RESEARCH LETTER

Kidney Function and Subclinical Arrhythmias: The Multi-Ethnic Study of Atherosclerosis

To the Editor:

Patients with chronic kidney disease (CKD) are at high risk for atrial fibrillation (AF), an arrhythmia associated with progression to kidney failure and increased risk for cardiovascular complications and death,[1-3] and ventricular arrhythmias, which contribute to the increased risk for sudden cardiac death.[4] Arrhythmias are often asymptomatic and not detected clinically; thus, the true incidence and prevalence among patients with CKD are unknown. Extended ambulatory cardiac monitoring is a sensitive and unbiased method for detecting both atrial and ventricular arrhythmias, allowing accurate estimation of arrhythmia burden. The aim of this study was to investigate the presence of cardiac monitor–detected arrhythmias and their cross-sectional associations with measures of kidney function in the setting of a community-based prospective cohort study.

In the Multi-Ethnic Study of Atherosclerosis (MESA), kidney function was assessed at the 2016 to 2018 study visit using 2 measures: glomerular filtration rate, estimated (eGFR) using the 2009 CKD Epidemiology Collaboration creatinine equation,[5] and urinary albumin-creatinine ratio (UACR), which was $\log_2$ transformed for analysis. At the same visit, extended ambulatory cardiac monitoring was conducted for up to two 14-day periods per participant using the Zio Patch XT (iRhythm Technologies, Inc).[6] Device information was consolidated for participants with 2 devices. Seven arrhythmia outcomes were studied: presence of subclinical AF or atrial flutter lasting more than 30 seconds (in those with no history of clinically recognized AF/flutter), presence of monitor-detected AF/flutter (>30 seconds), frequency of premature atrial contractions, frequency of runs of 4 or more beats of supraventricular tachycardia (SVT), frequency of premature ventricular contractions, presence of runs of 4 or more beats of ventricular tachycardia (VT), and frequency of runs of VT. Continuous outcome variables were natural log transformed. Analyses used logistic regression for binary outcomes and linear regression for continuous outcomes, adjusted for demographic and clinical risk factors. Participants who completed at least 24 hours of monitoring, had no paced rhythm, and did not receive renal replacement therapy were included in this analysis. Further details of the study methods are available in the supplementary methods (Item S1).

Of 1,518 eligible participants, 1,459 had eGFR measures, 1,369 had UACR measures, and 178 had a history of clinically recognized AF/flutter (Table 1). Mean age was 74 (standard deviation, 8) years, 52% were women. Median kidney function measures were eGFR of 77 (interquartile range [IQR], 62, 88) mL/min/1.73 m^2 and UACR of 6 (IQR, 3, 18) mg/g, and median total monitoring duration was 14.0 (IQR, 13.6, 26.4) days. AF/flutter was detected in 7%, all but 1 participant had supraventricular ectopy, and 98% had ventricular ectopy (Table S1). Prevalence of arrhythmias among participants with eGFR < 60 mL/min/1.73 m^2 is presented in Table S2.

In primary analyses with continuous kidney function measures (Table 2), a doubling of UACR was associated with increased odds of monitor-detected AF/flutter (odds ratio, 1.18; 95% CI, 1.06-1.32) while eGFR was not significantly associated with AF/flutter. Neither eGFR nor UACR was associated with subclinical AF/flutter or ventricular arrhythmias. The analysis of eGFR and frequency of runs of SVT yielded results opposite of the expected direction: a 10 mL/min/1.73 m^2 greater eGFR was associated with 7% greater frequency of SVT (95% CI, 1%-12%).

In a multiethnic community-based population of older adults with a wide range of kidney function, higher UACR was associated with increased risk for monitor-detected AF/flutter but not subclinical AF/flutter. Also, higher eGFR was associated with a slightly greater frequency of runs of SVT. We found no association of these 2 kidney function measures with other measures of supraventricular or ventricular ectopy.

Previous studies of kidney function and clinically recognized AF among patients with CKD have also found significant associations for UACR but not creatinine-based eGFR.[1,7,8] However, the literature on arrhythmias other than AF in adults with CKD is sparse.[9,10] Our study is one of the first to use extended ambulatory monitoring to evaluate the risk for other arrhythmias in relation to kidney function in a community-based sample of adults with and without CKD (Table S2).

Strengths of our study include the large number of participants with extended cardiac monitoring, permitting accurate estimation of the burden of supraventricular and ventricular arrhythmias. Participants ranged in age from 60 to 98 years, an age span during which decreased kidney function and cardiac arrhythmias are common. Limitations include the small proportion of participants with eGFR < 45 mL/min/1.73 m^2 and the possibility that the few significant results in our study arose by chance alone given the examination of 2 measures of kidney function and 7 arrhythmia measures.

In summary, in a large population of older individuals across a wide range of kidney function, we found little evidence that decreased kidney function was associated with increased monitor-detected arrythmias other than AF. Additional studies in larger groups of people with CKD are needed to better understand the association of kidney function with subclinical arrhythmias.

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Table 1. Characteristics of Participants as of the 2016-2018 Study Examination in MESA, Stratified by eGFR and UACR

			eGFR Category, mL/min/1.73 m^2				UACR Category, mg/g		
	All Participants	All With eGFR	≥60	45-59	<45	All With UACR	<10	10-29	≥30
No. of participants	1,518	1,459	1,139	227	93	1,369	855	263	251
Age, y	74 (8)	74 (8)	72 (8)	79 (8)	82 (7)	74 (8)	72 (8)	76 (9)	77 (8)
Women	783 (52%)	750 (51%)	592 (52%)	101 (45%)	57 (61%)	701 (51%)	439 (51%)	150 (57%)	112 (45%)
Race									
White	615 (41%)	605 (42%)	468 (41%)	96 (42%)	41 (44%)	565 (41%)	368 (43%)	107 (41%)	90 (36%)
Chinese American	208 (14%)	195 (13%)	158 (14%)	29 (13%)	8 (9%)	189 (14%)	114 (13%)	41 (16%)	34 (14%)
African American	378 (25%)	353 (24%)	270 (24%)	59 (26%)	24 (26%)	330 (24%)	193 (23%)	60 (23%)	77 (31%)
Hispanic	317 (21%)	306 (21%)	243 (21%)	43 (19%)	20 (22%)	285 (21%)	180 (21%)	55 (21%)	50 (20%)
History of clinically recognized AF or atrial flutter	178 (12%)	170 (12%)	100 (9%)	44 (19%)	26 (28%)	162 (12%)	71 (8%)	40 (15%)	51 (20%)
History of MI or HF	57 (4%)	55 (4%)	30 (3%)	15 (7%)	10 (11%)	51 (4%)	23 (3%)	17 (7%)	11 (4%)
BMI, kg/m^2	28.3 (5.5)	28.3 (5.5)	28.2 (5.5)	28.7 (5.2)	28.6 (5.6)	28.3 (5.5)	28.0 (5.1)	28.6 (6.1)	29.2 (5.9)
Systolic blood pressure, mm Hg	127 (20)	127 (20)	126 (20)	129 (19)	128 (18)	127 (20)	123 (17)	130 (20)	138 (25)
Diastolic blood pressure, mm Hg	69 (10)	69 (10)	70 (10)	67 (9)	64 (9)	69 (10)	69 (9)	68 (10)	70 (12)
Hypertension	978 (64%)	937 (64%)	672 (59%)	186 (82%)	79 (85%)	883 (65%)	470 (55%)	195 (74%)	218 (87%)
Smoking									
Never	704 (46%)	677 (47%)	536 (47%)	96 (42%)	45 (48%)	635 (46%)	409 (48%)	125 (48%)	101 (40%)
Former	722 (48%)	694 (48%)	531 (47%)	118 (52%)	45 (48%)	655 (48%)	392 (46%)	129 (49%)	134 (53%)
Current	90 (6%)	86 (6%)	70 (6%)	13 (6%)	3 (3%)	79 (6%)	54 (6%)	9 (3%)	16 (6%)
Glucose status									
Normal	806 (53%)	788 (54%)	636 (56%)	115 (51%)	37 (40%)	727 (54%)	496 (59%)	133 (51%)	98 (39%)
Impaired fasting glucose	360 (24%)	351 (24%)	270 (24%)	60 (26%)	21 (23%)	336 (25%)	210 (25%)	64 (24%)	62 (25%)
Diabetes	337 (22%)	320 (22%)	233 (21%)	52 (23%)	35 (38%)	297 (22%)	142 (17%)	65 (25%)	90 (36%)
Education									
≤High school	426 (28%)	403 (28%)	301 (27%)	68 (30%)	34 (37%)	378 (28%)	216 (25%)	79 (30%)	83 (33%)
>High school	1089 (72%)	1053 (72%)	836 (74%)	158 (70%)	59 (63%)	988 (72%)	636 (75%)	184 (70%)	168 (67%)
β-Blocker use	335 (22%)	326 (23%)	200 (18%)	88 (39%)	38 (41%)	307 (22%)	150 (18%)	71 (27%)	86 (34%)
Antiarrhythmic use	16 (1.0%)	15 (1.0%)	12 (1.1%)	1 (0.4%)	2 (2.2%)	16 (1.2%)	7 (0.8%)	3 (1.2%)	6 (2.4%)
UACR, mg/g	6 [3, 18]	6 [3, 18]	6 [3, 13]	10 [3, 38]	23 [8, 78]	6 [3, 18]	4 [2, 6]	15 [12, 21]	73 [42, 138]
eGFR, mL/min/1.73 m^2	77 [62, 88]	77 [62, 88]	82 [72, 90]	53 [49, 57]	39 [31, 43]	77 [62, 88]	79 [67, 89]	75 [57, 86]	68 [52, 85]

Note: Values expressed as mean (standard deviation), number (percent), or median [interquartile range]. Conversion factor for glucose in mg/dL to μmol/L, ×0.05551. Abbreviations and Definitions: AF, atrial fibrillation; BMI, body mass index; Diabetes, use of an oral hypoglycemic agent or insulin, or fasting glucose level ≥ 126 mg/dL; eGFR, estimated glomerular filtration rate; HF, heart failure; Hypertension, systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or use of an antihypertensive medication with self-reported history of hypertension; Impaired glucose status, no use of a medication for diabetes and fasting glucose level of 100 to 125 mg/dL; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; UACR, urinary albumin-creatinine ratio.

Table 2. Association of Kidney Function Measures With Monitor-Detected Arrhythmias

	Presence of Monitor-Detected AF/Flutter[a]		Presence of Subclinical AF/Flutter[b]		Runs of SVT per Day		PACs per Hour	
Atrial Arrhythmias	**N Events/Total**	**OR (95% CI)**	**N Events/Total**	**OR (95% CI)**	**N Events/Total**	**GMR[c] (95% CI)**	**N Events/Total**	**GMR (95% CI)**
eGFR/10	93/1,459	0.88 (0.77-1.01)	43/1,289	1.09 (0.87-1.36)	1,207/1,415	1.07 (1.01-1.12)	1,414/1,415	1.02 (0.96-1.08)
eGFR category								
≥60	56/1,139	1.0 (ref)	35/1,039	1.0 (ref)	951/1,121	1.0 (ref)	1,120/1,121	1.0 (ref)
45-59	21/227	1.22 (0.69-2.16)	4/183	0.36 (0.12-1.09)	187/211	0.89 (0.71-1.11)	211/211	1.12 (0.84-1.49)
<45	16/93	2.38 (1.21-4.68)	4/67	1.18 (0.38-3.72)	69/83	0.51 (0.37-0.71)	83/83	0.76 (0.52-1.12)
$\log_2$ UACR[d]	88/1,369	1.18 (1.06-1.32)	39/1,207	1.05 (0.88-1.26)	1,134/1,327	1.01 (0.96-1.05)	1,326/1,327	1.03 (0.98-1.09)
UACR category								
<10	39/855	1.0 (ref)	23/784	1.0 (ref)	714/843	1.0 (ref)	842/843	1.0 (ref)
10-29	20/263	1.42 (0.78-2.57)	6/223	0.89 (0.34-2.33)	209/251	0.82 (0.67-1.02)	251/251	0.96 (0.74-1.25)
≥30	29/251	2.33 (1.32-4.09)	10/200	1.87 (0.79-4.46)	211/233	1.04 (0.84-1.30)	233/233	1.10 (0.84-1.43)

	Presence of Runs of VT		Runs of VT per Day[e]		PVCs per Hour	
Ventricular Arrhythmias	**N Events/Total**	**OR (95% CI)**	**N Events/Total**	**GMR (95% CI)**	**N Events/Total**	**GMR (95% CI)**
eGFR/10	416/1,459	1.06 (0.98-1.15)	416/416	0.95 (0.88-1.03)	1,437/1,459	1.08 (0.99-1.17)
eGFR category						
≥60	318/1,139	1.0 (ref)	318/318	1.0 (ref)	1,119/1,139	1.0 (ref)
45-59	71/227	0.87 (0.62-1.22)	71/71	1.05 (0.72-1.53)	225/227	0.92 (0.63-1.34)
<45	27/93	0.82 (0.49-1.38)	27/27	1.14 (0.67-1.92)	93/93	0.57 (0.31-1.02)
$\log_2$ UACR	389/1,369	1.07 (1.00-1.14)	389/389	1.05 (0.97-1.13)	1,347/1,369	1.01 (0.94-1.10)
UACR category						
<10	217/855	1.0 (ref)	217/217	1.0 (ref)	838/855	1.0 (ref)
10-29	89/263	1.46 (1.06-2.02)	89/89	1.26 (0.96-1.66)	259/263	0.94 (0.65-1.36)
≥30	83/251	1.28 (0.91-1.81)	83/83	1.13 (0.82-1.55)	250/251	1.06 (0.71-1.58)

Note: All models adjusted for continuous age, height, weight, and systolic blood pressure and categorical sex, race, glucose status, hypertension, clinic site, and history of myocardial infarction or heart failure. Logistic models were also adjusted for total analyzable monitor time. Abbreviations: AF/flutter, atrial fibrillation or atrial flutter; eGFR/10, per 10 mL/min/1.73 m^2 increment greater estimated glomerular filtration rate; GMR, geometric mean ratio; OR, odds ratio; PAC, premature atrial contraction; PVC, premature ventricular contraction; ref, reference; SVT, supraventricular tachycardia; UACR, urinary albumin-creatinine ratio; VT, ventricular tachycardia.

[a]Monitor-detected AF/flutter is defined as AF or atrial flutter identified by the monitor.

[b]Subclinical AF/flutter is defined as newly identified AF or atrial flutter detected solely by the monitor, with no known history of clinically recognized AF or atrial flutter.

[c]For a log-transformed outcome variable, such as runs of SVT per day, the GMR gives the average percent change in the outcome per increment increase in the exposure variable. For example, an increase of 10 mL/min/1.73 m^2 in eGFR was associated with 7% more runs of SVT per day.

[d]When an exposure variable is $\log_2$ transformed, an increment increase in the log-transformed variable equals a 2-fold increment in the variable. For example, per 2-fold increment in UACR, the odds of monitor-detected AF/flutter increased by 18%.

[e]Runs of VT per day includes only participants with at least 1 run of VT.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Supplementary Methods

Table S1: Prevalence of monitor-detected arrhythmias, overall and stratified, by estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR) in Multi-Ethnic Study of Atherosclerosis participants

Table S2: Among individuals with chronic kidney disease, comparison of the MESA results with published studies reporting detection rates of arrhythmias

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