

Chronic Renal Diseases: Renoprotective Benefits of Renin–Angiotensin System Inhibition

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Progression to renal parenchymal damage and end-stage renal disease, which seems to be largely independent of the initial insult, is the final common pathway for chronic, proteinuric nephropathies in animals and humans. The key event is enhanced glomerular capillary pressure; this impairs glomerular permeability to proteins and permits excessive amounts of proteins to reach the lumen of the proximal tubule. The secondary process of reabsorption of filtered proteins can contribute to renal interstitial injury by activating intracellular events, including upregulation of the genes encoding vasoactive and inflammatory mediators. Both interstitial inflammation and progression of disease can be controlled by such drugs as angiotensin-converting enzyme inhibitors, which strengthen the glomerular permeability barrier to proteins and

thereby limit proteinuria and filtered protein-dependent inflammatory signals. Clinical data strongly suggest that remission can now be achieved in some patients with chronic renal disease. Because of the current lag time between starting treatment and remission, however, a substantial proportion of patients still progress to end-stage renal disease before renal function begins to stabilize. A multimodal approach that centers on reducing or removing all risk factors associated with the progression of renal disease may decrease the time to remission of the disease for most patients with proteinuric nephropathies.

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Certain renal diseases seen in clinical practice, such as rapidly progressive glomerulonephritis, have a very rapid course that soon leads to irreversible end-stage renal failure caused by complete structural damage. These diseases, however, are rare. The more common nephropathies, which progress more slowly, still evolve to end-stage renal failure. Diabetes mellitus or hypertension can, in some patients, cause renal injury that progresses to renal failure and the need for kidney replacement therapy.

The number of patients requiring kidney replacement therapy in 1997 was 304 083 in the United States, 175 988 in Japan, and 197 721 in Europe. The number of new patients entering kidney replacement programs has increased constantly in the past 10 years and will probably continue to increase. In the United States, 450 000 patients are expected to require treatment for end-stage renal disease by 2005 (1, 2). With so many patients involved, the costs of treatment will become extremely high and prohibitive, and not just for developing countries (3). Thus, efforts must be directed toward stopping renal diseases from progressing to end-stage renal failure.

METHODS

We identified papers mentioned in this review by searching the MEDLINE database from 1966 to 2000.

We selected the most relevant articles (original research and reviews) for this topic using the following individual or combined search terms: *progressive chronic nephropathies, proteinuria, clinical trials, experimental models, renal function, ACE inhibitors, angiotensin II receptor blockers, blood pressure, lipid lowering agents, low protein diet, and smoke*. Selected articles were published in the most recognized nephrology journals and in general medicine journals with the highest impact factor.

THE PROGRESSIVE NATURE OF RENAL DISEASES

In 1952, Robert Platt (4) reported that when 80% of the renal tissue was removed from rats, the remaining nephrons became hypertrophied as they assumed a volume of work that a normal kidney would never have to perform. This was interpreted as a possible adaptation to compensate for the effects of nephron loss; renal function then progressively deteriorated. In 1982, however, investigators at Brigham and Women's Hospital in Boston, Massachusetts, first presented the concept that progressive deterioration of renal function was the result of compensatory glomerular hemodynamic changes in response to nephron loss related to the original insult; the hemodynamic changes then caused relentless injury of the remaining intact nephrons (5, 6).

In animal models, high intraglomerular capillary pressure impairs the size-selective function of the glo-

merular permeability barrier and causes protein ultrafiltration (7, 8). In 1986 (9), Bertani and colleagues suggested that proteins filtered through the glomerular capillary wall might have intrinsic renal toxicity and could contribute to the progression of renal damage. Consistent with these experimental observations was evidence that in humans with nephropathy, disease progressed more quickly when proteinuria was more severe (10–13).

Even in normal conditions, proteins cross the glomerular capillary wall in large amounts and return to the blood by a transtubular mechanism involving proximal tubular cells (14, 15) (**Figure 1**). Abundant evidence from *in vitro* cell culture studies (16–18) and *in vivo* rat models of proteinuric renal disease (19–25) indicates that reabsorption of filtered proteins activates the proximal tubular epithelium. Biochemical events associated with tubular cell activation in response to protein stress include upregulation of the genes encoding vasoactive and inflammatory substances and synthesis of the corresponding protein products, such as endothelin-1 (16), monocyte chemoattractant protein (MCP-1) (17), and RANTES (regulated upon activation, normal T-cell expressed and secreted) (18, 26).

Inflammatory and vasoactive substances formed in excessive amounts by proximal tubuli are secreted toward the basolateral compartment of the cell and give rise to an inflammatory reaction in the interstitium that consistently precedes renal scarring. These processes can be accelerated by cytokines released by tubular epithelial cells and by inflammatory cells that accumulate in the interstitium when proteinuria is present (27–31).

LIMITING PROTEIN TRAFFIC PREVENTS THE PROGRESSION OF RENAL DISEASE IN ANIMALS

In chronic proteinuric nephropathies, if the interstitial inflammatory reaction and the subsequent fibrosis were indeed a feature of protein overloading, limiting protein traffic or the biological effect of excessive tubular protein reabsorption should prevent or slow the progression of renal disease. This is precisely what happens in animals treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (**Figure 2**). In experimental diabetes, short- or long-term treatment with enalapril or the angiotensin II receptor blocker losartan reduced proteinuria and conferred pro-

tection (32, 33). Use of ACE inhibitors reduced proteinuria and limited progressive deterioration of renal function in other models of renal disease, including spontaneous proteinuria in aging male Munich Wistar Fromter/Ztm rats (34) and rats with passive Heymann nephritis (35), an experimental model that mimics membranous nephropathy in humans.

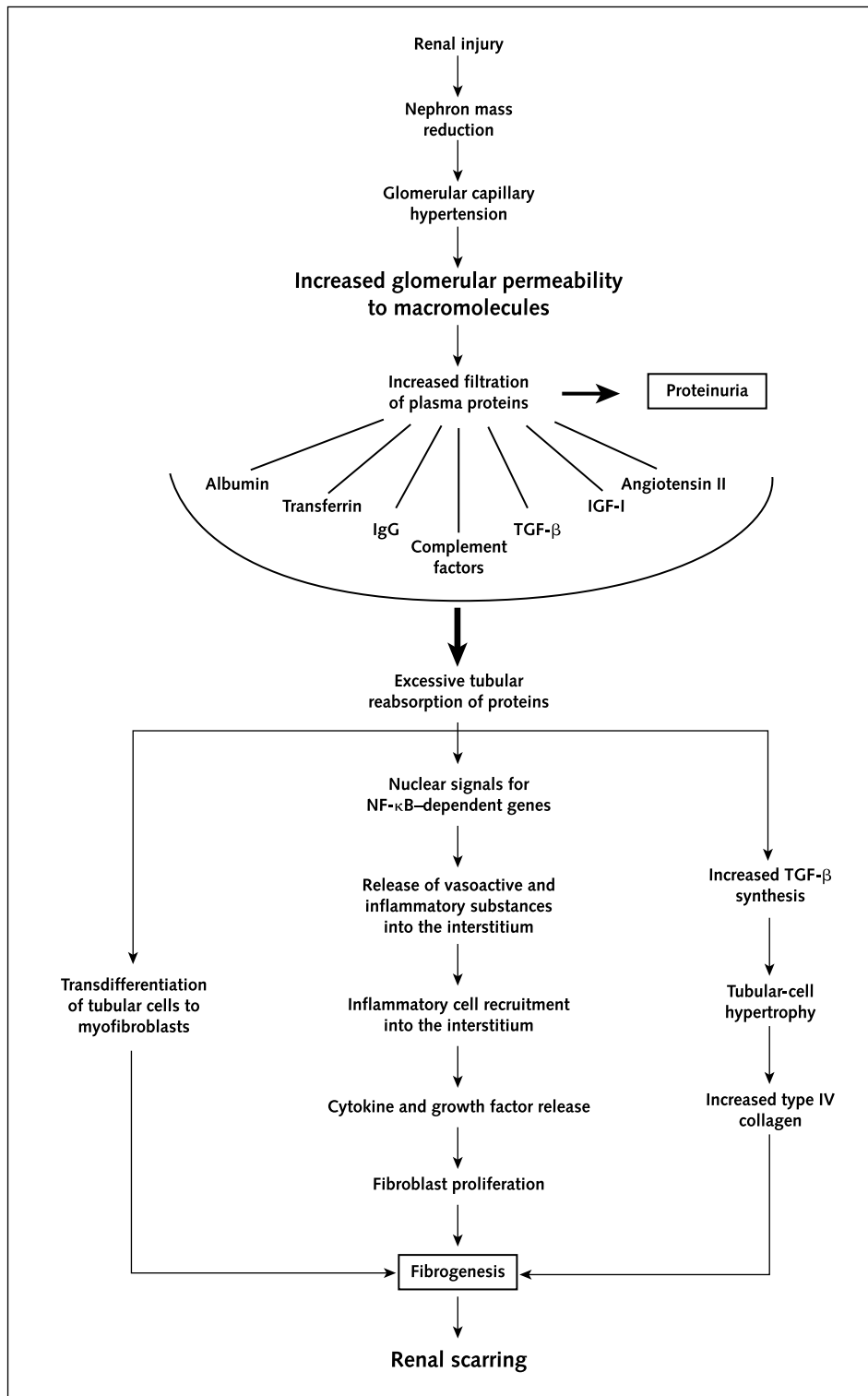
In a recent study of rats with Heymann nephritis and severe proteinuria, simultaneous blocking of angiotensin II and endothelin-1 activity by an ACE inhibitor, together with an endothelin type A receptor antagonist, was more renoprotective than either drug alone (36). Thus, in animals, limiting protein excretion and the resulting activation of tubular epithelial cells is instrumental in protecting the kidney from further damage.

FROM ANIMAL EXPERIMENTS TO DESIGNING A CLINICAL STUDY

Clinical studies and clinicopathologic correlations in patients with progressive proteinuric nephropathies indicate that the observations in experimental models are relevant to understanding human disease (37). Among several baseline measures, proteinuria was a strong and independent predictor of renal outcome in a series of 840 patients with nondiabetic renal disease entering the Modification of Diet in Renal Disease (MDRD) study (38) and in 409 patients with type 1 diabetes and nephropathy (39). Moreover, in patients with nephroangiosclerosis (40), the onset of *de novo* proteinuria after years of stable renal function indicated subsequent decline in renal function.

Minimal-change disease seems to be an exception to the rule that interstitial infiltrates develop with time in proteinuric glomerulopathies. This type of disease is the only example of a human proteinuric nephropathy in which a substantial percentage of patients consistently respond to steroids. Thus, periods of elevated protein excretion are relatively limited in minimal-change disease and may be inadequate to generate injury (41). Patients with this disease who have only a few relapses are protected from progressive renal damage (42), whereas those who initially responded to glucocorticoid therapy but then have frequent relapses tend to develop focal glomerulosclerosis (43–46). In patients with permanent proteinuria and nephrotic syndrome caused by minimal-change disease that is resistant to treatment,

Figure 1. Effect of increased glomerular permeability to proteins on progressive renal injury.



renal function inevitably deteriorates with time (47). The few patients who have undergone repeated renal biopsies show interstitial inflammation and fibrosis, with an increasing number of sclerotic glomeruli over time (48).

Primary tubulointerstitial nephritis also appears to be indolent with regard to progression to end-stage renal disease, despite the hypothetical relationship between the degree of interstitial damage and the rate of renal function decline (49). This may occur because during the early stages of interstitial nephritis, tubular functional abnormalities are more pronounced than is the decline in glomerular filtration rate (GFR). At the time of the initial insult, injury is limited to segmental loci of the tubulointerstitial areas, with almost all glomeruli structurally and functionally intact; thus, renal functional reserve is completely preserved (50). Glomerular abnormalities arise only in advanced stages of primary tubulointerstitial nephritis; they are a consequence of adaptive alterations to glomeruli or of the injurious effects of tubulointerstitial processes. In such circumstances, excess protein leakage from glomeruli into the tubular lumen and the resulting reabsorption of excess proteins by proximal tubular cells may have additional interstitial damaging effects, which accelerate the progression of renal disease.

The pivotal role of enhanced protein traffic as a predictor of end-stage renal disease and its impact on renal outcome are clearly illustrated by the Ramipril Efficacy in Nephropathy (REIN) study. This study formally investigated whether excessive ultrafiltration of proteins influenced the progression of renal disease and whether an ACE inhibitor (ramipril) was superior to placebo and other antihypertensive drugs in reducing proteinuria, limiting the decline in GFR, and preventing end-stage renal disease in patients with and without hypertension; blood pressure was controlled at similar levels in both treatment groups (51). The REIN study is a randomized, double-blind, placebo-controlled, multi-

center clinical trial in 352 nondiabetic patients with clinical proteinuria (≥ 1 g/24 hours). Patients were randomly assigned to receive ramipril or conventional antihypertensive therapy to maintain diastolic blood pressure at 90 mm Hg or less. A prestratification strategy recognized two levels of proteinuria (stratum 1: >1 and <3 g/24 hours; stratum 2: ≥ 3 g/24 hours) in patients randomly assigned to ramipril or conventional antihypertensive therapy.

In this trial, the only baseline variable that correlated significantly with decline in GFR and progression of disease to end-stage renal failure was urinary protein excretion. Thus, patients with baseline urinary protein excretion less than 2.5 g/24 hours had a low rate of GFR decline over 3 years of follow-up, whereas in those with proteinuria in the nephrotic range (>4.3 g/24 hours), GFR decreased by 10 mL/min per 1.73 m² of body surface area per year and the kidney failure rate exceeded 50% at 3 years (52).

THE RENOPROTECTIVE EFFECT OF RENIN-ANGIOTENSIN SYSTEM INHIBITION: THE REIN STUDY

The REIN study showed that despite similar blood pressure control in the two treatment groups, patients with proteinuria of 3 g/24 hours or more who received the ACE inhibitor had a significantly lower rate of decline in GFR and lower risk for doubling of serum creatinine levels or end-stage renal failure than did patients receiving conventional antihypertensive therapy (51). On the other hand, the authors found that the ramipril-induced reduction in rate of urinary protein excretion was the only time-dependent covariate that predicted a lower decline in GFR and lower incidence of progression to end-stage renal disease; this finding clearly indicated that renoprotection is linked to reduction of protein traffic (51).

On the basis of interim data analysis, the core study of the REIN trial was stopped by an independent adju-

Compensatory glomerular hemodynamic changes in response to nephron loss caused by the original renal insult lead to increased intraglomerular capillary pressure, which impairs the size-selective function of the glomerular permeability barrier and causes protein ultrafiltration. Excessive reabsorption of proteins as a consequence of the increased glomerular permeability results in protein accumulation in proximal tubular cells. Congestion of endolysosomes and endoplasmic reticulum in proximal tubular cells may trigger the activation of genes encoding vasoactive and inflammatory mediators (endothelin, RANTES [regulated upon activation, normal T-cell expressed and secreted], monocyte chemoattractant protein-1, and other cytokines). In addition, enhanced generation of transforming growth factor- β (TGF- β) causes tubular cell hypertrophy and collagen type IV production. Tubular cells may also become activated to transdifferentiate into myofibroblasts. Release of excessive vasoactive and inflammatory substances from the proximal tubular cells into the interstitium contributes to interstitial inflammation and fibroblast proliferation, eventually inducing increased synthesis of extracellular matrix and renal scarring. IGF-I = insulin-like growth factor-I; NF- κ B = nuclear factor- κ B.

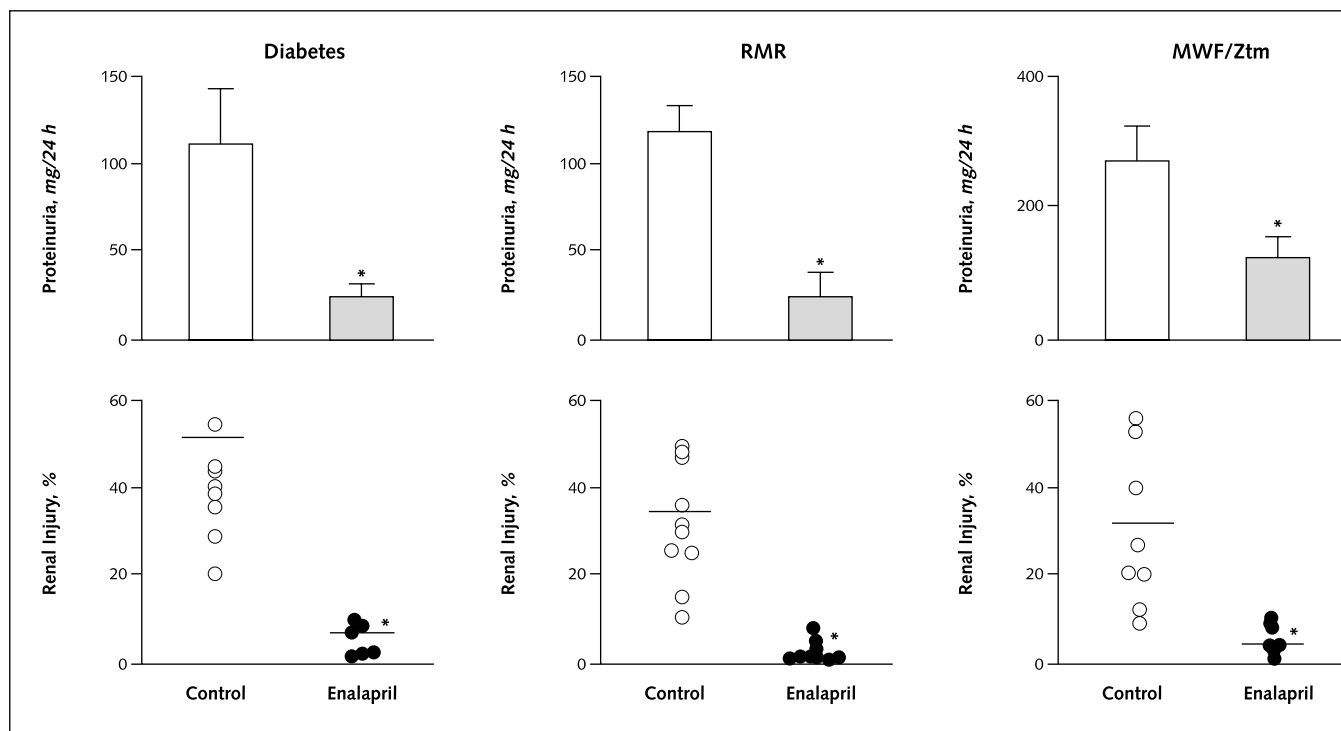
dicating panel; the panel recommended that all patients in stratum 2 be given the most effective treatment. Thus, patients who were receiving ramipril at the start of the study, as well as those originally randomly assigned to conventional therapy and then switched to ramipril, were formally followed for another 2 years (the REIN follow-up study) (53). In patients continuing to receive ramipril, GFR further decreased by approximately 1 mL/min per year during follow-up (Figure 3). The decrease was similar to that associated with normal aging. This finding is reminiscent of early results in patients with diabetic nephropathy. Antihypertensive therapy continued for a long enough period was associated with a progressive reduction in GFR decline; GFR decline was only 1.2 mL/min per year after 6 years of treatment (54). Patients who switched from conventional therapy to ramipril also benefited from the treatment, as shown by a greater reduction in GFR during follow-up than during the core study (Figure 3).

Results of an analysis of outcome events were con-

sistent with the GFR data. Considering both the core and follow-up phases of the REIN study, patients originally randomly assigned to ramipril had a significantly lower incidence of progression to end-stage renal disease (51, 53). Perhaps most impressive is the finding that after about 36 months of treatment with ramipril, no additional patients progressed to the point of requiring dialysis, whereas patients switched from conventional therapy to ramipril continued to develop end-stage renal disease. During the core study, ramipril was associated with a 41.5% reduction in the risk for end-stage renal disease, whereas during the follow-up phase, patients initially randomly assigned to ramipril had a 66.1% reduction in the risk for reaching this end point.

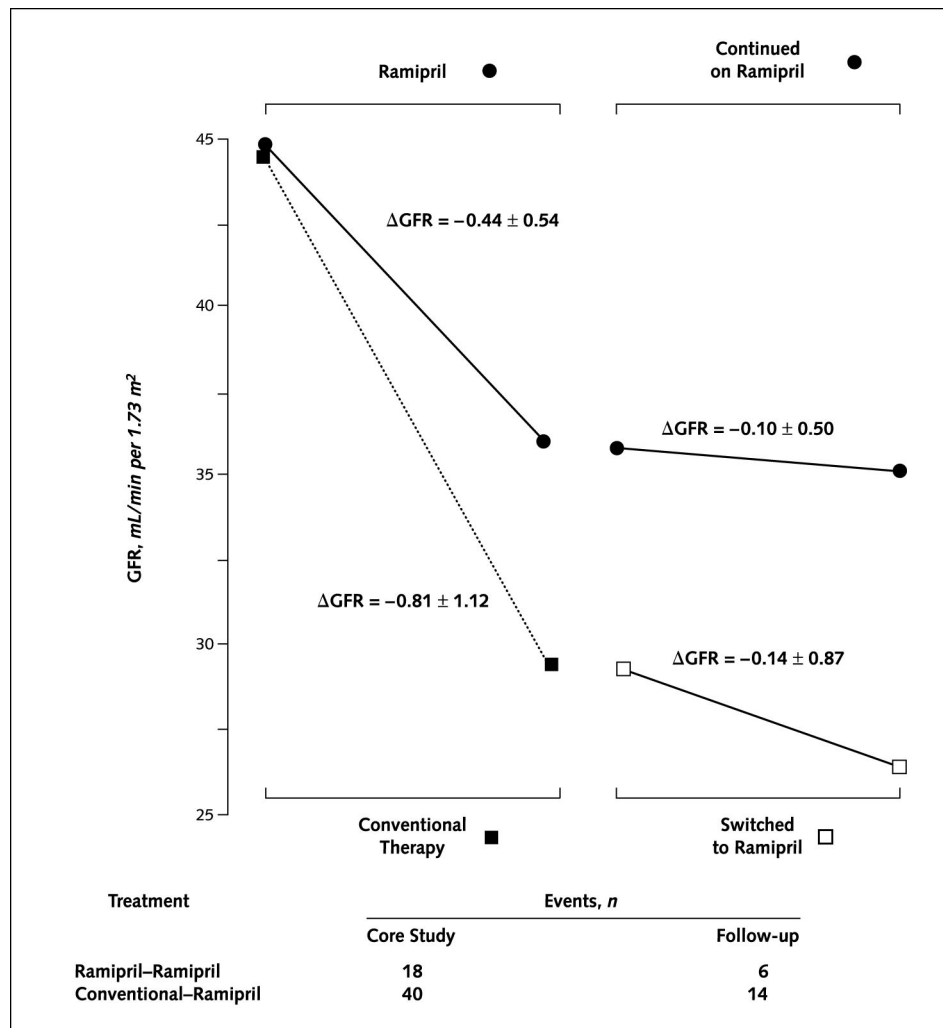
How can we explain the continued improvement in patients who continued to receive ramipril? In patients who initially received ramipril, a small increase in GFR over the first 3 months was followed by a slow decline. After 30 to 36 months of treatment, however, GFR did not decrease further, and, from 36 to 48 months, the

Figure 2. Limiting protein traffic prevents progression of renal disease in animals.



In experimental diabetes among rats with a remnant kidney and male Munich Wistar Fromter/Ztm (*MWF/Ztm*) rats (all animal models in which progressive proteinuria and renal injury develop with time), inhibition of angiotensin-converting enzyme with enalapril consistently exerts antiproteinuric and renoprotective properties. * $P < 0.01$ versus control. In the top panel, white bars represent control rats and gray bars represent rats receiving enalapril. In the bottom three panels, each circle represents an individual rat. Diabetes = streptozotocin-induced diabetes; RMR = renal mass reduction.

Figure 3. Mean decline in glomerular filtration rate (GFR) during the Ramipril Efficacy in Nephropathy (REIN) core and follow-up study in patients with nondiabetic chronic proteinuric nephropathies.



Solid lines indicate ramipril therapy and the dotted line indicates conventional therapy. Black circles indicate continued ramipril therapy during the core and follow-up study; black and white squares indicate a switch in treatment from conventional therapy (during the core study) to ramipril (during the follow-up study). The decline in GFR (in mL/min per 1.73 m² per month) was significantly lower during the follow-up study than during the core study in the patients originally randomly assigned to ramipril or to placebo plus conventional antihypertensive therapy. The GFR was better preserved and the number of renal outcome events (for example, end-stage renal failure) was lower in patients receiving ramipril during the core and follow-up studies than in those who originally received conventional antihypertensive therapy and switched to ramipril in the follow-up phase.

mean GFR actually increased, suggesting that patients may have reached a stage of disease regression (55). This remarkable outcome should be considered in light of the fact that all these patients had proteinuria greater than 3 g/24 hours before the study and therefore would have been expected to have a rapid decline in GFR. Thus, after 60 months of ramipril treatment, the rate of renal function decline was less than one tenth of the decline

seen in patients receiving conventional therapy during the core study (0.9 mL/min per month) (55).

We must concede, however, that these findings may have been affected by a selection bias resulting from different periods of follow-up. We have formally analyzed this issue and found that in all the cohorts of patients with different periods of follow-up, the GFR decline was slower in patients who continued to receive

ramipril therapy than in those who switched to ramipril during follow-up (55). More important, in each cohort of patients receiving continued ramipril therapy, renal function tended to improve progressively as the follow-up period (18 to 60 months) increased.

To further investigate the nature of the time-dependent improvement in GFR change, we looked for a breakpoint in the individual GFR slopes of patients receiving continued ramipril therapy. We predicted that after the breakpoint, 10 patients receiving continued ramipril therapy would never progress to end-stage renal disease and that another 10 had such improved GFR slopes that progression to end-stage renal disease would be delayed by about 5 years (55).

This analysis provides evidence that the tendency of GFR to decline with time can be halted in some patients with chronic nephropathies. The clinical relevance of these findings rests on the fact that patients recruited in the REIN study were selected for severe disease, which resulted in a study sample expected to rapidly progress to end-stage renal disease if left untreated. These findings agree with previous findings in proteinuric Munich Wistar Fromter rats (a genetic model of progressive nephropathy) that late-onset ACE inhibition normalized blood pressure and gradually reduced the high protein excretion rate toward normal values, arresting the progression of tissue damage (56). The same is true for remission of the nephrotic syndrome in diabetic patients receiving long-term ACE inhibitor treatment (57). Thus, both experimental and clinical data strongly suggest that remission is now achievable in some patients with chronic renal disease.

A STEPWISE MULTIMODAL PROTOCOL FOR MANAGING RENAL DISEASE PROGRESSION

Because of the current lag time between start of treatment and remission, a substantial proportion of patients still progress to end-stage renal disease before their renal function begins to stabilize. The goal should be to investigate strategies for limiting the number of patients progressing to end-stage renal disease during the initial treatment periods. Ad hoc studies should explore whether this can be achieved by starting therapy very early in patients with chronic renal disease, when GFR is greater than 60 mL/min. Transplantation of a single kidney merits special attention because a single kidney theoretically supplies

half the number of nephrons usually available to healthy patients. This implies an increased workload per nephron to maintain homeostasis. In the transplanted kidney, the pool of functioning nephrons is also likely to decrease as a result of the initial ischemic injury, acute rejection, and long-term drug toxicity. Thus, self-perpetuating adaptive hemodynamic changes occur (as in progressive proteinuric nephropathies); these changes may ultimately contribute to renal function deterioration and scarring (58, 59).

The potential renoprotective effect of renin-angiotensin system blockade in clinical transplantation has been seen only in studies with short-term follow-up; these studies show that these agents can reduce urinary protein excretion. However, it is too soon to predict the long-term impact of these drugs on kidney graft survival.

When early treatment is not feasible because of late referral to nephrologists, the current therapeutic approach, based on ACE inhibitors, can be optimized by adding other agents to reduce the risk for progression to end-stage renal disease. The first step in this multimodal approach relies on a low-sodium diet in addition to pharmacologic blockade of the renin-angiotensin system with ACE inhibitors. Low but not high sodium intake activates the intrarenal renin-angiotensin system, which potentiates the efficacy of ACE inhibitors. In patients with chronic nephropathies, treatment with lisinopril and a low-salt diet (3 g/d) provided a higher anti-proteinuric effect than did the same ACE inhibitor with a high-salt diet (12 g/d) (60). Moreover, the blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored with diuretics, as was recently documented in patients receiving an ACE inhibitor and hydrochlorothiazide in addition to a high-sodium diet (61).

If progression of renal disease is still not satisfactorily controlled, an attempt should be made to maximize the antiproteinuric effect of the currently used ACE inhibitor. One possibility is to increase the drug dose to a level higher than the recommended threshold. The rationale for this suggestion rests on experimental data from rats with subtotal nephrectomy. In that study, the ACE inhibitor was given in dosages exceeding the required antihypertensive dose; this resulted in additional benefit to the glomerular structure (that is, reversing early glomerulosclerosis) compared with a low antihypertensive dose (62).

We evaluated the effects of different dosages of ramipril, from a minimum of 5 mg/d to a maximum of 20 mg/d (four times the recommended maximum dosage) on the level of proteinuria. Although the higher dosages had no additional effect on blood pressure, urinary protein excretion rates were further reduced, suggesting that the use of blood pressure alone to titrate the dosage may not achieve the maximum renoprotective effect (63). Similarly, doses of angiotensin II receptor antagonist higher than the maximum recommended doses further reduced urinary protein excretion, without causing significant changes in blood pressure or serum creatinine and potassium levels (64). Because of the preliminary nature of these data, caution should be used in adopting this regimen, and blood pressure control as well as potential side effects must be closely monitored.

An alternative is the multidrug approach that combines ACE inhibitors and angiotensin II receptor antagonists. The advent of angiotensin II receptor blockers extended the therapeutic options to slow the progression of chronic renal disease because these drugs inhibit the renin-angiotensin system at different levels than do ACE inhibitors; thus, they may act synergistically. Data on the use of combinations of an ACE inhibitor and an angiotensin II receptor antagonist in humans are extremely limited. Preliminary studies in sodium-depleted persons with normal blood pressure and in diabetic patients with normal renal function found a greater reduction in blood pressure after the addition of losartan to enalapril treatment than after doubling of the enalapril dose; this suggests that the combination more effectively inhibited the renin-angiotensin system (65).

In a pilot study of 11 patients with chronic renal disease of various causes, the investigators reported that 2 weeks after the addition of an angiotensin II receptor antagonist to ACE inhibitor therapy, there were an additional 30% reduction in proteinuria, a 6-mm Hg decrease in mean arterial pressure, and no changes in creatinine clearance (66). Proteinuria and blood pressure were significantly lower in patients with type 2 diabetes and overt nephropathy when an angiotensin II receptor antagonist was added to the initial treatment regimen with maximum recommended doses of an ACE inhibitor (67). An additive antiproteinuric effect of ACE inhibition and angiotensin II receptor antagonism has been reported in normotensive patients with IgA nephropathy; systemic blood pressure was not affected (68).

Taken together, these preliminary studies suggest that adding an angiotensin receptor antagonist may help maximize the antiproteinuric effect of ACE inhibitors. Prospective trials will reveal whether combined therapy is actually more renoprotective than single therapy.

A potential side effect of these treatments is hyperkalemia, especially in patients with renal failure and those with diabetes. However, in a pooled analysis of six published trials that included 154 diabetic and nondiabetic patients with chronic proteinuric nephropathies (51, 53, 69–72), the incidence of dropout due to uncontrolled hyperkalemia was similar: less than 2% in the renin-angiotensin system blockade and conventional treatment groups. The risk for hyperkalemia can be minimized by excluding patients with renovascular disease. In patients being treated with drugs that inhibit the renin-angiotensin system, serum potassium levels should be closely monitored, hyperglycemia and metabolic acidosis should be promptly treated, and thiazide or loop diuretics should be recommended.

Calcium-channel blockers are often used in patients with renal disease. Whether these drugs add benefit to the renoprotective properties of ACE inhibitors is controversial. Nondihydropyridine calcium-channel blockers reduced proteinuria in humans with type 2 diabetes and overt nephropathy (73) and, combined with ACE inhibitors, produced a greater reduction in proteinuria than did higher doses of either agent alone; similar levels of blood pressure control were maintained. Despite the lack of controlled studies, these observations suggest that combined treatment with nondihydropyridine calcium-channel blockers and ACE inhibitors may be more renoprotective than either treatment alone.

Data on dihydropyridine calcium-channel blockers are less encouraging because they indicate that these agents may worsen the progression of chronic nephropathies. In the REIN study, patients receiving dihydropyridine calcium-channel blockers had a higher level of proteinuria and faster decline in GFR than patients treated with other antihypertensive drugs; in both groups, blood pressure control and severity of underlying renal disease were similar (74). The excess proteinuria was greater for patients with poor blood pressure control or without concomitant ACE inhibition. These findings, combined with the evidence that these drugs may increase cardiovascular risk (75), particularly in patients with diabetes with or without renal disease, sug-

gest that dihydropyridine calcium-channel blockers should not be given to patients with chronic nephropathies of nondiabetic or diabetic origin. An exception is when ACE inhibitors, diuretics, and β -blockers fail to reduce blood pressure to the appropriate level.

THE NEED TO CONTROL BLOOD PRESSURE AND THE LIPID PROFILE

The proposed strategies to reduce proteinuria should be combined with other pharmacologic interventions aimed at controlling blood pressure and the lipid profile, as well as modifying the diet and habits of patients with chronic renal disease.

Hypertension, the hallmark of most chronic nephropathies, is a strong independent risk factor for end-stage renal disease (38, 76); reducing blood pressure consistently slows the progression of renal disease and reduces injury (77). A meta-analysis found a strong relationship between the extent of blood pressure control and reduction in proteinuria in patients who have type 1 and type 2 diabetes with microalbuminuria and macroalbuminuria (78). Whenever blood pressure was well controlled, all antihypertensive drugs except the dihydropyridine calcium-channel blocker nifedipine significantly reduced proteinuria. Thus, close monitoring of blood pressure is essential in slowing the progression of both diabetic and nondiabetic renal disease.

Dyslipoproteinemia is seen with chronic renal insufficiency from the early stages of renal functional impairment (79); it accelerates atherosclerosis and progression of the renal disease (80). A meta-analysis of 13 prospective controlled trials supports the possibility of a causal relationship between dyslipidemia and disease progression; the analysis found that lipid reduction may reduce proteinuria and preserve GFR in patients with chronic renal disease (81).

A few initial studies showed a low-protein diet to be beneficial, but larger trials were less encouraging. A meta-analysis of 13 randomized trials (1919 patients) and 11 nonrandomized, controlled trials (2248 patients) indicate that protein restriction had significantly more effect in the nonrandomized trials (82). In the randomized trials, low protein intake was associated with only a mild (not significant) reduction in the decline in GFR. Thus, the benefit of a low-protein diet in slowing the progression of renal failure is negligible or, at best, small.

The poor nutritional status often seen in patients adherent to the diet must also be considered.

Finally, impressive findings indicate the importance of smoking cessation. This is perhaps the single most important measure to protect kidneys from progressive disease (83–85). Unfortunately, patients and their physicians do not tend to appreciate the importance of smoking cessation.

CONCLUSIONS

We now have compelling clinical evidence of the renoprotective effects of ACE inhibitors in patients with nondiabetic chronic renal disease. In hypertensive patients with chronic renal failure, ACE inhibition slows progression toward end-stage renal disease more than β -blockers do, through a mechanism at least partially independent of blood pressure control (71). Therapy with ACE inhibitors also improves long-term dialysis-free survival in patients with progressive chronic renal failure, an outcome influenced by the magnitude of protein excretion rate and the initial antiproteinuric response to therapy (70).

A meta-analysis of 10 randomized trials confirmed that ACE inhibitors are more effective than other antihypertensive agents in slowing the progression to end-stage renal disease in nondiabetic patients, although it was not clear whether this benefit was due to the greater decline in blood pressure or to other effects (86). The REIN core study showed that at similar levels of blood pressure control, ACE inhibitors are more effective than conventional antihypertensive therapy in reducing proteinuria, slowing GFR decline, and limiting progression to end-stage renal disease. Finally, in the follow-up phase of the REIN study, prolonged (>36 months) ACE inhibitor therapy helped arrest the decline in GFR (disease remission). In a small number of patients with the longest follow-up, there was even a small increase in GFR with time, possibly signifying regression of the disease.

In the future, we should be able to reduce the time required to induce remission by optimizing renoprotection with multimodal interventions (87) achieved by combining antihypertensive medications, lowering lipids, and stopping smoking; in addition, for patients with diabetes, tight blood glucose control is critical. Several new compounds are under evaluation in animal studies,

and it is hoped that they will soon become part of the treatment strategy.

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