Taking confidence from CREDENCE and navigating with SONAR: new evidence for reducing renal failure in diabetes

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Apart from the use of renin–angiotensin–aldosterone system (RAAS) blockade in albuminuric chronic kidney disease (CKD) in diabetes, we have had precious little to help reduce the ever growing numbers with diabetes and advancing CKD. The impact of tight glycaemic control is best evidenced in type 1 diabetes over the 25 years of follow up in DCCT-EDIC. In type 2 diabetes I do not believe the outcomes are anything like as clear cut, and the intensive insulin regime in ACCORD delivered more adverse outcomes without clear hard renal end points.

The renal outcomes in studies are important in that reliance on albuminuria development and progression may be better considered a functional measure rather than more robust composite end points – doubling of serum creatinine, estimated glomerular filtration rate (eGFR) <15 mL/min, dialysis, transplantation or death from renal failure.

Over the last 10 years there is a litany of false dawns with treatment that were intended to address inflammatory or advanced glycated contributions to renal disease in diabetes. They on occasion reduced albuminuria but had no impact on the key renal outcomes mentioned, and often had additional adverse effects.

The cardiovascular safety trials with gliflozins and glucagon-like peptide-1 (GLP-1) analogues have changed the landscape in clearly demonstrating the potential to reduce overall cardiovascular disease (CVD) events, and most notably heart failure with gliflozins. Renal outcomes were pre-specified but secondary end points in these studies and the gliflozin CVD safety studies showed reductions in progression to hard renal end points as well as albuminuria. The GLP-1 CVD studies have predominantly found that albuminuria reduction was clearly the major contributor to reduced renal end points. However, the criticism applied to the gliflozin studies in respect of renal prognosis was that the studies did not specifically focus on an exclusive cohort with CKD.

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CREDENCE (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation) set out to specifically evaluate the impact of 100 mg canagliflozin on established albuminuric CKD and was a well-designed double-blind placebo-controlled study with appropriate end points.[1] The sample size was large (4,401) and the study was terminated early based on planned interim analysis after a median follow-up of 2.6 years. There was a 30% risk reduction on the primary renal outcome as well as a 20% reduction in major adverse cardiovascular events (MACE) and an almost 40% reduction in hospitalised heart failure. Importantly, and in distinction to the findings with canagliflozin in the earlier CANVAS and CANVAS-R pooled studies, there was no difference in rates of amputation or fractures.

In the same week as the publication of this paper, the SONAR (Study Of diabetic Nephropathy with AtRasentan) study of the selective endothelin antagonist atrasentan was published.[2] The study design was very similar with 2,648 albuminuric patients with CKD randomised with a follow-up of 2.6 years, again stopped early albeit for lower than expected primary event rates. There was a 35% reduction in the same hard renal primary endpoint as in CREDENCE.

There are interesting comparisons to be made between CREDENCE and SONAR. There was somewhat higher albuminuria and less advanced CKD based on eGFR in CREDENCE compared with SONAR (median albumin creatinine ratio (ACR) 920–930 vs. 797–805 mg/g and eGFR 56 vs. 44 mL/min/1.73 m^2).

There were recognised adverse effects of the drug classes in both studies. In CREDENCE the hazard ratio for ketoacidosis was 10.8 in the active treatment group (0.5% event rate), whilst in SONAR anaemia and fluid retention were seen more frequently with atrasentan ($p<0.0001$ and $p=0.022$, respectively).

Both studies selected patients with established albuminuria (ACR 300–5000 mg/g). However, the vast majority of patients with type 2 diabetes and CKD have either normal or only modestly elevated albumin excretion. Albuminuria reduction was seen with both active treatments and this is known to be beneficial for renal filtration function. It cannot be stated with certainty that the extent of benefits would be so clear in CKD without albuminuria, although in the case of gliflozins, the earlier CVD safety studies included less advanced degrees of CKD with less albuminuria and similar renal outcome benefits were shown. The numbers needed to treat (NNT) to avoid the primary end point or CVD-renal deaths was 22 in CREDENCE whereas the number needed to harm (NNH) based on ketoacidosis was 200. Similar figures can be estimated

in SONAR as an NNT of 51 for primary renal outcome benefit.

As ever with new studies and exciting positive findings, the practical question of applicability to clinical practice comes to mind.

Current licensing restrictions are the most frustrating issue. At present canagliflozin is a licensed treatment for hyperglycaemia initiated at eGFR >60 mL/min and maintained whilst eGFR remains ≥45 mL/min. The renal (and cardiovascular) benefits seen in CREDENCE (and indeed in the earlier CVD safety studies with canagliflozin, empagliflozin and dapagliflozin) were independent of glycaemia benefit. Indeed, given the study design, the overall mean HbA_{1c} difference was only 0.25% (2.5 mmol/mol) at conclusion of the CREDENCE study.

Although the renal benefits in CREDENCE were consistent with no significant interaction with respect to baseline eGFR (or ACR), almost 60% had a baseline eGFR that would currently preclude licensed use. There is probably a meta-analysis in the wings that may, I suspect, suggest that those with eGFR of ≤45 mL/min may benefit particularly from gliflozins. Something needs to change to realise the full potential of this class of therapy.

Atrasentan will need to undergo further evaluation and regulatory review before approval in the UK. Tantalisingly, the adverse effects of atrasentan would be ameliorated by canagliflozin, raising the inevitable question as to cumulative benefits from a combination of these two strategies which would, of course, require further studies.

We are definitely at a point now where we can reasonably state we have a new class of therapy that benefits renal function in type 2 diabetes. The demonstrable benefit of gliflozins at a lower eGFR than currently licensed justifies regulatory approval. Furthermore a cardio-renal protective role in appropriately defined cohorts should be considered independent of glycaemia lowering, although the blood pressure lowering effects of gliflozins need to be taken into consideration.

An analogy might be the established role of antiplatelet therapy in secondary CVD prevention without any requirement to assess the impact on platelet reactivity.

There does remain in my mind the need to ensure this real advance in diabetes renal care is not compromised by what I believe to be a real – albeit relatively lower – risk of ketoacidosis, often euglycaemic.

Whereas the reports of gliflozin-related ketoacidosis might be more amongst type 1 and insulin deficient type 2 diabetes, the CREDENCE cohort aged 63 with body mass index >31 kg/m^2 does not fit the classic stereotype of such cases, and ketoacidosis has been recorded in several acute clinical scenarios that predispose to ketone production including starvation, vomiting, dehydration, excess alcohol and surgery. The roll-out of effective sick day guidelines and pre-emptive temporary withdrawal of gliflozins in particular circumstances, as advocated by ABCD and ADA, will I hope minimise the risk that a valuable new approach is not held back.

We should already be managing temporary withdrawal and reinstitution of, for example, metformin and RAAS blockade in certain situations, so why not gliflozins?

Conflict of interest Dr Peter H Winocour has received honoraria for delivering educational meetings and/or attending advisory boards and support to attend overseas meetings from Napp Pharmaceuticals.

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References

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2. Heerspink HJL , Parving H-H, Andress DL, *et al*, on behalf of the SONAR Committees and Investigators. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double blind randomised placebo controlled trial. *Lancet* 2019;**393**:1937–47. https://doi.org/10.1016/S0140-6736(19)30772-X

Diary dates 2019

1 July	**Cardiovascular, Metabolic and Kidney Disease: Crosscutting Science and Best Practice in Multi-morbidity** RCP, London https://www.rcplondon.ac.uk/events/cardiovascular-metabolic-and-kidney-disease-crosscutting-science-and-best-practice
4 July	**2nd National Conference – Diabetes and Eating Disorders** Bournemouth Football Stadium Contact: Julia.Knott@nhs.net to register
4 July	**Royal College Advanced Certificate in Clinical Education** Glasgow: 17–18 September, Heathrow: 20–21 September, Leeds: 8–9 November, although a number of other dates are available. https://rcpsg.ac.uk/events/postgrad
16–20 September	**EASD 2019** Barcelona, Spain https://www.easd.org/
18 October	**EXTOD/PEAK: Exercising for Type 1 Diabetes and Performing at your PEAK** Radisson Blu, Glasgow https://abcd.care/extod-peak/conference-2019
28-29 November	**ABCD Autumn Meeting 2019** Holiday Inn, Regents Park, London https://abcd.care/events/abcd-autumn-meeting-2019
2-6 December	**ABCD Consultant Development Programme 2019** Hornton Grange, Birmingham https://abcd.care/events/abcd-consultant-development-programme-2019

For other meetings see https://www.abcd.care/events