DIABETES

Dapagliflozin DECLAREd safe

The sodium–glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin is safe and does not increase the rate of adverse cardiovascular events in patients with type 2 diabetes mellitus, according to the results of the DECLARE–TIMI 58 trial presented at the AHA Scientific Sessions 2018. The findings are consistent with those from previous trials on canagliflozin and empagliflozin.

A total of 17,160 patients with diabetes (40.6% with established atherosclerotic cardiovascular disease and 59.4% with multiple cardiovascular risk factors) were randomly assigned to receive dapagliflozin or placebo and followed up for a median of 4.2 years. Dapagliflozin was noninferior to placebo for the occurrence of major adverse cardiovascular events (MACE; defined as cardiovascular death, myocardial infarction or ischaemic stroke), which was the primary safety outcome. For the co-primary efficacy outcomes, dapagliflozin did not reduce the rate of MACE compared with placebo (8.8% versus 9.4%) but did reduce the rate of cardiovascular death or hospitalization for heart failure (4.9% versus 5.8%; HR 0.83, 95% CI 0.73–0.95, $P = 0.005$), mainly driven by a significantly lower rate of hospitalization for heart failure (HR 0.73, 95% CI 0.61–0.88). The rate of renal events was 4.3% with dapagliflozin and 5.6% with placebo (HR 0.76, 95% CI 0.67–0.87).

Collectively, SGLT2 inhibitors seem to have more robust and consistent effects on prevention of heart failure and renal outcomes than on atherosclerotic events, which is consistent with their mechanism of action in the kidneys and promotion of glycosuria.

"Current international guidelines for the management of diabetes have focused on the use of SGLT2 inhibitors in patients with atherosclerotic cardiovascular disease," comment the authors. "These new data suggest that in patients without established atherosclerotic cardiovascular disease, SGLT2 inhibitors can prevent serious clinical events, particularly hospitalization for heart failure."

Gregory B. Lim

ORIGINAL ARTICLE Wiviott, S. D. et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1812389 (2018)
FURTHER READING Nassif, M. & Kosiborod, M. Effect of glucose-lowering therapies on heart failure. *Nat. Rev. Cardiol.* **15**, 282–291 (2018)

HEART FAILURE

A new link for heart failure and diabetes

Diabetes mellitus increases the risk of heart failure, but the mechanisms underlying this relationship are unclear. New research shows that, compared with muscle from nonfailing hearts, the heart muscle from patients with heart failure and diabetes has increased levels of post-translational modifications induced by the glycolysis by-product methylglyoxal (MG). "We further showed that MG modifications depress the function of the molecular motors of the heart, which could explain the increased risk of heart failure in patients with diabetes," says lead investigator Jonathan Kirk.

Kirk and colleagues examined left ventricular samples of explanted and rejected donor hearts and found higher levels of MG modifications of the myofilaments in patients with diabetes and heart failure than in patients with nonfailing hearts or with heart failure but without diabetes. Ex vivo exposure to pathological MG levels reduced contractility and Ca^{2+} sensitivity in nonfailing cardiomyocytes from humans or mice, but cardiomyocytes from patients with diabetes were resistant to functional changes from MG treatment, suggesting that these cells had already been exposed to MG in vivo. Proteomic analysis of samples from patients with diabetes and heart failure and from MG-treated mice showed increased MG modifications on the myofilament proteins actin and myosin, but not on the thin-filament regulatory proteins tropomyosin and troponin complex. MG modifications on actin and myosin independently depressed thin-filament regulation, and the functional effects required the presence of Ca^{2+}-regulated thin-filament proteins.

These findings highlight the potential of MG modifications as a therapeutic target to prevent or ameliorate heart failure in patients with diabetes. "Although MG modifications are irreversible, the myofilament is a highly tunable system," notes Kirk. "We are interested in determining whether the detrimental effects of the MG modifications in patients with diabetes could be reversed using existing small molecules," he adds.

Irene Fernández-Ruiz

ORIGINAL ARTICLE Papadaki, M. et al. Diabetes with heart failure increases methylglyoxal modifications in the sarcomere, which inhibit function. *JCI Insight* https://doi.org/10.1172/jci.insight.121264 (2018)

HEART FAILURE

Safety and efficacy of sacubitril–valsartan in acute heart failure

In patients with acute decompensated heart failure (HF), treatment with the angiotensin receptor–neprilysin inhibitor sacubitril–valsartan is safe and results in greater reduction in the plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) than treatment with the angiotensin-converting enzyme inhibitor enalapril. These results from the PIONEER-HF trial, presented at the AHA Scientific Sessions 2018, support the in-hospital initiation of sacubitril–valsartan therapy in patients with acute HF.

In 2015, the FDA approved the use of sacubitril–valsartan for the treatment of patients with chronic HF, after data from the PARADIGM-HF trial showed that this therapy led to greater reductions in cardiovascular deaths and HF-related hospitalizations in these patients than enalapril therapy. Patients with acute HF were excluded from the PARADIGM-HF trial, and the multicentre, double-blind PIONEER-HF trial was designed to investigate the effects of the drug in the context of acute HF.

A total of 881 patients who were hospitalized for acute decompensated HF were randomly assigned after haemodynamic stabilization to receive sacubitril–valsartan or enalapril. The primary efficacy outcome, defined as the time-averaged change in plasma levels of NT-proBNP from baseline to weeks 4 and 8, was −46.7% in the sacubitril–valsartan group and −25.3% in the enalapril group (HR 0.71, 95% CI 0.63–0.81; $P < 0.001$). Safety outcomes, such as rates of worsening renal function or hyperkalaemia, were similar between the two groups.

These results extend the findings of the PARADIGM-HF trial to an inpatient setting. However, NT-proBNP levels were used as a surrogate; therefore, a trial to confirm the effect of the drug on cardiovascular outcomes is warranted.

Alexandra Le Bras

ORIGINAL ARTICLE Velazquez, E. J. et al. Angiotensin–neprilysin inhibition in acute decompensated heart failure. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1812851 (2018)