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.