Appendix E. Available glucose-lowering agents

When evaluating the clinical evidence of the following interventions, high-quality, long-term prospective trials on clinical outcomes specific to type 2 diabetes and its complications are useful. Of note, agents recently listed for glycaemic management have short-term trials that have reported cardiovascular safety but no cardiovascular benefits.

Metformin

Prospective trials have demonstrated reduced progression (31%) from impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) to diabetes when metformin is used. However, metformin is not currently Therapeutic Goods Administration (TGA) indicated for this use.

In patients with type 2 diabetes, the UK Prospective Diabetes Study (UKPDS) has demonstrated cardiovascular benefits with metformin use in overweight patients.

Metformin:

- is the medication of first choice for people with type 2 diabetes
- reduces hepatic glucose output and improves muscle cell insulin receptor resistance
- does not stimulate insulin release
- significantly reduces the risk of diabetes-related morbidity and mortality in overweight patients
- should be used with caution in people with hepatic or cardiac disease, and those with a heavy alcohol intake or dehydration (eg acute gastroenteritis) and renal impairment due to risks of lactic acidosis.

Contraindication:

- Advanced renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) is the only absolute contraindication to metformin. It should be used with caution in people with an eGFR of 30–45 mL/min/1.73 m^2 with dose reduction is recommended.

Main side effects:[278]

- anorexia, nausea, vomiting
- diarrhoea, abdominal cramps, flatulence
- lactic acidosis (uncommon, but may occur with dehydration and co-existing renal, liver or cardiovascular disease [CVD])
- possible vitamin B12 deficiency.

Sulphonylureas

The UKPDS has demonstrated microvascular benefits with sulphonylurea use. Cardiovascular benefits only emerged with long-term, post-trial follow-up of newly diagnosed patients previously intensively treated with sulphonylureas and insulin. This has been called the 'legacy' effect. Clear microvascular benefits have also been shown in the Advance in Diabetes and Vascular Disease (ADVANCE) trial, which used the more contemporary sulphonylurea agent gliclazide.

Sulphonylureas:

- act to increase insulin secretion in a non-glucose dependent fashion and rely on some residual β-cell function
- can be considered after a trial of healthy lifestyle and used in combination with agents such as metformin.

Main side effects:

- weight gain
- symptomatic hypoglycaemia
- anorexia, nausea, diarrhoea, skin rashes
- occasionally blood dyscrasias
- glibenclamide and glimepiride may cause high rates of hypoglycaemia (in older patients and in patients with autonomic neuropathy or nephropathy).

Acarbose

One prospective trial Study to Prevent Non-Insulin-Dependant Diabetes Mellitus (STOP-NIDDM) has shown reduced progression to diabetes in patients with IGT, as well as macrovascular benefits.[279] As yet, no prospective cardiovascular trials have reported on acarbose use in type 2 diabetes.

Acarbose:

- can be used when blood glucose values remain high after meals despite dietary modification
- inhibits the digestion of carbohydrate and thus slows the rate of glucose delivery into the circulation
- needs to be taken at the time of starting the meal and introduced gradually to avoid flatulence and abdominal discomfort.

If hypoglycaemia occurs (because of concurrent sulphonylurea or insulin treatment), glucose rather than other carbohydrates is required. Care is necessary in those with renal impairment or gastrointestinal disease, and liver enzymes need to be monitored.

Main side effects:

- flatulence and abdominal bloating
- nonresponse to carbohydrates other than glucose if hypoglycaemic
- liver abnormalities (rare).

Glitazones (pioglitazone and rosiglitazone)

The Prospective pioglitazone clinical trial in macrovascular events (PROactive) trial did not demonstrate benefit for the primary outcome of major adverse cardiovascular events (MACE) but did report significantly increased risk of heart failure (11% versus 8% in placebo).[116]

Several meta-analyses have reported that glitazones (including rosiglitazone) increase risk of hospitalisation with heart failure or heart failure death.

Glitazones:

- sensitise the liver and peripheral tissues to insulin and are effective in lowering blood glucose by reducing insulin resistance
- can (pioglitazone and rosiglitazone) be used as combination therapy with metformin, sulphonylureas or insulin.

Contraindications:[280,281]

- moderate to severe cardiac failure (pioglitazone and rosiglitazone)
- increased risk of bladder cancer.

Rosiglitazone is not recommended in patients with known ischaemic heart disease, particularly in those taking nitrates.

Rosiglitazone is not listed on the Pharmaceutical Benefits Scheme (PBS) for triple therapy with metformin and a sulphonylurea, or in combination with insulin.

Main side effects:

- increased subcutaneous fat and/or fluid
- decreased haemoglobin levels
- increased risk of peripheral fractures in women
- possible increased risk of myocardial infarction (rosiglitazone)
- increased LDL-C (rosiglitazone).

Incretins

Two classes of incretin medications exist – dipeptidyl peptidase-4 inhibitor (DPP-4i) and glucagon-like peptide-1 receptor agonist (GLP-1 RA).[282]

DPP-4i

DPP-4i includes sitagliptin, linagliptin, saxagliptin, vildagliptin and alogliptin.

Saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction [SAVOR-TIMI] trial) showed secondary endpoint data: statistically significant increase in hospital admissions for congestive heart failure. No demonstrated macrovascular benefits.

Alogliptin (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE] trial) and sitagliptin (Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin [TECOS] trial) showed no increased cardiovascular risks, but also did not demonstrate macrovascular benefits.

Other DPP-4i have no reported prospective cardiovascular trials demonstrating benefits.

DPP-4i:

- are oral agents and act by increasing levels of circulating incretins – glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) – which are released by intestinal cells in response to food
- block the enzyme dipeptidyl peptidase-4 (DPP-4), which is responsible for rapid breakdown of GLP-1 and GIP
- cause elevated and prolonged action of physiologically released incretin hormones
- such as GLP-1 and GIP act on pancreatic cells to increase insulin levels and also suppress α-cell secretion of glucagon (elevated in type 2 diabetes)
- are weight neutral and improve postprandial control
- rarely cause hypoglycaemia except in combination with agents such as sulphonylureas and insulin
- dose reduction in renal impairment eGFR <60 mL/min/1.73 m^2 for alogliptin, saxagliptin, sitaglitpin, and vildagliptin; no dose adjustment required for hepatically metabolised linagliptin; saxagplitin may not be used in end-stage renal failure stage five of chronic kidney disease.[283]

Main side effects:

- nasopharyngitis
- headache
- upper respiratory tract symptoms.

GLP-1 RA

GLP-1 RA includes exenatide, liraglutide and lixisenitide.

Lixisenatide (Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA] trial) showed no increased cardiovascular risks but also did not demonstrate macrovascular benefits. A prospective cardiovascular safety outcomes trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER]) for liraglutide, another GLP-1 RA in high risk patients, had a 13% reduction in major adverse cardiac events and 22% reduction in cardiovascular death.[130]

GLP-1 RAs:

- are injectable medications that bind to the GLP-1 receptor (exenatide is currently PBS subsidised; once weekly exenatide, liraglutide and lixisenitide are TGA approved for use in Australia but are currently not PBS-listed)
- cause weight loss through actions on cerebral hormonal responses to insulin and appetite
- may affect gastric emptying
- only cause hypoglycaemia in combination with other medications such as sulphonylureas and insulin.

Main side effects:

- nausea, vomiting
- pancreatitis (rarely)
- weight loss.

Sodium glucose co-transporter 2 inhibitors

The EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial) OUTCOME trial (empagliflozin) showed reduced rates of death from cardiovascular causes (38% relative risk reduction) and any cause (32% relative reduction). In secondary endpoint analyses, a 35% reduction in hospitalisation for heart failure was observed. The mechanism through which empagliflozin may mediate these outcomes is still under investigation.

The other sodium glucose co-transporter 2 (SGLT2) inhibitors have no reported prospective cardiovascular trials.

SGLT2 inhibitors:

- are novel oral medications that selectively inhibit SGLT2, the main renal glucose reabsorptive mechanism
- result in glycosuria with resultant lowering of glucose in a non-insulin dependent manner and modest weight loss plus lowered BP
- rely on adequate renal function
- promote weight loss.

Side effects:

- weight loss
- increased urogenital mycotic and urinary tract infections
- aggravate dehydration
- euglycaemic diabetic ketoacidosis (DKA).