Supplementary Materials

Supplementary Methods

Individuals with ADPKD (n=864) who participated in the Halt Progression of Polycystic Kidney Disease (HALT-PKD) study A (NCT00283686) or B (NCT01885559) and had genotype data with either a *PKD1* or *PKD2* mutation were included in this analysis. In addition, a subset of individuals (n=449) who underwent cardiac magnetic resonance imaging (MRI) in HALT Study A were included in a secondary analysis.

The HALT-PKD study design and implementation have been previously reported in detail.[S11] In brief, the trials were multicenter, randomized, double-blind, placebo-controlled including hypertensive ADPKD patients enrolled across a 3-year time span with 5 to 8 years of follow-up. Study A included 548 participants with an estimated glomerular filtration rate (eGFR) of >60 ml/min per 1.73 m^2 and study B included 470 participants with an eGFR of 25 to 60 ml/min per 1.73 m^2.[7,8] All participants had a known diagnosis of ADPKD and either hypertension or high-normal blood pressure. Study A employed a 2x2 factorial design and evaluated the effect of 1) multilevel renin angiotensin aldosterone system (RAAS) blockade with an angiotensin converting enzyme inhibitor (ACEi) + angiotensin receptor blocker (ARB) compared to ACEi + placebo and 2) low (95-110 / 60-75 mmHg) compared to standard (120-130 / 70-80 mmHg) blood pressure control.[7] Study B evaluated only the effect of ACEi + ARB compared to ACEi + placebo.[8]

Hospitalizations were adjudicated by investigators who were unaware of the treatment-group assignments and who determined the principal diagnosis and related procedures.[7] The number of cardiac events in the HALT-PKD studies was very small; thus, we determined the

association of genotype with the adverse cardiac event with the highest frequency (cardiac hospitalization; defined according to the Common Terminology Criteria for Adverse Events v.4.0 of the National Cancer Institution and adjudicated by an endpoints committee). Cardiac hospitalization was defined as the first hospitalization during the duration of participation in the HALT-PKD trials with a primary, secondary, or tertiary ICD9 code adjudicated as cardiovascular while participants were enrolled in the HALT-PKD trials. The cardiac MRI protocol, described previously by Perrone et al.[S5], was standardized and executed in 1.5T scanners. In brief, images of the left ventricle were acquired using ECG-gated, breath-hold 2D true-FISP (FIESTA) imaging sequences and involved 10-mm-thick contiguous slices encompassing the left ventricle from base to apex in the cardiac short-axis orientation. Image analysis was performed in the Analyze software system (Mayo Foundation, Biomedical Imaging Resource, Rochester, MN). Left ventricular volume was calculated as the sum of the myocardial area over the total ventricle times slice thickness. LVM was defined by the product of the volume and the specific gravity of myocardium (1.05 g/ml).[S5]

Confounders were selected *a priori* and all were measured at baseline. Race was categorized as White and non-White, as determined by self-report. Seated SBP was reported as the average of the final two readings within 10 mmHg, with three measurements taken following at least 5 minutes of rest and 30 seconds between readings. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) prediction equation using serum creatinine measured by a centralized laboratory.[S12] Body mass index was calculated using baseline body weight in kilograms divided by baseline height in meters squared (measured at clinical research clinics) and rounded to the nearest tenth.

Statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC). Mean and standard deviations were calculated for continuous variables, frequency and proportion were calculated for categorical variables. The comparison between genotype groups was performed by a two-sample t-test for continuous variables and using chi-square tests for categorical variables. Independent t-tests were used to compare continuous variables between two genotype groups. The association of genotype with time to first cardiac hospitalization was assessed using Cox models. We checked the assumption of proportional hazard, which was not met even after adjusting for covariates, and thus interaction terms with time were included in the unadjusted and adjusted models. Hazard ratios were calculated at 66.3 months, which was the mean follow-up time. A sequence of multivariable models was evaluated for each analysis. Model 1 adjusted for age, sex, race, and randomization assignment. Model 2 added cardiac history, systolic blood pressure, body mass index, smoking history, and baseline estimated glomerular filtration rate. Linear regression models were used to assess associations of genotype with continuous outcomes LVM and LVMI. A sequence of multivariable models was evaluated for each analysis. Model 1 adjusted for age, sex, and race. Model 2 added cardiac history, systolic blood pressure, body mass index, smoking history, and baseline estimated glomerular filtration rate. A significance level of $p< 0.05$ was set *a priori* for all statistical tests.

Supplementary References

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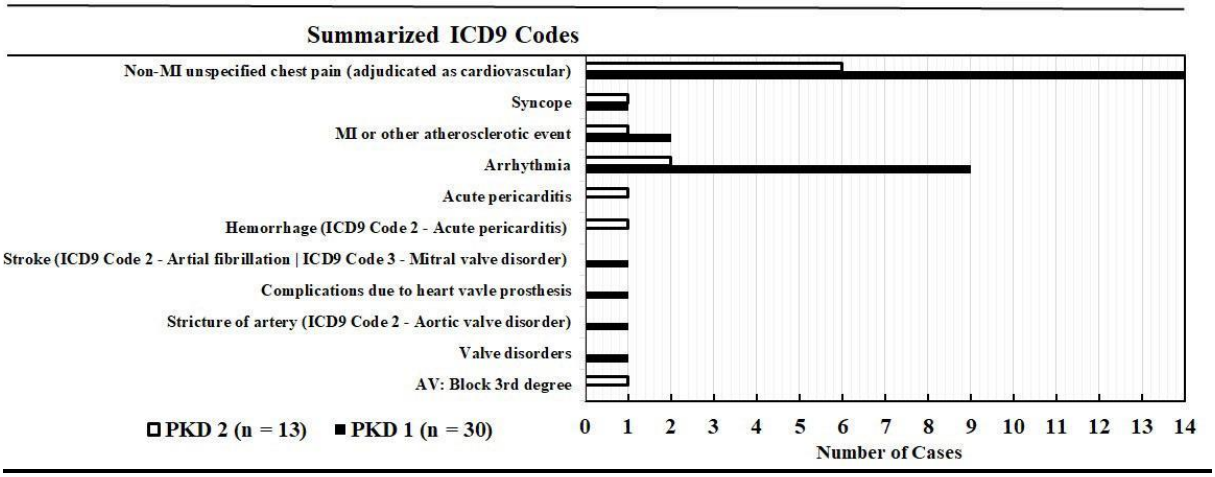
Supplementary Figures

Figure S1. Summary of first cardiac hospitalizations categorized by ICD9 codes.



*ICD9 code 1 listed first is primary, followed by code 2 (secondary) and code 3 (tertiary), if applicable.

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