Electrocardiographic Measures and Prediction of Cardiovascular and Noncardiovascular Death in CKD

Rajat Deo,* Haochang Shou,† Elsayed Z. Soliman,‡ Wei Yang,† Joshua M. Arkin,* Xiaoming Zhang,† Raymond R. Townsend,§ Alan S. Go,‖¶** Michael G. Shlipak,**†† and Harold I. Feldman†§

*Cardiac Electrophysiology Section, Division of Cardiovascular Medicine, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; †Center for Clinical Epidemiology and Biostatistics and the Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; ‡Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology and Prevention, and Department of Internal Medicine, Cardiology Section, Wake Forest University School of Medicine, Winston Salem, North Carolina; §Renal Electrolyte and Hypertension Division, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; ‖Division of Research, Kaiser Permanent Northern California, Oakland, California; ¶Department of Health Research and Policy, Stanford University, Palo Alto, California; **Department of Epidemiology, Biostatistics, and Medicine, University of California San Francisco, San Francisco, California; and ††Department of General Internal Medicine, San Francisco VA Medical Center, San Francisco, California

ABSTRACT

Limited studies have assessed the resting 12-lead electrocardiogram (ECG) as a screening test in intermediate risk populations. We evaluated whether a panel of common ECG parameters are independent predictors of mortality risk in a prospective cohort of participants with CKD. The Chronic Renal Insufficiency Cohort (CRIC) study enrolled 3939 participants with eGFR<70 ml/min per 1.73 m^2 from June 2003 to September 2008. Over a median follow-up of 7.5 years, 750 participants died. After adjudicating the initial 497 deaths, we identified 256 cardiovascular and 241 noncardiovascular deaths. ECG metrics were independent risk markers for cardiovascular death (hazard ratio, 95% confidence interval): PR interval ≥200 ms (1.62, 1.19–2.19); QRS interval 100–119 ms (1.64, 1.20–2.25) and ≥120 ms (1.75, 1.17–2.62); corrected QT (QTc) interval ≥450 ms in men or ≥460 ms in women (1.72, 1.19–2.49); and heart rate 60–90 beats per minute (1.21, 0.89–1.63) and ≥90 beats per minute (2.35, 1.03–5.33). Most ECG measures were stronger markers of risk for cardiovascular death than for all-cause mortality or noncardiovascular death. Adding these intervals to a comprehensive model of cardiorenal risk factors increased the C-statistic for cardiovascular death from 0.77 to 0.81 ($P<0.001$). Furthermore, adding ECG metrics to the model adjusted for standard risk factors resulted in a net reclassification of 12.1% (95% confidence interval 8.1%–16.0%). These data suggest common ECG metrics are independent risk factors for cardiovascular death and enhance the ability to predict death events in a population with CKD.

J Am Soc Nephrol 27: 559–569, 2016. doi: 10.1681/ASN.2014101045

The use of a resting 12-lead electrocardiogram (ECG) as a screening test in intermediate risk populations such as those with CKD remains controversial. Although the US Preventive Services Task Force does not recommend routine ECG screening for the purposes of cardiovascular risk stratification in asymptomatic adults at low risk for coronary heart disease events,[1,2] inadequate data exist on utilizing ECGs in intermediate risk populations. CKD comprises greater than 10% of the world's population[3] and is a known risk factor for cardiovascular events and death.[4] ECGs are not routinely obtained in most general internal

Received October 27, 2014. Accepted May 1, 2015.

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

Correspondence: Dr. Rajat Deo, 3400 Spruce Street, 9 Founders Cardiology, Philadelphia, PA 19146. Email: Rajat.Deo@uphs.upenn.edu

medicine or nephrology practices where most CKD patients are being managed in the United States.

The ECG, which provides a comprehensive overview of cardiac rhythms and conduction, is obtained routinely in nearly all inpatients and in the preoperative setting. Most ECGs obtained in clinical practice are produced from digital signaling. In addition, ECG interpretation software is built into many modern ECG systems and contains algorithms to assess reliably the cardiac rhythm and measure the heart rate and PR, QRS, and QT intervals.[5] These metrics provide important insight into autonomic function, atrioventricular conduction, ventricular depolarization, and repolarization. In community-based elderly participants with early CKD, ECG measures were independently associated with all-cause mortality.[6,7] The mean age in these studies was 75 years, the mean eGFR was 50–60 ml/min per 1.73m^2 and greater than 80% of the study population was white thus limiting the generalizability of these findings to a larger CKD population, especially those with moderate to advanced CKD. In contrast, among participants with end stage renal disease on hemodialysis from the German Diabetes and Dialysis (4D) Study, common ECG measures including the QRS duration, QT interval and heart rate were not independently associated with clinical events.[8] Given its ubiquitous availability and the potential for further risk stratifying kidney disease patients, a more detailed understanding of the utility of ECG testing in a diverse CKD population is necessary. Further, limited studies have assessed rigorously the utility of ECG metrics in improving risk stratification of individuals with CKD above and beyond the assessment of cardiorenal risk factors. To address this knowledge gap, we evaluated a panel of five commonly available ECG parameters including measures of standard intervals and left ventricular hypertrophy (LVH). We assessed each as a potential independent risk factor for and predictor of all-cause mortality, cardiovascular death, noncardiovascular death, and incident cardiovascular disease in a diverse cohort of individuals with CKD.

RESULTS

Among 3587 participants included in this analysis, the mean (SD) age was 58 ($\pm$11) years, 45% were women, and 41% were black. Approximately one-third of participants had a baseline history of cardiovascular disease. In addition, the prevalence of abnormal ECG metrics in the The Chronic Renal Insufficiency Cohort (CRIC) study included the following: 542 (15%) had a PR$\geq$200 ms, 1065 (30%) had a QRS$\geq$100 ms, 295 (8%) participants had a $QT_c \geq$450 ms in men or 460 ms in women, and 315 (9%) had LVH (Table 1, Supplemental Table 1). In addition, the distribution of heart rates included 1196 (33%) individuals with a rate $<$60 beats per minute (bpm), 2285 (64%) with a rate between 60 and 90 bpm, and 105 (3%) with a rate $\geq$90 bpm. In general, participants with longer PR, QRS, and QT_c intervals were more likely than those with shorter intervals to be older, have more prevalent cardiovascular disease, diabetes, hypertension, and a lower eGFR at entry. Participants with higher heart rates were younger, had more diabetes, a lower eGFR, and more proteinuria than those with lower heart rates, but there were no significant differences in the prevalence of cardiovascular disease and hypertension. Finally, we noted that higher left ventricular mass index and lower left ventricular ejection fraction were associated with longer PR, QRS, and QT_c intervals. Abnormalities in these echocardiographic measures were also associated with the presence of ECG-based LVH. Higher heart rate was associated with lower left ventricular ejection fraction, but not with left ventricular mass index.

During a median follow-up of 7.5 (interquartile range, 6.2–8.6) years, there were 750 deaths in this cohort with an annual mortality rate of 3.0% per year. We adjudicated the initial 497 deaths and identified 256 cardiovascular (1.1% per year) and 241 noncardiovascular deaths (1.0% per year). Finally, in the subgroup of 2492 CRIC participants without any baseline history of heart failure, coronary heart disease, or stroke, we identified 242 cases of incident heart failure (incident rate 1.5% per year) and 136 cases of incident myocardial infarction (MI) (incident rate 0.8% per year).

An abnormality in any of the five ECG metrics was associated with either death or cardiovascular death in unadjusted analysis (Figure 1A and B). Only QT_c and heart rate were associated with noncardiovascular death in the unadjusted models (Figure 1C). After multivariable adjustment, the PR interval was an independent risk marker for cardiovascular death in both the categorical and linear analyses (Table 2). In addition, both the QRS and QT_c intervals were associated with death and cardiovascular death after multivariable adjustment. Abnormalities in QRS and QT_c appeared to be stronger risk factors for cardiovascular death than all-cause mortality. In particular, compared with participants with a normal QRS ($<$100 ms) or QT_c ($<$450 ms men or $<$460 ms women) interval, those with a wide QRS interval or prolonged QT_c had an adjusted 65–80% higher incidence of cardiovascular death. An increase in heart rate was independently associated with all three mortality outcomes. It was also the only ECG measure that was an independent marker for noncardiovascular death. Electrocardiographic-based LVH and the associated Cornell voltage (reflecting the severity of LVH) were not associated with any of these outcomes.

Among the subgroup of 2492 CRIC participants without any baseline history of heart failure, coronary heart disease, or stroke, we detected modest associations between the ECG intervals and incident heart failure and MI (Table 3). Compared with participants with a QRS duration $<$100 ms, individuals with a QRS, 100–119 ms had an approximate 60% increase in both incident heart failure and MI after multivariable analysis. The risk was 116% higher among those with a QRS$\geq$120 ms. A long QTc was associated with incident heart failure only. The PR interval, heart rate, and ECG-LVH were not associated with any of the incident cardiovascular disease outcomes.

Table 1. Baseline characteristics across the QRS and corrected QT intervals

	QRS interval		Corrected QT interval (QT_c)		
Range (ms)	<100 ms	100–119 ms	≥120 ms	<450 M/460 W ms	≥450 M/460 W ms
Number of participants	2522	766	299	3292	295
Demographics					
Age (years)±SD	57±11	59±10	64±8	58±11	60±10
Female, n (%)	1304 (52)	225 (29)	94 (31)	1500 (46)	123 (42)
Race, n (%)					
White	1045 (41)	320 (42)	125 (42)	1402 (43)	88 (30)
Black	1037 (41)	319 (42)	126 (42)	1320 (40)	162 (55)
Hispanic	332 (13)	97 (13)	41 (14)	437 (13)	33 (11)
Prevalent cardiovascular disease					
Coronary artery disease, n (%)	434 (17)	205 (27)	130 (44)	666 (20)	103 (35)
Heart failure, n (%)	154 (6)	85 (11)	88 (29)	253 (8)	74 (25)
Peripheral vascular disease, n (%)	146 (6)	57 (7)	32 (11)	205 (6)	30 (10)
Stroke, n (%)	220 (9)	93 (12)	41 (14)	312 (10)	42 (14)
Cardiovascular disease risk factors					
Systolic BP (mmHg)±SD	128±22	131±22	131±24	128±22	138±27
Diastolic BP (mmHg)±SD	72±13	72±14	69±13	71±13	73±16
Hypertension, n (%)	2116 (84)	697 (91)	271 (91)	2815 (86)	269 (91)
Diabetes, n (%)	1190 (47)	359 (47)	181 (61)	1548 (47)	182 (62)
Body mass index (kg/m^2)±SD	31.7±8.0	32.5±7.2	33.0±7.1	31.8±7.7	34.0±7.8
Smoking status, n (%)					
Current	335 (13)	96 (13)	36 (12)	419 (13)	48 (16)
Past	996 (40)	341 (45)	153 (51)	1367 (42)	123 (42)
Never	1191 (47)	329 (43)	110 (37)	1506 (46)	124 (42)
Total cholesterol (mg/dl)±SD	187±46	180±44	172±42	185±46	175±43
HDL (mg/dl)±SD	49±16	45±14	44±14	48±16	45±14
LDL (mg/dl)±SD	105±36	101±35	95±34	104±36	98±35
Triglycerides (mg/dl)±SD	157±115	164±132	155±115	158±117	158±139
Echocardiographic variables					
Left ventricular mass index (g/m$^{2.7}$)±SD	102±23	116±28	125±30	105±24	129±34
Left ventricular ejection fraction (%)±SD	55±7	53±9	48±13	55±8	49±13
Left ventricular ejection fraction categories					
<35%, n (%)	31 (2)	33 (5)	46 (19)	74 (3)	36 (16)
35–50%, n (%)	310 (15)	134 (21)	59 (24)	440 (16)	63 (28)
>50%, n (%)	1770 (84)	467 (74)	139 (57)	2248 (81)	128 (56)
Kidney function					
eGFR (ml/min per 1.73m^2)±SD	46±17	45±16	39±14	46±17	39±16
eGFR categories (ml/min per 1.73m^2)					
<15, n (%)	8 (0.3)	3 (0.4)	0 (0)	8 (0.2)	3 (1)
15–30, n (%)	473 (19)	160 (21)	90 (30)	623 (19)	100 (34)
30–60, n (%)	1544 (61)	474 (62)	184 (62)	2038 (62)	164 (56)
60–90, n (%)	453 (18)	123 (16)	25 (8)	575 (18)	26 (9)
≥90, n (%)	44 (2)	6 (1)	0 (0)	48 (2)	2 (1)
Cystatin C (mg/l)±SD.	1.48±0.54	1.53±0.55	1.72±0.56	1.49±0.53	1.75±0.62
Proteinuria (mg/24 hours),					
Median [IQR]	170 [70–920]	220 [80–960]	210 [80–840]	170 [70–890]	300 [90–1290]
Serum measures					
Serum calcium (mg/dl)±SD	9.2±0.5	9.2±0.5	9.1±0.5	9.2±0.5	9.0±0.6
Serum phosphate (mg/dl)±SD	3.7±0.7	3.7±0.7	3.8±0.7	3.7±0.7	3.9±0.7
Serum potassium (mmol/l)±SD	4.4±0.5	4.3±0.5	4.3±0.6	4.4±0.5	4.2±0.6
Serum albumin (g/dl)±SD	3.9±0.5	3.9±0.5	3.9±0.4	4.0±0.5	3.8±0.5
Hemoglobin (g/dl)±SD	12.6±1.8	12.7±1.8	12.4±1.7	12.7±1.8	12.1±1.8
Medications, n (%)					
Aspirin	1013 (40)	361 (48)	175 (59)	1403 (43)	146 (50)
Beta blockers	1137 (45)	422 (56)	191 (65)	1565 (48)	185 (63)
Calcium channel blockers	945 (38)	367 (48)	124 (42)	1301 (40)	135 (46)
Statins	1323 (53)	449 (59)	192 (65)	1800 (55)	164 (56)

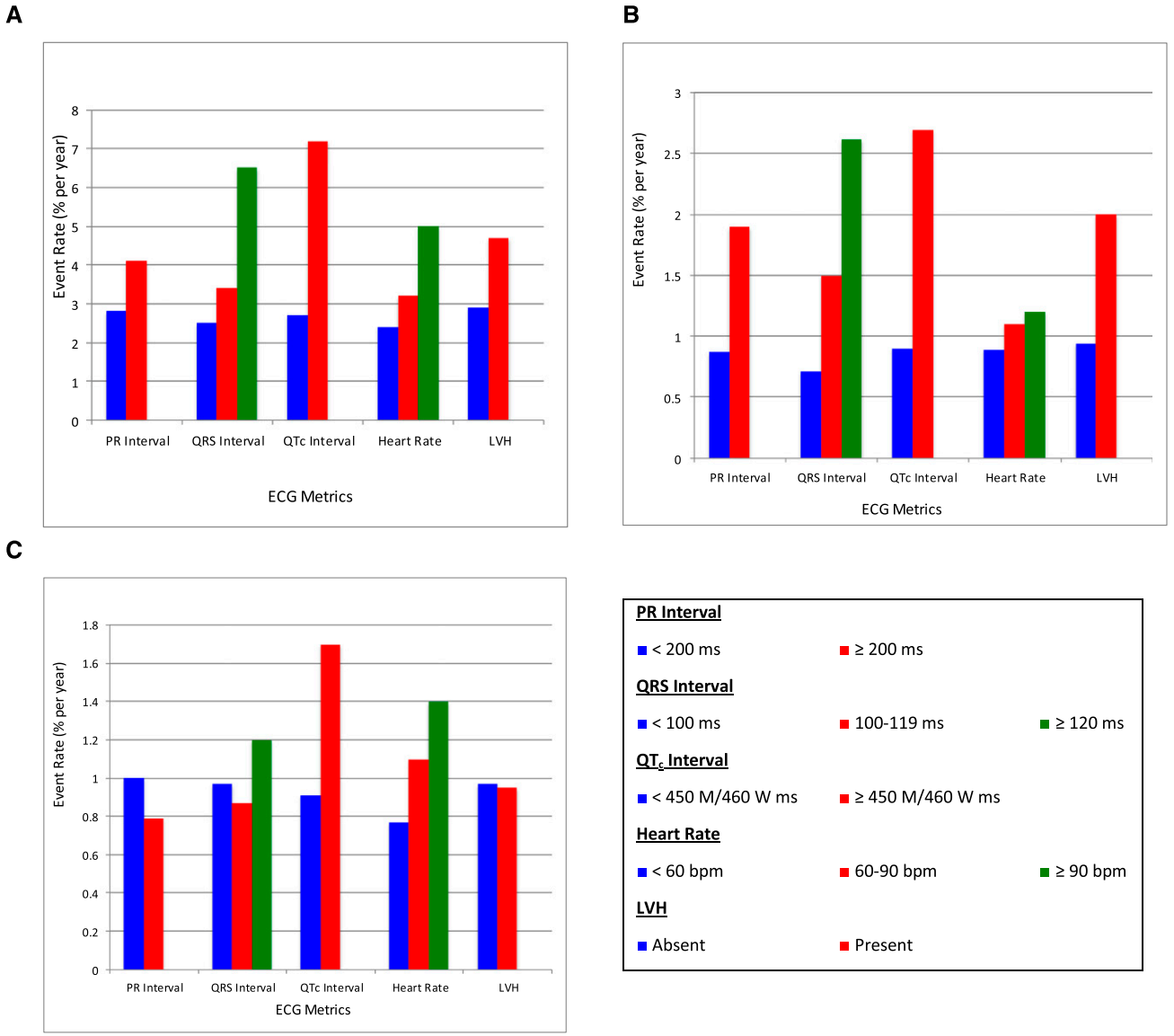

Figure 1. Mortality rates across ECG intervals. ECG measures and (A) rates of all-cause mortality; (B) rates of cardiovascular death; (C) rates of noncardiovascular death.

Additional evaluation of the corrected QT interval and left ventricular voltage in the subgroup of participants with a QRS<120 ms yielded similar findings to the primary analysis. An increased QT_c was associated with higher risk for all three mortality outcomes after adjustment for age, sex, race, clinical site, history of cardiovascular disease, systolic and diastolic blood pressure, total cholesterol, HDL, body mass index (BMI), smoking, diabetes, eGFR, proteinuria, serum calcium, serum phosphate, serum potassium, and medication use (per 10 ms increase in the QT_c, hazard ratio [HR], 1.09; 95% confidence interval [95% CI], 1.05–1.13 for all-cause mortality; HR, 1.14; 95% CI, 1.07–1.22 for cardiovascular death; HR, 1.08; 95% CI, 1.01–1.16 for noncardiovascular death). An increase in left ventricular voltage was now an independent risk factor for mortality (per 1 mm increase in voltage, HR, 1.02; 95% CI, 1.00–1.03 for all-cause mortality; HR, 1.03; 95% CI, 1.00–1.05 for cardiovascular death; HR, 1.01; 95% CI, 0.99–1.04 for noncardiovascular death).

Subgroup Analyses and Interaction Testing for Cardiovascular Death

In the additional analyses that included echocardiographic measures of left ventricular mass index and left ventricular ejection fraction, we noted that PR, QRS, and heart rate remained significant risk markers for cardiovascular death (Supplemental Table 2). In addition, the corrected QT interval was no longer associated with cardiovascular death after the addition of these two echocardiographic measures.

After assessing potential effect modification between each ECG interval and either sex or race, we detected significant

Table 2. Association of ECG metrics with all-cause mortality, cardiovascular mortality and noncardiovascular mortality

	All-cause mortality	Cardiovascular mortality	Noncardiovascular mortality
PR interval			
PR<200 ms; HR (95% CI)	1.00 (ref)	1.00 (ref)	1.00 (ref)
PR≥200 ms;[a] HR (95% CI)	1.15 (0.95–1.40)	1.62 (1.19–2.19)	0.61 (0.40–0.93)
Per 10 ms increase;[a] HR (95% CI)	1.01 (0.99–1.03)	1.05 (1.01–1.09)	0.95 (0.90–1.00)
QRS interval			
QRS<100 ms; HR (95% CI)	1.00 (ref)	1.00 (ref)	1.00 (ref)
QRS 100–119 ms;[a] HR (95% CI)	1.13 (0.93–1.36)	1.64 (1.20–2.25)	0.90 (0.64–1.28)
QRS≥120 ms;[a] HR (95% CI)	1.41 (1.11–1.80)	1.75 (1.17–2.62)	0.77 (0.46–1.28)
Per 10 ms increase;[a] HR (95% CI)	1.05 (1.01–1.10)	1.08 (1.01–1.16)	0.94 (0.87–1.03)
QT_c interval			
QT_c<450 ms M/460 ms W; HR (95% CI)	1.00 (ref)	1.00 (ref)	1.00 (ref)
QT_c≥450 ms M/460 ms W;[a] HR (95% CI)	1.46 (1.16–1.84)	1.72 (1.19–2.49)	1.35 (0.85–2.16)
Per 10 ms increase;[a] HR (95% CI)	1.06 (1.02–1.09)	1.09 (1.03–1.15)	1.03 (0.97–1.10)
Heart rate			
HR<60 bpm; HR (95% CI)	1.00 (ref)	1.00 (ref)	1.00 (ref)
HR 60–90 bpm;[a] HR (95% CI)	1.28 (1.07–1.53)	1.21 (0.89–1.63)	1.52 (1.11–2.09)
HR≥90 bpm;[a] HR (95% CI)	2.44 (1.59–3.76)	2.35 (1.03–5.33)	2.35 (1.03–5.32)
Per 50 ms decrease;[a] HR (95% CI)	1.06 (1.03–1.09)	1.05 (1.00–1.10)	1.10 (1.04–1.15)
LVH			
Absent; HR (95% CI)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Present;[a] HR (95% CI)	1.15 (0.90–1.47)	1.25 (0.85–1.85)	0.94 (0.57–1.55)
Per 1 mm increase in Cornell voltage;[a] HR (95% CI)	1.01 (0.99–1.02)	1.01 (0.99–1.03)	1.01 (0.99–1.03)

LVH, left ventricular hypertrophy.
[a]The adjusted analysis included the following covariates: age, sex, race, clinical site, history of cardiovascular disease (coronary artery disease, congestive heart failure, peripheral vascular disease, and stroke), systolic blood pressure, diastolic blood pressure, total cholesterol, HDL, body mass index, current smoking status, diabetes, eGFR, log (urine total protein excretion), serum calcium, serum phosphate, serum potassium, medication use (β-blockers, calcium channel blockers, and statins). In addition, with the exception of the assessed ECG parameter, the adjusted analysis included the other four metrics.

interactions between the RR interval and sex (RR per 50 ms×sex, $P_{interaction}$=0.01; RR categorical×sex, $P_{interaction}$=0.02). A higher heart rate appeared to be a stronger risk factor for cardiovascular death among women compared with men. For each 50 ms decrease in the RR interval, women had a 14% higher incidence of cardiovascular death after multivariable analysis (HR, 1.14; 95% CI, 1.05–1.24). No significant association was observed in men (HR, 1.00; 95% CI, 0.94–1.06). Similar findings were observed in the categorical analysis. Compared with women with a heart rate <60 bpm, those with higher heart rates had significant risks for cardiovascular death (heart rate 60–90 bpm, HR, 2.27; 95% CI, 1.28–4.02; heart rate ≥90 bpm, HR, 3.60; 95% CI, 0.96–13.50). Similar to the linear analysis, no significant associations were observed between these categorical cut points and cardiovascular death among men. In addition, there were no other significant interactions between PR, QRS, QTc, and Cornell voltage and sex. Further, no significant interactions were observed between any of the five ECG metrics and race ($P_{interaction}$>0.01).

ECG Metrics and the Prediction of Cardiovascular Death

Over a 5-year period, the inclusion of the five ECG metrics enhanced the prediction of cardiovascular death. In this population of individuals with CKD, the prediction of cardiovascular death using a set of standard risk factors including age, sex, race, history of cardiovascular disease, blood pressure, total cholesterol, HDL, BMI, diabetes, smoking, eGFR, and proteinuria yielded a C-statistic of 0.77; 95% CI, 0.75–0.80 (Figure 2). After adding the five ECG metrics to this comprehensive risk factor model, the C-statistic increased to 0.81; 95% CI, 0.78–0.83. A similar improvement was observed in the different CKD subgroups including blacks, whites, men, and women. The integrated discrimination improvement was 2.7%; 95% CI, 0.8%–4.6%, P=0.001. The addition of ECG metrics to the model that adjusted for a comprehensive panel of kidney disease and cardiovascular risk factors resulted in a net reclassification of 12.1%; 95% CI, 8.1%–16.0% of the overall sample (Table 4). The upward reclassification of participants that eventually died of cardiovascular causes was greater than the downward reclassification of individuals who survived.

DISCUSSION

In this multicenter cohort of 3587 CKD participants, we demonstrated that the PR interval, QRS duration, and corrected QT interval were independent risk markers for cardiovascular death. These measures had stronger associations with cardiovascular death than they did with either all-cause mortality or noncardiovascular death. Higher heart rates were associated with a similar increase in risk across all three mortality outcomes. Only modest associations were observed between the QRS and QT intervals and incident cardiovascular disease. Our analyses included common electrocardiographic

Table 3. Association of ECG metrics with incident heart failure and myocardial infarction

	Heart failure	Myocardial infarction
PR interval		
PR<200 ms; HR (95% CI)	1.00 (ref)	1.00 (ref)
PR≥200 ms;[a] HR (95% CI)	1.11 (0.76–1.63)	0.53 (0.29–0.98)
Per 10 ms increase;[a] HR (95% CI)	1.00 (0.95–1.05)	0.93 (0.86–1.00)
QRS interval		
QRS<100 ms; HR (95% CI)	1.00 (ref)	1.00 (ref)
QRS 100–119 ms;[a] HR (95% CI)	1.60 (1.14–2.23)	1.56 (1.00–2.42)
QRS≥120 ms;[a] HR (95% CI)	1.37 (0.81–2.31)	2.16 (1.14–4.08)
Per 10 ms increase;[a] HR (95% CI)	1.00 (0.92–1.09)	1.09 (0.98–1.21)
QT_c interval		
QT_c<450 ms M/460 ms W; HR (95% CI)	1.00 (ref)	1.00 (ref)
QT_c≥450 ms M/460 ms W;[a] HR (95% CI)	1.59 (1.01–2.50)	0.81 (0.40–1.64)
Per 10 ms increase; HR (95% CI)	1.12 (1.05–1.20)	1.04 (0.96–1.14)
Heart Rate		
HR<60 bpm; HR (95% CI)	1.00 (ref)	1.00 (ref)
HR 60–90 bpm;[a] HR (95% CI)	1.11 (0.80–1.55)	1.23 (0.81–1.89)
HR≥90 bpm;[a] HR (95% CI)	2.07 (0.95–4.51)	2.65 (0.95–7.39)
Per 50 ms decrease;[a] HR (95% CI)	1.02 (0.96–1.07)	1.05 (0.98–1.13)
LVH		
Absent; HR (95% CI)	1.00 (ref)	1.00 (ref)
Present;[a] HR (95% CI)	1.20 (0.76–1.88)	1.19 (0.64–2.22)
Per 1 mm increase in Cornell voltage;[a] HR (95% CI)	1.04 (1.02–1.06)	1.02 (0.99–1.05)

LVH, left ventricular hypertrophy.
[a]The adjusted analysis included the following covariates: age, sex, race, clinical site, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL, body mass index, current smoking status, diabetes, eGFR, log (urine total protein excretion), serum calcium, serum phosphate, serum potassium, medication use (β-blockers, calcium channel blockers, and statins). In addition, with the exception of the assessed ECG parameter, the adjusted analysis included the other four metrics.

measurements that are reported automatically during ECG acquisition by most software programs and do not require additional interpretation by a physician reviewer. This combination of measures resulted in enhanced discrimination for cardiovascular mortality, with a significant increase in the C-statistic and improved reclassification that was driven by identifying higher risk participants. These findings along with the modest expense and widespread availability of electrocardiography suggest that broader use of ECGs among individuals with CKD may positively impact the care of the CKD population by permitting improved targeting of cardiovascular risk reduction strategies.

Recent reports from the US Preventive Services Task Force have highlighted the importance of evaluating a series of ECG metrics simultaneously for the purposes of screening, especially intermediate risk populations.[1,9] The 3587 CKD participants in our sample had a mortality rate of 3% per year, which is significantly higher than that observed in most population-based cohorts. The addition of common ECG metrics resulted in significant improvement in the discrimination (C-statistic) for cardiovascular death. Further, ECG metrics appeared to enhance prediction for cardiovascular death to a greater degree in blacks compared with whites. Our analysis also identifies a significant risk reclassification that was driven primarily by identifying higher risk participants. The highest risk category in the reclassification table consisted of a >5% per year cardiovascular death rate and equals the corresponding death rate observed in patients with systolic heart failure.[10–12] These findings suggest that routine ECG evaluation in the CKD population is likely to be more helpful than screening low risk populations.

One of the important questions arising from these data remains how abnormalities in common ECG measures can be utilized to alter cardiovascular mortality risk in this population. ECG abnormalities reflect the electrophysiologic health of the myocardium and may reflect a combination of dysregulation in ionic currents, metabolic changes, alterations in serum electrolytes, and secondary effects of medications. Our analyses also demonstrate strong electromechanic correlations as abnormalities in all five ECG measures were associated with left ventricular dysfunction and increased left ventricular mass. These findings help to explain the stronger associations observed between ECG measures and cardiovascular death compared with noncardiovascular death. Further, the modest associations observed with heart failure and MI suggest that alternative cardiac diseases and pathways contribute to the higher mortality risk. Individuals with CKD are known to be at higher risk for fatal arrhythmias and sudden cardiac death.[13,14] Future clinical trials should evaluate whether the additional information from an ECG can identify a subgroup that may benefit from additional cardiac work-up such as stress testing, echocardiography, or cardiac/coronary computed tomography scanning. A further understanding of the cardiac substrate through additional diagnostic tests may identify CKD patients that will benefit from aggressive cardioprotective therapies including β-blockers, mineralocorticoid receptor blockers, revascularization, and even implantable cardioverter defibrillator placement.

Our sample of 3587 CKD participants is the largest population of kidney disease individuals to undergo systematic assessment of the significance of abnormalities of common ECG measures across various subgroups. ECG measures had a similar association with cardiovascular death in the various subgroups including blacks and whites, and men and women. We were able to assess the independent effects of ECG metrics after adjusting for a series of potential confounders including a cystatin C and creatinine-based eGFR equation, 24-hour proteinuria, and serum concentrations of calcium, phosphorus, and potassium. Our study findings, especially pertaining to the enhanced prediction of cardiovascular mortality, will need to be validated in other populations of individuals with CKD. Also, this study was composed of research volunteers. As such, the results may

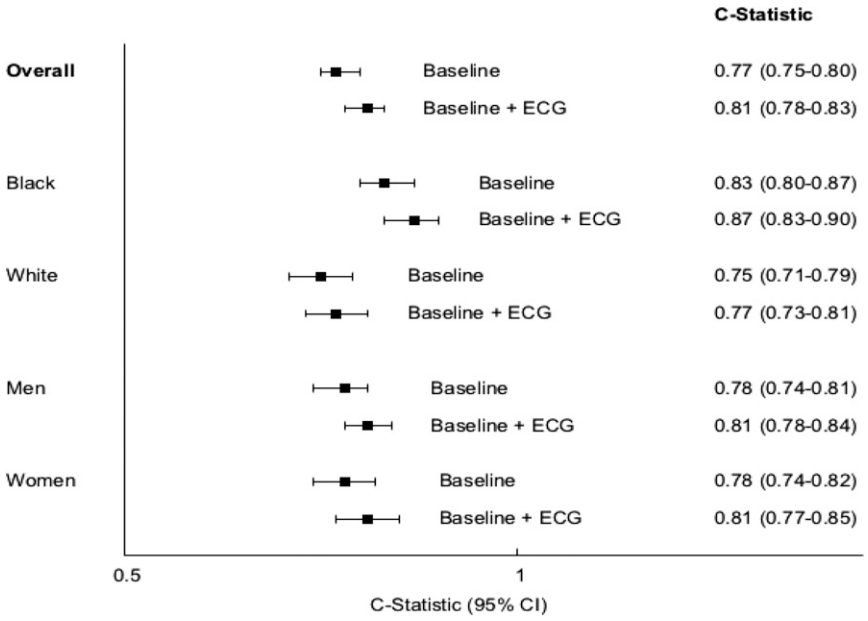

Figure 2. C-statistics for cardiovascular death. The plot depicts the C-statistics for cardiovascular death across the entire study population followed by subgroups of race and sex. The baseline model includes age, sex, race, history of cardiovascular disease, smoking, diabetes, systolic and diastolic blood pressure, BMI, total cholesterol, HDL, eGFR, and proteinuria (24 hour collection). The baseline plus ECG model includes all the variables above plus the PR, QRS, QT_c, and RR intervals, and Cornell voltage.

not be generalizable to all individuals with CKD of similar severity.

In summary, several common ECG metrics appear to have stronger independent associations with cardiovascular death compared with noncardiovascular death among individuals with CKD. These measures also improve the prediction of cardiovascular death in the setting of CKD above and beyond standard clinical risk factors. Future research is needed to evaluate the clinical effectiveness of ECG-based screening strategies linked to targeted interventions.

CONCISE METHODS

Study Population

The CRIC study is a large, multicenter, multiracial cohort study established to understand the progression of cardiovascular and renal disease among individuals with CKD. The study enrolled participants between June 2003 and September 2008. Individuals who were between 21 and 74 years and had an eGFR between 20 and 70 ml/min per 1.73 m^2 were eligible for the study. The age and eGFR criteria were specifically designed to facilitate evaluation of the progression and implications of CKD across a wide spectrum of mild to moderate kidney dysfunction and age. Details on recruitment and design have been published previously.[15] The study protocol complies with the Declaration of Helsinki, and the institutional review boards at the seven participating centers approved the study protocol. All study participants provided written informed consent.

In brief, CRIC recruited 3939 men and women aged 21–74 years. The participants underwent clinical evaluations at baseline and

Table 4. Risk Reclassification for cardiovascular death after the addition of ECG Metrics

Base Model[a]	Base Model[a] + ECG parameters (PR, QRS, QT_c, heart rate, and LVH)				Reclassified as Higher Risk	Reclassified as Lower Risk
	< 5%	5%-25%	>25%	Total		
<5%[b]	23	11	1	35	12 (34.3%)	N/A
5%-25%	6	69	8	83	8 (9.6%)	6 (7.2%)
>25%	0	2	10	12	N/A	2 (16.7%)
Total	29	82	19	130	20 (15.4%)	8 (6.2%)
EVENTS						
Base Model[a]	Base Model[a] + ECG parameters (PR, QRS, QT_c, heart rate, and LVH)				Reclassified as Higher Risk	Reclassified as Lower Risk
	< 5%	5%-25%	>25%	Total		
<5%[b]	2076	62	2	2140	64 (3.0%)	N/A
5%-25%	164	483	32	679	32 (4.7%)	164 (24.2%)
>25%	0	14	21	35	N/A	14 (40%)
Total	2240	559	55	2854	96 (3.4%)	178 (6.2%)
NON-EVENTS						

LVH, left ventricular hypertrophy.
[a]The base model includes age, sex, race, history of cardiovascular disease, smoking, diabetes, systolic and diastolic blood pressure, body mass index, total cholesterol, HDL, eGFR and proteinuria (24 hour collection).
[b]Rate of cardiovascular death over a 5 year period.

annual visits with interim telephone interviews at 6-month intervals. Among the 3939 participants enrolled at baseline, we excluded 269 participants who were missing at least one of the five ECG metrics assessed in this study. From the remaining 3670 participants, we excluded those with a baseline ECG demonstrating either atrial fibrillation, atrial flutter, or atrial tachycardia (n=51). Atrial fibrillation and atrial flutter result in variations of heart rate and the QT interval and thus do not provide a reliable measure of these parameters. We also excluded participants with a nonphysiologic PR interval defined as one that is less than 100 ms, suggestive of accessory pathway conduction (n=42). In total, 83 participants had either atrial fibrillation/atrial tachycardia or a PR interval <100 ms on the baseline ECG resulting in a final analytical sample of 3587 study participants.

Information on baseline confounders was obtained during the initial visit and included sociodemographics, lifestyle risk factors, medical history, and medication use. Blood pressure,[16] anthropometrics,[17] and other clinical variables such as smoking status and diabetes were collected using standard protocols. Prevalent cardiovascular disease included any history of coronary heart disease, heart failure, peripheral arterial disease, and stroke. Blood was obtained from participants in the fasting state and assayed for serum creatinine, cystatin C, calcium, sodium, potassium, phosphorus, total cholesterol, HDL, LDL, triglycerides, albumin, and hemoglobin. Hemoglobin was measured locally at a laboratory associated with each clinical center. All other measurements were performed at a central laboratory at the University of Pennsylvania. Estimated GFR was calculated from serum creatinine and cystatin C using the CRIC-based equation.[18] Twenty-four hour urine samples were obtained and measured for albumin.

Cardiac Measurements

Twelve-lead electrocardiograms were recorded in all participants using standardized procedures[19] and identical electrocardiographic equipment (MAC 1200; GE Medical Systems Information Technologies, Milwaukee, WI). Digitally recorded ECGs were transmitted for analysis to the CRIC ECG reading center located at Wake Forest University, Winston Salem, NC. After being visually checked for quality, the study ECGs were automatically processed using the 2001 version of the GE Marquette 12-SL program (GE Medical Systems Information Technologies). The PR and QT intervals were calculated as single global measures from the earliest onset to the latest off-set of the relevant waveforms. Heart rate was calculated from the RR interval (heart rate [in bpm]=60/RR [in ms]*1000). The PR, QRS, QT, and heart rate (RR) durations were evaluated automatically in normal sinus rhythm using these recordings. Additional details on how each ECG metric was assessed are provided: the PR interval was assessed both as a linear variable (per 10 ms) and a dichotomous one (≥200 ms) based on clinical criteria that define PR prolongation or first degree atrioventricular block. The QRS interval was evaluated as a linear variable (per 10 ms) and categorized into three groups (<100 ms, 100–119 ms, and ≥120 ms). A QRS interval between 100 and 119 ms reflects intraventricular conduction delay and is suggestive of fibrosis and conduction system disease.[20] In addition, a QRS interval ≥120 ms is defined as bundle branch block. The QT_c interval was calculated using Bazett's formula[21] and was assessed both as a linear variable (per 10 ms) and dichotomous one. QT_c prolongation was defined according to national guidelines, which recommend cut points of 460 ms or longer in women and 450 ms or longer in men.[21] Since the QT interval, which includes the QRS duration, will automatically prolong in any ventricular conduction defect, special considerations and adjustments for the QRS duration were necessary.[22–24] As a result, we also evaluated the significance of the QT_c interval among the subgroup of participants who were not considered to have significant delays in ventricular conduction (*i.e.*, QRS duration <120 ms). Heart rate was assessed as both a linear variable (per 50 ms) and categorized into three groups (in units of bpm): less than 60, 60–90, and greater than 90. Electrocardiographic LVH was assessed utilizing the Cornell voltage criteria based on the sum of the S-wave in V3 and R-wave in aVL.[25,26] LVH was evaluated both as a linear variable (per 100 microvolts) and dichotomized by the presence or absence of LVH, which is defined as a Cornell voltage greater than 28,000 microvolts in men and greater than 20,000 microvolts in women.[25,26] Both LVH and intraventricular conduction delay alter QRS patterns, and a prolonged QRS duration may impact the accuracy of the ECG criteria for LVH. Multiple studies have also suggested that the diagnosis of LVH should not be attempted in the setting of bundle branch block.[27] As a result, in addition to evaluating LVH in all CRIC participants, we also evaluated its significance in the subgroup with a QRS duration <120 ms.

Echocardiography was performed approximately one year after enrollment into the CRIC study. Studies were performed at the individual sites according to the American Society of Echocardiography guidelines and assessed cardiac structure and function.[28] All data were sent to the core echocardiography laboratory (University of Pennsylvania) for measurement and analysis. Left ventricular mass was calculated using the area-length method and indexed to $height^{2.7}$.[28] In addition, left ventricular systolic function was assessed. Left ventricular end-diastolic and end-systolic volumes were calculated using the modified biplane method, and ejection fraction was calculated as [(end-diastolic volume minus end-systolic volume)/(end-diastolic volume)].

Outcome Variables

We assessed all-cause mortality, cardiovascular death, and noncardiovascular death. In addition, incident heart failure and MI were evaluated. Deaths were ascertained from next of kin, retrieval of death certificates or obituaries, review of hospital records, and linkage with the social security death master file. All deaths to March 31, 2013, were included in these analyses.

We also adjudicated cardiovascular death and noncardiovascular death events. For inpatient deaths, two physicians reviewed medical records, death certificates, and autopsy reports when available. Based on this review, the physician reviewers adjudicated the death as one being due to MI, coronary heart disease, congestive heart failure, or another cardiovascular cause. The etiology for other deaths especially those that occurred among outpatients were adjudicated by a nurse research coordinator using death certificate data. As part of their evaluation, a mortality event was attributable to a cardiovascular cause when the primary diagnosis on the death certificate included MI, coronary heart disease, cardiorespiratory arrest, or congestive heart failure. Individuals who had a diagnosis of a severe, noncardiovascular

illness such as cancer, sepsis, systemic inflammatory response syndrome, dementia, gastrointestinal bleeding, or severe hemorrhage were labeled as having a noncardiovascular death.

Incident heart failure and MI were also assessed in the subgroup of 2492 CRIC participants without a baseline history of heart failure, coronary heart disease, or stroke. These outcomes were adjudicated using well defined criteria that have been described previously.[15,29]

Statistical Analysis

The baseline characteristics of CRIC participants are described across the *a priori* specified ECG categories. Separate Cox proportional hazards models were fitted to assess the association between each ECG measure and outcome. Each ECG parameter was modeled both as a linear and categorical variable, with quadratic splines used to explore a potential non-linear relationship between each ECG measure and outcome.[30]

For the evaluation of the three mortality outcomes, multivariable analysis adjusted for potential confounders of the association between each ECG metric and death. Adjusted models included the following covariates: demographic characteristics (age, sex, and race/ethnicity), clinical center, cardiovascular disease at baseline, cardiovascular risk factors including current smoking and diabetes, systolic blood pressure, diastolic blood pressure, BMI, total cholesterol, HDL, eGFR, 24-hour proteinuria (log of urinary protein excretion), serum calcium, serum phosphorus, serum potassium, and baseline medications (β-blocker, calcium channel blocker, and statin). In addition, multivariable models included all five ECG variables that were assessed. For incident heart failure and MI, the multivariable modeling included the same covariates except prevalent heart failure, coronary heart disease or stroke. Additional analyses were performed to evaluate the QT_c interval and LVH as potential risk factors in the subgroup with a QRS$<$120 ms. There was no evidence of violation of the proportional hazards assumption based on cumulative Martingale residuals.[31] We also performed additional evaluation for cardiovascular death and adjusted for echocardiographic-based measures of left ventricular mass index and ejection fraction. Based on *a priori* hypotheses, we tested for interactions between each of the five ECG metrics and sex and race for the outcome of cardiovascular death.

We evaluated the ability of ECG metrics to improve cardiovascular mortality prediction within 5 years of follow-up in this CKD cohort. We first calculated the c-statistic, a measure of discrimination,[32] for the base model for cardiovascular mortality, which included a standard set of predictors including age, sex, race, history of cardiovascular disease, smoking, diabetes, systolic and diastolic blood pressure, BMI, total cholesterol, HDL, eGFR, and proteinuria (24 hour collection). We then evaluated the C-statistic after adding the five ECG metrics to the model. We calculated the net reclassification improvement (NRI)[33] to assess how well the addition of ECG metrics reclassified cases into higher risk strata and non-cases into lower risk categories. The NRI is estimated according to the method by Pencina[33] and is defined as {([number of events reclassified higher – number of events reclassified lower]/number of events)+([number of non-events reclassified lower–number of non-events reclassified higher]/number of non-events)}. Since the mortality rate in the CRIC study is 3% per year, we used annualized cut points of 1% and 5% to define the low, medium, and high risk groups. In particular, we assessed reclassification over a 5-year period and defined the low risk group as having an annualized rate of death $<$1% (corresponds to less than 5% over 5 years). The intermediate risk group was composed of participants who had an annual death rate between 1% and 5% (corresponds to 5–25% over 5 years). We defined the high risk group as having a death rate $\geq$5% per year. Finally, we estimated the integrated discrimination improvement,[33] defined as the average increase in predicted risk among cases, plus the analogous average decrease among non-cases, afforded by information of ECG metrics. In contrast to the three-category NRI measures, the integrated discrimination improvement is calculated using predicted risks and is not affected by choice of cutoff values. Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). All statistical tests were two-sided, and P values $<$0.05 were considered significant.

ACKNOWLEDGMENTS

We appreciate the support of the other CRIC Study Investigators including Lawrence J. Appel, Jiang He, John W. Kusek, James P. Lash, Akinlolu Ojo, and Mahboob Rahman. The CRIC ancillary study was supported by the National Institutes of Health (NIH) grant K23-DK089118 (to R.D.). The CRIC study is supported by cooperative agreement project grants from the National Institute of Diabetes and Digestive and Kidney Diseases (U01-DK060990, U01-DK060984, U01-DK061022, U01-DK061021, U01-DK061028, U01-DK060980, U01-DK060963, and U01-DK060902).

In addition, this work was supported in part by the Perelman School of Medicine at the University of Pennsylvania Clinical and Translational Science Award NIH/ National Center for Advancing Translational Sciences (NCATS) Grant UL1-TR000003, Johns Hopkins University Grant UL1-TR000424, University of Maryland GCRC Grant M01-RR16500, Clinical and Translational Science Collaborative of Cleveland Grant UL1-TR000439 from the NCATS component of the NIH and NIH roadmap for Medical Research, Michigan Institute for Clinical and Health Research Grant UL1-TR000433, University of Illinois at Chicago CTSA Grant UL1-RR029879, Tulane University Translational Research in Hypertension and Renal Biology Grant P30-GM103337, and Kaiser Permanente NIH/NCRR UCSF-CTSI Grant UL1-RR024131.

DISCLOSURES

None.

REFERENCES

1. Moyer VA; U.S. Preventive Services Task Force: Screening for coronary heart disease with electrocardiography: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 157: 512–518, 2012
2. Chou R, Arora B, Dana T, Fu R, Walker M, Humphrey L: Screening asymptomatic adults with resting or exercise electrocardiography: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 155: 375–385, 2011

3. Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Köttgen A, Levey AS, Levin A: Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet* 382: 158–169, 2013
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
5. Shah AP, Rubin SA: Errors in the computerized electrocardiogram interpretation of cardiac rhythm. *J Electrocardiol* 40: 385–390, 2007
6. Kestenbaum B, Rudser KD, Shlipak MG, Fried LF, Newman AB, Katz R, Sarnak MJ, Seliger S, Stehman-Breen C, Prineas R, Siscovick DS: Kidney function, electrocardiographic findings, and cardiovascular events among older adults. *Clin J Am Soc Nephrol* 2: 501–508, 2007
7. Dobre M, Brateanu A, Rashidi A, Rahman M: Electrocardiogram abnormalities and cardiovascular mortality in elderly patients with CKD. *Clin J Am Soc Nephrol* 7: 949–956, 2012
8. Krane V, Heinrich F, Meesmann M, Olschewski M, Lilienthal J, Angermann C, Störk S, Bauersachs J, Wanner C, Frantz S; German Diabetes and Dialysis Study Investigators: Electrocardiography and outcome in patients with diabetes mellitus on maintenance hemodialysis. *Clin J Am Soc Nephrol* 4: 394–400, 2009
9. van der Werf C, Postema PG: Using the electrocardiogram as a crystal ball for cardiovascular and all-cause mortality. *Eur Heart J* 35: 1303–1305, 2014
10. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 346: 877–883, 2002
11. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators: Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 352: 225–237, 2005
12. Packer DL, Prutkin JM, Hellkamp AS, Mitchell LB, Bernstein RC, Wood F, Boehmer JP, Carlson MD, Frantz RP, McNulty SE, Rogers JG, Anderson J, Johnson GW, Walsh MN, Poole JE, Mark DB, Lee KL, Bardy GH: Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the sudden cardiac death in heart failure trial. *Circulation* 120: 2170–2176, 2009
13. Deo R, Lin F, Vittinghoff E, Tseng ZH, Hulley SB, Shlipak MG: Kidney dysfunction and sudden cardiac death among women with coronary heart disease. *Hypertension* 51: 1578–1582, 2008
14. Deo R, Sotoodehnia N, Katz R, Sarnak MJ, Fried LF, Chonchol M, Kestenbaum B, Psaty BM, Siscovick DS, Shlipak MG: Cystatin C and sudden cardiac death risk in the elderly. *Circ Cardiovasc Qual Outcomes* 3: 159–164, 2010
15. Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J, Fink JC, Franklin-Becker ED, Go AS, Hamm LL, He J, Hostetter T, Hsu CY, Jamerson K, Joffe M, Kusek JW, Landis JR, Lash JP, Miller ER, Mohler ER 3rd, Muntner P, Ojo AO, Rahman M, Townsend RR, Wright JT; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators: The Chronic Renal Insufficiency Cohort (CRIC) Study: Design and Methods. *J Am Soc Nephrol* 14[Suppl 2]: S148–S153, 2003
16. Perloff D, Grim C, Flack J, Frohlich ED, Hill M, McDonald M, Morgenstern BZ: Human blood pressure determination by sphygmomanometry. *Circulation* 88: 2460–2470, 1993
17. McDermott MM, Criqui MH, Liu K, Guralnik JM, Greenland P, Martin GJ, Pearce W: Lower ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial pressures, and association with leg functioning in peripheral arterial disease. *J Vasc Surg* 32: 1164–1171, 2000
18. Anderson AH, Yang W, Hsu CY, Joffe MM, Leonard MB, Xie D, Chen J, Greene T, Jaar BG, Kao P, Kusek JW, Landis JR, Lash JP, Townsend RR, Weir MR, Feldman HI; CRIC Study Investigators: Estimating GFR among participants in the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 60: 250–261, 2012
19. Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ, Hancock EW, van Herpen G, Kors JA, Macfarlane P, Mirvis DM, Pahlm O, Rautaharju P, Wagner GS, Josephson M, Mason JW, Okin P, Surawicz B, Wellens H; American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society: Recommendations for the standardization and interpretation of the electrocardiogram: part I: The electrocardiogram and its technology: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation* 115: 1306–1324, 2007
20. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, Rautaharju PM, van Herpen G, Wagner GS, Wellens H; American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society: AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation* 119: e235–e240, 2009
21. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, van Herpen G, Wagner GS, Wellens H; American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society: AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation* 119: e241–e250, 2009
22. Das G: QT interval and repolarization time in patients with intraventricular conduction delay. *J Electrocardiol* 23: 49–52, 1990
23. Rautaharju PM, Zhang ZM, Prineas R, Heiss G: Assessment of prolonged QT and JT intervals in ventricular conduction defects. *Am J Cardiol* 93: 1017–1021, 2004
24. Crow RS, Hannan PJ, Folsom AR: Prognostic significance of corrected QT and corrected JT interval for incident coronary heart disease in a general population sample stratified by presence or absence of wide QRS complex: the ARIC Study with 13 years of follow-up. *Circulation* 108: 1985–1989, 2003
25. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, Phillips MC: Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. *J Am Coll Cardiol* 6: 572–580, 1985
26. Havranek EP, Emsermann CD, Froshaug DN, Masoudi FA, Krantz MJ, Hanratty R, Estacio RO, Dickinson LM, Steiner JF: Thresholds in the relationship between mortality and left ventricular hypertrophy defined by electrocardiography. *J Electrocardiol* 41: 342–350, 2008
27. Hancock EW, Deal BJ, Mirvis DM, Okin P, Kligfield P, Gettes LS, Bailey JJ, Childers R, Gorgels A, Josephson M, Kors JA, Macfarlane P, Mason JW, Pahlm O, Rautaharju PM, Surawicz B, van Herpen G, Wagner GS, Wellens H; American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society: AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part V: electrocardiogram changes associated with cardiac chamber hypertrophy: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology

Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation* 119: e251–e261, 2009
28. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography: Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 18: 1440–1463, 2005
29. Deo R, Yang W, Khan AM, Bansal N, Zhang X, Leonard MB, Keane MG, Soliman EZ, Steigerwalt S, Townsend RR, Shlipak MG, Feldman HI; CRIC Study Investigators: Serum aldosterone and death, end-stage renal disease, and cardiovascular events in blacks and whites: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Hypertension* 64: 103–110, 2014
30. Greenland S: Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. *Epidemiology* 6: 356–365, 1995
31. Lin DY, Wei LJ, Ying Z: Model-checking techniques based on cumulative residuals. *Biometrics* 58: 1–12, 2002
32. Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 15: 361–387, 1996
33. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS: Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 27: 157–172, discussion 207–212, 2008

This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2014101045/-/DCSupplemental.