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Can we further enrich autosomal dominant polycystic kidney disease clinical trials for rapidly progressive patients? Application of the PROPKD score in the TEMPO trial

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ABSTRACT

Background. The PROPKD score has been proposed to stratify the risk of progression to end-stage renal disease in autosomal dominant polycystic kidney disease (ADPKD) subjects. We aimed to assess its prognostic value in a genotyped subgroup of subjects from the Tolvaptan Phase 3 Efficacy and Safety Study in Autosomal Dominant Polycystic Kidney Disease (TEMPO3/4) trial.

Methods. In the *post hoc* analysis, *PKD1* and *PKD2* were screened in 770 subjects and the PROPKD score was calculated in mutation-positive subjects (male: 1 point; hypertension <35 years: 2 points; first urologic event <35 years: 2 points;

nontruncating *PKD1* mutation: 2 points; truncating *PKD1* mutation: 4 points). Subjects were classified into low-risk (LR; 0–3 points), intermediate-risk (IR; 4–6 points) and high-risk (HR; 7–9 points) groups.

Results. The PROPKD score was calculated in 749 subjects (LR = 132, IR = 344 and HR = 273); age was inversely related to risk (LR = 43.6 years, IR = 39.5 years, HR = 36.2 years; P < 0.001). Subjects from the HR group had significantly higher height-adjusted total kidney volume (TKV) and rates of TKV growth. While baseline renal function was similar across all risk groups, the rate of estimated glomerular filtration rate (eGFR) decline significantly increased from LR to HR in the placebo

group. Tolvaptan treatment effectiveness to reduce TKV growth was similar in all three risk categories. While tolvaptan significantly slowed eGFR decline in the IR (tolvaptan = −2.34 versus placebo = −3.33 mL/min/1.73 m^2/year; P = 0.008) and HR groups (tolvaptan = −2.74 versus placebo = −3.94 mL/min/1.73 m^2/year; P = 0.002), there was no difference in the LR group (tolvaptan = −2.35 versus placebo = −2.50 mL/min/1.73 m^2/year; P = 0.72). Excluding the LR subjects from the analysis improved the apparent treatment effect of tolvaptan on eGFR decline.

Conclusion. This study confirms the prognostic value of the PROPKD score and suggests that it could reduce costs and enhance endpoint sensitivity by enriching future study populations for rapidly progressing ADPKD subjects.

Keywords: autosomal dominant polycystic kidney disease, genetics, *PKD1*, *PKD2*, TEMPO 3/4

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the fourth leading cause of end-stage renal disease (ESRD) worldwide [1], with a prevalence of renal replacement therapy (RRT) calculated at 91.1 per million in Europe [2]. The course of ADPKD varies considerably among individuals, with some reaching ESRD before 40 years of age and others living a normal lifespan without requiring RRT. Two principal genes, *PKD1* and *PKD2*, are involved in ∼72–77% and ∼13–18% of cases, respectively [3–8]. A third gene, *GANAB*, has recently been described, which causes milder polycystic kidney disease but in some cases severe polycystic liver disease [9]. Genetic variability strongly influences the severity of ADPKD, with *PKD1* truncating mutations typically associated with an earlier age at ESRD (median age ∼58 years) than *PKD1* nontruncating mutations (∼67 years) and *PKD2* mutations (∼79 years) [3].

Substantial progress in understanding the pathogenesis of ADPKD has triggered the development of new therapeutic strategies [10]. Tolvaptan, a vasopressin 2 receptor antagonist, was demonstrated to slow the rate of total kidney volume (TKV) growth and the rate of kidney function decline in the Tolvaptan Efficacy and Safety in Autosomal Dominant Polycystic Kidney Disease (TEMPO) trial [11]. A *post hoc* analysis suggested clinically similar beneficial effects of tolvaptan in ADPKD across chronic kidney disease (CKD) Stages 1–3, as defined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [12].

Two major factors have made the design of clinical trials in ADPKD particularly challenging. First, the significant variability of renal disease severity complicates the evaluation of candidate drugs, as nonselected cohorts are highly heterogeneous. Second, the loss of kidney function [evaluated by estimated glomerular filtration rate (eGFR)] usually happens gradually, when irreversible structural damage has occurred and intervention is unlikely to be successful. Consequently, classic clinical endpoints such as doubling of serum creatinine or onset of ESRD are difficult to study in a placebo-controlled trial of

reasonable length. Ideally, patients at risk of rapid progression should be selected and treatment should be initiated early to maximize the chance of detecting therapeutic effects in a limited population size [13].

Several approaches have been developed to assess the severity and the prognosis of ADPKD. Previous studies from the Consortium for Radiologic Imaging Study of PKD (CRISP) provided a strong rationale for the prognostic value of TKV, including height adjusted (HtTKV), in ADPKD [14–19]. The Mayo imaging classification (MIC) was developed to predict the rate of decline of eGFR according to the HtTKV at a given age [20]. The authors recommended enriching clinical trials with patients who present with typical imaging presentations and higher HtTKV/age, specifically imaging categories 1C–1E. Aside from the imaging-based prognostic strategies, a different approach was developed in the French cohort Genkyst, which aims to include all the consenting ADPKD patients from the western part of France, irrespective of their disease severity. The Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score, based on clinical and genetic data, was shown to stratify the risk of progression to ESRD [4]. The authors suggested enriching clinical trials with subjects classified as high risk by the PROPKD score.

In this *post hoc* analysis involving a subgroup of subjects from the TEMPO 3/4 trial with genetic data available, we first aimed to assess the prognostic value of the PROPKD score. Our second objective was to investigate whether risk stratification using the PROPKD score in the TEMPO 3/4 trial, by excluding subjects from the low-risk group, where progression of TKV and eGFR would be expected to be slowest, may have further enriched the population for subjects with rapidly progressing ADPKD enhancing discriminative ability.

MATERIALS AND METHODS

Study design

This is a *post hoc* exploratory analysis of TEMPO 3/4, a prospective, randomized, double-blinded trial in 1445 ADPKD adult patients (18–50 years) with an estimated creatinine clearance (Cockroft and Gault) >60 mL/min and a TKV >750 mL/min. The participants were randomized in a 2:1 ratio to receive tolvaptan or placebo [11, 21].

Study participants

TEMPO 3/4 participants with available genetic analysis were included in this study, namely subjects enrolled in the open-label extension trial TEMPO 4/4 who consented to provide a blood sample for DNA analysis [22]. The PROPKD score was calculated in all the subjects in whom a mutation of *PKD1* or *PKD2* was identified (n = 749).

Molecular analysis of the *PKD1* and *PKD2* genes

The entire coding regions of the *PKD1* and *PKD2* genes and their flanking intronic regions were screened by Sanger sequencing, followed if negative by the detection of gross rearrangements using multiplex ligation-dependent probe amplification [23, 24].

Calculation of the PROPKD

The PROPKD score, ranging from 0 to 9 points, was calculated in the mutation-positive subjects as the sum of the following factors: being a male: 1 point; hypertension onset before age 35 years: 2 points; first urologic event before age 35 years (including cyst infection, gross hematuria and/or flank pain related to cysts): 2 points; *PKD2* mutation: 0 points; nontruncating mutation of *PKD1*: 2 points; truncating mutation of *PKD1*: 4 points (Supplementary data, Table S1). Subjects were classified into low-risk (LR; 0–3 points), intermediate-risk (IR; 4–6 points) and high-risk (HR; 7–9 points) groups (Supplementary data, Table S1) [4]. For subjects <35 years of age who had not developed hypertension and/or urological events, a score of 0 was allocated to these clinical variables and the score calculated as the sum of the remaining factors.

Outcome measure

Two endpoints of the TEMPO 3/4 trial were considered in this analysis: the primary outcome measure, which was the annual rate of change in TKV over time, and the secondary outcome measure, the rate of kidney function decline.

Statistical analyses

Annualized TKV growth rate was calculated in each risk subgroup by regressing logarithm-transformed kidney volume data against time and then displaying regression slope exponentials. All eGFR values presented were calculated using the CKD-EPI formula [25]. The rate of eGFR decline was obtained in each risk subgroup by regressing eGFR from steady-state after baseline (i.e. Week 3 and beyond) against time by subject. Treatment effects for both endpoints corresponded to the difference between the slopes of tolvaptan and placebo.

RESULTS

Description of the study population and comparison of risk groups defined by the PROPKD score at baseline

Molecular analysis of *PKD1* and *PKD2* was conducted in 770 subjects. The mutation detection rate was high, with mutations identified in 749 subjects (97.3%; 583 different mutations), of whom 61.3% had a truncating *PKD1* mutation, 26.3% had a nontruncating *PKD1* mutation and 12.4% had a *PKD2* mutation. A majority of the mutations identified were private, the two most frequent variants were the missense c.8311G>A (p.Glu2771Lys) and the frameshifting deletion c.5014_5015delAG (p.Arg1672fs97X), each identified in 2% of the subjects ($n = 15$). Baseline and demographic characteristics in these 749 tolvaptan- and placebo-treated subjects were well-balanced overall and similar to baseline characteristics in the TEMPO 3/4 trial (Supplementary data, Table S2). After calculation of the PROPKD score in the 749 mutation-positive patients, most subjects were categorized to the more severe risk groups [$n = 132$ (17.6%) in LR, 344 (45.9%) in IR and 273 (36.5%) in HR], with the mean age inversely related to risk (LR = 43.6 years, IR = 39.5 years, HR = 36.3 years; P < 0.001) (Table 1).

At baseline, while HtTKV was significantly higher in the HR group than in the IR and LR groups (respective median values of 947, 784 and 785 mL/m; P < 0.005), eGFR was similar in the three groups (Table 1, panel A).

Patients with no mutation detected

While age and eGFR at baseline were similar in the 21 patients with no mutation detected (NMD) and the 749 mutation-positive subjects, median baseline TKV (1167 mL) and HtTKV (648 mL/m) were lower (P-values 0.015 and 0.018, respectively) and these subjects were more frequently classified at lower risk by the MIC (Class 2 or 1B) (38.1% versus 10.2%; P = 0.009).

Rate of TKV growth and PROPKD risk categories

Rate of TKV growth was significantly higher in subjects classified in the HR group than those in the IR and LR groups for both treatment arms. Indeed, in placebo-treated subjects, the rate of TKV growth in the HR group was 32–43% higher than in the LR and IR groups, whereas in the tolvaptan-treated subjects, TKV growth in the HR group was 48–80% higher than in the LR and IR groups (Table 2, panel A). In the LR group, TKV at baseline was significantly higher in the tolvaptan- versus placebo-treated subjects (Table 1, panel B). However, TKV growth was significantly lower in tolvaptan- versus placebo-treated subjects in each of the risk groups. Treatment effect was similar in the three risk groups (Table 2, panel A).

Rate of eGFR decline and PROPKD risk categories

In the placebo-treated subjects, the eGFR decline was greater from the HR to the LR groups. While tolvaptan significantly reduced the rate of renal function decline in the IR and HR groups, with relative treatment effects of 30.3% and 30.6%, there was no significant difference between the tolvaptan- and placebo-treated subjects in the LR group (Table 2, panel A). In the latter group, however, the eGFR at baseline was significantly higher in the placebo-treated group (Table 1, panel B).

Effect of the exclusion of subjects from the LR group on the outcome measures

We investigated the effect of excluding subjects from the LR group [$n = 132$ (17.6%)]. While this exclusion did not change the tolvaptan-mediated decrease in TKV growth rate (Figure 1A), there was a nonsignificant trend of increased treatment effect on the rate of eGFR decline (treatment effect 30.6% after exclusion of LR versus 27.1%). In the three combined groups, tolvaptan reduced the rate of eGFR decline from −3.40 to −2.48 mL/min/1.73 m^2/year (P = 0.0001). Excluding subjects in the LR group from the analysis increased this difference (−3.62 to −2.51 mL/min/1.73 m^2/year; P < 0.0001) (Figure 1B).

Stability of PROPKD risk groups in subjects <35 years of age during the trial follow-up

The clinical variables included in the PROPKD score, i.e. hypertension and urological events, are set as binary variables occurring before 35 years (2 points) or not (0 points). Among the 749 mutation-positive subjects, 168 were <35 years of age, almost exclusively in the more severe groups (7 in LR, 61 in IR, 100 in HR). Fourteen of these subjects changed risk category

Table 1. Baseline characteristics

(A) Comparison of the baseline characteristics in the three PROPKD risk groups				P-values		
	LR PROPKD 1–3	IR PROPKD 4–6	HR PROPKD 7–9			
	(n = 132)	(n = 344)	(n = 273)	LR to IR	IR to HR	LR to HR
Age (years), mean (SD)	43.6 (5.3)	39.5 (6.6)	36.3 (6.8)	<0.0001	<0.0001	<0.0001
Caucasian, n (%)	124 (93.9)	339 (98.5)	259 (94.9)	0.01	0.7	0.003
Male, n (%)	80 (60.6)	101 (29.3)	209 (76.6)	<0.0001	<0.0001	0.002
Age at diagnosis of ADPKD (years), mean (SD)	35.4 (8.6)	26.7 (8.9)	23.6 (7.7)	<0.0001	<0.0001	<0.0001
HTN, n (%)	108 (81.8%)	277 (80.5%)	252 (92.3%)	0.80	<0.0001	0.003
Age at diagnosis of HTN, (years), mean (SD)	38.3 (5.77)	33.1 (7.9)	26.5 (6.5)	<0.0001	<0.0001	<0.0001
Median TKV (mL) (IQR)	1367 (838–1896)	1338 (916–1759)	1682 (1181–2182)	0.15	<0.0001	0.002
Median HtTKV (mL/m), (IQR)	785 (492–1077)	784 (545–1022)	947 (663–1231)	0.28	<0.0001	0.005
eGFR$_{CKD-EPI}$ (mL/min/1.73 m^2, mean (SD)	84.8 (21.1)	83.4 (20.9)	82.3 (23.1)	0.56	0.49	0.32
Genotype, n (%)						
PKD1 truncating	0 (0.0)	219 (63.7)	240 (87.9)	<0.0001	<0.0001	<0.0001
PKD1 nontruncating	53 (40.2)	111 (32.2)	33 (12.1)	0.11	<0.0001	<0.0001
PKD2	79 (59.8)	14 (4.1)	0 (0.0)	<0.0001	0.304	<0.0001
Mayo imaging class, n (%)						
Class 2	10 (7.6)	7 (2)	1 (0.4)	0.097	0.0831	<0.0001
Class 1B	17 (12.9)	35 (10.2)	6 (2.2)	0.41	<0.0001	<0.0001
Class 1C	62 (47)	151 (43.9)	70 (25.6)	0.61	0.0119	0.003
Class 1D	36 (27.2)	113 (32.8)	117 (42.9)	0.27	<0.0001	<0.0001
Class 1E	7 (5.3)	36 (10.5)	76 (27.8)	0.11	<0.0001	<0.0001
Missing	0	2 (0.6)	3 (1.1)			

(B) Comparison of the baseline characteristics in the tolvaptan-(T) and placebo (P)-treated patients within each PROPKD risk group						
	LR PROPKD 1–3		IR PROPKD 4–6		HR PROPKD 7–9	
	T (n = 79)	P (n = 53)	T (n = 226)	P (n = 118)	T (n = 167)	P (n = 106)
Age (years), mean (SD)	43.7 (5.0)	43.5 (5.8)	39.2 (6.7)	40.2 (6.5)	36.3 (6.4)	36.1 (7.3)
Caucasian, n (%)	75 (94.9)	49 (92.5)	222 (98.2)	117(99.2)	157 (94)	102 (96.2)
Male, n (%)	50 (63.3)	30 (56.6)	74 (32.7)	27 (22.9)	135* (80.8)	74* (69.8)
TKV (mL), median (IQR)	1574* (1009–2138)	1241* (943–1538)	1330 (905–1754)	1352 (950–1754)	1699 (1163–2235)	1677 (1216–2138)
HtTKV (mL/m), median (IQR)	917* (596–1238)	705* (538–871)	756 (520–991)	793 (553–1032)	952 (666–1238)	939 (663–1215)
eGFR$_{CKD-EPI}$, mean mL/min/1.73 m^2 (SD)	81.1* (18.5)	90.3* (23.6)	83.7 (20.7)	82.9 (21.4)	82.0 (22.5)	82.8 (24.1)

HTN, hypertension; IQR, interquartile range.
*P-value between T and P < 0.05.

after 3 years of follow-up: 3 from LR to IR and 11 from IR to HR (Figure 2).

Combination of the MIC and PROPKD approaches

To investigate whether the PROPKD score and the MIC could be used as complementary enrichment strategies, we studied the distribution of LR, IR and HR subjects in the different classes of the MIC. As expected, HR subjects were more represented in the more severe classes (1C, 1D and 1E; Table 1, panel A and Figure 3). While 75.7% of subjects were defined at higher risk of significant progression by both methods (Group 1, i.e. IR and HR by the PROPKD and MIC groups 1C, 1D and 1E), only 3.6% were defined at low risk of progression by both methods (Group 2), 14.1% were considered at higher risk only by the MIC (Group 3) and 6.6% only by the PROPKD score (Group 4). Consistent with the entry criteria of the TEMPO trial, a majority of the subjects classified at lower risk by each method were >35 years of age (96% for the MIC and 94% for the PROPKD). Inversely, subjects from Group 1 had similar baseline kidney function but were significantly younger than patients from Group 3 and Group 4 [mean age 37 versus 43 and 43 years, respectively (P < 0.001)]. The proportion of subjects

from MIC Class 1C was significantly higher in the discordant Group 3 than in the concordant Group 1 (59% versus 39.3%; P < 0.001). Similarly, the proportion of subjects from the PROPKD IR group was higher in the discordant Group 4 than in the concordant Group 1 (85.7% versus 40%; P < 0.001). This suggests an overall milder disease in these two discordant subgroups. The most frequent missense variant, p.Glu2771Lys, was more frequently identified in the discordant Group 3 than in the rest of the cohort (5.7% versus 1.4%; P = 0.004).

To evaluate whether the PROPKD further improved the imaging stratification in Classes 1C, 1D and 1E, we excluded subjects classified as Class 2 (n = 18) and 1B (n = 58). In subjects from Classes 1C, 1D and 1E, while tolvaptan reduced TKV growth in each of the three PROPKD risk groups, it was associated with significantly slower renal function decline in the IR and HR groups, but not in the LR group (Table 2, panel B).

DISCUSSION

Designing optimal clinical trials in ADPKD is a difficult task given the lifelong progression of the disease and the high variability of its severity. Inclusion criteria in the TEMPO trial

Table 2. Rate of change in TKV and eGFR by PROPKD risk categories

(A) Analysis in the 749 individuals included in the *post hoc* analysis						
Variable	LR		IR		HR	
	T (n = 79)	P (n = 53)	T (n = 226)	P (n = 118)	T (n = 167)	P (n = 106)
Rate of TKV growth (%/year)	2.80	5.11	2.30	4.72	4.15	6.75
P-value	0.0022		<0.0001		<0.0001	
Relative treatment effect (%)	45.8		51.8		38.2	
	T (n = 79)	P (n = 52)	T (n = 214)	P (n = 115)	T (n = 159)	P (n = 103)
Rate of eGFR$_{CKD-EPI}$ decline (mL/min/1.73 m^2)	−2.35	−2.50	−2.34	−3.33	−2.74	−3.94
P-value	0.72		0.008		0.002	
Relative treatment effect (%)	6.9		30.3		30.6	
(B) Subgroup analysis in patients from MICs C, D and E (n = 668)						
Variable	LR		IR		HR	
	T (n = 65)	P (n = 40)	T (n = 196)	P (n = 104)	T (n = 160)	P (n = 103)
Rate of TKV growth (%/year)	2.71	5.36	2.47	5.08	4.27	6.9
P-value	0.0010		<0.0001		<0.0001	
Relative treatment effect (%)	50.4		52.2		38.1	
	T (n = 65)	P (n = 39)	T (n = 186)	P (n = 101)	T (n = 152)	P (n = 100)
Rate of eGFR$_{CKD-EPI}$ decline (mL/min/1.73 m^2)	−2.55	−2.58	−2.47	−3.53	−2.74	−4.11
P-value	0.91		0.009		0.0003	
Relative treatment effect (%)	2.3		30.5		33.7	

P, placebo; T, tolvaptan.

combined volume and age thresholds in individuals with pre-served kidney function, thus enriching for patients with rapidly progressive ADPKD. Reflecting this enrichment, when compared with the Genkyst cohort, *PKD1* truncating mutations were more frequent in TEMPO patients (61.3% versus 53%) and *PKD2* mutations less frequent (12.4% versus 20.2%).

The PROPKD score was developed in a population-based cohort representative of the wide spectrum of disease severity in adult ADPKD. Herein, we confirm the prognostic value of the PROPKD score in a genotyped subgroup of subjects from the TEMPO trial. Indeed, subjects from the HR group, although younger, had higher HtTKVs at baseline and higher rates of TKV growth. While subjects from the three risks groups had similar average eGFR at baseline, we observed increasingly steeper rates of eGFR decline from the LR to the HR group. This study provides strong validation of the prognostic value of the PROPKD score for two reasons. First, it demonstrates that the PROPKD score stratifies the risk for disease progression even in ADPKD patients selected to have rapidly progressive disease. Second, although the PROPKD score was developed to predict age at ESRD, we show here that it also predicts rates of eGFR decline and TKV growth.

Our second objective was to investigate whether excluding subjects from the LR group defined by the PROPKD score may have enhanced the discriminative ability of the TEMPO trial. As a result of the TEMPO entry criteria, a higher proportion of subjects was classified in the HR (36.5%) and IR groups (45.9%) when compared with the Genkyst cohort, where the HR and IR groups represented 14% and 46.7% of the subjects, respectively

[4]. In this *post hoc* analysis, exclusion of the 132 LR group subjects (17.6%) slightly maximized the difference in the rate of eGFR decline between the tolvaptan- and the placebo-treated subjects. The treatment effect on the rate of TKV growth was similar in the three risk groups.

This analysis demonstrates that the PROPKD score can be used to enrich clinical trial cohorts for rapidly progressive patients, and complement enrichment from TKV criteria, to increase the chances of observing significant differences in the rate of kidney function decline. Such strategies in future trials may allow cost reductions by decreasing the number of subjects to recruit while maximizing the chance of positive results. While the high cost of a comprehensive analysis of *PKD* genes has long been a disincentive, the current wide-spread use of next-generation sequencing allows significant cost reductions and is likely to facilitate access to genetic testing [26–30].

Two recent studies evaluating an enrichment strategy using the MIC have been published [31, 32]. The first *post hoc* analysis was conducted in early disease in the HALT-PKD study, a randomized controlled trial that studied the effect of rigorous versus standard blood pressure control on rates of TKV increase and eGFR decline in ADPKD subjects ages 15–49 years with preserved renal function (eGFR > 60 mL/min/1.73 m^2) at inclusion [33]. Treatment was more beneficial in subjects from Classes 1D and 1E, both in terms of TKV increase and eGFR decrease. This cohort of subjects was more heterogeneous in terms of disease severity than in the TEMPO 3/4 trial. Analysis of the PROPKD score performance in that population would be
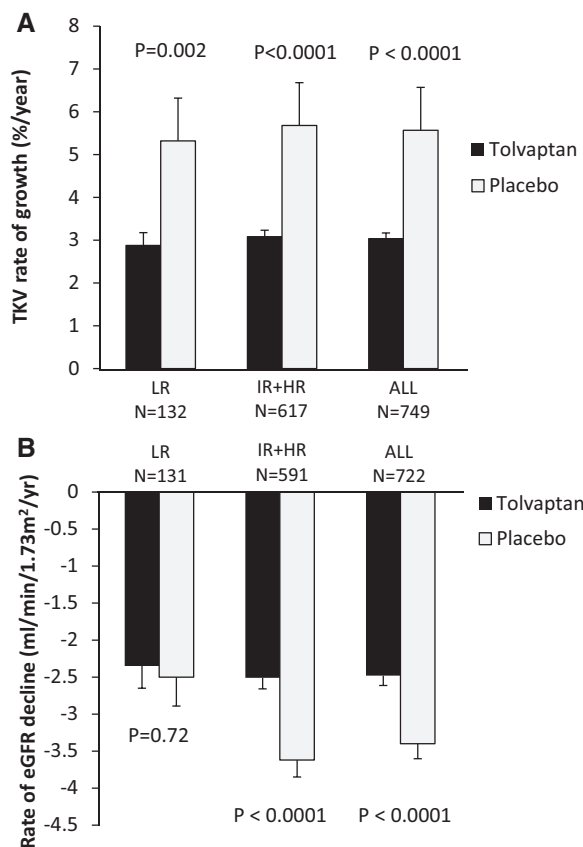
FIGURE 1: (**A**) Rate of TKV growth in the LR group, in the combined HR and IR group and in the three combined groups. (**B**) Rate of eGFR decline in the LR group, in the combined HR and IR group and in the three combined groups. Error bars represent the standard error of the mean.

FIGURE 2: Classification remains stable in most patients over time. Flowchart representing the classification of the 749 subjects in the three PROPKD risk groups at baseline and after 3 years of follow-up. Fourteen of these subjects changed risk category after 3 years of follow-up: 3 from LR to IR and 11 from IR to HR as a consequence of a diagnosis of hypertension in 10 subjects and the occurrence of a first urological event in 6 subjects.

FIGURE 3: Distribution of LR, IR and HR groups in each category of the MIC model.

interesting, but age at the first urological event was not systematically collected. The second *post hoc* analysis was conducted in the TEMPO trial [32]. Exclusion of Class 2A and 1B subjects resulted in a slightly higher treatment effect on TKV and eGFR slopes, although nonsignificant. Interestingly in our study, 105 subjects from MICs 1C–1E were categorized in the PROPKD LR group. Subjects in this subgroup were significantly older and more frequently classified as MIC 1C, suggesting an overall milder disease in this discordant subgroup. In subgroup analysis including only the 668 subjects from MICs 1C–1E, the rate of eGFR decline was lower in the LR than in the IR and HR groups. And while treatment was associated with a slower renal function decline in the HR and IR groups, there was no difference from placebo in the LR group. This suggests that combining imaging, genetics and clinical criteria in a single scoring system may be of interest to develop future prognostic tools in ADPKD. Such an approach will allow evaluation of the relative contributions of the different predictors and provide accurate prognostic information earlier: before the occurrence of significant volume enlargement and/or hypertension or a urological event. Meanwhile, the use of both tools seems particularly interesting in patients at intermediate risk, for instance using PROPKD to reclassify subjects from MIC 1C and MIC to reclassify subjects from the PROPKD IR group, depending on which prognosis tool was used first.
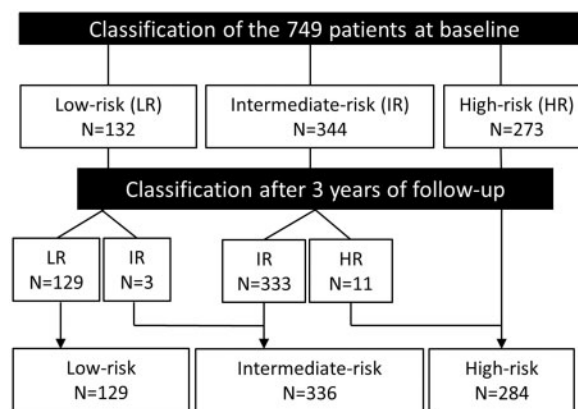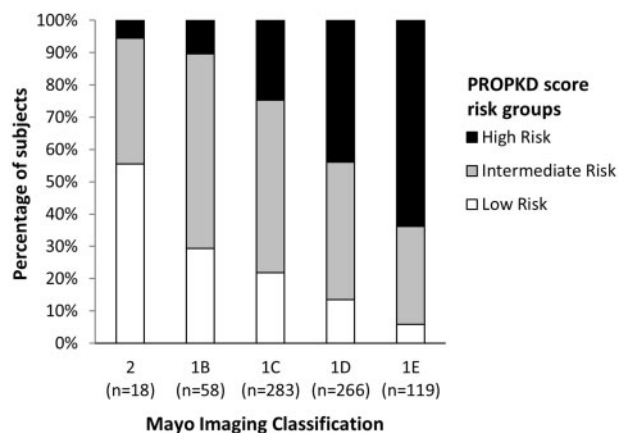
Tolvaptan is now available in Canada, Japan, Europe, South Korea and Switzerland and a position statement for the use of tolvaptan has recently been issued by a European group of experts [34]. One of the objectives of this group was to define the definition of 'evidence of rapid disease progression'. Besides historical kidney growth and eGFR decline, demonstrated by sequential imaging or creatinine measurements, the authors suggested that subjects from MICs 1C–1E or from the PROPKD HR group were likely to have rapid progression. Taking into account the results of the present study, subjects from the PROPKD IR group should also be considered at risk for rapid progression, although we must keep in mind that these subjects met the inclusion criteria for the TEMPO trial and so potentially had more rapid progression than nonpreselected IR group subjects.

This study has some limitations. First, this is a *post hoc* analysis, which was run in a subgroup of the TEMPO trial, and a sample for genetic analysis was collected on only ∼53% of

subjects. As a consequence, the LR group was quite small and baseline characteristics between placebo- and tolvaptan-treated patients differed significantly in this subgroup. Reassuringly, baseline characteristics in the genotyped subgroup were similar to the full TEMPO 3/4 cohort [11]. Second, while disease severity is overall milder in patients with nontruncating variants, a handful of missense variants has been shown *in vitro* to be fully penetrant, including p.Glu2771Lys, which disrupts cleavage of polycystin 1 at the G-protein coupled receptor proteolytic site [35, 36], and was more frequent in subjects considered at higher risk only by the MIC. Attributing four points (truncating mutation) rather than two points (nontruncating mutation) for the genetic component of the PROPKD score in the ~2% of ADPKD patients harboring this mutation would improve their prognostic assessment. In the future, the development of functional assays will allow more refined variant classification. Moreover, in 21 patients no mutation of *PKD1* or *PKD2* was identified and thus the PROPKD score could not been calculated. Aside from missed mutations in the complex *PKD1* gene, or in the intronic portions of both genes, missense variants of unknown significance or mosaic cases may explain some of these genetically unresolved cases, which is suggested by the higher proportion of subjects from MIC 2, i.e. with segmental, asymmetric or lopsided imaging presentation. Mutations in *GANAB* are unlikely to be involved here, as none of the 20 *GANAB* patients reported so far would have met the age and TKV inclusion criteria of the TEMPO 3/4 trial [9]. Nevertheless, the mutation detection rate was particularly high in this cohort, with only 2.7% of the subjects having NMD, compared with 7–10% in other recent ADPKD cohorts [3, 4, 7, 24]. A potential explanation is that subjects with NMD tend to have milder disease [7] and were hence less likely to be included in the TEMPO trial. Last, due to the scoring criteria, the PROPKD score can increase in subjects <35 years of age if they develop hypertension or experience a first urological event. Therefore, excluding young LR group subjects from studies and treatment has the risk of removing a few subjects with rapidly progressive disease. The follow-up analysis in the TEMPO trial timeframe is reassuring, as only three subjects moved from the LR to the IR group.

In conclusion, the PROPKD score is an efficient strategy to enrich future randomized control trials cohorts for rapidly progressive patients. Ultimately, the combination of imaging and genetic-based approaches will likely enhance our capacity to predict renal outcomes and tailor therapeutic approaches to individual ADPKD patients.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxford journals.org.

CONFLICT OF INTEREST STATEMENT

None declared.

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