A new blood glucose management algorithm for type 2 diabetes

A position statement of the Australian Diabetes Society

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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 HbA1c 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.

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.

LIST OF ABBREVIATIONS
ADS = Australian Diabetes Society
BGL = Blood glucose level
DPP4i = Dipeptidyl peptidase inhibitor
GLP-1 = glucagon like peptide-1
GLP1RA = GLP-1 receptor agonist
HbA1c = glycosylated haemoglobin
PBS = Pharmaceutical benefits scheme
RCT = Randomised controlled trial
SGLT2i = Sodium glucose co-transporter 2 inhibitor
TZD = Thiazolidinedione

Introduction

Type 2 diabetes is an increasingly common condition in Australia and worldwide. In Australia alone the annual costs of treating diabetes and its complications are estimated at over $10 billion. Large randomised trials have demonstrated that controlling blood glucose levels (BGL) is important for the prevention of the microvascular complications of diabetes, which include retinopathy, nephropathy and neuropathy (1, 2). The role of glucose in the development of macrovascular complications is less clear. The UKPDS showed benefits with metformin for myocardial infarction and potential long-term benefits of intensive glucose management for diabetes-related mortality with prolonged follow up. A meta-analysis of the large randomised trials (UKPDS, ADVANCE, ACCORD and VADT) reported a 17% relative risk reduction in non-fatal myocardial infarction for every ~ 9 mmol/mol (0.9%) HbA1c reduction over a 5-year period but no benefits for 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 BGL and HbA1c targets*.*

In 2009, the Australian Diabetes Society (ADS) published in this journal a position statement describing the need for 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 for most people with diabetes the general HbA1c target is 53mmol/mol (7%), however:

- In people without known cardiovascular disease, a long duration of diabetes, severe hypoglycaemia or another contraindication, the HbA1c 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%).
- In people with limited life expectancy, aim for symptom control and
- In women planning a pregnancy, aim for the tightest achievable control without severe hypoglycaemia before and during pregnancy; preferably ≤42mmol/mol (6%).

Despite these new recommendations and the increased range of glucose lowering drugs available, achieving glycaemic targets in people with type 2 diabetes can be difficult. For that reason, the Australian Diabetes Society have formulated this position statement to assist with choosing appropriate treatments for people with type 2 diabetes.

Method: ADS council appointed the authors to draft the position statement with a focus on results of recent trials of triple therapy and newer agents. The statement was reviewed by the current ADS council (September 2014) and revised and then sent to all ADS members for comment and revision before submission of shorter version of the text to MJA.

In this position statement we briefly describe the classes of drugs and their place in the glucose lowering therapeutic algorithm (**Figure 1**). We also discuss the 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).**

Australian Blood Glucose Treatment Algorithm for Type 2 Diabetes

Lifestyle measures: diet, exercise, weight control.
Determine the individual's HbA1c target, see text and (1). If not at target, mostly commonly 53mmol/mol (7%), move down the algorithm.

1st Line. Metformin is the usual 1st line therapy unless contraindicated or not tolerated.

Metformin | SU | DPP-4 inhibitor | SGLT2 inhibitor | Insulin # | Acarbose | TZD

2nd Line. If metformin was not used 1st line, add it now if not contraindicated.

- SUs are the recommended initial agent to add to metformin.
- If SUs are contra-indicated or not tolerated, another agent is recommended

SU | **DPP-4 inhibitor** | GLP-1 RA | SGLT2 inhibitor | Insulin # | Acarbose | TZD

3rd Line. Consider triple oral therapy *or* GLP-1R agonist *or* insulin.

DPP-4 inhibitor | **SU** | **GLP-1 RA** | **Insulin #** | SGLT2 inhibitor | Acarbose | TZD

THEN:

If on triple oral therapy:
Switch ≥1 oral agent to:
GLP-1RA *or* insulin #
or another oral agent*

OR

If on a GLP-1RA
Change to: Premixed # *or* Basal insulin #
Add: Basal # *Or* Premixed insulin #

OR

If on insulin #:
Intensify insulin: Basal bolus Insulin *or* Basal plus #

Figure 1. Recommended treatment algorithm. PBS = pharmaceutical benefits scheme/ SU=sulfonylurea. TZD= thiazolidinedione. DPP-4 = dipeptidyl peptidase. GLP1RA= glucagon like peptide 1 receptor agonist. SGLT2 = sodium glucose transporter. Blue boxes indicate usual therapeutic strategy. White boxes indicate alternate approaches. Red outlines indicate potentially PBS subsidised therapies. Compliance should be assessed before changing or adding new therapies. Therapies which do not improve glycaemia should be ceased. *switching an oral agent is likely to have the smallest impact on glycaemia. # Unless metformin is contraindicated, or not tolerated, it is often therapeutically useful to continue it in combination with insulin in people with type 2 diabetes.

Drugs

Metformin

Metformin has a long safety track record of over 50 years. It decreases hepatic glucose output, is particularly useful for decreasing fasting glucose and is generally weight-neutral when used by people with diabetes. It decreases Hba1c by up to 15-22 mmol/mol (1.5-2%) if starting HbA1c is high (5, 6). The most common side effects are gastrointestinal and as such metformin should be started at low doses and titrated up. People who have gastrointestinal side effects may be changed to the slow-release formulations, which cost approximately 40% more per dose (see **Table 3**) but produce fewer gastrointestinal side effects. Metformin is contraindicated where patients have significant renal impairment (see **Table 1** for alternatives), or severe hepatic or cardiac failure.

Sulfonylureas

Sulfonylureas have been available for many years, have long-term safety and beneficial outcome data, and are cheap and decrease HbA1c by 6-16mmol/mol (0.6-1.5%) (7-9). They bind to the sulfonylurea receptor on beta-cells and trigger insulin-release in a glucose-independent manner. Their main side effects are hypoglycaemia and weight gain. The risk of hypoglycaemia differs with different sulfonylureas and appears highest with agents that have long half-lives and renally excreted active metabolites such as glibenclamide (8).

Dipeptidyl peptidase 4 inhibitors (DPP4i)

DPP4i are a more recently available class which inhibit the inactivation of glucagon-like peptide-1 (GLP-1), thereby increasing its availability. GLP-1 improves beta-cell function and insulin secretion, and slows gastric emptying. A meta-analysis reported average decreases in HbA1c of 7-8mmol/mol (0.60-0.71%), except for vildagliptin (11mmol/mol) after adjustment for baseline HbA1c in the included studies (10). Common side-effects are mild gastrointestinal disturbance and nasopharyngitis which often subside during the first 10-14 days. Rash is a rare but potentially serious side effect. One large randomised controlled trial (RCT) reported no change in overall cardiovascular safety but increased hospital admissions for heart failure amongst patients with or at risk of cardiovascular events (11). To date, long-term RCT safety and efficacy data are limited to around 3 years.

Post-marketing surveillance reports an association between all currently used DPP4i and pancreatitis. As the background risk of pancreatitis in people with diabetes is increased (1-2 cases per 1000 person years), it remains unclear whether DPP4i further increases this risk (12).

At the time of writing, there are 5 DPP4i available in Australia approved for PBS-subsidised use with *either* metformin *or* a sulfonylurea but not both. For triple therapy, the patient is required to buy the DPP4i on a private script (see **Table 2**). DPP4i are not subsidised for use as monotherapy, with insulin or with SGLT inhibitors.

Thiazolidinediones (TZDs)

Thiazolidinediones are PPAR-gamma ligands which lower BGL through insulin-sensitising actions. One large RCT of rosiglitazone reported longer monotherapy treatment durability

than glibenclamide or metformin (13). Another large RCT of pioglitazone treatment demonstrated a trend to a reduced risk of developing at least one event in the primary composite macrovascular outcome in high-risk patients, (HR 0.9, 95%CI 0.80-1.02, p=0.095) (14). There was a 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). Side effects include weight gain, fluid retention and heart failure, and an increased risk of non-axial fractures in women(15). Rosiglitazone was reportedly associated with an increased risk of cardiovascular events (16) but in 2013 the FDA concluded that the cumulative evidence did not support this premise and removed the prescribing and dispensing restrictions. Pioglitazone is also associated with an increased risk of bladder cancer. Use of TZDs has declined in recent years. Nonetheless, in selected 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 thus reduces post-prandial but not basal glycaemia. Its main side effects are gastrointestinal, especially bloating and flatulence. This leads to its discontinuation in approximately 25% of people. In people in whom it is tolerated it can be a useful drug, particularly in combination with metformin. Acarbose is weight neutral.

Sodium glucose co-transporter 2 inhibitors (SGLT2i)

Two SGLT2i were listed on the PBS in Australia in late 2013 (canagliflozin and dapagliflozin) and there are a number of others in development. These drugs inhibit the eponymously named transporter, which exchanges sodium and glucose in the kidney. The kidneys normally filter approximately 180g of glucose per day, and the SGLT2i allow renal loss of glucose, thereby decreasing BGL. Their side-effects relate to the mechanism of action and the most common are dehydration, dizziness, and increased risk of genito-urinary infections. The former two can be prevented with adequate fluid intake and the latter diminished with meticulous hygiene.

The SGLT2i class is associated with weight loss due to caloric loss via the urine and decreased blood pressure due to tubuloglomerular feedback. They cause an approximately 10% decrease in serum urate (versus a >30% decrease with classic anti-gout drugs) and lower systolic blood pressure by 3-6mmHg. They have diminished or no efficacy with increasing renal impairment. Because of their diuretic effect, their use with loop diuretics should be avoided. PBS reimbursement requires use with metformin *or* sulfonylureas but not both.

Glucagon-like peptide 1 (GLP-1) receptor agonists (GLP1RA)

These agents, two of which are currently available in Australia (exenatide and liraglutide), are analogues of human GLP-1 that are administered by subcutaneous injection. 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 the DPP4i. This and perhaps central nervous system effects contribute to weight loss, but also to nausea and

vomiting which are recognised side effects. The improvement in glycaemic control associated with the GLP1RA is slightly superior to oral agents. The shorter acting GLP1RA such as exenatide act primarily to reduce post-prandial BGL while the longer-acting analogues such as liraglutide have greater effect on basal glycaemia. The GLP1RA have a beneficial effect on blood pressure that appears independent of weight loss, albeit with an associated mild increase in resting heart rate.

Other potential adverse effects of this drug class are pancreatitis and medullary C-cell tumours of the thyroid. A recent meta-analysis (12) suggests that the increased risk of pancreatitis is about 50% above a baseline of 1-2 episodes per 1,000 patient-years in type 2 diabetes. 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 the rare people with a history of this disorder. In the case of GLP1RA that are not closely homologous with the human GLP-1 peptide such as exenatide, there is the potential for antibody formation with long-term use that may impair blood glucose-lowering efficacy.

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 BGLs are very high or there are signs of metabolic decompensation. Other situations where it should be considered include perioperatively 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 glucose levels.

Treatment Algorithm

The algorithm outlined in **Figure 1** summarises the available clinical evidence on the efficacy of BGL lowering strategies to achieve target HbA1c in people with type 2 diabetes. At each step there are a number of proven and effective approaches. The previous Australian algorithm focused only on therapies which were reimbursed through the PBS. This updated algorithm also incorporates other 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 2**, 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 and "alternative approaches" at each stage.

First Line Treatment (See Figure 1)

All guidelines, including this position statement, agree that first line treatment for type 2 diabetes is appropriate diet and exercise. Diet and exercise should be reinforced at each step at which titration of medication is considered. Weight loss in the overweight or obese, and prevention of weight gain are important.

If BGL are very high, or remain high overnight, insulin should be considered early. After diet and exercise no longer achieve the individualised treatment target, the first step for people in whom there is no contraindication should be metformin. If metformin is not tolerated or is contraindicated, a sulfonylurea should be used. Other medications are also available but apart from acarbose and insulin, are not PBS reimbursed for use as initial treatment with lifestyle measures.

Second Line Treatment

If glucose control is not achieved with a single agent, there are many options for second line treatment, as shown in **Figure 1.** Sulfonylureas are a good initial second line agent. They achieve similar decreases in HbA1c to other oral second line agents for approximately one quarter of the daily cost (**Table 2)**. In 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 should be considered (**Figure 1**).

The most common alternative second line agent is a DPP4i. 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 after trial of combination metformin and sulfonylurea. They can also be tried if glycaemic control is not achieved with a DPP4i.

In some people acarbose can 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.

GLP1RA 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. There are no data on use of GLP1RA with a DPP4i or SGLT2i. As always, insulin is an option and should be considered, especially in patients in whom HbA1c is above 75mmol/mol (9%) on oral therapy.

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

Third Line Therapy

When dual oral therapy cannot achieve glucose targets, treatment of type 2 diabetes becomes more complex. Metformin normally should be continued for its other benefits unless contraindications develop. If other therapies are ineffective, they should be ceased and a different medication trialled. Comparative RCT evidence to inform prescribing is relatively scarce. The options here are triple oral therapy or the addition of injectable GLP1RA or insulin (**Figure 1**).

Triple oral therapy

Metformin, Sulfonylurea and DPP4i

Limited RCTs examining the addition of sitagliptin (17) and linagliptin (18) to metformin and sulfonylurea have demonstrated a reduction in HbA1c of 7-10 mmol/mol (0.62-0.90%) relative to baseline or placebo, as well as an increase in body weight of 0.4-0.8 kg. With triple therapy, the advantage of a lower hypoglycaemia rate with DPP4i use appears to be lost (approximately 10% rate of hypoglycaemia after adding DPP4i). Most episodes are not severe.

Whilst it is a reasonable clinical approach to escalate from metformin+sulfonylurea or metformin-DPP4i dual therapy to metformin-sulfonylurea-DPP4i triple therapy, it should be recognised that this triple therapy combination is not currently PBS subsidised.

Metformin, Sulfonylurea and TZDs

Triple oral therapy with metformin, SU and a TZD has been tested in a few trials. These show benefit of ~11mmol/mol (1%) in HbA1c. However, an increase in weight of 3-5kg, oedema associated seen with TZDs and an increase in hypoglycaemia is reported. The rate of hypoglycaemia is over 20% in some studies (19) and if this combination is initiated, a pre-emptive decrease in the sulfonylurea dose should be considered, with later up-titration if necessary. For TZDs, only pioglitazone is PBS-reimbursed for triple oral therapy in Australia.

Metformin, Sulfonylurea and SGLT2i

Limited trials indicate that metformin, sulfonylurea and SGLT2i is an effective combination for improving glycaemic control but this form of triple-therapy is not PBS-reimbursed. An RCT compared adding a DPP4i versus adding canagliflozin to metformin plus sulfonylurea. At 52 weeks, the HbA1c change with the SGLT2i was 11mmol/mol (1.0%) versus 7mmol/mol (0.66%) with the DPP4i, with reduced weight and systolic blood pressure with the SGLT2i (17). There was no significant difference in rate of hypoglycaemia which was high in both groups. Similar results were reported for dapagliflozin in abstract form at EASD 2013 and ADA 2014.

Metformin, Sulfonylurea and Acarbose

Acarbose is approved for PBS-subsidy for triple oral therapy with metformin and sulfonylurea. One double-blinded cross-over trial of this combination reported a 1.9kg decrease in weight, and a 15mmol/mol (1.4%) decrease in HbA1c with the addition of acarbose (20). Acarbose in other dual therapy studies more commonly decreases HbA1c by 6-9mmol/mol (0.5-0.9%).

Parenteral Agents

Metformin, Sulfonylurea and GLP1RA

Triple therapy studies with metformin, sulfonylurea and GLP1RA are few but show effective BGL-lowering when the GLP1RA is added to maximal dual oral therapy in patients with poor glycaemic control (21-23). The average HbA_{1c} reduction is 11mmol/mol (1.0%) and there is typically 1-2 kg weight loss over 6-12 months. The risk of hypoglycaemia can be attenuated by initially reducing the sulfonylurea and later up-titrating it if necessary. The GLP1RA currently available in Australia have TGA approval for use with metformin plus sulfonylurea but 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 drugs, 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 or combining long-acting insulin with one or more injections of short-acting insulin, or by continuous subcutaneous insulin infusion (this latter strategy is not commonly used in type 2 diabetes). Recent studies have explored combining insulin with newer therapies, including DPP4i, SGLT2i and GLP1RA, with good effect, however these combination are not currently PBS-reimbursed.

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 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 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 is acceptable without dose adjustment with 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 DPP4i, TZD and insulin) do not need to be discontinued in patients 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 patients 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). This may mean that the glycaemic-target could be symptom-control only, or 64mmol/mol (8%). Assessment of eGFR is important, as serum creatinine is not as 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 anti-hyperglycaemic agents.

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. If the patient experiences adverse effects with a glucose lowering therapy then another should be instituted. This will often take the form of a combination of therapies. With diabetes education and an engaged patient it is now possible to achieve good glycaemic control with the currently available therapies in even more people with type 2 diabetes.

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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 1500 mg/d.	Avoid	Avoid	Reduced clearance	GI disturbance, Lactic acidosis
		If eGFR30-45, max 850mg/d			Reduced clearance	
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 1 mg	Avoid	Avoid	Reduced clearance	Hypoglycaemia, increased transaminases
Glipizide	5-20 mg	Max dose 5-10 mg/day	Use at low doses 2.5 mg/day	Avoid	Hepatically metabolised	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 in dialysis

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 in dialysis
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 change 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 in dialysis
Incretin mimetics						
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

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	NO
Insulin	YES	YES	YES	YES	NO	NO	NO	NO	n/a
Triple therapy with									
M + SU	n/a	n/a	YES	YES	NO	NO	NO	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	NO	NO	NO	NO	n/a	NO	NO	NO
M + SGLT2i	n/a	NO	NO	NO	NO	NO	n/a	NO	NO
M + GLP-1a	n/a	YES	NO	NO	NO	NO	NO	n/a	NO
M + Insulin	n/a	YES	YES	NO	NO	NO	NO	NO	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	NO	n/a	NO	NO	NO	n/a	NO	NO	NO
SU + SGLT2i	NO	n/a	NO	NO	NO	NO	n/a	NO	NO
SU + GLP-1a	YES	n/a	NO	NO	NO	NO	NO	n/a	NO
SU + Insulin	YES	n/a	YES	NO	NO	NO	NO	NO	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	NO	NO	NO	NO	NO	NO	n/a	NO	n/a
GLP-1a + Insulin	NO	NO	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	$10.67	$0.21	$16.01	$0.32	Note lower dose
Metformin	Diabex	500	1bd	2	100	$13.52	$0.27	$18.86	$0.38	Brand price premium
Metformin	Various	1000	1 bd	2	90	$13.57	$0.30	$18.91	$0.42	
Metformin	Diabex	1000	1bd	2	90	$16.42	$0.36	$21.76	$0.48	Brand price premium
Metformin XR	Various	500	4 daily	4	120	$13.02	$0.43	$18.36	$0.61	
Metformin XR	Diabex	1000	2 daily	2	60	$15.87	$0.53	$21.21	$0.71	
Glibenclamide	Glimel	5	2 bd	4	100	$11.73	$0.47	$17.07	$0.68	
Glibenclamide	Daonil	5	2 bd	4	100	$13.17	$0.53	$18.51	$0.74	Brand price premium
Gliclazide	Various	80	2 bd	4	100	$13.50	$0.54	$18.84	$0.75	
Gliclazide MR	Various	30	4 daily	4	100	$13.69	$0.55	$19.03	$0.76	
Gliclazide MR	Diamicron	60	2 daily	2	60	$17.03	$0.57	$22.37	$0.75	Brand price premium
Glimepiride *	Various	4	1 daily	1	30	$11.02	$0.37	$16.36	$0.55	
Glimepiride *	Amaryl	4	1 daily	1	30	$13.86	$0.46	$19.20	$0.64	Brand price premium
Glipizide	Melizide	5	2 bd	4	100	$12.61	$0.50	$17.95	$0.72	
Glipizide	Minidiab	5	2 bd	4	100	$17.12	$0.68	$22.46	$0.90	Brand price premium
Metformin+ Glibenclamide *	Glucovance	500+5	2 bd	4	90	$15.60	$0.69	$20.94	$0.93	
Acarbose	Glucobay	50	1 tds	3	90	$34.87	$1.16	$36.90	$1.23	Note lower dose
Acarbose	Glucobay	100	1 tds	3	90	$45.87	$1.53	$36.90	$1.23	
Linagliptin	Trajenta	5	1 daily	1	30	$62.95	$2.10	$36.90	$1.23	Streamline authority required
Linagliptin+Met *	Trajentamet	2.5+ 1000	1 bd	2	60	$67.29	$2.24	$36.90	$1.23	Streamline authority required
Saxagliptin	Onglyza	5	1 daily	1	28	$59.20	$2.11	$36.90	$1.32	Streamline authority required
Saxagliptin+Met *	Kombiglyze	2.5+ 1000	1 bd	2	56	$63.26	$2.26	$36.90	$1.32	Streamline authority required
Vildagliptin	Galvus	50	1 bd	2	60	$62.95	$2.10	$36.90	$1.23	Streamline authority required
Vildagliptin+ Met *	Galvumet	50+ 1000	1 bd	2	60	$64.21	$2.14	$36.90	$1.23	Streamline authority required
Sitagliptin *	Januvia	100	1 daily	1	28	$59.20	$2.11	$36.90	$1.32	Streamline authority required
Sitagliptin+ Met *	Janumet	50+ 1000	1 bd	2	56	$63.26	$2.26	$36.90	$1.32	Streamline authority required
Alogliptin *	Nesina	25	1 daily	1	28	$59.20	$2.11	$36.90	$1.32	Streamline authority required

Alogliptin+ Met *	Nesina Met	12.5+1000	1 bd	2	56	$63.26	$2.26	$36.90	$1.32	Streamline authority required
Canagliflozin*	Invokana	300	1 daily	1	30	$96.61	$3.22	$36.90	$1.23	Phone authority required
Dapagliflozin	Forxiga	10	1 daily	1	28	$58.66	$2.10	$36.90	$1.32	Streamline authority required
Rosiglitazone	Avandia	8	1 daily	1	28	$90.94	$3.25	$36.90	$1.32	Authority required
Rosi+Met 1000*	Avandamet	4	1 bd	2	56	$95.00	$3.39	$36.90	$1.32	Authority required
Pioglitazone	Various	30	1 daily	1	28	$40.64	$1.45	$36.90	$1.32	Note lower dose, streamline authority required
Pioglitazone	Various	45	1 daily	1	28	$49.56	$1.77	$36.90	$1.32	Streamline authority required
Exenatide *	Byetta	10	S/C bd	2	60	$131.65	$4.39	$36.90	$1.23	Streamline authority required
Liraglutide *	Victoza	1.2	S/C bd	1	45	$253.35	$5.63	N/A	N/A	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	$224.66	75	$3.00	$36.90	$0.49	
Actrapid or Humulin R	Vials	10	Usually with meals	5	$134.16	50	$2.68	$36.90	$0.74	
Humalog, Novorapid, Apidra	Pens or penfills	3	Usually with meals	25	$264.56	75	$3.53	$36.90	$0.49	
Humalog, Novorapid, Apidra	Vials	10	Usually with meals	5	$159.61	50	$3.19	$36.90	$0.74	
Humalog mix 25 or Novomix 30	Pens or penfills	3	Usually bd	25	$264.56	75	$3.53	$36.90	$0.49	Short + long acting
Humalog mix 50	Pens or penfills	3	Usually bd	25	$264.56	75	$3.53	$36.90	$0.49	Short + long acting
Protophane or Humulin NPH	Pens or penfills	3	Usually bd	25	$224.66	75	$3.00	$36.90	$0.49	
Protophane or Humulin NPH	Vials	10	Usually bd	5	$134.16	50	$2.68	$36.90	$0.74	
Detemir(Levemir)#	Pens or penfills	3	Usually bd	25	$433.06	75	$5.77	*N/A*	$0.49	***Type 1*** diabetes only
Glargine (Lantus) #	Pens or penfills	3	Usually daily	25	$433.06	75	$5.77	$36.90	$0.49	
Insulin hypurin (Bovine)	Vials	10	Variable	5	$401.06	50	$8.02	$36.90	$0.74	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 1st December 2014.
* = 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.