An update on proteinuric chronic kidney disease: The dual-goal approach

**ABSTRACT**

Lowering both blood pressure and urinary albumin excretion to specific goals may slow the progression of proteinuric chronic kidney disease. However, this dual-goal approach needs to be validated prospectively.

**KEY POINTS**

Evidence is emerging that urinary albumin is toxic to the kidney.

Lowering both blood pressure and urinary albumin excretion, as a means to prevent progressive renal disease, appears to require aggressive inhibition of the renin-angiotensin-aldosterone system, often with several complementary drugs, ie, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, aldosterone receptor antagonists, and possibly, direct renin inhibitors.

Volume status and potassium levels may help suggest which of several available drugs could be added at different times.

Serum potassium levels must be managed aggressively when using renin-angiotensin-aldosterone inhibitors in combination.

When angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs) were introduced, we hoped that these drugs would slow or stop the inexorable progression of chronic kidney disease. This hasn’t come to pass: the incidence of end-stage renal disease continued to increase throughout the 1990s, and although it may have finally reached a plateau, it remains unacceptably high.1 One reason may be that, used singly, drugs that block the renin-angiotensin-aldosterone system are only moderately successful, as approximately 20% to 40% of patients still reach unfavorable renal end points such as doubling of the serum creatinine level or dialysis.2-7

In view of these disappointing results, some experts are advocating a new strategy in which they advise that both blood pressure and urinary albumin excretion be lowered to specific goals. To achieve these goals, we will generally have to give higher doses of ACE inhibitors and ARBs alone or use a combination of these and other drugs that block the renin-angiotensin-aldosterone system at various sites.

This article describes how the dual-goal approach, with a focus on renin-angiotensin-aldosterone system inhibition, may be applied in the therapy of proteinuric chronic kidney disease. This appears to be a reasonable approach, based on current evidence, to address the epidemic of renal failure. However, further studies are needed to establish the effectiveness of this approach, and the risk of hyper-
kalemia following aggressive inhibition of the renin-angiotensin-aldosterone system poses a significant management problem.

**ALBUMIN MAY BE TOXIC**

While hypertension has long been associated with poor renal outcomes, urinary albumin has more recently been implicated by observational and experimental evidence as a tubular-interstitial toxin that may also accelerate the progression of renal disease.

For example, in both the Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) study\(^8\) and the Ramipril Efficacy in Nephropathy study\(^4\), baseline proteinuria was almost linearly related to worse renal outcomes. In RENAAL, patients who excreted more than about 3 g of albumin per day had an 8.1-fold higher risk of progressing to end-stage renal disease.\(^8\) Moreover, the more that protein excretion could be reduced, the better the renal outcomes, down to a level of about 500 mg/day.\(^9\)

Of importance, lowering blood pressure did not always decrease protein excretion—nearly 40% of patients had a dissociation between the two.\(^9\) In fact, prescribing a single ACE inhibitor or ARB while targeting only blood pressure has not predictably reduced protein excretion to 500 mg/day (the proposed goal).\(^2–7\)

To reduce protein excretion to minimal levels, we need to use specific “renoprotective” medicines (TABLE 1)\(^2–7,10–14\) that lower protein excretion more than expected from their antihypertensive effect alone. We also need to set a goal level of proteinuria, continually adjusting the renoprotective medicines until the goal is achieved.

Although albumin has not been conclusively proven to be a renal toxin, targeting the reduction of proteinuria may also succeed if urinary albumin simply serves as a marker of the success of chronic kidney disease treatment and reflects prognosis.

**A DUAL-GOAL APPROACH**

In view of the observational and experimental evidence, many experts\(^10,15–18\) are advocating a dual-goal approach that stresses lowering both blood pressure and urinary protein (albumin) excretion. The recommended goal for systolic blood pressure is less than 120 to 125 mm Hg; the goal for proteinuria is less than 300 to 500 mg/24 hours,\(^16,17,19\) aiming to slow the decline in glomerular filtration rate to less than 2 mL/min/year.\(^11,20\)

The strategy of targeting both proteinuria and blood pressure has recently received further support. In a prospective randomized controlled study,\(^21\) nondiabetic patients with proteinuria received either an ACE inhibitor or an ARB. In one group, the dose was adjusted to lower the blood pressure to less than 130/80 mm Hg; in the other group, the dose was adjusted to lower the blood pressure to 130/80 and to reduce protein excretion maxi-

---

**TABLE 1**

**Renoprotective antihypertensive drugs**

- Angiotensin-converting enzyme inhibitors\(^2–4,7\):
  - Benazepril (Lotensin)
  - Captopril (Capoten)
  - Enalapril (Vasotec)
  - Fosinopril (Monopril)
  - Lisinopril (Prinivil, Zestril)
  - Moexipril (Univasc)
  - Perindopril (Aceon)
  - Quinapril (Accupril)
  - Ramipril (Altace)
  - Trandolapril (Mavik)
- Angiotensin II type 1 receptor blockers\(^5,6\):
  - Candesartan (Atacand)
  - Eprosartan (Teveten)
  - Irbesartan (Avapro)
  - Losartan (Cozaar)
  - Olmesartan (Benicar)
  - Telmisartan (Micardis)
  - Valsartan (Diovan)
- Aldosterone receptor antagonists\(^18–20\):
  - Eplerenone (Inspra)
  - Spironolactone (Aldactone)
- Nondihydropyridine calcium channel blockers\(^26\):
  - Diltiazem (Cardizem, others)
  - Verapamil (Calan, others)
- Renin inhibitors\(^31\):
  - Aliskiren (Tekturna)

*The relative efficacy of renin inhibitors is not yet established.*

---

Proposed goals:
- Systolic pressure: < 120–125 mm Hg
- Urinary protein: < 300–500 mg/day
- Decline in GFR: < 2 mL/min/year
mally. Only about half as many patients in
the group with the dual-goal strategy reached
the composite primary end point (doubling of
serum creatinine, end-stage renal disease, or
death) over a median of 3.7 years of follow-up,
as compared with those treated by targeting
the blood pressure alone.

In retrospect, the suboptimal success in the
earlier landmark studies2–7 may have derived
from the failure of ACE inhibitors and ARBs,
used by themselves at moderate doses, to ei-
ther lower the blood pressure to the recently
advised goal (the actual results obtained var-
ied from about 128 to about 145 mm Hg sys-
tolic) or, perhaps, to reduce proteinuria to the
goal level.

Not all nephrologists currently pursue
the stringent proteinuria goal of 500 mg per
day—the targeted reduction of proteinuria
requires further prospective evidence to sup-
port it. However, nephrologists do commonly
follow the broad theme that antihypertensive
therapy in proteinuric chronic kidney disease
should accentuate medicines that protect the
kidney beyond their antihypertensive effect
(TABLE 1), and that proteinuria is an important
metric that, at the very least, reflects the re-
sponse to therapy and prognosis.

### BLOCKING RENIN-ANGIOTENSIN-
ALDOSTERONE MORE COMPLETELY

These issues may be addressed by more com-
plete inhibition of the renin-angiotensin-
aldosterone system, now achievable with the
addition of aldosterone receptor antagonists
and direct renin inhibitors to the ACE inhibi-
tors and ARBs. Although we lack long-term
studies of the relative efficacy of these medi-
cines alone or in various combinations, the
multistep sequence of the renin-angiotensin-
aldosterone system allows for the possibility
that more complete suppression via coordi-
nated pharmacologic attention to multiple
sites will yield beneficial results.

### Combining an ACE inhibitor and an ARB

Even in the absence of ACE, angiotensin II is
also produced by other kinases and therefore
is not completely suppressed by an ACE in-
hibitor. For this and other reasons, there are
theoretical advantages to adding an ARB to
an ACE inhibitor.

In the Combination Treatment of Angio-
tensin 2 Receptor Blocker and Angiotensin-
Converting-Enzyme Inhibitor in Non-Diabet-
ic Renal Disease (COOPERATE) study,20 the
combination of an ACE inhibitor and an ARB
protected the kidneys better than either medi-
cine alone, not only in terms of less protein
in the urine but also in terms of significantly
fewer patients progressing to the primary end
points of doubling of serum creatinine or end-
stage renal disease after 3 years of follow-up
(11% of patients on combination therapy vs
23% on single therapy).

### Aldosterone receptor antagonists or renin
inhibitors plus ACE inhibitors and ARBs

Aldosterone escape is common during long-
term therapy with ACE inhibitors and ARBs,
and an aldosterone-receptor antagonist reduc-
es proteinuria11–13 and stabilizes kidney func-
tion13 in a manner additive to that of ACE
inhibitors and ARBs.

Direct renin inhibitors overcome the reac-
tive rises in renin activity and in angiotensin
II that complicate therapy with ACE inhibi-
tors and ARBs, and they also reduce urinary
aldosterone excretion.14

### When to consider combination therapy

Inhibition of the renin-angiotensin-aldoster-
one system at multiple sites may be considered
in cases of persistent hypertension or proteinu-
ria, or of progression of chronic kidney disease
despite single-drug therapy, or more broadly,
with increasing evidence that combination
therapy may preserve the glomerular filtration
rate.13,20 This article suggests one way to apply
the several available renin-angiotensin-aldos-
terone inhibitors, keeping in mind extensive
interindividual variations, uncertain respons-
es, and the absence of a linear evidence-based
strategy known to be broadly successful.

### INITIAL CONSIDERATION:
WHAT IS THE BLOOD PRESSURE GOAL?

Determining the blood pressure goal for a
patient may not be as straightforward as usu-
ally assumed. Typically, advisories suggest a
discrete goal; for example, the Seventh Joint
National Committee22 recommended a sys-
tolic blood pressure of 130 mm Hg or lower for patients with chronic kidney disease or diabetes. However, if we weigh the risks and benefits, we find that the situation is more nuanced. The blood pressure goal should vary among patients, depending on age, amount of proteinuria, whether the patient can tolerate the lowered blood pressure, and whether lowering the blood pressure to this goal stabilizes kidney function.

Long-term follow-up of the Modification of Diet in Renal Disease (MDRD) study demonstrated a benefit of setting the goal mean arterial pressure to less than 92 mm Hg (about 125 mm Hg systolic) regardless of proteinuria. In addition, a meta-analysis suggested that nondiabetic proteinuric patients benefit from even lower systolic blood pressures (110–119 mm Hg).

In older patients

However, in the MDRD study, the goal of approximately 125 mm Hg systolic pertained only to patients no older than 60 years. The goal was increased to about 130 mm Hg for patients 61 to 70 years old. In addition, major clinical studies of chronic kidney disease have excluded patients older than 70 years. Therapeutic studies of chronic kidney disease in this older age group are essentially unstudied, and we should be cautious about extrapolating results of aggressive blood pressure-lowering (and renin-angiotensin-aldosterone inhibition) from younger patients to older patients, who may have extensive vascular disease. However, some of these patients may have had premorbid systolic blood pressures of 90 to 110 mm Hg, so systolic pressures of 110 to 120 mm Hg would be “hypertensive” by 10 to 30 mm Hg for them. It is possible that some patients in this cohort will tolerate a systolic pressure lower than 110 mm Hg, and that the lower blood pressure may provide additional long-term renal protection for them. This notion is theoretical, however, and has not been verified by clinical studies.

No one pressure fits all

In summary, an initial target systolic pressure for proteinuric patients, based on available evidence, might be less than 130 mm Hg for patients 61 to 70 years old, less than 125 mm Hg for patients younger than 61 years, and perhaps as low as 110 to 119 mm Hg for non-diabetic patients. Caution is advised against targeting systolic blood pressure less than 140 mm Hg for patients older than 70 years. These are only initial goals and should be reevaluated as treatment progresses. The achieved blood pressure must be clinically tolerated—symptoms of tissue hypoperfusion indicate that the blood pressure is too low for the patient. In addition, the blood pressure goal (like the proteinuria goal) is only a surrogate end point, and if kidney function declines even though the surrogate end points are attained, then those end points should be reevaluated.

Tailoring blood pressure goals to the individual patient dovetails with the recent suggestion that blood pressure should not be perceived as a rigid dichotomy of “hypertension” vs “normal.” There is, in general, a continuous correlation between blood pressure, beginning at low levels, and the risk of cardio renal disease, and choosing an optimal blood pressure goal for an individual...
patient requires an ongoing assessment of benefits, risks, and side effects.

### STARTING ANTIHYPERTENSIVE THERAPY

The question of which antihypertensive drug to try first is moot in chronic kidney disease because almost all patients need multiple medicines to reach their blood pressure goals.

The Seventh Joint National Committee recommended an ACE inhibitor for initial therapy in hypertensive patients with chronic kidney disease, although an ARB is a reasonable first choice for those with type 2 diabetes.

Diuretics potentiate the effects of ACE inhibitors and ARBs and are generally prescribed concomitantly or as the second choice.

A beta-blocker may be recommended as a third medicine (when needed), to provide a complementary class of antihypertensive, to address the high incidence of concomitant coronary artery disease and systolic dysfunction, and because of evidence that sympathetic excess contributes to the hypertension and progression of chronic kidney disease.

The National Kidney Foundation suggests that the dose of beta-blocker be increased if the heart rate is greater than 84.

### INTENSIFYING RENIN-ANGIOTENSIN-ALDOSTERONE INHIBITION: WHICH DRUGS, AND WHEN?

When hypertension and proteinuria persist despite the use of an ACE inhibitor or an ARB, additional inhibition of the renin-angiotensin-aldosterone system is generally recommended to lower both the blood pressure and the protein excretion. Increasing the dose of ACE inhibitor or ARB, combining an ACE inhibitor and an ARB, or adding an aldosterone receptor antagonist to either an ACE inhibitor or an ARB have all been shown to reduce proteinuria (as a surrogate end point), and several studies have, importantly, found that these combinations preserve kidney function over time.

However, lacking long-term studies that compare these options, we cannot insist upon specific treatment choices or sequences in these situations.

### An approach based on serum potassium and volume status

Nevertheless, physicians need to make decisions when hypertension or proteinuria persists despite initial therapy. In the absence of definitive clinical studies, one possible approach is to choose among the various drugs on the basis of the serum potassium level and volume status (Table 2).

For example, if a patient has obvious signs of volume excess (eg, edema, jugular venous distention, rales) and the serum potassium concentration is less than about 5.0 or 5.5 mEq/L, then an aldosterone receptor antagonist may logically be added or increased in dose.

### Aldosterone is more than a kidney hormone

Of note, we now know that aldosterone does not act only on the renal tubule: recent stud-

---

### TABLE 2

<table>
<thead>
<tr>
<th>SERUM POTASSIUM LEVEL (APPROXIMATE)</th>
<th>IF OBVIOUS VOLUME EXCESS, THEN GIVE:</th>
<th>IF NORMAL VOLUME THEN GIVE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5.5 mEq/L</td>
<td>Aldosterone receptor antagonist</td>
<td>ACE inhibitor or ARB</td>
</tr>
<tr>
<td>&gt; 5.5 mEq/L</td>
<td>Loop diuretic</td>
<td>Nondihydropyridine CCB or loop diuretic</td>
</tr>
</tbody>
</table>

*Almost all patients with chronic kidney disease need multiple drugs to reach their blood pressure goals.*

---

*ACE = angiotensin-converting enzyme; ARB = angiotensin II type 1 receptor blocker; CCB = calcium channel blocker.*
‘Ultra-high’ doses of ACEs and ARBs appear to reduce protein excretion without lowering blood pressure further

**TABLE 3**

Possible indications for aldosterone receptor antagonists

- To complement angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers in reducing proteinuria
- To treat significant systolic dysfunction
- To augment the diuresis of loop and thiazide diuretics via an effect on a different tubule site
- To counter the hypokalemic and alkaline effects of loop and thiazide diuretics
- For hypertension related to obesity and sleep apnea
- For hypertension related to primary hyperaldosteronism

Increasing the diuretic or renin-angiotensin-aldosterone inhibition

For patients who have obvious signs of volume excess and a serum potassium level greater than 5.0 mEq/L, the dosage of kaliuretic (potassium-excreting) diuretic (usually a loop diuretic in chronic kidney disease) can be increased. Although kaliuretic diuretics do not specifically lower proteinuria, they will help control volume and blood pressure and, by lowering the serum potassium level, facilitate the subsequent augmentation of renin-angiotensin-aldosterone inhibition.

When a hypertensive patient does not seem to have excess volume or tachycardia and the serum potassium level is less than 5.5 mEq/L, then additional renin-angiotensin-aldosterone inhibition is indicated. This may be accomplished either by increasing the ACE inhibitor or the ARB to its maximal antihypertensive dose or by starting combination therapy.

Starting a calcium channel blocker

When the serum potassium level is higher than about 5.5 mEq/L, further inhibition of the renin-angiotensin-aldosterone system is contraindicated, and a nondihydropyridine calcium channel blocker can be added for its antihypertensive and antiproteinuric effects. When nondihydropyridine calcium channel blockers are contraindicated due to their anti-inotropic effect, an attractive alternative may be to cautiously increase the dose of kaliuretic diuretics. Given the high prevalence of (often covert) volume excess in chronic kidney disease, empiric diuresis may lower blood pressure, particularly in patients already receiving several vasodilators. Moreover, as mentioned, by reducing serum potassium, kaliuretic diuretics help allow for a subsequent increase in renin-angiotensin-aldosterone inhibition.

**IF BLOOD PRESSURE IS NORMAL, BUT PROTEINURIA PERSISTS**

Because lowering blood pressure does not necessarily reduce protein excretion, some patients achieve their blood pressure goal but still have excessive proteinuria. Proponents of the dual-goal approach suggest that these patients require further treatment modifications to reach the proteinuria goal and their optimal renal prognosis.

A number of options are available (Table 4), although none of them has been shown to be clearly superior to the others in clinical studies.

A cautious increase in renin-angiotensin-aldosterone inhibition is possible but is likely to be limited by low blood pressure. When applicable, any nonessential antihypertensive drug that does not specifically reduce proteinuria (ie, dihydropyridine calcium channel blockers and central and direct vasodilators) should first be discontinued. This allows additional renin-angiotensin-aldosterone inhibition to reduce proteinuria without causing hypotension.

In addition, “ultra-high” doses of these drugs—two or more times the maximal antihypertensive dose—appear to reduce proteinuria without further reducing blood pressure.

Various combinations of an ACE inhibitor, an ARB, and an aldosterone receptor antagonist (and possibly a renin inhibitor) may also be prescribed, striving for more complete sup-
pression of the renin-angiotensin-aldosterone system, with dose adjustments to prevent hypotension.

**KEEPING SERUM POTASSIUM AT SAFE LEVELS**

Intensive inhibition of the renin-angiotensin-aldosterone system, via higher doses or combination therapy, increases the risk of hyperkalemia. This risk must be addressed energetically to prevent a potentially life-threatening complication.

When prescribed by nephrologists in clinical studies, renin-angiotensin-aldosterone inhibition has proven safe, with minimal adverse events (including hyperkalemia), even with high doses,32–34 in stage 4 chronic kidney disease (ie, with a glomerular filtration rate of 15 to 29 mL/min/1.73 m², inclusively)7 and with combination therapy.11–13,20

However, the increased incidence of hyperkalemia reported with spironolactone in patients with congestive heart failure following publication of the Randomized Aldactone Evaluation Study38 suggests that safety in clinical studies should not be extrapolated to mean safety in routine, community use. Patients with chronic kidney disease should not be given high doses or combinations of these drugs unless the treating physician is experienced in the prevention and treatment of hyperkalemia; typically such therapy should be guided by a nephrologist.

*When serum potassium levels exceed 5.6 mEq/L, renin-angiotensin-aldosterone inhibitors should be decreased in dose or discontinued.*39 Ideally, the drug or drugs should be restarted (to provide the potential benefits of these classes of drugs) when hyperkalemia has resolved, but this requires not only resolution of hyperkalemia but also steps to prevent this serious problem from recurring. The serum potassium level should be checked frequently, particularly after any increase in renin-angiotensin-aldosterone inhibition.

**Treating hyperkalemia**

Potential treatments for hyperkalemia include dietary restriction, sodium bicarbonate,39 fludrocortisone (Florinef),40 kaliuretic diuretics, and sodium polystyrene sulfonate (Kayexalate). Nonsteroidal anti-inflammatory drugs should be avoided.

**Dietary restriction** should be particularly emphasized: if potassium intake is decreased to the same extent as renin-angiotensin-aldosterone inhibitors reduce its excretion, then the serum potassium level will remain acceptable. All dietary supplements whose contents are not precisely known should be proscribed. A list of high-potassium foods to avoid should be given with the initial prescription for the drug. If briefly reviewed at each visit, with

| TABLE 4 |
| Options for treating normotensive proteinuric patients |
| Discontinue any antihypertensive drug that does not reduce proteinuria and increase inhibition of the renin-angiotensin-aldosterone system, adjusting doses to maintain blood pressure at goal |
| Increase the renin-angiotensin-aldosterone inhibitor to an “ultra-high” dose |
| Increase renin-angiotensin-aldosterone inhibition with combinations of two or more of the following: an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin II type 1 receptor blocker (ARB), an aldosterone receptor antagonist, and a renin inhibitor, with dose adjustments to prevent hypotension |
| Restrict protein intake |
| Change the ACE inhibitor to an ARB, or vice versa |
| Change the ACE inhibitor to ramipril (Altace) or quinapril (Accupril) to increase tissue ACE inhibition |
| Prescribe statins, vitamin D, weight loss |
| Consider additional reduction of blood pressure in young, nondiabetic patients |
feedback given based on measured serum potassium levels, dietary treatment is typically effective (personal observation).

Fludrocortisone is an option when dietary potassium restriction fails.

An increase in the dose of diuretic is typically required with fludrocortisone to prevent sodium retention. The combination of dietary potassium restriction, fludrocortisone (0.1 mg/day, 3–5 days a week), and furosemide (Lasix) allowed high doses of an ACE inhibitor or a combination of an ACE inhibitor and an ARB to be given in 132 patients with chronic kidney disease.40 Over several years, their mean peak potassium level was 4.87 mEq/L, and no instance of acute hyperkalemia required stopping the ACE inhibitor or ARB.

However, fludrocortisone is an aldosterone analogue with potentially long-term aldosterone-mediated injurious effects on heart and renal function, even though only low doses were required in the three-pronged approach to hyperkalemia.40 The long-term effect of a regimen of an ACE inhibitor plus an ARB plus fludrocortisone on cardiac and renal outcomes is unknown and of concern.

Therefore, fludrocortisone should probably be avoided in patients with systolic heart dysfunction and should be used cautiously in general. Its use might be limited to patients with proteinuric chronic kidney disease that progresses despite therapy, particularly when that progression is in the context of inability to give significant renin-angiotensin-aldosterone inhibition because of hyperkalemia.

MORE STUDY NEEDED

Chronic kidney disease treatment is becoming increasingly complex, with a lengthening list of potentially effective drugs, difficult-to-reach goals, and a less structured approach. This complexity is magnified by issues of potassium homeostasis and interindividual variations in response to renin-angiotensin-aldosterone inhibition.

More prospective studies are needed to confirm the benefits of targeting proteinuria along with blood pressure and the metrics of the goals in tandem, but, based on available information, the dual-goal approach has been recommended for proteinuric patients,10,15–18 and evidence is accumulating for greater renal protection from larger doses of renin-angiotensin-aldosterone inhibitors and from using these drugs in combination.

REFERENCES


ADDRESS: Sheldon Hirsch, MD, 516 Meadow Drive East, Wilmette, IL 60091; e-mail shelman100@aol.com.

LET US HEAR FROM YOU

Let us hear your opinions about the Cleveland Clinic Journal of Medicine.
Do you like current articles and sections?
What topics would you like to see covered and how can we make the Journal more useful to you?

PHONE 216.444.2661
FAX 216.444.9385
E-MAIL ccjm@ccf.org
WWW http://www.ccjm.org

CLEVELAND CLINIC JOURNAL OF MEDICINE
Cleveland Clinic
9500 Euclid Avenue, NA32
Cleveland, Ohio 44195