Meeting Impression

ESC Heart Failure Congress 2016, May 21, 2016, Florence, Italy

DIABETES & HEART FAILURE: EVALUATING NOVEL STRATEGIES TO ADDRESS OUTCOMES

During the ESC Heart Failure Congress 2016, held in Florence, Italy, the Physicians' Academy for Cardiovascular Education (PACE) organised a satellite symposium on diabetes and heart failure, two debilitating diseases, that aggravate each other when they co-exist. During the symposium, current treatment options of diabetes in heart failure were discussed. The results of recent trials with SGLT2 inhibitors were summarised, and potential mechanisms of the observed clinical benefit were considered.

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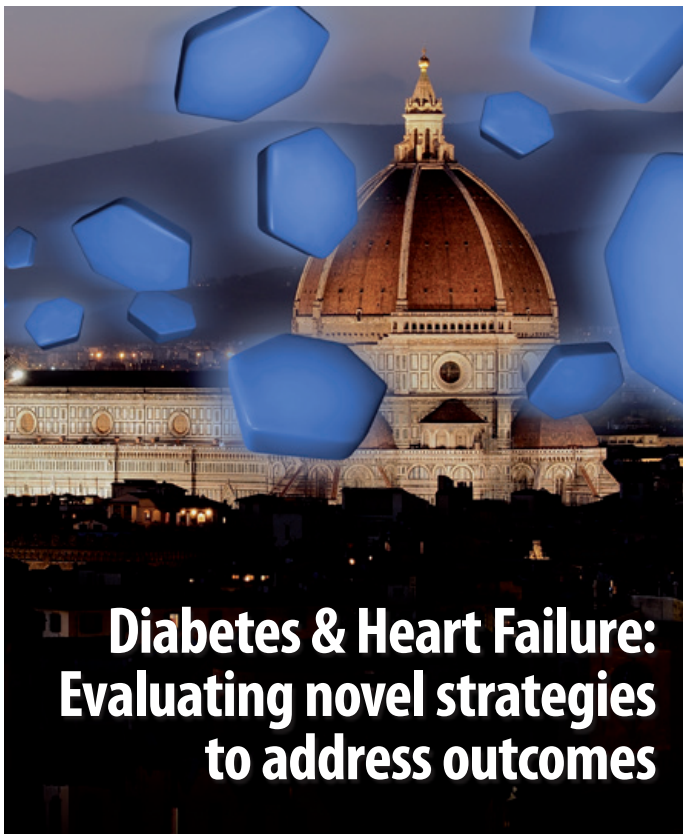

Current treatment of diabetes in heart failure

Adriaan Voors, MD – *University Medical Center Groningen, Groningen, The Netherlands*

The number of acute and chronic HF patients with diabetes (DM) increased tremendously over the last decade. The prevalence of DM in these patients now ranges between 13 and 47% and is even higher in HF patients with preserved ejection fraction (25-33%). Both diseases are deleterious, and prognosis is even worse when the two co-exist. 'Diabetes and heart failure are fatal twins', states professor Voors.

Medication that reduces glucose and haemoglobulin A1c (HbA1c) levels may have devastating effects on heart function. Both too loose and too strict control of HbA1c may be harmful, as a U-shaped relation has been reported between death and Hb1Ac level upon antidiabetic treatment[1]. It is therefore crucial to define and select the most optimal drug and dose. Prof. Voors provided an overview of currently available antidiabetic drugs, their effect on HF and current guideline recommendations on treatment.

'Diabetes and heart failure are fatal twins'

First, clinical data were presented that demonstrated the inferior prognosis for DM patients with advanced HF and who were treated with insulin compared to those that did not get insulin[2]. However, Voors noted that these data may be biased, as insulin-treated patients generally have more severe DM. Nevertheless, the CHARM trial[3] supports the potential harmful effects of insulin, since insulin-treated DM was the third strongest predictive factor of all-cause mortality in a wide variety of HF patients.

Second, the relation of antidiabetic sulfonylureas to HF was discussed. A direct interaction has not been studied, however it has been shown that sulfonylurea-treated

patients experienced HF more frequently compared to patients treated with the antidiabetic metformin[4].

Metformin has been investigated in quite a number of studies, including two meta-analyses of several antidiabetic drugs. These data demonstrated that metformin was actually the only drug that did not show any harm and was even suggested to be beneficial for HF patients[5, 6].

In contrast, a meta-analysis with various antidiabetic thiazolidinediones (TZDs) in prediabetic and diabetic patients showed an increased risk of congestive HF and cardiovascular (CV) death in almost all studies[7]. Therefore, the FDA officially warns for treatment with TZDs in DM patients with increased risk of HF: it is discouraged and should be handled with care.

At last, the effect of GLP-1 receptor antagonists and DPP-4 inhibitors on HF were discussed, but strong evidence is currently lacking. GLP-1 analogues may increase the risk of CV events and worsening HF[8], but the 2016 ESC HF guidelines state that no safety data in HF is available. Saxagliptin showed a significant increase in HF hospitalisation in the SAVOR-TIMI 53 trial, but this was not confirmed for other DPP-4 inhibitors[9].

Voors concluded that metformin is the antidiabetic treatment of choice in patients with HF, although it cannot be used in all DM patients. All other drugs either worsen HF, should be used with caution or are even discouraged, or lack data that ensure its safety.

SGLT2 inhibition and cardiovascular outcomes: lessons from recent clinical trials

David Fitchett, MD – *University of Toronto, Toronto, ONT, Canada*

Sodium-glucose co-transporter 2 (SGLT2) is a glucose transporter and SGLT2 inhibitors can improve glycaemic control. They block kidney reabsorption of filtered glucose and thereby reduce blood glucose levels. So far, only one clinical trial evaluating SGLT2 inhibitor results on CV outcome has been published[10]. This trial is called the EMPA REG OUTCOME trial in which empagliflozin is evaluated. Two other trials investigating the SGLT2 inhibitors canagliflozin (CANVAS) and dapagliflozin (DECLARE-TIMI) are currently ongoing.

EMPA REG OUTCOME is the first diabetes trial that shows a positive outcome in the primary endpoint: triple MACE including CV death, non-fatal myocardial infarct (MI) and non-fatal stroke. It is a double blind randomised placebo-controlled trial with the aim to examine the long-term effects of empagliflozin versus placebo, in addition to standard of care treatment in type 2 diabetes patients with a high CV risk. In this trial, patients received standard of care and were, on top of that, treated with either placebo (n=2333), empagliflozin 10 mg (n=2345) or empagliflozin 25 mg (n=2342). The trial was ended when 691 patients experienced triple MACE. This resulted in a median on-treatment time of 2.6 years and observation time of 3.2 years. At the end of the study, 99% of patients were still alive.

At baseline, median age was 63.1 years, 72% were male and a bit less than half of the patients were current or ex-smoker. Fifty-seven percent of patients had diabetes for more than 10 years and over a quarter had chronic kidney disease. Patients were at a high risk of CV events of which 75% had coronary disease, including 10.5% with heart failure. For this, patients were well-treated with CV and/or antidiabetic medicine.

In EMPA REG OUTCOME, a 14% reduction of the primary triple MACE outcome was seen in HF patients treated with empagliflozin, as compared with those on placebo

Results of this trial showed a drop of 0.7% in HbA1c in patients treated with empagliflozin during the first 12 weeks. After these first weeks, investigators were allowed to adjust glycaemic medication. This resulted in a final HbA1c decrease of 0.24%, which was insufficient to reach the local target. Also the systolic and diastolic blood pressure (BP) dropped during these first weeks (4 mmHg systolic) which was sustained throughout the study. A similar pattern was observed for weight (reduction of 4 kg), whereas the haematocrit increased (3-4%).

There was a 14% reduction of the primary triple MACE outcome for patients treated with empagliflozin as compared with placebo (HR 0.86; 95% CI: 0.74-0.99, P=0.0382), which was already observed during the first months of the study. This result was driven by a 38% reduction in CV death (HR 0.62; 95% CI: 0.49-0.77, P<0.0001). This effect is noticeable early during the trial, but since the curves further separated throughout the trial, this suggests an ongoing benefit. Subgroup analysis showed that older patients (≥65 yrs), males, Asian people, patients with a low HbA1c, body mass or average renal function (eGFR 60-90 mL/min) have a non-statistical increased benefit regarding CV death probabilities. The type of CV deaths that most significantly reduced, were sudden death (28%) and unexplained CV deaths (40%). Contribution of MI or stroke (16%), worsening HF (14%) or cardiogenic shock was only modest (2%). Furthermore, all-cause mortality was significantly reduced

by 32%, with CV death accounting for about two third of the reduction.

Regarding HF outcome specifically, HF hospitalisation (hHF), hHF or CV mortality, investigator-reported HF, hHF or HF mortality, and the introduction of loop diuretics as a surrogate for acute HF, were investigated in the trial. hHF (HR 0.65; 95% CI: 0.50-0.85, P=0.0017) as well as hHF/CV mortality (HR 0.66; 95% CI:0.55-0.79, P<0.001) and hHF or HF mortality (HR 0.61; 95% CI: 0.47-0.79, P=0.002) in empagliflozin-treated patients were persistently reduced throughout the study. No difference in treatment benefit was seen in investigator-reported HF and serious HF. The reduction of hHF/CV mortality between empagliflozin- and placebo-treated patients was similar for patients with or without prior HF at baseline. Furthermore, there was no difference in risk for CV mortality nor for risk of hHF observed, between patients taking loop diuretic at baseline and those who did not. HHF patients had a high risk of mortality: the placebo group showed almost 24.2% of CV mortality and 30.5% all-cause mortality, which was non-significantly reduced by empagliflozin treatment to 14.3% and 21.4% respectively.

No serious adverse events were reported. The frequency of most events was not increased by empagliflozin, however candida infections were relatively more common in empagliflozin-treated patients (6.8% with 10 mg, 6.8% with 25 mg versus 1.8% with placebo). Interestingly, the incidence of acute kidney injury was lower in empagliflozin-treated patients (5.2% in 10 mg, 5.3% in 25 mg versus 6.6% in placebo).

Altogether, during 3 years of treatment this reflects a benefit of 25 lives and 14 fewer hHFs, but at the costs of 53 additional genital infections, per 1000 DM patients who are at increased risk for CV disease. The number needed-to-treat was 39 patients, which is consistent with other preventive CV medications. Thus in the EMPA REG OUTCOME trial with high-risk DM patients, empagliflozin treatment was associated with a large early mortality benefit and reduced frequency of hospitalisations. The treatment benefit was consistent with both doses and not associated with serious events.

Heart failure and SGLT2 inhibition: understanding the mechanism for potential benefit

Naveed Sattar, MD – *Glasgow University, Glasgow, United Kingdom*

As shown in the previous talk, the treatment reduction of CV death by the SGLT2 inhibitor empagliflozin was significant and this occurred almost immediately after the start of therapy. These findings were very unexpected, according to Professor Sattar. In his presentation, he explained the thoughts about the proposed mechanism of action of empagliflozin before, and after the EMPA REG trial (10).

SGLT2 inhibitors were known to lower BP and arterial stiffness and to reduce sympatic nervous system activity, albuminuria, weight, visceral adiposity, oxidative stress, triglyceride, HDL and LDL levels, uric acid and most importantly, glucose and insulin levels. However, previously nothing was known about the haemodynamic benefits of empagliflozin. So what makes empagliflozin superior to other SGLT2 inhibitors regarding CV mortality reduction?

According to Sattar, this cannot be explained by the drop in haemoglobulin A1c levels, as this was comparable with that seen in other trials with SGLT2 inhibitors. Furthermore, it probably was neither a result of glucose reduction nor an effect of any other known associated mechanism. Furthermore, it does not look like an athero-thrombotic benefit, since there were no clear benefits observed for MI and stroke. In contrast, the pattern of change in HF and CV death by empagliflozin suggests an effect on the vascular system. Cardiac pre- and afterload may be reduced and renal function may be affected, which can thereby reduce extracellular fluid volume and cardiac pre-load. Moreover, it may effect cardiac metabolism such that the systolic and diastolic function are enhanced.

The observed CV benefit of empagliflozin is not just a diuretic effect

More specifically, it is postulated that empagliflozin has a renal effect that improves hemodynamic factors and will then have a secondary benefit on the heart. This is proposed as follows: as SGLT2 inhibitors will block the reabsorption of glucose by the renal glomeruli, also sodium reabsorption will become blocked. Herein, glucose and sodium blood levels are lowered but sodium delivery is increased in the macula densa. In turn, this results in urinary excretion. Besides excretion, this also leads to restoration of the tubuloglomerular feedback and subsequent afferent arteriole constriction. In diabetic patients, this normalises pressure in the glomeruli as well as the glomerular filtration rate.

However, regarding heart function, enhanced urinary excretion may decrease intravascular and extracellular fluid volume. This is indeed true as increased haematocrit values and reduced systolic blood pressures were observed during the EMPA REG OUTCOME trial. The consequences of decreased fluid volumes are a reduced cardiac pre- and afterload, increased myocardial oxygen supply and perhaps

still unknown improved cardiac mechanisms. Also a reduced heart stress will improve systolic and diastolic dysfunction, and the likelihood of pulmonary congestion is reduced. Less cardiac stretch may lower the risk of fatal arrhythmic death. Remarkably, many risk factors of diabetic patients are associated with increase in body fluid and may thereby particularly increase the risk for HF.

The observed beneficial effect of empagliflozin is not just a diuretic effect. For example, the diuretic furosemide increases distal tubular sodium concentrations and will not normalise proximal tubular sodium reabsorption and thereby arterial constriction. BP reduction itself can also contribute to risk reduction of HF. Studies have shown that even a modest reduction in BP can yield quite a reduction in HF. In the SPRINT trial[11], in which diuretics were used, BP was strongly decreased and the frequency of HF was reduced. However, in the EMPA REG trial, BP-lowering was not as substantial. This means that BP itself reduces HF risk, but that this only partly explains the decreased risk of HF observed in the EMPA REG trial.

To conclude, the CV benefit of empagliflozin is probably predominantly due to its haemodynamic effects. However, it is not just a diuretic result but reduced glucose levels, weight loss and a better renal function probably also contribute to the treatment benefits.

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