Implantable Loop Recorder Monitoring and the Incidence of Previously Unrecognized Atrial Fibrillation in Patients on Hemodialysis

Bruce A. Koplan[1,12], Wolfgang C. Winkelmayer[2,12], Alexandru I. Costea[3], Prabir Roy-Chaudhury[4,5], James A. Tumlin[6], Vijay Kher[7], Don E. Williamson[8], Saurabh Pokhariyal[9] and David M. Charytan[10]; on behalf of the Monitoring in Dialysis (MiD) Investigators and Committees[11]

[1]Cardiology Division, Brigham & Women's Hospital, Boston, Massachusetts, USA; [2]Section of Nephrology, Baylor College of Medicine, Houston, Texas, USA; [3]Cardiology Division, University of Cincinnati School of Medicine, Cincinnati, Ohio, USA; [4]Department of Medicine, University of North Carolina Kidney Center, Chapel Hill, North Carolina, USA; [5]Department of Medicine, WG (Bill) Hefner VA Medical Center, Salisbury, North Carolina, USA; [6]Georgia Nephrology Clinical Research Institute, Atlanta, Georgia, USA; [7]Medanta Kidney & Urology Institute, Medanta, The Medicity, Gurugram, India; [8]Southeastern Clinical Research Institute, Augusta, Georgia, USA; [9]Division of Nephrology and Renal Transplantation, Manipal Hospitals, Dwarka, New Delhi, India; and [10]Nephrology Division, NYU Grossman School of Medicine, New York, New York, USA

Introduction: Atrial fibrillation (AF) is common in patients with kidney failure on hemodialysis (KF-HD). We determined both AF incidence and burden in patients with KF-HD using implantable loop recorder (ILR) monitoring.

Methods: Patients with KF-HD were enrolled and received an ILR. In 6 monitoring months, the incidence of AF events lasting ≥6 minutes was captured. Demographic, clinical, and dialysis characteristics were collected, and associations with incident AF were estimated using negative binomial regression models and expressed as incidence rate ratios and 95% CIs.

Results: We enrolled 66 patients with KF-HD (mean age = 56 years, 70% male); 59 (90%) were without previously diagnosed AF. AF lasting ≥6 minutes was detected in 18 of 59 subjects (31%) without previously diagnosed AF and in 5 of 7 subjects (71%) with a previous AF diagnosis. Among the 23 with detected AF, episodes were present on 16% of patient days. Although 14 of 23 patients (61%) had AF on <5% of monitored days, the average duration of AF episodes was <1 hour in 13 of 23 patients (52%). Among patients with AF ≥6 minutes, 19 of 23 (83%) had a CHA_2DS_2-VASc score ≥2. When investigating individual HD parameters, higher dialysate calcium (>2.5 vs. 2.5 mEq/l: incidence rate ratio = 0.62; 95% CI, 0.48–0.80) was associated with lower AF risk whereas higher dialysate bicarbonate concentrations (>35 vs. 35 mEq/l: incidence rate ratio = 3.18; 95% CI, 1.13–8.94) were associated with higher AF risk.

Conclusion: New AF was detected in approximately one-third of patients with KF-HD. AF affects a substantial proportion of patient days and may be an underappreciated cause of stroke in KF-HD.

AF is the most common arrhythmia and has been estimated to be present in 3 to 5 million Americans and >33 million individuals worldwide. AF is associated with 4- to 5-fold rates of ischemic stroke and with increased risks of several other important health events, including heart failure and mortality, and a significant burden of health care-related costs.[1]

The burden of AF is particularly high in persons with kidney disease.[2] Chronic kidney disease is associated with an increased incidence of AF, wherein both reduced estimated glomerular filtration rate and higher proteinuria associate with AF risk.[3] AF is particularly common in persons with KF-HD, a population in which both its incidence and its prevalence have been

Correspondence: Wolfgang C. Winkelmayer, Section of Nephrology, Baylor College of Medicine, One Baylor Plaza, MS: 395, Houston, Texas 77030, USA. E-mail: winkelma@bcm.edu

[11]Members of Monitoring in Dialysis (MiD) Investigators and Committees are listed in the Appendix.

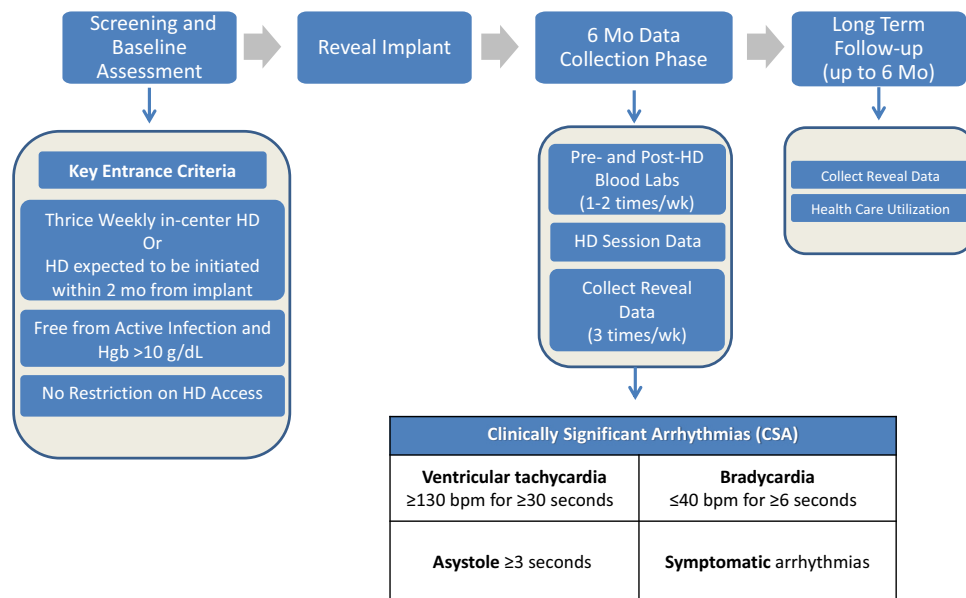[12]BAK and WCW contributed equally to this work.

Figure 1. Overview of the Monitoring in Dialysis study design. The primary outcome was the occurrence of CSAs. Atrial fibrillation data were collected as a secondary outcome. bpm, beats per minute; CSA, clinically significant arrhythmia; HD, hemodialysis; Hgb, hemoglobin; mo, month; wk, week.

increasing.[4,5] Patients with KF-HD are also at a dramatically higher risk of hospitalization for hemorrhagic and ischemic strokes compared with the general population,[6] and even short durations of AF in this population can increase stroke risk.[7] These data suggest that patients with KF might have a high incidence of undetected AF, but subclinical AF in the dialysis population has not been well studied. Previous monitoring studies identified a significant proportion of patients with new-onset AF during follow-up,[8,9] and the present study sought to confirm and expand on these observations.

To address the incidence and burden of AF in persons with KF-HD, we conducted a prospective study using ILRs in persons with KF undergoing regular-maintenance HD. We hypothesized that ILR monitoring would provide potentially actionable information by detecting and quantifying AF in patients on HD.

METHODS

Study Design—Patients and Procedures

The Monitoring in Dialysis study was a prospective multicenter, single-arm observational study designed to characterize arrhythmias in patients with KF-HD (Figure 1).[10,11] The primary objective was to estimate the proportion of subjects experiencing clinically significant arrhythmias in a 6-month period of continuous monitoring using an ILR (Reveal XT or LINQ, Medtronic USA, Ltd., Minneapolis, MN). Quantification of atrial arrhythmias, including AF, was a prespecified, key secondary objective. The study was approved by the governing institutional review board or ethics committee at each center, and all eligible patients

provide informed consent. Patients ≥21 years old undergoing HD thrice weekly were enrolled at 10 sites in the United States and India. Key exclusion criteria included presence of an implantable defibrillator or pacemaker, recent infection, or expected survival <6 months.

After the implant procedure, subjects downloaded device tracings at each dialysis session for 6 months. Long-term follow-up continued for a maximum of 12 months or until the last enrolled subject completed the primary observation period. During long-term follow-up, devices were downloaded at least once weekly. Study coordinators and cardiologists reviewed transmissions regularly to identify prespecified, potentially dangerous arrhythmias, which mandated clinical intervention. The study sponsor reviewed all patient-marked events and transmissions with ILR-detected arrhythmia. A core laboratory adjudicated all events potentially consistent with the prespecified primary objective; ventricular tachycardia ≥ 130 beats per minute for ≥30 seconds, bradycardia of ≤40 beats per minute lasting ≥6 seconds, asystole ≥3 seconds, or patient-marked events with possible arrhythmia.

Outcome—AF

AF episodes, and their duration, were identified using ILR, which allows detection of AF events that would be missed with short-term observation. Studies comparing this technology against Holter monitoring revealed 92% sensitivity and 80% positive predictive value for ILR-detected AF episodes of ≥6 minutes in duration.[12] The utility of this approach was demonstrated by the

Table 1. Baseline characteristics according to presence or absence of atrial fibrillation during follow-up

Characteristics	All Subjects (N = 66)	No Atrial Fibrillation (n = 43)	Atrial Fibrillation (n = 23)	P value
Age at implant, yrs	56.3 ± 12.2	56.6 ± 10.8	55.9 ± 14.7	0.83
Male sex	69.7% (46/66)	69.8% (30/43)	69.6% (16/23)	1.00
Race				0.05
Asian	34.8% (23/66)	44.2% (19/43)	17.4% (4/23)	
Black	53.0% (35/66)	48.8% (21/43)	60.9% (14/23)	
Other	1.5% (1/66)	0.0% (0/43)	4.3% (1/23)	
White	10.6% (7/66)	7.0% (3/43)	17.4% (4/23)	
Systolic blood pressure, mm Hg	140.8 ± 23.4	142.7 ± 22.2	137.2 ± 25.6	0.37
Diastolic blood pressure, mm Hg	80.0 (70.0–84.0)	80.0 (67.0–84.0)	76.0 (70.0–85.0)	0.99
Weight (kg)	81.7 (68.2–95.2)	80.4 (67.6–90.0)	88.7 (68.2–119.6)	0.15
Body mass index, kg/m^2	27.2 (24.3–32.5)	26.1 (23.8–31.6)	27.9 (25.4–35.4)	0.16
Presumed cause of KF				
Diabetes	42.4% (28/66)	44.2% (19/43)	39.1% (9/23)	0.75
Hypertension	37.9% (25/66)	34.9% (15/43)	43.5% (10/23)	
Glomerulonephritis	9.1 (6/66)	11.6% (5/43)	4.3% (1/23)	
Other	10.6% (7/66)	9.3% (4/43)	13.0% (3/23)	
Time since onset of KF (yrs)	2.4 (1.2–5.3) (n = 65)	2.2 (1.0–5.2) (n = 42)	3.8 (1.2–6.6) (n = 23)	0.28
Previous kidney transplant	13.6% (9/66)	9.3% (4/43)	21.7% (5/23)	0.26
Previous peritoneal dialysis	10.6% (7/66)	7.0% (3/43)	17.4% (4/23)	0.23
Vascular access				0.22
Arteriovenous fistula	69.2% (45/65)	72.1% (31/43)	63.6% (14/22)	
Arteriovenous graft	26.2% (17/65)	20.9% (9/43)	36.4% (8/22)	
Central venous catheter	4.6% (3/65)	7.0% (3/43)	0.0% (0/22)	
Diabetes	63.6% (42/66)	62.3% (27/43)	65.2% (15/23)	1.00
Atrial fibrillation	10.6% (7/66)	4.7% (2/43)	21.7% (5/23)	0.05
Other arrhythmia	31.8% (21/66)	20.9% (9/43)	52.2% (12/23)	0.01
Previous myocardial infarction	9.1% (6/66)	7.0% (3/43)	13.0% (3/23)	0.42
Previous stroke	12.1% (8/66)	14.0% (6/43)	8.7% (2/23)	0.70
Hyperlipidemia	60.6% (40/66)	55.8% (24/43)	69.6% (16/23)	0.30
Hypertension	84.8% (56/66)	86.0% (37/43)	82.6% (19/23)	0.73
Ischemic heart disease	48.5% (32/66)	46.5% (20/43)	52.2% (12/23)	0.80
Heart failure	25.8% (17/66)	20.9% (9/43)	34.8% (8/23)	0.25
Coronary artery bypass surgery	13.6% (9/66)	16.3% (7/43)	8.7% (2/23)	0.48
Smoking				0.84
Current	7.6% (5/66)	7.0% (3/43)	8.7% (2/23)	
Never	69.7% (46/66)	72.1% (31/43)	65.2% (15/23)	
Past	22.7% (15/66)	20.9% (9/43)	26.1% (6/23)	
Ejection fraction, %	55 (55–60) (n = 65)	55 (55–60) (n = 42)	55 (55–60) (n = 23)	0.83
CHA$_2$DS$_2$-VASc score	3 (2–5)	3 (1–4)	3 (2–5)	0.48

KF, kidney failure.
P value from unpaired t test or Wilcoxon-ranked sum test for continuous variables and χ^2 or Fisher exact tests for categorical variables.

Cryptogenic Stroke and Underlying AF trial,[13] in which ILRs identified episodes of AF lasting ≥30 seconds 6.4 times more often than standard clinical monitoring techniques. More importantly, it was found that 12.4% of the patients in the ILR group had newly diagnosed AF at 12 months of monitoring, whereas detection of AF was 30% at 36 months of follow-up. Conversely, a previous study revealed that monitor-detected, subclinical AF was associated with significantly increased risks of strokes and systemic embolism.[14]

Patient Characteristics

We recorded patients' age, sex, race, several comorbid conditions, and their reported causes of KF. We also calculated the CHA$_2$DS$_2$-VASc score, a recommended tool to identify persons at elevated stroke risk.[15] We recorded any history of peritoneal dialysis or kidney transplant and the duration of kidney replacement therapy ("vintage"). HD parameters included blood pressure measurements and ion concentrations in the prescribed dialysate, which were collected each session; predialysis and postdialysis serum electrolyte concentrations were measured at least weekly for 6 months. The primary findings of the Monitoring in Dialysis study have been reported previously.[11]

Statistical Analyses

We present baseline demographic characteristics for the entire study sample and separately for subjects with at least 1 AF event versus those without. Data are tabulated

Table 2. Number and rate of AF events

Parameter	Reveal-detected AF	Reveal-detected AF of at least 6 min in duration
Number of events	4419	1710
Subjects with events (% of subjects with any reveal data)	27 (41%)	23 (35%)
Estimated events per patient mo [95% confidence bounds]	11.9 [4.9–28.7]	4.6 [1.8–11.5]

AF, atrial fibrillation.

as count (%), mean (± SD), or median (interquartile range) as appropriate. Characteristics were compared between subjects with versus those without at least 1 AF episode using an unpaired t test or Wilcoxon-ranked sum test for continuous variables, whereas χ^2 or Fisher exact test was used for categorical variables.

Generalized negative binomial mixed effects regression models with unstructured working correlation structure and using the SAS default optimization method of Dual Quasi-Newton were used to evaluate potential effects of electrolytes on the incidence of AF during the 12-hour period beginning with the start of each dialysis session. This interval was chosen because it is the period of maximal intradialytic fluid and electrolyte flux and postdialytic re-equilibration. In addition, AF events were clustered during this time period. A random intercept was included in the model to account for repeated measures within subjects. In the presence of convergence issues or problems with estimating variance, an alternative optimization method was used. Associations of AF with hospitalization were analyzed using univariate Cox regression. A $P < 0.05$ was considered statistically significant. All analyses were completed using SAS version 9.3 (The SAS Institute, Cary, NC; www.sas.com).

RESULTS

Baseline Characteristics
A total of 66 patients underwent ILR placement and were followed for a median of 177 days (range 14–180 days). Baseline demographics are found in Table 1 and Supplementary Table 1. A previous diagnosis of AF or atrial flutter was present in 7 subjects (11%): 2 had paroxysmal AF, 1 had permanent AF, and 2 reported atrial flutter. The baseline history of AF was unclassified in the remaining 2 subjects. There were few meaningful differences between subjects with versus those without AF during follow-up. Mean age was 56.3 years, and 30% were of female sex (vs. 30%), both similar between groups. Nevertheless, history of ischemic heart disease and history of heart failure were more common in the AF group, albeit not statistically significant, whereas ejection fraction did not differ between groups. In contrast, a history of arrhythmia was more common in subjects in whom AF was recorded during follow-up than among

those without (52% vs. 21%, $P = 0.01$). In addition, severe obesity (body mass index ≥ 40 kg/m^2) was more prevalent among individuals with AF than those without (22% vs. 2%, $P = 0.02$).

AF Episodes and Stroke Risk Factors
During up to 6 months of rhythm monitoring, any AF was detected in 27 subjects (41%) and AF episodes ≥ 6 minutes long were recorded in 23 subjects (35%; Table 2), Excluding the 7 subjects with a history of AF (2 of whom did not have AF detected during monitoring), 18 of 59 subjects (31%) had *de novo* detection of AF episodes lasting ≥ 6 minutes during the 6-month observation period. During 4016 monitoring days, 2967 hours of AF were detected. There were 1710 episodes lasting ≥ 6 minutes, which occurred on 627 patient days (16%) , with an average ventricular response rate of 103 beats per minute. In the subgroup of 23 subjects with any AF episodes of ≥ 6 minutes in duration, the median number of days with AF was 7, ranging from 1 subject with a single AF episode to a different subject with 161 days with AF (Table 3 and Figure 2a–c).

The mean CHA$_2$DS$_2$-VASc score in the subjects without previous AF in whom *de novo* AF was detected was 3.2. In addition, 2 patients in this cohort had a history of a cerebrovascular accident or transient ischemic attack and were not on baseline anticoagulation. Data from individual subjects in the study with AF detected are found in Table 3.

AF Predictors and Hospitalizations
In unadjusted analyses, no associations with AF were found between predialysis ion concentrations or their intradialytic changes, except for a borderline association between higher predialysis phosphorus concentration and AF (Table 4). By contrast, there were associations with AF of ion concentrations in the dialysis bath (Supplementary Table 2), specifically for dialysate calcium and bicarbonate concentrations. Compared with a dialysate calcium concentration of 2.5 mEq/l, those in whom it was >2.5 mEq/l were less likely to have AF. Compared with persons whose dialysate bicarbonate concentration was 35 mEq/l, those in whom it was >35 mEq/l had a higher AF risk (Table 4). No episodes of AF were detected within 8 hours of dialysis performed with sodium modeling. No associations with AF were found for dialysate potassium, dialysate temperature, and intradialytic weight change. Nevertheless, there was evidence of a significant interaction ($P_{interaction} = 0.01$) between the intradialytic change in calcium and the weight change during dialysis such that a greater increase in serum calcium concentration during dialysis was more strongly associated with increased incidence

Table 3. Atrial fibrillation duration, stroke history, anticoagulation, and CHA_2DS_2-VASc score in subjects with AF ≥6 minutes detected during the observation period

Patient number	Monitoring days	Hours of AF	Days with ≥6min of AF (n)	AF episodes ≥6 min (n)	Mean ventricular rate during AF (bpm)	Previous CVA or TIA	Previous AF	Anticoagulation at baseline	CHA_2DS_2-VAS score
1	168	1304.4	55	3	111	–	–	+	2
2	177	868.1	161	620	86	–	+	–	6
3	161	423.4	133	564	86	–	–	–	5
4	177	150.8	22	154	67	–	+	+	5
5	177	64.7	32	60	106	–	–	–	5
6	179	55.7	98	180	62	+	–	–	6
7	177	26.2	40	54	72	–	–	+	6
8	178	24.8	4	3	120	–	–	+	2
9	177	16.3	9	9	104	–	–	–	4
10	168	5.9	3	4	150	–	–	+	3
11	177	5.3	18	9	125	+	–	–	5
12	158	5.2	13	19	117	–	–	–	2
13	179	4.6	4	4	110	–	–	–	3
14	177	4.1	2	2	166	–	+	–	4
15	175	1.8	7	4	113	–	–	–	1
16	177	1.7	6	3	135	–	–	–	1
17	179	1.5	7	7	99	–	+	+	1
18	177	0.9	5	4	89	–	+	+	2
19	177	0.5	2	2	137	–	–	–	2
20	178	0.5	2	1	79	–	–	–	5
21	179	0.3	2	2	109	–	–	–	1
22	177	0.3	1	1	81	–	–	–	3
23	167	0.2	1	1	39	–	–	–	2
Total/mean:	4016	2967.2	627	1710	103	2	5	7	3.3

AF, atrial fibrillation; bpm, beats per minute; CVA, cerebrovascular accident; TIA, transient ischemic attack.

of AF as the volume of fluid removed during dialysis increased (Figure 3a). There was also suggestion of a borderline significant interaction between the intradialytic change in sodium concentration and weight change during dialysis ($P_{interaction} = 0.06$, Figure 3b). There was no evidence of interaction between the intradialytic weight and change in magnesium, potassium, or bicarbonate. We found that CHA_2DS_2-VASc score (continuous) was associated with number of AF episodes among patients with AF. Nevertheless, episode duration was not associated with CHA_2DS_2-VASc score.

There were 18 hospitalizations during the follow-up. The number of AF episodes >6 minutes was significantly associated with hospitalization (hazard ratio per 0.1 event/d = 1.06; 95% CI, 1.01–1.11). Having AF > 6 minutes during the last 7 days (hazard ratio = 3.17; 95% CI, 1.02–9.86) had a borderline association with hospitalization, and more remote episodes within the last 14 (hazard ratio = 1.64; 95%CI, 0.46–5.38) or 21 days (hazard ratio = 1.39; 95% CI, 0.39–4.94) were not associated with hospitalization risk.

DISCUSSION

Patients with KF requiring dialysis continue to have unacceptably high mortality (18% per year), with roughly 1 quarter of deaths attributed to sudden

(cardiac) death.[16] Less is known on the incidence of nonfatal arrhythmias, especially using modern heart rhythm monitoring technologies. In our prospective study of patients with KF on HD who were equipped with an ILR to capture both symptomatic and asymptomatic arrhythmias, we found that 35% of the patients had at least 1 sustained AF episode lasting at least 6 minutes in a 6-month monitoring period. Among patients not previously diagnosed with having AF, the proportion of newly diagnosed patients was 31%.

This incidence of AF likely underestimated the true population incidence because we monitored patients for only 6 months, but it is nevertheless significantly higher than what has previously been reported using other means of AF ascertainment.[4,17] One study used diagnostic codes in Medicare-insured US patients on HD (1995–2006) and estimated the prevalence of diagnosed AF to be 13%, 19%, and 23% in those aged 65 to 74, 75 to 84, and ≥85 years, respectively.[5] More recently, using electrocardiogram and electronic health record review, 27% of patients on HD in the greater Vienna, Austria metropolitan area were found to have AF, or a history of AF, in 2014/2015.[18] The high incidence in the Monitoring in Dialysis cohort is remarkably similar to that of a recent French study of 71 patients with KF on HD of whom 12 (17%) had previously diagnosed AF or flutter. When using ILR, the
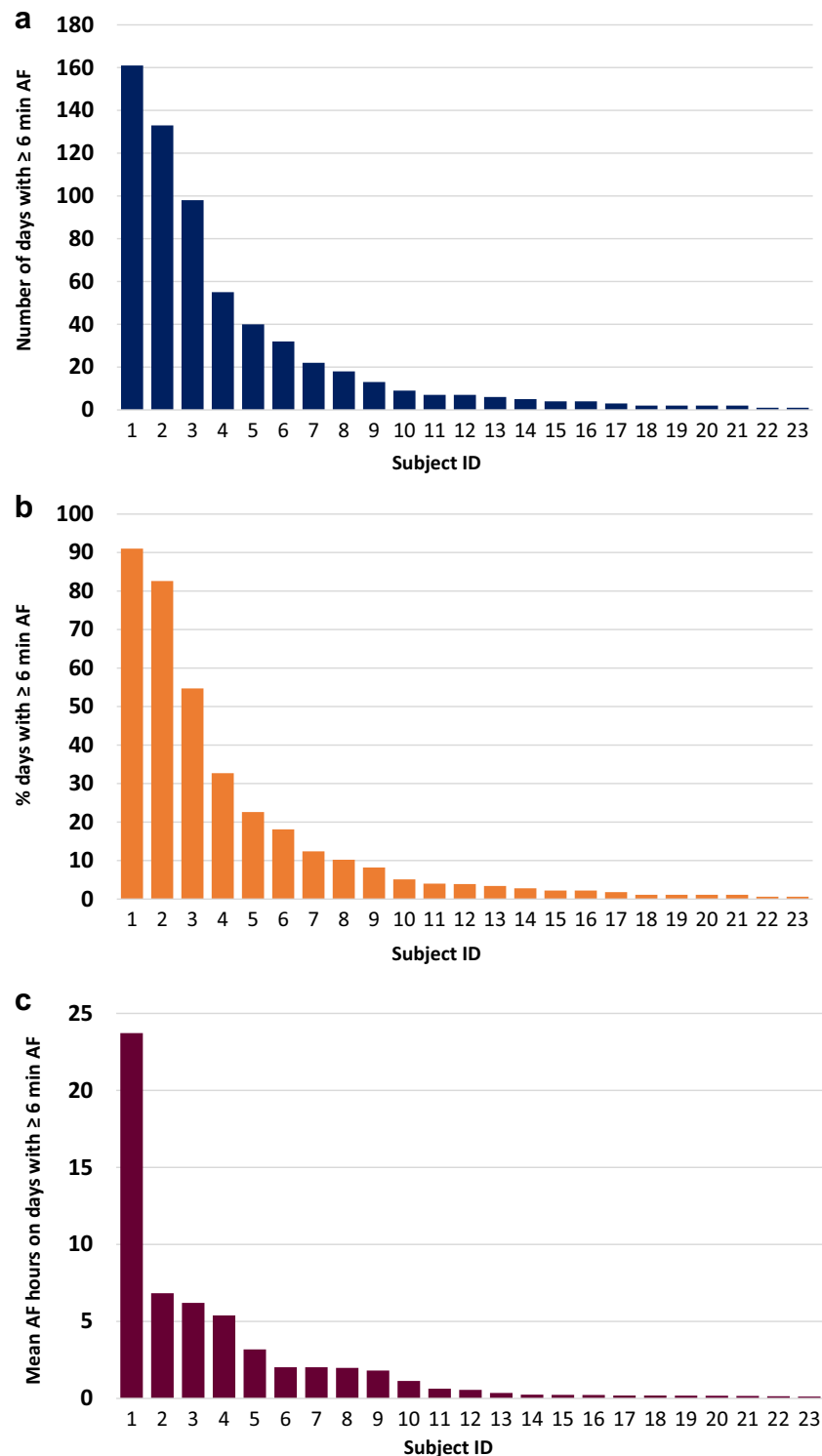
Figure 2. AF burden detected in MiD subjects who experienced at least 1 AF episode lasting ≥6 mins during the monitoring period. (a) Number of days with at least 6 mins of AF detected. (b) Percentage of days with AF episodes ≥ 6 mins detected. (c) Total duration of AF in hours on days with at least 1 episode of AF ≥ 6 mins. AF, atrial fibrillation; ID, identification; min, minute; MiD, Monitoring in Dialysis.

overall AF prevalence was 37% and *de novo* AF was detected in 20% during a mean follow-up of 21 months.[8] Similarly, an Australian study of 50 patients with KF on HD found new-onset paroxysmal AF in 28% of patients over a mean follow-up of 18 months.[9] These high AF rates are likely explained by the

continuous nature of the longer-term monitoring in these studies and the ability to pick up asymptomatic events which had previously not been feasible. These findings suggest that the already high prevalence of AF previously documented in this population has underestimated the true prevalence of this condition.

Table 4. Associations of electrolytes and dialysis parameters with atrial fibrillation rate from the beginning of each dialysis session to 8-hour postdialysis

Parameter	IRR (95% CI)	P Value
Electrolyte concentration		
Predialysis potassium	0.76 (0.40–1.44)	0.40
Intradialytic potassium change	1.10 (0.80–1.50)	0.56
Predialysis calcium	0.98 (0.64–1.51)	0.93
Intradialytic calcium change	0.82 (0.51–1.33)	0.43
Predialysis magnesium	0.94 (0.15–5.67)	0.94
Intradialytic magnesium change	0.32 (0.05–2.00)	0.22
Predialysis phosphorus	1.18 (1.01–1.37)	0.04
Intradialytic phosphorus change	0.80 (0.63–1.02)	0.08
Predialysis bicarbonate	1.02 (0.92–1.14)	0.70
Intradialytic bicarbonate change	1.06 (0.93–1.21)	0.40
Sodium predialysis	0.99 (0.84–1.16)	0.87
Intradialytic sodium change	1.05 (0.87–1.26)	0.64
Dialysis prescription parameters		
Dialysate temperature ≥37 vs. 36–36.9 °C	1.83 (0.04–81.0)	0.76
Dialysis potassium 3 vs. 2 mEq/l	1.22 (0.92–1.64)	0.17
Dialysate calcium	—	—
<2 vs. 2.5 mEq/l	0.03 (0.001–1.18)	0.06
2.0–2.4 vs. 2.5 mEq/l	5.04 (1.11–22.9)	0.04
>2.5 vs. 2.5 mEq/l	0.62 (0.48–0.80)	<0.001
Dialysate sodium	—	—
>135–139 vs. 140 mEq/l	0.15 (0.01–3.49)	0.24
≤135 vs. 140 mEq/l	4.52 (0.31–65.6)	0.27
Dialysate bicarbonate	—	—
≤28 vs. 35 mEq/l	21.32 (0.08–5927)	0.29
>28–34 vs. 35 mEq/l	3.41 (0.12–96.4)	0.47
>35 vs. 35 mEq/l	3.18 (1.13–8.94)	0.03
Intradialytic weight change (per % of weight)	0.93 (0.75–1.16)	0.51
CHA_2DS_2-VASc score (per unit)	2.59 (1.99–3.37)	<0.001

IRR, incidence rate ratio.
Unadjusted associations of characteristics with presence of any atrial fibrillation episode of >6 minutes in duration for the 8-hour time window from the start of the dialysis session using negative binomial regression. All sessions were included; analyses accounted for repeated measures within subjects.

Furthermore, when comparing our findings with previous data evaluating the incidence of AF in a general population (with largely normal kidney function) at similar age ranges, the incidence of AF in this cohort of persons with KF on HD was >10-fold higher.[19]

There are important public health implications to the possibility that approximately 31% to 42% of patients on HD without known AF experience sustained subclinical episodes during a relatively short period of follow-up and that the burden of time spent in AF in many of these patients is high. Monitor-detected AF has been associated in other populations with substantially increased risks of ischemic stroke,[14] and a high incidence of subclinical AF has been identified in individuals with otherwise cryptogenic stroke.[13,20] Although we did not detect any strokes during a relatively short-term observation period, we did find a potential association of these monitor-detected AF events and hospitalization. Moreover, our findings raise the possibility that the extraordinarily high stroke

incidence in patients on chronic HD (4 to 10 times that of age- and sex-matched non–end-stage renal disease individuals) may at least partly be explained by a high prevalence of asymptomatic or undiagnosed AF that may only become clinically apparent at the time of cerebral embolism.[6]

Even using conservative estimates of the range of AF detection after 6 months (i.e., no further AF detection after 6 months), our data suggest that surveillance with continuous monitoring technology has potential value in identifying patients on HD at risk for ischemic stroke in whom chronic anticoagulation may be beneficial in suitable patients. Indeed, CHA_2DS_2-VASc scores, which help identify patients at elevated ischemic stroke risk in the general population with AF and in patients on dialysis, were above the threshold in which anticoagulation is recommended in the general population with AF according to standard guidelines.[21–23] Thus, a strategy of routine ILR insertion followed by anticoagulation based on monitoring results may have potential as a novel strategy for improving outcomes in the population on HD by preventing ischemic stroke. Previous studies have struggled to enroll patients for ILR placement and subsequent observation. Modern devices such as external patches that allow several weeks of monitoring and smart watches have additional convenience and may carry promise for broader use but have not yet been validated, and studies in persons on HD are needed. Future research will need to elucidate the relationship between subclinical AF and AF burden on stroke and embolic events in patients with KF on dialysis, including to provide more solid evidence in stronger support of net-benefit from oral anticoagulation in these patients.[23]

Additional findings from this study raise important questions regarding modifiable aspects of the dialysis prescription that may serve to reduce the incidence and burden of AF in patients undergoing HD. Although we found that high dialysate calcium was associated with lower and high bicarbonate concentrations with higher AF incidence, these results were unadjusted and can only generate hypotheses motivating more targeted studies focusing on elements of dialysis prescription that may affect AF incidence. Furthermore, although unadjusted, these results are consistent with previous investigations using signal-averaged electrocardiograms that revealed significant associations between intradialytic electrolyte changes or fluid removal and P-wave morphology.[24–26]

Several limitations of this study merit discussion. We enrolled prevalent patients with KF undergoing HD and may miss the period of highest AF incidence, which is during the first few months after dialysis
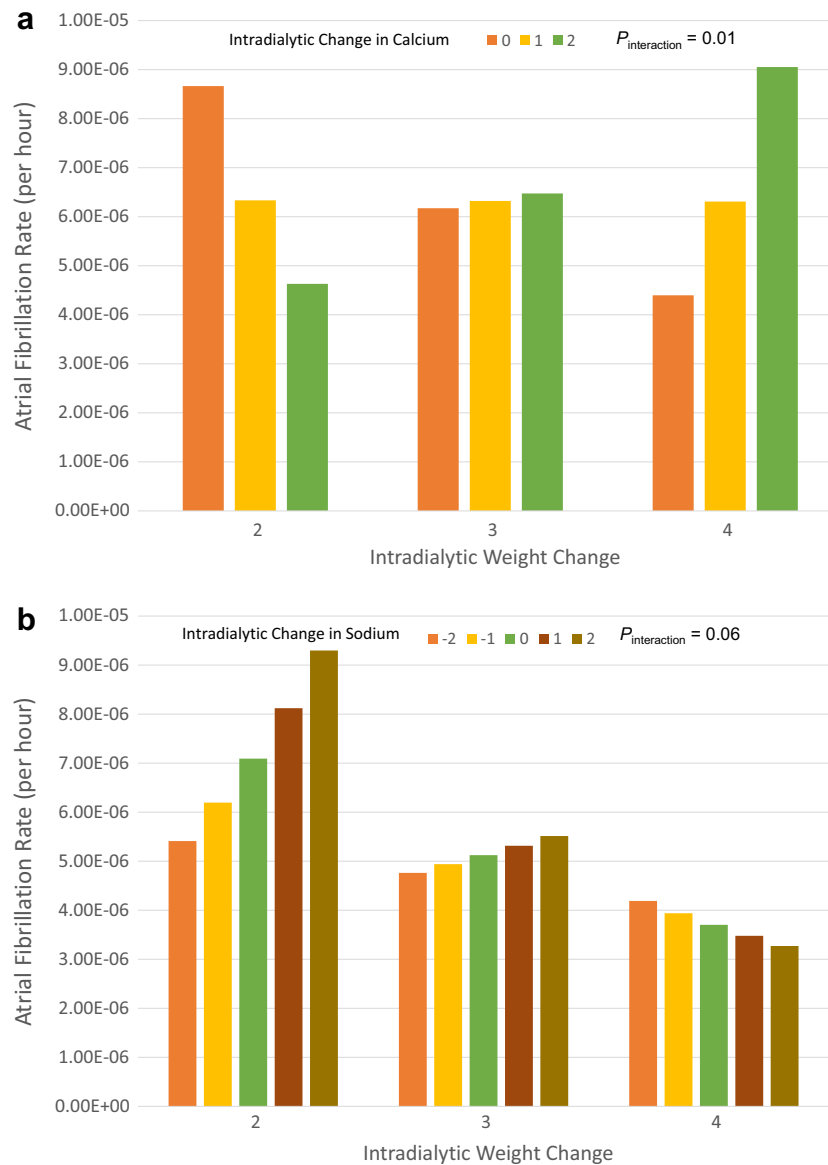
Figure 3. Interactions of intradialytic weight gain with intradialytic changes in calcium and sodium. Rate of atrial fibrillation during dialysis through 8 hours after dialysis according to intradialytic weight change in kilograms and (a) serum calcium or (b) sodium.

initiation.[27] Although 7 subjects (10%) had been previously diagnosed with having AF, several others may have had AF episodes that would have remained asymptomatic, undetected, or undiagnosed. The study used a convenience sample of patients that may not be generalizable to the overall population of patients with KF on HD in either country. In particular, certain racial/ethnic groups were not represented in our study, including Hispanic or Native American patients. In addition, the average dialysis vintage was relatively high and it would be useful to conduct a similar study in patients with incident KF commencing dialysis. A larger cohort size and/or longer follow-up time are necessary to perform subgroup analyses and to determine the association between the occurrence or time-burden of subclinical

AF and subsequent ischemic stroke risk and other health outcomes. Reporting of concurrent symptoms during AF episodes was poor, which precludes reporting this information with confidence. Finally, it is conceivable that if we had continued to monitor the patients for the duration of the implantable recorder's battery life (3 years), more silent AF would have been diagnosed.

In conclusion, our data demonstrate that there is a higher rate of AF in patients on HD than previously appreciated. In many, the burden of AF regarding the number of events and duration of time spent in AF was high. These data suggest the possibility that unrecognized AF is an important cause of stroke in the population on HD and that personalizing fluid removal or dialysate electrolyte prescription, or alternatively a

strategy of continuously monitoring for arrhythmia and anticoagulating patients with detected AF, may have the potential to reduce stroke and mortality in this vulnerable population.

APPENDIX

List of Monitoring in Dialysis (MiD) Investigators and Committees
Affiliations at the time of study.

Nephrology Investigators
Don Williamson, MD (Southeastern Clinical Research Institute, Augusta, GA, Augusta, GA), Prabir Roy-Chaudhury, MD, (University of Cincinnati Medical Center, Cincinnati, OH), James Tumlin, MD (Georgia Nephrology Clinical Research Institute, Atlanta, GA), Vijay Kher, MD (Medanta – The Medicity- Kidney & Urology Institute, Gurgaon, India), Vikranth Reddy, MD (CARE Hospital Hyderabad, India), Kowdle Chandrasekhar Prakash, MD, (Apollo Hospitals –Chennai, India), David Charytan, MD MSc (Brigham & Women's Hospital, Boston, MA), Suresh Chandra Tiwari, MD (Fortis Vasant Kunj Hospital Delhi, India), Saurabh Pokhariyal, MD (Fortis Memorial Research Institute Gurgaon, India), Amber Podoll, MD (University of Texas-Houston, Houston, TX), Sanjeev Jasuja, MD (Apollo Hospitals – Delhi, Delhi, India).

Cardiology Investigators
G. Leslie Walters, MD (Augusta Cardiology Clinic, Augusta, GA), Kraig Wangsnes, MD (Cardiovascular Associates, Augusta, GA), Alexandru Costea, MD (University of Cincinnati Medical Center, Cincinnati, OH), Selcuk Tombul, MD (Diagnostic Cardiology Group, Chattanooga, TN), Balbir Singh, MD (Medanta – The Medicity- Heart Institute, Gurgaon, India), Brajesh Mishra, MD (Medanta – The Medicity- Heart Institute, Gurgaon, India), Sachin Yalagudri, MD (CARE Hospital, Hyderabad, India), Abhijeet Shelke, MD (CARE Hospital Hyderabad, India), Calambur Narasimhan, MD (CARE Hospital, Hyderabad, India), A.M. Karthigesan, MD (Apollo Hospitals – Chennai, Chennai, India), Abraham Oomman, MD (Apollo Hospitals – Chennai, Chennai, India), K P Pramod Kumar, MD (Apollo Hospitals – Chennai, Chennai, India), Bruce Koplan, MD (Brigham & Women's Hospital, Boston, MA), Upendra Kaul, MD (Fortis Vasant Kunj Hospital, Delhi, India), Tapan Ghose, MD (Fortis Vasant Kunj Hospital, Delhi, India), Ripen Gupta, MD (Fortis Vasant Kunj Hospital, Delhi, India), Arvind Sethi, MD (Fortis Escorts Hospital, Delhi, India), Nikhil Kumar, MD (Fortis Memorial Research Institute, Gurgaon, India), Ramesh Hariharan, MD, (University of Texas-Houston, Houston, TX), Rajnish Sardana, MD (Apollo Hospitals – Delhi, Delhi,

India), Arif Wahab, MD (Apollo Hospitals – Delhi, Delhi, India) N.N Khanna, MD (Apollo Hospitals – Delhi, Delhi, India)

Nephrology Coinvestigators
Mark Smith, MD (Southeastern Clinical Research Institute, Augusta, GA), Suresh Kamath, MD (University of Cincinnati Medical Center, Cincinnati, OH), Claude Galphin, MD (South East Renal Research Institution (SERRI), Chattanooga, TN), Puneet Sodhi, MD (Medanta – The Medicity- Heart Institute, Gurgaon, India), Rajsekara Chakravarthy, MD (CARE Hospital, Hyderabad, India), Subba Rao Budithi, MD (Apollo Hospitals – Chennai, Chennai, India), Finnian McCausland, MB, MMSc (Brigham & Women's Hospital, Boston, MA), Sanjeev Gulati, MD (Fortis Vasant Kunj Hospital, Delhi, India), Munawer Dijoo, MD (Fortis Vasant Kunj Hospital, Delhi, India), Upendra Singh, MD (Fortis Escorts Hospital, Delhi, India), Salil Jain, MD (Fortis Memorial Research Institute, Gurgaon, India), Vishal Saxena, MD (Fortis Memorial Research Institute, Gurgaon, India), Gaurav Sagar, MD (Apollo Hospitals – Delhi Delhi, India)

Advisory Committee
David Charytan, MD, MSc, (Brigham & Women's Hospital, Boston, MA), Rachel Fissell, MD (Vanderbilt University, Nashville, TN), Robert Foley, MD (Hennepin County Medical Center, Minneapolis, MN), Charles A. Herzog, MD (Hennepin County Medical Center, University of Minnesota, Minneapolis, MN), Peter A. McCullough, MD (Baylor University Medical Center, Baylor Heart and Vascular Institute, Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas), John D. Rogers, MD (Scripps Clinic-Torrey Pines, La Jolla, CA), James A. Tumlin, MD (South East Renal Research Institution (SERRI), Chattanooga, TN), Peter Zimetbaum, MD (Beth Israel Deaconess Medical Center, Boston, MA)

Adverse Events Committee
Manish Assar, MD (Baylor University Medical Center, Dallas, TX), Mark Kremers, MD (Mid Carolina Cardiology Charlotte, North Carolina), Wolfgang C. Winkelmayer, MD, ScD (Baylor College of Medicine, Houston, TX)

DISCLOSURE
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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Table S1. Detailed subject characteristics, United States *versus* India, for all subjects and for those with detected atrial fibrillation.

Table S2. Distribution of dialysate prescription characteristics, at the level of the individual dialysis session.

REFERENCES

1. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol*. 2014;11:639–654. https://doi.org/10.1038/nrcardio.2014.118

2. Turakhia MP, Blankestijn PJ, Carrero JJ, et al. Chronic kidney disease and arrhythmias: conclusions from a kidney disease: Improving Global Outcomes (KDIGO) controversies conference. *Eur Heart J*. 2018;39:2314–2325. https://doi.org/10.1093/eurheartj/ehy060

3. Alonso A, Lopez FL, Matsushita K, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123:2946–2953. https://doi.org/10.1161/CIRCULATIONAHA.111.020982

4. Goldstein BA, Arce CM, Hlatky MA, Turakhia M, Setoguchi S, Winkelmayer WC. Trends in the incidence of atrial fibrillation in older patients initiating dialysis in the United States. *Circulation*. 2012;126:2293–2301. https://doi.org/10.1161/CIRCULATIONAHA.112.099606

5. Winkelmayer WC, Patrick AR, Liu J, Brookhart MA, Setoguchi S. The increasing prevalence of atrial fibrillation among hemodialysis patients. *J Am Soc Nephrol*. 2011;22:349–357. https://doi.org/10.1681/ASN.2010050459

6. Seliger SL, Gillen DL, Longstreth WT, Kestenbaum B, Stehman-Breen CO. Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int*. 2003;64:603–609. https://doi.org/10.1681/ASN.2010050459

7. Chao TF, Liu CJ, Wang KL, et al. Incidence and prediction of ischemic stroke among atrial fibrillation patients with end-stage renal disease requiring dialysis. *Heart Rhythm Off J Heart Rhythm Soc*. 2014;11:1752–1759. https://doi.org/10.1016/j.hrthm.2014.06.021

8. Sacher F, Jesel L, Borni-Duval C, et al. Cardiac rhythm disturbances in hemodialysis patients: early detection using an implantable loop recorder and correlation with biological and dialysis parameters. *JACC Clin Electrophysiol*. 2018;4:397–408. https://doi.org/10.1016/j.jacep.2017.08.002

9. Wong MC, Kalman JM, Pedagogos E, et al. Temporal distribution of arrhythmic events in chronic kidney disease: highest incidence in the long interdialytic period. *Heart Rhythm*. 2015;12:2047–2055. https://doi.org/10.1016/j.hrthm.2015.06.033

10. Charytan DM, Foley R, McCullough PA, et al. Arrhythmia and sudden death in hemodialysis patients: protocol and baseline characteristics of the monitoring in dialysis study. *Clin J Am Soc Nephrol*. 2016;11:721–734. https://doi.org/10.2215/CJN.09350915

11. Roy-Chaudhury P, Tumlin JA, Koplan BA, et al. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. *Kidney Int*. 2018;93:941–951. https://doi.org/10.1016/j.kint.2017.11.019

12. Hindricks G, Pokushalov E, Urban L, et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: results of the XPECT trial. *Circ Arrhythm Electrophysiol*. 2010;3:141–147. https://doi.org/10.1161/CIRCEP.109.877852

13. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;370:2478–2486. https://doi.org/10.1056/NEJMoa1313600

14. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke [published correction appears in *N Engl J Med*. 2016;374:998]. *N Engl J Med*. 2012;366:120–129. https://doi.org/10.1056/NEJMoa1105575

15. Lip GY, Nieuwlaat R, Pisters R, Lane DA. Crijns HJ Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272. https://doi.org/10.1378/chest.09-1584

16. USRDS 2018 Annual data report: atlas of end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. https://www.usrds.org/annual-data-report/previous-adrs/. Accessed January 2, 2021.

17. Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int*. 2010;77:1098–1106. https://doi.org/10.1038/ki.2009.477

18. Königsbrügge O, Posch F, Antlanger M, et al. Prevalence of atrial fibrillation and antithrombotic therapy in hemodialysis patients: cross-sectional results of the Vienna. In:Vestigation of AtriaL Fibrillation and Thromboembolism in Patients on HemoDIalysis (VIVALDI). *PLoS One*. 2017;12:e0169400. https://doi.org/10.1371/journal.pone.0169400

19. Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27:949–953. https://doi.org/10.1093/eurheartj/ehi825

20. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370:2467–2477. https://doi.org/10.1056/NEJMoa1311376

21. Olesen JB, Lip GY, Lindhardsen J, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost*. 2011;106:739–749. https://doi.org/10.1160/TH11-05-0364

22. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society [published

correction appears in *Circulation*. 2014;130:e270-e271]. *Circulation*. 2014;130:2071–2104. https://doi.org/10.1161/CIR.0000000000000040

23. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons [published correction appears in *Circulation*. 2019;140:e285]. *Circulation*. 2019;140:e125–e151. https://doi.org/10.1161/CIR.0000000000000665

24. Shimada K, Tomita T, Kamijo Y, et al. Hemodialysis-induced P-wave signal-averaged electrocardiogram alterations are indicative of vulnerability to atrial arrhythmias. *Circ J*. 2012;76:612–617. https://doi.org/10.1253/circj.cj-11-1000

25. Szabo Z, Kakuk G, Fulop T, et al. Effects of haemodialysis on maximum P wave duration and P wave dispersion. *Nephrol Dial Transplant*. 2002;17:1634–1638. https://doi.org/10.1093/ndt/17.9.1634

26. Ozben B, Toprak A, Koc M, et al. P wave dispersion increases during hemodialysis sessions. *Nephron Clin Pract*. 2009;112:c171–c176. https://doi.org/10.1159/000214213

27. Niu J, Shah MK, Perez JJ, et al. Dialysis modality and incident atrial fibrillation in older patients with ESRD. *Am J Kidney Dis*. 2019;73:324–331. https://doi.org/10.1053/j.ajkd.2018.09.011