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Review

Sudden death prophylaxis in heart failure

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Abstract

Sudden cardiac death (SCD) is the leading cause of mortality in heart failure (HF). Today the implantable cardioverter-defibrillator (ICD) has become a commonplace therapy around the world for patients with both ischemic and non-ischemic cardiomyopathy and an ejection fraction (EF) ≤35%. However, EF alone does not discriminate between the modes of death from HF (sudden arrhythmic death vs. non-sudden death). Other risk statifiers, such as electrophysiologic study and microvolt T-wave alternans testing, should therefore be used in the appropriate settings to minimize the number of unnecessary device implants. In addition, left ventricular mechanical dyssynchrony has now become recognized as an additional major marker of cardiac mortality. Its assessment should entail echocardiography rather than measurement of the QRS duration. This will allow us to better integrate the ability of cardiac resynchronization therapy (CRT) in enhancing cardiac function with the ability of an ICD in preventing SCD. This review aims to: 1) give a synthesis of the published evidence regarding the value of implantable ICDs and CRT in the primary prophylaxis of SCD in HF; 2) discuss controversial clinical issues in this area; and 3) recommend practical device-based management strategies.

Keywords: Sudden death; ICD; Resynchronization; Mortality; Arrhythmia

Sudden cardiac death (SCD) is defined as natural death due to cardiovascular causes in a patient with or without known preexisting heart disease, in whom the mode and time (≤1 h) of death are unexpected [1]. In the vast majority of cases, SCD is heralded by an episode of ventricular tachycardia (VT), which degenerates to ventricular fibrillation (VF) and ultimately collapses to asystole [2]. It accounts for nearly 60% of all cardiovascular deaths, which means that 250,000 to 460,000 Americans succumb to SCD annually [3]. These fatalities number more than the annual fatalities from most other medical diseases combined, including HIV, lung and breast cancers, and stroke. Unfortunately, SCD remains difficult to predict and treat.

Severe left ventricular (LV) systolic dysfunction has long been recognized as a risk factor for SCD and all-cause mortality. It is estimated to account for 250,000 deaths annually with an economic burden of $20 billion per year [3]. Given that about 4.8 million individuals in the United States are afflicted with systolic heart failure (HF), that 400,000 to 700,000 new cases are diagnosed yearly, and that baby boomers are aging and life expectancy is lengthening, the occurrence of HF and SCD will probably continue to rise in tandem [3]. Therefore, there is a strong impetus to reduce HF mortality, either by enhancing cardiac function or by preventing SCD.

The intentions of this review are: 1) to give a synthesis of the published evidence on the value of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) to assist the clinician in the primary

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prophylaxis of SCD in HF; 2) to discuss controversial issues in this area; and 3) to recommend practical device-based management strategies.

1. Prophylactic ICD and unresolved issues

Because pharmacologic strategies, other than β-blockers, have been largely ineffective in preventing SCD, device-based SCD prevention has become critically important from a public health standpoint. It was during the early 1990s, when the technique of pectoral ICD implantation with use of transvenous leads was developed, that the number of ICD implants increased substantially [4]. It was not, however, until the publication of three randomized controlled trials in the late 1990s – Antiarrhythmics Versus Implantable Defibrillators (AVID), Canadian Implantable Defibrillator Study (CIDS), and Cardiac Arrest Study Hamburg (CASH) – that the ICD became widely accepted [5–7]. These studies demonstrated that ICDs produced a nearly 30% relative risk reduction in all-cause mortality in survivors of spontaneous episodes of ventricular tachyarrhythmias [8]. Regrettably, only a small minority of patients who experience out-of-hospital cardiac arrest are successfully resuscitated. Consequently, there is a relative paucity of candidates for secondary prevention of SCD, giving the ICD in this scenario a cost-effectiveness ratio of approximately $125,000 per year of life saved. This is much higher than the acceptable benchmark for a cost-effective intervention [3,4,8]. In contrast, ICD therapy has found wider applicability for the primary prevention of SCD in high-risk patients.

The prophylactic era began in 1996 with the publication of the Multicenter Automatic Defibrillator Implantation Trial (MADIT), which showed that ICDs provided effective protection against death in patients with coronary artery disease (CAD), LV dysfunction with ejection fraction (EF) <35%, spontaneous asymptomatic non-sustained VT (NSVT), and inducible, non-suppressible VT on electrophysiologic study (EPS) [9]. This small trial of 196 patients, who were followed for an average of 27 months, demonstrated a 54% reduction in all-cause mortality in patients with ICDs compared with those treated by conventional therapy.

Three years later, the results of the Multicenter Un-Sustained Tachycardia Trial (MUSTT) came out [10]. This study tested the electrophysiologic inducible suppression hypothesis by randomizing 704 patients with CAD, EF ≤40%, asymptomatic NSVT, and inducible sustained ventricular tachyarrhythmia to receive antiarrhythmic therapy or no antiarrhythmic therapy. While some patients in the arrhythmic therapy arm were offered an ICD, it should be emphasized that MUSTT was not a randomized ICD trial. Nonetheless, the all-cause mortality and SCD rates at 5 years were 24% and 9%, respectively, among patients assigned to EPS-guided ICD implantation, compared with 55% and 37% among those who did not receive an ICD. The results of MUSTT therefore taught us that we can expect to save lives by implanting ICDs in the appropriate patients, but not by suppressing inducible VT with antiarrhythmic drugs.

Six years after the first MADIT, the second MADIT (MADIT II) came out. This study of 1232 demonstrated that those with a history of myocardial infarction (MI) and an EF ≤30% had a 31% relative risk reduction in mortality after a mean follow-up of 20 months when *empirically* treated with an ICD one month or more after the MI, as compared with conventional medical therapy [11]. Because the investigators did not use EPS to risk-stratify patients, MADIT II raised one of the big unanswered questions in rhythm-management devices: *Should all patients with LV dysfunction and an EF ≤30% due to CAD but with no other risk markers of SCD receive an ICD?*

While LV dysfunction appears to be an important risk stratifier for SCD, it is clear that not all patients with impaired systolic dysfunction benefit from devices. LV dysfunction is only part of a puzzle and does not provide the entire picture. For example, patients with NYHA class IV HF are at lower risk of arrhythmic death than patients with less severe symptoms (e.g., NYHA class II) [12]. Also, if EF were a perfect risk stratification test, then both its sensitivity and specificity for SCD should approach 100%, with its predictive accuracy remaining stable over time. Several lines of evidence, however, suggest that EF lacks sufficient sensitivity when used alone. In the Maastricht prospective registry that included 492 patients who had SCD, only 19% had an EF <30% prior to the event [13]. In the Autonomic Tone and Reflexes After acute MI (ATRAMI) study which enrolled 1284 patients, an EF of <35% was found in only 22 patients who died of SCD among a total of 49 cardiac deaths [14]. Furthermore, most of the patients enrolled in the largest trials of secondary prophylaxis of SCD had an EF >30% [5–7]. Thus, with the current ACC/AHA ICD guidelines, the majority of patients who die of SCD would have never qualified for an ICD for primary prophylaxis [15]. Along these lines, a recent MUSTT subgroup analysis suggested that EF alone might not be helpful in distinguishing how patients die [16]. Not unexpectedly, patients with CAD and an EF <30%, regardless of inducibility of VT, had a higher all-cause mortality rate than those with an EF ≥30% even if inducible sustained VT was present. However, with regard to arrhythmic death, patients with an EF <30% with no inducible sustained VT had a slightly lower risk of SCD than patients with an EF ≥30% and VT inducibility [16]. Therefore, EF alone may not predict the mode of death, whereas VT inducibility identifies patients for whom death, if it occurs, is more likely to be arrhythmic, even if the EF is ≥30%. If one assumes that ICDs reduce mortality primarily by preventing arrhythmic events, these findings suggest that such devices have the potential to significantly reduce mortality not only in patients with an EF <30% but also in those whose EFs are ≥30%. Therefore, as pointed out by Buxton, we must strive to identify the characteristics of patients who are most likely to benefit from ICD therapy and minimize the number of these expensive implants in patients who do not require them [17].