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PERSPECTIVE

Treating Heart Failure With Antihyperglycemic Medications

Is Now the Right Time?

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A transformation in diabetes mellitus care has occurred over the past several years in patients with cardiovascular disease. We have transitioned from a time of Food and Drug Administration–mandated trials executed primarily to prove that new drugs do not exacerbate cardiovascular disease risk, to the present era where we not only expect demonstration of cardiovascular safety, but also meaningful improvements in cardiovascular outcomes. Members of 2 categories of newer antihyperglycemic medications, the sodium glucose cotransporter 2 inhibitors (SGLT2-is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), now have a growing evidence base demonstrating precisely this. It is notable that 3 large SGLT2-i trial programs encompassing >28 000 patients have shown a consistent signal for reductions in hospitalizations for heart failure (HF) in patients with type 2 diabetes mellitus (T2DM) with prevalent or multiple risk factors for atherosclerotic cardiovascular disease. As a result, we now have evidence that SGLT2-is prevent HF hospitalization in patients with T2DM. This is a remarkable advancement in care, over just a span of 3 years, and has appropriately generated great optimism, and multiple large randomized clinical trials are now testing the hypothesis that these agents can also treat HF.

The American Diabetes Association and the European Association for the Study of Diabetes recently released a consensus report recommending that, after lifestyle interventions and metformin, patients with T2DM who have HF should be preferentially treated with SGLT2-is, and if that is not possible (eg, intolerance or an inadequate estimated glomerular filtration rate), a GLP-1 RA should be used.[1] In light of the strong and consistent signals for HF prevention with SGLT2-is, the first recommendation seems intuitive. If a patient with diabetes mellitus who has HF needs to start a new glucose-lowering therapy, why not have it be a drug that seems to specifically benefit HF? However, we should pause and ask whether now is the time to make these recommendations given the rapidly evolving evidential landscape.

First, are medicines that prevent HF reproducibly good treatments for preexisting HF? Unfortunately, not always. We have learned that prevention and treatment of HF are not one and the same. The most applicable example is the story of statins. Just like the SGLT2-i trials, in atherosclerotic cardiovascular disease populations, statins were frequently associated with a substantial reduction in HF events.[2,3] Also like the SGLT2-i trials, a similar benefit of statin therapy was often seen in the subgroups of patients with preexisting HF. However, when studied prospectively in the GISSI-HF (Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF) and the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trials of patients with HF with reduced ejection fraction (HFrEF), there was no benefit on time to death or first HF hospitalization.[2,3] It is notable that the CORONA trial only enrolled patients with ischemic HF, a group in

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which the benefit of statins would seem almost guaranteed.[3] Similarly, from the ALLHAT trial (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), a substantially greater reduction in HF events occurred with the thiazide-like diuretic, chlorthalidone, in comparison with the angiotensin-converting enzyme inhibitor, lisinopril.[4] Although the mechanisms for this observation remain debated, we certainly would not recommend chlorthalidone as first-line treatment for HF over angiotensin-converting enzyme inhibitors based solely on this prevention signal.

The American Diabetes Association/European Association for the Study of Diabetes recommendation for the use of GLP-1 RAs in patients with T2DM who have HF may be of even greater concern. Liraglutide is described by the American Diabetes Association/European Association for the Study of Diabetes document as the GLP-1 RA with the strongest cardiovascular benefit.[1] In the large diabetes mellitus cardiovascular safety trial of liraglutide, the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), there was technically no difference with regard to the improvement in the primary outcome (cardiovascular death, myocardial infarction, or stroke) between patients with and without baseline HF (*P* interaction=0.53).[1] However, the point estimate for benefit trended closer to unity for the relatively small subset of patients in the trial (n=1305/9340; ≈14%) who had preexisting HF (hazard ratio, 0.94; 95% CI, 0.72–1.21) in comparison with those without (hazard ratio, 0.85; 95% CI, 0.76–0.96). It is notable that the reduction in HF hospitalizations was not statistically significant in the LEADER trial or in any of the cardiovascular outcomes trials of GLP-1 RAs cited in the consensus report, with a trend toward increased hospitalization with semaglutide in the SUSTAIN 6 trial (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes).[1] Taken as a whole, the published data on HF prevention from large T2DM cardiovascular outcomes trials with GLP-1 RAs is substantially less compelling than that of the trials with SGLT2-is. However, with the GLP-1 RAs, we now have 2 small prospective HF treatment trials published, both of which demonstrated the lack of efficacy and perhaps concerning safety signals with liraglutide versus placebo in patients with HFrEF with or without T2DM.[1] In the LIVE trial (Effect of Liraglutide, a Glucagon-like Peptide-1 Analogue, on Left Ventricular Function in Stable Chronic Heart Failure Patients With and Without Diabetes; n=241), there was a statistically significant increase in cardiac adverse events, with the caveat that the event rate was low.[1] In the FIGHT trial (Functional Impact of GLP-1 for Heart Failure Treatment) (n=300), a trend toward harm was seen with liraglutide on 180-day outcomes such as death, rehospitalization, and emergency department visits, with several of these reaching borderline statistical significance.[1] It is notable that these adverse safety signals in FIGHT were no better in the subset of patients with T2DM, and, if anything, the point estimates suggested greater risk in that subgroup.[1] We would not propose that the available evidence requires us to recommend the avoidance of GLP-1 RA therapy in patients with HF, but we would certainly suggest that it should give us substantial pause before specifically recommending their use for the treatment of patients with HF who have T2DM, especially for HFrEF.

One could argue that the subgroups of patients with T2DM in the SGLT2-i trials who had HF at study entry (10%–15% of the overall study populations) provide sufficient evidence of a treatment benefit. First, we have learned time and time again to be cautious about subgroup analyses. Perhaps more importantly, the history of HF was largely an historical report in the SGLT2-i trials, with little information published to date on left ventricular ejection fraction, New York Heart Association class, natriuretic peptides, HF cause, and medication, to ensure that these patients actually had HF and, if so, how HFrEF and HF with preserved ejection fraction were distributed. This lack of detail is problematic beyond the treatment versus prevention argument, because it is well established that the benefit of pharmacotherapy is different in HF with preserved ejection fraction versus HFrEF. This is of critical importance because, if SGLT2-is are ineffective in either HF with preserved ejection fraction or HFrEF, treating all patients who have HF with these agents would unnecessarily expose roughly half them to increased cost, side effects, and potentially even harm. Of note, in a subanalysis of the DECLARE trial (Dapagliflozin Effect on Cardiovascular Events) comparing known HFrEF (n=671, 3.9% of the population) and HFpEF (n=808, 4.7%) at trial entry, there was heterogeneity in the effect of dapagliflozin on cardiovascular death (p interaction=0.01).[5] While there seemed to be a benefit in those with HFrEF (HR=0.55; 95% CI, 0.034–0.9), this was not observed in patients with HFpEF (HR=1.4; 95% CI, 0.93–2.1). Although we should be careful not to over-interpret post-hoc subgroup analyses from a trial, these trends underscore the need to wait for results of dedicated HF outcomes trials before recommending widespread use of these agents to treat HF.

In the end, we all remain highly optimistic that the HF prevention observations with SGLT2-is will translate into treatment benefit in HF. We are similarly optimistic that SGLT2-is may be the first class of medications that improves outcomes in all types of HF, independent of left ventricular function. We will soon have definitive data in this regard, with several dedicated HF treatment trials ongoing with SGLT2-is, with the first of the large outcomes trials expected to be complete as early as this year. These studies should answer the yet unresolved

question whether SGLT2-is will be effective to treat HF and, if so, which type. Widespread adoption of recommendations to preferentially use these medications in patients withT2DM who have HF may not only be premature, but may also threaten the completion and data fidelity of these trials (because of drop-in SGLT2-i use and early withdrawal from randomized treatment). As such, until definitive data are available, formally recommending the treatment of patients with both T2DM and HF with specific antihyperglycemic agents may be premature.

ARTICLE INFORMATION

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