The Contradiction of Appropriate Shocks in Primary Prevention ICDs
Increasing and Decreasing the Risk of Death

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Do I contradict myself? Very well, then I contradict myself, I am large, I contain multitudes.
—Walt Whitman

It is a common fault of true believers to celebrate successful reinforcement of their belief system and to dismiss failures. Such has been the case with the evolution of implantable cardioverter-defibrillator (ICD) therapy. Evidence-based guidelines, national health care coverage determinations (CAG-00157R3, January 27, 2005), and clinical practice have been transformed by large randomized clinical trials demonstrating that ICDs reduce mortality in patients with reduced left ventricular ejection fraction (EF), regardless of etiology or accompanying symptoms of heart failure, and with no history of sustained ventricular tachyarrhythmia (VTA) or cardiac arrest.\(^1\)^\(^2\) This reduction in mortality is due entirely to prevention of sudden cardiac death (SCD) by VTA.\(^3\) Consequently, primary prevention ICDs have become an important healthcare industry, with heavily invested stakeholders (implanting physicians, medical device manufacturers, and hospitals) pursuing the same relentless mission: how can we get more ICDs into qualifying patients?

A few years ago, in an editorial arguing for national coverage determinations to align with evidence-based medicine, I wrote that in an earlier era intellectual opposition to the idea of the ICD was antivisionary.\(^4\)^\(^5\) However, it now seems that contemporary application of primary prevention ICD therapy has become an anti-intellectual endeavor. Twenty years later, the translation to clinical practice has devolved to low EF, needs ICD have not been helpful. Thus, the anti-intellectual status quo persists.

Unexpected failure in clinical investigation provides the best opportunity for insight and learning. Proving what you know to be true is not nearly as illuminating as working out why you got it entirely wrong. The latter outcome composes another important purpose of clinical trial failures: to protect us from hubris.

Two recent and notable clinical trial failures of primary prevention ICD therapy would seem to offer an opportunity for illumination. The highest risk period for SCD is immediately following acute myocardial infarction (MI). This risk declines exponentially after the first 6 to 12 months and then persists indefinitely for low-EF patients.\(^6\) Because clinically significant EF improvement is sometimes noted after medical therapy and revascularization accompanying acute MI, such patients were excluded from most primary prevention ICD trials. However, the high risk, early post-MI patient remained an irresistibly tempting and untreated target for ICD therapy to conquer. This population constituted the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT),\(^7\) which randomized 653 patients with EF <35%, recent MI (6 to 40 days), and low heart rate variability or high resting heart rate to primary prevention ICD (311) or medical therapy (342). Randomization to ICD was associated with a 67% reduction in relative risk of sudden, presumed arrhythmic, death. Curiously, and unexpectedly, this reduction in SCD was completely offset by a parallel increase in nonarrhythmic death (70% relative risk compared to non-ICD arm), which was confined to the ICD minority subgroup that recorded electric therapies (mostly shocks) for VTA. Consequently, no survival difference was observed between treatment arms (hazard ratio: 1.08, 95% confidence interval: 0.76 to 1.55).

For the first time in a large randomized clinical trial, a significant reduction in SCD did not transfer a reduction in mortality, and DINAMIT did not join the glitterati of primary prevention ICD trials MADIT-II\(^8\) and SCD-HeFT.\(^2\)

The response to the failure of DINAMIT was suspended disbelief. The true believers, who were also the strongest stakeholders, attributed the DINAMIT failure to an error of the second kind (\(\beta\)) and cited with personal conviction N of 1 experiences of ICD or life-vest saves in similar patients. Mostly, DINAMIT was ignored, except by the national coverage determination which, citing this failure, excluded early post-MI patients from primary prevention ICD coverage. Subsequently, and to the dismay of true believers, DINAMIT was reloaded in the Immediate Risk Stratification Improves Survival trial (IRIS)\(^9\) with the same result: an offsetting increase in nonsudden deaths cancelled out the presumed mortality.

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benefit of electric therapy for VTA in the ICD arm. For IRIS, like DINAMIT, the denouement was a fizzle.

The duplicative negative outcomes of DINAMIT and IRIS proved that in the case of ICDs early after MI, the failure to observe a mortality difference is because the truth is there isn’t one. But what is the explanation for this contradiction? The explanation for the contradictory failure of DINAMIT and IRIS is unavoidably linked to the paradox that has recently emerged in secondary analyses of MADIT II, SCD-HEFT, and other ICD trials: an immediate and accelerating decline in survival after shocked VTA episodes.9–13 I believe this paradox is the premier thought problem facing ICD therapy and the pursuit of the answer provides the greatest opportunity for learning about the factors and conditions that limit its life-saving benefit.

In this issue of Circulation, Dorian et al attempt to shine a light on the mortal contradiction of DINAMIT.14 Some of the abstracted elements of the current secondary analysis were presented during the 2004 Scientific Sessions of the American Heart Association, 11 months after publication of the primary manuscript. It is worth asking why it took 6 years for the current analysis to appear as a full manuscript. I suspect vindication by IRIS and emerging interest in the paradox of VTA shocks and increased mortality risk were enough for the authors to recognize new significance in a failed trial and to overcome whatever inertia previously limited the horizon of their enthusiasm for the topic.

Characteristic of complex modeling analyses, translation of the numeric results to the meaning of the results is not straightforward. However, Dorian et al do provide enough raw materials to frame the thought experiment; the foundation can be summarized as follows: (1) A minority of ICD patients (59, 17.3%) had electrogram-adjudicated (appropriate) VTA therapies; 2/3 of these events occurred within the first year. (2) These patients appeared to be sicker at enrollment (more heart failure, prior MI, less β-blocker use) and had nearly double the intermittent event rates (acute coronary syndrome, heart failure) during follow up compared to other subgroups. (3) Mortality was higher in these patients (36%) compared to ICD patients without VTA therapies (13%) or the control group (16%); VTA therapies (70% shocks) transferred a ≥5 times increased risk of death. (4) Among these ICD patients with VTA therapies, mortality was highest (50%) for those with intercurrent events versus those without such events (18.5%). (5) The majority of deaths (61% to 67%) in the ICD group (with/without VTA therapies) were cardiac nonarrhythmic; conversely, the majority (54%) of deaths in the control group were sudden and presumed arrhythmic.

The 5-fold increased relative risk of death after VTA therapies (mostly shocks) in DINAMIT replicates the 3.4-fold increased risk of death after VTA shocks in MADIT II and 5.7-fold increased risk after VTA shocks in SCD-HeFT.12 This consistently reproducing relationship between shocked VTA episodes and mortality risk can be summarized as follows: patients with VTA and shocks have higher mortality than otherwise similar patients with neither, and patients with more VTA and more shocks have higher mortality than patients with less of both.

The authors’ interpretation of this line of evidence is congruent with the most often held view of the link between shocked VTA episodes and increased mortality risk in other primary prevention ICD randomized clinical trials: patients with VTA and shocks are at higher risk for dying, and the former is a marker for, but mechanistically unrelated to, the latter. In simpler terms, the lack of a mortality benefit in the ICD group despite VTA electric therapies is not a device failure, but a patient failure. This is the safe fall-back position of the true believer. When annualized survival rates are constituted, no credit is given for a life saved by VTA electric therapy at 6 months, nor is fault assigned for the subsequent death at 11 months.

This default argument persists because it is the easiest to make and always within reach. DINAMIT is no exception and the most obvious problem is that the enrollment criteria guaranteed a study population enriched with a huge burden of uncorrected peri-MI coronary disease superimposed on low EF. The qualifying (index) MI was preceded by chronic MI in 30% to 50% of patients; only 2/3 had any form of acute reperfusion, and those who were candidates for complete coronary revascularization (percutaneous or surgical) were intentionally excluded. If the goal was enrollment of a supremely high risk population, the strategy was a success, but it may have unintentionally doomed the possibility of an ICD mortality benefit due to severely competing threats to survival. This is an old argument of logic that remains relevant.

While lack of adequate revascularization may actively counterbalance ICD mortality benefit in a negative direction, robust revascularization may passively neutralize mortality benefit by suppressing cardiac arrest. This lesson is provided by the Coronary Artery Bypass Graft (CABG) Patch Trial,16 another almost forgotten, failed primary prevention ICD randomized clinical trial, which is the Gemini twin, Pollux to Castor, of DINAMIT. Among 900 patients with severe ischemic cardiomyopathy (EF <36%) randomized to ICD or no antiarrhythmic therapy at the time of bypass surgery, no mortality difference was recorded. Though ICDs reduced arrhythmic death by 54%, annualized arrhythmic mortality was very low overall (6.9% control, 4.0% ICD). Yet, programmed ventricular stimulation induced sustained VTA in 43% of patients,17 similar to MADIT-I, in which prophylactic ICDs delivered a huge mortality benefit.18 This suggests that the CABG-Patch population, which was demographically similar to MADIT-I, also had sufficient substrate for spontaneous VTA, but that complete coronary revascularization “unlinked” arrhythmic substrate from mortality outcome (SCD),17 probably by preventing lethal ventricular fibrillation (VF), even if risk for less lethal ventricular tachycardia (VT) due to stable reentry persisted. This hypothesis is consistent with the observation that coronary artery bypass grafting suppresses inducible VF, but not stable VT, in cardiac arrest survivors.19 Coronary artery bypass grafting reduces the risk of sudden death in low EF20,21 and weakens the mortality benefit of primary prevention ICDs for up to 2 years following revascularization.22,23

There are, however, nagging inconsistencies that nurture more subtle and troubling possibilities. The timing of inter-
current (mostly ischemic) events appeared to be randomly related to the timing of VTA electric therapies: 56% occurred after therapy, 34% prior, and 10% on the same day. Yet survival time after VTA electric therapies was similarly poor (<1 day-<1 year), regardless of the timing of intercurrent events. The authors failed to examine the distribution of intercurrent events and SCD in the control group. This was a missed opportunity to dissociate and isolate any independent effects of intercurrent events and VTA electric therapies on mortality.

The problem with the thesis that the lack of a mortality benefit from shocked VTA is strictly a patient failure is that it excludes the possibility for understanding alternative and more disruptive explanations which might lead to improved patient survival. The argument becomes a little involved here. The increasing risk relationship between VTA shocks and mortality could be explained by the adverse effects of VTA in failing hearts, cardiac electric trauma associated with shocks, or both, because almost all episodes in these studies were shocked. VTA shocks saved enough lives in MADIT-II and SCD-HeFT to achieve a mortality advantage compared to medical therapy, and the increased mortality risk of shocked VTA episodes did not completely counterbalance the mortality benefit of VTA termination. Yet in DINAMIT, and presumably in IRIS, the mortality benefit of VTA termination (mostly shocks) was completely offset by an immediate and dramatic increased risk of death after electric therapy.

The relationship between shocked VTA episodes and death must be complex. This complexity invokes the benefit versus harm paradox of high voltage shocks. Large electric currents destroy cardiac myocytes. Sufficiently strong shocks terminate VF but cause temporary or permanent damage to the heart, whereas weaker shocks cause less damage but do not defibrillate. Extensive literature over the past 35 years describes adverse cellular, tissue, and cardiac mechanical responses to large electric currents during defibrillation shocks in animals and humans. These effects are directly related to increasing shock energy and VTA duration and are enhanced by recent or ongoing ischemia. This latter finding has critically important interpretive implications for DINAMIT and IRIS.

In DINAMIT, the risk of death increased as a dramatic step function immediately after VTA electric therapy (mostly shocks). Survival time after electric therapy for VF (all shocks) was substantially less compared to electric therapy for VT (mostly shocks). There were too few treated VTA events, insufficiently differentiated by electric therapy type, to isolate the effect of VTA type and therapy type on mortality. A recent analysis of 2135 ICD patients from 4 trials for VT (mostly shocks) was substantially less compared to electric therapy for VF (all shocks). Qualified by VTA type and electric therapy type, 18 patients (30.5%) received ATP-only, 15 (25.4%) received ATP + shocks, and 26 (44.1%) received only shocks. This is a substantially higher frequency distribution of VF and shocks compared to other contemporary ICD trials that excluded early post-MI patients, where VF accounts for <5% to 10% of VTA and ATP terminates up ≥80% of all remaining VTA (VT and FVT). This is important because though VF must be treated with shocks it may also be the worst conditioning rhythm for shock harm.

The explanation for the contradiction of increased and reduced risk of death after VTA shocks is undetermined. Understanding whether high voltage shocks delivered into the failing heart preconditioned by VTA have an adverse effect on mortality is the most important question facing ICD therapy delivery and development. To dismiss the link between shocked VTA and death as an inevitable consequence of a patient doomed to die is to dismiss the possibility of improving survival. Even proponents of the shock-only subcutaneous ICD concept, facing an increasingly challenged argument that shocks are inconsequential amid a groundswell of concern that they are and that we should be doing something about it, wisely hedged their position with intellectual property for future application of subcutaneously delivered ATP. Ongoing clinical trials to suppress shocks and improve mortality using drugs, VTA substrate modification, and device-based strategies should provide enlightenment.

Disclosures
None.

References
1a. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of all types increased the risk of death by 20%, whereas ATP-terminated Vr and fast Vr episodes did not increase mortality risk. Inappropriate shocks were associated with increased mortality risk in MADIT-II and SCD-HeFT, but the magnitude of effect was substantially less than appropriate shocks. Shock-free ATP termination, though sparingly applied, did not transfer increased mortality risk in MADIT-II. ICD shocks during implant testing and transthoracic shocks for induced VTA result in high intensity cardiac specific biomarker release, whereas ATP for induced VTA and cardioversion shocks for AF do not. Collectively, these observations suggest an interaction between conditioning rhythm type (supraventricular versus ventricular) and adverse effects of high voltage shocks. Furthermore, there may be differences between VTA subtypes (Vr, fast Vr, VF) and shock effects, where greater consequences are observed for VF shocks, and patients with more VTA may be more susceptible to harm from shocks.

The distribution of VTA type + electric therapy type in DINAMIT is therefore important. There were 81 treated VTA events in 59 patients who were electrogram-classified as Vr (50, 61.7%) or VF (31, 38.2%). Qualified by VTA type + electric therapy type, 18 patients (30.5%) received ATP-only, 15 (25.4%) received ATP + shocks, and 26 (44.1%) received only shocks. This is a substantially higher frequency distribution of VF and shocks compared to other contemporary ICD trials that excluded early post-MI patients, where VF accounts for <5% to 10% of VTA and ATP terminates up ≥80% of all remaining VTA (VT and FVT). This is important because though VF must be treated with shocks it may also be the worst conditioning rhythm for shock harm.

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A defibrillator in patients with myocardial infarction and reduced ejection fraction.


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