Meta-analysis: age and effectiveness of prophylactic implantable cardioverter-defibrillators


CRD summary
The review concluded that available data did not conclusively show that prophylactic ICD therapy improved survival in elderly patients with severe left ventricular dysfunction. That this conclusion was based on a small number of studies should be borne in mind when interpreting the results.

Authors' objectives
To determine the effectiveness of implantable cardioverter-defibrillators (ICDs) for the primary prevention of sudden cardiac death in different age groups of patients with severe left ventricular dysfunction.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), BioMed Central, Cardiosource, ClinicalTrials.gov and Web of Science were searched without language restrictions from 1970 to April 2010. Search terms were reported. Proceedings from the annual American Heart Association, American College of Cardiology, European Society of Cardiology, Heart Rhythm and Europace for the past five years were manually searched. Websites of key journals were searched for relevant oral and expert-slide presentations.

Study selection
Randomised controlled trials (RCTs) that compared ICD therapy with standard medical therapy in patients with ischaemic and non-ischaemic cardiomyopathy and severe left ventricular dysfunction who had not previously had major arrhythmic events were eligible for inclusion. Trials that reported estimated risks for all-cause mortality in patients categorised by age (elderly patients ≥60 years and younger patients <60 years) were included. Trials of prophylactic ICD therapy associated with cardiac resynchronisation therapy were excluded.

ICD therapy was transvenous in all trials, although programming varied. Trial populations included: patients with ischaemic cardiomyopathy (with or without acute myocardial infarction); patients with acute myocardial infarction within the preceding 40 days, left ventricular ejection fraction of 0.5 or less and evidence of cardiac autonomic dysfunction; patients with high risk criteria early after myocardial infarction; and non-ischaemic cardiomyopathy and non-sustained ventricular tachycardia. The age cut-off for defining the older population group differed slightly across trials (≥60 and ≥65 years). Mean follow-up duration was 32 months (range 20 to 45 months). At study entry, 69% to 87% of participants were on beta-blockers and 69% to 97% received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Adverse events were reported in the review.

Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
Trials were assessed for methodological quality using methods proposed by the Cochrane Collaboration that considered selection, performance, detection and attrition bias. Allocation concealment and masking were not considered possible due to ICD implantation being an invasive procedure and were not included as part of the quality assessment.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the hazard ratio (HR) for all-cause mortality and 95% confidence intervals (CIs). The standard error (SE) of logarithm of the hazard ratio was estimated from the 95% CI reported in each study. Investigators of trials that did not report mortality by age were contacted in order to obtain this data. Disagreements were resolved by a third blinded reviewer.

Methods of synthesis
Summary hazard ratios (HRs) together with 95% CIs were estimated using DerSimonian-Laird random-effects models. Heterogeneity was assessed qualitatively. Differences between younger and older patients were assessed using Altman and Bland test for interaction.

Subgroup analysis was conducted of trials considered most relevant to current primary prevention and trials that enrolled patients early after acute myocardial infarction. Sensitivity analyses removed one study at a time and investigated age cut-off and trial populations.

Results of the review
Five RCTs were included in the meta-analysis (n=5,783). None of the included trials had evidence of selection, performance, detection or attrition biases. All trials used a masked committee for adjudication of events and used intention-to-treat analysis.

ICD survival benefit in elderly patients: No statistically significant difference between prophylactic ICD and standard medical therapy was found for all-cause mortality (HR 0.81, 95% CI 0.62 to 1.05; three RCTs). Results were stable after including studies that enrolled patients early after acute myocardial infarction. Sensitivity analysis (age cut-off) did not affect the significance of results.

ICD survival benefit in younger patients: Compared with standard medical therapy, prophylactic ICD therapy significantly reduced all-cause mortality (HR 0.65, 95% CI 0.50 to 0.83; three RCTs). Inclusion of studies that enrolled patients early after acute myocardial infarction and sensitivity analyses (sequential exclusion of studies and age cut-off) did not change the results.

No significant difference was found between younger and older patients (ratio comparison 0.80, 95% CI 0.56 to 1.14). Adverse effects associated with ICD and medical therapy were summarised in an online appendix.

Authors’ conclusions
Available data did not conclusively show that prophylactic ICD therapy improved survival in elderly patients with severe left ventricular dysfunction.

CRD commentary
The review addressed a focused question supported by clearly defined inclusion criteria. A number of relevant sources were searched without language restriction and some attempts were made to identify unpublished studies, which reduced risks of publication and language biases. Appropriate steps were taken to minimise bias and errors during study selection and data extraction; it was unclear whether similar methods were used to assess methodological quality. Study quality was assessed with appropriate criteria and results were reported. Appropriate methods were used to pool studies. There was apparent heterogeneity in both trial design and trial populations; some potential sources of heterogeneity were investigated.

The authors conclusions are supported by the results, but are based on a small number of studies and should be treated with some caution.

Implications of the review for practice and research
Practice: The authors did not state any implication for practice.

Research: The authors stated that well-conducted RCTs of implantable device therapy in elderly patients were needed to confirm these findings. Trials should compare optimal medical therapy plus cardiac resynchronisation therapy, optimal medical therapy plus ICD and optimal medical therapy alone in elderly patients (75 years plus) with severe left ventricular function and should focus on total mortality as the primary outcome. Economic and social analyses were recommended. Such trials should help identify the subgroup of elderly patients at greater risk of sudden cardiac death who may receive the most benefit from prophylactic ICD therapy.
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