Letters to the Editor

Effects of the Angiotensin-1 Receptor Blocker Valsartan Compared With Amlodipine on Renal Hemodynamics

To the Editor:

Delles et al investigated the effects of the angiotensin-1 (AT₁) receptor blocker valsartan compared with those of the calcium antagonist amlodipine on renal hemodynamics and the renal microcirculation using inferences derived from Gomez’ formulas assessing renal hemodynamics. They concluded that at similar blood pressure (BP) control, valsartan maintained glomerular filtration rate and glomerular pressure, whereas amlodipine led to glomerular hyperfiltration and an increase in P_{Gloc}. They proposed that these results might explain the favorable renal outcome with AT₁ receptor blocker therapy. They then imply that the observed hemodynamic profiles may support the adverse effect of amlodipine on albuminuria in patients with type 2 diabetes mellitus. Regrettfully, their report is confounded by both the lack of rigor of inferences of Gomez’ formulas and the discrepancies between the current isolated renal hemodynamic findings and clinical outcomes.

“Therapeutic decisions” are based on a number of considerations. Early in the course of the development of a therapeutic pathway, decisions are often made on the basis of pathophysiologic considerations. Most physicians prefer a later stage, in which therapeutic decisions can be made on the basis of the outcome of well-designed, randomized controlled clinical trials. In the arena of renal injury and progressive renal disease, surely we have reached this advanced stage.

Most experts in the field would argue that blocking the renin-angiotensin system (RAS) with a specific agent is a requisite intervention in the management of the patient with diabetes and nephropathy and possibly the management of all patients with diabetes. That conclusion is consistent with the findings in the study by Delles et al, which confirmed a salutary profile for valsartan.

Citing the MicroAlbuminuria Reduction With VALsartan (MARVAL) study as indicative of the effects of DHPs on the kidney, however, is misleading. As detailed in a recent review, several large studies have indicated a beneficial effect of the DHPs on renal function in the setting of hypertension.

A substudy analysis from the Systolic Hypertension in Europe study evaluated 390 patients with proteinuria, a higher baseline serum creatinine concentration, and lower levels of creatinine clearance at baseline. Compared with placebo, patients treated with the dihydropyridine calcium antagonist nitrendipine showed a reduction in proteinuria and serum creatinine concentration.

Additional data about the renal protective effects of DHP calcium antagonists derive from the recently published results of 5.3 years of follow-up of 470 patients with hypertension in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial. This study demonstrated no statistical difference between the use of the long-acting calcium antagonist nisoldipine and the angiotensin-converting enzyme (ACE) inhibitor enalapril on diabetic nephropathy as measured by creatinine clearance and the log urine albumin excretion (UAE) during 5 years of follow-up. The percentage of patients advancing from normoalbuminuria to microalbuminuria and from microalbuminuria to overt albuminuria was similar for both groups. In summary, the weight of studies cited in Epstein do not indicate that DHPs are harmful to the kidney.

A second principle in therapeutics of nephropathy involves the overriding importance of BP control. Most advisory agencies and guidelines today recommend that the goal for BP control in the patient at risk of nephropathy involves a systolic BP <130 mm Hg and a diastolic BP <85 or 80 mm Hg. Regrettfully our ability to achieve that goal is difficult and often demands the use of a dihydropyridine calcium antagonist such as amlodipine or other vasodilator calcium channel blocking agents. Fortunately, we have excellent data from therapeutic trials to indicate that amlodipine and similar agents are not injurious to the kidney.

The conclusion of the RENAAL investigators is a reasonable summary of outcomes from several large randomized studies that DHPs when added to either an ACE inhibitor or angiotensin receptor blocker are not deleterious with respect to either cardiovascular or renal outcomes. As cited in the RENAAL report, the addition of a calcium antagonist to an angiotensin receptor blocker “did not detract from the beneficial effects of losartan, despite the recent controversy regarding the role of calcium antagonists in the protection of the kidneys and the heart.” Consequently, we have major concerns that the second half of the conclusions of the article by Delles et al are misleading and not indicative of the weight of current clinical outcomes.

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In Reply:

We thank Epstein and Hollenberg for their interest in our recent comparison of the effects of valsartan and amlo-
dipine on renal hemodynamics in patients with essential hy-
pertension. They offer us the opportunity to discuss some aspects of our report in more detail.

The formulas of Gomez have always been subject to criticism. As already discussed in our report, we are fully aware of the shortcomings of any models applied in humans to calculate intraglomerular hemodynamic parameters that cannot be determined directly. Nonetheless, the derived parameters are used in a homogenous group of patients and are fully in accordance with data from experiments that measured the parameters directly, but Epstein and Hollenberg may have noticed that we were cautious not to draw conclusions about “therapeutic decisions” from our data.

We fully agree with Epstein and Hollenberg that any treatment of arterial hypertension is superior to placebo treatment to delay hypertensive renal disease, including calcium channel blockers being chosen as first-line therapy. This has been impressively demonstrated by the Systolic Hypertension in Europe (Syst-Eur) Study. We also read with great interest that renal events were similar between the enalapril and nisoldipine group in a 5.3 years follow-up of the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial, although a previous 3.5-year follow-up suggested superiority of the angiotensin-converting enzyme (ACE) inhibitor. However, with regard to “therapeutic decisions” the significantly lower cardiovascular event rate in enalapril treated patients leading to the termination of the nisoldipine arm by the U.S. Data and Safety Monitoring Committee should be balanced against the renal outcome data.

The ABCD Trial clearly demonstrates the uncertainties we are still facing in our efforts to reduce renal damage in patients with arterial hypertension. First, it is evident that renal disease is a slowly developing disorder and that long-term follow-up over probably more than a decade is mandatory to draw definite conclusions. None of the large-scale outcome studies about the treatment of arterial hypertension reviewed by Epstein and Hollenberg provides us with renal follow-up data over 10 to 20 years, a time period that is needed to develop hypertensive nephrosclerosis. Glomerular hemodynamic alterations in early diabetic nephropathy include glomerular hyperfiltration, a process that is also an early step in hypertensive renal disease. For this reason, we believe that data from studies in early diabetic nephropathy can to some degree be transferred to patients at risk of hypertensive renal disease. Thus, we referred to results from the MicroAlbuminuria Reduction With VALsartan (MARVAL) Study and think that this citation is not misleading in this context.

Second, the ABCD Trial also demonstrates that due to the long time course of the development of renal damage in diabetes and hypertension, surrogate parameters such as reduction of albuminuria have to be used as measures of therapeutic effects in clinical trials instead of hard endpoints unless patients with advanced renal disease are included. Our study about short-term effects of valsartan and amlo- dipine on glomerular hydrostatic pressure examined another surrogate parameter of early renal damage. Against the background of well-founded criticism of such surrogate parameters, we almost exclusively cited other studies examining renal hemodynamic effects of antihypertensive agents.

Third, head-to-head comparisons of renal outcome between angiotensin receptor blockers and calcium channel blockers in arterial hypertension are rare. However, such comparisons have been made in patients with type 2 diabetes, each suggesting better renoprotection by angiotensin receptor blockers than by calcium channel blockers when chosen as the first-line therapy. Having in mind the above-mentioned similarities between early diabetic and early hypertensive kidney disease, we referred to the MARVAL Study since this study compared valsartan with amlo- dipine which were actually the drugs compared in our study about their effects on glomerular hemodynamics.

Fourth, Epstein and Hollenberg correctly point out that it is more and more evident that rigorous blood pressure control is the cornerstone of successful prevention of nephropathy but can only be achieved by combination therapy in most cases. Although our recent study demonstrated a favorable renal hemodynamic profile of valsartan when