HEART FAILURE HIGHLIGHTS FROM THE 2019 ESC CONGRESS IN PARIS

MICHAEL BÖHM, MD**; YVONNE BEWARDER**, MD**; INGRID KINDERMANN**, MD**; JONATHAN SLAWIK**, MD**; CHRISTIAN WERNER**, MD**; JAN WINTRICH**, MD

Author affiliations: *Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg/Saar, Saarland University, Germany*
Address for correspondence: *Michael Böhm, MD, Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Saarland University, Kardiologie, Angiologie und Internistische Intensivmedizin, Kirrberger Str. 1, 66421 Homburg/Saar, Germany (email: michael.boehm@uks.eu)*

Heart failure is one of the most prevalent health care problems affecting high-risk patients, particularly elderly individuals not only in high-income, but also in middle- and low-income countries. Of these patients, 50% have a reduced ejection fraction (HFREF), while the other 50% have a preserved (HFPEF, EF ≥50%) or mildly reduced EF (mid-range EF, 40% to 49%) as defined by the European Society of Cardiology (ESC). At the ESC congress, two landmark studies in either of the two conditions were presented.

DIABETES: A COMORBIDITY FOR HEART FAILURE

Comorbidities affect the heart failure syndrome, thus strongly impairing outcomes and increasing health care costs. One comorbidity, among others, is diabetes mellitus. Diabetes is one of the most important and growing health care problems in middle-income countries, as well as in low-income countries. When diabetes is diagnosed between the ages of 40 and 50 years, about 6.2 lifetime years are lost due to diabetes in men and 6.8 lifetime years are lost in women. This not only relates to cardiovascular death, but also to cancer-related death and all-cause death.[1] Cardiovascular events are increased in diabetic patients compared with nondiabetic patients by about 30% to 60%. Controlling cardiovascular risk factors completely eliminates the effects of diabetes on acute myocardial infarction and stroke, but not on heart failure where, despite controlling the risk factors, a residual risk (hazard ratio [HR], 2.4; 95% CI, 16.3-3.54) remains in diabetic patients.[2]

All oral antidiabetic drugs have been the mainstay of diabetes mellitus therapy for many years. However, several antidiabetic drugs, such as those in the glitazone class, exhibited an increase in hospitalizations for heart failure (PROACTIVE [PROspective pioglitAzone Clinical Trial In macroVascular Events] and RECORD trial [Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes] trials). This led the FDA to mandate safety studies for all novel antidiabetic drugs. In 2015, the EMPA-REG-OUTCOME trial (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) was published as a designed safety study for the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin. There

was a reduction in the primary end point of cardiovascular death, myocardial infarction, and stroke, which was primarily carried by a reduction in cardiovascular death. However, as an exploratory end point, EMPA-REG OUTCOME showed a 35% reduction in hospitalizations for heart failure worsening, which was a very rapid effect that was stable over 48 months.[3] This data was then later supported by data from the CANVAS study (CANagliflozin cardioVascular Assessment Study), as well as data from the DECLARE study (Dapagliflozin Effect on CardiovascuLAR Events). It is notable that these data were generated in a diabetes population with only a few heart failure patients, which were not characterized in detail. The information on heart failure was only provided by the investigators from their medical history. However, recently, many potential mechanisms beneficially affecting myocardial function and myocardial outcomes have been identified, such as an increase in ketones, unloading of the heart by sodium and glucose excretion, weight loss, reduction in blood pressure, and protective effects on the kidney by inhibiting the tubuloglomerular reflex.

DAPA-HF TRIAL

The positive effects on heart failure hospitalization led to the hypothesis that SGLT2 inhibitors might be efficient in treating heart failure. Since the pharmacological effects, such as glucose and sodium excretion, also apply for nondiabetic patients, the hypothesis in the recently published DAPA-HF study (DAPAgliflozin on the incidence of worsening heart failure or cardiovascular death in patients with chronic Heart Failure) and other ongoing heart failure studies is testing whether the beneficial effects of SGLT2 inhibition on heart failure outcomes in heart failure patients also apply to patients without diabetes.

At the ESC-congress in Paris, data from the DAPA-HF study were presented. Dapagliflozin is an SGLT2 inhibitor that has shown beneficial effects in the DECLARE study for cardiovascular death and heart failure hospitalization, while the effects on vascular end points were neutral in a diabetes population with cardiovascular risk factors. In this placebo-controlled trial, 4744 patients were assigned either to dapagliflozin or to placebo on top of optimal medical treatment. The hypothesis of this trial was whether dapagliflozin reduces cardiovascular and heart failure–related outcomes in patients with or without diabetes and HFREF. Patients were screened and randomized to placebo or 10 mg of dapagliflozin. Individuals were evaluated 14 and 16 days after randomization, with follow-up visits at 4-month intervals thereafter. The primary outcome was the composite of worsening of heart failure or death from cardiovascular causes. Heart failure worsening was either an unplanned hospitalization for heart failure or an urgent visit resulting in intravenous therapy for heart failure. Secondary outcomes involved hospitalization for heart failure and cardiovascular death (the classic heart failure end point), as well as other outcomes, such as the total number of hospitalizations, recurrent

heart failure hospitalizations, and cardiovascular death, as well as improvements in the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores.[4] The trial was of high quality because only 2 patients out of 4744 randomized patients had an unknown vital status at the end of the study. A total of 386 patients (16.3%) in the dapagliflozin group and 502 patients (21.2%) in the placebo group reached the primary end point (HR, 0.74; 95% CI, 0.65-0.85; P<0.001). Components of the composite end point all favored the treatment effect of dapagliflozin with risk reductions of 22% to 25% for all secondary outcomes. In the nonadjusted forest plot, there was no interaction between any of the subgroups, particularly not between sex, age, previous heart failure hospitalization, etc. In DAPA-HF, patients were excellently pretreated with a majority of patients on optimal background, guideline-directed therapy. The results have been recently published.[5]

This trial showed that, in a specific heart failure population with reduced ejection fraction, dapagliflozin added on top of guideline-recommended therapies at high-intensity treatment, resulted in a significant reduction in heart failure outcomes. Interestingly, this effect was also similar in patients without diabetes. This study extends the armamentarium of heart failure treatment to a drug, which was initially developed to treat diabetes.

DAPA-HF showed add-on effects to guideline-directed therapies of dapagliflozin in patients with and without diabetes, showing that the myocardium in heart failure and in diabetes might exhibit similar metabolic problems, which can be addressed by SGLT2 inhibitors. Many attractive mechanisms have been discovered, which could potentially explain the effect of dapagliflozin. However, the role and importance of each individual mechanism, such as increasing ketones, affecting sodium/hydrogen cotransporters, or unloading the heart, remains to be elucidated. Nevertheless, the study extends not only the armamentarium of heart failure treatments, but also the physiological insights into heart failure. Many secondary analyses will elucidate specific effects, such as those on quality of life and renal outcomes. In the comments to the Paris congress, DAPA-HF was commented as one of the most influential studies that might affect clinical practice in the future. It gained great visibility and provided great hope in patients with heart failure.

TREATMENT OF HFPEF

Studies on HFPEF with renin-angiotensin system (RAS) inhibitors (I-PRESERVE [Irbesartan in heart failure with PRESERVEd systolic function], CHARM-Preserved [Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-patients with Preserved LV function], PEP-CHF [Perindopril in Elderly People with Chronic Heart Failure]), ivabradine (EDIFY), spironolactone (TOPCAT [Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist], mixed results!), as well as β-blockers (subanalysis from SENIORS [Study

of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure]) have obtained more or less neutral results. The sacubitril/valsartan combination blocks maladaptive remodeling by valsartan and accentuates adaptive responses by augmenting the effects of natriuretic peptides. In HFREF, the PARADIGM-HF study (Prospective comparison of Angiotensin Receptor–neprilysin inhibitor with an Angiotensin-converting enzyme inhibitor to Determine Impact on Global mortality and Morbidity in Heart Failure trial) demonstrated a 20% reduction in the composite end point of cardiovascular death and heart failure hospitalization, an effect that was homogeneous through all secondary exploratory end points as well throughout all subgroups.

PARAGON-HF TRIAL

Given the fact that there are no available treatments improving cardiovascular outcomes in patients with HFPEF and that the antihypertrophic effect of valsartan together with maladaptive and antihypertrophic effects of natriuretic peptides have been convincingly shown in experimental and observational studies, this background provides solid hypotheses to test the sacubitril/valsartan combination on clinical outcomes in patients with HFPEF.

The PARAGON-HF trial (Prospective comparison of ARNi with Arb Global Outcomes in heart failure with preserved ejectioN fraction) randomly assigned 4822 patients with ejection fractions of 45% or higher to either placebo or sacubitril/valsartan. The study aimed to investigate 894 primary events. The primary outcome was cardiovascular death and all heart failure hospitalizations. The active comparator was valsartan. The quality of the study was high because only 9 patients (4 on valsartan and 5 on sacubitril/valsartan) had an unknown vital status at the end of the trial.

Overall, the results were neutral. On sacubitril/valsartan, 894 primary events occurred in 526 patients and, on valsartan, 1009 primary events occurred in 557 patients (HF, 0.87; 95% CI, 0.75 to 1.01; *P*=0.06). Both drugs were well tolerated. For the secondary end points, there were no significant differences in KCCQ score changes, no differences in renal outcomes (low incidence), and no differences in all-cause-death (HR, 0.97; 95% CI, 0.84-1.13). The nonadjusted analysis of prespecified subgroups was a significant interaction between sexes with females having a benefit (HR, 0.73; 95% CI, 0.59-0.90), while there was no effect in males (HR, 1.03; 95% CI, 0.85-1.25). Furthermore, patients with a mildly reduced ejection fraction (eg, below the median ≤57%) showed a benefit, while at higher ejection fractions, sacubitril/valsartan (vs valsartan) had no effect (HR, 1.00). The data have been recently published.[6]

Overall, the results of PARAGON, comparing sacubitril/valsartan with valsartan, showed neutral results. However, the results were very tight. Evidence in prespec-

ified special populations, such as in females and in patients with mildly reduced ejection fraction, might provide information that a benefit might exist from neprilysin inhibition add-on to angiotensin antagonism, which could be prospectively studied. Although, in the discussions after the presentation of the PARAGON results, there was a trend by presenters, investigators, and sponsors to interpret PARAGON as a positive trial (only about 6 events were lacking on valsartan to receive a significant result), PARAGON should be considered as neutral. Similar trial results with nonsignificant trends have also been reported for PEP-CHF, which was underpowered and was prematurely interrupted due to problems in recruitment. However, PARAGON is important in showing subgroups and providing information to inform investigators and the medical community on special subgroups, in whom these drug interventions should be specifically investigated.

It is difficult to explain the differences in the results between PARADIGM-HF and PARAGON-HF.

1. In patients with HFREF, neprilysin activity (above and below the median) was associated with poor or favorable outcomes (cardiovascular death or heart failure hospitalization or cardiovascular death).[7] In contrast, in patients with HFPEF, circulating neprilysin activity does not correlate with outcomes in patients with HFPEF.[8] Therefore, there may be principal differences in the role of neprilysin in the pathophysiology of outcomes in HFPEF and HFREF.
2. PEP-CHF and potentially other studies, such as CHARM-Preserved, showed trends for a beneficial effect of RAS inhibition in patients with HFPEF. Notably, the comparator was not placebo, but valsartan. If valsartan has a slight, but nonsignificant, effect on outcomes, it could have diluted the effect of the outcome of sacubitril/valsartan.
3. PARAGON did not use the ESC classification of HFPEF (≥50%), but included patients with an ejection fraction >45%. Patients with mildly reduced EF (<50%) might benefit from the combination, which could explain the trends in the overall population. Here, further secondary analyses must be awaited.
4. Specific causes of HFPEF, such as amyloidosis, sarcoidosis, hemochromatosis, etc, were not excluded. Therefore, the treatment effect could also have been diluted by specific cardiac pathologies, which cannot be addressed by RAS inhibition combined with neprilysin inhibition.

Sacubitril/valsartan did not improve outcomes in an overall population with HFPEF. However, PARAGON showed subgroups that might benefit from this treatment. Prospective randomized trials in more specific populations are needed to scrutinize potential benefits in dedicated heart failure subgroups. There are many controversial discussions expected from this trial.

CONCLUSIONS

Two recent landmark trials have again provided positive trial results in patients with HFREF, but neutral data in patients with HFPEF. Nevertheless, DAPA-HF extends the treatment armamentarium in HFREF, but PARAGON, as a well-conducted large investigation, might provide clues to do the next trial in more specific HFPEF populations. ■

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