COMMENTARY

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Cardiovascular Benefits of Digoxin and Empagliflozin in Patients with Chronic Heart Failure: The DIG Trial Revisited

Cardiovascular benefits of empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, in treating heart failure continue to accumulate. Two large-scale trials have evaluated the effect of empagliflozin in patients with heart failure and a reduced ejection fraction (HFrEF) and patients with heart failure with a preserved ejection fraction (HFpEF).[1,2] Based on the empagliflozin outcome trial in patients with chronic heart failure with reduced ejection fraction (EMPEROR-Reduced) trial, the Food and Drug Administration (FDA) recently approved empagliflozin to treat patients with HFrEF. The 2021 European Society of Cardiology Guidelines for heart failure has given a Class IA indication for empagliflozin to treat patients with HFrEF.[3] The recommendation for empagliflozin to treat HFpEF may come soon. In contrast, the use of digoxin, once one of the commonly used treatments for heart failure, has been declining substantially.[4] The background use of digoxin in these two trials was not even mentioned. The major heart failure guideline-issuing societies have downgraded digoxin as a second-line treatment for patients with heart failure.[3,5] It may be the time to revisit the DIG trial, a landmark trial in heart failure done 25 years ago and to compare digoxin with empagliflozin in terms of cardiovascular benefits.

CARDIOVASCULAR BENEFITS OF EMPAGLIFLOZIN AND DIGOXIN IN PATIENTS WITH HFREF

The EMPEROR-Reduced trial, a phase III trial, randomized 3730 patients with heart failure and an ejection fraction ≤ 40% to placebo or empagliflozin for a median follow-up of 16 months. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure. Empagliflozin led to a significant 5.3% absolute risk reduction (ARR) of this composite outcome versus placebo (19.4% vs 24.7%; hazard ratio [HR]: 0.75; 95% confidence interval [CI]: 0.65-0.86). The difference was mainly driven by a reduction in hospitalization for heart failure (13.2% vs 18.3%, ARR: 5.1%; HR: 0.69; 95% CI: 0.59-0.82). Cardiovascular death was not reduced (10% vs 10.8%; HR: 0.92; 95% CI; 0.75-1.12).

The Digitalis Investigation Group (DIG) trial is the only randomized trial investigating the impact of digoxin on mortality risk in HFrEF. The trial randomized 6800 patients with heart failure and an ejection fraction ≤ 45% to placebo or digoxin for a median follow-up of 33 months.[6] Digoxin had no impact on the primary outcome of all-cause mortality. However, digoxin led to a significant 3.3% ARR of cardiovascular death or hospitalization for heart failure as a secondary composite outcome versus placebo (13.8% vs 17.1%; HR: 0.79; 95% CI: 0.69-0.90). The difference was mainly related to a significant 7.9% ARR of hospitalization for heart failure (26.8% vs 34.7%; HR: 0.72; 95% CI: 0.66-0.79). Cardiovascular death was not reduced (29.9% vs 29.5%; HR: 1.01; 95% CI: 0.93-1.10).

In both trials, the primary effect was on hospitalization for heart failure and the magnitude of the effect was similar. There was no significant effect on cardiovascular death.

CARDIOVASCULAR EFFECTS OF EMPAGLIFLOZIN AND DIGOXIN IN PATIENTS WITH HFPEF

The Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR-Preserved) trial was a double-blind and placebo-controlled trial of empagliflozin in patients with HFpEF. A total of 5988 patients with heart failure and an ejection fraction >40% were randomly assigned to placebo or empagliflozin for a median follow-up of 26 months. Empagliflozin reduced the primary composite endpoint of cardiovascular death or hospitalization for heart failure by 3.3% ARR compared with placebo

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(13.8% vs17.1%; HR: 0.79; 95% CI: 0.69-0.90). This was driven by a 3.2% ARR of hospitalization for heart failure (8.6% vs 11.8%; HR: 0.71; 95% CI :0.60-0.83). Cardiovascular death was not reduced (7.3% vs 8.2%; HR: 0.91; 95% CI: 0.76-1.09).

In the DIG trial, there was an ancillary trial running in parallel to the main trial in patients with HFpEF and the data was analyzed separately,[7] in which 988 patients with an ejection fraction >45% were randomly assigned to placebo or digoxin for a median follow-up of 37 months. During the first 2 years after randomization (protocol prespecified), digoxin led to a significant 5% ARR of cardiovascular death or hospitalization for heart failure versus placebo (18% vs 23%; HR: 0.75; 95% CI: 0.57-0.99). This was related to the reduction of hospitalization for heart failure only, and there was a significant 5% ARR of hospitalization for heart failure (12% vs 17%; HR: 0.66; 95% CI: 0.47-0.91). Cardiovascular death was not reduced by digoxin (16.3% vs 16.5%; HR: 0.89; 95% CI: 0.59-1.36).

Although not statistically significant, at the end of the study (37 months of follow-up) in the ancillary DIG trial, there was an absolute 3.7% lower risk of hospitalization for heart failure (18.1% vs 21.8%; HR: 0.79; 95% CI: 0.59-1.04). This was consistent with the effect of digoxin in the main trial. The magnitude of the reduction in hospitalization for heart failure is similar to that observed in the EMPEROR-Preserved trial. The lack of statistical significance is likely due to a much smaller sample size of the trial and the relatively low event rate in the patients with HFpEF.

The benefit size for reducing hospitalization for heart failure of empagliflozin is similar to digoxin for both HFrEF and HFpEF. Empagliflozin and digoxin have no net beneficial effect on all-cause mortality or cardiovascular mortality in heart failure. The median follow-up period in DIG trial was 2 times longer than in EMPEROR-Reduced (33 months vs 16 months) and the sample size of DIG trial was almost twice as large as of EMPEROR-Reduced. DIG trial was done more than two decades ago and treatment for heart failure was quite different from EMPEROR-Reduced. In DIG trial, 94% patients were on angiotensin-converting enzyme (ACE) inhibitors, 81% on diuretics, and 42% on nitrates. In EMPEROR-Reduced, 88% patients were on renin-angiotensin inhibitors, 70% on mineralocorticoid receptor antagonists, 94% on beta-blockers, and 95% on diuretics. The change of policies and practice may shift many worsening heart failure events to be managed on an outpatient basis during EMPEROR-Reduced. All these may explain the higher mortality and hospitalization for heart failure rate in DIG trial. The differences in background therapy from the current practice when the DIG trial was conducted may limit the applicability of the data to the current practice. However, in the Randomized Aldactone Evaluation Study (RALES) trial, the mortality benefit of spironolactone was only significant in patients receiving digoxin.[8] Cardiovascular benefits of digoxin for patients with heart failure with current standard treatment or a head-to-head comparison with empagliflozin needs to be evaluated in a randomized trial.

Digoxin toxicity is a major concern for its clinical use. Ventricular fibrillation or ventricular tachycardia was the most common reason for suspected serious digoxin toxicity in the DIG trial. However, there was no significant difference of these events between the digoxin and placebo group (1.1% vs 0.8 %; HR: 1.4; 95% CI: 0.84-2.30; P = .20). In the ancillary trial, out of 48 patients with suspected or confirmed digoxin toxicity in the digoxin group, only 1 patient was hospitalized. In a recent randomized trial in patients with atrial fibrillation and heart failure symptoms, concerns regarding the use of digoxin, such as narrow therapeutic window and drug interactions were not an issue when the low-dose approach (the mean dose was 161 μg/d) was used.[9] My experience of digoxin use in clinical practice has been consistent with these findings.

Digoxin is one of the least expensive drugs for managing heart failure. In the United States, the monthly cost of digoxin is less than $10; in contrast, the monthly cost of empagliflozin is more than $600. The debate over the use of digoxin, a 200-year-old drug, will continue.[10] However, there is no compelling evidence supporting the widespread use of empagliflozin over digoxin. Nevertheless, consideration of using digoxin, especially at a low dose, should be part of standard treatment for symptom relief and hospitalization for heart failure reduction in patients with chronic HFrEF, especially in the developing countries where patients cannot afford the guideline-recommended treatments.

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