Nephropathy

When should we start renin–angiotensin system blockade in type 2 diabetes?

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This question has been debated for decades since studies emerged showing the superiority of renin–angiotensin system (RAS)-blocking agents over other antihypertensive therapies in terms of reducing albuminuria in people with diabetes. However, few of these trials were powered to demonstrate an effect on hard clinical endpoints such as end-stage renal disease (ESRD) or mortality. Part of the problem is the slow rate of glomerular filtration rate (GFR) decline in people with developing or early diabetic nephropathy (DN). Newly diagnosed people with type 2 diabetes in the UKPDS (UK Prospective Diabetes Study) took almost 30 years on average to develop ESRD (Bilous, 2008). Even people with established DN have an average decline in GFR of only 2.4–4.0 mL/min/year. In the IDNT (Irbesartan Diabetic Nephropathy Trial; Evans et al, 2012), RAS blockade with irbesartan cut the rate of GFR decline by approximately 38% (1.42 mL/min/year), making the logistics of performing ESRD outcome trials impractical.

In the paper summarised alongside, Schievink and colleagues tried to overcome this problem by modelling patient-level data from four trials in people with different severities of DN to see whether there was an optimum time for intervention with RAS blockade. For participants aged 60 years with early DN at baseline, RAS blockade led to a 20% increase in the median time to ESRD, a delay which increased to 30–33% in those with more advanced DN. In 45-year-olds, the effect was even greater for those with early and intermediate DN, with a 28% and 41% delay, respectively, and similar for those with advanced nephropathy (29% delay).

What can we make of these findings? The strength of the analysis is its use of patient-level data. These are always much more powerful, in that they allow individual covariates to be entered into the model. As such, the analysis adds to the consensus of support for RAS blockade in people with DN. However, as with all meta-analyses and *post hoc* studies, there is inherent bias from the entry criteria of the four selected studies (see the full article for details). All of the subjects were hypertensive with varying levels of glycaemic control (mean HbA_{1c} ranged from 37 to 69 mmol/mol [5.5–8.5%]). Mean follow-up ranged from 2.0 to 3.7 years, which is short in the context of the natural history of DN. In one of the studies, the frequency of retinopathy was only 40%; therefore, it is possible that many of the participants had non-diabetic renal disease.

It is impossible to determine clinical costs and benefits from this study. On the face of it, delaying the onset of ESRD by around 4 years sounds impressive, but we have no idea of the numbers needed to treat or the possible risks (e.g. acute kidney injury) of RAS blockade for ≥20 years. Furthermore, the confidence intervals of the estimates lack precision in participants at low risk of ESRD, as the authors acknowledge.

An additional finding of no delay in ESRD in participants who showed a ≤30% reduction in albuminuria after 6 months' RAS blockade needs further investigation, as it has important clinical implications in terms of prognosis. It would be interesting to know other clinical concomitants in these participants: was their blood pressure higher or glycaemia worse, for example?

Should we review our current guidance for the initiation of RAS blockade in type 2 diabetes as a result of this paper? All of the participants in the four studies had hypertension and/or albuminuria, so RAS blockers are recommended as first-line therapy anyway. This *post hoc* analysis cannot support RAS blockade in people with normal blood pressure. What it does show, however, is that, in those for whom such therapy is indicated, the sooner therapy is started the better; furthermore, even those at late stages of DN will benefit. ■

References on opposite page

Diabetes Obes Metab

Importance of early RAS blockade in delaying ESRD

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 Progression of diabetic nephropathy (DN) to end-stage renal disease (ESRD) can take decades to manifest, and so randomised controlled trials to compare the effects of early versus late renin–angiotensin system (RAS) inhibition are unlikely to be performed.

2 Therefore, these authors modelled DN progression over time using data from four trials (total $n=5027$) in which RAS treatment was initiated at different disease stages.

3 Participants were classed as having early, intermediate or advanced DN according to albumin:creatinine ratio and estimated glomerular filtration rate.

4 Among placebo recipients with a mean age of 60 years, the median time to ESRD was 21.4, 10.8 and 4.7 years in those who received treatment in the early, intermediate and advanced stages of DN, respectively.

5 Compared with the placebo group, RAS inhibition delayed ESRD onset by 4.2, 3.6 and 1.4 years in early, intermediate and advanced DN, respectively.

6 The benefits of earlier RAS inhibition were greater in younger participants. For example, in those with a mean age of 40 years, early RAS inhibition delayed ESRD by 6.9 years compared with placebo.

7 These findings, combined with the fact that T2D diagnoses are becoming more common in people aged <40 years, suggest that early intervention with RAS inhibitors is important to delay ESRD onset.

Schievink B, Kröpelin T, Mulder S et al (2015) Early renin–angiotensin-system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes. *Diabetes Obes Metab* **18**: 64–71

Am J Kidney Dis

Associations between eGFR, ACR, diabetes, hypertension and AKI

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 The authors of this meta-analysis sought to determine whether estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (ACR) remain risk factors for acute kidney injury (AKI) in the presence of diabetes and/or hypertension.

2 Eight general-population and five chronic kidney disease cohorts were pooled (total *n*=1 364 564) over a mean follow-up of 4 years.

3 Lower eGFRs and higher ACRs were found to be independently associated with AKI regardless of diabetes or hypertension status.

4 People with diabetes had higher risk of AKI across all eGFR levels, but the difference was attenuated at lower eGFRs, with no interaction between diabetes, ACR and AKI.

5 Although hypertension was linked to AKI risk overall, it did not affect risk at low eGFRs and high ACRs.

6 Therefore, eGFR and ACR remain powerful prognostic markers for AKI in people with diabetes or hypertension.

James MT, Grams ME, Woodward M et al (2015) A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. *Am J Kidney Dis* **66**: 602–12

Diabetologia

Diabetic nephropathy endpoints compared between T1D and T2D

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 These authors compared the incidence of death and end-stage renal disease (ESRD) and the rate of estimated glomerular filtration rate (eGFR) decline between 277 people with T1D and 942 with T2D.

2 The incidence of death was greater in people with T2D than in those with T1D (67.0 vs 24.6 per 1000 patient-years); however, after adjustment for age, the risk between the two types of diabetes was not significant.

3 Conversely, the incidence of ESRD was lower in T2D compared with T1D (18.4 vs 47.1 per 1000 patient-years, but the difference in risk was not significant after adjustment for gender, age and baseline serum creatinine level.

4 In a mixed linear model, the rate of eGFR decline was similar between the two types of diabetes.

5 In conclusion, the adjusted risk of death, ESRD and renal function decline did not significantly differ between T1D and T2D.

Hadjadj S, Cariou B, Fumeron F et al (2015) Death, end-stage renal disease and renal function decline in patients with diabetic nephropathy in French cohorts of type 1 and type 2 diabetes. *Diabetologia* 20 Oct [Epub ahead of print]

J Diabetes Complications

Improved measure of glycaemic control for people with CKD

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 While glycated albumin (GA) is arguably a better indicator of glycaemic control than HbA_{1c} because it also reflects glycaemic excursion, both measurements are inaccurate in people with severe chronic kidney disease (CKD) as a result of renal proteinuria and anaemia, respectively.

2 Therefore, these authors evaluated the use of GA adjusted for serum albumin levels (adjGA) as an indicator of glycaemic control in 30 people with T2D and severe CKD who were not on dialysis.

3 While HbA_{1c} showed no significant correlation with any indicator of glycaemic excursion, adjGA was strongly associated with all measured parameters except for mean amplitude of glucose excursion (MAGE).

4 The authors conclude that adjGA is a useful measure of glycaemic control in this patient group and call for large trials to assess whether strict glycaemic control using adjGA as an indicator can help improve outcomes.

Fukami K, Shibata R, Nakayama H et al (2015) Serum albumin-adjusted glycated albumin reflects glycemic excursion in diabetic patients with severe chronic kidney disease not treated with dialysis. *J Diabetes Complications* **29**: 913–7

"These findings, combined with the fact that type 2 diabetes diagnoses are becoming more common in people aged <40 years, suggest that early intervention with renin–angiotensin system inhibitors is important to delay end-stage renal disease onset."

Diabet Med

CSII superior to MDI in terms of HbA_{1c} and kidney function

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓

1 In this single-centre study, the authors compared the effects of 4 years of continuous subcutaneous insulin infusion (CSII) with multiple daily injections (MDI) on albuminuria and kidney function in people with T1D.

2 A total of 193 people who initiated CSII therapy were compared with 386 (1:2 ratio) who stayed on MDI. Baseline characteristics were similar between the two groups.

3 Compared with the MDI group, the CSII group had a rapid improvement in HbA_{1c} in the first year of treatment, so that the average HbA_{1c} was significantly lower over the 4-year study period (62 mmol/mol [7.8%] vs 69 mmol/mol [8.4%]).

4 After 4 years, the mean urinary albumin:creatinine ratio (ACR) was significantly lower in the CSII group (0.9 mg/mmol vs 1.2 mg/mmol; average yearly reduction, 10.1% vs 1.2%).

5 In the multivariate analysis, CSII was independently associated with reduced ACR. The authors posit that this may have been a result of lower glycaemic variability in the CSII group.

Rosenlund S, Hansen TW, Andersen S, Rossing P (2015) Effect of 4 years subcutaneous insulin infusion treatment on albuminuria, kidney function and HbA_{1c} compared with multiple daily injections: a longitudinal follow-up study. *Diabet Med* **32**: 1445–52

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Bilous R (2008) Microvascular disease: what does the UKPDS tell us about diabetic nephropathy? *Diabet Med* **25**(Suppl 2): 25–9

Evans M, Bain SC, Hogan S, Bilous RW; Collaborative Study Group participants (2012) Irbesartan delays progression of nephropathy as measured by estimated glomerular filtration rate: *post hoc* analysis of the Irbesartan Diabetic Nephropathy Trial. *Nephrol Dial Transplant* **27**: 2255–63