Renin-Angiotensin System Blockade Versus Endothelin Antagonism for Halting Progression of Chronic Kidney Disease

By George Bakris

R enin-angiotensin system (RAS) blockers (e.g., angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers) have enjoyed a great deal of notoriety under the heading of being “renoprotective.” There is no question that they can reduce very high albuminuria or macroalbuminuria (>300 mg/day) to a greater extent than other agents (1). The issue of renoprotection, however, across all stages of nephropathy is questionable and is not evidence based. Moreover, albuminuria reduction is not a proven surrogate for slowing the progression of chronic kidney disease (CKD), inasmuch as all of the data for this premise are based on retrospective or observational studies (2).

The totality of the evidence from prospective clinical trials supports the concept that RAS blockers significantly slow CKD progression compared with other agents in patients with advanced stage 3b or higher CKD who have, on average, more than 500 mg/day of albuminuria (2). This was true in the Captopril trial, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartin trial, and Irbesartan Diabetic Nephropathy Trial involving patients with diabetes and the Angiotensin-converting-enzyme Inhibition Progressive Renal Insufficiency, Ramipril Efficacy In Nephropathy, and Modification of Diet in Renal Disease trials, and the trial by Hou et al., involving patients with nondiabetic kidney disease (2, 3). The one exception, wherein RAS blockade slowed nephropathy progression in the absence of very high albuminuria, was the African American Study of Kidney Disease and Hypertension trial, in which most participants had stage 3b CKD and high albuminuria or microalbuminuria (4). Thus, in advanced albuminuric CKD, RAS blockade has level 1 A or B evidence, depending on the source for slowing CKD progression (5). This is not true for RAS blockers in stages 1 or 2 CKD with hypertension with or without high albuminuria or microalbuminuria, nor for individuals with normotension with or without diabetes (5). Hence, RAS blockers are an optional but not mandated antihypertensive therapy in the aforementioned patients.

Well-known markers of the perceived development of CKD, such as high albuminuria, are not accepted by regulatory authorities and are not indicative of kidney disease in diabetes, on the basis of biopsy evidence (6, 7). Moreover, reductions in high albuminuria or microalbuminuria in early nephropathy relate largely to reduction in blood pressure rather than inflammatory condition and are not consistent with arresting CKD progression, as noted when microalbuminuria returns to baseline within in a month after the RAS blocker is discontinued (8). And, if RAS blockers are used in people at risk for CKD progression are clearly beneficial only when used at maximal doses, like those used in trials. In individuals without macroalbuminuria, RAS blockers are beneficial in that they lower blood pressure and may improve endothelial function, but nothing else. Therefore, it is incorrect to conclude that a patient has “renoprotection” if he or she is taking an ACE inhibitor or ARB, regardless of dose, especially if blood pressure is not controlled. Outcome trials used the highest tolerated dose of RAS blockers, with most patients getting the maximum dose.

From an evidence-based perspective, the ACE inhibitors shown to slow nephropathy progression in trials are captopril, ramipril, and benazepril (8). The most commonly used ACE inhibitor, lisinopril, has not been formally tested in clinical trials against conventional therapy to assess its effects on CKD progression. The only ARBs approved to slow CKD progression are losartan and irbesartan. Telmisartan is the only approved ARB to reduce mortality in patients who are tolerant to ACE inhibitors (9). ARBs should be started at the maximal dose, as now recommended by the U.S. Food and Drug Administration, because they do not have dose-dependent side effects.

The only evidence that supported dual RAS blockade was additional reduction in albuminuria (1). We now have conclusive evidence showing a failure of dual RAS blockers to slow CKD progression, as assessed by ALTITUDE, Veterans Administration Diabetes in Nephropathy Study (VA NEPHRON D), and the On-going Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET). All three of these trials evaluated dual ACE inhibitor/ARB therapy of CKD progression, with ALTITUDE and VA NEPHRON D powered for primary renal outcomes. All failed to show a benefit, and all showed increased risk for hyperkalemia and risk for acute kidney injury. It should be noted that the mean estimated GFR in all of these trials was well below 60 mL/min per 1.73 m². When the combination of valsartan and aliskiren was tested for its effect on ambulatory blood pressure changes in people with a mean estimated GFR of 84 mL/min per 1.73 m², it was well tolerated, with no hyperkalemia and additive blood pressure lowering (10). These data, taken together with the questions regarding dual RAS blockade on CKD progression, by lowering albuminuria, clearly indicate that it is inappropriate to use dual RAS blockade in advanced CKD. The question of aldosterone blockade in this context has not yet been answered fully. Hence, the aforementioned statement does not apply to the use of aldosterone blockade with an ACE inhibitor or ARB.

Endothelin antagonists

Endothelin receptor antagonists (ETA) have been available for almost two decades. As a class, ETAs have not made it to the forefront of antihypertensive therapy. They are efficacious for blood pressure reduction, especially in specific situations such as pulmonary hypertension and post-transplant calcineurin inhibitor hypertension mechanistically caused by increases in endothelin (11). Their side-effect profile, however, is high, and this class has not been evaluated for its effect on CKD progression. The major side effects that lead to limited use of this class are profound sodium retenion and peripheral edema; thus, they are poorly tolerated (11).

Bosentan is a nonspecific endothelin blocker approved for the treatment of pulmonary hypertension, but it is expensive and causes edema; hence, it is not commonly used.

Darusentan, a selective ETA-1 blocker, showed great promise as an antihypertensive agent, although it also had dose-dependent edema and worsening heart failure symptoms as side effects (12). Atrasentan is also a good antihypertensive agent, especially in the post-transplantation setting, but it too had dose-limiting side effects, including edema, worsening heart failure symptoms, and liver function abnormalities (13, 14). Interestingly, nonhypotensive doses of atrasentan reduce macroalbuminuria without an effect on blood pressure (14). This agent is in clinical trials to evaluate its effects as a possible “renoprotective” agent independent of blood pressure lowering. Hence, this class of agents has utility in limited circumstances. Given their dose-dependent side effects, they can be useful in only a limited number of patients with specific conditions at this time.

References


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