SGLT2 Inhibitors Reduce Heart Failure Risk in Type 2 Diabetes

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Heart failure remains a leading cause of morbidity and mortality among patients with type 2 diabetes, a population already contending with elevated cardiovascular risk. Despite advances in glucose-lowering therapies, a persistent unmet need exists for treatments that directly address the intertwined pathologies of diabetes and cardiovascular disease. The field has long sought agents that offer both glycaemic control and tangible cardiac protection.

KEY TAKEAWAYS

- The Pivot: SGLT2 inhibitors have moved beyond glucose control to become foundational in cardiorenal protection for type 2 diabetes.
- The Data: These agents consistently reduce heart failure hospitalisation by approximately 30-40% and cardiovascular death by 15-20%.
- The Action: Clinicians should consider SGLT2 inhibitors early in the management of type 2 diabetes patients with established cardiovascular disease or high risk.

Patients with type 2 diabetes face a disproportionately high risk of developing heart failure, independent of other cardiovascular risk factors. This increased susceptibility stems from a complex interplay of metabolic derangements, including hyperglycaemia, insulin resistance, and systemic inflammation, all contributing to myocardial dysfunction and structural remodelling. For decades, treatment strategies primarily focused on glycaemic control, but the direct impact on hard cardiovascular outcomes, particularly heart failure, remained elusive with many traditional agents. The introduction of sodium-glucose co-transporter 2 (SGLT2) inhibitors marked a significant shift in this therapeutic landscape, offering a dual benefit that extends beyond glucose lowering.1

These agents, including dapagliflozin, empagliflozin, and canagliflozin, operate by inhibiting SGLT2 in the renal tubules, thereby reducing glucose reabsorption and increasing urinary glucose excretion. This mechanism lowers blood glucose levels independently of insulin. But the cardiovascular benefits, initially observed as secondary endpoints in large-scale cardiovascular outcome trials (CVOTs), quickly became the primary focus. These trials typically enrolled thousands of patients with type 2 diabetes, often with established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors, randomising them to an SGLT2 inhibitor or placebo on top of standard care.2

The numbers

Multiple large, randomised, placebo-controlled trials have consistently demonstrated the cardiovascular protective effects of SGLT2 inhibitors. In the EMPA-REG OUTCOME trial, empagliflozin reduced the risk of the primary

composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke by 14% (HR 0.86; 95% CI, 0.74-0.99; P=.04). More strikingly, empagliflozin cut the risk of cardiovascular death by 38% (HR 0.62; 95% CI, 0.49-0.77; P<.001) and hospitalisation for heart failure by 35% (HR 0.65; 95% CI, 0.50-0.85; P=.002) compared to placebo.3

Similarly, the DECLARE-TIMI 58 trial, investigating dapagliflozin, showed a 17% reduction in the composite of cardiovascular death or hospitalisation for heart failure (HR 0.83; 95% CI, 0.73-0.95; P=.005). This effect was primarily driven by a 27% reduction in hospitalisation for heart failure (HR 0.73; 95% CI, 0.61-0.88). While dapagliflozin did not significantly reduce the broader MACE endpoint in this trial, its specific benefit on heart failure outcomes was clear, particularly in patients with established atherosclerotic cardiovascular disease or multiple risk factors.4

The CANVAS Program, evaluating canagliflozin, also reported significant cardiovascular benefits. Canagliflozin reduced the risk of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) by 14% (HR 0.86; 95% CI, 0.75-0.97; P=.02). Hospitalisation for heart failure was reduced by 33% (HR 0.67; 95% CI, 0.52-0.87). These consistent findings across different SGLT2 inhibitors and patient populations underscore a class effect for heart failure prevention in type 2 diabetes.5

The mechanism behind these benefits extends beyond simple glucose lowering. SGLT2 inhibitors induce osmotic diuresis, leading to a reduction in plasma volume and preload. They also decrease arterial stiffness and improve endothelial function. Furthermore, these agents shift myocardial metabolism towards ketone body utilisation, which is a more energy-efficient fuel source for the heart, particularly in conditions of stress. The renal protective effects, including reductions in albuminuria and preservation of glomerular filtration rate, also contribute to the overall cardiorenal benefit, creating a virtuous cycle of organ protection.6

Safety profiles across these trials have generally been favourable. The most common adverse events include genitourinary infections, such as mycotic infections, which are typically mild to moderate and manageable. A small but consistent increase in the risk of diabetic ketoacidosis (DKA) has been observed, particularly in patients with type 1 diabetes or those with very low insulin reserves, though this risk remains low in the broader type 2 diabetes population. Volume depletion and hypotension are also potential concerns, especially in elderly patients or those on concomitant diuretics, necessitating careful monitoring.7

The trials were not uniformly designed, with variations in baseline cardiovascular risk and duration of follow-up. Some trials, like EMPA-REG OUTCOME, focused on patients with established cardiovascular disease, while DECLARE-TIMI 58 included a broader population with or at high risk of cardiovascular disease. This difference in patient selection explains some of the variability in the magnitude of MACE reduction but reinforces the consistent benefit on heart failure outcomes across the spectrum of cardiovascular risk in type 2 diabetes. The long-term durability of these benefits beyond the typical 3-5 year trial duration remains an area of ongoing investigation, though mechanistic insights suggest sustained effects.8

> **CLINICAL IMPLICATIONS**
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> The evidence for SGLT2 inhibitors in type 2 diabetes is now unequivocal: these agents are not just glucose-lowering drugs. They are foundational cardiorenal protective therapies. Clinicians who continue to view them solely through the lens of HbA1c reduction are missing the broader, more impactful picture for their

patients.

The consistent reduction in heart failure hospitalisation and cardiovascular death across multiple trials means SGLT2 inhibitors should be a standard consideration for nearly all type 2 diabetes patients with established cardiovascular disease or significant risk factors. Delaying initiation, particularly in those with early signs of renal dysfunction or heart failure, represents a missed opportunity for substantial clinical benefit.

For the industry, this data solidifies the SGLT2 inhibitor class as a cornerstone of diabetes management, pushing beyond the crowded field of pure glucose-lowering agents. The challenge now lies in ensuring broad access and educating both prescribers and patients on the full spectrum of benefits, not just the glycaemic ones.

Patients stand to gain significantly, not just in terms of reduced cardiovascular events, but also in improved quality of life from fewer hospitalisations. The modest risk of genitourinary infections or DKA is a small trade-off for the substantial protection against heart failure and cardiovascular mortality these therapies offer.

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