Meeting Impression

EBAC-Accredited Satellite symposium during ESC 2017 Congress
August 28, 2017 – Barcelona, Spain

Modern Management of Diabetes in Cardiology: Impact of SGLT2 Inhibition on CV Outcomes and Heart Failure

In this educational program chaired by David Fitchett and John Deanfield, which was held at the ESC Congress 2017 in Barcelona, Spain, Naveed Sattar, John Deanfield, and Stefan Anker discussed the role of diabetes treatment in the management of heart failure, as well as novel interventions targeted to improve cardiovascular (CV) outcomes. More specifically, the epidemiology and pathophysiology of patients with diabetes and at increased CV risk were summarized, and the role of the kidney in glucose homeostasis was explained. In addition, current interventions and the unmet need of impacting CV outcomes in diabetes were discussed, the effects of SGLT2 inhibition described, as well as future strategies in these multi-risk patients.

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SGLT2 inhibition in cardiology: What a cardiologist needs to know

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Multiple randomized trials have demonstrated that statins, blood pressure (BP) reduction, smoking cessation and prevention, and healthy lifestyle result in a lower cardiovascular (CV) risk in patients with diabetes and overall in the general population. While lowering glucose has only a slow and modest effect on CV risk, having diabetes and CVD results in a high CV risk and loss of years of life. For example, 40-year-old patients with diabetes and stroke have a reduction of 16 years in life expectancy.[1]

The EMPA-REG OUTCOME trial enrolled 7020 diabetes patients with established CVD, who were randomized to treatment with two different doses of the SGLT2 inhibitor empagliflozin or placebo. The HbA1c range of 7-10% decreased by 0.5% after 12 weeks of treatment with empagliflozin and reached a decrease of ~0.3% after 4 years. The overall primary outcome of MACE, which was a combination of fatal and non-fatal MI and stroke, was reduced by 15%. This was an important finding as, until then, no other drug than metformin was found to reduce fatal and non-fatal stroke. Surprisingly, treatment with empagliflozin gave a substantial 38% reduction in CV death. In addition, HF hospitalization was reduced by 35% in the empagliflozin group with an early effect after the start of therapy.

Altogether, improving kidney function and reducing flow and volume by empagliflozin results in beneficial effects on the heart, in addition to possibly directly benefitting the heart.

Prior to the trial, the idea was that empagliflozin acts by removing glucose in the kidney, which also improves many other risk factors like uric acid, oxidative stress and lipids, resulting in a range of beneficial effects on glycemia, blood pressure, arterial stiffness, albuminuria, weight, and differential effects on lipids, thereby reducing atherogenesis. However, the pattern of the results suggests that these are not the causal factors and thus the focus has shifted. Although no significant finding for non-fatal MI and stroke was demonstrated, the trial showed substantial and rapid effects on CV death and HF hospitalization, suggesting that the mechanism of action is not mediated by atherothrombosis, but by vascular actions, renal actions or improved cardiac metabolism. It is suggested that empagliflozin improves the cardiac-renal axis by reducing fluid in the system, which benefits cardiac function. In addition to inhibiting glucose reabsorption resulting in glycosuria, empagliflozin also causes profound natriuresis by interfering with the sodium-hydrogen exchange in the kidney leading to sodium excess and thereby resulting in decreased body weight, BP and hemoconcentration. The combination of these effects on blood volume result in decreased cardiac wall stress. In addition, the interference of empagliflozin on the sodium-hydrogen exchange in the heart results in cardiac benefits. SGLT2 inhibition causes afferent vasoconstriction resulting in reduction of hypofiltration, less pressure on nephrons, and reduction of albuminuria thereby protecting the kidneys.[2] RAAS blockade works on the efferent axis by causing vasodilation, resulting also in a decrease of glomerular pressure, but by a different mechanism. Furthermore, SGLT2 inhibition causes glucose and sodium reabsorption in the proximal tubules and reduces nephron hyperfiltration leading to generalized fluid reduction and generalized decongestion, which affects cardiac preload/afterload, systolic and potentially diastolic dysfunction, HF hospitalization, and potentially fatal arrhythmias.[3] Altogether, improving kidney function and reducing flow and volume by empagliflozin results in beneficial effects on the heart, in addition to possibly directly benefitting the heart. A study by Wanner *et al.* showed a 45% reduction in deterioration of renal function in patients during treatment with empagliflozin, which underwrites the idea that empagliflozin has beneficial effects on the kidney.[4]

Considering the observed clinical benefit of lower CVD mortality, potential HF and renal benefit, the clinical implications of the EMPA-REG OUTCOME trial are that empagliflozin should be used in patients with diabetes and CV risk. The use of empagliflozin in patients with diabetes without CVD needs further testing. Patients with CVD should be tested for diabetes by HbA1c or fasting glucose levels and those with known or newly developed diabetes without contraindications should be treated with empagliflozin, as is now included in the guidelines.[5]

The GLP-1 receptor agonist liraglutide also resulted in a decrease of CV mortality, glucose, weight, and showed renal benefits in the LEADER trial, but no reduction of HF hospitalization was seen. Cardiologists should work in tandem with endocrinologist to implement these novel therapies, most likely with a preference for empagliflozin, because it is orally administered.

The EMPA-REG OUTCOME trial introduced a new class of drugs with great CV benefits including reduction in CV death, HF hospitalization, MACE and potential renal benefits in patient with diabetes and CVD.

The CANVAS study, which evaluated the SGLT2 inhibitor canagliflozin, showed substantial HF benefits and similar MACE benefits as with empagliflozin treatment (reduction of ~14%). It did, however, not show a reduction in CVD and all cause death as was observed in the EMPA-REG OUTCOME trial. Moreover, unlike in the EMPA-REG OUTCOME trial, there was a significant amputation and fracture risk, and the risk for CVA was somewhat lower with canagliflozin, while with empagliflozin a non-significantly higher CVA risk was seen. It is unknown whether the differences in findings between the CANVAS and EMPA-REG OUTCOME trials are statistically significant, by lack of a head-to-head comparison. There might be possible population differences; the EMPA-REG OUTCOME trial included only patients with CVD, whereas in the CANVAS trial two-thirds of the patients had existing CVD. It will be interesting to examine whether there are real drug differences for CV death due to the molecular mechanisms of the drugs. Right now, clinicians should take these results at face value; personally, Sattar thinks that the results of empagliflozin look more favorable in terms of outcome and safety than canagliflozin. But, he adds, further trials are needed.
One should be aware that SGLT2 inhibitors should not be used in moderate to severe CKD, not in pregnant and breast-feeding women, and in acute stressful states. Caution should be exercised in the following categories: risk of volume depletion, complicated or recurrent UTIs, conditions of fasting (starvation) because those can precipitate diabetic ketoacidosis with euglycemia, and patients with already elevated hematocrit.

In conclusion, the EMPA-REG OUTCOME trial introduced a new class of drugs with great CV benefits including reduction in CV death, HF hospitalization, MACE and potential renal benefits in patient with diabetes and CVD. Empagliflozin was generally safe and the results changed the guideline recommendations due to the substantial reduction in CV mortality of 30%. The results give new insights in the mechanism of CV death in patients with diabetes and CVD, which is not only mediated by atherogenesis, but also by fluid effects.

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Management of CV Risk & T2DM: Implications of novel outcome trials

Prof. John Deanfield, MD – *University College London, United Kingdom*

Diabetes has a tremendous impact on the outcome of patients in CV practice, and therefore on the treatment of these patients. For example, life expectancy is shortened by 6 years in the presence of diabetes. The biggest impact is observed in younger patients from 40 to 60 years old in the study by Seshasai *et al.*[6] The Swedish National Diabetes Register also demonstrated the biggest impact of type 2 diabetes (T2DM) on premature CV mortality in patients <55 years old and 55-64 years old.[7] A large epidemiology study has shown that diabetes adds to the risk conferred by other known major CV risk factors, such as cholesterol, BP and smoking.[8]

In the past decade, clinicians have done very well in reducing glucose-related complications, but less in decreasing CV complications. A review from Gregg *et al.*[9] showed that the number of hyperglycemic deaths since 1988 has declined, however admissions due to CV complications have not decreased to the same extent. Most clinicians have focused on reducing traditional CV risk factors rather than lowering glucose. This can be explained by the impressive impact of BP and cholesterol on CV risk in patients with diabetes, and a much weaker association of CV risk with fasting blood glucose.[10] The CARDS trial was the first trial to evaluate the effect of a statin in diabetes patients, which resulted in a lower cumulative hazard for myocardial infarction (MI) and CV death with atorvastatin as compared to placebo and the trial was stopped early due to great success.[11] Similar data but to a lesser degree were seen regarding the impact of BP lowering on CV and renal outcomes.[12] Altogether, a recent meta-analysis confirmed these results, with disappointing results for traditional glucose lowering on CV risk reduction.[13]

Empagliflozin showed the best benefit in terms of CV death and HF hospitalization and due to the early benefits, guideline recommendations now already include the use of empagliflozin.

Metformin has long been used by cardiologists in routine clinical practice. Other glucose lowering drugs, however, may be harmful by increasing CV risk. Rosiglitazone for instance was demonstrated to increase the risk of MI and death by CV causes and has therefore been withdrawn from clinical use.[14] Other classic glucose lowering drugs, such as sulphonyl ureas, thiazolidinediones, DPP-4 inhibitors, and insulin, might also increase CV risk. As a result, both FDA and EMA have changed the study requirements and they now demand stringent demonstration of CV safety of new diabetes agents. These types of requirements have been applied to the newer approaches in development to reduce blood glucose.

The most recent additions to the therapeutic options in diabetes are the GLP-1 receptor agonists and SGLT2 inhibitors. Although the trials evaluating these drugs were designed to show noninferiority, two drugs showed a possible CV advantage in patients with diabetes and CVD. First, the LEADER trial evaluating the GLP-1 receptor agonist liraglutide showed an overall 13% reduction in hazard of CV endpoints over a 5-year period. Not much benefit was seen in the first year, but progressive benefit was seen up to 5 years.[15] Second, treatment with the SGLT2 inhibitor empagliflozin, which inhibits renal reabsorption of blood glucose, in the EMPA-REG OUTCOME trial, resulted in a reduction of almost 40% in CV mortality and 35% HF hospitalization in diabetes patients. The benefit was apparent within a rather short time after start of therapy, which was very different from the pattern seen with liraglutide treatment.[16] The finding of the reduction in HF hospitalization with empagliflozin has drawn great interest, as the presentation of patients with diabetes has changed over time from CV events to a large portion of patients now presenting with HF. The drugs tested in the EMPA-REG OUTCOME, LEADER and SUSTAIN-6 (testing the GLP-1 receptor agonist semaglutide) trials all showed a reduction in MI, however, there were differential effects on stroke, which needs further research.[17] Empagliflozin showed the best benefit in terms of CV death and HF hospitalization and due to the early benefits, guideline recommendations now already include the use of empagliflozin. Empagliflozin should be considered for patients with T2DM to prevent or delay the onset of HF and to prolong life.

An area of interest in the next few years is the potential opportunity to combine SGLT2 inhibitors and GLP-1 receptor agonists, due to their differential effects on atherosclerosis/atherogenesis as opposed to CV hemodynamics, which may underlie the CV benefits seen with SGLT2 inhibition.[17] It will be interesting to see if combining these agents yields incremental benefit in different categories of patients. The unexpected CV benefit from these drugs has raised the question how these drugs work to result in the observed clinical benefit. Also, it will be interesting to examine the benefit of SGLT2 inhibition in patients who do not have diabetes (yet). Two trials are currently being undertaken; dapagliflozin and empagliflozin are tested in the DAPA-HF trial in patients with HF with reduced ejection fraction and the EMPEROR-Preserved trial tests empagliflozin in patients with chronic HF with preserved ejection fraction.

This is a new era for CVD management in diabetes patients; both diabetologists and cardiologists should work together. Besides lowering traditional CV risk factors, patients can

also benefit from new diabetes drugs, in particular SGLT2 inhibitors. Future studies will give more insight in broader implications, early treatment, and prevention with this new class of drugs, even in patients who do not have diabetes.

Heart failure & Diabetes: Time for a more unified approach

Prof. Stefan Anker, MD PhD – *Berlin, Germany*

In management of HF, it is most important to consider comorbidities in HF, and to individualize therapy by patients' comorbidities. Diabetes is one of many comorbidities in chronic (C)HF, and associated with a 9-fold increase in mortality for patients with both diabetes and HF compared to those with diabetes alone.[18] In the past, HbA1c-guidance was considered as an approach to treat HF patients. Epidemiology studies have, however, described several different shapes of relationships, thus discrediting HbA1c as a suitable marker to guide treatment of HF patients. In CHF trials, about 20-40% of patients had T2DM.

Because most patients in the EMPA-REG OUTCOME trial did not have HF at baseline, the data suggest that empagliflozin may prevent development of HF.

A number of trials have targeted patients with CVD including HF, but did not specifically focus on HF patients. Nevertheless, we can learn about the treatment of HF patients from these trials, such as the EMPA-REG OUTCOME trial.[19] The SGLT2 inhibitor empagliflozin reduced glucose by renal excretion, resulted in loss of calories, body weight, and fluid, and BP was decreased, which are all beneficial effects for HF patients.[20] Patients had to have established CVD, but HF was a not a qualifying criterium for this study. Patients with HF in the trial (about 700) were older, had a higher percentage from Europe and a higher BMI compared to patients without HF. Other than CVD, it is possible that patients with HF were included at baseline. Unfortunately, EF, NYHA class or the BNP value are not known. Many of them had kidney dysfunction with GFR <60. Interestingly, the EMPA-REG OUTCOME trial had 3-point MACE as primary outcome and secondary endpoints included hospitalization for HF as an important prospectively specified endpoint. In patients on empagliflozin, all-cause and CV mortality decreased, as did hospitalization for HF. Because most patients did not have HF at baseline, the data suggest that empagliflozin may prevent development of HF. Statements about treatment of existing HF are difficult to make, because it is not known who had HF at baseline. However, comparing the 700 HF patients with the rest of the patient population showed similar results for empagliflozin, regardless of type of outcome event, indicating that these HF patients with T2DM benefitted equally as those without HF.

To get an idea what kind of HF patients these were, Anker compared event rates in the EMPA-REG OUTCOME trial with those in several HF trials. Event rates in the overall EMPA-REG OUTCOME trial showed 15 hospitalization per 1000 patient years of follow-up, but in the subgroup of patients with HF this was 52. This is about in the middle of what has been observed in HFpEF trials. The CHARM trial in patients with systolic HF reported ~1 in 10 deaths for all-cause mortality per 1000 patient years of follow-up. HFpEF trials showed about half that mortality rate, as did the EMPA-REG OUTCOME trial with 55 events per 1000 patient years. Anker concludes that this suggests that the EMPA-REG OUTCOME trial may have consisted of a HFpEF patient population. Thus, he thinks that these results indicate that empagliflozin may be used to treat HFpEF patients, although this was not a prespecified idea in the trial. In addition, EF and precise details are not known. The guidelines for CHF patients with diabetes recommend using standard HF medication (ACE-I, ARB, β-blockers) or metformin (level IIa with level of evidence C (expert consensus) recommendation) and glitazones should not be used. For the prevention of development of HF, empagliflozin should be considered, but it has a IIa indication with level of evidence B (based on 1 trial).[21]

Considering treatment of HF, the results of the EMPA-REG OUTCOME trial should be cautiously interpreted, as other trials have shown to misguide us in the past. For example the trials on vesnarinone; a small trial first showed surprisingly positive results, which could not be confirmed in a larger trial.[22,23] In addition, we cannot conclude anything on prediabetes in HF patients. About 20-50% of HF patients have prediabetes, but these patients have not been included in trials.
To answer these outstanding questions, new trials have been designed. The use of empagliflozin in patients with HF with reduced EF will be tested in the EMPEROR-Reduced trial with a total of 3000 patients, and later it will be tested in patients with HFpEF in EMPEROR-Preserved (4100 patients). Treatment with dapagliflozin is tested in a HFpEF population in the DAPA-HF trial enrolling 4500 patients. The difference between these trials is the BNP inclusion criterium. In all these trials, CV death and HF hospitalization are the primary endpoints.
These trials are essential, because no data on SGLT2 inhibitors are available in the treatment of HF patients, and it is necessary to validate the results of the EMPA-REG OUTCOME trial. It is unknown whether the benefits demonstrated in the EMPA-REG OUTCOME study population will extend to a true HF population. For instance, the CORONA and GISSI-HF programs have demonstrated that statins did not yield benefit for HF patients, unlike in patients

with CVD. In addition, it is not clear which type of HF patients were included in EMPA-REG-OUTCOME (HFrEF, HFpEF, HFmrEF). Thus, we need to better understand in which patients these drugs are most beneficial.

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