






Australasian Paediatric Endocrine Group

Australian Diabetes Society

National Evidence-Based Clinical Care Guidelines for Type 1 Diabetes in Children, Adolescents and Adults

TECHNICAL REPORT

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This *Technical Report* is designed as a systematic review support document to the *National Evidence-Based Clinical Care Guidelines in Type 1 Diabetes for Children, Adolescents, and Adults*. It should not be read or used in isolation from the main document, *National Evidence-Based Clinical Care Guidelines in Type 1 Diabetes for Children, Adolescents, and Adults* which contains the *Executive Summary.*

Contents

1 Introduction

This technical report accompanies the *National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults*. It presents the findings from the systematic literature reviews that underpin the guidelines. The methods for the review are given in Chapter 2 of the guidelines document.

This document covers questions that were developed at the start of the review process and were systematically reviewed.

2 Methods

The development of evidence-based clinical practice guidelines involves developing a set of clinical research questions, systematically reviewing the scientific literature for evidence related to those questions, and then developing and grading recommendations based on a structured assessment of the evidence (NHMRC 1999; NHMRC (National Health and Medical Research Council) 2007; NHMRC 2009). The methods used in applying this process to the development of these guidelines are outlined in Chapter 2 of the guidelines and a summary of the overall process of guideline development is given in Appendix B (Process report).

3 Natural History and Prevention

Question 3.1

What interventions delay or prevent the onset of type 1 diabetes?

This section of the report is a systematic review of the evidence behind interventions used to prevent or delay the onset of type 1 diabetes in at-risk populations.

3.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 3.1

Table 3.1 Criteria for determining study eligibility, question 3.1

Study design	Systematic review, meta-analysis, randomised controlled trial
Population	Subgroup of general population at increased risk of developing type 1 diabetes, as defined by relationship to proband, diabetes autoantibody and/or HLA status
Intervention	Oral or parenteral immunomodulatory agents, insulin or dietary supplements
Comparator	Placebo or no intervention
Outcomes	Development of type 1 diabetes

HLA, human leukocyte antigen

3.1.2 Assessment of study eligibility

Publications identified in the literature search were reviewed using the criteria shown in Table 3.2, applied hierarchically, to determine which publications to exclude.

A total of 1386 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with 1355 publications excluded, as shown in Table 3.2. A total of 31 publications remained, and the full-text version of each of these publications was retrieved and reviewed.

3.1.3 Literature search summary

Table 3.2 Search results, question 3.1

Stage	Notes	Number
Search summary	Manual	4
	Cochrane Library	0
	EMBASE	51
	Medline	1331
	INAHTA	0
	Total	1386
Duplicates	Duplicates identified	181
Identified	Total identified	1205
Exclusion criteria	Wrong study type (narrative review, cohort studies, case control studies)	131
	Wrong population (patients who already have diagnosed type 1 diabetes)	919
	Wrong intervention (not an intervention to prevent or delay diabetes)	29
	Wrong outcome (not diagnosis of type 1 diabetes)	91
	Not in English	4
	Total excluded	1174
Meeting criteria	Total meeting inclusion criteria	31
Included	Total included studies	9

3.1.4 Included studies

After review of the 31 full-text articles, 4 were found to be narrative reviews, 15 were found to be cohort studies and 1 examined the wrong outcomes.

Two systematic reviews were found, one examining the effects of vitamin D supplementation (Zipitis and Akobeng 2008) and the other day-care exposure (Kaila and Taback 2001). Both meta-analyses were performed on cohort or case–control studies. No RCTs were identified in either systematic review. Thus these studies could not be included.

A total of nine Level I studies were included (Fuchtenbusch et al 1998; Lampeter et al 1998; Diabetes Prevention Trial – Type 1 Diabetes Study Group 2002; Gale et al 2004; Harrison et al 2004; Skyler et al 2005; Cabrera-Rode et al 2006; Olmos et al 2006; Nanto-Salonen et al 2008).

3.1.5 Results of included studies

Insulin interventions

The results of the studies looking at insulin interventions are summarised in Table 3.3.

Table 3.3 Summary for insulin interventions

Reference and setting	Study type, intervention, quality	Population	Duration (years)	Results
Nanto-Salonen et al (2008) Finland	RCT Actrapid intranasal Good	n=24 Positive for two types of antibodies and with at-risk alleles (HLA-DQB1)	10	Effect of insulin treatment (HR insulin ITT 0.98, 95%CI: 0.67 to 1.43, p=0.91)
				Yearly rates of progression insulin group 16.8% (95%CI: 11.7 to 21.9) Placebo group 15.3% (95%CI: 10.5 to 20.2)
Skyler et al (2005) US, Canada	Randomised placebo control Oral insulin Fair	n=372 First-degree relatives, ICA pos with 26–50% projected 5 year risk of diabetes	6	Proportion of participants who developed diabetes (annual average over follow-up) insulin group 6.4%, placebo group 8.2%. Cumulative incidence of diabetes similar in both groups (HR 0.764, 95%CI: 0.511 to 1.142, p=0.189)
Harrison et al (2004) Australia	Randomised double blind crossover Intranasal insulin Good (but not designed to determine whether intranasal insulin could prevent development of clinical diabetes)	n=38 First-degree relatives, IA/GAD/IA2 positive	3.75	12 participants, 6 randomised to each arm developed diabetes
Diabetes Prevention Trial – Type 1 Diabetes Study Group (2002) United States, Canada	Randomised control SC and IV insulin Good	n=339 First or second-degree relatives, ICA positive with >50% projected 5 year risk	6	Proportion of subjects developing diabetes was 15.1% in intervention group and 14.6% in observation group
				Cumulative incidence of diabetes HR in intervention group compared with observation group of 0.96 (95%CI: 0.69 to 1.34, p=0.80) Incidence of definite hypoglycaemia (blood glucose <50 mg/dL) 13.4 in intervention group compared with 2.6 in observation group (p<0.001)
Fuchtenbusch et al (1998)	Randomised controlled pilot study IV and SC insulin Poor	n=14 First-degree relatives, ICA>20, reduced FPIR, normal OGTT	7	Risk of diabetes after 1 year in insulin group mean 14% (95%CI: 0% to 40%) and in control group mean 43% (95%CI: 6% to 80%)
				Mean diabetes free survival time in insulin group 5 years (95%CI: 3.2 to 6.8 years) and in control group 2.3 years (95%CI: 1.0 to 3.6) years (p<0.03 log-rank test)

CI, confidence interval; FPIR, first phase insulin response ; HR, hazard ratio; ICA, islet cell antigen; ITT, intention to treat; IV, intravenous; OGTT, oral glucose tolerance test; SC, subcutaneous

Nicotinamide

The results of the studies examining nicotinamide interventions are summarised in Table 3.4.

Table 3.4 Summary of studies examining nicotinamide interventions

Reference and setting	Type and intervention	Comparator	N	Population	Follow up (years)	Quality	Result
Cabrera-Rode et al (2006) Cuba	RCT Oral nicotinamide 1.2 g/m^2 to a maximum of 3 g/day	Placebo	40	First degree relatives, 2-55 years of age with ICA>10 JDFU on two consecutive occasions	5	Good	Two participants in each group developed type 1 diabetes within 5 years
Olmos et al (2006) Chile	RCT Oral nicotinamide 1.2 g/m^2/day	Placebo	24	First-degree relatives ICA>20 JDFU; FPIR>10th centile	5	Good	60-month cumulative probability of staying diabetes-free was 100% in nicotinamide group and 62.5% in placebo group (95%CI: 17.0 to 100.0, p=0.0483)
Gale et al (2004) Europe, Canada, United States	RCT 1.2 g modified release nicotinamide	Placebo	552	First-degree relatives ICA>20 JDFU	5	Good	Unadjusted HR for development of diabetes (intervention) of 1.07 (95%CI: 0.78 to 1.45, p=0.69) High withdrawal rate (30.4%)
Lampeter (1998) Holland	RCT 1.2 g/m^2/day nicotinamide	Placebo	55	First-degree relatives ICA>20 JDFU twice, and normal OGTT	5	Good	5 cases of diabetes observed in placebo group (17%) and 6 in intervention group (24%)

CI, confidence interval; FPIR, first phase insulin response ; HR, hazard ratio; ICA, islet cell antigen; ITT, intention to treat; IV, intravenous; JDFU, Juvenile Diabetes Foundation units; OGTT, oral glucose tolerance test; SC, subcutaneous

3.1.6 Discussion

Insulin

Of the six studies included in this review, four found no difference in type 1 diabetes incidence after exposure to intranasal (Harrison et al 2004; Nanto-Salonen et al 2008), oral (Skyler et al 2005) or subcutaneous plus intravenous insulin (Diabetes Prevention Trial – Type 1 Diabetes Study Group 2002). The total numbers studied were lower in the two pilot studies (n=14–38). The other trials involved between 224 and 372 participants. The dissenting study (Fuchtenbusch et al 1998) reported on the results of a pilot study; it only gave results of delayed time to development, with no incidence statistics. The diabetes-free survival time was significantly increased compared to the observation group (mean 5 years, [95%CI: 3.2 to 6.8 years] vs 2.3 years [95%CI: 1.0 to 3.6 years], p<0.03). However, this was a small pilot study that was underpowered to detect the reduction in diabetes risk from 80% to 30%. Other reasons for this difference include the differing eligibility criteria. Fuchtenbusch et al (1998) used first degree relatives with FPIR to intravenous glucose tolerance test below the fifth centile whereas, in Skyler et al (2005), the FPIR was above the

tenth centile. Thus, this group is of higher risk of diabetes than if a normal threshold FPIR was used.

Nicotinamide

The four studies reporting on the effects of nicotinamide on the development of type 1 diabetes were of good quality. Three studies found no difference between treatment and placebo groups (Lampeter et al 1998; Gale et al 2004; Cabrera-Rode et al 2006). The dissenting study was a smaller study of 24 participants, and did not have development of diabetes as an a priori outcome measure; this study was also underpowered (Olmos et al 2006).

3.1.7 Conclusion

Overall, the results of the included studies found that the interventions studied did not delay or prevent the development of type 1 diabetes.

The Level II studies (RCTs) found were mainly of good quality, with one of fair quality and one of poor quality. Risk of bias was lower in the studies of good quality. For each intervention, results were consistent, apart from in one study. The inconsistent studies were in both cases smaller and underpowered, and one did not have diabetes development as an a priori outcome. The countries involved have well-developed health-care systems; they included North America, Europe and Australia. The at-risk populations were usually identified in the first instance as relatives of newly diagnosed patients with type 1 diabetes. One study was based on the availability of general population cord blood collection, which allowed the at-risk population to be identified from laboratory testing. This is relevant to the applicability of results if the local country does not have access to a similar database.

3.1.8 Literature search strategy

The search was conducted between 5 July 2010 and 12 July 2010. Level I studies were considered first, with the plan to update with Level II studies as required. The Medline search strategy and a summary of citations retrieved from other searches are shown in Table 3.5.

Table 3.5 Search strategy, question 3.1

Database	Date searched	#	Search terms	Citations
Medline		1	Diabetes Mellitus, type 1/	52 390
		2	(IAA or anti-insulin antibodies).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2916
		3	(IA2A or insulinoma-associated protein 2 or IA–2 or IA–2B or anti-IA2 or islet antigen–2).mp.	705
		4	(ICA or islet cell antibodies or islet cell autoantibodies).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	7812
		5	(GADA or GAD or anti-GAD or anti-glutamic-acid decarboxylase).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	5097
		6	(GAD antibodies or glutamic-acid decarboxylase antibodies or GAD autoantibodies).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	441
		7	Milk Proteins/	7960
		8	Vitamin D3.mp. or Cholecalciferol/	8030

Database	Date searched	#	Search terms	Citations
		9	Docosahexaenoic Acids/	4052
		10	gluten.mp. or Glutens/	7256
		11	Niacinamide/	5674
		12	Insulin/	139 149
		13	Cyclosporine/	23 266
		14	Azathioprine/	12 050
		15	OKT3.mp. or Muromonab-CD3/	4168
		16	Mycophenolic Acid/	4743
		17	Antineoplastic Agents/ or Antibodies, Monoclonal/ or rituximab.mp.	286 886
		18	Immunosuppressive Agents/ or Receptors, Tumor Necrosis Factor/ or etanercept.mp.	73 238
		19	Recombinant GAD.mp.	22
		20	thymoglobulin.mp.	369
		21	anti CD3.mp. or Antibodies, Monoclonal/	153 888
		22	Interleukin–2/	33 001
		23	Sirolimus/	8289
		24	randomised controlled trial/	294 963
		25	controlled clinical trial.mp.	87 580
		26	(randomi?ed or rct).ab,ti. or random allocat*.ti,ab.	258 513
		27	Double-Blind Method/ or Placebos/	126 201
		28	islet autoantibodies.mp.	171
		29	diabetes autoantibodies.mp.	25
		30	Prediabetic State/ or pre-diabetes.mp.	2826
		31	nicotinamide.mp.	12 100
		32	BHT–3021.mp.	1
		33	DNA plasmid.mp.	635
		34	1 or 2 or 3 or 4 or 5 or 6 or 28 or 29 or 30	67 912
		35	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 31 or 32 or 33	584 514
		36	34 and 35	15 064
		37	24 or 25 or 26 or 27	488 740
		38	35 and 36 and 37	1439
		39	limit 38 to (english language and humans)	1331
EMBASE	6 July 2010	#9	#1 AND #7 AND #8	51
		#8	#4 OR #6	80 817
		#7	randomised AND controlled AND trial OR controlled AND clinical AND trial OR randomi?ed OR rct.ab,ti OR random AND allocat*, AND ti, AND ab. OR 'double blind' AND 'method'/exp OR 'placebos'/exp	173 690
		#6	'insulin'/exp OR cyclosporine OR 'azathioprine'/exp OR 'okt3'/exp OR 'muromonab cd3'/exp OR mycophenolic AND 'acid'/exp OR antineoplastic AND agents OR monoclonal AND 'antibodies'/exp OR 'rituximab'/exp OR immunosuppressive AND agents OR 'etanercept'/exp OR 'gad'/exp OR 'thymoglobulin'/exp OR anti AND	78 124

Database	Date searched	#	Search terms	Citations
			'cd3'/exp OR 'interleukin 2'/exp OR 'sirolimus'/exp	
		#4	'milk'/exp AND 'proteins'/exp OR 'cholecalciferol'/exp OR 'vitamin'/exp AND d3 OR docosahexaenoic AND 'acid'/exp OR 'gluten'/exp OR 'niacinamide'/exp AND [humans]/lim AND [english]/lim AND [embase]/lim AND [medline]/lim	2756
		#1	type AND 1 AND ('diabetes'/exp OR diabetes) AND ('prevention'/exp OR prevention)	19 768
Cochrane				0
INAHTA				0
Manual search				4
Total citations				1386
Total non-duplicate citations				1205

3.1.9 Evidence Matrix

Question 3.1 – nicotinamide

Q3.1	What interventions delay or prevent the onset of type 1 diabetes?	
Evidence statement	There is no evidence to support the use of any intervention to delay or prevent the onset of type 1 diabetes.	
Evidence base	A	Four RCTs, all of good quality.
Consistency	A	Studies consistent in showing no effect.
Clinical impact	NA	Given that nicotinamide is not used routinely to delay or prevent type 1 diabetes, the clinical impact of this intervention is not applicable.
Generalisability	C	The target population was people without type 1 diabetes. The evidence base included only high-risk populations (but with differences in definitions), who represent only 10% of people who develop type 1 diabetes.
Applicability	A	The studies included one from Australia; the remainder were from countries with well-established health-care systems.
Other factors	None identified.	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 3.1 – insulin

Q3.1	What interventions delay or prevent the onset of type 1 diabetes?	
Evidence statement	There is no evidence to support the use of any intervention to delay or prevent the onset of type 1 diabetes.	
Evidence base	A	Five RCTs – three of low risk of bias, one of moderate risk of bias and one of high risk of bias.
Consistency	A	All studies reporting diabetes as an outcome were consistent (excluding the one poor-quality study).
Clinical impact	NA	Given that insulin is not used routinely to delay or prevent type 1 diabetes, the clinical impact of this intervention is not applicable.
Generalisability	C	The target population was people without type 1 diabetes. The evidence base included only high-risk populations (but with differences in definitions), who represent only 10% of people who develop type 1 diabetes.
Applicability	A	The studies included one from Australia; the remainder were from countries with well-established health-care systems.
Other factors	None identified.	
Recommendation		
R3.1	No interventions are recommended for use in clinical practice to delay or prevent the onset of type 1 diabetes (Grade A).	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

4 Impact of type 1 diabetes on the individual and society

4.1 Prevalence of psychological disorders

> Question 4.1
>
> Is there an increased prevalence of psychological disorders in people with type 1 diabetes across the lifespan, including clinical depression, anxiety disorder and eating disorder?

This section of the report addresses the prevalence of psychological disorders including depression, anxiety and eating disorders in people with type 1 diabetes, compared with the nondiabetic population where controlled data are available.

4.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown inTable 4.1 .

Table 4.1 Criteria for determining study eligibility, question 4.1

Study design	All, including systematic review or meta-analysis of controlled studies, controlled cross-sectional studies, uncontrolled studies in paediatric population
Population	Type 1 diabetic subjects
Intervention	Assessment of prevalence of psychological disorders
Comparator	Control group of nondiabetic subjects, noncontrolled studies included for paediatric population
Outcomes	Prevalence of psychological disorders

4.1.2 Assessment of study eligibility

Publications identified in the literature search were reviewed using the criteria shown in Table 4.2, applied hierarchically, to determine which publications to exclude.

All study types reporting prevalence were included. Studies that did not report prevalence data specifically for type 1 diabetes were excluded. The assessment test used in the individual study was not part of the exclusion criteria. Studies without a concurrent control population of nondiabetic subjects were excluded unless no other controlled studies for that disorder or age group (paediatric or adolescent) were found.

The exclusion criteria were applied to all citations by reviewing the abstract and title, with 120 publications excluded. A total of 15 publications remained, and the full-text version of each of these publications was retrieved and reviewed.

4.1.3 Literature search summary

Table 4.2 Search results, question 4.1

Stage	Notes	Number
Search summary	Manual	0
	Medline	61
	Psychinfo	74
Duplicates	Duplicates identified	23
Identified	Total identified	135
Exclusion criteria	Wrong study type	17
	Wrong population (not type 1 diabetic subjects)	23
	Wrong intervention or test (not assessment of psychological disorder, depression, eating disorder or anxiety)	24
	Wrong comparator (no nondiabetic subject population as comparator (adult population)	7
	Wrong outcome (not a psychological disorder; depression, eating disorder or anxiety)	20
	Not in English	6
	Total excluded	120
Meeting criteria	Total meeting inclusion criteria	15
Included	Total included studies	15

4.1.4 Included studies

Two systematic reviews were found that addressed the prevalence of depression in adults (Anderson et al 2001; Barnard et al 2006). The study by Andersen et al was updated by Barnard et al, and is not discussed individually here. The full text of one systematic review on depression prevalence was not able to be retrieved by the time of writing this report (Gavard et al 1993).

One systematic review on anxiety in the adult population was found (Grigsby et al 2002); however, this review included only one controlled study of subjects with type 1 diabetes (Friedman et al 1998). That single study is detailed here separately.

Three systematic reviews were found on eating disorders in the adult and adolescent populations (Nielsen 2002; Mannucci et al 2005; Young-Hyman and Davis 2010). On examination of the full text, the review by Young Hyman et al was found to be conducted in a nonsystematic way and was therefore excluded.

The systematic reviews were updated with primary studies of a more recent publication date. These included a study in American youth regarding psychiatric disorders (Kovacs et al 1997), a cross-sectional study of adults with depression (Gendelman et al 2009) and three studies in adolescents regarding eating disorders (Colton et al 2004; Colton et al 2007; Ackard et al 2008).

No studies specifically reported on diabetes distress as an outcome. In adults, one study reporting on psychological distress in a diabetic subject population was included. Studies reporting paediatric psychosocial well-being or psychosocial functioning were included.

4.1.5 Characteristics of included studies

The characteristics of the included studies are shown in Table 4.3, below.

Table 4.3 Characteristics of included studies

Study reference	Studies included, setting	Study type	Population	Control	Screening test or assessment method
Psychological distress					
Li et al (2009)	United States	Cross sectional	Adults	Subjects without diabetes	Kessler 6
Paediatric psychosocial well-being or psychosocial functioning					
Northam et al (2010)	Australia	Prospective cohort	Youth aged 1–14 years	Age and sex matched	YSR and YASR: CBCL, and semistructured interview
Nardi et al (2008)	Italy	Cross sectional	Youths aged 6–18 years	Subjects without diabetes	CBCL, YSR, PedsQL
Helgeson et al (2007)	United States	Prospective cohort	Adolescents aged 10–14 years	Healthy adolescents	CDI, modified RCMAS, DES, EDI, BASC, SPPC via interview
Psychiatric disorders (depression, anxiety, conduct disorder)					
Barnard et al (2006)	4	Systematic review	Adults	First degree relatives/ medically well	Diagnostic interview: DIS/DSM-III, BDI≥14, PSE ID≥5, DIMD, M-CIDI
Gendelman et al (2009)	America	Cross sectional	Adults	Subjects without diabetes from the community	Self-report questionnaire: BDI-II>14
Kovacs 1997	America, single site	Prospective	Youth aged 8–13 years	No control	Diagnostic interview with mental health professional
Anxiety					
Herzer (2010)	America	Cross sectional	Adolescents	Noncontrolled	STAI
Grigsby et al (2002)	Only 1 study fulfilling criteria	Systematic Review	Adults	As per Friedman et al (1998)	As per Friedman et al (1998)
Friedman et al (1998)	France	Cross sectional	Adults	General outpatients Nursing students	Self-report questionnaire and diagnostic interview
Eating disorders					
Mannucci et al (2005)	8	Systematic review and meta-analysis	Adults and adolescents females	Subjects without diabetes	Diagnostic interview: DSM-III
Nielsen (2002)	8	Systematic review and meta-analysis	Adults and adolescent females	Subjects without diabetes	Diagnostic interview: DSM-III

Study reference	Studies included, setting	Study type	Population	Control	Screening test or assessment method
Ackard et al (2008)	Minnesota, United States	Cross sectional	Adolescents	Unconventional control	Self-reported survey
Colton et al (2004)	Canada	Cross sectional	Preteen and early teenage girls	Case–controlled	Diagnostic interview – Children's EDE
Colton et al (2007)	Canada	Longitudinal	Preteen and early teenage girls	No control group	Diagnostic interview – Children's EDE

BASC, Behaviour Assessment System for Children; BDI, Beck Depression Inventory; CBCL, Child Behaviour Check List; CDI, Children's Depression Inventory; DES, Differential Emotions Scale; DICA-IV, Diagnostic Interview for Children and Adolescents; DIMD, Diagnostic Interview for Mental Disorders; DIS/DSM-III, Diagnostic Interview Schedule/Diagnostic and Statistical Manual-III; EDE, Eating Disorder Examination; M-CIDI, Munchener Composite International Diagnostic Interview; PedsQL, Pediatric Quality of Life Inventory; PSE ID, Present State Examination; RCMAS, Revised Children's Manifest Anxiety Scale; SPPC, Self-Perception Profile for Children; STAI, State-Trait Anxiety Inventory; YASR, Young Adult Self Report; YSR, Youth Self Report

4.1.6 Results of included studies

Psychological distress

Li et al (2009)

The aim of the study by Li et al (2009) was to estimate the prevalence of severe psychological distress (SPD) among people with and without diagnosed diabetes, using data from the Behavioural Risk Factor Surveillance System (BRFSS). The BRFSS was a survey conducted in 2007 in the United States that involved monthly standardised telephone surveys. The survey data were used to assess the prevalence of key behavioural risk factors and chronic disease conditions in all states annually. The Kessler 6 (K6) scale was used to measure nonspecific serious psychological distress. Psychological distress was determined on the basis of how frequently participants reported having felt, during the previous 30 days, 1) nervous, 2) hopeless, 3) restless or fidgety, 4) so depressed that nothing could cheer them up, 5) that everything was an effort and 6) worthless. A 5-point Likert scale was used to rank the frequency with which participants reported experiencing these symptoms: 0 = 'None of the time', 1 = 'A little of the time', 2 = 'Some of the time', 3 = 'Most of the time' and 4 = 'All of the time'. Total scores could thus range from 0 to 24. Respondents were considered to have probable SPD if their total K6 score was 13 or above. Among the 220 235 participants aged over 18 years, 24 039 (8.4%) reported having diabetes. Of those, the type of diabetes was reported for 15 605 subjects, of whom 713 had type 1 diabetes. The prevalence of SPD was found to be 11% (standard error [SE] 2.4) among people with type 1 diabetes. The prevalence of SPD among those with no diagnosed diabetes was 3.6% (SE 0.1). In comparison, the prevalence of SPD in diagnosed diabetes of any type was 7.6% (SE 0.4). For any type of diagnosed diabetes, the unadjusted prevalence ratio was 2.09 (95% confidence interval [CI]: 1.87 to 2.34). Although not specified for the type 1 population, the authors found that the prevalence ratio of SPD between people with and without diagnosed diabetes was greatly attenuated after adjustments for all correlates. The following factors were also found to be independent correlates of SPD among people with diagnosed diabetes: young age, low education level, low annual household income, obesity, current smoking, no leisure-time physical activity, the presence of one or more microvascular or macrovascular complications, and disability.

The limitations of this study were the self-reporting of symptoms rather than an actual diagnosis, and the necessity of a landline telephone for participation.

Paediatric psychological adjustment, psychosocial well-being and psychosocial functioning

Northam et al (2010)

The prospective cohort study by Northam et al (2010) compared functional outcomes in youth with type 1 diabetes to community controls. After 12 years of follow-up, relationships between psychosocial variables at diagnosis and functional outcomes were examined. Consecutive admissions to a tertiary hospital, together with age and sex-matched controls, were recruited between 1990 and 1992. There were 133 newly diagnosed subjects with type 1 diabetes, aged 1–14 years. At 12 years of follow-up, 110 participants with type 1 diabetes and 76 controls participated in the current study.

Follow-up measures of psychosocial well-being were the Youth Self Report (YSR) and Young Adult Self Report (YASR), which provide scores for internalising (anxiety, withdrawal and somatic concerns) and externalising (aggression and delinquency) problems. A semistructured interview was conducted to obtain information about referral rates for mental health services over the previous 12 years, as an indicator of overall psychological morbidity.

The mean age of participants was 20.7 years. Group differences on sex ratio and age were small. Regarding current psychiatric status and functional outcome, youth with type 1 diabetes were more likely than control subjects to have had contact with mental health services (37% vs 18%, chi-square=8.30, p=0.004). The authors concluded that youth with type 1 diabetes reported similar levels of current psychosocial well-being compared with healthy control subjects, but that referrals for mental health services were 19% higher than in the control group. This prospective cohort study employed consecutive recruitment for the diabetic subject group, and had a long and relatively complete follow-up. It was the only study in this review to have used referral to mental health services as an indicator of psychological morbidity.

Nardi et al (2008)

Nardi et al (2008) evaluated self and parent reports on quality of life (QoL) and psychological adjustment of youths with type 1 diabetes in a cross-sectional study with a control group of subjects without diabetes, in Italy. The recruitment was of 90 consecutive eligible families from a diabetes centre. The Child Behaviour Check List (CBCL) questionnaire was filled in by parents and the YSR completed by the children or adolescents. The instruments generated a total problems score, which is an index of psychopathological severity. The total problem score was within the normal range for 86.8% of youth with type 1 diabetes and 82.2% in controls (chi-square test, p=0.76). In the group of children and adolescents considered together, self-report questionnaires showed that children and adolescents had a psychological adjustment similar to the controls. Adolescents showed a worse QoL and more frequent psychological disturbances.

Helgeson et al (2007)

The prospective cohort study by Helgeson et al (2007) examined the association with diabetes and psychosocial difficulties over the transition to adolescence. The study enrolled 132 adolescents with type 1 diabetes who responded to a letter of invitation from a local children's hospital. A control group was recruited from area malls and a physician network. The adolescents with diabetes and the control group were compared on indices of psychosocial functioning for 3 years, via yearly interview. The retention rate over 3 years was 96%. The assessments used were the Children's Depression Inventory (CDI), Self-Perception Profile for Children (SPPC), Eating Disorder Inventory (EDI) and Behaviour

Assessment System for Children (BASC). There were no differences between groups and no group effects for depressive symptoms, anxiety or anger. None of the parameters were significant in the final model for bulimia. There was evidence of greater difficulties for those with diabetes compared with peers in drive for thinness. The group-by-time interaction revealed an increase in drive for thinness for adolescents with diabetes over time, and a decrease for healthy adolescents when averaging across males and females. The limitations of the study were the homogenous sample demographics, the effect of interviewing the diabetic subject group in hospital compared to home interviews for the controls, and lack of full matching of controls. The strengths were the large sample, high retention rate and wide array of standardised instruments.

Psychiatric disorders

Northam et al (2005)

The prospective cohort study by Northam et al (2005) described psychiatric status and relationship to metabolic control in a group of adolescents with type 1 diabetes. There was no control group. A total of 41 adolescents completed a self-report measure of psychiatric status, 10 years after disease onset. The cohort of 133 patients was recruited at diagnoses of type 1 diabetes from a single centre in Melbourne. The adolescents completed the Diagnostic Interview for Children and Adolescents (DICA)-IV questionnaire during a routine diabetic subject clinic outpatient visit. This was a computerised version of DICA that has been found to be more acceptable to adolescents than face-to-face administration. The individual disorders were grouped into mood, anxiety, eating and behaviour disorders. Interview times ranged from 50 minutes to 120 minutes. The DICA-IV is reported to have high agreement with the CBCL, and moderate agreement with clinical diagnoses. It was found that 37% (n=15) of the sample received a Diagnostic and Statistical Manual (DSM)-IV diagnosis. Diagnoses included mood, anxiety, eating and behaviour disorders. Of those who received a diagnosis, 60% met criteria for two or more psychiatric disorders. Although the study was not controlled, the authors report that levels were 2–3 times higher than in the general community. This was the only study found in this body of evidence to have used a computerised self-administered interview to assess the level of psychiatric morbidity.

Kovacs et al (1997)

The single site prospective study by Kovacs et al (1997) reported the rates, associated features and risk factors for psychiatric disorders in young people aged 8–13 years at onset of type 1 diabetes, and who were studied longitudinally from initial diagnosis for a median interval of 9 years. The focus was on psychiatric disorders that began after onset of type 1 diabetes. The study reported results of 92 patients who represented 97% of the original sample recruited. The patients were sequential admissions to the diabetes inpatient service in Pittsburgh, and were newly diagnosed with classic acute onset type 1 diabetes. The mean age was 11 years, and there were 49 girls and 43 boys. The assessment consisted of an interview with a mental health professional. Psychiatric status was assessed by means of the standardised, semistructured, symptom-based Interview Schedule for Children and Adolescents (ISCA). After each evaluation, the symptom ratings and clinical history were used to determine whether the subject met DSM-II criteria for a psychiatric disorder.

The study found that 15 children (16.3%) had a psychiatric disorder at study entry that predated onset of type 1 diabetes. The authors reported this rate as within the range reported for population samples of youths. Of the children, seven had anxiety disorders, two had attention deficit disorder and one had conduct disorder. None had a history of depressive disorder. Operational criteria were used to diagnose an adjustment disorder in

response to the medical condition. A total of 31 children had an adjustment disorder within 3 months of diabetes onset.

The results after a median of 9.1 years of follow-up were that 39 youths (42.4%) developed at least one episode of psychiatric disorder during the follow-up, and 24 youths had two or more different diagnoses. The disorders were mostly grouped into the broad categories of depressive, anxiety and behaviour (conduct/substance use) disorders:

- 24 patients (26.1%) had major depressive disorder
- 18 patients (19.6%) developed some type of anxiety disorder, most commonly generalised anxiety disorder (n=9) that can be diagnosed with DSM-III only after age 18 or an overanxious disorder of childhood (n=6)
- 15 patients (16.3%) had behaviour disorders
- 5 patients had both conduct and substance use disorders.

According to life-table analyses, the first year of the type 1 diabetes was associated with the highest incidence of a psychiatric disorder in general, and with depressive and anxiety disorders in particular. The corresponding first year hazard rates are 0.165 for any psychiatric disorder, 0.103 for depressive and 0.0559 for anxiety disorders in particular. The authors reported that the prevalence of major depression in their subjects was higher than rates in similarly aged cohorts in the general population. The risk of any anxiety disorder was lower in their subjects than rates in the national probability sample and community sample. However, the rate found of generalised anxiety disorder of 12% appeared to be elevated compared to the general population rate. The limitations of this study were the small sample size and absence of control group.

Depression

Barnard et al (2006)

Barnard et al (2006) conducted a systematic review of the literature to estimate the cross-sectional prevalence of clinical depression in adults with type 1 diabetes. Fourteen studies were identified from a systematic search of studies published between January 2000 and June 2004. A previous meta-analysis was used to identify studies prior to 2001 (Anderson et al 2001). Of the studies found, only four were controlled studies of a population with type 1 diabetes. Of these four studies, diagnostic interviewing techniques were used in three studies, with only a questionnaire used in the remaining study. The depression assessment method was different in each study and included the Beck Depression Inventory (BDI), Diagnostic Interview for Mental Disorders (DIMD), the Diagnostic Interview Schedule/Diagnostic and Statistical Manual-III (DIS/DSM-III), the Munchener Composite International Diagnostic Interview (M-CIDI) and the Present State Examination (PSE).

The overall prevalence of depression identified in the primary studies ranged from 5.8% to 43.3% in the type 1 diabetes population. In the control populations, the prevalence ranged from 2.7% to 2.9%. The weighted mean prevalence rate was 12.0% for individuals with diabetes and 3.2% for the control population. When the study that did not use a diagnostic interview was excluded, the weighted prevalence rate for depression dropped to 7.8%. Although the prevalence for subjects with diabetes was double that of the control subjects, the weighted effect was not significant (odds ratio [OR] 2.36, 95%CI: –0.69 to 5.4). The authors noted there is currently insufficient evidence to conclude that depression is more prevalent in those with type 1 diabetes than in matched control groups. They also noted that the duration of illness or age of onset was recorded in only three studies.

One of the strengths of this study was that controlled studies were used for summary statistic calculations. This exclusion of noncontrolled studies reduced the recruitment bias inherent in noncontrolled surveys. In addition, the authors excluded the questionnaire-assessment method, due to its overestimation of prevalence. The control groups used in the four studies could not be considered comparable because in two of the studies, the control group was half the size of the diabetic subject group and had a markedly different gender distribution. One of the four studies was considered to be of adequate methodological rigour. This study indicated significantly increased rates of major depression for women with diabetes (9.3% in the diabetes group compared with 3.2% in the reference group), but not for men (3.6% type 1 diabetes compared with 2.2% control). The participants in this study were newly diagnosed; thus, the results may reflect response to diagnosis and may not be representative of the general type 1 diabetes population.

Gendelman et al (2009)

Gendelman et al (2009) reported data collected as part of the third study visit in the Coronary Artery Calcification in type 1 diabetes (CACTI) study from 2006 to 2008. A total of 1130 participants had completed the third study visit. Controls were recruited from the community; they included spouses, neighbours and friends of type 1 diabetic subject participants. The ascertainment method used was a mail out of the BDI questionnaire. Questionnaires were completed by 1004 participants, including 458 with type 1 diabetes. Of these, 47% were male aged 44 ±9 years, with a duration of diabetes of 29±9 years. The control population were aged 47 ±9 years and 51% were male. Depression was defined as use of at least one antidepressant medication or a BDI-II score above 14 (or both).

In this sample, the prevalence of depression as defined above in participants with type 1 diabetes was significantly higher than that of age and sex-adjusted participants without diabetes (32.1 vs 16%, $p<0.0001$). A BDI-II score above 14 was seen in 17.5% of participants with diabetes compared with 5.7% of controls ($p<0.0001$). Antidepressant use was reported in 20.7% of type 1 diabetes participants compared with 12.1% of controls ($p=0.0003$). When depression was defined as a BDI-II above 14 or antidepressant medication use, significantly more women than men with type 1 diabetes had depression (37.9 vs 25.5, $p=0.005$). When defined by BDI score alone, there was no difference.

The authors concluded that their results were some of the first to specifically demonstrate an increased prevalence of depression among adults with type 1 diabetes compared with age and sex-matched controls. Results also suggested that adults with type 1 diabetes were more than twice as likely as adults without diabetes to have depression, as assessed by BDI-II above 14 or current antidepressant use, or both. Previous studies have shown lower rates of depression. The authors postulated that this was because of differing criteria for the diagnosis of depression, and that a BDI-II score above 14 was considered indicative of mild depression. In addition, other studies may have reported a mixed sample of type 1 and 2 diabetes. The inclusion of current antidepressant medication use as an indicator of depression may have captured individuals successfully treated for depression who may no longer score high on the depression assessments. The limitations of this study were the use of a self-report questionnaire rather than diagnostic interview, as such questionnaires may overestimate prevalence compared with diagnostic interview.

Anxiety symptoms

Herzer et al (2010)

The cross-sectional study by Herzer et al (2010) was conducted in multiple sites in the United States, and examined the rates of anxiety in adolescents with type 1 diabetes. A total of 276

adolescents aged 13–18 participated by completing the State-Trait Anxiety Inventory (STAI) questionnaire during a clinic visit. The STAI does not provide clinical cut offs to denote elevated levels of anxiety suggestive of further evaluation. The mean age of participants was 15.63 years, and there was no control group. Adolescents had a mean STAI anxiety state score of 29.82 and a trait score of 32.15. The authors reported that this was comparable to published norms for children otherwise healthy, and noted that the STAI only provides a broad measure of anxiety symptoms; it does not provide a clinical cut off point nor convey a diagnosis of an anxiety disorder.

Anxiety

Grigsby et al (2002)

The aim of the review by Grigsby et al (2002) was to estimate the prevalence of clinically significant anxiety in adults with diabetes. A systematic search was performed, and studies were included if they had a sample size above 25 and were published before 2001. Anxiety disorders were assessed with structured or semistructured diagnostic interviews such as the Diagnostic Interview Schedule (DIS), or the Schedule for Affective Disorders and Schizophrenia Lifetime Version (SADS-LA), and diagnosed according to the criteria specified in the version of the DSM current at the time of the study.

This review identified two controlled studies in people with type 1 diabetes. One of these studies examined anxiety symptoms rather than anxiety disorder prevalence. The remaining included study was by Friedman et al (1998), and is described below. Grigsby et al (2002) state that the number of studies that reported prevalence by type of diabetes was insufficient to statistically assess the influence of these factors to calculate the adjusted prevalence.

Friedman et al (1998)

The frequency of anxiety and depressive disorders was examined in the controlled study by Friedman et al (1998) of 69 French young adults with type 1 diabetes. Eighty patients were included from an outpatient cohort; 69 completed a self-report questionnaire and, of these, 41 participated in a diagnostic interview. Control subjects were recruited from patients without diabetes attending a general outpatient clinic; 54 female nursing students were also recruited.

The questionnaires used were the Hopkins Symptom Checklist (HSCL) which assesses psychological symptoms of anxiety and depression, and somatic symptoms. The results from the self-questionnaires on anxiety and affective disorders comparing the HSCL and BDI scores were that medical outpatients reported more anxiety and affective disorders, and had higher mean BDI and HSCL 58 scores than patients with diabetes (HSCL: t=–2.2, p=0.03).

Among the 41 patients who completed the SADS-LA-R (modified for the study of anxiety disorders), 14 men and 19 women had at least one lifetime episode of anxiety disorder. Almost half of the diabetic subject population (48.6%) had in their life time suffered from a disorder of generalised anxiety, as expressed in terms of a specific DSM-III-R diagnosis (14.6%) or in terms of an anxiety disorder not meeting DSM-III-R criteria due to the short duration of the symptoms. A total of 24.4% of patients had a simple phobia at the time of the study. The mean age of the participants with diabetes was 26.7 years. The prevalence of DSM-III-R anxiety disorders in type 1 diabetes are summarised in Table 4.4 below.

Table 4.4 Prevalence of DSM-III-R anxiety disorders in type 1 diabetes

DSM-III-R disorder	Men: n=19		Women: n=22		All: n=41	
	Life time (%)	Present (%)	Life time	Present	Life time	Present
Not specified anxiety disorder	8(42)	8(42)	8(36)	7(31)	16(39)	15(36)
Simple phobia	4(21)	4(21)	7(31)	7(31)	11(26)	11(26)
Panic disorder	1(5.3)	1(5.3)	0	0	1(2.4)	11(2.4)
Generalised anxiety	1(5.3)	0	1(4.5)	0	2(4.8)	
PTSD	0	0	2(9)	1(4.5)	2(4.8)	1(2.4)

DSM-III-R, Diagnostic and Statistical Manual-III-R; PTSD, post-traumatic stress disorder

This study did not find a higher frequency of emotional disorders in a young adult population of type 1 diabetes patients than in two control populations. The prevalence of anxiety based on DSM-II criteria was not different compared to control groups. However, the authors reported that the lifetime prevalence of generalised anxiety disorder was higher than that reported for the general French population.

The limitations of this study included the small sample size, a possibly nonrepresentative population of participants with diabetes, and a control population that was not submitted to a diagnostic interview of emotional disorders.

Eating disorder

Mannucci et al (2005)

Mannucci et al (2005) performed a meta-analysis of controlled studies on prevalence of eating disorders in type 1 diabetes, to assess differences between type 1 diabetic and nondiabetic female subjects. All controlled studies published between 1987 and 2003 using the DSM-III or DSM-IV criteria using structured or nonstructured interviews were included.

Eight studies were included in the analysis, but only two included male patients with diabetes and control subjects. The total number of patients with diabetes was 847 (99 males, 748 females), while controls were 1745 (158 males, 1587 females). Male subjects were excluded from the analysis because of insufficient sample size. Differences in current prevalence of eating disorders were assessed using the chi-square test. The variance in the prevalence of eating disorders in type 1 diabetic patients and control subjects was calculated, as well as the sampling error variance. The age of the subjects included in the individual trials was not specified.

The prevalence of anorexia nervosa in type 1 diabetic subjects was not significantly different from that of controls (0.27% vs 0.06%); however, the prevalence of bulimia nervosa and of the two conditions combined was significantly higher in diabetic patients (1.73 vs 0.69%, and 2.00 vs 0.75%, respectively; both $p<0.05$). The authors concluded that type 1 diabetes is associated with a higher prevalence of bulimia nervosa in females.

Nielsen (2002)

The systematic review and meta-analysis by Nielsen et al (2002) aimed to provide a quantitative summary of existing studies on the occurrence of eating disorders in females with type 1 diabetes. The studies included differed slightly to the meta-analysis conducted

by Mannucci et al (2005), with one study included published in 1986 that was not included by Mannucci et al (2005). The effect of inclusion or omission of this study did not affect the statistical significance of the overall finding, but the estimated OR was increased by 30% if it was included. The omission of the study was justified by the author on the basis that it used self-report measures only. Thus, the findings were similar to that of Mannucci et al (2005), as the OR for bulimia nervosa was increased three fold but the statistical significance was marginal (p=0.04). Anorexia nervosa does not seem to be increased in type 1 diabetes populations. The findings for eating disorders not otherwise specified (ED-NOS) and subthreshold eating disorder were more substantive; in both cases the ORs were increased two fold and the increases were statistically significant (p<0.001).

Ackard et al (2008)

The aim of the cross-sectional study by Ackard et al (2008) was to compare the prevalence of disordered eating and body dissatisfaction between adolescents with type 1 diabetes and a population-based sample of youth. A clinic-based sample of 143 adolescents (58% of all eligible) chose to participate as the subject group with diabetes. This population had participated in Assessing Health and Eating among Adolescents with Diabetes (AHEAD). The control population was drawn from a population-based sample of 4746 youths who participated in Project Eating Among Teens (Project EAT). Both populations had answered common survey questions regarding weight perception and weight-control behaviours. The control population were not identified as to whether or not they had diabetes; thus, it is likely some of the control population had diabetes, but the number is unknown. Data sets from the separate studies were merged, and the authors report that variables were recoded when necessary to harmonise the surveys. A propensity matching method was used to approximate a 1:4 sampling ratio. Due to the different sources of population, all analyses were adjusted for age, race and socioeconomic status, as well as body mass index (BMI). There was a nonsignificant difference between groups regarding diagnosis of eating disorder. The prevalence of unhealthy weight control behaviour specific to type 1 diabetes is also shown in Table 4.5 below.

Table 4.5 Prevalence of unhealthy weight control behaviour in type 1 diabetes

	Males: type 1 diabetes (n=73)	Males: population (n=2377)	P value	Females: type 1 diabetes (n=70)	Females: population (n=2357)	P value
Diagnosed with eating disorder (%, SE)	1.8(1.8)	2.1(0.3)	0.864	1.6(1.6)	2.9(0.4)	0.560
Omitted insulin	1.4(1.4)	NA	NA	10.3(3.7)	NA	NA
Did not take insulin as directed	1.4(1.4)	NA	NA	7.4(3.2)	NA	NA

NA, not applicable; SE, standard error

The authors concluded that the findings from the study indicated that male and female youth with type 1 diabetes were not at increased risk for unhealthy weight control behaviours or weight dissatisfaction. However, of concern was that 10.3% females and 1.4% boys with type 1 diabetes reported skipping insulin in the past year, in an effort to lose weight or avoid gaining weight. The strengths of this study included its comparative nature, and the limitations included the dissimilar population used as a control group and unknown prevalence of diabetes in the 'control' population. The relatively small sample size of the youth participants with diabetes also reduces the power to detect clear differences. The

participants in the diabetes group may not have been representative of the population with diabetes as a whole.

Colton et al (2004)

Colton et al (2004) compared the prevalence of disturbed eating behaviour and eating disorders in preteen and early teenage girls with type 1 diabetes compared with age-matched, female control subjects without diabetes. The assessment measure was the Children's Eating Disorder Examination interview. Girls with type 1 diabetes aged 9–13 years were recruited during their clinic appointments at a children's hospital in Canada. The control group were recruited from local schools. Exclusion criteria for both groups were lack of fluency in English and developmental delay and, for the group with diabetes, a diagnosis for type 1 diabetes less than 6 months before the study. A total of 101 girls with type 1 diabetes (71% participation rate) and 439 controls without diabetes completed the assessment. The controls were age matched at a ratio of 3:1. Participants completed a private, semistructured, standardised diagnostic interview administered by trained interviewers with high inter-rater reliability. The authors acknowledged that there was little psychometric work done in the preteen age group, and that diagnostic criteria fluctuate over time. For this study, diagnoses of anorexia nervosa and bulima nervosa were based on DSM-IV criteria. ED-NOS was not considered a full-syndrome disorder in this study. Insulin dosage omission or reduction was diagnosed only if it was primarily a purging strategy to promote weight loss.

The results reported in 2004 were that there were no current diagnoses of anorexia nervosa or bulimia nervosa among any of the female subjects. In the girls with diabetes, there were two cases of ED-NOS and 6 cases of subthreshold disorders; in the control group, all three cases were subthreshold disorders. Binge eating, intense excessive exercise for weight control, reporting two or more current disturbed eating behaviours and ED-NOS or subthreshold eating disorders were all significantly more common among girls with diabetes than among girls without diabetes. All differences were confirmed or heightened when analyses were limited to participants aged 11 years or older. In addition, the prevalence of insulin omission for weight control was 2% in preteen girls, 14% in teenage girls and 34% in young adult women. The limitations of this study were that the rates of disturbed eating behaviours may have been underestimated, because individuals with significant eating problems have been shown to be less likely to participate in studies of eating problems. The strengths of the study were a large sample size, control group and use of standardised diagnostic interviewers.

Colton et al (2007)

The results from the Colton et al (2004) study published in 2007 reported on the data from baseline to 5 year follow-up. Point prevalence and cumulative prevalence were recorded. A total of 98 of 126 girls were still participating at 5 year follow-up. Girls who dropped out at 5 years were not more likely to have disordered eating behaviour at baseline than those who stayed in the study. At 5 years, 48 of 98 (49%) participants reported current disordered eating behaviour. Thirteen participants met criteria for an eating disorder, three girls had bulimia nervosa, three had an eating disorder not otherwise specified and 7 had a subthreshold eating disorder. The authors concluded that, using a validated diagnostic interview, one half of girls reported disordered eating behaviour at some point during the longitudinal study, and early disordered eating behaviour almost universally persisted. There was no control group for this part of the study.

4.1.7 Discussion

Psychological distress

The study by Li et al (2009) examined SPD in adults. This cross-sectional self-report survey found that there was an increased prevalence of SPD as measured by a K6 score of more than 13/24 in subjects with type 1 diabetes (11.1%, SE 2.4) compared to subjects without diabetes (3.6%, SE 0.4). This study was limited by the self-report nature of the symptoms.

Paediatric psychosocial well-being/psychosocial functioning

Two of the four studies addressing psychosocial well-being or functioning reported no difference in levels between subjects with diabetes and controls (Northam et al 2005; Nardi et al 2008). Helgeson et al (2007) reported no differences in depressive symptoms, anxiety, anger or behavioural problems between groups (Helgeson et al 2007). Northam et al (2005) reported higher level of psychiatric morbidity, as measured by referral to mental health services, in the group with diabetes compared to the control group. In addition, Northam et al (2005) reported that 37% of adolescents met criteria for a DSM-IV psychiatric disorder according to a self-report measure (DICA-IV). Although the study was not controlled, the authors reported that this was 2–3 times higher than community levels. Regarding overall psychological morbidity assessment, one study used a structured clinical interview using accepted tools for assessment (Helgeson et al 2007). Another study used a semistructured interview using self-reported referral to mental health services, as well as the CBCL, YSL and YASR self-report measures (Northam et al 2010). Self-report measures were used by Nardi et al (2008) and Northam et al (2005).

Psychiatric disorder

Two studies described psychiatric status accorded a DSM-IV diagnosis. The study by Northam et al (2005) described psychiatric status and relationship to metabolic control in a group of adolescents, with subjects completing a computerised self-report questionnaire. There was no confirmatory diagnostic clinical interview. It was found that 37% (n=15) of the sample received a DSM-IV diagnosis. Diagnoses included mood, anxiety, eating and behaviour disorders. Of those who received a diagnosis, 60% met criteria for two or more psychiatric disorders. Although the study was not controlled, the authors report this was 2–3 times higher than community levels.

The study by Kovacs et al (1997) focused on psychiatric disorders that began after the onset of type 1 diabetes. The study reported results of 92 sequential admissions to a diabetes inpatient service. The assessment consisted of an interview with a mental health professional. Psychiatric status was assessed by means of the standardised, semistructured, symptom-based ISCA. After each evaluation, the symptom ratings and clinical history were used to determine whether the subject met DSM-II criteria for a psychiatric disorder.

The study found that 15 children (16.3%) had a psychiatric disorder at study entry that predated onset of type 1 diabetes. The authors reported this rate as within the range reported for population samples of youths. A total of 31 children had an adjustment disorder within 3 months of diabetes onset.

The results after a median of 9.1 years of follow-up were that 39 youth (42.4%) developed at least one episode of psychiatric disorder during the follow-up. Although the study was uncontrolled, the authors reported that the prevalence of major depression in their subjects was higher than rates in similarly aged cohorts in the general population. They also reported that the risk of any anxiety disorder was lower in their subjects than in the national

probability sample and community sample. However, the rate of generalised anxiety disorder of 12% appeared to be higher than that found in the general population.

Depression

The prevalence of depression among adults with diabetes was not significantly different to that of the matched control groups in the meta-analysis by Barnard et al (2006). The weighted effect compared to control subjects (OR 2.36, 95%CI: –0.69 to 5.4). Only one of the four studies included was considered to be of adequate methodological rigour, and the findings from that study (Petrak et al 2003) were in contrast to the pooled findings. However, that study was conducted in newly diagnosed diabetic subjects and its findings may not be generalisable to the wider population. The only primary study published since that date that fulfilled inclusion criteria reported a significantly increased prevalence in subjects with type 1 diabetes compared to the control group (32.1% vs 16%, $p<0.0001$) (Gendelman et al 2009). The ascertainment was from a questionnaire, and the cut off score for indicating depression differed from other current studies. In the paediatric population, an uncontrolled study (Kovacs et al 1997) reported that 26.1% of a 92 patient cohort had major depressive disorder. The limitations of the study were the small sample size and lack of control group.

Anxiety

A controlled study in France of 69 young adults with type 1 diabetes reported that, based on self-report measures, there was less anxiety and affective disorders among subjects with diabetes than in medical outpatients. As expressed in terms of a specific DSM-III-R diagnosis following diagnostic interview, almost half (48.6%) the subjects with diabetes had in their life time suffered from a disorder of generalised anxiety. The authors did not report a comparison of the prevalence of this diagnosis in type 1 diabetes subjects versus the control groups.

The study by Kovacs et al (1997) in youth with type 1 diabetes reported that 19.6% had developed some type of anxiety disorder. The study by Herzer et al (2010) reported that adolescents had a mean STAI state anxiety score of 29.8, and STAI trait anxiety of 32.15; these results were comparable to published norms for children who were otherwise healthy. This was an uncontrolled study.

Eating disorders

Two systematic reviews and meta-analyses on eating disorders found that there was no significant difference in the prevalence of anorexia nervosa in subjects with type 1 diabetes, but that bulimia nervosa was significantly higher in subjects with diabetes compared to controls (1.73 vs 0.69%, $p<0.05$) (Mannucci et al 2005). A more recent publication examining prevalence of eating disorders in youth (Ackard et al 2008) found that male and female youth with type 1 diabetes were not at increased risk for unhealthy weight control behaviours or weight dissatisfaction compared with controls. However, the control population included some subjects with diabetes. Another primary study published since the meta-analysis reported no current diagnoses of anorexia nervosa or bulimia nervosa among either population studied.

4.1.8 Conclusion

Meta-analyses report no difference in the prevalence of depression or anxiety in the adult population with or without diabetes. Pooled analysis shows an increased prevalence of bulimia nervosa in the adult and adolescent subject population with diabetes compared with controls, but no difference in the prevalence of anorexia nervosa.

In the paediatric population, data from controlled studies showed that youth with type 2 diabetes were more likely than control subjects to have had contact with mental health services, and had higher rates of referral to mental health services. In addition, primary uncontrolled data demonstrated a 26% prevalence of major depressive disorder and 19.6% prevalence of anxiety disorder in youth with type 1 diabetes (Kovacs et al 1997). Data from uncontrolled studies showed that 37% of adolescents met criteria for a DSM-IV psychiatric disorder, according to a self-report measure (Northam et al 2005), and among these, 60% met criteria for two or more psychiatric disorders. Although the study was not controlled, this was 2–3 times higher than community levels. Primary studies examining prevalence of eating disorders in youth reported no significant difference between groups with and without diabetes regarding the incidence of anorexia nervosa. However, binge eating, intense excessive exercise for weight control, reporting two or more current disturbed eating behaviours and ED-NOS or subthreshold eating disorders were all significantly more common among girls with rather than without diabetes (Colton et al 2004).The generalisability of these data may be limited by the varied selection and inclusion criteria, as well as the variability in control group selection. The lack of control group in some paediatric studies may influence the interpretation of the findings.

The studies were mostly conducted in Australia, North America or Europe.

4.1.9 Literature search strategy

The search was conducted on 28 September 2010. Level I studies were considered first, with the plan to update with Level II studies as required. The Medline search strategy and the PsycInfo search strategy are shown in Table 4.6 below.

An additional search was performed to capture the terms ‘diabetes distress’, ‘adjustment disorder’, ‘psychological adjustment’ and ‘eating disorder not otherwise specified’. The search was conducted on 24 December 2010 and is shown in Table 4.6 below.

Only one additional study was found in the new search: a systematic review that was excluded because it was not in English (Papelbaum et al 2004). No studies were found reporting specifically on diabetes distress or adjustment disorder. ‘Serious psychological distress’ in subjects with diabetes was reported in one study.

Table 4.6 Search strategy, question 4.1

Database	Date searched	#	Search terms	Citations
Medline	28 September 2010	1	Diabetes Mellitus, type 1/	54 087
		2	exp Eating Disorders/	8 587
		3	Depression/	58 835
		4	Anxiety Disorders/	18 480
		5	psychological disorders.mp. or Stress, Psychological/	70 574
		6	2 or 3 or 4 or 5	148 955
		7	1 and 6	630
		8	Prevalence/	144 995
		9	7 and 8	54
		10	limit 9 to english language	50
		11	Yield	50

Database	Date searched	#	Search terms	Citations
Medline (revised search strategy)	24 December 2010	1	Diabetes Mellitus, type 1/	54 087
		2	diabetes distress.mp.	18
		3	psychological adjustment.mp. or Adaptation, Psychological/	62 764
		4	Adjustment Disorders/	3 674
		5	(eating disorder not otherwise specified).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	3 825
		6	2 or 3 or 4 or 5	69 642
		7	1 and 6	629
		8	Prevalence/	144 995
		9	7 and 8	11
		10	limit 9 to (english language and humans)	11
			Yield	11
PsycInfo	22 November 2010	1	exp Diabetes Mellitus/	2 726
		2	prevalence.mp.	53 488
		3	exp Eating Disorders/	18 902
		4	exp Anxiety Disorders/ or exp Anxiety/	49 072
		5	exp Major Depression/ or exp Atypical Depression/ or exp Endogenous Depression/ or exp Anaclitic Depression/ or exp 'Depression (Emotion)'/ or exp Beck Depression Inventory/ or exp 'Long-term Depression (Neuronal)'/	91 973
		6	3 or 4 or 5	151 874
		7	1 and 2 and 6	69
		8	Limit Human and English	64
		9	Yield	64
PsycInfo (revised search strategy)	24 December 2010	1	exp Diabetes Mellitus/ or type 1 diabetes.mp.	3 136
		2	(eating disorder not otherwise specified).mp. [mp=title, abstract, heading word, table of contents, key concepts]	6 052
		3	diabetes distress.mp.	9
		4	exp Adjustment Disorders/	399
		5	psychological adjustment.mp.	3 844
		6	2 or 3 or 4 or 5	10 284
		7	1 and 6	66
		8	prevalence.mp.	53 488
		9	7 and 8	10
		10	Yield	10
Manual search				0
Total citations				135
Total non-duplicate citations				112

4.1.10 Evidence Matrix

Q4.1	Is there an increased prevalence of psychological disorders in people with type 1 diabetes across the life span, including clinical depression, anxiety disorder and eating disorder?	
Evidence statement	Level I evidence shows that the prevalence of depression in people with type 1 diabetes is greater in certain subgroups – women and the newly diagnosed – than in the general population. Level I evidence shows that there is increased prevalence of bulimia nervosa in adults and adolescents with type 1 diabetes compared to the general population. Level II evidence indicates that there are higher referral rates to mental health services in children and young adults with type 1 diabetes, compared with the general population. Level IV evidence shows an increased prevalence of depression and anxiety in young people and adolescents with type 1 diabetes, compared with the general population. Level IV evidence shows that the prevalence of anxiety in adults with type 1 diabetes is high, but similar to that in the general population.	
Evidence base	A	• Eating disorders: Two Level I, one Level II and two Level IV studies, (adolescent and adult). • Depression: One Level I and one Level IV studies (adults); one Level II study (paediatric) (no control group). • Anxiety: One Level I study (adults), two Level IV studies (one paediatrics, one adult). • Psychosocial: One Level IV study (adults), two Level II studies and one Level IV study (paediatrics).
Consistency	B	• Psychosocial: Increased rate of referral to mental health services in paediatrics and adolescents (one Level II study); no differences in psychological adjustment and psychosocial difficulty in one Level II and one Level IV study in paediatrics and adolescents. • Depression: No difference in Level I study, but a significant difference in Level IV study (adults). • Anxiety: Not applicable (adults, one study only); studies uncontrolled (paediatrics). • Eating disorders: Anorexia – no difference in both Level I studies; bulimia – increased in both Level I studies (adults and adolescents); Level IV studies showed increase prevalence of disordered traits in type 1 diabetes, but no difference in diagnosed eating disorders (adolescents).
Clinical impact	C	Adults.
	A	Children and adolescents.
Generalisability	A	Paediatric, adolescent and adult populations were delineated in most studies.
Applicability	B	Studies were from North America and Europe; thus, they were from countries with well-established health-care systems.
Other factors	None identified.	
Recommendation		
R4.1	Clinicians should be aware that the co-occurrence of psychological disorders in type 1 diabetes is common (Grade A).	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

4.2 Cognitive outcomes and type 1 diabetes

Question 4.2
What is the impact of type 1 diabetes on cognitive performance?

This section of the report includes a systematic review of evidence concerning the impact of type 1 diabetes on the cognitive performance of children and adults with type 1 diabetes.

4.2.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 4.7.

Table 4.7 Criteria for determining study eligibility, question 4.2

Study design	NHMRC Level I or prospective cohort studies [a]
Population	Children and adults with type 1 diabetes
Intervention	Measures of cognitive performance
Comparator	Any
Outcomes	Cognitive performance

NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies

4.2.2 Assessment of study eligibility

A total of 33 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the title, with 24 publications excluded. The abstracts of the remaining publications were reviewed and the exclusion criteria applied, with 6 publications excluded, as shown. A total of 3 publications remained, and the full-text version of each of these publications was retrieved and reviewed.

Citations for full-text review

The full text of the three remaining publications were reviewed. They included two meta-analyses in children and adolescents and one in adults (Brands et al 2005; Gaudieri et al 2008; Naguib et al 2009).

The meta-analyses by Gaudieri et al (2008) (search date 1985–2006) and Naguib et al (2009) (search date 1985–2005) were both in children. The study by Naguib et al (2009) is not discussed further because it did not add to the study by Gaudieri et al (2008). Both of the remaining publications included predominantly Level III and Level IV studies (case–control and cross-sectional); as such, they did not constitute Level I evidence. Therefore, a search for Level II evidence was undertaken in the Medline and EMBASE databases, using the search terms listed in Table 4.13, and including filters for case–control and cohort studies.

Of the full papers retrieved, four publications met the inclusion criteria (DCCT/EDIC Research Group 2007; Musen et al 2008; Kent et al ; Northam et al 2009). These studies are discussed below.

4.2.3 Literature search summary

Table 4.8 Search results, question 4.2

Stage	Notes	Number
Search summary	Medline	21
	Cochrane Library	0
	EMBASE	17
	INAHTA	0
	Manual	0
	Total	38
Duplicates	Duplicates identified	5
Identified	Total non-duplicates identified	33
Exclusion criteria	Wrong study type (not level I or prospective cohort studies)	4
	Wrong population (not children or adult with type 1 diabetes)	
	Wrong intervention or test (not measure of cognitive performance)	2
	Wrong outcome (not cognitive performance)	
	Not in English	

4.2.4 Included studies

The included Level II studies were Kent et al (2009), DCCT/EDIC Study Research Group (2007), Musen et al (2008) and Northam et al (2009). The two meta-analyses included were Brands et al (2005) and Gaudieri et al (2008).

4.2.5 Characteristics of included studies

Musen et al 2008

Musen and colleagues reported on the subgroup of Diabetes Control and Complications Trial (DCCT) participants aged between 13 and 19 years at randomisation. The aim was to evaluate whether severe hypoglycaemia or intensive therapy affects cognitive performance over time in this group. A total of 249 subjects were in this age group at entry to the DCCT. A comprehensive battery of cognitive tests was obtained during the Epidemiology of Diabetes Interventions and Complications (EDIC) study 18 years later, and was compared with baseline performance. A total of 294 episodes of coma or seizure were reported. Frequency of hypoglycaemia and previous treatment group were not associated with decline on any cognitive domain. As in an earlier analysis of the entire study cohort regarding cognitive function (DCCT/EDIC Research Group (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group) et al 2007), higher glyated haemoglobin (A1c) values were associated with declines in psychomotor and mental efficiency domain ($p<0.01$); however, the previous finding of improved motor speed with lower A1c values was not replicated in this subgroup analysis.

Kent et al 2009

Kent and colleagues used an accelerated longitudinal study design with individual growth curve analysis to examine the potential effects of disease risk factors on memory over 3 years. Children and adolescents aged 9–17 years were recruited from two paediatric endocrine clinics. Baseline data included children from a prior cross-sectional study (n=248, aged 9–17 years) with approximately 100 of these children participating in this longitudinal

study (Soutor et al 2004). The study was restricted to children with type 1 diabetes for over 6 months, with no other chronic medical condition or documented head trauma. Participants completed the Wide Range Assessment of Memory and Learning (WRAML) tool, and were assessed at follow-up with a complementary cognitive battery to aid retention and to avoid memory practice effects. The authors concluded that, of the risk factors studied, only metabolic control had a significant impact on visual memory after 3 years; verbal memory was unaffected. However, given that the level of metabolic control tends to remain relatively consistent over time, the effect of continued poor metabolic control on memory should be monitored.

DCCT/EDIC Study Research Group 2009

Jacobson and colleagues reported on the cognitive outcomes of the cohort followed for up to 18 years duration in the DCCT and the follow-up EDIC study. The DCCT was a multicentre, randomised clinical trial designed to compare intensive with conventional diabetes therapy, with regard to effects on the development and progression of early vascular and neurologic complications. Neuropsychological outcomes were measured as one of the secondary outcomes. The major criteria for eligibility included insulin dependence, as evidenced by deficient C-peptide secretion, an age of 13–39 years, and the absence of hypertension, hypercholesterolemia and severe diabetic complications or medical conditions. From 1983–1989, 1441 patients were recruited at 29 centres. The entire cohort was followed for a mean of 6.5 years, with 99% of patients completing the study. The randomised controlled trial (RCT) phase of the DCCT was stopped prematurely after a mean follow up of 6.5 years by the Data Safety and Quality Committee. The benefits of intensive treatment were deemed incontrovertible and highly unlikely to be reversed with time. All participants were encouraged and advised to implement or continue intensive treatment (with DCCT staff) during a closeout period. The observational phase of the DCCT/EDIC study then commenced.

The EDIC study was designed to use the DCCT cohort of patients to determine the long-term effects of prior separation of glycaemic levels on microvascular and macrovascular outcomes. Of the 29 DCCT clinics, 28 opted to participate as EDIC clinical centres. There were 1375 participants in total – 687 from the intensive treatment group and 688 from the conventional group. At the end of the first year of EDIC, 95% of the former intensive group and 75% of the former conventional group reported that they were using intensive treatment. The mean HbA_{1c} levels were 7.9% in the former intensive group and 8.3% in the former conventional group.

A comprehensive battery of cognitive tests were carried out at entry to the DCCT and repeated at a mean of 18 years duration. HbA_{1c} levels were measured, and the frequency of severe hypoglycaemic events leading to coma or seizures was recorded during follow-up. The effects of the original DCCT treatment-group assignment, mean HbA_{1c} levels, and frequency of severe hypoglycaemic events were assessed on measures of cognitive ability, with adjustment for age at baseline, sex, years of education, length of follow-up, visual acuity, self-reported sensory loss due to peripheral neuropathy, and the number of cognitive tests taken since the start of the DCCT. Frequency of severe hypoglycaemia and treatment-group assignment were not associated with a decline in any cognitive domain. High HbA_{1c} values were associated with moderate declines in motor speed ($p=0.001$) and psychomotor efficiency ($p<0.001$), with no other cognitive domain effected.

Northam et al 2009

Northam and colleagues reported on a prospective cohort from consecutive patients with newly diagnosed type 1 diabetes attending an Australian paediatric diabetes clinic. A total of

106 participants were matched with 75 healthy controls for age and sex, and followed up for 12 years. There were no significant differences between the groups in full scale intelligence quotient (IQ), socioeconomic status, age, sex ratios or psychiatric symptoms. Time between baseline and current assessment was shorter in the type 1 diabetic subjects (12.7 ±1.1 vs 12.0 ±1.1; 95% confidence interval [CI] 0.37 to 1.0 years). The Wechsler Abbreviated Scale of General Intelligence, with full scale (FSIQ), verbal (VIQ), and performance (PIQ) measures were administered at blood glucose levels more than 5.0 mmol/L, at baseline and at follow-up. Magnetic resonance spectroscopy and imaging was also undertaken. A subanalysis to determine the illness-specific risk factors of severe hypoglycaemia (defined as coma or hypoglycaemic seizure), and early age at onset (defined as less than five years of age) was also undertaken.

People with type 1 diabetes had lower VIQ (p=0.03) and FSIQ (p=0.05) than controls. In the subanalysis of illness-related predictors of central nervous system (CNS) outcome, hypoglycaemia predicted lower VIQ (R^2 change=0.032, p<0.01) and early onset of diabetes predicted lower PIQ (R^2 change=0.135, p<0.001) and FSIQ (R^2 change=0.064, p<0.001). The authors concluded that group differences were marginal and appeared to reflect the selective impact of illness-specific risk factors. The effects were small but statistically significant; however, even mild decrements in ability may have functional significance during childhood, when new knowledge is being acquired.

Brands et al 2005

The main aim of the systematic review and meta-analysis undertaken by Brands and colleagues was to determine the pattern and magnitude of cognitive impairments in adults with type 1 diabetes compared with non-diabetic control subjects. The secondary aim was to evaluate the possible effects of level of metabolic control, occurrence of diabetes complications, and repeated episodes of hypoglycaemia on cognitive dysfunction. The authors searched the Medline and Psychlit databases to identify studies including non-diabetic control groups or different groups of patients with type 1 diabetes, where cognitive performance had been measured using standard neuropsychological methods at normal blood glucose values. A total of 33 studies met the inclusion criteria. The studies comparing adults with type 1 diabetes and non-diabetic controls were homogeneous with respect to age. Ten studies matched subjects for education, occupation or both, with nine studies matching participants for age only. The results of one study where there was a significant difference with respect to educational level were not used to calculate domain scores. There was heterogeneity with respect to complications and associated disorders of diabetes. Four of the studies excluded patients with complications or co-morbid conditions, whereas eight studies did not define any exclusion criteria. Compared with non-diabetic control subjects, the group with type 1 diabetes demonstrated a significantly lowered performance on the following cognitive domains: intelligence (d=–0.7), speed of information processing (d=–0.3), psychomotor efficiency (d=–0.6), visual (d=–0.4) and sustained attention (d=–0.3), cognitive flexibility (d=–0.5), and visual perception (d=–0.4). Lowered cognitive performance in people with diabetes appeared to be associated with the presence of microvascular complications but not with the occurrence of severe hypoglycaemic episodes or with poor metabolic control.

Gaudieri et al 2008

Gaudieri and colleagues undertook a systematic review and meta-analysis of studies in children with type 1 diabetes, matched to non-diabetic controls, to examine the effect of diabetes on cognitive performance. The authors searched Medline and Psychinfo databases (1985–2008), and found 19 studies meeting the inclusion criteria. The meta-analysis sample

of 2144 children comprised 1393 study subjects with type 1 diabetes and 751 control subjects. Subanalyses were undertaken to determine the effect of early onset diabetes (EOD) (defined as <7 years of age), and hypoglycaemic seizures, with the aim of identifying risk factors for cognitive dysfunction. Overall, type 1 diabetes was associated with slightly lower overall cognition (effect score [ES] –0.13), with small differences compared with control subjects across a broad range of domains, excluding learning and memory, which were similar for both groups. Learning and memory skills, both verbal (–0.28) and visual (–0.25), were more affected in children with EOD than with late onset diabetes (LOD), together with attention and executive function skills (–0.27). Compared with non-diabetic control subjects, EOD effects were larger (up to one-half standard deviation [SD] lower), particularly for learning and memory (–0.49). Generally, seizures were associated with a negligible overall cognition ES of –0.06, with slight and inconsistent cognitive effects found on some measures, possibly reflecting the opposing effects of poorer versus better metabolic control.

4.2.6 Results of included studies

4.2.6.1 Cognitive outcomes in children and adolescents

Musen et al 2008

This study found no significant effect of treatment assignment or cumulative number of hypoglycaemic events on any cognitive domain. Higher values of A1c were associated with modest declines in psychomotor and mental efficiency ($p < 0.01$).

Kent et al 2009

Glycaemic control and memory

The effect of metabolic control on verbal memory was not significant, but the predicted effect of metabolic control on visual memory as per growth curve modelling was significant.

Table 4.9 Growth curve model predicting effect of A1c on visual memory scores over time

Solution for fixed effects					
	Standard effect	Estimate	Error df	t value	Pr>
Intercept	104.33	7.70	1451	3.55	<0.0001
A1c	–1.99	0.71	176	–2.78	0.006
Age	0.79	0.35	176	2.22	0.03
Gender	4.32	1.50	176	2.89	0.004
Duration	–0.22	1.19	176	–0.18	0.85
A1c duration	0.02	0.14	176	0.12	0.91

A1c, glycated haemoglobin; df, degrees of freedom

Severe hypoglycaemia and memory

With seizures used as a dichotomous variable (1 = one or more seizures in the past year and 0+ no seizures in the past year), growth curve analysis indicated no effect of hypoglycaemic seizures in the past year, and no effect of hypoglycaemic seizures on verbal or visual memory over time.

Early disease onset and visual memory

Growth curve analysis revealed no influence of disease onset on change in visual memory. Dichotomisation of onset age into earlier versus later age groups did not affect the findings.

Disease duration and verbal memory

Growth curve analysis showed no effect of disease duration on verbal memory over time.

Northam et al 2009

Intelligence – type 1 diabetes versus non-diabetic controls

Children with type 1 diabetes had significantly lower verbal and full scale IQ than the controls.

Table 4.10 Comparison of intelligence in type 1 diabetes versus non-diabetic controls

Outcome	Type 1 diabetes	Control	Estimate	95%CI	P
VIQ	96.2	100.4	–3.64	–6.97 to –0.30	0.03
PIQ	106.4	109.1	–2.02	–5.46 to 1.43	0.25
FSIQ	101.3	105.1	–3.03	–6.07 to 0.00	0.05

CI, confidence interval; FSIQ, full scale IQ; IQ, intelligence quotient; PIQ, performance IQ; VIQ, verbal IQ

Regression analysis illness related risk factors

Hypoglycaemia was found to be predictive of lower VIQ (R^2 change=0.032, p<0.01) and early onset of diabetes predicted lower PIQ (R^2 change=0.135, p<0.001) and FSIQ (R^2 change=0.064, p<0.001).

Table 4.11 Regression analysis illness related risk factors

Outcome	VIQ		PIQ		FSIQ	
Overall model	Adjusted R^2 =0.50, F=18.08, p <0.001		Adjusted R^2=0.46, F=15.79, p <0.001		Adjusted R^2=0.58, F=25.24, p <0.001	
Predictor	B(95%CI)	P value	B(95%CI)	P value	B(95%CI)	P value
Diabetes onset age (years)	–3.12 (–7.33, 1.10)	0.15	–12.01 (–16.68, –7.34)	<0.001	–7.9 (–11.81, –3.98)	<0.001
Hypoglycaemia	–4.51 (–7.99, –1.04)	0.01	–0.21 (–4.06, 3.64)	>0.9	2.85 (–6.07, 0.38)	0.08
Metabolic control	–0.07 (–0.72, 0.59)	0.8	–0.25 (–0.98, 0.48)	0.5	–0.18 (–0.79, 0.43)	0.6
FSIQ baseline	3.95 (2.65, 5.25)	<0.001	4.67 (3.23, 6.12)	<0.001	4.89 (3.68, 6.10)	<0.001
SES	–3.34 (–5.19, –1.50)	0.001	–2.31 (–4.35, –0.27)	0.03	–3.04 (–4.75, –1.33)	0.001
Time between assessments (years)	–0.02 (–1.90, 1.85)	>0.9	–1.12 (–3.20, 0.96)	0.3	–0.64 (–2.39, 1.10)	0.5

CI, confidence interval; FSIQ, full scale IQ; IQ, intelligence quotient; PIQ, performance IQ; SES, socioeconomic status; VIQ, verbal IQ

Gaudieri et al 2008

Overall, type 1 diabetes was associated with slightly lower overall cognition, with small differences compared with control subjects across a broad range of domains, excluding learning and memory, which were similar for both groups. Both verbal and visual learning and memory were significantly affected in children with EOD compared to healthy controls and to children with LOD.

Table 4.12 Effect scores (ES) as per Cohen's *d* (negative scores indicate poorer cognitive performance expressed in standard deviation [SD] unit, weighted for sample size)

Cognitive domains	Type 1 diabetes versus control	EOD versus LOD	EOD versus control	LOD versus control	Hypoglycaemic seizures
Overall cognition	–0.13 p=0.00	–0.20 p=0.00	–0.29	–0.13	–0.06
Intelligence –crystallised –fluid	 –0.18 p=0.00 –0.15 p=0.00	 –0.15 p=0.03 –0.18 p=0.07	 –0.35 –0.28	 –0.20 –0.14	 –0.19 –0.21
Verbal learning and memory –verbal learning –verbal memory	 –0.07 p=0.18 –0.17 p=0.07 –0.03 p=0.62	 –0.28 p=0.00 –0.26 p=0.00 –0.32 p=0.13	–0.49	–0.03 NS	
Visual learning and memory –visual learning –visual memory	 –0.04 p=0.37 0.06 p=0.39 –0.04 p=0.38	 –0.25 p=0.04 –0.23 p=0.10 0.18 p=0.32	–0.44	–0.17	 0.12 0.13
Psychomotor activity –psychomotor efficiency –motor speed	 –0.10 p=0.01 –0.16 p=0.00	 –0.38 p=0.13 –0.16 p=0.45	–0.37 NS	–0.17 –0.04 NS	
Attention or executive function	–0.10 p=0.04	–0.27 p=0.01	–0.39		
Academic achievement	–0.13 p=0.01	–0.19 p=0.00		–0.10 NS	–0.10
Visual motor integration	–0.18 p=0.02	0.01 p=0.96	–0.16 NS	–0.17	–0.06

EOD, early onset diabetes; LOD, late onset diabetes; NS, nonsignificant

4.2.6.2 Cognitive outcomes adults

DCCT/EDIC Study Research Group 2007

Neither treatment assignment nor frequency of severe hypoglycaemia were associated with a decline in any cognitive domain. Higher A1c values were associated with moderate declines in motor speed (p=0.001) and psychomotor efficiency (p<0.001).

Brands et al 2005

Compared with non-diabetic control subjects, the group with type 1 diabetes demonstrated a significantly lower performance on the following cognitive domains: intelligence (d=–0.7), speed of information processing (d=–0.3), psychomotor efficiency (d=–0.6), visual (d=–0.4) and sustained attention (d=–0.3), cognitive flexibility (d=–0.5) and visual perception (d=–0.4).

Lower cognitive performance in patients with diabetes appeared to be associated with the presence of microvascular complications, but not with the occurrence of severe hypoglycaemic episodes or with poor metabolic control.

4.2.7 Discussion

The impact of type 1 diabetes on cognitive function has been demonstrated in studies that compared children and adults with type 1 diabetes with healthy non-diabetic controls. Marginally lower differences in FSIQ, PIQ and VIQ were found in a prospective cohort of 106 Australian children (Northam et al 2009). In a meta-analysis of both cross-sectional and

prospective cohort studies including 1393 children with type 1 diabetes matched to healthy controls, slightly lower cognition was reported, with small differences across a range of cognitive domains, excluding memory and learning (Gaudieri et al 2008). In adults, a meta-analysis of predominately cross-sectional studies demonstrated significantly lower performance across a number of cognitive domains, again excluding learning and memory (Brands et al 2005).

A number of studies have also examined the effects of specific disease variables including severe hypoglycaemia, metabolic control, early age at diagnosis and duration of type 1 diabetes. These are discussed below.

Severe hypoglycaemia

Occurrence of severe hypoglycaemia was not associated with a decline in cognitive function in the 1441 patients, or in a subgroup analysis of the 249 adolescents enrolled in the DCCT/EDIC studies after 18 years of follow-up (Musen et al 2008). No association was found between severe hypoglycaemia and verbal or visual memory in a study in children (Kent et al). A meta-analysis of studies in children found that hypoglycaemic seizures were associated with a negligible effect on overall cognition, with slight and inconsistent effects found on some measures (Gaudieri et al 2008). A meta-analysis of studies in adults found no association between severe hypoglycaemia and a negative impact on cognitive function (Brands et al 2005). However, another study reported that the occurrence of severe hypoglycaemia predicted lower VIQ, with children scoring nearly one-third of a SD below children with type 1 diabetes with no hypoglycaemia (Northam et al 2009).

Glycaemic control

Poorer glycaemic control was associated with significant declines in both the psychomotor and mental efficiency domains ($p<0.01$) of the adolescents enrolled in the DCCT/EDIC studies at 18 years follow-up (Musen et al 2008). In the entire cohort, higher A1c was associated with moderate declines in both motor speed ($p=0.001$) and psychomotor efficiency ($p<0.001$) (DCCT/EDIC Research Group (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group) et al 2007). In a qualitative assessment of the studies reported by Brands et al (2005), there was no consistent difference between the 'well' and 'poorly' controlled groups. Northam and colleagues found no significant relationship between intelligence and metabolic control (Northam et al 2009), whereas Kent et al (2009) found a significant relationship between A1c ($p<0.01$) and declines in visual memory in children over time.

Early age of onset

EOD (defined as <5 years of age) was found to predict both lower PIQ and FSIQ in children (Northam et al 2009). Both verbal and visual learning and memory skills, and attention or executive function skills were negatively affected by EOD (defined as <7 years) in the meta-analysis by Gaudieri et al (2008). Compared with non-diabetic control subjects, EOD effects were larger, up to one-half SD lower, particularly for learning and memory (–0.49).

4.2.8 Conclusion

This systematic review of the evidence for the impact of type 1 diabetes on the cognitive function of children, adolescents and adults is based on three Level II studies (two of low risk of bias and one of moderate risk of bias) and two meta-analyses of high risk of bias. Most of the studies included in the meta-analyses were of cross-sectional design, making derivation of casual inferences problematic. When compared with healthy controls, children and adolescents demonstrated marginal negative effects on several cognitive domains, excluding

learning and memory, and scored marginally lower on IQ. Adults demonstrated a small-to-moderate negative impact on several cognitive domains, again excluding learning and memory. Where the association between occurrence of severe hypoglycaemia and negative impact on cognitive function was examined, a significant effect was reported in one prospective cohort of children, with severe hypoglycaemia predicting lower VIQ. No other significant effects were reported. Where the association between metabolic control and impact on cognitive function was examined, significant negative effects were reported in one prospective cohort including adults and adolescents, and in one prospective cohort including children over 9 years of age. No significant effects on IQ were reported in one prospective cohort of Australian children, and no significant effects were reported in a qualitative analysis of studies included in a meta-analysis in adults. EOD was associated with lower performance and FSIQ, verbal and visual learning and memory skills, and attention or executive function skills. The exclusions reported included diabetes complications, history of head injury and depression. One study was carried out in Australia, and the remainder in countries with a well-developed health care system.

4.2.9 Literature search strategy

The search was conducted on 30 September 2010. Level I studies were considered first, with the plan to update with Level II studies as required. The Medline search strategy and a summary of citations retrieved from other searches are shown in Table 4.13.

Table 4.13 Search strategy, question 4.2

Database	Date searched	#	Search terms	Citations
Medline		1	exp Diabetes Mellitus, type 1/ or diabetes mellitus type 1.mp.	53 304
		2	cognitive.mp.	136 672
		3	behavioural.mp.	34 989
		4	attention.mp. or exp Attention/	202 769
		5	exp Learning/ or learning.mp.	299 620
		6	memory.mp. or Memory/	130 407
		7	executive functioning.mp.	1 716
		8	information processing.mp.	10 698
		9	spatial.mp.	115 649
		10	intelligence.mp. or exp Intelligence/	98 737
		11	intellectual.mp.	15 670
		12	neuropsychological.mp.	58 661
		13	meta-analysis.mp. or exp Meta-Analysis/	42 189
		14	systematic review.mp.	19 563
		15	pooled analysis.mp.	1 907
		16	(review and medline).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	29 565
		17	(systematic* and (review* or overview*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	45 767
		18	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	810 378
		19	13 or 14 or 15 or 16 or 17	96 011
		20	1 and 18 and 19	22
		21	limit 20 to English language	21
Cochrane				0
EMBASE				17

Database	Date searched	#	Search terms	Citations
INAHTA				0
Manual search				0
Total citations				38
Total non-duplicate citations				33

4.2.10 Evidence Matrix

Q4.2	What is the impact of type 1 diabetes on cognitive performance?	
Evidence statement	Evidence from Level I and II studies show a longitudinal association between glycaemic control and some aspects of cognitive function. The magnitude of this effect is greatest in children with early onset type 1 diabetes.	
Evidence base	B	Three Level II studies (two of low risk of bias, one of moderate risk of bias), and two Level IV studies, both of high risk of bias.
Consistency	B	Compared with healthy controls, children and adolescents demonstrated marginal effect on several domains and scored marginally lower on IQ, but with no effect on learning and memory. Adults demonstrated a small-to-moderate effect on several cognitive domains, again with no effect on learning and memory. Hypoglycaemia predicts a lower verbal IQ in children (one study), with no other significant effect reported. In relation to metabolic control, a higher HbA_{1c} is associated with a negative impact on cognitive function (reported in two studies including children >9 years, adolescents and adults). One study reported no significant effect on IQ. In early-onset diabetes, a negative association was reported in one prospective study and one meta-analysis.
Clinical impact	A	Children.
	B	Adolescents and adults.
Generalisability	B	Studies included children, adolescents and adults. Exclusions included diabetes complications, history of head trauma and depression. There is no evidence from the older adult or the elderly population (especially with respect to dementia).
Applicability	A	One study was in Australian children, two were from the United States (i.e. a country with a well-established health-care system).
Other factors	The mechanism is not known.	
Recommendation		
R4.2	To minimise the impact of diabetes on cognitive function, every effort should be directed toward achieving glycaemic targets (Grade B).	

HbA_{1c}, glycated haemoglobin; IQ, intelligence quotient

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

5 Importance of glycaemic control

This chapter was not systematically reviewed.

6 Blood glucose monitoring

6.1 Continuous real time monitoring

Question 6.1

Does real-time continuous glucose monitoring (CGM) versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?

HbA_{1c}, glycated haemoglobin

Standard management of diabetes involves self-monitoring of blood glucose (SMBG) through a finger prick at least four times per day, and measurement of glycated haemoglobin (HbA_{1c}) every 3–4 months. Continuous glucose monitoring (CGM) systems measure glucose in the interstitial fluid to provide semicontinuous information about glucose levels. Such information may identify fluctuations that would not have been identified with self-monitoring alone. Currently, the use of CGM is not common practice (Wentholt et al 2007). CGM is considered to be particularly useful in:

- children (to reduce the often very high number of finger punctures in this group)
- patients with poorly controlled diabetes
- pregnant women in whom tight glucose control is essential with respect to the outcome of pregnancy
- patients with hypoglycaemia unawareness (to prevent dangerous episodes of hypoglycaemia).

There are two types of CGM system:

- retrospective systems that measure the glucose concentration during a certain time span – the information is stored in a monitor and can be downloaded later
- real-time systems that continuously provide the actual glucose concentration on a display.

This systematic review reports on the evidence on how real-time CGM systems compare with standard management in improving HbA_{1c}, minimising fluctuations of blood glucose and reducing severe hypoglycaemia.

6.1.1 Criteria for eligibility

The criteria for determining if publications were eligible for inclusion for this clinical question are shown in Table 6.1.

Table 6.1 Criteria for determining study eligibility: clinical question 6.1

Study design	A systematic review or meta-analysis (NHMRC Level I evidence using the intervention accuracy scale a), or a randomised controlled trial (Level II evidence)
Population	Person with type 1 diabetes
Intervention	Real-time continuous glucose monitoring systems
Comparator	Conventional self-monitoring of blood glucose
Outcomes	Changes in HbA_{1c} Number of episodes of severe hypoglycaemia

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

6.1.2 Assessment of study eligibility

A total of 400 citations were identified in the initial literature search (see Table 6.14). The exclusion criteria were applied to all citations by reviewing the abstract and title, with 386 publications excluded. A total of 14 publications remained, and the full-text version of each publication was retrieved and reviewed. The same exclusion criteria were then applied to the full-text articles. A total of 13 publications met the inclusion criteria. Of these, 12 were RCTs (Chase et al 2003; Chase 2005; Deiss et al 2006; Hirsch et al 2008; JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) et al 2008; Cosson et al 2009; Hermanns et al 2009; JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) 2009; Logtenberg et al 2009; O'Connell et al 2009; Peyrot and Rubin 2009; Raccah et al 2009). The authors were contacted and provided the final version of this systematic review (Langendam et al In preparation). This unpublished review included all of the studies of CGM systems captured by our search.

6.1.3 Literature search summary

Table 6.2 Search results, question 6.1

Stage	Notes	Number
Search summary	Manual	1
	Cochrane Library	42
	EMBASE + Medline	366
Duplicates	Duplicates identified	9
Identified	Total identified	400
Exclusion criteria	Wrong study type (e.g. nonsystematic reviews or RCTs)	39
	Wrong population (not in individuals with type 1 diabetes)	54
	Wrong intervention (not evaluating real-time continuous glucose monitoring)	239
	Wrong outcome (not changes in HbA_{1c} or number of episodes of severe hypoglycaemia)	54
	Not in English	0
	Total excluded	386
Meeting criteria	Total meeting inclusion criteria	14
Included	Total included studies	9

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

6.1.4 Included studies

6.1.5 Characteristics of included studies

The systematic review (Langendam et al In preparation) aimed to capture all published data from randomised controlled trials (RCTs) that involved assessing the effect of CGM systems compared to SMBG in patients with type 1 diabetes. The review included studies in both real-time and retrospective CGM systems. For this question, we report only on the evidence from RCTs in real-time CGM systems. Of the 13 studies identified, 3 were excluded because they compared the GlucoWatch Biographer to SMBG (Chase et al 2003; Chase 2005; Wysocki et al 2006). This device has now been removed from the market worldwide. Another study was excluded from our analysis because it included patients who used continuous intraperitoneal insulin infusion (CIPII) (Logtenberg et al 2009). At present, CIPII is only available in a few European countries. As there was considerable clinical and methodological heterogeneity between the studies, Langendam et al (In preparation) were unable to pool the results and perform a meta-analysis. Table 6.3 details the characteristics of the nine included studies.

Table 6.3 Question 6.1: Characteristics of included studies

Study reference	N	Study type	Population Country	Intervention	Comparator	Outcomes
JDRF CGM Study Group (2008)[a]	Children (n=114) Adolescents (n=110) Adults (n=98)	RCT	Children, adolescents and adults United States	Continuous use of CGM, in addition to SMBG	SMBG	Change in mean HbA_{1c} Severe hypoglycaemia
Deiss et al (2006)	162	RCT	All age groups Europe and Israel (poorly controlled diabetes)	Arm 1: continuous use of CGM Arm 2: intermittent use of CGM	SMBG	Change in HbA_{1c}
JDRF CGM Study Group (2009)	129	RCT	All age groups United States	Continuous use of CGM, in addition to SMBG	SMBG	Change in mean HbA_{1c} Severe hypoglycaemia
Hirsch et al (2008)	146	RCT	Adolescents and adults United States	Continuous use of CGM	Insulin pump and SMBG	Change in mean HbA_{1c} Severe hypoglycaemia
Raccah et al (2009)	115	RCT	All age groups France (poorly controlled diabetes)	Continuous use of CGM	Conventional pump therapy and SMBG	Change in HbA_{1c} Hypoglycaemia
O'Connell et al (2009)	62	RCT	All age groups Australia	Continuous use of CGM	Usual insulin pump therapy and SMBG regimen	Change in HbA_{1c} Severe hypoglycaemia
Hermanns et al (2009)	50	RCT	Adults Germany	Real-time access to CGM values	Retrospective access to CGM values	Hypoglycaemia

Study reference	N	Study type	Population Country	Intervention	Comparator	Outcomes
Cosson et al (2009)	9	RCT	Adults France (poorly controlled diabetes)	48 hours CGM for all patients; intervention= patient evaluation using CGM data	48 hours CGM for all patients; control=patient evaluation with SMBG	Change in HbA_{1c}
Peyrot and Rubin (2009)	28	RCT	Adults United States	Continuous CGM use + SMBG	Conventional treatment: MDI=SMBG	Change in HbA_{1c}

CGM, continuous glucose monitoring; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections; RCT, randomised controlled trial; SMBG, self-monitoring of blood glucose

[a] Trial consists of three sub-RCTs, on children, adolescents and adults

6.1.6 Results of included studies

Studies in children

Juvenile Diabetes Research Foundation (JDRF) (trial in children) (2008)

An RCT reported in the systematic review by Langendam et al (In preparation) investigated the effectiveness of real-time CGM systems in children (JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) et al 2008) In this trial, the CGM group used three different types of CGM systems: a Dexcom SEVEN, a Paradigm or a Freestyle Navigator device. The Paradigm system combines an insulin pump with a CGM system. This trial included 114 children (age 8–14 years) and was of 6 months duration. The baseline HbA_{1c} level was 7–10%.

During the study period, the HbA_{1c} levels in both the CGM and SMBG group declined. The difference in the change was not statistically significant (change in HbA_{1c} –0.37% vs –0.22%, mean difference [MD] –0.15%, 95% confidence interval [CI]: –0.42 to 0.12). However, the proportion of patients who improved their HbA_{1c} level by at least 0.5% was significantly higher in the CGM group (54% vs 31%, rate difference [RD] 23%, 95%CI: 5% to 40%). The occurrence of severe hypoglycaemia after 6 months of follow-up was lower in the CGM study arm, but the difference was not statistically significant (7% vs 12%, RD 5%, 95%CI: –16% to 6%). Ketoacidosis events did not occur.

At baseline and after 6 months, glucose values were measured with (blinded) CGM in both study arms. The change in mean number of minutes per day with glucose level below 3.9 mmol/L was not different between the CGM and SMBG group (–2 vs 0 minutes, p=–0.29), nor was the change in number of minutes per day with glucose level above 10.0 mmol/L (hyperglycaemia), although the change was larger in the CGM group (–102 vs –36 minutes, p=0.58).

Studies in adolescents

JDRF (adolescent trial) (2008) and Hirsch (2008)

Two RCTs reported results for adolescents (Hirsch et al 2008; JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) et al 2008). In one RCT (JDRF adolescents) the CGM group used three different CGM devices: a Dexcom SEVEN, a Paradigm or a Freestyle Navigator device (all real-time systems) (JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) et al 2008). The trial included 110 adolescents (15–24 years of age) and was of 6 months duration. All patients had a baseline HbA_{1c} level of 7–10%. In the other trial, the

use of the Paradigm system was compared with insulin pump use and SMBG (Hirsch et al 2008). The age of the patients was 12–18 years, and their initial HbA_{1c} values were above 7.5%. All were previously treated with an insulin pump for at least 6 months. The duration of the trial was 6 months. The results are presented in **Error! Reference source not found.**.

In both trials, both the CGM group and the SMBG group had lower HbA_{1c} levels after 6 months from baseline, but there was no statistically significant difference in change between the two study arms (MD in change 0.03, 95%CI: –0.21 to 0.27 for JDRF CGM Study Group et al [2008], and –0.42, 95%CI: –0.92 to 0.08 for Hirsch et al [2008]) and no difference in absolute HbA_{1c} level (8.0% vs 8.2%, MD –0.19, 95%CI: –0.85 to 0.47). Also, the proportion of patients that had improved their HbA_{1c} level by at least 0.5% was equal in both groups (36% vs 37% in JDRF CGM Study Group et al [2008]). Severe hypoglycaemic and ketoacidotic events were infrequent; there were no significant differences between the groups (severe hypoglycaemia: 5% vs 9%, RD –4%, 95%CI: –14% to 6% in JDRF CGM Study Group et al [2008]). At baseline and after 6 months, glucose values were measured with CGM in both groups in JDRF CGM Study Group et al (2008). The number of minutes per day with glucose level <3.9 mmol/L (hypoglycaemia) and with glucose level >10.0 mmol/L (hyperglycaemia) decreased for both groups between the two time points, but by largely the same amount (JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) et al 2008).

Studies in adults

In adults the effectiveness of real-time CGM systems was investigated in six trials (Hirsch et al 2008; JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) et al 2008; Cosson et al 2009; Hermanns et al 2009; Logtenberg et al 2009; Peyrot and Rubin 2009). One of these trials included patients from 12 years of age, and reported the results for HbA_{1c} for adults separately (Hirsch et al 2008). As mentioned earlier, we have excluded the results of the cross-over trial by Logtenberg et al (2009) because it included patients from an outpatient clinic who used CIPII.

Hermanns (2009)

Another cross-over trial (n=50, GlucoDay system) had an inpatient setting, and included both insulin pump users and patients who used multiple daily injections (MDI) of insulin. The trial compared open versus blinded use of real-time CGM. Treatment decisions in the open phase were made based on real-time CGM values, and in the blinded phase on retrospective access of the CGM data. Patients used CGM for a short period (6 days and approximately 2 days) and switched over to the other CGM option (open or blinded). HbA_{1c} was not an outcome measure in these studies.

In the GlucoDay trial, the time spent in hypoglycaemia while having real-time access to the CGM values was almost one hour per day longer compared to having retrospective access to the CGM values, the difference showed a tendency towards significance, as shown in Table 6.4.

Table 6.4 Results from Hermanns (2009)

3 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
Hypoglycaemia (hours/day)	3.3	2.9	50	2.4	5.5	50	0.9	p=0.08 [a]

CGM, continuous glucose monitoring; CI, confidence interval; MD, mean difference; RD, rate difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

[a] Two-way analysis of variance analysis with a three level within-subjects factor and a between factor

Cosson et al (2009)

The study by Cosson et al (2009) (n=9) was in patients with poorly controlled diabetes (HbA_{1c} >8.0%). In this RCT, all patients used a CGM device for 2 days, in addition to SMBG. In the intervention group, diabetes treatment was managed using the CGM data; in the control group, treatment was adjusted using SMBG values. The absolute HbA_{1c} level and the change in HbA_{1c} were not statistically significantly different between the CGM group and the SMBG group at the end of the intervention; however, the decrease in HbA_{1c} was larger in the CGM group, as shown in Table 6.5.

Table 6.5 Results from Cossons (2009)

3 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
HbA_{1c}	8.47	0.83	3	8.72	0.89	6	–0.25	–1.43 to 0.93
Change in HbA_{1c}	–0.53	0.27	3	–0.22	0.23	6	–0.31	–0.67 to 0.05

CGM, continuous glucose monitoring; CI, confidence interval; HbA_{1c} glycated haemoglobin; MD, mean difference; RD, rate difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

Peyrot and Rubin (2009)

The study by Peyrot and Rubin (2009) was in patients with 'suboptimal metabolic control' (n=28). In this study, patients were pump naïve (i.e. had never used an insulin pump). The absolute HbA_{1c} level and the change in HbA_{1c} were not statistically significantly different between the CGM group and SMBG group at the end of the intervention; however, the decrease in HbA_{1c} was larger in the CGM group, as shown in Table 6.6.

Table 6.6 Results from Peyrot (2009)

4 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
HbA_{1c}	7.16	0.75	14	7.30	0.92	13	–0.14	–0.78 to 0.50
Change in HbA_{1c}	–1.71		14	–1.02		13	–0.69	p=0.07 [a]

CGM, continuous glucose monitoring; CI, confidence interval; MD, mean difference; RD, rate difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

[a] No standard deviation provided in the paper

Hirsch et al (2008)

The study by Hirsch et al (2008) was in patients with poorly controlled diabetes (HbA_{1c} >7.5%). In this study (n=98), the Paradigm device was used by the intervention group, and patients had used an insulin pump for at least 6 months before intake.

After 6 months, the HbA_{1c} levels were not different between the study arms, as shown in Table 6.7.

Table 6.7 Results from Hirsch (2008)

6 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
HbA_{1c}	7.68	0.84	49	7.66	0.67	49	–0.02	–0.28 to 0.32
Change in HbA_{1c}	–0.69	0.73	49	–0.64	0.57	49	–0.05	–0.31 to 0.21

CGM, continuous glucose monitoring; CI, confidence interval; HbA_{1c} glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

JDRF (adult trial) (2008)

In the JDRF CGM Study Group et al (2008) adults trial, the change in HbA_{1c} from baseline to 6 months was significantly higher in the CGM group compared to the SMBG group; also, in the CGM group, a larger proportion of patients improved their HbA_{1c} by at least 0.5%, as shown in Table 6.8. There were no differences in the occurrence of severe hypoglycaemia, but the absolute numbers were small.

At baseline and after 6 months, glucose values were measured with (blinded) CGM in the CGM and SMBG group in one trial. The number of minutes per day with glucose level <3.9 mmol/L (hypoglycaemia) decreased for the CGM group, but not for the SMBG group (change from baseline to 6 months: –29 vs 1 minutes, p=0.41); however, the difference was not statistically significant. The number of minutes per day with glucose level >10.0 mmol/L (hyperglycaemia) decreased for both groups between baseline and 6 months. The decrease for the CGM group was 73 minutes larger, and the difference between the CGM and SMBG group was statistically significant (change from baseline to 6 months: –103 vs –30 minutes, p=0.002).

Table 6.8 Results from JDRF (Adult trial) (2008)

6 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
Change in HbA_{1c}	–0.50	0.56	52	0.02	0.45	46	–0.52	–0.72 to –0.32
Patients (%) with HbA_{1c} level improved ≥0.5%	24(46%)		52	5(11%)		46	35%	19% to 52%
Severe hypoglycaemia (n,%)	5(10%)		52	4(9%)		46	2%	–9% to 13%
Severe hypoglycaemia with seizure or coma (n,%)	1(2%)		52	1(2%)		46	0%	–6% to 5%

CGM, continuous glucose monitoring; CI, confidence interval; HbA_{1c} glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

Studies in all age groups

Five trials investigated real-time CGM systems in patients of all ages (Deiss et al 2006; Hirsch et al 2008; JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) 2009; O'Connell et al 2009; Raccah et al 2009). The five studies were different in patient group and comparisons, therefore pooling was not appropriate. Langendam et al (In preparation) discuss the trials separately.

O'Connell et al (2009)

In the study by O'Connell et al (2009), the patients (n=62) had an HbA_{1c} level below 8.5%, and used an insulin pump for at least 3 months before randomisation. According to the authors' definition, these patients were considered to have well-controlled diabetes. The trial was of 3 months duration, and included adolescents and adults, but no children.

The results of this trial (Table 6.9) showed that the CGM users had a significantly lower HbA_{1c} 3 months after baseline compared to the SMBG users. The change in HbA_{1c} from baseline to the end of the study was larger for CGM users compared to SMBG users and was statically significant. Severe hypoglycaemia and ketoacidosis events did not occur. The percentage of time spent in hypo- or hyperglycaemic range did not differ significantly between the study arms.

Table 6.9 Results from O'Connell (2009)

3 months	CGM			SMBG			CGM	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N	MD/RD	
Glycaemic control								
HbA_{1c}	7.1	0.8	26	7.8	0.9	29	–0.70	–1.16 to –0.24
Change in HbA_{1c}	–0.2		26	0.3		29	–0.43	–0.19 to –0.75
Severe hypoglycaemia (n)	0		26	0		29		
CGM derived glycaemic control								
% time spent ≤3.9 mmol/L [a]	9.2	8.7	26	9.1	6.9	29	0.10	–4.17 to 4.37
% time spent ≥10.1 mmol/L [a]	33.6	12.7	26	37.0	17.3	29	–3.40	–11.65 to 4.85

CGM, continuous glucose monitoring; CI, confidence interval; HbA_{1c} glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

[a] Data pertain to the 26/31 participants in the intervention group and the 29/31 participants in the control group who completed the study

Hirsch et al (2008)

In the trial by Hirsch et al (2008) (n=138), which was of 6 months duration, the patients had an HbA_{1c} level of at least 7.5%, and had used an insulin pump in the 6 months preceding the study (Hirsch et al 2008).

In the trial with insulin pump users with HbA_{1c} levels of at least 7.5%, neither the absolute HbA_{1c} levels, nor the change in HbA_{1c} were different between the CGM and SMBG users (Table 6.10). The CGM users spent less time in the hypoglycaemic range at the end of the trial compared to baseline; however, for the SMBG users, there was no such decline. There was also no difference for the hyperglycaemic ranges.

Table 6.10 Results from Hirsch et al (2008)

6 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
Glycaemic control								
HbA_{1c}	7.77	0.92	66	7.84	0.81	72	–0.07	–0.36 to 0.22
Change in HbA_{1c}	–0.71	0.71	66	–0.56	0.72	72	–0.15	–0.39 to 0.09
CGM derived glycaemic control								
AUC ≤3.9 mmol/L to change from baseline (mean mmol/L/minute)	–0.01		66	0.02		72	–0.03	P <0.0001 [a]
AUC >10 mmol/L to change from baseline (mean mmol/L/minute)	–0.63	1.07	66	–0.54	0.92	72	–0.09	–0.43 to 0.25

AUC, area under the curve; CGM, continuous glucose monitoring; CI, confidence interval; HbA_{1c} glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

[a] Proportion of time over 6 days of CGM at the end of the study

Raccah (2009)

In the third Paradigm system trial (n=115), the patients were insulin pump naïve and their diabetes was poorly controlled (HbA_{1c} >8.0%) (Raccah et al 2009). In this trial, the Paradigm system was compared to treatment with an insulin pump and SMBG, in patients naïve to both treatment forms.

Among insulin pump naïve patients with poorly controlled diabetes there was no difference between the study arms in change in HbA_{1c} between baseline and end of CGM for diabetes treatment (Table 6.11). At the end of the study, CGM users had a slightly increased, but nonsignificant, duration of hypoglycaemic episodes, and a statistically significant decreased duration of hyperglycaemic episodes. The number of hypoglycaemic and hyperglycaemic episodes did not change.

Table 6.11 Results from Raccah et al (2009)

6 months	CGM			SMBG				
	Mean/ events	SD	N	Mean/ events	SD	N	MD/RD	95%CI
Glycaemic control								
Change in HbA_{1c}	–0.81	1.09	41	–0.57	0.94	55	–0.20	–0.61 to 0.21
Severe hypoglycaemia (n,%)	1(2%)		41	0(0%)		55	2%	–4% to 7%
CGM derived glycaemic control[a]								
Change in time <3.9 mmol/L (hours/day)	0.3	1.4	41	0.0	1.2	55	0.31	–0.04 to 0.64
Change in episodes <3.9 mmol/L (mean/day)	0.1	0.9	41	0.1	0.7	55	0.00	–0.30 to 0.30
AUC <3.9 mmol/L; change from baseline (mean mmol/L/day)	0.4	1.3	41	0.0	1.8	55	0.40	–0.05 to 0.85
Change in time spent >10.6 mmol/L (hours/day)	–3.5	4.8	41	–0.7	3.8	55	–2.80	–4.48 to –1.02
Change in episodes >10.6 mmol/L (mean/day)	–0.2	0.7	41	–0.2	0.7	55	0.00	–0.26 to 0.26
AUC >10.6 mmol/L; change from baseline (mean mmol/L/day)	–17.1	37.1	41	–5.8	26.7	55	–11.3	–22.3 to 0.70

AUC, area under the curve; CGM, continuous glucose monitoring; CI, confidence interval; HbA_{1c} glycated haemoglobin; MD, mean difference; RD, rate difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

[a] Proportion of time over 6 days of CGM at the end of the study

Deiss (2006)

One RCT (n=162) investigated the Guardian real-time CGM system. Patients in this trial had poorly controlled diabetes (HbA_{1c} >8.1%), despite intensified insulin treatment (pump or MDI). The study was of 3 months duration and had three arms: continuous and intermittent use (i.e. bi-weekly for 3-day periods) was compared with SMBG.

In the Guardian trial, the improvement in HbA_{1c} between baseline and end of the intervention (3 months) was significantly better for the continuous CGM users compared to the SMBG users (Table 6.12). The HbA_{1c} of the intermittent CGM users showed also a greater improvement than the SMBG group, but the difference was not statistically significant.

Table 6.12 Results from Deiss et al (2006)

3 months	Continuous CGM			Intermittent CGM			SMBG			Continuous CGM		Intermittent CGM	
	Mean/ events	SD	N	Mean/ events	SD	N	Mean/ events	SD	N	MD/RD	95%CI	MD/RD	95%CI
Glycaemic control													
Change in HbA_{1c}	–1.0	1.1	54	–0.7	1.3	54	–0.4	1.0	54	–0.60	–1.00 to –0.20	–0.30	–0.74 to 0.14
CGM derived glycaemic control													
Episodes <3.9 mmol/L (number)	0.62	0.71	54	1.04		54	0.71	0.88	54	–0.10	–0.40 to 0.20	–0.30	–0.74 to 0.14
AUC hypoglycaemia (<3.9 mmol/L) (mmol/L/24 hours)	0.026	0.050	54	0.024		54	0.023	0.046	54	0.01	–0.01 to 0.03	0.30	–0.08 to 0.68
Episodes >10.6 mmol/L (number)	2.3	1.1	54	2.4		54	2.4	1.1	54	–0.10	–0.51 to 0.31	0.00	–0.02 to 0.02
AUC hyperglycaemia (>10.6 mmol/L) (mmol/L/24 hours)	1.07	1.08	54	1.12		54	1.39	1.27	54	–0.32	–0.77 to 0.13	–0.27	–0.75 to 0.21

AUC, area under the curve; CGM, continuous glucose monitoring; CI, confidence interval; HbA_{1c} glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

JDRF CGM Study Group (2009)

In the JDRF trial (n=129), the participants had well-controlled diabetes (HbA_{1c} <7.0%) and the CGM group used three different real-time CGM systems (including the Paradigm system) (JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) 2009). The duration of this trial was 6 months.

The CGM group of patients with well-controlled diabetes had better glycaemic control (consistent for different outcomes) after 6 months CGM use, compared to the SMBG group (Table 6.13).

Table 6.13 Results from JDRF CGM Study Group (2009)

6 months	CGM			SMBG			CGM	
	Mean/ events	SD	N	Mean/ events	SD	N	MD/RD	95%CI
Glycaemic control								
HbA_{1c}	6.4	0.5	67	6.8	0.5	62	–0.40	–0.57 to –0.23
Change in HbA_{1c}	0.0	0.5	67	0.3	0.4	62	–0.30	–0.46 to –0.14
Decrease in HbA_{1c} ≥3% (n,%)	21(31%)		67	3(5%)		62	27%	14% to 39%
Severe hypoglycaemia (n)	7(10%)		67	7(11%)		62	–1%	–12% to 10%
CGM derived glycaemic control								
AUC <3.9 mmol/L (median, IQR)	0.3(0.1–0.6)		67	0.5(0.1–1.7)		60		p=0.01
BG <10.6 mmol/L minute/day (median, IQR)	54(28–108)		67	91(27–188)		62		p=0.04
BG >10.6 mmol/L minute/day (median, IQR)	283(173–423)		67	341(232–502)		60		p=0.09

AUC, area under the curve; BG, blood glucose; CGM, continuous glucose monitoring; CI, confidence interval; HbA_{1c} glycated haemoglobin; IQR, inter quartile range; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

6.1.7 Discussion

Glycaemic control was an outcome measure in all RCTs, and most studies reported change in HbA_{1c} level. In power analyses, a clinically significant difference of 0.5% HbA_{1c} is used to calculate sample size (Deiss et al 2006; JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) et al 2008; Raccah et al 2009). Hermanns et al (2009) reported CGM-derived hypoglycaemia and hyperglycaemia. Severe hypoglycaemia and ketoacidosis occurred infrequently. Most studies were therefore underpowered to detect differences for this outcome.

All RCTs compared CGM with SMBG; there were no head-to-head comparisons between CGM systems.

One trial compared real-time access of CGM with retrospective access and SMBG (Hermanns et al 2009). Another trial involved use of three different types of CGM, but subgroup analyses of the different CGM systems were not reported (JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) 2009).

The results for children, adolescents and adults are summarised below.

Children

For children, there is limited evidence, based on one RCT with low risk of bias, for the effectiveness of real-time CGM systems on glycaemic control. After 6 months, more patients in the CGM group had a decrease of at least 0.5% in HbA_{1c} compared to the SMBG group. However, the mean change in HbA_{1c} did not differ significantly between the two groups, and there were no differences for the other outcomes (JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) et al 2008).

Adolescents

For adolescents, no statistically significant differences in any outcome were found. However, among experienced insulin pump users, the improvement in HbA_{1c} over 6 months was 0.42% larger in the group that used real-time CGM than in the SMBG group (Hirsch et al 2008a). However, this study did not use an intention-to-treat analysis; thus, the effect may have been overestimated.

Adults

Short-term results (<6 months) showed no statistically significant differences in glycaemic control for the real-time CGM systems, although one study found a relatively large and clinically relevant difference in change in HbA_{1c} (0.69%) between the CGM and SMBG groups (Peyrot and Rubin 2009).

Long-term glycaemic control outcomes (≥6 months) showed conflicting results. One RCT (with a low risk of bias) showed a statistically and clinically significant higher improvement in HbA_{1c} for the CGM group (MD in change –0.52%, 95%CI: –0.72 to –0.32) (JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) et al 2008), while in another RCT (with a moderate risk of bias) there was no difference (Hirsch et al 2008).

6.1.7.1 Patients with poorly controlled diabetes

Three RCTs using real-time CGM were performed in patients with poorly controlled diabetes (HbA_{1c} >8.0%) (Deiss et al 2006; Cosson et al 2009; Raccah et al 2009). There was limited evidence for improved glycaemic control. The change in HbA_{1c} was larger in the CGM group than in the SMBG group in all three RCTs, but statistically significant in only one high-quality RCT (MD in change –0.60%, 95%CI: –1.00 to –0.20) (Deiss et al 2006).

In one of these RCTs (Raccah et al 2009) a subgroup of patients who were fully protocol-compliant (including CGM sensor wear ≥70% of the time) was analysed according to a prespecified analysis. Fully compliant CGM-users showed a larger improvement in HbA_{1c} than CGM-users in the total group (mean change in 6 months –0.96% [SD 0.93] vs –0.81% [SD 1.09%]). In this per-protocol analysis, the difference in improvement between the CGM and SMBG groups was statistically significant (p-value for difference between study arms=0.004), in contrast to the intention-to-treat analysis (Raccah et al 2009).

6.1.8 Conclusion

Langendam et al (In preparation) conclude that there is limited evidence for the effectiveness of real-time CGM use in children and patients with poorly controlled diabetes. Against expectations, CGM is not associated with a lower incidence of severe hypoglycaemia in type 1 diabetes. Most studies, however, were underpowered to detect a difference, and studies in patients with hypoglycaemia unawareness are lacking.

6.1.9 Literature search strategy

The search was conducted between 17 March 2010 and 24 March 2010. Studies published after this time were not eligible for inclusion in the systematic review. The search strategy is shown in Table 6.14. (Note: this search strategy was also used for Question 6.2). We replicated the search strategy by Langendam et al (2009).

Table 6.14 Search strategy, question 6.1

Database	Date searched	#	Search terms	Citations
EMBASE + Medline	17 March 2010 to 24 March 2010	1	Exp diabetes mellitus, type 1/	52 113
		2	exp diabetic ketoacidosis/	4 463
		3	(IDDM or T1DM or T1D).tw,ot.	8 596
		4	(insulin depend$ or insulindepend$ or insulin-depend$).tw,ot.	26 908
		5	((diabet$ or dm) adj5 ((typ? adj3 (one or '1' or I)) or typ?1 or typ?I)).tw,ot.	26 225
		6	((earl$ or acidos$ or juvenil$ or child$ or keto$ or labil$ or britt$ or p?ediatric) adj6 (diabet$ or dm)).tw,ot.	24 134
		7	((auto-immun$ or autoimmun$ or sudden onset) adj6 (diabet$ or dm)).tw,ot.	4 910
		8	(insulin$ defic$ adj6 absolut$).tw,ot.	81
		9	or/1–8	86 239
		10	exp Blood Glucose Self-Monitoring/	3 003
		11	(cgm or cgms).tw,ot.	515
		12	(GlucoWatch or (navigator and freestyle) or Medtronic or guardian or glucosemeter$).tw,ot	3 555
		13	((gluco$ or sugar or HbA$) adj6 (sensor$ or monitor$)).tw,ot	7 011
		14	or/10–13	12 101
		15	randomised controlled trial.pt.	291 363
		16	controlled clinical trial.pt.	81 622
		17	randomi?ed.ab.	237 196
		18	placebo.ab.	119 122
		19	clinical trials as topic.sh.	148 655
		20	randomly.ab.	144 530
		21	trial.ti	85 961
		22	or/15–21	688 197
		23	Meta-analysis.pt.	24 732
		24	exp Technology Assessment, Biomedical/	8 229
		25	hta.tw,ot.	833
		26	(health technology adj6 assessment$).tw,ot.	956
		27	(meta analy$ or metaanaly$ or meta?analy$).tw,ot.	29 311
		28	((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinhal or psychinfo or psychlit or healthstar or biosis or current content$ or systemat$)).tw,ot.	196 733
		29	or/23–28	226 712

Database	Date searched	#	Search terms	Citations
		30	(comment or editorial or historical-article).pt.	841 724
		31	29 not 30	222 322
		32	9 and 14 and 22	427
		33	9 and 14 and 31	46
		34	(animals not (human and animals)).sh	4 566 751
		35	32 not 34	419
		36	limit 35 to yr="1990–2010"	366
Cochrane	17 March 2010 to 24 March 2010	1	MeSH descriptor Diabetes Mellitus, type 1 explode all tress	
		2	MeSH descriptor Diabetic Ketoacidosis explode all trees	
		3	(IDDM or TIDM or TID)	
		4	(insulin* depend* or insulindepend* or insulin-depend*	
		5	((diabet* or dm) near5 ((typ? Near3 (one or '1' or I)) or typ?1 or typ?1))	
		6	((earl* or acidos* or juvenile* or child* or keto* or labil* or britt* or p?ediatric)near6 (diabet* or dm))	
		7	((auto-immun* or autoimmun* or sudden onset) near6 (diabet* or dm))	
		8	(insulin* defic* near6 absolut*)	
		9	(#1 OR #2 OR #3 OR #4 OR #5 or #6 or #7 or #8)	
		10	MeSH descriptor Blood Glucose Self-Monitoring explode all trees	
		11	(cgm or cgms)	
		12	(Gluco Watch or (navigator and freestyle) or Medronic or guardian or glucosemeter*)	
		13	((glucose* or sugar or HbA*) near6 (sensor* or Monitor**)	
		14	(#10 OR #11 OR #12 OR #13)	
		15	(#9 and #14)	42
Manual search				1
Total citations				409
Total non-duplicate citations				400

6.1.10 Evidence Matrix

HbA_{1c}

Q6.1	Does continuous real-time monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous real-time monitoring to improve HbA_{1c} and reduce severe hypoglycaemia.	
Evidence base	A	Level I evidence with a low risk of bias. Systematic review comprised nine RCTs with a low or moderate risk of bias.
Consistency	C	There was significant clinical and methodological heterogeneity across the nine RCTs, but some consistency regarding the magnitude and direction of effect. There was a nonsignificant advantage to real-time monitoring, with the direction fairly consistent across studies. Children – limited evidence (two RCTs). Adolescents – two RCTs. Adults – consistent up to 6 months, but inconsistent beyond that time, possibly due to lack of adherence (six RCTs). All age groups – (five RCTs).
Clinical impact	D	
Generalisability	C	Studies included children and adolescents, or adults, but some had a small sample size.
Applicability	B	The studies included one Australian study.
Other factors	Continuous real-time monitoring is not used routinely in Australia, but is a rapidly developing technology. The clinical role of real-time blood glucose monitoring is expected to increase with time; therefore, the current evidence statement may become outdated.	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Hypoglycaemia

Q6.1	Does continuous real-time monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous real-time monitoring to improve HbA_{1c} and reduce severe hypoglycaemia.	
Evidence base	A	
Consistency	C	There were no reports of severe hypoglycaemia; there was insufficient evidence on this outcome, because studies lacked power due to low event rates.
Clinical impact	D	
Generalisability	C	
Applicability	B	
Other factors	None identified.	
Recommendation		
R6.1	Real-time CGM may be considered for individuals expected to adhere with therapy, but routine use is not currently recommended (Grade C).	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

6.2 Retropsective continuous glucose monitoring systems

Question 6.2

Does CGM (retrospective systems) versus standard management improve HbA1c, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?

HbA_{1c}, glycated haemoglobin

This chapter expands on Chapter 8, to report on the available evidence on how continuous glucose monitorg systems (CGMS) compare with standard management in improving glycated haemoglobin (HbA_{1c}), minimising fluctuations of blood glucose and reducing severe hypoglycaemia.

6.2.1 Criteria for eligibility

The criteria for determining if publications were eligible for inclusion for this clinical question are shown in Table 6.15.

Table 6.15 Criteria for determining study eligibility, question 6.2

Study design	A systematic review or meta-analysis (NHMRC Level 1 or Level II evidence, using the intervention accuracy scale[a])
Population	Person with type 1 diabetes
Intervention	Continuous glucose monitoring systems, not real time
Comparator	Conventional self-monitoring of blood glucose
Outcomes	• Changes in HbA_{1c} • Variations in glycaemic control • Number of episodes of severe hypoglycaemia

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

6.2.2 Literature search summary

Table 6.16 Search results, question 6.2

Stage	Notes	Number
Search summary	Manual	1
	Cochrane Library	42
	Medline + EMBASE	366
Duplicates	Duplicates identified	9
Identified	Total identified	400
	Total excluded	389
Meeting criteria	Total meeting inclusion criteria	11
Included	Total included studies	10

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

6.2.3 Included studies

A total of 400 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with 389 publications excluded. A total of 11 publications remained, and the full-text version of each publication

was retrieved and reviewed. The same exclusion criteria were then applied to the full-text articles. A total of nine publications met the inclusion criteria. Of these, two were systematic reviews (Chetty et al 2008; Golicki et al 2008) and seven were randomised controlled trials (RCTs) (Chase et al 2001b; Chico et al 2003; Ludvigsson and Hanas 2003; Tanenberg et al 2004; Lagarde et al 2006; Yates et al 2006; Deiss et al 2006b).

The search also identified a Cochrane protocol on this topic (Langendam et al In preparation). The authors were contacted and provided the final version of this systematic review (Langendam et al In preparation). This unpublished review included all of the studies of continuous glucose monitoring systems (CGMS) captured by our search.

6.2.4 Characteristics of included studies

The systematic review by Langendam et al (In preparation) aimed to capture all published data from RCTs that involved assessment of the effect of CGMS compared to standard self-monitoring of blood glucose (SMBG) in patients with type 1 diabetes. That review included studies in both real-time and retrospective CGMS; thus, the authors were unable to pool the results and perform a meta-analysis, because of considerable clinical and methodological heterogeneity. Chetty et al (2008) only included studies using retrospective devices, and could therefore perform a meta-analysis.

Here, we report only on the evidence from RCTs in retrospective CGMS. Table 6.17 details the characteristics of the seven RCTs included in this review.

Table 6.17 Characteristics of included studies, question 6.2

Reference, study type	N, population, country	Intervention	Comparator	Outcomes
Chase et al (2001a) RCT	n=11 Children (poorly controlled diabetes HbA_{1c} >8.0%) United States	CGMS; the children were asked to wear 6 sensors (18 total sensor days) within a 1-month period. While using the CGMS, the children had to perform at least 4 SBGM tests per day. All insulin dose adjustments were made by telephone by one person using the CGMS and SBGM values.	SMBG; ≥4 times a day. All insulin dose adjustments were made by telephone by one person using both the SMBG values.	HbA_{1c} level
Ludvigsson et al (2003) RCT	n=32 Children (poorly controlled diabetes HbA_{1c} >8.0%) Sweden	Open CGMS use for 3 days every 2 weeks during 3 months; participants were instructed to complete at least 2 SMBG tests at different times during the day and a 7-point SMGB once every week.	Blinded CGMS use for 3 days every 2 weeks during 3 months; participants were instructed to complete at least 2 SMBG tests at different times during the day and a 7-point SMGB once a week. During the blinded study arm, neither the patient nor the diabetes team reviewed the results.	HbA_{1c} level Severe hypoglycaemic episodes

Reference, study type	N, population, country	Intervention	Comparator	Outcomes
Deiss et al (2006b) RCT	n=30 Children Germany	Open CGMS use for 3 days at the beginning of the study, at 3 and at 6 months. Patients were instructed to assess SMBG ≥5 times a day and additionally when hypoglycaemic symptoms were expected. Evaluation and interpretation of CGM curves conducted by two physicians experienced in this system.	Blinded CGM use for 3 days at the beginning of the study, at 3 and at 6 months. Patients and/or parents were instructed to assess SMBG measurements at least 5 times/day and additionally when hypoglycaemic symptoms were expected. Patients and investigators were concealed from CGMS data.	HbA_{1c} level Average glucose and AUC during the day Average glucose and AUC during the night Excursions, AUC and time >180 mg/dL and <60 mg/dL
Lagarde et al (2006) RCT	n=27 Children United States	Open CGMS; 72-hour periods of CGMS data collection were initiated at baseline, 2 months and 4 months. Therapeutic decisions were made based on CGMS and SMBG data.	Blinded CGMS; 72-hour periods of CGMS data collection were initiated at baseline, 2 months and 4 months. Therapeutic decisions were made based on SMBG data.	HbA_{1c} level Severe hypoglycaemic episodes Minor hypoglycaemic episodes AUC <70 mg/dL Mean daily time 70 mg/dL AUC >180 mg/dL
Yates et al (2006) RCT	n=36 Children Australia	CGM monitoring for 3 days every 3 weeks over a 3-month period (4 cycles), in addition to traditional intermittent SMBG. Every 3 weeks, the insulin doses were reviewed and adjusted based on CGMS and SMBG by the principal investigator.	SMBG 4–6 times daily. Every 3 weeks, the insulin doses were reviewed and adjusted based on SMBG by the principal investigator.	HbA_{1c} level Severe hypoglycaemia
Chico et al (2003) RCT	n=75 Adults Spain	CGM; the CGMS group was monitored for 3 days using the CGMS, and the information obtained was used to modify treatment. Glucose data from each day were analysed at 5 different times. Responses to hypoglycaemia and exercise and the presence of unrecognised hypoglycaemias were also evaluated.	SMBG; the control group members' treatment was modified using the information obtained from capillary glucose measurements (>8 measurements/day for 3 days).	HbA_{1c} level
Tanenberg et al (2004) RCT	n=109 Adults United States	CGM in addition to SMBG (4 times per day and in response to symptoms of hypoglycaemia). Patients in the CGMS group wore the monitors for 3 days during week 1, and for 3 days during week 3.	SMBG; 4 times per day and in response to symptoms of hypoglycaemia.	HbA_{1c} level Hypoglycaemia (sensor value ≥3.3 mmol/L) Hyperglycaemia (sensor value ≥11.1 mmol/L)

AUC, area under the glucose curve; CGM, continuous glucose monitoring; CGMS, continuous glucose monitoring systems; HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial; SMBG, self-monitoring of blood glucose
Results of included studies

Studies in children

Five RCTs studied the effectiveness of the retrospective Minimed CGMS (Chase et al 2001b; Ludvigsson and Hanas 2003; Lagarde et al 2006; Yates et al 2006; Deiss et al 2006b). Two trials were crossover studies (Ludvigsson and Hanas 2003; Deiss et al 2006b). The duration of the parallel group trials were 3 months, 6 months, and 3 months intervention plus a 3-month follow-up period. The duration of the crossover trials was two times 3 months. In all trials, the CGM sensors were used for 3 days at several time points or intervals. The control group used SMBG alone or blinded CGM with SMBG.

Chase et al (2001)

The trial by Chase et al (2001b) included only children (n=11) with poorly controlled diabetes (HbA_{1c}>8.0%). Participants were recruited from paediatric diabetes clinics. The study measured HbA_{1c} levels after using the CGMS for 3 months. As shown in Table 6.18, CGM users had a significantly higher HbA_{1c} level after 3 months (8.8% vs 8.4%).

Table 6.18 Results from Chase et al (2001)

3 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
Glycaemic control								
HbA_{1c}	8.8	0.3	5	8.4	0.2	6	0.40	0.09 to 0.71

CI, confidence interval; CGM, continuous glucose monitoring; HbA_{1c}, glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

Ludvigsson and Hanas (2003)

The trial by Ludvigsson and Hanas (2003) was a crossover study of 6 months duration (two periods of 3 months) in children (n=32) with poorly controlled diabetes (HbA_{1c}>8.0%). Participants were recruited from paediatric diabetes clinics. As shown in Table 6.19, the HbA_{1c} level at the end of the study was significantly lower in the CGM group than in the control group.

Table 6.19 Results from Ludvigsson and Hanas (2003)

3 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
Glycaemic control								
HbA_{1c}	7.31		13	7.65		14	–0.34	p=0.012[a]
Severe hypoglycaemia (n, %)	1 (8%)		13	1 (7%)		14	1%	–19% to 20%

CI, confidence interval; CGM, continuous glucose monitoring; HbA_{1c}, glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

[a] No standard deviation

Deiss et al (2006b)

The trial by Deiss et al (2006b) was another crossover study. Patients (n=30) were randomised into an open (A) or blind (B) study arm. This trial did not use HbA_{1c} as an eligibility criterion; results are shown in Table 6.20.

Table 6.20 Results from Deiss et al (2006b)

3 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
Glycaemic control								
HbA_{1c}	7.8	1.1	15	8.3	1.1	15	–0.50	–1.29 to 0.29
CGM derived glycaemic control[b]								
AUC >10 mmol/L	24		15	38		15		p=0.49[a]
Time >10 mmol/L (min)	620		15	720		15		p=0.19[a]
Excursions >10 mmol/L	4		15	3		15		p=0.24[a]
AUC <3.3 mmol/L	0		15	0		15		p=0.42[a]
Time <3.3 mmol/L (min)	30		15	0		15		p=0.60[a]
Excursions <3.3 mmol/L (number)	1		15	0		15		p=0.36[a]

AUC, area under the glucose curve; CI, confidence interval; CGM, continuous glucose monitoring; HbA_{1c}, glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring of blood glucose

[a] No standard deviation

[b] Median + range

Lagarde et al (2006)

The trial by Lagarde et al (2006) (n=27) did not use HbA_{1c} as an eligibility criterion. Participants were 5–17 years of age and had been diagnosed with type 1 diabetes for at least 1 year. The study measured HbA_{1c} after 6 months, and found that HbA_{1c} was significantly lower in the CGM group than in the SMBG group (Table 6.21). The decrease in HbA_{1c} was statistically significant in the intervention group, but not in the control group. The difference in HbA_{1c} between groups did not reach statistical significance.

The occurrence of severe hypoglycaemia was measured in this trial. There were no reports of severe hypoglycaemia. The trial also measured minor hypoglycaemia and found that, compared to the control group, the CGM group had a slightly higher, but nonsignificant, number of episodes. CGM-derived glycaemic control was also measured in this trial, with none of the outcomes showing a significant difference between the study arms.

Table 6.21 Results from Lagarde et al (2006)

6 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
Glycaemic control								
HbA_{1c}	7.8	0.88	18	8.6	0.95	9	–0.80	–1.54 to –0.06 p=0.02
Change in HbA_{1c}	–0.61	0.68	18	–0.28	0.78	18	–0.33	–0.93 to 0.27 p=0.13
Severe hypoglycaemia (n, %)	0		18	0		18		
Minor hypoglycaemia (episodes)[a]	1.2	2.2	18	0.7	1.0	18	0.53	–0.68 to 1.74 p=0.24
CGM derived glycaemic control								
AUC <3.9 mmol/L (mmol/L x min/day)	2061	2061	18	1415	1256	9	646	–515 to 1807
Time <3.9 mmol/L (min)	133	133	18	84	66	9	49	–18 to 116
AUC >10 mmol/L (mmol/L x min/day)	662	622	18	656	243	9	6	–185 to 197

AUC, area under the glucose curve; CI, confidence interval; CGM, continuous glucose monitoring; HbA_{1c}, glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring blood glucose

[a] Minor hypoglycaemic episodes were defined as the presence of hypoglycaemic symptoms (sweating, shakiness, weakness, dizziness, hunger, unsteadiness, tingling hands or lips, and headache) associated with a capillary blood glucose <3.9 mmol/L

Yates et al (2006)

The trial by Yates et al (2006) included children (n=36) with HbA_{1c} lower than 10%. There was a significant improvement in HbA_{1c} from baseline values in both groups, but there was no difference in the degree of improvement of HbA_{1c} at 12 weeks between the groups, as shown in Table 6.22.

Table 6.22 Results from Yates et al (2006)

6 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
Glycaemic control								
HbA_{1c}	8.2		19	7.8		17	0.40	p=0.25 [a]
Change in HbA_{1c}	–0.1		19	–0.1		17	0.00	p=0.87 [a]
Severe hypoglycaemia (n, %)	0		19	0		17		

CI, confidence interval; CGM, continuous glucose monitoring; HbA_{1c}, glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring blood glucose

[a] No standard deviation

Studies in adults

Two RCTs studied the effectiveness of retrospective Minimed CGMS on glycaemic control in adults (Chico et al 2003, Tanenberg et al 2004). Both were parallel group trials with duration of 3 months, in patients with inadequate metabolic control.

Chico et al (2003)

In the trial by Chico et al (2003) (n=75), the CGM device was used for a period of 3 days. The control group used SMBG. Three months after baseline, the mean HbA_{1c} levels were equal in the CGM and SMBG groups, as shown in Table 6.23.

Table 6.23 Results from Chico et al (2003)

3 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
Glycaemic control								
HbA_{1c}	7.5	1.6	40	7.5	0.8	35	0.00	–0.56 to 0.56

CI, confidence interval; CGM, continuous glucose monitoring; HbA_{1c}, glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring blood glucose

Tanenberg et al (2004)

In the trial by Tanenberg et al (2004) (n=109), the CGM device was used for two periods of 3 days. The control group used SMBG. Three months after baseline, the mean HbA_{1c} levels were equal in the CGM and SMBG group, as shown in Table 6.24. Change in HbA_{1c} was analysed, and there was no difference in change between the study arms.

Severe hypoglycaemia was also measured in this trial; in both the CGM and the SMBG group, 2% of patients had an episode of hypoglycaemia. The occurrence and duration of CGM-derived hypoglycaemic and hyperglycaemic events were registered for a 3-day period at the end of the study (3 months). The number of events per day did not differ between the study arms, but the mean duration of the hypoglycaemic events was 32 minutes per event shorter in the CGM group. The mean duration of the hyperglycaemic periods was 37 minutes longer in the CGM group, but the difference was not statistically significant.

Table 6.24 Results from Tanenberg et al (2004)

3 months	CGM			SMBG			MD/RD	95%CI
	Mean/ events	SD	N	Mean/ events	SD	N		
Glycaemic control								
HbA_{1c}	8.3	0.9	51	8.3	0.9	58	0.00	–0.34 to 0.34
Change in HbA_{1c}	–0.74	0.95	51	–0.73	1.17	58	–0.01	–0.41 to 0.39
Severe hypoglycaemia (n, %)	1 (2%)		51	1 (2%)		58	0%	–5% to 5%
CGM derived glycaemic control								
BG <3.3 mmol/L (events/day)	1.4	1.1	51	1.7	1.2	58	–0.30	–0.73 to 0.13
BG <3.3 mmol (min per event)	49.4	40.8	51	81.0	61.1	58	–31.6	–50.9 to –12.3
BG >11.1 mmol/L (events/day)	2.9	1.2	51	2.8	1.2	58	0.10	–0.35 to 0.55
BG >11.1 mmol/L (min per event)	208.5	135.3	51	171.6	90.6	58	36.9	–7.0 to 80.8

BG, blood glucose; CI, confidence interval; CGM, continuous glucose monitoring; HbA_{1c}, glycated haemoglobin; MD, mean difference; RD, risk difference; SD, standard deviation; SMBG, self-monitoring blood glucose

Chetty et al (2008)

The seven studies included in Langendam's systematic review were also included in a previous systematic review conducted by Chetty et al (2008). The authors of this latter review performed a meta-analysis of the seven RCTs that compared CGMS and SMBG in patients with type 1 diabetes. The authors also investigated the effect of subcutaneous CGM on the frequency of hypoglycaemic episodes.

With respect to the primary outcome, use of a CGMS was associated with a nonsignificant reduction in HbA_{1c} (0.22), compared to SMBG. The p-value for the heterogeneity test was not statistically significant (I^2 [inconsistency] = 0%). In view of the marked heterogeneity in the definition and assessment of hypoglycaemia, the authors did not perform a pooled analysis of the secondary endpoint (i.e. hypoglycaemic episodes).

Sensitivity analyses

Sensitivity analysis using the three high-quality studies (Tanenberg et al 2004; Lagarde et al 2006; Yates et al 2006) further eroded the differences, with a nonsignificant 0.044% reduction in HbA_{1c}.

When Chetty et al (2008) analysed the paediatric population separately, they observed a significant reduction in HbA_{1c} in favour of CGMS (0.37%).

6.2.5 Conclusion

In summary, Chetty et al (2008) found that, compared with SMBG, CGMS was associated with a nonsignificant reduction in HbA_{1c} (0.22%; 95% confidence interval [CI]: –0.439% to

0.004%; p=0.055). Sensitivity analysis using the three high-quality studies gave similar results (0.044%; 95%CI: –0.35% to 0.26%; p=0.775). Interestingly, when we analysed the paediatric population separately, we observed a significant reduction in HbA_{1c} in favour of the CGMS (0.37%; 95%CI: –0.71% to –0.02%; p=0.036).

The authors concluded that there is insufficient evidence to support CGMS as more beneficial than intensive SMBG in improving HbA_{1c} in patients with type 1 diabetes. There may be a benefit in the paediatric population.

Langendam et al (In preparation) did not perform a meta-analysis because of considerable clinical and methodological heterogeneity between the trials. They summarised the results as shown below.

Children

Unlike Chetty et al (2008), the authors found the evidence for retrospective CGMS in children conflicting. Significantly lower (Ludvigsson and Hanas 2003; Lagarde et al 2006), as well as significantly higher (Chase et al 2001b) HbA_{1c} levels for the CGM group at the end of the study were found. In one RCT, the difference in change after 3 months was not statistically significant (Deiss et al 2006b). In another RCT, the absolute HbA_{1c} level was significantly lower in the CGM group, but the difference in change in HbA_{1c} did not reach significance (Lagarde et al 2006).

Adults

For adults, the authors concurred with Chetty et al (2008), concluding that there were no differences between CGM and SMBG in the primary glycaemic control outcome measures.

Patients with poorly controlled diabetes

Three RCTs (retrospective CGMS) were performed in patients with poorly controlled diabetes (HbA_{1c} >8.0%) (Chase et al 2001b; Ludvigsson and Hanas 2003; Tanenberg et al 2004). The evidence for improved glycaemic control is conflicting. Ludvigsson and Hanas (2003) found significantly lower HbA_{1c} levels for the CGM group at the end of the study; Chase et al (2001b) found higher levels and Tanenberg et al (2004) found no difference.

Literature search strategy

The search was conducted between 17 March 2010 and 24 March 2010. Studies published after this time were not eligible for inclusion in the systematic review. The search strategy, shown in Table 6.25, replicated that of Langendam et al (2009).

Table 6.25 Search strategy, question 6.2

Database	Date searched	#	Search terms	Citations
Medline + EMBASE	17–24 March 2010	1	Exp diabetes mellitus, type 1/	52 113
		2	exp diabetic ketoacidosis/	4 463
		3	(IDDM or T1DM or T1D).tw,ot.	8 596
		4	(insulin depend$ or insulindepend$ or insulin-depend$).tw,ot.	26 908
		5	((diabet$ or dm) adj5 ((typ? adj3 (one or '1' or I)) or typ?1 or typ?I)).tw,ot.	26 225
		6	((earl$ or acidos$ or juvenil$ or child$ or keto$ or labil$ or britt$ or p?ediatric) adj6 (diabet$ or dm)).tw,ot.	24 134
		7	((auto-immun$ or autoimmun$ or sudden onset) adj6 (diabet$ or dm)).tw,ot.	4 910
		8	(insulin$ defic$ adj6 absolut$).tw,ot.	81
		9	or/1-8	86 239
		10	exp Blood Glucose Self-Monitoring/	3 003
		11	(cgm or cgms).tw,ot.	515
		12	(GlucoWatch or (navigator and freestyle) or Medtronic or guardian or glucosemeter$).tw,ot	3 555
		13	((gluco$ or sugar or HbA$) adj6 (sensor$ or monitor$)).tw,ot	7 011
		14	or/10-13	12 101
		15	randomised controlled trial.pt.	291 363
		16	controlled clinical trial.pt.	81 622
		17	randomi?ed.ab.	237 196
		18	placebo.ab.	119 122
		19	clinical trials as topic.sh.	148 655
		20	randomly.ab.	144 530
		21	trial.ti	85 961
		22	or/15-21	688 197
		23	Meta-analysis.pt.	24 732
		24	exp Technology Assessment, Biomedical/	8 229
		25	hta.tw,ot.	833
		26	(health technology adj6 assessment$).tw,ot.	956
		27	(meta analy$ or metaanaly$ or meta?analy$).tw,ot.	29 311
		28	((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinhal or psychinfo or psychlit or healthstar or biosis or current content$ or systemat$)).tw,ot.	196 733
		29	or/23-28	226 712
		30	(comment or editorial or historical-article).pt.	841 724
		31	29 not 30	222 322
		32	9 and 14 and 22	427
		33	9 and 14 and 31	46
		34	(animals not (human and animals)).sh	4 566 751

Database	Date searched	#	Search terms	Citations
		35	32 not 34	419
		36	limit 35 to yr="1990-2010"	366
Cochrane	17–24 March 2010			42
Manual search				1
Total citations				409
Total non-duplicate citations				400

6.2.6 Evidence Matrix

HbA_{1c}

Q6.2	Does continuous glucose monitoring (retrospective systems) versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous retrospective blood glucose monitoring systems to improve HbA_{1c} and reduce severe hypoglycaemia.	
Evidence base	A	Level I evidence with a low risk of bias, comprising seven RCTs: three with a low risk of bias and four with a moderate risk of bias.
Consistency	C	There was a nonsignificant reduction in this outcome. A sensitivity analysis of the high-quality studies reduced the magnitude of the effect. A subgroup analysis of the paediatric group found a significant effect, but results in adults were conflicting.
Clinical impact	D	The magnitude of change in the meta-analysis was –0.4%.
Generalisability	B	
Applicability	B	The studies included one Australian study in children.
Other factors	None identified.	

Hypoglycaemia

Q6.2	Does continuous real-time monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous retrospective blood glucose monitoring systems to improve HbA_{1c} and reduce severe hypoglycaemia.	
Evidence base	A	
Consistency	C	There were no reports of severe hypoglycaemia; there was insufficient evidence on this outcome, because studies lacked power due to low event rates.
Clinical impact	D	
Generalisability	B	
Applicability	B	
Other factors	None identified.	
Recommendation		
R6.2	Retrospective CGM systems are not recommended for routine use to improve glycaemic control or reduce severe hypoglycaemia, but may be considered for children and adolescents (Grade C).	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

7 Insulin and pharmacological therapies

7.1 Insulin analogues versus human insulin

7.1.1 Effect of insulin analogues vs human insulin on hypoglycaemia and glycaemic control

Question 7.1

(i) How effective are insulin analogues versus human insulin at reducing hypoglycaemia and HbA1c?

HbA_{1c}, glycated haemoglobin

This section of the report investigates the effectiveness of insulin analogues at reducing glycated haemoglobin (HbA_{1c}) and hypoglycaemia, in comparison to human or regular insulin (e.g. neutral protamine Hagedorn [NPH], insulin zinc). The analogues investigated were insulin lispro, insulin aspart, insulin glulisine, insulin glargine and insulin detemir.

7.1.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 7.1.

Table 7.1 Criteria for determining study eligibility, question 7.1 (i)

Study design	NHMRC evidence Level I or II (using the intervention accuracy scale) [a]
Population	Patients with type 1 diabetes
Intervention	An insulin analogue
Comparator	An insulin analogue
Outcomes	Change in HbA_{1c} Hypoglycaemia

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

7.1.1.2 Assessment of study eligibility

A total of 181 citations were identified in the initial literature search (see Table 7.2). The exclusion criteria were applied to all citations by reviewing the abstract and title, with 166 publications excluded. A total of 15 publications remained, and the full-text version of each of these publications was retrieved and reviewed.

7.1.1.3 Citations for full-text review

The literature search identified 15 Level I studies; these were:

- studies that included both short- and long-acting insulin analogues (Colquitt et al 2003; Singh et al 2009)
- studies that included short-acting insulin analogues only (Davey et al 1997; Brunelle et al 1998; Haycox 2004; Siebenhofer et al 2004; Plank et al 2005; Siebenhofer et al 2006; Banerjee et al 2007)

- studies that included long-acting insulin analogues only (NICE (National Institute for Clinical Excellence) 2002; Wang et al 2003; Warren et al 2004; Goldman-Levine and Lee 2005; Tran et al 2007; Monami et al 2009).

The included studies were reviewed to see whether any one study captured all identified studies, and thus could be used as the primary piece of evidence for this clinical question. The meta-analysis by Singh et al (2009) captured all of the relevant citations from the earlier studies. Some of recent systematic reviews included more studies (Siebenhofer et al 2006; Vardi et al 2008) due to their broader inclusion criteria (subjects with type 2 diabetes or gestational diabetes). However, the study by Singh et al (2009) was the most comprehensive in terms of outcomes of interest to this review; it was also the most recent. It included 68 randomised controlled trials (RCTs) in the analysis of rapid-acting insulin analogues, and 49 in the analysis of long-acting insulin analogues.

Although Singh et al (2009) was the most comprehensive systematic review identified here, the literature search for this publication was performed in April 2007. It was therefore decided that an updated literature search for Level II studies was needed, to identify any recent RCT evidence. The additional search strategy and yield is shown in Table 7.8.

The systematic literature search identified 136 publications from Medline and 53 from EMBASE. None of the EMBASE articles were relevant; 23 articles from the Medline search were relevant for review of the full text, and of these, 3 were not already included in the meta-analysis and met the inclusion criteria.

7.1.1.4 Literature search summary

Table 7.2 (a) Search results – (a) initial search and (b) RCTs published since April 2007

Stage	Notes	Number
Search summary	Manual	0
	Medline	28
	Cochrane Library	48
	INAHTA	10
	DARE	13
	EMBASE	80
	NHS (NICE)	2
	Total	181
Exclusion criteria	Wrong study type (not NHMRC evidence Level I or II) [a]	124
	Wrong population (not in patients with type 1 diabetes)	18
	Wrong intervention or test (not an insulin analogue)	16
	Wrong comparator (not regular human insulin or NPH)	
	Wrong outcome (not change in HbA_{1c} or hypoglycaemia)	6
	Not in English	2
	Total excluded	166
Meeting criteria	Total meeting inclusion criteria	15

Table 7.3 (b)

Stage	Notes	Number
Search summary	Manual	0
	Medline	53
	Total	53
Included	Total included studies	4

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council; NPH, neutral protamine Hagedorn
[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

7.1.1.5 Included studies

Three Level I studies were included (Banerjee et al 2007; Tran et al 2007; Singh et al 2009), and four Level II studies (Chatterjee et al 2007; Mullins et al 2007; Bartley et al 2008; Chase et al 2008).

7.1.1.5.1 Systematic reviews

Singh et al (2009) aimed to provide a systematic review and meta-analysis of outcomes associated with the use of rapid and long-acting insulin analogues in type 1 and type 2 diabetes (adult and paediatric patients), and gestational diabetes. The study was an update of two earlier systematic reviews of the efficacy and safety of rapid and long-acting insulin analogues from the Canadian Agency for Drugs and Technologies in Health (CADTH), published in 2007 (Banerjee et al 2007; Tran et al 2007).

The outcomes measured were HbA_{1c}, hypoglycaemia, quality of life, patient satisfaction, complications of diabetes and adverse effects. The update included recently published studies and additional outcomes of interest, such as intraclass comparisons of the rapid and long-acting insulin analogues. Only RCTs were included in the original and updated studies. The studies included for the update were RCTs published up to April 2007. Studies of insulin glulisine were excluded from the systematic review because that agent was not available in Canada at the time of the review.

Short-acting analogues

The original meta-analysis regarding short-acting insulin analogues on which the update was based described 47 RCTs on type 1 diabetes. There were 29 crossover trials and 18 parallel trials. Patient numbers in the RCTs ranged between 21 and 876. Some of the trials were multicentre and multinational.

The updated studies found by Singh et al (2009) regarding short-acting insulin analogues were largely on populations not relevant to this review. The relevant study from the update was a randomised crossover trial on 35 children from Australian diabetes clinics (Fairchild et al 2000).

Long-acting analogues

The meta-analysis on long-acting insulin analogues on which the update was based included 23 studies on subjects with type 1 diabetes. The number of patients ranged between 14 and 756. Most studies were conducted in adults; only three involved paediatric or young adult populations. On average, the RCTs were of low quality. The evaluation was made according to a modified Jadad scale (Jadad et al 1996) which evaluated the extent of allocation concealment, blinding of assessors and reporting of intention-to-treat analysis. Most of the trials were multicentre, and many were also multinational.

The authors reported that funnel plots were used to assess the potential for publication bias in meta-analyses that included more than five studies. However, these data were not found in the body of the report or appendices.

Regarding long-acting insulin, 20 trials were selected for inclusion and were analysed together with the 28 trials from the original report. Of these studies, seven were in cohorts of subjects with type 2 diabetes. The updated studies were not analysed separately.

Most of the trials included in the meta-analysis were multinational and sponsored by industry. The number of patients in each study ranged from 7 to 1008. Of the 48 crossover studies, most lacked or did not mention a wash-out period. All studies were of open-label design, and trial duration ranged from 4 weeks to 30 months. The methodologic quality of most of the trials was poor; no study was double blinded, and allocation concealment was rarely described. A sensitivity analysis was performed for studies of low methodologic quality.

Outcomes of interest

The outcomes considered for this systematic review were hypoglycaemia and HbA_{1c}. Data on hypoglycaemia were analysed using the relative risk (RR) of experiencing one or more episodes of hypoglycaemia during the study period. The rate ratio was used for the frequency of episodes (i.e. number of episodes per patient per unit time). Definitions of hypoglycaemia and subtypes were taken from the individual trials.

Adults: Insulin lispro

Compared with regular human insulin, use of insulin lispro resulted in a marginally lower HbA_{1c} (weighted mean difference [WMD] –0.09%, 95% confidence interval [CI]: –0.15% to –0.02%) and a lower risk of severe hypoglycaemia (RR 0.80, 95%CI: 0.67 to 0.96). There was also a lower rate of nocturnal hypoglycaemia in the overall analysis (rate ratio 0.51, 95%CI: 0.42 to 0.62). There was a high degree of heterogeneity – not explained by differences in patient characteristics or treatments – across the studies that reported rates of nocturnal hypoglycaemia in the overall analysis (I^2 = 73.1%). The rate of overall hypoglycaemia was similar between groups. Subgroup analysis by method of administration did not reveal substantial differences in treatment effects between patients using multiple daily injections (MDI) and those using continuous subcutaneous insulin infusion (CSII).

Adults: Insulin aspart

Insulin aspart also resulted in a slightly lower mean HbA_{1c} concentration compared with regular human insulin (WMD –0.13%, 95%CI: –0.20% to –0.07%). There were no significant differences between groups in the risk of severe hypoglycaemia or the rate of overall hypoglycaemia. In the only study reporting data on nocturnal hypoglycaemia, the rate among patients given insulin aspart via CSII was significantly lower than the rate among those given regular human insulin (rate ratio 0.55, 95%CI: 0.43 to 0.70).

Adults: Insulin glargine

Insulin glargine provided a small but significant improvement in HbA_{1c} compared to NPH insulin (WMD –0.11%, 95%CI: –0.21% to –0.02%). There were no significant differences in the risk or rate of any type of hypoglycaemia when the same bolus insulin was used in each treatment arm. The RR estimate for nocturnal hypoglycaemia demonstrated a high degree of heterogeneity, with an I^2 of 65.6%. This was reduced when the study of shortest duration (4 weeks) was removed from the meta-analysis. This study had demonstrated the largest risk reduction in favour of insulin glargine (RR 0.64, 95%CI: 0.47 to 0.87).

Adults: Insulin detemir

No differences were found in HbA_{1c} between insulin detemir and NPH insulin (WMD –0.06%, 95%CI: –0.13% to 0.02%). There was a slight reduction in the risk of severe hypoglycaemia (RR 0.74, 95%CI: 0.58–0.96) and nocturnal hypoglycaemia (RR 0.92, 95%CI: 0.85 to 0.98) in favour of insulin detemir, but not for overall hypoglycaemia (data not shown in Singh et al [2009]). It was reported that statistically significant reductions in the rates of nocturnal and overall hypoglycaemia in favour of insulin detemir was found; however, the data were not shown in the report published by Singh et al (2009).

Children: Insulin lispro

The pooled analysis of trials comparing insulin lispro and regular human insulin in pre-adolescent patients found no significant difference in HbA_{1c} (WMD 0.14%, 95%CI: –0.18% to 0.46%), risk of severe hypoglycaemia (RR 0.69, 95%CI: 0.24 to 2.01) or rates of nocturnal hypoglycaemia (rate ratio 0.96, 95%CI: 0.74 to 1.26) and overall hypoglycaemia (data not shown).

Adolescents: Insulin lispro

Only one study compared insulin lispro and human insulin in adolescents, and no differences were found in HbA_{1c} (WMD –0.01%, 95%CI: –0.21% to 0.19%) or risk of severe hypoglycaemia (RR 1.00, 95%CI: 0.29 to 3.43). The rate ratios for nocturnal hypoglycaemia (rate ratio 0.61, 95%CI: 0.57 to 0.64) and overall hypoglycaemia (data not shown) was reported as significantly favouring insulin lispro.

Children and adolescents: Insulin aspart

One study comparing insulin aspart and human insulin in pre-adolescents and one study of children and adolescent patients showed no significant difference in HbA_{1c} or risk of overall hypoglycaemia (data not shown).

Children and adolescents: Insulin glargine

No differences were found between insulin glargine and the conventional insulins (mostly NPH) in children and adolescents regarding HbA_{1c} (WMD –0.25%, 95%CI: –0.55% to –0.05%). Nor were there any differences for any type of hypoglycaemia (data not shown).

Children and adolescents: Insulin detemir

Regarding insulin detemir and NPH insulin, one trial showed no difference in HbA_{1c} (WMD 0.10%, 95%CI: –0.10% to 0.30%) or severe hypoglycaemia (RR 0.80, 95%CI: 0.50 to 1.28). There was a small, statistically significant benefit in favour of insulin detemir with regard to nocturnal hypoglycaemia (RR 0.85, 95%CI: 0.77 to 0.94), and also for overall hypoglycaemia (data not shown).

7.1.1.5.2 Randomised controlled trials

Four RCTs relevant to the clinical question and published since 2007 were identified. One study (Mullins et al 2007) met some prespecified inclusion criteria, but the results do not form part of this report. This study aimed to apply a statistical model to adjust for the potentially confounding interaction of hypoglycaemia and glycaemic control. The model was then used to compare rates of hypoglycaemia associated with the use of insulin glargine compared to NPH insulin. The secondary outcome met inclusion criteria for this report. However, the methodology used to arrive at the studies included for analysis of hypoglycaemia outcomes was in biased studies with patient-level data, and studies from a single source. Thus, although systematic, Mullins et al (2007) was not representative, and

the hypoglycaemia results were not included in this report. The main findings of this study are discussed in detail in the introductory section of this chapter.

Three RCTs compared long-acting insulin analogues with human insulin counterparts. The study duration ranged from 24 to 96 weeks. Two studies were in adults and one was in children and adolescents aged 9–17 years. The different populations and comparators precluded combination of these studies into a meta-analysis. The results of the RCTs are summarised in Table 7.4.

Table 7.4 Summary of randomised controlled trials, question 7.1 (i)

Study	Study design and type	Intervention	Comparator	Population	Setting	N	Study quality
Bartley et al (2008)	Randomised, open-label, parallel-group treat-to-target	Detemir daily	NPH daily	Adults	33 sites in 10 countries	495	Fair
Chase et al (2008)	Non-inferiority, randomised, open-label, parallel-group	Glargine	NPH or insulin lente	Adolescents	Multicentre 40 sites: 29 United States, 11 Canadian	175	Fair
Chattergee et al (2007)	Randomised, open-label, crossover trial	Glargine once daily	NPH twice daily	Adults: 58 white European, 2 South Asian	Single-centre United Kingdom	60	Fair

NPH, neutral protamine Hagendorn

Bartley et al (2008)

The longest trial of long-acting insulin compared to human insulin was of 24 months duration in 495 subjects (Bartley et al 2008). The mean diabetes duration was 13.0 years (range 1.0–50.4). The mean age was 35 years (range 18–75 years) and the mean baseline HbA_{1c} was 8.3% (range 5.0–11.6%).

In total, 497 patients were randomly allocated 2:1 to insulin detemir or NPH insulin:

- 100% of those allocated to insulin detemir received treatment, with 15.7% discontinuing treatment (3.9% due to an adverse event, and 1.8% because of noncompliance)
- 98.9% of those allocated to NPH insulin received treatment, with two patients withdrawing consent and 13.2% discontinuing treatment (0.6% due to an adverse event, and 3.6% because of noncompliance).

Insulin detemir or NPH insulin was initiated once daily, and titrated using a treat-to-target concept. Thus, a second basal morning dose was added according to a prespecified algorithm, which was used to adjust the basal insulin to a prebreakfast and dinner plasma glucose target of ±6.0 mmol/L. The short-acting insulin was also titrated according to local practice, to achieve a postprandial plasma glucose level of ≤9.0 mmol/L.

After 24 months, there was a small but significant difference in HbA_{1c} in favour of insulin detemir with a mean difference (insulin detemir–NPH insulin) of –0.22%.

In the analysis of hypoglycaemia, all self-monitored plasma glucose values below 3.1 mmol/L, as well as signs and symptoms of hypoglycaemia, were recorded in patients' diaries. Hypoglycaemic episodes were classified as:

- 'major' if assistance from another person was required
- 'minor' if plasma glucose was below 3.1 mmol/L and the individual dealt with the episode themselves
- 'symptoms only' if episodes were not confirmed by plasma glucose and no assistance was required.

The definition of nocturnal hypoglycaemic episodes was not recorded. The risk of major and nocturnal hypoglycaemia was lower with insulin detemir than with NPH insulin; however, the overall safety profile was similar in the two groups.

Chase et al (2008)

Chase et al (2008) compared insulin glargine with NPH insulin or insulin lente in 175 adolescents who were using insulin lispro as the bolus insulin. The mean age was 13.1 years in the insulin glargine group and 13.4 years in the NPH/insulin lente group. The mean duration of diabetes was 5.1 years in the insulin glargine group and 5.4 years in the NPH/insulin lente group. The mean HbA_{1c} was 7.8% in the insulin glargine group and 8.0% in the NPH/insulin lente group.

A total of 175 patients were randomised and analysed as the safety population. Of these, 168 patients were included in the intention-to-treat (ITT) population, with 1 patient from the insulin glargine group and 4 from the NPH/insulin lente group having no baseline HbA_{1c}; in addition, 2 patients from the NPH/insulin lente group had no treatment A_{1c}. Of the 168 patients in the ITT population, 8 were lost from the glargine arm (4 with treatment duration <148 days) and 4 with major protocol violations (screening A_{1c} <7%). In the NPH/insulin lente arm, 1 patient was lost with treatment duration <148 days and 2 were major protocol violations.

Insulin glargine once daily was compared to NPH/insulin lente twice daily. The investigators titrated the basal insulin doses weekly to achieve a target fasting plasma glucose value of 70–100 mg/dL (3.8–5.5 mmol/L). The mean change of A_{1c} from baseline to study end was similar in the two groups.

The adjusted mean difference between the groups in the per-protocol population was –0.2 (95%CI: –0.48 to 0.08; p=0.1725 between groups). This was within the predefined limit of ±0.4%, demonstrating non-inferiority.

In this study, 'severe hypoglycaemia' was defined as an event requiring assistance from another person and associated with either blood glucose of less than 2 mmol/L, or prompt recovery after oral carbohydrate or intramuscular (IM) or subcutaneous glucagon. Patients often did not record a blood glucose level during these events. Patients recorded the date, time and symptoms of suspected hypoglycaemic events, as well as the self-monitoring of blood glucose (SMBG) value. The rates of biochemical hypoglycaemia were ascertained by analysis of SMBG data, and divided into three categories: below 3.8 mmol/L, 2.7 mmol/L or 2 mmol/L. Rates of severe hypoglycaemia (hypoglycaemia requiring assistance, blood glucose values often not measured) were categorised separately to the biochemical hypoglycaemia. There was a significant difference between groups in terms of blood glucose

levels below 3.8 mmol/L, with a higher event rate in patients on insulin glargine. There were no other differences between groups.

Chatterjee et al (2007)

Of the adult trials, Chatterjee et al (2007) compared insulin glargine to NPH insulin with insulin aspart as the bolus insulin. This 36-week crossover trial consisted of 60 patients. The mean age was 42.9 years (standard deviation [SD] 12.5), the mean HbA_{1c} was 8.53% (SD 1.15) and the mean duration of diabetes was 18.2 years (SD 11.8%).

Insulin glargine was administered once daily and NPH insulin twice daily. The number of units equal to that administered at the end of the first period was prescribed for the next block, with the basal dose being increased by 20% when switching from insulin glargine to NPH insulin. When switching from NPH insulin to insulin glargine, the basal dose of insulin was reduced by 20%. It was reported that insulin dosage was adjusted according to a local algorithm, with targets of 4.0–6.7 mmol/L before meals, 4–8 mmol/L at bedtime and less than 8 mmol/L 2 hours before meals. Phone contact was made twice weekly to advise on changes in insulin dosage.

HbA_{1c} was significantly lower in the insulin glargine group.

Hypoglycaemia was categorised as symptoms only, documented or confirmed, severe and nocturnal (occurring between 24:00 and 08:00). Severe hypoglycaemia was defined as a hypoglycaemic episode requiring third party assistance, or intravenous (IV) glucose or IM glucagon. Documented or confirmed hypoglycaemia was defined as a capillary glucose measurement of less than 2.8 mmol/L.

The mean incidence of both severe and non-severe hypoglycaemia with insulin glargine was similar to the incidence with NPH insulin (80.7% vs 77.2%, 1.21 (0.56–2.64) p=0.63).

Summary of included randomised controlled trials

The results of the three included RCTs are summarised in Table 7.5.

Table 7.5 Summary of RCTs and results, question 7.1 (i)

Study reference	Difference between groups	95%CI	P value
Bartley et al (2008)	HbA_{1c}–0.22% in favour of detemir	–0.41 to –0.03	0.022
	Hypoglycaemia: RR of all hypoglycaemic episodes (detemir/NPH) 0.74	0.51 to 1.07	0.112
	RR nocturnal hypo 0.54	0.4 to 0.71	<0.001
Chase et al (2008)	HbA_{1c}:–0.2	–0.48 to 0.08	0.1725
	Hypoglycaemia <70 mg/dL (3.8 mmol) adjusted event rate per patient year 116.1 glargine	93.8 NPH/insulin lente	0.298
Chattergee et al (2007)	HbA_{1c}:–0.19	0.37 to 0.01	0.04
	Hypoglycaemia: all OR 1.2 (glargine vs NPH)	0.55 to 2.59	No significant difference in incidence

CI, confidence interval; HbA_{1c}, glycated haemoglobin; NPH, neutral protamine Hagendorn; OR, odds ratio; RR, relative risk

7.1.1.6 Discussion

The meta-analysis by Singh et al (2009) found that, where there were statistically significant differences in HbA_{1c} between groups, the differences were smaller than minimal clinically important differences described in the literature (i.e. less than 1%). There were statistically significant benefits of insulin analogues in terms of hypoglycaemia in some populations, but there were no statistically significant differences for insulin glargine versus NPH insulin, or insulin aspart versus human insulin. Several trials excluded subjects with a history of recurrent major hypoglycaemia. All head-to-head comparisons between insulin analogues of the same class showed little or no difference in glycaemic control or risk of hypoglycaemia.

The limitations of this meta-analysis included the restriction of the search to trials published in English, the significant heterogeneity across trial results and the lack of availability of long-term trials.

The authors concluded that insulin analogues offer few clinical advantages over conventional insulins in the management of most patients with type 1 diabetes.

The RCTs were limited by the lack of blinding in treatment assignment, and the lack of reported blinding of outcome assessor, patient and care giver.

Another difference between studies was that Bartley et al (2008) reported a prespecified aim of treating to target according to algorithm, whereas the other two studies had no such prespecified aim. These studies reported their treatment targets in their methods section, and the target fasting plasma glucose varied from less than 5 mmol/L (Bartley et al 2008) to 3.8–5.5 mmol/L (Chase et al 2008) and 4–6.7 mmol/L (Chatterjee et al 2007).

The classification of hypoglycaemia varied between trials, as shown in Table 7.6.

Table 7.6 Definitions, classification and measurement of hypoglycaemia in included RCTs

Study	Definition/classification of hypoglycaemia	Measurement
Bartley et al (2008)	PG <3.1 mmol/L, plus signs and symptoms of hypoglycaemia recorded in patient diaries Major: assistance required Minor: PG <3.1 mmol/L and patient dealt with episode themselves Symptoms only if episodes not confirmed by PG measurement and no assistance required Nocturnal hypoglycaemia (23:00 to 06:00)	RR: events per patient year
Chase et al (2008)	Severe hypoglycaemia: event requiring assistance from another person and associated with PG <35 mg/dL or prompt recovery after oral carbohydrate/IV glucose or IM glucagon Nocturnal hypoglycaemia: events between 24:00 and 06:00 Biochemical hypoglycaemia: 3 categories: <70 mg/dL, <50 mg/dL and <35 mg/dL	Event rate: events per patient year
Chattergee et al (2007)	Symptoms only Severe: requiring third party assistance and/or IV glucose or IM glucagon Nocturnal (occurring between 24:00 and 08:00) Documented or confirmed hypoglycaemia: capillary glucose of less than 2.8 mmol/L	Mean incidence Odds ratio

IM, intramuscular; IV, intravenous; PG, plasma glucose; RR, relative risk

Adults

Glycaemic control

Rapid-acting analogues

HbA_{1c} was significantly lower when insulin lispro (WMD –0.09%; 95%CI: –0.16% to –0.02%) and insulin aspart (WMD –0.13%, 95%CI: –0.2 to –0.07%) were compared to human insulin (Singh et al 2009).

Long-acting analogues

HbA_{1c} was lower with insulin glargine than with NPH insulin (WMD –0.11%, 95%CI:–0.21% to 0.02%). There was no significant difference between insulin detemir and NPH insulin (Singh et al 2009). Regarding the RCTs, a difference of –0.22% (95%CI: –0.41 to –0.03) in favour of insulin detemir was found (Bartley et al 2008). Reductions in HbA_{1c} in favour of insulin detemir and insulin glargine over NPH insulin were also found (Chatterjee et al 2007; Chase et al 2008).

Hypoglycaemia

Short-acting analogues

Severe hypoglycaemia was lower with insulin lispro than with human insulin (RR 0.8, 95%CI: 0.67 to 0.96) (Singh et al 2009). There was no difference between insulin aspart and human insulin (Singh et al 2009).

Nocturnal hypoglycaemia was lower with insulin lispro (rate ratio 0.51, 95%CI: 0.42 to 0.62) (Singh et al 2009) However, there was a high degree of heterogeneity (I^2=73.1%). In the one trial (Bode et al 2002) that compared insulin aspart with human insulin via CSII, there was a lower rate among those given human insulin (rate ratio 0.55, 96% CI: 0.43 to 0.70).

Overall, hypoglycaemia was similar between those receiving insulin lispro and human insulin, and between those receiving insulin aspart and human insulin (Singh et al 2009).

Long-acting analogues

Severe hypoglycaemia was slightly reduced with insulin detemir compared with NPH insulin (RR 0.74, 95%CI: 0.58 to 0.96). No difference with insulin glargine was found (Singh et al 2009). The risk of major hypoglycaemia was 69% lower with insulin detemir than NPH insulin (Bartley et al 2008).

Nocturnal hypoglycaemia was reduced with insulin detemir (RR 0.92, 95%CI: 0.85 to 0.98). There was no difference with insulin glargine (Singh et al 2009). Nocturnal hypoglycaemia was 46% lower with insulin detemir than with NPH (Bartley et al 2008).

There were no differences in the rate of overall hypoglycaemia with either insulin detemir or insulin glargine (Singh et al 2009). Also, there was no difference in any category of hypoglycaemia in an RCT of 60 adult patients (Chatterjee et al 2007).

Children and adolescents

Glycaemic control

Short-acting insulin analogues

There was no difference in HbA_{1c} in the one study where insulin lispro was compared with human insulin in adolescents or in the pooled analysis of preadolescent patients (Singh et al 2009).

Long-acting insulin analogues

There were no significant differences in HbA_{1c} when insulin glargine or insulin detemir were compared to NPH insulin in children and adolescents (Singh et al 2009). There was also no difference between insulin glargine and NPH/insulin lente groups in terms of HbA_{1c} in adolescents (Chase et al 2008).

Hypoglycaemia

Severe hypoglycaemia was no different between insulin lispro and human insulin in adolescents or children. There was no overall difference with insulin glargine or insulin detemir compared to human insulin in pooled data (Singh et al 2009).

Rates of nocturnal hypoglycaemia were significantly reduced in the one study of lispro in adolescents (rate ratio 0.96, 95%CI: 0.74 to 1.26) but no difference was found in pooled results on pre-adolescents (Singh et al 2009). Nocturnal hypoglycaemia was significantly lower with insulin detemir in children and adolescents (0.85, 95%CI: 0.77 to 0.94). There was no difference with insulin glargine.

Overall, hypoglycaemia was not significantly different in pre-adolescents using insulin lispro. There was no difference when insulin aspart was used. There was also no difference in overall hypoglycaemia when insulin glargine was compared to NPH insulin, and only a small statistically significant reduction with insulin detemir, although numerical values were not given (Singh et al 2009). In the RCT on adolescents (Chase et al 2008), there was a higher event rate of blood glucose levels of less than 3.8 mmol/L in patients on insulin glargine compared with NPH/insulin lente (see Table 7.5) but no difference in other categories of hypoglycaemia.

7.1.1.7 Conclusion

This systematic review is based on a comprehensive meta-analysis of good quality, which itself was an update of two good-quality systematic reviews. The results were consistent across other Level I studies identified. The reduction in HbA_{1c} with insulin analogues compared to human insulin was –0.06% to –0.13%. The results regarding hypoglycaemia were varied across studies. The populations and clinical settings were not well described in the studies, although most were multicentre and multinational. The countries involved were mainly European and American.

The Level II studies included in this report compared long-acting insulin analogues with NPH insulin. The findings regarding HbA_{1c} reduction were similar to those found in the pooled analysis by Singh et al (2009), with a small but statistically significant reduction in HbA_{1c} using long-acting insulin analogues. The results regarding hypoglycaemia varied in the method of measurement. Bartley et al (2008) found a relative risk of nocturnal hypoglycaemia of 0.54 in favour of insulin detemir compared with NPH insulin. No other statistically significant difference was found in any category in the other two studies. The populations involved in the RCTs were adults in two studies and adolescents in one study. Two of the RCTs were multicentre and multinational, one study was single centre and set in the United Kingdom.

The relationship between HbA_{1c} and hypoglycaemia was not a prespecified endpoint in this report. This concept will be discussed in the introduction to this chapter.

7.1.1.8 Literature search strategy

The search was conducted between 8 March 2010 and 13 May 2010. Level I studies were considered first, with the plan to update with Level II studies as required. The Medline search strategy and a summary of citations retrieved from other searches are shown in Table 7.7.

Table 7.7 Search strategy, question 7(i)

Database	Date searched	#	Search terms	Citations
Medline	25 February 2010	1	Diabetes Mellitus, type 1/	50 461
		2	(LADA or latent autoimmune diabetes mellitus).mp.	283
		3	insulin dependent diabet*.mp.	23 229
		4	(insulin analog* or insulin receptor ligands).mp.	1 285
		5	(rapid acting insulin or ultra short acting insulin).mp.	265
		6	(insulin lispro or insulin lispro-protamine suspension or humalog).mp.	700
Medline	Between 8 March 2010 and 13 May 2010	7	(insulin aspart or novorapid or novolog).mp.	416
		8	(insulin glulisine or apidra).mp.	83
		9	(insulin glargine or lantus).mp.	567
		10	(insulin detemir or levemir).mp.	284
		11	novomix 30.mp.	17
		12	Insulin/	135 311
		13	(human insulin or regular insulin or insulin zinc suspension or soluble insulin).mp.	5 515
		14	Insulin, Long-Acting/	770
		15	insulin isophane.mp. or Insulin, NPH/	537
		16	(humulin or mixtard).mp.	121
		17	protaphane.mp	19
		18	actrapid.mp.	169
		19	neutral insulin.mp.	29
		20	Hyperglycemia/	14 898
		21	Hemoglobin A, Glycosylated/	15 382
		22	Blood Glucose/	105 089
		23	(blood glucose control or glycemic control or glycaemic (control).mp.	12 399
		24	(metabolic control or diabetes control).mp.	8 311
		25	or/1–3	62 274
		26	or/4–11	2 320
		27	or/12–19	137 377
		28	or/20–24	130 372
		29	and/25–28	610
		30	Meta-Analysis/	23 338
		31	systematic review.mp.	16 972
		32	pooled analysis.mp.	1 679

Database	Date searched	#	Search terms	Citations
		33	(review and medline).mp.	26 722
		34	(systematic* and (review* or overview*)).mp.	41 342
		35	or/30–34	75 783
		36	29 and 35	28
Cochrane	22 February 2010			48
INAHTA	23 February 2010			10
DARE	23 February 2010			13
EMBASE	28 February 2010			80
NHS (NICE)	23 February 2010			2
Manual search				0
Total citations				181
Total non-duplicate citations				181

7.1.1.9 Search strategy for RCTs published since April 2007

Table 7.8 Search strategy for RCTs published since April 2007[a]

Database	Date searched	#	Search terms	Citations
Medline (Update analogue RCTs)	07 June 2010	1	Diabetes Mellitus, type 1/	51 765
		2	(LADA or latent autoimmune diabetes mellitus).mp.	294
		3	insulin dependent diabet*.mp.	23 779
		4	(insulin analog* or insulin receptor ligands).mp.	1 317
		5	(rapid acting insulin or ultra short acting insulin).mp.	271
		6	(insulin lispro or insulin lispro-protamine suspension or humalog).mp.	714
		7	(insulin aspart or novorapid or novolog).mp.	438
		8	(insulin glulisine or apidra).mp.	87
		9	(insulin glargine or lantus).mp.	597
		10	(insulin detemir or levemir).mp.	269
		11	novomix 30.mp.	18
		12	Insulin, Long-Acting/	784
		13	short acting insulin.mp.	304
		14	basal insulin.mp.	1 888
		15	Clinical Trial/	461 595
		16	randomised controlled trial.mp.	293 811
		17	Random Allocation/	68 229
		18	double blind method/ or triple blind method.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	106 419
		19	cross-over studies/	25 863

Database	Date searched	#	Search terms	Citations
		20	placebos/	28 814
		21	Prospective Studies/	278 706
		22	or/15–21	802 762
		23	or/1–3	63 863
		24	or/4–14	4 740
		25	22 and 23 and 24	441
		26	limit 25 to (english language and humans and yr="2005 - Current")	136
			Title and abstract cull	
			Wrong language	3
			Wong outcome	26
			Wrong population	9
			Wrong test	62
			Wrong study type	13
			Keep for full text	23
			Update analogue RCTs (EMBASE) 10/5/10	
			type AND 1 AND ('diabetes'/exp/mj OR 'diabetes'/mj) AND ('insulin'/exp/mj OR 'insulin'/mj) AND analogues AND [humans]/lim AND [english]/lim AND [embase]/lim AND [2005–2010]/py	53
Cochrane				0
Manual search				0
Total citations				53

[a] Last search date of Singh et al (2009)

7.1.1.10 Evidence Matrix

HbA_{1c}

Q7.1 (i)	How effective are insulin analogues versus human insulin at reducing HbA_{1c}?	
Evidence statement	Compared with human insulin, insulin analogues have no effect on overall hypoglycaemia, but lead to a slight reduction in severe and nocturnal hypoglycaemia in adults. Compared with NPH insulin, insulin detemir shows a small but significant benefit with respect to nocturnal and overall hypoglycaemia in children and adolescents.	
Evidence base	C	One good-quality systematic review (Level I evidence) was selected from 15 identified systematic reviews. The selected study was based on Level II evidence (17 RCTs) that was of poor quality (i.e. lack of double blinding and of ITT reporting). In addition, 3 RCTs (Level II) were included, all of which were of fair quality.
Consistency	B	The RCTs included in the Level I study were mostly consistent, as were findings across all the Level I studies identified.
Clinical impact	D	The reduction in HbA_{1c} was *statistically* significant, but was below the level commonly accepted as *clinically* significant (0.5% change in HbA_{1c}). Impact on patient satisfaction (which is considered to be a key benefit of analogues) was not captured by the Level I study selected.
Generalisability	B	Patients characteristics were HbA_{1c} 6–11% at baseline, with some exclusions of HbA_{1c} below 10% or 11%. Many studies excluded patients for severe hypoglycaemia.
Applicability	A	Studies included populations form Australia, Europe, South Africa and the United States and were thus from countries with well-established health-care systems.
Other factors	None identified.	

Hypoglycaemia

Q7.1 (i)	How effective are insulin analogues versus human insulin at reducing hypoglycaemia?	
Evidence statement	Compared with human insulin, insulin analogues have no effect on overall hypoglycaemia, but lead to a slight reduction in severe and nocturnal hypoglycaemia in adults. Compared with human insulin, insulin detemir shows a small but significant benefit with respect to nocturnal and overall hypoglycaemia in children and adolescents.	
Evidence base	C	One good quality systematic review (Level I evidence) was identified, but the study was based on poor-quality Level II evidence (i.e. lack of double blinding and lack of ITT reporting).
Consistency	C	The definitions of hypoglycaemia used in individual trials were not consistent. There was also variation in the units of measurement between trials. This resulted in high heterogeneity and it was thus not possible to make summary estimates for specific subgroups.
Clinical impact	D	The clinical impact of hypoglycaemia is significant. However, evidence on the clinical impact was lacking, apart from in one subtype of hypoglycaemia. Impact on patient satisfaction (which is considered to be a key benefit of analogues) was not captured by the Level I study selected.
Generalisability	B	Patient characteristics: HbA_{1c} 6–11% at baseline, with some exclusions of HbA_{1c} <10 or <11. Many studies excluded patients for severe hypoglycaemia.
Applicability	A	Studies included populations from Australia, Europe, South Africa and the United States.
Other factors	Impact of hypoglycaemia (and the associated disutility) not fully captured in the studies. Evidence base is missing the patient perspective.	

HbA_{ic}, glycated haemoglobin; ITT, intention to treat

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

7.1.2 Relative effectiveness between insulin analogues on hypoglycaemia and glycaemic control

> Question 7.1
>
> (ii) What is the relative effectiveness between insulin analogues at reducing hypoglycaemia and HbA_{1c}?

This section of the report covers clinical question 7.1 (ii), which investigates the relative effectiveness of the insulin analogues insulin lispro, insulin aspart, insulin glulisine, insulin glargine and insulin detemir.

7.1.2.1 Criteria for eligibility

The criteria for determining whether publications were eligible for inclusion for this clinical question are shown in Table 7.9.

Table 7.9 Criteria for determining study eligibility

Study design	NHMRC Evidence Level I or II (using the intervention accuracy scale)[a]
Population	Patients with type 1 diabetes
Intervention	An insulin analogue
Comparator	An insulin analogue
Outcomes	Change in HbA_{1c} Hypoglycaemia

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

7.1.2.2 Assessment of study eligibility

A total of 48 citations were identified in the initial literature search, as shown in Table 7.10. The exclusion criteria were applied to all citations by reviewing the abstract and title. One publication remained, and the full-text version was retrieved and reviewed. This study was then updated with another search for Level II studies published since the final reported search date of the meta-analysis (April 2007).

7.1.2.3 Literature search summary

Table 7.10 Search results, question 7.1 (ii)

Stage	Notes	Number (Level I)	Number (Level II)
Search summary	Manual	0	0
	Cochrane Library	3	–
	Medline	43	135
	INAHTA	2	–
	EMBASE	–	53
	Total	48	188
Duplicates	Duplicates identified		30
Identified	Total identified	48	158
Exclusion criteria	Wrong study type (Non-systematic reviews (i.e. narrative reviews), case reports, animal studies, short notes, letters, editorials, conference abstracts, in-vitro studies)	11	13
	Wrong population (Not in type 1 diabetes)	3	19
	Wrong intervention or test (Does not evaluate the intervention or test of interest)	28	91
	Wrong outcome (Does not report any of the outcomes listed for the research question)	1	27
	Not in English (Non-English publications will be excluded)	4	3
	Total excluded	47	153
Meeting criteria	Total meeting inclusion criteria	1	5
Included	Total included studies	1	5

7.1.2.4 Included studies

The included studies were one Level I study (Singh et al 2009) and five Level II studies (Bode et al 2002; Dreyer et al 2005; Pieber et al 2007; Weinzimer et al 2008; Heller et al 2009).

The characteristics of the included studies are shown in Table 7.11.

Table 7.11 Characteristics of included Level II studies

Reference	Study design and type	Intervention	Comparator	Population	N
Bode et al (2002)	Randomised open label parallel group	Insulin aspart via CSII	Human insulin vs insulin lispro via CSII	Type 1 diabetes, adults	146
Weinzimer et al (2008)	Randomised open parallel group	Insulin aspart via CSII	Insulin lispro via CSII	Type 1 diabetes; children and adolescents	298
Dreyer et al (2005)	Non-inferiority randomised parallel group	Insulin glulisine	Insulin lispro	Type 1 diabetes; adults	672
Heller et al (2009)	Non-inferiority open label parallel group treat to target	Insulin detemir	Insulin glargine	Type 1 diabetes; adults	443
Pieber et al (2007)	Randomised open label parallel group trial Non-inferiority	Insulin detemir twice daily	Insulin glargine once daily	Type 1 diabetes; adults	320

CSII, continuous subcutaneous insulin infusion

7.1.2.5 Results of included studies

Singh et al (2009)

The systematic review performed by Singh et al (2009) was an update of two earlier systematic reviews of the efficacy and safety of rapid and long-acting insulin analogues. The study was based on two health technology assessments of the insulin analogues from the Canadian Agency for Drugs and Technologies in Health (CADTH). The reports were updated to include recently published studies, additional outcomes of interest and intraclass comparisons of the rapid and long-acting insulin analogues. The studies included for the update were RCTs, published up to April 2007. Studies of insulin glulisine were excluded from the systematic review because that agent was not available in Canada at the time of the review.

Only two studies comparing insulin analogues were found in the systematic review by Singh et al (2009), Bode et al (2002) and Pieber et al (2007).

Singh reported that, in adults, only one trial (Bode et al 2002) of 87 subjects comparing insulin lispro with insulin aspart administered via continuous subcutaneous insulin infusion (CSII) was reported. Only one trial (Pieber et al 2007) of 320 subjects comparing insulin glargine with insulin detemir was found. No studies on intraclass comparison of analogues were found in children or adolescents.

Bode et al (2002) compared insulin lispro with insulin aspart administered via CSII. No significant differences were found in glycated haemoglobin (HbA_{1c}) or nocturnal hypoglycaemia. The rate of overall hypoglycaemia was significantly lower in insulin aspart over insulin lispro (rate ratio for insulin lispro vs insulin aspart 1.49, 95% confidence interval [CI]: 1.37 to 1.63).

Pieber et al (2007) compared insulin detemir and insulin glargine, and found there was no difference in HbA_{1c} (weighted mean difference [WMD] –0.03%, 95%CI: –0.26 to 0.20%). The

risk of severe hypoglycaemia (relative risk [RR] 0.25, 95%CI: 0.07 to 0.86) was statistically significant in favour of insulin detemir.

Due to the small number of updated studies found by Singh et al (2009), a more detailed report of these two studies is included below.

Bode et al (2002)

Insulin aspart, insulin lispro and regular insulin via CSII were compared in 146 adult patients in a multicentre open label parallel group study (Bode et al 2002). The study was conducted at 13 sites in the United States. Patients were randomised to insulin aspart, regular insulin or insulin lispro by CSII for 16 weeks. The 146 patients enrolled were aged 18–71 years and had been diagnosed with type 1 diabetes for at least 12 months (fasting C-peptide <0.5ng/ml) and treated with CSII therapy continuously for the previous 3 months. The baseline body mass index (BMI) of these patients was ≤35 kg/m^2 and baseline HbA_{1c} ranged from 5.7 to 9.7%. Subjects were excluded if they had impaired hepatic, renal or cardiac function, or recurrent major hypoglycaemia.

Hypoglycaemia was defined as 'minor' when the subject had a symptom confirmed with a blood glucose (BG) meter reading <50 mg/dL (2.8 mmol/L) and was able to deal with the episode on their own. It was defined as 'major' where the meter reading was <50 mg/dl and the event was associated with severe central nervous system dysfunction that either prevented the subject from treating themselves or required administration of parenteral glucose or glucagon.

Subjects underwent a 4-week run-in period using their own insulin pumps. The investigator and subject were blinded at the point of randomisation. Subjects assigned to insulin aspart or insulin lispro were instructed to take bolus doses just before the start of each meal; those assigned to regular insulin were instructed to take bolus doses 30 minutes before meals. Subjects were contacted weekly during the run-in period and every 2 weeks during the dose adjustment period (the first 4 weeks of the trial).

Mean baseline HbA_{1c} levels were <7.5%. After 16 weeks of treatment, the mean changes in baseline HbA_{1c} values were not significantly different among the three groups. Mean change in baseline HbA_{1c} were insulin aspart: 0.00 ±0.51%, regular insulin: 0.15 ±0.63% and insulin lispro: 0.18 ±0.84%.

Similar numbers of subjects (≥90%) in each treatment group reported one or more minor hypoglycaemic episodes during the treatment period. About 50% of the hypoglycaemic episodes were confirmed by a BG level <50 mg/dl. The rate of hypoglycaemic episodes with BG <50 was reported as mean number of hypo episodes reported per subject per 30 days. The rate was 3.7 ±3.6 in the insulin aspart group during the maintenance period and 1.1 ±4.7 in the insulin lispro group in the same period (p=0.841 for insulin lispro vs insulin aspart).

Regarding follow-up, 93% of subjects receiving insulin aspart, 85% receiving regular insulin, and 96% of those on insulin lispro completed the study. The authors concluded that insulin aspart is as effective as regular insulin and insulin lispro when used in CSII therapy. No significant differences were found in HbA_{1c} or hypoglycaemia between the analogues and regular insulin, or between the two analogues.

Peiber et al (2007)

Twice-daily insulin detemir was compared with once-daily insulin glargine in a 26-week parallel group study of 322 subjects from 39 centres in Germany, Austria and South Africa by

Pieber et al (2007). Both basal insulins were combined with premeal insulin aspart. Eligible subjects were over 18 years of age with a BMI ≤35kg/m^2 and HbA_{1c} of 7.5–12%. Subjects were excluded if they had significant medical problems, including proliferative retinopathy or maculopathy requiring acute treatment, recurrent severe hypoglycaemia, hypoglycaemic unawareness, impaired hepatic or renal function or uncontrolled cardiovascular problems. Mean HbA_{1c} at baseline was 8.9% in the insulin detemir group and 8.8% in the insulin glargine group.

After 26 weeks of treatment, the difference between groups was –0.03% (95%CI: –0.25 to 0.19).

The overall risk of hypoglycaemia was similar between groups (RR 0.95, 95%CI: 0.68 to 1.35), but a significantly lower risk of both severe (RR 0.28, 95%CI: 0.08 to 0.98) and nocturnal hypoglycaemia (RR 0.28, 95%CI: 0.08 to 0.98) was found with insulin detemir (p=0.047 severe and p=0.043 for nocturnal).

It was acknowledged that insulin glargine is often prescribed twice daily but was used only once daily during the trial, according to the labelling. The titration of insulin detemir against both prebreakfast and predinner targets would increase the daytime basal insulin dose, and possibly limit proper comparison between preparations.

Results of RCTs published since Singh et al (2009)

Three RCTs relevant to the clinical question were identified (Dreyer et al 2005; Weinzimer et al 2008; Heller et al 2009).The results are summarised below, in Table 13.4.

Dreyer et al (2005)

Dreyer et al (2005) reported a randomised parallel group study comparing insulin glulisine or insulin lispro with evening insulin glargine daily in 683 adults with type 1 diabetes. This was a multinational, multicentre parallel group open study. The trial was conducted at 62 sites in 13 European countries and 5 sites in South Africa. Patients were excluded if they had active proliferative retinopathy in the 6 months before the study, impaired hepatic or renal function, or hypersensitivity to insulin or excipients in the insulin glulisine formulation. Glycaemic control was similar in both groups at baseline in terms of HbA_{1c} (7.6% for insulin glulisine and 7.58% for insulin lispro). Patients in the insulin glulisine group had a longer duration of diabetes (17.4 yrs vs 15.6 years) and insulin therapy (17.1 yrs vs 15.3 years) compared with the insulin lispro group. These differences were statistically significant (p=0.01).

The treatment phase was conducted over 26 weeks with a 26-week clinical extension study to assess one full year of safety for insulin glulisine compared with insulin lispro. The primary efficacy endpoint was change in HbA_{1c} from baseline to endpoint (defined as the last available measurement after the start of treatment). Hypoglycaemic episodes were monitored. Symptomatic hypoglycaemia was defined as an event with clinical symptoms that were considered to result from hypoglycaemia. Severe symptomatic hypoglycaemia was defined as an episode requiring the assistance of another person.

The results showed a similar reduction in mean HbA_{1c} between both groups. There was no difference between groups regarding rates of symptomatic, severe or nocturnal hypoglycaemia. The authors concluded that insulin glulisine is as effective and well-tolerated as insulin lispro when used as part of a basal-bolus therapy in combination with insulin glargine.

Weinzimer et al (2008)

Insulin aspart was compared to insulin lispro in children and adolescents in the study by Weinzimer et al (2008). This was a 16-week open label multicentre parallel group study, with 298 children and adolescents with type 1 diabetes randomly assigned in a 2:1 manner to receive either insulin aspart or insulin lispro by CSII. The study was conducted in the United States. The mode of administration was CSII. Subjects were excluded from the study if they had impaired hepatic or renal function, abnormal thyroid function, proliferative retinopathy, a history of severe hypoglycaemia or a developmental disorder, or had received another investigational drug within 1 month before the trial. There was no difference between groups regarding rates of hypoglycaemic episodes. The authors concluded that insulin aspart CSII is as effective as insulin lispro CSII in children and adolescents aged 4–18 years.

Heller et al (2009)

Insulin detemir was compared with insulin glargine in a treat-to-target parallel group study of 443 adult patients in the study by Heller et al (2009). The trial sites were not reported. Subjects were over 18 years old and had type 1 diabetes for at least 12 months with an HbA_{1c} of less than 11% at screening. Exclusion criteria included proliferative retinopathy or maculopathy requiring acute treatment within 6 months before the study, any recurrent major hypoglycaemia, an anticipated change in any medication known to interfere with glucose metabolism, impaired hepatic or renal function and cardiac problems or uncontrolled hypertension. The mean age at baseline was 42 (standard deviation [SD 12]) years, duration of diabetes was 17.2 (SD 11.4) years and HbA_{1c} was 8.1% (SD1.1%). Patients were started on once-daily basal insulin with insulin detemir; this was increased to twice daily to reach predinner targets whereas insulin glargine was left at once daily according to labelling. The plasma glucose (PG) targets were ≤6 mmol/L before breakfast and dinner, with no episodes of significant hypoglycaemia (not defined). If patients in the insulin detemir arm were achieving the PG target before breakfast but not before dinner, a second daily dose was added.

After 52 weeks, the mean HbA_{1c} did not differ between groups. There were no significant differences between groups in the overall risk of having a hypoglycaemic episode (RR insulin detemir/insulin glargine=0.94; 95%CI: 0.74 to 1.18). There was also no difference in the risk of nocturnal hypoglycaemic episode (RR=1.12; 95%CI: 0.74 to 1.18) between groups.

7.1.2.6 Discussion

Rapid-acting insulin analogues

Dreyer et al (2005) reported that insulin glulisine provided equivalent glycaemic control to insulin lispro in adults with type 1 diabetes, with insulin glargine as the basal insulin. The baseline populations were statistically different because the insulin glulisine group had a longer duration of insulin therapy and a longer duration of diabetes. Patients with complications were excluded. Due to the formulation of the different insulins, blinding was not feasible. However, investigators were blinded to the centrally measured HbA_{1c} levels.

The study by Weinzimer et al (2008) aimed to evaluate and compare the safety and efficacy of insulin aspart versus insulin lispro via CSII in children and adolescents with type 1 diabetes in the US. Subjects with specified complications were excluded. The study was not treat-to-target and investigators reviewed subject diaries and subject-specific basal and bolus doses were determined at their discretion.

Bode et al (2002) compared insulin aspart with human insulin and insulin lispro via CSII in adults in a parallel study of 16 weeks. No significant difference in HbA_{1c} was found between

groups. The baseline populations were similar between groups and had relatively good glycaemic control, as well as experience with pumps. The investigator and subject were blinded at randomisation but, subsequent to this, blinding to the intervention by patients or investigators was not reported.

Long-acting insulin analogues

Limitations of the study by Heller et al (2009) included the strict inclusion and exclusion criteria, the open-label design and the off-label use of split-dose insulin glargine. The inclusion of these patients in the intention-to-treat (ITT) analysis may have introduced some bias into the insulin glargine data set.

The trial by Pieber et al (2007) comparing insulin detemir and once-daily insulin glargine with insulin aspart was also open label. Insulin detemir was injected twice daily with a pre-evening meal PG target, whereas the insulin glargine dose was injected at bedtime and the titration was terminated when the prebreakfast PG target was reached. The total daily dose was higher with insulin detemir; thus, the proper comparison of dose and efficacy may be limited. The overall risk of hypoglycaemia was not different between groups, but the risk of severe and nocturnal hypoglycaemia was lower with insulin detemir than with insulin glargine.

7.1.2.7 Summary

Overall, Bode et al (2002) found no significant difference in HbA_{1c} between insulin aspart, regular insulin and insulin lispro via CSII in adults. There was a significant reduction in the rate of nocturnal hypoglycaemia between insulin aspart and regular insulin. In Weinzimer et al (2008), no significant difference was found between insulin aspart and insulin lispro via CSII, in terms of HbA_{1c} or hypoglycaemia.

Dreyer et al (2005) found no significant difference in HbA_{1c} between insulin glulisine and insulin lispro. There was also no reduction between groups in the reporting of any symptomatic hypoglycaemia. Heller et al (2009) found no significant difference between insulin detemir and insulin glargine in terms of HbA_{1c}. There was no difference in relative risk for total and nocturnal hypoglycaemia. Pieber et al (2007) found no significant difference between groups regarding HbA_{1c}. A significant difference was found in favour of insulin detemir regarding all severe hypoglycaemia (assistance from third party required) and symptomatic nocturnal hypoglycaemia (PG ≥3.1 mmol/L and no assistance). Pieber et al (2007) found no difference in glycaemic control between insulin detemir and insulin glargine. There was no difference in overall risk of hypoglycaemia but the risks of both severe and nocturnal hypoglycaemia were significantly lower with insulin detemir.

Table 7.12 Summary of RCT results

Reference and setting	Intervention	Comparator	HbA_{1c}	Hypoglycaemia			
Bode et al (2002)	Insulin aspart via CSII	Vs human insulin vs insulin lispro via CSII	Mean change in baseline HbA_{1c}: Insulin aspart: 0.00 ±0.51%, Insulin lispro: 0.18 ±0.84% Regular: 0.15 ±0.63%	Rate [a] P values: Wilcoxon rank sum test, relative to rate in insulin aspart group during maintenance			
					All	BG<50	Nocturnal
				Insulin aspart	6.7	3.7	0.5
				Insulin lispro	10.5 (p=0.044)	4.4 (p=0.841)	0.6 (p=0.189)
				Regular insulin	10.5 (p=0.034)	4.8 (p=0.175)	0.9 (p=0.004)
Weinzimer et al (2008) (children and adolescents)	Insulin aspart via CSII	Insulin lispro via CSII	Change in A1c from baseline at end of study Insulin aspart: –0.15 ±0.05% Insulin lispro: –0.05 ±0.07% (95%CI: –0.27 to 0.07)	Rate: number of hypoglycaemic events per subject year			
					Insulin aspart	Insulin lispro	P=
				All	92.2	81.3	0.209
				Nocturnal	5.7	6.2	0.645
Dreyer et al (2005)	Insulin glulisine	Insulin lispro	Adjusted mean change from baseline at endpoint Insulin glulisine –0.14 ±0.709 Insulin lispro –0.14 Difference 0.00 ±0.049 (95%CI: –0.09 to 0.10)	Rate: number of events per patient month			
					Severe	Nocturnal	
				Insulin glulisine	0.03 ±0.685	0.55	
				Insulin lispro	0.02	0.53	
Heller et al (2009)	Insulin detemir	Insulin glargine	Mean difference between insulin detemir and insulin glargine at end of trial 0.01% (95%CI: –0.13 to 0.16)	Rate: episodes per patient year All hypoglycaemic episodes Insulin detemir 53.6 Insulin glargine 57.3			
Pieber et al (2007)	Insulin detemir twice daily	Insulin glargine once daily	Difference adjusted for baseline between groups at end of study –0.03 (95%CI: –0.25 to 0.19)	Relative risk insulin detemir/insulin glargine Significant results shown only			
				All nocturnal		0.68	(95%CI 0.46, 0.99) p=0.046
				All severe		0.28	(95%CI 0.08, 0.98) p=0.047
				Symptomatic nocturnal		0.52	(95%CI 0.28, 0.98) p=0.043

BG, blood glucose; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin

[a] (mean number of hypos reported per subject per 30 days)

7.1.2.8 Conclusion

One Level I study of fair quality was identified. The results from the included studies were consistent regarding the HbA_{1c} outcome. Four out of five studies were consistent regarding the hypoglycaemia outcome. The populations studied included children, adolescents and adults, and were multicentre and multinational. The participating countries included those from Europe and North America.

No study found a significant difference in mean change from baseline HbA_{1c} when different insulin analogues were compared. One study (Pieber et al 2007) found a difference in the relative risk of all nocturnal, all severe and symptomatic nocturnal hypoglycaemia between insulin detemir and insulin glargine.

7.1.2.9 Literature search strategy

The search was conducted between 8 March 2010 and 13 May 2010. Level I studies were considered first with the plan to update any Level I studies with Level II studies as required. The Medline search strategy for Level I studies is shown in Table 7.13 and the search strategy for Level II studies is given in Table 7.14.

Table 7.13 Search strategy Level I studies, question 7.1 (ii)

Database	Date searched	#	Search terms	Citations
Medline	9 March 2010	1	Diabetes Mellitus, type 1/	50 607
		2	(LADA or latent autoimmune diabetes mellitus).mp.	287
		3	insulin dependent diabet*.mp.	23 236
		4	(insulin analog* or insulin receptor ligands).mp.	1290
		5	(rapid acting insulin or ultra short acting insulin).mp.	265
		6	(insulin lispro or insulin lispro-protamine suspension or humalog).mp.	702
		7	(insulin aspart or novorapid or novolog).mp.	422
		8	(insulin glulisine or apidra).mp.	83
		9	(insulin glargine or lantus).mp.	569
		10	(insulin detemir or levemir).mp.	253
		11	novomix 30.mp.	17
		12	Insulin, Long-Acting/	770
		13	short acting insulin.mp.	294
		14	basal insulin.mp.	1842
		15	or/1–3	62 426
		16	or/4–14	4622
		17	15 and 16	1350
		18	Meta-Analysis/	23 338
		19	systematic review.mp.	16 972
		20	pooled analysis.mp.	1679
		21	(review and medline).mp.	26 722
		22	(systematic* and (review* or overview*)).mp.	41 342
		23	or/18–22	75 783
		24	17 and 23	43

Database	Date searched	#	Search terms	Citations
INAHTA				2
Cochrane				3
Manual search				0
Total citations				48
Total non-duplicate citations				

Table 7.14 Search strategy Level II studies, question 7.1 (ii)

Database	Date searched	#	Search terms	Citations
Medline	13 April 2010	1	Diabetes Mellitus, type 1/	51 765
		2	(LADA or latent autoimmune diabetes mellitus).mp.	294
		3	insulin dependent diabet*.mp.	23 779
		4	(insulin analog* or insulin receptor ligands).mp.	1317
		5	(rapid acting insulin or ultra short acting insulin).mp.	271
		6	(insulin lispro or insulin lispro-protamine suspension or humalog).mp.	714
		7	(insulin aspart or novorapid or novolog).mp.	438
		8	(insulin glulisine or apidra).mp.	87
		9	(insulin glargine or lantus).mp.	597
		10	(insulin detemir or levemir).mp.	269
		11	novomix 30.mp.	18
		12	Insulin, Long-Acting/	784
		13	short acting insulin.mp.	304
		14	basal insulin.mp.	1888
		15	Clinical Trial/	461 595
		16	randomised controlled trial.mp.	293 811
		17	Random Allocation/	68 229
		18	double blind method/ or triple blind method.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	106 419
		19	cross-over studies/	25 863
		20	placebos/	28 814
		21	Prospective Studies/	278 706
		22	or/15–21	802 762
		23	or/1–3	63 863
		24	or/4–14	4740
		25	22 and 23 and 24	441
		26	limit 25 to (91nglish language and humans and yr=”2005 – Current”)	135
			Title and abstract cull	
			Wrong language	0
			Wrong outcome	27

Database	Date searched	#	Search terms	Citations
			Wrong population	9
			Wrong test	62
			Wrong study type	13
			Keep for full text	22
			Not included in Singh (2009)	4
EMBASE	10 May 2010		type AND 1 AND ('diabetes'/exp/mj OR 'diabetes'/mj) AND ('insulin'/exp/mj OR 'insulin'/mj) AND analogues AND [humans]/lim AND [92nglish]/lim AND [embase]/lim AND [2005–2010]/py	53
			Excluded	53
Manual search				
Total citations				
Total non-duplicate citations				22

The systematic literature search identified 135 publications from Medline and 53 from EMBASE, of which 22 were found to be relevant for review of the full text; of those, 5 were not already included in the meta-analysis. One study (Dreyer et al 2005) was published within the search span of Singh et al (2009), but was not included in the systematic review because the intervention was not part of the inclusion criteria (insulin glulisine not marketed in the country of publication).

7.1.2.10 Evidence Matrix

HbA_{1c}

Q7.1 (ii)	What is the relative effectiveness between insulin analogues on HbA_{1c}?	
Evidence statement	Level II evidence is consistent in showing no significant difference between insulin analogues in relation to their effect on HbA_{1c}.	
Evidence base	C	One good-quality systematic review was identified that included two RCTs (Level II evidence) of fair and poor quality; three RCTs (Level II) of fair quality were also identified.
Consistency	A	Different agents were compared; thus, the results could not be pooled.
Clinical impact	D	The studies did not capture patient satisfaction or preference.
Generalisability	B	The population was aged 20–40 years, HbA_{1c} was 7–8% at baseline, and severe hypoglycaemia was an exclusion criterion in most studies.
Applicability	A	No Australian studies or sites were included in the studies, but the results are considered applicable to the Australian health-care context.
Other factors	Based on a literature review of economic evaluations of analogues, the EAG concluded that analogues are unlikely to be cost effective at the published prices in Australia. However, the true cost effectiveness has probably not been captured, because none of the published economic analyses captured the patient perspective.	

Hypoglycaemia

Q7.1 (ii)	What is the relative effectiveness between insulin analogues at reducing hypoglycaemia?	
Evidence statement	Level II evidence is consistent in showing no significant difference between insulin analogues in relation to their effect on HbA_{1c}.	
Evidence base	C	One good-quality systematic review was identified that included two RCTs (Level II evidence) of fair and poor quality; three RCTs (Level II) of fair quality were also identified.
Consistency	C	One Level II study showed a significant difference in hypoglycaemia rate between insulin analogues; the remaining four studies did not show a significant different. The agents compared were different in all but two studies; thus, consistency was limited across the body of evidence.
Clinical impact	D	The studies did not capture patient satisfaction or preference.
Generalisability	B	Population was aged 20–40 years; HbA_{1c} was 7–8% at baseline; severe hypoglycaemia was an exclusion criterion in most studies.
Applicability	A	No Australian studies or sites were included in the studies, but the results are considered applicable to the Australian health-care context.
Other factors	Based on a literature review of economic evaluations of analogues, the EAG concluded that analogues are unlikely to be cost effective at the published prices in Australia. However, the true cost effectiveness has probably not been captured, because none of the published economic analyses captured the patient perspective.	
Recommendation		
R7.1	Human insulin or insulin analogues may be used as treatment for glycaemic control (Grade C).	

EAG, Expert Advisory Group; HbA1c, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

7.1.3 Cost and cost effectiveness of insulin analogues

> Question 7.1
>
> (iii) What are the cost and cost effectiveness of insulin analogues at reducing hypoglycaemia and reducing (HbA_{1c})?
>
> HbA_{1c}, glycated haemoglobin

This section of the report covers clinical question 7.1 (iii), which relates the cost and cost-effectiveness of insulin analogues. Insulin analogues selected for inclusion in this systematic literature review were insulin aspart, insulin glulisine, insulin lispro, insulin detemir and insulin glargine.

7.1.3.1 Criteria for eligibility

Studies were eligible for inclusion if they were cost effectiveness studies on the use of insulin analogues in subjects with type 1 diabetes.

7.1.3.2 Assessment of study eligibility

Publications identified in the literature search were reviewed and the exclusion criteria shown in Table 7.15 applied hierarchically. A total of 102 citations were identified in the initial literature search. After applying the exclusion criteria shown, a total of 15 publications remained, and the full-text version of each publication was retrieved and reviewed. The same exclusion criteria were then applied to the full-text articles.

7.1.3.3 Literature search summary

Table 7.15 Search results, question 7.1 (iii)

Stage	Notes	Number
Search summary	Cochrane Library	5
	Medline	102
	Total	107
Duplicates	Duplicates identified	5
Identified	Total identified	102
Exclusion criteria	Wrong study type (Not a study of cost or cost effectiveness)	34
	Wrong population (Not of type 1 diabetes)	7
	Wrong intervention (Does not evaluate an insulin analogues)	41
	Wrong outcome (Does not report on costs)	5
	Not in English (Non-English publications will not be included)	3
	Total excluded	90
Meeting criteria	Total meeting inclusion criteria	12
Included	Total included studies	12

7.1.3.4 Included studies

The literature search identified 12 publications that met the inclusion criteria for clinical question 7.1 (iii) (Palmer et al 2004; Valentine et al 2006; Banerjee et al 2007; Grima et al 2007; Palmer et al 2007; Tran et al 2007; Brixner and McAdam-Marx 2008; Reviriego et al 2008; Cameron and Bennett 2009; Gschwend et al 2009; Pratoomsoot et al 2009; Tunis et al 2009).

7.1.3.5 Results of Included studies

Studies of both long and short-acting insulin analogues

Two studies of both long and short-acting insulin analogues were identified from the search. The full-text article was available for only one study. Cameron and Bennett (2009) studied the cost effectiveness of long and short-acting insulin analogues in Canada, and found only the short-acting analogues to be cost effective.

Cameron and Bennett (2009)

Cameron and Bennett (2009) compared the cost effectiveness of insulin analogues and conventional insulins used to treat type 1 and type 2 diabetes mellitus in adults. A cost-effectiveness evaluation of insulin analogues versus conventional insulins was performed using the Center for Outcomes Research Diabetes Model. Rapid-acting analogues (insulin aspart and insulin lispro) were compared with regular human insulin, and long-acting analogues (insulin glargine and insulin detemir) with neutral protamine Hagedorn (NPH) insulin. Clinical information for the comparisons came from meta-analyses of randomised controlled trials (RCTs). Cost and utility estimates from published sources and sensitivity analyses were used to test the robustness of results. The mean daily dose for each treatment was based on data from a patient sample supplied by a single endocrinologist.

For type 1 diabetes, insulin aspart was more effective and less costly than regular human insulin. Insulin lispro was associated with an incremental cost of C$28 996 per quality-adjusted life year (QALY). The incremental cost per QALY was C$87 932 for insulin glargine and C$387 729 for insulin detemir, compared with NPH insulin. The model was sensitive to changes in the effect size of glycated haemoglobin (HbA_{1c}) and to decrements applied to utility scores when fear of hypoglycaemia was included as a factor. Rapid-acting insulin analogues only were found to be cost effective.

Assessment

This study posed a well-defined question in an answerable form and examined both costs and effects with a comparison of alternatives. The viewpoint was from a Canadian third party payer. A time horizon of 60 years was used. The relevant costs were identified and measured. The source of values was credible. An incremental analysis was performed.

Brixner and McAdam-Marx (2008)

Brixner and McAdam-Marx (2008) undertook a systematic review on cost-effectiveness studies for insulin analogues used in the United States. Most of the modelling studies identified in the analysis used the Center for Outcomes Research (IMS-CORE) Diabetes Model. Cost per QALY was reported in four studies of patients with type 1 diabetes. The cost per QALY ranged from US$14 974 for insulin detemir versus NPH insulin and C$20 799 for insulin glargine versus NPH insulin.

Thus, in the United States, insulin detemir is cost effective when compared to NPH insulin and insulin glargine.

Assessment

The systematic review methods were sufficiently rigorous. The results of the studies were not combined in a meta-analysis.

Studies of short-acting insulin analogues

Three studies of the cost effectiveness of the short-acting insulin analogues were found. The study by Pratoomsoot et al (2009) was based in the United Kingdom and found that insulin lispro was more likely to improve quality-adjusted life expectancy (QALE) and reduce lifetime medical costs compared with regular insulin. Reviriego et al (2008) studied the costs of severe hypoglycaemia in Spain, and the cost effectiveness of insulin lispro over regular insulin in preventing severe hypoglycaemic episodes. Insulin lispro was found to be associated with reductions in annual costs because of severe hypoglycaemia, and possibly cost neutral or cost saving overall. A systematic review and meta-analysis undertaken by Banerjee et al (2007) concluded that insulin lispro and human insulin were similar when examined in cost comparison studies, but that insulin lispro was more favourable than human insulin when willingness to pay studies were performed.

Pratoomsoot et al (2009)

The aim of the study by Pratoomsoot et al (2009) was to determine the long-term health economic benefits associated with insulin lispro versus regular human insulin in patients in the United Kingdom, with type 1 diabetes. Clinical benefits were derived from a Cochrane meta-analysis. All costs were accounted in 2007 Great British pounds from a National Health Service (NHS) perspective. Future costs and clinical benefits were discounted at 3.5% annually. Insulin lispro was associated with improvements in QALE of approximately 0.10 QALYs compared to regular human insulin (RHI) (7.60 vs 7.50 QALYs). Lifetime direct medical costs per patient were lower with lispro treatment, £70 576 vs £72 529. Severe hypoglycaemia rates were the key driver in terms of differences in QALE and lifetime costs. Sensitivity analyses with assumptions around time horizon, discounting rates and benefits in terms of glycaemic control or hypoglycaemic event rates revealed that lispro remained dominant. The conclusion was that insulin lispro is likely to improve QALE, reduce frequency of diabetes-related complications and lifetime medical costs compared with regular human insulin.

Assessment

This study examined both costs and effects of the intervention. The clinical effects of the intervention and comparator were derived from the results of a good-quality meta-analysis rather than on an individual trial; this lowers the risk of bias. However, there is an inherent uncertainty in making long-term projections based on short-term trial data. This limitation applies to all studies of the cost effectiveness of insulin analogues.

Reviriego et al (2008)

A study by Reviriego et al (2008) examined the costs of severe hypoglycaemia in a population of patients with type 1 diabetes in the Spanish health-care system and the cost effectiveness of insulin lispro over regular insulin in preventing severe hypoglycaemia episodes. Resource use data were collected for interventions specifically relating to hypoglycaemic episodes. The direct medical costs determined in the analyses were costs of hospitalisation, diagnostic tests carried out, costs of treatment administered and other associated costs (e.g. visits to the endocrinologist and re-training in glucose control, transportation and assistance of a care giver). In addition, indirect costs (e.g. days of lost productivity) were measured. The incidence rates of severe hypoglycaemia for insulin lispro and regular insulin were obtained from the literature. The incremental cost effectiveness of insulin lispro over regular insulin was calculated. The overall mean cost per episode of severe hypoglycaemia was €366, comprising 65.4% direct costs and 35.6% indirect costs. The largest cost was for hospitalisation at €183 per episode. The severe hypoglycaemia episode incidence rates for 100 patients per year were 33 and 73 for insulin lispro and 48 ($p<0.05$)

and 117 ($p<0.01$) for regular insulin, in the two clinical trials found in the literature. The additional cost to prevent one episode of severe hypoglycaemia with insulin lispro over regular insulin ranged from €277 to insulin lispro dominance.

It was concluded that severe hypoglycaemia has a significant impact on the total cost of diabetes. The use of insulin lispro is associated with reductions in annual costs because of severe hypoglycaemia; the overall effect may be cost neutral or cost saving when total costs are considered. The cost of severe hypoglycaemia should be included in the analysis of total socioeconomic burden of diabetes.

Assessment

This study considered the costs of hypoglycaemia and the cost effectiveness of insulin lispro in preventing hypoglycaemia. The clinical data was derived from a retrospective study of clinical records of 100 people with type 1 diabetes from three hospitals in Spain. The direct medical costs measured were comprehensive. The total costs varied significantly between hospitals; therefore, minimum and maximum hospitalisation costs were used with the average resource use, to give an estimate of the sensitivity of overall costs. The incidence rates of severe hypoglycaemia for insulin lispro and human insulin were derived from two randomised open-label trials. An incremental analysis was performed.

Banerjee et al (2007)

Banerjee et al (2007) performed a systematic review evaluating the clinical and economic implications of using short-acting insulin analogues in subjects with type 1 diabetes compared to human insulin. However, one of the included studies did not separate the outcomes of type 1 from type 2 diabetes. Five economic studies were included after a systematic search and application of exclusion criteria. The BMJ checklist was used to assess the quality of included economic studies. Three studies were set in Canada. One study (Davey et al 1997) was set in Australia, but the outcomes were not separated for type 1 and type 2 diabetes. Overall, two cost comparison studies concluded that insulin lispro and human insulin were similar, and three willingness to pay studies found that insulin lispro or a lispro-based mix was more favourable than human insulin or a human insulin-based mix. One of these studies included both people with type 1 and type 2 diabetes.

Assessment

The questions and methods of this systematic review were clearly stated. The search procedure was sufficiently rigorous. The included studies were not entirely specific to the population of interest to this review; however, the results of the studies were discussed separately. The design, time horizon, perspective and population of the included studies were all described.

Studies of long-acting insulin analogues

Seven studies regarding the cost effectiveness of long-acting insulin analogues were found. One was a systematic review (Tran et al 2007). The study by Tunis et al (2009) was set in Canada and found that insulin detemir was cost effective compared with NPH. A European study by Gschwend et al (2009) found that insulin detemir was cost saving compared with NPH in three of five countries studied. Grima et al (2007) found that the NPH group had lower total costs than the insulin glargine group. However, the insulin glargine group had greater total and quality-adjusted life expectancy. The weighted incremental cost per QALY was $20 799. The systematic review by Tran et al (2007) included only one study of relevance to this report (Palmer et al 2004).

Tunis et al (2009)

The study by Tunis et al (2009) was conducted to quantify the long-term cost effectiveness of insulin detemir versus NPH insulin for the treatment of type 1 and type 2 diabetes in Canada, and to assess the sensitivity of results to dis-utilities for hypoglycaemic events. The IMS-CORE Diabetes Model was used to project lifetime (60 years for type 1 and 35 years for type 2 diabetes), and clinical and economic outcomes. Cohort characteristics, utilities and costs were derived from published literature. For type 1 diabetes, clinical trial data for HbA_{1c} improvement (insulin detemir –0.94% ±1.07; NPH –0.82% ±1.01) from baseline, and rates of hypoglycaemic events (major events: 0.20 vs 0.80 per patient year for insulin detemir vs NPH, respectively) were modelled. Sensitivity analyses were conducted on discount rate and hypoglycaemia dis-utility. Outcomes included costs of treatment or management, and costs (and incidence) of diabetes-related complications. Incremental cost-effectiveness ratios (ICERs) were calculated from differences in total costs and QALYs. Average total costs for type 1 diabetes were C$83 622 ±4585 for insulin detemir and C$72 016 ±4593 for NPH. QALYs increased by 0.475 years with insulin detemir, with an ICER of C$24 389/QALY. The analysis demonstrated that insulin detemir had a 65.2% probability of being cost effective for adult type 1 diabetes patients.

Assessment

The theoretical cohort of adult type 1 diabetes patients used in this study was defined, with baseline characteristics taken from the Diabetes Control and Complications Trial (DCCT) secondary intervention cohort and from an online source of Canadian demographic information. The perspective was stated. The list of diabetes complications was comprehensive.

Gschwend et al (2009)

The analysis by Gschwend et al (2009) evaluated the long-term clinical and economic outcomes associated with insulin detemir and NPH insulin, in combination with mealtime insulin aspart in patients with type 1 diabetes in Belgian, French, German, Italian and Spanish settings. The IMS-CORE Diabetes Model was used to make long-term projections of life expectancy, QALE and direct medical costs. The analysis was based on patient characteristics and treatment effects from a 2-year RCT. Events were projected for a time horizon of 50 years. Basal-bolus therapy with insulin detemir was projected to improve QALE by 0.45 years versus NPH in the German setting, with similar improvements in the other countries. Insulin detemir was associated with cost savings in Belgium, Germany and Spain. In France and Italy, lifetime costs were slightly higher in the insulin detemir arm, leading to ICER of €519 per QALY gained and €3256 per QALY gained, respectively.

Assessment

This study based patient characteristics on a 2-year multinational RCT of 497 patients. Costs were accounted from a third party payer perspective. Costs were obtained from credible sources. Time horizons were stated. Incremental costs were calculated. A sensitivity analysis was performed and the results were most sensitive to differences in major hypoglycaemic event rates. Removing the difference between the treatments did not affect overall outcome.

Grima et al (2007)

The objective of the study by Grima et al (2007) was to assess the cost effectiveness of insulin glargine compared with NPH insulin in patients with type 1 or 2 diabetes who had inadequate glycaemic control. A long-term, state-transition model was developed to simulate the natural history of type 1 and 2 diabetes. Risks of diabetes-related

macrovascular and microvascular complications and mortality by HbA_{1c} levels were estimated based on the United Kingdom Prospective Diabetes Study (UKPDS). Outcome measures included complication rates and associated costs, insulin costs, life years (LYs) and QALYs. The baseline analysis was conducted for patients with type 1 and 2 diabetes (aged 27 and 53 years, respectively) with HbA_{1c} levels above 7%, using a 36-year time horizon and a Canadian public payer perspective. Costs and effects were discounted at 5% per annum. All costs were reported in Canadian dollars (2005 values). The NPH insulin group had lower total costs than the insulin glargine group for patients with inadequately controlled diabetes (HbA_{1c} above 7%; lifetime difference C$1398 and C$1992, respectively, in type 1 and 2 diabetes). However, patients treated with insulin glargine had greater total life expectancy and QALE than those who received NPH insulin (incremental LY=0.08 and QALYs=0.07 in type 1 diabetes, and incremental LY=0.25 and QALYs=0.23 in type 2 diabetes). The weighted incremental cost per LY gained and QALY gained were C$18 661 and C$20 799, respectively, in type 1 diabetes. The authors concluded that the cost-effectiveness ratios for insulin glargine use for type 1 diabetes provide evidence for its adoption from a Canadian health-care payer perspective.

Assessment

The rates of complications and deaths used in the analyses were based on an RCT. Seven complications of diabetes were considered. The perspective was stated as a public payer perspective. Costs were comprehensive and from a credible source. A sensitivity analysis was employed using a reduction in HbA_{1c} of 0.14% to 0.53%, based on the range of reductions observed in clinical trials. Incremental costs were analysed.

Tran et al (2007)

A systematic review was undertaken by Tran et al (2007) to evaluate the economic implications of using long-acting insulin analogues relative to human insulin. Due to the heterogeneity of economic studies, results were not combined. Three studies were included. Only one of these studies analysed type 1 diabetes separately to type 2. This was the study by Palmer et al (2007) summarised below. Tran commented that the results of Palmer et al (2007) are not generalisable, due to the lack of significant differences in HbA_{1c} between insulin detemir and NPH. Palmer et al (2007) based their analysis on differences in HbA_{1c} value of –0.15 with insulin detemir compared with NPH, and assumed this difference was maintained over a life time. The meta-analysis of eight RCTS performed by Tran et al (2007) showed no significant differences.

Assessment

The systematic review stated a clear question and method. The search procedure was sufficiently rigorous. Only one study was included; thus, heterogeneity was not an issue. The methodological quality of the study was discussed and critiqued.

Palmer et al (2007)

Palmer et al (2007) used a computer simulation model to project long-term economic and clinical outcomes in a simulated cohort of type 1 diabetes patients treated with either insulin detemir plus insulin aspart (analogue) or NPH plus human soluble insulin (human), in a United Kingdom setting. Probabilities of complications and $HbA1_c$-dependent adjustments were derived from major clinical and epidemiological studies. Complication and treatment costs were projected over patient lifetimes from an NHS perspective. Costs and clinical benefits were discounted at 3.5% annually.

QALE was 0.66 QALYs higher in the analogue insulin versus the human insulin group (mean ±standard deviation[SD]) (7.65 ±0.09 vs 6.99 ±0.08). Direct lifetime costs were £1654 greater with analogue versus human insulin treatment (£40 876 ±1119 vs £39 222 ±1141), producing an ICER of £2500 per QALY gained. Sensitivity analyses showed the results were robust under a range of plausible scenarios. The authors concluded that treatment with analogue insulin was associated with a decreased incidence of long-term complications and improved QALE, but slightly higher treatment costs compared to human insulin therapy. Analogue insulin treatment had an ICER within the range generally considered to represent good value for money in the United Kingdom.

Assessment

This study posed a well-defined question. The baseline demographics of the cohort was based on a meta-analysis, which reduces the risk of bias. An NHS reimbursement perspective was taken. The list of costs and complications was comprehensive. This study assumed a reduction in HbA_{1c} of insulin detemir compared with NPH that was greater than that found in recent meta-analyses. The sensitivity analysis revealed that differences in HbA_{1c} had the greatest impact on the ICER. As the underlying assumed reduction in HbA_{1c} was not consistent with recent studies, the findings of this study may be exaggerated.

Valentine et al (2006)

The purpose of the study by Valentine et al (2006) was to compare, in clinical and economic terms, the long-acting insulin analogue detemir with NPH insulin and with long-acting insulin glargine. Investigators used the validated IMS-CORE Diabetes Model to project clinical and cost outcomes over a 35-year base case time horizon; outcome data were extracted directly from RCTs designed to compare insulin detemir with NPH and with insulin glargine. Modelled patient characteristics were derived from corresponding trials, and simulations incorporated published quality-of-life utilities, with cost data obtained from a Medicare perspective. Insulin detemir, when compared with NPH, increased QALE by 0.698 QALYs. Lifetime direct medical costs were increased by US$10 451 per patient, although indirect costs were reduced by US$4688. On the basis of direct costs, the cost per QALY gained with detemir was US$14 974. In comparison with glargine, detemir increased QALE by 0.063 QALYs, reduced direct medical costs by US$2072 per patient, and decreased indirect costs by US$3103 (dominant). Reductions in diabetes-related comorbidities were also associated with insulin detemir in both instances – most notably in the complications of retinopathy and nephropathy. Relative reductions in rates of complications were greatest in the comparison of insulin detemir with NPH. Results were most sensitive to variation in HbA_{1c} levels. However, variation among any of the key assumptions, including HbA_{1c}, did not alter the relative results. It was concluded that insulin detemir represents an attractive clinical and economic intervention in the United States health-care setting compared with both NPH insulin and insulin glargine.

Assessment

The question was well defined and answerable. Model projections were based on results generated from an RCT. The direct and indirect costs were not specified, and the units were not recorded. The source of cost values was credible. The ICER was measured. Sensitivity analysis was performed. The findings were similar to other reports of these agents.

Palmer et al (2004)

In the study by Palmer et al (2004), the IMS-CORE Diabetes Model was used to project short-term results obtained from the fixed-effects (weighted average) meta-analysis to long-term incidence of complications, improvements in QALY, long-term costs and the cost

effectiveness for insulin detemir combinations versus NPH combinations in type 1 diabetes patients. Probabilities of complications and HbA_{1c}-dependent adjustments were derived from the DCCT and other studies. Costs of treating complications in the United Kingdom were retrieved from published sources. Total direct costs (complications + treatment costs) for each arm were projected over patient lifetimes from an NHS perspective. Both costs and clinical outcomes were discounted at 3.5% annually. The results showed improved glycaemic control, decreased hypoglycaemic events and body mass index with insulin detemir-based basal/bolus therapy, which led to fewer diabetes-related complications, an increase in QALE of 0.09 years, increased total lifetime costs per patient of £1707 and an ICER of £19 285 per QALY gained. Results were stable under a wide range of reasonable assumptions. The conclusions made were that short-term improvements seen with insulin detemir combinations versus NPH combinations led to decreased complications, improvements in QALYs and reductions in complication costs, which partially offset the additional costs of insulin detemir, leading to a cost-effectiveness ratio that fell within a range considered to represent excellent value for money (<£35 000/QALY gained).

Assessment

The question was well defined and answerable. Model projections were based on a meta-analysis. Baseline patient characteristics were taken from a meta-analysis and from an RCT. The assumption was made that insulin detemir led to a 0.37% point drop in HbA_{1c} from baseline compared to 0.22% with NPH (nonsignificant difference). An NHS perspective was taken, and costs were valued credibly. The listed costs of complications was comprehensive. The incremental analysis was performed, as was a sensitivity analysis.

7.1.3.6 Overall summary tables

Table 7.16 Characteristics of included studies, Question 7.1 (iii)

Reference	Study type	Model population	Intervention	Comparator	Setting
Banerjee et al (2007)	Meta-analysis	T1d, T2d adults	Aspart, lispro, glargine, detemir	Human, NPH	Canada (includes Australian primary study)[a]
Brixner and McAdam-Marx (2008)	Systematic review	T1d, T2d adults	Detemir, glargine	NPH	United States
Cameron and Bennett (2009)	Meta-analysis	T1d, T2d adults	Aspart, lispro, glargine, detemir	Human NPH	Canada
Grima et al (2007)	Cost effective-ness	T1d, T2d	Glargine	NPH	Canada
Gschwend et al (2009)	Cost effective-ness	T1d	Detemir	NPH	Belgium, France, Germany, Italy, Spain
Palmer et al (2004)	Cost effective-ness	T1d adults	Detemir	NPH	United Kingdom
Palmer et al (2007)	Cost effective-ness	T1d	Detemir and aspart	NPH and human	United Kingdom
Pratoomsoot et al (2009)	Cost effective-ness	T1d	Lispro	Human	United Kingdom
Reviriego et al (2008)	Cost effective-ness	T1d	Lispro	Human	Spain
Tran et al (2007)	Meta-analysis				
Tunis et al (2009)	Cost effective-ness	T1d, T2d	Detemir	NPH	Canada
Valentine et al (2006)	Cost effective-ness	T1d	Detemir	NPH	United States

NPH, neutral protamine Hagedorn; T1d, type 1 diabetes; T2d, type 2 diabetes

[a] Study by (Davey et al 1997) not included in this review because outcomes not separately extracted for type 1 diabetes

Table 7.17 Results of included studies, Question 7.1 (iii)

Reference	Base case results: ICER per QALY unless otherwise stated	Sensitivity analyses: HbA_{1c}	Sensitivity analysis: hypoglycaemia	Summary
Banerjee et al (2007)				Lispro and human similar (cost comparison) Lispro or mix more favourable than human (WTP)
Brixner and McAdam-Marx (2008)	Individual studies reported in this table			In the United States, detemir cost effective vs NPH and glargine
Cameron and Bennett (2009)	Lispro C$28 996 Glargine C$87 932 Detemir C$387 729	Model sensitive to changes in effect size of HbA_{1c}	Sensitive to decrements applied to utility scores when fear of hypoglycaemia included as factor	Rapid-acting insulin analogues only found to be cost effective
Grima et al (2007)	Glargine C$18 661 NPH C$20 799			
Gschwend et al (2009)	Detemir ICER €519 per QALY (France) ICER €3256 (Italy)			Detemir associated with cost savings in Belgium, Germany and Spain
Palmer et al (2004)	ICER £19 285 per QALY gained			Detemir cost effectiveness ratio within range representing excellent value for money
Palmer et al (2007)	ICER £2500 per QALE gained			Analogue associated with increased QALE but higher treatment costs. ICER in range considered good value
Pratoomsoot et al (2009)	Lispro: improvement in QALE 0.10 vs RHI Lifetime direct medical costs Lispro £70 576 vs £72 529	Lispro benefit 0.034 QALYs	Lispro remained dominant	ICER based on QALE: lispro dominant
Reviriego et al (2008)	Lispro vs human: cost to prevent one episode of severe hypoglycaemia is €277			
Tran et al (2007)				Included studies not fully comparable: 1. Detemir favoured over NPH 2. Glargine favoured over NPH 3. Glargine associated with proportional reduction in hypoglycaemia-related inpatient claims
Tunis et al (2009)	ICER: C$24 389/QALY			Detemir 62.5% probability of being cost effective
Valentine et al	Cost per QALY gained	When no difference in		Favours detemir vs NPH

Reference	Base case results: ICER per QALY unless otherwise stated	Sensitivity analyses: HbA_{1c}	Sensitivity analysis: hypoglycaemia	Summary
(2006)	US$14 974 detemir	efficacy with respect to HbA_{1c}, detemir associated with ICER or $20 386 per QALY gained		

HbA_{1c}, glycated haemoglobin; ICER, incremental cost-effectiveness ratio; NPH, neutral protamine Hagedorn; QALE, quality adjusted life expectancy; QALY, quality-adjusted life year; RHI, regular human insulin; WTP, willingness to pay

7.1.3.7 Literature search strategy

The search was conducted on 22 March 2010. Studies published after this time were not eligible for inclusion in the systematic review. A total of 101 non-duplicate citations were identified.

7.2 Continuous subcutaneous insulin infusion pumps

7.2.1 Effect of CSII versus MDI on hypoglycaemia, glycaemic control and QoL

Question 7.2

(i) How effective are modern CSII pumps versus MDI at reducing hypoglycaemia and HbA_{1c}, and improving QoL?

(ii) How effective are sensor augmented CSII pumps versus MDI at reducing hypoglycaemia and HbA_{1c}, and improving QoL?

CSII, continuous subcutaneous insulin infusion; HbA_{1c}glycated haemoglobin; MDI, multiple daily injections; QoL, quality of life

This section of the report covers clinical question 7.2 (i), which compares the effectiveness of continuous subcutaneous insulin infusion (CSII) pumps and multiple daily injections (MDI) at reducing hypoglycaemia and glycated haemoglobin (HbA_{1c}), and improving quality of life (QoL). A subquestion, question 7.2 (ii), was developed after the publication of a major study on sensor augmented pumps, which prompted the development of a question on this topic. Thus, question 7.2 (ii) compares the effectiveness of sensor augmented pumps and MDI.

7.2.1.1 Criteria for eligibility

Question 7.2 (i)

Studies were eligible for inclusion if they met the criteria shown in Table 7.18.

Table 7.18 Criteria for determining study eligibility, question 7.2 (i)

Study design	Level II or higher published >1999
Population	children and adults with type 1 diabetes
Intervention	CSII - modern pumps - at least 12 weeks duration
Comparator	MDI - at least 3 injections (adults) at least 2 injections (children)
Outcomes	HbA_{1c}, hypoglycaemia, QoL

CSII, continuous, subcutaneous insulin infusion; $HbA_{1c,}$ glycated haemoglobin; QoL, quality of life; NHMRC, National Health and Medical Research Council; MDI, multiple daily injections

[a] NHMRC intervention scale: Level I, a systematic review of Level II studies; Level II, a randomised controlled trial

Question 7.2 (ii)

Studies were eligible for inclusion if they met the criteria shown in **Error! Reference source not found.**.

Table 7.19 Criteria for determining study eligibility, question 7.2 (ii)

Study design	Level I or Level II[a]
Population	Children and adolescents with diabetes
Intervention	Sensor augmented pump
Comparator	Multiple daily injections
Outcomes	HbA_{1c}, hypoglycaemia, QoL

$HbA_{1c,}$ glycated haemoglobin; QoL, quality of life; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I, a systematic review of Level II studies; Level II, a randomised controlled trial

7.2.1.2 Assessment of study eligibility

Question 7.2 (i)

A total of 38 citations were identified in the initial literature search (see Table 7.21). The exclusion criteria were applied to all citations by reviewing the abstract and title, with 20 publications excluded (shown in Table 7.20). A total of 18 publications remained (shown in Table 7.20), and the full text version of each publication was retrieved and reviewed. The same exclusion criteria were then applied to the full text articles. A total of three publications met the inclusion criteria.

Table 7.20 Assessment of study eligibility, question 7.2 (i)

Exclusion criteria	Number
Total citations	38
Citations excluded after review of abstract/title	20
Wrong study type	14
Wrong population	0
Wrong intervention	5
Wrong outcome	0
Not in English	1
Total excluded citations	20
Full papers reviewed	18
Citations excluded after review of full publication	15
Wrong study type	13
Wrong population	0
Wrong intervention	1
Wrong outcome	1
Not in English	0
Total excluded citations	15
Total included citations	3

Question 7.2 (ii)

Publications identified in the literature search were reviewed using the criteria shown in Table 7.22, applied hierarchically, to determine which publications to exclude.

A total of four nonduplicate citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with three publications excluded, as shown in Table 7.22. One publication remained, and the full text version of this publication was retrieved and reviewed (Bergenstal et al 2010).

7.2.1.3 Citations for full text review

The three systematic reviews that met the inclusion criteria for question 7.2 (i) comprised one in adults and children (Misso et al 2010), one in children (Pankowska et al 2009), and one in both children and adults, with a focus on the effect on hypoglycaemia (Fatourechi et al 2009).

A search was undertaken in Medline and EMBASE to find published Level II evidence to update the three included systematic reviews; the search span was January 2007 to 16 April 2010. The abstract and title of 292 non-duplicate citations were reviewed. The selection criteria were applied, with two Level II studies meeting the inclusion criteria (Opipari-Arrigan et al 2007; Bolli et al 2009).

7.2.1.4 Literature search summary

The results of the literature search for question 7.2 (i) is shown in Table 7.21 and for question 7.2 (ii) in Table 7.22.

Table 7.21 Search results, question 7.2 (i)

Stage	Notes	Number
Search summary	Medline/EMBASE	293
Duplicates	Duplicates identified	1
Identified	Total identified	292
Exclusion criteria	Wrong study type (not RCT)	45
	Wrong population (not type 1 diabetes)	7
	Wrong intervention (not CSII (modern pumps) versus MDI (at least 3 injections/day in adults and at least 2 injections/day in children AND of at least 12 weeks duration)	237
	Wrong outcome (not HbA_{1c}, hypoglycaemia, QoL)	0
	Not in English	1
	Total excluded	290
Meeting criteria	Total meeting inclusion criteria	2
Included	Total included studies	2

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections, QoL, quality of life; RCT, randomised controlled trial

Table 7.22 Search results, question 7.2 (ii)

Stage	Notes	Number
Search summary	Medline	5
	Total	5
Duplicates	Duplicates identified	1
Identified	Total identified	4
Exclusion criteria	Wrong study type (not Level II[a])	0
	Wrong population (not type 1 diabetes)	0
	Wrong intervention (not sensor augmented pump)	1
	Wrong comparator (not MDI)	1
	Wrong outcome (not HbA_{1c}, hypoglycaemia, QoL)	1
	Not in English	0
	Total excluded	3
Meeting criteria	Total meeting inclusion criteria	1
Included	Total included studies	1

HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections; QoL, quality of life; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

7.2.1.5 Included studies

A total of six Level I and Level II studies were included for questions 7 (i) and (ii) (Opipari-Arrigan et al 2007; Bolli et al 2009; Fatourechi et al 2009; Pankowska et al 2009; Bergenstal et al 2010; Misso et al 2010).

7.2.1.6 Characteristics of included studies, question 7.2 (i)

Misso et al 2010

The Cochrane review by Misso et al (2010), included 23 RCTs comparing the efficacy of CSII versus MDI (defined as three or more injections per day). The review was of good quality with well-described method of literature search, quality assessment and data extraction, with search span to July 2009. Ten of the included studies were published before 2000 and thus did not meet the inclusion criteria for this systematic review, and are not discussed further. The authors report the results of a pooled analysis of the effect on HbA_{1c} and a qualitative assessment of evidence relating to hypoglycaemia and quality of life. They concluded that CSII might be better than MDI for glycaemic control in people with type 1 diabetes; however, CSII appears to provide no benefit for reducing non-severe hypoglycaemic events. The characteristics of the studies included in this review are summarised in Table 7.23.

Table 7.23 Studies included in Misso et al (2010) and published after 1999

Reference	Study type Study quality	Population	Intervention	Comparator	Outcomes
Bruttomesso et al (2008)	Crossover RCT Good	42 adults already on CSII for at least 6 months, mean HbA_{1c} 7.6% no exclusions based on hypoglycaemia	8 months	CSII for 4 months then crossover multiple pumps	MDI (insulin lispro/insulin glargine) for 4 months then crossover
Cohen et al (2003)	Crossover RCT Poor	16 teenagers (mean age 14.2 years, range 14.5–17.9) with diabetes >2 years patients with hypoglycaemia unawareness excluded	12 months	CSII for 6 months then crossover Disetronic pump	MDI (regular/ NPH) for 6 months then crossover
DeVries et al (2002)	Parallel RCT Good	79 adults with persistent poor control (HbA_{1c} >8.5% for 6 months before trial)	4 months	CSII	MDI (insulin lispro/NPH)
Doyle et al (2004)	Parallel RCT Fair	32 children/teenagers with diabetes >6 months naive to CSII and insulin glargine no exclusions based on hypoglycaemia experience	4 months	CSII (Medtronic 508 or Paradigm 511)	MDI (insulin lispro, insulin glargine)
Hanaire-Broutin et al (2000)	RCT crossover Fair	41 adults with HbA_{1c}<10%		CSII (Medtronic 506/507 or H-tron)	MDI (insulin lispro/NPH)
Hirsch et al (2005)	RCT-crossover Poor	100 adults mean age 43 years, diabetes duration 22 years, mean HbA_{1c} 7.5% excluded patients with: history of severe hypoglycaemia or hypoglycaemia unawareness experience with CSII for at least 3 months prior to trial	5 weeks	CSII – multiple pumps	MDI – insulin aspart/ insulin glargine
Hoogma et al (2006)	Crossover RCT Good	256 adults – mean age 36 years, mean duration of diabetes 15 years, mean HbA_{1c} 7.9% excluded if history of severe hypoglycaemia or hypoglycaemia unawareness	12 months	CSII (H-tron v100 or H-tron plus v100) for 6 months then crossover	MDI (insulin lispro/NPH) for 6 months then crossover
Lepore et al (2003)	Parallel RCT Fair	32 adults mean age 40 years, with persistent poor control (HbA_{1c} >8% for 1 year prior to trial) on MDI for >1 year prior to trial, mean HbA_{1c} 8.8% no exclusion based on hypoglycaemia 4 patients with history of severe hypoglycaemia	12 months	CSII - Minimed 508, Disetronic H-tron plus	MDI (insulin lispro, insulin glargine)

Reference	Study type Study quality	Population	Intervention	Comparator	Outcomes
Nuboer et al (2008)	Parallel RCT Fair	39 children/teenagers with diabetes >1 year	14 months	CSII (H-tron)	MDI (insulin lispro or regular/NPH or insulin glargine)
Pozzilli et al (2003)	Parallel RCT Fair	23 teenagers/ adults with diabetes <4 weeks Mean age 18 years (range 12–35) Mean HbA_{1c} 11% No exclusion based on hypoglycaemia	6 months	CSII (Medtronic 507c)	MDI (short-acting insulin /NPH)
Skogsberg et al (2008)	Parallel RCT	72 children	24 months	CSII (H-tron)	MDI (insulin aspart/NPH)
Tsui et al (2001)	Parallel RCT	27 adults with diabetes duration >2 years	9 months	CSII (Minimed 507)	MDI (insulin lispro/NPH)
Weintrob et al (2004)	Crossover RCT	23 children with diabetes >2 years mean age: 12 years, range 9–14 mean HbA_{1c} 8.2%	32 weeks with 2-week run-in/washout	CSII - Medtronic 508	MDI (regular insulin / NPH)

CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections; NPH, neutral protamine Hagendorn; RCT, randomised controlled trial

Pankowska et al 2009

Pankowska et al (2009) systematically reviewed the evidence in children and adolescents. The review was of good quality, with methods of literature search, assessment for study and publication bias, and data extraction well described. Six RCTs, comparing the efficacy of CSII with MDI (defined as two or more injections per day), were included, and a pooled analysis of the effect on HbA_{1c} and severe hypoglycaemia were reported. The authors concluded that CSII provided a more effective form of metabolic control in the short term. However, the results should be assessed in the context of the methodological limitations of the studies included in the pooled analysis. The characteristics of the included studies are summarised in Table 7.24.

Table 7.24 Studies included in Pankowska et al (2009)

Reference	Study type Study quality	Population Country (ethnicity)	Intervention	Comparator	Outcomes
Dimeglio et al (2004)	RCT - parallel Fair	42 patients - mean age 3.8 years - range 1.8–4.7 mean duration of diabetes 1.8 years mean Hba_{1c} 8.8% some experienced with MDI no exclusions based on hypoglycaemia experience	6 months	CSII - Medtronic minimed 508	MDI- insulin lispro and NPH (2 pts- insulin lente, 1 – insulin glargine)
Doyle et al (2004)	Parallel RCT Fair	32 children/teenagers with diabetes >6 months naive to CSII and insulin glargine no exclusions based on hypoglycaemia experience	4 months	CSII (Medtronic 508 or Paradigm 511)	MDI (insulin lispro, insulin glargine)
Fox et al (2005)	RCT- parallel Poor	26 patients - mean age 3.9 years, range 1–6 mean duration of diabetes 1.5 years mean HbA_{1c} 7.5% experienced with MDI	6 months	CSII - Medtronic minimed 508	MDI - insulin lispro/insulin aspart and NPH
Weintrob et al (2004)	Crossover RCT Poor	23 children with diabetes >2years mean age 12 years, range 9–14 mean HbA_{1c} 8.2%	32 weeks with 2 week run-in/washout	CSII - Medtronic 508	MDI (regular/NPH)
Wilson et al (2005)	RCT - parallel Fair	19 children - mean age 3.6 years, range 1.7–6.1 years mean HbA_{1c} 7.9% >6 months duration diabetes	12 months	CSII - (Minimed 508)	MDI - 2–3 injections per day

CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections; NPH, neutral protamine Hagendorn; RCT, randomised controlled trial

Fatourechi et al (2009)

Fatourechi et al (2009) specifically undertook to examine the effectiveness of CSII in reducing hypoglycaemia when compared with MDI. The review was of good quality with the method of literature search, assessment for study and publication bias, and data extraction well described. The search aimed to capture the most recent studies using modern insulin pumps, and the search span was dated 2002 to March 2008. The review included 15 RCTs, with 13 of these studies including a total of 669 participants with type 1 diabetes. The authors report the results of a pooled analysis of effect on HbA_{1c} and the risk of hypoglycaemia. The authors conclude that CSII results in a slightly reduced HbA_{1c} in adults with type 1 diabetes, with unclear impact on hypoglycaemia. They note that the effect in patients with hypoglycaemia unawareness or recurrent severe hypoglycaemia remains unclear because of lack of data. The characteristics of the included studies are summarised in Table 7.25.

Table 7.25 Studies included in Fatourechi et al (2009)

Reference	Study type Study quality	Population Country (ethnicity)	Intervention	Comparator	Outcomes
Bruttomesso et al (2008)	Crossover RCT Good	42 adults already on CSII for at least 6 months, mean HbA_{1c} 7.6% no exclusions based on hypoglycaemia	8 months	CSII for 4 months then crossover multiple pumps	MDI (lispro/ glargine) for 4 months then crossover
Cohen et al (2003)	Crossover RCT Poor	16 teenagers (mean age 14.2 years, range 14.5–17.9) with diabetes >2 years patients with hypoglycaemia unawareness excluded	12 months	CSII for 6 months then crossover Disetronic pump	MDI (regular/ NPH) for 6 months then crossover
Dimeglio et al (2004)	Parallel RCT Fair	42 patients - mean age 3.8 years - range 1.8–4.7 mean duration of diabetes 1.8 years mean Hba_{1c} 8.8% some experienced with MDI no exclusions based on hypoglycaemia experience	6 months	CSII - Medtronic minimed 508	MDI - lispro and NPH
Doyle et al (2004)	Parallel RCT Fair	32 children/teenagers with diabetes >6 months naive to CSII and glargine no exclusions based on hypoglycaemia experience	4 months	CSII (Medtronic 508 or Paradigm 511)	MDI (lispro, glargine)
Fox et al (2005)	Parallel RCT Poor	26 patients - mean age 3.9 years, range 1–6 mean duration of diabetes 1.5 years mean hba_{1c} 7.5% experienced with MDI	6 months	CSII - Medtronic minimed 508	MDI - lispro/aspart and NPH
Hirsch et al (2005)	Crossover RCT Poor	100 adults mean age 43 years, diabetes duration 22 years, mean HbA_{1c} 7.5% excluded patients with history of severe hypoglycaemia or hypoglycaemia unawareness experience with CSII for at least 3 months prior to trial	5 weeks	CSII - multiple pumps	MDI - aspart/ glargine
Hoogma et al (2006)	Crossover RCT Good	256 adults - mean age 36 years, mean duration of diabetes 15 years, mean HbA_{1c} 7.9% excluded if history of severe hypoglycaemia or hypoglycaemia unawareness	12 months	CSII (H-tron v100 or H-tron plus v100) for 6 months then crossover	MDI (lispro/NPH) for 6 months then crossover

Reference	Study type Study quality	Population Country (ethnicity)	Intervention	Comparator	Outcomes
Lepore et al (2003)	Parallel RCT Fair	32 adults mean age 40 years, with persistent poor control (HbA_{1c}>8% for 1 year prior to trial) on MDI for >1 year prior to trial, mean HbA_{1c} 8.8% no exclusion based on hypoglycaemia 4 patients with history of severe hypoglycaemia	12 months	CSII - Minimed 508, Disetronic H-tron plus	MDI (lispro, glargine)
Nuboer et al (2008)	Parallel RCT Fair	39 children/teenagers with diabetes >1 year	14 months	CSII (H-tron)	MDI (lispro or regular/ NPH or glargine)
Opipari-Arrigan et al (2007)	Parallel RCT N=16 (CSII) N=8 (MDI) N=8 Fair	Children, mean age 4.4 years with >1 year diabetes duration mean HbA_{1c} 8.1%	CSII - Animas pump using insulin lispro 24 weeks	MDI - insulin lispro and NPH (except one patient on lispro and glargine)	HbA_{1c} Hypo-glycaemia QoL
Pozzilli et al (2003)	Parallel RCT Fair	23 teenagers/adults with diabetes <4 weeks mean age 18 years (range 12–35) mean HbA_{1c} 11% no exclusion based on hypoglycaemia	6 months	CSII (Medtronic 507c)	MDI (short acting/NPH)
Thomas et al (2007)	Parallel RCT I	21 adults mean age 43, mean diabetes duration 25 years; mean HbA_{1c} 8.5% inclusions - 1 or more episodes of severe hypoglycaemia in past 6 months and evidence of hypoglycaemia unawareness	6 months	CSII - (Minimed 508)	MDI (lispro/ glargine)
Weintrob et al (2004)	Crossover RCT Poor	23 children with diabetes >2 years mean age: 12 years, range: 9–14 mean HbA_{1c} 8.2%	32 weeks with 2 week run-in/washout	CSII - Medtronic 508	MDI (regular/ NPH)
Wilson et al (2005)	Parallel RC Fair	19 children - mean age: 3.6 years, range: 1.7–6.1 years mean HbA_{1c} 7.9% >6 months duration diabetes	12 months	CSII - (Minimed 508)	MDI - 2–3 injections per day

CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections; NPH, neutral protamine Hagendorn; QoL, quality of life; RCT, randomised controlled trial

Bolli et al (2009)

The study reported by Bolli and colleagues (2009) was a multicentre, open parallel designed RCT in 48 adult participants with type 1 diabetes, with the intervention including a 1-week run-in period followed by a 24-week treatment period. The participants were naive to CSII and MDI at enrolment, with the MDI arm receiving insulin glargine once daily and insulin

lispro three times per day, and the CSII arm receiving insulin lispro via Medtronic 508 insulin pump. The authors concluded that optimisation of basal NPH insulin replacement with insulin lispro by CSII or an MDI-based regimen of once daily glargine plus insulin lispro results in similar improvement in glycaemic control.

Opipari-Arrigan et al (2007)

The study reported by Opipari-Arrigan et al (2007) was an RCT of parallel design, including 16 children less than 5 years of age with type 1 diabetes, randomised to either CSII or MDI for 6 months. The outcomes measured included HbA_{1c}, glycaemic variability assessed by continuous blood glucose sensing, quality of life and adverse events. The authors concluded that, for young children with type 1 diabetes, CSII therapy is comparable to MDI therapy with regard to glucose control, but is associated with higher treatment satisfaction and improved quality of life.

7.2.1.7 Characteristics of included studies, question 7.2 (ii)

Bergenstal et al (2010)

In this multicentre (n=30) study of fair study quality, 485 patients (n=329 adults, n=156 children) were randomised to receive either sensor augmented CSII or MDI with insulin glargine and insulin aspart (Bergenstal et al 2010). Inclusion criteria were HbA_{1c} 7.4–9.5%, at least 3 months of MDI before enrolment, and monitoring of BGLs at least four times per day. Exclusions included CSII in the past 3 years, two or more severe hypoglycaemic episodes in the 12 months before enrolment, and pregnancy. Baseline characteristics in both groups were similar. The primary outcome was change from baseline in $HbA_{1c,}$ with secondary outcome rate of severe hypoglycaemia. Follow-up measures occurred at 3, 6, 9 and 12 months duration. There was no significant difference between groups in the rate of severe hypoglycaemia.

7.2.1.8 Results of included studies, question 7.2 (i)

Glycaemic control

Results of pooled analysis

A pooled analysis of the effect on HbA_{1c} was undertaken using a random effects model, based on the data reported by Misso et al (2010) and Bolli et al (2009). Results are reported as the weighted mean difference (WMD) at endpoint.

The studies included in this analysis were in children and adults with type 1 diabetes (n=697; CSII n=351, MDI n=346).

Table 7.26 Results from Misso et al (2010) and Bolli et al (2009): HbA_{1c} – weighted mean difference at endpoint

	HbA_{1c} WMD at end of treatment: 95%CI	Statistical significance	Heterogeneity
Children (n=204)	–0.25(–0.46 to –0.05)	p=0.01	I^2=29%
Adults (n=493)	–0.16(–0.33 to 0.01)	p=0.06	I^2=35%
Overall	–0.20(–0.28 to –0.12)	p<0.00001	I^2=24%

Pankowska et al (2009)

Pankowska and colleagues (2009) pooled the results of five studies (n=136), with the meta-analysis showing a significant lower HbA_{1c} value in the children treated with CSII compared with MDI group, 0.24% lower in the CSII (95%CI: –0.41 to –0.07) with I^2=0%. Pankowska and colleagues concluded that, in the short term, CSII is more effective than MDI at lowering HbA_{1c}. Methodological limitations included small sample sizes, unclear randomisation methods and lack of ITT analysis.

Results of primary studies

Opipari-Arrigan et al (2007)

The study reported by Opipari-Arrigan (2007) was a relatively small study reporting on the results of 16 preschool children, with mean age 4.4 years, randomised to either CSII or MDI. The authors reported no significant difference between the groups or from baseline to 6 months. The WMD 95%CI was 0.15 (95%CI: –0.49 to 0.79) in favour of MDI.

The results of this study should be considered in the context of methodological limitations. The method of randomisation was not described in this study, and no intention to treat (ITT) analysis was carried out. A total of 23% of randomised participants were lost to follow up, and the authors noted that sample size was a limitation. The authors concluded that CSII is comparable to MDI with regard to glucose control.

Fatourechi et al (2009)

All of the studies included in the meta-analysis by Fatourechi et al (2009) have been analysed in either the current meta-analysis or that of Pankowska et al (2009), except for one study, by Thomas et al (2007). This study was carried out in a relatively small group of adults (n=21), who had recently experienced at least one severe hypoglycaemic episode and had hypoglycaemia unawareness. This study was not included in our meta-analysis due to its heterogeneity.

Hypoglycaemia

Misso et al (2010)

Misso et al (2010) provide a descriptive analysis of hypoglycaemia reported in the individual studies. Due to the different scales used to measure hypoglycaemia a pooled analysis was not possible. The authors suggest that data from the 17 studies reporting on hypoglycaemia indicate no relevant benefit of one intervention over the other for reducing non-severe hypoglycaemic events; however, CSII may be better than MDI for reducing the incidence of severe hypoglycaemic events.

Pankowska et al (2009)

Pankowska et al (2009) assessed episodes of severe hypoglycaemia in a pooled analysis. A pooled analysis of non-severe hypoglycaemia was not undertaken due to the different definitions of mild and moderate hypoglycaemia used in each of the studies. The pooled analysis resulted in no significant difference between CSII and MDI, with a pooled relative risk of 0.87 (95%CI: 0.06 to 11.66; p=0.8659).

Fatourechi et al (2009)

Fatourechi et al (2009) undertook a pooled analysis of the effect on hypoglycaemia. A random effects model was used to estimate the pooled odds ratio and 95% confidence intervals for hypoglycaemic events between groups. Outcomes from crossover studies were analysed separately, and sensitivity analyses were carried out. The authors found no

significant difference in severe or nocturnal hypoglycaemia. Adolescents and adults enrolled in crossover trials had non-significantly fewer minor hypoglycaemia episodes per patient week with CSII than MDI; children enrolled in parallel trials had significantly more episodes of minor hypoglycaemia. The main limitation of the study was the paucity of evidence in patients with a history of severe hypoglycaemia and patients with hypoglycaemia unawareness, because these conditions were often cited as exclusions to participation in studies.

Table 7.27 Results from Fatourechi et al (2009) – hypoglycaemia

	Pooled relative risk (95%CI)	Statistical significance	Heterogeneity
Severe hypoglycaemia	0.48; 95%CI: 0.23 to 1.00	NS	NR
Nocturnal hypoglycaemia	0.82, 95%CI: 0.33 to 2.03	NS	I^2=0%
Minor hypoglycaemia Cross-over	–0.08; 95%CI: –0.21 to 0.06	NS	I^2=9%
Minor hypoglycaemia Parallel	0.68;95%CI: 0.16 to 1.20	p=0.03	I^2=0%

CI, confidence interval; NR, not reported; NS, not significant

Bolli et al (2009)

Bolli and colleagues (2009) found the incidence of overall hypoglycaemia (41± 43 vs. 35± 35events/patient; p=0.93), non-severe hypoglycaemia (35 ±37 vs. 31 ±32 events/patient; p=0.97), symptomatic hypoglycaemia (13 ±12 vs. 14 ±15 events/patient; p=0.84) and asymptomatic hypoglycaemia (1.2 ±2.0 vs. 1.4 ±2.3; p=0.95) to be similar in both groups. Two participants in both groups experienced one severe hypoglycaemic event.

Quality of life

The results on QoL from eight studies included in Misso et al (2010) are shown in Table 15.14.

Table 7.28 Summary of results for quality of life from Misso et al (2010)

Reference	Measure	CSII	MDI	Difference – statistical significance
Cohen et al (2003)	DQoLY	82.7 ±13 satisfaction subscale	76.4 ±14.3 satisfaction subscale	p<0.05
DeVries et al (2002)	SF36 general health perceptions	General health - change in baseline 5.9 Mental health - change in baseline 5.2	General health - change in baseline –1.2 Mental health - change in baseline –0.06	p=0.048 p=0.050
Doyle et al (2004)	DQoLY	NR	NR	No statistical difference
Hoogma et al (2006)	DQoL	75	71	p<0.001
Hoogma et al (2006)	SF–12 questionnaire			(p<0.01) in favour of CSII (perception of mental health)

Reference	Measure	CSII	MDI	Difference – statistical significance
Nuboer et al (2008)	PedsQL mean ± SD	88.8 ±9.0	82.3 ±12.8	p<0.05 in favour of CSII
Tsui et al (2001)	Diabetes quality of life score (DQoL)	75.6	68.3	No statistical difference
Wilson et al (2005)	DQol	–0.24 ±0.25 change from baseline	–0.08 ± 0.19 change from baseline	p=0.03
Fox et al (2005)	DQol	NR	NR	Score NR, no difference between groups; fathers of children on MDI significantly more stress
Opipari Arrigan et al (2007)	PedSQL	50.0±39.4 to 73.6±38.2	54.2±17.3	CSII P<0.05 diabetes-related worry decrease from baseline

CSII, continuous subcutaneous insulin infusion; DQoL, diabetes quality of life; DQoLY, diabetes quality of life for youth scale; MDI, multiple daily injection; NR, not reported; PedSQL, Pediatric Quality of Life Inventory

Treatment satisfaction

Four of the studies included by Misso et al (DeVries et al 2002; Cohen et al 2003; Bruttomesso et al 2008; Skogsberg et al 2008) used the validated diabetes treatment satisfaction questionnaire DTSQ; two of these studies were of participants less than 18 years of age (Cohen et al 2003; Skogsberg et al 2008). In all four studies the CSII group scored higher, representing better treatment satisfaction, than the MI group. In two of the studies (Bruttomesso et al 2008; Skogsberg et al 2008) the difference was statistically significant.

The authors report that the data suggests that the majority of participants were more satisfied with CSII than MDI.

Of the studies included by Pankowska et al (2009) in one study (Weintrob et al 2004) DTSQ scores were significantly higher in patients treated with CSII (30.6 ± 3.7 vs. 21.9 ± 3.8, p<0.001).

Bolli et al (2009) found a significant increase in DTSQ treatment satisfaction score in the CSII group compared with the MDI group (3.1 95%CI 0.1, 6.1 p=0.042).

7.2.1.9 Results of included studies, question 7.2 (ii)

Glycaemic control

At 1 year, the baseline mean HbA_{1c} level had decreased to 7.5% in the pump-therapy group, as compared with 8.1% in the injection therapy group (p<0.001). The proportion of patients who reached the target of less than 7.0% HbA_{1c} was greater in the pump-therapy group than in the injection therapy group.

Table 7.29 Results from Bergenstal et al (2010) – HbA_{1c}

Sensor augmented pump	MDI	Between group difference
8.3–7.5% Absolute reduction of 0.8 ±0.8%	8.3–8.1% Absolute reduction of 0.2 ±0.9%	–0.6% (95%CI: –0.7 to 0.4; p<0.001) in favour of pumps
Adults 8.3–7.3 Absolute reduction of 1.0 ±0.7%	Adults 8.3–7.9% absolute reduction of 0.4 ±0.8%	–0.6% (95%CI: –0.8 to 0.4; p<0.001) in favour of pumps
Children 8.3–7.9% Absolute reduction of 0.4 ±0.9%	Children 8.3–8.5% Increase of 0.2 ±1.0%	–0.5% (95%CI: –0.8 to –0.2; p<0.001 in favour of pumps

CI, confidence interval; MDI, multiple daily injections; p, probability

An increased use of sensor was associated with a greater reduction in HbA_{1c} at 12 months in the entire group (p=0.003).

There were significant differences between groups in the number of patients reaching a target of less than 7% in the group as a whole, and in adults alone. There was no significant difference between groups in the number of children reaching a target HbA_{1c} of <7%.

Table 7.30 Results from Bergenstal et al (2010)

Sensor augmented pump	MDI	Between group difference
67/244 (27%)	23/241 (10%)	p<0.001
Adults 57/166 (34%)	Adults 19/163(12%)	p<0.001
Children 10/78 (13%)	Children 4/78 (5%)	p=0.15 NS

MDI, multiple daily injections; NS, nonsignificant

Severe hypoglycaemia

There were no significant differences between groups in rate of severe hypoglycaemia.

Table 7.31 Results from Bergenstal et al (2010) – severe hypoglycaemia

Sensor augmented pump	MDI	Between group difference
13.31 cases per 100 patient years	13.48 per 100 patient years	p=0.58
Adults 15.31 cases per 100 patient-years	Adults 17.62 cases per 100 patient years	p=0.66
Children 8.98 cases per 100 patient-years	Children 4.95 cases per 100 patient-years	p=0.35

MDI, multiple daily injections

7.2.1.10 Discussion

Our systematic search of the literature for evidence regarding the efficacy of CSII compared with MDI in the treatment of type 1 diabetes resulted in numerous Level I studies. Most of these studies report the results of primary studies of various designs, from RCTs, to before and after studies, including data in patients treated with insulin pumps that are now obsolete and insulins that are no longer available. We narrowed the included studies to include only RCTs in which participants were managed on modern insulin pumps. The

technology behind insulin pump therapy is constantly evolving, necessitating further assessment of the benefits of this therapy as new methods are introduced. A study published after our search date, comparing sensor augmented insulin pumps and MDI (Bergenstal et al) has prompted a review of evidence about the efficacy of the sensor augmented pump in managing type 1 diabetes.

The pooled data on the effect of CSII on metabolic control indicates that insulin pump therapy results in an improvement in HbA_{1c} of approximately 0.2% versus treatment with MDI, and 0.24% in paediatric patients (Pankowska et al 2009). The pooled data on the effect of CSII on the risk of severe hypoglycaemia indicates that insulin pump therapy has no additional benefit over and above treatment with MDI (Fatourechi et al 2009; Pankowska et al 2009). A qualitative assessment of the effect of CSII on QoL found that various measurement scales had been used, with varied results. Of 10 studies where QoL was evaluated with a valid measurement tool, seven reported a statistically significant improvement in QoL with CSII as compared with MDI. CSII was associated with higher treatment satisfaction in five of these studies, with a statistically significant result reported in three studies (Misso et al 2010). These results should be considered in the context of the generally low methodological quality of the studies included in the pooled results, and the paucity of evidence in people with a history of recurrent severe hypoglycaemia or hypoglycaemia unawareness.

One study into the effectiveness of sensor augmented pumps versus MDI met the inclusion criteria. This was a multicentre study involving 485 patients with type 1 diabetes, of medium risk of bias. The study is generalisable to the target population, including children and adults with type 1 diabetes; however, it did not include children under the age of 7 years, pregnant women, or patients with a recent history of severe hypoglycaemia. The study did not include Australian diabetes clinics; however, it was carried out in a setting with a well-developed health-care system.

7.2.1.11 Conclusion

Question 7.2 (i)

There is Level I evidence to suggest that CSII may be better than MDI for lowering HbA_{1c} in children and adults with type 1 diabetes. There is Level I and Level II evidence that, in children and adults using CSII or MDI, the rates of severe hypoglycaemia are similar. There is Level II evidence to suggest that CSII may be more beneficial than MDI on quality of life measures in children and adults with type 1 diabetes. There is Level II evidence that CSII results in a higher level of treatment satisfaction than MDI in children and adults with type 1 diabetes. The evidence reported is not generalisable to people who have recurrent severe hypoglycaemia or hypoglycaemic unawareness. The results are applicable to the Australian setting.

Question 7.2 (ii)

There is Level II evidence to suggest that sensor augmented pumps are more effective than MDI for lowering HbA_{1c} in children and adults with type 1 diabetes.

7.2.1.12 Literature search strategy

Question 7.2 (i)

The search strategy for Level I evidence is shown in Table 7.32, which also summarises the citations retrieved from other searches.

Table 7.32 Search strategy, question 7.2 (i)

Database	Date searched	#	Search terms	Citations
Medline/ EMBASE	24 February 2010	1	Diabetes Mellitus, Type	52 521
		2	(continuous subcutaneous insulin infusion or CSII).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1 141
		3	(insulin pump therapy or IPT).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1 136
		4	2 or 3	2 154
		5	meta analysis.mp. or exp Meta-Analysis/	41 224
		6	systematic review.mp.	18 904
		7	pooled analysis.mp.	1 856
		8	exp "Review"/ or review.mp.	1 802 967
		9	5 or 6 or 7 or 8	1 823 065
		10	exp Meta-Analysis/	25 688
		11	meta analysis.mp.	41 224
		12	systemat*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	135 075
		13	pool*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	105 113
		14	10 or 11 or 12 or 13	263 576
		15	9 and 14	83 486
		16	1 and 4 and 15	40
		17	limit 16 to English language	37
Cochrane/ INAHTA	24 February 2010	1	diabetes mellitus insulin dependent.mp. or exp insulin dependent diabetes mellitus/	
		2	continuous subcutaneous insulin infusion or insulin pump therapy	
		3	1 and 2- Cochrane	6
			1 and 2- INAHTA	5
			total non-duplicate studies	38
Manual search				0
Total citations				48
Total non-duplicate citations				38

Question 7.2 (ii)

The search strategy is shown in Table 7.33.

Table 7.33 Search strategy, question 7.2 (ii)

Database	Date searched	#	Search terms	Citations
Medline	14 September 2010	1	exp Diabetes Mellitus, type 1/	53 054
		2	IDDM.tw.	6 808
		3	insulin$ depend$.mp. or insulin?depend$.tw. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	27 087
		4	((typ$ 1 or typ$ 1) adj diabet$).tw.	17 373
		5	(earl$ adj diabet$).tw.	1 054
		6	((auto?immun$ or sudden onset) adj diabet$).tw.	2 034
Medline		7	(insulin$ defic$ adj absolut$).tw.	3
		8	((juvenil$ or child$ or keto$ or labil$ or britt$) adj diabet$).tw.	2 970
		9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	72 329
		10	exp Injections/	221 177
		11	exp Infusion Pumps/	9 957
		12	(infusion$ or injection$).mp. or CSII.tw. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	687 853
Medline		13	10 or 11 or 12	696 332
		14	exp Insulin/	140 678
		15	insulin$.tw.	219 568
		16	14 or 15	249 600
		17	13 and 16	32 169
		18	9 and 17	6 882
Medline		19	exp Clinical Trial/	625 069
		20	clinical trial.pt.	465 191
		21	random$.tw.	497 620
		22	(doubl$ or singl$ or trebl$).mp. and blind$.tw. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	114 130
		23	exp Randomised Controlled Trial/	298 721
		24	19 or 20 or 21 or 22 or 23	906 018
Medline		25	18 and 24	1 447
		26	limit 25 to (English language and yr="1990 -Current")	1 125
		27	limit 26 to yr="2007 -Current"	253
		28	sensor augmented pump.mp.	9
		29	27 and 28	5
		30		
Total citations				1
Total non-duplicate citations				1

7.2.1.13 Evidence Matrix

HbA_{1c}

Q 7.2	How effective are modern CSII versus MDI at reducing HbA_{1c}?	
Evidence statement	Across all individuals with type 1 diabetes, Level I evidence demonstrates a small but statistically significant reduction in HbA_{1c} with CSII compared to MDI. Level II evidence shows that CSII has a minor benefit for HbA_{1c} levels compared to MDI.	
Evidence base	C	One good-quality systematic review (Level I) was identified, but the study was based on Level II studies with a moderate to high risk of bias. Also, the systematic review included evidence with pumps that are now obsolete. The systematic review undertaken for these guidelines was updated and was limited to modern pumps; however, many of the included studies had a moderate risk of bias.
Consistency	B	The included studies were fairly consistent in relation to changes in HbA_{1c}, showing a statistical difference in favour of CSII.
Clinical impact	D	The accuracy of HbA_{1c} measurement is 0.2%; hence, the magnitude of the observed changes in adults was within the bounds of measurement error, but this was not the case for children and adolescents younger than 18 years.
Generalisability	B	The meta-analysis conducted for the current systematic review included 697 patients. However, the individual studies were small, and the total sample for children younger than 5 years was very small. Exclusions included severe hypoglycaemia, hypoglycaemia unawareness and complications of diabetes.
Applicability	B	No studies were conducted in Australia. However, all studies were undertaken in countries with an established health-care system.
Other factors	A systematic search of the literature for published economic evaluations of insulin pumps found that pumps are typically only cost effective when the magnitude of change in HbA_{1c} is at least 0.51%. This sensitivity analysis is modelled on reductions in consequent diabetes complications over a lifetime horizon. A second cost-effectiveness analysis was based on the incremental costs per severe hypoglycaemia attack avoided over 6 years.	

Hypoglycaemia

Q7.2	How effective are modern CSII versus MDI at reducing hypoglycaemia?	
Evidence statement	There is no evidence to support a reduction in hypoglycaemia in adults. There is Level I evidence of a slight, but statistically significant increase in mild hypoglycaemia in children using CSII. There is no statistically significant evidence to support a reduction in severe and nocturnal hypoglycaemia in adults and children.	
Evidence base	C	One good-quality systematic review (Level I) was identified, but the study was based on Level II studies with a moderate to high risk of bias. Also, the systematic review included evidence with pumps that are now obsolete. The systematic review undertaken for these guidelines was updated and was limited to modern pumps; however, many of the included studies had a moderate risk of bias.
Consistency	C	Definitions of hypoglycaemia varied between studies, making comparisons difficult. In one systematic review, an evaluation of individual studies indicated no difference in nonsevere hypoglycaemia between groups, and a tendency towards less severe hypoglycaemia in the CSII group. In two other reviews, a meta-analysis of studies showed no difference between groups in relation to severe hypoglycaemia. In one systematic review, a meta-analysis of studies showed significantly more episodes of hypoglycaemia in children treated with CSII.
Clinical impact	D	The clinical impact is unclear.
Generalisability	B	The meta-analysis conducted for the current systematic review included 697 patients. However, the individual studies were small, and the total sample for children younger than 5 years was very small. Some of the studies included in this systematic review had hypoglycaemia unawareness and one or more recent severe hypoglycaemia episodes as exclusion criteria.

Applicability	B	No studies were conducted in Australia. However, all studies were undertaken in countries with an established health-care system.
Other factors	A systematic search of the literature for published economic evaluations of insulin pumps found that pumps are typically only cost effective when the magnitude of change in HbA_{1c} is at least 0.51%. This sensitivity analysis is modelled on reductions in consequent diabetes complications over a lifetime horizon. A second cost-effectiveness analysis was based on the incremental costs per severe hypoglycaemia attack avoided over 6 years.	

CSII, continuous subcutaneous infusion pumps; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections

Notes: MDI is defined as three injections per day for adults, and three or more injections per day for children and adolescents; modern pumps are defined as those that are available in Australia or overseas and are not obsolete.

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Quality of life

Q7.2	How effective are modern CSII versus MDI at improving QoL?	
Evidence statement	Level II evidence shows an improvement in QoL with CSII compared to MDI. Level II evidence consistently shows improved treatment satisfaction with CSII compared to MDI.	
Evidence base	C	One good-quality systematic review (Level I) was identified, but the study was based on Level II studies with a moderate to high risk of bias. Also, the systematic review included evidence with pumps that are now obsolete. The systematic review undertaken for these guidelines was updated and was limited to modern pumps; however, many of the included studies had a moderate risk of bias. QoL was poorly reported, and was measured using a variety of instruments. Results were not pooled.
Consistency	D	The results of the Level II studies were inconsistent in relation to QoL: • 7 studies (n=425) found statistical difference in favour of CSII • four studies (n=85) found no statistical differences between MDI and CSII. The results of the Level II studies were consistent where: • PedsQL was used • treatment satisfaction was measured.
Clinical impact	D	The clinical impact is unclear.
Generalisability	B	The meta-analysis conducted for the current systematic review included 697 patients. However, the individual studies were small, and the total sample for children younger than 5 years was very small.
Applicability	B	No studies were conducted in Australia. However, all studies were undertaken in countries with an established health-care system.
Other factors	A systematic search of the literature for published economic evaluations of insulin pumps found that pumps are typically only cost effective when the magnitude of change in HbA_{1c} is at least 0.51%. This sensitivity analysis is modelled on reductions in consequent diabetes complications over a lifetime horizon. A second cost-effectiveness analysis was based on the incremental costs per severe hypoglycaemia attack avoided over 6 years.	
Recommendation		
R7.2	Nonsensor-augmented CSII should be considered for use in individuals in whom the expected magnitude of benefit is clinically significant in terms of reducing HbA_{1c}, reducing hypoglycaemia or improving QoL (Grade C).	

CSII, continuous subcutaneous infusion pumps; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections; PedsQL, Pediatric Quality of Life Inventory; QoL, quality of life

Notes: MDI is defined as three injections per day for adults, and three or more injections per day for children; modern pumps are defined as those that are available in Australia or overseas and are not obsolete; QoL is defined as DQoL, SF–36 or others.

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

7.2.2 Cost of treatment with CSII pumps versus MDI

Question 7.2 (iii)
What are the cost (upfront plus ongoing) and cost-effectiveness of treatment with CSII pumps versus MDI?
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections

This section of the report covers clinical question 7.2 (ii), which compares the cost and cost-effectiveness of treating type 1 diabetes with continuous subcutaneous insulin infusion (CSII) pumps and multiple daily injections (MDI).

7.2.2.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 7.34.

Table 7.34 Criteria for determining study eligibility, question 7.2 (ii)

Study design	Existing HTA reports, published economic evaluations
Population	Children and adults with type 1 diabetes
Intervention	CSII – modern pumps
Comparator	MDI – at least three injections (adults) or at least two injections (children)
Outcomes	Cost and cost-effectiveness

CSII, continuous subcutaneous insulin infusion; HTA, health technology assessments; MDI, multiple daily injections

7.2.2.2 Assessment of study eligibility

A total of 15 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with 10 publications excluded (see Table 7.35). A total of 5 publications remained. A systematic review by Campbell et al (2008), identified in the review of clinical effectiveness of CSII versus MDI (see Chapter 15 of this report), reports on four of these studies, as shown in Table 16.3. The full-text version of the review by Campbell et al (2008), and the remaining study by St Charles et al (2009), were retrieved and reviewed. The same exclusion criteria were then applied to these full-text articles, with both publications meeting the inclusion criteria.

7.2.2.3 Literature search summary

Table 16.2 shows the results of the literature search for question 7.2 (ii).

Table 7.35 Search results, question 7.2 (iii)

Stage	Notes	Number
Search summary	Manual	1
	Medline and EMBASE	15
Duplicates	Duplicates identified	0
Identified	Total identified	16
Exclusion criteria	Wrong study type (Not HTA report or economic evaluation)	8
	Wrong population (Not in children or adults with type 1 diabetes)	0
	Wrong intervention (Not CSII vs MDI)	2
	Wrong outcome (Not cost or cost-effectiveness)	0
	Not in English	
	Total excluded	10
Meeting criteria	Total meeting inclusion criteria	6
Included	Total included studies	6

7.2.2.4 Included studies

The literature search identified two publications, describing five economic evaluations, which met the inclusion criteria for this question (Campbell et al 2008; St Charles et al 2009).

7.2.2.5 Characteristics of included studies

The main characteristics of the studies are summarised in Table 7.36.

The systematic review undertaken by Campbell et al (2008) for the New Zealand Ministry of Health was an update of the National Health Service (NHS) technology assessment report (Colquitt et al 2004), which had informed the National Institute for Clinical Excellence (NICE) guidance for use of CSII in diabetes. The authors used a systematic method of searching, study selection, data extraction and appraisal. NHMRC dimensions of evidence, levels of evidence and quality assessment criteria were used to evaluate each of the included studies. The search strategy for economic evaluations identified a total of four relevant publications. All four studies were also identified by our search. All of the analyses were taken from the perspective of the health-care funder. All studies were in patients with type 1 diabetes, with one study, Cohen et al (2007), including a separate analysis in both adolescents and adults.

Campbell et al (2008) also reported on their analysis of the cost-effectiveness of CSII compared with MDI for a patient with type 1 diabetes. The economic model used by the authors was based on the method and approach presented in the NICE report, with some modifications to inputs, to suit New Zealand data, where possible. The authors presented the additional costs associated with CSII, the health benefits of CSII, the cost-effectiveness of CSII versus MDI, and sensitivity analyses.

Cohen at al (2007) published an economic evaluation of CSII versus MDI in Australian adults and adolescents, from the perspective of the health-care provider. The evaluation was a modelling analysis using the health economic model (IMS CORE Diabetes Model) to determine incremental cost-effectiveness, using a lifetime horizon. Patient baseline characteristics were taken from the Australian National Diabetes Information Audit and Benchmarking (ANDIAB) in Australia, a meta-analysis by Weissberg-Benchell et al (2007), and the Diabetes Control and Complications Trial (DCCT) secondary intervention cohort. The

adult cohort had a mean age of 43.3 years, mean duration of diabetes 17.2 years, and mean glycated haemoglobin (HbA_{1c}) of 8.2%. The adolescent cohort had a mean age of 17.1 years, mean duration of diabetes 6.3 years, and mean HbA_{1c} of 8.9%. Base-case data inputs were taken from the Weissberg-Benchell (2007) meta-analysis, with reduction in HbA_{1c} of 1.2% and no difference in number of hypoglycaemic events. Sensitivity analyses were undertaken.

St Charles et al (2009) aimed to evaluate the projected long-term cost-effectiveness of CSII versus MDI. The authors used the IMS CORE Diabetes Model to determine the incremental cost-effectiveness of CSII compared with MDI, in Canadian adults with type 1 diabetes, from the perspective of the health-care provider. They used a theoretical sample based on data from the DCCT secondary intervention group. Data points for base-case analysis were taken from the 2007 meta-analysis by Weissberg-Benchell (2007), as above. The simulation time horizon was set to 60 years, to capture the remainder of a lifetime of a patient with type 1 diabetes. A discount rate of 5.0% per annum on costs and clinical outcomes was used. Sensitivity analyses were undertaken.

Table 7.36 Characteristics of included studies

Reference	Study type	Studies included	Model population	Intervention	Comparator	Time horizon
Campbell et al (2008)	Systematic review	Scuffham and Carr (2003)	Adults with type 1 diabetes	CSII	MDI	8 years
		Roze 2004	Adults with type 1 diabetes United Kingdom	CSII	MDI	Lifetime
		Colquitt 2004	Adults with type 1 diabetes	CSII	MDI	4 years
		Cohen 2007	Adults and adolescents with type 1 diabetes Australia	CSII	MDI	Lifetime
		Campbell 2008 Economic evaluation	Adults with type 1 diabetes New Zealand	CSII	MDI	6 years
St Charles et al (2009)	Economic evaluation		Adults with type 1 diabetes Canada	CSII	MDI	Lifetime

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections

7.2.2.6 Results of included studies

Campbell et al 2008 – systematic review

Campbell et al (2008) found that all four studies reported results favouring insulin pump therapy; they therefore concluded that CSII could be a worthwhile investment. Two of the evaluations reached their conclusion based on a cost–utility analysis that incorporated a reduction in diabetic complications and mortality as a result of improved glycaemic control with CSII (Roze et al 2005; Cohen et al 2007). Scuffham and Carr (2003) also conducted a cost–utility analysis, based mainly on a reduction in severe hypoglycaemic events. Finally, the NHS assessment conducted for NICE (Colquitt et al 2004) reported cost-effectiveness as costs per severe hypoglycaemic events avoided. The cost per quality-adjusted life year (QALY) is not reported in this assessment. However, it is clear from the results of the

sensitivity analyses that the model results are reasonably dependent upon the model parameters associated with severe hypoglycaemic event rate and %HbA_{1c}.

Table 7.37 Results from Campbell et al (2008) – costs and clinical outcomes

Reference	Base-case results	Sensitivity analyses: HbA_{1c}	Sensitivity analyses: severe hypoglycaemic event rate
Scuffham and Carr (2003)	£11 338 per QALY	Not incorporated in the model	Base-case: 0.404 Sensitivity: 0.1=£13 766
Roze et al (2005)	£25 648 per QALY	Base-case: –1.2% Sensitivity: –0.51% =£61 564	Base-case: no difference Sensitivity: 50% reduction =£20 104
Colquitt et al (2004)	£1 305–1 526 cost per severe hypoglycaemic event avoided	-	-
Cohen et al (2007)	Adult: A$74 147 per QALY Adolescent: A$74 661 per QALY	Base-case (adult): –1.2% Sensitivity: –0.51% =A$124 201	

HbA_{1c}, glycated haemoglobin; QALY, quality-adjusted life year

Campbell et al (2008) – economic evaluation for New Zealand setting

In the analysis undertaken by Campbell et al (2008), cost-effectiveness was reported as the incremental cost per severe hypoglycaemic attack avoided over 6 years (i.e. the lifetime of the pump). The authors presented incremental costs associated with the introduction of CSII over 6 years.

Table 7.38 Results from Campbell et al (2008) – incremental costs associated with the introduction of CSII over 6 years

Item	Incremental cost
Insulin pump	$5625
Consumables	$10 800
Additional general patient management	$69
Additional patient education	$2203
Reduction in insulin usage	($1332)
Reduction in treatment costs for severe hypoglycaemic events	($371)
Total incremental cost over 6 years (undiscounted)	$16 993
Total incremental cost over 6 years (discounted)* *Discount rate of 5% applied	$15 976

The authors postulate that CSII reduces the number of severe hypoglycaemic events compared with MDI; however, they point out that the evidence to support this hypothesis is equivocal. They therefore suggest that the cost-effectiveness they report be considered as indicative only. The following table presents the incremental cost per severe hypoglycaemic attack avoided per patient annum, over a 6-year time horizon.

Table 7.39 Results from Campbell et al (2008) – cost savings associated with reduction in number of severe hypoglycaemic events

	Number of severe hypoglycaemic events avoided per patient per year							
	0.10	0.20	0.30	0.40	0.50	0.60	0.70	1
Incremental *cost*-effectiveness ratio	$30 533	$15 236	$10 137	$7587	$6057	$5037	$4309	$2998

Campbell et al (2008) noted some limitations of this economic evaluation, namely that the analysis does not capture any quality of life gain associated with the use of pump over MDI. Additionally the model used did not capture the small improvement in glycaemic control (HbA_{1c}) over MDI (0.37% improvement in HbA_{1c}) found in their review of clinical effectiveness. In the base-case it would cost a total of NZ$16 000 if this benefit were to be maintained over 6 years. They also note the economic model does not include any reduction in the long-term complications of diabetes that may occur due to improved glycaemic control, and their associated costs, quality of life, and survival implications. The authors suggest referring to the sensitivity analyses of Cohen et al (2007) and Roze et al (2005) that reported the lifetime cost per QALY, which would be expected with a change in HbA_{1c} of this magnitude. This exceeds NZ$100 000.

Cohen et al (2007)

Annual costs of CSII and MDI in Australia were reported by Cohen et al as below.

Table 7.40 Annual costs (A$) of CSII and MDI in Australia – Cohen et al (2007)

Resource	CSII – adults	MDI – adults	CSII – adolescents	MDI – adolescents
Pump (based on lifespan of 8 years)	987.50		987.50	
Insulin	1174.99	1334.33	1001.03	1136.79
Consumables	2761.83	401.50	2761.83	401.50
Self monitoring	1326.41	1326.41	1326.41	1326.41
Medical professional assistance	1036.20	326.80	1036.20	326.80
Total: year 1	7286.93	3389.04	7112.96	3191.50
Total: year 2 beyond	6577.53	3389.04	6403.58	3191.50

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections

The mean discounted lifetime direct medical costs associated with CSII in Australian adults was projected to be $A123 402 ±2113 compared with MDI $A88 760 ±2055. And in adolescents $A148 918 ±2498 compared with MDI $A107 139 ±2320. The authors report the incremental difference in costs of A$34 642 translated into a cost per life-year gained (LYG) of $A88 220 with CSII versus MDI in adults, and in the incremental difference of A$41 779 translated into a cost per LYG of $A77 851. These results are both near the threshold value of $A76 000/LYG considered to represent good value for money in Australia. The results

were sensitive to changes in HbA_{1c} and rate of hypoglycaemic events with incremental cost-effectiveness ratios (ICERs) reported as below.

Table 7.41 Incremental costs (A$) of use of CSII in Australia – Cohen et al (2007)

HbA_{1c}	–1.2% base-case	–0.91%	–0.51%
ICER – adult	74 147	97 297	124 201
ICER – adolescent	74 661	97 238	114 818
Reduction in hypoglycaemic events (%)	50	75	
ICER – adult	63 537	57 936	
ICER – adolescent	62 950	56 472	

CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; ICER, incremental cost-effectiveness ratio

The authors conclude that the results suggest that CSII is associated with ICERs in the range of $A53 022–$259 646 per QALY gained, with most ICERs representing good value for money in Australia under the majority of scenarios explored. The authors point out some limitations including the fact that a large number of studies in the Weissberg-Benchall meta-analysis were published prior to 1987, representing data on older insulin device technology. A second limitation is the base-case analysis does not take into account non-medical costs such as loss of productivity, and so may have underestimated total costs from a complete societal perspective. A further limitation of modelling studies is that the data used to design most models are primarily from clinical trials, and as such miss many real-life factors such as compliance, effectiveness and treatment withdrawal rates.

St Charles et al (2009)

The mean direct lifetime costs were C$15 591 higher with CSII treatment than MDI. Treatment with CSII was associated with an improvement in discounted life expectancy of 0.655 QALYs over a 60-year time horizon, compared with MDI. ICERs were C$27 797 per QALY for CSII compared with MDI. The results were most sensitive to HbA_{1c} assumptions.

Table 7.42 Results from St Charles et al (2009)

Variable	CSII	MDI	Difference	ICER
Life expectancy, mean (SD), year	14.562 (0.146)	13.990 (0.114)	0.572	
Quality-adjusted life expectancy, mean (SD), year	10.029 (0.133)	9.374 (0.076)	0.655	
Total direct costs, mean (SD), year – 2006 C$	162 807 (3544)	147 216 (3462)	15 591	
Ratio of difference in costs to difference in life expectancy, year – 2006 C$ per life year gained				27 264
Ratio of difference in costs to difference in QALY, year 2006 C$ per QALY gained				23 797
Sensitivity analysis – HbA_{1c} (base-case –1.2%)				–0.15% $50 768/ QALY
Sensitivity analysis – hypoglycaemia (base-case – no difference)				50% less in CSII (20 570) 75% less in CSII (18 696)

C$, Canadian dollars; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; ICER, incremental cost-effectiveness ratio; MDI, multiple daily injections; QALY, quality-adjusted life year; SD, standard deviation;

The authors concluded that CSII may be a cost-effective medical intervention, compared with MDI, for the treatment of adult patients with type 1 diabetes in Canada.

7.2.2.7 Discussion and conclusion

Campbell et al (2008) present cost-effectiveness as the incremental cost per severe hypoglycaemic attack avoided over 6 years. The analysis projects costs saved per severe hypoglycaemic attack, but the authors note that the current evidence regarding reduction in severe hypoglycaemic events in patients treated with CSII compared to MDI is equivocal. The total additional costs of using CSII relative to improvements seen in glycaemic control, and the reduction in consequent diabetic complications, have been considered and modelled by Cohen et al (2007), Roze et al (2005) and St Charles (2009), based on a lifetime horizon. All three studies used a base-case of a 1.2% reduction in HbA_{1c} in the patients treated with CSII compared to MDI. All three also presented sensitivity analyses based on a reduction of HbA_{1c} of 0.51%, which is much closer to the reduction of HbA_{1c} of 0.2% reported in the systematic review of the clinical effectiveness of CSII versus MDI associated with this report.

7.2.2.8 Literature search strategy

The search was conducted on 13 May 2010. Studies published after this time were not eligible for inclusion in the systematic review. The search strategy is shown in Table 7.43. A total of 15 citations were identified.

Table 7.43 Search strategy, question 7.2 (ii)

Database	Date searched	#	Search terms	Citations
Medline and EMBASE	1990 – 13 May 2010	1	Diabetes Mellitus, type 1/	26 832
		2	(continuous subcutaneous insulin infusion or CSII) or (insulin pump therapy or IPT)	1 322
		3	Cost-Benefit Analysis/ or cost effectiveness analysis or economic evaluation or health economics or cost minimization analysis or cost utility analysis or Quality-Adjusted Life Years/ or quality adjusted life year or Quality-Adjusted Life Years/ or qaly or life year saved	36 419
		4	#1 and #2 and #3	15
Total citations				15
Total non-duplicate citations				15

7.3 Comparison of metformin plus insulin and insulin alone

Question 7.3

How effective is metformin plus insulin versus insulin alone at glycaemic control (achieving HbA1c) targets and reducing insulin requirement?

HbA_{1c}, glycated haemoglobin

The potential role of adjunctive therapy in type 1 diabetes is to improve insulin action, and make it easier for individuals with type 1 diabetes to achieve and maintain 'better' metabolic control (Jefferies et al 2004). Metformin is a biguanide that is commonly used in the treatment of type 2 diabetes. It lowers glucose by reducing hepatic glucose production (i.e. it inhibits gluconeogenesis) and increasing insulin-stimulated glucose uptake in skeletal muscle and adipocytes. Since the effect of metformin on glucose metabolism is independent of residual β-cell activity, the drug may have potential for use in patients with type 1 diabetes (Jacobsen et al 2009).

This systematic review reports on the evidence on the effect of metformin plus insulin versus insulin alone at achieving glycated haemoglobin (HbA_{1c}) targets and reducing insulin requirement.

7.3.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 7.44

Table 7.45 Criteria for determining study eligibility, question 7.3

Study design	A systematic review or meta-analysis (Level I evidence) or RCTs (Level II evidence) of at least three months duration
Population	Person with type 1 diabetes
Intervention	Metformin added to insulin therapy
Comparator	Insulin alone
Outcomes	Changes in HbA_{1c} Change in insulin requirements Change in body weight Adverse effects

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

7.3.2 Literature search

The search strategy for Medline is shown in Table 7.5. This search strategy was adapted slightly for the other databases. A total of 439 non-duplicate citations were identified.

Table 7.46 shows the number of publications identified at different stages of the search.

Table 7.46 Search results, question Table 7.47

Stage	Notes	Number
Search summary	Manual	0
	Cochrane Library	0
	EMBASE	374
	Medline	80
Duplicates	Duplicates identified	24
Exclusion criteria	Wrong study type (not a systematic review or meta-analysis or RCT)	
	Wrong population (not in individuals with type 1 diabetes)	
	Wrong intervention (does not evaluate the correct intervention [metformin added to insulin therapy])	
	Wrong outcome (does not report changes in HbA_{1c} or changes in insulin requirement)	
	Not in English (non-English publications will not be included)	
	Total excluded	430
Meeting criteria	Total meeting inclusion criteria	9
Included	Total included studies	1

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

7.3.3 Included studies

A total of nine publications remained, and the full-text version of each publication was retrieved and reviewed. Three systematic reviews (Pang and Narendran 2008; Abdelghaffar and Attia 2009) and six RCTs (Meyer et al 2002; Hamilton et al 2003; Särnblad et al 2003; Khan et al 2006; Lund et al 2008; Jacobsen et al 2009) met the inclusion criteria. All of the RCTs identified in the literature search and the identified systematic reviews were identified by Vella et al (2010). Therefore, only this publication is presented in the results section of this report.

7.3.4 Characteristics of included studies

The systematic review and meta-analysis by Vella et al (2010) aimed to capture all published data from RCTs that involved using metformin in people of any age with type 1 diabetes. In total, nine RCTs were included in that review. For formal meta-analysis, only the five studies listed in Table 7.48 reported the necessary means and standard deviations for insulin dose and HbA_{1c}.

Table 7.48 Details of studies included in meta-analysis, question 7.3

Study	Country	Mean age (years)	Number of patients randomised (completed)	Duration in months	HbA_{1c} (%) at baseline
Meyer et al (2002)	France	41	62 (59)	6	7.6
Hamilton et al (2003)	Canada	16 (adolescents)	30 (27)	3	9.4 (MF) 8.9 (PL)
Särnblad et al (2003)	Sweden	17 (adolescents)	30 (26)	3	9.3
Lund et al (2008)	Denmark	46	100 (92)	12	9.5
Jacobsen et al (2009)	Denmark	40	24 (23)	6	8.9 (MF) 9.3 (PL)

MF, metformin; PL, placebo

7.3.5 Results of included studies

Vella et al (2010)

In Vella et al (2010), analysing all five studies, the overall effect on %HbA_{1c} was a standardised mean difference between treatment groups of −0.10 (i.e. 0.10 standardised units lower in the metformin group, 95% confidence interval [CI]: standardised mean difference reduction of –0.36 to 0.15, p=0.42). This translates into an absolute difference of 0.11 units lower in the metformin than in the placebo groups (not statistically significant).

As there was some suggestion of heterogeneity (p=0.175), the authors carried out a sensitivity analysis of the four smaller and shorter studies. Excluding the largest study (Lund et al 2008), the overall effect on %HbA_{1c} was a standardised mean difference between treatment groups of −0.30 (i.e. 0.30 standardised units lower in the metformin group; 95%CI: standardised mean difference of −0.64 to 0.037, p=0.081). This translates into an absolute difference of 0.28 units lower %HbA_{1c} (not statistically significant) in the metformin than in the placebo groups, with little evidence of heterogeneity (p=0.353).

All five studies showed a reduction in daily insulin dose with metformin, with the overall measure of effect being a standardised mean difference between treatment groups of –0.65 (i.e. 0.65 standardised units lower in the metformin group; 95%CI: standardised mean difference of –0.92 to –0.39 units, p<0.001). This translates into an absolute difference in insulin dose requirement of 6.6 units/day lower in the metformin than placebo groups. The χ2 test of heterogeneity was not statistically significant (p=0.41), with most of the information coming from the Lund et al (2008) study.

A similar sensitivity analysis of the four smaller and shorter studies, excluding Lund et al (2008), confirmed a reduction in daily insulin dose with metformin, with the overall measure of the treatment effect being a standardised mean difference between treatment groups of −0.55 (i.e. 0.55 standardised units lower in the metformin group; 95%CI: standardised mean difference of −0.90 to −0.21 units, p=0.002). This translates into an absolute difference of 7.16 units/day lower in the metformin than in the placebo groups. The χ2 test of heterogeneity was not statistically significant (p=0.365), with most of the information coming from Meyer et al (2002).

The seven studies were of sufficient duration to report data on changes in weight or body mass index (BMI) (weight baseline characteristics are given in Table 7.49, below). Metformin reduced weight by 1.7–6.0 kg in three studies (Walravens et al 2000; Lund et al 2008; Jacobsen et al 2009), but not in three other studies (Meyer et al 2002; Särnblad et al 2003; Khan et al 2006). A sustained and statistically significant reduction (mean 1.74 kg) was reported in the largest study, which was also of the longest duration (Lund et al 2008).

Table 7.49 Weight at baseline

Study	Mean weight (kg)	Daily dose metformin (mg)
Gin et al (1985)	62	1700
Keen et al (1987)	84	1500
Walravens et al (2000)	68	1000
Meyer et al (2002)	76	1700
Hamilton et al (2003)	63 (MF) 71 (PL)	Up to 2000 (weight-dependent)
Särnblad et al (2003)	68	Forced titration to 2000
Khan et al (2006)	92	Forced titration to 2550
Lund et al (2008)	80	Forced titration to 2000
Jacobsen et al (2009)	90	Forced titration to 2000

MF, metformin; PL, placebo
Source: Vella et al (2010)

There was insufficient data on weight for the authors to conduct a formal meta-analysis of this outcome.

7.3.6 Discussion

A predicted associated decrease in weight gain with lowering of required insulin doses was seen in the largest and longest trial (Lund et al 2008), which was twice the duration of any other study. A reduction in weight was also reported over 6 months' treatment in the most recently published study (Jacobsen et al 2009), in which use of a specific algorithm for insulin titration resulted in a mean dose reduction of 20%.

In terms of adverse effects, there was a statistically significant increase in hypoglycaemic events with metformin therapy in two studies (Hamilton et al 2003; Jacobsen et al 2009). Furthermore, although the largest trial did not report increased rates of metformin-associated major or minor hypoglycaemia, there were significantly more major hypoglycaemic events leading to unconsciousness among metformin-treated individuals with type 1 diabetes (Lund et al 2008). No reports of lactic acidosis were associated with metformin therapy. Rates of gastrointestinal adverse effects were systematically reported in only two studies (Lund et al 2008; Jacobsen et al 2009), with rates being similar in metformin and placebo groups in the largest study (metformin: n=43; placebo: n=39; p=0.310) (Lund et al 2008).

The authors concluded that, even with this weak evidence, physicians contemplating a recommendation of metformin therapy for patients with type 1 diabetes should advise the patients carefully about insulin dose adjustment and blood glucose monitoring.

7.3.7 Conclusion

The literature search identified three systematic literature reviews and six RCTs comparing metformin and placebo. All these studies were captured by Vella et al (2010). This paper found nine RCTs of metformin therapy in type 1 diabetes, two of which were small and experimental (Gin et al 1985; Keen et al 1987). There were only 192.8 patient years of randomised follow-up in the literature. Reflecting the lack of evidence underpinning metformin in type 1 diabetes, the recent publication by Lund et al (2008) doubled the available patient years of randomised follow-up. Other limitations were that not all studies

provided treatment effects derived by the authors from absolute units of outcome as baseline values, and that the magnitude of treatment effect can be influenced by differences in entry criteria between trials (e.g. for HbA_{1c}).

Overall, the mean difference in HbA_{1c} was −0.10 (95%CI: –0.36 to 0.15, p=0.42). A sensitivity analysis excluding Lund et al (2008) showed a mean difference of −0.30 (95%CI: −0.64 to 0.037, p=0.081). This translates into an absolute difference of 0.28 units lower $\%HbA_{1c}$ (not statistically significant) in the metformin groups compared to the placebo groups.

Therefore, there was no evidence of a statistically significant change in HbA_{1c} when metformin was compared with placebo.

The mean difference in daily insulin dose with metformin was –0.65 (i.e. 0.65 standardised units lower in the metformin group; 95%CI: standardised mean difference of –0.92 to –0.39 units, p<0.001). A sensitivity analysis excluding Lund et al (2008) confirmed a reduction in daily insulin dose with metformin, with a mean difference of –0.90 to –0.21 units, p=0.002). The $\chi 2$ test of heterogeneity was not statistically significant (p=0.365).

A predicted associated decrease in weight gain with lowering of required insulin doses was seen in the largest and longest trial (Lund et al 2008), which was twice the duration of any other study. A reduction in weight was also reported over 6 months' treatment in the most recently published study (Jacobsen et al 2009), in which use of a specific algorithm for insulin titration resulted in a mean dose reduction of 20%.

7.3.8 Literature searches

Table 7.50 Search strategy, question 7.2 (iii)

Database	Date searched	#	Search terms	Citations
Medline	22 February to 4 March 2010	1	Diabetes Mellitus, type 1/	51 874
		2	(LADA or latent autoimmune diabetes mellitus).mp. (mp=title, original title, abstract, name of substance word, subject heading word, unique identifier)	295
		3	1 or 2	51 968
		4	(metformin and insulin).mp. (mp=title, original title, abstract, name of substance word, subject heading word, unique identifier).	3 234
		5	3 and 4	110
		6	Limit 5 to English language	80
Cochrane	22 February to 4 March		(search strategy above adapted for Cochrane database)	9
EMBASE	22 February to 4 March		(search strategy above adapted for EMBASE database)	374
Manual search				0
Total citations				463
Total non-duplicate citations				439

7.3.9 Evidence Matrix

HbA_{1c}

Q7.3	How effective is metformin plus insulin versus insulin alone at achieving HbA_{1c} targets?	
Evidence statement	Level I evidence demonstrates a small but not statistically significant reduction in HbA_{1c} with metformin plus insulin compared to insulin alone.	
Evidence base	C	One systematic review was identified that included nine RCTs (with a meta-analysis of five of the RCTs). Change in HbA_{1c} was an outcome reported in the meta-analysis.
Consistency	B	Most studies reporting this outcome were consistent. The authors of the systematic review conducted a sensitivity analysis of the four smaller RCTs, excluding the largest RCT because of issues of heterogeneity. The outcome was confirmed in both analyses.
Clinical impact	D	Benefit is small and therefore will have a restricted impact on clinical management. In addition, due to the small sample size, safety could not be adequately addressed.
Generalisability	B	Adults.
	C	Children and adolescents (the evidence base is limited by age and weight, and there is no evidence in children under 16 years of age).
Applicability	B	There were no studies from Australia; however, all the studies were undertaken in countries with an established health-care system.
Other factors	Metformin is not TGA-approved for use in type 1 diabetes, so any current use is off label. There are likely to be issues with compliance, and with safety (especially lactic acidosis). There are no publications on cost effectiveness of metformin in type 1 diabetes, but metformin is a low-cost drug.	

Body-mass index

Q7.3	How effective is metformin plus insulin versus insulin alone at reducing BMI or weight?	
Evidence statement	Level II evidence shows no consistent effect of metformin plus insulin versus insulin alone on reduction in BMI or body weight.	
Evidence base	C	One systematic review was identified that included nine RCTs with a moderate risk of bias; six of these RCTs reported changes in BMI or body weight.
Consistency	D	Metformin plus insulin versus insulin alone was associated with weight loss of 1.7–6.0 kg (mean of 1.74 kg in longest duration study), but three studies found no difference in weight. There were insufficient data on weight for the authors to conduct a formal meta-analysis of this outcome.
Clinical impact	D	Benefit is small and therefore will have a restricted impact on clinical management. In addition, due to the small sample size, safety could not be adequately addressed.
Generalisability	B	Adults.
	C	Children and adolescents (the evidence base is limited by age and weight, and there is no evidence in children under 16 years of age).
Applicability	B	There were no studies from Australia; however, all the studies were undertaken in countries with an established health-care system.
Other factors	Metformin is not TGA-approved for use in type 1 diabetes, so any current use is off-label. There are likely to be issues with compliance, and with safety (especially lactic acidosis). There are no publications on economic populations in type 1 diabetes, but metformin is a low-cost drug.	

BMI, body-mass index; RCT, randomised controlled trial; TGA, Therapeutic Goods Administration

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Insulin requirements

Q7.3	How effective is metformin plus insulin versus insulin alone at reducing insulin requirements?	
Evidence statement	Level I evidence demonstrates a small but statistically significant reduction in insulin requirement with metformin plus insulin compared to insulin alone.	
Evidence base	C	One systematic review that included nine RCTs (with a meta-analysis of five of the RCTs). Insulin dose was an outcome reported in the meta-analysis.
Consistency	A	All five studies reporting this outcome were consistent; overall, they showed a mean reduced insulin requirement of 6.6 U/day. The authors of the systematic review conducted a sensitivity analysis of the four smaller RCTs, excluding the largest RCT because of issues of heterogeneity. The outcome was confirmed in both analyses.
Clinical impact	D	Benefit is small and therefore will have a restricted impact on clinical management. In addition, due to the small sample size, safety could not be adequately addressed.
Generalisability	B	Adults.
	C	Children and adolescents (the evidence base is limited by age and weight, and there is no evidence in children younger than 16 years).
Applicability	B	There were no studies from Australia; however, all the studies were undertaken in countries with an established health-care system.
Other factors	Metformin is not TGA-approved for use in type 1 diabetes, so any current use is off label. There are likely to be issues with compliance, and with safety (especially lactic acidosis). There are no publications on economic populations in type 1 diabetes, but metformin is a low-cost drug.	
Recommendation		
R7.3	Metformin should not be used in routine clinical practice for type 1 diabetes (Grade C).	

RCT, randomised controlled trial; TGA, Therapeutic Goods Administration

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

8 Health Care Delivery

8.1 Ambulatory Care

Question 8.1

What is the effectiveness of ambulatory care versus hospital inpatient care of patients with newly diagnosed disease?

This section of the report examines the efficacy and safety of ambulatory care in the management of children, adolescents and adults at the time of diagnosis of type 1 diabetes. It considers approaches to the initial management of patients diagnosed with type 1 diabetes who are not acutely unwell, including home management, ambulatory care in which initial insulin therapy and education is delivered in an outpatient setting, and hospital inpatient admission.

8.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 8.1.

Table 8.1 Criteria for determining study eligibility, question 8.1

Study design	Any comparative study
Population	Children, adolescents or adults with type 1 diabetes
Intervention	Ambulatory care at diagnosis of type 1 diabetes (including patients with brief hospitalisation)
Comparator	Hospital inpatient care at diagnosis of type 1 diabetes
Outcomes	Metabolic control-HbA_{1c}, complications- DKA, severe hypoglycaemia Diabetes knowledge in parents, adolescents and adults

DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin

8.1.2 Assessment of study eligibility

A total of 271 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with 250 publications excluded, as shown in Table 8.2. A total of 21 publications remained.

8.1.3 Literature search summary

Table 8.2 Search results, question 8.1

Stage	Notes	Number
Search summary	Manual	2
	Cochrane Library	1
	EMBASE	172
	Medline	219
	INAHTA	0
	Total	392
Duplicates	Duplicates identified	121
Identified	Total identified	271

Stage	Notes	Number
Exclusion criteria	Wrong study type (not a comparative study)	47
	Wrong population (not child, adolescent or adult with type 1 diabetes)	16
	Wrong intervention or test (not ambulatory care at diagnosis of type 1)	183
	Wrong comparator (not hospital inpatient care at diagnosis of type 1)	0
	Wrong outcome (not HbA_{1c}, DKA, severe hypoglycaemia, diabetes knowledge)	4
	Not in English (not English language)	0
	Total excluded	250
Meeting criteria	Total meeting inclusion criteria	21
Included	Total included studies	3

8.1.4 Citations for full-text review

Of the 21 full texts reviewed, one was a randomised controlled trial (RCT) in children that compared home care and inpatient care (Dougherty et al 1999). There were also 2 systematic reviews by Clar et al; one of which was an update of a previous study (Clar et al 2003; Clar et al 2007). Most of the studies included in the systematic review were of retrospective cohort design; therefore, the systematic review was designated as Level IV evidence. Several of the full-text studies reviewed were also included in this systematic review. In addition there was one retrospective cohort study in children that met the inclusion criteria (Swift et al 1993). Of the remaining studies, 13 were excluded as being of the wrong study design and 2 were excluded as reporting the wrong outcome. No comparative studies in adults were found that met the inclusion criteria.

8.1.5 Included studies

The included studies were Swift et al (1993), Dougherty et al (1999) and Clar et al (2007).

8.1.6 Characteristics of included studies

Dougherty et al (1999)

The randomised, unblinded, controlled trial of Dougherty et al (1999) was of good quality. It involved 63 consecutive children newly diagnosed with type 1 diabetes, in an emergency department of a paediatric teaching hospital in Montreal, Canada, who were randomised to either home-based care (n=32) or hospital-based care (n=31). Children were eligible for the study if they were over 2 years of age, living at home and within 1 hour of the hospital, and had no sibling with type 1 diabetes. The participants were randomised within 72 hours of diagnosis, with a short admission to hospital for metabolic stabilisation if necessary. Home-based care consisted of insulin treatment and teaching at home by a diabetes nurse educator making one or two visits daily for 2–3 days, with follow-up every 3–4 months in the outpatient clinic. The control group received the same education sessions, and the same treatment team, with an average length of hospitalisation of 4.7 days, and follow-up in the outpatient clinic as per the intervention group. Follow-up measures of HbA_{1c}, diabetes-related adverse events, knowledge of diabetes, adherence to diabetes regime, psychosocial impact and social (total) costs incurred were assessed for 24 months. The severity of diabetes at onset was not described. HbA_{1c} levels were significantly lower in the home-based group at 12, 24 and 36 months. There were no significant differences between groups in diabetes-related adverse events or level of diabetes knowledge. The authors concluded that management for children newly diagnosed with diabetes can result in better metabolic control and similar psychosocial outcomes, compared with hospital-based care.

Clar et al (2007)

The systematic review by Clar et al (2007) included seven comparative studies – mainly of high risk of bias – involving 626 children and adolescents, 298 of whom received ambulatory care at diagnosis either on an outpatient basis or at home or a combination of both. Two of the studies were RCTs (Simell et al 1995; Dougherty et al 1999), but one (Simell et al 1995) was only available as an abstract, and thus did not meet the inclusion criteria. The remaining five studies were of cohort design (Spaulding and Spaulding 1976; Galatzer et al 1982; Chase et al 1992; Siminerio et al 1999; Srinivasan et al 2004). Three of the studies included patients in the outpatient/home group who had been hospitalised for a short period for metabolic stabilisation (Chase et al 1992; Dougherty et al 1999; Srinivasan et al 2004). Follow-up was for up to 5 years, and outcomes included physiological measures of metabolic control, complications reported as hospital admissions and emergency presentations, diabetic ketoacidosis and severe hypoglycaemia, and psychosocial and behavioural measures. One of the included studies found a slightly improved metabolic control at 2 and 3 years follow-up in the ambulatory group (Dougherty et al 1999). No other differences in metabolic control, hospitalisations or acute diabetic complications were found between groups. The authors report the results of this review as inconclusive, due to the generally low quality or limited applicability of the studies identified. The characteristics of the individual studies included in the Clar systematic review (Clar et al 2007), except for the study by Dougherty et al (1999), are summarised in Table 19.3.

Table 8.3 Summary of studies included in Clar et al (2007)[a]

Reference and level	Study type and quality	Treatment duration	Population Country (ethnicity)	Intervention	Comparator	Outcomes
Chase et al (1992) Level IV	Retrospective cohort Poor	4–5 days education at diagnosis, with outcomes measured up to 5 years	n=121 Intervention: n=41 Age: 13.0 ±4.6 vs 12.9 ±4.5 years US	Outpatient education at diagnosis of 4–5 days, with follow-up every 3 months and possible hospitalisation of 1 night Taught sugar-restricted diet	Hospitalisation at diagnosis (mean 4.5 days) Education and follow-up as per intervention group, except taught exchange diet not sugar-restricted diet	HbA_{1c}; hospitalisations; severe hypoglycaemia; ketoacidosis
Galatzer et al (1982) Level IV	Retrospective cohort Poor	Continuous intensive phase lasted 2 months Outcomes measured at the time of the study (3–15 years post diagnosis)	n=223 Age: 7–24 years (mean 15 years – at time of study, not diagnosis) Diabetes severity not described Intervention: n=107 Israel	Outpatient and home care Patient seen daily for first week, then twice per week for 3 weeks, then once per month for 2 months, then every 3 months	Hospitalisation at diagnosis, duration not described Diabetes management not described	Psychosocial

Reference and level	Study type and quality	Treatment duration	Population Country (ethnicity)	Intervention	Comparator	Outcomes
Siminerio et al (1999) Level III	Prospective cohort Poor	Education 3–5 days Outcomes measured at diagnosis and at 1 month	n=32 Diabetes severity not reported Intervention: n=16 Age: mean 10.2 years (range 6–18 years) n=9 male Control: n=16 Age: mean 10.1 (range 6–18) years n=10 male US	Outpatient setting Individualised education, total of 10–12 hours over 3 days Daily telephone calls for at least 1 week post discharge from outpatient program Follow-up at 1 month post diagnosis	Inpatient hospitalisation of 3–5 days Same education and follow-up as per intervention group	Re-admission for DKA or severe hypoglycaemia; knowledge; psychosocial
Spaulding and Spaulding (1976) Level IV	Retrospective cohort Poor	2 weeks; followed for at least 6 months	n=20 (18 matched in pairs, 2 unmatched) Intervention: age 12 ±3 (range 7–19) years n=7 male Control: age 12 ±5 (range 4–20) years n=5 male Canada	Outpatient and home patient attends day care 2–3 times during first 2 weeks post diagnosis; home visits by nurse and daily phone calls	Admission to hospital duration –12 days on average No description of treatment	Composite diabetes score: urine glucose; urine ketones; DKA; hypoglycaemia; hyperglycaemia; blood glucose; costs
Srinivasan et al (2004) Level IV	Cohort study with historic control Fair	Outcomes measured at baseline, 3, 6 and 12 months post diagnosis	n=110 Intervention: n=61 Age: 8.1 (1.1–15.9) years Control: n=49 8.8 (1.2–16.2) years Australia	Outpatient setting; 16 hours of education over 6–8 visits, follow-up at 4–6 weeks post diagnosis, then 3 monthly follow-up	Admission to hospital for 4–7 days Education by same team Follow-up at 3–6 weeks, then every 3 months	Parental diabetes knowledge; HbA_{1c}; hospital stays; psychosocial

[a] Excluding Dougherty et al (1999)

Swift et al (1993)

The study by Swift et al (1993) was a retrospective cohort study of poor quality, involving the analysis of patient records over 10 years. The study included children aged under 15 years diagnosed with type 1 diabetes and referred to consultants in Leicestershire, United Kingdom. During this period, 236 children were diagnosed with diabetes, with 138 managed in the home or outpatient setting. The age, sex or severity of diabetes at diagnosis was not reported. Significantly fewer children who received management at home were re-admitted for diabetes-related reasons (p=0.004). There was no difference between the groups in metabolic control as measured by HbA_{1c}.

8.1.7 Results of included studies

Metabolic control

One study reported a significant difference in HbA_{1c} between the groups, with the ambulatory care group having a lower HbA_{1c} (of 0.7%) at 2 years and 3 years duration (Dougherty et al 1999). Three other studies that reported HbA_{1c} found no statistical difference between groups (Chase et al 1992; Swift et al 1993; Srinivasan et al 2004).

Table 8.4 Glycaemic control

Reference	HbA_{1c} ambulatory care	HbA_{1c} inpatient care	Statistical significance
Chase et al (1992)	1 year (n=37) 10.7 ±2.4 5 years (n=37) 11.5 ±2.1	1 year (n=76) 11.0 ±1.8 5 years (n=76) 11.4 ±1.7	NS NS
Dougherty et al (1999)	(n=32) baseline: 10.8 ±2.5 1 month: 7.5 ±1.6 2 years: 6.1 ±1.3 3 years: 6.4 ±1.4	(n=31) baseline: 10.0 ±2.0 1 month: 6.6 ±1.0 2 years: 6.8 ±1.3 3 years: 7.1 ±1.3	 NS NS p<0.05 p<0.02
Srinivasan et al (2004)	(n=61) 3 months: 8.1 (95%CI: 6.8 to 9.9) 6 months: 8.0 (95%CI: 6.9 to 9.0) 12 months: 8.3 (95%CI: 6.7 to 9.6)	(n=49) 3 months: 8.3 (95%CI: 7.1 to 9.9) 6 months: 8.0 (95%CI: 6.0 to 9.6) 12 months: 8.3 (95%CI: 6.5 to 10.0)	 NS NS NS
Swift et al (1993)	10.2%	10.1%	NS

CI, confidence interval; NS, not significant

Adverse events

Four studies reported adverse events in terms of hospital admissions and emergency admissions, with three reporting no significant difference between the groups (Chase et al 1992; Swift et al 1993; Srinivasan et al 2004). One study reported a significant difference between groups in diabetes-related re-admissions, with the ambulatory care group having significantly fewer admissions post diagnosis (p=0.004) (Swift et al 1993).

Diabetic ketoacidosis

Two studies reported episodes of diabetic ketoacidosis; both found no significant differences between the groups (Chase et al 1992; Dougherty et al 1999).

Table 8.5 Diabetic ketoacidosis

Study ID	Ambulatory care	Inpatient care	Statistical significance
Chase et al (1992)	4 cases over mean of 6.5 years (n=37)	18 cases over mean of 6.6 years (n=76)	NS
Dougherty et al (1999)	2 cases over 2 years (n=32)	0 cases over 2 years (n=31)	NS

NS, not significant

Severe hypoglycaemia

Two studies reported episodes of severe hypoglycaemia; both found no significant differences between the groups (Chase et al 1992; Dougherty et al 1999).

Table 8.6 Severe hypoglycaemia

Reference	Ambulatory care	Inpatient care	Statistical significance
Chase et al (1992)	12 cases over mean of 6.5 years (n=37)	19 cases over mean of 6.6 years (n=76)	NS
Dougherty et al (1999)	7 cases over 2 years (n=32)	6 cases over 2 years (n=31)	NS

NS, not significant

Patient knowledge

Three studies measured patient knowledge, with no significant difference found between groups (Dougherty et al 1999; Siminerio et al 1999; Srinivasan et al 2004).

Table 8.7 Patient knowledge

Reference	Scale	Population	Intervention	Control	Statistical significance
Dougherty et al (1999)	Diabetes knowledge scale	Parents and adolescents >12 years	1 month (n=31): 82.5% ±14.0 (n=15): 71.5% ±17.5 2 years (n=30): 88.5% ±13 (n=19): 85.0% ±15.0	1 month (n=31): 84.5% ±13.5 (n=12): 79.0% ±13.0 2 years (n=30): 84.0% ±13.5 (n=16): 83.5% ±11.0	NS NS NS NS
Siminerio et al (1999)	Test of diabetes knowledge	Parents	NR	NR	NS
Srinivasan et al (2004)	Test of diabetes knowledge	Parents	12 months (n=41): 96% (64–100%)	12 months (n=40): 96% (75–100%)	NS

NR, not reported; NS, not significant

Other psychosocial factors reported by Clar et al (2007) included treatment adherence, family impact, coping and stress, treatment satisfaction and quality of life, and child behaviour and sociability. No differences were found between groups.

8.1.8 Discussion

The included studies compared the initial management of children at diagnosis of type 1 diabetes on an ambulatory basis with management in a hospital setting; however, there are a number of issues that must be considered. First, only one of the included studies is of low risk of bias and of a randomised controlled design (Dougherty et al 1999); the rest were predominantly of high risk of bias and based on a retrospective analysis of data (Spaulding and Spaulding 1976; Galatzer et al 1982; Chase et al 1992; Swift et al 1993). Second, in several of the studies, children in the intervention group were initially hospitalised fometabolic stabilisation (Chase et al 1992; Swift et al 1993; Dougherty et al 1999; Srinivasan

et al 2004) before receiving education either as an outpatient or in the home. Third, in a number of studies, the treatment received in the control group was either poorly described (Spaulding and Spaulding 1976; Galatzer et al 1982), or the educational content delivered was not equivalent (Chase et al 1992). Also, in several studies, the baseline description of the groups did not include details such as the severity of diabetes or metabolic control (Galatzer et al 1982; Swift et al 1993; Siminerio et al 1999; Srinivasan et al 2004), making comparison of baseline characteristics difficult. Finally, several of the studies were carried out more than 20 years ago, in an era that may not now reflect contemporary care of children with diabetes.

8.1.9 Conclusion

This systematic review of evidence examining the efficacy and safety of ambulatory management of children, adolescents and adults at diagnosis of type 1 diabetes is based on one RCT of low risk of bias, one retrospective cohort study of high risk of bias, and one systematic review of low risk of bias (based predominantly on comparative studies of high risk of bias). Of the outcomes reported, one study reported a difference of 0.7% HbA_{1c} between the intervention and control groups, with those children managed in the home setting having a significantly lower HbA_{1c} at 12, 24 and 36 months duration, whereas three other studies found no significant difference in HbA_{1c} between groups. This inconsistency may relate to the differing study designs, interventions and study quality. There were consistently no significant differences reported in the rate of diabetic ketoacidosis, severe hypoglycaemia or diabetes knowledge, between the intervention or control group. When compared to a hospital inpatient setting, management of children with newly diagnosed type 1 diabetes on an ambulatory basis:

- may have a slight advantage in terms of metabolic control
- does not increase the rate of diabetic ketoacidosis or severe hypoglycaemia
- does not impact negatively in terms of patient knowledge.

The evidence reported is not generalisable to children aged under 2 years, or to adults. The results are applicable to the Australian setting.

8.1.10 Literature search strategy

The search was conducted on 16 July 2010. Level I studies were considered first, with the plan to update with Level II studies as required. The Medline search strategy and a summary of citations retrieved from other searches are shown in Table 8.8.

Table 8.8 Search strategy, question 8.1

Database	Date searched	#	Search terms	Citations
Medline	16 July 2010	1	Diabetes Mellitus, type 1/	52 585
		2	(new or newly or first or initial near diagnos* or onset or on-set).mp	1 647 492
		3	(in-patient* or inpatient* or hospital* or in-hospital*).mp	1 637 766
		4	(outpatient* or out-patient* or home* or ambulatory*).mp	458 585
		5	#1 and #2 and #3 and #4	254
		6	Limit to english language	219
EMBASE	16 July 2010	1	Diabetes Mellitus, type 1/	42 508
		2	(new or newly or first or initial near diagnos* or onset or on-set).mp	1 437 227
		3	(in-patient* or inpatient* or hospital* or in-hospital*).mp	1 285 436
		4	(outpatient* or out-patient* or home* or ambulatory*).mp	3 316 112
		5	#1 and #2 and #3 and #4	199
		6	Limit to English language	172
INAHTA	15 July 2010			0
Cochrane	15 July 2010			1
Manual search				2
Total citations				392
Total non-duplicate citations				271

8.1.11 Evidence Matrix

Q8.1	What is the effectiveness of ambulatory care versus hospital inpatient care of patients with newly diagnosed disease?	
Evidence statement	Ambulatory care, delivered by a multidisciplinary team in a tertiary referral diabetes service, at diagnosis of type 1 diabetes in children over 2 years of age: results in a lower HbA_{1c} (0.7%) at 3 years follow-up compared to in-hospital care at diagnosis does not increase the risk of severe hypoglycaemia or diabetic ketoacidosis, or result in poorer levels of diabetes knowledge at 2 years follow-up compared to in-hospital care at diagnosis.	
Evidence base	A	One Level II study (of low risk of bias) in children older than 2 years. One Level IV study (of high risk of bias) in children. One Level IV systematic review of low level of bias (included five studies in addition to the Level II study above – four of high risk of bias, one of medium risk of bias).
Consistency	B	• HbA_{1c} – one Level II study demonstrated 0.7% difference between groups in favour of home care. All other studies found no significant difference. • Severe hypoglycaemia – no significant difference (consistent). • Diabetic ketoacidosis – no significant difference (consistent). • Patient knowledge – no significant difference (consistent).
Clinical impact	B	Ambulatory care is as effective as inpatient care in terms of glycaemic targets, rates of severe hypoglycaemia and diabetic ketoacidosis, and diabetes knowledge.
Generalisability	C	No adults in evidence base, no children younger than 2 years
Applicability	C	Setting – One study was conducted in Australia, and the others in countries with an established health-care system. Evidence was from tertiary centres only, and may not be applicable to rural and remote settings.
Other factors	From Dougherty et al (1999): Parents in the home-based group spent significantly fewer hours on diabetes care and incurred significantly lower out-of-pocket expenses during the first month. Health-care sector costs were significantly higher. Hospital costs were $889 higher, and government costs $890 higher per child. Social (total) costs were only $48 higher per case (nonsignificant) with home care, when parents' time was valued at $11.88 per hour. Implementation issues: infrastructure, demographically appropriate.	
Recommendation		
R8.1	Children and adolescents presenting with newly diagnosed type 1 diabetes should be managed in an appropriately resourced ambulatory care or inpatient hospital setting (Grade B).	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

8.2 Telemedicine and other technology-based delivery methods

> Question 8.2
>
> What is the effectiveness of telemedicine and other technology-based delivery methods for rural and remote individuals?

This section of the report addresses the effectiveness of telemedicine and other technology-based delivery methods for rural and remote individuals.

8.2.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 8.9.

Table 8.9 Criteria for determining study eligibility, question 8.2

Study design	Level I to Level IV evidence (NHMRC intervention scale[a])
Population	Type 1 diabetes, rural or remote setting
Intervention	Telemedicine or other technology-based methods
Comparator	Usual care
Outcomes	Change in HbA_{1c}, time saving, cost saving, weight, random blood glucose, insulin dose, hypoglycaemic episodes, frequency of day and night blood sugar testing, frequency of clinic visits, all adverse events of therapy (e.g. severe hypoglycaemia or ketotic states)

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial, Level III-1: A pseudorandomised controlled trial, Level III-2: A comparative study with concurrent controls, Level III-3: A comparative study without concurrent controls, Level IV: Case series with either post-test or pre-test/post-test outcomes

8.2.2 Literature search summary

The search results for this question are summarised in Table 8.10.

Table 8.10 Search results, question 8.2

Stage	Notes	Number
Search summary	Manual	0
	Cochrane Library	28
	EMBASE	47
	Medline	28
	INHATA	9
	Total found	112
Duplicates	Duplicates identified	46
Identified	Total identified	66
Exclusion criteria	Wrong study type (not NHMRC Level I, II, III or IV)[a]	2
	Wrong population (not type 1 diabetic, not rural or remote)	30
	Wrong intervention (not telemedicine or other technology-based delivery method)	29
	Wrong comparator (conventional care)	0
	Wrong outcome (No change in HbA_{1c}, time saving, cost saving, weight, random blood glucose, insulin dose, hypoglycaemic episodes, frequency of day and night blood sugar testing, frequency of clinic visits, adverse events of therapy, for example, severe hypoglycaemia or ketotic states)	0
	Not in English	1
	Total excluded	62

Stage	Notes	Number
Meeting criteria	Total meeting inclusion criteria	4
Included	Total included studies	4

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial, Level III-1: A pseudorandomised controlled trial, Level III-2: A comparative study with concurrent controls, Level III-3: A comparative study without concurrent controls, Level IV: Case series with either post-test or pre-test/post-test outcomes

8.2.3 Included studies

Four studies were included (Ahring et al 1992; Liesenfeld et al 2000; Biermann et al 2002; Corriveau et al 2008).

8.2.4 Characteristics of included studies

Ahring et al (1992)

Ahring et al (1992) examined whether the use of telephone modems for the transmission of self-monitoring of blood glucose (SMBG) data could present an advantage to the management of the patient with type 1 diabetes in rural communities. Forty-two patients participated in the study, and were followed for 12 weeks. The patients were randomly divided into two groups at baseline – a modem group and a control group. The modem group transferred their data over the phone once a week. The control group brought in their results on their regular visits every 6 weeks.

Biermann et al (2002)

Biermann et al (2002) conducted a prospective randomised trial (n=43) that focused on the fiscal and administrative aspects of telemanagement. Patients were randomly assigned to telecare (n=27) or conventional care (n=16). The intervention group used blood glucose (BG) meters and transmitted their data over a combined modem and interface via telephone line to the diabetes centre.

Corriveau et al (2008)

Corriveau et al (2008) conducted a comparative study with concurrent controls to determine whether use of the internet-based insulin pump monitoring system, Carelink, improved glycaemic control in rural and urban children treated with insulin pump therapy. The researchers reviewed records of 94 children treated with insulin pump therapy between the years 2004 and 2007, and compared glycaemic control, diabetes self-care measures, frequency of clinic visits and geographic location associated with Carelink use.

Liesenfeld et al (2000)

Liesenfeld et al (2000) conducted a case series study of a telemedical care program aimed at overcoming geographical isolation of patients on intensive insulin therapy. Sixty-one children and adolescents with type 1 diabetes participated in the program. They stored daily information on blood glucose, injected insulin, meals and exercise in a glucosemeter with electronic memory, and transferred the data via modem to a remote diabetes centre outside the region. By individual telephone consultations from home, they reviewed the data with an endocrinologist at the diabetes centre and adjusted their intensive insulin therapy, to achieve predefined treatment goals.

8.2.5 Results of included studies

Table 8.11 shows the details of the included studies.

Table 8.11 Details of studies included, question 8.2

Reference, country and duration	Level and type of study, and N	Outcomes	Results
Ahring et al (1992) Canada 3 months	Level II RCT 42	Change in HbA_{1c}, weight, random blood glucose, insulin, hypoglycaemic episodes	HbA_{1c} Significantly reduced after 6 weeks (0.094 ±0.012 vs 0.106 ±0.028, p=0.05). After 12 weeks, further reduced and significantly reduced (0.092 ±0.011, p=0.05). The change between the groups was significant after 6 weeks but not after 12 weeks. Weight reduction There was a gradual but nonsignificant weight reduction in the modem group at 6 and 12 weeks compared with the start of the study. Random blood glucose No significant difference (p=0.10). Mean insulin dose Change was not significant.
Biermann et al (2002) Germany 8 months	Level II RCT 43	Time saving, cost saving, metabolic control – HbA_{1c}	HbA_{1c} Improved to 6.9 ±1.3% after 4 months (n=27) and 7.1 ±0.7% after 8 months (n=11) in the telecare group; and 7.0 ±1.0% after 4 months (n=16) and 6.8 ±1.1% after 8 months (n=10) in the control group. Differences between the groups were not statistically significant. Time required (minutes per month) Patients of the telecare group spent an average total of 554 minutes (range: 220–1056) for their consultation after 4 months; and of 974 minutes (range: 399–1762) after 8 months.[a] Costs[b] (Cost-comparison analysis) (costs per year) €389 Resulting in savings of €650 per year per patient.

Reference, country and duration	Level and type of study, and N	Outcomes	Results
Corriveau et al (2008) United States 2004–07	Level III-2 Comparative study with concurrent control 94	HbA_{1c}, Carelink uploads per month, frequency of day and night blood sugar testing, self-adjustment of insulin dose, frequency of clinic visits	HbA_{1c} *Rural patients* Rural Carelink users showed improvement in HbA_{1c} levels after Carelink use (7.9 ±0.2 [SE] vs 7.4 ±0.2 [SE], p=0.001), whereas rural non-users (9.2 ±0.5 [SE] vs 9.2 ±0.5 [SE], p=0.96) and rural no-access patients (8.1 ±0.3 [SE] vs 8.0 ±0.4 [SE], p=0.79) did not change. *Urban patients* There were no statistically significant changes in HbA_{1c} before and after Carelink use in the groups of urban patients. Clinical visits Rural patients had significantly fewer annualised clinic visits (2.8 ±0.2 [SE] vs 3.5 ±0.1 [SE] for urban patients, p=0.003). Carelink uploads per month Rural Carelink users uploaded 2.3 ±0.5 (SE) times per month versus urban Carelink users who uploaded 2.1 ±0.3 (SE) times per month, p=0.75. No-access patients and Carelink users had similar diabetes self-care behaviours. They did not differ significantly in frequency of adjusting doses (50 vs 68%), testing overnight (50 vs 64%), or tests per day. Non-users differed significantly from the other groups in adjusting insulin doses (23%), p=0.03, and testing overnight (15%), p=0.01, but not in frequency of blood glucose monitoring. The mean frequency of blood glucose monitoring per day was 5.4 ±2.3 (SD) for no-access patients, 4.3 ±1.9 (SD) for non-users, and 5.3 ±1.5 (SD) for Carelink users, p=0.13.
Liesenfeld et al (2000) Germany 1 month	Level IV Case series with pre- and post-test outcomes 61	Blood glucose values, the number of hypoglycaemic events. All adverse events of therapy (e.g. severe hypoglycaemia or ketotic states) were also recorded	HbA_{1c} had dropped by 0.4% (range –3.8 to +2.2%; n=47; p<0.05) at the end of the program. This corresponds to the reduction of mean blood glucose by 11 mg/dL even though the rate of hypoglycaemic events was significantly reduced, whereas the proportion of readings below 80 mg/dL remained stable. The event rates for severe adverse events during the program and the retrospectively recorded events since time of diabetes manifestation but before the entry of the program did not differ (data not shown).

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial; SD, standard deviation; SE, standard error

[a] The times include travel, waiting, consultation, data transmission times and times for completing the study protocol in all patients. Consultation times were taken from the patients' chart records and all other times were recorded by questionnaire.
[b] Data collected in the questionnaire included travel distance and time to the diabetes centre. A cost analysis was carried out, estimating average travel costs and average telephone costs by distance for all patients.

8.2.6 Discussion

Glycaemic control

Glycaemic control was an outcome measure in all four studies; all reported changes in glycated haemoglobin (HbA_{1c}) level. The evidence for improved glycaemic control is conflicting. One randomised controlled trial (RCT) (Ahring et al 1992) found a significant reduction in HbA_{1c} compared to baseline, both at 6 weeks and at 12 weeks. The control group showed a nonsignificant improvement in HbA_{1c} after both 6 and 12 weeks compared with the start of the study. The change between the groups was significant after 6 weeks but not after 12 weeks. Another RCT (Biermann et al 2002) found that HbA_{1c} levels improved in both the telecare and control groups after 4 and 8 months; differences between the groups were not statistically significant. A comparative study with concurrent controls (Corriveau et al 2008) found that rural, but not urban, Carelink users showed improvement in HbA_{1c} levels after Carelink use. HbA_{Ic} was reduced in a case-series study (Liesenfeld et al 2000).

Time and cost savings

The RCT by Biermann et al (2002) focused on the fiscal and administrative aspects of telemanagement. The researchers found that a substantial amount of time on the patients' side could be saved through replacing personal communications by telephone contacts and data transmission reduction (96 vs 163 min/month including data transmission time). A cost analysis indicated that setting up an optimal telemanagement scenario could yield savings of €650 per year per patient. The study by Corriveau et al (2008) reported that rural patients had significantly fewer annualised clinic visits.

Adverse events

Only Liesenfeld et al (2000) reported on adverse events. The authors stated that the event rates for severe adverse events during the program and the retrospectively recorded events since time of diabetes manifestation but before the entry of the program did not differ.

8.2.7 Conclusion

The literature search identified four studies that examined the effectiveness of telemedicine and other technology-based delivery methods for rural and remote individuals. Two were RCTs (Level II), one was a comparative study (Level III-2) and the other was a case-series study (Level IV). All four studies reported changes in HbA_{1c} as an outcome measure. Of the four studies, only one (Ahring et al 1992) showed a statistically significant change in HbA_{1c}. A study by Biermann et al (2002) reported cost and time savings of a telemedicine intervention. The authors developed a cost-analysis scenario that showed a saving of €650 per year per patient. The four included studies were of limited methodological quality and involved small numbers of participants.

8.2.8 Literature search strategy

Table 8.12 Search strategy, question 8.2

Database	Date searched	#	Search terms	Citations
Medline		1	Diabetes Mellitus, type 1/	52 442
		2	Telemedicine/	7 554
		3	telehealth.mp.	866
		4	telemonitoring.mp.	284
		5	Telecommunications/	3 200
		6	(diabetes and internet).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	654
		7	web-based.mp.	6 998
		8	(diabetes management and internet).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	42
		9	telecare.mp.	223
		10	Telephone/	7 679
		11	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	25 284
		12	rural.mp. or Rural Health/	85 804
		13	remote.mp.	30 451
		14	distance.mp.	94 170
		15	12 or 13 or 14	205 092
		16	1 and 11 and 15	28
Cochrane				28
ENAHTA				9
EMBASE				47
Manual search				0
Total citations				
Total non-duplicate citations				4

8.2.9 Evidence Matrix

Q8.2	What is the effectiveness of telemedicine and other technology-based delivery methods for rural and remote individuals?	
Evidence statement	There is insufficient evidence to determine the effect of telemedicine and other technology-based delivery methods for rural and remote individuals on glycaemic control or time and cost savings.	
Evidence base	D	Four studies: two Level II studies, one Level III study and one Level IV study; all with high risk of bias, in which telemedicine replaced standard care.
Consistency	C	One RCT found a significant reduction; three showed no effect.
Clinical impact	C	If compared to tertiary outreach.
Generalisability	B	Three in adults, one in children.
Applicability	C	In the study by Biermann et al (2000), the definition of remote was only 50 minutes to clinic. Most studies were either old or out of date.
Other factors	None identified.	
Recommendation		
	There was insufficient evidence to make a recommendation.	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

9 Education and psychological support

9.1 Diagnostic performance of specified psychological screening tools

Question 9.1

What is the diagnostic performance of the following psychological screening tools: CDI, BASC, EDE, CHQ, BAI, BDI, HADS, EDI, ADS, ATT19?

ADS, Appraisal of Diabetes Scale; ATT19, Diabetes Integration Scale; BAI, Beck Anxiety Inventory; BASC, Behaviour Assessment System for Children; BDI, Beck Depression Inventory; CDI, Children's Depression Inventory; CHQ, Child Health Questionnaire; EDE, Eating Disorders Examination; Eating Disorder Inventory, EDI, HADS, Hospital Anxiety and Depression Scale

This section of the report addresses the diagnostic performance of a range of psychological screening tools. The tools studied in children were the Behaviour Assessment System for Children (BASC), the Children's Depression Inventory (CDI), the Child Health Questionnaire (CHQ) and the Eating Disorders Examination (EDE). The tools studied in adults were the Appraisal of Diabetes Scale (ADS), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI), the Diabetes Integration Scale (ATT19), the Eating Disorder Inventory (EDI), and the Hospital Anxiety and Depression Scale (HADS).

9.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 9.1.

Table 9.1 Criteria for determining study eligibility, question 9.1

Study design	Level I to Level IV evidence (NHMRC intervention scale[a])
Population	Type 1 diabetes
Intervention	Psychological screening tools Children and adolescents Children's Depression Inventory (CDI); Behaviour Assessment System for Children (BASC); Eating Disorders Examination (EDE); Child Health Questionnaire (CHQ) Adults Beck Anxiety Inventory (BAI); Beck Depression Inventory (BDI); Hospital Anxiety and Depression Scale (HADS); Eating Disorder Inventory (EDI); Appraisal of Diabetes Scale (ADS); Diabetes Integration Scale (ATT19)
Comparator	"Gold standard", as defined by the studies or other psychological screening tool
Outcomes	Diagnosis of anxiety; depression; or eating disorder.

NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial, Level III-1: A pseudorandomised controlled trial; Level III-2: A comparative study with concurrent controls; Level III-3: A comparative study without concurrent controls; Level IV: Case series with either post-test or pre-test/post-test outcomes.

9.1.2 Literature search summary

The results of the literature search are summarised in Table 9.2.

Table 9.2 Search results, question 9.1

Stage	Notes	Number
Search summary	EMBASE	42
	Medline	25
	Total	67
Duplicates	Duplicates identified	37
Identified	Total identified	30
Exclusion criteria	Wrong study type (not NHMRC Level I, II, III or IV) [a]	22
	Wrong population (not type 1 diabetic)	3
	Wrong intervention (not the following psychological screening tools: CDI, BASC, EDE, CHQ, BAI, BDI, HADS, EDI, ADS, ATT19)	1
	Wrong outcome (not diagnosis of depression; anxiety or eating disorder)	0
	Not in English	1
	Total excluded	27
Meeting criteria	Total meeting inclusion criteria	
Included	Total included studies	3

NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial, Level III-1: A pseudorandomised controlled trial; Level III-2: A comparative study with concurrent controls; Level III-3: A comparative study without concurrent controls; Level IV: Case series with either post-test or pre-test/post-test outcomes.

9.1.3 Included studies

The included studies were Cameron et al (2003), Hermanns et al (2006) and Lustman et al (1997).

The characteristics and results of the three included studies are summarised in Table 9.3. The sensitivities and specificities of selected BDI cut-off scores, using the entire 21-item test, are shown in Table 9.4.

Table 9.3 Details of studies included, question 9.1

Reference, country, level of evidence	N, population	Aim of the study	Screening tool	Comparator	Results
Cameron et al (2003) Australia Level II (Diagnostic accuracy)	n=103 (type 1) Children (aged 7–12 years)	To assess the validity of the CHQ as a screening tool for detecting 'at risk' emotional and behavioural maladjustment in children with diabetes, using the BASC as a gold standard	CHQ	BASC	The BASC Externalizing Problems scale correlated strongly with CHQ Behaviour, Global Behaviour, Mental Health, Family Activities and Family Cohesion scales (*r*-values –0.68, –0.54, –0.51, –0.59 and –0.42, respectively). BASC Internalizing Problems scale correlated strongly with CHQ Behaviour, Mental Health and Family Cohesion scales (r-values –0.40, –0.43, and –0.45, respectively).

Reference, country, level of evidence	N, population	Aim of the study	Screening tool	Comparator	Results
		measure			Using receiver operating characteristic curve analysis, the CHQ Mental Health scale most effectively indentified children classified as borderline on the BASC Internalizing Problems scale (sensitivity 87%, specificity 78%), while the CHQ Global Behaviour scale most effectively identified children classified as borderline on the BASC Externalizing Problems scale (sensitivity 73%, specificity 82%).
Hermanns et al (2006) Germany Level III–2 (Diagnostic accuracy)	n=376 (37.2% type 1; 62.8% type 2) Adults	Compare the screening performance of different measures of depression (for this review, extracted data relating to the BDI only)	BDI	CIDI	BDI yielded the highest sensitivity for the detection of clinical depression Sensitivity: 86.8% (83.4–90.2) Specificity: 81.4% (77.5–85.3) PPV: 43.4% (38.4–48.4) NPV: 97.4% (95.8–99.0)
Lustman et al (1997) United States Level II (Diagnostic accuracy)	n=59 (type 1) Adults	To determine the utility of the BDI as a screening tool for major depression in diabetes, using the complete 21-item measure as well as the cognitive (13 items) and somatic (eight items) symptom subgroups	BDI	DSM-III-R	BDI total scores between 12 and 14 inclusive displayed the best balance between sensitivity (0.90–0.82) and specificity (0.84–0.89). A cut-off score ≥16 for the entire 21-item measure exhibited the best balance between sensitivity and positive predictive value when prediction values were extrapolated to a diabetic population with a depression prevalence rate of 20%. This cut-off score would capture >70% of the patients diagnosed with major depression, yet provide >70% certainty that a person screening positive actually has the psychiatric disorder.

BASC, Behaviour Assessment System for Children; BDI, Beck Depression Inventory; CHQ, Child Health Questionnaire; CIDI, Composite International Diagnostic Interview; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders; NPV, negative predictive value; PPV, positive predictive value

Table 9.4 Sensitivity and specificity of the BDI using selected cut-offs for identifying major depression in diabetes

BDI cut-off score	Sensitivity	Specificity
≥8	0.99	0.52
≥10	0.98	0.70
≥12	0.90	0.84
≥14	0.82	0.89
≥16	0.73	0.93

BDI, Beck Depression Inventory

9.1.4 Discussion

Cameron et al (2003) found that sequential use of the CHQ, as a screening tool, followed by an established mental health measure such as BASC, may help to identify children with diabetes 'at risk' for chronic maladjustment and poor health outcomes.

Hermanns et al (2006) found that among patients with type 1 diabetes, the prevalence of clinical depression was 30% and a further 31% were diagnosed with subclinical depression. Using receiver operating characteristic (ROC) analysis, BDI was more sensitive and specific than the other tools evaluated, including the Problem Areas in Diabetes (PAID) questionnaire, for the detection of clinical depression. However, for the evaluation of the screening tools, patients with type 1 and type 2 diabetes were combined.

Lustman et al (1997) found that a cut-off score ≥16 for the entire 21-item measure exhibited the best balance between sensitivity and positive predictive value when prediction values were extrapolated to a diabetic population with a depression prevalence rate of 20%. Cut-off scores between 12 and 14 inclusive displayed the best balance between sensitivity and specificity. Higher cut-off scores may be utilised to minimise false positives, but at the expense of decreasing sensitivity. As with Hermanns et al (2006), the study included both type 1 and type 2 diabetic patients.

9.1.5 Conclusion

The literature search identified three studies on the performance of psychological screening tools in diabetes (Lustman et al 1997; Cameron et al 2003; Hermanns et al 2006). One of these studies was conducted in children with type 1 diabetes (Cameron et al 2003) and the other two were in adult populations of people with either type 1 or type 2 diabetes (Lustman et al 1997; Hermanns et al 2006). This is a limited evidence base for acceptance performance of BDI in adults and of CHQ in children with type 1 diabetes.

9.1.6 Literature search strategy

Table 9.5 Search strategy, question 9.1

Database	Date searched	#	Search terms	Citations
Medline		1	Diabetes Mellitus, type 1/	53 229
		2	childrens depression inventory.mp	405
		3	CDI.mp.	1 416
		4	Behaviour Assessment System for Children.mp.	5
		5	Behavior Assessment System for Children.mp.	44
		6	BASC.mp.	106
		7	Eating Disorders Examination.mp.	68
		8	EDE.mp.	316
		9	Child Health Questionnaire.mp.	335
		10	CHQ.mp.	339
		11	Beck Anxiety Inventory.mp.	357
		12	BAI.mp.	711
		13	Beck Depression Inventory.mp.	4 851
		14	BDI.mp.	2 910
		15	(Hospital Anxiety and Depression Scale).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2 359
		16	HADS.mp.	1 269

Database	Date searched	#	Search terms	Citations
		17	Eating Disorder Inventory.mp.	429
		18	EDI.mp.	1 020
		19	Appraisal of Diabetes Scale.mp.	9
		20	ADS.mp.	2 377
		21	Diabetes Integration Scale.mp.	2
		22	ATT19.mp.	1
		23	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	1 480
		24	exp sensitivity-and-specificity/	324 367
Medline		25	exp False negative reactions/	14 563
		26	exp False positive reactions/	21 812
		27	exp Diagnosis, differential/	335 977
		28	exp Mass screening/	84 356
		29	Du.fs.	298 391
		30	Di.fs.	1 678 191
		31	Sensitivit$.tw.	411 316
		32	Specificit*.tw.	274 288
		33	(Predictive and value$).tw.	61 670
		34	(False and reaction$).tw.	5 320
		35	(Likelihood and ratio$).tw.	12 001
		36	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	2 688 669
		37	1 and 23 and 36	25
EMBASE				42
Total citations				67

9.1.7 Evidence Matrix

Q9.1	Psychological screening tools	
Evidence statement	There is one Level II and one Level III study demonstrating the diagnostic accuracy of the BDI in a mixed population of type 1 and type 2 diabetes. There is one Level II study examining the diagnostic accuracy of the CHQ administered to the parents of children with type 1 diabetes. No evidence was identified for the performance of other psychological screening tools in type 1 diabetes.	
Evidence base	C	Two Level II studies (diagnostic accuracy) of fair quality and one Level III-II study (diagnostic accuracy) of fair quality.
Consistency	B	Studies were broadly consistent, with difference related to instruments.
Clinical impact	C	
Generalisability	B	One study in children with type 1 diabetes and two studies in adults (both with type 1 and type 2 diabetes).
Applicability	A	One Australian study (in children). The adult studies were in Germany and the United States.
Other factors	None identified.	
Recommendation		
	There was insufficient evidence to make a recommendation.	

CHQ, Child Health Questionnaire

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

9.2 Education and psychological support programmes

Question 9.2

What is the effectiveness of education and/or psychological support programmes in type 1 diabetes?

i) on metabolic outcomes

ii) on psychological outcomes.

9.2.1 Introduction

This section of the report addresses the effectiveness of education and psychological support programmes in the management of type 1 diabetes. For the purpose of this review, education and psychological programmes are defined as interventions that are delivered in either a group or one-on-one format, and are focused on changing either knowledge, behaviour, or self-management skills, or have a psychological focus, such as coping skills, problem solving or family therapy.

9.2.2 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 9.6.

Table 9.6 Criteria for determining study eligibility, question 9.2

Study design	Level I evidence (NHMRC intervention scale[a])
Population	Children, adolescents and adults with type 1 diabetes
Intervention	Education and/or psychological support programme
Comparator	Any
Outcomes	Metabolic – glycaemic control (HbA_{1c}), severe hypoglycaemia, DKA Knowledge Self-management behaviours Psychosocial Quality of life

DKA, diabetes ketacidosis; HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

9.2.3 Assessment of study eligibility

Publications identified in the literature search were reviewed using the criteria shown in Table 9.7, applied hierarchically, to determine which publications to exclude.

9.2.4 Literature search summary

A total of 245 non-duplicate citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with 216 publications excluded, as shown in Table 9.7. A total of 28 publications remained, and the full-text version of each of these publications was retrieved and reviewed.

Table 9.7 Search results, question 9.2

Stage	Notes	Number
Search summary	Manual	0
	Cochrane Library	16
	EMBASE	198
	Medline	81
	Psychinfo	38
	CINAHL	0
	INAHTA	35
	Total	319
Duplicates	Duplicates identified	74
Exclusion criteria	Wrong study type (not NHMRC Level I)[a]	128
	Wrong population (not children, adolescents or adults with type 1 diabetes)	19
	Wrong intervention (not diabetes education/psychological programme)	67
	Wrong outcome (not glycaemia control [HbA_{1c}], severe hypoglycaemia, DKA, knowledge, self-management, psychosocial or quality of life)	2
	Not in English	0
	Total excluded	216
Meeting criteria	Total meeting inclusion criteria	28
Included	Total included studies	11

DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

9.2.5 Citations for full-text review

Of the 28 full-text studies reviewed, 4 were excluded because they were either narrative reviews or editorials; 10 because they reported studies in type 2 diabetes, or in both type 1 and type 2 diabetes, but did not report outcomes separately; 1 because of wrong outcomes; and 3 because of wrong intervention. Of the remaining 10 Level I studies, 4 specifically examined the effectiveness of interventions in adolescents (Hampson et al 2000; Hampson et al 2001; Gage et al 2004; Urban et al 2004) and 1 updated a Health Technology Assessment (HTA) report to include studies in children as well as adolescents (Murphy et al 2006). One study reviewed the effectiveness of problem-solving interventions in both children and adults (Hill-Briggs and Gemmell 2007), and another the effectiveness of diabetes self-management education across the age spectrum (Norris et al 2002). These systematic reviews are not discussed further because they do not provide any further evidence than that reported in the three remaining Level I studies, which are listed in Table 9.8.

Table 9.8 Level I studies

Study reference	Included interventions	Included studies Level II studies in type 1
Couch et al (2008)	General diabetes education Cognitive behavioural therapy Family therapy Skills training Diabetes camps Psycho-education Physical activity program	(Gross et al 1983; Mann et al 1984; Campaigne et al 1985; Gross et al 1985; Kaplan et al 1985; Anderson et al 1989; Hackett et al 1989; Massouh et al 1989; Satin et al 1989; Delamater et al 1990; Horan et al 1990; Szumowski 1990; Cigrang 1991; Delamater et al 1991; Kennedy-Iwai 1991; Boardway et al 1993; Pichert et al 1993; McNabb et al 1994; Pichert et al 1994a; Pichert et al 1994b; Mitchell 1996; Sundelin et al 1996; Wolanski et al 1996; Brown et al 1997; Hakimi 1998; Anderson et al 1999; Dougherty et al 1999; Webb 1999; Grey et al 2000; Hains et al 2000; Wysocki et al 2000; Olmsted et al 2002; Laffel et al 2003; Panagiotopoulos et al 2003; Svoren et al 2003; Hoff et al 2005; Howe et al 2005; Nordfeldt et al 2005; Wadham et al 2005; Nunn et al 2006; Wysocki et al 2007)
Loveman et al (2003)	Diabetes self-management	Reichard 1988–96: includes multiple publications (Reichard et al 1988; Reichard and Rosenqvist 1989; Reichard et al 1990; Reichard et al 1991a; Reichard et al 1991b; Reichard et al 1991c; Reichard et al 1993; Reichard and Pihl 1994; Reichard et al 1994; Reichard 1996; Reichard et al 1996), Terent et al (1985)
Winkley et al (2006)	Supportive or counselling therapy Cognitive behavioural therapy Psychoanalytically informed therapies Family systems therapy	(Gross et al 1985; Kaplan et al 1985; Feinglos et al 1987; Anderson et al 1989; Satin et al 1989; Delamater et al 1990; Belendez and Mendez 1991; McGrady et al 1991; Daley 1992; Boardway et al 1993; Manning et al 1994; Spiess et al 1995; Glasgow et al 1996; Wolanski et al 1996; Fosbury et al 1997; Halford 1997; Mendez and Belendez 1997; Olivares et al 1997; Forsander et al 1998; Grey et al 1998; Wysocki et al 2000; Pouwer et al 2001; Didjurgeit et al 2002; Howells et al 2002; Weinger et al 2002; Stenstrom et al 2003; Svoren et al 2003; Wysocki et al 2003; van der Ven et al 2005)

Couch et al (2008) is a comprehensive report from the Agency for Healthcare Research and Quality (AHRQ), evaluating the effectiveness of diabetes education programmes in children and adolescents under 18 years of age. Loveman et al (2003) is an HTA report on the effectiveness of diabetes self-management education in adults (including type 1 and type 2 diabetes), with a subanalysis on results in studies of type 1 diabetes. Winkley et al (2006) is a systematic review including meta-analysis of the effect of psychological interventions in both children and adults.

A search of Medline, EMBASE and Psychinfo databases to find published Level II evidence to update the three systematic reviews was undertaken on 23 September 2010, with the search terms as per Table 9.24, plus the term 'therapeutic patient education', filters for randomised controlled trials (RCTs), and limited to papers published from 2002 in adults and from 2007 in children and adolescents. The abstract and title of 1150 nonduplicate citations were reviewed. The exclusion criteria were applied hierarchically with the full-text version of 37 publications reviewed for inclusion. Of these 37 publications, 8 met the inclusion criteria (DAFNE Study Group 2002; Channon et al 2007; George et al 2007; Viklund et al 2007; Snoek et al 2008; Amsberg et al 2009; Grey et al 2009b; Ismail et al 2010).

9.2.6 Included studies

9.2.7 Characteristics of included studies

A total of 11 studies were included (DAFNE Study Group 2002; Loveman et al 2003; Winkley et al 2006; Channon et al 2007; Viklund et al 2007; Couch et al 2008; George et al 2008; Snoek et al 2008; Amsberg et al 2009; Grey et al 2009b; Ismail et al 2010). These studies are discussed below.

Couch et al (2008)

Couch et al (2008) undertook a systematic review of published research, with search date up to 2 March 2007, to determine the effectiveness of diabetes education for children and adolescents with type 1 diabetes and their families. Study selection, quality assessment and data extraction were conducted independently by several investigators in duplicate. A descriptive analysis was presented. The authors reported on RCTs, case–control studies and observational studies that met their inclusion criteria. The results of the RCTs are reported and discussed here. Most of the 41 RCTs were of low quality. The authors concluded that, due to the heterogeneity of interventions, outcome measures and duration of follow-up, there was insufficient evidence to identify a particular intervention that was more effective than standard care to improve metabolic control or quality of life (QoL), or to reduce short-term complications. The RCTs reported by Couch et al (2008) are summarised in Table 9.9.

Table 9.9 Characteristics of randomised controlled trials included in Couch et al (2008)

Study reference Quality	Study design Country	Population (n and other characteristics)	Intervention Setting	Outcomes
Anderson et al (1999) Low	RCT (parallel) United States	89 adolescents	Diabetes responsibilities versus didactic diabetes education versus standard care Diabetes centre	HbA_{1c} Pychosocial – family/social support, family/social relationships
Anderson et al (1989) Low	RCT (parallel) United States	70 adolescents	Self-management skills, problem solving versus standard care Clinic	HbA_{1c} Self-monitoring skills
Boardway et al (1993) Low	RCT (parallel) United States	31 adolescents Noncompliance and/or poor metabolic control	Stress management plus self-management skills versus standard care Outpatient clinic	HbA_{1c} Self-management/ adherence Psychosocial – stress Coping
Brown et al (1997) Low	RCT (parallel) United States	59	Diabetes video game versus pinball video game Home	HbA_{1c} Knowledge Psychosocial – family/social relationships, self-efficacy
Campaigne et al (1985) Low	RCT (parallel) United States	16 adolescents	Exercise sessions versus standard care	HbA_{1c} Hypoglycaemia

Study reference Quality	Study design Country	Population (n and other characteristics)	Intervention Setting	Outcomes
Cigrang (1991) Low	RCT (parallel) United States	37 adolescents Poor metabolic control	Stress coping strategies versus diabetes lectures versus standard care Hospital	HbA_{1c} Coping Psychosocial – self-perception, depression
Delamater et al (1991) Low	RCT (parallel) United States	13 Noncompliance and/or poor metabolic control	Self-management skills, psychosocial skills versus standard care Hospital outpatient clinic	HbA_{1c}, Self-management/ adherence Psychosocial
Delamater et al (1990) Moderate	RCT (parallel) United States	36 children Newly diagnosed	Self-management skills and problem solving versus psychosocial adjustment versus standard care Hospital, home	HbA_{1c}
Dougherty et al (1999) Moderate	RCT (parallel) Canada	63 children Newly diagnosed	General diabetes knowledge Home General diabetes knowledge Hospital	HbA_{1c}, DKA Severe hypoglycaemia Knowledge Self-management/ adherence Psychosocial – stress Coping
Grey et al (2000) Moderate	RCT (parallel) United States	77 adolescents	Coping skills training versus standard care Hospital, home	HbA_{1c}, Severe hypoglycaemia DKA Psychosocial – self-efficacy QoL Coping
Gross et al (1985) Low	RCT (parallel) United States	14 children	Behaviour modification versus open-ended discussions	HbA_{1c} Knowledge Self-management/ adherence Psychosocial
Gross et al (1983) Low	RCT (parallel) United States	11	Social training versus no social training	HbA_{1c}, Psychosocial – social skills
Hackett et al (1989) Low	RCT (parallel) United Kingdom	119 children	General diabetes knowledge and reinforcement sessions versus general diabetes knowledge versus general diabetes knowledge, 10 months after versus no intervention Clinic	HbA_{1c} Knowledge
Hains et al (2000) Low	RCT (parallel) United States	15	Cognitive behavioural stress training versus no intervention Hospital	HbA_{1c} Psychosocial – anxiety, stress Coping

Study reference Quality	Study design Country	Population (n and other characteristics)	Intervention Setting	Outcomes
Hakimi (1998) Low	RCT (parallel) United States	35 children Newly diagnosed	General knowledge plus psychosocial issues versus general diabetes knowledge	Psychosocial – stress
Hoff et al (2005) High	RCT (parallel) United States	46 Newly diagnosed	Construct of illness uncertainty management versus standard care Clinic	Psychosocial – depression, internalising, externalising problems
Horan et al (1990) Low	RCT (parallel) United States	20	Dynamic and colourful education modules versus static, black-and-white education modules	HbA_{1c} Knowledge Self-management/ adherence
Howe et al (2005) Low	RCT (parallel) United States	89 adolescents and children	General diabetes knowledge (family session) versus general diabetes knowledge (family session) plus telephone class versus standard care Diabetes centre, home	HbA_{1c} Knowledge Psychosocial
Kaplan et al (1985) Low	RCT (parallel) United States	21 adolescents	Social skills training versus general diabetes knowledge (lectures) Summer school	HbA_{1c}
Kennedy-Iwai (1991) Low	RCT (parallel) United States	19 children Newly diagnosed	Communication program for parents versus general diabetes education home	HbA_{1c} Psychosocial
Laffel et al (2003) Low	RCT (parallel) United States	105 children	General diabetes education, responsibility sharing versus standard care Diabetes centre, home	HbA_{1c} Psychosocial QoL
Mann et al (1984) Low	RCT (parallel) United Kingdom	39 children Poor metabolic control	Home visits, instructional videos, telephone contact versus same plus graphically tracking BG data Home, community, outpatient clinic	HbA_{1c}
Massouh et al (1989) Low	RCT (parallel) United States	33 children	General diabetes knowledge, plus social learning intervention versus general Diabetes knowledge	HbA_{1c}
McNabb et al (1994) Low	RCT (parallel) United States	24 children	Goal setting, self-management (youths) parenting skills (parents) versus standard care Diabetes centre	HbA_{1c} Self-management/ adherence Psychosocial
Mitchell (1996) Low	RCT (parallel) Canada	32 children Newly diagnosed	Adherence behaviours versus standard care Diabetes centre	HbA_{1c} Psychosocial Coping

Study reference Quality	Study design Country	Population (n and other characteristics)	Intervention Setting	Outcomes
Nordfelt et al (2005) Low	RCT (parallel) Sweden	332 children and adolescents	Self-management skills, 2 instructional videos, 2 brochures versus standard care, 1 video, 1 brochure, versus standard care	Hypoglycaemia
Nunn et al (2006) High	RCT (parallel) Australia	123 children and adolescents Poor metabolic control	General diabetes knowledge (telephone calls) versus standard care Home, diabetes centre	HbA_{1c} Knowledge Psychosocial
Olmsted et al (2002) Moderate	RCT (parallel) Canada	85 adolescents Eating disorder	Eating disorder intervention versus standard care Diabetes centre	HbA_{1c} Psychosocial
Panagiotopoulos et al (2003) High	RCT (parallel) Canada	50 adolescents Poor metabolic control	Self-management skills (telephone calls) versus standard care Home, diabetes centre	HbA_{1c}
Pichert et al (1994a) Low	RCT (parallel) United States	83	Anchored instruction, nutrition education Camp	Knowledge Self-management skills
Pichert et al (1994b) Moderate	RCT (parallel) United States	84	Anchored instruction, sick day management Camp	Knowledge
Pichert et al (1993) Low	RCT (parallel) United States	70	Anchored instruction, problem-solving skills	Knowledge
Satin et al (1989) Low	RCT (parallel) United States	32 adolescents	Group process and teamwork, adherence versus simulated diabetes management (parent) versus no intervention Hospital	HbA_{1c} Psychosocial
Sundelin et al (1996) Low	RCT (parallel) Sweden	38 children Newly diagnosed	General diabetes knowledge (hospital apartment) versus general diabetes knowledge (hospital) Hospital, apartment	HbA_{1c} Psychosocial
Svoren et al (2003) Moderate	RCT (parallel) United States	301 children and adolescents	Care ambassador to assist families versus care ambassador plus psycho-education versus no intervention Diabetes centre	Hypoglycaemia
Szumowski (1990) Moderate	RCT (parallel) United States	27 children	Goal setting, adherence behaviours versus general diabetes knowledge Outpatient clinic	HbA_{1c} Hypoglycaemia Knowledge Psychosocial Self-management/ adherence

Study reference Quality	Study design Country	Population (n and other characteristics)	Intervention Setting	Outcomes
Wadham (2005) Low	RCT (parallel) United Kingdom	63 children	General diabetes knowledge, teamwork, communication responsibilities versus no intervention Clinic	HbA_{1c}
Webb (1999) Low	RCT (parallel) United States	66	Goal setting (5 goal setting guidelines) versus goal setting (without guidelines) Outpatient clinic	HbA_{1c} Self-management/ adherence
Wolanski et al (1996) Low	RCT (parallel) Canada	Poor self-management skills	SMBC skills versus usual teaching activities Camp	
Wysocki et al (2007) Low	RCT (parallel) United States	104 adolescents	Group meetings, emphasised education and social support versus behavioural family systems therapy versus standard care Diabetes centre	HbA_{1c} Self-management/ adherence Psychosocial
Wysocki et al (2000) High	RCT (parallel) United States	119 adolescents Poor metabolic control, moderate levels of parent-adolescent conflict	Behavioural family systems therapy versus group meetings, emphasised education, and social support versus standard care Doctor's office	HbA_{1c} Self-management/ adherence Psychosocial

BG, blood glucose; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; QoL, quality of life; RCT, randomised controlled trial; SMBG, self-monitored blood glucose

Loveman (2003)

Loveman et al (2003) aimed to evaluate the clinical and cost effectiveness of educational interventions in adults with type 1 and type 2 diabetes. Interventions that included a focus on diabetes self-management were included. Studies evaluating psychological interventions or targeting specific complications (e.g. foot care) were excluded. Of the included studies presented, two RCTs were in adults with type 1 diabetes. The intervention in one of the included studies (Reichard et al 1988) also involved the intensification of diabetes management, confounding the effects of the education provided. The authors concluded that education as part of intensification of treatment improves metabolic control in adults with type 1 diabetes. The characteristics of the included RCTs are summarised in Table 9.10.

Table 9.10 Characteristics of randomised controlled trials included in Loveman et al (2003)

Study reference Quality	Study design Country	Population	Intervention Setting	Outcomes
Reichard et al 1998 (see Table 9.8) (SDIS) Low	RCT Sweden	102 adults	Self-management education with intensified management versus usual treatment Outpatient clinic	HbA_{1c} Hypoglycaemia DKA

Study reference Quality	Study design Country	Population	Intervention Setting	Outcomes
Terent et al (1985) Low	RCT Sweden	37 adults	Self-management education plus SMBG versus self-management education versus SMBG versus usual care Community	HbA_{1c} Hypoglycaemia DKA

DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial; SDIS, Stockholm Diabetes Intervention Study; SMBG, self-monitored blood glucose

Winkley et al (2006)

Winkley et al (2006) undertook to assess the effectiveness of psychological interventions in improving glycaemic control and psychological distress in people with type 1 diabetes. A systematic method of literature search was undertaken with search date September 2004. Data extraction and quality assessment was undertaken independently by two authors. Psychological therapy was defined as individual, group and family, and studies were included where the control group was nonpsychological (either usual diabetes care, education, attention control or waiting list) or less intensive psychological treatment. A total of 29 trials were eligible for inclusion (16 in children, 13 in adults), and 21 studies (10 in children and 11 in adults) reported sufficient data to be included in a meta-analysis. The included studies were assessed by the authors for quality, and only two were assessed as having a low risk of bias. Fourteen of the studies used a continuous measure of psychological status, with 10 having data on psychological outcomes that could be pooled in a meta-analysis (4 in children and 6 in adults). Psychological distress was significantly lower in the intervention groups in children and adolescents, but not in adults. The characteristics of the included studies that were not included by Couch et al (2008), are presented in Table 9.11.

Table 9.11 Characteristics of randomised controlled trials included in Winkley et al (2006) but not in Couch et al (2008)

Study reference Quality[a]	Study design Country	Population	Other characteristics	Intervention
Studies in children and adolescents				
Daley (1992) C	RCT United States	54 adolescents		Individual counselling
Forsander et al (1998) C	RCT Sweden	38 children and adolescents	Newly diagnosed	Family systems therapy versus usual care
Grey et al (1998) C	RCT United States	75 adolescents		Group CBT
Howells et al (2002) A	RCT United Kingdom	91 adolescents and young adults		Problem solving and telephone support versus usual care

Study reference Quality[a]	Study design Country	Population	Other characteristics	Intervention
Mendez and Belendez (1997) C	RCT Spain	38 children		Family CBT versus usual care
Olivares et al (1997) C	RCT Spain	28 children		Family CBT versus usual care
Wysocki et al (2003) C	RCT United States	147 children and adolescents		Intensive education and medical therapy and support groups versus usual care
Studies in adults				
Belendez and Mendez (1991) C	RCT Spain	20		Group CBT versus usual care
van der Ven et al (2005) B	RCT Netherlands	107		Group CBT versus blood glucose awareness training
Didjurgeit et al (2002) B	RCT Germany	46	Microvascular complications	Individual CBT versus routine care
Feinglos et al (1987) C	RCT United States	20		Individual and group CBT versus no intervention
Fosbury et al (1997) B	RCT United Kingdom	32		Individual psychotherapy versus individualised education
Glasgow et al (1996) C	RCT United States	34	Combined type 1 and type 2	Computer assessed barriers to dietary self-care plus follow-up phone calls versus usual care
Halford (1997) C	RCT Australia	40		Group CBT versus usual care
Manning et al (1994) C	RCT United Kingdom	19	Combined type 1 and type 2	Group CBT versus intensive individual education
McGrady et al (1991) C	RCT United States	19		Individual CBT versus diabetes education
Pouwer et al (2001) B	RCT Netherlands	166	Combined type 1 and type 2	Individual counselling versus usual care
Spiess et al (1995) A	RCT Austria	23	Newly diagnosed	Psychoanalytical therapy versus usual care

Study reference Quality[a]	Study design Country	Population	Other characteristics	Intervention
Stenstrom et al (2003) C	RCT Sweden	36		Group CBT
Weinger et al (2002) B	RCT United States	74		Group CBT versus cholesterol education program

CBT, cognitive behavioural therapy; RCT, randomised controlled trial

[a] A, low risk of bias; B, medium risk of bias; C, high risk of bias

Primary studies

The characteristics of the included primary studies are summarised in Table 9.12.

Table 9.12 Primary studies included in the review

Study reference Quality	Study design Country	Population (n and other characteristics)	Intervention	Outcomes
Channon et al (2007) Good	RCT– parallel United Kingdom	Teenagers n=66	MI versus control (support visits)	HbA_{1c} Psychosocial
Grey et al (2009b) Good	RCT– parallel United States	111 children (8–12 years) and parents	Coping skills training versus group education; 12 months duration sessions, 1.5 hours intervention n=82 comparator n=53	Psychosocial
Viklund et al (2007) Fair	RCT (WLC) Sweden	Teenagers n=32	Empowerment group education weekly meetings × 6 weeks versus usual care (WLC) Invited to include parents	HbA_{1c} Psychological
Amsberg et al (2009) Good	RCT (WLC) Sweden	Adults n=94 Poor control (HbA_{1c}>7.5%)	CBT 8 × weekly 2-hour sessions (7 × group, 1 × individual) + CGMS × 2 (delivered by diabetes nurse and psychologist) Maintenance program – 2 × group and 2 × individual sessions Control – usual care plus CGMS × 2 (WLC)	HbA_{1c} Hypoglycaemia Psychological
DAFNE Study Group (2002) Good	RCT – parallel (WLC) Multicentre n=3 United Kingdom	Adults n=169	Flexible intensive insulin management 5-day education program aimed at teaching participants to adjust insulin to food and lifestyle versus usual care (WLC)	HbA_{1c} QoL

Study reference Quality	Study design Country	Population (n and other characteristics)	Intervention	Outcomes
George et al (2008) Good	RCT – parallel (WLC) United Kingdom	Adults n=117	Flexible intensive insulin management 2.5-day education program aimed at teaching insulin adjustment to food and lifestyle versus usual care (WLC)	HbA_{1c} Hypoglycaemia Psychological
Ismail et al (2010) Good	RCT – 3 arm parallel Multicentre United Kingdom	Adults with poor control (HbA_{1c}>8.5%) n=344 MET + CBT n=106 MET alone n=117 usual care n=121 Poor control HbA_{1c}>8.5%	Control. Usual diabetes care (at least 3-monthly visits) MET – 4 × individual sessions over a 2-month period MET + CBT – MET as above plus 8 CBT sessions for a further 4 months Delivered by nurses trained in method	HbA_{1c} Depression QoL
Snoek et al (2008) Fair	RCT Netherlands	Adults n=86 Poor control (HbA_{1c} ≥ 8%)	CBT versus BGAT 6 weekly group meetings with either CBT or BGAT	HbA_{1c} Psychological

BGAT, blood glucose awareness training; CBT, cognitive behavioural therapy; CGMS, continuous glucose monitoring system; HbA_{1c}, glycated haemoglobin; MET, motivational enhancement therapy; MI, motivational interviewing; QoL, quality of life; RCT, randomised controlled trial; WLC, waiting-list control

Metabolic outcomes

HbA_{1c} in children and adolescents

In the study by Couch et al (2008), 33 RCTs reported the effect of education programmes on glycated haemoglobin (HbA_{1c}). Twenty-six of these studies were assessed as being of low quality, 4 of moderate quality and 3 of high quality. HbA_{1c} levels were significantly decreased in 8 studies, 3 of which were categorised as family therapy, 4 as cognitive behavioural therapy (CBT) and 1 as general diabetes education. In 9 studies, either the intervention group or both intervention group and control group reported a nonsignificant change in HbA_{1c}; in the remaining 16 studies, there was no difference between groups. The authors concluded that, due to the heterogeneity across the studies and the general low methodological quality, it is difficult to determine which interventions may have an affect over and above standard care.

Table 9.13 Results of Couch et al (2008), HbA_{1c} in children and adolescents

Reference	Quality	N	Result
General diabetes education			
Brown et al (1997)	Low	59	No significant improvement in either group at 6 months
Hackett et al (1989)	Low	119	No significant improvement in any groups at 8 months
Howe et al (2005)	Low	89	HbA_{1c} decreased in all groups; no significant difference between groups
Wadham et al (2005)	Low	67	No significant change in either group at 6 months

Reference	Quality	N	Result
Dougherty et al (1999)	Moderate	63	Intervention group significantly lower HbA_{1c} compared to control at 24–36 months
Coupland (1990)	Low	32	Significant decreases in both groups at 6 months; no significant difference between groups
Nunn (2006)	High	123	No significant change in either group at 8 months
Cognitive behavioural therapy			
Anderson et al (1989)	Low	70	Significant difference between groups at 18 months
Anderson et al (1999)	Low	89	No significant difference between groups
Grey et al (2000)	Moderate	77	Intervention group significantly lower HbA_{1c} compared to control at 12 months
Gross et al (1985)	Low	14	No significant difference between groups
Horan et al (1990)	Low	20	No significant change in either group at 15 weeks
Kaplan et al (1985)	Low	21	Intervention group significant lower HbA_{1c} compared to control at 4 months
McNabb et al (1994)	Low	24	No significant difference between groups
Szumowski (1990)	Moderate	27	No significant change in either group at 3 months
Webb (1999)	Low	66	No significant change in either group at 3 months
Delamater et al (1990)	Moderate	36	Intervention group significantly lower HbA_{1c} compared to control at 24 months
Boardway et al (1993)	Low	31	No significant change in either group at 6 months
Cigrang (1991)	Low	37	No significant difference between groups
Delamater et al (1991)	Low	13	No significant change in either group at 4 months
Hains et al (2000)	Low	15	No significant change in either group at 1 month
Family therapy			
Laffel et al (2003)	Low	105	Intervention group significantly lower HbA_{1c} compared to control at 12 months
Satin et al (1989)	Low	32	Intervention group significantly lower HbA_{1c} compared to control at 6 months
Wysocki et al (2007)	Low	104	Intervention group significantly lower HbA_{1c} compared to control at 12 months
Kennedy-Iwai (1991)	Low	19	No significant change in HbA_{1c} for either group
Wysocki et al (2000)	High	119	No significant change in HbA_{1c} for either group at 3 months
Diabetes camp			
Massouh et al (1989)	Low	33	No significant change in either group at 3.5 months
Skills			
Mitchell et al (1996)	Low	32	HbA_{1c} lower for intervention group over control over 24 months; no significant difference except at 10–13 months
Mann et al (1984)	Low	39	No significant change in either group at 18 months
Panagiotopoulos et al (2003)	High	50	No significant difference between groups
Physical training			
Campaigne et al (1985)	Low	16	No significant change in either group at 12 weeks

Reference	Quality	N	Result
Pychoeducation			
Olmsted et al (2002)	Moderate	85	No significant change iin either group at 6 months

HbA_{1c}, glycated haemoglobin

Winkley et al (2006) presented a pooled analysis of 21 studies (10 in children and adolescents) reporting the effect of psychological interventions on glycaemic control. The mean percentage of HbA_{1c} was significantly reduced in the intervention group. There was significant heterogeneity; –0.35 (95% confidence interval [CI]: –0.66 to –0.04) equivalent to 0.48% (0.05% to 0.91%) absolute reduction in HbA_{1c}. Cochran's Q test indicated heterogeneity (p=0.002).

Table 9.14 Pooled analysis of the effect of psychological interventions on HbA_{1c} in children and adolescents (Winkley et al 2006)

Reference	Weight (%)	Effect size (95% confidence interval)
Wysocki et al (2003)	7	–0.76 (–1.10 to 0.42)
Anderson et al (1989)	5.7	–0.47 (–0.98 to 0.04)
Mendez and Belendez (1997)	4.6	–0.88 (–1.54 to –0.21)
Satin et al (1989)	3.1	–1.20 (–2.14 to –0.25)
Boardway et al (1993)	2.9	0.89 (–0.09 to 1.87)
Grey et al (1998)	6.0	–0.67 (–1.14 to –0.20)
Wysocki et al (2000)	6.1	0.16 (–0.29 to 0.61)
Delamater et al (1990)	3.4	0.13 (–0.74 to 0.99)
Howells et al (2002)	5.5	–0.32 (–0.85 to 0.22)
Sundelin et al (1996)	4.8	0.03 (–0.61 to 0.66)
Pooled	49.1	–0.35 (–0.66 to –0.03)

HbA_{1c}, glycated haemoglobin

Primary studies

Channon et al (2003) reported a significant difference in HbA_{1c} between those receiving motivational interviewing and the control group, with the intervention group having an HbA_{1c} 0.5% lower at 12 months (–0.5 ±1.81 [–1.55 to 0.55] p=0.04) and 0.4% lower at 24 months (–0.4 ±1.73 [–1.4 to 0.60] p=0.003). Viklund et al (2007) found no difference between those enrolled in the intervention and those enrolled in the control group at the end of the study. In a post hoc analysis of data, in the subgroup of teenagers who had parental involvement in the intervention program, there was a significant decrease in HbA_{1c} 12 and 24 months after intervention, from 8.9% (standard deviation [SD]=1.1) to 7.6% (SD=1.3; p<0.05, CI: 0.37 to 2.26).

HbA_{1c} in adults

Loveman et al (2003) present the results of two RCTs, both assessed as being of low quality. One study showed a significant difference between groups at all time points during follow-up to 10 years, the other showed no significant differences between groups (Table 9.15).

Table 9.15 Results of Loveman et al (2003), HbA_{1c}

Study reference Study type	N	Timepoint	Intervention (mean% ±SEM unless otherwise stated)			Control	Differences between groups
Reichard et al (1996) (SDIS) RCT	Initial total: 102 3 years=97 5 years=96 7.5 years=89 10 years=43	Baseline 18 months 3 years 5 years 7.5 years 10 years	9.5 7.5 (from graph) 7.4 (0.1) 7.2 (0.1) 7.1 (0.7) 7.2 (0.6)			9.4 9.0 (est.) 9.0 (0.2) 8.7 (0.1) 8.5 (0.7) 8.3 (1.0)	 p<0.01 p<0.01 p<0.01 p<0.01 p<0.01
Terent et al (1985) RCT	Initial total: 37 (10/8/9/10) In analysis: 37 (10/8/9/10)	 Baseline 12 months 18 months	Education + SMBG 12.3 (SD3.2) 11.0 (SD2.6) 10.2 (SD1.9)	SMBG alone 11.8 (SD1.4) 10.8 (SD1.0) 9.8 (SD3.0)	Education alone 11.2 (SD2.0) 9.9 (SD2.5) 10.2 (SD2.1)	 11.2 (SD2.3) 9.5 (SD3.2) 10.4 (SD2.1)	 NS NS

est., estimated; HbA_{1c}, glycated haemoglobin; NS, not significant; RCT, randomised controlled trial; SD, standard deviation; SDIS, Stockholm Diabetes Intervention Study; SEM, standard error of mean; SMBG, self-monitored blood glucose

Winkley et al (2006) presented a pooled analysis of 21 studies (11 in adults) reporting the effect of psychological interventions on glycaemic control. The mean percentage of HbA_{1c} was significantly reduced in the intervention group; –0.17 (95%CI: –0.45 to 0.10) equivalent to 0.22% (–0.13% to 0.56%) absolute reduction in HbA_{1c}. Cochran's Q test indicated heterogeneity (p=0.02).

Table 9.16 Pooled analysis of the effect of psychological interventions on HbA_{1c} in adults (Winkley et al 2006)

References	Weight (%)	Effect size (95% confidence interval)
Pouwer et al (2001)	6.9	–0.28 (–0.63 to 0.07)
Van der Ven et al (2005)	6.4	–0.45 (–0.88 to –0.03)
Feinglos et al (1987)	3.2	0.93 (0.00 to 1.86)
Fosbury et al (1997)	3.7	–0.78 (–1.60 to 0.04)
Weinger et al (2002)	6.1	–0.12 (–0.58 to 0.33)
Spiess et al (1995)	3.6	0.47 (–0.37 to 1.31)
Didjurgeit et al (2002)	4.9	–0.71 (–1.32 to –0.10)
Manning et al (1994)	3.2	–0.48 (–1.40 to 0.43)
Halford (1997)	4.2	0.72 (–0.01 to 1.45)
Stenstrom et al (2003)	4.3	–0.14 (–0.85 to 0.57)
Glasgow et al (1996)	4.5	–0.17 (–0.45 to 0.10)
Pooled	50.9	–0.17 (–0.45 to 0.10)

HbA_{1c}, glycated haemoglobin

Primary studies

In the two studies testing the effectiveness of training in flexible intensive insulin management, one reported a significant reduction in HbA_{1c} in the intervention group at 6 months of 1.0% (8.4% vs 9.4%; t=6.1, p<0.0001) (DAFNE Study Group 2002) and the second reported no difference between groups at any time up to 12 months follow-up (George et al 2008).

In the three studies testing the effectiveness of psychological interventions, CBT was found to reduce HbA_{1c} by approximately 0.5% at 48 weeks follow-up (–0.49 [–0.87 to –0.11] p=0.012) (Amsberg et al 2009). CBT in combination with motivational enhancement therapy (MET) significantly reduced HbA_{1c} by 0.45% over usual care (95%CI: 0.16% to 0.79%, p=0.008), and when delivered without MET resulted in a nonsignificant reduction of 0.16% over usual care (95%CI: 0.20% to 0.51%, p=0.38) (Ismail et al 2010). In another study, CBT had no effect on HbA_{1c} (Snoek et al 2008).

Severe hypoglycaemia and diabetic ketoacidosis in children and adolescents

Couch et al (2008) found six RCTs reporting the acute complications of severe hypoglycaemia and diabetic ketoacidosis (DKA). Four studies were assessed as of moderate quality and two of low quality. Three studies reported a significant effect of the intervention; one was a general diabetes education intervention, one a CBT intervention and one a skill-based intervention. The remaining studies showed either no change or no statistically significant difference between the groups.

Table 9.17 Results of Couch et al (2008), acute complications

Study reference	Quality	N	Result
General diabetes education			
Svoren et al (2003)	Low	299	Severe hypoglycaemia event rate significantly reduced in intervention group compared with control at 24 months
Dougherty et al (1999)	Moderate	63	No significant difference for severe hypoglycaemia and DKA
Cognitive behavioural therapy			
Grey et al (2000)	Moderate	77	Significantly lower event rates of severe hypoglycaemia and DKA
Szumowski (1990)	Moderate	27	No significant decrease in event rate of severe hypoglycaemia for either group at 3 months
Skills			
Nordfelt et al (2002)	Low	332	Significant reduction in event rate for severe hypoglycaemia compared with control groups at 12 and 24 months
Physical training			
Campaigne et al (1985)	Low	16	No significant difference in event rate for hypoglycaemia at 12 weeks

DKA, diabetic ketacidosis

Severe hypoglycaemia and DKA in adults

Loveman et al (2003) reported hypoglycaemia as an outcome; however, the authors did not distinguish between the different levels of hypoglycaemia (e.g. severe hypoglycaemia). Only one of the included studies reported differences between groups in ketoacidotic episodes – Terent et al (1985) found no statistical difference between groups.

Primary studies

The two studies in which severe hypoglycaemia was reported as an outcome both found no significant effect on the rate of severe hypoglycaemia (DAFNE Study Group 2002; George et al 2007).

Psychological outcomes

Knowledge in children and adolescents

The study by Couch et al (2008) included 11 RCTs that assessed the impact of interventions on knowledge. Seven studies were assessed as of low quality, 3 as moderate quality and 1 as high quality. The interventions included general diabetes education (n=5), CBT (n=3) and diabetes camps (n=3). The results of studies were inconsistent, with 3 studies of low quality reporting a statistically significant increase in knowledge, 4 studies (1 of low quality and 3 of moderate quality) reporting knowledge gains that were not statistically significant, and 4 studies (3 of low quality and 1 of high quality) reporting no change.

Table 9.18 Results of Couch et al (2008), knowledge in children and adolescents

Study reference	Quality	N	Result
General diabetes education			
Brown et al (1997)	Low	59	Intervention group significantly improved knowledge scores compared to control group at 6 months; difference was not significant
Hackett et al (1989)	Low	119	Significant increase in knowledge scores in intervention group
Howe et al (2005)	Low	89	No significant difference among groups at 6 months
Dougherty et al (1999)	Moderate	63	No significant difference between groups at 36 months
Nunn et al (2006)	High	146	No significant difference between groups
Cognitive behavioural therapy			
Gross et al (1985)	Low	14	Intervention group significantly higher knowledge scores than control at 6 months
Horan et al (1990)	Low	20	No significant difference between groups post intervention
Szumowski (1990)	Moderate	27	No significant difference
Diabetes camp			
Pichert et al (1993)	Low	146	Significant improvement in knowledge in intervention group
Pichert et al (1994a)	Low	83	Both groups significant improvement; difference not significant post camp
Pichert et al (1994b)	Moderate	84	No significant difference between groups at 8 months

Knowledge in adults

In the one study reporting knowledge as an outcome, a diabetes knowledge test demonstrated no significant change as a result of the intervention (George et al 2008).

Self-management behaviour in children and adolescents

Couch et al (2008) reported that 15 studies assessed self-management and regimen adherence; 1 study of moderate quality and 7 of low quality reported significant improvement in self-management in the intervention group. Successful interventions included general diabetes education (n=3), CBT (n=3) and family therapy (n=2). The remaining studies did not show a significant change.

Table 9.19 Results of Couch et al (2008), self-management behaviour in children and adolescents

Study reference	Quality	N	Result
Diabetes education			
Brown et al (1997)	Low	59	Intervention group had significant gains in self care compared with control group at 6 months
Hackett et al (1989)	Low	119	No significant difference for either group in nutritional management
Howe et al (2005)	Low	89	Significant group × time interaction; significant increase in roles/responsibilities at 12 months
Dougherty et al (1999)	Moderate	63	No significant change for either group at 36 months
Coupland (1990)	Low	32	Self-management significantly higher in intervention group compared to control at 6 months; adherence – intervention group significantly different from control at 6 months
Cognitive behavioural therapy			
Gross et al (1985)	Low	14	Adherence – intervention group showed increase in compliance compared with control at 6 months
Horan et al (1990)	Low	20	Adherence – intervention group showed greater behavioural change at 6 months than control
McNabb et al (1994)	Low	24	No significant difference between groups at 12 weeks
Szumowski (1990)	Moderate	27	Self-management – significant interaction comparing baseline at 3 months; no other significant improvement in either group at 3 months in roles/responsibilities or physical activity or nutritional management
Webb (1999)	Low	66	No significant differences between groups at 3 months
Boardway et al (1993)	Low	31	Adherence – no significant change for either group at 6 months
Delamater et al (1991)	Low	13	Adherence – intervention group higher compared to control at 4 months, but difference not significant
Family therapy			
Laffel et al (2003)	Low	105	Intervention group – significantly more involvement in roles/responsibilities compared to control at 12 months
Wysocki et al (2007)	Low	104	Adherence – significantly higher scores in intervention than control at each follow-up
Wysocki et al (2000)	High	119	Improvement in younger children at 3 months, but effect not significant

Psychosocial outcomes in children and adolescents

Couch et al (2008) reported that 21 RCTs examined one or more psychosocial outcomes including family or social relationships, family or social support, social skills, coping, self-perception, self-efficacy, stress, depression and anxiety. The authors concluded that diabetes education was effective in improving several psychosocial outcomes; however, the study quality was generally low and there was considerable heterogeneity across interventions, time points and measures used.

Table 9.20 Results of Couch et al (2008), psychosocial outcomes in children and adolescents

Study reference	Quality	N	Result
General diabetes education			
Brown et al (1997)	Low	59	Significant increased communication skills compared to control at 6 months Self-efficacy – no significant difference between groups at 6 months
Coupland (1990)	Low	32	Family and social support – no significant difference between groups at 6 months
Hoff et al (2005)	High	46	Self-efficacy – no significant difference between groups at 6 months
Dougherty et al (1999)	Moderate	63	No significant difference between groups on family impact at 24 months
Nunn et al (2006)	High	123	Social skills – no significant change for either group at 5–8 months
Cognitive behavioural therapy			
Anderson et al (1999)	Low	89	Significantly less conflict; significant decrease in unsupportive behaviour compared to control at 12 months
Grey et al (2000)	Moderate	77	Coping – no significant difference between groups Self-efficacy – intervention group significantly better at 12 months Depression – no significant difference between groups
Gross et al (1985)	Low	14	Significantly less conflict; significant increase in social skills
Szumowski (1990)	Moderate	27	Conflict – no significant difference between groups
Boardway et al (1993)	Low	31	Coping and self-efficacy – no significant difference between groups at 6 months Stress – significantly less in intervention group at 6 months
Cigrang (1991)	Low	37	Coping, self-perception, depression – no significant difference between groups
Delamater et al (1991)	Low	13	No difference between groups – parent–teenager relationship at 4 months; social support measures
Hains et al (2000)	Low	15	Coping, stress and anxiety – no significant difference between groups at 1 month
Family therapy			
Laffel et al (2003)	Low	105	Conflict – no significant difference between groups 12 months
Satin et al (1989)	Low	32	No significant change in family environment at 12 months
Wysocki et al (2007)	Low	104	Family conflict – no significant difference between groups at 12 months
Kennedy-Iwai (1991)	Low	19	No difference between groups – family environment or conflict at 3 months
Wysocki et al (2000)	High	119	Problem resolution, negative communication, intervention group significantly improved at 12 months Coping – no significant difference between groups at 12 months

Study reference	Quality	N	Result
Sundelin et al (1996)	Low	38	Family/social relationships and self-perception – no significant difference between groups at 24 months
Hakimi (1998)	Low	35	Anxiety and depression – no significant difference between groups at 6 weeks
Skills			
Mitchell (1996)	Low	32	Family/social relationships and coping – no significant difference between groups at 12 months Depression/anxiety – significant improvement at 12 months

Winkley et al (2006) using a random effects meta-analysis reported a significant reduction in psychological distress with psychological therapy in children and adolescents (pooled estimate –0.46, –0.83 to –0.10, p=0.013). There was no evidence for heterogeneity in psychological distress effects (Cochran's Q test p=0.23).

Table 9.21 Psychological distress in children and adolescents (Winkley et al 2006)

Study reference	Measure	Weight (%)	Effect size (95%CI)
Boardway et al (1993)	Diabetes stress questionnaire	3.9	–1.00 (–2.00 to –0.01)
Grey et al (2000)	Child depression inventory	17.3	–0.71 (–1.18 to –0.25)
Howells et al (2002)	Self-efficacy for diabetes	13.2	–0.28 (–0.82 to 0.26)
Sundelin et al (1996)	Self-efficacy scale	9.4	–0.05 (–0.83 to –0.10)
Pooled		43.8	–0.46 (–0.83 to –0.10)

CI, confidence interval

Primary studies

Channon and colleagues (2007) reported significant benefits on various psychosocial measures as a result of motivational interviewing. There were differences in psychosocial variables at 12 months, with the MI group reporting more positive well-being (p<0.001), less depression (p=0.044) and anxiety (p=0.001) and differences in their personal models of illness (p=0.001). In the study by Grey et al (2009a) both the coping skills training group and the control group improved over time, reporting lower impact of diabetes, better coping with diabetes, better diabetes self-efficacy, fewer depressive symptoms, and less parental control. The authors suggested that group-based interventions may be effective in teenagers. Viklund and colleagues reported that teenagers felt more ready for changes after the empowerment programme (3.9 SD=0.5 to 4.1 SD=0.5; p<0.05) (Viklund et al 2007).

Psychosocial outcomes in adults

Winkley et al (2006), using a random effects meta-analysis, reported some evidence for a reduction in psychological distress with psychological therapy in adults; however, this did not reach statistical significance (pooled estimate –0.25, 95%CI: –0.51 to 0.01, p=0.059). There was no evidence for heterogeneity in psychological distress effects (Cochran's Q test p=0.74).

Table 9.22 Effect size from different measures

Study references	Measure used	Weight (%)	Effect size (95%CI)
van der Ven et al (2005)	Centre for epidemiological studies scale for depression	21.8	–0.10 (–0.52 to 0.32)
Fosbury et al (1997)	Inventory of interpersonal problems	6.1	–0.02 (–0.81 to 0.77)
Spiess et al (1995)	Beck depression inventory	5.5	–0.28 (–1.11 to 0.55)
Didjurgeit et al (2002)	Zerssen depression scale	10.8	–0.25 (–0.84 to 0.35)
Belendez and Mendez (1991)	State trait anxiety inventory	4.6	–0.74 (–1.65 to 0.17)
Stenstrom et al (2003)	Mood adjective checklist	7.3	–0.57 (–1.30 to 0.15)
Pooled		56.2	–0.25 (–0.51 to 0.01)

CI, confidence interval

Primary studies

In the two studies testing the effectiveness of training in flexible intensive insulin management, one reported a positive effect of the intervention on the impact of diabetes on dietary freedom (t=5.4, p<0.0001) (DAFNE Study Group 2002), and the other reported significant improvements in treatment satisfaction at 3 months (difference=9.4, 95%CI: 5.2 to 13.6, p=0.0005), 6 months (difference=10.4, 95%CI: 6.0 to 14.8, p=0.0005) and 12 months (difference=7.1, 95%CI: 2.1 to 12.1, p=0.006); significant improvement in two dimensions of the diabetes empowerment scale, 'managing psychological aspects' and 'setting and achieving goals' at 3, 6 and 12 months; and no significant effect as measured by the Illness Perception Questionnaire, Hypoglycaemia Fear Scale and Short Form 36 (George et al 2008).

In the three studies testing the effectiveness of psychological interventions, CBT was found to have a significant effect on various psychosocial measures in one study, with a significant difference between groups in well-being (p<0.05), diabetes-related distress (p<0.05), frequency of blood glucose level (BGL) testing (p<0.05), avoidance of hypoglycaemia (p<0.05), perceived distress (p<0.05), anxiety (p<0.05), and depression (p<0.05) (Amsberg et al 2009). CBT had no effect on psychosocial outcomes in a second study (Ismail et al 2010). In the third study, which compared CBT with blood glucose awareness training, both interventions resulted in lower depressive symptoms (Center for Epidemiologic Studies Depression Scale 15.7–13.3, p=0.01) up to 12 months (Snoek et al 2008).

Quality of life in children and adolescents

Couch et al (2008) concluded that, overall, there was limited evidence for QoL and the results were mixed. Of the studies included in this review, one study of moderate quality (Grey et al 2000) found that adolescents who received coping skills training along with intensive diabetes management experienced less negative impact on QoL compared to controls. The RCT by Laffel et al (2003) found no difference in QoL scores between the family therapy group and control group.

Table 9.23 Primary studies examining the effect of educational and/or psychosocial interventions on quality of life in children and adolescents

Study reference	Quality	N	Result
Cognitive behavioural therapy			
Grey et al (2000)	Moderate	77	Intervention group experienced less negative quality of life than control at 10 months
Family therapy			
Laffel et al (2003)	Low	105	No significant differences between groups at 12 months

Primary studies

In the study by Channon et al (2007) significant improvement in QoL (as measured by the diabetes QoL [DQOL]) was reported for the group receiving motivational interviewing in measures of satisfaction ($p<0.001$), impact of diabetes ($p=0.003$) and worries ($p<0.001$).

Quality of life in adults

Neither of the RCTs reported by Loveman et al used validated QoL measurement tools, so results were therefore not reported in this review (Loveman et al 2003).

Primary studies

The DAFNE Study Group (2002) reported a positive impact on QoL of training in flexible intensive insulin management ($t=2.9$, $p<0.01$). CBT had no effect on QoL in the study reported by Ismail and colleagues (2010).

9.2.8 Discussion

Level I studies – metabolic outcomes

Where studies were assessed individually, there was no clear evidence that any specific educational or psychological programmes improved HbA_{1c} in children and adolescents; however, more intensive interventions (e.g. CBT and family therapy) appeared to have a small benefit (Couch et al 2008). The pooled effect of psychological interventions on lowering HbA_{1c} in children and adolescents was approximately 0.5%, but significant heterogeneity was reported (Winkley et al 2006). In adults, a long-term significant improvement (up to 10 years of follow-up) in HbA_{1c} was demonstrated where education was delivered in conjunction with intensification of treatment (Loveman et al 2003). The pooled effect of psychological interventions in lowering HbA_{1c} in adults was not found to be significant (Winkley et al 2006), but again, significant heterogeneity was reported. Results of the effect of interventions on rates of DKA and severe hypoglycaemia in children and adolescents are unclear. Couch et al (2008) pointed out that most studies did not have high enough rates of DKA to show significant differences, and that it is possible that both standard care and standard diabetes education effectively reduce the incidence of hypoglycaemia, making it difficult to demonstrate differences among different educational interventions. In adults, the rate of severe hypoglycaemia was not reported as an outcome (Loveman et al 2003; Winkley et al 2006) and there were no differences between treatment groups in the one study reporting the rate of DKA (Loveman et al 2003).

Level II studies – metabolic outcomes

The inconsistency in the effect of educational or psychological interventions on HbA_{1c} as reported by Couch et al (2008), was also reflected in the primary studies, with motivational

interviewing resulting in a significant reduction in HbA_{1c} of 0.5% (Channon et al 2007) and MET having no effect on HbA_{1c} (Viklund et al 2007). The effect on HbA_{1c} in the Level II studies in adults was also inconsistent. However, this may well be a reflection of the heterogeneity in interventions, and in study quality.

Level I studies – psychological outcomes

Studies in children and adolescents reported inconsistent results on the effect on knowledge, with most studies reporting no significant difference between groups (Channon et al 2007). The effect of interventions on knowledge in adults was not reported (Loveman et al 2003). The effect of education or psychological interventions on self-management behaviours was not consistent across studies in children and adolescents, with 8 of 15 studies reporting a significant effect (Couch et al 2008), and was not reported in adults (Loveman et al 2003). In children and adolescents, interventions had significant effects on various psychosocial outcomes; however, there was significant heterogeneity across interventions, time points and measures used (Couch et al 2008). A pooled analysis of psychological interventions in children demonstrated a significant reduction in psychological distress, with no significant heterogeneity reported (Winkley et al 2006). The results of the same analysis in adults was not significant (Winkley et al 2006). There were inconsistent results between two studies reporting QoL measures in children and adolescents (Couch et al 2008); in the studies in adults, a validated tool for measurement of QoL was not used and the results were not reported (Loveman et al 2003).

Level II studies – psychological outcomes

In children and adolescents there were a number of significant improvements in psychological outcomes reported (Channon et al 2007; Viklund et al 2007; Grey et al 2009a), reflecting evidence from the Level I studies. In adults, training in flexible intensive insulin management had significant benefit in terms of treatment satisfaction, dietary freedom, empowerment and QoL (DAFNE Study Group 2002; George et al 2008). CBT had an inconsistent effect on psychological outcomes in the primary studies in adults (Amsberg et al 2009; Ismail et al 2010).

9.2.9 Conclusion

This systematic review into the evidence for the effectiveness of education and/or psychological interventions in reducing HbA_{1c}, severe hypoglycaemia and DKA, and improving psychological outcomes, is based on three Level I studies of low risk of bias, and eight Level II studies, six of which were of low risk of bias and two of moderate risk of bias. The studies included in the three Level I studies were predominantly of high risk of bias.

In children and adolescents, educational or psychological interventions were heterogeneous, and results were inconsistent for their effect on HbA_{1c}, severe hypoglycaemia, DKA, knowledge, self-management behaviours and psychological outcomes. A pooled analysis of the effect of psychological interventions found a 0.5% reduction in HbA_{1c}, but with significant heterogeneity.

In adults, self-management education was found to have a significant effect in lowering HbA_{1c} (0.5–1.0%) when delivered in conjunction with intensive diabetes management, but this was not a consistent finding, reflecting heterogeneity of interventions and study quality. Specific psychological interventions (e.g. CBT) also resulted in a significant reduction in HbA_{1c} of approximately 0.5%, whereas a pooled analysis of psychological interventions found no significant effect on HbA_{1c}, with significant heterogeneity reported. Self-management education in the context of intensive insulin management consistently resulted in significant

improvements in a number of psychological outcomes, including QoL. A pooled analysis of psychological interventions found no significant effect on the psychosocial outcome of psychological distress.

Reported exclusions included mental illness, pregnancy, diabetes complications, hypoglycaemia unawareness and low literacy levels or lack of fluency in English language. One study was carried out in Australia, the rest in countries also with a well-established health-care system.

9.2.10 Literature search strategy

The search was conducted between 25 August 2010 and 30 August 2010. Level I studies were considered first, with the plan to update with Level II studies as required. The Medline search strategy and a summary of citations retrieved from other searches is shown in Table 9.24.

Table 9.24 Search strategy, question 9.2

Database	Date searched	#	Search terms	Citations
Medline	25 August 2010	1	exp Diabetes Mellitus, type 1/	52 843
		2	Education/	16 235
		3	patient education.mp. or exp Patient Education as Topic/	65 880
		4	health education.mp. or exp Health Education/	124 349
		5	(((diabet$ or lifestyle or education$) and intervention$) or program$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	530 965
		6	(psycholog$ or psychotherap$ intervention).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	444 209
		7	(psycholog$ or psychotherap$ intervention).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	444 209
		8	psychosocial intervention.mp.	708
		9	meta-analysis.mp. or exp Meta-Analysis/	41 431
		10	systematic review.mp.	19 034
		11	pooled analysis.mp.	1 866
		12	(review and medline).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	29 126
		13	(systematic* and (review* or overview*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	44 893
		14	2 or 3 or 4 or 5 or 6 or 7 or 8	1 039 212
		15	9 or 10 or 11 or 12 or 13	94 422
		16	1 and 14 and 15	88
		17	limit 16 to (english language and humans)	81
EMBASE	25 August 2010	1	exp Diabetes Mellitus, type 1/	58 964
		2	Education/	234 555
		3	patient education.mp. or exp Patient Education as Topic/	72 930

Database	Date searched	#	Search terms	Citations
		4	health education.mp. or exp Health Education/	188 110
		5	(((diabet$ or lifestyle or education$) and intervention$) or program$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	674 362
		6	(psycholog$ or psychotherap$ intervention).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	635 205
		7	(psycholog$ or psychotherap$ intervention).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	635 205
		8	psychosocial intervention.mp.	936
		9	meta-analysis.mp. or exp Meta-Analysis/	62 285
		10	systematic review.mp.	46 786
		11	pooled analysis.mp.	2 415
		12	(review and medline).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	40 644
		13	(systematic* and (review* or overview*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	76 570
		14	2 or 3 or 4 or 5 or 6 or 7 or 8	1 520 988
		15	9 or 10 or 11 or 12 or 13	137 938
		16	1 and 14 and 15	216
		17	limit 16 to (english language and humans)	198
Psychinfo	25 August 2010	1	type 1 diabetes.mp.	625
		2	exp Diabetes/	6 560
		3	education/	12 016
		4	health education.mp. or exp Health Education/	11 123
		5	(self-management or self care).mp. [mp=title, abstract, heading word, table of contents, key concepts]	9 168
		6	(psycholog$ or psychotherap$ intervention).mp. [mp=title, abstract, heading word, table of contents, key concepts]	278 620
		7	psychosocial intervention.mp.	927
		8	meta-analysis.mp. or exp Meta Analysis/	8 884
		9	(systematic* and (review* or overview*)).mp. [mp=title, abstract, heading word, table of contents, key concepts]	11 087
		10	pooled analysis.mp.	174
		11	3 or 4 or 5 or 6 or 7	306 698
		12	8 or 9 or 10	19 152
		13	1 or 2	6 596
		14	11 and 12 and 13	39
		15	limit 14 to (human and english language)	38
CINAHL	25 August 2010			0

Database	Date searched	#	Search terms	Citations
Cochrane	25 August 2010			16
INAHTA	25 August 2010			35
Manual search				0
Total citations				319
Total non-duplicate citations				245

9.2.11 Evidence Matrix

Children and adolescents: (i) metabolic outcomes

Q9.2	What is the effectiveness of education and/or psychological support programs in type 1 diabetes?	
Evidence statement	There is some evidence from Level I and II studies for a beneficial effect of psychological support programs and education on glycaemic control in children and adolescents. There is insufficient evidence to identify a particular intervention that is more effective than standard care to improve glycaemic control.	
Evidence base	C	Two Level I studies with a low risk of bias. HbA_{1c} – Level II studies – 25 with a high risk of bias, 5 with a moderate risk of bias and 3 with a low risk of bias. Severe hypoglycaemia – Level II studies – 3 with a high risk of bias and 3 with a low risk of bias. Diabetic ketoacidosis – Level II studies – 2 with a moderate risk of bias.
Consistency	D	HbA_{1c} (meta-analysis – 0.5% difference in HbA_{1c} – significant heterogeneity) – findings inconsistent. Severe hypoglycaemia and diabetic ketoacidosis – findings inconsistent.
Clinical impact	C	
Generalisability	B	Exclusions were not reported.
Applicability	A	One study was conducted in Australia, the others in countries with a well-established health-care system.
Other factors	None identified.	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Children and adolescents (ii): psychological outcomes

Q9.2	What is the effectiveness of education and/or psychological support programs in type 1 diabetes?	
Evidence statement	There is Level I and II evidence that educational or psychological interventions improve some psychological outcomes, including psychological distress and self-management behaviours in young people with type 1 diabetes.	
Evidence base	A	Two Level I studies of low risk of bias (most studies of low or moderate risk of bias) and three Level II studies (one of moderate risk of bias and two of low risk of bias).
Consistency	D	(Couch et al 2008) Knowledge – inconsistent (5/11 significant difference). Self-management behaviour – inconsistent (6/15 significant effect, 4/15 positive effect not significant, 5/15 not significant). Psychosocial – inconsistent (7/15 significant effect). QoL – inconsistent (1/2 positive effect). (Winkley et al 2006) Psychological interventions – significant effect on psychological distress. Level II studies. QoL – significant improvement in one study, no effect in two studies.
Clinical impact	D	The findings are unlikely to alter current clinical practice.
Generalisability	B	Exclusions were not reported.
Applicability	A	One study was conducted in Australia, the others in countries with a well-established health-care system.
Other factors	None identified.	

QoL, quality of life

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Adults (i): education and psychological interventions on metabolic outcomes

Q9.2	What is the effectiveness of education and/or psychological support programs in type 1 diabetes?	
Evidence statement	The evidence base shows that the intensified education programs delivered in Reichard et al (1996) and the DAFNE Study Group (2002) are associated with reductions in HbA_{1c} compared with usual care. However, the intensified education programs delivered in the BITES program and by Terent et al (1985) were not associated with reductions in HbA_{1c} compared with usual care.	
Evidence base	B	One Level I study with a low risk of bias (including two Level II studies with a high risk of bias), and two Level II studies with a low risk of bias.
Consistency	B	• HbA_{1c} –Results from the Level I study were inconsistent. In the larger study with a long intervention involving phone calls, etc, and a long follow-up, the intervention had a significant effect in combination with intensification of therapy. In the smaller study that was of poor quality and involved a relatively brief intervention, there was no effect. The Level II studies found a significant effect in one study but not in the other. • Severe hypoglycaemia was not reported (NA). • Diabetic ketacidosis was reported in one study, which showed no effect (NA).
Clinical impact	B/C	HbA_{1c} – B Psychological outcomes – C
Generalisability	B	Reported exclusions included pregnancy, non-English speaking, mental illness and diabetes complications.
Applicability	A	The studies were in countries with an established health-care system.
Other factors	The heterogeneity of interventions contributed to differences in findings. The focus here is on the incremental benefit associated with intensified education compared to standard education. However, issues around how to define standard education may affect interpretation. It is taken as given that education is an effective and critical component of care.	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Adults (ii): psychological outcomes

Q9.2	What is the effectiveness of education and/or psychological support programs in type 1 diabetes?	
Evidence statement	There is Level II evidence that educational and psychological interventions improve some psychological outcomes (including psychological wellbeing, diabetes-related distress, self-care behaviours, distress, anxiety and depression) in adults.	
Evidence base	B	One Level I study with a low risk of bias (most included studies were of moderate and high risk of bias) and three Level II studies (two with a low risk of bias and one of moderate risk of bias).
Consistency	C	• Educational interventions and psychological outcomes – both Level II studies reported a significant effect in terms of dietary freedom, quality of life, diabetes empowerment and treatment satisfaction (B). • Psychological outcomes – the meta-analysis found no significant effect on psychological distress; of the Level II studies, one found a significant effect on wellbeing, diabetes-related distress, self-care behaviours, distress, anxiety and depression; the other two studies found no significant effect on psychological outcomes.
Clinical impact	D	The findings are unlikely alter current clinical practice.
Generalisability	B	Reported exclusions included pregnancy, non-English speaking, mental illness and diabetes complications.
Applicability	A	The studies were conducted in countries with an established health-care system.
Other factors	None identified.	
Recommendation		
R9.2	Education and psychological support are an essential component of standard diabetes care. Intensified education and psychological support programs should be considered when treatment goals are not being met (Grade B).	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

10 Nutrition

This chapter of the technical report addresses the safety and efficacy of nutritional interventions in the management of type 1 diabetes. The interventions reported here include:

- following a meal plan of fixed carbohydrate versus a liberalised intake of dietary carbohydrate, and matching of insulin to the estimated carbohydrate content of the meal
- low glycaemic index or high fibre diet versus moderate or high glycaemic index diet
- high protein diet versus no modification of protein intake
- high monounsaturated fat diet versus no modification of fat intake

10.1 Carbohydrate quantification

Question 10.1

What are the efficacy and safety of

(i) regulating or quantifying dietary carbohydrate and

(ii) insulin-to-carbohydrate ratios in type 1 diabetes?

10.1.1 Criteria for eligibility

Studies were eligible for inclusion in question 10.1 if they met the criteria shown in Table 10.1.

Table 10.1 Criteria for determining study eligibility, question 10.1

Study design	Level I or Level II (NHMRC intervention scale[a])
Population	Children and adults with type 1 diabetes
Intervention	Variable carbohydrate intake and matching insulin dose to estimated carbohydrate of more than 4 weeks duration
Comparator	Fixed carbohydrate meal plan
Outcomes	HbA_{1c} Body mass index and weight Quality of life Severe hypoglycaemia

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

10.1.2 Literature search summary

The results of the literature search for questions 10.1 to 10.4 are shown in Table 10.2. The initial search was for Level I studies, then Medline and EMBASE were searched again, restricted to RCTs.

Table 10.2 Search results, questions 10.1 – 10.4

Stage	Notes	Level I and II (n)	RCTs (n)
Search summary	Manual	0	2
	Cochrane Library	9	–
	EMBASE	56	182
	Medline	15	281
	INAHTA	1	–
Duplicates	Duplicates identified	32	
Identified	Total identified	456	
Exclusion criteria	Wrong study type	94	
	Wrong population	28	
	Wrong intervention	249	
	Wrong outcome	8	
	Not in English		
	Total excluded		
Meeting criteria	Total meeting inclusion criteria	79	
Included	Total included studies (for questions 10.1 – 10.4)	8	

10.1.3 Included studies

Three Level II studies that met the inclusion criteria were suitable for inclusion (Kalergis et al 2000; DAFNE Study Group 2002; Scavone et al 2010), but no Level I studies were suitable.

10.1.4 Characteristics of included studies

The characteristics of the three studies are shown inTable 10.3.

In the study by the DAFNE Study Group (2002), participants in the intervention group completed a 5-day course intended to help them develop skills and confidence in adjusting insulin to suit a flexible diet and lifestyle. This intervention was compared to usual care, which involved adapting the timing and content of food to more fixed doses of insulin.

The RCT by Kalergis et al (2000) compared three approaches to intensive insulin management:

- simplified (SIMP), which involved a set meal plan based on the exchange system with no self-adjustments of insulin for food, exercise and stress
- qualitative (QUAL), which involved a set meal plan based on the exchange system with qualitative adjustments of insulin for food, exercise and stress
- quantitative (QUANT), involving a meal plan based on carbohydrate gram counting and quantitative adjustments of insulin for food based on ratios of units of regular

insulin/10 g carbohydrate and qualitative adjustments of insulin for exercise and stress similar to QUAL.

Most participants had been following a treatment plan similar to SIMP before enrolling in the study; 12 subjects chose to continue with QUAL, 3 with QUANT, and none with SIMP.

In the study by Scavone et al (2010), patients were randomised to either a nutritional education program involving 4 sessions held over 1 month duration, aimed at teaching them to adjust insulin doses in relation to carbohydrate content of meals, or to no nutrition education program. Before enrolment, none of the participants had followed any dietetic or educational program.

Table 10.3 Characteristics of included studies, question 10.1

Reference	Study type and quality	Population	Intervention	Comparator	Outcomes
DAFNE Study Group (2002)	RCT, parallel design, multicentre (n=3) Good	n=169 adults mean age 40 ±9 years mean duration of diabetes 16.6 ±9.6 years United Kingdom	Flexible intensive insulin management 5-day education program aimed at teaching participants to adjust insulin to food and lifestyle	Usual care, placed on 6-month waiting list for intervention	HbA_{1c}, severe hypoglycaemia, QoL (ADDQoL)
Kalergis et al (2000)	RCT, duration 3.5 months with three approaches to intensive insulin management Washout period not reported Poor	n=21 adults mean age 38 (range 23–59) years sex (M/F) 6/9 duration of diabetes mean=18.1 (range 8–28) years Canada	Adjusting insulin doses for food intake using insulin/ carbohydrate ratios	No adjustment of insulin for food intake (SIMP) or qualitative adjustment of insulin for food intake (QUAL)	HbA_{1c}, weight, QoL (DQOL, MOS)
Scavone et al (2010)	RCT, parallel design Poor	n=256 adults intervention: n=100 age: 39 ±11 years n=51 female comparator: n=156 age 39 ±11 years n=82 female Italy	Nutritional education program Four educational sessions over 1 month teaching insulin adjustment to carbohydrate, exercise, and glycaemia	Usual care	HbA_{1c}, hypoglycaemia, weight

ADDQoL, Audit of Diabetes-Dependent Quality of Life; DQOL, diabetes quality of life; HbA_{1c}, glycated haemoglobin; MOS, Medical Outcomes Survey; QoL, quality of life; QUAL, qualitative; RCT, randomised controlled trial, SIMP, simplified

10.1.5 Results of included studies

Glycaemic control

All three studies reported glycated haemoglobin (HbA_{1c}) as an outcome (Table 10.4). One study reported a significant difference between the intervention and control groups at end of study, in favour of a flexible intake of carbohydrate (DAFNE Study Group 2002). Another study reported a statistical within-group difference, with the intervention group lowering

HbA_{1c} from baseline to end of study more than the control group (Scavone et al 2010). The third study found no statistical difference between treatments (Kalergis et al 2000).

Table 10.4 Results from included studies, question 10.1 (HbA_{1c})

Study reference	Flexible dietary intake		Fixed meal plan	Statistical difference between groups
DAFNE Study Group (2002)	8.4%		9.4%	t=6.1, p<0.0001
Scavone et al (2010)	7.8 ±1.3 baseline to 7.4 ±0.9%		7.5 ±0.8 baseline to 7.5 ±1.1%	p<0.01
Kalergis et al (2000)	QUAL 9.5 ±0.44	QUANT 10.2 ±0.43	SIMP 9.7 ±2.9	NS

NS, not significant; QUAL, qualitative; QUANT, quantitative; SIMP, simplified

Body mass index or weight

In the two studies that reported body mass index (BMI) or weight as an outcome, no significant differences between groups were found (Kalergis et al 2000; DAFNE Study Group 2002).

Quality of life

Quality of life (QoL) was reported as an outcome in two of the studies (Table 10.5). The DAFNE Study Group (2002) used a validated measurement tool (Audit of Diabetes-Dependent Quality of Life [ADDQoL]) and found a significant improvement in aspects of QoL in the intervention group. Kalergis et al (2000) measured QoL with a validated diabetes-specific tool (diabetes quality of life [DQOL]) and a validated generic tool (Medical Outcomes Survey [MOS]), and found no significant differences between treatment arms.

Table 10.5 Results from included studies, question 10.1 (quality of life)

Study reference	Measure	Flexible dietary intake		Fixed meal plan	statistical difference between groups
DAFNE Study Group (2002)	Impact of diabetes on dietary freedom	–1.8 (2.3)		–4.0 (2.9)	2.2 (1.3 to 3.1) t=5.4, p<0.0001
	Impact of diabetes on quality of life	–1.6 (1.6)		–1.9 (1.3)	0.4 (–0.1 to 0.9) t=2.9, p<0.01
Kalergis et al (2000)	DQOL	QUAL 1.9 ±0.13	QUANT 1.8 ±0.11	SIMP 2.0 ±0.13	NS

DQOL, diabetes quality of life; NS, not significant; QUAL, qualitative; QUANT, quantitative; SIMP, simplified

Severe hypoglycaemia

One of the three studies reported severe hypoglycaemia as an outcome (Table 10.6). No difference was found between groups at 6 months (DAFNE Study Group 2002).

Table 10.6 Results from included studies, question 10.1 (severe hypoglycaemia)

Study reference	Flexible dietary intake	Fixed meal plan	Statistical difference between groups
DAFNE Study Group (2002)	Proportion of participants with hypoglycaemia in past 6 months 12/67 (18)	Proportion of participants with hypoglycaemia in past 6 months 11/72 (15)	χ^2=0.17, p=0.68

10.1.6 Discussion

Three studies, all with adult participants, met the inclusion criteria. The studies examined interventions where the dietary management included flexible intake of carbohydrate with adjustment of insulin based on insulin to carbohydrate ratios (Kalergis et al 2000; DAFNE Study Group 2002; Scavone et al 2010). Two of the studies (n=425) reported a positive effect on HbA_{1c} in the flexible diet groups. The DAFNE Study Group (2002) also reported positive benefits on aspects of QoL. One of the studies (n=21) did not report a difference in HbA_{1c} or QoL between treatment arms; however, the sample size was small and the quality was poor (Kalergis et al 2000). No significant differences were found in weight, BMI and severe hypoglycaemia.

10.1.7 Conclusion

One study of low risk of bias and two of high risk of bias met the inclusion criteria for this question. The inconsistencies in the effect on metabolic control (HbA_{1c}) and QoL can probably be explained by differences in interventions and study quality. Where BMI and weight were measured, there was a consistent finding of no statistical difference between the intervention and control groups. The rate of severe hypoglycaemia was assessed in only one study, which found no difference between groups. These results are generalisable to an adult population with type 1 diabetes. There is some evidence to suggest an improvement in both HbA_{1c} and QoL in adults who have received education on the use of insulin to carbohydrate ratios to enable a liberalised carbohydrate intake.

10.1.8 Literature search strategy

Search terms included all terms relevant to the four nutrition questions (10.1 to 10.4) addressed in these guidelines, with an initial search including terms for Level I evidence and a subsequent search including terms for Level II evidence.

The search for Level I and Level II studies was conducted between 26 July 2010 and 29 July 2010. The search strategy is shown in Table 10.7. The search strategy for RCTs is shown in Table 10.7.

10.1.9 Evidence Matrix

Q10.1	What is the efficacy and safety of following a meal plan with a fixed carbohydrate intake versus a liberalised intake of dietary carbohydrate and/or matching insulin to estimated carbohydrate in type 1 diabetes?	
Evidence statement	Level II evidence (from three studies) shows that the use of insulin-to-carbohydrate ratios in multiple daily injection therapy reduces HbA_{1c} but has no clinically significant effect on weight, QoL or severe hypoglycaemia.	
Evidence base	C	Three Level II studies – one with a low risk of bias and two with a high risk of bias.
Consistency	C	HbA_{1c} – two studies were positive; 1% with the DAFNE Study Group (2002), 0.4% with Scavone et al (2010) (one study of high quality), and one study was negative (small sample size and high risk of bias).
	A	BMI/weight – no change in this outcome in two studies.
	D	QoL – reported in two studies, one showing a positive change and the other study (small sample size and high bias) showing no significant change.
	NA	Severe hypoglycaemic episodes – reported in one study.
Clinical impact	C	$HbA_{1c.}$
	D	BMI/weight.
	C	QoL.
	D	Severe hypoglycaemic episodes.
Generalisability	C	Studies included adults only, and excluded people with non-English speaking, psychiatric illness, pregnancy, complications and hypoglycaemia unawareness. The studies did not include children or the elderly, and may have included dietary naive subjects.
Applicability	B	Studies were conducted in Canada, Italy and the United Kingdom.
Other factors	None identified.	
Recommendation		
R10.1	Matching of meal-time insulin dose to carbohydrate intake should be considered for patients using multiple daily injection therapy (Grade C).	

BMI, body mass index; HbA_{1c}, glycated haemoglobin; QoL, quality of life; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Table 10.7 Search strategy for Level I and Level II studies and systematic reviews, questions 10.1 to 10.4

Database	Date searched	#	Search terms	Citations
Medline	26 July 2010	1	Diabetes Mellitus, type 1/ or diabetes mellitus type 1.mp.	52 503
		2	(diet$ adj5 diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	7 932
		3	(diet$ adj5 carbohydrate$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	22 970
		4	(diet$ adj5 fat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	56 804
		5	(diet$ adj5 glyc?em$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	945
		6	(diet$ adj5 protein$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	40 880
		7	(glycemic index or glyc?emic index).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1 727
		8	GI.mp.	21 509
		9	exp Dietary Carbohydrates/	20 970
		10	exp Dietary Fiber/ or dietary fibre.mp.	11 349
		11	dietary proteins.mp. or exp Dietary Proteins/	70 293
		12	dietary fats.mp. or exp Dietary Fats/	61 674
		13	medical nutrition therapy.mp. or exp Nutrition Therapy/	68 660
		14	carbohydrate counting.mp.	49
		15	carbohydrate exchanges.mp.	6
		16	insulin to carbohydrate ratio$.mp.	13
		17	nutritional education program.mp.	14
		18	meta analysis.mp. or exp Meta-Analysis/	40 860
		19	systematic review.mp.	18 685
		20	pooled analysis.mp.	1 846
		21	(review and medline).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	28 727
		22	(systematic* and (review* or overview*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	44 300
		23	18 or 19 or 20 or 21 or 22	93 257
		24	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	246 226
		25	1 and 23 and 24	15
EMBASE	29 July 2010	1	diabetes mellitus insulin dependent.mp. or exp insulin dependent diabetes mellitus/	58 647
		2	diet*.mp.	482 241
		3	systematic review.mp. or exp "systematic review"/	46 004
		4	1 and 2 and 3	62
		5	limit 4 to english language	58

Database	Date searched	#	Search terms	Citations
		6	limit 5 to human	56
INAHTA	29 July 2010			1
Cochrane	29 July 2010	1	diabetes mellitus type 1	
		2	diet*.mp.	
		3	#1 and #2	9
Manual search				0
Total citations				79
Total non-duplicate citations				8

Table 10.8 Additional search strategy for RCTs, questions 10.1 to 10.4

Database	Date searched	#	Search terms	Citations
Medline	26 July 2010	1	Diabetes Mellitus, type 1/ or diabetes mellitus type 1.mp.	52 503
		2	(diet$ adj5 diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	7 932
		3	(diet$ adj5 carbohydrat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	22 970
		4	(diet$ adj5 fat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	56 804
		5	(diet$ adj5 glyc?em$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	945
		6	(diet$ adj5 protein$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	40 880
		7	(glycemic index or glyc?emic index).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1 727
		8	GI.mp.	21 509
		9	exp Dietary Carbohydrates/	20 970
		10	exp Dietary Fiber/ or dietary fibre.mp.	11 349
		11	dietary proteins.mp. or exp Dietary Proteins/	70 293
		12	dietary fats.mp. or exp Dietary Fats/	61 674
		13	medical nutrition therapy.mp. or exp Nutrition Therapy/	68 660
		14	carbohydrate counting.mp.	49
		15	carbohydrate exchanges.mp.	6
		16	insulin to carbohydrate ratio$.mp.	13
		17	nutritional education program.mp.	14
		18	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	246 226
		19	clinical trial.mp. or exp Clinical Trial/	640 849
		20	randomised controlled trial.mp. or exp Randomised Controlled Trial/	298 693
		21	random allocation.mp. or exp Random Allocation/	69 884
		22	(double blind method or triple blind method).mp. [mp=title, original title, abstract, name of substance word, subject heading	107 739

Database	Date searched	#	Search terms	Citations
			word, unique identifier]	
		23	19 or 20 or 21 or 22	697 264
		24	1 and 18 and 23	303
		25	limit 24 to english language	281
EMBASE	29 July 2010	1	diabetes mellitus insulin dependent.mp. or exp insulin dependent diabetes mellitus/	58 642
		2	diet*.mp.	482 241
		3	randomised controlled trial	265 029
		4	1 and 2 and 3	202
		6	limit 4 to human and English language	182

10.2 Efficacy and safety of low glycaemic index or high fibre diets in type 1 diabetes

> Question 10.2
>
> What are the efficacy and safety of low glycaemic index or high fibre diets in type 1 diabetes?

This section addresses the safety and efficacy of a low glycaemic index (GI) or high fibre diet in type 1 diabetes. It should be read in conjunction with section 10.1.8, which contains details of the search strategy for this question.

10.2.1 Criteria for eligibility

Studies were eligible for inclusion in question 10.2 if they met the criteria shown in Table 10.9.

Table 10.9 Criteria for determining study eligibility, question 10.2

Study design	Level I or Level II (NHMRC intervention scale[a])
Population	Children and adults with type 1 diabetes
Intervention	Low glycaemic or high fibre diet >4weeks duration
Comparator	Moderate or high glycaemic diet
Outcomes	HbA_{1c} Body mass index and weight Quality of life Severe hypoglycaemia

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

10.2.2 Literature search summary

The literature search summary for this question is shown in Section 10.1.8.

10.2.3 Included studies

From the full texts reviewed, there were two systematic reviews with meta-analysis (Brand-Miller et al 2003; Thomas and Elliott 2009). The most recent was a systematic review with search date to June 2008 (Thomas and Elliott 2009); the other had a search date of 1981–2001 (Brand-Miller et al 2003). The systematic review by Brand-Miller et al (2003) is not discussed further here because it does not add to the review by Thomas and Elliott (2009). Three Level II studies examined the effect of low–GI test meals on post-prandial glucose levels; however, these studies did not meet the inclusion criteria because the interventions were of less than 4 weeks duration (O'Connell et al 2008; Ryan et al 2008; Rovner et al 2009). No other Level II studies met the inclusion criteria.

Table 10.10 Meta-analyses

Study ID	Search date	Included studies (type 1 Diabetes)
Brand-Miller et al (2003)	1981–2001	Collier et al (1988) Giacco et al (2000) Gilbertson et al (2001) Fontvielle et al (1992) – (type 1 and type 2 diabetes)
Thomas and Elliott (2009)	Up to June 2008	Collier et al (1988) Giacco et al (2000) Gilbertson et al (2001) Fontvielle et al (1992) – (type 1 and type 2 diabetes)

10.2.4 Characteristics of included studies

Thomas and Elliott (2009)

In a Cochrane review including meta-analysis, the authors aimed to assess the effects of low–GI diets on glycaemic control in subjects with diabetes (Thomas and Elliott 2009). A thorough method of literature search, data collection, data analysis and extraction was used. Randomised controlled trials (RCTs) of at least 4 weeks duration were considered for inclusion. Study quality was assessed according to the quality criteria specified by Schulz (1995) and Jadad et al (1996). Heterogeneity was assessed and reported. Of the 11 studies that met the inclusion criteria, 4 were carried out in subjects with type 1 diabetes, in a total of 186 subjects (Collier et al 1988; Fontvieille et al 1992; Giacco et al 2000; Gilbertson et al 2001). The characteristics and results of these 4 studies are discussed below.

Two of the studies were in adults (n=75) (Fontvieille et al 1992; Giacco et al 2000) and two in children (n=111) (Collier et al 1988; Gilbertson et al 2001). Although the studies were reported as randomised, the method of randomisation and of allocation concealment was not reported. Blinding of assessors was reported in one of the studies (Gilbertson et al 2001), and an intent-to-treat analysis was undertaken in three of the studies (Collier et al 1988; Fontvieille et al 1992; Gilbertson et al 2001). The largest of the studies was carried out in 104 Australian children (Gilbertson et al 2001).

Participants were stratified according to current dietary management; that is, those primarily following a low-GI diet and those following a fixed carbohydrate exchange diet. They were then randomised to either a low-GI flexible diet where they were advised to eat regular carbohydrate containing meals and snacks to satisfy appetite, with no specific quantity defined; or to a fixed carbohydrate diet, where participants followed a prescription of a set number of exchanges of carbohydrates (15 g) for each meal and snack. They were followed for 12 months, with 3-day food diaries and other outcome measures collected at 1, 3, 6 and 12 months. Most participants were on twice daily injections of insulin.

The characteristics of the four studies included by Thomas and Elliott (2009) are summarised below in Table 10.11.

Table 10.11 Characteristics of studies included by Thomas and Elliott (2009)

Reference	Study type study quality	Population	Intervention	Comparator	Outcomes
Collier et al (1988)	RCT – crossover Fair	n=7 children aged 12 ±2 years Canada	6 weeks (4 week washout) mean GI=68 ±3 SE	6 weeks (4 week washout) Mean GI=82 ±1	Glycosylated albumin levels
Fontvieille et al (1992)	RCT – crossover Poor	n=12 (type 1) Adults : age 47 ±12 years France	5 weeks GI=38 ±5SD	5 weeks high GI=64 ±2 SD	HbA_{1c} Fructasomine Body weight
Giacco et al (2000)	RCT – parallel Poor	n=63 Adults age- low GI- 29 ±11years High GI- 26 ±8 years Italy	24 weeks GI=70% 50 g/day fibre	24 weeks GI=90% 15 g/day fibre	HbA_{1c} Hypoglycaemia Body weight
Gilbertson et al (2001)	RTC – parallel Good	n=104 children age- low GI- 10.7 ±1.6 years High GI- –10.2 +_ 1.6 years Australia	Low GI diet 12 months mean GI 56.5 ±4.0	Measured carbohydrate exchange diet 12 months Mean GI 55.3 ±4.8	HbA_{1c} weight Hypoglycaemia Quality of life

GI, glycaemic index; HbA_{ic}, glycated haemoglobin; RCT, randomised controlled trial; SE, standard error

10.2.5 Results of included studies

Glycaemic control

Glycated haemoglobin (HbA_{1c}) was reported in two studies (Giacco et al 2000; Gilbertson et al 2001), both of which reported a statistically significant difference in endpoint HbA_{1c} between the study groups (Table 10.12). In a subanalysis of the included parallel studies, Thomas and Elliot (2009) report the pooled results of these two studies, showing a statistically significant decrease in HbA_{1c} of 0.5% in the low-GI group versus the conventional or high GI group.

Table 10.12 Summary of results of glycaemic control

Reference	Low GI N	Low GI HbA_{1c} (SD)	High GI N	High GI HbA_{1c} (SD)	Statistical significance
Giacco et al (2000)	29	8.80 (1.00)	25	9.10(1.30)	p<0.05
Gilbertson et al (2001)	51	8.00 (1.00)	38	8.60 (1.40)	p=0.05
Pooled analysis- WMD –0.5% with 95%CI: –0.9 to 1.0, p=0.02					

Fructasomine was reported in Fontvieille et al (1992), with a significant reduction with the low GI diet compared to the high GI diet (3.9 ±0.9 vs 3.4 ±0.4 mmol/L, p<0.05). The study had 18 participants, of whom 6 had type 2 diabetes.

HbA_{1c} levels were reported in the study by Collier et al (1988), with a significant reduction within the low-GI intervention group (13.2 ±1.5% to 10.7 ±2.2% , p<0.05).

Body mass index (BMI) and weight were not reported by Thomas and Elliott (2009).

Hypoglycaemia was reported in two studies, with no report of the degree (e.g. mild, moderate or severe) and no definition of hypoglycaemia (Table 10.5). Due to heterogeneity, the results were reported separately (Giacco et al 2000; Gilbertson et al 2001).

Table 10.5 Summary of results on hypoglycaemic episodes

	Low GI		High GI		
Reference	n	Mean no. of hypoglycaemic episode (SD) per month	n	Mean no. of hypoglycaemic episode (SD) per month	Statistical significance
Giacco et al (2000)	29	0.70 (0.70)	25	1.50 (1.20)	p<0.01
Gilbertson et al (2001)	51	6.90(6.80)	38	5.80(5.50)	NR

GI, glycaemic index; NR, not rejported; SD, standard deviation

QoL was reported in one trial and was found to be significantly influenced by type of diet, although the validation measures for the questionnaire were not reported (Gilbertson et al 2001). In this trial, twice as many parents in the low-GI group stated that their child had no difficulties in selecting their own meals at the 12-month time point (51% vs 24%, p=0.01). Almost twice as many parents from the low-GI group also reported that diabetes never limited the type of family activities pursued (53% vs 27%, p=0.02).

10.2.6 Discussion

The systematic review by Thomas and Elliott (2009) reported data on four trials in subjects with type 1 diabetes. The effect on metabolic control was reported in terms of change in HbA_{1c}, fructasomine and glycosylated albumin. In a pooled analysis of the effect of a low-GI diet on metabolic control, end of study HbA_{1c} showed a reduction of 0.5% in favour of the low-GI diet group. Individual studies showed a reduction of 0.5 mmol/L in end of study fructasomine, in favour of the intervention group, and a within-group reduction of glycosylated albumin was found following a low-GI diet. One study reported a significant difference in the number of hypoglycaemic events between the groups, in favour of the low-

GI group (Giacco et al 2000). The level of severity of the episodes of hypoglycaemia were not defined. One study reported a significant improvement in QoL; however, the measurement tool used was not a validated measure (Gilbertson et al 2001). The effect of a low–GI diet on BMI and weight were not reported.

Thomas and Elliott (2009) reported that the difference in the GI of the diets in the intervention and control groups reached statistical significance in two of the included studies (Collier et al 1988; Fontvieille et al 1992). From their original published study, Gilbertson et al (2001), reported no difference in level of GI between the intervention and control groups. About half the food intake records of the children enrolled in their study revealed dietary energy intakes that were not likely to reflect the child's habitual intake. The high rate of underreporting may have affected the ability to detect subtle differences in carbohydrate quality (mean GI) between the two study groups (Gilbertson et al 2001).

10.2.7 Conclusion

In this systematic review of evidence for the efficacy and safety of low-GI diets for individuals with type 1 diabetes, one Level I study of low risk of bias met the inclusion criteria. Of the studies included in this Level I study, two were of high risk of bias, one of moderate risk of bias and one of low risk of bias. A low-GI diet was consistently found to have a positive effect on metabolic control. The effect on BMI, weight, severe hypoglycaemia and QoL could not be determined because these outcomes were either not reported, not defined, or not measured with a validated tool. These results are generalisable to children aged 8–13 years and to adults with type 1 diabetes. There is some evidence that a low-GI diet has a beneficial effect on metabolic control.

10.2.8 Literature search strategy

See Section 10.1.8.

10.2.9 Evidence Matrix

Q10.2	What is the efficacy and safety of low glycaemic index/high-fibre diets in type 1 diabetes?	
Evidence statement	Level I evidence shows that a low GI diet has a beneficial effect on glycaemic control in adults and children. There is insufficient evidence to determine the effect of low-GI diets on body mass index, weight, severe hypoglycaemia or QoL in children, adolescents or adults with type 1 diabetes.	
Evidence base	A	One Level I study with a low risk of bias, comprising four Level II studies – one with a low risk of bias, one with a moderate risk of bias, and two with a high risk of bias. The rating is based on the Level I study, not the individual studies within it.
Consistency	A	HbA_{1c} – only reported in two studies, which together showed a pooled improvement of 0.5%.
	N/A	BMI – not reported in the systematic review.
	N/A	Weight – not reported in the systematic review.
	N/A	QoL – none of the studies used a validated tool.
	N/A	Severe hypoglycaemic episodes – not reported in the systematic review.
Clinical impact	C	For outcome of HbA_{1c}.
Generalisability	C	Evidence based on studies in children aged 8–13 years and adults; no studies included children aged under 8 years or those with complications. The studies from 1988 and 1992 are not relevant to current practice, because different regimens are now used.
Applicability	A	Studies were performed in countries with well-established health-care systems, including one Australian study.
Other factors	None identified.	
Recommendation		
R10.2	Individuals with type 1 diabetes should be educated on low-GI diets (Grade A).	

BMI, body mass index; GI, glycaemic index; HbA_{1c}, glycated haemoglobin; QoL, quality of life; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

10.3 Efficacy and safety of a high-protein diet in type 1 diabetes

Question 10.3

What are the efficacy and safety of a high-protein diet in type 1 diabetes?

This section addresses the efficacy and safety of a high-protein diet in type 1 diabetes. It should be read in conjunction with section 10.1.8, which contains details of the search strategy for this question.

10.3.1 Criteria for eligibility

Studies were eligible for inclusion in question 10.3 if they met the criteria shown in Table 10.13.

Table 10.13 Criteria for determining study eligibility, question 10.3

Study design	Level I or Level II (NHMRC intervention scale[a])
Population	Children and adults with type 1 diabetes
Intervention	High-protein diet >4 weeks duration
Comparator	No modification of protein content of diet
Outcomes	HbA_{1c} Body mass index and weight Quality of life Severe hypoglycaemia

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

10.3.2 Literature search summary

The literature search summary for this question is shown in section 10.1.8.

10.3.3 Included studies

From the full texts reviewed there were no Level I or Level II studies examining the efficacy or safety of moderate or high-protein diets in individuals with type 1 diabetes.

10.3.4 Conclusion

In this systematic review of evidence for the efficacy and safety of high-protein diets for individuals with type 1 diabetes, no Level I or Level II studies met the inclusion criteria. There is insufficient evidence to determine the effect of a diet high in protein in individuals with type 1 diabetes.

10.3.5 Evidence Matrix

Q10.3	What are the efficacy and safety of a high-protein diet in type 1 diabetes?	
Evidence statement	There is insufficient evidence to determine the effect of modifying protein intake in individuals with type 1 diabetes.	
Evidence base	NA	
Consistency	NA	
Clinical impact	NA	
Generalisability	NA	
Applicability	NA	
Other factors	NA	
Recommendation		
	There was insufficient evidence to make a recommendation.	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

10.4 Efficacy and safety of modifying dietary fat intake in type 1 diabetes

Question 10.4

What are the efficacy and safety of modifying dietary fat intake in type 1 diabetes?

This chapter addresses the efficacy and safety of modifying dietary fat intake in type 1 diabetes. It should be read in conjunction with section 10.1.8, which contains details of the search strategy for this question.

10.4.1 Criteria for eligibility

Studies were eligible for inclusion in question 10.4 if they met the criteria shown in Table 10.14.

Table 10.14 Criteria for determining study eligibility, question 10.4

Study design	Level I or Level II (NHMRC intervention scale[a])
Population	Children and adults with type 1 diabetes
Intervention	High monounsaturated fat diet >4 weeks duration
Comparator	No modification of fat intake
Outcomes	HbA_{1c} Body mass index and weight Quality of life Severe hypoglycaemia Lipid profile

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

10.4.2 Literature search summary

The literature search summary for this question is shown in section 10.1.8.

10.4.3 Included studies

From the full texts reviewed, no Level I studies and four Level II studies met the inclusion criteria (Donaghue et al 2000; Georgopoulos et al 2000; Strychar et al 2003; Strychar et al 2009).

10.4.4 Characteristics of included studies

The characteristics of the included studies are shown in Table 10.15.

Table 10.15 Characteristics of included studies

Reference	Study type study quality	Population	Intervention	Comparator	Outcomes
Donaghue et al (2000)	RCT – parallel design 12 weeks single arm Fair	n=25 adolescents Australia	High monounsaturated fat diet 43% total energy from fat (20% monounsaturated fats)	High CHO diet 30% total energy from fat 55% from CHO	HbA_{1c}, weight, total cholesterol, triglycerides, LDL, HDL Other outcomes – insulin dose, RCFAs

Georgopoulos et al (2000)	RCT – crossover design 4 weeks in each arm, washout period not reported Poor	n=19 adults United States	High monounsaturated fat diet containing 40% total fatty acids (25% monounsaturated, 6% polyunsaturated, 9% saturated) 45% CHO and 15% protein	High CHO diet containing 24% total fatty acids (9% mono, 6% poly, 9% saturated), 61% CHO and 15% protein	HbA_{1c}, weight, total cholesterol, TG, HDL, LDL Other outcomes – insulin dose, fructasomine, apolipoprotein A–1, apolipoprotein B
Strychar et al (2003)	RCT – crossover design phase 1 – 2 months optimising glycaemic control and normalising lipoprotein phase 2 and 3 – 2 months each of intervention and comparator diets Good	n=34 adults Canada	High monounsaturated fat diet containing 43–46% carbohydrate and 37–47% fat (17–20% monounsaturated fat)	High carbohydrate diet containing 54–57% carbohydrates and 27–30% fat (10–13% monounsaturated fat)	HbA_{1c}, weight, BMI, plasma total cholesterol, HDL-C, LDL-C; plasma total TG Other outcomes – VLDL-TG, LDL particle size, insulin, hyperglycaemia
Strychar et al (2009)	RCT – parallel design Fair	n=30 adults Exclusions: BMI ≥ 30, A_{1c}>8.4%, and major diabetes complications Canada	High monounsaturated fat diet containing 43–46% CHO and 37–47% fat (20% monounsaturated fat) n=15	High CHO diet containing 54–57% CHO and 27–30% fat (10% monounsaturated fat) n=15	HbA_{1c}, BMI, plasma lipids, weight Other outcomes – blood pressure, adhesion molecules, markers of oxidation, thrombosis and inflammation

BMI, body mass index; CHO, carbohydrate; HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; RCFA, red cell membrane fatty acid; RCT, randomised controlled trial; TG, trigylceride; VLDL, very low density lipoprotein

10.4.5 Results of included studies

Metabolic control

The four studies assessing the effect of high monounsaturated fat diets reported no differences between the intervention and control groups or treatments in terms of endpoint glycated haemoglobin (HbA_{1c}) (Donaghue et al 2000; Georgopoulos et al 2000; Strychar et al 2003; Strychar et al 2009). An association between increased monounsaturated fat intake and improvement in metabolic control was, however, reported in one study (Donaghue et al 2000). Donaghue et al (2000) reported that the whole study group had a significant increase in monounsaturated fat, as indexed by red cell phospholipid fatty acids (RCFAs), with an increase of *n–9* RCFAs from 14.9% (interquartile range [IQR]: 14.5–21.7%) to 21.7% (IQR: 18.8–25.6%; p=0.002). Changes in *n–9* RCFAs were found to be inversely related to changes in HbA_{1c} (coefficient of determination [R2]=0.26, p=0.02), such that a 10% increase in *n–9* RCFAs corresponded to a 0.64% improvement (i.e. a decrease) in HbA_{1c}. The authors concluded that this favourable effect on HbA_{1c} warrants further investigation.

Weight and BMI

One study reported a significant increase (2%) in weight in the high monounsaturated fat group (Strychar et al 2009). No other statistical effects of treatment diet on weight or body mass index (BMI) were found.

Table 10.16 Change in body mass index and weight (Strychar et al 2009)

	High carbohydrate / lower fat diet				Lower carbohydrate / higher monounsaturated fat diet			
BMI (kg/m2)	24.3 ±2.6	24.1 ±2.6	–0.24 ±1.0	Sig	24.3 ±2.7	24.8 ±2.7	+0.56 ±0.6	Sig
Weight (kg)	71.1 ±13.7	70.3 ±13.1	–0.83 ±3.0	Sig	71.8 ±13.4	73.4 ±13.6	+1.6 ±1.8	Sig

BMI, body mass index; Sig, significant

Quality of life

Quality of life (QoL) was not measured as an outcome in any of the included studies.

Severe hypoglycaemia

Severe hypoglycaemia was not measured as an outcome in any of the included studies.

Lipid profile

Of the studies reporting changes in lipid profiles – total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG), very low density lipoprotein triglycerides (VLDL-TG) and very low density lipoprotein cholesterol (VLDL-C) – two reported no significant differences between groups and study treatments (Georgopoulos et al 2000; Strychar et al 2009). Donaghue et al (2000) reported a significant change from baseline in HDL-C (p=0.03) in the high carbohydrate group, and an association between an increase in monounsaturated fat intake and improvements in plasma total cholesterol and plasma LDL cholesterol (Table 10.17) Changes in *n–9* RCFAs were found to be inversely related to changes in plasma total cholesterol (R2=0.38, p=0.002), and plasma LDL cholesterol (R2=0.21, p=0.03).

Table 10.17 Comparison of monounsaturated fat diet group to the control group

	Monounsaturated diet group		Carbohydrate group		
	Baseline	12 weeks	Baseline	12 weeks	P value for change (week 12 from baseline)
HbA_{1c}	8.8 (8.0 ±10.6)	8.8 (8.2–9.5)	9.1 (7.4–10.1)	9.3 (8.0–10.4)	0.8
Cholesterol (mmol/L)	4.6 ±0.6	4.1 ±0.7	4.2 ±0.9	4.0 ±0.8	0.4
HDL (mmol/L)	1.2 ±0.2	1.2 ±0.3	1.2 ±0.3	1.3 ±0.4	0.03
LDL (mmol/L)	3.0 ±0.7	2.6 ±0.6	2.8 ±0.8	2.4 ±0.7	0.9
Triglycerides (mmol/L)	0.8 ±0.3	0.9 ±0.3	0.6 ±0.2	0.8 ±0.2	0.6

HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein

Source: Donaghue et al (2000)

The results from Strychar et al (2003) are shown in Table 10.18.

Table 10.18 Effects of a high monounsaturated fat diet and a high carbohydrate diet on lipid and lipoprotein parameters

	Group of 26, intent-to-treat group					Group of 7, followed the two diet prescriptions				
	End phase 1	End of high-mono diet	End of high-CHO diet	% change	P	End phase 1	End of high- mono diet	End of high-CHO diet	% change	P
Total cholesterol (mmol/L)	4.57 ±0.81	4.53 ±0.69	4.52 ±0.82	0	0.896	4.64 ±0.78	4.84 ±0.70	4.60 ±0.97	5	0.128
LDL-C (mmol/L)	2.49 ±0.72	2.38 ±0.63	2.54 ±0.74	–7	0.034	2.63 ±0.69	2.66 ±0.64	2.62 ±0.70	2	0.499
HDL-C (mmol/L)	1.42 ±0.60	1.38 ±0.48	1.32 ±0.52	5	0.099	1.27 ±0.33	1.29 ±0.39	1.20 ±0.37	8	0.176
Total TG (mmol/L)	1.16 ±0.57	1.07 ±0.38	1.17 ±0.37	–9	0.129	1.30 ±0.54	1.17 ±0.48	1.42 ±0.43	–18	0.027
VLDL-TG (mmol/L)	0.52 ±0.50	0.44 ±0.36	0.52 ±0.30	–11	0.371	0.66 ±0.51	0.54 ±0.42	0.73 ±0.41	–26	0.043
VLDL-C (mmol/L)	0.20 ±0.16	0.17 ±0.20	0.20 ±0.13	–11	0.612	0.30 ±0.26	0.15 ±0.09	0.29 ±0.17	–48	0.043

C, cholesterol; CHO, carbohydrate; HDL, high density lipoprotein; LDL, low density lipoprotein; mono, monounsaturated fat; TG, trigylceride; VLDL, very low density lipoprotein

Source: Strychar et al (2003)

10.4.6 Discussion

Of the four studies that examined the effect of increasing monounsaturated fat intake, two reported low dietary adherence rates, demonstrating the difficulty in implementing dietary recommendations in the free-living population with type 1 diabetes (Donaghue et al 2000; Strychar et al 2003). In one study, meals and snacks were prepared in a metabolic kitchen and supplied to participants; however, food diaries were not recorded to assist with the verification of actual dietary intake (Georgopoulos et al 2000). Donaghue et al (2000) measured changes in the fatty acid concentration of RCFAs as a marker of dietary adherence (Donaghue et al 2000). Although the intervention group did not meet the dietary targets for monounsaturated fat intake, the study group as a whole showed a significant increase in monounsaturated fat. This was positively correlated with a reduction in HbA_{1c}, such that a 10% increase in dietary intake corresponded to a 0.64% improvement in HbA_{1c}. There were no other significant differences in HbA_{1c} found between groups or treatment diets. One study found a significant increase in weight of 2% in the monounsaturated diet group (Strychar et al 2009), whereas no other effects on body weight or composition were found. Donaghue et al (2000) reported a correlation between dietary intake and improvement in total cholesterol and LDL-cholesterol levels, and Strychar et al (2003) reported a statistically significant improvement in LDL-cholesterol in the intention-to-treat group following the monounsaturated diet intervention, and total TG, VLDL-TG and VLDL-cholesterol following the monounsaturated diet intervention in the subgroup of participants who had adhered to required dietary targets. There were no significant differences in lipid profiles found by Georgopoulos et al (2000) and Strychar et al (2009).

10.4.7 Conclusion

In this systematic review of evidence for the efficacy and safety of high monounsaturated fat intake for individuals with type 1 diabetes, four Level II studies – one of high risk of bias, two of moderate risk of bias and one of low risk of bias – met the inclusion criteria. Three studies included adult participants (n=83) and one included adolescents (n=25). A diet high in monounsaturated fat was consistently found to have no direct effect on lowering HbA_{1c}; however, an inverse relationship between intake of monounsaturated fat and an improvement on metabolic control was reported in one study involving adolescents. Most studies consistently reported no effect of a diet high in monounsaturated fat on body weight and composition, with one study reporting a slight increase (2%) in weight. The effect on severe hypoglycaemia and QoL could not be determined because these outcomes were not reported. There were inconsistent findings on the effect of diets high in monounsaturated fats on plasma lipid levels. The results of this systematic review are not generalisable to children with type 1 diabetes. There is evidence from a study of small sample size that increasing monounsaturated fats in the diet can have a beneficial effect on HbA_{1c}, total cholesterol and LDL-cholesterol in adolescents. There is evidence from a study of small sample size and good quality that increasing monounsaturated fats in the diet can have a beneficial effect on LDL-cholesterol, triglycerides, VLDL-triglycerides, and VLDL-cholesterol, in non-obese adults with well-controlled uncomplicated type 1 diabetes. There is insufficient evidence on the impact on weight, BMI, QoL and severe hypoglycaemia of diets high in monounsaturated fat in children, adolescents or adults with type 1 diabetes.

10.4.8 Literature search strategy

See section 10.1.8.

10.4.9 Evidence Matrix

Q10.4	What are the efficacy and safety of a high monounsaturated fat diet in type 1 diabetes?	
Evidence statement	Level II evidence (from one, good-quality study, small sample size) shows that, in nonobese adults with well-controlled, uncomplicated type1 diabetes, a diet high in monounsaturated fats can have a beneficial effect on LDL-cholesterol, triglycerides, VLDL-triglycerides and VLDL-cholesterol. There is insufficient evidence to determine any effect on weight, body mass index, quality of life and severe hypoglycaemia of diets high in monounsaturated fat in children, adolescents or adults with type 1 diabetes	
Evidence base	C	Four Level II studies – one of low quality, two of moderate quality and one of high quality.
Consistency	A	HbA_{1c} – all studies found no between-group differences.
	C	Weight and BMI – one study found a significant increase in favour of intervention; all other studies found a nonsignificant difference.
	NR	QoL – not reported.
	NR	Severe hypoglycaemic episodes – not reported.
	D	Results for lipids were variable – two studies showed no difference in lipids; one study (in adolescents) showed a significant increase in HDL in the comparator group and an inverse correlation between total cholesterol and LDL-cholesterol and dietary monounsaturated fat content in both groups; another study (in adults) showed a significant decrease in LDL in the intervention group.
Clinical impact	D	Slight or restricted impact for outcomes of HbA_{1c}, weight and BMI, and lipids.
Generalisability	C	The study groups was small (n=108 total), and participants found it difficult to follow the diet due to its difference from most western-style diets. The studies only included adults and adolescents.
Applicability	B	Studies were performed in countries with well-established health-care systems, and included one Australian study.
Other factors	None identified.	
Recommendation		
R10.4	Diets high in monounsaturated fats should not be used routinely in type 1 diabetes (Grade C).	

BMI, body mass index; HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; QoL, quality of life; RCT, randomised controlled trial; VLDL, very low density lipoprotein

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

11 Exercise

This chapter was not systematically reviewed.

12 Complementary and alternative medicines?

Question 12.2

What is the effectiveness of complementary and alternative medicines at achieving targets?

This section of the report addresses the effectiveness of complementary and alternative medicines at achieving targets.

12.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 12.1.

Table 12.1 Criteria for determining study eligibility, question 12.2

Study design	Level I to Level II evidence (NHMRC intervention scale) [a]
Population	Type 1 diabetes
Intervention	Complementary and alternative medicines (herbal medicines, antioxidants, vitamins or heavy metals)
Comparator	Placebo or regular therapy
Outcomes	Change in HbA_{1c}, insulin dose, lipid targets, adverse events

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

12.1.2 Assessment of study eligibility

A total of 529 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title. A total of 16 publications remained, and the full-text version of each of these publications was retrieved and reviewed.

Four systematic reviews met the inclusion criteria (Table 12.2 and Table 12.3). The studies captured by the Level I studies were supplemented by Level II studies that were identified in the search but had not been included because they were published after the Level I studies (Pozzilli et al 1996; Visalli et al 1999; Ludvigsson et al 2001; Crinò et al 2004; Manuel et al 2004; Pena et al 2004; Engelen et al 2005; Pitocco et al 2006; Giannini et al 2007; Huang and Gitelman 2008).

Table 12.2 Systematic reviews identified in the literature search, question 12.2

Reference	Included citations
Baker et al (2008)	Type 1 diabetes; Altschuler et al (2007)
Pilkington et al (2007)	Evidence from systematic reviews: Yeh et al (2003)
Yeh et al (2003)	Type 1 diabetes; Sharma et al (1990); Serraclara et al (1998)
Pozzilli et al (1996)	10 de-identified studies included

Table 12.3 Details of Level I studies

Reference	Type of study, quality and no. of participants	Intervention	Outcome	Result
Baker et al (2008)	1 RCT Fair N=72	Cinnamon	HbA_{1c}, FBG, lipid parameters	No significant differences in final HbA_{1c} (8.8 vs. 8.7, p=0.88), change in HbA_{1c} (0.3 vs. 0.0, p=0.13), total daily insulin intake, or number of hypoglycaemic episodes between the cinnamon and placebo arms
Pilkington et al (2007)	Summary of systematic review by Yeh et al (2003) Fair	Complementary therapies	See Yeh et al (2003)	See Yeh et al (2003) (This review included a wide variety of complementary therapies – the authors reported on the systematic review by Yeh et al (2003)
Yeh et al (2003)	2 RCTs Poor N=20	Serraclara et al (1998) study: *Ficus carica* (Fig leaf) Sharma et al (1990) study: *Trigonella foenum* (Fenugreek)	HbA_{1c}, FBG, insulin requirement	Serraclara et al (1998) – decrease in insulin requirement (not statistically significant), no change in HbA_{1c} Sharma et al (1990) decrease in FBG, no change in insulin requirement
Pozzilli et al (1996)	10 RCTs Poor N=291	Nicotinamide	HbA_{1c}, insulin requirement	No differences were observed in the insulin dose required or HbA_{1c} values between nicotinamide and control patients

FBG, fasting blood glucose; HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trials

12.1.3 Literature search summary

Table 12.4 Search results, question 12.2

Stage	Notes	Number
Search summary	Manual	
	Cochrane Library	
	EMBASE	
	PubMed	
	Total	529
Duplicates	Duplicates identified	
Identified	Total identified	
Exclusion criteria	Wrong study type (not a systematic review or meta-analysis or RCT)	230
	Wrong population (not type 1 diabetic)	193
	Wrong intervention (not complementary or alternative medicine [herbal, vitamins, antioxidants or heavy metals])	10
	Wrong comparator (placebo or regular therapy)	
	Wrong outcome (not change in HbA_{1c}, insulin dose, lipid targets, adverse events)	76
	Not in English	4
	Total excluded	513
Meeting criteria	Total meeting inclusion criteria	16

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trials

12.1.4 Characteristics of included studies

A total of 13 primary studies met the inclusion criteria. A number of trials studied the effect of herbs (Sharma et al 1990; Serraclara et al 1998) and vitamin supplements (Crinò et al 2004; Manuel et al 2004; Engelen et al 2005; Giannini et al 2007). Details and results of all the included studies are summarised in Table 12.5, below.

Table 12.5 Details of studies included, question 12.2

Reference and setting	Herb or supplement	Design, control and quality	Sample	Outcomes	Adverse effects or events
Altschuler et al (2007) United States	Cinnamon	Randomised, double blind Placebo controlled Fair	n=72 , type 1 diabetes (adolescents)	No difference in HbA_{1c}, insulin dose, hypoglycaemia	Reported: urticaria in 1 patient with family history of cinnamon allergy
Crino et al (2004) Italy	Vitamin E + nicotinamide	RCT, multicentre; nonblinded Control – nicotinamide only Fair	n=64, recent-onset type 1 diabetes (children and adolescents)	No difference in HbA_{1c}, C-peptide; higher insulin requirement in nicotinamide only vs nicotinamide vs vitamin E (not statistically significant)	Reported: none

Reference and setting	Herb or supplement	Design, control and quality	Sample	Outcomes	Adverse effects or events
Engelen et al (2005) Belgium	Fenofibrate + vitamin E or vitamin E alone	Randomised, double-blind Placebo controlled Fair	n=44, type 1 diabetes (adults)	Total cholesterol and LDL cholesterol did not change in the patients who received vitamin E; vitamin E alone had no effect on triglycerides	Adverse events reported for 7 patients (50%) in the vitamin E group; 10 patients (62.5%) in the fenofibrate + vitamin E group and for 8 patients (57.1%) in the placebo group (difference between groups not statistically significant). None of the events were considered to be serious
Giannini et al (2007) Italy	Vitamin E, 1200 mg/day	Randomised, double-blind Placebo controlled Poor	n=10, type 1 diabetes + microalbuminuria (adolescents)	No difference in HbA_{1c}	Not reported
Huang et al (2008) United States	Alpha-lipoic acid, 14–21 mg/kg/day	Randomised, double-blind Placebo controlled Fair	n=40, type 1 diabetes (adolescents)	No difference in HbA_{1c}; insulin dose, antioxidant status	No adverse events noted
Ludvigsson et al (2001) Sweden	Antioxidants tablets (containing nicotinamide, vitamin C, vitamin E, beta-carotene, selenium)	Randomised, double-blind Placebo controlled Fair	n=46, type 1 diabetes (children)	No difference in insulin requirement or HbA_{1c} between groups	Antioxidants demonstrated no positive or negative effect
Pena et al (2004) Australia	Folate, 5 mg/day	Randomised, double blind; crossover Placebo controlled Fair	n=36, type 1 diabetes (adolescents)	No change in HbA_{1c}	None reported
Manuel et al (2004) Belgium	Atorvastatin + vitamin E	Randomised Control – atorvastatin + placebo Fair	n=24, type 1 diabetes (adults)	No effect on lowering lipids	Not reported

Reference and setting	Herb or supplement	Design, control and quality	Sample	Outcomes	Adverse effects or events
Pitocco et al (2006) Italy	Vitamin D (calcitriol – 0.25 μg every 48 hour) + nicotinamide (25 mg/kg/day)	Randomised, open-label Control – nicotinamide Fair	n=70, recent-onset type 1 diabetes (adolescents)	No difference in HbA_{1c}, insulin dose	Not reported
Pozzilli et al (1997) Italy	Nicotinamide + vitamin E (15 mg/kg/day)	Randomised, multicentre, nonblinded Control – Nicotinamide 25 mg/kg/day Fair	84 recent-onset type 1 diabetes (adolescents)	No difference in HbA_{1c}, insulin requirement	Reported: leukopenia in 1 patient treated with vitamin E
Serraclara et al (1998) Spain	*Ficus carica* (fig leaf) tea (13 g/day decoction, for 4 weeks)	Open-label; crossover Control – bitter commercial tea blend Poor	n=10, type 1 diabetes (adults)	Decrease PPG, insulin requirement; no change in FPG, C-peptide, HbA_{1c}	No side effects
Sharma et al (1990) India	*Trigonella foenum* (fenugreek), as defatted, debitterised seed powder; 100 g/day in unleavened bread; for 10 days	Blinding unclear; crossover Control – no treatment Poor	n=10, type 1 diabetes; diet and insulin (dose decreased during study) (adolescents and adults)	Decrease FBG, PPG, urine glucose; no change in body weight, insulin	Not reported
Visalli et al (1999) Italy	Nicotinamide (25 mg/kg/day vs 50 mg/kg/day)	Randomised, single blind Control – different dose Fair	n=74, recent-onset type 1 diabetes (adolescents)	No difference in HbA_{1c}, insulin dose	Not reported

FBG, fasting blood glucose; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; LDL, low density lipoprotein; PPG, postprandial glucose; RCT, randomised controlled trial

12.1.5 Discussion

Glycaemic control

Glycaemic control was an outcome measure in 10 studies (Pozzilli et al 1997; Serraclara et al 1998; Visalli et al 1999; Ludvigsson et al 2001; Crinò et al 2004; Pena et al 2004; Pitocco et al 2006; Altschuler et al 2007; Giannini et al 2007; Huang and Gitelman 2008). All the included studies found no difference in HbA_{1c}. A meta-analysis conducted by Pozzilli et al (1996) that

looked at nicotinamide treatment in patients with recent-onset type 1 diabetes reported no differences in HbA_{1c} values between patients taking nicotinamide and the control group.

Insulin dose

Insulin dose was an outcome measure in nine studies (Sharma et al 1990; Pozzilli et al 1997; Serraclara et al 1998; Visalli et al 1999; Ludvigsson et al 2001; Crinò et al 2004; Pitocco et al 2006; Altschuler et al 2007; Huang and Gitelman 2008). Of these, eight studies found no difference in overall insulin requirement. The study by Serraclara et al (1998) did show a reduction in insulin dose (12% lower in the intervention group) (no raw data provided in study), and a decline in mean capillary glycaemia ($p<0.05$). However, this study was graded as poor quality (Yeh et al 2003).

The meta-analysis of 10 randomised controlled trials (RCTs) by Pozzilli et al (1996) also reported no difference in insulin dose required between nicotinamide and control patients.

Lipid targets

Lipid targets were an outcome in two studies, both of which examined the effect of vitamin E compared to conventional treatment (Manuel et al 2004; Engelen et al 2005). The study by Engelen et al (2005) was a double blind, placebo-controlled trial in which patients were randomised into three treatment groups after a wash-out period of 8 weeks: a placebo group (placebo during two consecutive periods of 8 weeks); a vitamin E group (vitamin E during two consecutive periods); and a fenofibrate/vitamin E group (fenofibrate during the first period, followed by fenofibrate and vitamin E during the consecutive period). Fenofibrate caused a significant decrease in total and low density lipoprotein (LDL) cholesterol and triglycerides ($p<0.05$). Combination with vitamin E for a period of 8 weeks caused no further decrease in cholesterol, nor LDL cholesterol levels. Total cholesterol and LDL cholesterol did not change in the patients who received vitamin E alone, and there was also no effect on triglycerides. Similarly, a study by Manuel et al (2004), found that vitamin E added to atorvastatin had no effect in lowering lipids.

Adverse events

The study by Engelen et al (2005) (n=44) reported adverse events in 7 patients in the vitamin E group, 10 in the fenofibrate plus vitamin E group, and 8 in the placebo group. Differences between groups were not statistically significant, and none of the events were considered to be serious.

The meta-analysis by Pozzilli et al (1996) noted that adverse effects were reported in few patients among the 291 receiving nicotinamide (transient elevation of transaminase, n=2; skin rash, n=2; recurrent hypoglycaemia, n=2). A subsequent study by Pozzilli et al (1997) compared the effect of vitamin E with nicotinamide (control group) on metabolic control in patients with recent-onset type 1 diabetes, and reported leukopenia in one patient treated with vitamin E.

The RCT by Altschuler et al (2007) examining the effect of cinnamon in type 1 diabetes reported urticaria in one patient with a family history of cinnamon allergy.

Five RCTs reported no adverse events in the studies (Serraclara et al 1998; Ludvigsson et al 2001; Crinò et al 2004; Pena et al 2004; Huang and Gitelman 2008). Five other studies did not report on adverse events (Sharma et al 1990; Visalli et al 1999; Manuel et al 2004; Pitocco et al 2006; Giannini et al 2007).

12.1.6 Conclusion

The literature search identified 4 systematic reviews and 13 RCTs on the effectiveness of complementary and alternative medicines at achieving targets. The 10 primary studies and a systematic review by Pozzilli et al (1996) that reported changes in HbA_{1c} as an outcome measure showed no difference between the intervention and control group. There was also no difference in insulin dose in eight of the nine studies that reported insulin dose requirement as an outcome measure.

One study assessed cinnamon and found no significant difference in HbA_{1c}, or change in HbA_{1c} and insulin dose (Altschuler et al 2007).

Two studies compared vitamin E with conventional therapy in achieving lipid targets (Manuel et al 2004; Engelen et al 2005). Engelen et al (2005) found no difference in total cholesterol and LDL cholesterol in patients in the intervention group (vitamin E) and there was also no effect on triglycerides. A similar result was reported by Manuel (2004). Another study by Giannini et al (2007) evaluated the effects of high-dose vitamin E supplementation compared to placebo. After 6 months, no significant differences in HbA_{1c} were observed between the two groups (8.44 ±0.58 vs 8.59 ±0.28%; p=0.73). A study by Crino et al (2004) found that vitamin E plus nicotinamide compared to nicotinamide alone resulted in no difference in HbA_{1c}.

The use of nicotinamide in the treatment of patients with type 1 diabetes has been examined in a number of studies. Pozzilli et al (1996)'s meta-analysis of 10 RCTs reported no differences in HbA_{1c} values or insulin requirement between nicotinamide and control patients. The meta-analysis by Pozzilli et al (1996) noted that adverse effects were reported in few patients (6 out of a total of 291 patients receiving nicotinamide).

12.1.7 Evidence Matrix

Adverse effects

Q12.1	Complementary and alternative medicines and outcome/population adverse effects	
Evidence Statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.	
Evidence base	C	One systematic review, of poor quality; eight Level II studies (seven with a low risk of bias; one with a high risk of bias).
Consistency	C	Five Level II studies (four with a low risk of bias; one with a high risk of bias) reported no adverse events. The systematic review reported that 6 of 291 patients treated with nicotinamide experienced an adverse effect. One study reported seven adverse events in the intervention (vitamin E) group, but this group was not statistically different from the other groups, and the adverse events were not considered serious. One study reported one adverse event (n=72; cinnamon intervention). One study reported one adverse event (n=82; vitamin E intervention).
Clinical impact	D	Interventions unlikely to be used in clinical practice.
Generalisability	A	Two studies were in adults – one study (fig leaf) reported no adverse events; one study (vitamin E) reported seven adverse events, but no statistically significant difference between groups. Four studies were in adolescents – two studies reported no adverse events; one study (cinnamon) reported one adverse event; one study (vitamin E) reported one adverse event. One study was in children (antioxidants) and reported no adverse events. One study was in children and adults (vitamin E + nicotinamide), and reported no adverse events.
Applicability	A	One study was conducted in Australia, five studies were in Europe and two were in the United States.
Other factors	None of the studies were powered to address adverse events.	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Glycaemic control

Q12.1	Complementary and alternative medicines and outcome/population – glycaemic control combined	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.	
Evidence base	C	One systematic review of poor quality and 10 Level II studies (8 with a moderate risk of bias and 2 with a high risk of bias).
Consistency	A	Studies were consistent. All included studies found no difference in HbA_{1c} (cinnamon, vitamin E + nicotinamide, vitamin E, alpha-lipoic acid, antioxidants, folate, vitamin D + nicotinamide, vitamin E + nicotinamide, fig leaf, and nicotinamide). Systematic review/meta-analysis (nicotinamide) showed no difference between intervention and control.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	B	Seven studies in adolescents (cinnamon, alpha-lipoic acid, vitamin D + nicotinamide, vitamin E + nicotinamide, nicotinamide, folate, and vitamin E). One study in children and adolescents (vitamin E + nicotinamide). One study in children (antioxidants). One study in adults (fig leaf). A systematic review: age range 10–26 (nicotinamide).
Applicability	A	One Australian study, two studies from the United States, and seven European studies.
Other factors	None identified.	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Insulin dose

Q12.1	Complementary and alternative medicines and outcome/population insulin dose	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.	
Evidence base	C	One systematic review/meta-analysis of poor quality. Nine Level II studies, seven of low risk of bias, two of high risk of bias.
Consistency	B	Systematic review (nicotinamide) and eight Level II studies (cinnamon, vitamin E+ nicotinamide, alpha-lipoic acid, antioxidants, vitamin D + nicotinamide, nicotinamide + vitamin E, fenugreek, and nicotinamide) showed no difference in insulin dose. One study (fig leaf) showed a decrease in insulin requirement, but the study was of poor quality and of high risk of bias.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	A	Systematic review (nicotinamide) – age range 10–26 years. Five studies in adolescents (cinnamon, alpha-lipoic acid, vitamin D + nicotinamide, vitamin E + nicotinamide, and nicotinamide). One study in children (antioxidants). One study in adults (fig leaf). One study in adolescents and adults (fenugreek). One study in children and adolescents (vitamin E + nicotinamide).
Applicability	A	Six studies were conducted in Europe, two in the United States and one in India.
Other factors	None identified.	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Lipid targets

Q12.1	Complementary and alternative medicines and outcome/population – lipid targets	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.	
Evidence base	C	Two Level II studies of low risk of bias.
Consistency	A	Studies were consistent – both found no effect of the intervention (vitamin E) in lowering lipids.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	C	Both studies were in adults. Exclusion criteria were only reported in one study; they were hypertension (systolic BP >140 mmHg or diastolic BP >90 mmHg), creatinine level ≥15 mg/L or positive microalbuminuria, total cholesterol >300 mg/dl or triglycerides >500 mg/dl, pregnancy, breast feeding, women of childbearing age without adequate contraception, recent or unstable cardiovascular or cerebrovascular disease.
Applicability	C	Both studies were conducted in Belgium.
Other factors	None identified.	
Recommendation		
R12.1	CAM should not be used in type 1 diabetes to target metabolic outcomes (Grade C).	

BP, blood pressure

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

12.2 Cost and cost-effectiveness of complementary and alternative medicines

Question 12.2

What are the cost and cost-effectiveness of complementary and alternative medicines at achieving targets? [herbal medicines, antioxidants, vitamins, heavy metals, or similar?

No evidence of effectiveness of complementary and alternative medicines was identified (see section 12.1 of this technical report). Therefore, it was not appropriate to undertake a systematic review of cost or cost-effectiveness of these agents.

13 Maternal pregnancy and fetal outcomes

Question 13.1

What is the effectiveness of preconception care in women with type 1 diabetes in improving maternal and fetal outcomes?

13.1 Effectiveness of preconception care

This section of the report investigates the effectiveness of preconception care in women with type 1 diabetes in improving maternal and fetal outcomes.

13.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 13.1.

Table 13.1 Criteria for determining study eligibility, question 13.1

Study design	NHMRC Levels I–IV (using the intervention scale [a])
Population	Women with type 1 diabetes
Intervention	Preconception care
Comparator	Women without type 1 diabetes
Outcomes	Maternal outcomes are defined as preconception HbA_{1c}, blood pressure control, foot care, folate levels, rubella status and miscarriage rates Fetal outcomes are defined as rates of congenital heart disease, respiratory distress syndrome, hypoglycaemia, anencephaly, congenital malformations and cordal regression

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of Level II studies, Level II: A randomised controlled trial, Level III-1: A pseudorandomised controlled trial; Level III-2: A comparative study with concurrent controls; Level III-3: A comparative study without concurrent controls; Level IV: Case series with either post-test or pre-test/post test outcomes.

13.1.2 Assessment of study eligibility

Publications identified in the literature search were reviewed using the criteria shown in Table 13.1, applied hierarchically, to determine which publications to exclude.

A total of 151 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with 120 publications excluded, as shown in Table 13.2. A total of 31 publications remained, and the full-text version of each of these publications was retrieved and reviewed. After further review, a total of 11 papers were included.

13.1.3 Literature search summary

Table 13.2 Search results, question 13.1

Stage	Notes	Number
Search summary	Manual	0
	Cochrane Library	8
	EMBASE	68
	Medline	72

Stage	Notes	Number
	INAHTA	3
	Total	151
Duplicates	Duplicates identified	49
Identified	Total identified	102
Exclusion criteria	Wrong study type (not NHMRC Levels I-IV [a])	42
	Wrong population (not women with type 1 diabetes)	6
	Wrong intervention or test (not preconception care)	17
	Wrong outcome (not maternal or fetal outcomes as listed above (Table 13.1)	5
	Not in English	1
	Total excluded	71
Meeting criteria	Total meeting inclusion criteria	31
Included	Total included studies	11

13.1.4 Included studies

The systematic review by Ray et al (2001) was included; it included 16 studies (Fuhrmann et al 1983; Fuhrmann et al 1984; Goldman et al 1986; Jensen et al 1986; Rowe et al 1987; Dicker et al 1988; Mills et al 1988; Damm and Molsted-Pedersen 1989; Steel et al 1990; Cousins 1991; Kitzmiller et al 1991; Rosenn et al 1991; Willhoite et al 1993; Janz et al 1995; DCCT Research Group 1996; Garcia-Patterson et al 1997; Dunne et al 1999; Herman et al 1999). The characteristics of this study are summarised in Table 13.3. Nine other studies were included; details are given in Table 13.4.

13.1.5 Characteristics of included studies

Table 13.3 Characteristics of Level I studies, question 13.1

Reference and setting	Included studies	Intervention	Outcome	Quality	Comments
Ray et al (2001) Denmark Israel Germany Scotland Spain United Kingdom United States	16 cohort studies (8 retrospective, 8 prospective) n=1192 offspring of mothers who had received preconception care n=1459 offspring of mothers who had not received preconception care	Preconception care	Major and minor congenital malformations, early first trimester HbA_{1c} values	Fair	Preconception care was associated with a significantly lower risk of major and minor congenital anomalies among offspring of women with established diabetes, in conjunction with significantly lower first trimester HbA_{1c} values

HbA_{1c}, glycated haemoglobin

Table 13.4 Characteristics of other included studies, question 13.1

Reference and setting	Study type and quality	Population	Intervention	Outcomes	Comments
Bar et al (1999) Israel	Interrupted time series (Level III–3 evidence) Fair	n=24 women with type 1 diabetes and diabetic nephropathy (proteinuria >500 mg/day) from Israel, mean age 26 ±2.9 years	All subjects received treatment with the ACE inhibitor captopril for at least 6 months before planned pregnancy and were maintained under strict glycaemic control from at least 3 months before pregnancy to delivery.	Maternal and neonatal complications	Pre-pregnancy captopril treatment combined with strict glycaemic control offers potential for improved pregnancy outcomes.
Boulot et al (2003) France	Cross-sectional (Level IV evidence) Fair	n=289 pregnancies from women with type 1 diabetes	Conducted in 12 perinatal centres in France. Preconception care was provided in 48.5% of women with type 1 diabetes. Preconception care included information about the need for optimisation of glycaemic control before pregnancy, assessment of diabetes complications, review of dietary habits, intensification of SMBG, and optimisation of insulin therapy.	Perinatal mortality, major congenital malformations, first trimester HbA_{1c}	Preconception care results in improved perinatal outcomes in women with type 1 diabetes.
Gold et al (1998) United Kingdom	Retrospective cohort (Level III–2 evidence) Poor	The case records of 57 deliveries to women with type 1 diabetes between 1992 and 1996 at the Simpson's Memorial Maternity Pavilion of the Royal Infirmary of Edinburgh were reviewed	Women were offered preconception counselling if they attended routine diabetes review clinics.	HbA_{1c}, birth weight	Glycaemic control in the immediate preconception period and early first trimester appears to have a greater influence on birth weight than does glycaemic control in the later weeks of pregnancy. Limitation: unclear how many subjects received preconception counselling
Goldman et al (1986) Israel	Comparative study (Level III–2 evidence) Poor	n=44 women with type 1 diabetes attending a preconception clinic in Israel (mean age 24.2 ±5.8 years) n=31 women with type 1 diabetes not attending a preconception clinic (mean age 21.4 ±2.3 years)	At the preconception clinic glycaemic control was obtained by intensified insulin therapy and monitored by SMBG. Subjects were also advised to adhere closely to their strict, prescribed diet.	Congenital anomalies, HbA_{1c}	The authors conclude that congenital malformations in pregnancy complicated by diabetes may be linked to disturbances in maternal metabolism during embryogenesis, and that tight glycaemic control is required prior to conception.

Reference and setting	Study type and quality	Population	Intervention	Outcomes	Comments
Heller et al (2010) Inter-national (18 countries)	Open-label, randomised, parallel-group trial (Level III–3 evidence) Fair	Preconception care: n=99 subjects (44 to IAsp and 55 to human insulin) Early pregnancy (<10 weeks) care: n=223 subjects (113 for IAsp and 110 for human insulin)	Prandial IAsp administered immediately before each meal versus human insulin administered 30 minutes before each meal in women with type 1 diabetes. Multicentre study conducted at 63 sites in 18 countries.	Severe hypoglycaemia (requiring outside assistance)	Initiation of insulin analog treatment preconception rather than during early pregnancy may lower the risk of severe hypoglycaemia in women with type 1 diabetes.
Hod et al (1999) Georgia	Interrupted time series (Level III–3 evidence) Fair	n=32 women with type 1 diabetes, mean age 27 ±6 years	A Diabetes-in-Pregnancy centre was established in Georgia. All subjects were placed under strict metabolic surveillance starting at least 3 months prior to conception. Subjects attended a compulsory 5 day course on diabetes in pregnancy and methods of self-monitoring.	HbA_{1c}, insulin dose, maternal and neonatal complications	Preconception care in the Diabetes-in-Pregnancy centre in Georgia led to improved maternal and neonatal outcomes in women with type 1 diabetes.
McElvy et al. (2000) United States	Comparative study (Level III–3 evidence) Fair	306 women were enrolled in three 5-year periods: PPG I (1978–1983) n=111 (age 24.7 ±2.3 years), PPG II (1983–1988) n=103 (26.2 ±5.0 years), and PPG III (1988–1993) n=92 (27.4 ±5.4 years) An emphasis on preconception care began in 1984, with preconception enrolment reaching 23% for PPG II and increasing in PPG III to 37%	Women were enrolled either during preconception or during the first trimester (up to 14 weeks) and had pregnancies continuing beyond 20 weeks gestation. Strict glucose control was implemented and adherence assessed. Intensive diabetes education was tailored to each subject and adjusted according to their progress. Antepartum fetal surveillance was started at 32 weeks gestation.	HbA_{1c}, perinatal mortality, congenital malformation rates, pre-eclampsia, hypertension, birth weight, pre-term delivery	A program emphasising preconception care and the use of antepartum fetal surveillance was associated with a significant decrease in the rate of perinatal mortality in infants of women with type 1 diabetes. Limitation: cohort was recruited either during preconception or the first trimester.
Pearson et al (2007) United Kingdom	Retrospective cohort (Level III–2 evidence) Poor	Using data from two national audit periods, information was collected on all pregnancies in Scotland in women with pre-gestational type 1 diabetes (n=423 singleton pregnancies; age 28.3 ±5.5 years)	Data were extracted from case records to determine if formal pre-pregnancy counselling was documented.	Adverse outcome (spontaneous miscarriage, ectopic pregnancy, molar pregnancy, major congenital anomaly or perinatal death)	The risk of adverse outcome was non-significantly lower in those who received preconception care. Limitation: no indication of what pre-pregnancy counselling involved.

Reference and setting	Study type and quality	Population	Intervention	Outcomes	Comments
Temple et al (2006) United Kingdom	Prospective observational cohort study (Level III–2 evidence) Good	n=110 women with type 1 diabetes who received pre-pregnancy care, mean age 29.4 ±4.3 years n=180 women with type 1 diabetes who did not receive pre-pregnancy care, mean age 28.6 ±5.4 years	Pre-pregnancy care involved SMBG, and education about glycaemic control, diet and medication.	Maternal HbA_{1c}, maternal severe hypoglycaemic episodes, macrosomia, pre-eclampsia, premature delivery, and adverse pregnancy outcome (defined as major malformation, stillbirth, and neonatal death)	This study shows that in women with type 1 diabetes, receiving pre-pregnancy care is associated with improved glycaemic control in early pregnancy and reduced adverse pregnancy outcomes.
Tripathi et al (2010) United Kingdom	Retrospective cohort (Level III–2 evidence) Fair	n=588 women with pre-gestational diabetes (77% had type 1 diabetes), mean age 29.6 ±6.3 years n=291 received preconception counselling n=297 did not receive preconception counselling	The preconception counselling provided was not well defined.	Glycaemic control, adverse pregnancy outcome (major congenital anomaly and/or perinatal death)	Women receiving preconception counselling had better indicators of care. Limitation: lack of detailed content and delivery format of preconception counselling.

ACE, angiotensin-converting enzyme; HbA_{1c}, glycated haemoglobin; IAsp, insulin aspart; PPG, Program Project Grant; SMBG, self-monitoring of blood glucose

13.1.6 Results of included studies

Ray et al (2001)

The meta-analysis by Ray et al (2001) included 16 cohort studies (8 retrospective and 8 prospective). These studies were conducted in the United States (7 studies), Europe (5 studies), the United Kingdom (3 studies) and Israel (1 study). All but 5 studies were conducted at a single centre. Most studies had only subjects with type 1 diabetes, but 3 included some women with type 2 diabetes (≤35% of the study population). Among 2561 offspring, the pooled rate of major anomalies was lower among preconception recipients (2.1%) than non-recipients (6.5%) (relative risk [RR] 0.36, 95% confidence interval [CI]: 0.22 to 0.59). In nine studies and among 2104 offspring, the risk for major and minor anomalies was also lower among women who received preconception care (RR 0.32, 95%CI: 0.17 to 0.59). In seven studies, early first trimester HbA_{1c} values were lower in the preconception care group (pooled mean difference: 2.3%, 95%CI: 2.1 to 2.4). However, heterogeneity was present for this pooled estimate ($p<0.20$).

Bar et al (1999)

Bar et al (1999) examined pregnancy outcome in subjects with type 1 diabetes and diabetic nephropathy treated with angiotensin-converting enzyme (ACE) inhibitors before pregnancy. A successful pregnancy outcome (live, healthy infant with no severe handicaps 2 years after delivery) was observed in 87.5% of subjects. In all subjects a significant decrease in HbA_{1c} was observed from baseline to conception (9.8 vs 7.9%; p=0.01).

Boulot et al (2003)

A French multicentre survey was conducted in 12 perinatal centres in France in 2000–2001 to examine perinatal outcome in pregnancies in women with pre-gestational diabetes (Boulot et al 2003). Perinatal mortality (0.7 vs 8.1%; p<0.0001), congenital malformation (0.7 vs 8.1%, p<0.005) and first trimester HbA_{1c} >8% (4.3 vs 55.0%; p<0.05) were all significantly lower in those who received preconception care (n=140) compared with those who did not (n=149).

Gold et al (1998)

The aim of the study by Gold et al (1998) was to examine the case records of 57 deliveries to women with type 1 diabetes to assess the relative effects of HbA_{1c} levels before conception, at booking, and during the three trimesters of pregnancy on birth weight. Significant correlations were found between birth weight and HbA_{1c} at 0–6 months preconception (r=0.44, p=0.002), at booking (r=0.43, p=0.001), at 0–12 weeks gestation (r=0.48, p=0.001), at 12–24 weeks gestation (r=0.45, p=0.001) and at 24 weeks to term (r=0.34, p=0.009).

Goldman et al (1986)

A comparative study by Goldman et al (1986) examined the association between pregnancy outcomes in women with type 1 diabetes and attendance at a preconception clinic in Israel. Congenital anomalies occurred in 9.6% of offspring of non-attendees, while none occurred in those with preconception counselling. Hypoglycaemia and respiratory distress syndrome in infants were not significantly different between the groups.

Heller et al (2010)

An open-label, randomised, parallel-group trial was performed to investigate the incidence of severe hypoglycaemia during pregnancy in women with type 1 diabetes receiving additional insulin treatment commenced during preconception compared to during early pregnancy (Heller et al 2010). In the first half of pregnancy the RR of severe hypoglycaemia in women randomly assigned to insulin aspart in early pregnancy/preconception was 1.70 (95%CI: 0.91 to 3.18; p=0.097). The RR in the second half of pregnancy was 1.35 (0.38–4.77; p=0.640).

Hod et al (1999)

Hod et al (1999) examined the effectiveness of a joint Israeli-Georgian twinning project aimed at improving perinatal care in Georgian women with pre-gestational diabetes. HbA_{1c} levels decreased significantly from the preconception period to conception (10.1 vs 7.5%; p<0.001) and were maintained at the lower level throughout pregnancy. Insulin dosage decreased significantly from pre-conception to conception and the first two trimesters (p<0.001) and then increased significantly in the third trimester (p<0.001). There were no significant maternal complications during the whole course of pregnancy. The only neonatal complications were mild respiratory distress syndrome (n=3, 16%), which resolved promptly, and hypoglycaemia (n=4, 22.2%). There were no spontaneous abortions, major congenital malformations or neonatal deaths.

McElvy et al (2000)

McElvy et al (2000) evaluated the impact of a focused preconception and early pregnancy program in women with type 1 diabetes on perinatal mortality and congenital malformations. Entry and interval HbA_{1c} concentrations significantly decreased with each consecutive Program Project Grant (PPG) ($p<0.05$). As preconception enrolment increased, perinatal mortality rate decreased from 3% for PPG I and 2% for PPG II, to 0% in PPG III ($p=0.15$), and the congenital malformation rate decreased from 9.0% in PPG I to a low of 2.2% by PPG III ($p=0.07$). There were no significant maternal and neonatal outcome differences among groups in regard to pre-eclampsia, pregnancy induced hypertension, birth weight or preterm delivery ≤34 or ≤37 weeks gestation. Comparison data collected for the period before PPG I (1973–1978) (n=79) revealed a perinatal mortality rate of 7% and a congenital malformation rate of 14%. Also, a post-program retrospective analysis of the period 1993–1999 (n=82) revealed an increase in perinatal mortality, with one death compared to none in PPG III, and a congenital malformation rate of 3.65% compared to 2.2% during PPG III. The preconception enrolment for this period decreased (19.5%). A major limitation of this study was that it was not strictly a preconception care intervention, as subjects were recruited either during preconception or during the first trimester.

Pearson et al (2007)

Using data from two national audit periods, information was collected on all pregnancies in Scotland in women with pre-gestational type 1 diabetes (n=423 singleton pregnancies; age 28.3 ±5.5 years) (Pearson et al 2007). Compared to those with no formal pre-pregnancy counselling, the adjusted odds ratio (OR) for an adverse outcome in those with documented formal pre-pregnancy counselling was 0.54 (95%CI: 0.28 to 1.05). However, there was no indication about what was involved in the pre-pregnancy counselling.

Temple et al (2006)

A prospective observational cohort study was conducted to examine the relationship between pre-pregnancy care, glycaemic control, maternal hypoglycaemia and pregnancy outcomes in 290 women with type 1 diabetes in the United Kingdom (Temple et al 2006). Adverse pregnancy outcomes and very premature deliveries (before 34 weeks) were significantly lower in women who received pre-pregnancy care (2.9 vs 10.2%; $p=0.03$ and 5.0 vs 14.2%; $p=0.02$, respectively). HbA_{1c} was significantly lower in women who received pre-conception care at registration (6.5 vs 7.6%; $p<0.0001$) and remained lower throughout early pregnancy. There was no difference between groups in HbA_{1c} after 24 weeks or in rates of macrosomia, pre-eclampsia, or maternal severe hypoglycaemic episodes.

Tripathi et al (2010)

A population-based study in the North of England investigated the association of preconception counselling with markers of care and maternal characteristics in 588 women with pre-gestational diabetes (mean age 29.6 ±6.3 years) (Tripathi et al 2010). Preconception counselling was associated with better glycaemic control 3 months preconception (OR 1.91, 95%CI: 1.10 to 3.04) and in the first trimester (OR 2.05, 1.39–3.03), and reduced risk of adverse pregnancy outcome ($p=0.027$). Uptake of preconception counselling was positively associated with type 1 diabetes (OR 1.87, 1.14–3.07). However, a major limitation of this study was a lack of detailed content and delivery format information regarding the preconception counselling.

13.1.7 Discussion

The literature search identified 1 systematic review and 10 cohort studies examining the effectiveness of preconception care in women with type 1 diabetes. The systematic review included 16 cohort studies (8 prospective and 8 retrospective). Most of the studies, including those in the systematic review, were of a low level of evidence. Due to the nature of the topic, randomised controlled trials (RCTs) for this question were not available. Most studies were considered to be of fair quality; the rest were of poor quality. Limitations in some studies included an unclear description of the preconception care intervention or the number of subjects who actually received preconception care, largely due to the problem of the studies being retrospective. In one study there was overlap of subjects recruited during either preconception or first trimester.

The systematic review by Ray et al (2001) reported a significantly lower rate of major congenital anomalies among preconception care recipients compared to non-recipients (Ray et al 2001). In addition, the risk for both major and minor congenital anomalies was lower among women who received preconception care, as were early first trimester HbA_{1c} values.

Of the remaining cohort studies, there were mixed results across various outcomes. Most studies found a reduced risk of an adverse outcome with preconception care. Five studies reported a reduced rate of perinatal mortality (McElvy et al 2000; Boulot et al 2003; Temple et al 2006; Pearson et al 2007; Tripathi et al 2010) and six found fewer congenital malformations with preconception care (Goldman et al 1986; McElvy et al 2000; Boulot et al 2003; Temple et al 2006; Pearson et al 2007; Tripathi et al 2010). However, for each of these outcomes, in two studies this association did not quite reach statistical significance (McElvy et al 2000; Pearson et al 2007). Three studies reported reduced HbA_{1c} at conception or during the first trimester with preconception care (Boulot et al 2003; Temple et al 2006; Tripathi et al 2010), while two studies noted a reduction in HbA_{1c} from baseline to conception in those receiving preconception care (Bar et al 1999; Hod et al 1999). There was no significant effect of preconception care on either the rate of hypoglycaemia (Goldman et al 1986) or on the risk of severe hypoglycaemia (Temple et al 2006; Heller et al 2010). Other studies also reported no significant effect of preconception care on birth weight (McElvy et al 2000), macrosomia (Temple et al 2006) or pre-eclampsia (McElvy et al 2000; Temple et al 2006).

13.1.8 Conclusion

The evidence supports a reduced risk of congenital malformations and perinatal mortality among women with type 1 diabetes who receive preconception care compared with women who do not. Preconception care also appears to be effective at reducing HbA_{1c} levels at or around the time of conception. There is no evidence to suggest that preconception care leads to improvements in other maternal and fetal outcomes, such as birth weight, macrosomia, pre-eclampsia or the risk of severe hypoglycaemia. However, many studies, including the systematic review of 16 cohort studies, did not focus on outcomes beyond congenital malformations and perinatal mortality. Therefore, further studies of preconception care in women with type 1 diabetes looking at a wide range of outcomes are warranted.

13.1.9 Literature search strategy

The search was conducted on 11 November 2010. Level I studies were considered first, with the plan to update with Level II studies as required. The Medline search strategy and a summary of citations retrieved from other searches is shown in Table 13.5.

Table 13.5 Search strategy, question 13.1

Database	Date searched	#	Search terms	Citations
Medline	11 November 2010	1	Diabetes Mellitus, type 1/	53 868
		2	Preconception Care/	1 022
		3	(preconception or pre-conception).tw.	1 205
		4	2 or 3	1 905
		5	1 and 4	82
		6	limit 5 to (English language and humans)	72
Cochrane	11 November 2010			8
INAHTA	11 November 2010			3
EMBASE	11 November 2010			68
Manual search				0
Total citations				151
Total non-duplicate citations				102

13.1.10 Evidence Matrix

Q13.1	What is the effectiveness of preconception care in women with type 1 diabetes in improving maternal and fetal outcomes?	
Evidence statement	Level III evidence shows that preconception care is effective at reducing congenital malformations, perinatal mortality and HbA_{1c} levels in women with type 1 diabetes,	
Evidence base	C	One systematic review (included 16 cohort studies – 8 prospective and 8 retrospective) and 10 cohort studies. Level III and IV evidence with a moderate risk of bias.
Consistency	A	Studies were generally consistent in their findings, particularly in regard to the primary outcomes (congenital malformations, perinatal mortality and HbA_{1c}).
Clinical impact	A	Results expected to affect clinical management.
Generalisability	A	For females of childbearing age.
Applicability	A	No studies from Australia, but studies undertaken in countries with a well-established health system.
Other factors	Question is not suitable for study by RCT.	
Recommendation		
R13.1	Females of childbearing age with type 1 diabetes should be aware of the need for pregnancy planning and receive preconception care (Grade B).	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

13.2 Effectiveness of blood glucose control in improving maternal and fetal outcomes in type 1 diabetes

> Question 13.2
>
> What is the effectiveness of blood glucose control during pregnancy in women with type 1 diabetes in achieving blood glucose targets and improving maternal and fetal outcomes?

This section of the report investigates the effectiveness of blood glucose control during pregnancy in women with type 1 diabetes in improving maternal and fetal outcomes.

13.2.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 13.6.

Table 13.6 Criteria for determining study eligibility, question 13.2

Study design	NHMRC Level I or Level II (intervention scale[a])
Population	Women with type 1 diabetes
Intervention	Blood glucose control
Comparator	Women without type 1 diabetes
Outcomes	Blood glucose targets Maternal outcomes are defined as preconception HbA_{1c}, blood pressure control, foot care, folate levels, rubella status and miscarriage rates Fetal outcomes are defined as rates of congenital heart disease, respiratory distress syndrome, hypoglycaemia, anencephaly, congenital malformations and cordal regression

HbA_{1c}, glycated haemoglobin; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

13.2.2 Assessment of study eligibility

Publications identified in the literature search were reviewed using the criteria shown in Table 13.6, applied hierarchically, to determine which publications to exclude.

A total of 35 non-duplicate citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with 25 publications excluded, as shown in Table 13.7. A total of 10 publications remained, and the full-text version of each of these publications was retrieved and reviewed. After further review, only one paper was included.

13.2.3 Literature search summary

Table 13.7 Search results, question 13.2

Stage	Notes	Number
Search summary	Manual	0
	Cochrane Library	5
	EMBASE	27
	Medline	13
	INAHTA	1
	Total	46
Duplicates	Duplicates identified	11
Identified	Total identified	35
Exclusion criteria	Wrong study type (not NHMRC Level I or II[a])	11
	Wrong population (not women with type 1 diabetes)	9
	Wrong intervention or test (not blood glucose control interventions)	4
	Wrong outcome (not blood glucose control targets or maternal or fetal outcomes as listed above in Table 13.6)	1
	Not in English	0
	Total excluded	25
Meeting criteria	Total meeting inclusion criteria	10
Included	Total included studies	1

NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

13.2.4 Included studies

The only systematic review included was that by Middleton et al (2010), which included the studies by Demarini et al (1994), Farrag (1987) and Sacks et al (2006).

13.2.5 Characteristics of included study

Table 13.8 Details of Level I study, question 13.2

Reference and setting	Included studies and quality	Intervention	Outcome	Comments
Middleton et al (2010) United States Saudi Arabia	3 RCTs, all in women with type 1 diabetes (n=223 women and babies) Good	Two trials compared very tight (3.33 to 5.0 mmol/L FBG) with tight–moderate (4.45 to 6.38 mmol/L) glycaemic control targets. Another trial compared tight (≤5.6 mmol/L FBG), moderate (5.6 to 6.7 mmol/L) and loose (6.7 to 8.9 mmol/L) glycaemic control targets	Perinatal deaths, perinatal morbidity, congenital malformations, glycaemic control, hypoglycaemia, caesarean section, pre-eclampsia	Based on very limited evidence, there were few differences in outcomes between very tight and tight-moderate glycaemic control targets in pregnant women with type 1 diabetes, including actual glycaemic control achieved. There is some evidence of harm (increased pre-eclampsia, caesareans, respiratory distress syndrome and birth weight greater than 90th percentile) for 'loose' glycaemic control (FBG above 7 mmol/L)

FBG, fasting blood glucose; RCT, randomised controlled trial

13.2.6 Results of included study

Middleton et al (2010)

Middleton et al (2010) completed a Cochrane systematic review examining different intensities of glycaemic control for pregnant women with pre-existing diabetes. Of the three included randomised controlled trials (RCTs), two (Demarini et al 1994; Sacks et al 2006) were conducted in the United States and one (Farrag 1987) in Saudi Arabia. Each trial used a different method to achieve glycaemic control targets. Demarini et al (1994) focused on clinician monitoring and several hospital admissions throughout pregnancy. Farrag (1987) used insulin adjustment (one unit for each 0.6 mmol/L above the set target). Sacks et al (2006) focused on diet and insulin adjustment based on self-monitoring. Two trials (Demarini et al 1994; Sacks et al 2006) compared very tight (3.33–5.0 mmol/L fasting blood glucose (FBG)) with tight to moderate (4.45–6.38 mmol/L) glycaemic control targets. The other trial (Farrag 1987) compared tight (≤5.6 mmol/L FBG), moderate (5.6–6.7 mmol/L) and loose (6.7–8.9 mmol/L) glycaemic control targets. One trial of 22 babies reported no perinatal deaths or serious perinatal morbidity; 2 birth defects in the very tight and no birth defects in the tight–moderate group (risk ratio (RR) 3.57, 95%CI: 0.19 to 66.61), with no differences in caesarean section between groups (RR 0.92, 0.49 to 1.73). In the first two trials, glycaemic control was significantly better in the very tight target group compared to the tight–moderate group in the first (mean difference (MD) –1.23 mmol/L, –2.19 to –0.27) and second (MD –0.99 mmol/L, –1.64 to –0.34), but not the third trimester (MD –0.66 mmol/L, –1.60 to 0.28). One trial of 22 women found significantly less maternal hypoglycaemia in the tight–moderate group. In the third trial with 60 women and babies there were two neonatal deaths in the loose and none in the tight or moderate groups (RR 0.07, 95%CI: 0.00 to 1.37). There were significantly fewer women with pre-eclampsia (RR 0.11, 0.01 to 0.99), fewer caesareans (RR 0.28, 95%CI: 0.10 to 0.78), and fewer neonates with respiratory distress syndrome (RR 0.17, 95%CI: 0.05 to 0.59) and birth weight greater than the 90th percentile (RR 0.01, 95%CI: 0.00 to 0.20) in the combined tight–moderate compared with the loose group. Based on this very limited evidence, few differences in outcomes were seen between very tight and tight–moderate glycaemic control targets in pregnant women with type 1 diabetes, including actual glycaemic control achieved. There is some evidence of harm (increased pre-eclampsia, caesareans and respiratory distress syndrome) for loose control (i.e. FBG above 7 mmol/L).

13.2.7 Discussion

Little evidence was found to address this question. Studies were identified on blood glucose control in gestational diabetes mellitus (GDM), and comparisons between continuous subcutaneous insulin infusion (CSII) using insulin pumps and intensive conventional insulin therapy using multiple daily injections (MDI) in pregnant women with diabetes. However, these issues were considered beyond the current guidelines. Other studies looked at the effectiveness of blood glucose monitoring in pregnant women, but again did not meet the criteria.

The only study that met the inclusion criteria – Middleton et al (2010) – was a Cochrane review of high quality and was classified as Level I evidence. The authors used a rigorous and detailed search methodology that was updated monthly until May 2010. This review included three RCTs, two from the United States and one from Saudi Arabia. There was a high risk of bias for all three trials due to unclear allocation concealment methods, lack of blinded outcome assessment and a high risk of selective outcome reporting bias. The studies were roughly divided into very tight (<5 mmol/L), tight (<6 mmol/L), moderate (<7 mmol/L) and loose (<9 mmol/L) categories of glycaemic control. In two small trials, very few differences were seen between very tight (3.33–5.0 mmol/L) and tight–moderate (4.45–

6.38 mmol/L) FBG targets. A single trial comparing tight (≤5.6 mmol/L), moderate (5.6–6.7 mmol/L) and loose (6.7–8.9 mmol/L) glycaemic control targets found few differences between tight and moderate groups. There was a greater amount of pre-eclampsia, caesareans and neonates with respiratory distress syndrome and birth weight greater than 90th percentile in the loose group.

13.2.8 Conclusion

Based on limited evidence, there were few differences in outcomes between very tight and tight–moderate glycaemic control targets in pregnant women with type 1 diabetes, including the actual level of glycaemic control achieved. There is some evidence of harm (increased pre-eclampsia, caesareans, respiratory distress syndrome and birth weight greater than 90th percentile) for loose glycaemic control (FBG above 7 mmol/L). Further studies with greater sample size are needed to confirm these results.

13.2.9 Literature search strategy

The search was conducted on 15 November 2010. Level I studies were considered first, with the plan to update with Level II studies as required. As an appropriate Level I study in the form of a Cochrane review was published in 2010, which itself included a thorough search strategy, the search was limited to 2010 to identify only those studies published since the publication of this Level I study. The Medline search strategy and a summary of citations retrieved from other searches are shown in Table 13.9.

Table 13.9 Search strategy, question 13.2

Database	Date searched	#	Search terms	Citations
Medline	15 November 2010	1	Diabetes Mellitus, type 1/	53 944
		2	Pregnancy/	623 207
		3	Blood Glucose Self-Monitoring/	3269
		4	(glucose control or glucose monitoring or glucose self-monitoring).tw.	6437
		5	(glycemic control or glycaemic control).tw.	12 510
		6	diabet$ control.tw.	4121
Medline		7	3 or 4 or 5 or 6	22 861
		8	1 and 2 and 7	471
		9	limit 8 to (English language and humans)	420
		10	limit 9 to yr="2010"	13
Cochrane	15 November 2010			5
INAHTA	15 November 2010			1
EMBASE	15 November 2010			27
Manual search				0
Total citations				46
Total non-duplicate citations				35

13.2.10 Evidence Matrix

Q13.2	What is the effectiveness of blood glucose control during pregnancy in women with type 1 diabetes in achieving blood glucose targets and improving maternal and fetal outcomes?	
Evidence statement	During pregnancy in women with type 1 diabetes, there is some evidence of harm for fasting blood glucose targeted at 6.7–8.9 mmol/L, compared to below 6.7 mmol/L.	
Evidence base	D	One Level I study that included three RCTs of high risk of bias, due to unclear allocation concealment methods, lack of blinded outcome assessment and high risk of selective outcome reporting bias.
Consistency	NA	Only one study was available.
Clinical impact	C	
Generalisability	B	
Applicability	A	No studies from Australia, but the studies were undertaken in countries with a well-established health system
Other factors	None identified.	
Recommendation		
	There was insufficient evidence to make a recommendation.	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

14 Effectiveness of hormonal versus nonhormonal contraceptives

Question 14.1

What is the effectiveness of hormonal versus nonhormonal contraceptives in women with type 1 diabetes?

This section of the report compares the effectiveness of hormonal and nonhormonal contraceptives in women with type 1 diabetes.

14.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 14.1.

Table 14.1 Criteria for determining study eligibility, question 14.1

Study design	A systematic review or meta-analysis (Level I evidence, NHMRC intervention scale[a])
Population	Women with type 1 diabetes
Intervention	Hormonal contraceptive
Comparator	Nonhormonal contraceptive
Outcomes	Contraceptive effectiveness, diabetes control, lipid metabolism and micro- and macrovascular complications.

NHMRC, National Health and Medical Research Centre

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

14.1.2 Assessment of study eligibility

Publications identified in the literature search were reviewed, and the exclusion criteria shown in Table 14.2 applied hierarchically.

The exclusion criteria were applied to all citations by reviewing the abstract and title, with 211 publications excluded (Table 14.2). One publication (a systematic review by Visser et al 2006) met the inclusion criteria, and the full-text version of the publication was retrieved and reviewed. This systematic review was updated and published in 2009.

14.1.3 Literature search summary

Table 14.2 Search results, question 14.1

Stage	Notes	Number
Search summary	Manual	1
	Cochrane Library	8
	EMBASE	2
	Medline	205
Duplicates	Duplicates identified	3
Exclusion criteria	Wrong study type (not a systematic review or meta-analysis)	82
	Wrong population (not in women with type 1 diabetes)	33
	Wrong intervention (not a hormonal contraceptives)	27

Stage	Notes	Number
	Wrong comparator (not a nonhormonal contraceptive)	
	Wrong outcome (does not report principal outcomes: contraceptive effectiveness, diabetes control, lipid metabolism and vascular complications)	69
	Not in English (Non-English publications will not be included)	0
	Total excluded	211
Meeting criteria	Total meeting inclusion criteria	1
Included	Total included studies	1

14.1.4 Characteristics of included studies

The systematic review by Visser et al (2006) aimed to capture all published data from randomised controlled trials (RCTs) and quasirandomised trials that compared differences between progestogen-only contraceptive methods, combined estrogen/progestogen contraceptives, and nonhormonal contraceptives, in women with diabetes, in terms of:

- effectiveness in preventing pregnancy
- side effects on carbohydrates and lipid metabolism
- long-term outcomes such as vascular complications.

Table 14.3 gives the characteristics of the four RCTs included in the review. The trials differed in terms of contraceptives studied, participant characteristics and methodological quality; thus, data could not be combined in a meta-analysis. The trial results were examined on an individual quantitative basis and narrative summaries were provided.

Table 14.3 Details of studies included in the systematic review (Visser et al 2006)

Reference	Country	Duration (months)	Number randomised (completed)	Interventions	Outcomes
Grigoryan et al (2006)	Russia	12	58	20 µg ethinylestradiol and 150 µg desogestrel 30 µg ethinylestradiol and 150 µg desogestrel 30 µg ethinylestradiol and 75 µg gestodene T-shaped copper-containing IUD LNG-releasing IUD	HbA_{1c} Average insulin requirement Total cholesterol; triglycerides LDL-cholesterol HDL-cholesterol
Rogovskaya et al (2005)	Russia	12	62	LNG-releasing IUD Copper T 380A IUD	Glycosylated haemoglobin levels Fasting serum-glucose levels Daily insulin requirements

Reference	Country	Duration (months)	Number randomised (completed)	Interventions	Outcomes
Skouby et al (1986)	Denmark	6	27	4 mg 17ß-estradiol, 2 mg estriol and 3 mg norethindrone 35 µg ethinyl estradiol + 500 µg norethindrone 300 µg norethindrone Triphasic combination of ethinylestradiol (30, 40, 30 µg) + levonorgestrel (50, 75, 125 µg) for 6/5/10 days	Fasting plasma glucose 24-hour insulin requirement HbA_{1c} levels Plasma free fatty acids Triglycerides Total cholesterol HDL, LDL, VLDL Body weight Blood pressure
Radberg et al (1982)	Sweden	6	25	Lynestrenol 0.5 mg Ethinyl estradiol 50 µg and lynestrenol 2.5 mg	Insulin requirement Urinary glucose Fasting blood sugars Serum-cholesterol, serum-triglycerides, serum-phospholipids HDL-cholesterol, HDL-triglycerides, HDL-phospholipids, LDL-cholesterol Body weight Blood pressure

HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; IUD, intrauterine device; LDL, low density lipoprotein; LNG, levonorgestrel; VLDL, very low density lipoprotein

14.1.5 Results of included studies

Grigoryan et al (2006)

Grigoryan et al (2006) examined changes in glucose and lipid metabolism. Only perimenopausal insulin-dependent women (n=58) with type 1 diabetes were included. Participants were assigned to three different types of combined oral contraceptives, a T-shaped copper-containing intrauterine device (IUD) or a levonorgestrel (LNG)-releasing IUD for a period of 12 months.

As shown in Table 14.4, mean insulin requirement increased significantly ($p<0.001$) in women using 30 µg ethinyl-estradiol (EE2) plus 75 µg gestodene (GSD). During all other interventions, mean insulin requirement and HbA_{1c} remained unchanged. Women using 20 µg EE2 plus 150 µg desogestrel (DSG) showed a statistically significant decrease ($p<0.05$) of triglycerides and increase ($p<0.05$) of high density lipoprotein (HDL) cholesterol after 12 months of use. Blood lipid profile remained unchanged when using 30 µg EE plus 75 µg GSD or an LNG-releasing IUD.

Table 14.4 Results from Grigoryan et al (2006)

Regimen	HbA_{1c}	Total cholesterol	Total triglycerides	HDL-cholesterol	LDL-cholesterol
Before 20 µg EE2 + 150 µg DSG	7.5 ±0.3	6.88 ±0.95	0.88 ±0.75	1.68 ±0.68	2.75 ±0.85
After 20 µg EE2 + 150 µg DSG	7.5 ±0.4	7.02 ±1.25	0.81 ±0.55 ($p<0.05$)	1.89 ±1.12 ($p<0.05$)	2.84 ±1.13
Before 30 µg EE2 + 150 µg	7.5 ±0.3	7.78 ±1.45	0.86 ±0.37	1.66 ±0.68	2.75 ±0.75

Regimen	HbA_{1c}	Total cholesterol	Total triglycerides	HDL-cholesterol	LDL-cholesterol
DSG					
After 30 µg EE2 + 150 µg DSG	7.5 ±0.6	7.72 ±1.23	0.88 ±0.57	1.75 ±0.50 (p<0.05)	2.83 ±0.76
Before 30 µg EE2 + 75 µg GSD	7.5 ±0.3	7.87 ±1.75	0.76 ±0.37	1.68 ±0.68	2.95 ±0.55
After 30 µg EE2 + 75 µg GSD	7.5 ±0.4	7.65 ±0.29	0.78 ±1.57	1.70 ±1.63	2.89 ±0.66
Before copper IUD	7.8 ±0.3	NA	NA	NA	NA
After copper IUD	7.8 ±0.7	NA	NA	NA	NA
Before LNG-releasing IUD	7.6 ±0.5	NA	NA	NA	NA
After LNG-releasing IUD	7.7 ±0.3	NA	NA	NA	NA

DSG, desogestrel; EE2, ethinyl-estradiol; GSD, gestodene; HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; IUD, intrauterine device; LDL, low density lipoprotein; LNG, levonorgestrel; NA, not available

Rogovskaya et al (2005)

Rogovskaya et al (2005) examined glucose metabolism in women (n=62) randomly assigned to either a copper IUD or an LNG-releasing IUD for a period of 12 months. As shown in Table 14.5, there were no significant changes in insulin requirement, glycated haemoglobin (HbA_{1c}) and fasting blood sugars during any of the treatments. The authors also found no differences in glucose metabolism between the treatment groups after 12 months. No adverse effects were reported.

Table 14.5 Results from Rogovskaya et al (2005)

Regimen	HbA_{1c}	Fasting glucose	Daily insulin dosage
Before LNG-releasing IUD	5.6 ±1.3	5.2 ±0.9	35.2 ±12.7
After LNG-releasing IUD	6.3 ±1.5	7.4 ±4.2	35.1 ±12.8
Before copper IUD	5.5 ±1.4	5.0 ±0.6	36.4 ±9.7
After copper IUD	6.3 ±1.3	7.5 ±4.2	36.4 ±9.0

HbA_{1c}, glycated haemoglobin; IUD, intrauterine device; LNG, levonorgestrel

Skouby et al (1986)

Skouby et al (1986) examined changes in glucose and lipid metabolism. Twenty-seven women were assigned to four different oral contraceptive preparations (4 mg 17ß-estradiol [E2] + 2 mg estriol + 3 mg norethindrone; 35 µg ethinyl estradiol + 500 µg norethindrone; 300 µg norethindrone; triphasic combination of EE2 (30, 40, 30 µg) + LNG (50, 75, 125 µg) for 6/5/10 days) for a period of 6 months. No changes in fasting blood glucose, HbA_{1c} or mean insulin requirement were observed during treatment in any of the groups. Also, no differences in glucose metabolism were found between the four different oral contraceptive preparations after 6 months.

As shown in Table 14.6, no changes in triglycerides, low density lipoprotein (LDL) cholesterol and very low density lipoprotein (VLDL) cholesterol were observed during treatment in any of the groups. HDL-cholesterol was significantly lower after 6 months in users of 4 mg E2 plus 2 mg estriol plus 3 mg norethindrone. After 6 months, triglycerides were significantly decreased in users of 4 mg E2 plus 2 mg estriol plus 3 mg norethindrone, and the triphasic preparation of EE2 + LNG, compared with users of 35 µg EE2 plus 500 µg norethindrone

(p<0.01). Similarly, after 6 months, VLDL-cholesterol was significantly decreased in users of 4 mg E2 + 2 mg estriol + 3 mg norethindrone when compared with users of 35 µg EE2 + 500 µg norethindrone (p<0.01).

Blood pressure and body weight remained unchanged throughout the study. No adverse effects were reported.

Table 14.6 Results from Skouby et al (1986)

Regimen	Fasting glucose	HbA_{1c}	Daily insulin dosage	Free fatty acids	Serum-triglycerides	HDL-cholesterol	LDL-cholesterol	VLDL-cholesterol
Before 4 mg E2 + 2 mg estriol + 3 mg norethindrone	15.6 ±1.9	8.6 ±0.7	51 ±6	986 ±151	1.07 ±0.2	1.54 ±0.1	3.17 ±0.4	0.49 ±0.1
After 4 mg E2 + 2 mg estriol + 3 mg norethindrone	14.6 ±2.0	8.8 ±0.4	55 ±5	1033 ±145	0.95 ±0.1	1.33 ±0.1 (p<0.01)	3.12 ±0.4	0.41 ±0.1
Before 35 µg EE2 + 500 µg norethindrone	12.8 ±1.8	9.5 ±0.7	48 ±4	854 ±99	1.28 ±0.2	1.42 ±0.1	3.13 ±0.3	0.58 ±0.1
After 35 µg EE2 + 500 µg norethindrone	12.9 ±2.2	9.1 ±0.7	50 ±4	756 ±118	1.93 ±0.3	1.52 ±0.1	3.48 ±0.4	0.88 ±0.1
Before 300 µg norethindrone	14.1 ±1.7	8.9 ±0.5	47 ±3	969 ±138	1.25 ±0.1	1.23 ±0.1	3.26 ±0.2	0.57 ±0.1
After 300 µg norethindrone	16.9 ±2.0	9.5 ±0.9	47 ±3	783 ±123	1.17 ±0.1	1.30 ±0.1	3.15 ±0.2	0.53 ±0.1
Before triphasic preperation of EE2 + LNG	17.1 ±1.7	9.1 ±0.5	45 ±5	594 ±61	1.25 ±0.3	1.51 ±0.1	3.23 ±0.2	0.57 ±0.1
After triphasic preperation of EE2 + LNG	13.2 ±1.5	9.1 ±0.5	44 ±4	761 ±105	1.12 ±0.2	1.54 ±0.1	3.35 ±0.3	0.53 ±0.1

E2, 17ß-estradiol; EE2, ethinyl-estradiol; HbA_{1c}, glycated haemoglobin; LNG, levonorgestrel

Radberg et al (1982)

Radberg et al (1982) examined changes in glucose and lipid metabolism. Twenty-three women were assigned to either 0.5 mg lynoestrenol (LYN) or 50 µg EE2 plus 2.5 mg LYN, and after 6 months were re-assigned to the other preparation.

As shown in Table 14.7, mean insulin requirement remained unchanged during LYN treatment but increased significantly (p<0.01) in the combined oral contraceptive group. In both groups, urinary glucose excretion increased significantly (p<0.05), although fasting blood glucose levels did not change. After 6 months, users of LYN had a statistically significant lower mean insulin requirement when compared with users of EE2 plus LYN (p<0.05).

As shown in Table 14.8, treatment with LYN caused a significant (p<0.001) decrease in serum cholesterol, triglycerides, phospholipids and LDL. Conversely, combined oral contraceptives

caused a significant increase in serum triglycerides. After 6 months, users of LYN had a significant lower level of serum cholesterol (p<0.01), serum triglycerides (p<0.001), serum phospholipids (p<0.001) and HDL-triglycerides (p<0.05) when compared to users of EE2 plus LYN.

No signs or symptoms of thromboembolic incidents or visual disturbances were observed during any of the interventions. Blood pressure remained unchanged throughout the study.

Table 14.7 Results from Radberg et al (1982) – glucose levels

Regimen	Daily insulin dosage	Urinary glucose	Blood glucose
Before 0.5 mg LYN	43.9 ±3.1	180 ±30	10.5 ±0.9
After 0.5 mg LYN	43.1 ±3.0	270 ±45 (p<0.05)	10.5 ±0.9
Before 50 µg EE2 + 2.5 mg LYN	42.1 ±3.2	237 ±45	10.1 ±0.6
After 50 µg EE2 + 2.5 mg LYN	44.9 ±3.4 (p<0.01)	302 ±47 (p<0.05)	10.6 ±0.7

EE2, ethinyl-estradiol; LYN, lynoestrenol

Table 14.8 Results from Radberg et al (1982) – lipid levels

	Serum cholesterol	Serum triglycerides	Serum phospholipids	HDL-cholesterol	HDL-triglycerides	HDL-phospholipids	LDL-cholesterol
Before 0.5 mg LYN	5.17 ±0.16	0.66 ±0.1	2.77 ±0.09	1.28 ±0.06	0.09 ±0.02	1.07 ±0.05	3.33 ±0.13
After 0.5 mg LYN	4.56 ±0.12 (p<0.001)	0.46 ±0.05 (p<0.001)	2.45 ±0.07 (p<0.01)	1.23 ±0.04	0.06 ±0.01	1.05 ±0.03	3.10 ±0.1 (p<0.01)
Before 50 µg EE2 + 2.5 mg LYN	4.89 ±0.22	0.63 ±0.1	2.71 ±0.09	1.20 ±0.04	0.07 ±0.01	1.13 ±0.08	3.42 ±0.18
After 50 µg EE2 + 2.5 mg LYN	4.91 ±0.23	0.75 ±0.11 (p<0.05)	2.84 ±0.06	1.22 ±0.05	0.08 ±0.02	1.21 ±0.08	3.22 ±0.22

EE2, ethinyl-estradiol; LYN, lynoestrenol

14.1.6 Discussion

Effectiveness

No unintended pregnancies occurred during any of the included trials. Since pregnancy is a rare event in contraceptive users, the sample size and duration of the included trials were too small and too short, respectively, to detect differences among the various contraceptives. From large trials conducted among contraceptive users we know that when used properly, as in the included trials, combined oral contraceptives and the minipill give a 0.3% chance of experiencing an unintended pregnancy within the first year. This chance is 0.6% for a copper IUD and 0.1% for a progestogen-releasing IUD (WHO (World Health Organization) 2004). The chance of experiencing an unintended pregnancy is likely to be similar in women with or without diabetes.

Diabetes control

Two of the included studies compared diabetes control in women using an LNG-releasing IUD versus a copper IUD (Rogovskaya et al 2005; Grigoryan et al 2006). These studies found that glucose metabolism remained stable during both interventions. Three of the included

studies compared progestogen-only methods and different types of combined oral contraceptives (Radberg et al 1982; Skouby et al 1986; Grigoryan et al 2006). These studies also found no changes in glucose metabolism during use of progestogen-only pills, and reported slight impairment of glucose homeostasis in users of high-dose oral contraceptives and 30 µg EE2 plus 75 µg GSD. Other low-dose oral contraceptives appeared to have no effect on glucose metabolism.

The studies had some limitations. Reporting of study methods and the methodological quality were poor. For example, three of the four included studies did not report the method of generating the allocation sequence, the method of concealing the treatment allocation sequence or the use of blinding. Bias can arise from nonrandom methods of generating the allocation sequence, inadequate allocation concealment, failure to blind the participants or the outcome assessors, and exclusion of participants after randomisation.

Lipid metabolism

The three included studies found conflicting results in relation to lipid metabolism (Radberg et al 1982; Skouby et al 1986; Grigoryan et al 2006). Radberg et al (1982) found a significant increase in serum cholesterol, triglycerides and phospholipids levels in the combined oral contraceptives group, and the opposite effect in the progestogen-only group. In spite of the significant change, all lipid levels were within normal range before and after contraceptive use. Skouby et al (1986) found no significant changes in lipid metabolism in the treatment groups. However, this study did find significant differences between the users of the different combined oral contraceptive regimens, in relation to serum triglycerides and VLDL-cholesterol before and after contraceptive use. Grigoryan et al (2006) found a slightly favourable effect on lipid metabolism after 12 months in the groups using 20 µg EE2 plus 150 µg DSG, 30 µg EE plus 150 µg DSG and the T-shaped copper-containing IUD. However, the study found no significant changes in the group using 30 µg EE plus 75 µg GSD and an LNG-releasing IUD. Again, the study limitations should be taken into account when considering the results of these studies.

14.1.7 Conclusion

The four RCTs included in this systematic review provided insufficient evidence to assess whether progestogen-only and combined oral contraceptives differ from nonhormonal contraceptives in diabetes control, lipid metabolism and long-term complications. Unintended pregnancies were not observed during any of the studies. Three of the four studies were of limited methodological quality and described surrogate outcomes.

14.1.8 Literature search strategy

The search was conducted between 13 May 2010 and 22 June 2010, and covered the period from 1990 to 22 June 2010. Studies published after 22 June 2010 were not eligible for inclusion in the systematic review. The search strategy for Medline (Table 14.9) was slightly adapted for the other databases. A total of 211 non-duplicate citations were identified.

Table 14.9 Search strategy, question 14.1

Database	Date searched	#	Search terms	Citations
Medline	13 May 2010 – 22 June 2010	1	Diabetes Mellitus/	76 375
		2	Diabetes Mellitus/ type 1/ or Diabetic Ketoacidosis/ or DKA.mp.	55 482
		3	IDDM.mp.	6 793
		4	1 or 2 or 3	128 816
		5	Contraceptive Agents, Female/	4 188
		6	(Contraceptive and device).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2 432
		7	(oral and contraceptive).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	14 362
		8	progestogen.mp. or Progestins/	9 930
		9	progestagen.mp.	1 120
		10	progesteron.mp.	460
		11	levonorgestrel.mp. or Levonorgestrel/	3 820
		12	norethisteron.mp.	22
		13	(Norethindron or norgestimat or desogestr or gestode or norgestrel or estrogen or estragen or oestrogen or oestragen or ethiny or estradiol or oestradiol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	160 360
		14	(low and dose).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	149 885
		15	progestagen-only.mp.	84
		16	progestogen-only.mp.	361
		17	norplant.mp.	1 012
		18	barrier method.mp.	220
		19	IUD.mp. or Intrauterine Devices/	9 670
		20	IUS.mp.	426
		21	(intra-uterine and system).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	247
		22	(menopause or estorgen replacement therapy).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	29 129
		23	neplasms.mp.	3
		24	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	346 099
		25	meta analysis/exp or meta analysis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	40 290
		26	systematic review.mp.	18 330
		27	pooled analysis.mp.	1 820
		28	exp review/	1 534 431
		29	25 or 26 or 27 or 28	1 560 813
		30	4 and 24 and 29	314
		31	limit 30 to (english language and yr="1990 -Current")	205

Database	Date searched	#	Search terms	Citations
Cochrane	22 June 2010		(adapting search strategy above)	8
EMBASE	6 July 2010	1	"insulin dependent diabetes mellitus"	132 970
		2	"contraceptive"	21 132
		3	"systematic review"	34 651
		4	1 and 2 and 3	2
Manual search				1
Total citations				215

14.1.9 Evidence Matrix

HbA_{1c}

Q14.1	What is the metabolic effect of hormonal versus nonhormonal contraceptives in women with type 1 diabetes?	
Evidence statement	The four RCTs included in this systematic review provided insufficient evidence to assess whether progesterone-only and combined oral contraceptives differ from nonhormonal contraceptives in their impact on glycaemic control.	
Evidence base	D	Level 1 evidence comprising four RCTs, three of high risk of bias and one of moderate risk of bias.
Consistency	A	HbA_{1c} – only two studies reported this outcome, and no difference was found in either study. No safety outcomes were reported.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	D	Sample size was small (n=62), and studies were not recent.
Applicability	C	All studies were conducted in Europe.
Other factors	None identified.	

Lipids

Q14.1	What is the metabolic effect of hormonal versus nonhormonal contraceptives in women with type 1 diabetes?	
Evidence statement	The four RCTs included in this systematic review provided insufficient evidence to assess whether progesterone-only and combined oral contraceptives differ from nonhormonal contraceptives in their impact on lipid metabolism.	
Evidence base	D	Level I evidence comprising four RCTs, three of high risk of bias and one of moderate risk of bias.
Consistency	C	Lipids – results were conflicting; one study reported a significant increase and three studies reported changes that were not clinically meaningful (i.e. they were within the normal range). No safety outcomes were reported.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	D	Sample size was small (n=62), and studies were not recent.
Applicability	C	All studies were conducted in Europe.
Other factors	None identified.	
Recommendation		
	There was insufficient evidence to make a recommendation.	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

15 Essential elements in transitional care

This chapter was not systematically reviewed.

16 Hypoglycaemia

Question 16

i) What are the predictive factors for severe hypoglycaemia?

ii) What is the effect of intensive diabetes management on the incidence of severe hypoglycaemia?

This chapter examines the predictive or risk factors for severe hypoglycaemia (SH), including those that are a consequence of treatment of diabetes and those that are inherent in the individual with diabetes. Question 16 (i) addresses risk factors not related to the treatment regimen; Question 16 (ii) addresses the evidence surrounding the risk of SH with intensive diabetes management as the intervention. The definition of SH varies between studies. For the purposes of this report, any hypoglycaemia requiring the assistance of a third party was taken as SH.

16.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 16.1.

Table 16.1 Criteria for determining study eligibility, question 16

Study design	i) Aetiology: NHMRC Levels I, II, III–1, III–2, III–3, III–4, IV (NHMRC aetiology scale[a]) ii) Intervention: Levels I or II
Population	Type 1 diabetic subjects
Intervention	ii) Intensive diabetes management
Comparator	ii) Conventional management
Outcomes	Severe hypoglycaemia, as defined by study

NHMRC, National Health and Medical Research Council

[a] NHMRC aetiology scale: Level I, a systematic review of Level II studies, Level II, a prospective cohort study, Level III–1, all or none, Level III–2, a retrospective cohort study, Level III–3, a case–control study, Level IV, a cross-sectional study or case series.

16.1.2 Assessment of study eligibility

Publications identified in the literature search were reviewed using the criteria shown in Table 16.2, applied hierarchically, to determine which publications to exclude.

A total of 295 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with 248 publications excluded, as shown in Table 16.2. A total of 34 publications remained, and the full-text version of each of these publications was retrieved and reviewed.

16.1.3 Literature search summary

Table 16.2 Search results, question 16

Stage	Notes	38(i)
		Number
Search summary	Manual	6
	Cochrane Library	14
	INAHTA	2
	Medline	273
	Total	295
Duplicates	Duplicates identified	12
Exclusion criteria	Wrong study type: i) not NHMRC Levels I, II, III–1 or III–2, III–3(n<500), Level IV (n<500), ii) not NHMRC Levels I or II	69
	Wrong population (not type 1 I subjects, studies on subjects with type 1 diabetes during pregnancy were excluded)	83
	Wrong intervention or test (ii) not intensive diabetes management/intensive treatment (IT)	24
	Wrong comparator (ii) not conventional treatment	
	Wrong outcome (not SH as defined by the study)	67
	Not in English	5
	Total excluded	248
Meeting criteria	Total meeting inclusion criteria	34
	N<500 Levels III or IV	10
Included	Total included studies	25

16.1.4 Included studies

Question 16 (i) What are the predictive factors for severe hypoglycaemia?

Included studies for this subquestion were Allen et al (2001), Barkai et al (1998), Bognetti et al (1997), Bragd et al (2003), Bulsara et al (2004), Bulsara et al (2007), Chaturvedi et al (1995), Cox et al (1999), Danne et al (2001), Davis et al (1998), Gonder-Frederick et al (2008), The Diabetes Control and Complications Trial (DCCT) Research Group (1997), Hirai et al (2007), Kilpatrick et al (2007), Levine et al (2001), Mortensen et al (1997), Nordfeldt et al (2003), Pedersen-Bjergaard et al (2001), Pedersen-Bjergaard et al (2008), Rewers et al (2002), Rosilio et al (1998), Salti et al (2004), Stephenson et al (1996), The Diabetes Control and Complications Trial (DCCT) Research Group (1994).

Question 16 (ii) What is the effect of intensive diabetes management on the incidence of severe hypoglycaemia?

Included studies for this subquestion were Wang et al (1993b) and Egger et al (1997).

16.1.5 Characteristics of included studies

Question 16 (i) What are the predictive factors for severe hypoglycaemia?

No Level I evidence was found that addressed this part of the question; 10 Level II (prospective cohort) studies on children and adolescents were found. The Level II studies

ranged from 61 person years (Gonder-Frederick et al 2008) to over 7605 (Bulsara et al 2007) person years in follow-up. One cohort study used retrospective outcome ascertainment (Bognetti et al 1997). Three cross-sectional studies were identified that surveyed paediatric populations of over 2000 subjects (Mortensen and Hougaard 1997; Rosilio et al 1998; Danne et al 2001). Cross-sectional or case–control studies of fewer than 500 subjects were not included. The study by Allen et al (2001) used a population range of 0–34 years, with most participants being 5–14 years of age. Thus, results applicable to the adolescent cohort were included in this section, and the overall statistics in the adult section (Allen et al 2001). These studies were mostly of good or fair quality, based on the question asked, reporting of results and representative population. Total persons and years were also taken into account. The study by Gonder-Frederick et al (2008) was rated as poor quality.

In the adult population, the highest level evidence came from a randomised control trial (RCT), the Diabetes Control and Complications Trial (DCCT) (DCCT Research Group 1993). As this report addressed a question of aetiology, it was classified as Level II evidence (prospective cohort study). Two analyses of this population were included (DCCT Research Group 1991; DCCT Research Group 1997). This cohort has a follow-up time of over 9000 person years. The other adult prospective cohort study was more recent, but smaller, with 171 person years (Pedersen-Bjergaard et al 2008). The only Level III and Level IV studies included in this systematic review were those with a population of more than 500 subjects. The search identified six cross-sectional studies. The population ranged from 537 (Hirai et al 2007) to 12914 (Salti et al 2004), with the EURODIAB population examined in three separate reports on smoking (Chaturvedi et al 1995), autonomic neuropathy (Stephenson et al 1996) and fibre intake (Buyken et al 1998). Characteristics of the included studies are shown in Table 16.3. These studies were of generally good to fair quality.

Table 16.3 Characteristics of included studies for question 16 (i), in order of publication date

Reference	Risk factor	Population	Study type	Persons and years
Pedersen-Bjergaard et al (2008)	Gene polymorphisms Angiotensin concentration Serum ACE activity	Adult type 1 diabetes more than 2 years duration	Prospective cohort	171 over 1 year
Gonder-Frederick et al (2008)	Poor hypoglycaemia detection	Parents of children aged 6–11 years, and 1 parent	Prospective cohort	53 parents 6 months
Kilpatrick et al (2007)	Mean blood glucose and/or glucose variability	DCCT data	Data re-analysis	1441 over 9 years
Hirai et al (2007)	Smoking	Type 1 diabetes	Cross-sectional	537 patients
Bulsara et al (2007)	ACE genotype	Children and adolescents	Prospective cohort	585 subjects over 13 years
Salti et al (2004)	Fasting during Ramadan	Type 1 diabetes; adults	Cross-sectional	1070
Bulsara et al (2004)	HbA_{1c} Demographic features	Children	Prospective cohort	1335 over 4 years
Nordfeldt et al (2003)	Serum ACE level	Intensively treated type 1 diabetes; children and adolescents aged 7–19 years	Prospective cohort	86 over median 4 years

Reference	Risk factor	Population	Study type	Persons and years
Bragd et al (2003)	Demographic and clinical features	Adults	Repeat cross-sectional/cohort	434 in 1985, 641 in 1999 178 answered both (cohort)
Rewers et al (2002)	Underinsurance Psychiatric disorder Mean dose Mean HbA_{1c} BMI Diabetes education Clinic visits	Children, median age 13 years	Prospective cohort	3994 1243 over average 3.5 years
Levine et al (2001) USA	HbA_{1c} tertile	Youth age 7–16 years Type 1 diabetes; receiving specialty care	Prospective cohort	300 over 1 year
Danne et al (2001) Canada, Europe, Japan	HbA_{1c} Different diabetes centres	Paediatric; median age 11.9 years	Repeat cross-sectional/cohort (results from cross-sectional)	2780 patients in 1995; 2101 patients in 1998; 891 in both (3 year) cohorts
Pedersen-Bjergaard et al (2001)	ACE activity	Type 1 diabetes; adults Untreated with ACEI or ARB	Cross-sectional	204
Allen et al (2001)	HbA_{1c} IT SMBG Socioeconomic Health insurance Frequent hypoglycaemia	4th to 6th year after diagnosis of type 1 diabetes; age range at time of study <5–34 years	Prospective cohort	415 over 4–6.5 years
Cox et al (1999)				
Barkai et al (1998)	Impaired hypoglycaemic awareness	Children and adolescents	Prospective cohort	130 over 1 year
Davis et al (1998) Australia	Strict glycaemic control	Children and adolescents	Prospective cohort	709 patients, 2027 patient years
Rosilio et al (1998) France	Medical and nonmedical factors	Children and adolescents	Cross-sectional	2579 patients
DCCT (1997) North America	Risk factors for severe hypo: baseline characteristics, HbA_{1c} during trial. (non-IT factors)	Adolescents and adults	Randomised controlled trial	1441 (3.5–9)

Reference	Risk factor	Population	Study type	Persons and years
Mortensen and Hougaard (1997) United States, Europe, Japan	Estimate of current level metabolic control	Children and adolescents	Cross-sectional	2873 children
Bognetti et al (1997)	Demographic and clinical factors	Children and adolescents	Retrospective cohort	187 patients over 3 years
Stephenson et al (1996)	Autonomic neuropathy	EURODIAB cohort	Cross-sectional	3248 patients
Chaturvedi et al (1995)	Smoking	EURODIAB cohort Adults	Cross-sectional	3250 patients
Pinkey et al (1994)	Gender Age History	Mean age at diagnosis 12 years	Prospective cohort	161 over 4 years
DCCT (1994) 13–17 years at entry	Intensive glycaemic control	Adolescents	Prospective cohort	195 over 7.4 years

ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BMI, body mass index; DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycated haemoglobin; IT, intensive treatment; SMBG, self-monitoring blood glucose

Question 16 (ii) What is the effect of intensive diabetes management on the incidence of hypoglycaemia?

Level I evidence was found for this part of the question in two meta-analyses that examined the risk of adverse effects of intensive treatment (IT) in insulin-dependent diabetes. Wang et al (1993b) was published in 1993, before the results of the large DCCT trial, and was of fair quality. The meta-analysis by Egger et al (1997) included the results of the DCCT and was of good quality.

16.1.6 Results of included studies

Question 16 (ii)

Paediatric

Prospective cohort

Table 16.4 Results of paediatric, prospective cohort studies for question 16 (ii)

Reference, setting, age	Person years	Incidence or frequency	Variable with increased risk of severe hypoglycaemia	Statistics	
DCCT (1994) Adolescents 1994	195	85.7 per 100 PY; IT vs 27.8 in CT	IT	Difference between CT and IT p<0.001	
Bulsara et al (2004) Australia (0–18 years)	6928	In 1992: 7.8 per 100 PY In 2002: 16.6 per 100 PY	Young age, <6 years	IRR 1.76 , 95%CI 1.1 to 2.81	
			Male sex 13–18 years	1.44 (1.11–1.86)	
			Higher insulin dose	IRR 1.62 (1.19–2.2) MV	
			Duration diabetes >9 years (<1 year IRR=1)	IRR 5.3 (2.9–9.5)	
			Duration diabetes 1–5 years	IRR 3.7 (2.3–6)	
			Social disadvantage (highest=1) Lowest	IRR 0.7 (0.5–0.9)	
Rewers et al (2002) United States (<18 years)	3994	19 per 100 PY	Non-Hispanic white ethnicity	UV	MV (age stratification <13>13 and sex adjusted)
			Longer duration diabetes	UV	<13 years RR 1.39 per 5-year increment (1.16–1.69)
			Psychiatric disorder	UV	>13 years RR 1.56 (1.23–1.98)
			Underinsurance	UV	>13 years RR1.42 (1.11–1.81)
			Decreased HbA_{1c}	_	>13, RR 1.22 per 1% decrease (1.12–1.32)
Allen et al (2001) United States (0–29 years: data given for age <15)	415x(4–6.5)	Overall rate (age 0–29) 1987 observations in 415 subjects			
			Older age compared with age 0	MV	OR 2.2 (1.1–4.5) 5 years old OR 5.7(1.3–24.4) 15 years of age
Levine et al (2001) United States 7–16 years	300	62 per 100 PY	Trend for lower incidence SH in highest HbA_{1c} tertile, total events small, no statistically significant difference was found	chi-squared 4.3, df=4, p=0.116 for the 3-way comparison	

Reference, setting, age	Person years	Incidence or frequency	Variable with increased risk of severe hypoglycaemia	Statistics	
Davis et al (1998) Australia (0–18 years)	2027	7.8 episodes/100 PY	Diabetes duration<1year reduced incidence SH	1.19 vs 8.8 episodes/100 PY	p<0.001
			Age<6, SH rate higher than >6 years	14.9 vs 7.2 episodes/PY	p<0.05
			HbA_{1c} 7–8% vs 8–9% (independent of age, duration, method of treatment)	45.9 vs 23.5 episodes/100 PY	p<0.01
			Final year of study (1992 vs 1995)	4.8 vs 15.6 episodes/100 PY	p<0.01
Bulsara et al (2007) Australia (≤18 years)	7605	14 per 100 PY	(Difference between patients with 0 SH and 1 SH) Age at onset (9.9 vs 8.3 years)	<0.0001	
			Duration (5.4 vs 7.9 years)	<0.0001	
			Mean HbA_{1c} (8.6 vs 8.8%)	0.003	
			Presence of the D allele of the ACE gene does not predict higher risk of SH		
Gonder-Frederick et al (2008) USA 6–11	61	13/53 reported 1 SH	Lower hypoglycaemia AI in children with SH than those without	T=4.4, p<0.0001	
Pinkey et al (1994) England	664	Overall risk 0.062 admissions per pt year of follow up	No relationship with sex, family history of diabetes, social class or DKA or hospital admission at original presentation	Of the 55 pts reporting SH, 44% had admissions for poor control compared with 23% of the remainder (p<0.01)	
Nordfeldt et al (2003) Sweden (7–19 years)	86 x1	1.8 events per PY	S-ACE at or above median level had mean of 3-yearly SH vs mean 0.5 in S-ACE lower than median (median 1.03 microkat/L)	p=0.0079	

AI, accuracy index (subtraction of % of clinically significant errors from % accurate estimates); CI, confidence interval; CT, conventional therapy; df, degrees of freedom; DKA, diabetic ketacidosis; HbA_{1c}, glycated haemoglobin; IRR, incidence rate ratio; IT, intensive treatment; MV, multivariate analysis; OR, odds ratio; PY, person years; RR, rate ratio; S-ACE, serum angiotensin-converting enzyme; SH, severe hypoglycaemia; UV, univariate analysis

Paediatric

Retrospective cohort

Table 16.5 Results of paediatric, retrospective cohort studies for question 16 (ii)

Reference	Person years	Frequency of SH	Variable	Stat significance
Bognetti et al (1997)	187 x 2	14.9 episodes/100 PY	Frequency of SH decreased significantly with age, independent of duration of diabetes duration	chi-squared=24.1 p<0.0001
			Hypoglycaemia and duration diabetes	No correlation chi-squared=5.79
			Statistical correlation b/w HbA_{1c} and age was at occurrence of hypoglycaemia	R=0.12 (not significant)

HbA_{1c}, glycated haemoglobin; PY, person years; S-ACE, serum angiotensin converting enzyme; S-ACE, serum angiotensin-converting enzyme; SH, severe hypoglycaemia

Paediatric

Cross-sectional studies

Table 16.6 Results of paediatric, cross-sectional studies for question 16 (ii)

Reference, setting, age	N	Prevalence/ frequency	Variable with significant effect on severe hypoglycaemia	Statistical significance
Mortensen and Hougaard (1997) Denmark (1–18)	2873	22 per 100 PY	Age: decrease by 8.4%/year	SE 2% p<0.0001
			HbA_{1c}: decrease by 21% for 1% increase HbA_{1c}	SE 6% p<0.001
Danne et al (2001) 17 countries Europe, Japan, North America	1995: n=2780 age 0–18 years 1998: n=2101 age 11–18 years	Not reported	Paired comparison of the three centre groups with average, above average and below average glycaemic control showed relative risk of SH lowest in group with best glycaemic control regardless of year of data. The centre effect did not reach significance due to low rates of hypoglycaemia (chi-squared=5.46, 2 df, p=0.07)	
Rosilio et al (1998) France (1–19)	2579	593 events in 338 patients 45 per 100 PY	Number of SH correlated only to diabetes duration and number of inpatient days. Its variance was poorly explained by the other variables with an r squared of 0.11. No relationship was found between level of HbA_{1c} and occurrence of SH (standard coefficient –0.06, p=0.01)	

df, degrees of freedom; HbA_{1c}, glycated haemoglobin; PY, person years; SE, standard error; SH, severe hypoglycaemia

Adult

Prospective cohort

Table 16.7 Results of adult, prospective cohort studies for question 16 (ii)

Reference, setting	Person years	Prevalence/ frequency	Variable	Statistical significance
Kilpatrick et al (2007) (DCCT) United States	9508	3103 episodes hypoglycaemia in 655 patients	Baseline confounders for one or more SH	Effect size (HR and p)
			Intervention group (IT vs CT)	2.28 p<0.001UV
			Prior hypoglycaemia	1.98 p<0.001UV
			Age (years)	0.99 p=0.097UV
			C-peptide (<0.2 vs >0.2 mmol/l)	1.002 p=0.51UV
			Duration diabetes	1.002 p=0.03UV
			HbA_{1c}	0.93 p<0.001UV
			Mean blood glucose (without reference to HbA_{1c})	HR 0.95 (0.92–0.97)
DCCT (1997) United States		3788 episodes (required assistance) 1027 (coma/seizure) overall rate 61.2/100 PY in IT 18.7 per 100 PY in CT	IT vs CT	RR 3.28
			Subgroup: Males vs females	RR 4.35 vs2.52 p<0.05
			CT patients with lower screening HbA_{1c} (%) levels have a higher rate of hypoglycaemia (episodes per 100 PY) during the trial (also had lower HbA_{1c} during trial)	<7.8, rate 27.2
				7.8–8.8, rate 18.8
				8.8–10, rate 16
				10+, rate 12.6
			In both treatment arms: C-peptide <0.20 vs >0.2	Significantly lower risk p<0.004
			Adolescents: higher rate hypoglycaemia than adults in CT and IT arms	No difference in relative risks
			Increased risk with increasing years of duration of diabetes in CT group	
			Patients using higher insulin doses at baseline higher rates hypoglycaemia in both treatment groups	p<0.002
			History of hypoglycaemia with coma and/or seizure before entry into trial had higher rate; no difference between IT and CT	p<0.001 each group

Reference, setting	Person years	Prevalence/ frequency	Variable	Statistical significance
Allen et al (2001) United States (0–29 years)	415 x (4–6.5)	1987 observations in 415 subjects	HbA_{1c}	OR 1.5 (1.2–2.0)
Pedersen-Bjergaard et al (2008)	SH 1.1 (SE 0.2) episodes/PY SH with coma/parenteral treatment 0.3 episodes/PY	Older age compared with age 0	OR 2.2 (1.1–4.5) 5years old OR 5.7 (1.3–24.4) 15 years age	MV
		Serum ACE upper quartile	RR 2.9 (1.3–6.2)	UV
		Homozygosity. Hemizygosity for A allele AT2R 1675G/A	2.5 (1.4–5.0)	UV
		Impaired hypoglycaemia awareness significantly associated with SH	RR 4.6 (2.5–8.6) p<0.0001	(Multiple regression)

ACE, angiotensin converting enzyyme; CT, conventional treatment; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; IT, intensive treatment; MV, multivariate analysis; OR, odds ratio; RR, risk ratio; SD, standard deviation; SE, standard error; SH, severe hypoglycaemia UV, univariate analysis

Adult

Cross-sectional

Table 16.8 Results of adult, cross-sectional studies for question 16 (ii)

Reference, setting	N	Prevalence	Variable	Statistical significance (OR, 95%CI)
Hirai et al (2007) (Wisconsin)	537	14.3%	Current vs never smoker	2.40 (1.3 to 4.4) p=0.01 UV
Chaturvedi et al (1995) (EURODIAB)	3 250	35% men 29% women	Ex-smoker males vs never smokers; not significant when adjusted for age, duration, HbA_{1c}, education and centre	1.48 times more likely to have had at least one hypoglycaemic episode (p<0.01)
Stephenson et al (1996) (EURODIAB)	3 000	32% pts with one or more SH over past year	Abnormal response to change in HR and SBP on standing	OR 1.7 (1.3 to 2.2) adjusted for age, duration, HbA_{1c} and centre.
Salti et al (2004)	12 914	0.03 episodes/month (non-Ramadan)	Fasting during Ramadan	0.14 episodes/month (significantly more frequent than other months, p=0.0174)
Bragd et al (2003) Sweden	712	17% in 1984, 27% in 1998	Hypoglycaemia unawareness Inverse relation to HbA_{1c}	chi-squared 4.4 r2 0.06, p=0.04 chi-squared 4.7, r^2 0.03, p=0.03
Buyken et al (1998) (EURODIAB)	2 687	31% subjects reported SH required third party help	SH not related to fibre intake	No risk reduction in higher quartiles of fibre intake after adjustment

HbA_{1c}, glycated haemoglobin; OR, odds ratio; R^2, proportion of explained variation; SH, severe hypoglycaemia; UV, univariate analysis

Children and adolescents

Age

All studies of Australian children found a significant relationship between age and incidence of SH. Age under 6 years was associated with increased risk compared to the oldest age group (age 12–18 years), with an incidence rate ratio (IRR) of 1.76 (Bulsara et al 2004). Younger age was reported to be a significant risk factor for SH, with age having an IRR of 0.96 on multivariate analyses (Bulsara et al 2007). Davis et al (1998) also found that children under 6 years of age had a higher incidence of SH compared with those more than 6 years of age (rate 14.9 vs 7.2 episodes/100 person years, $p<0.05$). This effect was independent of diabetes duration and HbA_{1c}.

In contrast, in an American population, the odds ratio from multivariate analysis found an increased risk of SH with increasing age: 2.2(1.2–2) for age 5 years compared to age 0 years, 5.7 (95%CI: 1.3 to 24.4) age 15 years (Allen et al 2001). However, the confidence intervals are quite wide, and the relationship is not linear, with a plateau after 15 years of age. This finding is in contrast to most other studies, and the authors report that in a multivariate model including glycaemic control, the effect of age seen in their population was not present in multivariate analyses in most others. The contrast in findings compared with Davis et al (1998) may be attributed to the different levels of glycaemic control (average HbA_{1c} in Allen et al higher at 11.5% vs approx 9% in Davis et al).

In the DCCT, adolescents had a significantly higher rate of hypoglycaemia than adults: $p=0.025$ in the conventional group and $p=0.004$ in the IT group, with no difference in relative risk. The increased risk among adolescents was observed within each of the categories of duration of diabetes within the secondary cohort.

Of the three large cross-sectional studies, Mortensen and Hougaard (1997) found an association of SH incidence with age. They reported a decrease in SH by 8.4% per year with age (SE 2% $p<0.001$).

Duration of diabetes

An increased risk of SH was associated with increased duration of diabetes in Bulsara et al (2004), where duration of more than 9 years, compared with less than 1 year, gave an IRR of 3.7 (2.3–6). This was also shown in Bulsara et al (2007). Davis et al (1998) reported that children who had diabetes for less than 1 year had a reduced incidence of SH (1.9 vs 8.8 episodes/100 person years: duration<1 year vs duration >1 year, $p<0.001$). The largest American study, with 3994 person years, showed an increased risk ratio (RR) of 1.39 per 5-year increment of diabetes duration in children under 13 years of age (95%CI: 1.16 to 1.69) in univariate analysis (Rewers et al 2002).

Glycaemic control

Lower HbA_{1c} was associated with increased risk of hypoglycaemia in the DCCT (1994) adolescent cohort and also in 6 other prospective cohort studies of children and adolescents. The hazard ratio was 0.63 (0.59–0.72) in a recent Australian study (Bulsara et al 2007). The study by Allen et al (2001) reported an OR of 1.5(1.2–2.0) per 2% decrease in HbA_{1c}.

One study stratified subjects by age and reported increased risk with lower HbA_{1c} in children over 13 years, but did not report a significant association with those under 13 years (Rewers et al 2002). Due to the small number of total events, Levine et al found a trend but no significant difference between HbA_{1c} tertiles and incidence of SH (Levine et al 2001). The

study by Davis et al (1998) found a significant difference in the incidence of SH in subjects with an HbA_{1c} or 7–8% vs 8–9% (45.9 vs 23.5 episodes/person year) independent of age, duration or treatment method.

Of the cross-sectional studies, Mortensen and Hougaard (1997) found an association between HbA_{1c} and SH, with a decrease in SH of 21% for an increase in HbA_{1c} of 1% (SE 6% $p<0.001$). The authors also reported that the eight centres with HbA_{1c} levels significantly below the grand mean did not show a significantly greater incidence of hypoglycaemia than those with HbA_{1c}s above the mean (21.8 events/100 person years vs 19).

Gender

Bulsara et al (2004) found an IRR of 1.44 (1.111–1.86) for male sex as a risk factor for SH at the age group 13–18 years. In contrast, Pinkey et al (1994) found no relationship of SH with sex. Rewers et al (2002) found a significant decrease in incidence of SH with age between girls and boys of all age groups (incidence girls vs boys: age <7: 24 vs 23/100 person years; age 7–12: 19 vs 22/100 person years; age >13 years: 14 vs 20 per 100 person years; $p<0.001$ for trend).

Hypoglycaemia unawareness and hypoglycaemia awareness accuracy

Gonder-Frederick et al (2008) studied a small group of children aged 6–11 years, and found that lower hypoglycaemia accuracy index scores were significantly lower in children with SH than those without ($p<0.0001$).

Other

Rewers et al (2002) found that psychiatric disorders were additional predictors of SH in older children, with an of RR 1.56 (1.23–1.98). Psychiatric comorbidity was an exclusion criterion in most other studies. Higher insulin dose was associated with an IRR of 1.62 in the DCCT publication. Social disadvantage was found to have an IRR of 0.7 when the highest level was compared to the lowest (Bulsara et al 2004). Rewers et al (2002) found an association between underinsurance and SH ,with an RR of 1.42. Presence of the D allele of the ACE gene was found not to be a significant predictor of SH by Bulsara et al (2007). Nordfeldt et al (2003) reported that serum-ACE at or above median level was associated with a significantly higher incidence of SH (3 yearly SH vs mean 0.5 in S-ACE below median). Pinkey et al (1994) found no relationship between SH with sex, social class, diabetic ketacidosis (DKA) or hospital admission at original presentation.

Adults

Glycaemic control

Three prospective cohort studies in adults reported the relationship between HbA_{1c} and SH. Two cross-sectional studies also reported correlation statistics for this risk factor. The largest and highest level evidence was from the DCCT (1997). In both treatment groups, protocol mandated that glycaemic goals be modified in response to recurrent hypoglycaemia. Thus, HbA_{1c} levels could be expected to increase following episodes of SH. Analyses were performed separately to assess the influence of the current level of HbA_{1c} on the risk of the first of any episodes of hypoglycaemia requiring assistance. In the unadjusted models, the relationship between risk and HbA_{1c} (log) was linear. In the conventional group, the risk of the first episode of SH increased by 60% (49–72%) for a 10% lower quarterly HbA_{1c} value during the trial. In the IT group, the increase in risk was 27% (19–37%) for a 10% lower monthly HbA_{1c}. These models accounted for an R^2 of 5.9 and 1% within the conventional and IT groups. When background variation in risk over time was adjusted for using a proportional hazards model, the unadjusted risk of one episode of SH was increased 2.53-fold with IT,

compared to conventional treatment. The authors reported that an IT patient with a given HbA_{1c} had on average a 45% greater risk of SH than a patient on conventional treatment with the same level of HbA_{1c}. This finding was supported by the use of an additional proportional hazards model with the two groups combined; after adjusting for the quarterly HbA_{1c} level, the RR for the IT versus the conventional treatment group was 1.45 (1.22–1.73) (DCCT Research Group 1997). The more recent publication using the DCCT cohort (Kilpatrick et al 2007) reported a hazard ratio of 0.93 ($p<0.001$) for HbA_{1c} and SH.

Prior severe hypoglycaemia

The hazard ratio associated with prior SH and SH was 1.98 ($p<0.001$) from the DCCT cohort (Kilpatrick et al 2007).

Gender

Subgroup analysis of the DCCT according to baseline characteristics showed a difference in relative risk (RR) between males and females (4.35 vs 2.52 for IT, $p=0.01$).

Duration

The DCCT found a significant increase of risk of SH with increasing years of duration of diabetes on entry in the conventional group. The RR was approximately the same for duration categories (DCCT Research Group 1997).

C-peptide

The DCCT (1997) found that patients with residual C-peptide secretion (0.2–0.5pmol/µL after stimulation) also had significantly lower risks of hypoglycaemia in both treatment groups ($p<0.004$), with no difference in relative risk. The more recent publication of the same cohort reported a hazard ratio of 1.002 (<0.2 vs≥0.2nmol/l) $p=0.51$ (Kilpatrick et al 2007)

Other

Kilpatrick et al (2007), analysing DCCT data, found that a 1 mmol/L rise in mean blood glucose (BG) was associated with a 1.05 fold reduction in risk of first SH, while a 1 mmol/L increase in daily standard deviation of BG led to a 1.07 fold rise in risk. This was without reference to HbA_{1c}. These remained predictive for repeated hypoglycaemia, independently of HbA_{1c}, but not for SH incidence. Although the markers of glycaemia are not the main predictors of hypoglycaemia risk, they add to the predictive value of HbA_{1c} alone.

The cross-sectional Wisconsin retinopathy study (Hirai et al 2007) reported associations between SH and smoking. Current smokers having an OR of 2.4 (1.3–4.4) compared to those who never smoked (univariate analysis). The larger EURODIAB study reported that male ex-smokers were 1.48 times more likely to have had at least one hypoglycaemic episode compared to never smokers; however, this was not significant when adjusted for age, duration, HbA_{1c} and centre (Chaturvedi et al 1995). The same cohort was examined with regard to autonomic neuropathy status and SH. Patients with an abnormal response to standing in both HR and BP had an OR of 1.7 adjusted for age, duration, HbA_{1c} and centre (Stephenson et al 1996). Another analysis of this cohort found no association between fibre intake and SH (Buyken et al 1998). The large cross-sectional study of largely Islamic countries found an association between fasting during Ramadan and SH compared to other months of the year ($p=0.017$) (Salti et al 2004).

Question 16 (ii) What is the effect of intensive diabetes management on the incidence of hypoglycaemia?

Egger et al (1997)

The systematic review and meta-analysis by Egger et al (1997) examined the risk of SH, DKA and death in RCTs comparing intensive glycaemic control to conventional therapy. A systematic search was undertaken. RCTs with at least 6 months follow up and reported HbA_{1c} levels with at least one outcome event were included. Each study was assigned a quality grading. A total of 14 studies were identified, which included 1028 patients allocated to IT and 1039 to conventional treatment. Patients randomised to IT received pump therapy in 9 arms, multiple daily injections (MDI) in 4 arms or could choose (3 arms). Mean HbA_{1c} in conventional treatment groups ranged from 41% to 88% above the mean of a reference population without diabetes. In most trials, HbA_{1c} levels were lower among IT patients (0–22%). The mean age of study participants ranged from 18–42 years, and diabetes duration from 3–20 years.

Regarding SH, the incidence was 0–66.6 (median 7.9) episodes per 100 person years among IT patients and 0–33.3 (median 4.6) among conventionally treated patients. SH in all studies was defined as episodes with typical signs requiring intervention by a third party. The combined OR was 2.99 ($p<0.0001$) for the risk of suffering one or more episodes of SH. However, the test for heterogeneity was significant ($p=0.06$). Sensitivity analysis was performed with removal of the DCCT results (OR reduced to 1.59, 95%CI: 1.01–2.52) for SH. Excluding poor-quality trials did not affect results. The type of regimen used also did not influence risk. Important heterogeneity between trials could be shown and accounted for. This SR was of good quality.

Wang et al (1993b)

The meta analysis by Wang et al (1993b) was undertaken to estimate the impact of IT on the progression of diabetic subject retinopathy and nephropathy, and the risks of severe side effects. This meta-analysis did not include the large DCCT study published that year. The databases searched were not reported, nor was there any report of quality rating of the studies. Studies were excluded if they were nonrandomised or had data that could not be analysed. A total of 16 papers were identified, with duration of follow up ranging from 8 to 60 months. All studies but one achieved better or near normal control by IT. The difference by study end between groups was –1.4% HbA_{1c} (95%CI: –1.8 to –1.1).

Six studies were reported to have provided combinable data on SH. There was no mention of the definitions used in the individual studies. The overall estimated difference in SH reactions among intensively treated patients was reported as 9.1 (95%CI: –1.4 to 19.6). There was no significant difference; however, there was a trend towards more frequent SH. One study presented a distinct trend different from the rest, but the overall conclusion did not change when that study was excluded. The variable frequency of hypoglycaemia could not be explained by how tightly blood glucose was controlled, because two different studies achieved similar levels of control but recorded different frequencies of hypoglycaemia. The reasons postulated were variations in patient population, methods of insulin delivery, structure of programmes and practising style of physicians. This study was of fair quality.

16.1.7 Discussion

Question 16 (i) What are the predictive factors for SH?

Children and adolescents

The evidence for HbA_{1c} as a risk factor for SH came from five Level II studies (DCCT Research Group 1997; Davis et al 1998; Allen et al 2001; Rewers et al 2002; Bulsara et al 2007). Levine et al (2001) found a trend but, due to small event numbers, statistical significance was not reached. One Level III–2 study (Bognetti et al 1997) and one of the three Level IV studies (Mortensen and Hougaard 1997) also provided evidence. In some studies, an HbA_{1c} threshold of 8% was used. Other studies used tertiles or quartiles of HbA_{1c}. Some studies reported HbA_{1c} after adjustment for age and sex (Bulsara et al 2004). The confounders adjusted for in multivariate analysis was not always reported (Allen et al 2001).

There was also Level II evidence for the risk factors of intensive treatment, male sex, diabetes duration, higher insulin dose, social disadvantage, psychiatric disorder and younger age, although one study found older age predicted SH.

There was conflicting evidence for age as a risk factor for SH in children. The DCCT found an increased IRR at age under 6 years. Bulsara et al (2004) and Davis et al (1998) also found that younger age was associated with a higher risk of SH. Allen et al (2001) found an increasing OR with increasing age; this plateaued after 15 years or age. Nordfeldt et al (2003) reported that frequency of SH decreased with age, independent of duration of diabetes.

The studies of children and adolescents were consistent with regard to lower HbA_{1c}, male sex and duration of diabetes. Other risk factors (e.g. psychiatric disorder, social disadvantage, higher insulin dose and genetic factors) were each not reported by more than one study.

Adults

The evidence base for this question consisted of Level II studies for the impact of IT on SH in adolescents and adults. There was also Level II evidence for an association between prior hypoglycaemia, age, C-peptide, duration of diabetes, HbA_{1c}, mean blood glucose, gender, impaired hypoglycaemia awareness, serum ACE levels and genetic factors. There was Level IV evidence for increased risk of SH with current smoking, ex-smokers and autonomic neuropathy, hypoglycaemia unawareness and fasting during Ramadan, but not for increased fibre intake.

The adult studies were consistent regarding the impact of IT, lower HbA_{1c}, increased duration of diabetes, lower C-peptide, age and prior hypoglycaemia. Most of the other risk factors (e.g. insulin dose, plasma angiotensin, serum ACE and smoking) were each not reported by more than one study.

Regarding the general studies included in this report, the definition of SH varied. Most studies followed the DCCT definition of ‘hypoglycaemia requiring the assistance of a third party’. Some defined SH further as ‘that resulting in seizure or coma or hospital admission or requiring parenteral therapy’. The prevalence statistics for these events may underestimate the prevalence of any SH requiring third party help. In addition, the threshold at which children need assistance from a third party may differ from that of adults. Davis et al (1998) attempted to address this by including only episodes accompanied by obvious neuroglycopenia. The issue of recurrent SH was not always addressed in the included studies; it was not included as an outcome for this report, but may be a confounding factor.

The use of retrospective outcome ascertainment in the retrospective cohort and cross-sectional studies introduces recall bias. However, the definition of SH as requiring third party help may improve the objectivity of the reports.

Duration of follow-up varied in the included studies, and this may also have affected the risk prediction.

Thorough documentation of a nonselected population is important to study quality in questions of risk factors. However, some prospective cohort studies do not report consecutive or completeness of enrolment.

Most studies did not report non-significant correlations. In addition, adjustment for confounders varied among studies. Univariate models were noted where possible, to allow for comparison between studies. Multivariate analyses were reported with adjustments if reported in the study. Due to the large number of risk factors studied, data were extracted according to the most frequent outcomes reported, statistical significance and clinical relevance. Due to time constraints, some outcomes were not summarised here.

Question 16 (ii) What is the effect of intensive diabetes management on the incidence of hypoglycaemia?

There was Level I evidence that intensified diabetes management significantly increased the risk of SH. From the meta-analysis by Egger et al (1997) examining a total of 2067 patients, the incidence of SH ranged from 0 to 66.6 (median 7.9) episodes per 100 patient years among the IT patients and from 0 to 33.3 (median 4.6) among conventionally treated patients. The combined OR reported by Egger et al was 2.99 ($p<0.0001$) for IT patients. The test for heterogeneity was significant ($p=0.06$).

The DCCT trial itself reported a relative risk of 3.28 for SH in subjects from the IT arm compared to the conventional group.

The meta-analysis published before the DCCT results showed a trend towards at increase in SH with IT patients; however, this was not statistically significant (Wang et al 1993b); the estimated difference between arms was 9.1 (95%CI: –1.4 to 19.6). These results were pooled from six small studies (n=20–94) with low incidence rates.

16.1.8 Conclusion

Overall, there is high-level evidence supporting the increased risk of SH with intensive diabetes management in adults and adolescents. The combined OR from meta-analysis was reported as 2.99 (Egger et al 1997) and the RR from the DCCT trial was reported as 3.28 with IT compared to conventional treatment.

There is lower level evidence showing associations between SH and various factors including age, duration of diabetes, residual C-peptide secretion, HbA_{1c} and hypoglycaemic unawareness.

The generalisability of these findings is good, in that the populations studied were Australian or mostly European and American, and the age cohorts were well defined. However, genetic factors may vary in the Australian population, as may cultural factors, and these may limit generalisability.

16.1.9 Literature search strategy

The search was conducted between 22 and 27 September 2010. Level I–II studies were considered first. The Medline search strategy is shown in Table 16.9.

For question 16 (i) it was decided to include any Level III–IV studies found in the original search, but no separate search for all cross-sectional or case series was not performed. A cut-off of n≥500 was set for Level IV evidence.

The search strategy for question 16 (ii) was taken from question 18.1 (What is the effect of intensive glycaemic management on microvascular and macrovascular complications?). Citations examining the outcome of SH were identified from the search result. In addition, a separate search was conducted, as reported below. The results of these two searches were supplemented by reviewing bibliographies of relevant articles. A summary of citations retrieved from other searches is shown in Table 16.9.

Table 16.9 Search strategy, question 16

Database	Date searched	#	Search terms	Citations
		Q38	What are the predictive factors for severe hypoglycaemia?	
Medline	Between 22 September 2010 and 27 September 2010	1	Diabetes Mellitus, type 1/	51808
		2	Risk Factors/ or predictive factors.mp.	428566
		3	(hypoglycaemia unawareness or alcohol or duration of diabetes or diabetic autonomic neuropathy or brittle diabetes).mp.	171249
		4	age or glycemic control or exercise or meals.mp	5697566
		5	(liver disease or renal disease or adrenal insufficiency or acute illness or thyroid disease).mp.	79093
		6	(previous hypoglycemia or insulin regimen or psychiatric disease).mp.	1417
		7	intensive diabetes management.mp.	58
		8	(cohort studies or risk factor or (odds and ratio*) or (relative and risk) or (case and control)).mp.	499680
		9	(predict* or prognosis or survival analysis).mp.	1019605
		10	(incidence or mortality or follow-up studies).mp.	1105384
		11	OR/2–7	5952159
		12	OR/8–10	2235407
		13	1 AND 11 AND 12	10914
		14	limit 13 to (English language and humans)	
		15	Yield	273
		Q38ii	What is the effect of intensive diabetes management on the incidence of severe hypoglycaemia?	
		1	Diabetes Mellitus, type 1/	51808
		2	Intensive diabetes management.mp.	58
		3	(intensive glycemic control or intensive glycaemic control).mp.	177
		4	(intensive blood glucose control or blood glucose target or glycaemic target or glycemic target).mp.	105
		5	(intensive blood pressure control or intensive blood pressure target).mp.	38

Database	Date searched	#	Search terms	Citations
		6	(glycem* target or glycaem* target).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	40
		7	(intensive follow up or frequent follow up or frequent monitoring or intensive monitoring).mp.	1844
		8	(intensive dose adjustment or frequent dose adjustment).mp.	5
		9	Hypoglycaemia/	18231
		10	2 or 3 or 4 or 5 or 6 or 7 or 8	2221
		11	1 and 9 and 10	18
		12	limit 11 to (English language and humans)	17
Cochrane			Yield	14
INAHTA			Yield	2
Manual search				6
Total citations				25
Total non-duplicate citations				25

16.1.10 Evidence Matrix

(i) Prediction of hypoglycaemia

Q16.1 (i)	What are the predictive factors for severe hypoglycaemia?	
Evidence statement	Level II evidence indicates that younger age, longer duration of diabetes and hypoglycaemia unawareness are associated with higher risk of severe hypoglycaemia.	
Evidence base	B	Younger age is associated with increased risk (e.g. OR 2.2): four Level II studies and one Level IV study in children; one Level II study in older children. Longer duration is associated with increased risk: (e.g. IRR 5.3, RR 1.39/5 years), four Level II studies in children and two Level II studies in adults. Lower HbA_{1c}: (RR 1.2 per 1%), three Level II studies in children; one Level IV study in children showing no relationship; three Level II studies and one Level IV study in adults. Sex: one Level I study in males; one Level I study showing no effect and one Level I study in adults. Psychological disorder: (RR1.56), one Level II study in children. Decreased hypoglycaemic awareness: one Level II study in children (RR4.6), one Level II and one Level IV study in adults. Prior hypoglycaemia: (HR 1.98) one Level I study and one Level IV study in adults.
Consistency	B	Generally consistent.
Clinical impact	B	
Generalisability	A	Populations were mostly clearly defined as paediatric or adult.
Applicability	A	Large Australian studies as well as American and European.
Other factors	None identified.	

HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, rate ratio

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

(ii) Incidence of hypoglycaemia

Q16.1 (ii)	What is the effect of intensive diabetes management on the incidence of hypoglycaemia?	
Evidence statement	Level I evidence from studies published before 1997 (including the DCCT) shows that intensive management is associated with a higher risk of severe hypoglycaemia.	
Evidence base	A	Two Level I studies one with a low risk of bias and one with a moderate risk of bias.
Consistency	B	Direction of effect is consistent, but magnitude of effect varies when the results from DCCT are excluded: OR of experiencing one or more severe hypoglycaemic episode, 2.99 changed to 1.59. Significant interaction between effect and HbA_{1c}.
Clinical impact	C	Limitations regarding currency of evidence.
Generalisability		Intensity of control may not be replicable. All studies included adults or adolescents, with a mean age of 18–42 years across included studies. No studies in children.
	B	Adults.
	C	Children.
Applicability	C	Studies in America, Europe and North America (DCCT). Management practices have changed, so current delivery of care may be different from that in the evidence base.
Other factors	None identified.	
Recommendation		
R16.1	Risk factors for severe hypoglycaemia should be identified (Grade B).	

DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycated haemoglobin; OR, odds ratio

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

16.2 Acute effect of hypoglycaemia and hyperglycaemia on cognitive function

Question 16.2

What are the acute effects of hypoglycaemia and hyperglycaemia on cognitive function?

This section addresses the acute effects of hyperglycaemia and hypoglycaemia on cognitive function in children, adolescents and adults with type 1 diabetes. The question is addressed as a prognosis question.

16.2.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 16.10. As the question is a prognosis question, prospective cohort studies provide Level II evidence. Studies were restricted to at least Level II evidence. Studies where hypoglycaemia or hyperglycaemia were experimentally induced or manipulated were not eligible for inclusion.

Table 16.10 Criteria for determining study eligibility, question 16.2

Study design	Any comparative study
Population	Children, adolescents and adults with type 1 diabetes
Intervention	Cognitive function test at time of hypoglycaemia or hyperglycaemia
Comparator	Cognitive function test at time of euglycaemia
Outcomes	Cognitive performance

16.2.2 Assessment of study eligibility

Publications identified in the literature search were reviewed using the criteria shown in Table 16.11, applied hierarchically, to determine which publications to exclude.

16.2.3 Literature search summary

A total of 323 non-duplicate citations were identified in the initial literature search. After reviewing the abstract and title, a total of 45 publications remained, and the full-text version of each of these publications was retrieved and reviewed.

Table 16.11 Search results, question 16.2

Stage	Notes	Number
Search summary	Manual	
	Cochrane Library	0
	EMBASE	268
	Medline	232
	INAHTA	9
	Total	509
Duplicates	Duplicates identified	186
Identified	Total identified	323
Exclusion criteria	Wrong study type (not a comparative study)	278
	Wrong population (not child, adolescent or adult with type 1 diabetes)	0

Stage	Notes	Number
	Wrong intervention or test (not cognitive function test during hypoglycaemia or hyperglycaemia)	0
	Wrong comparator (not cognitive function test during euglycaemia)	
	Wrong outcome (not cognitive performance)	0
	Not in English	
	Total excluded	278
Meeting criteria	Total meeting inclusion criteria	45

16.2.4 Included studies

The included Level II studies were Blackman et al (1992), Cheyne et al (2004), Cox et al (1993), Cox et al (1999), Cox et al (2005), Davis et al (1996), Draelos et al (1995), Ewing et al (1998), Fanelli et al (1998), Geddes et al (2008), Gold et al (1995), Gonder-Frederick et al (1994), Gonder-Frederick et al (2009), Gschwend et al (1995), Hoffman et al (1989), Hoi-Hansen et al (2009), Holmes et al (1983), Holmes et al (1986), Holmes et al (1984), Lingenfelser et al (1992), Maassen et al (1990), Maran et al (1995), McAulay et al (2006), Pramming et al (1986), Ryan et al (1990), Sommerfield et al (2003), Strachan et al (2003), Widom and Simonson (1990), Wright et al (2009) and Ziegler et al (1992).

16.2.5 Characteristics of included studies

Prospective cohort studies

Cox et al (1999)

In a prospective cohort study, Cox et al (1999) assessed a proposed biopsychobehavioural model of severe hypoglycaemia (SH) in differentiating patients with and without a history of SH, and in predicting occurrence of future SH. The proposed model included the physiological consequences of hypoglycaemia, including impact on cognitive function. A total of 93 adults, 42 of whom had a recent history of SH, performed cognitive-motor function tests (visual vigilance, mental subtraction and choice reaction time) on a hand-held computer, immediately followed by a blood glucose (BG) reading, completing 70 trials over a period of 1 month. Following this, patients were required to record any episodes of SH, defined as 'episodes requiring help from another person due to confusion, disorientation or unconsciousness', over a period of 6 months. The physiological consequences of low BG was quantified by calculating the relative slowing in seconds of cognitive motor performance on the neuropsychological tests during low BG (<3.9 mmol/L) relative to a patient's mean euglycaemic performance (BG 4.7–10 mmol/L). Participants with a recent history of SH demonstrated significantly greater cognitive-motor impairments during hypoglycaemia, and the magnitude of hypoglycaemia-impaired ability to do mental subtraction correlated positively with number of SH episodes in the subsequent 6 months.

Table 16.12 Reduction in performance speed during hypoglycaemia

	SH group	No SH group	p-value	Correlation
Visual vigilance	2.8	1.5	0.11	0.11
Mental subtraction	11.4	4.3	<0.001	0.28
Choice reaction time	1.1	0.5	0.02	0.13

SH, severe hypoglycaemia

Cox et al (2005)

Cox et al (2005) reported on three prospective cohort studies examining the effect of acute hyperglycaemia on cognitive function in adults with diabetes within naturalistic conditions. Two of the studies were carried out in adults with type 1 diabetes. In the first of these two studies, 105 adults who had been recruited to participate in a BG awareness training study were required to perform three psychomotor tasks, immediately before a BG level, using a handheld computer, 3–4 times per day over a period of 1 month, for a total of 50 trials. In the second study, 91 adults with type 1 diabetes followed the same study protocol as the first study, however only one psychomotor task, the metal subtraction test, was required, in order to reduce subject burden. Hyperglycaemia was associated with slowing of all cognitive performance tests ($p<0.02$) and an increased number of mental subtraction errors. The effects of hyperglycaemia were highly individualised, affecting about half of the participants.

Table 16.13 Group effects of hyperglycaemia on cognitive function

Study and n	Group effects of hyperglycaemia (blood glucose level >15 mmol/L)		
Study 1 n=105	Number of 'A' words retrieved in 30-second intervals	F=5.08	p=0.0004
	Mental subtraction speed	F=3.71	p=0.005
	Number of subtraction errors	F=2.72	p=0.02
	Choice reaction time	F=2.08	p=0.09
Study 2 n=91	Mental subtraction speed	F=7.73	p<0.0001
	Number of subtraction errors	F=3.87	p=0.003

Table 16.14 Individual effects of hyperglycaemia on cognitive function

Individual effects of hyperglycaemia (blood glucose level >15 mmol/L)		
	Study 1	Study 2
Mean number of SMBG >15	17.8	17.9
% participants with significant disruptions in 0, 1, 2, and 3 of any of the cognitive tasks at BGL >15	0–45% 1–24% 2–16% 3–11%	0–41% 1–48% 2–12% 3–NR
% participants with specific tests significantly affected by BGL >15	Subtractions speed – 21% Subtractions errors – 20% 'A' words – 20% Reaction time – 28%	Subtraction speed – 19% Subtraction errors – 52%
Correlations		
HbA_{1c} % BGL >15 Mean euglycaemic performance	r=0.20, p<0.1 r=0.20, p<0.05 r=–0.18, p<0.1	r=0.34, p<0.01 r=0.39, p<0.01 r=–0.19, p<0.05

BGL, blood glucose level; HbA_{1c}, glycated haemoglobin; NR, not reported; SMBG, self-monitoring of blood glucose

Gonder-Frederick et al (2009)

Gonder-Frederick et al (2009) studied the effect of hypoglycaemia and hyperglycaemia in school-aged children using a field procedure, to test the hypothesis that naturally occurring episodes of hypoglycaemia and hyperglycaemia are associated with deterioration in cognitive function. In this prospective cohort study, 61 children aged 6–11 years performed two brief cognitive tests (mental mathematics and choice reaction time) immediately before a BG test. The children completed several trials per day over 4–6 weeks for a total of 70 trials. Time to complete both mental mathematics and reaction time was significantly longer during hypoglycaemia. During hyperglycaemia, time to complete mathematics was significantly longer, and reaction time was marginally significant. There were no differences on task accuracy. Decline in mental mathematics ability was equivalent at glucose level of less than 3.0 mmol/L and more than 22.2 mmol/L. Level of impairment across individuals varied greatly, with no age or sex differences.

There were significant effects for mathematics time ($F=5.0$, $p<0.001$) and a strong trend for reaction time ($F=2.2$, $p=0.053$).

Table 16.15 Performance across blood glucose levels, compared with euglycaemia

Test	Blood glucose <3.0 mmol/L	Blood glucose >22.2 mmol/L
Mathematics time	Significantly longer p=0.017	Significantly longer (p=0.0001)
Reaction time	Significantly longer p=0.01	Trend toward significance (p=0.08)
Seconds to task completion	Mathematics – 12.6 seconds longer Reaction time – 2.6 seconds longer	Mathematics – 16.8 seconds longer (NS) Reaction time – 1.5 seconds longer (NS)
No significant differences in number of correct responses across ranges		

NS, not significant

Individual impairment scores (IISs) were computed for each child at BG levels below 3.0 mmol/L and above 22.2 mmol/L, by using the child's mean performance during euglycaemia (4.3–9.9 mmol/L) as their baseline or 'normal' performance. The difference, in Z scores, between mean baseline performance and mean performance during hypoglycaemia and hyperglycaemia was then computed. Positive Z scores indicated poorer performance compared with euglycaemia, and negative scores indicated better performance.

Table 16.16 Mean individual impairment scores at different levels of blood glucose

Test	Blood glucose <3.0 mmol/L (n=34)	Blood glucose >22.2 mmol/L (n=41)
Mathematics time	0.57 ±1.6	0.33 ±1.1
% of children with IIS >1.0, indicating performance deteriorated on average >1 SD	21%	27%
Correlations with HbA_{1c}, number of severe hypoglycaemic episodes, diabetes duration, glucose variability, depression and anxiety measures	None found	HbA_{1c} correlated with IIS for reaction time r=0.40, p=0.02 Number of SH in past year correlated with IIS for mathematics time r=0.39, p=0.04 reaction time r=0.40, p=0.02

HbA_{1c}, glycated haemoglobin; IIS, individual impairment score; SD, standard deviation; SH, severe hypoglycaemia

Exploratory analyses were also carried out to identify practice effects over time, by comparing results for the first 35 trials with results of the second 35 trials. During euglycaemia, mathematics time was significantly shorter for the second of 35 trials, but there was no improvement for reaction time. During hypoglycaemia and hyperglycaemia, there were no practice effects over time.

Insulin clamp studies

The insulin clamp studies involve experimentally induced and manipulated BG levels by way of the insulin clamp method. The studies were heterogeneous in terms of methodologies used, including glycaemic thresholds at which cognitive function was assessed, the tests that were used to measure cognitive function, the timeframe in which assessment was undertaken and the outcomes measured. A qualitative assessment of the studies is summarised in Table 16.17 below.

Table 16.17 Qualitative assessment of insulin clamp studies

Reference, country, quality	Study type and outcome/ method	Population	Type of glycaemia	Relevant results	Conclusions
Blackman et al (1992) United States Fair	Interrupted time series with controls without diabetes Recovery of cognitive function after hypoglycaemia P300 and reaction time to visual stimuli	10 adults without diabetes 5 male/ 5 female Age: 26.7 ±1.9 years 14 age-matched subjects with type 1 diabetes 6 male/ 8 female Age: 29.5 ±1.6 years	Hypoglycaemia PGL of euglycaemia, 3.5 and 2.5	P300 latency during recovery from hypoglycaemia vs baseline (for subjects with type 1 diabetes): 430 ±9 minutes vs 403 ±9 minutes ($p<0.05$) In subjects with type 1 diabetes, during recovery from hypoglycaemia reaction time was increased by 39 minutes over baseline ($p<0.05$)	Hypoglycaemia appears to slow decision-making processes in IDDM Subjects with type 1 diabetes had a lag in recovery of cognitive function of 45 to 75 minutes following hypoglycaemia
Cheyne et al (2004) United Kingdom Good	RCT-crossover, double blinded Four-choice reaction time (primary outcome), general intellectual skills and digit symbol substitution and visual information processing driving performance	n=17 adults	Hypoglycaemia PGL of 4.5, 2.8	Reduction in reaction time reported at plasma glucose 2.8 Marked reduction in all cognitive tests where plasma glucose 2.8 and modest alcohol intoxication	Both hypoglycaemia and alcohol independently impair cognitive function and together the effects are additive
Cox et al (1993) (Abstract only)	Interrupted time series with matched control Cognitive and motor neuro-psychological test	n=10 adults	Hypoglycaemia PGL of 5.4, 2.6, 3.6, 6.7	Only cognitive tasks demonstrated impairment at 2.6 mmol/L ($p<0.04$) Individual differences correlated with BGL at nadir (2.6) and baseline performance	Cognitive tasks appear to be more sensitive to neuroglycopenia than motor tasks. Cognitive impairment caused by hypoglycaemia is reliable and differs across subjects

Reference, country, quality	Study type and outcome/ method	Population	Type of glycaemia	Relevant results	Conclusions
Davis et al (1996) (Abstract only) Australia	RCT cross over, double blinded IQ assessed with subtests from the Wechsler Intelligence Scale for Children	n=12 children, mean age 12.4 years	Hyperglycaemia PGL of 20–30 and 5–10	Hyperglycaemia resulted in reduction in performance IQ p<0.05	Acute hyperglycaemia results in impairment of complex cognitive function in children with IDDM. This may have important implications for school performance
Draelos et al (1995) (Abstract only)	Interrupted time series with no control Reaction time (simple and choice), digit vigilance, trail making part B, word recall, digit sequence learning, and verbal fluency	n=42 adults 20 male/ 22 female, aged 18–44 years HbA_{1c} from 5.8% to 18%	Hypoglycaemia and hyperglycaemia PGL of 2.2, 5.6, 8.9, 14.4, and 21.1 mmol/L	Compared with basal levels of performance at 8.9 mmol/L, no alterations of neuro-psychological function were observed at 14.4 or 21.1 mmol/L	Cognitive function was generally well-preserved even at substantially elevated BGL
Ewing et al (1998) United Kingdom Poor	Crossover single blind not randomised; tests of visual processing and cognitive function	n=16 adults mean age 26.9 years, with no evidence of lens opacities or retinopathy	Hypoglycaemia PGL of 5.0, 2.6	Significant disruption in general cognitive ability; visual information processing deteriorated p<0.005	Hypoglycaemia impairs important aspects of early visual information processing
Fanelli et al (1998) United States Poor	Interrupted time-series with control Insulin clamp to induce nocturnal hypoglycaemia or nocturnal euglycaemia Tests of pattern recognition, memory, attention and information processing	n=12 non-diabetic controls n=15 adults with type 1 diabetes mean age 27 ±6 years	Hypoglycaemia PGL of 4.7, 4.2, 3.6, 3.1, 2.5	Less deterioration in cognitive function in participants who had had prior nocturnal hypoglycaemia p=0.0065	Glycaemic thresholds for hypoglycaemic cognitive dysfunction shift to lower plasma glucose concentrations after recent antecedent hypoglycaemia

Reference, country, quality	Study type and outcome/ method	Population	Type of glycaemia	Relevant results	Conclusions
Geddes et al (2008) United Kingdom Fair	Interrupted time-series with control, single blind Psychomotor function	n=20 adults without diabetes n=16 adults with type 1 diabetes	Hypoglycaemia PGL of 4.5, 2.5	Type 1 diabetes – significant impairment of psychomotor function as measured by reaction time, p=0.023 and pursuit rotor p=0.045 Without diabetes, significant impairment in reaction time, manual dexterity, hand steadiness, pursuit rotor and total body coordination	Compared with those without diabetes, type 1 participants had a lower magnitude of impairment (study not powered for between-group comparison)
Gold et al (1995) United Kingdom Poor	Crossover, single blinded Rapid visual information processing trail making B, paced auditory serial addition test and digit symbol substitution test	n=20 adults (n=10 with impaired hypo-glycaemia awareness)	Hypoglycaemia PGL of 4.5 and 2.5	Multivariate analysis of variance demonstrated a significant effect of hypoglycaemia on cognitive function ($p<0.01$) Cognitive dysfunction more profound and persisted longer following blood glucose recovery in those with hypoglycaemia unawareness	
Gonder-Frederick et al (1994) United States Fair	Randomised crossover, single blind Writing name and address, coin flipping, serial subtractions, twos and sevens, verbal fluency, trail making B	n=26 adults n=15 retested 3 months after original testing	Hypoglycaemia PGL of 6.4, 3.6, 2.6, 6.3	Both mild and moderate hypoglycaemia significantly disrupted performance. However, performance deterioration varied substantially across individual subjects. Men exhibited significantly more deterioration than women at mild hypoglycaemia, and subjects with a history of unconsciousness due to hypoglycaemia exhibited more deterioration than subjects with no such history	Glycaemic threshold for onset and recovery from neurobehavioural deterioration with hypoglycaemia, as well as degree of impairment experienced, varies across individuals. Furthermore, these individual differences are stable across time

Reference, country, quality	Study type and outcome/ method	Population	Type of glycaemia	Relevant results	Conclusions
Gschwend et al (1995) United States Fair	Interrupted time-series with no control, single blind 3 x clamp studies over 4 years Simple reaction time, choice reaction, trail making	n=36 children 9–19 years, mean age 14.7 years n=13 studied during hypo-glycaemia n=13 studied during euglycaemia n=10 studied during hyper-glycaemia	Hypoglycaemia and Hyperglycaemia PGL of 20, 5.5, 3.3	Cognitive test performance did not decline during hyperglycaemia Significant decline in performance on all cognitive tests during mild hypoglycaemia	Mild hypoglycaemia causes transient decrements in cognitive function. In contrast, neither hyperglycaemia, nor the rapid drop from acute hyperglycaemia to euglycaemia, affected cognitive function
Hoffman et al (1989) United States Fair	Crossover study, single blind Motor speed and reaction time; vigilance and motor control; sensory motor and higher cortical functioning with trail making test; driving performance	n=18 adults mean age 29.3 ±1.2 years	Hypoglycaemia and hyperglycaemia PGL of 2.8, 5.6 and 16.7 mmol/L	Performance on tasks requiring visual tracking, visuomotor speed, concentration, and planning ability (pursuit rotor and trails B) were significantly impaired under conditions of hypoglycaemia compared with normoglycaemic levels. Visual reaction time was not significantly impaired under conditions of hypoglycaemia or hyperglycaemia	
Hoi-Hansen et al (2009) Denmark Fair	Controlled crossover, single blind Four different reaction time tasks, two tests of working memory, measures of cognitive and perceptual speed	n=18 adults (n=9 with high basal RAS and n=9 with low RAS activity) (drawn from larger observational study on risk of SH and ACE activity and ACE genotype)	Hypoglycaemia PGL of euglycaemia and 2.2	The high RAS group displayed significant deterioration in cognitive performance during hypoglycaemia in the three most complex reaction time tasks. In the low RAS group, hypoglycaemia led to cognitive dysfunction in only one reaction time task	High RAS activity is associated with increased cognitive dysfunction and blunted symptoms during mild hypoglycaemia compared to low RAS activity

Reference, country, quality	Study type and outcome/ method	Population	Type of glycaemia	Relevant results	Conclusions
Holmes et al (1983) (Abstract only)	Interrupted time series with no control group Attention and fine motor skills		Hypoglycaemia and hyperglycaemia PGL of 3.3, 6.1 and 16.7 mmol/L	Slowed attention and visual reaction time were found during low and high glucose levels	
Holmes et al (1986) United States Fair	Crossover, double blind Sensory motor and cognitive processing	n=24 adults, males aged 18–35 years	Hypoglycaemia and hyperglycaemia PGL of 3.3, 6.1 and 16.7 mmol/L	The rate of cognitive processing as measured by reaction time was influenced by glucose levels. Significantly poorer during hypoglycaemia Performance change more subtle during hyperglycaemia, not significant but with a trend toward poorer performance	The demonstrated sensitivity of cognitive processing skills to brief disruptions of euglycaemia suggests the need to consider acute impairments when planning treatment regimens
Holmes et al (1984) United States Fair	Crossover, double blinded Verbal function	n=12 adults, males aged 18–35 years	Hypoglycaemia and hyperglycaemia PGL of 3.3, 6.1 and 16.7 mmol/L	Significantly disrupted naming or labelling skills at hypoglycaemia, with a trend toward poorer performance at hyperglycaemia During hypoglycaemia, rate of responding was slowed from 6% to 18%, compared with euglycaemic performance, but accuracy was not impaired. In contrast, word recognition skills were not affected by deviations in glucose	Hyperglycaemia does not produce the striking acute cognitive effects that hypoglycaemia does, although subtle performance deviations may occur
Lingenfelser et al (1992) (Abstract only)	Interrupted time-series with control without diabetes Cognitive and psychomotor function	n=10	Hypoglycaemia PGL of euglycaemia, 2.2 mmol/L	There was a significant performance decrement in all but two neuropsychological tests (aiming center I, aiming center II, line tracing errors, reaction time, $p<0.01$; digit symbol, $p<0.05$) Performance of simple motor tasks as well as cognitive tasks	

Reference, country, quality	Study type and outcome/ method	Population	Type of glycaemia	Relevant results	Conclusions
Maassen et al (1990) (Abstract only)	Interrupted time-series with control without diabetes Cognitive and psychomotor function	n=8 type 1 diabetes n=8 controls without diabetes	Hypoglycaemia PGL of 5.6, 3.6, 2.8 and 2.2 mmol/L	Hypoglycaemia resulted in a significant increase in the reaction time (p=0.012). These effects were not dependent on the type of insulin being used (porcine or human) nor were they typical of a particular study group	
Maran et al (1995) United Kingdom Fair	Study 1 – interrupted time-series with no control Study 2 – interrupted time-series with control Comparing IT versus CT Four choice reaction time	Study 1 – n=5 adult males, aged 33 ±4 years Study 2 – n=8 adults type 1 diabetes, HbA_{1c} 7.7% ±0.3, hypo unaware n=10 adults type 1 diabetes, HbA_{1c} 10.1 ±0.2%, good hypo awareness n=8 non-diabetic controls	Hypoglycaemia PGL of 5.0 mmol/L, 2.0 mmol/L	Study 1 – no significant effect Study 2 – during stepped hypoglycaemia hormonal response and subjective awareness of hypoglycaemia started at significantly lower BGL in the intensive treatment group No difference between groups in BGL level at which deterioration of cognitive performance occurred	
McAulay et al (2006) United Kingdom Fair	Crossover, single blinded Attention and intelligence	n=16 adults, aged 18–39 years	Hypoglycaemia PGL of 4.5, 2.6 mmol/L	Hypoglycaemia caused a significant deterioration in tests sensitive to visual and auditory selective attention Attentional flexibility deteriorated and speed of information processing was delayed Sustained attention and intelligence scores were preserved	Hypoglycaemia causes a significant deterioration in attentional abilities, while non-verbal reasoning is preserved

Reference, country, quality	Study type and outcome/ method	Population	Type of glycaemia	Relevant results	Conclusions
Pramming et al (1986) Fair	Interrupted time-series with no control Various psychological skills from simple motor tasks to more complex problems in memory and control	n=16 adult men with diabetes n=6 patients in 'sham' study	Hypoglycaemia BGL levels of 6.3, 2.9, 1.8, 6.1 mmol/L	Total score deteriorated from BGL 6.3 to 2.9, 6.3 to 1.8 and 2.9 to 1.8, whereas improvement occurred from 1.8 to 6.3 (all $p<0.02$) The changes were consistent for the whole group	
Sommerfield et al (2003) United Kingdom Fair	Randomised crossover single blinded Tests of immediate and delayed verbal and visual memory, and tests of working memory Also trail making B test and digit symbol test	n=16 adults median age 28.5 years	Hypoglycaemia PGL of 4.5, 2.5	Performance in tests of immediate verbal and immediate visual memory was significantly impaired The effect on working memory and delayed memory was more profound Performance in the memory tests, the trail making B test, and the digit symbol test also deteriorated during hypoglycaemia	All of the memory systems examined in the present study were affected significantly by acute hypoglycaemia, particularly working memory and delayed memory
Strachan et al (2003) United Kingdom Fair	Crossover, single blinded Auditory information processing	n=15 adults, mean age 26.5 ±9.1 years	Hypoglycaemia PGL of 5.0, 2.6	Hypoglycaemia caused deterioration in mental efficiency (digit symbol $p<0.001$; trail making B $p=0.004$) and in auditory processing (single-tone loudness, $p=0.001$; auditory temporal processing $p=0.007$)	Our findings are consistent with other recognised disruptive effect of acute hypoglycaemia on sensory information processing
Widom and Simonson (1990) United States Fair	Interrupted time-series with control, single blinded Attention, short-term memory, visual motor skills, visual conceptual and visual spatial skills	n=17 adults n=8 HbA_{1c} <8.6% n=9 HbA_{1c} >10.6% n=10 non-diabetic control	Hypoglycaemia PGL of 5.0, 4.4, 3.9, 3.3, 2.8, 2.2 mmol/L	No difference between groups in threshold for cognitive dysfunction in visual spatial skills, visual motor skills or global cognition Glycaemic thresholds for adrenergic symptoms was significantly lower in well-controlled group ($p<0.05$)	Diabetic patients with good control are at increased risk for developing cognitive impairment before the onset of adrenergic symptoms during hypoglycaemia

Reference, country, quality	Study type and outcome/ method	Population	Type of glycaemia	Relevant results	Conclusions
Wright et al (2009) United Kingdom Fair	Randomised crossover, single blinded Spatial ability tests	n=16 adults, median age 28 years	Hypoglycaemia PGL of 4.5, 2.5	Significantly lower score on all of the spatial ability tests except the Map Memory Test. Cohen's d results have shown that the impact of hypoglycaemia was medium to large	Acute hypoglycaemia causes significant decrements in most spatial cognitive abilities in a group of adults with uncomplicated diabetes
Ziegler et al (1992) Germany Fair	Interrupted time series with no control group P300 event-related potential – its latency reflects speed of information processing and is associated with attention and short-term memory	n=18 adults (n=7 HbA_{1c} ≤7.0% group 1, n=11 HbA_{1c} ≥7.5% group 2)	Hypoglycaemia PGL of 5.6, 1.6, 5.6 mmol/L	No significant difference in P300 latency between groups at baseline; glycaemic threshold for dysfunction 1.6 ±0.2 mmol/L group 1 vs 3.5 ±0.2 mmol/L group 2, p<0.05	The glycaemic threshold for and magnitude of cognitive dysfunction during hypoglycaemia are reduced in strictly controlled as compared with poorly controlled patients with type 1 diabetes

ACE, angiotensin converting enzyme; BGL, blood glucose level; CT, conventional treatment; HbA_{1c}, glycated haemoglobin; IDDM, insulin-dependent diabetes mellitus (type 1 diabetes), IQ, intelligence quotient; IT, intensive treatment; PGL, plasma glucose levels; RAS, renin-angiotensin system; RCT, randomised controlled trial; SH, severe hypoglycaemia

16.2.6 Discussion

Both hypoglycaemia and hyperglycaemia were associated with impairment of cognitive function in the prospective cohort studies included as evidence for this systematic review (Cox et al 1999; Cox et al 2005; Gonder-Frederick et al 2009). In adults, hyperglycaemia (defined as BG level >15 mmol/L, had a significant impact on cognition, with slowing in all cognitive performance tests ($p<0.02$) and an increased number of mental subtraction errors (Cox et al 2005). In children during blood glucose extremes (defined as <3.0 mmol/L and >22.2 mmol/L), cognitive function was significantly affected, as demonstrated by longer time taken to do mental mathematics and choice reaction time (Gonder-Frederick et al 2009). The studies, however, reported large individual differences in the degree of impairment at different BG levels (Cox et al 2005; Gonder-Frederick et al 2009). Exploratory analyses undertaken to determine the basis of these individual differences demonstrated a mild relationship between greater exposure to BG readings over 15 mmol/L and higher glycated haemoglobin (HbA_{1c}) in adults (Cox et al 2005). In adults, the negative impact on cognitive function when BG was less than 3.9 mmol/L was significantly greater when compared with the impact on those without a recent history of SH (Cox et al 1999). In children, demographic variables such as age and sex were not associated with individual differences; however, a relationship was demonstrated between higher HbA_{1c}, frequency of SH and greater cognitive impairment when BG levels were high (Gonder-Frederick et al 2009). The reported limitations of these studies included the relatively small number of participants, who were a fairly homogenous sample, almost all of whom were Caucasian (Gonder-Frederick et al 2009). The participants were studied over a relatively short period of time, yielding a limited number of extreme BG readings (Gonder-Frederick et al 2009). The authors suggest that the results be considered preliminary and be interpreted with caution. There were large

individual differences found and there are likely to be numerous, unidentified variables that affect the impact of acute BG extremes on cognitive function.

The studies in which BG levels were artificially manipulated through the insulin clamp method were predominately carried out in adults, with only two of these studies carried out in children (Gschwend et al 1995; Davis et al 1996). In those studies measuring the effect of hypoglycaemia on cognitive function, significant effects on both simple and more complex cognitive tasks were demonstrated in comparison to measures of cognitive function during euglycaemia. Decrements in psychomotor function, motor speed and reaction time, attention, verbal function, memory, visual spatial skills and auditory information processing were demonstrated in response to acute hypoglycaemia. Gonder-Fredrick et al (1994) found that glycaemic thresholds for and recovery from cognitive dysfunction varied greatly across individuals, ranging from BG levels of below 2.6 mmol/L to levels above 3.6 mmol/L. Hypoglycaemia unawareness was found to be associated with more profound and longer lasting cognitive dysfunction (Gold et al 1995). Recent occurrence of nocturnal hypoglycaemia was associated with lower glycaemic thresholds for cognitive dysfunction (Fanelli et al 1998). Lower HbA_{1c} was also associated with lower glycaemic thresholds for cognitive dysfunction in one study (Ziegler et al 1992) but not in another (Maran et al 1995). Where the effects of hyperglycaemia were studied, assessment of cognitive function was undertaken during plasma glucose levels ranging from 16.7 mmol/L to as high as 30 mmol/L. There was inconsistency in the results reported concerning the effects of hyperglycaemia on cognitive function in the two studies in children, with one study finding a significant impact on performance intelligence quotient (IQ) in a group of 12 Australian children (Davis et al 1996), and another finding no impact of hyperglycaemia on cognitive performance as measured by choice reaction time and the trail making test, in 10 teenagers (Gschwend et al 1995). This inconsistency may be due to the different methodologies used and the outcomes measured. In studies assessing the impact of hyperglycaemia on cognitive function in adults, no effect on cognitive function was reported in two studies (Hoffman et al 1989; Draelos et al 1995), and subtle trends towards poorer performance during hyperglycaemia were reported in three studies by Holmes et al (1983; 1984; 1986).

16.2.7 Conclusion

This systematic review of the evidence for the acute impact of hypoglycaemia and hyperglycaemia on the cognitive function of children, adolescents and adults was based on three Level II studies, all of moderate risk of bias, which included 289 adults and 61 primary school aged children; and 27 (Level II and Level III studies, of predominately moderate risk of bias, which included 398 adults and 48 children under 6 years of age. No studies in children less than 6 years of age were found. Level II evidence demonstrated a negative impact on cognition at BG levels below 3.9 mmol/L and above 15 mmol/L in adults, and at below 3.0 mmol/L and above 22.2 mmol/L in children, when compared with cognitive function at euglycaemia. There was Level II evidence that a recent history of SH attenuates the effect of hypoglycaemia on cognitive function in adults, and that poorer metabolic control (as assessed by higher HbA_{1c}, and greater exposure to BG levels >15 mmol/L) were mildly associated with level of impairment during hyperglycaemia in adults. In children, there was Level II evidence that poorer metabolic control (as assessed by higher HbA_{1c} and frequency of SH) were mildly associated with degree of impairment at BG levels above 22.2 mmol/L. The exclusions reported include diabetes duration of less than 1 year, inability to read English, psychiatric disorder, substance abuse and pregnancy. One study was carried out in Australia; the remainder in countries also with a well-developed health care system.

16.2.8 Literature search strategy

The search was conducted between 3 November 2010 and 15 November 2010. The Medline search strategy and a summary of citations retrieved from other searches is shown in is shown in Table 16.18.

Table 16.18 Search strategy, question 16.2

Database	Date searched	#	Search terms	Citations
Medline	Between 3 November 2010 and 15 November 2010	1	exp Diabetes Mellitus, type 1/ or diabetes mellitus type 1.mp.	54 307
		2	exp Cognition Disorders/ or cognitive disorder.mp.	47 359
		3	cognitive.mp.	141 105
		4	exp Neuropsychological Tests/ or neuropsychological.mp.	62 065
		5	cognitive function.mp.	12 018
		6	2 or 3 or 4 or 5	192 400
		7	1 and 6	506
		8	hyperglycemia.mp. or exp Hyperglycemia/	33 616
		9	exp Hypoglycemia/ or hypoglycemia.mp.	26 495
		10	8 or 9	57 216
		11	7 and 10	247
		12	limit 11 to english language	236
		13	limit 12 to human	232
Cochrane				0
EMBASE				268
INHATA				9

16.2.9 Evidence Matrix

Q16.2	What are the acute effects of hypoglycaemia and hyperglycaemia on cognitive function?	
Evidence statement	Level II evidence shows that acute hypoglycaemia causes a temporally related impairment in cognitive performance. Level III evidence shows that acute hyperglycaemia may cause cognitive impairment in children and adults. One Level II study shows that acute hyperglycaemia above 22 mmol/L in children is associated with a comparable impairment to acute hypoglycaemia (<3 mmol/L).	
Evidence base	B/C	Three Level II studies of moderate risk of bias (n=289 adults, n=61 primary school aged children) and 27 Level II or III studies, predominately of moderate risk of bias (clamp studies) (n=398 adults, n=48 children aged >6 years). B for hypoglycaemia. C for hyperglycaemia.
Consistency	A/C	BG level below 3.9 mmol/L and above 15 mmol/L in adults has a negative impact on cognition. BG level below 3.0 mmol/L and above 22.2 mmol/L in children has a negative impact on cognition. In adults, a recent history of severe hypoglycaemia attenuates the effect of hypoglycaemia, and higher HbA_{1c} and greater exposure to BG levels above 15 mmol/L are associated with a greater level of impairment during hyperglycaemia. In children, higher HbA_{1c} and frequency of severe hypoglycaemia are associated with a degree of impairment at BG levels above 22.2 mmol/L. Effects of hyperglycaemia and hypoglycaemia were highly individualised. A for hypoglycaemia. C for hyperglycaemia.
Clinical impact	A/C	'Hyperglycaemia resulted in increased errors and slower responses when performing basic verbal and mathematical tasks, which are important to numerous daily functions, such as balancing cheque books, calculating insulin dosing, and school and work performance.' (Cox et al 2005) Individual scores indicated that performance declines by more than 1 SD during hypoglycaemia and hyperglycaemia for more than 20% of children (Gonder-Frederick et al 2009). Group scores – during hypoglycaemia and hyperglycaemia there was, on average, a 20% decrease in speed (Gonder-Frederick et al 2009). A for hypoglycaemia. C for hyperglycaemia.
Generalisability	B	No studies in children younger than 6 years. Reported exclusions included diabetes duration of less than 1 year, inability to read English, psychiatric disorder, substance abuse and pregnancy.
Applicability	A	One study was in Australia; the rest were from countries with a well-established health-care system.
Other factors	N/A	
Recommendation		
R16.2	Acute hypoglycaemia (Grade B) and hyperglycaemia (Grade C) should be minimised to maintain optimal cognitive performance.	

BG, blood glucose; HbA_{1c}, glycated haemoglobin; SD, standard deviation

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

16.3 Prevention of severe hypoglycaemia

Question 16.3

How can severe hypoglycaemia be prevented?

The objective of this question was to evaluate the evidence for any intervention primarily designed to prevent, reduce or avoid severe hypoglycaemia. The reduction of severe hypoglycaemia as a secondary outcome of specific interventions has been addressed by other systematic review in this series. Thus a specific search strategy as detailed below was carried out. The NHMRC 'Intervention' Hierarchy was used to designate levels of evidence

16.3.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 16.19

Table 16.19 Criteria for determining study eligibility, question 16.2

Study design	Level I-IV as designated by the NHMRC 'Intervention' scale
Population	Children, adolescents and adults with type 1 diabetes
Intervention	Any test that is not already covered by another systematic review in this series
Comparator	No intervention
Outcomes	Primary outcome to prevent, reduce or avoid severe hypoglycaemia as defined by the individual study

16.3.2 Literature search summary

A systematic method of literature searching and selection was employed in the preparation of this review. Searches were conducted in Medline, INAHTA and the Cochrane database. Search terms were searched for as keywords, exploded where possible, and as free text within the title or abstract in the Medline databases. Variations on these terms were used for the Cochrane and INAHTA databases, modified to suit their keywords and descriptors.

The reference lists of included papers were reviewed to identify any peer-reviewed evidence that may have been missed in the literature search. Authors were not contacted for unpublished research, and conference abstracts were not eligible for inclusion.

The search was conducted between 8 November 2010 and 13 November 2010. The Medline search strategy is shown in Table 16.20

Table 16.20 Search results, question 16.3

Stage	Notes	Number
Search summary	Total	174
Exclusion criteria	Wrong study type	25
	Wrong population (not child, adolescent or adult with type 1 diabetes)	8
	Wrong intervention	56
	Wrong outcome	71
	Not in engish	2
Total excluded		162
Full papers reviewed		12

16.3.3 Included studies

No Level I studies were identified in this search. Seven studies were excluded after retrieval of the full text as the primary outcome studied was not severe hypoglycaemia. The sub population of subjects with type 1 diabetes and impaired hypoglycaemia awareness was of particular interest however no studies were found which fulfilled inclusion criteria in this search. One study of a population with impaired hypoglycaemia awareness was excluded as it was a pilot study with no power calculations

16.3.4 Characteristics of included studies

Nordfeldt 2003

This randomised controlled study tested the hypothesis that good quality self study material for home use would be used and disseminated, be perceived as helpful in self treatment and reduce severe hypoglycaemia without worsening in metabolic control as measured by mean HbA1c. The primary outcome was the yearly incidence of severe hypoglcaemia (SH). The population studied were the 332 children with t1d treated at the paediatric centres of the general hospitals in Sweden. The intervention studied was two video programmes consisting of interview clips of young patients and their parents regarding diabetes treatment and prevention of hypoglycaemia with comments from a diabetologist. A self study brochure was mailed out 1 month later which contained FAQs regarding the practical aspects of severe hypoglycaemia management. The control material was a video of general diabetes information and corresponding brochure. 110 control subjects had traditional treatment only. The yearly incidence of SH was obtained by postal surveys at baseline and 12 months later. The question asked was “Did you experience episodes of severe hypoglycaemia (needing assistance) during the last 12 months?”.

After the intervention (mail out of video programmes), the incidence of SH was reduced in the intervention group (change from baseline) from 42% to 27%. N=38 episodes of SH vs n=22. The risk difference was 15%, 95%CI 1% to 29% p=0.0394. It was not reduced in the control and traditional groups. There was no difference between the intervention and control group when results were not adjusted for baseline. The difference being 10 with the 95%CI (-4 to 24). There were no differences in yearly mean HbA_{1c} levels compared with control and traditional groups or compared with baseline. The reading and viewing levels were reported as the brochure and video had been read/viewed a median of twice in the family (range 1-10 for brochure and 2-10 for video). The cost of this intervention was estimated at 1000 euros per 100 pateints. The yearly sociaoeconomic cost for SH per 100 diabetes patients has been estimated at 17440 as a conservative measure. This study was of fair quality. Randomisation and blinding were described and ITT was used. There was a high drop out rate. The real world effectiveness of an intervention in a complete geographical population was a strength of this study. Self reported compliance may not be accurate. Recall bias from a 12 monthly reporting of SH may cause some inaccuracies.

Nordfeldt 2005

This article reported 24 month follow up data from the same cohort tested in the study described above. At 24 months, 249 patients provided data. The patients were asked via questionnaire ‘ Have you experience episodes of severe hypoglycaemia (needing assistance) during the last 12 months? Yes/No”. The number of SH episodes was also reported in the results. There were 20 episodes of SH in the intervention group after 24 months and 34 episodes in the control group and 29 in the traditional group. The difference between intervention and control reported in percentage as -15, 95%CI (-1 to -29) p=0.0448. The yearly incidence of SH decreased at 24 months from 42% to 25% (difference 17% , 95%CI 3-

31, p=0.0241) in the intervention group but not in the control group. 218 (66%) of the original 332 randomised patients returned data for this variable at 24 months. 18/80 (26%) of intervention group patients reported SH after 24 months compared with 29/92 (41%) patients at baseline. There was no significant difference in the number of patients reporting SH at 24 months compared to baseline in the control or traditional groups. After 24 months, there was a significant difference between intervention and controls when unadjusted for baseline of -15% 95%CI (-1 to -29) p=0.0448. This finding was in contrast to the 12 month results reported above which showed no difference between intervention and control group. It was reported that video use was higher in the intervention group but not in control groups in this study. Retrospective ascertainment of SH was used in this study as an outcome measure as was in the previous report. There was a high drop out rate at 24 months.

Schachinger 2005

In this RCT, Schachinger et al tested the effect of Blood Glucose Awareness Training (edition 3) on blood glucose measurements, severe hypoglycaemia and diabetes specific locus of control and general quality of life measures in patients with type 1 diabetes. The German version of BGATIII was delivered by a physician-psychologist team to groups of 5-12 subjects in 8 weekly sessions. Each session lasted 2 hours. The sessions focus on internal cues, disruptions in cognitive and motor performance and mood changes. Patients are taught to use these signals to recognise when their BGL is too high or low. Exogenous cues eg insulin dose, food and exercise is reviewed subsequently. Weekly homework and preparatory readings were required. The control group participated in 3 monthly sessions by one physician. Focus topics were set out with participants determining the specific issues and timing. The population was recruited from university hospitals with patients known to physicians as having recurrent severe hypoglycaemia being encouraged to participate. Patients were on a 'state of the art' intensified insulin regimen at recruitment and performed at least 3 BGL measurements per day. 138 subjects participated. Patients were grouped as pairs of approximately the same age and diabetes duration (important confounders favouring the occurence of SH). The authors report a random decision was made as to which of the two patients received the intervention or control. 14 subjects were excluded from analyses due to poor attendance at the intervention programme. 13 subjects were lost to follow up at 6 months. These patients had a higher HbA_{1c} than that of those participating subjects.

Regarding results, there was a decrease in severe hypoglycaemic episodes in the BGAT group comparing baseline SH incidence to 7-12 months follow up F(1,109)=4.04 p=0.04. The between group comparison showed a significant difference between the BGAT and control group with F(2,218)=3.14 p=0.04. The absolute numbers were 1.61 SH episodes/6 months at baseline in the BGAT group and 0.13 at 7-12 months. In the control group, the baseline was 1.76 and at 7-12 months 1.78. The higher incidence of SH at baseline compared to non selected populations was attributed to the older age, longer duration and intensive treatment of the study population. In addition, patients with known recurrent SH were selectively encouraged to participate. This study is of fair quality.

Broers 2005

This case series with pre-test/post-test outcomes evaluated the aforementioned BGAT program among Dutch patients in a pre-post. 59 patients participated in either group or individual training. The incidence of severe hypoglycaemia was assessed by a questionnaire at baseline and at 12 months after they had attended the BGAT program. The BGAT program was modified from the original to involve 6 sessions rather than 8 and was also translated

into Dutch. The subject was asked to report the frequency of SH episodes during the preceding year. Severe hypoglycaemia was defined as an episode of hypoglycaemia which the patient was unable to correct themselves. Only 26 out of 59 subjects returned questionnaires at 12 months follow up regarding severe hypoglycaemia. The frequency ws reported at baseline for the group BGAT participants as 7.9 episodes per year and 1.7 at follow up. For the individual BGAT participants, the baseline number of SH episodes per year was 6.6 and at follow up was 0.3. The p Time reported as 0.001 and pInteraction 0.26. This study is of poor quality.

Cox 2001

Cox et al described the effects of a psychoeducational program targeted at improving accuracy of patient's detection and interpretation of BG symptoms. The effects on severe hypoglycaemia was a primary endpoint. This study was a case series with pre-post test outcomes. Baseline assessments were performed for 6 months after recruitment then exposure to the BGAT program followed by 12 month measurements post exposure. The Blood Glucose Awareness Training II programme was used. This differed from the original programme as it had separate chapters on the effect of insulin, food and exercise influence BG. The program was delivered to groups of 5-15 subjects in 8 weekly sessions. The population were 78 subjects with t1d from university diabetes centers in North America. The mean age was 38.3 years, the mean duration of disease 19.5 years and the mean HbA_{1c} was 10.2%. Severe hypoglycaemia was defined as stupor or unconsciousness necessitating assistance in the treatment of low BG and was recorded in a monthly diary by the subjects. Severe hypoglycaemia was 1.6+/- 2.0 episodes per month at baseline. At 6 months follow up, SH was reduced to 1.2+/-1.9 episodes and at 12 months was 1.1+/-2.0 episodes per month F=3.9 p<0.002. Contrast I P levels compared the 6 month baseline with the 6 and 12 month follow up data to determine whether there was a long term benefit of BGAT-2. The t was 2.3 and P=0.002 for Contrast 1 P levels. The authors conclude there was a reduction of severe hypoglycaemia after BGAT-II training. They report theirs was the first study to show reduc tion in SH without manipulating diabetic subject regimen or metabolic control. Post hoc analyses showed that improvement in self treatment decisions only marginally correlated with improvement in SH (r=0.19, P=0.086). This study consists of low level evidence and is of fair quality.

16.3.5 Discussion

This systematic review identified five studies which examined the effect of educational interventions on the reduction of severe hypoglycaemia. Two studies by Nordfeldt et al reported the results of the same study, the article published in 2005 reporting results after 24 month follow up. Three of the studies were randomised controlled trials(level II evidence) and two studies were case series with pre-test/post-test outcomes (level IV evidence) with significant potential for bias. Four studies were of fair quality and one was of poor quality.

Three studies examined the same intervention: Blood Glucose Awareness Training with slight differences in edition and language. Although all studies reported a significant reduction in severe hypoglycaemia after intervention, most studies were of either low level evidence or had unclear randomisation methods. The largest study which was also an RCT of fair quality reported a reduction of SH in the intervention group compared to control. The difference in incidence of SH at 24 months between the two groups reported as -15% 95%

CI (-1 to -29). There were 20 episodes of Shin the intervention group compared to 34 in the control group. In contrast, the 12 month results of the same study showed no difference between intervention and control 95%CI (-4 to 24) but a difference in change from baseline

in the intervention group (-15% 95% CI 1 to 29 p=0.039) but not the control group (+3% 95%CI -11 to 17). The RCT published by Schachinger et al reported that BGAT led to a decrease in SH episodes. This was reported as a time.group interaction of F(2,218) = 3.14 p=0.04 and a change in SH episodes/6 months in the BGAT group compared to baseline (F(1,109)=4.04 p=0.04. Change from post exposure to baseline was significant in the non-randomised study by Broers et al. The number of SH episodes decreased after intervention with p=0.001. There were 7.9 episodes per year at baseline reported in the Group BGAT participants and 1.7 at 12 month follow up. The individual BGAT participants reported 6.6 episodes per year baseline and 0.3 at follow up. Cox reported severe hypoglycaemia was reduced by a third across the first and last 6 months of follow up (p<0.002) with a mean episodes/month of 1.6 at baseline and 1.2 at 6 months, 1.1 at 12 months. As these studies do not have a control group, the observed change may not be necessarily attributable to the intervention only.

The population studied was most representative in the study by Nordfeldt et al where all patients in a geographic catchment area were recruited. The selection of the population studied was biased towards patients with a history of recurrent severe hypoglycaemia in the study by Schachinger et al, in addition the randomisation method used in this trial was not made clear. The population sample studied by Broers et al were those that had participated in a research project by the same authors published 3 years prior. In all studies, the definition of severe hypoglycaemia was defined as an episode of hypoglycaemia requiring assistance. Subject's reports of SH were confirmed by BGL diary in one study. The primary outcome of severe hypoglycaemia was retrospectively ascertained by yearly survey in two studies.

16.3.6 Conclusion

There is evidence to support the use of educational interventions in the reduction but not prevention of severe hypoglycaemia. The evidence base for this question consists of 2 level II studies of moderate risk of bias and 2 level IV studies of high risk of bias. All studies are consistent in showing a reduction in the incidence of SH after intervention compared to baseline. Two RCTs showed a significant difference in SH incidence between intervention and control groups. The results from the early follow up of one RCT did not show a difference at 12 months but the 24 month follow up did show a difference. The populations studied were more representative in one study of an entire geographic catchment area. The other populations studied showed some selection bias. The studies were set in Europe and North America and are applicable to the Australian Health care setting.

16.3.7 Evidence Matrix

Q16.3	How can severe hypoglycaemia be prevented?	
Evidence statement	Level II and Level IV evidence shows that specific educational interventions (in particular, BGAT) reduce the rate of severe hypoglycaemia.	
Evidence base	C	Two Level II studies (1 with 12 months follow-up) with moderate risk of bias, and two Level IV studies; one with low risk of bias and one with high risk of bias.
Consistency	B	Reduction of severe hypoglycaemia –the 24-month and 12-month results from the same study were conflicting (no effect at 12 months and a significant effect at 24 months). This may be explained by length of follow-up and the overall effect being positive. The other Level II study found a significant effect compared to control. The two Level II studies were consistent in reporting significant improvement compared to baseline. (Different definitions of severe hypoglycaemia and reporting methods were used.)
Clinical impact	A	Level II studies used a method not described in detail. Level IV studies used published BG awareness training methodology.
Generalisability	B	Populations were representative with studies in adolescents and adults. Compliance of the populations may vary. Children were not represented.
Applicability	A	Studies were set in Europe and North America.
Other factors	One study reported the cost of intervention per 100 patients at €1000, and the yearly socioeconomic cost for severe hypoglycaemia at €17 440. Issues regarding language. Cost effectiveness should be considered with regard to implementation.	
Recommendation		
R16.3	Structured education specifically targeting prevention of severe hypoglycaemia should be provided (Grade B).	

BG, blood glucose; BGAT, blood glucose awareness training

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

17 Ketone monitoring

Question 17.1

How effective is blood ketone monitoring versus urine ketone monitoring in prevention of diabetic ketoacidosis or hospital admission?

This question examines the effectiveness of ketone monitoring in preventing diabetic ketoacidosis (DKA) and hospitalisation. Ketone monitoring is used for the detection of insulin deprivation and to guide insulin replacement during sick days. There are two methods of monitoring ketone bodies; the measurement of beta-hydroxybutyric acid by capillary blood sample and measurement of acetoacetic acid by urine dipstick test.

17.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 17.1.

Table 17.1 Criteria for determining study eligibility, question 17.1

Study design	Level I or Level II (NHMRC intervention scale[a])
Population	Children, adolescents or adults with type 1 diabetes
Intervention	Measurement of ketone bodies by capillary blood sample
Comparator	Measurement of ketone bodies by urine sample
Outcomes	Diabetic ketoacidosis Hospitalisation

NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

17.1.2 Assessment of study eligibility

Publications identified in the literature search were reviewed using the criteria shown in Table 17.2, applied hierarchically, to determine which publications to exclude.

A total of 156 non-duplicate citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with 155 publications excluded, as shown in Table 17.2. One publication remained, and the full-text version of this publication was retrieved and reviewed.

17.1.3 Literature search summary

Table 17.2 Search results, question 17.1

Stage	Notes	Number
Search summary	Manual	
	Cochrane Library	8
	INAHTA	11
	EMBASE	112
	Medline	62
Duplicates	Duplicates identified	39
Identified	Total identified	

Stage	Notes	Number
Exclusion criteria	Wrong study type (not NHMRC Level I or Level II[a])	99
	Wrong population (not type 1 diabetes)	
	Wrong intervention (not measurement of ketone bodies by capillary sample)	54
	Wrong comparator (not measurement of ketone bodies by urine test)	
	Wrong outcome (not rate of DKA or hospitalisation)	
	Not in English	2
	Total excluded	
Meeting criteria	Total meeting inclusion criteria	
Included	Total included studies	1

DKA, diabetic ketoacidosis; NHMRC, National Health and Medical Research Council
[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

17.1.4 Included study

No Level I studies were found in the literature search. The citation of one Level II study was retrieved for full-text review (Laffel et al 2006).

17.1.5 Results of included study

Laffel et al (2006)

Laffel et al (2006) was a prospective, two-centre study that assessed sick day management using blood 3-hydroxybutyrate (3-OHB) monitoring compared with traditional urine ketone testing, with the aim of averting emergency assessment and hospitalisation. In total, 123 children, adolescents and young adults, aged 3–22 years, and their families received sick day education. Participants were randomised to receive either a blood glucose monitor that also measured blood 3-OHB (blood ketone group, n=62) or a monitor plus urine ketone strips (urine ketone group, n=61). To avoid confounding, participants were randomised according to insulin pump use and level of glycated haemoglobin (HbA_{1c}) (<8.5% or >8.5%). All participants were encouraged to check glucose levels at least three times daily, and to check ketones during acute illness or stress, when glucose levels were consistently elevated (≥13.9 mmol/L on two consecutive readings), or when symptoms of DKA were present. Patients and families were counselled to contact their local diabetes team for sick day management during illness, as necessary. Frequency of sick days, hyperglycaemia, DKA, and hospitalisation or emergency assessment were ascertained prospectively for 6 months. Participants were supplied with logbooks that included written sick day guidelines reflecting the method of ketone assessment. The logbooks and blood glucose meters were reviewed at 3 and 6 months; a questionnaire to ascertain diabetes care and sick day management was administered; and intercurrent illnesses, hospitalisations and emergency visits were recorded.

There were 578 sick days during 21 548 days of follow-up.

Participants in the blood ketone group checked ketones significantly more during sick days (276 of 304 episodes, 90.8%) than participants in the urine ketone group (168 of 274 episodes, 61.3%) (p<0.001).

Table 17.3 Comparison of number of acute complications

	Blood ketone group	Urine ketone group
Number of acute complications	n=11 in 10 patients (n=8 emergency room visits / n=3 hospitalisations)	n=22 in 15 patients (n=14 emergency room visits / n=8 hospitalisations)

The incidence of hospitalisation or emergency assessment was significantly lower in the blood ketone group (38/100 patient years) than in the urine ketone group (75/100 patient years) (p=0.05).

The authors concluded that routine implementation of blood 3-OHB monitoring for the management of sick days and impending DKA can potentially reduce hospitalisation or emergency assessment compared with urine ketone testing, and offers potential cost savings.

The study was supported by an investigator-initiated industry research grant.

17.1.6 Discussion

DKA is a life-threatening acute complication of type 1 diabetes, which may be preventable with frequent monitoring of blood glucose and ketosis, and adequate replacement of insulin. Laffel et al (2006) attempted to determine the efficacy of monitoring blood ketones versus urine ketones in a group of 123 children, adolescents and young adults. In the patient characteristics reported there was no note of prior experience with the blood ketone monitoring method. There was also no description of ethnicity, level of education or presence of diabetes complications. The outcomes reported included hospitalisation or emergency assessment. A detailed description of the type of acute complication encountered was not provided; therefore, the study did not provide evidence about the effect of the method of ketone monitoring used and frequency of DKA.

17.1.7 Conclusion

This systematic review of evidence for the effectiveness of blood ketone monitoring versus urine ketone monitoring for the prevention of DKA or hospital admission was based on one randomised controlled trial (RCT) of low risk of bias, including 123 children, adolescents and young adults aged under 22 years. No studies were found in adults aged over 22 years. Use of blood ketone monitoring resulted in a significant reduction (of about 50%) in the incidence of hospitalisation or emergency assessment. The included study did not report on rates of DKA. Exclusions reported included recurrent episodes of DKA or known emotional problems. The study was carried out in the United States, which has a well-developed health-care system.

17.1.8 Literature search strategy

The search was conducted between 10 November 2010 and 17 November 2010. The Medline search strategy and a summary of citations retrieved from other searches are shown in Table 17.4.

Table 17.4 Search strategy, question 17.1

Database	Date searched	#	Search terms	Citations
Medline	Between 10 November 2010 and 17 November 2010	1	Diabetes Mellitus, type 1/	53 959
		2	ketone Bodies/ or Ketones/ or Diabetic Ketoacidosis/	18 871
		3	(ketoacidosis or ketones or diabetic ketoacidosis).mp.	20 970
		4	monitor*.mp.	472 926
		5	measur*.mp.	1 868 939
		6	2 or 3	25 089
		7	4 or 5	2 208 470
		8	6 and 7	2 991
		9	1 and 8	375
		10	exp Clinical Trial/	637 902
		11	clinical trial.pt.	469 434
		12	random$.tw.	512 753
		13	(doubl$ or singl$ or trebl$).mp. and blind$.tw. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	116 508
		14	exp Randomised Controlled Trial/	305 777
		15	10 or 11 or 12 or 13 or 14	928 721
		16	9 and 15	64
		17	limit 16 to (english language and humans)	62
Cochrane				8
INAHTA				11
EMBASE				112

17.1.9 Evidence Matrix

Q17.1	Does ketone monitoring prevent ketoacidosis or hospital admission?	
Evidence statement	Blood ketone measurement compared with urine ketone measurement, as part of a sick-day management plan, reduces the rate of emergency presentations and hospitalisations.	
Evidence base	B	One Level II study of low risk of bias.
Consistency	N/A	Blood ketone monitoring resulted in a significant reduction (about 50%) in the incidence of hospitalisation and emergency assessment.
Clinical impact	A	This is an important clinical procedure that is easy to do at home.
Generalisability	B	Participants aged 3–22 years, and population not defined in terms of ethnicity. Exclusions included 'known emotional problems' and recurrent episodes of DKA.
Applicability	A	The study was undertaken in the United States, which has a well-developed health-care system.
Other factors	None identified.	
Recommendation		
R17.1	Blood ketone measurement should be available as part of a comprehensive sick-day management plan (Grade C).	

DKA, diabetic ketoacidosis

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable.

18 Microvascular and macrovascular complications

18.1 Effect of intensive glycaemic management on microvascular and macrovascular complications

Question 18.1

What is the effect of intensive glycaemic management on microvascular and macrovascular complications?

This section of the report addresses the evidence regarding the effect of intensive glycaemic management on micro and macrovascular complications. This question will cover the effects of intensive glycaemic control as implemented by the Diabetes Control and Complications Trial (DCCT) study, which defined such control as 'maintenance of glycaemic control as close to normal range as possible'.

18.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 18.1.

Table 18.1 Criteria for determining study eligibility, question 18.1

Study design	NHMRC Level I or II
Population	Type 1 diabetes
Intervention	Intensive glycaemic control as defined by the DCCT trial
Comparator	Conventional care
Outcomes	Microvascular and/or macrovascular complications : retinopathy, nephropathy, neuropathy, coronary artery, peripheral vascular disease and cerebrovascular disease Adverse events and cost of intensive glycaemic management

DCCT, Diabetes Control and Complications Trial; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

Publications identified in the literature search were reviewed using the criteria shown in Table 18.2, applied hierarchically, to determine which publications to exclude.

A total of 239 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with publications excluded, as shown in Table 18.2. A total of 14 publications remained, and the full-text version of each of these publications was retrieved and reviewed. Two meta-analyses examined the effect of glycaemic control on macrovascular disease. One systematic review examined the risk of adverse effects of intensified treatment and was included in this review. A systematic review of observational studies did not meet inclusion criteria. Randomised controlled trials (RCTs) of less than 200 subjects were not included in this review (Selvin et al 2004).

18.1.2 Literature search summary

Table 18.2 Search results, question 18.1

Stage	Notes	Number
Search summary	Manual	6
	Cochrane Library	128
	Medline	105
	Total	239
Duplicates	Duplicates identified	26
Exclusion criteria	Wrong study type (Not NHMRC level I or II evidence)	101
	Wrong population (Not type 1 diabetes)	43
	Wrong intervention or test (Not intensive glycaemic management)	34
	Wrong comparator (Not conventional treatment)	0
	Wrong outcome (Not a micro or macrovascular complication of diabetes)	17
	Not in English	0
Meeting criteria	Total meeting inclusion criteria	19
Included	Total included studies	19

18.1.3 Included studies

The included studies were 4 Level I studies (Wang et al 1993a; Egger et al 1997; Lawson et al 1999; Stettler et al 2006) and 15 Level II studies (DCCT 1993; DCCT 1994; Anonymous 1995b; Anonymous 1995a; Anonymous 1996b; Anonymous 1998; Anonymous 2000; DCCT/EDIC Research Group2000; Anonymous 2001; Writing Team for the DCCT/EDIC Research Group 2002; Writing Team for the DCCT/EDIC Research Group 2003; Nathan et al 2005; Martin et al 2006; Pop-Busui et al 2009; White et al 2010).

18.1.4 Characteristics of included Level 1 studies

Stettler et al (2006)

Stettler et al (2006) is a systematic review and meta-analysis of RCTs comparing interventions to improve glycaemic control with conventional treatment in type 1 and type 2 diabetes. The aim was to identify all randomised controlled comparisons of improved glycaemic control that assessed macrovascular disease in type 1 and type 2 diabetes. Multiple databases were searched in a thorough and systematic method. In addition to the above criteria, the trials had to have a follow up of at least 2 years, and have prospective recording of macrovascular events (which were clearly defined). Methodological assessment of study quality was made. For each comparison the incidence rate ratio (IRR) was obtained by dividing the incidence in the intensified group with the incidence in the control group. The extent to which the effect of improved glycaemic control was modified by study level variables was explored in univariate meta-regression models. The following variables were considered: reduction of glycated haemoglobin (HbA_{1c}), duration of diabetes, age at baseline, gender, date of study and study quality. Analyses were repeated after excluding one study where the prevalence of smoking was much higher in the intensive group (Veterans Affairs study in type 2 diabetes). Numbers were presented as IRR with 95% confidence intervals (CIs) and number needed to treat (NNT) to prevent one macrovascular event.

The study found eight randomised comparisons including 1800 patients with type 1 diabetes; these studies were set in Europe, North America and Asia. Mean follow-up ranged from 2 to 8 years. Intensified treatment typically consisted of multiple daily injection (MDI) therapy or CSII with intensive self monitoring of blood glucose. Conventional treatment was based on 1–3 injections with or without occasional blood glucose monitoring. Mean HbA_{1c} ranged from 8.8% to 11.8% in type 1 diabetes at the end of the study; differences between intensified and conventional groups ranged from –0.5% to –1.9%. The prevalence of cardiac risk factors was similar between treatment groups.

The absolute numbers of events in 11 293 person years of follow up were as follows: 134 macrovascular events consisting of 40 cardiac events, 88 peripheral vascular events and 6 cerebrovascular events. The results of fixed effects meta-analyses are summarised below. There was a statistically significant reduction in IRR for any macrovascular, cardiac or peripheral vascular event (see 95%CI in table below). However, the 95%CI for cerebrovascular events crossed unity, indicating that it was not significant.

Nine deaths occurred in patients with type 1 diabetes in 3 studies; no macrovascular deaths occurred.

Table 18.3 Incidence rate ratios (95%CI) for any macrovascular event and cardiac, peripheral vascular and cerebrovascular events

	Any macrovascular	Cardiac	Peripheral vascular	Cerebrovascular
Combined IRR (fixed effect)	0.38	0.41	0.39	0.34
95%CI	0.26 to 0.56	0.19 to 0.87	0.25 to 0.62	0.05 to 2.57
Heterogeneity (I^2)	0.0% p=0.579	13.6% p=0.326	0.0% p=0.957	16.9% p=0.273

The incidence of macrovascular events in conventionally treated patients ranged from 0.6 to 4.7 per 100 person years. To calculate NNT, a typical incidence of 1 per 100 person years was assumed. Using the IRR, the number of patients that need to receive intensified treatment for 10 years to prevent one macrovascular event was 16.

There was little evidence of funnel plot asymmetry (p>0.3 for all endpoints). The reduction in risk for macrovascular events associated with improved glycaemic control was greater in studies that achieved larger reductions in HbA_{1c} levels (p–0.05).

Lawson et al (1999)

The objective of the systematic review by Lawson et al (1999) was to determine the effect of intensive insulin therapy on macrovascular complications in type 1 diabetes. Medline and reference lists were used to identify RCTs of more than 2 years duration comparing intensive therapy (IT) to conventional therapy. Data were extracted on macrovascular disease and cardiovascular risk factors.

The search was undertaken systematically. IT was defined as a method of intensifying diabetes management with the goal of improving metabolic control over that achieved by conventional therapy. Quality assessment was performed and definition of outcome measures was made prior to data extraction. Odds ratios (OR) were calculated. Six studies met inclusion criteria. Each study had a follow up of >90%. The duration ranged from 2–

9 years. The studies all achieved a statistically significant difference in HbA_{1c} between the two groups and the studies were all similar in quality.

Most of the RCTS included relatively young subjects. The mean age at entry ranged from 18 to 42 years. The duration of diabetes ranged from 1.7 to 18.6 years.

IIT was found to decrease the number of first major macrovascular events (OR 0.55, 95%CI: 0.35 to 0.88, p=0.015) but had no significant effect on the number of patients developing macrovascular disease (OR 0.72, 95%CI: 0.44 to 1.17, p=0.22) or on macrovascular mortality (OR 0.91, 95%CI: 0.31 to 2.65, p=0.93). There was no significant statistical heterogeneity (p=0.76 for all analyses).

Publication bias, assessed through funnel plot analysis, did not appear to be present.

Wang et al (1993a)

The meta-analysis by Wang et al (1993a) was undertaken to estimate the impact of IT on the progression of retinopathy and nephropathy and the risks of severe side effects in people with type 1 diabetes. The analysis did not include the large DCCT study published that year. The databases searched were not reported, nor was there report of quality rating of the studies. Studies were excluded if they were nonrandomised or had data that could not be analysed. In total, 16 papers were identified with duration of follow up ranging from 8 to 60 months. All studies but one achieved better or near normal control by IT. The difference by study end between groups was –1.4% HbA_{1c} (95%CI: –1.8 to –1.1).

Regarding retinopathy, after 2–5 years of IT, the risk of retinopathy progression was significantly reduced (OR 0.49, 95%CI: 0.28 to 0.85. p=0.011) and there was little or no heterogeneity (p=0.885). Progression within background retinopathy is clinically different to progression to proliferative retinopathy, but not all studies separated this. In those that did, IT significantly retarded retinopathy progression to more severe states such as proliferative retinopathy or changes requiring laser treatment (OR 0.44, 95%CI: 0.22 to 0.87, p=0.018, heterogeneity p=0.991).

Regarding nephropathy, IT significantly reduced the risk of nephropathy progression (OR 0.34, 95%CI: 0.2 to 0.58, p<0.001), with no heterogeneity (p=0.99). Most studies included patients with normal albumin excretion (AE) or microalbuminuria, or normal serum creatinine.

Egger et al (1997)

The systematic review and meta-analysis by Egger et al (1997) examined the risk of severe hypoglycaemia, ketoacidosis and death in RCTs comparing intensive glycaemic control to conventional therapy. A systematic search was undertaken. RCTs with at least 6 months follow up and reported HbA_{1c} levels with at least one outcome event were included. Each study was assigned a quality grading. A total of 14 studies were identified; these included 1028 patients allocated to IT and 1039 to conventional treatment. Patients randomised to IT received pump therapy in 9 arms, MDI in 4 arms and could choose in 3 arms. Mean HbA_{1c} in conventional treatment groups ranged from 41% to 88% above the mean of a reference population without diabetes. In most trials, HbA_{1c} levels were lowered among IT patients, with a range of 0–22%. The mean age of study participants ranged from 18 to 42 years, and diabetes duration from 3 to 20 years.

Regarding severe hypoglycaemia, the incidence ranged from 0 to 66.6 (median 7.9) episodes per 100 person-years among IT patients and from 0 to 33.3 (median 4.6) among

conventionally treated patients. Severe hypoglycaemia in all studies was defined as episodes with typical signs requiring intervention by a third party. The combined OR was 2.99 ($p<0.0001$) for the risk of suffering one or more episodes of severe hypoglycaemia. However, the test for heterogeneity was significant ($p=0.06$)

The incidence of ketoacidosis ranged from 0 to 37.5 episodes per 100 person years among IT patients and from 0 to 6.3 among those on conventional treatment. The combined OR indicated an increased risk with IT (OR 1.74, $p=0.0003$). Again, the test for heterogeneity was significant ($p=0.06$).

Mortality rates ranged from 0 to 6.3 per 100 person years among IT patients and from 0 to 5.5 among those on conventional treatment. A total of 15 all-cause deaths occurred with IT and 11 with conventional treatment (OR 1.4, 95%CI: 0.65 to 3.01, $p=0.39$).

Sensitivity analysis was performed after removal of the DCCT results (OR reduced to 1.59, 95%CI: 1.01 to 2.52) for severe hypoglycaemia. Excluding poor quality trials did not affect the results. The type of regimen used also did not influence risk. The authors reported that important heterogeneity between trials could be shown and accounted for, but there was no further description of this.

The significant heterogeneity statistics should be taken into account when the pooled results are interpreted. This SR was of fair quality.

Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications

The DCCT was a multicenter RCT designed to compare IT with conventional diabetes therapy, with regard to effects on the development and progression of the early vascular and neurologic complications.

IT included the administration of insulin three or more times daily by injection or an external pump. The dosage was adjusted according to the results of self-monitored blood glucose (SMBG) at least four times daily, diet and exercise. The patients initially chose either MDI or pump therapy, and could change to the other method according to preference or targets. Patients visited the study centre each month, and were contacted even more frequently by telephone for review and dose adjustment.

Conventional therapy consisted of one or two daily injections of insulin, including mixed intermediate and rapid-acting insulins, daily self-monitoring of urine or blood glucose, and education about diet and exercise. Conventional therapy did not usually include daily adjustments in the insulin dosage. Patients were examined every three months.

In total, 1441 patients were recruited at 29 centres from 1983 to 1989. The entire cohort was followed for a mean of 6.5 years, which gave a total of more than 9300 patient years. A total of 99% of patients completed the study; 11 patients died and 32 were assigned to inactive status.

The clinical RCT phase of the DCCT was stopped prematurely, by the data safety and quality committee, after a mean follow-up of 6.5 years. The benefits of IT were deemed incontrovertible and highly unlikely to be reversed with time. During a closeout period, all participants were encouraged and advised to implement or continue IT using DCCT staff.

The observational phase of the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study then commenced.

The EDIC study was a multicentre, longitudinal, observational study designed to use the DCCT cohort of patients to determine the long-term effects of prior separation of glycaemic levels on microvascular and macrovascular outcomes.

At completion of the DCCT, 96% subjects consented to participate in EDIC. There were 1375 participants in total, 687 from the IT group and 688 from the conventional treatment group.

At the end of EDIC year 1, 95% of the former IT group and 75% of the former conventional group reported that they were using IT. The mean HbA_{1c} levels were 7.9% for the former IT group and 8.3% in the former conventional group. The HbA_{1c} levels converged further and have remained similar during the ensuing 7 years. The overall mean HbA_{1c} levels for the entire EDIC follow up til 2002 were 8.3% for the former conventional group and 8.1% for the IT group.

Cardiovascular disease

The effect of prior IT on the long-term incidence of cardiovascular disease (CVD) was published by the DCCT/EDIC study group in 2005 (Nathan et al 2005).This paper reported the results at year 11 of DCCT. The research group had specified in 1996 that no analyses comparing the cardiovascular events between groups would be performed until 50 patients in the original conventional treatment group had had a cardiovascular event. This occurred in 2005. At baseline, no patient in the DCCT had hypertension or hypercholesterolaemia, and only 5% had microalbuminuria. There were no significant differences between the IT and conventional group in terms of risk factors for CVD apart from a minimally higher systolic blood pressure (SBP) in the conventional group. At the end of the DCCT, microalbuminuria and albuminuria were more prevalent in the conventional group (13% vs 7%, $p<0.01$ for microalbuminuria) and (3% vs 1%, $p<0.05$ for albuminuria). This continued to be the case at year 11 of EDIC. In addition, the prevalence of a serum creatinine value of at least 2 mg per decilitre was also significantly greater in this group (2% vs 0%, $p<0.05$). The absolute difference in the HbA_{1c} value between groups was only 0.1% at year 11 of EDIC.

Regarding event rate, a total of 144 cardiovascular events occurred in 83 patients during the mean 17 years of follow up: 46 among 31 patients in the IT group and 98 among 52 patients in the conventional group. The respective event rates were 0.38 and 0.8 per 100 patient years ($p=0.007$). The risk of the first occurrence of nonfatal myocardial infarction (MI), stroke or death from CVD was reduced 57% with IT as compared with conventional treatment (96%CI: 12 to 79%, $p=0.02$).

Proportional hazards models, adjusted for selected baseline factors, were used to assess the association of time-dependent co-variates with the risk of CVD. A history of renal disease did not have a significant effect on the risk of CVD perhaps because of the small number of such patients. A history of microalbuminuria or of albuminuria was significantly associated with an increase in the risk of CVD by a factor of more than 2.5. The difference in CVD outcomes between groups remained significant after adjustment for these factors. A mean HbA_{1c} updated to the time of the CVD event of 10% lower represented a 20% reduction in the risk of a cardiovascular event in one patient compared to another with a higher HbA_{1c} (95%CI: 9 to 30%, $p<0.001$)

Regarding risk factors, the baseline characteristics of the entire DCCT cohort that were associated with the occurrence of the CVD outcome independent of treatment assignment

were older age, longer duration of diabetes, presence of retinopathy, current smoking, higher body-mass index (BMI), higher total and low-density lipoprotein (LDL) cholesterol levels, higher $HJbA_{1c}$ and higher albumin excretion rate as well as assignment to conventional treatment.

Retinopathy

The most recent publication reported on the persistence of the benefits of IT after 10 years of follow-up and the comparison between subjects who were adolescents at enrolment and those who were adults (White et al 2010). At EDIC year 10, HbA_{1c} (A_{1c}) was similar between original IT and conventional groups, and between former adolescents and adults. At EDIC year 10, adults in the former IT group continued to show slower progression of diabetic retinopathy than those in the conventional group (adjusted hazard reduction 56%, p<0.0001), whereas in adolescents this beneficial effect had disappeared (32%, p=0.13). It was reported that 79% of observed differences in the prolonged treatment effect between adults and adolescents at year 10 were explained by differences in mean A_{1c} during the DCCT between adolescents and adults (8.9 vs. 8.1%), particularly between IT adolescents and adults (8.1 vs. 7.2%)

An earlier publication (DCCT 1993) showed that, in the primary prevention cohort, IT (median HbA_{1c} 7.3%) reduced the adjusted mean risk for the development of retinopathy by 76% (95%CI: 62% to 85%) compared with conventional therapy (HbA_{1c} 9.1%). Patients in the primary prevention cohort with duration of diabetes of less than 2.5 years at entry into the trial had 89% reduction in the risk of retinopathy compared with 70% in patients with duration of more than 2.5 years (p<0.001). In the secondary intervention cohort, IT slowed the progression of retinopathy by 54% (95%CI: 39% to 66%), and reduced the development of proliferative or severe nonproliferative retinopathy by 47% (95%CI: 14% to 67%)

In the primary prevention cohort, there was an early worsening of retinopathy. This occurred in 22% of patients in the IT group compared with 13% in the conventional group. The progression consisted of the development of soft exudates or intraretinal microvascular abnormalities. This occurred mainly in the secondary intervention cohort in during the first year of therapy. The abnormalities often disappeared by 18 months. The patients with early worsening who were treated intensively ultimately had a 74% reduction (95%CI: 46% to 88%) in the risk of subsequent progression, compared with patients with early worsening who received conventional therapy (p<0.001)

Epidemiological analysis of the DCCT data demonstrated a strong exponential relationship between the risk of retinopathy and the mean HbA_{1c} measured quarterly (Anonymous 1996a). For each 10% decrease in HbA_{1c}, there was a 39% decrease in risk of retinopathy over the range of HbA_{1c} values. There was no glycaemic threshold at which the risk of retinopathy was eliminated above the nondiabetic range of Hb_{1c} (4.0%–6.05%). The risk of retinopathy at any mean HbA_{1c} level also increased with the duration of follow-up during the DCCT (e.g. the same risk of retinopathy was reached within 2.5 years at an HbA_{1c} level of 11% as was reached in 9 years at an HbA_{1c} level of 8%).

Nephropathy

The original publication from the DCCT reported that, in the combined cohorts (primary prevention and secondary intervention), IT reduced the occurrence of microalbuminuria (urinary albumin excretion of ≥40 mg/24 hours) by 39%. Albuminuria was reduced by 54%. The risk of developing nephropathy was exponentially related to the mean HbA_{1c}. For each 10% decrease in HbA_{1c}, there was a 25% decrease in the risk of microalbuminuria. No glycaemic threshold for nephropathy was detected above the nondiabetic range of HbA_{1c}.

The DCCT found no influence of IT on glomerular filtration rate; however, these values remained within normal range for most subjects during the DCCT.

The more recent report (Writing Team for the DCCT/EDIC Research Group 2003) was published after 7–8 years of follow-up. During the EDIC study, in the IT group, new cases of microalbuminuria occurred in 6.8% of participants compared to 15.8% who were in the CT group. The odds reduction was 59% (95%CI: 39% to 73%), adjusted to baseline values. This compares to a 59% (95%CI: 36% to 74%) reduction at the end of the DCCT (p<.001 for both comparisons). At the end of the DCCT, new cases of clinical albuminuria occurred in 9 (1.4%) of the participants in the original IT group compared to 59 (9.4%) of those in the original conventional group, representing an 84% reduction in odds (95%CI: 67% to 92%), compared with a reduction of 57% (95%CI: –1 to 81%) at the end of the DCCT.

Although small numbers of patients required dialysis or transplantation, fewer patients experienced either of these outcomes in the intensive group (4 vs 7, p=36).

Neuropathy

A study published in 2006 reported on the impact of prior IT on neuropathy at 8 years after the end of DCCT (Martin et al 2006). The former IT group showed a lower prevalence of neuropathy based on questionnaire or examination at the first EDIC examination (1.8% vs 4.7%, p=0.003 for the questionnaire; and 17.8% vs 28%, p<0.0001 on examination). At the beginning of the EDIC study, prior IT reduced the odds of having symptoms and signs of neuropathy using MNSI criteria (see data extraction table) by 64% (p=0.0044) and 45% (p<0.0001), respectively, with similar odds reductions observed for both neuropathic symptoms (515, p<0.0001)

The study published in 2002 reported that neuropathy, whether assessed by a neurologist's standardized clinical exam, nerve conduction studies or autonomic nerve function testing, was benefited by intensive treatment (Writing Team for the DCCT/EDIC Research Group 2002). After 5 years of DCCT follow up, the prevalence of confirmed clinical neuropathy in those without neuropathy at baseline was reduced by 69% in the primary cohort and 57% in the secondary cohort.

Autonomic neuropathy

The most recent publication regarding cardiac autonomic neuropathy (CAN) was published in 2009 (Pop-Busui et al 2009). This report detailed the incidence and prevalence of CAN in the IT and conventional cohort 13–14 years after closeout of the DCCT. The DCCT autonomic measures (R-R variation with paced breathing, valsalva ratio, postural blood pressure [BP] changes and autonomic symptoms) were repeated in 1226 EDIC subjects in EDIC year 13–14. The prevalence of CAN using the DCCT composite definition was significantly lower in the former IT group compared to the former conventional group (28.9% vs 35.2%, p=0.018). The adjusted R-R variation was significantly greater in the former IT group. Prior DCCT IT reduced the risks of incident CAN by 31% (OR 0.69, 95%CI: 0.51 to 0.93) and of incident abnormal R-R variation by 30% (OR 0.70, 95%CI: 0.51 to 0.96) in EDIC year 13–14. The authors concluded that although CAN prevalence increased in both groups, the incidence was significantly lower in the former IT group compared with the former conventional therapy group.

Adolescent cohort

The subgroup of DCCT participants who were aged 13–19 years at randomisation in the DCCT have been subjects of various reports. The most recent of these was published in 2010 (White et al 2010). This report showed that, of the 195 adolescents originally enrolled in the

DCCT, 175 were enrolled in EDIC and, of those, 156 were evaluated at year 10. Prolonged beneficial treatment effects continued to be observed in the adult cohort (metabolic memory). In the adolescent cohort, there was no longer evidence of metabolic memory. After 10 years, 40% of both the IT and conventionally treated adolescents had further retinopathy progression (odds reduction 0%) compared with 23% in the conventional and 8% in IT 4 years after closeout of the DCCT (odds reduction 72%, 95%CI: 17% to 90%, p=0.0165).

Adverse events and safety

Mortality did not differ significantly between the treatment groups, nor did diabetic ketacidosis (DKA) events. The death rate in the conventional group was 0.084 deaths per 100 person years, and the rate in the IT group was 0.148 (p=0.38).The only death directly due to diabetes was from DKA in an IT group patient treated with MDIs, who lapsed into a coma at home without seeking medical attention. Three deaths were related to cardiovascular conditions. In two of these deaths, diabetes was determined to have a minor contributing role (Anonymous 1995a). Hypoglycaemia was the most common adverse event observed in the trial. The incidence of severe hypoglycaemia, including multiple episodes in some patients, was approximately three times higher in the IT group than in the conventional therapy group (p<0.001). In the IT group, there were 62 hypoglycaemic episodes per 100 patient years in which assistance was required. There were 16 episodes of coma or seizure per 100 patient years. In the conventional group, there were 19 episodes per 100 patient years of hypoglycaemic episodes requiring assistance, and 5 episodes of coma or seizure per 100 patient years. Almost half of the DCCT cohort – 714 patients – had one or more episodes of hypoglycaemia requiring assistance. The event rate of hypoglycaemia requiring assistance was 61.2 episodes per 100 patient years of follow-up for the IT group compared to 18.7 for the conventional group (RR: 3.28, p<0.001) (Anonymous 1995a).

Despite the higher risk of severe hypoglycaemia with IT, there was no difference between the two groups in the occurrence of clinically important changes in neuropsychological function, nor where there any significant differences in the mean total scores in the quality of life (QoL) questionnaire.

The purpose of a report published in 2008 was to evaluate whether severe hypoglycaemia or IT affects cognitive performance over time in adolescents (Musen et al 2008). A total of 249 subjects were adolescents at entry to the DCCT. A comprehensive battery of cognitive tests were obtained during the EDIC study 18 years later, and were compared with baseline performance. It was found that there were 294 reported episodes of coma or seizure. Neither frequency of hypoglycaemia nor previous treatment group was associated with decline of any cognitive domain, as found in an earlier analysis of the entire study cohort regarding cognitive function (DCCT/EDIC Research Group 2007). Higher HbA_{1c} values were associated with declines in psychomotor and mental efficiency domain; however, the previous finding of improved motor speed with lower A_{1c} values was not replicated in this subgroup analysis.

Diabetic ketoacidosis

DKA event rates were 2.0 per 100 patient years in the IT group (10.0% of patients) and 1.8 per 100 patient years in the conventional group (8.1% of patients). Among IT patients, rates were higher during periods of use of CSII pump (3.09/100 patient years) than during use of MDI (1.39/100 patient years, p=0.003) (Anonymous 1995a).

Weight gain

There was an increase of 33% in the mean adjusted risk of becoming overweight in the IT group compared with 9.3% in the conventional group. At 5 years, patients in the IT group had gained a mean of 4.6 kg more than patients receiving conventional therapy (Anonymous 2001).

Costs

Regarding costs, it was found that the annual cost of IT was approximately three times the cost of conventional therapy. MDI IT cost $4000 and CSII cost $5800 per year compared to conventional therapy ($1700 per year). Most of the difference in cost was related to more frequent outpatient visits and greater resources used in self care (DCCT 1995).

Quality of life

The effect of intensive diabetes treatment on patient QoL was assessed by the Diabetes QoL Measure, the Symptom Checklist–90R, the Medical Outcome Study 36-Item Short Form Survey, and intercurrent psychosocial events (Anonymous 1996b). The volunteers were followed for a mean of 6.5 years (range 3–9 years). QoL data were collected during annual visits. Of the volunteers, 99% completed the study, and more than 95% of scheduled tests were completed. The results showed that all analyses of quality of life, psychiatric symptom indexes, and psychosocial event data showed no differences between IT and conventional diabetes treatment.

18.1.5 Results of included studies

The study results are summarised in the table below for microvascular and macrovascular outcomes.

Table 18.4 Effects of intensive treatment on microvascular and macrovascular outcomes

Study ID	Outcome	Result		(95%CI) p	Comment
Macrovascular disease/risk factors					
NEJM 2005 (Nathan et al 2005)	Long-term incidence of cardiovascular disease: Mean 17 years follow-up				Decrease in HbA_{1c} significantly associated with decreased risk. Microalbuminuria and albuminuria were associated with a significant increase in the risk of CVD
	Cardiovascular events	46 among 31 IT	98 among 52 CT		
	Event rate per 100 patient years	0.38 IT	0.80 CT	p=0.007	
	Life table analysis of cumulative incidence of first cardiovascular event	IT reduced risk of any cardiovascular disease event by 42%		(9% to 63%) p=0.02	
		Risk of nonfatal MI, stroke or death from CVD decreased by 57% in IT group		(12% to 79%) p=0.02	
NEJM 1993 (DCCT 1993)	Progression of carotid intima-media thickness (measure of atherosclerosis)	Mean progression 0.032 mm in IT group and 0.046 mm in CT. Difference 0.013 mm		(0.003 to 0.24) p=0.01	After 6 years follow-up, no difference in thickness at baseline.
NEJM 1993 (DCCT 1993)	All major cardiovascular and peripheral vascular events combined; 41% risk reduction in IT group	(0.5 event per 100 pt years vs 0.8 event)		(–10% to 68%)	Young age of patients and exclusion at baseline of patients with risk factors contributed to small event number
	Development of hypercholesterolaemia (LDL >4.14 mmol/L)	34% reduction		(7% to 54%) p=0.02	

Study ID	Outcome	Result		(95%CI) p	Comment
Retinopathy and nephropathy					
JAMA 2002, NEJM 2000 (Anonymous 2000; DCCT/EDIC Research Group 2000; Writing Team for the DCCT/EDIC Research Group 2002)	Microvascular complications between end of DCCT and year 4 of EDIC Adjusted Odds Reduction (%)	3 step progression from no retinopathy	66%	(26% to 84%) p=0.006	Regarding risk of retinopathy, for each 10% decrease in HbA_{1c}, there was a 39% decrease in risk over the range of HbA_{1c} values. No glycaemic threshold above the nondiabetic range (4.0–6.05%) at which the risk of retinopathy was eliminated Regarding nephropathy, for every 10% decrease in HbA_{1c} there was a 25% decrease in the risk of microalbuminuria No glycaemic threshold for nephropathy was detected above the nondiabetic range of HbA_{1c}.
		Severe nonprolif or worse	76%	(52% to 88%) p<0.001	
		Microalbuminuria:	53%	(26% to 70%) p=0.002	
		Albuminuria	86%	(60% to 95%) p<0.001	
NEJM 1993 (DCCT 1993)	Microvascular complications after mean 6.5 yrs IT both prim prev and secondary intervention cohorts Risk reduction (%)	>3 step sustained retinopathy	63%	(52% to 71%) p<0.002	
		Severe non/proliferative retinopathy	47%	(15% to 67%) p<0.04	
		Microalbuminuria (>40 mg/24hr)	39%	(21% to 52%) p<0.0002	
		Albuminuria (>300 mg/24 hr)	54%	(19% to 74%) p<0.04	
Neuropathy					
NEJM 1993 (DCCT1993)	Clinical neuropathy at 5 years Exam+Nerve Conduction Studies (NCS) Both cohorts Excluding patients with neuropathy at baseline	Risk reduction 60%		(38% to 74%) p<0.04	Treatment effect results more from a significant deterioration in CT group rather than improvement in IT group

Study ID	Outcome	Result		(95%CI) p	Comment
Autonomic neuropathy					
Circulation 2009 (Pop-Busui et al 2009)	Cardiac autonomic neuropathy (CAN) 13–14 years after DCCT closeout	Prevalence of CAN significantly lower in IT group		(28.9% vs 35.2%) p=0.018	Although CAN prevalence increased in both groups, the incidence was significantly lower in the IT group.
Diabetologia 1998 (1998)	Cardiovascular autonomic nervous system function	Abnormally low RR less prevalent in IT group		(p<0.002)	Young , healthy subjects with low baseline rate of abnormality. Less than 3% DCCT subjects reported symptoms consistent with autonomic dysfunction.
		Incomplete bladder emptying		Statistically different between groups	
		confirmed orthostatic hypotension		No significant difference between groups	
		Decreased awareness of hypoglycaemia was greater in the IT group		p<0.0012	
Adolescents					
Diabetes 2010 (White et al 2010)	10-year progression of retinopathy; comparison of adults and adolescents	Adults: slower progression of diabetic retinopathy IT group		Adjusted hazard reduction 56% p<0.0001	
		Adolescents: no beneficial effect		32% p=0.13	
Diabetes Care (2008)	Severe hypoglycaemia or IT effects on cognitive performance in patients aged 13–19 years at entry	Neither hypo frequency nor ITT was associated with decline on any cognitive domain.			Higher values of A_{1c} were associated with modest declines in psychomotor and mental efficiency p<0.0.1
Journal of Pediatrics 1994 (DCCT 1994)	Microvascular complications in adolescents (13–17 years of age at entry) Combined cohorts	>3 step sustained retinopathy	61% RR	(30% to 78%) p<0.02	Major adverse event was nearly 3-fold increase in severe hypoglycaemia with IT
		Microalbuminuria	35% RR	(–7% to 60%)	

Study ID	Outcome	Result		(95%CI) p	Comment
Adverse effects					
Diabetes Care (2008) (18 yrs follow up)	Adolescents: Severe hypoglycaemia (coma or seizure)	200 episodes in 51 IT subjects 94 episodes in CT subjects			
Diabetes Care 2001 (Anonymous 2001)	Adults: Weight gain after 1 year	3.3kg in IT group	1.2kg in CT group		
	Weight gain at study end	4.75 kg more than CT group		p<0.0001	IT group more likely to be overweight than CT group by study end
Diabetes Care 1996* (Anonymous 1996b)	QoL	No difference in DQOL or SCL–90R		No significant difference	

A_{1c}, glycated haemoglobin: CT, conventional therapy; CAN, cardiac autonomic neuropathy; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; DQOL, Diabetes Quality of Life; LDL, low density lipoprotein; MI, myocardial infarction; QoL, quality of life; SCL-90R, Symptom Checklist–90R

18.1.6 Discussion

The body of evidence surrounding the issue of intensive diabetic management is dominated by the large DCCT/EDIC study (DCCT 1993; Nathan et al 2005). Two Level 1 studies incorporated the findings from the RCT phase of the DCCT published in 1993 (Lawson et al 1999; Stettler et al 2006). They both found that intensive diabetes management significantly reduced the risk of macrovascular events in people with type 1 diabetes. The NNT was 16 patients needing to receive IT for 10 years to prevent one macrovascular event (Stettler et al 2006) (assuming a typical incidence of 1 event per 100 person years. In the same study, the total number of events is small with an absolute number of 134 events in 11 293 person years. There was no significant difference found in macrovascular mortality between groups nor in the subgroup cardiac, peripheral or cerebrovascular disease.

The longer term follow up of the EDIC stage of the DCCT study provided more data on the less common macrovascular complications. This showed a significant reduction in risk of any cardiovascular disease event in the IT group (42% 95%CI: 9 to 63 p=0.02) (Nathan et al 2005). The risk of nonfatal MI, stroke or death from CVD decreased by 57% in the IT group. The decrease in HbA_{1c} was significantly associated with decreased risk. A 10% lower HbA_{1c} was associated with a hazard ratio of 0.80 (95%CI: 9% to 30%, p<0.001).

Regarding microvascular complications, data from the DCCT/EDIC showed a significant reduction in retinopathy progression. For every 10% decrease in HbA_{1c}, there was a 39% decrease in risk over the range of HbA_{1c} values. Regarding nephropathy, for every 10% decrease in HbA_{1c}, there was a 25% decrease in the risk of microalbuminuria. For both outcomes, no glycaemic threshold was detected above the nondiabetic range of HbA_{1c}.

There was a transient worsening of retinopathy with IT. The abnormalities found often disappeared by 18 months. Those with early worsening who were treated with IT ultimately had a 74% reduction (95%CI: 46% to 88%, p<0.001) in the risk of subsequent progression, compared with patients with early worsening who received conventional treatment. Hypoglycaemia was significantly higher in the IT group. The risk of severe hypoglycaemia was three times higher with IT. Weight gain was also significantly higher in the IT group.

The most recent publication from this trial examined differences between adolescents and adults in the persistence of the benefits of IT 10 years after completion of the study. The cohort comprised 1055 adults and 156 adolescents. It was reported that, at EDIC year 10, adults in the former IT group continued to show slower progression of diabetic subject retinopathy than those in the conventional group (adjusted hazard reduction 56%, p<0.0001), whereas in adolescents, this beneficial effect had disappeared (32%, p=0.13) (White et al 2010). It was reported that 79% of observed differences in the prolonged treatment effect between adults and adolescents at year 10 were explained by differences in mean HbA_{1c} during DCCT between adolescents and adults (8.9% vs 8.1%), particularly between the IT groups where the HbA_{1c} difference was greater (8.1% vs 7.2%).

18.1.7 Conclusion

Intensive diabetes management reduces the risk of both microvascular and macrovascular complications in type 1 diabetes. The adverse effects of this intervention include hypoglycaemia and weight gain. The evidence base for this question consists of two good quality Level I studies examining the effects of intensive glycaemic management on macrovascular outcomes, one fair-quality Level I study examining microvascular outcomes before the results of the DCCT and a series of Level II publications on the same RCT, published by the DCCT/EDIC group. Adverse effects of intensive glycaemic control are

summarised by a good-quality Level I study. Adverse events and the costs of IT are also reported by the DCCT trial writers. The evidence is consistent in the studies found. The findings are generalisable to the broader population; however, the applicability is limited to health-care systems that can provide the same level of resources demanded by intensive diabetes management.

18.1.8 Literature search strategy

The search was conducted between 18 November 2009 and 16 September 2010. Level I studies were considered first, with the plan to update with Level II studies as required.

Table 18.5. Search strategy, question 18.1

Database	Date searched	#	Search terms	Citations
Medline		1	Diabetes Mellitus, Type 1/	
		2	Intensive diabetes management.mp.	
		3	(Intensive glycemic control or intensive glycaemic control).mp.	
		4	(Intensive blood glucose control or blood glucose target or glycaemic target or glycemic target).mp.	
		5	(Glycem* target or glycaem* target).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	
		6	(Dcct edic research group or dcct edic study group or dcct research group or dcct skin collagen ancillary study group).au.	
		7	(Diabetes Control and Complications Trial).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	
		8	(Epidemiology of Diabetes Interventions and Complications Research Group).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	
		9	DCCT.mp.	
		10	EDIC.mp.	
		11	OR 2-10	
		12	AND 1-11	105
Cochrane				128
EMBASE				
Dare				
INAHTA				
Manual search				6
Total citations				239
Total non-duplicate citations				213

18.1.9 Evidence Matrix

Macrovascular

Q18.1	What is the effect of intensive glycaemic management on macrovascular complications?	
Evidence statement	Intensive glycaemic control in adolescents and adults with type 1 diabetes reduces the risk of cardiovascular disease.	
Evidence base	A	Level I evidence – two systematic reviews of low risk of bias and the DCCT/EDIC studies (Level II/III).
Consistency	A	Any cardiovascular event – a statistically significant difference was observed in all studies.
Clinical impact	A	
Generalisability	B	The DCCT was a large trial (n=1441). Children were not included in the DCCT; the age at baseline was 13–39 years. The age in the two systematic reviews was 18–42 years.
Applicability	A	The studies were not conducted at sites in Australia (the DCCT/EDIC studies were in the United States), but did include some rural and remote centres.
Other factors	None identified.	

Microvascular

Q18.1	What is the effect of intensive glycaemic management on microvascular complications?	
Evidence statement	Intensive glycaemic control in adolescents and adults with type 1 diabetes reduces the risk of microvascular outcomes.	
Evidence base	B	One Level II study of low risk of bias (DCCT), plus the long-term follow-up of the DCCT cohort (EDIC).
Consistency	NA	Only one study.
Clinical impact	A	
Generalisability	B	The DCCT was a large trial (n=1441). Children were not included in the DCCT; the age at baseline was 13–39 years.
Applicability	A	The studies were conducted in the United States, but did include some rural and remote centres.
Other factors	Intensive management in the DCCT referred to intensive glycaemic management, through a package of methods including MDI or CSII, frequent insulin dose adjustment, blood glucose monitoring at least four times per day and a weekly 3-am BG level, formal diabetes education, medical nutrition therapy, and physical activity advice. Such a package is not necessarily available at all centres in Australia. The incremental cost per life year gained was US$28 661, but this is not necessarily informative for the Australian setting (see Chapter 4 of the guidelines on costs of diabetes).	
Recommendation		
R18.1	Intensive glycaemic control should be implemented to reduce the risk of onset or progression of microvascular and development of macrovascular diabetes complications (Grade B).	

BG, blood glucose; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; MDI, multiple daily injections

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

18.2 Effectiveness of antihypertensive agents at controlling blood pressure and reducing complications

18.2.1 Blood pressure control

> Question 18.2 (i)
>
> How effective are antihypertensive agents at controlling blood pressure in type 1 diabetes?

This section of the report details studies examining the effect of antihypertensive agents on the blood pressure (BP) of patients with type 1 diabetes.

18.2.1.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 18.6.

Table 18.6 Criteria for determining study eligibility, question 18.2 (i)

Study design	NHMRC Level I or Level II (NHMRC intervention scale[a])
Population	Type 1 diabetes
Intervention	Antihypertensive agents: ACEI, ARB, beta antagonists, alpha antagonists, aldosterone antagonists, CCB, diuretics, centrally acting agents (see specific drugs in search table below)
Comparator	Any
Outcomes	Change in blood pressure reported as a primary outcome

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

18.2.1.2 Literature search summary

A total of 440 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title, with 416 publications excluded, as shown in Table 18.7. A total of 24 publications remained, and the full-text version of each of these publications was retrieved and reviewed.

Table 18.7 Search results, question 18.2 (i)

Stage	Notes	Number
Search summary	Manual	0
	Cochrane Library	41
	EMBASE	67
	Medline	200
	Dare	3
	INAHTA	0
Duplicates	Duplicates identified	18
Identified	Total identified	
Exclusion criteria	Wrong study type (Not NHMRC Level I or II)[a]	122
	Wrong population (Not in type 1 diabetes)	95
	Wrong intervention (Not an antihypertensive agent)	76
	Wrong comparator (Did not include a comparator)	
	Wrong outcome (Did not report BP as a primary outcome)	97
	Not in English	8
	Total excluded	416

Stage	Notes	Number
Meeting criteria	Total meeting inclusion criteria	24
Included	Total included studies	3

BP, blood pressure; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial

18.2.1.3 Included studies

After application of the exclusion criteria and consideration of full texts, three studies met the inclusion criteria (Parving et al 1989; Gerdts et al 1998; Andersen et al 2000).

18.2.1.4 Characteristics of included studies

Interventions

All studies were randomised controlled trials (RCTs).

Table 18.8 Characteristics of included studies

Reference and setting	Population	Intervention	Control	N	Duration
Andersen et al (2000) Denmark	Adult type 1 diabetes Nephropathy Hypertension	Losartan 50 mg Losartan 100 mg Enalapril 10 mg Enalapril 20 mg	Placebo	16	10 months
Gerdts et al (1998) Norway	Adult type 1 diabetes Hypertension Half nephropathy	Captopril	Doxazosin	35	31 weeks
Parving et al (1989) Denmark	Adult type 1 diabetes Nephropathy Normotension	Captopril 25–100 mg	no treatment	32	12 months

Andersen et al (2000)

Andersen et al (2000) aimed to compare the renal and haemodynamic effects of angiotensin II receptor blockers (ARB) and angiotensin converting enzyme inhibitors (ACEI) with placebo. Patients with BP >145/85 mmHg, persistent albuminuria (>300 mg/24 hour), diabetic retinopathy and duration of diabetes more than 10 years were allocated to 2 months of treatment with placebo or antihypertensive medication, in random order, and both participants and investigators were blinded. All antihypertensive medications were withdrawn before enrolment; however, five patients received frusemide during all treatment periods to prevent oedema. BPs were measured every 15 minutes during the day and 30 minutes during the night, over 24 hours. Values were averaged for each hour before calculating the 24-hour BP. There were no drop outs and no adverse effects. The 24-hour mean arterial BP and the 24-hour systolic and diastolic BPs were significantly reduced in all interventions compared with placebo ($p<0.05$). There were no significant differences between the interventions, as shown in Table 18.9. This small, short-term study showed that treatment with ACEI and ARB significantly reduced BP compared with placebo, in patients with more than 10 years of diabetes with hypertension, retinopathy and nephropathy.

Table 18.9 Results of Andersen et al (2000)

Intervention	Losartan 50 mg	Losartan 100 mg	Enalapril 10 mg	Enalapril 20 mg	Placebo
24-hour systolic BP mmHg – mean (±SD)	137 (4) [a]	135 (3) [a]	141 (4) [a]	135 (4) [a]	147 (3) [a]
24-hour diastolic BP mmHg – mean (±SD)	75 (1) [a]	76 (2) [a]	77 (2) [a]	73 (2) [a]	82 (2) [a]
24-hour mean BP – mean (±SD)	95 (2) [a]	96 (2) [a]	98 (3) [a]	93 (3) [a]	104 (2) [a]

BP, blood pressure; SD, standard deviation

[a] p<0.05 versus placebo

Gerdts et al (1998)

Gerdts et al (1998) studied the effect of doxazosin or captopril on left ventricular mass, BP and albuminuria. Of the 35 patients recruited, 23 had been previously treated with antihypertensive agents – of these, 19 were receiving ACEI and 3 had received doxazosin. A total of 11 patients had clinical nephropathy and 8 had incipient nephropathy. These patients were evenly split between intervention groups. No patient had serum creatinine more than twice the upper normal limit. Patients were randomised for treatment for 6 months. Neither patient nor investigator was blinded. Casual BP was the mean of the last 2 out of 3 consecutive readings while sitting using a conventional mercury sphygmomanometer. Patients' 24-hour BP was recorded at baseline and at the end of the study. The patients were started on 12.5 mg captoril twice daily with dose titration up to 200 mg per day. The doxazosin was started at 1 mg daily with dose titration up to 16 mg per day. The aim was a casual BP of 135/85 mmHg. Casual BPs were measured 2-weekly during the first month, and 4-weekly thereafter. Both agents resulted in a statistically significant reduction in BP from baseline, as shown in Table 18.10. It was reported that the reduction in mean 24-hour BP was similar in two groups although the p value was not reported. This was a small, nonblinded study showing statistically significant reductions in BP with ACEI or alpha–1 receptor blocker in hypertensive type 1 diabetics.

Table 18.10 Results of Gerdts et al (1998)

Intervention	Doxazosin		Captopril	
	Baseline	After treatment	Baseline	After treatment
Casual BP mmHg – mean (±SD)	116 (14)	106 (11) [a]	118 (11)	103 (11) [a]
24-hour systolic BP mmHg – mean (±SD)	156 (20)	147 (21)	152 (18)	145 (19)
Diastolic BP mmHg – mean (±SD)	86 (8)	79 (8) [a]	86 (10)	81 (10) [a]
24-hour BP – mean (±SD)	109 (12)	101 (11) [a]	108 (11)	103 (13) [a]

BP, blood pressure; SD, standard deviation

[a] p<0.05 versus baseline within group

Parving et al (1989)

The objective of Parving et al (1989) was to assess whether angiotensin converting enzyme (ACE) inhibition protects kidney function in diabetic nephropathy. The main outcome measures were albuminuria, arterial BP and glomerular filtration rate (GFR). The records of all patients with type 1 diabetes attending the outpatient clinic in a tertiary hospital were examined. Patients were invited to participate if they were normotensive with nephropathy (persistent albuminuria >300 mg/24 hour), and had serum creatinine <120 μmol/L and had an average of three or more BP readings below 150/90 mmHg. The 33 patients who gave informed consent were matched in pairs according to albuminuria, BP and GFR. These pairs were randomly assigned to receive captopril or no antihypertensive treatment. Treatment with captopril was aimed primarily at preventing the rise in arterial BP and secondarily at reducing the mean BP by 5 mmHg. Captopril doses were adjusted every 3 months to a maximum of 50 mg twice daily. There were no drop outs after randomisation, and no severe side effects occurred. In two patients a diuretic was added to control BP. Mean arterial BP fell by 3 mmHg (standard error [SE] 2) in the captopril group and rose by 6 (SE 1) mmHg in the controls. Arterial BP was significantly lower in the captopril treated group than in the untreated controls ($p<0.05$). This was due to a significant rise in mean arterial BP in the control group ($p<0.01$) and a nonsignificant reduction in these values in the captopril treated group, as shown in Table 18.11. The authors concluded that ACE inhibition with captopril can arrest the progressive rise in albuminuria in normotensive type 1 diabetes with nephropathy.

Table 18.11 Results of Parving et al (1989)

Change in arterial BP after 12 months (mmHg)	Captopril	Control
Systolic BP – mean (SE)	–6.0 (2.8)	6.8 (1.9) [a]
Diastolic BP – mean (SE)	–0.9 (2.0)	5.2 (1.5) [a]

BP, blood pressure; SE, standard error

[a] Captopril treated group versus controls ($p<0.01$)

18.2.1.5 Discussion

Andersen et al (2000) showed a statistically significant reduction in 24-hour mean, 24-hour systolic and 24-hour diastolic BP after 2 months' treatment with ACEI or ARB compared to placebo. Baseline BP was 147/82 (3/2) and baseline albuminuria was 1156 (643–2080) mg per 24 hours. There were no significant differences between the two classes of drugs. The reduction compared to placebo using ACEI or ARB ranged from 12/9 mmHg to 6/5 mmHg for the systolic and diastolic BPs, respectively, and from 11 to 6 mmHg mean BP, comparing the various antihypertensive treatments with placebo. This was a small, short-term trial with only 16 subjects and a wide range of baseline albuminuria. The long-term effects are unknown.

Gerdts et al (1998) demonstrated a statistically significant reduction in casual and 24-hour BP from baseline to the end of treatment, with both doxazosin and captopril, of about 10 mmHg in all readings. The baseline population were patients with known hypertension and half had nephropathy (microalbuminuria or macroalbuminuria). The doses of both drugs were titrated 2-weekly during the first month of treatment to a target of 135/85 mmHg, but only a minority of patients reached the target.

Parving et al (1989) demonstrated, in a nonplacebo controlled study of captopril 25–50 mg daily, that mean arterial BP (not 24-hour BP monitoring as in the previous studies) fell by

3 mmHg (SE 2) in the captopril group and rose by 6 (SE 1) mmHg in the controls, compared to baseline. There was a significant rise in mean arterial BP and a nonsignificant reduction in the captopril group. The dose of captopril used started at 12.5 mmHg and was adjusted every 3 months to a maximum of 50 mg twice daily.

18.2.1.6 Summary of results

Table 18.12 Comparison of results of included studies

Reference	Intervention	Comparator	Difference in 24-hour mean BP (mmHg) (intervention versus comparator)	p
Andersen et al (2000)	Losartan 50 mg	Placebo	9	<0.05
	Losartan 100 mg	Placebo	8	<0.05
	Enalapril 10 mg	Placebo	6	<0.05
	Enalapril 20 mg	Placebo	11	<0.05
Gerdts et al (1998)	Captopril	Baseline	5	<0.05
	Doxazosin	Baseline	8	<0.05
Parving et al (1989)	Captopril (mean 40 mg)	No treatment	9	<0.01

BP, blood pressure

18.2.1.7 Conclusion

Only three Level II studies addressing this question were found. This was because of the almost universal use of proteinuria rather than BP control as a primary outcome for studies on antihypertensive medications in type 1 diabetes. Although all studies included randomisation, only one was double blinded. The results of two of the three studies were consistent in that use of an antihypertensive agent reduced BP compared to baseline (Gerdts et al 1998) or to placebo (Andersen et al 2000). Parving et al (1989) showed that arterial BP was statistically significantly lower in the captopril group compared to the nontreated group at study end, but also that there was a significant increase in BP in the nontreatment group, and a nonsignificant reduction in BP in the captopril group compared to baseline.

No statistically significant differences between the various antihypertensive agents were found in any study. The reduction in BP was approximately 4–10 mmHg comparing ACEI or ARB to placebo, or alpha antagonist to ACEI. These readings were made with 24-hour ambulatory BP machines. Casual BP (mean of the last two of three seated BP readings taken with a conventional mercury sphygmomanometer) was reported by Gerdts et al (1998). The authors showed the casual BP was statistically significantly reduced in both the captopril and doxazosin groups. The difference being 19 mmHg systolic and 12 mmHg diastolic in the captopril group (end of study compared to baseline) and 15 mmHg systolic and 7 mmHg diastolic in the doxazosin group. Parving et al (1989) did not use 24-hour continuous BP monitoring, and measured two BP readings during outpatient clinic visits every 3 months. The authors showed a statistically significant difference in casual BP of 6 mmHg systolic and 0.9 mmHg diastolic ($p<0.01$) between treatment and control arms. The data for change from baseline for each group was not given, although the difference was reported as a significant rise in arterial BP in the control group ($p<0.01$) and a nonsignificant reduction in these values in the captopril group.

All of these studies were quite small, with only 16–35 participants. Two studies used hypertensive populations, one (Parving et al 1989) did not. Two of the studies had nephropathy as an inclusion criteria and one (Gerdts et al 1998) did not. All studies were set

in Scandinavia, and the populations were recruited from tertiary institutions' outpatient clinics. The drop out rate was negligible in each study, and compliance as measured by tablet count was good. The dose titration required 2-weekly follow-up to achieve targets in the study by Gerdts et al (1998). All studies were of short duration; thus, the long-term beneficial and adverse effects are unknown.

18.2.1.8 Literature search strategy

The search was conducted in July 2010. Level I studies were considered first, with the plan to update with Level II studies as required. The Medline search strategy and a summary of citations retrieved from other searches are shown in Table 18.13.

Table 18.13 Search strategy, question 18.2 (i)

Database	Date searched	#	Search terms	Citations
Medline		1	Diabetes Mellitus, type 1/	52 390
		2	Antihypertensive Agents/	43 503
		3	Adrenergic alpha-Antagonists/	13 383
		4	(Prazosin or terazosin or phenoxybenzamine).mp.	17 460
		5	Adrenergic alpha-Agonists/	10 352
		6	(Methyldopa or clonidine or moxonidine).mp.	19 642
		7	Aldosterone Antagonists/	2 545
		8	(Spironolactone or eplerenone).mp.	6 198
		9	Adrenergic beta-Antagonists/	32 907
		10	(Atenolol or metoprolol or carvedilol or bisoprolol).mp.	13 774
		11	Angiotensin-Converting Enzyme Inhibitors/	25 141
		12	(Captopril or enalapril or fosinopril or lisinopril or perindopril arginine or perindopril erbumine or Quinapril or ramipril or trandolapril).mp.	21 572
		13	Angiotensin II type 1 Receptor Blockers/	4 945
		14	(Candesartan or eprosartan or irbesartan or olmesartan or temisartan).mp.	3 712
		15	Calcium Channel Blockers/	30 920
		16	(Non dihydropyridine or diltiazem or verapamil or Dihydropyridine or amlodipine or felodipine or lercanidipine or nifedipine).mp.	50 519
		17	Diuretics/	22 424
		18	(Thiazide or hydrochlorothiazide or indapamide or Potassium-sparing diuretic or amiloride).mp.	19 609
		19	(Hydralazine or minoxodil).mp.	5 098
		20	or/2–19	239 015
		21	1 and 20	934
		22	limit 21 to (english language and humans)	745

Database	Date searched	#	Search terms	Citations
		23	randomised controlled trial.mp. or 'single blind procedure'/exp or 'single blind procedure'.mp. or 'double blind procedure'/exp or 'double blind procedure'.mp. or 'triple blind procedure'/exp or 'triple blind procedure'.mp. or 'crossover procedure'/exp or 'crossover procedure'.mp. or 'placebo'/exp or placebo.mp. or randomi?ed:ab,ti.mp. or rct:ab,ti.mp. or 'random allocation':ab,ti.mp. or 'randomly allocated':ab,ti.mp. or 'allocated randomly':ab,ti.mp. or 'single blind':ab,ti.mp. or 'single blinded':ab,ti.mp. or 'double blind':ab,ti.mp. or 'double blinded':ab,ti.mp. or 'treble blind':ab,ti.mp. or 'treble blinded':ab,ti.mp. or 'triple blind':ab,ti.mp. or 'triple blinded':ab,ti.mp. or placebo*:ab,ti.mp. or 'prospective study'/exp or 'prospective study'.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	419 296
		24	22 and 23	200
		25	limit 21 to (english language and humans)	
Cochrane				41
EMBASE				67
Dare				3
INAHTA				0
Manual search				0
Total citations				24
Total non-duplicate citations				3

18.2.1.9 Evidence Matrix

Q18.2 (i)	How effective are antihypertensives at reducing blood pressure in type 1 diabetes?	
Evidence statement	Level II evidence shows that antihypertensive agents are effective at lowering blood pressure.	
Evidence base	B	Three RCTs, two of high risk of bias and one of low risk of bias.
Consistency	A	The studies were consistent in magnitude and direction.
Clinical impact	C	A 10 mmHg reduction in systolic pressure and a 5 mmHg reduction in diastolic pressure. The impact is most applicable to the adult population; this evidence has already been incorporated into clinical practice.
Generalisability	C	The studies had small sample sizes (n=16–35) and were in people with diabetes, with complications.
Applicability	B	All studies were conducted in northern Europe.
Other factors	None identified.	

ACE, Angiotensin converting enzyme; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

18.2.2 Effectiveness of antihypertensive agents at reducing complications

> Question 18.2 (ii)
>
> How effective are antihypertensives at reducing or preventing retinopathy, nephropathy, neuropathy, cardiovascular disease and autonomic neuropathy?

This chapter examines the effectiveness of antihypertensives (AHT) at reducing or preventing retinopathy, nephropathy, neuropathy, cardiovascular disease and autonomic neuropathy.

18.2.2.1 Criteria for determining study eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 18.14.

Table 18.14 Criteria for determining study eligibility, question 18.2 (ii)

Study design	NHMRC Level I or II[a]
Population	Type 1 diabetic subjects
Intervention	Antihypertensive agents: alpha-blockers, beta-blockers, calcium channel blockers, diuretics, centrally acting agents
Comparator	Placebo or no treatment
Outcomes	Retinopathy, neuropathy, autonomic neuropathy, cardiovascular disease, nephropathy

NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I, a systematic review of Level II studies; Level II, a randomised controlled trial

18.2.2.2 Assessment of study eligibility

Publications identified in the literature search were reviewed using the criteria shown in Table 18.15 and Table 18.16, applied hierarchically, to determine which publications to exclude. Microalbuminuria was included under the definition of nephropathy. Studies regarding nephropathy were excluded if there was no measurement of urine albumin or protein excretion.

18.2.2.3 Literature search summary

Table 18.15 Search results for Level I studies, question 18.2 (ii)

Stage	Notes	Number
Search summary	Manual	0
	PubMed	7
	Cochrane Library	5
	EMBASE	98
	INAHTA	0
	Bibliographies etc	1
	Total	111
Duplicates	Duplicates identified	4
Identified	Total identified	0
Exclusion criteria	Wrong study type (not NHMRC Levels I or II) [a]	55
	Wrong population (not type 1 diabetic subjects or results not extracted for type 1 diabetic subjects)	24
	Wrong intervention or test (not an antihypertensive agent)	11

Stage	Notes	Number
	Wrong outcome (not nephropathy, neuropathy, retinopathy, cardiovascular disease or autonomic neuropathy)	8
	Not in English	7
	Only 1 RCT included	1
Meeting criteria	Total meeting inclusion criteria	
Included	Total included studies	1

NHMRC, National Health and Medical Research Council; RCT, randomised controlled trial

[a] NHMRC intervention scale: Level I, a systematic review of level II studies; Level II, a randomised controlled trial

Table 18.16 Search results for Level II studies, question 18.2 (ii)

Stage	Notes	Number
Search summary	Manual	0
	PubMed	200
	Cochrane Library	0
	EMBASE	83
	INAHTA	0
	Bibliographies etc	3
	Total	286
Duplicates	Duplicates identified	39
Exclusion criteria	Wrong study type (not NHMRC Levels I or II)[a]	74
	Wrong population (not type 1 diabetic subjects or results not extracted for type 1 diabetic subjects)	67
	Wrong intervention or test (not an antihypertensive agent)	34
	Wrong outcome (not nephropathy, neuropathy, retinopathy, cardiovascular disease or autonomic neuropathy)	30
	Not in English	8
	Included in Level 1 study above	10
	Studies with n<100	17
Included	Total included studies	7

18.2.2.4 Characteristics of included studies

Level I studies

After applying exclusion criteria, six Level I publications remained, and the full-text version of each of these publications was retrieved and reviewed. Four of these publications did not extract separate results for subjects with type 1 diabetes (Strippoli et al 2004; 2006; Strippoli et al 2006; Sarafidis et al 2008). Of the two remaining studies, the angiotensin converting enzyme (ACE) Inhibitors in Diabetic Nephropathy Trialists (ACEI Trialists 2001) examined the effects of AHTs on nephropathy on patient-level data for 698 subjects with type 1 diabetes and microalbuminuria. The most recent included study of this meta-analysis was published in 2001. The other Level I study that met the inclusion criteria, Mohamed et al (2007), examined retinopathy as the outcome of interest. Only one randomised controlled trial (RCT) was included in that systematic review and a large Level II study – DIRECT 2008

(Chaturvedi et al 2008) – had been published since then. Thus, the primary study – EUCLID (Chaturvedi et al 1998) – was included in this review, rather than the Level I study itself.

Level II studies

A total of 200 Level II studies were identified in the Medline search, filtered for RCT study type. These studies were supplemented by searches of EMBASE and references identified in bibliographies. As two large Level II studies that examined nephropathy were found, Level II studies of fewer than 100 participants were not included in the body of evidence for this outcome.

Studies by outcome measure

One Level I study (ACEI Trialists 2001) and three Level II studies regarding nephropathy were included. The systematic review analysed patient level data on 698 people with type 1 diabetes with microalbuminuria. One of the RCTs not in the Level I study reported the results of the three DIRECT studies (Bilous et al 2009). The report by Mauer et al (2009) (referred to here as the RASS study) reported change in fractional glomerular volume in normotensive normoalbuminuric patients with type 1 diabetes (Mauer et al 2009). The other RCT included in this systematic review was on patients with macroalbuminuria (Lewis et al 1993). A report by the Microalbuminuria Captopril Study Group (1996) was excluded because the original data was included in the Level I study by the ACE Inhibitors in Diabetic Nephropathy Trialists.

Regarding retinopathy, three articles met the inclusion criteria. Chaturvedi et al (2008) reported on the DIRECT-Prevent 1 and DIRECT-Protect 1 trials. These authors also published a report using retinopathy data from the EUCLID trials (Chaturvedi et al 1998). The other study examined nephropathy and retinopathy as outcomes (Mauer et al 2009).

For neuropathy, two studies were found (Malik et al 1998; Maser and Lenhard 2003) that did not separate the results of patients with type 1 and type 2 diabetes, and therefore did not meet inclusion criteria. No other studies examining neuropathy were found.

Regarding autonomic neuropathy, three studies met inclusion criteria. These studies examined cardiac autonomic neuropathy (Ebbehøj et al 2002; Ebbehøj et al 2004; Lanza et al 2007).

No studies examining the effect of AHT on cardiovascular disease in patients with type 1 diabetes were found in this search; however, a protocol for a trial in adolescents with type 1 diabetes examining the effect of ACE or statin on renal and cardiovascular outcomes was found (AdDIT Research Group 2009). A study of ACE or angiotensin II receptor blocker (ARB) on lung volume function in patients with autonomic neuropathy did not separate the results for type 1 and type 2 diabetes, and thus was not included (Didangelos et al 2006).

18.2.2.5 Results of included studies

Nephropathy

Table 18.17 Study characteristics

Reference and setting	Population characteristics	n	Duration active treatment	Intervention	Comparator	Outcome	Quality
Mauer et alet al (2009)	Adult, type 1 diabetes Normotensive Normoalbuminuric	285	5 years	Enalapril or losartan or placebo		Change in Vv (mes/glom) AER, GFR, BP, retinal fundus photography	Good
DIRECT Renal – Bilous et al (2009) 309 study sites in 30 countries	Adult type 1 diabetes Normotensive Normoalbuminuric	1421	4 years	Candesartan 32 mg	Placebo	Primary: incidence of microalbuminuria Secondary: rate of change in urinary AER	Good
ACEI Trialists (2001) meta-analysis	Type 1 diabetes subjects Normotensive Microalbuminuric Trial: n=10, >1year follow-up. AER measured twice	12 trials 698 patients	At least 1 year follow-up	ACE inhibitors	Placebo or nonintervention group	AER	Good
Lewis et al (1993) Collaborative study group; 30 clinical centres	Type 1 diabetes Adult Retinopathy and macroalbuminuria Creatinine <221	207	3 years	Captopril	Placebo	Serum creatinine Combined: death, dialysis and transplantation	Good

ACE, angiotensin converting enzyme; AER, albumin excretion rate; BP, blood pressure; GFR, glomerular filtration rate; Vv (mes/glom), mesangial fractional volume

Mauer et alet al (2009)

The aim of the 5-year multicentre, double-blind placebo-controlled RCT by Mauer et alet al (2009) was to assess the effect of renin-angiotensin system (RAS) blockade with either an ACE or ARB on both renal and retinal morphologic features in normotensive patients with type 1 diabetes and normoalbuminuria. This study was set in the United States and Canada. The prespecified primary endpoint was a change in the fraction of glomerular volume occupied by mesangium (the mesangial fractional volume). Secondary renal endpoints included changes in AER and glomerular filtration rate (GFR). After the study started, another study was added with an a priori endpoint of a progression of diabetic retinopathy of two or more steps. A total of 285 patients of more than 18 years with blood pressure (BP) below 135/85 mmHg, not on AHT and with an AER above 20 mcg/minute were randomised to either enalapril 10 mg daily, losartan 50 mg daily or daily placebo. During the study, doses were doubled due to new data indicating generated reduction in proteinuria with higher doses. Fifteen patients received the doubled dose for an average of 2.9 years. Follow-up was for 5 years with measures of BP, pill counts and AER quarterly. Biopsy was performed before randomisation and 5 years later. Retinopathy was graded via stereoscopic photography as per the Early Treatment Diabetic Retinopathy Study (ETDRS) fields at baseline and 5 years.

There was no significant difference between the groups at baseline. Medication adherence was about 85%, and overall rate of visit attendance was over 93%, with rates similar across all groups. Change in mesangial fractional volume between baseline and 5 years compared with placebo was not significant, with either enalapril (p=0.15) or losartan (p=0.17). The 5-year cumulative incidence of microalbumiuria was 6% in the placebo group; the incidence was higher with losartan (17% p=0.01) but not with enalapril (4% p=0.96)

The AER increased significantly from baseline in the losartan group (p=0.04) but not in any other group. Compared with placebo, the 5-year average rate was higher by 4 mcg/minute with losartan (p=–0.3) but was not significantly higher with enalapril (p=0.47). The 5-year cumulative incidence of microalbuminuria was higher with losartan than placebo (17% vs 6%, p=0.01) but was not significantly higher with enalapril (4% vs 6%, p=0.96).

Serious adverse events were few and similar between groups. There were three deaths. Similar numbers in each group had hypoglycaemia or ketoacidoses. Chronic cough occurred in more patients in the enalapril group. There were three biopsy-related adverse events.

This was a good quality RCT with less than 15% loss to follow-up. Study doses were doubled during the study due to new data and the doubled dose was received for an average of 3 years. The original study was powered to detect a change in mesangial fractional volume. The study findings are generalisable to those patients matching the inclusion criteria (normotensive, microalbuminuric adult patients with good compliance) and the health-care settings are applicable to Australia.

DIRECT (Bilous et al 2009)

This publication reported on the results of three multicentre RCTs that were set up to investigate whether candesartan could prevent development or progression of diabetic subject retinopathy in normoalbuminuria subjects with type 1 and 2 diabetes. The incidence of microalbuminuria was a prespecified primary endpoint. The primary outcome was incidence and progression of retinopathy. The rate of change in urinary AER (UAER) was a prespecified secondary endpoint. These analyses make up the DIRECT-Renal study.

The DIRECT-Prevent 1 trial was set up to investigate the effect of candesartan on the incidence of retinopathy. A total of 1421 normotensive (sitting BP ≤130/85 mmHg), normoalbuminuric (UAER<20 microg/min) adult type 1 diabetic patients without retinopathy were recruited. The baseline population had a mean age of 30 years and mean duration of diabetes of 6.7 years. The average HbA_{1c} was 8.1% and the baseline UAER was 4.5 (standard deviation [SD] 3.0–6.5) (Sjolie et al 2005). These patients were randomly assigned to either candesartan or placebo. All patient results were available for intention-to-treat (ITT) analysis; however, 106 discontinued from the treatment arm of the trial compared to 92 from the placebo arm. UAER was measured in two, timed overnight collections by using nephelometry at baseline and annually thereafter. The lower limit of detection of albumin concentration was 20 mcg/L, with a maximum coefficient of variation of 5%. The patients who developed microalbuminuria (UAER ≥20 mcg/minute) in one or both urine samples at any time were asked to provide two more samples. If three of four of these samples were positive, this was considered microalbuminuria and was treated with open label ACE inhibitor (ACEI) therapy. Patients who were or became hypertensive (BP >140/85 mmHg) but whose UAER remained normal could be prescribed any non-RAS blocking AHT. The number of patients who developed microalbuminuria did not differ between the intervention and control groups. The incidence of microalbuminuria per 1000 patient years was 6 (95% confidence interval [CI]: 3.5 to 9.3) in the candesartan arm and 5 (95%CI: 3.1 to 8.7) in the placebo arm. The hazard ratio (HR) was 1.08 (0.54 to 2.19).

The DIRECT-Protect 1 trial investigated the effect of candesartan on the progression of mild or moderate retinopathy. A total of 1905 adult, normotensive and normoalbuminuric patients with type 1 diabetes were recruited. These patients scored between 20/10 and 47/47 as a retinal grading level, as opposed to the DIRECT-Prevent 1 cohort who scored 10/10. The mean age of these patients was 32 years, duration of diabetes 11 years (compared to 6.7 in the primary prevention cohort) and mean HbA_{1c} 8.5%, with baseline UAER 5.0 (SD 3.5–7.5) (Sjolie et al 2005). These patients were randomly assigned to candesartan or placebo, with complete data for ITT analysis; 132 discontinued from the treatment arm and 165 from the placebo arm. The UAER measurements were as noted above. There was no difference in the number of patients who developed microalbuminuria between groups. The incidence of microalbuminuria per 1000 patient years (95%CI) was 16 (12.8 to 20.9) in the candesartan arm and 16 (12.6 to 20.7) in the placebo arm. The HR was 1.03 (0.72 to 1.46).

In summary, this analysis shows that candesartan had no effect on the incidence of microalbuminuria over 4.7 years in normoalbuminuric and normotensive patients with type 1 diabetes. This study was not powered for a renal endpoint. The microalbuminuria event rate was lower than in many previously published studies. The overall median baseline UAER of 6 mcg/minute in DIRECT-Renal was low, such that the rate of change from baseline may have been too slow to detect over the 4.7-year follow-up. The patients also had a low baseline burden of vasculopathy.

ACE Trialists (2001)

This meta-analysis set out to determine whether response of albumin excretion rate to ACEI has a threshold in patients with type 1 diabetes and microalbuminuria, and to examine treatment effect according to covariates. The trials were restricted to nonhypertensive adult patients, to obviate the confounding factor of other AHT being used in control groups for trials including hypertensive type 1 diabetic subjects. The definition of normotension used in early trials differs to current usage, and about two thirds of the patients included in this meta-analysis had normal BP according to current standards. Patients also had microalbuminuria (albumin excretion rate of 20–200 micrograms/minute at baseline). Trials had to include at least 10 patients and at least 1 year of follow-up. Absolute rates of progression to macroalbuminuria and regression to normoalbuminuria were considered as outcomes. These were defined as an albumin excretion rate greater than 200 mcg/minute on two successive occasions at least 3 months apart. Regression to normoalbuminuria was defined as an AER less than 20 mcg/minute at two consecutive visits.

The results of a systematic search were raw data for 698 patients from 12 identified trials. The included trials had a modal follow-up period of 2 years with only two trials continuing for 4 years. The most common ACEI were captopril and lisinopril.

The pooled analysis showed that in patients receiving ACE inhibitors, progression to macroalbuminuria was reduced (odds ratio [OR] 0.38 (95%CI: 0.25 to 0.57) and the OR for regression to normoalbuminuria was 3.07 (CI: 2.15 to 4.44). At two years, AER was 50.5% (CI: 29.2% to 65.5%) lower in treated patients than placebo.

The estimated treatment effect varied by baseline albumin excretion rate: 74.1% in patients with a rate of 200 mcg/minute and 17.8% in patients with a rate of 20 mcg/minute (p=0.04). Adjustment for change in BP attenuated the treatment difference in AER at 2 years to 45.1% (CI: 18.6% to 63.1%, p<0.001).

Power was retained by restricting analyses to studies with at least 2 years of follow up (10 of 12 studies) and using the full 2 years of data for analysis. When the 2-year data were used, the albumin excretion rate was 53.6% lower at 2 years in patients receiving ACEI than in those receiving placebo (CI: 37.4% to 65.6%). Adjustment for baseline covariates (sex, age, diabetes duration, HbA_{1c} and BP), in addition to the initial adjustment for baseline albumin excretion rate, had no impact on the treatment effect. The model selected for analyses provided different estimates of the treatment effect according to length of follow-up because the treatment effect plateaued with longer follow-up. Thus, the analysis was performed using a standard follow-up length of 2 years. Adjustment for BP after randomisation had little impact on treatment effects of ACE on AER. However, the treatment effect was strongly influenced by baseline AER; patients with the highest levels at baseline showed the greatest reduction at follow-up.

This meta-analysis described a relevant question and the search strategy was restricted to one database. Patient level data was obtained from all investigators. There was no record of study quality assessment. The heterogeneity statistic was insignificant. The study population was all adults. This was a good quality study.

Lewis et alet al (1993)

This study by the Collaborative Study Group was set in 30 clinical centres, although the locations were not specified. This was a double-blind RCT to determine whether captopril is more effective in slowing the progression of diabetic subject nephropathy than agents that act primarily by reducing BP. Adult patients with diabetes diagnosed before 30 years of age who had retinopathy, urinary protein excretion of at least 500 mg/24 hours and a serum creatinine of less than or equal to 221 micromol/L. Eligibility was not affected by previous BP status or previous need for AHTs. Patients receiving ACE or calcium channel blocker (CCB) were eligible, provided the trial BP range could be met without these treatments. The intervention was captopril 25 mg three times a day or placebo. The blood pressure goals were a diastolic BP of less than 90 mmHg and a systolic BP of less than 140 mmHg. The average of two consecutive seated BPs taken 30 seconds apart was recorded as the BP for that visit. Serum creatinine and 24-hour urinary excretion of creatinine, protein and urea were measured at each visit. The primary study endpoint was doubling of creatinine to at least 177 micromols/L. Secondary endpoints were time to death or dialysis and renal transplantation, changes in renal function in terms of creatinine, and 24-hour protein excretion.

A total of 409 patients were randomised. The baseline characteristics were similar, except that the urinary protein excretion was higher in the placebo group than in the captopril group (p=0.02). A total of 59% of patients in the placebo group and 60% in the treatment group were receiving AHT at baseline; 301 patients completed their final scheduled visit.

Regarding doubling of creatinine, 25 patients in the captopril group and 43 in the placebo group had a doubling of serum creatinine (p=0.007). There was a 48% risk reduction in the captopril group (95%CI: 16 to 69%). Treatment with captopril was associated with a reduction in the risk of the combined endpoints of death, dialysis and transplantation (95%CI: 18% to 70%, 23 patients in the captopril group and 42 in the placebo group, p=0.006). An aggregate analysis over the 4 years of the study revealed significantly less proteinuria in the captopril group (p=0.001). The most frequent condition that prompted discontinuation of treatment was myocardial infarction (MI), congestive cardiac failure (CCF) and stroke.

There was a significant difference between groups in the use of beta-blockers during the first 12 months of the study, but no significant differences in the use of other agents except for diuretic use at 24 months. Other agents used included labetalol, clonidine, methyldopa, prazosin, hydralazine, guanabenz, terazosin and minoxidil.

The study was designed to determine whether captopril was associated with an effect that was independent of its role as an AHT. The BP reduction between groups was similar. The inclusion of mean arterial pressure as a time-dependent covariate did not alter the estimated risk ratio for the primary endpoints.

This was a good quality study based in the reporting of randomisation, blinding and ITT. The results are generalisable to adult type 1 diabetes patients with nephropathy, who are not taking calcium channel blockers and have blood pressure kept to the study target.

Table 18.18 Summary of results: nephropathy

Mauer et alet al (2009)	No significant difference in mesangial fractional volume between groups Albumin excretion rate increased by 4.0 mcg/minute with losartan (p=0.03) vs placebo (5 year average). No increase with enalapril. Significant increase in 5-year cumulative incidence microalbuminuria in losartan (17% p=0.01) vs placebo but not with enalapril (4%, p=0.96)			
DIRECT: Renal Bilous et al (2009)		Candesartan	Placebo	Hazard ratio (95%CI)
	DIRECT-Prevent 1			
	Incidence of microalb/1000 patient years	6 (3.5–9.2)	5 (3.1–8.7)	1.08 (0.54 to 2.19)
	DIRECT-Protect 1			
	Incidence of microalb/1000 patient years	16 (12.8–20.9)	16 (12.6–20.7)	1.03 (0.72 to 1.46)
	Pooled study population, HR (candesartan vs placebo) 0.95 (95%CI: 0.078 to 1.16,p=0.06)			
ACEI Trialists (2001)	Progression to macroalbuminuria with ACEI vs placebo (OR 0.38 95%CI: 0.25 to 0.57) Regression to normoalbumiuria with ACEI vs placebo (OR 3.07CI: 2.15 to 4.44)			
Lewis et al (1993)	RR 48% in doubling of serum creatinine in captopril group (95%CI: 16 to 69%) RR 50% combined death, dialysis and transplantation (95%CI: 18 to 70%)			

ACEI, angiotensin converting enzyme inhibitor; CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, risk ratio

Retinopathy

Table 18.19 Study characteristics

Reference	Population	N	Median follow-up	Intervention	Comparator	Outcome	Quality
Mauer et alet al (2009)	Adult Type 1 diabetes Normotensive Normoalbuminuria	285	5 years	Losartan 100 mg or enalapril 20 mg or placebo		Progression of 2 steps or more	Good
DIRECT-Prevent 1 – Chaturvedi et al (2008) 309 centres	Adult Type 1 diabetes normoalbuminuric Normotensive No retinopathy	1 421	4.7 yrs	Candesartan 32 mg	Placebo	Incidence of retinopathy	Good
DIRECT-Protect 1 – Chaturvedi et al (2008) 309 centres	Adult Type 1 diabetes Normoalbuminuric Normotensive Mild nonproliferative to mod severe nonproliferative)	1 905	4.8yrs	Candesartan 32 mg	Placebo	Progression of retinopathy	Good
EUCLID 1998 – Chaturvedi et al (1998) 15 European centres	Type 1 diabetes Adults Normotensive Normoalbuminuric or microalbuminuric	409	2 years	Lisinopril 20 mg	Placebo	Progression, development and regression of retinopathy	Fair

Mauer et alet al (2009)

This study has been described above. Regarding retinopathy, 88% competed the study. There were no significant differences at baseline. At baseline 34% of patients had no diabetic subject retinopathy, 40% had minimal nonproliferative retinopathy, and 9% had moderate to severe nonproliferative retinopathy.

Progression in diabetic retinopathy of two steps or more occurred in 38% patients on placebo and 25% on enalapril (p=0.02) and 21% on losartan (p=0.008). The odds of progression was reduced by 65% with enalapril (OR vs placebo 0.35 95%CI: 0.14 to 0.85) and by 70% with losartan (OR vs placebo 0.3; 95%CI: 0.12 to 0.73). These effects remained the same after adjustment for BP and time to doubled AHT dose.

The quality of this study is good, but the original study was powered to detect a change in mesangial fractional volume and retinopathy was added as an outcome after the trial had started.

DIRECT-Prevent 1 (Chaturvedi et al 2008)

Described above, DIRECT-Prevent 1 recruited normotensive, normoalbuminuric patients with type 1 diabetes, without retinopathy, to assess whether candesartan could reduce the incidence of retinopathy. Retinopathy was assessed by seven-field stereo photographs according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Individuals with other eye conditions that affect photography were excluded, as were those with

valvular disease, MI, cerebrovascular accident (CVA) history or renal impairment (creatinine ≥110 women, 130 men). Assessors were blinded to treatment group. The prespecified outcome measure was overall change in retinopathy status from baseline to final visit. A total of at least a two-step change (one step in each eye or at least two steps in one eye) for the participant defined incidence of retinopathy. 1421 participants with a median age of 29 years were randomised. The baseline BP was 116/72 and the baseline diabetes duration was 6.8 years. Similar numbers withdrew from each arm of the trial; however, ITT was complete. Incidence of retinopathy was 31% in the placebo group and 25% in the candesartan group, resulting in a nonsignificant relative risk reduction of 18% due to candesartan (95%CI: 0.67 to 1.00, p=0.051).

A post hoc analysis was performed to define incidence as a total of at least a three-step change for the participant from baseline. The application of this more stringent definition resulted in statistical significance in the candesartan group. The overall quality of this study was good.

DIRECT-Protect 1 (Chaturvedi et al 2008)

This study recruited type 1 diabetes subjects with baseline retinopathy according to the same protocol described above. Retinopathy was defined as ETDRS scale at least 20/10 (mild nonproliferative) up to 47/47 (moderately severe nonproliferative). A total three-step or more change for the participant was counted as progression of retinopathy (i.e. the primary endpoint). The secondary endpoint was progression to proliferative retinopathy or macular oedema. In all, 1905 patients were randomised, and all results were included in the ITT analysis. Adverse events were similar in both groups, the most common being nasopharyngitis, hypoglycaemia, hypotension and headache.

There was no significant difference between arms of the trial regarding progression to the combined secondary endpoint (HR 1.02, 95%CI: 0.8 to 1.31, p=0.849). There was an identical 13% progression of retinopathy in the placebo and candesartan arms.

This was a good quality study. It was powered on a 25% event rate in the placebo arm, whereas only about half that rate was achieved. Thus, the ability to detect effect was reduced. The duration of follow-up may have been insufficient to detect treatment effect. Individuals with high BP or microalbuminuria were excluded and those with more severe disease may have shown more of a response.

EUCLID 1998 (Chaturvedi et al 1998)

This randomised double-blind study set out to examine the effects of lisinopril on 'normotensive' adults with type 1 diabetes. The primary outcome was urinary albumin excretion rate with retinopathy being a secondary endpoint. The authors report that, with the assumption that there would be 250 patients in each group, of whom half would have retinopathy at baseline, they would be able to detect a reduction in retinopathy progression from 24% in placebo to 10% on lisinopril (OR 0.35) with 80% power at 5% significance.

In all, 530 patients from 18 European countries were recruited if they had type 1 diabetes, were aged between 20–59 years and their resting blood pressure was 75–90 mmHg diastolic and 155 mmHg or less systolic. Of these, 409 subjects had gradeable baseline retinal photographs and were randomised to placebo (n=207) or 10 mg lisinopril (n=202), to be titrated to 20 mg if diastolic BP was more than 75 mmHg at 3 months.

The main outcome for retinopathy was progression of retinopathy by at least one grade. Those who could not show progression (photocoagulated and proliferative at baseline) were

excluded from the analyses. Patients whose retinopathy progressed by at least two grades or to proliferative retinopathy were also compared. Incident retinopathy and regression was also compared.

There was a significant difference between groups ($p<0.05$) in terms of baseline HbA_{1c} with the intervention group having a mean HbA_{1c} of 6.9% compared to 7.3% in the placebo group. Most of the patients were normoalbuminuric, 15% had an albumin excretion rate 20–200 mcg/minute. Retinopathy was present in 65% of patients in the placebo group and 59% in the lisinopril group (nonsignificant difference, p=0.2).

After 2 years of treatment with lisinopril, the progression of diabetic retinopathy by one level was reduced by 50% (95%CI: 28 to 89%, p=0.02). Progression by two levels was of dubious significance. The unadjusted OR was 0.27 with a wide confidence interval (95%CI: 0.07 to 1.00, p=0.06). Progression to proliferative diabetic retinopathy was reduced in the lisinopril group by 82% (OR 0.18 95%CI: 0.04 to 0.82, p=0.03). There was a nonsignificant reduction in incidence of retinopathy and regression of retinopathy (OR 0.69, 0.3 to 1.59, p=0.4) and (OR 1.48, 82 to 2.68, p=0.2) respectively.

On logistic regression only HbA_{1c} was related to progression of retinopathy. Adjustment for HbA_{1c} at baseline made the OR 0.55 (0.30 to 1.03, p=0.06). A stratified analysis by HbA_{1c} resulted in a reduced but significant OR in those with HbA_{1c} below 7% (OR 0.34 95%CI: 0.13 to 0.94, p=0.04) and a larger but not significant OR in those with HbA_{1c} above 7% (OR 0.61 95%CI: 0.29 to 1.29, p=0.2).

EUCLID was limited by differences in baseline glycaemic levels between groups (the treatment group had lower HbA_{1c} levels) and a relatively short follow-up of 2 years. The study was not primarily designed to assess the effects of ACEI on retinopathy, and was underpowered to detect a reduction in retinopathy progression. Data was analysed only on patients who completed the trial (i.e. ITT not achieved). This study is of fair quality. The randomisation and blinding were appropriately documented; however, the 77% follow-up and lack of ITT reduced the control of selection bias after treatment assignment.

Table 18.20 Summary of results: retinopathy

Study	Outcome	Result
Mauer et alet al (2009)	Reduction in retinopathy progression by two steps or more with enalapril and losartan vs placebo	Enalapril: OR 0.35 (95%CI: 0.12 to 0.73) Losartan: OR 0.30 (95%CI: 0.12 to 0.73)
DIRECT-Prevent 1 – Chaturvedi et al (2008)	Incidence (≥two-step increase on EDTRS scale)	No significant effect HR 0.82 (95%CI: 0.37 to 1.00, p=0.051)
DIRECT-Protect 1 – Chaturvedi et al (2008)	Progression of diabetic subject retinopathy, primary endpoint (two steps on ETDRS scale)	No significant effect HR 1.02 (95%CI: 0.8 to 1.31, p=0.849)
	Progression to combined secondary endpoint (proliferative retinopathy and/or macular oedema)	No significant effect n=110 treatment, n=107 placebo
EUCLID – Chaturvedi et al (1998)	Incidence of retinopathy	No significant effect OR 0.69 (0.30–1.59, p=0.4)
	Progression of retinopathy by 1 grade	Significant effect OR 0.50 (95%CI: 0.28 to 0.89, p=0.02)
	Progression of retinopathy by 2 grades	Borderline significance OR 0.27 (0.07 to 1.00, p=0.05)
	Regression of retinopathy	No significant effect OR 1.48 (0.82 to 2.68, p=0.2)

CI, confidence interval; EDTRS, Early Treatment Diabetic Retinopathy Study; HR, hazard ratio; OR, odds ratio

Neuropathy and autonomic neuropathy

Table 18.21 Study characteristics – neuropathy and autonomic neuropath

Study ID Setting	Population	n	Duration	Intervention	Comparator	Outcome	Quality
Lanza et alet al (2007) Italy	Type 1 diabetes Adults Depressed HRV	21	4 weeks	Atenolol	No treatment	CRP HRV parameters	Poor
Ebbehøj et alet al (2002) Denmark	Type 1 diabetes Micro or macroalbuminuria BP <160/90 No other AHT	20	6 weeks	Metoprolol 100 mg	Placebo	HRV 24-hour BP UAER	Good
Ebbehøj et alet al (2004)	Type 1 diabetes Abnormal albuminuria (>20)	20	6 weeks	Metoprolol 100 mg	Placebo	QT interval and QT dispersion	Good

AHT, antihypertensives; BP, blood pressure; CRP, C-reactive protein; HRV, heart rate variability; UAER, urinary albumin excretion rate

Lanza et alet al (2007)

This two-phase study set in Italy was aimed at answering two questions: (i) whether there was a relationship between impaired cardiac autonomic function and inflammation, and (ii) whether beta-blockade might also improve both abnormalities in these patients. Heart rate variability (HRV) – a marker of cardiac autonomic dysfunction – was an outcome

measure for study phase two. A consecutive group of type 1 diabetes patients were enrolled from an outpatient diabetes care unit if they had no symptoms of heart disease, normal physical exam, normal echocardiogram, normal stress test and no inflammatory disease. The first phase was a cross-sectional study to examine the relationship between HRV and CRP. The power of the RR-interval variations in the whole frequency range of the spectrum were obtained. It was found that low frequency (LF) power was the HRV variable that showed the best correlation with CRV (r coefficient –0.39, p=0.005). Thus, the 24 patients with an LF power value below median level (not reported) were invited to participate in phase two, the RCT phase. Three of these patients were excluded due to a history of asthma, use of aspirin and refusal to participate. Thus, 21 patients were randomised to add atenolol 25 mg once daily for 3 days then 50 mg od) to their standard treatment or to continue their standard treatment for 3–4 weeks. After this time a blood sample and a 24-hour Holter monitor were repeated. The patients were not blinded; however, the outcome assessors were. There were no significant baseline differences between groups at randomisation. The mean age was 54 and the mean duration of diabetes was 29 years. A total of 50–54% had microalbuminuria and 64–70% had retinopathy. Four patients in each group were on either ACE or ARB. There were no significant differences in HRV values at baseline. At follow up, it was reported that HRV variables were higher in the beta-blocker group than in the nontreatment group. RR interval was increased in the atenolol group 924 ±168 ms, compared to 752 ±115 ms in the no atenolol group p=0.0001 (p value referring to beta-blocker × variable interaction according to two-way analysis of variance on log-transformed data). Low frequency power improved in atenolol-treated patients compared to baseline (low frequency power, p=0.018). It was reported that there was significant improvement of HRV in the group of patients with clear impairment of cardiac autonomic function treated with atenolol.

This was a small, short-term study in a highly selective population of people with type 1 diabetes. Participants were not blinded, and there was no placebo group. From phase two randomisation, there was ITT and less than 15% drop out. However, the selective recruitment of these patients for the RCT increased bias. Adverse effects, especially hypoglycaemia or hypoglycaemia unawareness, were not reported. The overall quality of this study was poor. The generalisability and applicability of these results are limited by the small and selected study population.

Ebbehøj et al (2002)

The aim of this crossover RCT set in Denmark was to assess the effect of additional metoprolol on cardiac autonomic function, blood pressure and UAER in ACEI-treated people with type 1 diabetes with abnormal albuminuria. Twenty adult subjects with a disease duration of at least 5 years, intact hypoglycaemia awareness, UAER of above 20 mcg/minute despite ongoing ACE, no heart disease and BP of less than or equal to 160/90 mmHg were randomised to 100 mg metoprolol or placebo. A 4-week washout period was interposed between treatment periods. The outcomes measured were HRV, 24-hour BP and 24-hour urine collections. HRV was measured by 24-hour ambulatory monitoring as well as HR response to standing and deep breathing, and BP response to standing up.

The baseline clinical characteristics were a mean age of 38 years, diabetes duration 21 years, ramipril dose 5.5 mg, 2.7-year duration of ACEI, UAER of 109.7 mcg/minute and HbA_{1c} 9.2%. All patients were taking ramipril at baseline. No patients reported symptoms of autonomic neuropathy; however, baseline measurements revealed abnormal tests in 15 of the 20 patients. Regarding adverse effects, one patient received 50 mg metoprolol due to bradycardia, and no patient experienced hypoglycaemic episodes. Regarding the bedside tests of cardiac autonomic neuropathy; metoprolol treatment reduced the inspiratory–expiratory difference in beats per minute compared to placebo (p=0.001). There was no

significant effect on the change of BP from supine to upright posture. Regarding the 24-hour time domain analysis of HRV, metoprolol resulted in an increment in mean RR interval (p<0.0001). The broad-band measures of total 24-hour HRV, which are summations of short-term and long-term HRV, were unchanged during metoprolol treatment. There was a statistically significant effect of metoprolol in some short-term spectral measures of HRV (i.e. mean RR, HF power both supine and upright and ratio of LF to high frequency (HF), which was due to a drop in HF in the upright position). Measures reflecting sympatovalgal modulation of heart rate were not influenced by metoprolol.

This was a small, short-term study in patients with nephropathy and on ACEI treatment. The overall study quality was good. The generalisability and applicability are affected by the strict inclusion criteria and small size of the study.

Ebbehøj et alet al (2004)

This article reported a separate outcome from a trial performed by the same author reported above. The aim of this Danish study was to describe the effects of metoprolol treatment on QT interval and QT dispersion in type 1 diabetic subjects with abnormal albuminuria (UAER >20 mcg/ml). All patients completed the trial. The QTc interval (ms) was significantly reduced by metoprolol treatment (estimated treatment effect ±standard error [SE] 7.70±3.52 p=0.035, approximately 2%). No difference in QTc dispersion was observed following metoprolol treatment. To rule out a possible confounding effect of heart rate correction, data was also analysed using QT dispersion without correction for heart rate; the results and associations were similar.

Table 18.22 Summary of results: neuropathy and autonomic neuropathy

Study	Result
Lanza et alet al (2007)	Total power frequency[a] in atenolol vs no treatment group (p=0.052)
Ebbehøj et alet al (2002)	Improvement in IE difference (bpm) with metoprolol (p=0.001)[b]
Ebbehøj et alet al (2004)	Reduction in Qtc interval with metoprolol (p=0.035)

[a] power of the high and low frequency oscillation. High frequency oscillation considered a pure estimate of parasympathetic activity. Low frequency oscillation reflects para and sympathetic modulation of HR and is strongly influenced by baroreflex activity.
The LF:HF can be considered an indicator of sympatovagal balance
RR interval mean of all normal RR intervals
[b] estimate of vagal function

18.2.2.6 Discussion

This systematic review covers the published evidence around the effect of AHT on the development or progression of specific complications of diabetes. The limitations of this report include possible inaccuracies of applying study type filters on the search yield. The exclusion of studies with less than 100 subjects should also be noted when interpreting the results.

Nephropathy

The study by Mauer et alet al (2009) showed no significant effect of ACE or ARB on the primary endpoint of change in mesangial fractional volume on renal biopsy. The study reported an increase in the 5-year cumulative incidence of microalbuminuria with losaratan versus placebo but not with captopril versus placebo. The lack of treatment effect of ARB on incidence of microalbuminuria in normoalbuminuric normotensive adults with type 1

diabetes was consistent in both the RASS and DIRECT studies. However, there was no increase in incidence of microalbuminuria with ARB in the DIRECT study as there was in the RASS. The dose of ARB used was 100 mg losartan (RASS) and 32 mg candesartan. Follow-up time was similar. In both studies, the subjects recruited were at low overall risk, which resulted in a low rate of microalbuminuria. The average age at baseline was 29–30 years in both studies, with diabetes duration being approx 6.8 years in DIRECT-Prevent 1 and about 11 years in DIRECT-Protect 1 and RASS. The average HbA_{1c}, AER and BP were similar in the two studies. Both studies were originally powered for other primary endpoints than incidence of microalbuminuria.

In patients with baseline microalbuminuria, ACEI use significantly reduced progression to macroalbuminuria, but the OR for regression to normoalbuminuria was 3.07. At 2 years, UAER was 50.5% lower in treated than in placebo patients. The much older study (Lewis et al 1993) reported a decrease of 0.3 g/day in median urinary protein excretion in the captopril group, and significantly less proteinuria over the 4 years of the study (p=0.001). The primary endpoint was the doubling of serum creatinine, which was significantly reduced by captopril.

Retinopathy

The DIRECT studies were large, good quality RCTs in adult normotensive normoalbuminuric patients. They showed no significant effect of lisinopril on the incidence of retinopathy. There was also no significant difference between arms of the trial regarding two-step progression (pre-specified outcome). This finding was in contrast to the two other included studies. RASS was powered for structural renal change, and the study on retinopathy outcomes was added after the trial had begun. However, the odds of retinopathy progression by two steps or more was reduced by 65% with enalapril as well as with losartan.

The EUCLID study (Chaturvedi et al 1998) reported that lisinopril decreased progression of retinopathy (main outcome) by at least one grade. Progression of retinopathy by two levels was also reduced with ACEI use compared to placebo, but the statistical significance of this result was borderline, with a wide CI.

There was no significant effect on incidence or regression of retinopathy. The EUCLID study was not primarily designed to assess the effect of ACEI on retinopathy but rather nephropathy. Other biases of this study included the difference in baseline glycaemia and the lack of ITT analysis.

Neuropathy and autonomic neuropathy

Due to the paucity of RCTs addressing these outcomes, studies were not excluded by population size. Both studies were small and of short duration. The study by Lanza et alet al (2007) reported a significant increase in RR interval, very LF, LF and HF HRV in patients treated with atenolol. Atenolol appeared to improve HRV and markers of inflammation (i.e. CRP). It was reported that there was no change in the clinical status of patients. Other appropriately designed trials would be needed to establish whether beta-blockers may improve clinical outcomes.

Metoprolol improved vagal tone as assessed by short-term spectral analysis Ebbehøj et alet al (2002). The 24-hour ambulatory HRV analysis showed improvement in some parameters reflecting vagal function. A minor decrease in daytime diastolic BP was shown, but no alterations in diurnal variation of BP was shown. The authors reported that metoprolol improved all short-term HRV parameters known to reflect parasympathetic function. Clinical outcomes (e.g. morbidity and mortality) were not addressed.

The effect of metoprolol on QTc interval in the same population was reported in a separate publication. This showed a treatment effect of 7.7 ms reduction in QTc interval (p=0.035)

18.2.2.7 Conclusion

The evidence base for this question consists of one good quality Level I study and eight Level II studies, mostly of good quality.

Nephropathy

The nephropathy studies were heterogenous regarding baseline population proteinuric status. In normoalbuminuric patients, RASS showed no therapeutic effect of ACE or ARB on renal endpoints; rather, there was a significantly increased 5-year cumulative incidence of microalbuminuria with losartan compared to placebo.

A meta-analysis found that all included studies tended toward a beneficial effect of ACE on progression to macroalbuminuria. Only one study (DIRECT-Renal) (Chaturvedi et al 2008) examined incident microalbuminuria and found no effect with ACEI. An older study (Lewis et al 1993) was of a proteinuric population; thus, the measurement of progression of disease differed to the other studies. A significant reduction in doubling of serum creatinine and combined death or dialysis and transplantation with ACEI was found. The generalisability of the body of evidence is limited by the inclusion of only adult subjects in all trials. The baseline hypertensive status of populations varied between trials, as did the proteinuric state. Regarding applicability, populations were drawn from multiple study sites in multiple countries including Australia, New Zealand, Europe and America.

Retinopathy

The body of evidence consisted of three large Level II studies, two of which were of good quality, and one of fair quality. Two studies were not powered for retinopathy as a primary outcome. The studies were consistent in showing no effect of ACEI on the incidence of retinopathy. However, the studies were conflicting regarding progression of retinopathy, with DIRECT-Protect showing no effect and RASS showing a significant reduction in the progression of retinopathy. EUCLID (Chaturvedi et al 1998) reported that progression by two levels was reduced, but this was supported by a wide CI and a borderline p value. Both positive studies were initially powered for renal endpoints, and the statistical significance of secondary endpoints would be made more robust with larger numbers or other variables, to improve statistical power. The generalisability was limited because only adult patients were studied. Patients were normotensive and varied according to baseline retinopathy status. Both studies were multicentre and included populations from Europe, the United Kingdom and America.

Cardiac autonomic neuropathy

The body of evidence consisted of three small, short-term Level II studies of poor and good quality. The risk of bias was high. The studies were consistent in showing a statistically significant improvement in various aspects of cardiac autonomic neuropathy (CAN) measurement; however, apart from an increase in RR interval in both studies, the measurements showing improvement differed between studies. As neither study examined clinical endpoints, the impact of these studies is slight. The small size and short-term nature of the studies limit generalisability. The studies were conducted at single sites in Europe.

18.2.2.8 Literature search strategy

The search was conducted between 27 July 2010 and 30 August 2010. Level I studies were considered first, with the plan to update with Level II studies as required.

Table 18.23 Search strategy, question 18.2

Database	Date searched	#	Search terms	Citations
Medline	27 July 2010	1	Diabetes Mellitus, Type 1/	
		2	Antihypertensive Agents/	
		3	Adrenergic alpha-Antagonists/	
		4	(Prazosin or terazosin or phenoxybenzamine).mp.	
		5	Adrenergic alpha-Agonists/	
		6	(Methyldopa or clonidine or moxonidine).mp.	
		7	Aldosterone Antagonists/	
		8	(Spironolactone or eplerenone).mp.	
		9	Adrenergic beta-Antagonists/	
		10	(Atenolol or metoprolol or carvedilol or bisoprolol).mp.	
		11	Angiotensin-Converting Enzyme Inhibitors/	
		12	(Captopril or enalapril or fosinopril or lisinopril or perindopril arginine or perindopril erbumine or Quinapril or ramipril or trandolapril).mp.	
		13	Angiotensin II Type 1 Receptor Blockers/	
		14	(Candesartan or eprosartan or irbesartan or olmesartan or temisartan).mp.	
		15	Calcium Channel Blockers/	
		16	(Non dihydropyridine or diltiazem or verapamil or Dihydropyridine or amlodipine or felodipine or lercanidipine or nifedipine).mp.	
		17	Diuretics/	
		18	(Thiazide or hydrochlorothiazide or indapamide or Potassium-sparing diuretic or amiloride).mp.	
		19	(Hydralazine or minoxodil).mp.	
		20	or/2-19	
		21	1 and 20	
		22	limit 21 to (nglish language and humans)	
		23	'meta analysis'/exp or 'meta analysis'.mp. or 'systematic review'/exp or 'systematic review'.mp. or 'pooled analysis'.mp. or (('review'/exp or 'review'.mp.) and ('meta analysis'/exp or 'meta analysis'.mp. or systemat*.mp. or pool*.mp.)) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	
		24	22 and 23	
		25	limit 21 to (english language and humans)	
		26	randomized controlled trial.mp. or 'single blind	

Database	Date searched	#	Search terms	Citations
			procedure'/exp or 'single blind procedure'.mp. or 'double blind procedure'/exp or 'double blind procedure'.mp. or 'triple blind procedure'/exp or 'triple blind procedure'.mp. or 'crossover procedure'/exp or 'crossover procedure'.mp. or 'placebo'/exp or placebo.mp. or randomi?ed:ab,ti.mp. or rct:ab,ti.mp. or 'random allocation':ab,ti.mp. or 'randomly allocated':ab,ti.mp. or 'allocated randomly':ab,ti.mp. or 'single blind':ab,ti.mp. or 'single blinded':ab,ti.mp. or 'double blind':ab,ti.mp. or 'double blinded':ab,ti.mp. or 'treble blind':ab,ti.mp. or 'treble blinded':ab,ti.mp. or 'triple blind':ab,ti.mp. or 'triple blinded':ab,ti.mp. or placebo*:ab,ti.mp. or 'prospective study'/exp or 'prospective study'.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	
Level I studies		27	24 22 and 23	7
Cochrane				5
EMBASE				98
INAHTA				0
Manual search				1
Total citations				111
Total non-duplicate citations				107
Level II studies		27	24 22 and 23	200
Cochrane				0
EMBASE				83
INAHTA				0
Manual search				3
Total citations				286
Total non-duplicate citations				247

18.2.2.9 Evidence Matrix

Retinopathy

Q18.2 (ii)	How effective are antihypertensives at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?	
Evidence statement	Primary prevention: In normotensive patients with type 1 diabetes and no retinopathy, there is insufficient evidence to determine the effect of ACEI or ARB on the onset of retinopathy. Secondary prevention: In normotensive patients with type 1 diabetes and nonproliferative diabetic retinopathy, ACEI or ARB reduce the progression of retinopathy. Prespecified outcomes were two grades of retinopathy progression on the ETDRS scale (DIRECT and RASS) or one grade (EUCLID), thus with differing study outcome measures.	
Evidence base	B	Two Level II studies with combined low risk of bias.
Consistency	B	All studies were consistent in showing no effect on incidence of retinopathy. Evidence was conflicting about the progression of retinopathy. RASS: reduction with ACE (OR 0.35) and ARB (OR 0.3). DIRECT: No effect on predefined progression (2 steps), signify effect on post hoc analysis of three steps. No effect on proliferative retinopathy. EUCLID: Underpowered, and retinopathy not a primary outcome of this study.
Clinical impact	D	
Generalisability	B	Large, good or fair-quality trials in normotensive, normoalbuminuric and microalbuminuric patients. All adult participants.
Applicability	B	Both large multicentre studies undertaken in Europe, the United Kingdom and the United States.
Other factors	None identified.	

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; OR, odds ratio; RASS, Renin Angiotensin System Study

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Nephropathy

Q18.2 (ii)	How effective are antihypertensives at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?	
Evidence statement	Primary prevention: In normotensive normoalbuminuric patients with type 1 diabetes, there is consistent evidence that neither ACEI nor ARB prevent the onset of microalbuminuria. Secondary prevention (progression): There is evidence that the use of ACEI prevents the progression from microalbuminuria to macroalbuminuria. There is evidence that ACEI attenuates or delays the progression from macroalbuminuria to doubling of creatinine or end-stage renal disease (combined death, dialysis and transplantation).	
Evidence base	B	Primary.
	A	Secondary.
Consistency	B	Primary (results inconsistent for ACEI and ARB).
	A	Secondary – ACEI.
	B	Secondary – ARB.
Clinical impact	D	Primary.
	A	Secondary.
Generalisability	B	Large, good to fair-quality trials in normotensive, normoalbuminuric and microalbuminuric patients. All adult participants.
Applicability	A	Both large multicentre studies undertaken in Europe, the United Kingdom and the United States.
Other factors	Children and adolescents are not represented in the evidence base.	
Recommendation		
R18.2	ACEI therapy should be used to prevent progression of diabetic nephropathy (Grade B).	

ACEI; angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; OR, odds ratio

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

18.3 What is the effect of statins on lipid levels and cardiovascular outcomes in type 1 diabetes?

Question 18.3

What is the effect of statins on lipid levels and cardiovascular outcomes in type 1 diabetes?

This chapter reviews the evidence for the effect of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG CoA) inhibitors (referred to as statins) on lipid levels and cardiovascular outcomes in type 1 diabetes.

18.3.1 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 18.24.

Table 18.24 Criteria for determining study eligibility, question 18.3

Study design	NHMRC Level I or Level II or Level III (NHMRC intervention scale[a])
Population	Type 1 diabetes
Intervention	HMG CoA reductase inhibitors (statins): pravastatin, atorvastatin, simvastatin, rosuvastatin, lovastatin, fluvastatin
Comparator	
Outcomes	Change in blood lipid levels, clinical cardiovascular outcomes

HMG CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of level II studies, Level II: A randomised controlled trial, Level III-3: A comparative study without concurrent controls; Level IV: Case series with either post-test or pre-test/post test outcomes.

18.3.2 Assessment of study eligibility

Publications identified in the literature search were reviewed using the criteria shown in Table 18.25, applied hierarchically, to determine which publications to exclude.

A total of 229 citations were identified in the initial literature search. The exclusion criteria were applied to all citations by reviewing the abstract and title (see Table 18.25. The full-text version of 17 publications was retrieved and reviewed. After further review, a total of 12 papers were included (Biesenbach and Zazgornik 1992; Hommel et al 1992; Kjaer et al 1992; Zhang et al 1995; Rustemeijer et al 1997; Noutsou and Georgopoulos 1999; Mullen et al 2000; Fried et al 2001; Manuel et al 2003; Baigent et al 2005; de Vries et al 2005; Kearney et al 2008).

18.3.3 Literature search summary

Table 18.25 Search results, question 18.3

Stage	Notes	Number
Search summary	Manual	
	Cochrane Library	0
	EMBASE	150
	Medline	51
	INAHTA	1
	Dare	20
	Total	222
Exclusion criteria	Wrong study type (Not NHMRC Level I or II or III) [a]	87
	Wrong population (Not type 1 diabetes)	20
	Wrong intervention or test (Not a statin)	37
	Wrong outcome (Effect on plasma lipid levels not reported)	21
	Not in English	9
Meeting criteria	Total meeting inclusion criteria	11
Included	Total included studies	11

18.3.4 Characteristics and results of included studies

Table 18.26 Characteristics and results of included studies, question 18.3

Reference	Type	Population	Intervention	Comparator	n	Duration
Kearney (2008)	Prospective meta-analysis	Type 1 and type 2 adult diabetes; type 1 diabetes results extracted	Simvastatin 20–40 mg Pravastatin 40 mg Lovastatin 40–80 mg Fluvastatin 40–80 mg Atorvastatin 10 mg	Included studies: 4S 94 WOSCOPS95 CARE95 Post-CABG97 LIPID98 GISSI-I00 LIPS02 HPS02 PROSPER02 ALERT03 CARDS04	18 686 1466 type 1 diabetes 14 RCTs	4.3 years
de Vries et al (2005)	Randomised crossover trial	Adults Moderate hyper-cholesterolaemia Type 1 diabetes	Simvastatin: 10, 20, 40 mg	Placebo	14	24 weeks
Manuel et al (2003)	RCT	Total/HDL >4	Atorvastatin 40 mg	Placebo	24	12 weeks
Fried et al (2001)	Randomised controlled pilot trial	Type 1 diabetes	Simvastatin	Placebo	39	2 years
Mullen et al (2000)	Double blind 2 x 2 factorial study	Type 1 diabetes	L-arginine and atorvastatin 40 mg	Placebo	84	6 weeks

Reference	Type	Population	Intervention	Comparator	n	Duration
Noutsou and Georgopoulos (1999)	Randomised crossover trial	Type 1 diabetes	Simvastatin	Placebo	8	Not reported
Rustmeijer et al (1997)	RCT	Type 1 diabetes and type 2 diabetes with hyper-cholesterolaemia	Pravastatin 20 mg	Placebo	22 type 1 diabetes	24 weeks
Zhang et al (1995)	Randomised crossover trial	Diabetes incipient nephropathy	Pravastatin 20 mg		20	24 weeks
Kjaer et al (1992)	Randomised crossover trial	Type 1 diabetes	Simvastatin 10–40 mg	Placebo	10	24 weeks
Hommel et al (1992)	RCT	Type 1 diabetes, hyper-cholesterolaemia	Simvastatin 10–20 mg	Placebo	26	12 weeks

HDL, high density lipoprotein; RCT, randomised controlled trial

Kearney et al (2008)

Kearney et al (2008) analysed the data from 18 686 individuals with diabetes from a previously published prospective meta-analysis of statins on coronary heart disease (CHD) and other major vascular events. The aim of this meta-analysis was to examine the effects of statins on major coronary and major vascular events in diabetic patients. The studies included in the original meta-analysis had an intervention that modified lipid levels, and they were not confounded with respect to the intervention (i.e. no other differences in modification of risk factors between the relevant treatment groups were intended). The original studies were also trials that aimed to recruit 1000 or more participants, with treatment lasting at least 2 years.

Of the 14 studies in the original paper, 11 provided data on patients with type 1 diabetes and were included in the meta-analysis. Trial participants were considered to have diabetes if they had a recorded history of diabetes at randomisation. Subdivision of diabetes type was done according to the definitions used in the individual trials.

Baseline characteristics of patients presenting with type 1 diabetes included mean age of 55.1 years; 21% of the type 1 diabetes population were smokers; 56% had a history of any vascular disease (previous myocardial infarction [MI]/coronary heart disease [CHD], stroke or peripheral arterial disease). The mean blood pressure (BP) was 140/78 mmHg. The mean total cholesterol was 5.7 mmol/L, low density lipoprotein (LDL) 3.4 mmol/L and high density lipoprotein (HDL) 1.3 mmol/L.

The interventions studied included simvastatin 20–40 mg, pravastatin 40 mg, lovastatin 40–80 mg, fluvastatin 40–80 mg and atorvastatin 10 mg. For subgroup analyses, the prespecified categories in the original protocol were used, together with three new subgroups. The new subgroups categorised participants according to LDL/HDL ratio; estimated glomerular filtration rate (GFR) and predicted yearly risk of major vascular event.

In patients with type 1 diabetes, the mean (standard error [SE]) difference in plasma lipid concentrations at 1 year, in participants exposed to statins and controls were as follows: total cholesterol –1.04 (0.08) mmol/L, LDL –0.96 mmol/L (0.15) and triglycerides –0.09

(0.08). There was no change in HDL. The statistical significance of these results was not reported.

The incidence of major vascular events showed no significant evidence of benefit in the 1466 patients with type 1 diabetes. The risk ratio (RR) was 0.79 (99% confidence interval [CI]: 0.62 to 1.01) and the test for heterogeneity was not significant (p=1.0).

Regarding adverse events, there were too few cases of rhabdomyolysis reported in patients with diabetes for meaningful analysis. Statin therapy was not associated with an increased incidence of rhabdomyolysis in all participants (9 vs 6 cases, p=0.4). In the meta-analysis of all patients, statin therapy did not increase the risk of nonvascular causes of death or cancer when used for an average of 5 years.

This was a large, fair-quality meta-analysis with results extracted for type 1 diabetic subjects.

de Vries et al (2005)

The aim of the randomised crossover trial by de Vries et al (2005) was primarily to determine the capacity of plasma to induce cholesterol efflux out of Fu5AH cells and fibroblasts. Conventional plasma lipid profiles were also measured. After a diet run in, 14 male patients with type 1 diabetes were assigned to simvastatin (10 mg, 20 mg and 40 mg) or placebo in random order for 6 weeks each. Participants had a fasting plasma total cholesterol between 5.0 and 8.0 mmol/L. All participants had fasting triglycerides of less than 2.5 mmol/L and a body mass index (BMI) of less than 30kg/m^2. They also had no (cardiovascular disease) CVD, drank less than three standard drinks of alcohol per day, and had normal urinary albumin excretion, blood pressure, thyroid function and liver function. The mean age was 45 years and mean glycated haemoglobin (HbA_{1c}) was 7.8% at baseline. Adverse effects were not reported. It was found that there was a significant reduction in LDL and significant increase in HDL on 10 mg simvastatin compared with placebo ($p<0.05$). There was no significant change in total cholesterol or triglycerides. Simvastatin at 20 mg and 40 mg reduced total cholesterol, triglycerides and LDL to a statistically significant degree. HDL was statistically significantly increased with simvastatin 20 mg and 40 mg. This study had small numbers and strict inclusion criteria.

Manuel et al (2003)

The aim of the placebo controlled randomised controlled trial (RCT) by Manuel et al (2003) was to investigate the effects of atorvastatin on lipoprotein composition, LDL subfractions and peroxidation in patients with type 1 diabetes and high serum levels of cholesterol. Patients with atherogenic index (total cholesterol/HDL cholesterol) of at least 4 were randomised to atorvastatin 40 mg or placebo. Fasting blood samples were collected at inclusion, and after 6 and 12 weeks. Randomisation resulted in two groups with a statistically significant difference in total and LDL cholesterol. Each group contained 12 patients. The mean age was 44 years and the mean HbA_{1c} was 7.8–8.2%. Those in the intervention group had a higher total cholesterol and LDL than the mean in the placebo group. There was no difference in the atherogenic index. There were also no other significant differences between groups. After correcting for the significant difference at inclusion, the total and LDL levels decreased by 40–50% after 6 weeks of atorvastatin compared with baseline, with no further change after 12 weeks. There was no change in the placebo group. There was a significant difference after 12 weeks of treatment compared to placebo, with lower total cholesterol, LDL and triglycerides in the treatment group. There was no significant difference in HDL levels. Adverse effects were not reported.

Fried et al (2001)

The aim of the study by Fried et al (2001) was to examine the effect of lipid reduction on microvascular complications. The reduction in lipid levels was also reported. Thirty-nine patients with type 1 diabetes and LDL cholesterol of 2.5–4.16 mmol/L were randomised to simvastatin (maximum dose 20 mg) or placebo. Both groups also had their diets reviewed. The trial was terminated early due to lowering of drug initiation levels by the American Diabetes Association (ADA). This study reported results up to that point. There were no differences between groups at randomisation. The mean age was 31–33 years, and the mean HbA_{1c} was 8.8–9.2%. All subjects completed 6 months, 92% completed 1 year, 43% reached 18 months and only two subjects reached 2 years. No patient dropped out of the study because of side effects. At 6 months, most patients were on 10 mg simvastatin. At this time, total cholesterol and LDL had declined to a significant degree (p=0.028 total cholesterol and p<0.001 LDL). There was no change in HDL or triglycerides. At 12 months, about half the patients were taking 20 mg simvastatin. The effect of simvastatin on LDL and total cholesterol was maintained throughout the trial (LDL: mean on treatment 2.73 versus 3.3, p<0.001 – lower in simvastatin than placebo throughout trial; total cholesterol: mean on treatment 4.5 versus 3.3, p–0.02 – lower in simvastatin group throughout trial). No adverse effects were reported.

Mullen et al (2000)

The 2 x 2 RCT by Mullen et al (2000) studied the effect of L-arginine and atorvastatin 40 mg on conduit artery vascular function in 84 normocholesterolaemic young adults. The mean age was 34 years, with mean LDL 2.96 mmol/L. Atorvastatin resulted in a significant reduction in serum LDL compared to baseline (48 ±10% p<0.001); total cholesterol was also significantly reduced, as were triglycerides and HDL. A total of 88% of participants were included in the follow-up; reasons for withdrawal included postoperative ketosis, hypoglycaemia and dizziness.

Noutsou and Georgopoulos (1999)

The small randomised crossover trial by Noutsou and Georgopoulos (1999) sought to assess the effect of simvastatin on fasting and postprandial triglyceride-rich lipoproteins in type 1 diabetes, in subjects with elevated LDL levels. The starting dose of simvastatin was 5 mg per day, and this was increased every 2 weeks until the LDL dropped below 3.35 or the maximum dose of 40 mg was reached. The duration of the intervention was not reported. There was no change in liver function test results or creatine kinase. No side effects were reported by patients. A statistically significant reduction in total cholesterol, triglycerides and LDL was seen in the simvastatin group compared with the placebo group.

Table 18.27 Results of Noutsou and Georgopoulos (1999)

Lipid (mmol/L mean/SD)	Simvastatin	Placebo	p
Total cholesterol	4.01/1.47	6.13/0.91	0.01
Triglycerides	1.07/0.38	1.33/0.64	0.09
Low density lipoprotein	2.82/0.39	4.27/0.67	<0.001
High density lipoprotein	1.32/0.36	1.27/0.34	NS

NS, not significant; SD, standard deviation

There was no significant difference in the HDL cholesterol between groups. This was a small study of undefined duration where blinding was not described.

Rustemeijer et al (1997)

The double blind RCT by Rustemeijer et al (1997), set in the Netherlands, investigated the efficacy and safety of pravastatin in type 1 and type 2 diabetes, with hypercholesterolaemia. Patients aged between 18 and 70 years, with total cholesterol between 6.5 mmol/L and 8 mmol/L, were recruited. The report does not mention whether fasting lipid levels were taken. The lipid profile was taken every 8 weeks. There were 22 patients with type 1 diabetes, with a mean age of 46 years and mean HbA_{1c} of 9.3%. After 24 weeks, total cholesterol, triglycerides and LDL were lower compared to baseline (see Table 18.28). Pravastatin was well tolerated. Two serious adverse events were noted in the study: libido loss in the pravastatin group and muscle pain in the placebo group. Both patients dropped out of the study.

Table 18.28 Results of study by Rustemeijer et al (1997)

Change from baseline (mmol/L)	Mean	Standard deviation	Percentage change	p
Total cholesterol	5.56	0.72	–24	<0.001
Triglycerides	1.3	0.51	–21.8	<0.05
Low density lipoprotein	3.62	0.75	–29.1	<0.001
High density lipoprotein	1.41	0.43	5.5	NS

NS, not significant

Zhang et al (1995)

The randomised crossover trial by Zhang et al (1995), of 20 patients with type 1 diabetes with persistent microalbuminuria (20–200 µg/minute), studied the effects of pravastatin on lipid levels. Patients were recruited from the Antwerp University hospital, and the median age was 43 years. All patients had more than one diabetes-related complication. Blood samples were taken after an overnight fast at baseline, and after 12 and 24 weeks. Compared to baseline, it was found that after 12 weeks, pravastatin reduced plasma cholesterol by 22% and LDL by 19%, as shown in Table 18.29. There was no report of blinding, intention-to-treat (ITT) analysis or adverse effects.

Table 18.29 Results of Zhang et al (1995)

Lipid levels mmol/L mean	Baseline	12 weeks pravastatin	p
Total cholesterol	5.46	4.81	<0.05
Triglycerides	1.2	1.1	NS
Low density lipoprotein	3.2	2.6	<0.05
High density lipoprotein	1.6	1.6	NS

NS, not significant

Kjaer et al (1992)

The randomised controlled crossover study by Kjaer et al (1992), set in Denmark, studied the effect of simvastatin on hypercholesterolaemic patients with type 1 diabetes. Ten patients were randomised to 20 mg simvastatin or placebo for a period of 12 weeks each. There was a washout period of 4 weeks in between. The mean age of the patients was 44 years and the fasting plasma cholesterol was above 6 mmol/L. All patients completed the study, and one patient complained of mild nausea. There were no other side effects. It was found that simvastatin reduced total cholesterol by 19% ($p<0.001$) and LDL by 24% ($p<0.001$).

Simvastatin reduced triglycerides by 8% and increased HDL by 8%, but neither of these effects were significant (p>0.05).

Table 18.30 Results of Kjaer et al (1992)

mmol/L (mean/SD)	Baseline	12 weeks simvastatin	p
Total cholesterol	6.8/0.7	5.3/0.3	<0.001
Triglycerides	1.2/0.4	1.1/0.4	NS
Low density lipoprotein	4.5/1.0	3.1/0.6	<0.001
High density lipoprotein	1.7/0.5	1.7/0.6	NS

NS, not significant; SD, standard deviation

Hommel et al (1992)

The aim of the study by Hommel et al (1992) was to assess the effect of simvastatin on lipid profiles and renal function in patients with type 1 diabetes, hypercholesterolaemia and diabetic nephropathy. A total of 26 patients aged 35–41 years, with total cholesterol above 5.5 mmol/L and nephropathy, were randomised. Patients were assigned to either simvastatin 10 mg/day or placebo. Cholesterol was checked at 6 weeks to titrate dosages to a maximum of 20 mg if total cholesterol increased to 5.2 mmol/L or more. At 12 weeks, the average dose was 12.5 mg. Two patients in the treatment group were withdrawn due to gastrointestinal symptoms and myalgia. Three patients were removed from the study because baseline cholesterol dropped with dietary modification alone. In the treatment group, there was a significant reduction in total cholesterol and LDL (p<0.01) (as shown in Table 18.31). There were significant differences (p<0.01) in mean changes from baseline to 12 weeks between the treatment and control groups, as shown below.

Table 18.31 Results of Hommel et al (1992)

mmol/L (mean/SD)	Placebo 12 weeks	Simvastatin 12 weeks	p	Change from baseline placebo	Change from baseline simvastatin	p (difference in change between groups)
Total cholesterol	6.8/1	4.8/0.7	<0.01	0.078/0.25	–1.58/0.25	<0.01
Triglycerides	2.06/0.8	1.49/0.6	NS			
Low density lipoprotein	4.7/1	2.6/0.5	<0.01	0.013/0.21	–1.67/0.21	<0.01
High density lipoprotein	1.26/0.3	1.53/0.5	NS			

NS, not significant; SD, standard deviation

Table 18.32 Summary of results from included studies

Reference, quality	Intervention	Comparator	Result	Lipid	95%CI/SE	p
Kearney et al (2008) Fair	Any statin (meta-analysis)	No treatment	Mean difference at 1 year	TC –1.04 TG – 0.09 LDL – 0.96 HDL 0.00	0.08 0.08 0.15 0.03	NS
de Vries et al (2005)	Simvastatin 10 mg	Placebo	Difference (mean in mmol/L) Treatment versus placebo	TC	–0.86	*p<0.05
				TG	–0.17	
				LDL	–0.85*	

Reference, quality	Intervention	Comparator	Result	Lipid	95%CI/SE	p
Good				HDL	+0.06*	
	Simvastatin 20 mg	Placebo	Difference (mean in mmol/L) Treatment versus placebo	TC	–1.23*	*p<0.05
				TG	–0.4*	
				LDL	–1.08*	
				HDL	+0.06*	
	Simvastatin 40 mg	Placebo	Difference (mean in mmol/L) Treatment versus placebo	TC	–1.3*	*p<0.05
				TG	–0.27*	
				LDL	–1.18*	
				HDL	0.05*	
Manuel et al (2003) Fair	Atorvastatin 40 mg	Placebo	Difference (mean in mmol/L) Treatment versus placebo	TC	–1.86*	p<0.0001
				TG	–0.30*	p=0.04
				LDL	1.71*	p<0.001
				HDL	+0.02	p<0.001
Fried et al (2001) Good	Simvastatin 20 mg	Placebo	Difference (median in mmol/L) Treatment versus placebo	TC	–1.2	p<0.001
				TG	Mean on treatment not given	NS
				LDL	–0.6	p=0.02
				HDL	Mean on treatment not given	NS
Mullen et al (2000) Good	Atorvastatin 20 mg	Placebo	Decrease compared to baseline (mean/SD%)	TC	33.3/9.4	p<0.001
				TG	12.1/25.6	p=0.028
				LDL	48.3/10	p<0.001
				HDL	6.1/21.3	p=0.045
Noutsou and Georgopoulos (1999) Poor	Simvastatin	Placebo	Difference treatment vs placebo mean mmol/L	TC	2.1	0.01
				TG	0.26	0.09
				LDL	1.45	<0.001
				HDL	0.05 (simvastatin higher)	NS

Reference, quality	Intervention	Comparator	Result	Lipid	95%CI/SE	p
Rustemeijer et al (1997) Good	Pravastatin 20 mg	Placebo	Percentage change from baseline (statin group)	TC	–24.0	p<0.001
				TG	–21.8	p<0.05
				LDL	–29.1	p<0.001
				HDL	5.5	NS
Zhang et al (1995) Poor	Pravastatin 20 mg	Placebo	Percentage change from baseline (statin group)	TC	–22	p<0.05
				TG		NS
				LDL	–19	p<0.05
				HDL		NS
Kjaer et al (1992) Fair	Simvastatin 20 mg	Placebo	Percentage change from baseline (statin group)	TC	–21.8	<0.001
				TG	–12.3	NS
				LDL	–29.2	<0.001
				HDL	+1.3	NS
Hommel et al (1992) Fair	Simvastatin 20 mg	Placebo	Mean absolute change in mmol/L from baseline (statin group)	TC	–1.6	<0.01
				TG	–0.13	NS
				LDL	–1.6	0.01
				HDL	+0.04	NS

CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein; NS, not significant; SD, standard deviation; SE, standard error ; TC, total cholesterol; TG, triglycerides

[a] Indicates significance

18.3.5 Discussion

The studies that met the inclusion criteria for this question were 1 systematic review and meta-analysis (Kearney et al 2008) of fair quality and 10 RCTs, mostly of good or fair quality. The Level II studies did not meet the inclusion criteria for the systematic review (Kearney et al 2008) because they did not aim to recruit more than 1000 subjects.

The meta-analysis by Kearney et al (2008) prospectively included any RCT that studied an intervention that modified lipid levels, was not confounded and aimed to recruit 1000 or more participants with treatment duration of more than 2 years. The primary outcome for the study was reduction in occlusive vascular events, and the primary meta-analyses were of the effects on clinical outcomes. Each trial was weighted by the absolute LDL cholesterol difference in that trial at the end of the first year of follow-up, and outcomes were reported as the effects per 1.0 mmol/L reduction in LDL cholesterol. To make allowance for repeated subdivision of data, only summary rate ratios were presented with 95%CI; all other rate ratios were presented with 99%CI.

Fourteen statin trials were included in the original meta-analysis. This gave data from 90 056 participants. Of these, 18 686 (20%) had diabetes. Further subdivision showed that 1466 (1.6% of the 20%) of these had type 1 diabetes. The percentage of people with diabetes in each trial ranged from 0.9% to 13.3%.

There was some limited direct evidence of benefit in the 1466 people with type 1 diabetes (RR 0.79, 99%CI: 0.62 to 1.01; p=0.01) regarding reduction of predicted yearly risk of major vascular event in terms of proportional reduction per mmol/L LDL cholesterol. Also, the incidence of major vascular events was reduced by about a fifth in terms of per mmol/L LDL cholesterol reduction in all prognostic subgroups of participants with diabetes that were examined. Data on lipid levels was extracted for this subgroup. The efficacy of statins on lipid levels in type 1 diabetics was reported but not as a major outcome. There was no report of the statistical significance of this data. The magnitude of difference was about 1 mmol/L reduction in total cholesterol and LDL, with very small or no change in HDL or triglycerides.

The Level II studies were consistent in reporting a statistically significant reduction in total cholesterol and LDL with statin use. The order of magnitude in statistically significant difference in total cholesterol ranged from –1.2 mmol/L to –2.1 mmol/L treatment compared to placebo at the end of each study. The percentage reduction in total cholesterol from baseline to end of treatment in the statin groups ranged from –21% to –33%. Regarding LDL, the magnitude of difference ranged from –0.85 mmol/L to –1.7 mmol/L in the treatment group compared to placebo. In terms of percentage reduction in the treatment groups from baseline to study end, the range was 29–48%.

Several studies showed a nonsignificant effect of statins on triglyceride levels (Hommel et al 1992; Kjaer et al 1992; Zhang et al 1995; Mullen et al 2000; Fried et al 2001). Noutsou and Georgopoulos (1999) and Rustemeijer et al (1997) reported a significant reduction in triglycerides, and de Vries et al (2005) showed a significant reduction in triglycerides with doses of 20–40 mg simvastatin but not 10 mg simvastatin.

A statistically significant increase in HDL with statins was reported by de Vries (2005) with all doses of simvastatin. Manuel et al (2003) also showed a significant increase, but this was not replicated in any of the other studies.

18.3.6 Conclusion

The overall body of evidence is consistent in showing a statistically significant reduction in total and LDL cholesterol with statin use in type 1 diabetes. The evidence is less consistent regarding reduction in triglycerides and effect on HDL. The body of evidence consisted of a large meta-analysis that examined clinical endpoint but did not report the statistical significance of the effect on lipid profiles of statin use.

The meta-analysis for type 1 diabetes included 11 large studies. The studies were also selected for inclusion before their results were known, thus reducing publication bias. The large numbers involved would improve the generalisability of the results on a population basis. However, the percentage of subjects with type 1 diabetes was small in the original trials, which may increase the risk of allocation bias. The inclusion and exclusion criteria of the individual studies were not reported, and may affect the applicability of the results. The trials gave an average follow-up period of 4 years. The quality of the included studies was not reported. Most of the included studies were set in Europe or America. This study was of fair quality due to the increased risk of bias involved in retrospective analysis of original

studies not initially powered to examine the effects of statins on subjects with type 1 diabetes.

Four level II studies were of good quality, three were of fair quality and two were of poor quality (mostly based on a lack of reporting of randomisation methods). The trial numbers were relatively small, ranging from 8 to 84 subjects. The maximum duration was 2 years and most trials were of 6 months duration. The studies were consistent in the effect of statins on total cholesterol and LDL, but inconsistent regarding triglycerides and HDL. Most studies were set in Europe or America. There were no Australian studies. Five studies included patients with hypercholesterolaemia, one study included patients with nephropathy (Hommel et al 1992) and one with incipient nephropathy (Zhang et al 1995).

18.3.7 Literature search strategy

The search was conducted between 2 August 2010 and 4 August 2010. Level I studies were considered first, with the plan to update with Level II studies as required. The Medline search strategy and a summary of citations retrieved from other searches is shown in Table 18.33.

Table 18.33 Search strategy, question 18.3

Database	Date searched	#	Search terms	Citations
Medline	Between 2 August 2010 and 4 August 2010	1	Diabetes Mellitus, type 1/	52 442
		2	Hydroxymethylglutaryl CoA Reductases/	3 088
		3	Anticholesteremic Agents/	11 300
		4	Pravastatin/	2 667
		5	Simvastatin/	4 441
		6	atorvastatin.mp.	4 026
Medline		7	rosuvastatin.mp.	1 089
		8	fluvastatin.mp.	1 359
		9	or/2–8	21 141
		10	1 and 9	72
		11	limit 10 to (english language and humans)	51
Cochrane				0
EMBASE				150
INAHTA				1
Dare				20
Manual search				
Total citations				229
Total non-duplicate citations				44

18.3.8 Evidence Matrix

Q18.3	How effective are statins at correcting dyslipidaemia in type 1 diabetes?	
Evidence statement	Level I and II evidence demonstrates that statins are effective at reducing total and LDL cholesterol in adults with type 1 diabetes. Level I evidence demonstrates that statins reduce cardiovascular events in adults with type 1 diabetes.	
Evidence base	A	Level I study with inclusion criteria (>1000 patients) that ensure a low risk of bias. The Level II studies included four of low risk of bias, four of moderate risk of bias and two of high risk of bias.
Consistency	A	LDL/total cholesterol –all studies show a statistically significant effect on lowering total cholesterol and LDL-cholesterol. Two studies showed a statistically significant increase in HDL, in contrast to the other studies.
	B	HDL/triglycerides.
Clinical impact	A	There was a large effect size and the finding has the potential to affect all patients with type 1 diabetes.
Generalisability	B	Systematic review was large (n=1466 total). Numbers in individual studies were 8–82. Children and young adults were not represented in the evidence base.
Applicability	A	Studies were conducted in Europe or the United States.
Other factors	PBS prescribing restrictions limit access to statins (e.g. microalbuminuria, Indigeneous). PBS guidelines use total cholesterol as the indicator, whereas paediatric guidelines recommend LDL cholesterol as the indication for therapy.	
Recommendation		
R18.3	Statins are recommended for use in adults with type 1 diabetes, to reduce total and LDL cholesterol, and to reduce cardiovascular risk (Grade B).	

HDL, high density lipoprotein; LDL, low density lipoprotein; PBS, Pharmaceutical Benefits Scheme

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

19 Screening for foot complications

This chapter was not systematically reviewed.

20 Other complications and associated conditions

20.1.1 Coeliac disease

Question 20.1

How often should people with type 1 diabetes be screened for coeliac disease?

Coeliac disease is a disorder of the small intestine caused by the immune response to ingested wheat gluten and similar proteins of rye and barley. As shown in Table 20.1, coeliac disease is more common in people with type 1 diabetes than in the general population. The reported prevalence is 0.8–6.4% in adults and 0.6–16.4% in children with type 1 diabetes. In Australia, the prevalence in children has been reported as 2.2% (1992) and more recently as up to 8.4% (Doolan et al 2005), with an incidence of 0.72 per 100 patient years (Glastras et al 2005).

Table 20.1 Prevalence of coeliac disease

Reference, country	Total participants	Screening test/s	Prevalence by serology (%)	Prevalence by biopsy (%)	Notes
Adults					
Aygun et al (2005) Turkey	122			2.45	
Bouguerra et al (2005) Tunisia	348			2.30	
Collin et al (1989) Finland	195	Reticulin		4.10	
Page et al (1994) United Kingdom	767	Gliadin		2.00	
Picarelli et al (2005) Italy	94	Endomysium		6.40	
Remes-Troche et al (2008) Mexico	84	Transglutaminase		5.90	
Rensch et al (1996) United States	47	EMA	6.3	6.3	
Sategna-Guidetti et al (1994) Italy	383	EMA	3.1	2.6	10/12 biopsied
Sjoberg et al (1998) Germany	848	AGA, EMA	2.6	0.8	Only 14/22 biopsied
Talal et al (1997) United States	185	EMA	4.9	2.1	Only 5/9 biopsied

Reference, country	Total participants	Screening test/s	Prevalence by serology (%)	Prevalence by biopsy (%)	Notes
Children					
Abu-Zekry et al (2008) Egypt	250	Endomysium, transglutaminase		4.7	
Al-Ashwa et al (2003) Saudi Arabia	123	Gliadin, reticulin		4.9	
Arato et al (2003) Hungary	205	Endomysium		8.3	
Ashabani et al (2003) Libya	234	Gliadin, endomysium, transglutaminase		10.3	
Baptista et al (2005) Brazil	104	Endomysium		4.8	
Barera et al (1991) Italy	498	Gliadin		3.2	
Barera et al (2002) Italy	274	Endomysium		6.2	
Boudraa et al (1996) Algeria	116	Gliadin, endomysium,		16.4	
Calero et al (1996) Spain	141	Gliadin		2.85	
Carlsson et al (1999) Sweden	115	Gliadin, endomysium,		6.0	
Crone et al (2003) Austria	157	Endomysium		5.1	
Doolan et al (2005) Australia	131	Endomysium, transglutaminase, human leukocyte antigen		8.4	
Fraser-Reynolds et al (1998) United States	236	Endomysium	6.5	4.6	17/19 biopsied
Gadd et al (1992) Australia	180	Gliadin		2.2	
Gillett et al (2001) Canada	233	Endomysium or gliadin	8.1	6.0	18/19 biopsied
Glastras et al (2005) Australia	173	Endomysium		Incidence 0.72 per 100 patient years	

Reference, country	Total participants	Screening test/s	Prevalence by serology (%)	Prevalence by biopsy (%)	Notes
Goh and Banerjee (2007) United Kingdom	113	Gliadin, endomysium, transglutaminase		4.40	
Hansen et al (2001) Denmark	106	Gliadin, endomysium, transglutaminase		10.4	
Hansen et al (2006) Denmark	269	Endomysium, transglutaminase		12.3	
Kaspers et al (2004) Germany	19 796	Gliadin, endomysium, transglutaminase		0.6	
Koletzko et al (1988) Germany, Switzerland	1 032	Gliadin		0.97	
Mankai et al (2007) Tunisia	205	Endomysium		5.3	
Peretti et al (2004) France	284	Gliadin, endomysium, transglutaminase		3.9	
Poulain et al (2007) France	950	Gliadin, endomysium, transglutaminase		1.6	
Roldan et al (1998) Spain	177	Gliadin, endomysium		3.9	
Sakly et al (2005) France	165	Gliadin, endomysium, transglutaminase		4.85	
Salardi et al (2008) Italy	331	Endomysium		6.6	
Saukkonen et al (1996)	776	Reticulin, gliadin		2.4	
Sigurs et al (1993) Sweden	459	Reticulin, gliadin		4.6	
Spiekerkoetter et al (2002) Germany	205	Transglutaminase		4.0	
Tanure et al (2006) Brazil	236	Gliadin, endomysium		2.6	
Valerio et al (2002) Italy	383	Gliadin, endomysium		8.3	
Verge et al (1994) Australia	273	Gliadin, endomysium		1.8	

Reference, country	Total participants	Screening test/s	Prevalence by serology (%)	Prevalence by biopsy (%)	Notes
Vitoria et al (1998) Spain	93	Gliadin, endomysium		6.4	
Children/adults					
DeVitis et al (1996) Italy	1114	Gliadin, endomysium,		7.0/5.6	
Kordonouri et al (2000) Germany	520	Gliadin, endomysium, transglutaminase		1.70	
Lorini et al (1996) Italy	133	Gliadin, endomysium,		3.75	
Mahmud et al (2005) United States	158	Endomysium, transglutaminase		7.0	
Sanchez-Albisua et al (2005) Cuba	281	Gliadin, endomysium		3.9	

AGA, antigliadin antibodies; EMA, antiendomysium antibodies

In people with diabetes, coeliac disease commonly presents as a silent disease, with few if any symptoms (Collin et al 1989; Sategna-Guidetti et al 1994; Calero et al 1996; Kordonouri et al 2000; Goh and Banerjee 2007).

Metabolic complications of seropositivity to coeliac antigens have been demonstrated in children with type 1 diabetes. For example, Artz et al (2008) found a significant difference in weight and bone mineral density between seropositive and seronegative children(Artz et al 2008), and Simmons et al (2007) found a significant difference in weight and body mass index (BMI). In a large, multicentre retrospective study involving 19 796 German children with type 1 diabetes, coeliac-specific antibodies were significantly related to lower height at onset ($p<0.05$) and lower BMI ($p<0.05$) (Kaspers et al 2004).

No studies were found regarding these outcomes in the adult population.

20.1.2 Focus of review

The aim of this systematic review was to identify evidence to inform recommendations for the frequency of screening for coeliac disease in children and adults with type 1 diabetes.

Antibody screening tests include those for antigliadin antibodies (AGA), either IgA or IgG; antireticulin antibodies (ARA), (IgA); antiendomysium antibodies (EMA), (IgA); and anti-tissue transglutaminase (tTGA and tTGG). These tests can give a false-negative result in IgA-deficient populations; therefore, a measure of total IgA is recommended at the time of screening (APEG (Australasian Paediatric Endocrine Group) 2005). The diagnostic accuracy of these tests has been examined, however, as the 'gold standard' reference test involves a small biopsy, there are few studies where both the reference test and the antibody measures have been carried out in nonsymptomatic people with type 1 diabetes (Dretzke et al 2004). The National Institute of Health and Clinical Excellence (NICE) recommend using IgA tTGA as the initial test for the recognition and assessment of coeliac disease; IgA EMA if the result of the tTGA test is equivocal; IgA deficiency if serology is negative; and IgG tTGA or IgG

EMA (or both) for people with confirmed IgA deficiency (NICE (National Institute for Clinical Excellence) 2009).

Recommendations for screening for coeliac disease in people with type 1 diabetes are inconsistent (Silverstein et al 2005; Kordonouri et al 2009; NICE (National Institute for Clinical Excellence) 2010). For example, guidelines from the American Diabetes Association (ADA) recommends testing for coeliac disease on presentation of symptoms, the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends routine testing for coeliac disease at diagnosis and at follow-up, and the National Institute of Health and Clinical Excellence (NICE) recommends routine testing for coeliac disease at diagnosis (in children, adolescents and adults), with no recommendation to continue screening in those who are not symptomatic individuals after the initial test.

20.1.3 Criteria for eligibility

Studies were eligible for inclusion if they met the criteria shown in Table 20.2.

Table 20.2 Criteria for determining study eligibility, question 20.1

Study design	Level IV or higher (NHMRC intervention scale[a])
Population	Children and adults with type 1 diabetes
Intervention	Antibodies to endomysium or tissue transglutaminase
Comparator	Any
Outcomes	Measure of antibodies on two or more occasions

NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of Level II studies, Level II: A randomised controlled trial, Level III-1: A pseudorandomised controlled trial, Level III-2: A comparative study with concurrent controls, Level III-3: A comparative study without concurrent controls, Level IV: Case series with either post-test or pre-test/post-test outcomes

20.1.4 Literature search summary

Publications identified in the literature search were reviewed using the criteria shown in Table 20.3 applied hierarchically, to determine which publications to exclude.

The exclusion criteria were applied to all citations identified in the initial search by reviewing the abstract and title. A total of 49 publications remained, and the full-text version of each publication was retrieved and reviewed. The same exclusion criteria were then applied to the full-text articles. Seven publications met the inclusion criteria (Barera et al 2002; Crone et al 2003; Cerutti et al 2004; Glastras et al 2005; Poulain et al 2007; Larsson et al 2008; Salardi et al 2008).

Table 20.3 Search results, question 20.1

Stage	Notes	Number
Search summary	Manual	1
	Cochrane Library	1
	Medline	233
Duplicates	Duplicates identified	1
Identified	Total identified	234
Exclusion criteria	Wrong study type (Not NHMRC Level IV or higher[a])	74
	Wrong population (Not type 1 diabetes)	27
	Wrong intervention (Not antibodies to endomysium or tissue transglutaminase)	11
	Wrong outcome (Not measure of antibodies on two or more occasions)	107
	Not in English (Not reported in English language)	
	Total excluded	
Included	Total included studies	7

NHMRC, National Health and Medical Research Council

[a] NHMRC intervention scale: Level I: A systematic review of Level II studies, Level II: A randomised controlled trial, Level III-1: A pseudorandomised controlled trial, Level III-2: A comparative study with concurrent controls, Level III-3: A comparative study without concurrent controls, Level IV: Case series with either post-test or pre-test/post-test outcomes

20.1.5 Characteristics of included studies

The main characteristics of the seven included studies are summarised in Table 20.4.

Table 20.4 Characteristics of included studies, question 20.1

Reference and evidence level	Study type and quality	Population and country	Intervention	Outcomes
Barera et al (2002) Level II	Longitudinal prospective cohort follow-up from diagnosis for up to 6 years Study quality – fair	273 eligible children, with newly diagnosed type 1 diabetes (116 female, 159 male) Age (mean ±SD): 8.28 ±4.6 years, range 0.6–18.7 years Attending a paediatric endocrinology clinic Italy	Tested for EMA at onset of type 1 diabetes, and tested annually for up to 6 years Also tested for IgG EMA and AGA if IgA deficient Small bowel biopsy recommended in antibody-positive people or those with 2 weak EMA results	Prevalence of seropositivity and biopsy-proven coeliac disease
Cerutti et al (2004) Level III	Retrospective cohort multicentre (n=25) Study quality – fair	4322 children and adolescents (2388 boys and 1034 girls) attending 25 paediatric diabetes clinics (representing those from 60% of Italian clinics for childhood diabetes) Ages at recruitment and diabetes diagnosis 11.8 ±4.2 and 7.4 ±3.9 years 292 of the cohort diagnosed with coeliac disease Italy	Tested for IgA/IgG AGA and/or IgA EMA annually for 5 years Assessed age, sex, age at diagnosis of diabetes, and presence or absence of thyroid disorder, as independent variables for the development of coeliac disease	Prevalence of biopsy-confirmed coeliac disease

Reference and evidence level	Study type and quality	Population and country	Intervention	Outcomes
Crone et al (2003) Level II	Longitudinal prospective cohort at least 3 years follow-up (tested the hypothesis that EMA positivity can occur at any time during the course of type 1 diabetes) 1993–2001 Study quality – fair	157 children (mean age 14.8 years, range 4–21 years; male n=83) Group 1: n=37 first screened at diagnosis Group 2: n=120 first screened during the course of diabetes (mean duration 33.6 months, range 11–105 months) Group 1 were younger (mean age 8.5 years, range 1–17 years) compared with entire group Ethnic origin, comorbidity, disease status not reported Austria	Screening at diagnosis with at least 3 years follow-up and at least 2 EMA measurements Small-bowel biopsy in EMA-positive people	Prevalence of seropositivity and biopsy-proven coeliac disease
Glastras et al (2005) Level II	Longitudinal prospective cohort 13 years follow-up (to test hypothesis that antibody positivity at diagnosis predicts development of associated disease and thus determine appropriate screening frequency for associated disease) Study quality – fair	173 children diagnosed with type 1 diabetes 1990–1991 n=173, median age 8.2 years (0.9–14.9) at onset of diabetes, 52% male. Statistically younger at age of onset than nonparticipants (8.3 vs 11.6 years, p<0.0001 No more likely to come from an urban than a rural area (63% vs 64%, not significant) Australia	EMA at diagnosis, with follow-up screening for AGA (1992–98) and EMA thereafter (Also screened at diagnosis for TPOA, EMA, ICAs, GADA, IAAs and TSH Small bowel biopsy if AGA or EMA positive	Incidence of seropositivity and biopsy-proven coeliac disease
Larsson et al (2008) Level II	Longitudinal prospective cohort, 5 years follow-up, multicentre- n=6 Study quality – fair	300 children and adolescents with newly diagnosed with type 1 diabetes Mean age at diagnosis of diabetes 9.2 years (range 1.3–18.7 years) 160 (53.3%) boys Sweden	Annual IgA EMA screening and small-bowel biopsy in antibody-positive patients	Prevalence of biopsy-confirmed coeliac disease and cumulative frequency of biopsy-confirmed coeliac disease over 5 years
Poulain et al (2007) Level III	Single centre retrospective cohort 1994–2001 Study quality – fair	950 children attending paediatric diabetes clinic (1994–2001) France	Routine screen (no description of frequency) of AGA, ARA, EMA, tTGA; each patient tested 1–7 times Antibody-positive subjects biopsied	Prevalence of histologically documented coeliac disease
Salardi et al (2008) Level II	Single-centre, longitudinal prospective cohort study 18 years follow-up Study quality – fair	331 consecutive unselected people attending a diabetes clinic Mean age at diagnosis of diabetes 8.1 ±4.3 years (range 0.08–14.9 years) Italy	Screened from diagnosis of type 1 diabetes every 6–12 months with measures of EMA EMA positive subjects given intestinal biopsy Average length of follow-up 9 years	Prevalence of seropositivity and of biopsy-confirmed coeliac disease

AGA, antigliadin antibodies; ARA, antireticulin antibodies; EMA, antiendomysium antibodies; GADA, glutamic acid decarboxylase antibodies; IAA, insulin autoantibody; ICA, islet cell antigen; SD, standard deviation; TPOA, thyroperoxidase antibodies; TSH, thyroid stimulating hormone; tTGA, anti-tissue transglutaminase

20.1.6 Results of included studies

Barera et al (2002)

The results of the study by Barera et al (2002) are shown in Table 20.5. The age at onset of type 1 diabetes was not different between those with or without coeliac disease.

Table 20.5 Results (Barera et al 2002)

	n (%)						
	At diagnosis	1 year	2 years	3 years	4 years	5 years	6 years
EMA	15 (5.5%)	4 (1.4%)	5 (1.8%)	5 (1.8%)	3 (1.1%)	0	0
Coeliac disease	9 (3.3%)	2 (0.7%)	2 (0.7%)	2 (0.7%)	1 (0.35%)	0	0

EMA, antiendomysium antibodies

The authors reported that prevalence of coeliac disease was 20 times higher than in the general population. In 60% of cases, coeliac disease was already present at diagnosis of type 1 diabetes, with the remaining 40% developing coeliac disease a few years after the onset of diabetes. The authors recommended extending screening programs after the onset of type 1 diabetes.

Cerutti et al (2004)

In the study by Cerutti et al (2004), 292 of 4322 children and adolescents had biopsy-confirmed coeliac disease. Prevalence was 6.8%; 95% confidence interval [CI]: 6.0 to 7.6). The rate was higher in girls than in boys (odds ratio [OR] 1.93, 1.51–2.47). The prevalence of biopsy-confirmed coeliac disease, by duration of diabetes was as shown in Table 20.6.

Table 20.6 Prevalence of biopsy-confirmed coeliac disease, by duration of diabetes

Duration of type 1 diabetes (years)	Confirmed coeliac disease as a percentage (95%CI)
≤1.0	3.3 (2.6 to 4.1)
1.1–2.0	1.5 (1.0 to 2.0)
2.1–3.0	0.9 (0.6 to 1.4)
3.1–4.0	0.7 (0.4 to 1.2)
4.1–5.0	0.8 (0.5 to 1.4)
5.1–6.0	0.7 (0.3 to 1.2)
6.1–7.0	0.5 (0.2 to 1.1)
7.1–8.0	0.7 (0.3 to 1.5)
8.1–9.0	0.8 (0.3 to 1.7)
9.1–10.0	0.3 (0.04 to 1.2)
>10.0	0.6 (0.2 to 1.2)

CI, confidence interval

Multiple logistic regression analyses were performed to assess variables independently associated with the risk of having both type 1 diabetes and coeliac disease, compared with having diabetes alone, as shown in Table 20.7.

Table 20.7 Assessment of variables

	OR (95%CI)	p
Boys	1.00	
Girls	1.75 (1.35 to 2.29)	<0.0001
Age at diagnosis of diabetes (years)		
<4	3.27 (2.20 to 4.85)	<0.0001
4–6	2.61 (1.73 to 3.92)	
7–9	1.04 (0.65 to 1.67)	
>9	1.00	
Thyroid disorder		
No	1.00	0.001
Yes	1.82 (1.29 to 2.55)	

CI, confidence interval; OR, odds ratio

The results provide evidence of the high prevalence of biopsy-confirmed coeliac disease in children and adolescents with type 1 diabetes. They also demonstrate:

- that the risk of having both type 1 diabetes and coeliac disease is three times higher in children diagnosed with type 1 diabetes at age less than 4 years than those aged more than 9 years
- that girls have a higher risk of having both diseases than boys
- a decreasing trend of prevalence of coeliac disease by duration of diabetes, indicating that coeliac disease is rarely found after 10 years duration of diabetes.

Crone et al (2003)

The results from Crone et al (2003) are summarised in Table 20.8. Group 1 were those whose first screening test occurred at diagnosis, and group 2 were those whose first screening test occurred during the course of diabetes. Follow-up for group 1 was at 11, 12 and 39 months. Of the five cases in group 1 who were positive at diagnosis, three had biopsy-proven coeliac disease, and one of the three who had seroconverted had biopsy-proven coeliac disease.

In group 2, four children had biopsy-proven coeliac disease. There was no transient EMA positivity in group 2. The longest duration from first negative result to seroconversion was 8 years.

Table 20.8 Results (Crone et al 2003)

	Entire cohort (n=157)	Group 1 (n=37) at diagnosis	Group 1 at follow-up	Group 2 (n=120)
Prevalence of EMA	n=16 10.2% cumulative prevalence (incidence not reported)	n=5 (13.5%) positive at diagnosis	n=3 (8.1%) positive at follow-up	n=8 (6.6%)
Prevalence of biopsy-proven coeliac disease	n=8 5.1% cumulative prevalence (incidence not reported)	n=3 (8.1%) positive on biopsy	n=1 (2.7%) positive on biopsy	n=4 (3.3%)

EMA, antiendomysium antibodies

The authors concluded that screening for coeliac disease should be included at diagnosis. Also, based on their observation that seroconversion may occur at any time during the course of diabetes, the authors suggested that patients should be screened annually for a long period.

Glastras et al (2005)

The results of the study by Glastras et al (2005) are shown in Table 20.9. The median time interval between negative to positive titres for EMA was 3.6 years. People with negative EMA titres at diagnosis were more likely than those with positive titres to remain disease free ($p<0.00001$). There were no false negative EMA tests from initial screening, as all patients with biopsy-proven disease had another negative screening test before seroconversion.

Table 20.9 Results (Glastras et al 2005)

	At diagnosis	At follow-up (2.8–10.2 years)
Prevalence of positive antibodies	n=4 (2.4%)	n=4 (2.8%)
Prevalence of coeliac disease (confirmed by small bowel biopsy)	n=4 (2.4%)	n=4 (2.8%)
Incidence of coeliac disease	0.72/100 patient years (95%CI: 0.31 to 1.41)	

CI, confidence interval

The study demonstrated the high positive predictive value of screening with EMA at diagnosis, because all four patients with positive EMA were diagnosed with biopsy-proven coeliac disease within 12 months. Given the high negative predictive value of EMA at diagnosis and the low cumulative incidence of disease, the authors concluded that screening annually is not justifiable in patients who test negative to antibodies at diagnosis. The authors recommended screening at 2-year intervals in this subgroup of patients, but also recommended screening as clinically indicated in children in whom there is suspicion of disease.

Larsson et al (2008)

Of the 300 patients in the study in Sweden by Larsson et al (2008), 2 had a diagnosis of coeliac disease before onset of type 1 diabetes and 10 at onset (EMA and biopsy-confirmed). During the 5-year follow-up, a total of 17 patients developed EMA and biopsy-confirmed coeliac disease. The authors did not find a statistically significant effect of age at diagnosis of type 1 diabetes.

Table 20.10 Results (Larsson et al 2008)

	Before onset of diabetes	At onset of diabetes	Years after onset of diabetes			
			1	2	3	5
Prevalence of coeliac disease	0.7% n=2	3.3% n=10	3.3% n=10	1.7% n=5	0.3% n=1	0.3% n=1

This results of this study demonstrate the high prevalence of coeliac disease in the cohort, and showed that most (93%) of the children who went on to develop coeliac disease did so within 2 years of onset of type 1 diabetes. The authors therefore suggested that screening for coeliac disease should be carried out at diagnosis and annually at least for 2 years.

Poulain et al (2007)

The study by Poulain et al (2007) was a retrospective analysis of the 15 (1.6%) out of 950 children who had coeliac disease diagnosed by positive biopsy during the study period. Of these 15 children, 1 had developed coeliac disease before the diagnosis of type 1 diabetes, 2 at diagnosis of diabetes and 12 (73%) on follow-up (mean 4 years; range 4 months to 13 years). Seroconversion was documented in two cases, 2 and 6 years after the diagnosis of diabetes. The authors did not report on prevalence of seropositivity in the whole cohort, or on the number of patients with positive screen and subsequent negative biopsy. The authors noted that their results lend support to repeat screening for coeliac disease.

Salardi et al (2008)

The results of the study by Salardi et al (2008) of 331 children are shown in Table 20.11. In total, 31 were found to be EMA positive. Seroconversion occurred up to 6.2 years after diagnosis of type 1 diabetes.

Table 20.11 Results (Salardi et al 2008)

	Before diagnosis of type 1 diabetes	At diagnosis of type 1 diabetes	9–18 months after diagnosis of type 1 diabetes	3–6 years after diagnosis of type 1 diabetes
Prevalence of EMA positivity	0.6% n=2	4.5% n=15	3.0% n=10	1.2% n=4

EMA, antiendomysium antibodies

This study demonstrated a high prevalence of seropositivity and biopsy-confirmed coeliac disease in a cohort of Italian children with type 1 diabetes, followed longitudinally for up to

18 years. Of the children found to have positive EMA at diagnosis of type 1 diabetes and during follow-up, 25 (86%) had seroconverted within 18 months of diagnosis of type 1 diabetes. These results suggest that screening for coeliac disease should be undertaken at diagnosis of type 1 diabetes and annually for at least 2 years.

20.1.7 Discussion

The included studies demonstrate the high prevalence of antibodies for coeliac disease or of biopsy-proven coeliac disease in children and adolescents with type 1 diabetes and a decreasing trend in prevalence with duration of diabetes, with most cases being detected by screening at diagnosis of diabetes or up to 2 to 4 years post diagnosis (Barera et al 2002; Crone et al 2003; Cerutti et al 2004; Larsson et al 2008; Salardi et al 2008). The results therefore provide the rationale for routine screening at the time of diagnosis of type 1 diabetes and repeated at follow-up until the risk declines. Cerutti et al (2004) suggest that, using a conservative approach, coeliac disease is rarely found after 10 years duration of diabetes (Cerutti et al 2004). There are also some subgroups of patients for whom the risk of developing coeliac disease may be higher, with female sex and age of less than 4 years at diagnosis of type 1 diabetes being independently associated with the risk for having both coeliac disease and diabetes (Cerutti et al 2004). Additionally, positive antibodies at diagnosis are highly predictive of future disease (Glastras et al 2005), suggesting the need for closer surveillance of patients falling into these subgroups.

20.1.8 Conclusion

In this systematic review of evidence for the screening for coeliac disease in individuals with type 1 diabetes, five Level II studies, all of medium risk of bias, and two Level III studies, both of medium risk of bias, met our inclusion criteria. All of the studies were in children and adolescents (n=6506), with no prospective or retrospective, longitudinal studies found in adults. The findings of the studies were consistent in demonstrating the high prevalence of antibodies for coeliac disease or biopsy-proven coeliac disease, mostly detected at the time of diagnosis of type 1 diabetes or within 2–4 years post diagnosis.

20.1.9 Literature search strategy

The search was conducted on 16 June 2010. Studies published after this time were not eligible for inclusion in the review. The search strategy is shown in Table 20.12. A total of 234 non-duplicate citations were identified.

Table 20.12 Search strategy, question 20.1

Database	Date searched	#	Search terms	Citations
Medline and EMBASE	16 June 2010	1	exp Diabetes Mellitus, type 1/ or diabetes mellitus, type1.mp.	42 418
		2	(celiac disease or coeliac disease).mp.	10 669
		3	(celiac sprue or coeliac sprue).mp.	395
		4	(celiacs or coeliacs).mp.	265
		5	(silent celiac or silent coeliac).mp.	96
		6	(asymptomatic celiac or asymptomatic coeliac).mp.	48
		7	subclinical celiac or subclinical coeliac).mp.	44
		8	gluten sensitive enteropathy.mp. or exp Celiac Disease/	10 142
		9	#2 or#3 or#4 or#5 or #6 or#7 or#8	10 775
		10	reticulin.mp. or exp Reticulin/	1 234
		11	gliadin.mp. or exp Gliadin/	2 538
		12	(endomysial or endomysium).mp.	2 093
		13	tissue transglutaminase.mp.	1 548
		14	antireticulin.mp.	85
		15	antigliadin.mp.	539
		16	antiendomysial.mp.	262
		17	antiendomysium.mp.	181
		18	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	6 052
		19	1 and 9 and 18	270
		20	limit 19 to English language	233
Cochrane	16 June 2010	1	diabetes Mellitus, type 1	
		2	celiac disease or coeliac disease	
		3	#1 and #2	1
Manual search				1
Total citations				234
Total non-duplicate citations				226

20.1.10 Evidence Matrix

Q20.1	How often should individuals with type 1 diabetes be screened for coeliac disease?	
Evidence statement	There is an increased risk of coeliac disease in children and adolescents with type 1 diabetes compared to general population historical rates. The number of new cases detected 1 and 2 years after diagnosis is similar to the number of cases at diagnosis. The number of new cases detected after 10 years of diabetes duration is similar to the general population.	
Evidence base	C	Five Level II studies of moderate risk of bias, and two Level III studies of moderate risk of bias.
Consistency	B	Prevalence of coeliac disease by duration was similar across the studies; it ranged from 1.6% to 8.1%. All studies demonstrated an increased risk of coeliac disease in type 1 diabetes. The direction of the effect was consistent, but the magnitude varied.
Clinical impact	B	Detection of coeliac disease will have a major impact on patients.
Generalisability	B	Most of the evidence is in children and adolescents. Only study in adults was a cross-sectional study not a longitudinal study.
Applicability	A	
Other factors	None identified.	
Recommendation		
R20.1	Screening for coeliac disease should occur at diagnosis of type 1 diabetes in children and adolescents; individuals with negative tests at diagnosis should be rescreened (Grade B).	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

20.2 Thyroid disease

Question 20.2

How and how often should people with type 1 diabetes be screened for thyroid disease?

Thyroid disease is the most common autoimmune disease in patients with type 1 diabetes and occurs more co mmonly than in the general population (Dretzke et al 2004). It commonly presents as a subclinical disease with few if any symptoms. Screening methods include measures of antibodies against thyroperoxidase (TPOA) and thyroglobulin (TGA) or thyroid function tests (e.g. thyroid stimulating hormone [TSH], T4 and T3).

20.2.1 Criteria for eligibility

The criteria for determining whether publications were eligible for inclusion for this clinical question are shown in Table 20.13. Studies were eligible for inclusion if they were primary research published in English, as full original reports and secondary research (systematic reviews and meta-analyses) with a study design that provided at least Level III evidence.

Table 20.13 Criteria for determining study eligibility: clinical question

Study design	Prospective cohort study
Population	Children and adults with type 1 diabetes
Intervention	Screening for thyroid disease at multiple time points
Comparator	
Outcomes	Incidence and/or probability of thyroid autoimmunity and/or thyroid disease

Publications identified in the literature search were reviewed and the exclusion criteria applied hierarchically. Publications were excluded if they were the wrong study type, (nonsystematic reviews, nonprospective cohort studies or narrative reviews); if they were in the wrong population (not in children or adults with type 1 diabetes) or evaluated the wrong intervention (not screening for thyroid antibodies at multiple time points). Publications were excluded if they reported the wrong outcomes (not thyroid autoimmunity or thyroid disease). Only English language publications were eligible for inclusion.

A total of 78 citations were identified in the initial literature search and 6 publications were identified from hand searching. After applying exclusion criteria, 17 publications remained, and the full-text version of each publication was retrieved and reviewed. The same exclusion criteria were then applied to the full-text articles; 6 publications met the inclusion criteria (Perros et al 1995; Umpierrez et al 2003; Kordonouri et al 2004; Glastras et al 2005; Kordonouri et al 2005; Severinski et al 2009).

20.2.2 Literature search strategy

The search was conducted on 8th February 2010. Studies published after this time were not eligible for inclusion in the systematic review. The search strategy is shown in Table 20.14.

Table 20.14 Search strategy, question 20.2

Database	Date searched	#	Search terms	Citations
Medline and EMBASE	8 February 2010	1	Diabetes Mellitus, type 1/ or latent autoimmune diabetes in adults.mp or LADA.mp.	51 978
		2	(anti-thyroid peroxidase antibody or anti-TPO or ATPO) or (anti-thyroid stimulating hormone receptor or TSHR)or thyroid receptor antibody.mp. or anti-thyroid antibodies.mp. or (anti-thyroglobulin antibodies or anti-TG) or Goiter/ or thyromegaly.mp. or Thyrotropin/ or (thyroid stimulating hormone or TSH).orThyroxine/ or (Free T4 Index or FT4I or FTI)	64 081
		3	Thyroiditis, Autoimmune/ or AIT or Graves Disease/ or hashimoto's thyroiditis.mp or hyperthyroidism/ or hypothyroidism	53 041
		4	1 and 2 and 3 (english language and humans)	77
Cochrane				1
INAHTA				4
Manual search				6

20.2.2.1 Characteristics of included studies

The main characteristics of the included studies are discussed below and summarised in Table 20.15.

Glastras et al (2005)

In this longitudinal, prospective, population-based incident cohort, 173 children had TPOAs measured at diagnosis; thyroid function was assessed by measuring TSH at diagnosis and then at routine follow-up visits. The authors reported incidence rates for thyroid disease of 0.9 per 100 patient years , and a significant difference between those patients negative to TPOA at diagnosis and those positive to TPOA tests. The authors concluded that positive TPOA at diagnosis predicts development of thyroid disease. They suggested that screening in those with positive TPOA at diagnosis should be undertaken annually, with measurement of thyroid function. In those with negative TPOA at diagnosis, the authors suggested that screening should be undertaken less frequently, with thyroid function test at 2-yearly intervals unless clinically indicated otherwise.

Kordonouri et al (2004)

Kordonouri and colleagues reported the results of screening for autoimmune thyroid disease in 147 German children, followed for 12 years. The children underwent screening at diagnosis and annually, with measurement of TPOAs, TGAs, TSH, T3 and T4. In those children with positive thyroid autoantibodies, the risk of developing thyroid disease was high, with thyroid disease usually occurring within 3–5 years of diagnosis of type 1 diabetes. The authors recommended screening for thyroid disease with TPOAs,TGAs,T3 and T4 at diagnosis, and then annually in those patients with an initial positive screen.

Kordonouri et al (2005)

In this prospective, longitudinal cohort study, 659 German children were screened at diagnosis and annually for thyroid disease with TSH,T3 and T4 measurements from 1990,

with TPOAs and TGAs included from 1996. The authors aimed to examine the incidence and course of autoimmune thyroiditis using a long-term regular screening programme for thyroid disease. Cumulative incidence of autoimmune thyroiditis (AIT) and thyroid disease requiring treatment was reported, with girls being more predisposed than boys. The authors recommended screening with TPOAs, TGAs, TSH, T3, and T4 at diagnosis, repeated annually in those children who are initially positive. In those children with a negative screen at diagnosis, the authors recommended annual screening with TPOA and TSH, particularly from 12 years of age or from onset of puberty.

Perros et al (1995)

In this cohort study, a randomly selected sample of 1310 adults with diabetes, in whom a subgroup of 406 participants had type 1 diabetes, were screened for thyroid disease (TSH, free T4, thyroid microsomal antigen and thryoglobulin); tests were repeated at one year duration. The annual incidence rate of new cases of thyroid disease in this group was reported; the authors recommended annual screening with TSH to detect thyroid disease.

Severinski et al (2009)

The aim of this study was to evaluate the natural course and potential risk factors of AIT and thyroid dysfunction in children with type 1 diabetes. A total of 148 children who underwent annual measures of TPO and thyroglobulin, as well as thyroid function tests (TSH and T4) were followed for 12 years. The authors reported the cumulative incidence of AIT; the number of new cases peaked at puberty, and girls were significantly more predisposed than boys at any age. The cumulative incidence of hypothyroidism was reported, with boys with AIT significantly more predisposed than girls with AIT. The authors recommended annual screening of thyroid antibodies, and of TSH in those with detected thyroid antibodies.

Umpierrez et al (2003)

Umpierrez and colleagues (2003) aimed to analyse the incidence of thyroid dysfunction over time, to evaluate the natural history of thyroid disorders in patients with type 1 diabetes. A prospective cohort of 58 adults enrolled in the DCCT were followed for 18 years. Patients underwent measurement of thyroid function tests annually and TPOA every 4 years. Patients who were TPO positive were 18 times as likely to develop hypothyroidism as patients who were TPO negative (95%CI: 3.89 to 82.54). The authors concluded that annual screening by TSH measurements to detect asymptomatic thyroid dysfunction should be undertaken, particularly in those with positive TPO antibodies. They also suggested that long-term follow-up is indicated, because onset of diabetes usually precedes the development of thyroid disease by about 10 years.

Table 20.15 Characteristics of included studies

Study ID	Study type Study quality	Population Country (ethnicity)	Intervention	Comparator	Outcomes
Glastras et al (2005) Level III Fair	Longitudinal prospective cohort 13 years follow-up	n=173 children <15 years Australia	TPOAs, TFTs at diagnosis TFTs annually		Incidence of thyroid disease OR for thyroid disease
Kordonouri et al (2004) Level III Fair	Longitudinal prospective cohort 12 years follow-up	n=147 children Germany	TPOA, TGA, TSH,T4 T3 at diagnosis and annually		Cumulative incidence of AIT
Kordonouri et al (2005) Level III Fair	longitudinal prospective cohort 13 years follow-up	n=659 children Germany	TPOA, TGA, TSH,T4 T3 at diagnosis and annually		Cumulative incidence of AIT cumulative incidence of thyroid disease requiring treatment
Perros et al (1995) Level III Low	longitudinal prospective cohort 1 year follow-up	n=406 adults (mean age of all patients , type and type 2 53.8 ±16.3(SD)) United Kingdom	TSH, T4, Retrospective review of charts for reports of TMA (thyroid microsomal antigen)		Annual incidence of thyroid disease
Severinski et al (2009) Level III Fair	Longitudinal prospective cohort 12 years follow-up	n=148 children Croatia	TPOAs, TFTs at diagnosis and annually		Incidence of thyroid disease
Umpierrez et al (2003) Level III Fair	Longitudinal prospective cohort 18 years follow-up	n=58 adults United States	TFTs annually TPOAs every 4 years		OR for thyroid disease

AIT, autoimmune thyroiditis; OR, odds ratio; SD, standard deviation; TFT, thyroid function test; TGA, thyroglobulin antibody; TPOA, thyroid peroxidase antibody; TSH, thyroid stimulating hormone

20.2.3 Results of included studies

Results of included studies are shown in Table 20.16.

Table 20.16 Combined results of included studies

Study ID	N	Incidence or probability
Glastras et al (2005)	173 children	0.9 (95%CI: 0.45 to 1.62) per 100 patient years Positive TPOA at diagnosis = 18 times more likely to develop thyroid disease than those with negative TPOA (95%CI: 5.6 to 94.0)
Kordonouri et al (2004)	147 children	AIT at 5 years 0.08 ±0.03 AIT at 5 years in positive TPOA 0.4 ±0.13 AIT at 5 years in positive TGA 0.38 ±0.15. These were significantly different to those without antibodies (p<0.001)
Kordonouri et al (2005)	659 children	AIT at the age of 18 years was 0.14 (0.02) females vs males 0.19 (0.03) vs 0.09 (0.02), p<0.015 AIT at 10 years diabetes duration was 0.14 (0.02) females vs males 0.18 (0.03) vs 0.10 (0.02) p=0.030 Disease requiring treatment at 10 years 0.69 (0.08) in positive TPOAs vs 0.12 (0.05) in negative TPOAs, p<0.001 Disease requiring treatment at 10 years 0.79 (0.10) in positive TGAs vs 0.12 (0.04) in negative TGAs, p<0.001
Perros et al (1995)	406 adults	Annual incidence 6.5% males and 12.3% in females (including subclinical forms) annual incidence 1.6% in males and 3.2% in females (excluding subclinical forms)
Severinski et al (2009)	148 children	AIT at 6 years diabetes duration was 22% females vs males 30% vs 15%; p=0.03, hazard ratio 0.3823, 95%CI: 0.169 to 0.89 Hypothyroidism at 3.5 years antibody positive duration was 55% males vs females 85% vs 40% ;p<0.01; hazard ratio 3.8386; 95%CI: 1.939 to 43.5512
Umpierrez et al (2003)	58 adults	Positive TPO = 17.91 times as likely to develop hypothyroidism as patients who were TPO negative (95%CI: 3.89 to 82.54) p=0.0002

AIT, autoimmune thyroiditis; CI, confidence interval; TGA, thyroglobulin antibody; TPOA, thyroid peroxidase antibody; TSH, thyroid stimulating hormone

20.2.4 Discussion

The studies that met the inclusion criteria involved 1127 children and adolescents, and 464 adults with type 1 diabetes. Participants were screened on multiple occasions for thyroid disease and were followed for up to 18 years.

The method of screen used included measurement of thyroid function (TSH, T4 and T3) and autoantibodies (TPOA and TGA) at diagnosis of type 1 diabetes. Follow-up screening with thyroid function tests alone was carried out in one study (Glastras et al 2005), and in combination with antibody testing in five studies (Perros et al 1995; Umpierrez et al 2003; Kordonouri et al 2004; Kordonouri et al 2005; Severinski et al 2009). Transient autoimmunity was only reported in one study in five children, in all cases the initial TPOA and TGA titres were only slightly elevated (<100U/ml) (Kordonouri et al 2004). In the studies measuring

thyroid antibodies at multiple time points, most patients with thyroid antibodies were detected at the initial screening (Umpierrez et al 2003; Kordonouri et al 2004; Kordonouri et al 2005; Severinski et al 2009).

The results of the included studies demonstrate the high prevalence of thyroid autoimmunity and thyroid disease in individuals with type 1 diabetes. The prevalence of thyroid autoimmunity ranged from 5.4% to 15.5% in children and adolescents, and the prevalence of hypothyroidism was reported as 8.1% in the study by Severinski (2009). In adults, the prevalence of thyroid disease, including subclinical disease, was reported as 12.4% in males and 31.4% in females (Perros et al 1995). The incidence in a cohort of Australian children was 0.9 per 100 patient-years (Glastras et al 2005). By duration of diabetes, the cumulative incidence of AIT was reported as 14% after 10 years duration in children (Kordonouri et al 2005) and as high as 22% after 6 years duration in a group of Croatian children (Severinski et al 2009). In both those studies, the cumulative incidence in girls was significantly greater than in boys. In adults, the annual incidence of thyroid disease was reported as 6.5% in males and 12.3% in females, including subclinical forms (Perros et al 1995). Three studies, two in children and one in adults, reported statistically significant differences in the probability of developing thyroid disease between those patients lacking thyroid antibodies at diagnosis of diabetes and those that have such antibodies, with those with a positive screen being about 18 times more likely to develop thyroid disease (Umpierrez et al 2003; Glastras et al 2005; Kordonouri et al 2005). The presence of antibodies is associated with higher risk; therefore, it may be appropriate to undertake a higher level of surveillance for this subgroup of patients.

The results of these studies provide the rational for screening at diagnosis of type 1 diabetes, with the authors consistently recommending screening for thyroid disease at diagnosis of type 1 diabetes through measurement of thyroid function and thyroid autoantibodies.

For follow-up screening, three authors recommend annual thyroid function tests, particularly in patients with an initial positive thyroid autoantibody test (Perros et al 1995; Umpierrez et al 2003; Glastras et al 2005); Glastras et al recommended biannual thyroid function tests in those initially negative to thyroid autoantibodies (Glastras et al 2005). Kordonouri et al (2005) recommend a combination of both thyroid function tests and thyroid autoantibody tests annually in those who have positive thyroid autoantibody test at diagnosis, and annually from onset of puberty in those with an initial negative thyroid autoantibody test (Kordonouri et al 2005). Severinski et al recommended annual screen with a thyroid autoantibody test with thyroid function tests in those with a positive result(Severinski et al 2009).

20.2.5 Conclusion

This systematic review of evidence to inform screening practices for thyroid disease in children and adults with type 1 diabetes is based on the results of six prospective longitudinal cohort studies, five of which were of moderate risk of bias and one of high risk of bias. A significant difference in the cumulative incidence of thyroid disease between patients with a positive thyroid antibody screen and those with a negative screen were consistently reported in three of the studies (two in children and one in adults). Another consistent finding was that transient autoimmunity was not reported in any patients with thyroid antibody titres above 100U/mL. In one study, transient autoimmunity was reported in five children in whom thyroid antibodies were only slightly elevated. The studies measuring thyroid antibodies at multiple time points consistently reported that most patients with positive results were detected at their initial screening. All studies consistently

recommend screening for thyroid disease and thyroid autoimmunity at diagnosis. Annual screening for thyroid disease in patients with a positive thyroid antibody titre was recommended by the authors of five of the studies, with less frequent screening in those that have negative antibody titres. Annual screening for thyroid autoimmunity in all patients was recommended by the authors of one study. The evidence is generalisable to both children and adults with type 1 diabetes, with the only exclusions reported as patients who had developed thyroid disease before the diagnosis of diabetes. The results are applicable to the Australian population, with one study carried out in a cohort of Australian children and all other studies carried out in countries with a well-developed health-care system.

20.2.6 Evidence Matrix

Q20.2	How and how often should patients with type1 diabetes be screened for thyroid disease?	
Evidence statement	Thyroid dysfunction is common in type 1 diabetes, and positive antibodies are strongly predictive of thyroid dysfunction.	
Evidence base	C	Five Level III studies with a moderate risk of bias, and one Level III study with a high risk of bias.
Consistency	B	Consistent findings included the following: • A significant difference in the cumulative incidence of thyroid disease in patients positive to thyroid antibodies at diagnosis versus those negative to thyroid antibodies at diagnosis (four studies). • In studies measuring thyroid antibodies at multiple time-points, most patients were found to be positive at diagnosis of type 1 diabetes, rather than at follow-up testing (four studies). • Transient autoimmunity was not found in any patients who had highly positive thyroid antibody screen (>100 U/mL) (four studies). • Children and adults should be screened for thyroid disease and autoimmunity at diagnosis of type 1 diabetes (six studies). • Annual screening is suggested in antibody-positive patients, with less frequent screening in antibody negative patients (five studies).
Clinical impact	B	Thyroid dysfunction is common in type 1 diabetes, and often requires treatment. Antibodies to TPO or TG are predictive of development of hypothyroidism.
Generalisability	A	There is evidence in both children (n=1127) and adults (n=464) with type 1 diabetes. Follow-up was of 18 years' duration.
Applicability	A	One study was conducted in a group of Australian children younger than 15 years; all other studies were undertaken in countries with a well-developed health-care system.
Other factors	N/A	
Recommendation		
R20.2	Screening for thyroid dysfunction and testing for antibodies to thyroid peroxidase (TPO Ab) should be performed at diagnosis of type 1 diabetes; screening for thyroid dysfunction should be performed regularly thereafter (Grade B).	

TG, thyroglobulin; TPO, thyroid peroxidase

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Abbreviations and acronyms

A_{1c}	glycated haemoglobin
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ADA	American Diabetes Association
ADC	Australian Diabetes Council
ADDQoL	audit of diabetes-dependent quality of life
ADEA	Australian Diabetes Educators Association
ADIPS	Australasian Diabetes in Pregnancy Society
ADS	Australian Diabetes Society
AER	albumin excretion rate
AHT	antihypertensive
AN	autonomic neuropathy
ANOVA	analysis of variation
APEG	Australasian Paediatric Endocrine Group
APS	autoimmune polyglandular syndrome
APS	Australian Psychological Society
ARA	antireticulin antibodies
ARB	angiotensin II receptor blocker
AUC	area under the glucose curve
BAI	Beck Anxiety Inventory
BASC	Behaviour Assessment System for Children
BDI	Beck Depression Inventory
BG	blood glucose

BGAT	blood glucose awareness training
BGL	blood glucose level
BMI	body mass index
BP	blood pressure
BRFSS	Behavioural Risk Factor Surveillance System
C	cholesterol
CACTI	coronary artery calcification in type 1 diabetes
CAN	cardiac autonomic neuropathy
CBGM	continuous blood glucose monitoring
CBCL	child behaviour check list
CBT	cognitive behavioural therapy
CCB	calcium channel blocker
CCF	congestive cardiac failure
CDI	Children's Depression Inventory
CFRD	cystic fibrosis related diabetes
CGM	continuous glucose monitoring
CGMS	continuous glucose monitoring systems
CHD	coronary heart disease
CHO	carbohydrate
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CIMT	carotid intima-media thickness
CIPII	continuous intraperitoneal insulin infusion
CNS	central nervous system
CORE	Center for Outcomes Research

CRP	C-reactive protein
CSII	continuous subcutaneous insulin infusion
CT	conventional treatment
CVA	cardiovascular accident
CVD	cardiovascular disease
DA	Diabetes Australia
DAA	Dietitians Association of Australia
DAFNE	dose adjustment for normal eating
DARE	database of abstracts of reviews of effects
DCCT	Diabetes Control and Complications Trial
df	degrees of freedom
DIDMOAD	diabetes insipidus diabetes mellitus optic atrophy deafness
DIMD	Diagnostic Interview for Mental Disorders
DIS	Diagnostic Interview Schedule
DKA	diabetic ketoacidosis
DPT	Diabetes Prevention Trial
DQOL	diabetes quality of life
DSG	desogestrel
DSM	*Diagnostic and statistical manual of mental disorders*
E2	17ß-estradiol
EDE	Eating Disorders Examination
EDI	Eating Disorder Inventory
EDIC	Epidemiology of Diabetes Interventions and Complications
ED-NOS	eating disorders not otherwise specified
EDTRS	Early Treatment Diabetic Retinopathy Study

EE2	ethinyl-estradiol
ELISA	enzyme linked immunosorbent assay
EMA	antiendomysial antibodies
ENDIT	European Nicotinamide Diabetes Intervention Trial
EOD	early onset diabetes
ES	effect score
FBG	fasting blood glucose
FPG	fasting plasma glucose
FPIR	first phase insulin response
FSIQ	full scale intelligence quotient
GAD	glutamic acid decarboxylase
GADA	glutamic acid decarboxylase antibodies
GFR	glomerular filtration rate
GI	glycaemic index
GSD	gestodene
HADS	Hospital Anxiety and Depression Scale
HbA_{1c}	glycated haemoglobin
HDL	high density lipoprotein
HF	high frequency
HLA	human leukocyte antigen
HMG CoA	3-hydroxy-3-methylglutaryl-coenzyme
HNF	hepatic nuclear factor
HR	hazard ratio
HSCL	Hopkins Symptom Checklist
HRV	heart rate viability

HTA	health technology assessments
IA-2	insulinoma-associated 2 molecule
IAA	insulin autoantibodies
IAsp	insulin aspart
ICA	islet cell antigen
ICER	incremental cost-effectiveness ratio
IDDM	Insulin dependent diabetes mellitus
IDF	International Diabetes Federation
IFG	impaired fasting glycaemia
IGT	impaired glucose tolerance
IIS	individual impairment score
IM	Intramuscular
INAHTA	International Network of Health Technology Assessment
IQ	intelligence quotient
IQR	interquartile range
IRR	incidence rate ratio
ISCA	Interview Schedule for Children and Adolescents
IT	intensive treatment
ITT	intention to treat
IUD	intrauterine device
IV	intravenous
IVGTT	intravenous glucose tolerance test
JDFU	Juvenile Diabetes Foundation Unit
JDRF	Juvenile Diabetes Research Foundation
K6	Kessler 6 scale

LADA	latent autoimmune diabetes of the adult
LDL	low density lipoprotein
LF	low frequency
LNG	levonorgestrel
LOD	late onset diabetes
LY	life year
LYN	lynoestrenol
M-CIDI	Munchener Composite International Diagnostic Interview
MD	mean difference
MDI	multiple daily injections
MET	motivational enhancement therapy
MF	metformin
MHC	major histocompatibility complex
MI	myocardial infarction
MNSI	Michigan Neuropathy Screening Instrument
MODY	maturity onset diabetes in the young
mono	monounsaturated
MOS	Medical Outcomes Survey
MRDM	malnutrition related diabetes mellitus
mtDNA	mitochondrial DNA
NA	not available
NATA	National Association of Testing Authorities
NICE	National Institute for Clinical Excellence
NIDDM	non-insulin dependent diabetes mellitus
NHMRC	National Health and Medical Research Council

NHS	National Health Service
NPH	neutral protamine Hagedorn
NR	not reported
NS	not significant
OR	odds ratio
OCP	oral contraceptive pill
PAID	Problem Areas in Diabetes program
PedsQL	Pediatric Quality of Life Inventory
PG	plasma glucose
PGL	plasma glucose levels
PIQ	performance intelligence quotient
PL	placebo
poly	polyunsaturated
PPG	program project grant
PSE	present state examination
PTSD	post-traumatic stress disorder
OGTT	oral glucose tolerance test
QALE	quality-adjusted life expectancy
QALY	quality-adjusted life years
QoL	quality of life
QUAL	qualitative
QUANT	quantitative
RACP	Royal Australian College of Physicians
RACGP	Royal Australian College of General Practitioners
RAS	renin-angiotensin system

RCFA	red cell fatty acids
RCMAS	Revised Children's Manifest Anxiety Scale
RCT	randomised controlled trial
RD	risk difference
ROC	receiver operating characteristic
RR	relative risk
S-ACE	serum angiotensin converting enzyme
SADS	Schedule for Affective Disorders and Schizophrenia
SADS-LA	Schedule for Affective Disorders and Schizophrenia Lifetime Version
SC	subcutaneous
SCL-90R	Symptom Checklist–90R
SD	standard deviation
SDS	standard deviation score
SE	standard error
SES	socioeconomic status
SH	severe hypoglycaemia
SIMP	simplified
SMBG	self-monitoring of blood glucose
SPD	severe psychological distress
SPPC	self-perception profile for children
SR	systematic review
STAI	State-Trait Anxiety Inventory
TG	trigylceride
TPOA	thyroperoxidase antibodies
TRIGR	Trial to Prevent Type 1 Diabetes in the Genetically at Risk

TSH	thyroid stimulating hormone
tTG	anti-tissue transglutaminase
tTGA	anti-tissue transglutaminase antibody
UKPDS	United Kingdom Prospective Diabetes Study
VIQ	verbal intelligence quotient
VLDL	very low density lipoprotein
WHO	World Health Organization
WMD	weighted mean difference
YASR	Young Adult Self Report
YSR	Youth Self Report
ZnT-8	zinc transporter 8

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