The unexpected benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors

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ABSTRACT

The sodium glucose co-transporter 2 (SGLT2) inhibitor empagliflozin is currently funded in New Zealand for management of patients with type 2 diabetes who have an HbA1c >53mmol/mol and a high cardiovascular (CV) risk. Large clinical trials now provide strong evidence that SGLT2 inhibitors decrease the risk of cardiovascular death, heart failure, progressive kidney dysfunction, myocardial infarction, stroke and gout. Patients with or without diabetes who have a history of heart failure, including those with a preserved left ventricular ejection fraction and patients with chronic kidney impairment are likely to benefit most from treatment with an SGLT2 inhibitor. These findings make a strong case for extending funding of SGLT2 inhibitors to include patients with heart failure or kidney dysfunction without diabetes, so many more New Zealanders could benefit.

The sodium glucose co-transporter 2 (SGLT2) inhibitors were developed in the 1990s, over a century after an isolate from an apple tree bark was found to be glucosuric. The isolate, phlorizin, was found to inhibit active co-transport of sodium and glucose in the proximal kidney tubules and this was later modified to develop the first orally active SGLT2 inhibitor. The United States Food and Drug Administration approved canagliflozin for management of type 2 diabetes in 2013 after clinical trials confirmed that canagliflozin lowered blood glucose concentrations, reduced body weight, lowered blood pressure, and was safe.[1] Since early 2021 PHARMAC has funded empagliflozin in New Zealand with special authority criteria for patients with diabetes at increased cardiovascular (CV) risk. However, the criteria for using SGLT2 inhibitors now need to be revised because of accumulating evidence from large clinical trials which indicate the benefits of SGLT2 inhibitors go beyond glucose lowering. These include decreasing the risk of heart failure hospitalisation and CV death, improving quality of life in patients with heart failure, decreasing progression of chronic kidney impairment and preventing gout. Remarkably, many of these benefits are similar in patients with and without type 2 diabetes. The mechanisms responsible are currently only partly understood.

Clinical trials showing benefits of SGLT2 inhibitors in heart failure

The first large clinical trials to demonstrate improved clinical outcomes with SGLT2 inhibitors were in patients with type 2 diabetes and increased CV risk.[1–4] In these trials, SGLT2 inhibitors reduced progressive kidney dysfunction and the risk of myocardial infarction, stroke, heart failure hospitalisation and CV death. Because the benefit was greatest for heart failure hospitalisation and CV death, further trials were undertaken in patients with heart failure.

The "DAPA-HF"[5] and "EMPEROR-reduced"[6] trials investigated dapagliflozin and empagliflozin, respectively, in patients with heart failure and reduced left ventricular ejection fraction (<40%) who were also treated with other evidence-based treatments. In a meta-analysis of the two trials, which included 8,474 patients followed for 16 to 18 months, the SGLT2 inhibitors decreased CV death or hospitalisation for heart failure by 25% (p=0.0001) and all-cause mortality by 13% (p=0.018).[7] The "EMPEROR-preserved trial", randomised 5,988 patients with symptoms of heart failure and raised natriuretic peptide levels, but preserved left ventricular ejection fraction (>40%) to empagliflozin or placebo. During a median follow-up of 26 months, hospitalisation for heart failure or cardiovascular death was 21% lower on

empagliflozin (p=<0.001).[8] These trials provided the first clear evidence that medication treatment improved outcomes for patients with heart failure who have preserved, as well as reduced left ventricular ejection fraction. In patients hospitalised for acute heart failure, empagliflozin has also been shown to decrease heart failure exacerbations and improve quality of life during the next 90 days.[9] Favourable effects of SGLT2 inhibitors were evident early in all trials, and were similar for non-diabetic and diabetic patients.

Effects of SGLT2 inhibitors on the risk of cardiovascular death or hospitalisation for heart failure in clinical outcome trials are summarised in Table 1. The absolute benefits from treatment with a SGLT2 inhibitor were much higher for patients with heart failure, in part because heart failure patients have a much higher absolute risk. The risk reduction was similar for diabetic and non-diabetic patients with heart failure. The absolute decrease in CV death or heart failure hospitalisation, chosen for this comparison across trials, is modest, but these outcomes do not capture all the benefits of SGLT2 inhibitors. These include reducing the risk of myocardial infarction and stroke, slowing progression of kidney dysfunction, improving quality of life in patients hospitalised with acute heart failure and halving the risk of gout.[10]

Clinical trials showing benefits of SGLT2 inhibitors in kidney disease

Reduced progression of kidney dysfunction on SGLT2 inhibitors was observed in the early clinical trials which evaluated patients with type 2 diabetes.[1,3] Subsequent trials have shown that SGLT2 inhibitors have a similar benefit on kidney outcomes in patients who do not have diabetes. In the '*Dapagliflozin in patients with chronic kidney disease trial*',[11] 4,304 patients with an estimated glomerular filtration rate (eGFR) of 25–75ml/1.73m^2 and urinary albumin/creatinine 200–5000mg/g, were randomised to dapagliflozin 10mg per day or placebo. After a median follow-up of 2.4 years, doubling of serum creatinine, end stage kidney disease or kidney death were nearly halved on dapagliflozin (HR 0.56, 95%CI 0.45–0.68, p<0.001) and CV death was decreased. Results were similar for patients with and without diabetes. The EMPA-KIDNEY trial was recently stopped early because of clear evidence that empagliflozin decreased progression of chronic kidney disease, CV and kidney-related death. This trial evaluated empagliflozin in more than 6,600 adults with chronic kidney disease from a wide range of causes. Full results are expected in late 2022.[12]

Adverse effects

SGLT2 inhibitors were generally well tolerated in clinical trials. Side effects include a modest increase in urinary and genital infections from glucosuria in patients with diabetes. Although SGLT2 inhibitors do not directly cause hypoglycaemia, the dose of other glucose-lowering medications may need to be decreased. There is a small risk of euglycemic ketoacidosis with starvation, dehydration or intercurrent illness, particularly if the patient is insulin deficiency. To decrease this risk, it is currently recommended that SGLT2 inhibitors are withheld for three days prior to major surgery, or when the patient is unwell, missing meals or dehydrated. The benefits of SGLT2 inhibitors on kidney outcomes occur despite a physiological decrease in eGFR of up to 30% during the first few weeks after starting, which can be exaggerated by diuretic therapy. Usually this does not require cessation of the SGLT2 inhibitor

Comparison of SGLT2 inhibitors with other glucose-lowering medications

The accumulating evidence for benefit with SGLT2 inhibitors contrasts with the relative lack of evidence for improved CV outcomes for metformin, sulphonylureas and gliptins. Despite widespread clinical use, there is no clear evidence that metformin[13] sulphonylureas[14] or gliptins[15] lower CV mortality. In three large trials (16–18) with >23,000 diabetic patients at high CV risk, there was no decrease in CV mortality with more intensive, compared to standard, glucose control using combinations of these medications and insulin, and there was a possible increase in sudden death.[17] The glucagon-like receptor one agonists, which includes dulaglutide, are also funded in New Zealand for diabetic patients who have a high CV risk, reduce the risk of myocardial infarction and stroke; but reduction of CV death and hospitalisation for heart failure were less than for SGLT2 inhibitors.[19] Lowering glucose is important to prevent complications related to microvascular disease and other adverse consequences of hyperglycaemia. However, large clinical trials indicate the benefits and risks of different treatments are not simply related to glucose lowering. Treatment

decisions should, therefore, consider the impact of medications on major adverse CV and kidney events, and mortality.

The need to broaden indications for SGLT2 inhibitors in New Zealand

Changing evidence demands a rethink of clinical practice guidelines and funding criteria. SGLT2 inhibitors are currently funded for treatment of patients with type 2 diabetes who also have a high CV risk. However, international guidelines now recommend SGLT2 inhibitors for prevention and treatment of heart failure and progressive kidney impairment in patients both with and without diabetes.[20,21] This should also be the case in New Zealand.

In patients with type 2 diabetes, special authority requirements related to HbA1c levels and the need to first use other glucose medications should be reconsidered. It is important to consider HbA1c and CV risk, but the most important predictors of benefit are a history of heart failure or kidney dysfunction. It should be possible to start treatment early and in hospital, particularly in patients admitted with decompensated heart failure.

Ensuring access for Māori and Pacific peoples is important because they have a greater burden of ill health and premature death from diabetes, as well as kidney failure, heart failure, stroke, coronary artery disease, and gout.[22,23] It is possible that SGLT2 inhibitors are more beneficial for Māori and Pacific peoples, but more data are needed to confirm this. In secondary analyses from clinical trials, Asian and African American patients had a greater benefit from SLGT2 inhibitors compared to Caucasian patients.[7]

Conclusion

The SGLT2 inhibitors benefit patients with diabetes and increased CV risk, but the absolute benefits are greater for patients with heart failure or chronic kidney impairment, including for patients without diabetes. Funding for SGLT2 inhibitors should reflect this evidence, so these medications can be prescribed for the many more New Zealanders who could benefit.

Table 1: Relative and absolute reductions in cardiovascular death or heart failure hospitalisation in clinical outcome trials on a sodium glucose co-transporter 2 (SGLT2) inhibitor compared to placebo.

Clinical trials stratified by inclusion of patients with diabetes and/or heart failure	CV death or HF / 1,000 patient years		Reduction in CV death or HF hospitalisation / 1,000 patient years	Hazard Ratio (95%CI)
	SGLT2 inhibitor	Placebo		
1. Diabetes, No history of HF				
CANVAS	13.6	15.2	2	0.87 (0.72–1.06)
DECLARE TIMI 58	8.9	10.5	2	0.84 (0.72–0.99)
EMPA REG outcome	15.5	24.9	10	0.63 (0.51–0.78)
				0.79 (0.71–0.88)[+]
2. Diabetes + history of HF				
EMPEROR reduced	162	214	52	0.72 (0.60–0.87)
DAPA HF	132	168	36	0.75 (0.63–0.90)
EMPEROR preserved	75	91	16	0.79 (0.67–0.94)
				0.76 (0.68–0.84)[+]
3. No diabetes + history of HF				
EMPEROR preserved	53	67	14	0.78 (0.64–0.95)
DAPA-HF	87	117	30	0.73 (0.60–0.88)
EMPEROR reduced	130	158	28	0.78 (0.64–0.97)
				0.76 (0.68, 0.85)[+]

Outcomes are reported in clinical trials which compared SGLT2 inhibitors with placebo 1) in patients with type 2 diabetes at increased cardiovascular risk but with no history of heart failure, 2) patients with type 2 diabetes and a history of heart failure and, 3) patients with heart failure (HF) but no diabetes.
The composite outcome of cardiovascular death or heart failure hospitalisation are reported to allow comparison across trials. The risk reductions therefore do not include a reduction in myocardial infarction, stroke or progressive kidney dysfunction also observed with SGT2 inhibitors.
Risk reductions / 1,000 patient years were estimated from the events rates and median follow-up times for each trial and rounded to the nearest whole number.
[+] For each diagnostic group the Hazard ratio (HR) and 95% confidence intervals (95%CI) across trials were calculated using generic inverse variance analysis and a random effects model with Review Manager 5.4.[1–6,8]

COMPETING INTERESTS
Nil.

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