Research digest: new horizons in heart failure therapy

When the concept of tackling type 2 diabetes with a drug that enhances urinary excretion of glucose was first mooted, many felt the idea was speculative; for years, doctors had been trying to lessen urinary glucose loss, not accentuate it. Undeterred, several companies pressed on with their development of sodium-glucose co-transporter-2 (SGLT2) inhibitors.

Fast forward to the present day and major trials have now shown unequivocally that, when given to patients with type 2 diabetes, this drug class lessens the chances of cardiovascular events and heart failure in patients with cardiovascular disease and, remarkably, also slows renal decline. The emergence of a diabetes drug with haemodynamic effects has resulted in closer interactions between diabetology and cardiology. The recent publication of the DAPA-HF trial—coinciding with its presentation at the Annual Meeting of the European Association for the Study of Diabetes (EASD) in Barcelona, Spain in September—will make cardiologists take further notice of this drug class.

DAPA-HF was a phase 3 trial in which 4744 patients with class II–IV reduced ejection fraction heart failure (HFrEF; 42% with diabetes) were randomly assigned to dapagliflozin 10 mg or matching placebo once daily. Both groups were well treated with drugs known to improve outcomes in HFrEF. After 18 months, dapagliflozin recipients had a 26% (95% CI 15–35, p<0·001) reduced risk of the primary outcome of worsening heart failure or cardiovascular death, as well as an impressive 17% (3–29) reduced risk of death from any cause. Previous studies have shown that SGLT2 inhibition in people without type 2 diabetes leads to urinary glucose excretion and reductions in blood pressure and bodyweight, but these changes are modest compared with effects in those with type 2 diabetes. Therefore, perhaps the most notable finding in DAPA-HF was that the primary outcome benefit was near identical in participants with and without type 2 diabetes. This finding should widen the trialling of these drugs—eg, to patients following a recent myocardial infarction who do not have diabetes. No new safety issues emerged in the trial, with no excesses of hypoglycaemia, fluid volume depletion, or renal dysfunction, and no cases of Fournier gangrene. The results were so impressive that when presented at the European Society of Cardiology (ESC) Congress in Paris, France in August, the audience spontaneously applauded, recognising arguably the biggest advance in the treatment of HFrEF since angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

An ideal heart failure drug would, in addition to lowering risk of adverse outcomes, improve symptoms and functional capacity. The DEFINE-HF trial—also presented at the EASD Annual Meeting—tested this possibility for SGLT2 inhibition in 263 patients with HFrEF, randomly assigning participants to the same treatment regimens as in DAPA-HF for 12 weeks. Dapagliflozin-treated patients had an 80% (95% CI 3–206%) greater chance of either a five-point improvement in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score or a reduction of at least 20% in N-terminal pro-B-type natriuretic peptide (dual primary outcome). Improvements in many KCCQ subdomains were also noted and, as in DAPA-HF, benefits were similar in patients with or without type 2 diabetes.

If the link between type 2 diabetes and HFrEF is strong, its link with preserved ejection fraction heart failure (HFpEF) is even stronger. HFpEF is now the most common form of heart failure, mortality rates remain high, and almost half of affected individuals have type 2 diabetes. Patients with type 2 diabetes and HFpEF have thicker left ventricles, higher B-type natriuretic peptide concentrations, more severe symptoms, and poorer outcomes than those with HFpEF but without diabetes. Unlike HFrEF, where incremental improvements in outcomes have been heralded in recent decades by landmark trials of

several drugs, HFpEF has largely resisted any similar trend. Trials of ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists have generally not shown clear benefit.

In the PARAGON-HF trial—also presented at the ESC Congress—investigators assessed whether treatment of patients with HFpEF with sacubitril–valsartan would improve outcomes compared with use of valsartan alone. The trial follows on from the PARADIGM-HF trial, in which sacubitril–valsartan proved clinically superior to enalapril in patients with HFrEF. Of 4882 participants in PARAGON-HF, 43% had diabetes at baseline. The primary outcome was a composite of total hospital admissions for heart failure and cardiovascular deaths. Over the average follow-up of 35 months, 1903 events occurred in 1083 participants, and those with diabetes again fared poorly, with a 60% higher event rate than in those without diabetes. Sacubitril–valsartan narrowly failed to show significant improvement in the primary outcome (rate ratio 0·87, 95% CI 0·75–1·01), but did improve heart failure symptoms and lower systolic blood pressure compared with valsartan alone. Even though the trial was negative in conventional statistical terms, it is notable that the comparator was not placebo but valsartan. It will be interesting to see how these mixed results are viewed in future guidelines. Whether SGLT2 inhibition has a role in treating HFpEF is now an even bigger question: ongoing trials (EMPEROR-Preserved [NCT03057951], DELIVER [NCT03619213]) should provide that answer in the next 2 years.

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For the PARAGON-HF trial see N Engl J Med 2019; published online Sept 1.
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