Sudden Cardiac Death
Lessons Learned from Cardiac Implantable Rhythm Devices

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KEYWORDS

• Sudden cardiac death • Implantable rhythm devices • Cardiac arrest • Left ventricular dysfunction • Left ventricular ejection fraction • Implantable cardioverter-defibrillator

KEY POINTS

- Multiple randomized controlled trials have clearly demonstrated that implantable–cardioverter defibrillators (ICDs) are highly effective in preventing sudden cardiac death (SCD).
- In patients who have suffered a cardiac arrest, there is consistent evidence supporting a benefit of ICDs to reduce mortality owing to recurrent cardiac arrest events.
- Left ventricular dysfunction is currently the only parameter to identify primary prevention populations at higher risk of SCD, in which prophylactic implantation of ICDs may reduce the longitudinal mortality risk.
- Application of current risk stratification approaches based on left ventricular ejection fraction (LVEF) alone has failed to prevent most SCD in the general population without LV dysfunction.
- Future studies should focus on the discovery and validation of newer arrhythmic risk markers, to improve the predictive value of LVEF and improve SCD prevention.

INTRODUCTION

Sudden cardiac death (SCD) accounts for 450,000 deaths yearly in the United States,[1] with similar incidence in Europe. Analyses of disease progression patterns over the last 20 years have consistently shown a decrease in overall cardiovascular mortality, mostly driven by an expanded use of evidence-based medical therapies as well as changes in risk factors and lifestyle modifications.[2–4] Although overall cardiovascular mortality has decreased, the proportion of SCD mortality to overall cardiovascular mortality has remained stable over the years.[5] Despite a large evidence base from randomized, controlled, clinical trials and the tremendous advances with implantable cardioverter–defibrillator (ICD) technologies shown to reduce SCD in high-risk patients, defined solely on the clinical history of prior resuscitated cardiac arrest or based on the degree of left ventricular (left ventricular) dysfunction (indexed as the LV ejection fraction [LVEF]),[6–8] there is increasing recognition that the use of these established criteria as standalone risk factors to define who will benefit from an ICD is insufficient. In this regard, many patients who qualify per current guidelines for an ICD will never experience a major arrhythmic event, thus blunting the potential benefit of ICDs and unnecessarily exposing these patients to risky and costly procedures.[9,10] In addition, the absolute number of SCDs prevented using current guidelines is small when compared to the large number of SCDs that occur in the

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general population as the first and last manifestation of subclinical cardiac disease.[11,12] In this context, there remains an unmet need for more effective preventive and treatment strategies to reduce the morbidity and mortality of out-of-hospital cardiac arrest.[13] Survival rates with good neurologic status remain poor, averaging 8.5%. Despite early data suggesting a benefit of antiarrhythmic medications to improve survival in out-of-hospital ventricular tachycardia (VT) and ventricular fibrillation (VF) cardiac arrest that is refractory to cardiopulmonary resuscitation and defibrillation,[14,15] recent data suggest a more limited role of antiarrhythmic medications such as lidocaine or amiodarone in this context.[16]

In this article, we summarize the cumulative evidence on SCD learned from major cardiac implantable rhythm device trials, reviewing the positive and negative lessons learned from these trials and providing a critical overview of the merits and pitfalls of current SCD risk stratification methods.

ESTABLISHMENT OF IMPLANTABLE CARDIOVERTER–DEFIBRILLATOR DEVICES

Secondary Prevention Implantable Cardioverter–Defibrillator Trials

Three major randomized controlled trials, the CASH (Cardiac Arrest Study Hamburg),[17] the AVID (Antiarrhythmics versus Implantable Defibrillators) trial,[18] and the CIDS (Canadian Implantable Defibrillator Study)[19] were consistent in demonstrating a survival benefit from ICD implantation compared with antiarrhythmic drug therapy (primarily amiodarone) for survivors of life-threatening ventricular arrhythmias (Table 1).[17–20] The AVID study was the largest of these trials and included 1016 patients. The populations studied in these trials were fairly homogeneous, although some differences were present. In particular, CASH included only patients with previously documented cardiac arrest owing to VF, whereas CIDS and AVID included patients with either VF or symptomatic sustained VT (and syncope with inducible VT and an LVEF <35% in CIDS). CASH compared ICD with propafenone, metoprolol, and amiodarone therapy, whereas CIDS compared ICD treatment with amiodarone, and AVID compared it with class III antiarrhythmic drugs, although amiodarone was used primarily. The combined results of these trials were summarized in an excellent metaanalysis by Connolly and colleagues.[20] After a mean duration of follow-up of 2.33 $\pm$ 1.89 years, ICD therapy was associated with a significant reduction in death from any cause compared with amiodarone (hazard ratio [HR], 0.72; 95% CI, 0.60–0.87; $P = .0006$). Based on these results, current guidelines give a class I indications for ICD therapy for the secondary prevention of SCD in survivors of cardiac arrest, unstable VT, and sustained VT that occurs in the setting of structural heart disease, either stable or unstable.[21] However, it is important to emphasize that, in these trials, the treatment effect with ICD therapy was not homogeneous across all the subgroups of patients. In particular, subgroup analyses showed that the survival benefit from ICD therapy was largely driven by a positive effect in patients with severe LV dysfunction (LVEF $\leq$35%), whereas no conclusive benefit was found for patients with an LVEF of greater than 35%.[20,22] Although this heterogeneous treatment effect did not translate in specific treatment recommendations by device guidelines, it constituted one of the major drivers for further clinical studies testing ICDs in broader primary prevention populations.

Primary Prevention Implantable Cardioverter–Defibrillator Trials

Table 2 shows a summary of major primary prevention ICD trials. The first randomized study that tested the ICD in primary prevention of SCD was

Table 1
Clinical trials evaluating implantable cardioverter–defibrillators for the secondary prevention of sudden cardiac death

Study[Ref#]	Year	No. of Patients	Medical Treatment	Clinical Presentation for Inclusion	Follow-up (mo)
AVID[18]	1997	1016	Amiodarone/sotalol	Cardiac arrest, VF, VT	18
CASH[17]	2000	191	Amiodarone/propafenone/ metoprolol	Cardiac arrest, VF	54
CIDS[19]	2000	659	Amiodarone	Cardiac arrest, VF, VT, syncope	36

Abbreviations: AVID, The Antiarrhythmics versus Implantable Defibrillators; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study; VF, ventricular fibrillation; VT, ventricular tachycardia.
Follow-up represents mean value.