Primary prevention of sudden cardiac death: indications for cardioverter-defibrillator implantation

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Sudden cardiac death accounts for 400 000 to 450 000 deaths annually in Europe and in the United States. In patients with previous life-threatening arrhythmia, several perspective, randomized, controlled studies have demonstrated that implantable cardioverter-defibrillator (ICD) therapy is superior to the best antiarrhythmic therapy in prolonging survival. Furthermore, in a stratified-risk population with coronary artery disease, left ventricular ejection fraction ≤ 35%, non-sustained ventricular arrhythmias, and inducible ventricular tachycardia, the ICD supports the class I level of recommendation by the guidelines published in 1998. The American College of Cardiology, American Heart Association, and North American Society of Pacing and Electrophysiology have updated the 1998 guidelines on the implantation of arrhythmia devices including in a class IIa level of recommendation also patients with a previous Q wave myocardial infarction and left ventricular ejection fraction ≤ 30%, independently of their arrhythmic risk profile.

In the recent years several randomized studies assessed the role of ICD treatment for primary prevention of sudden cardiac death and total mortality reduction in high-risk groups of patients with ischemic and non-ischemic dilated cardiomyopathy, with special reference to those with heart failure and ventricular dysfunction.

This article reviews those trials that have resulted in defining indications for ICD, and that will expand its use in the future.

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Introduction

Sudden cardiac death (SCD) accounts for 450 000 deaths annually in the United States[1] and for 400 000 in Europe[2]. In patients with previous sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), several prospective, randomized, controlled study have demonstrated that implantable cardioverter-defibrillator (ICD) therapy is superior to the best antiarrhythmic therapy in prolonging survival[3-5].

Because patients with previous sustained VT/VF account for < 1% of patients who died suddenly[6], in the recent years several randomized studies assessed the role of ICD treatment for primary prevention of SCD and total mortality reduction in particular high-risk groups of patients with ischemic and non-ischemic dilated cardiomyopathy (CMP). This article reviews trials that have resulted in defining and expanding indications for ICDs.

Primary prevention trials in ischemic cardiomyopathy

Survivors of cardiac arrests or life-threatening ventricular arrhythmic events constitute a high-risk but relatively small subset of post-infarction patients. The invasive and non-invasive risk stratification methods aims to identify patients who might be much more numerous but at lower risk than cardiac arrest survivors[6].

Multicenter Automatic Defibrillator Implantation Trial (MADIT). The study assessed whether prophylactic therapy with an ICD, as compared with conventional medical therapy, would improve survival in patients with prior myocardial infarction (MI), a left ventricular ejection fraction (LVEF) < 35%, a documented episode of asymptomatic non-sustained VT, and inducible, non-suppressible by antiarrhythmic drugs ventricular tachyarrhythmia on electrophysiologic study[7]. The patients

were randomly assigned to receive an ICD (n = 95) or conventional medical therapy (n = 101). During an average follow-up of 27 months, there were 15 (12%) deaths in the defibrillator group (11 from cardiac causes) and 39 (39%) deaths in the conventional therapy group (27 from cardiac causes) (hazard ratio [HR] for overall mortality 0.46, 95% confidence interval [CI] 0.26-0.82, p = 0.009). Amiodarone, beta-blockers, or any other antiarrhythmic therapy did not influence the observed HR; on the contrary, prophylactic therapy with ICD improved survival. The majority of the benefit was seen in patients with LVEF < 26% and in patients with a QRS interval ≥ 120 ms, contrary to the belief at the time the study was designed. Therefore the sickest patients benefit the most. MADIT was the first randomized trial to demonstrate that ICD therapy could improve survival in a high-risk population after an acute MI. Although there was only one trial, the guidelines committee recommended a class I indication given the magnitude in beneficial effect[8].

Multicenter Unsustained Tachycardia Trial (MUSTT). The randomized, controlled MUSTT trial tested the hypothesis that electrophysiologically guided therapy would reduce the risk of SCD among patients with coronary artery disease, LVEF ≤ 40%, and asymptomatic, non-sustained VT[9]. A total of 704 patients in whom sustained ventricular tachyarrhythmias were inducible were randomly assigned to receive either antiarrhythmic therapy, including drug and ICD, as indicated by the results of electrophysiologic testing, or no antiarrhythmic therapy. The 5-year incidence of the primary endpoint of cardiac arrest or death from arrhythmia were 25% among those receiving electrophysiologically guided therapy and 32% among the patients assigned to no antiarrhythmic therapy (HR 0.73, 95% CI 0.53-0.99, p = 0.04), representing a reduction in risk of 27%. The risk of cardiac arrest or death from arrhythmia among the patients who received treatment with ICD was significantly lower than that among the patients discharged without ICD (HR 0.24, 95% CI 0.13-0.45, p < 0.001). Neither the rate of cardiac arrest or death from arrhythmia nor the overall mortality rate was different among the patients assigned to electrophysiologically guided therapy and treated with antiarrhythmic drugs and the patients assigned to no antiarrhythmic therapy. The 5-year estimate of total mortality regarded 55% of patients treated with antiarrhythmic drugs and 24% of patients treated with ICD (24 lives saved every 100 patients implanted with an ICD). The conclusion of the MUSTT trial is that ICD reduces the risk of SCD in high-risk patients with coronary disease, very similar to the MADIT trial, supporting the indication for an ICD in this population. These data support the class I level of recommendation by the guidelines committee[8].

Coronary Artery Bypass Graft (CABG) Patch Trial. The study evaluated the effect on survival of the prophylactic implantation of an ICD in patients with coronary heart disease, LVEF < 36%, and abnormalities on signal-averaged ECG at the time of coronary artery bypass graft (CABG) surgery[10]. The trial randomly assigned 900 patients to CABG plus ICD (446 patients) or to CABG alone (454 patients). The primary endpoint of the study was overall mortality, and the two groups were compared in an intention-to-treat analysis. The trial was prematurely terminated because mortality was equal in the two groups. During an average follow-up of 32 months, there were 101 deaths in the ICD group (71 from cardiac causes) and 95 in the control group (72 from cardiac causes). The HR for death from any cause was 1.07 (95% CI 0.81-1.42, p = 0.64). Thus the CABG Patch trial demonstrated no benefit of the prophylactic ICD in patients with an ischemic burden and a depressed LVEF undergoing appropriated coronary revascularization.

Multicenter Automatic Defibrillator Implantation Trial (MADIT II). This randomized trial was designed to evaluate the effect of an ICD on survival in a lower-risk group of patients with LVEF ≤ 30% and prior Q wave MI[11]. The patients were randomly assigned in a 3:2 ratio to receive an ICD (742 patients) or conventional medical therapy (490 patients) including beta-blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering drugs. Total mortality from any cause was the main endpoint. Patients were excluded if they had a MI within the past month, an approved indication for an ICD, NYHA class IV congestive heart failure, or coronary revascularization in the preceding 3 months. During an average follow-up of 20 months, the mortality rates were 19.8% in the conventional therapy group and 14.2% in the defibrillator group (HR 0.69, 95% CI 0.51-0.93, p = 0.016), representing a reduction in risk of 31%. The effect of ICD therapy on survival was similar in subgroup analyses stratified according to age, sex, LVEF, NYHA class, but, with increasing QRS duration, an incremental benefit was shown for survival. CI were highly significant for the subset of QRS duration > 150 ms. Zareba et al. (unpublished data) presented at the NASPE meeting in 2002 survival data from the MADIT II groups with QRS duration > 120 ms. At 3 years, mortality in the conventional treated group was 53% and in the ICD group 21% (HR 0.37, p = 0.016). However, this analysis was retrospective and cannot be accurately applied to exclude patients who may not benefit from prophylactic ICD, moreover, whether there is a lower cut-off at which benefit is lost, is unknown. The conclusion is that prophylactic implantation of an ICD should be considered as a recommended therapy in patients with a prior MI and advanced left ventricular dysfunction, independently of spontaneous ventricular arrhythmias. Because there was only one trial to support this position, a class IIa instead of a class I recommendation was made by the committee to update the 1998 guidelines[12]. However given the results of recent trials, future guidelines probably will support a class I indication for ICDs in MADIT II patients (Table I).

Table I. Future implantable cardioverter-defibrillator recommendations based on the results of recent trials.

Class I
Patients with LVEF < 30%, at least 45 days after myocardial infarction and at least 3 months after coronary revascularization surgery (MADIT II plus DINAMIT indication).
Class IIa
NYHA class III-IV congestive heart failure, LVEF < 35%, QRS duration > 120 ms, on optimal medical therapy, irrespective of substrate of cardiomyopathy (COMPANION indication).
NYHA class II-II congestive heart failure, LVEF < 35%, on optimal medical therapy, irrespective of substrate of cardiomyopathy (SCD-HeFT indication).

LVEF = left ventricular ejection fraction.

Defibrillator in Acute Myocardial Infarction Trial (DINAMIT). DINAMIT was a randomized trial to test the hypothesis that an ICD will reduce the risk of death in patients with recent MI (6-40 days) who are at high risk of arrhythmic death due to LVEF < 35%, and autonomic imbalance (low heart rate variability or high resting heart rate)[13]. Exclusion criteria included NYHA class IV congestive heart failure, CABG surgery or three-vessel angioplasty since MI. The primary outcome was mortality from all causes, and the secondary outcomes included arrhythmic death. A total of 674 patients were enrolled; 332 were randomly assigned to ICD therapy and 342 to conventional medical therapy. Mean age was 62 years. Men comprised 76% of the study population. Mean LVEF was 28%. During a mean follow-up of 30 months there were 62 deaths in the ICD group compared to 58 deaths in the conventional therapy group (HR 1.08, 95% CI 0.76-1.55, p = 0.66). For the secondary endpoint, there were 12 arrhythmic deaths in the ICD group compared to 29 deaths in the conventional therapy group (HR 0.42, 95% CI 0.22-0.83, p = 0.009). The conclusion of the DINAMIT trial is that ICD therapy does not improve survival in patients with severe ischemic heart disease and recent MI. Future guidelines should state that patients must be evaluated at least 45 days after the target MI before receiving prophylactic ICD (Table I).

Primary prevention trials in non-ischemic cardiomyopathy

Currently there are no accepted indications for the prophylactic implantation of ICDs in patients with non-ischemic CMP who have not experienced VT/VF. Unfortunately, all antiarrhythmic drug trials to date have shown that these drugs, with the exception of amiodarone, either have a deleterious effect on mortality or neutral effect. On the other hand, angiotensin-converting enzyme inhibitors and beta-blockers significantly reduce mortality in these patients, and thus should be the standard of care[14]. Despite these data, mortality remains unacceptably high in patients with congestive heart failure[15], and ICDs may provide an adjunctive benefit to drug therapy.

Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). The CAT was a randomized trial to compare ICD therapy to standard medical therapy in patients with idiopathic dilated CMP with symptoms of recent onset (≤ 9 months), LVEF < 30%, NYHA class II or III[16]. The primary endpoint was all-cause mortality at 1 year of follow-up. A total of 104 patients were enrolled in the CAT pilot phase: 50 patients were randomly assigned to ICD treatment and 54 to the control group. Mean follow-up was 5.5 years. Mean age was 52 years. Men comprised 83% of the study population. Mean LVEF was 24%. Approximately 65% of the patients had NHYA class II heart failure and 35% had class III. There were a total of 30 deaths: 13 in the ICD group compared to 17 in the control group (p = 0.554). Eleven patients received adequate ICD therapy. The investigators concluded "this trial did not provide evidence in favor of prophylactic ICD implantation in patients with idiopathic dilated CMP of recent onset" and that "short- and long-term overall mortality rates in patients with idiopathic dilated CMP and significantly impaired left ventricular function were surprisingly low". The trial may not have been adequately powered because the overall mortality at 1 year did not reach the expected 30% in the control group.

Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia (AMIOVIRT). The AMIOVIRT trial compared prospectively total mortality rates of patients with non-ischemic dilated CMP, LVEF < 35%, NYHA class I-III, and asymptomatic non-sustained VT who were randomized to therapy with amiodarone or an ICD[17]. Patients with symptoms within 6 months were excluded. The primary endpoint was total mortality. A total of 103 patients were enrolled: 51 patients were randomly assigned to ICD treatment and 52 to amiodarone. Mean age was 59 years. Men comprised 70% of the study population. Mean LVEF was 23%. Approximately 63% of the patients had NYHA class II and 20% had class III. During mean follow-up of 2.0 years there were a total of 13 deaths: 6 in the ICD group compared to 7 in the amiodarone group (p = 0.8). The percent of patients surviving at 1 year (90 vs 96%) and 3 years (88 vs 87%) in the amiodarone and ICD groups, respectively, were not statistically different (p = 0.8). The study was stopped due to the prospective rule used to identify inability to differentiate between ICD and amiodarone therapy.

Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE). The DEFINITE trial was a prospective, randomized and large study to test the hypothesis that an ICD will reduce the risk of death in patients with non-ischemic CMP, LVEF ≤ 35%, ambient arrhythmias (non-sustained VT or > 10 premature ventricular contractions per hour), and history of symptomatic heart failure[18]. Patients were excluded if they had NYHA class IV, had undergone electrophysiological testing within the prior 3 months, had permanent pacemakers, or familial CMP associated with SCD. The primary endpoint was death from any cause. The secondary endpoint was sudden death from arrhythmia. A total of 458 patients were enrolled: 229 patients were randomly assigned to receive standard medical therapy and 229 to receive standard medical therapy plus a single-chamber ICD. During a mean follow-up of 29 months there were 68 deaths: 28 in the ICD group, 40 in the standard therapy group (HR 0.65, 95% CI 0.40-1.06, p = 0.08). There were 17 sudden deaths from arrhythmia: 3 in the ICD group, as compared with 14 in the standard therapy group (HR 0.20, 95% CI 0.06-0.71, p = 0.006). The ICDs were programmed to back up VVI pacing at a rate of 40 b/min and to detect VF at a rate of 180 b/min. Forty-one patients (17.9%) received appropriate ICD shocks. Forty-nine patients (21.4%) received inappropriate ICD shocks, primarily for atrial fibrillation or sinus tachycardia. In this study the implantation of an ICD significantly reduced the risk of sudden death from arrhythmia and was associated with a non-significant reduction in the risk of death from any cause in patients with severe, non-ischemic dilated CMP who were optimally treated with cardiac drugs.

Primary prevention trials in chronic heart failure (both ischemic and non-ischemic cardiomyopathy) with or without cardiac resynchronization therapy

SCD accounts for 28 to 68% of all deaths in heart failure patients[15]. Class I and II patients primarily die from arrhythmias, whereas class III and IV patients die mostly from pump failure. Identifying patients at high risk for SCD is important because only 3 to 28% of patients survive an episode of SCD. The ICD is superior to antiarrhythmic drugs in secondary prevention of overall death and SCD in the general heart failure population[3]; similar results were shown in primary prevention of total death and SCD in ischemic CMP[11]. However, efficacy of ICD in primary prevention of death in non-ischemic CMP and advanced functional class heart failure has not been established.

Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION). The COMPANION was a randomized trial to test the hypothesis that prophylactic cardiac resynchronization therapy with a pacemaker (CRT) or with a pacemaker-defibrillator (CRT-D) would reduce the risk of death and hospitalization among patients with advanced chronic heart failure (NYHA class III or IV, LVEF < 35%), intraventricular conduction delays (QRS interval > 120 ms), who were hospitalized for the treatment of heart failure in the preceding 12 months[19]. The primary endpoint was a composite of all-cause mortality and all-cause hospitalization. The secondary endpoints included all-cause mortality and cardiac morbidity. A total of 1520 patients were enrolled with a 1:2:2 randomization: 308 were randomly assigned to receive optimal pharmacologic therapy, 617 to optimal pharmacologic therapy plus CRT and 595 to optimal pharmacologic therapy plus CRT-D. Mean age was 67 years. Men comprised 68% of the study population. Mean LVEF was 21% and ischemic CMP was detected in 55% of patients. The study was prematurely terminated because both device arms improved the primary endpoint. The 12-month rate of death from any cause or hospitalization for any cause was 68% in the pharmacologic therapy group as compared with 56% in the CRT group (HR 0.81, 95% CI 0.69-0.96, p = 0.014) and 56% in the CRT-D group (HR 0.80, 95% CI 0.68-0.95, p = 0.010). For the secondary endpoint, there were 77 deaths (25%) in the pharmacologic therapy group, 131 deaths (21%) in the CRT group (HR 0.76, 95% CI 0.58-1.01, p = 0.0059), and 105 deaths (18%) in the CRT-D group (HR 0.64, 95% CI 0.48-0.86, p = 0.003). The conclusion of the COMPANION trial is that in patients with advanced heart failure and a prolonged QRS interval, CRT decreases the combined risk of death from any cause or first hospitalization and, when combined with an implantable defibrillator, significantly reduces mortality. The Cardiac Resynchronization Heart Failure (CARE-HF) study[20] should have the power to determine whether biventricular pacing alone can improve survival. The COMPANION results should lead to an expanding role for biventricular pacing-ICDs in similar types of patients (Table I).

Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). SCD-HeFT was a prospective, randomized trial to test the hypothesis that amiodarone or an ICD will improve survival compared to placebo in patients with systolic dysfunction (LVEF < 35%) from ischemic or non-ischemic causes, heart failure duration of at least 3 months, stable NYHA class II or class III, and no previous history of sustained ventricular arrhythmia[21]. The primary endpoint was all-cause mortality based on a minimum of 2.5 years of follow-up. The secondary endpoints included arrhythmic mortality, non-arrhythmic cardiac mortality, and morbidity. A total of 2521 patients were enrolled; 847 were randomly assigned to placebo plus conventional heart failure therapy, 845 to amiodarone plus conventional heart failure therapy, and 829 to single-lead ICD plus conventional heart failure therapy. Mean age was 59.5 years. Men comprised 77%

of the study population. Mean LVEF was 23.8%. Ischemic CMP was present in 52% of patients. Single-lead, shock-only defibrillators were used in all patients in the ICD group. During a median follow-up of 45.5 months there was a significant reduction in mortality in the ICD group compared to the placebo and amiodarone groups (HR 0.77, 95% CI 0.62-0.96, p = 0.007). The benefit was the highest in patients with QRS duration ≥ 120 ms or LVEF ≤ 30%, and in NYHA class II patients. Main conclusion of SCD-HeFT is that amiodarone therapy does not improve survival with respect to placebo plus optimal drug treatment, while ICD significantly ameliorates prognosis in comparison to placebo and amiodarone treatments, irrespective of substrate. These results will have an effect on future guideline recommendations (Table I).

Conclusion

The application of lifesaving ICD technology continues to evolve with the completion of multiple randomized clinical trials. Recent data from SCD-HeFT strongly support the MADIT II indication for ICDs, especially for patients with LVEF < 30%. This will warrant a class I indication for MADIT II patients. Waiting for all the subanalysis of SCD-HeFT (most of which had prospective endpoint) it seems reasonable, given a 23% reduction in mortality in the overall group, to give a class IIa indication for ICDs in patients meeting SCD-HeFT criteria. Finally, considering the results of the COMPANION trial, the role of biventricular pacemaker plus ICD will expand in the near future. This data should warrant at least a class IIa indication in incoming guidelines. The further of controversy in terms of superiority of biventricular pacemaker plus ICD vs biventricular pacemaker alone may wait for the results of the CARE-HF study.

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