Updated meta-analysis on implantable cardioverter defibrillator detection programming to reduce mortality.

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Abstract

Objective: The purpose of this study was to perform a meta-analysis to better gauge the impact of prolonged arrhythmia detection times or high arrhythmia detection rates on ICD shock therapy and other adverse outcomes.

Background: Programming long arrhythmia detection time or high arrhythmia detection rate reduce the incidence of implantable cardioverter defibrillator (ICD) shock therapy. However, potential concerns exist regarding the impact on mortality and incidence of syncope.

Methods: PUBMED database was systematically searched. We included only randomized, prospective studies that examined the impact of programming longer vs shorter ICD arrhythmia detection times or higher vs lower ICD arrhythmia detection rates on clinical outcomes. Summary estimates of the relative risk (RR) of death, syncope, and total, appropriate and inappropriate shocks were calculated using random effects model.

Results: Six studies enrolling 6,543 patients were identified. During a mean/median follow-up of 1 to 1.5 years, there were 405 deaths, 156 patients experienced syncope, 367 received an appropriate shock, and 291 an inappropriate shock. In the experimental group there were significant reductions in mortality (RR=0.73, 95% confidence interval [CI] 0.60-0.88), and inappropriate shocks (RR=0.50 0, 95% CI 0.39-0.63), without affecting syncope (RR=1.31, 95% CI 0.95-1.80).

Conclusion: ICD reduction programming therapy is an important strategy, decreasing the burden of inappropriate shocks and all-cause mortality in ICD recipients, without significant increase in syncope.

Keywords: Defibrillators, Implantable, Mortality, Meta-analysis, Shock.

Introduction

Implantable cardioverter-defibrillator (ICD) is the cornerstone in the prevention of death in patients at risk of life-threatening ventricular arrhythmias (primary prevention), and in patients rescued from ventricular tachycardia (VT) or ventricular fibrillation (VF) (secondary prevention). Whether ICD efficacy is largely proven, shock delivery (appropriate or inappropriate) has been reported to negatively impact survival (1). Appropriate ICD programming is the key to prevent nonessential or inappropriate shock delivery, while maintaining the efficacy to detect and terminate VT or VF. Two meta-analyses have examined weather programming faster rate criteria, or longer detection duration reduced ICD therapies, particularly shocks. Tan et al. included 4 randomized and 2 prospective studies and demonstrated a 30% reduction in all-cause mortality with appropriate ICD therapy reduction programming (2). Scott et al. included 3 randomized and 1 prospective studies and demonstrated a 23% reduction in mortality, a 50% reduction in appropriate shocks without significant increase in syncope (3). Since these publications, other studies were available. The purpose of our study was to perform an updated meta-analysis to better evaluate the impact of ICD therapy reduction strategies on ICD shock therapy and other adverse outcomes.

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(4)

Search Strategy

We searched the PUBMED database for articles on appropriate ICD programming to reduce therapies, as well as clinicaltrials.gov. The search is considered up to date as of December 31, 2019. The following search terms were used: ("defibrillators, implantable"[MeSH Terms] OR ("defibrillators"[All Fields] AND "implantable"[All Fields]) OR "implantable defibrillators"[All Fields] OR ("implantable"[All Fields] AND "cardioverter"[All Fields] AND "defibrillator"[All Fields]) OR "implantable cardioverter defibrillator"[All Fields]) AND (icd[All Fields] AND programming[All Fields])) AND (("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND reduction[All Fields]). In addition, we searched for meeting abstracts in Embase and hand-searched references and related citations in review articles and commentaries.

Study Selection and Eligibility Criteria

We selected studies that examined the impact of arrhythmia detection programming settings to limit the delivery of ICD therapies. We included RCTs of both primary and secondary prevention ICD therapy, that specifically compared programming faster VT/VF detection rate or longer detection duration vs conventional settings. Studies in which the programmed detection parameters were not specifically stated or were not predetermined (e.g., they were at the discretion of the treating physician) were excluded. Studies were assessed for eligibility, and demographic and clinical data were extracted by 2 independent investigators (CB and MP). The following outcomes were evaluated: (1) all-cause mortality, (2) number of patients with syncope, (3) number of patients with total, appropriate and inappropriate shocks.

Quality Assessment

The internal validity of included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (5).

Data Synthesis and Statistical Analysis

Data were pooled and analyzed using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. The summary estimates of the relative risk (RR) were calculated using the random effects model based on DerSimonian and Laird's meta-analytic statistical method. Statistical heterogeneity was evaluated using Cochran's $\chi 2$ and quantified with the I2 statistic. In all analyses, $P < 0.05$ was considered significant.

Results

Study Selection. We identified 6 RCTs that met the inclusion criteria and were included in the analyses (Figure 1). The included studies were: (1) Multicenter Automatic Defibrillator Implantation Trial - Reduce Inappropriate Therapy [MADIT-RIT] (6); (2) Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III [ADVANCE III] (7); (3) Programming Implantable Cardioverter-Defibrillators in Patients with Primary Prevention Indication to Prolong Time to First Shock [PROVIDE] (8); (4) Reduction of inappropriate ICD therapies in patients with approved indication for primary prevention of sudden cardiac death [DECREASE] (9); (5) Reduction of Inappropriate ShockS bY InCreaseD zones [RISSY-ICD) (10); (6) PainFree SST [SmartShockTM technology] (11). Figure 1 reported the quality assessment of the studies included.

Study quality

The risk of bias in the 6 RCTs was low (Figure 2).

Study Characteristics.

The characteristics of the 6 included trials are shown in Table 1. The 6 studies enrolled 6,543 (3,020 conventional and 3,523 appropriate programming) patients. All studies were multicenter and included both patients with ischemic and non-ischemic cardiomyopathy. Four of the studies included only patients with a primary prevention indication for ICD therapy, whereas ADVANCE III included a minority of patients (25%) and PAINREE SST enrolled only patients with a secondary prevention device. MADIT-RIT had 2 experimental study arms: (1) the "high-rate therapy" and (2) the "delayed therapy".

Therapy reduction programming consisted of long detection interval (ADVANCE III, MADIT-RIT, PAINFREE SST and PROVIDE) (6-8, 11), and high detection rate (DECREASE, MADIT-RIT, RISSY-ICD) (6, 9, 10). ICD programming parameters varied significantly between studies, partly because devices from different manufacturers were used. However, in all the included studies, the arrhythmia detection duration was longer and the detection rate was higher in the experimental group than the control group.

Mortality

During a mean/median follow-up of 1 to 1.5 years 405 deaths (6.2%) were observed; 183 (5.2%) in the enhanced programming group and 222 (7.4%) in the control group. Pooled analysis demonstrated a statistically significant 27% (95% CI, 12% to 40%; P=0.001) risk reduction in all-cause mortality in favour of therapy reduction programming group without significant statistical heterogeneity (P=0.85, I2=0%) (Figure 3).

The effect size was greater when the analysis evaluated the impact of increasing the cut-off arrhythmia rate detection (40% relative reduction, 95% CI, 2% to 63%; P=0.04) rather than prolonging the arrhythmia detection time (25% relative reduction, 95% CI 1% to 42%; P=0.04). Furthermore, the effect size was somewhat different when the secondary prevention groups were assessed separately (30% relative reduction, 95% CI, -0.5%–54%; P=0.08).

Syncope

During follow-up, 156 patients with syncope events (2.4%) were reported. These included 99 (2.8%) patients in the therapy reduction programming group and 57 (1.9%) patients in the control group. No statistically significant difference in the rate of patients with syncope was observed, (31% increase; 95% CI, 5% reduction to 80% increase; P=0.10), without significant statistical heterogeneity (P=0.89, I2=0%) (Figure 4).

ICD Shocks

PAINFREE SST (11) did not report the overall incidence of shocks and RISSY-ICD (10) only evaluated the occurrence of first shock either inappropriate or appropriate. These 2 studies were excluded from the respective analyses.

During follow-up, a total of 367 patients experienced appropriate shocks and 291 patients had inappropriate shocks. Overall, the number of patients who received ICD shocks was significantly reduced by 31% (95% CI, 29% to 41%; P<0.00001) in the therapy reduction programming arm, without statistical heterogeneity (P=0.70, I2=0%) (Figure 5).

There was no significant reduction in the number of patients with an appropriate shock (RR=0.99, 95%CI 0.81 to 1.21; P=0.95), without statistical heterogeneity (P=0.93, I2=0%) (Figure 6). However, the number of patients with an inappropriate shock was significantly reduced (RR=0.50, 95% CI 0.39 to 0.63; P<0.00001), without statistical heterogeneity (P=0.57, I2=0%) (Figure 7).

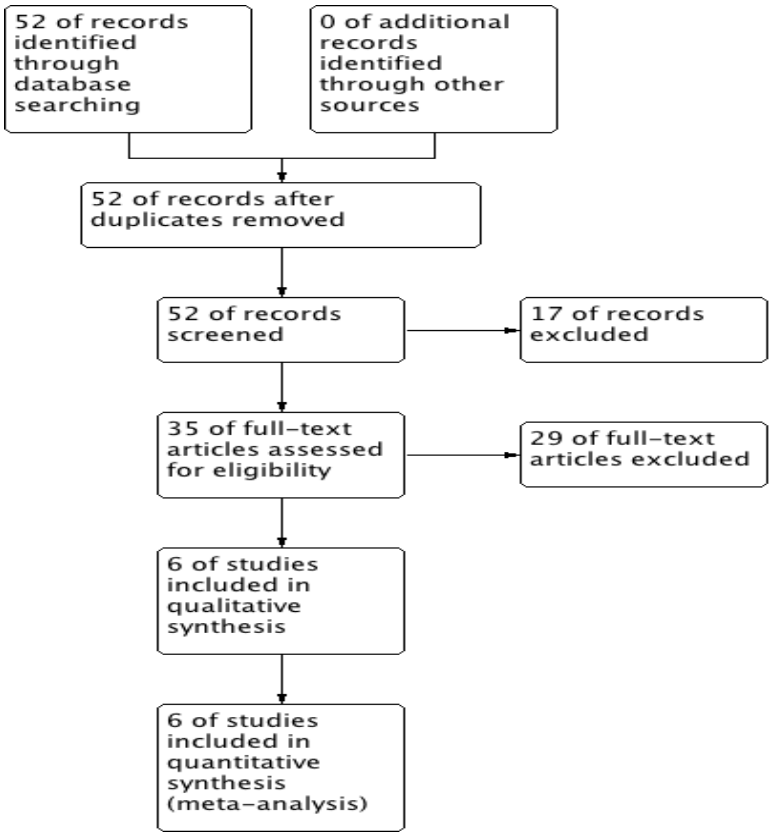

Figure 1. *QUORUM diagram of selection process for articles included in the meta-analysis.*

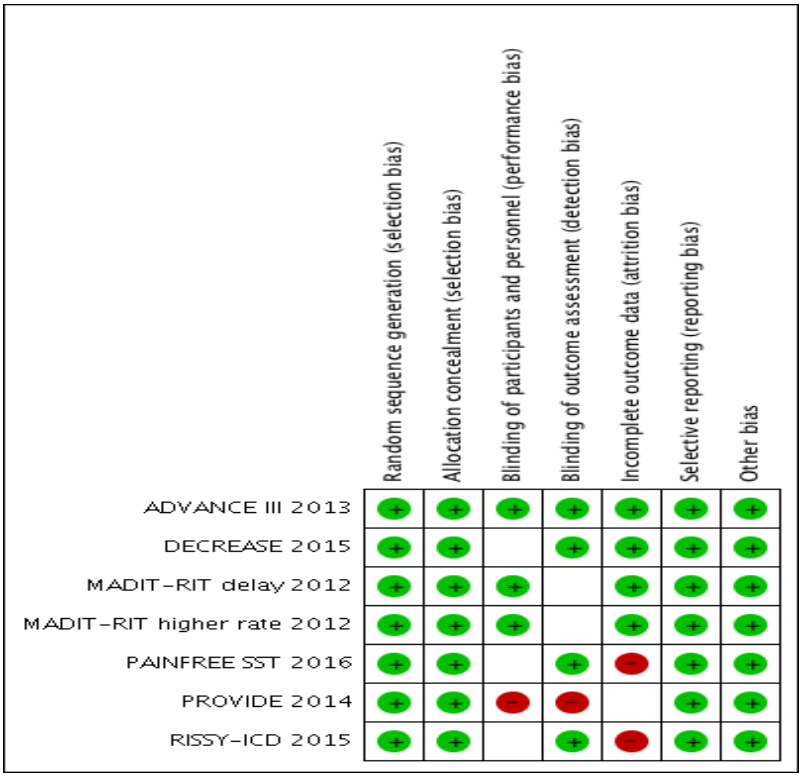

Figure 2. *Risk of bias in individual studies assessed using the Cochrane Collaboration's bias assessment tool.*

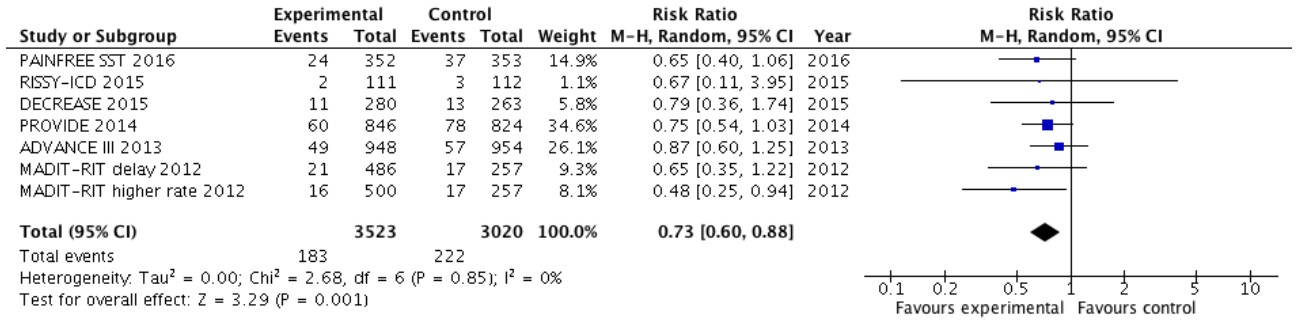

Figure 3. *Enhanced vs convention programming and risk of death. Random effects meta-analysis of enhanced ICD programming vs conventional programming on the outcome of all-cause mortality*

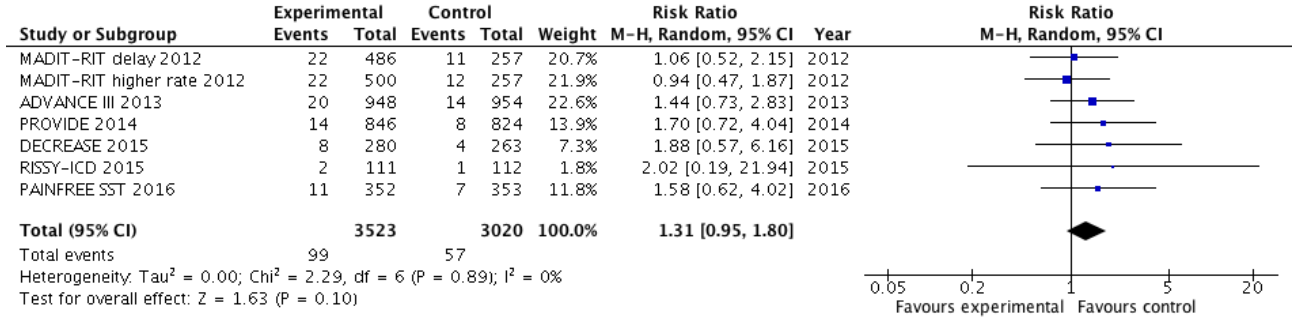

Figure 4. *Enhanced vs convention programming and risk of death. Random effects meta-analysis of enhanced ICD programming vs conventional programming on the outcome of syncope.*

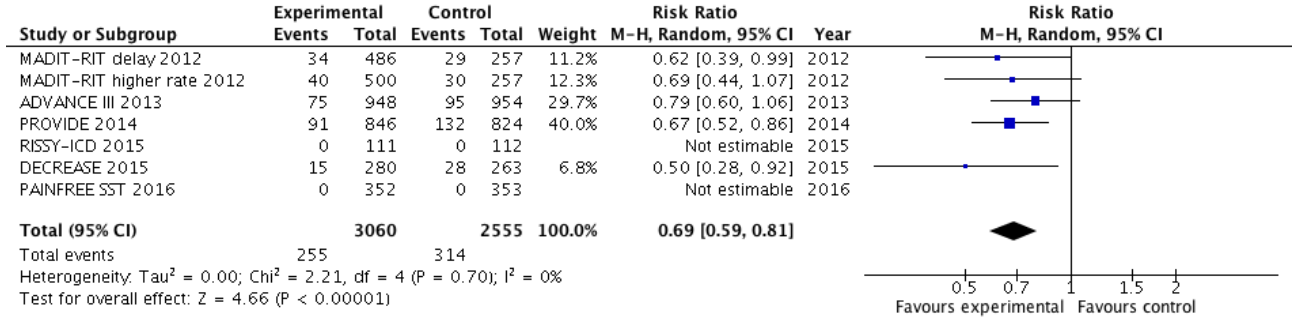

Figure 5. *Enhanced vs convention programming and risk of death. Random effects meta-analysis of enhanced ICD programming vs conventional programming on the outcome of total shocks.*

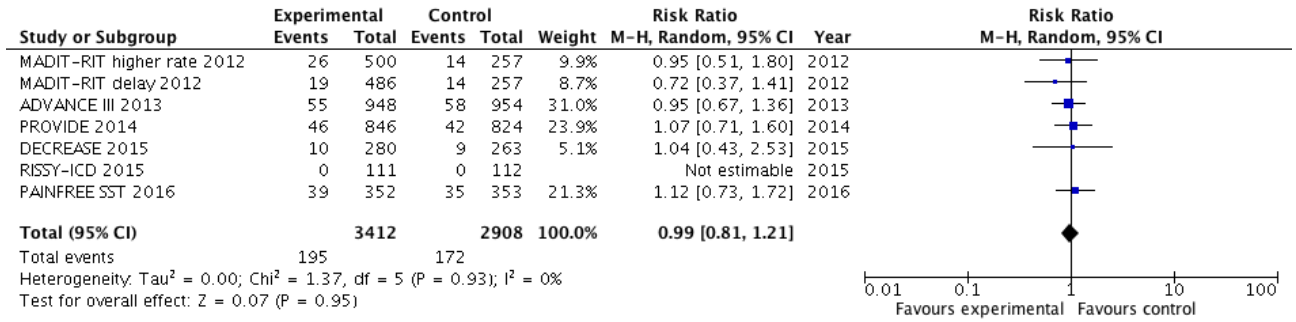

Figure 6. *Enhanced vs convention programming and risk of death. Random effects meta-analysis of enhanced ICD programming vs conventional programming on the outcome of appropriate shocks.*

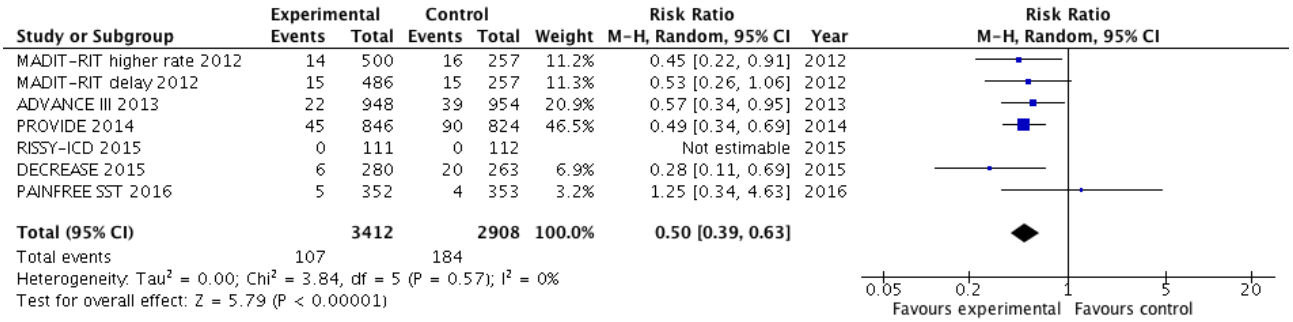

Figure 7. *Enhanced vs convention programming and risk of death. Random effects meta-analysis of enhanced ICD programming vs conventional programming on the outcome of inappropriate shocks.*

Table 1: *Study Characteristics*

Study, y	Paients, n	Mean/Median follow-up, y	Study population	ICD indication	ICD manufacter	Therapy Reduction Programming	Conventional Programming
MADIT-RIT, 2012	**1500**	**1.4**	**NICM/CAD**	**Primary**	**Boston**	Zone 1–200 bpm; 2.5 s delay (8–10 beats); ATP×1	Zone 1–200 bpm; 1 s delay (3–4 beats); ATP×1
						Zone 2–170 bpm; monitor only	Zone 2–170 bpm; 2.5 s delay (7–8 beats); ATP×1
						Zone 1–250 bpm; 2.5 s delay; ATP×1	Zone 1–200 bpm; 1 s delay (3–4 beats); ATP×1
						Zone 2–200 bpm; 12 s delay (40–50 beats); ATP×1	Zone 2–170 bpm; 2.5 s delay (7–8 beats); ATP×1
						Zone 3–170 bpm; 60 s delay (169–99 beats); ATP×1	
ADVANCE III, 2013	**1902**	**1**	**NICM/CAD**	**Mixed (25% secondary)**	**Medtronic**	VF–188 bpm; NID 30 of 40; ATP×1	VF–188 bpm; NID 18 of 24; ATP×1
						VT–150 bpm; NID 32; monitor only	VT–150 bpm; NID 32; monitor only
PROVIDE, 2013	**1670**	**1.5**	**NICM/CAD**	**Primary**	**St. Jude Medical**	VF–250 bpm; NID 12	VF–214 bpm; NID 12
						VT 2–214 bpm; NID 18; ATP×1	VT 2–181 bpm; NID 12; ATP×2
						VT 1–181 bpm; NID 25; ATP×2	VT 1–150 bpm; NID 12; monitor only
RISSY-ICD, 2015	**223**	**1**	**NICM/CAD**	**Primary**	**Medtronic**	VF–230 bpm; NID 30 of 40	VF–200 bpm; NID 30 of 40
						FVT–200 to 230 bpm; NID 30 of 40; ATP×4	FVT–182 to 200 bpm; NID 30 of 40; ATP×4
						VT–171 bpm; NID 32; ATP×6	VT–167 bpm; NID 32; ATP×6
DECREASE, 2015	**543**	**1**	**NICM/CAD**	**Primary**	**St. Jude Medical**	VF–240 bpm; NID 12	VF–214 bpm; NID 12
						VT–187 bpm; NID 12; ATP×1	VT–171 bpm; NID 12; ATP×1
PAINFREE SST, 2016	**705**	**1**	**NICM/CAD**	**Secondary**	**Medtronic**	VF–188 bpm; NID 30 of 40; ATP×1	VF–188 bpm; NID 18 of 24; ATP×1
						VT–162 bpm; NID 24; monitor only	VT–162 bpm; NID 24; monitor only
						or	or
						VF–200 bpm; NID 30 of 40; ATP×1	VF–200 bpm; NID 30 of 40; ATP×1
						VT 2–longest known VT CL 2 + 50 ms; NID minimum of 24	VT 2–longest known VT CL 2 + 50 ms; NID minimum of 24
						VT 1–VT 2 zone CL + ≥ 40 ms; NID minimum of 24; monitor only	VT 1–VT 2 Zone + ≥ 40 ms; NID minimum of 24; monitor only

NICM = non-ischemic cardiomyopathy; CAD = coronary artery disease; VT = ventricular tachycardia; FVT = fast ventricular tachycardia; VF = ventricular fibrillation; NID = number of intervals to detect; ATP = anti-tachycardia pacing

Discussion

This meta-analysis, which included data on nearly 6500 ICD recipients, demonstrated that ICD programming with faster VT/VF detection rate, or longer detection duration, decreases the inappropriate shocks by 50%, and is associated with a reduction in all-cause mortality by 27%, without statistically significant increase in syncope.

It is known that ICD shocks are associated with worse prognosis. Proietti et al. performed a meta-analysis examining the association between ICD shocks and mortality in major ICD trials. Data from 10 studies, including nearly 200,000 patients, were evaluated. The pooled analysis demonstrated a significant relationship between ICD shocks and mortality, greater for appropriate (HR=2.95, 95 % CI 2.12 to 4.11, p<0.001) than inappropriate shocks (HR=1.71, 95 % CI 1.45 to 2.02, p<0.001) (1). The association between ICD shocks and increased mortality may be explained by either the detrimental effects of shocks themselves, the progression of underlying

disease process (shocks could be merely a marker of disease progression) or both. Appropriate ICD programming can reduce the occurrence of ICD shocks without altering the underlying myocardial substrate, and provide evidence implicating shocks as directly influencing mortality risk (12). In this regard, two meta-analyses have examined the effect of ICD programming strategies on mortality reduction. Tan et al. sought to quantify the overall effect of ICD therapy reduction programming strategies on mortality from six major trials: Comparison of Empiric to Physician-tailored Programming of Implantable Cardioverter Defibrillators (EMPIRIC), Primary Prevention Parameters Evaluation (PREPARE), Role of Long Detection Window Programming in Patients With Left Ventricular Dysfunction, Non-ischemic Etiology in Primary Prevention Treated with a Biventricular ICD (RELEVANT), MADIT-RIT, ADVANCE III and PROVIDE. A total of 4,089 patients used combinations of long detection time, or high detection rate with SVT discriminators and were compared with 3,598 conventionally programmed patients. Over 1-year follow-up showed a 50 % reduction in inappropriate shocks in the strategic programming group, though appropriate shock rates were similar between the groups. Therapy reduction programming was associated with a 30 % reduction in mortality (95 % CI 16 to 41 %, P<0.001) compared with the conventional arm (2). Then, the mortality benefit of programming long detection times was addressed in the meta-analysis by Scott and colleagues. Four studies enrolling 4,896 patients were included: RELEVANT, MADIT-RIT, ADVANCE III and PROVIDE. A mortality reduction of 23 % (RR=0.77, 95 % CI 0.62 to 0.96, P=0.02) was seen in the long detection arm. In keeping with the analysis of Tan and colleagues there was a 50 % reduction in inappropriate shocks, without significant difference in the occurrence of appropriate shocks. Importantly, no increase in risk of syncope was seen (3).

Our meta-analysis updated the number of included patients, adding data from the other RCTs. We confirmed that appropriate ICD programming, based on longer detection time or higher detection rate, reduces unnecessary therapies without withholding intervention for life-threatening VT/VF. These results are consistent among the 6 included studies, despite variations in optimized programming strategies, and strengthen the evidence that shocks themselves contribute to the risk of death. By prolonging the time of detection to longer settings or raising the cutoff detection rate, it is not surprising that fewer inappropriate therapies were delivered. Interestingly, despite the general concerns that this result would likely come at the price of a higher rate of syncopal episodes, a low number of events occurred with no difference between the 2 arms of the meta-analysis. These data suggest that a relevant proportion of true ventricular arrhythmias may be self-terminating as well as that most inappropriate therapies are determined by high-rate conducted atrial arrhythmias, and therefore, a programming strategy that combines long detection intervals or high detection rates with ATP during charging should be recommended in these patients (12). However, there are some limitations. Each study used ICDs from a single manufacturer with programmed parameters that were different among the studies. Thøgersen et al. determined the reasons why contemporary ICDs failed to deliver therapy for life-threatening VT/VF in the era of strategic programming. In a series of cases, the authors showed that most patients who did not receive timely VF shocks had devices programmed consistent with indications extrapolated from evidence obtained using another manufacturer's ICD with different sensing and detection features. They conclude that more data are needed to assess both the benefits and risks of applying generic programming recommendations to specific ICDs in which these recommendations have not been validated clinically (13). Finally, most of the patients included in our analysis received an ICD for primary prevention indication and caution should be used to generalize our findings to secondary prevention patients.

Conclusions

Our meta-analysis updated data from all available RCTs, enrolling both primary and secondary ICD recipients. We demonstrated that long arrhythmia detection time or high rate treatment zone cutoff significantly reduce all-cause mortality by about one third and decrease by about half the rate of inappropriate shocks. No significant difference in the risk of syncope or appropriate shocks was observed. These results provide further support to the existing HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal ICD programming (12)

Acknowledgment

Thank all the participants for their continuously efforts in conducting the survey.

Conflict of Interest

The authors declare that they have no conflicts of interest.

References

1. Proietti R, Labos C, Davis M, Thanassoulis G, Santangeli P, Russo V, et al. A systematic review and meta-analysis of the association between implantable cardioverter-defibrillator shocks and long-term mortality. Can J Cardiol. 2015;31(3):270-7.
2. Tan VH, Wilton SB, Kuriachan V, Sumner GL, Exner DV. Impact of programming strategies aimed at reducing nonessential implantable cardioverter defibrillator therapies on mortality: a systematic review and meta-analysis. Circ Arrhythm Electrophysiol. 2014;7(1):164-70.
3. Scott PA, Silberbauer J, McDonagh TA, Murgatroyd FD. Impact of prolonged implantable cardioverter-defibrillator arrhythmia detection times on outcomes: a meta-analysis. Heart Rhythm. 2014;11(5):828-35.
4. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
5. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
6. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in inappropriate therapy

and mortality through ICD programming. N Engl J Med. 2012;367(24):2275-83.
7. Gasparini M, Proclemer A, Klersy C, Kloppe A, Lunati M, Ferrer JB, et al. Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. JAMA. 2013;309(18):1903-11.
8. Saeed M, Hanna I, Robotis D, Styperek R, Polosajian L, Khan A, et al. Programming implantable cardioverter-defibrillators in patients with primary prevention indication to prolong time to first shock: results from the PROVIDE study. J Cardiovasc Electrophysiol. 2014;25(1):52-9.
9. Schwab JO, Bonnemeier H, Kleemann T, Brachmann J, Fischer S, Birkenhauer F, et al. Reduction of inappropriate ICD therapies in patients with primary prevention of sudden cardiac death: DECREASE study. Clin Res Cardiol. 2015;104(12):1021-32.
10. Cay S, Canpolat U, Ucar F, Ozeke O, Ozcan F, Topaloglu S, et al. Programming implantable cardioverter-defibrillator therapy zones to high ranges to prevent delivery of inappropriate device therapies in patients with primary prevention: results from the RISSY-ICD (Reduction of Inappropriate ShockS bY InCreaseD zones) trial. Am J Cardiol. 2015;115(9):1235-43.
11. Sterns LD, Meine M, Kurita T, Meijer A, Auricchio A, Ando K, et al. Extended detection time to reduce shocks is safe in secondary prevention patients: The secondary prevention substudy of PainFree SST. Heart Rhythm. 2016;13(7):1489-96.
12. Wilkoff BL, Fauchier L, Stiles MK, Morillo CA, Al-Khatib SM, Almendral J, et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Heart Rhythm. 2016;13(2):e50-86.
13. Thogersen AM, Larsen JM, Johansen JB, Abedin M, Swerdlow CD. Failure to Treat Life-Threatening Ventricular Tachyarrhythmias in Contemporary Implantable Cardioverter-Defibrillators: Implications for Strategic Programming. Circ Arrhythm Electrophysiol. 2017;10(9)

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