NEWSLETTER 14

SGLT2 Inhibitors: Cardiorenal Mechanisms

How a glucose-lowering drug became a foundational heart and kidney therapy

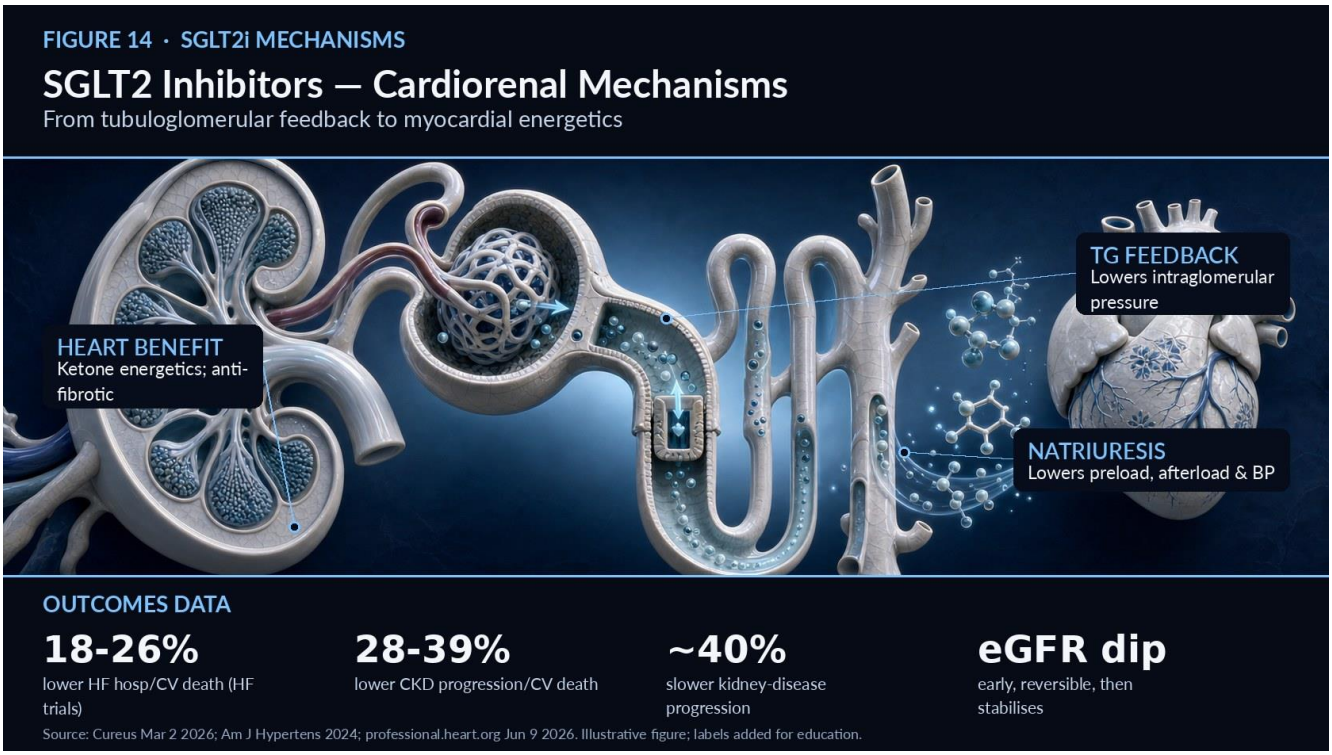

Figure 14. SGLT2 Inhibitors: Cardiorenal Mechanisms — mechanism overview (illustrative; labels added for education).

SGLT2 inhibitors have moved far beyond glucose control, and understanding their mechanisms clarifies why. A key renal mechanism is restoration of tubuloglomerular feedback: increased sodium delivery to the macula densa triggers afferent arteriolar vasoconstriction, reducing intraglomerular pressure and curbing the maladaptive hyperfiltration that damages nephrons over time.[1]

This explains the characteristic early, modest eGFR “dip” seen after initiation. The dip stabilises over time and is followed by a slower long-term loss of kidney function—a hemodynamic signature of protection rather than injury, which clinicians should anticipate and not misinterpret as harm.[1]

The cardiac and systemic benefits arise through complementary pathways. Natriuresis and osmotic diuresis reduce plasma volume, blood pressure, and ventricular filling pressures, unloading both preload and afterload. Additional mechanisms include ketone-mediated improvements in myocardial energetics, anti-inflammatory and anti-fibrotic signalling, and reductions in uric acid and oxidative stress.[1] The net effect is protection that is largely independent of glucose lowering.

Outcomes data validate the biology. Across landmark trials, SGLT2 inhibitors reduced heart-failure hospitalisation or cardiovascular death by 18–26% (DAPA-HF HR 0.74; EMPEROR-Reduced HR 0.75; EMPEROR-Preserved HR 0.79; DELIVER HR 0.82) and reduced CKD progression or cardiovascular death by 28–39% (DAPA-CKD HR 0.61; EMPA-KIDNEY HR 0.72; CREDENCE HR 0.70).[1] On top of standard care, they cut acute kidney injury risk by roughly 25% and slow kidney-disease progression by about 40%, with similar effects independent of type 2 diabetes.[2]

A useful clinical corollary is how to counsel patients about the initial eGFR dip. Anticipating it, explaining that it reflects reduced intraglomerular pressure rather than injury, and avoiding reflexive discontinuation are key to keeping patients on a therapy that pays off over years.[1] The convergence of hemodynamic, metabolic, and anti-inflammatory mechanisms—largely independent of glucose lowering—also explains why benefit extends to patients without diabetes, a point the outcomes trials confirm and the guidelines now reflect.[2]

These mechanisms and outcomes underpin the drug class's central role in the 2026 CKM guideline, which recommends SGLT2 inhibitors as cardioprotective and kidney-protective guideline-directed therapy and as first-line treatment in HFmrEF and HFpEF.[3] For any CKM patient, the mechanistic story is now a clinical mandate.

References

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