Prospective Change in Renal Volume and Function in Children with ADPKD

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Background and objectives: Autosomal dominant polycystic kidney disease (ADPKD) is a progressive hereditary disorder affecting children and young adults. Early intervention may be necessary to significantly affect the long-term consequences of this disease.

Design, setting, participants, & measurements: The authors conducted a 5-yr randomized clinical trial to assess the effect of BP control with angiotensin-converting enzyme inhibition (ACEI) on disease progression in 85 children and young adults with ADPKD. Study groups were determined by subject BP, including hypertension (BP ≥ 95th percentile), borderline hypertension (BP 75 to 95th percentile), and severe ADPKD (BP ≤75th percentile with > 10 renal cysts). The primary outcome variable was renal volume by ultrasound, with secondary outcome variables including left ventricular mass index (LVMI) and microalbuminuria. In secondary analysis, the authors compared results between hypertensive and normotensive groups.

Results: The authors were not able to demonstrate a significant effect of ACEI on renal growth in young subjects with ADPKD. Hypertensive children were at particular risk for increases in renal volume and LVMI and decreased renal function as compared with the other study groups, and borderline hypertensive children were at high risk to develop hypertension over time. However, ACEI treatment was associated with stable renal function and LVMI in this group of children.

Conclusions: Close monitoring of cardiovascular and renal status is indicated in ADPKD children with hypertension or borderline hypertension. In contrast to effects in hypertensive ADPKD children, ACEI treatment in normotensive or borderline hypertensive ADPKD children may prevent the development of increased LVMI and deterioration in renal function.

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Autosomal dominant polycystic kidney disease (ADPKD) is a common hereditary disorder, affecting 1 in 400 to 1 in 1000 people. Although previously considered to be an adult disease, it has become clear that systemic manifestations can occur early in childhood, with diagnosis possible as early as *in utero*(1,2). Given that ADPKD is a progressive condition, it seems most appropriate to initiate intervention as early in life as possible to delay or prevent long-term consequences, including renal failure and cardiac complications. In this regard, we have recently completed a prospective randomized clinical trial designed to assess the effect of BP control with the angiotensin-converting enzyme inhibitor (ACEI) enalapril on renal and cardiac disease progression over a 5-yr period in children and young adults with ADPKD. The primary outcome variable was renal volume as assessed by ultrasound, with secondary outcome variables including left ventricular mass index (LVMI) and microalbuminuria. The results of this clinical trial are presented here.

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Materials and Methods

Recruitment and Regulatory Monitoring

This clinical trial was conducted at the Clinical Translational Research Center (CTRC) at The Children's Hospital in Denver, CO. Recruitment began in 1998. Subjects were recruited nationally from our ongoing studies of ADPKD, from physician referrals, and from family responses to preliminary information from the Polycystic Kidney Disease Research Foundation. The Colorado Multiple Institutional Review Board reviewed and approved the study protocol. Informed consent and assent as appropriate were obtained from all parents and/or subjects. A data safety monitoring board was established and met annually to review the progress of participants in the clinical trial as well as any adverse events.

Inclusion/Exclusion Criteria

Inclusion criteria included being between ages 4 and 21 yr, having ADPKD, and having normal renal function. Patients were considered to have ADPKD when radiographic imaging demonstrated at least one renal cyst in the setting of a family history of ADPKD or when multiple cysts were present and were clinically consistent with a new diagnosis of ADPKD. Creatinine clearance was estimated from the patient's height and serum creatinine concentration obtained within 6 mo before enrollment using the Schwartz formula (3). Exclusion criteria included

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past history of allergy to study medications or inability to comply with the study protocol.

Study Protocol

The study protocol has been extensively described (4). Once eligibility was confirmed, each subject was seen for a two-day visit at the CTRC. All subjects underwent a detailed history and physical examination. Blood was drawn for routine serum chemistries and complete blood count. A routine urinalysis was obtained. Two 24-h urine collections were obtained for assessment of creatinine clearance and microalbumin excretion. Abdominal ultrasound and echocardiography were performed as described below.

On the first day of the visit, BP measurement was determined in each arm after 5 min of quiet sitting. All subsequent BP measurements were taken in the arm with the highest BP, with a cuff appropriate for the size of the subject's arm according to guidelines set forth by the National High Blood Pressure Education Program (5–7), after 5 min of quiet sitting. A total of 12 sitting BP measurements were obtained during the visit using a programmable oscillometric BP monitor (Dinamap 1846 SX, Critikon). Subjects were assigned to a study group on the basis of BP results, with norms determined from the subject's sex, height, and age according to guidelines set forth by the National High Blood Pressure Education Program (5–7). Hypertension (high blood pressure; HBP) was defined as systolic BP (SBP) and/or diastolic BP (DBP) at or above the 95th percentile for sex, age, and height on three or more measurements. If a subject was already receiving antihypertensive medication, hypertension was documented by reviewing records or by close monitoring during a one-week washout period before the initial visit. During this washout period, medications were held as deemed clinically safe by the principal investigators, and BP was assessed within 2 d of stopping antihypertensive medication. Once hypertension was documented, the subject's usual antihypertensive regimen was resumed. For the vast majority of subjects, hypertension could be documented from previous records. Borderline BP (BBP) was defined as SBP and/or DBP between the 75th and the 95th percentiles for sex, age, and height on 3 or more measurements. Prehypertension in pediatric patients has been defined as BP between the 90th and the 95th percentile for age, height, and sex, which represents a very narrow range of BP as compared with prehypertension in adults (120 to 139/80 to 89 mmHg). We did not anticipate that we would be able to enroll enough prehypertensive children to achieve reasonable statistical power. The broader borderline hypertension definition was therefore adapted. This designation of borderline hypertension is supported by the observation that at baseline these children have an increase in LVMI as compared with children with BP less than the 75th percentile for age, height, and sex (8). Children with ADPKD with at least 10 renal cysts with BP at or below the 75th percentile for sex, age, and height on three or more measurements were assigned to the severe ADPKD (SPKD) study group.

Imaging

Renal volumes were measured by performing standard abdominal ultrasonography. Volume was calculated as the volume of a modified ellipse for each kidney using the following formula: volume = $\pi/6$ x length x width $\times$ depth. Length, width, and depth were measured in centimeters. Length and width were obtained from longitudinal images acquired in planes ranging from sagittal to coronal, whereas depth was obtained from transverse images of the mid-kidney acquired in the plane perpendicular to the longitudinal plane. Total renal volume was obtained by summing the volumes of both kidneys. Cyst number was recorded as the actual number when <15 or as >15 cysts per kidney. The ultrasonographer and the radiologist were not aware of the subject's BP or treatment status.

Standard two-dimensional and Doppler echocardiography was performed with the subject in a supine position using an Accuson 128 XP/5 ultrasound. Left ventricular mass (LVM) was determined by the formula $LVM = 0.80\,[1.04 \times (LVDd + PWT + IVSd)^3 - (LVDd)^3] + 0.6$, where LVDd is left ventricular diameter in diastole, PWT is posterior wall thickness in diastole, and IVSd is ventricular septal thickness in diastole (9). LVM was then corrected by body surface area (BSA) and reported as LVMI in g/m^2. BSA was utilized for correction of LVM to maintain consistency with our previous reports (8,9). The echocardiography technician and the cardiologist were not aware of the subject's BP or treatment status.

Home BP Monitoring

All subjects were given an autoinflation digital BP monitor with an appropriately sized cuff (A&D UA-767H, A&D Medical, San Jose, CA) and were instructed in its use. The accuracy and reliability of this BP monitor has been previously demonstrated in children and adults by comparison to simultaneous auscultatory measurements (10,11). Participants were instructed to obtain the subject's arm BP at home on at least a monthly basis. Measurements were to be taken six times, 3 min apart after 5 min of quiet sitting, 24 h after the last medication dose for daily dosing or 12 h after the last medication dose for twice daily dosing. Results were submitted for review on at least a monthly basis by either regular mail or by subject/parent entry of results onto a secure web-based data entry form. Results from home BP monitoring were then used for adjustment of medications as described below.

Patient Population

At the initial visit, subjects were stratified into hypertensive (HBP), borderline hypertensive (BBP), or severe ADPKD with normal BP (SPKD) groups on the basis of BP assessment and prior renal imaging (Figure 1). Subjects were randomized according to the scheme described in *Statistical Analyses* below. Hypertensive subjects were randomized to receive initial treatment with enalapril (Merck & Co., Inc., Whitehouse Station, NJ) to maintain goal BP either below the 90th percentile (HBP90) or below the 50th percentile (HBP50) for age, sex, and height. Borderline hypertensive subjects were randomized to either receive treatment with enalapril to a goal BP below the 50th percentile (BBP+ACEI) or to no ACEI treatment (BBP-ACEI). SPKD normotensive subjects were randomized to receive either treatment with enalapril to maintain goal BP less than the 50th percentile (SPKD+ACEI) or to no ACEI treatment (SPKD-ACEI).

Hypertensive children who were not previously taking enalapril underwent adjustment of medications at the discretion of the supervising physician (M.A.C.), on the basis of the subject's BP control, previous medications, and body size, with frequent monitoring. Enalapril was increased to a maximum of 0.6 mg/kg per d or 40 mg/d to reach the subject's BP goal (at least four of six SBP and at least four of six DBP readings at or slightly below the target level). Additional antihypertensive medications were added in a step-wise fashion if the goal BP was not reached with the maximum dose of enalapril. The second-line medication for management of hypertension was amlodipine (starting dose 2.5 mg/d [0.1 mg/kg per d], with dose increases of 2.5 mg/d every 4 wk to a maximum dose of 10 mg twice a day (12;13). The third-line antihypertensive medication was metoprolol (starting dose 0.5 mg/kg per d up to 50 mg/d with dose increases of 25 mg/d every 4 wk to a maximum dose of 2 mg/kg per d or 150 mg/d). The metoprolol dose was adjusted as needed to maintain heart rate $>$ 75 beats per minute (bpm) in children 6 to 12 yr of age and $>$60 bpm in

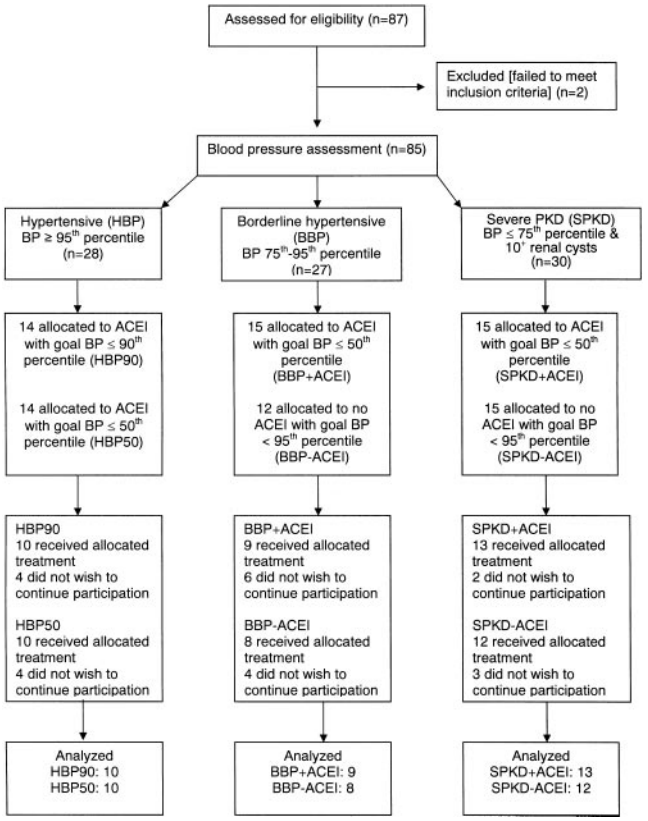

Figure 1. Flow of participants through study.

children ≥ 13 yr of age. Metoprolol was not used in subjects younger than 6 yr of age or subjects with a history of wheezing or asthma. Hydrochlorothiazide could also be added if needed (starting dose 6.25 mg/d for children weighing less than 25 kg, 12.5 mg/d for children weighing 25 to 50 kg, and 25 mg/d for children and adolescents weighing > 50 kg, with maximum 50 mg/d). For all medications, more rapid adjustments could be made by the supervising physician on the basis of the subject's BP control and size. Additional antihypertensive medications were prescribed as necessary to reach the subject's BP goal. Losartan was used for subjects who were unable to tolerate enalapril because of side effects such as cough or rash. Losartan was started at a dose of 0.7 mg/kg per d up to 50 mg/d in children age 6 yr and older, increasing incrementally to a maximum of 1.4 mg/kg per d (maximum 100 mg/d).

Borderline hypertensive and SPKD children who were randomized to treatment with enalapril were started at a dose of 2.5 mg/d, with adjustments in dose up to once per month at the discretion of the physician to reach the subject's BP goal (at least four of six SBP and at least four of six DBP at or slightly below the target level for each subject with maximum dose 40 mg/d). Any normotensive subject randomized to ACEI who demonstrated hypertension during follow-up despite maximal ACE inhibition was treated as described above for hypertensive patients. Any normotensive subject not randomized to ACEI who demonstrated hypertension (BP greater than the 95th percentile for age, sex, and height) was treated with enalapril to a BP goal at the 90th percentile.

All girls of possible childbearing potential (Tanner stage II or higher) who received medications were instructed in the use of home urine pregnancy tests (First Response Early Pregnancy Test; Church & Dwight, CO, Inc., Princeton, NJ) and were asked to perform tests each month and report the results to us. They also received counseling regarding medication risks in pregnancy and methods of birth control as appropriate.

Follow-Up

Subjects returned on an annual basis for repeat blood and urine testing, abdominal ultrasound, echocardiography, and BP monitoring as described above. Compliance with medication administration was assessed by monthly review of medication doses and BP results with subject/parent and by every third month review of medication supply. The study duration was 5 yr, including one baseline visit and five subsequent annual visits.

Conclusion of Study

Upon conclusion of the study, we attempted to decrease and/or discontinue enalapril in all subjects in the BBP and SPKD groups. Subjects in these groups who required enalapril to maintain BP below the 95th percentile for height, age, and sex were considered to have developed hypertension over the course of the study.

Statistical Considerations

Sample Size. Because this clinical trial represented a novel approach to treatment of ADPKD in children, no previous studies were available for calculation of the sample size required to achieve appropriate statistical power. Our preliminary data had demonstrated that subjects who had BP above the 75th percentile on 2 visits had a 9 ml greater increase in renal volume than subjects whose BP was less than the 75th percentile on 2 visits. The SD was 7 ml/yr. On the basis of these data, we estimated that the required sample size for 80% power at $\alpha = 0.05$ was 10 subjects in each subgroup (treated *versus* not treated). Therefore, our goal was to recruit at least 12 subjects in each subgroup to account for dropouts over the duration of the study.

Randomization Scheme. Block randomization was used to separately randomize HBP patients to HBP50 or HBP90, BBP patients to either BBP+ACEI or BBP-ACEI, and SPKD to SPKD+ACEI or SPKD-ACEI.

Statistical Analyses. In the current study we tested the hypothesis that treatment with ACEI would ameliorate the increase in renal volume, LVMI, and microalbuminuria in children and young adults with ADPKD. The primary outcome variable was renal volume, as assessed by ultrasound, with secondary outcome variables including LVMI as assessed by echocardiography and microalbuminuria. Baseline characteristics in the three primary study groups (HBP, BBP, SPKD) were reported as mean ± SEM and evaluated with ANOVA with Tukey test *post hoc*. Each of the three groups of children was analyzed separately. The normotensive (<95th percentile; BBP+ACEI, BBP-ACEI, SPKD+ACEI & SPKD-ACEI) *versus* hypertensive (≥ 95th percentile; HBP50 & HBP90) subjects were also analyzed separately. The data were first checked for the distributional assumption of normality. Since renal volume by ultrasound, LVMI, and urine microalbumin excretion (UMA) were highly skewed, a natural log transformation was performed, resulting in normal distributions for all three variables. Thus, the natural logs were used in analysis, then back-transformed and presented as the geometric mean and 95% confidence interval. Mixed-model repeated measures analysis was performed using an unstructured covariance structure and preplanned comparisons to test the difference between groups at baseline and final study visits. Sex and height were used as covariates in all models. Height was used in place of body mass index (BMI) because it was more highly correlated with the outcome variables than BMI.

Renal volume was also presented corrected for a BSA of 1.73 m^2

without additional adjustment for sex and height for assistance with clinical interpretation of data. The annual percent change in kidney volume for both kidneys combined was determined by regressing BSA-corrected kidney volumes against time (baseline to year 5) for each subject. Mixed-model repeated measures analysis with preplanned contrasts at baseline and year 5 was used to determine the least square means at those time points and to compute differences between groups using log transformed (on a base-10 scale) kidney volumes corrected for BSA. Annual increase (slope) in renal volume was calculated by regressing the untransformed corrected renal volume on years in the study and calculating a random slope and intercept for each individual. An estimate statement in SAS Proc Mixed was used to compare slopes between groups. Percent change per year in renal volume was obtained by regressing log 10 BSA-corrected renal volume on years, obtaining the log 10 base slope (which is the ratio), and back-transforming the slope to obtain the percent.

Fisher's exact test was used to compare the percentage of patients reaching their BP goal at each time point. Mixed-model analysis with random intercept and slope was used to test the hypothesis of equality of slopes between treatment arms. For this analysis, maximum likelihood estimates were calculated for untransformed data. A P value less than 0.05 was considered significant.

Results

A total of 85 subjects were enrolled in this clinical trial (Figure 1). Baseline characteristics are described in Table 1. There were no differences observed between the three study groups upon enrollment with respect to age, height, sex distribution, renal function as assessed by serum creatinine concentration and 24-h urine creatinine clearance, and microalbuminuria. SBP and DBP and index differed significantly between the study groups as per the study design. Renal volume was markedly increased in hypertensive subjects as compared with BBP and SPKD groups. LVMI was significantly increased in both HBP and BBP groups as compared with subjects with severe PKD. Of the 85 randomized patients, 62 (73%) completed the 5-yr study visit.

Hypertensive ADPKD children randomized to BP at or below the 50th percentile (HBP50) versus at or below the 90th percentile (HBP90)

A total of 28 hypertensive subjects were enrolled, including 14 in each treatment arm. Four subjects in both the HBP50 and the HBP90 groups dropped out during the course of the 5-yr study (Figure 1). We found significant difficulty in maintaining BP control in hypertensive ADPKD children. Specifically, at the conclusion of the study, four of 10 subjects in the HBP50 group were consistently at their BP goal with mean ± SEM 2.8 ± 0.3 antihypertensive drugs as compared with seven of 10 subjects in the HBP90 group with 1.6 ± 0.4 antihypertensive drugs. Thus, those in the HBP50 group required more medications in an attempt to control hypertension ($P < 0.05$). The SBP BP ($P =$

Table 1. Baseline characteristics of hypertensive (HBP), borderline hypertensive (BBP), and severe ADPKD (SPKD) subjects

Parameter	HBP	BBP	SPKD	*p-value for ANOVA*
N	28	27	30	
Male/female	17/11	15/12	13/17	NS
Age (years)	14 ± 1	12 ± 1	12 ± 1	NS
Height (cm)	160 ± 4	151 ± 5	151 ± 5	NS
SBP (mmHg)	130 ± 3	119 ± 2	109 ± 2	<0.0001
DBP (mmHg)	72 ± 2	68 ± 1	64 ± 1	<0.0002
SBP index	1.01 ± 0.02	0.95 ± 0.01	0.87 ± 0.01	<0.0001
DBP index	0.86 ± 0.02	0.84 ± 0.01	0.78 ± 0.01	<0.0004
Serum creatinine (mg/dl)	0.74 (0.68–0.81)	0.69 (0.62–0.77)	0.66 (0.57–0.70)	NS
24-h urine creatinine clearance (ml/min/1.73 m^2)	130 (120–141)	127 (117–138)	135 (127–145)	NS
Total renal volume corrected for BSA (ml/1.73m^2)	289 (247–339)	190 (162–223)	188 (162–220)	<0.0002
Total renal volume (ml)	238 (206–275)	163 (141–188)	156 (136–180)	<0.0001
LVMI (g/m^2)	75 (70–80)	71 (66–76)	61 (57–66)	<0.0004
UMA (mcg/day)	23 (16–33)	22 (14–35)	31 (19–51)	NS

Values for total renal volume corrected by body surface area are geometric mean (95% confidence interval). All others are height- and sex-adjusted mean ± SEM or geometric mean (95% confidence interval). ADPKD, autosomal dominant polycystic kidney disease; SBP, systolic blood pressure. DBP, diastolic blood pressure. US, ultrasound. BSA, body surface area. LVMI, left ventricular mass index. UMA, urine microalbumin excretion. NS, not significant.

SBP: HBP vs. BBP, $P < 0.002$; HBP vs. SPKD, $P < 0.0001$; BBP vs. SPKD, $P < 0.0001$
DBP: HBP vs. BBP, pNS; HBP vs. SPKD, $P < 0.0003$; BBP vs. SPKD, $P < 0.05$
SBP index: HBP vs. BBP, $P < 0.003$; HBP vs. SPKD, $P < 0.0001$; BBP vs. SPKD, $P < 0.0001$
DBP index: HBP vs. BBP, pNS; HBP vs. SPKD, $P = 0.0005$; BBP vs. SPKD, $P < 0.007$
Renal volume corrected for BSA (ml/1.73 m^2): HBP vs. BBP, $P = 0.0012$; HBP vs. SPKD, $P = 0.0007$; BBP vs. SPKD, pNS
Renal volume adjusted for sex and height: HBP vs. BBP, $P < 0.002$; HBP vs. SPKD, $P = 0.0002$; BBP vs. SPKD, pNS
LVMI: HBP vs. BBP, pNS; HBP vs. SPKD, $P = 0.0005$; BBP vs. SPKD, $P < 0.02$

0.0093) and DBP ($P = 0.0174$) index for HBP50 decreased over 5 yr, but SBP index and DBP index were not significantly different between the two groups. There was no significant difference between HBP50 and HBP90 groups for renal volume at baseline, but both groups demonstrated increased renal volume over time (Table 2A). There was no significant difference observed between baseline and year 5 in either group with respect to LVMI or UMA. A significant increase in serum creatinine occurred from baseline to year 5 in the HBP50 group ($P < 0.0001$) and in the HBP90 group ($P < 0.0001$). Similarly, 24-h urine creatinine clearance decreased in both groups ($P < 0.0001$ for baseline *versus* year 5). These changes were not different between the two arms.

Borderline Hypertensive ADPKD Children Randomized to Treatment with ACEI (BBP+ACEI) Versus *no ACEI Treatment (BBP-ACEI)*

A total of 27 borderline hypertensive subjects were studied, including 15 in the BBP+ACEI arm and 12 in the BBP-ACEI arm. Six subjects in the BBP+ACEI group and four subjects in the BBP-ACEI group dropped out during the course of the study (Figure 1). All subjects continuing in the study met their target BP goal (BBP+ACEI: ≤ 50th percentile; BBP–ACEI: < 95th percentile). Both SBP and DBP and BP index were lower in the BBP+ACEI as compared with BBP-ACEI at the conclusion of the study (Table 2B). There was no significant treatment effect in either arm on renal volume by ultrasound, LVMI, or UMA (Table 2B). Preplanned comparisons revealed no significant differences between BBP+ACEI and BBP-ACEI in LVMI (geometric mean [95% CI]: 76 [68–84] *versus* 66 [59–74] g/m^2, $P = 0.10$) at baseline after adjusting for height and sex, and there were no significant differences noted at year 5 of study. However, there was an increase in LVMI (geometric mean [95% CI]: 66 [59–74] *versus* 77 [67–88] g/m^2, $P < 0.05$) from baseline to year 5 in the BBP-ACEI arm. Both groups demonstrated increased renal volume by ultrasound (Table 2B). Subjects in the BBP+ACEI arm demonstrated no change in serum creatinine or 24-h urine creatinine clearance over time. However, subjects in the BBP-ACEI group demonstrated a mild decline in renal function over the 5-yr study period as assessed by serum creatinine ($P < 0.02$) and 24-h urine creatinine clearance ($P = 0.03$). At the conclusion of the 5 yr, enalapril was decreased or discontinued in the BBP+ACEI group. After this alteration in enalapril therapy, these subjects' follow-up BP monitoring demonstrated that nine of 15 subjects were unable to maintain normal BP to less than the 95th percentile without antihypertensive medication. Five of 12 subjects in the BBP-ACEI also developed BP greater than the 95th percentile for age, height, and sex over the course of the study. Thus, a total of 14 of 27 (52%) subjects within the borderline hypertensive group developed hypertension over the 5-yr study period.

Severe ADPKD Children Randomized to Treatment with ACEI (SPKD+ACEI) Versus *no ACEI Treatment (SPKD-ACEI)*

A total of 30 SPKD subjects were enrolled, including 15 each in the SPKD+ACEI and SPKD-ACEI arms. Two subjects in the SPKD+ACEI group and three subjects in the SPKD-ACEI group dropped out during the course of the study (Figure 1). We also found significant difficulty maintaining BP at or below the 50th percentile with a single agent (enalapril) in children with severe ADPKD, with only 8 of 13 (62%) at BP goal at the conclusion of the study. Within the study protocol, a second antihypertensive agent was only added if BP exceeded the 95th percentile on maximum enalapril dosing. There was no effect of ACEI on renal volume by ultrasound, UMA, serum creatinine, or 24-h urine creatinine clearance (Table 2C). LVMI increased in SPKD+ACEI from baseline to 5 yr ([95% CI]: 61 [55–68] *versus* 75 [67–83] g/m^2, $P < 0.003$). There was an increase in LVMI in SPKD-ACEI ([95% CI]: 61 [55–68] *versus* 71 [62–80] g/m^2, $P < 0.05$) from baseline to 5 yr. There was also a decrease in microalbumin excretion between baseline and 5 yr in SPKD+ACEI ([95% CI]: 36 [22–60] *versus* 22 (14–36) mg/d, $P < 0.0001$). Both groups demonstrated increased renal volume by ultrasound (Table 2C). At the conclusion of the study, enalapril was decreased or discontinued in SPKD+ACEI subjects. Follow up BP monitoring showed that four of 15 subjects could not maintain normal BP less than the 95th percentile without antihypertensive medication. Within the SPKD-ACEI group, 3 of 15 subjects developed hypertension over the course of the study. Thus, among children with severe ADPKD, 7 of 30 (23%) developed hypertension over the 5-yr study period.

The average change in renal volume per year across all groups was 32 ± 10 ml/1.73 m^2/yr or 9.3 ± 3.3 percent/1.73 m^2/yr, which was significantly different from zero ($P < 0.008$).

Normotensive Versus *Hypertensive ADPKD Children*

Results were then compared between all hypertensive (BP ≥ 95th percentile, HBP) and all normotensive (BP <95th percentile, NBP) subjects with adjustment for height and sex. Mixed-model repeated measures analysis with preplanned comparisons revealed that hypertensive children consistently had higher renal volume than normotensive children throughout the 5-yr study period (Figure 2, Table 3). These findings were consistent when renal volume was instead adjusted for sex and body mass index (data not shown). With adjustment for height and sex, hypertensive subjects demonstrated a greater but not statistically significant increase in renal volume over time as compared with normotensive subjects ($P = 0.19$). The increase in renal volume in the hypertensive and normotensive children was linear over the course of the study. However, a curvilinear relationship was present between renal volume and age in hypertensive children (Figure 3). Hypertensive children also had higher LVMI at baseline and tended to have higher LVMI throughout the study (Figure 4). These findings were consistent when LVMI was instead adjusted for sex and body mass index (data not shown). There was no difference between hypertensive and normotensive children in microalbumin excretion at baseline (23 [16–33] *versus* 26 [20–34], pNS) or at year 5 (34 [23–49] *versus* 22 [17–28], $P = 0.06$). Hypertensive children showed a significant decrease in renal function as assessed by both serum creatinine concentration and 24-h urine creatinine clearance over the 5-yr study period as compared with normotensive children (Table 4).

Table 2. Systolic blood pressure (SBP), SBP index, diastolic blood pressure (DBP), DBP index, renal volume by ultrasound, left ventricular mass index (LVMI) by echocardiography, and urine microalbumin (UMA) excretion over the 5-year study period in the different treatment arms

	A		B		C	
	HBP50	HBP90	BBP + ACEI	BBP-ACEI	SPKD + ACEI	SPKD-ACEI
N						
baseline	14	14	15	12	15	15
year 5	10	10	9	8	13	12
SBP (mmHg)						
baseline	131 ± 4	129 ± 4	119 ± 3	119 ± 3	109 ± 2	110 ± 2
year 5	125 ± 4	137 ± 4[a]	122 ± 3	132 ± 3[h,l]	117 ± 2	118 ± 3
SBP index						
baseline	1.02 ± 0.02	1.00 ± 0.02	0.95 ± 0.02	0.94 ± 0.02	0.86 ± 0.01	0.87 ± 0.01
year 5	0.93 ± 0.03[d]	1.03 ± 0.04	0.89 ± 0.02[k]	0.96 ± 0.02[h]	0.86 ± 0.01	0.90 ± 0.02
DBP (mmHg)						
baseline	70 ± 2	74 ± 2[b]	68 ± 2	67 ± 2	65 ± 2	63 ± 2
year 5	67 ± 2	77 ± 2[b]	71 ± 2	78 ± 2[h,m]	68 ± 2	71 ± 2
DBP index						
baseline	0.85 ± 0.02	0.86 ± 0.03	0.85 ± 0.02	0.83 ± 0.02	0.79 ± 0.01	0.77 ± 0.02
year 5	0.77 ± 0.03[c]	0.86 ± 0.04	0.78 ± 0.02[k]	0.87 ± 0.02[i]	0.74 ± 0.02[o]	0.83 ± 0.02[n,r]
BP goal met based on home reports						
year 5	4/10	7/10	9/9	8/8	8/13	12/12
Renal volume corrected for BSA (ml/1.73 m^2)						
baseline	255 (189–344)	328 (243–443)	188 (152–231)	193 (153–244)	184 (151–225)	194 (156–240)
year 5	399 (290–550)[e]	500 (366–682)[g]	276 (222–342)[j]	290 (227–372)[l]	307 (251–376)[p]	342 (273–428)[q]
Change in renal volume per year corrected for BSA (ml/1.73 m^2/yr)	43 ± 30	44 ± 30	20 ± 11	21 ± 14	24 ± 19	28 ± 21
Percent change in renal volume per year corrected for BSA (%/1.73 m^2/yr)	10.5 ± 8.8	8.7 ± 8.9	6.6 ± 5.3	8.1 ± 6.6	9.4 ± 5.7	11.6 ± 6.2
Renal volume adjusted for sex and height (ml)						
baseline	246 (174–350)	315 (226–439)	157 (125–196)	168 (132–214)	162 (133–198)	177 (142–220)
year 5	417 (290–600)[e]	516 (366–727)[f]	231 (184–290)[j]	263 (202–342)[l]	260 (214–318)[p]	311 (248–391)[q]
LVMI (g/m^2)						
baseline	76 (68–84)	76 (69–84)	76 (68–84)	66 (59–74)	61 (55–68)	61 (55–68)
year 5	79 (69–90)	80 (71–90)	77 (69–87)	77 (67–88)[l]	75 (67–83)[o]	71 (62–80)[s]
UMA (mcg/day)						
baseline	21 (14–32)	32 (20–50)	17 (9–32)	26 (14–48)	36 (22–60)	19 (11–34)
year 5	29 (18–46)	40 (25–63)	29 (11–35)	23 (12–46)	22 (14–36)[p]	20 (11–36)
SCr (mg/dl)						
baseline	0.70 (0.63–0.78)	0.78 (0.71–0.85)	0.77 (0.69–0.85)	0.67 (0.60–0.74)	0.66 (0.61–0.72)	0.69 (0.63–0.76)
year 5	0.98 (0.88–1.10)[e]	1.03 (0.93–1.15)[g]	0.73 (0.66–0.82)	0.80 (0.70–0.90)[l]	0.73 (0.67–0.80)	0.68 (0.61–0.76)
ClCr (ml/min/1.73 m^2)						
baseline	142 (129–156)	128 (117–140)	122 (111–135)	135 (121–150)	138 (127–150)	137 (125–149)
year 5	101 (90–112)[e]	97 (88–108)[g]	126 (113–140)	114 (100–129)[l]	127 (117–138)	136 (123–151)

A: hypertensive ADPKD children randomized to treatment with enalapril to goal blood pressure at the 50th percentile (HBP50) versus goal blood pressure at the 90th percentile (HBP90). B: borderline hypertensive children randomized to treatment with enalapril to goal blood pressure at or below the 50th percentile (BBP + ACEI) versus no treatment (BBP-ACEI): C: severe ADPKD children randomized to treatment with enalapril (SPKD + ACEI) versus no treatment (SPKD-ACEI). Values for renal volume (ml), LVMI, and UMA are geometric mean with 95% confidence interval adjusted for height and sex. Values for renal volume (ml/1.73 m^2) and change in renal volume over time (ml/1.73 m^2/yr) represent renal volume corrected for body surface area and are not adjusted for height or sex.

P values: [a]HBP50 vs. HBP90, $P < 0.05$. [b]HBP50 vs. HBP90, $P < 0.01$. [c]HBP50 year 5 vs. baseline, $P < 0.05$. [d]HBP50 year 5 vs. baseline, $P < 0.01$. [e]HBP50 year 5 vs. baseline, $P < 0.0001$. [f]HBP90 year 5 vs. baseline, $P < 0.05$. [g]HBP90 year 5 vs. baseline, $P < 0.0001$. [h]BBP + ACEI vs. BBP-ACEI, $P < 0.05$. [i]BBP + ACEI vs. BBP-ACEI, $P < 0.01$. [j]BBP + ACEI year 5 vs. baseline, $P < 0.05$. [k]BBP + ACEI, year 5 vs. baseline, $P < 0.01$. [l]BBP-ACEI year 5 vs. baseline, $P < 0.05$. [m]BBP-ACEI year 5 vs. baseline, $P < 0.01$. [n]SPKD + ACEI vs. SPKD-ACEI, $P < 0.01$. [o]SPKD + ACEI year 5 vs. baseline, $P < 0.01$. [p]SPKD + ACEI, year 5 vs. baseline, $P < 0.0001$. [q]SPKD-ACEI, year 5 vs. baseline, $P < 0.05$. [r]SPKD-ACEI, year 5 vs. baseline, $P < 0.01$. [s]SPKD-ACEI, year 5 vs. baseline, $P < 0.05$.

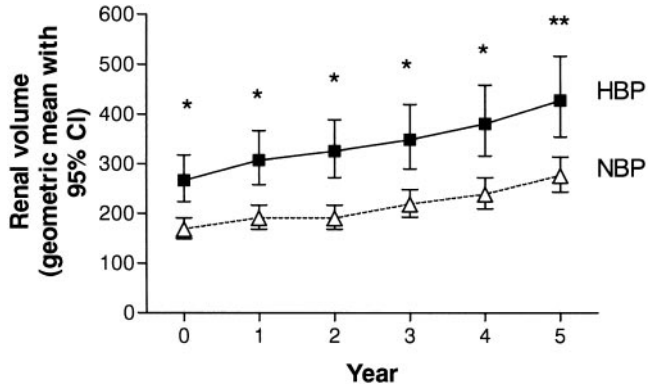

Figure 2. Hypertensive (HBP, n = 28) children had consistently higher renal volume than normotensive (NBP, n = 57) children throughout the 5-yr study period. Values are geometric mean (95% confidence interval) adjusted for height and sex. For HBP versus NBP: *P < 0.0001; **P < 0.0002.

Discussion

This is the first prospective longitudinal clinical study in children and adolescents with ADPKD. Although we were unable to demonstrate any significant effect of ACEI on our primary endpoint of renal volume in the present study, some interesting and important effects of ACEI on renal function and cardiovascular disease progression were evident in children with ADPKD. Previous studies in adults with ADPKD have implicated the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of the hypertension and left ventricular hypertrophy associated with this condition. In this regard, all components of the renin-angiotensin system including angiotensinogen, renin, angiotensin converting enzyme, angiotensin I and II, and angiotensin IA receptor have been identified in adult ADPKD kidneys (14). Circulating plasma renin activity has also been shown to be higher in ADPKD adults as compared with matched patients with essential hypertension in the supine and upright position and after stimulation with the ACE inhibitor captopril (15). In a 7 yr prospective adult study ACEI was shown to reverse left ventricular hypertrophy in hypertensive ADPKD patients, an effect significantly better than that of the calcium channel blocker amlodipine (16). ACEI has also been shown in adult ADPKD to prevent a rise in urinary albumin excretion over a 5-yr follow-up period as compared with amlodipine (17). These findings suggested the potential for ACE inhibition to slow renal and cardiovascular disease progression in children with ADPKD.

The inability of ACEI to diminish renal cyst growth in children with ADPKD could be explained by numerous factors. Despite the accumulated evidence in adults with ADPKD, the importance of RAAS in the pathogenesis of cyst growth and hypertension in children with ADPKD has not been well defined. Thus, it is possible that factors other than, or in addition to, RAAS are the primary mediators of renal cyst growth and hypertension in children with this condition. In this regard, although ACEI monotherapy was effective in controlling BP in children with borderline hypertension, multiple antihypertensive medications were necessary in hypertensive ADPKD children. Moreover, the role of angiotensin and aldosterone breakthrough was not characterized in the present study. Such breakthrough is known to occur in the presence of ACEI (18). It is not known whether more complete blockade with combined ACEI and angiotensin receptor blockade could have provided a more favorable result. Our results were also affected by sample size. The dropout rate of 27% exceeded that anticipated in the design of the clinical trial. Ambulatory BP monitoring would have been a useful tool to better characterize BP in individual subjects and to guide antihypertensive management in this research study (19). However, ongoing routine evaluation with this method would have been difficult with our distribution of subjects from across the United States. Our difficulty in consis-

Table 3. Renal volume over the 5-year study period in hypertensive (HBP) and normotensive (NBP) subjects with ADPKD

		HBP	NBP
N	Year 0	28	57
	Year 5	20	42
Renal volume corrected for BSA (ml/1.73 m^2)	Year 0	289 (244–343)	189 (168–213)[a]
	Year 5	451 (375–541)	304 (268–344)[b]
Change in renal volume per year corrected for BSA (ml/1.73 m^2/yr)		44 ± 15	24 ± 11
Percent change in renal volume per year corrected for BSA (%/1.73 m^2/yr)		9.4 ± 4.8	8.9 ± 3.4
Renal volume adjusted for sex and height (ml)	Year 0	267 (224–318)	169 (149–191)[a]
	Year 5	428 (354–516)	276 (243–313)[b]
Change in renal volume per year adjusted for sex and height (ml/yr)		41 ± 17	29 ± 12

Values for renal volume are geometric mean with 95% confidence interval. Values for change and percent change in renal volume are mean ± SEM. ADPKD, autosomal dominant polycystic kidney disease.
[a]HBP vs. NBP, $P < 0.0001$. [b]HBP vs. NBP, $P < 0.0005$.

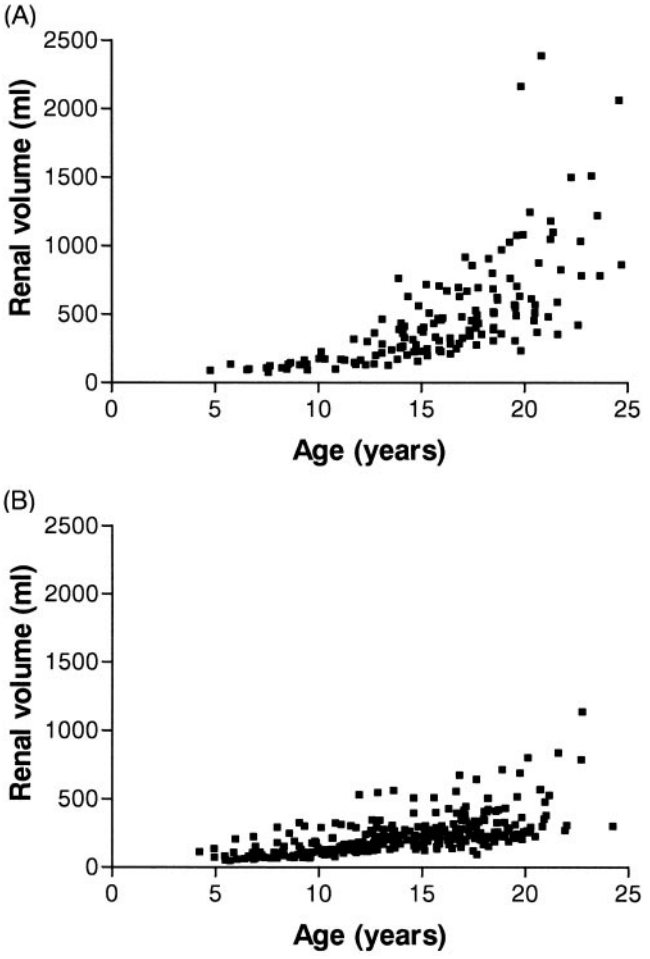

Figure 3. Relationship between renal volume and age in children with ADPKD who were (A) hypertensive; (B) normotensive.

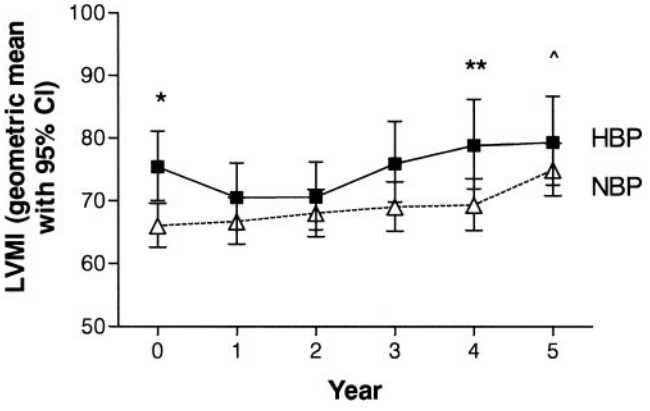

Figure 4. Hypertensive (HBP) subjects had higher left ventricular mass index (LVMI) at baseline as compared with normotensive (NBP) subjects with ADPKD. No significant differences in LVMI were noted between the groups at year 5 of study. Values are geometric mean (95% confidence interval) adjusted for height and sex. For HBP *versus* NBP: *$P < 0.005$; **$P < 0.05$. For NBP Year 0 *versus* Year 5: $\hat{P} < 0.0002$.

tently maintaining BP goals in hypertensive children with ADPKD also likely contributed to our negative findings with respect to the primary endpoint of renal volume. We attempted to optimize medication compliance via review of medication supplies and frequent communication with subjects to support compliance. However, it is likely in this group of subjects with many teenage participants that medication compliance may have affected BP control.

Nonetheless, several important findings were observed in the present study. It is important to note that a significant decline in renal function occurred over the course of the study in hypertensive children with ADPKD. Although this could represent an effect of ACEI inhibition to prevent glomerular hyperfiltration, this effect was not observed in the BBP+ACEI or SPKD+ACEI groups. Moreover, this finding is consistent with previous studies in adults with ADPKD, in whom the diagnosis of hypertension before 35 yr of age was associated with a median renal survival which was 14 yr shorter than those subjects with later onset hypertension (20). Thus we believe that children with ADPKD and hypertension are at particular risk of early chronic renal failure.

In ADPKD children with borderline hypertension, there was an apparent effect of ACEI on cardiovascular disease progression and renal function. Of the 17 children with borderline hypertension (75th–95th percentile) who completed the study, nine were treated with the ACEI enalapril to a proposed BP goal of the 50th percentile, whereas the BBP-ACEI group of eight patients was only treated if the BP exceeded the 95th percentile. In both groups the goals were met in those subjects completing the 5-yr follow-up. At the end of the study, antihypertensive medications were tapered or stopped and patients assessed for the presence of hypertension (BP ≥95th percentile). Thirteen of these 17 patients (77%) had become hypertensive. Thus, the results demonstrate that over a 5-yr period, children with borderline BP (75th–95th percentile) are at high risk to become overtly hypertensive. Moreover, control of BP in this borderline hypertensive group is possible with ACEI monotherapy. In these ADPKD children followed over 5 yr, the mean SBP and DBP were stable, and the SBP and DBP index decreased over time with ACEI. In contrast, the mean SBP and DBP rose significantly in the non-ACEI group, with no change in SBP or DBP index.

We have previously demonstrated that ADPKD children with borderline hypertension (75th–95th percentile) have increased LVMI as compared with children with BP below the 75th percentile in a baseline study (8). This elevation in LVMI was comparable to that observed in hypertensive ADPKD children. In the present prospective study, the BBP+ACEI group demonstrated stable LVMI over the course of the clinical trial while LVMI increased significantly in the same time period in the BBP-ACEI group. Similar to hypertensive children with ADPKD, elevated 24-h urine creatinine clearance was common at baseline in children with borderline hypertension. Some investigators have suggested that glomerular hyperfiltration may be an early marker of severe ADPKD (21,22). In this regard, it is important to note that the borderline hypertensive children receiving ACEI had stable renal function over the

Table 4. Renal function as assessed by serum creatinine (SCr) and 24-h urine creatinine clearance (ClCr) over the 5-year study period in hypertensive (HBP) and normotensive (NBP) subjects with ADPKD

		HBP	NBP
N	Year 0	28	57
	Year 5	20	42
SCr (mg/dl)	Year 0	0.73 (0.69–0.79)	0.70 (0.67–0.74)
	Year 5	0.98 (0.90–1.06)[a]	0.75 (0.71–0.79)[bc]
ClCr (ml/min/1.73 m^2)	Year 0	129 (121–138)	135 (128–141)
	Year 5	98 (90–106)	125 (119–132)[d]
Δ SCr (mg/dl/yr)		0.03 ± 0.01	0.00 ± 0.0[a]
Δ ClCr (ml/min/1.73 m^2/yr)		−6.1 ± 1.3	−1.4 ± 0.9[e]

Values for serum creatinine (SCr) and creatinine clearance (ClCr) are geometric mean with 95% confidence interval. Values for ΔSCr and ΔClCr are mean ± SEM.

[a]HBP Year 0 vs. Year 5. [b]HBP vs. NBP, $P < 0.0001$. [c]NBP Year 0 vs. Year 5, $P < 0.05$. [d]NBP Year 0 vs. Year 5, $P < 0.02$. [e]HBP vs. NBP, $P < 0.004$. $P < 0.0001$.

course of the study, whereas the BBP-ACEI group demonstrated a significant decline in renal function over time. It is not clear if these differences represent a protective effect of ACEI to prevent increased LVMI and glomerular hyperfiltration, the discrepancy in BP control between these study groups, or both.

Of the normotensive patients with severe ADPKD (BP <75th percentile with greater than 10 kidney cysts at baseline) followed for 5 yr, only seven of these 25 ADPKD children (28%) demonstrated persistent hypertension at the conclusion of the study. Both groups of normotensive children with greater than 10 renal cysts, however, demonstrated an increased LVMI from baseline to 5 yr. ACEI treatment was associated with a significant decrease in microalbuminuria in children with severe ADPKD.

We would anticipate a sigmoidal increase in renal volume with somatic growth in healthy children. Although renal volume increased in a linear manner over the course of the study (Figure 2), we observed exponential growth compared with age in children with ADPKD (Figure 3). The increase in renal volume was particularly impressive in hypertensive children and was reminiscent of the growth pattern observed in adults with ADPKD (23,24). These findings provide further evidence for the guarded prognosis of children with ADPKD and hypertension.

In summary, using ultrasonography, we observed progressive enlargement in renal volume in both normotensive and hypertensive children with ADPKD despite ACE inhibitor treatment. Hypertensive ADPKD children are clearly at increased risk for progressive renal and cardiovascular disease. Once hypertension is established, ACEI alone will not control hypertension nor prevent deterioration in renal function. In contrast, ACEI treatment may be of potential benefit to ameliorate cardiovascular disease progression and loss of renal function over time in ADPKD children with borderline hypertension (75th–95th percentile).

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Disclosures

None.

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See related editorial, "Renal Volume in Children with ADPKD: Size Matters," on pages 698–699.