Meeting Impression

55th ERA-EDTA Congress
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Diabetic Kidney Disease: Exploring mechanisms and outcomes of SGLT2 inhibition

This symposium was held during the 55th ERA-EDTA Congress 2018 in Copenhagen, Denmark. Christoph Wanner, Per-Henrik Groop and Colin Baigent discussed the mechanisms and outcomes of sodium glucose co-transporter 2 (SGLT2) inhibition in diabetic kidney disease. Key lessons from the EMPA-REG OUTCOME trial focusing on the effect of empagliflozin on renal and cardiovascular (CV) events were presented. Also, potential underlying mechanisms of the CV and renal protection seen with SGLT2 inhibition were discussed. Finally, three new trials on SGLT2 inhibition were presented and compared to address the question whether SGLT2 inhibitors have any value for patients with established chronic kidney disease (CKD).

TOPICS

Key lessons from the EMPA-REG OUTCOME trial
Prof. Christoph Wanner, University of Würzburg, Germany

Understanding CKD and SGLT2-inhibition: what are the key mechanisms?
Prof. Per-Henrik Groop, University of Helsinki, Finland

Addressing the remaining questions on SGLT2 and CKD: a review of new outcome trials
Prof. Colin Baigent, University of Oxford, United Kingdom

What are the key lessons from the EMPA-REG OUTCOME trial?

Prof. Christoph Wanner, *University of Würzburg, Germany*

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) OUTCOME trial was published in 2015. This trial randomly assigned type 2 diabetes mellitus (T2DM) patients with established cardiovascular disease (CVD) to receive placebo, or 10 mg or 25 mg of the SGLT2 inhibitor empagliflozin after a placebo run-in period. The treatment period was followed by 30 days consisting of a wash-out period and serum creatinine measurements for the kidney endpoint. 7020 Adults with body mass index ≤45 kg/m2, hemoglobin (Hb) A1c of 7-10% and an estimated glomerular filtration rate (eGFR) >30 ml/min/1.73m2 were included. The CV results of this trial were surprisingly positive as will be discussed next [1].

A reduction in CV outcomes was observed in the EMPA-REG OUTCOME trial after treatment with the SGLT2 inhibitor. Treatment of only 39 patients with empagliflozin on top of standard care (ACE-inhibitors, statins and aspirin), prevents one death over a period of three years [1]. This compares favorably with treating 56 persons over a period of five years with ramipiril [2] and 30 persons over a period of 5.4 years after treatment with simvastatin [3]. Prof. Wanner therefore concluded: 'The EMPA-REG OUTCOME has been an important study in the field of cardiovascular outcomes'.

Next, prof. Wanner discussed the secondary endpoints of the study , starting with the effect of empagliflozin on the kidneys. Treatment with empagliflozin in T2DM patients with well-preserved kidney function and a mean eGFR of 74 ml/min/1.73m2 initially resulted in eGFR reduction by about 3 to 4 mL/min/1.73m2 and then eGFR normalized over time by

gradually increasing about 2 mL/min/1.73m2/year, whereas the placebo group more often showed progression of CKD. During the follow-up after the treatment period (median: 34 days) without the use of empagliflozin, eGFR increased and returned to baseline. At the follow up visit, the difference in eGFR from baseline between placebo and empagliflozin was 4.7 ml/min/1.73m2, which translated into a reduction of kidney endpoints with empagliflozin[4].

New onset or worsening of nephropathy was significantly reduced by 39% after treatment with empagliflozin

The secondary kidney endpoint new onset or worsening of nephropathy was significantly reduced by 39% after treatment with empagliflozin compared with placebo (HR: 0.61, 95%CI: 0.53-0.70, P<0.0001). Also, new onset macroalbuminuria was significantly decreased by 38% in the empagliflozin group, suggesting that nephropathy is driven by macroalbuminuria. Although only a few patients showed doubled creatinine levels, a reduction of 44% was observed after treatment with empagliflozin as compared with placebo. Initiation of renal replacement therapy occurred in 0.3% of the patients treated with empagliflozin and in 0.6% of the patients treated with placebo (relative risk reduction: 55%) [4].

In macroalbuminuria patients (UACR ratio of 800 mg/gram) albuminuria was prominently reduced by 50% at the end of empagliflozin treatment, but albuminuria returned to half of baseline levels when patients stopped using the drug, suggesting there might be a structural benefit over time. When comparing different risk populations, macroalbuminuria patients (N=764) showed lower eGFR levels at a later stage of the study in comparison with normoalbuminuria (N=4042) and microalbuminuria patients (N=1995). This risk population mainly consisted of older patients, with more comorbid diseases, more long-standing diabetes, and their eGFR was reduced by 7 mL/min/1.73m2/year with placebo. This reduction in eGFR was stabilized after treatment with empagliflozin, showing a prominent and significant difference with placebo treatment [5].

A next step was to investigate the effect of empagliflozin in patients with pre-existing CKD, the so-called renal population. CKD was defined by an eGFR of 30-60 mL/min/1.73m2 and/or macroalbuminuria at baseline and the study included 2250 patients. To study the effect of the drug in this subpopulation, HbA1c levels were evaluated and compared with patients with normal kidney function (eGFR ≥60 mL/min/1.73m2 at baseline). HbA1c was reduced in patients with normal kidney function, whereas only 0.3% of the CKD patients showed a reduction, possibly due to lower glucose excretion. Thus, it might be that empagliflozin does not effectively lower HbA1c in patients with CKD. To further study this, a subanalysis was done focusing on groups with different eGFRs (≥90, 60 to <90, 45 to <60, 30 to <45 mL/min/1.73m2) and albuminuria patients. Surprisingly, the hazard ratio risk reduction for new onset or worsening of nephropathy was almost the same for each subgroup with different eGFRs, suggesting that patients with an eGFR of at least 30 ml/min/173m2 would benefit from the drug. Also, according to the results, albuminuria patients can benefit from treatment with empagliflozin [6].

Kaplan-Meyer survival curves showed a reduced incidence of nephropathy in prevalent CKD patients after treatment with empagliflozin as compared with placebo (HR: 0.58, 95%CI: 0.47-0.71, P<0.001). Similarly, CV death was decreased in CKD patients with empagliflozin (HR: 0.70, 95%CI: 0.51-0.96, P=0.0265).Of note, the curves for CV death separate after one year, indicating that treatment with empagliflozin is effective in later stages of CKD. When looking at hospitalization for heart failure (HF), again CKD patients showed reduced risk after treatment with empagliflozin compared to placebo (HR: 0.60, 95%CI: 0.42-0.86, P=0.0056), with a prominent effect already in a very early stage of the trial [6].

Prof. Wanner finished with a last slide about safety of empagliflozin. 'It is important to look at acute renal failure and acute kidney injury when evaluating the safety of this drug. In randomized trials there is no evidence of harm with empagliflozin in terms of kidney outcomes' [4].

In summary, the EMPA-REG OUTCOME trial results showed a reduction of new onset or worsening of nephropathy, CV death and hospitalization for HF in CKD patients after treatment with empagliflozin, as compared with placebo, on top of standard care.

Understanding CKD and SGLT2-inhibition: what are the key mechanisms?

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

Prof. Groop set out to explain the mechanisms and outcomes of SGLT2 inhibition. First, he started with a few words on the consequences of CKD. Prof. Groop: 'The consequences of CKD are grim. Data from many trials and observational studies show a many-fold increased risk of premature mortality in T2DM patients with albuminuria and/or impaired eGFR, which is due to CVD [7]. Every T2DM patient with CKD has a doubled risk of myocardial infarction, stroke, peripheral vascular disease and premature death [8] due to risk factors that come with CKD, such as hypertension, oxidative stress, insulin resistance, arterial calcification, inflammation, left ventricle

hypertrophy, endothelial dysfunction, activation of the reno-angiotensin-aldosterone system, activation of the sympathetic nervous system, anemia etc. Without doubt, CKD and CVD go hand in hand'.

Two big outcome trials demonstrated renal benefits in patients with T2DM after treatment with SGLT2 inhibitors

Next, Prof. Groop shared renal outcome findings from the EMPA-REG OUTCOME trial and the CANVAS Program . The CANVAS program evaluated another SGLT2 inhibitor, canagliflozin. As prof. Wanner had already mentioned, the EMPA-REG OUTCOME trial demonstrated a 39% reduction in new onset or worsening of CKD in patients who were exposed to either 10 or 25 mg empagliflozin compared to placebo on top of standard care. Also, the composite endpoint of doubling of serum creatinine level, initiation of renal replacement therapy or death due to renal disease was reduced with 46% and a 55% decrease in the likelihood of ending on dialysis was observed after treatment with empagliflozin. Besides, empagliflozin-treated patients showed an initial drop in the eGFR followed by preservation of kidney function, which was not observed in the placebo group [4].

The CANVAS Program, which included low renal risk patients, showed a very similar effect of 40% reduction in the composite endpoint of eGFR, end stage renal disease or renal death. Again, an initial drop in eGFR was found, followed by normalization and preservation of kidney function. Summarized, these two big outcome trials demonstrated renal benefits in patients with T2DM after treatment with SGLT2 inhibitors [9].

The next question was: 'Why do SGLT2 inhibitors work so well?'. Although SGLT2 inhibitors are not indicated for use in patient with type 1 diabetes (T1DM), we can learn a lot about SGLT2 inhibitors from a T1DM study. One study showed a reduction of the eGFR by 33 ml/min/1.73m2 in hyperfiltering T1DM patients after treatment with empagliflozin [10]. Hyperfiltering T1DM patients have glomerular hypertension and increased intra-glomerular pressure. T1DM patients with normal filtering did not show any effect on renal function measures after treatment with 25 mg empagliflozin. This drug did, however, reduce both the intra-glomerular pressure and the eGFR in hyperfiltering T1DM patients [11]. This was accompanied by a decrease in renal blood flow and an increase in renal vascular resistance, which is consistent with an increased tone in the afferent arteriole [10].

The renal effects of the SGLT2 inhibitors can be explained by the tubular hypothesis. Normally, the SGLT2 transporter in the proximal tubule absorbs glucose and sodium, which is a balanced process. Residual sodium reaches the macula densa next to the glomerulosa, where it is absorbed again by another counter-transporter that transports sodium, potassium and chloride. Absorption of sodium requires energy, which is generated from ATP. During ATP hydrolysis, adenosine is generated, which is a basal constrictor of the afferent arteriole.

Hyperfiltering T2DM and T1DM patients with established CKD show an exaggerated reabsorption of glucose and sodium in the proximal tubule, into the blood. In this case sodium does not reach the macula densa and consequently there is no vasoconstriction in the afferent arteriole, but instead vasodilation. SGLT2 inhibitors block the sodium reabsorption, and consequently sodium reaches the macula densa again. This allows adenosine to be generated, causing vasoconstriction [12]. Prof. Groop emphasized the effect of empagliflozin on glomerular hyperfiltration by displaying a diagram that shows a similar effect of ACE inhibitors (decrease of 35 mL/min versus 33 mL/min respectively) [13][10].

Hypoxia also seems to play a role, which he illustrated with observations in experimental studies. In diabetic mice, renal hypoxia, increased eGFR and a slight increase in proteinuria were observed within three days after diabetes induction [14]. Moreover, hypoxia was not only seen in the cortex, but also in the medulla of the kidneys. After administration of dinitrophenol, a mitochondrial uncoupler, increased proteinuria, kidney vimentin expression and infiltration of inflammatory cells were observed, which is similar to the phenotype of diabetes, obesity and hypertension [15].

According to the tubular hypothesis and results in diabetic mice, prof. Groop hypothesized: 'Due to administration of a SGLT2 inhibitor there is less sodium handling, leading to reduced oxygen consumption and hypoxia, which in the end results in renal benefit'.

In summary, CKD is a common complication with grim consequences. SGLT2 inhibitors have been shown to result in CV protection and renal protective effects, beyond their effects on glucose control. However, the renal protective effects have to be studied in dedicated renal trials in the future.

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Addressing the remaining questions on SGLT2 and CKD: a review of new outcome trials

Prof. Colin Baigent, *University of Oxford, United Kingdom*

Prof. Baigent reviewed ongoing SGLT2 outcome trials in CKD patients, set up to address the question whether SGLT2 inhibitors have any value for patients with established CKD.

Prof. Wanner already discussed the promising results of the EMPA-REG OUTCOME trial on the effects of empagliflozin in patients with a mild degree of renal impairment. The key question that needs to be answered is whether there is any impact of empagliflozin on the rate of progression from CKD to end-stage renal disease in patients with more severe CKD than those included in the EMPA-REG OUTCOME trial, before the drug may be more widely used in patients with CKD.

The starting point to consider a broader application, is the observation that, as eGFR declines, glycosuria is also lower [16], which has in turn an impact on HbA1c levels. Indeed, a pooled analysis of phase 3 trials with empagliflozin showed a difference in HbA1c levels of 0.9% in patients with well-preserved eGFR >90 ml/min/1.73m2 compared with placebo, whereas a much smaller impact was observed in patients with eGFR <30 ml/min/1.73m2. In contrast, the time to doubling of creatinine levels, initiation renal replacement therapy or renal death in EMPA-REG outcome was only slightly influenced by baseline levels of renal function [17]. Prof. Baigent: 'Thus, a reduction in CKD outcomes did not depend on renal function. There is a sort of uncoupling of the effects of the drug on glycemic parameters and its apparent effects on renal outcomes. This encourages us to think that we might be able to achieve a benefit even among patients with much more severe renal disease'.

Since the SGLT2 protein is also present in non-diabetic patients and it functions in exactly the same way, SGLT2 inhibition might work in non-diabetic CKD patients

Another question is how empagliflozin affects individuals without diabetes, who make up about 60% of all CKD patients depending on geographical region. Prof. Baigent: 'It would be great to find a drug that prevents CVD and prevents progression to end-stage renal disease in non-diabetic CKD patients. Since the SGLT2 protein is also present in non-diabetic patients and it functions in exactly the same way, SGLT2 inhibition might work in non-diabetic CKD patients'.

It has already been shown that empagliflozin has hemodynamic effects in overweight people, with an 8% reduced eGFR after treatment [18]. Similarly, reduced creatinine levels were found in pre-diabetic or obese people after treatment with empagliflozin [19]. 'These data suggest that the effects of SGLT2 inhibition may be relevant to the very large number of CKD patients without diabetes'.

Before translating data from the EMPA-REG OUTCOME trial and CANVAS program to clinical use of the drugs in CKD patients, there are some key areas of uncertainty that need to be addressed . About the efficacy, Baigent wondered: 'What happens to the effects of SGLT2 inhibition as eGFR declines and what will happen to the end-stage renal disease outcomes?' Beneficial effects on HF were observed, but the effect of the drugs on CV outcomes as eGFR decreases remain to be elucidated. Similarly, the effects of empagliflozin on CV and renal outcomes in patients without diabetes are unknown. About safety, prof. Baigent said: 'We would like to know the magnitude of known adverse effects as eGFR declines?' Naturally, it needs to be studied whether there are any unanticipated adverse effects in patients with severe renal impairment.

Three new trials will determine how the effect of SGLT2 inhibitors vary according to baseline levels of renal function, whether or not patients have diabetes

Next, Prof. Baigent summarized currently ongoing trials. First, the Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial recruited 4401 T2DM patients >30 years old (mean age: 63 years) with HbA1c levels between 6.5 and 12% (mean: 8.3%), eGFR 30-90 ml/min/1.73m2 (mean 56: mL/min/1.73m2), UACR between 300-5000 (median: 927), on a RAS blocker at baseline. Patients were randomized to either empagliflozin 100 mg daily or placebo. The primary endpoint is doubling of serum creatinine, end stage kidney disease, or death from CV or renal causes [20].

Secondly, the Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA CKD) is currently recruiting about 4000 patients aged >18 year, eGFR 25-75 ml/min/1.73m2, UACR between 200-5000, on RAS blockade at baseline. Patients are randomized to either 5 or 10 mg dapagliflozin or placebo. The primary endpoint is a 50% decline in eGFR, end stage renal disease, or death from renal or CV causes [21].

Prof. Baigent described the third study in more detail. The EMPA-KIDNEY study is about to start, and will recruit patients >18 years old who are at risk for progression

to end stage renal disease and who are on stable RAS blockade at baseline. A key element is that treatment with SGLT2 inhibitors is not part of standard care. There will be two groups of patients; the first group will have eGFR of 20-45 ml/min/1.73m2, with or without proteinuria, and is considered very likely to progress to end stage renal disease. This group is anticipated to potentially benefit from SGLT2 inhibition. The second group of patients will have eGFR between 45-90 ml/min/1.73m2, UACR of >200 mg/g or a protein creatinine ratio greater than 300 mg/g. Study enrollment will consist of a screening visit, followed by a run-in period with placebo of 8 to 12 weeks in order to identify people who are not likely to comply with their treatment long term, and also to ensure that they are on the appropriate RAS blockade. Eligible patients will then be randomized to either 10 mg empagliflozin or placebo and will be followed every six months for a fixed period until the beginning of June 2022 [22].

Prof. Baigent compared the three trials by discussing the inclusion criteria, primary endpoints and power, and secondary endpoints. The three studies have slightly different age criteria and a key difference is that the CREDENCE study only includes patients with T2DM, whereas the DAPA CKD study and the EMPA-KIDNEY study also include patients without diabetes. Another criterion that differs slightly is renal function, since the EMPA-KIDNEY study includes patients with an eGFR of 20-45 ml/min/1.73m2, irrespective of albuminuria, while the other two studies only include patients with an eGFR of ≥30 and <90 ml/min/1.73m2 (CREDENCE) and 25-75 ml/min/1.73m2 (DAPA-CKD).

A total of over 2000 primary endpoints is anticipated in these three studies. A substantial number of patients with CKD can quite reasonably and reliably demonstrate whether SGLT2 inhibition has an impact on the vascular and renal endpoints. The statistical assumptions are very similar for all three trials and each trial is well powered to detect an effect of around 20% in the primary composite renal outcome.

This drug class has the potential to cause major advances in the management of patients with CKD

The three studies have slightly different secondary outcomes, but in essence all of the studies try to understand the impact of SGLT2 inhibitors on or renal outcomes. Prof. Baigent: 'By the time these three trials have finished, it should be possible to determine to some extent how the effects of these drugs vary according to baseline levels of renal function, whether or not patients have diabetes, and according to other key parameters that vary among the different types of patients who are managed in renal programs'.

Prof. Baigent finished with the conclusion: 'By 2022 we will likely have data on the effects of SGLT2 inhibition on about 13,500 patients with CKD. And that will include about 3,000 patients without diabetes. We should have around 2000 primary outcomes and while it is a composite renal outcome, there should be substantial numbers, some hundreds of end stage kidney disease outcomes. Despite this, there will be limited power for subgroups, and so we do need to make sure that, if any new SGLT2 inhibitors come along, we have data on patients with CKD. That would potentially need new trials. This drug class is very interesting, and I think it has the potential to cause major advances in the management of patients with CKD.'

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