More on the pathophysiology and prevention of sudden death - Part II: ICD treatment

(Ital Heart J 2004; 5 (Suppl 1): 103S-107S)

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PRIMARY PREVENTION OF SUDDEN DEATH BY THE IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR CURRENT STATUS

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While major prospective randomized trials have established the role of the implantable cardioverter-defibrillator (ICD) for secondary prevention of sudden cardiac death in patients having survived an episode of life-threatening ventricular tachycardia or ventricular fibrillation, this is true for primary prevention of sudden death in asymptomatic patients only under welldefined circumstances. This article describes the entry criteria for studies on patients with coronary artery disease in whom a benefit of ICD implantation has been shown for primary prevention of sudden cardiac death, specifically MADIT, MUSTT and MADIT II. Special emphasis is placed on description of the type of patients included in MADIT, MUSTT and MADIT II. This analysis reveals that ICD implantation is established based on these studies only in patients in the chronic phase of coronary artery disease when special prerequisites are met, and that these results cannot be extrapolated to the patient after acute myocardial infarction. This patient population is under investigation, however, in current ICD trials.

Introduction

Three major prospective randomized trials have established the role of the implantable cardioverter-defibrillator (ICD) for secondary prevention of sudden cardiac death¹⁻³. This article concentrates on ICD implantation for primary prevention of sudden death in patients with coronary artery disease with emphasis on the time frame of coronary artery disease in the patients who were included in the trials.

The Multicenter Automatic Defibrillator Implantation Trial

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) was the first proof of the concept that primary prevention of sudden cardiac death by ICD implantation is possible⁴. In essence, a highly selected group of patients with myocardial infarction in the past, left ventricular ejection fraction $\leq 35\%$ and asymptomatic/ non-syncopal non-sustained ventricular tachycardia was studied. In order to be recruited, a sustained ventricular tachyarrhythmia had to be induced during baseline invasive electrophysiologic evaluation and inducibility not being suppressible by intravenous administration of procainamide. Patients with myocardial infarction within the past 3 weeks were excluded from enrolment, and the time interval between myocardial infarction and study entry was > 6 months in 75-76% of cases. No attempt was undertaken in this trial to assess the denominator of patients from whom the very small sample size of 196 patients was drawn.

The Multicenter Unsustained Ventricular Tachycardia Trial

Nevertheless, the results of the MADIT were confirmed by the Multicenter Unsustained Ventricular Tachycardia Trial (MUSTT) in 1999⁵. While several drawbacks of the former study were eliminated, MUSTT also included patients (underlying heart disease, coronary artery disease, left ventricular ejection fraction $\leq 40\%$, pres-

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ence of asymptomatic non-sustained ventricular tachycardia, induction of a sustained ventricular tachyarrhythmia in a baseline electrophysiologic study) mostly in the chronic phase after myocardial infarction: only 18% of the study population in MUSTT was included in the time frame between day 4 and 1 month after the most recent myocardial infarction, 38% within 1 year, and 52% after 3 years⁶.

The Multicenter Automatic Defibrillator Implantation Trial II

Very recently, the MADIT II demonstrated a significant survival benefit of a prophylactically implanted defibrillator in patients with remote myocardial infarction selected exclusively on the basis of a reduced left ventricular ejection fraction $\leq 30\%^7$. Of special note, patients with myocardial infarction within 1 month were not included, and the interval between the most recent myocardial infarction and enrolment was > 6 months in 87-88% of cases⁷.

Knowing that the risk of dying is highest in the first weeks and months after myocardial infarction⁸, it can be conceived that many more patients could be protected by implantation of an ICD early after myocardial infarction. This, however, cannot be derived from MADIT, MUSTT and MADIT II since these trials did not include a relevant number of patients after acute myocardial infarction. Recently, an interesting subgroup analysis was reported for the MADIT II population in abstract form with respect to the time-dependence of mortality risk and defibrillator benefit following myocardial infarction9. Dividing the patients into four quartiles according to time after myocardial infarction (quartile 1: month 1 to 17 after myocardial infarction, quartile 2: month 18 to 59, quartile 3: month 60 to 121, quartile 4: > 121 months), the mortality risk increased from 15.6% in quartile 1, to 15.8% in quartile 2, 21.1% in quartile 3, and finally 26.7% in quartile 4, all in the conventionally treated group. A clear-cut benefit of ICD implantation was apparent only in quartiles 2, 3 and 49.

This subgroup analysis is remarkable in two respects: • mortality of patients increased with longer time elapsed between index myocardial infarction and recruitment for study;

• ICD implantation had no benefit in patients recruited 1 to 17 months after myocardial infarction.

Hence, MADIT II results cannot at all be taken to justify ICD implantation in the first 1.5 years after myocardial infarction. Secondly, the increase in mortality with time after myocardial infarction in the MADIT II population, while a decrease would be expected in unselected populations⁸, indicates a selection bias in the MADIT II population, with outcome not primarily being determined by the status after myocardial infarction, but by other factors such as previous bypass surgery, heart failure or other predictors not being determined.

The patient after acute myocardial infarction

The role of ICD implantation for primary prevention of sudden cardiac death and improvement of outcome after acute myocardial infarction can only be determined by prospective randomized trials including exactly these patients. The risk of ICD implantation might be increased early after myocardial infarction. While a pilot study on 33 patients seems to indicate that this is not the case¹⁰, the safety of the procedure must be demonstrated in large groups of patients. Three trials have been initiated to determine the role of the ICD in this patient population.

The Beta-Blocker Strategy Plus Implantable Cardioverter Defibrillator Trial uses reduced left ventricular function (ejection fraction $\leq 35\%$) and SDNN < 70 ms, ≥ 10 premature ventricular contractions per hour or an abnormal signal-averaged ECG; tolerance of beta-blocker therapy is a prerequisite for inclusion, presence of nonsustained ventricular tachycardia a criterion for exclusion¹¹. Unfortunately, because of poor patient recruitment, this trial was terminated prematurely.

The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) uses for inclusion reduced left ventricular function (ejection fraction $\leq 35\%$) and impairment of cardiac autonomic function by depressed heart rate variability (SDNN ≤ 70 ms, or elevated average 24hour heart rate measured as mean 24-hour AA interval ≤ 750 ms by Holter monitoring)¹².

The Immediate Risk Stratification Improves Survival (IRIS) study compares ICD therapy with no ICD therapy in selected high risk patients early after myocardial infarction. Special emphasis is placed on optimal acute and long-term medical therapy in all patients including metoprolol CR/Zok. The hypothesis is tested that use of the ICD reduces overall mortality. For that purpose, consecutive acute ST elevation or non-ST elevation myocardial infarction patients are collected in a registry. From this denominator, patients are screened, and enrolled early after myocardial infarction (day 5 to day 31) if they exhibit both a reduced left ventricular ejection fraction $\leq 40\%$ and a heart rate > 100 b/min on the first available ECG (criterion I), or non-sustained ventricular tachycardia at a rate > 150/min during Holter (criterion II).

A flow chart of IRIS is depicted in figure 1.

In conclusion, DINAMIT and IRIS are two large scale prospective, randomized trials to evaluate the benefit of ICD therapy for primary prevention of sudden cardiac death in patients considered at high risk early after



Figure 1. *Flow-chart of the IRIS study. EF* = *ejection fraction; ICD* = *implantable cardioverter-defibrillator.*

acute myocardial infarction, and any conclusion regarding this mode of therapy must await the advent of these trial results in the years to come.

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IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR THERAPY AND CONGESTIVE HEART FAILURE

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Congestive heart failure (CHF) is one of the most important healthcare problems in the world because of the large size of the affected population. Despite pharmacological advances, mortality of CHF patients, due to progressive pump failure or ventricular tachyarrhythmias, remains high.

The efficacy of implantable cardioverter-defibrillators (ICDs) for primary and secondary prevention of sudden cardiac death has been well documented by several clinical trials even though they have not specifically targeted heart failure population. Nevertheless patients involved in the ICD trials were similar to patients suffering from CHF and involved in clinical trials with pharmacological therapy and the majority of them had a clinical history of heart failure and were in NYHA functional class II or III with a low o very low left ventricular ejection fraction (< 35%).

Cardiac resynchronization therapy (CRT) has been documented to significantly improve cardiac performance in patients with severe drug-refractory CHF and QRS enlargement (> 150 ms). The question remaining is whether to implant a device with pacemaker function only (CRT-P) or to include defibrillation therapy (CRT-ICD). In the COMPANION trial both CRT-P with pharmacological therapy and CRT-ICD with optimal pharmacological therapy demonstrated a statistically significant reduction in the composite endpoints (20%) while in the total mortality, that was the secondary endpoint, CRT-ICD demonstrated a greater reduction (43.4%) compared with CRT-P and pharmacological therapy (24%) and with optimal pharmacological therapy only (19%). This implies that defibrillator therapy conferred additional benefit over CRT alone in the total mortality.

Congestive heart failure (CHF) is one of the most important healthcare problems in the world because of the large size of the affected population. Nearly 6.5 million people in Europe and 5 million people in the United States currently suffer from CHF, especially in the very elderly, with an approximately 1 million new cases of CHF per year, making it the most rapidly growing cardiovascular disorder. The growing incidence of this syndrome reflects the increase in the mean age of the general population and the reduction of the mortality in patients suffering from acute coronary syndromes¹.

Despite advances in pharmacological therapy (ACEinhibitors, beta-blockers), mortality rate remains high, 5-15% per year in NYHA class I-II patients and 30-70% in NYHA class III-IV patients, as documented by epidemiological data and multicenter clinical trials.

The main causes of cardiac death in CHF patients are progressive worsening of functional performance of the heart, especially in NYHA class III-IV patients, and malignant ventricular tachyarrhythmias, especially in NYHA class II patients in which the risk of dying suddenly has been estimated at 50-60%. Clinical implications of these data are relevant considering that the identification of CHF patients at high arrhythmic risk will allow us to provide adequate systems, in particular implantable cardioverter-defibrillators (ICDs), for the primary prevention of sudden cardiac death (SCD) and to increase the life expectancy of those patients that have still a discrete quality of life.

The efficacy of ICDs for primary and secondary prevention of SCD has been well documented by several clinical trials²⁻⁵. Even though these randomized trials for ICDs have not specifically targeted heart failure population, some considerations of particular clinical value may derive from these: patients involved in the ICD trials were similar to patients suffering from heart failure involved in clinical trials with pharmacological therapy; two thirds of patients had a clinical history of heart failure with symptoms that may be referred to NYHA class II or III and significant depressed ventricular function (the left ventricular ejection fraction -LVEF - was between 25 and 35%); 50% of patients were in treatment with diuretics and ACE-inhibitors; almost 40% patients were taken digoxin at therapeutic dosages.

The AVID study (Antiarrhythmics Versus Implantable Defibrillators), comparing ICD therapy to antiarrhythmic drug treatment (empiric amiodarone-sotalol guided by electrophysiologic study) in survivors of life-threatening ventricular arrhythmias, documented that the improved survival with ICD as compared with antiarrhythmic drug therapy was statistically significant in patients with moderate to severe left ventricular dysfunction, while in patients with relatively well preserved left ventricular function (LVEF > 35%) the survival of patients treated with antiarrhythmic drug therapy and drug therapy may be modulated by the degree of left ventricular dysfunction².

In the CIDS study (Canadian Implantable Defibrillator Study), that compared ICD therapy with amiodarone, the study population was divided into quartiles of risk based on age, LVEF and functional class. ICD therapy produced a 50% reduction in death in the highest-risk quartile patients that were patients with advanced age, LVEF < 35% and poor NYHA functional class (III-IV), but conferred no benefit in the three lower-risk quartiles³.

In the MADIT (Multicenter Automatic Defibrillator Implantation Trial), that was the first prospective randomized trial to investigate the role of ICDs for primary prophylaxis of SCD in patients with prior myocardial infarction (3 weeks from the last myocardial infarction), unsustained ventricular tachycardia (mean 9-10 consecutive beats) on Holter monitoring, inducible nonsuppressible ventricular tachycardia by procainamide, LVEF < 35% and NYHA class I-III, the survival benefit of ICD therapy was almost entirely confined to patients with LVEF < 0.25^4 .

The MADIT II was the latest completed and published trial for primary prevention of SCD in patients with prior myocardial infarction and LVEF $\leq 30\%$. Patients (n = 1132) were randomized to receive an ICD or conventional medical therapy, trying the use of any antiarrhythmic drugs. For the average follow-up of 20 months, the mortality rates were 19.8% in the conventional therapy group and 14.2% in the ICD group with statistical difference between the two groups⁵. The concept of this trial was that ICD may provide clinicians with a powerful tool to prevent SCD in many high-risk patients and that patients with myocardial infarction and reduced left ventricular function are at high risk for CHF and arrhythmia-related SCD.

Recently, prospective randomized clinical trials⁶⁻¹⁰ demonstrated the benefits in cardiac performance and symptoms of cardiac resynchronization therapy (CRT) by simultaneous biventricular pacing at optimal atrioventricular delay in patients with severe drug-refractory CHF and QRS enlargement (> 150 ms). The positive hemodynamic effects were related to a restoration of ventricular contractile synchrony, resynchronization of ventricular septal motion, reduction of mitral regurgitation and prolongation in ventricular diastolic filling time; long-term clinical benefits were an improvement in functional capacity (as measured by peak oxygen consumption and 6-min walk) and in quality of life, a reduction of the CHF symptoms and the number of hospitalization as well, making patients feel better.

Considering the positive impact on cardiac performance, it has been postulated that biventricular pacing therapy might itself have antiarrhythmic effects through the elimination of the main factors that are related to the induction of malignant ventricular tachyarrhythmias, such as decrease in ventricular conduction delays, contributing to a decrease in macroreentry, avoidance of pause-dependent tachyarrhythmias, decrease in plasma catecholamine levels, reduction of frequency of premature ventricular beats, improvement of heart rate variability, increase of the electrical stability in the heart, reduction of left ventricular dimensions, and improvement of hemodynamic performance of the heart. However, it remains unknown what impact this novel and very attractive therapy may have on survival of patients with CHF, considering that in some retrospective and prospective trials, performed in patients with CHF refractory to medical therapy and submitted to permanent biventricular pacing, SCD due to ventricular tachyarrhythmias occurred during the follow-up with an incidence between 3-9% of the implanted patients.

So the question remaining is whether to implant a device with pacemaker function only or to include defibrillation therapy in CHF patients considered as candidates for biventricular pacing.

The impact of CRT in the treatment of CHF patients and the need for the contemporary use of an ICD in these patients were the objective of the COMPANION trial (Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure)¹¹. This was a randomized controlled study using three treatment arms. Patients were randomized to optimal pharmacological therapy alone, CRT plus optimal pharmacological therapy (CRT-P) or CRT with defibrillator backup (CRT-ICD) in addition to optimal pharmacological therapy. Inclusion criteria were symptomatic heart failure, NYHA class III or IV, prior heart failure hospitalization in the 12 months before enrolment, QRS duration > 120 ms, PR interval > 150 ms and LVEF < 35%.

The trial was terminated prematurely and the preliminary results were reported at the American College of Cardiology meeting in Chicago. Both CRT-P and CRT-ICD with optimal pharmacological therapy demonstrated a statistically significant 19% reduction in the composite endpoints (all-cause mortality and all-cause hospitalization) compared with optimal pharmacological therapy only. There was a non-significant 23.9% reduction in all-cause mortality with CRT-P, but a significant 43.4% reduction in all-cause mortality (secondary endpoint) with addition of the defibrillator (CRT-ICD). In this study long-term mortality benefit in patients with severe heart failure was maximized with combination of CRT to defibrillation therapy.

In conclusion, biventricular pacing with optimized atrioventricular delay, in combination with optimal pharmacological therapy, may be considered a novel interesting treatment in moderate-to-severe CHF patients with intraventricular conduction delay. It allows to improve functional status of the heart and quality of life of patients and to relieve symptoms related to heart failure. Until now, it is questionable if a defibrillator backup could find a rational indication in all CHF patients submitted to biventricular pacing and not only in those at high risk for SCD. High cost of the electrical system could not be considered a problem if the positive effects of this novel and very attractive therapy will be confirmed by other ongoing trials.

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