Introduction

Few patients with type 2 diabetes can successfully manage their glucose levels, and the risk of complications associated with them, using only monotherapy. Most will need to take at least two, more often three glucose-lowering agents to achieve and maintain optimal glucose control. Although each single agent will have some limitations as monotherapy, this is seldom a failing of any individual strategy. Rather, it reflects the complex multifactorial pathogenesis of hyperglycaemia and the progressive nature of type 2 diabetes.

So instead of accepting the traditional ‘treat-to-fail’ approach for managing diabetes that uses combination therapy only as a last resort, an early proactive use of combination therapies for glucose lowering may offer a number of advantages. This review will explore the potential benefits and limitations of combination therapy with SGLT2 and DPP4 inhibitors and their role in managing type 2 diabetes.

Take Home Messages

- SGLT2 inhibitors and DPP4 inhibitors can be safely and effectively used together in patients with type 2 diabetes.
- The glucose lowering achieved using combination therapy is better than each agent individually.
- Therapy combining SGLT2 inhibitors with DPP4 inhibitors are now subsidised through the Pharmaceutical Benefits Scheme (PBS) as triple therapy (added to metformin or a sulphonylurea).
- A range of fixed-dose formulations combining different SGLT2 inhibitors with DPP4 inhibitors are now available and subsided by the PBS.
More medication = better glucose control

Good glucose control is still important for the management of diabetes. Although recent cardiovascular outcome trials have demonstrated that some of the benefits of SGLT2 inhibitors\(^3\) and GLP-1 receptor agonists\(^2\) are independent of glucose lowering, achieving and maintaining the HbA1c at or close to the target appropriate for that individual is still fundamental and clearly has long-term benefits for preventing diabetic complications\(^4\), especially if undertaken without delay and early in the course of the disease.

RACGP guidelines specifically recommend adding additional glucose lowering therapy after no more than six months when patients are not achieving their desired level of control\(^6\).

The addition of SGLT2 inhibitors to DPP4 inhibitors and vice versa, achieves a valuable reduction in HbA1c in most patients. Overall, across a large number of clinical trials, the use of SGLT2 inhibitors is associated with reduction in HbA1c between 0.6 to 0.9% when compared to placebo, regardless of background therapy\(^6\). Specifically, adding an SGLT2 inhibitor onto background therapy with a DPP4 inhibitor reduces HbA1c by 0.62%, [95% CI: 0.73 to 0.51%; P < 0.001] compared to placebo\(^7\).

For example, in patients inadequately controlled on sitagliptin and metformin, treatment with ertugliflozin 5mg or 15mg lowered HbA1c by 0.7% [95% CI 0.9, 0.5] and 0.8% [95% CI 0.9, 0.6], respectively (P <0.001 for both comparisons; Figure 1)\(^8\).

However, patients with poor glucose control (HbA1c>8%) can achieve a greater response than those starting an SGLT2 inhibitor when closer to 7%\(^8,10\). This is simply because the amount of glucose that can be lost into the urine when using SGLT2 inhibitors is proportional to the ambient glucose\(^6\).

A key advantage of combining DPP4 inhibition and SGLT2 inhibition in an individual patient is that the fundamental differences in glucose-lowering by these two agents offer an opportunity for broader coverage. For example, in a patient with poor glucose control, treatment with an SGLT2 inhibitor reduces plasma glucose levels effectively, but their glycosuria wanes as HbA1c levels approach 7.0%. To achieve target control, adding in DPP4 inhibitors is a great way to get over the line, because unlike SGLT2 inhibitors, their efficacy is less glucose-dependent. Indeed, DPP4 inhibitors may be more effective for glucose lowering than SGLT2 inhibitors when the HbA1c is less than 7.5%\(^9,11\). Equally, in patients inadequately controlled on a DPP4 inhibitor, the better effects of SGLT2 on post-prandial glucose and insulin-independent glucose lowering can facilitate improved glucose control.

Overall, the effect of adding a DPP4 inhibitor onto background therapy with an SGLT2 inhibitor in recent trials is slightly less than the other way around [weighted mean difference 0.37%; 95% CI: 0.50 to 0.25%; P < 0.001]. However, this most likely reflects differences in glucose control at baseline. This is also why the glucose-lowering effects of simultaneously combining a DPP4 inhibitor together with an SGLT2 inhibitor are not additive with respect to HbA1c reduction, as each agent reduces the baseline glucose for the other to work off.

Importantly, the likelihood of achieving a target HbA1c <7% is increased to the same extent by adding a DPP4 inhibitor to an SGLT2 inhibitor, or by adding an SGLT2 inhibitor to a DPP4 inhibitor\(^7\).

More medication ≠ more side effects

The first reason why most patients and doctors dislike combination therapy is the notion that adding more medication will unnecessarily expose patients to more side effects. Take for example what happens when sulphonylurea is added to metformin, the addition opens up a whole world of monitoring and mitigation of hypoglycaemia risks. However, a perfect combination would add little or no extra risks to the patient (alongside the potential benefits).

One advantage of using DPP4 inhibitors in combinations is their highly favourable tolerability when added to background therapy, including SGLT2 inhibitors\(^12,13\).

Avoiding the worry of potential hypoglycaemia and weight gain helps for adherence when starting out as well as in the long term. But while the safety and tolerability of DPP-4 inhibitors is favourable compared to other glucose lowering agents, all DPP-4 inhibitors
may be associated with an increased risk of acute pancreatitis and bullous pemphigoid (although the absolute risk remains very low).

Adding an SGLT2 inhibitor to background therapy with a DPP4 inhibitor does not increase the risk of hypoglycaemia or weight gain. In fact, taking SGLT2 inhibitors results in rapid, significant and sustained weight loss (approximately two to three kilograms in six months of treatment), regardless of background therapy. For example, adding ertugliflozin 5mg or 15mg onto background therapy with a sitagliptin 100mg reduced body weight by 2.0 kg and 2.1 kg respectively more than placebo (p<0.001).

Clinical experience suggests patients don’t forget that this was the drug that helped them lose some weight, even if the weight loss subsequently plateaus after six months of therapy.

On the downside, adding an SGLT2 inhibitor to background therapy with a DPP4 inhibitor can be associated with increased urine output and frequency, especially if baseline plasma glucose levels are high. This is not usually a problem, and settles down quickly as glucose control improves and glycosuria declines. Starting the SGLT2 inhibitor early, while patients have an HbA1c below 8%, can also minimise polyuria at initiation. Subjects with pre-existing bladder, pelvic floor or prostate problems may be less accommodating to any increase in their urine output, and other glucose lowering strategies might be preferable in these contexts.

SGLT2 inhibition can also increase the risk of developing genital thrush (candidiasis), especially in women with urinary incontinence and/or poor genital hygiene. Although painful and unpleasant, thrush generally settles quickly with short courses of standard antifungal therapies (topical creams, suppositories or oral ‘azoles’). Furthermore, focused education programs to improve genital hygiene can significantly reduce the risks of thrush in patients with diabetes. Like polyuria, genital mycoses are glucose-dependent and minimised when starting therapy from an HbA1c of less than 8%. Some studies have reported that SGLT2/DPP4 inhibitor combinations resulted in a slightly lower risk of genital infection compared with an SGLT2 inhibitor alone (RR: 0.42, 95% CI: 0.18 to 0.99; P = 0.046). Whether this is due to less glycosuria or other actions of DPP4 inhibitors is unclear.

Ketoacidosis has been rarely reported in patients using SGLT2 inhibitors. Where it has occurred, it has almost always been when SGLT2 inhibitors have continued to be taken in stressful metabolic settings, like prolonged starvation, after surgery, excess alcohol intake or major intercurrent illness.

Inappropriate and excessive reductions of insulin doses may also increase ketone production. Although DPP4 inhibition may prevent the rise in glucagon following SGLT2 inhibition, it does not appear to prevent ketogenesis or lower the risk of ketoacidosis.

Combinations for patients with diabetes and renal impairment

At least one in four of all adult patients (>55 years) with type 2 diabetes in Australian general practice have moderate to severe renal impairment, denoted by the presence of an estimated GFR less than 60 mL/min/1.73m². Managing these patients can be challenging. Patients with diabetes and renal impairment are at increased risk for poor health outcomes including adverse drug reactions, cardiovascular disease, heart failure, and premature mortality. This makes the use SGLT2 inhibitors with their proven cardiovascular, heart failure and renoprotective benefits highly desirable, compared to other strategies that, at best, have demonstrated safety in this setting.

At the same time, the glucose-lowering effects of SGLT2 inhibitors are reduced in patients with an eGFR between 45-60 mL/min/1.73m² (Stage 3A CKD) and are non-significant in patients with reduced kidney function below this level. This is the reason that SGLT2 inhibitors are not currently recommended for use in patients with an eGFR less than 45 mL/min/1.73m², and are contraindicated in patients with an eGFR <30 mL/min/1.73m² or an eGFR persistently lower than 45 mL/min/1.73m². In fact, they are still working but too little glomerular filtration means insufficient urinary glucose loss, so little or no plasma glucose lowering. In order to achieve glucose control, as well as end organ protection, a combination of SGLT2 inhibition with an appropriate dose of DPP4 inhibitor in patients with renal impairment is therefore preferred. Empagliflozin/linagliptin is contraindicated in patients with an eGFR persistently below 45 mL/min/1.73m². Saxagliptin/dapagliflozin should not be used in patients with an eGFR persistently lower than 60 mL/min/1.73m².

DPP4 inhibition allows for safe and effective glucose control in patients with diminished renal function, with efficacy comparable to that observed in patients with normal renal function and a low incidence of adverse drug reactions including hypoglycaemia. Reductions in albuminuria with DPP4 inhibitors have also been reported in large trials. At the same time, SGLT2 inhibition can protect the heart and the kidneys, independent of glucose lowering.

Combinations for patients with diabetes and heart failure

Heart failure is an unwelcome companion to type 2 diabetes.

Patients with type 2 diabetes have over twice the risk of incident heart failure as people without diabetes.

Although historically-associated with comorbid ischaemic heart disease (e.g. a prior heart attack), increasingly patients are presenting with shortness of breath or ankle swelling as their first sign of cardiac disease.
Treatment with SGLT2 inhibitors has been shown to be associated with a substantial reduction in hospitalisation for heart failure, both in those with known heart failure and those without known cardiac disease\(^2\). Recent European guidelines recommend the use of SGLT2 inhibitors in all patients with diabetes and heart failure, as well as those at increased risk from heart failure, including those with cardiovascular disease and chronic kidney disease\(^3\).

By contrast, some DPP4 inhibitors have been associated with a borderline increase in the risk for hospitalisation from heart failure\(^4\), and have been generally discouraged for use in patients with heart failure. However, the large Cardiovascular Outcome Trial using sitagliptin showed no safety signal, including patients with known heart failure\(^5\). Limiting any risk from heart failure by combining SGLT2 and DPP4 inhibition is an attractive proposition, although there is currently no evidence to support this.

**Combinations for patients with diabetes and cardiovascular disease**

The burden of cardiovascular disease among people with diabetes is substantial.

Almost two in three adults with type 2 diabetes report having cardiovascular disease\(^6\). Reducing the risk of cardiovascular events, and certainly not adding to it, is a top priority of diabetes management.

Overall, data suggests that DPP4 inhibitors are generally a safe way to lower glucose levels in patients with type 2 diabetes\(^7\). Clinical trials including patients with established CVD have been completed with empagliflozin, canagliflozin (not available in Australia) and dapagliflozin (EMPA-REG Outcomes, CANVAS and DECLARE-TIMI53, respectively) and the VERTIS-CV trial with ertugliflozin is due to be reported in 2020.

Despite some variability between studies, taken as a whole these data suggest that all SGLT2 inhibitors have the potential to reduce the risk of major acute cardiovascular events, myocardial infarction, heart failure and mortality, when used in addition to standard care (Figure 3)\(^3\). As a consequence, recent global guidelines recommend the use of SGLT2 inhibitors in all patients with diabetes and atherosclerotic cardiovascular disease\(^8,9\).

**Fixed-dose combinations make a difference**

One of the major keys to long term therapy is adherence. The best medication does not work if it does not continue to be taken! One determinant of non-adherence is a medication’s tolerability and perceived safety, which is one reason why adherence with DPP4 inhibitors is greater than with other glucose-lowering agents.

Another factor that contributes to non-adherence is dosing complexity and the overall pill burden.

Fixed dose combinations of glucose lowering medications have a strong potential to improve adherence by consolidating therapy to reduce the pill burden of separate pills as well encouraging adherence with a stronger combination therapy\(^8\). Generally, fixed-dose combinations are also associated with better patient satisfaction\(^9\). And better adherence and satisfaction generally means better control. For example, the GIFT study observed a 0.3% to 0.4% reduction in HbA1c after a switch to a fixed dose combination from separate metformin and DPP4 inhibitor therapy\(^10\).

**What combination?**

As most patients with type 2 diabetes will need dual or triple therapy to achieve and maintain glucose control, almost everyone should consider some fixed-dose combination or another. Consolidating the SGLT2 and DPP4 inhibitor into a single once daily tablet, and

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**Figure 2. The glucose-lowering efficacy of SGLT2 inhibitors is reduced in patients with moderate renal impairment eGFR 45-60mL/min/1.73m2 (CKD stage 3A)**

![Graphs showing glucose-lowering efficacy of SGLT2 inhibitors](image-url)

taking the metformin separately has marginal cost advantages for
the patient compared to fixed-dose combinations with metformin.
However, as most patients will be using metformin combinations as
second line before using both SGLT2 and DPP4 inhibition together,
it is often simpler to add one (of DPP4 or SGLT2 inhibitor), rather
than change two.

Whether you are starting with an SGLT2 inhibitor and then adding
an DPP4 inhibitor or the other way around will be dependent
upon the patient and their individual needs. In high risk patients
with comorbidities including cardiovascular disease, heart failure
and chronic kidney disease, SGLT2 inhibition is now widely
recommended after metformin as first or second line therapy.20,23
Additional control can be easily achieved with the addition of a
DPP4 inhibitor as needed, to safely reach the desired target without
hypoglycaemia or weight gain.

Equally, in low-risk patients the priority is to reduce barriers to
long-term adherence by choosing agents with a reduced risk of
side effects like hypoglycaemia and weight gain. Generally,
DPP4 inhibition is a safe, well-tolerated second line agent. SGLT2
inhibition can then be added for patients who are non-responsive
with the added reinforcement of early weight loss.

In the future, it may well be that an early combination approach
will be the norm for managing type 2 diabetes. We are already
seeing a move away from a traditional glucose-centric approach,
to assessing the risks from comorbidities and complications which
influence the choice of a particular glucose-lowering medication or
medications.20,23 But even in early disease the sooner and better
the glucose is controlled, the more durable this control will be.31

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>FE Model p-value</th>
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<tbody>
<tr>
<td>3P-MACE*</td>
<td>0.86 (0.80, 0.93)</td>
<td>0.0002</td>
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<tr>
<td>Myocardial infarction</td>
<td>0.85 (0.76, 0.95)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.98 (0.84, 1.14)</td>
<td>0.78</td>
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<tr>
<td>Hospitalisation for heart failure</td>
<td>0.71 (0.62, 0.82)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Cardiovascular death</td>
<td>0.80 (0.71, 0.91)</td>
<td>0.0005</td>
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<tr>
<td>All-cause mortality</td>
<td>0.83 (0.75, 0.92)</td>
<td>0.0003</td>
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Figure 3. Pooled analysis of completed trials demonstrates a reduction in major cardiac outcomes associated with SGLT2 inhibitors in patients with established atherosclerotic cardiovascular disease (*3P-MACE = time to first myocardial infarction, stroke or cardiovascular death).


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