Utilization of implantable cardioverter-defibrillators for the prevention of sudden cardiac death in emerging countries: Improve SCA clinical trial

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BACKGROUND Implantable cardioverter-defibrillators (ICDs) are underutilized in Asia, Latin America, Eastern Europe, the Middle East, and Africa. The Improve SCA Study is the largest prospective study to evaluate the benefit of ICD therapy in underrepresented geographies. This analysis reports the primary objective of the study.

OBJECTIVES The objectives of this study was to determine whether patients with primary prevention (PP) indications with specific risk factors (1.5PP: syncope, nonsustained ventricular tachycardia, premature ventricular contractions >10/h, and low ventricular ejection fraction <25%) are at a similar risk of life-threatening arrhythmias as patients with secondary prevention (SP) indications and to evaluate all-cause mortality rates in 1.5PP patients with and without devices.

METHODS A total of 3889 patients were included in the analysis to evaluate ventricular tachycardia or fibrillation therapy and mortality rates. Patients were stratified as SP (n = 1193) and patients with PP indications. The PP cohort was divided into 1.5PP patients (n = 1913) and those without any 1.5PP criteria (n = 783). The decision to undergo ICD implantation was left to the patient and/or physician. The Cox proportional hazards model was used to compute hazard ratios.

RESULTS Patients had predominantly nonischemic cardiomyopathy. The rate of ventricular tachycardia or fibrillation in 1.5PP patients was not equivalent (within 30%) to that in patients with SP indications (hazard ratio 0.47; 95% confidence interval 0.38–0.57) but was higher than that in PP patients without any 1.5PP criteria (hazard ratio 0.67; 95% confidence interval 0.46–0.97) (P = .03). There was a 49% relative risk reduction in all-cause mortality in ICD implanted 1.5PP patients.

In addition, the number needed to treat to save 1 life over 3 years was 10.0 in the 1.5PP cohort vs 40.0 in PP patients without any 1.5PP criteria.

CONCLUSION These data corroborate the mortality benefit of ICD therapy and support extension to a selected PP population from underrepresented geographies.

KEYWORDS Implantable cardioverter-defibrillators; Mortality; Primary prevention; Risk stratification; Secondary prevention; Sudden cardiac arrest

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Introduction
Sudden cardiac death (SCD) remains a leading cause of mortality worldwide. The prevention of SCD is an important goal, and implantable cardioverter-defibrillators (ICDs) play a vital role by terminating sudden or unexpected arrhythmias leading to sudden cardiac arrest (SCA). Current clinical practice guidelines recommend the use of ICDs in the management of patients, both for primary prevention (PP) and for secondary prevention (SP) of SCD. However, PP ICD utilization remains low in some geographic regions and varies greatly, partly because of the heterogeneous degree of the reported benefit that ICDs confer to all patients with PP indications. For example, ICD utilization in the United States has been reported to be 280 per million, in comparison to 4.3 per million in China and 3.1 per million in India. Risk factors known to represent the severity of ventricular dysfunction and thus increase the risk of SCD include syncope or presyncope, low ventricular ejection fraction (LVEF, <25%), nonsustained ventricular tachycardia (NSVT), and frequent premature ventricular contractions (PVCs, >10/h). In a retrospective analysis of the OMNI study, Assessing Therapies in Medtronic Pacemaker, Defibrillator and Cardiac Resynchronization Therapy Devices (ClinicalTrials.gov ID: NCT002275524), a subset of patients with PP indications with at least 1 of these risk factors had a similar rate of ventricular tachyarrhythmias (ventricular tachycardia or fibillation [VT/VF]) as patients receiving ICDs for SP. Whether this is true in patients from underrepresented geographies remains poorly understood. We sought to further understand this by conducting a prospective observational study to test the hypothesis that patients with PP indications with these risk factors (termed 1.5PP) have a risk of VT/VF comparable to that of patients with SP.

Methods
Study design
The Improve SCA Study (ClinicalTrials.gov ID: NCT02099721) was a prospective, nonrandomized, nonblinded, multicenter global study designed to evaluate the rate of ICD therapy for VT/VF in PP ICD patients. Patients with PP indications with ≥1 of the following risk factors were identified as “1.5PP” patients: syncope or presyncope, LVEF <25%, NSVT, and PVCs ≥10/h. Patients with PP indications who were indicated for an ICD/cardiac resynchronization therapy-defibrillator (CRT-D) and did not have these risk factors were identified as “1.0PP.” The study design has been described previously. Briefly, patients were enrolled from geographies underrepresented in prior randomized clinical trials and where ICD utilization in clinically indicated patients is low: Asia, Latin America, Eastern Europe, the Middle East, and South Africa. Enrollment occurred between March 26, 2014, and July 15, 2017 Supplemental Appendix A. The primary objective of the study was to compare the time to first therapy for VT/VF between 1.5PP and patients with SP indications. The study also compared the mortality rates between patients with 1.5PP criteria who underwent ICD implantation and those who did not.

Patient population
All patients older than 18 years having a class I indication for a single- or dual-chamber ICD or CRT-D implant according to current clinical practice guidelines were eligible for participation. Patients were categorized as either patients with PP indications or patients with SP indications. At the baseline visit, patients with PP indications were assessed to determine whether they met 1.5PP criteria and were further categorized as either 1.5PP or 1.0PP patients. All implanted patients received a Medtronic ICD or CRT-D (Medtronic, Mounds View, MN).

Follow-up and data collection
The decision to implant an ICD (or CRT-D, if indicated) was left to the discretion of the patient and/or physician. The reasons for refusal were documented for patients who chose not to undergo implantation, and patients could select multiple reasons. Patient follow-ups were completed in person or by telephone every 6 months postimplantation or postrefusal until study closure. Patients with SP indications who did not receive an implant were exited, as they would not contribute to the objectives of the study.

End points
The primary end point of the study was the time to first VT/VF therapy (shock or antitachycardia pacing) to treat a confirmed VT/VF episode. This was compared between SP and 1.5PP ICD recipients. The hypothesis was that the rate of first VT/VF therapy between the 2 groups was comparable, defined as being within 30%. The study also compared the time to first VT/VF therapy between 1.5PP and 1.0PP post hoc. All device-detected and treated VT/VF episodes were reviewed and adjudicated by an independent episode review committee. The secondary end point for the study was mortality in 1.5PP patients who did and did not elect to undergo ICD implantation. Deaths were classified by the sites into the following categories: SCD, non-SCD, non-cardiac death, and unknown.

Device programming
The protocol required sites to program all devices, regardless of patient indication, to common settings for 32 parameters so that study outcomes would not be dictated by differences in device programming. The settings follow the principles of treating only high-rate, longer-duration episodes, utilizing extensive sustained ventricular tachycardia and oversensing
Physicians were allowed discretionary programming with a documented medical rationale. Each key parameter was programmed correctly at implantation in at least 85% of patients (Supplemental Table S1).

**Statistical analysis**

Continuous variables are reported as mean ± SD. Two-sample t tests and χ² tests were used to compare baseline characteristics. The objective of the study was to demonstrate that VT/VF therapy rates (defined as time to first appropriate VT/VF therapy) between 1.5PP and SP patients are within 30% (lower 95% confidence bound of the hazard ratio of 1.5PP/SP is >0.7). All patients who received an ICD at any time in the study were included in the primary objective analysis. Patients were followed from the date of implantation and were censored on the date of their last device follow-up.

An unadjusted log-rank test P value and hazard ratio are reported, though the secondary objective analysis of mortality used Cox proportional hazards adjustment (adjusted for the following prespecified factors: age, sex, QRS duration, ischemic cardiomyopathy, left bundle branch block, New York Heart Association class, diabetes, LVEF, syncope qualifying as 1.5PP, NSVT qualifying as 1.5PP, and PVCs qualifying as 1.5PP) because of the lack of randomization. Patients were followed from the date of implantation or date of implantation refusal and were censored at their last follow-up. Kaplan-Meier methods were used to produce incidence plots, and the curves within the plots were censored when <20 patients remained at risk. Comparisons between the 1.5PP and 1.0PP populations were post hoc. The sample size was determined using a simulation program and was recalculated midway through the study to achieve a statistical power of 90%.14

**Time to first VT/VF therapy**

There were 4870 VT/VF episodes treated with antitachycardia pacing and/or shock that had an electrogram available for adjudication. Of the adjudicated events, 4205 (86.3%) were found to be VT/VF and 665 (13.7%) were found to be sustained ventricular tachycardia or oversensing. The time to first VT/VF therapy for 1.5PP and SP was not within 30% (the prespecified definition of “similar”; hazard ratio 0.47; 95% confidence interval [CI] 0.38–0.57) (Figure 2). However, the rate of VT/VF therapy in the 1.5PP group was statistically significantly higher (P = .03) than in the 1.0PP group (observed hazard ratio 0.67; 95% CI 0.46–0.97). When each factor that made up the 1.5PP cohort (LVEF <25%, NSVT, PVCs, and syncope) was evaluated independently in comparison with the 1.0PP cohort (Figure 3), it was observed that NSVT and PVCs had the greatest effect on an increased relative risk of VT/VF therapy in the 1.5PP cohort compared with the 1.0PP cohort.

**All-cause mortality**

1.5PP patients with an ICD had a statistically significant (P < .0001) 49% adjusted relative risk reduction in all-cause mortality (hazard ratio 0.51; 95% CI 0.40–0.66) (Figure 4A) as compared with 1.5PP patients without an ICD. The 3-year mortality rate was 24.4% in the nonimplanted cohort, while it was 14.4% in the implanted cohort. This converts to 10.0 as the number needed to treat (NNT) to save 1 life at 3 years. Similarly, the implanted 1.0PP patients had a statistically significant adjusted hazard ratio of 0.50 (95% CI 0.27–0.93) (Figure 4B). However, the 1.0PP nonimplanted group's mortality rate was 10.4% at 3 years (the implanted rate was 7.9%), lower than the 24.4% of 1.5PP (P < .0001), leading to a higher observed NNT to save 1 life in this population (40.0 at 3 years). The most common cause of death in patients not implanted with an ICD was SCD (Figure 4C).

**Time to first VT/VF therapy and all-cause mortality in patients with nonischemic cardiomyopathy**

Because of the observed proportion of patients with nonischemic cardiomyopathy being higher than that reported in other large contemporary trials, the end points were examined as they relate to nonischemic cardiomyopathy status. Figure 5A shows that the rate of VT/VF therapy in patients with nonischemic cardiomyopathy had a similar trend as in the full cohort of studied patients. Compared with 1.5PP patients with nonischemic cardiomyopathy and without an ICD, 1.5PP patients with nonischemic cardiomyopathy and with an ICD had a statistically significant (P = .0001) 44% relative risk reduction in all-cause mortality (Figure 5B).

**Discussion**

Improve SCA was the first large prospective study to evaluate the 1.5PP criteria in clinically indicated ICD patients in countries where utilization of ICDs for SCA prevention is low.
The aims of the study were 2-fold: to determine whether 1.5PP patients had a similar time to first VT/VF therapy as patients with SP indications and to determine whether there was a mortality difference between 1.5PP patients who received an ICD and those who did not. The findings from this study did not support equivalence in time to first therapy between 1.5PP and SP ICD recipients; however, when evaluating the time to first VT/VF therapy within patients with PP indications only, it was clear that the time to first therapy was shorter for 1.5PP patients than for 1.0PP patients, implying that 1.5PP may still identify a subset of patients with PP indications who have a greater benefit from ICD therapy. The second metric (all-cause mortality in 1.5PP patients with vs without an ICD implant) gives evidence that ICD therapy confers a strong mortality benefit to 1.5PP patients.

The higher rates of ICD therapy in patients with PP indications in this study overall is in line with previous studies. Prior studies have noted that PVCs, NSVT, low LVEF, and syncope are all indicators that a patient is more likely to experience a VT or VF episode. This study included these 4 indicators to define a subgroup of patients with PP indications (1.5PP). Each of the factors that make up the 1.5PP criteria were evaluated independently, and all were associated with an increase in the risk of VT/VF events, greater than that observed in 1.0PP patients. In addition, the study found that 1.5PP patients had a higher mortality rate and smaller NNT to save 1 life by ICD at 3 years than did those (1.0PP patients) without any 1.5PP criteria.

ICD utilization in patients with PP indications to reduce all-cause mortality has been demonstrated in multiple studies; however, it has not been adopted in many areas of the world for several reasons. In our study, patients and their physicians elected whether to receive an ICD implant when they met class I indications. Despite this limitation,
and regardless of whether patients were in the 1.5PP group or 1.0PP group, mortality was significantly reduced in comparison to those patients who did not undergo ICD implantation. Furthermore, the 1.5PP patient population enrolled in this study exhibiting that a mortality benefit was largely nonischemic (74.0%), which contrasts with prior ICD trials where nonischemic cardiomyopathy patients represented only less than half of the population.20,23 This is an important and surprising finding given the preponderance of nonischemic patients in these parts of the world. More importantly, this

![Figure 2](image-url)

**Figure 2** Primary end point—time to first treated VT/VF episode. The faded blue line represents 70% of the SP rate, which was the prespecified noninferiority margin. CI = confidence interval; SP = secondary prevention; VT/VF = ventricular tachycardia or fibrillation.

### Table 1  
Baseline characteristics for implanted patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SP (n = 1066)</th>
<th>1.5PP (n = 1068)</th>
<th>1.0PP (n = 331)</th>
<th>P value: SP vs 1.5PP</th>
<th>P value: 1.5PP vs 1.0PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>57.1 ± 14.3</td>
<td>61.1 ± 11.7</td>
<td>61.3 ± 11.3</td>
<td>&lt;.0001</td>
<td>.80</td>
</tr>
<tr>
<td>Sex: male</td>
<td>812 (76.2)</td>
<td>815 (76.3)</td>
<td>236 (71.3)</td>
<td>.94</td>
<td>.07</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>233 (21.9)</td>
<td>218 (20.4)</td>
<td>85 (25.7)</td>
<td>.41</td>
<td>.04</td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy</td>
<td>349 (32.7)</td>
<td>790 (74.0)</td>
<td>217 (65.6)</td>
<td>&lt;.0001</td>
<td>.003</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>216 (20.3)</td>
<td>450 (42.1)</td>
<td>144 (43.5)</td>
<td>&lt;.0001</td>
<td>.66</td>
</tr>
<tr>
<td>Type 1 or type 2 diabetes</td>
<td>226 (21.2)</td>
<td>306 (28.9)</td>
<td>117 (35.6)</td>
<td>&lt;.0001</td>
<td>.02</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>43.3 ± 15.7</td>
<td>25.3 ± 5.9</td>
<td>29.4 ± 3.4</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>115 ± 33</td>
<td>132 ± 36</td>
<td>134 ± 34</td>
<td>&lt;.0001</td>
<td>.54</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>73 (6.9)</td>
<td>315 (29.5)</td>
<td>113 (34.1)</td>
<td>&lt;.0001</td>
<td>.11</td>
</tr>
<tr>
<td>New York Heart Association classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>149 (14.1)</td>
<td>14 (1.3)</td>
<td>4 (1.2)</td>
<td>&lt;.0001</td>
<td>.45</td>
</tr>
<tr>
<td>Class II</td>
<td>383 (36.1)</td>
<td>420 (39.4)</td>
<td>145 (43.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>241 (22.7)</td>
<td>631 (59.1)</td>
<td>182 (55.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>34 (3.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject does not have heart failure</td>
<td>253 (23.9)</td>
<td>2 (0.2)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>353 (33.1)</td>
<td>414 (38.8)</td>
<td>134 (40.5)</td>
<td>.007</td>
<td>.58</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>269 (25.2)</td>
<td>317 (29.7)</td>
<td>118 (35.6)</td>
<td>.02</td>
<td>.04</td>
</tr>
<tr>
<td>CRT-D Implanted</td>
<td>123 (11.5)</td>
<td>512 (47.9)</td>
<td>176 (53.2)</td>
<td>&lt;.0001</td>
<td>.10</td>
</tr>
<tr>
<td>ACE inhibitors/angiotensin II receptor blockers/inhibitors</td>
<td>494 (46.3)</td>
<td>749 (70.1)</td>
<td>258 (77.9)</td>
<td>&lt;.0001</td>
<td>.06</td>
</tr>
<tr>
<td>Diuretics</td>
<td>472 (43.8)</td>
<td>931 (87.2)</td>
<td>261 (78.9)</td>
<td>&lt;.0001</td>
<td>.002</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; CRT-D = cardiac resynchronization therapy-defibrillator; LVEF = left ventricular ejection fraction; PP = primary prevention; SP = secondary prevention. Values are presented as mean ± SD or as n (%).
lends further support that patients with nonischemic cardiomyopathy benefit from ICDs, despite prior studies being interpreted as suggesting the contrary.24

Limitations
There are a number of limitations that should be considered when applying the results of this study to other populations. First, patients were not randomized, since this study attempted to capture real-world clinical practice in the regions evaluated and ICD implantation was left to the discretion of the patient and/or physician. To control for potential bias, we adjusted the mortality analysis to account for baseline characteristics that would most likely have an impact on mortality. Second, it is important to recognize the limitations of considering VT/VF therapy events as a surrogate for SCA since appropriate therapy does not equate with survival, not all VTs cause

Figure 3  Time to first treated VT/VF episode, by 1.5 factors. Each of the four 1.5PP criteria are compared with all 1.0PP patients. The 1.5 curves are not mutually exclusive. Patients may be included in ≥1 curve. CI = confidence interval; LVEF = left ventricular ejection fraction; MI = myocardial fibrillation; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction; VT/VF = ventricular tachycardia or fibrillation.

Figure 4  Mortality summary. A: Prespecified secondary objective: comparison of mortality rates between implanted and nonimplanted 1.5PP patients. B: Post hoc analysis of mortality rates between implanted and nonimplanted 1.0PP patients. C: Cause of death summary in patients with PP indications. CI = confidence interval; CRT-D = cardiac resynchronization therapy-defibrillator; ICD = implantable cardioverter-defibrillator; PP = primary prevention.
syncope, and some VTs may terminate spontaneously. Third, deaths were not adjudicated by a central committee, and as such, the likelihood of inconsistencies in the classification of deaths must be taken into consideration. Nevertheless, the ICD benefit observed in this study is relevant to both patients with SP and PP indications, and risk stratification based on the 1.5 criteria can inform health care policy, physician training, and patient education on SCA risk and prevention and ICD benefit in underrepresented regions.

Clinical implications

While our recommendations regarding implantation decisions may be tempered by biases inherent to the nature of the study design, there are still a number of important observations in this study. First, Improve SCA is the largest prospective study of patients at risk of SCA in regions previously underrepresented in the literature and these findings are likely to raise awareness of the risk and prevalence of SCD worldwide. Second, a majority of the patients with PP indications enrolled in the study (>70%) had at least 1 of the risk factors (1.5PP patients) that have been previously recognized as harboring a higher risk of sudden death. Third, the 1.5PP group experienced a larger absolute risk reduction in mortality than the 1.0PP group. While this observation alone may support use of these metrics for risk stratification, caution must be exercised since this was not included as a prespecified analysis of the study. Finally, the findings generate a number of interesting hypotheses that could factor into the development of a future risk stratification tool and inform further studies needed to corroborate and validate these data and guide implantation decisions in resource-constrained environments. Ultimately, these data could inform education and awareness initiatives that further underscore the importance of equitable access to life-saving devices and therapies worldwide.

Conclusion

The time to first VT/VF therapy for patients with PP and SP indications with ICDs remains different among patients from underrepresented geographies. However, within the PP group, patients with 1.5PP risk factors have an earlier time to first VT/VF therapy than do 1.0PP patients. These data, along with the observation of lower mortality in 1.5PP ICD recipients than in those who did not undergo ICD implanta
tion, support the notion that ICDs remain an important intervention in the management of SCD globally, even in a population predominantly with nonischemic cardiomyopathy. The study suggests a clinically feasible risk stratification approach for identifying patients with a higher risk of SCA.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2019.09.023.

References


