

The holy grail of renal protection in diabetes mellitus: is SGLT2 inhibition fulfilling its promise?

Joaquim Calado

ToxOmics, Centre for Toxicogenomics and Human Health, NOVA Medical School, New University of Lisbon
Department of Nephrology, Hospital de Curry Cabral-Centro Hospitalar de Lisboa Central, Lisboa – Portugal

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The manuscript from Lambers-Heerspink *et al* that appeared in this year's January issue of the *J Am Soc Nephrol*¹ reports a secondary analysis of the Canagliflozin Treatment and Trial Analysis versus Sulphonylurea (CANTATA-SU)², that focus on the renal outcomes. A total of 1161 diabetic patients completed the 104-week double-blind treatment period. Over that period, canagliflozin-treated patients experienced a slower decrease of the estimated glomerular filtration rate (eGFR), compared to those on glimepiride (0.5, 0.9 and 3.3 ml/min per 1.73m² per year, for the 100, 300 mg of canagliflozin and glimepiride groups, respectively). Additionally, in the subset of patients presenting with baseline urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/g, canagliflozin significantly decreased albuminuria over time, respectively by an average of 31.7% (100 mg arm) and 49.3% (300 mg arm), relative to glimepiride.

The paper confirms, although less ambitiously, the previous findings on the *renoprotective* effects of another SGLT2 inhibitor, empagliflozin, that were recently published (EMPA-REG OUTCOMES)³. In this work, the renal outcomes, a secondary outcome of the EMPA-REG composite microvascular events that encompass incident albuminuria (UACR ≥ 30 mg/g), eGFR over time and incident or worsening nephropathy (new onset macro-albuminuria, doubling of serum creatinine, initiation of renal replacement therapy or death due to renal disease), were reported. Over 7000 diabetic patients (randomly assigned to 10 mg, 25 mg of empagliflozin or placebo) were followed for 48 months. At the end, there was a 44% reduction in the risk of doubling of serum creatinine, and a 55% reduction in renal replacement initiation in the empagliflozin-treated group, compared to placebo. However, no risk reduction was found in the rate of incident albuminuria.

It is tempting to compare both these results to the outcomes of the RENAAL study, published over 15 years ago⁴. Still, study populations are not entirely similar. The RENAAL cohort included a far more renal population, with an average creatinine of 1.9 mg/dl (based on which I dare to extrapolate an eGFR of 36 ml/min/1.73m² while considering the predominant 60-year-old Caucasian male that is representative of the RENAAL cohort); due to efficacy and safety concerns, the CANTATA and EMPA-REG only included patients with an eGFR ≥ 55 and ≥ 30 ml/min/1.73m², respectively, while merely 7.7% of the EMPA-REG study population presented at baseline with an eGFR between 30 and 39 ml/min/1.73m². So, it is somewhat surprising that this secondary outcome was ever published in the *New England Journal of Medicine*. The fact that in a previous issue of the journal, the results of the cardiovascular outcomes of the EMPA-REG OUTCOMES made quite an impact in the diabetic community is probably one reason⁵. Another, more appealing to nephrologists, lies in the circumstance that these renal outcomes were obtained in populations already under background inhibition of the renin angiotensin system (60% and 80.7%, for the CANTATA and EMPA-REG, respectively).

In the absence of mechanistic studies, the way SGLT2 inhibition accomplishes renoprotection remains speculative. One interesting clue comes from the observation that in either studies, SGLT2 inhibition caused an acute reduction of the mean eGFR in the first few weeks (~4) after which it stabilized. In the EMPA-REG study, after cessation of the study drug (last week of treatment to follow-up) the eGFR recovered from the initial acute reduction. This is highly suggestive that changes in renal haemodynamics may be operating. The hitch is that SGLT2 inhibition also

caused significant dose-dependent reduction in systolic blood pressure in both studies (-3 to -4 mmHg compared to glimepiride or placebo). Could this be the cause? Apparently not, because adjusting these effects on albuminuria or eGFR did not alter the results. And similar considerations apply to blood glucose control and body weight.

An alternative explanation for the haemodynamic effect resides in the interference with the tubuloglomerular feed-back (TGFB). There is supportive evidence that the proximal tubule of the diabetic kidney is hyperabsorptive. The renal threshold for glucose excretion (RT_G) is the key parameter in the kinetics of tubular glucose transport. Ralph DeFronzo⁶, using a stepped hyperglycaemic clamp technique, estimated the RT_G in type 2 diabetic patients to be increased compared to healthy controls (196 vs. 171 mg/dl). We have also shown that in renal glucosuric patients harbouring heterozygous mutations for SGLT2, those with coincidental type 2 diabetes display higher than expected RT_G values⁷. The immediate cause for this is not clear, but there are some plausible explanations. For instance, it has been shown *in vitro* that insulin is a SGLT2 agonist by means of phosphorylation⁸. It was Volker Vallon who first proposed that the enhanced SGLT2 mediated Na^+ /glucose reabsorption could account for the hyperabsorptive proximal tubule, leading to less Na^+ being offered to the *macula densa*, therefore reducing the TGFB with subsequent increase in the single nephron glomerular filtration rate⁹. In other words, hyperfiltration, the longtime assumed *sine qua non* for the development of diabetic nephropathy. In order to confirm the hypothesis that SGLT2 inhibition exerts its *renoprotective* effects by resetting the TGFB loop, one has to verify 2 premises: the first, to demonstrate that SGLT2 inhibition ameliorates hyperfiltration and secondly, that diabetic nephropathy can be prevented by doing so. Indeed, it was shown for individuals with type 1 diabetes *mellitus* that 8-week treatment with empagliflozin did attenuate hyperfiltration in both euglycaemic and hyperglycaemic clamp conditions¹⁰. But due to the unrealistic duration of a clinical trial designed to test the beneficial effects of hyperfiltration amelioration on the prevention of diabetic nephropathy, we have to rely on animal data to verify the second premise. And the existing evidence, although favouring a beneficial effect of SGLT2 inhibition on hyperfiltration and that is blood glucose independent, on the other hand indicates that the rescuing of the remaining changes of the early diabetic kidney (albuminuria, kidney growth and renal

inflammation) is entirely dependent on the blood glucose lowering effect of SGLT2 inhibition¹¹.

Nevertheless, more convincing evidence is expected to be provided by the ongoing Canagliflozin and Renal Events in Diabetes with an Established Nephropathy Clinical Evaluation Study (CREDENCE), for which the primary composite endpoint of the study includes end-stage kidney disease, doubling of serum creatinine, renal or cardiovascular death (clinical trials.gov NCT02065791).

The Na^+ /glucose co-transporter SGLT2 is responsible for the bulk of glucose reabsorption in the proximal tubule. Contrary to other proximal Na^+ co-transporters, such as NaPiIIa or NHE3, little is known about the regulation of SGLT2 expression and abundance in the proximal tubule cell. It is rather curious that precisely in the same *JASN* issue where the manuscript from Lambers-Heerspink appeared, another work regarding SGLT2 was published. In that collaborative study, MAP17 was identified as an accessory protein for SGLT2 and found to be mutated in one renal glucosuric individual negative for SGLT2 mutations¹². MAP17, similar to NaPiIIa and NHE3, is a PDZK1 (also known as NHERF3) interacting protein which is the major scaffold in the proximal tubule, orchestrating the abundance of major proximal tubule transporters at the apical cell surface. This is the first hint of the post-transcriptional regulation of SGLT2 activity.

So, definitely, these are exciting times for everyone in the field, and it is fortunate that contributions from both the clinical and basic sciences may come together to significantly impact on the natural history of one of the most fearful complications in diabetes *mellitus*.

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Correspondence to:

Joaquim Calado

ToxOmics, Centre for Toxicogenomics and Human Health, NOVA Medical School, New University of Lisbon

Department of Nephrology, Hospital de Curry Cabral

Centro Hospitalar de Lisboa Central, Lisboa – Portugal