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Albuminuria and tolvaptan in autosomal-dominant polycystic kidney disease: results of the TEMPO 3:4 Trial

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ABSTRACT

Background. The TEMPO 3:4 Trial results suggested that tolvaptan had no effect compared with placebo on albuminuria in autosomal-dominant polycystic kidney disease (ADPKD) patients. However, the use of categorical 'albuminuria events' may have resulted in a loss of sensitivity to detect changes. The aim of this study is to investigate the effects of tolvaptan on albuminuria as a continuous variable.

Methods. *Post hoc* analysis of a 3-year prospective, blinded randomized controlled trial, including 1375 ADPKD patients. Albuminuria was measured in a spot morning urine sample prior to tolvaptan dosing and expressed as albumin-to-creatinine ratio (ACR).

Results. Baseline median (interquartile range) ACR was 3.2 (1.7–7.1) mg/mmol. Of note, 47.9% of ADPKD patients had normal, 48.7% moderately increased and 3.4% severely increased ACR. Subjects with higher baseline ACR had higher blood pressure and total kidney volume (TKV) and lower estimated glomerular filtration rate (eGFR). During follow-up, higher baseline ACR was associated with more rapid eGFR loss ($P < 0.0001$ for trend), but not with rate of growth in TKV. During the 3-year trial, ACR rose in placebo- and decreased in tolvaptan-treated patients (+0.23 versus −0.40 mg/mmol). The difference ACR increased over time, reaching a maximum of 24% at Month 36 ($P < 0.001$). At that time only a minor difference in blood pressure was observed (mean arterial pressure −1.9 mmHg for tolvaptan). The decrease in ACR was similar in all subgroups investigated, and remained after withdrawal of study drug. The beneficial effect of tolvaptan on TKV growth and eGFR loss was stronger in patients with higher baseline ACR.

Conclusions. In ADPKD, higher baseline albuminuria was associated with more eGFR loss. Tolvaptan decreased albuminuria compared with placebo, independent of blood pressure. Treatment efficacy of tolvaptan on changes in TKV and eGFR was more readily detected in patients with higher albuminuria.

Keywords: ADPKD, albuminuria, chronic renal failure, eGFR, vasopressin

INTRODUCTION

In subjects with chronic kidney disease (CKD) higher [1] albuminuria has consistently been shown to be associated with worse kidney outcomes, e.g. with an increased risk for estimated glomerular filtration rate (eGFR) loss [2, 3]. Furthermore, it has been observed in CKD patients that treatments that prevent kidney function decline [such as low protein diet, strict blood pressure control and renin–angiotensin–aldosterone system inhibition (RAASi)] in general also lower albuminuria [4–6], and that in subjects with higher baseline albuminuria these renoprotective treatments are more effective [1, 7–11].

The aforementioned studies have in general been performed in patients with CKD due to various etiologies. In subjects with autosomal-dominant polycystic kidney disease (ADPKD), most of the information on the association of albuminuria with disease outcomes has been derived from cross-sectional studies [12–16]. Only limited prospective data are available on the prognostic value of albuminuria in this patient group [17, 18]. With respect to treatment, the initial TEMPO 3:4 Trial publication showed renoprotective effects of an intervention in ADPKD [19]. During 3 years of follow-up, the vasopressin V2 receptor antagonist tolvaptan decreased the rate of growth in total kidney volume (TKV) and the rate of eGFR loss. This publication also suggested that use of tolvaptan had no effect compared with placebo on albuminuria [19]. However, albuminuria was classified categorically as 'albuminuria events' instead of on a continuous scale, which may have resulted in a loss of sensitivity to detect treatment-induced changes.

Given these considerations the present investigation was designed to determine the associations between baseline albuminuria and ADPKD patient outcomes, the effect of tolvaptan on albuminuria expressed as a continuous variable and whether baseline albuminuria is associated with tolvaptan treatment efficacy.

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MATERIALS AND METHODS

Patients and study design

The present study is performed as a *post hoc* exploratory analysis of the TEMPO 3:4 Trial, a prospective, blinded, randomized controlled trial in patients with diagnosed ADPKD. Patients were enrolled at 129 sites worldwide between January 2007 and January 2009. Inclusion criteria were age between 18 and 50 years, TKV measured by magnetic resonance imaging (MRI) ≥750 mL and creatinine clearance estimated (eCrCl) by the Cockcroft–Gault formula ≥60 mL/min. Exclusion criteria were, among others, concomitant illnesses likely to confound endpoint assessments, such as known diabetes mellitus. Patients were randomized to tolvaptan or placebo (2:1) with stratification by hypertension status, eCrCl, TKV and geographic area. Tolvaptan dosing was started at 45 mg am/15 mg pm (daily split-dose) and increased weekly to 60/30 and 90/30 mg if tolerated. Patients remained on the highest tolerated dose for 36 months. Details of the study protocol [20] and the primary study results [19] have been published previously. For the present analyses, only subjects who had baseline information on albuminuria available were included ($n = 1375$ out of the original 1445 subjects). The Institutional Review Board or Ethics Committee at each site approved the protocol. Written informed consent was obtained for all participants.

Data collection, measurements and definitions

Evaluations were performed at baseline, randomization, Week 3 during the titration phase, every 4 months during treatment, and twice for 2–6 weeks after completion of treatment at 36 months. These evaluations included interviews, examinations, vital signs and blood, and single trough, mid-stream, spot morning urine samples. Standardized kidney MRIs were obtained at baseline and at Months 12, 24 and 36 (±2 weeks) or at early withdrawal (±2 weeks).

Information on drug use was obtained by patient interview. Blood pressure was measured seated, after at least 5 min resting, on the arm with highest diastolic pressure. Cholesterol, glucose and creatinine were determined centrally with a Roche Modular analyzer. For creatinine an IDMS-traceable enzymatic assay was used [intra- and interassay coefficient of variation (CV) 0.6 and 1.35%, respectively]. Serum creatinine was reported to two decimal points and used to estimate GFR (applying the CKD-EPI equation [21]). TKV was assessed as described in the original protocol [20]. Urinary albumin (mg/L) was determined by nephelometry (BNII, Siemens; intra and interassay CV 4.3 and 4.4%, respectively). Albuminuria was expressed as albumin-to-creatinine ratio (ACR, mg/mmol).

Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or the use of blood pressure lowering medication. Hypercholesterolemia was defined as a serum cholesterol ≥6.0 mmol/L or the use of cholesterol lowering medication, and diabetes mellitus as a fasting blood glucose ≥7.0 mmol/L, a non-fasting glucose ≥11.1 mmol/L or the use of blood glucose lowering medication.

Statistical analyses

Normally distributed variables are expressed as mean ± standard deviation (SD), whereas non-normally distributed variables are given as median with interquartile range (IQR), unless indicated otherwise. Baseline characteristics of the study population are given stratified for ACR, with thresholds 1.5, 3.0 and 15.0 mg/mmol to allow sufficient numbers of patients per subgroup for analyses. Differences between groups were tested with Fisher's exact test for categorical variables and a Mann–Whitney–Wilcoxon test for continuous variables.

The prognostic value of ACR was tested in placebo-treated patients, first, by assessing the associations of the four categories of baseline ACR with annual change in eGFR as well as annual change in TKV during follow-up using linear mixed models (crude analysis). Annual change in TKV was calculated as the slope of the regression over TKVs (on a log scale) obtained at baseline, Months 12, 24 and 36, and annual change in eGFR as the slope of regression over all eGFRs obtained during the treatment period. Second, multivariate regression was used to determine if the associations of ACR with these outcomes was independent of patient characteristics. Third, for change in TKV this multivariate model was additionally adjusted for baseline eGFR, and for change in eGFR additionally adjusted for baseline TKV. In these multivariate analyses ACR and TKV were logarithmically transformed to meet the assumptions for multivariate analyses.

Treatment group comparisons to assess the effect of tolvaptan on ACR during follow-up were determined at each time point ACR was collected using observed case analysis on log-transformed data (mixed model of repeated measurement analysis). Relevant subgroup analyses were performed to test whether the effect of tolvaptan on ACR at Month 36 was dependent on patient baseline characteristics. Possible interaction by these characteristics was tested by mixed models with factors of treatment, subgroup, and treatment and

subgroup interaction taken into account. A sensitivity analysis of tolvaptan treatment effect was performed that included only those patients that had ACR data available at Month 36.

In tolvaptan-treated patients the association of categorical baseline ACR data with change in TKV as well as eGFR during follow-up was tested by linear mixed models. In the four ACR subgroups also tolvaptan treatment induced effects on annual change in TKV as well as eGFR were calculated. Formal interaction between baseline ACR and tolvaptan treatment effect was tested by mixed models with annual changes in TKV and eGFR expressed on a continuous scale.

All analyses were performed with the statistical software package SAS 9.3, and a two-sided $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Study participants

The study population consisted of 1375 ADPKD patients, with a median ACR of 3.2 (IQR 1.7–7.1) mg/mmol. The baseline characteristics of these patients are listed in Table 1 stratified for ACR. Subjects with higher ACR had higher blood pressure and tended to have higher blood glucose. Other characteristics that are traditionally linked to higher albuminuria were similar or even lower in ADPKD patients with increased ACR when compared with those with lower ACR, i.e. they had similar age, were less likely to be male, and had a lower body mass index (BMI). When using the Kidney Disease: Improving Global Outcomes (KDIGO) thresholds to categorize ACR 47.9% of these patients had normal to mildly increased albuminuria (<3 mg/mmol), 48.7% moderately increased (3 to 29.9 mg/mmol) and 3.4% severely increased albuminuria (≥30 mg/mmol).

ACR was 3.4 (IQR 1.8–6.8) mg/mmol in the 459 patients randomized to placebo and 3.1 (IQR 1.7–7.1) mg/mmol in the 916 subjects randomized to tolvaptan ($P = 0.50$). Supplementary data, Tables S1 and S2 provide baseline characteristics for placebo- and tolvaptan-treated patients separately. No essential differences were observed in baseline characteristics between placebo and tolvaptan randomized patients, and in both groups ACR stratified baseline characteristics showed similar trends.

Albuminuria versus ADPKD outcome

At baseline patients with increased ACR had a significantly higher TKV and lower eGFR when compared with patients with lower ACR (Table 1). In placebo-treated patients the annual increase in TKV during follow-up was 5.6 ± 5.3%, and the annual decline in eGFR −3.57 ± 4.50 mL/min/1.73 m^2. In these placebo-treated patients a significant association was found for baseline ACR with decline in eGFR (Figure 1, left panel, and Supplementary data, Table S3). This association was independent of gender, age, race, BMI, systolic blood pressure, cholesterol and glucose ($P = 0.05$), but lost significance when additionally adjusted for baseline TKV ($P = 0.32$). In contrast, no association was found between baseline ACR with annual change in TKV during follow-up, neither crude (Figure 2, left panel, and Supplementary data, Table S3) nor after adjustment for covariates.

Albuminuria during tolvaptan treatment

During follow-up ACR rose in placebo-treated patients (+0.23 mg/mmol at Month 36), whereas it decreased in tolvaptan-treated patients (−0.40 mg/mmol at Month 36) (Figure 3). Consequently, tolvaptan induced a decrease in

Table 1. Baseline characteristics of TEMPO 3:4 Trial participants according to baseline ACR

	ACR (mg/mmol)				P for trend
	<1.5	1.5–2.99	3.0–14.99	≥15.0	
N	284	375	576	140	NA
ACR (mg/mmol)	1.0 (0.5)	2.1 (0.8)	5.6 (4.4)	25.4 (18.1)	<0.0001
Male (%)	67.3	48.8	46.7	52.1	<0.0001
Caucasian (%)	89.8	84.5	83.2	75.7	0.002
Age (years)	39.0 ± 7.1	38.6 ± 7.3	38.3 ± 7.1	38.0 ± 6.8	0.39
BMI (kg/m^2)	27.6 ± 5.4	26.1 ± 4.8	25.3 ± 4.8	26.4 ± 4.9	<0.0001
SBP (mmHg)	126.0 ± 13.7	128.8 ± 13.2	128.8 ± 13.1	133.6 ± 14.7	<0.0001
DBP (mmHg)	81.2 ± 9.8	82.2 ± 9.4	82.8 ± 9.4	85.0 ± 11.6	0.008
Use of BLD (%)	74.7	70.1	71.9	72.1	0.65
Use of RAASi (%)	74.7	70.1	71.9	72.1	0.65
Hypertension (%)	81.7	81.3	82.5	88.6	0.24
Cholesterol	5.0 ± 0.9	5.0 ± 0.9	5.0 ± 0.9	5.2 ± 1.0	0.06
Use of LLD (%)	14.8	9.9	11.5	16.4	0.10
Hypercholesterolemia (%)	28.2	19.7	24.0	32.1	0.01
Glucose (mmol/L)	5.2 ± 0.7	5.2 ± 0.7	5.1 ± 0.9	5.4 ± 1.1	0.004
Use of GLD (%)	0	0	0	0	NA
Diabetes mellitus (%)	0	0	0.2	0	NA
Uosmol (mosmol/kg)	562 ± 196	523 ± 177	480 ± 163	473 ± 165	<0.0001
eGFR (mL/min/1.73 m^2)	84.1 ± 20.6	84.3 ± 20.3	80.6 ± 22.3	73.6 ± 23.0	<0.0001
TKV (mL)	1266 (703)	1366 (879)	1602 (946)	1804 (1208)	<0.0001

Data are given as mean ± standard deviation or as median (interquartile range) unless otherwise stated.
N, number; SBP, systolic blood pressure; DBP, diastolic blood pressure; BLD, blood pressure lowering drugs; LLD, lipid lowering drugs; GLD, glucose lowering drugs; Uosmol, urine osmolality; NA, not applicable.

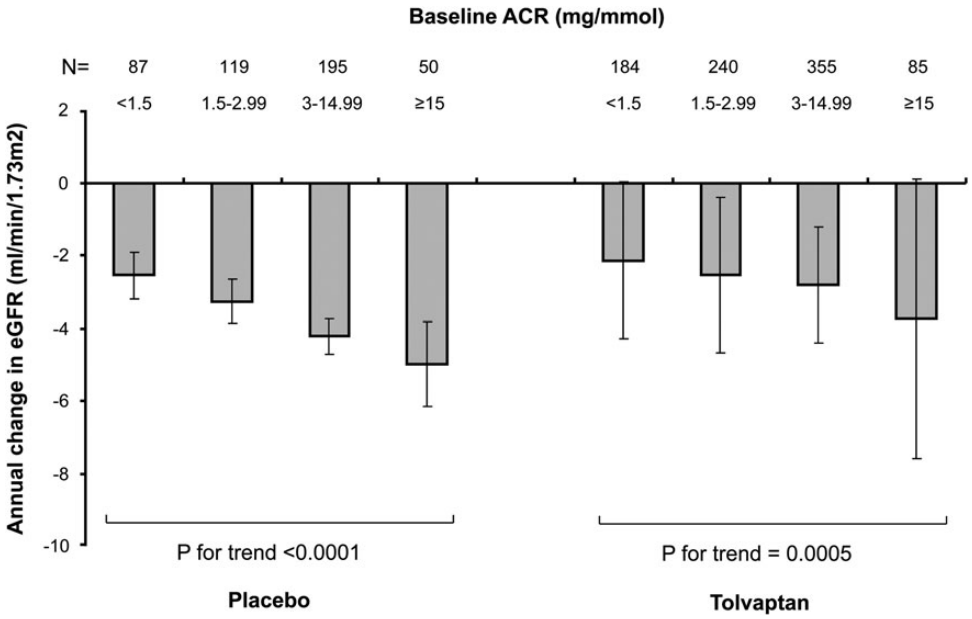


FIGURE 1: Annual change (mean and 95% CI) in eGFR according to randomization group and baseline ACR.

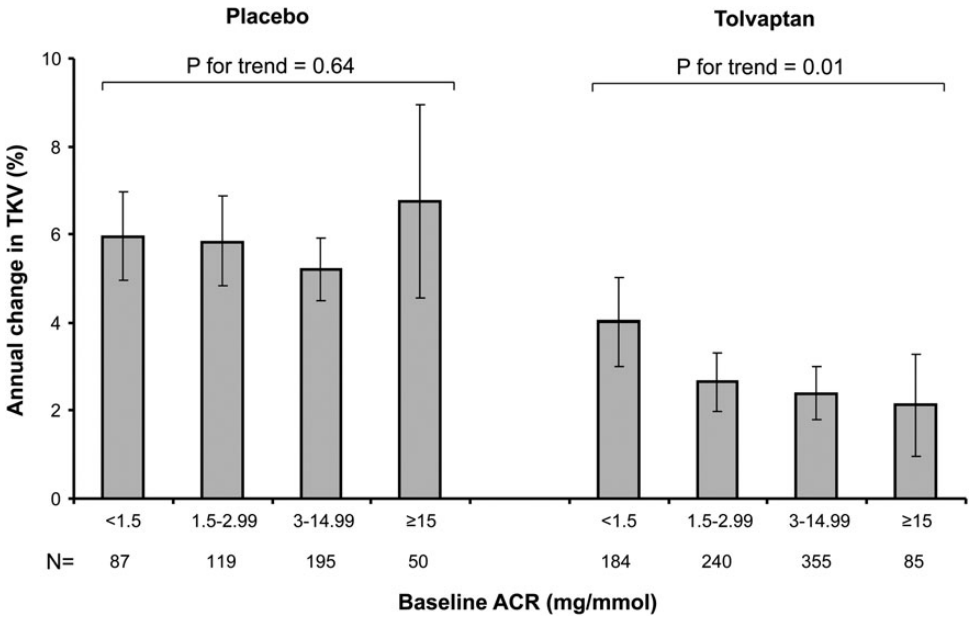
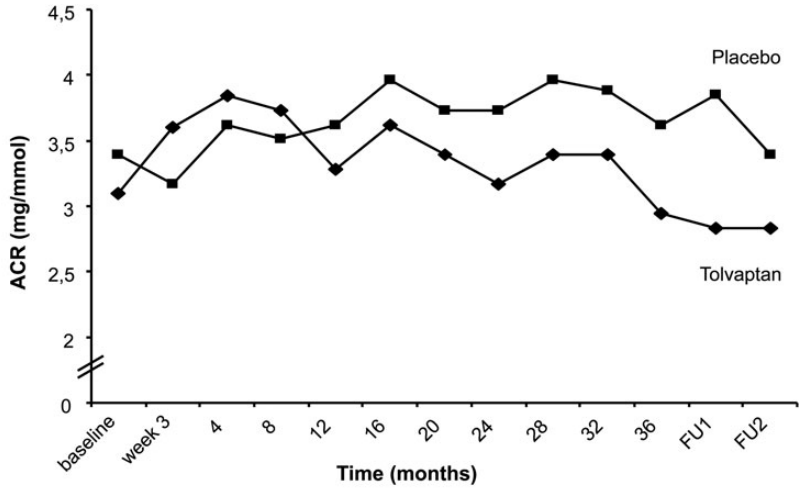


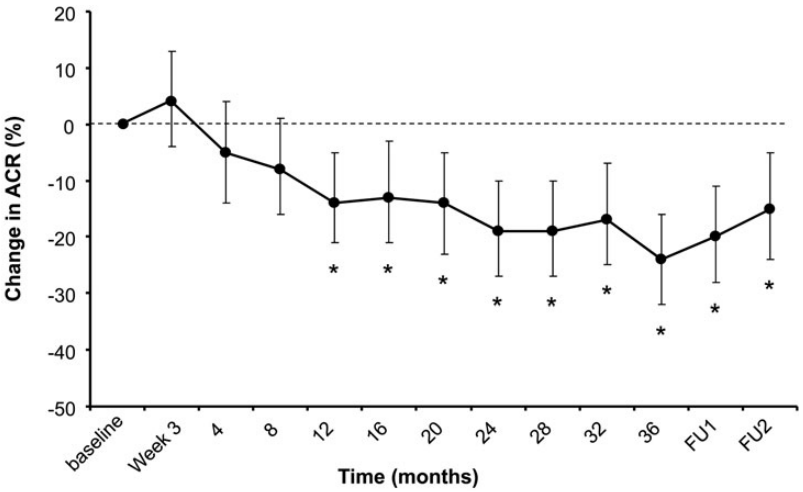
FIGURE 2: Annual change (mean and 95% CI) in TKV according to randomization group and baseline ACR.

ACR compared with placebo (Figure 4). The difference in ACR in tolvaptan- versus placebo-treated patients increased over time, reaching statistical significance at Month 12 and reaching a maximum of 24% [95% confidence interval (CI) 16–32%] at Month 36 ($P < 0.001$). During tolvaptan treatment only a slight decrease in blood pressure was observed compared with placebo, that reached statistical significance only between 28 and 36 months of treatment (difference in mean arterial pressure (MAP) −1.1 to −1.9 mmHg, $P < 0.05$). When adjusted for difference in MAP the difference in ACR between tolvaptan- and placebo-treated patients at Month 36 was −23% (95% CI 15–31%) ($P < 0.001$). At Month 36 of treatment there was no difference in RAASi drug use between the two treatment groups (tolvaptan group 71% and placebo group 72%). After tolvaptan withdrawal, the difference in ACR between the two treatment groups remained significant. At the second follow-up, mean 29 days after drug withdrawal, the difference in ACR was −15% (95% CI −5 to −24%), $P = 0.004$, whereas the difference in blood pressure fully disappeared [difference in MAP −0.3 mmHg (95% CI −1.3 to 0.7 mmHg), $P = 0.5$]. This difference



Placebo	N=	454	409	402	386	365
Tolvaptan	N=	900	563	585	547	669

FIGURE 3: Median albuminuria in tolvaptan- (diamonds) and placebo- (squares) treated patients during 36 months of treatment and after withdrawal of tolvaptan [follow-up visit 1(FU1) and FU2]. The number of subjects at FU2 in the tolvaptan-treated group is higher than at Month 36, because some patients withdrew and had their off-treatment follow-up visits before this date.



Placebo	N=	454	409	402	386	365
Tolvaptan	N=	900	563	585	547	669

FIGURE 4: Difference in albuminuria in tolvaptan- and placebo-treated ADPKD patients during 36 months of treatment and after withdrawal of tolvaptan [follow-up visit 1 ((FU1) and FU2]. The number of subjects at FU2 in the tolvaptan- treated group is higher than at Month 36, because some patients withdrew and had their off-treatment follow-up visits before this date.

in ACR was not changed when statistically adjusting for differences in MAP, i.e. still −15% (95% CI −5 to −24%), P = 0.003. The ACR lowering effect of tolvaptan was not different between patients using RAASi and patients not using such drugs, or in any other subgroup analysis (Table 2). During the trial relatively more patients that used tolvaptan withdrew when compared with those using placebo (23.0 versus 13.8%, respectively, P < 0.0001), partly because of adverse events (15.4 versus 5.0%). The patients using tolvaptan that withdrew were characterized by similar baseline ACR and TKV, but slightly higher eGFR than those who continued [3.3 (5.6) versus 3.0 (5.4), P = 0.91; 1449 (927) versus 1501 (986), P = 0.67, and 83.9 ± 22.0 versus 80.6 ± 20.7 mL/min/1.73 m^2, P = 0.05, respectively]. A sensitivity analysis was performed that included only those patients that had ACR data available at Month 36 (placebo n = 386, tolvaptan n = 547). This analysis showed essentially similar findings: ACR rose on placebo with (+0.23 mg/mmol at Month 36), whereas it decreased in tolvaptan-treated patients (−0.40 mg/mmol at Month 36), with a maximal ACR lowering effect being obtained at Month 36 [26% (95% CI 17 to

Table 2. Change in ACR (medians with 95% CIs) in tolvaptan- versus placebo-treated patients at Month 36 overall, and in subgroups according to baseline patient characteristics

Subgroups	*N*	Change in ACR	P	P for interaction
All	933	−24 (−32 to −16)%	<0.0001	
Male	502	−28 (−39 to −16)%	<0.0001	0.50
Female	431	−20 (−31 to −8)%	0.003	
Age <35 years	211	−29 (−43 to −12)%	0.002	0.39
Age ≥35 years	719	−23 (−33 to −13)%	<0.001	
Hypertension	772	−25 (−34 to −15)%	<0.001	0.65
No hypertension	151	−22 (−40 to 0)%	0.05	
RAASi	686	−26 (−35 to −15)%	<0.0001	0.96
No RAASi	247	−23 (−36 to −6)%	0.01	
Hypercholesterolemia	125	−28 (−47 to −4)%	0.03	0.92
No hypercholesterolemia	808	−24 (−33 to −15)%	<0.0001	
Glucose <5.3 mmol/L	617	−29 (−38 to −18)%	<0.0001	0.82
Glucose ≥5.3 mmol/L	316	−18 (−32 to −1)%	0.04	
Uosmol <500 mosmol/kg	450	−21 (−34 to −7)%	0.006	0.29
Uosmol ≥500 mosmol/kg	468	−27 (−37 to −16)%	<0.0001	
eGFR <80 mL/min/1.73 m^2	483	−27 (−38 to −14)%	0.0002	0.80
eGFR ≥80 mL/min/1.73 m^2	447	−22 (−32 to −10)%	0.0006	
TKV <1500 mL	449	−17 (−28 to −4)%	0.01	0.09
TKV ≥1500 mL	484	−32 (−42 to −19)%	<0.0001	
ACR <3.0 mg/mmol	390	−14 (−27 to −0)%	0.04	0.14
ACR ≥3.0 mg/mmol	501	−32 (−42 to −20)%	<0.0001	

Data are given as median (95% CI).
N, number; Uosmol, urine osmolality. Numbers of subgroups sometimes do not add up to the overall number of patients (*N* = 933) because of missing data.

33%), P < 0.0001] (Supplementary data, Figure S2). Of note, no association was found between ACR and incidence of (serious) adverse events or withdrawal rate (Supplementary data, Table S4).

Albuminuria and tolvaptan treatment efficacy

In tolvaptan-treated patients the annual increase in TKV during follow-up was 2.78 ± 5.65%, and the annual decline in eGFR −2.68 ± 7.63 mL/min/1.73 m^2. In these patients again a significant association was found for baseline ACR with decline in eGFR (Figure 1, right panel). Remarkably, in the current analysis ACR was associated with change in TKV, but opposite to what was expected: higher baseline ACR was associated with less increase in TKV during follow-up (Figure 2, right panel). When compared with placebo-treated patients a beneficial and significant effect of tolvaptan on TKV growth was observed in all ACR subgroups, but was stronger in patients with higher ACR (P for interaction <0.05). The tolvaptan treatment effect on annual change in TKV was an improvement of 36.1, 52.7, 54.7 and 64.2% in the four subgroups with increasing ACR, respectively (P = 0.006, P < 0.0001, P < 0.0001 and P < 0.001, respectively, Supplementary data, Table S3). Of note, tolvaptan dose was not different in the four ACR subgroups (median 103, 101, 103 and 114 mg/day, respectively). A beneficial effect of tolvaptan was found also on change in eGFR in all subgroups, and again was stronger in patients with higher ACR (P for interaction 0.09). Tolvaptan induced improvement in annual eGFR loss by 16.1, 21.8, 33.5 and 24.4% in the four subgroups with increasing ACR, respectively (P = 0.30, 0.07, <0.0001 and 0.09, respectively, Supplementary data, Table S3).

DISCUSSION

The present study shows that ACR is relatively low in ADPKD patients characterized by early-phase disease (eCrCl >60 mL/min). Yet, even in this low range ACR is predictive of eGFR loss. Tolvaptan induced a slowly appearing decrease in ACR, which remained after drug withdrawal. Interactions were found between baseline ACR and tolvaptan induced treatment effects on eGFR loss and especially TKV growth.

Only limited information is available on the significance of albuminuria in ADPKD. Most studies that investigated this issue were of cross-sectional design and suggested that higher TKV and lower eGFR are associated with higher albuminuria [12–16]. These associations can already be found at young age [13]. Only few prospective studies have been published [17, 18]. The Consortium of Radiologic Studies in Polycystic kidney disease (CRISP) found that albuminuria predicted eGFR loss as well as TKV growth, but not in multivariate models [18]. The present study corroborates that baseline albuminuria is associated with eGFR loss, and adds that this association is independent of baseline characteristics except TKV. In contrast, we did not find an association between baseline ACR and TKV growth rate. Differences in findings in the CRISP cohort and the present cohort may be explained by the inclusion criteria and the sample size of both studies. In the TEMPO 3:4 Trial one of the inclusion criteria limited enrollment to patients with a TKV ≥750 mL, whereas no inclusion criteria were defined for TKV in the CRISP Study. The enrichment for higher TKV in the TEMPO 3:4 Trial may have weakened the association between baseline albuminuria and TKV growth. Of note, both studies included patients with preserved eGFR. That we found a significant association between baseline albuminuria and eGFR loss during follow-up in contrast to the CRISP investigators may be due to the larger sample size in the present study ($n = 459$ versus $n = 241$), which provides more power for multivariate analyses. Our findings indicate that albuminuria may have value to predict prognosis in ADPKD patients with early-stage disease.

We observed that tolvaptan induced a significant decrease in ACR over time. This finding seems to contrast the initial TEMPO 3:4 report, which suggested that this drug had no effect on albuminuria as a component of the composite secondary endpoint of disease progression [19]. In the present report, however, we analyzed changes in ACR on a continuous scale, whereas the initial report analyzed tolvaptan-induced ACR effects as events, i.e. expressed as class changes. Classes were defined as normal, moderately elevated or severely elevated albuminuria, and an event was counted when a subject increased from one category to the next. Movement to a lesser category was not taken into account. The present results indicate that such an event-based analysis can lead to an underestimation of the true effect of a drug on ACR. The limitations of an event-based ACR analysis should therefore be

recognized before using this in the design of future randomized controlled trials.

From this study, only limited information can be obtained in regards to the mechanism of the ACR lowering effect of the vasopressin V2 receptor antagonist tolvaptan. Investigators have found in various non-ADPKD animal models that infusion of vasopressin induces albuminuria and that treatment with V1a and V2 receptor antagonists prevents an increase in albuminuria [22]. One of the most compelling investigations suggested that the albuminuric effect of vasopressin results from increased glomerular leakage, requires functional vasopressin V2 receptors and is mediated, at least in part, by the RAAS [23]. No mediating role was found in that study for changes in systemic or glomerular blood pressure [23]. In the current study the albuminuria lowering effect of the V2 receptor antagonist increased over time, reaching a maximum after 36 months of treatment, whereas at that time point only a minor effect on systemic blood pressure was observed. Of note, tolvaptan is known to cause an acute, reversible hemodynamic decrease in measured GFR [24, 25], which may be interpreted as a decrease in intraglomerular blood pressure. This effect is maximal within 1–3 weeks of treatment [24, 25]. The present findings, as well as those in a previous study [26], indicate that at that time the albuminuria lowering effect of tolvaptan is only minor. Considered together these data do not provide an indication that a decrease in systemic and/or intraglomerular blood pressure plays an important role in the albuminuria lowering effect of V2 receptor antagonist treatment. Importantly, the albuminuria lowering effect of tolvaptan was independent of RAASi in the TEMPO study, making a major role for this hormonal system also unlikely. In our opinion, the gradual onset of the ACR lowering response that remains after drug withdrawal indicates that the reduction in albuminuria with V2 receptor antagonists is a reflection of structural benefits that have been obtained, such as less growth in TKV during tolvaptan treatment. Whether such structural benefits are on the level of improved sieving characteristics of the glomerular filtration barrier or improved tubular reabsorption of albumin [27] is beyond the scope of the present study and requires additional investigation.

Treatments that prevent kidney function decline, such as low protein diets, strict blood pressure control and RAASi, are in general more effective in patients with CKD not due to ADPKD and high albuminuria [1, 7–11]. This has led the KDIGO organization to define in their guideline for treatment of CKD albuminuria-specific treatment goals for blood pressure- and albuminuria-specific thresholds when RAASi is preferred over other blood pressure lowering agents (KDIGO 2013). Our findings indicate that in ADPKD subjects with higher albuminuria a vasopressin V2 receptor antagonist had more effect on TKV growth and to a lesser extent also on eGFR decline. As such, these findings with a non-RAASi agent in ADPKD elevate the importance of baseline albuminuria as a modifying factor for the efficacy of renoprotective drugs. Of note, it should be emphasized that ADPKD is a relatively low albuminuria disease. The effect of tolvaptan on albuminuria *per se* is therefore of limited clinical relevance. The importance of the present findings is especially that they indicate that in ADPKD tolvaptan induces structural benefits and that assessing albuminuria status in this disease may be of help to identify ADPKD patients that may benefit more from tolvaptan treatment.

A limitation of the present study is that it was performed as a *post hoc* analysis of a randomized controlled trial with specific inclusion criteria for TKV and eGFR. As explained this may have led to an underestimation of the true association between baseline ACR and disease outcomes, especially TKV. Second, ACR is variable over time. Ideally, ACR is therefore determined as an average value based on three urine samples. Because of feasibility for patients, in this study (as in most studies) ACR was measured in one sample. This can influence reliability. On the other hand, the fact that despite this limitation significant associations between baseline ACR and outcomes and significant differences in ACR between tolvaptan and placebo were found makes these findings stronger instead of weaker. Third, relatively more tolvaptan-treated patients withdrew during the study than placebo-treated patients, partly because of adverse events. Details on reasons for withdrawal can be found in the original TEMPO 3:4 study report (reference 19 therein). These patients had on average similar ACR and TKV, but higher eGFR than the patients that continued study medication. Such patients in general have a more favorable prognosis with respect to TKV growth and eGFR loss. Still we found that higher baseline ACR was associated with better tolvaptan treatment efficacy on these outcome variables. The higher withdrawal rate in tolvaptan-treated patients is therefore not likely to have caused bias towards false-positive results. Strengths of this study are that it is performed in a relatively large dataset, and that it is the first to provide human data on the ACR lowering effect of long-term V2-receptor antagonist treatment.

In conclusion, in ADPKD patients increased albuminuria is associated with more rapid eGFR loss. Tolvaptan decreased albuminuria compared with placebo, independent of blood pressure. This effect remained after withdrawal of study drug, suggesting that tolvaptan induced structural renal benefits. Treatment efficacy of tolvaptan was more readily detected in patients with increased albuminuria. These results mimic those obtained with renoprotective drugs in patients with CKD not due to ADPKD.

SUPPLEMENTARY DATA

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

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CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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