Nephropathy

Hyperkalaemia in chronic kidney disease: New treatment for an old problem

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Blockade of the renin–angiotensin–aldosterone system (RAAS) remains the cornerstone of therapy in diabetic nephropathy (DN). For the most part, either angiotensin-converting enzyme inhibition (ACEI) or angiotensin receptor blockade (ARB) are well tolerated and about equivalent in terms of efficacy (Palmer et al, 2015). However, it is recognised that some patients remain albuminuric on therapy despite high doses of single therapy. This observation led to the concept of incomplete RAAS blockade as a result of escape from, or bypass of, the conventional system. Consequently, trials of multiple-level blockade using combination ACEI and ARB or aldosterone antagonists (such as spironolactone or eplerenone) were undertaken. A recent meta-analysis of these studies concluded that combination blockade reduced albuminuria and end-stage renal disease (ESRD) more than monotherapy, but was associated with increased hyperkalaemia and acute kidney injury (Palmer et al, 2015). As a result, multiple-level RAAS blockade is not currently recommended (National Kidney Function, 2013). However, hyperkalaemia can complicate mono-RAAS blockade in patients when glomerular filtration rate declines and often leads to cessation of therapy, possibly leading to more rapid progress to ESRD. In addition, some people with DN have hyporeninaemic hypoaldosteronism (also called renal tubular acidosis type 4), which is often associated with hyperkalaemia when patients commence RAAS blockade. There is thus considerable interest in developing agents to reduce serum potassium in people with chronic kidney disease (CKD), and, earlier in 2015, two studies showing short-term efficacy of novel agents were published (Inglefinger, 2015).

The AMETHYST-DN trial addressed the problem of hyperkalaemia in type 2 DN (see Bakris et al, summarised alongside). The investigators used patiromer (a potassium-binding polymer, which prevents absorption and increases faecal loss of potassium) over one year. Significant and sustained reductions in serum potassium to a mean of 4.8 mmol/L were observed, with a rapid onset (within 2 days) and equally rapid loss (3 days after cessation) of effect. The drug was generally well tolerated with expected gastrointestinal side effects of constipation and diarrhoea, but these led to discontinuation in only two participants over a year. Slightly more concerning was the observation of a reduction in serum magnesium, although the mean remained within the normal range (none developed severe hypomagnesaemia defined as <0.4 mmol/L). This is important as hypomagnesaemia (normal range 0.6–1.0 mmol/L in AMETHYST-DN) is associated with cardiac dysrhythmias, which are thought to be responsible, in part, for the increased incidence in sudden death observed in people with DN and CKD stage 4/5 (4.9% of AMETHYST-DN participants died during the year of study).

The AMETHYST-DN trial was limited by its unblinded design and lack of a comparator. This is partly due to the poor tolerability of existing potassium binders (such as calcium resonium), which would make blinding difficult. Nevertheless, it provides enough preliminary evidence of tolerability and effectiveness to make patiromer a potentially useful agent.

This is because there is still considerable interest in multiple-level RAAS blockade as a means of reducing ESRD in people with DN. Non-steroidal aldosterone antagonists are in development, and a phase 2b trial of one of them (finerenone) has recently been published (Bakris et al, summarised on the next page); this agent is now undergoing extensive phase 3 study. Another problem that is confronting many of our patients with DN is heart failure, which often requires therapies that are known to increase serum potassium. Patiromer, therefore, represents a potentially positive advance in managing hyperkalaemia in otherwise difficult-to-treat patients. Long-term studies (which are ongoing and hopefully suitably designed) in those with hyperkalaemia and worsening CKD are now required to firmly establish safety and efficacy. ■

References on opposite page

JAMA

Patiromer: Hyperkalaemia treatment

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

1 Hyperkalaemia (high potassium levels) is often seen in people who are treated with renin–angiotensin–aldosterone system (RAAS) inhibitors with stage 3 or greater chronic kidney disease (CKD) and who may also have diabetes, heart failure or both.

2 The researchers conducted a phase 2 long-term safety and efficacy trial of patiromer, a potassium-binding polymer, in people with hyperkalaemia.

3 The AMETHYST-DN trial was open-label, dose-ranging and randomised. It was conducted at 48 sites in Europe and all participants received RAAS inhibitors before and during the study period. In total, 306 outpatients with T2D were included.

4 The participants were grouped into mild or moderate hyperkalaemia groups. The mild hyperkalaemia group received a starting patiromer dose of 4.2 g, 8.4 g or 12.6 g twice daily and the moderate hyperkalemia group received a starting dose of 8.4 g, 12.6 g or 16.8 g twice daily. Patiromer was titrated to achieve and maintain serum potassium level 5.0 mEq/L or lower.

5 The treatment period lasted 8 weeks, following a 4-week run-in period, and the maintenance period after treatment took the study up to 52 weeks.

6 Over the 52 weeks, hypomagnesaemia was the most common treatment-related adverse event (7.2%). Patiromer starting doses of 4.2 to 16.8 g twice daily resulted in statistically significant decreases in serum potassium levels after 4 weeks of treatment, which lasted through 52 weeks.

Bakris GL, Pitt B, Weir MR et al (2015) Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease. *JAMA* **314**: 151–61

Diabetes Care

Nonalbuminuric CKD in people with T1D

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

1 The questions the authors aimed to answer were what is the prevalence of nonalbuminuric chronic kidney disease (CKD) in T1D, and does it increase the risk of cardiovascular and renal outcomes as well as all-cause mortality.

2 An observational study with 13 years follow-up was conducted using data from 3809 adults (37.6±11.8 years) from the Finnish Diabetic Nephropathy Study.

3 At baseline, 78 people had nonalbuminuric CKD. This was associated with older age, female sex, history of retinal laser treatment, cardiovascular events (CVEs) and the number of anti-hypertensive drugs used. It was not associated with blood pressure levels or specific anti-hypertensive drugs.

4 Nonalbuminuric CKD did not increase the risk of end-stage renal disease, but it did increase the risk of CVEs and all-cause mortality.

Thorn LM, Gordin D, Harjutsalo V et al (2015) The presence and consequence of nonalbuminuric chronic kidney disease in patients with type 1 diabetes. *Diabetes Care* **38**: 2128–33

Diabetologia

CVEs in T2D and renal impairment

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

1 In this study, the relationships between mean blood pressure, cardiovascular events (CVEs) and all-cause mortality were examined among people with T2D and renal impairment.

2 An observational study of data from the Swedish National Diabetes Register included over 33 300 adults aged 75±9 years with diabetes duration of 10±8 years who were followed for up to 6 years or death if sooner.

3 During the mean follow-up of 5 years, among those with renal impairment, the risk of CVEs and all-cause mortality increased significantly with both high and low blood pressures (BP), while a systolic BP of 135–139 mmHg and diastolic BP of 72–74 mmHg were associated with the lowest risks of CVEs and death.

Afghahi H, Svensson MK, Pirouzifard M et al (2015) Blood pressure level and risk of major cardiovascular events and all-cause of mortality in patients with type 2 diabetes and renal impairment: an observational study from the Swedish National Diabetes Register. *Diabetologia* **58**: 1203–11

JAMA

Finerenone safety for albuminuria

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

1 Steroidal mineralocorticoid receptor antagonists are known to reduce proteinuria in patients with chronic kidney disease, but are linked with a high risk of adverse events (AEs).

2 In a phase 2b study to evaluate the safety and efficacy of different oral doses of finerenone, a randomised, double-blind, placebo-controlled, parallel-group study was conducted at 148 sites in 23 countries.

3 The doses of finerenone under investigation were 1.25 mg; 2.5 mg; 5 mg; 7.5 mg; 10 mg; 15 mg; and 25 mg daily (plus placebo), and these were randomly distributed evenly among the cohort.

4 The addition of finerenone to people already receiving drug treatment for diabetic nephropathy saw an improvement in the urinary albumin–creatinine ratio. There was no difference in the secondary outcome of an estimated glomerular filtration rate decrease of 30% or any difference in the incidence of AEs and serious AEs between the placebo and finerenone groups.

Bakris GL, Agarwal R, Chan JC et al (2015) Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA* **314**: 884–94

Diabet Med

Increased physical activity leads to improved kidney function

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

1 The authors investigated the association between objectively measured physical activity and kidney function over 4 years in people with T2D.

2 As part of the ADDITION-Plus trial, the time spent in various levels of physical activity were measured alongside heart and kidney markers at baseline and after 4 years.

3 Multivariate regression was used to quantify the associations, which were adjusted for related factors such as waist circumference, HbA_{1c} and blood pressure.

4 In this study group of 120 women and 206 men, increases in sedentary time were associated with increases in serum creatinine after adjustment for moderate-to-vigorous-intensity physical activity and cardiovascular risk factors. Increases in total physical activity energy expenditure were associated with reductions in serum creatinine.

5 Increasing physical activity and reducing sedentary behaviour may improve kidney function among people with diabetes.

Guo VY, Brage S, Ekelund U et al (2015) Objectively measured sedentary time, physical activity and kidney function in people with recently diagnosed type 2 diabetes: a prospective cohort analysis. *Diabet Med* 18 Aug [Epub ahead of print]

"Increasing physical activity and reducing sedentary behaviour may improve kidney function among people with diabetes."

References from commentary

Ingelfinger JR (2015) *N Engl J Med* **372**: 275–7
National Kidney Foundation (2013) *Am J Kidney Dis* **60**: 850–86
Palmer SC et al (2015) *Lancet* **385**: 2047–56