Benefits of Continuing RAAS Inhibitors in Advanced CKD

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Renin-angiotensin-aldosterone system inhibitors (RAASi) have been repeatedly demonstrated to significantly slow progression of CKD in randomized controlled trials conducted in adults (1,2). The mechanisms by which RAASi slow progression of CKD include the reduction of proteinuria and optimized BP control (3). While the benefits of RAASi are undisputed in CKD stages 2–3, there is considerable controversy regarding the role of these agents in advanced CKD (stages 4–5) because few studies to date have included this population (2). Given that RAASi result in an acute drop in GFR, some have suggested that RAASi should be discontinued in patients with advanced CKD in an effort to restore some function and delay the need for KRT. One small observational study in adults with CKD stages 4–5 suggested improvement in kidney function after cessation of RAASi (4). In contrast, a randomized trial of 224 adults aged 18–70 years with CKD stage 4 showed a significantly slower decline in eGFR among those treated with the angiotensin-converting enzyme inhibitor benazepril compared with placebo (1). The major difference between these two studies was the age of the study population: the trial, which included younger adults, appeared to show benefits of RAASi treatment in patients with advanced CKD, whereas the observational study of an older population showed the opposite. Until now, no similar studies have been conducted in children with advanced CKD. Children represent a unique population, and are far less likely than adults to have comorbid conditions that may also influence outcomes.

In this issue of *CJASN*, van den Belt *et al.* (5) report an *acceleration* of the progression of CKD after discontinuation of RAASi in a prospective observational study of 69 children aged 6–17 years old with advanced CKD (mean eGFR 27.3 ml/min per 1.73 m^2). eGFR decreased by 3.9 (95% confidence interval [CI], 2.6 to 5.1) ml/min per 1.73/m^2 per year after discontinuation of RAASi, which represented a more than twofold larger decline in eGFR compared with the time before RAASi discontinuation (−1.5 [95% CI, −2.4 to −0.6] ml/min per 1.73 m^2 per year). Perhaps even more importantly, a group of propensity score-matched controls who continued RAASi showed a significantly *slower* decline in eGFR over the observation period than those in whom RAASi were discontinued. While this was an observational study, subject to bias in the selection of patients for discontinuation versus continued use of RAASi, the authors made impressive efforts to minimize such bias. Controls who continued RAASi were matched on important predictors of outcome with patients in whom RAASi were discontinued, including eGFR, change in eGFR since the previous visit, and follow-up time at the time point at which RAASi were stopped among those exposed to discontinuation of RAASi (termed "time zero"). Relevant characteristics (age, sex, primary disease, BP, eGFR, change in eGFR, degree of albuminuria, and serum potassium) of those who stopped and those who continued RAASi were almost identical. These well-matched controls showed a 1.8 (95% CI, 1.1 to 2.6) ml/min per 1.73 m^2 per year drop in eGFR before time zero, compared with a decline of 1.2 (95% CI, 0.4 to 2.0) ml/min per 1.73 m^2 per year after time zero ($P=0.30$). This represents a more than three times slower rate of decline in eGFR than was observed among those who stopped RAASi.

These findings in children are in sharp contrast to those of a case series of elderly patients (mean age 73.3±1.8 years) with advanced CKD in whom RAASi were discontinued. Ahmed *et al.* (4) reported impressive improvements in kidney function after discontinuation of RAASi, with 32/52 patients (62%) showing a >25% increase in eGFR.

Not surprisingly, both the pediatric and adult studies found slightly higher BP and higher albuminuria after stopping RAASi compared with before stopping. In the pediatric study, increases in BP after cessation of RAASi were mitigated by addition of another class of antihypertensive medication in 20% of children. Albuminuria more than doubled after RAASi were stopped in children, and each log unit increase in albuminuria was associated with 2.15 times higher hazards of reaching the end point of progression to KRT or a 50% decline in eGFR. These findings are consistent with the known mechanisms of action of RAASi and with the findings of prior randomized trials (1) showing preservation of kidney function with the use of RAASi. While Ahmed *et al.* emphasized the lack of a statistically significant increase in albuminuria after RAASi discontinuation in adults, the protein:creatinine ratio increased from 77±20 to 122±34 mg/mmol; power to detect a significant difference was very limited given the small sample and large variability.

Why, despite similar increases in BP and albuminuria after stopping RAASi, do children with CKD show an accelerated deterioration in eGFR while elderly adults appear to show an improvement in eGFR? Two important differences in the study populations must be

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acknowledged. First, the rate of decline in eGFR during treatment with RAASi among the children in the van den Belt *et al.* study (−1.5 ml/min per 1.73 m^2 per year) was substantially faster than in the adult study (−0.39 ml/min per 1.73 m^2 per year). This may reflect differences in primary kidney disease distributions between children and adults: congenital anomalies of the kidneys and the urinary tract are the most common cause of CKD in children, whereas diabetes is most common in adults. However, the physiologic rationale for the effectiveness of RAASi as renoprotective agents is stronger in proteinuric diseases such as diabetes (3,6) than in diseases without significant glomerular proteinuria, like congenital anomalies of the kidneys and the urinary tract. Therefore, solely on the basis of primary disease, one might expect less benefit of RAASi in children than adults, not more.

The most obvious major difference between the populations of the van den Belt *et al.* and Ahmed *et al.* studies is age. The pediatrician's (overused) refrain, "children are not just small adults," can be extended: adults are not just big children. The larger the age gap, the more numerous and larger the anatomic, biologic, and physiologic differences. The elderly are far more likely to have extensive, hemodynamically important vascular disease than children. Five of the patients in the adult study were presumed to have renovascular disease. Bilateral renovascular disease, compromising glomerular perfusion, may be unrecognized in some adults with CKD. RAASi in this setting are well known to result in substantial, *reversible* drops in eGFR (7).

It behooves pediatric and adult nephrologists alike to recall the mechanisms by which RAASi are believed to protect the kidneys. RAASi result in relatively greater dilation of the efferent than the afferent arteriole of the glomerulus, thereby reducing intraglomerular pressure. This will inevitably lead to a decrease in GFR. Indeed, the mechanism by which RAASi reduce proteinuria is by decreasing GFR; this is a desired effect, and does not reflect kidney injury. In fact, there is some evidence that the greater the initial acute drop in GFR with RAASi, the slower the subsequent decline in kidney function (8). However, when glomerular perfusion is already seriously compromised by vascular disease, additional reduction in glomerular pressure due to RAASi may result in an intolerable drop in GFR. Such extensive vascular disease is highly unlikely in children, likely explaining the major discrepancies between children and the elderly in the effect of RAASi in CKD. The results of the pediatric study by van den Belt *et al.* not only highlight the importance of avoiding generalization of observations made in adults to children, but the importance of considering the modifying effects of age even among adults.

The most frequently cited reasons for stopping RAASi in children were increased creatinine (33%) and hyperkalemia (23%). Whereas increased creatinine is rarely a welcome sign, it is important to remember that elevated creatinine alone, in the absence of other important signs or symptoms, is neither a definitive sign of AKI nor a signal that KRT is imminent. Asymptomatic elevated creatinine can be tolerated if reversible causes are excluded. Hyperkalemia, on the other hand, cannot be ignored. However, the mean decrease in potassium after stopping RAASi reported in the pediatric study (−0.17 mmol/L), although statistically significant, may not be clinically significant. There was large variability in the change in potassium after cessation of RAASi: potassium decreased by as much as 1.4 mmol/L but also increased by up to 1.4 mmol/L. Discontinuation of RAASi remains a reasonable response to hyperkalemia in advanced CKD, but if no improvement in potassium follows, van den Belt *et al.* findings suggest that reinitiation of RAASi should be considered. With the advent of newer potassium-binding medications, such as patiromer and sodium zirconium cyclosilicate, addition of these medications may allow RAASi to be prolonged (9).

A randomized trial of cessation versus continuation of RAASi (STOP-ACEi) is ongoing in a group of adults ≥18 years old with CKD stages 4–5 (10). The results of this trial may help inform practice in children. However, the work of van den Belt *et al.* reminds us that children, and even younger adults, may respond differently.

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