Published in final edited form as:

Clin Transplant. 2015 March ; 29(3): 261–267. doi:10.1111/ctr.12514.

Daily Fluid Intake and Outcomes in Kidney Recipients: Post hoc analysis from the randomized ABCAN trial

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Abstract

Generous and even excessive fluid intake is routinely recommended to kidney transplant recipients despite minimal evidence to support this practice. We hypothesized that increased fluid intake, ascertained by 24-hour urine volume output, may adversely affect graft outcomes as it would impose an extra workload on a limited number of nephrons. Kidney transplant recipients who were randomized to losartan vs. placebo in the ABCAN trial (n=153) underwent baseline, five-year biopsies and annual iothalamate GFR assessment. Recipients with higher urine volume at randomization had higher urinary sodium and also higher urinary protein. The proportion using diuretics or CNI based regimens were similar across urinary volume tertiles. The highest urinary volume tertile (>2.56 L/day) did not predict the development of interstitial volume doubling or ESRD from IF/TA (OR=3.52, 95% CI 0.4, 38.15, p=0.26), interstitial volume doubling or all-cause ESRD (OR=7.04, 95% CI 0.66, 74.87, p=0.10), and was not associated with the conventional endpoint of doubling serum creatinine, all cause ESRD, or death (OR=0.89, 95% CI 0.21, 3.71, p=0.87). These results suggest that the current practice of liberal fluid intake may not be beneficial in low risk and mostly Caucasian transplant recipients.

Keywords

fluid intake; kidney; graft failure

Introduction

The general public is inundated with messages to drink 8 glasses of water daily for good health; a prime example is the recent “Drink up” campaign sponsored by the Partnership for a Healthier America in collaboration with First Lady Michelle Obama. It is thought that high fluid intake may confer a renoprotective effect on kidney function in disease states (1). Work supporting this notion has been primarily based on rat models that attribute the beneficial effects of generous fluid intake to suppression of antidiuretic hormone which has

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Disclosure:

The authors of this manuscript have no conflicts of interest to disclose.

been linked to hyperfiltration-mediated injury (2,3). In clinical renal disease, however, Hebert et al. reported accelerated GFR decline in those with CKD stage 3–4 with increasing urine volume potentially explained by pressure-induced glomerulosclerosis (4,5). Furthermore, the benefit of high fluid intake for the prevention of chronic kidney disease is unproven, including in the setting of kidney transplantation (1,6–9). It is, of course, obvious that preventing volume depletion particularly early after transplant when the maximum concentrating ability has not been achieved is important particularly when calcineurin inhibitors are kept at higher blood levels.

The NIH sponsored Angiotensin II Blockade for Chronic Allograft Nephropathy (ABCAN) trial was a randomized double-blind placebo-controlled trial that provides a unique opportunity to assess the relationship between urine volume (as a surrogate of daily fluid intake) with a variety of important functional and structural indices of renal function (10). We hypothesized that a higher urine volume offers no protection from renal damage and may actually be associated with worse outcomes as it engenders a greater workload for a limited and already challenged number of nephrons.

Methods

The Angiotensin II Blockade for Chronic Allograft Nephropathy (ABCAN) trial (Clinical Trial # NCT00067990) was a 5-year randomized double-blind placebo-controlled trial that evaluated the efficacy of losartan (100 mg/day) vs. placebo in the prevention of interstitial fibrosis/tubular atrophy (IF/TA) in 153 kidney transplant recipients. Subjects were recruited from two transplant centers in Minneapolis, Minnesota and randomized at 58 ± 34 days following transplantation. The study was approved by the University of Minnesota Institutional Review Board, (IRB# 0007M59161), and informed consent was obtained from each participant. The primary endpoint was a composite of doubling of the cortical volume occupied by interstitium (VvInt/C) in biopsies obtained at baseline and five years later and also ESRD from biopsy proven IF/TA. At the end of the trial there was a modest but not statistically significant benefit in losartan treated recipients (OR=0.39, 95% CI 0.13–1.15, $p=0.08$). Moreover, there were no significant differences in time to end stage renal disease (ESRD), death, or doubling creatinine level though the losartan treated group did have a reduced risk of the a priori defined secondary endpoint of doubling interstitial volume or all-cause ESRD. A detailed description of the study design and results has been previously published (10).

Study Population

The ABCAN trial included adults who were recipients of a first or second kidney transplant. Exclusion criteria included serum creatinine ≥ 2.5 mg/dL, potassium >5.4 mEq/L, allograft artery stenosis, primary renal disease with high risk of recurrence including primary hyperoxaluria, dense-deposit disease, severe focal segmental glomerulosclerosis, or atypical hemolytic uremic syndrome. Recipients with HLA-identical donors (minimal risk of graft loss in 5 years), women of child-bearing age who were unable or unwilling to use contraceptives during the trial and recipients who required ACE inhibitors or AII blockers for a cardiovascular indication were also excluded (10). Participants were randomized

shortly after transplantation, underwent baseline and 5 year allograft biopsies in addition to annual iothalamate GFR measurements and 24 hour urine collection.

Clinical and laboratory measurements

Baseline and annual evaluations included multiple blood pressure measurements, iothalamate GFR and 24-hour urine protein and albumin measurements. Iothalamate GFR was determined utilizing 5 accurately timed urine and blood collections and measured by HPLC method; the coefficient of variation was <8%. Albumin was measured by immunoturbidimetry. All assays were performed at the University of Minnesota Laboratories. Baseline allograft biopsies were performed either intra-operatively or in the early post-transplant period with a follow up biopsy performed at five years. Cortical volume occupied by interstitium (VvInt/C) was estimated by point counting as previously described (11).

Statistical Analysis

Participants were divided into tertiles based on 24-hour urine volume (<1.73 L/day, 1.73–2.56 L/day, and >2.56 L/day) and 24-hour urine sodium (<128 meq/L/day, 128–191 meq/L/day, and >191 meq/L/day) at time of randomization. Demographic comparisons were performed using chi-squared tests for categorical variables and t-tests or ANOVA for continuous variables amongst the tertiles. Linear and mixed linear models were utilized using backwards selection to assess significant predictors of urine volume and urine sodium at baseline and also over time. In assessing both urine volume and urine sodium as a predictor variable, a multivariate logistic regression model was constructed to evaluate the association between baseline urine volume as well as potential confounders with the primary outcome of doubling of VvInt/C or ESRD from IF/TA, and for the secondary outcomes of 1) doubling of VvInt/C or all cause ESRD and 2) doubling of serum creatinine, all cause ESRD or death. A multivariate linear regression model was also used to evaluate the association between baseline variables including urine volume and VvInt/C at 5-years, last GFR, last urine albumin to creatinine ratio (ACR) and VvInt/C change from baseline to five years. A multivariate mixed linear regression model using fixed effects was used to evaluate the association between time-varying urine volume and time-varying GFR and ACR. In addition, ANOVA testing was performed to evaluate GFR change over five years by baseline urine volume tertile using Tukey adjustment. Cox proportional hazards regression with both fixed and time to event analysis was utilized to assess association of urine volume and urine sodium with allograft outcomes. Given the fact that doubling of the VvInt/C was assessed for participants at five years, this outcome was not considered in a time-dependent model. Instead, the secondary composite outcome of doubling of creatinine, ESRD or death was used. Adjustment in all models included urine volume, urine sodium, randomization group (losartan vs. placebo), recipient sex, age, race, BMI, iothalamate GFR, ACR, systolic blood pressure (SBP), diastolic blood pressure (DBP), diuretic use, donor age, gender, source and ethnicity, HLA matches (<3 vs. ≥3), cause of kidney disease, hypertension, acute rejection and immunosuppressive regimen (tacrolimus vs. cyclosporine and steroids use). All analyses were performed in SAS version 9.3 (Cary, NC). Results are expressed as mean ± SD, unless otherwise specified.

Results

A total of 148 subjects were studied in detail with a mean age of 49.2 ± 11.8 years; 61.5% were male, and 86.5% were Caucasian (Table 1). Baseline iothalamate GFR was 55.9 ± 16.9 ml/min/1.73m² and baseline biopsies revealed a cortical interstitium volume of 18.5 ± 4.9 %. Hypertension and diabetes were present in 71% and 40% of the participants, respectively. Tacrolimus based immunosuppression was prescribed in 44% and cyclosporine in 45%. In total, 33% of the participants were on a diuretic at the time of randomization. Graft and patient status at 5 years were known in all 153 participants.

Of the 148 participants with complete data, 49 had a 24 hour baseline urine volume <1.73 L/day, 50 were between 1.73–2.56 L/day and 49 exceeded 2.56 L/day. For each 10mEq/L/day increase in urine sodium at baseline, urine volume increased 50 mL/day ($p<0.01$). Those in the highest urine volume tertile had significantly higher urinary sodium and protein. There were no differences in age, gender, race, donor type, diabetes, iothalamate GFR, tobacco use, or medication regime across the tertiles. The final visit was completed by 88 subjects (60 subjects died, reached ESRD in the first 5 years or withdrew) of which, 28.4% had a baseline urine volume less than 1.73 L/day, 36.4% were between 1.73–2.56 L/day and 35.2% were greater than 2.56 L/day. The mean urine volume was 2.22 ± 1.03 L/day at visit one and 2.31 ± 0.92 L/day at exit with no significant difference amongst the visits in between (Figure 1). In contrast to the baseline visit, there was no relationship between 24-hour urinary sodium and volume at study end.

Baseline urinary volume and GFR, proteinuria and histological changes at study end

The highest urinary tertile (compared to lowest) was not associated with GFR, ACR, VvInt/C at study end or the change in these outcomes over the trial period (Table 2). The detailed results of the multivariate analysis addressing baseline urinary volume and these outcomes is provided in the supplemental material (Table S1).

Baseline urinary sodium and GFR, proteinuria and histological changes at study end

The highest urinary sodium tertile (compared to lowest) was not associated with GFR, ACR or VvInt at study end nor was it associated with change in ACR over the trial period, however the highest urinary sodium tertile was associated with change in GFR over time (OR = 4.32, 95% CI 0.13, 8.5, $p=0.04$).

Urinary volume and urinary sodium as predictors of the trial's primary and secondary endpoints

For the primary trial endpoint of doubling of interstitium or ESRD from IF/TA, there was no association with the highest urinary volume tertile (OR=3.52, 95% CI 0.4, 31.24, $p=0.26$) nor the highest urinary sodium tertile (OR=0.79, 95% CI 0.11, 5.62, $p=0.81$) (Table 3). Cyclosporine use was protective while having <3 HLA matches and acute rejection was associated with 8-fold and 21-fold increased risk of the outcome (OR=8.44, 95% CI 1.44, 49.47, $p=0.02$) and (OR=21.99, 95% CI 2.41, 200.58, $p=0.01$) respectively. When all causes of ESRD in addition to VvInt/C doubling were considered, the highest urinary volume tertile was associated with over a 7-fold increase in risk but this did not reach the conventional $p <$

0.05 (OR=7.04, 95% CI 0.66,74.87, p=0.11). Losartan use was protective (OR=0.16, 95% CI 0.03,0.87, p=0.03) while <3 HLA matches and acute rejection was associated with increased risk.. For the more conventional endpoint of doubling of creatinine, ESRD or death, acute rejection was associated with increased risk but neither the highest urine volume nor urine sodium teriles were associated with increased risk (Urine volume OR=0.89, 95% CI 0.21, 3.71, p=0.87; Urine sodium OR=1.19, 95% CI 0.27,5.33, p=0.82).

Urinary volume and urinary sodium as predictors of time to primary and secondary endpoints

In the Cox proportional hazard utilizing time dependent covariates we found that female sex, and receipt of a kidney from white donor reduced the risk of all cause ESRD while a higher albumin creatinine ratio and <3 HLA matches were associated with higher risk of all cause ESRD (Table 4). Neither urine volume nor urine sodium were associated with this outcome. For doubling of creatinine, ESRD or death, both urine volume and urine sodium were not predictive.

Discussion

These results suggest that high urine volume, a reasonable but imperfect surrogate of fluid intake, has neither a favorable nor adverse impact on multiple functional and structural endpoints in kidney transplant recipients within the first five years of receiving their allograft. The modest association (p=0.11) with VvInt/C doubling and all cause ESRD is curious but may simply reflect the small sample size or the imprecision of the estimate as evidenced by the extremely wide confidence interval (95% CI 0.66 – 74.87).

Our findings are consistent with two previous studies that have assessed the effects of increased water consumption on graft function (8,9). Gordon et al. interviewed 88 recipients 2 months after receiving a kidney regarding adherence to the center recommended >3 L/day fluid intake. The cohort was followed prospectively for 12 months and multivariate regression models were used to determine the impact of adherence to recommended fluid intake with mean change in eGFR (8). This group concluded there was no relationship between high fluid intake and eGFR at both 6 and 12 months post-transplant. This study had a 43% recruitment attrition rate making the practice of recommending high fluid intake questionable from a practical standpoint, above and beyond the finding that high fluid intake had no impact on change in eGFR in the first year after transplantation.

Similar observations were made by Magpantay et al. who randomized 62 long-term kidney transplant recipients to >4L/day (high fluid intake) or 2L/day (normal fluid intake) (9). This group found that increased fluid intake (compared to normal fluid intake) resulted in no immediate improvement in kidney function or change in progression of renal disease over 12 months. However, results from these studies were hindered by small sample size, short follow-up, self-reporting and non-adherence to the assigned fluid volume intake in many recipients. Also of note, patients in the normal fluid intake group were significantly older and had transplants of longer duration possibly putting this group at higher risk for worse outcomes.

Previously, Clark et al. reported an inverse relationship between 24-hour urine volume and rate of eGFR decline in 2148 subjects with preserved renal function (6). Outcomes were categorized as <1%, 1–4.9% (mild-to-moderate) or ≥5% (rapid) annual change in eGFR. Overall, participants had a decline in eGFR of 1% with 40% sustaining a mild-to-moderate decline, and 10% suffering a rapid decline. Those with a urine volume ≥3L/day were less likely to have GFR decline mild-to-moderate or rapid decline in eGFR over a median of 5.7 years. While our results do not corroborate these findings, inherent differences in the populations studied make it difficult to compare as Clark et al. studied only those with an eGFR >60ml/min/1.73m² whereas recipients contend with diseases necessitating transplant, half the number of functioning nephrons and the adverse hemodynamic effects of certain immunosuppression regimens. Thus, it is not surprising that kidney transplant recipients may not see the same beneficial effects encountered in those with preserved kidney function. Also, a more recent report from a general population study of 3858 older Australian adults found no significant relationship between fluid intake from the consumption of food and beverages (excluding water) and eGFR over a 10 year period (7). These results should be interpreted with caution as the mean age of participants was 70.3 ± 9.9 years and serial creatinine values were available for only 31% of those studied.

Hebert et al. performed a retrospective analysis of Modification of Diet in Renal Disease (MDRD) study consisting of 139 CKD patients with polycystic kidney disease (PKD) and 442 CKD patients without PKD (4). They demonstrated that higher urine volumes were associated with more rapid progression of GFR decline as estimated by iothalamate clearance in patients with and without PKD over a mean of 2.3 years. The greatest rate of GFR decline was observed in those with a urine volume >2.85 L/day (4). Reassuringly, our results are not in that direction except for the modest and non-statistical association with VvInt/c doubling and all cause ESRD. The association described by Hebert et al. may have been related to a higher likelihood of diuretic use in those who were already at high risk for progression. Of note, we did not find the use of diuretics to be associated with urine volume in this study. It is easily conceivable that patients with progressive CKD have higher urine output due to inability to concentrate their urine though in our study urine volume remained largely unchanged over the 5 year period (12–16).

This study is limited in that it is observational and does not compare the impact of high vs. low fluid intake on kidney allograft outcomes in a controlled fashion. Fluid intake was not directly measured in this study though urine volume appears to be a reasonable surrogate as detailed human fluid balance studies found that urine volume accounts for about 60% of total water output; the remaining being accounted for by insensible and gastrointestinal losses (17). It should also be noted that our participants were relatively low risk being predominately white and over half had a living donor, thus our results may not be applicable to the general transplant population. The conclusions drawn from this small study may not be relevant to higher risk individuals and those living in a different climate than Minnesota. Lastly, tacrolimus based regimens have now become almost universal and whether this practice would alter the association we observed remains to be seen.

In conclusion, volume depletion should certainly be avoided in transplant patients particularly early on as the concentrating ability of the new allograft is not yet complete. The

general recommendation to “push water”, however, seems to be of no benefit and may burden many recipients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding for this project was provided by NIDDK, U01 DK06070609 and Merck Inc. donated losartan and the placebo.

Abbreviations

ACR	albumin to creatinine ratio
ADH	antidiuretic hormone
CKD	chronic kidney disease
DBP	diastolic blood pressure
ESRD	end stage renal disease
IF/TA	interstitial fibrosis/ tubular atrophy
HR	hazard ratio
SBP	systolic blood pressure
VvInt/C	cortical volume occupied by interstium

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Figure 1. Urine Volume by Visit

Urine volume by visit. The mean urine volume ($\pm$ SD) did not vary significantly by visit with a mean volume of 2.22 (1.03), 2.38 (0.91), 2.39 (0.88), 2.30 (0.79), 2.39 (1.00) and 2.31 (0.92) L/day at visit 1, 2, 3, 4, 5, and 6 (exit) respectively.

Table 1

Description of participants, overall and by tertile of 24-hour urine volume at baseline.

Characteristics	Overall	Urine Volume (L/day)			p
		1.73	1.73–2.56	>2.56	
Number (n)	148	49	50	49	-
Age (yrs.)	49.2 ± 11.8	50.4 ± 12.7	49.4 ± 10.3	47.6 ± 12.3	0.49
Male	61.5%	27 (55.1)	34 (68.0)	30 (61.2)	0.42
Caucasian	86.5%	42 (85.7)	42 (84.0)	44 (89.8)	0.69
BMI (kg/m ²)	26.5 ± 5.1	26.4 ± 4.5	26.2 ± 5.8	27.0 ± 5.0	0.74
Hypertension	71.0%	32 (65.3)	40 (80.0)	33 (67.4)	0.22
Diabetes	39.9%	17 (34.7)	23 (46.0)	19 (38.8)	0.51
Smoking	23.0%	10 (20.4)	16 (32.0)	8 (16.3)	0.16
Living Donor	69.6%	30 (61.2)	40 (80.0)	33 (67.4)	0.12
Urine Sodium (mEq/L/day)	177.2 ± 96.7	114.8 ± 61.6 ^{ab}	182.5 ± 75.5 ^{ac}	231.9 ± 108.6 ^{bc}	<0.01
Urine Protein (g/day)	0.49 ± 0.55	0.28 ± 0.24 ^a	0.44 ± 0.33 ^b	0.76 ± 0.80 ^{ab}	<0.01
Iothalamate GFR	55.9 ± 16.9	56.2 ± 16.3	54.9 ± 18.8	56.5 ± 15.7	0.88
VvInt/C (%)	18.5 ± 4.9	18.8 ± 4.9	18.7 ± 4.8	18.1 ± 5.0	0.78
SBP (mmHg)	130.6 ± 18.2	130.3 ± 18.6	129.1 ± 18.9	132.5 ± 17.3	0.64
DBP (mmHg)	73.6 ± 10.7	74.2 ± 11.7	72.7 ± 10.2	73.7 ± 10.3	0.78
Diuretic	33.1%	28.6%	32.0%	38.8%	0.55
Tacrolimus Based	43.9%	38.8%	52.0%	40.8%	0.36
CSA Based	44.6%	44.9%	38.0%	51.1%	0.43
Other	11.5%	16.3%	10.0%	8.2%	0.41

Common superscripts denote significant difference after Tukey pairwise adjustment.

Body mass index (BMI); Glomerular filtration rate (GFR); Systolic Blood Pressure (SBP); Diastolic Blood Pressure (DBP); Cortical Volume occupied by interstitium (VvInt/C); Cyclosporine (CSA).

Table 2

Baseline urinary volume and urinary sodium as predictors for GFR, proteinuria and histological changes.

Outcome	Urine Volume				Urine Sodium			
	1.73–2.56 Liters		> 2.56 Liters		128 – 191meq/L/day		> 191meq/L/day	
	AOR	p	AOR	p	AOR	p	AOR	p
Final GFR	-3.15 (-14.69 – 8.39)	0.59	3.17 (-8.29 – 14.64)	0.58	-1.13 (-12.48 – 10.21)	0.84	7.04 (-6.03 – 20.10)	0.28
Final ACR	50.47 (-145.1 – 246.04)	0.61	-35.07 (-216.39 – 146.24)	0.70	64.42 (-113.18 – 242.02)	0.47	-171.84 (-381.46 – 37.77)	0.11
Final VvInt/C	-0.02 (-0.07 – 0.03)	0.40	-0.04 (-0.09 – 0.003)	0.07	-0.03 (-0.08 – 0.02)	0.19	-0.03 (-0.04 – 0.02)	0.23
VvInt Change	-0.07 (-0.16 – 0.02)	0.11	-0.06 (-0.15 – 0.03)	0.19	-0.09 (-0.19 – 0.02)	0.09	-0.061 (-0.178 – 0.056)	0.29
Serial GFR	2.233 (-1.731 – 6.198)	0.27	2.88 (-1.55 – 6.90)	0.21	0.36 (-3.09 – 3.81)	0.84	4.32 (0.13 – 8.5)	0.04
Serial ACR	14.21 (-27.84 – 56.25)	0.50	10.95 (-32.65 – 54.56)	0.62	-16.52 (-54.17 – 21.14)	0.39	-22.92 (-67.69 – 21.85)	0.31

* Urine Volume categories are compared to reference urine volume of < 1.73 L/day and urine sodium values are compared to a reference urine sodium of < 128 meq/L/day.

Adjusted Odds Ratio (AOR), adjusted for randomization group (losartan vs. placebo), recipient sex, age, race, BMI, iohalamate GFR, ACR, SBP, DBP, diuretic use, allopurinol use, donor age, gender, source and ethnicity, HLA matches, cause of kidney disease, hypertension, acute rejection and immunosuppressive regimen.

End Stage Renal Disease (ESRD); Human Leukocyte Antigen (HLA); Glomerular Filtration Rate (GFR); Body mass Index (BMI); Systolic Blood Pressure (SBP); Cortical Volume occupied by interstitium (VvInt/C).

Table 3

Urinary volume as a predictor of the primary and secondary endpoints.

Outcome	Variable	AOR (95%)	p
Doubling of Interstitium or ESRD from IF/TA	Urine Sodium > 191 meq/L/day [§]	0.79 (0.11–5.62)	0.81
	Urine Volume > 2.56 L/day [*]	3.52 (0.4–31.24)	0.26
	Cyclosporine	0.09 (0.01–0.83)	0.03
	< 3 HLA matches	8.44 (1.44–49.47)	0.02
	Acute rejection (ever)	21.99 (2.41–200.58)	0.01
Doubling of Interstitium or any ESRD	Urine Sodium > 191 meq/L/day [§]	0.72 (0.09–5.65)	0.76
	Urine Volume > 2.56 L/day [*]	7.04 (0.66–74.87)	0.11
	Losartan	0.16 (0.03–0.87)	0.03
	Female	0.14 (0.02–1.16)	0.07
	Cyclosporine	0.16 (0.02–1.14)	0.07
	< 3 HLA matches	12.4 (2.04–75.57)	0.01
	Acute rejection (ever)	20.27 (2.08–197.86)	0.01
Doubling of Serum Creatinine, All Cause ESRD or Death	Urine Sodium > 191 meq/L/day [§]	1.19 (0.27–5.33)	0.82
	Urine Volume > 2.56 L/day [*]	0.89 (0.21–3.71)	0.87
	Losartan	0.34 (0.11–1.1)	0.07
	SBP	1.05 (1.01–1.1)	0.02
	Cyclosporine	0.23 (0.06–0.87)	0.03
	White	0.18 (0.05–0.65)	0.01
	< 3 HLA matches	2.58 (0.8–8.28)	0.11
	Acute rejection (ever)	4.85 (1.25–18.83)	0.02

Adjusted Odds Ratio (AOR)

^{*} Urine Volume compared to reference of urine volume < 1.73L/day[§] Urine Sodium compared to reference of urine sodium < 128 meq/L/day.

End Stage Renal Disease (ESRD); Human Leukocyte Antigen (HLA); Systolic Blood Pressure (SBP); Interstitial Fibrosis/Tubular Atrophy (IF/TA)

Table 4

Cox proportional hazard with time-dependent covariates.

Outcome	Variable	AHR (95% CI)	p
All Cause ESRD	Urine Sodium >191 meq/L/day [§]	1.07 (0.07–16.05)	0.96
	Urine Volume > 2.56 L/day [*]	1.96 (0.15–24.94)	0.60
	Female	0.05 (0–0.92)	0.04
	Age	1.11 (0.99–1.24)	0.06
	White	0.02 (0.01–0.32)	0.01
	< 3 HLA matches	37.64 (1.91–740.47)	0.02
ACR		1.01 (1.00–1.01)	0.02
Doubling of Cr, ESRD or Death	Urine Sodium >191 meq/L/day [§]	0.99 (0.3–3.21)	0.98
	Urine Volume > 2.56 L/day [*]	1.25 (0.34–4.6)	0.73
	Losartan	0.47 (0.17–1.3)	0.14
	SBP	1.01 (0.98–1.05)	0.47
	Cyclosporine	0.5 (0.17–1.43)	0.20
	White	0.14 (0.05–0.42)	0.00
	< 3 HLA matches	4.73 (1.55–14.43)	0.01
	HTN	10.65 (2.49–45.58)	0.00
Acute rejection (ever)		3.81 (1.22–11.89)	0.02

Adjusted Hazards Ratio (AHR).

Acute rejection not considered as covariate due to lacking model fit.

^{*} Urine Volume compared to reference of urine volume < 1.73L/day.[§]Urine Sodium compared to reference of urine sodium < 128 meq/L/day.

Albumin to creatinine ratio (ACR); End Stage Renal Disease (ESRD); Human Leukocyte Antigen (HLA); Glomerular Filtration Rate (GFR); Body mass Index (BMI); Systolic Blood Pressure (SBP); Cortical Volume occupied by interstitium (VvInt/C).