Recent Trials in Heart Failure

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Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Mcmurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995-2008.

Trial Summary

Background: Sodium–glucose cotransporter 2 (SGLT2) inhibitors have shown to reduce the risk of cardiovascular mortality and risk of a first hospitalization for heart failure (HF), in patients suffering from Type 2 diabetes mellitus (T2DM). However, data are insufficient regarding the effects of SGLT2 inhibitors in patients with established HF and reduced ejection fraction (HFrEF), regardless of the presence or absence of type 2 diabetes.

Methods: This was a phase 3, placebo-controlled trial, in which around 4700 patients with NYHA classes II, III or IV HF with a left ventricular ejection fraction ≤40%, N-terminal pro BNP ≥600 pg/ml were included. Those with eGFR <30 ml/min/m², symptomatic hypotension, systolic blood pressure <95 mmHg or type 1 diabetes were excluded. The included patients were randomly assigned to receive either dagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended optimal therapy. The primary outcome was a composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular death.

Results: Over a median follow-up of around 18 months,

- The primary outcome occurred in 386 (16.3%) of 2373 patients in the dapagliflozin group as compared to 502 (21.2%) of 2371 patients in the placebo group (hazard ratio: 0.74; 95% confidence interval [CI]: 0.65–0.85; P < 0.001) [Figure 1]
- A first worsening HF event occurred in 10.0% of the dapagliflozin group and in 13.7% in the placebo group (hazard ratio: 0.70; 95% CI: 0.59–0.83)
- Death from cardiovascular causes occurred in 227 (9.6%) patients in the dapagliflozin group and in 273 (11.5%) patients in the placebo group (hazard ratio: 0.82; 95% CI: 0.69–0.98)
- In the dapagliflozin group, the percentage of patients with ≥5 point improvement in the Kansas City Cardiomyopathy Questionnaire (KCCQ) was increased and the percentage of patients with ≥5 point deterioration was lowered compared to the placebo group [Figure 2]
- Findings in patients with diabetes were similar to those in patients without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.

Conclusions: Among patients with HFrEF, the risk of worsening HF or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes.

Perspective

The results of the landmark DAPA-HF trial demonstrated that the SGLT2 inhibitor dapagliflozin provides consistent benefit in patients with HF, both with and without Type 2 diabetes. Thus, we now have a drug with proven and compelling benefit for patients with HFrEF, regardless of glycemic status. Moreover, the safety profile of dapagliflozin was also good.

The benefits observed among diabetic patients were expected, given the strong signal of lower hospitalization for HF observed in the cardiovascular outcome trials with dapagliflozin (DECLARE-TIMI 58), canagliflozin (CANVAS 2017 and CREDANCE 2019), and empagliflozin (EMPA-REG 2015). However, the magnitude of the benefit was similar to other foundational HF therapies (RAAS inhibitors, beta-blocker, and cardiac resynchronization therapy). This was quite unexpected and will result in a change in current practice approaches.

However, the most exciting result of the study was that the benefit was consistent even in those patients without diabetes. Although being a glucose-lowering drug, it is now clear that the mechanism of benefit is independent of glucose lowering.

The DAPA-HF findings also align with those of DEFINE-HF trial. Although there was no reduction of mean NT-proBNP after 12 weeks of therapy, it increased the proportion of patients experiencing clinically meaningful improvements in HF-related health status, as assessed by the Kansas City Cardiomyopathy Questionnaire in patients with or without diabetes.

Over coming years, we will learn more from the other ongoing trials of SGLT2 inhibitors in patients with HF and reduced ejection fraction such as EMPEROR-Reduced and perhaps even more importantly, in patients with preserved ejection fraction EMPEROR-Preserved. In the meantime, the DAPA-HF results should be considered a milestone for optimization of therapy for patients with heart failure, with or without diabetes.

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ANGIOTENSIN–NEPRILYSIN INHIBITION IN HEART FAILURE WITH PRESERVED EJECTION FRACTION (PARAGON-HF)

Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med 2019;381:1609-20.

TRIAL SUMMARY

Background: Studies proving benefits of angiotensin receptor–neprilysin inhibitor (ARNI) and sacubitril–valsartan in patients with HFrEF which led to a reduced risk of hospitalization or death from cardiovascular causes are well documented. The effect of ARNI in patients with HF with preserved ejection fraction (HFpEF) is unclear.

Methods: In this study, around 4800 patients with NYHA Class II to IV HF, ejection fraction of ≥45%, elevated level of natriuretic peptides, and structural heart disease were randomly assigned to receive sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or valsartan alone (target dose, 160 mg twice daily). The primary outcome was a composite of total hospitalizations for HF and death from cardiovascular causes. Primary outcome components, secondary outcomes (including NYHA class change, worsening renal function, and change in KCCQ clinical summary score [scale, 0–100, with higher scores indicating fewer symptoms and physical limitations]), and safety were also assessed.

Results: The mean duration of follow-up was 39 months.

- There were 894 primary events in the sacubitril–valsartan group (526 patients) and 1009 primary events in the valsartan group (557 patients) (rate ratio: 0.85; 95% CI: 0.72–1.00)
- NYHA class improved in 15.0% of the patients in the sacubitril–valsartan group and in 12.6% of those in the valsartan group (odds ratio (OR): 1.45; 95% CI: 1.13–1.86)
- The mean change in the KCCQ clinical summary score at 8 months was 1.0 point (95% CI: 0.0–2.1) higher in the sacubitril–valsartan group
- NYHA class improved in 15.0% of the patients in the sacubitril–valsartan group and in 12.6% of those in the valsartan group (odds ratio (OR): 1.45; 95% CI: 1.13–1.86)
- There were 690 and 797 total hospitalizations for HF, respectively, in the ARNI and valsartan groups (rate ratio: 0.85; 95% CI: 0.72–1.00)
- NYHA class improved in 15.0% of the patients in the sacubitril–valsartan group and in 12.6% of those in the valsartan group (odds ratio (OR): 1.45; 95% CI: 1.13–1.86)

Conclusions: Sacubitril–valsartan did not result in a significantly lower rate of total hospitalizations for HF and death from cardiovascular causes among patients with HF and an ejection fraction of ≥45%.

PERSPECTIVE

Although the desire for an evidence-based drug therapy for HFpEF was not fulfilled once again by the results of the PARAGON-HF trial, which did not show any significant advantage of sacubitril/valsartan for its primary clinical outcome, the data did suggest benefit in some patient groups.

Since HFpEF is not just heterogeneous with respect to phenotype, but also heterogeneous with respect to treatment with potential benefit in certain groups, such as women and patients with an ejection fraction below the median, i.e., patients with HF with ejection fraction in the 41%–49% range, it was evident that “one size might not fit all” in HFpEF.

However, the subgroup analyses are truly exploratory and are insufficient to drive clinical practice.

Investigational efforts for HFpEF should be to evaluate an “approach,” and not a therapy. It is the heterogeneity that must be dissected now, before therapy can be determined, with exploring specific therapies for specific HFpEF phenotypes,
rather than broad-spectrum approach with HFpEF defined only by left ventricular ejection fraction (LVEF) value.

**Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients with Heart Failure with Reduced Ejection Fraction**

Michael E. DEFINE-HF Investigators. Circulation. Circulation 2019;140:1463-76.

**Trial Summary**

**Background:** Three large cardiovascular outcome trials, and one kidney outcome trial, all conducted in patients with T2DM at increased cardiovascular risk, have demonstrated robust and consistent reductions in the risk of hospitalization for HF with three different agents in the SGLT-2i class. However, majority of patients in these trials did not have established HF with left ventricular dysfunction. Hence, this trial was designed to test the hypothesis that treatment with the SGLT-2i dapagliflozin will improve natriuretic peptides and health status in well-phenotyped and optimally treated HFrEF patients, both with and without T2DM.

**Methods:** DEFINE-HF was an investigator-initiated, multicenter, randomized controlled trial of HF patients with left ventricular ejection fraction ≤40%, NYHA Class II–III, eGFR rate ≥30 mL/min/1.73 m², and elevated natriuretic peptides.

In total, 263 patients were randomized to dapagliflozin 10 mg daily or placebo for 12 weeks. Dual primary outcomes were (1) mean NT-proBNP and (2) proportion of patients with ≥5-point increase in HF disease-specific health status on the KCCQ overall summary score or a ≥20% decrease in NT-proBNP.

**Results:** In the median follow up of 12 weeks,

- A total of 263 qualified for the trial and were subsequently randomized: 131 to dapagliflozin and 132 to placebo
- There was no significant difference in the average 6- and 12-week adjusted NT-proBNP with dapagliflozin versus placebo (1133 pg/dL [95% CI: 1036–1238] vs. 1191 pg/dL [95% CI: 1089–1304]; P = 0.43)
- In terms of a meaningful improvement in KCCQ, dapagliflozin-treated patients met this endpoint
- This was attributable to both higher proportions of patients with ≥5-point improvement in KCCQ overall summary score (42.9% vs. 32.5%, adjusted OR: 1.73, 95% CI: 0.98–3.05) and ≥20% reduction in NT-proBNP (44.0% vs. 29.4%, adjusted OR: 1.9, 95% CI: 1.1–3.3) by 12 weeks
- The results were consistent among patients with or without T2DM and other prespecified subgroups (all P values for interaction = nonsignificant).

**Conclusions:** In patients with HF and reduced ejection fraction on optimum medical therapy, use of dapagliflozin over 12 weeks did not affect mean NT-proBNP, but increased the proportion of patients experiencing clinically meaningful improvements in HF-related symptoms or natriuretic peptides. Benefits of dapagliflozin on clinically meaningful HF measures appear to extend to patients without T2DM.

**Perspective**

Once again, the antidiabetic drug dapagliflozin showed that the term “antidiabetic drug” does not really capture all that it might have to offer.

In this randomized trial in patients with HFrEF, the patients on dapagliflozin showed fewer symptoms and an improved quality of life within the first 12 weeks of initiation of therapy.

On the other hand, levels of the biomarker NT-proBNP did not fall significantly in those taking the drug compared with its placebo, although the proportion of patients whose NT-pro BNP decreased by at least 20% was greater in the dapagliflozin group, even if the overall average was not. This suggests that the principal mechanism is still not clear. It is though evident that fluid depletion is not the reason for benefit in these patients.

The DAPA-HF results show significant morbidity and mortality benefit with dapagliflozin in patients with HFrEF, and the DEFINE-HF results show improved KCCQ score, complementing the DAPA-HF results that the patients not only live longer but with better health status. The KCCQ results were not only positive in a relatively short timeframe, but also at a very meaningful level.

Over the coming years, we will learn more from the other ongoing trials of SGLT-2 inhibitors in patients with heart failure and reduced LVEF and perhaps even more importantly in patients with preserved LVEF. In the meantime, the DAPA-HF and DEFINE-HF results should challenge us to change our practice and optimize therapy for patients with HF (with or without Type-2 diabetes).

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Nil.

**Conflicts of interest**

There are no conflicts of interest.