CORRESPONDENCE

Aliskiren Combined with Losartan in Diabetes and Nephropathy

TO THE EDITOR: In the report on the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study by Parving et al. (June 5 issue),[1] there is convincing evidence that aliskiren, in addition to losartan, has a significant antiproteinuric effect, which supports the potential therapeutic role of a renin inhibitor in diabetic nephropathy. However, the authors do not indicate specifically the type of calcium-channel blocker the patients were concomitantly taking. Non-dihydropyridine calcium-channel blockers, such as diltiazem, have been shown to have antiproteinuric and renoprotective properties.[2] Since more than 50% of the patients were taking a calcium-channel blocker, this may have partially contributed to the observed decrease in proteinuria. Furthermore, the superiority of telmisartan over losartan in reducing proteinuria in patients with diabetes was recently reported.[3] We question whether aliskiren would have resulted in the same magnitude of reduction in proteinuria had telmisartan been used instead of losartan.

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Dr. Panesar reports serving on speakers' bureaus for Novartis and Boehringer Ingelheim. No other potential conflict of interest relevant to this letter was reported.

1. Parving H-H, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008;358:2433-46.
2. Pérez-Maraver M, Carrera MJ, Micaló T, et al. Renoprotective effect of diltiazem in hypertensive type 2 diabetic patients with persistent microalbuminuria despite ACE inhibitor treatment. Diabetes Res Clin Pract 2005;70:13-9.
3. Bakris G, Burgess E, Weir M, Davidai G, Koval S. Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. Kidney Int 2008;74:364-9.

TO THE EDITOR: Parving et al. report that the use of aliskiren and losartan in patients with diabetic nephropathy reduces proteinuria by 20% as compared with losartan and a placebo. Why was aliskiren tested against a placebo and not against an angiotensin-converting–enzyme (ACE) inhibitor or spironolactone? With a combination of trandolapril and losartan, proteinuria may be reduced in patients with nondiabetic nephropathy by more than 70%.[1] A combination of spironolactone and an ACE inhibitor or angiotensin II–receptor blocker leads to a reduction of proteinuria by more than 40%.[2] It can be assumed that a comparison of aliskiren and losartan with trandolapril and losartan would at best have shown the noninferiority of the new substance with regard to proteinuria reduction. If one changed the therapy from ramipril to aliskiren, medication costs would increase by a factor of four in my country, Ger-

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many.[3] Thus, economically speaking, aliskiren has a distinct drawback, without any apparent advantage in effectiveness.

Aliskiren is an interesting drug from both a pathophysiological and a pharmacologic point of view.[4] However, widespread use in everyday treatment is not justified at present, in my view.

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1. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet 2003;361:117-24.
2. Chrysostomou A, Pedagogos E, MacGregor L, Becker GJ. Double-blind, placebo-controlled study on the effect of the aldosterone receptor antagonist spironolactone in patients who have persistent proteinuria and are on long-term angiotensin-converting enzyme inhibitor therapy, with or without an angiotensin II receptor blocker. Clin J Am Soc Nephrol 2006;1:256-62.
3. Aliskiren (Rasilez). In: Wirkstoff aktuell. Berlin: Arzneimittelkommission der Ärzteschaft, January 2008. (Accessed August 20, 2008, at http://www.akdae.de/40/Aliskiren.pdf.)
4. Müller D, Luft F. Direct renin inhibition with aliskiren in hypertension and target organ damage. Clin J Am Soc Nephrol 2006;1:221-8.

TO THE EDITOR: Parving et al. report that the addition of the renin inhibitor aliskiren to the maximal recommended dose of losartan and optimal antihypertensive therapy was more effective in reducing proteinuria than losartan alone in patients who had type 2 diabetes with nephropathy. They conclude that their results support a renoprotective effect of aliskiren. Renin inhibition interferes with the major rate-limiting component of the renin–angiotensin system and offers a promising approach to achieving greater inhibition of the system and, consequently, better therapeutic outcomes in patients with diabetic nephropathy. However, we are concerned that the trial may not have really demonstrated renoprotection. Although a reduction in proteinuria is the best clinical surrogate for long-term protection, the antiproteinuric effect of aliskiren was quite modest, and the effect on the long-term renal prognosis is unknown. This short-term study, involving carefully selected patients, could not discern differences in decline in renal function. Of most importance for clinicians is the question of whether equivalent effects might have been achieved with the addition of an ACE inhibitor or a diuretic (both widely available at $4 per month).

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TO THE EDITOR: Parving et al. report that aliskiren may have renoprotective effects that are independent of its blood-pressure–lowering effect in patients with hypertension and type 2 diabetes. Although the data presented appear to be conclusive, blood pressure was measured only in the clinic. However, not only blood pressure as measured in the clinic but also night and morning blood pressures play an important role in the development of organ damage.[1] Blood pressure measured at home in the morning appears to have a stronger predictive power for the level of albuminuria than does blood pressure measured in the clinic.[2,3] Furthermore, ambulatory blood-pressure monitoring is useful for identifying high-risk groups and for monitoring subsequent measurements in patients with type 2 diabetes.[4] Therefore, in addition to the clinic blood-pressure measurements reported by Parving et al., blood-pressure measurements obtained for 24 hours or in the morning would be needed to confirm their conclusion that aliskiren provides sustained renoprotection.

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1. Imai Y, Okubo T, Asayama K, et al. Epidemiology of hypertension based on ambulatory blood pressure monitoring and self-measurement of blood pressure at home. J Health Sci 2004;50:113-9.
2. Kamoi K, Ikarashi T. The bedtime administration of doxazosin controls morning hypertension and albuminuria in patients with type-2 diabetes: evaluation using home-based blood pressure measurements. Clin Exp Hypertens 2005;27:369-76.
3. Kamoi K, Miyakoshi M, Soda S, Kaneko S, Nakagawa O. Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. Diabetes Care 2002;25:2218-23.
4. Leitao CB, Canani LH, Kramer CK, Boza JC, Pinotti AF, Gross JL. Masked hypertension, urinary albumin excretion rate, and echocardiographic parameters in putatively normotensive type 2 diabetic patients. Diabetes Care 2007;30:1255-60.

THE AUTHORS REPLY: In response to Panesar and Damodar: dihydropyridines were used as the predominant additional antihypertensive agent in both groups in the AVOID study, with no significant difference in the distribution: 93% (in the aliskiren group) and 90% (in the placebo group).

The suggestion that telmisartan has a slightly better antiproteinuric effect than losartan would not have any effect on the outcome in our study, since all patients received the maximal recommended dose of a renin–angiotensin–aldosterone system–blocking drug.

We do not agree with Lindner that dual renin–angiotensin–aldosterone system blockade should have been used in the control group. We used the recommended renoprotective therapy with a maximal dose of losartan and optimal blood-pressure–lowering treatment, as indicated in international guidelines. Dual renin–angiotensin–aldosterone system blockade is still regarded as an experimental treatment. The data reported by Nakao et al. on dual renin–angiotensin–aldosterone system blockade in patients with nondiabetic nephropathy[1] have recently been seriously questioned.[2] The suggestion by Lindner that the combination of an ACE inhibitor and an angiotensin II–receptor blocker is cheaper than aliskiren and an angiotensin II–receptor blocker is correct; however, he does not mention that the largest study evaluating the use of the maximal dose of ramipril and irbesartan in patients with type 2 diabetes failed to show any significant additional antiproteinuric effect, despite lower blood pressure, as compared with monotherapy.[3]

We do not agree with Anderson and Komers, who suggest that the antialbuminuric effect of aliskiren was modest (20%) on top of maximal recommended renoprotective therapy in our study. Furthermore, they suggest that the effect of such a reduction in albuminuria on the long-term renal prognosis is unknown. All previously published studies using different classes of renin–angiotensin–aldosterone system–blocking drugs have shown that the initial antiproteinuric effect (in the first 6 months, as in the AVOID study) is closely associated with beneficial long-term outcomes of kidney and cardiovascular disease, as reviewed in our report. As a result, a reduction in proteinuria has been widely used as a surrogate end point for renoprotection. Despite the short duration of the AVOID study, the rate of decline in the estimated glomerular filtration rate tended to be smaller in the aliskiren group than in the placebo group: 2.4 ml versus 3.8 ml per minute per 1.73 m^2 of body-surface area ($P=0.07$). Anderson and Komers ask whether equivalent effects might have been achieved with the addition of an ACE inhibitor or a diuretic. The answer, according to the Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events (IMPROVE) study, is no.[3] Diuretics were used in two thirds of the patients in the AVOID study.

We agree with Kamoi that blood pressure measured for 24 hours is a better predictor of target organ damage than blood pressure measured in the clinic alone.

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Dr. Persson reports having received lecture fees from Novartis since the publication of the study report. No further potential conflict of interest relevant to this letter was reported.

1. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination therapy of angiotensin-II receptor blocker and angiotensin-cenverting enzyme inhibitor in non-diabetic renal disease: a randomised, controlled trial in Japan (COOPERATE). Lancet 2003;361:117-24.
2. Kunz R, Wolbers M, Glass T, Mann JF. The COOPERATE trial: a letter of concern. Lancet 2008;371:1575-6.
3. Bakris GL, Ruilope L, Locatelli F, et al. Treatment of microalbuminuria in hypertensive subjects with elevated cardiovascular risk: results of the IMPROVE trial. Kidney Int 2007;72:879-85.

Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness

TO THE EDITOR: In their article on methylnaltrexone for opioid-induced constipation in patients with advanced illness, Thomas et al. (May 29 issue)[1] point out that the effectiveness of methylnaltrexone appeared to be undiminished throughout the 2-week, double-blind trial, as well as during the 3-month, open-label extension phase. However, during the trial, the percentage of pos-