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ROLE OF SGLT-2 INHIBITORS IN THE TREATMENT OF DIABETIC PATIENTS

20. Patophysiology of cardiovascular and renal benefits of SGLT-2 inhibitors and its implications for clinical practice

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The inhibition of sodium-glucose cotransporter-2 (SGLT-2) in the kidney proximal tubules is a new therapeutic approach in prevention of atherosclerosis in patients with type 2 diabetes. SGLT-2 inhibition is a mechanism in diabetes treatment independent of insulin resistance, insulin secretion or incretin effect. The primary aim of the treatment is the inhibition of compensatory increased glucose reabsorption in kidneys, which leads k increased glucose and sodium elimination by kidneys and subsequent improvement of glycemic control, weight reduction and blood pressure decrease. SGLT-2 inhibitors are alternatively called gliflozins. At the present time, three drugs from the mentioned group are available – dapagliflozin, empagliflozin and canagliflozin. So far, only one study of cardiovascular safety and efficacy has been finished in patients with diabetes, specifically with empagliflozin (EMPA-REG OUTCOME). Those patients with type 2 diabetes were included who had with previous cardiovascular disease and also a wide use of lipid-lowering, blood pressure-lowering and anti-platelet treatment. The study observed a significant effect of empagliflozin treatment on primary composite outcome which incidence was reduced significantly by 14 %. At the same time there was a significant reduction in cardiovascular mortality by 38 % and overall mortality by 32 %. Among the other endpoints a 35 % reduction in incidence of hospitalizations for heart failure and a 39 % reduction in the progression of diabetic nephropathy was observed. Meta-analyses of the studies with dapagliflozin observed also a significant reduction in incidence of hospitalizations for heart failure, in incidence of myocardial infarction, as well as in incidence of major cardiovascular events. In the present time, the studies of cardiovascular safety and prevention with canagliflozin (CANVAS) and dapagliflozin (DECLARE) are on the way. The patients included in the mentioned studies have type 2 diabetes and similar or lower cardiovascular risk in comparison with those included in EMPA-REG OUTCOME. The decreases in blood glucose, body weight and blood pressure do no fully explain the effect of gliflozins on the cardiovascular mortality. Further potential mechanisms are investigated and it seems that the benefit of SGLT-2 inhibitors is related mainly to it effect on heart failure by more effective use of energy by the myocardium as a result of ketoacids utilisation. Renal protective effect if gliflozins is explained by their protective effect on renal damage by the restoration of decreased tubuloglomerular feedback resulting in reduction of the glomerular filtration pressure. Further possible mechanisms of cardiovascular and renal protection are currently under investigation both in animal models, in healthy subjects and in the subjects with type 2 diabetes. The implication for the clinical practice include the widening in the spectrum of gliflozin indications from antidiabetic treatment only to the prevention of cardiovascular events, heart failure and the progression of nephropathy.

21. SGLT-2 inhibitors and cardiovascular risk

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Cardiovascular (CV) disease represents the major cause of morbidity and mortality of patients with type 2 diabetes mellitus (DM2T). The risk of CV incidents is not only 2–3 times higher than in non-diabetic population, but they also have worse prognosis and requires more complex treatment. Moreover, the try to normalize plasma glucose levels in CV high risk patients was associated with increased risk of mortality. Increased risk of heart failure (HF) and CV mortality was also observed in association with treatment with some antidiabetic drugs (glitasones, some sulphonylureas, some gliptins) and very high dosage of insulin, as well. The recent RCT and RWE studies focused on CV safety of new class of antidiabetic drugs – inhibitors of SGLT-2 cotransport (empagliflosine, dapagliflosine, canagliflosine) revealed not only CV safety of these drugs but also CV and renal benefits such as reduced risk of CV mortality, reduced hospitalization due to HF or slowing of progression of diabetic nephropathy. Moreover, the mechanism by which these drugs reduce plasma glucose is independent from insulin secretion and insulin sensitivity. Drugs also reduce body weight and visceral adiposity, blood pressure, triglycerides, uric acid, arterial stiffness, have

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diuretic effect. Effect of improving energetic metabolism of failing myocardium is also considered. Thus, after the years of some disappointments and embarrassment in treatment of DM2T, these studies brought a convincing evidence of CV and renal benefits, reviewed our current view on treatment goals, and indicated the new trends in treatment of DM2T. These findings were very promptly introduced also into the treatment algorithms of ADA/EASD as well as national treatment recommendations, including Slovak diabetes association.