Meeting Impression

Satellite Symposium during ESC Heart Failure 2018
May 28, 2018 – Vienna, Austria

Contemporary management of a patient with heart failure and diabetes: Implications from recent trials

This lunch symposium held during Heart Failure 2018 in Vienna, Austria, explored the role of diabetes treatment in the management of heart failure (HF), in light of recent findings that novel glucose-lowering drugs affect CV outcomes. Different classes of novel diabetes drugs were considered, along with their effects on HF in safety and outcome trials. Potential mechanisms underlying the observed effects are discussed, as well as how these drugs may be benefitted from in the management of patients with diabetes and HF.

TOPICS

Current management of heart failure & T2DM
Martin Cowie, MD – Imperial College London, United Kingdom

Understanding the mechanisms of SGLT2 inhibition in heart failure and diabetes
Naveed Sattar, MD – University of Glasgow, United Kingdom

Guidance from outcome trials: What are the clinical implications
Faiez Zannad, MD – CHU- Nancy University, France

Prof. **Adriaan Voors** (UMCG, Groningen, The Netherlands) chaired the symposium. To start of, he first introduced a patient he saw in his clinic, who illustrated relevance of the topic of this symposium; a 49-year old morbid obese (BMI: 51 kg/m^2) woman with heart failure with preserved ejection fraction (HFpEF) and type 2 diabetes (T2DM), who had to be hospitalized for acute decompensated HF. She showed a very poor response on furosemide, and renal function worsened. Recently, she had switched from metformin 2 dd 850 mg to insulin. The 2016 European Society of Cardiology (ESC) guidelines on the treatment of acute and chronic HF[1] state that insulin may exacerbate fluid retention, which may lead to worsening of HF. The latter risk is also seen with thiazolidinediones, as with sulphonylureas. This situation led to several questions on how this patient could best be managed, which culminate into 'should diabetic patients with HF be treated differently from patients with diabetes without HF'?

Challenges in heart failure management: Diabetes and renal impairment

Professor Martin Cowie – *Imperial College London, United Kingdom*

The question posed by prof. Voors is relevant one, as diabetes is very common in patients with HF. Prof. Cowie showed that over 33% of patients with both HF with reduced EF (HFrEF) and HFpEF have also been diagnosed with diabetes. Moving from patients with pre-diabetes, via newly diagnosed diabetes to long-lasting diabetes, patients show a higher risk of mortality or hospitalization for HF.[2] Nevertheless, the most recent ESC Guidelines for the diagnosis and management of HF[1] write little about patients with diabetes. The two main points state that metformin should be considered as first-line treatment of glycemic control, and that thiazolidinediones are not

recommended in patients with HF, as they may increase the risk of HF worsening due to increased fluid retention.

A position statement issued by the ESC Heart Failure Association states that HF patients with diabetes should not be treated any differently from HF patients without diabetes.

With regard to metformin, some evidence exists that it has CV benefits, but no specific data in the HF population is available. Metformin improves glycemic control, and patients do not tend to gain weight or retain fluid. Caution should be given to renal function, and metformin is contra-indicated if eGFR <30 ml/min/1.73 m^2, in light of the rare but serious metabolic complication of lactic acidosis. Hence, limited options are recommended to treat patients with both HF and diabetes. In management of diabetes alone however, more options are available, including:

- drugs that enhance insulin action in peripheral tissues: thiazolidinediones and metformin,
- drugs that enhance endogenous insulin secretion: sulphonylureas, glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidylpeptidase 4 (DPP-4) inhibitors,
- drugs that suppress endogenous glucose production: metformin and thiazolidinediones,
- drugs that delay the absorption of carbohydrate from the gastrointestinal tract: alpha glucosidase inhibitors.

Cowie likes to think of these agents in terms of oral tablets on the one hand, and injectables on the other hand. Injectables include insulin, and the incretin mimetics GLP-1RAs and GLP analogues. Oral agents include the new class of glucosurics, or sodium-glucose cotransporter-2 (SGLT2) inhibitors, which was discussed in more detail later in this symposium.

The list of actions that every patient with diabetes should expect from their treating physician, largely overlaps with all relevant actions in good care of patients with heart failure.

Treatment of patients with diabetes and HF is evolving rapidly. Before publishing an update of the ESC Guidelines on HF, a position statement has been issued by the Heart Failure Association (HFA) of the ESC, on treatment of T2DM and HF.[3] The document states that HF patients with diabetes should not be treated any differently from HF patients without diabetes when it comes to disease-modifying drugs and devices. There is no evidence that T2DM modifies the benefit of guideline-based therapies for HF. It is pointed out, however, that limited data are available on treatment with hypoglycemic agents in HF patients; no large randomized controlled trials (RCTs) have been conducted, let alone specifically in patients with HF.

When a patient with both HF and T2DM comes to the clinic, the treating cardiologist may wonder whether the diabetes is his/her responsibility. Cowie showed a list of actions that every patient with diabetes deserves and should expect from their treating physician, composed by a diabetes organization. The list contains 15 aspects, some of which need to be performed annually, such as checking glycemic control, blood pressure, cholesterol profile, and looking at legs and feet, doing a kidney function test, checking for proteinuria, ensuring a flu vaccination in autumn, and checking for retinopathy. Other items on the list include ongoing, individualized dietary advice, but also emotional and psychological support, education, seeing a specialist professional, in case of hospitalization high quality care, exploration of sexual problems, support to stop smoking, and specialist input if a pregnancy is desired and planned. Cowie showed the list of actions again, this time to demonstrate that these are, in fact, almost all relevant in good care of patients with HF. Only screening for retinopathy and cholesterol profile may not be performed so regularly, but he emphasized that all other things also apply to patients with HF. Thus, considering the overlap between what a diabetologist does and what a HF specialist thinks should be done with a patient, it is a missed opportunity if cardiologists do not check these things from a diabetic point of view if they are seeing their HF patients.

In conclusion, Cowie is of the opinion that it is important that HF physicians know what diabetes care looks like, and what the treatment options are. This can lead to better treatment choices and better support for patients. It is also useful for a cardiologist to develop a good relationship with the local diabetologist, as more complicated situations that need specialist input are likely to occur. In general, it is wise to check HF patients occasionally if they are developing diabetes, as many will. As patients may not expect their cardiologist to ask them about their diabetes, Cowie suggests to positively surprise patients by informing about other things they may be concerned about.

Understanding the mechanisms of SGLT2 inhibition in heart failure and diabetes

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

Professor Sattar continued by diving deeper into one of the latest developments in the diabetes field; what is known about the effects and mechanism of SGLT2 inhibition. The EMPA-REG OUTCOME trial[4] compared two doses of the SGLT2 inhibitor empagliflozin with placebo,

in patients with diabetes and high CV risk. 99% Of participants had existing CV disease. Average age was 63 years old, average HbA1c was 8.1%, and about a quarter of participants had eGFR <60 ml/min/1.73 m^2. About 7000 patients were followed over a median observation time of 3.1 years.[4]

When combining findings of EMPA-REG OUTCOME and the CANVAS program, a class effect for SGLT2 inhibitors of a benefit on HF hospitalization emerges, and a mortality reduction for empagliflozin.

It was anticipated that empagliflozin would mostly benefit myocardial infarction (MI) and stroke risk, as it modulates several factors related to CV risk, including glucose and insulin lowering. It was already known that empagliflozin reduces albuminuria, and affects some lipid factors, as well as weight and blood pressure.[5] When the first results were presented, however, non-fatal MI and stroke were not significantly affected by treatment with empagliflozin as compared with placebo, with a point-estimate above 1 for stroke, and below 1 for MI. The three-point MACE (major adverse CV events) endpoint was significantly reduced by 14% with empagliflozin vs. placebo (HR: 0.86, 0.74-0.99, P=0.0382), which was mostly driven by a reduction in CV death (HR: 0.62, 95%CI: 0.49-0.77, P=<0.0001). It was also striking that the Kaplan-Meier event curves separated early after start of treatment. In addition, empagliflozin showed a reduction of hospitalization for HF as compared with placebo, by 35% (HR: 0.65, 95%CI: 0.50-0.85, P=0.0017). Furthermore, empagliflozin also reduced all-cause death by 32% in the EMPA-REG OUTCOME trial.[5]

The CANVAS program compared another SGLT2 inhibitor, canagliflozin, with placebo.[6] The pooled CANVAS program also demonstrated a 14% reduction in MACE (CV death, nonfatal MI and non-fatal stroke) after treatment with canagliflozin (HR: 0.86, 95%CI: 0.75-0.97). Again, non-fatal MI and stroke were not significantly reduced. Like empagliflozin, treatment with canagliflozin also showed a significant reduction in HF hospitalization or CV death (HR: 0.78, 95%CI: 0.67-0.91), but less effect on CV death only (HR: 0.87, 95%CI: 0.72-1.06).[6] When combining the findings of both SGLT2 inhibitors, a class effect of a benefit on HF hospitalization emerges, and in addition to that, empagliflozin may give mortality reduction.

When speculating on the mechanism of action of SGLT2 inhibition, atherothrombosis does not seem relevant because the benefits occurred too fast, and no benefit on MI and stroke was seen. Thus, it may be a vascular or renal effect, or altered cardiac metabolism. Additionally, the ketone hypothesis has been proposed.[7] It is good to remember how these drugs work. SGLT2 inhibitors lead to reduction of sugar reabsorption in the proximal tubule. In diabetes patients, SGLT2 is upregulated, so that 90% of the sugar is reabsorbed early on in the proximal tubule. SGLT2 inhibitors suppress this mechanism, leading to reduced reabsorption of glucose into the bloodstream and consequently loss of sugar in the urine. This glucosuria also leads to loss of calories and water, which lowers blood pressure.

As the name suggests, *sodium*-glucose cotransporter-2 inhibitors also affect sodium levels. Normally, SGLT2 upregulation leads to sodium reabsorption and diabetes patients will likely be sodium overloaded and water overloaded. As a consequence of increased sodium reabsorption in the proximal tubule, less sodium reaches the macula densa in the kidney. This feeds back to lead to afferent arterial vasodilation, with consequently increased pressure in the kidney through elevated glomerular filtration rate (GFR). SGLT2 inhibition causes sodium to no longer be reabsorbed, and as sodium reaches the macula densa in high concentration, the feedback mechanism leads to arterial vasoconstriction. Consequently, the pressure on the kidneys is normalized. It is thought that this destresses the nephron.[8] Moreover, salt is excreted via the urine[7] and albuminuria is reduced. It is suggested that altogether, SGLT2 inhibition results in protection of the kidney.[7]

These effects of SGLT2 inhibition are also seen with RAAS blockade. Although these effects arise through different mechanisms, combining the two drug classes may have additive benefits. Concerning the proposed reno-protective effects, in EMPA-REG OUTCOME, in comparison with placebo, treatment with empagliflozin indeed reduced the progression to a decline in eGFR greater than 40%, a meaningful eGFR decline (HR: 0.55, 95%CI: 0.40-0.75, P=0.0001).[9]

The volume effects of SGLT2 inhibition go beyond what is seen with diuretics. The effects may reflect a more pathophysiologically targeted pathway in diabetes than diuretics.

The ketone hypothesis postulates a switch in cardiac use of ketones instead of glucose, with ketones being a more energy-efficient fuel for the failing heart. Normally in diabetes, a switch takes place in cardiac use from free fatty acids to glucose, which impairs cardiac function. Interestingly, SGLT2 inhibitors have been demonstrated to increase ketone synthesis, which may be beneficial for the heart.[10] However, it should be noted that not all researchers in this field are convinced that the ketone hypothesis is relevant to the effects of SGLT2 inhibition.[11] Research is ongoing to shed more light on the relevance of the ketone hypothesis.

With regard to the altered hemodynamics induced by SGLT2 inhibiting treatment, Sattar and colleagues developed an early hypothesis, by postulating that SGLT2 inhibition leads to glucose and sodium reduction in the blood, by reducing reabsorption of both factors in the kidneys. This lowers nephron hyperfiltration and in turn reduces generalized decongestion and intravascular volume, which destresses the heart. Cardiac afterload and preload are decreased. And because the heart is stressed less, fewer HF hospitalizations are seen. Also fatal arrhythmias occur less often.[12] Sattar recommends to read the review article by Butler *et al.*[13], which elaborates on the volume effects and this hypothesis, in addition to the metabolic effects of SGLT2 inhibition.

The volume effects of SGLT2 inhibition go beyond what is seen with diuretics. Loop diuretics and thiazides for instance only cause natriuresis, and vaptans only aquaresis. SGLT2 inhibition on the other hand affects both glucose and sodium, without causing a change in osmolality, serum potassium, and uric acid and sugar levels go down. This may reflect a more pathophysiologically targeted pathway in diabetes than diuretics. Still, these mechanisms should be explored further.

In a recent paper, Sattar and McGuire rethink how diabetes and obesity may lead to CV disease.[14] Not only by accelerating atherogenesis through the usual risk factors. It may have been overlooked that both diabetes and obesity, particularly when they interact, also lead to fluid overload and sodium and glucose overload. SGLT2 inhibitors may predominantly target this pathway, thereby addressing volume excess and the hemodynamic and glomerular stress directly.[14] Ongoing trials my confirm this hypothesis.

Guidance from outcome trials: What are the clinical implications?

Professor Faiez Zannad, MD – *CHU- Nancy University, France*

Professor Zannad set out to share ideas on how to deal with a patient with diabetes and HF, based on data of the latest trials. On the one hand, evidence comes from HF therapy outcome trials, in which a subset of patients had diabetes. Patients with diabetes benefit from various types of HF therapy in the same way as patient without diabetes. On the other hand, there are glucose-lowering diabetes outcome trials, in which it is interesting to look at the effect on HF outcomes. HF as an independent endpoint has long been neglected in diabetes trials[15], but this should be improved in future studies.

A meta-analysis of the effect of intensive glucose control as compared with less intense control, based on data of the pivotal ADVANCE, UKPDS, ACCORDS and VADT studies, showed a reduction in MI (by 15%) in patients with T2DM, while the effect on hospitalization or death from HF was neutral (HR: 1.00).[16] Although glucose control may improve microvascular and/or macrovascular disease, this does not necessarily translate into protection against HF. In the RECORD trial, rosiglitazone, as compared with metformin, showed better glucose control, but was neutral on CV outcomes. Most strikingly, the risk of HF was increased with rosiglitazone.[17]

Recent trial data suggest that glucose control, which is a property common to all novel glucose-lowering medications, is not associated to an effect on heart failure.

When comparing the newest glucose-lowering drug classes DPP-4 inhibitors, GLP-1 receptor agonists (GLP-1RAs) and SGLT-2 inhibitors, various effects on HF events are seen. In the first category, saxagliptin showed an excess of HF events in the SAVOR-TIMI 53 trial, while in the latter category, both empagliflozin and canagliflozin showed a reduction of HF events. In the middle category, at least so far, the GLP-1RAs seem to be neutral on HF events. This suggests that glucose control, which is a property common to all these medications, is not associated to an effect on HF.

The class of DPP-4 inhibitors shows the broadest range of effects on HF; different members have shown different outcomes. While the results of the SAVOR-TIMI 53 trial surprised the field with an increase in hospitalization for HF in patients receiving saxagliptin (HR: 1.80, 95%CI: 1.29-2.55, P=0.001 at 180 days after randomization, and HR: 1.27, 95%CI: 1.07-1.51, P=0.007 at 720 days)[18], alogliptin showed total neutrality with respect to the outcome of CV death and hospitalization for HF (HR: 0.997, 95%CI: 0.820-1.212, at 30 months), as did sitagliptin in TECOS (HR: 1.00, 95%CI: 0.83-1.20). These findings suggest that there is no class effect for the DPP-4 inhibitors.

As Sattar had already touched upon, a big positive surprise came form the EMPA-REG OUTCOME trial, in which the SGLT2 inhibitor empagliflozin improved mortality, CV death and MACE. HF was a secondary outcome. Much improvement was seen very soon after initial exposure to the drug.[4] Thus, empagliflozin appeared to be a glucose-lowering agent, which is not only safe, but also improves CV outcomes including HF. Irrespective of the definition of HF that was applied, the finding that empagliflozin treatment was beneficial for HF outcomes was very robust. Also in patients without HF at baseline, empagliflozin reduced HF events, thus new onset symptomatic HF was prevented.[19]

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Protection against heart failure seems to be a class effect of SGLT2 inhibitors.

HF, especially when it co-exists with diabetes, is often accompanied with chronic kidney disease (CKD). But patients with eGFR <60 ml/min/1.73m^2 have been excluded in many trials. The proportion of patients with reduced renal function ranged between 5 and 30% in outcome trials evaluating novel glucose-lowering drugs. Thus, current findings cannot be extrapolated to patients with CKD and moderate to severe renal dysfunction. Two dedicated trials (CREDENCE with canagliflozin and CARMELINA with linagliptin) study these subpopulations, to evaluate whether the HF protection extends to patients with the frequent comorbidity of CKD, diabetes and HF.

When comparing empagliflozin and canagliflozin, results seen in the EMPA-REG OUTCOME trial and the CANVAS program are largely consistent. Thus, the protection against HF seems to be a class effect of SGLT2 inhibitors. A hint at potential mechanisms underlying this benefit comes from the increase in hematocrit, seen with empagliflozin. A consistent and persistent increase in hematocrit of 45 % over the course of follow-up was seen, which was not related to the number of red blood cells, suggestive of hemoconcentration.[20] Thus, diuretic decongestion effect takes place. Moreover, the sodium and water excretion induced by SGLT2 inhibition can help prevent HF events. A mediation analysis suggested that the effect of empagliflozin on hematocrit and hemoglobin, and also albumin, explained most of the clinical benefit on HF seen in EMPA-REG OUTCOME (37.3, 44.4 and 25.3% respectively).[20]

GLP-1RAs are thought to be more effective in prevention of atherosclerotic events.

GLP-1RAs showed a benefit on CV death and MI in LEADER and SUSTAIN-6, but not on HF. Thus, considering equal glucose control, different CV outcomes are to be expected with different glucose-lowering agents.21 GLP-1RAs are thought to be more effective in prevention of atherosclerotic events. Novel guidelines and treatment recommendations introduce new sub-groups and different phenotypes of HF, as not all diabetes patients should be considered the same. Empagliflozin is now considered the preferred second line or third line therapy in addition to metformin, especially in patients at risk of HF and CVD. Based on the LEADER trial data, liraglutide is considered second or third line therapy in patients with stage three kidney disease, and in patients with atherosclerotic disease.[21] Thus, treatment of patients with diabetes and HF is increasingly finetuned.

More trials are ongoing or coming up, which will teach us more about the use of these glucose-lowering agents in various patient populations. For instance, the EMPEROR trial investigates the effect of empagliflozin in patients with HFrEF (LVEF ≤40%, n=2850) or HFpEF (LVEF ≥40%, n=4126), in parallel trials. In each HF arm, patients will be randomized to empagliflozin 10 mg or placebo, on top of standard of care. EMPEROR includes both patients with and without T2DM, thus the results may inform us whether empagliflozin may become HF therapy, independent of diabetes.[22]

Similarly, DAPA-HF includes patients with HFrEF (LVEF ≤40%), also including patients with eGFR <30 ml/min/1.73m^2. The primary outcome is a composite of CV death, hospitalization for HF or an urgent HF visit, and a number of secondary outcome measures focus on aspects of HF, making DAPA-HF a typical HF trial.[23]

Some of these recent insights are the unintended consequence of the 2008 FDA Guidance on trials of new antidiabetic medications, which mandated that all these new agents should be evaluated for CV safety. Some trials were also designed to test for superiority. As described above, certain trials have demonstrated that a drug that lowers glycated hemoglobin, can also affect major CV events within five years of use, which has nothing to do with glycemic control. Ultimately, these novel glucose-lowering drugs may turn out to become HF therapy. This is an important paradigm shift, and the consequence of serendipity: an accident and sagacity while in pursuit of something else. Zannad concluded by citing Louis Pasteur, who said 'in the fields of observation, chance favors only the prepared mind' and stating that fortunately HF specialists were prepared to capture this signal from SGLT2 inhibitors.

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