CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Electrocardiographic Abnormalities and Reclassification of Cardiovascular Risk: Insights from NHANES-III

Apurva O. Badheka, MD,[a,1] Nileshkumar Patel, MD,[a,1] Tushar A. Tuliani, MD,[b,1] Ankit Rathod, MD,[c] George R. Marzouka, MD,[a] Sandip Zalawadiya, MD,[b] Abhishek Deshmukh, MD,[d] Mauro Moscucci, MD,[a] Mauricio G. Cohen, MD[a]

[a]University of Miami Miller School of Medicine, Miami, Fla; [b]Wayne State University/Detroit Medical Center, Detroit, Mich; [c]Cedars-Sinai Medical Center, Los Angeles, Calif; [d]University of Arkansas, Little Rock.

ABSTRACT

BACKGROUND: We aimed to assess the additive value of electrocardiogram (ECG) findings to risk prediction models for cardiovascular disease.

METHODS: Our dataset consisted of 6025 individuals with ECG data available from the National Health and Nutrition Examination Survey-III. This is a self-weighting sample with a follow-up of 79,046.84 person-years. The primary outcomes were cardiovascular mortality and all-cause mortality. We compared 2 models: Framingham Risk Score (FRS) covariates (Model A) and ECG abnormalities added to Model A (Model B), and calculated the net reclassification improvement index (NRI).

RESULTS: Mean age of our study population was 58.7 years; 45.6% were male and 91.7% were white. At baseline, 54.6% of individuals had ECG abnormalities, of which 545 (9%) died secondary to a cardiovascular event, compared with 194 individuals (3.2%) ($P < .01$) without ECG abnormalities. ECG abnormalities were significant predictors of cardiovascular mortality after adjusting for traditional cardiovascular risk factors (hazard ratio 1.44; 95% confidence interval, 1.13-1.83). Addition of ECG abnormalities led to an overall NRI of 3.6% subjects ($P < .001$) and 13.24% in the intermediate risk category. The absolute integrated discrimination index was 0.0001 ($P < .001$).

CONCLUSION: Electrocardiographic abnormalities are independent predictors of cardiovascular mortality, and their addition to the FRS improves model discrimination and calibration. Further studies are needed to assess the prospective application of ECG abnormalities in cardiovascular risk prediction in individual subjects.

© 2013 Elsevier Inc. All rights reserved. • *The American Journal of Medicine (2013) 126, 319-326*

KEYWORDS: ECG screening; Epidemiology; Net reclassification index; Risk score.

The role of the resting 12-lead electrocardiogram (ECG) is well established in cardiology. Per the recommendations of the US Preventive Services Task Force, there is no role for screening subjects at low risk for coronary heart disease with resting or exercise ECG (D recommendation) and insufficient evidence to use it in subjects with increased risk (I recommendation).[1,2] The low prevalence of resting ECG abnormalities in subjects aged <50 years could be the cause of insufficient data supporting its use in cardiovascular risk prediction.[3]

The Framingham Heart Study helped identify traditional cardiovascular risk factors.[4] The INTERHEART study demonstrated that most, but not all, the risk of cardiovascular disease is explained by these traditional risk factors across populations.[5]

Over the past couple of decades, many "novel risk factors" of cardiovascular disease have been identified. Reclassification has been attempted utilizing coronary artery calcium score (CACS), C-reactive protein, and homocysteine, to name a few.[6-8] However, of these novel risk factors, only

Funding: None.

Conflicts of Interest: None.

Authorship: All authors have contributed to the analysis design and oversight, manuscript conception and drafting, statistical analysis, or editorial review of the manuscript, and they have all read and approved the final manuscript.

[1]These authors share equal contribution.

Requests for reprints should be addressed to Mauricio G. Cohen, MD, University of Miami Hospital, 1400 NW 12th Avenue, Suite 1179 Miami, FL 33136.

E-mail address: mgcohen@med.miami.edu

0002-9343/$ -see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjmed.2012.10.020

a handful, like CACS, have proven to be of diagnostic utility in clinical practice.[9]

There is an unmet need for a low-cost, easily available diagnostic tool for further stratifying intermediate-risk (10-year Framingham Risk of 10%-20%) individuals into higher or lower risk strata. Baseline ECG abnormalities suggesting ischemia, ST-T wave changes,[10,11] abnormal Q-QS patterns,[12] and left ventricular hypertrophy by ECG criteria[13] have been associated with cardiovascular events on follow-up.[3,14-16] A study conducted in asymptomatic postmenopausal women showed that minor and major ECG abnormalities are independent predictors of cardiovascular events and mortality.[17] The additive value of ECG abnormalities to cardiovascular risk prediction models has been investigated recently in an elderly population.[18] We hypothesize that the use of ECGs can improve the predictive ability of the Framingham Risk Score Model in the National Health And Nutrition Examination Survey-III (NHANES-III) database, which was a nationwide survey conducted to assess the health and nutrition of adults and children in the US.[19]

CLINICAL SIGNIFICANCE

- Electrocardiography is a low-cost, widely available, easily interpretable tool which is not recommended in screening for cardiovascular disease, as per the US Preventive Services Task Force.
- Baseline resting electrocardiogram (ECG) screening helps reclassify patients in the intermediate-risk category for a 10-year cardiovascular event.
- The addition of baseline resting ECG abnormalities improves the predictive ability of the Framingham Risk Score Model.

METHODS

Design

We performed a secondary analysis of the NHANES-III (1988-1994) to compare survival estimates in subjects with and without any ECG abnormality. The outcome measures were cardiovascular mortality and all-cause mortality. We assessed the additive value of "ECG abnormalities" to risk prediction models for cardiovascular mortality.

Study Sample

Our cohort was selected from all adults enrolled into NHANES-III with ECG data available (n = 8561). To ensure a population without known coronary artery disease or risk equivalent, subjects with a self-reported history of being told by a physician that they have had a heart attack (n = 620), congestive heart failure (n = 164), stroke (n = 228), self-reported history of chest pain suggestive of angina (n = 423), and history of leg pain suggestive of intermittent claudication (n = 54) were excluded. Subjects with self-reported history of diabetes, medication use, or glycohemoglobin levels ≥6.5% (n = 1032) were considered diabetic and excluded. The presence of any of these risk factors would have warranted a baseline point-of-care ECG by a care provider. Subjects with missing follow-up mortality data (n = 2), implanted pacemaker (n = 7), and non-classified ECG (n = 6) also were excluded. Our study population included 6025 participants, with a follow-up period of 13.1 ± 4.1 years (Mean ± SD) and 79,046.8 person-years (**Figure 1**).

ECG Measures

In the NHANES-III, subjects older than 40 years underwent a supine resting 12-lead baseline ECG using the Marquette MAC 12 (Marquette Medical Systems Inc., Milwaukee, Wis) and analyzed using the NOVACODE ECG program, which classified the ECGs as per the Minnesota Coding (MC) System. The details have been discussed previously elsewhere.[20]

Definitions

ECG abnormalities were defined as the presence of major and minor ECG abnormalities by the MC, possible or probable myocardial infarction by the MC, cardiac infarction/injury score of ≥10, possible or probable left ventricular hypertrophy by the MC, any axis deviation, and any rhythm abnormalities other than sinus (**Supplementary Table 1**). Individuals without the aforementioned abnormalities were considered to have no ECG abnormalities at baseline.

We used strict definitions for hypertension, which included self-reported history or use of antihypertensive medication(s) or systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg on physical examination. Similarly, hypercholesterolemia was defined as self-reported history or use of lipid-lowering medication or LDL-cholesterol values above the normal cutoff as per the National Cholesterol Education Program guidelines.[21] Serum LDL cholesterol was calculated as: LDL cholesterol = Total cholesterol − HDL cholesterol − (0.20 × Serum triglycerides).

Outcome Measures

The primary outcomes were cardiovascular and all-cause mortality. Mortality status was obtained from the NHANES-III-linked mortality file with mortality data provided until December 31, 2006.[13,22] In the present study, underlying cause of death for 24 subjects was unknown. The underlying causes of death were provided by death certificate data contained in the mortality files and classified according to the 10th revision of the International Classification of Diseases (ICD-10). Cardiovascular mortality was defined by ICD-10 codes I00-I99, which included deaths secondary to ischemic heart disease, hypertensive

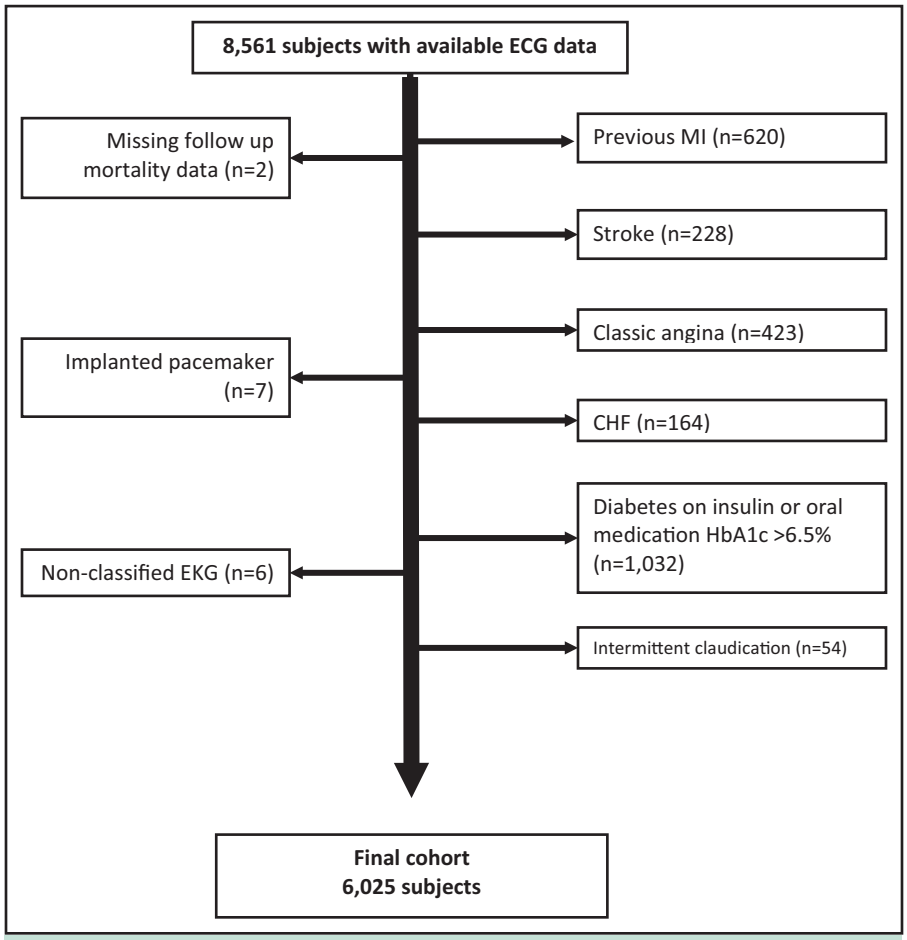

Figure 1 Flowchart for cohort selection.
ECG = electrocardiogram; MI = myocardial infarction; CHF = congestive heart failure.

heart disease, and cerebrovascular diseases[23] (**Supplementary Table 2**).

Statistical Analysis

NHANES-III had a complex nonrandom multistage stratified sample design.[19] Analyses were performed using the designated weighting specified in the NHANES-III dataset to minimize biases. We used the total NHANES-III pseudo-stratum as our strata variable, the total NHANES-III pseudo-primary sampling units as our survey sampling units, and the total mobile examination center final weight as our sampling unit weight.[24]

Differences in baseline characteristics were examined using simple linear regression for continuous variables and chi-squared test for categorical variables.

The sample was divided into 2 groups according to the presence or absence of ECG abnormalities. Kaplan-Meier survival analysis was used to evaluate differences in all-cause and cardiovascular mortality between these 2 groups. Univariate and multivariate Cox proportional hazard regression models were built to calculate the hazard ratio of all-cause and cardiovascular mortality for all possible predictors. A P-value of $<.05$ was considered significant. Missing data in the covariates were imputed based on 10 sets of simulated values generated from nonmissing variables using the multiple imputation method. STATA SE 11.1 (StataCorp LP, College Station, Tex) was used for performing the statistical analysis.

Calibration, Discrimination, and Clinical Net Reclassification Index (NRI)

We compared 2 models: Framingham Risk Score (FRS) covariates, which include age, sex, systolic blood pressure, smoking history, serum cholesterol level, and serum high-density lipoprotein level (Model A), and ECG abnormalities added to the FRS covariates (Model B). Because Model B was a "special case" of Model A, we used the likelihood ratio test to assess the differences in global measure of model fit. The Bayes Information Criterion (BIC) (lower values imply better fit) was calculated to evaluate the improvement in the global measure of model fit after addition of ECG abnormalities to Model A. BIC is a likelihood-based measure that takes into account the number of vari-

ables in the predictive model and prefers a model with fewer variables if it provides equally good prediction.[25]

In order to test the ability of the new model to distinguish those who develop a cardiovascular-related event from those who do not (discrimination), we used the Harrell's concordance c-statistic, wherein larger values imply better discrimination.[26,27] Harrell's c-statistics for these 2 models were compared with bootstrap sampling. In order to test the ability of the new model to predict the risk of future events (calibration), we calculated the Hosmer-Lemeshow statistic (chi-squared value >20 and P value <.01 implies lack of calibration).[28]

Clinical re-stratification helps in comparing the new model, which includes the preexisting model, with the added variable. We calculated predicted 10-year risk estimates based on both models for all study participants with available data (n = 5729) and directly compared with the actual risk observed during follow-up period. A score of 1 is assigned to every correct reclassification, which implies that every individual who experiences an event or nonevent is upgraded or downgraded in the risk category, respectively. A score of −1 is assigned to every incorrect classification based on the aforementioned criteria. A score of 0 is assigned to every "non-reclassification."[26] The Integrated Discrimination Index (IDI) was calculated, which is the difference in the integral of sensitivity and one minus specificity over all possible cutoff values.[26] This is the measure of improvement imparted by the ECG abnormalities to the FRS model.

RESULTS

Baseline Characteristics

The baseline characteristics of the 6025 healthy individuals are displayed in **Table 1**. The mean age of our study population was 58.7 years. In our study, 45.6% were male and 8.3% were black.

ECG Abnormalities

At baseline, 3291 (54.6%) individuals demonstrated ECG abnormalities. Subjects with ECG abnormalities at baseline were significantly (P <.05) older, more likely to be male and black, and had a higher proportion of subjects with a history of hypertension, hypercholesterolemia, and current smoking (**Table 1**).

Mortality

A total of 1824 (30.3%) subjects died during the mean follow-up period, of which 739 (12.3%) deaths could be attributed to cardiovascular events. There were 545 (9.0%) and 194 (3.3%) (P <.01) cardiovascular deaths in people with and without ECG abnormalities, respectively. **Figures 2** and **3** display the survival curves according to the presence of baseline ECG abnormalities, showing a significant difference in cardiovascular and all-cause mortality in the 2 groups (log-rank P <.01). On multivariable analysis, age, male sex, black race, hypertension, current smoking, and ECG abnormalities were significant predictors of cardiovascular mortality. The hazard ratios (95% confidence interval) for cardiovascular and all-cause mortality for ECG abnormalities were 1.43 (1.13-1.84, P = .004) and 1.38 (1.2-1.57, P <.01), respectively, after adjusting for demographic variables and traditional cardiovascular risk factors (**Supplementary Table 3**).

Table 1 Baseline Characteristics

Variable	Any ECG Abnormalities Absent (n = 2734)	Any ECG Abnormalities Present (n = 3291)
Demographics		
Age (years)*, Mean ± SD	54.97 ± 12.43	61.81 ± 13.71
Male sex*†	43.1	48.1
Race*†		
White	89.1	87.4
Black	6.9	9.8
Other	4	2.8
Measurements		
Body mass index (Kg/m^2), Mean ± SD‡	27.10 ± 4.91	27.23 ± 5.59
Past history		
Hypertension*†	31.6	47.4
Current smoker*†	20.1	25.6
Family history of myocardial infarction before the age 50†	9.5	10.5
History of hypercholesterolemia*†	56	59.9
Laboratory parameters, Mean ± SD		
Serum cholesterol§	215.46 ± 42.26	217.64 ± 43.15
Serum HDL cholesterol§	52.19 ± 15.97	52.12 ± 16.58
Serum triglycerides§	145.82 ± 101.90	150.01 ± 102.32
Serum LDL cholesterol§‖	135.43 ± 38.03	136.49 ± 38.96
Glomerular filtration rate*¶	66.77 ± 19.62	64.03 ± 21.34
Serum potassium**	4.06 ± 0.31	4.06 ± 0.36
Serum normalized calcium**	1.23 ± 0.05	1.23 ± 0.05

*P value <.05.

†Expressed as a percentage.

‡Body mass index is in weight in kilograms divided by the square of the height in meters.

§Expressed in milligrams per deciliter.

‖Serum LDL cholesterol was calculated by the following formula: LDL cholesterol = Total cholesterol − HDL cholesterol − (0.20 × serum triglycerides).

¶Modification of Diet in Renal Disease Study (MDRD) formula was used to calculate glomerular filtration rate (GFR). $GFR = 186 * (\text{serum creatinine})^{-1.154} * (\text{age})^{-0.203} * 1.210$ (for African American) * 0.742 (for female). GFR is in mL/min/1.73 m^2 BSA (body surface area).

**Serum potassium and serum normalized calcium are expressed in millimole per liter. Normalized calcium value derived from adjusting the measured ionized calcium for pH (Laboratory Procedures Used for NHANES III).[29]

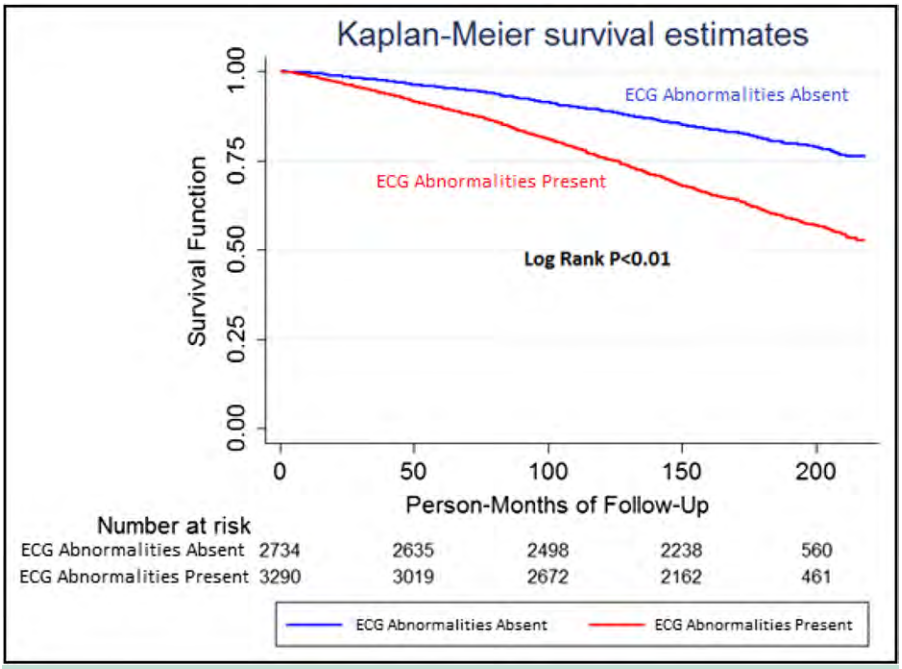

Figure 2 Kaplan-Meier curves for all-cause mortality in subjects with and without electrocardiogram (ECG) abnormalities.

Reclassification

In order to calculate the net reclassification improvement index (NRI), we divided the data on the basis of 10-year risk of a cardiovascular event into the following categories: <5%, 5%-10%, 10%-20%, and >20%. The addition of the ECG abnormalities to the FRS model led to an overall NRI of 3.6% ($P = .0001$) in the entire cohort and 13.24% in the intermediate risk cohort (**Table 2**). Furthermore, in the intermediate risk category, 137 (2.4%) and 187 (3.3%) individuals were reclassified to higher and lower risk

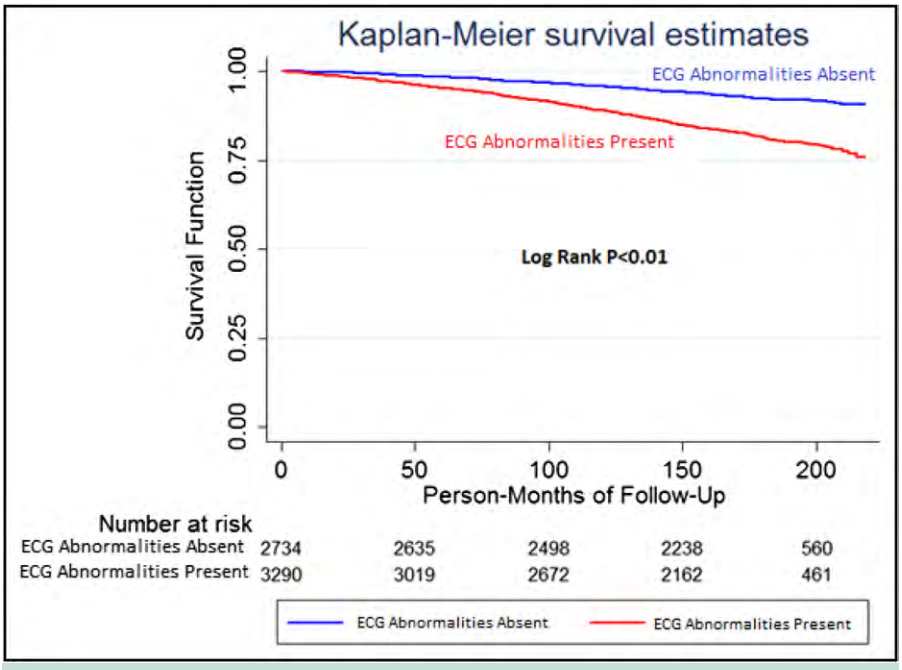

Figure 3 Kaplan-Meier curves for all cardiovascular mortality in subjects with and without electrocardiogram (ECG) abnormalities.

Table 2 Net Reclassification Index with and without ECG Abnormalities

	Model B†					Risk Reclassified	
Model A*	<5%	5%-10%	10%-20%	>20%	Total	Higher	Lower
Events							
<5%	92	11	0	0	103	11 (10.7%)	NA
5% to <10%	4	98	26	0	128	26 (20.3%)	4 (3%)
10% to <20%	0	14	205	21	240	21 (8.8%)	14 (5.8%)
≥20%	0	0	19	208	227	NA	19 (8.4)
Total	96	123	250	229	698	58 (8.3%)	37 (5.3%)
NRI for events							3.0% ($P = .03$)
No events							
<5%	3209	79	0	0	3288	79 (2.4%)	NA
5% to <10%	104	702	53	0	859	53 (6.2%)	104 (12.1%)
10% to <20%	0	65	512	37	614	37 (6.0%)	65 (10.6%)
≥20%	0	0	31	239	270	NA	31 (11.5%)
Total	3313	846	596	276	5031	169 (3.4%)	200 (4.0%)
NRI improvement for nonevents							0.6% ($P = .11$)
NRI improvement overall							3.6% ($P < .001$)

ECG = electrocardiogram; NRI = net reclassification improvement index.

*Model A was adjusted for only traditional risk factors, which include age, sex, systolic blood pressure, smoking history, serum cholesterol level, and serum high density lipoprotein level.

†Model B was adjusted for all the variables in model A plus any ECG abnormalities.

groups, respectively, of which 47 (25.6%) and 18 (9.6%), respectively, experienced death secondary to a cardiovascular cause. The absolute IDI was 0.0001 (*P*-value for improvement = .0007) (**Table 3**).

The c-statistic improved from 0.851 (0.836-0.865) to 0.852 (0.838-0.866) ($P = .05$) with the addition of ECG abnormalities to the FRS model, indicating improved discrimination of Model B over Model A. Similarly, the BIC decreased from 3360.54 to 3358.28 and the Hosmer-Lemeshow chi-squared value decreased from 15.14 to 10.98 (*P* value, Model A: 0.05, Model B: 0.2), representing improved global measure of model fit and calibration, respectively. The *P* value for the likelihood ratio test was .001.

Table 3 Comparison of Models with and without ECG Abnormalities

Tests	Model A*	Model B†	*P* Value
Tests for discrimination			
C-statistic	0.851	0.852	.05
Absolute IDI	<.001		<.001
Tests for calibration			
Hosmer-Lemeshow χ^2	15.14	10.98	–
Tests for Goodness of Fit			
Likelihood ratio test	.001		–
Bayesian Information Criterion	3360.54	3358.28	–

ECG = electrocardiogram; IDI = Integrated Discrimination Index.

*Model A was adjusted for only traditional risk factors, which include age, sex, systolic blood pressure, smoking history, serum cholesterol level, and serum high density lipoprotein level.

†Model B was adjusted for all the variables in model A plus any ECG abnormalities.

DISCUSSION

Screening for cardiovascular disease is based on prognostic models, such as the Framingham and Reynolds Risk scores, as opposed to screening tests for other diseases (Pap smear for cervical cancer, colonoscopy for colon cancer), which are based on diagnostic studies.[30]

Per our findings, ECG abnormalities were independently associated with adverse cardiovascular and all-cause mortality in a nationally representative population. Our study demonstrates that the mortality risk associated with ECG abnormalities is similar to that associated with known traditional risk factors like age, smoking, hypertension, diabetes, dyslipidemia, and family history of myocardial infarction.

The addition of ECG abnormalities to the FRS model resulted in overall NRI of 3.6%, and 13.24% in the intermediate risk category. The NRI was more balanced in the intermediate risk category. The mere association of a biomarker with cardiovascular disease is not sufficient.[26] Novel statistical tools like NRI and IDI add practical utility to mere numbers and statistical tests. NRI is superior to area under the receiver operating curve in assessing the additive value of a novel biomarker to an existing validated risk prediction model.[30]

Clinical Utility of ECG Abnormalities

For subjects who are in the lowest risk category of 10-year cardiovascular event (<10%), doubling of their risk would fail to upgrade them to a higher category.[2] Subjects in the highest risk category of 10-year cardiovascular event (>20%) would be unlikely beneficiaries of ECG screening. Individuals in the intermediate risk category of 10-year

cardiovascular event (>10% to <20%) would be most likely to benefit from ECG screening, as it would help reclassify them to higher or lower risk strata, where preventive measures are better delineated. On the downside, screening and reclassifying patients with ECG might precipitate further testing, which could be a cause for concern.[2]

Our results are comparable with the NRI of 5.3%, with the inclusion of highly sensitive C-reactive protein, and parental history of myocardial infarction before age 60 years in the Reynold's Risk Score for men (end-point of all-cardiovascular events), and NRI of 20.2% in the intermediate risk category.[7] Other studies have attempted risk reclassification and demonstrated higher or lower reclassification percentages than those in our study.[6,8] Of note is the commendable NRI achieved by the incorporation of CACS in the FRS model, resulting in an overall NRI of 25% and an NRI of 55% in the intermediate risk category.[6] However, the utility of CACS needs to be assessed in view of the inherent risks of radiation exposure and high costs.[31,32] Variations in the NRI between studies should be interpreted with prudence, as the values vary depending on the cut-points used to define risk categories and population characteristics.[33]

Auer et al[18] recently demonstrated an overall NRI of 7.4%, and 13.6% in the intermediate risk category, with the addition of ECG abnormalities to traditional cardiovascular risk factors in an elderly population. The main outcome in their study included myocardial infarction, death secondary to coronary heart disease, and hospital admission for angina or coronary intervention. We utilized the NHANES-III dataset, which is larger, nationally representative, includes individuals 40 years and older, and had a longer follow-up. However, NHANES-III did not include a follow-up ECG to elucidate changes in the ECG abnormalities captured at the initiation of the study and lacked information on interval myocardial infarction, angina, and coronary revascularization. In addition to the ECG abnormalities included by Auer et al,[18] we also included axis deviations, probable/possible myocardial infarction, artificial pacemaker, ST elevation, minor Q waves, minor T-wave codes, prolonged PR interval, RR' in chest lead V1 and V2, and left anterior fascicular block (**Supplementary Table 1**).

Our study adds to the wealth of data being gathered in "remodeling of risk prediction models." The use of MC to classify ECG into watertight compartments based on predetermined criteria helped maintain uniformity and eliminate interpreter variability.[34]

Limitations

Despite the benefit of a large nationally representative dataset and using strict definitions and ECG classification, our study had some drawbacks. The endpoint of Adult Treatment Panel-III FRS is nonfatal myocardial infarction, angina, and death secondary to coronary heart disease.[21] We did not have data on nonfatal myocardial infarction, angina, and interval revascularization procedures (percutaneous coronary intervention/coronary artery bypass graft) on the study subjects. It has been established that ECG-interpreting software like the NOVACODE assign "severer MC with similar prognostic importance" when compared with human ECG interpretation.[35] We did not control for medication use, which could modify the disease process being studied. We could not account for diseases developing in the follow-up period.

Our outcome measures were dependent on diagnoses mentioned on the death certificate. Although the accuracy of the cause of death could be a concern, vital status and date of death were documented accurately and have been used in other epidemiologic studies.[36]

CONCLUSION

ECG is a widely available, low-cost tool. There is a paucity of prospective randomized controlled trials for evaluating the utility of ECG data in prevention and guiding intervention. Our study supports further investigation in the utility of ECG screening in healthy populations.

Part of the findings discussed here were presented as a poster presentation at American College of Cardiology 2012, Chicago, Ill.[37]

References

1. Screening for coronary heart disease: recommendation statement. *Ann Intern Med*. 2004;140:569-572.
2. Chou R, Arora B, Dana T, et al. Screening asymptomatic adults with resting or exercise electrocardiography: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011;155: 375-385.
3. Strom Moller C, Zethelius B, Sundstrom J, Lind L. Persistent ischaemic ECG abnormalities on repeated ECG examination have important prognostic value for cardiovascular disease beyond established risk factors: a population-based study in middle-aged men with up to 32 years of follow-up. *Heart*. 2007;93:1104-1110.
4. Kannel WB, Anderson K, McGee DL, et al. Nonspecific electrocardiographic abnormality as a predictor of coronary heart disease: the Framingham Study. *Am Heart J*. 1987;113:370-376.
5. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-952.
6. Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA*. 2010;303:1610-1616.
7. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation*. 2008;118: 2243-2251, 4p following 2251.
8. Veeranna V, Zalawadiya SK, Niraj A, et al. Homocysteine and reclassification of cardiovascular disease risk. *J Am Coll Cardiol*. 2011;58: 1025-1033.
9. Hochholzer W, Morrow DA, Giugliano RP. Novel biomarkers in cardiovascular disease: update 2010. *Am Heart J*. 2010;160:583-594.
10. De Bacquer D, De Backer G, Kornitzer M, Blackburn H. Prognostic value of ECG findings for total, cardiovascular disease, and coronary heart disease death in men and women. *Heart*. 1998;80:570-577.
11. Badheka AO, Rathod A, Marzouka GR, et al. Isolated nonspecific ST-segment and T-wave abnormalities in a cross-sectional United States population and mortality (from NHANES III). *Am J Cardiol*. 2012;110:521-525.
12. Caird FI, Campbell A, Jackson TF. Significance of abnormalities of electrocardiogram in old people. *Br Heart J*. 1974;36:1012-1018.

13. Larsen CT, Dahlin J, Blackburn H, et al. Prevalence and prognosis of electrocardiographic left ventricular hypertrophy, ST segment depression and negative T-wave; the Copenhagen City Heart Study. *Eur Heart J*. 2002;23:315-324.
14. Daviglus ML, Liao Y, Greenland P, et al. Association of nonspecific minor ST-T abnormalities with cardiovascular mortality: the Chicago Western Electric Study. *JAMA*. 1999;281:530-536.
15. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol*. 1976;38:46-51.
16. Liao Y, Liu K, Dyer A, et al. Sex differential in the relationship of electrocardiographic ST-T abnormalities to risk of coronary death: 11.5 year follow-up findings of the Chicago Heart Association Detection Project in Industry. *Circulation*. 1987;75:347-352.
17. Denes P, Larson JC, Lloyd-Jones DM, et al. Major and minor ECG abnormalities in asymptomatic women and risk of cardiovascular events and mortality. *JAMA*. 2007;297:978-985.
18. Auer R, Bauer DC, Marques-Vidal P, et al. Association of major and minor ECG abnormalities with coronary heart disease events. *JAMA*. 2012;307:1497-1505.
19. National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–94. Series 1: programs and collection procedures. *Vital Health Stat 1*. 1994;(32):1-407.
20. Wu CC, Yeh WT, Crow RS, et al. Comparison of electrocardiographic findings and associated risk factors between Taiwan Chinese and US White adults. *Int J Cardiol*. 2008;128:224-231.
21. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-3421.
22. National Center for Health Statistics, Centers for Disease Control and Prevention.Analytic and Reporting Guidelines: The Third National Health and Nutrition Examination Survey, NHANES III (1988-1994): Linked Mortality File Public use. 1996. Available at: http://www.cdc.gov/nchs/data/datalinkage/nh3_file_layout_public_2010.pdf.).
23. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18-e209.
24. Mohadjer L, Montaquila JM, Waksberg J, et al. *National Health and Nutrition Examination Survey III: Weighting and Estimation methodology*. Hyattsville, MD: Westat Inc. for National Center for Health Statistics; 1996.
25. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York: Springer; 2001.
26. 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*. 2008;27:157-172; discussion 207-112.
27. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29-36.
28. D'Agostino RB, Nam BH. Evaluation of the performance of survival analysis models: discrimination and calibration measures. In: Balakrishnan N, Rao CR, eds. *Handbook of Statistics, 23*. London: Elsevier; 2004.
29. Centers for Disease Control and Prevention (CDC): National Health and Nutrition Examination Survey. NHANES III. Available at: http://www.cdc.gov/nchs/nhanes/nh3data.htm.
30. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem*. 2008;54:17-23.
31. Kim KP, Einstein AJ, Berrington de Gonzalez A. Coronary artery calcification screening: estimated radiation dose and cancer risk. *Arch Intern Med*. 2009;169:1188-1194.
32. O'Malley PG, Greenberg BA, Taylor AJ. Cost-effectiveness of using electron beam computed tomography to identify patients at risk for clinical coronary artery disease. *Am Heart J*. 2004;148:106-113.
33. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30:11-21.
34. Macfarlane PW. Minnesota coding and the prevalence of ECG abnormalities. *Heart*. 2000;84:582-584.
35. Kors JA, Crow RS, Hannan PJ, et al. Comparison of computer-assigned Minnesota Codes with the visual standard method for new coronary heart disease events. *Am J Epidemiol*. 2000;151:790-797.
36. Calle EE, Terrell DD. Utility of the National Death Index for ascertainment of mortality among cancer prevention study II participants. *Am J Epidemiol*. 1993;137:235-241.
37. Badheka AO, Patel N, Tuliani TA, et al. Electrocardiographic Changes and Reclassification of Cardiovascular Risk: Insights from NHANES-III. *J Am Coll Cardiol*. 2012;59:E1761-E1761

Supplementary Table 1 Minnesota Coding of ECG Abnormalities

	Minnesota Codes
Major ECG abnormalities	
Major Q, QS waves	1.1 or 1.2 except 1.2.8
ST-depression	4.1 or 4.2
Negative T-waves	5.1 or 5.2
Complete AV block	6.1
Wolff Parkinson White pattern	6.4
Artificial pacemaker	6.8
Ventricular conduction defect	7.1 or 7.2 or 7.4
Atrial fibrillation or atrial flutter	8.3
ST-elevation	9.2
Minor ECG abnormalities	
Minor Q-waves	1.2.8 or 1.3
High R-waves	3.1 or 3.3
Minor ST-codes	4.3 or 4.4
Minor T-wave codes	5.3 or 5.4
Prolonged PR-interval	6.3
RR' in V1 or V2	7.3 or 7.5
Left anterior fascicular block	7.7
Possible myocardial infarction	
Moderate Q/QS waves without ST-depression or T-wave inversion	1.2.1-1.2.7 without 4.1, 4.2, 5.1, and 5.2
Minor Q/QS waves with ST-depression or T-wave inversion	1.2.8 or 1.3.1-1.3.6 and 4.1, 4.2, 5.1, or 5.2
Probable myocardial infarction	
Major Q/QS waves	1.1.1-1.1.7
Moderate Q/QS waves with ST-depression or T-wave inversion	1.2.1-1.2.7 and 4.1, 4.2, 5.1, or 5.2
Infarction/injury score≥10	—
Left ventricular hypertrophy	
Possible left ventricular hypertrophy	3.1 without 5.1, 5.2 and 5.3, or any code 3.3
Probable left ventricular hypertrophy	3.1 with 5.1, 5.2, or 5.3
Axis	
Left axis deviation	2.1.2
Right axis deviation	2.2.2
Extreme axis deviation	3.3
Borderline left axis deviation	2.1.1
Borderline right axis deviation	2.2.1
Rhythm other than sinus	—

ECG = electrocardiogram.

Supplementary Table 2 ICD codes for Cardiovascular Mortality

Cardiovascular Diseases	ICD Codes
Acute rheumatic fever and chronic rheumatic heart diseases	I00-I09
Essential hypertension, hypertensive heart and kidney diseases	I10-I13
Ischemic heart diseases	I20-I25
Acute and subacute endocarditis	I33
Diseases of pericardium and acute myocarditis	I30-I31, I40
Other heart diseases	I26 to I51
Heart failure	I50
All other forms of heart diseases	I26-I28, I34-I38, I42-49, I51
Cerebrovascular diseases	I60 to I69
Atherosclerosis	I70
Other diseases and disorders of the circulatory system	I71-I78, I80-I99

ICD = International Classification of Diseases.

Supplementary Table 3 Multivariate Predictors of Cardiovascular and All-cause Mortality

Adjusted Hazard Ratios* During the Follow-up Period of 13.12 ± 4.12 Years

	CVD-Related Mortality		All-Cause Mortality	
Variables	Hazard Ratio (95% CI) (n = 739)	*P* Value	Hazard Ratio (95% CI) (n = 1824)	*P* Value
Age	1.13 (1.11-1.14)	<.01	1.11 (1.10-1.12)	<.01
Male sex	1.40 (1.16-1.68)	.001	1.48 (1.34-1.63)	<.01
White race	1.45 (0.60-3.51)	.41	1.26 (0.79-2.01)	.33
Black race	1.86 (0.72-4.78)	.20	1.48 (0.93-2.33)	.1
Hypertension	1.68 (1.30-2.16)	<.01	1.30 (1.10-1.52)	.003
Current smoker	2.05 (1.50-2.76)	<.01	2.53 (2.11-2.99)	<.01
Hypercholesterolemia	1.22 (0.98-1.50)	.07	1.34 (1.18-1.52)	<.01
GFR	0.99 (0.98-1.00)	.01	1.00 (0.99-1.00)	.20
Any ECG abnormalities	1.43 (1.13-1.84)	.004	1.38 (1.20-1.57)	<.01

CVD = cardiovascular disease; CI = confidence interval; GFR = glomerular filtration rate; ECG = electrocardiogram.

*Here multivariate model was adjusted for age, sex, race, hypertension, smoking, hypercholesterolemia, glomerular filtration rate, and any ECG abnormalities.