The new class war: SGLT2 inhibitors versus DPP-4 inhibitors

Merlin Thomas

Over 90% of people with type 2 diabetes will need more than metformin monotherapy to achieve their targets for optimal glucose levels. There are many second-line options for glucose management in type 2 diabetes, including the sodium–glucose cotransporter 2 (SGLT2) inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor classes. This article provides a framework for Australian general practices to compare the associated benefits and risks of SGLT2 inhibitors and DPP-4 inhibitors when added to metformin for the management of type 2 diabetes.

Over 90% of people with type 2 diabetes will need more than metformin monotherapy to achieve their targets for optimal glucose levels. Dual therapy may begin early in their management, when it is clear that metformin is insufficient (primary failure) or later as the efficacy of metformin gradually wanes (secondary failure). The Royal Australian College of General Practitioners (RACGP) and Diabetes Australia (2014) guidelines recommend that when optimal glycaemic levels are not met, no more than 3–6 months should pass before a second-line agent is added. Of course, earlier initiation of combination therapy may be appropriate in some cases, especially when diabetes is clearly managed suboptimally.

There are many second-line options for glucose management of type 2 diabetes, including the sodium–glucose cotransporter 2 (SGLT2) inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor classes. These newer classes have a number of advantages compared to older classes, including reduced risk of hypoglycaemia and weight gain, and no need for dose-titration. So the question, rather than whether to use them, is which agent will be best for the patient you have in front of you? This article provides a framework to compare the associated benefits and risks of SGLT2 inhibitors and DPP-4 inhibitors, when added to metformin for the management of type 2 diabetes in Australian general practice.

Question #1: efficacy

The most obvious first question when deciding between an SGLT2 and a DPP-4 inhibitor is how well does each class lower glucose? Across clinical trials, SGLT2 inhibitors have been shown to lower HbA_{1c} by 7.2 mmol/mol (–0.66%; 95% confidence interval [CI], –0.73%, –0.58%; Vasilakou et al, 2013). Very similar results have also been reported for DPP-4 inhibitors in participants who were not achieving their glycaemic target on metformin alone (7.2 mmol/mol [–0.69%] 95% CI, –0.79%, –0.61%; Liu et al, 2012). It has been considered that there is no significant difference in glucose lowering achieved by either drug class (Goring et al, 2014). However, recent head-to-head studies have suggested that SGLT2 inhibitors may result in a greater glucose-lowering effect than DPP-4 inhibitors in people with type 2 diabetes very suboptimally managed diabetes at baseline (HbA_{1c} >75 mmol/mol [9%]; Rosenstock et al, 2014; DeFronzo et al, 2015). In contrast, for people with type 2 diabetes who have an HbA_{1c} around 53 mmol/mol (7%), a DPP-4 inhibitor may achieve a greater glucose-lowering effect. The effect of DPP-4 inhibitors on fasting plasma glucose may be modestly greater than with SGLT2 inhibitors in combination with metformin, while the converse may be true for post-prandial glucose levels (Rosenstock et al, 2014; DeFronzo et al, 2015). In people with type 2 diabetes who have renal impairment, there may be a reduction in SGLT2 inhibitor efficacy. The glucose-lowering effects of DPP-4 inhibitors are unaffected or

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Article points

1. Over 90% of people with type 2 diabetes will require additional medication after metformin.
2. Dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter 2 inhibitors provide an alternative to the older glucose-lowering medications.
3. Drug regimens should be individualised and patient-centred.

Key words

– DPP-4 inhibitors
– Dual therapy
– SGLT2 inhibitors

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Page points

1. DPP-4 inhibitors have highly favourable tolerability. This is important, as most Australians with type 2 diabetes are over 65 years of age, and for whom polypharmacy, inconstant health and comorbidities are common.
2. Because of their mode of action, SGLT2 inhibitors are not recommended for glucose lowering in people with renal impairment.
3. While some antidiabetes medications are potentially weight promoting, DPP-4 inhibitors are weight neutral and SGLT2 inhibitors are weight negative.

even modestly improved in people with renal impairment (Thomas et al, 2016).

Question #2: tolerability

All treatments have the potential for adverse effects, so the doctor's mantra must be *prius minus noceant* (first do least harm). The key advantage of using DPP-4 inhibitors is their highly favourable tolerability (Karagiannis et al, 2012; Kawalec et al, 2014). This is critical, given that the most Australians with type 2 diabetes are over 65 years of age, in whom polypharmacy, inconstant health and comorbidities are common. Recent studies have confirmed a very small risk of pancreatitis with DPP-4 inhibitors (DeVries et al, 2017).

SGLT2 inhibitors block the SGLT2 protein involved in 90% of glucose reabsorption in the proximal renal tubule, resulting in increased renal glucose excretion and lower blood glucose levels. SGLT2 inhibitors also increase the urine output, especially when therapy has just been started and glucose levels are high. This can be a positive experience for people using an SGLT2 inhibitor, as within hours of taking the drug, it begins to take effect. As glucose levels improve, the amount and frequency of urination usually settles down.

The glucose-lowering efficacy of SGLT2 inhibitors is dependent on sufficient glomerular filtration to deliver a glucose load to the proximal tubule. SGLT2 inhibitors are not recommended for glucose lowering in patients with renal impairment (estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2 for empagliflozin or <60 mL/min/1.73 m^2 for dapagliflozin), although action on weight, renal and cardiac outcomes appear to be maintained even in patients with severe renal impairment.

In the long-term, people with type 2 diabetes taking SGLT2 inhibitors will void on average an extra 300–400 mL/day (Kilov et al, 2013). This is the same volume as a can of soft drink and taking an SGLT2 inhibitor will generally mean individuals will go to the toilet once or maybe twice more every day, especially if the medication is taken in the morning (Johnsson et al, 2013). Individuals with type 2 diabetes who have pre-existing bladder, pelvic floor or prostate problems may not feel comfortable with any increase in their urine output, and other glucose-lowering strategies should be considered.

The modest volume losses associated with SGLT2 inhibition should not cause dehydration, constipation or dizziness in the long term (Vasilakou et al, 2013). However, alternative glucose-lowering strategies should be considered for individuals prone to postural hypotension, fainting or dizziness.

About 1 in 12 women with diabetes using an SGLT2 inhibitor will develop genital thrush (candidiasis), usually in the first 3–4 months of treatment (Wilding, 2014). Thrush is easy to recognise and treat with short courses of standard antifungal therapies (topical creams, suppositories or oral "azoles"). Once treated, recurrent infections are uncommon. Although SGLT2 inhibitors add glucose to the urine, surprisingly, urinary tract infections (UTIs) are not significantly more common or more severe in participants receiving SGLT2 inhibitors, even in women with a previous history of chronic or recurrent UTIs (Vasilakou et al, 2013). This is possibly because people taking an SGLT2 inhibitor empty their bladder more often, and just like encouraging drinking, this reduces bladder stasis and offsets the risk of UTIs.

Question #3: optimising body weight

Optimising body weight is a key element of the management of type 2 diabetes in overweight or obese people, especially in early diabetes when weight loss is a high priority and can be hard to achieve, reinforce or sustain. When glucose levels are suboptimal, it is common to recommend intensification of lifestyle interventions to lose weight while also adding in additional glucose-lowering agents. It is important to be aware that some antidiabetes medications are potentially weight promoting (sulfonylureas, insulin and thiazolidinediones), and so will be antagonist with the advice to intensify lifestyle interventions for weight loss. DPP-4 inhibitors are weight neutral while SGLT2 inhibitors are weight negative. Glucose loss and thus calorie loss in the urine, as a result of an SGLT2 inhibitor, can result in rapid, significant and sustained weight loss (approximately 2–3 kg in 6 months). Most of the weight loss seen with SGLT2 inhibition is loss of fat, including visceral fat (Bolinder et al, 2012), which is important for the waistline and overall health. Interestingly, after 6 months of SGLT2 inhibition, weight loss stops even though glycosuria continues. SGLT2 inhibition can contribute to weight loss, but is not the solution.

Question #4: cardiovascular safety

Reducing the risk of cardiovascular events is a priority of diabetes management as heart attacks and strokes account for over a third of all deaths in people with type 2 diabetes. If an agent reduces glucose levels, it must be shown to not increase the risk of cardiovascular disease, and as such, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) now mandate that all new antidiabetes agents undergo rigorous testing to demonstrate cardiovascular safety.

Cardiovascular safety data for DPP-4 inhibitors suggest that the class does not pose an unacceptable cardiovascular risk (Patil et al, 2012; Scirica et al, 2013), although there is a small increase in heart failure admissions observed in trials of participants using DPP-4 inhibitors (odds ratio, 1.13 [95% CI, 1.00–1.26]; Li et al, 2016).

Cardiovascular safety data for empagliflozin from the EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial suggested that its use may be associated with reduced rates of heart failure and cardiovascular death in people with established cardiovascular disease (Zinman et al, 2016). The mechanism behind this is still unclear and it is yet to be determined whether such benefits will also be seen in high-risk individuals without cardiovascular disease. CANVAS (CANagliflozin cardioVascular Assessment Study) recently demonstrated a reduction in major adverse cardiovascular events with canagliflozin (Neal et al, 2017), suggesting there is a class effect. However, it is yet to be established whether dapagliflozin will have the same cardiovascular safety effect in the DECLARE-TIMI 58 (Dapagliflozin Effect on CardiovascuLAR Events – Thrombolysis in Myocardial Infarction) trial.

Question #5: renoprotection

Chronic kidney disease (CKD) is a major microvascular complication in diabetes. At least half of people with type 2 diabetes in Australian general practices have CKD, in whom its presence and severity are strongly associated with poor health outcomes, including premature mortality. Beyond glucose lowering, there are data to suggest that some agents used to treat diabetes provide renoprotection. Reductions in albuminuria have been reported in the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction; Mosenzon et al, 2017) and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin; Cornel et al, 2016) trials in over 10 000 participants using the DPP-4 inhibitors saxagliptin and sitagliptin, respectively. However, no significant effects were seen on declining renal function or the incidence of renal failure. The EMPA-REG study reported a slower decline in renal function and fewer participants developing renal failure or needing dialysis (Wanner et al, 2016). Similar renal benefits were also reported in the CANVAS trial (Neal et al, 2017). When renoprotection is a treatment priority, such benefits may be potentially valuable. However, it is important to remember that, unlike DPP-4 inhibitors, SGLT2 inhibitors are currently not recommended in people with severe or moderate renal insufficiency because of their reduced efficacy for lowering glucose levels in this setting.

Question #6: cancer

Today, every new agent must go through rigorous testing to ensure that it does not increase the risk of cancer. DPP-4 inhibition raises the levels of the incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which have the potential to promote the growth of the rare medullary carcinoma of the thyroid (MCT). Consequently, DPP-4 inhibitors are contraindicated in individuals with a personal or family history of MCT or multiple endocrine neoplasia type 2 (Vangoitsenhoven et al, 2012). Whether incretins have significant effects on other cancers is debatable. Certainly, large clinical trials have not observed any increased risk of cancers, including pancreatic cancer (Scirica et al, 2013; Cornel et al, 2016; Mosenzon et al, 2017), although from a practical point of view, it is reasonable not to prescribe a DPP-4 inhibitor in individuals with a history of pancreatitis or pancreatic cancer.

Early studies reported numerically more cases of bladder cancer in participants treated with dapagliflozin than with standard therapy, and on this basis, FDA approval for this agent was initially withheld (Lin and Tseng, 2014). However, most people who were diagnosed with bladder cancer in the trial had blood in the urine before starting

Page points

1. Cardiovascular safety data for DPP-4 inhibitors suggest that the class does not pose an unacceptable cardiovascular risk, although a small increase in heart failure admissions has been observed in trials.
2. Cardiovascular safety data for empagliflozin suggest that its use may be associated with reduced rates of heart failure and cardiovascular death in people with established cardiovascular disease.
3. Reductions in albuminuria have been reported in study participants using the DPP-4 inhibitors saxagliptin and sitagliptin. No significant effects were seen on declining renal function or the incidence of renal failure.
4. DPP-4 inhibitors are contraindicated in individuals with a history of medullary carcinoma of the thyroid. Whether they have significant effects on other cancers is debatable.

"As a simple rule of thumb, anytime it is considered to stop metformin, stopping the SGLT2 inhibitor may also be prudent."

treatment or it appeared only a short time after starting, which suggests a causal link to the drug itself is unlikely. Trials of other SGLT2 inhibitors have not observed any difference in the prevalence of cancers, including those of the bladder (Lin and Tseng, 2014). Additionally, there has been no excess risk for any cancers reported for people who are born without the SGLT2 protein (benign familial glycosuria), despite persistent glycosuria throughout life.

Question #7: ketoacidosis

Ketone bodies are fatty acid derivatives that are used by many tissues when glucose availability is limited. It is normal for a healthy human to increase production of ketones during prolonged fasting. Apart from during pregnancy, alcoholism and type 1 diabetes, ketoacidosis does not occur due to the buffering effects of bicarbonate. SGLT2 inhibitors trigger the increased production of ketone bodies by the liver, possibly to offset the glucose loss in the urine and, as such, SGLT2 inhibitors have been associated with diabetic ketoacidosis (DKA; FDA, 2015).

Most SGLT2-associated cases of DKA have been when SGLT2 inhibitors have been continued to be taken in stressful metabolic settings, like prolonged starvation, after surgery, excess alcohol intake or major inter-current illness. Inappropriate and excessive reductions of insulin doses may also induce excess ketone production. As a simple rule of thumb, any time it is considered to stop metformin, stopping the SGLT2 inhibitor may also be prudent. For this reason, SGLT2 inhibitors should never be used in people with type 1 diabetes, in which their use is contraindicated.

Summary

SGLT2 inhibitors and DPP-4 inhibitors are both second-line therapy options for type 2 diabetes. It is important to consider the individual when deciding what drug should be added to metformin. No two individuals with type 2 diabetes are exactly the same – what is best for one person may be unthinkable for another. The balance of benefits ("pluses") and negatives ("minuses") is vital to get right (*Figure 1*). ■

Competing interests

Merlin Thomas has received honoraria for educational symposia conducted on behalf of AstraZeneca, BMS and the Boehringer Ingelheim and Lilly alliances, and MSD respectively, manufacturers of sodium–glucose cotransporter 2 and dipeptidyl peptidase-4 inhibitors.

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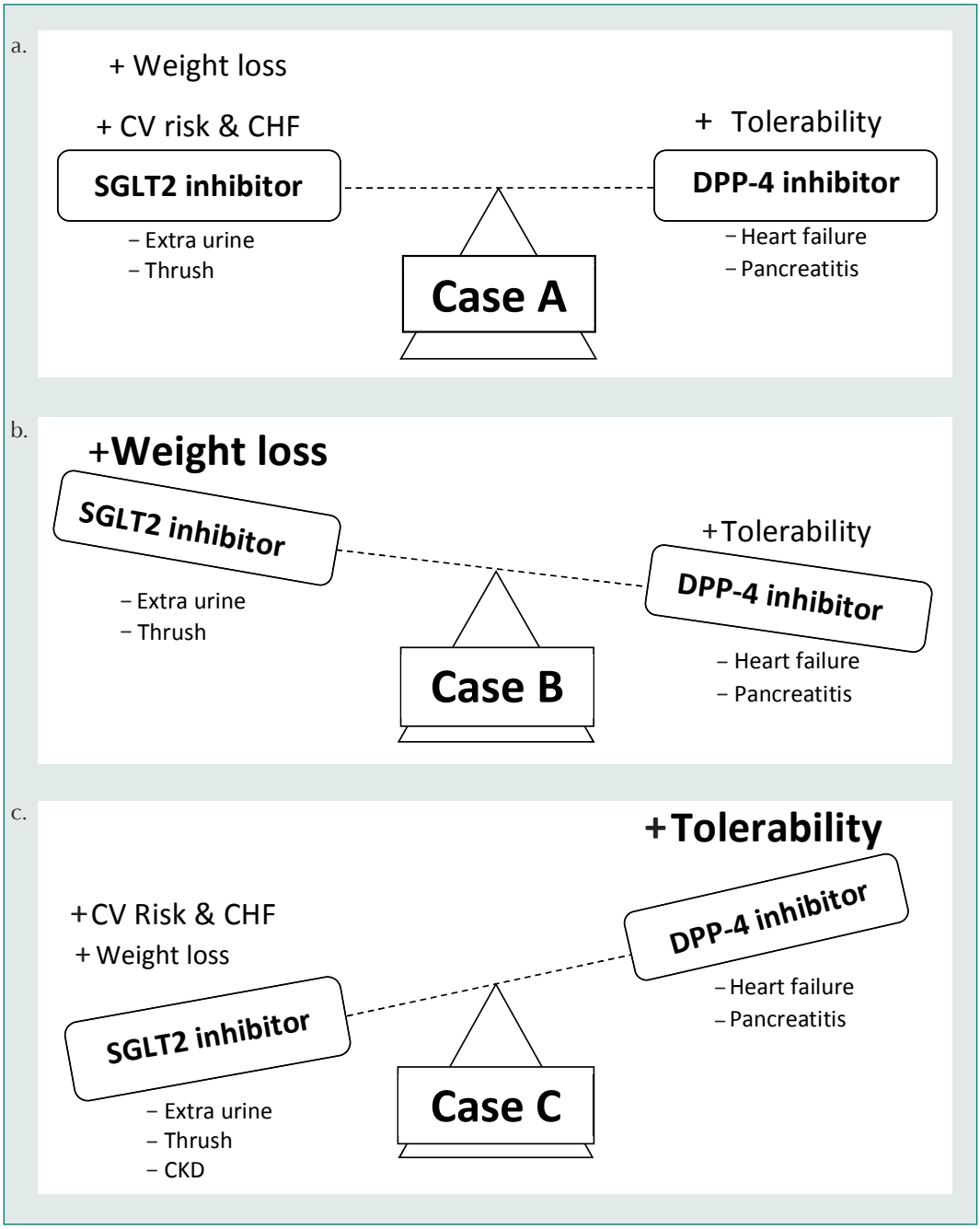

Figure 1a. The main advantages and negatives of SGLT2 and DPP-4 inhibitors.

1b. In a younger person with sub-optimal blood glucose management early in their disease course, in whom weight loss is a priority, and bladder dysfunction and comorbidity are not limiting, then an SGLT2 inhibitor could be advantageous.

1c. In an older person, in whom weight loss is not a priority, and bladder dysfunction and comorbidity are frequently limiting, then good tolerability and easy efficacy of a DPP-4 inhibitor could be advantageous.

CHF=congestive heart failure; CKD=chronic kidney disease; CV=cardiovascular; DPP-4=dipeptidyl peptidase-4; SGLT2=sodium–glucose cotransporter 2.

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