Primary Prevention Implantable Cardiac Defibrillator Trials
What Have We Learned?

Jakub Sroubek, MD, PhD, Alfred E. Buxton, MD*

KEYWORDS

• ICD • Primary prevention • Sudden cardiac death • Ischemic cardiomyopathy
• Nonischemic cardiomyopathy

KEY POINTS

- To date, a total of nine randomized controlled primary prevention ICD trials have been published and support the notion that patients with reduced left ventricular systolic function derive net mortality benefit from ICD therapy.
- However, this benefit is not uniformly distributed. ICDs most consistently improve outcomes in individuals with ischemic heart disease, who are greater than or equal to 40 days post acute MI.
- The role of ICDs in other patients, including those with nonischemic cardiomyopathies, is much less certain. In some individuals, ICDs may lower the rate of arrhythmic deaths at the price of disproportionately increasing the number of nonarrhythmic deaths.
- Current guidelines are inadequate for selection of appropriate ICD candidates, because risk stratification is not used. Although there are many ways of predicting all-cause mortality, specific assessment of arrhythmic sudden cardiac death risk remains a challenge.

INTRODUCTION

Reduced left-ventricular systolic function (generally meaning an ejection fraction [EF] $\leq$40%) is found in a heterogenous group of disorders. In general, reduced EF is associated with increased mortality, regardless of the underlying anatomic substrate. Although many deaths in cardiomyopathy patients are "expected" and are attributed to a clinically well-delineated process, such as progressive pump-failure or myocardial ischemia, numerous cardiomyopathy deaths are unexpected and sudden. These sudden cardiac deaths (SCDs) have traditionally been thought to be a consequence of ventricular tachyarrhythmias, arrhythmias known to be highly prevalent in this patient population.

Until three decades ago, limited efforts could be made to address out-of-hospital ventricular arrhythmias, either by directly attempting to prevent the arrhythmias (eg, using antiarrhythmic medications or surgical ablation) or indirectly by treating the underlying disorders (eg, through treatment of the underlying cardiac disorders using heart failure medical regimens or revascularization). The introduction of the implantable cardiac defibrillator (ICD) in the 1980s meant that ventricular arrhythmias could be treated effectively as they occurred with high probability of preventing cardiac arrest.

Disclosure Statement: Dr A.E. Buxton has research grants from Medtronic and Biosense-Webster.
Cardiovascular Division, Department of Medicine, Clinical Electrophysiology Laboratory, Beth Israel Deaconess Medical Center, Harvard Medical School, Baker 4, 185 Pilgrim Road, Boston, MA 02215, USA
* Corresponding author.
E-mail address: abuxton@bidmc.harvard.edu

Card Electrophysiol Clin ■ (2017) ■–■
http://dx.doi.org/10.1016/j.ccep.2017.08.006

Subsequent decades of experience with these devices have demonstrated that the ICD can reduce (but not eliminate) risk of SCD and total mortality, in selected patient groups. As a result of technological evolution, the ICD has matured from a bulky, experimental device to one of the mainstays in the ever-expanding armamentarium of contemporary cardiomyopathy treatments.

Despite the perceived benefit that the introduction of the ICD has had for many patients, these devices are not a risk-free panacea suitable for each and every individual with left ventricular (LV) dysfunction. Although the role of ICDs in secondary SCD prevention[1] is well-established and rarely challenged, their appropriate place in primary SCD prevention strategies is much less clear. Identifying the right individuals who will benefit from a primary prevention device, and pinpointing the proper timing of ICD implantation, remains a challenge.

To date, nine large, randomized trials have examined the utility of primary prevention ICDs in patients with either ischemic cardiomyopathy[2–8] or nonischemic cardiomyopathy (NICM)[7,9,10] with reduced LVEF (**Tables 1–3**). They have raised as many questions as they have provided answers. Awareness of the results of these pivotal studies and the controversies that they have provoked is therefore important for any electrophysiologist seeking to provide optimal, individualized care for patients with cardiomyopathy. Before discussing each of these trials in detail, it is worth summarizing the key conclusions that are drawn from the literature as a whole:

- Overall, the use of ICDs reduces all-cause mortality in patients with reduced LVEF.
- Not all patients with reduced LVEF derive equal benefit from ICDs.
- The greatest mortality benefit is seen in patients with infarct-related cardiomyopathy.
- That said, this benefit is only seen if ICDs are implanted greater than or equal to 40 days after index myocardial infarction (MI).
- Earlier ICD implantation in these patients may not be helpful or may actually cause harm.
- The least mortality benefit is seen in patients with NICM with reduced LVEF, presumably because of the lower incidence of sustained, life-threatening ventricular arrhythmias in this population.
- Reduced LVEF is currently the prime bench mark in societal guidelines for ICD use because it was used as the central entry criterion for all relevant clinical trials; however, low LVEF is primarily associated with increased all-cause mortality and has no direct physiologic link to specific arrhythmias, although it certainly modifies the rate of SCD.

PRIMARY PREVENTION IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS IN ISCHEMIC CARDIOMYOPATHY, 1990s

In the 1970s and 1980s, the understanding of mortality in patients with ischemic cardiomyopathy was derived from several key observations, reflected in the Multicenter Post Infraction Research Group (MPRG) study.[11] First, it was well established that survivors of acute MI had a very high overall out-of-hospital mortality rate. Second, it was recognized that many post-MI deaths were sudden (ie, SCDs) and therefore presumed caused by ventricular arrhythmias. Third, certain high-risk clinical features, such as low LVEF or frequent ventricular ectopy, portended worse prognosis. However, it should be said that there was insufficient evidence to parse out which of these risk factors were specific predictors of SCD risk as opposed to being mere markers of increased overall mortality.

These observations generated several questions: Can ICDs reduce the rate of SCD in post-MI patients? If so, would a lower SCD rate translate into lower all-cause mortality? Will this benefit be generalizable to the entire post-MI population or do we need to develop some sort of a risk stratification algorithm to identify a subset of individuals where ICDs are most cost-effective? Is there a reasonable alternative to ICDs, such as antiarrhythmic drugs (AADs)? This last question was particularly relevant because early ICDs (1980–1994) were epicardial devices that depended on surgical (thoracotomy) insertion associated with nonnegligible periprocedural risks.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT-I)[2] was the first major published effort to address these questions. This study, conducted across 32 centers (mostly in the United States), enrolled MI-survivors with reduced LVEF ($\leq$35%), who had spontaneous nonsustained ventricular tachycardia (NSVT) at least 3 weeks after an index MI and who developed sustained VT/ventricular fibrillation in response to programmed electrical stimulation (PES) that was not suppressible with procainamide. These individuals were randomized to ICD therapy (n = 95) versus conventional therapy (n = 101). Although the use of AADs was not protocol-mandated in either study arm, the control group was prescribed amiodarone much more frequently (45%–75% at 1 month and trial end, respectively) than the ICD cohort (2%–7% at 1 month and trial end, respectively). During an average follow-up period of 27 months, there were 39 all-cause deaths in the control arm compared with 15 all-cause deaths in the ICD arm, yielding a hazard ratio (HR) of 0.46 (95% confidence interval [CI], 0.26–0.92; P = .009) in favor of ICD use.