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Blood Pressure Control and Progression of CKD in Children

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Hypertension both accelerates and is exacerbated by progression of chronic kidney disease (CKD). In children with CKD, hypertension is common and often undertreated. A report by the North American Pediatric Renal Transplant Cooperative Study in 2002 showed that nearly half of the children enrolled in the Chronic Renal Insufficiency arm of the registry had hypertension based upon a casual blood pressure at the time of enrollment.(1) Hypertensive children with CKD developed either end-stage renal disease or loss of glomerular filtration rate (GFR) $> 10 \text{ ml/min/1.73m}^2$ significantly more often than normotensive children with CKD.

In a recent cross-sectional analysis of baseline blood pressure in almost 400 children in the CKiD (Chronic Kidney Disease in Children) cohort study, hypertension was common and frequently not adequately controlled.(2) The overall prevalence of systolic or diastolic hypertension was over 50%, with 13% of participants having uncontrolled hypertension. After multivariable adjustment, both nephrotic-range proteinuria and non-use of an agent to block the renin angiotensin system (RAS; angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker) were associated with having uncontrolled hypertension. More aggressive treatment of hypertension is a clear opportunity to improve the treatment of children with CKD.

Although substantial randomized controlled trial data in adults with CKD demonstrate that drugs blocking the renin-angiotensin II-aldosterone system, especially ACE inhibitors, both decrease proteinuria and slow CKD progression more than conventional antihypertensive therapy (3–6), little direct evidence has been available to support the generalization of these findings to children with CKD. Furthermore, although studies in adults have suggested that lower blood pressure targets may further slow CKD progression (7), this has not previously been shown in children. A recent study by the ESCAPE (Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients) trial group, published in 2009 in the *New England Journal of Medicine*, addresses both of these gaps in the current literature on slowing progression of CKD in children. (8)

WHAT DOES THIS IMPORTANT STUDY SHOW?

From 1998 – 2001, 33 pediatric nephrology units across Europe collaborated to randomize 468 children aged 3 – 18 years with estimated GFR by the Schwartz formula of $15 - 80 \text{ ml/min/1.73m}^2$ in order to assess the long-term effect on kidney disease progression of intensified blood pressure control among children who were receiving a fixed high dose of an ACE

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inhibitor. Hypertensive children either controlled with medications or with 24 hour mean arterial blood pressure above the 95th percentile for age, sex and height were included. Children were stratified by underlying kidney disease and rate of estimated GFR decline (fast or slow) during the 6 month run-in period and then were randomized to an intensive or conventional target for 24- hour mean arterial pressure (MAP), as assessed ambulatory blood pressure monitoring. Targets were based on normative ambulatory blood pressure monitoring data published by the same group in 2002 (9); the intensive target was a MAP less than 50th percentile for age, while the conventional target was a MAP corresponding to the 50th to 90th percentiles. After a 2 month wash-out period for those previously treated with RAS antagonists, all children received ramipril at the highest dose approved for hypertension for adults adapted for body size (6 mg/m²/day). Additional anti-hypertensive agents, except for other antagonists of the RAS, were added at the discretion of the local provider to achieve the target blood pressure goal for each study group. Study participants were seen in follow-up with clinic blood pressure monitored every 2 months and ambulatory blood pressure monitoring measured every 6 months for 5 years. The primary study endpoint was a 50% reduction in the estimated GFR or progression to end-stage renal disease, defined as estimated GFR < 10 ml/min/1.73m² or start of renal replacement therapy.

Of 468 children screened, 83 either did not meet entry criteria or were not adherent with therapy during the run-in period. Of 385 individuals randomized, 189 received intensified and 196 conventional blood pressure control. Baseline characteristics of treatment groups were comparable. The primary causes of kidney disease were hypodysplasia/dysplasia (66% and 71% in each treatment arm, respectively). Equal numbers of children in each arm were withdrawn over the course of follow-up as some transitioned to adult units or were non-adherent with study medications. Few had adverse events, specifically hyperkalemia or hypotension. The mean number of anti-hypertensive drugs prescribed in addition to ramipril was 0.9 ± 1.1 in the intensified-control group, as compared to 0.5 ± 0.9 in the conventional control group.

By Kaplan-Meier analysis, 29.9% of the intensified blood pressure control group versus 41.7% of the conventional blood pressure target group reached the primary endpoint. The hazard ratio for progression to end-stage renal disease with the intensified blood pressure treatment was 0.65 (95% CI 0.44– 0.94) compared to conventional therapy. The reduction in risk achieved with intensified blood pressure control remained significant after adjustment for baseline GFR, proteinuria, mean arterial pressure and age. Ambulatory blood pressure monitoring confirmed that the 24 hour mean arterial pressure was reduced in both groups with 24 hour mean arterial pressure 3–4 mm Hg lower on average in the intensified group. In this study, Cox proportional hazards analysis showed that the risk of attaining the composite endpoint was increased by 15.3 % for each mmHg above the 50th percentile (HR 1.153; CI 1.071–1.241, $p < 0.0001$), whereas any blood pressure below the 50th percentile did not significantly affect renal risk (HR 1.003, CI 0.898 – 1.119, $p=0.96$).

In the entire cohort, median urine protein to creatinine ratio was reduced from 0.82 to 0.36 g/g during the 1st 6 months of therapy but gradually increased again over time. Achievement of a 50% reduction in proteinuria within the first two months of ramipril administration was highly predictive of renal survival [HR 0.46 (0.27–0.79, $p=0.005$)], with actuarial five-year survival of 81.1% in patients who achieved >50% initial proteinuria reduction vs. 60.3% in patients with a less marked response independent of intervention group ($p=0.004$). Among the different groups of underlying kidney disorders, intensified blood pressure control clearly improved kidney survival in patients with glomerulopathies and was also effective in children with renal hypodysplasia/dysplasia. No significant effect was observed in patients with other congenital and hereditary nephropathies. Overall, achievement of blood-pressure targets and a decrease

in proteinuria were significant independent predictors of delayed progression of kidney disease in the children in this study.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

The renoprotective efficacy of RAS, which is in part independent of blood pressure, has been clearly demonstrated in animal models and in adults with acquired nephropathies (3–6). While both ACE inhibitors and angiotensin receptor blockers have been shown to reduce proteinuria in children with CKD,(10) the renoprotective efficacy of these medications in children and their potential impact on the epidemiology of CKD have not been previously studied in a large prospective randomized trial.

In adults with CKD, the REIN (Ramipril Efficacy in Nephropathy) trial demonstrated that patients with nephrotic range proteinuria had over a two-fold increase in risk of kidney disease progression compared to patients with less proteinuria.(11) Similarly, in a prospective multicenter trial of dietary protein restriction in children, proteinuria (partial $r^2 = 0.259$) and systolic blood pressure (partial $r^2 = 0.087$) were independent predictors of GFR decline.(12) In cross-sectional analysis of baseline data from the CKiD study, use of an ACE inhibitor or angiotensin receptor blocker was associated with a 54% (95% CI 15% to 75%) lower urine protein to creatinine ratio in individuals with underlying glomerular diagnosis, and a 9% (95% CI -29% to 18%) lower ratio in those with underlying urologic disease. (13)

In 2007, a case control study of 41 children treated with ACE inhibitors compared to 123 matched controls with CKD in the ItalKid registry led by Ardissino et al showed no clear evidence that the use of ACE inhibitors slowed the progression of CKD in children with hypoplastic nephropathy. Though the point estimates for rate of GFR decline were lower in the ACE inhibitor treated group, the difference in GFR decline between cases and controls was not statistically significant. The authors suggested that further studies were necessary before this treatment was routinely proposed to slow progression in children with hypoplasia.(14) While the study reported by the ESCAPE group does not directly address the question of ACE therapy vs no ACE therapy, it does provide evidence that improved blood pressure control utilizing ACE inhibitor therapy may slow GFR decline in children with CKD. Over the 5-year follow-up in the ESCAPE study, in which all children were treated with fixed dose ramipril, the annual reduction in the estimated GFR was 1.1 ± 7.8 ml/min/1.73m² in the intensified blood pressure control group and 2.5 ± 5.9 ml/min/1.73m² in the conventional blood pressure control group. These point estimates compare favorably with historic data in a prior study from the same group reporting change in estimated GFR (12) and with preliminary data on change in measured GFR decline in the CKiD study.

While hypertension is common in children with CKD (1,2), neither the relative degree of hypertension nor the effect of any class of antihypertensive medications on progressive kidney damage has been previously studied in a randomized controlled trial in children. The additional use of ambulatory blood pressure monitoring in the ESCAPE trial is another point of departure from prior studies of the management of elevated blood pressure in children with CKD. Ambulatory blood pressure monitoring has recently been shown to facilitate a more accurate diagnosis of hypertension in children and also to predict hypertensive target-organ damage (15) .

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The results of the ESCAPE study suggest that use of ACE inhibitors with targeting blood pressure control to the low range of normal in children with CKD is associated with slowing the rate of progression of kidney disease in children with primary glomerulopathies or renal hypodysplasia/dysplasia. Prior clinical practice guidelines on hypertension and anti-

hypertensive agents in CKD in children published by National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) in 2004 cited only weak evidence that ACE inhibitors or angiotensin receptor blockers may be preferred antihypertensive agents to slow the progression of CKD in children.⁽¹⁶⁾ The ESCAPE study suggests that the renoprotective effect of intensified blood pressure control appears to be additive to the potential benefit conferred by high-dose ACE inhibition. Prior KDOQI guidelines stated that there were insufficient data on the optimal level of blood pressure in children with CKD. Results of the ESCAPE study suggest that clinicians should target blood pressure in children with CKD below the 50th percentile for normal values. This study further suggests that ambulatory blood pressure monitoring may offer some additional benefit in blood pressure management for children with CKD. Further research on the advantages of combined therapies with ACE inhibitors and other therapies targeting the RAS in children are necessary.

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