Nephropathy

Combination blockade of the renin angiotensin aldosterone system in diabetic nephropathy

Rudy Bilous
Professor of Clinical Medicine, Newcastle University, Newcastle and Consultant Physician, James Cook University Hospital, Middlesbrough

The renin angiotensin aldosterone system (RAAS) is thought to play a pivotal role in the initiation and progression of renal disease in diabetes. In animals, its activation leads to an increase in glomerular capillary pressure that leads to glomerulosclerosis. Blockade of the RAAS in these models can prevent and slow progression of experimental nephropathy (Zatz et al, 1986).

The first class of agent in this area was the angiotensin-converting enzyme (ACE) inhibitors, and early studies in man demonstrated that ACE inhibitors reduced albuminuria and slowed clinical progression of advanced nephropathy (Lewis et al, 1993). Since then, the development of angiotensin II receptor blockers (ARBs) and direct renin inhibitors (e.g. aliskiren), together with aldosterone receptor blockers (spironolactone and eplerenone), means that the RAAS can be inhibited at multiple levels. These agents have also been shown to reduce albuminuria and, in the case of ARBs, slow the progression to end-stage renal disease (ESRD) in diabetic nephropathy in people with T2D (Brenner et al, 2001; Lewis et al, 2001).

Post hoc analysis of these latter studies (Evans et al, 2012) suggested that individuals with a greater reduction of albuminuria had a slower progression of kidney disease; so investigators explored methods of maximising the albuminuria response. One idea was to block the RAAS at multiple levels using different combinations of blocking agents, and short-term proof of concept studies suggested that this approach was effective.

On this basis, long-term trials were undertaken including ONTARGET (telmisartan added to ramipril [Mann et al, 2008]), ALTITUDE (aliskiren added to an ACE inhibitor or ARB [Parving et al, 2012]), and most recently the VA NEPHRON-D study (lisinopril added to losartan [summarised alongside]). However, all were terminated early due to lack of effect and excess serious adverse events despite all of them achieving a significant reduction in albuminuria. Why should this be?

Progression of diabetic renal disease is much slower nowadays. In the original captopril trial in people with T1D, the rate of loss of creatinine clearance was >11 mL/min/1.73 m^2/year (Lewis et al, 1993); by the time of the RENAAL and IDNT trials 10 years later, this rate of loss was down to <3 mL/min/1.73 m^2/year (Evans et al, 2012). Thus the VA NEPHRON-D study would have had to wait 10 years for its primary end-point of a 30 mL/min/1.73 m^2 decline, and in the event was terminated after a median duration of 2.2 years.

The RAAS preserves renal blood flow and protects the kidney at times of physiological stress. Complete blockade makes the kidney vulnerable, so it is perhaps not surprising that more episodes of acute kidney injury occurred in those on combination therapy (there were a large number of cardiovascular events in study participants, more than 18% of whom had heart failure, an acute myocardial infarction or stroke during the trial).

In the VA NEPHRON-D study, median entry albumin:creatinine ratio was around 850 mg/g (~850 mg albumin/day), which represents established overt nephropathy but is still much lower than in the captopril trial (~1250 mg albumin/day [Lewis et al, 1993]), IDNT (1900 mg albumin/day [Lewis et al, 2001]), or the RENAAL trial (1250 mg albumin/day [Brenner et al, 2001]). Although a significantly greater reduction in albuminuria was seen in the combination group compared to placebo (34% vs 15% respectively; $P<0.001$) it is possible that, in absolute terms, this reduction was not enough, or was not maintained long enough, to slow progression.

What does this mean for clinical practice? The VA NEPHRON-D study shows why suitably powered trials with hard clinical end-points are necessary to confirm findings from proof of concept short-term studies. The investigators are to be congratulated even though the study was effectively negative. We still need therapies to slow and prevent the development of diabetes-related ESRD. However, multiple-level RAAS blockade is neither effective nor safe, and has no place in the current management of people with diabetic nephropathy. ■

Study acronyms and references on next page

N Engl J Med

VA NEPHRON-D study terminated early

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

1 The VA NEPHRON-D (Veterans Affairs Nephropathy in Diabetes) study aimed to investigate the safety and efficacy of combined therapy of an angiotensin-converting enzyme inhibitor (lisinopril) with an angiotensin-receptor blocker (losartan) in overt diabetic nephropathy.

2 Losartan was prescribed to all participants at 50 mg/day and increased to 100 mg after 30 days if there were no adverse effects. Those with no adverse effects were later randomly assigned in a 1:1 ratio to receive the addition of lisinopril or placebo (combination therapy or monotherapy respectively).

3 The primary end-point was the first occurrence of a change in the estimated glomerular filtration rate (eGFR; an absolute decrease of ≥30 mL/min/1.73 m^2), end-stage renal disease or death.

4 Among 1448 randomly assigned participants followed for a median of 2.2 years, 152 primary end-points were recorded in the monotherapy group and 132 in the combined therapy group.

5 A trend towards a beneficial effect of combination therapy with respect to the secondary end-point decreased over time, and there was no benefit with respect to mortality or cardiovascular events.

6 Combination therapy increased the risk of hyperkalaemia and acute kidney injury compared to monotherapy.

7 The authors conclude combination therapy increased the risk of adverse events among people with diabetic nephropathy.

Fried LF, Emanuele N, Zhang JH et al (2013) Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* **369**: 1892–903

Diabetes Care

Glycaemia and mortality in dialysis

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

1 Guidelines suggest that people with diabetes receiving dialysis treatment should have tight glycaemic control; however, these people are often excluded from glucose-lowering trials so there is little evidence-based research in this area.

2 This study used observational data from the UK Renal Registry to investigate the association between glycaemia and mortality in adults with diabetes who started dialysis between 1997 and 2006.

3 Individuals were observed for at least 6 months and HbA_{1c} was catergorised into the following ranges: <48 mmol/mol (<6.5%); 48–57 mmol/mol (6.5–7.4% [reference value]); 58–68 mmol/mol (7.5–8.4%) and ≥69 mmol/mol (≥8.5%).

4 Of 3157 people observed for a median of 2.7 years, 1688 people died.

5 Among people >60 years of age, there was no association between HbA_{1c} and death. Among younger people the hazard ratio (HR) for HbA_{1c} level 58–68 mmol/mol (7.5–8.4%) compared to the reference value was 1.2 (95% confidence interval [CI], 0.9–1.5) and for HbA_{1c} level >69 mmol/mol (>8.5%) the HR was 1.5 (95% CI, 1.2–1.9).

6 After adjusted analyses for co-variates, there was no association between death and HbA_{1c} among people >60 years of age. The adjusted HR for younger people was 2.11 (95% CI, 1.45–3.07; $P<0.0001$).

7 The findings support tighter glycaemic control for younger people with diabetes prior to or during dialysis treatment.

Adler A, Casula A, Steenkamp R et al (2014) Association between glycemia and mortality in diabetic individuals on renal replacement therapy in the United Kingdom. *Diabetes Care* 26 Feb [Epub ahead of print]

Diabetes Care

Renal functional decline in T1D

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

1 Renal functional decline is observed in people with microalbuminuria (MA), but it is unclear if it begins before, when they are normoalbuminuric (NA), or during MA.

2 In total, 286 people with NA and 248 people with MA were followed for 4–10 years at the Joslin Diabetes Center, MA, USA.

3 Renal decline occurred in 10% of people with NA and 35% of people with MA ($P<0.001$). The strongest determinants of renal decline were baseline serum concentrations of uric acid and tumour necrosis factor receptor 1 or 2 (both $P<0.001$).

4 Other risk factors included baseline HbA_{1c}, age/diabetes duration and systolic blood pressure.

5 Renal decline in T1D begins during NA, but may cause or develop in parallel with MA.

Krolewski AS, Niewczas MA, Skupien J et al (2014) Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. *Diabetes Care* **37**: 226–34

Diabetes Care

Diabetes, ESRD and CV events

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

1 This study investigated the effect of the interaction between diabetes and end-stage renal disease (ESRD) on the risk of cardiovascular (CV) events.

2 In total, ~65 000 people without ESRD and ~71 000 people with ESRD (including ~53 000 and ~35 000 people with diabetes respectively) were included to determine the age- and sex-specific incidence and 20-year risk of incidence CV events stratified by the presence of diabetes, *de novo* diabetes after ESRD, or ESRD.

3 There was a multiplicatively synergistic effect of diabetes and ESRD for CV-related risk, especially for acute myocardial infarction and stroke. Adjusted hazard ratios were 5.24 (95% confidence interval [CI], 4.83–5.63) and 2.43 (95% CI, 2.32–2.55) respectively compared to healthy controls. There was a similar association between the risk of CV events and *de novo* diabetes after ESRD.

Chang YT, Wu JL, Hsu CC et al (2014) Diabetes and end-stage renal disease synergistically contribute to increased incidence of cardiovascular events. *Diabetes Care* **37**: 277–85

BMJ Open

Progression of renal function in T2D

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

1 The authors examined the 10-year progression of renal function for people with T2D and chronic kidney disease (CKD) and described the risk factors for a "severe decline" in renal function.

2 The primary outcome measure was kidney function calculated using the "modification of diet in renal disease" equation, and severe renal decline was defined as >4 mL/min/year.

3 Out of 4041 participants, 38% had CKD and 15% presented with severe decline in renal function after 10 years.

4 Severe decline was associated with younger age, male sex, higher mean HbA_{1c} and a higher number of "certain drops" (year-to-year decline in renal function of >10 mL/min [$P<0.05$]). Statins and higher diastolic blood pressure were significantly associated with the absence of severe decline ($P<0.001$).

Goderis G, Van Pottelbergh G, Truyers C et al (2013) Long-term evolution of renal function in patients with type 2 diabetes mellitus. *BMJ Open* **3**: e004029

"The findings support tighter glycaemic control for younger people with diabetes who are about to begin, or already receive, dialysis treatment."

Study acronyms from the commentary

ALTITUDE = Aiskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints
IDNT = Irbesartan Diabetic Nephropathy Trial
ONTARGET = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
VA NEPHRON-D = Veterans Affairs Nephropathy in Diabetes

References from commentary

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Lewis EJ et al (1993) *N Engl J Med* **329**: 1456–62
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Mann JF et al (2008) *Lancet* **372**: 547–53
Parving HH et al (2012) *N Engl J Med* **367**: 2204–13
Zatz R et al (1986) *J Clin Invest* **77**: 1925–30