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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: When should we consider SGLT-2 inhibitors in patients with acute decompensated heart failure?

A: Sodium-glucose cotransporter 2 (SGLT-2) inhibitors should be started as early as possible in patients hospitalized with acute decompensated heart failure who do not have clear contraindications to them, and continued after discharge (**Figure 1**). These medications are well tolerated, can aid in decongestion without worsening renal function, and have multiple cardiovascular benefits.

Introduced in 2012, SGLT-2 inhibitors were developed to treat type 2 diabetes by reducing reabsorption of glucose from the renal filtrate, but they have since been found to have multiple cardiovascular benefits beyond glucose-lowering,[1] which may be attributed to their natriuretic and osmotic diuretic effects and other metabolic effects.[2–4] Of note, they lower N-terminal pro-B-type natriuretic peptide levels, which may be a key determinant of improved clinical outcomes regardless of left ventricular ejection fraction.[3–5]

BENEFITS OF STARTING EARLY

Acute decompensated heart failure is one of the leading reasons for hospital admissions worldwide and is associated with considerable morbidity and mortality.[6] As outlined below and in **Table 1**,[3,4,7–11] studies have suggested that patients hospitalized for acute decompensated heart failure could tolerate SGLT-2 inhibitors and derive cardiac benefit from them, especially when these drugs were started early. While most of the patients in these trials had reduced left ventricular ejection fraction, the benefits were consistent across all left-ventricular-ejection-fraction groups.

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The EMPA-RESPONSE-AHF trial (Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure),[7] with 79 patients, found patients who were randomized to empagliflozin within 24 hours of admission had a significant reduction in the composite outcome of worsening heart failure, rehospitalization for heart failure, or death at 60 days compared with placebo.

The EMPULSE trial (Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized)[3] found that patients who were randomized to receive empagliflozin 10 mg daily within 5 days of admission had a significant reduction in the combined primary end point, ie, a hierarchical composite of death from any cause, number of heart failure events, and time to first heart failure event, or a 5-point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days compared with placebo.

The DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure),[12] in a prespecified analysis of 654 (10.4%) of the trial patients who were randomized to receive dapagliflozin or placebo while hospitalized for heart failure or within 30 days of hospital discharge, demonstrated a reduced risk of worsening heart failure or cardiovascular death. The investigators calculated that the number needed to treat with dapagliflozin to prevent 1 primary outcome event was 28 patient-years in recently hospitalized patients and 65 patient-years in patients not recently hospitalized.

The SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes

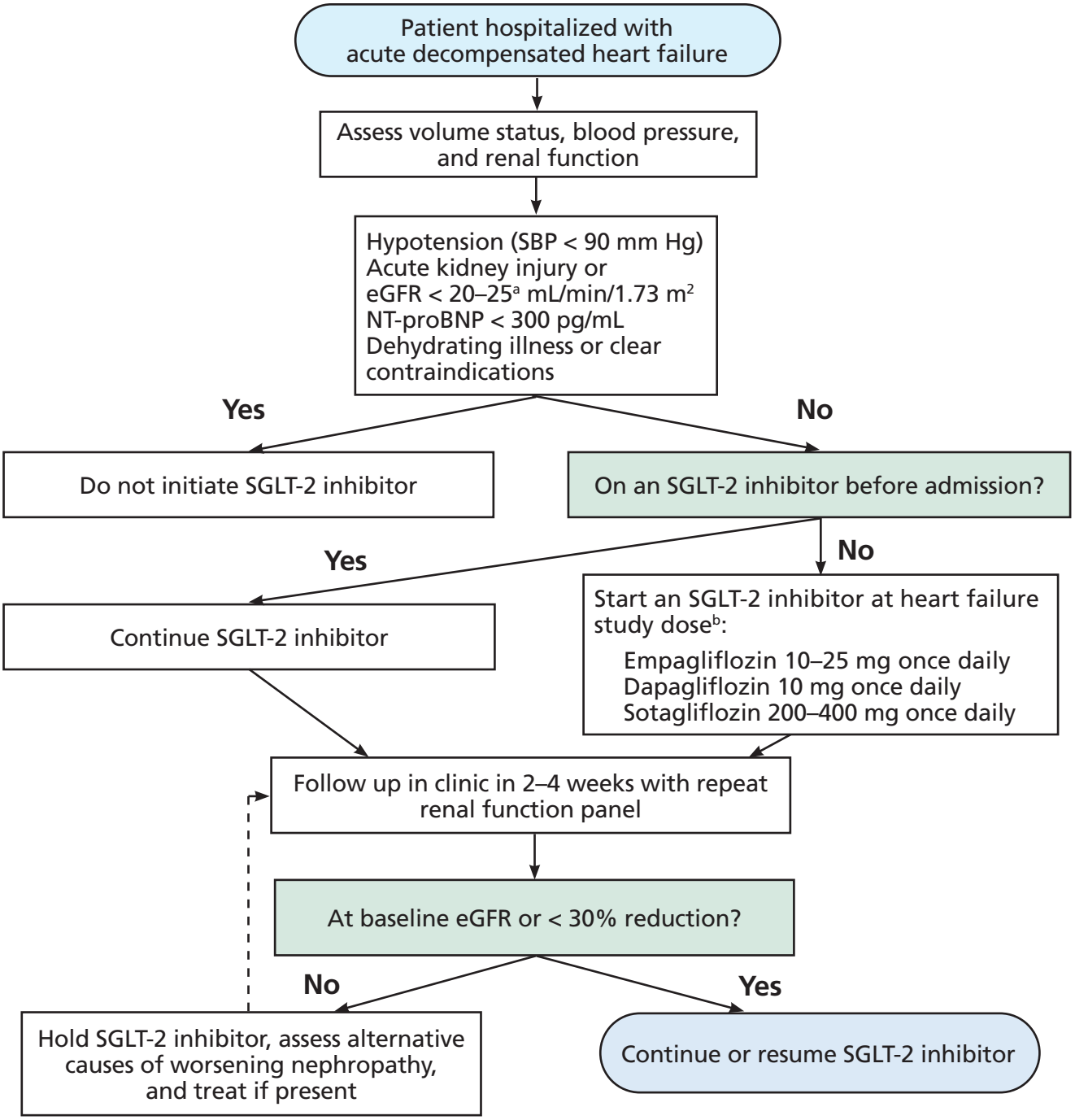

Figure 1. Proposed algorithm for initiating sodium-glucose cotransporter 2 inhibitors in acute decompensated heart failure.

[a]Dapagliflozin: No dosage adjustment for eGFR ≥ 25 mL/min/1.73 m². Manufacturer labeling does not recommend initiation of therapy at eGFR < 25 mL/min/1.73 m². Sotagliflozin is not indicated for patients with eGFR < 25 mL/min/1.73 m². For heart failure, empagliflozin is not indicated for eGFR < 20 mL/min/1.73 m². For type 2 diabetes mellitus, empagliflozin is not indicated for eGFR < 30 mL/min/1.73 m².

[b]Direct evidence on the effects of canagliflozin and ertugliflozin on heart failure outcomes is available only in patients with type 2 diabetes mellitus. It remains to be determined if they have similar effects in patients without type 2 diabetes.

eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure; SGLT-2 = sodium-glucose cotransporter 2

TABLE 1
Randomized controlled trials of sodium-glucose cotransporter 2 inhibitors in acute decompensated heart failure

Trial	Patients	Treatment	Results
EMPULSE[3]	N = 530, 67% with left ventricular ejection fraction (LVEF) < 40%	Empagliflozin 10 mg/day or placebo for 90 days, started a median of 3 days after hospital admission	Early benefit, defined by a hierarchical composite that incorporated all-cause mortality, time to heart failure events, and quality of life (measured by Kansas City Cardiomyopathy Questionnaire Total Symptom Score) with empagliflozin use
EMPAG-HF[4]	N = 59, mean LVEF 45 ± 16%	Empagliflozin 25 mg/day or placebo for 5 days, started within 12 hours of admission	A 25% increase in cumulative urine output over 5 days without affecting markers of renal function with empagliflozin use
SOLOIST-WHF[8,9]	N = 1,222, 79% with LVEF < 50%	Sotagliflozin 200–400 mg/day or placebo for a median of 9 months, initiated before or shortly after hospital discharge	A 33% reduction of a composite of cardiovascular death and hospitalizations or urgent visits for heart failure and apparent improvement in quality of life as measured by the Kansas City Cardiomyopathy Questionnaire 12 score at 4 months in sotagliflozin group
EMPA-RESPONSE-AHF[7]	N = 79, 100% with LVEF < 50%	Empagliflozin 10 mg/day or placebo for 30 days, initiated within 24 hours of presentation while on intravenous diuretics	Significantly reduced composite outcome of worsening heart failure, rehospitalization for heart failure, or death at 60 days in empagliflozin group
DAPA-RESIST[10]	N = 61, 44% with LVEF ≤ 40%	Dapagliflozin 10 mg or metolazone 5–10 mg for up to 3 consecutive days, initiated within 24 hours of trial screening	Significant weight reductions at up to 96 hours of dapagliflozin use compared with metolazone group
DICTATE-AHF[11]	N = 240, 52% with LVEF < 40%	Dapagliflozin 10 mg/day + protocolized diuretic titration or protocolized diuretic titration alone, initiated within 24 hours of presentation	Strong signal of improved diuretic efficiency (defined as weight change divided by loop diuretic dose) until day 5 of hospitalization or discharge if sooner

DAPA-RESIST = Dapagliflozin Versus Thiazide Diuretic in Patients With Heart Failure and Diuretic Resistance, DICTATE-AHF = Efficacy and Safety of Dapagliflozin in Acute Heart Failure, EMPAG-HF = Empagliflozin in Acute Decompensated Heart Failure, EMPA-RESPONSE-AHF = Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure, EMPULSE = Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized, SOLOIST-WHF = Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure

Post Worsening Heart Failure),[8] in a prespecified analysis based on timing of the first dose of the SGLT-1/2 inhibitor sotagliflozin, found the degree of benefit in the primary end point (the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure) was similar regardless of whether the drug was started during the admission (48.8% of the overall group) or within 3 days after discharge. Similarly, a post hoc analysis of this trial demonstrated that starting sotagliflozin before discharge in patients with type 2 diabetes hospitalized for acute decompensated heart failure significantly decreased cardiovascular deaths and heart failure events through 30 and 90 days after discharge.[9] However, no trials to date have directly compared SGLT-2 inhibitors with combined SGLT-1/2 inhibitors.

Another advantage of starting these medications while the patient is in the hospital is the opportunity to address medication reconciliation and potential barriers to adherence, which we usually do on discharge.

SGLT-2 INHIBITORS HELP REMOVE FLUID

Congestion is thought to be the primary reason patients are hospitalized with acute decompensated heart failure.[13] Excreting more sodium early during decongestive

therapy is strongly associated with better postdischarge outcomes, and sodium excretion is a better prognostic indicator than urine output, net fluid balance, or weight change.[14]

A concern about starting SGLT-2 inhibitors as an add-on therapy (in addition to loop diuretics) is the potential for excessively rapid intravascular volume removal and renal injury. Nevertheless, empagliflozin was shown to achieve decongestion without worsening renal function in patients with type 2 diabetes hospitalized for acute decompensated heart failure.[15] This might be explained by the natriuresis and osmotic diuresis caused by SGLT-2 inhibition, leading to reduced plasma volume and, subsequently, reduced preload.[2] Furthermore, SGLT-2 inhibitors may act synergistically with loop diuretics for decongestion and have other beneficial metabolic effects.[16]

The 2023 DAPA-RESIST trial (Dapagliflozin Versus Thiazide Diuretic in Patients With Heart Failure and Diuretic Resistance)[10] showed that dapagliflozin 10 mg daily was as effective as metolazone 5 to 10 mg daily in alleviating congestion in patients with acute decompensated heart failure with resistance to loop diuretics. Although patients in the dapagliflozin group received a higher total amount of furosemide, they encountered fewer biochemical disturbances than those in the metolazone group.

PATIENTS ALREADY ON SGLT-2 INHIBITORS

Although SGLT-2 inhibitors lowered blood pressure only slightly by themselves in large heart failure clinical trials, it is important to consider volume status, especially in those receiving other heart failure agents such as angiotensin receptor-neprilysin inhibitors and loop diuretics, which can increase the risk of orthostasis and falling after the patient goes home. Nevertheless, unless patients have a clear contraindication such as severe hypotension (systolic blood pressure < 90 mm Hg), shock, acute kidney injury, estimated glomerular filtration rate (eGFR) less than 20 or 25 mL/min/1.73 m^2 (depending on the specific agent), or diabetic ketoacidosis (including euglycemic ketoacidosis), those who are already receiving SGLT-2 inhibitors and are admitted with acute decompensated heart failure would benefit from continuing this therapy.[3,7–9,12]

Of note, evidence of the beneficial effects of canagliflozin and ertugliflozin on heart failure outcomes is available only in patients with type 2 diabetes, and there is even less evidence currently for outcomes with bexagliflozin. It remains to be determined if these drugs have similar effects in patients without type 2 diabetes.

PATIENTS WITH RENAL DYSFUNCTION

While SGLT-2 inhibitors have been shown to slow the progression of chronic kidney disease, they generally are not indicated for patients whose eGFR is less than 20 or 25 mL/min/1.73 m^2 (depending on the particular SGLT-2 inhibitor). A reason for caution in this situation is that SGLT-2 inhibitors cause a temporary drop in eGFR and persistent reductions in plasma volume. However, this initial nadir in eGFR early after starting SGLT-2 inhibitors partially reverses over the subsequent 6 to 8 weeks. Further, continuation is associated with improved renal and cardiovascular outcomes, and new studies suggest that SGLT-2 inhibitors should not be discontinued unless the eGFR decreases by more than 30%.[17]

DIABETIC KETOACIDOSIS AND INFECTIONS

SGLT-2 inhibitors are not approved for patients with type 1 diabetes, since their use may promote hypoglycemia in patients without sufficient insulin secretagogue activity, a situation also posing a risk for euglycemic diabetic ketoacidosis.[18] Also, prescribers have been cautioned about genital mycotic infections and the rare severe complication of Fournier gangrene in patients at high risk (eg, older men and those with diabetes, alcohol use disorder, obesity, or immunocompromising conditions).

Fortunately, none of the previously mentioned trials found a higher risk of these complications in patients started on SGLT-2 inhibitors during admissions for acute decompensated heart failure.

THE BOTTOM LINE

In patients with acute decompensated heart failure without clear contraindications to these agents, an SGLT-2 inhibitor should be started as early as possible or continued if the patient is already receiving one. As an adjuvant therapy for decongestion, they have been shown to be well tolerated and can aid in decongestion without worsening renal function. Their use early during hospitalization and their continuation after discharge may translate into long-term clinical benefits.

DISCLOSURES

Dr. Tang has disclosed consulting for Boston Scientific, CardiaTec Biosciences, Cardiol Therapeutics, Genomics, Intellia Therapeutics, Kiniksa Pharmaceuticals, preCARDIA, Relypsa, Renovacor, Sequana Medical, WhiteSwell, and Zehna Therapeutics; board examination writing/approval committee for American Board of Internal Medicine; and editorship/authorship for SpringerNature. The other 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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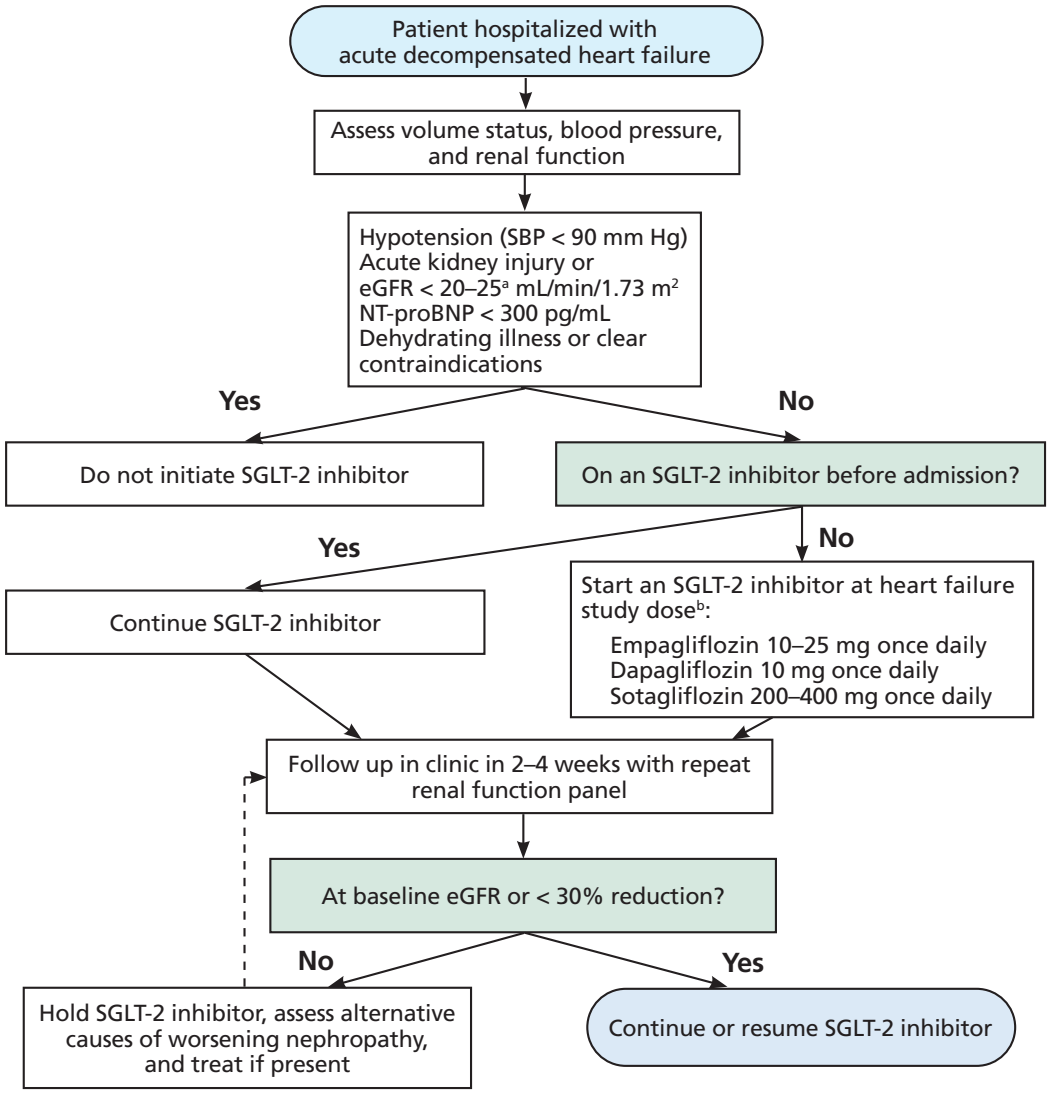
When should we consider SGLT-2 inhibitors in patients with acute decompensated heart failure?

In the January 2024 issue, the article by *Badwan OZ, Braghieri L, Skoza W, Agrawal A, Menon V, Tang WHW. When should we consider SGLT-2 inhibitors in patients with acute decompensated heart failure? Cleve Clin J Med 2024; 91(1):47–51. doi:10.3949/ccjm.91a.23034* contained an error in **Figure 1**. The dosage of empagliflozin was given as 10–25 mg twice daily. The correct dosage is 10–25 mg once daily. The corrected version appears below:



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