Progressive renal and cardiovascular disease: Optimal treatment strategies

Principal discussant: Matthew R. Weir
University of Maryland Medical System, Baltimore, Maryland, USA

CASE PRESENTATION

A 54-year-old white man was referred by his internist for evaluation of a serum creatinine of 1.9 mg/dL and nephrotic-range proteinuria (3.6 g/24 h). The patient had an approximate 10-year history of non–insulin-dependent diabetes mellitus and a 15-year history of hypertension. The patient also reported that he had a history of a mildly enlarged heart and an elevated cholesterol level but denied previous visual abnormalities, chest pain, shortness of breath, or peripheral edema. He reported that he has always been stocky but had gained approximately 10 pounds during the previous year. He stated that his glucose levels were reasonably controlled between 130-200 mg/dL with diet and oral medication, but that his blood pressure was hard to treat and his physician had prescribed many different medicines.

On physical examination, he was a middle-aged, overweight white male who was 5’10” tall and weighed 230 pounds. His blood pressure was 162/98 mm Hg and did not vary between arms or with position. Funduscopic examination revealed arteriolar narrowing, a rare microaneurysm, and two small hemorrhages in his left retina. His lungs were clear. Cardiovascular examination disclosed normal carotid upstrokes, a regular heart rate and rhythm, an S4 gallop, and 1+ peripheral pulses without pedal edema. His abdominal examination was remarkable for truncal obesity and no hepatosplenomegaly or vascular bruits. He had intact sensation and motor function of all four extremities as well as normal deep tendon reflexes.

Laboratory testing revealed a serum potassium of 4.8 mEq/L; BUN, 26 mg/dL; serum creatinine, 1.9 mg/dL; hematocrit, 38.8%; serum cholesterol, 287 mg/dL; 24-hour urinary protein, 3.6 g; and a creatinine clearance of 52 mL/min. His serum albumin was 2.2 g/dL. The urine sediment showed 0-2 red blood cells/high-power field and hyaline casts. Serum protein electrophoresis and urine protein electrophoresis did not reveal paraproteins. Serologic evaluation for other causes of renal dysfunction and proteinuria was negative.

The purpose of the consultation was to recommend the optimal treatment strategy for treating the blood pressure and proteinuria and for inhibiting his progressive renal disease.

DISCUSSION

Dr. Matthew R. Weir (Head, Division of Nephrology, and Director, Clinical Research Unit, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA): This case exemplifies the problem that clinicians face in the management of patients with hypertension and early renal insufficiency. What is the best strategy for preventing progression of both atherosclerotic cardiovascular disease and chronic renal failure? In my discussion, I will focus on the most relevant issues in the management of this patient. Among these, I will review the concept of renal autoregulation because it provides a rationale for optimal levels of blood pressure and for which medications might need to be prescribed. An understanding of renal autoregulation also provides a framework for understanding (1) the relationship between blood pressure and renal injury, (2) the option of intensive control of blood pressure, and (3) the particular role of drugs that block the renin-angiotensin-aldosterone system (RAAS). I will conclude with some comments about the importance of proteinuria as a prognostic and modifiable risk factor for cardiovascular and renal disease progression and why preventing renal failure is important for reducing the risk of cardiovascular events. These topics will provide a framework for an understanding of the optimal therapeutic strategies.
for delaying progression of renal and cardiovascular disease in the patient with incipient nephropathy.

Risk factors

Multiple risk factors affect the development of cardiovascular disease and progression of renal disease in patients with early renal insufficiency. These include non-modifiable risk factors such as genetics, but more important, they include modifiable risk factors such as glycemic control, dietary protein and salt intake, blood pressure, dyslipidemia, hyperhomocysteinemia, proteinuria, and cigarette smoking [1–3]. For the sake of clarity and brevity, I will focus here on factors related to blood pressure and proteinuria both as interdependent and independent modifiable risk factors for progression of renal insufficiency and ultimately cardiovascular disease.

Renal autoregulation

Renal autoregulation is the physiologic mechanism whereby glomerular capillary pressure varies by only about 5 mm Hg over a wide range (60 to 150 mm Hg) of alterations in the renal perfusion pressure. Increasing systemic blood pressure induces a myogenic reflex that stimulates smooth muscle cells in the afferent glomerular arterioles to initiate a reflex contraction that reduces renal blood flow [4]. A second mechanism that facilitates preglomerular vasoconstriction is the increased delivery of sodium chloride to the distal nephron, which stimulates a tubuloglomerular feedback mechanism that causes afferent arteriolar vasoconstriction [4, 5]. As a consequence of these two mechanisms, autoregulation of glomerular capillary pressure is carefully maintained within a tight range, thereby assuring stable glomerular filtration while simultaneously reducing the likelihood of mechanical injury to the delicate glomerular capillary vessels. Should glomerular capillary perfusion fall below the autoregulatory threshold of approximately 60 mm Hg because of systemic hypotension, then increasing activation of the RAAS enhances efferent glomerular arteriolar vasoconstriction and facilitates maintenance of glomerular capillary pressure in a range that is necessary for filtration [6].

Adequacy of control of glomerular capillary pressure is likely one of the most important factors in reducing risk for progression of renal injury (Fig. 1). Control of glomerular capillary pressure works well within the normal autoregulatory range of the kidney (60-150 mm Hg) [4–7]. Patients with pressures exceeding 150 mm Hg, or patients with damage to the autoregulation capacity of the afferent glomerular arterioles (as can occur in a patient with diabetes and vascular disease or who ingests a high-protein diet) can be vulnerable to injury from levels of systemic blood pressure within the so-called “normotensive” range (125-140 mm Hg). This level of blood pressure exceeds the usual range of pressures in the glomeruli and therefore can cause glomerular capillary hypertension in patients with damaged autoregulatory capacity. These circumstances, coupled with the increased vasodilation of the afferent glomerular arteriole in diabetes mellitus [8], markedly increase glomerular capillary pressure and the risk for injury. The increasing pressure can result in mechanical stretch and strain within the delicate glomerular capillary vascular beds and mesangial cells; this stress in turn results in an injury and repair response largely mediated by fibrogenic cytokines and angiotensin II [9]. Repetitive injury results in scarring, inflammation, and glomerulosclerosis and ultimately leads to loss of renal function. Subsequent loss
The Modification of Diet in Renal Disease (MDRD) study demonstrated important benefits of rigorous control of blood pressure in patients with non-diabetic renal disease and proteinuria (Fig. 2) [11, 15]. The proteinuric patients (defined as patients with \( > 1 \) g of proteinuria/day) demonstrated substantial benefits with better blood pressure control (125/75 mm Hg), perhaps because the proteinuria was a reflection, in part, of impaired renal autoregulation and glomerular capillary hypertension. Bakris demonstrated a nearly linear relationship between systolic blood pressure achieved with pharmacotherapy and rate of loss of renal function each year in an evaluation of non-diabetic patients and diabetic patients, both groups with renal disease [16]. Likewise, Jafar et al noted an increased risk for doubling of serum creatinine or reaching end-stage renal disease in a meta-analysis of patients with non-diabetic renal disease as a function of systolic blood pressure achieved with pharmacotherapy [17]. These and other clinical observations have provided important insights for establishing goals for optimal levels of blood pressure in patients with renal disease.

These analyses also have indicated that an average of 3 to 4 medications (or more) are needed to achieve lower, more intensive blood pressure control (125-130 mm Hg systolic) in patients with renal disease. However, these studies have not provided insight as to how early in the course of renal failure one should intensify treatment so as to optimally prevent progressive renal injury. As I will discuss in a moment, several clinical trials in diabetes will discuss in a moment, several clinical trials in diabetes indicate that the earlier the intervention, preferably in the so-called “pre-hypertensive stage” (blood pressure less than 130/80 mm Hg), the greater the likelihood of preventing progressive renal injury (as a reflection of preventing progression from microalbuminuria to clinical proteinuria). Needless to say, blood pressure is more easily controlled with less medication when the untreated systolic blood pressure is 130-140 mm Hg. Possibly, earlier treatment will prevent the need for more medication in subsequent years. This hypothesis is an important consideration that needs to be tested in clinical trials.

Proteinuria and renal injury

Evidence from clinical trials indicates that proteinuria is an independent predictor of progression of renal disease [15, 18, 19]. The severity of baseline proteinuria is an important predictor, not only of the rate, but also of the likelihood, of loss of renal function [15, 17]. Clinical trials also have demonstrated that the reduction in protein excretion with antihypertensive agents or dietary protein restriction correlates directly with the reduction of the rate of loss of renal function [20, 21]. Newer clinical trials indicate that the net reduction in proteinuria achieved with antihypertensive therapy ultimately predicts the rate of loss of renal function over time; the
initial severity of baseline proteinuria does not [19, 22]. These observations indicate that proteinuria is a modifiable risk factor of progressive renal disease. However, in clinical practice, attempting to reduce or abolish proteinuria is not common, as more emphasis has been placed on reducing blood pressure.

Microalbuminuria is an important predictor of subsequent risk for nephropathy in both type 1 and type 2 diabetes [23–25]. Its presence also is predictive of cardiovascular mortality in diabetic and non-diabetic patients [23–25]. Microalbuminuria likely reflects evidence of a systemic vasculopathy, with damage to the glomerular vascular bed being one of the first areas of damage that is clinically evident. Microalbuminuria also can represent evidence of glomerular capillary hypertension and hyperfiltration, perhaps due to loss of afferent glomerular arteriolar vasoconstriction and dysfunctional autoregulation of glomerular capillary blood pressure. Thus, the presence of microalbuminuria, like proteinuria, indicates the patient with a greater risk of developing both progression of renal disease and cardiovascular events.

Excessive proteins filtered by the glomerulus lead to an increase in both renal tubular cell reabsorption of proteins and overall protein catabolism. Remuzzi and Bertani have suggested that excessive renal tubular cell reabsorption of proteins activates vasoactive and inflammatory genes, thereby resulting in the synthesis and elaboration of several substances within the interstitium. These substances in turn result in fibrogenesis, collagen production, and scarring (Fig. 3) [26]. Glomerular capillary hypertension would likely accelerate this process, as it results in increased glomerular permeability to proteins and, at the same time, greater mechanical stretch and strain within the glomeruli and surrounding mesangial cells. This process results in greater production of angiotensin II, transforming growth factor-β1, and a subsequent increase in collagen synthesis [9, 26]. Consequently, both glomerular hyperfiltration and excessive tubular reabsorption of proteins are likely additional causes of renal injury.

The reduction of proteinuria is important in patients both with non-diabetic and diabetic renal disease. The Ramipril Efficacy in Nephropathy (REIN) study was in part designed to assess the relationship between proteinuria and progression of renal disease in non-diabetic patients. Investigators noted that the mean rate in decline in GFR of the patients whose urinary protein excretion was between 1 and 3 g/day was one-third that of the patients whose urinary protein excretion was greater than 3 g/day [18]. Moreover, this study also noted that the use of the ACE inhibitor ramipril was the only time-dependent variable that predicted the slower rate in decline of GFR. The report thus concluded that renal protection was linked to a reduction in urinary protein excretion and not blood pressure.

Jafar et al conducted a meta-analysis of 1860 patients enrolled in 11 randomized controlled trials comparing the effects of multidrug antihypertensive regimens, including or not including ACE inhibitors, on the progression of non-diabetic renal disease [17]. They demonstrated that the level of proteinuria achieved with pharmacotherapy was predictive of the rate of loss of renal function.
This finding indicated that urinary protein excretion was a modifiable risk factor for the progression of renal disease. It is interesting that they also noted that the beneficial effect of ACE inhibitors in retarding progression of renal disease remained significant, even after they controlled for the level of urinary protein excretion achieved.

The Collaborative Study Group demonstrated that only patients with type 1 diabetes who achieved at least a 50% reduction in urinary protein excretion derived benefit, defined as subsequent stabilization of renal function [27]. This study indicated that intensive antiproteinuric strategy, concurrent with an optimal blood pressure strategy, is important in reducing the likelihood of progressive nephropathy in type 1 diabetics. Information regarding the importance of reducing proteinuria on the rate of progression of renal disease in patients with type-2 diabetes is inconsistent, in large part because of the small size and short duration of the studies to date (abstract; Walker et al, *J Am Soc Nephrol* 3:339, 1992) [28–32].

With the completion of the Irbesartan Diabetic Nephropathy Trial (IDNT) and the Reduction of Endpoints in NIDDM with the Angiotensin II type-1 Antagonist Losartan (RENAAL) trial [33, 34], more information is now available to correlate the importance of reduction in proteinuria on renal outcomes in patients with type-2 diabetes and incipient nephropathy. Although not completely analyzed yet, both studies likely will show a direct correlation between the antiproteinuric effects of the angiotensin II receptor blocker and protection of renal function.

**Implications of lower blood pressure goals and proteinuria on antihypertensive medication selection**

Lower blood pressure goals in the presence of microalbuminuria or proteinuria are important considerations for treatment. Reaching the desired systolic blood pressure goal frequently requires one drug for every 10 mm Hg of systolic blood pressure reduction. The presence of microalbuminuria or proteinuria requires specific therapy including drugs that block the renin-angiotensin system, non-dihydropyridine calcium channel blockers, and restriction of dietary sodium and protein. Proteinuria and hypertension are separate and independent yet intertwined modifiable risk factors for progression of renal insufficiency.

Angiotensin-converting-enzyme (ACE) inhibitors attenuate the rate of progression of renal disease both in type 1 diabetics [13, 26] and patients with non-diabetic renal disease [17]. The benefit of ACE inhibitors likely is derived from antihypertensive/antiproteinuric properties and the anti-mitogenic/anti-fibrogenic effects of angiotensin II antagonism [9]. The meta-analysis by Jafar et al demonstrated the important benefit of ACE inhibitors in patients with non-diabetic renal disease [17]. These results are in concert with the observation by the Collaborative Study Group of the advantages of the ACE inhibitor captopril versus conventional therapy in preventing renal insufficiency in type-1 diabetes [27]. However, similar conclusive data showing nephroprotection are not available with ACE inhibitors in proteinuric type 2 diabetic patients with incipient nephropathy.

Two placebo-controlled studies indicated that ACE inhibitors could prevent the progression of microalbuminuria to macroproteinuria in “normotensive” (systolic 125-130 mm Hg) type-1 and type-2 diabetic patients [35, 36]. In both studies, modest but significant reductions in blood pressure occurred with ACE inhibitor therapy. Consequently, one cannot be sure whether the prevention of macroproteinuria is simply a blood pressure effect, a unique effect of the ACE inhibitor, or both. These studies also indicated that earlier therapeutic intervention, even with treatment of blood pressure in the “normotensive” range, could prevent the development of macroproteinuria.

In the Heart Outcomes Prevention Evaluation (HOPE) trial, patients with cardiovascular disease, type 2 diabetes, or both demonstrated important cardiovascular risk reduction when blood pressure was reduced below a traditionally acceptable level of 139/79 mm Hg by adding the ACE inhibitor ramipril, 10 mg/day, to the medical regimen [37]. Thus, earlier and more intensive efforts to control blood pressure with ACE inhibitors can have important cardiovascular benefits in patients with type 2 diabetes.

Six studies have compared ACE inhibitor versus non-ACE-inhibitor therapy in proteinuric patients with type 2 diabetes with two to five years of follow-up (abstract; Walker et al, *J Am Soc Nephrol* 3:339, 1992) [28–32]. Unfortunately, there are fewer than 400 patients in all six studies combined. Only one of these six studies showed significant differences between the decline in GFR in patients treated with or without ACE inhibitors [28]. Thus, one can only extrapolate the benefits of an ACE inhibitor in proteinuric patients with type 2 diabetes based on experience in type 1 diabetic patients or patients with non-diabetic renal disease.

Whether the benefits of ACE inhibitors in preventing or protecting against worsening of renal disease can be generalized to other classes of drugs that block the renin-angiotensin system can now be addressed with the results of two recently completed trials. The RENAAL and IDNT trials provide evidence that an angiotensin II type-1 receptor blocker protects against the progression of renal disease in type 2 diabetics, independent of blood pressure effects [33, 34]. Both these studies demonstrated statistically significant risk reduction for doubling of serum creatinine, end-stage renal disease (ESRD), and death (the primary composite end point of the trials) compared to traditional (diuretic, beta blocker, vasodila-
Fig. 4. Annual cardiovascular disease mortality for the general population (GP) and dialysis population based on gender, race, and age. The data were generated from the National Center for Health Statistics (1993) and from the United States Renal Data System Report of 1994-1996 [41].
Of those patients with doubled serum creatinine, 50% underwent dialysis within one year, and 25% were dead within three years. Consequently, any strategy that is effective in preventing a doubling of serum creatinine also will likely be beneficial in reducing the risk of cardiovascular events.

**Summary**

Let me summarize. I argue that optimal strategies to provide more effective prevention or protection against renal disease progression should focus on earlier and more intensive blood pressure reduction, proteinuria reduction (preferably eliminated), and renin-angiotensin-aldosterone system pharmacologic blockade. These are modifiable risk factors for development of progressive renal insufficiency. I believe that the weight of medical evidence supports the need for earlier and more intensive efforts to control blood pressure below traditionally acceptable levels (less than 130/80 mm Hg), particularly if evidence of microalbuminuria or proteinuria is present. We need to identify patients at risk earlier, use a relatively large number of drugs to achieve our goals, and better educate the public and clinicians of the need for earlier, more rigorous efforts for the control of all risk factors. Efforts at encouraging a healthier lifestyle by reducing smoking, reducing a high-salt and high-saturated-fat diet, and by increasing the frequency of exercise can help reduce cardiovascular risk and improve the efficacy of antihypertensive, antiproteinuric medications.

**QUESTIONS AND ANSWERS**

**Dr. Nicolaos E. Madias (Executive Academic Dean, Tufts University School of Medicine, Boston, Massachusetts):** You indicated that for certain groups with renal disease, a lower target for blood pressure control might apply, that is, lower might be better than low. Could you give us more specific recommendations about target blood pressures for a range of groups within the renal disease population?

**Dr. Weir:** I can give you some of my own thoughts, but I can’t back them up with any data, because clinical trials have not been completed that pursued either systolic blood pressure below 125 mm Hg or specific treatment for extinguishing proteinuria or albuminuria. With regard to the patient with chronic renal insufficiency with either the presence of micro- or macroalbuminuria/proteinuria, my clinical efforts are geared toward at least getting the systolic pressure into the 120s and extinguishing the proteinuria or albuminuria. If I am unsuccessful in attaining those two goals, then I continue to add specific medications to further lower the systolic pressure and extinguish the proteinuria, much in the same way that a cardiologist would advance ACE inhibition to reach doses demonstrated to be effective in the risk reduction trials in heart failure.

**Dr. Madias:** Despite reaching target blood pressure, many patients with renal disease continue to have significant proteinuria. Could you comment on additional strategies for controlling proteinuria, such as using “mega doses” of ACE inhibitors, combining ACE inhibitors with angiotensin II type 1 receptor antagonists, and the use of aldosterone antagonists?

**Dr. Weir:** The use of large or “mega” doses of ACE inhibitors is a fascinating area. In general, clinicians, and even many nephrologists, are concerned about using higher doses of ACE inhibitors, even doses in the approved dosing range, let alone “mega” doses. This is particularly true in patients who have early evidence of renal disease (serum creatinine, 1.4-2.0 mg/dL) despite demonstrated efficacy and safety of these drugs in clinical trials. Small studies have shown that titrating ACE inhibitors to higher doses can effectively reduce proteinuria [44]. This is also a function of higher doses providing more effective reduction in blood pressure. Adding an angiotensin II receptor blocker, thiazide diuretics, or a non-dihydropyridine calcium antagonist also can sometimes potentiate the antiproteinuric effects of ACE inhibitors. Several small clinical trials have indicated the benefit of this strategy (abstract; Hemmelder et al, J Am Soc Nephrol 6:420, 1995) [40, 45]. Again, how much the further reduction in blood pressure plays a role in decreasing proteinuria remains open to question. Also not resolved is the mechanism of incremental reduction of proteinuria: are there specific effects on the glomerular basement membrane, or are the additive effects of these specific drugs purely related to reducing systemic and glomerular capillary pressure?

Perhaps more demanding of our attention is the clinical importance of modifying dietary salt consumption. The scientific literature clearly indicates that the antiproteinuric and antihypertensive effects of all drugs are compromised by increasing dietary salt consumption (even in the physiologic range) [46–48]. Consequently, efforts at modifying salt consumption should always be part of every antiproteinuric strategy. Whether adding a thiazide diuretic, or another drug like an angiotensin II receptor blocker, or using higher doses of ACE inhibitors or angiotensin II receptor blockers would render the patient more tolerant to the hypertensive and proteinuric effects of higher dietary salt intake needs to be tested in clinical trials. Perhaps this is another reason why higher doses of ACE inhibitors and angiotensin II receptor blockers (in the approved dosing range, or possibly above) need to be considered in clinical practice as part of a strategy for facilitating better reduction in both blood pressure and proteinuria. Modifying dietary protein intake also might help reduce proteinuria, but it raises concern about adequacy of nutrition and requires expert nutritional counseling.

Another area of interest is the pharmacologic block-
ade of aldosterone. Some small clinical studies indicate that aldosterone blockade and ACE inhibition have additive antiproteinuric effects (abstract; Epstein et al, Am J Coll Cardiol 39(Suppl 4): 249A, 2002). This information needs to be substantiated in future clinical trials.

Dr. Madias: Although we have been using ACE inhibitors for many years, it might well be that we are far from knowing how to use them optimally. We tend to use virtually the same doses for a very wide range of clinical settings—asymptomatic hypertension, hypertension with left-ventricular hypertrophy, congestive heart failure, diabetic microalbuminuria, overt diabetic nephropathy, and advanced renal disease. We might find that widely different doses of ACE inhibitors are required for optimal response in various clinical settings.

Dr. Weir: Your point is excellent. All the dosing ranges have been driven by clinical trials focusing on blood pressure reduction. There might be other clinical disease states that require different dosing strategies. As I mentioned earlier, in patients with systolic heart failure, higher doses of ACE inhibitors than necessary to improve circulatory hemodynamics have demonstrated reductions in cardiovascular morbidity and mortality [49].

Dr. John T. Harrington (Dean, Tufts University School of Medicine): What’s the evidence in humans that proteinuria means an abnormality in glomerular capillary pressure regulation? Second, how much of the effect of angiotensin II blockade is hemodynamic, and how much is a nonhemodynamic effect?

Dr. Weir: Those two questions are excellent. I am not sure that microalbuminuria, in and of itself, indicates the presence of glomerular capillary hypertension. I am suspicious that it indicates either vasculopathy, inadequate renal autoregulation, or possibly both. How to quantify the contribution of each for a given patient is not yet known. I mention this to alert the clinician that the presence of microalbuminuria suggests a need for better blood pressure control (to less than 130 mm Hg systolic) and a therapeutic strategy designed to extinguish the microalbuminuria.

One important consideration as part of a therapeutic strategy is blocking the activity of the RAAS. How is the RAAS involved in the development of vascular disease? On one hand, the RAAS is well described as a neuroendocrine system that regulates circulatory homeostasis. But the RAAS also might have effector function in an autocrine or paracrine fashion by regulating vascular injury and repair responses, ultimately leading to remodeling and restructuring. From a clinical standpoint, there is an interrelationship between level of blood pressure with the resulting mechanical stretch and strain, vascular risk factors, and progression of vascular injury. These observations might explain why rigorous control of blood pressure coupled with therapeutic strategies that block the RAAS have more success in slowing the progression of vascular disease. Large-scale clinical trials, such as the Heart Outcomes Prevention Evaluation (HOPE), have shown unequivocal benefit of lower blood pressure and blocking the RAAS [37]. Other clinical trials in patients with cardiac or renal disease demonstrated similar, consistent benefits with better blood pressure control and blocking of the RAAS [37, 49].

Dr. James Strom (Division of Nephrology, St. Elizabeth’s Medical Center, Brighton, MA): One of the confounding features of the evaluation of proteinuria in an individual is the potential for “structural” protein loss. We all follow patients with class-IV lupus nephritis in whom one doesn’t really believe the proteinuria is due to hyperfiltration. Patients like this might have a combination of factors causing heavy proteinuria despite controlled systolic pressure. How would you advise proceeding in such a situation?

Dr. Weir: Your question raises the issues of the relative contribution of glomerular capillary pressure elevation and glomerular structural injury to proteinuria, and the most effective way to treat it. I would submit that the lower the glomerular capillary pressure, the less the hydraulic force of transglomerular passage of proteins. In a patient with glomerulonephritis and nephrotic-range proteinuria, I would employ more rigorous efforts to drive that systolic blood pressure down as low as comfortably possible (to avoid presyncope) with drugs that block the RAAS.

Dr. Allon Friedman (Renal Fellow, Division of Nephrology, New England Medical Center, Boston, MA): You spoke about how we can use proteinuria as a surrogate marker to titrate blood pressure to ideal levels. However, some of our clinic patients who have chronic renal disease do not exhibit proteinuria. What surrogate markers would you use with these patients?

Dr. Weir: We clearly need more effective means of determining which patients with renal disease are at risk for developing progressive renal disease and cardiovascular disease, particularly if they have minimal evidence of proteinuria. The NIDDK has just started an observational cohort study in patients with early renal insufficiency to look at biomarkers for progression of both renal and cardiovascular disease. When completed, this trial should provide much relevant information. Our center is evaluating different therapeutic strategies in renal transplant recipients with biopsy-proven chronic allograft nephropathy and low-grade proteinuria to determine the optimal level of blood pressure and specific benefits of drugs that block the RAAS. This study provides measurements of renal function and renal histology with sequential renal biopsies during follow-up. The observations of this study also might provide important insights into the management of patients with other forms of renal disease.

Clinical trials to evaluate optimal strategies in patients
with non-proteinuric renal disease will likely take longer and require larger numbers of patients to demonstrate statistically significant benefits in reducing end points. The MDRD trial demonstrates this point nicely. In the meantime, patients with renal disease, even those with minimal proteinuria, should still have rigorous efforts to control systolic blood pressure below 130 mm Hg, and preferably with drugs that block the RAAS.

Dr. Katrin Uhlig (Renal Fellow, Division of Nephrology, New England Medical Center): At the ASN meeting, Dr. Andrew Levey showed data from further analysis of the AIPRD (Angiotensin Converting Enzyme Inhibition in Progressive Renal Disease) study. These data showed that the beneficial ACE-inhibitor effect was only partially explained by lowering of both blood pressure and proteinuria (abstract; Jafar J, Am Soc Nephrol 11:A0345, 2000). Could you comment on that? Also, do any data suggest that ACE inhibitors or angiotensin receptor blockers work in different ways in diabetic versus non-diabetic renal disease?

Dr. Weir: It is likely that drugs that block the RAAS—the ACE inhibitors and angiotensin II receptor blockers—have blood pressure-dependent and blood pressure-independent benefits on slowing progression of renal disease in diabetics and non-diabetics. It will probably take more patients or longer follow-up to demonstrate this in a single clinical trial, unless a properly performed meta-analysis of many clinical trials is done. We still do not know with certainty the mechanism of action of either the ACE inhibitors or the angiotensin II receptor blockers. Until we do, it is hard to predict the long-term effects of these two therapeutic classes that block the RAAS.

Dr. Madias: We’re increasingly learning about the cluster of genes that importantly influence susceptibility to various chronic diseases. Could you talk about the genetic background of the individual in terms of the rate of progression of renal disease and the response to ACE inhibition?

Dr. Weir: I have not been overwhelmed with the available gene polymorphism data, particularly for the ACE gene, to make them clinically relevant at the present time. This is particularly true in patients with nephropathy due to type 2 diabetes, the most common clinical form of renal disease.

Dr. Harrington: Nick asked you earlier about the efficacy of the new aldosterone antagonists. Could you tell us more about it?

Dr. Weir: Eplerenone is a new selective aldosterone receptor antagonist that does not have the endocrine side effects of spironolactone. Thus, it might allow the study of higher doses of the drug to evaluate effects not just on blood pressure, but also on vascular and target organ function. One congestive heart failure study that utilized 12.5 to 25 mg of spironolactone with an ACE-inhibitor–based multidrug regimen demonstrated a powerful impact on reducing cardiovascular events [50].

Dr. Madias: You mentioned a number of interesting hypothetical trials. Do you want to use this Forum to specifically delineate two or three of those that you think are the most pressing in our field?

Dr. Weir: There is a substantial variation in physician use of drugs that block the RAAS in patients with chronic renal failure or end-stage renal disease despite the overwhelming evidence of increased cardiovascular disease in these patients. Perhaps doctors are concerned about changes in creatinine or potassium, or the perceived lack of need of these drugs after the kidneys have failed. For that reason, a clinical trial is needed to evaluate the benefit of drugs that block the RAAS on cardiovascular end points in patients with established renal disease or end-stage renal disease. Two outcome trials have been organized at our center to evaluate the benefits of ACE inhibitors and angiotensin II receptor blockers in patients on dialysis or who have received a renal transplant. Patients will receive similarly effective pharmacotherapies to control blood pressure. The difference in outcome for patients on a drug that blocks the RAAS versus a non-RAAS-blocking drug will be compared on cardiovascular end points. As part of our efforts to design these two trials, we are also evaluating physician use of drugs that block the RAAS in dialysis and transplant patients. There are some surprising differences among health care providers. In general, the usage is quite low, particularly in patients with renal transplants.

Dr. John Gill (Research Fellow, Division of Nephrology, New England Medical Center): In your previous comments, you alluded to the transplant population on a couple of occasions. You suggested that we ignore the potential benefits of angiotensin II receptor antagonists compared to ACE inhibitors. However, given the potential for complications, specifically hyperkalemia, if we decide to use these medications, might angiotensin II receptor blockers be favored given their known ability to decrease TGF-β?

Dr. Weir: Good point. Whether ACE inhibitors or angiotensin II blockers can more effectively reduce renal scarring, perhaps due to effects on angiotensin II or TGF-β, is unknown. Perhaps our current renal biopsy study in transplant patients will shed light on this subject. The potassium issue is an important one, as it frequently is a stumbling block for physicians who want to prescribe ACE inhibitors or angiotensin II receptor blockers. These drugs do raise serum potassium on average 0.3 to 0.5 mEq/L because of inhibition of aldosterone. One of the intriguing questions is whether it is healthier for you to have a potassium level of 5.5 to 6.0 mEq/L. That might be a more desirable potassium level in people with cardiovascular risk factors. This possibility needs to be
carefully explored in large data bases. If you look at the wealth of information from clinical trials in congestive heart failure or chronic renal insufficiency, the need for stopping an ACE inhibitor because of a potassium level of 6.0 mEq/L or greater occurs in less than 2% of patients. Thus, this is an infrequent clinical problem. It can largely be minimized if physicians ensure that their patients do not take NSAIDS or salt substitutes.

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Reprint requests to Dr. M. Weir, Division of Nephrology, University of Maryland Medical System, 22 South Greene Street, Room No. N3W143, Baltimore, Maryland 21201-1595, USA. E-mail: mwweir@medicine.umn.edu

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