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

Vern Hsen Tan, MBBS, MRCP; Stephen B. Wilton, MD, MSc; Vikas Kuriachan, MD, FHRS; Glen L. Sumner, MD; Derek V. Exner, MD, MPH, FHRS

Background—Patients who receive implantable cardioverter defibrillator therapies are at higher risk of death versus those who do not. Programmed settings to reduce nonessential implantable cardioverter defibrillator 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, implantable cardioverter defibrillator shocks, and syncope.

Methods and Results—MEDLINE, EMBASE, and clinicaltrials.gov databases were searched to identify relevant studies. Those that followed patients for ≥6 months and reported mortality were included. Six met the inclusion criteria; 4 randomized (Comparison of Empiric to Physician-Tailored Programming of ICDs [EMPIRIC], Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy [MADIT-RIT], Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III [ADVANCE III], and Programming Implantable Cardioverter-Defibrillators in Patients with Primary Prevention Indication to Prolong Time to First Shock [PROVIDE]) and 2 prospective studies (Role of Long Detection Window Programming in Patients With Left Ventricular Dysfunction, Non-ischemic Etiology in Primary Prevention Treated with a Biventricular ICD [RELEVANT] and Primary Prevention Parameters Evaluation [PREPARE]). These 6 studies included 7687 (3598 conventional and 4089 therapy reduction programming) patients. Most (77%) participants were men, had a history of ischemic heart disease (56%), and were prescribed β-blockers (84%). Therapy reduction programming was associated with a 30% relative reduction in mortality (95% confidence interval, 16%–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% confidence interval, 11%–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. (Circ Arrhythm Electrophysiol. 2014;7:164-170.)

Key Words: defibrillators, implantable ■ mortality ■ review ■ shock
publication, several large studies have been reported, including the Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy (MADIT-RIT),20 the Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III (ADVANCE III),21 and the Programming Implantable Cardioverter-Defibrillators in Patients with Primary Prevention Indication to Prolong Time to First Shock (PROVIDE)22 randomized trials. Further, prior individual trials that assessed the effect of therapy reduction programming were not powered to detect a difference in mortality.23 This systematic review and meta-analysis sought to quantify the effect of therapy reduction programming in 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 Systematic reviews and Meta-Analyses (PRISMA) statement on the quality of reporting of meta-analyses.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 ≥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 nonrandomized studies were included. A separate analysis was performed among the randomized trials before 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).25

Statistical Analysis
Data were pooled and analyzed using Stata version 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 F 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-RIT,20 ADVANCE III,21 and PROVIDE)22 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 7687 (3598 conventional and 4089 therapy reduction programming) patients.

Characteristics
The characteristics of the patients in these 6 trials are shown in Table 2. Most (77%) participants were men 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 β-blockers (84%) and few (14%) received antiarrhythmic drugs. Baseline

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>
</tr>
</thead>
<tbody>
<tr>
<td>EMPIRIC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>PREPARE</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
</tr>
<tr>
<td>RELEVANT</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MADIT-RIT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ADVANCE III</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PROVIDE</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ADVANCE III indicates Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III; EMPIRIC, Comparison of Empiric to Physician-Tailored Programming of ICDs; MADIT-RIT, Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy; PREPARE, Primary Prevention Parameters Evaluation; PROVIDE, Programming Implantable Cardioverter-Defibrillators in Patients with Primary Prevention Indication to Prolong Time to First Shock; and RELEVANT, Role of Long Detection Window Programming in Patients With Left Ventricular Dysfunction, Non-ischemic Etiology in Primary Prevention Treated with a Biventricular ICD.

Figure 1. Flow diagram of study selection. Progress through the systematic review.
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 PREPARE.

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 and noise from ventricular arrhythmias. Algorithms to discriminate supraventricular tachycardia 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, 20%–39%) lower risk of death compared with the conventional programming group.

Table 3. Summary of Therapy Reduction Programming Strategies and Comparator Groups

<table>
<thead>
<tr>
<th>Study, y</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</td>
<td>VF–rate not specified; NID 12 of 16 (50%) or 18 of 24 (49%)</td>
</tr>
<tr>
<td></td>
<td>FVT–200 bpm; NID 18 of 24; ATP×1</td>
<td>FVT–rate not specified (used in 70%)</td>
</tr>
<tr>
<td></td>
<td>VT–150 bpm; NID 16; ATP×2</td>
<td>VT–rate not specified; ≥1 ATP (95%)</td>
</tr>
<tr>
<td>PREPARE (2008)</td>
<td>VF–250 bpm; NID 30 of 40</td>
<td>VF–rate not specified; NID 12 of 16 (58%) or 18 of 24 (42%)</td>
</tr>
<tr>
<td></td>
<td>FVT–182 bpm; NID 30 of 40; ATP×1</td>
<td>FVT–rate not specified; ≥1 ATP (25%)</td>
</tr>
<tr>
<td></td>
<td>VT–167 bpm; NID 32; monitor only</td>
<td>VT–rate not specified; ≥1 ATP (29%)</td>
</tr>
<tr>
<td>RELEVANT (2009)</td>
<td>VF–250 bpm; NID 30 of 40</td>
<td>VF–250 bpm; NID 12 of 16</td>
</tr>
<tr>
<td></td>
<td>FVT–182 bpm; NID 30 of 40; ATP×1</td>
<td>FVT–182 bpm; NID 12 of 16; ATP×1</td>
</tr>
<tr>
<td></td>
<td>VT–167 bpm; NID 32; monitor only</td>
<td>VT–167 bpm; NID 32; monitor only</td>
</tr>
<tr>
<td>MADIT-RIT (2012)</td>
<td>High rate</td>
<td>Zone 1–200 bpm; 1 s delay (≥3–4 beats); ATP×1</td>
</tr>
<tr>
<td></td>
<td>Zone 1–200 bpm; 2.5 s delay (8–10 beats); ATP×1</td>
<td>Zone 2–170 bpm; 2.5 s delay (7–8 beats); ATP×1</td>
</tr>
<tr>
<td></td>
<td>Zone 2–170 bpm; monitor only</td>
<td>Duration delay</td>
</tr>
<tr>
<td></td>
<td>Zone 1–250 bpm; 2.5 s delay; ATP×1</td>
<td>Zone 1–200 bpm; 1 s delay (≥3–4 beats); ATP×1</td>
</tr>
<tr>
<td></td>
<td>Zone 2–200 bpm; 12 s delay (40–50 beats); ATP×1</td>
<td>Zone 2–170 bpm; 2.5 s delay (7–8 beats); ATP×1</td>
</tr>
<tr>
<td></td>
<td>Zone 3–170 bpm; 60 s delay (169–99 beats); ATP×1</td>
<td>Zone 3–170 bpm; 2.5 s delay (7–8 beats); ATP×1</td>
</tr>
<tr>
<td>ADVANCE III (2013)</td>
<td>VF–188 bpm; NID 30 of 40; ATP×1</td>
<td>VF–188 bpm; NID 18 of 24; ATP×1</td>
</tr>
<tr>
<td></td>
<td>VT–150 bpm; NID 32; monitor only</td>
<td>VT–150 bpm; NID 32; monitor only</td>
</tr>
<tr>
<td>PROVIDE (2013)</td>
<td>VF–250 bpm; NID 12</td>
<td>VF–214 bpm; NID 12</td>
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<tr>
<td></td>
<td>VT 2–214 bpm; NID 18; ATP×1</td>
<td>VT 2–181 bpm; NID 12; ATP×2</td>
</tr>
<tr>
<td></td>
<td>VT 1–181 bpm; NID 25; ATP×2</td>
<td>VT 1–150 bpm; NID 12; monitor only</td>
</tr>
</tbody>
</table>

ADVANCE III indicates Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III; ATP, antitachycardia pacing therapy; bpm, beats per minute; EMPIRIC, Comparison of Empiric to Physician-Tailored Programming of ICDs; FVT, fast ventricular tachycardia; MADIT-RIT, Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy; NID, number of intervals to detect; PREPARE, Primary Prevention Parameters Evaluation; PROVIDE, Programming Implantable Cardioverter-Defibrillators in Patients with Primary Prevention Indication to Prolong Time to First Shock; RELEVANT, Role of Long Detection Window Programming in Patients With Left Ventricular Dysfunction, Non-ischemic Etiology in Primary Prevention Treated with a Biventricular ICD; and VT, ventricular tachycardia.
16%–41%; \( P<0.001 \) lower risk of death versus with conventional programming (Figure 2A). No significant heterogeneity among the 6 studies was observed (\( I^2=0\% \); \( P=0.6 \)). However, the 95% CI surrounding the \( F \) 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 noncardiovascular deaths were not consistently reported separately in the studies, preventing analysis of the effect 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%–39%; \( P=0.002 \); Figure 2B). Furthermore, the effect size was somewhat larger when the 2 MADIT-RIT therapy reduction groups were combined (35% relative reduction, 95% CI, 9%–49%; \( P=0.004 \)) versus when they were assessed separately (Figure 2A).

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

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

**Secondary Outcomes**

**Syncope**

PREPARE did not report the number of patients with syncope in the conventional arm and that study was removed from the subanalysis 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%) nonarrhythmic. Ten of the 12 arrhythmic events or 25% of all syncopal were judged as related to therapy reduction programming.

A total of 179 syncopal 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).

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

When assessed using meta-regression, none of the baseline characteristics presented in Table 2, alone or in combination, significantly altered the relationship between reduced mortality with therapy reduction versus conventional programming.
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 compared with 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%–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 proarrhythmic.29,30 Furthermore, the receipt of ICD therapies, shocks and antiarrhythmia pacing therapies, has been linked to an increased risk of death from progressive heart failure.31 In both secondary prevention (Antiarrhythmic Versus Implantable Defibrillators [AVID])31 and primary prevention studies (Sudden Cardiac Death Heart Failure Trial [SCD-HeFT])32 and Multicenter Automatic Defibrillator Implantation Trial II [MADIT II]33), the receipt of ICD therapies is 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 proarrhythmia requiring ICD shocks or other adverse sequelae. Furthermore, the specific method by which a reduction in nonessential therapies is achieved does not seem critical because reductions in mortality were consistent among the 6 studies, despite variations in therapy reduction programming strategies (Table 3).

Initial concerns on a potential increase in rates of death or syncope with therapy reduction programming (prolonged...
detection) seem to be unfounded. As noted, only 1 death in the 6 studies included was possibly related to therapy reduction programming. Furthermore, syncope was uncommon in both the therapy reduction and conventional programming groups, and rates of syncope were similar in the 2 groups. However, only the PROVIDE trial further divided syncope into arrhythmic and nonarrhythmic 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 were not available, and only pooled study data were used. Hence, our ability to look at specific patient characteristics (eg, 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 was wide because of the small number of studies included. Cardiovascular deaths were not separately reported, preventing a separate analysis of cardiovascular versus noncardiovascular 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 because of a lack of such data. Moreover, only PROVIDE and PREPARE differentiated arrhythmic from nonarrhythmic 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 trade-off 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 ejection fraction and received an ICD for a primary prevention indication. Additional data are required to understand the use of therapy reduction programming in other groups of ICD recipients.

Conclusions
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 trade-off between avoidance of ICD therapies versus a risk of arrhythmic syncope likely exists, the reduction in ICD therapies was related largely to the reduction in inappropriate therapies.

Acknowledgments
Dr Exner is Canadian Institutes of Health Research Canada Research Chair in Cardiovascular Clinical Trials.

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. The other authors report no conflicts.

References
Controversy exists on optimal ICD programming. Conventional programming is designed to rapidly detect and treat tachyarrhythmias (primary prevention). Yet, ICD shocks are painful, reduce quality of life, and are linked to adverse outcomes. (secondary prevention) and those at high risk of sudden cardiac arrest because of the presence of left ventricular systolic dysfunction.

Implantable cardioverter defibrillator (ICD) therapy improves survival in patients with sustained ventricular arrhythmias and is based on the desire to reduce the risk of syncope via aggressive treatment of all potentially life-threatening arrhythmias. However, the rate of ICD shocks for potentially life-threatening arrhythmias is many times larger than the mortality benefit from an ICD. Further, many arrhythmias may self-terminate, and early, aggressive ICD treatment results in the delivery of shocks for non-life-threatening rhythms such as atrial fibrillation. Programmed settings to limit the delivery of ICD therapies only to arrhythmias that are both sustained and rapid (therapy reduction programming) aims to reduce the number of shocks but may undertreat arrhythmias and increase the risk of syncope. This systematic review and meta-analysis evaluated the effect of therapy reduction versus conventional programming on the risks of death and syncope in mostly primary prevention ICD recipients. A large and consistent reduction in mortality was observed with therapy reduction versus conventional programming, mostly because of a reduction in inappropriate ICD therapies. No apparent increase in the risk of syncope was observed. These data support the standard adoption of therapy reduction programming in primary prevention ICD recipients to improve clinical outcomes.
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_Circ Arrhythm Electrophysiol._ 2014;7:164-170; originally published online January 20, 2014; doi: 10.1161/CIRCEP.113.001217
_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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