(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.