Effectiveness of Implantable Cardioverter Defibrillators for Primary Prevention of Sudden Cardiac Death in Subgroups
A Systematic Review
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Background: Previous systematic reviews of implantable cardioverter defibrillators (ICDs) used for primary prevention of sudden cardiac death (SCD) concluded that ICDs are less effective in women and the elderly.

Purpose: To examine ICD effectiveness for primary prevention of SCD across subgroups by sex, age, New York Heart Association class, left ventricular ejection fraction, heart failure, left bundle branch block, QRS interval, time since myocardial infarction, blood urea nitrogen level, and diabetes.

Data Sources: MEDLINE and the Cochrane Central Register of Controlled Trials through 3 September 2013 with no language restriction.

Study Selection: Researchers screened articles for studies comparing ICD versus no ICD for primary prevention.

Data Extraction: Data were extracted about study design, patients, interventions, mortality and SCD outcomes, subgroup characteristics, and subgroup effects. Quality of subgroup analyses was determined by consensus. Relative odds ratios comparing subgroup effects were calculated, and random-effects model meta-analyses were conducted on these ratios.

Data Synthesis: Meta-analysis of 14 studies showed a decrease in deaths and SCDs due to ICD treatment. Ten studies provided subgroup analyses. Nine studies compared ICD versus no ICD, whereas one compared cardiac resynchronization therapy plus a defibrillator versus no ICD. Within-study interaction tests and across-study meta-analyses yielded weak evidence that did not show differences for all-cause mortality in subgroups by sex, age, and QRS interval. The evidence was indeterminate for other evaluated subgroups because of a paucity of data.

Limitation: Many subgroup analyses were underpowered, which may have resulted in false-negative findings.

Conclusion: Weak evidence fails to show differences for all-cause mortality in subgroups of sex, age, and QRS interval. Evidence is indeterminate for all-cause mortality in the other subgroups and for SCD.

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See also:
Web-Only Supplement
CME quiz
ICDs for Primary Prevention of Sudden Cardiac Death in Subgroups

Data Sources
We searched MEDLINE and the Cochrane Central Register of Controlled Trials from inception through 3 September 2013 with no language restrictions. Table 1 of the Supplement (available at www.annals.org) shows the search strategy.

Study Selection
We included randomized, controlled trials and longitudinal, nonrandomized, comparative studies with at least 10 participants per group. For nonrandomized studies, only those that used concurrent controls and reported a multivariable analysis were eligible.

The population of interest was adults eligible to receive an ICD for primary prevention of SCD. Participants had to be followed from the time of ICD implantation, not from an arbitrary time after ICD implantation. We examined effect modification in reported subgroups for different patient and clinical characteristics (including age, sex, race or ethnicity, NYHA class, LVEF, heart failure, left bundle branch block [LBBB], QRS interval, heart disease, time since MI, previous coronary revascularization, time since coronary revascularization, diabetes, blood urea nitrogen level, and kidney disease).

The comparison of interest was ICD with or without CRT versus no ICD. We did not implement a minimum follow-up duration. Outcomes of interest were all-cause mortality and death due to SCD.

Data Extraction and Quality Assessment
We screened titles and abstracts using Abstrackr (Brown University, Providence, Rhode Island) (19). Seven researchers double-screened the abstracts after iterative training of all reviewers on the same batches of abstracts. Discordant decisions and queries were resolved at group meetings. Full-text articles were retrieved for all potentially relevant abstracts and re-screened by the same researchers.

Each study was extracted by 1 experienced methodologist, and results and quality were reviewed and confirmed by 1 other methodologist. Data extraction included elements for population characteristics, sample size, study design, descriptions of the ICD and comparison interventions, outcomes, subgroup factors (demographic and clinical features at baseline), and relevant results analyses. When necessary, we estimated figure data using Engauge Digitizer, version 2.14 (SourceForge, Mountain View, California). We assessed the quality of the subgroup analyses on the basis of recently proposed criteria for reporting and interpreting subgroup analyses (Table 1) (20, 21). We examined published articles and related study design papers but did not contact investigators for unpublished data.

Data Synthesis and Analysis
For outcomes with subgroup data from at least 4 randomized, controlled trials with sufficiently similar comparisons of interest and adequate data, we conducted profile likelihood random-effects model meta-analyses because of the relatively small number of studies (22). If the profile likelihood model did not converge, we did a fixed-effect model meta-analysis. For each subgroup analysis, we calculated a relative odds ratio (ROR), dividing the odds ratio (OR) or similar measure of death for 1 subgroup by the other. We preferentially used adjusted ORs (or hazard ratios) when necessary, we calculated ORs on the basis of recently proposed criteria for reporting and interpreting subgroup analyses (Table 1) (20, 21). We examined published articles and related study design papers but did not contact investigators for unpublished data.

Table 1. Quality Assessment of Subgroup Analyses in Studies of ICD vs. No ICD

| Question                                                                 | CABG-Patch Trial (9) | Chan, 2009 (11) | COMPANION (10) | DEFINITE (15) |
|--------------------------------------------------------------------------|----------------------|-----------------|----------------|---------------|
| Which subgroup analyses were prespecified in design?                     | Age, sex, heart failure, NYHA class, LVEF, DM, and duration of QRS complex | Age, ischemic vs. nonischemic heart failure, LVEF, and DM | None | Age, sex, LVEF, QRS interval, NYHA class, and history of atrial fibrillation |
| Were subgroup categories for nonbinary variables prespecified in design?  | Yes (QRS complex >100 msec vs. ≤100 msec) | Yes (age <65 y vs. 65 to 74 y vs. ≥75 y and LVEF >25% vs. ≤25%) | NA | Unclear |
| Were a priori power calculations done for subgroups?                     | No                   | No              | No             | No            |
| Were subgroup results adjusted for baseline variables?                   | No                   | Yes             | No             | No            |
| Was a formal interaction testing for effect modification by subgroup done? | Yes                  | Yes             | No             | Yes           |

BUN = blood urea nitrogen; CABG = Coronary Artery Bypass Graft; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator in Acute Myocardial Infarction Trial; DM = diabetes mellitus; ICD = implantable cardioverter defibrillator; IRIS = Immediate Risk Stratification Improves Survival; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; NYHA = New York Heart Association; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.
* Randomization was stratified by the cause of heart failure (ischemic vs. nonischemic) and by NYHA class (II vs. III).
† This was implied when a study used words or context rather than actual P-values to describe the statistical significance or nonsignificance of the subgroup interaction test.
where A and B are the 2 subgroups. Statistical heterogeneity was assessed with the $I^2$ statistic and the chi-square $P$ value. Meta-analyses were conducted with the metaan package in Stata, version 11.2 (StataCorp, College Station, Texas). We extracted and tabulated the reported $P$ values of the difference in effect between the subgroups of interest.

Role of the Funding Source
The Agency for Healthcare Research and Quality participated in formulating the study questions and developing the protocol but did not participate in the literature search, determination of study eligibility criteria, data analysis or interpretation, preparation or review of the manuscript, or the decision to submit the manuscript for publication.

RESULTS
Figure 1 of the Supplement summarizes the search yield. Of 11 314 abstracts, 27 articles described 10 randomized and 4 nonrandomized comparative studies of ICD versus no ICD treatment (Table 2 of the Supplement). Of these, 10 studies (in 19 articles) provided data to our subgroup analyses (8–12, 14–18, 23–31).

Six of these studies were conducted in the United States and Canada, 1 in Germany, and 3 in both the United States and Europe. Nine studies examined the comparison of ICD only versus no ICD. A single U.S. study, however, compared CRT-D versus no ICD, which we treated as a comparison of ICD versus no ICD for the purpose of this review.

With regard to age and sex, the study by Hernandez and colleagues (12), which focused exclusively on Medicare patients, was an outlier: Mean age was 74.7 years, and 40% of patients were women. Across the other studies, mean age was 63 years (95% CI, 61 to 65), and 25% (CI, 21% to 28%) were women. Subgroup data from at least 2 studies with sufficiently similar comparisons of subgroups are shown in Table 2. Table 3 of the Supplement shows all subgroup comparisons, including those that were examined only once.

All-Cause Mortality
All 10 randomized (8–10, 14–18, 24–26, 29–38) and 4 nonrandomized studies (11, 12, 39, 40) provided consistent and precise findings of a statistically significant benefit of ICD to reduce all-cause mortality rates (Figure 2 of the Supplement) (1). Use of ICD for patients who had no recent MI (within 30 days) and no concurrent coronary revascularization reduced the risk for all-cause mortality by approximately 31% (CI, 21% to 40%) over the course of 3 to 7 years after implantation. Additional details about the overall meta-analysis can be found in the full Health Technology Assessment (1).

The 10 studies that conducted subgroup analyses did not support a statistical difference in the benefit of ICD for all-cause mortality across subgroups on the basis of age, sex, race or ethnicity, NYHA class, LVEF, heart failure, LBBB, QRS interval, heart disease, time since MI, previous coronary revascularization, time since coronary revascularization, diabetes, blood urea nitrogen level, and kidney disease. The single exception was 1 study that found that ICD placement was statistically significantly more effective in patients in NYHA class II versus NYHA class III (8) (Table 2).

Meta-analyses of the ROR of death for subgroups on the basis of sex (Figure 1), age (<65 years vs. ≥65 years) (Figure 2), and QRS interval (<120 msec vs. ≥120 msec)
### Table 2. Subgroup Analyses Data and Meta-analysis of ICD vs. No ICD for All-Cause Death*

| Author, Year (Reference) | Study Name | Subgroup Characteristic | Subgroup 1 vs. Subgroup 2, n= | Ratio | Ratio (95% CI) for Subgroup 1 | Ratio (95% CI) for Subgroup 2 | OR (95% CI) | Reported P Value |
|--------------------------|------------|-------------------------|-------------------------------|-------|-------------------------------|-------------------------------|-------------|------------------|
| Sex                      | Bristow et al, 2004 (10) | COMPANION NA | Subgroup 1 (female): 291; subgroup 2 (male): 612 | 0.6 (0.3–1.1) | 0.65 (0.4–0.9) | 0.92 (0.43–1.99) | ND |
|                          | Kadish et al, 2004 (15) | DEFINITE NA | Subgroup 1 (female): 132; subgroup 2 (male): 326 | 1.1 (0.5–2.6) | 0.49 (0.27–0.90) | 2.24 (0.81–6.23) | NS |
|                          | Hohnloser et al, 2004 (14) | DINAMIT NA | Subgroup 1 (female): 160; subgroup 2 (male): 514 | 1.0 (0.5–2.1) | 1.1 (0.7–1.7) | 0.91 (0.39–2.11) | 0.82 |
|                          | Hernandez et al, 2010 (12) | NA | Subgroup 1 (female): 1896; subgroup 2 (male): 2789 | 0.58 (0.41–0.83) | 0.80 (0.63–1.01) | 0.73 (0.47–1.11) | 0.31 |
|                          | Steinbeck et al, 2009 (18) | IRIS NA | Subgroup 1 (female): 209; subgroup 2 (male): 689 | 1.0 (0.6–1.7) | 1.1 (0.8–1.5) | 0.91 (0.49–1.67) | 0.15 |
|                          | Moss et al, 2002 (17) | MADIT II NA | Subgroup 1 (female): 192; subgroup 2 (male): 1040 | 0.6 (0.3–1.1) | 0.7 (0.5–0.9) | 0.86 (0.42–1.75) | 0.85 |
|                          | Russo et al, 2008 (29) | SCD-HeFT NA | Subgroup 1 (female): 382; subgroup 2 (male): 1294 | 0.90 (0.56–1.43) | 0.71 (0.57–0.88) | 1.27 (0.76–2.12) | 0.54†‡ |
|                          | Bigger, 1997 (9) | CABG-Patch NA | Subgroup 1 (female): 141; subgroup 2 (male): 795§§ | ND | ND | ND | NS |
|                          | Moss et al, 1996 (16) | MADIT NA | Subgroup 1 (female): 16; subgroup 2 (male): 1806§§ | ND | ND | ND | >0.2 |

**Meta-analysis:** Females vs. males

$I^2 = 0\%$

0.95 (0.75–1.27)

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**Age**

<65 y vs. ≥65 y

| Author, Year (Reference) | Study Name | Subgroup Characteristic | Subgroup 1 (<65 y): 383; subgroup 2 (≥65 y): 582 | Ratio | Ratio (95% CI) | OR (95% CI) | Reported P Value |
|--------------------------|------------|-------------------------|-------------------------------|-------|----------------|-------------|------------------|
| Chan et al, 2009 (11) | COMPANION Median: 79 y (IQR, 76–82 y) | Subgroup 1 (<65 y): 383; subgroup 2 (≥65 y): 582 | 0.74 (0.43–1.28) | 0.65 (0.47–0.90) | 1.14 (0.60–2.15) | ND |
| Bristow et al, 2004 (10) | COMPANION Median: 66 y | Subgroup 1 (<65 y): 395; subgroup 2 (≥65 y): 508 | 0.6 (0.3–0.95) | 0.7 (0.5–1.0) | 0.86 (0.44–1.68) | ND |
| Kadish et al, 2004 (15) | DEFINITE Mean: 58 y (range, 20–84 y) | Subgroup 1 (<65 y): 301; subgroup 2 (≥65 y): 157 | 0.7 (0.3–1.4) | 0.6 (0.3–1.2) | 1.17 (0.41–3.29) | NS |
| Steinbeck et al, 2009 (18) | IRIS Mean: 63 y (SD, 11) | Subgroup 1 (<65 y): 480; subgroup 2 (65–80 y): 418 | 0.95 (0.6–1.5) | 1.05 (0.8–1.5) | 0.90 (0.52–1.58) | 0.73 |
| Goldenberg and Moss, 2007 (25) | MADIT II Mean: 64 y (SD, 10) | Subgroup 1 (<65 y): 574; subgroup 2 (≥65 y): 659 | 0.79 (0.48–1.29) | 0.66 (0.47–0.91) | 1.20 (0.66–2.18) | 0.75*** |
| Barale et al, 2005 (8) | SCD-HeFT Median: 60 y (IQR, 52–69 y) | Subgroup 1 (<65 y): 1098; subgroup 2 (≥65 y): 578 | 0.68 (0.52–0.95) | 0.86 (0.65–1.14) | 0.79 (0.55–1.13) | ND |

**Meta-analysis:** (<65 y vs. ≥65 y):

$I^2 = 0\%$

0.93 (0.73–1.20)

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<75 y vs. ≥75 y

| Author, Year (Reference) | Study Name | Subgroup Characteristic | Subgroup 1 (<75 y): 696; subgroup 2 (≥75 y): 269 | Ratio | Ratio (95% CI) | OR (95% CI) | Reported P Value |
|--------------------------|------------|-------------------------|-------------------------------|-------|----------------|-------------|------------------|
| Chan et al, 2009 (11) | COMPANION Median: 79 y (IQR, 76–82 y) | Subgroup 1 (<75 y): 696; subgroup 2 (≥75 y): 269 | 0.75 (0.51–1.10) | 0.59 (0.39–0.90) | 1.27 (0.72–2.24) | 0.43§§ |
| Hernandez et al, 2010 (12) | COMPANION Mean: 74 y (SD, 5) | Subgroup 1 (65–74 y): 2039; subgroup 2 (75–84 y): 2646 | 0.65 (0.47–0.89) | 0.80 (0.62–1.03) | 0.81 (0.54–1.22) | 0.31 |
| Huang et al, 2007 (26) | MADIT II Mean: 64 y (SD, 10) | Subgroup 1 (<75 y): 1028; subgroup 2 (≥75 y): 204 | 0.62 (0.54–0.88) | 0.56 (0.29–1.08) | 1.11 (0.55–2.23) | 0.75 |

**Meta-analysis:** (<75 y vs. ≥75 y):

$I^2 = 0\%$

0.93 (0.73–1.20)

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<60 y vs. older

| Author, Year (Reference) | Study Name | Subgroup Characteristic | Subgroup 1 (<60 y): 796; subgroup 2 (≥60 y): 436 | Ratio | Ratio (95% CI) | OR (95% CI) | Reported P Value |
|--------------------------|------------|-------------------------|-------------------------------|-------|----------------|-------------|------------------|
| Moss et al, 2002 (17) | MADIT II Mean: 64 y (SD, 10) | Subgroup 1 (<60 y): 796; subgroup 2 (≥60 y): 436 | 0.70 (0.47–1.03) | 0.64 (0.45–0.95) | 1.09 (0.64–1.87) | ND |
| Hohnloser et al, 2004 (14) | DINAMIT Mean: 62 y (SD, 11) | Subgroup 1 (<60 y): 275; subgroup 2 (60–80 y): 399 | 0.9 (0.4–1.9) | 1.2 (0.8–1.9) | 0.75 (0.31–1.83) | 0.46 |
| Moss et al, 2002 (17) | MADIT II Mean: 64 y (SD, 10) | Subgroup 1 (<60 y): 370; subgroup 2 (60 y): 862 | 0.50 (0.20–0.90) | 0.66 (0.51–1.10) | 0.67 (0.29–1.55) | ND |
| Continuous | Moss et al, 1996 (16) | MADIT Mean: 62 y (SD, 9) | Continuous | – | – | ND | >0.2 |

Continued on following page
| Author, Year (Reference) | Study Name | Subgroup Characteristic | Subgroup 1 vs. Subgroup 2, n‡ | Ratio§ (95% CI) for Subgroup 1 | Ratio§ (95% CI) for Subgroup 2 | ROR|H14667|H14667|H14667| Reported P Value¶ |
|---------------------------|------------|-------------------------|-----------------------------|-----------------------------|-----------------------------|------|-----|-----|-----|------------------|
| **NYHA class**            |            |                         |                             |                             |                             |      |     |     |     |                   |
| Kadish et al, 2004 (15)   | DEFINITE   | NA                      | Subgroup 1 (NYHA class II): 262; subgroup 2 (NYHA class III): 96 | 1.0 (0.5–2.2) | 0.37 (0.15–0.90) | 2.70 (0.85–8.64) | **NS** |
| Bardy et al, 2005 (8)     | SCD-HeFT   | NA                      | Subgroup 1 (NYHA class II): 1160; subgroup 2 (NYHA class III): 516 | 0.54 (0.41–0.81) | 1.16 (0.87–1.44) | 0.47 (0.32–0.67) | <0.001 |
| Zareba et al, 2005 (31)   | MADIT II   | Mean: 64 y (SD, 10)    | Subgroup 1 (NYHA class II): 425; subgroup 2 (NYHA class III): 350 | 0.65 (0.38–1.10) | 0.65 (0.43–0.99) | 1.00 (0.51–1.97) | 0.95  |
| **Heart failure**         |            |                         |                             |                             |                             |      |     |     |     |                   |
| Bigger, 1997 (9)          | CABG-Patch | NA                      | Subgroup 1 (heart failure): 450; subgroup 2 (no heart failure): 450‡‡ | ND | ND | ND | NS  |
| Chan et al, 2009 (11)     |            | NA                      | Subgroup 1 (heart failure): 707; subgroup 2 (no heart failure): 258 | 0.69 (0.50–0.93) | 0.70 (0.35–1.41) | 0.99 (0.46–2.11) | 0.59  |
| Moss et al, 1996 (16)     | MADIT      | NA                      | Subgroup 1 (heart failure): 101; subgroup 2 (no heart failure): 95§§ | ND | ND | ND | >0.2 |
| Steinbeck et al, 2009 (18)| IRIS       | NA                      | Subgroup 1 (heart failure): 406; subgroup 2 (no heart failure): 491 | 1.0 (0.7–1.4) | 1.2 (0.8–1.8) | 0.83 (0.49–1.42) | 0.56  |
| **LBBB**                  |            |                         |                             |                             |                             |      |     |     |     |                   |
| Bristow et al, 2004 (10)  | COMPANION  | NA                      | Subgroup 1 (LBBB): 649; subgroup 2 (no LBBB): 254 | 0.5 (0.4–0.8) | 0.9 (0.5–1.6) | 0.56 (0.28–1.09) | ND  |
| Moss et al, 1996 (16)     | MADIT      | NA                      | Subgroup 1 (LBBB): 12; subgroup 2 (no LBBB): 184§§‡‡ | ND | ND | ND | >0.2 |
| Moss et al, 2002 (17)     | MADIT II   | NA                      | Subgroup 1 (LBBB): 229; subgroup 2 (no LBBB): 1003§§ | ND | ND | ND | NS  |
| **QRS interval**          |            |                         |                             |                             |                             |      |     |     |     |                   |
| Kadish et al, 2004 (15)   | DEFINITE   | Mean: 115 msec (range, 78–196 msec) | Subgroup 1 (QRS, <120 msec): 111; subgroup 2 (QRS, 120–196 msec): 147 | 0.75 (0.4–1.5) | 0.5 (0.2–1.1) | 1.50 (0.51–4.41) | NS  |
| Hohnloser et al, 2004 (14)| DINAMIT    | Mean: 107 msec (SD, 24) | Subgroup 1 (QRS, <120 msec): 494; subgroup 2 (QRS, ≥120 msec): 165 | 0.85 (0.5–1.4) | 1.5 (0.8–2.9) | 0.57 (0.25–1.29) | 0.13 |
| Moss et al, 2002 (17)     | MADIT II   | ND                      | Subgroup 1 (QRS, <120 msec): 618; subgroup 2 (QRS, ≥120 msec): 614 | 0.7 (0.5–1.2) | 0.6 (0.4–0.8) | 1.30 (0.73–2.30) | **NS**** |
| Bardy et al, 2005 (8)     | SCD-HeFT   | ND                      | Subgroup 1 (QRS, <120 msec): 977; subgroup 2 (QRS, ≥120 msec): 699 | 0.84 (0.64–1.11) | 0.67 (0.51–0.95) | 1.25 (0.88–1.79) | ND  |
| **Meta-analysis**         |            |                        |                             |                             |                             |      |     |     |     |                   |
|                           |            |                         |                             |                             |                             |      |     |     |     | $\hat{I}^{2} = 0\%$ | 1.13 (0.82–1.54) |
| **Time since MI**         |            |                         |                             |                             |                             |      |     |     |     |                   |
| Moss et al, 1996 (16)     | MADIT      | ND                      | Subgroup 1 (time since MI, <6 mo): 48; subgroup 2 (time since MI, ≥6 mo): 148‡‡ | ND | ND | ND | >0.2 |
| Moss et al, 2002 (17)     | MADIT II   | Mean: 81 mo             | Subgroup 1 (time since MI, <6 mo): 153; subgroup 2 (time since MI, ≥6 mo): 1079‡‡†† | ND | ND | ND | NS  |
| Wilber et al, 2004 (30)   | MADIT II   | Mean: 81 mo             | Subgroup 1 (time since MI, <18 mo): 300; subgroup 2 (time since MI, 18–59 mo): approximately 300 | 0.97 (0.51–1.81) | 0.52 (0.26–1.05) | 1.87 (0.73–4.79) | NS  |

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### Table 2—Continued

| Author, Year (Reference) | Study Name | Subgroup Characteristic | Subgroup 1 vs. Subgroup 2, n† | Ratio§ (95% CI) for Subgroup 1 | Ratio§ (95% CI) for Subgroup 2 | ROR¶ (95% CI) | Reported P Value¶¶ |
|--------------------------|------------|-------------------------|-------------------------------|-------------------------------|-------------------------------|----------------|---------------------|
| Piccini et al, 2011 (28) | SCD-HeFT   | ND                      | Subgroup 1 (time since MI, <18 mo): 178; subgroup 2 (time since MI, 18–59 mo): 178 | 0.7 (0.37–1.31) | 0.54 (0.3–0.98) | 1.30 (0.55–3.08) | 0.33*** |
| Wilber et al, 2004 (30)  | MADIT II   | Mean: 81 mo             | Subgroup 1 (time since MI, 18–59 mo) approximately 300; subgroup 2 (time since MI, 60–119 mo) approximately 300 | 0.52 (0.26–1.05) | 0.50 (0.26–0.91) | 1.04 (0.41–2.66) | ND |
| Piccini et al, 2011 (28) | SCD-HeFT   | ND                      | Subgroup 1 (time since MI, 18–51 mo): 178; subgroup 2 (time since MI, 52–111 mo): 178 | 0.54 (0.3–0.98) | 1.47 (0.75–2.87) | 0.37 (0.15–0.90) | 0.33*** |

### Blood urea nitrogen

| Author, Year (Reference) | Study Name | Subgroup Characteristic | Subgroup 1 (BUN level, ≤8.92 mmol/L): 154; subgroup 2 (BUN level, >8.92 mmol/L): 423§§ | Ratio§ (95% CI) for Subgroup 1 | Ratio§ (95% CI) for Subgroup 2 | ROR¶ (95% CI) | Reported P Value¶¶ |
|--------------------------|------------|-------------------------|--------------------------------|-------------------------------|-------------------------------|----------------|---------------------|
| Moss et al, 1996 (16)    | MADIT      | ND                      | ND                            | ND                            | ND                            | ND              | >0.2               |
| Moss et al, 2002 (17)    | MADIT II   | ND                      | ND                            | ND                            | ND                            | ND              | NS                 |

### DM

| Author, Year (Reference) | Study Name | Subgroup Characteristic | Subgroup 1 (DM): 345; subgroup 2 (no DM): 620 | Ratio§ (95% CI) for Subgroup 1 | Ratio§ (95% CI) for Subgroup 2 | ROR¶ (95% CI) | Reported P Value¶¶ |
|--------------------------|------------|-------------------------|---------------------------------------------|-------------------------------|-------------------------------|----------------|---------------------|
| Chan et al, 2009 (11)    | NA         | Subgroup 1 (DM): 345; subgroup 2 (no DM): 620 | 0.68 (0.45–1.03) | 0.69 (0.48–1.01) | 0.99 (0.56–1.72) | 0.95 |
| Hohnloser et al, 2004 (14) | DINAMIT   | Subgroup 1 (DM): 200; subgroup 2 (no DM): 474 | 0.9 (0.5–1.5) | 1.2 (0.8–2.0) | 0.75 (0.37–1.53) | 0.38 |
| Bardy et al, 2009 (8)    | SCD-HeFT   | Subgroup 1 (DM): 524; subgroup 2 (no DM): 1152 | 0.95 (0.71–1.24) | 0.67 (0.52–0.93) | 1.42 (0.99–2.03) | ND |
| Bigger, 1997 (9)         | CABG-Patch | Subgroup 1 (DM): 342; subgroup 2 (no DM): 558§§ | ND                            | ND                            | ND                            | ND              | NS                 |
| Steinbeck et al, 2009 (18)| IRIS      | Subgroup 1 (DM): 302; subgroup 2 (no DM): 996§§ | ND                            | ND                            | ND                            | ND              | NS                 |
| Moss et al, 2002 (17)    | MADIT II   | Subgroup 1 (DM): 431; subgroup 2 (no DM): 801§§ | ND                            | ND                            | ND                            | ND              | NS                 |

BUN = blood urea nitrogen; CABG = Coronary Artery Bypass Graft; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; DEFINITE = Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator in Acute Myocardial Infarction Trial; DM = diabetes mellitus; IQR = interquartile range; IRIS = Immediate Risk Stratification Improves Survival; LBBB = left bundle branch block; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; ND = no data; NS = nonsignificant; NYHA = New York Heart Association; ROR = relative odds ratio; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

* Includes only subgroup comparisons for which at least 2 trials reported analyses for similar subgroups. Meta-analyses were done only if there were at least 4 such studies with sufficient data for a given subgroup comparison.
† Data from ICD group.
‡ Number of participants analyzed, unless otherwise noted.
§ Reported odds ratios, relative risks, or hazard ratios.
¶ RORs and their CIs calculated from reported odds ratios, relative risks, or hazard ratios for each subgroup.
¶¶ The reported P value for the interaction among subgroups. We used the abbreviation NS in studies that reported only that the interaction test was “nonsignificant” without providing an exact P value.
∗∗ Data from participants in the Organized Program to Initiate Life-Saving Treatment in Hospitalized Patients With Heart Failure and Get With the Guidelines–Heart Failure program.
†† HR for the ICD vs. placebo group.
‡‡ For the analysis of ICD vs. amiodarone vs. placebo.
§§ Number of participants enrolled; number of participants analyzed was not documented.
|| Estimate is based on combining the 65–74-y (hazard ratio, 0.76 [95% CI, 0.45–1.29]) and ≥75-y (hazard ratio, 0.59 [CI, 0.39–0.90]) age subgroups.
||| Estimate is based on combining the 65–74-y (hazard ratio, 0.63 [95% CI, 0.41–0.95]) and ≥75-y (hazard ratio, 0.70 [CI, 0.41–1.20]) age subgroups.
| Estimate for the interaction across 3 subgroups (age <65, 65–74, and ≥75 y).
| Estimate is based on combining the <65-y (hazard ratio, 0.70 [95% CI, 0.43–1.28]) and 65–74-y (hazard ratio, 0.76 [CI, 0.45–1.29]) age subgroups.
| Estimate is based on combining the <60-y (hazard ratio, 0.5 [95% CI, 0.2–0.9]) and 60–69-y (hazard ratio, 0.8 [CI, 0.5–1.3]) age subgroups.
| Estimate is based on combining the 0.12–0.15-msec (hazard ratio, 0.6 [95% CI, 0.5–1.3]) and ≥0.15-msec (hazard ratio, 0.5 [CI, 0.3–0.9]) subgroups.
| For analysis of NYHA class I vs. class II vs. class III.
| Estimate is based on combining the 0.12–0.15-msec (hazard ratio, 0.6 [95% CI, 0.4–1.1]) and >0.15-msec (hazard ratio, 0.5 [CI, 0.3–0.9]) subgroups.
| For analysis of <120 msec vs. 120–150 msec vs. ≥150 msec.
| For analysis of <180 vs. 18–51 mo vs. 52–111 mo vs. >111 mo.
Figure 1. Men vs. women: RORs of implantable cardioverter defibrillators vs. no implantable cardioverter defibrillators for all-cause mortality.

| Author, Year (Reference) | ROR* (95% CI) | Ratio for Women† (95% CI) | Ratio for Men‡ (95% CI) |
|--------------------------|--------------|---------------------------|------------------------|
| Bristow et al, 2004 (10) | 0.92 (0.43–1.99) | 0.6 (0.3–1.1) | 0.65 (0.4–0.9) |
| Kadish et al, 2004 (15) | 2.24 (0.81–6.23) | 1.1 (0.5–2.6) | 0.49 (0.27–0.90) |
| Hohnloser et al, 2004 (14) | 0.91 (0.39–2.11) | 1.0 (0.5–2.1) | 1.1 (0.7–1.7) |
| Hernandez et al, 2010 (12) | 0.73 (0.47–1.11) | 0.58 (0.41–0.83) | 0.80 (0.63–1.01) |
| Steinbeck et al, 2009 (18) | 0.91 (0.49–1.67) | 1.0 (0.6–1.7) | 1.1 (0.8–1.5) |
| Moss et al, 2002 (17) | 0.86 (0.42–1.75) | 0.6 (0.3–1.1) | 0.7 (0.5–0.9) |
| Russo et al, 2008 (29) | 1.27 (0.76–2.12) | 0.90 (0.56–1.43) | 0.71 (0.57–0.88) |
| Overall, women vs. men (I² = 0%; Phet = 0.47) | 0.95 (0.75–1.27) | | |

P̄het = P value for the heterogeneity across studies; ROR = relative odds ratio.
* ROR, relative risk ratio, or relative hazard ratio, as reported by studies.
† Odds ratio, risk ratio, or hazard ratio, as reported by studies.
‡ Odds ratio, risk ratio, or hazard ratio, as reported by studies.

(Table 2) found no statistically significant differences and were statistically homogeneous. Other comparisons of subgroups were not meta-analyzed because too few studies compared them; however, no consistent differences between subgroups were found across studies (Table 2).

Table 1 summarizes quality criteria for the subgroup analyses in the 10 studies. Seven out of 10 studies prespecified some subgroup analyses, and 5 also prespecified subgroup categories for nonbinary variables. No study detailed an a priori power calculation, but 1 used the subgroup factors for stratified randomization (8). In 4 studies, analyses were adjusted for baseline characteristics. All but 1 study provided some data for interaction tests.

Sudden Cardiac Death

Seven randomized studies reported in 10 articles (8, 14–16, 18, 26, 28, 33, 39, 41), and 2 nonrandomized studies (11, 39) (Table 2 of the Supplement) provided consistent and sufficiently precise findings of a statistically significant benefit of ICD to reduce SCD (Figure 3 of the Supplement) (1). Use of ICD as primary prevention for patients with ischemic or nonischemic cardiomyopathy without recent MI or concurrent coronary revascularization reduced the risk for SCD by approximately 63% (CI, 48% to 74%) over the course of 2 to 6 years after implantation.

Only 2 of the studies reported subgroup analyses (Table 4 of the Supplement) (24–26, 28, 41). These were for age, time since MI, coronary revascularization, history of coronary revascularization, or presence of kidney disease. Due to the small number of analyses, evidence to evaluate differential effects of ICD on SCD in subgroups is indeterminate. The data for sudden cardiac death were sparse so no quality assessment for this outcome was done.

DISCUSSION

Implantable cardioverter defibrillator therapy for primary prevention of SCD versus no ICD therapy showed benefit for all-cause mortality and SCD. For all-cause mortality, there were 4 to 7 studies with subgroups by sex, age, and QRS interval. For these subgroups, within-study interaction tests and across-study meta-analyses yielded weak evidence that did not show differences. There were only 3 or fewer studies for other subgroups, including NYHA class, LVEF, heart failure, LBBB, time since MI, blood urea nitrogen level, and diabetes; for these, evidence was deemed indeterminate on the basis of the small number of subgroup analyses. Evidence for the SCD outcome was indeterminate for all subgroups.

Our findings differ from conclusions by others who proposed differential effects by age and sex (5–7). Two previous reviews have proposed no or less benefit from ICDs in women (6, 7) on the basis of a nonstatistically significant finding when pooling effect estimates within subgroups of women while finding a statistically significant pooled estimate in men. However, within each source study, interaction tests did not show statistically significant differences. We believe that the difference in statistical significance of pooled estimates in men and women was primarily because of less power for the analysis of women, resulting in lower precision and wider CIs. Of note, only one quarter of the patients enrolled in the studies were women.

Another review suggested a smaller benefit of ICD therapy for older compared with younger patients (5), but the estimate in the older age subgroup varied in size and statistical significance on the basis of the inclusion of different age subgroups from the source studies (42). Further,
the age cut point for older versus younger age groups was not uniform across the studies combined in the meta-analysis, making it difficult to apply the findings from the pooled analysis to a certain age group (for example, a patient aged 62 years may have been included in the older subgroup for those 60 years and older in 1 study and the younger group for those younger than 65 years in another). Our analysis combining studies with a threshold of 65 years did not find a difference. Three studies that provided data for a threshold of 75 years also found no differences between age subgroups with this cut point.

When a difference of effects is found in subgroups, interaction testing is recommended to help establish the credibility of subgroup effects (43). Our approach of calculating and pooling RORs across studies maintained the integrity of the within-study comparisons of the analyzed subgroups, in contrast to the previous reviews’ approach of separately pooling effect sizes of different subgroups across studies, which removed information about the within-study interactions from their analyses. On the basis of the ROR analyses, we do not see any evidence suggesting that men and women, or any other subgroups, should be treated differently. Nevertheless, differences in baseline risk for different characteristics can have important effects on absolute risk reduction and may change the balance of benefits and harms when making treatment decisions for individual patients (43).

Other differences between our study and previous reviews relate to study inclusion. One other review included the Multicenter Unsustained Tachycardia Trial (44), which compared therapy guided by electrophysiologic testing versus medical management without electrophysiologic testing in patients at risk for SCD. We excluded this study because not all patients assigned to electrophysiologic testing received an ICD. The study showed unfavorable results for women. However, again, women only constituted 23% of population in this study. Our study included the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure trial, which compared CRT-D versus medical management and was excluded by previous reviews (10).

On the basis of the representation in the source studies, our findings are predominantly applicable to the effect of ICD alone, with greater uncertainty for CRT-D interventions. We further considered how the trial subgroup findings apply to patients who have ICD implantation in

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**Figure 2. Younger vs. older subgroups: RORs of implantable cardioverter defibrillators vs. no implantable cardioverter defibrillators for all-cause mortality.**

| Author, Year (Reference) | Comparison | ROR* (95% CI) | Ratio for Younger Cohorts† (95% CI) | Ratio for Older Cohorts† (95% CI) |
|--------------------------|------------|---------------|----------------------------------|-------------------------------|
| Age <65 y vs. older cohorts | <65 y vs. ≥65 y | 1.14 (0.60–2.15) | 0.74 (0.43–1.28) | 0.65 (0.47–0.90)† |
| Chan et al, 2009 (11)    | ≤65 y vs. >65 y | 0.86 (0.44–1.68) | 0.6 (0.3–1.0) | 0.7 (0.5–1.0) |
| Bristow et al, 2004 (10) | ≥65 y vs. >65 y | 1.17 (0.41–3.29) | 0.7 (0.3–1.4) | 0.6 (0.3–1.2) |
| Kadish et al, 2004 (15)  | <65 y vs. ≥65 y | 0.90 (0.52–1.58) | 0.9 (0.6–1.5) | 1.1 (0.8–1.5) |
| Steinbeck et al, 2009 (18)| <65 y vs. ≥65 y | 0.79 (0.55–1.13) | 0.68 (0.50–0.93) | 0.86 (0.62–1.18) |
| Bardy et al, 2005 (8)    | ≥65 y vs. ≥65 y | 1.20 (0.66–2.18) | 0.79 (0.48–1.29) | 0.66 (0.47–0.91)† |
| Goldenberg and Moss, 2007 (25) | <65 y vs. ≥65 y | 0.93 (0.73–1.20) | — | — |
| Overall, age <65 y vs. older (I² = 0%; Phet = 0.83) | — | — | — | — |

**Comparisons of other cohorts (some studies repeated)**

| Author, Year (Reference) | Comparison | ROR* (95% CI) | Ratio for Younger Cohorts† (95% CI) | Ratio for Older Cohorts† (95% CI) |
|--------------------------|------------|---------------|----------------------------------|-------------------------------|
| Hohlonser et al, 2004 (14) | <60 y vs. ≥60 y | 0.75 (0.31–1.83) | 0.9 (0.4–1.9) | 1.2 (0.8–1.9) |
| Moss et al, 2002 (17)    | <60 y vs. ≥60 y | 0.67 (0.29–1.55) | 0.5 (0.2–0.9) | 0.66 (0.51–1.10)† |
| Moss et al, 2002 (17)    | <70 y vs. ≥70 y | 1.09 (0.64–1.87) | 0.7 (0.47–1.03)† | 0.64 (0.45–0.95) |
| Hernandez et al, 2010 (12) | 65–74 y vs. 75–84 y | 0.81 (0.54–1.22) | 0.65 (0.47–0.89) | 0.80 (0.62–1.03) |
| Chan et al, 2009 (11)    | <75 y vs. ≥75 y | 1.27 (0.72–2.24) | 0.75 (0.51–1.10)† | 0.59 (0.39–0.90) |
| Huang et al, 2007 (26)   | <75 y vs. ≥75 y | 1.11 (0.55–2.23) | 0.62 (0.54–0.88) | 0.56 (0.29–1.08) |

ROR = relative odds ratio.
* ROR, relative risk ratio, or relative hazard ratio, as reported by studies.
† Estimated by combining reported subgroups (see Table 2).
‡ Odds ratio, risk ratio, or hazard ratio, as reported by studies.
the real world. A recent publication compared characteristics for patients in 2 primary prevention trials of MADIT II (Multicenter Automatic Defibrillator Implantation Trial) and the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) and the primary prevention population in the National Cardiovascular Data Registry’s (NCDR) ICD Registry (45). Compared with NCDR, the patients in key trials were younger (mean ages were 64 years in MADIT II, 60 years in SCD-HeFT, and 68 years in NCDR) and were less often women (16% women in MADIT II, 23% women in SCD-HeFT, and 27% women in NCDR) but had similar LVEF (23% in MADIT II, 24% in SCD-HeFT, and 25% in NCDR). Also, the trial populations had a lower burden of comorbid conditions (45). Notable differences in the trials included less frequent NYHA class III (25% in MADIT II, 30% in SCD-HeFT, and 39% in NCDR), less frequent hypertension (53% in MADIT II, 55% in SCD-HeFT, and 73% in NCDR), less common LBBB (19% in MADIT II and 27% in NCDR), and more digoxin use (57% in MADIT II, 67% in SCD-HeFT, and 30% in NCDR). These differences highlight that the trials are not directly applicable to all patients receiving ICDs for primary prevention in contemporary practice, who are older, are more likely to be female, have more comorbid conditions, and have worse heart failure symptoms.

Another important question is how representative the trial findings are to the larger Medicare population eligible for ICD implantation for primary prevention. Six comparative studies in our review provided subgroup data for those older than 65 years, which made up 47% of the study populations, whereas the proportion in NCDR is greater than 60% (46). One cohort study followed Medicare beneficiaries (median age, 75 years) after primary ICD implantation and found a mortality rate of 31% at 3 years of follow-up (47). This mortality rate was greater than in the key trials, SCD-HeFT (mean age of 60 years, 3-year mortality rate of 16%) and MADIT-II (mean age of 64 years, 3-year mortality rate of 22%). However, nearly one half of the Medicare patients did not have previous heart failure hospitalizations and received an ICD on the admission day, suggesting that they were electively admitted for the procedure. In this subgroup, the mortality rate of 22% was similar to that of the key trials despite the difference in mean ages (47). Although most trials did not specify that patients were electively admitted for ICD implantation, this is assumed to be the case. Overall, this suggests that the trial findings may apply to a sizeable proportion of Medicare patients with similar baseline risk.

There are common limitations to the analysis of subgroups. These analyses are rarely prespecified as part of the study protocol and are often conducted post hoc on the basis of available data. For this reason, many subgroup analyses are underpowered and may lead to spurious “negative” findings of no difference between subgroups. Of note, although most of the studies included in our review prespecified the subgroups before analysis and conducted interaction tests, no study was designed and powered a priori to investigate differences across subgroups. Further adjustment for baseline variables was inconsistently done, which may also lead to a misinterpretation of results.

In our review, there were limited numbers of analyses for each subgroup. Subgroup analyses of SCD outcomes were rare, limiting our ability to draw conclusions about whether any differences may exist. It is likely that subgroup analyses were not done because many studies were not powered for SCD, further restricting the power of subgroup analyses. Despite expansive searches and detailed screening, we may not have captured all relevant subgroup papers because they are often not well-indexed with subgroup-related search terms.

Further exploration of treatment heterogeneity to identify groups of patients who may particularly benefit (or derive no benefit) from ICD use are needed, especially when the cause of the disease, pathophysiology, and competing risks for death differ. To date, the analyses of subgroups are underpowered and inconclusive. A patient-level meta-analysis across major trials may be able to provide greater power to further evaluate subgroups. The existing trials have not representatively enrolled the elderly, women, and persons with comorbid conditions and more symptomatic heart failure who make up a larger percentage of persons receiving ICDs in real-world practice. Determining at what age, if any, ICD use no longer adds benefit (but possibly causes harms from adverse events, including inappropriate shocks) would be of great interest. If there are differences in the effect of ICD between men and women, then it would be important to investigate the cause of the difference to mitigate it. Although future trials should focus on the elderly and women, there is also a need for better risk prediction tools that capture risk factors beyond commonly used demographic and clinical characteristics for stratification of trial participants.

Implantable cardioverter defibrillator therapy for primary prevention of SCD versus no ICD therapy shows benefit with regard to mortality and SCD. Weak evidence for all-cause mortality in subgroups of sex, age, and QRS interval does not show differences. Evidence is indeterminate for all-cause mortality in the other subgroups and for SCD. Regardless, each patient’s prognosis has to be considered to individualize treatment decisions in clinical practice.

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