Kidney Function, Electrocardiographic Findings, and Cardiovascular Events among Older Adults

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Chronic kidney disease (CKD) is associated with cardiovascular (CV) disease and mortality. It is not known whether cardiac rhythm disturbances are more prevalent among individuals with CKD or whether resting electrocardiogram findings predict future CV events in the CKD setting. Data were obtained from the Cardiovascular Health Study, a community-based study of adults aged ≥65 yr. After exclusions for prevalent heart disease, atrial fibrillation, implantable pacemaker, or antiarrhythmic medication use, 3238 participants were analyzed. CKD was defined by an estimated GFR <60 ml/min per 1.73 m^2. Outcomes were adjudicated incident heart failure (HF), incident coronary heart disease (CHD), and mortality. Participants with CKD had longer PR and corrected QT intervals compared with those without CKD; however, differences in electrocardiographic markers were explained by traditional CV risk factors and CV medication use. After adjustment for known risk factors, each 10-ms increase in the QRS interval was associated with a 15% greater risk for incident HF (95% confidence interval [CI] 1.04 to 1.27), a 13% greater risk for CHD (95% CI 1.04 to 1.24), and a 17% greater risk for mortality (95% CI 1.09, 1.25) among CKD participants. Each 5% increase in QTI was associated with a 42% (95% CI 1.23 to 1.65), 22% (95% CI 1.07 to 1.40), and 10% (95% CI 0.98 to 1.22) greater risk for HF, CHD, and mortality, respectively. Associations seemed stronger for participants with CKD; however, no significant interactions were detected. Resting electrocardiographic abnormalities are common in CKD and independently predict future clinical CV events in this setting.

Clin J Am Soc Nephrol 2: 501-508, 2007. doi: 10.2215/CJN.04231206

Chronic kidney disease (CKD) is associated with a markedly increased risk for cardiovascular (CV) events and mortality (1–4). Disturbances of the cardiac electrical cycle might be detectable in early stages of CKD. Prolonged QT intervals and greater QT dispersion have been reported among uncontrolled case series of long-term hemodialysis patients (5–7). In contrast, a recent study found no association of kidney function with QT interval duration among approximately 200 nondialysis patients with earlier stages of CKD (8). Existing data do not clarify whether electrocardiogram (ECG) disturbances are more prevalent among patients with CKD or which ECG markers might be particularly important.

Prolonged ventricular depolarization and repolarization, assessed from the resting ECG, predict CV events in the general population, particularly among individuals who are at high baseline CV risk (9–12). ECG abnormalities may be particularly strong predictors of CV events among people with CKD, as a result of their considerable baseline CV risk. Associations of resting ECG markers with clinical CV events could promote the 12-lead ECG as a useful clinical tool for CV risk stratification in the CKD setting, for which reliable markers of subclinical CV disease are otherwise lacking.

In this study, we examined two research questions regarding kidney disease, ECG findings, and incident CV events among an ambulatory cohort of older adults without known heart disease. First, we investigated whether CKD is associated with differences in ECG measurements of atrial conduction, ventricular depolarization, and ventricular repolarization, independent of traditional CV risk factors and CV medication use.

Received December 18, 2006. Accepted February 28, 2007.

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

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ISSN: 1555-9041/203–0501

Second, we evaluated and compared resting ECG measurements as predictors of incident heart failure (HF), coronary heart disease (CHD), and mortality among older adults with and without CKD.

Materials and Methods

Study Population

The Cardiovascular Health Study (CHS) is a community-based study of clinical and subclinical cardiovascular disease among 5888 adults aged ≥65 yr (13). In 1989 to 1990, 5201 participants were recruited from four communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. An additional 687 black participants were recruited in 1992 to 1993. Potentially eligible study participants were randomly sampled from age-stratified Medicare eligibility lists in each area; 57% of those invited chose to participate in the study. Patients were excluded from CHS when they were institutionalized, required a proxy to give consent, were planning to move out of the area within 3 yr, required a wheelchair in the home, were receiving hospice care, or were undergoing radiation or chemotherapy for cancer.

This study uses data from the 1992 to 1993 CHS examination. Patients were excluded when they had any history of HF or CHD, defined by participant responses to questionnaires, medical chart review, and interim events that occurred between the baseline and 1992 to 1993 CHS examinations (14). Patients were also excluded when they had atrial fibrillation on their 1992 to 1993 ECG (precluding reliable measurement of ECG conduction parameters), had an implantable pacemaker, were using a class Ia or class IIIa antiarrhythmic medication, had incomplete 1992 to 1993 ECG data, or were missing serum cystatin C measurements.

Assessment of Kidney Function

Serum creatinine was measured using the colorimetric method and calibrated to the Cleveland Clinic Laboratory (15). Estimated GFR (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) equation (16). CKD was defined by an eGFR <60 ml/min per 1.73 m^2, as proposed by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (17). An eGFR threshold of 60 ml/min per 1.73 m^2 has been used as a cut point to predict CV risk in previous epidemiologic studies (1,2). Only 33 CHS participants had an eGFR <30 ml/min per 1.73 m^2; therefore, stage IV CKD was not analyzed as a separate category. Serum cystatin C levels were also examined as an alternative marker of kidney function. Cystatin C was measured from frozen sera using the BNII nephelometer (Dade Behring, Deerfield, IL) (18).

Assessment of ECG Variables

Resting 12-lead ECG were recorded in the supine position and processed using the Marquette 12SL ECG analysis program (GEMS-IT, Milwaukee, WI), which clusters QRS-T complexes from a 10-s recording of eight independent simultaneous ECG leads and selects a median complex for QT measurement. QT intervals were corrected for heart rate using the QT prolongation index (QTI), which represents the percentile prolongation of the QT interval with respect to the median value of a large North American sample (19): QTI % = (QT/656) × (heart rate + 100). QT intervals were also corrected for heart rate using Bazett's equation (QTc) (20): $QTc = QT/\sqrt{(RR)}$. Bazett's adjustment is widely used in clinical practice but does not fully account for the impact of heart rate on the QT interval, particularly in the setting of QRS prolongation (21). Accordingly, analyses of the QTc were restricted to participants without intraventricular conduction delay or bundle branch block.

Other Risk Factors

Diabetes was defined by a history of diabetes, the use of a diabetes medication, or a fasting blood glucose level ≥126 mg/dl (22). Impaired fasting glucose was defined among individuals without diabetes by a fasting glucose ≥100 mg/dl (22). BP was calculated from the mean of two consecutive readings in the seated position.

Ascertainment of Events

Outcomes of interest were incident HF, incident CHD, and mortality. Potential CV events were identified semiannually in CHS using telephone surveillance and participant-initiated contact and annually by repeat interviews and examinations. CV events were adjudicated using hospital discharge summaries, diagnostic test reports, surgery and radiology findings, and consultation reports (23). HF, which may be systolic or diastolic, was defined using an algorithm that included a physician diagnosis of HF, documentation of symptoms and physical signs of HF, evidence of pulmonary edema, and specific medical treatment for HF (24). Echocardiography results, when available, were also considered during adjudication. Incident CHD was defined as the first occurrence of acute myocardial infarction, angina, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting. Acute myocardial infarction was defined using an algorithm that included elements of chest pain, cardiac enzymes, and ECG changes. HF outcomes include nonfatal and fatal cases of HF; CHD outcomes include nonfatal and cases of CHD.

Statistical Analyses

Differences in continuous and categorical ECG markers were compared among patients with and without CKD using the t test and χ^2 test, respectively. PR and QRS intervals were evaluated as continuous exposure variables and in categories that correspond to known definitions of first-degree atrioventricular block (PR >200 ms) and incomplete and complete ventricular conduction delay (QRS >100 and >120 ms, respectively). The QTI was examined on the basis of categories that have been previously described within CHS (12). Prolonged QTc intervals were defined as >440 ms for men and >450 ms for women (25).

Nested multiple linear regression models were fit to explore independent associations of kidney function with ECG measurements. Models progressively included terms for demographics, traditional CV risk factors, CV medications, and other CV risk factors as putative explanations for differences in ECG findings according to kidney function. In these models, kidney function was evaluated as eGFR ≥60 *versus* <60 ml/min per 1.73 m^2 and continuously using serum cystatin C levels.

Participants were considered at-risk from the date of their 1992 to 1993 CHS examination until the first occurrence of an outcome of interest or censoring as a result of death (for analyses of nonfatal events) or study closure on June 30, 2004. Incident event rates were defined as the number of first events during follow-up divided by the number of person-years at risk. Cox proportional hazards models were used to estimate independent associations of each ECG marker with the time to first CV event. Models were adjusted for age; race; gender; smoking and alcohol status; diabetes status; systolic BP; height; weight; heart rate; CV medications; and serum levels of albumin, hemoglobin, potassium, total cholesterol, and HDL. The difference in partial likelihoods was used to evaluate whether the strength of association of each ECG marker (measured continuously) with CV events differed accord-

ing to an eGFR greater than or less than 60 ml/min per 1.73 m^2 or according to continuous cystatin C levels. Analyses were performed using S-Plus v6.1 (Insightful, Seattle, WA).

Results

Description of the Study Population

A total of 4692 CHS participants completed the 1992 to 1993 examination. We excluded 281 (6.0%) participants with a history of HF and 833 (17.8%) participants with a history of CHD. We further excluded 79 (1.7%) participants with atrial fibrillation, 20 (0.4%) with an implantable pacemaker, 61 (1.3%) who were receiving a class Ia or IIIa antiarrhythmic agent, 159 (3.4%) with incomplete ECG data, and 21 (0.4%) without a cystatin C measurement. After these exclusions, 3238 participants were available for analysis; 600 of these participants had CKD. Patients with CKD were older and more likely to use a diuretic and/or an angiotensin-converting enzyme inhibitor and had higher serum potassium levels compared with those without CKD (Table 1). Other medications that specifically affect the QT interval were rarely used (macrolides [0.4%], antihistamines [0.03%], antipsychotics

Table 1. Baseline characteristics according to eGFR[a]

Characteristic	eGFR (ml/min per 1.73 m^2)	
	<60 (n = 600)	≥60 (n = 2638)
Age (yr)	76.7 ± 5.8	73.9 ± 4.8
Male	34 (204)	39 (1021)
Race		
white	85 (509)	82 (2161)
black	14 (83)	18 (468)
other	1.3 (8)	0.3 (9)
Diabetes status		
normal	77 (459)	77 (2022)
impaired fasting glucose	12 (71)	10 (258)
diabetes	11 (70)	13 (358)
Smoker status		
never smoked	48 (287)	46 (1216)
former smoker	42 (250)	42 (1093)
current smoker	9 (53)	11 (282)
Alcohol use		
none	59 (354)	53 (1387)
1 to 7 drinks/wk	33 (198)	35 (930)
>7 drinks/wk	8 (47)	12 (316)
Medication use		
digoxin	4 (22)	3 (81)
β blocker	11 (68)	7 (193)
calcium channel blocker	13 (76)	11 (297)
thiazide diuretic	25 (151)	15 (403)
potassium-sparing diuretic	15 (87)	6 (161)
loop diuretic	7 (43)	3 (76)
ACE inhibitor	13 (77)	8 (217)
aspirin	33 (196)	30 (792)
SBP (mmHg)	138.0 ± 22.2	136.0 ± 20.8
Weight (lb)	159.0 ± 33.4	159.0 ± 32.2
Laboratory values		
creatinine (mg/dl)	1.3 ± 0.55	0.9 ± 0.18
cystatin C (mg/L)	1.4 ± 0.44	1.0 ± 0.18
eGFR (ml/min per 1.73 m^2)	51.1 ± 8.76	83.6 ± 16.4
potassium (mEq/L)	4.2 ± 0.45	4.1 ± 0.38
albumin (g/dl)	3.9 ± 0.27	3.9 ± 0.27
hemoglobin (g/dl)	13.3 ± 1.42	13.8 ± 1.4
total cholesterol (mg/dl)	214.0 ± 39.0	209.0 ± 37.1
HDL cholesterol (mg/dl)	52.9 ± 14.4	54.9 ± 14.6

[a]Data are % (n) or means ± SD. ACE, angiotensin-converting enzyme; eGFR, estimated GFR; SBP, systolic BP.

[0.4%], and tricyclic antidepressants [1.7%]), and their use was similar across eGFR categories. Among participants who had CKD, the median eGFR was 53 ml/min per 1.73 m^2 (interquartile range 47 to 58 ml/min per 1.73 m^2).

CKD and ECG Findings

ECG findings of atrial conduction delay, prolonged ventricular depolarization, and prolonged ventricular repolarization were relatively common among CHS participants, with and without CKD (Table 2). Left bundle branch block was a relatively uncommon finding. Unadjusted PR and QTI intervals were significantly longer among participants with CKD, compared with the remainder of the study cohort (Table 2). However, differences in ECG markers across CKD status were surprisingly modest and were explained by differences in demographics, traditional CV risk factors, and CV medication use (Table 3). Incremental adjustment for these characteristics progressively attenuated the unadjusted associations. To explore whether the lack of association of eGFR with resting ECG findings might be due to imprecision of eGFR as a marker of kidney function among older adults, we explored cystatin C as an alternative marker of kidney function (Table 3). Higher serum cystatin C levels were associated with significantly higher unadjusted PR, QRS, and corrected QT intervals. However, adjustment for demographics, CV risk factors, and medication use also extinguished statistical associations of cystatin C with ECG findings (Table 3).

CKD, ECG Findings, and Incident CV Events

Median follow-up was 9.2 yr among patients who had CKD and 9.4 yr for the remainder of the cohort. Among participants with CKD, there were 127 and 169 incident cases of HF and CHD, respectively. Attributable risks for CV events that were associated with resting ECG markers were notably greater for participants with CKD (Table 4). For example, there 51.5 additional cases of CHD per 1000 person-years attributable to the highest *versus* the lowest QRS category among participants with CKD, compared with 12.4 additional cases among those without CKD. QRS intervals of ≤100, 101 to 120, and >120 ms were associated with absolute 5-yr mortality rates of 18, 26, and 40%, respectively among participants with CKD.

After adjustment, longer QRS and corrected QT intervals remained significantly associated with greater relative hazards for incident HF, CHD, and mortality among both participants with and without CKD (Table 4). Among individuals with CKD, each 10-ms increase in the QRS interval was associated with a 15% (95% confidence interval [CI] 1.04 to 1.27) greater adjusted hazard for incident HF, a 13% (95% CI 1.04 to 1.24) greater adjusted hazard for incident CHD, and a 17% (95% CI 1.09 to 1.25) greater adjusted hazard for mortality. Among participants with CKD, each 5% increase in the QTI was associated with a 42% (95% CI 1.23 to 1.65), 22% (95% 1.07 to 1.40), and 10% (95% CI 0.98 to 1.22) greater adjusted hazard for HF, CHD, and mortality, respectively. In contrast, longer PR intervals did not independently predict incident CV events or mortality. Associations of Bazett's QTc with CV events and mortality were somewhat weaker than those observed for the QTI. A prolonged Bazett's QTc (440 for men and 450 for women) was associated with adjusted hazards for HF, CHD, and mortality of 1.32 (95% CI 0.85 to 2.07), 1.19 (95% CI 0.80 to 1.77), and 1.11 (95% CI 0.81 to 1.54), respectively, among participants with CKD.

The strength of associations of ECG markers with incident CV events and mortality tended to be stronger for CKD participants compared with the remainder of the study cohort (Table 4). However, these differences were not significant (Table 4), except for a stronger association of QRS intervals with mortality among participants with CKD ($P = 0.01$ value for interaction). We also explored whether the strength of associations of ECG markers with incident CV events differed according to cystatin C levels, measured continuously, or according to an eGFR <45 ml/min per 1.73 m^2 compared with ≥45 ml/min per 1.73 m^2. Neither of these interactions was found to be statistically significant.

Table 2. Electrocardiographic characteristics according to eGFR[a]

Characteristic	eGFR (ml/min per 1.73 m^2)		*P*
	<60 (n = 600)	≥60 (n = 2638)	
PR interval (ms)	174.4 ± 32.7	169.9 ± 28.6	<0.01
PR >200 ms	18.5 (111)	14.1 (371)	0.01
QRS interval (ms)	92.4 ± 17.0	91.8 ± 16.4	0.43
QRS >100 ms	18.5 (111)	18.2 (479)	0.86
QRS >120 ms	8.3 (50)	6.2 (164)	0.06
Left bundle branch block	2.2 (13)	1.5 (39)	0.22
Right bundle branch block	6.0 (36)	5.0 (132)	0.32
Corrected QT interval (ms)[b]	428.7 ± 21.8	427.4 ± 21.1	0.19
Corrected QT > 450[b]	16.9 (91)	13.9 (341)	0.06
QTI	105.0 ± 5.6	104.0 ± 5.4	0.05
Heart rate (beats per minute)	66.0 ± 10.3	66.1 ± 10.7	0.83

[a]Data are % (n) or means ± SD.
[b]Excludes 250 participants with QRS interval >120 ms or bundle branch block.

Table 3. Mean differences in ECG markers associated with unit differences in estimated kidney function[a]

Parameter	Mean Difference in ECG Marker (95% CI)			*P* (Model 2)
	Unadjusted	Model 1	Model 2	
PR interval				
eGFR <60[b]	4.5 (1.88 to 7.11)	2.7 (0.1 to 5.3)	1.6 (−1.1 to 4.2)	0.24
cystatin C[c]	9.2 (5.74 to 12.73)	4.1 (0.5 to 7.8)	1.8 (−2.0 to 5.6)	0.36
QRS interval				
eGFR <60	0.7 (−0.77 to 2.18)	0.6 (−0.9 to 2.0)	0.0 (−1.5 to 1.5)	0.98
cystatin C	4.1 (2.13 to 6.08)	1.6 (−0.5 to 3.6)	0.4 (−1.8 to 2.5)	0.74
QTc interval				
eGFR <60	1.3 (−0.69 to 3.31)	0.8 (−1.1 to 2.6)	1.4 (−0.5 to 3.3)	0.16
cystatin C	3.3 (0.59 to 5.93)	1.5 (−1.2 to 4.1)	2.6 (−0.2 to 5.3)	0.07
QTI				
eGFR <60	0.5 (0.02 to 0.99)	0.3 (−0.2 to 0.8)	0.3 (−0.2 to 0.8)	0.26
cystatin C	0.9 (0.30 to 1.60)	0.5 (−0.2 to 1.2)	0.5 (−0.3 to 1.2)	0.21

[a]Model 1 was adjusted for age, race, gender, height, weight, heart rate, SBP, diabetes/impaired glucose tolerance, HDL and total cholesterol, smoking, and alcohol use. Model 2 adds cardiovascular medications (calcium channel blockers, β blockers, digoxin, diuretics, ACE inhibitors, aspirin) and serum potassium, albumin, and hemoglobin levels. Mean difference values were measured in milliseconds. CI, confidence interval; ECG, electrocardiogram.

[b]eGFR analyzed as $<$ *versus* $\geq$60 ml/min per 1.73 m^2.

[c]Cystatin C levels analyzed continuously in mg/L.

Discussion

In this population-based study, early-stage CKD was associated with only modest differences in ECG measurements of atrial conduction, ventricular depolarization, and ventricular repolarization. These differences were explained by CV risk factors and CV medication use. Longer QRS and corrected QT intervals but not longer PR intervals were independently associated with incident HF, CHD, and mortality among individuals with CKD, demonstrating these ECG markers to be useful markers of subclinical CV disease in the CKD setting. The strength of association between ECG markers and CV events seemed qualitatively stronger for participants with CKD compared with the remainder of the study cohort; however, these differences were not statistically significant. Strengths of this study include the use of a population-based cohort without known CV disease; the use of uniform and precise measurements of ECG markers, CV risk factors, and CV medication use; and the inclusion of formally adjudicated CV outcomes.

Previous reports have documented prolonged QT intervals among patients who have ESRD (5–8). In contrast, a recent evaluation of nearly 200 nondialysis patients with earlier stages of CKD reported minimal association of kidney function with QT interval duration (8). We found no association of CKD with QRS interval duration and weak unadjusted associations of CKD with PR and corrected QT intervals that were explained by differences in measured covariates. Misclassification of kidney function by serologic markers, misclassification of the cardiac electrical cycle by resting ECG, or true lack of association of early-stage CKD with cardiac electrical disturbances may explain this negative finding. Our results did not change appreciably when cystatin C levels were substituted for eGFR, suggesting that misclassification of kidney function is less likely to explain the observed lack of association. Misclassification of ventricular repolarization by resting ECG remains an important consideration, because of variable electrocardiographic projection of repolarization into the body surface, morphologic T wave variation, and the coexistence of U waves (26).

Our findings demonstrate the prognostic relevance of resting ECG markers for predicting incident CV events and mortality in the setting of CKD. Rates of incident HF, CHD, and mortality were two- to three-fold higher comparing the lowest with highest categories of QRS and corrected QTI among participants with CKD. Associations of QRS and corrected QT intervals with CV events were independent of clinically apparent heart disease and an array of established CV risk factors and laboratory findings. Longer QRS and QT intervals may reflect a combination of increased left ventricular mass, arising from longstanding hypertension, impaired left ventricular function, nonviable myocardium, and calcification of the cardiac conduction system (27,28). Associations of resting ECG markers with CV outcomes have been previously observed among nonrenal populations who have known or suspected heart disease (9–12,29,30). Longer QRS intervals predict CV morbidity and mortality among patients who have established congestive heart failure (11,30) and among patients who are referred for cardiac exercise testing (10). In contrast, associations of longer QRS intervals with incident CHD have not been observed among younger, healthier populations (31). Ventricular repolarization abnormalities are linked to the risk of Torsades De Pointes and arrhythmia and have been associated with an increased risk for death within a number of general population cohort studies (9,12,29).

Table 4. Associations of ECG markers with cardiovascular events according to estimated kidney function[a]

Parameter	eGFR < 60 ml/min per 1.73 m²			eGFR ≥ 60 ml/min per 1.73 m²		
	Rate (Events)	5-Yr Incidence (95% CI)	Adjusted HR (95% CI)[b]	Rate (Events)	5-Yr Incidence (95% CI)	Adjusted HR (95% CI)[b]
Incident HF						
PR ≤ 200 ms	27.3 (95)	0.11 (0.08 to 0.14)	Reference	18.4 (335)	0.07 (0.06 to 0.08)	Reference
PR > 200 ms	44.2 (32)	0.22 (0.14 to 0.30)	0.96 (0.63 to 1.46)	20.9 (62)	0.08 (0.05 to 0.10)	0.89(0.67 to 1.18)
P value for interaction[c]						0.62
QRS ≤ 100 ms	28.0 (99)	0.12 (0.09 to 0.15)	Reference	15.8 (280)	0.06 (0.05 to 0.06)	Reference
100 < QRS ≤ 120 ms	36.9 (14)	0.22 (0.10 to 0.32)	1.10 (0.61 to 1.97)	31.7 (75)	0.12 (0.08t to 0.16)	1.70 (1.30 to 2.23)
QRS > 120 ms	50.1 (14)	0.17 (0.04 to 0.28)	1.88 (1.06 to 3.33)	37.1 (42)	0.13 (0.07 to 0.18)	2.01 (1.44 to 2.80)
P value for interaction						0.88
QTi ≤ 98%	16.3 (6)	0.04 (0.00 to 0.10)	Reference	19.0 (39)	0.07 (0.03 to 0.10)	Reference
98 < QTi ≤ 102%	21.7 (26)	0.10 (0.05 to 0.15)	1.41 (0.57 to 3.46)	15.3 (92)	0.05 (0.03 to 0.07)	0.86 (0.59 to 1.26)
102 < QTi ≤ 107%	30.3 (44)	0.14 (0.09 to 0.18)	2.68 (1.13 to 6.36)	16.1 (133)	0.06 (0.04 to 0.07)	0.93 (0.65 to 1.34)
107 < QTi ≤ 112%	32.1 (25)	0.16 (0.08 to 0.22)	2.61 (1.05 to 6.48)	23.2 (77)	0.08 (0.05 to 0.10)	1.27 (0.85 to 1.89)
QTi > 112%	65.0 (26)	0.24 (0.12 to 0.34)	4.95 (1.99 to 12.34)	36.2 (56)	0.15 (0.10 to 0.20)	1.66 (1.08 to 2.53)
P value for interaction						0.11
Incident CHD						
PR ≤ 200 ms	39.7 (134)	0.16 (0.13 to 0.20)	Reference	25.7 (452)	0.12 (0.10 to 0.13)	Reference
PR > 200 ms	49.0 (35)	0.18 (0.10 to 0.25)	0.78 (0.53 to 1.16)	30.0 (84)	0.13 (0.10 to 0.16)	1.01 (0.79 to 1.29)
P value for interaction						0.32
QRS ≤ 100 ms	37.6 (130)	0.15 (0.12 to 0.19)	Reference	24.1 (409)	0.06 (0.05 to 0.06)	Reference
100 < QRS ≤ 120 ms	44.1 (17)	0.16 (0.06 to 0.24)	0.91 (0.54 to 1.55)	38.1 (87)	0.12 (0.08 to 0.16)	1.35 (1.06 to 1.72)
QRS > 120 ms	89.1 (22)	0.29 (0.14 to 0.41)	2.66 (1.67 to 4.24)	36.5 (40)	0.13 (0.07 to 0.18)	1.25 (0.89 to 1.74)
P value for interaction						0.26
QTi ≤ 98%	36.1 (13)	0.09 (0.00 to 0.17)	Reference	22.2 (44)	0.07 (0.03 to 0.10)	Reference
98 < QTi ≤ 102%	37.4 (43)	0.16 (0.10 to 0.21)	1.16 (0.60 to 2.22)	25.9 (148)	0.05 (0.03 to 0.07)	1.24 (0.89 to 1.75)
102 < QTi ≤ 107%	36.5 (52)	0.16 (0.10 to 0.21)	1.28 (0.68 to 2.42)	25.8 (205)	0.06 (0.04 to 0.07)	1.24 (0.89 to 1.73)
107 < QTi ≤ 112%	41.3 (31)	0.18 (0.10 to 0.25)	1.38 (0.70 to 2.74)	25.3 (82)	0.08 (0.05 to 0.10)	1.19 (0.82 to 1.72)
QTi > 112%	74.2 (30)	0.24 (0.13 to 0.34)	2.30 (1.15 to 4.60)	37.8 (57)	0.15 (0.10 to 0.20)	1.55 (1.03 to 2.32)
P value for interaction						0.13
All-cause death						
PR ≤ 200 ms	60.1 (224)	0.20 (0.16 to 0.24)	Reference	35.0 (669)	0.12 (0.11 to 0.13)	Reference
PR > 200 ms	76.6 (61)	0.23 (0.15 to 0.31)	0.81 (0.60 to 1.09)	34.1 (107)	0.10 (0.07 to 0.13)	0.87 (0.70 to 1.08)
P value for interaction						0.84
QRS ≤ 100 ms	56.2 (213)	0.18 (0.15 to 0.21)	Reference	32.4 (597)	0.11 (0.09 to 0.12)	Reference
100 < QRS ≤ 120 ms	92.9 (39)	0.26 (0.14 to 0.36)	1.71 (1.20 to 2.43)	44.3 (114)	0.13 (0.09 to 0.17)	1.32 (1.07 to 1.63)
QRS > 120 ms	105.7 (33)	0.40 (0.25 to 0.52)	2.61 (1.79 to 3.81)	51.7 (65)	0.23 (0.16 to 0.29)	1.39 (1.07 to 1.82)
P value for interaction						0.01
QTi ≤ 98%	63.6 (24)	0.17 (0.05 to 0.27)	Reference	35.0 (75)	0.14 (0.10 to 0.18)	Reference
98 < QTi ≤ 102%	63.0 (80)	0.19 (0.13 to 0.25)	0.94 (0.58 to 1.51)	31.8 (199)	0.11 (0.09 to 0.13)	1.05 (0.80 to 1.37)
102 < QTi ≤ 107%	62.4 (98)	0.23 (0.17 to 0.29)	1.25 (0.79 to 1.99)	33.0 (284)	0.11 (0.09 to 0.13)	1.07 (0.82 to 1.39)
107 < QTi ≤ 112%	53.5 (45)	0.16 (0.09 to 0.23)	1.07 (0.64 to 1.80)	38.9 (137)	0.13 (0.10 to 0.16)	1.27 (0.95 to 1.70)
QTi > 112%	82.2 (38)	0.27 (0.16 to 0.37)	1.53 (0.89 to 2.62)	47.1 (81)	0.14 (0.09 to 0.19)	1.31 (0.95 to 1.83)
P value for interaction						0.96

CHD, coronary heart disease; HF, heart failure.

[b]Adjustment variables are age; race; gender; smoking and alcohol status; prevalent diabetes; SBP; height; weight; heart rate; use of digoxin, β blockers, calcium channel blockers, diuretics, aspirin, and ACE inhibitors; and serum levels of albumin, hemoglobin, potassium, total cholesterol, and HDL cholesterol.

[c]*P* values for interaction test whether association of each continuous ECG marker with incident events differs according to an eGFR <60 *versus* ≥60 ml/min per 1.73 m².

There were no statistical differences in the magnitude of association between ECG markers and CV events, comparing patients who had CKD with the remainder of the cohort. The absence of statistical significance may have been due to inadequate study power, given the relatively small number of participants who had CKD. Despite not finding statistically significant effect modification, the consistent finding of stronger associations for participants with CKD across every CV outcome suggests that ECG conduction abnormalities could have greater prognostic importance in the setting of CKD. Furthermore, the greater overall risk for CV disease among participants with CKD resulted in substantially higher absolute risks for CV events that were attributable to prolonged QRS and QT intervals.

This study has some important limitations. There was no gold standard for measuring kidney function. Instead, kidney function was estimated using eGFR and cystatin C. Among populations with established kidney disease, creatinine, age,

race, and gender have been reported to explain approximately 85% of the variation in radioisotope-measured GFR (15,32). However, performance of creatinine-based estimates of GFR is significantly diminished among populations with normal kidney function and those with a high proportion of older people (15,32). Markers of kidney function were measured on a single occasion, potentially with some patients having acute changes in GFR. However, study measurements were performed in the outpatient setting, without a clinical indication; therefore, the prevalence of acute renal failure is likely to be low. The majority of study participants who had renal impairment had stage 3 CKD (96.8% with eGFR 30 to 60 ml/min per 1.73 m^2), precluding study of more advanced kidney disease in which associations of ECG markers and incident CV events may differ. This study population consisted exclusively of older adults; therefore, results may not apply to younger people who have CKD. Finally, our analyses focused on ECG markers of rhythm disturbances, whereas markers of ischemia, such as Q waves and ST-T segment changes, were not examined.

Conclusion

Longer QRS and corrected QT intervals were independently associated with incident HF, CHD, and mortality among participants with early CKD and without CKD. ECG findings may provide important prognostic information regarding long-term CV risk in the setting of CKD.

Acknowledgments

The research reported in this article was supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, and U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurologic Disorders and Stroke and National Institutes of Health Career Development Award K23 DK63274-01.

A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org.

Disclosures

None.

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