More Evidence for SGLT2 Inhibitors in Heart Failure

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In 2015, the *Journal* published the results of EMPA-REG OUTCOME, a cardiovascular outcomes trial of the sodium–glucose contransporter 2 (SGLT2) inhibitor empagliflozin in patients with type 2 diabetes at high cardiovascular risk.[1] Among the patients who received empagliflozin, the investigators found a significant reduction in major adverse cardiovascular events (cardiovascular death, myocardial infarction, or stroke), as well as in death from cardiovascular causes, death from any cause, progression of renal disease, and hospitalization for heart failure.

Subsequent cardiovascular outcomes trials of other SGLT2 inhibitors have varied in the extent to which they have confirmed the various benefits seen in EMPA-REG OUTCOME.[2,3] However, the benefit with respect to hospitalization for heart failure has been consistent across all the drugs in the class.[4] This observation led to the question of whether the benefit of SGLT2 inhibitors in heart failure might be independent of the presence of diabetes.

This question was answered in the affirmative in 2019 with the publication of the DAPA-HF trial.[5] In DAPA-HF, 4744 patients with heart failure and a reduced ejection fraction were randomly assigned to receive either dapagliflozin or placebo in addition to standard heart-failure therapy. Of the enrolled patients, 41.8% had diabetes mellitus. At a median of 18 months, the primary outcome of cardiovascular death or worsening heart failure was significantly lower in the dapagliflozin group than in the placebo group (16.3% vs. 21.2%; hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). A subgroup analysis indicated that the benefit seen was independent of the presence or absence of diabetes. DAPA-HF thus provided a rationale for a novel therapy for heart failure. On May 5 of this year, the Food and Drug Administration (FDA) approved dapagliflozin specifically for the treatment of patients with heart failure and a reduced ejection fraction.

Now reported in the *Journal* are the results of the EMPEROR-Reduced trial, which examines the potential benefit of another SGLT2 inhibitor, empagliflozin, in 3730 patients with heart failure and a reduced ejection fraction.[6] As in DAPA-HF, a substantial proportion of the patients (50.2%) did not have diabetes. The patients in this trial had on average more severe heart failure than those in the DAPA-HF trial, with a mean ejection fraction of 27% versus 31% and a median level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) of 1907 versus 1437; in addition, more than 70% of the patients enrolled in EMPEROR-Reduced had an ejection fraction of 30% or less. The median duration of follow-up was 16 months. As in DAPA-HF, the incidence of the primary outcome of cardiovascular death or hospitalization for heart failure was significantly lower with empagliflozin than with placebo (19.4% vs. 24.7%; hazard ratio, 0.75; 95% CI, 0.65 to 0.86; P<0.001). Again, the benefit was seen regardless of diabetes status.

In both DAPA-HF and EMPEROR-Reduced, the two components of the primary outcome were analyzed individually but were not formally tested for significance. In DAPA-HF, the hazard ratio for cardiovascular death considered alone was 0.82 (95% CI, 0.69 to 0.98), a result that is nominally significant if the inflation of the alpha error owing to multiple testing is disregarded. In contrast, in EMPEROR-Reduced, the hazard ratio for cardiovascular death alone was 0.92 (95% CI, 0.75 to 1.12), a result that is not nominally significant.

Is this apparent difference in the effect on cardiovascular death real? There are some reasons to consider this possibility. Two different drugs were used, and, as noted earlier, the individual SGLT2 inhibitors do not seem to have entirely consistent cardiovascular effects. On the other hand, as the authors point out in their Discussion section, the effects of dapagliflozin and empagliflozin on cardiovascular death in patients with diabetes without heart failure trend in the opposite direction, with empagliflozin showing a significant benefit on cardiovascular death that was not seen with dapagliflozin. Another possible consideration is that, as noted, the patients in EMPEROR-Reduced had on aver-

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age more severe heart failure than those in DAPA-HF; perhaps these drugs are less effective in more advanced heart failure. A subgroup analysis of cardiovascular death according to ejection fraction, baseline NT-proBNP level, or NYHA class might help in examining this question. It is also possible, of course, that the apparent difference in effect on cardiovascular death is a chance finding; the confidence intervals for the two point estimates certainly overlap. A definitive answer to this question would likely require a head-to-head randomized trial.

When new heart-failure therapies are investigated, it is important to consider whether they provide benefit in addition to established therapies. This question applies in particular to sacubitril–valsartan, which has been adopted rather gradually in clinical practice despite receiving FDA approval in 2015 and a class I guidelines recommendation in 2016.[7] In DAPA-HF, only 10.7% of the patients were receiving sacubitril–valsartan, as compared with 19.5% of those in EMPEROR-Reduced. In both trials, subgroup analyses did not suggest that the benefit of empagliflozin varied according to the use of sacubitril–valsartan.

The results of the EMPEROR-Reduced trial confirm that the findings in DAPA-HF were no fluke and substantially strengthen the rationale for the use of SGLT2 inhibitors in patients with heart failure and a reduced ejection fraction. Guidelines committees will now need to contend with the evidence. The Canadian Cardiovascular Society and the Canadian Heart Failure Society have already done so: they have recommended the use of SGLT2 inhibitors in patients with mild or moderate heart failure who have an ejection fraction of 40% or less to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality.[8] The EMPEROR-Reduced data will provide further impetus for other groups to address this question.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

This editorial was published on August 28, 2020, at NEJM.org.

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DOI: 10.1056/NEJMe2027915
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