Angiotensin-Converting Enzyme Inhibition and Renal Protection in Nondiabetic Patients: The Data of the Meta-Analyses

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ESRD represents a major health problem. The number of patients who enter kidney replacement programs has increased at an average of 7% per year in the past 10 yr. A large number of experimental and clinical studies have demonstrated that chronic nephropathies share common pathogenic mechanisms that contribute to renal disease progression, even independent of the original cause. Clinical studies found a significant correlation between the extent of urinary protein excretion and the rate of GFR decline in both diabetic and nondiabetic chronic nephropathies. Randomized trials, in particular the Ramipril Efficacy In Nephropathy (REIN) study, also showed that treatments that reduce proteinuria (namely angiotensin-converting enzyme [ACE] inhibitors) are renoprotective and limit progression to ESRD. Meta-analyses of randomized clinical trials also evaluated the role of proteinuria and of ACE inhibition therapy in chronic renal disease progression. Their findings were consistent with those of the REIN study and confirmed in larger series of patients the predictive value of proteinuria and the renoprotective effect of proteinuria reduction by ACE inhibition therapy. Thus, the meta-analyses may confirm and extend previous findings generated by randomized clinical trials. Conceivably, well-designed studies in properly selected and carefully monitored patients who are at increased risk continue to be the best approach to test novel hypotheses. The meta-analyses, however, represent a valuable tool to evaluate the consistency and generalizability of trial results to larger cohorts of patients.

E SRD represents a major health problem. The number of new patients who enter kidney replacement programs has increased constantly at an average of 7% per year in the past 10 yr (1). Approximately 1.1 million people are on renal replacement therapy today, and they will double in the next 10 yr. In the United States, 450,000 patients are expected to require treatment for ESRD by 2005 (2). Thus, the cost for renal replacement in the next decade will exceed $1 trillion, an amount that will be prohibitive also for the richest Western countries (3,4). Approximately two thirds of patients who were on ESRD irreversibly lost their kidney function because of progressive nephropathies, such as diabetic nephropathy and nondiabetic chronic nephropathies. Thus, halting the progression of chronic nephropathies to ESRD may be instrumental in substantially decreasing the need and cost for renal replacement therapy.

Mechanisms of Progression

A large number of experimental studies have demonstrated that chronic nephropathies share common pathogenic mechanisms that contribute to renal disease progression, even independent of the original cause. Actually, a variety of insults may result in a common pathway of systemic hypertension, increased glomerular pressure and permeability, proteinuria, interstitial inflammation, and, ultimately, scarring (5–8).

Role of Protein Traffic: Experimental Evidence

Glomerular hypertension in both diabetic and nondiabetic chronic nephropathies leads to increased glomerular permeability and excessive protein filtration. The protein ultrafiltrates are toxic to the proximal tubules, resulting in tubular damage, interstitial inflammation, and scarring (9). The degree of proteinuria correlates with the magnitude of renal damage in experimental models, and reducing the proteinuria helps to preserve renal function (10). Proteins in the urine are normally absorbed by endocytosis in the proximal tubules. During periods of heavy proteinuria, the filtered proteins accumulate in lysosomes in the proximal tubular cells, causing cell disruption and injury (reviewed in 9–12). Recent data are also in support of the possibility that the excessive protein load of the cells can be a factor underlying progressive podocyte injury and glomerulosclerosis (13).

Role of Proteinuria: Clinical Data

Clinical studies found a significant correlation between the extent of urinary protein excretion and the rate of GFR decline both in diabetic (14) and nondiabetic (15) chronic nephropathies. A 20-yr observational study in a large white population found that dipstick-positive proteinuria independently predicts risk for ESRD and overall mortality (16). On the same line, increased urinary albumin excretion predicted increased renal
and cardiovascular mortality 8 yr later in a remote Australian Aborigine community (17).

Studies showed that whenever proteinuria is decreased, progression to ESRD is consistently reduced. The Modification of Diet in Renal Disease (MDRD) study found that a reduction of proteinuria, independent of the reduction in BP, was associated with a decrease in the rate of decline in GFR and that the degree of protection of renal function achieved by lowering BP was dependent on the level of initial proteinuria (18). The Ramipril Efficacy In Nephropathy (REIN) study, which recruited patients with nondiabetic chronic nephropathies, also found that a rapid and sustained reduction in proteinuria prevented or limited long-term GFR decline (19). Patients who had more proteinuria to start with had more benefit from BP-lowering treatment. Finding that the extent of residual proteinuria was also a major determinant of disease progression provided further evidence of the pathogenic role of protein traffic (20).

BP

In animal models of chronic nephropathies, systemic hypertension is associated with increased intraglomerular pressure, an important determinant of renal disease progression (5,11,12). Lowering BP uniformly retards renal disease progression and reduces injury (11). Of great importance, angiotensin-converting enzyme (ACE) inhibitors are among the antihypertensive drugs that most effectively lower intraglomerular capillary pressure in animal models (21,22). In a seminal study published in 1976, Mogensen et al. (23) showed that five patients who had type 1 diabetes and whose decline in renal function was linear with time since several years had such tendency suddenly modified when antihypertensive treatment was instituted. These findings have subsequently been confirmed in many studies, and similar observations have been reported in nondiabetic renal disease (24). Hypertension, a hallmark of most chronic nephropathies, then was recognized as a strong, independent risk factor for ESRD (25). The MDRD study, which included patients with chronic renal failure of diverse causes, showed that those who progressed less were also those with the lowest BP (18). The Multiple Risk Factor Intervention Trial documented that elevated BP was a strong and independent risk factor for the development of ESRD (25) in men. In the MDRD study, patients who had >1 g of protein/24 h and were randomized to a mean arterial target of 92 mmHg had a greater reduction in proteinuria and a slower rate of loss of GFR than patients who were randomized to a mean arterial pressure of 107 mmHg (18). In a cohort of 163 patients with progressive chronic nephropathies of the REIN study, GFR decline was more reliably predicted by systolic as compared with diastolic BP and by pretreatment as compared with posttreatment BP. Systolic BP and pretreatment morning BP measurement were the most reliable predictors of disease outcome (26).

Low-Protein Diet

A low-protein diet in animal models of chronic nephropathy is consistently renoprotective (27). It has been more difficult to document this effect in humans. Low-protein diets may delay dialysis either through a reduction in uremic symptoms or through a specific renal protective effect (28). The MDRD study, the largest study to address this issue to date, found that a low-protein diet of 0.58 g protein/kg body wt per d compared with a usual intake of 1.3 g protein/kg body wt per d in patients with a GFR of 25 to 55 ml/min per 1.73 m² body surface area produced only a modest improvement in the rate of loss of GFR (18); this finding, however, has been challenged by subsequent analysis (29).

ACE Inhibition and Renal Protection: Evidence from Clinical Studies

Before 1995, several small randomized trials of ACE inhibitors in patients with nondiabetic renal disease were reported (30–34). These studies, however, did not have uniform results. Possible sources of variability included different methods of measuring renal function, different causes and severity of renal disease, use of different ACE inhibitors, and small sample sizes. Then, the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) study, a large-scale trial of patients with nondiabetic renal disease, provided evidence of a slower increase in serum creatinine on ACE inhibition (ACE-I) therapy (35). These results, however, were flawed by lack of data on hard end points such as dialysis or transplantation and did not allow the conclusion of whether the effect on this surrogate end point reflected a true renal protective effect. Moreover, a much more effective BP reduction on ACE inhibitors did not allow the establishment of whether this effect was specific for ACE-I or merely reflected better control of arterial hypertension. Much more convincing evidence of a specific renoprotective and dialysis saving potential of ACE-inhibition therapy was provided by the triad of Lancet publications generated by the REIN study from 1997 to 1999 (19,36,37). Analysis of the REIN study demonstrated that although BP control did not differ between the two treatment groups, patients who had proteinuria of ≥3 g/d and were treated with the ACE inhibitor showed a significant lower rate of decline in GFR and a reduced risk for doubling serum creatinine or end-stage renal failure as compared with patients who received conventional therapy (19). However, the finding that ramipril-induced reduction in urinary protein excretion rate was the only time-dependent covariate that predicted a lower rate of GFR decline and progression to ESRD indicated clearly that renoprotection is linked to reduction of protein traffic (38). After approximately 36 mo of treatment with ramipril, no additional patients progressed to the point of requiring dialysis, whereas patients who switched from conventional therapy to ramipril continued to develop ESRD (36). During the core study, ramipril therapy was associated with a 50% reduction in the risk for outcome events (ESRD or doubling of serum creatinine), whereas during the follow-up phase, patients who were originally randomized to ramipril had at most a threefold reduction in the risk for reaching end points. This remarkable outcome should be considered in light of the fact that these patients all had >3 g/d proteinuria before the study and, therefore, would have been expected to develop rapid decline in GFR (39).
A Valuable Tool to Test the Benefit of ACE-I in Chronic Renal Disease: Meta-Analysis of Clinical Trials

Background of the Meta-Analysis Approach

By using the meta-analytic method of pooling data from several clinical trials, the power to detect an effect of a given treatment may be increased. However, this type of analysis could have limitations. Sometimes they do not include small randomized trials that do not provide data on outcomes; secondarily, the appropriateness of combining data from different studies is questionable; also, the detection of relationships with covariates depends on the frequency and adequacy of measurements of the variables that could have true biologic variability as well as measurement error.

ACE-I and Renoprotection

Diverse meta-analyses examined whether ACE inhibitors in individuals with chronic nephropathy delay renal disease progression (40–47). An analysis, first of group (46) and then of individual-patient data (40), from 11 randomized, controlled trials revealed strong and consistent effects of ACE inhibitors in slowing the progression of nondiabetic renal disease. As in diabetic renal disease, ACE inhibitors decreased BP and urinary protein excretion, slowed the increase in serum creatinine, and reduced the risk for ESRD or for the combined outcome of doubling of the baseline serum creatinine concentration or ESRD by approximately 30% (40–44). These findings were consistent with data of a pooled analysis including patients with diabetic and nondiabetic renal disease, that was less consistently influenced by the underlying pathologies (43).

Role of Proteinuria Reduction

In a meta-analysis of >1100 patients, including 558 with nondiabetic renal disease, urinary proteins decreased by 40% on ACE-I and by 17% on other non–ACE-I despite almost equal BP reduction (−12.0% on ACE-I versus −11.4% on other drugs) (45). As also found in the REIN study, the beneficial effect of ACE inhibitors was stronger in patients with greater proteinuria at the onset of therapy and in patients with a greater decrease in BP and urinary protein excretion during ACE-I therapy (42).

These findings were consistent with data of a pooled analysis of 11 trials, including 2387 patients with chronic nephropathies of different causes, showing that, regardless of adopted treatments, the short-term changes in proteinuria had a major prognostic value in the long term (47). Actually, in 1710 patients, reduction of proteinuria was invariably associated with improved outcome (48). On the same line, in 638 patients without appreciable reductions in proteinuria, there was no benefit in the long term. In two other studies, lowering of proteinuria did not translate into a better outcome (48).

Role of BP Reduction

In a meta-analysis of 14 randomized, controlled trials that included patients with diabetic and nondiabetic renal disease, Maki et al. (42) found that the long-term beneficial effect of antihypertensive agents on proteinuria and GFR were proportional to BP reductions and were similar in diabetic and nondiabetic patients. Secondarily, they confirmed previous evidence that ACE-I has additional beneficial effects on proteinuria that are independent of BP reductions. A subsequent meta-analysis on 1860 nondiabetic patients showed that a systolic BP (SBP) of 110 to 129 mmHg in patients with urine protein excretion >2.0 g/d were associated with the lowest risk of kidney disease progression (44). No relationship between achieved BP control and outcome was found among patients with less proteinuria. These findings were consistent with previous evidence from the MDRD (18), REIN (19), and African American Study of Kidney Disease and Hypertension (AASK) (49) studies of the close relationship between BP reduction and renoprotection, in particular in patients with more proteinuria, and of a relatively slow progression in patients with less proteinuria (with the only exception of those with adult polycystic kidney disease) that was less consistently influenced by the achieved BP control (47).

The meta-analysis by Jafar et al. (50), however, found that SBP <110 mmHg was associated with an increased risk for doubling of serum creatinine or doubling of ESRD. The possibility of a detrimental effect, possibly mediated by a reduced kidney perfusion, was suggested. However, the possibility of a reverse causation could not be excluded by the meta-analysis. In other words, whether lower SBP was per se a risk factor or, alternatively, diseases often associated with lower BP (e.g., idiopathic membranous nephropathy, focal segmental glomerulosclerosis) independently contributed to more events in patients with SBP <110 mmHg could not be addressed by the analysis. Of note, unlike SBP, diastolic BP was not an independent predictor of progression and its reduction of improved outcome.

Interactions of ACE-I Therapy with Low-Protein Diet

A meta-analysis of five randomized controlled studies that included a total of 1413 patients who had nondiabetic renal disease and were followed for 18 to 36 mo failed to show any consistent benefit of a low-protein diet (51). On the same line, a more recent meta-analysis of 13 randomized and 11 nonrandomized trials found only a small benefit with the protein restriction in the randomized trials (52). Previous studies suggested the possibility that a low-protein diet could synergize the antiproteinuric effect of ACE-I. The hypothesis of a possible
beneficial interaction between the two therapeutic approaches, however, has not been evaluated formally so far.

Interaction of ACE-I with Gender

A number of studies suggested that renal disease progression is faster in men than in women regardless the ACE-I (53). Neugarten et al. (54) in a meta-analysis of 11,345 patients with nondiabetic chronic disease concluded that male gender adversely influenced the outcome of chronic renal disease. However, this analysis did not assess whether the effects of gender on renal disease progression was independent of other covariates such as diet, BP, or serum lipid levels. Moreover, the results were possibly confounded by the inclusion also of retrospective studies and by the analysis of group rather than of single patient. This may explain why Jafar et al. (55) recently published a patient-level meta-analysis with different findings. After adjusting for other factors associated with a faster rate of progression, they found that renal disease progression was comparable in women and men. Of note, their results were reminiscent of those of the REIN study, showing that disease progression in women is slower than in men (56). Actually, this study found a more consistent benefit from ACE-I therapy in women than in men. The possibility of an interaction between ACE-I therapy and gender, however, has not been explored formally by a meta-analysis approach.

Safety of ACE-I Therapy: Evidence from Clinical Studies and Meta-Analysis

A limited elevation in serum creatinine is common with ACE-I (57), but this is seldom reason for concern. In patients with chronic renal disease, ACE inhibitors usually increase serum K⁺ by 0.3 to 0.5 mEq/L. However, severe hyperkalemia that required treatment withdrawal was in no more than 1 to 2% of patients who were included in randomized trials of ACE-I therapy in nondiabetic renal disease (58). These findings were confirmed by the results of a meta-analysis of five clinical trials that included >1000 patients with nondiabetic nephropathy that found that only eight patients in the renin-angiotensin system inhibition group and seven in the non-renin-angiotensin system inhibition group had to be withdrawn because of severe hyperkalemia (Remuzzi G, personal communication, 2003). Further analysis showed ACE-I does not have clinically relevant effects on serum potassium when predisposing factors (e.g., hypovolemia, renal vascular disease) are excluded (58). Again, these data confirmed previous results of the REIN study showing that only one of 78 patients who were on ACE-I therapy had to be withdrawn from the study because of hyperkalemia (19).

Conclusion

In most cases, the meta-analyses confirmed and extended previous findings generated by randomized, clinical trials. Conceivably, well-designed studies in properly selected and carefully monitored patients who are at increased risk continue to be the best approach to test novel hypotheses. The meta-analyses, however, represent a valuable tool to evaluate the consistency and the generalizability of trial results to larger cohorts of patients.

References
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