

Prevention of cardiovascular disease and renal failure in type 2 diabetes: sodium-glucose cotransporter-2 (SGLT2) inhibitors

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End-stage renal failure is a common and devastating consequence of type 2 diabetes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, in combination with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists (ARBs), reduce cardiovascular events and deterioration of renal disease in patients with type 2 diabetes and renal impairment.

Type 2 diabetes is a global epidemic.¹ It is the third most frequent cause of disability in high-income countries and the most common cause in most low-income countries.¹ Much of this disability relates from renal impairment caused by uncontrolled blood glucose levels; as many as 40% of patients with diabetes will develop kidney disease.² The presence of renal impairment in patients with type 2 diabetes has many consequences—chiefly, these patients are at substantial risk of cardiovascular disease and, often in <10 years, progress to end-stage renal failure.³ Currently, the only medicines approved for renoprotective in patients with diabetes are renin–angiotensin blockers, namely ACEI and ARBs.⁴ The CREDENCE trial tested the effect of a new class of drugs—SGLT2 inhibitors—on renal and cardiovascular outcomes in patients with type 2 diabetes and renal impairment.

Investigators from 34 different countries recruited patients aged over 30 with some degree of renal impairment (30 to <90 mL/min/1.73 m²), type 2 diabetes (HbA1c: 6.5% to 12.0%) and treated with one renin–angiotensin blocker. Patients with a renal disease caused by diseases other than type 2 diabetes (including type 1 diabetes) were excluded. Participants were then randomised to 100 mg of canagliflozin (an SGLT2 medication) or a placebo (note both groups continued their renin–angiotensin blocker, either an ACEI or ARB). Participants were then followed up for a composite primary outcome of end-stage renal disease or death from renal impairment or cardiovascular disease. End-stage renal disease was defined as dialysis for at least 30 days, kidney transplantation, or 30 days of an estimated glomerular filtration rate of <15 mL/min per 1.73 m², 30 days doubling of a serum creatinine measurement (from baseline). Secondary outcomes included a number of cardiovascular events, such as myocardial infarction, stroke and heart failure hospitalisation.

Around 4400 participants were randomised and followed for approximately 2.5 years (median follow-up, 2.62 years). The trial was

EBM Verdict

EBM Verdict on: Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. Perkovic V, *et al*; CREDENCE Trial Investigators. *N Engl J Med* 2019;380:2295–2306.

► Sodium-glucose cotransporter-2 (SGLT2) inhibitors appear effective to reduce cardiovascular events and deterioration of renal disease in patients with type 2 diabetes and renal impairment.

stopped early after a prespecified interim analysis revealed a significant reduction in the primary outcome. Participants randomised to canagliflozin had a 30% lower rate of the primary outcome (end-stage renal disease, or renal impairment or cardiovascular death) (HR, 0.70; 95% CI: 0.59 to 0.82; *p*<0.001). This translates to a number needed to treat of 22 (95% CI: 15 to 38). The results of secondary analyses and prespecified subgroup analyses were also consistent with the direction of the result for the primary outcome, namely that canagliflozin provides renal protection. Similarly, a consistent protective effect for the cardiovascular system was also noted; there was a 31% and 20% reduction in the composites of (a) cardiovascular death or heart failure hospitalisation (HR, 0.69; 95% CI: 0.57 to 0.83; *p*<0.001) and (b) cardiovascular death, myocardial infarction or stroke (HR, 0.80; 95% CI: 0.67 to 0.95; *p*=0.01). Importantly, SGLT2 inhibitors appear relatively safe for this population group; there was no significant difference in cancer rates between groups, nor was there a difference in amputation, fracture, hyperkalaemia or acute kidney injury. There was, however, an increased risk of diabetic ketoacidosis.

The CREDENCE trial shows that SGLT2 inhibitors have cardiorenal protective effects for patients with type 2 diabetes and some degree of renal impairment. The trial was well-conducted; participants and investigators were both blinded (double-blinded), the randomisation protocol appears adequate, the outcomes were objective and outcomes were appropriately reported. However, some caution should be held when extrapolating these results to clinical practice. Most notably, there was no difference in all-cause mortality between the two groups, trials that stop early are at risk of their results being overinflated and the patient group that SGLT2 inhibitors currently appear effective for is a selective group of patients with diabetes (ie, those with renal impairment). Lastly, the results from the CREDENCE trial should only be applied to the population assessed in the study, that is, patients with type 2 diabetes aged over 30 years of age, already on a renin–angiotensin blocker medication (ACEI or ARB) and with some degree of renal impairment.

Nevertheless, SGLT2 inhibitors appear to be safe and effective to prevent a deterioration of renal disease and to reduce adverse cardiovascular events in patients with type 2 diabetes and some degree of renal impairment.

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