Making an earlier diagnosis of ADPKD: Implications for the treatment of hypertension

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Hypertension is a common finding in autosomal dominant polycystic kidney disease and frequently leads to its diagnosis. It develops earlier than in essential hypertension, usually during the second to third decade of life and before the loss of significant kidney function. It can even present in childhood, as shown in two studies where 18%–22%, or approximately one in five adolescents with ADPKD, had hypertension. The incidence increases with age and after age 30 years is present in more than 65% of individuals with normal kidney function and 80% of those with reduced kidney function (see Figure 1). Hypertension is associated with increased kidney size, a faster decline in kidney function, left ventricular hypertrophy, premature cardiovascular disease, and mortality. As an example of the high prevalence of cardiac disease, 48% of ADPKD individuals in one study had left ventricular hypertrophy at a mean age of only 44 years.

In recognition of the high cardiovascular risk of this population, the Joint National Committee 7 and the National Kidney Foundation 8 recommend a lower target of <130/80 mm Hg in individuals with chronic kidney disease, the latter including ADPKD patients with normal kidney function. This largely follows observational studies in the general population showing a continuous decline in cardiovascular mortality with blood pressure lowering that extends even below 130/80 mm Hg.

Only a few randomized clinical trials have assessed the role of aggressive blood pressure lowering on renal and cardiac outcomes specifically in a CKD population. The MDRD 9 and AASK 10 studies on patients with nondiabetic chronic kidney disease and African Americans with hypertensive nephrosclerosis, respectively, showed no benefit of aggressive BP lowering on renal progression. A meta-

Figure 1
Prevalence of hypertension in children and adults seen at the University of Colorado between 1985 to 2000. Hypertension was defined as systolic or diastolic BP above the 95th percentile for age-, sex-, and height-matched children for subjects <18 years of age and as BP >140/80 for subjects older than 18 years of age or the use of antihypertensive medications.

<table>
<thead>
<tr>
<th>Age</th>
<th>% with hypertension</th>
</tr>
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<tbody>
<tr>
<td>0-14</td>
<td>10</td>
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<tr>
<td>14-18</td>
<td>20</td>
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<td>18-24</td>
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<td>24-30</td>
<td>40</td>
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<tr>
<td>&gt;30</td>
<td>50</td>
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PKD offering research funding

The PKD Foundation is seeking applications for $3.7 million in research funding. The foundation will accept grant and fellowship applications. New this year is the application for bridge grants. Deadlines are as follows: Grant applications (August 15, 2006), Fellowship applications (August 15, 2006), and Bridge Grant applications (September 1, 2006, December 1, 2006, and March 1, 2007). Application guidelines and downloadable forms are available online at www.pkdcure.org. For questions on the application process, contact PKD Foundation Scientific Program Director Lorrie Rome at lorrierr@pkdcure.org

analysis of randomized trials of ACE inhibitors in patients with nondiabetic kidney disease showed a greater benefit of lower blood pressure, but only in those with significant proteinuria (>1g/day),[12] atypical of ADPKD. The most compelling evidence comes from a trial involving 75 hypertensive APKD subjects with left ventricular hypertrophy who were treated to a BP of <120/80 versus 135-140/85-90 mm Hg over seven years.[13] As shown in Figure 2, those treated to the low vs. usual goal had a greater regression of left ventricular mass. There was no effect on the rate of decline in renal function, although the study was of insufficient size for such an effect to be detected.

Long-term follow-up of the MDRD Study participants, including 200 subjects with ADPKD, suggests a benefit of aggressive BP lowering on renal progression.[14] After an average of six years of follow-up, those randomized to the low BP goal were noted to have a significant delay in reaching end-stage renal disease and mortality. A lower target of <110/70 mm Hg applied at an earlier stage of disease (GFR>60 ml/s/min) may provide an even greater benefit and will be assessed in the HALT-PKD Study, a five-year multicenter NIH-sponsored clinical trial in ADPKD subjects that is currently enrolling patients.[15]

Also supporting an earlier diagnosis of ADPKD, the choice of antihypertensive agent differs from the treatment of essential hypertension. Thiazide diuretics are the recommended first-line agent in essential hypertension.[7] In contrast, strong evidence supports the use of ACE inhibitors or angiotensin receptor block-
in ADPKD specifically has not yet been conducted. A trend towards a slowing of renal functional decline with ACE-I was observed in a subgroup of 142 ADPKD subjects from a meta-analysis of ACE-I trials, although it was not statistically significant.[16] A wealth of experimental and clinical evidence, however, implicates the renin angiotensin aldosterone system in the development of hypertension and renal progression.[8] With cyst enlargement, blood vessels are impinged upon and blood flow is reduced, leading to the release of renin, angiotensin II generation, and from there, a cascade of inflammatory and mitogenic proteins that cause fibrosis of the tubulointerstitium and cyst growth. Although there is a lack of conclusive data, the strong evidence supporting ACE-I in other forms of kidney disease and the wealth of experimental data implicating the RAAS in ADPKD has led to the widespread use of ACE-I or ARB as first-line agents for

Figure 2
Reversal of left ventricular hypertrophy was greater with rigorous vs. standard blood pressure control.

treatment of hypertension in ADPKD. Whether more complete blockade of the RAAS through combination ACE-I/ARB as compared with ACE-I alone will slow the growth of kidneys and/or renal progression will be studied as part of the HALT-PKD Study.

**Conclusion**

It is important to screen at-risk and already diagnosed adolescents and young adults for hypertension at least annually. Early detection and aggressive treatment will reduce the future likelihood of cardiac and renal injury. A blood pressure target of less than 130/80 mm Hg and use of ACE-I or ARBs as first-line therapy are achievable goals. There is no evidence to support a specific second line agent after ACE-I; however, most clinicians would first add a diuretic and then a beta- or calcium channel blocker, to achieve a target of 130/80 mm Hg. As kidney function declines, as many as four to five drugs may be necessary to reach a blood pressure of 130/80 mm Hg.

**References**