Impact of Programming Strategies Aimed at Reducing Non-Essential Implantable Cardioverter Defibrillator Therapies on Mortality – A Systematic Review and Meta-Analysis

Running title: Tan et al.; Therapy reduction programming improves survival

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Journal Subject Codes: [121] Primary prevention, [22] Ablation/ICD/surgery, [135] Risk factors
Abstract:

**Background** - Patients who receive implantable cardioverter defibrillator (ICD) therapies are at higher risk of death versus those who do not. Programmed settings to reduce non-essential ICD therapies (therapy reduction programming) have been developed, but may have adverse effects. This systematic review and meta-analysis assessed the relationship between therapy reduction programming with the risks of death from any cause, ICD shocks and syncope.

**Methods and Results** - MEDLINE, EMBASE and clinicaltrials.gov databases were searched to identify relevant studies. Those that followed patients for at least 6 months and reported mortality were included. Six met the inclusion criteria; 4 randomized (EMPIRIC, MADIT-RIT, ADVANCE III, and PROVIDE) and 2 prospective studies (RELEVANT and PREPARE). These 6 studies included 7,687 (3,598 conventional and 4,089 therapy reduction programming) patients. Most (77%) participants were male, had a history of ischemic heart disease (56%), and were prescribed beta-blockers (84%). Therapy reduction programming was associated with a 30% relative reduction in mortality (95% Confidence Interval [CI] 16% to 41%; p < 0.001). No significant heterogeneity among studies was observed (p = 0.6). A similar 26% reduction in mortality was observed when only the 4 randomized trials were included (95% CI 11% to 40%; p = 0.002). These results were not significantly altered after adjustment for baseline characteristics. No significant difference in the risk of syncope was observed with conventional versus therapy reduction programming (p = 0.5).

**Conclusions** - Therapy reduction programming results in a large, significant and consistent reduction in mortality with no apparent increase in the risk of syncope.

**Key words:** implantable cardioverter-defibrillator, systematic review, mortality, shock, syncope (fainting)
Introduction

Implantable cardioverter defibrillator (ICD) therapy is effective in reducing mortality in patients with left ventricular dysfunction and symptoms of heart failure.\textsuperscript{1-6} Non-essential ICD therapies, include those unrelated to a sustained ventricular tachyarrhythmia. They include inappropriate therapies (e.g., therapies for atrial fibrillation, supraventricular arrhythmias, or noise) and ICD therapies for non-sustained ventricular arrhythmias.\textsuperscript{7,8}

Recent data from a large prospective observational study found a 23\% incidence of appropriate ICD shocks and a 17\% incidence of inappropriate ICD shocks over 5 years.\textsuperscript{9} Receipt of painful ICD shocks, whether essential or not, is linked to significant morbidity\textsuperscript{10-13} and mortality.\textsuperscript{14,15} It is not known whether the receipt of ICD shocks is responsible for the higher risk of death or if the clinical deterioration that leads to the development of ventricular arrhythmias or atrial fibrillation is related to a higher risk of death.\textsuperscript{16-18} At the same time, extending the time to delivery of ICD therapies may increase the risk of adverse events, most notably syncope.

A prior systematic review by Ha et al\textsuperscript{19} found no compelling evidence that interventions aimed at reducing ICD shocks (antiarrhythmic drugs, ablation therapy, or ICD programming) significantly altered the risk of death. Since that publication several large studies have been reported, including the Multicenter Automatic Defibrillator Implantation Trial - Reduce Inappropriate Therapy (MADIT RIT)\textsuperscript{20}, the Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III (ADVANCE III)\textsuperscript{21} and the – Programming Implantable Cardioverter-Defibrillators in Patients with Primary Prevention Indication to Prolong Time to First Shock (PROVIDE)\textsuperscript{22} randomized trials. Further, prior individual trials that assessed the impact of therapy reduction programming were not powered to detect a difference in mortality.\textsuperscript{23} This systematic review and meta-analysis sought to quantify the impact of therapy reduction
programming on the risks of all-cause mortality, ICD shocks, inappropriate shocks and syncope.

Methods

This analysis was performed in adherence to the Preferred Reporting Items for Systemic reviews and Meta-Analyses (PRISMA) statement on the quality of reporting of meta-analyses.\textsuperscript{24} Therapy reduction programming included any ICD programming that was designed to prolong the time required to detect a sustained ventricular arrhythmia.

Search strategy

Two independent reviewers sought relevant articles on therapy reduction programming via searches of the MEDLINE and EMBASE databases, as well as clinicaltrials.gov. In addition, the reference lists of all published studies and the biographies of review articles were searched for additional articles. The search was not limited by language and is considered up to date as of October 1, 2013. Only studies that followed patients for at least 6 months and in which mortality data were reported or available from the authors were included. The primary authors of studies that appeared to be eligible, apart from mortality data, were contacted for these data.

Study selection and eligibility criteria

The primary outcome was all-cause mortality. Secondary outcomes included rates of syncope, appropriate shocks and inappropriate shocks as defined by the individual studies included. Both randomized and non-randomized studies were included. A separate analysis was performed among the randomized trials prior to pooling.

Bias assessment

The internal validity of included studies was assessed using Cochrane Collaboration’s tool for assessing risk of bias in randomized trials (Table 1).\textsuperscript{25}
Statistical analysis

Data were pooled and analyzed using Stata v.11 statistical software. A random effects model was used. The effect size is presented as the relative risk reduction. Statistical heterogeneity was evaluated using the I² statistic and its 95% confidence interval (CI). Meta-regression was used to assess the potential influence of baseline characteristics.

Results

Study Selection

A total of 307 records were identified. Twenty-one full text articles were assessed for eligibility (Figure 1). Six trials met the inclusion criteria. They included 4 randomized trials (Comparison of Empiric to Physician-Tailored Programming of ICDs [EMPIRIC]26, MADIT RIT20, ADVANCE III21, and PROVIDE21) and 2 prospective studies (the Primary Prevention Parameters Evaluation [PREPARE]27 and the Role of Long Detection Window Programming in Patients With Left Ventricular Dysfunction, Non-ischemic Etiology in Primary Prevention Treated with a Biventricular ICD [RELEVANT]28). These 6 studies included 7,687 (3,598 conventional and 4,089 therapy reduction programming) patients.

Characteristics

The characteristics of the patients in these 6 trials are shown in Table 2. Most (77%) participants were male and had history of coronary heart disease (58%). A minority of patients (19%) had history of atrial arrhythmias (atrial fibrillation, atrial flutter or atrial tachycardia). Few (12%) patients received an ICD for secondary prevention. Most patients received beta-blockers (84%) and few (14%) received antiarrhythmic drugs. Baseline characteristics were similar in the therapy reduction and conventional programming arms (not shown), apart from a lower mean left ventricular ejection fraction in the conventional (25%) versus therapy reduction group (28%) in
Therapy Reduction Programming

ICD programming for the comparator groups in each of the 6 studies is summarized in Table 3. Therapy reduction programming included combinations of longer detection intervals and higher detection rates. All but one of the programming strategies included algorithms designed to discriminate between supraventricular tachycardia (SVT) and or noise from ventricular arrhythmias. Algorithms to discriminate SVT from ventricular arrhythmias were not used in the MADIT RIT high rate programming strategy.

Primary Outcome (Mortality)

All-cause Mortality

A total of 469 deaths (6%) were observed; 207 (5.0%) in the therapy reduction and 262 (7.3%) in the conventional programming group. Therapy reduction programming was associated with a significant and consistent 30% (95% CI 16% to 41%; p<0.001) lower risk of death versus with conventional programming (Figure 2a). No significant heterogeneity among the 6 studies was observed (I² = 0%, p = 0.6). However, the 95% CI surrounding the I² statistic was wide, reflecting the small number of studies included.

One death in PREPARE was adjudicated as possibly related to therapy reduction programming. No other deaths were categorized as related to therapy reduction programming in the 5 remaining studies. Cardiovascular and non-cardiovascular deaths were not consistently reported separately in the studies, preventing analysis of the impact of therapy reduction programming on cardiovascular death.

Sensitivity Analyses

Similar reductions in mortality were observed when only the 4 randomized trials were included.
(26% relative reduction, 95% CI 11% to 39%; \( p = 0.002; \textbf{Figure 2b} \)). Further, the effect size was somewhat larger when the 2 MADIT RIT therapy reduction groups were combined (35% relative reduction, 95% CI 9% to 49%; \( p = 0.004 \)) versus when they were assessed separately (\textbf{Figure 2a}).

A significant reduction in mortality was also observed with therapy reduction versus conventional programming when only the 2 non-randomized were separately assessed (42% relative reduction, 95% CI 14% to 61%; \( p = 0.007 \)).

When assessed using meta-regression, none of the baseline characteristics presented in \textbf{Table 2}, alone or in combination, significantly altered the relationship between reduced mortality with therapy reduction versus conventional programming.

\textbf{Secondary Outcomes}

\textbf{Syncope}

PREPARE did not report the number of patients with syncope in the conventional arm and that study was removed from the sub-analysis of syncope. Nonetheless, PREPARE does provide insight into the frequency of syncope attributable to therapy reduction programming. A total of 40 syncopal events were reported in therapy reduction programming group in PREPARE. Of these, 12 (30%) were considered arrhythmic and 28 (70%) non-arrhythmic. Ten of the 12 arrhythmic events or 25% of all syncopal were judged as related to therapy reduction programming.

A total of 179 \textit{syncope} events (2.8%) were reported in the 5 remaining studies. This included 105 (3.1%) events among patients in the therapy reduction group and 74 (2.5%) events in the conventional programming group. No significant difference in the rate of syncope (9% increase; 95% CI 17% reduction to 44% increase; \( p = 0.5 \)) was observed with therapy reduction
versus conventional programming (Figure 3).

**ICD Shocks**

Shock density (number of shocks per 100 patient-year of follow-up) was reduced for both appropriate and inappropriate (except EMPIRIC) shocks in therapy reduction programming arm as compare to conventional arm. Neither EMPIRIC nor PREPARE separated out the numbers of patients receiving appropriate and inappropriate ICD therapies. Hence these analyses were limited to the remaining 4 studies (Table 4).

**Appropriate Shocks**

A minority of patients received appropriate ICD shocks in the 4 studies included. A total of 290 patients received appropriate ICD shocks (5.4%); 153 (5.2%) in the therapy reduction and 137 (5.6%) in the conventional group. No significant difference in the risk of appropriate ICD shocks (relative reduction 6%; 95% CI 25% reduction to 16% increase; p = 0.5) was observed with therapy reduction versus conventional programming.

**Inappropriate Shocks**

A somewhat lower proportion of patients in the 4 included studies received inappropriate ICD shocks. A total of 267 patients received inappropriate ICD shocks (4.9%); 99 (3.4%) in the therapy reduction and 168 (6.9%) in the conventional programming group. A 50% relative reduction (95% CI 37% to 61%; p < 0.001) in the risk of inappropriate ICD shocks with therapy reduction versus conventional programming was observed (Figure 4).

**Discussion**

This analysis demonstrates therapy reduction programming results in a 30% lower risk of death versus conventional programming. This was consistent among the 6 studies. The reduction in mortality with therapy reduction programming was similar in the 4 randomized trials and the 2
prospective studies. No significant difference in the risk of syncope or in the risk of appropriate shocks was observed with therapy reduction versus conventional programming. However, a 50% reduction in inappropriate shocks was found with therapy reduction versus conventional programming.

ICD shocks have been shown to cause myocardial injury and are potentially pro-arrhythmic.\textsuperscript{29, 30} Further, the receipt of ICD therapies, shocks and / or anti-tachycardia pacing therapies (ATP), has been linked to an increased risk of death from progressive heart failure.\textsuperscript{31} In both secondary prevention (Antiarrhythmic Versus Implantable Defibrillators [AVID]\textsuperscript{31}) and primary prevention studies, (Sudden Cardiac Death Heart Failure Trial [SCD-HeFT]\textsuperscript{14} and Multicenter Automatic Defibrillator Implantation Trial II [MADIT II]\textsuperscript{15}) the receipt of ICD therapies are associated with a 3 to 5-fold higher risk of death that is temporally related to the receipt of these ICD therapies.

Limiting ICD therapies to only sustained and potentially life-threatening arrhythmias (essential therapies) may improve patient outcomes by reducing pro-arrhythmia requiring ICD shocks or other adverse sequelae. Further, the specific method by which a reduction in non-essential therapies is achieved does not appear critical, since reductions in mortality were consistent among the 6 studies despite variations in therapy reduction programming strategies (Table 3).

Initial concerns regarding a potential increase in rates of death or syncope with therapy reduction programming (prolonged detection) appear to be unfounded. As noted, only one death in the 6 studies included was possibly related to therapy reduction programming. Further, syncope was uncommon in both the therapy reduction and conventional programming groups and rates of syncope were similar in the two groups. However, only the PROVIDE trial further
divided syncope into arrhythmic and non-arhythmic and provided data in both treatment arms. In PROVIDE there was no significant difference ($p = 0.49$) in arrhythmic syncope between therapy reduction (1%) and conventional programming groups (2%).

**Limitations**

Individual patient data was not available and only pooled study data was used. Hence, our ability to look at specific patient characteristics (e.g., secondary versus primary prevention or history versus no history if atrial arrhythmias) was limited and our analysis was not adequately powered to detect smaller, but clinically important differences for the characteristics assessed in the meta-regression models. As noted, the 95% CI surrounding the heterogeneity estimates were wide due to the small number of studies included. Cardiovascular deaths were not separately reported, preventing a separate analysis of cardiovascular versus non-cardiovascular death. We also relied on the definitions of syncope, inappropriate and appropriate therapies from each of the included studies and were not able to apply standard definitions due to a lack of such data. Moreover, only PROVIDE and PREPARE differentiated arrhythmic from non-arhythmic syncope. As noted, no difference in the rate of arrhythmic syncope among the comparator groups was identified in that trial. The trials included were not designed to assess risk of syncope events as a result of therapy reduction programming strategy and a tradeoff between avoidance of ICD therapies versus a risk of arrhythmic syncope likely exists and merits further study. Finally, caution should be exercised in extrapolating the results of this analysis to all ICD recipients. Most of the patients included had a low EF and received an ICD for a primary prevention indication. Additional data are required to understand the utility of therapy reduction programming in other groups of ICD recipients.
Conclusion

Therapy reduction programming is associated with a large, significant and consistent reduction in mortality without an apparent increase in the risk of syncope. Although a tradeoff between avoidance of ICD therapies versus a risk of arrhythmic syncope likely exists. The reduction in ICD therapies was largely related to the reduction in inappropriate therapies.

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Conflict of Interest Disclosures: Drs. Exner and Wilton receive research funding from St. Jude Medical. Drs. Exner and Sumner receive research funding from Medtronic. The University of Calgary receives fellowship support from Boston Scientific, Canada and Medtronic, Canada.

References:


Table 1: Risk of Bias in the Included Studies (Cochrane Collaboration’s Tool).

<table>
<thead>
<tr>
<th>Study</th>
<th>Adequate sequence generation</th>
<th>Concealment of allocation</th>
<th>Single or double blinding</th>
<th>Blinding to outcome</th>
<th>Incomplete outcome data addressed</th>
<th>Free of selective reporting</th>
<th>Free of other bias</th>
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</thead>
<tbody>
<tr>
<td>EMPIRIC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Yes</td>
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<td>PREPARE</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>PROVIDE</td>
<td>Yes</td>
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<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
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</table>

See text for study acronyms.
Table 2: Characteristics of Patients Included.

<table>
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<tr>
<th>Study</th>
<th>N</th>
<th>Trial Type</th>
<th>Mean FU (years)</th>
<th>Mean Age</th>
<th>Male (%)</th>
<th>CHD (%)</th>
<th>2° (%)</th>
<th>Mean LVEF (%)</th>
<th>NYHA III/IV (%)</th>
<th>VVI-ICD (%)</th>
<th>Atrial Arrhythmia (%)</th>
<th>BB (%)</th>
<th>AAD (%)</th>
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<tbody>
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<td>EMPIRIC</td>
<td>900</td>
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<td>81</td>
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<td>16</td>
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<td>64</td>
<td>76</td>
<td>0</td>
<td>0</td>
<td>25</td>
<td>NA</td>
<td>0</td>
<td>16</td>
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<td>27</td>
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<td>RCT</td>
<td>1.4</td>
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<td>RCT</td>
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<td>65</td>
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<td>60</td>
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<td>29</td>
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<td>81</td>
<td>20</td>
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<td>1,670</td>
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<td>64</td>
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<td>62</td>
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<td>48</td>
<td>60</td>
<td>27</td>
<td>89</td>
<td>10</td>
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</tbody>
</table>

**Table Notes:**
- **AAD** - antiarrhythmic drug therapy;
- **BB** - beta-blocker therapy;
- **CHD** - history of coronary heart disease;
- **FU** - Follow up;
- **RCT** - randomized clinical trial;
- **LVEF** - left ventricular ejection fraction;
- **ICD** - implantable cardioverter defibrillator;
- **N** - number of patients in study;
- **NYHA** - New York Heart Association functional class;
- **OBS** - Observational, non-randomized study.

**Additional Notes:**
- 
- **VVI** - single chamber ICD;
- **2°** - secondary prevention ICD therapy. See text for study acronyms.
Table 3. Summary of Therapy Reduction Programming Strategies and Comparator Groups.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Therapy Reduction Programming</th>
<th>Conventional Programming</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPIRIC (2006)</td>
<td>VF – 250 bpm; NID 18 of 24 FP – 200 bpm; NID 18 of 24; ATP x 1 VT – 150 bpm; NID 16; ATP x 2</td>
<td>VF – Rate not specified; NID 12 of 16 (50%) or 18 of 24 (49%)</td>
</tr>
<tr>
<td>PREPARE (2008)</td>
<td>VF – 250 bpm; NID 30 of 40 FVT – 182 bpm; NID 30 of 40; ATP x 1 VT – 167 bpm; NID 32; Monitor only</td>
<td>VF – Rate not specified; NID 12 of 16 (58%) or 18 of 24 (42%)</td>
</tr>
<tr>
<td>RELEVANT (2009)</td>
<td>VF – 250 bpm; NID 30 of 40 FVT – 182 bpm; NID 30 of 40; ATP x 1 VT – 167 bpm; NID 32; Monitor only</td>
<td>VF – 250 bpm; NID 12 of 16</td>
</tr>
<tr>
<td>MADIT-RIT (2012)</td>
<td>High Rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zone 1 – 200 bpm; 2.5 sec delay (8 to 10 beats); ATP x 1 Zone 2 – 170 bpm; Monitor only</td>
<td>Zone 1 – 200 bpm; 1 sec delay (3 to 4 beats); ATP x 1 Zone 2 – 170 bpm; 2.5 sec delay (7 to 8 beats); ATP x 1</td>
</tr>
<tr>
<td></td>
<td>Duration Delay</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zone 1 – 250 bpm; 2.5 sec delay; ATP x 1 Zone 2 – 200 bpm; 12sec delay (40 to 50 beats); ATP x 1</td>
<td>Zone 1 – 200 bpm; 1 sec delay (3 to 4 beats); ATP x 1 Zone 2 – 170 bpm; 2.5 sec delay (7 to 8 beats); ATP x 1</td>
</tr>
<tr>
<td></td>
<td>Zone 3 – 170 bpm; 60sec delay (169 to 199 beats); ATP x 1</td>
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</tr>
<tr>
<td>ADVANCE III (2013)</td>
<td>VF – 188 bpm; NID 30 of 40; ATP x 1 VT – 150 bpm; NID 32; Monitor only</td>
<td>VF – 188 bpm; NID 18 of 24; ATP x 1 VT – 150 bpm; NID 32; Monitor only</td>
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<tr>
<td>PROVIDE (2013)</td>
<td>VF – 250 bpm; NID 12 VT 2 – 214 bpm; NID 18; ATP x 1 VT 1 – 181 bpm; NID 25; ATP x 2</td>
<td>VF – 214 bpm; NID 12 VT 2 – 181 bpm; NID 12; ATP x 2 VT 1 – 150 bpm; NID 12; Monitor only</td>
</tr>
</tbody>
</table>

ATP – anti-tachycardia pacing therapy; BPM – beats per minute; FVT – Fast Ventricular Tachycardia; NID – number of intervals to detect; VF - Ventricular Fibrillation; VT - Ventricular Tachycardia. See text for study acronyms.
Table 4. Rates of Appropriate and Inappropriate Shocks (expressed per 100-Patient-Years of Follow-up) in the Four Studies that Separately Reported the Numbers of Patients Receiving Appropriate and Inappropriate Defibrillator Therapies.

<table>
<thead>
<tr>
<th></th>
<th>RELEVANT</th>
<th>MADIT RIT Delay</th>
<th>MADIT RIT High Rate</th>
<th>ADVANCE III</th>
<th>PROVIDE</th>
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<td>Therapy Reduction</td>
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<tr>
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<td>8 (6 - 10)</td>
<td>10 (8 - 13)</td>
<td>11 (9 - 13)</td>
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<td>Inappropriate Shocks (95% CI)</td>
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<td></td>
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<td>Therapy Reduction</td>
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<tr>
<td>Conventional</td>
<td>36 (26 - 48)</td>
<td>10 (8 - 12)</td>
<td>10 (8 - 12)</td>
<td>15 (13 - 18)</td>
<td>11 (9 - 13)</td>
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</table>

See text for study acronyms.
Figure Legends:

**Figure 1:** Flow Diagram of Study Selection. Progress through the systematic review.

**Figure 2A** Therapy Reduction Versus Convention Programming and Risk of Death – Randomized and Non-randomized Studies. Random effects meta-analysis of therapy reduction versus conventional programming on the outcome of all-cause mortality. All 6 studies are shown. The MADIT RIT groups are separately compared to the same control group. See text for study acronyms.

**Figure 2B** Therapy Reduction Versus Convention Programming and Risk of Death – Randomized Trials Only. Random effects meta-analysis of therapy reduction versus conventional programming on the outcome of all-cause mortality. The 4 randomized trials are shown. The MADIT RIT groups are combined. See text for study acronyms.

**Figure 3:** Risk of Syncope with Therapy Reduction Versus Conventional Programming. Random effects meta-analysis of therapy reduction versus conventional programming on the outcome of syncope. The 5 studies that reported syncope in both treatment arms are included. The two MADIT RIT groups are separately compared to the same control group. See text for study acronyms.

**Figure 4:** Risk of Inappropriate Implantable Cardioverter Defibrillator Shocks with Therapy Reduction Versus Conventional Programming. Random effects meta-analysis of therapy reduction versus conventional programming on the outcome of inappropriate implantable cardioverter defibrillator shocks. The 4 studies that separately reported inappropriate shocks in
both treatment arms are included. The two MADIT RIT groups are separately compared to the same control group. See text for study acronyms.
307 records identified via Medline, Embase, and clinicaltrials.gov databases

112 duplicate records excluded

195 records retained

174 records excluded after abstract review

21 articles retained

15 articles excluded
- 2 without mortality data
- 9 review articles
- 1 computer modeling only
- 3 lacked comparison group

6 studies included