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Associations of Serum and Dialysate Potassium Concentrations With Incident Atrial Fibrillation in a Cohort Study of Older US Persons Initiating Hemodialysis for Kidney Failure

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Introduction: Atrial fibrillation (AF) disproportionally affects persons on maintenance hemodialysis (HD). Associations of serum and dialysate potassium concentrations [K^+] with AF incidence are poorly understood.

Methods: We conducted a cohort study using Medicare claims merged with clinical data from a dialysis provider to determine whether serum-[K^+] and/or dialysate-[K^+] independently associated with AF incidence. Persons insured by fee-for-service Medicare aged ≥67 years at dialysis initiation and free from diagnosed AF prior to day 120 of dialysis were eligible. Serum-[K^+] and dialysate-[K^+] were assessed in 30-day intervals and patients were followed-up with for AF incidence in subsequent 30-day intervals.

Results: During 2006 to 2011, 15,190 persons (mean age = 76.3 years) initiating HD had no prior AF diagnosis. Mean serum-[K^+] was 4.5 mEq/l; dialysate-[K^+] was 3 mEq/l in 34% and 2 mEq/l in 52% of patients. Followed-up over 21,907 person-years, 2869 persons had incident AF (incidence/100 person-years, 13.1 [95% confidence interval [CI], 12.6–13.6]). The multivariable-adjusted association of serum-[K^+] with incident AF was J-shaped as follows: relative to a serum-[K^+] of 4.5 mEq/l, lower serum-[K^+] associated with increased AF risk, whereas confidence bands for higher serum-[K^+] indicated no association. Dialysis against a dialysate-[K+] of 3 mEq/l versus 2 mEq/l independently associated with a 14% (95% CI, 5%–24%) lower incidence of AF. No effect modification between serum-[K^+] and dialysate-[K^+] was detected ($P = 0.34$).

Conclusion: Lower serum-[K^+] was independently associated with incident AF whereas elevated serum-[K+] was not. The findings support adoption of dialysate solutions with a dialysate-[K^+] of 3 mEq/l, regardless of patients' serum-[K+], and elimination of lower dialysate-[K+] solutions from practice. Clinical trials randomizing patients to different dialysate-[K^+] are warranted to establish causality.

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Atrial fibrillation (AF) is the most common arrhythmia with an estimated prevalence of approximately 2% in the US population.[1] In contrast, the prevalence of AF among patients receiving HD has been estimated to be about 21%.[2] Although patients with end-stage kidney disease (ESKD) generally have a high burden of traditional risk factors for AF such as hypertension and heart failure,[2] there is emerging evidence that the dialysis procedure itself can further increase the risk of developing AF.[3] In one study, implanted loop-recording devices detected AF events at higher rates during and immediately following dialysis sessions than at any other time of the week,[3] raising the question of whether electrolyte and volume derangements and shifts during dialysis might contribute to AF incidence and burden.

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One potential culprit is the cation potassium. Potassium accumulation is a hallmark of ESKD, especially in persons with little or no residual kidney function.[4] Hyperkalemia is then managed by exposing the patient to a dialysate [K^+] that is below physiologic range, resulting in rapid and potentially large potassium shifts and the potential for inducing subsequent hypokalemia.[5] Dyskalemias in patients on HD have been associated with an increased risk for sudden cardiac arrest[6] but their associations with the incidence of AF in HD patients have not been well-studied. Similarly, the question of whether a large serum-to-dialysate [K^+] gradient poses a risk for incident AF is unknown. Therefore, we examined the associations between serum-[K^+], dialysate-[K^+], and their possible interaction on the incidence of diagnosed AF in a large, national population of patients undergoing HD.

METHODS

Data Source

We used data from the United States Renal Data System (USRDS), the national registry for patients with ESKD, linked with data from the electronic health records of a large US dialysis provider (2006–2011) using a person-level crosswalk file provided by the USRDS Coordinating Center.

Study Design and Population

We conducted a retrospective cohort study of older individuals with ESKD who initiated HD in the US and who did not have a previous AF diagnosis, to examine the associations of serum-[K^+] and dialysate-[K^+] with the incidence of AF. We used sequential 30-day exposure intervals to set up the study followed by adjoining 30-day intervals during which the outcome was ascertained (Figure 1). More specifically, the development of incident AF was ascertained during the period P_i with serum-[K^+] ascertained during the period P_{i-1} and other covariates ascertained during the period P_{i-2}, where i represents the 30 days' period indicator.

Similar to previously published research,[7,8] to assemble the cohort, we first identified all incident HD patients who were ≥67 years old when they initiated kidney replacement therapy between January 1, 2006, and August 31, 2011. This was necessary to ensure that all patients had at least 2 years of predialysis Medicare insurance, for which they qualify at 65 years of age, so that we could eliminate persons with preexisting AF. Though some persons under the age of 65 years have Medicare coverage prior to kidney failure (e.g., through disability) they cannot be considered representative and, in addition, the USRDS does not provide their pre-ESKD claims. We assigned day 121 after the initiation of kidney replacement therapy as the index date because of the well documented incompletion of the USRDS registry of persons with kidney failure who die early, which gave rise to the "90-day rule" usually applied in studies of the USRDS,[9] and to allow patients to establish routine dialysis with the provider as well as laboratory results and vital sign and treatment data to accumulate in the health record. We then used a 30-day exposure assessment period from days 91 to 120 to ascertain baseline serum-[K^+]. To ascertain minimum active system use, we required patients to have uninterrupted Medicare parts A and B coverage for at least 730 days prior to the incident ESKD date to the study

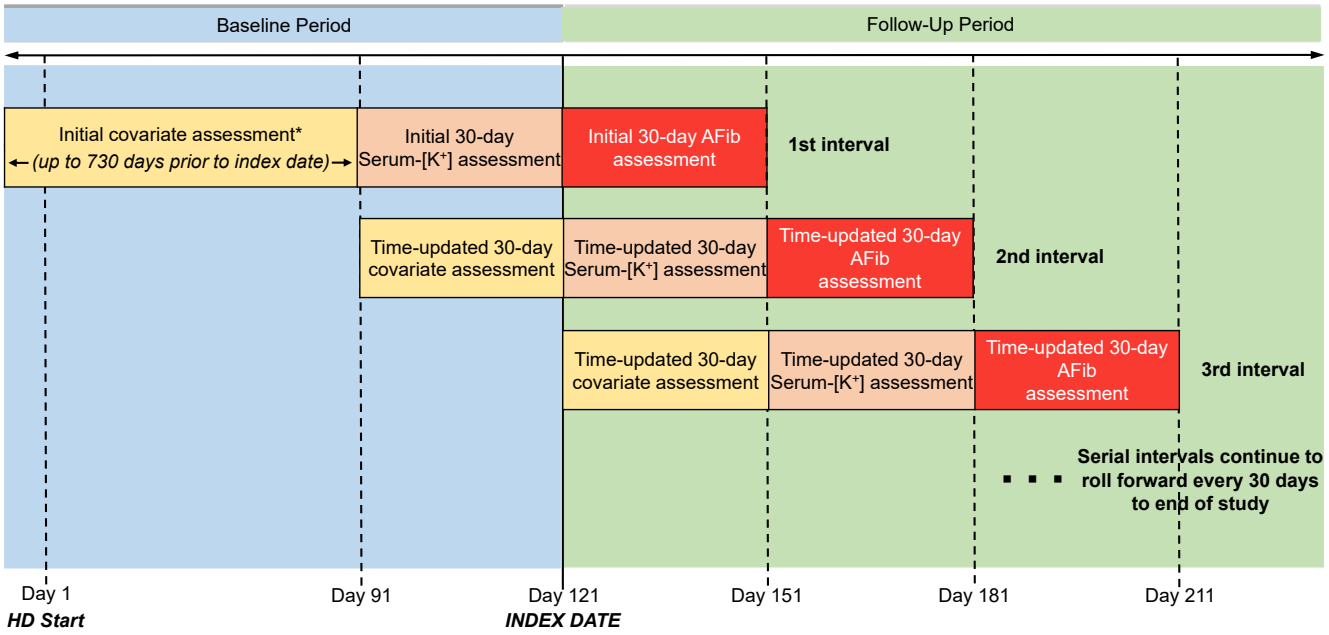

Figure 1. Study design and timelines. AFib, atrial fibrillation.

index date with at least 1 Medicare claim (part A or B) in the 730 to 366 days and 365 to 0 days preceding incident ESKD. We excluded patients who died, who were lost to follow-up, who received a kidney transplant, who recovered kidney function, who received any peritoneal dialysis treatments, or who lost continuous Medicare A and B coverage prior to the index date. We excluded patients with any documented history of AF (any billing claim with International Classification of Diseases-Ninth Revision (ICD-9) diagnosis code of 427.3× between January 1, 1996 and the index date). As done previously, to ensure capturing a stable cohort of patients on regular thrice-weekly dialysis, we further excluded those who had fewer than 10 or more than 16 clinic-based HD treatments in the 30 days prior to the index date. However, to appropriately retain patients who were hospitalized during the interval we credited patients with 3/7th of a HD session for each day spent in a hospital during that period. Finally, we excluded patients without any recorded dialysate-[K^+] and serum-[K^+] at baseline and all follow-up periods.

Outcome: Incident AF

The outcome was incident AF identified from a single inpatient claim with an International Classification of Diseases-ninth revision diagnosis code of 427.3× or from any outpatient claim with an ICD-9 diagnosis code of 427.3×, provided that there was a second, subsequent inpatient or outpatient code of 427.3×, in any position, separated by at least 1 day from the initial code appearance. This approach to increase specificity in outpatient coding is commonly used for AF ascertainment in Medicare claims, and we have used this approach in previous work.[7,8] The outcome was ascertained following the index date (day 121 from ESKD).

Exposures

Starting at day 91 and updated in 30-day intervals, we ascertained the exposure variable, predialysis serum-[K^+] (mEq/l), as the last laboratory measurement recorded in each 30-day period. Using a previously published algorithm,[10] we chose the quadratic form as the best parametrization for serum-[K^+].

The other exposure of interest was dialysate-[K^+]. Because the choice of dialysate-[K^+] may be based on the serum potassium value, we used the dialysate-[K^+] (mEq/l) that was prescribed on the same day or the closest day prior to the serum-[K^+] draw date. We modeled dialysate-[K^+] as a categorical variable because there are only a few, discrete choices for this value.

Covariates

We defined a large number of covariates, some of which were measured only at baseline and others that were updated during each subsequent 30-day interval (i.e., time-varying). For the baseline covariates, we included age, sex, Medicaid dual eligibility status, census region, year of incident ESKD, race (White, Black, Asian, Native American, Pacific Islander, and other), ethnicity (Hispanic vs. non-Hispanic), and estimated glomerular filtration rate reported at HD initiation, as well as neighborhood-level socioeconomic data (median rent, percentage living below the federal poverty line, percentage unemployed, and percentage with less than a high-school education) at the time of incident HD initiation using the Patient file, the Medicare Evidence Form, as well as corresponding zip code level US population census data. The time-varying covariates included comorbidities and number of hospital days during the 30-day interval, laboratory (serum albumin and calcium) and dialysis-related (predialysis systolic and diastolic blood pressures, mean HD ultrafiltration rate, and vascular access type) data. We ascertained all comorbid conditions listed in Table 1 using International Classification of Diseases-ninth revision diagnosis and procedure codes in any position requiring at least 1 inpatient or 2 outpatient encounters separated by at least 1 day, using all available claims and pre-ESKD data between January 1, 1996 and day 90 after the first ESKD date and then repeatedly updated using additional 30 days thereafter. The number of recent hospital days were ascertained from Medicare part A claims and updated every 30 days. We used dialysis electronic health records data to obtain the last laboratory values in the 90-day laboratory assessment period and then time-updated the variables using the last value in each subsequent 30-day interval. Vascular access type was designated as central venous catheter versus arteriovenous access based on ever use of a central venous catheter during the 30 days prior to the exposure period and then time-updated in subsequent 30-day intervals.

Statistical Analyses

We present baseline characteristics by baseline serum potassium, dichotomized at the median serum-[K^+] value $\geq$4.5 mEq/l or $<$4.5 mEq/l, and summarized categorical variables as frequencies (percentages) and continuous variables as means (SDs), or as medians (25th–75th percentiles).

We applied an extended Cox model as a function of a time-varying exposure to compute adjusted hazard ratios (HRs) and 95% CIs for the associations of serum-

Table 1. Patient characteristics, overall and by mean serum potassium concentration during baseline period

Patient characteristics	All (N = 15,190)	Serum-[K^+] ≥ 4.5 mEq/l (n = 7183)	Serum-[K^+] < 4.5 mEq/l (n = 6988)	Serum-[K^+] Missing (n = 1019)
Demographics				
Age, years, mean (SD)	76.3 (6.3)	76.3 (6.3)	76.3 (6.2)	75.8 (6.2)
Male sex	7491 (49.3%)	3629 (50.5%)	3367 (48.2%)	495 (48.6%)
Race				
White	10,465 (68.9%)	5218 (72.6%)	4567 (65.4%)	680 (66.7%)
Black	4014 (26.4%)	1591 (22.1%)	2124 (30.4%)	299 (29.3%)
Asian	559 (3.7%)	285 (4.0%)	240 (3.4%)	34 (3.3%)
Native American	135 (0.9%)	81 (1.1%)	48 (0.7%)	<10[a]
Other	17 (0.1%)	<10[a]	<10[a]	0 (0%)
Hispanic ethnicity	1214 (8.0%)	649 (9.0%)	478 (6.8%)	87 (8.5%)
Year of HD initiation				
2006	2914 (19.2%)	1428 (19.9%)	1279 (18.3%)	207 (20.3%)
2007	2730 (18.0%)	1280 (17.8%)	1235 (17.7%)	215 (21.1%)
2008	2592 (17.1%)	1226 (17.1%)	1200 (17.2%)	166 (16.3%)
2009	2632 (17.3%)	1277 (17.8%)	1196 (17.1%)	159 (15.6%)
2010	2620 (17.2%)	1241 (17.3%)	1220 (17.5%)	159 (15.6%)
2011	1702 (11.2%)	731 (10.2%)	858 (12.3%)	113 (11.1%)
Medicare/Medicaid dual eligibility	4088 (26.9%)	1943 (27.0%)	1842 (26.4%)	303 (29.7%)
Hemodialysis catheter	9585 (63.1%)	4608 (64.2%)	4313 (61.7%)	664 (65.2%)
Census data, median (Q1–Q3)				
% unemployed	9.3 (6.8, 12.4)	9.1 (6.7, 12.2)	9.4 (6.9, 12.7)	9.5 (7.0, 12.8)
% below poverty	13.9 (8.3, 20.9)	13.6 (8.0, 20.2)	14.2 (8.5, 21.6)	14.6 (8.7, 21.9)
% less than high school	14.1 (8.8, 21.1)	13.8 (8.5, 20.6)	14.2 (9.0, 21.5)	15.2 (9.4, 22.8)
% median rent ($)	858 (686, 1069)	871 (695, 1081)	842 (679, 1048)	841 (673, 1067)
History of comorbid conditions				
Myocardial infarction	2080 (13.7%)	987 (13.7%)	952 (13.6%)	141 (13.8%)
Coronary artery disease	8427 (55.5%)	4018 (55.9%)	3837 (54.9%)	572 (56.1%)
Coronary revascularization	3279 (21.6%)	1547 (21.5%)	1523 (21.8%)	209 (20.5%)
Unstable angina	2555 (16.8%)	1210 (16.8%)	1185 (17.0%)	160 (15.7%)
Heart failure	9397 (61.9%)	4452 (62.0%)	4293 (61.4%)	652 (64.0%)
Valvular disease	4511 (29.7%)	2154 (30.0%)	2064 (29.5%)	293 (28.8%)
Arrhythmia other than AF	2365 (15.6%)	1109 (15.4%)	1108 (15.9%)	148 (14.5%)
Pacemaker	931 (6.1%)	446 (6.2%)	428 (6.1%)	57 (5.6%)
Stroke/transient ischemic attack	2824 (18.6%)	1276 (17.8%)	1338 (19.1%)	210 (20.6%)
Peripheral artery disease	5601 (36.9%)	2642 (36.8%)	2549 (36.5%)	410 (40.2%)
Diabetes mellitus	10,367 (68.2%)	4904 (68.3%)	4760 (68.1%)	703 (69.0%)
Hyperlipidemia	11,316 (74.5%)	5336 (74.3%)	5218 (74.7%)	762 (74.8%)
Lung disease	5810 (38.2%)	2754 (38.3%)	2645 (37.9%)	411 (40.3%)
Liver disease	1122 (7.4%)	524 (7.3%)	523 (7.5%)	75 (7.4%)
Depression	2347 (15.5%)	1109 (15.4%)	1057 (15.1%)	181 (17.8%)
Number of hospital d in the previous 30 days	0.9 (3.0)	0.9 (2.9)	0.9 (2.9)	1.6 (4.5)
Number of HD sessions in the previous 30 days	12.1 (1.8)	12.2 (1.7)	12.1 (1.8)	11.9 (2.2)
Biometric/laboratory measurements, mean (SD)				
eGFR at dialysis initiation	12.2 (5.0)	11.9 (5.0)	12.4 (5.0)	12.3 (5.2)
eGFR, median (IQR)	11.5 (8.5, 15.0)	11.2 (8.3, 14.7)	11.8 (8.7, 15.3)	11.6 (8.6, 15.0)
Predialysis SBP (mm Hg)	147.3 (19.6)	148.0 (19.6)	146.6 (19.5)	146.7 (20.4)
Predialysis DBP (mm Hg)	72.4 (10.1)	72.7 (10.2)	72.1 (9.9)	72.3 (10.4)
Serum albumin (mg/dl)	3.6 (0.5)	3.6 (0.4)	3.6 (0.5)	3.6 (0.5)
Serum calcium (mmol/l)	8.9 (0.7)	8.9 (0.7)	8.9 (0.7)	8.9 (0.7)
Delivered UFR (ml/h/kg)	7.4 (4.0)	7.9 (3.9)	7.0 (4.0)	7.3 (4.1)
Main exposures				
Mean serum potassium (mEq/l)	4.5 (0.6)	5.0 (0.4)	4.0 (0.3)	
Mean (SD)				
Dialysate potassium (mEq/l)				
1	274 (1.8%)	222 (3.1%)	51 (0.7%)	<10
1.5	13 (0.1%)	<10	<10	
2	7828 (51.5%)	4016 (55.9%)	3805 (54.5%)	<10
2.5	23 (0.2%)	11 (0.2%)	12 (0.2%)	

(Continued on following page)

Table 1. (Continued) Patient characteristics, overall and by mean serum potassium concentration during baseline period

Patient characteristics	All (N = 15,190)	Serum-[K^+] ≥ 4.5 mEq/l (n = 7183)	Serum-[K^+] < 4.5 mEq/l (n = 6988)	Serum-[K^+] Missing (n = 1019)
3	5115 (33.7%)	2474 (34.4%)	2638 (37.8%)	<10
3.5	39 (0.3%)	15 (0.2%)	24 (0.3%)	
4	222 (1.5%)	84 (1.2%)	138 (2.0%)	
Median (IQR)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)

AF, atrial fibrillation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (in ml/min per 1.73 m^2); ESKD, end-stage kidney disease; HD, hemodialysis; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; UFR, ultrafiltration rate.
[a]Cell counts <10 were suppressed in compliance with federal research regulations and indicate "<10."
Missing data counts were 56 for Hispanic ethnicity, 202 for type of hemodialysis access, between 140 and 311 for the US census-based socioeconomic indicators, 171 for blood pressure, 299 for estimated glomerular filtration rate at dialysis initiation, 155 for serum albumin concentration, 144 for serum calcium concentration, 1019 for serum potassium concentration, and 1675 for dialysate potassium concentration.

[K^+] and dialysate-[K^+] with incident AF, whereas adjusting for the other. Estimates were further adjusted in 3 nested multivariable models as follows: Model 1, adjusted for year of incident ESKD; Model 2, additionally adjusted for age, sex, race, Hispanic ethnicity, census division, socioeconomic status variables, and Medicaid dual eligibility; Model 3, additionally adjusted for comorbid conditions (Table 1), number of recent hospital days and vascular access type, predialysis systolic and diastolic blood pressures, number of HD treatments, baseline estimated glomerular filtration rate, serum calcium concentration, serum albumin concentration, and average hemodialysis session ultrafiltration rate. We examined the correlation of the scaled Schoenfeld residuals with time and found no evidence that the log-HR changed with follow-up time either for the exposures or other Model 3 covariates (Schoenfeld test global P-value > 0.05). We present 2 separate plots to better interpret results from different vantage points. Both plots compare the hazard for AF between 2 patients that are similar for all covariates at a time t but differ in their serum [K^+] measurements. In one plot, serum-[K^+] values between 2.5 mEq/l and 8.0 mEq/l are compared with a fixed referent serum-[K^+] of 4.5 mEg/l, the population median. The other plot shows the HRs reflecting a comparison to a hypothetical 0.5 mEq/l higher serum-[K^+].

We primarily focused on the main, directly observable exposures, serum-[K+] and dialysate-[K+], but subsequently were interested in exploring the possible role of an exposure "derived" from these 2, namely the serum-to-dialysate [K+] gradient. Technically, this can be done by testing for statistical significance of an interaction test between the 2 "main (exposure) effects." Therefore, we examined the interaction between serum-[K^+] and dialysate-[K^+] by adding the interaction term between the 2 exposures of interest (including the quadratic term) directly into Model 3. If significant, it would support effect modification of the association between serum-[K+] and AF by levels of dialysate-[K+] and vice versa (i.e., the serum-to-dialysate [K+] gradient); absent significance, an importance of the gradient would not find support by the model and instead one would have to conclude that the 2 main exposure(s) solely associated with AF, regardless of the level of the other.

Sensitivity Analyses

When cleaning the data set we noted that many patients never had a change in their dialysate-[K^+]. Thus, we conducted a set of sensitivity analyses. We restricted analyses to persons whose dialysate-[K^+] remained unchanged prior to the index date, that is, up to day 120 from initiation of dialysis. Thus, we sought to identify a population whose nephrologists were apparently not inclined to ordering adjustments to dialysate-[K^+] regardless of their measured serum-[K^+].

Missing Data

In the 15,190-patient cohort, 10,364 patients (68.2%) had at least 1 variable missing at some point during follow-up. Overall, 37,221 (13.6%) of 273,152 records had at least 1 variable missing. Median rent was the most common missing baseline variable (2.0% of all records). Time-varying covariates were present most of the time (>99%). In addition, there was missingness for both exposure variables at baseline or during follow-up (serum [K^+]: missing 6.7% at baseline and in 8.3% of all follow-up periods; dialysate [K^+]: missing 11.3% at baseline and in 10.1% of all follow-up periods). Note that dialysate [K^+] was determined based on the day of serum [K^+] ascertainment. Therefore, for those periods where we were not able to determine serum [K^+], we were also not able to ascertain dialysate [K^+]. We assumed that the data were missing at random, conditional on observed variables, and used multiple imputation by chained equations as implemented in Stata to impute 15 data sets.[11-13] We combined the estimates and standard errors obtained from the analysis model applied to each imputed data set using Rubin's rules.[14] In addition to the exposures and

all covariates included in the analysis model, the imputation model also included the event indicator and the Nelson–Aalen estimator of the cumulative marginal hazard.[15] Auxiliary variables have been shown to help the imputation.[16,17] Some potential auxiliary variables were already included in the analysis model as covariates. For example, hospital stay in a certain period is an auxiliary variable for laboratory data, such as the exposure serum [K^+], being missing during that period. In this analysis, we included number of hospital days as a covariate. We ran a separate imputation model for testing the interaction between serum [K^+] and dialysate [K^+] by using the substantive-model compatible fully conditional specification approach.[18]

All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc, Cary, NC; www.sas.com) and Stata, version 16 (StataCorp LLC, College Station, TX; www.stata.com).[11] Institutional review boards at Stanford University (protocol #17904) and Baylor College of Medicine (protocol #H-36408) approved this work, and data use agreements for both USRDS, dialysis provider data, and their crosswalk were in place.

RESULTS

The final cohort consisted of 15,190 patients initiated on HD with no prior AF diagnosis, and who met the

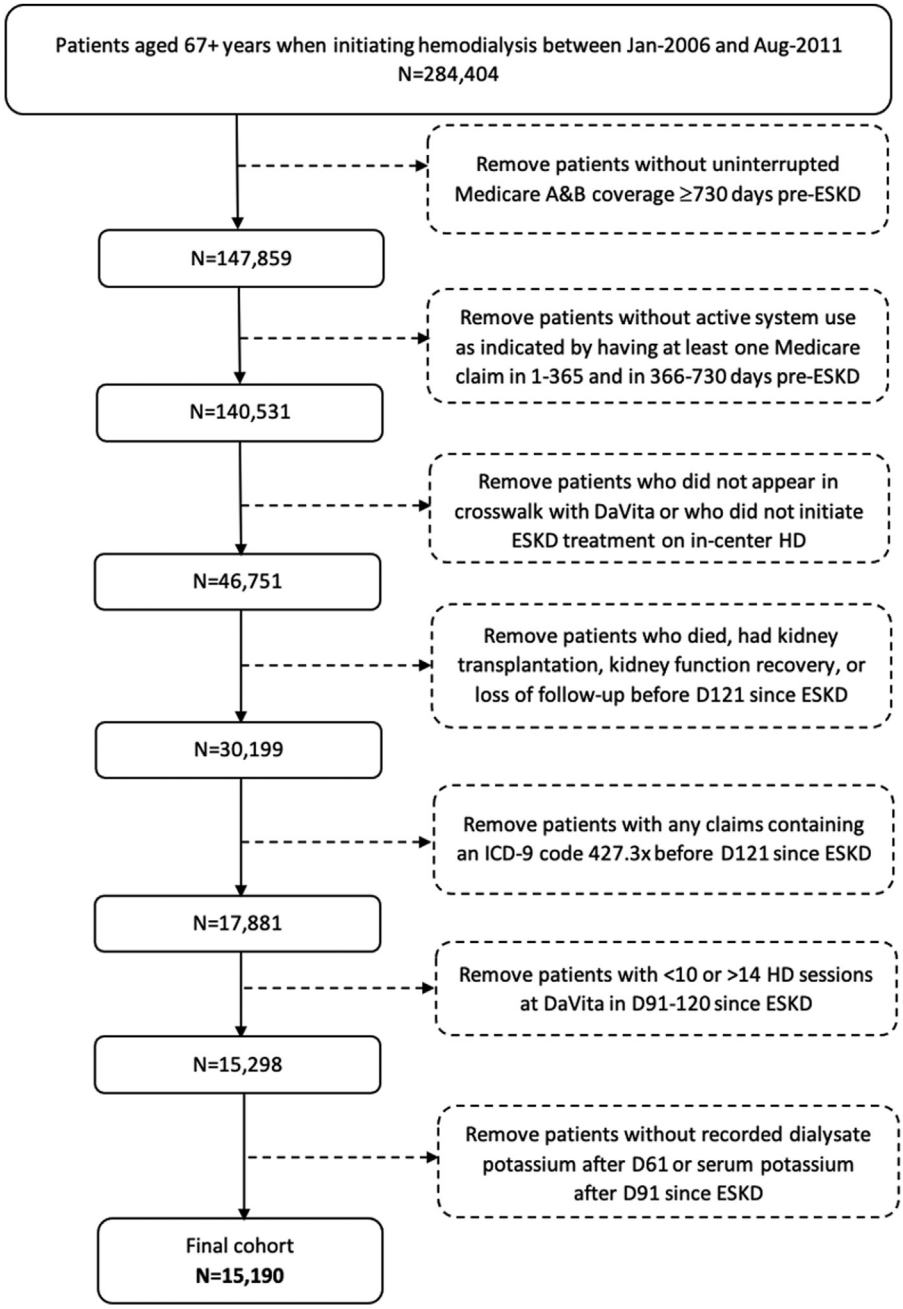

Figure 2. Flow chart illustrating cohort assembly. ESKD, end-stage kidney disease; HD, hemodialysis.

other specified inclusion and exclusion criteria (Figure 2). Overall, the cohort had an average age of 76 years, 49% were male, and 69% were of White race (Table 1). For their dialysate composition, at baseline, 52% were dialyzed with a $[K^+] = 2$ mEq/l bath and 34% with a $[K^+] = 3$ mEq/l bath. Patients with higher baseline serum-$[K^+]$ included a higher percentage of Caucasians, a lower percentage of Black patients, and a higher percentage of persons with Hispanic ethnicity than those whose mean predialysis serum-$[K^+]$ was <4.5 mEq/l; otherwise, the 2 groups were well balanced with respect to their demographic and clinical characteristics. The use of specific dialysate-$[K^+]$ baths between the 2 groups was also well balanced with a median (interquartile range) of 2.0 (2.0, 3.0) mEq/l in both groups (Table 1); use of a 1 mEq/l dialysate-$[K^+]$ bath was rare but slightly more common in the higher baseline serum-$[K^+]$ group (3.1 vs. 0.7%).

During follow-up a total of 2869 AF events were registered, whereas follow-up time was censored at the earliest occurrence of death ($n = 3575$), modality change ($n = 1700$), loss of Medicare part A or B coverage ($n = 348$), discontinuation of dialysis at a DaVita facility ($n = 1884$) or end of study period (January 1, 2012; $n = 4814$). With a mean follow-up of 527 days, the overall unadjusted AF incidence was 13.1 (95% CI, 12.6–13.6) events per 100 person-years. Patients whose average serum-$[K^+]$ was between 3.5 and 4 mEq/l had the lowest unadjusted AF incidence at 12.0 (95% CI, 10.8–13.2) events per 100 person-years followed by patients with a mean serum-$[K^+]$ between 4.5 and 5 mEq/l. However, patients who had average serum-$[K^+]$ <3.5 mEq/l experienced the highest rates of incident AF (15.9 events per 100 person-years, Table 2).

We modeled serum-[K+] as a quadratic variable anchored at a serum-[K+] of 4.5 mEq/l and found significantly higher rates of newly diagnosed AF both at lower and higher serum-[K+] (Figure 3a). The rate of incident AF remained significantly higher with serum-$[K^+]$ values below 4.5 mEq/l, even for values that were still within the normal serum-$[K^+]$ range. However, while hyperkalemia was significantly associated with an increased hazard for AF at severely elevated concentrations ($[K^+]$ >6.5 mEq/l), the association was attenuated in fully adjusted models (Figure 3a, Model 3). We also show the associated HR for incident AF associated with a 0.5 mEq/l increase in serum $[K^+]$ for any given serum $[K^+]$ value (Figure 3b). As shown in Figure 3b, a 0.5 meq/l increase in serum $[K^+]$ is associated with a lower hazard of AF for serum $[K^+]$ <5.5 mEq/l, and no significant association with incident AF when serum $[K^+]$ values rise above this value.

Table 2. Patient counts, event counts, person-time, and event rates by baseline serum potassium concentration

30-day averaged serum-$[K^+]$	N of patients	N of AF events	Person-time at risk (year)	Incidence rate (events/100 person-years)
Overall	15,190	2869	21,907	13.1 (12.6, 13.6)
$[K^+] < 3.5$	538	103	647	15.9 (13.1, 19.3)
$3.5 \le [K^+] < 4$	2189	368	3077	12.0 (10.8, 13.2)
$4 \le [K^+] < 4.5$	4261	801	6063	13.2 (12.3, 14.2)
$4.5 \le [K^+] < 5$	3978	762	5959	12.8 (11.9, 13.7)
$5 \le [K^+] < 5.5$	2168	422	3204	13.2 (12.0, 14.5)
$5.5 \le [K^+]$	1037	226	1490	15.2 (13.3, 17.3)
$[K^+]$ missing	1019	187	1466	12.8 (11.1, 14.7)

The incidence of AF with respect to different dialysate-$[K^+]$ baths with a 2 mEq/l $[K^+]$ bath as the reference is depicted in Table 3. Most subjects (86%) were either on a 2 mEq/l or 3 mEq/l $[K^+]$ bath. In the fully adjusted model, and independent of serum-$[K^+]$ adjustment in the model, a dialysate-$[K^+]$ bath of 3 mEq/l was associated with a 13% (95% CI, 4%–22%) lower rate for incident AF compared with those who dialyzed against a dialysate-$[K^+]$ of 2 mEq/l.

We next examined for effect modification between serum-$[K^+]$ and dialysate-$[K^+]$ using multiplicative interaction terms. No significant interaction was identified ($P = 0.35$ for Model 1, $P = 0.32$ for Model 3).

Finally, we conducted sensitivity analyses that included only patients who remained on the same dialysate $[K^+]$ bath, either 2 mEq/l or 3 mEq/l, during the first 120 days. They included 9743 patients (64.1% of the full cohort) who were similar in their observed characteristics to the cohort used in the main analysis (Supplementary Table S1). Of those, 5957 (61.1%) used a $[K^+]$ 2 mEq/l bath and 3786 (38.9%) used a $[K^+]$ 3 mEq/l bath. Patients dialyzing against a 2 mEq/l $[K^+]$ bath included more Black and fewer White patients and there was a slight tendency toward indicators reflecting lower socioeconomic status. Otherwise, the baseline characteristics were very similar between these groups, including virtually identical serum $[K^+]$ concentrations at a mean of 4.5 (SD = 0.6) mEq/l (Supplementary Table S1). Persons using a $[K^+] = 3$ mEq/l dialysate had a 14% lower AF incidence (HR = 0.86; 95% CI, 0.74–0.97) compared with those using a $[K^+] = 2$ mEq/l dialysate, consistent with the main results (Supplementary Table S2).

DISCUSSION

We examined the associations of serum-$[K^+]$ and dialysate-$[K^+]$ with the incidence of AF in persons with ESKD undergoing HD. We found that lower serum-$[K^+]$ was associated with a higher rate of incident AF, even after adjusting for multiple potential confounders. This association became evident even within the lower normal range for serum-$[K^+]$. In contrast, we found no

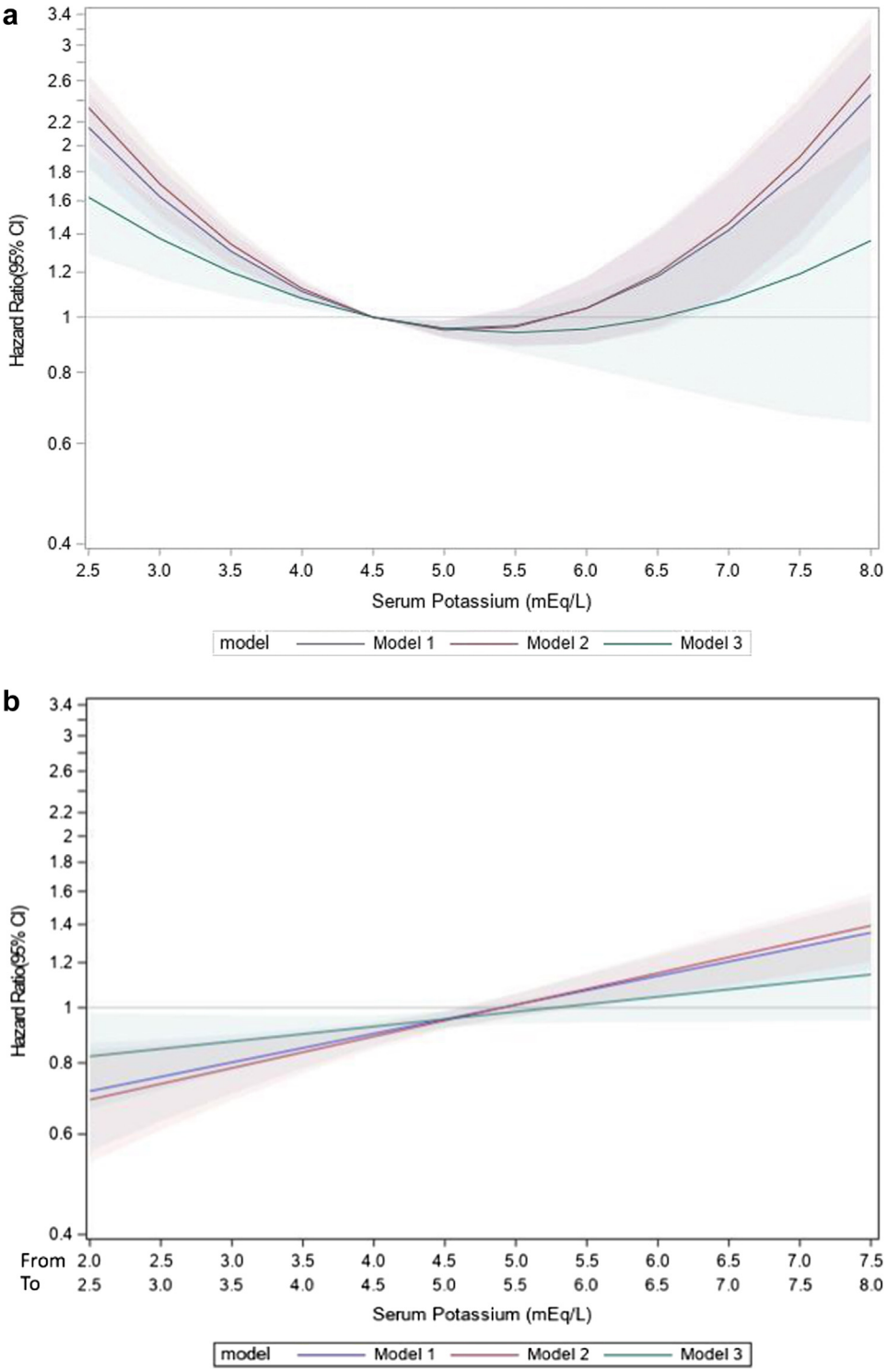

Figure 3. Association of time-averaged serum potassium concentration and incident atrial fibrillation. (a) Hazard ratios and 95% CIs comparing serum potassium concentrations to a referent of of 4.5 mEq/l.

Note: This figure uses a fixed serum potassium reference value: serum potassium concentrations from 2.5–8.0 mEq/l are compared with a fixed referent at serum potassium 4.5 mEq/l. Example of fully adjusted HR (serum potassium 4 vs. 4.5) = 1.08 (1.04–1.12) and fully adjusted HR (serum potassium 7 vs. 4.5) = 1.07 (0.71–1.43). All models were stratified by year of incident kidney failure. Model 1 − serum-[K^+] (continuous and quadratic term) + dialysate-[K^+] (categorical); Model 2 − model 1 + age, sex, race, Hispanic ethnicity, census division, socioeconomic status variables, and Medicaid dual eligibility; Model 3 − model 2 + comorbidities, number of hospital days, and type of vascular access, systolic blood pressure, diastolic blood pressure, count of monthly hemodialysis sessions, estimated glomerular filtration rate at hemodialysis initiation, serum calcium concentration, serum albumin concentration and delivered ultrafilitration rate. (b) Hazard ratios and 95% CIs representing the association of a 0.5 mEq/l increase in serum potassium concentration relative to a range of referent serum potassium concentrations

Note: This figure uses a varying serum potassium reference value. HRs at each serum potassium level represent a counterfactual (continued)

Table 3. Incidence of atrial fibrillation by dialysate potassium concentration

Models	Dialysate [K^+] (mEq/l)	Hazard ratio (95% CI)
Model 1	1	1.08 (0.90–1.26)
	2	–
	3	0.96 (0.84–1.03)
	4	1.15 (0.77–1.52)
Model 2	1	1.08 (0.90–1.25)
	2	–
	3	0.89 (0.80–0.99)
	4	1.08 (0.70–1.46)
Model 3	1	1.07 (0.90–1.25)
	2	–
	3	0.87 (0.78–0.96)
	4	1.06 (0.66–1.45)

CI, confidence interval.
Note: All models were stratified by year of incident kidney failure. Model 1 – serum-[K^+] (quadratic term) + dialysate-[K^+] (categorical); Model 2 – model 1 + age, sex, race, Hispanic ethnicity, census division, socioeconomic status variables, and Medicaid dual eligibility; Model 3 – model 2 + comorbidities, number of hospital days, and vascular access, systolic blood pressure, diastolic blood pressure, count of monthly hemodialysis sessions, estimated glomerular filtration rate at hemodialysis initiation, serum calcium concentration, serum albumin concentration, and delivered ultrafiltration rate.

significant association between higher serum-[K^+] and incident AF in fully adjusted models. We also found that patients who underwent dialysis on a 3 mEq/l dialysate-[K^+] bath had a lower adjusted rates of incident AF than those exposed to a 2 mEq/l dialysate-[K^+] bath, independent of their serum [K^+]. A test for interaction between serum-[K^+] and dialysate-[K^+] was not statistically significant. These findings bring into focus 2 distinct, yet related points worthy of discussion as follows: the effect of dyskalemias on arrhythmias in general, and the potential influence of the serum-to-dialysate [K^+] gradient on arrhythmogenicity.

Because potassium plays a crucial role in cardiac electrophysiology, potassium derangements are particularly arrhythmogenic. Hypokalemia causes cellular hyperpolarization and impairs membrane potassium conductance, which hinders cell repolarization and prolongs the action potential. Hypokalemia, via suppression of the sodium-potassium adenosine triphosphatase, also causes intracellular sodium and calcium ions to accumulate, which further prolongs repolarization and predisposes the cell to early afterdepolarizations. These early afterdepolarizations can cause widespread repolarization inhomogeneity and trigger reentrant arrhythmias.[19] Therefore, hypokalemia is strongly associated with abnormal cardiac excitability and ectopy with a proclivity toward atrial and ventricular tachyarrhythmias and sudden cardiac death.[4] These mechanisms are reflected in observational studies wherein hypokalemia was associated with an increased risk for AF in an older, community-based population,[20] and patients undergoing cardiac surgery with preoperative hypokalemia had increased rates of postoperative AF.[21] Moreover, potassium repletion can reduce or suppress arrhythmias and remains an important acute therapy. In the HD population, a study that implanted loop recorders in 71 HD patients found in (likely overfitted) multivariate analysis that AF was significantly associated with hypokalemia (serum-[K^+] <4 mmol/l) but not hyperkalemia (serum-[K^+] >5 mmol/l). In fact, the point estimate suggested that serum-[K^+] >5 mmol/l may even be mildly protective against AF, although the finding was not statistically significant.[22]

We did not find an association between hyperkalemia and incident AF. Whereas point-estimates suggest that very high levels of hyperkalemia (serum-[K^+] > 6.5 mEq/l) may be associated with incident AF, the confidence bands did not support statistical significance. One possible reason is that patients with ESKD can adapt and tolerate higher serum-[K^+] over time,[23] which may explain why patients with a serum-[K^+] between 5 and 5.5 mEq/l had the lowest risk for incident AF in our cohort. Hyperkalemia also differs from hypokalemia in how it exerts its arrhythmogenic effects. Hyperkalemia causes cell depolarization and lowers the resting membrane potential, initially making it easier for action potentials to fire. However, as the serum-[K^+] rises, the cell becomes further depolarized and action potential generating ion channels become inactivated, suppressing electrical conduction.[19] Thus, the hallmark of severe hyperkalemia is impaired conduction and progressive bradycardia.[19] Though there are mechanisms that can generate tachyarrhythmias in a hyperkalemic heart, the more typical cause of sudden cardiac death in hyperkalemia is asystole.[19] This is illustrated in a study that implanted loop recorders in HD patients and found that 87% of all clinically significant arrhythmias recorded were bradycardias, which predominantly clustered around the hours right

Figure 3. (continued) increase by 0.5 mEq/l in serum potassium across a range of serum potassium from 2.0–7.5 mEq/l. The referent serum potassium level is listed in the upper row of tick mark values ("FROM") and the counterfactually increased serum potassium level is stated in the lower row of values ("TO") for which the corresponding HR (95% CI) associated with the 0.5 mEq increase is shown vertically above. For example, the fully adjusted HR for a serum potassium increase from 4.5–5 mEq/l is estimated at 0.96 (0.92–0.99) and the fully adjusted HR for a serum potassium from 6.5–7 mEq/l is estimated at 1.08 (0.95–1.21). All models were stratified by year of incident kidney failure. Model 1 – serum-[K^+] (continuous and quadratic term) + dialysate-[K^+] (categorical); Model 2 – model 1 + age, sex, race, Hispanic ethnicity, census division, socioeconomic status variables, and Medicaid dual eligibility; Model 3 – model 2 + comorbidities, number of hospital days, and vascular access, systolic blood pressure, diastolic blood pressure, count of monthly hemodialysis sessions, estimated glomerular filtration rate at hemodialysis initiation, serum calcium concentration, serum albumin concentration, and delivered ultrafiltration rate. CI, confidence interval.

before the next dialysis session.[3,24] Asystole was the second highest clinically significant arrhythmia with 14 events whereas there was only 1 sustained ventricular tachycardia event.[3] Although the hours leading up to the next HD treatment constitute a period when potassium levels tend to be the highest, other derangements accumulate at the same time, such as interdialytic volume expansion, which may confound this potential association. Another study that monitored 66 HD patients with implantable loop recorders found that hyperkalemia (serum-[K^+] >5 mmol/l) was significantly associated with conduction disorders, including bradycardia and asystole whereas hypokalemia (serum-[K^+] <4 mmol/l) was more associated with ventricular arrhythmias.[22] No association of serum or dialysate-[K^+] with AF was identified in this cohort.[25]

Observational studies have generally found an association between a lower dialysate-[K^+] bath (<2 mEq/l) and increased risks for arrhythmias, sudden cardiac arrests, or mortality[6,26,27] (although this was not consistently found in all studies),[28,29] thereby generating the hypothesis that the generation of a large serum-to-dialysate [K^+] gradient with a low dialysate-[K+] bath could be arrhythmogenic.[30] In our study, whereas a dialysate-[K^+] of 2 mEq/l versus 3 mEq/l was associated with a higher risk for incident AF, a formal test for interaction was not statistically significant, suggesting that the choice of dialysate-[K^+] independently contributes to the associated risk for incident AF regardless of the predialysis serum dialysate-[K^+] and vice versa. Evidence that a large serum-to-dialysate [K^+] gradient is associated with adverse outcomes has been mixed. A study by Brunelli *et al*.[31] found that increasing serum-to-dialysate [K^+] gradients were associated with increased odds for emergency department visits and all-cause hospitalizations, and a trend toward increased odds for cardiovascular hospitalizations. In stratified analysis, Ferrey *et al*.[26] found that a 1 mEq/l dialysate [K^+] bath was associated with higher mortality for patients with a predialysis serum [K^+] ≥5 mEq/l versus <5 mEq/l suggesting that a higher potassium gradient leads to poor outcomes. However, a study by Pun *et al*.[6] showed that for subjects exposed to a dialysate-[K^+] <2 mEq/l, there was a trend toward a decreasing risk for sudden cardiac arrest as the serum-[K^+] (and the serum-to-dialysate [K^+] gradient) increased. Conversely, the risk for sudden cardiac arrest with a dialysate-[K^+] ≥2 mEq/l increased as the serum [K^+] increased, suggesting that the postdialysis serum [K^+] may play a greater role in determining risk for sudden cardiac death.[6] Kovesdy *et al*.[29] also found that dialyzing patients with a higher serum-[K^+] against a lower-[K^+] bath (and thus a higher serum-to-dialysate [K^+] gradient) was associated with decreased all-cause mortality. Yet, for patients with a serum-[K^+] between 3.5 and 4.0 mEq/l, there was a trend toward increasing harm with a lower dialysate-[K^+] bath.[29] Again, this study suggests that the postdialysis serum-[K^+] likely contributes more to outcomes than the serum-to-dialysate [K^+] gradient. Likewise, in the present study, it is possible that the lower 2 mEq/l dialysate-[K^+] bath predisposed subjects in our study to postdialysis hypokalemia more often than the 3 mEq/l dialysate-[K^+] bath, which then increased the risk for incident AF. Therefore, whether a large serum-to-dialysate [K^+] gradient in itself is arrhythmogenic and leads to poor outcomes still requires further investigation. However, assuming that the associations found in this study are causal, substituting dialysate-[K+] of 2 mEq/l with a bath that has a dialysate-[K+] of 3 mEq/l could lead to a reduction of 1.7 incident AF cases/100 person-years, which we would consider clinically important. Nevertheless, regardless of the arrhythmogenic mechanism, it is generally agreed upon that avoiding extremes of dyskalemias should be beneficial for reducing the risk for arrhythmias in patients on HD.[4,32]

The present study has several important strengths, but also limitations that merit discussion. Drawing data from the electronic health records of a large, nationally operating dialysis provider provided highly granular data on laboratory markers, vital parameters, and dialysis treatment parameters. This information was merged with billing claims data from Medicare, the national public payor for the vast majority of US persons older than 65 years, which allows comprehensive capture of all health care encounters, and associated diagnoses and procedures even prior to start of dialysis in older persons nearing kidney failure. Therefore, we were able to study a large number of subjects with excellent representation of racial and ethnic minority groups in real world settings, which enhances generalizability, but were unable to study individuals under the age of 67 years. We required survival to 121 days from dialysis initiation to be able to have patients establish their care with the dialysis provider and be able to ascertain exposure and important confounder information. This limited our ability to study these patients sooner after dialysis initiation during which incidence of AF is highest. Utilization of a time-updated approach ensured that both exposure and potential confounding variables were up-to-date, thus minimizing misclassification. However, a limitation inherent in the availability of data and reflection of clinical practice in dialysis care, we did not have predialysis serum [K^+] from each dialysis session, which required the chosen approach of using the most recent measurement from the preceding 30-day interval. Relatively few patients (<7%) had moderate to severe hyperkalemia, which may have limited our

power to detect any smaller, but clinically important associations with AF risk in the hyperkalemic range. We did not have access to electrocardiograms or rhythm monitoring device tracings, and instead relied on identifying AF from claims, an approach that is highly specific, but limited in sensitivity, and we therefore may have missed some AF events. We did not use data on prescription drugs, which were unavailable in a large number of patients, and had no data on residual kidney function. Finally, our study's observational nature precludes us from making causal inferences and there may be residual confounding, including time-dependent residual confounding, despite our comprehensive multivariate adjustment and time-updating approach.

We conclude that lower predialysis serum-[K+], even within the low normal range, associate with significantly elevated rates of incident AF. Similar associations with high serum [K^+] were not found, at least not within the mild to moderate hyperkalemic range. In contrast, choice of dialysate potassium concentration was robustly associated with AF risk in that persons dialyzed against a 2 mEq/l dialysate-[K^+] had significantly higher rates of AF, independent of their serum-[K^+]. The findings support broad adoption of dialysate solutions with a dialysate-[K^+] of 3 mEq/l, regardless of patients' serum-[K+], and elimination of lower dialysate-[K+] solutions. Clinical trials randomizing patients undergoing hemodialysis to different concentrations of dialysate-[K^+] are warranted to establish causality.

DISCLOSURE

WCW reports having served as a scientific advisor to Akebia/Otsuka, AstraZeneca, Bayer, Boehringer Ingelheim/Lilly, GlaxoSmithKline, Janssen, Merck, and Relypsa/Vifor Fresenius Medical Care Renal Pharma, and on clinical trial committees for Akebia, Bayer, Merck, and the Duke Clinical Research Institute. He gave a lecture at an event sponsored by Pharmacosmos. MPT reports personal fees from Medtronic Inc, personal fees from Abbott, grants from Bristol Myers Squibb, grants from American Heart Association, personal fees from Biotronik, personal fees from Sanofi, personal fees from Pfizer, grants from Apple, grants and personal fees from Bayer, personal fees from Myokardia, personal fees from Johnson & Johnson, personal fees from Milestone Pharmaceuticals, personal fees from InCarda Pharmaceuticals, personal fees from 100Plus, personal fees from AliveCor, grants from Food and Drug Administration, personal fees from Acutus Medical, personal fees from BrightInsight, outside the submitted work. TIC reports serving as a consultant for Bayer, Janssen Pharmaceuticals, Novo Nordisk, Fresenius Medical Care, Tricida, Gilead and AstraZeneca; and has received grant support from Satellite Healthcare, the American Heart Association and the National Institutes of Health. None is related to the current work. None of the remaining authors have any relationships with industry to disclose.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Sensitivity Analysis: Restricted to patients who had no change in dialysate-[K^+] prior to index date.

Table S1. Characteristics of the study cohort overall and by serum potassium baseline.

Table S2. Incidence of atrial fibrillation by dialysate potassium concentration, all 15,190 patients versus restriction to 9743 patients without change of dialysate composition prior to day 121 of dialysis.

STROBE Statement.

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