Association of Dialysate Bicarbonate with Arrhythmia in the Monitoring in Dialysis Study

Katherine Scovner Ravi[1,2] *James A. Tumlin*[3] *Prabir Roy-Chaudhury*[4,5] *Bruce A. Koplan*[6] *Alexandru I. Costea*[7] *Vijay Kher*[8] *Don Williamson*[9] *Candace K. McClure*[10] *David M. Charytan*[11] *and Finnian R. Mc Causland*[1,2]*, on behalf of the MiD Investigators and Committees**

Key Points

- Sudden cardiac death is a major concern for hemodialysis patients. Mortality is higher on dialysis days and is associated with higher dialysate bicarbonate (D_{BIC}).
- Contrary to our hypothesis, there was no consistent association of higher D_{BIC} with a higher risk of arrhythmia.
- Further research is needed to assess the optimal D_{BIC} and mechanisms by which it may improve outcomes for maintenance hemodialysis patients.

Abstract

Background Sudden death accounts for approximately 25% of deaths among maintenance hemodialysis patients, occurring more frequently on hemodialysis days. Higher dialysate bicarbonate (D_{BIC}) may predispose to alkalemia and arrhythmogenesis.

Methods We conducted a 12-month analysis of session-level data from 66 patients with implantable loop recorders. We fit logistic regression and negative binomial mixed-effects regression models to assess the association of D_{BIC} with clinically significant arrhythmia (ventricular tachycardia ≥115 beats per minute [BPM] for at least 30 seconds, bradycardia ≤40 BPM for at least 6 seconds, or asystole for at least 3 seconds) and reviewer confirmed arrhythmia (RCA—implantable loop recorder-identified or patient-marked event for which a manual review of the stored electrocardiogram tracing confirmed the presence of atrial fibrillation, supraventricular tachycardia, sinus tachycardia with rate >130 BPM, ventricular tachycardia, asystole, or bradycardia). Models adjusted for age, sex, race, hemodialysis vintage, vascular access, and prehemodialysis serum bicarbonate and additionally for serum and dialysate potassium levels.

Results The mean age was 56±12 years, 70% were male, 53% were Black, and 35% were Asian. Fewer RCA episodes were associated with D_{BIC} >35 than 35 mEq/L (incidence rate ratio 0.45 [0.27 to 0.75] and adjusted incident rate ratio 0.54 [0.30 to 0.97]), but the association was not significant when adjusting for serum and dialysate potassium levels (adjusted incident rate ratio, 0.60 [0.32 to 1.11]). Otherwise, no associations between D_{BIC} and arrhythmia were identified.

Conclusions We observed a lower frequency of RCA with higher D_{BIC}, compared with D_{BIC} of 35 mEql/L, contrary to our original hypothesis, but this association was attenuated in fully adjusted models. Validation of these findings in larger studies is required, with a further need for interventional studies to explore the optimal D_{BIC} concentration.

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Introduction

More than 550,000 patients are dependent on maintenance hemodialysis in the United States alone.[1] Their mortality rate is nearly 20% per year, with more than 40% dying from cardiovascular (CV) disease.[2,3] Sudden cardiac death (SCD) accounts for around a quarter of deaths in the maintenance hemodialysis patient population,[4] with cardiac arrhythmia likely to be a major etiological factor.[5] CV mortality and hospitalization rates are higher on the days on which hemodialysis occurs,[6] which suggests there may be something intrinsic to the hemodialysis procedure that contributes to adverse CV outcomes.

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence: Dr. Katherine Scovner Ravi, email: ksravi@bwh.harvard.edu

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Patients on maintenance hemodialysis are reliant on the delivery of base in the dialysate, in an attempt to minimize metabolic acidosis and its complications. This is achieved mostly *via* the use of dialysate bicarbonate (D_{BIC}) at each hemodialysis session, which is delivered thrice weekly, in a highly nonphysiologic fashion *via* the prescription of dialysate concentrations above the normal physiologic range of serum bicarbonate (S_{BIC}).[7,8] Practitioners prescribe D_{BIC} for millions of hemodialysis sessions per year. In light of observational evidence that higher D_{BIC} is associated with mortality and SCD,[9] and perhaps under duress from many highly publicized lawsuits against the use of higher D_{BIC}, some authorities are encouraging physicians to manipulate the D_{BIC} prescription, based on prehemodialysis S_{BIC} levels.[10] However, the optimal D_{BIC} prescription is unknown.

Previous reports on the Monitoring in Dialysis (MiD) study illustrate that S_{BIC} increases from prehemodialysis to posthemodialysis,[11] and in these data, the D_{BIC} is one of the most important contributors to changes in S_{BIC} that occur during and after each individual hemodialysis session. Furthermore, for any given D_{BIC}, the prehemodialysis S_{BIC} is a strong predictor of the posthemodialysis S_{BIC} concentration.[11] To assess the interplay between D_{BIC} and S_{BIC} in terms of arrhythmogenesis, this study assesses how D_{BIC} relates to arrhythmias described in the MiD study while accounting for prehemodialysis S_{BIC} levels.

Methods

Study Design and Population

This study is a secondary analysis of the MiD study.[12] MiD was a prospective cohort study that enrolled 66 patients on maintenance hemodialysis from 10 centers (n=43 from the United States; n=23 from India). The study used implantable loop recorders to record continuous electrocardiographic readings over a 6-month period. Patients were enrolled from January 2013 to January 2014 in the United States and from March 2014 to December 2015 in India. The primary eligibility criteria were age 21 or older, thrice weekly in-center hemodialysis, or eGFR <15 ml/min per 1.73 m^2 with expected hemodialysis initiation within 2 months, although no patients were enrolled before their hemodialysis initiation. Key exclusion criteria were unsuitability for implantation, expected survival <6 months, left-sided hemodialysis catheter interfering with implantation, thoracic surgery within the preceding 6 months, bacteremia within the preceding 60 days or nonbacteremic infection within the preceding 14 days, hemoglobin <10 g/dl on consecutive measurements within the preceding 2 months, end-stage liver failure, transplantation or modality transfer expected within 6 months, or existing pacemaker or implantable cardioverter defibrillator. The design and main results of the MiD study have been reported.[12,13] Dialysate prescriptions were as deemed clinically indicated by the patient's nephrologist (Figure 1).

Exposures and Outcomes

The primary exposure in this study was categorical D_{BIC} (<35, 35, and >35 mEq/L). D_{BIC} of 35 mEq/L was considered as the reference because it was the most common prescription used in the MiD cohort,[14] and it is commonly used in clinical practice.[15] Hemodialysis parameters, including D_{BIC}, were recorded for all hemodialysis sessions, and updated parameters were used for the analysis of each repeated measure of hemodialysis session within individuals. The primary outcomes were arrhythmias from the beginning of the respective hemodialysis sessions to the start of the next. Arrhythmia events were defined as per the definitions used in the MiD study: (*1*) clinically significant arrhythmia (CSA)—those most likely to be associated with SCD, defined as episodes of ventricular tachycardia ≥115 beats per minute (BPM) for at least 30 seconds; episodes of bradycardia ≤40 BPM for at least 6 seconds; instances of asystole for at least 3 seconds; and any symptomatic event during which the stored electrocardiogram showed a CSA and (*2*) reviewer-confirmed arrhythmia (RCA)—any implantable loop recorder-identified or patient-marked event in which a manual review of the stored electrocardiogram tracing confirmed the presence of atrial fibrillation, supraventricular tachycardia, sinus tachycardia with rate >130 BPM, ventricular tachycardia, asystole, or bradycardia. Implantable loop recorders were interrogated at each hemodialysis session for 6 months. As previously described, the RCA end point defines events that represent clinically relevant electrical instability and chronotropic dysfunction which likely share common physiologies with CSA. RCA thus merits analysis in conjunction with CSA.[14] Tracings were independently adjudicated by a core laboratory.[13] The number of CSA, RCA, and all their subtype events were assessed across groups of D_{BIC}. We included data where the number of events was sufficient to make a determination regarding associations.

Laboratory Analysis

Blood samples were obtained before hemodialysis twice weekly for the first 4 weeks and then once weekly through the remaining 5 months of the 6-month observation period. Blood samples were collected at study sites by trained personnel, centrifuged, refrigerated, and then shipped to a central laboratory in the United States or India according to the recruitment site for measurement, using standard techniques.[12]

Statistical Analysis

Continuous variables were examined graphically and recorded as means (±SD) for normally distributed data or medians (25th–75th percentile) for non-normally distributed data. Categorical variables were examined by frequency distribution and recorded as proportions. Associations between demographic, laboratory, and dialysis session data and D_{BIC} were assessed using ANOVA for continuous variables or chi-squared or Fisher exact tests for categorical variables, as appropriate.

The associations between D_{BIC} with the number of hemodialysis sessions complicated by arrhythmia from the beginning of the session until the initiation of the next hemodialysis session and with the number of arrhythmias occurring from the start of one hemodialysis session to the initiation of the next hemodialysis session were assessed using repeated measures logistic regression models and negative binomial mixed-effects regression models, respectively, with patient ID included as a

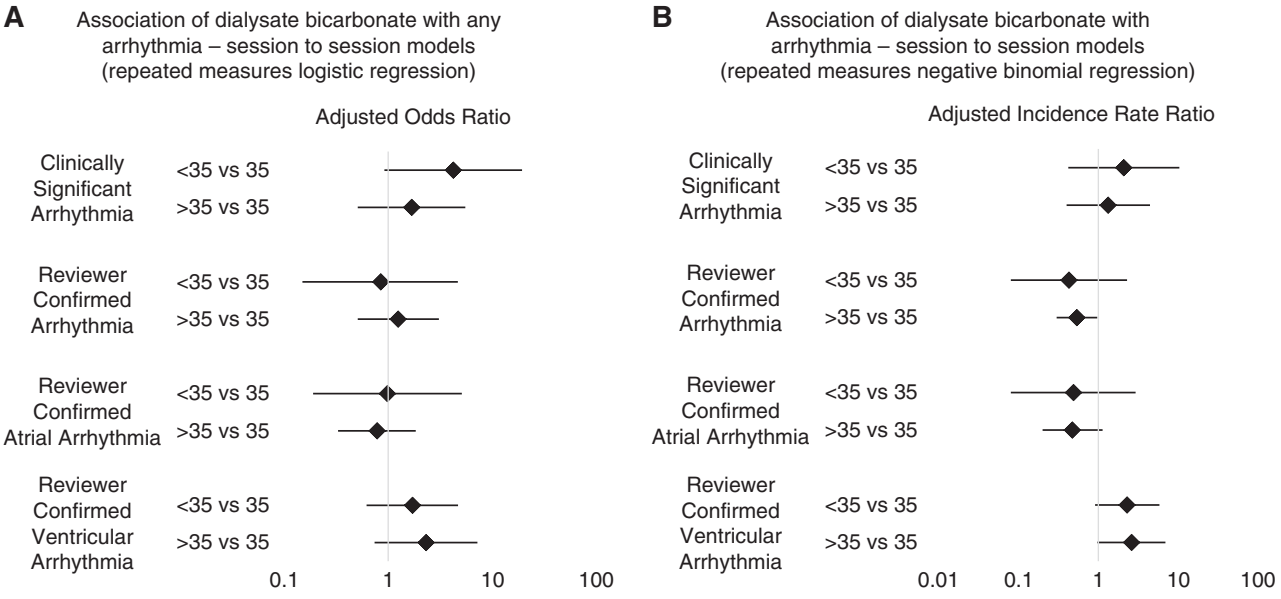

Figure 1. Association of dialysate bicarbonate with arrhythmia—forest plots. (A) Association of dialysate bicarbonate with any arrhythmia—session to session models (repeated measures logistic regression). (B) Association of dialysate bicarbonate with arrhythmia—session to session models (repeated measures negative binomial regression). The diamonds represent the adjusted incident rate ratio, and the horizontal lines through the diamonds represent the 95% CIs. Models adjusted for age, sex, race, dialysis vintage, vascular access, and pre-hemodialysis serum bicarbonate. Note: Estimates are provided on the log scale. CI, confidence interval; OR, odds ratio.

random effect. D_{BIC} was reviewed at each session and recorded if it was changed permitting accuracy of repeated measures. Initially, unadjusted models were fit; subsequently, adjusted models accounted for age, sex, race, hemodialysis vintage, and vascular access (covariates used in initial analyses)[13] (model 1). Our fully adjusted model included the aforementioned covariates and added prehemodialysis S_{BIC} as a time varying covariate with S_{BIC} from the respective session; sessions for which S_{BIC} was unavailable were not included in these results (model 2). The number of covariates was limited by the small sample size and number of outcomes. However, given the particular interest regarding the interactions with potassium, we included an exploratory model which included the aforementioned variables and added prehemodialysis serum potassium and dialysate potassium levels. All analyses were carried out using the statistical software package SAS version 9.4 (Cary, NC). Two-sided *P* values of <0.05 were considered statistically significant.

Ethics

The MiD study was approved by applicable institutional review boards or ethical review committees at each participating center. The investigation conforms with the principles outlined in the Declaration of Helsinki. Participants provided written informed consent before the beginning of the study.

Results

Baseline Characteristics

A total of 66 patients were included in the present analysis, contributing a total of 3655 sessions with recorded D_{BIC}. The mean age at baseline was 56±12 years, 70% were male, 53% were Black, and 35% were Asian. A total of 64% of participants had a history of diabetes, 26% had heart failure, and 11% had atrial fibrillation at baseline (Table 1). Patients with higher D_{BIC} were more likely to be Black, to have older hemodialysis vintage, and had higher prehemodialysis S_{BIC} levels. Baseline characteristics and hemodialysis treatment characteristics are presented by country of origin in Supplemental Tables 1 and 2, respectively. Laboratory data and dialysis characteristics across all sessions are shown in Supplemental Tables 3 and 4, respectively.

Hemodialysis Treatment Characteristics

The median duration of hemodialysis was 4.0 (3.5–4.0) hours, with a mean single-pool Kt/V of 1.5±0.4 and ultrafiltration rate of 12±6 ml/kg per hour across all participants (Table 2). Patients with higher D_{BIC} had shorter hemodialysis durations, were heavier and further above their target dry weight prehemodialysis, and were more likely to have higher blood flows, high-flux dialyzers, and higher dialysate calcium concentrations. Of the sessions for which D_{BIC} was <35 mEq/L, the baseline mean was 30.9±2.4 mEq/L, and the mean for all sessions was 30.4±4.1 mEq/L. Of the sessions for which D_{BIC} was >35 mEq/L, the baseline mean was 38.8±1.7 mEq/L, and the mean for all sessions was 38.5±1.6 mEq/L. Regarding intraparticipant prescription variability, 3408/3655 (93.2%) hemodialysis sessions had D_{BIC} that was the same as the participant's baseline.

Laboratory Analysis

Blood samples were obtained twice weekly for the first 4 weeks after the insertion of internal loop recorders and

Table 1. Characteristics of the participants at baseline

Baseline Characteristic	All Patients (N=66)	Baseline D_{BIC} Recorded (n=62)	Baseline D_{BIC} <35 (n=15)	Baseline D_{BIC}=35 (n=27)	Baseline D_{BIC} >35 (n=20)	P Value[a]
Age, yr	56±12	56±12	59±15	59±10	51±12	0.09
Male, No. (%)	46 (70)	42 (68)	11 (73)	19 (70)	12 (60)	0.70
Race, No. (%)						
Asian	23 (35)	19 (31)	8 (53)	11 (41)	0 (0)	<0.001
Black	35 (53)	35 (57)	7 (47)	13 (48)	15 (75)	
White	7 (11)	7 (11)	0 (0)	3 (11)	4 (20)	
Other	1 (2)	1 (2)	0 (0)	0 (0)	1 (5)	
ESKD vintage, yr	2.4 (1.2–5.3)	2.5 (1.1–5.5)	2.9 (1.3–4.8)	2.2 (0.9–4.8)	3.4 (1.2–11.9)	0.02
Vascular access, No. (%)						0.58
AV fistula	45 (68)	41 (66)	10 (67)	20 (74)	11 (55)	
AV graft	17 (26)	17 (27)	5 (33)	5 (19)	7 (35)	
Catheter	3 (5)	3 (5)	0 (0)	2 (7)	1 (5)	
Comorbid conditions, No. (%)						
Diabetes mellitus	42 (64)	38 (61)	9 (60)	17 (63)	12 (60)	1.00
Hyperlipidemia	40 (61)	39 (63)	8 (53)	17 (63)	14 (70)	0.63
Hypertension	56 (85)	56 (86)	12 (80)	22 (82)	19 (95)	0.35
Ischemic heart disease	32 (49)	28 (45)	7 (47)	12 (44)	9 (45)	1.00
Congestive heart failure	17 (26)	17 (27)	5 (33)	4 (15)	8 (40)	0.15
Arrhythmia	21 (32)	21 (34)	4 (27)	8 (30)	9 (45)	0.49
Atrial fibrillation	7 (11)	7 (11)	1 (7)	2 (7)	4 (20)	0.40
Systolic BP, mm Hg	141±23	140±23	142±25	140±23	137±24	0.83
Diastolic BP, mm Hg	77±13	76±13	75±12	75±11	79±17	0.62
Medication use, No. (%)						
Aspirin	24 (36)	22 (36)	5 (33)	8 (30)	9 (45)	0.59
Antilipidemic	32 (49)	31 (50)	10 (67)	12 (44)	9 (45)	0.37
ACEI or ARB	22 (33)	21 (34)	4 (27)	6 (22)	11 (55)	0.06
β blockers	38 (58)	36 (58)	9 (60)	15 (56)	12 (60)	1.00
Predialysis serum laboratory values						
BUN, mg/dl	60±18	60±18	51±18	64±20	60±14	0.11
Creatinine, mg/dl	10.0±3.4	10.2±3.4	9.2±3.2	10.0±3.4	11.2±3.5	0.25
Sodium, mEq/L	137±5	137±4	137±5	137±3	138±5	0.71
Potassium, mEq/L	5.0±1.0	4.9±0.9	4.5±0.7	5.1±1.2	4.8±0.7	0.14
Calcium, mg/dl	8.7±0.8	8.7±0.9	8.8±0.9	8.7±0.9	8.8±0.9	0.86
Bicarbonate, mEq/L	22±4	22±4	22±4	21±4	24±3	0.04
Magnesium, mg/dl	2.4±0.5	2.4±0.5	2.3±0.7	2.5±0.5	2.3±0.3	0.47
Phosphorus, mg/dl	5.5±2.0	5.5±2.0	4.5±1.0	6.0±2.5	5.5±1.8	0.13
Hemoglobin, g/dl	11±1	11±1	10±2	11±1	11±1	0.16
Serum albumin, g/dl	3.9±0.3	4.0±0.3	3.9±0.5	3.9±0.3	4.0±0.2	0.28

Continuous variables are presented as means ± SD or median (25th–75th percentiles). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, arteriovenous; D_{BIC}, dialysate bicarbonate.
[a]P value from ANOVA for continuous variables or chi-squared or Fisher exact tests for categorical variables, as appropriate.

then weekly for the subsequent 5 months.[12] Regarding the day of the week blood was obtained, 1040/1229 (84.6%) blood samples were obtained on a Monday or a Tuesday, and 189/1229 (15.4%) were obtained on other days of the week.

Risk of Arrhythmia by D_{BIC}

The association of variable D_{BIC} with the various types of arrhythmia is reported in Tables 3 and 4. There were fewer episodes of RCA for D_{BIC} >35 mEq/L compared with 35 mEq/L in unadjusted (incidence rate ratio [IRR], 0.45; 95% CI, 0.27 to 0.75) and fully adjusted (model 2, adjusted incident rate ratio [aIRR], 0.54; 95% CI, 0.30 to 0.97) models, respectively. Although the trend persisted, the association lost significance in the exploratory model. Otherwise, no association between D_{BIC} and the frequency of other arrhythmia subtypes was observed (D_{BIC} >35 mEq/L compared with 35 mEq/L, aIRR [95% CI] in fully adjusted model 2 for each arrhythmia subtype: CSA: 1.33 [0.40 to 4.44]; reviewer-confirmed atrial arrhythmia: 0.47 [0.20 to 1.13]; reviewer-confirmed ventricular arrhythmia 2.60 [0.97 to 6.93]). For D_{BIC} <35 mEq/L compared with 35 mEq/L, aIRR (95% CI) in fully adjusted model 2 for each arrhythmia subtype: CSA: 2.09 (0.42 to 10.36); RCA: 0.43 (0.08 to 2.29); reviewer-confirmed atrial arrhythmia: 0.49 (0.08 to 2.93); reviewer-confirmed ventricular arrhythmia 2.30 (0.91 to 5.83).

An association of D_{BIC} with the presence of arrhythmias was not observed using logistic regression models (Table 3). For D_{BIC} >35 mEq/L compared with 35 mEq/L, aOR (95%

Table 2. Characteristics of the dialysis prescriptions at baseline

Baseline Characteristic	All Patients (*N*=66)	Baseline Dialysate Recorded (*n*=62)	Baseline D_{BIC} <35 (*n*=15)	Baseline D_{BIC}=35 (*n*=27)	Baseline D_{BIC} >35 (*n*=20)	*P* Value[a]
Duration of hemodialysis, h	4.0 (3.5–4.0)	4.0 (3.5–4.0)	4.0 (4.0–4.0)	3.7 (3.5–4.0)	3.6 (3.5–4.0)	0.02
spKt/V	1.5±0.4	1.5±0.3	1.5±0.3	1.4±0.3	1.5±0.3	0.53
Predialysis weight, kg	86.7±28.8	88.5±28.8	72.4±16.8	85.3±19.1	104.7±38.2	<0.01
Kilogram over dry weight target before dialysis	4.2 (2.7–5.2)	4.3 (2.8–5.5)	3.9 (2.3–4.8)	4.3 (2.3–5.0)	4.9 (3.5–6.9)	0.01
UFR, ml/kg per hour	12±6	12±6	12±6	11±5	13±6	0.64
Dialysate flow, ml/min	600 (500–800)	600 (500–800)	500 (500–800)	600 (500–800)	600 (600–800)	0.20
Blood flow, ml/min	387 (300–467)	400 (300–475)	314 (294–500)	375 (300–400)	471 (407–500)	<0.001
High-flux dialyzer, No. (%)	42 (64)	41 (66)	7 (47)	15 (56)	19 (95)	<0.01
Membrane reuse, No. (%)	18 (27)	17 (27)	1 (7)	11 (41)	5 (25)	0.06
Cellulose membrane, No. (%)	5 (8)	4 (7)	1 (7)	3 (11)	0 (0)	0.35
Dialysate temperature, °C, No. (%)						0.06
35.5	1 (2)	1 (2)	0 (0)	0 (0)	1 (5)	
36.0	3 (5)	3 (5)	0 (0)	1 (4)	2 (10)	
36.5	5 (8)	5 (8)	0 (0)	5 (19)	0 (0)	
37.0	57 (86)	53 (86)	15 (100)	21 (78)	17 (85)	
Dialysate potassium, mEq/L, No. (%)						0.77
1.0	1 (2)	1 (2)	0 (0)	0 (0)	1 (5)	
2.0	53 (80)	49 (79)	11 (73)	22 (82)	16 (80)	
3.0	11 (17)	11 (18)	4 (27)	4 (15)	3 (15)	
4.0	1 (2)	1 (2)	0 (0)	1 (4)	0 (0)	
Dialysate calcium, mEq/L, No. (%)						<0.001
1.5 and 1.6	13 (20)	11 (18)	1 (7)	10 (37)	0 (0)	
2.0 and 2.5	39 (59)	39 (63)	7 (47)	16 (59)	16 (80)	
3.0 and 3.5	14 (21)	12 (19)	7 (47)	1 (4)	4 (20)	
Dialysate sodium, mEq/L, No. (%)						0.36
135	6 (10)	5 (9)	1 (9)	4 (15)	0 (0)	
138	6 (10)	5 (9)	1 (9)	3 (11)	1 (5)	
140	49 (80)	48 (83)	9 (82)	20 (74)	19 (95)	

Continuous variables are presented as means ± SD or median (25th–75th percentiles). D_{BIC}, dialysate bicarbonate; spKt/V, single-pool Kt/V; UFR, ultrafiltration rate.
[a]*P* value from ANOVA for continuous variables, or chi-squared or Fisher exact tests for categorical variables, as appropriate.
Note: Blood flow rate is the mean of 12 time points during the baseline dialysis session.

CI) in fully adjusted model 2 for each arrhythmia subtype: CSA: 1.68 (0.51 to 5.51); RCA: 1.25 (0.51 to 3.07); reviewer-confirmed atrial arrhythmia: 0.78 (0.33 to 1.84); reviewer-confirmed ventricular arrhythmia 2.31 (0.74 to 7.20). For D_{BIC} <35 mEq/L compared with 35 mEq/L, aOR (95% CI) in fully adjusted model 2 for each arrhythmia subtype: CSA: 4.22 (0.92 to 19.33); RCA: 0.85 (0.15 to 4.67); reviewer-confirmed atrial arrhythmia: 0.98 (0.19 to 5.10); reviewer-confirmed ventricular arrhythmia 1.71 (0.62 to 4.69).

Discussion

In this secondary analysis of the MiD study, we tested whether higher D_{BIC} is associated with cardiac arrhythmia in patients with implantable loop recorders. We observed a lower frequency of RCA with higher D_{BIC} (>35 mEq/L), compared with D_{BIC} of 35 mEq/L. Within RCA, a majority of events were atrial arrhythmia. We found no association of D_{BIC} with CSA or other arrhythmia subtypes.

Cardiac arrhythmias are common in patients receiving hemodialysis, with mean estimates of 2 (95% confidence interval, 1.8 to 2.2) episodes of cardiac arrhythmia (defined as sinus bradycardia, asystole, high degree atrioventricular block, sustained ventricular tachycardia, ventricular fibrillation, or atrial fibrillation) per patient year[16] and are thought to predispose to SCD. The highest incidence of CV death, hospitalization, and SCD occur on the days that patients receive hemodialysis treatments.[6,17] Arrhythmias appear to cluster around the hemodialysis procedure, with previous studies demonstrating a three-fold increased risk of SCD in the 12 hours preceding and 1.7-fold increased risk of SCD in the 12 hours after hemodialysis sessions.[18] The MiD study previously demonstrated that CSA occurs most frequently just preceding hemodialysis sessions and after the first hemodialysis session of the week.[13] Because patients are at an increased risk of SCD in the perihemodialysis period,[18] it is tempting to hypothesize that extremes of electrolyte derangement before hemodialysis and/or rapid changes during hemodialysis may contribute to the development of malignant cardiac arrhythmia. Although higher D_{BIC} was shown to be associated with mortality and a trend toward more SCD (OR

Table 3. Association of dialysate bicarbonate with any arrhythmia—session to session models (repeated measures logistic regression)

Model		D_{BIC} (mEq/L) <35 versus 35 OR (95% CI) *n/N*	D_{BIC} (mEq/L) >35 versus 35 OR (95% CI) *n/N*	D_{BIC} (mEq/L) <35 versus >35 OR (95% CI) *n/N*	*n/N* *P* Value[a]
Arrhythmia subtype					
CSA	Unadjusted	1.68 (0.49 to 5.72)	1.22 (0.41 to 3.58)	1.38 (0.36 to 5.23)	221/3655
		87/816 versus 56/1552	78/1287 versus 56/1552	87/816 versus 78/1287	0.71
	Model 1	2.00 (0.55 to 7.22)	1.01 (0.32 to 3.16)	1.99 (0.37 to 10.76)	218/3528
		87/795 versus 56/1552	75/1181 versus 56/1552	87/795 versus 75/1181	0.57
	Model 2	4.22 (0.92 to 19.33)	1.68 (0.51 to 5.51)	2.52 (0.37 to 17.13)	116/1186
		46/249 versus 29/549	41/388 versus 29/549	46/249 versus 41/388	0.13
	Exploratory model	3.28 (0.66 to 16.39)	1.65 (0.49 to 5.60)	1.98 (0.26 to 15.29)	114/1176
		44/240 versus 29/548	41/388 versus 29/548	44/240 versus 41/388	0.24
RCA	Unadjusted	0.43 (0.09 to 2.10)	0.61 (0.25 to 1.51)	0.71 (0.16 to 3.20)	1391/3655
		271/816 versus 533/1552	587/1287 versus 533/1552	271/816 versus 587/1287	0.44
	Model 1	0.41 (0.06 to 2.67)	0.58 (0.24 to 1.38)	0.72 (0.10 to 4.95)	1339/3528
		265/795 versus 533/1552	541/1181 versus 533/1552	265/795 versus 541/1181	0.35
	Model 2	0.85 (0.15 to 4.67)	1.25 (0.51 to 3.07)	0.68 (0.10 to 4.54)	452/1186
		86/249 versus 173/549	193/388 versus 173/549	86/249 versus 193/388	0.87
	Exploratory model	0.91 (0.16 to 5.07)	1.47 (0.58 to 3.71)	0.62 (0.09 to 4.24)	450/1176
		84/240 versus 173/548	193/388 versus 173/548	84/240 versus 193/388	0.71
RCA subtypes					
Reviewer-confirmed atrial arrhythmia	Unadjusted	0.45 (0.13 to 1.54)	0.77 (0.43 to 1.39)	0.58 (0.18 to 1.83)	1113/3655
		238/816 versus 421/1552	454/1287 versus 421/1552	238/816 versus 454/1287	0.41
	Model 1	0.60 (0.11 to 3.25)	0.61 (0.35 to 1.09)	0.98 (0.17 to 5.50)	1068/3528
		235/795 versus 421/1552	412/1181 versus 421/1552	235/795 versus 412/1181	0.23
	Model 2	0.98 (0.19 to 5.10)	0.78 (0.33 to 1.84)	1.25 (0.19 to 8.11)	353/1186
		73/249 versus 139/549	141/388 versus 139/549	73/249 versus 141/388	0.85
	Exploratory model	1.00 (0.19 to 5.29)	0.86 (0.36 to 2.07)	1.16 (0.18 to 7.55)	351/1176
		71/240 versus 139/548	141/388 versus 139/548	71/240 versus 141/388	0.95
Reviewer-confirmed ventricular arrhythmia	Unadjusted	1.94 (0.49 to 7.75)	2.33 (0.54 to 10.01)	0.83 (0.20 to 3.42)	368/3655
		117/816 versus 108/1552	143/1287 versus 108/1552	117/816 versus 143/1287	0.48
	Model 1	2.44 (0.75 to 7.93)	2.22 (0.60 to 8.21)	1.10 (0.28 to 4.33)	364/3528
		116/795 versus 108/1552	140/1181 versus 108/1552	116/795 versus 140/1181	0.27
	Model 2	1.71 (0.62 to 4.69)	2.31 (0.74 to 7.20)	0.74 (0.23 to 2.36)	125/1186
		34/249 versus 38/549	53/388 versus 38/549	34/249 versus 53/388	0.32
	Exploratory model	1.45 (0.53 to 3.97)	2.47 (0.75 to 8.13)	0.59 (0.17 to 1.99)	125/1176
		34/240 versus 38/548	53/388 versus 38/548	34/240 versus 53/388	0.33

Model 1 adjusted for age, sex, race, dialysis vintage, and vascular access. CSA, clinically significant arrhythmia; D_{BIC}, dialysate bicarbonate; *n/N*, number of sessions with event/number of sessions; OR, odds ratio; RCA, reviewer confirmed arrhythmia.
Model 2 adjusted for age, sex, race, dialysis vintage, vascular access, and prehemodialysis serum bicarbonate.
Exploratory model adjusted for age, sex, race, dialysis vintage, vascular access, prehemodialysis serum bicarbonate, prehemodialysis serum potassium, and dialysate potassium levels.
[a]Overall *P* value from repeated measures model F test.

Table 4. Association of dialysate bicarbonate with arrhythmia—session to session models (repeated measures negative binomial regression)

Model		D_{BIC} (mEq/L) <35 versus 35 IRR (95% CI) *n/N*	D_{BIC} (mEq/L) >35 versus 35 IRR (95% CI) *n/N*	D_{BIC} (mEq/L) <35 versus >35 IRR (95% CI) *n/N*	*n/N* *P* Value[a]
Arrhythmia subtype					
CSA	Unadjusted	1.35 (0.33 to 5.53)	0.92 (0.27 to 3.15)	1.47 (0.33 to 6.60)	1211/3655
		586/816 versus 170/1552	455/1287 versus 170/1552	586/816 versus 455/1287	0.87
	Model 1	1.39 (0.30 to 6.37)	0.72 (0.21 to 2.39)	1.94 (0.29 to 12.83)	1208/3528
		586/795 versus 170/1552	452/1181 versus 170/1552	586/795 versus 452/1181	0.78
	Model 2	2.09 (0.42 to 10.36)	1.33 (0.40 to 4.44)	1.57 (0.22 to 11.09)	505/1186
		205/249 versus 83/549	217/388 versus 83/549	205/249 versus 217/388	0.61
	Exploratory model	1.59 (0.29 to 8.85)	1.51 (0.46 to 4.95)	1.05 (0.13 to 8.35)	503/1176
		203/240 versus 83/548	217/388 versus 83/548	203/240 versus 217/388	0.69
RCA	Unadjusted	0.27 (0.07 to 1.02)	0.45 (0.27 to 0.75)	0.60 (0.20 to 1.82)	9718/3655
		2127/816 versus 3617/1552	3974/1287 versus 3617/1552	2127/816 versus 3974/1287	<0.01
	Model 1	0.30 (0.03 to 2.66)	0.40 (0.26 to 0.61)	0.75 (0.09 to 6.30)	9360/3528
		2120/795 versus 3617/1552	3623/1181 versus 3617/1552	2120/795 versus 3623/1181	<0.001
	Model 2	0.43 (0.08 to 2.29)	0.54 (0.30 to 0.97)	0.79 (0.14 to 4.36)	3036/1186
		565/249 versus 1221/549	1250/388 versus 1221/549	565/249 versus 1250/388	0.09
	Exploratory model	0.52 (0.08 to 3.21)	0.60 (0.32 to 1.11)	0.86 (0.14 to 5.25)	3024/1176
		553/240 versus 1221/548	1250/388 versus 1221/548	553/240 versus 1250/388	0.25
RCA subtypes					
Reviewer-confirmed atrial arrhythmia	Unadjusted	0.30 (0.07 to 1.30)	0.53 (0.26 to 1.10)	0.57 (0.15 to 2.12)	5832/3655
		1387/816 versus 2391/1552	2054/1287 versus 2391/1552	1387/816 versus 2054/1287	0.15
	Model 1	0.39 (0.05 to 3.05)	0.45 (0.24 to 0.87)	0.86 (0.11 to 6.75)	5547/3528
		1384/795 versus 2391/1552	1772/1181 versus 2391/1552	1384/795 versus 1772/1181	0.05
	Model 2	0.49 (0.08 to 2.93)	0.47 (0.20 to 1.13)	1.03 (0.16 to 6.72)	1751/1186
		342/249 versus 862/549	547/388 versus 862/549	342/249 versus 547/388	0.21
	Exploratory model	0.45 (0.07 to 2.93)	0.51 (0.21 to 1.23)	0.87 (0.13 to 5.92)	1739/1176
		330/240 versus 862/548	547/388 versus 862/548	330/240 versus 547/388	0.28
Reviewer-confirmed ventricular arrhythmia	Unadjusted	2.24 (0.58 to 8.69)	2.13 (0.68 to 6.66)	1.05 (0.28 to 3.93)	737/3655
		246/816 versus 161/1552	330/1287 versus 161/1552	246/816 versus 330/1287	0.35
	Model 1	3.00 (0.93 to 9.70)	2.18 (0.80 to 5.94)	1.38 (0.40 to 4.77)	733/3528
		245/795 versus 161/1552	327/1181 versus 161/1552	245/795 versus 327/1181	0.12
	Model 2	2.30 (0.91 to 5.83)	2.60 (0.97 to 6.93)	0.89 (0.32 to 2.47)	244/1186
		72/249 versus 58/549	114/388 versus 58/549	72/249 versus 114/388	0.09
	Exploratory model	2.03 (0.01 to 276.52)	2.86 (0.20 to 41.06)	0.71 (0.07 to 6.92)	244/1176
		72/240 versus 58/548	114/388 versus 58/548	72/240 versus 114/388	<0.001

Model 1 adjusted for age, sex, race, dialysis vintage, and vascular access. CSA, clinically significant arrhythmia; D_{BIC}, dialysate bicarbonate; IRR, incidence rate ratio; *n/N*, number of events/number of sessions; RCA, reviewer-confirmed arrhythmia.
Model 2 adjusted for age, sex, race, dialysis vintage, vascular access, and prehemodialysis serum bicarbonate.
Exploratory model adjusted for age, sex, race, dialysis vintage, vascular access, prehemodialysis serum bicarbonate, prehemodialysis serum potassium, and dialysate potassium levels.
[a]Overall *P* value from repeated measures model F test.

per 4 mEq/L higher D_{BIC}, 1.03 [95% confidence interval, 0.88 to 1.19]) in the Dialysis Outcomes and Practice Patterns Study,[9] this analysis used administrative codes and was unable to granularly define the presence or timing of an underlying arrhythmia in relation to hemodialysis sessions. Using MiD study data, we are able to address some of these issues, as well as adjust for the prehemodialysis S_{BIC} concentrations in our models.

In this study, we describe the association of D_{BIC} with CSA, RCA, and RCA subtypes, reviewer-confirmed atrial arrhythmia and reviewer-confirmed ventricular arrhythmia. Overall, we did not observe any meaningful association of D_{BIC} >35 or <35 (versus 35 mEq/L) with CSA in either the logistic or negative binomial regression models. Regarding RCA, the observed effect estimates were on the side of a lower risk of RCA with D_{BIC} >35 versus 35 and for D_{BIC} <35 versus 35, which was mostly driven by a lower risk of reviewer-confirmed atrial arrhythmia. Conversely, the effect estimates were on the side of higher risk of reviewer-confirmed ventricular arrhythmia for D_{BIC} >35 versus 35 and <35 versus 35. However, these estimates should be interpreted with caution, given the relative paucity of events in some models, wide confidence intervals, and inability to perform further multivariable adjustment. Ultimately, larger studies and trials are warranted to further assess for the potential associations of D_{BIC} with arrhythmia.

In other MiD analyses of RCA in the 8 hours subsequent to respective hemodialysis sessions, Tumlin *et al.* reported that D_{BIC} of >35 mEq/L was associated with fewer RCA events, compared with D_{BIC} of 35 mEq/L (incidence rate ratio, 0.51 [0.27 to 0.97]).[14] Our analysis adds clarity to the duration of this association in that it assessed the association in the full intradialytic and subsequent interdialytic interval (allowing for potential delayed events), and it also adjusted for S_{BIC}. Soomro *et al.* assessed the association between D_{BIC} and clinically significant bradycardia or asystole in the final 12 hours of the interdialytic interval and from the end of one dialysis session to the initiation of the next.[19] Similar to our data, their study did not show evidence of an association of D_{BIC} with clinically significant bradycardia or asystole during these time frames, but did not adjust for S_{BIC}. Our study confirms these findings, even after adjustment for S_{BIC}.

There are several mechanisms by which changing pH rapidly with higher D_{BIC} could lead to arrhythmia. Alkalemia can promote intracellular shifts in serum potassium[20] and lead to a change in the electrical charge of proteins, which promotes protein-to-calcium complexes and results in lower ionized calcium concentrations.[10] Both lower serum calcium and potassium levels are associated with longer QTc durations,[21] which may partially explain previous observations of QTc prolongation during hemodialysis with higher D_{BIC}.[22] However, other mechanisms for the association of higher D_{BIC} with mortality warrant consideration.[9] Metabolic alkalosis during hemodialysis may result in vasodilation and hemodynamic instability.[23–25] Furthermore, metabolic alkalosis during hemodialysis may lead to decreased cerebral blood flow and respiratory suppression.[26,27] High D_{BIC} may lead to posthemodialysis alkalosis which promotes precipitation of calcium phosphate in the vasculature potentially contributing to vascular disease.[28–30] Furthermore, higher D_{BIC} is associated with mortality due to infections,[9] possibly as alkalosis inhibits dendritic cell antigen-presenting capacity.[31] Our findings demonstrate that mechanisms beyond arrhythmia for explaining the association of D_{BIC} with mortality also warrant exploration.

This study has several notable strengths. First, it uses data from the MiD study, a multicenter prospective cohort with detailed session-level arrhythmia data as has rarely previously been obtained. Furthermore, our analysis includes the full intradialytic and interdialytic periods and accounts for S_{BIC}, which to our knowledge has not previously been done using these data. A limitation of this study includes its assessment of a modest sample of patients. This precluded adjustment for or subgroup analysis by country of origin and thus country of origin remains a potential confounder. In addition, the inclusion/exclusion criteria of this cohort could limit generalizability. Furthermore, the modest sample size and concerns for overfitting precluded extensive adjustment for many potential confounders. Therefore, the possibility of residual confounding remains, and the results must be interpreted with caution. The added power that binomial regression, compared with logistic regression, gave by incorporating assessment of multiple episodes of an arrhythmia per session rather than simply asking if an episode occurred versus not in association with a given session may explain why significant results were found with binomial regression but not with the logistic regression model. However, multiple comparisons were examined, and the fact that our analyses did not correct for the multiple tests performed must be considered as a limitation. Another issue is that dialysate prescriptions reflect nephrologists' orders rather than the measured concentration of D_{BIC} in dialysate baths. Furthermore, the inclusion and exclusion criteria in this study may have led to selection of healthier patients, which could limit the generalizability of the present findings to a sicker patient population.

In conclusion, this study suggests that, contrary to our original hypothesis, there was no consistent association of higher D_{BIC} which is a higher risk of arrhythmia among participants of the MiD study. Owing to small numbers of events and multiple hypothesis testing, these results should be considered hypothesis generating. Larger studies and randomized controlled trials that assess variable D_{BIC} and arrhythmia are required to fully understand how our management of acid-base in the maintenance hemodialysis patient population may affect a patient's risk of arrhythmia.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/KN9/A623.

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Author Contributions

Conceptualization: David M. Charytan, Finnian R. Mc Causland, Katherine Scovner Ravi.

Data curation: Alexandru I. Costea, Vijay Kher, Bruce A. Koplan, Prabir Roy-Chaudhury, James A. Tumlin, Don Williamson.

Formal analysis: David M. Charytan, Finnian R. Mc Causland, Candace K. McClure, Katherine Scovner Ravi.

Methodology: David M. Charytan, Finnian R. Mc Causland, Katherine Scovner Ravi.

Writing – original draft: David M. Charytan, Candace K. McClure, Katherine Scovner Ravi.

Writing – review & editing: Alexandru I. Costea, Vijay Kher, Bruce A. Koplan, Finnian R. Mc Causland, Prabir Roy-Chaudhury, James A. Tumlin, Don Williamson.

Data Sharing Statement

All data are included in the manuscript and/or supporting information.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A622.

Supplemental Table 1. Characteristics of the participants at baseline according to country of origin.

Supplemental Table 2. Characteristics of the dialysis prescription at baseline according to country of origin.

Supplemental Table 3. Laboratory values by hemodialysis sessions.

Supplemental Table 4. Characteristics of the hemodialysis prescriptions by hemodialysis sessions.

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*MiD Investigators and Committees: Nephrology Investigators—Don Williamson, MD (Southeastern Clinical Research Institute, Augusta, GA, Augusta, GA), Prabir Roy-Chaudhury, MD, (University of Cincinnati Medical Center Cincinnati, OH; now at the University of Arizona Tuscon, AZ), James Tumlin, MD (Nephronet Clinical Research Institute, Atlanta, GA), Vijay Kher, MD (Medanta - The Medicity-Kidney and Urology Institute, Gurgaon, India), Vikranth Reddy, MD (CARE Hospital Hyderabad, India), Kowdle Chandrasekhar Prakash, MD, (Apollo Hospitals–Chennai, Chennai, India), David Charytan, MD MSc (Brigham and Women's Hospital, Boston, MA; now at NYU Langone Medical Center, New York, NY), 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 and 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 Co-investigators—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 Mc Causland, MBBCh, MMSc (Brigham and 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, India). Advisory Committee—David Charytan, MD, MSc, (Brigham and Women's Hospital, Boston, MA; now at NYU Langone Medical Center, New York, NY), 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 McCullough, MD (Baylor University Medical Center, Baylor Heart and Vascular Institute, Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, TX), 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, NC), Wolfgang C. Winkelmayer, MD, ScD (Baylor College of Medicine, Houston, TX).

AFFILIATIONS

[1]Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts
[2]Harvard Medical School, Boston, Massachusetts
[3]NephroNet Clinical Research Consortium, Atlanta, Georgia
[4]UNC Kidney Center, Chapel Hill, North Carolina
[5]WG (Bill) Hefner VA Medical Center, Salisbury, North Carolina
[6]Cardiology Division, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts
[7]The Christ Hospital, Cincinnati, Ohio
[8]Medanta Kidney and Urology Institute, Medanta The Medicity, Gurugram, India
[9]Southeastern Clinical Research Institute, Augusta, Georgia
[10]NAMSA, Minneapolis, Minnesota
[11]New York University School of Medicine and NYU Langone Medical Center, New York, New York