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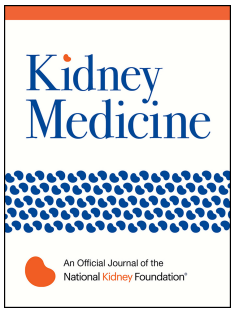

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Quality of Life in Autosomal Dominant Polycystic Kidney Disease Patients Treated With Tolvaptan

Manuel A. Anderegg[1], MD,PhD; Nasser A. Dhayat[1], MD; Grit Sommer[2], PhD; Mariam Semmo[1], MD; Uyen Huynh-Do[1], MD; Bruno Vogt[1], MD; Daniel G. Fuster[1], MD

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ABSTRACT

Rationale and objective: The impact of Tolvaptan on health-related quality-of-life (HRQoL) in autosomal dominant polycystic kidney disease (ADPKD) patients is unknown. To address this knowledge gap, we studied patient-reported health-related quality of life (HRQoL) in patients enrolled in the Bern ADPKD registry.

Study design: Prospective cohort study.

Settings and participants: Inclusion criteria were age ≥18y, clinical diagnosis of ADPKD and informed consent. The main exclusion criterion was need for kidney replacement therapy.

Outcome: HRQoL was assessed with the standardized Kidney Disease Quality of Life Short Form (KDQOL-SF) questionnaire at start of the study (baseline) and after one year (follow-up). The KDQOL-SF has two parts: a generic Short Form-36 instrument with eight subscores and two summary scores, and a kidney disease-specific instrument to assess health concerns. Higher scores indicate better HRQoL. The influence of Tolvaptan treatment on HRQoL and on kidney-specific health concerns was analysed using analysis of covariance (ANCOVA), adjusting for HRQoL and health concerns before start of the study, sex and age.

Results: In 38 of 121 registry patients, Tolvaptan treatment was initiated. Within the first three months, treatment had to be discontinued in six patients (16%) due to aquaretic side effects (N=4, 11%) or elevated liver enzymes (N=2, 5%), and a dose reduction was necessary in eight patients (21%). We included 98 patients (30 with and 68 without Tolvaptan treatment) in the analysis for which baseline and 1-year follow-up data were available. At follow-up, and after adjusting for baseline scores, sex and age, HRQoL and

kidney-specific health concerns were not influenced by Tolvaptan treatment, except for "patient satisfaction" which was increased.

Limitations: Observational study design, monocentric study at tertiary referral hospital, almost exclusively white study population, grant support by Otsuka Pharmaceuticals.

Conclusions: Our results indicate that Tolvaptan does not significantly affect HRQoL in ADPKD patients who tolerate treatment beyond the first three months of therapy.

Index words: ADPKD, Tolvaptan, HRQoL, quality of life.

INTRODUCTION

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease worldwide, occurs in all ethnic groups and accounts for up to 10 % of patients with end-stage renal disease (ESRD) [1]. Mutations in *PKD1* and *PKD2* genes account for the overwhelming majority of ADPKD cases [2].

The disease is characterized by a progressive enlargement of the kidneys due to cyst growth, resulting in chronic flank pain, abdominal fullness and in advanced cases early satiety. Kidney cysts are associated with arterial hypertension and urological complications such as cyst hemorrhage, gross hematuria, recurrent urinary tract infections and nephrolithiasis. ADPKD manifestations are not restricted to the kidneys; well-known extrarenal manifestations include intracranial aneurysms that may cause fatal bleeding due to rupture, liver cysts, colonic diverticular disease, abdominal hernias and cardiac valve abnormalities.

Due to its progressive nature, the associated co-morbidities and that it is hereditary, ADPKD imposes a significant burden on affected patients. The association of patient-reported health-related quality-of-life (HRQoL) with ADPKD disease severity markers has been assessed in several previous studies, but results were inconclusive, at least partially attributed to small sample size, patient selection or use of generic HRQoL instruments only [3-7]. A recent meta-analysis of nine studies employing standardized HRQoL assessments with the generic SF-36 questionnaire encompassing 1623 patients concluded that overall physical and mental component scores were significantly reduced in ADPKD patients compared to the reference population, even after age correction [8]. Interestingly, larger liver volume, but not eGFR or total kidney volume displayed a

significant negative correlation with age-corrected HRQoL in ADPKD patients. In support of these findings, treatment of severe polycystic liver disease by somatostatin analogues but not with placebo improved HRQoL in a pooled analysis of two randomized, placebo-controlled trials [9].

Recently, Tolvaptan, an orally active, non-peptide selective arginine vasopressin V2R antagonist has been approved for the treatment of ADPKD in many countries, including Switzerland. In two randomized, double-blind, controlled phase III trials, TEMPO 3:4 and REPRISE, respectively, Tolvaptan lowered the increase in total kidney volume (TEMPO 3:4 only) and kidney function decline (both studies) compared to placebo [10, 11]. However, a high frequency of aquaresis-related adverse events (thirst, polydipsia, polyuria, nocturia) was noted in these clinical trials. Although regular HRQoL assessment in patients with Tolvaptan treatment was advocated in recent treatment guidelines [12], the impact of the drug on patient's HRQoL has not been studied systematically and thus is largely unknown at the moment.

To address this knowledge gap, we compared baseline (treatment-naïve) and follow-up (with or without Tolvaptan treatment) HRQoL using the KDQOL-SF questionnaire in participants of the Bern ADPKD registry.

METHODS

Study population

The Bern ADPKD registry is a prospective, observational cohort of ADPKD patients at the Department of Nephrology and Hypertension at the Bern University Hospital, Bern, Switzerland. Inclusion criteria are: (1) ADPKD based on the criteria by Ravine et al. [22]; (2) minimum age of 18 years; (3) written informed consent. Need for kidney replacement therapy was an exclusion criterion. The Bern ADPKD registry

adheres to the Declaration of Helsinki and was approved by the ethical committee of the Kanton of Bern (approval # BE 124/15). Between October 2015 and March 2019, 121 patients were included in the Bern ADPKD registry. In 98 of 121 registry participants, baseline and one-year follow-up data were available as of March 2019.

Tolvaptan treatment

Tolvaptan became available for patients in Switzerland on November 1 2016. Treatment is reimbursed by health care insurance companies if the following criteria are met: i) age ≥ 18 years, ii) typical class I ADPKD, iii) CKD stages I – III, iv) total kidney volume ≥ 750 ml and v) evidence of rapid progression. Rapid progression is defined as Mayo class 1C-1E or eGFR decline ≥ 5 ml/min per 1.73 m^2 or growth of kidney volume > 5 %/year or truncating *PKD1* mutation and a PROPKD-Score >6 [23]. The decision on Tolvaptan treatment initiation was left to the responsible investigator, always a board-certified Nephrologist. Treatment was always initiated with the lowest split dose regimen of 45/15 mg and uptitrated in monthly intervals to 60/30 mg and ultimately to 90/30 mg, as tolerated by the patient.

Data collection and measurements

Patients in the registry are seen at baseline and yearly thereafter. At each visit, patients undergo a physical examination including measurement of height and weight, office and 24-hour blood pressure measurements. Office blood pressure measurements were done in supine position after at least 5 minutes of rest using the oscillometric method. At baseline, total kidney volume (TKV) was determined by MRI using the ellipsoid method and patients were subclassified according to height-adjusted TKV (HtTKV) ranges for age into Mayo classes 1A-E [24]. Standardized blood and urine

analysis, including a 24-hour urine collection, are conducted at baseline and then annually. All blood analyses were performed after at least a 6 hour fast in the morning before noon. Urine and blood analyses were performed at the Central Laboratory of the Bern University Hospital, Bern, Switzerland using standard laboratory methods. The creatinine-based CKD-EPI 2009 equation was used to estimate the glomerular filtration rate eGFRcr [25].

Diabetes was defined as reported, treated, or fasting glycemia ≥7 mmol/L. Hypertension was defined as either systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medications.

Quality of life assessment

At baseline and then at each yearly visit, the kidney disease quality of life questionnaire KDQOL-SF 1.2 was used to assess patient-reported health-related quality of life. KDQOL-SF is an instrument developed for individuals with kidney disease by the RAND corporation (https://www.rand.org/health-care/surveys_tools/kdqol.html) and consists of 36 items that provide a generic score and an overall health rating item (SF-36) as well as 43 kidney-disease targeted items [18]. The SF-36 consists of 36 items (questions) that measure eight health-related subscales: physical functioning (PF), role limitations caused by physical health problems (RP), role limitations caused by emotional health problems (RE), social functioning (SF), emotional well-being/mental health (MH), bodily pain (BP), vitality (energy/fatigue; VT) and general health perceptions (GH) and two summary scores: physical component summary (PCS) and mental component summary (MCS). Responses were scored into T-scores, with a mean of 50, SD of 10 and a range of 0–100, based on age-stratified Swiss normative population assessed during 2015-2016

(N=1209). Higher scores reflect better HRQoL [13, 26-28]. The kidney-disease targeted items include symptom/problem, effects of kidney disease, burden of kidney disease, work status, cognitive function, quality of social interaction, sexual function, sleep, social support, patient satisfaction and an overall health item and were scored (0–100) a higher score representing better quality-of-life [14]. One question from the KDQOL-SF (related to dialysis) was omitted because our patients were not on dialysis. The KDQOL-SF has been used previously in health-related quality of life studies in patients with CKD not on dialysis [4, 29, 30].

Statistical analysis

Categorical data are described by number of individuals N (%), continuous variables are described by their mean and standard deviation or by their median and 25th-75th percentile. All statistical tests were two-sided and a *p* value <0.05 was considered statistically significant. The means of the eight subscales of the SF-36 and the PCS and MCS were used to compare ADPKD patients to Swiss norms, between different treatment groups and time points by calculating exact confidence intervals. Questionnaires with >50% missing data in subscales or compound scales were excluded from statistical analysis. Analysis of covariance (ANCOVA) was used to examine the impact of Tolvaptan treatment on HRQOL and on kidney disease-specific health concerns after one year of follow-up[31]. For each scale (of HRQoL and of kidney disease-specific health concerns), we ran an ANCOVA. The models included the score of the scale at follow-up as dependent variables and the score of the same scale at baseline as independent variables,, Tolvaptan treatment status (yes/no), sex and age at follow-up (continuous, in years) regardless of their significance. If meaningful interaction was

present, we included second level interaction terms in the models. All statistical analyses were conducted using Stata, release 15.1 (College Station, TX, USA: StataCorp LLC) 15 and the R software, version 3.2.2 [32]. We used the Stata package coefplot for plotting mean differences in HRQoL and kidney-specific health concerns between patients treated with vs. those not treated with Tolvaptan [33].

RESULTS

Characteristics of the study population

The Bern ADPKD registry is a prospective, observational cohort of ADPKD patients without kidney replacement therapy at the Department of Nephrology and Hypertension at the Bern University Hospital, Bern, Switzerland. Between October 2015 and March 2019, 121 ADPKD patients were included in the Bern ADPKD registry (Fig. 1). In the final analysis, we included 98 registry participants for whom baseline and at least one-year follow-up HRQoL data were available. Baseline characteristics of the overall study population as well as separated in patients with (N = 30) and without (N = 68) future Tolvaptan treatment are shown in Table 1. Patients with future Tolvaptan treatment had a median age of 45.8 years, were more often men and had higher total as well as height-adjusted kidney volumes than patients without future Tolvaptan treatment. Tolvaptan treatment has been initiated in 38 of 121 (31.4 %) registry patients thus far. Tolvaptan was discontinued within the first three months of treatment in four patients due to aquaretic side effects (10.5 %) and in two patients due to elevated liver function tests (5.3 %). In the 32 patients remaining on Tolvaptan treatment, 24 patients (75 %) were on the maximal dose 90/30 mg, in eight patients (25 %), a dose reduction to 60/30 (N = 6) or 45/15 mg (N = 2) was necessary.

HRQoL of Swiss ADPKD patients – comparison to general population and impact of Tolvaptan treatment

General HRQoL was assessed by SF-36 subscales (physical functioning, role-physical, bodily pain, general health, energy/vitality, social functioning, role-emotional, mental health), and two summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS). Raw scores were transformed into T-scores (mean=50, SD=10, range 0-100) stratified by age, using contemporaneous Swiss general population norms [13]. ADPKD patients without future Tolvaptan treatment had lower scores in physical functioning and general health, but scored similar as the general population in all other subscales and summary scales of the SF-36 (Table 2). In contrast, ADPKD patients with future Tolvaptan treatment had a better score in bodily pain (i.e. less bodily pain) and a higher PCS than the general population.

After one year follow-up, patients with Tolvaptan treatment continued to score better in bodily pain and had a higher score in physical functioning than the general population (Table 2). Patients without Tolvaptan treatment continued to score lower in general health than the general population, but scored higher than the general population in bodily pain at one-year follow-up.

Results from analysis of covariance (ANCOVA) showed that Tolvaptan treatment status did not affect HRQoL after one year of follow-up after adjusting for HRQoL at baseline, sex and age (Table 3, Fig. 2). As expected, we found a strong association of HRQoL at baseline on HRQoL at follow-up.

In a next step, we analyzed the kidney disease-specific health concerns, for which no normative data from the general population exist. Kidney disease-specific health

concerns (symptoms/problems, effects of kidney disease, burden of kidney disease, work status, cognitive function, quality of social interaction, sexual function, sleep, social support, patient satisfaction and overall health) were scored (0–100), with a higher score representing better health perception[14]. In the analyses of covariance models, after adjusting for baseline scores of health concern, sex and age, Tolvaptan treatment had no influence on health concerns at follow-up, except for patient satisfaction, which was better in patients treated with Tolvaptan (Table 4, Table 5, Fig. 3). Higher scores of kidney-specific health concerns were significantly associated with higher scores at baseline.

DISCUSSION

Previous HRQoL assessments in ADPKD patients have been mostly cross-sectional [9]. Only for laparoscopic cyst decortication [15] and lanreotide treatment in patients with advanced polycystic liver disease, HRQoL was assessed prospectively [16, 17]. Our study represents the first report of a systematic HRQoL assessment of Tolvaptan treatment on HRQoL in ADPKD patients. For HRQoL assessments in our cohort of 98 ADPKD patients, we used the well-validated KDQOL-SF questionnaire that contains the generic SF-36 and 43 kidney-disease targeted items [18]. While the generic SF-36 part has been used in several previous studies with ADPKD patients [3-8, 15-17, 19], the more extensive and thus more informative kidney-disease item part of the KDQOL-SF questionnaire has only been employed in one previous study [4]. The generic SF-36 part allowed us to compare HRQoL outcomes in AKPKD patients with the Swiss general population [13]. Our results demonstrate that overall self-reported HRQoL in our cohort of Swiss non-dialysis ADPKD patients is similar to the general population, as reported previously in other cohorts [3, 6, 19]. However, HRQoL assessments in ADPKD patients yielded conflicting

results in the past and some studies, including a recent meta-analysis, reported significantly reduced HRQoL in non-dialysis dependent ADPKD patients [4, 8, 16, 17, 20]. These differences may be due to variability in patient demographics, co-morbidities, degree of liver involvement and CKD stage of patients studied. In support of this, our observation that patients with future Tolvaptan treatment had a higher PCS score at baseline compared to the general population may be due to selection bias. Only patients with relatively preserved health without significant comorbidities are candidates for a Tolvaptan prescription. Obviously, up-to-dateness and representativeness of normative data from the general population will also significantly influence results. Normative values of the general population used for our study were derived from a contemporaneous and representative sample of the Swiss population, supporting the validity of our results [13].

The systematic inclusion of all ADPKD patients treated at our site in the ADPKD registry reveals that 11% of patients elected to suspend treatment with Tolvaptan due to aquaretic side effects, similar to the discontinuation rate observed in the TEMPO 3:4 trial [10]. In an additional two patients (5 %), Tolvaptan had to be withdrawn due to elevated liver enzymes. All treatment cessations occurred within the first three months of treatment. Prospective HRQoL assessment in patients continuing Tolvaptan beyond the first three months of treatment indicates that the therapy is well tolerated without significant impact on overall physical or mental health scores, as assessed by the generic SF-36 part of the KDQOL-SF questionnaire. Patient-reported feedback evaluation of kidney-disease specific items revealed increased patient satisfaction at follow-up. The reasons for increased satisfaction in Tolvaptan-treated patients can only be speculated.

Positive selection of patients that tolerated this novel disease-modifying drug in the analysis and close patient-physician relationship due to monthly visits for liver function tests are likely causes. Surprisingly, however, neither the categories work status nor sleep were affected by Tolvaptan treatment.

Our study has a number of limitations. First, because of the limited number of patients on Tolvaptan therapy, we may have missed effects due to the lack of statistical power. Likewise, the number of follow-up questionnaires available from patients who stopped Tolvaptan was too low for a sub-set analysis. Larger studies are needed to definitively establish the impact of Tolvaptan treatment on HRQoL in ADPKD patients. Second, our results apply to a selected group of patients who tolerated long-term treatment of Tolvaptan. Importantly, however, we included all patients with reduced dose Tolvaptan in our analysis who continued treatment beyond the first three months. In all of the eight patients on submaximal Tolvaptan dose, dose reductions were necessary because of aquaretic side effects. Third, selection bias may have caused differences observed in both general and kidney-specific HRQoL scores between patients with and without Tolvaptan treatment. Fourth, we may have missed important aspects of HRQoL in our study population because we did not use an ADPKD-specific HRQoL instrument. The ADPKD impact scale HRQoL instrument was developed only after our study was initiated [21].

In summary, our study reveals that HRQoL in Swiss ADPKD patients is comparable to HRQoL in the general Swiss population. Furthermore, our results indicate that Tolvaptan does not significantly affect HRQoL in ADPKD patients who tolerate treatment beyond the first three months of therapy.

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FIGURE LEGENDS

Figure 1. Overview of patients with and without Tolvaptan treatment in the Bern ADPKD registry. Tolvaptan treatment was started in 38 of 121 ADPKD registry patients (n = 31.4 %), therapy was stopped within the first three months of treatment in 6 patients (n= 15.8 %) due to aquaretic side effects or elevated liver function tests (LFTs). Eight patients (n= 21.1 %) did not tolerate the maximal Tolvaptan dose (90/30 mg) and a dose reduction to 60/30 mg or 45/15 mg was necessary. In 68 patients without Tolvaptan treatment and 30 patients with Tolvaptan treatment, baseline and 1 year follow-up HRQoL data were available for analysis.

Figure 2. Change in HRQoL after one year of Tolvaptan treatment vs. no Tolvaptan treatment. Abbreviations: PF, physical functioning; RP, role limitations caused by physical health problems; RE, role limitations caused by emotional health problems; SF, social functioning; MH, emotional well-being/mental health; BP, bodily pain; VT, vitality (energy/fatigue); GH, general health perceptions; PCS, physical component summary; MCS, mental component summary. Filled diamonds indicate differences in HRQoL T-scores for ADPKD patients treated with Tolvaptan vs. those not treated with Tolvaptan (reference) derived from multivariable linear regression involving HRQoL as dependent and Tolvaptan status, sex and age as independent variables. A positive difference indicate better HRQoL in patients with Tolvaptan vs those without Tolvaptan. Capped spikes indicate 95% confidence intervals.

Figure 3. Change in kidney-specific health concerns after one year of Tolvaptan treatment vs. no Tolvaptan treatment. Abbreviations: symptom**,** symptom/problem; effect, effects of kidney disease; burden, burden of kidney disease; work, work status; cognition, cognitive function; interact, quality of social interaction; sexfunction, sexual function; support; social support; satisfaction, patient satisfaction; health, overall health. Filled diamonds indicate differences in health concern scores for ADPKD patients treated with Tolvaptan vs. those not treated with Tolvaptan (reference) derived from multivariable linear regression involving health concerns as dependent and Tolvaptan status, sex and age as independent variables. A positive difference indicate better scores in health concerns of patients with Tolvaptan vs those without Tolvaptan. Capped spikes indicate 95% confidence intervals.

Table 1 | Characteristics of the study population at baseline visit.

Characteristics	N	All patients	N	No Tolvaptan	N	Tolvaptan	*p*-value
Women	55	56.1%	44	64.7%	11	36.7%	0.02
Age, years	98	45.8;37.6-52.7	68	45.95;35.4-57.6	30	45.8;40.2-49.7	0.94
Body mass index, kg/m^2	97	24.7;22.2-27.5	68	24.6;21.8-27.6	29	24.7;22.3-27.1	0.89
Hypertension	74	76.3%	49	72.1%	25	86.2%	0.22
Antihypertensive medication intake	62	63.9%	41	60.3%	21	72.4%	0.36
ACE inhibitors or sartans	54	55.7%	33	48.5%	21	72.4%	0.05
Calcium channel blockers	21	21.6%	14	20.6%	7	24.1%	0.91
Beta blockers	9	9.3%	6	8.8%	3	10.3%	1
Diuretics	20	20.6%	14	20.6%	6	20.7%	1
Diabetes	2	2.1%	2	2.9%	0	0.0%	0.88
eGFR creatinine Equation CKD-EPI 2009, mL/min per 1.73 m^2 BSA	98	70.9;47.1-93.4	68	78.1;44.5-97.8	30	64.4;49.9-90.7	0.39
eGFR subgroups							
≥90	27	27.6%	19	27.9%	8	26.7%	0.04
60-89	36	36.7%	27	39.7%	9	30.0%	0.003
30-59	24	24.5%	15	22.1%	9	30.0%	0.22
15-30	9	9.2%	5	7.4%	4	13.3%	0.74
≤15	2	2.0%	2	2.9%	0	0.0%	-
Total kidney volume (TKV), mL	84	1220;672-2171	56	871;529-1662	28	1743;1225-2329	<0.001
Height-adjusted TKV (htTKV), mL/m	84	731;396-1255	56	526;340-1123	28	950;735-1439	0.002
ADPKD Mayo classification available	84	85.7%	56	82.4%	28	93.3%	0.22
ADPKD Mayo classification subgroups							
Class 1A	5	6.0%	5	8.9%	0	0.0%	-
Class 1B	27	32.1%	26	46.4%	1	3.6%	<0.001
Class 1C	33	39.3%	19	33.9%	14	50.0%	0.38
Class 1D	13	15.5%	3	5.4%	10	35.7%	0.05
Class 1E	6	7.1%	3	5.4%	3	10.7%	1
Tolvaptan intake	30	30.6%	-	-	-	-	-

Table 1 footnote: Categorical variables are expressed as number of participants N (%), continuous variables are expressed as median and 25^{th}-75^{th} percentile. Abbreviations: BP, blood pressure; ACE inhibitor, angiotensin-converting-enzyme inhibitor; BSA, body surface area; eGFR, estimated glomerular filtration rate.

Table 2: Mean SF-36 T-scores of AKPKD patients with and without Tolvaptan treatment at baseline and follow-up

	Time point	Tolvaptan		No Tolvaptan	
		N	Mean scores (95% CI)[a]	N	Mean scores (95% CI)[a]
Subscales					
Physical functioning	Baseline	30	51.8 (49.8; 53.9)	68	**46.9** (43.9; 49.9)
	Follow-up	23	**52.6** (51.3; 53.9)	45	49.9 (47.7; 52.1)
Role physical	Baseline	29	53.2 (49.0; 57.4)	66	46.4 (42.2; 50.7)
	Follow-up	23	51.7 (47.0; 56.3)	43	50.6 (47.0; 54.2)
Bodily pain	Baseline	30	**54.5** (52.0; 57.1)	68	49.6 (47.2; 52.1)
	Follow-up	22	**54.9** (51.5; 58.2)	45	**53.5** (50.8; 56.2)
General health	Baseline	29	47.2 (43.0; 51.4)	67	**45.0** (42.0; 47.9)
	Follow-up	22	49.8 (44.6; 55.1)	44	**46.7** (43.7; 49.7)
Vitality	Baseline	29	51.6 (48.5; 54.7)	67	49.3 (46.5; 52.1)
	Follow-up	22	49.8 (45.9; 53.8)	44	49.4 (46.0; 52.7)
Social functioning	Baseline	30	51.2 (48.1; 54.2)	68	50.2 (47.8; 52.6)
	Follow-up	23	**53.4** (50.5; 56.4)	45	52.5 (49.9; 55.1)
Role emotional	Baseline	29	50.5 (46.0; 54.9)	67	47.5 (43.3; 51.8)
	Follow-up	23	53.2 (48.6; 57.7)	43	52.5 (48.7; 56.4)
Mental health	Baseline	29	49.1 (45.4; 52.8)	67	49.1 (46.5; 51.8)
	Follow-up	22	51.9 (49.7; 54.1)	43	50.8 (47.6; 53.9)
Summary Scores					
Physical Component Summary	Baseline	28	**52.8** (50.2; 55.3)	65	46.8 (43.7; 50.0)
	Follow-up	21	52.4 (49.4; 55.4)	41	50.4 (47.6; 53.2)
Mental Component Summary	Baseline	28	49.6 (46.1; 53.0)	65	49.6 (46.9; 52.3)
	Follow-up	21	51.3 (48.2; 54.3)	41	51.4 (48.1; 54.6)

Results from multivariable linear regression. Abbreviations: CI, confidence interval; N, number;

[a]Mean T-scores with 95 % CIs are standardized to age-stratified Swiss general population norms with a mean of 50 and a standard deviation of 10. Higher scores indicate better HRQoL. Bold numbers indicate deviation from general population with a probability of >95%.

Table 3. Influence of baseline HRQoL, Tolvaptan treatment, sex and age on HRQoL during follow up					
	Covariable	**N**	**SS**	**p-value[a]**	**Coef[b] (95% CI)**
Physical functioning	Baseline Score	66	1051	<0.001	0.6 (0.4; 0.8)
	Tolvaptan[c]		3	0.71	0.5 (-2.2; 3.2)
	Sex[d]		0.1	0.95	0.1 (-2.4; 2.5)
	Age at survey[e]		58	0.12	0.1 (-0.02; 0.2)
Role physical	Baseline Score	62	1736	<0.001	0.4 (0.2; 0.6)
	Tolvaptan[c]		31	0.59	-1.5 (-7.3; 4.2)
	Sex[d]		0.001	1.00	0.01 (-5.4; 5.4)
	Age at survey[e]		51	0.49	-0.1 (-0.3; 0.2)
Bodily pain	Baseline Score	65	1940	<0.001	0.8 (0.5; 1.1)
	Tolvaptan[c]		7	0.69	-0.7 (-4.3; 2.9)
	Sex[d]		123	0.10	21.5 (-3.9; 46.8)
	Age at survey[e]		9	0.55	0.1 (-0.2; 0.3)
	Baseline Score*Sex[d]		116	0.11	-0.3 (-0.7; 0.1)
	Sex[e]*Age at survey[e]		9	0.65	-0.1 (-0.4; 0.2)
General health	Baseline Score	63	3411	<0.001	0.7 (0.5; 0.9)
	Tolvaptan[d]		3	0.82	0.5 (-3.7; 4.7)
	Sex[d]		14	0.62	-1.0 (-5.1; 3.1)
	Age at survey[e]		148	0.11	0.1 (-0.03; 0.3)
Vitality	Baseline Score	62	2211	<0.001	0.6 (0.4; 0.8)
	Tolvaptan[c]		8	0.74	-0.8 (-5.4; 3.9)
	Sex[d]		1	0.90	-0.3 (-4.7; 4.1)
	Age at survey[e]		4	0.80	-0.02 (-0.2; 0.2)
Social functioning	Baseline Score	66	650	0.001	0.4 (0.2; 0.6)
	Tolvaptan[c]		2	0.85	-0.4 (-4.4; 3.7)
	Sex[d]		152	0.11	-3.1 (-7.0; 0.7)
	Age at survey[e]		17	0.59	0.05 (-0.1; 0.2)
Role emotional	Baseline Score	62	711	0.02	0.3 (0.1; 0.5)
	Tolvaptan[c]		25	0.65	1.4 (-4.6; 7.4)
	Sex[d]		50	0.52	-1.9 (-7.6; 3.9)
	Age at survey[e]		4	0.85	0.02 (-0.2; 0.3)
Mental health	Baseline Score	61	1244	<0.001	0.5 (0.3; 0.7)
	Tolvaptan[c]		43	0.40	1.8 (-2.5; 6.1)
	Sex[d]		1	0.90	0.3 (-3.9; 4.4)
	Age at survey[e]		16	0.61	0.05 (-0.1; 0.2)
Summary Scores					
Physical Component Summary	Baseline Score	58	1379	<0.001	0.5 (0.3; 0.7)
	Tolvaptan[c]		4	0.76	-0.6 (-4.6; 3.4)
	Sex[d]		66	0.24	2.2 (-1.5; 5.8)
	Age at survey[e]		18	0.53	0.05 (-0.1; 0.2)
Mental Component Summary	Baseline Score	58	1116	<0.001	0.5 (0.2; 0.7)
	Tolvaptan[c]		3	0.84	0.5 (-4.1; 5.1)
	Sex[d]		46	0.41	-1.8 (-6.3; 2.6)
	Age at survey[e]		34	0.48	0.07 (-0.1; 0.3)

Results from the analysis of covariance models. Abbreviations: CI, confidence interval; Coef, coefficient; N, number; SS, sum of squares

[a]p-value derived from Wald tests, testing for the null hypothesis that the coefficients of respective covariables are equal to zero.

[b]Coefficient derived from linear regression models involving follow-up score as independent and covariables as dependent variables. In all regression models, we a priori included baseline score, tolvaptan treatment, sex, age at survey and added interaction terms where appropriate.

[c]Reference: No Tolvaptan treatment.

[d]Reference: Male sex.

[e]Age at survey in years (continuous variable).

Table 4: Mean scores of kidney-specific health concerns of AKPKD patients with and without Tolvaptan treatment at baseline and follow-up

	Time point	Tolvaptan		No Tolvaptan	
		N	Mean scores (95% CI)	N	Mean scores (95% CI)
Symptom/ Problem	Baseline	29	89.5 (86.2; 92.8)	67	83.7 (80.5; 86.9)
	Follow-up	23	86.3 (81.8; 90.7)	47	83.7 (79.9; 87.5)
Effects of kidney disease	Baseline	30	95.1 (92.8; 97.4)	68	90.6 (88.0; 93.3)
	Follow-up	23	92.6 (89.4; 95.9)	45	92.9 (89.0; 96.7)
Burden of kidney disease	Baseline	29	86.9 (81.7; 92.0)	66	80.2 (74.7; 85.7)
	Follow-up	23	81.5 (75.7; 87.4)	47	83.9 (77.8; 90.0)
Work status	Baseline	29	94.8 (87.0; 102.6)	65	86.9 (79.6; 94.3)
	Follow-up	23	100.0 (100.0; 100.0)	46	87.0 (78.4; 95.5)
Cognitive function	Baseline	30	88.2 (83.5; 93.0)	68	82.8 (78.8; 86.8)
	Follow-up	23	88.7 (84.9; 92.5)	46	85.1 (81.0; 89.1)
Quality of social interaction	Baseline	30	82.0 (76.9; 87.1)	68	82.6 (79.4; 85.9)
	Follow-up	23	81.6 (76.5; 86.7)	47	81.7 (77.6; 85.8)
Sexual function	Baseline	29	89.2 (81.0; 97.4)	63	84.1 (77.7; 90.6)
	Follow-up	22	88.6 (78.2; 99.0)	46	85.9 (78.4; 93.4)
Sleep	Baseline	30	68.2 (62.2; 74.2)	68	70.1 (65.8; 74.4)
	Follow-up	23	66.8 (60.1; 73.6)	47	70.9 (64.5; 77.3)
Social support	Baseline	30	76.1 (67.4; 84.9)	68	69.9 (62.8; 76.9)
	Follow-up	23	81.9 (75.4; 88.4)	47	75.9 (67.8; 84.0)
Patient satisfaction	Baseline	24	68.8 (56.8; 80.7)	55	70.9 (65.5; 76.3)
	Follow-up	21	79.4 (72.6; 86.1)	45	71.5 (66.4; 76.6)
Overall health	Baseline	29	83.1 (79.6; 86.6)	65	77.2 (73.2; 81.3)
	Follow-up	23	82.2 (77.7; 86.7)	47	78.3 (74.1; 82.5)

Results from multivariable linear regression. Abbreviations: CI, confidence interval;

Table 5. Influence of baseline health concern, Tolvaptan treatment, sex and age on health concern during follow up

	Covariable	N	SS	p-value[a]	Coef[b] (95% CI)
Symptom/ Problem	Baseline Score	64	4800	<0.001	0.8 (0.6; 0.9)
	Tolvaptan[c]		217	0.06	-4.1 (-8.4; 0.2)
	Sex[d]		287	0.03	-4.4 (-8.4; -0.4)
	Age at survey[e]		7	0.73	-0.03 (-0.2; 0.1)
Effects of kidney disease	Baseline Score	66	763	0.01	0.4 (0.1; 0.7)
	Tolvaptan[c]		4	0.85	-2.9 (-32.8; 27.0)
	Sex[d]		15	0.72	-1.0 (-6.4; 4.4)
	Age at survey[e]		208	0.07	-0.2 (-0.5; 0.02)
	Tolvaptan[c]#Age at survey[e]		0.4	0.95	0.02 (-0.6; 0.7)
Burden of kidney disease	Baseline Score	62	1725	<0.001	0.6 (0.3; 0.8)
	Tolvaptan[c]		302	0.16	47.4 (-20.0; 114.9)
	Sex[d]		22	0.70	-1.3 (-7.8; 5.3)
	Age at survey[e]		408	0.24	0.2 (-0.1; 0.5)
	Tolvaptan[c]#Baseline Score		19	0.73	-0.1 (-0.7; 0.5)
	Tolvaptan[c]#Age at survey[e]		1008	0.01	-1.0 (-1.8; -0.2)
Work status	Baseline Score	59	2591	<0.001	0.5 (0.2; 0.7)
	Tolvaptan[c]		177	0.28	3.7 (-3.1; 10.5)
	Sex[d]		231	0.22	-4.1 (-10.6; 2.5)
	Age at survey[e]		30	0.66	0.1 (-0.2; 0.4)
Cognitive function	Baseline Score	65	5428	<0.001	0.6 (0.5; 0.8)
	Tolvaptan[c]		30	0.47	-1.5 (-5.6; 2.7)
	Sex[d]		80	0.25	-2.3 (-6.2; 1.6)
	Age at survey[e]		6	0.76	-0.03 (-0.2; 0.1)
Quality of social interaction	Baseline Score	66	3827	0.009	0.6 (0.2; 1.1)
	Tolvaptan[c]		10	0.70	10.2 (-42.3; 62.7)
	Sex[d]		3	0.91	-2.4 (-45.2; 40.4)
	Age at survey[e]		5	0.22	0.2 (-0.1; 0.6)
	Tolvaptan[c]#Baseline Score		0.01	0.99	0.002 (-0.5; 0.5)
	Tolvaptan[c]#Sex[d]		16	0.68	-2.5 (-14.4; 9.4)
	Tolvaptan[c]#Age at survey[e]		47	0.48	-0.2 (-0.9; 0.4)
	Sex[d]#Baseline Score		46	0.48	0.2 (-0.3; 0.7)
	Sex[d]#Age at survey[e]		173	0.17	-0.3 (-0.7; 0.1)
Sexual function	Baseline Score	60	18117	<0.001	0.8 (0.7; 1.0)
	Tolvaptan[c]		135	0.33	-3.3 (-10.0; 3.4)
	Sex[d]		71	0.48	-2.3 (-8.7; 4.1)
	Age at survey[e]		124	0.35	-0.1 (-0.4; 0.1)
Sleep	Baseline Score	66	9637	<0.001	0.8 (0.5; 1.0)
	Tolvaptan[c]		571	0.11	-6.4 (-14.3; 1.6)
	Sex[d]		385	0.19	-5.0 (-12.6; 2.6)
	Age at survey[e]		36	0.69	-0.1 (-0.4; 0.3)
Social support	Baseline Score	56	1524	0.02	0.3 (0.04; 0.5)
	Tolvaptan[c]		378	0.24	5.5 (-3.9; 14.9)
	Sex[d]		1856	0.01	12.0 (2.8; 21.2)
	Age at survey[e]		528	0.17	-0.3 (-0.7; 0.1)
Patient satisfaction	Baseline Score	52	6232	<0.001	0.6 (0.4; 0.8)
	Tolvaptan[c]		777	0.03	8.6 (0.7; 16.5)
	Sex[d]		217	0.25	4.2 (-3.1; 11.6)
	Age at survey[e]		944	0.02	-0.3 (-0.6; -0.1)
Overall health	Baseline Score	63	3863	<0.001	0.6 (0.4; 0.8)
	Tolvaptan[c]		3	0.86	-0.5 (-5.8; 4.9)
	Sex[d]		128	0.24	3.0 (-2.0; 8.0)
	Age at survey[e]		28	0.57	-0.1 (-0.3; 0.2)

Results from multivariable linear regression. Abbreviations: CI, confidence interval; Coef, coefficient; N, number; SS, sum of squares.

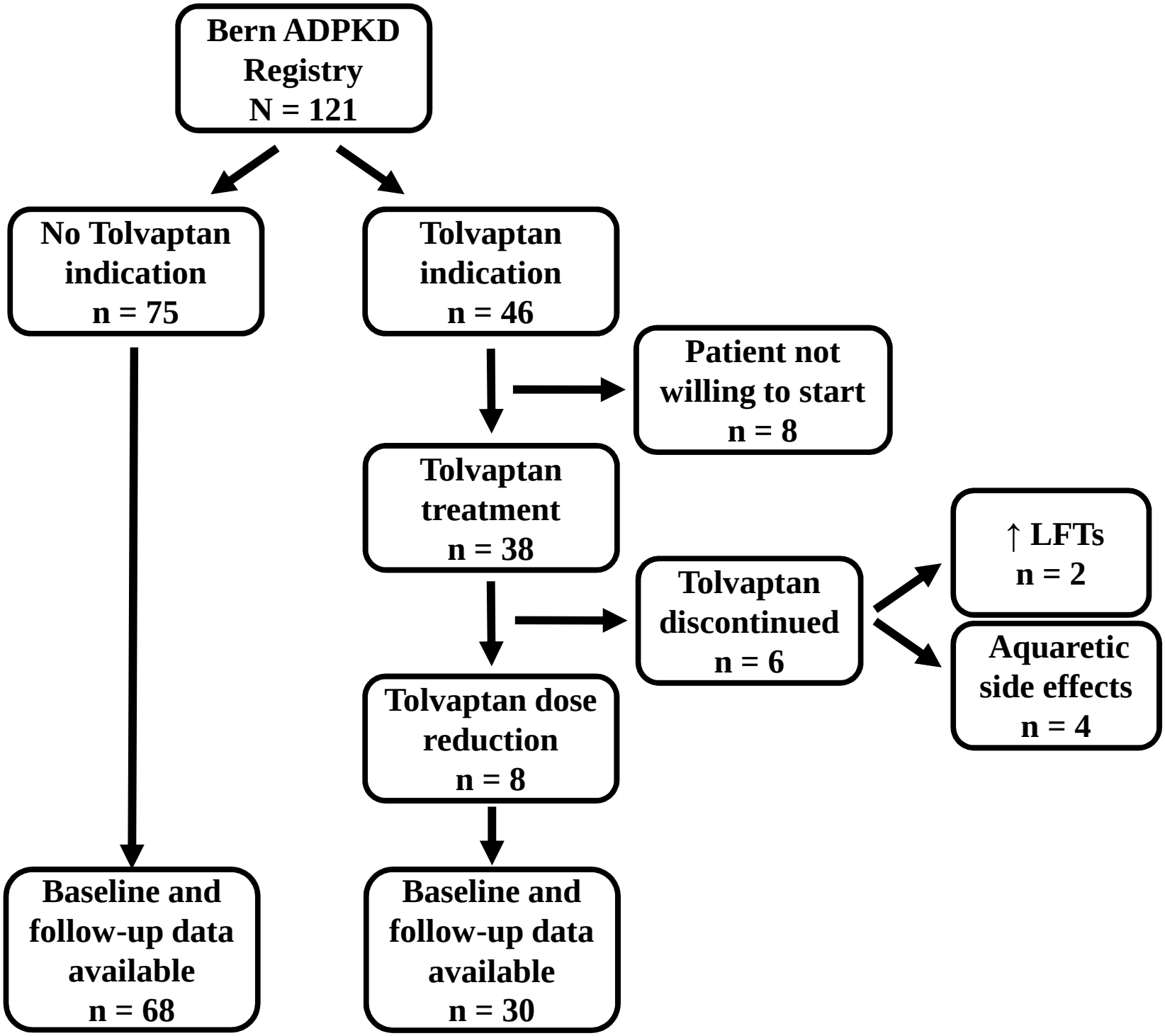
[a]p-value derived from Wald tests, testing for the null hypothesis that the coefficients of respective covariables are equal to zero.

[b]Coefficient derived from linear regression models involving follow-up score as independent and covariables as dependent variables. In all regression models, we a priori included baseline score, tolvaptan treatment, sex, age at survey and added interaction terms where appropriate.

[c]Reference: No Tolvaptan treatment.

[d]Reference: Male sex.

[e]Age at survey in years (continuous variable).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Tolvaptan indication n = 46
Patient not willing to start n = 8
Tolvaptan treatment n = 38
Tolvaptan discontinued n = 6
↑ LFTs n = 2
Aquaretic side effects n = 4
Tolvaptan dose reduction n = 8
Baseline and follow-up data available n = 68
Baseline and follow-up data available n = 30