# Early repolarization is associated with a significantly increased risk of ventricular arrhythmias and sudden cardiac death in patients with structural heart diseases

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**BACKGROUND** Early repolarization pattern (ERP) has been proved to increase risk of arrhythmia death in the general population, but its prognostic significance in subjects with structural heart disease (SHD) is controversial.

**OBJECTIVE** The purpose of this study was to conduct a meta-analysis of studies assessing the association between ERP and risk of ventricular arrhythmias (VTAs) and sudden cardiac death (SCD) in patients with SHD.

**METHODS** We performed a literature search using MEDLINE (January 1, 1966, to September 25, 2016) and EMBASE (January 1, 1980, to September 25, 2016) with no restrictions. Studies that reported odds ratio (OR) estimates with 95% confidence intervals (CIs) for the associations of interest were included.

**RESULTS** The search yielded 19 observational studies, involving 7268 subjects that reported 1127 cases of VTAs or SCD. In the selected studies, the point estimates of the ORs were consistently greater than 1. Compared with those without ERP, subjects with ERP experienced a significantly increased risk of developing VTAs or SCD (OR 4.76; 95% CI 3.62–6.26), ventricular fibrillation (OR 7.14; 95% CI 4.31–11.82), and SCD (OR 4.07; 95% CI 1.58–10.51). The results were consistent and statistically significant in all subgroups. ERP with J-point elevation in inferior leads, notching configuration, and horizontal or descending ST segment connote higher risk.

**CONCLUSION** ERP is associated with a significant increased risk of VTAs or SCD in patients with SHD. Future research should attempt to understand the exact mechanisms for the arrhythmia risk and to introduce ERP in the risk stratification in this patient group.

**KEYWORDS** Early repolarization pattern; Ventricular tachycardia; Ventricular fibrillation; Sudden cardiac death; Structural heart disease

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## Introduction

Early repolarization pattern (ERP) is a common electrocardiographic variant manifested as J-point elevation or QRS notching or slurring on the standard 12-lead electrocardiogram (ECG).[1] It is prevalent in 2.3%–29.3% of the population, depending on race, age, and sex category.[2] Although ERP generally used to be considered a benign electrocardiographic sign, several recent reports and our previous study indicated that ERP was associated with an increased risk of ventricular arrhythmias (VTAs) and sudden cardiac death (SCD) in the general population.[3–5]

As VTAs and SCD remain leading causes of mortality in patients with structural heart disease (SHD) despite sufficient medication and device therapy, identification of patients at high risk of VTAs and SCD is of particular importance to help frame appropriate prevention and therapeutic decisions. Currently, however, a reliable way to risk stratify the patients is lacking. Some recent studies pointed out that ERP might increase sudden death risk under certain cardiovascular conditions such as acute myocardial infarction and heart failure.[6,7] Therefore, we conducted a meta-analysis to

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summarize all published cohort studies and case-control studies to examine the link between ERP and VTAs or SCD in selected patients with SHD.

## Methods

### Study end point and definitions

The study end point was SCD or VTAs, as defined by *International Classification of Diseases, 10th Revision* codes as ventricular tachycardia (VT), torsades de pointes, ventricular fibrillation (VF), ventricular flutter, sudden cardiac arrest (SCA), and SCD. *SCD* was defined as a natural death from cardiac causes heralded by abrupt loss of consciousness within 1 hour (or 6 hours) of the onset of acute symptoms or an unwitnessed, unexpected death of someone seen in a stable medical condition 24 hours previously with no evidence of a noncardiac cause.

### Search strategy

We searched the publications listed in the electronic databases MEDLINE (source PubMed; January 1, 1966, to September 25, 2016) and EMBASE (January 1, 1980, to September 25, 2016) using the following text and key words in combination both as MeSH terms and text word: *early repolarization*, *J-wave*, *ventricular arrhythmias*, *ventricular tachycardia*, *ventricular fibrillation*, *sudden cardiac death*, *cardiac arrest*, *acute coronary syndrome*, *myocardial infarction*, *coronary heart disease*, *heart failure*, and *cardiomyopathy*. We searched articles published in any language and scrutinized references from these studies to identify other relevant studies.

### Study selection and data abstraction

To minimize differences between studies, we imposed the following methodological restrictions for the inclusion criteria: (1) studies that contained the minimum information necessary to estimate the odds ratio (OR) associated with ERP and a corresponding measure of uncertainty (ie, 95% confidence interval [CI], standard error, variance, or *P* value of the significance of the estimate); (2) cohort studies and case-control studies published as original articles; and (3) studies that were independent. In the case of multiple reports on the same population or subpopulation, we considered the estimates from the most recent or most informative reports. In instances of multiple publications, the most up-to-date or comprehensive information was used.

Two authors (Y.-J.C. and Z.-Y.L.) independently extracted the data. The following data were extracted from each study: first author's name, baseline heart disease, publication year, geographical location, sex category, mean age, study size, study design, number of cardiovascular events, covariates adjusted for in the multivariable analysis, and ORs and the associated measure of variance. When available, we used the most comprehensively adjusted risk estimates.

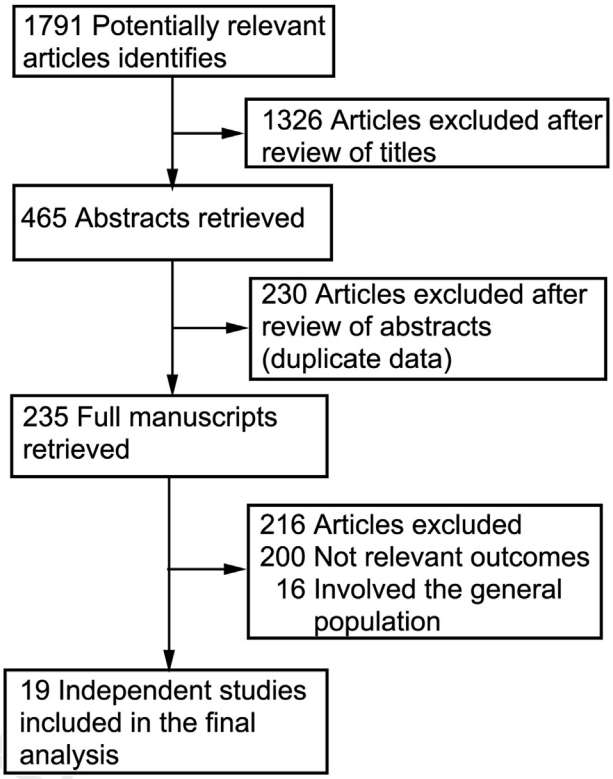


**Figure 1** Flowchart of the selection of studies included in meta-analysis.

### Statistical analysis

The OR was used as a measure of the association between ERP and risk of VTAs or SCD. When the actual OR was not available, we calculated ORs and 95% CIs using Stata version 12.0 (StataCorp LP, College Station, TX).[8] Summary ORs (95% CIs) were calculated by pooling the study-specific estimates using a random-effects model that included between-study heterogeneity (parallel analyses used fixed-effects models), because significant heterogeneity was anticipated in studies.[9] Pooled ORs were expressed with 95% CIs. We calculated the $I^2$ (95% CI) statistic to assess heterogeneity across studies, applying the following interpretation for $I^2$: <50%, low heterogeneity; 50%–75%, moderate heterogeneity; >75%, high heterogeneity.[8] Subgroup analyses and meta-regression models were carried out to investigate potential sources of between-study heterogeneity.[10] We assessed the possibility of publication bias using the Begg test and visual inspection of a funnel plot. The nonparametric "trim and fill" procedure was also performed to further assess the possible effect of publication bias.[11] We used Stata version 12.0 for all analyses. Statistical tests were 2-sided and used a significance level of $P < .05$.

## Results

### Study selection

With the search strategy, 1791 unique citations were initially retrieved. Of these, 235 articles were considered of interest and full text was retrieved for detailed evaluation. Two