Consider this SGLT2 inhibitor for patients with HF with preserved ejection fraction

The addition of empagliflozin to usual therapy reduced hospitalization risk, regardless of patients' diabetes status.

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PRACTICE CHANGER

Consider adding empagliflozin 10 mg to usual therapy to reduce hospitalization of symptomatic patients with heart failure with preserved ejection fraction (HFpEF; EF > 40%) and an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level > 300 pg/mL, regardless of diabetes status.

STRENGTH OF RECOMMENDATION

B: Based on a single, good-quality, multicenter, randomized controlled trial.[1]

Anker SD, Butler J, Filippatos G, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451-1461. doi: 10.1056/NEJMoa2107038

ILLUSTRATIVE CASE

A 72-year-old man with a history of hypertension, permanent atrial fibrillation, and heart failure (HF) comes into your clinic for follow-up. He was hospitalized a few months ago for HF requiring diuresis. His echocardiogram at that time showed an EF of 50% and no significant valvular disease. He does not have a history of diabetes or tobacco use. His medication regimen includes metoprolol, lisinopril-hydrochlorothiazide, apixaban, and atorvastatin. The patient is still symptomatic from his HF and asks you if there is anything else he can do to prevent another hospitalization for HF.

HFpEF was first defined as HF in patients with a left ventricular ejection fraction (LVEF) > 40%. However, HF with an LVEF between 41% and 49% has been reclassified as its own category: heart failure with mildly reduced ejection fraction (HFmrEF).[2] HFpEF is now diagnosed when the patient has HF symptoms and an LVEF ≥ 50%, mimickers (lung disease, pulmonary embolism, pulmonary hypertension, and renal disease) have been excluded, and there is evidence of elevated left ventricular filling pressure or noninvasive correlates such as elevated natriuretic peptides. It is estimated that HFpEF comprises half of all patients with HF.[3]

In comparison with HF with reduced ejection fraction (HFrEF), there are limited proven treatment options with cardiovascular (CV) benefit in HFpEF.[4] Spironolactone is associated with a slight decrease in HF-related hospitalizations but not with a reduction in CV or all-cause mortality for patients with HFpEF.[4,5] Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and beta-blockers have not been shown to reduce morbidity or mortality in HFpEF when not indicated for another reason.[6,7]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are known to decrease the development and progression of HFrEF[8]; however,

the effect of SGLT2 inhibition in patients with HFpEF remains unclear. Post hoc analyses of a multicenter trial of dapagliflozin in type 2 diabetes indicated no reduction in CV death, hospitalization, or all-cause mortality in HFpEF.[9] Another study found improved CV mortality and decreased HF-related urgent visits and hospitalizations with sotagliflozin, but the number of events was too small to estimate a treatment effect.[10] Given this uncertainty, the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) was conducted to evaluate the effects of SGLT2 inhibition with empagliflozin in patients with HFpEF.[1]

For patients with HFpEF, empagliflozin added to usual care significantly reduced the risk of hospitalization for heart failure, regardless of whether patients had diabetes.

STUDY SUMMARY

Confirmation of benefit of empagliflozin for patients with HFpEF

The EMPEROR-Preserved study was a double-blind, placebo-controlled trial that randomized adult patients with HFpEF (defined by an LVEF > 40%) to either placebo or empagliflozin 10 mg/d, in addition to usual therapy. Patients were randomized in a 1:1 ratio stratified by geographic region, diabetes status, renal function (estimated glomerular filtration rate [eGFR] either < 60 or ≥ 60 mL/min/1.73 m^2), and LVEF > 40% to < 50% or LVEF ≥ 50%.

Included patients were 18 years or older and had an NT-proBNP level > 300 pg/mL (or > 900 pg/mL if the patient had atrial fibrillation at baseline), an LVEF > 40%, and New York Heart Association (NYHA) class II-IV symptoms at baseline. Patients with a CV event in the preceding 90 days, systolic blood pressure ≥ 180 mm Hg, or significant valvular disease were excluded from the study.

The primary outcome was a composite of CV death or first hospitalization for HF. The secondary outcomes were all hospitalizations for HF and the rate of decline in eGFR.

Of the 5988 patients in the trial, 2997 were randomized to receive empagliflozin and 2991 were randomized to placebo. The average age was 72 years in each group, 45% of patients were women, about 76% were White, and 12% were from North America. About 81% of patients were classified as NYHA class II, nearly half had diabetes, and half had an eGFR < 60 mL/min/1.73 m^2. The median body mass index (BMI) was 30, and the median LVEF was 54%. At baseline, the groups were similar in BMI, history of HF hospitalization in the past 12 months, history of common risk factors for HFpEF (atrial fibrillation, diabetes, and hypertension), and prescribed CV medications (ACE inhibitor or ARB with or without a neprilysin inhibitor, spironolactone, beta-blocker, digitalis glycosides, aspirin, and statins). Patients were followed for a median of 26.2 months.

The primary composite outcome of death from CV causes or HF-related hospitalization occurred in 415 patients (13.8%) in the empagliflozin group and in 511 patients (17.1%) in the placebo group (hazard ratio [HR] = 0.79; 95% CI, 0.69-0.90; P < .001). The number needed to treat to prevent 1 primary outcome event was 31 (95% CI, 20-69). Hospitalization for HF occurred in 259 patients (8.6%) with empagliflozin vs 352 patients (11.8%) with placebo (HR = 0.71; 95% CI, 0.60-0.83), and CV death occurred in 219 patients (7.3%) with empagliflozin vs 244 patients (8.2%) with placebo (HR = 0.91; 95% CI, 0.76-1.09). The effect was consistent in patients with or without diabetes at baseline; however, the largest reduction in the primary composite outcome was seen in those with an LVEF < 50%, age ≥ 70 years old, BMI < 30, and NYHA class II status.

The secondary outcome of total number of hospitalizations for HF was 407 with empagliflozin vs 541 with placebo (HR = 0.73; 95% CI, 0.61-0.88; P < .001). The rate of decline in the eGFR per year was –1.25 in the empagliflozin group vs –2.62 in the placebo group (P < .001), indicating that those taking empagliflozin had preserved renal function compared with those taking placebo.

Death from any cause occurred in 422 patients (14.1%) in the empagliflozin group and 427 patients (14.3%) in the placebo group (HR = 1.00; 95% CI, 0.87-1.15). Empagliflozin treatment was associated with higher rates of genital infections (2.2% vs 0.7%; P value not provided), urinary tract infections (9.9% vs 8.1%; P value not provided), and hypotension (10.4% vs 8.6%; P value not provided), compared to placebo.

WHAT'S NEW

Risk of hospitalization significantly reduced for patients with HFpEF

In the EMPEROR-Preserved study, empagliflozin led to a lower incidence of hospitalization for HF in patients with HFpEF but did not significantly reduce the number of deaths from CV disease or other causes. In comparison, in the similarly designed EMPEROR-Reduced trial, treatment with empagliflozin reduced CV and all-cause mortality in individuals with HFrEF.[8]

CAVEATS

HF criteria, study population may limit generalizability

The reduction in the primary outcome of CV death or first hospitalization was most pronounced in patients with an LVEF > 40% to < 50%, typically defined as HFmrEF, who often have clinical features similar to those with HFrEF. This raises the question of how generalizable these results are for all patients with HFpEF.

The study's generalizability was further limited by its significant exclusion criteria, which included elevated blood pressure, chronic obstructive pulmonary disease on home oxygen, liver disease, renal disease with an eGFR < 20 mL/min/1.73 m^2 or requiring dialysis, and BMI ≥ 45.

Finally, only 12% of patients were from North America, and results were not significant for this subgroup (HR = 0.72; 95% CI, 0.52-1.00), which may challenge its external validity. The authors noted that 23% of patients discontinued treatment for reasons other than death, which may have driven the null effect.

CHALLENGES TO IMPLEMENTATION

Empagliflozin is expensive, but coverage may improve

Cost could be a major barrier to implementation. Retail pricing for empagliflozin is estimated to be more than $550 per month, which may be prohibitive for patients with no insurance or with higher-deductible plans.[11] However, the US Food and Drug Administration has approved empagliflozin to reduce the risk of CV death and hospitalization for HF in adults,[12] which may help to improve insurance coverage. JFP

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Empagliflozin treatment, however, was associated with higher rates of genital infections, urinary tract infections, and hypotension, compared to placebo.