Dual therapy and diabetic kidney disease

T. Desai
Creator, Nephrology On-Demand,
Charlotte, NC, USA 28075
Address for correspondence:
Dr. T. Desai,
1601 Brenner Ave, Salisbury NC 28144, United States.
E-mail: tejas.p.desai@gmail.com

In this issue of the Indian Journal of Nephrology, Singh *et al*.[1] present a study that shows dual therapy with an angiotensin-converting enzyme (ACE) inhibitors and a fourth-generation dihydropyridine can reduce the amount of microalbuminuria in patients with diabetic kidney disease. Nephrologists have known for some time that albuminuria is an independent predictor of cardiovascular mortality, and that microalbuminuria (defined as a urine albumin: creatinine ratio of 30–300 mg/g) is an early detector of diabetic kidney disease. The results of this investigation are impressive; a reduction in microalbuminuria by more than 50% in patients administered both ACE inhibitors and dihydropyridine. These results, however, should be cautiously interpreted.

Interventions in the last five (5) years have suggested a disconnect between reductions in albuminuria and the progression of chronic kidney disease. In the BEAM and BEACON trials, an initial enthusiasm surrounding bardoxolone was dampened as reductions in albuminuria did not result in slowing of glomerular filtration rate (GFR) decline or death.[2,3] Subgroup analyses in the ALTITUDE trial showed a reduction in proteinuria with dual renin-angiotensin-aldosterone blockade; when looked at as a primary outcome in the Veterans Affairs Nephropathy in Diabetes trial, these results were complicated by higher rates of hyperkalemia and acute kidney injury.[4,5]

Thus far, only intensive glycemic control (glycosylated hemoglobin levels of < 6.5% as in the ADVANCE and ADVANCE-ON trials) has been proven to slow the progression of diabetic kidney disease.[6,7] Newer therapies, including endothelin receptor antagonists (e.g. atrasentan), have shown promise as anti-fibrotic agents, but their efficacy has been measured by reductions in albuminuria (RADAR trial).[8] The use of ACE inhibitors with dihydropyridines shows reductions in proteinuria similar to that seen with bardoxolone, dual ACE/angiotensin II receptor blockers, and atrasentan. Our hope is that additional studies with these agents show improvements in GFR decline and mortality.

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