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Kidney Disease Progression in Autosomal Recessive Polycystic Kidney Disease

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Abstract

Objective—To define glomerular filtration rate (GFR) decline, hypertension (HTN) and proteinuria in subjects with autosomal recessive polycystic kidney disease (ARPKD) and compare with two congenital kidney disease control groups in the Chronic Kidney Disease in Children (CKiD) cohort.

Study design—GFR decline (iohexol clearance), rates of HTN (ambulatory/casual blood pressures (BPs)), antihypertensive medication usage, left ventricular hypertrophy (LVH) and proteinuria were analyzed in subjects with ARPKD (n=22) and two control groups: aplastic/hypoplastic/dysplastic (n=44) and obstructive uropathies (n=44). Differences between study groups were examined by Wilcoxon rank sum test.

Results—Annualized GFR change in subjects with ARPKD was −1.4 ml/min/1.73m^2 (−6%), with higher decline in subjects age >10 years (−11.5%). However, overall rates of GFR decline did not differ significantly in subjects with ARPKD vs. controls. There were no significant differences in HTN or LVH rates, but subjects with ARPKD had a higher percent on ≥3 BP medications (32% vs.0%, p<0.0001), more ACE inhibitor use (82% vs. 27% vs. 36%, p<0.0005), and less proteinuria (urine protein: creatinine=0.1 vs.0.6, p<0.005).

Conclusions—This study reports rates of GFR decline, HTN and proteinuria in a small but well-phenotyped ARPKD cohort. The relatively slow rate of GFR decline in subjects with ARPKD and absence of significant proteinuria suggest that these standard clinical measures may have limited utility in assessing therapeutic interventions and highlight the need for other ARPKD kidney disease progression biomarkers.

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[*]List of additional members of CKiD Study is available at www.jpeds.com (Appendix).

The authors declare no conflicts of interest.

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Keywords

GFR decline; pediatric; hypertension; proteinuria

Autosomal recessive polycystic kidney disease (ARPKD) affects approximately 1 in 20,000 children and is genetically and clinically distinct from the more common autosomal dominant form (ADPKD).[1] ARPKD was previously considered a uniformly fatal disease in affected newborns, but with modern neonatal care, overall mortality has improved significantly More than 70% survive beyond the newborn period and >80% of those survive beyond ten years of age.[2] ARPKD still carries significant morbidity, with over 40% of patients progressing to end-stage renal disease (ESRD) by age 15 years.[2] The phenotype of ARPKD, however, is quite variable: some patients progress to ESRD in infancy, whereas others may not require renal replacement therapy until later childhood and adolescence.[3] A smaller subset present primarily with liver manifestations, typically in adolescence and young adulthood.[4]

Despite the significant mortality and morbidity in this population, prospectively collected data on ARPKD progression are very limited. Most studies have relied on retrospective analyses and/or registries, which have inherent limitations.[3-5] One prospective study reported measured glomerular filtration rates (GFRs) obtained by 24-hour creatinine clearance measurements, but did not report rates of GFR decline over time.[6] Factors that may contribute to kidney disease progression, specifically hypertension and proteinuria, have also not been well characterized.

The need for these progression data is highlighted by the emergence of novel therapies that may slow disease progression. Although there are currently no disease-specific therapies that have been applied in patients with ARPKD, a number of therapies have shown promise in ARPKD animal models.[7,8] Unfortunately, development of treatment trials in patients with ARPKD is hampered by the paucity of prospective data on GFR decline. In addition, surrogate markers for kidney disease progression, especially magnetic resonance imaging (MRI) measurements of kidney volume used to quantitate kidney disease progression in ADPKD,[9] are not valid in ARPKD, as kidney size does not increase with progressive disease.[10]

The objective of this study was to describe the rates of GFR decline, hypertension and proteinuria in subjects with ARPKD currently enrolled in the prospective Chronic Kidney Disease in Children (CKiD) study. We also compared findings in the subjects with ARPKD with those of two control groups with other congenital renal diseases also enrolled in CKiD in order to better identify ARPKD-specific kidney disease progression features that might differ from those of other congenital renal diseases.

METHODS

Subjects with ARPKD and controls were selected from among those enrolled in CKiD, a longitudinal, prospective study of children with mild-moderate chronic kidney disease (CKD). Over 50 pediatric nephrology sites in the United States and Canada have

participated and/or continue to participate in the study. The inclusion and exclusion criteria for participation in the study have been reported in detail elsewhere[11] (ClinicalTrials.gov: NCT00327860). Specific entry criteria relevant to this study include age 1-16 years, estimated GFR of 30-90 ml/min/1.73m^2, absence of prior solid organ or hematopoietic stem cell transplant and absence of severe syndromic disease. Subjects enrolled in CKiD undergo baseline evaluations, then yearly follow-up visits. The current study included all subjects with ARPKD currently enrolled in CKiD. Matched controls were obtained from two diagnostic groups with other congenital renal diseases: (1) aplastic/hypoplastic/dysplastic disorders (A/H/D); and (2) obstructive uropathies (OU). These groups were chosen as they were likely to have a similar age distribution as the subjects with ARPKD and are also primarily tubulointerstitial diseases. Matching was performed in order to distinguish ARPKD-specific clinical features from those related to early onset CKD in general.

Participants enrolled in CKiD undergo yearly determination of estimated GFR (eGFR) by the updated biomarker-based Schwartz GFR estimating formula, eGFR (ml/min per 1.73 m^2) = 39.8[ht(m)/Scr(mg/dl)]$^{0.456}$ [1.8/cystatin C (mg/l)]$^{0.418}$ [30/BUN(mg/dl)]$^{0.079}$ [1.076^{male}] [ht(m)/1.4]$^{0.179}$ and every other year measurements of GFR utilizing iohexol clearance (iGFR).[12] This eGFR formula has show strong correlation with corresponding iGFR measurements (R=0.92).[12] An analysis of subjects with ARPKD confirmed a similar strong correlation between eGFR and iGFR (R = 0.96, data not shown). Only subjects with at least two GFR measurements, whether iohexol-measured or estimated, were included. Subjects with ARPKD were matched 1:2 with A/D/H or OU controls for baseline GFR, age at study entry and at diagnosis. The primary outcome examined in this study was rate of GFR decline, reported both as percent (%) decline and absolute decline (expressed as GFR change in ml/min/1.73m^2/year). Both iGFR and eGFR were used in progression calculations, with preference given to iGFR where available.[13] Blood pressure control and rates of LVH and proteinuria were also investigated as secondary outcomes.

Casual blood pressures were obtained by standardized auscultatory methods at yearly visits. Ambulatory blood pressure monitoring (ABPM) was performed every two years utilizing the SpaceLabs 90217 oscillometric device (SpaceLabs Healthcare, Issaquah, WA). Echocardiography was also performed every two years to assess for the presence of left ventricular hypertrophy (LVH), defined as LV mass ≥95th percentile (indexed to Ht$^{2.7}$ for age and sex). Methods for obtaining casual blood pressures, ABPMs and echocardiograms have been described elsewhere.[14,15] A subject was considered to have casual hypertension (HTN) if the baseline blood pressure at the first visit was ≥95th percentile for age/sex/height percentile.[16] Ambulatory HTN was defined as mean wake or sleep systolic blood pressure (SBP) or diastolic blood pressure (DBP) ≥ 95th percentile or wake or sleep SBP or DBP load ≥ 25% according to published data.[17] Proteinuria was defined as a urine protein to creatinine ratio (UP/C) of ≥0.2 mg/mg from first morning specimens obtained at yearly visits.

Statistical analyses

Demographic and clinical characteristics were reported as median [interquartile range] or number, n (percent, %) for each group and compared descriptively between groups. Annualized percent and absolute change in GFR were calculated using individual

regressions (loglinear and linear, respectively) for each subject incorporating all available follow-up measurements. Differences (ARPKD vs. each control group) were tested by Wilcoxon rank-sum test or Fisher's exact test. Matched differences were calculated as the difference between the value of a subject with ARPKD and the average value of the two matched controls, and these distributions were tested for difference from zero by Wilcoxon signed rank test. As a subanalysis, we stratified subjects with ARPKD and control groups by baseline GFR (≥45 and <45 ml/min/1.73m^2) or age at study entry (≥10 and <10 years). All analyses were performed in SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

The baseline demographic and clinical features of the subjects with ARPKD and two control groups are shown in **Table I**. Subjects with ARPKD and controls were successfully matched on the selected factors; specifically, baseline GFR, age at study entry and age at diagnosis were not significantly different between the subjects with ARPKD and both control groups. The vast majority of subjects were diagnosed before one year of age. Notably, there were more males in the OU group, likely due to the preponderance of subjects with posterior urethral valves in that subgroup. There were also more African Americans in the OU control group compared with the ARPKD group, but this difference was not seen in comparisons of subjects with ARPKD with the A/H/D control group. Similarly, the ARPKD group had more subjects who were of Hispanic ethnicity compared with the A/H/D group, but this difference was not seen in comparisons with the OU group. Rates of prematurity (gestational age less than 36 weeks) or low birth weight (less than 2500 g) were similar in all three groups.

Renal function (GFR) decline

Baseline GFR and rates of GFR decline, including both annualized absolute and percent change, for the subjects with ARPKD and two control groups are summarized in **Table II**. Subjects with ARPKD showed a median absolute decline in GFR of −1.4 ml/min/1.73m^2 per year and a percent decline of 6% per year. This was not significantly different from that of the A/H/D group or the OU group. Analysis of the paired differences in percent GFR decline showed no significant differences between the subjects with ARPKD and either control group (data not shown). Because baseline GFR and puberty/older age have been associated with more rapid decline in renal function,[18,19] we performed subanalyses to examine the impact of these two factors on GFR decline. Subjects with ARPKD and control subjects were stratified into two baseline GFR groups: GFR <45 or ≥45 ml/min/1.73m^2 and two age groups: <10 vs. ≥10 years of age. Results are summarized in **Table III**. For both ARPKD and control groups, subjects with baseline GFR<45 ml/min/1.73m^2 showed increased rates of GFR decline compared with those with higher GFRs. In terms of differences related to age, it was notable that subjects with ARPKD who were ≥10 years of age showed an 11.5% per year decline in GFR, which was more than double the rate in subjects with ARPKD <10 years of age. The OU group also showed faster GFR decline in older subjects, whereas the A/H/D group did not. Statistical testing was not performed due to small numbers in some subgroups.

Hypertension, LVH and proteinuria

Rates of hypertension, LVH, anti-hypertensive medication use, and proteinuria are summarized in **Table IV**. Subjects with ARPKD had similar baseline blood pressures when compared with the A/H/D and OU controls, and there were no significant differences in rates of casual or ambulatory hypertension between subjects with ARPKD and either control group. Rates of LVH also did not differ significantly between subject and control groups. The subjects with ARPKD did, however, have more antihypertensive use, with over 80% requiring anti-hypertensive medications. Notably, 32% of subjects with ARPKD were on 3 or more anti-hypertensive medications, whereas none of the control subjects required that number. Subjects with ARPKD also had more angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) use compared with the controls. In contrast, the subjects with ARPKD had significantly less proteinuria than either control group. Median urine UPC in ARPKD was 0.1 vs. 0.6 in both of the control groups ($p<0.005$). Only 27% of subjects with ARPKD had proteinuria (UPC>0.2 mg/mg) whereas 68% of the A/H/D control group and 77% of the OU control group had proteinuria ($p<0.005$ subjects with ARPKD vs. each control group).

DISCUSSION

Cystic kidney disease in ARPKD is characterized by normal collecting tubule (CT) formation followed by development of progressive fusiform dilatation of the CTs.[1] The disorder affects all CTs, with fusiform cysts progressively replacing normal parenchyma over time. This ongoing active cystogenic process is accompanied by development of tubulointerstitial fibrosis. This pathophysiology is in contrast to obstructive uropathies and congenital dysplasias, in which damage or abnormalities occur during tubular development. Despite these differences in underlying pathogenesis, there were no significant differences in percent or absolute GFR decline in the subjects with ARPKD compared with the two control groups. The subjects with ARPKD had a relatively slow median annualized GFR decline (−1.4 ml/min/1.73m^2 or 6% per year) but also showed substantial variability (IQR, 1-10% decline per year). Overall, the absolute declines in all three groups were relatively slow, with overall rates of GFR decline less than 3 ml/min/1.73m^2/year.

Specific risk factors for ARPKD kidney disease progression have not been reported previously. Older age/puberty and lower baseline GFR, however, were recently shown to impact pediatric CKD progression.[18-20] In subanalyses, we examined rates of GFR decline in the subjects with ARPKD and two control groups, stratified by subject age or baseline GFR. subjects with ARPKD with lower baseline GFRs had higher rates of GFR decline than those with more intact baseline function. Although small numbers precluded statistical comparisons, both control groups also demonstrated higher rates of GFR decline in subjects with lower baseline GFRs. Strikingly, we found a strong association between age and GFR decline in the subjects with ARPKD with those ≥10 years of age having a decline rate of 11.5% per year, over twice that of younger children. The OU control group also showed higher rates of decline with older age, though not as dramatic, whereas the A/H/D group did not.

Hypertension is a well-established risk factor that is known to influence kidney disease progression in a wide variety of kidney diseases.[20] A previous publication that examined neurocognition in ARPKD reported data on hypertension and blood pressure medication use in this ARPKD cohort and the A/H/D control group.[21] In the current study, we expanded on those findings by examining the rates of hypertension and antihypertensive medication use in subjects with ARPKD in comparison with both A/H/D and OU patient groups. We also examined LVH rates, which had not been previously reported in the ARPKD cohort. Consistent with the well-known early and severe hypertension that is characteristic of ARPKD kidney disease, and with the previous published data, the subjects with ARPKD had significantly greater anti-hypertensive medication use compared with either control group. In fact, one-third of subjects with ARPKD were taking 3 or more anti-hypertensive medications, whereas none of the control subjects were. Despite the high anti-hypertensive requirements in the subjects with ARPKD, the rates of LVH did not differ among the three groups, suggesting that blood pressure control was similar in the three groups.

Proteinuria is also an important risk factor for kidney disease progression and several recent studies have highlighted its association with progression in both glomerular and non-glomerular disease in pediatric patients.[13,20] Although progression rates were similar in the subjects with ARPKD compared with the two control groups, the subjects with ARPKD had significantly lower rates of proteinuria compared with either of the control groups. There were, in fact, no subjects with ARPKD with heavy proteinuria (UPC >2 g/g, data not shown). Because all three groups encompass subjects with non-glomerular/primary tubulointerstitial diseases, one might not have expected them to differ with respect to the degree of proteinuria. The subjects with ARPKD, however, had substantially higher rates of ACEI use, likely reflecting the prevailing practice of using these agents as first line therapy for management of hypertension in this disease.[22] The decreased proteinuria rates in the subjects with ARPKD, therefore, may reflect greater ACEI use, although they may also reflect the underlying tubulointerstitial disease pathogenesis. Regardless of the underlying cause for the diminished proteinuria, the findings suggest that proteinuria does not predict progression in subjects with ARPKD.

This study had several important limitations. Most notably, the number of subjects with ARPKD was relatively small. Several other studies have included larger numbers of subjects, but, as noted previously, these were primarily retrospective studies and registry data that relied on voluntary self-reporting.[3,4] The ARPKD natural history study included 73 genetically confirmed adult and pediatric subjects with ARPKD and prospectively collected data.[6] However, although baseline GFR values on those subjects were reported, no data on serial GFRs or rates of progression were presented. That study also utilized 24-hour urine creatinine clearances rather than “gold standard” plasma clearance-based GFR measurements, such as the iohexol clearance methodology utilized in the CKiD study. In addition, a significant proportion of their population had undergone liver or kidney transplants at the time of evaluation. Another limitation of our study is the fact that the diagnosis of ARPKD in the CKiD cohort was made by the treating nephrologist on the basis of clinical information, genetic testing or both. Thus, we are not able to definitively exclude disorders that phenocopy ARPKD (eg, isolated cystic dysplasia).[23] Finally, the CKiD cohort includes subjects with ARPKD with mild to moderate renal disease. Those who were most

severely affected were typically excluded from entry based on GFR criteria (i.e., eGFR requirement of >30 ml/min/1.73m^2) and/or a history of antecedent solid organ transplantation (including liver or kidney transplant). Thus, the data presented may not be generalizable to all patients with ARPKD.

Whereas this study provides data on rates of GFR decline, it also highlights the ongoing challenges of quantifying kidney disease progression in these subjects. The subjects with ARPKD had relatively low rates of GFR decline as well as substantial variability in GFR decline; their rates of proteinuria were also very low, in part likely the result of ACEI usage which also had a favorable impact on BP control. These findings suggest that a large number of patients would need to be studied for a long period of time in order to assess the impact of a therapeutic intervention using these standard clinical measures of progression. Given the rare occurrence of this disease, alternative biomarkers for ARPKD kidney disease progression are urgently needed in order to undertake therapeutic trials in ARPKD.

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Appendix

APPENDIX

Additional CKiD sites and principal investigators by clinical coordinating center

Principal Investigator	Site
Alvaro Munoz, PhD	Johns Hopkins Bloomberg School of Public Health
Allison Dart, MD, MSc, FRCPC	Children's Hospital of Winnipeg
Larry Greenbaum, MD, PhD	Egleston Children's Hospital, Emory University
Jens Goebel, MD, Mark Mitsnefes, MD	Cincinnati Children's Hospital and Medical Center
Joseph Flynn, MD	Seattle Children's Hospital
Craig Wong, MD	University of New Mexico Children's Hospital
Sahar Fathallah, MD	Children's Hospital of Alabama
Isidro Salusky, MD; Ora Yadin, MD	University of California, Los Angeles
Bruce Morgenstern, MD	Phoenix Children's Hospital
Tom Blydt-Hansen, MD, FRCPC	British Columbia Children's Hospital
Keefe Davis, MD	St. Louis Children's Hospital
Cynthia Pan, MD	Medical College of Wisconsin
Amira Al-Uzri, MD; Randall Jenkins, MD	Oregon Health and Science University
Anthony Portale, MD	UCSF Children's Hospital
Mouin Seikaly, MD	University of Texas Southwestern Medical Center
Martin Turman , MD, PhD	Oklahoma University Health Sciences Center
Cynthia Wong, MD; Steven Alexander, MD	Stanford University Medical Center
Colleen Hastings, MD	LeBonheur Children's Medical Center
Randall Jenkins, MD	Northwest Pediatric Kidney Specialist
Nancy Rodig, MD; William Harmon, MD	Children's Hospital of Boston
Sharon Bartosh, MD	University of Wisconsin
Nadine Benador, MD; Robert Mak, MD, PhD	University of California, San Diego
Ellen Wood, MD	Cardinal Glennon Hospital
Randall Jenkins, MD	Children's Kidney Specialists, Idaho
Gary Lerner, MD	Children's Hospital of Los Angeles
Susan Massengill, MD	Carolinas Medical Center
Guillermo Hidalgo, MD	East Carolina University
Meredith Atkinson, MD	Johns Hopkins Children's Center

Principal Investigator	Site
Debbie Gipson, MD	University of Michigan, Mott Hospital
Poyyapakkam Srivaths, MD	Texas Children's Hospital, Baylor
Joshua Samuels, MD	University of Texas, Houston
Frederick Kaskel, MD, PhD	Children's Hospital at Montefiore
Debora Mattosian, MD	Children's Hospital at Dartmouth
Yi Cai, MD	DeVos Children's Hospital at Spectrum
Sharon Andreoli, MD, PhD	Riley Hospital for Children at Indiana Univ. Health
Jeffrey Saland, MD	Icahn School of Medicine at Mount Sinai
Hiren Patel, MD	Nationwide Children's Hospital, Ohio State Univ.
Victoria Norwood, MD	University of Virginia
Rulan Parekh, MD; Lisa Robinson, MD	Hospital for Sick Children (Sick Kids)
Susan Mendley, MD	University of Maryland
Marc Lande, MD, George Schwartz, MD	University of Rochester Medical Center, Golisano Children's Hospital at Strong
Patrick Brophy, MD	University of Iowa
Eunice John, MD	University of Illinois, Chicago
Kiran Upadhyay, MD	University of Florida
Maria Ferris, MD	University of North Carolina, Chapel Hill
Tej Matoo, MD	Children's Hospital of Michigan
Juan Kupferman, MD	Maimonides Medical Center
Lynne Weiss, MD	RBHS - Robert Wood Johnson Medical School
Craig Langman, MD	Ann & Robert H. Lurie Children's Hospital of Chicago
Patricia Seo-Mayer, MD	INOVA Fairfax Hospital for Children
Kanwal Kher, MD	Children's National Medical Center
Dmitry Samsonov, MD	Maria Fareri Children's Hospital at Westchester

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Table 1

Baseline Demographic and Clinical Characteristics of ARPKD Subjects and Controls

Characteristic	ARPKD Subjects (n=22)	A/H/D Controls (n=44)	p-value	OU Controls (n=44)	p-value
Age (in years) at study entry[a]	7.9 [4.8,10.1]	7.4 [6.1,9.6]	0.99	8.6 [4.9,10.2]	0.55
Age (in years) at diagnosis[a]	0.1 [0.0,0.4]	0.0 [0.0,1.1]	0.51	0.0 [0.0,0.8]	0.75
Male sex[b]	9 (41%)	22 (50%)	0.60	36 (82%)	**0.002**
African-American[b]	1 (5%)	10 (23%)	0.08	12 (27%)	**0.046**
Hispanic ethnicity[b]	8 (36%)	4 (9%)	**0.02**	7 (16%)	0.12
Premature birth (<36 weeks)[b]	6 (27%)	7 (17%)	0.34	4 (9%)	0.08
Low birth weight (<2500g)	4 (18%)	15 (36%)	0.16	5 (12%)	0.47

[a] Median [interquartile range]

[b] Number (percent). Significant p values ($p<0.05$) are shown in **bold.**

Table 2

Summary of Renal Disease Progression

	ARPKD Subjects (n=22)	A/H/D Controls (n=44)	p-value	OU Controls (n=44)	p-value
Baseline GFR (ml/min/1.73m^2)[a]	43 [30,57]	46 [29,55]	0.77	48 [31,56]	0.77
GFR annual absolute change (ml/min/1.73m^2)[a]	−1.4 [−3.5,−0.3]	−1.0 [−3.0,0.5]	0.72	−2.7 [−4.3,−0.4]	0.55
GFR annual percent change[a]	−6 [−10,−1]	−2 [−10,1]	0.21	−7 [−12,−1]	0.80

[a]Median [interquartile range].

Table 3

Subanalyses of Annualized Percent GFR Decline Stratified by Baseline GFR or Age at Study Entry.

	ARPKD Subjects (n=22)	A/H/D Controls (n=44)	OU Controls (n=44)
GFR <45 ml/min/1.73m^2	−6.52 (n=11)	−4.36 (n=21)	−9.17 (n=20)
GFR ≥45 ml/min/1.73m^2	−4.91 (n=11)	−0.71 (n=23)	−5.73 (n=24)
Age <10 years	−5.01 (n=16)	−2.79 (n=35)	−4.54 (n=32)
Age ≥10 years	−11.5 (n=6)	0.65 (n=9)	−11.20 (n=12)

Table 4

Hypertension and Proteinuria in ARPKD Subjects and Controls

Characteristic	ARPKD Subjects (n=22)	A/H/D Controls (n=44)	p-value	OU Controls (n=44)	p-value
Baseline (casual) systolic blood pressure (SBP) percentile[a]	83 [44,97]	68 [31,94]	0.31	72 [60,89]	0.56
Casual hypertension[b],	7 (32%)	9 (20%)	0.37	6 (14%)	0.10
Ambulatory hypertension[c]	6/12 (50%)	8/22 (36%)	0.49	20/28 (71%)	0.28
LVH[b,c]	4 (20%)	4 (10%)	0.42	2 (6%)	0.19
Anti-hypertensive medication use[b]	19 (86%)	18 (41%)	**0.0004**	15 (34%)	**0.0001**
ACEIs[b]	18 (82%)	16 (36%)	**0.0004**	12 (27%)	**<0.0001**
ARBs[b]	2 (9%)	0 (0%)	0.11	2 (5%)	0.60
# of Anti-hypertensives					
0	3 (14%)	26 (59%)	**<0.0001**	29 (66%)	**<0.0001**
1-2	12 (55%)	18 (41%)		15 (35%)	
≥3	7 (32%)	0 (0%)		0 (0%)	
Urine protein: Creatinine ratio (mg/mg)[a]	0.1 [0.1,0.2]	0.6 [0.1,1.5]	**0.003**	0.6 [0.2,0.9]	**0.0001**
Urine protein: creatinine > 0.2 (mg/mg)[b]	6 (27%)	28 (68%)	**0.003**	33 (77%)	**0.0002**

[a]Median [interquartile range]

[b]Number (percent)

[c]Number positive/number studied (percent). Significant p values (p<0.05) are shown in **bold** ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVH, left ventricular hypertrophy