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Impact of age and sex on the long-term prognosis associated with early repolarization in the general population

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Declarations of interest:

None

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Abstract

Background

Early repolarization (ER) has been linked to the risk of sudden cardiac death (SCD) in the general population, although controversy remains regarding risks across various subgroups.

Objective

We investigated whether age and sex influence the prognostic significance of ER.

Methods

We evaluated the 12-lead electrocardiograms of 6631 Finnish general population subjects aged ≥30 years (mean age 50.1 ± 13.9 years, 44.5% men) for the presence of ER (J-point elevation ≥0.1 mV in ≥2 inferior/lateral leads), following them for 24.4 ± 10.3 years. We analyzed the association between ER and the risk of SCD, cardiac death, and all-cause mortality in subgroups according to age (<50 or ≥50 years) and sex.

Results

ER was present in 367 of the 3305 subjects under 50 and in 426 of 3326 subjects aged ≥50 years. ER was not associated with any of the endpoints in the entire study population. After adjusting for clinical factors, ER was associated with SCD (hazard ratio [HR] 1.88; 95% confidence interval [CI] 1.16–3.07) in subjects under 50, but not in older subjects (interaction between ER and age group, *P* = .048). Among the younger subgroup, women with ER had a high risk of SCD (HR 4.11; 95% CI 1.41–12.03), whereas among men ER was not associated with SCD. Finally, ER was not associated with cardiac mortality or all-cause mortality in either age group.

Conclusion

ER associates with SCD in subjects younger than 50 years, particularly in women, but not in subjects 50 years and older.

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Keywords

Electrocardiography; Sudden cardiac death; Early repolarization; Epidemiology; Age groups

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Introduction

An early repolarization (ER) pattern was previously considered a benign electrocardiogram (ECG) pattern, until it was shown to be associated with idiopathic ventricular fibrillation in three separate case-control studies in 2008.[1–3] Subsequently, researchers found that ER was also associated with all-cause mortality, cardiac death, and sudden cardiac death (SCD) in the general population.[4–8] However, some studies found no link between ER and adverse events.[7] Consequently, researchers attempted to distinguish benign ER patterns from patterns that associate with more unfavorable prognoses.[5,9–12] Furthermore, other studies examined whether the prognosis associated with ER varies across different patient subgroups.[6,9,11] In some studies ER was associated with cardiac mortality, particularly among younger middle-aged subjects, whereas in studies among older subjects ER was not associated with an excess risk.[6,13] In young adult populations, however, ER is a prevalent finding and considered a benign phenomenon.[14–16] Whether age affects the risk of SCD associated with ER in adult subjects remains unclear.

Here, we present our investigation of the association between ER and SCD, cardiac mortality, and all-cause mortality in a Finnish general population cohort and examine whether this association differs between subjects younger than 50 years old and those ≥50 years. Furthermore, we assess whether sex impacted the risk associated with ER in these age groups.

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Methods

Study population

The study population consisted of participants of the Mini-Finland Health Survey, a representative sample of the Finnish population, conducted in 1978–1980. The survey consisted of health interviews regarding the subjects' health status, diseases, medications, symptoms, and lifestyle, together with health examinations that measured blood pressure, body mass index, and serum cholesterol, and included an electrocardiogram (ECG). In total, 8000 subjects aged ≥30 years were invited to take part, among whom 7217 participated in the health examination. The extensive survey methods are reported elsewhere.[17] In total, 17 survey participants in this study also participated in a previous cohort study by Tikkanen et al.[4]

Electrocardiographic measurement and analyses

A standard 12-lead ECG was recorded with a paper speed of 50 mm/s for all study subjects during the health examinations conducted in 1978–1980, and subsequently stored for later assessment. The presence of an ER pattern was assessed manually from the original paper ECGs by three physicians in 2016–2018, with assistance from a cardiologist when needed.

An ER pattern was defined and assessed based on a slightly modified version of the recommendations from a published consensus paper.[18] Briefly, we defined an ER pattern as an end-QRS notch or slur on the downward slope of the prominent R-wave at the J-point, with an amplitude of ≥0.1 mV measured with respect to the true baseline determined as the T–P segment. The presence of a pathological Q-wave in the lead with an end-QRS notch or slur was considered a possible peri-infarction block and not classified as an ER pattern.[19] A subject's ECG was considered positive for ER if an ER pattern was present in either ≥2 of the inferior (II, III, or aVF) or ≥2 of the lateral (I, aVL, V4, V5, or V6) leads. An ER amplitude was classified as ≥0.1 mV, but

<0.2 mV or ≥0.2 mV. Each ECG positive for ER was classified according to the configuration of the ER patterns as a slur, notch, or undetermined (no predominant form). The ST-segment was regarded horizontal or descending if the amplitude of the ST-segment 100 ms after the J-point was less than or equal to the amplitude at the J-point end, and ascending if the amplitude was greater than the amplitude at the J-point end.[18] An ECG was classified as a low amplitude T-wave if any T-wave in leads I, II, or V4–V6 was inverted, biphasic, or had an amplitude ≤0.1 mV and ≤10% of the R-wave amplitude in the same lead.[12]

We excluded subjects (n = 248) with missing or unreadable ECGs and subjects (n = 331) with II/III-degree atrioventricular block, ventricular pre-excitation, complete or incomplete bundle branch block, left anterior or posterior fascicular block, QRS duration >110 ms, a pacemaker rhythm, or rare ECG findings not representing the general population. We also excluded subjects (n = 7) with missing data.

Follow-up

Subjects were followed from the baseline examinations in 1978–1980 until the end of 2011 using the Causes of Death Register maintained by Statistics Finland. SCDs likely caused by terminal arrhythmias were determined by two cardiologists. These cardiologists reviewed the data for all deaths from cardiovascular causes from death, hospital, and autopsy records using the SCD definitions based on the modified Cardiac Arrhythmia Suppression Trial (CAST) criteria.[20] In cases of disagreement, a third cardiologist reviewed and classified the case. The primary endpoint was SCD, and the secondary endpoints were cardiac death and death from any cause.

The Mini-Finland Health Survey preceded the current legislation on ethics in medical research. All participants were fully informed about the survey and its implications, participated in the study voluntarily, and were advised that their information would be used for medical research. Agreeing to participate in the baseline health examination was taken to indicate their informed

consent. Record linkage with national health registers to the survey data was approved by the register authorities.

Statistical analysis

Continuous data are presented as the mean ± standard deviation, while categorical data appear as the number of cases and prevalence in the study population in parentheses. We used the general linear model to compare the age- and sex-adjusted mean values for continuous variables, and the prevalence of categorical variables in cross-sectional baseline data. Hazard ratios (HRs), 95% confidence intervals (95% CIs), and *P* values were calculated using the Cox proportional hazards model. We tested the assumption for proportional hazards for each covariate in the final Cox regression model. Age, sex, systolic blood pressure, total serum cholesterol, smoking, diabetes, and coronary artery disease (CAD) were used as covariates in the multivariate models. The statistical significance of the effect modification by age group (subjects aged <50 years and ≥50 years, respectively) and sex were tested using the Wald test by entering an interaction term for ER and age group, and ER and sex, respectively. We considered $P < .05$ as statistically significant. All statistical analyses were performed using IBM SPSS Statistics (version 24) and R (version 3.6.1, https://www.r-project.org/).

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Results

Baseline characteristics of subjects

Table 1 summarizes the baseline characteristics. ER was slightly more prevalent among subjects aged ≥50 years compared to subjects under 50 years (12.8% vs 11.1%; *P* = .033). Subjects with ER were more likely male than subjects without ER among subjects aged <50 (68.1% vs 45.7%; *P* < .001). Yet, we found no significant sex difference in subjects ≥50 years. Subjects under 50 with ER had a lower systolic blood pressure, a lower heart rate, and a shorter QRS duration and QTc interval compared to subjects without ER after adjusting for age and sex. Subjects ≥50 years with ER had a lower heart rate and were less likely to have diabetes, but were more likely to take beta blocker medication compared to subjects without ER after adjusting for age and sex.

Impact of age and sex on ER prognosis

Among 3305 subjects under 50, 748 (22.6%) died during a mean follow-up of 30.2 ± 6.4 years, among whom 237 died from cardiac causes (31.7% of all deaths), and 95 from SCD (12.7% of all deaths). Among those ≥50 years old, 2819 of 3326 subjects (84.8%) died during a mean follow-up of 18.7 ± 10.2 years. Among those who died, 1283 deaths resulted from cardiac causes (45.5% of all deaths) and 251 from SCD (8.9% of all deaths).

Across the entire study population, ER was not associated with any of the endpoints (see Supplemental Material). Furthermore, from the different ER patterns, only ER with a low amplitude T-wave (n=158 [19.9% of ER subjects], multivariate-adjusted HR 1.75; 95% CI 1.06–2.87; *P* = .027) was associated with SCD in the entire study population when compared to subjects without ER (see Supplemental Material). Table 2 shows the risk for SCD and the secondary endpoints associated with ER in the age subgroups, and the interaction between ER and age group. ER was not associated with cardiac death or all-cause mortality in either age group. During the

follow-up period, 5.7% of subjects with ER and 2.5% of subjects without ER under 50 suffered an SCD, compared to 7.7% with and 7.5% without ER, respectively, ≥50 years old. We detected a significant interaction between ER and the age group in SCD (multivariate-adjusted $P = .048$). In addition, ER was associated with an increased risk of SCD in subjects under 50 in the multivariate analysis (HR 1.88; 95% CI 1.16–3.07; $P = .011$), whereas among subjects ≥50 years ER was not associated with an increased SCD risk. Figure 1 provides the survival plots according to age group for SCD adjusted for confounders.

Among subjects under 50, we detected a significant interaction between ER and sex in SCD after adjusting for age ($P = .024$), which did not remain significant in the multivariate analysis ($P = .092$). When women under 50 were analyzed separately, ER was associated with a high risk of SCD in both the age-adjusted (HR 5.34; 95% CI 1.88–15.19; $P = .002$) and multivariate-adjusted (HR 4.11; 95% CI 1.41–12.03; $P = .010$) analyses when compared to subjects without ER. Figure 2 provides an example ER pattern from a woman under 50 years old. In comparison, ER was not associated with SCD among men under 50. Neither men nor women under 50 with ER exhibited an increased risk for cardiac death or all-cause mortality.

Risk of SCD based on the ER pattern in subjects under 50

Table 3 summarizes the risks of SCD based on the ER pattern among subjects under 50 in the multivariate analyses. When assessed by ER localization, both inferior (HR 1.92; 95% CI 1.04–3.56; $P = .038$) and lateral (HR 2.08; 95% CI 1.10–3.95; $P = .024$) ER localizations were associated with SCD risk among subjects under 50. Furthermore, a slurred ER (HR 2.09; 95% CI 1.19–3.67; $P = .010$), ER with a horizontal or descending ST-segment (HR 3.12; 95% CI 1.56–6.26; $P = .001$), and ER with a low amplitude T-wave (HR 4.47; 95% CI 1.75–11.42; $P = .002$) were associated with SCD risk among subjects under 50 years old.

Discussion

We evaluated the prognosis associated with ER based on sex and age groups in a large representative population cohort with a long follow-up period. We found that ER was associated with an increased risk of SCD among adults aged 30–50 years, whereas no increased SCD risk was observed among subjects with ER aged ≥50 years. Furthermore, among subjects under 50, women with ER exhibited a high SCD risk, whereas ER was not associated with SCD among men.

In this study, ER prevalence reached 12.0% in the entire study population. In previous studies, the prevalence of ER ranged from 0.9% to 23.9%.[7,8,21] We defined ER following minor adjustments as recommended in a recent consensus paper. We measured the ER amplitude with respect to the true baseline determined as the T–P segment, compared to with respect to the QRS onset suggested by the consensus paper. This difference could have had an effect on the ER amplitude measurements, especially on tachycardic subjects. The ER definition used in the present study is similar albeit somewhat modified to that used in a previous Finnish middle-aged general population cohort study in which ER prevalence was 5.8%.[4,10,18] A possible explanation for the difference in the ER prevalence between these studies may lie in the improved ECG quality in the present study given the more modern recording device, as borderline cases would be determined ER positive in the present study and negative in the previous study. Concordant with previous studies, ER was more prevalent among men younger than 50, whereas no sex difference was identified among older subjects.[16] One possible explanation for this may lie in the association between ER and testosterone levels in men, which begin declining before the age of 50.[22]

Previously, few studies examined ER prognosis in different age groups. In a German cohort study, ER was associated with all-cause and cardiac mortality among subjects aged 35–54, while ER was not associated with an adverse prognosis in older age groups.[6] Similarly, in a Japanese cohort study, subjects aged <60 years with ER exhibited an increased risk for cardiac

death, while subjects with ER ≥60 years carried no such increased risk.[13] However, in young adults aged 18–30 in the United States, ER with an ascending ST-segment was not associated with adverse outcomes, and the prevalence of ER markedly decreased during the follow-up period.[14] Interestingly, the prevalence of ER with an ascending ST-segment appears to change in male and female subjects throughout puberty, while the prevalence of ER with a horizontal or descending ST-segment remains fairly constant among children, adolescents, and middle-aged subjects.[10,15,23]

To our knowledge, no previous studies examined the impact of age on SCD risk related to ER. In our study, subjects aged 30–50 years exhibited an increased risk of SCD, while ≥50-year-old subjects with ER showed no increase in SCD risk. Previous studies demonstrated that ER may predispose an individual to a fatal arrhythmia during ischemic or nonischemic events.[11,24] This vulnerability could manifest after a longer time period, perhaps explaining why ER was associated with SCD only among the younger subjects in our study. Furthermore, older subjects may have died due to other comorbidities before a critical event occurred. A plausible explanation could then be that ER in young adults, particularly with an ascending ST-segment, represents a benign ECG finding that normally disappears before middle age. This stands in contrast to a more constant and unchanging ER with a descending or horizontal ST-segment, which associates with a long-term vulnerability to more nefarious arrhythmias.[14–16] It may also be that the most malign ER phenotypes manifest at a younger age and, thus, the more benign ER phenotypes may be overrepresented among the very old. Moreover, as the risk of SCD increases with age, other factors may associate with SCD risk more strongly than ER in older individuals.

Previous studies have provided contradictory results on the impact of sex on ER prognosis. For example, a German study found that ER was associated with cardiac mortality in a subgroup of men, but not among women.[6] In contrast, a cohort study from the United States demonstrated an association between ER and SCD only among women.[9] However, in the same study population, automatically detected ER was associated with cardiovascular mortality only

among men.[25] We, however, observed an association between ER and the risk of SCD in women under 50, but not among men.

Various studies provide a large degree of heterogeneous results in their examinations of the risk associated with ER among general populations, with several studies finding no link between ER and an increased risk of adverse outcomes.[7,9,21] In the present study, we found that ER was not associated with SCD, cardiac mortality, or all-cause mortality across the entire study population. Possible explanations for these contradicting results across studies include the different study population characteristics, follow-up periods, and ER definitions applied. In addition, only a small minority of subjects with ER will eventually experience SCD, while the majority will enjoy benign prognoses. Therefore, future research should continue to refine or better define the specific patient characteristics and ER pattern features to more accurately identify that minority of individuals who will suffer an SCD. Better identifying such individuals will ultimately serve to improve their prognosis.

Limitations

Although the subjects underwent extensive health interviews and examinations at the beginning of the survey, the subjects' health status or the presence of ER in ECG were not reassessed during the follow-up period. Therefore, we had no information on whether participants' health status, comorbidities, or ER status changed during the follow-up period. Yet, ER has been shown to be relatively stable ECG finding among middle-aged subjects.[4] A further limitation to this study lies in the study population, which consisted of only Caucasian subjects. Thus, these results are not directly generalizable to other ethnicities.

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Conclusions

In conclusion, among adults aged 30–50 years, ER associates with SCD. In particular, women under 50 years old with ER exhibited a higher risk of SCD, while ER was not associated with SCD among men <50 years old. In addition, we found that among subjects ≥50 years old, ER was not associated with an adverse prognosis at all. Future research should focus on identifying factors that account for the differences between age groups, and improving the risk stratification in younger patient populations with ER.

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Conflicts of Interest

None declared.

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References

1. Haïssaguerre M, Derval N, Sacher F, et al.: Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008; 358:2016–2023.

2. Nam G-B, Kim Y-H, Antzelevitch C: Augmentation of J waves and electrical storms in patients with early repolarization. N Engl J Med 2008; 358:2078–2079.

3. Rosso R, Kogan E, Belhassen B, et al.: J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. J Am Coll Cardiol 2008; 52:1231–1238.

4. Tikkanen JT, Anttonen O, Junttila MJ, et al.: Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2009; 361:2529–2537.

5. Rollin A, Maury P, Bongard V, et al.: Prevalence, prognosis, and identification of the malignant form of early repolarization pattern in a population-based study. Am J Cardiol 2012; 110:1302–1308.

6. Sinner MF, Reinhard W, Müller M, et al.: Association of early repolarization pattern on ECG with risk of cardiac and all-cause mortality: a population-based prospective cohort study (MONICA/KORA). PLoS Med 2010; 7:e1000314. 7. Cheng Y-J, Lin X-X, Ji C-C, et al.: Role of Early Repolarization Pattern in Increasing Risk of Death. J Am Heart Assoc 2016; 5:e003375.

8. Haruta D, Matsuo K, Tsuneto A, et al.: Incidence and prognostic value of early repolarization pattern in the 12-lead electrocardiogram. Circulation 2011; 123:2931–2937.

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9. Olson KA, Viera AJ, Soliman EZ, Crow RS, Rosamond WD: Long-term prognosis associated with J-point elevation in a large middle-aged biracial cohort: the ARIC study. Eur Heart J 2011; 32:3098–3106.

10. Tikkanen JT, Junttila MJ, Anttonen O, et al.: Early repolarization: electrocardiographic phenotypes associated with favorable long-term outcome. Circulation 2011; 123:2666–2673.

11. Adler A, Rosso R, Viskin D, Halkin A, Viskin S: What do we know about the "malignant form" of early repolarization? J Am Coll Cardiol 2013; 62:863–868.

12. Roten L, Derval N, Maury P, et al.: Benign vs malignant inferolateral early repolarization: Focus on the T wave. Heart Rhythm 2016; 13:894–902.

13. Hisamatsu T, Ohkubo T, Miura K, et al.: Association between J-point elevation and death from coronary artery disease--15-year follow up of the NIPPON DATA90. Circ J 2013; 77:1260–1266.

14. Ilkhanoff L, Soliman EZ, Prineas RJ, et al.: Clinical characteristics and outcomes associated with the natural history of early repolarization in a young, biracial cohort followed to middle age: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Circ Arrhythm Electrophysiol 2014; 7:392–399.

15. Sager SJ, Hoosien M, Junttila MJ, et al.: Comparison of inferolateral early repolarization and its electrocardiographic phenotypes in pre- and postadolescent populations. Am J Cardiol 2013; 112:444–448.

16. Lanza GA, Mollo R, Cosenza A, et al.: Prevalence and clinical correlates of early repolarization and J wave in a large cohort of subjects without overt heart disease. J Electrocardiol 2012; 45:404–410.

17. Knekt P, Rissanen H, Järvinen R, Heliövaara M: Cohort Profile: The Finnish Mobile Clinic Health Surveys FMC, FMCF and MFS. Int J Epidemiol 2017; 46:1760–1761i.

18. Macfarlane PW, Antzelevitch C, Haissaguerre M, et al.: The Early Repolarization Pattern: A Consensus Paper. J Am Coll Cardiol 2015; 66:470–477.

19. Castle CH, Keane WM: Electrocardiographic "Peri-Infarction Block" A Clinical and Pathologic Correlation. Circulation 1965; 31:403–408.

20. Pratt CM, Greenway PS, Schoenfeld MH, Hibben ML, Reiffel JA: Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. Circulation 1996; 93:519–524.

21. Klatsky AL, Oehm R, Cooper RA, Udaltsova N, Armstrong MA: The early repolarization normal variant electrocardiogram: correlates and consequences. Am J Med 2003; 115:171–177.

22. Junttila MJ, Tikkanen JT, Porthan K, et al.: Relationship between testosterone level and early repolarization on 12-lead electrocardiograms in men. J Am Coll Cardiol 2013; 62:1633–1634.

23. Rosso R, Glikson E, Belhassen B, et al.: Distinguishing "benign" from "malignant early repolarization": the value of the ST-segment morphology. Heart Rhythm 2012; 9:225–229.

24. Holmström LTA, Haukilahti MA, Tikkanen JT, et al.: Inferolateral early repolarization among non-ischaemic sudden cardiac death victims. Europace 2018; 20:f93–f98.

25. O'Neal WT, Wang YG, Wu H-T, et al.: Electrocardiographic J Wave and Cardiovascular Outcomes in the General Population (from the Atherosclerosis Risk In Communities Study). Am J Cardiol 2016; 118:811–815.

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Tables

Table 1

Baseline characteristics

	All n = 6631			Age <50 years n = 3305			Age ≥50 years n = 3326		
	No ER n = 5838 (88.0%)	ER n = 793 (12.0%)	*P*	No ER n = 2938 (88.9%)	ER n = 367 (11.1%)	*P*	No ER n = 2900 (87.2%)	ER n = 426 (12.8%)	*P*
Male (%)†	2522 (43.2%)	432 (54.5%)	< .001	1342 (45.7%)	250 (68.1%)	< .001	1180 (40.7%)	182 (42.7%)	.405
Age (years)‡	51.0 ±13.9	52.1 ±13.8	.006	39.3 ±5.8	39.6 ±5.9	.434	62.7 ±8.8	62.9 ±8.6	.680
Systolic blood pressure (mmHg)§	143.2 ±23.2	143.0 ±22.3	.074	132.3 ±16.6	131.9 ±15.2	.033	154.3 ±23.7	152.5 ±23.0	.114
Diastolic blood pressure (mmHg)§	86.8 ±11.5	87.2 ±11.5	.633	84.9 ±11.2	85.6 ±10.9	.397	88.8 ±11.5	88.6 ±11.9	.661
Body mass index (kg/m^2)§	25.9 ±4.1	26.2 ±4.1	.082	25.0 ±3.8	25.3 ±3.6	.583	26.8 ±4.2	26.9 ±4.4	.425
Cholesterol (mmol/l, *mg/dl*)§	6.9 ±1.4 *268* *±53*	7.1 ±1.5 *274* *±57*	.008	6.6 ±1.3 *254* *±48*	6.7 ±1.3 *260* *±49*	.293	7.3 ±1.4 *283* *±53*	7.4 ±1.6 *286* *±61*	.164
Heart rate (bpm)§	69 ±14	65 ±12	< .001	67 ±12	63 ±11	< .001	71 ±15	66 ±14	< .001
QRS duration (ms)§	85	85	.079	86	86	.001	85	85	.793

	±9	±8		±9	±8		±9	±8	
QTc interval (ms)§	404 ±24	400 ±25	.004	400 ±23	393 ±25	.009	407 ±24	405 ±24	.254
Smoking (%)§	1266 (21.7%)	199 (25.1%)	.291	779 (26.5%)	118 (32.2%)	.544	487 (16.8%)	81 (19.1%)	.301
Diabetes (%)§	320 (5.5%)	27 (3.4%)	.002	34 (1.2%)	4 (1.1%)	.662	286 (9.9%)	23 (5.4%)	.002
Coronary artery disease (%)§	603 (10.3%)	76 (9.6%)	.067	55 (1.9%)	8 (2.2%)	.987	548 (18.9%)	68 (16.0%)	.107
Beta blocker medication (%)§	370 (6.3%)	73 (9.2%)	.007	88 (3.0%)	17 (4.6%)	.136	282 (9.7%)	56 (13.1%)	.029

ER = early repolarization; QTc = QT corrected for heart rate using Bazett's formula. Continuous data are presented as means ± standard deviation, while categorical data are presented as the number of cases (% of study population). Statistical test for the difference between subjects with and without ER in all subjects, subjects aged <50 years, and subjects aged ≥50 years.

†Adjusted for age.

‡Adjusted for sex.

§Adjusted for age and sex.

354 *Table 2*

355 Risk of sudden cardiac death, cardiac death, and death from any cause associated with ER in

356 subjects aged <50 years and subjects aged ≥50 years

357

	Age <50 years n = 3305		Age ≥50 years n = 3326		ER*age group interaction
	No ER n = 2938	ER n = 367	No ER n = 2900	ER n = 426	*P*
SCD					
# of SCDs	74	21	218	33	
(# of SCDs in men)	(62)	(16)	(123)	(19)	
Age- and sex-adjusted HR (95% CI)	1	1.72 (1.05–2.80)	1	1.01 (0.70–1.46)	.045
Multivariate-adjusted HR (95% CI)	1	1.88 (1.16–3.07)	1	1.01 (0.70–1.46)	.048
Cardiac death					
# of cardiac deaths	199	38	1112	171	
(# of cardiac deaths in men)	(150)	(31)	(507)	(82)	
Age- and sex-adjusted HR (95% CI)	1	1.20 (0.85–1.70)	1	1.03 (0.88–1.21)	.170
Multivariate-adjusted HR (95% CI)	1	1.13 (0.79–1.60)	1	1.08 (0.92–1.27)	.175
Death					
# of deaths	649	99	2442	377	
(# of deaths in men)	(404)	(75)	(1052)	(166)	

Age- and sex-adjusted HR (95% CI)	1	1.05 (0.85–1.30)	1	1.04 (0.93–1.16)	.585
Multivariate-adjusted HR (95% CI)	1	1.03 (0.83–1.28)	1	1.07 (0.96–1.19)	.620

358

359 ER = early repolarization; SCD = sudden cardiac death. The hazard ratios (HRs) and 95%
360 confidence intervals (CIs) were calculated using the Cox proportional hazards model. Variables
361 included in the multivariate analyses were age as a continuous variable, sex, systolic blood pressure,
362 total serum cholesterol, coronary artery, diabetes, smoking, and ER. The effect modification was
363 tested by entering an interaction term for ER and the age group in the multivariate analysis.

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Table 3

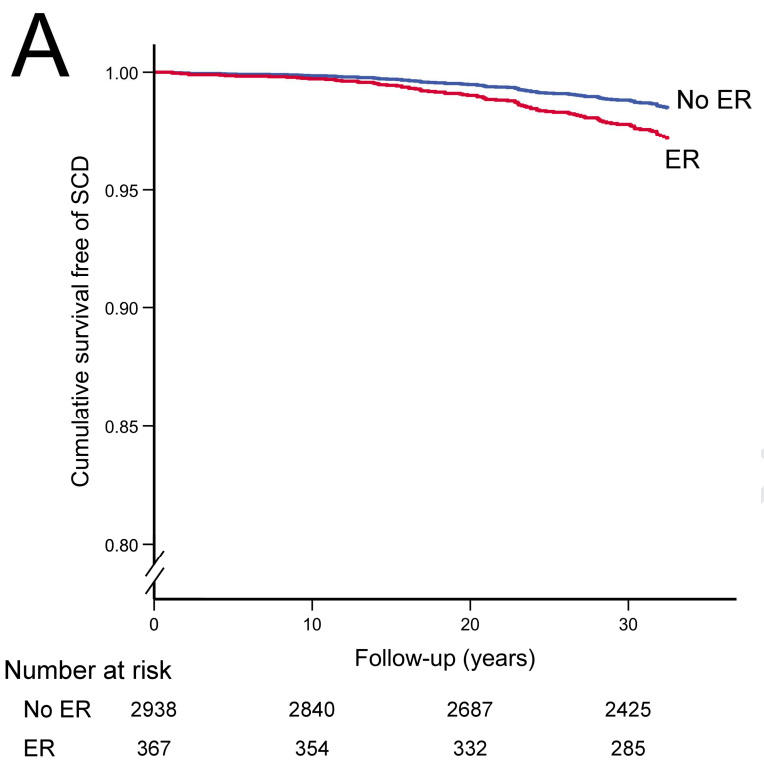
Risk of sudden cardiac death according to the ER pattern in subjects aged <50 years

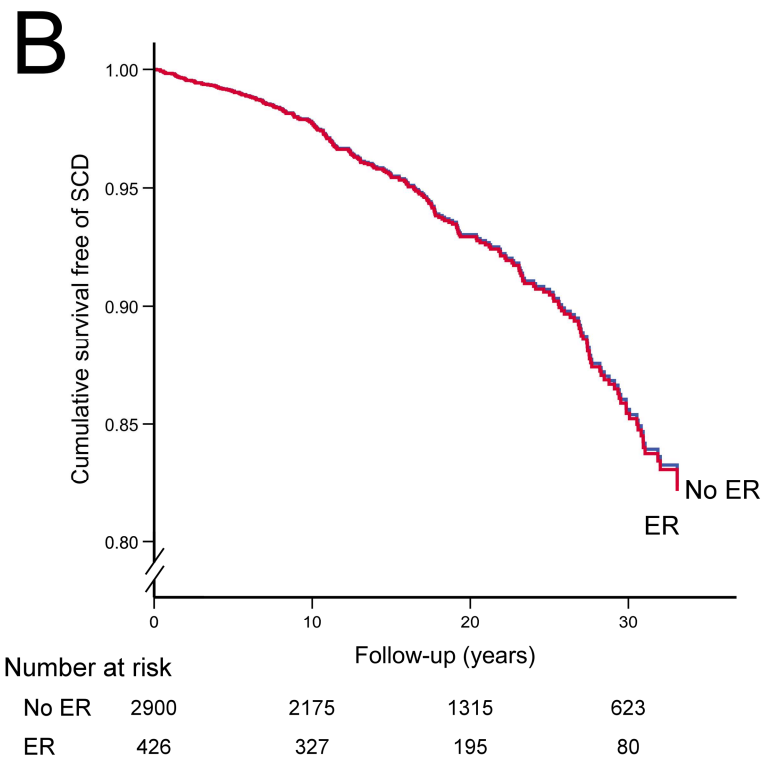
	Age <50 years n = 3305			
	# of subjects	# of SCDs	Age- and sex-adjusted HR (95% CI)	Multivariate-adjusted HR (95% CI)
No ER	2938	74	1	1
Inferior/lateral ER	367	21	1.72 (1.05–2.80)	1.88 (1.16–3.07)
Inferior ER	213	12	1.72 (0.93–3.19)	1.92 (1.04–3.56)
Lateral ER	174	11	1.80 (0.95–3.39)	2.08 (1.10–3.95)
Slurred inferior/lateral ER	251	15	1.82 (1.04–3.18)	2.09 (1.19–3.67)
Notched inferior/lateral ER	74	4	1.59 (0.58–4.37)	2.28 (0.82–6.31)
Inferior/lateral ER, ascending ST-segment	253	12	1.34 (0.72–2.47)	1.45 (0.78–2.67)
Inferior/lateral ER, horizontal or descending ST-segment	114	9	2.74 (1.37–5.47)	3.12 (1.56–6.26)
Inferior/lateral ER ≥0.1 mV but <0.2 mV	300	21	2.00 (1.23–3.25)	2.16 (1.33–3.52)
Inferior/lateral ER ≥0.2 mV	46	0	—	—
Low amplitude T-wave	29	5	6.79 (2.73–16.89)	4.47 (1.75–11.42)

The hazard ratios (HRs) and 95% confidence intervals (CIs) for sudden cardiac death were calculated using the Cox proportional hazards model. Variables included in the multivariate analyses were age, sex, systolic blood pressure, total serum cholesterol, diabetes, smoking, coronary artery disease, and the ER pattern.

Figures

Figure 1





375 *Figure 1 legend*

376 Survival plots of A) subjects aged <50 years and B) subjects aged ≥50 years with and without ER
377 for sudden cardiac death (SCD), adjusted for age, sex, systolic blood pressure, total serum
378 cholesterol, smoking, diabetes, and coronary artery disease.

379

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Figure 2

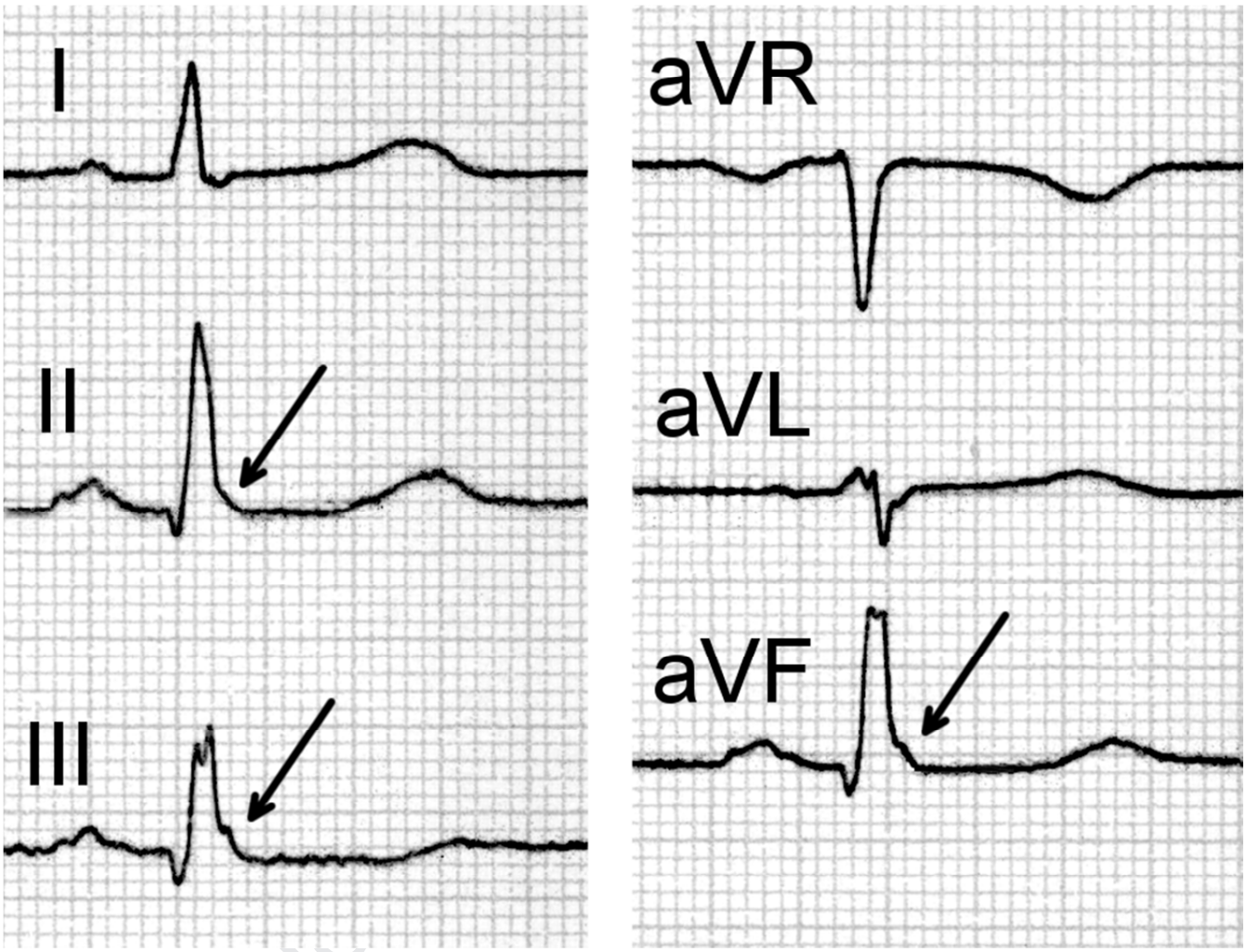


Figure 2 legend

Forty-five-year-old woman with typical inferior ER pattern with horizontal ST-segments. She died of sudden cardiac death during the follow-up period. Paper speed is 50 mm/s. Arrows indicate the ER patterns.

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Table 1
Baseline characteristics

	All n = 6631			Age <50 years n = 3305			Age ≥50 years n = 3326		
	No ER n = 5838 (88.0%)	ER n = 793 (12.0%)	*P*	No ER n = 2938 (88.9%)	ER n = 367 (11.1%)	*P*	No ER n = 2900 (87.2%)	ER n = 426 (12.8%)	*P*
Male (%)†	2522 (43.2%)	432 (54.5%)	< .001	1342 (45.7%)	250 (68.1%)	< .001	1180 (40.7%)	182 (42.7%)	.405
Age (years)‡	51.0 ±13.9	52.1 ±13.8	.006	39.3 ±5.8	39.6 ±5.9	.434	62.7 ±8.8	62.9 ±8.6	.68
Systolic blood pressure (mmHg)§	143.2 ±23.2	143.0 ±22.3	.074	132.3 ±16.6	131.9 ±15.2	.33	154.3 ±23.7	152.5 ±23.0	.114
Diastolic blood pressure (mmHg)§	86.8 ±11.5	87.2 ±11.5	.633	84.9 ±11.2	85.6 ±10.9	.397	88.8 ±11.5	88.6 ±11.9	.661
Body mass index (kg/m^2)§	25.9 ±4.1	26.2 ±4.1	.082	25.0 ±3.8	25.3 ±3.6	.583	26.8 ±4.2	26.9 ±4.4	.425
Cholesterol (mmol/l, *mg/dl*)§	6.9 ±1.4, *265* *±53*	7.1 ±1.5, *274* *±57*	.008	6.6 ±1.3, *254* *±48*	6.7 ±1.3, *260* *±49*	.293	7.3 ±1.4, *283* *±53*	7.4 ±1.6, *286* *±61*	.164
Heart rate (bpm)§	69 ±14	65 ±12	< .001	67 ±12	63 ±11	< .001	71 ±15	66 ±14	< .001
QRS duration (ms)§	85 ±9	85 ±8	.079	86 ±9	86 ±8	.001	85 ±9	85 ±8	.793
QTc interval (ms)§	404 ±24	400 ±25	.004	400 ±23	393 ±25	.009	407 ±24	405 ±24	.254
Smoking (%)§	1266 (21.7%)	199 (25.1%)	.291	779 (26.5%)	118 (32.2%)	.544	487 (16.8%)	81 (19.1%)	.301
Diabetes (%)§	320 (5.5%)	27 (3.4%)	.002	34 (1.2%)	4 (1.1%)	.662	286 (9.9%)	23 (5.4%)	.002
Coronary artery disease (%)§	603 (10.3%)	76 (9.6%)	.067	55 (1.9%)	8 (2.2%)	.987	548 (18.9%)	68 (16.0%)	.107

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Beta blocker medication (%)§	370 (6.3%)	73 (9.2%)	.007	88 (3.0%)	17 (4.6%)	.136	282 (9.7%)	56 (13.1%)	.004

ER = early repolarization; QTc = QT corrected for heart rate using Bazett's formula. Continuous data are presented as means ± standard deviation, while categorical data are presented as the number of cases (% of study population). Statistical test for the difference between subjects with and without ER in all subjects, subjects aged <50 years, and subjects aged ≥50 years.

† Adjusted for age.

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Table 2

Risk of sudden cardiac death, cardiac death, and death from any cause associated with ER in subjects aged <50 years and subjects aged ≥50 years

	Age <50 years n = 3305		Age ≥50 years n = 3326		ER*age group interaction
	No ER n = 2938	ER n = 367	No ER n = 2900	ER n = 426	*P*
SCD					
# of SCDs	74	21	218	33	
(# of SCDs in men)	(62)	(16)	(123)	(19)	
Age- and sex-adjusted HR (95% CI)	1	1.72 (1.05–2.80)	1	1.01 (0.70–1.46)	0.045
Multivariate-adjusted HR (95% CI)	1	1.88 (1.16–3.07)	1	1.01 (0.70–1.46)	0.048
Cardiac death					
# of cardiac deaths	199	38	1112	171	
(# of cardiac deaths in men)	(150)	(31)	(507)	(82)	
Age- and sex-adjusted HR (95% CI)	1	1.20 (0.85–1.70)	1	1.03 (0.88–1.21)	0.170
Multivariate-adjusted HR (95% CI)	1	1.13 (0.79–1.60)	1	1.08 (0.92–1.27)	0.175
Death					
# of deaths	649	99	2442	377	
(# of deaths in men)	(404)	(75)	(1052)	(166)	
Age- and sex-adjusted HR (95% CI)	1	1.05 (0.85–1.30)	1	1.04 (0.93–1.16)	0.585
Multivariate-adjusted HR (95% CI)	1	1.03 (0.83–1.28)	1	1.07 (0.96–1.19)	0.620

intervals (CIs) were calculated using the Cox proportional hazards model. Variables included in the multivariate analyses were age as a continuous variable, sex, systolic blood pressure, total serum cholesterol, coronary artery, diabetes, smoking, and ER. The effect modification was tested by entering an interaction term for ER and the age group in the multivariate analysis.

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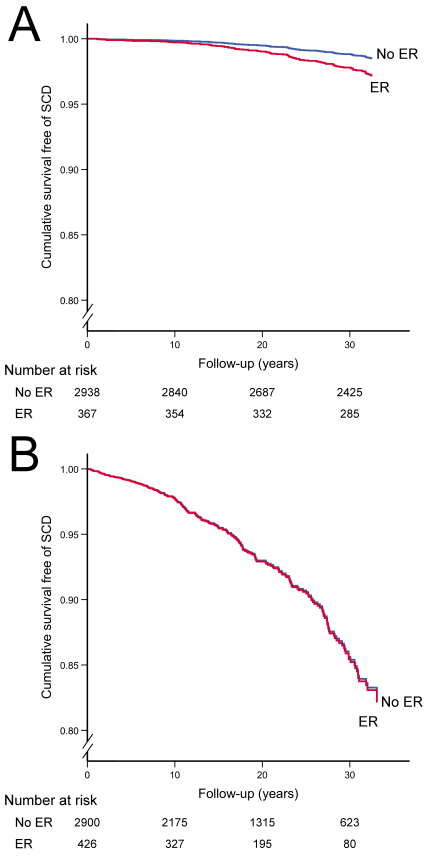
Table 3
Risk of sudden cardiac death according to the ER pattern in subjects aged <50 years

	Age <50 years n = 3305			
	# of subjects	# of SCDs	Age- and sex-adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)
No ER	2938	74	1	1
Inferior/lateral ER	367	21	1.72 (1.05–2.80)	1.88 (1.16–3.07)
Inferior ER	213	12	1.72 (0.93–3.19)	1.92 (1.04–3.56)
Lateral ER	174	11	1.80 (0.95–3.39)	2.08 (1.10–3.95)
Slurred inferior/lateral ER	251	15	1.82 (1.04–3.18)	2.09 (1.19–3.67)
Notched inferior/lateral ER	74	4	1.59 (0.58–4.37)	2.28 (0.82–6.31)
Inferior/lateral ER, ascending ST segment	253	12	1.34 (0.72–2.47)	1.45 (0.78–2.67)
Inferior/lateral ER, horizontal or descending ST segment	114	9	2.74 (1.37–5.47)	3.12 (1.56–6.26)
Inferior/lateral ER ≥0.1 mV but <0.2 mV	300	21	2.00 (1.23–3.25)	2.16 (1.33–3.52)
Inferior/lateral ER ≥0.2 mV	46	0	-	-
Low amplitude T-wave	29	5	6.79 (2.73–16.89)	4.47 (1.75–11.42)

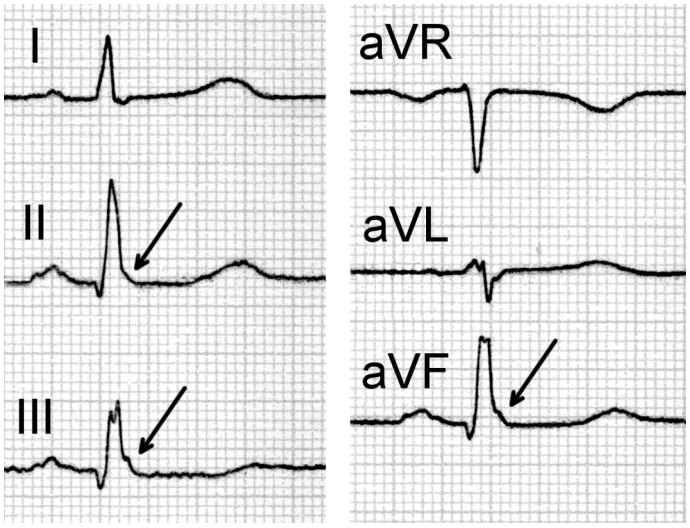
The hazard ratios (HRs) and 95% confidence intervals (CIs) for sudden cardiac death were calculated using the Cox proportional hazards model. Variables included in the multivariate analyses were age, sex, systolic blood pressure, total serum cholesterol, diabetes, smoking, coronary artery disease, and the ER pattern.

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SUPPLEMENTAL MATERIAL

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Supplemental Table 1

Risk of sudden cardiac death, cardiac death, and death from any cause associated with ER in the entire study population

	All n = 6631	
	No ER n = 5838	ER n = 793
SCD		
# of SCDs	292	54
Age- and sex-adjusted HR (95% CI)	1	1.22 (0.91-1.63)
Multivariate-adjusted HR (95% CI)	1	1.23 (0.92-1.64)
Cardiac death		
# of cardiac deaths	1311	209
Age- and sex-adjusted HR (95% CI)	1	1.07 (0.93-1.24)
Multivariate-adjusted HR (95% CI)	1	1.12 (0.96-1.29)
Death		
# of deaths	3091	476
Age- and sex-adjusted HR (95% CI)	1	1.05 (0.95-1.15)
Multivariate-adjusted HR (95% CI)	1	1.07 (0.97-1.18)

ER = early repolarization; SCD = sudden cardiac death.

The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. Variables included in the multivariate analyses were age as a continuous variable, sex, systolic blood pressure, total serum cholesterol, coronary artery, diabetes, smoking, and ER.

Supplemental Table 2

Risk of sudden cardiac death according to the ER pattern in the entire study population

	All n = 6631			
	# of subjects	# of SCDs	Age- and sex-adjusted HR (95% CI)	Multivariate-adjusted HR (95% CI)
No ER	5838	292	1	1
Inferior/lateral ER	793	54	1.22 (0.91–1.63)	1.23 (0.92–1.64)
Inferior ER	392	27	1.29 (0.87–1.92)	1.26 (0.85–1.88)
Lateral ER	429	30	1.20 (0.82–1.75)	1.25 (0.86–1.82)
Slurred inferior/lateral ER	555	38	1.25 (0.89–1.75)	1.26 (0.90–1.76)
Notched inferior/lateral ER	138	10	1.26 (0.67–2.37)	1.29 (0.68–2.43)
Inferior/lateral ER, ascending ST segment	470	28	1.04 (0.71–1.54)	1.10 (0.75–1.63)
Inferior/lateral ER, horizontal or descending ST segment	323	26	1.49 (1.00–2.23)	1.39 (0.93–2.09)
Inferior/lateral ER ≥0.1 mV but <0.2 mV	680	47	1.27 (0.93–1.73)	1.27 (0.93–1.73)
Inferior/lateral ER ≥0.2 mV	113	7	0.98 (0.46–2.07)	1.00 (0.47–2.12)
Low amplitude T-wave	158	17	1.85 (1.13–3.03)	1.75 (1.06–2.87)

The hazard ratios (HRs) and 95% confidence intervals (CIs) for sudden cardiac death (SCD) were calculated using the Cox proportional hazards model. Variables included in the multivariate analyses were age, sex, systolic blood pressure, total serum cholesterol, diabetes, smoking, coronary artery disease and the ER pattern.