EDITORIAL

Heart-Failure Therapy — New Drugs but Old Habits?

James C. Fang, M.D.

In 2015, empagliflozin, an inhibitor of sodium–glucose cotransporter 2 (SGLT2), lowered the composite cardiovascular end point in the EMPA-REG trial[1] involving patients with type 2 diabetes mellitus who were at increased cardiovascular risk. What was remarkable in that finding was that the benefit was driven by reductions in hospitalization for heart failure and cardiovascular mortality but not by a lower frequency of myocardial infarction or stroke. Moreover, empagliflozin appeared to slow deterioration in renal function, and the heart-failure benefits persisted in the presence of renal dysfunction. These early observations regarding heart failure were extended and confirmed in two subsequent trials of SGLT2 inhibitors involving patients with type 2 diabetes: the CANVAS trial of canagliflozin[2] and the DECLARE–TIMI 58 trial of dapagliflozin.[3] Since these heart-failure benefits were independent of glucose lowering, it was postulated that SGLT2 inhibitors might be a treatment for heart failure associated with a reduced ejection fraction (i.e., systolic heart failure), regardless of diabetes status.

In this context, McMurray et al. now report in the *Journal* the primary results of the DAPA-HF randomized trial,[4] in which they tested the hypothesis that dapagliflozin would reduce the primary composite outcome of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death in patients with heart failure and a reduced ejection fraction, with or without type 2 diabetes mellitus. Among the patients who received dapagliflozin, the frequency of the primary composite outcome was 26% lower than that among the patients who received placebo (386 [16.3%] and 502 [21.2%], respectively; hazard ratio, 0.74; 95% confidence interval, 0.65 to 0.85; P<0.001), with a number needed to treat of 21. Multiple secondary cardiovascular outcomes were also positive, including a reduction in the total number of first and recurrent hospitalizations for heart failure, a decrease in all-cause mortality, and an improvement in quality of life. There were many adjudicated events, and the benefits were remarkably consistent among outcomes and prespecified subgroups, which bolsters confidence in the conclusions. Dapagliflozin was associated with few adverse effects and with no excess of dangerous but rare adverse events, as was seen in some previous trials of SGLT2 inhibitors.[1-3] In addition, hypoglycemia and volume depletion were uncommon.

Other observations are worth highlighting. First, the benefit was additive to background therapies for heart failure, although the baseline systolic blood pressure and heart rate suggested room for dose titration. Second, the magnitude of benefit was similar regardless of the presence or absence of type 2 diabetes. Third, the magnitude of benefit was similar to and reminiscent of the benefits of sacubitril–valsartan, an angiotensin-receptor neprilysin inhibitor, in the PARADIGM-HF trial.[5]

Although the overall results of DAPA-HF are compelling, several matters will require clarification. For example, almost all the patients had moderate heart failure, so the benefit and side-effect profile in patients with more severe heart failure will need further study. Furthermore, the background use of sacubitril–valsartan was limited (in approximately 10% of the patients), so definitive conclusions about the benefits and side effects associated with SGLT2 inhibition in com-

bination with sacubitril–valsartan remain unclear. Finally, data regarding the individual doses of background heart-failure therapies were not reported. Thus, the magnitude of benefit of SGLT2 inhibition might have been attenuated if the patients had been treated with higher doses of heart-failure medications. Multiple mechanisms for the benefit associated with dapagliflozin have and will be hypothesized[6] but cannot be defined from this trial.

Nonetheless, the results are important and impressive, especially since they substantiate observations from previous trials of SGLT2 inhibitors. Will clinicians incorporate this new class of heart-failure medications into their daily practice? That remains to be seen, since there are barriers to the use of additional drugs in patients with heart failure, despite the evidence of benefit.[7] Providers and patients are concerned about polypharmacy because of questions regarding the potential side effects of complex medical regimens, unanticipated drug interactions, and challenges with adherence. Furthermore, administrative hurdles and the cost of new medications present additional difficulties. Paradoxically, these various issues may create a risk–treatment mismatch, in which patients at greatest risk are those least likely to receive appropriate treatment.[8] Finally, medications that are used for the treatment of diabetes are complex and intimidating to many providers, particularly with the explosion of new drug classes for patients with diabetes and the multiple nuances to their use.

In the end, it is not a question of having too many medications for heart-failure therapy but rather of using these drugs at doses that have been shown to be effective. It behooves us as clinicians to learn more about using such newer agents effectively, but we have a long way to go. In 2014, the PARADIGM-HF trial showed the benefits of a combination of sacubitril and valsartan for heart failure with a reduced ejection fraction. In 2017, it was estimated that fewer than 15% of eligible patients were receiving that combination drug.[9] Will we be waiting until 2022 before SGLT2 inhibitors are used in 15% of eligible patients with heart failure with a reduced ejection fraction?

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

From the Division of Cardiovascular Medicine, University of Utah Health, Salt Lake City.

This editorial was published on September 19, 2019, at NEJM.org.

1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
3. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.
4. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. DOI: 10.1056/NEJMoa1911303.
5. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
6. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia 2018;61:2108-17.
7. Rankin A, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev 2018;9:CD008165.
8. Lee DS, Tu JV, Juurlink DN, et al. Risk-treatment mismatch in the pharmacotherapy of heart failure. JAMA 2005;294:1240-7.
9. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. J Am Coll Cardiol 2018;72:351-66.

DOI: 10.1056/NEJMe1912180