SGLT2 Inhibitors in the Prevention and Treatment of Cardiovascular Disease: A Review

Michael J. Rheaume¹; Aditya Khetan¹; Marie Pigeyre¹,²

¹Department of Medicine, McMaster University, Hamilton, ON, Canada; ²Population Health Research Institute, Hamilton, ON, Canada

Corresponding Author: Michael Rheaume: michael.rheaume@medportal.ca

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Abstract
Over the last decade, sodium-glucose transport (SGLT2) inhibitors have become one of the most exhaustively studied classes of medications for cardiometabolic diseases. Although multiple trials have established their benefit, one of the crucial tasks of the medical community is to accelerate their effective adoption into clinical practice by identifying the most appropriate patient population who could benefit from it. To date, this class of medications is indicated in patients with symptomatic (NYHA class II-IV) congestive heart failure with preserved or reduced ejection fraction, chronic kidney disease, or type 2 diabetes with cardiovascular (CV) risk factors. This article focuses on best implementing these medications into clinical practice and reviews their proposed mechanisms of action.

Résumé
Au cours de la dernière décennie, les inhibiteurs du transport du sodium et du glucose (SGLT2) sont devenus l'une des classes de médicaments les plus étudiées dans le traitement des maladies cardiométaboliques. Bien que de multiples essais aient établi leur bénéfice, l'une des tâches cruciales de la communauté médicale est d'accélérer leur adoption effective dans la pratique clinique en identifiant la population de patients la plus appropriée qui pourrait en bénéficier. À ce jour, cette classe de médicaments est indiquée chez les patients souffrant d'insuffisance cardiaque congestive symptomatique (classe II-IV de la NYHA) avec fraction d'éjection préservée ou réduite, de maladie rénale chronique ou de DT2 avec facteurs de risque cardiovasculaire (CV). Cet article se concentre sur la meilleure façon de mettre en œuvre ces médicaments dans la pratique clinique et fournit un examen de leurs mécanismes d'action proposés.

Keywords: SGLT2 inhibitors, cardiovascular disease, chronic kidney disease, type 2 diabetes
Case

A 68-year-old male with a history of coronary artery disease, ischemic cardiomyopathy with reduced ejection fraction (EF) of 35%, chronic kidney disease (CKD), and type 2 diabetes (T2DM) is admitted to hospital for congestive heart failure exacerbation. His home medications include aspirin 81 mg daily, sacubitril/valsartan 49/51 mg BID, bisoprolol 2.5 mg daily, spironolactone 25 mg daily, furosemide 60 mg po BID, rosvastatin 40 mg daily, metformin 1000 mg BID, insulin glargine 40 units at bedtime, and insulin aspart 10 units with meals. In the past, his heart failure therapy has been limited by symptomatic hypotension and hyperkalemia. Over the past year, he has had two admissions for heart failure exacerbations, with escalating need for diuretic therapy as an outpatient. He is appropriately decongested on intravenous diuretics, is hemodynamically stable with a blood pressure of 105/80, and is starting to ambulate without needing oxygen. His renal function has stabilized since being admitted to hospital, settling to his baseline eGFR of 40. His sacubitril/valsartan has been on hold since being admitted to hospital for acute kidney injury. As you are preparing to discharge the patient in the next 48 hours, you consider what to do with his medication regimen.

Over the last decade, sodium-glucose transport (SGLT2) inhibitors have become one of the most exhaustively studied classes of medications for cardiometabolic diseases. Although multiple trials have established their benefit, one of the crucial tasks of the medical community is to accelerate their effective adoption into clinical practice by identifying the most appropriate patient population who could benefit from it. To date, this class of medications is indicated in patients with symptomatic (NYHA class II-IV) congestive heart failure with preserved or reduced EF, CKD or T2DM with cardiovascular (CV) risk factors (Figure 1).

Figure 1. Flow chart for clinical use of SGLT2 inhibitors.
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Major Trials

SGLT2 inhibitors are often described as a “diamond in the rough” discovery due to the serendipity with which their CV benefit was established. Initially formulated as an oral glucose-lowering medication for T2DM, early trials evaluating CV outcomes were mainly performed as a regulatory requirement to demonstrate safety. The EMPA-REG trial was the first trial specifically designed to evaluate CV mortality, non-fatal myocardial infarction, and stroke in patients with T2DM and established CV disease. It demonstrated a reduction in its composite primary outcome and secondary outcomes of all-cause mortality and heart failure hospitalizations (HFH). Following these findings, multiple subsequent trials (CANVAS, DECLARE-TIMI-58, and VERTIS) further evaluated CV mortality, non-fatal myocardial infarction (MI), and stroke outcomes. Moreover, within the secondary outcomes evaluated in these trials, a clear and consistent benefit in HFH emerged. This benefit was consistent across a diverse set of trial populations and different SGLT2 inhibitors, which led to evaluating these medications in heart failure patients.

The EMPEROR-reduced and DAPA-HF trials were critical milestones in establishing these agents as foundational therapy for heart failure patients with and without type 2 diabetes. Both trials demonstrated a benefit in symptomatic (NYHA class II-IV) ambulatory participants with heart failure and reduced ejection fraction (EF) with respect to CV death and HFH. Subsequent subgroup analyses stratified by the Kansas City Cardiomyopathy Questionnaire have shown improvement in participants quality of life and heart failure symptom burden. Importantly, these trials demonstrated that the benefits were additive to patients already on appropriate guideline-based therapy for HF. More recently, SGLT2 inhibitors have been shown to have favourable benefits in patients across a broad range of EF. The EMPORER-preserved and DELIVER trial have now extended their use to patients with preserved EF (>40%), reducing HFH in a population where many traditional heart failure medications have failed in the past. With accumulating evidence, SGLT2 inhibitors have become a core therapy component for patients with heart failure, regardless of left ventricular (LV) EF, mainly for their capacity to prevent heart failure exacerbations.

Heart failure exacerbations are seminal moments in the overall disease trajectory of heart failure patients. These episodes provide a critical opportunity to initiate or improve therapy. Paradoxically, patients hospitalized for heart failure commonly experience medication discontinuation, and many eligible patients never receive therapies to extend survival, prevent hospitalization, and improve quality of life. Multiple studies have demonstrated that failure to discharge eligible patients on goal-directed medical therapy significantly increases the risk of future clinical events and the chance that therapies will not be initiated in the future or at considerable delay. With multiple therapeutic options, a major challenge of contemporary heart failure management is facilitating titration of therapies before discharge.

The initial trials evaluating SGLT2 inhibitors involved participants who were stable outpatients. Therefore, there was concern about starting these medications in patients acutely hospitalized due to the possibility of precipitating ketoacidosis or worsening renal function. However, four randomized controlled trials have supported safe initiation of SGLT2 inhibitors in hospitals. The first of these was the SOLOIST-WHF study, which was conducted on stable inpatients off inotropes and oxygen support. This study established that the initiation of SGLT2 inhibitors is safe and effective during hospital stay or early after discharge. These trials demonstrated benefit in urine output, NT-proBNP levels, and overall body weight. There was also a significant reduction in HFH and early urgent HF visits within 1 month of randomization, with early divergence of the primary outcome. A secondary analysis of the DELIVER trial demonstrated that the absolute risk reduction was nearly three times greater in the peri-hospitalized population compared to stable outpatients, suggesting that this tenuous population derives significantly more benefit. Additionally, a recent meta-analysis evaluating safety outcomes demonstrated no significant difference in acute kidney injury, hypoglycemia, or hypotension.

Overall, these trials provide robust data to suggest substantial early clinical benefit occurring within days to weeks of initiation, and this strategy is safe. Ongoing major trials of SGLT2 inhibitors in cardiovascular disease are summarized in Table 1.

Clinical Use of SGLT2 Inhibitors

Early initiation of SGLT2 inhibitors is also complementary to existing baseline therapy for heart failure. Not only do they provide significant clinical benefit regardless of baseline therapy, but they can also help facilitate tolerability and minimize notable side effects of other heart failure therapies. Due to their renal benefits and ability to reduce hyperkalemia, simultaneous introduction with renin-angiotensin-aldosterone system (RAAS) inhibitors and mineralocorticoid receptor antagonists can be done to maximize
Although SGLT2 inhibitors are better tolerated than many other medications for heart failure or type 2 diabetes, there are some considerations to minimize side effects. Due to glycosuria, there is a 2-4 fold increase in genital mycotic infections and urinary tract infections, which is more common in females. These are generally mild, with only case reports of severe urosepsis and necrotizing fasciitis. Notably, prior history of urinary tract infection is not a contraindication to therapy, and all patients should be counselled on proper hygiene to minimize risk. As previously mentioned, SGLT2 inhibitors are also associated with euglycemic DKA, although the overall incidence is extremely low (<1%) and typically precipitated by an intercurrent illness. As such, this complication is preventable with appropriate education. All patients require “sick day management” education to temporarily discontinue SGLT2 inhibitors while unwell and at least 3 days before any planned surgery to reduce the risk of hypovolemia and perioperative ketoacidosis.

Due to these medications’ diuretic and anti-glycemic effects, other therapies may need to be adjusted. For stable euvoletic patients, baseline diuretic therapy should be decreased by 30–50% to avoid hypovolemia. Patients should also be educated on orthostatic symptoms and instructed to monitor blood pressure. Although blood pressure effect is typically minimal, it can be more prominent in elderly patients and may require dose adjustment of other anti-hypertensive therapies. Anti-glycemic therapies also require adjustment if HbA1c is well controlled (<7.0%), with insulin dosing often reduced by 10–20% and sulfonylureas discontinued or reduced.

Table 1. Summary of major trials of SGLT2 inhibitors for the prevention and treatment of cardiovascular disease

<table>
<thead>
<tr>
<th>Trial name, clinical-trials.gov identifier</th>
<th>Drug</th>
<th>Number of participants</th>
<th>Key inclusion criteria</th>
<th>Primary outcome</th>
<th>Estimated study completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 DAPA-MI, NCT04564742</td>
<td>Dapagliflozin 10 mg</td>
<td>6,400</td>
<td>Confirmed MI, either STEMI or NSTEMI</td>
<td>CV death or hospitalization for heart failure</td>
<td>September 2023</td>
</tr>
<tr>
<td>2 EMPACT-MI, NCT04509674</td>
<td>Empagliflozin 10 mg</td>
<td>6,500</td>
<td>Confirmed MI, either STEMI or NSTEMI</td>
<td>All-cause mortality or hospitalization for heart failure</td>
<td>March 2023</td>
</tr>
<tr>
<td>3 DAPA ACT HF-TIMI 68, NCT04363697</td>
<td>Dapagliflozin 10 mg</td>
<td>2,400</td>
<td>Hospitalized for acute heart failure, regardless of LVEF</td>
<td>CV death or worsening heart failure</td>
<td>May 2023</td>
</tr>
<tr>
<td>4 EMPA-AHF, NCT05392764</td>
<td>Empagliflozin 10 mg</td>
<td>500</td>
<td>Hospitalized for acute heart failure, regardless of LVEF, requiring IV diuretics</td>
<td>Death, HF worsening or rehospitalization for HF, and urine output (48 hours after initiation), assessed by win ratio</td>
<td>April 2023</td>
</tr>
</tbody>
</table>

CV, cardiovascular; HF, heart failure; LVEF, left-ventricular ejection fraction; MI, myocardial infarction
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Regarding patient monitoring following initiation, patients with CKD and borderline eGFR ($<30\text{mL/min/1.73m}^2$) should have baseline bloodwork 1–2 weeks after initiation. Treatment initiation is typically accompanied by increased serum creatinine (15–20%), reflecting reduced renal intraglomerular pressure. However, this effect is transient and should not prompt medication withdrawal, as long-term use is associated with slowing the progression of kidney disease.

Mechanisms of Benefits

SGLT2 inhibitors act by inhibiting glucose reabsorption in the proximal tubule of the kidneys. Their clinical effects are not yet fully understood, but their action as blood glucose-lowering agents cannot fully explain their CV benefits, given the early onset of their beneficial effects after initiation. Because SGLT2 receptors are expressed in the kidneys as opposed to the heart, their effects on left ventricular structure and function are indirect and are suspected to be predominantly mediated by systemic hemodynamic and metabolic effects. Potential mechanisms have been extensively reviewed elsewhere, and can be grouped into two distinct pathways: an increase in natriuresis and diuresis or an increase in glycosuria. Given that the resorption of glucose and sodium in the proximal convoluted tubule of the kidneys is coupled, SGLT2 inhibition is associated with a negative sodium-water balance and an initial decrease in extracellular fluid and plasma volume, which result in osmotic diuresis and hemoconcentration. These osmotic and diuretic effects are associated with a reduction in systolic and diastolic blood pressure on average, which may lower cardiac afterload, resulting in an improvement of the ventricular arterial coupling and cardiac efficiency. Moreover, the reduction in blood pressure in the absence of an increasing heart rate indirectly suggests that SGLT2 inhibitors may also be associated with a reduction in sympathetic nervous system (SNS) activity. As for the increased hematocrit, SGLT2 inhibitors may promote erythropoiesis via enhanced erythropoietin (EPO) secretion by the kidneys. An increase in EPO may improve cardiomyocyte mitochondrial function, angiogenesis, cell proliferation, and inflammation and directly enhance myocardial tissue oxygen delivery. SGLT2 inhibitors also improve vascular function by attenuating endothelial cell activation, inducing direct vasorelaxation, reducing endothelial cell dysfunction and molecular changes associated with early atherogenesis, decreasing arterial wall stiffness, and decreasing vascular resistance. The glycosuria induced by SGLT2 inhibitors results in a loss of approximately 200–250 kcal per day, resulting in a decrease in adipose tissue mass of 2 kg in both visceral and subcutaneous regions. It is known that an increase in epicardial adipose tissue is associated with an increased risk of coronary artery disease, cardiometabolic disease, atrial fibrillation, and possibly cardiomyopathy due to a release of profibrotic and pro-inflammatory cytokines. By reducing the accumulation and inflammation of peri-vascular adipose tissue, which minimizes the secretion and paracrine action of adipocytokines (such as leptin, tumor necrosis factor [TNF]), SGLT2 inhibitors can reduce heart fibrosis, and thus may contribute to a decrease in the adverse remodeling of the failing heart.

Heart failure is associated with a progressive decline in mitochondrial oxidative metabolism, making the heart more dependent on glycolysis as a source of energy, leading to decreased energy production. This uncoupling between glycolysis and glucose oxidation also leads to decreased cardiac efficiency in both cases of reduced and preserved EF. SGLT2 inhibitors can improve cardiac energetics and efficiency by shifting towards ketone body production. By reducing glucose oxidation, SGLT2 inhibitors increase fat oxidation in the liver, subsequently increasing circulating ketone bodies even in the absence of diabetes. Increasing plasma ketone levels increases cardiac ketone oxidation rates and therefore improves the energy supply to the starving heart. It is also established that excessive cardiac mitochondrial reactive oxygen species (ROS) production contributes to contractile dysfunction in heart failure. Improving glycemic control with SGLT2 inhibition decreases myocardial ROS production and cardiac fibrosis. Indeed, SGLT2 inhibitors reduce molecular processes related to inflammation directly by decreasing certain cytokines (i.e., Interleukin 6 (IL-6), TNF, Chemokine (C-X-C motif) ligand 2 (CXCL2), Nuclear factor kappa B (NF-κB)), and indirectly by affecting oxidative stress, hemodynamics, production of hyperglycaemia-induced cytokines, activation of RAAS, immune system function and obesity-related inflammation. Finally, increased glycosuria induced by SGLT2 inhibitors reduces urate absorption in the proximal convoluted tubule, and thus decreases plasma uric acid level, which has been strongly associated with cardiovascular outcomes in epidemiological studies.

In total, the renal effects of SGLT2 inhibitors are important mechanisms of action and mostly contribute to their cardiovascular benefits (Figure 2). Indeed, SGLT2 inhibition results in an early hemodynamic effect at the level of
the proximal renal tubule, which in turn promotes sodium and water loss while also, through tubulo-glomerular feedback, promoting afferent arteriolar constriction. The reduction in intraglomerular (IG) pressure leads to renal protection. Improving renal function and/or reducing renal stress can indirectly improve cardiac function through several pathways, including reducing afferent SNS activation, inflammation, and ROS generation. Furthermore, the renal hemodynamic effects are observed independently of diabetes status. The increase in EPO production may also be secondary to an improvement in kidney health and may explain why the hematocrit is increased similarly in people with and without diabetes. Additional suspecting mechanisms for the benefits of SGLT2 inhibition in heart failure include improving cardiac energy metabolism and decreasing cardiac inflammation. However, further studies are still required to fully disentangle the mechanisms underlying the clinical benefits of SGLT2 inhibitors.

Returning to the case, our patient with heart failure and multiple hospitalizations in the past year, T2DM, and CKD would be an excellent candidate for initiation of an SGLT2 inhibitor (Table 2). Now that he is appropriately decongested, early pre-discharge implementation is crucial to maximize clinical benefit. There are many clinical approaches to this, but one consideration would be to reduce baseline diuretic dose, start dapagliflozin or empagliflozin 10 mg daily, and maintain his other heart failure therapies. This would

![Figure 2. Mechanisms of cardiovascular benefits of SGLT2 inhibitors.](image)

<table>
<thead>
<tr>
<th>Population</th>
<th>Benefits</th>
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<tbody>
<tr>
<td>SGLT2i benefits</td>
<td>Increased risk of MI, stroke, or CV mortality</td>
</tr>
<tr>
<td>T2DM and established CV disease/additional risk factors</td>
<td>Decreased risk of hospitalization for heart failure</td>
</tr>
<tr>
<td>EF ≤ 40% and NYHA II, III or IV</td>
<td>Decreased risk of adverse kidney outcomes</td>
</tr>
<tr>
<td>EF &gt; 40% and NYHA II, III or IV (NT-proBNP &gt; 300 pg/ml [-600 in patients with atrial fibrillation])</td>
<td>Decreased risk of CV death or hospitalization for heart failure</td>
</tr>
<tr>
<td>T2DM and current admission for heart failure (with intravenous diuretics)</td>
<td>Decreased risk of CV death or hospitalization for heart failure</td>
</tr>
<tr>
<td>Confirmed MI, either STEMI or NSTEMI</td>
<td>Being explored</td>
</tr>
<tr>
<td>Hospitalized for heart failure, regardless of LVEF or T2DM status</td>
<td>Being explored</td>
</tr>
</tbody>
</table>

CV, cardiovascular; EF, ejection fraction; HF, heart failure; LVEF, left-ventricular ejection fraction; MI, myocardial infarction.
provide an additive effect to diuresis, reduce possible hyperkalemia, and facilitate tolerability for quadruple heart failure therapy. Based on his overall glycemic control, consideration of reducing his insulin doses is also reasonable.

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