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Prognostic enrichment design in clinical trials for autosomal dominant polycystic kidney disease: the HALT-PKD clinical trial

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ORIGINAL ARTICLE

ABSTRACT

Background. Patients with mild autosomal dominant polycystic kidney disease (ADPKD) are less likely to be informative in randomized clinical trials (RCTs). We previously developed an imaging classification of ADPKD (typical diffuse cyst distribution Class 1A–E and atypical cyst distribution Class 2) for prognostic enrichment design in RCTs. We investigated whether using this classification would have increased the power to detect a beneficial treatment effect of rigorous blood pressure (BP) control on HALT-PKD participants with early disease (Study A).

Methods. *Post hoc* analysis of the early disease HALT-PKD study, an RCT that studied the effect of rigorous versus standard BP control on rates of total kidney volume (TKV) increase and estimated glomerular filtration rate (eGFR) decline in ADPKD patients with eGFR >60 mL/min/1.73 m^2.

Results. Five hundred and fifty-one patients were classified by two observers (98.2% agreement) into Class 1A (6.2%), 1B (20.3%), 1C (34.1%), 1D (22.1%), 1E (11.8%) and 2 (5.4%). The TKV increase and eGFR decline became steeper from Class 1A through 1E. Rigorous BP control had been shown to be associated with slower TKV increase, without a significant overall effect on the rate of eGFR decline (faster in the first 4 months and marginally slower thereafter). Merging Classes 1A and 2 (lowest severity), 1B and 1C (intermediate severity) and 1D and 1E (highest severity) detected stronger beneficial effects on TKV increase and eGFR decline in Class 1D and E with a smaller number of patients.

Conclusions. Strategies for prognostic enrichment, such as image classification, should be used in the design of RCTs for ADPKD to increase their power and reduce their cost.

Keywords: autosomal dominant polycystic kidney disease, eGFR, HALT-PKD study, image classification, total kidney volume

INTRODUCTION

In recent years there has been an enormous increase in the number of therapeutic agents and successful interventions in animal models of polycystic kidney disease (PKD) (mostly at early stages of disease); however, the number of randomized controlled clinical trials (RCTs) is disproportionately small [1–10]. Large phenotypic variability among patients with autosomal dominant polycystic kidney disease (ADPKD) and maintenance of normal glomerular filtration rate (GFR) until late stages of the disease are major obstacles to the implementation of RCTs [11, 12]. Including patients with milder phenotypes and lower risk of progression may reduce the chance and decrease the power to detect a treatment effect.

We have previously developed and validated an image classification of ADPKD that can be used to select patients with progressive disease most likely to be informative in RCTs and to benefit from an effective therapy [13]. Most ADPKD patients (∼95%) present with bilateral and diffuse distribution of the disease are classified as Class 1 (typical), while a minority of patients (∼5%) presenting with focal (unilateral, segmental, asymmetric or bilateral atypical presentation) or atrophic disease (bilateral or unilateral acquired atrophy) are classified as Class 2 (atypical; Class 2A and 2B, respectively) [13]. A longitudinal mixed-effect regression model to predict future estimated GFR (eGFR) decline showed that height-adjusted total kidney volume (HtTKV) and age were the only parameters to significantly interact with time in Class 1 patients. However, HtTKV

and age were not significant predictors of change in eGFR over time in Class 2 patients. Accordingly, we proposed to exclude Class 2 patients from RCTs or therapies aimed at reducing kidney growth. Further stratification of Class 1 patients into A, B, C, D and E, based on HtTKV and age, showed that the risk for declining GFR and end-stage renal disease (ESRD) increased progressively from Class A to Class E.

HALT-PKD Study A is an RCT that was designed to test two hypotheses [14]. The first was that rigorous blood pressure (BP) control (95–110/60–75 mmHg) with drugs that block the renin–angiotensin system would slow the increase in TKV (primary endpoint) and the decline in eGFR (secondary endpoint) compared with standard BP control (120–130/70–80 mmHg) in 15- to 49-year-old patients with eGFR >60 mL/min/1.73 m^2. The second was that an angiotensin-converting enzyme inhibitor (ACEI) and an angiotensin II receptor blocker (ARB) combination would be more effective than an ACEI alone on these endpoints. Here we applied this image classification to early ADPKD HALT participants and found that the power to detect a beneficial treatment effect of rigorous BP control was increased in the classes with the highest disease severity.

MATERIALS AND METHODS

Study design

We used a *post hoc* analysis of the early ADPKD population in the HALT-PKD Study A to investigate the performance of a previously developed imaging classification of ADPKD for prognostic enrichment design in clinical trials. The study was approved by the HALT-PKD Ancillary Studies Committee. A detailed description of the imaging classification and the HALT-PKD study was published previously [13–17].

Study participants

All HALT-PKD study participants who met inclusion criteria for Study A and underwent randomization ($N = 558$) were considered for this ancillary study [14]. Seven participants were excluded from analysis due to lack of baseline images ($n = 5$) or patient's height ($n = 2$). Baseline magnetic resonance imaging (MRI) studies were used to classify these patients using our classification system [10]. HALT participants included in the late ADPKD HALT study (Study B) [17] were excluded as MRIs were not acquired for the study, thus preventing further classification of these patients. Detailed information about the HALT-PKD Study A participants has been published previously [14].

Evaluation of baseline MRI, TKV measurements and classification of ADPKD into typical (Class 1) and atypical (Class 2) patients

All available baseline MRIs were transferred to the Mayo Translational PKD Center and later retrieved to a work station for further analysis. Patients were classified into typical (Class 1) and atypical (Class 2) cases based on prespecified imaging findings [10]. Simultaneously, patients were classified at the University of Pittsburgh by a second observer. Image classifications were performed blinded to clinical data. TKVs were previously measured for the HALT-PKD study [18]. Class 1 ADPKD patients were further stratified into five subclasses based on HtTKV and age as previously described [13]. Representative images of Class 1 and Class 2A patients are shown in Figure 1.

Outcome measures

The primary outcome was the same as for the early ADPKD HALT study, the annualized percent change in TKV over time. TKVs from HALT-PKD were utilized for this calculation. The first secondary outcome, rate of change in the eGFR and additional secondary outcomes were also the same as for the early ADPKD study [14]. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [19, 20]. Patient's characteristics, i.e. age, sex, race and laboratory measurements i.e. serum creatinine and urine albumin excretion, were obtained with permission from the main HALT database.

Statistical analysis

We compared baseline and clinical characteristics across the classification groups (separately for five- and three-level classifications) using analysis of variance and χ^2 tests of significance, or their nonparametric counterparts when necessary. Several variables such as TKV and urine albumin were log-transformed to normalize them. Linear mixed models were run separately within each classification group to assess the effect of rigorous BP control (versus standard) and telmisartan (versus placebo) on primary and secondary outcomes. For most models, predictors included month, month × BP arm and month × drug arm. For the eGFR and left ventricular mass index (LVMI) models in subclass 1A and 1B, respectively, we included the main effect for BP group to account for potential between-arm imbalances at baseline. We also included covariates for age, sex, race, baseline eGFR and clinical site. Baseline LVMI was also included as a covariate for all models in subclass 1B to account for between-arm differences at baseline. Of interest was whether either of the interactions was significant, which would indicate an effect of drug or BP. To account for multiple comparisons, we controlled the false discovery rate (FDR) at 5% by utilizing the Benjamini–Hochberg step-up procedure for each of the 12 outcome × subclass investigations [21]. SAS 9.2 was used for all statistical programming.

RESULTS

Image classification and baseline clinical, laboratory and genetic characteristics

We first evaluated interobserver agreement in classifying early ADPKD HALT participants by having two separate observers classify the patients using study baseline images. We found a high degree of agreement in the imaging classification, where 541 (98.2%) of the patients were assigned the same class and only 10 (1.8%) of the patients were assigned a discrepant class (κ coefficient = 0.83). Most of the patients [521 (94.6%)] presented typical imaging characteristics of ADPKD and were classified as Class 1, while the remaining 30 (5.4%) patients were classified as atypical or Class 2 (all Class 2A) (Table 1). Class 1 patients were younger (36.2 ± 8.3 versus 41.9 ± 5.6 years old; $P < 0.001$), had similar eGFRs (91.6 ± 17.6 versus

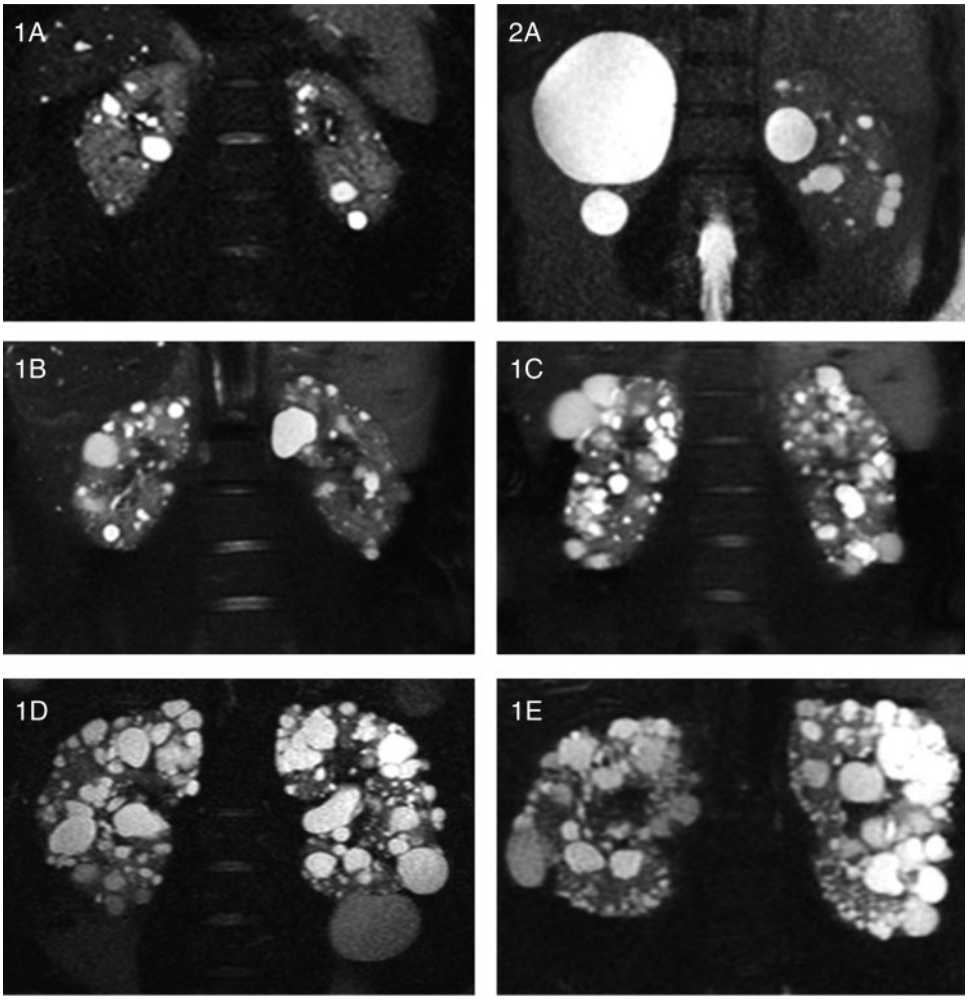

FIGURE 1: Coronal T_2-weighted MRIs from patients with Class 1A (49-year-old male PKD2), 2A (49-year-old male PKD2), 1B (38-year-old male PKD1), 1C (37-year-old male PKD1), 1D (37-year-old male PKD1) and 1E (37-year-old male PKD1) ADPKD. Classes 1A and 2A are considered mild, 1B and 1C intermediate and 1D and 1E severe disease.

Table 1. Baseline characteristics of study patients

Class		Patients, *n* (M/F)	Age, mean ± SD	eGFR, mean ± SD	HtTKV, mean ± SD	Genetic analysis, *n* (%)[a]	NMD, *n* (%)[b]	PKD1, *n* (%)[b]	PKD2, *n* (%)[b]
1	All	521 (268/253)	36.2 ± 8.3	91.6 ± 17.6	685.1 ± 394.1	480 (94.5)	42 (8.8)	366 (76.2)	72 (15.0)
	A	34 (9/25)	40.9 ± 8.0	95.0 ± 12.5	233.1 ± 39.6	29 (85.3)	11 (37.9)	7 (24.1)	11 (37.9)
	B	112 (37/75)	39.9 ± 7.3	91.7 ± 14.5	383.4 ± 87.6	104 (92.9)	8 (7.7)	64 (61.5)	32 (30.8)
	C	188 (104/84)	37.1 ± 7.6	90.9 ± 17.7	607.3 ± 188.7	178 (94.7)	12 (6.7)	144 (80.9)	22 (12.4)
	D	122 (73/49)	34.7 ± 7.6	89.7 ± 18.8	936.8 ± 344.2	113 (92.6)	7 (6.2)	99 (87.6)	7 (6.2)
	E	65 (45/20)	28.0 ± 6.4	95.6 ± 20.9	1200.3 ± 498.2	56 (86.2)	4 (7.1)	52 (92.9)	0 (0.0)
2[c]	A	30 (9/21)	41.9 ± 5.6	90.3 ± 14.8	818.2 ± 518.2	28 (93.3)	4 (14.3)	13 (46.4)	11 (39.3)
Total		551 (277/274)	36.5 ± 8.2	91.6 ± 17.4	692.3 ± 402.3	508 (92.2)	46 (9.1)	379 (74.6)	83 (16.3)

eGFR estimated using CKD-EPI equation (mL/min/1.73 m^2); HtTKV calculated by stereology, HALT-PKD baseline images (mL/m).
NMD, no mutation detected.
[a]Percentage is based on the total number of patients for each class.
[b]Percentage is based on the patients with genetic analysis within each class.
[c]No patient classified as 2B in this study.

90.3 ± 14.8 mL/min/1.73 m^2; P = 0.79) and had slightly lower HtTKVs (685.1 ± 394.1 versus 818.2 ± 518.2 mL/m; P = 0.17) compared with Class 2 patients. The gender distribution was similar in Class 1 patients [253 (48.6% female)], but the proportion of female patients was higher in Class 2 [21 (70.0%)]. A blood sample for genetic analysis was available in 508 (480 Class 1 and 28 Class 2) patients, of whom 379 (74.6%) had a mutation in the *PKD1* gene, 83 (16.3%) in *PKD2* and 46 (9.1%) had no mutation detected (NMD). The percentages of *PKD2* and NMD cases were higher in Class 2 patients compared with Class 1 (39.3 and 14.3% versus 15.0 and 8.8%, respectively), while that of *PKD1* was lower (46.4 versus 76.2%).

Class 1 ADPKD patients were further stratified into five subclasses (1A–E) as previously described [13]: 1C [n = 188 (36.1%)], 1D [n = 122 (23.4%)] and 1B [n = 112 (21.5%)], 1E [n = 65 (12.5%)] and 1A [n = 34 (6.5%)] (Figure 2). The main clinical, laboratory and genetic characteristics at baseline are shown in Table 1. Baseline age decreased from Class 1A through 1E (41 to 28 years old) while HtTKV increased (223–1200 mL/m); eGFR was similar for all classes. Interestingly, the male:female ratio increased from 1A to 1E (Figure 3A). The percentage of PKD1 cases increased from Class 1A through 1E (1A, 24.1%; 1B, 61.5%; 1C, 80.9%; 1D, 87.6%; 1E, 92.9%), whereas PKD2 cases decreased from class 1A through 1E (1A, 37.9%; 1B, 30.8%; 1C, 12.4%; 1D, 6.2%; 1E, 0.0%). Class 1A had a higher NMD rate, but it decreased and remained similar through Classes 1B to 1E (1A, 37.9%; 1B, 7.7%; 1C, 6.7%; 1D, 6.2%; 1E, 7.1%) (Figure 3B).

Outcome measures by class

Primary outcome: annualized percent change in TKV over time. In Class 1 patients, the annualized percent TKV increase became steeper from Class 1A to 1E and was lower in patients randomized to low BP compared with standard BP except in Class 1A (1A, 4.04%; 1B, 4.31%; 1C, 6.04%; 1D, 5.89%; 1E, 7.27% and 1A, 2.55%; 1B, 4.91%; 1C, 7.17%; 1D, 7.55%; 1E, 8.60% for low BP and standard BP groups, respectively). However, the difference was statistically significant only in Class 1D (P = 0.018) (Table 2). In Class 2A patients, annualized percent TKV increases, 4.51% in the low and 5.73% in the standard BP groups, were not significantly different (Table 2).

Secondary outcomes: eGFR slopes. Analysis of overall (F0–96) eGFR slopes in Class 1 patients showed increasingly steeper declines from Class 1A to 1E for both BP groups (1A, −1.12; 1B, −2.06; 1C, −3.27; 1D, −3.09; 1E, −4.42 and 1A, −0.98; 1B, −1.96; 1C, −2.82; 1D, −3.72; 1E, −5.69 mL/min/1.73 m^2/year for low and standard BP groups, respectively). Although the rates of eGFR decline tended to be less in the low compared with the standard BP groups, particularly in 1D and 1E, the differences did not reach statistical significance (Table 2). The analysis of eGFR slopes after the first 4 months of treatment (F596) also showed increasingly steeper slopes from Class 1A to 1E for both BP groups (1A, −1.14; 1B, −1.85; 1C, −3.13; 1D, −2.96; 1E, −4.08; and 1A, −1.14; 1B, −2.16; 1C, −2.94; 1D, −3.74; 1E, −5.81 mL/min/1.73 m^2/year for low and standard BP groups, respectively). Although the rates of eGFR decline tended to be lower in the low compared with the standard BP groups, the difference was significant in Class 1E only (P = 0.036) (Table 2). In Class 2 patients, rigorous BP control had no significant impact on decreasing the rate of eGFR decline overall or after the first 4 months of treatment (Table 2).

Urinary albumin excretion. At baseline, the urinary albumin excretion was 17.7 mg/24 h [interquartile range (IQR) 11.7–33.3] and 19.1 (IQR 12.8–31.8) in the low and standard BP groups, respectively. During the trial, the urinary albumin excretion tended to decrease in the low BP group and increase in the standard BP group in all classes, but the difference between the study arms was statistically significant in Classes 1A and 1C only (both P < 0.01) (Table 3).

Renal vascular resistance and LVMI. At baseline, the renal vascular resistance was 12 853 ± 6936 and 13 387 ± 7024 dynes/cm^5 in the low and standard BP groups, respectively. During the trial, renal vascular resistance tended to decrease in

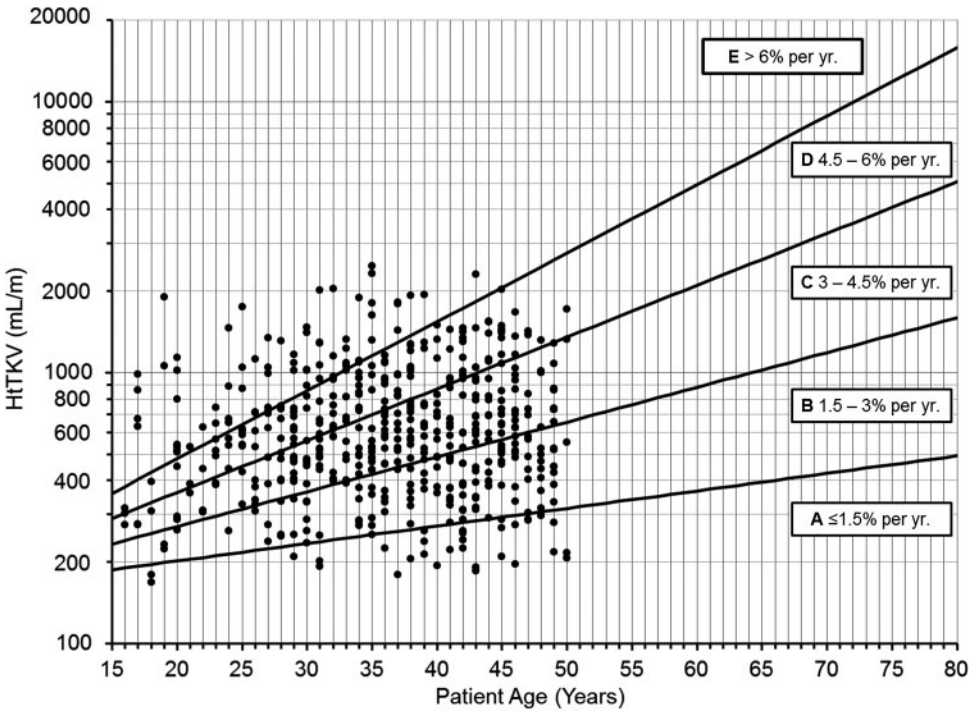

FIGURE 2: Distribution of Class 1 early ADPKD HALT study patients at baseline based on HtTKV limits for their age. Limits are defined based on estimated kidney growth rates of 1.5, 3.0, 4.5 and 6.0%.

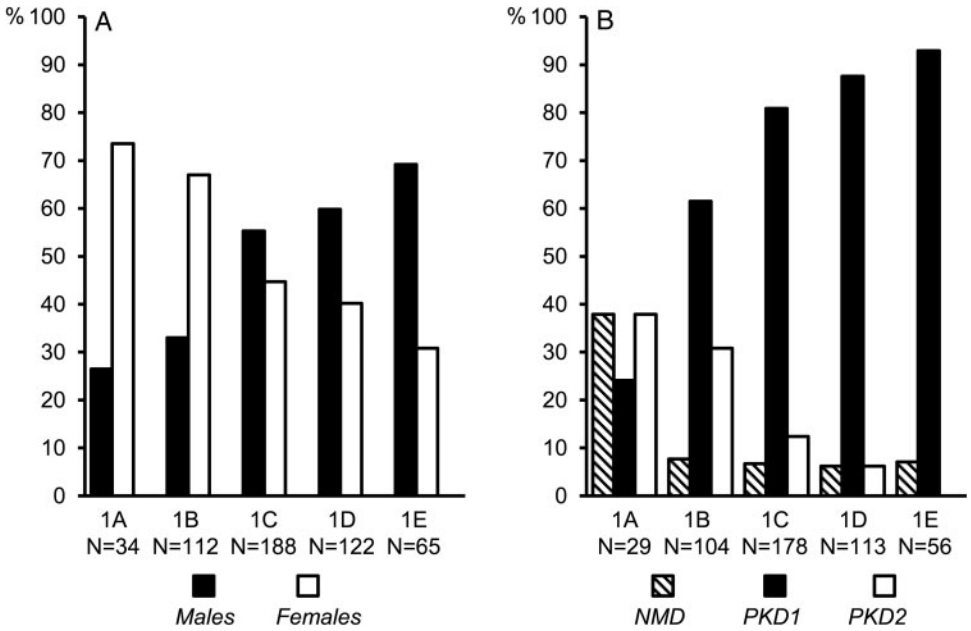

FIGURE 3: Distribution of (**A**) gender and (**B**) genotype of early ADPKD HALT study patients by baseline classes. (A) The male:female ratio increased from 1A to 1E (0.36, 0.49, 1.24, 1.49 and 2.25); *N* = total number of patients per class. (B) Similarly, the PKD1:PKD2 case ratio increased from Class 1A through 1E (0.64, 2.0, 6.55, 14.14 and 52.0). Proportionately to the total in each class, Class 1A had the highest NMD rate (37.9%), but this decreased and remained similar through Classes 1B to 1E (1B, 7.7%; 1C, 6.7%; 1D, 6.2%; 1E, 7.1%); *N* = number of patients with genetic analysis per class.

the low BP group and increase in the standard BP group in most classes, but the difference between the study arms was statistically significant only in Classes 1C ($P = 0.023$) and 1E ($P = 0.043$) (Table 3). At baseline, LVMI was 63.9 ± 12.2 and 63.8 ± 13.8 g/m^2 in the low and standard BP groups, respectively. During the trial, LVMI tended to decrease in both groups, significantly more in the low compared with the standard BP group in Class 1C patients only ($P < 0.001$; Table 3).

Outcome measures by groups of low, intermediate and high disease severity. Because small sample sizes may have hindered the ability to detect statistically significant differences between the low and the standard BP patients after stratification into different classes according to the image classification [13], we decided to pool the patients into larger groups reflecting low (Class1A and 2A), intermediate (Class 1B and 1C) and high (Class 1D and 1E) disease severity. The baseline characteristics (age, gender, eGFR, TKV and PKD1 versus PKD2 mutations) of the patients randomized to standard compared with rigorous BP control were not different in any of the three groups of disease severity (Table 4). In the patients randomized to standard BP control, the progression of ADPKD as reflected by the annual percent TKV increase, overall decline in eGFR and decline in eGFR after the first 4 months of treatment increased from Class 1A–2A (4.61%; −1.16 and −1.40 mL/min/1.73 m^2/year, respectively) to Class 1B–C (6.20%; −2.47 and −2.63 mL/min/1.73 m^2/year, respectively) and to Class 1D–E (7.80%; −4.37 and −4.45 mL/min/1.73 m^2/year, respectively). Furthermore, the effect of the rigorous BP intervention was statistically significant for the annual percent increase in TKV ($P = 0.034$), for the eGFR decline after the first 4 months of treatment ($P = 0.011$) and at borderline statistical significance for the overall eGFR decline ($P = 0.052$) in Class 1D–E, but not in the other groups (Table 5).

The effect of rigorous BP control on urinary albumin excretion was statistically significant in all classes ($P = 0.018$, 0.001 and 0.047 for Class 1A–2, 1B–C and 1D–E, respectively). Renal vascular resistance tended to increase in the standard BP group and decrease in the rigorous BP group in all classes, but the difference between the patients randomized to low and standard BP control was statistically significant in Class 1B–C ($P = 0.005$) and of borderline statistical significance in Class 1D–E ($P = 0.057$) (Table 6). The effect of rigorous BP control on the LVMI was only statistically significant in Class 1B–C ($P < 0.001$).

Another goal of the early ADPKD HALT study was to determine whether combined administration of an ACEI (lisinopril) and an ARB (telmisartan) would slow the progression of ADPKD compared with an ACEI alone. No difference between the two treatment groups was found in Class 1A–2A, 1B–C or 1D–E (results not shown).

DISCUSSION

A goal of the early ADPKD HALT study was to determine whether rigorous BP control (95–110/60–75 mmHg) would slow the progression of ADPKD compared with standard BP control (120–130/70–80 mmHg) in 15–49-year-old patients with eGFR >60 mL/min/1.73 m^2. The results of the early ADPKD HALT study showed that the annualized percent

Table 2. Effect of BP intervention on TKV and eGFR by image-based classification

	Class 1A ($n = 34$)		Class 1B ($n = 112$)		Class 1C ($n = 188$)		Class 1D ($n = 122$)		Class 1E ($n = 65$)		Class 2A ($n = 30$)	
Log-transformed TKV slope (%/year)												
Group	Std ($n = 16$)	Low ($n = 18$)	Std ($n = 56$)	Low ($n = 56$)	Std ($n = 86$)	Low ($n = 102$)	Std ($n = 71$)	Low ($n = 51$)	Std ($n = 34$)	Low ($n = 31$)	Std ($n = 17$)	Low ($n = 13$)
Slope	2.55	4.04	4.91	4.31	7.17	6.04	7.55	5.89	8.60	7.27	5.73	4.51
Diff (95% CI)	1.45 (−0.77, 3.72)		−0.58 (−1.80, 0.66)		−1.05 (−2.13, 0.04)		−1.54 (−2.80, −0.27)		−1.22 (−3.57, 1.18)		−1.15 (−3.71, 1.48)	
P-value	0.196		0.359		0.058		0.018		0.312		0.381	
eGFR slope, overall (F0F96) (mL/min/1.73 m^2/year)												
Group	Std	Low	Std	Low	Std	Low	Std	Low	Std	Low	Std	Low
Slope	−0.98	−1.12	−1.96	−2.06	−2.82	−3.27	−3.72	−3.09	−5.69	−4.42	−1.11	−1.31
Diff (95% CI)	−0.14 (−1.67, 1.39)		−0.10 (−0.80, 0.61)		−0.45 (−1.12, 0.21)		0.62 (−0.20, 1.45)		1.26 (−0.30, 2.82)		−0.20 (−1.56, 1.17)	
P-value	0.857		0.786		0.179		0.140		0.113		0.779	
eGFR slope, chronic (F5–F96) (mL/min/1.73 m^2/year)												
Group	Std	Low	Std	Low	Std	Low	Std	Low	Std	Low	Std	Low
Slope	−1.14	−1.14	−2.16	−1.85	−2.94	−3.13	−3.74	−2.96	−5.81	−4.08	−1.32	−0.92
Diff (95% CI)	−0.002 (−1.60, 1.60)		0.31 (−0.43, 1.05)		−0.18 (−0.87, 0.50)		0.79 (−0.08, 1.65)		1.72 (0.11, 3.33)		0.40 (−1.06, 1.86)	
P-value	0.998		0.405		0.600		0.075		0.036		0.592	

Table 3. Effect of BP intervention on other secondary outcomes by image-based classification

	Class 1A ($n = 34$)		Class 1B ($n = 112$)		Class 1C ($n = 188$)		Class 1D ($n = 122$)		Class 1E ($n = 65$)		Class 2A ($n = 30$)	
Logarithm urine albumin excretion (%/year)												
Group	Std ($n = 16$)	Low ($n = 18$)	Std ($n = 56$)	Low ($n = 56$)	Std ($n = 86$)	Low ($n = 102$)	Std ($n = 71$)	Low ($n = 51$)	Std ($n = 34$)	Low ($n = 31$)	Std ($n = 17$)	Low ($n = 13$)
Slope	11.74	−5.92	−0.49	−5.50	1.01	−4.97	4.19	−1.78	6.82	−0.90	−1.98	−1.09
Diff (95% CI)	−15.79 (−24.98, −5.47)		−5.03 (−10.21, 0.45)		−5.95 (−9.68, −2.05)		−5.76 (−11.91, 0.83)		−7.30 (−15.10, 1.22)		0.89 (−7.29, 9.79)	
P-value	0.004[a]		0.072		0.003[a]		0.085		0.091		0.836	
Left ventricular mass index (g/m^2/year)												
Group	Std	Low	Std	Low	Std	Low	Std	Low	Std	Low	Std	Low
Slope	0.01	0.16	−0.47	−1.31	−0.38	−1.33	−0.85	−1.42	−1.50	−1.34	0.80	0.31
Diff (95% CI)	0.15 (−1.52, 1.83)		−0.83 (−1.58, −0.08)		−0.95 (−1.44, −0.46)		−0.57 (−1.24, 0.11)		0.16 (−1.00, 1.32)		−0.49 (−2.12, 1.14)	
P-value	0.855		0.030		0.0002[a]		0.098		0.785		0.550	
Renal vascular resistance (dyne s/cm^5/year)												
Group	Std	Low	Std	Low	Std	Low	Std	Low	Std	Low	Std	Low
Slope	−194.41	183.27	273.94	−219.88	784.14	−31.73	74.46	−117.72	497.63	−505.64	−107.83	−240.21
Diff (95% CI)	377.68 (−428.49, 1183.85)		−493.82 (−1100.88, 113.24)		−815.87 (−1515.54, −116.19)		−192.18 (−725.12, 340.76)		−1003.27 (−1975.20, −31.33)		−132.38 (−727.44, 462.67)	
P-value	0.349		0.110		0.023[a]		0.477		0.043		0.656	

Diff, difference; CI, confidence interval; Std, standard.

[a]Significant after controlling for 5% false discovery rate (FDR) using Benjamini–Hochberg step-up procedure.

Table 4. Baseline characteristics of the study patients by group severity and assignment to standard versus rigorous BP control

Group	Low (1A, 2A) ($n = 64$)			Intermediate (1B, 1C) ($n = 300$)			Severe (1D, 1E) ($n = 187$)		
	Std ($n = 33$)	Low ($n = 31$)	P-value	Std ($n = 142$)	Low ($n = 158$)	P-value	Std ($n = 105$)	Low ($n = 82$)	P-value
Age, years, mean ± SD	41.8 ± 5.5	40.8 ± 8.2	0.57	37.8 ± 8.0	38.4 ± 7.2	0.51	32.2 ± 7.7	32.7 ± 8.2	0.67
Male, *n* (%)	8 (24.2)	10 (32.3)	0.48	63 (44.4)	78 (49.4)	0.39	68 (64.8)	50 (61.0)	0.59
HtTKV, mL (log), mean ± SD	6.0 ± 0.7	5.9 ± 0.7	0.56	6.2 ± 0.3	6.2 ± 0.4	0.60	6.8 ± 0.4	6.9 ± 0.4	0.85
eGFR (mL/min/1.73 m^2), mean ± SD	90.6 ± 14.0	95.1 ± 13.3	0.20	91.9 ± 17.4	90.5 ± 15.9	0.46	92.0 ± 19.5	91.5 ± 20.1	0.86
PKD1 mutation, *n* (%)	13 (46.4)	7 (24.1)	0.21	103 (77.4)	105 (70.5)	0.37	86 (89.6)	65 (89.0)	0.51
PKD2 mutation, *n* (%)	9 (32.1)	13 (44.8)	–	21 (15.8)	33 (22.1)	–	3 (3.1)	4 (5.5)	–
No mutation detected, *n* (%)	6 (21.4)	9 (31.0)	–	9 (6.8)	11 (7.4)	–	50 (47.6)	43 (52.4)	–

increase in TKV was 14.2% lower (5.6 versus 6.6%; P = 0.006), whereas the rate of decline in eGFR was faster in the first 4 months (P < 0.001) and marginally slower thereafter (P = 0.05), without a significant overall effect (−2.9 and −3.0 mL/min/1.73 m^2/year, respectively; P = 0.55) in the rigorous BP group compared with the standard BP group [14].

The results of the early ADPKD HALT study have received different interpretations. Some authors viewed them as showing that rigorous BP control did not affect the decline in eGFR, despite attenuating the increase in kidney volume, thus dissociating kidney volume growth from a decline in renal function [22]. Others suggested that an acute, reversible eGFR reduction induced by achievement of the low BP target likely accounted for the failure to detect an effect of rigorous BP control on the overall eGFR decline [23]. Unfortunately, the HALT-PKD protocol did not include a measurement of eGFR after allowing a return of BP to standard control levels at the end of study in the low BP patients. Additionally, because a decrease in GFR occurs late in the clinical course of the disease, it is possible that only the patients with more rapidly progressive disease would have benefited from a low BP target. On the other hand, it has also been suggested that the effect of rigorous BP control on the rate of growth of kidney volume, although statistically significant, may not be clinically significant or even spurious because of a non–statistically significant (P = 0.09) imbalance in the frequency of *PKD1* and *PKD2* mutations in the patients randomized to rigorous (70.6 and 19.8%, respectively) compared with standard BP control (78.5 and 13.1%, respectively).

In this *post hoc* analysis of the early ADPKD HALT study, participants were stratified according to an image classification of disease severity that was developed to assist in the selection of patients most likely to be informative in clinical trials for ADPKD. As expected, the majority of patients enrolled into HALT-PKD were typical Class 1 patients and all atypical Class 2 patients were Class 2A. Stratification from Class 1A through 1E was associated with increasing rates of kidney growth and eGFR decline, whereas Class 2A patients experienced substantial increases in kidney volume with minimal declines in eGFR. Effects of rigorous versus standard BP control on kidney growth and eGFR decline after Month 4 tended to be greater in Classes 1C, 1D and 1E compared with Classes 1A and 1B and, for eGFR only, Class 2A. Likely due to the small sample size of the different class groups, differences only reached statistical significance in Class 1D for kidney growth and 1E for eGFR decline after Month 4. When the HALT-PKD participants were stratified into three larger groups by disease severity (Class 1A and 2A, low; 1B and 1C, intermediate; 1D and 1E, high), the patients with high disease severity (1D–1E) randomized to rigorous BP control not only had a slower annual increase in TKV compared with those randomized to standard BP (6.4 versus 7.8%; P = 0.034), but also had a slower decline in eGFR after the first 4 months of treatment [−3.36 versus −4.45 (P = 0.011), low and standard BP, respectively], and of borderline statistical significance overall [−3.57 versus −4.37 (P = 0.052), low and standard, respectively]. Furthermore, the favourable outcome associated with rigorous BP control in Group 1D–E could not be explained by an imbalance in the frequency of *PKD1* and *PKD2* mutations since they were similar in the patients randomized to rigorous (89.0 and 5.5%, respectively) and standard (89.6 and 3.1%, respectively) BP control.

Whereas this *post hoc* analysis uncovered a stronger effect of rigorous BP control on outcomes in the participants with the highest disease severity by the image classification, stratification by class individually or by groups of low, intermediate or high disease severity was not associated with different outcomes in the patients treated with lisinopril and telmisartan compared with those treated with lisinopril and placebo, further supporting the conclusion that the intensity of suppression of the renin–angiotensin system, as implemented in the HALT-PKD clinical trials, did not affect the progression of ADPKD.

This study has the limitation of being *post hoc* in nature and carries the risk of a false-positive result. While subgroup analyses of the primary and secondary endpoints were prespecified in the HALT-PKD protocol, the study was not powered to analyze these endpoints by classes of disease severity. Nevertheless, the analysis suggests that the treatment effects of rigorous BP control increased with class severity. In the patients with the most severe disease (Class 1D–E), rigorous BP control was associated with slower eGFR decline after Month 4 and overall. Restriction of enrollment to Class 1D–E patients would have detected a stronger effect of rigorous BP control on TKV growth and eGFR decline, with a smaller number of patients (187 versus 551). Because this is a *post hoc* analysis, these conclusions need to be interpreted cautiously.

In summary, with the limitations inherent to a *post hoc* analysis, the results of this study suggest that young patients with ADPKD and rapidly progressing renal disease are likely to benefit from rigorous BP control and support the use of strategies for prognostic enrichment, such as image classification, in the

Table 5. Effect of BP intervention on TKV and eGFR by disease severity

	All patients ($n = 553$)		Low (1A, 2A) ($n = 64$)		Intermediate (1B, 1C) ($n = 300$)		High (1D, 1E) ($n = 187$)	
Log-transformed TKV slope (%/year)								
Group	Std	Low	Std ($n = 33$)	Low ($n = 31$)	Std ($n = 142$)	Low ($n = 158$)	Std ($n = 105$)	Low ($n = 82$)
Slope	6.58	5.62	4.61	4.20	6.20	5.47	7.80	6.44
Diff (95% CI)	−0.90 (−1.53, −0.26)		−0.39 (−2.04, 1.29)		−0.68 (−1.51, 0.15)		−1.26 (−2.40, −0.10)	
P-value	0.006		0.645		0.108		0.034	
eGFR slope, overall (F0–F96) (mL/min/1.73 m^2/year)								
Group	Std	Low	Std	Low	Std	Low	Std	Low
Slope	−2.99	−2.85	−1.16	−1.20	−2.47	−2.84	−4.37	−3.57
Diff (95% CI)	0.13 (−0.30, 0.57)		−0.04 (−1.01, 0.93)		−0.37 (−0.88, 0.13)		0.80 (−0.01, 1.61)	
P-value	0.547		0.940		0.145		0.052	
eGFR slope, chronic (F5–F96) (mL/min/1.73 m^2/year)								
Group	Std	Low	Std	Low	Std	Low	Std	Low
Slope	−3.12	−2.67	−1.40	−0.97	−2.63	−2.67	−4.45	−3.36
Diff (95% CI)	0.45 (0.00, 0.90)		0.43 (−0.60, 1.46)		−0.04 (−0.56, 0.48)		1.09 (0.25, 1.92)	
P-value	0.048		0.412		0.878		0.011[a]	

Diff, difference; CI, confidence interval; Std, standard.
[a]Significant after controlling for 5% false discovery rate (FDR) using Benjamini–Hochberg step-up procedure.

Table 6. Effect of BP intervention on other secondary outcomes by disease severity

	All patients ($n = 553$)		Low (1A, 2A) ($n = 64$)		Intermediate (1B, 1C) ($n = 300$)		High (1D, 1E) ($n = 187$)	
Log-transformed urine albumin (%/year)								
Group	Std	Low	Std ($n = 33$)	Low ($n = 31$)	Std ($n = 142$)	Low ($n = 158$)	Std ($n = 105$)	Low ($n = 82$)
Slope	2.38	−3.76	3.97	−4.46	0.41	−5.00	4.89	−0.66
Diff (95% CI)	−6.00 (−8.48, −3.45)		−8.10 (−14.33, −1.42)		−5.39 (−8.41, −2.26)		−5.30 (−10.24, −0.08)	
P-value	<0.0001		0.018[a]		0.001[a]		0.047[a]	
Renal vascular resistance (dynes/cm^5/year)								
Group	Std	Low	Std	Low	Std	Low	Std	Low
Slope	343.21	−171.56	7.61	−78.25	567.14	−123.83	219.23	−208.55
Diff (95% CI)	−514.77 (−814.25, −215.29)		−85.86 (−542.71, 370.98)		−690.98 (−1166.34, −215.61)		−427.78 (−867.79, 12.24)	
P-value	0.001		0.709		0.005[a]		0.057	
Left ventricular mass index (g/m^2/year)								
Group	Std	Low	Std	Low	Std	Low	Std	Low
Slope	−0.57	−1.17	0.46	0.21	−0.49	−1.27	−1.07	−1.42
Diff (95% CI)	−0.60 (−0.91, −0.29)		−0.25 (−1.31, 0.80)		−0.78 (−1.16, −0.39)		−0.35 (−0.92, 0.23)	
P-value	0.0002		0.635		<0.0001[a]		0.239	

Diff, difference; CI, confidence interval; Std, standard.
[a]Significant after controlling for 5% false discovery rate (FDR) using Benjamini–Hochberg step up procedure.

design of RCTs for ADPKD to increase their power and reduce their cost.

AUTHORS' CONTRIBUTION

M.V.I. and V.E.T. designed the ancillary study. K.Z.A. supervised the statistical analyses. M.V.I. and V.E.T. drafted the manuscript. M.V.I. and K.T.B. classified the patients. All coauthors provided comments and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

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