



EMPA-REG Renal: Are we there yet?

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There are few trials that have caught the attention of the diabetes world more than EMPA-REG OUTCOME. It was the first cardiovascular outcome trial using an agent designed to control glycaemia that showed significant mortality benefit (Zinman et al, 2015). Now the analysis of the microvascular endpoints has also been published. These findings (summarised alongside) showed a significant benefit on some of the pre-specified endpoints. These benefits were, however, limited to the kidney; no benefit on retinal outcomes was observed. Is the impact on diabetic kidney disease the paradigm shift in therapeutic options that some are claiming?

The renal outcomes were incident or progression of nephropathy, defined as a urinary albumin:creatinine ratio (ACR) ≥ 300 mg/g (approximately 30 mg/mmol) and/or a doubling of serum creatinine in combination with an estimated glomerular filtration rate (eGFR) ≤ 45 mL/min/1.73 m²; the need for renal replacement therapy; and renal death. In addition, the authors assessed the impact on a combined cardiorenal endpoint and on incident microalbuminuria (defined as an ACR ≥ 30 mg/g [around 3.0 mg/mmol]).

Results from both doses of empagliflozin were combined. Compared with placebo, there was a 5% absolute risk reduction (ARR) for incident and progressive nephropathy, a 1.1% ARR for a doubling of serum creatinine and a 0.3% ARR for renal replacement therapy. These translate into numbers needed to treat to prevent one endpoint of 52, 236 and 867, respectively, over the study duration of 2.6 years. There was no impact on renal death. Not surprisingly, the impact on a combined cardiorenal endpoint was positive but, importantly, empagliflozin had no significant effect on incident microalbuminuria, despite a high overall incidence. eGFR declined sharply after starting empagliflozin but then stabilised for the duration of the study, whereas placebo recipients showed a steady decline of 1.67 mL/min/1.73 m² per year. Of note is the fact that eGFR rose to pre-trial levels in the empagliflozin group at a median of 34 days after study cessation but did not change in the placebo group.

Reviewing the data in the supplementary appendix, it is clear that:

- The reduction in incident/progressive nephropathy began early (within 6 months).
- The effect on doubling of serum creatinine and renal replacement therapy was not apparent until much later (after 24 months).
- The benefit on creatinine doubling was mostly seen in those with a higher eGFR at baseline (≥ 90 mL/min/1.73 m²), although this might be a reflection of the proportion (25%) of subjects with GFR ≤ 60 mL/min/1.73 m².
- The impact on change in eGFR was mostly seen in those with a baseline eGFR of ≥ 60 mL/min/1.73 m².
- Haematocrit increased by around 5% in the empagliflozin groups, consistent with haemoconcentration.

The main outcomes showing benefit were creatinine-based: GFR estimated from serum and ACR derived from urine. If serum creatinine levels increase

due to haemoconcentration then eGFR will fall (as was seen within 6 months of commencing empagliflozin). Urine creatinine excretion might increase either by increased filtration (less likely) or increased secretion (known to occur as serum levels rise); the result of this would be a reduced ACR. Consistent with this interpretation is the observation that eGFR increased after stopping empagliflozin (possibly due to a reduction in serum creatinine with resolution of haemoconcentration). For this increase in GFR to be a return to true glomerular hyperfiltration, there should have been a concomitant deterioration in glycaemia (but we are not given the HbA_{1c} levels at that time) and/or a reduction in glycosuria. What happened to ACR at washout? If this increased as well, then this might call into question any long-term renal benefit. ACR was measured on a single spot urine sample collected at baseline, 12 weeks, 28 weeks, 52 weeks and every 14 weeks thereafter. This introduces considerable variation in the measure, and thus an unquantifiable bias, although recent analysis suggests that the frequency of sampling may be less of an issue than was once thought (Kröppel et al, 2016).

The reduction in doubling of serum creatinine is perhaps more noteworthy, particularly as the oft-quoted relative risk reduction of 44% sounds very impressive. Absolute numbers were small and the benefit was largely confined to people with higher eGFRs, leaving some uncertainty as to when to introduce empagliflozin. Waiting for an increase in ACR may be too late as eGFR may have already declined too much. The impact on those requiring renal replacement therapy was also modest and must have been seen in people with advanced rather than early nephropathy, suggesting that later introduction of empagliflozin might be better – but why wasn't there an effect on doubling serum creatinine in these participants?

Perhaps most perplexing is the absence of an effect on incident microalbuminuria. If the benefit of sodium–glucose cotransporter 2 (SGLT2) inhibitors on diabetic kidney disease depends upon their ability to reduce single-nephron GFR and thus intraglomerular capillary pressure, then we should have anticipated a positive primary preventative effect on albuminuria. Indeed, short-term trials using empagliflozin and employing direct measurement of GFR and timed albumin excretion confirmed these expectations (Cherney et al, 2016). These results are somewhat analogous to those seen in trials of renin–angiotensin system blockers, in which, as with empagliflozin, there is undoubted reduction of established albuminuria but more inconsistent results with respect to primary prevention of microalbuminuria (Bilous et al, 2009).

So are we there yet? Not quite. These results from a relatively short-term study are encouraging but, as with all trials of new agents, they raise intriguing questions relating to the unknown mechanisms. We need a better understanding of the effects of SGLT2 inhibitors on the renal handling of creatinine and timed (preferentially fractional) clearances of albumin. Other longer-term studies are due to report in a few years' time. In the meantime, we should exercise caution before claiming a paradigm shift. ■

References on opposite page

N Engl J Med

EMPA-REG: Renal outcomes

Readability ////

Applicability to practice ////

WOW! Factor ////

1 EMPA-REG OUTCOME was a randomised controlled trial comparing empagliflozin and placebo in terms of cardiovascular safety. In this prespecified subanalysis, published simultaneously at ADA 2016 and in the *New England Journal of Medicine*, the authors sought to determine the agent's effects on renal outcomes.

2 A total of 7020 people with long-standing T2D and a history of cardiovascular disease were randomised 2:1 to empagliflozin or placebo for a median of 2.6 years. Most were already taking renin-angiotensin system blockers.

3 Incident or worsening nephropathy was significantly less common in the empagliflozin group compared with placebo (12.7% vs 18.8%; hazard ratio, 0.61; 95% confidence interval, 0.53–0.70). However, there was no significant between-group difference in the rate of incident albuminuria.

4 Progression to macroalbuminuria (albumin:creatinine ratio [ACR], ≥ 300 mg/g) occurred in 11.2% of empagliflozin recipients and 16.2% of placebo recipients (relative risk reduction [RRR], 38%; $P < 0.001$).

5 Doubling of serum creatinine levels was significantly less common in the empagliflozin group (1.5% vs 2.6%; RRR, 44%), as was initiation of renal replacement therapy (0.3% vs 0.6%; RRR, 55%).

6 The adverse event profile in those with impaired renal function at baseline was similar to that in the overall trial population.

7 The authors conclude that empagliflozin slows kidney disease progression and lowers the risk of clinically relevant renal events.

Wanner C, Inzucchi SE, Lachin JM et al (2016) Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* **375**: 323–34

ADA 2016

Slowing of renal disease progression with canagliflozin



1 Canagliflozin, a sodium-glucose cotransporter 2 inhibitor, decreases HbA_{1c}, body weight, blood pressure and albuminuria in people with T2D, and may confer renoprotection.

2 This ADA session reported on a secondary analysis of trial data to determine whether canagliflozin decreases albuminuria and reduces renal function decline independently of its glycaemic effects.

3 1450 participants with T2D were randomly assigned to once-daily canagliflozin 100 mg or 300 mg, or glimepiride 6–8 mg. The endpoints were change in estimated glomerular filtration rate (eGFR) and albuminuria over 2 years of follow-up.

4 Annual eGFR declines for the glimepiride, canagliflozin 100 mg and canagliflozin 300 mg groups were 3.3, 0.5 and 0.9 mL/min/1.73 m², respectively ($P < 0.01$ for each canagliflozin group vs glimepiride).

5 In a subgroup with baseline albumin:creatinine ratio ≥ 30 mg/g, the ratio decreased significantly more with canagliflozin than with glimepiride.

6 Those receiving glimepiride, canagliflozin 100 mg or canagliflozin 300 mg had HbA_{1c} reductions of 8.9, 9.0 and 10.2 mmol/mol (0.81%, 0.82% and 0.93%), respectively, after 1 year, and 6.0, 7.1 and 8.1 mmol/mol (0.55%, 0.65% and 0.74%), respectively, after 2 years.

7 The authors concluded that canagliflozin slows the progression of renal disease in T2D compared to glimepiride over 2 years, and may confer protective effects independently of its glycaemic effects.

Heerspink HJL, Desai M, Jardine M et al (2016) Canagliflozin (CANA) slows progression of renal function decline independent of glycaemic effects. *ADA 76th Scientific Sessions: abstract 70-OR*

Diabetes Care

Persistent effects of intensive glycaemic control on retinopathy

Readability ////

Applicability to practice //

WOW! Factor ////

1 The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Eye Study, a subset of participants in the ACCORD study, established that intensive glycaemic control and fenofibrate treatment both reduced retinopathy progression in people with established T2D and additional cardiovascular (CV) risk factors.

2 The findings of the ACCORD Follow-On (ACCORDION) Eye Study were simultaneously announced at ADA 2016 and published in *Diabetes Care*.

3 In the follow-on study, a subset of 2856 participants who underwent eye examination throughout the original study were re-examined 4 years after its close-out.

4 This re-examination revealed that intensive glycaemic control reduced the risk of diabetic retinopathy progression compared with standard treatment (5.8% vs 12.7%; adjusted odds ratio, 0.42; $P < 0.001$). This was despite HbA_{1c} levels having equalised between the groups since the close of the original study.

5 This is the first study in people with T2D of 10 years' duration and established CV disease to demonstrate this effect.

6 The benefit of fenofibrate seen during the original trial did not persist once its use was discontinued. This suggests that treatment needs to be ongoing to maintain benefit, although further study is required to confirm this.

ACCORDION Eye Study Group, ACCORDION Study Group (2016) Persistent effects of intensive glycaemic control on retinopathy in type 2 diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. *Diabetes Care* **39**: 1089–100

“The authors conclude that empagliflozin slows kidney disease progression and lowers the risk of clinically relevant renal events.”

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