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COMMENTARY

Long-term blockade of the renin–angiotensin system: an adequate evaluation is still needed

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Blockade of the renin–angiotensin system (RAS) with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) is considered a possible tool, in combination with other therapies, for improving the outcome of patients at different stages of established cardiovascular disease (CVD) and for delaying the evolution of chronic kidney disease (CKD) to end-stage renal disease (ESRD), particularly in those with high levels of albuminuria and in diabetics.[1] The previous statement separates the positive effects of RAS blockade in the cardiovascular and renal systems, but CVD and CKD very frequently have a common origin, and related factors that require similar therapeutic attitudes initiate and participate in the progress of simultaneous cardiorenal damage.[2]

Seminal studies on this topic include the Anglo-Scandinavian Cardiac Outcomes Trial,[3] the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial,[4] and the Action in Diabetes and Vascular Disease—PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) trial,[5] which have shown simultaneous positive results for cardiovascular and renal outcomes with similar therapies. Equally important, the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) study indicated that futility could be simultaneous for both systems even in the presence of a significant diminution in albuminuria levels.[6] The ADVANCE and ALTITUDE studies were conducted in type 2 diabetics, and in the ACCOMPLISH trial approximately two-thirds of the patients were type 2 diabetics. The presence of albuminuria, which is related to high cardiovascular risk and more frequent events or death, is particularly interesting because, in addition to the data reported from the ALTITUDE study, the favorable ACCOMPLISH trial outcomes in the arm receiving the renal and cardiovascular RAS blocker and amlodipine occurred in the presence of changes in albuminuria that were significantly lower than those obtained when the diuretic was in the fixed combination.[4]

What does the study to which this commentary is devoted add to our knowledge? First, it is a *post hoc* analysis, and therefore none of its conclusions can be considered definitive. It is clearly shown that olmesartan had the expected effect of decreasing BP and albuminuria. Second, another expected finding was that the ability to diminish albuminuria was significant but lower in the presence of an ACEi. Third, the findings of the study contradict the negative comments regarding the cardioprotective capacity of olmesartan that were made after the publication of the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study.[7] The improved cardiovascular outcomes indicate that the explanation for cardiovascular death given in the publication is reasonable and was not specifically related to the drug. The completed data from the follow-up study at the end of the ROADMAP study will substantially clarify this point. Fourth, the study confirms the absence of positive effects of the dual blockade with an ACEi and an ARB on cardiovascular and renal outcomes, confirming previous data from the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial,[8] the ALTITUDE[6] trial, and other, smaller trials related specifically to renal prognosis. Fifth, studies on the use of high doses of an ARB in Japanese patients are infrequent in the literature, and the good tolerability of 40 mg of olmesartan presents a new possibility for dosing RAS blocker in these patients. Sixth, the long follow-up of this study at least partially augments the data on the evolution of renal function. Previous studies investigating renal function in type 2 diabetics had follow-up periods that lasted slightly longer than 2 years. This will be required in the future to make an adequate simultaneous validation of renal and cardiovascular outcomes.

Can the cardiorenal prognosis of type 2 diabetic patients be improved through other variations of RAS blockade? Whereas additional data on renal outcomes with dual blockade are forthcoming, the excellent results obtained with aldosterone blockers in heart failure patients, as well as their improved effects on albuminuria with the addition of an aldosterone blocker compared with the dual blockade of an ACEi plus an ARB,[9] reinforce the need to perform trials of cardiorenal outcomes using aldosterone blockers in type 2 diabetics. The confirmation that new non-steroidal antialdosterone drugs are equally efficacious and produce significantly less hyperkalemia[10] and that the new potassium binders, which can be administered chronically, impede the appearance of hyperkalemia in the presence of aldosterone blockers[11] will contribute to facilitating the use of these drugs.

In summary, the findings of this *post hoc* analysis of the Olmesartan Reducing

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Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial[12] data confirm that an adequate evaluation of the long-term suppression of RAS is still needed.

CONFLICT OF INTEREST

Dr Ruilope has served as an advisor/speaker of Daiichi-Sankyo and has been a member of the ROADMAP study Executive Committee.

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