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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

# Q: Should I start an SGLT-2 inhibitor in my patient with heart failure and chronic kidney disease?

*A 57-year-old male is admitted to the cardiology inpatient service for acute decompensated heart failure. He has a history of heart failure with reduced ejection fraction (HFrEF) with a left ventricular ejection fraction of 35% and stage 4 chronic kidney disease (CKD). His estimated glomerular filtration rate (eGFR) is 27 mL/min/1.73m$^2$. Should I start him on a sodium-glucose cotransporter 2 (SGLT-2) inhibitor?*

**A:** Large-scale trials have demonstrated the beneficial impacts of SGLT-2 inhibitors in patients with CKD and heart failure, and thus they should be utilized with the goal of rendering renoprotective and cardiovascular benefits. The potential risks and benefits must be weighed, and patients should be monitored closely for adverse events and significant changes in renal function.

Heart failure and CKD are both increasing in prevalence globally, corresponding with an aging patient population with shared comorbidities. These 2 medical conditions are seen commonly in the primary care, cardiology, and nephrology settings, and they often co-exist.[1] They have complex interactions, with progression of kidney disease increasing the risk of major adverse cardiovascular events.[1] Moreover, patients with both heart failure and CKD have a significantly increased morbidity and mortality risk, with previously limited treatment options. With the emergence of new medications to treat HFrEF, it is necessary to critically evaluate the data regarding these medications in patients with additional medical comorbidities.

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## WHAT ARE THE CARDIOVASCULAR AND RENAL BENEFITS OF SGLT-2 INHIBITORS?

Initial trials first detailed the beneficial impact of SGLT-2 inhibitors in patients with type 2 diabetes mellitus, demonstrating their ability to reduce heart failure hospitalizations.[2] Additional studies, including the landmark Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial,[3] expanded on these findings by evaluating SGLT-2 inhibitors in patients with confirmed HFrEF, regardless of the presence or absence of diabetes. The trial showed that patients with HFrEF had a lower risk of worsening heart failure or death from any cardiovascular cause when compared with placebo,[3] and this was validated in patients with more advanced HFrEF in the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction.[4] More recently, trials evaluating SGLT-2 inhibitors in patients with heart failure with preserved ejection fraction have demonstrated a reduction in cardiovascular deaths or hospitalizations for heart failure compared with placebo, thus improving the armamentarium for clinicians in this difficult to treat disease.[5]

These studies suggested possible beneficial effects of SGLT-2 inhibitors on progression of renal dysfunction in addition to a positive impact in patients with heart failure, but did not specifically evaluate SGLT-2 inhibitors in patients with CKD. Consequently, these drugs are often used conservatively in patients with impaired renal function. Further studies explored the



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renoprotective effects of SGLT-2 inhibitors, including a meta-analysis that evaluated 3 separate trials and more than 34,000 patients and showed that SGLT-2 inhibitors reduced progression of renal disease by 45%.[6] This reduction in progression of renal disease was demonstrated irrespective of the presence of known atherosclerotic cardiovascular disease, indicating direct renal protection by SGLT-2 inhibitors.[6]

## WHAT eGFR IS VALIDATED FOR SGLT-2 INHIBITORS IN CHRONIC KIDNEY DISEASE?

The recent Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY)[7] further evaluated SGLT-2 inhibitors in patients with CKD. This trial included patients with an eGFR between 20 and 45 mL/min/1.73m$^2$ regardless of the degree of albuminuria, or patients with an eGFR between 45 and 90 and a urinary albumin-to-creatinine ratio of at least 200. Primary outcomes included progression to end-stage renal disease (ie, initiation of dialysis or transplant), death from renal causes, sustained decline in eGFR of 40% or greater, or cardiovascular death. The trial showed a 28% lower risk of progression of kidney disease or cardiovascular death in patients taking empagliflozin vs placebo.[7]

In the context of these data, the 57-year-old male in our scenario should be placed on an SGLT-2 inhibitor. He is within the eGFR range of the study population included in EMPA-KIDNEY[7] and would likely benefit from an SGLT-2 inhibitor from both a cardiovascular and a renoprotective standpoint.

## WHAT IS THE UNDERLYING MECHANISM OF ACTION OF SGLT-2 INHIBITORS?

Clinicians and researchers alike are encouraged by the prospect of revolutionizing the management of comorbid cardiovascular disease, CKD, and diabetes, while simultaneously hypothesizing about the pathophysiologic mechanism of their pleiotropic effects. SGLT-2 inhibitors block sodium and glucose reabsorption in the proximal tubule, thereby increasing the delivery of sodium to the distal tubule and downregulating the renin-angiotensin-aldosterone system.[8] This increased delivery of sodium to the macula densa (ie, natriuresis) activates tubuloglomerular feedback, thus reducing single nephron filtration and opposing glomerular hyperfiltration via afferent arteriole vasoconstriction.[8] This initial reduction in glomerular hyperfiltration has been postulated to lead to long-term preservation of kidney structure and function and to a lower risk of kidney disease progression.

## WHEN SHOULD A CLINICIAN INITIATE SGLT-2 INHIBITORS?

While SGLT-2 inhibitors had historically been started in the outpatient setting, the Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized trial[9] evaluated the effects of starting empagliflozin in patients admitted with acute heart failure and found a statistically significant benefit in terms of symptomatic improvement, death from any cause, and heart failure events, and the benefit persisted months after randomization.

When initiating SGLT-2 inhibitors, clinicians must keep in mind that these medications have not been validated in patients with end-stage renal disease (eGFR < 15), those on dialysis, or those with previous renal transplant. While diuresis is not the predominant mechanism of SGLT-2 inhibitors in improving cardiovascular outcomes, adjustment of concomitant diuretic therapy may often be needed after starting SGLT-2 inhibitors.

The most commonly prescribed SGLT-2 inhibitors include empagliflozin (starting dose 10 mg daily), dapagliflozin (starting dose 5 mg daily), and canagliflozin (starting dose 100 mg daily). While some differences were seen in studies of these drugs, their long-term outcomes have not been compared directly in randomized controlled trials.

## WHAT ARE THE SIDE EFFECTS TO BE AWARE OF?

Clinicians should monitor patients for adverse effects including acute kidney injury, euglycemic ketoacidosis, hyperkalemia, urinary tract infection, hypotension, dehydration, risk factors for lower-limb amputation (seen specifically with canagliflozin), Fournier gangrene, and volume depletion.[10] Clinicians should note that after initiation of SGLT-2 inhibitors, there is an acute, dose-dependent reduction in eGFR of about 5 mL/min/1.73m$^2$ in the first 2 to 4 weeks, similar to that seen with other classes of renin-angiotensin-aldosterone system inhibitors, and this reduction typically stabilizes thereafter. If such a drop in eGFR is noted, abruptly stopping these medications is not advisable, as patients may require time to benefit from SGLT-2 inhibitors. Patients can be followed with laboratory testing, and a basic metabolic panel should be obtained 2 to 4 weeks after starting an SGLT-2 inhibitor to monitor these parameters.

Overall, many large-scale trials have demonstrated the beneficial impacts of SGLT-2 inhibitors in patients with CKD and heart failure, and thus they should be used for their renoprotective and cardiovascular bene-



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fits. The potential risks and benefits must be weighed, and patients should be monitored closely for adverse events and significant changes in renal function.

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## DISCLOSURES

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