FPIN's Clinical Inquiries

SGLT-2 Inhibitors for Cardiovascular Outcomes in Heart Failure With Preserved Ejection Fraction

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Clinical Question

Do sodium-glucose cotransporter-2 (SGLT-2) inhibitors improve cardiovascular outcomes in patients who have heart failure with preserved ejection fraction (HFpEF)?

Evidence-Based Answer

SGLT-2 inhibitors can reduce hospitalizations from heart failure but do not significantly reduce cardiovascular-related mortality. (Strength of Recommendation [SOR]: A, based on three meta-analyses of seven randomized controlled trials [RCTs] and one high-quality RCT.) Dapagliflozin (Farxiga) decreases symptoms of heart failure and improves distance walked in a six-minute walk test (mean increase = 8.3%). (SOR: B, based on one good-quality RCT.)

Evidence Summary

A 2020 systematic review and meta-analysis included two RCTs and a pooled analysis of two additional RCTs evaluating the effect of SGLT-2 inhibitors compared with placebo in patients who had heart failure with reduced ejection fraction and HFpEF.[1] The authors performed subgroup analyses of patients with preserved ejection fraction (n = 2,554). Patients (average age = 64 to 70 years) with diabetes mellitus and an ejection fraction greater than 45% were randomized to treatment with ertugliflozin (Steglatro), 5 or 15 mg per day; dapagliflozin, 10 mg per day; sotagliflozin (Zynquista; not available in the United States), 200 or 400 mg per day; or placebo with a follow-up of nine to 50 months. The primary outcome, a composite of hospitalization for heart failure and cardiovascular mortality, was not significantly different between the SGLT-2 inhibitors and placebo (four studies; n = 2,554; hazard ratio [HR] = 0.80; 95% CI, 0.63 to 1.00; P = .05). The SGLT-2 inhibitors did reduce the first hospitalization from heart failure (two studies; n = 1,815; HR = 0.71; 95% CI, 0.52 to 0.97; P = .03) but did not decrease cardiovascular mortality (two studies; n = 1,815; HR = 1.27; 95% CI, 0.92 to 1.76; P = .15). The validity of the primary outcome was limited by significant heterogeneity (I^2 = 63.9%).

A 2021 meta-analysis included two RCTs that evaluated the effect of SGLT-2 inhibitors on all-cause mortality, cardiovascular mortality, and hospitalization in patients with HFpEF (n = 2,323) using one of the studies in the previous review and one more recent study.[2] Patients (average age = 64 years) with diabetes and an ejection fraction greater than 45% were randomized to ertugliflozin, 5 or 15 mg per day, or dapagliflozin,

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10 mg per day, vs. placebo and were followed for 42 to 50 months. There was no difference between SGLT-2 inhibitors and placebo for all-cause mortality (two studies; n = 2,323; HR = 1.02; 95% CI, 0.81 to 1.29), cardiovascular mortality (two studies; n = 2,323; HR = 1.26; 95% CI, 0.93 to 1.73), or hospitalization (two studies; n = 2,323; HR = 0.74; 95% CI, 0.55 to 1.00).

A 2022 meta-analysis evaluated the effect of SGLT-2 inhibitors vs. placebo on all-cause mortality, cardiovascular mortality, and hospitalization from heart failure.[3] The meta-analysis included three RCTs in patients with HFpEF (one RCT from the previous meta-analysis and two newer RCTs; n = 8,610). Patients (mean age = 68 to 71 years) with and without diabetes were included if the ejection fraction was greater than 50%. The interventions were empagliflozin (Jardiance), canagliflozin (Invokana), and sotagliflozin (doses were not provided); patients were followed for six to nine months. The meta-analysis of all three studies showed that, compared with placebo, SGLT-2 inhibitors decreased hospitalization from heart failure (three studies; n = 8,610; relative risk = 0.72; 95% CI, 0.5 to 0.96) but had no effect on all-cause or cardiovascular mortality.

Two more recent RCTs evaluated the effect of SGLT-2 inhibitors compared with placebo in patients with HFpEF. The largest RCT, a multinational, randomized, double-blind trial (n = 5,988), evaluated the effect of empagliflozin, 10 mg per day, vs. placebo in patients 62 to 82 years of age with New York Heart Association class II to IV heart failure and an ejection fraction greater than 40%.[4] The study included patients with an N-terminal pro–brain natriuretic peptide level greater than 300 pg per mL without rhythm disturbance or greater than 900 pg per mL for patients with atrial fibrillation. Nearly one-half of the patients had type 2 diabetes. The outcomes studied were cardiovascular death and hospitalization from heart failure. During a median of 26.2 months, a primary outcome event occurred in 415 (13.8%) of 2,997 patients in the empagliflozin group and 511 (17.1%) of 2,991 patients in the placebo group (HR = 0.79; 95% CI, 0.69 to 0.90; number needed to treat = 31). Empagliflozin decreased hospitalization for heart failure (8.6% vs. 11.8% with placebo; attributable risk = 3.2%; number needed to treat = 32; HR = 0.71; 95% CI, 0.60 to 0.83). A nonsignificant decrease in cardiovascular death was noted in the empagliflozin group vs. the placebo group (7.3% vs. 8.2%; 95% CI, 0.76 to 1.09). There was a high discontinuation rate (23%) in both groups.

A multicenter, randomized, double-blind, placebo-controlled study (n = 324) evaluated the effect of dapagliflozin, 10 mg per day, vs. placebo. Patients (63 to 78 years of age) were from the United States with New York Heart Association class II to IV heart failure and an ejection fraction of 45% or greater.[5] The primary outcome was symptomatic improvement evaluated at 12 weeks by the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS; a 0 to 100 scale of symptoms and physical limitations from heart failure; higher scores are better). Secondary outcomes were distance walked on a six-minute walk test and a 5-point or greater increase (considered clinically meaningful) in the KCCQ-CSS. Compared with placebo, dapagliflozin increased the KCCQ-CSS by a mean of 5.8 points (95% CI, 2.3 to 9.2), significantly improved the six-minute walk test distance (mean difference = 20.1 m; 95% CI, 5.6 to 34.7), and improved KCCQ-CSS by 5 points or more (odds ratio = 1.73; 95% CI, 1.05 to 2.85). Study limitations include the short duration of the study and that the participants were all from the United States.

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