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Meta-analysis: Age and Effectiveness of Prophylactic Implantable Cardioverter-Defibrillators

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Background: Implantable cardioverter-defibrillators (ICDs) for the primary prevention of sudden cardiac death have been proven effective in several clinical trials.

Purpose: To summarize evidence about the effectiveness of ICDs versus standard medical therapy for the primary prevention of sudden cardiac death in different age groups of patients with severe left ventricular dysfunction.

Data Sources: MEDLINE, Embase, CENTRAL, BioMed Central, Cardiosource, ClinicalTrials.gov, and ISI Web of Science (January 1970 to April 2010) were searched with no language restrictions.

Study Selection: Two independent reviewers screened titles and abstracts to identify randomized, controlled trials of prophylactic ICD versus medical therapy in patients with severe left ventricular dysfunction that provided data about mortality outcomes for different age groups.

Data Extraction: Two independent reviewers assessed risk for bias of trials and extracted patient and study characteristics and hazard ratios (HRs) relevant to all-cause mortality.

Data Synthesis: Five trials (MADIT-II, DEFINITE, DINAMIT, SCD-HeFT, and IRIS) that enrolled 5783 patients (44% were elderly) were included. The primary analysis, which excluded the 2 trials enrolling patients early after acute myocardial infarction (DINAMIT and IRIS), found that prophylactic ICD therapy reduced mortality in younger patients (HR, 0.65 [95% CI, 0.50 to 0.83]; $P < 0.001$). A smaller survival benefit was found in elderly patients (HR, 0.75 [95% CI, 0.61 to 0.91]) that was not confirmed when MADIT-II patients older than 70 years were excluded or when data from DINAMIT and IRIS were included.

Limitations: Four potentially eligible trials were not included in the meta-analysis because mortality data by age group were not available. Adjustment for differences in comorbid conditions and medical therapies among patients enrolled in the trials was not possible.

Conclusion: Available data suggest that prophylactic ICD therapy may be less beneficial for elderly patients with severe left ventricular dysfunction than for younger patients.

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Several clinical trials show that implantable cardioverter-defibrillators (ICDs) can prevent sudden cardiac death and reduce overall mortality in some patients with severe left ventricular dysfunction (1). The benefit of such therapy, however, may not be the same across different patient subgroups (2–6). Widespread implementation of current ICD recommendations for the primary prevention of sudden cardiac death has resulted in a substantial number of patients receiving an ICD without any clinical benefit, while being exposed to a potentially risky and costly procedure (7, 8).

Although none of the ICD trials excluded elderly patients, the real benefit of prophylactic ICD therapy in this subgroup has not been consistently demonstrated (2–6). Because the relative weight of sudden cardiac death decreases steadily as a function of age in patients with heart failure (9), it would be reasonable to expect that elderly patients with severe left ventricular dysfunction would not gain the same survival benefit from prophylactic ICD therapy as younger patients. Indeed, the survival benefit of ICD therapy is directly dependent on the effect of sudden cardiac death—the only preventable outcome with ICDs—on overall mortality.

We summarize the evidence on the effectiveness of ICD therapy versus standard medical therapy for the primary prevention of sudden cardiac death in different age groups of patients with severe left ventricular dysfunction.

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METHODS

We followed a standard protocol that was adapted from Cochrane Collaboration procedures and work previously published by our group (10, 11).

Data Sources and Selection

Three trained investigators performed independent searches of MEDLINE, Embase, CENTRAL, BioMed Central, Cardiosource, ClinicalTrials.gov, and ISI Web of Science (January 1970 to April 2010). Search keywords included *randomized AND, implantable cardioverter defibrillator, ICD, defibrillator, sudden cardiac death OR sudden*

Context

Prophylactic implantable cardioverter-defibrillators (ICDs) can prevent sudden cardiac death, but do they improve survival in older patients?

Contribution

This systematic review summarizes subgroup data from 5 trials that compared prophylactic ICD therapy with medical therapy in patients with severe left ventricular dysfunction. Implantable cardioverter-defibrillator therapy reduced mortality in patients younger than 60 years. The observed survival benefit in older patients was smaller though still statistically significant.

Implication

Whether prophylactic ICD therapy benefits older patients with severe left ventricular function, who might have a higher risk for dying of causes other than sudden death compared with younger patients, is unclear.

—The Editors

death, *ventricular arrhythmias*, *dilated cardiomyopathy*, *ejection fraction*, *ischemic cardiomyopathy*, *nonischemic cardiomyopathy*, *cardiomyopathy*, and *cardiomyopath** (where * denotes a wildcard). No language restriction was used. Proceedings from the annual American Heart Association, American College of Cardiology, European Society of Cardiology, Heart Rhythm, and Europace meetings for the past 5 years were also manually searched. Web sites of the American Heart Association, American College of Cardiology, and European Society of Cardiology were searched for oral presentations and expert slide presentations.

Study Selection

Two independent reviewers screened and selected studies. A preliminary screening of titles and abstracts was done, and complete manuscripts deemed potentially relevant were retrieved. Studies selected for inclusion were randomized, controlled trials that tested ICD therapy versus standard medical therapy in patients with ischemic and nonischemic cardiomyopathy and severe left ventricular dysfunction (left ventricular ejection fraction [LVEF] $\leq$0.40) who had not previously had major arrhythmic events (that is, primary prevention indication). Studies that provided estimates of the risk for all-cause mortality of the ICD group compared with the medical therapy group in elderly ($\geq$60 years) and younger patients ($<$60 years) were included. Investigators of trials that met eligibility criteria but did not report mortality by age were contacted in an attempt to obtain such data. Trials that evaluated prophylactic ICD therapy associated with cardiac resynchronization therapy (CRT) were excluded because CRT has demonstrated effects on all-cause mortality (12, 13).

Data Extraction and Quality Assessment

The end point of interest of the meta-analysis was the survival benefit of prophylactic ICD therapy compared with standard medical therapy. Two independent reviewers evaluated the studies for inclusion in the meta-analysis and extracted data on inclusion criteria, the total number of patients randomly assigned, the number of elderly and younger patients, a relative risk measure (hazard ratio [HR]) of all-cause mortality with its 95% CI of the ICD group compared with the medical therapy group, ICD type, duration of follow-up, and adverse effects associated with ICD and medical therapy. Adverse effects related to ICD therapy included but were not limited to the following: pneumothorax, pericardial effusion or tamponade, mechanical malfunction of the device, infection related to the implant, hematoma or hemorrhage, inappropriate shocks (shocks not occurring for rapid sustained ventricular tachycardia or fibrillation), and any other complication resulting in permanent injury or death. Disagreements between reviewers were resolved by a third blinded reviewer.

Study quality was evaluated by using methods proposed by the Cochrane Collaboration to assess risk for bias (10). We separately estimated the risk for selection bias (systematic differences in baseline characteristics of the groups compared), performance bias (systematic differences between groups in the background care that was provided), detection bias (systematic differences between groups in how outcomes were measured), and attrition bias (systematic differences between groups in withdrawal or crossover rates) (10). Because the tested intervention (ICD implantation) was an invasive procedure, allocation concealment and masking were not possible in the original trials (14). We did not consider such items in these trials as part of our quality assessment.

Data Synthesis and Analysis

We critiqued and described several characteristics of the trials and paid particular attention to patient populations that were enrolled in the different trials. We then did meta-analyses of groups of the trials. For meta-analyses, outcome data from each study were entered as a logarithm of HR with its SE and combined with a DerSimonian–Laird random-effects model to obtain the summary estimate of the end point, expressed as an HR (95% CI) (15). The SE of logarithm of the HR was estimated from the 95% CI reported in each study (10). Our primary meta-analysis focused on the 3 studies that we considered most relevant to current primary prevention ICD practice (MADIT-II [Multicenter Automatic Defibrillator Implantation Trial II], DEFINITE [Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation], and SCD-HeFT [Sudden Cardiac Death in Heart Failure Trial]) (2, 4, 5). Our secondary meta-analysis then included the 2 trials that enrolled patients early after acute myocardial infarction (DINAMIT [Defibrillator in Acute Myocardial Infarction Trial] and IRIS [Immediate Risk Stratification Improves Survival]) (3, 6). We tested statistical significance between the results for younger versus

Table 1. **Characteristics of ICD Studies Not Reporting Outcome Data in Different Age Subgroups**

Variable	MADIT-I	CABG-Patch	CAT	AMIOVIRT
Characteristic				
Trial				
Year	1996	1997	2002	2003
Design	ICD vs. standard medical therapy	ICD vs. standard medical therapy	ICD vs. standard medical therapy	ICD vs. amiodarone
Clinical scenario	LVEF ≤0.35, previous MI, NSVT, inducible SVT	LVEF <0.36, scheduled CABG, LPs at SAECG	LVEF ≤0.30, nonischemic cause, onset ≤9 mo	LVEF ≤0.35, nonischemic cause, NSVT
Primary end point	Total mortality	Total mortality	Total mortality	Total mortality
Total patients, *n*	196	900	104	103
Duration of follow-up, *mo**	27	32	66	24
Demographic				
Mean age (SD), *y*	63 (9)	64 (9)	52 (11)	59 (11)
Men, *n (%)*	184 (94)	759 (84)	83 (80)	73 (71)
Mean LVEF (SD)	0.26 (0.07)	0.27 (0.06)	0.24 (0.07)	0.23 (0.09)
Ischemic cause, *n (%)*	196 (100)	900 (100)	0 (0)	0 (0)
Medication, *n (%)*†				
β-Blocker	32 (16)	183 (20)	4 (4)	53 (51)
ACE inhibitor or ARB	107 (55)	473 (53)	100 (96)	88 (85)
HR for ICD survival benefit (95% CI)	0.46 (0.26–0.82)	1.07 (0.81–1.42)	0.76 (0.33–1.80)‡	0.86 (0.27–2.75)‡

ACE = angiotensin-converting enzyme; AMIOVIRT = Amiodarone versus Implantable Cardioverter-Defibrillator Trial; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass graft; CABG-Patch = Coronary Artery Bypass Graft Patch Trial; CAT = Cardiomyopathy Trial; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LP = late potential; LVEF = left ventricular ejection fraction; MADIT-I = Multicenter Automatic Defibrillator Implantation Trial I; MI = myocardial infarction; NSVT = nonsustained ventricular tachycardia; SAECG = signal-averaged electrocardiogram; SVT = sustained ventricular tachycardia.
* Mean value.
† One month after enrollment in MADIT-I; at last follow-up in AMIOVIRT.
‡ Not provided in the original trials and calculated by the meta-analysis authors.

elderly patients by using the test for interaction of Altman and Bland (16), which calculates the zeta value (the ratio of the difference between the treatment effect estimates of 2 subgroups to the SE of this difference). The zeta value, when referred to a table of normal distribution, gives the corresponding *P* value.

We assessed the sensitivity of results. Statistical analyses were done after excluding each study in turn. We conducted analyses by excluding in turn studies enrolling ischemic cardiomyopathy patients only, studies that mixed ischemic with nonischemic cardiomyopathy patients, and studies that enrolled nonischemic cardiomyopathy patients only. Heterogeneity among studies was evaluated only qualitatively because of the few studies included. The statistical level of significance was $P < 0.05$ (2-tailed). We did analyses by using STATA software, version 10.1 (StataCorp, College Station, Texas).

Role of the Funding Source

No funding was received for any aspect of this study.

RESULTS

Search Results and Study Selection

We screened 3422 citations and identified 10 randomized trials to consider for review (**Appendix Figure**, available at www.annals.org). We excluded one of these, MUSTT (the Multicenter Unsustained Tachycardia Trial) (17), because it was not designed specifically to test ICD therapy versus placebo for the primary prevention of sudden cardiac death.

Four of the remaining 9 trials did not report mortality outcomes in different age groups. We contacted the principal investigators of these trials to obtain such data, which, however, were not retrievable. These studies were the MADIT-I (18), the CABG-Patch (Coronary Artery Bypass Graft Patch) trial (19), CAT (Cardiomyopathy Trial) (20), and AMIOVIRT (Amiodarone versus Implantable Cardioverter-Defibrillator Trial) (21). **Table 1** shows the baseline characteristics and main results of these trials. In brief, MADIT-I enrolled patients with ischemic cardiomyopathy (LVEF ≤0.35), nonsustained ventricular tachycardia, and inducible sustained ventricular tachycardia not suppressible by procainamide (18). The CABG-Patch trial focused on patients with ischemic cardiomyopathy (LVEF <0.36) undergoing coronary artery bypass surgery and with late potentials on signal-averaged electrocardiography (19). CAT and AMIOVIRT enrolled patients with nonischemic cardiomyopathy (LVEF ≤0.30 and ≤0.35, respectively) (20, 21), with nonsustained ventricular tachycardia being an additional enrollment criterion in AMIOVIRT (21). A survival benefit associated with prophylactic ICD therapy was shown only in MADIT-I (18), whereas CABG-Patch (19), CAT (20), and AMIOVIRT (21) reported negative results (**Table 1**).

Description of Trials With Mortality Outcomes, by Age Groups

Table 2 shows characteristics of the 5 trials that reported mortality outcomes in younger and older patients (2–6). All were multicenter trials, but patient populations and trial design were heterogeneous. Three studies were designed to test ICD therapy versus medical therapy for the primary prevention of sudden cardiac death in patients with ischemic cardiomyopathy. MADIT-II (2) enrolled patients with ischemic cardiomyopathy (LVEF ≤0.30) without acute myocardial infarction; DINAMIT (3) enrolled patients with acute myocardial infarction within the preceding 40 days, an LVEF of 0.35 or less, and evidence of cardiac autonomic dysfunction (reduced heart rate variability); and the IRIS (6) enrolled patients with high-risk criteria early after acute myocardial infarction (LVEF ≤0.40, increased heart rate, and nonsustained ventricular tachycardia). DEFINITE (4) enrolled patients with nonischemic cardiomyopathy (LVEF <0.36) and nonsustained ventricular tachycardia, and SCD-HeFT (5) enrolled both ischemic and nonischemic cardiomyopathy patients (LVEF ≤0.35).

The quality of all 5 included trials seemed similar (**Table 2**). None had evidence of selection, performance, detection, or attrition bias. Follow-up data were available for nearly all of the included patients. All trials used a masked committee for adjudication of events and used intention-to-treat analyses providing detailed accounting of withdrawal and crossover rates.

Overall, 5783 patients were included in the 5 trials, of whom 4105 (71%) had ischemic cardiomyopathy. Elderly patients totaled 2414 of the enrolled participants (**Table 3**). The age cutoff for defining the elderly population differed slightly among trials. Elderly patients were persons 65 years or older in DEFINITE, SCD-HeFT, and IRIS (4–6) and persons 60 years or older in MADIT-II and DINAMIT (2, 3). Mean follow-up duration was 32 months (SD, 9; range, 20 to 46 months).

Quantitative Data Synthesis

ICD Survival Benefit in Elderly Patients

In elderly patients, pooled analysis of trials showed that prophylactic ICD therapy was associated with a small reduction in all-cause mortality compared with medical therapy (HR, 0.75 [95% CI, 0.61 to 0.91]) that was not confirmed when MADIT-II patients older than 70 years were excluded or when data from DINAMIT and IRIS were included (**Figure 1**). Analyses that included the 2

Table 2. **Baseline Characteristics of ICD Studies Included in the Meta-analysis**

Trial Characteristic	MADIT-II	DINAMIT	DEFINITE	SCD-HeFT	IRIS
Year	2002	2004	2004	2005	2009
Design	ICD vs. standard medical therapy	ICD vs. standard medical therapy	ICD vs. standard medical therapy	ICD vs. amiodarone vs. standard medical therapy	ICD vs. standard medical therapy
Clinical scenario	LVEF ≤0.30, previous MI	LVEF ≤0.35, recent MI, depressed HRV	LVEF <0.36, nonischemic cause, PVCs or NSVT	LVEF ≤0.35, previous MI and nonischemic cause	LVEF ≤0.40, recent MI, HR ≥90 beats/min, NSVT
Primary end point	Total mortality	Total mortality	Total mortality	Total mortality	Total mortality
Events committee	Blinded	Blinded	Blinded	Blinded	Blinded
Internal validity					
Follow-up, %	99.8	100*	100	100	100
Crossover rate, %					
To ICD	4.5	0	10	11.1	10.1
To medical therapy	4.3	6	1.7	19.5	8.6
Risk for bias					
Selection	No	No	No	No	No
Performance	No	No	No	No	No
Detection	No	No	No	No	No
Intention-to-treat analysis	Yes	Yes	Yes	Yes	Yes
Run-in phase	No	No	No	No	Yes†
ICD type	Transvenous	Transvenous	Transvenous	Transvenous	Transvenous
ICD programming	Discretional	ATP or shock for VT ≥175 beats/min; shock for VF ≥200 beats/min	Shock only for VF ≥180 beats/min	Shock only for VF ≥187 beats/min	Shock only for VF ≥200 beats/min
Industry sponsorship‡	Guidant	St. Jude Medical	St. Jude Medical	Medtronic, Wyeth-Ayerst, Knoll	Medtronic, AstraZeneca

ATP = antitachycardia pacing; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator in Acute Myocardial Infarction Trial; HR = heart rate; HRV = heart rate variability; ICD = implantable cardioverter-defibrillator; IRIS = Immediate Risk Stratification Improves Survival; LVEF = left ventricular ejection fraction; MADIT-II = Multicenter Automatic Defibrillator Implantation Trial II; MI = myocardial infarction; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular complex; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; VF = ventricular fibrillation; VT = ventricular tachycardia.

* Only partial follow-up was available for 4 patients in DINAMIT.

† Duration of the run-in phase was 5 to 31 d after acute MI.

‡ Guidant, Indianapolis, Indiana; St. Jude Medical, West Berlin, New Jersey; Medtronic, Fridley, Minnesota; Wyeth-Ayerst, Madison, New Jersey; Knoll, Mt. Olive, New Jersey; AstraZeneca, London, United Kingdom.

Table 3. **Baseline Characteristics of Patients Enrolled in ICD Studies Included in the Meta-analysis**

Variable	MADIT-II	DINAMIT	DEFINITE	SCD-HeFT	IRIS
Characteristic					
Trial					
Total patients, *n*	1232	674	458	1676‡	898
Elderly patients, *n (%)**	862	399 (59)	157 (34)	578‡	418 (47)
Duration of follow-up, *mo*†	20	30	29	45	37
Demographic					
Mean age (SD), *y*	65 (10)	62 (11)	58 (NR)	60 (NR)	62 (11)
Men, *n (%)*	1041 (85)	514 (76)	326 (71)	1933 (77)	689 (77)
NYHA class III or IV, *n (%)*	355 (29)	49 (13)	96 (21)	756 (30)	107 (11)
Mean LVEF (SD)	0.23 (0.05)	0.28 (0.05)	0.21 (0.14)	0.25 (0.05)	0.34 (0.09)
Ischemic cause, *n (%)*	1232 (100)	674 (100)	0 (0)	1310 (52)	898 (100)
Medication at baseline, *n (%)*					
β-Blocker	862 (70)	585 (87)	389 (85)	1738 (69)	782 (87)
ACE inhibitor or ARB	857 (69)	638 (95)	443 (97)	2133 (85)	734 (82)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; 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; LVEF = left ventricular ejection fraction; MADIT-II = Multicenter Automatic Defibrillator Implantation Trial II; NR = not reported; NYHA = New York Heart Association; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.
* Patients ≥65 y in DEFINITE, SCD-HeFT, and IRIS and patients ≥60 y in MADIT-II and DINAMIT.
† Mean value in MADIT-II, DINAMIT, DEFINITE, and IRIS; median value in SCD-HeFT.
‡ Numbers apply to the placebo and ICD groups and exclude the amiodarone group of the trial.

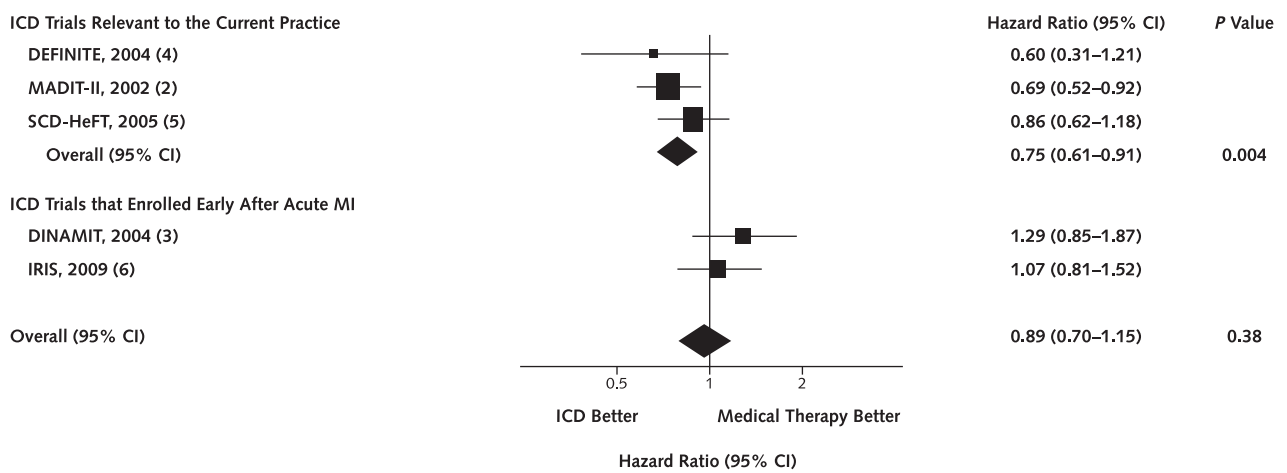
studies that enrolled patients early after acute myocardial infarction (DINAMIT and IRIS) also showed no statistically significant reduction in mortality with prophylactic ICD therapy (HR, 0.97 [CI, 0.78 to 1.19]; $P = 0.75$) (**Figure 1**). None of the sensitivity analyses affected the significance of the results. The HR was 0.90 (CI, 0.70 to 1.16; $P = 0.43$) for studies that used an age cutoff of 65 years or older and 1.10 (CI, 0.72 to 1.68; $P = 0.67$) for studies that used an age cutoff of 60 years or older.

ICD Survival Benefit in Younger Patients

Pooled analysis of the 3 primary prevention trials relevant to current clinical practice (MADIT-II, DEFINITE, and SCD-HeFT) showed that prophylactic ICD therapy in younger patients reduced all-cause mortality compared with medical therapy (HR, 0.65 [CI, 0.50 to 0.83]; $P < 0.001$; ratio of HR for comparison with elderly patients, 0.80 [CI, 0.56 to 1.14]; $P = 0.2$) (**Figure 2**). The inclusion of the 2 studies that enrolled patients early after acute myocardial infarction (DINAMIT and IRIS) did not change the results (HR, 0.72 [CI, 0.58 to 0.89]; $P = 0.003$; ratio of HR for comparison with elderly patients, 0.74 [CI, 0.55 to 1.00]; $P = 0.052$) (**Figure 2**).

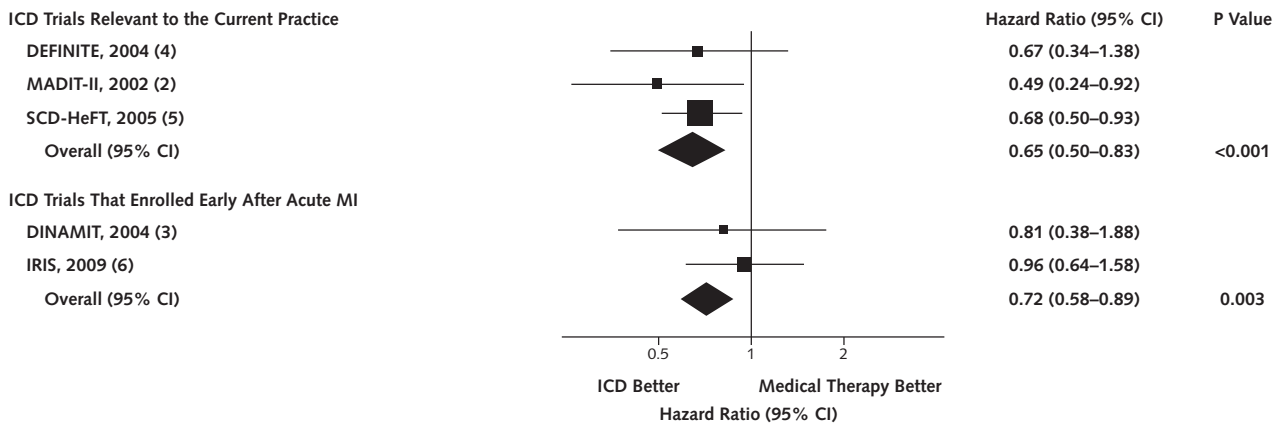
Sensitivity analyses showed results similar in direction and statistical significance: Point estimates for HRs were all

Figure 1. **Individual and pooled hazard ratios for all-cause mortality with prophylactic ICD implantation versus standard medical therapy in elderly patients with severe left ventricular dysfunction.**



ICD = implantable cardioverter-defibrillator; MI = myocardial infarction. Study acronyms are defined in the Results section. The size of each hazard ratio box indicates the weight from random-effect analysis.

Figure 2. **Individual and pooled hazard ratios for all-cause mortality with prophylactic ICD implantation versus standard medical therapy in younger patients with severe left ventricular dysfunction.**



ICD = implantable cardioverter-defibrillator; MI = myocardial infarction. Study acronyms are defined in the Results section. The size of each hazard ratio box denotes the weight from random-effect analysis.

less than 1.0 (range of HRs, 0.66 to 0.76; range of 95% CIs, 0.52 to 0.94) when the 5 studies were sequentially excluded 1 at a time. Similar results were seen among studies that used an age cutoff for defining the younger population of younger than 65 years, although the degree of the survival benefit seemed slightly less (HR, 0.75 [CI, 0.59 to 0.95]; $P = 0.02$).

Adverse Effects

Appendix Table 1 (available at www.annals.org) summarizes adverse effects associated with ICD and medical therapy. Overall, complications associated with ICD therapy occurred in 442 patients (17%), including 1 death during ICD implantation in IRIS (6). Mechanical malfunctions of the device (mainly lead-related) were reported in MADIT-II (2), DEFINITE (4), and IRIS (6); malfunctions occurred in 30 of 1416 (2%) patients who received an ICD. Data on device-related infection, reported in MADIT-II (2) and DEFINITE (4), occurred in 6 of 971 (0.6%) of the patients with ICDs. Inappropriate ICD shocks, reported in MADIT-II (22), DEFINITE (4), and SCD-HeFT (5), occurred in 214 of 1800 (12%) of ICD recipients. Adverse effects associated with standard medical therapy were not reported in the original trials.

Discussion

Our meta-analysis shows that age may have an effect on prophylactic ICD benefit in patients with severe left ventricular dysfunction and that evidence about benefit in elderly patients is inconclusive. The clinical implications of these findings are potentially very important. The elderly population is steadily increasing in Western countries; it is projected that the population older than 65 years will have doubled by 2030 in the United States (23). Because prophylactic ICD implantation is a costly and potentially risky procedure (**Appendix Table 1**), definitive data on effectiveness of this therapy in elderly patients are clearly warranted to optimize resource distribution and costs.

In primary prevention ICD trials, which constitute the basis for current clinical practice (1), more than 50% of enrolled patients were younger than 60 years (2–6). In real-world practice, nearly 70% of ICDs are implanted in patients older than 60 years, and more than 40% are implanted in patients older than 70 years (24). A primary prevention indication accounts for two thirds of cases in which such devices are used.

To date, no consistent evidence supports a similar benefit of ICD therapy among younger and elderly patients (25–29). A previous pooled analysis of secondary prevention ICD trials showed that ICD therapy was not associated with a reduction in all-cause and arrhythmic mortality in elderly patients (28). Our meta-analysis, which included only primary prevention ICD studies, suggested a smaller survival benefit of prophylactic ICD implantation in elderly patients than in younger patients. The survival benefit in elderly patients was driven by inclusion of MADIT-II patients older than 70 years who constituted 18% of the elderly population in the meta-analysis. These findings may be explained by a marked increase in nonarrhythmic mortality in this subgroup because of noncardiac and heart failure mortality (9). Accordingly, in a cohort study of 769 ICD recipients, elderly patients had higher overall mortality than younger patients because of an increased rate of nonarrhythmic death (27).

Of note, the benefit of CRT, which reduces predominantly nonarrhythmic mortality (for example, heart failure mortality), seems consistent across different age groups (12, 13, 30). Subgroup analyses of CRT trials have reported a similar degree of CRT benefit in elderly and

younger patients (**Appendix Table 2**, available at www.annnals.org) (12, 13, 30). Taken together, these findings support that CRT alone may be the best device therapy in elderly persons with severe left ventricular dysfunction. Of interest, a recently published U.S. registry of more than 26 000 cardiac device implantations showed that older patients are more likely to receive CRT alone (31).

In contrast, whether prophylactic ICD therapy reduces specifically arrhythmic death in elderly persons cannot be addressed by our meta-analysis because none of the primary prevention ICD trials reported the cause of death in elderly and younger patients (2–6).

Our study has limitations. Because of the lack of prophylactic ICD studies that focused on elderly patients, we pooled data from subgroup analyses of primary prevention ICD trials to evaluate the survival benefit of prophylactic ICD therapy across different age groups. Such an analytical approach is susceptible to type I error. We acknowledge substantial qualitative heterogeneity among included trials; however, we found no statistically significant interactions that were based on different trial designs, the enrolled population of patients, or a different age cutoff for defining the elderly population. Regardless, it would be improper to derive from our study an exact age cutoff above which it is justifiable to withhold ICD therapy in patients meeting primary prevention ICD criteria. Indeed, a statistically significant but smaller survival advantage associated with prophylactic ICD therapy in younger patients was seen when studies with an age cutoff of 65 years were analyzed. It is possible that a higher cutoff for age would still result in a statistically significant mortality reduction in younger patients. A post hoc analysis of the MADIT-II showed no statistically significant differences in ICD survival benefit between older and younger patients when an age cutoff of 75 years was used (29). However, only 204 of the 1232 patients of the MADIT-II were aged 75 years or older, and the relative risk measure for mortality reduction associated with ICD therapy in this subgroup had wide confidence limits (CI, 0.29 to 1.08) (29).

The nonsignificant statistical interaction between the results for older and younger patients in the 3 primary prevention trials relevant to the current clinical practice (MADIT-II, DEFINITE, and SCD-HeFT) calls for further caution in concluding that prophylactic ICD therapy is ineffective in elderly patients. However, the nonsignificant results of the interaction test should not be interpreted as proving a lack of difference because the statistical power of such analysis is very limited when based on very few studies (10). Of note, repeating the interaction test including the DINAMIT and IRIS studies, which increased the sample size of patients and thus the statistical power of analysis, led to a borderline statistically significant P value.

Our analysis also does not take into account the potential differences in baseline comorbid conditions and medical therapies between elderly and younger patients, and important follow-up information, such as the occurrence of ICD shock therapy in the 2 subgroups, were not retrievable. However, serious comorbid conditions (usually more prevalent among elderly patients) were exclusion criteria in all of the included trials (2–6), and it is likely that the rate of ICD shocks (at least of appropriate shocks) would be even lower in elderly patients because of the smaller effect of arrhythmic mortality on overall mortality in this subgroup (27, 28). Therefore, our analysis may even overestimate the survival benefit of ICD in elderly persons, when prophylactic ICD indications are generalized to the real-world, unselected population.

We excluded 4 primary prevention ICD studies (MADIT-I, CABG-Patch, CAT, and AMIOVIRT) (18–21) because they did not report the outcome of interest in elderly patients and unpublished data were not retrievable. Although inclusion of unpublished material risks inclusion of invalid and biased information (10), 3 of the 4 excluded trials (CABG-Patch, CAT, and AMIOVIRT) (19–21) reported negative results. Therefore, we believe it is unlikely that including the elderly population of these trials would change the results of our pooled analysis.

Our findings call for a properly designed randomized trial of prophylactic device therapy in elderly patients. We believe that such a trial should compare optimal medical therapy plus CRT, optimal medical therapy plus ICD, and optimal medical therapy alone in elderly patients with severe left ventricular dysfunction and should focus on total mortality as the primary end point. Because of the overall increase in life expectancy of the population and the fact that elderly patients benefit from medical therapies that were not always used in the older ICD trials, such as β-blockers and angiotensin-converting enzyme inhibitors, we suggest that future trials consider enrolling elderly patients aged 75 years or older. Finally, because the results of our analysis strongly support a smaller survival benefit associated with prophylactic ICD implantation in the elderly, appropriate economic and social analyses are warranted also to measure the cost-effectiveness of this therapy in elderly patients.

Prophylactic ICD therapy in elderly patients with severe left ventricular dysfunction may be less effective than in younger patients. Randomized, controlled, prospective trials that evaluate implantable device therapy in elderly patients are needed to confirm this finding and identify the subgroup of elderly patients at higher risk for sudden cardiac death, rather than other causes of death, who may receive the greatest benefit from prophylactic ICD therapy.

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Note: Drs. Santangeli and Di Biase contributed equally to the study and should both be considered as first authors.

Potential Conflicts of Interest: Dr. Di Biase: *Consultancy:* Hansen Medical. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-0999.

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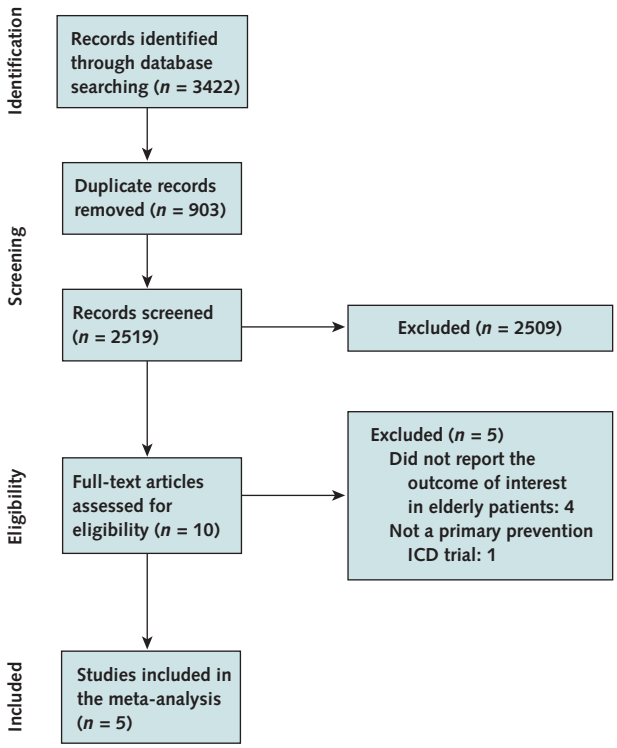
Appendix Figure. **Summary of evidence search and selection.**



ICD = implantable cardioverter-defibrillator.

Appendix Table 1. Adverse Events Related to ICDs in Studies Included in the Meta-analysis

Adverse Event	MADIT-II	DINAMIT	DEFINITE	SCD-HeFT	IRIS
Mechanical complications, *n (%)*	13 (2)	–	6 (3)	NR	NR
Pneumothorax, *n (%)*	NR	–	1 (0.4)	NR	NR
Device-related infection, *n (%)*	5 (0.7)	NR	1 (0.4)	NR	NR
Hematoma or hemorrhage, *n (%)*	NR	NR	1 (0.4)	NR	NR
Venous thrombosis, *n (%)*	NR	NR	3 (1.3)	NR	NR
Pericardial effusion or tamponade, *n (%)*	NR	NR	1 (0.4)	NR	NR
Death during implantation, *n (%)*	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)
Inappropriate shocks, *n (%)**	83 (11)	–	49 (21)	82 (10)	NR
Total, *n (%)*	101 (14)	25 (8)†	62 (27)	173 (21)	81 (18)

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; MADIT-II = Multicenter Automatic Defibrillator Implantation Trial II; NR = not reported; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.
* Shocks not for rapid sustained ventricular tachycardia or fibrillation. Adverse events related to standard medical therapy were not reported in original trials.
† Includes lead dislodgment, pneumothorax, and inappropriate shocks.

Appendix Table 2. Characteristics of CRT Trials

Variable	COMPANION*	CARE-HF	MADIT-CRT
Characteristic			
Trial			
Year	2004	2005	2009
Design	CRT vs. standard medical therapy	CRT vs. standard medical therapy	CRT + ICD vs. ICD
Clinical scenario	LVEF ≤0.35, NYHA III/IV, QRS ≥120 ms	LVEF ≥0.35, NYHA III or IV, QRS ≥140 ms or ≥120 ms + dyssynchrony	LVEF ≤0.30, NYHA I or II, QRS ≥130 ms
Primary end point	Total mortality + total hospitalization	Total mortality + hospitalization for cardiovascular causes	Total mortality + heart failure events
Total patients, *n*	925	813	1820
Elderly patients, *n (%)*†	530 (57)	407 (50)	968 (53)
Duration of follow-up, *mo*‡	16	29	29
Demographic			
Mean or median age (SD or IQR), *y*	66 (NR)	66 (59–73)	64 (11)
Men, *n (%)*	629 (68)	597 (73)	1367 (75)
Mean or median LVEF (SD or IQR)	0.21 (NR)	0.25 (0.22–0.29)	0.24 (0.05)
Ischemic cause, *n (%)*	523 (56)	309 (38)	999 (55)
Medication at baseline, *n (%)*			
β-Blocker	620 (67)	586 (72)	1697 (93)
ACE inhibitor or ARB	823 (89)	770 (95)	1777 (98)
HR for CRT benefit in younger patients (95% CI)	0.57 (0.32–0.93)	0.55 (0.40–0.75)	0.80 (0.50–1.10)
HR for CRT benefit in elderly patients (95% CI)	0.86 (0.68–1.07)	0.68 (0.52–0.89)	0.56 (0.41–0.76)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CARE-HF = Cardiac Resynchronization-Heart Failure; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CRT = cardiac resynchronization therapy; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LVEF = left ventricular ejection fraction; MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; NR = not reported; NYHA = New York Heart Association.
* Only the CRT alone and medical therapy groups are included.
† Patients ≥65 y in COMPANION and MADIT-CRT and patients ≥66.4 y in CARE-HF.
‡ Mean value in CARE-HF and MADIT-CRT; median value in COMPANION.

Correction: Age and Effectiveness of Prophylactic Implantable Cardioverter-Defibrillators

In their meta-analysis, Santangeli and colleagues (1) incorrectly excluded some elderly patients from MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) (2). Corrections that include the subgroup of patients older than 70 years in MADIT-II are as follows:

The last 2 sentences of the abstract's Results section should be replaced with: "A smaller survival benefit was found in elderly patients (HR, 0.75 [95% CI, 0.61 to 0.91]) that was not confirmed when MADIT-II patients older than 70 years were excluded or when data from DINAMIT and IRIS were included."

The abstract's Conclusion section should read: "Available data suggest that prophylactic ICD therapy may be less beneficial for elderly patients with severe left ventricular dysfunction than for younger patients."

In the article's Results section, the second sentence of the fifth paragraph (on page 595) should read: "Elderly patients totaled 2414 of the enrolled participants (Table 3)." The first sentence of the Quantitative Data Synthesis section (on page 595) should read: "In elderly patients, pooled analyses of trials showed that prophylactic ICD therapy was associated with a small reduction in all-cause mortality compared with medical therapy (HR, 0.75 [95% CI, 0.61 to 0.91]) that was not confirmed when MADIT-II patients older than 70 years were excluded or when data from DINAMIT and IRIS were included (Figure 1)."

In Table 3, the number of elderly patients in MADIT-II should be 862 and the numbers of total and elderly patients in SCD-HeFT should be 1676 and 578. Of note, the SCD-HeFT numbers apply to the placebo and ICD groups and exclude the amiodarone group of the trial.

Figure 1 has also been corrected.

The first sentence of the article's Discussion section should read, "Our meta-analysis shows that age may have an effect on prophylactic ICD benefit in patients with severe left ventricular dysfunction."

The third sentence of the third paragraph of the Discussion section should read: "Our meta-analysis, which included only primary prevention ICD studies, suggested a smaller survival benefit of prophylactic ICD implantation in elderly patients than in younger patients. The survival benefit in elderly patients was driven by inclusion of MADIT-II patients older than 70 years who constituted 18% of the elderly population in the meta-analysis."

The first sentence of the last paragraph in the article should read: "Prophylactic ICD therapy in elderly patients with severe left ventricular dysfunction may be less effective than in younger patients."

Finally, in the Editors' Notes on page 593, the last sentence in the Contribution section should read: "The observed survival benefit in older patients was smaller though still statistically significant."

These corrections have been made in the online version.

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