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SGLT-2 INHIBITION, DIABETES AND CVD: WHERE DOES THIS FIT IN CV RISK MANAGEMENT?

Patients with diabetes have an increased risk for cardiovascular (CV) morbidity and mortality. Great benefit on CV outcome in these patients has been achieved with SGLT-2 inhibitors, which represent the newest class of anti-diabetic medication. During a satellite symposium at the ESC 2016 in Rome, organised by the Physicians' Academy for Cardiovascular Education (PACE), the impact of CV disease in patients with diabetes, SGLT-2 inhibitor trial outcome data as well as the mechanism by which SGLT-2 inhibitors may affect heart function, were discussed.

TOPICS

Challenging CV risk in diabetes: ready for a new approach?

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Diabetes is increasing in all areas of the world and once you have diabetes, it has a tremendous impact on CV morbidity and mortality. Fortunately, great efforts in CV research over the past years substantially reduced morbidity and mortality rates. Although, emphasised Dr. John Deanfield, there is still a considerable residual CV morbidity and mortality that represents a challenge.
It was recently shown by the Swedish National Diabetes Register that CV mortality mostly occurred in the younger population; the hazard ratio decreased stepwise with age[1]. Furthermore, CV mortality was predominantly driven by type 2 diabetes as compared to type 1 diabetes[2], which suggests the impact of other damaging risk factors on mortality, such as hypertension and hypercholesterolaemia. The multifactorial influence on CV morbidity and mortality was further supported by the notion that multiple risk factors drive CV death in both diabetic and non-diabetic patients. In this regard, the MRFIT trial[4] showed that the more risk factors one has, the worse the outcome. This relationship was much more pronounced in diabetic patients compared to non-diabetic patients. The benefit of treating multiple risk factors has been shown in a follow-up of the Steno-2 trial[5]. This means that not only the lower is better, but also the broader is better, in terms of CV intervention.

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These data suggest that diabetes should be prevented in the young and in a multifactorial fashion. In this light, there is increasing evidence showing that prevention of obesity and other modifiable risk factors in the young reduced the

number of diabetic patients. Moreover, early intervention reversed diabetes and modern treatment reduced CV impact. For example, statin therapy was able to achieve a huge benefit for diabetic patients in terms of myocardial infarction and CV death, which in the CARD study corresponded to a relative risk reduction of 37%[3].

Also lowering blood pressure or cholesterol levels showed a very strong association with CV outcome, however a less clear benefit in CV endpoints has been observed with traditional glucose-lowering medication. In contrast, some studies demonstrated that these medications were even associated with an increased risk. So how can we manage glycaemic control?

In the past few years, two classes of glycaemic drugs have been developed that seem to make a difference in terms of CV outcome; GLP-1 receptor agonists and SGLT-2 inhibitors. Liraglutide is a GLP-1 receptor agonists that was tested in the LEADER trial and demonstrated an event and mortality reduction benefit in patients with established diabetes, although this benefit was only notable after 2 years. The second group of drugs is represented by the SGLT-2 inhibitors, which target renal reabsorption of glucose and therefore stimulate glucose excretion in the urine. One of the SGLT-2 inhibitors is empagliflozin, which was evaluated in the EMPA-REG OUTCOME trial[6]. In this trial, CV death was impressively reduced by 38%, which is equivalent to the effects seen with statins in patients with diabetes. It is hypothesised that the clinical effects seen with SGLT-2 inhibitors are due to haemodynamic changes. Furthermore, it was recently reported that empagliflozin also has an effect on kidney function as it reduced progression of nephropathy as well as a composite renal outcome in diabetic patients. Besides empagliflozin, trials with different SGLT-2 inhibitors are currently ongoing, including canagliflozin and dapagliflozin.

SGLT-2 inhibitors in T2DM management: current position & future promise

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Since the 1950s on, new medications for diabetes had not been discovered until midway 1990s. Before that, insulin and sulfonylureas were the only options for treatment. As of 1995, the discovery of new medicines suddenly took off, which started with the introduction of metformin. Since then, every 3 to 4 years new medicines for diabetes were introduced.

The introduction of SGLT-2 inhibitors occurred in 2013. SGLT-2 inhibitors belong to the "glucose excreters". These transporters of sodium and glucose serve to augment glucose excretion by the kidney. Until a certain threshold, SGLT-2 proteins can reabsorb glucose that is filtered by the glomerulus. Beyond this threshold, glucose is being excreted. By blocking SGLT-2 proteins, more glucose is being excreted.

Since 1995, every 3-4 years a new anti-hyperglycemic category of medication has been introduced, including the SGLT-2 inhibitors in 2013

There are three SGLT-2 inhibitors currently on the American and European market, three others in Japan and one is still under phase III investigation. But how effective are these inhibitors? Most important differences of SGLT-2 inhibitors compared to traditional drugs are the 6-fold fewer events of hypoglycaemia as well as the more durable haemoglobulin A1c (HbA1c) reduction, the modest body weight reduction, blood pressure reduction and triglyceride reductions, a small increase in HDL-c, a decrease in the albumin:creatinin ratio and the insulin-independent fashion of these drugs. In contrast, SGLT-2 inhibitors can go together with an increased risk for genital mycotic infections, urinary tract infections, diabetic ketoacidosis, polyuria, a reversible decrease in glomerular filtration rate (GFR), a small increase in LDL-c and fractures.

The benefits of SGLT-2 inhibitors can also be linked to CV risk benefit, like body weight and blood pressure reduction. In this light, the EMPA-REG OUTCOME trial evaluated the CV outcomes of diabetic patients treated with the SGLT-2 inhibitor empagliflozin. This trial showed a 14% risk reduction in the 3-point MACE outcome that was primarily driven by the impressive reduction in CV deaths (38%) and this effect already occurred very early during treatment[6]. This early effect suggests a haemodynamic effect rather than a reduction in atherosclerosis.

So how deleterious are these drugs for renal function? As said before, there is a small but reversible decrease in GFR and it is known that the drugs are less effective when kidney function is reduced. But there is a positive effect on albuminuria and patients with a genetic abnormality resulting in loss of glucose reabsorption prove that loss of glucose reabsorption is safe in non-diabetic patients with normal GFR. Furthermore, the EMPA-REG OUTCOME study showed a 41% reduction in worsening nephropathy with SGLT-2 inhibitors[6].

The current position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) regarding treatment of diabetic patients advocate that weight control, healthy eating and physical activity should be the foundation of therapy. This is followed by metformin as monotherapy, which after three months can be extended with dual or triple therapy with metformin and sulfonylureas, thiazolidinedione's, DPP4-inhibitors, GLP-1 receptor agonists, insulin or SGLT-2 inhibitors. However, the choice of medication should be driven by the patient.

Heart failure & diabetes: SGLT2 inhibition, a paradigm shift?

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Until very recently, heart failure as a problem in diabetes was largely ignored, although it is one of the most common and most important complications in diabetes. But the EMPA-REG OUTCOME study[6] put heart failure on the map; SGLT-2 inhibitors showed a remarkable reduction in heart failure hospitalisation and mortality.

How is heart failure prevented and mortality reduced by SGLT-2 inhibitors, and can these medications be used to treat established heart failure?

There are multiple possible explanations for the prevention of heart failure and reduction of mortality by these medications. These include the direct and indirect action on the myocardium, other myocardial effects such as through the extracellular matrix, antiarrhythmic effects, blood pressure-lowering and reducing sodium or extracellular fluid volume by the kidneys or other renal effects. Dr. McMurray further elaborated on these mechanisms.

A direct action of SGLT-2 inhibitors on the myocardium could be through a shift in myocardial energetics, resulting in a more fuel efficient heart. It is proposed that the heart metabolism is shifted away from fatty acids and glucose towards ketones. Indirect actions on the myocardium may also involve increased efficacy, thereby resulting in anti-ischaemic effects or reduced myocyte necrosis. But there is no evidence for this. Nevertheless, the EMPA-REG OUTCOME trial excluded a direct effect of SGLT-2 inhibitors on myocardial infarction as the number of these events were not reduced. Furthermore, SGLT-2 inhibitors may potentially cause an antiarrhythmic effect through a reduction in extracellular fluid volume, reducing atrial pressure and subsequently atrial arrhythmias. But so far, this remains only speculation.

More evidence exists on the effect of SGLT-2 inhibitors on blood pressure-lowering and heart failure. Many studies have shown the benefit of blood pressure-lowering on heart failure. Although the EMPA-REG OUTCOME study showed only a marginal reduction of 4-5 mmHg systolic blood pressure by SGLT-2 inhibitors, a meta-analysis showed that even a modest decrease in blood pressure reduction can result in a substantial decrease in the development of new-onset heart failure[7]. Moreover, blood pressure acts on the cardiac volume as well as on sodium concentrations. And on the other hand, sodium concentrations can also be altered by the diuretic effect of SGLT-2 inhibitors. The strong effect of diuretics on heart failure reduction has been evidenced by multiple studies. The diuretic and natriuretic effects of SGLT-2 inhibitors also reduce intravascular volume and thereby preload and perhaps also afterload. It is known that reducing the cardiac afterload and also preload improves the cardiac function. Taken together, the cardiac load, diuretic effect as well as the blood pressure-lowering may be critical in explaining the significant reduction in heart failure observed in the EMPA-REG OUTCOME trial. In addition, as it has been shown in several trials that blood pressure-lowering can have a very fast effect on heart failure incidence, this may explain the early benefit from SGLT-2 inhibitors observed in the EMPA-REG OUTCOME trial. Other large evidence regarding the heart failure benefit with SGLT-2 inhibitors comes from the renal function, as is known that the cardio-renal axis is critical in heart failure. Moreover, it was very recently shown that the incidence of worsening renal function in the EMPA-REG OUTCOME trial was remarkably decreased with SGLT-2 inhibitors.

Heart failure is related to mortality, which may explain the reduced number of mortality seen with SGLT-2 inhibitors. This relationship has been shown in the RECORD and SAVOR-TIMI-53 trials[8,9], patients who develop heart failure have a 3- to 4-fold and 4-5-fold increased risk of mortality, respectively. Death as a result from heart failure is caused by either worsening heart failure or lethal ventricular arrhythmias. It is, however, not clear yet whether deaths are related to heart failure with a preserved or reduced left-ventricular ejection fraction.

Using SGLT-2 inhibitors to treat heart failure is an interesting thought and needs further investigation. Remarkably in the EMPA-REG OUTCOME study, patients with heart failure at baseline had a treatment benefit with SGLT-2 inhibitors similar to patients without heart failure, which seems promising.

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