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Total Kidney Volume Is a Prognostic Biomarker of Renal Function Decline and Progression to End-Stage Renal Disease in Patients With Autosomal Dominant Polycystic Kidney Disease

Ronald D. Perrone[1], Mohamad-Samer Mouksassi[2], Klaus Romero[3], Frank S. Czerwiec[4], Arlene B. Chapman[5], Berenice Y. Gitomer[6], Vicente E. Torres[7], Dana C. Miskulin[1], Steve Broadbent[3] and Jean F. Marier[2]

[1]Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, Massachusetts, USA; [2]Pharsight, Montreal, Quebec, Canada; [3]Critical Path Institute, Tucson, Arizona, USA; [4]Otsuka Pharmaceutical Development and Commercialization Inc., Global Clinical Development, Rockville, Maryland, USA; [5]Division of Nephrology, University of Chicago, Chicago, Illinois, USA; [6]Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA; and [7]Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Minnesota, USA

Introduction: Autosomal dominant polycystic kidney disease is the most common hereditary kidney disease. TKV is a promising imaging biomarker for tracking and predicting the natural history of autosomal dominant polycystic kidney disease. The prognostic value of TKV was evaluated, in combination with age and eGFR, for the outcomes of 30% decline in eGFR and progression to ESRD. Observational data including 2355 patients with TKV measurements were available.

Methods: Multivariable Cox models were developed to assess the prognostic value of age, TKV, height-adjusted TKV, eGFR, sex, race, and genotype for the probability of a 30% decline in eGFR or ESRD.

Results: TKV was the most important prognostic term for 30% decline in eGFR in autosomal dominant polycystic kidney disease patients with and without preserved baseline eGFR. For a 40-year-old subject with preserved eGFR (70 ml/min per 1.73 m^2), the adjusted hazard ratios for a 30% decline in eGFR were 1.86 (95% CI, 1.65–2.10) for a 2-fold larger TKV (600 vs. 1200 ml) and 2.68 (95% CI, 2.22–3.24) for a 3-fold larger TKV (600 vs. 1800 ml), respectively. Hazard ratios for progression to ESRD for 2- and 3-fold larger TKV were 1.72 (95% CI, 1.49–1.99) and 2.36 (95% CI, 1.88–2.97), respectively.

Discussion: The capability to predict 30% decline in eGFR is a novel aspect of this study. TKV was formally qualified, both by FDA and EMA, as a prognostic enrichment biomarker for selecting patients at high risk for a progressive decline in renal function for inclusion in interventional clinical trials.

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. There is a strong body of evidence demonstrating that the kidneys of patients with ADPKD progressively increase in size from birth throughout life, and the clinical symptoms and signs of ADPKD including hypertension, gross hematuria, flank and abdominal pain, and declining glomerular filtration rate (GFR) are associated with increased kidney volume.[1–3] Irazabal *et al.*[4] reported that future estimated glomerular filtration rate (eGFR) decline in ADPKD could be predicted based on total kidney volume (TKV) growth rate, estimated by height-corrected TKV, and age.

Currently there are no therapies approved in the United States to prevent or delay disease progression in patients with ADPKD, although the vasopressin V2 receptor antagonist tolvaptan has been approved for use in Japan, Canada, and Europe. Scientific progress has been made in understanding the mechanisms of disease and pathophysiological processes underlying ADPKD. This has resulted in several potential therapeutic targets, some of which have shown great promise in animal studies.[5,6] However, development of early therapeutic interventions has proceeded slowly in the absence of a universally acceptable and practical

Correspondence: Ronald D. Perrone, Tufts Medical Center, 800 Washington Street, Boston, Massachusetts 02111-1526, USA. E-mail: rperrone@tuftsmedicalcenter.org

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regulatory path with respect to an endpoint that could be used to establish the efficacy of a therapy intended to treat ADPKD early in its disease course. The clinical course of ADPKD is marked by a decades-long period of apparently stable kidney function, as measured by eGFR, despite progressive loss of nephron reserve and the relentless expansion of TKV due to growth of cysts.[1–3] Accepted registration endpoints for trials in chronic kidney disease progression, including doubling of serum creatinine or development of end-stage renal disease (ESRD), occur late in the disease course, after irreversible fibrosis and distortion of kidneys has taken place.[7]

The only biomarker proposed to date as a surrogate endpoint for ADPKD clinical trials is TKV; the US Food and Drug Administration (FDA) did not accept TKV as a registration endpoint for the Phase 3, Multi-center, Double-Blind, Placebo-Controlled, Parallel-Arm Trial to Determine Long-term Safety and Efficacy of Oral Tolvaptan Tablets Regimens in Adult Subjects With Autosomal Dominant Polycystic Kidney Disease (TEMPO 3:4) trial.[8] The European Medicines Agency (EMA), Health Canada, and the Pharmaceuticals and Medical Devices Agency of Japan have approved tolvaptan, based on the endpoint of TKV, but there is no formal regulatory recognition of TKV as a biomarker.

To address the lack of an approved biomarker for ADPKD clinical trials, the Polycystic Kidney Disease Outcomes Consortium engaged in a process with FDA and EMA to formally qualify TKV as a prognostic biomarker.[9] The Polycystic Kidney Disease Outcomes Consortium has developed the first-ever Clinical Data Interchange Standards Consortium therapeutic area–specific data standard for ADPKD to allow for the mapping and integrating of observational data from both patient registries and Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort studies into a common dataset.[10] The current research used this large dataset to determine whether baseline TKV and other covariates such as age, sex, genotype, or eGFR predicts future decline in renal function. The outcome of these studies is that TKV was formally qualified, both by FDA and EMA, as a prognostic enrichment biomarker for selecting patients at high risk for a progressive decline in renal function for inclusion in interventional clinical trials. The present and accompanying manuscripts form the basis of this accomplishment.

METHODS

Populations and Endpoints

Observational data from 5 sources were integrated into a standardized Clinical Data Interchange Standards Consortium structure: (i) University of Colorado–Denver, (ii) Mayo Clinic, (iii) Emory University, (iv) CRISP1, and (v) CRISP2. The content of these databases is described elsewhere.[10] A brief description of the timeframe of enrollment, number of subjects enrolled, and process of each study/registry as outlined in the STROBE statement is presented in Supplementary Table S1.[11]

Because the goal of this project was to determine whether TKV, along with other prognostic factors such as baseline age and eGFR, can accurately predict the risk of eGFR decline and progression to ESRD, only endpoint measurements that occurred after the first baseline TKV measurement were considered.

- 30% decline of eGFR: This endpoint represents a 30% decline in eGFR relative to the baseline.[12,13] A subsequent measurement within any timeframe was required to confirm that the original 30% decline was not transient.
- 57% decline of eGFR: This endpoint represents a 57% decline in eGFR relative to the baseline.[12,13] A subsequent measurement within any timeframe was required to confirm that the original 57% decline was not transient.
- ESRD: This endpoint was defined as a patient with either dialysis or transplant.

A summary of subjects included in the analysis is presented in Figure 1. A total of 2355 patients with ADPKD with TKV data collected up to 30 years of follow-up were available in the database. Baseline TKV was defined as the first TKV measurement for a subject, whereas baseline age was the age associated with the first TKV measurement. TKV measurements were used, irrespective of modality, including computed tomography (CT), magnetic resonance imaging (MRI), and

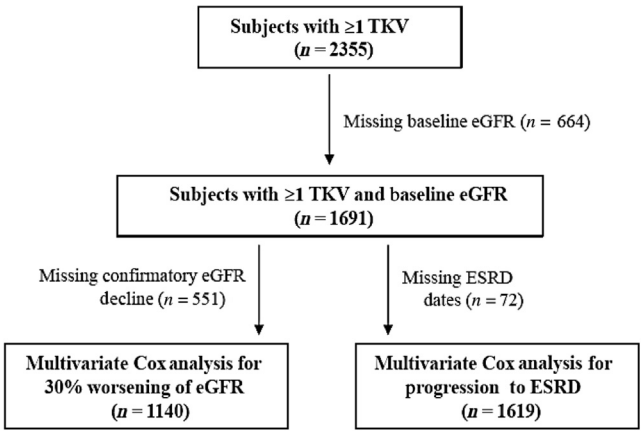

Figure 1. Summary of subjects included in the analysis, missing baseline characteristics, and disease endpoints. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; TKV, total kidney volume.

ultrasound. Baseline eGFR was calculated from the first valid serum creatinine measurement on the 365th day or within 365 days of the baseline TKV. The original MDRD equation was used to derive eGFR for creatinine methods that were not calibrated to an isotope dilution mass spectrometry (IDMS) reference method.[14] For creatinine methods calibrated to an IDMS reference method, the IDMS-traceable Modification of Diet in Renal Disease (MDRD) study equation was used to derive eGFR.[15] The majority of creatinine measurements were not calibrated to an IDMS reference method as they were obtained prior to the development of this methodology.

A total of 664 patients did not have a baseline eGFR (i.e., time-matched eGFR with baseline TKV). For the assessment of 30% decline of eGFR, a total of 551 patients did not have ≥2 eGFR measurements. As a result, the population for the assessment of a 30% decline of eGFR included 1140 patients with a complete set of baseline characteristics and ≥2 eGFR measurements after baseline. For the assessment of ESRD, 664 patients did not have a baseline eGFR and 72 patients did not have a time record at the time of ESRD. As a result, the population for the assessment of ESRD included 1619 patients with a complete set of baseline characteristics.

Statistical Methodology

The following baseline characteristics were summarized with descriptive statistics: age, TKV, eGFR, sex, race, and ADPKD mutations (*PKD1*, *PKD2*, or unknown). Baseline characteristics (TKV, age, and eGFR) in patients who progressed to a 30% decline in eGFR and ESRD were compared with those who did not reach the endpoint using a t-test at an alpha level of 0.05. Median values with quartile 1 and 3 (Q1 to Q3) for time to events of each endpoint were derived.

Time-to-event (30% decline of eGFR or ESRD) times were derived endpoints as a function of follow-up times. Censoring was defined as the last date where information from patients was available in the database before an event could be observed. Kaplan-Meier figures were presented for each endpoint as a function of follow-up times and as a function of baseline TKV (<1000 or ≥1000 ml) and eGFR (<50 or ≥50 ml/min per 1.73 m^2). Survival curves were compared using the G-rho family of tests.[16] Briefly, the G-rho family of tests includes weights on each death of $S(t)^{\rho}$, where S is the Kaplan-Meier estimate of survival. With $\rho = 0$ this is the log-rank or Mantel-Haenszel test, and with $\rho = 1$ it is equivalent to the Peto and Peto modification of the Gehan-Wilcoxon test.

Univariate Cox models (1-by-1) were developed in a first step to assess the effect of various candidate predictors for the probability of disease outcome. The following predictors were considered: baseline age (age at first TKV measurement), baseline TKV (first TKV measurement), height-adjusted baseline TKV, sex, race (white and nonwhite), and genotype (*PKD1* and *PKD2* or no mutation detected). The predictive performance of individual terms was assessed by deriving receiver-operating characteristics (ROC) at 1 and 3 years.[17] It is well known that TKV, age, and eGFR are not completely independent.[18] Therefore, the following interaction terms were tested in the multivariable Cox model: (i) interaction between ln-transformed baseline TKV and baseline age, (ii) interaction between baseline eGFR and baseline age, and (iii) interaction between baseline eGFR and ln-transformed baseline TKV. Models with different interaction terms were compared by deriving Akaike information criterion and ROC at 1 and 3 years. The final interaction model was selected based on the Akaike information criterion and ROC values. Hazard ratios for individual predictors were derived with the final multivariable Cox model with interactions. Covariates were tested through forward stepwise model building and backward elimination testing. Missing data were not imputed.

Several imaging modalities have been used to determine TKV in patients with ADPKD.[19] These included ultrasound as determined using the ellipsoid method, MRI and CT scan.[20] The primary analysis was performed based on TKV measured using any of these imaging modalities. Furthermore, to understand potential differences in using TKV data collected by different imaging modalities, separate multivariable Cox models were constructed for TKV measured by ultrasound and compared with analyses based on TKV measured by magnetic MRI or CT scan.

Kaplan-Meier figures, Cox modeling, and area under the curve for ROC were performed using R 3.0.2 (64-bit; R Foundation, Vienna, Austria).

RESULTS

Baseline Characteristics

Baseline characteristics of the patient population included in the analysis of a 30% decline of eGFR or ESRD are presented in Table 1. Median (Q1– Q3) follow-up times for a 30% decline of eGFR and ESRD were 4.10 (1.77–8.03) and 5.89 (2.61–10.1) years. The populations used in modeling the probability of a 30% decline of eGFR consisted of 1140 subjects with mean baseline TKV, age, and eGFR of 1494.6 ml, 38.8 years, and 70.1 ml/min per 1.73 m^2, respectively. A total of 361 (31.7%) subjects experienced a 30% decline of eGFR over a median (interquartile range) of 3.11 years (1.59–6.60) of follow-up. Baseline characteristics of the

Table 1. Baseline characteristics of ADPKD population

Baseline characteristics	Population for the analysis of 30% decline of eGFR (n = 1140)[a]	Population for the analysis of progression to ESRD (n = 1619)
TKV (ml)[b]	1494.6 ± 1426.7	1460.7 ± 1456.2
Age (yr)	38.8 ± 15.8	38.8 ± 16.0
Age (yr)		
0–<20	156 (13.7)	230 (14.2)
20–<40	404 (35.4)	569 (35.1)
40–<60	489 (42.9)	682 (42.1)
60–<80	83 (7.3)	128 (7.9)
80–100	8 (0.7)	10 (0.6)
eGFR (ml/min per 1.73 m^2)	70.1 ± 37.8	69.9 ± 37.6
CKD stages[c]		
1	281 (24.6)	398 (24.6)
2	406 (35.6)	579 (35.8)
3	274 (24.0)	385 (23.8)
4	117 (10.3)	169 (10.4)
5	62 (5.4)	88 (5.4)
Sex		
Male	464 (40.7)	641 (39.6)
Female	676 (59.3)	978 (60.4)
Race		
White	1042 (91.4)	1452 (89.7)
Black	40 (3.5)	50 (3.1)
Other	58 (5.1)	117 (7.2)
Genotype		
PKD1	585 (51.3)	740 (45.7)
PKD2	70 (6.1)	76 (4.7)
Missing	466 (40.9)	780 (48.2)
No mutation detected	20 (1.8)	23 (1.4)
Data source[b]		
CRISP studies	233	236
University of Colorado	359	568
Emory University	177	253
Mayo Clinic	498	690
Imaging modality[b]		
Ultrasound	90	801
CT	528	558
MRI	392	663

ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; CRISP, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; CT, computed tomography; eGFR, estimated glomerular filtration; ESRD, end-stage renal disease; MRI, magnetic resonance imaging; TKV, total kidney volume.
Values are mean ± SD or n (%).
[a]The population for the analysis of a 57% decline of eGFR presented the same baseline characteristics.
[b]TKV measured using all imaging modalities (i.e., ultrasound and MRI/CT).
[c]CKD stages 1, 2, 3, 4, and 5: eGFR >90, 89 to 60, 59 to 30, 29 to 15, and <15 ml/min per 1.73 m^2, respectively.

patient population for the analysis of a 57% decline of eGFR were the same as those for the analysis of a 30% decline of eGFR. Because the number of subjects presenting a 57% decline of eGFR was very low (approximately 10%), only exploratory analyses were performed for this endpoint.

Baseline characteristics of subjects for the analysis of ESRD were consistent with those observed for the 30% eGFR decline analysis. A total of 354 (21.9%) subjects progressed to ESRD over a median (Q1–Q3) 4.0 years (1.10–8.16) of follow-up. Baseline characteristics were consistent with those reported in randomized controlled clinical trials of ADPKD.[21,22]

Similar baseline age and baseline eGFR were observed in patients with or without a 30% decline of eGFR, whereas a 32% higher baseline TKV ($P < 0.001$) was observed in patients experiencing a 30% decline of eGFR (Supplementary Tables S2 and S3). Higher baseline TKV was also observed in patients who progressed to ESRD compared with those who did not ($P < 0.001$), although these patients were also older and had a lower baseline eGFR.

Exploratory Data Analysis

Kaplan-Meier figures for the probability of avoiding a 30% decline of eGFR as a function of baseline eGFR (<50 or ≥50 ml/min per 1.73 m^2) and baseline TKV (<1000 or ≥1000 ml) are presented in Figure 2. For patients with "preserved" kidney function (GFR ≥50 ml/min per 1.73 m^2) and "reduced" kidney function (GFR <50 ml/min per 1.73 m^2), the risk of a 30% decline of eGFR in ADPKD patients with larger TKV (≥1000 ml) was markedly greater than that observed in patients with smaller TKV (<1000 ml) (red dashed vs. red solid lines). Kaplan-Meier figures for the probability of avoiding ESRD as a function of baseline eGFR (<50 or ≥50 ml/min per 1.73 m^2) and baseline TKV (<1000 or ≥1000 ml) are presented in Figure 3.

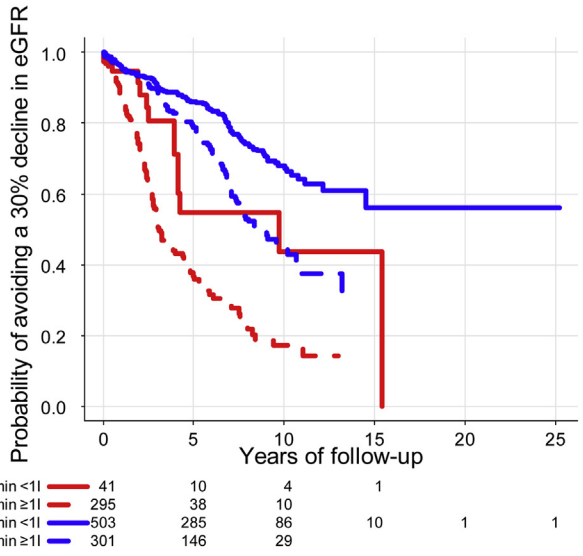

Figure 2. Probability of avoiding a 30% decline in estimated glomerular filtration rate (eGFR) as a function of baseline total kidney volume (TKV) and baseline eGFR. Solid red line represents preserved eGFR (≥50 ml/min per 1.73 m^2) and small TKV (<1000 ml). Dashed red line represents preserved eGFR (≥50 ml/min per 1.73 m^2) and large TKV (≥1000 ml). Solid blue line represents reduced eGFR (<50 ml/min per 1.73 m^2) and small TKV (<1000 ml). Dashed blue line represents reduced eGFR (<50 ml/min per 1.73 m^2) and large TKV (≥1000 ml).

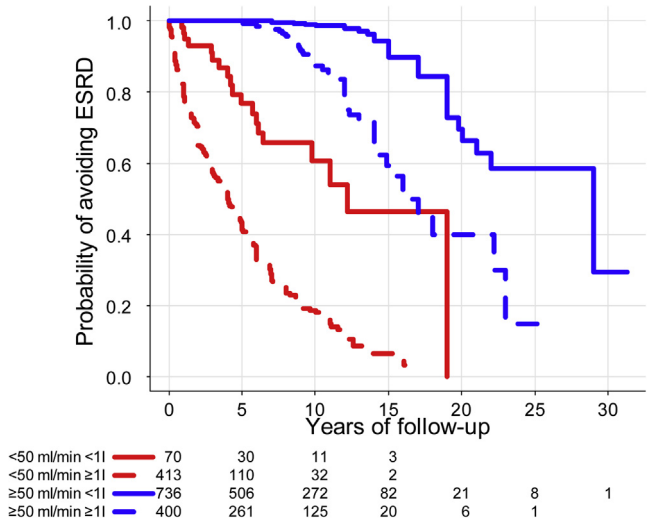

Figure 3. Probability of avoiding end-stage renal disease (ESRD) as a function of baseline total kidney volume (TKV) and baseline estimated glomerular filtration rate (eGFR). Solid red line represents preserved eGFR (≥50 ml/min per 1.73 m^2) and small TKV (<1000 ml). Dashed red line represents preserved eGFR (≥50 ml/min per 1.73 m^2) and large TKV (≥1000 ml). Solid blue line represents reduced eGFR (<50 ml/min per 1.73 m^2) and small TKV (<1000 ml). Dashed blue line represents reduced eGFR (<50 ml/min per 1.73m^2) and large TKV (≥ 1000 ml).

Risks of progression to ESRD in patients with larger TKV (≥1000 ml) were markedly greater than those observed in patients with smaller TKV (<1000 ml), regardless of kidney function. Median (Q1–Q3) time to events for each endpoint and each subpopulation of patients with preserved or reduced eGFR, with either small or large TKV are presented in Table 2. Based on a log-rank or Mantel-Haenszel test, the 4 survival curves for the probability of a 30% decline of eGFR and ESRD (Figures 2 and 3, respectively) were all statistically different ($P < 0.001$). Kaplan-Meier figures for the probability of avoiding a 57% decline of eGFR as a function of baseline eGFR (<50 or ≥50 ml/min per 1.73 m^2) and baseline TKV (< 1000 or ≥1000 mL) are presented in Supplementary Figure S1.

Table 2. Median time (yr) to reach endpoint

Populations	Median (Q1–Q3) time to 30% decline of eGFR	Median (Q1–Q3) time to progression to ESRD
Overall	10.4 (4.76–NC)	19.0 (10.0–29.0)
eGFR <50 ml/min per 1.73 m^2		
With TKV <1000 ml	9.72 (3.92–15.4)	12.2 (5.75–19.0)
With TKV ≥1000 ml	3.11 (1.90–7.54)	4.00 (1.41–7.94)
eGFR ≥50 ml/min per 1.73 m^2		
With TKV <1000 ml	NA (7.73—NC)	29.0 (19.01—NC)
With TKV ≥1000 ml	8.68 (5.43—NC)	16.0 (16.0—23.0)

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NA, not available; NC, not calculated; Q, quartile; TKV, total kidney volume.

Statistical Analyses

Univariate Cox models (1-by-1) were used in a first step to assess the effect of individual candidate predictors for the probability of a 30% decline of eGFR and ESRD (Supplementary Tables S4 and S5). Because TKV was shown to increase in an exponential manner, the use of ln-transformed TKV values was a natural choice because it was shown to be more prognostic than a raw untransformed TKV.[2,19] In general, the effect of ln-transformed baseline height-adjusted TKV and ln-transformed baseline TKV resulted in the highest ROC values for all endpoints. The effect of baseline eGFR and age were also statistically significant. In univariate analyses, genotype and race were not significant for the probability of a 30% decline of eGFR and ESRD.

In order to tease out confounding effects between baseline TKV and other covariates such as baseline age and baseline eGFR, multivariable Cox analyses were performed for the probability of a 30% decline of eGFR and ESRD. Although ln-transformed baseline height-adjusted TKV and ln-transformed baseline TKV resulted in a similar predictive power (ROC at 1 and 3 years), ln-transformed baseline TKV was used in multivariable Cox models because it was deemed more convenient to use in a clinical setting. Of all covariates, ln-transformed baseline TKV was associated with the lowest P value for all endpoints ($P < 0.001$). For the 30% decline of eGFR endpoint, baseline age ($P < 0.001$) and baseline eGFR ($P < 0.001$) were included in the model during the second and third iterations. Statistically significant interaction terms between TKV and age, as well as eGFR and age were included in all models due to the well-known correlations between these covariates.[4] None of the covariates or interaction terms were removed during the backward elimination testing. At 1 year, ROC area under the curve values for the probability of a 30% decline of eGFR and progression to ESRD were 0.748 and 0.952, respectively. At 3 years, ROC area under the curve values for the probability of a 30% decline of eGFR and progression to ESRD were 0.707 and 0.944, respectively.

The final multivariable Cox models for the probability of a 30% decline of eGFR or progression to ESRD with 95% confidence intervals (CIs) are presented in Table 3. The effect of baseline age, baseline eGFR, and baseline TKV on the hazard ratio of a 30% decline of eGFR in the setting of preserved eGFR (GFR, 50 ml/min per 1.73 m^2) and a TKV 1000 ml shows that age and baseline eGFR have minimal impact whereas TKV has a substantial effect (Figure 4a). Independent of baseline age and baseline eGFR, baseline TKV was also a strong prognostic factor for progression to ESRD (Figure 4b). A dramatic increase in hazard ratio for ESRD with

Table 3. Multivariable Cox models for probabilities of a 30% decline of eGFR or progression to ESRD

Parameters	Coefficient	(SE)	Z score	*P* value
30% decline of eGFR				
Prognostic factors				
Ln baseline TKV (l)	2.755	(0.367)	7.50	<0.001
Baseline age (yr)	0.260	(0.0434)	5.99	<0.001
Baseline eGFR (ml/min per 1.73 m^2)	0.0966	(0.0166)	5.77	<0.001
Interaction terms				
TKV-age	−0.0291	(0.00586)	−4.96	<0.001
eGFR-age	−0.00079	(0.00014)	−5.65	<0.001
ESRD				
Prognostic factors				
Ln baseline TKV (l)	1.502	(0.296)	5.07	<0.001
Baseline age (yr)	0.173	(0.0458)	3.77	<0.001
Baseline eGFR (ml/min per 1.73 m^2)	−0.0275	(0.0106)	−2.58	0.01
Interaction terms				
TKV-age	−0.0180	(0.00553)	−3.25	0.001
eGFR-age	−0.00168	(0.000242)	−6.98	<0.001

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ln, natural log; TKV, total kidney volume.
For a 30% decline of eGFR, exponent of ln baseline TKV, baseline age, and baseline eGFR for a difference of 1 log (i.e., 2.7-fold increase in TKV), 1 year, and 1 ml/min per 1.73 m^2 correspond to 15.7, 1.30, and 1.10, respectively. For ESRD, exponent of ln baseline TKV, baseline age, and baseline eGFR for a difference of 1 log (i.e., 2.7-fold increase in TKV), 1 year, and 1 ml/min per 1.73 m^2 correspond to 4.49, 1.19, and 0.97, respectively.

decreasing age (with TKV and eGFR held constant) is likely to be associated to the fact that patients with the same TKV at younger age have faster growing kidneys. Based on the multivariable Cox models, an interactive research tool was developed (https://pharmacometrics.shinyapps.io/KIreports) to assess the risk of disease progression according to different reference values of baseline age, baseline eGFR, and baseline TKV in ADPKD subjects.[23] For example, adjusted hazard ratios for 30% decline of eGFR in a 40-year-old subject with preserved eGFR (50 ml/min per 1.73 m^2) for a doubling of TKV (600 vs. 1200 ml) was 1.86 (95% CI, 1.65–2.10) and for a tripling of TKV (600 vs. 1800 ml) was 2.68 (95% CI, 2.22–3.24) Adjusted hazard ratios for ESRD for a doubling and tripling of TKV were 1.72 (95% CI, 1.49–1.99) and 2.36 (95% CI, 1.88–2.97), respectively.

In a sensitivity analysis to assess whether the relationship of TKV with outcomes was dependent on the imaging modality, we find TKV as measured by ultrasound is strongly associated with 30% eGFR decline and ESRD and has nearly the same point estimate as in models using TKV measured by CT/MRI (Supplementary Tables S6 and S7). In addition, an exploratory analysis was performed by including in the analysis a population of patients likely to be enrolled in a clinical study (i.e., baseline eGFR ≥ 20 ml/min per 1.73 m^2, age range, >15 to <51 years). Median time to 30% decline of eGFR and ESRD (10.4 years and 19.2 years, respectively) and parameters derived with the multivariable Cox model in the above subpopulation were consistent with those derived with the main analysis (refer to Supplementary Table S8).

DISCUSSION

This study provides clear evidence that TKV is prognostic for a 30% decline in eGFR, a threshold recommended for its utility in predicting ESRD and its sensitivity to early renal function decline, and for actual events of ESRD independent of baseline age, mutation type, and eGFR.[11] Moreover, our results suggest that TKV is a strong prognostic biomarker where large kidneys in young patients with preserved eGFR, which corresponds to the population most likely to be enrolled in clinical trials, are associated to a worse outcome, as also reported by Irazabal *et al.*[4] The present study also demonstrates the capability to predict likelihood of ESRD. The clinical and research implication of this finding is that TKV can be used in combination with age and eGFR as an enrichment biomarker to identify patients most likely to have a

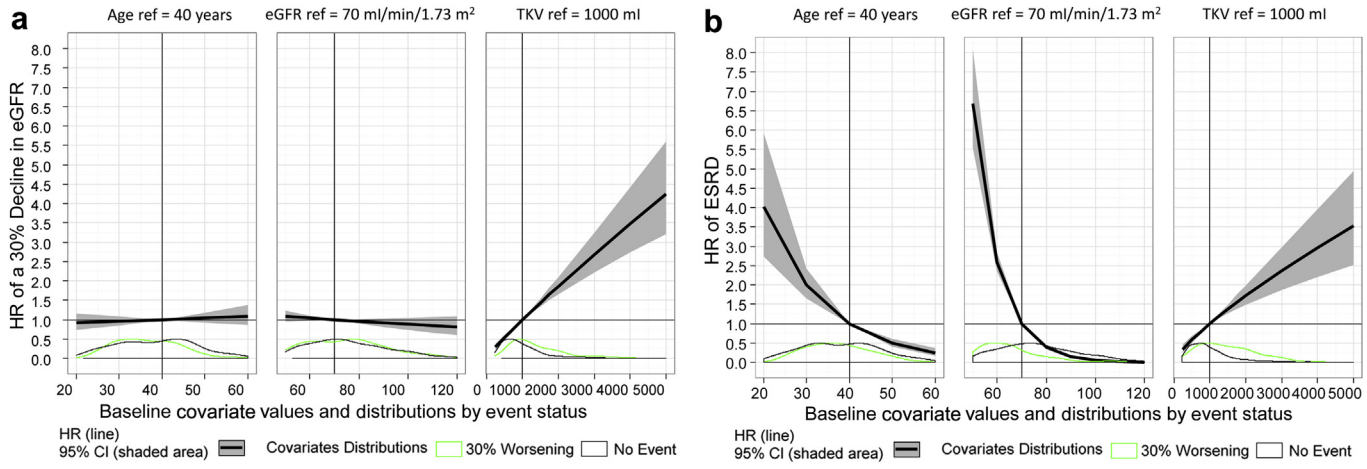

Figure 4. Effect of age, estimated glomerular filtration rate (eGFR), and total kidney volume (TKV) on hazard ratio (HR) of (a) 30% of decline of eGFR and (b) progression to ESRD for a reference autosomal dominant polycystic kidney disease subject (reference: 40 years, eGFR of 70 ml/min per 1.73 m^2 and TKV of 1000 ml, respectively). CI, confidence interval.

decline in kidney function and these would be the participants to target in an interventional trial.

Individuals with the *PKD1* genotype typically exhibit earlier progression to ESRD compared with those with *PKD2*.[24] The CRISP Investigators have documented that the *PKD1* genotype manifests with larger TKV and greater cyst burden at any age;[25] similarly, the HALT Polycystic Kidney Disease study demonstrated an association between *PKD1* and larger TKV at all ages.[26] Based on the current analysis, median time to progression to a 30% decline of eGFR in patients with *PKD1* was shorter than that observed in *PKD2* (35.2 and 42.5 years, respectively). On the other hand, baseline TKV in patients with *PKD1* was higher than those with PKD2 (1052.5 and 759.0 ml, respectively). Likewise, median time to progression to ESRD in patients with *PKD1* was shorter than that observed in *PKD2* (35.1 and 42.6 years, respectively) whereas baseline TKV in patients with *PKD1* was higher than those in patients with *PKD2* (1014.6 and 769.7 ml, respectively). These results support the hypothesis that the higher risk of eGFR decline in *PKD1* is associated with larger TKV, confirming the findings of Irazabal *et al*.[4] Overall, our findings confirm an earlier report from the CRISP Investigators that in multivariable analyses of renal progression that include TKV, genotype loses statistical significance.[18] Thus, TKV remains a readily available prognostic marker, obviating the need for expensive and complex genetic analysis.

Indeed, based on these analyses and those in the accompanying manuscript,[27] TKV was qualified as a prognostic biomarker for the selection of patients in clinical trials for new therapies for the treatment of ADPKD by the FDA in the form of a draft guidance and by the EMA in the form of a qualification opinion.[28,29]

The strengths of the present study include the large dataset representing a diverse group of patients with measurements of TKV receiving medical care or participating in observational cohorts at major centers in the USA, the long duration of follow-up, in some cases individuals' entire lifespan, and with follow-up measures of kidney function or ESRD. Additionally, our findings demonstrate that the predictive power of TKV is not limited to measurements performed with MRI, but also with CT or ultrasound. One limitation of the current work is that the prognostic value of baseline TKV was not evaluated in an external dataset. Another limitation common to registry data is irregular follow-up and missing data, as compared to data from robust observational studies or clinical trials. Despite these limitations, abundant data with long-term follow-up has allowed the creation of predictive models that can prognosticate long-term outcomes in ADPKD.

The imaging classification system for ADPKD developed by Irazabal *et al*.[4] is based on MRI assessment of TKV and provides an assessment of risk of GFR decline by attempting to discriminate between rapid and slow progressors. The novelty of the Polycystic Kidney Disease Outcomes Consortium model is that it can more specifically identify individuals at risk for a 30% decline in GFR and therefore be used for purposes of study design and power calculations. The present model was built using ultrasound, CT, or MRI measurements of TKV and is not dependent on MRI measurements. Furthermore, the Irazabal classification has not been examined or validated by regulatory authorities.

The qualification of TKV as an imaging biomarker for tracking and predicting the natural history of ADPKD represents a significant confirmation of the commitment of health authorities to provide tools to researchers and patient volunteers to more efficiently address the unmet research needs for this debilitating condition. Access to such tools aids clinical trial designers and mitigates risks to patient volunteers, thereby encouraging development of promising new therapies in ADPKD.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Figure S1. Probability of avoiding a 57% decline in estimated glomerular filtration rate (eGFR) as a function of baseline total kidney volume (TKV) and baseline eGFR (panels A and B, respectively).

Table S1. Description of timeframe of enrollment, number of subjects enrolled, and process of each study/registry (Strengthening the Reporting of Observational Studies in Epidemiology [STROBE]).[11]

Table S2. Baseline characteristics of subjects with and without a 30% decline of estimated glomerular filtration rate (eGFR).

Table S3. Baseline characteristics of subjects with and without progression to end-stage renal disease (ESRD).

Table S4. Univariate Cox model—30% decline of estimated glomerular filtration rate (eGFR).

Table S5. Univariate Cox model— end-stage renal disease (ESRD).

Table S6. Multivariable Cox models for probabilities of a 30% decline of estimated glomerular filtration rate (eGFR) and progression to end-stage renal disease (ESRD)—ultrasound dataset.

Table S7. Multivariable Cox models for probabilities of a 30% decline of estimated glomerular filtration rate (eGFR) and progression to end-stage renal disease (ESRD)—magnetic resonance imaging/computed tomography (MRI/CT) dataset.

Table S8. Multivariable Cox models for probabilities of a 30% decline of estimated glomerular filtration rate (eGFR) and progression to end-stage renal disease (ESRD)—clinical trial population (baseline eGFR $\geq$ 20 ml/min per 1.73 m^2, age range $>$15 to $<$51 years).

Supplementary material is linked to the online version of the paper at http://www.kireports.org/.

REFERENCES

1. Grantham JJ, Chapman AB, Torres VE. Volume progression in autosomal dominant polycystic kidney disease: the major factor determining clinical outcomes. *Clin J Am Soc Nephrol*. 2006;1:148–157.
2. Grantham JJ, Cook LT, Torres VE, et al. Determinants of renal volume in autosomal-dominant polycystic kidney disease. *Kidney Int*. 2008;73:108–116.
3. Grantham JJ, Mulamalla S, Swenson-Fields KI. Why kidneys fail in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol*. 2011;7:556–566.
4. Irazabal MV, Rangel LJ, Bergstralh EJ, et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol*. 2015;26:160–172.
5. Torres VE, Harris PC. Strategies targeting cAMP signaling in the treatment of polycystic kidney disease. *J Am Soc Nephrol*. 2014;25:18–32.
6. LaRiviere WB, Irazabal MV, Torres VE. Novel therapeutic approaches to autosomal dominant polycystic kidney disease. *Transl Res*. 2015;165:488–498.
7. Levey AS, Cattran D, Friedman A, et al. Proteinuria as a surrogate outcome in CKD: report of a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis*. 2009;54:205–226.
8. Food and Drug Administration, Center for Drug Evaluation and Research. Meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC). Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm364579.pdf. Accessed December 30, 2016.
9. US Food and Drug Administration. Biomarker Qualification Program. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm. Accessed December 30, 2016.
10. Perrone RD, Neville J, Chapman AB, et al. Therapeutic area data standards for autosomal dominant polycystic kidney disease: a report from the Polycystic Kidney Disease Outcomes Consortium (PKDOC). *Am J Kidney Dis*. 2015;66:583–590.
11. von Elm E, Altman DG, Egger M, et al., for the STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147:573–577.
12. Coresh J, Turin TC, Matsushita K, et al., for the CKD Prognosis Consortium. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA*. 2014;311:2518–2531.
13. Chang WX, Asakawa S, Toyoki D, et al. Predictors and the subsequent risk of end-stage renal disease - usefulness of 30% decline in estimated GFR over 2 years. *PLoS One*. 2015;10:e0132927.
14. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(suppl 1):S1–S266.
15. Miller WG. Estimating glomerular filtration rate. *Clin Chem Lab Med*. 2009;47:1017–1019.
16. Harrington DP, Fleming TR. A class of rank test procedures for censored survival data. *Biometrika*. 1982;69:553–566.
17. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics*. 2000;56:337–344.
18. Chapman AB, Bost JE, Torres VE, et al. Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2012;7:479–486.
19. Grantham JJ, Torres VE, Chapman AB, et al. Volume progression in polycystic kidney disease. *N Engl J Med*. 2006;354:2122–2130.
20. O'Neill WC, Robbin ML, Bae KT, et al. Sonographic assessment of the severity and progression of autosomal dominant polycystic kidney disease: the Consortium of Renal Imaging

Studies in Polycystic Kidney Disease (CRISP). *Am J Kidney Dis*. 2005;46:1058–1064.

21. Caroli A, Perico N, Perna A, et al., for the ALADIN Study Group. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. *Lancet*. 2013;382:1485–1495.
22. Torres VE, Abebe KZ, Chapman AB, et al. Angiotensin blockade in late autosomal dominant polycystic kidney disease. *N Engl J Med*. 2014;371:2267–2276.
23. Interactive Tool for Computation of Hazard Ratio According to eGFR, TKV and Age. Available at: https://pharmacometrics.shinyapps.io/KIreports. Accessed December 30, 2016.
24. Cornec-Le Gall E, Audrézet MP, Rousseau A, et al. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2016;27:942–951.
25. Harris PC, Bae KT, Rossetti S, et al. Cyst number but not the rate of cystic growth is associated with the mutated gene in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2006;17:3013–3019.
26. Heyer CM, Sundsbak JL, Abebe KZ, et al., for the HALT PKD and CRISP Investigators. Predicted mutation strength of nontruncating *PKD1* mutations aids genotype-phenotype correlations in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2016;27:2872–2884.
27. Perrone RD, Mouksassi M-S, Romero K, et al. A drug development tool for trial enrichment in patients with autosomal dominant polycystic kidney disease. *Kidney Int Rep*. 2017;2:451–460.
28. US Food and Drug Administration. Qualification of Biomarker—Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458483.pdf. Accessed December 30, 2016.
29. European Medicines Agency. Qualification opinion. Total Kidney Volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196569.pdf. Accessed December 30, 2016.