

Predicting Sudden Cardiac Death in a General Population Using an Electrocardiographic Risk Score

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Short title:

Predicting SCD Using ECG Score

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Declarations of interest:

None

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Abstract

Objective

We investigated whether combining several electrocardiogram (ECG) abnormalities would identify general population subjects with a high sudden cardiac death (SCD) risk.

Methods

In a sample of 6830 participants in (mean age 51.2 ± 13.9 years; 45.5% male) the Mini-Finland Health Survey, a general population cohort representative of the Finnish adults aged ≥ 30 years conducted in 1978–1980, we examined their ECGs, following subjects for 24.3 ± 10.4 years. We analyzed the association between individual ECG abnormalities and 10-year SCD risk and developed a risk score using 5 ECG abnormalities independently associated with SCD risk: heart rate >80 bpm, PR duration >220 ms, QRS duration >110 ms, left ventricular hypertrophy, and T-wave inversion. We validated the score using an external general population cohort of 10,617 subjects (mean age 44.0 ± 8.5 years; 52.7% male).

Results

No ECG abnormalities were present in 4563 subjects (66.8%), while 96 subjects (1.4%) had ≥ 3 ECG abnormalities. After adjusting for clinical factors, the SCD risk increased progressively with each additional ECG abnormality. Subjects with ≥ 3 ECG abnormalities had a hazard ratio (HR) of 10.23 (95% confidence interval [CI] 5.29–19.80) for SCD compared with those without abnormalities. The risk score similarly predicted SCD risk in the validation cohort, in which subjects with ≥ 3 ECG abnormalities had HR 10.82 (95% CI 3.23–36.25) for SCD compared with those without abnormalities.

Conclusion

The ECG risk score successfully identified general population subjects with a high SCD risk.

Combining ECG risk markers may improve the risk stratification for SCD.

Key Questions

What is already known about this subject?

Almost half of sudden cardiac death (SCD) victims do not have previously diagnosed heart disease, with SCD being the first manifestation of the underlying condition. Current risk stratification tools are insufficient at predicting the majority of SCDs. Combining known SCD risk markers may improve the risk stratification.

What does this study add?

The presence of multiple ECG abnormalities associated with mortality and SCD was associated with increased SCD risk in general population subjects, with the risk increasing progressively with each additional ECG abnormality. Subjects with 3 or more of the 5 ECG abnormalities assessed had more than tenfold risk of SCD compared to subjects with no ECG abnormalities.

How might this impact on clinical practice?

Better SCD risk stratification in the general population could identify subjects with high SCD risk and potentially improve SCD prevention in these subjects.

Keywords

electrocardiography, sudden cardiac death, prognosis, general population

Introduction

Globally, sudden cardiac death (SCD) remains a major cause of mortality, accounting for 10–20% of deaths in industrialized countries.[1,2] However, in many cases SCD can represent the first manifestation of an underlying cardiac condition, as almost half of all SCD victims have no previously diagnosed heart disease.[2,3]

Currently, risk stratification for the primary prevention of SCD, with an implantable cardioverter defibrillator (ICD), primarily relies on the reduced left ventricular ejection fraction (LVEF), despite numerous other SCD risk markers with low individual predictive values identified.[1,4] However, most SCD victims have a normal or only a mildly reduced ejection fraction.[1,3,5] Combining several SCD risk markers, e.g. electrocardiographic (ECG) parameters, into integrated risk models may potentially improve risk stratification. Accordingly, several combinations of ECG risk markers have been associated with a markedly increased risk for SCD.[6–8] However, these studies have used different ECG markers with varying complexity, and no ECG risk model is currently in clinical use.

To evaluate the optimal combination of ECG markers for SCD prediction, we assessed several ECG parameters previously associated with SCD, developed a cumulative ECG risk score, and evaluated its ability to identify subjects at high risk for SCD using the Mini-Finland Health Survey, a large Finnish general population cohort. Furthermore, we validated the ECG risk score using a separate large Finnish general population cohort.

Methods

Mini-Finland Health Survey Population

The primary study population consisted of participants of the Social Insurance Institution's Mini-Finland Health Survey, conducted in 1978 through 1980. The detailed descriptions of the survey protocol and methods appeared previously.[9,10] Briefly, the survey consisted of health interviews, including questionnaires about subjects' health status, diseases, medications, symptoms, and lifestyles, as well as health examinations, including measurements of the heart rate, blood pressure, body mass index, serum cholesterol, and a standard 12-lead ECG. A total of 8000 subjects ≥ 30 years old representative of the Finnish population were invited to take part, from which 7217 participated in the health examination. The baseline diagnoses were assessed using structured criteria based on health interviews and health examination findings.

Electrocardiographic (ECG) Measurements

A resting paper ECG was recorded from all subjects with a paper speed of 50 mm/s. After excluding missing or unreadable ECGs, a total of 6969 ECGs underwent digitization and digital analysis as described previously.[11] We excluded subjects (n=106) with atrial fibrillation, atrial flutter, left or right bundle branch block, II/III degree atrioventricular block, ventricular pre-excitation, a pacemaker rhythm, or rare ECG findings not representative of the general population. We also excluded subjects (n=33) with missing data.

After these exclusions, the remaining 6830 ECGs were analyzed for the presence of ECG variables associated with mortality and SCD risk relatively easily obtainable in clinical practice: heart rate >80 beats per minute (bpm), a PR interval >220 ms, a QRS duration >110 ms, a prolonged QTc interval (QTc >450 ms in men and >460 ms in women), left ventricular hypertrophy (LVH), early repolarization (ER) pattern, delayed

intrinsicoid deflection, frontal QRS-T angle $>90^\circ$, a T-peak to T-end interval >90 ms, a delayed QRS transition zone, a T-wave inversion, and ST-segment depressions. The used ECG parameter definitions are presented in the Supplemental Material.

Follow-up

Subjects were followed from the baseline examinations in 1978 through 1980 until the end of 2011 using nation-wide health registers (Causes of Death Register maintained by Statistics Finland and Care Register for Health Care maintained by the National Institute for Health and Welfare). The validity of these registers has been well established.[12] Of all the Mini-Finland Health Survey subjects, 1077 subjects (27% of all deceased) were autopsied during the complete follow-up, of which 194 were SCD cases (48% of SCD cases). Two cardiologists reviewed all deaths due to cardiovascular causes using death certificates, hospital records, and autopsy records in order to determine SCDs, and using the SCD definitions based on the modified CAST criteria.[13] When disagreements occurred, a third cardiologist reviewed the case and established the final classification. The primary endpoint was SCD, and the secondary endpoints consisted of non-sudden cardiac death (non-SCD), death from any cause, and cardiac hospitalization due to coronary artery disease (CAD) or heart failure. The follow-up time was limited to 10 years in the primary analyses in order to clarify the role of ECG in assessing risk since the cardiovascular risk profile could ultimately change during a longer follow-up period.

Cumulative ECG Risk Score

The cumulative ECG risk score was developed using a stepwise method. The age- and sex-adjusted association between individual ECG parameters and the risk of SCD was first analyzed, omitting from further analysis ECG parameters with no statistically significant

association. The remaining ECG parameters were entered simultaneously into an age- and sex-adjusted model, and those ECG parameters not independently associated with SCD were then excluded from further analysis. Any ECG parameters that remained statistically significant were used to calculate the cumulative ECG risk score. In addition to the primary risk score, we developed for comparison a secondary ECG risk score from all the ECG parameters individually associated with the risk of SCD.

External Validation Cohort

The validity of the ECG risk score was assessed using the Coronary Heart Disease (CHD) Study cohort, a general population cohort study representing the Finnish middle-aged population conducted from 1966 through 1972. Detailed descriptions of the study design appeared previously.[14,15] In short, a total of 12,310 subjects aged 30–59 years were invited to the survey, from which 10,957 subjects participated in the study. Subjects completed a questionnaire regarding their medical history, underwent baseline examinations, including measurement of blood pressure, total serum cholesterol level, and recording of a 12-lead ECG, and were then followed until the end of 2007 using the same health registers as those used for the Mini-Finland Health Survey. SCDs were determined based on definitions presented in the Cardiac Arrhythmia Pilot Study.[16,17] After applying the same exclusion criteria as those applied to Mini-Finland Health Survey subjects, the presence of ECG abnormalities used for the risk score was determined manually from the 10,617 subjects' ECGs.

All participants of the CHD Study and Mini-Finland Health Survey were fully informed about the study, they participated in the study voluntarily, and the use of information for medical research was explained to them. Agreeing to participate in the baseline health examination was taken to indicate informed consent. The participants were

free to unconditionally withdraw their consent at any time, in which case their data were deleted. It was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research. The study protocol and the practice of the subjects' voluntary participation indicating informed consent were approved by the Institutional Review Board (IRB) of National Institute for Health and Welfare (IRB 00007085, Federalwide Assurance (FWA) 00014588).

Statistical Analysis

The general linear model was used to compare the age and sex adjusted mean values for continuous variables and the prevalence of categorical variables. We calculated the hazard ratios (HRs) and their 95% confidence intervals (CIs) using the Cox proportional hazards model. Age, sex, systolic blood pressure, total serum cholesterol, smoking, diabetes, and CAD served as covariates in the multivariate models in both the Mini-Finland Health Survey and CHD Study populations. Kaplan–Meier plots were used to compare the survival of subjects with different ECG risk scores. The effect modification by baseline heart failure and CAD was tested using the Wald test by entering an interaction term of heart failure and the ECG risk score, and CAD and the ECG risk score, respectively. C-statistics, an integrated discrimination index (IDI), continuous net reclassification improvement (NRI), and categorical NRI with predicted probability risk groups of <5%, 5% to 20%, and >20% were used for model comparisons. Model calibration was assessed using Greenwood-Nam-D'Agostino test and by visually comparing the predicted and observed SCD incidences.[18] All reported P-values are two-sided and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics (version 25) and R (version 3.6.1, <https://www.r-project.org/>).

Results

The Prognostic Significance of Individual ECG Parameters

Among 6830 Mini-Finland Health Survey participants (mean age 51.2 ± 13.9 years; 45.5% male), 986 subjects (14.4%) died during the 10-year follow-up (mean 9.3 ± 2.0 years), of which 123 deaths resulted from SCD (12.5% of all deaths). When the ECG parameters were analyzed individually, ER, delayed intrinsicoid deflection, delayed QRS transition, and T-peak to T-end >90 ms did not associate with an increased risk for SCD and, thus, were excluded from further analysis. When the remaining ECG parameters were included in the same model, prolonged QTc, frontal QRS-T angle $>90^\circ$, and ST-segment depressions did not remain associated with SCD and, thus, were excluded from further analysis. Consequently, the final ECG risk score consisted of five ECG abnormalities: heart rate >80 bpm, PR duration >220 ms, QRS duration >110 ms, LVH, and T-wave inversion. Table 1 summarizes the prevalence of ECG parameters, as well as the risks associated with ECG parameters when analyzed individually and when included in the same model simultaneously.

Baseline Characteristics

The subjects' baseline characteristics according to the ECG risk score appear in Table 2. No ECG abnormalities were present in 4563 subjects (66.8%), 1859 subjects (27.2%) exhibited 1 ECG abnormality, 312 subjects (4.6%) had 2 ECG abnormalities, and ≥ 3 ECG abnormalities were identified in 96 subjects (1.4%). Subjects with ≥ 1 ECG abnormalities were older, had higher systolic blood pressure, and were more likely to present with diabetes, CAD or heart failure compared to subjects with no ECG abnormalities ($P < 0.001$ for all).

ECG Risk Score and Outcomes

Table 3 provides the HRs and 95% CIs for SCD and the secondary endpoints according to the ECG risk score. The ECG risk score associated with SCD and all of the secondary endpoints. The risk for SCD progressively increased with each additional ECG abnormality, whereby subjects with ≥ 3 ECG abnormalities exhibited the highest risk (HR 10.23; 95% CI 5.29–19.80; $P < 0.001$) for SCD. In contrast, subjects with ≥ 3 ECG abnormalities exhibited a moderate risk (HR 2.83; 95% CI 1.79–4.48; $P < 0.001$) for non-SCD. Figure 1 illustrates the risk for non-SCD and SCD according to the ECG risk score. The Kaplan-Meier survival curves for SCD and overall mortality in the 10-year follow-up appear in Figure 2.

The association between the ECG risk score and SCD risk persisted in the complete follow-up of 24.3 ± 10.4 years in the multivariate model, with subjects with ≥ 3 ECG abnormalities having HR 5.42 (95% CI 3.23–9.08; $P < 0.001$) for SCD (Supplemental Material). Furthermore, the ECG risk score associated with SCD risk in both subjects with and without a CAD diagnosis, and in both subjects with and without heart failure diagnosis, with no statistically significant effect modifications (Supplemental Material).

The secondary risk score, consisting of all the 8 ECG parameters individually associated with SCD risk, associated with progressively increasing SCD risk, but not as strongly as the primary ECG risk score (Supplemental Material).

Model Improvement with ECG Risk Score

Compared to the baseline model of age, sex, systolic blood pressure, total serum cholesterol, current smoker, diabetes, and CAD, the addition of the ECG risk score significantly improved the model's ability to estimate the risk for SCD. The C-statistics for the baseline model was 0.871, improving to 0.898 using the ECG risk score, representing a statistically significant improvement of 0.028 ($P < 0.05$). Furthermore, IDI of 0.037 ($P < 0.001$), continuous NRI of

0.397 ($P<0.001$), and categorical NRI of 0.125 ($P<0.05$) improved significantly. With the addition of the ECG risk score to the baseline model, 21.1% of the SCD cases were appropriately reclassified into a higher risk group and 9.8% inappropriately reclassified into a lower risk group, whereas of the subjects without SCD 4.0% were appropriately reclassified into a lower risk group and 2.9% inappropriately reclassified into a higher risk group (Table 4). The predicted and observed SCD incidences were similar, with some overestimation of the risk in high risk subjects (Figure 3). However, the Greenwood-Nam-D'Agostino test showed poor calibration ($P<0.05$).

ECG Risk Score Validation in the CHD Study

Baseline characteristics of the CHD Study validation cohort and the association between individual ECG parameters and SCD risk are presented in the Supplemental Material. Among 10,617 CHD Study subjects (mean age 44.0 ± 8.5 years; 52.7% male), 115 SCDs occurred during the 10-year follow-up. Subjects ($n=4887$, 46.0%) with 1 ECG abnormality (HR 1.51; 95% CI 0.96–2.38; $P=0.072$), subjects ($n=1023$, 9.6%) with 2 ECG abnormalities (HR 2.36; 95% CI 1.35–4.12; $P=0.002$), and subjects ($n=26$, 0.2%) with ≥ 3 ECG abnormalities (HR 10.82; 95% CI 3.23–36.25; $P<0.001$) exhibited a progressively increased risk for SCD compared to subjects ($n=4681$, 44.1%) with no ECG abnormalities. Model improvement with ECG risk score in the CHD Study population are demonstrated in the Supplemental Material.

Discussion

In this study, by combining five ECG parameters which independently associate with SCD risk, we successfully identified general population subjects with a high risk of SCD. That is, subjects with ≥ 3 ECG abnormalities had a more than tenfold risk for SCD compared to subjects with no ECG abnormalities, with similar results found in an external validation cohort. Furthermore, the risk score associated more strongly with SCD compared to non-SCD risk.

In previous studies, multiple ECG patterns associated with SCD risk both in general populations and in cardiac patient populations.[1] However, since the predictive value of a single ECG parameter remains relatively low, combining ECG parameters into a SCD risk score provides appeal.[6–8] In a case–control study, adding the heart rate, QRS duration, and JTc interval markedly improved the SCD risk prediction with LVEF.[7] Similarly, in a study combining two large population cohorts, adding the spatial ECG parameter global electric heterogeneity improved the selective SCD risk prediction over non-SCD and non-cardiac death risk.[8] In another study using the same two cohorts, the addition of an increased heart rate, QTc prolongation, and T-wave inversion improved the differentiation of SCD risk from the risk of a non-sudden CHD event.[19] More recently, the prognostic value of combining six ECG abnormalities was examined using case–control population comparing SCD cases with control subjects with the majority having diagnosed CAD, the findings of which were validated using an established general population cohort, with the cumulative number of ECG abnormalities associating with progressively increasing SCD risk.[6] In contrast to these studies, the present risk score was developed and validated using two large general population cohorts and used relatively simple parameters easily obtainable in clinical practice. Moreover, it assessed not only the score’s ability to predict SCD risk but also its specificity for SCD.

To identify the optimal combination of ECG risk markers, we analyzed the SCD risk associated with 12 ECG parameters previously shown to associate with an increased mortality or SCD risk, of which 5 parameters persistently associated with SCD risk when analyzed simultaneously.[1,14,20–25] During the 10-year follow-up, 70% of Mini-Finland Health Survey subjects with ≥ 3 of the 5 ECG abnormalities died, of which 24% were SCDs compared to the 9% of subjects with no ECG abnormalities who died, among which only 7% were SCDs.

After adjusting for multiple cardiovascular risk factors, the cumulative number of ECG abnormalities associated with progressively increasing risk for SCD. Importantly, the ECG risk score more strongly predicted SCD than it did non-SCD. Furthermore, the ECG risk score also associated with SCD risk in subgroup analyses of subjects with and without heart failure or CAD. As almost half of SCD victims do not previously receive a cardiac disease diagnosis, the presence of ECG abnormalities may indicate subclinical or undetected cardiac disease, with the first manifestation (without or in conjunction with acute myocardial ischemia) possibly being SCD.[1]

The validity of the ECG risk score was evaluated among subjects from another general population cohort, the CHD Study. Due to the inclusion of subjects aged 30-59 years, the CHD Study subjects were on average 7 years younger and, consequently, exhibited different prevalences of ECG abnormalities compared with Mini-Finland Health Survey subjects. In both study populations, the risk of SCD progressively increased with each additional ECG abnormality and subjects with ≥ 3 ECG abnormalities exhibited a more than tenfold higher risk for SCD after adjusting for multiple risk factors.

Currently, the criteria for the primary prevention of SCD with ICD primarily rely on reduced LVEF, since the risks associated with other individual markers are typically only modest.[1,4] However, LVEF carries major limitations as a risk predictor and some patient

groups with a reduced LVEF do not benefit from ICD.[26,27] Furthermore, only one-third of SCD victims meet the reduced LVEF criteria for prophylactic ICD.[5] Consequently, some population-based studies demonstrated that by combining multiple risk markers into predictive models, the SCD risk prediction greatly improves and subjects with a high SCD risk can be identified.[28,29]

Limitations

The present study has some limitations. The use of only Sokolow-Lyon ECG criterion to assess LVH may have underestimated the role of LVH, as the composite of LVH criteria may perform better in SCD risk prediction.[30] Furthermore, echocardiography was not performed to survey participants, whereby the effect of LVEF on the performance of the ECG risk score could not be evaluated. We tested the performance of the ECG risk score using diagnosed heart failure as a substitute for reduced LVEF. However, the presented ECG risk score's performance should be assessed when combined with LVEF assessment in future studies. Although the predicted and observed SCD incidences were relatively similar, the risk model showed imperfect calibration when assessed statistically, likely due to mild risk overestimation in high risk subjects. The low number of SCDs during the follow-up relative to the large study population may have also affected the calibration statistics. Nevertheless, the ECG risk score was able to discriminate successfully low and high-risk subjects, highlighting the usefulness of the score in identifying high SCD risk general population subjects.

Conclusions

The ECG risk score based on parameters available also in the primary care setting presented in our study significantly improved the ability to predict SCD risk in a general population and

successfully identified subjects at a high SCD risk. Future research should investigate how to improve SCD prevention in these high-risk general population subjects.

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Disclosures

None.

References

- 1 Wellens HJJ, Schwartz PJ, Lindemans FW, *et al.* Risk stratification for sudden cardiac death: current status and challenges for the future. *Eur Heart J* 2014;**35**:1642–51. doi:10.1093/eurheartj/ehu176
- 2 Chugh SS, Reinier K, Teodorescu C, *et al.* Epidemiology of sudden cardiac death: clinical and research implications. *Prog Cardiovasc Dis* 2008;**51**:213–28. doi:10.1016/j.pcad.2008.06.003
- 3 Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001;**345**:1473–82. doi:10.1056/NEJMra000650
- 4 Priori SG, Blomström-Lundqvist C, Mazzanti A, *et al.* 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793–867. doi:10.1093/eurheartj/ehv316
- 5 Stecker EC, Vickers C, Waltz J, *et al.* Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. *J Am Coll Cardiol* 2006;**47**:1161–6. doi:10.1016/j.jacc.2005.11.045
- 6 Aro AL, Reinier K, Rusinaru C, *et al.* Electrical risk score beyond the left ventricular ejection fraction: prediction of sudden cardiac death in the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study. *Eur Heart J* 2017;**38**:3017–25. doi:10.1093/eurheartj/ehx331

- 7 Reinier K, Narayanan K, Uy-Evanado A, *et al.* Electrocardiographic Markers and the Left Ventricular Ejection Fraction have Cumulative Effects on Risk of Sudden Cardiac Death. *JACC Clin Electrophysiol* 2015;**1**:542–50. doi:10.1016/j.jacep.2015.07.010
- 8 Waks JW, Sitlani CM, Soliman EZ, *et al.* Global Electric Heterogeneity Risk Score for Prediction of Sudden Cardiac Death in the General Population: The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. *Circulation* 2016;**133**:2222–34. doi:10.1161/CIRCULATIONAHA.116.021306
- 9 Knekt P, Rissanen H, Järvinen R, *et al.* Cohort Profile: The Finnish Mobile Clinic Health Surveys FMC, FMCF and MFS. *Int J Epidemiol* 2017;**46**:1760–1761i. doi:10.1093/ije/dyx092
- 10 Holkeri A, Eranti A, Haukilahti MA, *et al.* Prevalence and Prognostic Significance of Negative U-waves in a 12-lead Electrocardiogram in the General Population. *Am J Cardiol* 2019;**123**:267–73. doi:10.1016/j.amjcard.2018.10.010
- 11 Holkeri A, Eranti A, Kenttä TV, *et al.* Experiences in digitizing and digitally measuring a paper-based ECG archive. *J Electrocardiol* 2018;**51**:74–81. doi:10.1016/j.jelectrocard.2017.09.007
- 12 Rapola JM, Virtamo J, Korhonen P, *et al.* Validity of diagnoses of major coronary events in national registers of hospital diagnoses and deaths in Finland. *Eur J Epidemiol* 1997;**13**:133–8.
- 13 Pratt CM, Greenway PS, Schoenfeld MH, *et al.* Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. *Circulation* 1996;**93**:519–24.

- 14 Aro AL, Anttonen O, Tikkanen JT, *et al.* Intraventricular conduction delay in a standard 12-lead electrocardiogram as a predictor of mortality in the general population. *Circ Electrophysiol* 2011;**4**:704–10. doi:10.1161/CIRCEP.111.963561
- 15 Reunanen A, Aromaa A, Pyörälä K, *et al.* The Social Insurance Institution's coronary heart disease study. Baseline data and 5-year mortality experience. *Acta Med Scand Suppl* 1983;**673**:1–120.
- 16 Greene HL, Richardson DW, Barker AH, *et al.* Classification of deaths after myocardial infarction as arrhythmic or nonarrhythmic (the Cardiac Arrhythmia Pilot Study). *Am J Cardiol* 1989;**63**:1–6.
- 17 Tikkanen JT, Anttonen O, Junttila MJ, *et al.* Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med* 2009;**361**:2529–37.
doi:10.1056/NEJMoa0907589
- 18 Demler OV, Paynter NP, Cook NR. Tests of Calibration and Goodness of Fit in the Survival Setting. *Stat Med* 2015;**34**:1659–80. doi:10.1002/sim.6428
- 19 Soliman EZ, Prineas RJ, Case LD, *et al.* Electrocardiographic and clinical predictors separating atherosclerotic sudden cardiac death from incident coronary heart disease. *Heart* 2011;**97**:1597–601. doi:10.1136/hrt.2010.215871
- 20 Jouven X, Zureik M, Desnos M, *et al.* Resting heart rate as a predictive risk factor for sudden death in middle-aged men. *Cardiovasc Res* 2001;**50**:373–8.
doi:S0008636301002309 [pii]
- 21 Aro AL, Anttonen O, Tikkanen JT, *et al.* Prevalence and prognostic significance of T-wave inversions in right precordial leads of a 12-lead electrocardiogram in the middle-

- aged subjects. *Circulation* 2012;**125**:2572–7.
doi:10.1161/CIRCULATIONAHA.112.098681
- 22 Kannel WB, Doyle JT, McNamara PM, *et al.* Precursors of sudden coronary death. Factors related to the incidence of sudden death. *Circulation* 1975;**51**:606–13.
- 23 Darouian N, Narayanan K, Aro AL, *et al.* Delayed intrinsicoid deflection of the QRS complex is associated with sudden cardiac arrest. *Heart Rhythm* 2016;**13**:927–32.
doi:10.1016/j.hrthm.2015.12.022
- 24 Aro AL, Eranti A, Anttonen O, *et al.* Delayed QRS transition in the precordial leads of an electrocardiogram as a predictor of sudden cardiac death in the general population. *Heart Rhythm* 2014;**11**:2254–60. doi:10.1016/j.hrthm.2014.08.014
- 25 Dekker JM, Schouten EG, Klootwijk P, *et al.* ST segment and T wave characteristics as indicators of coronary heart disease risk: the Zutphen Study. *J Am Coll Cardiol* 1995;**25**:1321–6. doi:10.1016/0735-1097(95)00017-X
- 26 Goldenberg I, Vyas AK, Hall WJ, *et al.* Risk Stratification for Primary Implantation of a Cardioverter-Defibrillator in Patients With Ischemic Left Ventricular Dysfunction. *J Am Coll Cardiol* 2008;**51**:288–96. doi:10.1016/j.jacc.2007.08.058
- 27 Køber L, Thune JJ, Nielsen JC, *et al.* Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *N Engl J Med* 2016;**375**:1221–30.
doi:10.1056/NEJMoa1608029
- 28 Bogle BM, Ning H, Goldberger JJ, *et al.* A Simple Community-Based Risk-Prediction Score for Sudden Cardiac Death. *Am J Med* 2018;**131**:532-539.e5.
doi:10.1016/j.amjmed.2017.12.002

- 29 Deo R, Norby FL, Katz R, *et al.* Development and Validation of a Sudden Cardiac Death Prediction Model for the General Population. *Circulation* 2016;**134**:806–16.
doi:10.1161/CIRCULATIONAHA.116.023042
- 30 Porthan K, Kenttä T, Niiranen TJ, *et al.* ECG left ventricular hypertrophy as a risk predictor of sudden cardiac death. *Int J Cardiol* 2019;276:125–9.
doi:10.1016/j.ijcard.2018.09.104

Tables

Table 1. Sudden Cardiac Death Risk Associated with ECG Parameters in a 10-year Follow-Up in the Mini-Finland Health Survey

| ECG parameter | n (%) | ECG parameters individually | | ECG parameters in the same model | |
|------------------------------|--------------|-----------------------------|----------------|----------------------------------|----------------|
| | | HR (95% CI) | <i>P</i> value | HR (95% CI) | <i>P</i> value |
| Heart rate >80 bpm | 1067 (15.6%) | 2.43 (1.65–3.58) | <0.001 | 2.19 (1.45–3.31) | <0.001 |
| PR >220 ms | 143 (2.1%) | 3.23 (1.88–5.54) | <0.001 | 2.10 (1.20–3.68) | 0.010 |
| QRS >110 ms | 310 (4.5%) | 3.07 (1.94–4.86) | <0.001 | 2.05 (1.23–3.41) | 0.006 |
| Left ventricular hypertrophy | 947 (13.9%) | 2.42 (1.66–3.52) | <0.001 | 1.73 (1.15–2.60) | 0.009 |
| T-wave inversion | 328 (4.8%) | 4.89 (3.21–7.46) | <0.001 | 2.29 (1.29–4.08) | 0.005 |
| Prolonged QTc | 522 (7.6%) | 2.26 (1.46–3.51) | <0.001 | 1.27 (0.79–2.05) | 0.328 |
| Frontal QRS-T angle >90° | 847 (12.4%) | 3.14 (2.12–4.64) | <0.001 | 1.30 (0.78–2.19) | 0.315 |
| ST-segment depressions | 336 (4.9%) | 4.02 (2.57–6.28) | <0.001 | 1.45 (0.85–2.46) | 0.176 |

Number of subjects with ECG parameters (% of the total study population). Age- and sex-adjusted hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values for SCD risk associated with ECG parameters calculated using the Cox proportional hazards model. Each ECG parameter was first analyzed individually and then simultaneously with other ECG parameters in the same model. When analyzed individually, early repolarization pattern, delayed intrinsicoid deflection, delayed QRS transition, and T-peak to T-end >90 ms did not

associate with an increased risk for SCD, and were excluded from further analysis.

Prolonged QTc = QTc over 450 ms in men and over 460 ms in women.

Table 2. Baseline Characteristics of the Mini-Finland Health Survey Population According to the ECG Risk Score

| | ECG risk score | | | |
|--------------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| | 0 n=4563 | 1 n=1859 | 2 n=312 | ≥3 n=96 |
| Male (%) | 1985 (43.5%) | 926 (49.8%) | 158 (50.6%) | 41 (42.7%) |
| Age (years) | 48.9 ± 12.9 | 54.1 ± 14.5 | 61.9 ± 14.0 | 70.1 ± 10.1 |
| Systolic blood pressure (mmHg) | 138.6 ± 20.8 | 150.1 ± 23.2 | 163.3 ± 27.5 | 166.5 ± 28.2 |
| Diastolic blood pressure (mmHg) | 85.4 ± 10.9 | 89.3 ± 11.7 | 91.8 ± 13.8 | 88.6 ± 14.0 |
| Body mass index (kg/m ²) | 25.8 ± 4.0 | 26.1 ± 4.3 | 26.3 ± 4.0 | 25.2 ± 4.2 |
| Total cholesterol (mmol/l, mg/dl) | 6.9 ± 1.4 267 ± 53 | 7.1 ± 1.4 274 ± 53 | 7.2 ± 1.5 279 ± 58 | 7.1 ± 1.4 276 ± 54 |
| Current smoker (%) | 1048 (23.0%) | 408 (21.9%) | 65 (20.8%) | 17 (17.7%) |
| Diabetes (%) | 140 (3.1%) | 145 (7.8%) | 55 (17.6%) | 27 (28.1%) |
| Coronary artery disease (%) | 348 (7.6%) | 251 (13.5%) | 90 (28.8%) | 48 (50.0%) |
| Heart failure (%) | 201 (4.4%) | 216 (11.6%) | 99 (31.7%) | 58 (60.4%) |
| Beta blocker medication (%) | 261 (5.7%) | 148 (8.0%) | 37 (11.9%) | 9 (9.4%) |

Continuous data are presented as means ± standard deviations and categorical data as the number of cases (% of the total study population). The ECG risk score consisted of 5 ECG

abnormalities: heart rate >80 bpm, PR duration >220 ms, QRS duration >110 ms, LVH, and T-wave inversion.

Table 3. Risk of SCD, Non-SCD, All-Cause Mortality, and Cardiac Hospitalization Associated with the ECG Risk Score in a 10-Year Follow-Up in the Mini-Finland Health Survey

| | ECG Risk Score | | | |
|--|-----------------------|---------------------|----------------------|-----------------------|
| | 0 | 1 | 2 | ≥3 |
| | n=4563 | n=1859 | n=312 | n=96 |
| SCD | | | | |
| # of SCDs | 30 | 55 | 22 | 16 |
| Age- and sex- adjusted HR (95% CI) | 1 | 3.42 (2.18–5.36) | 6.79 (3.85–11.98) | 15.89 (8.42–29.97) |
| Multivariate adjusted HR (95% CI) | 1 | 3.11 (1.98–4.89) | 5.59 (3.13–9.98) | 10.23 (5.29–19.80) |
| Non-SCD | | | | |
| # of non-SCDs | 105 | 102 | 58 | 25 |
| Age- and sex- adjusted HR (95% CI) | 1 | 1.55 (1.17–2.04) | 3.65 (2.62–5.09) | 4.84 (3.09–7.57) |
| Multivariate adjusted HR (95% CI) | 1 | 1.37 (1.03–1.80) | 2.90 (2.07–4.07) | 2.83 (1.79–4.48) |
| Death from any cause | | | | |
| # of deaths | 414 | 366 | 139 | 67 |

| | | | | |
|---------------------------|-----|---------------------|---------------------|---------------------|
| Age- and sex- adjusted | 1 | 1.50 (1.31–1.74) | 2.57 (2.11–3.13) | 3.85 (2.96–5.02) |
| HR (95% CI) | | | | |
| Multivariate adjusted | 1 | 1.41 (1.22–1.62) | 2.23 (1.82–2.73) | 2.80 (2.14–3.68) |
| HR (95% CI) | | | | |
| Cardiac hospitalization | | | | |
| # of hospitalizations | 489 | 383 | 141 | 53 |
| Age- and sex- adjusted | 1 | 1.41 (1.23–1.61) | 2.58 (2.13–3.13) | 2.98 (2.23–3.98) |
| HR (95% CI) | | | | |
| Multivariate adjusted | 1 | 1.26 (1.10–1.44) | 2.05 (1.68–2.50) | 2.01 (1.49–2.70) |
| HR (95% CI) | | | | |

The ECG risk score consisted of 5 ECG abnormalities: heart rate >80 bpm, PR duration >220 ms, QRS duration >110 ms, LVH, and T-wave inversion. The age- and sex-adjusted and the multivariate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for sudden cardiac death (SCD), non-sudden cardiac death (non-SCD), all-cause mortality, and hospitalization due to coronary artery disease or heart failure (cardiac hospitalization) in the 10-year follow-up were calculated using the Cox proportional hazards model. Variables included in the multivariate analyses consisted of age, sex, systolic blood pressure, total serum cholesterol, diabetes, current smoker, coronary artery disease, and the ECG risk score.

Table 4. Risk Stratification Improvement with the Addition of the ECG Risk Score to the Baseline Clinical Risk Model

| Baseline Model | | Baseline Model + ECG Risk Score | | | |
|----------------|----------------------------------|---------------------------------|---------|---------|---------|
| | | <5% | 5-20% | >20% | Total |
| <5% | No. of subjects | 5853 | 141 | 4 | 5998 |
| | (% of all subjects) | (85.7%) | (2.1%) | (0.1%) | (87.8%) |
| | No. of subjects with SCDs | 44 | 11 | 1 | 56 |
| | (% of all subjects with SCDs) | (36%) | (8.9%) | (0.8%) | (45.6%) |
| | No. of subjects without SCD | 5809 | 130 | 3 | 5942 |
| | (% of all subjects without SCDs) | (86.6%) | (1.9%) | (0.0%) | (88.6%) |
| 5-20% | No. of subjects | 244 | 409 | 73 | 726 |
| | (% of all subjects) | (3.6%) | (6.0%) | (1.1%) | (10.6%) |
| | No. of subjects with SCDs | 8 | 36 | 14 | 58 |
| | (% of all subjects with SCDs) | (6.5%) | (29.3%) | (11.4%) | (47.2%) |
| | No. of subjects without SCD | 236 | 373 | 59 | 668 |
| | (% of all subjects without SCDs) | (3.5%) | (5.6%) | (0.9%) | (10.0%) |
| >20% | No. of subjects | 0 | 36 | 70 | 106 |
| | (% of all subjects) | (0%) | (0.5%) | (1.0%) | (1.6%) |
| | No. of subjects with SCDs | 0 | 4 | 5 | 9 |
| | (% of all subjects with SCDs) | (0%) | (3.3%) | (4.1%) | (7.3%) |
| | No. of subjects without SCD | 0 | 32 | 65 | 97 |
| | (% of all subjects without SCDs) | (0%) | (0.5%) | (1.0%) | (1.4%) |

| | | | | |
|-------|----------------------------------|---------|---------|---------|
| | No. of subjects | 6097 | 586 | 147 |
| | (% of all subjects) | (89.3%) | (8.6%) | (2.2%) |
| Total | No. of subjects with SCDs | 52 | 51 | 20 |
| | (% of all subjects with SCDs) | (42.3%) | (41.5%) | (16.3%) |
| | No. of subjects without SCD | 6045 | 535 | 127 |
| | (% of all subjects without SCDs) | (90.1%) | (8.0%) | (1.9%) |

SCD = sudden cardiac death.

SUPPLEMENTAL MATERIAL

Supplemental Table 1

Definition

| | |
|--|--|
| Heart rate >80 bpm | Heart rate >80 bpm |
| PR >220 ms | PR duration >220 ms in lead II or V5, whichever was longer |
| QRS >110 ms | QRS duration >110 ms in lead II or V5, whichever was longer |
| Prolonged QTc | QT interval measured from lead II or V5, whichever was longer. Corrected for heart rate using Bazett's formula. QTc >450 ms in men and >460 ms in women was considered prolonged |
| Left ventricular hypertrophy (Sokolow–Lyon criterion) | SV1+RV5 \geq 35 mm or SV1+RV6 \geq 35 mm |
| Early repolarization pattern | End-QRS notch or slur with an amplitude of \geq 0.1 mV in either \geq 2 of the inferior (II, III, aVF) or \geq 2 of the lateral (I, aVL, V4–V6) leads |
| Delayed intrinsicoid deflection | R-wave peak time \geq 50 ms in leads V5 and V6 |
| Frontal QRS-T angle >90° | The absolute difference of >90° in value between the frontal plane QRS axis and T-wave axis |
| T-peak to T-end interval >90 ms | T-peak to T-end interval >90 ms in lead V5 |
| Delayed QRS transition zone | R-wave amplitude exceeding or equaling the S-wave amplitude at lead V4 or later |
| T-wave inversion | Negative T-wave with an amplitude of \geq 0.1 mV in \geq 1 of the following leads: I, II, V4–V6 |
| ST-segment depressions | Negative ST-segment of \geq 0.1 mV at 60 ms from the J point in \geq 2 of the following leads: I, II, III, aVL, aVF, and V1–V6 |

Supplemental Table 2

Risk of SCD, Non-SCD, All-Cause Mortality, and Cardiac Hospitalization Associated with the ECG Risk Score in the Complete Follow-Up in the Mini-Finland Health Survey

| | | ECG Risk Score | | | |
|-----------------------|-----------------|------------------|------------------|-------------|--------|
| | | 0 | | | |
| n=4563 | 1 | | | | |
| n=1859 | 2 | | | | |
| n=312 | ≥3 | | | | |
| n=96 | | | | | |
| SCD | | | | | |
| | No. of SCDs | 170 | 144 | 46 | 18 |
| Age- and sex-adjusted | | | | | |
| HR (95% CI) | 1 | 2.02 (1.62–2.53) | 4.60 (3.29–6.44) | 7.29 (4.40– | 12.07) |
| Multivariate adjusted | | | | | |
| HR (95% CI) | 1 | 1.79 (1.43–2.25) | 3.72 (2.63–5.26) | 5.42 (3.23– | 9.08) |
| Non-SCD | | | | | |
| | No. of non-SCDs | 697 | 406 | 99 | 39 |
| Age- and sex-adjusted | | | | | |
| HR (95% CI) | 1 | 1.30 (1.15–1.47) | 2.10 (1.69–2.62) | 2.83 (2.04– | 3.94) |
| Multivariate adjusted | | | | | |
| HR (95% CI) | 1 | 1.19 (1.05–1.35) | 1.82 (1.46–2.27) | 2.04 (1.46– | 2.84) |

| | | | | | |
|-------------------------|-------------------------|------------------|------------------|-------------|-------|
| Death from any cause | | | | | |
| | No. of deaths | 2139 | 1199 | 266 | 94 |
| | Age- and sex-adjusted | | | | |
| HR (95% CI) | 1 | 1.29 (1.20–1.39) | 1.98 (1.74–2.26) | 2.51 (2.04– | 3.10) |
| | Multivariate adjusted | | | | |
| HR (95% CI) | 1 | 1.23 (1.14–1.32) | 1.80 (1.57–2.05) | 2.06 (1.66– | 2.55) |
| Cardiac hospitalization | | | | | |
| | No. of hospitalizations | 1942 | 1017 | 224 | 65 |
| | Age- and sex-adjusted | | | | |
| HR (95% CI) | 1 | 1.39 (1.28–1.50) | 2.53 (2.19–2.92) | 2.91 (2.26– | 3.75) |
| | Multivariate adjusted | | | | |
| HR (95% CI) | 1 | 1.30 (1.20–1.41) | 2.21 (1.91–2.55) | 2.25 (1.74– | 2.91) |

The age- and sex-adjusted and the multivariate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for sudden cardiac death (SCD), non-sudden cardiac death (non-SCD), all-cause mortality, and hospitalization due to coronary artery disease or heart failure (cardiac hospitalization) in the complete follow-up were calculated using the Cox proportional hazards model. Variables included in the multivariate analyses consisted of age, sex, systolic blood pressure, total serum cholesterol, diabetes, current smoker, coronary artery disease, and the ECG risk score.

Supplemental Table 3

Risk of SCD Associated with the ECG Risk Score in Subjects without and with Diagnosed Coronary Artery Disease in a 10-Year Follow-Up in the Mini-Finland Health Survey

| | | ECG Risk Score | | | |
|-----------------------|----|-------------------|----|-------------------|---|
| No CAD | | | | | |
| n=6093 | | 0 | | | |
| n=4215 | 1 | | | | |
| n=1608 | 2 | | | | |
| n=222 | ≥3 | | | | |
| n=48 | | | | | |
| No. of SCDs | | 19 | 37 | 12 | 3 |
| Age- and sex-adjusted | | | | | |
| HR (95% CI) | 1 | 3.82 (2.19–6.68) | | 6.17 (2.92–13.05) | |
| | | 7.38 (2.15–25.38) | | | |
| Multivariate adjusted | | | | | |
| HR (95% CI) | 1 | 3.49 (1.98–6.14) | | 4.92 (2.27–10.66) | |
| | | 5.83 (1.65–20.65) | | | |

| | | ECG Risk Score | | | |
|-------------|----|----------------|----|----|----|
| CAD | | | | | |
| n=737 | | 0 | | | |
| n=348 | 1 | | | | |
| n=251 | 2 | | | | |
| n=90 | ≥3 | | | | |
| n=48 | | | | | |
| No. of SCDs | | 11 | 18 | 10 | 13 |

Age- and sex-adjusted

| | | | |
|-------------|---|------------------|--------------------|
| HR (95% CI) | 1 | 2.26 (1.06–4.81) | 5.09 (2.15–12.04) |
| | | | 14.23 (6.15–32.95) |

Multivariate adjusted

| | | | |
|-------------|---|------------------|--------------------|
| HR (95% CI) | 1 | 2.33 (1.09–4.99) | 5.37 (2.24–12.86) |
| | | | 14.77 (6.21–35.17) |

CAD = coronary artery disease. SCD = sudden cardiac death. The age- and sex-adjusted and the multivariate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for SCD, in a 10-year follow-up, were calculated using the Cox proportional hazards model. Variables included in the multivariate analyses consisted of age, sex, systolic blood pressure, total serum cholesterol, diabetes, current smoker, and the ECG risk score. There was no significant interaction between the ECG risk score and CAD in the age- and sex-adjusted analysis (P=0.366) or in the multivariate analysis (P=0.518).

Supplemental Table 4

Risk of SCD Associated with the ECG Risk Score in Subjects without and with Diagnosed Heart Failure in a 10-Year Follow-Up in the Mini-Finland Health Survey

| | | ECG Risk Score | |
|------------------|----|----------------|--|
| No heart failure | | | |
| n=6256 | | 0 | |
| n=4362 | 1 | | |
| n=1643 | 2 | | |
| n=213 | ≥3 | | |
| n=38 | | | |

| | | | | |
|-----------------------|----|------------------|-------------------|--------------------|
| No. of SCDs | 26 | 39 | 15 | 5 |
| Age- and sex-adjusted | | | | |
| HR (95% CI) | 1 | 3.12 (1.89–5.14) | 6.75 (3.51–12.97) | 11.53 (4.34–30.63) |
| Multivariate adjusted | | | | |
| HR (95% CI) | 1 | 2.78 (1.68–4.60) | 5.51 (2.81–10.79) | 6.97 (2.57–18.89) |

ECG Risk Score

Heart failure

n=574 0

n=201 1

n=216 2

n=99 ≥3

n=58

| | | | | |
|-------------|---|----|---|----|
| No. of SCDs | 4 | 16 | 7 | 11 |
|-------------|---|----|---|----|

Age- and sex-adjusted

| | | | | |
|-------------|---|-------------------|-------------------|--------------------|
| HR (95% CI) | 1 | 3.80 (1.26–11.45) | 4.83 (1.41–16.57) | 14.97 (4.69–47.76) |
|-------------|---|-------------------|-------------------|--------------------|

Multivariate adjusted

| | | | | |
|-------------|---|-------------------|-------------------|--------------------|
| HR (95% CI) | 1 | 3.89 (1.29–11.74) | 5.08 (1.47–17.53) | 15.19 (4.60–50.16) |
|-------------|---|-------------------|-------------------|--------------------|

The age- and sex-adjusted and the multivariate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for sudden cardiac death (SCD), in a 10-year follow-up, were

calculated using the Cox proportional hazards model. Variables included in the multivariate analyses consisted of age, sex, systolic blood pressure, total serum cholesterol, diabetes, current smoker, coronary artery disease, and the ECG risk score. There was no significant interaction between the ECG risk score and diagnosed heart failure in the age- and sex-adjusted analysis (P=0.771) or in the multivariate analysis (P=0.754).

Supplemental Table 5

Risk of Sudden Cardiac Death Associated with the Secondary ECG Risk Score in a 10-Year Follow-Up in the Mini-Finland Health Survey

| | Secondary ECG Risk Score | | | |
|--------------------------|--------------------------|------------------|--------------------|----|
| | 0 | 1 | 2 | >3 |
| n=4510 (60.8%) | | | | |
| n=1646 (24.1%) | | | | |
| n=591 (8.7%) | | | | |
| n=443 (6.5%) | | | | |
| SCD | | | | |
| No. of SCDs | 25 | 34 | 17 | 47 |
| Age- and sex-adjusted | | | | |
| HR (95% CI) ¹ | 2.71 (1.61–4.56) | 3.32 (1.77–6.25) | 11.10 (6.55–18.81) | |
| Multivariate adjusted | | | | |

| | | | |
|--------------------------|------------------|------------------|----------------------|
| HR (95% CI) ¹ | 2.42 (1.43–4.08) | 2.58 (1.36–4.92) | 8.00 (4.61–13.87) |
|--------------------------|------------------|------------------|----------------------|

SCD = sudden cardiac death. The secondary ECG risk score consisted of all the 8 ECG parameters associated with SCD when analyzed individually: heart rate >80 bpm, PR duration >220 ms, QRS duration >110 ms, left ventricular hypertrophy, T wave inversion, prolonged QTc, frontal QRS-T angle >90°, and ST-segment depressions. Compared to the baseline model of age, sex, systolic blood pressure, total serum cholesterol, current smoker, diabetes, and coronary artery disease, the addition of the secondary ECG risk score significantly improved the model's ability to estimate the risk of SCD. The C-statistics for the baseline model was 0.871, improving to 0.897 using the secondary ECG risk score, representing a statistically significant improvement of 0.026 (P<0.05). Furthermore, IDI of 0.033 (P<0.05), continuous NRI of 0.298 (P<0.05), and categorical NRI of 0.114 (P<0.05) improved significantly. With the addition of the secondary ECG risk score to the baseline model, 26.0% of the SCD cases were appropriately reclassified into a higher risk group and 13.0% inappropriately reclassified into a lower risk group, whereas of the subjects without SCD 4.2% were appropriately reclassified into a lower risk group and 3.7% inappropriately reclassified into a higher risk group.

Supplemental Table 6

Sudden Cardiac Death Risk Associated with ECG Parameters in a 10-year Follow-Up in the Coronary Heart Disease Study

| ECG parameters | ECG parameters individually | | ECG parameters in the |
|----------------|-----------------------------|--------------------------|--------------------------|
| | n (%) | HR (95% CI) ^P | same model |
| | | | HR (95% CI) ^P |

| | | | |
|------------------------------|------------------|-------------------|------------------|
| Heart rate >80bpm | 3397 (32.0%) | 1.63 (1.11–2.39) | 0.13 |
| | 1.72 (1.17–2.53) | 0.006 | |
| PR >220ms | 122 (1.1%) | 3.08 (1.25–7.54) | 0.014 |
| | 0.014 | | 3.08 (1.25–7.60) |
| QRS >110ms | 66 (0.6%) | 6.22 (2.88–13.41) | <0.001 |
| | (2.21–10.81) | <0.001 | 4.89 |
| Left ventricular hypertrophy | 3352 (31.6%) | 1.41 (0.98–2.04) | |
| | 0.067 | 1.42 (0.98–2.06) | 0.064 |
| T-wave inversion | 74 (0.7%) | 6.88 (3.19–14.83) | <0.001 |
| | (2.28–11.21) | <0.001 | 5.05 |

Association between individual ECG parameters used in the ECG risk score and SCD risk in the validation cohort. The number of subjects with ECG parameters (% of the total study population). Age- and sex-adjusted hazard ratios (HRs), 95% confidence intervals (CIs), and P values for SCD risk associated with ECG parameters calculated using the Cox proportional hazards model. Each ECG parameter was first analyzed individually and then simultaneously with other ECG parameters in the same model.

Supplemental Table 7

Baseline Characteristics of the Coronary Heart Disease Study Population According to the ECG Risk Score

| | ECG risk score | | | |
|-------------|----------------|------------|--------------|-------------|
| | 0 | 1 | 2 | ≥3 |
| | n=4681 | n=4887 | n=1023 | n=26 |
| Male (%) | 2532 (50.2%) | | 2621 (53.6%) | 598 (58.5%) |
| Age (years) | 43.7 ± 8.3 | 44.0 ± 8.5 | 45.0 ± 8.8 | 49.4 ± 7.8 |

| | | | | |
|--------------------------------------|--------------|--------------|--------------|--------------|
| Systolic blood pressure (mmHg) | 132.2 ± 18.3 | 141.4 ± 21.5 | 152.2 ± 24.4 | 159.6 ± 26.7 |
| Diastolic blood pressure (mmHg) | 80.1 ± 11.2 | 83.2 ± 12.7 | 87.0 ± 14.4 | 92.0 ± 17.4 |
| Body mass index (kg/m ²) | 26.0 ± 3.8 | 25.9 ± 4.0 | 25.6 ± 3.6 | 26.0 ± 4.9 |
| Cholesterol (mmol/l) | 6.5 ± 1.3 | 6.5 ± 1.3 | 6.5 ± 1.5 | 6.4 ± 1.2 |
| Smoking (%) | 1576 (33.7%) | 1665 (34.1%) | 371 (36.3%) | 11 (42.3%) |
| Diabetes (%) | 28 (0.5%) | 48 (0.9%) | 9 (0.9%) | 0 (0%) |
| Cardiovascular disease (%) | | 342 (7.3%) | 394 (8.1%) | 105 (10.3%) |

Continuous data are presented as means ± standard deviations and categorical data as the number of cases (% of the total study population). The ECG risk score consisted of 5 ECG abnormalities: heart rate >80 bpm, PR duration >220 ms, QRS duration >110 ms, LVH, and T-wave inversion.

Supplemental Table 8

Discrimination and Calibration with ECG Risk Score in the CHD Study Population

| | Value | P | |
|--|-------|-------|---------------|
| C-statistics of the baseline model | 0.861 | - | |
| C-statistics of the baseline model + ECG risk score | 0.865 | - | |
| C-statistics improvement with the addition of the ECG risk score | 0.004 | | insignificant |
| Categorical NRI | 0.015 | | insignificant |
| Continuous NRI | 0.249 | 0.006 | |
| IDI | 0.007 | 0.016 | |
| GND statistics (chi-squared test) | 114 | | insignificant |

NRI = net reclassification improvement; IDI = integrated discrimination index; GND =

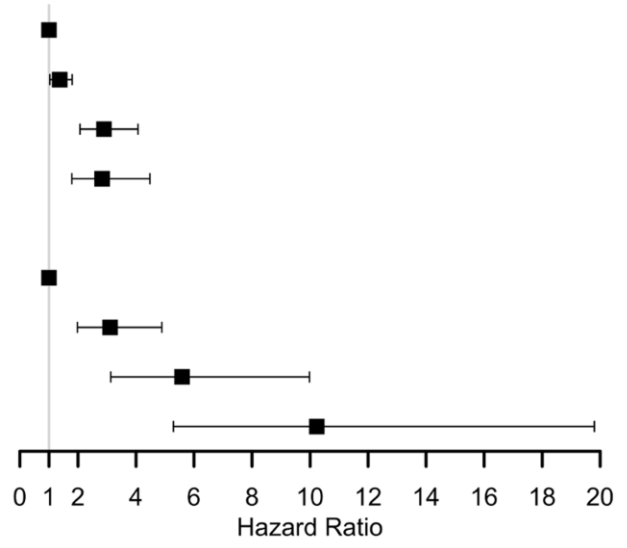
Greenwood-Nam-D'Agostino

Supplemental Figure 1

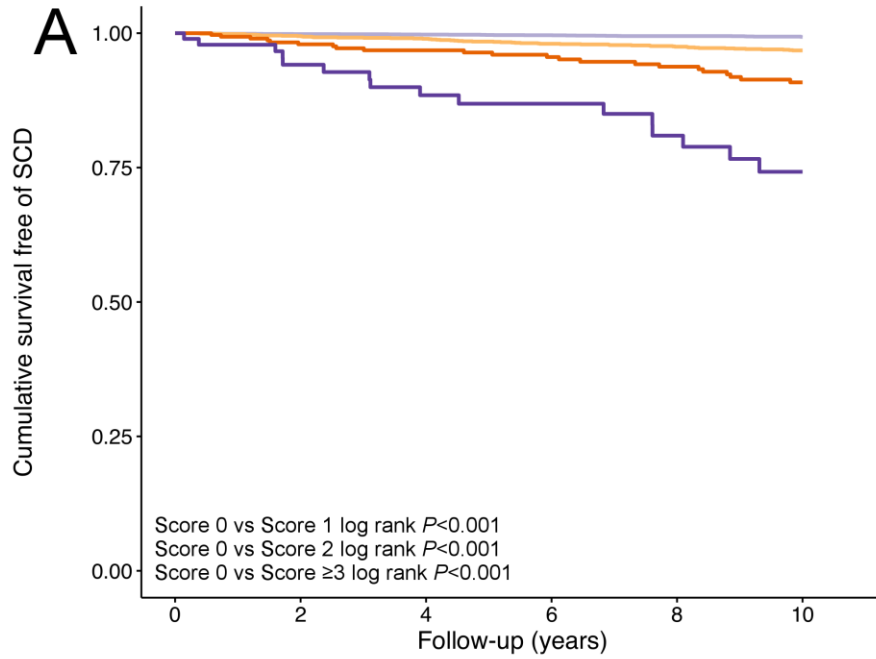
Calibration of the ECG Risk Score with Baseline Model in the CHD Study population

Endpoint Group Subjects Cases

| | | | |
|---------|-----------|------|-----|
| Non-SCD | Score = 0 | 4563 | 105 |
| | Score = 1 | 1859 | 102 |
| | Score = 2 | 312 | 58 |
| | Score ≥ 3 | 96 | 25 |
| SCD | Score = 0 | 4563 | 30 |
| | Score = 1 | 1859 | 55 |
| | Score = 2 | 312 | 22 |
| | Score ≥ 3 | 96 | 16 |



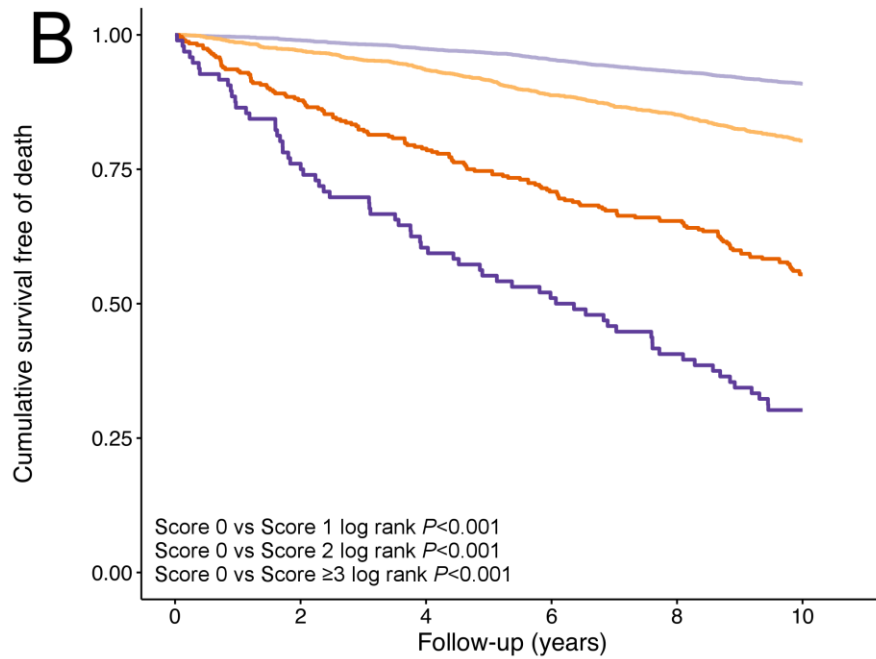
Score 0 — Score 1 — Score 2 — Score ≥ 3 —



Number at risk

| | 0 | 2 | 4 | 6 | 8 | 10 |
|----------------|------|------|------|------|------|------|
| Score = 0 | 4563 | 4517 | 4444 | 4352 | 4250 | 4149 |
| Score = 1 | 1859 | 1805 | 1738 | 1650 | 1583 | 1493 |
| Score = 2 | 312 | 274 | 246 | 221 | 204 | 173 |
| Score ≥ 3 | 96 | 73 | 58 | 49 | 39 | 29 |

Follow-up (years)



Number at risk

| | 0 | 2 | 4 | 6 | 8 | 10 |
|----------------|------|------|------|------|------|------|
| Score = 0 | 4563 | 4517 | 4444 | 4352 | 4250 | 4149 |
| Score = 1 | 1859 | 1805 | 1738 | 1650 | 1583 | 1493 |
| Score = 2 | 312 | 274 | 246 | 221 | 204 | 173 |
| Score ≥ 3 | 96 | 73 | 58 | 49 | 39 | 29 |

Follow-up (years)

