What Is an SGLT2 Inhibitor? Mechanism, Indications, and Evidence

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SGLT2 inhibitors are a class of oral agents that reduce blood glucose by blocking glucose reabsorption in the proximal tubule of the kidney. Beyond glycaemic control, they reduce cardiovascular mortality, hospitalisation for heart failure, and progression of chronic kidney disease.12 This primer outlines their mechanism, approved indications, and the clinical evidence that reshaped non-communicable disease management.

KEY TAKEAWAYS

- SGLT2 inhibitors block renal glucose reabsorption, lowering blood glucose independently of insulin
- Approved indications extend beyond type 2 diabetes to HFrEF, HFpEF, and CKD
- Landmark trials established 26-38% reductions in cardiovascular death, heart failure hospitalisation, and kidney disease progression
- Common side effects include genital mycotic infections and UTIs; withhold perioperatively to reduce DKA risk
- ESC and ADA/EASD guidelines recommend early use in high-risk cardiometabolic patients regardless of HbA1c

What Is an SGLT2 Inhibitor?

An SGLT2 inhibitor (sodium-glucose cotransporter-2 inhibitor) is an oral medication that lowers blood glucose by preventing its reabsorption in the proximal convoluted tubule of the kidney. Under normal physiology, the kidneys filter approximately 180 g of glucose per day, nearly all of which is reabsorbed via the SGLT2 transporter. By blocking this transporter, SGLT2 inhibitors cause excess glucose to be excreted in the urine (glycosuria), reducing circulating glucose levels independent of insulin.

Mechanism of Action

SGLT2 accounts for approximately 90% of renal glucose reabsorption. When inhibited, urinary glucose excretion increases by 60-100 g per day, producing a clinically meaningful HbA1c reduction of approximately 0.5-1.0% and modest weight loss of 1-3 kg. Because the mechanism is insulin-independent, efficacy is maintained across a wide range of beta-cell function and is additive with metformin, GLP-1 receptor agonists, and insulin.1

Approved Agents and Indications

Four SGLT2 inhibitors are in routine clinical use across Europe and North America:

• Empagliflozin (Jardiance) - type 2 diabetes, HFrEF, HFpEF, and CKD

• Dapagliflozin (Farxiga/Forxiga) - type 2 diabetes, type 1 diabetes (selected markets), HFrEF, HFpEF, and CKD

• Canagliflozin (Invokana) - type 2 diabetes and CKD with albuminuria

• Ertugliflozin (Steglatro) - type 2 diabetes

Key Clinical Evidence

The cardiovascular and renal benefits were established in landmark outcomes trials:

• EMPA-REG OUTCOME (2015): Empagliflozin reduced cardiovascular death by 38% in patients with type 2 diabetes and established cardiovascular disease.2

• CREDENCE (2019): Canagliflozin reduced end-stage kidney disease by 32% in patients with CKD and type 2 diabetes.3

• DAPA-HF (2019): Dapagliflozin reduced the composite of worsening heart failure or cardiovascular death by 26% in HFrEF, regardless of diabetes status.4

• EMPEROR-Preserved (2021): Empagliflozin reduced heart failure hospitalisation in HFpEF patients regardless of diabetes status.5

Safety Considerations

Common adverse effects include genital mycotic infections (particularly in women) and urinary tract infections attributable to glycosuria. Diabetic ketoacidosis is a rare but serious risk, predominantly in patients with type 1 diabetes or severely reduced insulin secretion. Volume depletion may occur in elderly patients or those on loop diuretics; eGFR and blood pressure warrant monitoring at initiation. SGLT2 inhibitors should be withheld perioperatively and during acute illness to reduce DKA risk.

Bottom Line for Clinicians

SGLT2 inhibitors have extended well beyond glycaemic management. Current ESC and ADA/EASD guidelines recommend them as first-line or early add-on therapy in patients with type 2 diabetes and established or high-risk cardiovascular disease, CKD, or heart failure - independent of baseline HbA1c. Their insulin-independent mechanism, favourable weight and blood pressure profile, and demonstrated organ protection make them among the most clinically versatile agents in non-communicable disease management.

Emerging Evidence and Future Directions

Beyond their established benefits, ongoing research continues to explore the broader therapeutic potential of SGLT2 inhibitors. Studies are investigating their role in specific populations, such as patients post-myocardial infarction without heart failure, or those with non-diabetic kidney disease, to further delineate their renoprotective mechanisms. The anti-inflammatory and anti-fibrotic properties observed in preclinical models suggest potential applications in other organ systems, though these remain largely speculative in human clinical practice.

Furthermore, the mechanistic understanding of SGLT2 inhibitors is evolving. While glycosuria is the primary driver of glucose lowering, other effects, such as improved renal haemodynamics (afferent arteriolar vasoconstriction), modest natriuresis, and shifts in myocardial fuel substrate utilisation, contribute to their cardiovascular and renal benefits. These pleiotropic effects underscore the complex interplay between glucose metabolism, fluid balance, and organ function, offering avenues for novel therapeutic strategies.

Limitations in current evidence include a relative paucity of head-to-head trials comparing different SGLT2 inhibitors for specific non-glycaemic outcomes. While class effects are often assumed for cardiovascular and renal protection, subtle differences in selectivity, pharmacokinetics, and off-target effects may exist, necessitating careful interpretation of individual trial data. Future research will likely focus on optimising patient selection, exploring combination therapies, and refining risk stratification to maximise the benefits of SGLT2 inhibitors across a wider spectrum of chronic diseases.

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