

AMGEN International Prize

The history and future of renoprotection

BARRY M. BRENNER

Samuel A. Levine Professor of Medicine, Harvard Medical School, Director Emeritus, Renal Division, Brigham and Women's Hospital, Boston, Massachusetts

These comments were delivered upon receiving the inaugural AMGEN International Prize at the World Congress of Nephrology in Berlin, Germany, June 9, 2003.

I am extremely pleased to be named the first recipient of the AMGEN International Prize and express my appreciation to the International Society of Nephrology and to AMGEN, Inc. for this high honor. Please be assured that the prize recognizes the efforts of many devoted colleagues to whom I am indebted and delighted to cite in the references to follow. To place our studies on renoprotection in its proper context, let me remind you that when we began our studies in the 1970s, much of the effort in nephrology was concerned with improving the effectiveness of renal replacement therapies for patients with otherwise fatal end-stage renal disease (ESRD). At that time, we fortuitously gained access to a strain of rats with glomeruli situated on the renal cortical surface, accessible to direct study by new microtechniques developed in our laboratory [1]. We were therefore in the unique position to address the following questions: What are the precise hemodynamic forces and biophysical properties that govern glomerular capillary function in health? How are these elements modified by renal injury? Do these modifications contribute to the relentless progression of renal disease? If so, can they be reversed so as to prevent or retard the development of ESRD?

When glomerular filtration rate (GFR) in humans falls below about half of normal, further loss of function often ensues, even when the original disease becomes inactive. In response to reduced renal mass, surviving nephrons undergo adaptations in structure and function that raise single-nephron GFR to meet excretory demands. In our initial study [2], we found that the glomerular hemodynamic adaptations responsible for increased single-nephron GFR actually proved to initiate and perpetuate glomerular injury following partial nephrectomy, suggesting that similar events may occur when nephrons are lost through disease. In addition to the detrimental effects of acquired nephron loss [3, 4], we have also argued that inborn deficits in total nephron number in

association with low birth weight contribute to hypertension and progressive glomerular injury in adult life [5, 6], an hypothesis now confirmed in several recent reports [7–9].

The most unfavorable glomerular hemodynamic adaptation to congenital deficits or focal nephron obliteration by disease is elevated glomerular capillary pressure, which ultimately leads to glomerular scarring and nephron dropout. Among a variety of measures that slow progression of experimental renal disease, alleviation of glomerular capillary hypertension has been found to be the common denominator. Meyer, Hostetter and I, working with the partial nephrectomy model [3], and Zatz, Meyer, Rennke, and I [10], with the streptozotocin diabetes model, showed that dietary protein restriction reduces glomerular pressure and ameliorates renal structural injury. Glomerular capillary hypertension is maintained largely by angiotensin-dependent mechanisms, via increased systemic blood pressure and efferent arteriolar vasoconstriction [11]. In addition to their potent systemic antihypertensive actions, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are highly effective in controlling glomerular capillary hypertension and thereby in retarding disease progression. In rats with partial renal ablation, Anderson, Rennke, and I observed that ACE inhibitors reduced the glomerular capillary pressure gradient, ΔP , and slowed renal disease progression, as reflected by less proteinuria and glomerulosclerosis, whereas, with a combination of hydralazine, reserpine, and hydrochlorothiazide, despite equivalent systemic blood pressure lowering, glomerular hypertension persisted and disease progression continued unabated [12]. Subsequent studies by my group and others consistently demonstrated renal protection with inhibitors of the renin-angiotensin system (RAS) in a variety of experimental models of renal injury [13].

Thus, angiotensin II emerged as a central mediator of the glomerular hemodynamic changes associated with progressive renal injury. It soon became apparent that several *nonhemodynamic* effects of angiotensin II are also important in mediating renal disease progression. These include oxidant and aldosterone-induced injury, increased filtration of plasma proteins, and coordinated

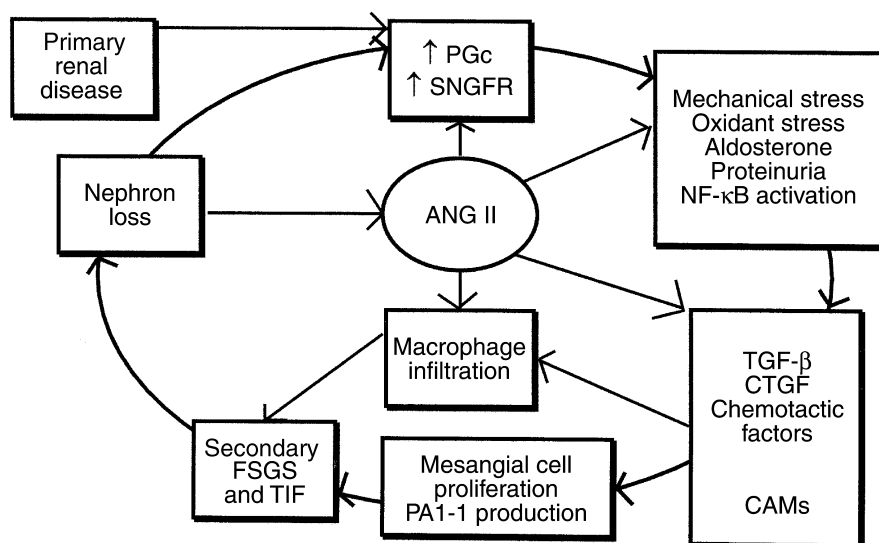


Fig. 1. Final common pathway for progression of chronic renal disease. Angiotensin II (ANG II) promotes injury in at least five separate steps in the cycle. Abbreviations are: PG_C, glomerular capillary pressure; SNGFR, single-nephron glomerular filtration rate (GFR); GS, glomerulosclerosis; TIF, tubulointerstitial fibrosis; FSGS, focal segmental glomerulosclerosis; NF-κB, nuclear factor-kappaB; PAI-1, plasminogen activation inhibitor-1; TGF-β, transforming growth factor-β; CTGF, connective tissue growth factor; CAMs, cell adhesion molecules.

nuclear factor-kappa B (NF-κB)-induced up-regulation of cytokines, chemokines, transforming growth factor-β (TGF-β), connective tissue growth factor (CTGF), and chemotactic and cell adhesion molecule expression, all of which in turn give rise to mesangial cell proliferation, increased synthesis of extracellular matrix proteins, stimulation of plasminogen activation inhibitor-1 production by endothelial and vascular smooth muscle cells, and macrophage activation and infiltration [14–17]. Together, these factors promote focal and global glomerulosclerosis and tubulointerstitial fibrosis, culminating in further nephron loss and a vicious cycle or final common pathway of progressive renal damage (Fig. 1).

I will now review the key clinical trials that have emanated from these studies in experimental animals. Our initial studies in the partial nephrectomy model showing that dietary protein restriction abrogates the adaptive rise in glomerular pressure and slows the tendency to renal disease progression helped motivate the National Institutes of Health Modification of Diet in Renal Disease (NIH-MDRD) trial. Although the overall study results reported by Klahr et al [18] were ambiguous, subsequent subgroup analyses by Levey et al [19, 20] provided clear evidence of benefit from dietary protein restriction. Furthermore, a meta-analysis of ten randomized, controlled studies of the effects of protein restriction on the progression of diabetic and nondiabetic renal disease by Pedrini et al [21] determined that the overall relative risk of renal failure or death was indeed reduced with protein restriction, as compared with nonrestricted protein intake.

With regard to pharmacologic approaches, our studies in rodents, showing that control of glomerular capillary hypertension with ACE inhibitors retards the development of glomerular lesions of experimental diabetic ne-

phropathy [22], soon motivated a number of clinical trials. Results of several small clinical studies performed to assess the effects of antihypertensive treatment in general, and ACE inhibitors in particular, on the rate of progression of diabetic nephropathy appeared to show a favorable response to therapy. However, none was sufficiently robust statistically to establish benefit conclusively. These shortcomings were resolved by the clinical trial entitled “The Effect of Angiotensin-Converting Enzyme Inhibition on Diabetic Nephropathy” performed by the Collaborative Study Group led by Dr. Edmund Lewis [23]. A total of 407 patients with type 1 diabetes and proteinuria (>500 mg/day) were randomized to receive either the ACE inhibitor, captopril, or placebo. If needed, blood pressure was managed independently of the experimental treatment, using agents other than ACE inhibitors or calcium channel blockers. Captopril treatment was associated with a 50% reduction in the combined risk of ESRD or death. These results yielded solid clinical proof of the concept that ACE inhibitors provide effective retardation of nephropathy, in this case due to type 1 diabetes, and led to the first federally approved treatment in the United States for slowing the progression of kidney disease.

It must be noted, however, that most diabetic patients who develop ESRD suffer from type 2 diabetes, reflecting its approximately 20-fold greater prevalence over type 1 diabetes. Type 2 diabetic patients develop glomerular hyperfiltration, proteinuria, and progressive declines in GFR, much as in type 1 diabetes and with essentially the same time course. Most renal protection studies with ACE inhibitors demonstrated significant reduction in proteinuria but failed to address the hard end point of ESRD, as these trials generally enrolled patients at rela-

tively early stages of diabetic nephropathy and their durations were usually 2 years or less.

Since 1995, ARBs have also been available to inhibit the RAS, by blocking angiotensin II subtype 1 (AT_1) receptors. Thus, whereas ACE inhibitors depress ACE-dependent angiotensin II production, ARBs block the effects of angiotensin II from any source at the receptor level. Despite these differences in mechanisms of action, experimental studies reveal that ACE inhibitors and ARBs produce similar improvements in glomerular hemodynamics and afford equivalent renoprotection in a variety of experimental models of kidney disease [13].

Two large, recently completed, prospective, multicenter, randomized clinical trials showed that interruption of the RAS with ARBs in type 2 diabetic patients with overt nephropathy delays the progression of renal disease. The Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT) evaluated the effects of the ARB, irbesartan, on renal and cardiovascular morbidity and mortality versus the effects of conventional therapy (placebo group) or the calcium channel blocker, amlodipine, in 1715 subjects [24]. The primary composite end point of the study was the time to a first event, namely, doubling of baseline serum creatinine, ESRD, or death from any cause. For subjects receiving irbesartan, the adjusted relative risk of reaching the primary composite end point was 20% lower than for those receiving placebo and 23% lower than for those receiving amlodipine. There was no significant difference between placebo and amlodipine for the primary composite end point. The relative risk of ESRD in the irbesartan group was 17% lower than that in the placebo group and 24% lower than that in the amlodipine group, but these differences did not achieve statistical significance. Secondary cardiovascular outcomes also failed to show significant differences among the various arms of the IDNT study. Proteinuria was reduced an average of 33% in the irbesartan arm, compared with 6% and 10% in the amlodipine and placebo arms, respectively. The more favorable renal outcomes in the irbesartan group were in excess of effects directly attributable to blood pressure control.

The Reduction of End Points in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) study was also undertaken to determine whether the ARB, losartan, reduces the number of patients with type 2 diabetes who experience a doubling of serum creatinine, ESRD or death, as compared with placebo-treated subjects [25]. The primary and secondary end points of the study were similar to those in the IDNT study, but treatment was of longer average duration in the RENAAL study (3.4 vs. 2.6 years). In RENAAL, 1513 subjects were randomized to receive either losartan or placebo once daily on a background of conventional antihypertensive therapy, excluding ACE inhibitors or other ARBs. Losartan treatment significantly reduced the risk of the

primary composite end point by 16% relative to placebo. Losartan lowered the risk of doubling of serum creatinine, the risk of reaching ESRD, and the combined risk of ESRD or death by 25%, 28%, and 20%, respectively, relative to placebo. RENAAL is thus the only study to date to specifically reduce the risk of ESRD in diabetes, in this case with losartan. Proteinuria declined by 35% in the losartan arm and increased slightly in the placebo group, and losartan slowed the estimated rate of loss of GFR by 18% relative to placebo. No significant difference was observed between the losartan and placebo arms for the secondary composite end point of cardiovascular morbidity or mortality, or for most of the cardiovascular components, although the losartan arm showed a significant reduction of 32% in the risk of a first hospitalization for heart failure. Once again, these consistent benefits of losartan in the RENAAL study were above and beyond effects that could be attributed to measured reductions in blood pressure.

Several studies investigated the potential of ACE inhibitors to afford renoprotection in nondiabetic forms of clinical renal disease. In the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) trial, Maschio et al [26] randomly assigned 583 patients with renal disease of diverse etiologies to treatment with benazepril or placebo. After 3 years of follow-up, the study found a 53% reduction with ACE inhibitor treatment in the combined risk of doubling of the baseline serum creatinine or need for dialysis. However, a significantly lower blood pressure among patients receiving ACE inhibitor versus placebo made it difficult to separate the beneficial effects of blood pressure reduction from any unique renoprotective effects of ACE inhibition.

In the more recent Ramipril Efficacy in Nephropathy (REIN) study [27], 352 patients with nondiabetic renal disease, randomly assigned to receive either ACE inhibitor or placebo, achieved similar control of blood pressure. Among patients with proteinuria of at least 3g/day at baseline, a significantly lower rate of decline of GFR was seen after 2 years in patients receiving the ACE inhibitor, ramipril (-0.44 vs. -0.81 mL/min/month with non-ACE conventional therapy). In the extension phase of the study [28], patients who initially received placebo were switched to ACE inhibitors, and those already on ACE inhibitors continued this treatment. Consistent with the findings in the first 2-year phase of the study, those switched from conventional therapy to ramipril treatment enjoyed a significant reduction in the rate of GFR decline, while patients continuing on the ACE inhibitor enjoyed a further reduction in the rate of GFR decline to levels similar to those associated with normal aging. Indeed, from 36 to 54 months of follow-up, no patients in the latter group reached ESRD, and a small number actually experienced a rise in GFR [29]. Another

186 REIN study patients with less than 3 g/day of proteinuria at baseline also benefited from ramipril with reduced incidence of ESRD [30].

In the AIPRID data study, a recent patient-based meta-analysis of 1860 nondiabetic subjects from 11 randomized ACE inhibitor versus placebo-treatment trials, Jafar et al [31] also concluded that ACE inhibitors are more effective than other antihypertensive treatment regimens in slowing renal disease progression and reducing proteinuria. Significantly lower values were seen with ACE inhibitors for several outcome measures, including level of proteinuria and incidence of ESRD. A similar conclusion emerged from the AASK trial in hypertensive African Americans [32], in which ramipril proved more renoprotective than the comparator drugs, amlodipine or metoprolol.

In addition to the renoprotective effects of ACE inhibitor treatment, the recent Heart Outcomes Prevention Evaluation (HOPE) [33] and Losartan Intervention for End Point Reduction in Hypertension Study (LIFE) [34] trials reported substantial reductions in all-cause mortality, cardiac, and stroke events in patients receiving ramipril or losartan, respectively. Because cardiovascular disease is the single largest cause of morbidity and mortality among patients with even mild chronic kidney disease, the HOPE and LIFE trial data provide a further compelling argument for the use of drugs that interrupt the RAS in patients with kidney disease.

Large randomized clinical studies of the renoprotective effects of ARBs in nondiabetic kidney disease are still awaited, but preliminary data suggest that ARBs are likely to be as effective as ACE inhibitors. In small studies, ARBs and ACE inhibitors produced similar antihypertensive and antiproteinuric effects in patients with essential hypertension or chronic kidney disease. One important advantage of ARBs over ACE inhibitors is their more favorable side-effect profile, as ARBs are seldom associated with the cough that may occur in up to 40% of patients receiving ACE inhibitors. Finally, the differing effects of ACE inhibitors and ARBs on the RAS imply that in combination they may have additive or even synergistic effects, and early evidence appears to support this contention [35–39].

In the largest combination trial to date, the COOPERATE trial, involving 336 patients with nondiabetic renal disease treated for 3 years with maximally effective doses of the ACE inhibitor, trandolapril, or the ARB, losartan, alone or in combination, the combination clearly was more effective in reducing progression and urinary protein excretion than either drug alone [38].

Let's now take a moment and ask about other new and novel approaches that might enhance our efforts at renoprotection. I would like to comment upon a promising new drug class referred to as vaso-peptidase inhibitors (VPIs). ACE and neutral endopeptidase (NEP) are mech-

Table 1. A comprehensive strategy for therapy in chronic kidney disease

Intervention	Therapeutic goal
Specific renoprotective therapy	
ACE inhibitors or ARB treatment (consider combination therapy if goals not achieved with full dose monotherapy)	Proteinuria <0.5 g/day GFR decline <2 mL/min/year
Adjunctive cardiorenal protective therapy	
Additional antihypertensive therapy (if needed)	<130/80 mm Hg
Dietary protein/salt restriction	0.6 to 0.8 g/kg/day and 3 to 5 g/day
Tight glycemic control in diabetes	HbA _{1c} <6.5%
Reduce elevated calcium × phosphate product	Normal values
Lipid-lowering therapy	LDL-cholesterol <100 mg/dL
Antiplatelet therapy	Thrombosis prophylaxis
Consider correction of anemia	Hemoglobin >12 g/dL
Smoking cessation	Abstinence
Weight control	Ideal body weight
Avoid nephrotoxic drugs, including some herbal remedies and dietary supplements	Avoidance

Abbreviations are: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; GFR, glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; LDL, low-density lipoprotein.

anistically similar metallopeptidases. ACE cleaves two peptides from the decapeptide angiotensin I to form the vasoactive octapeptide, angiotensin II. ACE also degrades the vasodilator, bradykinin, to inactive metabolites. The chief substrates for NEP are the vasodilators, bradykinin, and atrial and brain natriuretic peptides. Thus, a single molecule capable of inhibiting these two metallopeptidases results in reduced angiotensin II-mediated vasoconstriction as well as enhanced vasodilation due to accumulation of bradykinin, atrial natriuretic peptide, and brain natriuretic peptide. Taal et al [40] recently evaluated one such dual ACE-NEP inhibitor, omapatrilat, in comparison to the ACE inhibitor, enalapril, in the rat partial nephrectomy model. Enalapril extended the time to high-grade proteinuria well beyond the time course seen in placebo-treated rats, whereas omapatrilat extended the period of renoprotection indefinitely, as we were forced by budgetary considerations to terminate the study at 1 year when renal injury was still less marked. Furthermore, the greater renoprotection with omapatrilat compared to enalapril was not because of better blood pressure control as systolic blood pressures were similarly well controlled in both treatment groups. We await with interest a suitable clinical renoprotection trial of this new drug class as our rat studies clearly predict that VPI will provide even greater renoprotection than ACE inhibition alone.

Based on the evidence reviewed, let me now propose what might be considered a reasonable comprehensive strategy for therapy of patients with chronic kidney disease (Table 1). I think a strong case can be made for

prescribing an ACE inhibitor, ARB, or both in any patient with kidney disease in doses sufficient to achieve two distinct goals, namely, to reduce proteinuria to less than 0.5 g/day, and to show, by at least twice yearly checks, that some reliable estimate that GFR is falling by no more than 2 mL/min/year. Beyond this effort, other adjunctive treatments should be prescribed to address the heightened risk of cardiovascular disease that exists in all patients with kidney disease. These include additional antihypertensive drugs as needed to achieve the Joint National Committee Seventh Report recommended blood pressure target of less than 130/80 [41]. I also recommend moderate dietary protein and salt restriction, tight glycemic control in diabetics, statins, aspirin, erythropoietin, and measures to reduce calcium phosphorus product, excess body weight, tobacco use, and exposure to nephrotoxic drugs, including many herbal remedies and dietary supplements.

Clearly, this aggressive and comprehensive strategy will require substantial economic outlays from government or private insurers, as well as greater involvement of physicians and other health care professionals in overseeing attainment of treatment goals. But hopefully these added costs and efforts will translate into reduced morbidity and mortality from cardiovascular disease and fewer patients in need of expensive renal replacement therapy.

As we move forward with these efforts in regions with well-developed systems of medical care, let us also ask whether newer approaches are also needed in medically less advantaged societies where routine health screening, secondary and tertiary care facilities, and specialists in cardiovascular and renal medicine are lacking or in short supply. In such a setting, is it time to make available a once-a-day, low-cost cardiovascular and renoprotective pill, not unlike the all-purpose daily multivitamin so many of us now take? One such proposal might be an all-in-one clinically proven effective dose combination pill containing aspirin, lovastatin, and lisinopril, all now generic and therefore very low in cost. This combination pill, which I call ASTACE (for aspirin, statin, and ACE inhibitor), would be no larger than the daily multivitamin we now take. Clearly, government regulatory approvals would be required but I believe the time has come to consider this low-cost, universal approach to vital target organ protection. An even more ambitious proposal for a polypill containing folic acid and three antihypertensives (thiazide, ARB, and a calcium antagonist) together with low-dose aspirin and a statin has recently been advocated [42].

CONCLUSION

In less than two decades, the use of ACE inhibitors and ARBs as therapeutic interventions for slowing renal disease progression has made the giant leap from laboratory to universal clinical practice. In all likelihood, other

novel renoprotective agents will emerge from future laboratory and clinical studies, such as the dual ACE-NEP inhibitor described, but it is already clear that currently available strategies not only delay the need for dialysis, but actually prevent many patients from ever progressing to ESRD. It may be worth emphasizing that while the original studies from my laboratory centered upon basic issues in glomerular capillary physiology, it soon became evident that our investigations could shed light on mechanisms of renal disease progression and on rational approaches to their interruption. That this has come to pass serves to reinforce the important and unique role played by physician-scientists in the pursuit of fundamental and initially untargeted biomedical research.

Let me close by again thanking the International Society of Nephrology for selecting me to receive the first AMGEN International Prize which honors me and my coworkers and also celebrates the currently robust ongoing effort by basic and clinical investigators everywhere who seek therapies to improve the lives of patients with chronic kidney disease.

*Correspondence to Barry M. Brenner, M.D., Renal Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.
E-mail: Bbrenner@partners.org*

REFERENCES

1. BRENNER BM, TROY JL, DAUGHARTY TM: The dynamics of glomerular ultrafiltration in the rat. *J Clin Invest* 50:1776-1780, 1971
2. HOSTETTER TH, OLSON JL, RENNKE HG, *et al*: Hyperfiltration in remnant nephrons: A potentially adverse response to renal ablation. *Am J Physiol* 241:F85-F93, 1981
3. BRENNER BM, MEYER TW, HOSTETTER TH: Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* 307:652-659, 1982
4. BRENNER BM: Nephron adaptation to renal injury or ablation. *Am J Physiol* 249:F324-F337, 1985
5. BRENNER BM, GARCIA DL, ANDERSON S: Glomeruli and blood pressure. Less of one, more the other? *Am J Hypert* 1:335-347, 1988
6. BRENNER BM, CHERTOW GM: Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 23:171-175, 1994
7. NELSON RG: Intrauterine determinants of diabetic kidney disease in disadvantaged populations. *Kidney Int* 63(Suppl 83):S13-S16, 2003
8. KELLER G, ZIMMER G, MALL G, *et al*: Nephron number in patients with primary hypertension. *N Engl J Med* 348:101-108, 2003
9. HUGHSON M, FARRIS AB, DOUGLAS-DENTON R, *et al*: Glomerular number and size in autopsied kidneys: The relationship to birth weight. *Kidney Int* 63:2113-2122, 2003
10. ZATZ R, MEYER TW, RENNKE HG, BRENNER BM: Predominance of hemodynamics rather than metabolic factors in the pathogenesis of diabetic glomerulopathy. *Proc Natl Acad Sci USA* 82:5963-5967, 1985
11. MYERS BD, DEEN WM, BRENNER BM: Effects of norepinephrine and angiotensin II on the determinants of glomerular ultrafiltration and proximal tubule fluid reabsorption in the rat. *Circ Res* 37:101-110, 1975
12. ANDERSON S, RENNKE HG, BRENNER BM: Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 77:1993-2000, 1986

13. TAAL MW, BRENNER BM: Renoprotective benefits of RAS inhibition: From ACEI to angiotensin II antagonists. *Kidney Int* 57:1803–1817, 2000
14. EDDY AA, GIACHELLI CM: Renal expression of genes that promote interstitial inflammation and fibrosis in rats with protein-overload proteinuria. *Kidney Int* 47:1546–1557, 1995
15. GREENE EL, KREN S, HOSTETTER TH: Role of aldosterone in the remnant kidney model in the rat. *J Clin Invest* 98:1063–1068, 1996
16. ABBATE M, ZOJA C, CORNA D, *et al*: In progressive nephropathies, overload of tubular cells with filtered proteins translates glomerular permeability dysfunction into cellular signals of interstitial inflammation. *J Am Soc Nephrol* 9:1213–1224, 1998
17. RUIZ-ORTEGA M, LORENZO O, SUZUKI Y, *et al*: Pro-inflammatory actions of angiotensins. *Curr Opin Nephrol Hypertens* 10:321–329, 2001
18. KLAHR S, LEVEY AS, BECK GL, *et al*: The effect of dietary protein restriction and blood pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease study group. *N Engl J Med* 330:877–884, 1994
19. LEVEY AS, ADLER S, GREENE T, *et al*: Effects of dietary protein restriction on the progression of moderate renal disease in the Modification of Diet in Renal Disease Study. *J Am Soc Nephrol* 7:2616–2626, 1996
20. LEVEY AS, ADLER S, CAGGIULA AW, *et al*: Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 27:652–663, 1996
21. PEDRINI MT, LEVEY AS, LAU J, *et al*: The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: A meta-analysis. *Ann Intern Med* 124:627–632, 1996
22. ZATZ R, DUNN BR, MEYER TW, *et al*: Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 77:1925–1930, 1986
23. LEWIS EJ, HUNSICKER LG, BAIN RP, ROHDE RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 329:1456–1462, 1993
24. LEWIS EJ, HUNSICKER LG, CLARKE WR, *et al*: Renoprotective effects of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851–860, 2001
25. BRENNER BM, COOPER ME, DE ZEEUW D, *et al*: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
26. MASCHIO G, ALBERTI D, JANIN G, *et al*: Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 334:939–945, 1996
27. THE GISEN GROUP (GRUPPO ITALIANO DI STUDI EPIDEMIOLOGICI IN NEFROLOGIA): Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 349:1857–1863, 1997
28. RUGGENENTI P, PERNA A, GHERARDI G, *et al*, FOR THE GRUPPO ITALIANO DI STUDI EPIDEMIOLOGICI IN NEFROLOGIA (GISEN): Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Ramipril efficacy in nephrology. *Lancet* 352:1252–1256, 1998
29. RUGGENENTI P, PERNA A, BENINI R, *et al*, FOR THE GRUPPO ITALIANO DI STUDI EPIDEMIOLOGICI IN NEFROLOGIA (GISEN): In chronic nephropathies prolonged ACE inhibition can induce remission: Dynamics of time-dependent changes in GFR. *J Am Soc Nephrol* 10:997–1006, 1999
30. RUGGENENTI P, PERNA A, GHERARDI G, *et al*: Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 354:359–364, 1999
31. JAFAR TH, SCHMID CH, LANDA M, *et al*: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 135:73–87, 2001
32. WRIGHT JT: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 288:2421–2431, 2002
33. YUSUF S, SLEIGHT P, POGUE J, *et al*: Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 342:145–153, 2000
34. DAHLÖF B, DEVEREUX R, SJELDSSEN S, *et al*: Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE): A randomised trial against atenolol. *Lancet* 359:995–1003, 2002
35. JACOBSEN P, ANDERSEN S, ROSSING K, *et al*: Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. *Kidney Int* 63:1874–1880, 2003
36. SEGURA J, PRAGA M, CAMPO C, *et al*: Combination is better than monotherapy with ACE inhibitor or angiotensin receptor antagonist at recommended doses. *J RAAS* 4:43–47, 2003
37. CAMPBELL R, SANGALLI F, PERTICUCCI E, *et al*: Effects of combined ACE inhibitor and angiotensin II antagonist treatment in human chronic nephropathies. *Kidney Int* 63:1094–1103, 2003
38. NAKAO N, YOSHIMURA A, MORITA H, *et al*: Combination treatment of angiotensin-II receptor blocker and angiotensin-converting enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. *Lancet* 361:117–124, 2003
39. TAAL MW, BRENNER BM: Combination ACEI and ARB therapy: Additional benefit in renoprotection? *Curr Opin Nephrol Hypertens* 11:377–382, 2002
40. TAAL MW, NENOV VD, WONG W, *et al*: Vasopeptidase inhibition affords greater renoprotection than angiotensin-converting enzyme inhibition alone. *J Am Soc Nephrol* 12:2051–2059, 2001
41. CHOBANIAN A, BAKRIS G, BLACK H, *et al*: The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. The JNC 7 report. *JAMA* 289:2560–2574, 2003
42. WALD NJ, LAW MR: A strategy to reduce cardiovascular disease by more than 80%. *Br Med J* 326:1419–1424, 2003