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RESEARCH LETTER

PKD1 Compared With *PKD2* Genotype and Cardiac Hospitalizations in the Halt Progression of Polycystic Kidney Disease Studies

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INTRODUCTION

Autosomal dominant polycystic disease (ADPKD) is a genetic disorder characterized by progressive development and enlargement of kidney cysts that ultimately lead to loss of kidney function in most individuals.[1] ADPKD is primarily caused by mutations in the *PKD1* and *PKD2* genes.[1] Although the hallmark of ADPKD is an increase in total kidney volume with progressive loss of kidney function owing to the accumulation of kidney cysts, cardiovascular complications are a leading cause of death.[2] Notably, polycystin 1 and 2 are expressed in vascular endothelial and vascular smooth muscle cells.[3,4] Primary cilia defects that characterize ADPKD are associated with dysfunction in endothelial cilia, affecting calcium and nitric oxide signaling that can consequentially lead to vascular disorders, such as hypertension.[5]

Hypertension occurs in >60% of individuals with ADPKD before the loss of kidney function, resulting in a much earlier diagnosis of hypertension than the general population and is closely associated with total kidney volume.[2] Although hypertension occurs earlier and more frequently in patients with *PKD1* versus those with *PKD2*, both genotypes seem to confer an equal risk of developing intracranial aneurysms.[3,6] ADPKD has also been associated with cardiomyopathies.[S1,S2] Nevertheless, it is currently unknown whether mutations in *PKD1* or *PKD2* confer different risks of cardiovascular events. Given the known difference in the prevalence of hypertension, we hypothesized that patients with *PKD1* would have a higher risk of cardiovascular hospitalizations than those with *PKD2* who participated in the Halt Progression of Polycystic Kidney Disease (HALT-PKD) study A (NCT00283686) and B (NCT01885559).[7,8]

RESULTS

The baseline characteristics of the research subjects with ADPKD (n = 864) in the HALT-PKD study A (NCT00283686) or B (NCT01885559) with *PKD1* or *PKD2* mutations are found in Table 1. In addition, a subset of individuals (n = 449 from study A) who underwent cardiac magnetic resonance imaging were included in a secondary analysis (Table 1).

Among the 864 included participants, individuals with the *PKD1* genotype (84%) were slightly younger than those with the *PKD2* genotype. In addition, left ventricular mass (LVM) was significantly greater in

Table 1. Baseline characteristics of participants and cardiac hospitalizations

Baseline characteristics				
	Total (N = 864)	**PKD1 (n = 723)**	**PKD2 (n = 141)**	***P* value**
Age (yr)	42 ± 10	42 ± 10	46 ± 10	<0.01[a]
Systolic blood pressure (mm Hg)	128 ± 14	128 ± 14	125 ± 13	0.01[a]
Body mass index (kg/m^2)	27.5 ± 5.0	27.4 ± 4.9	28.0 ± 5.1	0.17
eGFR (ml/min per 1.73 m^2)	70.8 ± 26.3	70.1 ± 26.3	74.6 ± 26.2	0.06
Sex				
Male (%)	50.2	49.8	52.5	0.58
Female (%)	49.8	50.2	47.5	
Race				
Non-White (%)	6.1	6.8	2.8	0.08
White (%)	93.9	93.2	97.2	
	Total (N = 449)	**PKD1 (n = 367)**	**PKD2 (n = 82)**	***P* value**
Left ventricular mass (g)	126.5 ± 33.5	128.2 ± 34.0	119.2 ± 30.4	0.03[a]
Left ventricular mass index (g/m^2)	63.9 ± 12.7	64.4 ± 12.8	61.5 ± 11.6	0.06

eGFR, estimated glomerular filtration rate.
[a]$P < 0.05$.
Baseline characteristics are presented as mean ± SD or %. eGFR estimated by Chronic Kidney Disease Epidemiology Collaboration prediction equation. *t* tests or chi-square tests were used to calculate *P* values.

those with *PKD1* in comparison to those with *PKD2* in the subset of individuals who underwent cardiac magnetic resonance imaging, with a similar trend for LVM index (LVMI).

First cardiac hospitalization (N = 43) during trial participation was more common in individuals with a *PKD2* genotype (n = 13, 9.2%) compared with those with a *PKD1* genotype (n = 30, 4.1%; P = 0.01) (Supplementary Figure S1). Individuals with *PKD2* mutations were more likely to have cardiac hospitalization over time (Supplementary Figure S2). After adjustment for age, sex, race, and study randomization, *PKD2* was associated with an increased hazard of cardiac hospitalization (hazard ratio = 46.43, 95% CI: 9.97–216.34 vs. *PKD1*) (Table 2). This association remained after further adjustment for cardiac history, baseline systolic blood pressure, body mass index, smoking history, and baseline estimated glomerular filtration rate. In the study A subgroup, the *PKD2* genotype was associated with lower LVM at baseline as compared with *PKD1* (unadjusted: β-estimate = −8.91, 95% CI: −16.93 to −0.90). Nevertheless, in the adjusted models, there was no longer an association between genotype and baseline LVM (Table 2). There was also no association between genotype and LVMI at baseline.

DISCUSSION

In early and late-stage participants in the HALT-PKD studies, mutations in *PKD2* were independently associated with an increased hazard of cardiac hospitalization.[2] The association remained even after adjustment for demographics, study randomization, and cardiovascular risk factors. After adjustment, there was no association between genotype and LVM or LVMI at baseline.

Cardiac disease has been identified as a major cause of death in those with ADPKD associated with cardiac hypertrophy and coronary artery disease.[S3] Hypertension in the ADPKD population is associated with progression to end-stage renal disease and increased cardiovascular complications.[S4] Left ventricular hypertrophy, a risk factor for cardiovascular disease, is more prevalent in patients with ADPKD than in the general population.[9] Nevertheless, the prevalence of left ventricular hypertrophy in HALT-PKD was reported to be 3.9%, determined by cardiac magnetic resonance imaging using nonindexed LVM, and 0.93% using LVMI, which is a much lower proportion than reported previously in patients with ADPKD using echocardiography.[S5] Notably, hypertension and LVMI are significantly correlated in adults with ADPKD.[2,S6] Furthermore, normotensive patients with ADPKD have increased LVM when compared with healthy matched controls.[S7] We did not observe differences in LVMI between genotypes; however, the low prevalence of left ventricular hypertrophy in this sample may have limited the ability to detect differences between genotypes.

Genetic mutations in *PKD1* (∼80% of cases) are more prevalent when compared with mutations in *PKD2* (∼15% of cases).[S8] Similarly, our sample consisted of 84% of *PKD1* (chromosome 16p13.3) cases and 16% of *PKD2* (mutation chromosome 4q22.1) cases. *PKD1* cases are linked to an increased risk of progressive renal failure and more severe symptoms when compared with *PKD2*.[S9] Reduced kidney function is

Table 2. Associations between genotype and first cardiac hospitalization, baseline LVM, and baseline LVMI

Associations (hazard ratios [95% CI]) of genotype with first cardiac hospitalization (PKD2 vs. PKD)		
Model	**PKD1 (n = 723)**	**PKD2 (n = 141)**
Months to admission		
Unadjusted	Ref	29.58 [6.72–130.20]
[a]Model 1	Ref	46.43 [9.97–216.34]
[b]Model 2	Ref	50.24 [10.42–242.35]
Associations (β-estimates [95% CI]) of genotype with LVM (PKD1 vs. PKD2)		
Model	**PKD1 (n = 723)**	**PKD2 (n = 141)**
Unadjusted	Ref	−8.91 [−16.93 to −0.90]
[c]Model 1	Ref	−5.41 [−11.30 to 0.48]
[d]Model 2	Ref	−1.55 [−7.24 to 4.14]
Associations (β-estimates [95% CI]) of genotype with LVMI (PKD1 vs. PKD2)		
Model	**PKD1 (n = 723)**	**PKD2 (n = 141)**
Unadjusted	Ref	−2.93 [−5.97 to 0.10]
[c]Model 1	Ref	−1.61 [−4.18, 0.97]
[d]Model 2	Ref	−0.06 [−2.66, 2.53]

LVM, left ventricular mass; LVMI, left ventricular mass index.
[a]Model 1: Adjusted for age, sex, race, and study randomization.
[b]Model 2: Adjusted for model 1+ cardiac history, systolic blood pressure, body mass index, smoking history, and baseline estimated glomerular filtration rate.
[c]Model 1: Adjusted for age, sex, and race.
[d]Model 2: Adjusted for model 1+ cardiac history, systolic blood pressure, body mass index, smoking history, and baseline estimated glomerular filtration rate.
Hazard ratios were calculated at 66.3 months, which was the mean follow-up time.

associated with a higher cardiac event risk; however, we unexpectedly found that patients with *PKD2* had an increased risk of cardiac hospitalization. Of note, HALT inclusion criteria required preexisting hypertension, therefore likely selecting more severely affected patients within the *PKD2* spectrum. Notably, idiopathic dilated cardiomyopathy has been described to associate more strongly with *PKD2* versus *PKD1* mutations in humans, and polycystin-2 modulates intracellular calcium cycling contributing to the development of heart failure in *PKD2*-mutant fish.[S1] Chebib *et al.*[S2] observed that both *PKD1* and *PKD2* mutations may be predisposing factors for the development of cardiomyopathy. Also of note, the *PKD2* locus (4q21) is relatively close to genetic loci (4q25) that has been associated with an increased risk of atrial fibrillation.[S10] These factors could all influence cardiac hospitalization risk; however, there is not yet a molecular basis for the clinical observation of this study. If our findings are confirmed in other populations with ADPKD, further mechanistic studies need to be conducted to explain differences between genotypes and find therapeutic targets.

Strengths of this analysis include the use of a sizable multicenter trial with a well-characterized cohort. Our assessment is also novel as the association between PKD genotype and cardiac hospitalization to our knowledge has not been evaluated previously. Hospitalizations were adjudicated by an independent committee. Furthermore, as *PKD2* is known to confer an overall milder phenotype than *PKD1*, this information may be of clinical significance to this population.

Our study was limited to HALT-PKD participants who may not be reflective of the general ADPKD population. In addition, the CIs in some analyses were quite wide, and the small number of cardiac hospitalizations and limited power may have led to a chance finding. Another limitation was the high proportion of events identified as non-myocardial infarction unspecified chest pain adjudicated as cardiovascular. We also recognize that it would have been preferable to define cardiovascular death or major adverse cardiac events as an end point; however, this was not possible owing to the low incidence of these events in the trial. Finally, although significant, these statistical associations do not reveal causality, and residual confounding may exist, including cardiovascular risk factors we are unable to adjust for, such as medication use and lipoproteins.

In conclusion, we have revealed for the first time a possible association of a *PKD2* mutation with an increased hazard of cardiac hospitalization as compared with *PKD1*. Nevertheless, owing to the limitations of this analysis, the findings should be interpreted cautiously, and further research is needed to validate and further elucidate this observation.

DISCLOSURE

ACB is a consultant for Otsuka, Reata, and Sanofi. ASLY is a consultant for Regulus Therapeutics, Calico Life Sciences, and Navitor Pharmaceuticals and has served on an advisory board for Otsuka Pharmaceuticals. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Summary of first cardiac hospitalizations categorized by ICD-9 codes.

Figure S2. Survival probability of time to first cardiac hospitalization.

STROBE Statement.

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