Management of Glomerular Proteinuria: A Commentary

WILLIAM A. WILMER,* BRAD H. ROVIN,* CHRISTOPHER J. HEBERT,[†]
SUNIL V. RAO,[‡] KAREN KUMOR,[§] and LEE A. HEBERT*

Department of Internal Medicine, The Ohio State University Medical Center, Columbus, Ohio; [†]Case Western Reserve University, Louis Stokes VA Medical Center, Cleveland, Ohio; [‡]Department of Medicine, Duke University, Durham, North Carolina; and [§]Alexion Pharmaceuticals, Inc., Cheshire, Connecticut.

Abstract. It is widely accepted that proteinuria reduction is an appropriate therapeutic goal in chronic proteinuric kidney disease. Based on large randomized controlled clinical trials (RCT), ACE inhibitor (ACEI) and angiotensin receptor blocker (ARB) therapy have emerged as the most important antiproteinuric and renal protective interventions. However, there are numerous other interventions that have been shown to be antiproteinuric and, therefore, likely to be renoprotective. Unfortunately testing each of these antiproteinuric therapies in RCT is not feasible. The nephrologist has two choices: restrict antiproteinuric therapies to those shown to be effective in RCT or expand the use of antiproteinuric therapies to include those that, although unproven, are plausibly effective and prudent to use. The goal of this work is to provide the documentation needed for the nephrologist to choose between these strategies. This work describes 25 separate interventions that are either antiproteinuric or may block injurious mechanisms of proteinuria. Each intervention is assigned a level of recommendation (Level 1 is the highest; Level 3 is the lowest) according to the strength of the evidence supporting its antiproteinuric and renoprotective efficacy. Pathophysiologic mechanisms possibly involved are also discussed. The number of interventions at each level of recommendation are: Level 1, $n = 7$; Level 2, $n = 9$; Level 3, $n = 9$. Our experience indicates that we can achieve in most patients the majority of Level 1 and many of the Level 2 and 3 recommendations. We suggest that, until better information becomes available, a broad-based, multiple-risk factor intervention to reduce proteinuria can be justified in those with progressive nephropathies. This work is intended primarily for clinical nephrologists; therefore, each antiproteinuria intervention is described in practical detail.

This work focuses on therapies that can be expected to be antiproteinuric in all forms of glomerulopathy. Not considered are disease-specific therapies such as insulin for diabetic nephropathy. In chronic glomerular diseases, the greater the proteinuria the greater is the risk of "progression" (irreversible and progressive GFR decline) (1,2) (Table 1). The exceptions are glomerulopathies that manifest highly selective proteinuria such as minimal change disease and certain forms of hereditary glomerulopathy (3). In these conditions, heavy proteinuria can be present for years without evidence of kidney damage.

Why Is Greater Proteinuria Associated with Faster Kidney Disease Progression?

The historic explanation is that greater proteinuria indicates a more severe glomerulopathy, and this accounts for the faster GFR decline (1). Recently, it has become clear that proteinuria, particularly when heavy and nonselective, can be nephrotoxic through a variety of mechanisms (reviewed in references 4–6).

Thus, there is strong evidence that proteinuria is both a marker for and a mechanism of kidney disease progression. Consistent with this hypothesis are the clinical studies showing that proteinuria reduction is associated with slower subsequent GFR decline (7–9), whereas maintained or worsened proteinuria is associated with faster GFR decline (10,11). Nevertheless, to critically test the hypothesis that proteinuria causes progression requires studies in which proteinuria, or a damaging mechanism attributed to proteinuria, is changed independent of all other progression mechanisms. Presently the only possible approach is to block a mechanism by which proteinuria could cause kidney damage. This has recently been accomplished in experimental nephropathies in which complement activation in the tubular compartment was either attenuated by complement inhibitors (12,13) or abrogated by genetic deficiency of the sixth component of complement (14). The rationale is that nonselective proteinuria contains the entire alternative and terminal complement pathways, which activate and deposit the membrane attack complex (C5b-9) on tubular epithelium (12–15). Furthermore, activated renal tubular epithelium can synthesize and secrete C3 (6). Studies in the C6 genetically deficient rat (14) provide particularly compelling evidence that proteinuria itself is nephrotoxic. In these studies, the normal PVG rats subjected to 5/6 nephrectomy manifested proteinuria, tubular C5b-9 deposition, and progressive kidney damage. By

Table 1. GFR decline during follow-up in chronic proteinuric glomerulopathies according to baseline proteinuria

MDRD[a] (n = 585) Baseline GFR: 38.6 ± 0.4 ml/min			
Baseline proteinuria (g/d)	<1.0	1–3	>3.0
GFR decline[c] (ml/min per yr per 1.73 m²)	1.7 ± 0.3	4.9 ± 0.5	8.3 ± 0.7

REIN[b] (n = 352) Baseline GFR: 43.8 ± 1.0 ml/min				
Baseline proteinuria (g/d)	<2.0	2–3	3–4.5	>4.5
GFR decline[c] (ml/min per yr per 1.73 m²)	2.5 ± 0.04	4.6 ± 0.1	6.5 ± 0.1	9.5 ± 0.2

[a] Modification of Diet in Renal Disease (MDRD) Study A (7). Includes BP and diet intervention groups. Results adjusted for race, kidney disease diagnosis, baseline BP, and plasma transferrin level.
[b] Ramipril Efficacy in Nephropathy (REIN) Study (8) Strata 1 and 2, includes both ramipril and placebo groups.
[c] Mean GFR decline ± SE.

contrast, the C6 genetically deficient rats with 5/6 nephrectomy manifest only the proteinuria (14).

If Proteinuria Is Reduced, How Much Slowing of GFR Decline Can Be Expected?

Of the studies examining this question (7–9,16,17), Study A of the Modification of Diet in Renal Disease (MDRD) study is among the largest (585 patients) and most detailed (adjustment for 11 relevant baseline and 6 relevant follow-up co-variates). The MDRD study showed that for each 1-g/d reduction in proteinuria observed at 4 mo of the antiproteinuria therapies (the BP and dietary interventions), subsequent GFR decline was slowed by about 1 ml/min per year (7). The REIN study showed that for each 1-g/d reduction in proteinuria observed at 3 mo of ACEI therapy, subsequent GFR decline adjusted for baseline GFR was slowed by about 2.0 ml/min per year (18). In most proteinuric kidney diseases, GFR loss occurs at about 4 to 10 ml/min per year (7). Thus proteinuria reductions of 1.0

g/d or more should prolong time to ESRD (Figure 1) and may reduce cardiovascular deaths because chronic kidney disease (CKD) is independently related to cardiovascular death rate (19).

Monitoring Glomerular Proteinuria
Spot versus 24-h Urine Collection to Assess Proteinuria

The Work Group of the Kidney Disease Outcome Quality Initiative (K-DOQI) of the National Kidney Foundation recommends first morning or random spot urine collections to monitor proteinuria in established kidney disease (20). Spot urine testing is a convenient and acceptable practice; but we suggest that 24-h urine testing is a "best practice" for the following reasons.

1. Twenty-four–hour urine collections estimate proteinuria rate more accurately than spot urine collections. In the typical nephrotic patient, the urine protein/creatinine ratio (P/C ratio) at midday is about 1.7-fold greater than that in the morning (21,22). Thus, the closer the urine collection approaches 24 h, the closer the urine P/C ratio approaches the 24-h proteinuria rate. The notion that the spot urine/creatinine ratio accurately predicts 24-h proteinuria is based on cross-sectional studies in which the between-patient variation in proteinuria rate was great, generally 600-fold or greater (20, 23). Thus, the high correlation coefficients do not apply to individual proteinuric patients followed longitudinally (24).

2. The urine P/C ratio of even an inaccurately timed 24-h urine collection is likely to yield a better estimate of 24-h proteinuria rate than that of a random spot urine. This follows from Point #1 (above).

3. Kidney disease progression attributable to proteinuria is probably related to the absolute 24-h proteinuria rate. Spot or overnight urine collections tend to overestimate or underestimate the absolute 24-h proteinuria rate. Morning spot or fractional urine collections usually represent nadir proteinuria rates. Midday spot or fractional urine collections usually represent peak proteinuria rates (21,22).

4. Large daily changes in urinary creatinine excretion can occur independently of urine protein excretion, causing the
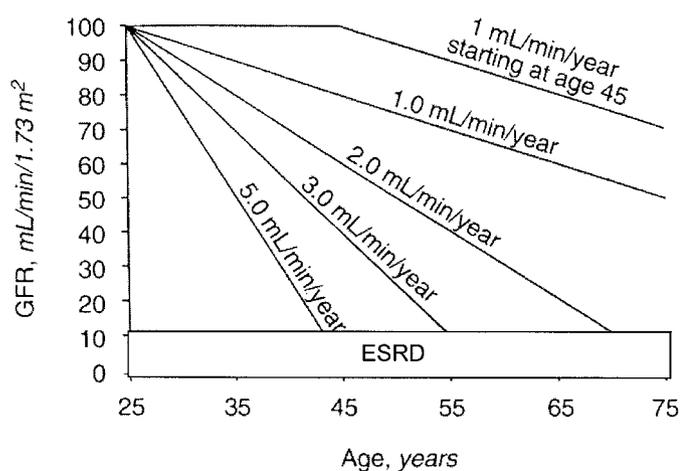

Figure 1. Rate of GFR decline in normals an in hypothetical patients with onset of progressive renal disease at age 25 yr. The course of GFR decline with normal aging (top curve) is based on a cross-sectional study of iothalamate clearance in 357 patients aged 17 to 70 years. Note also that small differences in rates of GFR decline can result in large differences in time to onset of ESRD. Reprinted with permission from Hebert et al. (4).

urine P/C ratio to be an inaccurate estimate of proteinuria rate. Spot urine testing cannot detect this confounder, but 24-h urine testing can. In the average carnivorous North American adult, about one third of urine creatinine is from eating cooked meat (cooking converts meat creatine to creatinine) (25), particularly beef (26). Sustained heavy exercise can increase 24-h urine creatinine by nearly two-fold (27). Creatine, a nutritional supplement usually taken at 2 to 5 g daily is metabolized to creatinine (28). Fenofibrate increases urinary creatinine excretion by as much as 35% (29). Thus, creatinine excretion can be changed substantially depending on whether the 24-h urine was collected in relation to vigorous exercise, high-meat or no-meat meal, a creatine supplement, or fenofibrate. Measuring the 24-h urine creatinine content should detect these confounders; a spot urine cannot.

5. Twenty-four–hour urine testing provides relevant information regarding nutrient and fluid intake that a spot urine cannot. Our practice in CKD management is to test 24-h urine collections at 2- to 6-mo intervals for volume, creatinine, protein, urea, sodium, and potassium if abnormalities of serum potassium are present (4). The relevance is discussed later.

To assist the patient in obtaining an accurate and informative 24-h urine collection, we suggest that the patient should do the following. (*1*) Pick a day that is convenient and typical of their usual regimen. (*2*) Obtain the 24-h urine within 1 wk of the clinic visit. Store it in the cold. It is OK if individual voidings must be held at room temperature for up to 12 h. (*3*) Avoid missed voidings by carrying in purse or duffle bag a leak-proof 500-ml plastic wide-mouth container (*e.g.* Rubbermaid Sipp'n Sport 590 ml). (*4*) Inform their physician if voidings are lost. It is better to submit an incomplete 24-h urine collection than none at all.

Table 2 summarizes the advantages of 24-h *versus* spot urine testing. Table 3 is an algorithm to interpret 24-h urine collections to assess proteinuria and nutrient intake.

Urine Albumin Versus Urine Total Protein for Monitoring Proteinuria

The K-DOQI Work Group recommends urine albumin measurement to monitor CKD (20). Certainly microalbuminuria measurement for the early detection of CKD and cardiovascular risk (30) is appropriate. However, in established glomerulopathies (proteinuria >500 mg/d) or to screen for tubular proteinuria (where albuminuria may be at normal levels), we suggest measurement of total urine protein (albumin + other proteins). The rationale is that in established glomerulopathies, there is no evidence that albuminuria rate is more informative than total proteinuria rate. Indeed, albuminuria and total proteinuria rates are generally highly correlated (20). Nevertheless, recent studies demonstrate differences in the renal tubular reclamation and degradation of filtered albumin compared with IgG and transferrin (31,32). Thus, measurement of albuminuria alone might provide spurious information regarding the status of glomerular and tubular function. Furthermore, urine albumin

Table 2. Advantages of 24-h *versus* "spot" urine testing in monitoring chronic kidney disease (the column containing the dot indicates the advantage)

	24-h Urine	"Spot" urine
Convenience		●
Accuracy of proteinuria rate estimate	●	
Estimate of nutrient intake		
sodium	●	
protein	●	
water	●	
potassium	●	
Detects change in urine creatinine	●	
Proven to predict kidney disease progression	●	
Cost[a]		

[a] At most laboratories the charge is the same for analysis of a spot or 24-h urine specimen.

measurement is more costly. In a survey of four Ohio hospitals and one commercial laboratory, median charge for a urine albumin/creatinine ratio was $77 compared with $25 for a P/C ratio.

Antiproteinuric Therapies

Antiproteinuric therapies of proven effectiveness, or plausibly effective and prudent to use, are listed in Table 4 according to level of recommendation. Level 1 (highest) recommendation is based on one or more large high-quality controlled clinical trials. Level 2 (intermediate) recommendation is based on a secondary analysis of the high-quality trials or randomized controlled trials. Level 3 (lowest) recommendation is based on observational or experimental kidney disease studies.

The goal of antiproteinuric therapy is to reduce proteinuria as much as possible, ideally to <500 mg daily, which appears to approach the maximum benefit of proteinuria reduction (33,34). The antiproteinuric therapies listed in Table 4 are discussed below.

1. Control BP (Level 1)

Three large trials have randomized kidney disease patients to two different levels of BP control, a usual goal (approximately 140/85 mmHg) or a low goal (approximately 125/75 mmHg), and observed the effects on proteinuria. The studies are the MDRD study (7), the Appropriate Blood Pressure Control in Diabetes (ABCD) study (35), and the African American Study of Kidney Disease and Hypertension (AASK) (11). The low BP goal either reduced proteinuria by 50% (7) or prevented the

Table 3. Interpretation of urine collections submitted as 24-h collections to estimate proteinuria and nutrient excretion rate

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Step 1. Determine the accuracy of the timed urine collection. Calculate the ratio measured creatinine (MC)/expected C (EC). EC is determined by the formula [(140 − age) × lean weight (kg)] × 0.2 [if female, result × 0.85] (Cockroft-Gault). To interpret urine protein/creatinine (P/C) ratios and nutrient excretion, triage the MC/EC ratio as follows.

MC/EC ratio 0.9–1.1
- The urine collection is probably an accurate 24-h collection. The P/C ratio is probably a valid estimate of the proteinuria rate. This P/C ratio can be compared to that of other valid urine P/C ratios to assess proteinuria trends.
- The urine volume and content of sodium, urea, etc. are probably accurate 24-h values. Trends of these values can be compared with those of other valid 24-h urine collections.

MC/EC ratio 0.75–1.25
- The urine collection is probably not an accurate 24-h collection. However, the P/C ratio from this collection was determined from urine collected during the *majority* of the diurnal variation in protein excretion. This ratio is likely superior to a "spot" urine in assessment of proteinuria rate. Therefore, this urine P/C ratio can be compared with other valid urine P/C ratios to assess proteinuria trends.
- A reasonable estimate of 24-h urine volume and content of sodium, urea, etc. can be extrapolated by dividing each urine value by the MC/EC ratio.

MC/EC ratio <0.75 or >1.25
- The urine collection is probably not an accurate 24-h collection. Proceed to Step 2.

Step 2. Problem solving for urine collections in which the MC/EC ratio is <0.75 or >1.25. Begin by determining whether the patient understands the instructions for a 24-h urine collection. Then triage as follows.

The patient acknowledges that the urine collection is inaccurate
- The urine P/C ratio may not be a valid estimate of the proteinuria rate. However, because this ratio was obtained from a urine collected during *much* of the diurnal variation in protein excretion, it probably is superior to that of a "spot" urine in assessment of proteinuria rate.
- An accurate urine volume and content of sodium, urea, etc. probably cannot be extrapolated from the collection.
- A repeat 24-h collection is recommended.

The patient insists that the urine collection is accurate
- The MC/EC ratio is <0.75
  a. If serum creatinine is stable compared with previous values, it is likely that an undercollection has occurred. Alternatively, GFR has declined in proportion to a decline in creatinine production (low-meat diet, muscle wasting, limb amputation).
  b. If serum creatinine is decreased compared with previous values, it is likely that a decline in creatinine production has occurred (see above).
  c. If creatinine production has decreased, the urine P/C ratio of the current 24-h urine cannot be validly compared with previous P/C ratios.
- The MC/EC ratio is >1.25
  a. If serum creatinine is stable compared with previous values, it is likely an overcollection has occurred. Alternatively, GFR has increased in proportion to an increase in creatinine production (high-meat diet, increased muscle mass, creatine supplementation, fenofibrate therapy).
  b. If serum creatinine is increased compared with previous values, an increase in creatinine production has occurred (see above). If creatinine production has increased, the urine P/C ratio of the current 24-h urine cannot be validly compared to previous P/C ratios.

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twofold to threefold increase in proteinuria observed in the usual BP goal patients (11,35). In the MDRD study, the greater the baseline proteinuria, the greater was the percent reduction in proteinuria in the low goal group (7). The low BP goal was well tolerated in the large randomized trials (7,11,35) and in the smaller studies of the effect of the low BP goal (36,37). Compared with the usual BP goal, the low BP goal reduced stroke rate (35) and left ventricular mass index (38). A recent meta-analysis showed that the higher mortality rates associated with lower BP (the J-curve phenomenon) is explained by association of low BP with poor health, not the low BP itself (39). Benefits of the low goal have also been confirmed in

hypertensive non-kidney disease patients (40,41). Thus, the low BP goal, sitting systolic BP in the 120s or less if tolerated, is recommended. The systolic BP is specified because it correlates better than diastolic pressure with kidney disease progression (7,10).

BP should be taken in the sitting position and after taking the antihypertensive medications at the usual times. However, if the antihypertensive medication has rapid onset (clonidine tablets, labetalol, captopril, hydralazine), this needs to be taken into account. At the first evaluation, BP is taken in both arms. The arm with the higher BP is used for future BP measurement (42). We recommend home BP monitoring using proper tech-

*Table 4.* Antiproteinuric strategies ranked according to level of recommendation

Intervention	Goal/Comment
1. Control BP (Level 1)	The goal is a sitting systolic BP in the 120s or less, if tolerated. The greater the proteinuria, the greater the benefit of the low goal. Text has recommended antihypertensive regimens.
2. ACEI therapy (Level 1)	Use ACEI even if normotensive. ACEI is first choice because of proven cardio protection. Use maximum recommended doses if tolerated. Goal is proteinuria <0.5 g/d.
3. ARB therapy (Level 1)	Proven antiproteinuric and renoprotective therapy. Studies are underway to assess cardiovascular protection compared with ACEI. ARB is first choice if ACEI–intolerant. Use maximum recommended doses, if tolerated. Goal is proteinuria <0.5 g/d.
4. Combination ACEI and ARB therapies (Level 1)	Adding ARB to maximum ACEI appears to reduce proteinuria further. However, BP may not be reduced further.
5. Avoid DHCCB unless needed for BP control (Level 1)	DHCCBs are excellent antihypertensive agents but they are not antiproteinuric and may promote kidney disease progression. ARB therapy may mitigate these effects.
6. β-blocker therapy (Level 1)	β-blocker therapy is antiproteinuric compared to DHCCB–therapy.
7. Control protein intake (Level 1)	Goal is 0.7 to 0.8 g/kg/d. Effect on proteinuria is nearly the same as that of the low BP goal. Soy proteins may offer advantages over other protein sources.
8. Restrict NaCl intake (Level 2) (Level 1 for BP control)	Goal is 80 to 120 mmol/d ($\approx$2.0 to 3.0 g Na) to optimize the antiproteinuric effects of ACEI, ARB, or NOH-CCB therapy. Lower salt intake controls BP, which may further reduce proteinuria.
9. Control fluid intake (Level 2)	Goal is urine volume <2.0 L/d unless higher fluid intake is needed for specific reasons. In the MDRD Study A, each 1% greater urine volume was associated with a 1% increase in urine protein/creatinine ratio. Also, urine volumes >2.0 L/d were associated with faster GFR decline.
10. NDH-CCB therapy (Level 2)	This CCB class is antiproteinuric. It might also be renal protective based on observational studies.
11. Control blood lipids (Level 2) (Level 1 for cardiovascular benefit)	There is good evidence that statins are antiproteinuric and renoprotective.
12. Aldosterone antagonist therapy (Level 2)	Spironolactone is antiproteinuric in humans and in animal models independent of BP control.
13. Smoking cessation (Level 2)	Cigarette smoking in humans increases proteinuria/albuminuria and is associated with faster kidney disease progression. Smoke condensate worsens proteinuria and glomerulosclerosis in experimental kidney disease in rats.
14. Avoid estrogen/progestin replacement therapy in postmenopausal women with kidney disease (Level 2)	Estrogens may have renoprotective effects that explain slower progression of kidney disease in premenopausal women compared with men of the same age. However, estrogens induce microalbuminuria and have other adverse effects in postmenopausal women.
15. Supine/recumbent posture when feasible. Avoid severe exertion (Level 2)	Nephrotic-range proteinuria decreases by as much as 50% during recumbency. Severe exercise may increase proteinuria substantially.
16. Reduce obesity (Level 2)	Obesity apparently causes glomerulomegaly and proteinuria. Reducing obesity reduces proteinuria.
17. Decrease elevated homocysteine (Level 3)	Hyperhomocystinuria is associated with microalbuminuria and increased cardiovascular risks. Folic acid, B6, and B12 may lower homocysteine levels.
18. Antioxidant therapies (Level 3)	Antioxidant therapies of several types reduce proteinuria in both experimental models and in patients with diabetic nephropathy.
19. Sodium bicarbonate therapy to correct metabolic acidosis (Level 3)	$NaHCO_3$ therapy is not antiproteinuric; however, it blocks complement activation in the tubular compartment and, therefore, may block tubular injury caused by proteinuria. Correction of metabolic acidosis also decreases protein catabolism, which may provide general benefit.
20. NSAID therapy in severe untreatable nephrotic syndrome (Level 3)	NSAIDs (both COX 2 and nonspecific COX inhibitors) are antiproteinuric but are also nephrotoxic. Thus, NSAID use should be reserved for severe untreatable nephrotic syndrome to reduce proteinuria and achieve symptomatic relief.
21. Other therapies based on animal studies (Level 3)	Avoid excessive caffeine, iron overload. Allopurinol, pentoxifylline, mycophenolate therapy. See text.

nique and calibrated equipment, particularly if office BP is not at goal (4). Ambulatory BP monitoring (ABPM) may be useful to assess cardiovascular risk if the clinic BP is not at goal (43). Also ABPM tests for increased nocturnal BP, which may promote proteinuria progression (44). Thus, consider ABPM if the proteinuria goal is not met (discussed later). ABPM may also be useful in identifying whether BP control is better than that estimated by clinic BP. A striking example is that observed in the HOPE trial, where ABPM results showed much better BP control than suggested by the clinic BP (45).

Recommended Antihypertensive Regimens. Nonpharmacologic Therapy. Restrict salt intake and lose excess weight (discussed later). Avoid alcohol more than 2 drinks daily, vasoconstrictor nose drops and eye drops, decongestants, amphetamines, anabolic steroids, high-dose estrogen therapy, cocaine, and nonsteroidal antiinflammatory agents (NSAIDs) (4).
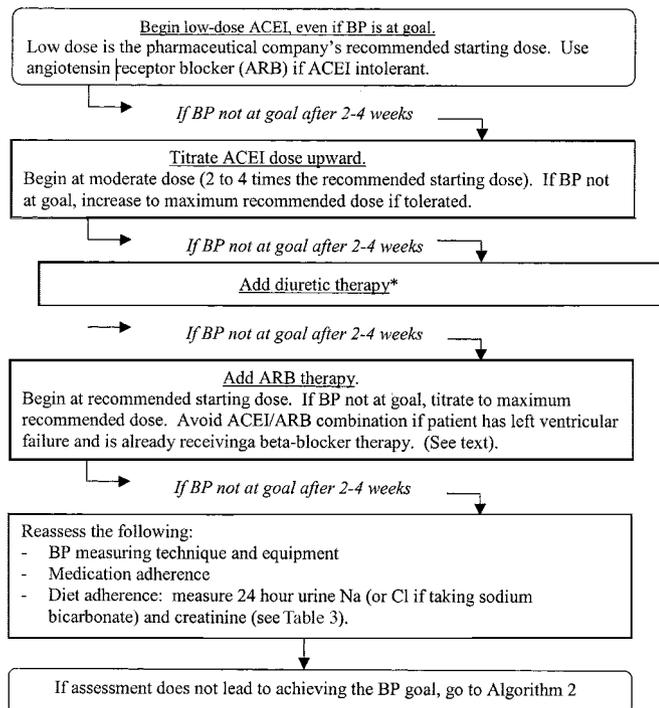
Figure 2. Algorithm 1: Initial Pharmacologic Blood Pressure Management in Kidney Disease. Assumes nonpharmacologic therapy to control BP is in place (see text) and that the patient does not have renovascular hypertension, congestive heart failure, ischemic heart disease, or hypertensive urgency. The above approach focuses on BP control in proteinuric nephropathies, but it may also be appropriate for nephrosclerosis, polycystic kidney disease, and interstitial nephropathies. *The suggestion to add diuretic before ARB is arbitrary but can be justified by the evidence that diuretic increases the antihypertensive effect of angiotensin-converting enzyme inhibitor (ACEI), is often needed in chronic kidney disease (CKD) to control fluid retention, is inexpensive, and may increase the renoprotective effects of ACEI, angiotensin receptor blocker (ARB), or the combination (93). Emphasize salt restriction in autosomal dominant polycystic kidney disease (ADPKD) rather than diuretic therapy, which may promote cyst growth (4). Details of diuretic therapy are discussed previously (4) and in the text.
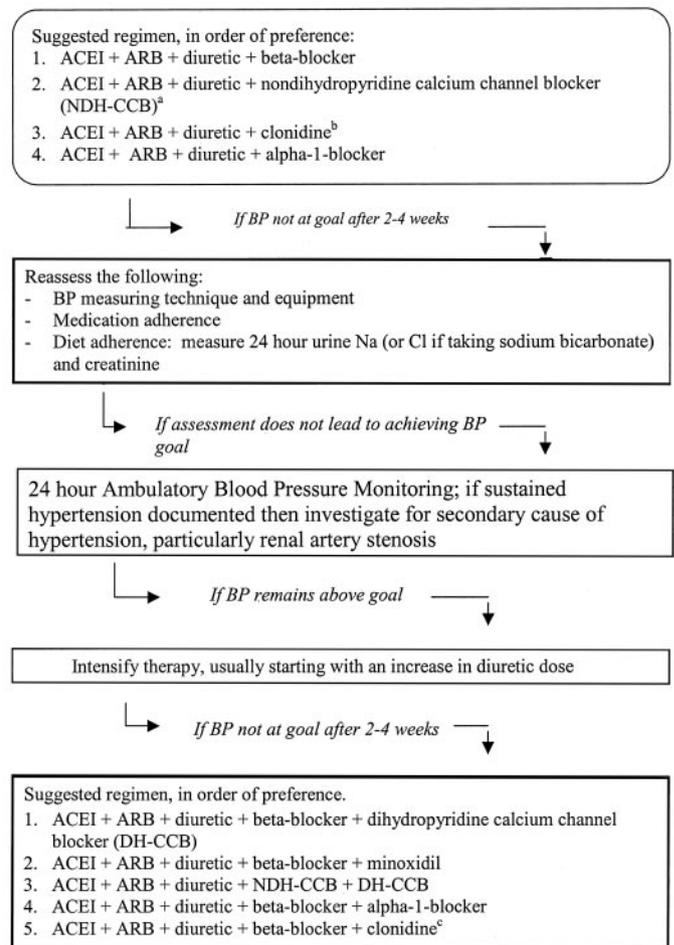
Figure 3. Algorithm 2: BP Management in Kidney Disease if Initial Therapy (Algorithm 1) Fails. (a) Diltiazem and verapamil sustained release preparations are recommended. (b) Clonidine recommended for individuals receiving insulin, because it does not importantly affect glucoregulation, and for those who have difficulty with beta-blocker (e.g., bronchospasm, cardiac conduction). (c) Beta-blocker/clonidine combination is usually well tolerated, but may cause bradycardia.

Pharmacologic Therapy. This is shown in Figures 2 and 3. The strategy is to achieve the BP goal using drugs that are antiproteinuric and attenuate angiotensin II (AngII) and aldosterone. The recommended starting point is ACEI or ARB, not diuretics. ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) showed that chlorthalidone reduced certain cardiovascular risks better than ACEI, dihydropyridine calcium channel blocker (DH CCB), or doxazosin (46). On this basis, diuretics are recommended as first-line therapy in hypertension (47). However, diuretics stimulate the renin-angiotensin system, which is probably undesirable in CKD (discussed later). Furthermore, in ALLHAT, the main benefit of diuretics was reduction in congestive heart failure and stroke in African Americans (48). Both are salt-sensitive states. Thus, unless heart failure or another edema-forming state is present, the preferred initial antihypertensive/antiproteinuric therapy in CKD is ACEI or ARB because they atten-

uate AngII effects. This should not compromise BP control in CKD. Note that about 60% of MDRD Study A patients and about 40% of the AASK patients received no diuretics, and most achieved their BP goal (11,49). Consistent with our recommendation of ACEI rather than diuretic as initial therapy of hypertension is the outcome of the second Australian National Blood Pressure Study (50), and the May 5, 2003, nationally promulgated joint statement of the American Society of Nephrology and the National Kidney Foundation recommending that ACEI, ARB, or both is the preferred initial therapy of hypertension in CKD. If diuretic therapy is needed in CKD, furosemide is recommended (4,51).

2. ACEI Therapy (Level 1)

ACEI, rather than ARB, is the initial choice because, although both ACEI (4,5,33,52) and ARB (16,17,53) are antiproteinuric and renal protective, it is unclear whether ARB are cardioprotective to the level of ACEI. A detailed discussion of this issue is beyond the scope of this work; however, we cite the two largest controlled cardiovascular trials involving ACEI or ARB. The HOPE trial ($n > 9000$ patients) showed that ramipril significantly reduced the composite endpoint of death, stroke, and myocardial infarction, and each component of the composite endpoint (54). In the LIFE trial ($n > 9000$ patients), the composite endpoint of death, stroke, and myocardial infarction was reduced significantly by losartan but of the individual components of the composite endpoint, only stroke was significantly reduced (55). Furthermore, in the recent OPTIMAAL trial ($n = 5477$ patients), which compared losartan to captopril in patients with acute myocardial infarction and heart failure (56), captopril was numerically better than losartan in reducing death, the primary endpoint ($P = 0.069$), and in reducing each of the twelve secondary cardiac and non-cardiac endpoints, although statistical significance was reached only for cardiovascular death, $P = 0.032$. In the captopril trial (57), the combined endpoint of death or ESRD was reduced significantly. By contrast, such benefit was not observed in RENAAL or the IDNT study (16,17,58). Further insight into ACE and ARB cardiovascular protection may be provided by the VALIANT, which is currently underway and much larger than HOPE or LIFE, and will compare valsartan, captopril, and the combination in patients post–myocardial infarction with evidence of heart failure, left ventricular dysfunction, or both.

Theoretical advantages of ACEI over ARB include the increased bradykinin levels during ACEI therapy, which can be additionally vasodilatory and antifibrotic (59,60). ACEI also decrease elevated plasminogen activation inhibitor-1 (PAI-1) levels. Lower PAI-1 levels are antifibrotic by promoting higher plasmin levels, which degrade matrix proteins (61). ACEI also suppresses profibrotic aldosterone (62) better than ARB (63). Both ACEI and ARB appear to reduce the rate of new-onset diabetes mellitus: ACEI, 34% reduction in HOPE (54); ARB, 25% reduction in LIFE (55). Some suggest that the lower rates of new-onset diabetes in the ACEI or ARB groups in these trials are not truly protection against diabetes but rather reflect induction of diabetes by the beta-blocker or diuretic therapy of the control group. The ALLHAT results, however, suggest true

protection against diabetes by ACEI because the chlorthalidone group had more new cases of diabetes mellitus and the ACEI group had fewer new cases of diabetes mellitus than the group receiving DH CCB (46), which does not affect glucose metabolism (64). A further ACEI advantage is that captopril, enalapril, and lisinopril are available as generics. There are no generic ARB.

Benefits of ACEI are believed to be a property of the drug class. Nevertheless, there are differences among ACEI with respect to binding to plasma proteins, tissue penetration, lipid solubility, ACE affinity, and off rate (65,66), each of which could influence efficacy. Most ACEI have relatively low plasma protein binding. Benazepril and fosinopril have higher protein binding (67). ACEI with the highest affinity for tissue ACE are benazepril, quinapril, and ramipril (67). In heart tissue, ACE is expressed mainly on endothelial cells with its catalytic site toward the vessel lumen (68). In kidney, tissue ACE is expressed mainly on the apical portion of the proximal tubular epithelial cell (69). ACEI block both plasma and tissue ACE. Tissue ACE primarily regulates BP (70). Indeed, ACE knockout mice, which lack tissue ACE but have abundant plasma ACE, are hypotensive (70).

ACEI therapy reduces proteinuria by about one third (33,52,71). At maximum recommended doses, ACEI may be more antiproteinuric than ARB (72). Concomitant use of low-salt and reduced-protein diet enhances ACEI antiproteinuria (4,73) as does diuretic therapy (74), the low BP goal (11), and statin therapy (75). The greater the proteinuria, the greater the benefits of ACEI therapy in slowing CKD progression (33). ACEI are antiproteinuric and renoprotective even in inflammatory glomerulopathies (76). ACEI is generally well tolerated in renal insufficiency (serum creatinine >3 mg/dl, reviewed in reference 4). However, greater caution is advised. Hyperkalemia can usually be controlled by restricting potassium intake, increasing diuretic therapy, and adding sodium bicarbonate therapy (4). Serum creatinine increases of up to 50% can occur with ACEI therapy. There is no need to discontinue ACEI therapy if it is a stable increase (4,11,77); however, awareness to possible renal artery stenosis is indicated.

ACEI Dose. Antiproteinuric and renoprotective effects of ACEI have been shown with four different ACEI (captopril, enalapril, benazepril, and ramipril) used in relatively low doses (78). High-dose ACEI therapy may be more antiproteinuric and more renoprotective than usual doses (4,72,79–81), although mild anemia has been reported with ramipril at 20 mg daily (82). Current trends are to use the maximum recommended dose of ACEI, if tolerated (4,11,72,79–81). Tolerance to ACEI occurs on lower-dose ACEI, which can be overcome by increased ACEI dose (83). Thus, preemptively increasing ACEI dose to tolerance may avoid undertreatment.

Choosing an ACEI. Based on reported efficacy and safety in achieving both cardiovascular and renoprotection in large patient populations, ramipril would be the ACEI of choice (11,54,84). Also to be considered is that in the nephropathy of type 1 diabetes, captopril reduced the risk of death or ESRD (57). Nevertheless, as discussed above, ACEI benefits may be a drug class effect.

3. ARB Therapy (Level 1)

ARB are recommended in ACEI-intolerant patients (cough, angioedema, or allergy [4]). Also, ARB may raise serum potassium less than ACEI (63). ARB are antiproteinuric and renoprotective in the nephropathy of type II diabetes (16,17). The American Diabetes Association recommends ARB as first-line therapy in type II diabetic patients with nephropathy (85) because no large-scale trials demonstrate efficacy of ACEI in this group (4,5). However, we and others recommend ACEI as initial therapy in the nephropathy of type II diabetes (4,53,79) because ARB may not be cardioprotective to the level of ACEI (discussed above) and may be less antiproteinuric (72). Theoretically, ARB might be more cardioprotective than ACEI therapy (86) in part because most myocardial AngII is formed by chymase, not ACE (87), and ACEI do not inhibit chymase. Myocardial chymase is in interstitial cells, mast cells, and bound to extracellular matrix (87). If ARB can efficiently penetrate myocardial interstitium, they should be more effective than ACEI in attenuating myocardial AngII effects such as myocardial hypertrophy and fibrosis. However, ARB are highly protein bound, which could affect tissue penetration. A reduced salt intake increases the antiproteinuric effects of ARB (4).

Choosing an ARB. Both losartan and inrbesartan have been shown to be both antiproteinuric and renoprotective in the nephropathy of type II diabetes mellitus (16,17). There are no generic ARB.

ARB Dose. The maximum recommended ARB dose, if tolerated, is recommended because it is more antiproteinuric (72,88) and more likely to regress left ventricular hypertrophy (89) than the usual ARB dose.

4. Combination ACEI and ARB (Level 1).

There is now clear evidence that combination ACEI/ARB therapy is more antiproteinuric than ACEI or ARB alone (72,90–94). Also combination ACEI/ARB may be more renoprotective than either drug alone as demonstrated in a recent large-scale trial in nondiabetic kidney disease (93). Therefore, early deployment of combination ACEI/ARB therapy can be recommended. The optimum antiproteinuric strategy appears to be addition of ARB to maximum ACEI in those who fail to achieve their proteinuria goal on ACEI alone (72). The theoretical benefits of combination therapy include those of ACEI therapy (increased bradykinin, decreased aldosterone, decreased AngII levels) and those of ARB therapy (blockade of AngII produced by chymase, and increased AT2 receptor activation, which may be vasodilatory, antiproliferative, and antifibrotic) (5,90,95). The VAL-HEFT study results suggested that in patients with systolic dysfunction and heart failure, addition of an ARB to beta-blocker and ACEI increases mortality. However, the longer CHARM study showed no adverse effect of combinations of ACEI, ARB, and β-blocker therapies (96). Diuretic therapy may increase the renoprotective effects of combination therapy (93). Combination ACEI/ARB therapy might be particularly effective in those with the ACE gene DD genotype where resistance to ACEI may be present. The D allele encodes for high ACE, both circulating and tissue, and

might contribute to kidney disease progression and resistance to ACEI therapy (71,97–101). A low salt intake may restore responsiveness to ACEI in the DD genotype (71). Not all studies show resistance to ACEI in DD genotypes, particularly in males (99). The reason for this difference is not clear. The incidence of hyperkalemia in combination ACEI/ARB therapy in CKD is similar to that of ACEI alone (93), even when ACEI and ARB are given in maximum recommended doses (72,92).

5. Avoid Dihydropyridine Calcium Channel Blocker (DH CCB) Therapy Unless Needed for BP Control (Level 1)

DH CCB are excellent antihypertensive agents, and a non-randomized intervention suggested that DH CCB may be antiproteinuric if good BP control is achieved (102). However, the randomized trials do not support this suggestion. In the ABCD trial, despite good BP control, nisoldipine resulted in threefold greater albuminuria rate compared with enalapril (103). In the IDNT, despite substantial BP reduction in the amlodipine group, proteinuria remained at baseline. By contrast, at the same BP level as the amlodipine group, the irbesartan group achieved a 33% reduction in proteinuria (17). In the AASK, although amlodipine achieved better BP control than ramipril or metoprolol, proteinuria increased about twofold on amlodipine therapy but generally remained at or below baseline levels on ramipril or metoprolol therapy (11). These results confirm previous observational studies suggesting that DH CCB are not antiproteinuric and may actually promote proteinuria and more rapid CKD progression (10). Also, the AASK showed that, compared with ACEI and beta-blocker therapy, DH CCB increased the risk of the composite endpoint of doubling of serum creatinine, ESRD, or death, compared with ACEI or beta-blocker (10). If DH CCB is needed for BP control, concomitant use of ARB (16), ACE (102), combination ACEI/ARB (93), or beta-blocker may mitigate the vasodilatory effects of DH CCB to cause glomerular hypertension (11) and, apparently, promote proteinuria. This strategy may also limit RAS stimulation by DH CCB.

6. Beta-Blocker Therapy (Level 1)

The AASK showed that sustained-release metoprolol had antiproteinuric effects nearly equal that of ramipril and better than that of amlodipine (11). Sympathicoplegic effects may be involved (104).

7. Control Protein Intake (Level 1)

In proteinuric renal diseases, reducing protein intake from usual levels (about 1.0 to 1.5 g/kg ideal body weight per d) to about 0.7 g/kg ideal body weight per d decreases proteinuria about 50% (4), even with nephrotic-range proteinuria (105). Reduced protein intake lowers fibrinogen levels (105), possibly reducing cardiovascular risk (4), and inhibits glomerular hypertrophy (106), possibly contributing to renoprotection (4). In patients with proteinuria < 250 mg/d, the low-protein diet does not reduce proteinuria; however, it does slow the progression from minor to major proteinuria, which is a strong risk factor for CKD progression (4). Thus, the low-protein diet is

recommended even in low-level proteinuria (4). Substituting soy proteins for animal proteins is antiproteinuric and inhibits glomerulosclerosis (107,108). Soy proteins are high in antioxidants (isoflavones) and L-arginine, a nitric oxide donor, which may be renoprotective. A reduced protein diet is recommended in both diabetic and nondiabetic CKD (4,109). However, malnutrition must be avoided (110). To monitor dietary protein intake, we recommend measurement of 24-h urine urea excretion (4).

8. Restrict NaCl Intake (Level 2)

High salt intake (*e.g.*, 200 mmol NaCl/d or 4.6 g sodium/d) can completely override the antiproteinuric effects of ACEI or NDH CCB (4). The average adult North American daily dietary NaCl intake is 170 mmol or 3.9 g of sodium, or 10 g of NaCl. Counseling the patient in dietary salt restriction is usually necessary. We recommend in CKD that dietary salt intake be monitored with 24-h urine collection at 2- to 6-mo intervals, particularly if hypertension, edema, or heart failure are present. Sodium bicarbonate usually does not contribute importantly to sodium retention and should not be included in the estimates of salt intake. Because virtually all dietary chloride is as NaCl, urine chloride rather than urine sodium should be measured to estimate NaCl intake for patients receiving sodium bicarbonate therapy (4). Urine chloride of 88 mEq/d corresponds to a 2.0-g sodium diet. Concomitant KCl therapy must be taken into account when interpreting urine chloride levels.

9. Control Fluid Intake (Level 2)

A retrospective analysis of the MDRD Study A showed that each 1% greater urine volume was associated with a 1% greater urine P/C ratio (111). Higher urine volume was associated with higher BP, lower serum sodium, and frankly hypotonic urine, suggesting excessive fluid intake, not renal sodium and water wasting, as the mechanism of the increased urine volume. Also, higher fluid intake was associated with faster GFR decline (111). We found no benefit of a high fluid intake in CKD (111).

10. NDH CCB Therapy (Level 2)

This class includes diltiazem and verapamil. NDH CCB are antiproteinuric and may be renoprotective (4,10). Sustained release forms are recommended. Verapamil is available as a generic. Combination NDH CCB and DH CCB is potent antihypertensive therapy (112,113), which should be considered when quadruple therapy is required (Figure 3).

11. Control Blood Lipids (Level 2)

Controlled clinical trials show an antiproteinuric effect of lipid-lowering therapy, particularly statins (75,114–117) and niceritrol, a nicotinic acid derivative (118). The mechanisms may include decreasing oxidative stress and prevention of lipid-induced podocyte damage from decreased nitric oxide production (119). The maximum recommended statin dose may be the appropriate starting dose, based on the remarkable benefits and safety of 40 mg/d simvastatin in the MRC/BHF study (120). This study also suggested that there may not be a

blood lipid threshold for cardiovascular benefit of statin therapy (121). Combining ACEI and statins may further reduce proteinuria (122). Note that fenofibrate increases serum creatinine by as much as 35% because of increased creatinine production (29). Lisinopril therapy may contribute to lipid control by effects independent of proteinuria reduction (123).

12. Aldosterone Antagonists (Level 2)

In stroke-prone hypertensive rats, spironolactone prevents the progressive proteinuria independent of BP control (124). In CKD, 25 mg/d spironolactone added to ACEI therapy for 4 wk reduced mean proteinuria from 3.8 g/d to 1.8 g/d (125), perhaps by blocking the profibrotic effects of aldosterone (126). Combination spironolactone and ACEI therapy can cause serious hyperkalemia (127). Eplerenone (currently under study) is similar to that of spironolactone, but with fewer side effects (128), and is antiproteinuric (129,130).

13. Smoking Cessation (Level 2)

Cigarette smoking is associated with proteinuria and faster progression of CKD of all types (131,132). Cigarette smoke condensate worsened experimental renal injury and increases proteinuria (133).

14. Avoid Hormone Replacement Therapy in Postmenopausal Women (Level 2 for Kidney Protection, Level 1 for General Benefit)

CKD occurs less frequently and progresses more slowly in premenopausal women compared to men (4). However, estrogen replacement therapy or estrogens contained in oral contraceptives are associated with microalbuminuria (134). Combination estrogen and progestin therapy also is not recommended because it increased cancer and cardiovascular disease in the Women's Health Initiative study (135). Whether estrogen therapy alone can be justified in younger menopausal women, particularly those with hysterectomy, has not been determined (136).

15. In Heavy Proteinuria, Supine or Recumbent Posture Is Encouraged, Severe Exertion Is Discouraged (Level 2)

Exercise and erect posture increase proteinuria. In experimental nephritis, severe exercise worsens proteinuria (137). Nephrotic-range proteinuria decreases by as much as 50% during recumbency (138). In severely nephrotic patients, encouraging recumbent posture may decrease proteinuria and raises serum albumin. This could improve edema, hyperlipidemia, nutrition, and Ig depletion. However, there should be sufficient exercise (for example, 100 min per week of walking at a moderate pace [2–3 miles/h] [139]), and measures to avoid thrombosis such as low-dose aspirin therapy (4).

16. Reduce Obesity (Level 2)

Obesity is associated with glomerulomegaly, focal and segmental glomerulosclerosis (FSGS), and proteinuria that can be progressive (140). Reducing obesity can reduce proteinuria

(140–142) but may not affect progression of primary glomeru-lopathies (143).

17. Decrease Elevated Homocysteine (Level 3)

Elevated plasma homocysteine is associated with microalbuminuria (4) and increased cardiovascular risk (144). We recommend 5 mg of folic acid, 50 mg of Vitamin B_6, and 1 mg of Vitamin B_{12} daily, which is the vitamin intervention of the NIH multicenter trial in kidney transplant patients (FAVORIT). During folic acid therapy, B_{12} levels must be normal to avoid neurologic damage (4).

18. Antioxidant Therapies (Level 3)

Antioxidants, d-α-tocopherol (145), Vitamin C (146), α-lipoic acid (147), and selenium (148) decrease proteinuria in experimental kidney disease, and a 50% reduction of proteinuria was noted in diabetic nephropathy after 3 mo of α-lipoic acid therapy (147). However, Vitamin E does not decrease cardiovascular risks (149).

19. Sodium Bicarbonate (NaHCO₃) to Correct Metabolic Acidosis (Level 3)

$NaHCO_3$ is not antiproteinuric, but it may block alternative complement pathway in the renal tubules in nonselective proteinuria. Oral bicarbonate therapy sufficient to raise urine pH to >5.0, the optimum pH for alternative pathway activation, decreases complement activation in the tubular compartment in proteinuric humans (150) and rats (151). Metabolic acidosis correction also decreases protein catabolism, which may benefit proteinuric renal disease (152).

20. NSAIDs in Severe Untreatable Nephrotic Syndrome (Level 3)

NSAIDs, both COX 2 and nonspecific COX inhibitors, are antiproteinuric but nephrotoxic in humans (153) and should be avoided in kidney disease (4,77). However in untreatable severe nephrotic syndrome, NSAIDs can substantially reduce proteinuria and provide symptomatic relief (154).

21. Other Therapies Based on Animal Studies (Level 3)

(1) Avoid excessive caffeine consumption. Obese diabetic rats develop heavy proteinuria if fed caffeine, equivalent to 3 cups of coffee daily in humans (155). (2) Avoid iron overload. In experimental proteinuric renal disease, iron depletion reduces proteinuria and kidney injury (156). Thus, iron overload might worsen proteinuria. Iron catalyzes formation of free oxygen radicals and reactive iron-oxygen complexes (156). Low plasma transferrin, which favors iron glomerular filtration, is an independent risk factor for CKD progression (157). Transferrin induces C3 biosynthesis by human proximal tubular epithelial cells in culture (158). In proteinuric CKD, filtration of iron-bearing transferrin could contribute to tubular injury. (3) Allopurinol therapy to reduce elevated serum uric acid levels (Level 3). Hyperuricemia in the rat induces proteinuria and CKD, perhaps by activation of the renin-angiotensin system and induction of COX-2 (159). Allopurinol or a urico-

suric agent attenuates these changes (160). Also, allopurinol may improve endothelial cell dysfunction in humans (161). (4) Pentoxifylline. In rats with 5/6 nephrectomy, this drug prevented progression of proteinuria and renal disease. The mechanism may involve suppression of mitogenic and profibrotic genes (162). (5) Mycophenolate mofetil (MMF). This widely used immunosuppressive drug is antiproteinuric and renoprotective in the 5/6 nephrectomy model (163). The benefit of MMF may be related to suppression of nonspecific trapping by the kidney of circulating inflammatory cells (4, 163)

Kidney Conditions for which Antiproteinuria Therapy Is Usually Indicated

Any patient with a CKD is a candidate for antiproteinuric therapy, even in those with low-level proteinuria. CKD with low-level proteinuria generally manifests slow GFR decline, but progression of proteinuria during follow-up is the rule (7,11,35). Thus, those with low level proteinuria and slow GFR decline tend to become those with greater proteinuria and greater GFR decline.

The ability of antiproteinuric therapy to slow GFR decline has been documented at proteinuria levels starting as low as 500 mg/d (33). A plausible explanation for the benefit of antiproteinuric therapy, even at low-level proteinuria, is that current methods underestimate the actual protein load to the proximal tubule by about 2.0 g/d (31,32). The underestimate occurs because filtered plasma proteins are extensively absorbed, degraded, and then largely excreted in urine in forms not measured by clinical methods (31,32). Thus interventions that reduce only microalbuminuria (Table 4) may have greater benefit than would be inferred from the magnitude of microalbuminuria reduction. Microalbuminuria is a risk factor for progression of autosomal-dominant polycystic kidney disease (ADPKD) (38). However, there is no clear rationale for suggesting that reducing microalbuminuria in ADPKD would slow progression. Nevertheless, because microalbuminuria is also a cardiovascular risk factor (164), we suggest that it is appropriate to use antiproteinuric therapies in ADPKD, especially Level 1 therapies. Patients with directly treatable forms of nephropathy such as lupus nephritis should also be managed with concomitant antiproteinuric therapies to hasten resolution of proteinuria and thereby lessen kidney damage (165). Those with congenital solitary kidney or solitary kidney that was acquired in childhood should be considered at least for Level 1 antiproteinuric therapies (166) because the only renal diagnosis in 27 patients in the MDRD Study A was solitary kidney (7).

Chronic Kidney Diseases for which Antiproteinuric Therapies Usually Are Not Indicated

Aggressive use of kidney protective therapies are not recommended in CKD at low risk for ESRD (4). These include steroid-responsive minimal change disease, a solitary kidney that is normal and acquired in adulthood (e.g., a kidney donor),

hereditary nephritis, or thin GBM disease in the normotensive adult whose only renal manifestation is microscopic hematuria, and in elderly patients with idiopathic and moderately elevated serum creatinine (1.3 to 2.0 mg/dl) and minor proteinuria (<1 g/d) that have been stable for a least 1 yr.

Practicality of a Multiple Risk Factor Intervention for Proteinuria

Our experience suggests that most of the Level 1 and Level 2 interventions are achievable in the majority of patients with chronic proteinuria. A strategy that appears to help our patients achieve compliance is to provide written documentation for our recommendations (4). We suggest that the current work could serve this purpose, especially Table 4. With regard to drug interactions, there is no *a priori* reason to believe that any of the antiproteinuria interventions antagonize any of the others. Indeed, there is already evidence that specific combinations have at least additive effects (see discussion of BP, ACEI, ARB, statins, diet, aldosterone antagonists and NDH CCB). Given the benefits of even modest proteinuria reductions in CKD progression (4), Figure 1, a broad therapeutic approach to antiproteinuric therapy seems prudent.

Acknowledgment

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