JACC: HEART FAILURE VOL. 7, NO. 2, 2019

PUBLISHED BY ELSEVIER

PERSPECTIVE

Practical Guide to Prescribing Sodium-Glucose Cotransporter 2 Inhibitors for Cardiologists

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ABSTRACT

The sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of glucose-lowering therapies that have been shown to reduce risks of heart failure (HF) events in patients with type 2 diabetes mellitus (T2DM) at high-risk for or with cardiovascular disease. The United States Food and Drug Administration has expanded the regulatory label for empagliflozin and canagliflozin for use to lower cardiovascular risk in patients with T2DM and cardiovascular disease. SGLT2 inhibitors are being actively studied in the treatment of patients with HF, including in those without diabetes mellitus. Despite the accumulating data supporting this class of therapies in HF prevention, cardiologists infrequently prescribe SGLT2 inhibitors, potentially due to lack of familiarity with their use. We provide an up-to-date practical guide highlighting important elements for treatment initiation, dosing, anticipated adverse effects, and barriers to uptake.
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The sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of glucose-lowering therapies that block renal tubular glucose reabsorption with distinct multisystem metabolic and hemodynamic benefits. Over the last 5 years, 4 SGLT2 inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for glycemic control in type 2 diabetes mellitus (T2DM). Beyond their glucose-lowering potential, canagliflozin, dapagliflozin, and empagliflozin have each been shown to reduce rates of hospitalization for heart failure (HF) in at-risk patients with T2DM, irrespective of history of atherosclerotic cardiovascular disease or HF (1). Appropriately selected patients with T2DM at high cardiovascular risk stand to benefit from the initiation of SGLT2 inhibitors for the prevention of HF. As only a minority of patients (~10% to 15%) carried a baseline diagnosis of HF and data capture of key HF-related elements (e.g., ejection fraction) was incomplete in cardiovascular outcomes trials of SGLT2 inhibitors to date, several dedicated clinical trials (NCT03036124; NCT03619213; NCT03057977; NCT03057951; and NCT03521934) are now underway to evaluate the utility of SGLT2 inhibitors in the treatment of manifest HF.

Given robust cardiovascular health benefits, comparable to that of established therapies actively prescribed in cardiology practices, cardiologists represent an important prescribing pathway. In fact, the FDA has broadened the labeling of empagliflozin and canagliflozin specifically for use to lower cardiovascular risk in patients with T2DM and established cardiovascular disease. Unfortunately, only ~5% of eligible patients are treated with SGLT2 inhibitors in clinical practice (2), and <5% of current prescriptions appear to be initiated by cardiologists (3). We provide a practical guide to SGLT2 inhibitor initiation, monitoring, and patient counseling by cardiologists (**Central Illustration**).

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Manuscript received October 14, 2018; revised manuscript received November 20, 2018, accepted November 24, 2018.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2018.11.013

ABBREVIATIONS AND ACRONYMS

CKD = chronic kidney disease

DKA = diabetic ketoacidosis

eGFR = estimated glomerular filtration rate

FDA = Food and Drug Administration

HF = heart failure

SGLT2 = sodium-glucose cotransporter 2

T2DM = type 2 diabetes mellitus

STEP-WISE TREATMENT AND DRUG SEQUENCING

The recent American Diabetes Association and European Association for the Study of Diabetes consensus guidance (4) provided strong support for upfront cardiovascular risk assessment and consideration of SGLT2 inhibitors as second-line therapies. Metformin is still preferred as backbone therapy given clinician familiarity, low cost, and widespread availability. Moreover, baseline metformin use exceeded 70% in cardiovascular safety programs of SGLT2 inhibitors. The latest iteration of the European Society of Cardiology HF guidelines also prefers metformin as first-line glucose-lowering therapy in patients with HF.

Glycemic targets remain an important adjunct in the comprehensive care of patients with T2DM. If glycated hemoglobin levels remain above individualized targets despite metformin (or if metformin is not tolerated or contraindicated) in patients with T2DM and cardiovascular disease, an SGLT2 inhibitor should be strongly considered. If glycated hemoglobin levels are below desired targets, then other non-metformin oral glucose-lowering therapies (such as sulfonylureas) should be switched to SGLT2 inhibitors. Combination formulations (metformin + SGLT2 inhibitors) are available and may be considered to limit polypharmacy and nonadherence.

COSTS OF SGLT2 INHIBITORS

Median national average drug acquisition costs ($411/month to $415/month) and median average wholesale prices ($512/month to $517/month) are comparable across marketed SGLT2 inhibitors (5), but costs paid by patients may vary by insurance coverage. Cost-effectiveness data are needed accounting for long-term cardiorenal outcome benefits and safety hazards. We anticipate affordability and access to SGLT2 inhibitors will remain major barriers to uptake.

SELECTION AND DOSING OF SPECIFIC SGLT2 INHIBITORS

Treatment-related benefits with respect to HF risk appear relatively consistent for canagliflozin, dapagliflozin, and empagliflozin. Safety concerns with canagliflozin have potentially led to tempered recent use in clinical practice (3). All SGLT2 inhibitors can be taken once daily and should be started at the following doses: canagliflozin (100 mg), dapagliflozin (5 mg), empagliflozin (10 mg), and ertugliflozin (5 mg). Pharmacokinetic drug interactions with SGLT2 inhibitors are minimal. There is limited evidence of dose heterogeneity with respect to cardiovascular outcome benefits; uptitration is thus guided by the need for additional glycemic control, tolerability, and renal function.

CHRONIC KIDNEY DISEASE AND RENAL FUNCTION MONITORING

SGLT2 inhibitors have been shown to prevent renal progression, especially in patients with preserved baseline estimated glomerular filtration rate (eGFR) (1). Although clinical trials have included cohorts with eGFR as low as 30 ml/min/1.73 m^2, regulatory labels vary with respect to acceptable eGFR cutoffs for initiation: 60 ml/min/1.73 m^2 (dapagliflozin, ertugliflozin) and 45 ml/min/1.73 m^2 (canagliflozin, empagliflozin). Patients on dialysis should not be started on SGLT2 inhibitors. Baseline and periodic monitoring of renal function is recommended, especially if used in chronic kidney disease (CKD). A modest decline in eGFR (~3 to 4 ml/min/1.73 m^2) is expected after initiation, but SGLT2 inhibitors result in long-term renoprotection and reduced albuminuria. SGLT2 inhibitors are being actively studied in established CKD (± albuminuria), and dedicated trials in HF are enrolling patients with eGFR down to 20 ml/min/1.73 m^2. A phase 3 trial (NCT02065791) evaluating canagliflozin in T2DM and CKD was recently stopped early for efficacy.

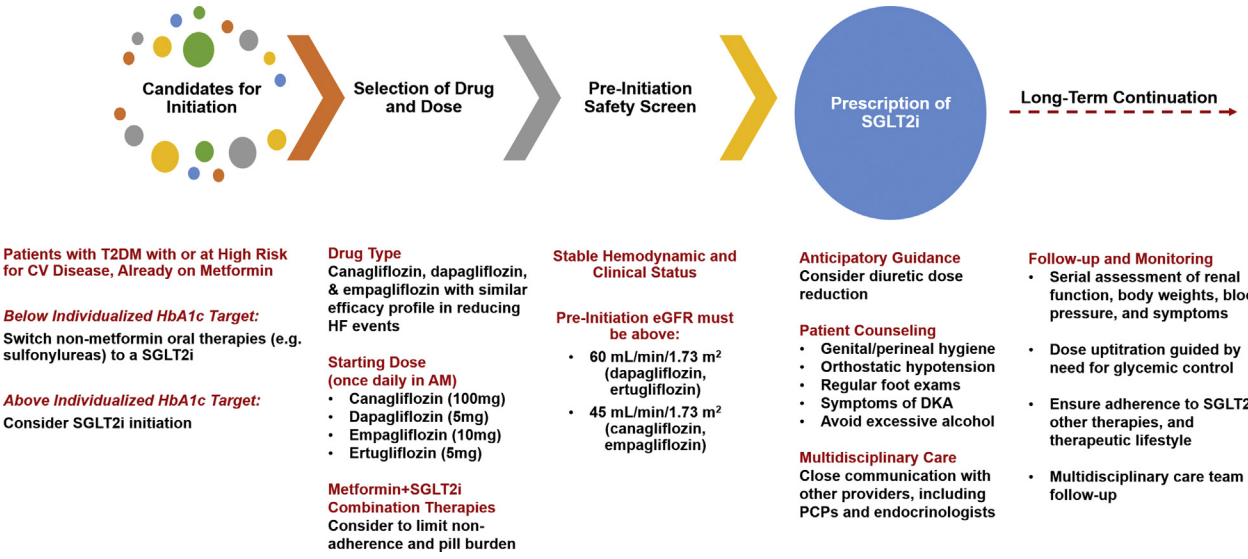
GENITAL AND URINARY INFECTIONS

Cardiologists may be reluctant to prescribe SGLT2 inhibitors due to concerns for adverse effects (**Table 1**). Ongoing clinical trials and accruing real-world evidence will continue to expand our composite understanding of other safety issues not discussed here, including fractures and acute pancreatitis. Genital mycotic infections (vaginitis/balanitis) are most common, occurring more frequently among women and uncircumcised men. Mild-to-moderate infections are responsive to topical antifungals, and occasionally oral fluconazole is required. Patients may experience polyuria, but urinary tract infections are not significantly increased with SGLT2 inhibitors. In August 2018, the FDA released a class-wide warning related to 12 cases of perineal necrotizing fasciitis (Fournier's gangrene), a rare, but serious and potentially disfiguring infection. Patient education and self-monitoring of genital/perineal symptoms are important (**Table 1**).

HYPOGLYCEMIA AND DIABETIC KETOACIDOSIS

SGLT2 inhibitors exhibit a low risk for hypoglycemia due to their insulin-independent mechanism of

CENTRAL ILLUSTRATION **Stepwise Approach to Prescription of SGLT2 inhibitors by Cardiologists**



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A proposed pathway of candidate selection, initiation, monitoring, and patient counseling related to prescription of SGLT2i in clinical practice by cardiologists.
AM = morning; CV = cardiovascular disease; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HF = heart failure; PCP = primary care physician; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus.

TABLE 1 **Practical Considerations With Use of SGLT2 inhibitors**

Potential Adverse Effect	Practical Considerations
Adverse drug-drug interaction	Pharmacokinetic drug-drug interactions are minimal Canagliflozin is a P-glycoprotein substrate (modest inhibition); co-administration with digoxin may increase plasma levels of digoxin; monitor digoxin levels and for signs and symptoms of toxicity when both are used together
Genital and urinary infections	Mycotic infections more common among females and in uncircumcised males Reinforce importance of adequate hygiene Counsel patients to urgently report genital/perineal tenderness, redness, or swelling No significant increase in risk of urinary tract infections
Hypoglycemia	Uncommon; risk increased with concomitant use of sulfonylureas and insulin
Diabetic ketoacidosis	Avoid pre-emptive substantial reductions in insulin dose Hold dose if acutely ill with limited oral intake, and 3 days before major surgery Use caution with low carbohydrate diets to minimize excessive ketosis Discourage excessive alcohol intake Asymptomatic elevations in beta-hydroxybutyrate are frequent with SGLT2 inhibitors, but only a fraction lead to overt diabetic ketoacidosis Counsel patients regarding potential symptoms of diabetic ketoacidosis (fruity odor on breath, thirst, polyuria, nausea, vomiting, abdominal pain, confusion, and fever)
Renal injury	Baseline and periodic monitoring of renal function is recommended, especially if used in chronic kidney disease Modest decrease in eGFR (3 to 4 ml/min/1.73 m^2) is expected with initiation Currently being investigated in eGFR <30 ml/min/1.73 m^2 Cases of acute kidney injury are rare, except in concert with volume depletion
Volume depletion	Increased risk with concomitant diuretic use; consider diuretic dose adjustment Educate patient about potential for orthostatic hypotension and necessity to monitor daily weights and blood pressure, particularly in the first week of therapy Anticipatory guidance to call healthcare provider if home weight decreases by 3 or more pounds over 24 h, or 5 or more pounds in a week, or in the setting of symptomatic hypotension
Lower limb amputations	Predominantly toe and metatarsal More apparent with canagliflozin Increased risk among those with previous amputations or in patients with peripheral artery disease Remind patients to perform regular foot exams and to see a podiatrist annually

eGFR = estimated glomerular filtration rate; SGLT2 = sodium-glucose cotransporter 2.

action. Concomitant insulin/sulfonylureas increase hypoglycemia risk with SGLT2 inhibitors, particularly early after initiation. However, pre-emptive substantial reductions in insulin dose are not recommended and could increase the risk for diabetic ketoacidosis (DKA). SGLT2 inhibitor-related DKA is infrequent (~0.5 patient-years/1,000 patient-years), but may occur at lower than expected glucose levels (euglycemic DKA). Early recognition and holding SGLT2 inhibitors in situations that could precipitate DKA are essential (Table 1).

VOLUME DEPLETION AND BLOOD PRESSURE LOWERING

Treatment with SGLT2 inhibitors is associated with sustained lowering of systolic (4 to 6 mm Hg) and diastolic (1 to 2 mmHg) blood pressure, stemming from reductions in plasma volume and direct effects on vascular function. Osmotic diuresis with SGLT2 inhibitors may lead to dehydration and orthostatic hypotension (frequency of 1.2% to 1.5%), especially among the elderly.

The safety and efficacy of SGLT2 inhibitors started at the time of discharge after hospitalization for HF is under active evaluation (NCT03521934). However, at the present time, given variation in renal function and hemodynamics immediately after cardiovascular events, procedures, or hospitalizations, we recommend restricting initiation to stable patients in the outpatient setting. It is important to assess the patient's volume status and correct hypovolemia before initiating an SGLT2 inhibitor, which may entail reduction of loop diuretic doses as deemed appropriate. Close monitoring of symptoms, hemodynamics, weights, and volume status after SGLT2 inhibitor initiation is recommended (Table 1).

LOWER LIMB AMPUTATIONS

The FDA issued a safety warning regarding risks of lower limb amputations (mainly toes) in patients receiving canagliflozin. The risk appears highest among individuals with history of amputation or peripheral artery disease, and is not dose-dependent. The occurrence of lower limb amputations is very low in trials and observational studies relative to number of patients exposed to SGLT2 inhibitors, and amputation risk was not observed in trials of empagliflozin or dapagliflozin. Nonetheless, regular foot exams and avoidance of SGLT2 inhibitors in those with previous amputation or active foot ulceration appear prudent (Table 1).

MULTIDISCIPLINARY CARE PATHWAYS

Effective integration of SGLT2 inhibitors in cardiovascular clinical care will require restructuring current care models and improved interdisciplinary communication. Many eligible patients who stand to benefit from SGLT2 inhibitors are encountered in cardiology practices. We believe cardiologists are well-positioned to initiate SGLT2 inhibitors in appropriately selected patients in collaboration with other health care providers. As the scope of cardiometabolic therapeutics rapidly expands, reenvisioned training models could better prepare the next generation of cardiologists in managing cardiometabolic diseases and risk factors. Furthermore, collaborative care models with joint or clustered visits with primary care providers, cardiologists, endocrinologists, and allied health professionals may streamline communication and optimize therapeutic efforts. Because of the complexity involved with SGLT2 inhibitor initiation in patients with T2DM and cardiovascular disease, clinical pharmacists embedded in primary care and cardiology clinics are in a unique position to identify and facilitate safe initiation in appropriately selected patients. The SGLT2 inhibitor class represents an important, but underutilized treatment pathway by cardiologists to improve global cardiovascular care.

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KEY WORDS comorbidities, diabetes mellitus, heart failure, prevention