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High water vs. *ad libitum* water intake for autosomal dominant polycystic kidney disease: a randomized controlled feasibility trial

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Summary

Background: Vasopressin stimulates cyst growth in autosomal dominant polycystic kidney disease (ADPKD) and is a key therapeutic target. Evaluation of high water intake as an alternative to pharmacological vasopressin blockade is supported by patients. However feasibility, safety and adherence-promoting strategies required to deliver this remain unknown.
Aims: Assess the feasibility of a definitive randomized high water intake trial in ADPKD.
Methods: In this prospective open-label randomized trial, adult ADPKD patients with eGFR $\geq$ 20 ml/min/1.73 m^2 were randomized to prescribed high water (HW) intake targeting urine osmolality (UOsm) $\leq$270 mOsm/kg, or *ad libitum* (AW) intake (UOsm >300 mOsm/kg). Self-management strategies including home-monitoring of urine-specific gravity (USG) were employed to promote adherence.
Results: We enrolled 42 participants, baseline median eGFR (HW 68.4 [interquartile range (IQR) 35.9–107.2] vs. AW 75.8 [IQR 59.0–111.0 ml/min/1.73 m^2, $P = 0.22$) and UOsm (HW 353 [IQR 190–438] vs. AW 350 [IQR 240–452] mOsm/kg, $P = 0.71$) were similar between groups. After 8 weeks, 67% in the HW vs. 24% in AW group achieved UOsm $\leq$270 mOsm/kg, $P = 0.001$. HW group achieved lower UOsm (194 [IQR 190–438] vs. 379 [IQR 235–503] mOsm/kg, $P = 0.01$) and higher urine volumes (3155 [IQR 2270–4295] vs. 1920 [IQR 1670–2960] ml/day, $P = 0.02$). Two cases of hyponatraemia occurred in HW group. No acute GFR effects were detected. In total 79% (519/672) of USG were submitted and 90% (468/519) were within target. Overall, 17% withdrew during the study.
Conclusion: DRINK demonstrated successful recruitment and adherence leading to separation between treatment arms in primary outcomes. These findings suggest a definitive trial assessing the impact of high water on kidney disease progression in ADPKD is feasible.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the commonest inherited kidney disorder, affecting 12 million people globally.[1] Continued cyst growth compresses the surrounding kidney parenchyma causing hypertension and kidney function decline,[2] with over 70% developing end stage kidney disease by the sixth decade of life.[3]

Current treatment options for ADPKD are limited. Rigorous blood pressure control targeting the renin angiotensin system slows total kidney volume (TKV) growth but has no effect on kidney function decline.[4,5] Advancing knowledge of signalling pathways implicated in cyst growth and disease progression identified several potential therapies including somatostatin analogues, mammalian target of rapamycin inhibitors and metformin.[6,7]

The greatest advance has come from the recognition that vasopressin modulates cystogenesis. It binds to V2 receptors in the distal nephron and upregulates intracellular cyclic adenosine monophosphate production resulting in disrupted tubulogenesis, excessive epithelial proliferation and secretion, culminating in cyst formation and growth.[8–10] This understanding has led to licencing of the vasopressin receptor antagonist tolvaptan for ADPKD.[11,12] However, Tolvaptan access is limited through cost, geographic location and considerable side effect burden, restricting its use to more advanced disease.[3]

Vasopressin plays a pivotal role in osmoregulation.[13] and reducing its release by maintaining high water intake (HWI) is a viable alternative to tolvaptan, with the additional benefit of being a widely accessible affordable therapy commenced in early disease given the favourable risk-benefit balance.[14,15] Previous studies have indicated that HWI and solute restriction successfully lower urine osmolality (UOsm) and copeptin in ADPKD patients over the short-term.[16–18] However, none of these studies were performed in the tolvaptan-era. Furthermore a non-randomized study paradoxically found a possible detrimental effect of HWI on kidney function.[19] Demonstrating biological feasibility through measuring vasopressin is a challenge given its short half-life and concerns persist over reliability of copeptin, a surrogate for vasopressin, in CKD.[13,15,20–22] Alternative surrogates of vasopressin suppression include plasma and UOsm. UOsm is highly correlated with copeptin and vasopressin concentrations in ADPKD,[23] its ease of measurement makes it an ideal surrogate for large-scale trials. Although, a small intermediate-endpoint trial is currently underway to assess the effect of hydration on TKV[24] controversies regarding use of TKV as a surrogate for renal endpoints remain.[25] Therefore questions persist over feasibility of HWI trials in the presence of Tolvaptan access, safety of the intervention and the optimal renal outcome selection which is influenced by acute GFR effects.

We conducted a randomized controlled trial of high (HW) vs. *ad libitum* (AW) water intake in patients with ADPKD to assess the feasibility and inform the design of a large definitive trial in a developed healthcare setting with access to tolvaptan.

Materials and methods

Study design and participants

In this prospective, single-centre, open-label, randomized controlled Phase 2 trial, the objective was to determine feasibility of a definitive HWI trial. The study was co-produced by the PKD Charity and Patient Led Research Hub,[26] and the design and protocol have been reported previously.[27]

Participants were recruited from the Renal Genetics clinic at Addenbrooke's Hospital, Cambridge. The trial was advertised nationally via PKD Charity and RaDaR (National Registry of Rare Kidney Diseases) websites. We recruited subjects aged 16 years or over, with ADPKD and an estimated GFR $\geq$20 ml/min/1.73 m^2, able to self-monitor urine-specific gravity (USG). ADPKD Diagnosis was confirmed using the modified Pei-Ravine criteria,[28] with supportive evidence of a pathogenic ADPKD mutation if available. Exclusion criteria were; (i) advanced renal failure (eGFR <20 ml/min/1.73 m^2), (ii) fluid overload states or diuretics, (iii) other renal diseases and (iv) participants taking tolvaptan within 4-weeks of screening (Supplementary Table S1). All participants provided written informed consent. The study was approved by the East of England Essex Research Committee (16/EE/0026).

Randomization and masking

Participants were randomized (1:1) to either HW or AW intake groups using a sealed envelope system. The study was unblinded.

Procedures

HW group participants were given an individualized daily fluid prescription derived from the free-water clearance formula (Supplementary eTable S2a).[27] The AW group was advised to drink to thirst with a target UOsm $\geq$300 mOsm/Kg. At baseline, both groups were guided through trial smartphone application installation and given secure login details. They were provided with Siemens Multistix GP indicator strips and shown how to test their urine and read the USG. The HW group was asked to maintain a USG $\leq$ 1.010 (consistent with vasopressin suppression) and those in the AW group were asked to maintain USG > 1.010. Participants tested USG twice weekly between 4 and 8 pm, and recorded results via the app. Fluid intake was then titrated by participants according to USG using instructions signposted through the app (Supplementary Table S2b). Results could also be telephoned, emailed or texted.

Participants taking diuretics which could be stopped safely underwent a 2-week washout prior to inclusion.

Study evaluations were performed at baseline, Weeks 2, 4 and 8 and included physical examination with fluid-balance assessment (Supplementary Table S3). Blood pressure was assessed using an automated device (DINAMAP Carescape). Three measurements were taken after 5 min rest and the average of the second and third reported. Creatinine was measured using the Siemens Advia_2400 autoanalyser. Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[29] Plasma and spot UOsm were measured by the freezing point depression method (Advanced Instruments Model_3320). Urine indicator strip testing for proteinuria, haematuria and USG was performed using Siemens Multistix GP indicator strips, read by Siemens CliniTek Status+auto-analyser. Patients underwent dietary review to ensure moderate solute intake (sodium <2 g/day and protein 0.75–1 g/kg/day). Twenty-four-hour urine collections for osmolality and volume were obtained. In exploratory analyses, serum copeptin was analysed by the Department of Clinical Chemistry at the Royal Victoria Infirmary, Newcastle.

Outcomes

The primary outcomes were (i) the recruitment rate and potential, defined as the proportion of eligible participants enrolled and (ii) the proportion of the HW group that achieved a UOsm ≤270 mOsm/kg at Week 8.

Secondary outcomes included demonstration of separation in UOsm between treatment arms at Week 8, the proportion of participants able to reliably self-monitor and report USG, change in copeptin, determinations of acute changes in measured and estimated GFR between baseline and Week 4, and incidence of adverse events.

Statistical analysis

Data from a previous RCT has shown that Tolvaptan resulted in UOsm < 300 mOsm/kg in 81% vs. 17% (placebo).[30] We considered that similar proportions would be required for a clinically meaningful difference in kidney function decline rate. A minimum of 30 patients would yield 99% power at a two-sided alpha of 0.05 to detect target UOsm in 85% of the HW group, allowing for a 15% drop-out.

Categorical variables were reported as frequency (percent). Continuous variables were expressed as mean ± SD or median (interquartile range [IQR]). We assessed the change in UOsm over time using multi-level mixed effects models. In a basic model the outcome variable was assessed using an interaction term between visit number and treatment group as a fixed effects regression coefficient, with a random intercept accounting for between-subject variations. Further models added the following covariates to the fixed part of the model; age, gender, and eGFR. The odds of maintaining a low USG (≤1.010) were explored using logistic regression. Data were analysed by intention-to-treat. All tests were two-sided with ≤0.05 significance level. Analyses were performed using STATA-V.15 (College Station, TX).

Results

Between January 2017 and January 2018, 45% (42/93) of all eligible participants were enrolled at an average rate of 3.5 patients per month (Figure 1). Actual patient accrual exceeded this, but enrolment was limited by staffing capacity. Tolvaptan prescribing was introduced at our centre during the second study month in accordance with NICE guidelines.[31] There was some overlap in eligibility criteria between the study and Tolvaptan; however, DRINK did not require evidence of rapid disease progression and permitted the inclusion of lower eGFR cut-off (Tolvaptan cut-off eGFR ≥30 ml/min/1.73 m^2). Although 38% (35/93) were eligible for Tolvaptan, only 13% (12/93) commenced the drug. Forty-two participants were subsequently randomized to the HW ($n = 21$) or AW ($n = 21$) group (Figure 2). Thirty five participants completed the trial, with 7 (17%) withdrawals during the study (HW 4/21, 19%; AW 3/21, 14%). One participant (HW) was withdrawn due to a serious urinary tract infection requiring hospitalization; the remaining six subjects withdrew consent.

Baseline characteristics were similar between groups (Table 1). In total 57% were female, 88% (37) were of White British ethnicity and the mean age was 46 ± 13 years. Both median spot (352 mOsm/kg IQR 202–452) and 24-h (319 mOsm/kg IQR 251–420) UOsm were above the HW treatment target. Median eGFR was 75.8 ml/min/1.73 m^2 (IQR 46.5–107.5) and 81% of patients had at least one risk factor for progression (hypertension, microscopic haematuria, large kidney size).

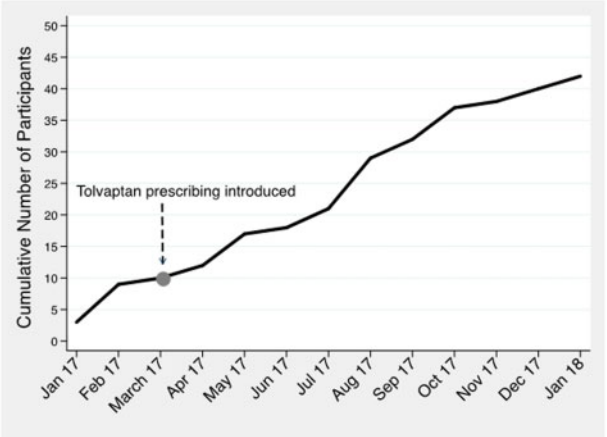

Figure 1. Cumulative number of participants enrolled each month from January 2017 until January 2018. Average recruitment was 3.5 participants per month. Tolvaptan prescribing was introduced in our centre in March 2017. Participants taking Tolvaptan were ineligible for the DRINK study.

In the HW group, mean fluid prescription at baseline was 3566 ± 834 ml. UOsm ≤270mOsm/kg was achieved in 14/21 (67%) patients in the HW group and 5/21 (24%) in the AW group at Week 8 ($P = 0.001$). In a *post hoc* per-protocol analysis (excluding withdrawals) this increased to 82 vs. 26%, respectively.

The 8-week median spot UOsm was 194 (IQR 157–255) mOsm/Kg for HW vs. 379 (IQR 235–503) for AW ($P = 0.01$). Mean difference from baseline to Week 8 in UOsm was −82 (SD ±158) mOsm/kg (HW) vs. 47 (SD ±141) mOsm/kg (AW, $P = 0.01$, Figure 3A). In a mixed effects regression model randomization to HW was associated with lower UOsm (ß −34.60 CI −67.26 to −1.93, $P = 0.04$). In a multivariable model adjusting for age, eGFR, and gender, only allocation to HW predicted a lower UOsm (Supplementary Table S4). By Week 8, median 24-h urine volume was higher in the HW group (3155 IQR 2270–4295 ml) compared with the AW group (1920 IQR 1670–2960 ml), $P = 0.02$. Although effects of HWI on UOsm and volume appeared to be greater at Week 2, this was not statistically significant.

Median USG was consistently ≤1.010 in the HW group and ≥1.015 in the AW group ($P = 0.0031$, Figure 3E). In the logistic regression model randomization to HW was associated with lower USG over time (β −0.20, 95% CI −0.31 to −0.08, $P = 0.001$). Increasing median spot UOsm correlated with higher USG category ($P = 0.0156$); for USG 1.005 the median UOsm 174 (IQR 139–210) compared with USG 1.030 where the median UOsm 462 (IQR 406–652) mOsm/kg (Supplementary Figure S2).

USG was performed and recorded for 79% (519/672) of time points, and this was similar between groups (HW 75% vs. AW 79%, $P = 0.232$). In total 70% (364/519) were submitted using the app (Supplementary Table S5).

In the HW group, serum osmolality decreased from baseline to Week 2 (290 ± 8–286 ± 8 mOsm/kg, $P = 0.09$, Figure 3B), but increased to 291 ± 7 mOsm/kg by Week 8. Conversely in the AW group serum osmolality increased by 2.5 ± 4 mOsm/kg, $P = 0.02$.

A small reduction in serum sodium concentration occurred in the HW arm after 2 weeks (138 (IQR 137–140) mmol/l vs. 139 (IQR 139–140) mmol/l, $P = 0.02$), although this was no longer significantly by Week 8 ($P = 0.27$, Figure 3C).

Baseline copeptin concentrations were low in both trial arms. In the HW arm, copeptin decreased from baseline after 2

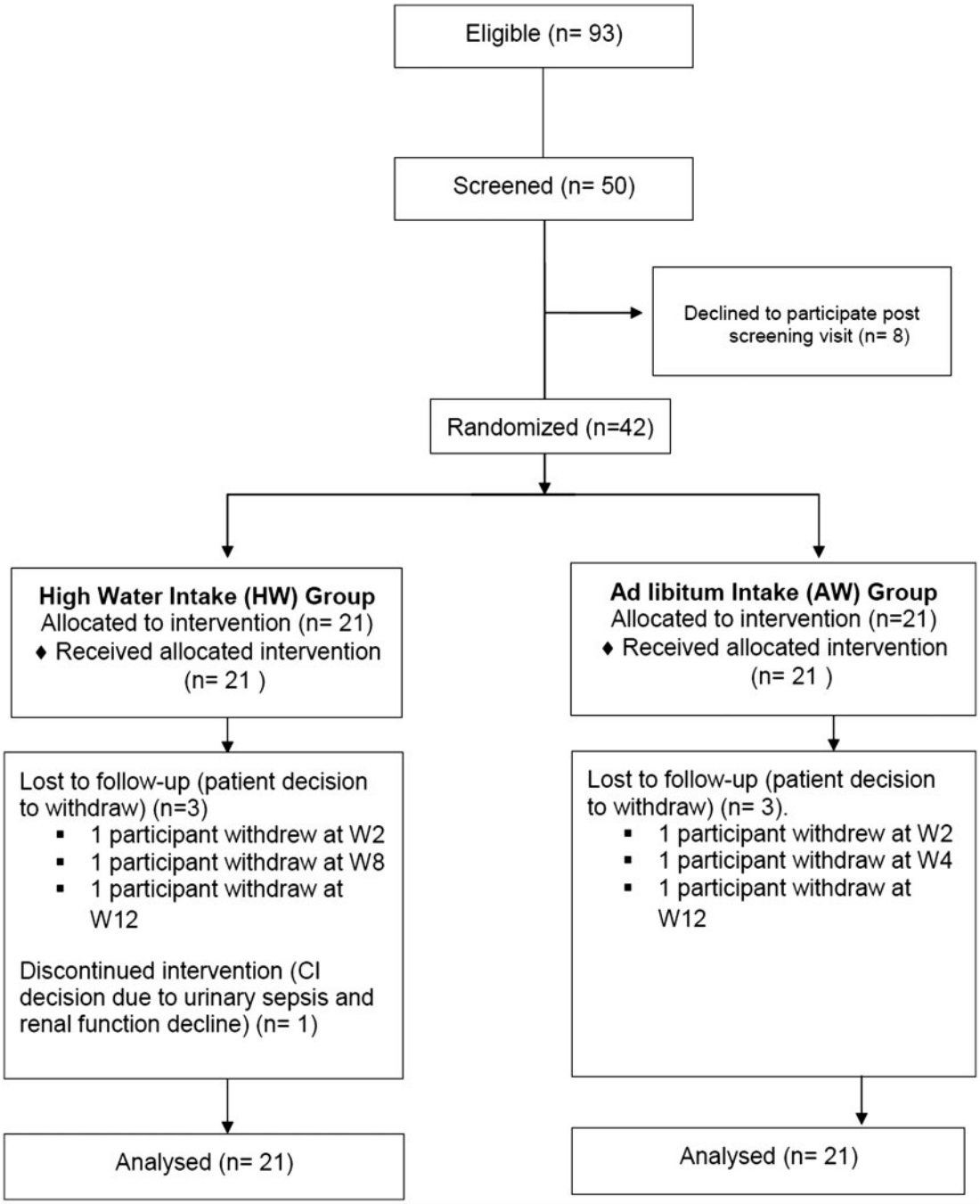

Figure 2. DRINK Study CONSORT flow diagram. A total of 50 patients were screened, 42 were randomized (HW = 21, AW = 21). Thirty-five participants completed the trial. One participant was withdrawn by the chief investigator for clinical reasons, two participants (one from HW and one from AW group) withdrew after the Week 8 visit as they were unable to attend the final appointment due to work commitments, three participants (two from HW and one from the AW) were unable to attend further appointments due to work/family commitments, and one participant in the AW group was uncontactable after the Week 2 visit.

weeks (mean difference −0.2 ± 0.5, $P = 0.0475$, Figure 3D). In the AW group copeptin increased from baseline to Week 8 (mean difference 0.2 ± 0.3, $P = 0.0093$). Median copeptin was lower in the HW group at Week 8 (HW 3.6 vs. AW 4.1, $P = 0.25$).

Estimated GFR after 8 weeks did not differ between the HW (79.3, 45.4–109.6 ml/min/1.73 m^2) and AW groups (77.5, 50.1–112.8 ml/min/1.73 m^2, $P = 0.56$). Change in eGFR from baseline to Week 8 was similar between HW (0.7, −0.8 to 6.2 ml/min/1.73 m^2) and AW (0.6, −5.0 to 3.6 ml/min/1.73 m^2) groups ($P = 0.52$, Figure 3F). In a substudy including 8 HW participants, 51Cr-EDTA measured GFR did not change from baseline (68, IQR 32–75 ml/min) to 4 weeks (71, IQR 47–76 ml/min, $P = 0.95$; Supplementary Figure S1).

Other parameters including weight, blood pressure, potassium, urea and creatinine levels, and 24-h urine solute excretion showed no change (Table 2).

There was no significant difference in adverse events between treatment groups (Table 3). In total 63% (5/8) were disease-related and included cysts infection, bleeding and pain. One serious adverse event (renal cyst infection requiring

Table 1. Baseline characteristics by treatment group. Values are reported as number (%), mean ± SD, median (IQR)

Baseline demographic and clinical characteristics	AW group ($n = 21$)	HW group ($n = 21$)
Female	12 (57)	12 (57)
White British	18 (86)	18 (86)
Age (years)	44 ± 12	49 ± 13
Age at diagnosis (years)	31 ± 14	32 ± 15
Positive family history	18 (86)	18 (86)
Previous surgical intervention	0 (0)	1 (5)
Extra-renal manifestations	10 (48)	13 (62)
Hepatic cysts	10 (48)	12 (57)
Intracranial aneurysms	0 (0)	4 (19)
Cardiac valve abnormalities	0 (0)	2 (10)
Anti-hypertensives	10 (48)	17 (81)
Renin–angiotensin inhibition	8 (38)	13 (62)
Calcium channel blockers	6 (29)	10 (48)
Diuretics	3 (14)	2 (10)
Alpha blocker	2 (10)	4 (19)
Other	3 (14)	4 (19)
Comorbidities	16 (76)	17 (81)
Hypertension	11 (52)	16 (76)
Stroke	0 (0)	1 (5)
Liver disease	1 (5)	2 (10)
Ischaemic heart disease	0 (0)	0 (0)
Lung disease	2 (10)	2(10)
Migraine	2 (10)	1 (5)
Large kidney size	14 (67)	15 (71)
Physical parameters		
Height centimetres	176.6 ± 10.4	172.0 ± 10.7
Weight kilograms	79.0 (67.1–88.6)	75.0 (66.5–84.0)
Body mass index	25 (21–31)	25 (22–31)
Systolic BP (mmHg)	134 ± 19	139±12
Diastolic BP (mmHg)	79 (74–87)	84 (76–91)
MAP (mmHg)	95 (91–104)	102 (97–107)
Blood biochemical parameters		
Sodium (mmol/l)	139 (138–140)	139 (138–140)
Potassium (mmol/l)	4.2 (4.0–4.2)	4.5 (4.2–4.6)
Creatinine (μmol/l)	91 (62–115)	94 (66–149)
eGFR ml/min/1.73 m^2 (CKD-EPI)	75.8 (59.0–111.0)	68.4 (35.9–107.2)
eGFR ≥ 60 ml/min/1.73 m^2	15 (71)	11 (52)
Serum osmolality (mOsm/kg)	290 ± 6	290 ± 8
24-h urine parameters		
Urine volume (ml/day)	2680 (2145–3480)	2403 (2042–3545)
UOsm (moSm/kg/day)	338 (259–409)	308 (229–437)
Urine solute excretion (mOsm)	757 (658–1068)	762 (672–957)
Spot urine parameters		
UOsm (mOsm/kg)	350 (240–452)	353 (190–438)
Automated USG	1.015 (1.010–1.015)	1.010 (1.010–1.015)
Haematuria	7 (33)	4 (19)
Proteinuria	2 (10)	3 (14)

hospitalization) occurred in the HW group. There were two cases of hyponatraemia (Na <132 mmol/l) in the HW group, in patients with an eGFR of 28 and 57 ml/min/1.73 m^2. Participants received dietary reviews to ensure adequate salt intake and fluid prescriptions were reduced with resolution in both cases.

Discussion

This randomized trial confirms the willingness of patients in a developed healthcare setting with tolvaptan access to be randomly assigned to HW or AW intake, at a rate of enrolment that implies successful recruitment to a multi-centre large-scale trial is feasible. A high degree of sustained adherence resulted in important differences between trial arms in UOsm, self-monitored USG, plasma osmolality, sodium and urine volume. Our findings are congruent with previous reports indicating that HWI in ADPKD[17,19] and unselected CKD[32] could result in vasopressin suppression, and suggest that it is plausible to observe a biological effect on kidney function in a definitive trial.

Baseline copeptin was lower in our trial population than in other interventional studies,[17,19] reflecting contemporary specialist clinic advice to consume HWI exceeding 3 l/day. The magnitude of copeptin reduction may therefore have been smaller compared with populations where HWI is not current practice. Further, copeptin was not a primary

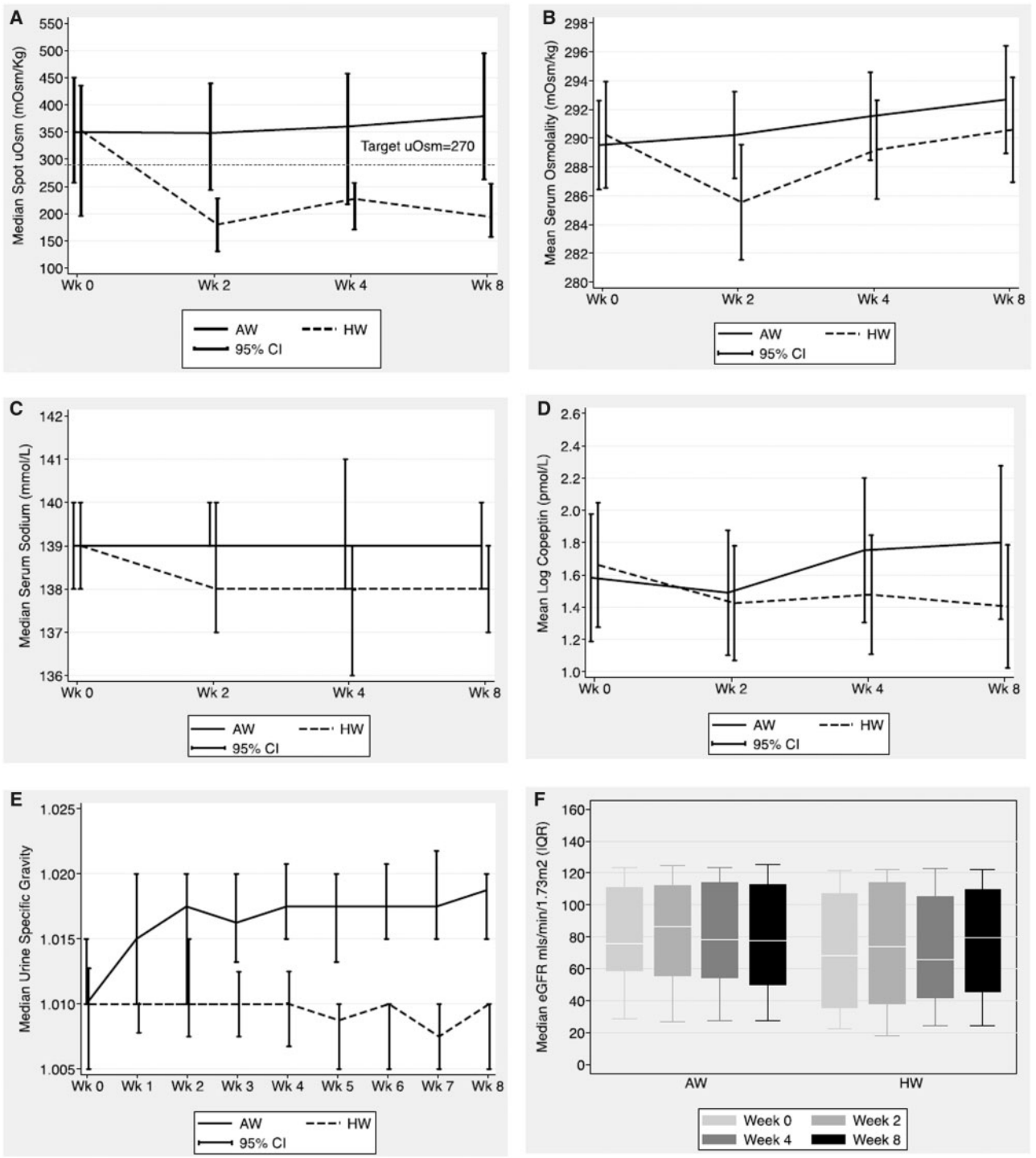

Figure 3. Median spot UOsm was lower in the HW intake arm (**A**). By Week 2 there was a small decrease in serum osmolality (**B**) and sodium (**C**) in the HW group, but this difference was not maintained at Week 8. Log copeptin (**D**) increased in the AW group, and although there was a decrease in the HW group by Week 2 this was not maintained. Median USG was maintained at $\leq$1.010 in the HW group (**E**) and there were no acute effects on estimated glomerular filtration rate (**F**).

measure of separation in the present trial due to uncertainty over whether it is a reliable surrogate for vasopressin in CKD.[21,33] Nevertheless, we observed only modest changes in copeptin.

We report adherence to allocated treatment, sustained for two months. Patients' self-monitored USG, submitting data remotely with a high degree of completeness. As USG reliably predicted measured UOsm, remotely monitored USG can be incorporated in an efficient, pragmatic large trial design.

Although our trial was not powered to detect differences in adverse events, two patients in the HWI arm developed hyponatraemia. Given current recommendations[1] of maintaining HWI in ADPKD, along with previous reports of an unexpected association with more rapid kidney function decline,[19] there is an

Table 2. Results for surrogate biomarkers of vasopressin (UOsm and urine volume, serum sodium, serum osmolality and copeptin levels) and secondary outcomes (serum potassium, creatinine and urea, mean arterial blood pressure, weight and urine solute excretion) are shown for each time point

Time point	AW group ($n = 21$)	HW group ($n = 21$)	P-value
24-h UOsm, median (IQR) (mOsm/kg)			
Week 0	338 (259–409)	308 (229–437)	
Week 2	356 (271–437)	208 (181–244)	0.0004
Week 8	369 (341–461)	257 (223–296)	0.0017
24-h urine volume, median (IQR) (ml)			
Week 0	2680 (2145–3480)	2403 (2042–3545)	
Week 2	2380 (2170–3200)	3460 (2420–4670)	0.04
Week 8	1920 (1670–2960)	3155 (2270–4295)	0.02
Serum sodium, median (IQR) (mmol/l)			
Week 0	139 (138–140)	139 (138–140)	
Week 2	139 (139–140)	138 (137–140)	0.03
Week 4	139 (138–141)	138 (136–139)	0.04
Week 8	139 (138–140)	138 (137–139)	0.17
Serum copeptin, median (IQR) (pmol/l)			
Week 0	3.9 (3.0–7.6)	4.0 (3.2–7.2)	
Week 2	3.9 (2.7–7.6)	3.4 (2.5–6.7)	0.56
Week 4	4.6 (2.6–10.3)	3.6 (2.4–7.0)	0.37
Week 8	4.1 (2.9–11.2)	3.6 (2.7–5.7)	0.25
Serum osmolality, mean (SD) (mOsm/kg)			
Week 0	290 (6)	290 (8)	
Week 2	290 (6)	286 (8)	0.05
Week 4	292 (6)	289 (7)	0.3
Week 8	293 (8)	291 (7)	0.4
Serum potassium, median (IQR) (mmol/l)			
Week 0	4.2 (4.0–4.2)	4.5 (4.2–4.6)	
Week 8	4.2 (4.1–4.4)	4.3 (4.1–4.8)	0.44
Serum creatinine (mmol/l)			
Week 0	91 (62–115)	94 (66–149)	
Week 8	97 (61–124)	85 (65–135)	0.65
Serum urea, median (IQR) (mmol/l)			
Week 0	6.5 (5.2–8.4)	7.0 (5.2–12.1)	
Week 8	6.5 (4.9–8.7)	6.0 (4.6–9.0)	0.99
Mean arterial blood pressure, median (IQR) (mmHg)			
Week 0	95 (91–104)	102 (92–107)	
Week 8	94 (88–102)	95 (90–111)	0.33
Weight, median (IQR) (kg)			
Week 0	79.0 (67.1–88.6)	75.0 (66.5–84.0)	
Week 8	78.4 (64.2–96.4)	74.7 (66.0–85.0)	0.48
Total urine solute excretion[a], median (IQR) (mOsm)			
Week 0	757 (658–1068)	762 (672–957)	
Week 8	828 (669–1011)	802 (677–907)	0.72

[a]Total urine solute was calculated from the UOsm and urine volume derived from 24 h urine collections.

Table 3. Incidence of adverse events by treatment group allocation, $P > 0.05$

Adverse event	AW group	HW group
Hyponatraemia	0	2 (10%)
Hypertension	0	1 (5%)
Renal cyst infection	0	1 (5%)
Loin pain and haematuria	0	2 (10%)
Macroscopic haematuria	2 (10%)	0
Urinary tract infection	2 (10%)	1 (5%)
Feeling bloated	0	1 (5%)

urgent need to conduct a definitive trial to assess safety and efficacy.

Our trial has several strengths, including its randomized nature, assessment of pragmatic design components, use of efficient self-monitoring approaches, patient engagement and conduct in a setting with tolvaptan access. Further, the exclusion of acute effects on measured GFR allows simple approaches to renal function endpoints in future trials. However, we demonstrated adherence over 8 weeks, long-term sustainability is unknown and will require monitoring in a definitive trial. Our study did not enrich the population for high risk progressors[34,35] and some uncertainty regarding replication in higher risk populations remains. Finally, the study was not powered to assess safety or efficacy.

Conclusion

Our findings suggest that a HWI trial in ADPKD is feasible, and the adherence-promoting methods were effective and acceptable. The risks of HWI in patients with ADPKD and reduced GFR remain unknown and benefits unproven, yet HWI advice is routine. This study provides data of fundamental importance for the design of a large-scale HWI trial. Several challenges remain a definitive trial with primary kidney function outcomes necessitates a reasonable sample size and therefore enrichment with high risk progressors. This may be a particular challenge in developed countries as tolvaptan adoption increases along with the emergence of other competing studies.

Supplementary material

Supplementary material is available at *QJMED* online.

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Conflict of interest: None declared.

References

1. Chapman AB, Devuyst O, Eckardt K-U, Gansevoort RT, Harris T, Horie S, *et al.* Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2015; **88**:17–27.
2. Antignac C, Calvet JP, Germino GG, Grantham JJ, Guay-Woodford LM, Harris PC, *et al.* The future of polycystic kidney

disease research—as seen by the 12 Kaplan awardees. *J Am Soc Nephrol* 2015; **26**:2081–95.
3. Gansevoort RT, Arici M, Benzing T, Birn H, Capasso G, Covic A, *et al*. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. *Nephrol Dial Transplant* 2016; **31**:337–48.
4. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, *et al*. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med* 2014; **371**:2255–66.
5. Torres VE, Abebe KZ, Chapman AB, Schrier RW, Braun WE, Steinman TI, *et al*. Angiotensin blockade in late autosomal dominant polycystic kidney disease. *N Engl J Med* 2014; **371**: 2267–76.
6. Chang M-Y, Ong A. New treatments for autosomal dominant polycystic kidney disease. *Br J Clin Pharmacol* 2013; **76**: 524–35.
7. Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. *Lancet* 2019; **393**:919–35.
8. Devuyst O, Torres VE. Osmoregulation, vasopressin, and cAMP signaling in autosomal dominant polycystic kidney disease. *Curr Opin Nephrol Hypertens* 2013; **22**:459–70.
9. Belibi FA, Edelstein CL. Novel targets for the treatment of autosomal dominant polycystic kidney disease. *Expert Opin Investig Drugs* 2010; **19**:315–28.
10. Torres VE, Harris PC. Autosomal dominant polycystic kidney disease: the last 3 years. *Kidney Int* 2009; **76**:149–68.
11. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, *et al*. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; **367**:2407–18.
12. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Koch G, *et al*. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med* 2017; **377**:1930–42.
13. Bankir L, Bichet DG, Morgenthaler NG. Vasopressin: physiology, assessment and osmosensation. *J Intern Med* 2017; **282**: 284–97.
14. Torres VE, Bankir L, Grantham JJ. A case for water in the treatment of polycystic kidney disease. *Clin J Am Soc Nephrol* 2009; **4**:1140–50.
15. van Gastel MDA, Torres VE. Polycystic kidney disease and the vasopressin pathway. *Ann Nutr Metab* 2017; **70**:43–50.
16. Barash I, Ponda MP, Goldfarb DS, Skolnik EY. A Pilot clinical study to evaluate changes in urine osmolality and urine cAMP in response to acute and chronic water loading in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2010; **5**:693–7.
17. Amro OW, Paulus JK, Noubary F, Perrone RD, OWAMD MS, ScD JKP, *et al*. Low-osmolar diet and adjusted water intake for vasopressin reduction in autosomal dominant polycystic kidney disease: a pilot randomized controlled trial. *Am J Kidney Dis* 2016; **68**:882–91.
18. Wang CJ, Creed C, Winklhofer FT, Grantham JJ. Water prescription in autosomal dominant polycystic kidney disease: a pilot study. *Clin J Am Soc Nephrol* 2011; **6**:192–7.
19. Higashihara E, Nutahara K, Tanbo M, Hara H, Miyazaki I, Kobayashi K, *et al*. Does increased water intake prevent disease progression in autosomal dominant polycystic kidney disease? *Nephrol Dial Transplant* 2014; **29**:1710–9.
20. Bolignano D, Cabassi A, Fiaccadori E, Ghigo E, Pasquali R, Peracino A, *et al*. Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology. *Clin Chem Lab Med* 2014; **52**:1–10.
21. Ettema EM, Heida J, Casteleijn NF, Boesten L, Westerhuis R, Gaillard C, *et al*. The Effect of renal function and hemodialysis treatment on plasma vasopressin and copeptin levels. *Kidney Int Rep* 2017; **2**:410–9.
22. Engelbertz C, Brand E, Fobker M, Fischer D, Pavenstädt H, Reinecke H. Elevated copeptin is a prognostic factor for mortality even in patients with renal dysfunction. *Int J Cardiol* 2016; **221**:327–32.
23. Zittema D, Casteleijn NF, Bakker SJL, Boesten LSM, Duit AAM, Franssen CFM, *et al*. Urine concentrating capacity, vasopressin and copeptin in ADPKD and IgA nephropathy patients with renal impairment. *PLoS One* 2017; **12**:e0169263–14.
24. Wong ATY, Mannix C, Grantham JJ, Allman-Farinelli M, Badve SV, Boudville N, *et al*. Randomised controlled trial to determine the efficacy and safety of prescribed water intake to prevent kidney failure due to autosomal dominant polycystic kidney disease (PREVENT-ADPKD). *BMJ Open* 2018; **8**: 1–13.
25. Smith KA, Thompson AM, Baron DA, Broadbent ST, Lundstrom GH, Perrone RD. Addressing the need for clinical trial end points in autosomal dominant polycystic kidney disease: a report from the polycystic kidney disease outcomes consortium (PKDOC). *Am J Kidney Dis* 2019; **73**:533–41.
26. Mader LB, Harris T, Kläger S, Wilkinson IB, Hiemstra TF. Inverting the patient involvement paradigm: defining patient led research. *Res Involv Engagem* 2018; **4**:367.
27. El-Damanawi R, Lee M, Harris T, Mader LB, Bond S, Pavey H, *et al*. Randomised controlled trial of high versus ad libitum water intake in patients with autosomal dominant polycystic kidney disease: rationale and design of the DRINK feasibility trial. *BMJ Open* 2018; **8**:e022859.
28. Pei Y, Obaji J, Dupuis A, Paterson AD, Magistroni R, Dicks E, *et al*. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009; **20**:205–12.
29. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**:604–12.
30. Devuyst O, Chapman AB, Gansevoort RT, Higashihara E, Perrone RD, Torres VE, *et al*. Urine osmolality, response to tolvaptan, and outcome in autosomal dominant polycystic kidney disease: results from the TEMPO 3: 4 trial. *J Am Soc Nephrol* 2017; **28**:1592–602.
31. *Tolvaptan for Treating Autosomal Dominant Polycystic Kidney Disease | Guidance | NICE*. NICE. https://www.nice.org.uk/guidance/ta358/chapter/1-Guidance (3 September 2019, date last accessed).
32. Clark WF, Sontrop JM, Huang S-H, Gallo K, Moist L, House AA, *et al*. Effect of coaching to increase water intake on kidney function decline in adults with chronic kidney disease. *JAMA* 2018; **319**:1810–70.
33. van Gastel MDA, Meijer E, Scheven LE, Struck J, Bakker SJL, Gansevoort RT, *et al*. Modifiable factors associated with copeptin concentration: a general population cohort. *Am J Kidney Dis* 2015; **65**:719–27.
34. Irazabal MV, Rangel LJ, Bergstralh EJ, Osborn SL, Harmon AJ, Sundsbak JL, *et al*. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol* 2015; **26**:160–72.
35. Cornec-Le Gall E, Audrezet MP, Rousseau A, Hourmant M, Renaudineau E, Charasse C, *et al*. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2016; **27**:942–51.