23.1.17

Dear Jin-Xin Kong, Dear Dr.

Re: Manuscript No. 29158.

Thank you for the opportunity to submit a revised version of our review.

Please pass on out thanks to the reviewers for their useful comments.

Our responses are shown below and modifications to the text are highlighted in red.

Reviewer 1:

1. In Tables, unit for each value was not showed in clear.

Thank you for this comment. We have now included units and the term "hazard ratio or risk reduction" for the decrease in events observed with empagliflozin or liraglutide.

2. In animal studies, agents with antioxidant
like action are useful to delay the renal damage without reduction of hyperglycemia.

In response to this I have the following sentence on page 9 "Despite these promising experimental studies like those mentioned above, clinical trials to date have failed to establish that non-glucose lowering based approaches that specifically target pathways linked to oxidative stress or inflammation are renoprotective"

3.
To establish a reliable HbA1c threshold for the development of kidney dysfunction s eems important in Diabetes Clinics.

In response to this comment I have added the following to the end of the second paragraph on page 12…

"This result together those of the already mentioned observational study from ADVANCE suggest that ideally a HbA1c threshold of 6.5% (48mmolmol) should be targeted as a means of preventing the development and progression of DKD (ref 19). However, the importance of individualising glycaemic targets according to a patient's age, co-morbidities and type of glucose lowering therapies prescribed is appreciated.

I had already mention threshold previously and it is again mentioned in the summary.

4.
Disadvantaged points for Empagliflozin or Liraglutide in renal disorders were not c onducted.

In response to this comment I have included new paragraphs at the end of the incretins (page 27) and SGLT-2 inhibitor (page 32)sections, respectively

Overall medications that target the incretin effect are generally well tolerated. The DPP-4 inhibitors are virtually free from side-effects and usually can be used at any level of renal function with an appropriate dose reduction. It should however, be noted that Linagliptin is not renally excreted and therefore does require a dose reduction at lower GFR levels. The side-effects of GLP-1 receptor agonists are mainly related to the gastrointestinal tract and include nausea, vomiting and gallstone disease. Concerns that medications targeting the incretin effect may promote the development of pancreatitis and pancreatic cancer have been raised but have not been supported by the results of large randomised clinical trials. A possible link between the use of liraglutide and semiglutide and the promotion of diabetic retinopathy has been raised. The significance of these findings remains to be fully established. An important point practice point to highlight for patients with CKD is that the GLP-1 receptor agonists are currently not recommended for used in patients with an eGFR < 30 ml/min/1.73m^2.

Potential side-effects or concerns related to the use of SGLT-2 inhibitors include increased rates of urinary tract infections, genital tract infections, postural hypotension, diabetic ketoacidosis, acute kidney injury and possible increased rates of fractures (REF 54 (Thomas), Vlotides and Merens NDT 2015, 30, 1272-6, Wu Lancet Diabetes Endocrinol 2106 4, 411-9, Heerspink Circulation 2016, 134, 752-772). Furthermore, the main disadvantage of the mode of action of the SGLT-2 inhibitors is that their effectiveness for lowering blood glucose levels is dependent on renal function. Hence they are not recommended as glycaemic management agents in patients with significantly impaired renal function.

Please note that we have also added the following on page 26 to highlight the recent results of the SUSTAIN-6 trial

After this manuscript was submitted for review the results of the Trial to Evaluate Cardiovascular and other long-term outcomes with semaglutide (SUSTAIN-6) have been released. This trial showed that a once weekly injection of semaglutide significantly reduced CV endpoints in high risk vascular patients with type 2 diabetes. In a similar fashion to liraglutide it also reduces progression to macroalbuminuria (HR 0.54, 0.37-0.77, $p < 0.001$). It should also be noted that currently, liragludite and semaglutide have only been shown to reduce progression to macroalbuminuria and that their ability to reduce progression to ESKD remains to be proven (ref: 51 NEJM 2016, 37, 1834-1844, Maraso SP)

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5. Limitation of this review article is helpful.

The limitations of the review are now stated on page 7

"A review of glycaemic management and the optimum way to assess glycaemic control in ESKD patients is beyond the scope of this review. We have also not reviewed the impact of failing kidney function on glucose and insulin metabolism".

Reviewer 2:

1.The induction of natrediuresis result in increasing of adenosine by TGF mechanism may not do good to the kidney as well as the reduction of ECBV and renal perfusion may more activate RAAS with more reduction of peritubular capillary flow and intr a-glomerular hypertension.

The reviewer raises a very interesting point. I believe that we still do not fully understand the relationship between SGLT- inhibition and RAS system.

However, to highlight this point, I have added the following paragraph under the one on page 22, that discusses the reduction in intraglomerular pressure with SGLT-2 inhibition.

The relationship between SGLT-2 inhibition and the renin-angiotensin system (RAS) is complex and as yet not fully elucidated. The decrease in intraglomerular pressure and the modest volume depletion volume depletion seen with SGLT-inhibition has the potential to result in RAS activation. In contrast, the increased delivery of sodium to the macular densa may result in a reduction in RAS activation. Despite the above, SGLT-2 inhibition appears to result in an increase in RAS activity (REF: 42). It has been suggested that increased RAS activity may in fact play an important role in maintain adequate glomerular filtration in the setting of SGLT-2 inhibition (Musetti C et al Kidney International 2014, 86, 1058). In any event, the cardiac and renal protective effects of empagliflozin appear to be consistent in patients treated or not treated with agents that block RAS activity (REF: 55 & 56).

2. UTI risks due to glycosuria should also be considered.

We have mentioned a possible increase in UTI rates with SGLT-2 inhibition in our response to reviewer 1 (page 31)

I now hope that the manuscript is now acceptable for full acceptance.

I look forward to your response.

Regards

Richard MacIsaac