

## 1-MINUTE CONSULT

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## Q: Should all patients with significant proteinuria take a renin-angiotensin inhibitor?

**A:** Most patients with proteinuria benefit from a renin-angiotensin-aldosterone system (RAAS) inhibitor. Exceptions due to adverse effects are discussed below.

### Trials discussed in this article

**AASK**—African American Study of Kidney Disease and Hypertension<sup>6</sup>

**ALTITUDE**—Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints<sup>19</sup>

**DETAIL**—Diabetics Exposed to Telmisartan and Enalapril<sup>13</sup>

**IDNT**—Irbesartan Diabetic Nephropathy Trial<sup>11</sup>

**ONTARGET**—Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial<sup>16–18</sup>

**REIN**—Ramipril Efficacy in Nephropathy<sup>4,5</sup>

**RENAAL**—Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan<sup>12</sup>

**VA NEPHRON-D**—Veterans Affairs Nephropathy in Diabetes study<sup>20</sup>

### WHY RAAS INHIBITORS?

RAAS inhibitors—particularly angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)—reduce proteinuria and slow the progression of chronic kidney disease by improving glomerular hemodynamics, restoring the altered glomerular barrier function, and limiting the nonhemodynamic effects of angiotensin II and aldosterone, such as fibrosis and vascular endothelial dysfunction.<sup>1</sup> Studies have shown that these protective effects are, at least in part, independent of the reduction in systemic blood pressure.<sup>2,3</sup>

### EVIDENCE FOR USING RAAS INHIBITORS IN PATIENTS WITH PROTEINURIA

In nondiabetic kidney disease, there is strong evidence from the REIN and AASK trials that treatment with ACE inhibitors results in slower decline in glomerular filtration rate (GFR), and this risk reduction is more pronounced in patients with a higher degree of proteinuria.<sup>4–6</sup>

In type 1 diabetes, treatment with an ACE inhibitor in patients with overt proteinuria was associated with a 50% decrease in the risk of the combined end point of death, dialysis, or renal transplant.<sup>7</sup> Patients with moderately increased albuminuria who were treated with an ACE inhibitor also had a reduced incidence of progression to overt proteinuria.<sup>8</sup> Angiotensin inhibition may be beneficial even in normotensive patients with type 1 diabetes and persistent moderately increased albuminuria.<sup>9,10</sup>

In type 2 diabetes, the IDNT and RENAAL trials showed that treatment with an ARB in patients with overt nephropathy was associated with a statistically significant decrease (20% in IDNT, 16% in RENAAL) in the risk of the combined end point of death, end-stage renal disease, or doubling of serum creatinine.<sup>11,12</sup> While there are more data for ARBs than for ACE inhibitors in type 2 diabetes, the DETAIL study showed that an ACE inhibitor was at least as effective as an ARB in providing long-term renal protection in type 2 diabetes and moderately increased albuminuria.<sup>13</sup>

Data are limited on the role of angiotensin inhibition in normotensive patients with type 2 diabetes and persistent moderately increased albuminuria, but consensus opinion suggests treatment with an ACE inhibitor or ARB in these patients if there are no contraindications.

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## LIMITATIONS

Adverse effects of ACE inhibitors and ARBs include cough (more with ACE inhibitors), angioedema (more with ACE inhibitors), and hyperkalemia.

The use of ARBs in patients with a history of ACE inhibitor-related angioedema has been previously discussed in this *Journal*.<sup>14</sup> Guidelines advocate caution when prescribing ARBs for patients who will benefit from RAAS inhibition and have had ACE inhibitor-related angioedema.<sup>15</sup>

RAAS inhibitor therapy can cause a modest rise in creatinine due to reduction in intraglomerular pressure. An elevation in creatinine of up to 30% that stabilizes in the first 2 months is not necessarily a reason to discontinue therapy. However, a continued rise in creatinine should prompt evaluation for excessive fall in blood pressure (especially with volume depletion from concomitant diuretic use), possible bilateral renal artery stenosis, or both. There is no level of GFR or serum creatinine at which an ACE inhibitor or ARB is absolutely contraindicated, and this decision should be made on an individual basis in conjunction with a nephrologist.

Risks for hyperkalemia should always be kept in mind at lower GFR levels. It would be prudent to check serum creatinine and potassium levels within the first week or two after starting or intensifying RAAS inhibition in these patients.

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## CAUTION

Combination therapy with an ACE inhibitor and an ARB was hypothesized to provide more complete RAAS blockade, with the hope of better clinical outcomes. However, this strategy has been questioned with results from three studies—ONTARGET, ALTITUDE, and the VA NEPHRON-D study—all of which showed worse renal outcomes, hypertension, and hyperkalemia with use of dual RAAS blockade.<sup>16–20</sup> The combined evidence so far suggests that dual RAAS blockade should not be routinely prescribed.

## RAAS INHIBITION IN PRACTICE

RAAS inhibition should be instituted and continued in patients with proteinuria who are able to tolerate the therapy and do not experience adverse effects as discussed above. Although there is no specific consensus guideline on the frequency of assessment of albumin excretion after diagnosis of albuminuria and institution of RAAS inhibition and blood pressure control in patients with diabetes, periodic surveillance at least once a year is reasonable to assess response to therapy and possible disease progression.<sup>21</sup> If there is significant proteinuria or possibility of nondiabetic kidney disease, the patient should be referred to a nephrologist. ■

**These drugs should be instituted and continued in patients with proteinuria who can tolerate them without adverse effects**

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