Australian Diabetes Society Position Statement:

Individualization of HbA1c Targets

for Adults with Diabetes Mellitus

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The Australian Diabetes Society: Supporting its members to enhance the welfare of people with diabetes

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SUMMARY

Tight glycaemic control reduces the risk of development and progression of organ complications in people with both type 1 and type 2 diabetes. A number of large clinical trials aiming for tight control have recently added to the knowledge in this field. On the basis of these trials, and earlier landmark studies, the Australian Diabetes Society recommends a general target HbA1c of ≤7.0% for most patients. HbA1c targets however, need to be individualised to a tighter or lesser degree, with a recommended target HbA1c level of ≤6.0% in some people, or up to ≤8.0% in others.

Individualization of the HbA1c target is based on patient specific factors such as the type of diabetes and its duration, pregnancy, diabetes medication being taken, presence of cardiovascular disease, risk of, and problems from hypoglycaemia, and co-morbidities. In particular, intensive glycaemic control is likely to be of greatest benefit early in the disease process. Management of diabetes mellitus also includes adequate control of other cardiovascular risk factors including obesity, blood pressure and lipids, anti-platelet therapy and smoking cessation.

BACKGROUND

The prevalence of diabetes mellitus is increasing in Australia, with the AusDiab survey finding that in the year 2000, diabetes affected 7.4% of the population (Dunstan 2002). Both type 1 and type 2 diabetes are associated with increased microvascular and macrovascular disease, disability and premature mortality. Diabetes is therefore a National Health Priority Area for the Commonwealth.

There is strong evidence from randomised controlled trials that better glycaemic control can reduce some diabetic complications. This is a principal goal of diabetes management. Most authorities have recommended an HbA1c target of ≤7.0%, largely based on the results of the Diabetes Complications and Control Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS), which demonstrated that intensive glucose control substantially reduced onset and delayed progression of microvascular disease.

In the DCCT, tight glycaemic control, achieving a mean HbA1c of 7.0% with intensive insulin therapy given by 3-4 injections per day or insulin pump (vs 9.2% in the conventional-therapy arm) over 6.5 years, reduced retinopathy by 47-76%, nephropathy by 39-54%, and clinical neuropathy by 60% in subjects with type 1 diabetes.[2] In the UKPDS, intensive therapy with insulin or sulphonylurea in people with newly diagnosed type 2 diabetes (mean age 53 years) achieved a median HbA1c of 7% over 10 years (vs 7.9% with standard treatment). This resulted in a 12% reduction in diabetes-related endpoints, mainly in microvascular events.[3] Additionally, in an obese sub-group of the intensive-therapy group, metformin used as first line therapy reduced the incidence of myocardial infarction by 39% and all cause mortality by 36%.[4] This did not reach statistical significance amongst subjects primarily assigned to sulphonylureas or insulin (relative risk 0.84, 95%CI 0.71-1.00, p=0.052).[3] Further support comes from a smaller Japanese trial which randomized people with insulin requiring type 2 diabetes to basal bolus insulin therapy or conventional once daily or twice daily insulin, achieving a mean HbA1c of 7.2% vs 9.4%.[5] The intensive therapy group developed less (or had less progression of) retinopathy, nephropathy and neuropathy.

In 2008, the results of several large studies designed to examine the effect of even tighter glycaemic control on cardiovascular outcomes and the long-term follow-up of UKPDS were published. The conflicting results have raised questions regarding the appropriateness of existing HbA1c targets, and created some confusion amongst clinicians. This has prompted the Australian Diabetes Society to develop recommendations for HbA1c, with a focus on the individualization of targets. These will complement the NHMRC Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes, which recommends a general HbA1c target of ≤7.0%.[6] ADS members were invited to make submissions to this process, and these were taken into consideration by the writing party. The pregnancy guidelines were developed in collaboration with the Australasian Diabetes in Pregnancy Society. It should be noted that this Position Statement serves as a guide to assist management, and it is not our intention for it to be dogmatically applied. Furthermore, these guidelines only apply to adults with diabetes; there are separate NHMRC guidelines for type 1 diabetes in children and adolescents.[7]

RECENT STUDIES OF TIGHT GLYCAEMIC CONTROL IN TYPE 2 DIABETES

ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD)

In the ACCORD Study, 10,251 adults with type 2 diabetes (mean age 62 years, disease duration 10 yrs) were randomised to intensive therapy (target HbA1c <6% using any anti-diabetic agent) or conventional therapy (target HbA1c 7%-7.9%).[8] All subjects had established or increased risk for cardiovascular disease (CVD). At one year, the intensive-therapy group achieved a median HbA1c of 6.4%, and the conventional group, 7.5%. After 3.5 years follow-up, the intensive regimen was discontinued due to an unexpected increase in all-cause mortality (a secondary endpoint) in this arm (5.0% vs 4.0%, hazard ratio 1.22, 95%CI 1.01-1.46, p=0.04). At this point, the pre-specified primary outcome, which was the first occurrence of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death, was showing a non-significant trend favouring intensive control (6.9% vs 7.2%, HR 0.90, 95%CI 0.78-1.04, p=0.16). No cause for the increased mortality in the intensive-therapy group was identified, though the incidence of hypoglycaemia requiring assistance was higher (10.5% vs 3.5%, p<0.001). On post-hoc sub-analysis, increased mortality was observed in the intensive group amongst subjects with known CVD or HbA1c >8.5% at baseline. Weight gain >10kg was also more common in the intensive group. The increased mortality in the intensive-therapy group has raised questions as to whether an HbA1c target around the normal range is appropriate in patients with or at high risk of CVD.

ACTION IN DIABETES AND VASCULAR DISEASE: PRETERAX AND DIAMICRON MODIFIED RELEASE CONTROLLED EVALUATION (ADVANCE)

The ADVANCE trial randomised 11,140 people with type 2 diabetes (age 66 years, duration 8 years) and major macrovascular or microvascular disease, or at least one other risk factor, to intensive or standard glycaemic control.[9] The intensive-therapy group was treated with Diamicron (gliclazide) Modified-Release, with the suggested sequential addition of metformin, a thiazolidinedione, acarbose and insulin as required to achieve a target HbA1c ≤6.5%. The standard-therapy group was treated in accordance with local guidelines. After 5 years, the mean HbA1c was 6.5% in the intensive-therapy group and 7.3% in the standard-therapy group. Intensive control resulted in a reduction in the primary outcome of combined major micro- and macrovascular events (18.1% vs 20.0%, HR 0.90, 95%CI 0.82-0.98, p=0.01), which were solely due to fewer microvascular events, mainly nephropathy. There were no differences in major macrovascular events, or mortality. Severe hypoglycaemia was more common in the intensive group (2.7% of subjects having at least one episode vs 1.5%, HR 1.86, 95%CI 1.42-2.40, p<0.001), with this contributing to increased hospitalisation (44.9% vs 42.8%, HR 1.07, 95%CI 1.01-1.13, p=0.03).

VETERANS AFFAIRS DIABETES TRIAL (VA-DT)

The VA-DT recruited 1791 subjects (age 60 years, 97% male, duration 12 years) with suboptimally controlled type 2 diabetes, to receive either intensive or standard treatment.[10] The HbA1c target was <6% for the intensive group, and 8-9% for the standard group. Stable median HbA1c levels of 6.9% and 8.4% respectively were achieved. After a median 5.6 years follow-up, no difference was demonstrated in the primary outcome of time to the first occurrence of any one of myocardial infarction, stroke, cardiovascular death, congestive heart failure, surgery for vascular disease, inoperable coronary artery disease or amputation for ischaemia (HR 0.88, 95%CI 0.74-1.05, p=0.14). There was no difference in all-cause mortality (HR 1.07, 95%CI 0.81-1.42, p=0.62). A post-hoc sub-analysis suggested that there was a benefit of intensive control on cardiovascular events for subjects who had diabetes of less than 20 years duration; conversely there appeared to be a detrimental effect in subjects who had a longer duration of diabetes. Severe hypoglycaemia was 3 times more likely in the intensive group. Weight gain was 4 kgs greater in the intensive-therapy group.

UKPDS FOLLOW-UP
The 10 year observational post-trial monitoring of the original randomised UKPDS cohorts has provided additional data regarding longer-term type 2 diabetes outcomes.[11] Upon completion of the UKPDS, all study subjects were advised to aim for lower blood glucose levels than previously targeted, with 3277 patients entering post-trial monitoring. Although the difference in HbA1c between the intensive and standard-therapy groups was lost within one year of completing the original study, the previously demonstrated reductions in risk of diabetes endpoints and microvascular disease persisted at 20 years. A reduction in myocardial infarction (15%, p=0.01) and all-cause mortality (13%, p=0.007) emerged amongst patients originally under intensive treatment with sulphonylureas or insulin compared with subjects in the standard treatment group, and even greater reductions were observed in those originally treated with metformin (21% in any diabetes endpoint; 33% in myocardial infarction; 27% in all-cause mortality). Therefore the benefits of better glycaemic control from the time of diagnosis of type 2 diabetes persisted and strengthened. Furthermore, the cardiovascular benefits may take many years to become evident.

KEY STUDIES COMPARED
ACCORD showed an overall detrimental effect of tight glycaemic control on mortality; ADVANCE and VADT have not shown any overall effect, either positive or detrimental, of tight glycaemic control on mortality; and, UKPDS showed a reduction in all-cause mortality.

One limitation of ACCORD, ADVANCE and VA-DT is that, compared to the UKPDS, they recruited older subjects at increased risk of CVD with poorly controlled diabetes. These patients may have had sub-optimal control for many years, resulting in irreversible end-organ damage. Instituting tight control in such patients may be very different from maintaining excellent control from the outset, especially when other risk factors are addressed. Therefore, these three studies do not provide guidance for the management of younger patients, patients with lower risk of CVD or patients with long-standing, well-controlled type 2 diabetes. In contrast, UKPDS indicates that maintaining good glycaemic control after achieving it early in the disease process is beneficial. However, as the benefits on CVD were only observed in the post-trial monitoring period of UKPDS, appropriate trials in newly presenting young patients are much needed.

Whilst the increase in all cause mortality seen in ACCORD is of concern, the neutral effect of intensive control in ADVANCE and VA-DT provide some reassurance. Furthermore, a recent meta-analysis including ACCORD, ADVANCE, VA-DT, UKPDS and PROactive[12] (a randomized controlled trial of intensified therapy with pioglitazone compared against placebo) has found that overall, tight glycaemic control does not increase the risk of death, though there was heterogeneity in outcome between the studies, and differences in patient population were not considered.[13]

The results of the major randomized controlled trials of intensive glycaemic control for type 2 diabetes are summarized in table 1.

Table 1: Details of major randomized controlled trials of glycaemic control in type 2 diabetes

	Subjects	Intervention Strategy	Targets	Median HbA1c Achieved	Primary Outcome (s)	Primary Results	All Cause Mortality	CVD Mortality	Microvascular	Myocardial Infarction	Hypos	Duration	Comment
UKPDS (sulphonyl ureas / insulin) including post-trial monitooring	N=3867 newly diagnosed T2DM, fasting BGL>6	Diet, chlorpropamide, glibenclamide, insulin	Intensive FBGL<6, preprandial 4-7 if on insulin Standard FBGL<15	Intensive 7.0% Standard 7.9%	i) Any diabetes related endpoint, ii) Diabetes related death, iii) all cause mortality + others	i) RR 0.88 (0.79-0.99) p=0.029; After 20yrs RR 0.91 (0.83-0.99) p=0.04 ii) RR 0.90 (0.73-1.11) p=0.34; After 20yrs RR 0.83 (0.73-0.96) p=0.01	RR 0.94 (0.8-1.1) p=0.44; After 20yrs RR 0.87 (0.79-0.96, p=0.007	RR 0.8 (071-1.00) p=0.052 (AMI)	RR 0.75 (0.60-093) p=0.0099, mainly ↓ retinal photocoagulation, microalbuminuria. After 20yrs RR 0.76 (0.64-0.89), p=0.001	Fatal RR 0.94 (0.68-1.30) p=0.63; Non-fatal RR 0.79 (0.58-1.09) p=0.057; After 20yrs RR 0.85 (0.74-0.97), p=0.01	Increased in intensive group	Median 10 yrs for RCT, + 10 yrs post-trial monitoring	1% increase HbA1c increases CAD by 11%, HbA1c rose gradually over 10 yrs. No differences in BP between groups in post-trial monitoring, but lipids were not assessed.
UKPDS (metformin)	N=753 newly diagnosed overweight T2DM, fasting BGL>6	Metformin ± glibenclamide ± insulin		Intensive 7.4% Standard 8.0%		i) RR 0.68 (0.53-0.87) p=0.0023; After 20yrs RR 0.79 (0.66-0.95), p=0.01 i) RR 0.58 (0.37-0.91) p=0.017; After 20yrs RR 0.70 (0.53-0.92), p=0.01	RR 0.64 (0.45-0.91) p=0.011; After 20yrs RR 0.73 (0.59-0.89), p=0.002	RR 0.5 (0.23-1.09) p= 0.02	RR 0.71 (0.43-1.19, p=0.71); After 20yrs RR 0.84 (0.60-1.17), p=0.31	RR 0.61 (0.41-0.89) p=0.01; After 20yrs RR 0.67 (0.51-0.89), p=0.005		Median 10 yrs for RCT + 10 yrs post-trial monitoring	
Kumamoto	N=110 T2DM on o.d. or b.d. insulin, age<70, no significant microvascular complicartions	Basal bolus insulin vs b.d. insulin	Intensive: FBGL<7.8, 2h pc <11.1, HbA1c<7.0%,. Control: Asymptomatic + FBGL<7.8	Intensive Mean 7.2±1.0% Standard 9.4±1.3%	Microvascular complications	Retinopathy progression ↓63% Nephropathy progression ↓74%, ↓neuropathy					35 vs. 22 events /100 patient-years		
ACCORD	N=10251 T2DM HbA1c ≥7.5, age 40-79, evidence of CVD risk	Any	Intensive HbA1c <6 Standard HbA1c 7-7.9%	Intensive 6.4% Standard 7.5%	First AMI, stroke or CVD death	2.11% vs 2.29% p.a. (HR 0.90 (0.78-1.04) p=0.16	1.41% vs 1.14% p.a. HR 1.22 (1.01-1.46) p=0.04	2.63% vs 1.83% p.a. HR 1.35 (1.04-1.76) p=0.02	Not reported	Non-fatal 1.11% vs 1.45% p.a. HR 0.76 (0.62-0.92) p=0.004; Fatal 0.4% vs 0.3%	Requiring medical assistance 10.5% vs 3.5%, p<0.001	Mean 3.5 yrs	Primary outcome less if no CVD or HbA1c<8%. Rapid ↓ in HbA1c achieved (1.4% in first 4/12).
ADVANCE	N=11140 age ≥55 T2DM after age 30, h/o macro or microvascular disease or 1 risk factor	Gliclazide MR plus other drugs as required	Intensive HbA1c ≤6.5 Standard local guidelines	Intensive 6.4% Standard 7.0%	Major macrovascular and microvascular events*	18.1% vs 20.0%, HR 0.9 (0.82-0.98), p=0.01	HR 0.93 (0.83-1.06), p=0.28	HR 0.88 (0.74-1.04), p=0.12	9.4% vs 10.9%, HR 0.86 (0.77-0.97), p=0.01, mainly due to a reduction in nephropathy	Non-fatal HR 0.98 (0.78-1.23) p=NS	2.7% vs 1.5%, HR 1.86 (1.42-2.40), p<0.001	Median 5 yrs	Effects consistent across subgroups. ↓ in microvascular disease due to ↓ nephropathy
VA-DT	N=1791 T2DM, age≥41, HbA1c ≥7.5%	Combination metformin, sulphonylurea, insulin	Intensive HbA1c <6% Standard HbA1c 8-9%	Intensive 6.9% Standard 8.4%	AMI, stroke, CVD death, CCF, inoperable CAD, amputation, intervention for CVD & PVD	HR 0.88 (0.74-1.05) p=0.14	HR 1.07 (0.81-1.42, p=0.62)	4.5% vs 3.7%, p=0.29	Differences in retinopathy or nephropathy NS except for worsening of albuminuria, p=0.05	HR 0.82 (0.59-1.14) p=0.24	8.5% vs 3.1%, p<0.001	Mean 6.25 yrs	Shorter duration diabetes benefited from intensive treatment.

HR = hazard ratio, RR = relative risk, NS = not significant, yrs = years

RECENT ADDITIONAL EPIDEMIOLOGICAL AND OBSERVATIONAL DATA

Epidemiological and observational studies have shown a continuum of risk of diabetic complications and mortality with increasing HbA1c. The threshold for increased risk lies within or at the upper limit of the normal range for HbA1c. Published in 2004, the European Prospective Investigation of Cancer in Norfolk (EPIC-Norfolk) prospectively followed 10,132 individuals aged 40-79 for an average of 6 years.[14] A continuous increase in cardiovascular events and all-cause mortality was observed with increasing baseline HbA1c from 5% upwards in men, even in the absence of diabetes. Amongst women, this was significant at HbA1c >6%.

Also published in 2004, a meta-analysis of prospective cohort studies in people with type 2 diabetes estimated that for every 1% increase in HbA1c, there was an 18% (95%CI 10-26%) higher risk of CVD.[15] For people with type 1 diabetes the risk increased by 15% (95%CI −8%-43%). In the UKPDS and published in 2000, each 1% reduction in HbA1c was associated with a 37% decrease in risk of microvascular complications, 14% decrease risk of myocardial infarction, and 14% decrease in risk of all-cause mortality with no threshold effect.[16]

IMPLICATIONS OF RECENT STUDIES FOR THE MANAGEMENT OF TYPE 2 DIABETES

The main concern arising from ACCORD is that tight glycaemic control in individuals with or at high risk of CVD, increases the risk of death. When considered together with the other trials above, there remains a clear benefit of maintaining an HbA1c ≤7.0% for the majority of patients. The risk-benefit balance however, is complex, and the following conclusions can also be drawn:

- Tight glycaemic control early in the diabetes disease process is desirable, and is likely to yield the greatest benefit for the prevention of micro- and macrovascular complications, as well as overall mortality. There is no evidence that maintenance of tight glycaemic control (e.g. HbA1c <6.0-6.5%) in a patient with long-standing well-controlled type 2 diabetes increases mortality risk.
- Attaining tight glycaemic control in advanced disease yields little, if any, benefit for macrovascular disease but this is still effective in retarding the development and progression of microvascular disease.
- Attempts to achieve tight glycaemic control need to be balanced against the increased risk of severe hypoglycaemia. In the UKPDS, the annual incidence of hypoglycaemia was 0.1% among subjects on diet alone, 0.3% for metformin monotherapy, 1.2% for sulphonylurea therapy, 3.8% for subjects taking basal insulin only, and 5.5% where prandial insulin was used.[17] Caution is necessary in people with CVD or the elderly. When such patients are on insulin or sulphonylureas, a low HbA1c warns of a heightened risk of hypoglycaemia. For patients prone to severe hypoglycaemia or who have hypoglycaemia unawareness, it is prudent to maintain an HbA1c >7%.
- Intensive correction of HbA1c requires caution as the risk of hypoglycaemia may be increased. This is particularly important in subjects with CVD or diabetes duration for more than 10-20 years. Weight gain is also more likely.

Therefore practitioners need to individualise the HbA1c target for people with type 2 diabetes, taking into consideration the presence of CVD, diabetes duration, diabetes medication(s) taken, co-morbidities, and problems with severe hypoglycaemia (table 2, with detailed rationale in appendix 2). It is important to remember that the prevention of hypoglycaemia does not rely purely on adjustment of medication, but also on patient education, including blood glucose monitoring.

Table 2: Recommended HbA1c target range for adults with type 2 diabetes

		HbA1c target (%)
General Target		≤7.0[a]
Specific clinical situations		
	Therapy	
Diabetes of short duration[b] and no clinical cardiovascular disease	Requiring lifestyle modification ± metformin	≤6.0[a]
	Requiring any anti-diabetic agents other than metformin or insulin	≤6.5[a]
	Requiring insulin	≤7.0[a]
Pregnancy or planning pregnancy		≤6.0[a]
Diabetes of longer duration[b] or clinical cardiovascular disease	Any	≤7.0[a]
Recurrent severe hypoglycaemia or hypoglycaemia unawareness	Any	≤8.0
Patients with major co-morbidities likely to limit life expectancy[c]	Any	Symptomatic therapy of hyperglycaemia[d]

Notes
- [a]Achievement of HbA1c targets must be balanced against risk of severe hypoglycaemia, especially in the elderly.
- [b]In an older adult long duration might be considered to be >10-20 years, but for a person who develops type 2 diabetes at a young age, it may be considerably longer.
- [c]Examples of major co-morbidities include chronic medical conditions such as chronic kidney disease stages 4 or 5; NYHA heart failure stages III or IV; incurable malignancy; and moderate to severe dementia.
- [d]Where practical, suggest BGL target <15 to help minimise risk of infection

RECENT DATA REGARDING GLYCAEMIC CONTROL IN TYPE 1 DIABETES

DIABETES COMPLICATIONS AND CONTROL TRIAL (DCCT) / EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS (EDIC) STUDY

Upon the completion of the DCCT, follow-up of 1394 subjects (96% of DCCT survivors) continued in the observational EDIC Study. Among the primary aims of EDIC were to examine the long-term effects of the earlier differences in glycaemic control on both microvascular and CVD. All EDIC subjects were advised regarding intensive insulin therapy, and returned to their usual medical practitioner for diabetes care. Subsequently, the HbA1c levels converged, with the HbA1c in the original intensive group rising to 8.0±1.2% and the conventional group decreasing to 8.2±1.2%. The rate of progression of retinopathy[18], nephropathy[19] and neuropathy[20] remained lower in the prior intensive group, though there was some attenuation of the effect on retinopathy after 4-10 years.[21] Over 17 years of follow-up in DCCT and EDIC, subjects in the DCCT intensive treatment group had a 42% lower risk of CVD events (p=0.02) and nonfatal myocardial infarction, stroke, or cardiovascular death fell by 57% (p=0.02).[21]

These long-term results of DCCT/EDIC on both microvascular and macrovascular outcomes support the target HbA1c of ≤7.0% for people with type 1 diabetes. Situations where it is suggested that the HbA1c target should be less strict are outlined in table 2 (detailed rationale in appendix 2). In particular, it is advisable that the HbA1c be maintained at higher levels (e.g. 7.0%-8.0%) for patients who suffer severe hypoglycaemic episodes or have hypoglycaemia unawareness.

Table 3: Recommended HbA1c target range for adults with type 1 diabetes

	HbA1c target (%)
General target	≤7.0[a]
Specific clinical situations	
Pregnancy or planning pregnancy	≤7.0[a,b]
Recurrent severe hypoglycaemia or hypoglycaemia unawareness	≤8.0
Patients with major co-morbidities likely to limit life expectancy	Symptomatic therapy of hyperglycaemia[c] and avoid ketosis

Notes
[a]achievement of HbA1c targets must be balanced against risk of severe hypoglycaemia.
[b]an HbA1c ≤6.0% is desirable if it can be achieved safely
[c]Where practical, suggest BGL target <15 to help minimise risk of infection

PREGNANCY

Pre-gestational diabetes is associated with serious adverse pregnancy outcomes such as miscarriage, congenital malformation, pre-eclampsia and perinatal death. There is a continuous relationship between elevated HbA1c at conception and these outcomes, with increased risk at even slight elevations above the non-pregnant normal range. A meta-analysis which included 1977 pregnancies (the vast majority with type 1 diabetes) from seven prospective cohort studies, found that for every one standard deviation (SD) increase in HbA1c (equivalent to 0.5% where the normal range is 4.0-6.0%), the risk of congenital malformation increased by 20%.[22] Even where the HbA1c was only 2 SD above the mean (ie. 6.0%), there was approximately a 50% increase in risk (absolute risk 3%), compared with subjects where the HbA1c was at the population mean (5%). There are no detailed data defining the relationship between HbA1c and fetal outcome in type 2 diabetes, beyond the recognition that high HbA1c in early pregnancy is associated with serious adverse fetal outcomes.[23]

The only randomised controlled trial data come from the 270 pregnancies in the DCCT.[24] Women in the intensive arm had a lower HbA1c at conception than the control arm (7.4±1.3% vs 8.1±1.7%). Despite intensification of management during pregnancy resulting in a convergence in HbA1c between the two groups, eight congenital malformations occurred in the conventional-therapy group, compared with only one in the intensive group (p=0.06).

We recommend that the HbA1c at conception and during pregnancy should be ≤6.0%. This is achievable for many women with type 2 diabetes. Although this HbA1c target is also desirable in women with type 1 diabetes, there is a heightened risk of severe hypoglycaemia with such tight glycaemic control. Therefore unless a lower A1c can be achieved safely, a conservative target of ≤7.0% is recommended for them. Pre-pregnancy planning is essential. Other aspects of pregnancy care for women with pre-gestational diabetes have previously been outlined in the MJA.[25]

CAVEATS TO THE USE OF HbA$_{1C}$ AS A MEASURE OF GLYCAEMIC CONTROL

Whilst the risk of diabetic complications is primarily assessed by HbA1c, it is important to note that there are circumstances in which HbA1c measurement is unreliable. HbA1c is a measure of glycosylation of the haemoglobin molecule, which occurs in proportion to the glucose concentration over time. If exposure time (red cell life-span) is decreased, HbA1c will be decreased. Causes of decreased red cell life span include haemolysis, ineffective erythropoiesis (eg. iron, folate or B12 deficiency), and renal failure.[26] Additionally, misleading results may be seen in patients with haemoglobinopathies due to interference with the measurement of HbA1c or altered red cell life span,[27] and in recipients of recent blood transfusion. In one Australian study, 7 of 29 patients (24%) with an HbA1c result lower than expected based on home glucose monitoring had a haemoglobinopathy detected on Hb-electrophoresis.[28]

The reader should also be aware that in addition to HbA1c, many laboratories are now reporting "estimated average glucose levels" (eAG). This can be calculated from the formula: eAG = (1.6 x HbA1c) – 2.6 mmol/L.[29] The purpose of this approach is to aid in the presentation of HbA1c results to patients in terms of average blood glucose.

MANAGEMENT OF CO-EXISTENT CARDIOVASCULAR RISK FACTORS

Diabetes is not only a disorder of glucose control. Weight control, anti-hypertensive therapy, lipid control and anti-platelet therapy are also critical in diabetes management. There are specific data in people with diabetes that controlling these other risk factors reduces cardiovascular mortality. The Steno-2 Study addressed multiple risk factors through control of HbA1c, blood pressure and lipids, aspirin and ACE inhibitor therapy, healthy diet, physical activity and smoking cessation.[30] This long-term target driven intervention among people with type 2 diabetes and microalbuminuria more than halved the risk of CVD, nephropathy, retinopathy and autonomic neuropathy.

The UKPDS and ADVANCE have also demonstrated improved macro- and microvascular outcomes with better blood pressure control.[31,32] The blood pressure target is <130/80 mmHg, and for those with ≥1g/day of proteinuria, ≤125/75 mmHg. In addition to lifestyle management, ACE inhibitor or angiotensin-II receptor blocker therapy is the preferred first line agent for hypertension, but preferably they should not be used together as this may accelerate renal failure.[33] However, two or more agents are often required to control blood pressure. In patients with increased cardiovascular risk (without cardiovascular disease), ACEI or A2RB therapy could be commenced even with the blood pressure in the target range. Statin therapy markedly reduces macrovascular events in type 2 diabetes.[34,35] The main lipid target is a LDL-C<2.5 mmol/L for primary prevention and <1.8 mmol/L in secondary prevention.

For most people with type 2 diabetes, the high absolute risk for macrovascular disease justifies statin treatment and ACE inhibitor (or angiotensin-II receptor blockade), even if lipids and blood pressure are in the target range. Anti-platelet therapy (especially aspirin at 75-325 mg daily) is indicated for both secondary and in many cases, primary prevention in those with high absolute cardiovascular risk.[36]

Anti-hypertensive therapy, lipid control, anti-platelet therapy and weight control are thus key elements in the management of diabetes. The NHMRC and ADS have developed detailed guidelines for the management of these risk factors[37-39] which are available on the NHMRC website (summarized in table 4).

Table 4. NHMRC / ADS evidence based guidelines for blood pressure, lipids and antiplatelet therapy in diabetes mellitus

Blood Pressure	
Normoalbuminuria or microalbuminuria	<130/80 mmHg
proteinuria of 1 g or more daily	<125/75 mmHg
Established microalbuminuria with BP<130/80 mmHg	Commence ACEI or A2RB, if blood pressure allows
Primary Lipid Target	
no clinical macrovascular disease	LDL-C <2.5 mmol/L
clinical macrovascular disease present	LDL-C <1.8 mmol/L
Anti-platelet therapy	
Known macrovascular disease	aspirin 75-325 mg daily, as tolerated
No known macrovascular disease	consider aspirin 75-325 mg daily on the basis of calculated cardiovascular risk

Appendix 1: Rationale and level of evidence for recommended HbA1c target range for adults with type 2 diabetes

		HbA1c target (%)	Rationale for recommendation	Level of Evidence For the Target Category
General Target		≤7.0	UKPDS demonstrated improved outcomes with median HbA1c ≤7%, supported by NHMRC systematic review	I
Specific clinical situations				
	Therapy			
Diabetes of short duration <u>and</u> no clinical cardiovascular disease	Requiring lifestyle modification ± metformin	≤6.0	UKPDS showed benefits with early treatment of diabetes. Epidemiological data indicates increased mortality and cardiovascular events with threshold below 6%. Negligible risk of hypoglycaemia with lifestyle or Metformin.	Consensus
	Requiring any anti-diabetic agents other than metformin or insulin	≤6.5	UKPDS showed benefits with early treatment of diabetes. The risk of hypoglycaemia increases with use of most antidiabetic agents other than Metformin hence we do are not recommending a target HbA1c ≤6.0% for this group. ADVANCE demonstrated reduced microvascular disease with an HbA1c target ≤6.5%.	II
	Requiring insulin	≤7.0	UKPDS demonstrated improved outcomes with median HbA1c 7%, in people with newly diagnosed diabetes, including people treated with insulin. The Kumamoto Study demonstrated improved outcomes with intensive insulin with mean HbA1c 7.2%.	II
Pregnancy or planning pregnancy		≤6.0	Almost all observational data (albeit mainly in type 1 diabetes) demonstrate a relationship between HbA1c and adverse pregnancy outcomes with a threshold below 6%.	Consensus

Diabetes of longer duration[2] or clinical cardiovascular disease	Any	≤7.0	UKPDS demonstrated improved outcomes with median HbA1c ≤7%. ACCORD indicates that attempts for even tighter control in people with relatively long duration of diabetes and cardiovascular disease associated with increased mortality. VADT found tighter control associated with increased cardiovascular events in people with diabetes >20 years (unpublished). We therefore do not routinely recommend tighter control in this group.	II
Recurrent severe hypoglycaemia or hypoglycaemia unawareness	Any	≤8.0	Severe hypoglycaemia is associated with significant morbidity and mortality. The risks of tight glycaemic control outweigh the benefits for such patients	Consensus
Patients with major co-morbidities likely to limit life expectancy	Any	Symptomatic therapy of hyperglycaemia	Tight glycaemic control will be of no benefit as diabetic complications take many years to develop.	Consensus

Appendix 2: Rationale and level of evidence for recommended HbA1c target range for adults with type 1 diabetes

	HbA1c target (%)	Rationale for recommendation	Level of Evidence for the Target Category
General target	≤7.0	DCCT/EDIC have shown that achieving a mean HbA1c of 7.0% was associated with improved outcomes	II
Specific clinical situations			
Pregnancy or planning pregnancy	≤7.0	Better pregnancy outcomes (borderline significance) in intensive group of DCCT (mean HbA1c 7.4%). Observational data demonstrate a relationship between HbA1c and adverse pregnancy outcomes with a threshold below 6%, but there is a heightened risk of hypoglycaemia at such low levels. Therefore for most women we recommend a target HbA1c ≤7.0%.	II
Recurrent severe hypoglycaemia or hypoglycaemia unawareness	≤8.0	Severe hypoglycaemia is associated with significant morbidity and mortality. The risks of tight glycaemic control outweigh the benefits for such patients	Consensus
Patients with major co-morbidities likely to limit life expectancy	Symptomatic therapy of hyperglycaemia and avoid ketosis	Tight glycaemic control will be of no benefit as diabetic complications take many years to develop.	Consensus

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