Editorial

ACE Inhibitors and ARBs: Are They Better Than Other Agents to Slow Nephropathy Progression?

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Chronic kidney disease is the most common medically treatable cause of secondary hypertension. It most often results from poorly controlled diabetes and/or elevated blood pressure (BP).[1] Kidney disease has various stages and may present with albuminuria (>200 mg/d) or proteinuria (>300 mg/d) as a laboratory marker. Some of the most common antihypertensive therapies used in the treatment of hypertension in people with kidney disease involve agents that inhibit the renin-angiotensin system (RAS). The compelling indications for use of these medications in kidney disease derives from data from a variety of studies in advanced (stage 3 or 4) nephropathy (ie, glomerular filtration rate [GFR] >15 but <60 mL/min).[1,2]

The RAS is an important mediator of blood volume, arterial pressure, and cardiac and vascular function. Components of this system are present in many tissues. The primary site of renin release is the kidney. The system is triggered by sympathetic stimulation, lowered BP in the renal artery, and decreased sodium delivery to the distal tubule. Angiotensin II, the end product of RAS stimulation, acts directly on the resistance vessels to increase systemic vascular resistance and arterial pressure; stimulates the adrenal cortex to release aldosterone, leading to increased sodium and water reabsorption and potassium excretion; promotes secretion of antidiuretic hormone, which results in fluid retention; stimulates thirst; promotes adrenergic function; and increases cardiac and vascular hypertrophy. In addition, both angiotensin II and aldosterone promote fibrosis in the kidney and heart.[3–5] Given these effects, it would be predicted that blocking this system would have at least theoretic benefits over other antihypertensive drugs in slowing progression of nephropathy, but is this so?

The major antihypertensive drug classes that inhibit the RAS include the angiotensin-converting enzyme inhibitors (ACEIs) and the angiotensin II receptor blockers (ARBs). These medications are approved for treatment of hypertension, heart failure, myocardial infarction (MI), diabetes, and renal disease. In one of the largest meta-analysis performed to date using original data from 27 randomized trials (N=158,709 participants) 33,395 individuals with diabetes and 125,314 without diabetes were included. With the exception of proteinuric kidney disease (ie, patients with a serum creatinine of >1.4 mg/dL and >300 mg/d of proteinuria), the use of ACE inhibitors and ARBs resulted in similar outcomes on nephropathy progression when compared with other classes of antihypertensive drugs. This was true for cardiovascular outcomes including stroke.[6]

In a more recent analysis by Casas and colleagues,[7] databases were searched up until January 2005 for randomized trials reviewing the use of antihypertensive drugs and progression of kidney disease. Primary end points in 127 trials were evaluated (ie, doubling of serum creatinine and/or development of end-stage renal disease, as well as secondary continuous markers of renal outcomes

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such as changes in creatinine, albuminuria, or estimated GFR). The use of ACE inhibitors or ARBs (usually with other medications) resulted in a risk reduction of 29% for doubling of serum creatinine and a 13% risk reduction for development of end-stage renal disease when compared to other regimens that did not include these agents. Analyses of the results by study size showed a smaller benefit in large studies. In patients with diabetic nephropathy, no benefit was seen in comparative trials with ACE inhibitors or ARBs on the doubling of serum creatinine or end-stage renal disease. In placebo-controlled trials of ACE inhibitors or ARBs, greater benefits were noted in all renal outcomes, but were accompanied by substantial reductions in BP in favor of ACE inhibitors or ARBs. The authors interpreted these data on the benefits of ACE inhibitors or ARBs on renal outcomes as being consistent with better BP lowering.

This paper suggests a number of issues about clinical trials in nephropathy progression. First, the mean weighted GFR of the studies evaluated by Casas and colleagues was 84.5 mL/min, about 35 mL/min higher than any single clinical trial demonstrating clear benefit of ACE inhibitors or ARBs. Moreover, many of the studies reviewed did not report the measurement of proteinuria or albuminuria and were underpowered for the primary end point. It should also be noted that the largest study in the analysis, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), also did not report urine protein or albumin. Lastly, in trials that had patients with either albuminuria or proteinuria, there was a uniform benefit for ACE inhibitors or ARBs to a greater degree than other active agents independent of BP levels. Thus, it appears that in advanced (stage 3 or 4) nephropathy with albuminuria or proteinuria, the use of an ACE inhibitor or an ARB is beneficial and indicated as one medication in a treatment program. Is this true for earlier stage nephropathy or nonproteinuric kidney disease?

The Kidney Dialysis Outcomes and Quality Initiative (KDOQI)[2] and the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guideline recommendations[8] put all outcome studies of kidney disease progression in proper context. It is clear that patients with a serum creatinine of >1.4 mg/dL and >300 mg/d of proteinuria progress more slowly when ACE inhibitors or ARBs are used in appropriate doses early in the antihypertensive regimen than when other agents are used without RAS inhibition. This is why there is a compelling indications for their use in such conditions.

In very early nephropathy (stage 1 or 2) (ie, GFR >60 mL/min with microalbuminuria or normoalbuminuria regardless of diabetes status), it is also clear that BP and glycemic control are critical to preserve kidney function, with no clear advantage for using an ACE inhibitor or ARB except for possible better tolerability. Progression of microalbuminuria (>30 but <300 mg/d) to macroalbuminuria (>300 mg/d) is reduced by these agents but this has not been shown to prevent doubling of creatinine or end-stage renal disease (ESRD) in a carefully controlled outcome study. The best examples of this are the Appropriate Blood Pressure Control in Diabetes (ABCD) trial[9] and the United Kingdom Prospective Diabetes Study (UKPDS)[10] where early intervention with ACE inhibitors (plus other agents) failed to offer superior results to either a calcium antagonist or β-blocker (with other medications), respectively. Note that the first study was underpowered for a renal outcome and UKPDS primarily evaluated cardiovascular events. These results coupled with other analyses by Casas and associates suggest that in early diabetes where nephropathy is in its early stages the focus should be on BP, glucose, and lipid control more than the use of a particular medication. This was demonstrated in the Steno Diabetes Center's Steno-2 study,[11] an intervention trial that controlled for these risk factors and showed a benefit of more aggressive control with no preference for an ACE inhibitor or ARB. Microalbuminuria is a cardiovascular risk marker and reflects underlying vascular inflammation rather than the presence of kidney disease.[12] Recent evidence also fails to link microalbuminuria to early diabetic kidney disease.[13] Thus, it should be appreciated that it is the kidney producing a physiologic product (urine) that may contain higher concentrations of protein indicative of diffuse increased vascular permeability rather than specific disease in the kidney.

Lastly, the question—Is there a difference between ACE inhibitors and ARBs on renoprotection?—remains partially unanswered. There is no clear answer to this question, and only a single center study addresses this issue. In the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial,[14] 250 patients with type 2 diabetes with a baseline GFR around 90 mL/min and microalbuminuria were randomized to an ACE inhibitor or ARB titrated to appropriate doses for BP lowering and followed for 5 years. There was no difference in the primary end point of change in GFR.

In conclusion, there is good evidence from 5 large outcome trials supporting the use of an ACE inhibitor or an ARB as part of an antihypertensive drug regimen in patients with proteinuric kidney disease and a GFR of <60 mL/min. The evidence for their use in early stage nephropathy is weak and, in the absence of albuminuria, nonexistent. Thus, in early-stage nephropathy from the most common causes (ie, diabetes and hypertension), the goal is to achieve the recommended goals for BP and glucose with the agents that are well tolerated. In the presence of albuminuria or proteinuria and a GFR of ≤60 mL/min, however, it is clear that an ACE inhibitor or ARB must be part of the antihypertensive regimen.

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