

Editorial

RENOPROTECTIVE EFFECTS OF SGLT2 INHIBITORS

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Recent data indicate that non-communicable chronic diseases represent a major health threat, representing the main cause of premature mortality [1], with diabetes contributing largely to this [2]. Moreover, diabetes constitutes a major cause of morbidity and mortality worldwide, with latest IDF data estimating healthcare expenditures related to diabetes to roughly 727 billion USD in 2017 [2]. The bulk of these costs are induced by the chronic complications of the disease, both microvascular and cardiovascular. Progresses in the treatment of diabetes and associated cardiovascular risk factors (dyslipidemia and high blood pressure) have led to a decline in mortality of diabetes subjects with increased survival, with a concomitant increase in the prevalence of microvascular complications, including diabetes chronic kidney disease (CKD) [3].

Diabetes related CKD (also known as diabetic kidney disease) represents currently the main cause of end stage renal disease (ESRD) requiring replacement therapy in developed countries [4]. For example, the prevalence of ESRD in the USA has doubled from 1990 to 2016, with a current prevalence of 2.2‰ [5]. In

the same time, prevalence of CKD in diabetes subjects is estimated to be up to 30-50% [6]. In addition, the presence of CKD greatly increases the risk of cardiovascular events, making this condition one of the costliest diabetes complications. Diagnosis is based on the presence of increased urinary albumin-to-creatinine ratio (UACR) or reduced glomerular filtration rate (GFR) with proof of persistence for over 3 months [6].

Strict glycemic control was repeatedly shown to prevent or at least delay the onset/progression of diabetic kidney disease both in type 1 (T1DM) and type 2 (T2DM) subjects. Thus, intensive glycemic control in the Diabetes Complications and Control Trial (DCCT) was shown to reduce albuminuria and decline of the eGFR both during the randomized part of the study and in the long-term follow-up of T1DM subjects in the EDIC study [7]. The same was true in T2DM subjects in the UKPDS trial (including patients with new onset/recently diagnosed diabetes) and the ACCORD, ADVANCE and VADT trials (including subjects with more advanced diabetes), with stronger effects on progression of albuminuria and almost

no impact on the decrease of eGFR [8]. In addition, control of blood pressure values, especially using blockers of the renin angiotensin aldosterone system (both angiotensin converting enzyme and angiotensin receptor blockers) reduce the risk of albuminuria and delays progression towards ESRD in both T1DM and T2DM subjects [9]. More recently, some of the modern classes of glucose lowering medications were shown to exhibit some intrinsic renal protective properties.

Inhibitors of the renal type 2 sodium glucose co-transporter (SGLT2i) reduce blood glucose by inducing glycosuria following inhibition of the SGLT2 transporters mainly located in the proximal convoluted tubules of nephrons. Consequently, to calorie loss via glycosuria, SGLT2i also reduce weight. In the same time, they promote natriuresis and osmotic diuresis with a decrease in blood pressure, with putative positive cardiovascular and renal effects [10]. Largely available SGLT2i in Europe include empagliflozin, canagliflozin and dapagliflozin. The large-scale cardiovascular outcome trials (CVOTS) with these three drugs were amongst the first to also indicate the potential renoprotective effects of SGLT2i.

The first published SGLT2i CVOT was the EMPA-REG OUTCOME trial with empagliflozin in September 2015 [11] followed by the CANVAS trial with canagliflozin in June 2017 [12] and the DECLARE-TIMI 58 trial with dapagliflozin in November 2018 [13]. All these trials established the cardiovascular benefits of these drugs, nowadays recommended by diabetes guidelines as first option after metformin in T2DM subjects with established CVD or heart failure [14]. In addition to CV endpoints, all these trials included as secondary or exploratory outcomes the renal effect of the drugs, including the impact on albuminuria and renal function.

In the EMPA-REG OUTCOME trial, treatment with empagliflozin in patients with T2DM and established CVD was associated with a 39% decrease in incident or worsening nephropathy, a 38% decrease in progression to macroalbuminuria, a 44% reduction in doubling of serum creatinine (with eGFR below 45 ml/min), a 55% reduction in the initiation of renal replacement treatment. Overall, this led to a 46% reduction in the composite endpoint including doubling of serum creatinine, initiation of renal replacement treatment and death from renal disease [15].

In the CANVAS trial programme, treatment with canagliflozin in patients with T2DM at high CV risk was associated with a 20% decrease of new onset albuminuria (driven mainly by the decrease of new onset macroalbuminuria), a 50% reduction in doubling of serum creatinine and a 47% reduction of the composite outcome including sustained doubling of serum creatinine, ESRD or death from renal causes [16].

In the DECLARE TIMI 58 trial, treatment with dapagliflozin in T2DM subjects with established CVD or CV risk factors was associated with a 46% reduction in the sustained decline of eGFR to CKD stage 3a, a 59% reduction in the composite of ESRD or renal death and a 47% reduction of the renal specific composite outcome including sustained decrease of eGFR by 40% below 60 ml/min, ESRD or renal death [17].

Overall, these trials offered some proof that SGLT2i could prevent the development of diabetic CKD or delay its progression in those already having nephropathy. However, it should be noted that being only secondary/exploratory endpoints in these trials, renal outcomes with SGLT2i had to be reconfirmed in trials specifically projected to assess this kind of objectives.

Recently, the results of the first renal specific endpoint study with a SGLT2i – the CREDENCE trial – were published [18]. The trial included 4401 T2DM subjects with established chronic renal disease, all having an eGFR between 30 and 90 ml/min and albuminuria (evidenced by an uACR higher than 300 mg/g). All patients were treated with medication blocking the renin-angiotensin system and were randomized to canagliflozin 100 mg QD or matching placebo, both on top of standard of care diabetes treatment. Median duration of follow-up was 2.62 years, the trial being stopped prematurely due to the evident benefits of the active treatment. The primary outcome in the study was the composite of ESRD, doubling of serum creatinine or death from renal or CV cause. The final analysis of data showed that canagliflozin treatment led to a highly significant 30% reduction of the primary endpoint ($p=0.00001$). The secondary composite that included only renal death instead of renal plus CV death was reduced even stronger, with a HR of 0.66. Other renal specific secondary endpoints including ESRD and the composite of dialysis, kidney transplantation or renal death were reduced also by ~30% [18].

There are several hypotheses regarding the potential mechanisms for cardioprotection of the SGLT2i [10,19]. These include the positive impact on the traditional “risk factors” for CKD mentioned above, namely glycemic control, weight and blood pressure, the last even in the presence of established CKD. An interesting postulated effect is the “loop diuretic sparing” effect of these drugs, with a reduced volume overload but with preserved intravascular volume that contributes to the preservation of glomerular filtration [19,20]. In addition, SGLT2i seem to reduce hyperfiltration by

increasing distal renal sodium delivery, restoring the physiologic tubule-glomerular feedback with consequent increased tone of the afferent arteriole [19,21]. Other mechanisms include improved oxygenation of tubular cells, decrease of the direct toxic effect of albuminuria on renal tubules, inhibition of some proinflammatory and profibrotic pathways etc. [19].

Finally, it should be noted that some other large-scale randomized trials with SGLT2i in patients with T2D and established renal disease are currently going on, with results expected in the following years. These include the DAPA-CKD (NCT03036150) testing the effect of dapagliflozin and the EMPA-KIDNEY (NCT03594110) testing the effect of empagliflozin. In contrast with the CREDENCE trial, these studies include both diabetic and non-diabetic subjects with CKD.

In conclusion, clinically relevant renal protective effects of SGLT2i in T2DM subjects have been already demonstrated in randomized controlled trials with empagliflozin, canagliflozin and dapagliflozin. Amongst diabetes drugs, the SGLT2i seem to be unique by having renal benefits beyond the decrease in albuminuria (reported for example also for GLP-1 receptor agonists), including on “harder” endpoints such as the decline in eGFR. Consequently, this class of diabetes medications is recommended in current guidelines for those patients with diabetes and CKD [14].

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