Are SGLT2 and GLP-1 the missing link in cardiorenal-metabolic care?

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Cardiovascular, renal, and metabolic diseases frequently co-exist, creating a complex web of interconnected pathologies that challenge clinicians. For decades, treatment strategies focused on managing individual risk factors in isolation, often with limited success in preventing the progression of multi-organ damage. The emergence of SGLT2 inhibitors and GLP-1 receptor agonists has fundamentally altered this approach, offering therapies that provide benefits far beyond their initial indications.

KEY TAKEAWAYS

- The Pivot: SGLT2 inhibitors and GLP-1 receptor agonists are now foundational therapies for cardiorenal-metabolic syndrome, not just diabetes.
- The Data: SGLT2 inhibitors reduce major adverse cardiovascular events (MACE) by 14% (HR 0.86; 95% CI, 0.80-0.93) and GLP-1 RAs by 14% (HR 0.86; 95% CI, 0.80-0.93) in patients with type 2 diabetes and established CVD.
- The Action: Clinicians should consider these agents early in patients with type 2 diabetes, heart failure, or chronic kidney disease, regardless of glycaemic status.

The burden of cardiorenal-metabolic (CRM) diseases, encompassing type 2 diabetes, heart failure, and chronic kidney disease, continues to rise across Europe. These conditions share common pathophysiological pathways, including inflammation, oxidative stress, and endothelial dysfunction, leading to a vicious cycle of organ damage. Traditional therapies, while effective for specific endpoints, often failed to address the systemic nature of CRM disease progression. The advent of SGLT2 inhibitors and GLP-1 receptor agonists has provided a new therapeutic paradigm, offering integrated benefits across these interconnected systems.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, initially developed for glycaemic control in type 2 diabetes, block glucose reabsorption in the renal tubules, leading to increased urinary glucose excretion. This mechanism lowers blood glucose independently of insulin. But their clinical trials, such as EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58, revealed a much broader impact. These trials enrolled thousands of patients with type 2 diabetes, many with established cardiovascular disease or multiple cardiovascular risk factors, and assessed major adverse cardiovascular events (MACE), heart failure hospitalisations, and renal outcomes. The patient populations in these trials were diverse, ranging from those with high cardiovascular risk to those with established atherosclerotic cardiovascular disease (ASCVD) or heart failure with reduced ejection fraction (HFrEF).

Beyond glucose: SGLT2 inhibitors' cardiorenal protection

SGLT2 inhibitors consistently reduced cardiovascular events. In the EMPA-REG OUTCOME trial, empagliflozin cut 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, it reduced 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). These benefits were observed early in the trial, suggesting mechanisms beyond glycaemic control.

The CANVAS Program, evaluating canagliflozin, showed a 14% reduction in MACE (HR 0.86; 95% CI, 0.80-0.93; P<.001) and a 33% reduction in hospitalisation for heart failure (HR 0.67; 95% CI, 0.57-0.79). DECLARE-TIMI 58, with dapagliflozin, demonstrated 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). These trials established SGLT2 inhibitors as essential agents for patients with type 2 diabetes and established cardiovascular disease or high risk.

But the story did not end with diabetes. Subsequent trials, DAPA-HF and EMPEROR-Reduced, extended the benefits of SGLT2 inhibitors to patients with HFrEF, regardless of their diabetes status. Dapagliflozin in DAPA-HF reduced the composite of worsening heart failure or cardiovascular death by 26% (HR 0.74; 95% CI, 0.65-0.85; P<.001) in patients with HFrEF (LVEF ≤40%). Empagliflozin in EMPEROR-Reduced showed a similar 25% reduction (HR 0.75; 95% CI, 0.65-0.86; P<.001). These results led to guideline updates recommending SGLT2 inhibitors as a foundational therapy for HFrEF.

The renal protective effects of SGLT2 inhibitors are equally compelling. The CREDENCE trial, specifically designed for patients with type 2 diabetes and chronic kidney disease (CKD), showed canagliflozin reduced the composite renal endpoint (ESKD, doubling of serum creatinine, or renal/cardiovascular death) by 30% (HR 0.70; 95% CI, 0.59-0.82; P=.00001). The DAPA-CKD trial, which included patients with CKD both with and without type 2 diabetes, found dapagliflozin reduced the composite of sustained decline in eGFR, ESKD, or renal/cardiovascular death by 39% (HR 0.61; 95% CI, 0.51-0.72; P<.001). These data confirm SGLT2 inhibitors as a cornerstone of CKD management, irrespective of diabetes status.

The proposed mechanisms for SGLT2 inhibitor benefits extend beyond diuresis and glycaemic control. They include improved renal haemodynamics by reducing intraglomerular pressure, enhanced myocardial energetics through substrate shift, reduced inflammation and oxidative stress, and favourable effects on arterial stiffness and blood pressure. These pleiotropic effects explain their broad utility across the CRM spectrum. Clinicians should consult resources like the Oxford Handbook of Cardiology for detailed guidance on integrating these agents into heart failure management.

GLP-1 receptor agonists: Metabolic and cardiovascular benefits

Glucagon-like peptide-1 (GLP-1) receptor agonists, another class initially for type 2 diabetes, stimulate insulin secretion, suppress glucagon, slow gastric emptying, and promote satiety. Their cardiovascular outcome trials (CVOTs) also demonstrated significant benefits. LEADER, SUSTAIN-6, Harmony Outcomes, and REWIND are key examples. These trials enrolled patients with type 2 diabetes, often with established ASCVD or high cardiovascular risk, and evaluated MACE as the primary endpoint.

Liraglutide in the LEADER trial reduced the primary composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke by 13% (HR 0.87; 95% CI, 0.78-0.97; P=.01). Semaglutide in SUSTAIN-6 showed a 26% reduction in the same composite endpoint (HR 0.74; 95% CI, 0.58-0.95; P=.02). Dulaglutide in REWIND, which included a larger proportion of patients without established ASCVD but with cardiovascular risk factors, reduced MACE by 12% (HR

0.88; 95% CI, 0.79-0.99; P=.026). These findings established GLP-1 RAs as having cardiovascular protective effects in patients with type 2 diabetes and high cardiovascular risk.

The mechanisms underlying GLP-1 RA cardiovascular benefits are thought to involve improvements in endothelial function, reduction in inflammation, direct effects on myocardial contractility, and favourable changes in lipid profiles and blood pressure. Their weight loss effects also contribute to overall metabolic improvement, which indirectly benefits cardiovascular health. The Oxford Handbook of Endocrinology and Diabetes provides comprehensive details on the metabolic actions of these agents.

Safety profiles and clinical considerations

Both SGLT2 inhibitors and GLP-1 RAs are generally well-tolerated. SGLT2 inhibitors carry a risk of genitourinary infections, particularly mycotic infections, which occurred in 2-6% of patients in trials. Diabetic ketoacidosis, though rare, is a serious adverse event, particularly in type 1 diabetes or during periods of stress or reduced caloric intake. Volume depletion and hypotension are also considerations, especially in elderly patients or those on diuretics. Bone fractures were a concern with canagliflozin in CANVAS, but this signal has not consistently appeared with other SGLT2 inhibitors.

GLP-1 RAs commonly cause gastrointestinal side effects, including nausea, vomiting, and diarrhoea, especially during dose escalation. These are usually transient. Pancreatitis is a rare but serious concern, though a causal link has not been definitively established in all studies. Medullary thyroid carcinoma (MTC) was observed in rodent studies, leading to a contraindication in patients with a personal or family history of MTC or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). However, human data have not confirmed this risk. These safety considerations necessitate careful patient selection and monitoring.

The open-label design of some early SGLT2 inhibitor trials, while common for long-term outcome studies, is an obvious caveat. Patients and investigators knew the treatment assignment, which could introduce bias, particularly for subjective endpoints. But the hard endpoints, like cardiovascular death and hospitalisation for heart failure, are less susceptible to such bias. The trials were also not uniformly powered to detect differences in all subgroups, meaning some observed benefits or lack thereof in specific populations require further investigation.

Still, the consistent and robust benefits across multiple large-scale, placebo-controlled trials for both drug classes provide strong evidence for their efficacy. The inclusion of diverse patient populations, including those with and without established cardiovascular disease, strengthens the generalisability of the findings. The long follow-up periods, often exceeding three years, allowed for the observation of sustained benefits, which is critical for chronic conditions like CRM diseases. The cumulative evidence supports a paradigm shift in managing these interconnected conditions.

> **CLINICAL IMPLICATIONS**
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> The data from the SGLT2 inhibitor and GLP-1 receptor agonist trials demand a re-evaluation of current prescribing practices. These agents are no longer merely glucose-lowering drugs; they are foundational therapies for cardiovascular and renal protection. Clinicians must consider their use early in patients with type 2 diabetes, heart failure with reduced ejection fraction, or chronic kidney disease, irrespective of baseline HbA1c.
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> Integrating these classes into treatment algorithms requires a holistic approach to patient care, moving

> beyond single-organ specialisation. Cardiologists, nephrologists, and endocrinologists now share a common therapeutic toolkit. This necessitates cross-specialty education and collaboration to ensure optimal patient outcomes and adherence to evolving guidelines.
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> The pharmaceutical industry, having invested heavily in these outcome trials, now faces the challenge of ensuring equitable access and affordability. The long-term societal benefits of reducing hospitalisations for heart failure and slowing CKD progression are substantial, but initial drug costs remain a barrier for some healthcare systems and patients. Value-based discussions are critical.
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> For patients, these medications offer a tangible prospect of improved quality of life and extended survival, reducing the burden of recurrent hospitalisations and dialysis. But adherence to complex regimens remains a challenge, underscoring the importance of patient education and shared decision-making in the clinic.

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