DIABETIC NEPHROPATHY

Aliskiren as an add-on treatment reduces albuminuria in patients with diabetes

The addition of aliskiren to standard therapy including an optimal dose of the angiotensin-receptor blocker losartan and antihypertensive medication reduces albuminuria and slows the development of renal dysfunction in patients with chronic kidney disease (CKD), hypertension and type 2 diabetes, say investigators from a post-hoc analysis of the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study. "The most significant finding [from this analysis] was that the addition of aliskiren to standard therapy was effective independent of baseline CKD status," explains researcher Frederik Persson.

Patients with type 2 diabetes, hypertension and nephropathy are at risk of renal disease progression and adverse cardiovascular events. Results from the randomized controlled AVOID study published in 2008 demonstrated that the direct renin inhibitor aliskiren could reduce proteinuria in patients with type 2 diabetes, hypertension, and nephropathy, when given in combination with standard therapy. "The publication of the AVOID study led to a number of questions being raised by the nephrology community with regard to the use of aliskiren as an add-on therapy in patients with type 2 diabetes and nephropathy," explains Persson. "One of these questions was whether this new treatment is safe and effective in patients with impaired renal function."

To answer this question, Persson and colleagues performed a post-hoc analysis of data from the AVOID study by grouping patients according to baseline CKD stage. All participants had hypertension, type 2 diabetes, and nephropathy. The trial consisted of an initial 3-month open-label phase, during which use of drugs that block the renin–angiotensin–aldosterone system were discontinued and use of losartan was initiated. Antihypertensive therapy was optimized to achieve a target blood pressure <130/80 mmHg. After

3 months, 599 patients were randomly assigned to receive either aliskiren (150 mg once daily for 3 months and then 300 mg once daily for a further 3 months) or placebo. Patients were followed for a median of 6 months.

In the current post-hoc analysis, the AVOID investigators compared the effect of aliskiren according to baseline stage of CKD. "For each of the CKD groups [stages 1–3], we compared the safety and efficacy results between patients who received aliskiren and those who received placebo added to a standard losartan-based regimen", explains Persson. "We used this approach so that clinicians would be able to translate the AVOID results into specific patient groups."

The researchers found that patients on aliskiren were more likely than those on placebo to achieve the primary end point of a reduction in early morning urinary albumin-to-creatinine ratio (UACR). In patients with stage 3 CKD, UACR decreased by 9% in those on aliskiren and increased by 13% in those on placebo ($P = 0.045$). In patients with stage 2 CKD, UACR decreased by 23% in those on aliskiren and by 1% in those on placebo ($P = 0.021$). In patients with stage 1 CKD, UACR decreased by 27% in those on aliskiren and by 11% in those on placebo, although this difference was not statistically significant ($P = 0.202$).

A higher proportion of patients on aliskiren than on placebo also achieved a ≥50% reduction in UACR. The researchers did not observe any significant differences in changes in estimated glomerular filtration rate between treatments; however, they found that a greater proportion of patients with stage 3 CKD on placebo developed renal dysfunction, defined as development of serum creatinine level >176.8 μmol/l (29.2% versus 13.6%, $P = 0.032$).

Persson and colleagues also found that elevations in serum potassium level >5.5 mmol/l were more frequent with aliskiren than with placebo in patients with stage 3 CKD (22.5% versus 13.6%, $P = 0.07$). Although this difference was nonsignificant, the researchers warn that this finding indicates that caution is needed when considering aliskiren for patients with stage 3 CKD.

The AVOID investigators acknowledge that the post-hoc nature of their study is a limitation, and advise that studies of longer duration are required to properly assess the benefits of direct renin inhibition in patient subgroups. "Results from the ongoing ALTITUDE study will provide us with more information regarding the potential cardiorenal benefits of renin inhibition", concludes Persson.

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Original article Persson, F. *et al*. Impact of baseline renal function on the efficacy and safety of aliskiren added to losartan in patients with type 2 diabetes and nephropathy. *Diabetes Care* **33**, 2304–2309 (2010)

Further reading Parving, H. H. *et al*. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N. Engl. J. Med*. **358**, 2433–2446 (2008) | Parving, H. H. *et al*. Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design. *Nephrol. Dial. Transplant*. **24**, 1663–1671 (2009)