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Association of Major and Minor ECG Abnormalities With Coronary Heart Disease Events

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Abstract

Context—In populations of older adults, prediction of coronary heart disease (CHD) events through traditional risk factors is less accurate than in middle-aged adults. Electrocardiographic (ECG) abnormalities are common in older adults and might be of value for CHD prediction.

Objective—To determine whether baseline ECG abnormalities or development of new and persistent ECG abnormalities are associated with increased CHD events.

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Design, Setting, and Participants—A population-based study of 2192 white and black older adults aged 70 to 79 years from the Health, Aging, and Body Composition Study (Health ABC Study) without known cardiovascular disease. Adjudicated CHD events were collected over 8 years between 1997–1998 and 2006–2007. Baseline and 4-year ECG abnormalities were classified according to the Minnesota Code as major and minor. Using Cox proportional hazards regression models, the addition of ECG abnormalities to traditional risk factors were examined to predict CHD events.

Main Outcome Measure—Adjudicated CHD events (acute myocardial infarction [MI], CHD death, and hospitalization for angina or coronary revascularization).

Results—At baseline, 276 participants (13%) had minor and 506 (23%) had major ECG abnormalities. During follow-up, 351 participants had CHD events (96 CHD deaths, 101 acute MIs, and 154 hospitalizations for angina or coronary revascularizations). Both baseline minor and major ECG abnormalities were associated with an increased risk of CHD after adjustment for traditional risk factors (17.2 per 1000 person-years among those with no abnormalities; 29.3 per 1000 person-years; hazard ratio [HR], 1.35; 95% CI, 1.02–1.81; for minor abnormalities; and 31.6 per 1000 person-years; HR, 1.51; 95% CI, 1.20–1.90; for major abnormalities). When ECG abnormalities were added to a model containing traditional risk factors alone, 13.6% of intermediate-risk participants with both major and minor ECG abnormalities were correctly reclassified (overall net reclassification improvement [NRI], 7.4%; 95% CI, 3.1%–19.0%; integrated discrimination improvement, 0.99%; 95% CI, 0.32%–2.15%). After 4 years, 208 participants had new and 416 had persistent abnormalities. Both new and persistent ECG abnormalities were associated with an increased risk of subsequent CHD events (HR, 2.01; 95% CI, 1.33–3.02; and HR, 1.66; 95% CI, 1.18–2.34; respectively). When added to the Framingham Risk Score, the NRI was not significant (5.7%; 95% CI, −0.4% to 11.8%).

Conclusions—Major and minor ECG abnormalities among older adults were associated with an increased risk of CHD events. Depending on the model, adding ECG abnormalities was associated with improved risk prediction beyond traditional risk factors.

In populations of older adults, prediction of coronary heart disease (CHD) through traditional risk factors is less accurate than among middle-aged adults.[1] Resting electrocardiographic (ECG) abnormalities have been shown to be independently associated with incident CHD and cardiovascular disease (CVD) events,[2–8] and ECG is a good candidate to consider for risk stratification of asymptomatic participants given its low cost, wide use, and safety.[9,10] However, performing routine ECG among asymptomatic adults is not supported by current evidence.[11]

Considering the higher prevalence of both CVD and ECG abnormalities in older adults, risk prediction incorporating ECG might be more useful in this group.[2,9] To date, few studies have examined the improvement of CVD risk prediction using ECG abnormalities in a population of older adults and none could adequately adjust the analyses for presence of previous CVD and traditional cardiovascular risk factors (CVRFs).[12,13] Moreover, no studies have examined the effect of ECG on net reclassification of participants, a method of reporting the prognostic properties of markers of cardiovascular risk.[14–16]

Our study goal was to determine whether baseline major and minor ECG abnormalities, development of new ECG abnormalities, and persistent ECG abnormalities during follow-up were associated with incident CHD events, independent of traditional CVRFs, in a population-based study of black and white older adults without preexisting CVD.

METHODS

Study Population

Participants were part of the Health, Aging, and Body Composition Study (Health ABC Study), a population-based cohort study of 3075 community-dwelling men and women aged 70 to 79 years at study entry in 1997–1998.[17] Participants were identified from a random sample of white and black Medicare-eligible adults living in designated zip code areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. Participants identified themselves as black or white race. Details of the eligibility criteria have been previously described.[17] All participants gave written informed consent and the institutional review board approved the protocol.

Among the 3075 participants, we excluded 842 who had overt CVD at baseline, defined as a diagnosis of CHD (angina, prior myocardial infarction [MI], angioplasty of coronary arteries, or coronary artery graft surgery), stroke or transient ischemic attack, peripheral arterial revascularization, carotid artery disease, heart failure, or having a pacemaker (based on algorithms mirroring those of the Cardiovascular Health Study).[18] We also excluded 41 participants with missing data for any of the traditional risk factors. The final sample for our analyses of baseline ECG abnormalities was 2192 participants.

ECG Data

Standard 12-lead ECGs were recorded at baseline and at the year 4 visit in the resting supine position and using strictly standardized procedures in all clinical centers. Electrocardiograms were sent electronically to an ECG core laboratory at St Louis University Medical Center, St Louis, Missouri. Each ECG was reviewed by 2 trained coders and discordant results were adjudicated by a senior coder. Electrocardiograms were coded according to the Minnesota Code (MC).[19] Independent data entry operators entered data twice in an electronic database and data were adjudicated by a supervisor. Among a random sample of 5% of baseline ECGs, κ values for the categorization described were 0.90 for major, 0.71 for minor, and 0.82 for no ECG abnormalities.

Electrocardiographic abnormalities were divided into major and minor abnormalities on the basis of the MC and according to previous publications.[7,8,10] Criteria for major prevalent ECG abnormalities were any of the following: Q-QS wave abnormalities (MC 1-1 to 1-2-8); left ventricular hypertrophy (MC 3–1); Wolff-Parkinson-White syndrome (MC 6-4-1 or 6-4-2); complete bundle branch block or intraventricular block (MC 7-1-1, 7-2-1, 7–4, or 7–8); atrial fibrillation or atrial flutter (MC 8–3); or major ST-T changes (MC 4–1, 4–2, 5–1, and 5–2). Criteria for minor prevalent ECG abnormalities were minor ST-T changes (MC 4–3, 4-4, 5–3, and 5–4). Participants with both major and minor abnormalities were classified

as having major abnormalities. Participants without minor or major ECG abnormalities were classified as having marginal or no abnormalities and their ECG was considered normal.

At 4 years, we analyzed repeat ECG data among 1670 of the participants who had not had any CHD events during the first 4 years of follow-up. From the base-line sample of 2192 participants, we excluded 424 participants without ECG data at 4 years and 98 participants who had had a CHD event during the first 4 years of follow-up. These 522 participants were more likely to be older, of black race, smokers, have hypertension and less education, be less physically active, and have an increased creatinine level than the participants included in the repeat ECG analyses at 4 years. For these analyses, participants were classified according to the presence of any (major, minor, or both) abnormalities at baseline and follow-up. These participants were then categorized as abnormalities at baseline only, persistent abnormalities (both baseline and follow-up), incident abnormalities (follow-up only), and no abnormalities (neither baseline nor follow-up).

CHD Events

We assessed incident CHD events among participants without preexisting CVD at baseline. Using algorithms mirroring those of the Cardiovascular Health Study,[18] diagnoses and cause of death were adjudicated until 2006–2007, based on interview, review of all hospital records, death certificates, and other documents by a panel of clinicians blinded to the results of ECG data at baseline and 4 years. CHD events were defined as acute MI, coronary death, hospitalization for angina, or coronary revascularization (angioplasty of coronary arteries and coronary artery bypass graft surgery).[20] We also separately analyzed hard CHD events, defined as MI and CHD deaths (as defined in current guidelines[21]) and soft CHD events, defined as hospitalization for angina and coronary revascularization.

Follow-up time was defined by the time from the baseline visit until the first event date (for those participants who had an event) or was censored at the last contact date (for those participants who did not have any event or were lost to follow-up) or the day of death (for those participants who died of noncardiovascular causes). For the analyses of repeat ECGs at 4 years, the baseline visit was defined as the date of the repeat ECG at 4 years.

Covariates

Covariates included sociodemographic variables (age, sex, self-reported race, study site, education) as well as physical and biological parameters, including smoking status (current, past, or never smokers assessed by questionnaire), body mass index (calculated as weight in kilograms divided by height in meters squared), and total cholesterol, high-density lipoprotein cholesterol, and creatinine (all measured by a colorimetric technique on a Johnson & Johnson Vitros 950 analyzer, New Brunswick, New Jersey). Hypertension was defined via self-report and use of antihypertensive medications, or measured blood pressure, with systolic of 140 mm Hg or higher, diastolic of 90 mm Hg or higher, or both. Diabetes was defined as self-reported diagnosis, using any hypoglycemic medication, or both.[20] The use of lipid-lowering drugs, angiotensin-converting enzyme inhibitors, estrogen therapy, and aspirin was assessed using Iowa Drug Information System codes.

Statistical Analyses

Differences in proportions and means of covariates across participants with and without incident CVD events during follow-up were assessed by use of χ^2 and analysis of variance statistics, respectively. For covariates that were not normally distributed, median values with interquartile ranges were reported and the use of Mann-Whitney *U* statistics. We used Cox proportional hazard regression models to assess the improvement in prediction of future CHD events by including ECG data.[22,23] The level of significance was established a priori at 2-sided $P<.05$. Primary analyses were adjusted for traditional risk factors included in the current Framingham Risk Score (FRS),[21] as well as diabetes, a strong independent CHD risk factor.[24] Systolic blood pressure was used as a continuous variable. In sensitivity analyses, we examined associations in models further adjusted for other potential riskfactors or confounders (ie, self-reported race, education, site, low-density lipoprotein cholesterol, creatinine level, alcohol consumption, physical activity, and use of statins, angiotensin-converting enzyme inhibitors, and estrogen). We further examined the overall reclassification rate of ECG abnormalities over the FRS categories (without diabetes). We did not use the FRS in the main analyses, because it has not been validated among adults aged older than 75 years. We also performed stratified analyses by race (white vs black). We addressed the potential concern of competing causes of death in this older population in a competing risk Fine and Gray model.[25]

To assess model calibration, we used Parzen adaptation of the Hosmer-Lemeshow test to the Cox proportional hazard regression model.[26] We verified the proportional hazards assumption using graphical methods and Schoenfeld tests. We examined several statistical measures according to recommendations for the assessment of novel markers.[15] To assess improvements in discrimination, we used Harrell C index,[27] an adaptation of the C statistic or area under the receiver operating characteristic curve to the Cox proportional hazard regression model. We adjusted the C index for optimism by using 10-fold cross-validation and obtained confidence intervals using bootstrap resampling with 500 repetitions. Net reclassification rates were computed as described previously.[14,28] To avoid extrapolation beyond the range of our data, we used Cox proportional hazard regression models to estimate 7.5-year risks rather than 10-year risks.[29] We used 7.5% to 15% risk over 7.5 years corresponding with the thresholds used in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines to define intermediate-risk categories (10%–20% over 10-year risk).[21] We also assessed net reclassification improvement (NRI) in intermediate-risk categories (10%–20% over 10-year risk), defined as 7.5% to 15% risk for 7.5-year time-frame.[30] The NRI is estimated according to the method by Pencina et al[14] 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)}. In addition, we estimated an alternate reclassification method for the intermediate-risk group (7.5%–15% over 7.5-year risk), the adjusted clinical NRI,[31] which takes into account the observed reclassification rates for the expected rates under the null hypothesis of no net reclassification. In addition, we estimated integrated discrimination improvement (IDI),[14] defined as the average increase in predicted risk among cases, plus the analogous average decrease among controls, afforded

by information on ECG abnormalities. In contrast to both NRI measures, the IDI is calculated using predicted risks before grouping into categories and is therefore not affected by choice of cutoff values.[14]

Statistical analyses were conducted using Stata version 12 (Stata Corporation) and R version 2.14.1 (R Project for Statistical Computing, http://www.r-project.org).

RESULTS

Baseline ECGs

At baseline, mean (SD) age was 73.5 (2.8) years, 55% were women, and 41% were of black race (Table 1). Of the 2192 participants, 506 (23%) had major and 276 (13%) had minor ECG abnormalities. During a median follow-up of 8.2 years (range, 9 days-10.2 years), 351 participants had CHD events (96 CHD deaths, 101 acute MIs, and 154 hospitalizations for angina or coronary revascularizations) and 602 died (96 deaths from CHD).

Major and minor ECG abnormalities at baseline were both associated with an increased risk of CHD. The Kaplan-Meier estimates of CHD cumulative hazard over time for those participants without ECG abnormalities vs any (minor and/or major) ECG abnormalities (Figure 1) and for those participants without ECG abnormalities vs major and minor ECG abnormalities (Figure 2) were calculated. The CHD rate per 1000 person-years in participants with no ECG abnormalities was 17.2 (29.3 per 1000 person-years in those with minor ECG abnormalities and 31.6 per 1000 person-years in those with major ECG abnormalities at baseline) (Table 2). After adjustment for CVRFs including age, sex, total and high-density lipoprotein cholesterol, systolic blood pressure, smoking, and diabetes, hazard ratios (HRs) and 95% CIs for CHD events for participants with minor ECG abnormalities vs participants without abnormalities was 1.35 (95% CI, 1.02–1.81) and 1.51 (95% CI, 1.20–1.90) for those with major ECG abnormalities at baseline. Results were similar when further adjusting for race, education, site, low-density lipoprotein cholesterol, creatinine (as natural logarithm), alcohol consumption, physical activity, statins, angiotensin-converting enzyme inhibitors, and estrogen use (Table 2).

Stratification of analyses by race showed similar findings between white and black participants (eTable 1, http://www.jama.com). The HRs adjusted for CVRFs were 1.58 (95% CI, 1.19–2.09) for hard CHD events (absolute risk, 16.1 vs 9.4 per 1000 person-years among those without ECG abnormalities) and 1.67 (95% CI, 1.21–2.31) for soft events (absolute risk, 13.6 vs 7.5 per 1000 person-years among those without ECG abnormalities) (eTable 2). Overall, associations with minor ECG abnormalities were less strong in these stratified analyses, although associations with major or any ECG abnormalities remained similar. A Fine and Gray model treating all-cause mortality as a competing risk yielded an HR of 1.63 (95% CI, 1.32–2.01), which was similar to the HR found for the main model adjusted for traditional CVRFs.

The addition of ECG abnormalities to the model adjusted for traditional CVRFs resulted in reclassification of 13.6% of intermediate-risk participants and 7.1% in the overall sample (Table 3). When ECG abnormality was added to the model adjusted for traditional CVRFs,

176 intermediate-risk participants (8%) were reclassified as high risk, of whom 27 (15.2%) experienced events. Conversely, 136 participants (6.2%) were reclassified as low risk, of whom 7 (5.2%) experienced events. Using the alternate reclassification method, which takes into account the observed rates vs the expected rates under the null hypothesis, 7.9% of intermediate-risk participants without events and −1.2% of participants with events were reclassified into the highest- and lowest-risk categories (adjusted clinical NRI, 6.7%; 95% CI, 1.2%–19.3%). With this method, the greatest effect of adding ECG abnormalities to the model was on reclassifying intermediate-risk participants without events into the lowest-risk category. Including ECG abnormality in the model adjusted for CVRFs placed 65% of the overall population into either the highest-risk or lowest-risk categories vs 49% with traditional risk factors alone. With the addition of ECG abnormality to the model, 0.9% fewer of those who experienced events were reclassified as high risk and an additional 8% of those who did not experience events were reclassified as low risk (NRI for the overall sample, 7.4%; 95% CI, 3.1%–19.0%; and IDI, 0.99%; 95% CI, 0.32%–2.15%). When using the FRS alone, the reclassification rates achieved with additional ECG abnormalities were lower (NRI, 5.7%; 95% CI, −0.4% to 11.8%; and IDI, 1.03%; 95% CI, 0.56%–1.50%).

In addition to age and sex, the model fit and discrimination (measured by C index) was greater for ECG abnormalities than for each traditional risk factor for the prediction of CHD events (eTable 3). Overall, a model with all CVRFs included did not show a good calibration (goodness of fit P=.03) and was not improved by the addition of ECG abnormalities (goodness of fit P=.01) (eTable 3).

Follow-up ECGs

Of the 1670 adults with a second ECG after 4 years, 208 had a new abnormality and 416 had a persistent abnormality. During a median follow-up of 6.4 years (maximum, 7.3 years), 185 participants had CHD events and 348 died (57 from CHD).

After adjustment for CVRFs, both new and persistent ECG abnormalities at 4 years were associated with an increased risk of subsequent CHD events (for new abnormalities: HR, 2.01; 95% CI, 1.33–3.02; and for persistent abnormalities: HR, 1.66; 95% CI, 1.18–2.34). The absolute risk was 33.2 per 1000 person-years in those with new and 27.8 per 1000 person-years in those with persistent ECG abnormalities (Table 4). Risk increased from those with no ECG abnormality and abnormality at baseline only compared with those with persistent abnormality at 4-year follow-up (P for trend=.01) in multivariate-adjusted models (Table 4).

The associations between major and minor ECG abnormalities at baseline and all-cause mortality were not statistically significant (Table 2). The all-cause mortality rate in participants with no ECG abnormalities was 31.0 per 1000 person-years, in those with minor ECG abnormalities at baseline was 32.9 per 1000 person-years, and in those with major ECG abnormalities at baseline was 37.8 per 1000 person-years. After adjustment for CVRFs, the HRs were 0.95 (95% CI, 0.75–1.22) for minor ECG abnormalities and 1.17 (95% CI, 0.97–1.41) for major ECG abnormalities.

COMMENT

Our results demonstrate that in a population-based study of elderly men and women without preexisting CVD, ECG abnormalities were associated with an increased risk of CHD and significantly improved the prediction of CHD events beyond traditional CVRFs. Addition of ECG data reclassified 13.6% of the intermediate-risk participants. New and persistent abnormalities in the ECG performed 4 years later were associated with CHD beyond CVRFs.

Several previous studies reported an association between ECG abnormalities and CHD outcomes, but none assessed reclassification and few examined a population of older adults.[10,12,13] In postmenopausal women aged 55 to 79 years, Denes et al[10] found that baseline major and minor as well as incident ECG abnormalities were associated with significantly increased risks for CHD events, independent of established risk factors and hormone treatment. Although 20% of the sample (n=2911) were older than 70 years, complete data on CVRFs was only available in 10% of the participants and reclassification was not assessed (85% of the participants included were white and 6% were black). The authors observed an interaction of borderline significance between ECG abnormalities and race on CVD events, suggesting that white women with an abnormal baseline ECG had a higher risk for CVD than nonwhite women. In our study, 41% of our sample population was black. We found the HR associated with ECG abnormalities to be similar in black and white individuals (eTable 1). Other previous studies of the ability of baseline ECG to predict CVD mortality did not exclude those individuals with a history of CVD[32] or did not measure CVD.[13]

When we restricted our sample to the intermediate-risk category, 14% of participants were reclassified into higher-risk and lower-risk categories. Using a recent method that takes into account the expected number of participants reclassified, 6.7% (95% CI, 1.2%–19.3%) of intermediate-risk participants were reclassified, with ECG mainly reclassifying participants without events into the lowest-risk category. The NRI for ECG in our study was similar or higher than the NRI for biomarkers in previous studies. We found an NRI of 6.6% in the Health ABC Study for interleukin 6 (IL-6) and an NRI of 3.3% for ankle brachial index beyond CVRFs.[29] The net risk reclassification with ECG in our population of older adults vs traditional CVRFs was similar to that reported with C-reactive protein in middle-aged women (5.7% overall).[30] The association between C-reactive protein and CHD events in our previous publication on this population of older adults was weaker and not statistically significant after adjusting for additional CVRFs.[29] However, even if the NRI of 7.1% was better than other markers of inflammation, it is much lower than the NRI recently found for coronary artery calcification score measured with computed tomography.[33] Polonsky et al[33] found an NRI of 25% for the entire population and an NRI of 55% for individuals at intermediate risk in a population of 5931 adults aged 45 to 85 years, without known CVD and diabetes at baseline and followed up for 5 years. No specific NRI were reported for older adults. Cautious interpretation should be made when comparing the NRI between the 2 studies—reclassification is highly dependent on the cut-points used to define risk categories and these differed between studies, as did primary outcome definitions and length of follow-up.[34]

What are the implications of our study? The US Preventive Services Task Force recommends against systematic screening with ECG in asymptomatic populations.[11] They based their recommendations on the lack of clinical trials studying clinical outcomes after ECG screening and mentioned the low prevalence of ECG abnormalities in younger populations. In contrast with the low prevalence of ECG in younger populations, 36% of our studied population had any ECG abnormality at baseline. The ECG screening may be useful among populations of older adults, but the benefit was small and our results need to be validated in additional cohorts. The benefits of ECG screening should also be examined in clinical trials, as recommended by the US Preventive Services Task Force. Among different noninvasive screening methods studied to date with the NRI, coronary artery calcification score seems the most promising tool to predict CHD events.[33] The intrinsic risk of computed tomography of induced cancer[35,36] might be lower in older adults,[36] but the benefit of reclassification would need to be analyzed in the context of its high costs. The safety, low cost, and wide availability of ECG are advantages as a screen for subclinical CVD. An electronic method of reading the ECGs might facilitate the use of ECG data in clinical practice by permitting direct inclusion of data into an individual risk calculator alongside other CVRFs of electronic health records.[9]Further research should compare the NRI of coronary artery calcification score to a model with traditional risk factors alone and a model with traditional risk factors and ECG or other novel promising biomarkers.

Our study has several strengths and limitations. The data were drawn from a well-characterized population-based cohort of older adults and contained a high number of CHD events during 8 years of follow-up. All CHD events were formally adjudicated.[20] However, CHD events that did not require hospitalization were not tracked and potential associations between ECG and these more minor CHD events might be lower. Presence of ECG abnormalities might have led to an increased risk of being hospitalized for suspected angina, thereby producing a bias toward higher hospitalization rates for angina in participants with ECG abnormalities at baseline. To evaluate this possibility, we analyzed “hard” CHD outcomes and still found a positive association.

The association between ECG abnormalities and CHD events also could be confounded by participants who died without experiencing CHD during follow-up. A sensitivity analysis treating all-cause mortality as a competing risk showed that all-cause mortality did not substantially influence our analyses. Our study sample did not permit subgroup analyses to assess risk of CHD events associated with each specific ECG abnormality. When we used the traditional CVRFs included in the FRS, the C index was 0.58 (eTable 3), which was consistent with prior studies in older adults.[1,29] When we used the FRS, which has not been validated in those participants older than 75 years, the additional contribution of the ECG was not significant. Traditional risk factors have weaker associations with CHD events in older adults than in younger adults.[37] Furthermore, our model with all CVRFs and ECG abnormalities did not achieve good calibration. For possible development of a future risk score using ECG abnormalities (not the study goal), a better calibrated model would need to account for nonlinear responses to the CVRFs, as well as potential interactions between them.

We also conducted analyses on repeat ECGs, but 424 participants with no repeat ECG data at 4 years had significantly different baseline characteristics than participants with repeat ECG data, leading to a potential selection bias. Therefore, the HRs between the main analyses at baseline and secondary analyses on repeat ECG data at 4 years should not be directly compared. Reclassification was not assessed for participants with new abnormalities on 4-year ECG data, given the limited follow-up thereafter and the low number of participants with new abnormalities (n=208).

Another consideration is whether our study conditions can be replicated in the clinical setting. The ECG reading was not automated and each ECG was reviewed by 2 trained coders; discordant results were adjudicated by a senior coder. Our results are concordant with studies using different ECG classification and reading methods. For example, Denes et al[10] used the Nova-code, which permits automated ECG reading through a computer, to code ECGs and found similar associations between minor ECG changes and CHD events. Considering that previous literature shows large variations in accuracy of ECG reading in the clinical setting,[38] precise estimation of how our results may vary in the clinical setting is not possible. Reproducibility and reclassification using ECG may be lower in the clinical setting compared with our results.

In conclusion, we found that major and minor ECG abnormalities are associated with future CHD events and provide modestly improved risk reclassification beyond traditional risk factors. Risk prediction with traditional risk factors is less accurate in older persons compared with middle-aged adults.[1] Given the safety, the low cost, and the wide availability of ECG, ECG data might be useful to improve CHD risk prediction in older adults. Whether ECG should be incorporated in routine screening of older adults should be evaluated in randomized controlled trials.

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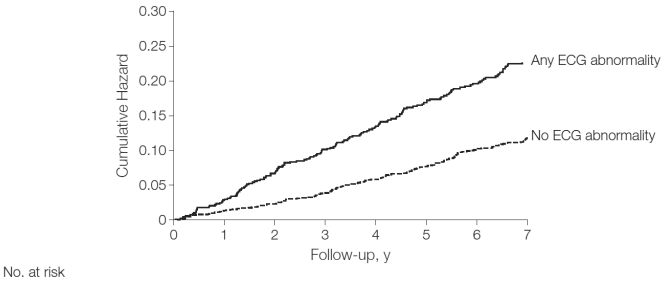
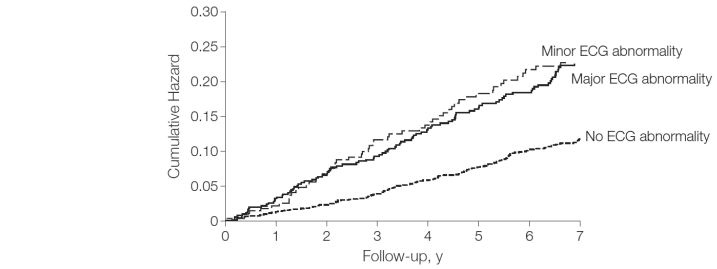


No. at risk								
No ECG abnormality	1410	1385	1353	1307	1259	1204	1134	1085
Any ECG abnormality	782	753	717	674	642	598	570	537

CHD indicates coronary heart disease; ECG, electrocardiographic. Any ECG abnormality included minor, major, or both. All 351 CHD events were included.

Figure 1.

Kaplan-Meier Estimates of CHD Cumulative Hazard Over Time of Any vs No ECG Abnormality



No. at risk								
No ECG abnormality	1410	1385	1353	1307	1259	1204	1134	1085
Minor ECG abnormality	276	268	254	239	229	212	200	191
Major ECG abnormality	506	485	463	435	413	386	370	346

CHD indicates coronary heart disease; ECG, electrocardiographic. All 351 CHD events were included.

Figure 2.

Kaplan-Meier Estimates of CHD Cumulative Hazard Over Time of Major and Minor vs No ECG Abnormality

Table 1

Baseline Characteristics of the Study Population[a]

Characteristics	No. (%) of Participants				*P* Value
	All (N = 2192)	No ECG Abnormality (n = 1410)	Minor ECG Abnormality (n = 276)	Major ECG Abnormality (n = 506)	
Age, mean (SD), y	73.5 (2.8)	73.4 (2.8)	73.5 (2.7)	73.8 (3.0)	.01
Women	1211 (55.3)	796 (56.5)	153 (55.4)	262 (51.8)	.19
White race	1292 (58.9)	896 (63.6)	139 (50.4)	257 (50.8)	<.001
Site					
Memphis, TN	1125 (51.3)	704 (49.9)	148 (53.6)	273 (53.9)	.21
Pittsburgh, PA	1067 (48.7)	706 (50.7)	128 (46.4)	233 (46.1)	
Education					
<High school	532 (24.3)	299 (21.2)	79 (28.6)	154 (30.4)	<.001
High school graduate	733 (33.5)	491 (34.8)	86 (31.2)	156 (30.8)	
Postsecondary	922 (42.2)	617 (43.8)	111 (40.2)	194 (38.3)	
Smoking status					
Never	1015 (46.3)	662 (46.9)	120 (43.5)	233 (46.0)	.36
Current	221 (10.1)	145 (10.3)	34 (12.3)	42 (8.3)	
Former	956 (43.6)	603 (42.8)	122 (44.2)	231 (45.7)	
Alcohol, drinks/wk					
<1	1534 (70.3)	969 (69.0)	195 (71.2)	370 (73.4)	.46
1–7	482 (22.1)	317 (22.6)	60 (21.9)	105 (20.8)	
>7	166 (7.6)	118 (8.4)	19 (6.9)	29 (5.8)	
Physical activity, kcal/wk					
<500	1147 (52.3)	697 (49.4)	163 (59.1)	287 (56.7)	.007
500–1499	598 (27.3)	409 (29.0)	67 (24.3)	122 (24.1)	
≥1500	447 (20.4)	304 (21.6)	46 (16.7)	97 (19.2)	
Hypertension	1257 (57.3)	748 (53.0)	165 (59.8)	344 (68.0)	<.001
Diabetes mellitus	292 (13.3)	162 (11.5)	50 (18.2)	80 (15.8)	.002
BMI, mean (SD)	27.4 (4.9)	27.0 (4.7)	28.6 (5.4)	27.9 (5.0)	<.001
Systolic BP, mean (SD)	136 (21)	133 (20)	136 (19)	142 (23)	<.001

Characteristics	No. (%) of Participants				*P* Value
	All (N = 2192)	No ECG Abnormality (n = 1410)	Minor ECG Abnormality (n = 276)	Major ECG Abnormality (n = 506)	
Diastolic BP, mean (SD)	72 (12)	71 (11)	72 (12)	73 (13)	<.001
Cholesterol, mean (SD), mg/dL					
Total	205 (38)	206 (39)	203 (37)	204 (37)	.51
HDL	55 (17)	56 (17)	54 (16)	55 (17)	.09
LDL	123 (34)	123 (35)	122 (35)	122 (33)	.81
Triglycerides, median (IQR)	116 (87–160)	116 (87–159)	120 (87–167)	115 (85–159)	.41
Creatinine, median (IQR), mg/dL	1.0 (0.9–1.1)	1.0 (0.8–1.1)	1.0 (0.9–1.2)	1 (0.9–1.2)	<.001
FRS, mean (SD), %[b]	12.6 (7.3)	12 (7.2)	13.2 (7.4)	13.9 (7.2)	<.001
Categories of FRS, %					
<5.0	297 (13.6)	220 (15.6)	34 (12.3)	43 (8.5)	<.001
5.0–9.9	525 (23.9)	353 (25.0)	62 (22.5)	110 (21.7)	
10.0–19.9	853 (38.9)	535 (38.0)	106 (38.4)	212 (41.9)	
≥20.0	517 (23.6)	302 (21.4)	74 (26.8)	141 (27.9)	
Medication use					
Lipid-lowering	228 (10.4)	138 (9.8)	39 (14.1)	51 (10.1)	.09
ACE inhibitors	272 (12.4)	158 (11.2)	37 (13.4)	77 (15.2)	.06
Hormone therapy in women	285 (23.5)	213 (26.8)	31 (20.3)	41 (15.7)	<.001
Aspirin	411 (18.8)	257 (18.2)	50 (18.1)	104 (20.6)	.50

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; BP, blood pressure; ECG, electrocardiographic; FRS, Framingham Risk Score; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

SI conversions: To convert total, HDL, and LDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; and creatinine to μmol/L, multiply by 88.4.

[a] See "Methods" section for definitions of hypertension and minor and major ECG abnormalities. Statistical analysis was by analysis of variance or χ^2 test. Systolic BP was used as a continuous variable. Mann-Whitney rank sum test was performed for triglycerides. Creatinine was used on log-transformed values.

[b] Estimation of 10-year risk of coronary heart disease with information about age, sex, smoking status, total cholesterol, HDL cholesterol, and BP.[21]

Table 2

Incidence Rates and HRs for CHD Events and All-Cause Mortality in Older Adults According to ECG Abnormalities

	No ECG Abnormality (n = 1410)	Minor ECG Abnormality (n = 276)	Major ECG Abnormality (n = 506)	Any ECG Abnormality (n = 782)
CHD events (n = 351)[a]				
Rate per 1000 person-years (95% CI)	17.2 (14.8–19.8)	29.3 (22.2–38.0)	31.6 (26.0–38.0)	30.8 (26.3–35.8)
CVRFs, adjusted HR (95% CI)[b]	1.00	1.35 (1.02–1.81)	1.51 (1.20–1.90)	1.64 (1.32–2.03)
Multivariate-adjusted HR (95% CI)[c]	1.00	1.39 (1.04–1.85)	1.47 (1.16–1.86)	1.63 (1.31–2.02)
All-cause mortality (n = 602)				
Rate per 1000 person-years (95% CI)	31.0 (27.9–34.3)	32.9 (25.9–41.3)	37.8 (32.1–44.2)	36.1 (31.1–41.0)
CVRFs, adjusted HR (95% CI)[b]	1.00	0.95 (0.75–1.22)	1.17 (0.97–1.41)	1.11 (0.94–1.31)
Multivariate-adjusted HR (95% CI)[c]	1.00	0.97 (0.76–1.24)	1.09 (0.90–1.31)	1.06 (0.89–1.25)

Abbreviations: CHD, coronary heart disease; CVRFs, cardiovascular risk factors; ECG, electrocardiographic; HRs, hazard ratios.

[a] Includes acute myocardial infarction, coronary death, hospitalization for angina, angioplasty of coronary arteries, and coronary artery bypass graft surgery.

[b] Adjusted for age, sex, total and high-density lipoprotein cholesterol, systolic blood pressure, smoking, and diabetes.

[c] Adjusted for CVRFs (including age, sex, total and high-density lipoprotein cholesterol, systolic blood pressure, smoking, and diabetes) and race, education, site, low-density lipoprotein (LDL) cholesterol, creatinine (as natural logarithm), alcohol consumption, physical activity, statins, angiotensin-converting enzyme inhibitors, and estrogen use. A total of 2168 participants analyzed (23 participants with missing data for LDL cholesterol, 10 for alcohol consumption, 5 for education, and 1 for creatinine, resulting in 24 participants with 1 or more missing values excluded from the multivariate analysis).

Table 3

Predicted Risk of CHD Events Using a Multivariate Risk Prediction Model With and Without Inclusion of ECG Data[a]

	Model With ECG				
	Frequency, %				
Model Without EGC	<7.5	7.5–<15.0	≥15.0	Total	Rate Reclassified, %[b]
Participants who experience a CHD event, %					
<7.5	4	2	0	6	
7.5–<15.0	7	91	27	125	
≥15.0	0	25	195	220	
Total	11	118	222	351	−0.9
Participants who do not experience a CHD event, %					
<7.5	74	17	0	91	
7.5–<15.0	129	678	149	956	
≥15.0	0	189	605	794	
Total	203	884	754	1841	8.3

Abbreviations: CHD, coronary heart disease; ECG, electrocardiographic.

[a] Net reclassification improvement (sum of the percentages of correctly reclassified participants with and without CHD events): 7.4%; 95% CI, 3.1%–19.0%. Identification discrimination improvement: 0.99%; 95% CI, 0.32%–2.15%.

[b] Proportion of all participants who were “correctly” reclassified minus the proportion of each group reclassified in the “wrong” direction.

Table 4

Hazard Ratios (HRs) for Incidence of CHD Events in Older Adults According to the Presence of Any ECG Abnormality at Baseline and Any Incident and Persistent ECG Abnormalities at Follow-up[a]

	No ECG Abnormality (n = 902)	Abnormality at Baseline Only (n = 144)	Persistent Abnormality at 4-Year Follow-up (n = 416)	New Abnormality at 4-Year Follow-up (n = 208)	*P* Value[b]
CHD events (n = 185)[c]					
No. of events	77	18	57	33	
Rate per 1000 person-years (95% CI)	16.5 (12.3–20.6)	24.9 (14.7–39.2)	27.8 (21.0–36.0)	33.2 (22.8–46.6)	
Age-adjusted HR (95% CI)	1.00	1.51 (0.90–2.52)	1.66 (1.18–2.34)	2.01 (1.33–3.02)	.003
CVRFs, adjusted HR (95% CI)[d]	1.00	1.43 (0.85–2.39)	1.52 (1.07–2.16)	1.97 (1.31–2.96)	.01
All-cause mortality (n = 348)					
No. of events	172	22	100	54	
Rate per 1000 person-years (95% CI)	32.2 (27.6–37.4)	25.8 (16.2–39.0)	41.4 (33.7–50.3)	45.9 (34.4–59.9)	
Age-adjusted HR (95% CI)	1.00	0.83 (0.53–1.29)	1.25 (0.98–1.61)	1.45 (1.07–1.97)	.01
CVRFs, adjusted HR (95% CI)[d]	1.00	0.77 (0.49–1.20)	1.19 (0.92–1.53)	1.40 (1.03–1.91)	.02

Abbreviations: CHD, coronary heart disease; CVRFs, cardiovascular risk factors; ECG, electrocardiographic.

[a] Any ECG abnormality indicates major and/or minor ECG abnormality. Inclusion of 1670 participants without events during first 4 years of follow-up and ECG data at baseline and 4-year follow-up only.

[b] *P* value for linear trend across no abnormality, abnormality at baseline, and persistent abnormality at follow-up.

[c] Includes acute myocardial infarction, coronary death, hospitalization for angina, angioplasty of coronary arteries, and coronary artery bypass graft surgery.

[d] Adjusted for age, sex, total and high-density lipoprotein cholesterol, systolic blood pressure, smoking, and diabetes.