Slowing Nephropathy Progression: Focus on Proteinuria Reduction

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Learning Objectives:
1. To examine the epidemiology and pathophysiology of stroke and cardiovascular disease in the chronic kidney disease population
2. To evaluate the efficacy of current therapies for the treatment of cardiovascular risk in patients with renal disease
3. To apply new clinical insights for the identification and treatment of cardiovascular risk to improve outcomes for patients with chronic kidney disease

Target audience: Physicians in internal medicine, nephrology, endocrinology, and other health care providers who are interested in the treatment of hypertension and kidney disease.

Categories: Chronic kidney disease, proteinuria, renoprotection, risk reduction

Blood pressure control reduces decline of kidney function. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers offer renoprotection to a small extent beyond that attributable to blood pressure lowering. These agents also reduce proteinuria, a risk marker for renal disease progression. Accumulating evidence indicates that their anti-proteinuric effect correlates with their additional renal benefits.

Blood pressure control is essential to slow the progression of nephropathy in patients who are at risk for or have developed chronic kidney disease (CKD). Proteinuria also is another important therapeutic target, because it is a major risk factor for renal disease progression (1–4).

Patients with hypertension typically require multiple agents to control BP (5). Therapies that target the renin-angiotensin system (RAS) offer particular benefit to hypertensive, proteinuric patients with kidney disease because these agents reduce proteinuria as well as BP (6,7). Reduction of proteinuria by >30% of baseline within the first 6 to 12 mo of treatment in patients with kidney disease has been shown to predict long-term renal (2) and cardiovascular (CV) outcomes (8).

The management of albuminuria in normotensive or hypertensive patients with diabetes is outlined in the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (9). Reduction in albuminuria levels may slow progression of diabetic kidney disease and improve clinical outcomes, even in normotensive patients; therefore, albuminuria may be identified as a target for treatment in diabetic kidney disease (9). In hypertensive patients with diabetes and CKD stages 1 through 4, the treatment guidelines recommend the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), in combination with a diuretic, to reach a target BP of <130/80 mmHg (9). ACEI or ARB should be used to treat macroalbuminuria in normotensive patients with diabetes and should be considered...
to treat microalbuminuria in normotensive patients with diabetes (9).

It should be noted that nephropathy progression can occur in the absence of albuminuria, and multiple examples in the literature show large samples of patients who have type 2 diabetes and for whom this is true (10,11). In these studies, patients with clear advanced nephropathy (e.g., stage 3 or higher) progressed and had no obvious evidence of albuminuria. Hence, although the majority of patients do have albuminuria and it is relevant and important to monitor, it is not absolutely clear that only those with albuminuria will progress (10,11).

ACEI have decreased the risk for nephropathy progression in patients without diabetes (12,13). In patients with both diabetes and high CV risk, ACEI therapy has reduced the risk for nephropathy and CV events (14). ARB have decreased the risk for End Stage Renal Disease (ESRD) and nephropathy progression in people with diabetes-related nephropathy (15,16). Some evidence suggests that a combination of ACEI and ARB therapy can slow renal disease progression more than can monotherapy with either drug class in patients with non–diabetes-related nephropathy (17). This article summarizes clinical evidence regarding the role of ACEI and ARB in people with non–diabetes- and diabetes-related nephropathy.

**ACE Inhibition, Proteinuria, and Renoprotection in Patients without Diabetes**

Several trials have demonstrated the renoprotective benefits of controlling proteinuria as well as BP in people with moderate to severe renal disease. These investigations have attempted to separate the impact of reductions in proteinuria from that of reductions in BP. Table 1 summarizes their findings (1,12,13,18–20).

**Higher Proteinuria Linked to Faster Decline in GFR**

One of the early clinical trials supporting the concept of proteinuria as an independent risk factor for renal disease progression was the Modification of Diet in Renal Disease (MDRD) (1). Patients were grouped by higher or lower baseline GFR and were assigned to either a normal or low BP goal. Patients with higher baseline proteinuria experienced a relatively faster rate of GFR decline and benefited more from the lower BP goal (1). Numerous analyses have since confirmed this observation (21–23). Thus, the selection of BP-lowering medications for patients with renal disease should be based on the efficacy of these agents in reducing proteinuria (1).

**ACE Inhibition Slows Renal Disease Progression in Patients with Mild Renal Insufficiency and High Proteinuria**

Among the first prospective clinical studies to demonstrate that ACE inhibition has a renoprotective benefit in patients with hypertensive nephropathy was the Angiotensin-Converting-Enzyme Inhibitor in Progressive Renal Insufficiency (AIPRI) study. Therapy with benazepril significantly reduced the risk for a composite renal outcome (doubling of baseline serum creatinine or need for dialysis) compared with placebo. This reduction in risk was attenuated but remained significant after adjustment for benazepril’s effect on diastolic BP (DBP) and urinary protein excretion (18).

After adjustment for DBP and proteinuria changes, the benefit of benazepril remained significant in the subgroup of patients with mild renal impairment at baseline (risk reduction 65 to 66%) and those with baseline urinary protein excretion ≥3 g/d (risk reduction 52 to 56%). However, the benefit was no longer significant in those with moderate renal impairment or lower levels of urinary protein excretion (18).

**ACE Inhibition Reduces the Risk for ESRD in Patients with CKD and Proteinuria**

In the Ramipril Efficacy in Nephropathy (REIN) study, ramipril therapy prevented the need for dialysis when used for 3 to 4 yrs in patients with proteinuria and CKD (19,20). These and other results were consistent with a renoprotective effect exceeding that attributable to BP lowering alone (13,20).

The trial was stopped early in patients with higher baseline proteinuria (≥3 g/d), because ramipril was associated with a significantly slower rate of GFR decline per month, the primary outcome (13). Ramipril also reduced the risk for a combined secondary end point (doubling of baseline serum creatinine or development of ESRD) in this stratum of patients (P = 0.02). This relationship remained significant after adjustment for changes in BP (P = 0.04), suggesting a mechanism other than BP lowering (13).

Findings in both strata of patients suggested that proteinuria reduction accounted for at least some of the renoprotection. In the higher proteinuria stratum, proteinuria was the only time-dependent variable that predicted ramipril’s renoprotective effect (13). In the ramipril group, early (1 mo after randomization) percentage reduction in urinary protein excretion from baseline was inversely correlated with long-term (≥6 mo) change in GFR (P = 0.035; Figure 1) (13). Percentage reduction from baseline in urinary protein excretion during the entire treatment period predicted the risk for reaching the combined end point (P = 0.04) (13).

**ACEI Therapy Slows GFR Decline in African Americans**

The incidence of ESRD is 3.7-fold higher in African Americans than in Caucasians (24). The African American Study of Kidney Disease (AASK) was the first outcome trial to demonstrate a renoprotective effect with an ACEI in an African American population (12).

When used with a diuretic to achieve BP control, ramipril significantly reduced the risk for a composite renal outcome (reduced GFR, development of ESRD, or death) when compared with either metoprolol or amlodipine given concurrently with a diuretic (12). The risk for the composite outcome did not differ significantly between patients who received amlodipine and those who received metoprolol, although the risk for ESRD and death was significantly lower with metoprolol than with amlodipine (12). Change in GFR slope, another primary outcome, showed no consistent significant differences among agents (12).

Patients were randomly assigned not only to an antihypertensive agent but also to a normal or lower mean arterial
Table 1. Renoprotection in patients without diabetes

<table>
<thead>
<tr>
<th>Study, Study Design, Subjects</th>
<th>Outcome Measure(s)</th>
<th>Findings</th>
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<td>Peterson et al. (1)</td>
<td>Effect of normal (MAP (\leq 107) mmHg if (\leq 60) yr or (\leq 113) mmHg if (\geq 61) yr) versus low BP goal ((\leq 92) mmHg if (\leq 60) yrs or (\leq 98) mmHg if (\geq 61) yrs) on GFR, and relationship to baseline proteinuria; any antihypertensive agent allowed, ACEI suggested as first choice; mean follow-up 2.2 yrs</td>
<td>GFR declined faster in those with higher BL proteinuria (&gt;0.25 g/d if higher GFR ([P = 0.02]) or &gt;1 g/d if lower GFR ([P = 0.01])); higher BL proteinuria was associated with greater benefit of low MAP goal.</td>
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<td>Maschio et al. (18)</td>
<td>Composite outcome: time to doubling of BL SC or ESRF; duration 3 yrs</td>
<td>ACEI reduced risk by 53% (95% CI 27 to 70%) in overall population; RR 38% (95% CI 3 to 61%) when adjusted for DBP; RR 39% (95% CI 5 to 61%) when adjusted for change in proteinuria</td>
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<td>GISEN group (13); Ruggenenti et al. (19,20)</td>
<td>Primary outcome if proteinuria (\geq 3) g/d ((n = 166)): Rate of GFR decline; secondary outcomes: composite of time to doubling of BL SC or ESRF, change in proteinuria; trial stopped early</td>
<td>Proteinuria (\geq 3) g/d: ACEI slowed rate of GFR decline: 0.53 (SE 0.08) versus 0.88 (SE 0.13) ml/min ((P = 0.03)); reduced risk for secondary composite outcome ((P = 0.02)); reduced urinary protein excretion versus BL (median 55% at 36 mo)(^c) (\geq 3) g/d: ACEI reduced risk for ESRF (RR 2.72; 95% CI 1.22 to 6.08) and of proteinuria (\geq 3) g/d (RR 2.40; 95% CI 1.27 to 4.52)</td>
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<td>Wright et al. (12)</td>
<td>Composite outcome: (\geq 50%) reduction in GFR versus BL or (\geq 25) ml/min per 1.73 m(^2), ESRD, or death; follow-up (\leq 4) yrs</td>
<td>ACEI reduced risk versus metoprol by 22% (95% CI 1 to 38%; (P = 0.04)) and versus amldipine by 38% (95% CI 14 to 56; (P = 0.004)); metoprol versus amldipine NS; lower MAP goal, NS effect</td>
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\(^a\)ACEI, angiotensin-converting enzyme inhibitor; BL, baseline; CI, confidence interval; CrCl, creatinine clearance; CV, cardiovascular; DBP, diastolic BP; ESRF, end-stage renal failure; MAP, mean arterial pressure; RR, relative risk; SC, serum creatinine.

\(^b\)Other antihypertensive therapy allowed as needed; roughly two thirds of patients received diuretic therapy.

\(^c\)Urinary protein excretion did not change significantly in the placebo group (13).
pressure (MAP) goal (12). The mean BP achieved were 141/85 mmHg in the normal group and 128/78 mmHg in the lower BP group (12). The lower MAP goal did not significantly affect the rate of the composite renal outcome or the change in GFR slope (12).

Use of ACEI on renal disease progression has not been tested in patients with type 2 diabetes, and, likewise, ARB have not been tested in patients with type 1 diabetes; however, on the basis of their mechanism of action of inhibiting of the RAS, it is logical to hypothesize that the protective effects will be similar. Moreover, the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial supports this concept in type 2 diabetes (25,26).

Impact of ACE Inhibition, ARB Therapy, BP, and Proteinuria on Renal and CV Risk in Diabetes

Diabetes is the leading cause of ESRD in the United States (24). Studies in populations with diabetes support the renoprotective effects of RAS inhibition (Table 2) (14–16).

ACE Inhibition Reduces Proteinuria in Patients with Diabetes-Related Nephropathy

Early data demonstrated that captopril could reverse proteinuria in patients with diabetes-related nephropathy. Captopril therapy led to remission of nephrotic proteinuria (>3.5 g/d) in 16.5% of patients, compared with 1.5% of those who received placebo (P = 0.005). This finding comes from a post hoc analysis of the subset of patients who entered the Captopril Study with this condition (n = 108) (27). Remission of proteinuria was associated with achieving a lower systolic BP (126 ± 8 versus 140 ± 13 mmHg; P = 0.002).

Intensive DBP Control Decreases CV Risk

The UK Prospective Diabetes Study Group (UKPDS) further evaluated the effect of tight BP control on diabetes-related outcomes in hypertensive patients with type 2 diabetes (n = 1,148; median follow-up 8.4 yr) (28). First-choice antihypertensive therapy was captopril or atenolol (28). Intensive BP control (<150/85 mmHg) significantly reduced rates of diabetes-related disease and death and of CV disease when compared with less stringent control (<180/105 mmHg) (28). The reduction in risk for fatal and nonfatal renal failure was NS (28). The lower BP target group showed a reduced risk for urinary albumin concentration ≥50 mg/L after 6 yrs of therapy (risk reduction 29%; P = 0.009) (28).

ACEI Therapy Favorably Reduces CV Risk When Compared with Calcium Channel Blockers

The Appropriate Blood Pressure Control in Diabetes trial was powered to detect differences in renal outcomes between two different BP-lowering strategies but failed to reach its primary end point. This occurred in part because renal function was well preserved at baseline, BP control was superb, and no proteinuria was present. Early in this trial, however, enalapril was associated with a reduced risk for CV events compared with nisoldipine in a subgroup of patients with both hypertension and type 2 diabetes (n = 470) (29). This finding comes from analysis of a secondary end point (29).

ACEI Therapy Reduces Risk for CV Events and Nephropathy in High-Risk Patients with Diabetes

The impact of ACEI therapy (ramipril) on CV risk in patients with diabetes was a primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) (14). Ramipril significantly lowered the risk for the combined primary CV end point by 25% (14). Adjustment for change in BP did not alter this result. Ramipril also significantly reduced the risk for overt nephropathy and lowered albuminuria (14).

ARB Therapy Slows Renal Disease and Reduces ESRD in Hypertensive Patients with Nephropathy Resulting from Type 2 Diabetes

ARB therapy also has demonstrated a renoprotective effect in hypertensive patients with diabetes-related nephropathy. Irbesartan significantly lowered the risk for a primary composite renal end point by 19% compared with placebo and 24% compared with amlopidine after adjustment for MAP during treatment (16). Proteinuria fell by an average of 33% with irbesartan therapy, compared with 6% with amlopidine and 10% with placebo (16).

In a similar study population, losartan significantly reduced
Table 2. Renoprotection in patients with diabetesa

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<td><strong>HOPE Study (14)</strong></td>
<td>Combined primary end point: MI, stroke, CV death; secondary end point: overt nephropathy (defined as clinical proteinuria); follow-up 4.5 yrs</td>
<td>ACEI reduced risk for primary end point by 25% (95% CI 12 to 36%; (P = 0.0004)); ACEI reduced risk for overt nephropathy by 24% (95% CI 3 to 40%; (P = 0.027)); ACEI reduced albumin/creatinine ratio at 1 yr ((P = 0.001)) and at study end ((P = 0.02)).</td>
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Lewis et al. (16)  
Prospective; patients randomly assigned to irbesartan, amlodipine, or placebo\(^b\) (\(n = 1,715\)); hypertension, type 2 diabetes, nephropathy (SC 1 to 3 mg/dl; urinary protein excretion \(\geq 900\) mg/d)

| Primary outcome: time to doubling of BL SC, ESRD, or death; outcomes adjusted for MAP during follow-up; mean follow-up 2.6 yrs | ARB reduced risk for primary end point by 19% (adjusted RR 0.81; 95% CI 0.67 to 0.99; \(P = 0.03\)) versus placebo and by 24% (adjusted RR 0.76; 95% CI 0.63 to 0.92; \(P = 0.005\)) versus amlodipine |

Brenner et al. (15)  
Prospective; patients randomly assigned to losartan or placebo\(^c\) (\(n = 1,513\)); hypertension, type 2 diabetes, nephropathy

| Primary outcome: time to doubling BL SC, ESRD, or death; outcomes adjusted for BP; mean follow-up 3.4 yrs | ARB reduced risk for primary end point by 15% (\(P = 0.03\)) versus placebo; ARB reduced risk for ESRD by 26% (\(P = 0.007\)) |

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aARB, angiotensin II receptor blocker; CV, cardiovascular; MI, myocardial infarction.
bTotal protein excretion \(\geq 500\) mg/d, urine albumin \(\geq 300\) mg/d, or albumin-to-creatinine ratio \(> 36\) mg/mmoL.
cOther antihypertensive therapy allowed as needed.

the risk not only for the primary composite outcome (time to doubling of baseline serum creatinine concentration, development of ESRD, or death) but also for ESRD alone when compared with placebo (15). These findings persisted after adjustment for BP (15). Losartan also decreased estimated GFR decline by 15.2% (4.4 \(\text{versus}\) 5.2 ml/min per 1.73 m\(^2\); \(P = 0.01\)) and lowered the risk for first heart failure–related hospitalization by 32% (\(P = 0.005\)) (15).

ACEI and ARB Therapy Provide Equivalent Renal and CV Protection for Hypertensive Patients with Diabetes and Early Nephropathy

No large outcome trial has compared the renal effects of ACEI and ARB therapy. One small (\(n = 250\)) trial of patients with type 2 diabetes, hypertension, and early nephropathy (mean GFR 91.4 to 94.3 ml/min per 1.73 m\(^2\)) demonstrated that telmisartan was not inferior to enalapril in GFR change from baseline over 5 yrs (26).

Early Changes in Proteinuria Predict Long-Term Renal and CV Outcome

Multiple studies that demonstrated renoprotection with ACEI or ARB therapy also reported reduction in proteinuria (2–4).

An analysis of trials in patients with hypertension and diabetes-related nephropathy (2,3,15) and in patients without diabetes and with hypertension and nephropathy (4) revealed that initial changes in proteinuria showed a roughly inverse relationship to the degree of long-term renal deterioration.

Every 50% decrease in proteinuria during the first 6 mo of losartan or placebo treatment was associated with a 36% reduction in risk for the composite renal end point, a 45% reduction in risk in risk for ESRD, and an 18% reduction in risk for CV events during subsequent follow-up (2,8). Losartan reduced average proteinuria by 35% from baseline during the 3.4-yr follow-up period (15). Much of this occurred in the first 6 mo of therapy, when proteinuria fell by 28% (2). Patients with a 15-mmHg decrease in systolic BP but a >30% increase in proteinuria had a four-fold elevated risk for ESRD (30).

Analysis of irbesartan’s effects identified a similar pattern. For every 50% reduction in proteinuria in the first 12 mo of ARB therapy, risk for the combined renal outcome (doubling of baseline serum creatinine, serum creatinine = 6.0 mg/dl, or development of ESRD) fell by more than half (hazard ratio 0.44; 95% confidence interval [CI] 0.40 to 0.49; \(P < 0.001\)) (3). Proteinuria decreased by an average of 41% during the first year of
irbesartan therapy, compared with an 11% reduction with amlopidine and a 16% reduction with placebo (3). Most of the reduction in proteinuria associated with ARB treatment occurred during the first 12 mo of the study (3).

Data from AASK demonstrate this relationship in patients without diabetes. Change in proteinuria at 6 mo predicted subsequent risk for ESRD (Figure 2) (4). This relationship extended to patients with baseline urinary protein excretion <300 mg/d. A 50% reduction in proteinuria at 6 mo was associated with a 72% reduction in risk for ESRD at 5 yrs (4). This was the first analysis to demonstrate that changes in low levels of proteinuria predict ESRD in patients with nondiabetic renal disease (4).

Role of ACEI and ARB Therapy in Management of Chronic Renal Disease Progression

On the basis of the previously summarized trials, treatment guidelines state that ACEI and ARB delay progression of renal disease and advise their use in hypertensive patients with kidney disease (5). Still, some researchers have questioned whether ACEI and ARB offer renoprotection independent of BP lowering (31). A meta-analysis of 13 trials (n = 37,089) that compared the effect of ACEI or ARB with that of other antihypertensive agents found that ACEI or ARB therapy was associated with a small reduction in risk for ESRD (risk reduction 0.87; 95% CI 0.75 to 0.99; P = 0.04). This benefit was not observed in an analysis that was restricted to trials of patients with diabetes (four trials; n = 14,437) (31). These authors found that ACEI and ARB therapy did not reduce the risk for doubling serum creatinine or slowing GFR decline when compared with other antihypertensive agents (31).

ACEI or ARB therapy reduced daily albumin excretion in patients without diabetes (−15.73 mg/d; 95% CI −24.72 to −6.74; P = 0.001; 44 trials; n = 5,266) and in patients with diabetes (−12.21 mg/d; 95% CI −21.68 to −2.74) (31). These findings were clouded by evidence of small-study bias (P < 0.001) and significant study heterogeneity (P < 0.0001) (31). Authors of the meta-analysis concluded that BP lowering is more important than the drug class prescribed (31). Still, the significant reduction in risk for ESRD is noteworthy.

Renoprotection with ACEI Plus ARB Therapy

Some people develop ESRD even with ACEI or ARB therapy. This suggests a need for further reduction of renal progression than is possible with either agent alone. Investigators therefore compared the effect of ACEI (trandolapril) and ARB (losartan) therapy separately and in combination in 263 patients without diabetes and with moderately reduced renal function (mean calculated GFR 37.5 to 38.4 ml/min per 1.73 m²). Most patients (≥90%) were hypertensive (17). The combined primary end point was time to doubling of serum creatinine concentration or development of ESRD (17). Patients were followed for a median of 2.9 yrs (17).

The trial was stopped early because of the benefit of combination therapy. Combination therapy favorably reduced the risk for reaching the combined end point when compared with either losartan (risk reduction 23 versus 11% for losartan; hazard ratio 0.40; 95% CI 0.17 to 0.69; P = 0.016) or trandolapril (reduction 23 versus 11% for trandolapril; hazard ratio 0.38; 95% CI 0.18 to 0.63; P = 0.018; Figure 3) (17). Change in proteinuria was independently associated with outcome (for every 10% proteinuria reduction: hazard ratio 0.58; 95% CI 0.24 to 0.88; P = 0.022) (17). BP reductions were similar across all three treatment groups (17).

Efficacy results were stratified on the basis of baseline proteinuria. Combining ACEI and ARB therapy significantly slowed renal disease progression in all three patient strata (<1 g/d, P = 0.049; 1 to <3 g/d, P = 0.029; ≥3 g/d, P = 0.033) (17). Urinary protein excretion decreased in all treatment groups but demonstrated the greatest reduction with combination therapy (maximum median reduction 42.1% with losartan, 44.3% with trandolapril, and 75.6% with combination therapy). In the combination-therapy group, patients with higher proteinuria (≥3 g/d) had greater reductions in proteinuria than did those with lower levels (<1 g/d) (17).

Ongoing Investigations

More information about the benefit of ACEI and ARB therapy will come from two major trials that are in progress. The Ongoing Telmisartan Alone and in Combination with Ramipril Global End-point Trial (ONTARGET) is a large (n = 25,620), double-blind, parallel-group trial that includes patients from 40 countries and is comparing ramipril, telmisartan, and combination treatment with both agents (32). The study population is similar to that for the HOPE trial (≥55 yr of age with a history of coronary artery disease, peripheral vascular disease, cerebro-
vascular disease, or diabetes with end-organ damage) (32). The end point is a composite of CV mortality, myocardial infarction, stroke, or hospitalization for heart failure. Patients will be followed for 3.5 to 5 yrs (32).

A similarly designed trial (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease [TRANSCEND]) compares the effect of telmisartan and placebo on the same primary end point and in patients with the same profile as those in ONTARGET except for their intolerance of ACEI (n = 6,000) (32). Results of both trials are expected in 2008.

In addition to these studies, there is a large VA cooperative study planned to compare ACEI therapy alone versus combinations of ACEI and ARB on renal disease progression. It is believed that the study will start in 2008.

Conclusions
Results of multiple trials point to the renal benefits of ACEI and ARB therapy beyond those attributable to BP lowering. Evidence strongly suggests that these effects derive from a reduction in proteinuria. Most hypertensive patients require multiple-drug treatment to achieve target BP goals (5). Patients with hypertension and proteinuric renal disease should receive an ACEI or an ARB as an integral part of their therapy.

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