A new blood glucose management algorithm for type 2 diabetes

A position statement of the Australian Diabetes Society

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This position statement from the Australian Diabetes Society (ADS) outlines the risks, benefits and costs of the available therapies and suggests a treatment algorithm incorporating the older and newer agents.

ABSTRACT

Lowering blood glucose levels in people with type 2 diabetes has clear benefits for preventing microvascular complications and potential benefits for reducing macrovascular complications and death. Treatment needs to be individualised for the person with diabetes. This should start with selection of the appropriate glucose and glycated haemoglobin targets, taking into account life expectancy, and the wishes of the person with diabetes. For most people, early use of glucose lowering therapies is warranted.

A range of recently available therapies have added to our range of options for lowering glucose but this has made the clinical pathway for treating diabetes more complicated.

LIST OF ABBREVIATIONS

ADS	Australian Diabetes Society
DPP-4	Dipeptidyl peptidase-4
GLP-1	glucagon like peptide-1
GLP1RA	GLP-1 receptor agonist
HbA_{1c}	Glycosylated haemoglobin
PBS	Pharmaceutical Benefits Scheme
RCT	Randomised controlled trial
SGLT2	Sodium-glucose co-transporter2
TZD	Thiazolidinedione

INTRODUCTION

Type 2 diabetes is an increasingly common condition in Australia and worldwide. The annual costs of treating diabetes and its complications are estimated at over $10 billion in Australia alone. Large randomised controlled trials (RCTs) have demonstrated that intensive blood glucose control in people with type 2 diabetes (T2D) reduces microvascular complications (1, 2). A meta-analysis of the large RCTs (UKPDS, ADVANCE, ACCORD and VADT) has also demonstrated that intensive blood glucose control modestly reduces major cardiovascular events and myocardial infarction but not stroke or all-cause mortality (3).

Given the clear benefits of glucose lowering for microvascular complications and the potential benefits for macrovascular complications and death, early use of effective and safe glucose lowering therapies is warranted with appropriate individualisation of blood glucose levels and glycated haemoglobin targets.

In 2009, the Australian Diabetes Society (ADS) published a position statement recommending individualisation of glycaemic targets (4). In 2012, the American Diabetes Association and European Association for the Study of Diabetes adopted a similar strategy in a consensus statement. The key conclusions were that general glycated haemoglobin (HbA_{1c}) target for most people with T2D is ≤53mmol/mol (7.0%), however:

- in people without known cardiovascular disease, a long duration of diabetes, severe hypoglycaemia or another contraindication, the target is ≤48mmol/mol (6.5%)
- in people with reduced hypoglycaemia awareness or major co-morbidities, the
- target may increase to ≤64 mmol/mol (8.0%)
- in people with limited life expectancy, aim for symptom control
- in women planning a pregnancy, aim for the tightest achievable control without severe hypoglycaemia before and during pregnancy; preferably ≤42mmol/mol (6.0%).

Despite these recommendations and the increasing range of therapies available, achieving glycaemic targets can be difficult. To assist with selecting glucose-lowering pharmacotherapy for people with T2D, the ADS developed this position statement (**Figure1**).

METHOD

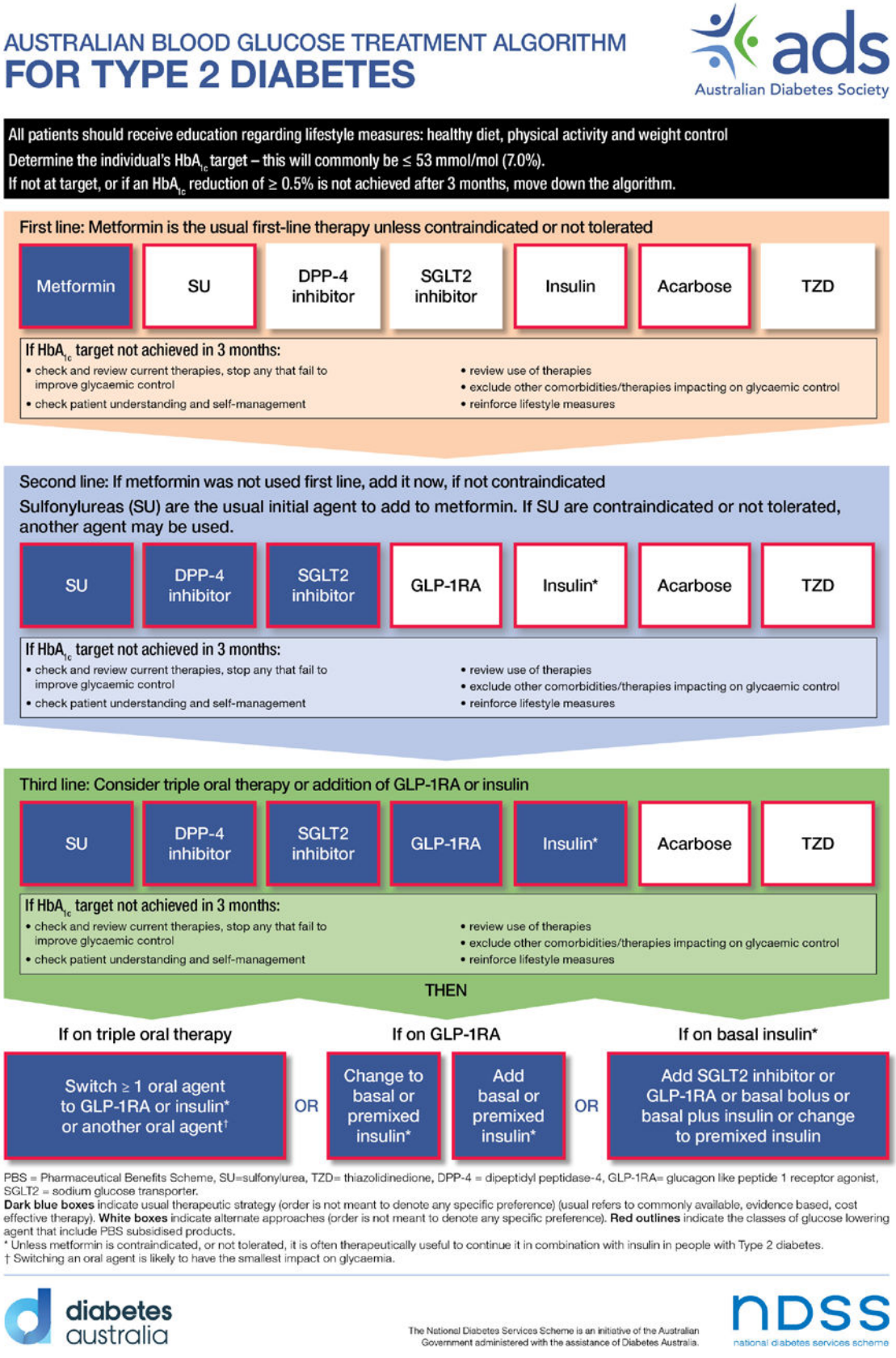
The ADS appointed the original authors to draft the position statement with a focus on the results of recent RCTs of glucose lowering agents.

The statement was reviewed by ADS council and then sent to all ADS members for comment before publication by MJA (5) in 2014.

The position statement briefly describes the classes of drugs and their place in the glucose lowering therapeutic algorithm (**Figure 1**), drug options in the setting of renal or hepatic impairment (**Table 1**), the Pharmaceutical Benefits Scheme (PBS) prescribing restrictions to obtain subsidised products (**Table 2**) and cost of various drugs to patients with and without PBS subsidy (**Table 3).**

In 2015 the ADS convened a working group to oversee the development of tools to assist with implementation of the algorithm. As part of this work, the original position statement and algorithm have been updated to include new RCT evidence (June 2016). In addition, a new table summarising the evidence and properties of the different classes of glucose lowering agents was developed (**Table 4**).

FIGURE 1. AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM FOR TYPE 2 DIABETES



DRUGS

Metformin

Metformin reduces hepatic glucose output, lowers fasting glucose and is generally weight-neutral. It decreases HbA1c by up to 15-22 mmol/mol (1.5-2.0%) if starting HbA1c is high (6, 7). It has long-term safety data (over 50 years). Gastrointestinal side effects are common and as such it should be started at low doses and titrated up. People with gastrointestinal side effects should be offered one of the slow-release formulations, which cost approximately 40% more per dose (see Table 3). Metformin is contraindicated for patients who have severe renal, hepatic or cardiac failure (see Table 1 for alternatives).

Sulfonylureas

Sulfonylureas bind to their receptor found on the surface of beta-cells, triggering insulin release in a glucose-independent manner. Their main side effects are hypoglycaemia and weight gain. They are inexpensive and effective, with decreases in HbA1c level of up to 7-16mmol/mol (0.6-1.5%) when combined with metformin (8-10). Sulfonylureas have favourable long-term safety and outcome data. The risk of hypoglycaemia is highest with sulfonylureas with long half-lives and renally-excreted active metabolites such as glibenclamide (9).

Two large RCTs (UKPDS (1) and ADVANCE (2)) have examined sulfonylurea's effects on cardiovascular outcomes. The UKPDS reported overall cardiovascular safety and reduced microvascular complications with either sulphonylurea or insulin based intensive glucose control compared with conventional treatment in patients with newly diagnosed type 2 diabetes and the ADVANCE trial reported overall cardiovascular safety and reduced new or worsening nephropathy including end-stage kidney disease with a sulphonylurea (gliclazide MR) based intensive glucose control approach compared with standard glucose control approach.

Dipeptidyl peptidase-4 inhibitors **(DPP-4)**

Dipeptidyl peptidase-4 inhibitors are reversible, competitive agents which bind to the DPP-4 active site, inhibiting the inactivation of glucagon-like peptide-1 (GLP-1), thereby increasing its availability. GLP-1 improves beta-cell function and insulin secretion. A meta-analysis has reported decreases in HbA1c of 7-8mmol/mol (0.6-0.7%) for most gliptins and 11mmol/mol for vildagliptin (11) after adjustment for baseline HbA1c. Common side-effects include mild gastrointestinal disturbance and nasopharyngitis, which often subside after 10-14 days. Rash is a rare but potentially serious side effect. Three large RCTs examining different DPP-4 inhibitors (SAVOR-TIMI: saxagliptin, EXAMINE: alogliptin, TECOS: sitagliptin) have reported overall cardiovascular safety (12-14) except for SAVOR-TIMI which also reported increased hospital admissions for heart failure amongst patients with or at risk of cardiovascular events (12). A recent meta-analysis of DPP-4 inhibitors has reported an increased risk of acute pancreatitis (RR 1.79; CI 1.13–2.81) that equates to a small increase in absolute risk (5.5 extra cases/10 000 patients/year) (15). Five DPP-4 inhibitors are approved for PBS subsidised use with either metformin or a sulfonylurea; saxagliptin, sitagliptin, linagliptin and vildagliptin are approved for use with metformin and sulfonylurea (listing date not available as yet for linagliptin and vildagliptin) (Table 2) and linagliptin sitagliptin are approved for use with insulin (listing date

not available as yet). DPP-4 inhibitors are not PBS subsidised for use as monotherapy.

Thiazolidinediones (TZD)

Thiazolidinediones are transcription factor peroxisome proliferator-activated receptor PPAR-gamma antagonists, which lower blood glucose levels through insulin sensitisation. A large RCT of rosiglitazone reported longer treatment durability as monotherapy than glibenclamide or metformin (16). Two large RCTs have examined thiazolidinedione's effects on cardiovascular outcomes. The PROACTIVE (pioglitazone) trial reported a trend to a reduced risk of the primary composite macrovascular outcome in high-risk patients, (HR 0.9, 95%CI 0.8-1.0, p=0.095) (17) and a significant reduction in the composite secondary outcome of all-cause mortality, non-fatal myocardial infarction, and stroke (0·84, 0·72–0·98, p=0·027). The RECORD (rosiglitazone) trial reported no reduction in cardiovascular death, myocardial infarction or stroke but increased heart failure (18). The side effects of thiazolidinediones include weight gain, fluid retention and heart failure, and an increased risk of non-axial fractures in women (19). Rosiglitazone has in the past been associated with an increased risk of cardiovascular events (20) but in 2013 the FDA concluded that the cumulative evidence did not support this premise and removed the prescribing and dispensing restrictions. Pioglitazone is associated with an increased risk of bladder cancer. In a limited number of people, TZDs combine well with metformin and sulfonylureas. Notwithstanding issues with weight gain and fluid retention, pioglitazone may be suitable for use with insulin.

Acarbose

Acarbose is an alpha-glucosidase inhibitor, which slows intestinal carbohydrate absorption and reduces post-prandial blood glucose level excursions. Its main side effects are gastrointestinal (bloating and flatulence), which lead to discontinuation in up to 25% of people. If tolerated, it can be effective, particularly when combined with metformin. Acarbose is weight neutral.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors

These drugs inhibit a renal sodium-glucose cotransporter, which exchanges sodium and glucose in the kidney. The kidneys normally filter approximately 180g of glucose per day, and the SGLT2 inhibitors allow renal loss of glucose, thereby decreasing. The SGLT2 inhibitor class is associated with weight loss due to caloric loss via the urine and decreased blood pressure due to tubuloglomerular feedback. Because of their diuretic effect, their use with loop diuretics should be avoided. SGLT2 inhibitors also decrease serum urate levels by approximately 10% (versus a >30% decrease with classic anti-gout drugs) and lower systolic blood pressure by 3-6mmHg. Side-effects of SGLT2 inhibitors relate to the mechanism of action and include dehydration, dizziness and increased risk of genitourinary infections. The former two can be prevented with adequate fluid intake and the latter diminished with meticulous hygiene. Case reports of ketoacidosis in people with type 2 diabetes has also been reported though this has been rare in the larger trials (21). One large RCT (EMPA-REG trial) has reported major cardiovascular benefits including reduced total mortality and heart failure with use of empagliflozin (22). SGLT2 inhibitors have diminished or no efficacy with increasing renal impairment. Dapagliflozin and empagliflozin are PBS subsidised for use with metformin or sulfonylureas, as triple oral therapy and for use with insulin.

Glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RA)

These agents, two of which are currently available in Australia (exenatide and liraglutide but not lixisenatide), are analogues of human GLP-1 and are administered by subcutaneous injection. They stimulate beta-cell insulin release and slow gastric emptying, which contributes to weight loss. Because pharmacological rather than physiological GLP-1-like activity is achieved with recommended doses, there is an effect on gastric emptying that is not observed with dipeptidyl peptidase-4 (DPP-4) inhibitors. This and perhaps central nervous system effects contribute to weight loss, but also to nausea and vomiting. The improvement in glycaemic control associated with the GLP-1RA is slightly superior to oral agents. The shorter acting GLP-1RA such as exenatide act primarily to reduce post-prandial blood glucose levels while the longer-acting analogues such as liraglutide have greater effect on basal glycaemia. The GLP-1RA have a beneficial effect on blood pressure that appears independent of weight loss, albeit with an associated mild increase in resting heart rate. An increased risk of pancreatitis (about 50% above a baseline of 1-2 episodes per 1,000 patient-years in T2D) and medullary C-cell tumours of the thyroid has been reported. Routine monitoring of lipase and amylase is not recommended but these agents should be avoided in patients with a history of pancreatitis or pancreatic malignancy. The evidence for medullary C-cell neoplasia comes from animal studies, which may have limited relevance to humans, but the agents should not be used in people with a history of this rare disorder. In the case of GLP-1RA that are not closely homologous with the human GLP-1 peptide such as exenatide, there is potential for antibody formation with long-term use that may impair their glucose-lowering efficacy. Two large RCTs examining GLP-1RA (ELIXA: lixisenatide (23, 24), LEADER: liraglutide (25)) have reported on the overall cardiovascular safety of these agents. The ELIXA trial reported overall cardiovascular safety with lixisenatide whilst the LEADER trial reported major cardiovascular benefits, reduced major cardiovascular events and total mortality with liraglutide.

Insulin

Insulin has extensive effects on metabolism and is necessary for the uptake of glucose into most of the body's cells where it is stored as glycogen in skeletal muscle and the liver. Insulin should be considered if blood glucose levels are very high or there are signs of metabolic decompensation. Other situations where it should be considered include preoperatively and when high dose corticosteroids are used.

A number of short-, intermediate- and long-acting analogue and human insulins are available, in addition to a number of pre-mixed preparations of rapid-acting/short-acting and intermediate-acting insulins. The major side effects of insulin are hypoglycaemia and weight gain. Unfortunately, due to a combination of clinician and patient reluctance, insulin is often initiated very late in the treatment cascade after an unnecessarily prolonged period of sustained poor diabetes control. Insulin is the most potent glucose lowering agent available, and with adequate dosage and dietary adherence, will almost always achieve target blood glucose levels. Insulin should be considered early if blood glucose levels are very high.

Two large RCTs (UKPDS (2) and ORIGIN (26)) have examined insulin's effects on cardiovascular outcomes. The UKPDS reported overall cardiovascular safety and reduced microvascular complications with either sulphonylureas or insulin compared with conventional treatment in patients with newly diagnosed type 2 diabetes and the ORIGIN trial reported overall

cardiovascular safety with insulin glargine compared to standard care in people with impaired fasting glucose, impaired glucose tolerance or established type 2 diabetes.

TREATMENT ALGORITHM

The algorithm outlined in Figure 1 summarises the available clinical evidence for pharmacotherapeutic strategies to achieve target HbA1c in people with type 2 diabetes. At each step, there are proven and effective approaches. The previous Australian algorithm focused only on therapies that were subsidised through the PBS. This updated algorithm incorporates all effective therapies approved by the Therapeutic Goods Administration (TGA) of Australia.

It should be noted that use of a medication outside PBS-approved indications requires the patient to purchase the medication on a private prescription. An estimate of the current cost of these medications on private prescription is given in Table 3, although this may vary in different areas and will vary over time.

Indications that may be PBS-subsidised are highlighted in Figure 1 by a red border. The algorithm is structured with a "usual approach" to treatment initiation and intensification (usual pertaining to commonly available, evidence based, cost effective therapy) and "alternative approaches" at each stage.

The order of listed therapies does not denote any specific preference.

An important rationale for the treatment of hyperglycaemia in type 2 diabetes is prompt management of any symptoms occurring due to hyperglycaemia. These symptoms may be acute or chronic in onset, and include fatigue, polyuria, bilateral vision disturbance, muscle cramps, and in institutionalised care in patients with chronic cognitive disturbance, urinary incontinence. In the most severe hyperglycaemia, coma may ensue requiring emergency treatment. Some agents act more promptly than others to reduce blood glucose levels and may be preferred in people with symptomatic hyperglycaemia. In particular, supervised insulin therapy has the greatest efficacy to promptly improve high blood glucose levels.

First Line Treatment

All guidelines, including this position statement, agree that treatment for type 2 diabetes is underpinned by lifestyle measures including diet and exercise. This should be reinforced at each stage. Both weight loss and prevention of weight gain are important. If blood glucose levels are very high, or remain high overnight, insulin should be considered early.

When diet and exercise no longer achieve the individualised treatment target, the first treatment step for people in whom there is no contraindication should be metformin. If metformin is not tolerated or is contraindicated, a sulfonylurea may be introduced. Other medications are also available but apart from acarbose and insulin are not currently PBS subsidised for use as initial monotherapy.

Second Line Treatment

If glycaemic control is not achieved with a single agent, there are many second-line treatment

options (Figure 1). Sulfonylureas are good second-line agents, achieving similar decreases in HbA1c levels as other second-line oral agents for approximately 25% of the daily cost (Table 3). For patients who experience problematic hypoglycaemia, weight gain, other side effects, or in whom it is considered that the potential for hypoglycaemia should be minimised, an alternate agent may be considered (Figure 1).

The most commonly used alternative second-line agent is a DPP-4 inhibitor. These are now all available in combination tablets with metformin, which may improve patient compliance.

SGLT2 inhibitors are another option and are also PBS subsidised for use with either metformin or a sulfonylurea. They can also be tried if glycaemic control is not achieved with a DPP-4 inhibitor.

In some people acarbose may be a useful agent, particularly where post-prandial hyperglycaemia and/or obesity are issues. Where the patient remains keen to avoid injectable therapy, this can be trialled.

In carefully selected insulin-resistant individuals, a TZD may be used, preferably in combination with metformin.

GLP-1RA have excellent therapeutic efficacy with the added benefit of facilitating weight and blood pressure reduction, and can be used in combination with metformin or a sulfonylurea as second-line therapy. Currently there are no data examining the efficacy of GLP-1RA in combination with a DPP-4 inhibitor or SGLT2 inhibitor.

As always, insulin is an option and should be considered, especially in patients in whom HbA1c is above 75mmol/mol (9.0%) on oral therapy.

When a decision has been made that a second agent is needed, the choice of second-line agent should be individualised, based on issues such as potency, body weight, risk of hypoglycaemia, comorbidities, patient acceptance of injection therapy, PBS subsidy and cost.

Third Line Treatment

After failure of dual oral therapy, treatment of type 2 diabetes becomes more complex. Metformin should be continued for its insulin-sensitising effects unless contraindications develop. Ineffective therapies should be ceased and substituted with a different medication. Comparative evidence from RCTs to inform prescribing is relatively scarce.

The options are triple oral therapy or the addition of injectable GLP-1RA or insulin (Figure 1).

Triple oral therapy

Metformin, Sulfonylurea and DPP-4 inhibitors

RCTs examining the addition of sitagliptin (27) or linagliptin (28) to metformin and sulfonylurea have demonstrated a reduction in HbA1c of 7-10 mmol/mol (0.6-0.9%) relative to baseline or placebo, as well as an increase in body weight of 0.4-0.8 kg. With this triple oral combination, the advantage of a lower hypoglycaemia rate with DPP-4 inhibitors appears to be lost

(approximately 10% rate of hypoglycaemia after adding DPP-4 inhibitors). However, most episodes are not severe. It is reasonable to escalate from metformin and a sulfonylurea or metformin and a DPP-4 inhibitor to triple therapy with all three. This triple therapy combination (metformin, sulfonylurea and DPP-4 inhibitor) is PBS subsidised.

Metformin, Sulfonylurea and TZDs

Triple oral therapy with metformin, sulfonylurea and a TZD has been reported by RCTs to lower HbA1c by approximately 11mmol/mol (1%) but with an increase in weight of 3-5kg, and increased hypoglycaemia. The rate of hypoglycaemia is over 20% in some studies (29). If this combination is initiated, a pre-emptive decrease in the sulfonylurea dose should be considered with later up-titration if necessary. Only pioglitazone is PBS subsidised for triple oral therapy in Australia.

Metformin, Sulfonylurea and SGLT2 inhibitors

RCTs have reported that the combination of metformin, sulfonylurea and SGLT2 inhibitor is effective for improving glycaemic control. One RCT compared adding canagliflozin or sitagliptin to metformin and sulfonylurea among patients with type 2 diabetes who did not have adequate glycaemic control. At 52 weeks, the HbA1c reduction with the SGLT2 inhibitor was 11mmol/mol (1.0%) versus 7mmol/mol (0.7%) with the DPP-4 inhibitor. Greater reductions in blood glucose levels, body weight, and systolic BP occurred with canagliflozin versus sitagliptin with similar rates of adverse events (30). There was no significant difference in rate of hypoglycaemia, which was high in both groups. Triple therapy with metformin, sulfonylurea and SGLT2 inhibitors (dapagliflozin or empagliflozin) is PBS subsidised.

Metformin, Sulfonylurea and Acarbose

Acarbose is approved for triple therapy with metformin and a sulfonylurea. One double-blinded cross-over trial of this combination reported a 1.9kg decrease in weight, and a 15mmol/mol (1.4%) reduction in HbA1c with the addition of acarbose (31). In other dual therapy studies acarbose has more commonly decreased HbA1c by 6-9mmol/mol (0.5-0.9%) (32).

Notably, in people receiving oral or injectable therapy, self-monitoring of blood glucose levels will need to be individualised.

Parenteral therapy

Metformin, Sulfonylurea and GLP-1RA

Triple therapy studies with metformin, sulfonylurea and GLP-1RA are few but show effective blood glucose-lowering when the GLP-1RA is added to maximal dual oral therapy in patients with poor glycaemic control (33-35). The average HbA1c reduction is 11mmol/mol (1.0%) and typically 1-2 kg weight loss occurs over 6-12 months. The immediate risk of hypoglycaemia may be attenuated by initially reducing the sulfonylurea dose and later up-titrating it if necessary. The GLP1-RA agents currently available in Australia have TGA approval for use with metformin plus sulfonylurea. Only exenatide has PBS reimbursement.

Insulin

Insulin can be used at any stage in the treatment cascade but is often reserved for when other therapies fail to achieve glycaemic targets. Insulin is commonly initiated as once daily basal insulin added to oral agents, particularly metformin (Figure 1). Alternatively, it can be initiated as once- or twice-daily premixed insulin, again usually in combination with metformin. Insulin therapy can be intensified by increasing the frequency of insulin injections, combining long-acting insulin with one or more injections of short-acting insulin, or by continuous subcutaneous insulin infusion (this latter strategy is not very commonly used in type 2 diabetes). Recent studies have explored combining insulin with newer therapies, including DPP-4 inhibitors, SGLT2 inhibitors and GLP-1RAs, with good effect. The DPP-4 inhibitors linagliptin and sitagliptin are PBS subsidised for use with insulin. The SGLT2 inhibitors dapagliflozin and empagliflozin are PBS subsidised for use with insulin. Only the GLP-1RA exenatide is PBS subsidised for use with insulin.

Notably, in people receiving insulin therapy self-monitoring of blood glucose levels is indicated in order to safely titrate insulin and to minimise hypoglycaemia risk.

GLUCOSE LOWERING THERAPY IN THE SETTING OF RENAL OR LIVER IMPAIRMENT

With loss of renal function, metabolic changes and drug pharmacokinetic changes (altered absorption, distribution, metabolism, and clearance) develop and these may increase risk of hypoglycaemia and other drug related side effects. The metabolic changes include reduced renal gluconeogenesis, increased insulin resistance with elevated counter-regulatory hormones, reduced renal degradation and clearance of insulin, altered lipid metabolism, electrolyte abnormalities, acidosis and uraemic toxins. These changes are most evident with advanced chronic kidney disease (chronic kidney disease (CKD) stages 4 and 5), and must be considered when deciding on therapy and dose for patients with CKD (Table 1). In some people, drug doses may need reduction. In others, drugs may need to be stopped and alternatives initiated that maintain effectiveness and also safety in CKD. Among the oral agents, glipizide and gliclazide can be used at reduced dose to CKD stage 4, and linagliptin can be used without dose adjustment by people receiving dialysis. Insulin should be considered if treatment targets are no longer met.

In the setting of liver disease, there may also be metabolic changes and drug pharmacokinetic changes that influence prescribing decisions. Most drugs (including metformin, sulfonylureas, acarbose, some DPP-4 inhibitors, TZD and insulin) do not need to be discontinued in people with mild to moderate hepatic impairment but drug half-lives, dosing, interactions, and risks of drug-specific adverse effects such as lactic acidosis and hypoglycaemia should be considered in addition to the potential for the drugs themselves to cause liver dysfunction. There is little clinical experience with use of the newer glucose lowering drug classes in patients with advanced hepatic impairment. In people with renal or liver impairment, close monitoring for hypoglycaemia and drug side effects and interactions is critically important.

GLUCOSE LOWERING THERAPY IN THE ELDERLY

In the elderly, glycaemic targets need to be considered in light of life-expectancy and general frailty (4-5). This may mean that the glycaemic-target could be symptom-control only, or 64mmol/mol (8.0%). Calculation of estimated GFR is important as serum creatinine is not a reliable a marker of renal function in this population. Significant cardiac dysfunction is more common, and severe congestive cardiac failure is a contraindication to metformin therapy. Use of multiple drugs should prompt regular review to minimise polypharmacy. Drugs should be used at the minimum doses needed to achieve practical and safe glycaemic targets. The avoidance of hypoglycaemia should be prioritised, and this should be considered in the choice and dosage of agent.

CONCLUSIONS

Diabetes is a progressive condition, and as such glycaemic targets should be reviewed at regular intervals. Diet and exercise should be reinforced at each step of the therapeutic pathway.

With the range of therapies now available in Australia, there is considerable room for individualising therapy. This will often take the form of a combination of therapies.

With education and an engaged patient it is now possible to achieve good glycaemic control with available therapies in even more people with type 2 diabetes.

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Updated position statement 2016

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DISCLAIMER

Review of this position statement will be undertaken in June 2017.

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TABLE 1. MEDICATIONS AND CHRONIC KIDNEY DISEASE.

Drug/Class	Usual daily dose	CKD 3 30-60ml/min	CKD 4 15-30ml/min	CKD 5 <15ml/min	Pharmacokinetic changes	Specific Concerns or Comments
Metformin						
metformin	500-1000 mg bd-tds	eGFR 45-60 max 1500mg/d If eGFR30-45, max 850mg/d	Avoid	Avoid	Reduced clearance Reduced clearance	GI disturbance, Lactic acidosis
Sulfonylureas						
gliclazide	40-320 mg	Use at low doses, titrate	Use at low doses, titrate	Avoid	Hepatically metabolised	Hypoglycaemia
gliclazide MR	30-120 mg	Use at low doses, titrate	Avoid	Avoid	Hepatically metabolised	Hypoglycaemia
glibenclamide	2.5-20 mg	Avoid	Avoid	Avoid	Reduced clearance	Hypoglycaemia, hepatic complications
glimepiride	2-4 mg	Max dose 1mg	Avoid	Avoid	Reduced clearance	Hypoglycaemia, increased transaminases
glipizide	5-20 mg	Max dose 5-10 mg/ day	Use at low doses, 2.5mg/day		Reduced clearance	Hypoglycaemia, increased transaminases
Acarbose						
acarbose	50-300 mg	No dose change	Avoid	Avoid	Increased plasma levels	GI disturbances
TZDs						
pioglitazone	15-45 mg	No dose change	No dose change	Limited data, not recommended		Weight gain, fluid retention, bladder cancer, peripheral fractures (women)
rosiglitazone	2-8mg	No dose change	Limited data, not recommended	Limited data, not recommended		Weight gain, fluid retention, peripheral fractures (women)
DPP4i						
sitagliptin	100 mg/d	50 mg daily	25 mg daily	25 mg daily	Increased plasma levels	GI disturbances, rare liver complications, use with dose reduction

vildagliptin	50 mg bd	50 mg daily	50 mg daily	50 mg daily	Increased plasma levels	GI disturbances, rare liver complications, use with dose reduction
saxagliptin	5 mg/d	2.5 mg/ day	2.5 mg/ day	Not recommended	Increased plasma levels	GI disturbances, rare liver complications
linagliptin	5 mg/d	No dose change	No dose change	No dose change	Hepatically metabolised	GI disturbances, rare liver complications, use with*out* dose reduction in dialysis
alogliptin	25 mg/d	12.5 mg/ day	6.25 mg/ day	6.25 mg/day	Increased plasma levels	GI disturbances, rare liver complications, use with dose reduction
GLP1-RA						
exenatide	5-10 µg bd	5 µg bd	Avoid	Avoid	Reduced clearance	GI disturbances
exenatide XR	2 mg/ week	No dose change	Avoid	Avoid	Reduced clearance	GI disturbances
liraglutide	0.6-1.2 mg	No dose change	Limited data, not recommended	Limited data, not recommended		GI disturbances
SGLT2i						
dapagliflozin	5-10 mg	Avoid	Avoid	Avoid	Increased plasma levels	Reduced efficacy, volume depletion, genitourinary infections
canagliflozin	300 mg	eGFR 45-60 Use 100 mg/day eGFR 30-45 Avoid	Avoid	Avoid	Increased plasma levels	Reduced efficacy, volume depletion, genitourinary infections
empagliflozin	10-25mg	eGFR 45-60 No Dose change eGFR <45 Avoid	Avoid	Avoid	Increased plasma levels and reduced clearance	Reduced efficacy, volume depletion, genitourinary infections

eGFR=estimated glomerular filtration rate. CKD=chronic kidney disease. Max=maximum. TZD= thiazolidinedione. DPP4i = di-peptidyl peptidase 4 inhibitor. SGLT2i = sodium glucose co-transporter inhibitor.

TABLE 2. MEDICATION COMBINATIONS POTENTIALLY ATTRACTING PBS SUBSIDY

Medication	Met	SU	Acar.	Pio	Rosi	DPP4i	SGLT2i	Exen.	Insulin*
Monotherapy									
	YES	**YES**	**YES**	**NO**	**NO**	**NO**	**NO**	**NO**	**YES**
Dual therapy with									
Metformin	n/a	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**
Sulfonylurea	**YES**	n/a	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**
Acarbose	**YES**	**YES**	n/a	**NO**	**NO**	**NO**	**NO**	**NO**	**YES**
Pioglitazone	**YES**	**YES**	**NO**	n/a	**NO**	**NO**	**NO**	**NO**	**YES**
Rosiglitazone	**YES**	**YES**	**NO**	**NO**	n/a	**NO**	**NO**	**NO**	**NO**
DPP4 inhibitor	**YES**	**YES**	**NO**	**NO**	**NO**	n/a	**NO**	**NO**	**NO**
SGLT2 inhibitor	**YES**	**YES**	**NO**	**NO**	**NO**	**NO**	n/a	**NO**	**NO**
Exenatide	**YES**	**YES**	**NO**	**NO**	**NO**	**NO**	**NO**	n/a	**YES**
Insulin	**YES**	**YES**	**YES**	**YES**	**NO**	**NO**	**NO**	**NO**	n/a
Triple therapy with									
M + SU	n/a	n/a	**YES**	**YES**	**NO**	**YES**	**YES**	**YES**	**YES**
M + Acarbose	n/a	**YES**	n/a	**NO**	**NO**	**NO**	**NO**	**N0**	**YES**
M + Pioglitazone	n/a	**YES**	**NO**	n/a	**NO**	**NO**	**NO**	**NO**	**NO**
M + Rosiglitazone	n/a	**NO**	**NO**	n/a	**NO**	**NO**	**NO**	**NO**	**NO**
M + DPP4i	n/a	**YES**	**NO**	**NO**	**NO**	n/a	**NO**	**NO**	**NO**
M + SGLT2i	n/a	**YES**	**NO**	**NO**	**NO**	**NO**	n/a	**NO**	**NO**
M + GLP-1a	n/a	**YES**	**NO**	**NO**	**NO**	**NO**	**NO**	n/a	**YES**
M + Insulin	n/a	**YES**	**YES**	**YES**	**NO**	**NO**	**YES**	**YES**	n/a
SU + Acarbose	**YES**	n/a	n/a	**NO**	**NO**	**NO**	**NO**	**NO**	**NO**
SU + Pioglitazone	**YES**	n/a	**NO**	n/a	**NO**	**NO**	**NO**	**NO**	**NO**
SU + Rosiglitazone	**NO**	n/a	**NO**	n/a	**NO**	**NO**	**NO**	**NO**	**NO**
SU + DPP4i	**YES**	n/a	NO	**NO**	**NO**	n/a	**NO**	**NO**	**NO**
SU + SGLT2i	**YES**	n/a	**NO**	**NO**	**NO**	**NO**	n/a	**NO**	**NO**
SU + GLP-1a	**YES**	n/a	**NO**	**NO**	**NO**	**NO**	**NO**	n/a	**YES**
SU + Insulin	**YES**	n/a	**YES**	**NO**	**NO**	**NO**	**NO**	**YES**	n/a
Ac + Pioglitazone	**YES**	**NO**	n/a	n/a	n/a	**NO**	**NO**	**NO**	**NO**
Ac + Rosiglitazone	**YES**	**NO**	n/a	n/a	n/a	**NO**	**NO**	**NO**	**NO**
Ac + DPP4i	**YES**	**NO**	n/a	**NO**	**NO**	n/a	**NO**	**NO**	**NO**
Ac + SGLT2i	**YES**	**NO**	n/a	**NO**	**NO**	**NO**	n/a	**NO**	**NO**
Ac + GLP-1a	**YES**	**NO**	n/a	**NO**	**NO**	**NO**	**NO**	n/a	**NO**
Ac + Insulin	**YES**	**YES**	n/a	**NO**	**NO**	**NO**	**NO**	**NO**	n/a
TZD + DPP4i	**NO**	**NO**	**NO**	n/a	n/a	n/a	**NO**	**NO**	**NO**
TZD + SGLT2i	**NO**	**NO**	**NO**	n/a	n/a	n/a	**NO**	**NO**	**NO**
TZD + GLP-1a	**NO**	**NO**	**NO**	n/a	n/a	**NO**	**NO**	n/a	**NO**
TZD + insulin	**NO**	**NO**	**NO**	n/a	n/a	**NO**	**NO**	**NO**	n/a
DPP4i + SGLT2i	**NO**	**NO**	**NO**	**NO**	**NO**	n/a	n/a	**NO**	**NO**
DPP4i + GLP-1a	**NO**	**NO**	**NO**	**NO**	**NO**	n/a	**NO**	n/a	**NO**
DPP4i + Insulin	**NO**	**NO**	**NO**	**NO**	**NO**	n/a	**NO**	**NO**	n/a
SGLT2i +exenatide	**NO**	**NO**	**NO**	**NO**	**NO**	n/a	**NO**	n/a	**NO**
SGLT2i + Insulin	**YES**	**YES**	**NO**	**NO**	**NO**	**NO**	n/a	**NO**	n/a

GLP-1a + Insulin	**YES**	**YES**	**NO**	**NO**	**NO**	**NO**	**NO**	n/a	n/a

PBS=pharmaceutical benefits scheme. Met=metformin. SU=sulfonylurea. Acar=acarbose. Pio=pioglitazone. Rosi=rosiglitazone. DPP4i= dipeptidyl peptidase 4 inhibitor.
SGLT2i = sodium glucose cotransporter 2 inhibitor. Exen = exenatide. M=metformin. Ac=acarbose. TZD=thiazolidinedione. YES=potentially PBS-subsidised, NO=not, n/a = not applicable.

TABLE 3. COSTS OF GLUCOSE-LOWERING MEDICATIONS FOR THE TREATMENT OF TYPE 2 DIABETES

Drug	Trade name	mg or mcg / dose	Dose	No / day	Doses / script	DPMQ (private script)	Cost / day (DPMQ)	Max PBS price to consumer	Cost/ day (PBS)	Comments
Metformin *	Various	500	1 bd	2	100	$13.42	$0.26	$18.92	$0.38	Note lower dose
Metformin	Diabex	500	1bd	2	100	$16.27	$0.32	$21.77	$0.43	Brand price premium
Metformin	Various	1000	1 bd	2	90	$15.65	$0.35	$21.15	$0.47	
Metformin	Diabex	1000	1bd	2	90	$18.49	$0.41	$23.99	$0.53	Brand price premium
Metformin XR	Various	500	4 daily	4	120	$18.08	$0.60	$23.58	$0.79	
Metformin XR	Diabex	1000	2 daily	2	60	$18.08	$0.60	$23.58	$0.79	
Glibenclamide	Glimel	5	2 bd	4	100	$14.74	$0.59	$20.24	$0.81	
Glibenclamide	Daonil	5	2 bd	4	100	$15.99	$0.64	$21.49	$0.86	Brand price premium
Gliclazide	Various	80	2 bd	4	100	$16.28	$0.65	$21.78	$0.87	
Gliclazide MR	Various	30	4 daily	4	100	$16.45	$0.66	$21.95	$0.88	
Gliclazide MR	Diamicron	60	2 daily	2	60	$19.61	$0.65	$25.11	$0.84	Brand price premium
Glimepiride *	Various	4	1 daily	1	30	$13.70	$0.46	$19.20	$0.64	
Glimepiride *	Amaryl	4	1 daily	1	30	$15.89	$0.53	$21.39	$0.71	Brand price premium
Glipizide	Melizide	5	2 bd	4	100	$17.24	$0.69	$22.74	$0.91	
Glipizide	Minidiab	5	2 bd	4	100	$24.75	$0.99	$30.25	$1.21	Brand price premium
Metformin + Glibenclamide	Glucovance	500+5	2 bd	4	90	$19.34	$0.86	$24.84	$1.10	
Acarbose	Glucobay	50	1 tds	3	90	$34.86	$1.16	$38.30	$1.27	Note lower dose
Acarbose	Glucobay	100	1 tds	3	90	$45.03	$1.50	$38.30	$1.28	
Linagliptin	Trajenta	5	1 daily	1	30	$61.50	$2.05	$38.30	$1.28	Streamline authority required
Linagliptin+Met *	Trajentamet	2.5+ 1000	1 bd	2	60	$64.99	$2.17	$38.30	$1.28	Streamline authority required
Saxagliptin	Onglyza	5	1 daily	1	28	$58.09	$2.07	$38.30	$1.37	Streamline authority required
Saxagliptin+Met *	Kombiglyze	2.5+ 1000	1 bd	2	56	$61.34	$2.19	$38.30	$1.37	Streamline authority required
Vildagliptin	Galvus	50	1 bd	2	60	$61.50	$2.05	$38.30	$1.28	Streamline authority required

Vildagliptin+ Met *	Galvumet	50+ 1000	1 bd	2	60	$62.19	$2.07	$38.30	$1.28	Streamline authority required
Sitagliptin *	Januvia	100	1 daily	1	28	$58.09	$2.07	$38.30	$1.37	Streamline authority required
Sitagliptin+ Met *	Janumet	50+ 1000	1 bd	2	56	$61.34	$2.19	$38.30	$1.37	Streamline authority required
Alogliptin *	Nesina	25	1 daily	1	28	$58.09	$2.07	$38.30	$1.37	Streamline authority required
Alogliptin+ Met *	Nesina Met	12.5+1000	1 bd	2	56	$61.34	$2.19	$38.30	$1.37	Streamline authority required
Canagliflozin*	Invokana	100	1 daily	1	30	$93.69	$3.12			TGA, not PBS subsidised
Dapagliflozin	Forxiga	10	1 daily	1	28	$57.60	$2.06	$38.30	$1.37	Streamline authority required
Empagliflozin	Jardiance	25	1 daily	1	30	$60.97	$2.03	38.30	$1.28	
Rosiglitazone	Avandia	8	1 daily	1	28	$86.95	$3.10	$38.30	$1.37	Authority required
Rosi+Met 1000*	Avandamet	4	1 bd	2	56	$90.20	$3.22	$38.30	$1.37	Authority required
Pioglitazone	Various	30	1 daily	1	28	$34.63	$1.24	$38.30	$1.37	Note lower dose, streamline authority required
Pioglitazone	Various	15	1 daily	1	28	$23.29	$0.83	$28.79	$1.02	Streamline authority required
Exenatide *	Byetta	10	S/C bd	2	60	$93.00	$3.10	$38.30	$1.28	Streamline authority required
Liraglutide *	Victoza	1.2	S/C bd	1	45	$253.35	$5.63			TGA, not PBS subsidised

Insulins	**Presentation**	**Size mls**	**Timing**	**No.**	**DPMQ**	**mls / script**	**$/ml**	**Max PBS price to consumer**	**Max PBS price ($/ml)**	**Comments**
Actrapid or Humulin R	Pens or penfills	3	Usually with meals	25	211.03	75	2.81	$38.30	0.51	
Actrapid or Humulin R	Vials	10	Usually with meals	5	$126.23	50	$2.52	$38.30	$0.77	
Humalog, Novorapid, Apidra	Pens or Penfills	3	Usually with meals	25	$252.33	75	$3.36	$38.30	$0.51	

Humalog, Novorapid, Apidra	Vials	10	Usually with meals	5	$149.38	50	$2.99	$38.30	$0.77	
Humalog mix 25 or Novomix 30	Pens or penfills	3	Usually bd	25	$252.33	75	3.36	$38.30	0.51	Short + long acting
Humalog mix 50	Pens or penfills	3	Usually bd	25	$252.33	75	3.36	$38.30	0.51	Short + long acting
Protaphane or Humulin NPH	Pens or penfills	3	Usually bd	25	$211.03	75	$2.81	$38.30	$0.51	
Protophane or Humulin NPH	Vials	10	Usually bd	5	$126.23	50	$2.52	$38.30	$0.77	
Detemir (Levemir)#	Pens or penfills	3	Usually bd	25	$426.73	75	$5.69	$38.30	$0.51	***Type 1*** diabetes only
Glargine (Lantus) #	Pens or penfills	3	Usually daily	25	$426.73	75	$5.68	$38.30	$0.51	
Insulin hypurin (Bovine)	Vials	10	Variable	5	$393.58	50	$7.87	$38.30	$0.77	Authority required

DPMQ = PBS dispensed price for maximum quantity without additional fees that the pharmacist may charge general patients if the DPMQ is below the co-payment of $36.90. Max price to consumer = general patient co-payment ($36.90) or if the DPMQ is below this threshold equals DPMQ + $4.19 (allowable additional patient charge) + $1.15 (additional fee for safety net) to maximum of general patient co-payment.
Prices were supplied by the Department of Health. PBS effective date 21st May 2016.
* = other strengths available. bd= twice daily. TGA=therapeutic goods administration. Met=metformin. S/C = subcutaneous injection. # = Special pricing arrangements exist where *actual* costs to the government are less than the disclosed DPMQ. The estimates of price per day are calculated by dividing the cost by the number of tablets/doses per script, multiplied by the 'usual' dose (3rd column). Levemir is not PBS subsidised for use in type 2 diabetes.

TABLE 4. TABLE OF EVIDENCE AND PROPERTIES OF GLUCOSE-LOWERING AGENTS

AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM FOR TYPE 2 DIABETES

Table of Evidence and Properties of Glucose-Lowering Agents†

Glucose-lowering Class and Drugs	Mechanism of Action	Outcome data	Contraindications	Precautions, Side Effects and Administration	Cost and Accessibility
Biguanide • metformin • metformin XR	Reduces hepatic glucose output, lowers fasting glucose levels	**UKPDS**[1]	Renal impairment (eGFR<30 ml/min/m²) Severe hepatic impairment	**Precautions** Suspend treatment during acute disease/ conditions with the potential to cause tissue hypoxia or alter renal function. **Side Effects** GI side effects, lactic acidosis, weight neutral **Administration** Oral administration Start at low dose and up-titrate Slow release preparations available	General schedule on PBS
Sulfonylureas • glibenclamide • gliclazide • gliclazide MR • glimepiride • glipizide	Triggers insulin release in a glucose-independent manner	**UKPDS**[2] **ADVANCE**[3] - Gliclazide MR	Severe renal or hepatic impairment	**Precautions** Hypoglycaemia **Side Effects** Weight gain **Administration** Oral administration Start at low dose and up-titrate Slow release preparation available	General schedule on PBS
Dipeptidyl peptidase-4 (DPP-4) inhibitors • alogliptin • linagliptin • saxagliptin • sitagliptin • vildagliptin	Decreases inactivation of glucagon-like peptide (GLP-1) thereby increasing its availability GLP-1 stimulates beta cell insulin release	**EXAMINE**[4,5] - Alogliptin **SAVOR-TIMI 53**[6,7] - Saxagliptin **TECOS**[8] - Sitagliptin	Pancreatitis[9]	**Precautions** Nasopharyngitis-often subsides in 10-14 days **Side Effects** Rash, pancreatitis, GI disturbances, weight neutral **Administration** Oral administration Dosage adjustment in renal impairment (except Linagliptin)[10]	Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin are PBS subsidised for use with either Metformin or Sulfonylurea (i.e. dual therapy) Linagliptin, Saxagliptin, Sitagliptin and Vildagliptin are PBS subsidised for use with Metformin and Sulfonylurea (i.e. triple therapy) Linagliptin and Sitagliptin are PBS subsidised for use with insulin
Thiazolidinediones (TZD) • pioglitazone • rosiglitazone	Transcription factor peroxisome proliferator-activated receptor PPARγ agonists Lowers glucose levels through insulin sensitisation	**PROACTIVE**[11] - Pioglitazone **RECORD**[12] - Rosiglitazone		**Precautions** Symptomatic heart failure **Side Effects** Fluid retention, heart failure, increased risk of non-axial fractures in women, increased risk of bladder cancer, weight gain **Administration** Oral administration	PBS subsidised for use in combination with Metformin or Sulfonylurea or both Patient must have a contraindication or intolerance to Metformin- Sulfonylurea combination PBS subsidised for use with insulin
Alpha 1 glucosidase inhibitors • acarbose	Slows intestinal carbohydrate absorption and reduces postprandial glucose levels		Severe renal impairment (creatinine clearance < 25 ml/min/m²)	**Precautions** Gastrointestinal disorders associated with malabsorption **Side effects** Bloating and flatulence, weight neutral **Administration** Oral administration Take with meals as tolerated	General schedule on PBS
Sodium-glucose co-transporter-2 (SGLT2) inhibitors • canagliflozin • dapagliflozin • empagliflozin	Inhibits a Sodium-glucose cotransporter to induce urinary glucose loss and decrease blood glucose levels	**EMPA-REG OUTCOME**[13] - Empagliflozin	Diminished efficacy with renal impairment (eGFR < 60 ml/min/m²)	**Precautions** Avoid use with loop diuretics **Side effects** Dehydration, dizziness, genitourinary infections (advise adequate fluid intake and meticulous toileting hygiene), ketoacidosis, weight loss **Administration** Oral administration	Dapagliflozin and Empagliflozin: PBS subsidised for use in combination with Metformin, Sulfonylurea or both PBS subsidised for use with insulin Not PBS subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1 Canagliflozin: PBS subsidisation withdrawn
Glucagon-like peptide-1 (GLP-1) receptor agonists • exenatide • exenatide ER • liraglutide • lixisenatide	Stimulates beta-cell insulin release and slows gastric emptying	**ELIXA**[14,15] - Lixisenatide **LEADER**[16] - Liraglutide	Avoid with history of pancreatitis or pancreatic malignancy	**Precautions** Dosage adjustment in moderate-severe renal impairment Increased risk of pancreatitis **Side effects** Nausea, vomiting, weight loss **Administration** Subcutaneous injection	Exenatide and Exenatide ER: PBS subsidised for use in combination with Metformin, Sulfonylurea or both Exenatide: PBS subsidised for use with insulin Not PBS subsidised for use as monotherapy or in combination with dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a SGLT2 inhibitor
Insulin	Directly activates the insulin receptor.	**UKPDS**[2] **ORIGIN**[17] - Insulin Glargine		**Precautions** Consider need for dosage adjustment in moderate-severe renal disease **Side effects** Hypoglycaemia, weight gain **Administration** Subcutaneous injection Considered early if BGL is very high	General schedule on PBS Levemir Insulin: PBS subsidisation restricted to Type 1 diabetes

† Gunton JE et al. MJA 2014, 201(11), 650-53.

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