Nephropathy

Strategies for blocking the renin–angiotensin–aldosterone system in diabetic nephropathy: What works?

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Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are effective in lowering blood pressure and reducing albuminuria in patients with diabetic nephropathy. However, for most people treated with these agents, progression of nephropathy is slowed but not halted.

ACEi and ARB inhibit the renin–angiotensin–aldosterone system at different sites, and the question of whether a combination of these drugs – a dual blockade – might yield additional benefits has arisen. A number of small, short-term studies, often using submaximal ACEi doses, have yielded conflicting results in regard to both blood pressure and albuminuria. The largest randomised trial to date (albeit only for 6 months in 20 people with type 2 diabetes), showed that dual blockade reduced albuminuria, with no apparent deleterious effects on renal function (Rossing et al, 2003). The effect on blood pressure was minimal, with a reduction of only 3/2mmHg.

Analysis of renal outcomes in the ONTARGET study (summarised on page 241) raises some concerns over the long-term safety and efficacy of dual blockade therapy. Although albuminuria was reduced, combination therapy appeared to worsen primary renal outcomes for the entire cohort with established atherosclerotic vascular disease. Despite the observed reductions in albuminuria with dual blockade, no clear benefit was evident in the sizeable subset of patients with diabetic nephropathy.

Given that, despite ACEi or ARB therapy, aldosterone levels return to normal in 40% of people with diabetic nephropathy, a different approach might be to block aldosterone action using spironolactone (or eplerenone). Again, a number of small, short-term studies have shown that the addition of these agents to an ACEi and/or ARB regimen will also lower albuminuria, but there does appear to be a more clinically significant effect on blood pressure, with reductions of up to 10/5mmHg reported (Rossing et al, 2005).

On top of this comes the study by Parving et al (summarised alongside) where the direct renin inhibitor aliskiren was added to losartan in people with well-controlled hypertension and diabetic nephropathy. Again, this combination produced significant reductions in albuminuria, with no real impact on blood pressure.

So what is the clinician to make of these results? Until long-term clinical trials clearly demonstrate that any of the suggested combination therapies are more efficacious in the prevention of progressive renal failure than an ACEi or ARB alone, there remains no convincing case for combination therapy. However, if blood pressure remains inadequately controlled with conventional therapies, a case might be made for a trial of spironolactone (a regimen of no more than 25mg/day) in order to lower both blood pressure and albuminuria. The use of any agent that blocks the renin–angiotensin–aldosterone system always needs to be balanced against the associated risks, in particular that of hyperkalaemia. Careful selection and supervision of those being treated with any combination therapy is advised (Palmer, 2004).

Palmer BF (2004) Managing hyperkalemia caused by inhibitors of the renin–angiotensin–aldosterone system. *New England Journal of Medicine* **351**: 585–92

Rossing K, Jacobsen P, Pietraszek L et al (2003) Renoprotective effects of adding angiotensin II receptor blocker to maximal recommended doses of ACE inhibitor in diabetic nephropathy: A randomized double-blind crossover trial. *Diabetes Care* **26**: 2268–74

Rossing K, Schjoedt KJ, Smidt UM et al (2005) Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: A randomized, double-masked, cross-over study. *Diabetes Care* **28**: 2106–12

⇨ **Continues on page 241.**

NEW ENGLAND JOURNAL OF MEDICINE

Aliskiren effective as renoprotective agent in patients with diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The main cause of end-stage renal disease is diabetes-related nephropathy; this study evaluated the efficacy of treatment with the oral renin inhibitor aliskiren, typically used as a blood-pressure-lowering agent, in addition to standard renoprotective treatment with losartan.

2 A total of 599 participants were randomly allocated to one of two combination treatment groups: the first group received aliskiren in addition to losartan, and the second received placebo with losartan, both over a period of 6 months.

3 Success of treatment was defined as a significant reduction in the albumin:creatinine ratio after 6 months of treatment.

4 At the end of this study, 20% of patients in the aliskiren/losartan treatment group exhibited a reduction in their mean albumin:creatinine ratio, compared with the placebo/losartan group ($P<0.001$). In addition, the albumin:creatinine ratio was reduced by 50% or more in 24.7% of patients treated with aliskiren, compared with 12.5% of the placebo group ($P<0.001$).

5 Blood pressure levels were also decreased in patients treated with aliskiren compared with placebo ($P=0.08$).

6 In addition to its blood-pressure-lowering properties, aliskiren is effective as a renoprotective agent when used in combination with standard renoprotective treatment.

Parving HH, Persson F, Lewis JB et al (2008) Aliskiren combined with losartan in type 2 diabetes and nephropathy. *New England Journal of Medicine* **358**: 2433–46

KIDNEY INTERNATIONAL

Telmisartan is more effective than losartan for proteinuria

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 Effective treatment of both high blood pressure and proteinuria can help slow progression to kidney failure in patients with diabetes with concomitant nephropathy.

2 This prospective, randomised, double-blind, multicentre trial compared the efficacy of treatment with two different angiotensin-receptor-blocking agents, telmisartan and losartan, for the treatment of people with diabetes and high blood pressure (>130/80mmHg) and a high urinary protein:creatinine ratio (≥700mg/g).

3 A total of 860 participants were randomly assigned to one of two treatment groups for a period of 52 weeks, with 80% of those randomised completing the study.

4 The mean urinary protein:creatinine ratio was reduced significantly for both treatment groups by study end ($P<0.0001$); however, the reduction from baseline was greater for those receiving telmisartan, compared with those receiving losartan.

5 Both groups experienced a significant reduction in mean blood pressure by study end, though no significant between-group difference for either diastolic or systolic blood pressure were found.

6 Thus, although the effects on blood pressure are not significantly better, telmisartan is more effective at treating proteinuria in people with diabetes and nephropathy.

Bakris G, Burgess E, Weir M (2008) Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. *Kidney International* **74**: 364–9

DIABETES

Risk of diabetes-related nephropathy not associated with a single kidney

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓

1 Having one kidney is thought to be a risk factor for diabetes-related nephropathy, however few data are available to support this hypothesis.

2 This study compared the rate of onset of kidney disease in people with type 1 diabetes with a single kidney (from a transplant) with those with two natural kidneys, and control participants with two natural kidneys and no diabetes.

3 Although serum creatinine, systolic blood pressure and rate of albumin excretion were higher in people with one kidney compared with those with two ($P<0.001$), there was no evidence indicating faster development of glomerulopathy lesions between groups.

Chang S, Caramori ML, Moriya R et al (2008) Having one kidney does not accelerate the rate of development of diabetic nephropathy lesions in type 1 diabetic patients. *Diabetes* **57**: 1707–11

LANCET

Ramipril–telmisartan combination therapy not effective in treating nephropathy

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓

1 This randomised study compared the efficacy of ramipril, telmisartan or a combination in the treatment of proteinuria in 25 620 people aged >55 years with diabetes or established atherosclerotic vascular disease.

2 Treatment with either telmisartan or ramipril was more effective for treating proteinuria compared with combination treatment ($P=0.037$); the incidence of dialysis and the doubling of serum creatinine levels was also greater when using combination therapy compared with either agent alone ($P=0.038$).

3 Individual treatment with telmisartan or ramipril was similarly effective for the treatment of renal disease; combination treatment with both drugs was effective at reducing proteinuria, but worsened major renal outcomes.

Mann JF, Schmieder RE, McQueen M et al (2008) Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* **372**: 547–53

MAYO CLINIC PROCEEDINGS

Atorvastatin effective in reducing heart disease in diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 This study aimed to compare the efficacy of high-dose versus low-dose treatment with atorvastatin, a lipid-lowering agent, for the reduction of major cardiovascular events in patients with diabetes and coronary artery disease, with and without concomitant chronic kidney disease (CKD).

2 A total of 10 001 patients were randomly allocated to receive treatment with either 80mg/day or 10mg/day atorvastatin over 8 weeks, with a median follow-up of 4.8 years ($P=0.01$).

3 High-dose atorvastatin was more effective in reducing the risk of major cardiovascular events in patients with diabetes, both with and without CKD.

Shepherd J, Kastelein JP, Bittner VA et al (2008) Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease. *Mayo Clinic Proceedings* **83**: 870–9

"Telmisartan–ramipril combination treatment was effective in reducing proteinuria, but worsened major renal outcomes."