ESC Heart Failure 2017 Congress, May 1, 2017 - Paris, France

HEART FAILURE, DIABETES, AND RENAL DYSFUNCTION: TIME FOR A MORE UNIFIED APPROACH

This lunch symposium held during ESC Heart Failure 2017 explored mechanisms and common pathways underlying the development of cardiovascular disease (CVD) and heart failure (HF) and the particular risk of patients with diabetes. Innovation in the field of HF management is ongoing. This has yielded several new agents in recent years, which are likely to change clinical practice. The role of anti-diabetic therapy, in particular the use of SGLT2 inhibitors, was discussed in the context of a risk-based intervention strategy that targets glucose control and CV risk factors.

Prof. **Adriaan Voors** (UMCG, Groningen, The Netherlands) gave an introduction to the topic, by pointing out that globally, an estimated 422 million adults are living with diabetes (WHO 2016). Projections predict this number to almost double by 2030. It is relevant to discuss diabetes at a HF congress, since diabetes is a risk factor for new-onset HF.[1]

In registries of patients with HF, the prevalence of diabetes varies between 13 and 47%. Interestingly, over a 10-year period, the percentage of patients with diabetes who were included in HF trials increased. Prognosis is worse in HF patients with diabetes, as compared with those without.

In the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[2], the following is stated with regard to anti-diabetic drugs: Insulin 'may exacerbate fluid retention, leading to HF worsening', sulphonylureas 'should be used with caution', metformin 'treatment of choice in patients with HF', thiazolidinediones 'not recommended', GLP-1 inhibitors and DPP-4 inhibitors: 'no safety data in HF' and SGLT2 inhibitor 'empagliflozin reduced risk of HF hospitalization'.

Challenges in Heart Failure management: Diabetes and Renal Impairment

Prof. Martin Cowie – *Imperial College London, United Kingdom*

Patients with HF, diabetes and renal dysfunction are commonly seen in clinical practice, but it remains a challenge to accurately diagnose a patient and to select the best therapeutic option. Moreover, it remains challenging to improve outcomes for patients. Knowing epidemiological data and what is known of risk factors, can help.

At first presentation of heart failure, almost 40% of patients have impaired renal function

Prof. Cowie therefore showed the course of serum creatinine levels over time in a 'typical' chronic HF patient, who is treated with an ACE-inhibitor, a beta-blocker and an MRA. Over the years, creatinine was relatively stable, while eGFR was relatively reduced (51 ml/min/1.73m²). A peak in serum creatinine was observed when the patient was admitted for IV diuretics. Volume depletion led to another admission for IV diuretics, which was accompanied by a drop in eGFR to severely impaired renal function (eGFR 20 ml/min/1.73m²). Treatment with the aldosterone antagonist had to be stopped. This patient thereby illustrates the complex interplay of what you would like to do for HF, complicated by co-existing comorbidities, such as renal dysfunction.

It has been shown that even at first presentation of HF, almost 40% of patients have impaired renal function (creatinine >125 µmol/L), and 20% even show severe impairment (>150 µmol/L).[3] The creatinine level at presentation affects the disease trajectory thereafter, with significantly better survival in HF with preserved ejection fraction (HFpEF) with <113 µmol/L as compared with those with ≥113 µmol/L (the median at presentation).[3]

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A prospective study in European patients with HF with reduced ejection fraction (HFrEF) showed that 29% of patients developed worsening HF (WHF, rise in serum creatinine by at least 26 µmol/L) during admission.[4] Baseline serum creatinine, pulmonary edema on chest X-ray and history of atrial fibrillation were factors independently associated with risk of WHF. WHF prolonged length of hospital stay, but did not affect mortality.

The MAGGIC meta-analysis revealed that in HFrEF, as renal function gets worse (lower eGFR), this negatively impacts mortality. In HFpEF, this relationship is less clear, since it is a much more heterogeneous patient group, often displaying various comorbidities.[5] In HFrEF, renal function is thus an important indicator of prognosis.

The EuroHeart Survey found prevalences of HF patients with kidney disease and diabetes of around 20%, but up to 37% of all HF admissions in European countries.[6] The Framingham Study has shown that diabetes confers a threefold (HR: 3.15) higher risk of HF in females, while in men it is almost doubled (HR: 1.82).[7] In an American, retired population, a third (33%) of diabetic men and almost half (45%) of diabetic women developed HF over the course of 5.5 years.[7] These proportions are also reflected in recent outcome trials, thus the evidence base of disease-modifying treatment in HF also applies to diabetic patients.

How are HF and diabetes related? The UKPDS study in diabetes patients showed a linear relationship between control of diabetes (HbA1c) and subsequent risk of HF (16% lower risk per 1% reduction in HbA1c).[8] Analysis of Swedish registry data of patients with type 1 diabetes shows that the risk of HF increases as HbA1c control gets poorer.[9] These data also showed that in patients with T2DM, having AF (HR: 1.89), ischemic heart disease (HR: 2.9) and in particular myocardial infarction (HR: 6.42) is associated with higher HF risk.

A lot of the CV benefit seen with the SGLT2 inhibitor empagliflozin seems to be related to HF, for instance the rate of hospitalization for HF was dramatically reduced.

The question then rises whether that CV risk can be reversed by tightly controlling diabetes. It has been known for a while that better diabetic control protects one from microvascular complications. An effect on macrovascular complications has not been demonstrated convincingly until recently.[10] Fortunately, nowadays therapeutic options are broader. The most exciting addition to the therapeutic options is empagliflozin. This SGLT2 inhibitor gave tight diabetic control, and reduced CV mortality. A lot of the benefit seems to be related to HF, for instance the rate of hospitalization for HF (HHF) was dramatically reduced.[11]

SGLT2 inhibition & Heart Failure: Lessons from EMPA-REG Outcome

Prof. Per-Henrik Groop – *University of Helsinki, Finland*

In persons of 60 years old without pre-existing CVD, but with diabetes, life expectancy is about 6 years shorter than in those without diabetes. In those with previous myocardial infarction (MI), the reduction in expected lifespan is even 12 years.[12] Having diabetes confers a twofold hazard of mortality, equivalent to having had stroke or MI. A combination of two of these conditions yields approximately a fourfold risk, and all three together yield a sevenfold risk of mortality.[12] Diabetes is also associated with a worse prognosis in patients with HF. A cumulative higher risk of CV death or hospitalization for HF was seen in both HFrEF (unadj HR: 1.60, 95%CI: 1.44-1.77, P<0.0001) and HFpEF (unadj HR: 2.0, 95%CI: 1.70-2.36, P<0.0001) patients with diabetes, as compared with those without diabetes.[13]

The more signs of kidney disease a patient with diabetes has, the more likely one is to suffer from premature mortality

When diabetes coincides with chronic kidney disease (CKD), the situation is even worse. The more signs of kidney disease one has, the more likely one is to suffer from premature mortality. The ADVANCE trial showed that the risk of CV events increases as albumin excretion rate increases and as eGFR gets worse, up to a 3.2 higher risk in case of macroalbuminuria and eGFR <60 ml/min/1.73m2.[14] Moreover, as compared with T2DM without CKD, diabetic kidney disease confers an approximately double risk of acute MI, CVA/TIA, peripheral vascular disease or death.[15]

In order to treat this risk, focus has been directed to lowering glucose. The UKPDS study showed that intensive glycemic control (median HbA1c was 7.0% in the intensive group and 7.9% in the conventional group) reduced microvascular but not macrovascular outcomes in newly diagnosed diabetic patients, over a median follow-up of 10 years.[16] The more recent ADVANCE trial, in patients with long-standing diabetes, also showed no effect on macrovascular events (HR: 0.94; 95%CI: 0.84–1.06; P=0.[32]), but a significant 14% risk reduction of microvascular events with intensive glycemic control over a median of 5 years of follow-up (HR 0.86; 95%CI: 0.77–0.97; P=0.01).[17] The UKPDS trial, however, after another ten years of follow-up, also showed a beneficial effect on macrovascular effects, implying that if we focus on glucose, it takes time to sort this type of effect. The ADVANCE-ON showed that intensive glycemic control also had significant benefit for end-stage renal disease (HR: 0.54, 95%CI: 0.34-0.85, P=0.007 during a 6-year post-trial follow-up).[18]

No effect of intensive glycemic control, as compared with less intensive control, on the risk of HF has been described (HR: 1.00, 95%CI: 0.86-1.16) in a meta-analysis of data of ACCORD, ADVANCE, UKPDS and VADT.[19]

The EMPA-REG Outcome trial gave insight into the effect of SGLT2 inhibition on diabetic late complications. About 7000 patients with T2DM were randomized to placebo, empagliflozin 10 mg or empagliflozin 25 mg, in addition to standard of care.[11] The three point MACE composite outcome was reduced by 14% with empagliflozin as compared with placebo (HR: 0.86, 95%CI: 0.74-0.99, P=0.0382). CV death was found to be reduced by 38% (HR: 0.62, 95%CI: 0.49-0.77, P<0.0001), all-cause mortality by 32% (HR: 0.68, 95%CI: 0.57-0.82, P<0.0001) and HHF by 35% (HR: 0.65, 95%CI: 0.50-0.85, P=0.0017) upon treatment with empagliflozin as compared with placebo.[11]
When specifically looking at the HF data of the EMPA-REG Outcome trial, consistent results are seen with regard to HHF in those without HF at baseline (HR: 0.59, 95%CI: 0.43-0.82) and those with HF at baseline (HR: 0.75, 95%CI: 0.48-1.19), although in those with HF, the risk reduction is not statistically significant.[20] This is due to lower numbers, according to Groop.
The composite outcome of HHF or CV death was reduced by 34% upon treatment with empagliflozin (HR: 0.66, 95%CI: 0.55-0.79, P<0.001).[21] Again, when stratifying for with or without HF at baseline, a consistent direction of the effect on HHF or CV death was seen, albeit with a non-significant reduction for those with HF at baseline (no HF: HR: 0.63, 95%CI: 0.51-0.78, with HF: HR: 0.72, 95%CI: 0.50-1.04).[20]
Consistent results are also seen upon stratification for kidney function or baseline medication.[21] A reduction of 39% was seen with empagliflozin for the composite of HHF or death from HF (HR: 0.61, 95%CI: 0.47-0.79, P<0.001). Moreover, time to first introduction of loop diuretics was reduced with empagliflozin as compared with placebo (HR: 0.62, 95%CI: 0.53-0.73, P=0.001).[20,21]

Upon exposure to empagliflozin, eGFR shows an initial drop, after which kidney function is preserved, while patients on placebo show a gradual decline over time

Pre-specified renal endpoints showed a reduction by 39% of new onset or worsening diabetic kidney disease (HR: 0.61, 95%CI: 0.53-0.70, P<0.001). This effect already appeared early in the study.[22] The composite renal endpoint of doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease was reduced by 46% (HR: 0.54, 95%CI: 0.40-0.75). The risk of ending with dialysis was reduced by 55% (HR: 0.45, 95%CI: 0.21-0.97, P=0.0409). In patients with kidney disease at baseline, the risk of new or worsening diabetic kidney disease was reduced by 42% (HR: 0.52, 95%CI: 0.47-0.71, P<0.001).[22]
Upon exposure to 10 or 25 mg of empagliflozin, eGFR (according to the CKD-EPI formula) shows an initial drop, after which kidney function is preserved. In patients on placebo, eGFR showed a gradual decline over the course of 192 weeks.[22]

The results of the EMPA-REG Outcome trial are interesting in comparison with those of the RENAAL and IDNT trials, which led to inclusion of losartan and irbesartan into the guidelines, respectively. The effects seen with empagliflozin on top of standard of care on doubling of serum creatinine, end-stage renal disease and HHF were at least as large as seen with losartan and irbesartan, and for the first time, now with empagliflozin, also a benefit on all-cause mortality was seen.

Being a little provocative, prof. Groop postulated that SGLT2 inhibition is as important as RAAS inhibition. Groop emphasized that the trial results were obtained with treatment of empagliflozin on top of standard of care. To illustrate the added benefit of empagliflozin, he superimposed the CV mortality curve of EMPA-REG Outcome on the curve of the HOPE trial[23]. The placebo-curve of the EMPA-REG Outcome fits well on the ramipril ACE inhibition arm of the HOPE trial, and from there an absolute risk reduction of 2.1% to 3.7% is seen at 48 months with SGTL2 inhibition. A similar picture is seen with other outcomes, namely MI, stroke, all-cause mortality, HF and overt CKD, as they are all lower in EMPA-REG Outcome than in HOPE.

New diabetes drugs and heart failure: What have we learnt?

Prof. John McMurray – *University of Glasgow, United Kingdom*

Prof. McMurray emphasized that HF is not only one of the most common CV complications of T2DM, it is also one of the most disabling and deadly complications of diabetes. On the other hand, many HF patients also have diabetes or prediabetes, which is why we need to know about the effects of glucose-lowering drugs in patients with HF, and whether they are safe.

In the past ten years have a great number of major CV outcome trials in T2DM were executed, as opposed to the decades before. This is the consequence of an FDA guidance that demanded studies that demonstrate the CV safety of new glucose-lowering drugs, because smaller studies of rosiglitazone had suggested an increased risk of MI. The guidance recommends that the sponsor of a new drug demonstrates that there is no increase of risk of CV death, MI or stroke. HF is not mentioned in the guidance, although it should have been addressed, since

an increased risk of congestive HF was seen with rosiglitazone in the RECORD trial[24], but not an increase in the outcomes now demanded by the FDA.

So, what have we learnt from these recent outcome trials of glucose-lowering drugs? The first group to consider is the incretin-based therapies, that increase the action of glucagon-like peptide-1 (GLP-1). This can be done by inhibiting breakdown of GLP-1, by inhibiting an enzyme involved in its breakdown: DPP4. Alternatively, endogenous GLP-1 can be increased by GLP-1 analogues/receptor agonists.

The first CV outcome trial in this category was the SAVOR-TIMI 53 trial, investigating the DPP4 inhibitor saxagliptin in T2DM patients with established CV disease.[25] This study showed no difference in major CV endpoints between treatment with saxagliptin and placebo. Patients receiving saxagliptin did show a significant increase in HF.[25] Fortunately, two trials with two other DPP4-inhibitors, the EXAMINE trial on alogliptin[26] and the TECOS trial on sitagliptin[27], did not show the same increased risk of HF. When all outcome trial data on DPP4 inhibitors are put together, this drug class does not appear to be associated with an increased risk of HF.[28] By lack of explanation why DPP4 inhibitors could increase the risk of HF and since no such signal was seen in the other DPP4 inhibitor outcome trials, the signal seen in SAVOR-TIMI 53 is currently thought to probably reflect a play of chance. Still, saxagliptin and alogliptin have a warning in their labelling about the risk of developing HF.

The only hypothesis put forward to explain the increased risk of developing HF is that DPP4 may cause breakdown of neuropeptide Y, which is a potent vasoconstrictor. If this is indeed the case, inhibiting DPP4 may cause tissue levels of neuropeptide Y to increase, and the increased vasoconstriction could plausibly lead to HF. No good experimental or clinical evidence exists to support this hypothesis.

Other drugs that act on the same pathway are now available, namely the aforementioned GLP-1 analogues. Three outcome trials have already reported on data with semaglutide[29], liraglutide[30] and lixisenatide[31], respectively. In the ELIXA trial (n=6068), lixisenatide did not change the risk of CV death, MI, stroke or unstable angina, in patients with T2DM and recent acute coronary syndrome, as compared with placebo.[31] The larger and longer LEADER trial (n=9340) showed a different picture. Liraglutide reduced the incidence of the primary composite MACE endpoint by 13% (HR: 0.87, 95%CI: 0.78-0.97, P<0.001 for noninferiority, P=0.01 for superiority) in patients with T2DM at high CV risk, over a median follow-up of 3.8 years. CV mortality was also significantly reduced.[30] Semaglutide was then shown to also reduce the incidence of the MACE composite outcome (HR: 0.74, 95%CI: 0.58-0.95, P<0.001 for non-inferiority, P=0.02 for superiority) in 3297 patients with T2DM at high CV risk in the SUSTAIN-6 trial, over a median follow-up of 2.1 years.[29] The results were slightly different from those of liraglutide, as CV mortality was not significantly reduced, and the major effect seemed to be on the risk of stroke. It is to date unclear why the results differ among these trials, other than that the trial populations are different.

Unfortunately, no reduction in HF was seen in either LEADER (HR: 0.87, 95%CI: 0.73-1.05, P=0.14)[30], SUSTAIN-6 (HR: 1.11, 95%CI: 0.77-1.61)[29] or ELIXA (with prior HF: HR: 0.93, 95%CI: 0.66-1.30, without prior HR: 0.97, 95%CI: 0.67-1.40)[31]. One reason why we might need to be a little cautious with the potential of these drugs, is that they increase heart rate. It is unclear why this happens, but in patients with HF it might not be good. Indeed, the small FIGHT study suggested that in patients with established, advanced decompensated HF leading to hospitalization, outcomes were a little bit worse in those treated with the GLP-1 analogue liraglutide.[32] Although not definitive at all, this should make us think carefully about the role of these agents in patients with established HF. Soon, the results of a fourth drug in this class will be reported, which is being tested the EXSCEL trial.

The rapid onset of the effect on HF seen in EMPA-REG Outcome is postulated to reflect a hemodynamic or diuretic effect that occurs more quickly, or it could be an effect on energy utilization by the myocardium.

The SGLT2-inhibitors act at another point in the glucose metabolism, namely by reducing renal glucose reabsorption in the proximal tubule, thereby inducing an osmotic diuresis and a natriuresis. The surprising finding of this trial was the reduction in the development of HF. It is not known what type of HF this was, thus a lot remains to be learned on SGLT2 inhibition and HF. The rapid onset of the effect on HF seen in EMPA-REG Outcome has led some to believe that metabolic benefits cannot explain the observations, and that another way of thinking is required. It has been postulated that this rapid effect may rather reflect a hemodynamic or diuretic effect that occurs more quickly, or it could be an effect on energy utilization by the myocardium. Animal experiments have yielded intriguing hypotheses, but the truth is that a heart of a patient with both HF and diabetes is a black box. We have a lot more to learn about the metabolic pathophysiology in this condition. Ongoing trials will hopefully give more insight in this question.

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