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# SGLT-2 inhibitors in heart failure and chronic kidney disease: A review for internists

## ABSTRACT

Despite current therapies, heart failure and chronic kidney disease continue to be major causes of morbidity and mortality. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors have recently become standard-of-care therapy for these conditions. This review summarizes important randomized controlled trials of SGLT-2 inhibitors and guidelines for using these agents in patients with heart failure and chronic kidney disease in both clinic and hospital settings.

## KEY POINTS

SGLT-2 inhibitors decrease the risk of cardiovascular events in patients with heart failure regardless of ejection fraction and the presence of diabetes.

SGLT-2 inhibitors decrease the risk of chronic kidney disease progression in patients with chronic kidney disease regardless of the presence of diabetes.

SGLT-2 inhibitors are relatively safe and generally well tolerated.

**H**EART FAILURE AND CHRONIC KIDNEY DISEASE are common diseases that lead to considerable morbidity and mortality.<sup>1-3</sup> Modern medical therapy has substantially reduced the burden associated with both conditions.<sup>4</sup> A recent addition to the standard of care is therapy with sodium-glucose cotransporter 2 (SGLT-2) inhibitors. Though initially approved for glycemic control in type 2 diabetes, SGLT-2 inhibitors use novel mechanisms that further improve outcomes for individuals with these conditions.

This review summarizes recent data and guidelines regarding the use of SGLT-2 inhibitors in heart failure and chronic kidney disease and provides practical guidance for their use in both the general medical clinic and hospital ward.

## ■ SGLT-2 INHIBITORS IN HEART FAILURE

### Chronic heart failure with reduced ( $\leq 40\%$ ) ejection fraction

*A 68-year-old man with hypertension and hyperlipidemia was admitted to the hospital for acute decompensated heart failure. During the hospitalization, echocardiography revealed a reduced ejection fraction of 35%, and he was started on a low-dose beta-blocker, sacubitril-valsartan, spironolactone, and daily furosemide before discharge. Two weeks after discharge, he presented to the clinic with a blood pressure of 105/68 mm Hg and heart rate of 69 beats per minute. Serum creatinine was normal. He was still experiencing some exertional dyspnea but otherwise felt well and was euvolemic on examination. He asked about any additional therapy that would improve his prognosis.*

The beneficial effect of SGLT-2 inhibition in the management of heart failure with reduced ejection fraction (HFrEF) was first noted after reduced rates of incident heart failure hospitalization were observed in the initial trials of SGLT-2 inhibitors in patients with diabetes and increased cardiovascular risk.<sup>5,6</sup> Mechanisms of this benefit are complex and unclear and appear to involve improved diuretic effect, myocardial metabolism, and vascular function.<sup>7</sup> Several randomized controlled trials were eventually conducted to investigate the benefits of SGLT-2 inhibitors in heart failure regardless of the presence of diabetes.

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial<sup>8</sup> randomized 4,744 patients with reduced ejection fraction ( $\leq 40\%$ ) and symptomatic heart failure to receive dapagliflozin 10 mg or placebo, in addition to otherwise-prescribed guideline-directed medical therapy. Patients with severe renal disease, acute decompensated heart failure, recent myocardial infarction, recent percutaneous coronary intervention, recent coronary artery bypass grafting, type 1 diabetes, or life expectancy less than 2 years were excluded from the trial. In this trial, the primary composite outcome of worsening heart failure (unplanned hospitalization or urgent visit for heart failure) or death from cardiovascular causes occurred at a lower rate in patients receiving dapagliflozin compared with placebo (16.3% vs 21.2%;  $P < .001$ ; number needed to treat = 21).<sup>8</sup> Notably, compared with placebo, dapagliflozin treatment demonstrated a reduction in the risk of each component of the primary end point, fewer serious safety events, and improved quality of life scored via the Kansas City Cardiomyopathy Questionnaire.<sup>8</sup>

Another randomized controlled trial, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced),<sup>9</sup> randomized 3,730 patients with symptomatic HFrEF (ejection fraction  $\leq 40\%$ ) and with or without diabetes to empagliflozin 10 mg daily or placebo in addition to other guideline-directed medical therapies. This trial also reported a significant reduction in the primary composite outcome of hospitalization for heart failure or cardiovascular death in the empagliflozin group (19.4% vs 24.7% in the placebo group; number needed to treat = 19).

The DAPA-HF and EMPEROR-Reduced trials led to a paradigm shift in the use of SGLT-2 inhibitors in patients with HFrEF. The 2022 guideline for the management of heart failure from the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Failure Society of America

(HFSA)<sup>10</sup> provides Class 1a (highest level of benefit and highest level of evidence) recommendations for SGLT-2 inhibition for the management of symptomatic chronic HFrEF (ejection fraction  $\leq 40\%$ ), regardless of diabetes status.<sup>8-10</sup> Maximizing doses of all 4 guideline-directed medical therapy classes (beta blockade, renin-angiotensin inhibition, mineralocorticoid receptor antagonism, and SGLT-2 inhibition) maximizes clinical benefit.<sup>10</sup>

*In our case, the patient continued with maximum-tolerated doses of beta blockade, renin-angiotensin inhibition with a neprilysin inhibitor, and mineralocorticoid inhibition. SGLT-2 inhibitor therapy was considered with either dapagliflozin 10 mg daily or empagliflozin 10 mg daily. Given that the patient appeared to be euolemic, it was likely that furosemide could be safely discontinued, as the natriuretic effects of the SGLT-2 inhibitor would offset the loss of the loop diuretic.*

### Chronic heart failure with mildly reduced or preserved ( $\geq 50\%$ ) ejection fraction

*A 48-year-old man with obesity and hypertension was hospitalized owing to progressive shortness of breath. At admission, his examination was notable for elevated jugular venous pressure and mild lower-extremity edema. His echocardiogram demonstrated an ejection fraction of 55% and grade 2 diastolic dysfunction. He was treated with intravenous furosemide, which improved his symptoms. At the time of his clinic follow-up visit, the patient inquired about any therapies that would reduce his risk of returning to the hospital.*

Heart failure with preserved ejection fraction accounts for approximately half of all hospitalizations for acute decompensated heart failure.<sup>11</sup> Unlike HFrEF, many trials involving these patients have been unsuccessful in demonstrating the benefit of traditional heart failure therapies including beta-blockers, mineralocorticoid inhibitors, or renin-angiotensin inhibitors.<sup>12-14</sup>

In response to the benefit observed with SGLT-2 inhibitors in patients with HFrEF, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved)<sup>15</sup> was designed to test the hypothesis that empagliflozin benefits patients with heart failure with preserved ejection fraction. This randomized controlled trial assigned 5,988 patients with New York Heart Association class II to IV heart failure and ejection fraction greater than 40% to either empagliflozin 10 mg or placebo. Notable exclusion criteria were acute decompensated heart failure, atrial fibrillation or flutter, history of infiltrative cardiomyopathy, severe valvular disease, chronic severe pulmonary disease,

impaired renal function with an estimated glomerular filtration rate less than 20 mL/minute/1.73 m<sup>2</sup>, or severe anemia. This study found a significant reduction in the primary composite end point of hospitalization for heart failure and cardiovascular death in the empagliflozin group (13.8% vs 17.1% in the placebo group;  $P < .001$ ; number needed to treat = 31).<sup>15</sup> This finding was primarily driven by a 29% relative risk reduction in the rate of hospitalization for heart failure. Notably, subgroup analyses demonstrated a consistent effect across all prespecified ejection fraction ranges, including an ejection fraction of greater than 50%.

Subsequently, the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER-HF) trial<sup>16</sup> investigated the benefit of dapagliflozin in patients with symptomatic heart failure with preserved ejection fraction. In this trial, 6,263 patients with symptomatic heart failure with preserved ejection fraction were randomized to dapagliflozin 10 mg or placebo. The trial reported a significant reduction in the primary composite end point of worsening heart failure and cardiovascular death (16.4% vs 19.5%; number needed to treat = 32), also driven by a reduction in worsening heart failure.

The results from the DELIVER-HF trial<sup>16</sup> were not incorporated into the 2022 ACC/AHA/HFSA guideline,<sup>10</sup> which gives SGLT-2 inhibitors a class 2a recommendation (likely benefit with moderate quality evidence). The 2023 ACC expert consensus statement,<sup>17</sup> however, suggested using SGLT-2 inhibitors in patients with heart failure with preserved ejection fraction given the results of the DELIVER-HF and EMPEROR-Preserved trials.<sup>15,16</sup>

*In our case, the patient appeared to be stable with residual symptomatic heart failure with preserved ejection fraction. An SGLT-2 inhibitor was indicated, either empagliflozin 10 mg or dapagliflozin 10 mg daily.*

### Acute heart failure

*A 55-year-old man with hypertension presented to the hospital with shortness of breath. He had not been to his primary care physician for several years and had stopped taking his antihypertensive medication. In the hospital, his blood pressure was 190/110 mm Hg with jugular venous distention, bilateral rhonchi, and pitting edema on examination. Echocardiography demonstrated an ejection fraction of 40%, and he was informed of his diagnosis of congestive HFrEF. He was given intravenous diuretic therapy that significantly improved his symptoms. He asked whether any therapies could be suggested to take in the hospital to improve his prognosis.*

Acute decompensated heart failure accounts for about 1.2 million hospitalizations in the United States.<sup>18</sup> Management of this serious condition is challenging, and often relies on diuretic therapy. SGLT-2 inhibition in acute heart failure exacerbation has been suggested as a possible adjunctive therapy to current care.

To examine this question, the Study to Test the Effect of Empagliflozin in Patients Hospitalized for Acute Heart Failure Who Have Been Stabilized (EMPULSE)<sup>19</sup> randomized 530 patients regardless of ejection fraction to either empagliflozin 10 mg daily or placebo at the time of clinical stability. The primary outcomes were a hierarchical assessment of time to all-cause death, number of heart failure events, and change in Kansas City Cardiomyopathy Questionnaire total symptom score. The trial demonstrated significant benefit in all 3 elements of the primary composite outcome for patients administered empagliflozin.<sup>19</sup>

The Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial<sup>20</sup> evaluated sotagliflozin, a combined SGLT-1/2 inhibitor, in patients soon after recent hospitalization for worsening heart failure. Despite loss of sponsorship leading to limited enrollment, this trial found that patients receiving sotagliflozin had a significant reduction ( $P < .001$ ) in the primary composite end point of total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure compared with patients receiving placebo.<sup>20</sup>

It is important to note that the 2022 ACC/AHA/HFSA guideline<sup>10</sup> does not specifically recommend SGLT-2 inhibitors in treating acute decompensated heart failure. However, it does suggest the continuation and optimization of guideline-directed medical therapy, as initiation of these therapies at maximum doses before discharge can help reduce adverse outcomes.

*Based on the results of the EMPULSE trial, it would be reasonable to initiate empagliflozin 10 mg daily in our patient, after he was stable and before he was discharged.*

Clinical trials of SGLT-2 inhibitors in heart failure are summarized in **Table 1**.<sup>8,9,15,16,19,20</sup>

### ■ SGLT-2 INHIBITORS AND CHRONIC KIDNEY DISEASE

*A 54-year-old woman with type 2 diabetes complicated by diabetic nephropathy presented to the medical office for routine follow-up. Her medications included metformin and semaglutide. Hemoglobin A1c was 6.9%, estimated glomerular filtration rate was 24 mL/minute/1.73 m<sup>2</sup> and stable, and the urine albumin-to-creatinine ratio was 239 mg/g. Should this patient be started on an SGLT-2 inhibitor?*

**TABLE 1**  
**Trials of sodium-glucose cotransporter 2 inhibitors in heart failure**

Trial	Patients	Intervention	Primary composite end point	Primary composite results
<b>Heart failure with reduced ejection fraction</b>				
DAPA-HF (2019) <sup>8</sup>	4,744 adults EF ≤ 40% Established HF eGFR < 30 mL/minute/1.73 m <sup>2</sup>	Dapagliflozin 10 mg	Cardiovascular death or worsening heart failure	16.3% vs 21.2% (NNT = 21)
EMPEROR-Reduced (2020) <sup>9</sup>	3,730 adults EF ≤ 40% Established HF eGFR < 20 mL/minute/1.73 m <sup>2</sup>	Empagliflozin 10 mg	Cardiovascular death or worsening heart failure	19.4% vs 24.7% (NNT = 19)
<b>Heart failure with preserved ejection fraction</b>				
EMPEROR-Preserved (2021) <sup>15</sup>	5,988 adults EF > 40% New York Heart Association class II–IV HF eGFR < 20 mL/minute/1.73 m <sup>2</sup>	Empagliflozin 10 mg	Cardiovascular death or hospitalization for heart failure	13.8% vs 17.1% (NNT = 31)
DELIVER-HF (2022) <sup>16</sup>	6,263 adults EF > 40% Stabilized HF eGFR > 25 mL/minute/1.73 m <sup>2</sup> With or without diabetes mellitus	Dapagliflozin 10 mg	Cardiovascular death or worsening heart failure	16.4% vs 19.5% (NNT = 32)
<b>Acute decompensated heart failure</b>				
EMPULSE (2022) <sup>19</sup>	530 adults Any EF Acute decompensated HF eGFR < 20 mL/minute/1.73 m <sup>2</sup>	Empagliflozin 10 mg	All-cause death, heart failure events, <sup>a</sup> Kansas City Cardiomyopathy Questionnaire score	53.4% vs 39.7% Win ratio <sup>b</sup> 1.36 (95% confidence interval: 1.09–1.68)
SOLOIST-WHF (2021) <sup>20</sup>	1,222 adults Any EF Acute decompensated HF eGFR < 30 mL/minute/1.73 m <sup>2</sup> Type 2 diabetes	Sotagliflozin 200 or 400 mg	Events of cardiovascular deaths, hospitalizations and urgent visits for heart failure	51% vs 76.3% (NNT = 4)

<sup>a</sup>EMPULSE: heart failure events include heart failure hospitalizations, urgent heart failure visit, unplanned outpatient heart failure visit, and worsening symptoms or intensification of therapy.

<sup>b</sup>Win ratio in favor of empagliflozin; the primary outcome analysis defined a “win” as when, in the common follow-up time, the patient did not die, have an increased number of exacerbations, have an earlier time to first exacerbation, or have a change in Kansas City Cardiomyopathy Questionnaire score < 5 points in hierarchal fashion. If any end point was achieved, it was considered a loss. The “wins ratio” was calculated for each group as the ratio of “wins” to “losses.”

DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER-HF = Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EF = ejection fraction; eGFR = estimated glomerular filtration rate; EMPEROR-Preserved = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPEROR-Reduced = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; EMPULSE = Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized; HF = heart failure; NNT = number needed to treat; SOLOIST-WHF = Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure

As with heart failure, recent trials<sup>21–24</sup> have shown that SGLT-2 inhibitors reduce the risk of kidney disease progression and death among individuals with chronic kidney disease. A recent systematic review and meta-analysis of 12 randomized controlled trials that included 38,949 participants

with an estimated glomerular filtration rate less than 60 mL/minute/1.73 m<sup>2</sup> found that use of an SGLT-2 inhibitor was associated with a 23% lower incidence of chronic kidney disease progression compared with placebo (relative risk 0.77; 95% confidence interval 0.68–0.88).<sup>21</sup>



**TABLE 2**  
**Trials of sodium-glucose cotransporter 2 inhibitors in chronic kidney disease**

Trial	Patients	Intervention	Primary composite end point	Primary composite results
CREDESCENCE (2019) <sup>24</sup>	4,401 adults eGFR 30–89 mL/minute/1.73 m <sup>2</sup> and UACR 301–5,000 mg/g Type 2 diabetes	Canagliflozin 100 mg	End-stage kidney disease, <sup>a</sup> double serum creatinine, or cardiovascular or renal death	43.2 vs 61.2 events/1,000 patient years (NNT = 22)
DAPA-CKD (2020) <sup>22</sup>	4,304 adults eGFR 25–75 mL/minute/1.73 m <sup>2</sup> and UACR 200–5,000 mg/g With or without diabetes mellitus	Dapagliflozin 10 mg	≥ 50% sustained decline in eGFR, end-stage kidney disease, <sup>b</sup> or cardiovascular or renal death	9.2% vs 14.5% (NNT = 19)
EMPA-KIDNEY (2023) <sup>23</sup>	6,609 adults eGFR 20–44 mL/minute/1.73 m <sup>2</sup> or eGFR 45–89 mL/minute/1.73 m <sup>2</sup> and UACR ≥ 200 mg/g With or without diabetes mellitus	Empagliflozin 10 mg	Kidney disease progression <sup>c</sup> or cardiovascular death	13.1% vs 16.9% (NNT = 26)

<sup>a</sup>CREDESCENCE: dialysis for at least 30 days, kidney transplantation, or eGFR < 15 mL/minute/1.73 m<sup>2</sup>.

<sup>b</sup>DAPA-CKD: maintenance dialysis ≥ 28 days, kidney transplantation, or eGFR < 15 mL/minute/1.73 m<sup>2</sup>.

<sup>c</sup>EMPA-KIDNEY: initiation of maintenance dialysis, receipt of kidney transplant, eGFR < 10 mL/minute/1.73 m<sup>2</sup>, sustained decrease in eGFR ≥ 40%, or renal death.

CREDESCENCE = Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD = Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR = estimated glomerular filtration rate; EMPA-KIDNEY = Study of Heart and Kidney Protection with Empagliflozin; NNT = number needed to treat; UACR = urine albumin-to-creatinine ratio

A pivotal randomized controlled trial focused on chronic kidney disease has been conducted for each of the 3 SGLT-2 inhibitors on the US market: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDESCENCE),<sup>24</sup> Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD),<sup>22</sup> and Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY)<sup>23</sup> (Table 2).<sup>22–24</sup> Although all participants had chronic kidney disease, eligibility for these trials varied in terms of estimated glomerular filtration rate and urine albumin-to-creatinine ratio limits. Also, the CREDESCENCE trial<sup>24</sup> was restricted to participants with type 2 diabetes, whereas the DAPA-CKD trial<sup>22</sup> and EMPA-KIDNEY trial<sup>23</sup> included participants with and without diabetes. Importantly, patients were required to be taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker unless a contraindication or intolerance was documented. Major common exclusion criteria of these trials included a history of polycystic kidney disease or kidney transplantation.

All 3 trials<sup>22–24</sup> showed benefit in reducing the risk of chronic kidney disease progression or cardiovascular death, with relative risk reductions ranging from 28% to 39%. This effect did not vary by the presence

or absence of diabetes at baseline. Because the lower limits of the estimated glomerular filtration rate ranged from 20 to 30 mL/minute/1.73 m<sup>2</sup>, there are different minimum estimated glomerular filtration rate thresholds for approved use of SGLT-2 inhibitors for indications other than type 2 diabetes (Table 3).<sup>8–10,15,16,19–27</sup>

Of note, the glucosuric effect of SGLT-2 inhibition declines with the estimated glomerular filtration rate.<sup>28</sup> Therefore, at estimated glomerular filtration rates below 30 to 45 mL/minute/1.73 m<sup>2</sup>, SGLT-2 inhibitors have minimal effect on blood glucose levels. However, in recognition of the compelling trial data, the American Diabetes Association recommends that an SGLT-2 inhibitor be used to reduce the risk of chronic kidney disease progression and cardiovascular events in patients with type 2 diabetes, diabetic kidney disease with a urinary albumin-to-creatinine ratio of 200 mg/g or greater, and an estimated glomerular filtration rate as low as 20 mL/minute/1.73 m<sup>2</sup>, as in the patient presented in our case.<sup>29</sup>

**The estimated glomerular filtration rate dip**

Despite slowing the decline of the estimated glomerular filtration rate over time, SGLT-2 inhibitors decrease the estimated glomerular filtration rate by about 5 mL/minute on average within 1 to 2 weeks of

TABLE 3

**Indications, doses, and estimated glomerular filtration rate thresholds for sodium-glucose cotransporter 2 inhibitors**

Indication	Sodium-glucose cotransporter 2 inhibitor		
	Canagliflozin	Dapagliflozin	Empagliflozin
Glycemic control in type 2 diabetes	100 or 300 mg	5 or 10 mg	10 or 25 mg
Major adverse cardiovascular events risk in type 2 diabetes and cardiovascular disease	100 or 300 mg		10 mg
CVE risk in heart failure		10 mg	10 mg
Heart failure hospitalization in type 2 diabetes and cardiovascular disease or cardiovascular risk		10 mg	10 mg
Chronic kidney disease progression or CVE risk in type 2 diabetes and diabetic kidney disease	100 or 300 mg		
Chronic kidney disease progression or CVE risk in chronic kidney disease		10 mg	10 mg
<b>Minimum estimated glomerular filtration rate (mL/minute/1.73 m<sup>2</sup>)</b>			
For type 2 diabetes	30	45	30
For other indications	30 <sup>a</sup>	25 <sup>a</sup>	20

CVE = cardiovascular events (cardiovascular death, hospitalization for heart failure, urgent heart failure visits)

<sup>a</sup>May continue therapy.

Data from references 8–10,15,16,19–27.

drug initiation.<sup>28</sup> Subsequently, the estimated glomerular filtration rate returns to baseline over the next 3 to 9 months.<sup>28</sup> Because this temporary dip in the estimated glomerular filtration rate is not associated with kidney injury—the risk of acute kidney injury is actually decreased with SGLT-2 inhibitor use<sup>21</sup>—and these drugs do not cause electrolyte abnormalities, we agree with the opinion that routine monitoring of serum creatinine after SGLT-2 inhibitor initiation is not necessary unless a patient is at high risk of volume depletion (blood pressure < 120/70 mm Hg, orthostatic symptoms, taking high-dose diuretics).<sup>30</sup>

## ■ PRACTICAL PRESCRIBING CONSIDERATIONS

### Initiation and titration

Table 3 shows indications, doses, and estimated glomerular filtration rate thresholds for SGLT-2 inhibitors approved by the US Food and Drug Administration.<sup>8–10,15,16,19–27</sup> The recommended dosage for both empagliflozin and dapagliflozin for the indications of reducing cardiovascular event risk and chronic kidney disease progression is 10 mg daily without titration.

They are also indicated for chronic kidney disease with persistently elevated urinary albumin excretion ( $\geq 200$  mg/g) in patients on other first-line therapies for albuminuria.<sup>25–27</sup> Canagliflozin has an indication for patients specifically with diabetic kidney disease with urinary albumin excretion greater than 300 mg/day at a dose of 100 mg daily without titration, although 300 mg may be used for additional glycemic control.

The cost of empagliflozin and canagliflozin is about \$600 per month.<sup>25–27,31–33</sup> Currently, there is a generic form of dapagliflozin that costs \$200 per month.<sup>32</sup> A variety of patient-assistance programs are available for patients to reduce the cost of these medications depending on income level and insurance coverage.

No current guideline offers a specific sequence to initiate or titrate guideline-directed medical therapy.<sup>17</sup>

### In our experience

When starting these medications in patients with type 2 diabetes, it may be necessary to down-titrate insulin or insulin secretagogues (eg, sulfonylureas) to decrease the risk of hypoglycemia. We suggest this down-titration if blood glucose levels are often less than 100 mg/dL.

Anecdotally, some clinicians use a urine glucose test to confirm adherence to and the effect of the medication. As SGLT-2 inhibitors increase urinary glucose excretion, urine glucose tests may remain positive while on the drug.

Volume status is another consideration. Before starting an SGLT-2 inhibitor, assess volume status and renal function in elderly ( $\geq 75$  years) patients, those with renal impairment or low systolic blood pressure, and those on diuretics. At the time of initiation, it may be necessary to down-titrate diuretics to maintain euvolemia, and volume status should be monitored during therapy. Conversely, it is reasonable to consider increasing or restarting diuretics if an SGLT-2 inhibitor should need to be stopped.

The effect of SGLT-2 inhibition on blood pressure is minimal and mediated mostly by volume depletion.

Lastly, starting therapy below drug-specific estimated glomerular filtration rate thresholds is not recommended, and these drugs provide little glycemic benefit at lower estimated glomerular filtration rates. Close collaboration with cardiology, endocrinology, and nephrology clinicians may be helpful in the initiation and use of SGLT-2 inhibitors.

Major drug interactions for canagliflozin include uridine 5'-diphospho-glucuronosyltransferase inducers such as rifampin, phenytoin, and ritonavir. Canagliflozin area under the curve is reduced with these agents, which may reduce efficacy. Co-administration of canagliflozin and digoxin can lead to increased mean peak drug concentrations of digoxin. Digoxin levels should be monitored appropriately when co-administered with canagliflozin.<sup>26,31</sup>

There are no major drug interactions listed for empagliflozin or dapagliflozin.

### Adverse effects

SGLT-2 inhibitors are generally well-tolerated, with most side effects being mild or moderate.<sup>34-37</sup> A common mild side effect is increased urination. Some, but not all, meta-analyses of clinical trials of SGLT-2 inhibitors report a significant increase in the risk of genitourinary infections, with risk of genital mycotic infection greater than risk of urinary tract infection.<sup>34-37</sup> SGLT-2 inhibitors should therefore be avoided in patients with a history of recurrent genitourinary infections. There have been some reports of urosepsis and pyelonephritis; thus, patients with urinary tract infection symptoms should be evaluated and treated promptly.<sup>37</sup>

In our opinion, it is reasonable to continue an SGLT-2 inhibitor through a single occurrence of an uncomplicated urinary tract infection and to discon-

tinue therapy if more severe infection or multiple infections occur.

Some studies have revealed an increased risk of diabetic ketoacidosis with use of SGLT-2 inhibitors in patients with type 2 diabetes.<sup>38-40</sup> These agents should therefore be avoided in patients with a history of diabetic ketoacidosis, pancreatic insufficiency, or alcohol abuse. Additionally, euglycemic diabetic ketoacidosis has been reported with SGLT-2 inhibitor use, which can lead to diagnostic delay.<sup>34,37</sup> Patients on SGLT-2 inhibitor therapy should be counseled regarding common symptoms of diabetic ketoacidosis (nausea, vomiting, abdominal pain, malaise, dyspnea), and patients with these symptoms should have ketone levels measured even in the absence of hyperglycemia. SGLT-2 inhibitors should be discontinued if ketosis is confirmed. Clinicians should consider counseling patients to stop these medications in situations known to predispose patients to ketoacidosis, such as prolonged fasting, gastrointestinal illness, and surgery. Current US Food and Drug Administration guidance is to consider holding these drugs for at least 3 days before scheduled surgery to reduce the risk of ketoacidosis.

There are some less common and more severe side effects of note. All 3 approved SGLT-2 inhibitors have been associated with necrotizing fasciitis of the perineum (Fournier gangrene).<sup>41</sup> Canagliflozin has been associated with an increased risk for lower-limb amputation as well as bone fracture,<sup>34,39</sup> and alternative SGLT-2 inhibitors should be considered in patients with risk factors for these conditions.

### Contraindications

SGLT-2 inhibitors are not approved by the US Food and Drug Administration for patients with type 1 diabetes as they increase the risk for diabetic ketoacidosis. These drugs are also not appropriate for patients on dialysis.

### CONCLUSION

SGLT-2 inhibitors are standard care for heart failure and chronic kidney disease as they decrease the risk of cardiovascular events in patients with heart failure regardless of ejection fraction and presence of diabetes, decrease the risk of chronic kidney disease progression regardless of the presence of diabetes, and are relatively safe and generally well tolerated. ■

### DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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