Rates of Cardiac Rhythm Abnormalities in Patients with CKD and Diabetes

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Abstract

Background and objectives Cardiac arrhythmias increase mortality and morbidity in CKD. We evaluated the rates of subclinical arrhythmias in a population with type 2 diabetes and patients with moderate to severe CKD who were not on dialysis.

Design, setting, participants & measurements This is a prospective observational study, using continuous ambulatory cardiac monitors to determine the rate of atrial and ventricular arrhythmias, as well as conduction abnormalities in this group.

Results A total of 38 patients (34% women), with mean eGFR of 38±13 ml/min per 1.73 m^2, underwent ambulatory cardiac monitoring for 11.2±3.9 days. The overall mean rate of any cardiac arrhythmia was 88.8 (95% confidence interval [95% CI], 27.1 to 184.6) episodes per person-year (PY). A history of cardiovascular disease was associated with a higher rate of detected arrhythmia (rate ratio, 5.87; 95% CI, 1.37 to 25.21; $P<0.001$). The most common arrhythmia was atrial fibrillation, which was observed in two participants with known atrial fibrillation and was a new diagnosis in four patients (11%), none of whom experienced symptoms. Overall, atrial fibrillation episodes occurred at a rate of 37.6 (95% CI, 2.4 to 112.3) per PY. Conduction abnormalities were found in eight patients (21%), a rate of 26.5 (95% CI, 4.2 to 65.5) per PY. Rates of ventricular arrhythmias were low (14.5 per PY; 95% CI, 4.3 to 32.0) and driven by premature ventricular contractions.

Conclusions Cardiac rhythm abnormalities are common in patients with diabetes with moderate to severe CKD not requiring dialysis. Rates of atrial fibrillation are high and episodes are asymptomatic. Future studies are needed to determine the role of screening and upstream therapy of cardiac arrhythmias in this group.

Clin J Am Soc Nephrol 14: 549–556, 2019. doi: https://doi.org/10.2215/CJN.09420818

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Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients with CKD (1,2). Cardiac rhythm abnormalities, including atrial fibrillation and ventricular arrhythmias, are also more prevalent in patients with CKD compared with the general population (3), and lead to poor clinical outcomes such as higher rates of death (4), including sudden cardiac death (5). Identification of preclinical cardiac arrhythmias may allow earlier opportunities for therapies to improve the poor cardiovascular outcomes in this vulnerable population.

Some studies have been conducted to assess preclinical arrhythmic burden in patients with ESKD requiring hemodialysis, using implantable cardiac monitors or loop recorders (6,7). In a study of 50 patients receiving hemodialysis, five deaths were classified as sudden cardiac death, which were due to bradycardia and asystole (8,9). However another study of 75 patients on hemodialysis reported that 79% of sudden cardiac arrest events were preceded by ventricular arrhythmias (10). A recent paper of 66 patients on dialysis found a high prevalence of bradycardia. Furthermore, 41% of these patients were noted to have atrial fibrillation, with temporal associations with timing of dialysis (11). A study of 77 dialysis patients also found higher rates of supraventricular arrhythmias, which were linked to a four-fold increased risk of cardiovascular events (7). Although these studies are informative, they have not provided data on the larger, nondialysis-requiring CKD population. With the widespread availability of noninvasive external mobile cardiac telemetry monitors, there is an opportunity to characterize the burden of preclinical cardiac arrhythmias in patients with CKD.

Therefore, in this study, we used mobile cardiac telemetry monitors to study the rate of cardiac rhythm abnormalities in a cohort of patients with moderate to severe CKD (eGFR 15–60 ml/min per 1.73 m^2; not requiring dialysis) and type 2 diabetes. We hypothesized that similar to the dialysis population, rates of preclinical cardiac arrhythmias would be high in this high-risk population.

Materials and Methods

Study Population

The Continuous Glucose Monitoring to Assess Glycemia in CKD (CANDY) study is an observational

study of patients with type 2 diabetes mellitus and CKD conducted at the University of Washington. Participants were recruited from the outpatient diabetes care centers and nephrology clinics at the University of Washington, Harborview Hospital, and the Puget Sound Veteran's Administration Hospital. The main goal of the CANDY study was to characterize glucose variability, hypoglycemia, and hyperglycemia using state-of-the-art continuous glucose monitoring. To be included, participants had to have a clinical diagnosis of type 2 diabetes and moderate to severe kidney disease (eGFR 15–60 ml/min per 1.73 m^2 but not yet requiring dialysis). Exclusion criteria included active treatment for cancer, use of continuous glucose monitoring for clinical care, erythropoietin use, ESKD needing dialysis, solid organ transplant, pregnancy, or inability to provide informed consent. A total of 81 participants with CKD were recruited between August 2015 and July 2017 and completed the study.

For the arrhythmia substudy of the CANDY study, participants were offered mobile cardiac telemetry monitoring with the SEEQ device (SEEQ; Medtronic Inc., Minneapolis, MN), for a minimum of 7 days of monitoring (and up to 28 days) (Supplemental Figure 1). Of the 81 participants with CKD in the CANDY study, 68 participants were approached to participate in the arrhythmia substudy. Of these, 38 participants (56%) agreed to wear the SEEQ and participate in the arrhythmia substudy, with no loss to follow-up.

The study protocol was reviewed and approved by the University of Washington Human Subjects Research Board and was compliant with the Declaration of Helsinki (IRB#45106).

Mobile Cardiac Telemetry

The SEEQ monitor is a patch that attaches to the patient's pectoral area and provides a single-lead electrocardiogram recording. Data are stored on the monitor then submitted to a monitoring center for analysis through a wireless transmitter. A summary report is provided at the end of the monitoring period, which includes sample tracings illustrating abnormal findings. Findings meeting criteria for urgent notification were reported to the study team by the monitoring center as soon as they were received. Urgent notification criteria are provided in the supplement file. Arrhythmias automatically detected by the monitor include bradycardia and pauses, resulting from sinus node or atrioventricular conduction block, bundle branch block, premature atrial and ventricular beats, as well as atrial and ventricular tachyarrhythmias. In addition, patients can use the monitor to manually record at any time and were encouraged to do so if they felt symptoms such as palpitations, lightheadedness, or syncope. CANDY study participants were asked to wear the SEEQ monitor for a minimum of 7 days and up to 28 days (consecutive or nonconsecutive). Each monitoring period was up to 7 days long, after which a new SEEQ monitor was placed.

All individual patient tracings were independently adjudicated by a board-certified electrophysiologist, who was blinded to CKD status, who either agreed with or corrected findings provided from the monitoring center and reclassified the arrhythmia type if indicated.

Cardiac Arrhythmias

We ascertained the following arrhythmia types: supraventricular arrhythmias (including atrial tachycardias, premature atrial and junctional beats, and junctional and ectopic atrial rhythms), atrial fibrillation/flutter, conduction abnormalities (including first, second [Mobitz types 1 and 2] and third-degree atrioventricular block, as well as bundle branch block), and ventricular arrhythmias (including premature ventricular beats and ventricular tachycardia).

The definitions used for each of these reported arrhythmias were as follows: sinus bradycardia slower than 30 beats per minute, any occurrence of second (Mobitz type 1 or type 2) or third-degree atrioventricular block, and pauses longer than 2 seconds. Premature atrial or ventricular beats were reported when more frequent than six occurrences in a 45-second recording period. Atrial fibrillation episodes lasting longer than 30 seconds were all reported. Any supraventricular tachycardia and wide complex tachycardia (ventricular tachycardia or supraventricular tachycardia with aberrant conduction) lasting longer than three consecutive beats were also reported.

Covariates

Patient demographic information, including age, sex, ethnicity, and educational level, was recorded at study entry as reported by the patients. Health history, including prior diagnoses of diabetes, hypertension, coronary artery disease, congestive heart failure, stroke, hyperlipidemia, peripheral vascular disease, atrial fibrillation, or cardiac arrest, was obtained through interviews conducted by study coordinators at study entry, ascertained through medical record review. Drug therapy at study entry was ascertained and updated at every study visit. Patients were classified as either taking or not taking (binary) medications including β-blockers, dihydropyridine (DHP) and non-DHP calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and other lipid-lowering agents. Height, weight, body mass index, eGFR, blood glycated hemoglobin, serum albumin and transferrin saturation, and urine albumin-to-creatinine ratio were reported as continuous variables at cohort entry.

Statistical Analyses

We summarized the demographic characteristics of study participants with means and SD for continuous variables, or number and percentages for categorical variables. For the primary analysis, the rate of physician-adjudicated arrhythmias was calculated as the number of arrhythmia occurrences divided by the total number of person years of valid ambulatory cardiac monitoring; bootstrap methods were used to obtain corresponding 95% confidence intervals (12). In exploratory analyses, we stratified rates of arrhythmias by the presence of clinical history of atrial fibrillation (yes/no); cardiovascular disease (yes/no) including clinical history of coronary disease, heart failure, or stroke; and use of β-blockers and non-DHP calcium channel blockers (yes/no). Associations of demographic and clinical predictors with any arrhythmia during the monitoring period were evaluated by Poisson regression with robust Huber–White SEM (13). All analyses were conducted using the R version 3.4.0 computing environment (R Foundation for Statistical Computing).

Results

Overview of Cardiac Monitoring

Cardiac monitoring was obtained on 38 patients with CKD, of whom 19 (50%) wore the SEEQ for one monitoring period (mean [SD] 7.9 [1.3] days), 18 (47%) for two monitoring periods (mean [SD] 14.1 [2.0] days), and 1 (3%) for three monitoring periods (22 days). The mean (SD) duration of overall monitoring per patient was 11.2 (3.9) days.

Characteristics of Study Participants

The mean age of study participants was 68 (9) years, 66% were men and the majority of participants were white (Table 1). A total of 39% of study participants had a history of cardiovascular disease, with the most common type being heart failure. Most patients (71%) were obese. Mean eGFR was 38 (13) ml/min per 1.73 m^2. The majority of participants were taking antihypertensive medications (92%), with a high proportion on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (76%) and β-blockers (55%). The vast majority of patients were on insulin, either alone or in combination with other oral hypoglycemic. Thyroid supplementation was also prescribed in 11% of patients. (Table 1).

Rates of Cardiac Arrhythmias

Among the 38 participants, there were 104 arrhythmic episodes among 18 unique participants (47%). The overall rate of any cardiac arrhythmia in patients with CKD was 88.8 (95% confidence interval, 27.1 to 184.6) episodes per person-year. Of the arrhythmia subtypes, atrial fibrillation and conduction abnormalities occurred at the highest rates (Figure 1, Table 2), as detailed below.

Conduction abnormalities occurred at a rate of 26.5 per person-year, with 31 episodes among eight participants (Figure 1, Table 2). Second-degree atrioventricular block had the greatest number of episodes but was limited to one participant. In contrast, sinus bradycardia occurred among 8% of participants.

Ventricular arrhythmias occurred at the lowest rate compared with the other cardiac arrhythmias (Figure 1, Table 2). There were 17 episodes of ventricular arrhythmias occurring among nine (24%) unique participants. The most common type of ventricular arrhythmia were premature ventricular complexes (Table 2).

Of the characteristics of the population, age ≥65 years, body mass index ≥30 kg/m^2, β-blocker/non-DHP calcium channel blocker usage, and a prior history of cardiovascular disease (including coronary disease, heart failure, or stroke) were significantly associated with greater rates of cardiac arrhythmias (of any type) (Table 3).

Exploratory Analyses: Stratified by History of atrial fibrillation

A prior diagnosis of atrial fibrillation was present in seven out of 38 patients with CKD, whereas a new diagnosis of atrial fibrillation was made in four of the remaining 31 patients without known atrial fibrillation (13%). There were 44 individual episodes of atrial fibrillation observed overall, with a rate of 37.6 per person-year. None of the participants reported symptoms during any of the 44 atrial fibrillation episodes. The duration of most atrial fibrillation episodes was between 5 minutes and 1 hour (59%), followed by 1–6 hours (38%) and >6 hours in 2.7%.

Table 1. Baseline characteristics of study participants with type 2 diabetes and moderate to severe CKD (*n*=38)

Demographics	*N* (%) or Mean (SD)
Age, yr	68 (9)
Men	25 (66)
Race/ethnicity	
White	32 (84)
Black	4 (11)
Other	2 (5)
Highest level of education	
High school	11 (29)
Trade school	5 (13)
College	13 (34)
Graduate school	9 (24)
Health history	
General health	
Excellent/very good	8 (21)
Good	10 (26)
Fair or poor	20 (53)
Current smoking	0 (0)
History of cardiovasular disease	15 (39)
History of myocardial infarction	4 (11)
History of congestive heart failure	7 (18)
History of stroke	5 (13)
History of peripheral vascular disease	4 (11)
History of atrial fibrillation	7 (18)
History of cardiac arrest	0 (0)
Duration of DM, yr	20.1 (10.7)
Physical characteristics	
BMI, kg/m^2	34.0 (6.2)
Systolic BP, mm Hg	134 (17)
Diastolic BP, mm Hg	70 (12)
eGFR, ml/min per 1.73 m^2	38 (13)
Serum electrolytes	
Potassium, mmol/L	4.5 (0.5)
Calcium, mg/dl	9.0 (0.5)
Urine ACR, mg/g[a]	128.6 (33.1–600.7)
HbA1c, %	7.9 (1.5)
Serum albumin, mg/dl	3.6 (0.4)
Transferrin saturation, %	28 (11)
Medication use	
Antihypertensive medications	35 (92)
ACEi/ARBs	29 (76)
β-blockers	21 (55)
Calcium channel blockers	21 (55)
DHP calcium channel blockers	19 (50)
Non-DHP calcium channel blockers	2 (5)
Diuretics	20 (53)
Statins	35 (92)
Lipid-lowering medications	35 (92)
Thyroid supplementation	4 (11)
Any insulin use	34 (89)
Insulin secretagogues	7 (18)
Other glucose-lowering medications	15 (39)

Entries are mean (SD) or *N* (%), as appropriate. DM, diabetes mellitus; BMI, body mass index; ACR, albumin-to-creatinine ratio; HbA1C, hemoglobin A1C; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DHP, dihydropyridine.
[a]Urine ACR is presented as median (interquartile range).

Exploratory Analyses: Stratified by History of Cardiovascular Disease

There were 15 patients with known cardiovascular disease and 23 patients without known cardiovascular disease. There appeared to be a trend in higher rates rate of any arrhythmia

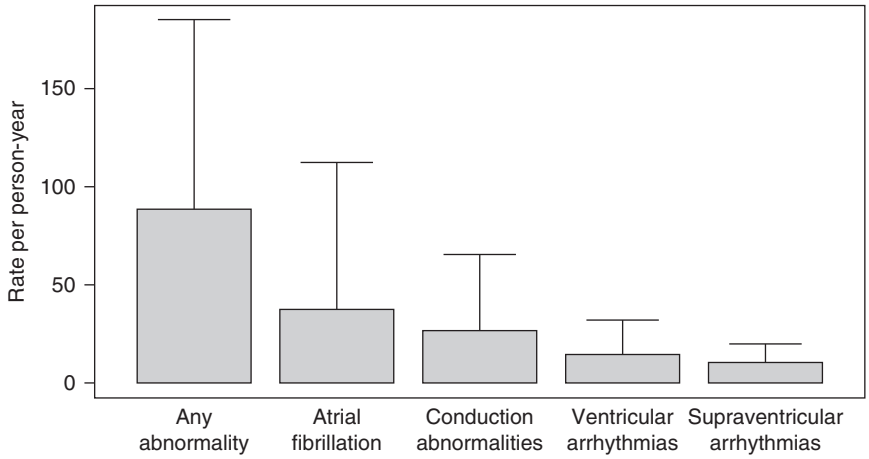

Figure 1. | **Rates of physician-adjudicated arrhythmias in participants with CKD (*n*=38).** Bars indicate the upper limit of a 95% bootstrapped confidence interval.

overall or by subtype in participants with a history of cardiovascular disease compared with those without (Supplemental Figure 2). There also appeared to be a trend for a particularly large difference in rates of atrial fibrillation and conduction abnormalities between participants with versus without history of cardiovascular disease (although these analyses were exploratory because of limited power).

Exploratory Analysis: Stratification by Use of β-Blockers and Non-DHP Calcium Channel Blockers

In the study population, 23 (61%) participants were taking either β-blockers or non-DHP calcium channel blockers. There appeared to be a trend toward higher rates of all arrhythmia types among participants who were taking β-blockers or non-DHP calcium channel blockers. The differences between β-blockers or non-DHP calcium channel blocker users versus nonusers appeared largest for risk of atrial fibrillation and conduction abnormalities (Supplemental Figure 3).

Discussion

In this study of 38 participants with moderate to severe CKD and type 2 diabetes, we demonstrate a high rate of cardiac rhythm abnormalities, with nearly half of the study population experiencing a significant cardiac arrhythmia and an overall mean rate of 88.8 episodes per person-year. The rates of atrial fibrillation were highest followed by conduction abnormalities (*e.g.*, atrioventricular conduction disease) and ventricular arrhythmias. Among the participants without known history of atrial fibrillation new atrial fibrillation was noted in 13% of the participants. These data suggest that patients with nondialysis-requiring CKD likely have a high burden of subclinical cardiac arrhythmias, which in turn may contribute to the high rates of cardiovascular morbidity and mortality in this population.

Prior studies in the ESKD population who are treated with hemodialysis have reported high rates of cardiac

Table 2. Rates of physician-adjudicated arrhythmias in participants with CKD (*n*=38)

Measurement	No. of Episodes	No. of Unique Participants	Rate per Person-Year (95% Bootstrapped CIs)
Any abnormality	104	18	88.8 (27.1 to 184.6)
Conduction abnormalities	31	8	26.5 (4.2 to 65.5)
Sinus bradycardia	4	3	3.4
Second-degree atrioventricular block	20	1	17.1
Junctional Rhythm	3	2	2.6
Intraventricular conduction delay	2	2	1.7
Pauses	2	1	1.7
Atrial fibrillation	44	6	37.6 (2.4 to 112.3)
Supraventricular arrhythmias	12	8	10.3 (3.4 to 20.1)
Preamture atrial or junctional complexes	9	8	7.7
Other supraventricular tachycardia	3	1	2.6
Ventricular arrhythmias	17	9	14.5 (4.3 to 32.0)
Premature ventricular contractions	16	8	13.7
Monomorphic ventricular tachycardia	0	0	0
Wide complex tachycardia	1	1	0.9

95% CI, 95% confidence interval;

Table 3. Associations of clinical characteristics with arrhythmia of any type

Variable	No. of Participants	No. (%) of Participants with at Least One Event	No. of Events	Rate (95% CI), per Person-Year	Rate Ratio (95% CI)
Sex					
Women	13	5	52	128.4 (7.5 to 383.8)	1.0 (Ref.)
Men	25	13	52	69.3 (23 to 137.4)	0.56 (0.09 to 3.38)
Age, yr					
<65	13	4	10	25.4 (5.4 to 53.4)	1.0 (Ref.)
≥65	25	14	94	122.7 (30.1 to 265.1)	4.91 (1.28 to 18.78)
Race/ethnicity					
White	32	16	92	96.3 (25.1 to 211.6)	1.0 (Ref.)
Nonwhite	6	2	12	61.9 (0 to 199.8)	0.59 (0.09 to 3.85)
BMI					
<30	11	5	5	14.3 (4.2 to 27.7)	1.0 (Ref.)
≥30	27	13	99	123.2 (34.3 to 261.9)	8.87 (2.62 to 30.04)
eGFR, ml/min per 1.73 m^2					
<30	11	3	14	40.8 (0 to 109.2)	1.0 (Ref.)
30–44	14	10	82	230.3 (49 to 527.3)	5.86 (1.05 to 32.8)
45–59	13	5	8	18.1 (3.4 to 42.5)	0.44 (0.08 to 2.51)
β-blocker/non-DHP CCB usage					
No	15	6	14	29.1 (6.6 to 57.9)	1.0 (Ref.)
Yes	23	12	90	133.5 (26.8 to 301.6)	4.64 (1.22 to 17.65)
History of cardiovascular disease					
No	23	7	23	32.3 (6.9 to 68.1)	1.0 (Ref.)
Yes	15	11	81	185.7 (35.4 to 436.3)	5.87 (1.37 to 25.21)
History of atrial fibrillation					
No	31	13	88	89.8 (20.5 to 201.5)	1.0 (Ref.)
Yes	7	5	16	89.9 (17.8 to 217.7)	0.97 (0.21 to 4.4)

95% CI, 95% confidence interval; BMI, body mass index; DHP, dihydropyridine; CCB, calcium channel blocker, CVD, cardiovascular disease.

arrhythmias, as detected by implantable cardiac monitors. In a recent study of 66 patients on dialysis, 66.7% experienced a cardiac arrhythmia with a rate of 20.1 events per month (11). In the dialysis population, there have been interesting temporal trends noted in arrhythmia burden corresponding to the timing of dialysis (9,11), which can lead to hemodynamic alterations, electrolyte shifts, and myocardial stunning, which are all possible triggers for cardiac arrhythmias. In our study of earlier stages of kidney disease, we found similar rates of cardiac arrhythmias as that reported in the dialysis population, even without a trigger such as kidney replacement therapy. We found that a known history of cardiovascular disease to be associated with arrhythmia risk in this CKD population. Other studies of non-CKD populations utilizing implantable heart monitors and conventional external monitors showed an atrial fibrillation detection rate of around 30% with loop monitors after 3 years (14) and 16% with conventional monitors up to 4 weeks in duration (15), in patients with cryptogenic stroke.

The proportion of patients who were newly diagnosed with atrial fibrillation during our study was 13% and the overall atrial fibrillation incidence rate was 37.6 per person-year. By comparison, the proportion of dialysis patients diagnosed with atrial fibrillation using implantable loop recorders was 33.3% with an incidence rate of 11.88 per person-month (142.56 per person-year), as reported recently in study by Roy-Chaudhury *et al*. (11). Another study reported that supraventricular tachycardias occurred in 49% of patients on dialysis, as detected by a Holter electrocardiogram (7). A third study reported new diagnosis of atrial fibrillation in 28% of patients on dialysis(9). Atrial fibrillation is the most common cardiac arrhythmia in CKD and is estimated to affect up to 25% of patients with CKD (16–19). Ascertainment of atrial fibrillation in prior studies of patients on CKD have relied on 12-lead electrocardiograms and International Classification of Diseases, Ninth Revision codes, which likely underestimates the incidence rate of atrial fibrillation compared with continuous monitoring performed in our study. Therefore, the true rate of atrial fibrillation in patients with CKD is likely higher than previous reports. This has important clinical implications because atrial fibrillation has been linked with poor clinical outcomes, including stroke, heart failure, death, and progression to ESKD. The minimum duration of atrial fibrillation episodes associated with clinical outcomes such as stroke or heart failure is not conclusively defined, and remains an area of active research in the general population. It is of particular interest in patients with CKD who are generally considered at increased risk for these outcomes (4,20,21). Restoration of sinus rhythm with catheter ablation has been shown to be associated

with improvement kidney function (22,23). Thus, subclinical atrial fibrillation may be an important therapeutic target in patients with CKD.

In our study, we noted high rates of conduction abnormalities (bradycardia and atrioventricular nodal disease). This is consistent with studies of patients on dialysis as well, which have shown high rates of bradycardia, which is linked with sudden cardiac death (6,8,9). Factors implicated in reentrant arrhythmia including fibrosis may also involve the sinus node, causing clinically significant sinus node dysfunction with sinus bradycardia, sinus arrhythmia, and pauses as manifestations.

The rate of malignant ventricular arrhythmias was low in our study. Prior reports have noted high rates of sudden cardiac death in patients with CKD and those on dialysis.(5,24) Some recent studies have also noted high rates of ventricular tachycardia and ventricular fibrillation in patients on dialysis, as detected by continuous cardiac monitoring (6). In our study of patients with CKD, although we did not find high rates of ventricular tachycardia or ventricular fibrillation, we found high rate of premature ventricular contractions. Preamture ventricular contractions are often seen as clinically insignificant; however, they may increase the risk of developing malignant arrhythmias such as ventricular tachycardia or ventricular fibrillation. Furthermore, premature ventricular contractions and atrial fibrillation are also associated with development of ectopy-related cardiomyopathy (25).

In exploratory analyses, there was a trend toward higher rates of all types of cardiac arrhythmias among participants treated with β-blockers and calcium channel blockers. Although these analyses were limited in power, the trends are interesting. β-blockers and non-DHP calcium channel blockers exacerbate sinus node and atrioventricular nodal disease, which may explain the higher rates of conduction abnormalities seen in these participants. It was intriguing that we noted higher rates of other types of cardiac arrhythmias (*e.g.*, supraventricular tachycardia, atrial fibrillation, and ventricular arrhythmias) in participants treated with these medications. In this small, observational study, the reasons for these findings are unclear; however, they may reflect that sicker patients at higher risk for arrhythmias are being appropriately treated (confounding by indication). These exploratory analyses warrant further study in a larger and potentially interventional study of patients with CKD.

The pathophysiologic basis for arrhythmias in the CKD population is multifactorial. Most re-entrant arrhythmia mechanisms, including atrial fibrillation, involve an abnormal tissue substrate. Patients with CKD have endothelial dysfunction, inflammation, and atherosclerosis, which leads to perfusion defects and fibrosis of atrial and ventricular tissue (26). Electrolyte disturbances in potassium, calcium, and magnesium are often common even in moderate stages of CKD, and may lead to arrhythmias. Metabolic disturbances and left ventricular hypertrophy seen in CKD may also contribute to myocardial fibrosis (27). In addition, there is a shift in the autonomic balance toward increased sympathetic activation due to uremic neuropathy, which leads to increased activity of focal triggers and provides an arrhythmogenic milieu for re-entrant tachyarrhythmias.

The findings of our study have potentially important next steps. Further work is needed to understand the implications of these arrhythmias on subsequent risk of cardiovascular disease and death. It is possible that preclinical cardiac arrhythmias may represent an important therapeutic target, treatable with widely available cardiovascular therapies. If so, mobile cardiac telemetry may be a feasible, noninvasive diagnostic tool to help stratify patients with CKD according to risk, and personalize their cardiovascular disease prevention strategies.

Our study had several strengths. We used state-of-the-art, noninvasive, and clinically available technology to detect cardiac arrhythmias. All arrhythmias were adjudicated by a board-certified electrophysiologist. We recognize some limitations as well. This is a relatively small study of 38 participants with moderate stages of CKD. However, previous published studies of patients on dialysis have had similar small sample sizes (7–9,11). Not all participants in the parent study consented to wear the heart monitor, which may have introduced selection bias. The population only included participants with type 2 diabetes. Although diabetes is the leading cause of CKD, the findings may not be generalizable to all patients with CKD. The sample size's effect on the generalizability of our study is also reflected by the wide confidence intervals in the overall rate of arrhythmias (88.8; 95% confidence interval, 27.1 to 184.6) as well as 62% of arrhythmia episodes contributed by seven patients in the cohort (of whom, some had a history of known atrial fibrillation). The study did not examine long-term outcomes. Our sample included patients with known coronary artery disease and congestive heart failure, both known to be risk factors for arrhythmias; it is unknown whether the rates of arrhythmias would be similar in patients with CKD without prior heart disease. Echocardiograms were not performed as part of this research study, and so we were not able to include data on left ventricular structure and function. In this observational study, we could not determine the reasons for prescription or nonprescription of important cardiovascular medication such as renin-angiotensin-aldosterone system inhibitors and β-blockers. We also recognize that our study did not include a control group without CKD to allow for a comparison of the rates of arrhythmia in the presence and absence of CKD.

In conclusion, in this study of participants with moderate CKD and type 2 diabetes, we found subclinical cardiac arrhythmias to be common, as nearly half of the participants experienced cardiac arrhythmias detected by mobile cardiac telemetry. Subclinical cardiac arrhythmias may be important precursors to clinically significant cardiovascular events, including sudden cardiac death. Further data are needed to determine whether treatment of subclinical cardiac arrhythmias reduce cardiovascular complications and improve overall survival in this high-risk CKD population.

Acknowledgments

N.A. and N.B. contributed to the conception, design, data acquisition, analysis and interpretation of the data, and manuscript drafting and critical revisions. L.R.Z. contributed to the data analysis and manuscript draft editing. C.H. and N.R. contributed to data acquisition. I.H.d.B., I.B.H., and D.T. contributed to the critical editing and reviewing of the manuscript. All of the authors gave their

final approval to this version of the manuscript and are accountable for all aspects of this work.

This work was supported by an American Diabetes Association grant (number 4-15-CKD-20) (Principal Investigator I.H.d.B.) and an unrestricted fund from the Northwest Kidney Centers. The SEEQ devices were supplied by Medtronic.

Because I.H.d.B. is a Deputy Editor of the *Clinical Journal of the American Society of Nephrology*, he was not involved in the peer review process for this manuscript. Another editor oversaw the peer review and decision-making process for this manuscript.

Disclosures

None.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.09420818/-/DCSupplemental.

Supplemental Figure 1. Continuous Glucose Monitoring to Assess Glycemia in CKD (CANDY) study activities.

Supplemental Figure 2. Rates of physician-adjudicated arrhythmias in participants with CKD with and without a history of clinical cardiovascular disease. Bars represent rate per person-year. CVD, cardiovascular disease including clinical diagnosis of coronary disease, heart failure, or stroke.

Supplemental Figure 3. Rates of physician-adjudicated arrhythmias in participants with CKD using and not using β-blockers or non-DHP CCBs. Bars represent rate per person-year. CCB, calcium channel blocker.

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Received: August 5, 2018 **Accepted:** January 18, 2019

Published online ahead of print. Publication date available at www.cjasn.org.