

Dual inhibition with losartan and aliskiren: a promising therapeutic option for type 2 diabetic nephropathy?

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SUMMARY

This Practice Point commentary discusses the findings and limitations of a randomized, double-blind study conducted by Parving and colleagues. The study evaluated the renoprotective effects of dual blockade of the renin–angiotensin–aldosterone system by adding aliskiren (an oral, direct renin inhibitor) or placebo to treatment with 100 mg daily losartan in patients who had hypertension and type 2 diabetes with nephropathy. Addition of daily aliskiren for 6 months (150 mg/day for 3 months and 300 mg/day for 3 months) reduced the mean urinary albumin:creatinine ratio by 20% ($P < 0.001$), with a reduction of 50% or more in 24.7% of the patients who received aliskiren versus only 12.5% of those who received placebo ($P < 0.001$). At study end, mean blood pressure levels were only slightly lower in the aliskiren group than in the placebo group (2/1 mmHg lower). The authors concluded that aliskiren might have renoprotective effects that are independent of its blood-pressure-lowering effect in patients who have hypertension, type 2 diabetes and nephropathy and are receiving the recommended renoprotective treatment.

KEYWORDS aliskiren, dual inhibition of RAAS, microalbuminuria, renin inhibition, renoprotection

COMMENTARY

Diabetic nephropathy is now the leading cause of end-stage renal failure worldwide. This devastating disorder seems to occur when metabolic and hemodynamic factors interact and cause the activation of common pathways that result in renal damage.¹ The renin–angiotensin–aldosterone system (RAAS) is an important target for both metabolic and hemodynamic disturbances in diabetic nephropathy. Currently available therapies are usually only started at the more-advanced stages of diabetic nephropathy characterized by clinically overt manifestations such as increased urinary albumin excretion and decreased glomerular filtration. Blood pressure is an important determinant of the risks of macrovascular and microvascular complications of type 2 diabetes, and guidelines recommend the intensive lowering of blood pressure in patients with diabetes and hypertension. Previous studies have indicated that the use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers is beneficial in preventing or slowing progression of diabetic nephropathy. Despite their proven efficacy in slowing the progression of diabetic nephropathy, however, these agents cannot prevent end-stage renal disease.¹

In the recently published AVOID (Aliskiren in the Evaluation of Proteinuria in Diabetes) trial, Parving *et al.*² investigated the renoprotective effects of dual blockade of the RAAS by randomizing 599 patients who had type 2 diabetes with nephropathy and hypertension and were on the maximum recommended renoprotective dose of the angiotensin-receptor blocker losartan (100 mg), to the addition of either aliskiren (an oral, direct renin inhibitor; $n = 301$) or placebo ($n = 298$). The addition of daily aliskiren for 6 months (150 mg/day for 3 months followed by 300 mg/day for 3 months) was associated with a 20% reduction in the mean urinary albumin:creatinine ratio (vs no change with placebo; $P < 0.001$). A reduction in the mean urinary albumin:creatinine ratio of 50% or more was observed in 24.7% of the patients who received aliskiren (vs 12.5% of those who received placebo ($P < 0.001$), which indicates that a considerable number of patients might not have responded to renin inhibition. The authors found that the benefits of aliskiren seemed to be independent of systemic blood pressure. At study end (6 months), mean blood pressure levels were only slightly lower (2/1 mmHg lower) in the aliskiren group than in the placebo group. This finding is surprising as previous studies have

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shown a significant blood-pressure-lowering effect with aliskiren.^{3,4} In fact, the combination of aliskiren and valsartan at maximum recommended doses has been shown to provide significantly greater reductions in blood pressure (within the ranges 4.0–4.5 mmHg systolic and 2.5–3.0 mmHg diastolic) than monotherapy with either agent in patients with hypertension.³ Since only single blood pressure—not 24 h blood pressure—measurements were taken in the AVOID trial,² however, it is possible that blood pressure differences between the two treatment arms were greater at different times of day. Remarkably, a recent study from the same group⁴ reported a significant reduction in mean 24 h systolic blood pressure from baseline (6–8 mmHg; $P=0.006$) after only 2 weeks of aliskiren treatment in 15 patients with type 2 diabetes and an elevated urinary albumin:creatinine ratio. Thus, future studies investigating the potential beneficial effects of aliskiren should measure 24 h blood pressure.

Another limitation of the AVOID study is the relatively poor glycemic control of the participants (mean glycosylated hemoglobin [HbA_{1c}] $8.0 \pm 1.4\%$ at baseline in the aliskiren group). It is unclear whether aliskiren would have had the same effect in patients with type 2 diabetes who were receiving more-effective antidiabetic therapy. Interestingly, the recently published ADVANCE study⁵ showed that lowering HbA_{1c} from about 7.5% to 6.5% reduced new or worsening nephropathy by 21% in patients with type 2 diabetes ($P=0.006$).

The AVOID trial lasted only 6 months, and much longer studies conducted over several years that include end-stage renal disease as an end point are needed. In 2000, a study evaluating dual blockade of the RAAS with candesartan and lisinopril in patients with hypertension, microalbuminuria, and type 2 diabetes showed rather promising results in terms of reductions in blood pressure and albuminuria.⁶ However, the effectiveness of dual blockade of the RAAS could not be confirmed in larger and longer studies.^{7,8} In the IMPROVE study, which randomized 405 patients with hypertension and diabetes to either ramipril plus irbesartan or ramipril plus placebo, dual RAAS blockade with ramipril and irbesartan did not reduce microalbuminuria to a greater extent than treatment with ramipril alone.⁷ The ONTARGET study⁸ evaluated dual blockade of the RAAS in 25,620 patients with vascular disease or

high-risk diabetes over a median of 56 months. The combination of telmisartan and ramipril did not reduce the primary composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure compared with either monotherapy. Moreover, the combination therapy group had a significantly increased risk of renal dysfunction compared with the ramipril group (hazard ratio 1.33; 13.5% vs 10.2%; $P<0.001$).⁸ The percentage of patients with an increase in potassium level of more than 5.5 mmol/l was similar in the ramipril and in the telmisartan group (3.3% vs 3.4%, respectively), but significantly higher in the combination-therapy group (5.6%; $P<0.001$ for comparison between ramipril and combination group). During the AVOID trial, 4.7% of patients in the aliskiren group had at least one value for serum potassium level that was 6.0 mmol/l or more, compared with 1.7% of patients in the placebo group ($P=0.06$).² Further studies are needed to determine whether dual blockade of the RAAS provides sustained renal protection and to confirm the long-term safety of this strategy.

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PRACTICE POINT

In the AVOID trial, dual blockade of the renin-angiotensin-aldosterone system reduced albuminuria, but further studies are needed to determine whether dual blockade provides sustained renal protection and to confirm the long-term safety of this strategy.

Competing interests

The author declared no competing interests.