Title: Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF)

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Key Points:

This phase 3, placebo-controlled trial, conducted on 4744 patients with a primary outcome of a composite of worsening heart failure or cardiovascular death in patients receiving dapagliflozin 10 mg once daily, versus placebo. There a many large clinical trial describing the effectiveness of Sodium-Glucose Cotransporter 2 (SGLT-2) inhibitors at reducing the risk of hospitalisation in heart failure patients in type 2 diabetes; such as the EMPA-REG OUTCOME trial.1 This study was conducted to establish if similar results were achieved in non-diabetic patients.

Patient Selection:

At least 18 years old and, a New York Heart Association Class II, III or IV and, ejection fraction of less than or equal to 40% and, N-terminal pro–B-type natriuretic peptide (NT-proBNP) of at least 600 pg per mil- liliter (or ≥400 pg per milliliter if they had been hospitalized for heart failure within the previous 12 months).

The patients were randomly assigned placebo or dapagliflozin. Kaplan–Meier estimates and Cox proportional-hazards models were used to evaluate time-to-event data and calculate the hazard ratio.

There is a 26% relative reduction in the primary outcome, defined as worsening heart failure, in patients receiving dapagliflozin versus placebo over a median follow up period of 18.2 months. There is also a 30% relative reduction in hospitalisations for heart failure, 18% relative reduction in death from cardiovascular causes and 17% relative reduction in death from any cause; demonstrated in the group taking dapagliflozin.

Conclusion:

Dapagliflozin had a lower risk of worsening heart failure or death from cardiovascular causes, regardless of a diagnosis of diabetes.

Limitations:

Rates of important adverse effects, such as genitourinary infections were not reported in this study. Patients with mild or moderate heart failure were included in this study; thus further investigation of those with severe heart failure is required.

Interpretation:

This is a landmark trial that will influence our clinical practice of heart failure management. The benefits of dapagliflozin were seen in patients on optimal heart failure therapy; loop diuretics and mineralocorticoid receptor antagonists. It mimics the benefit of sacubitiril/valsartan in the PARADIGM-HF trial. The outcomes of this trial will lead to increased quality of life for patients; as well as a cost benefit reduction in hospitalisation and worsening of disease. It has an impact on both cardiologists and diabetologists. The EMPORER-reduced trial is near completion and will give us insight on SGLT2 efficacy in patients with more severe heart failure.

References:

Zinman B, Wanner C, Lachin J, Fitchett D, Bluhmki E, Hantel S et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New England Journal of Medicine. 2015;373(22):2117-2128.

McMurray J, Packer M, Desai A, Gong J, Lefkowitz M, Rizkala A et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. New England Journal of Medicine. 2014;371(11):993-1004.

Packer M. Lessons learned from the DAPA-HF trial concerning the mechanisms of benefit of SGLT2 inhibitors on heart failure events in the context of other large-scale trials nearing completion. Cardiovascular Diabetology. 2019;18(1).

McMurray J, Solomon S, Docherty K, Jhund P. The Dapagliflozin And Prevention of Adverse outcomes in Heart Failure trial (DAPA-HF) in context. European Heart Journal. 2020;.

Seferović P, Coats A, Ponikowski P, Filippatos G, Huelsmann M, Jhund P et al. European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. European Journal of Heart Failure. 2019;.