A n irrefutable body of evidence from multiple well-powered clinical trials and numerous clinical studies in patients with type 1 and type 2 diabetes mellitus (DM) has demonstrated that inhibition of the renin-angiotensin system (RAS) retards the progression of diabetic nephropathy (1–11). The consistency of these clinical trial outcomes has resulted in guidelines from diabetes and renal societies to treat all patients with diabetes and diabetic nephropathy with drugs that inhibit the RAS (angiotensin-converting enzyme inhibitors [ACEI]) and/or angiotensin receptor antagonists (ARB) (12,13). The article by Ficociello et al. in this issue of CJASN documents the challenges and pitfalls of transporting these clinical trial and study results to a general population of patients (14). It is disheartening to read that, even in the most recent time of observation, 33% of patients with diabetic nephropathy did not receive any ACEI therapy despite current guideline recommendations. The transportability of clinical trial results is affected by differences between the study population and the general clinic population. By design, patients in clinical trials are judged to be compliant, do not have diseases other than diabetic nephropathy that could affect their kidney function, have clearly defined and accurately measured kidney function, and must meet many other inclusion and exclusion criteria. Certainly the general population of patients differs from those in a clinical trial, and those differences can affect the perceived efficacy of the intervention. The large number of patients in the observational study by Ficociello et al. with HgA1C levels far above those recommended by guidelines despite attendance in a dedicated diabetes clinic would suggest noncompliance. Interventions cannot benefit patients if they are not compliant or if the interventions are not properly implemented. Patients entering clinical trials are likely more compliant on average than a general clinic population. In addition, important areas to explore are the differences in health care delivery in a clinical trial that foster better compliance. The coordinators of clinical trials have to ensure timely visits and must educate patients, which may empower them to participate in their care more freely. Compliance with prescribed ACEI therapy is more carefully monitored, and there is consistency of ACEI therapy dosing in a trial, which is not necessarily reproduced in the clinic. This could have important effects on outcomes, as the Irbesartan Microalbuminuria II (IRMA 2) trial showed greater efficacy in patients randomized to the higher dose of irbesartan (11). Variation in compliance can be seen not only in the clinic but in clinical trials as well. Only recently has it become general knowledge that 50% of patients randomized to the ACEI, lis-inopril, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial either never received the drug or received it at such a low dose that it was unlikely to be renoprotective (15). This variation in patient compliance in ALLHAT raises serious doubt regarding reports derived from this study that question the renoprotective value of RAS blockade. These observations serve to emphasize the importance of accurate compliance data, whether in a clinical trial or in the clinic.

Another explanation for the difference in outcomes in the Joslin Clinic and the published clinical trials may be that the actual measurement of the outcome differed. Urine albumin:creatinine ratios on random specimens at different times of day associated with different levels of activity are going to be far less consistent than those measures of microalbuminuria used in clinical studies that employ consistent urine collection techniques. The authors give little information about the variability among the values for microalbuminuria that established their median values for each time interval in the Joslin study.

Is it surprising that, despite treatment with ACEI, some patients have progression of their diabetic nephropathy? Although clinical studies show a clear benefit of inhibition of the RAS, even in the treated group, progression of diabetic nephropathy does occur. For example, in the Collaborative Study Group Trial of Angiotensin-Converting Enzyme Inhibition in Type 1 Diabetic Nephropathy, during the median follow-up time of 1.7 yr there were 68 events in which serum creatinine was doubled: 43 in the placebo group and 25 in the group treated with captopril (1). This is an impressive beneficial effect, but as seen in the Joslin Clinic observational study not all treated patients are completely protected. Many variables could account for this included biologic variability in response to treatment, compliance, exposure to other “nephrotoxins,” and how advanced the disease was histologically at the time of treatment initiation (not necessarily coinciding with clinical measurements).

Also, there may be subsets of patients who are more or less
responsive to inhibition of the RAS because of differences in the pathogenesis of the chronic complex disease process that results in the clinical entity of diabetic nephropathy. Indeed, in chronic illnesses with multifactorial pathogenesis, a heterogeneity of response to treatment is expected. In the Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolemia Trial, cholesterol-lowering drugs (statins) reduced the risk of a primary myocardial event by 31%, but 174 of the patients in the treated group still experienced a myocardial event compared with 248 events in the control group during the average follow-up time of 4.9 yr (16). Despite this, statins are widely recommended to prevent myocardial events just as inhibitors of the RAS are recommended to prevent progression of diabetic nephropathy.

One must consider not only the hypothesis that a subset of patients responds in an all or none fashion to a specific therapy, but also the hypothesis that most or perhaps all patients are responsive, but to different degrees. Because the Joslin Clinic experience does not have patients randomized to treatment or no treatment, the ability to predict outcomes in the treated population, if untreated, is nonexistent. In the published clinical trials, it is not just the discrete end point events such as the previously mentioned doubling of serum creatinine events but the average rate of decline in creatinine clearance in the treated group as a whole compared with the untreated group that reveal the ACEI effect. What was seen was an average rate of decline of creatinine clearance of 11 ± 21% per year in the captopril group versus 21 ± 20% per year in the placebo group (P = 0.03) (1). This strongly suggests a more uniform slowing of the rate of decline in renal function in the treated group. In an analogous manner, the Joslin Clinic patients treated with varying doses of inhibitors of the RAS who progressed from microalbuminuria to proteinuria may have done so far sooner if untreated. This delay in progression when projected forward to a delay in the onset of end-stage renal disease translates into a better quality of life for a longer time for the patients and large health care cost savings.

By the nature of its design, the Joslin Clinic observational study is unable to discriminate between the possibility that there is a small subset of patients with microalbuminuria who, in response to treatment with ACEI, do not progress to proteinuria, or an alternative explanation that even the patients who are treated and progress do so at a slower rate than they would have if untreated, and hence there is a more uniform beneficial effect of treatment. The latter would lead one to look for additional therapies for diabetic nephropathy, not “alternate” therapies as suggested by the authors. Indeed, there are several ongoing pilot studies and clinical trials that examine the efficacy of new therapies on a background of therapy with inhibitors of the RAS in all participants.

The Joslin Clinic observational study best identifies potentially modifiable risk factors for progression of diabetic nephropathy in patients already treated with ACEI. This is very important information because risk factors may vary in the presence or absence of ACEI. Poor glycemic control and elevated serum cholesterol were identified as the major risk factors for progression in patients treated with ACEI. This is certainly consistent with the known detrimental effects of poor blood sugar control on the development of retinopathy, microalbuminuria, and neuropathy, and the known detrimental effects of dyslipidemia on the cardiovascular system. Well-designed clinical trials could rigorously examine these identified risk factors but would be complex to develop. There are already many indications for tight blood sugar control and treating dyslipidemia in this population of patients. With the epidemic of end-stage renal disease secondary to diabetic nephropathy, efforts must be made to more widely and more successfully implement existing therapies and to identify potentially modifiable additional risk factors for progressive renal disease.

Disclosures

J.L. was an investigator in the ACE Inhibition in Type 1 Diabetic Nephropathy Trial sponsored by the National Institutes of Health and Bristol-Myers/Squibb.

References

9. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA,
See the related article, “Determinants of Progression from Microalbuminuria to Proteinuria in Patients Who Have Type 1 Diabetes and Are Treated with Angiotensin-Converting Enzyme Inhibitors,” on pages 461–469.

Ficociello et al. (pages 461–469) and the editorial by Lewis in this month’s CJASN point to the fact that high urinary albumin excretion and high blood pressure, as well as the duration of diabetes, are major factors allowing microalbuminuria to evolve into overt proteinuria despite ACE inhibitors. The article in this month’s JASN by Eijkelkamp et al. (pages 1540–1546) emphasizes the importance of albuminuria as a target for renoprotective therapies independent of blood pressure control. Obviously, this is a continuum that needs to be appreciated by all nephrologists caring for patients with diabetes.