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DIPAK Consortium; Kramers, Bart J; Koorevaar, Iris W; De Boer, Rudolf; Pena, Michelle J; Gansevoort, Ron T; Meijer, Esther

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ORIGINAL ARTICLE

Thiazide diuretics and the rate of disease progression in autosomal dominant polycystic kidney disease: an observational study

Bart J. Kramers[1], Iris W. Koorevaar[1], Rudolf De Boer[2], Ewout J. Hoorn[3], Michelle J. Pena[4], Ron T. Gansevoort[1] and Esther Meijer[1] on behalf of the DIPAK Consortium

[1]Departments of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [2]Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [3]Division of Nephrology and Transplantation, Department of Internal Medicine, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, The Netherlands and [4]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University Hospital Groningen, Groningen, The Netherlands

Correspondence to: Esther Meijer; E-mail: esther.meijer@umcg.nl

ABSTRACT

Background. In autosomal dominant polycystic kidney disease (ADPKD), hypertension is prevalent and cardiovascular events are the main cause of death. Thiazide diuretics are often prescribed as second-line antihypertensives, on top of renin–angiotensin–aldosterone system (RAAS) blockade. There is a concern, however, that diuretics may increase vasopressin concentration and RAAS activity, thereby worsening disease progression in ADPKD. We aimed to investigate the validity of these suggestions.

Methods. We analysed an observational cohort of 533 ADPKD patients. Plasma copeptin (surrogate for vasopressin), aldosterone and renin were measured by enzyme-linked immunosorbent assay and radioimmunoassay, respectively. Linear mixed models were used to assess the association of thiazide use with estimated glomerular filtration rate (eGFR) decline and Cox proportional hazards models for the association with the composite kidney endpoint of incident end-stage kidney disease, 40% eGFR decline or death.

Results. A total of 23% of participants ($n = 125$) used thiazide diuretics at baseline. Compared with non-users, thiazide users were older, a larger proportion was male, they had lower eGFRs and similar blood pressure under more antihypertensives. Plasma copeptin was higher, but this difference disappeared after adjustment for age and sex. Both renin and aldosterone were higher in thiazide users. There was no difference between thiazide users and non-users in the rate of eGFR decline {difference −0.35 mL/min/1.73 m^2 per year [95% confidence interval (CI) −0.83 to −0.14], P = 0.2} during 3.9 years of follow-up (interquartile range 2.5–4.9). This did not change after adjustment for potential confounders [difference final model: 0.08 mL/min/1.73 m^2 per year [95% CI −0.46 to −0.62], P = 0.8). In the crude model, thiazide use was associated with a higher incidence of the composite kidney endpoint [hazard ratio (HR) 1.53 (95% CI 1.05–2.23), P = 0.03]. However, this association lost significance after adjustment for age and sex and remained unassociated after adjustment for additional confounders [final model: HR 0.80 (95% CI 0.50–1.29), P = 0.4].

Conclusions. These data do not show that thiazide diuretics have a detrimental effect on the rate of disease progression in ADPKD and suggest that these drugs can be prescribed as second-line antihypertensives.

Keywords: ADPKD, diuretics, hypertension, polycystic kidney disease, thiazide diuretics

INTRODUCTION

One of the first symptoms in patients with autosomal dominant polycystic kidney disease (ADPKD) is hypertension, typically occurring at ∼30 years of age [1]. In addition to being a risk factor for rapid kidney function decline, hypertension is also associated with increased cardiovascular morbidity and mortality [2, 3].

Limited evidence exists as to which antihypertensives should be prescribed in ADPKD. TheKidney Disease: Improving

KEY LEARNING POINTS

What is already known about this subject?

- hypertension is highly prevalent in autosomal dominant polycystic kidney disease (ADPKD), cardiovascular events are the main cause of death;
- thiazide diuretics are often the treatment of second choice (after renin–angiotensin–aldosterone system blockade) in non-ADPKD populations as large randomized controlled trials have shown that thiazide diuretics are superior to β-blockers for cardiovascular protection; and
- recent literature has suggested that thiazide diuretics may be detrimental to the progression of ADPKD, as thiazide diuretics may cause an increase in plasma vasopressin.

What this study adds?

- after adjustment for age and sex, the use of thiazide diuretics is not associated with higher plasma copeptin (a surrogate marker of vasopressin);
- during a median of 4 years of follow-up, the use of thiazide diuretics is not associated with accelerated estimated glomerular filtration rate (eGFR) decline in a large and diverse cohort of ADPKD patients; and
- after adjustment for age and sex, the use of thiazides is not associated with a higher incidence of end-stage kidney disease, a 40% eGFR decline or death.

What impact this may have on practice or policy?

- thiazide diuretics should be considered a viable treatment option as a second-line antihypertensive, on top of RAAS blockade in ADPKD patients.

Global Outcomes (KDIGO) ADPKD Conference Report from 2015 states that renin–angiotensin–aldosterone (RAAS) blockade should be the drug of first choice based on expert opinion and limited clinical data [4] . The second-line treatment options are under debate, due to the absence of clinical evidence. In non-ADPKD hypertensive populations, thiazide diuretics are the preferred first- or second-line drugs, as large randomized controlled trials have shown that thiazide diuretics are superior to β-blockers for cardiovascular protection [5, 6]. Furthermore, thiazides are known to potentiate the renoprotective effects of RAAS blockade in patients with chronic kidney disease [7]. There are theoretical concerns that impede the use of diuretics in ADPKD. Diuretics may increase plasma vasopressin levels, and vasopressin is detrimental in ADPKD. Furthermore, thiazide diuretics increase RAAS activity, which may also be harmful. These theoretical concerns have been described in the KDIGO Conference Report and are repeated in recent publications [8, 9].

While there is evidence to suggest that loop diuretics increase plasma vasopressin concentrations, this is unknown for thiazide diuretics [10–14]. In contrast, it is well established that thiazide diuretics increase RAAS activity [7, 10], but it is unknown whether this is harmful in ADPKD. We therefore aimed to evaluate the effects of thiazide diuretic use on vasopressin concentrations and on the rate of disease progression in ADPKD.

MATERIALS AND METHODS

For this study, we used the data from the Developing Intervention Strategies to Halt Progression of Autosomal Dominant Polycystic Kidney Disease (DIPAK) observational cohort study that was designed to investigate the natural course of polycystic kidney disease. The cohort was established to continue the follow-up of participants of the DIPAK 1 randomized controlled trial in which the renoprotective effect of the somatostatin analogue lanreotide was assessed ($n = 305$) and to include additional patients from the outpatient clinic ($n = 489$). Follow-up is still ongoing. Data were collected in the University Medical Centers of Groningen, Leiden, Nijmegen and Rotterdam. The design and methods of the DIPAK 1 trial have been published elsewhere [15]. In brief, patients were included between 2012 and 2015 if they were 18–60 years of age, had ADPKD (modified Ravine criteria [16]) and had an estimated glomerular filtration rate (eGFR) of 30–60 mL/min/1.73 m^2. After a baseline visit, participants were seen after 4, 8, 12, 48, 96, 120 and 132 weeks and blood was collected every 12 weeks. Lanreotide treatment did not influence plasma copeptin or the annual change in eGFR [17, 18]. After the end of the trial, 175 patients agreed to continue follow-up. Inclusion criteria for other participants in the observational cohort study were $\geq$18 years of age and had an eGFR $\geq$15 mL/min/1.73 m^2. Contraindications for participation in the trial and the observational cohort were concomitant diseases or medication use that might influence the natural course of ADPKD (e.g. diabetes mellitus or chronic non-steroidal anti-inflammatory drug use). For the present analyses, we included ADPKD patients with a minimum of three eGFR assessments during at least 2 years of follow-up, and patients using non-thiazide diuretics were excluded, leaving 533 patients for analysis. The DIPAK observational study was approved by the Institutional Review Board of

the University Medical Center Groningen and was conducted in adherence with the International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent was obtained from all participants.

Measurements

Creatinine was measured using anisotope dilution mass spectrometry–traceable enzymatic method in samples stored at −80°C. eGFR was estimated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [19]. Fasting plasma copeptin concentrations were measured using a sandwich immunoassay (Thermo Fisher Scientific BRAHMS, Hennigsdorf/Berlin, Germany). Renin (Renin III Generation RIA Cisbio Bioassays, Codelet, France) and aldosterone (Demeditec Diagnostics, Kiel, Germany) were measured by radioimmunoassay. Osmolality was measured by the freezing point depression method, sodium and potassium concentration by ion-specific electrodes and urea by an enzyme kinetic assay. Magnetic resonance imaging (MRI) was performed using a standardized MRI protocol without the use of intravenous contrast. Total kidney volume (TKV) was assessed by manual tracing of T2-weighted coronal magnetic resonance images using AnalyzeDirect 9.0 software (AnalyzeDirect, Overland Park, KS, USA).

Statistical analyses. For the statistical analyses, we used SPSS version 23 (IBM, Armonk, NY, USA) and Stata SE 14 (StataCorp, College Station, TX, USA). Variables that are normally distributed are presented as mean ± standard deviation (SD), whereas variables that are not normally distributed are presented as median and interquartile range (IQR). Categorical variables are presented as the percentage of the overall study population. For all analyses, a two-sided P-value <0.05 was considered statistically significant. In all analyses, 'use of thiazides' was the predictor variable, defined as 'use of a thiazide diuretic at baseline'.

Linear regression analysis was performed to evaluate the association of the use of thiazide diuretics with plasma copeptin and plasma osmolality as measured at baseline. Subsequent models were adjusted for age, sex and BMI, blood pressure, the known markers of disease severity [baseline eGFR, height-adjusted toal kidney volume (htTKV), DNA mutation and albuminuria] and, in the final model, use of RAAS blockade. N-terminal pro-brain natriuretic peptide (NT-proBNP; as a marker of volume status), renin and aldosterone were only measured in subjects that participated in the DIPAK 1 study. The same analysis was performed in these participants.

A mixed model repeated measures analysis was used to evaluate the primary outcome (slope of eGFR decline). All measurements during the study were included for slope analysis. Linear mixed models used an unstructured covariance structure. Intercept and slope were allowed to vary randomly. Baseline use of specific antihypertensives (yes/no), time and the interaction with time were added to the model as fixed effects. Potential confounders and their interaction with time were added to further models. Models were adjusted for age, sex, BMI, systolic blood pressure, number of antihypertensives used (in daily defined dose) and for the known risk factors of disease progression in ADPKD (eGFR, htTKV, DNA mutation and albuminuria). Due to a skewed distribution, htTKV was $\log_{10}$ transformed. Covariates were added to the models as measured at baseline, except for systolic blood pressure, which was added as a time-varying covariate. As a sensitivity analysis, we also performed an 'as treated' analysis, in which the follow-up was censored when thiazide use status change (i.e. when a patient started or stopped thiazide use during the study). Furthermore, we repeated the primary analysis in the separate cohorts (DIPAK 1 and DIPAK observational) as a sensitivity analysis. In each model, participants with missing data were excluded list wise.

To ensure that the results were not influenced by overfitting of the models, we repeated the analysis of the association of thiazide diuretic use with eGFR slope in a simpler mixed model. In this model, we first analysed univariable associations with eGFR slope and adjusted the analyses only for variables that were univariably associated with a P-value <0.1.

Subgroup analyses were performed for the primary outcome by including an interaction term between subgroup and thiazide use to the multivariable mixed model [that included all variables of the final (fifth) model]. If the interaction term was significant, the subgroup was considered a significant moderator for the association. The mixed model was run for each separate subgroup and graphed in a forest plot.

The change in htTKV was assessed in participants of the DIPAK 1 trial only using $\log_{10}$-transformed htTKV data at baseline and Week 132; the antilog of the estimated effect was derived from the mixed model analysis to provide annual percentage change of htTKV. As lanreotide influences htTKV, growth analyses were adjusted for the DIPAK 1 randomization group.

To study the association between the use of thiazide diuretics and a composite kidney endpoint (occurrence of ESRD, 40% eGFR decline or death), we performed Cox proportional hazards models. ESKD was defined as an eGFR <15 mL/min/1.73 m^2 or initiation of renal replacement therapy. In these analyses, we adjusted for the same covariates as in the mixed model analysis that evaluated eGFR decline.

RESULTS

Baseline characteristics

This analysis includes 533 patients, 257 of whom participated in the DIPAK 1 trial and an additional 276 in the DIPAK observational study. Of all the participants, 76% used antihypertensives at baseline. RAAS blockade with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers was the most commonly used first-line antihypertensive treatment, used by 69% of the participants. As second-line treatment, the most commonly used were thiazide diuretics, β-blockers and calcium channel blockers (Figure 1). α-Blockers were infrequently used (1% of participants). Of the specific thiazides that were used, hydrochlorothiazide was most common (89%), followed by chlorthalidone (6%) and indapamide (5%). Of the 125 participants who used thiazide diuretics at baseline, 45 stopped during the study, whereas 23 participants started using a thiazide diuretic during the study.

Table 1 shows the baseline characteristics of participants who used thiazide diuretics ($n = 125$) and participants who did not ($n = 408$). Compared with non-users, thiazide users were older, were more frequently male, used more antihypertensives and had larger kidney volume. Blood pressure and DNA mutations were similar.

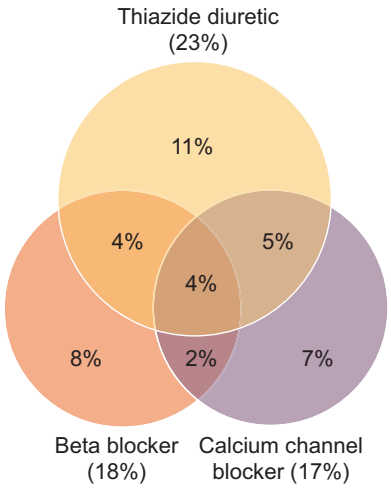

FIGURE 1: Percentage of participants that use specific antihypertensives and combinations of antihypertensives. Of thiazide diuretic users, 91% also used an RAAS inhibitor. Of calcium channel blocker users, this was 83% and of β-blocker users it was 77%. Percentages are of the total analysed population ($N = 533$).

Markers of volume status, osmolar intake and osmolality at baseline

Plasma copeptin and plasma potassium were significantly different in thiazide users compared with non-users (Table 2). After adjustment for age and sex, the difference in plasma copeptin disappeared, the difference in plasma potassium remained and plasma sodium and osmolality were significantly lower. Plasma NT-proBNP, aldosterone and renin were only measured in subjects who participated in the DIPAK 1 trial. NT-proBNP was similar in thiazide users and non-users. Aldosterone and renin were significantly higher in thiazide users. We performed linear regression analysis to investigate whether the use of thiazide diuretics was associated with markers of volume status and osmolality when adjusted for other potential confounders (Table 3). In the adjusted model, there was a significant negative association between thiazide use and plasma osmolality. Both plasma renin and aldosterone remained significantly associated after full adjustment. Thiazide use was not significantly associated with NT-proBNP after full adjustment. The crude model showed a positive association of thiazide use with plasma copeptin. This association disappeared after adjustment for age, sex and BMI. Further adjustment for potential confounders did not reveal a positive association, nor was there a trend towards a positive association.

Association with kidney function decline

The median follow-up time was 3.9 years (IQR 2.5–4.9), during which a median of 6 (IQR 5–14) eGFR assessments took

Table 1. Baseline characteristics

Characteristics	Not using thiazides ($n = 408$)	Thiazide users ($n = 125$)	P-value
Age (years), mean ± SD	46 ± 11	50 ± 8	**<0.001**
Sex (female), *n* (%)	254 (62)	57 (46)	**0.001**
Weight (kg), mean ± SD	80.7 ± 16.3	85.3 ± 17.9	**0.006**
Height (m), mean ± SD	1.76 ± 0.09	1.77 ± 0.10	0.3
SBP (mmHg), mean ± SD	132 ± 14	130 ± 14	0.6
DBP (mmHg), mean ± SD	82 ± 9	80 ± 9	0.05
Antihypertensives (DDD), *n* (%)	1.00 (0.00–2.00)	2.67 (2.00–3.92)	**<0.001**
RAASi	254 (62)	114 (91)	**<0.001**
β-blocker	55 (14)	39 (31)	**<0.001**
Calcium channel blocker	48 (12)	44 (35)	**<0.001**
eGFR (mL/min/1.73m^2)[a], mean ± SD	67 ± 24	54 ± 17	**<0.001**
Albuminuria (mg/24 h), median (IQR)	29 (13–62)	34 (18–70)	0.05
htTKV (mL/m), median (IQR)	775 (508–1207)	1207 (810–1851)	**<0.001**
MAYO risk class,[b] *n* (%)			**0.03**
ADPKD Class 2/1A/1B	130 (34)	23 (19)	
ADPKD Class 1C/1D/1E	254 (66)	95 (81)	
DNA mutation, *n* (%)			0.07
PKD1 truncating	177 (43)	49 (40)	
PKD1 non-truncating	114 (28)	32 (26)	
PKD2	80 (20)	37 (30)	
No mutation detected/other	36 (9)	6 (5)	

Participants that used non-thiazide diuretics are excluded.
Bold values indicate significance at $P < 0.05$.
[a]Estimated by CKD-EPI equation.
[b]MAYO ADPKD classification predicts prognosis and is based on TKV indexed for height and age [20]. Class 2 is atypical. Classes 1A and 1B indicate a more favourable prognosis than Classes 1C, 1D and 1E.
SBP, systolic blood pressure; DBP, diastolic blood pressure; DDD, daily defined dose; RAASi, RAAS inhibitor (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker).

Table 2. Markers of volume status, osmolar intake and osmolality at baseline

Markers	Not using thiazides	Thiazide users	P-value	Age- and sex-adjusted P-value
All participants ($N = 533$), n	408	125		
Plasma sodium (mmol/L), mean ± SD	140.9 ± 2.1	140.5 ± 2.5	0.1	**0.008**
Plasma potassium (mmol/L), mean ± SD	4.2 ± 0.4	3.9 ± 0.4	**<0.001**	**<0.001**
Plasma osmolality (mOsm/L), mean ± SD	287.8 ± 5.5	287.5 ± 7.8	0.6	**0.007**
Plasma copeptin (pmol/L), median (IQR)	6.8 (4.0–12.8)	9.3 (4.9–15.5)	**0.005**	0.2
Urine volume (mL/24 h), mean ± SD	2273 ± 782	2278 ± 877	0.9	0.7
Sodium excretion (mmol/24 h), mean ± SD	153 ± 64	155 ± 62	0.7	0.8
Osmol excretion (mOsm/24 h), mean ± SD	830 ± 286	868 ± 289	0.2	0.7
DIPAK 1 participants only ($n = 257$), n	170	87		
Plasma NT-proBNP (ng/L), median (IQR)	77 (45–148)	79 (32–150)	0.7	0.6
Plasma aldosterone (pg/L), median (IQR)	225 (169–302)	272 (204–367)	**0.001**	**0.003**
Plasma renin (pg/L), median (IQR)	30 (12–72)	65 (22–167)	**<0.001**	**<0.001**

NT-proBNP, aldosterone and renin were only measured in participants of the DIPAK 1 trial. Age- and sex-adjusted P-values were obtained using linear regression analysis.
Bold values indicate significance at $P < 0.05$.

Table 3. Associations of the use of thiazide diuretics with markers of volume and osmolality

Model	All participants ($N = 533$)				Participants DIPAK 1 trial only ($n = 257$)					
	ln(copeptin)		Plasma osmolality		ln(NT-proBNP)		ln(aldosterone)		ln(renin)	
	St. β	P-value	St. β	P-value	St. β	P-value	St. β	P-value	St. β	P-value
Model 1	**0.14**	**0.004**	−0.03	0.6	−0.09	0.2	**0.22**	**<0.001**	**0.38**	**<0.001**
Model 2	0.05	0.3	**−0.11**	**0.02**	−0.07	0.3	**0.24**	**<0.001**	**0.29**	**<0.001**
Model 3	0.02	0.7	−0.08	0.1	−0.08	0.3	**0.30**	**<0.001**	**0.16**	**0.01**
Model 4	−0.02	0.7	**−0.11**	**0.04**	−0.09	0.2	**0.31**	**<0.001**	**0.16**	**0.02**
Model 5	−0.02	0.7	**−0.11**	**0.04**	−0.10	0.2	**0.30**	**<0.001**	**0.19**	**0.001**

Standardized (St.) β's and P-values were calculated using linear regression analysis. NT-proBNP (ng/L), copeptin (pmol/L), renin (pmol/L) and aldosterone (pmol/L) were log-transformed to fulfil the criteria of linear regression analysis. Plasma osmolality (mOsm/L) was not transformed. Plasma copeptin and plasma osmolality were measured in all participants; NT-proBNP, aldosterone and renin were only measured in participants of the DIPAK 1 trial. Model 1: use of thiazides, unadjusted. Model 2: Model 1 + age, sex, body mass index. Model 3: Model 2 + systolic blood pressure. Model 4: Model 3 + eGFR, htTKV, DNA mutation, randomization group. Model 5: Model 4 + use of RAAS inhibitor.
Bold values indicate significance at $P < 0.05$

place per individual, which showed an average annual eGFR decline of 3.50 mL/min/1.73 m^2 [95% confidence interval (CI) 3.71–3.29). In the crude linear mixed model, thiazide diuretic users had similar eGFR slopes as non-users (Table 4). This remained unchanged after adjustment for the use of other hypertensives and after further adjustment for blood pressure, number of antihypertensives used or markers of disease severity (Figure 2). All data were available in >99% of participants except for baseline htTKV [$n = 29$ missing (5.4%)] and baseline albuminuria [$n = 24$ missing (4.5%)]; list wise, all data were available in 471 participants. Subgroup analysis showed a significantly different association of thiazide use and eGFR decline in subgroups based on htTKV, albuminuria, plasma sodium and urine volume, with a significantly less steep eGFR decline in patients with low plasma sodium and low urine volume (Figure 3). There were no subgroups in which thiazide use was associated with more rapid eGFR decline. In the patients who participated in the DIPAK 1 trial, a linear mixed model evaluated possible associations of the use of specific antihypertensives with growth in htTKV (Supplementary data, Table S1). The use of thiazide diuretics was neither associated with TKV growth in the crude model nor in the fully adjusted model.

Association with kidney end points

During follow-up, 131 composite endpoints occurred, 95 of which consisted of a 40% decline in eGFR, 36 were due to incident ESKD and none due to death. In univariable analysis, the use of thiazide diuretics was associated with a higher risk of the composite kidney endpoint [hazard ratio (HR) 1.53 (95% CI 1.05–2.23)] (Table 5). This association disappeared after adjustment for potential confounders [HR final model: 0.80 (95% CI 0.50–1.29)]. We performed subgroup analysis in the same subgroups as in the analysis of eGFR slope (Supplementary data, Figure S1). Here we found a near-significant interaction term for 24-h urine volume and use of thiazides ($P = 0.1$): in patients with urine volume <2200 mL ($n = 226$), use of thiazides was associated with a lower risk of the composite kidney endpoint [HR 0.35 (95% CI 0.16–0.77); $P = 0.009$], while there was no association in patients with urine volume >2200 mL [$n = 238$; HR 1.48 (95% CI 0.75–2.91); $P = 0.3$]. The interaction term of 24-h sodium excretion and use of thiazides was statistically significant ($P = 0.009$), with a statistically significant lower risk of the composite kidney endpoint in patients with sodium excretion <140 mmol/24 h [$n = 237$; HR 0.34 (95% CI 0.16–0.73)]; in patients with sodium excretion >140 mmol/24 h, the use of thiazide diuretics was not associated with the composite kidney

Table 4. Association of the use of specific antihypertensives with annual eGFR decline (mL/min/1.73 m^2 per year)

Variables	Model 1		Model 2		Model 3		Model 4		Model 5	
	Est.	P-value	Est.	P-value	Est.	P-value	Est.	P-value	Est.	P-value
Thiazide use[a]	−0.35	0.2	−0.04	0.9	−0.01	0.9	0.09	0.8	0.08	0.8
β-blocker use[a]			−0.37	0.2	0.35	0.2	0.28	0.3	−0.28	0.3
Calcium channel blocker use[a]			−0.53	0.07	−0.42	0.1	−0.36	0.3	−0.55	0.1
RAASi use[a]			−0.43	0.07	−0.36	0.1	−0.22	0.5	0.23	0.4
Age (years)[a]					0.02	0.07	**0.02**	**0.02**	0.06	0.7
Sex (female)[a]					**0.48**	**0.02**	0.36	0.2	0.3	0.1
BMI (kg/m^2)					**−0.05**	**0.04**	**−0.05**	**0.03**	−0.03	0.2
SBP (mmHg)[a]							**−0.01**	**0.008**	−0.003	0.4
Antihypertensives (DDD)[a]							−0.1	0.4	−0.02	0.9
eGFR (mL/min/1.73 m^2)[a]									0.004	0.5
Log_{10} htTKV (mL/m)[a]									**−1.81**	**<0.001**
Albuminuria (ref: <30 mg/24 h)[a]										
30–300 mg/24 h									−0.52	0.1
>300 mg/24 h									−1.36	0.07
DNA mutation (ref: PKD1 truncating)										
PKD1 non-truncating									0.11	0.6
PKD2									**1.26**	**<0.001**
No mutation detected/other									**0.84**	**0.04**

All variables entered into the model as measured at baseline, except for SBP, which was added as a time-varying covariate.
Bold values indicate significance at $P < 0.05$
[a]Estimations and P-values are shown for the interactions of variables with time. The interaction with time signifies the effect of said variable on eGFR over time, i.e. the effect on eGFR slope. Every model also included the variable time and all variables without the interaction with time. The estimations for the variables not interacted with time (not shown) signify the effect of said variable on baseline eGFR (the intercept).
RAASi: RAAS inhibitor (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker); BMI: body mass index; SBP: systolic blood pressure.

endpoint [HR 1.41 (95% CI 0.73–2.72); P = 0.3]. There were no differences in associations with the endpoint in any other subgroups, including subgroups based on htTKV, albuminuria or plasma sodium ($P_{interaction}$ = 0.6, 0.6 and 0.5, respectively).

Sensitivity analyses

In the first sensitivity analysis, we censored follow-up at the moment the status of thiazide use changed. This 'as-treated' analysis showed results similar to those of the primary analysis of eGFR slope (Supplementary data, Table S2). The primary analysis of the association of thiazide use with eGFR decline was similar when only performed in patients who participated in the DIPAK 1 trial (adjusted difference in eGFR decline 0.33 mL/min/1.73 m^2 per year in the final model; P = 0.3) as when performed in patients who only participated in the DIPAK observational study (fully adjusted difference in eGFR decline −0.39 mL/min/1.73 m^2 per year in the final model; P = 0.5). Performing the main analysis in a simpler model also did not change the results (Supplementary data, Table S3).

DISCUSSION

In ADPKD, there is a theoretical concern that thiazide diuretics may accelerate disease progression [4, 8, 9]. We evaluated the association of the use of thiazide diuretics with disease progression in 533 ADPKD patients participating in the DIPAK 1 trial and the DIPAK observational cohort. No differences in the rate of disease progression were found between users and non-users of thiazide diuretics. The use of thiazides was associated with a higher incidence of the composite kidney endpoint; however, this association lost significance after adjustment for age, sex, BMI and use of other antihypertensives.

The use of diuretics has been suggested to increase plasma vasopressin concentration, which could be unfavourable in ADPKD [4]. Vasopressin leads to cyst growth both *in vitro* and *in vivo*, and vasopressin V2 receptor antagonists slow the rate of kidney function decline in ADPKD patients [21, 22]. While the use of loop diuretics is known to increase plasma vasopressin concentration [12–14], this has never been convincingly shown for thiazide diuretics [10, 11]. On the contrary, a recent study found similar plasma vasopressin levels in thiazide users as in non-users and even lower vasopressin levels in hyponatraemic thiazide users [23]. With loop diuretics, the increase in vasopressin concentration is thought to be a consequence of volume depletion [24]. Compared with loop diuretics, volume depletion is less pronounced during thiazide treatment [25]. Importantly, the regulation of vasopressin is more sensitive to osmotic fluctuations than changes in volume status [26]. Hydrochlorothiazide can lower plasma osmolality and could therefore lead to decreased vasopressin levels [23, 27]. In this study, we found no differences between thiazide users and non-users in plasma osmolality or plasma sodium. However, after adjustment for age, sex and BMI, there was a significant negative association between thiazide use and lower plasma osmolality, an effect that can be explained by the mechanism of action of these drugs. This effect on plasma osmolality did not translate into an association between thiazide use and copeptin concentration (as a surrogate marker for vasopressin) after basic adjustment for age and sex, or after further adjustments. Perhaps this could be explained by a counteracting effect of thiazide diuretics on volume status, although we did not find a significant association of thiazide use with NT-proBNP.

In concordance with other studies, we found that thiazide therapy was associated with increased RAAS activity [7, 10].

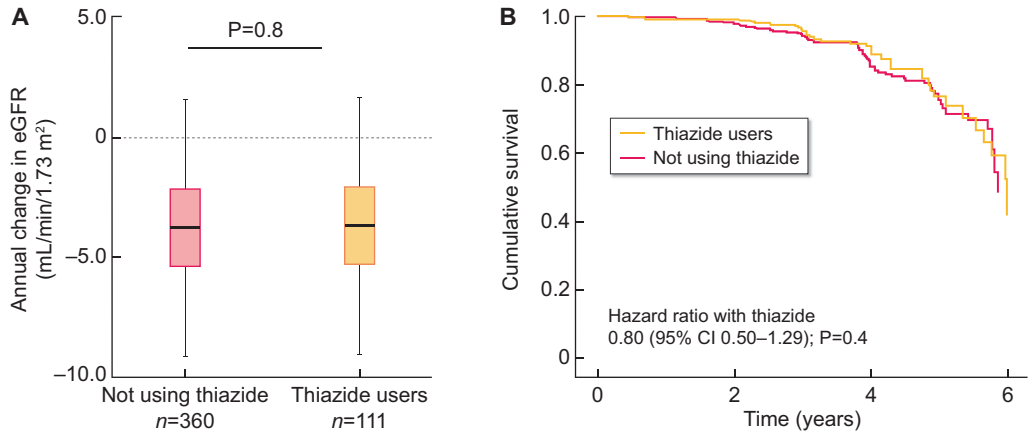

FIGURE 2: Association of the use of thiazide diuretics and eGFR decline and the composite kidney endpoint. (**A**) The predicted annual eGFR decline. The boxplot shows predicted mean and 25th and 75th percentiles, lower and upper limit error bars show predicted 2.5th and 97.5th percentiles as derived from the adjusted mixed model analyses (Model 5 of the primary analysis, adjusted for use of other antihypertensives, age, sex, BMI, systolic blood pressure, DNA mutation, baseline eGFR, htTKV and albuminuria). (**B**) The cumulative survival of thiazide users ($n = 111$) and participants not using thiazides ($n = 360$) in the Cox proportional hazards model at the mean of the covariates of the final model (age, sex, BMI, systolic blood pressure, number of antihypertensives used, baseline eGFR, htTKV, albuminuria and DNA mutation).

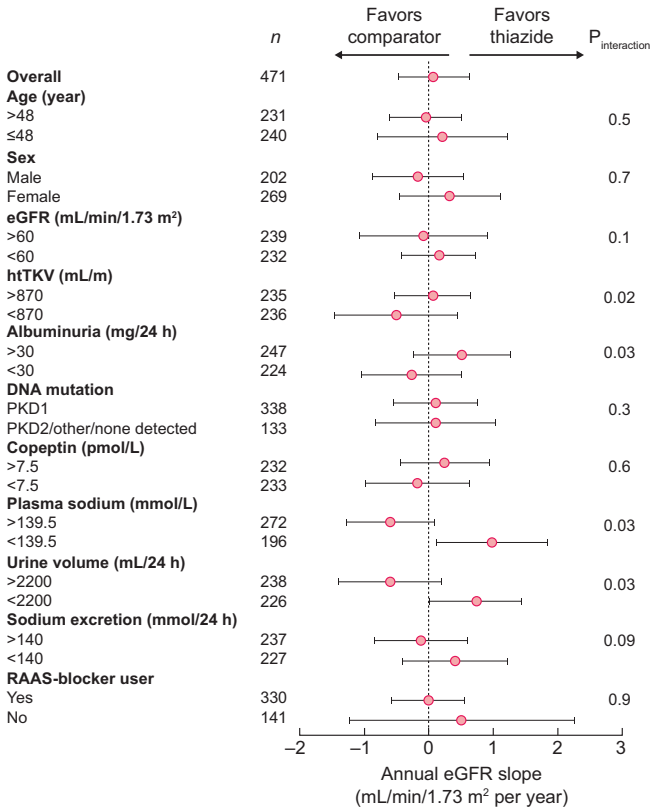

FIGURE 3: Association of the use of thiazide diuretics with the slope of estimated GFR (mL/min/1.73 m^2 per year) in subgroups. Analyses were adjusted for use of specific other antihypertensives, age, sex, BMI, systolic blood pressure, number of antihypertensives used, baseline eGFR, htTKV, albuminuria and DNA mutation. The analyses were performed in the 471 patients without missing values in any of these variables.

Table 5. Associations between the use of a thiazide diuretic and the occurrence of ESKD, −40% eGFR decline or death

Model	HR (95% CI)	P-value
Model 1 (univariable)	1.53 (1.05–2.23)	0.03
Model 2	1.41 (0.96–2.07)	0.08
Model 3	1.02 (0.66–1.59)	0.9
Model 4	1.07 (0.68–1.67)	0.8
Model 5	0.80 (0.50–1.29)	0.4

Model 1: crude; Model 2: Model 1 + adjustment for age and sex; Model 3: Model 2 + adjustment for BMI, systolic blood pressure and number of antihypertensives (daily defined dose); Model 4: Model 3 + adjustment for use of calcium channel blocker, use of β-blocker and use of RAAS inhibitor; Model 5: Model 4 + adjustment for eGFR, $_{10}$Log-transformed htTKV, DNA mutation and albuminuria. All covariates added to the model as assessed at baseline.

Theoretically, RAAS activation might lead to cyst growth independent of blood pressure by stimulating angiogenesis and growth factor secretion [28]. There are indeed several animal studies that suggest a beneficial effect of RAAS blockade. However, it is unclear whether this is an effect of RAAS inhibition *per se* or just an effect of lower blood pressure. The HALT-A study showed that there was no beneficial effect of dual RAAS blockade versus single RAAS blockade [29]. Based on the primary analysis and a *post hoc* study, it was concluded that beneficial effects of RAAS blockade were (primarily) the result of a blood pressure decrease as opposed to RAAS blockade [29, 30]. Moreover, if RAAS activation by thiazide use is detrimental, it is important to note that thiazides are typically prescribed as second-line agents on top of RAAS blockade, as was the case in 91% of thiazide users in our study. It is possible that the combination with RAAS blockade negates any possible detrimental effects induced by thiazide diuretics.

No differences were found in the rate of disease progression between thiazide users and non-users. The use of thiazides was univariably associated with the composite kidney endpoint (occurrence of ESRD, 40% eGFR decline or death). However, this seems to be attributable to differences in baseline characteristics

between thiazide users and non-users, as the association disappeared after adjustment for age and sex and remained insignificant after further adjustment. In subgroup analysis, thiazide use was not associated with more rapid eGFR decline or a higher incidence of the composite kidney endpoint in any of the subgroups. Interestingly, the use of thiazide diuretics was associated with a less steep eGFR decline in patients with lower urine volume and lower plasma sodium. The use of thiazide diuretics was associated with a lower incidence of the kidney endpoint in patients with low urine volume and low sodium excretion. Future studies are needed to further investigate these findings.

There are limitations to this study, most notably, the risk of bias by indication. The most common indication for thiazides is hypertension. Indeed, hypertension was more pronounced in the thiazide group as evaluated by the number of antihypertensives used. In ADPKD, early development of hypertension is associated with larger TKV and a known risk factor for disease severity [2, 31]. This is consistent with our finding of larger htTKV and more severe Mayo risk class at baseline in the thiazide group [20]. Although this difference could be a source of bias, confounding would be to the disadvantage of thiazide diuretics, whereas we found no negative effect associated with this class of drugs. Another limitation is that this study is observational and thus does not allow definitive conclusions with respect to causality. Such a conclusion would only be allowed after a dedicated randomized controlled clinical trial that studies intervention with a thiazide diuretic. However, considering the resources needed for a randomized trial, and the issue of whether it is ethical to investigate an agent that is hypothesized to have a negative effect, it is questionable whether such an intervention study will ever take place. Strengths of this study are that we were able to combine cohorts of patients that used exactly the same methodology. We therefore had sufficient power to analyse the eGFR slope as well as kidney endpoints, both of which showed the same results. Furthermore, participants of the DIPAK 1 trial as well as the DIPAK observational study were well phenotyped, including measurement of volume status and copeptin concentration. Finally, this study includes participants with a wide range of baseline kidney function and frequent assessments of eGFR, allowing precise estimation of the slope in a representative group of participants.

At present, there is no compelling evidence as to the most suitable second-line antihypertensive in ADPKD in addition to RAAS inhibition. This study shows that caution does not seem warranted in the case of thiazide diuretics. In our opinion, the choice for a specific antihypertensive should be made based on individual patient preferences and comorbidities. The use of thiazide diuretics in ADPKD could offer additional benefits to blood pressure control, for instance, in case of fluid overload or in combination with a vasopressin V2 receptor antagonist to limit the aquaretic side effects of that drug [32, 33]. However, this study did not investigate this specific combination of drugs and such a combination should be avoided until future research confirms its safety and efficacy.

In conclusion, thiazide use was not associated with plasma copeptin concentration or with the rate of ADPKD disease progression when used in addition to RAAS blockade. Therefore this study suggests that thiazide diuretics, especially hydrochlorothiazide, can be prescribed safely in addition to RAAS blockade in ADPKD.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

B.J.K., R.T.G. and E.M. contributed to the research idea, study design and data acquisition. B.J.K., I.W.K., R.T.G., R.D.B., E.J.H., M.J.P. and E.M. contributed to data analysis/interpretation. B.J.K., M.J.P. and E.M. contributed to the statistical analysis. R.T.G. and E.M. provided supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work.

CONFLICT OF INTEREST STATEMENT

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