

Review Article

SGLT2 Inhibitors and GLP-1 Receptor Agonists in Cardiorenal-Metabolic Syndrome: Canadian Evidence, Mechanistic Complementarity, and Pharmacotherapeutic Strategies

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Abstract

Background: Cardiorenal-metabolic disease reflects the interdependence of obesity, type 2 diabetes, chronic kidney disease (CKD), heart failure (HF), and atherosclerotic cardiovascular disease (ASCVD). Sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shifted management from glucose lowering alone toward organ protection. Canada provides a useful practice framework because national and specialty guidance now prioritizes these therapies according to cardiovascular, kidney, heart-failure, and weight-related risk.

Objective: To summarize the complementary mechanisms, outcome evidence, and practical use of SGLT2 inhibitors and GLP-1 RAs in Canadian cardiorenal-metabolic care.

Summary: Diabetes Canada recommends prioritizing agents with demonstrated cardiorenal benefit in people with type 2 diabetes and high cardiovascular risk, HF, or CKD, even when A1C is already at target. The Canadian Cardiovascular Society recommends SGLT2 inhibitors across HF and albuminuric CKD and supports

either an SGLT2 inhibitor or GLP-1 RA in type 2 diabetes with established ASCVD or multiple risk factors. Obesity Canada further recommends semaglutide 2.4 mg for selected patients with obesity and established ASCVD and recognizes its benefits in obesity-related HFpEF. Mechanistically, SGLT2 inhibitors predominantly reduce intraglomerular pressure, volume stress, and HF events, whereas GLP-1 RAs provide greater weight loss, glycemic lowering, and atherosclerotic risk reduction. Combination therapy is biologically attractive and endorsed as reasonable in selected Canadian patients, but additive hard-outcome benefit has not been definitively established in randomized combination trials.

Conclusion: Canadian practice increasingly supports phenotype-driven selection of these classes, with combination therapy considered when cardiovascular, kidney, HF, glycemic, and weight-related priorities overlap.

Keywords: SGLT2 inhibitors; GLP-1 receptor agonists; cardiorenal-metabolic syndrome; Canada; chronic kidney disease; heart failure; obesity; type 2 diabetes

1. Introduction

Cardiorenal-metabolic disease describes the clinical overlap among excess adiposity, insulin resistance, type 2 diabetes, CKD, HF, and ASCVD. These conditions amplify one another through inflammation, neurohormonal activation, endothelial dysfunction, altered renal hemodynamics, and progressive metabolic injury. In Canada, this overlap is clinically important: Diabetes Canada estimates that approximately 10% of people live with diagnosed diabetes and that diabetes or prediabetes affects about 30% of the population.[1]

SGLT2 inhibitors and GLP-1 RAs have changed treatment priorities because their benefits extend beyond A1C reduction. Canadian recommendations increasingly direct clinicians to select therapy according to organ risk rather than glycemia alone.[2,3]

2. Canadian Guideline Positioning

The 2024 Diabetes Canada pharmacologic update recommends that agents with proven cardiorenal benefit be prioritized in people with type 2 diabetes who have high cardiovascular risk, HF, or CKD; these therapies may be indicated even when A1C is already at target.[2] The 2022 Canadian Cardiovascular Society (CCS) guideline

recommends SGLT2 inhibitors for adults with HFrEF and for HF with LVEF >40% to reduce HF hospitalization, and for albuminuric CKD to reduce kidney and cardiovascular events.[3]

For people with type 2 diabetes and established ASCVD or multiple ASCVD risk factors, CCS recommends either a GLP-1 RA or SGLT2 inhibitor to reduce major cardiovascular events, while SGLT2 inhibitors have particular strength for HF and kidney outcomes and GLP-1 RAs for atherosclerotic events, including nonfatal stroke.[3]

The 2025 Obesity Canada guideline extends this cardiorenal-metabolic approach. Semaglutide 2.4 mg is recommended for selected adults with obesity and established ASCVD to reduce major cardiovascular events and may improve symptoms in obesity-related HFpEF.[4] Thus, in Canadian practice, indication is increasingly determined by phenotype: ASCVD, HF, CKD, obesity, or combinations of these conditions.

3. Mechanistic Complementarity

SGLT2 inhibitors act primarily in the proximal renal tubule. Glycosuria and natriuresis lower plasma glucose, modestly reduce weight and blood pressure, restore tubuloglomerular feedback, and reduce intraglomerular pressure. Hemodynamic and metabolic effects appear to contribute to rapid reductions in HF events and slower CKD progression, including in many patients without diabetes.[3,5]

GLP-1 RAs enhance glucose-dependent insulin secretion, suppress inappropriate glucagon secretion, slow gastric emptying, and increase satiety. Their most clinically important cardiorenal-metabolic effects are substantial weight reduction, improved glycemia, lower blood pressure, and reduction in atherosclerotic cardiovascular events. The FLOW trial also showed that semaglutide 1 mg weekly reduced major kidney disease events by 24% in people with type 2 diabetes and CKD.[6]

The two classes therefore target overlapping disease through different dominant pathways: SGLT2 inhibitors are especially powerful for HF and kidney protection, whereas GLP-1 RAs provide greater effects on weight, glycemic control, and atherosclerotic risk. This mechanistic complementarity provides the rationale for combined therapy when several risks coexist.

4. Practical Canadian Selection

A useful Canadian approach is to identify the dominant clinical problem before selecting therapy. In established HF, an SGLT2 inhibitor should generally be prioritized because Canadian HF guidance supports benefit across the ejection-fraction spectrum.[3] In albuminuric CKD, an SGLT2 inhibitor is also foundational when kidney function permits; EMPA-KIDNEY confirmed a 28% relative reduction in kidney-disease progression or cardiovascular death with empagliflozin in a broad CKD population.[5]

In established ASCVD or high atherosclerotic risk, either class may be appropriate. A GLP-1 RA is particularly attractive when weight reduction, A1C lowering, or stroke-risk reduction is a major priority. For patients with obesity and established cardiovascular disease, semaglutide 2.4 mg also has direct cardiovascular-outcome evidence from SELECT and is incorporated into the 2025 Canadian obesity guideline.[4,7]

When type 2 diabetes, CKD, obesity, and ASCVD coexist, use of both classes may be clinically reasonable if tolerated and accessible. CCS specifically notes that combination therapy might improve cardiorenal benefit when clinical status or glycemic needs justify both agents.[3] However, clinicians should describe this as complementary evidence-based therapy rather than a proven pharmacologic synergy, because dedicated randomized trials testing the combination against either class alone for hard outcomes remain limited.

5. A Simple Phenotype-Based Strategy

For Canadian practice, treatment can be simplified as follows:

Dominant phenotype	Preferred emphasis
Heart failure	Prioritize an SGLT2 inhibitor; benefit is independent of diabetes status.
Albuminuric CKD	Prioritize an SGLT2 inhibitor; add other kidney-protective therapy as indicated.
ASCVD / high CV risk	Use an SGLT2 inhibitor or GLP-1 RA; choose according to HF/CKD versus weight/atherosclerotic priorities.
Obesity with T2D	GLP-1 RA is often favoured when clinically meaningful weight loss is a major goal; SGLT2 inhibition can add cardiorenal protection.
Multiple overlapping risks	Consider both classes when each has a distinct indication and treatment burden, tolerance, cost, and access are acceptable.

6. Safety and Monitoring in Canadian Practice

SGLT2 inhibitors can cause genital mycotic infection, volume depletion, and rarely euglycemic diabetic ketoacidosis. A small early fall in eGFR is expected and should not automatically prompt discontinuation. Canadian guidance emphasizes assessment of volume status and temporary interruption during dehydrating illness; Diabetes Canada includes SGLT2 inhibitors in its SADMANS sick-day medication framework.[2,3] Excessive insulin reduction should be avoided because it can increase ketoacidosis risk.

GLP-1 RAs most commonly cause nausea, vomiting, diarrhea, or constipation, particularly during dose escalation. Slow titration improves tolerability. When A1C is near target, sulfonylurea or insulin doses may need reduction to prevent hypoglycemia. Rapid improvement in marked hyperglycemia may transiently worsen pre-existing diabetic retinopathy in susceptible patients, so retinal status and pace of glucose lowering should be considered.[3]

Neither class should be viewed as a substitute for comprehensive therapy. Blood pressure management, statin therapy, renin-angiotensin system blockade when indicated, mineralocorticoid receptor antagonism in appropriate CKD/HF patients, smoking cessation, nutrition, physical activity, and vaccination remain important components of Canadian risk reduction.

7. Access and Implementation in Canada

A practical limitation is that access and reimbursement vary across provinces, territories, public plans, and private insurers. The most evidence-based choice may therefore differ from the most immediately accessible choice. Clinicians should document the specific indication—diabetes, HF, CKD, obesity, or cardiovascular risk—because eligibility can depend on indication and provincial criteria.

Canadian implementation also favours shared care. Primary-care clinicians, cardiologists, nephrologists, endocrinologists, obesity specialists, nurses, dietitians, and pharmacists increasingly manage the same patients. Pharmacists can support renal-function assessment, sick-day education, dose titration, injection counselling, adherence, and medication-access navigation.

8. Conclusion

SGLT2 inhibitors and GLP-1 RAs are central to modern cardiorenal-metabolic therapy in Canada. National guidance has moved beyond a glucose-centred sequence toward phenotype-driven treatment. SGLT2 inhibitors have their strongest role in HF and CKD, while GLP-1 RAs provide major advantages for weight reduction, glycemic control, and ASCVD risk; semaglutide now also has dedicated kidney and cardiovascular outcome evidence.

For patients with overlapping type 2 diabetes, obesity, ASCVD, HF, and CKD, the most rational strategy is not to ask which class is universally superior, but which organ risks require treatment. In selected patients, both classes can be used because they address different components of the same disease continuum. The Canadian model therefore supports individualized, multidisciplinary, and indication-based cardiorenal-metabolic pharmacotherapy.

Declarations

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