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Journal
American Heart Journal, 167(6)

ISSN
0002-8703

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Publication Date
2014-06-01

DOI
10.1016/j.ahj.2014.03.020

Peer reviewed

Published in final edited form as:
Am Heart J. 2014 June ; 167(6): 869–875.e3. doi:10.1016/j.ahj.2014.03.020.

Association of electrocardiogram abnormalities and incident heart failure events

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Abstract

Background—Unless effective preventive strategies are implemented, aging of the population will result in a significant worsening of the heart failure (HF) epidemic. Few data exist on whether baseline electrocardiographic (ECG) abnormalities can refine risk prediction for HF.

Methods—We examined a prospective cohort of 2,915 participants aged 70 to 79 years without preexisting HF, enrolled between April 1997 and June 1998 in the Health, Aging, and Body Composition (Health ABC) study. Minnesota Code was used to define major and minor ECG abnormalities at baseline and at year 4 follow-up. Using Cox models, we assessed (1) the association between ECG abnormalities and incident HF and (2) the incremental value of adding ECG to the Health ABC HF Risk Score using the net reclassification index.

Results—At baseline, 380 participants (13.0%) had minor, and 620 (21.3%) had major ECG abnormalities. During a median follow-up of 11.4 years, 485 participants (16.6%) developed incident HF. After adjusting for the Health ABC HF Risk Score variables, the hazard ratio (HR) was 1.27 (95% CI 0.96–1.68) for minor and 1.99 (95% CI 1.61–2.44) for major ECG abnormalities. At year 4, 263 participants developed new and 549 had persistent abnormalities; both were associated with increased subsequent HF risk (HR 1.94, 95% CI 1.38–2.72 for new and HR 2.35, 95% CI 1.82–3.02 for persistent ECG abnormalities). Baseline ECG correctly reclassified 10.5% of patients with HF events, 0.8% of those without HF events, and 1.4% of the overall population. The net reclassification index across the Health ABC HF risk categories was 0.11 (95% CI 0.03–0.19).

Conclusions—Among older adults, baseline and new ECG abnormalities are independently associated with increased risk of HF. The contribution of ECG screening for targeted prevention of HF should be evaluated in clinical trials.

The prevalence of heart failure (HF) is rising, especially in older adults,[1] and remains one of the most frequent causes of hospitalization in persons older than 65 years.[2–4] Most HF research focuses on treatment of patients with manifest HF, but few studies have assessed the prediction of incident HF hospitalization in primary prevention.[5,6] The guidelines emphasize the importance of identifying subjects at risk for HF at an early stage and controlling risk factors such as hypertension, diabetes, metabolic syndrome, and atherosclerotic disease.[7,8] Subclinical changes in cardiac structure and function often precede clinical manifestations of HF and may alter the morphology of electrocardiographic (ECG) recording.[9]

Although it remains controversial whether screening ECG should be routinely done in clinical practice,[10] we[11] and others[12,13] have shown that resting ECG abnormalities are (1) common among older individuals, (2) associated with incident coronary heart disease (CHD), and (3) improve the prediction of CHD events beyond traditional risk factors.[11] In contrast, few studies have examined the association between ECG abnormalities and incident HF,[14–17] and no study has specifically assessed (1) the impact of ECG changes on HF risk in older adults, (2) the association between dynamic ECG changes and HF risk over time, and (3) the impact of ECG on net reclassification of HF risk beyond traditional risk factors.[5] In this study, we sought to assess the association between baseline major and minor ECG abnormalities and the risk of incident HF among older adults in the Health, Aging, and Body Composition Study ABC (Health ABC) as well as the risks associated with dynamic ECG changes over time. We also evaluated the impact of ECG on reclassification in the Health ABC HF Risk Score.[5]

Methods

Study design and population

We analyzed data from the Health ABC study, a prospective cohort study of 3,075 community-dwelling men and women aged 70 to 79 years enrolled between April 1997 and June 1998 and who were without overt physical disability at enrollment. Participants were identified from a sample of white and black Medicare-eligible adults living in designated zip coded areas surrounding Pittsburgh, PA, and Memphis, TN. Details of eligibility and exclusion criteria have been previously described.[18] All participants gave written informed consent, and the local institutional review boards approved the protocol. We excluded participants with preexisting HF (97 participants), those with missing baseline HF data (43 participants), those with a pacemaker (19 participants), and those with missing baseline ECG data (1 participant). The final sample consisted of 2,915 participants.

Electrocardiographic classification

As previously described,[11] standardized procedures were used at all clinical centers for the recording of the 12-lead resting ECGs at baseline and at the year 4 follow-up visit. Briefly, 2 trained coders read ECG records, and cases with discrepancies were resolved by a third

senior coder. All ECGs were assessed according to the Minnesota Code, as in previous large prospective cohorts.[11,13,19–22] Electrocardiographic abnormalities were classified into minor and major abnormalities, as previously described.[11–13,21] Minor baseline ECG abnormalities were defined as any minor ST-segment or T-wave abnormalities. Criteria for major baseline ECG abnormalities were any of the following: (1) Q-QS wave abnormalities, (2) major ST-T abnormalities, (3) left ventricular hypertrophy (LVH), (4) atrial fibrillation or atrial flutter, (5) Wolff-Parkinson-White, (6) complete bundle-branch block or intraventricular block (Supplementary Table I). Participants with both minor and major abnormalities were classified as having major ECG abnormalities. A random sample of 5% of baseline ECG underwent the same coding process to assess reproducibility of the readings. κ Values for the categorization described above were 0.90 for major, 0.81 for minor, and 0.82 for no abnormalities. At year 4, we analyzed repeat ECG data among 2,300 participants. From the baseline sample of 2,915 participants, 212 died within the first 4 years of non-HF causes. In addition, we excluded 59 participants who had interim HF events and 396 participants who had no available data on ECG.

Incident HF

All participants were contacted every 6 months to report any cardiovascular events.[18] *Incident HF* was defined as any overnight hospitalization related to HF among participants without HF at baseline. The presence of clinical HF at baseline was based on self-reported history, use of selected drugs, and 5-year review of Medicare data.[23] The HF criteria required at least a diagnosis of HF from a physician and treatment for HF, including current prescription for a diuretic agent and either digitalis or vasodilator or β-blocker. Clinicians at each center adjudicated HF events based on symptoms, clinical signs, chest x-ray, and echocardiographic findings, using criteria similar to those used in the Cardiovascular Health Study.[24] The available data on left ventricular ejection fraction (LVEF), as assessed by echocardiography or left ventriculography, were abstracted from medical records during the index hospitalization for HF events. *Follow-up time* was defined as the time from baseline ECG to the first HF event, death, or last contact date.

Covariates definition

The Health ABC HF Risk Score was developed in the Health ABC[5] Study and validated in the Cardiovascular Health Study to assess the 5-year risk of HF among older adults.[25] The model had a C-statistic of 0.73 in the derivation data set, 0.72 by internal validation, and 0.74 in the external validation data set. The Health ABC Risk Score classifies patients into 4 groups of 5-year HF risk (<5%, 5%–10%, 10%–20%, >20%) and includes the following variables: age, smoking, systolic blood pressure, CHD at baseline, heart rate, fasting glucose, LVH, serum albumin, and creatinine.

Statistical analysis

Differences in proportions and mean of covariates across participants with and without incident HF events during follow-up were assessed using χ^2 and analysis of variance statistics, respectively. For covariates that were not normally distributed, median values with interquartile ranges were reported and compared with the use of Mann-Whitney *U* statistics.

We used Cox proportional hazards models to assess the association between ECG abnormalities and HF events in multivariate analyses. We examined the proportionality of hazards using graphical methods and Schoenfeld residual tests. A Fine-Gray competing risks models treating all-cause mortality as a competing risk for HF were used to estimate cumulative HF incidence curves.[26] Estimates were adjusted for a number of confounders in 3 nested models including (1) age and sex; (2) Health ABC HF Risk Score variables[5]; and (3) in secondary analyses self-reported race, total cholesterol, body mass index, alcohol intake, and cardiovascular medications. We did not include LVH in the multivariate models because LVH was already included as a major ECG abnormality according to Minnesota Code. Sensitivity analyses including LVH in multivariate models showed similar results. To explore the impact of CHD on the association between ECG abnormalities and HF, we performed subgroup analyses according to preexisting CHD at baseline defined as the combination of possible and definite CHD. In a secondary analysis, we evaluated the association between ECG abnormalities and HF events with reduced (≤45%) versus preserved (>45%) LVEF.

For the reclassification analysis, we censored follow-up participants at 5 years as previously described.[5] We classified participants into 4 groups of HF risk (<5%, 5%–10%, 10%–20%, and >20%) according to the Health ABC HF Risk Score.[5] We assessed the reclassification among HF events and nonevents, as well among the overall population. We evaluated the net reclassification improvement (NRI) as described by Pencina et al[11,27–30] across categories with the addition of any ECG abnormality (minor or major). This method weighs the reclassification rates for events and nonevents equally. All analyses were performed with Stata version 12.1 (StataCorp, College Station, TX) and R version 2.13.0 (Project for Statistical Computing, http://www.r-project.org/). All tests were 2-sided, and $P < .05$ was considered statistically significant. The National Institute of Aging funded the Health ABC Study, reviewed the manuscript, and approved its publication.

The authors are solely responsible for the design and conduct of this analysis, all study analyses, and drafting and editing of the manuscript.

Results

Baseline characteristics

Among 2,915 participants without preexisting HF, 1,915 (65.7%) had no ECG abnormalities, 380 (13.0%) had minor ECG abnormalities, and 620 (21.3%) had major ECG abnormalities (Table I). The mean age was 73.6 years, 52.2% of participants were women, 41.3% were black, and 19.4% had baseline CHD. Participants with any ECG abnormality were older; had a higher systolic blood pressure, fasting glucose, creatinine, body mass index, and alcohol consumption; and were more likely to be men, black, and have a history of diabetes, hypertension, and CHD.

Electrocardiographic abnormalities and incident HF

During a median follow-up time of 11.4 years (inter-quartile range [IQR] 7.0–11.7 years), 485 participants developed incident HF. The risk of HF increased with baseline ECG

abnormalities. The Figure shows the cumulative incidence of HF events according to the presence of baseline ECG abnormalities. In age and gender-adjusted analyses, the hazard ratio (HR) for HF events was 2.09 (95% CI 1.75–2.50) in those with any (minor and/or major) ECG abnormalities compared with those without ECG abnormalities (Table II). The risk of HF increased according to the severity of ECG abnormalities: HR was 1.54 (95% CI 1.18–2.01) for minor and 2.46 (95% CI 2.02–2.99) for major abnormalities (*P* value for trend <.001). The association remained significant after adjustment for the Health ABC HF Risk Score variables (HR 1.70, 95% CI 1.41–2.05 for any ECG abnormalities) and persisted after additional adjustment for other potential confounding risk factors (body mass index, race, cholesterol, and alcohol intake) and for cardiovascular medications (Online Appendix Supplementary Table II). The Fine-Gray model treating all-cause mortality as a competing risk yielded a subdistribution HR of 1.58 (95% CI 1.31–1.81) for any ECG abnormality, which was similar to the estimate obtained with the main model. Self-reported race and gender did not show significant interactions with ECG abnormalities for HF risk (*P* value for interaction >.10), although the association was stronger among blacks (Online Appendix Supplementary Table III). The association between baseline ECG abnormalities and HF events did not significantly differ according to preexisting CHD (*P* value for interaction >.20) (Table II). In secondary analyses according to LVEF on index HF admission, ECG abnormalities at baseline were associated with risk of HF with preserved LVEF (HR 1.87, 95% CI 1.38–2.53) and reduced LVEF (HR 2.68, 95% CI 2.04–3.54) (Online Appendix Supplementary Table IV).

Reclassification

Among the 2,835 participants with complete data on covariates, 172 participants had HF events during the first 5 years of follow-up. The addition of ECG abnormalities to the Health ABC HF Risk Score resulted in an NRI of 0.11 (95% CI 0.03–0.19, *P* = .005) (Table III). Electrocardiogram correctly reclassified 10.5% of participants with HF events, 0.8% of those without HF events, and 1.4% of the overall population. There was no evidence of a violation of the proportional assumptions through graphical assessment and using Schoenfeld's test and the NRI was similar in sensitivity analyses dealing with censoring.

New ECG changes and HF risk

Among 2,248 participants who did not have an HF event before the year 4 follow-up, 1,269 (56.5%) had normal ECG in both examinations (baseline and year 4), 167 (7.4%) had abnormalities at baseline only, 263 (11.7%) had new abnormalities at year 4, and 549 (24.4%) had persistent abnormalities at both examinations (Online Appendix Supplementary Table V). During a median follow-up of 8.5 years (IQR 6.0–8.7 years) after the second ECG, 328 participants had incident HF. The risk of HF events increased both with new and persistent ECG abnormalities. Online Appendix Supplementary Figure shows the cumulative incidence after the second ECG according to normal ECG, baseline, incident, and persistent ECG abnormalities. In age- and gender-adjusted analyses, HR was 1.93 (95% CI 1.38–2.69) for new ECG abnormalities and 2.67 (95% CI 2.10–3.41) for persistent ECG abnormalities (*P* value for trend <.001). Risks did not significantly differ according to preexisting CHD at 4 years (*P* value for interaction >.20).

Discussion

Main findings

In this prospective cohort study, baseline ECG abnormalities in older adults were associated with an increased risk of incident HF after adjustment for clinical HF risk factors. The risk of HF increased significantly with the severity of ECG abnormalities. The association persisted after excluding participants with CHD at baseline and was present for HF with preserved and reduced LVEF. The addition of ECG data reclassified participants with HF events in higher risk categories, but its impact was modest regarding the entire population. New or persistent ECG abnormalities at 4 years were also associated with an increased risk of incident HF events.

Previous studies

A previous analysis in the same cohort has reported that ECG abnormalities were associated with incident CHD.[11] In this study, we reported that the same abnormalities were associated with HF events even in the absence of known CHD. Few studies have previously examined the associations between ECG changes and incident HF, and none examined specifically older (>70 years) adults.[14,16,17] In a middle-aged adult cohort (the Multi-Ethnic Study of Atherosclerosis), a long QRS duration >100 ms was significantly associated with incident HF suggesting that ECG abnormalities might be a marker of ventricular structural changes in asymptomatic subjects.[9]

Strengths and limitations

This study has several strengths and limitations. The data were drawn from a well-characterized cohort of older adults with a large number of HF events over 11 years of follow-up. However, participants were selected based on no disability at baseline, and therefore, this cohort might not be fully representative of the general older adult population. All HF events were adjudicated by independent reviewers. However, HF events were based on hospital admissions, which might underestimate the true incidence of HF. Nevertheless, this should similarly affect all ECG groups. Although ECG records were reviewed by 2 trained coders,[11] the reproducibility and reclassification using ECG might be lower in the clinical setting.[31] We also had limited power to perform analyses considering each specific ECG abnormality. We assessed the reclassification improvement with ECG using the Health ABC HF Risk Score with a follow-up of 5 years. Using Cox regression models over a longer follow-up period might violate the assumption of nonproportionality, but we did not find evidence of nonproportionality in our models. Finally, our results might not be applicable to individuals younger than 70 years old.

Clinical implications

In our study, ECG improved modestly classification in the overall sample across categories of the Health ABC HF Risk Score over 5 years. The Health ABC HF Risk Score aims to evaluate the individual HF risk over 5 years to target those who should benefit from intensive preventive efforts. Our study suggests that the presence of ECG abnormalities might be an independent risk factor for HF. Traditional risk factors as well ECG

abnormalities change and modify the risk of HF over time and should be assessed regularly. The American College of Cardiology/American Heart Association HF staging classification defines stage A as individuals at risk for HF without structural heart disease and stage B as individuals with structural heart disease but without clinical symptoms of HF.[7] Early detection of structural heart changes by ECG holds promise for an improved classification of HF risk at the population level. Electrocardiographic abnormalities might precede clinical manifestation of HF even in the absence of clinical CHD. A strategy based on ECG screening in asymptomatic older individuals and further investigation (echocardiography, Brain natriuretic peptide) for those with abnormalities should be assessed in a prospective trial.[32] Echocardiographic abnormalities in asymptomatic subjects have been associated with HF events even in patients without ECG abnormalities, suggesting that both tests could add complementary information for HF risk prediction.[9,32,33]

Conclusions

In conclusion, ECG abnormalities are independently associated with risk of incident HF events in older adults. The addition of ECG information improves modestly risk reclassification for HF over routine clinical risk factors. Given its safety, noninvasive nature, low cost, and wide availability, ECG might be a useful test to identify subjects at risk for HF who might benefit from further investigations and preventive efforts. The contribution of ECG in the prevention of HF among asymptomatic subjects should be evaluated further in randomized controlled trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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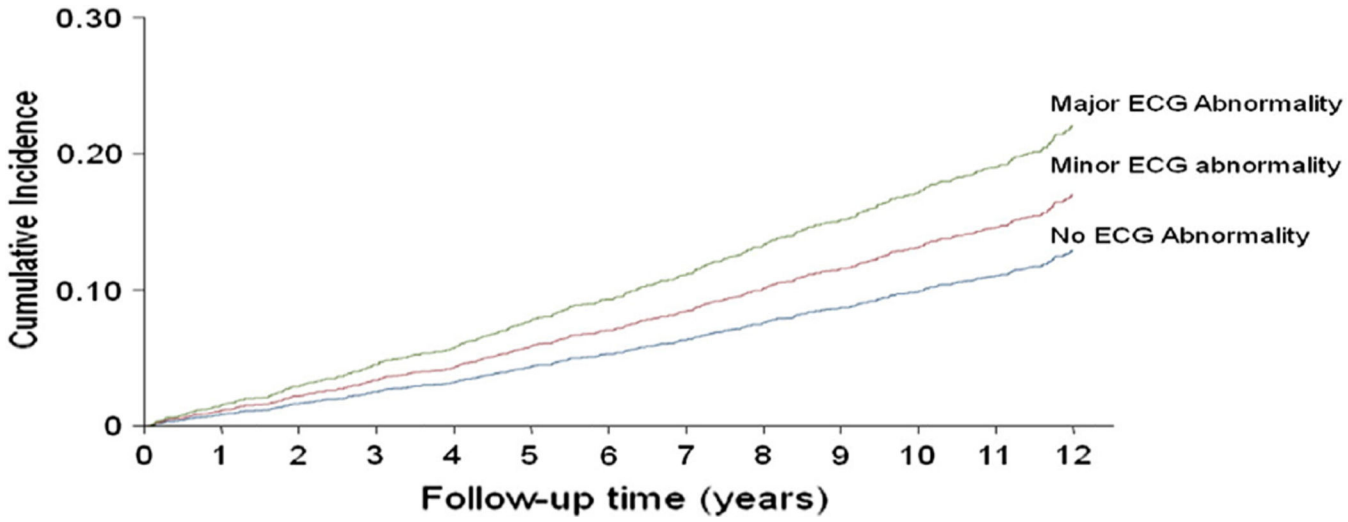

Figure.

Cumulative incidence of HF events according to the presence of baseline ECG abnormalities.

Table I

Baseline characteristics of the study population (N = 2,915)

Characteristics	All	No ECG abnormalities	Minor ECG abnormalities	Major ECG abnormalities	*P**
Total population	2915	1915	380	620	
Age (y), mean (SD)	73.6 (2.9)	73.5 (2.9)	73.5 (2.7)	74.0 (2.9)	<.001
Women, n (%)	1521 (52.2)	1029 (53.7)	202 (53.2)	290 (46.8)	.010
Self-reported race, n (%)					<.001
White	1710 (58.7)	1203 (62.8)	192 (50.5)	315 (50.8)	
Black	1205 (41.3)	712 (37.2)	188 (49.5)	305 (49.2)	
Smoking status, n (%)					.019
Never	1296 (44.5)	879 (46.0)	159 (41.8)	258 (41.8)	
Former	1308 (44.9)	835 (43.7)	168 (44.2)	305 (49.4)	
Current	307 (10.6)	199 (10.4)	53 (14.0)	55 (8.9)	
Body mass index (kg/m2), mean (SD)	27.3 (4.8)	27.1 (4.7)	28.5 (5.1)	27.5 (4.8)	<.001
Heart rate (beat/min), mean (SD)	65.3 (11.0)	65.2 (11.0)	65.5 (10.6)	65.6 (11.4)	.655
Systolic blood pressure (mm Hg), mean (SD)	136.0 (21.0)	133.6 (19.6)	137.6 (19.7)	142.4 (24.1)	<.001
Fasting glucose (mg/dL), median (IQR)	94 (87–105)	93 (87–103)	97 (91–117)	95 (88–110)	<.001
Albumin (g/dL), mean (SD)	4.0 (0.3)	4.0 (0.3)	4.0 (0.3)	4.0 (0.3)	.853
Creatinine (mg/dL), median (IQR)	1.0 (0.9–1.2)	1 (0.9–1.1)	1 (0.9–1.2)	1 (0.9–1.2)	<.001
Total cholesterol (mg/dL), mean (SD)	203.3 (38.3)	204.3 (38.6)	202.5 (38.3)	200.7 (37.9)	.117
CHD, n (%)					<.001
No	2311 (80.6)	1614 (85.3)	284 (76.8)	413 (68.3)	
Yes	556 (19.4)	278 (14.7)	86 (23.2)	192(31.7)	
Alcohol intake/week, n (%)					.109
<1	821 (28.3)	540 (28.4)	111 (29.4)	170 (27.5)	
1–7	1453 (50.1)	980 (51.4)	178 (47.1)	295 (47.7)	
>7	627 (21.6)	385 (20.2)	89 (23.5)	153 (24.8)	
Diabetes, n (%)	429 (14.7)	239 (12.5)	83 (21.8)	107 (17.3)	<.001
Hypertension, n (%)	1252 (43.3)	761 (40.0)	179 (47.7)	312 (50.8)	<.001
Cardiovascular medication, n (%)	2016 (69.4)	1265 (66.3)	276 (72.8)	475 (76.9)	<.001

Missing values were 4 for smoking status, 1 for heart rate, 27 for fasting glucose level, 26 for albumin level, 26 for creatinine level, 32 for cholesterol level, 48 for CHD, 14 for alcohol drinking, 3 for diabetes, and 22 for hypertension.

* Statistical analysis by analysis of variance if continuous variables and $\chi 2$ if categorical variables.

Table II

Hazard ratios for HF events according to ECG abnormalities (N = 2,915)

ECG abnormalities	No. of HF events	No. of participants	HR adjusted for age and gender (95% CI)	HR adjusted for Health ABC HF Risk Score variables* (95% CI)
No ECG abnormalities	246	1915	1 (ref)	1 (ref)
Minor ECG abnormalities	69	380	1.54 (1.18–2.01)	1.27 (0.96–1.68)
Major ECG abnormalities	170	620	2.46 (2.02–2.99)	1.99 (1.61–2.44)
P for trend			<.001	<.001
Any ECG abnormality	239	1000	2.09 (1.75–2.50)†	1.70 (1.41–2.05)†

*Age, CHD, systolic blood pressure, heart rate, smoking, albumin, fasting glucose, creatinine. Eighty participants had missing data. Left ventricular hypertrophy was not included in the multivariate models, as LVH was classified as major abnormalities.

†The interaction test according to preexisting CHD was not significant (*P* = .545). See Online Appendix Supplementary Table III.

Table III

Predicted risk of HF events using the Health ABC HF Risk Score with and without inclusion of ECG abnormalities

Model without ECG [*,†]	Model with ECG					
	<5%	5%–10%	10%–20%	>20%	Total	
Frequency	**n**	**n**	**n**	**n**	**n**	**% Correctly reclassified**
No. presenting with HF over 5 y (n = 172)						
<5%	38	8	0	0	46	
5%–10%	4	27	12	0	43	
10%–20%	0	5	25	12	42	
>20%	0	0	5	36	41	
Total	42	40	42	48	172	10.5%[‡]
No. not presenting with HF over 5 y (n = 2663)						
<5%	1496	169	0	0	1665	
5%–10%	191	332	90	0	613	
10%–20%	0	101	153	36	290	
>20%	0	0	25	70	95	0.8%[‡]
Total	1687	602	268	106	2663	
NRI Index [§]						0.11 (95% CI 0.03–0.19)

[*] Eighty participants were omitted because of missing data (≥1 variables of the Health ABC HF Risk Score were not available for those participants).

[†] Adjustment for LVH was not performed in both multivariate models with and without ECG data (see text). Left ventricular hypertrophy was included in the ECG abnormalities.

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

[§] Net reclassification improvement index is the sum of net percentages of correctly reclassified subjects with and without HF events.