Item S1: Detailed methods and additional results.

Contents:

Detailed Methods

a. **Experimental Design, and Major Results of the Early HALT-PKD Trial[1]; Distinctions from the Present Study.** The present study is a post hoc analysis of ADPKD patients enrolled in the Early HALT-PKD Trial and includes its trial design, interventions, and study oversight[1,2]. A steering committee of investigators designed the trial, and the protocol was approved by the institutional review board at each study site. An external advisory committee selected by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institutes of Health (NIH) reviewed the protocol and served as the data and safety monitoring board.[1,2] All the participants provided written informed consent.[1,2] Other than the obligatory oversight function of NIDDK/NIH, the funders of this study did not have a role in the study design; collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication. The contribution of NIDDK/NIH included its obligatory oversight role for the study. There were 512 hypertensive genetically tested ADPKD patients (418 families), ages 15-49 years, with an eGFR >60 mL/min/1.73m^2, who were randomized and treated to obtain either a standard blood pressure (BP) target of 120/70 to130/80 mmHg or a low BP target of 95/60 to 110/75 mmHg using an angiotensin-converting-enzyme (ACE) inhibitor (lisinopril) with either placebo or an angiotensin II-receptor blocker (ARB, telmisartan) in a double blinded pattern[1]. The relevant results of that study were: (a) low blood pressure control, as compared to standard blood- pressure control, was associated with a slower annual increase in TKV (5.6% vs 6.6%, P=0.006), no significant difference in the annual decline of overall eGFR or chronic eGFR (≥ 4 months), a greater decrease in acute eGFR (baseline to 4 months) (-3.1 vs 0.5 mL/min/1.73m^2, P<0.001), and a greater annual reduction in urinary albumin excretion (P<0.001); (b) the type of blood pressure treatment had no significant effect on any of these factors[1].

In the four patient groups of the present study (FH+/PKD1/PKD2, FH+/NMD, FH-/PKD1/PKD2, and

FH-/NMD), there was no significant effect of the degree of blood pressure control or the type of blood pressure treatment on the annual increase in TKV (P=0.6 and P=0.8, respectively), htTKV (P=0.6 and P=0.9, respectively) overall eGFR (P=0.09 and P=0.6, respectively), or 24-hour urine albumin excretion (P=0.2 and P=0.2, respectively).

b. **Clinical Methods.** Kidney and Liver MRI Imaging, eGFR, and 24-hour Urine Albumin Excretion. Patients had standardized imaging in a 1.5-T MRI scanner in order to determine total kidney volume (TKV) at baseline, 24, 48, and 60 months (Table 1).[1] The annual change in height-adjusted TKV (htTKV) was measured at these same intervals (table c).[3] The MRI images were analyzed with strict quality control measures[1]. Baseline MRI height-adjusted total liver volume (TLV), liver cyst volume (LCV), and liver parenchymal volume (LPV) were also measured (table b).[4] Serum creatinine was measured in a central lab at baseline, at 4 and 12 months, and every 6 months thereafter[1]. Estimated GFR (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration formula[5] at each of the times that serum creatinine was measured. Twenty-four hour urine albumin excretion was measured in a central lab at baseline, 4 and 12 months, and every 12 months thereafter[1]. The final MRI was done at 60 months, and eGFR and 24-hour urinary albumin excretion results conformed to the same duration.

c. **Statistical Methods.** Baseline and clinical characteristics were compared across the four patient groups using analysis of variance and chi square tests of significance, or their nonparametric counterparts when necessary. Several variables (e.g., TKV, htTKV, htTLV, htLCV, htLPV, and albuminuria) were log- transformed in order to normalize them.[1] Linear mixed models were used to assess whether the classified group moderated the effect of BP control and type of treatment on outcomes (TKV, htTKV, and eGFR) (part *a* of Detailed Methods).[1] Predictors included month, month-by-treatment arm, month-by-blood-pressure arm, patient classification groups, and all resulting 2- and 3-way interactions. A significant 3-way interaction (i.e. month-by-treatment arm-by-group interaction) would indicate a potential moderating effect of the group classification. In the absence of this effect, (TKV: P=0.6 for month-by-BP arm-by-group and P=0.8 for month-by-drug arm-by-group arm; htTKV: P=0.6 for month-by-BP arm-by-group and P=0.9 for month-by-drug arm-by-group arm; eGFR: P=0.09 for month-by-BP arm- by-group and P=0.6 for month-by-drug arm-by-group arm), the 2- and 3-way interactions were removed and the model was rerun to assess the impact of classification group on the outcome, independent of other predictors. As a result, the final model included predictors for month, month-by-treatment arm, month-by-blood-pressure arm, patient classification group, and month-by-patient classification group. For all log-transformed measures, we converted per-month slopes (β) into annual percentage changes according to the following formula: $100(e^{(12 \times \beta)} - 1)$,where e is the base of the natural logarithms. With piecewise linear mixed models, the overall eGFR slope was also partitioned into acute (baseline to 4 months) and chronic (≥4 months) phases with low or standard BP control and treatment groups which were then tested for any impact of patient group.[1]

An F test from a linear mixed model was used to statistically compare the TKV, htTKV and eGFR slopes across the four patient groups in Table 1, table *c*, and table *d*, respectively. The corresponding hypothesis is whether or not there are any differences in slope across the four groups. We did not further investigate pairwise differences between groups.

d. **Genetic Methods.** The entire coding regions of PKD1 and PKD2, as well as flanking intronic regions (± 50bp), were screened by Sanger sequencing.[6-8] Patients with no pathogenic mutation detected by Sanger sequencing were screened for gross rearrangements using multiplex ligation-dependent probe amplification (MLPA: MRC-Holland SALSA MLPA probemix P351/P352 PKD1-PKD2 Kit).[6-8] The designation of NMD in this study represents the results of Sanger sequence analysis and screening for larger rearrangements by MLPA with a protocol that was state-of-the-art when the HALT-PKD population was screened. If there still was no detectable mutation, a designation of NMD was made. Subsequently, in a multiconsortia study in which whole-exome sequencing in six families was followed by targeted Sanger sequencing of 11q12.3 in 327 genetically unresolved (GUR) ADPKD patients, a

single FH+ patient in the HALT-PKD cohort was found to have a GANAB mutation.[9] In order to thoroughly investigate NMD patients and their biological parents, one would need repeat testing with even more advanced next generation sequencing, but these studies are beyond the original scope of this paper.[1,6-8]

e. **Acute and Chronic eGFR.** In the acute eGFR period (baseline to 4 months), low BP patients did show a greater eGFR decrease than did those with standard BP (-14.944 vs –6.9305 mL/min/1.73 m^2, respectively, $P<0.001$). However, the effect of low BP on acute eGFR did not differ across the four patient groups ($P=0.5$). In the chronic eGFR period (≥ 4 months) low BP was not associated with a significant eGFR change ($P=0.09$), and there was no difference across the four patient groups ($P=0.2$).

f. **Baseline Height-Adjusted Liver Volumes.**[4] Height-adjusted total liver volume (htTLV), liver cyst volume (htLCV), and liver parenchymal volume (htLPV) were not significantly different across the four patient groups ($P=0.9$, $P=0.7$, and $P=0.7$, respectively) (table *b*). (see also part *a* of Detailed Methods)

Works Cited

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Table *a*. Patient Groups Based on Family History, PKD1 or PKD2 Mutation, or NMD

	Positive Family History (FH+)	**Negative Family History (FH-)**
PKD1 or PKD2 Mutation	*FH+/PKD1/PKD2*	*FH-/PKD1/PKD2*
N (%)	414 (93.5)	52 (75.4)
NMD	*FH+/NMD*	*FH-/NMD*
N (%)	29 (6.5)	17 (24.6)*
TOTAL 512	443 (100.0)	69 (100.0)

*There is a significantly higher percentage of NMD patients in the FH- Group (FH-/NMD) compared to the FH+ Group (FH+/NMD) in Early ADPKD, $P<0.001$.

Table *b*. Baseline Characteristics of Four Patient Groups: Positive Family History (FH+) and a PKD1 or PKD2 Mutation, FH+ and No Mutation Detected (NMD), a Negative Family History (FH-) and a PKD1 or PKD2 Mutation, and FH- and NMD

	FH+/PKD1/PKD2 (N=414)	*FH+/NMD* (N=29)	*FH-/PKD1/PKD2* (N=52)	*FH-/NMD* (N=17)	*P**
Age at baseline (years, mean ± SD) (N)†	36.6±8.3 (414)	38.7±8.7	36.6±8.5	40.3±6.7	0.2
Age at diagnosis of hypertension (years, mean ± SD) (N)	30.4±8.6 (412)	32.2±11.0	28.8±9.4	36.9±7.0	0.01
Age at diagnosis of ADPKD (years, mean ± SD) (N)	26.7±9.5 (412)	30.1±11.5	31.5±9.4	37.4±7.7	<0.001
Male, % (N)	52.2 (216)	41.4 (12)	50.0 (26)	52.9 (9)	0.7
White, % (N)	92.8 (384)	89.7 (26)	94.2 (49)	100.0 (17)	0.6
African American, % (N)	2.2 (9)	3.4 (1)	3.8 (2)	0.0 (0)	0.8
American Indian or Alaska Native, % (N)	1.2 (5)	3.4 (1)	0.0 (0)	0.0 (0)	0.5
Asian, % (N)	1.2 (5)	3.4 (1)	0.0 (0)	0.0 (0)	0.5
Some Other Race, % (N)	3.1 (13)	0.0 (0)	0.0 (0)	0.0 (0)	0.4
Body Mass Index (kg/m^2) (N)	27.2±4.8 (406)	29.6±7.8 (28)	27.5±6.1 (50)	27.0±6.1	0.1
Baseline average systolic blood pressure (mmHg) (N)	121.7±13.7 (409)	128.3±14.2 (28)	124.4±17.3 (51)	115.4±14.4	0.01
Baseline average diastolic blood pressure (mmHg) (N)	77.0±11.3 (409)	79.7±8.9 (28)	82.5±12.0 (51)	70.6±11.9	<0.001
Baseline average mean arterial pressure (mmHg) (N)	91.9±11.2 (409)	95.9±9.9 (28)	96.4±13.2 (51)	85.5±11.9	0.01
Left ventricular mass index (g/m^2) (N)	64.2±12.6 (402)	61.5±11.6 (28)	61.8±12.9 (50)	66.3±23.5	0.4
Urine volume (mL/24hrs) (N)	2615±1195 (412)	2412±976 (28)	2266±1150	2303±976	0.1
Urine sodium (mEq/24hrs) (N)	178±80 (405)	190±93 (28)	170±75	205±80 (15)	0.4
Total kidney volume (mL) (N)	1216±709 (410)	1097 ± 671	1355±791	1091±976	0.4
Height-adjusted total kidney volume (mL/m) (N)	692±393 (403)	645±371 (28)	781±439 (50)	611±524	0.3
Estimated GFR ($mL/min/1.73m^2$) (N)	91.6±17.4	87.1±15.8	89.5±18.9	90.4±15.7	0.5
Urinary albumin (mg/24hrs, median, p25, p75) (N)	18.4 (12.7,31.6) (405)	16.6 (9.9,37.4) (28)	20.2 (10.2,50.9)	13.5 (8.4,22.1) (15)	0.2
Height-adjusted Total liver volume (mL/m) (N)	1128±457 (402)	1077±313 (28)	1158±339 (50)	1211±798 (17)	0.9
Height-adjusted Liver cyst volume (mL/m) (N)	171±475 (302)	103±247 (17)	206±515 (39)	393±1015 (7)	0.7
Height-adjusted Liver parenchymal volume (mL/m) (N)	999±185 (402)	1015±241 (28)	998±247 (50)	1049±207 (17)	0.7

**P* values are calculated by chi-square for sex and race, and by probF for all other factors.
†N values are given if different from group total

Table *c*. Estimated Mean Change in htTKV (mL/m) from Baseline Measurements in Four Patient Groups During 60 Months of Follow-Up with 95% Confidence Intervals

Increase in htTKV (mL/m) over 60 months (mean and 95% confidence intervals)*				
	Model Estimated value at baseline	Change from baseline		
Month	**0**	**24**	**48**	**60**
FH+PKD1/PKD2	687.36	93.05	204.68	266.56
Lower 95% CI	622.14	85.60	187.31	243.10
Upper 95% CI	772.17	100.50	222.05	290.01
FH+NMD	638.82	84.83	188.96	232.88
Lower 95% CI	574.26	47.81	100.02	108.71
Upper 95% CI	727.66	121.84	277.89	357.05
FH-/PKD1/PKD2	776.78	123.33	273.49	320.60
Lower 95% CI	696.79	84.60	179.79	203.93
Upper 95% CI	890.49	162.05	367.18	437.26
FH-/NMD	594.53	55.69	121.05	155.42
Lower 95% CI	544.42	25.92	48.76	62.09
Upper 95% CI	649.28	85.46	193.33	248.75

$P = 0.03$ (see part *c* of Detailed Methods)

*See part *c* of Detailed Methods for formula to convert per month slopes into annual percentage changes.

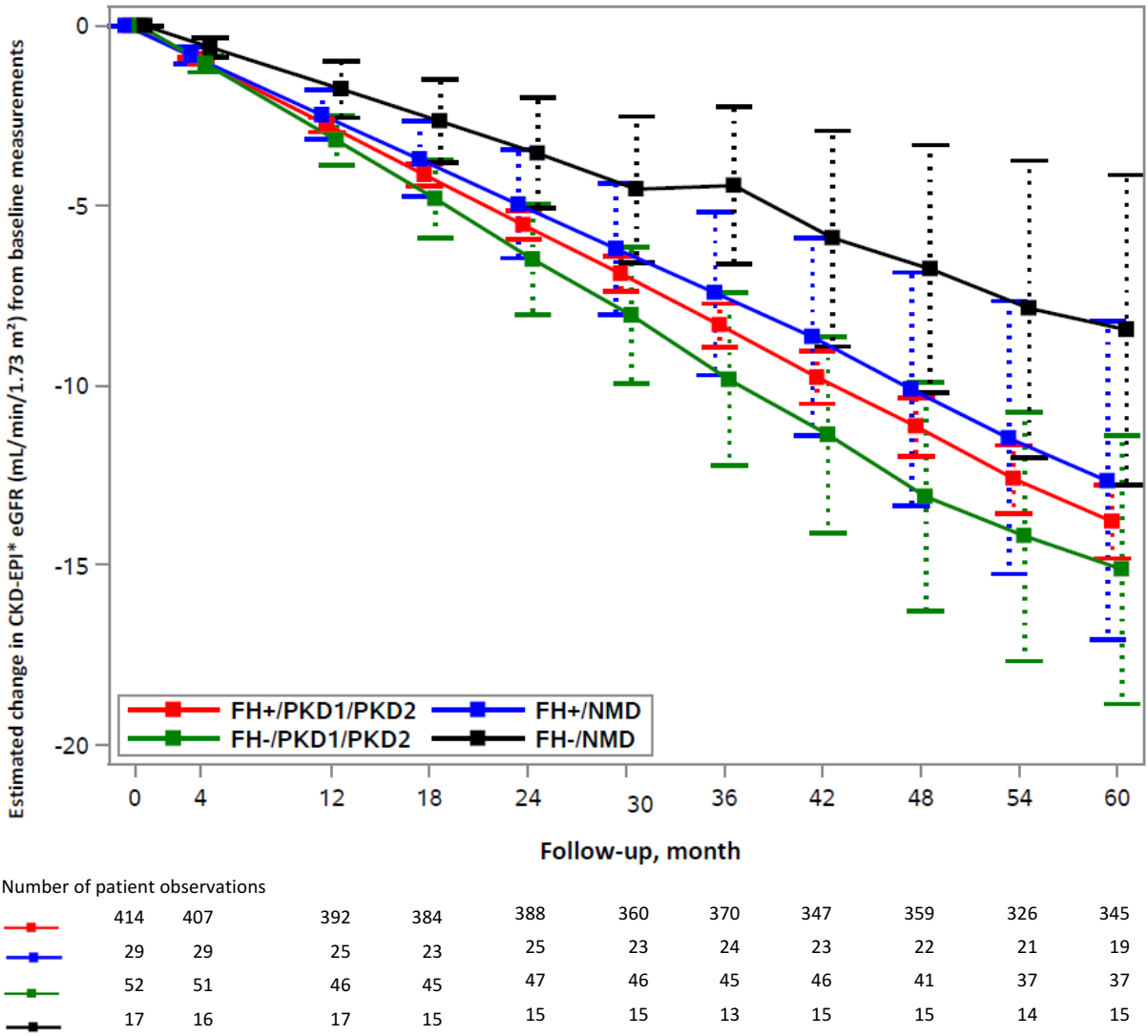
Table *d*. Estimated Mean Change in CKD-EPI* eGFR (mL/min/1.73m^2) from Baseline Measurements in Four Patient Groups During 60 Months of Follow-Up with 95% Confidence Intervals

Decrease in CKD-EPI-eGFR (mL/min/1.73m^2) over 60 months (mean and 95% confidence intervals)											
	Model Estimated value at baseline	Change from baseline									
Month	**0**	**4**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
FH+/PKD1/PKD2	91.19	-0.92	-2.76	-4.13	-5.53	-6.88	-8.34	-9.77	-11.16	-12.6	-13.8
Lower 95% CI	84.16	-0.98	-2.95	-4.43	-5.93	-7.38	-8.95	-10.5	-11.97	-13.55	-14.83
Upper 95% CI	98.21	-0.85	-2.56	-3.84	-5.13	-6.39	-7.72	-9.04	-10.34	-11.66	-12.77
FH+/NMD	87.28	-0.83	-2.48	-3.7	-4.96	-6.21	-7.44	-8.65	-10.12	-11.47	-12.65
Lower 95% CI	80.04	-1.05	-3.16	-4.75	-6.48	-8.04	-9.72	-11.41	-13.38	-15.26	-17.07
Upper 95% CI	94.52	-0.6	-1.8	-2.64	-3.45	-4.39	-5.17	-5.89	-6.86	-7.67	-8.24
FH-/PKD1/PKD2	88.78	-1.06	-3.17	-4.8	-6.49	-8.06	-9.83	-11.38	-13.09	-14.2	-15.13
Lower 95% CI	81.63	-1.29	-3.86	-5.91	-8.02	-9.94	-12.22	-14.12	-16.28	-17.67	-18.85
Upper 95% CI	95.93	-0.83	-2.48	-3.7	-4.96	-6.18	-7.44	-8.65	-9.9	-10.74	-11.41
FH-/NMD	89.79	-0.59	-1.77	-2.65	-3.54	-4.56	-4.45	-5.92	-6.76	-7.86	-8.46
Lower 95% CI	82.7	-0.85	-2.54	-3.81	-5.08	-6.59	-6.65	-8.93	-10.21	-12	-12.76
Upper 95% CI	96.88	-0.33	-1	-1.5	-2	-2.53	-2.25	-2.9	-3.32	-3.73	-4.15

$P = 0.09$ (see part *c* of Detailed Methods)

**Levey AS, Stevens IA, Schmid CH, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) A new equation to estimate glomerular filtration rate. Ann Intern Med 2009 May;150(9): 604-12.*

Figure *a*. Estimated mean change in CKD-EPI* eGFR (mL/min/1.73m^2) from baseline measurements in four patient groups during 60 months of follow-up with 95% confidence intervals. There was no significant difference across patient groups (*P* = 0.09) (see also table *d*).



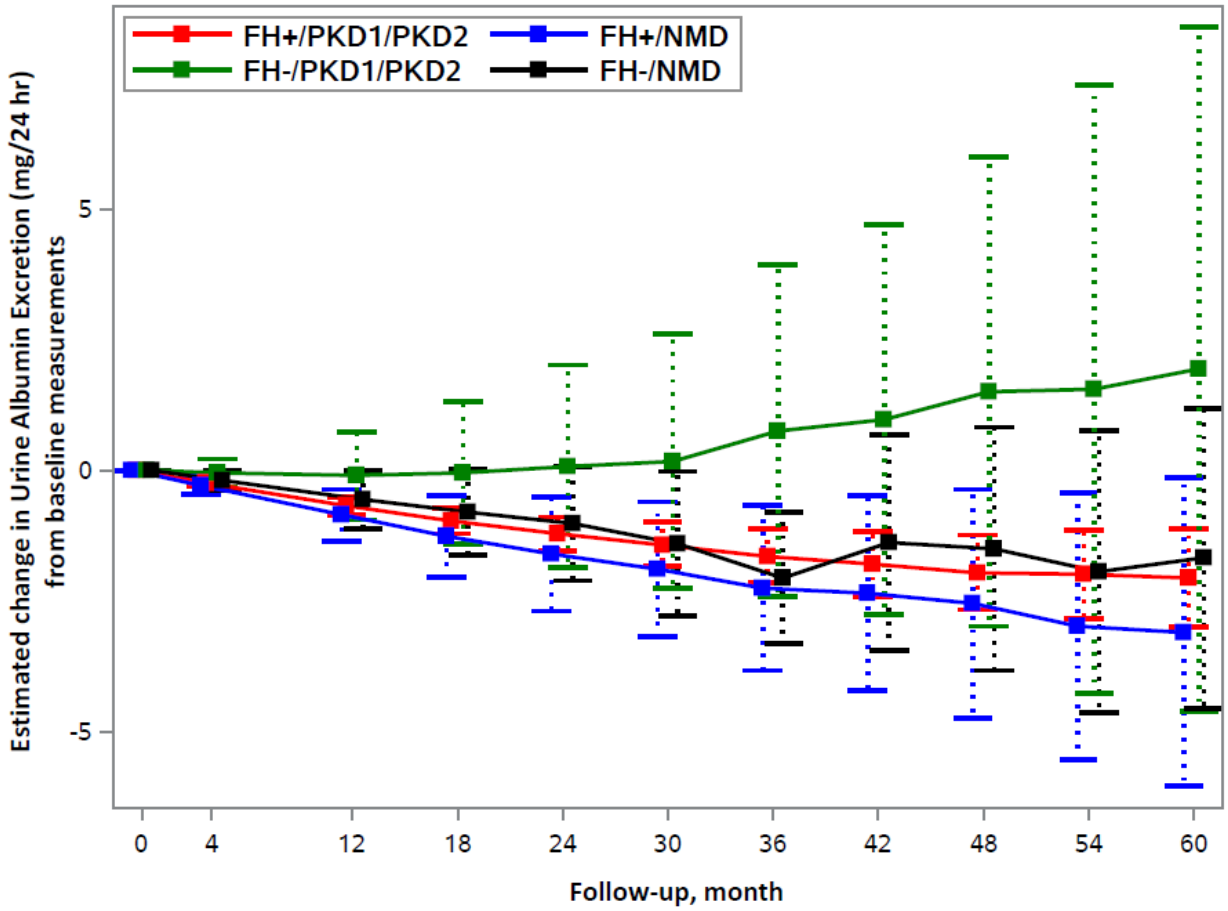
Number of patient observations

	414	407	392	384	388	360	370	347	359	326	345
	29	29	25	23	25	23	24	23	22	21	19
	52	51	46	45	47	46	45	46	41	37	37
	17	16	17	15	15	15	13	15	15	14	15

**Levey AS, Stevens IA, Schmid CH, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) A new equation to estimate glomerular filtration rate. Ann Intern Med 2009 May;150(9): 604-12.*

P = 0.09 (see part *c* of Detailed Methods)

Figure *b*. Estimated mean change in urine albumin excretion (mg/24 hr) from baseline measurements in four patient groups during 60 months of follow-up in early ADPKD with 95% confidence intervals. There was no significant difference across patient groups. (*P* = 0.1).



Number of patient observations†

405	384	367	247	312	331
28	28	21	19	15	17
52	48	46	41	36	36
15	14	17	14	10	14

†46 patients had a missing genotype

P = 0.1 (see part *c* of Detailed Methods)