
Copyright © 2009 Massachusetts Medical Society.

---

**Blood-Pressure Control and Delay in Progression of Kidney Disease in Children**

Julie R. Ingelfinger, M.D.

Many children with chronic kidney disease, even those in whom the disease is discovered very early, ultimately lose renal function; some ultimately progress to stage 5 chronic kidney disease (end-stage renal disease). Causes of chronic kidney disease in children differ substantially from those in adults; the largest diagnostic categories in children are congenital renal and genitourinary abnormalities; obstructive uropathy or renal hypoplasia—dysplasia are most common, followed by reflux nephropathy and focal segmental glomerulosclerosis.1,2

Despite much evidence that blocking the renin–angiotensin system is helpful in treating adults with various nephropathies,3 comparable data from randomized, controlled trials involving children are lacking. Although case reports, case series, and nonrandomized trials have been published, randomized studies examining potential renoprotection in children have been much awaited. More than 20 years ago, Trachtman and Gauthier reported that angiotensin-converting–enzyme (ACE) inhibition decreased proteinuria in eight children with chronic kidney disease.4 Subsequently, Lama et al.5 reported a decrease in proteinuria and a slowing of the progression of renal disease with ACE-inhibitor therapy in a small 2-year observational study. More recently, a case–control study from the Italian Pediatric Registry of Chronic Renal Insufficiency (the ItalKid Project), a database of children with glomerular filtration rates less than 90 ml per minute per 1.73 m² of body-surface area, concluded that the evidence that ACE inhibition was effective in halting the progression of chronic kidney disease in children with the most common form of pediatric renal disease — hypoplasia or dysplasia — was unclear.6 However, finding sufficient patients to study in pediatric trials, including in the ItalKid Project, is difficult; of 162 patients with chronic renal insufficiency due to renal hypoplasia or dysplasia in the registry, only 41 were available for study after children younger than 2 years of age, those with less than 2 years of follow-up, and those with fewer than three data points were excluded. Thus, prospective trials examining the effects of treatment in preventing progression have been awaited.

In this issue of the *Journal*, the results of a 5-year randomized trial, the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients trial (ESCAPE; ClinicalTrials.gov number, NCT00221845),7 show that intensified blood-pressure control in children 3 to 18 years of age with chronic kidney disease (glomerular filtration rates of 15 to 80 ml per minute) who received fixed high-dose ACE inhibition consisting of ramipril at a daily dose of 6 mg per square meter offers an advantage. After a 6-month run-in period, during which any ACE inhibitor or other blocker of the renin–angiotensin system was withdrawn at least 2 months before the active phase of the study, participants were randomly assigned to intensified blood-pressure control (24-hour mean arterial pressure below the 50th percentile for age) or conventional blood-pressure control (mean arterial pressure in the 50th to 95th percentile). To achieve the tar-
get blood pressure, antihypertensive agents from classes that do not block the renin–angiotensin system were added, if necessary. The primary efficacy measure was the time to a 50% decline in glomerular filtration rate or progression to end-stage renal disease. Secondary end points included changes in blood pressure, changes in glomerular filtration rate, and proteinuria.

The results of the ESCAPE trial indicate that fewer patients in the intensified-control group than in the conventional-control group reached the primary end point, (29.9% vs. 41.7%; hazard ratio, 0.65; 95% confidence interval, 0.44 to 0.94; \( P=0.02 \)). This result suggests that controlling blood pressure to reach a target of less than the 50th percentile — strict blood-pressure control — improves outcome.

Several features of the ESCAPE study are unusual. First, the target blood pressure for the intensified-control group was not just within the normal range but was below the 50th percentile, whereas the target in the conventional-control group was between the 50th and 95th percentiles. Second, the study dose of ramipril was fixed; further blood-pressure control was attained by adding agents that do not block the renin–angiotensin system.

The primary and secondary end points in the ESCAPE trial relied on changes in glomerular filtration rate that were estimated on the basis of the original Schwartz formula for estimating glomerular filtration rate in children,\(^8\) a formula that was recently refined.\(^9\) However, assessments of endogenous creatinine clearance were performed in 82% of the participants, and the values for estimated and measured clearance in those patients in whom both measurements were available did not differ significantly. Still, it would have been optimal to obtain direct measurements in all participants, although anyone who cares for children understands how technically difficult it is to obtain repeated direct measurements of glomerular filtration rate.

Unexpectedly, the proteinuria in the participants initially decreased by half but then gradually increased, despite good blood-pressure control in both study groups. This proteinuria rebound seems surprising, in that the authors report that a 50% reduction in proteinuria within the first 2 months after starting ramipril was highly predictive of not progressing to end-stage renal disease. Furthermore, we know that proteinuria per se is harmful,\(^10\) so one would think that continued control of proteinuria would be helpful. Why did the breakthrough proteinuria occur? The authors speculate that the recurrence of proteinuria might be due to an “aldosterone breakthrough” phenomenon, which has been reported with ACE-inhibitor therapy\(^11\); the theory behind the aldosterone breakthrough phenomenon is that enzymes other than ACE, such as chymase, increase, resulting in the production of more angiotensin II, which, in turn, stimulates the adrenal production of aldosterone. Furthermore, other vasoactive substances, such as endothelin-1, might increase over time, increasing proteinuria. The authors also speculate that progression of underlying diseases may result in more proteinuria, despite blood-pressure control.

Many of the patients in the ESCAPE trial had received ACE-inhibitor therapy before being screened for inclusion in the study (about 33% of those in the intensified-control group and 36% in the conventional-control group). Though the results indicate that pre-study ACE-inhibitor therapy did not influence the intervention’s effect on a delay in the progression of renal disease, there is evidence that ACE-inhibitor therapy may decrease inflammation and fibrosis — an effect that is of potential importance in the prevention of progression of renal disease and that is, therefore, relevant to all participants in the study.

The cumulative withdrawal rates for reasons other than reaching an end point were similar in the two study groups — 28.0% in the intensified-control group and 26.5% in the conventional-control group. Most such patients transitioned to adult units; the others left by their own request, because of nonadherence, or for other reasons. The authors note that the rate of withdrawal for reasons other than reaching the primary end point was 5.5% annually, as compared with 10 to 21% per year in similar trials of renoprotective strategies in adults.

The ESCAPE study shows that renoprotective therapy slows the progression of renal disease in children. One hopes that this study will set a precedent for long-term, randomized, controlled treatment trials involving children with renal disease.


Copyright © 2009 Massachusetts Medical Society.

ICMJE SEEKING TWO NEW MEMBER JOURNALS

The International Committee of Medical Journal Editors (ICMJE) is seeking two new member journals to be represented by their editors-in-chief. Information about the ICMJE is available at www.icmje.org. Given the small number of applicants and the ICMJE’s recent awareness that many journals interested in applying had not seen the initial announcement posted in late June, the ICMJE has decided to extend the deadline for applications to November 30, 2009. Candidate journals should meet the following criteria:

• peer reviewed, general medical journal
• represent geographic areas (Latin America, Asia, Africa) or publication models (open access) not well represented by current ICMJE members
• editor who is knowledgeable about publication ethics
• editor who expects to be in the position for at least 3 years

To apply, editors-in-chief of interested journals should send electronic copies of the following to the ICMJE secretariat (Christine Laine at claine@acponline.org) by November 30, 2009:

• brief curriculum vitae
• description of journal, including age, sponsor/publisher, publishing model (subscription model, author pays, open access, etc.), target audience, circulation, number of manuscript submissions per year, description of peer review process used to select material for publication, acceptance rate, bibliographical databases where indexed, Web site address if applicable, and copy of guidelines for authors
• statement on why the journal/editor-in-chief wants to be an ICMJE member (should not exceed 1000 words in length)
• contact information

Copyright © 2009 Massachusetts Medical Society.