Commentary

An Issue of Dependence: Implications From the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) Trial

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The direct renin inhibitor aliskiren is a new antihypertensive agent that appears to be equivalent to other agents in blood pressure reduction. It is well tolerated, has a long half-life, and has a sustained duration of action. At present, aliskiren as monotherapy is not widely used despite these potential benefits. There are many other available options for the treatment of hypertension with demonstrated morbidity and mortality outcomes and economic advantages. The role of aliskiren as part of combination therapy is, however, evolving. Two- or three-drug therapy is necessary for many hypertensive patients, and rational combinations to maximize blood pressure control and influence comorbid conditions should continue to be identified. The characteristics of aliskiren and the broader application of this new class of medications will require further assessment and demonstration of long-term effects, particularly before treatment practices will change.

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The recently published Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study evaluated the potential renoprotective effect of direct renin inhibition in patients with hypertension, type 2 diabetes, and proteinuria. Aliskiren, titrated to maximum doses over 6 months, or placebo were added to full-dose angiotensin II receptor blocker (ARB) (losartan) and antihypertensive therapy with other agents in 599 patients. The primary outcome was reduction in the urinary albumin-to-creatinine ratio.[1] Parving and colleagues[1] concluded that aliskiren may have renoprotective effects independent of blood pressure lowering in this patient population that was already receiving treatment with currently recommended renoprotective therapy, an ARB.[1,2] While this conclusion is plausible, we contend that the authors provide insufficient discussion on the contribution of several dependent variables, including the long-term effect of losartan, potential differences in 24-hour blood pressure between groups and, in particular, confounding baseline demographics.

Theoretically, as observed with the combination of angiotensin-converting enzyme inhibitors (ACEIs) and aldosterone antagonists in heart failure, optimization of renin-angiotensin system (RAS) inhibition may potentially offer benefits, particularly in patients with comorbid diseases. Treatment with an ACEI or ARB has been reported to provide benefits in the treatment of diabetic nephropathy. The rationale for attempting more complete blockade by combining agents targeting the RAS relates to the recognition of angiotensin-converting enzyme–independent pathways and further generation of angiotensin II by these pathways or to the

long-term effects of ARBs on renin activity. However, any benefit of combining ACEI and ARB therapy in patients with diabetic nephropathy is, at least, debatable. With the recent concerns and issues regarding interpretation of dual RAS blockade in nondiabetic renal disease (Combination Treatment of Angiotensin-II Receptor Blocker and Angiogtensin-Converting Enzyme Inhibitor in Nondiabetic Renal Disease [COOPERATE])[3] and the lack of benefit from dual RAS blockade in high-risk patients with vascular disease,[4] it is interesting to review the evidence for dual RAS blockade in diabetic nephropathy.

In a recent meta-analysis, Jennings and colleagues[5] suggested short-term benefits of ACEI and ARB combination therapy when compared with ACEI monotherapy on 24-hour urinary protein excretion in patients with diabetic nephropathy. However, the authors advised caution when interpreting results because of the trial durations and differences in blood pressure. Most of the studies available for conclusion had small treatment groups and were of short duration (8–12 weeks). The majority of trials also reported statistically significant correlations between improvement in blood pressure and proteinuria. The authors highlight earlier long-term studies (12 months' duration) using multiple-drug therapy and the lack of benefit on protein excretion, suggesting that an early effect of combination therapy may not translate into long-term benefits.[5]

The Candesartan and Lisinopril Microalbuminuria (CALM) study, one of the larger and more frequently cited multiple-drug studies, was not included in the meta-analysis as it did not report 24-hour urinary protein excretion.[5,6] This study compared once-daily doses of lisinopril 20 mg, candesartan 16 mg, or the 2 medications in combination over 24 weeks in patients with diabetes, microalbuminuria, and hypertension.[6] This therapy, using relatively low doses of both medications, was more effective in decreasing blood pressure and the urinary albumin-to-creatinine ratio; the authors, however, could not conclude that the proteinuria reduction was independent of the decrease in blood pressure observed.[6]

In the recently published Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), therapy with both agents did not confer renoprotective benefits despite a decrease in blood pressure. ONTARGET established the equivalence of an ACEI or ARB in the management of patients with vascular disease and high-risk diabetes, but it failed to demonstrate an additional advantage from 2-drug therapy. This large international trial randomized 25,620 patients, many of whom were not hypertensive, to receive ramipril 10 mg/d, telmisartan 80 mg/d, or both. Over a median follow-up of 56 months, there was no statistical difference among the groups in the primary outcome (death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure).[4] There were also no differences in secondary outcomes except for renal dysfunction, reported as renal impairment (a nonspecific definition based on a report of an event leading to study drug discontinuation) or renal failure requiring dialysis. Dual RAS blockade was associated with higher overall rates of renal dysfunction, with 13.5% in the 2-drug group compared with 10.2% with ramipril and 10.6% with telmisartan.[4] A significant increase in relative risk of renal impairment was observed in the ACEI/ARB group (1.33); relative risk was comparable with the monotherapy telmisartan and ramipril groups (1.04). Similarly, the rate of renal failure requiring dialysis increased with combination therapy (0.85% compared with 0.6% with ramipril or telmisartan).[4] All groups had a comparable number of patients who experienced a doubling of serum creatinine concentration. Although proteinuria increased to a lesser extent and the risk of new proteinuria developing was less in those receiving combination therapy, this therapy was associated with more adverse effects on typical renal outcomes and on the decline in estimated glomerular filtration rate.[7] The lack of positive findings with multiple-drug therapy is surprising; even the small differences observed in blood pressure reduction with the combination (ramipril, −6.4/−4.3 mm Hg; telmisartan, −7.4/−5.0 mm Hg; combination, −9.8/−6.3 mm Hg) would be expected to confer some additional benefits.[4] As the authors note, based on epidemiologic data, this 2- to 3-mm Hg blood pressure reduction should have translated into a risk reduction of 4% to 5%.[4] The CALM and ONTARGET results are somewhat different than the AVOID study findings, in which alternative dual RAS blockade with a renin inhibitor and an ARB has been reported to have renoprotective benefits independent of blood pressure lowering.[1,8]

Blood pressure reduction is clearly renoprotective. A decrease in the progression of renal disease has been reported in numerous blood pressure–lowering trials with many different antihypertensive agents including diuretics, hydralazine, and β-blockers. While blood pressure reduction was optimized with

other antihypertensive agents and was not a goal of aliskiren treatment in the AVOID study, it is difficult not to speculate on the AVOID conclusions while considering data from other previously reported studies. Only small office or clinic blood pressure reductions were observed in the Heart Outcomes Prevention Evaluation (HOPE) study group treated with ramipril (3/2 mm Hg compared with patients treated with medications that did not include an RAS blocker; in AVOID, there was a 2/1-mm Hg difference).[1,9] Subsequent review of ambulatory blood pressure in a small number of patients in HOPE identified significant differences in blood pressure over the 24-hour period, particularly at night. Thus, the effects on cardiovascular morbidity and mortality observed in HOPE may relate more than initially ascribed to changes in blood pressure if nocturnal blood pressure differences are considered.[9]

In the AVOID study, it is possible that differences between the aliskiren (plus other medications) and placebo (plus other medications) groups in 24-hour ambulatory blood pressure values could have occurred. Blood pressure differences in clinic blood pressure values may have significantly underestimated these differences. Losartan, the ARB selected presumably because of previous trials in patients with proteinuria, is, however, less effective than other ARBs in reducing blood pressure over the dosing interval.[10] In contrast, aliskiren has sustained effects, with some reports that blood pressure levels increase only gradually several weeks after treatment is stopped.[11]

Based on previous clinical studies in patients with diabetic nephropathy, ARB therapy is independently associated with a rapid and significant reduction in proteinuria. In the Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) study, Brenner and colleagues[12] observed a rapid and continual decline in the albumin-to-creatinine ratio with losartan. Patients treated with 50 to 100 mg/d of losartan (usually in addition to other medications) experienced an average reduction in the level of proteinuria of 35%.[12] Proteinuria continued to decline over a mean follow-up of 3.4 years, along with trough blood pressure. In comparison with AVOID, patients in RENAAL had higher baseline blood pressure values and more significant baseline proteinuria.[1,12] Higher initial blood pressure levels often predict better outcomes when they are reduced.

The AVOID study showed a similar rapid reduction in the albumin-to-creatinine ratio when aliskiren 150 mg/d was added to losartan 100 mg/d and other antihypertensive therapy.[1] The baseline reduction in proteinuria from losartan in the open-label phase was not reported, and there was no washout of previous RAS-blocking therapy, limiting comparison to the RENAAL study. After 3 months, the aliskiren dosage was increased to 300 mg once daily with an additional 3 months of follow-up.[1,12] Proteinuria decreased further, with reductions appearing to level off after approximately 4 weeks at each dosage (week 4 of 12, week 16 of 24). In contrast, the albumin-to-creatinine ratio decreased initially in the group not treated with the renin inhibitor but returned to baseline by week 24. A 20% mean reduction in the albumin-to-creatinine ratio was observed with aliskiren 300 mg as compared with placebo, which suggests that aliskiren may have renoprotective benefits. Because the AVOID study was short in duration (9 months on losartan, 6 months on aliskiren), the robustness of this conclusion should be carefully considered. RENAAL results indicate that long-term administration of losartan is associated with continued improvements in albuminuria, while previously observed benefits of dual RAS blockade with other agents have not persisted in studies longer than 12 months.[5,12] Considering the lack of continued reduction in the albumin-to-creatinine ratio in the aliskiren group and the rapid progression back to baseline in the group that did not receive the renin inhibitor between weeks 16 and 24, we contend that factors other than an independent aliskiren effect are responsible for the short-term significance of the improved albumin-to-creatinine ratio (a dual-dependent end point).

With a cursory review of the AVOID study, it is also easy to overlook other measures that may have implications in interpretation. Serum creatinine values and estimated glomerular filtration rates were similar at baseline between the aliskiren and placebo groups (creatinine for both groups: men, 1.3 mg/dL and women, 1.1 mg/dL; estimated glomerular filtration rate: 68.5 mL/min/1.73 m^2 for aliskiren and 66.8 for placebo groups). Relative changes in serum creatinine concentration or subgroup responses according to baseline serum creatinine level were not reported. In the Collaborative Study Group (CGS) trial of the effect of angiotensin-converting enzyme inhibition on diabetic nephropathy, higher baseline levels of serum creatinine (more advanced disease) predicted rates of renal decline (increase in serum creatinine level, decline in 24-hour creatinine clearance). A baseline serum creatinine level of $\geq$1.5 mg/dL predicted both a more pronounced decline in renal function over time and a benefit of captopril in protection

against further renal deterioration when compared with placebo. Captopril reduced proteinuria overall in the CGS trial, although subgroup responses based on creatinine values were not reported.[13] Relative changes in creatinine level or any significant differences in response among creatinine subgroups even over this short period of time may have further clarified interpretation in the AVOID study.

At study conclusion, there was no significant difference in the estimated glomerular filtration mean rate of decline between the aliskiren and placebo groups in the AVOID study.[1] In RENAAL, albeit over a much longer duration of study, losartan was associated with a reduction in the estimated decline in glomerular filtration rate compared with placebo.[12] Estimated glomerular filtration rate declined the least with ramipril compared with either telmisartan or combination therapy in ONTARGET, although mean final blood pressure levels were lower in both the ARB and combination groups.[4,7] Differences in baseline blood pressure values between these studies can obviously influence these findings.[1,4,12]

The issue of dependence is a critical one. Although the authors used appropriate randomization techniques in AVOID, there were statistically significant differences in age and known duration of diabetes between the 2 treatment groups.[1] In addition, the placebo group had a rise in glycated hemoglobin A_{1c} (HbA_{1c}) values throughout the study period (+0.2%), whereas the aliskiren group had no change in HbA_{1c}.[1] The National Kidney Foundation recognizes these factors (older age, longer duration of diabetes, and poorer glycemic control) as well as high blood pressure as risk factors for worsening chronic kidney disease.[14] Each of these dependent variables favored the aliskiren group and may have biased the results in favor of this group. A beneficial effect on the aliskiren group dependent end point (urinary albumin-to-creatinine ratio) might have been expected. There was no attempt in the trial to compensate for these or other confounding variables.

The concern with interpretation of a dual-dependent end point (ie, albumin-to-creatinine ratio) is that independent variables can play a key role in outcomes. The lack of improvement in other measures of renal function, coupled with the influence of the obvious dependent population confounding characteristics on chronic kidney disease, may raise questions about concluding an independent aliskiren effect. The progressive nature of renoprotection with losartan as demonstrated in RENAAL provides some explanation for the documented improvement in albumin-to-creatinine ratio, regardless of aliskiren use. While we admit that aliskiren may be beneficial in diabetic nephropathy—a disease of dependency—proven strategies (ie, blood pressure reduction, tight glycemic control, and maximization of single RAS blockade) should be the focus of treatment in all patients until unquestionable benefit of dual RAS blockade is demonstrated. The conclusions of ONTARGET bring this further into focus. Surrogate markers remain less than optimal for defining risk. The lack of renal benefits with ACEI and ARB combination therapy despite a reduction in proteinuria in ONTARGET demonstrates this point.[7] Clinical data are needed to establish the equivalence of aliskiren with single RAS blockade (with an ACEI or an ARB) in diabetic nephropathy and support the renoprotective capacity observed in animals.[15] As the authors point out, long-term studies must be conducted to determine whether the short-term benefits on proteinuria observed in AVOID can be sustained and translate to other markers of renoprotection or risk reduction.[1]

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