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Review Article

Prevention of sudden cardiac death beyond the ICD: Have we reached the boundary or are we just burning the surface?

Niyada Naksuk [a], *Christopher V. DeSimone* [a], *Suraj Kapa* [a], *Samuel J. Asirvatham* [a,b,*]

[a] *Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA*
[b] *Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA*

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ABSTRACT

Preventing sudden cardiac death (SCD) remains a major unsolved problem in contemporary medical practice. As the most common cause of SCD, treatment for ventricular arrhythmias is the target area of interest in research field. While implantable cardioverter-defibrillator (ICD) effectively decreases death from ventricular arrhythmias in highly selected patients, risk of inappropriate shocks, mortality from frequent therapy, chance of failing in abortion of arrhythmias despite having a defibrillator, and our inability to recognize which of several hundreds of thousands of patients at risk for sudden death but do not meet current criteria for defibrillator, limit ICD effectiveness. In this article, a brief review of mechanism leading to SCD, the existing evidence for a defibrillator and the lacunae in present guidelines for patients clearly at risk for sudden death but without proven benefit from a defibrillator are presented in Section I. Following this, interventional approaches, both catheter-based and general measures that may serve as adjuncts to a defibrillator in preventing this all too common catastrophic end event, are summarized in Section II.

1. Section I

Sudden cardiac death (SCD) represents perhaps the greatest challenge confronted by cardiologists, epidemiologists, as well as the socioeconomic fabric of most societies. For decades, we have recognized that hundreds of thousands of lives can potentially be saved by an effective, cost effective, and safe preventive therapy. Despite a great survival benefit from the revolution in interventional electrophysiology with the advent of the implantable cardioverter-defibrillator (ICD), it has been postulated that the overall number of SCD cases

Abbreviations: ICD, implantable cardioverter-defibrillator; LCSD, left cardiac sympathetic denervation; NICM, non-ischemic cardiomyopathy; PVC, premature ventricular contractions; SCD, sudden cardiac death; TEA, thoracic epidural anesthesia; VF, ventricular fibrillation; VT, ventricular tachycardia.

* *Corresponding author*. Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA. Tel.: +1 507 293 3376; fax: +1 507 255 2550.
E-mail addresses: asirvatham.samuel@mayo.edu, Bisco.Sue@mayo.edu (S.J. Asirvatham).

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will continue to grow because of the alarming rise in the prevalence of coronary artery disease, obesity and diabetes, and the rise in the average age of the population.[1] Furthermore, painful defibrillator discharges, relatively high incidence of inappropriate ICD shocks, the cost of offering this therapy to all patients potentially at risk for sudden death, and the lack of effective methods to prevent the ventricular arrhythmias that lead to sudden death are all contributory to our very limited success to date.

1.1. *Etiology of SCD*

An estimated 50%–70% of SCDs are due to lethal arrhythmias, mainly those that are related to coronary artery disease.[1–3] Ischemic heart disease has three major mechanisms for placing a patient at risk of developing ventricular arrhythmias. The first mechanism is related to acute coronary syndrome, which can result in ventricular fibrillation (VF) and polymorphic ventricular tachycardia (VT). The second, which can occur in a more "stable" state, is scar-related macroreentry, resulting in monomorphic VT, which is a major mechanism of all ischemic heart patients. The third major mechanism of VT is a reentrant circuit through the bundle branch, though this accounts for less than 10% of VTs.[4,5] Furthermore, focal, non-reentrant mechanisms are responsible for less than 5%–10% of VTs.

Other patients can have VTs that are not related to coronary artery disease. These are the non-ischemic cardiomyopathy (NICM) patients, which account for about 10%–15% of SCD[1,4] and the major mechanism at play is a scar-related monomorphic VT. Finally, the remaining 5%–10% of SCD are due to congenital cardiac conditions or in those with apparent normal heart. For this later group, caution is needed to identify *idiopathic* VT and vigorous searching for other channel abnormalities may further identify underlying mechanisms. Thus, the incidence of *truly* idiopathic VT may be less than estimated. Furthermore, idiopathic VT is thought to have more benign prognosis, although rare cases may experience SCD. Idiopathic VF is another clinical entity that poses high-risk for SCD. Taken all together, idiopathic VF and rare cases of idiopathic VT may account for ≈5% of SCD in all age groups.[6]

1.2. *Primary prevention of SCD: the Use of ICDs*

Several trials have shown that ICD implantation decreases mortality and is currently the mainstay in SCD preventive therapy in selected patients (Fig. 1).[7] The largest trial conducted in ischemic cardiomyopathy patients, the MADIT II study, showed that ICD was associated with a 31% decrease in mortality over 20 months, for an absolute decrease of 5.6%[8] while the SCD-HeFT trial enrolling NICM patients found a 23% decrease in mortality over a 5-year period, for an absolute decrease of 7.2% in primary prevention ICD implantation.[9] Consequently, a dramatic increase in ICD prescriptions has resulted in approximately 10,000 newly implanted defibrillators a month in the United States, and almost 75% of those were for primary prevention of SCD.[10]

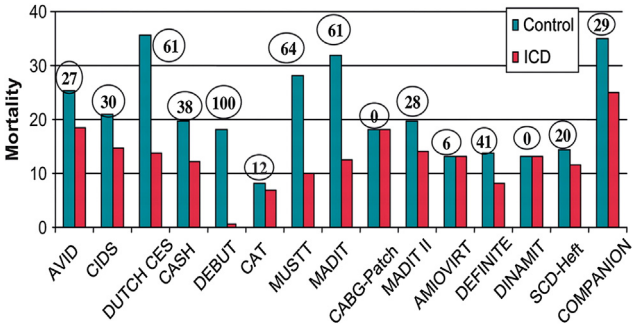

Fig. 1 – Major randomized trials performed that evaluated efficacy of ICD therapy for reduction in mortality (Reproduced with Permission from *Europace*).

1.3. *Limitations of ICDs in prevention of SCD*

Several limitations of the ICD device have been recognized. For example, even though they are highly effective in abortion of ventricular arrhythmias, ICDs do not prevent recurrent VT episodes, and furthermore, the underlying arrhythmogenic substrate remains unchanged or may even progress over time.[11] A pooled analysis of all randomized ICD trials indicated an ICD-unresponsive SCD rate of 5%.[12] Unfortunately, the retrospective post-hoc analyses have not revealed any distinguishing causes or characteristics of those who have had ICD-unresponsive events. Moreover, the Oregon Sudden Unexpected Death Study found that among ICD patients with SCD, 17% of patients had VT/VF, suggesting failure of ICD therapy to abort the lethal rhythm.[13]

Of great concern, firing of an ICD by itself can be associated with increased mortality. This observation was found in both appropriate and inappropriate defibrillator shocks as shown in a post-hoc analysis from the SCD-HeFT study.[14] Poole, et al showed data to suggest that an appropriate ICD shock is associated with a six-fold increase in the risk of death whereas an inappropriate ICD shock was also associated with a two-fold increase in the risk of death.[14] Indeed, the incidence of inappropriate shocks is common and may be as high as 12%–30%, while the incident-appropriate ICD shock is 20%–30% (Fig. 2).[15] To reduce ICD therapy, optimal ICD programming has been studied. The MADIT-RIT trial showed that a new stepwise ICD programming results in an impressively low incidence of ICD therapy (8% appropriate and 5% inappropriate therapy) during 1.4 years follow-up.[16] This strategy also further decreases overall mortality. However, the aforementioned problems of ICD (i.e. chance of recurrent ICD shock) still remain. In addition, ICD implantation and therapy can negatively impact patients and their families' quality of life because of significant psychological distress and depression since they have to adjust to the fact of uncertain health conditions and potentially painful ICD shocks.

2. Section II. Radiofrequency ablation to prevent sudden death – can we do this?

Although radiofrequency ablation has been remarkably successful in treating symptomatic arrhythmias of many