# Effect of left ventricular ejection fraction and QRS duration on the survival benefit of implantable cardioverter-defibrillators: Meta-analysis of primary prevention trials

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**BACKGROUND** Implantable cardioverter-defibrillators (ICDs) are recommended for the primary prevention of sudden cardiac death in patients with left ventricular dysfunction, but it is unclear whether treatment benefits are diminished in patients with very low baseline left ventricular ejection fraction (LVEF) ($<25\%$) or increased in those with prolonged QRS duration ($>120$ ms).

**OBJECTIVE** To study the effects of very low LVEF and prolonged QRS duration on the mortality benefits of ICD therapy.

**METHODS** We performed a meta-analysis of primary prevention randomized controlled trials comparing ICD and standard medical therapy. All-cause mortality hazard ratios (HRs) in subgroups according to thresholds of 25% for LVEF and 120 ms for QRS duration were extracted from published reports or contributed by trial investigators and synthesized.

**RESULTS** There was no significant difference of ICD effectiveness in LVEF subgroups of 25%–35% (random effects HR 0.81; 95% confidence interval [CI] 0.70–0.94) vs $<25\%$ (HR 0.71; 95% CI 0.55–0.93). Results were also similar in the narrow and wide QRS subgroups (HR 0.78; 95% CI 0.68–0.90 and HR 0.70; 95% CI 0.51–0.95, respectively). Within the LVEF $<25\%$ and wide QRS subgroups, there was large heterogeneity driven by the Defibrillator in Acute Myocardial Infarction Trial that included patients with early post-myocardial infarction and its results (HR 1.49; 95% CI 0.84–2.68 and HR 1.51; 95% CI 0.83–2.83, respectively) differed significantly from other trials ($P = .008$ and $P = .01$, respectively).

**CONCLUSIONS** LVEF values and QRS duration do not appear to directly modify the survival benefit of ICD in patients with baseline LVEF $<35\%$. However, patients with a recent myocardial infarction do not benefit from ICD, especially when they have LVEF $<25\%$ and/or wide QRS.

**KEYWORDS** Implantable-cardioverter defibrillator; Left ventricular ejection fraction; QRS duration; Primary prevention; Meta-analysis

**ABBREVIATIONS** **CAT** = Cardiomyopathy Trial; **CI** = confidence interval; **DEFINITE** = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; **DINAMIT** = Defibrillator in Acute Myocardial Infarction Trial; **ICD** = implantable cardioverter-defibrillator; **IRIS** = Immediate Risk Stratification Improves Survival; **HR** = hazard ratio; **LVEF** = left ventricular ejection fraction; **MADIT** = Multicenter Automatic Defibrillator Implantation Trial; **MI** = myocardial infarction; **SCD** = sudden cardiac death; **SCD-HeFT** = Sudden Cardiac Death in Heart Failure Trial

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## Introduction

Implantable cardioverter-defibrillators (ICDs) are considered effective in the primary prevention of sudden cardiac death (SCD) in patients with low left ventricular ejection fraction (LVEF) $\leq 35\%$.[1–4] However, patients within this LVEF range may have substantial differences in absolute risk and treatment benefits, depending on their exact LVEF and presence of other potential risk factors.[5–9] Ischemic patients whose only risk factor is LVEF $\leq 30\%$ may have a predicted 2-year arrhythmic death risk $< 5\%$.[5] Also, based on the results from the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)[6] and Immediate Risk Stratification Improves Survival (IRIS)[7] trial, ICD implantation is not considered beneficial within 40 days after myocardial infarction (MI)[3] and may even be harmful after MI in patients with LVEF $\leq 25\%$.[6] Given the considerable risk heterogeneity, it is useful to study more systematically the treatment benefit conferred by ICD to patients with different levels of LVEF.[8]

The benefit of ICD therapy may also depend on QRS duration.[9] Prolonged QRS duration is often associated with enlarged left ventricular volumes and reduced LVEF. In some trials, there has been a nonsignificant trend toward increased benefit from ICD in patients with prolonged QRS duration $> 120$ ms.[10–12]

This meta-analysis aimed at investigating whether ICD benefits for primary SCD prevention differ across LVEF and QRS duration subgroups, specifically whether benefits are diminished in patients with very low LVEF or increased in those with prolonged QRS duration. Given that different trials have published results using different definitions for the pertinent subgroups, we sought to obtain standardized data from eligible trials using consistent definitions of subgroup analyses.

## Methods

### Literature search and eligibility of studies

By using the terms *implantable cardioverter-defibrillator* and *implanted cardioverter-defibrillator*, we searched the MEDLINE database (limited by "Randomized Controlled Trial (Type of Study)" in PubMed) and the Cochrane Central Register of Controlled Trials without year or language restrictions. We also searched the ClinicalTrials.gov and Current Controlled Trials (controlled-trials.com) registries for any studies not yet published in journals as well as the Web sites of recent major cardiology meetings in the United States and Europe (ESC Congress 2011, AHA Scientific Sessions 2011, and ACC Annual Scientific Session 2012) for abstracts and presentations of pertinent studies. Finally, we assessed the references of all eligible papers and the citations (per SCOPUS database) of the earliest trial in the field—the Multicenter Automatic Defibrillator Implantation Trial I (MADIT-I).[13]

We considered trials that randomly assigned patients with ischemic or non-ischemic left ventricular dysfunction to implantation of an ICD vs no ICD or conventional heart failure therapy for the primary prevention of SCD. We accepted the left ventricular dysfunction definition as adopted by each trial's investigators. Studies were eligible regardless of whether they included only MI survivors or not and regardless of the interval between MI and enrollment. We excluded secondary prevention trials (patients surviving near-fatal arrhythmic events), trials comparing ICD vs medical therapy with specific antiarrhythmic agent except beta-blockers, trials combining ICD with resynchronization therapy, trials comparing different types of ICDs or different ICD monitoring modalities, and trials that randomized patients to therapy guided by electrophysiologic testing (followed by ICD implantation as indicated) vs conventional therapy.

### Data extraction and evaluation of bias in trials

For each trial included in the meta-analysis, we recorded general trial characteristics, including enrollment period, eligibility criteria, modes of LVEF and QRS assessment, primary outcome, length of follow-up, and effect of ICDs on overall survival, as well as patient characteristics per treatment arm, including demographics, baseline LVEF and QRS duration, medical history, and medications at enrollment.

In each trial, we assessed the following design/quality characteristics: mode of randomization, allocation concealment, reporting of losses to follow-up, blinding of outcome adjudicators, early trial termination for benefit, and whether analysis followed the intention-to-treat principle. Assessment of publication bias with funnel plot asymmetry testing was not considered appropriate, given the small number of studies.[14]

Finally, we recorded the hazard ratios (HRs) and 95% confidence intervals (CIs) for the effect of ICDs on all-cause mortality overall and specifically in the subgroups of interest based on LVEF and QRS values. We selected cutoffs of 25% for LVEF and 120 ms for QRS duration for the definition of subgroups and applied these consistently across all trials. We selected the 25% cutoff for LVEF because the DINAMIT trial had suggested that ICD may even be harmful, particularly in patients with LVEF $\leq 25\%$.[6] For QRS width, we selected the 120-ms cutoff since this separates patients with normal/narrow QRS from those with wide QRS. Given that subgroup risk estimates were often not reported in primary publications or were reported using different cutoffs, we invited the primary trial investigators to join the meta-analysis protocol and provide these standardized HR estimates from their trials. The longest available follow-up was considered for all trials.

Two authors independently searched the literature, assessed study eligibility, extracted data, and evaluated bias in trials. Discrepancies were resolved by consensus and arbitration by 2 other investigators.

### Analysis

We presented descriptive patient characteristics as frequencies and percentages for categorical data and as means or medians for continuous measures. All-cause mortality HR estimates and 95% CIs for ICD vs control comparisons overall, per LVEF 25%–35% and $< 25\%$, and wide and narrow QRS were log-transformed and quantitatively combined across trials by both fixed effects (inverse

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