Primary Prevention of Sudden Cardiac Death Early Post-Myocardial Infarction

Root Cause Analysis for Implantable Cardioverter–Defibrillator Failure and Currently Available Options

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The rate of death, including sudden cardiac death (SCD), is highest during the early period after a myocardial infarction (MI).[1] Implantable cardioverter–defibrillators (ICDs) improve survival rates of patients with various heart conditions who are at high risk of ventricular tachyarrhythmia (VTA), by terminating those VTA.[2–5] However, ICDs in conjunction with optimal medical therapy have failed to improve survival when implanted for primary prevention early after an MI in 2 prospective randomized controlled trials when compared with optimal medical therapy alone: the DINAMIT (Defibrillator in Acute Myocardial Infarction Trial)[6] and the IRIS (Immediate Risk Stratification Improves Survival Trial).[7] Therefore, current guidelines[8] indicate that patients should not receive an ICD within 40 days after an MI without revascularization (DINAMIT criteria) or within 3 months after an MI with revascularization which leaves patients at risk for SCD during this gap of vulnerability period.[9]

Different hypotheses that may underlie the negative results of the DINAMIT and IRIS trials will be reviewed here in detail. A meta-analysis of the outcomes of these 2 studies is performed. In addition, we estimate annualized mortality through 3 years for these 2 trials and all other major primary prevention ICD trials with ischemic cardiomyopathy, creating a basis for comparison across studies. The current options available to reduce SCD post-MI will be discussed, including the potential impact of a wearable cardioverter–defibrillator (WCD; LifeVest; Zoll, Pittsburgh, PA) as a bridging therapy, in light of the various hypotheses underlying the lack of ICD benefit in DINAMIT and IRIS patients.

SCD Post-MI: Incidence, Mechanisms, and Risk Stratification

The incidence of SCD is increased within the first few months post-MI. It is highest within the first month after an MI (1.2%–1.4%),[1–10] followed by a progressive decline until a plateau after a few months. The mechanism of SCD post-MI, adjudicated initially to VTA in studies such as VALIANT (Valsartan in Acute Myocardial Infarction Trial),[1] was only accurate in ≈50% of cases. Autopsy studies demonstrated that nearly 50% of SCDs were in fact caused by recurrent infarction or other mechanical complications, such as myocardial wall rupture.[11,12] However, controversy remains concerning how representative these autopsy data are because autopsies were not routine in VALIANT, leading to potential referral bias or study site differences.

The mechanisms (and thus the prognostic importance) of VTA after an MI vary based on temporal proximity to the MI. At the acute phase of an MI, VTAs (usually polymorphic ventricular tachycardia [VT] of ventricular fibrillation [VF]) are related to electric instability associated with the interaction of ischemia, necrosis, reperfusion, and autonomic changes. Over time, VTA occurs as a consequence of ventricular remodeling with reentry in heterogeneous areas of unexcitable scar and diseased myocardial tissue. Reentrant VTA is further enhanced by the temporal dispersion of repolarization in dilated ventricles.[13] VTA can be considered an epiphenomenon when they occur within 48 hours of an acute MI or when they complicate ongoing heart failure or ischemia after an MI.

Left ventricular (LV) dysfunction and heart failure are among the most powerful predictors of SCD post-MI.[10,14] With LV ejection fraction (EF) in particular, several studies demonstrated that the rate of SCD increases as the LVEF decreases. In VALIANT, for instance, patients with an EF <30% had the highest rate of SCD or resuscitated cardiac arrest the first month after the MI (2.3%). In addition, each decrease of 5% in EF was associated with a 21% increase in the risk of SCD or resuscitated cardiac arrest.[1] Similar findings were reported in MADIT (Multicenter Automatic Defibrillator Implantation Trial) where patients with EF <26% had worse outcomes compared with those with EF from 26% to 35%.[15]

Several other clinical risk factors have been associated with an increased risk of SCD post-MI, including prolonged QRS duration, spontaneous premature ventricular contraction, nonsustained VTA, late potential on signal averaged ECG, reduced heart rate variability, or T-wave repolarization alternans.[16] Additional risk factors, such as VTA induced by an electrophysiology study, the extent of a magnetic resonance

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imaging scar, and clinical factors are promising means of risk stratification[17,18] but have yet to be incorporated into practice or guidelines[16] because of lack of randomized trials. It remains, however, challenging to develop a comprehensive risk stratification strategy for several reasons. Most studies evaluated the value of individual parameters to predict SCD, in which case the sensitivity and specificity are relatively poor. When clinical parameters are considered together, however, the sensitivity and specificity seem to improve.[19,20] It is also difficult to compare different studies because of the heterogeneity of inclusion criteria (eg, SCD-HeFT [SCD in Heart Failure Trial] enrolled only patients with stable NYHA [New York Heart Association] class II or III heart failure, whereas MADIT II did not require the presence of clinical heart failure for enrollment), treatment (eg, before versus during the era of acute reperfusion), or timing after an MI (eg, the heart rate variability (HRV) varies considerably when evaluated immediately versus few weeks post-MI). Therefore, the current risk stratification ≥40 days after MI for primary prevention defibrillators is mainly based on the LVEF and heart failure.[8]

DINAMIT and IRIS Trials: Hypotheses for the Lack of Improvement in Survival

The main characteristics of the 2 early post-MI ICD trials (DINAMIT and IRIS) are presented in Table 1. A key observation is the significant decrease in the estimated hazard of SCD (58% and 45%, respectively, based on estimated hazard ratios (HazR) of 0.42 and 0.55), which was anticipated but completely offset by an unexpected increase in the hazard of cardiac death from other causes (72% and 92%, respectively) presumably related to heart failure, ischemia, or both. As a result, those trials were considered negative because prophylactic ICD did not reduce all-cause mortality among patients with recent MI. There are several potential explanations for the results of these 2 trials. A first possibility is that the reduction in SCD is an artifact created during the determination of the cause of death. When the clinician determining the cause of death is not blinded to the presence of an ICD, his adjudication might theoretically be influenced by the presence of an ICD. To eliminate this bias, the IRIS adverse-event committee that classified death as being cardiac sudden versus cardiac nonsudden was blinded to the presence of an ICD.[7] If present, significant differences between the randomized groups of patients in terms of baseline characteristics and treatment, or substantial study-group crossovers, could also impact results. However, the baseline characteristics and treatment were generally similar in DINAMIT and IRIS.[6,7] Similarly, the low rates of crossover in both studies seem unlikely to distort results.[6,7] Therefore, more plausible explanations beyond the ones aforementioned will be discussed. It is also important to recognize that these studies looked at long-term mortality benefit for early ICD implant, which is appropriate for a long-term, implanted therapy.

Complications Related to ICD Implantation

One potential explanation for the increased nonarrhythmic death, and thus negative primary outcome in these studies, is that ICD implantation (including general anesthesia and defibrillation testing [DFT]) in the early post-MI period may have led to increased risk, either from early complications or long-term, unknown effects on cardiac remodeling. ICD implantation can be associated with multiple complications, including potentially life-threatening cardiac perforations and pneumothorax.[21,22] However, only 1 patient died directly during the ICD implantation in IRIS (none in DINAMIT), in which mortality at 1 month was similar in the ICD group (9/445, 2.02%) versus the control group (11/453, 2.43%).

DFT during the early phase after the MI may also have contributed to adverse remodeling or somehow increased nonarrhythmic mortality over time because ICDs were systematically tested at implant in both trials. In a large study that randomized patients to DFT versus no DFT during ICD implantation, however, DFT did not increase all-cause mortality during a mean follow-up of 3.1 years,[23] although there was a trend toward an increased risk of perioperative complications among patients with DFT. Importantly, this study did not include early post-MI patients who may be most vulnerable to adverse effects of remodeling. Therefore, the long-term effects of DFT on an ongoing remodeling myocardium during the recovery phase of MI are unknown. DFT has indeed been associated with a significant increase in biomarkers, including those related to apoptosis.[24] Likewise, the impact of other factors related to ICD implantation (use of sedation, pain peri- and postprocedure) has not been evaluated in the early post-MI area, but theoretically could alter remodeling.[25]

Finally, frequent right ventricular pacing can be deleterious and has been associated with increased mortality.[26] There was, however, minimal right ventricular pacing in DINAMIT and IRIS because (1) ICDs were programmed to VVI 40 to 50 beats per minute in both studies (Table 1) and (2) many patients enrolled in these studies had high heart rates at baseline as required by enrollment criteria (Table 1). The exact percentage of pacing is not available in either trial.

Overall, immediate complications related to ICD implantation are an unlikely explanation for the negative results of DINAMIT and IRIS (such as pneumothorax, cardiac perforation, or right ventricular pacing). However, the impact of early implant (DFT, pain, sedation) on long-term remodeling and outcomes is less certain.

Population Risk for SCD and Statistical Power Analysis

Any factor that modified the prespecified statistical power calculations for DINAMIT and IRIS may dilute the apparent efficacy of ICD and potentially lead to a false-negative trial result (type II error). This can be related to the study subjects having less arrhythmic death than expected (eg, EF better than anticipated) or to an erroneous estimation of arrhythmic death among SCD.

Marked LVEF Recovery Leading to Less SCD

Significant EF recovery may occur over time after an initial myocardial stunning after an acute MI for some patients. Therefore, early measurements of the EF may be misleading because improvement in LVEF, beginning within 3 days, is largely complete by 14 days, especially among reperfused patients.[27,28] The extent of this phenomenon was not widely recognized and accounted for when the DINAMIT and IRIS trials were designed. Because the mortality rate is based on the extent of

Table 1. Main Characteristics of the DINAMIT and IRIS Trials

Study Characteristics	DINAMIT Study	IRIS Study
No. of patients screened	n/a	62 944
No. of patients enrolled	674	898
No. in ICD group/control group	332/342	445/453
Inclusion criteria	EF ≤35% and either:	EF ≤40% and either:
	1. Heart rate (RR intervals) variability ≤70 ms on Holter	1. Heart rate >90 beats per minute on initial ECG (67.04%)
	2. Mean heart rate >80 beats per minute on Holter	2. Nonsustained VT >150 beats per minute on Holter (23.16%)
		3. Both (9.80%)
Enrollment period	04/1998–09/2003	06/1999–10/2007
Post-MI enrollment timing (range)	6–40 d	5–31 d (86% of patients still hospitalized)
Randomization time	18 d (±na); ICD implanted 6.3±7.3 d after randomization	13±7 d
Device company and type	Saint Jude medical (100% single chamber)	Medtronic (81% single chamber; 21% Fidelis leads)
ICD programming*	VVI pacing mode 40 to 45 beats per minute typically, maximum 55 beats per minute (99% were VVI ≤50 beats per minute)	VVI pacing mode 40 beats per minute
		VT zone 150–200 beats per minute (32 intervals to detect, stability criterion at 30 ms, electrogram width criterion set ON, no ATP)
	VT zone 175–200 beats per minute with at least 16 beats (4 bursts of 6–10 beats, 81% of TCL first then 10 ms decrements of intervals between bursts then defibrillation)	VF zone ≥200 beats per minute (18 of 24 intervals to detect): defibrillation
	VF zone ≥200 beats per minute: defibrillation	
β Blocker use at baseline	585 (86.8%)	782 (87.4%)
Reperfusion therapy	448 (66.5%)	597 (86.8%)
Ejection fraction	28±5%	35±9%
Mo of follow-up	30±13	37 [range: 0–106]
No. of deaths		
ICD group/control group		
Total	62/58	116/117
SCD	12/29	27/60
Cardiac non-SCD	34/20	68/39
HazR for mortality (ICD vs no ICD)	1.08 [0.76–1.55], *P*=0.66	1.04 [0.81–1.35], *P*=0.78
Annualized mortality rate		
ICD group/control group		
As reported by authors	7.5%/6.9%	n.a./n.a.
As estimated from height of KMC at 3 y	7.4%/6.2%	8.1%/8.3%
Hazard changes (ICD vs no ICD)		
For SCD	–58%	–45%
For Cardiac non-SCD	+72%	+92%

Data are expressed as mean±SD for quantitative variables and number (%) for qualitative variables, unless otherwise indicated or clear from the context. ATP indicates antitachycardia pacing; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; EF, ejection fraction; HazR, estimated hazard ratio; ICD, implantable cardioverter–defibrillator; IRIS, Immediate Risk Stratification Improves Survival Trial; KMC, Kaplan–Meier curve; MI, myocardial infarction; n/a, not available; RR, beat to following beat in milliseconds; SCD, sudden cardiac death; TCL, tachycardia cycle length; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*For comparison, MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy) standard programming was VT zone 170–199 beats per minute; VF zone ≥200 beats per minute with ATP and shocks both zones.

EF impairment, the expected rates of death used for power calculations in these studies may have been overestimated, perhaps because lower EFs after the MI were anticipated to persist over time. For example, in the PREDICTS study (Prediction of ICD Treatment Study), 57% of patients with an initial EF ≤35% post-MI had an EF >35% at 3-month follow-up, including 26% who had an improved EF ≥50%.[29] Having EFs higher than expected may lead to less VTA, SCD, and better long-term outcomes. On

the other hand, EF improvement was comparatively modest in DINAMIT because EF only improved by an average of 2% (SD, 11%) among nearly half of the patients (321) with a repeat echo 6 to 8 weeks after the initial EF. Thus, most of the EF recovery already took place in patients before enrollment in DINAMIT (mean of 18 days after the index MI). Overall, it is likely that most EFs did not continue to improve markedly during follow-up in IRIS and DINAMIT patients, making this hypothesis not a predominant one.

Overestimation of the Rates of VTA Deaths Among SCD Occurring Post-MI

It is now recognized that nearly 50% of clinical SCD occurring early after MIs cannot be prevented by ICD shocks because they are related to causes, such as recurrent ischemia or cardiac rupture.[12,13,30] Thus, ICD would be potentially effective only in 50% of SCD post-MI, which could have affected the sample size calculations in DINAMIT and IRIS. Moreover, the mortality rates underlying these calculations (control group) were 29.4% at 2 years and 30% at 3 years for DINAMIT and IRIS, respectively. These percentages were noticeably larger than the actual estimates of 3-year mortality obtained from the studies (18.6% and 24.3%).

The question of power, however, has been at least partially addressed in the IRIS study. Because of a lower than-expected mortality rate, the steering committee increased the total number of patients from 700 to 900 and extended the follow-up. The power issue can be further addressed by a meta-analysis combining the outcomes of DINAMIT and IRIS.

DINAMIT and IRIS Mortality Outcomes: Meta-Analysis

We combined results on selected mortality outcomes from the DINAMIT and IRIS trials by random effects meta-analysis, using HazR/confidence intervals as ingredients for computations instead of contingency table entries and using Excel 2013 (Microsoft Corporation, Redmond, WA). The HazR for all-cause mortality based on the 1572 patients from both studies was 1.05 (95% confidence interval, 0.86–1.30; P=0.62) for patients assigned to ICD versus the control group. The combination of the 2 trials results diminishes the amplitude of the potential benefit of ICD early after an MI, if any, to a maximum realistic reduction of 14% in the hazard of all-cause mortality, versus 19% and 24% in IRIS and DINAMIT individually as evidenced by the reduction in the upper bounds of the hazard ratios (Table 1). Moreover, the HazR from DINAMIT and IRIS is not suggestive of a low statistical power hypothesis. If indeed low power were the main explanation for the negative results on all-cause mortality in DINAMIT and IRIS, the upper limits of the confidence intervals from these studies should have been barely >1 (for instance, around 1.10 or so), whereas the HazR themselves should have been <1. However, the HazRs were slightly >1 (1.08 and 1.04, respectively); this is more suggestive of a neutral or slight deleterious effect of ICD on all-cause mortality than of a meaningful salutary effect which could not be detected statistically.

On the other hand, the HazR for SCD based on the 1572 patients from both studies was 0.49 (95% confidence interval, 0.32–0.76; P=0.001) for patients randomized to ICD versus the control group. An important salutary effect from ICD on this outcome was detected and was statistically significant, both in the meta-analysis and in the studies individually. In sum, while possibly a contributing factor, lack of power is not plausible as the main explanation for the negative results on all-cause mortality in DINAMIT and IRIS.

Patient Selection Bias

A possible patient selection bias relates to the enrollment criteria required in DINAMIT and IRIS. More specifically, whereas the MADIT II study included patients exclusively based on EF (<30%), IRIS required additional criteria for enrollment, mainly an elevated heart rate (HR) which applied to 76.8% of patients; this criterion was initially >100 beats per minute before being reduced to >90 beats per minute to improve enrollment (Table 1). Therefore, among 62 944 patients screened for IRIS, only 1311 met both EF and HR or heart rhythm criteria (<2.1% of screened patients), among which 898 agreed to participate. Similarly, DINAMIT required HR >80 beats per minute or fulfillment of an HRV criterion (SD of normal-to-normal RR intervals ≤70 ms) for enrollment, in addition to low EF. Therefore, HR and HRV criteria may have selected a subgroup of patients with higher adrenergic stimulation and abnormal autonomic system function. Even if higher sympathetic activity promotes ventricular arrhythmia by various mechanisms,[31] it has been suggested that HRV may identify patients at high risk for death in general,[32] not necessarily arrhythmic.[33,34] These additional inclusion criteria may have selected for patients who may be more likely to die of heart failure, recurrent ischemia, or other nonarrhythmic causes. The precise significance and optimal use of HRV parameters remain uncertain.

The early post-MI patients in DINAMIT and IRIS included a subgroup not enrolled in landmark primary prevention trials for ischemic heart disease, which only included patients who survived months to years after MI (Figure 1). These latter patients presumably had well-compensated remodeled LV function more prone to reentrant scar-mediated VTA, successfully terminated by ICD. Importantly, these patients survived the first 3 months post-MI, which perhaps differentiates them from the groups studied in IRIS and DINAMIT. Thus, patients similar to the early post-MI patients in DINAMIT and IRIS may have died or had an EF recovery >35% and not been represented in successful primary prevention ICD trials (Figure 1). The potential impact of this subgroup of patients on DINAMIT and IRIS results may not be negligible because the risk of death is highest during the first month after an MI, before the progressive decrease over time until the plateau as described earlier.[1,35] It seems plausible that some patients in this subgroup might indeed die during the initial post-MI period with a severe cardiac condition despite ICDs. If that were the case, however, one would expect the Kaplan–Meier curves representing the ICD and control groups for cardiac nonarrhythmic death to separate early on after the MI and stay parallel over time; instead, those 2 curves continued to diverge during the entire study in both DINAMIT and IRIS, suggesting another ongoing or long-term effect (see Figure 3 in both the DINAMIT and IRIS studies).[6,7]

An important question on this hypothesis is whether patients enrolled in DINAMIT or IRIS with the aforementioned

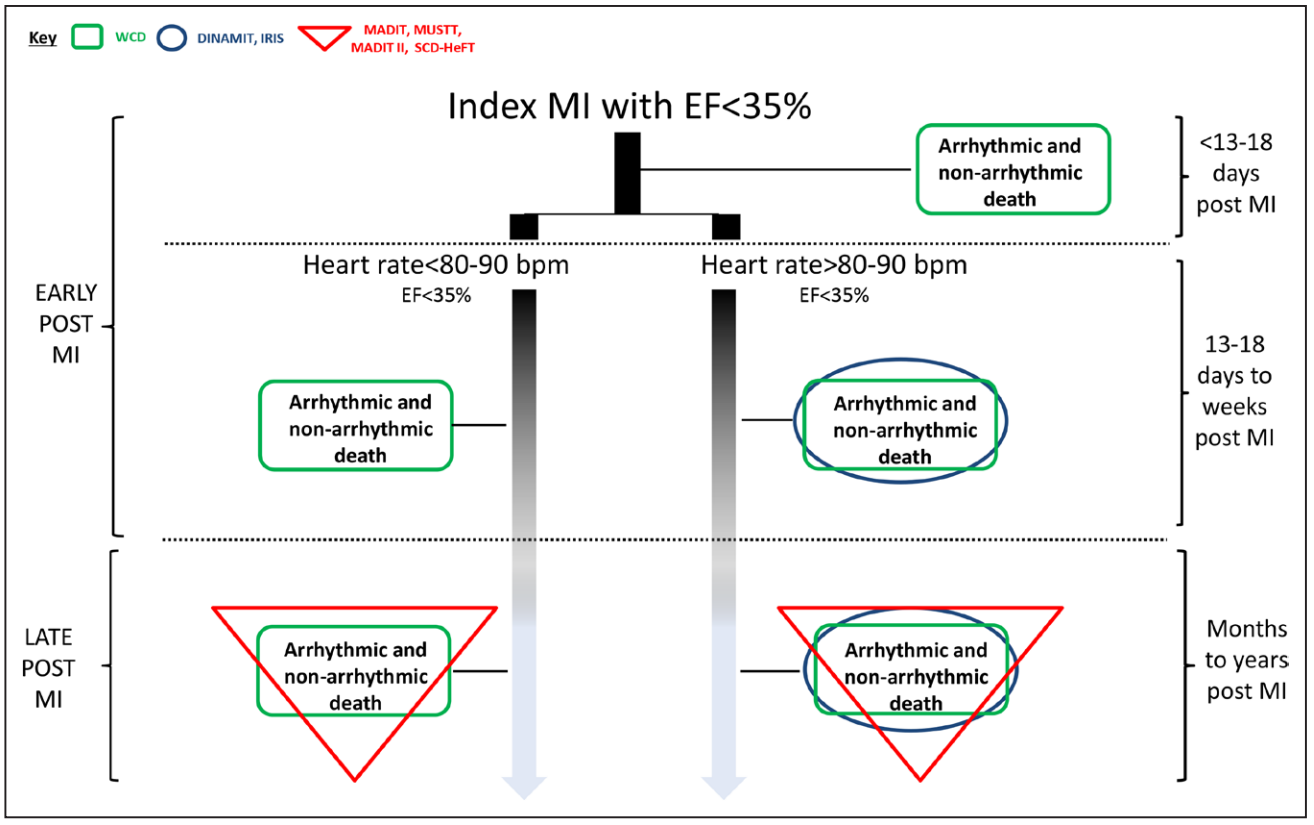

Figure 1. Patient populations included in the different defibrillator trials. This figure describes which subgroups of post-myocardial infarction (MI) patients with ejection fraction (EF) <35% were included in the main primary prevention implantable cardioverter–defibrillator (ICD) trials versus IRIS (Immediate Risk Stratification Improves Survival Trial) and DINAMIT (Defibrillator in Acute Myocardial Infarction Trial), based on the temporal enrollment after the index MI. The wearable cardioverter–defibrillator (WCD) trial will have the broadest enrollment base of post-MI patients, also including those patients that had a very early post-MI death within 2 wk after an MI.

selection bias were objectively sicker than those included in all other primary prevention ICD trials with positive outcomes. This is not the case in terms of EF, with mean EF in DINAMIT or IRIS actually being higher compared with mean EF from 3 other trials (Table 2). Another important objective measure of patients' morbidity and general condition in any trial is the annualized mortality rate of the control group. Most ICD trials do not report this outcome, negating a standardized comparison of patients' overall condition between trials. Therefore, we estimated annualized mortality for the primary prevention ICD trials using a method based on Kaplan–Meier curves, as illustrated with a hypothetical Kaplan–Meier plot (Figure 2) generated using Version 3.2.0 of R (R Foundation for Statistical Computing, Vienna Austria). Using this method, the estimated annualized mortality for the primary prevention ICD trials, including IRIS and DINAMIT, is reported in Table 2. Interestingly, the annualized mortality rate is in fact lower in DINAMIT and IRIS than in any of the other primary prevention trials. Therefore, the patient selection bias hypothesis does not

Table 2. Comparison of Selected Parameters for Primary Prevention ICD Trials in Ischemic Heart Disease

	MADIT	MUSTT	MADIT II	SCD-HeFT	DINAMIT	IRIS
MI diagnosis to study entry	Planned: ≥3 wk; Actual: 75% ≥6 mo	Planned: ≥4 d from MI; Actual: 17% ≤1 mo, 50% ≥3 y	Planned: ≥1 mo after MI; Actual: 88% ≥ 6 mo	Planned: 3 mo from diagnosis of HF, 30 d from MI/CABG	Actual: 6–40 d, mean 18 d	Actual: 5–31 d, mean 13 d
EF (%)	26±7	30	23±5	25	28±5	35±9
Annualized mortality rate (ICD group/control group)						
Reported by authors	n.a./n.a.	n.a./n.a.	n.a./n.a.	n.a./n.a.	7.5%/6.9%	n.a./n.a.
Estimated from height of KMC at 3 y	6.1%/17.0%	11.0%/13.6%	8.0%/11.5%	6.1%/8.0%	7.4%/6.2%	8.1%/8.3%

Temporal enrollment after MI, EF, and estimated annualized mortality in the main primary prevention ICD trials are described here. The method for estimated annualized mortality is described in Figure 2. EF is summarized as mean (±SD if available). For SCD-HeFT, the control group was defined to be those receiving placebo. CABG indicates coronary artery bypass graft; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; EF, ejection fraction; ICD, implantable cardioverter–defibrillator; IRIS, Immediate Risk Stratification Improves Survival Trial; KMC, Kaplan–Meier curve; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; and SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

seem to fully account for the negative results in DINAMIT and IRIS.

Mortality Directly Related to ICD Shocks

This hypothesis relates to the paradox of high-voltage ICD shocks, which are immediately lifesaving but may subsequently increase mortality by direct deleterious myocardial effects. Over the last few decades, several animal and human studies have described the deleterious effects of large amounts of current on the myocardium,[36] especially when the shock is delivered directly via an electrode in direct contact with the heart and results in electroporation.[37] Transient or permanent cellular damage with myocardial injury[38,39] can occur, with the release of various biomarkers, including those for apoptosis.[24] These shocks are also associated with transient myocardial stunning and may in turn be proarrhythmic.[40] The consequences of ICD shocks on the myocardium may be enhanced by various factors associated with VTA, such as ischemia and cardiac remodeling,[41,42] which may apply to DINAMIT and IRIS patients.

The association between ICD shocks and increased mortality was initially reported in subanalyses of MADIT II, SCD-HEFT, and DINAMIT, with receipt of shocks (appropriate or not) multiplying the estimated hazard of death by 3.4, 5.7, and 5.6, respectively, despite adjustment for confounders.[43–45] A subsequent analysis pooling 4 major ICD trials uncoupled VTA type (slow VT <190 beats per minute, fast VT 190–250 beats per minute, and VF >250 beats per minute) and ICD therapy type (shocks versus antitachycardia pacing) and demonstrated that mortality was highest for patients with VF undergoing ICD shocks.[46] The latest evidence was provided in the MADIT-RIT (Reduce Inappropriate Therapy) study, which randomized patients to different ICD therapy programs for VTA. This study essentially compared the outcomes of standard ICD programming (group 1) versus nonstandard programming design to ignore both slower VT (high-rate therapy >200 beats per minute, group 2) or arrhythmias of shorter duration (delayed therapy, group 3).[47] The 2 nonstandard programming designs (group 2 and 3) resulted in substantial ICD therapy reduction over 1-year follow-up compared with standard programming, with a nearly 50% reduction in all-cause mortality. Similar findings were reported in a meta-analysis of 6 trials comparing standard versus other programming options to reduce ICD therapies,[48] with an estimated 30% relative reduction in mortality for the latter, mainly related to a large reduction in inappropriate shocks. Because the VT/VF programs in DINAMIT and IRIS were similar to the standard ICD programming (group 1) in MADIT-RIT with a VT and VF zone, DINAMIT and IRIS patients likely received significant numbers of appropriate and inappropriate shocks (Table 1 for MADIT-RIT programming). These shocks may account for the increased nonarrhythmic mortality in DINAMIT and IRIS.

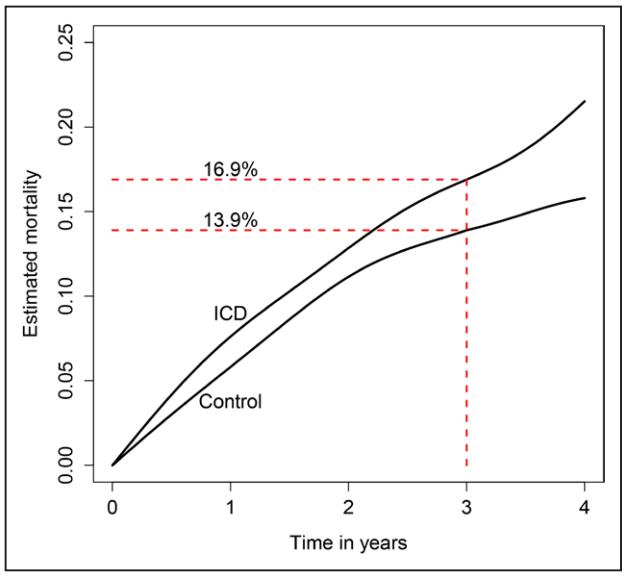

Figure 2. Illustration of annualized mortality estimation method. The method used to estimate annualized mortality for the main implantable cardioverter–defibrillators (ICD) trials is illustrated here with a hypothetical Kaplan–Meier plot. We retrieved 3-y estimated mortalities for ICD and control patients from the Kaplan–Meier plots (or text) presented in the main article for each ICD trial. In our hypothetical example, the 3-y estimated mortalities are 16.9% and 13.9%, respectively. We then used the formula $1-(1-m)^{1/3}$ to estimate annualized mortality, m representing a 3-y estimated mortality and superscript 1/3 representing a cube root. For instance, when m=16.9% or 13.9%, one obtains from the formula 6.0% or 4.9%, respectively. To confirm the first answer (6.0%), one can check that 0.940×0.940×0.940=0.831 (83.1% survival at 3 y); thus, for an annual mortality of 6.0%, the 3-y mortality would be about 16.9%. The second answer (4.9%) can be confirmed similarly.

Overall, a causal link between ICD shocks for VTA and mortality has been established. ICD shocks, however, might be more detrimental in specific arrhythmias (VF or polymorphic VT versus monomorphic VT) and specific myocardial substrates (eg, early post-MI phase during ventricular remodeling, ongoing ischemia, and failing heart with neurohormonal pathway activation). The importance of the substrate's vulnerability to shocks is further supported by a secondary analysis from the SCD-HeFT study, which found that the risk for death after shocks was nearly 3× as high in ischemic versus nonischemic patients.[45] The shock paradox, with a concomitant reduction in SCD at the expense of increased non-SCD, was not widely recognized initially. However, it is now associated with a growing body of evidence and reasonably provides at least a partial explanation for the negative results of DINAMIT and IRIS.[49]

In summary, the negative results for DINAMIT and IRIS do not seem to be due in large part to underpowering or adverse early complications of ICD implantation but may be more plausibly explained by a combination of multiple other factors, such as the important deleterious effects of ICD shocks and patient selection bias.

Current Options to Reduce Arrhythmic Death Early Post-MI

The current options to reduce arrhythmic death early post-MI (primary prevention), besides appropriate cardiac revascularization, include medications, electrophysiology study–directed ICD implantation and the use of a WCD.

Medications

β Blockers are a cornerstone to reduce total mortality and arrhythmic death post-MI and should be used unless there is an absolute contraindication.[50] Similarly, angiotensin-converting

enzyme inhibitors are an important medication to prevent arrhythmic and total death post-MI.[50] Eplerenone also reduces SCD in the presence of LV dysfunction post-MI.[50]

The role of other drugs in the post-MI setting is less clear. Amiodarone reduces arrhythmic death but not total mortality and has significant side effects.[51] D,l-Sotalol can be considered to reduce ICD shocks[52] but has not been shown to reduce mortality. The impact on SCD is inconclusive for statins and Ranolazine.

Electrophysiology Study–Directed ICD Implantation

Ventricular programmed stimulation during an electrophysiology study has been shown for 2 decades to be predictive of arrhythmic death in the chronic phase post-MI and might be useful to direct ICD implantation in the post-MI population. This was demonstrated in post-MI patients enrolled in MADIT[2] and MUSTT (Multicenter Unsustained Tachycardia Trial),[3] although a criticism was that there were large proportions of patients not on β blockers in both studies. More recently, a single-center, prospective study evaluated a systematic ventricular programmed stimulation early post-MI (median 9 days) to predict the subsequent risk of arrhythmic death.[17] Patients with a positive electrophysiology study were offered an ICD, whereas those with a negative result were not. Most patients (90%) were on β blockers at discharge. Patients with an initial positive ventricular programmed stimulation and subsequent ICD implanted had a substantial reduction in arrhythmic events (SCD, VT, or VF treated by the ICD) during the follow-up versus those with a negative ventricular programmed stimulation and no ICD implant. Several limitations were noted in this trial, but these promising results warrant a larger randomized clinical trial.

Wearable Cardiac Defibrillator

The WCD is effective in terminating VTA in some high-risk populations.[53] The WCD delivers shocks through 3 defibrillation electrodes incorporated into a chest strap assembly connected to a defibrillation unit carried on a waist belt[53] when ECG criteria for VTA detection are met (based on heart rate and ECG morphology). The WCD has several advantages and drawbacks compared with an ICD in the early post-MI period.

WCD Advantages

The WCD offers a potential alternative to ICDs to reduce arrhythmic death early after an MI, as a bridging therapy for the period before 40 or 90 days post-MI. However, to date, only nonrandomized studies have been published, so its efficacy cannot be confidently assessed.[54–56] The WCD can be viewed as a noninvasive strategy that allows waiting and monitoring for potential EF recovery before committing a patient to a lifetime ICD. The WCD does not share many of the potential complications of ICD implantation because it is a noninvasive device while still having an effective defibrillation capability. The WCD could be given to post-MI patients with an EF <35% before hospital discharge, which might prevent arrhythmic death occurring within a week or 2 after MI (patients not represented in DINAMIT and IRIS; Figure 1). The mechanisms of shocks and voltage delivered with a WCD are more similar to external cardioversion/defibrillation than to internal defibrillation via ICD. The WCD can provide a maximum of 150 J of a biphasic truncated exponential wave form (versus 200 J for classic external biphasic defibrillators). In contrast to internal shocks, external shocks are typically not associated with electroporation and biomarker increase. In 1 large retrospective analysis, external cardioversion for atrial fibrillation was not associated with increased mortality regardless of the number of external shocks, even in the subgroup of patients with low EF and heart failure.[36] Therefore, shocks from the WCD might be less deleterious than those from ICDs, although this remains to be demonstrated early post-MI. In addition, inappropriate shocks, a strong contributor to cardiac mortality with ICD,[47] can be averted with WCD as an escalating alarm sequence (vibration, noise, voice warning of impending shock) that allows a responsive patient to suspend therapy. Another indirect potential benefit of the WCD is that patients are likely more closely monitored and therefore potentially more compliant to other aspects of their therapy (eg, medication, follow-up visits).

WCD Potential Disadvantages

There are no options for pacing with the WCD for bradyarrhythmia or antitachycardia pacing for VTAs. Even though a few nonrandomized studies seem favorable to the WCD early post-MI, we learned from the randomized trials discussed in this article (DINAMIT and IRIS) and from other nonrandomized series on the same topic that nonrandomized data can be misleading. Previously unknown consequences can indeed be detected when prospective randomized trials are performed. For the WCD, it is not known, for example, what the compliance for wearing the WCD is in the post-MI period, whether the alarms for false detection cause stress that might affect recurrent ischemia or remodeling, whether appropriate or inappropriate shocks affect non-SCD mortality, or whether there are other unknown deleterious effects. For this reason, the WCD is not currently part of guidelines recommendation for treatment of early post-MI patients. A large, multicenter randomized control trial (VEST) is currently nearing completion with results anticipated in late 2017 (Unique identifier: NCT01446965; http://www.clinicaltrials.gov).

Conclusions

Despite the high rate of SCD early after MI, ICDs have not been shown to improve survival. The WCD could theoretically overcome many potential limitations encountered in IRIS and DINAMIT that may have led to ICD failure to improve survival. The results of the VEST, a prospective, multicenter randomized controlled trial will address whether the WCD is an effective therapy in the immediate post-MI patient population. The results will likely impact the management of SCD early post-MI over the next few decades.

Disclosures

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KEY WORDS: defibrillation, electric ■ electric shock cardiac stimulators ■ meta-analysis ■ myocardial infarction ■ root cause analysis ■ sudden cardiac death ■ ventricular fibrillation

Primary Prevention of Sudden Cardiac Death Early Post-Myocardial Infarction: Root Cause Analysis for Implantable Cardioverter–Defibrillator Failure and Currently Available Options

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