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Early Repolarization Pattern and Risk for Arrhythmia Death

A Meta-Analysis

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Objectives A meta-analysis was performed to determine the risk and incidence rate of arrhythmia death, cardiac death, and all-cause death in the general population with the early repolarization pattern (ERP).

Background The ERP has recently been associated with vulnerability to ventricular fibrillation in case-control studies. However, the prognostic significance of the ERP in the general population is controversial.

Methods Relevant studies published through July 31, 2012, were searched and identified in the MEDLINE and Embase databases. Studies that reported risk ratio estimates with 95% confidence intervals (CIs) for the associations of interest were included. Data were extracted, and summary estimates of association were obtained using a random-effects model.

Results Of the 9 studies included, 3 studies reported on arrhythmia death (31,981 subjects, 1,108 incident cases during 726,741 person-years of follow-up), 6 studies reported on cardiac death (126,583 subjects, 10,010 incident cases during 2,054,674 person-years of follow-up), and 6 studies reported on all-cause death (112,443 subjects, 22,165 incident cases during 2,089,535 person-years of follow-up). The risk ratios of the ERP were 1.70 (95% CI: 1.19 to 2.42; $p = 0.003$) for arrhythmia death, 0.78 (95% CI: 0.27 to 2.25; $p = 0.63$) for cardiac death, and 1.06 (95% CI: 0.87 to 1.28; $p = 0.57$) for all-cause death. The estimated absolute risk differences of subjects with the ERP were 70 cases of arrhythmia death per 100,000 subjects per year. J-point elevation $\geq$ 0.1 mV in the inferior leads and notching configuration had an increased risk for arrhythmia death in subgroup studies.

Conclusions The ERP was associated with increased risk and a low to intermediate absolute incidence rate of arrhythmia death. Further study is needed to clarify which subgroups of subjects with the ERP are at higher risk for arrhythmia death. (J Am Coll Cardiol 2013;61:645–50) © 2013 by the American College of Cardiology Foundation

The early repolarization pattern (ERP), which is characterized by an elevation $\geq$ 0.1 mV of the QRS-ST junction (J point) in the inferior and/or lateral leads on 12-lead electrocardiography, has recently been associated with vulnerability to ventricular fibrillation in case-control studies (1–4). However, the prognostic significance of the ERP in the general population is controversial. Some studies have found no significant association between the ERP and cardiac mortality (5–7), whereas other studies recently showed that the ERP was associated with increased risk for arrhythmia death, cardiac death, or all-cause death (7–12).

At the same time, most studies of the ERP have reported only the association between the ERP and risk for death from arrhythmia or cardiac causes, although with routine follow-up, little is known about the incidence of arrhythmia death or cardiac death in the general population with the ERP.

Therefore, we conducted a meta-analysis to summarize all published prospective studies and case-control studies to date on the risk and incidence of cardiac death, arrhythmia death, and all-cause death in the general population with the ERP.

Methods

The meta-analysis was conducted according to the checklist of the Meta-Analysis of Observational Studies in Epidemiology group (13). We performed a systematic search of relevant studies published through July 31, 2012, in the MEDLINE and Embase databases.

Search strategy. Accessing MEDLINE and Embase, we performed a search for studies published through July 31, 2012,

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Abbreviations and Acronyms

CI = confidence interval

ERP = early repolarization pattern

RD = risk difference

RR = risk ratio

using the following search terms and key words: "early repolarization" and "J-wave." We manually checked the reference list of each report. In addition, we reviewed the reference lists of retrieved reports to identify any studies that were not identified from the preliminary searches.

Study selection. Studies were included in the meta-analysis if they met the following criteria: published in the English language, used a prospective design or case-control design, and presented estimates of risk ratios (RRs) or hazard ratios with 95% confidence intervals (CIs) or reported data necessary to calculate these. Seven prospective observational cohort studies and 3 case-control studies have been conducted in which the association between the ERP and risk for cardiac death, arrhythmia death, or all-cause death was assessed.

Data extraction. From each retrieved report, we extracted the following data: name of the lead investigator, year of publication, country where the study was performed, primary and secondary end points, follow-up time, methods for assessment of end points, proportions of men and women, total number of subjects, person-years of follow-up, number of events, confounding factors that were adjusted for in the analysis, and RRs or hazard ratios with 95% CIs. We extracted multivariate-adjusted estimates with and without adjustment for the variables of sex, age, body mass index, left ventricular hypertrophy, diabetes mellitus, coronary artery disease, and smoking status.

Statistical analysis. RRs and 95% CIs were calculated or recalculated for each study and pooled in both fixed-effects and random-effects models. Heterogeneity among studies was formally assessed using Q and I^2 statistics. Publication bias was tested using Egger's regression test. We calculated absolute risk differences (RDs) on the basis of the obtained summary estimate and incidence rates of subjects without the ERP during follow-up. We performed the analysis using Stata version 11 (StataCorp LP, College Station, Texas), RevMan 5 (Cochrane Collaboration, Oxford, United Kingdom), and SPSS version 13 (SPSS, Inc., Chicago, Illinois). Two-sided p values ≤0.05 were considered statistically significant.

Results

The results of the search are shown in Figure 1. We retrieved 1,408 reports in our preliminary search. Of these, 10 were identified for full review (some reported analyses on ≥1 relevant outcome). Three studies reported the association between the ERP and the risk for arrhythmia death, 6 studies reported the association between the ERP and the risk for cardiac death, 6 studies reported the association between the ERP and the risk for all-cause death, and 3 case-control studies reported the association between the ERP and the risk for arrhythmia death. After full review, 1 study of arrhythmia death was excluded because it defined the ERP as an elevation ≥ 0.05 mV of the QRS-ST junction (J point) in the inferior and/or lateral leads on 12-lead electrocardiography. Of the 10 studies, 9 were included in the meta-analysis.

Study characteristics. The characteristics of the included studies are shown in Table 1. For risk for arrhythmia death (3 studies), the total number of subjects was 31,981, with 1,108 events during 726,741 person-years of follow-up. For risk for cardiac death (6 studies), the total number of subjects was 126,583, with 10,010 events during 2,054,674 person-years of follow-up. For risk for all-cause death (6 studies), the total number of subjects was 112,443, with 22,165 deaths during 2,089,535 person-years of follow-up. The mean follow-up durations were 24 years for arrhythmia death, 18 years for cardiac death, and 20 years for all-cause death. The number of potential confounding factors included in the multivariate-adjusted model varied.

In 2 case-control studies, the ERP was more commonly observed among patients with idiopathic ventricular fibrillation than among matched control subjects (31.1% vs. 5.9%, $p < 0.001$). Compared with subjects without the ERP, case subjects with the ERP were at increased risk for recurrent ventricular fibrillation (RR: 2.1; 95% CI: 1.2 to 3.5).

Risk for death. Table 2 shows the results of the random-effects meta-analysis of the relationships between the ERP and arrhythmia, cardiac, and all-cause death. The ERP was associated with a higher risk for death from arrhythmia (RR: 1.70; 95% CI: 1.19 to 2.42; p = 0.003) but not cardiac causes (RR: 0.78; 95% CI: 0.27 to 2.25; p = 0.640) or all causes (RR: 1.06; 95% CI: 0.87 to 1.28; p = 0.570). In the subgroup studies, J-point elevation ≥ 0.2 mV and ≥ 0.1

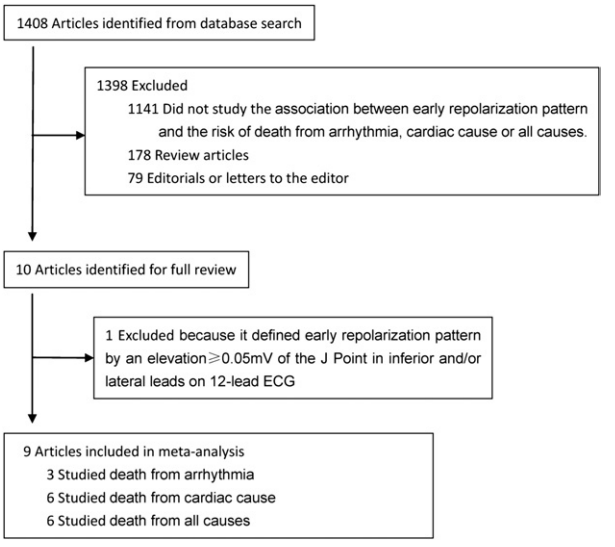

Figure 1 Selection of Studies Included in the Meta-Analysis

ECG = electrocardiography.

Table 1 Characteristics of the Included Studies

First Author (Year) (Ref. #)	Location	Men (%)	Mean Age (yrs)	Follow-Up (yrs)	Ratio of ERP (%)	Number of Events	Total Number of Subjects/ Person-Years	End Point
Cohort studies								
Sinner et al. (2010) (9)	Germany	48.9	52 ± 10	18.9	13.1	2,251	6,213/323,076	Cardiac death, all-cause death
Tikkanen et al. (2009) (8)	Finland	52.4	44 ± 8	30 ± 11	5.8	8,897	10,864/325,920	Cardiac death, all-cause death, arrhythmia death
Haruta et al. (2011) (7)	Japan	43.7	47 ± 15	24 ± 15	23.9	3,515	5,976/143,424	All-cause death, cardiac death, arrhythmia death
Olson et al. (2011) (11)	United States	44.3	54	17 ± 4	12.3	3,555	15,141/257,397	Arrhythmia death, all-cause death,
Uberoi et al. (2011) (6)	United States	87	55 ± 15	7.6 ± 3.8	3.2	1,995	29,281/222,536	Cardiac death
Klatsky et al. (2003) (5)	United States	44	42.5	14	0.9	11,075	73,088/102,3232	All-cause death, cardiac death
Rollin et al. (2012) (12)	France	1.6	49.8 ± 8.6	14.2 ± 2.0	13.2	77	157/16,254	All-cause death, cardiac death
Case-control studies								
Haissaguerre et al. (2008) (1)	Multinational	63.6	36 ± 12	5.1 ± 4.2	31.0	796	206/1,047	Recurrent VF
Rosso et al. (2008) (4)	United States	71	38	3	31.1	45	169/NA	NA

ERP = early repolarization pattern; NA = not available; VF = ventricular fibrillation.

mV in the inferior leads had a higher risk for death from arrhythmia (RR: 3.02; 95% CI: 1.84 to 4.96; $p \leq 0.001$; and RR: 1.58; 95% CI: 1.27 to 1.96; $p \leq 0.001$, respectively) and from cardiac causes (RR: 2.98; 95% CI: 1.85 to 4.94; $p \leq 0.001$; and RR: 1.48; 95% CI: 1.27 to 1.73; $p \leq 0.001$, respectively). Notching configuration had an increased risk for death from arrhythmia (RR: 1.48; 95% CI: 1.06 to 2.08; $p = 0.022$). There was no evidence of publication bias ($p = 0.22$) in the subject risk estimates for arrhythmia death.

Incidence rate of death. Events per 1,000 person-years of arrhythmia, cardiac, and all-cause death were 1.68, 4.81, and 17.06 in subjects with the ERP during follow-up, respectively. The ERP was associated with a higher risk for arrhythmia mortality (RR: 1.70; 95% CI: 1.19 to 2.42; $p = 0.003$) (Fig. 2, Table 3) but not cardiac mortality (RR: 0.78; 95% CI: 0.27 to 2.21; $p = 0.63$) or all-cause mortality (RR: 1.06; 95% CI: 0.85 to 1.31; $p = 0.62$) (Fig. 2, Table 3). The absolute RD of arrhythmia death was 0.07% ($p = 0.005$) (Fig. 3). The corresponding absolute RD on the basis of subjects without the ERP was estimated to be 70 cases of arrhythmia death per 100,000 subjects per year for subjects with the ERP.

Sensitivity analysis. The summary estimates were consistent when analyses were repeated using a fixed-effects model. Omitting 1 study at a time and recalculating the pooled RRs for the remainder of the studies showed that none of the individual studies substantially influenced the pooled RR for any of the outcomes.

Discussion

The ERP has been considered to be a benign finding in the asymptomatic, healthy population (14–17). However, the prognostic significance of the ERP in general population has recently become controversial (5–12,18–26).

The results of this meta-analysis of prospective studies suggest that the ERP is consistently associated with higher risk for arrhythmia death but not cardiac death or all-cause

Table 2 Risk for Death From Arrhythmia, Cardiac Causes, and All Causes in Subjects With ERP

	All-Cause Death			Cardiac Death			Arrhythmia Death		
	Events (Subjects)	RR (95% CI)*	p Value	Events (Subjects)	RR (95% CI)*	p Value	Events (Subjects)	RR (95% CI)*	p Value
ERP									
All ERP positive	1,899 (5,566)	1.06 (0.87–1.28)	0.57	387 (4,364)	0.78 (0.27–2.25)	0.64	142 (3,925)	1.70 (1.19–2.42)	0.003
All ERP negative	20,503 (106,877)			9,570 (122,219)			966 (28,056)		
J-point elevation									
≥0.1 mV in inferior leads	393 (858)	1.42 (0.75–2.71)	0.285	164 (1,043)	1.48 (1.27–1.73)	<0.001	97 (1,161)	1.58 (1.27–1.96)	<0.001
≥0.2 mV in inferior leads	18 (36)	1.54 (1.06–2.24)	0.03	17 (36)	2.98 (1.85–4.92)	<0.001	16 (72)	3.02 (1.84–4.96)	<0.001
≥0.1 mV in lateral leads	169 (262)	1.19 (1.02–1.39)	0.04	76 (741)	1.12 (0.72–1.77)	0.618	38 (1,092)	0.88 (0.60–1.27)	0.484
≥0.1 mV in both inferior and lateral leads	10 (16)	1.30 (0.70–2.43)	0.42	8 (179)	1.22 (0.54–2.73)	0.632	13 (462)	2.14 (1.01–4.54)	0.047
Configuration									
Notching	NA	NA	NA	6 (292)	0.60 (0.30–1.30)	0.200	38 (1,028)	1.48 (1.06–2.08)	0.022
Slurring	NA	NA	NA	13 (319)	0.90 (0.50–1.50)	0.600	31 (438)	1.23 (0.86–1.78)	0.263

*Adjusted for sex, age, body mass index, left ventricular hypertrophy, diabetes mellitus, coronary artery disease, and smoking status.
CI = confidence interval; ERP = early repolarization pattern; NA = not available; RR = risk ratio.

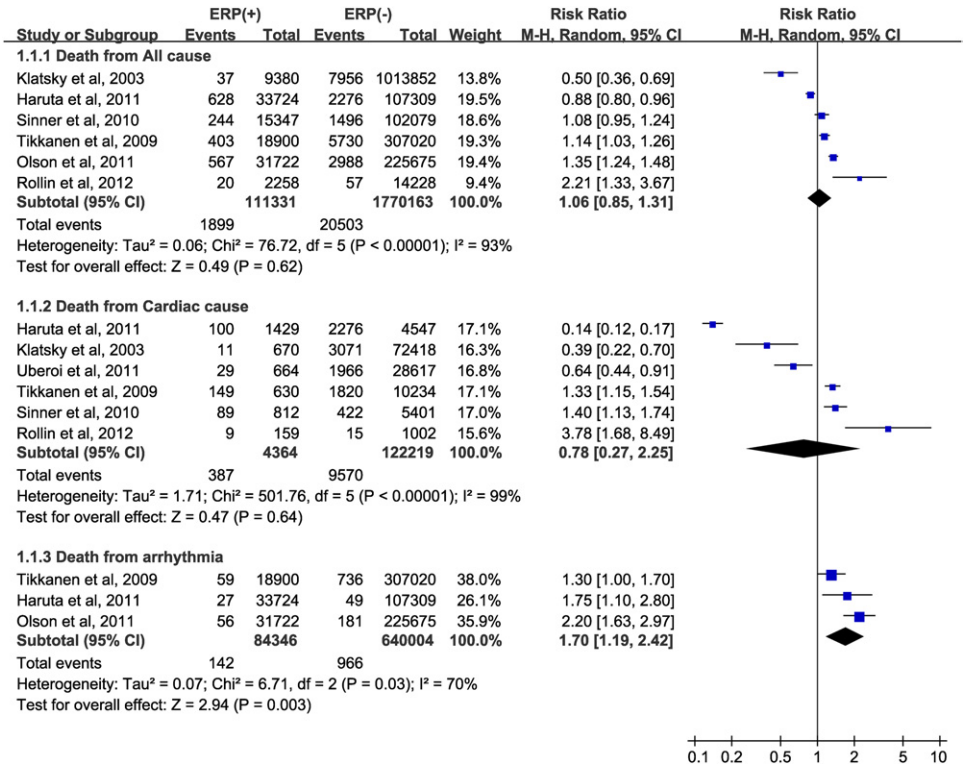

Figure 2 **Incidence Rates and RRs of Arrhythmia, Cardiac, and All-Cause Death in Subjects With the ERP During Follow-Up**

The early repolarization pattern (ERP) was associated with a higher risk for arrhythmia mortality (risk ratio [RR]: 1.70; 95% confidence interval [CI]: 1.19 to 2.42; p = 0.003) but not cardiac mortality (RR: 0.78; 95% CI: 0.27 to 2.21; p = 0.63) or all-cause mortality (RR: 1.06; 95% CI: 0.85 to 1.31; p = 0.62). "Events" represents arrhythmia, cardiac, and all-cause deaths during follow-up. "Total" represents person-years during follow-up. M-H = Mantel-Haenszel.

death. We observed RRs of 1.70 for arrhythmia death, 0.78 for cardiac death, and 1.06 for all-cause death in subjects with the ERP. On the basis of incidence rates in subjects without the ERP, we estimated that the absolute RD was 70 cases per 100,000 subjects per year for arrhythmia death. In subgroup studies, J-point elevation ≥ 0.1 mV in the inferior leads (RR: 1.58) and notching configuration (RR: 1.48) were associated with a higher risk for arrhythmia death in subjects with the ERP.

How the ERP increases the risk for arrhythmia death remains unclear. The current experimental studies support that J-point elevation is a marker of increased transmural heterogeneity of ventricular repolarization, which increases the vulnerability to ventricular fibrillation (27–30).

Table 3 **Incidence Rates and Risks for Arrhythmia Death, Cardiac Death, and All-Cause Death in Subjects With ERP During Follow-Up**

	Events per Person-Years			
	ERP Positive	ERP Negative	RR (95% CI)	p Value
Primary end point				
All-cause death	1,899/111,331	20,503/1,771,583	1.06 (0.85–1.31)	0.62
Cardiac death	387/80,388	9,570/1,747,749	0.78 (0.27–2.21)	0.63
Arrhythmia death	142/84,346	966/640,004	1.70 (1.19–2.42)	0.003
Subgroup study: J-point elevation				
≥0.1 mV in inferior leads	90/22,170	—	1.72 (1.39–2.13)	<0.00001
≥0.2 mV in inferior leads	16/2,196	—	3.06 (1.87–4.99)	<0.00001
≥0.1 mV in lateral leads	31/16,106	—	0.8 (0.56–1.14)	0.22
Configuration				
Notching	38/25,852	—	1.54 (1.11–2.15)	0.01
Slurring	31/12,483	—	1.36 (0.95–1.94)	0.09

CI = confidence interval; ERP = early repolarization pattern; RR = risk ratio.

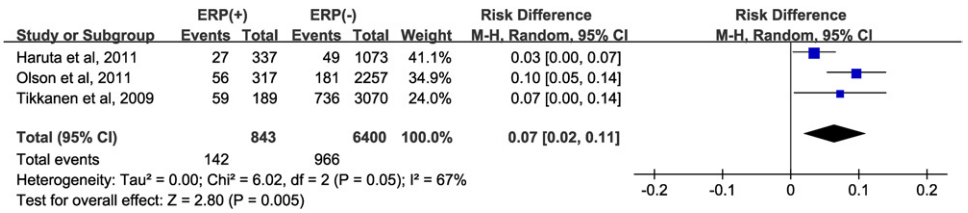

Figure 3 **Absolute RDs of Arrhythmia Death in Subjects With the ERP During Follow-Up**

The risk difference (RD) was 0.07% (p = 0.005) per person-year. The estimated absolute RD was 70 cases per 100,000 person-years for arrhythmia death. "Events" represents arrhythmia deaths during follow-up. "Total" represents person-years per 100 during follow-up. CI = confidence interval; ERP = early repolarization pattern; M-H = Mantel-Haenszel.

Although we identified a higher risk for arrhythmia death, the data from this meta-analysis also reveal a low to intermediate absolute incidence rate of arrhythmia death (70 cases per 100,000 person-years of follow-up) in subjects with the ERP. Therefore, future clinical and experimental studies should focus on understanding the exact mechanisms and reasons for the ERP and clarifying which subgroups of subjects with ERP are at higher risk for arrhythmia death.

Study limitations. There were some limitations to this meta-analysis. First, the relatively small number of studies limited our ability to identify which subgroups were at higher risk for reported events. Second, the small number of studies also limited our ability to determine whether heterogeneity in summary estimates was explained by factors related to study quality. Third, we cannot exclude the possibility of subject confounding and bias due to misclassification. Although the included studies attempted to control various known risk factors, the possibility of subject or unmeasured confounding cannot be ruled out.

Strengths of this study include large sample sizes, long durations of follow-up, and well-established prospective studies or case-control studies. In addition, our pooled estimates were based on prospective analyses with detailed adjustment for confounding variables.

Conclusions

The findings of our meta-analysis of prospective studies suggest the ERP is associated with increased risk and a low to intermediate absolute incidence rate of arrhythmia death. Future clinical and experimental studies should focus on understanding the exact mechanisms and reasons for the ERP and clarifying which subgroups of subjects with the ERP are at higher risk for arrhythmia death.

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Key Words: arrhythmia ■ early repolarization ■ meta-analysis.