

# Implantable Cardioverter-Defibrillator Therapy for Primary Prevention of Sudden Cardiac Death

C Jarman, L Wang

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## Abstract

Primary prevention trials have focused on differing sub-groups of patients at high-risk of sudden cardiac death (SCD) and this includes patients with coronary artery disease (CAD), a history of myocardial infarction, congestive heart failure (CHF), and ventricular arrhythmias on electrophysiology study or with a non-sustained episode of ventricular tachycardia on Holter and/or in hospital monitoring, and syncope from unidentified causes and patients with differing forms of cardiomyopathy. The purpose of this article is to provide an up-to-date review of the use of an implantable cardioverter-defibrillator (ICD) in the primary prevention of SCD based on information obtained from randomised clinical trials, particularly in those focusing on high-risk patients with CAD.

## INTRODUCTION

Sudden cardiac death (SCD) resulting from fatal ventricular arrhythmias is one of the most common causes of death in the developed world. Patients suffering from a potentially fatal arrhythmia are at risk of death before they even reach medical intervention and out-of-hospital survival rates are as low as 2-15% (1). Immediate defibrillation treatment is the only remedy for arrhythmic sudden death caused by hemodynamically compromising ventricular tachycardia (VT) and ventricular fibrillation (VF) (2). The implantable cardioverter-defibrillator (ICD) has seen dramatic changes in design to accommodate its role in preventing sudden cardiac death, particularly given the fact that anti-arrhythmic drug therapy has proven to be of limited use and in some instances increased the risk of death (3). This said, it is still universally accepted that treatment with beta-blockers and ACE-inhibitors reduce the risk of sudden cardiac death and should therefore be administered to those patients that are not contraindicated (4, 5).

Of those patients who do survive a potentially fatal arrhythmia, the implantation of an ICD has proved invaluable to their continued survival as these patients are at an especially high-risk of ventricular arrhythmia recurrence. A number of randomised trials, the Antiarrhythmics Versus Implantable Defibrillators (AVID), Cardiac Arrest Study Hamburg (CASH), and the Canadian Implantable Defibrillator Study (CIDS) have been conducted to assess

the role of ICDs in the secondary prevention of SCD and have proven to be effective with a reduction in all-cause mortality of 20-30% (6,7,8). Given the large battery of trials supporting the use of the ICD in the secondary prevention of SCD, further trials have been envisioned to assess the use of an ICD in the primary prevention of SCD to address the large number of patients who have not experienced fatal arrhythmias before ICD therapy. Addressing the question of who should be prophylactically implanted with an ICD in order to prevent SCD is one that can not be answered easily, and ethical considerations should not be overlooked when contemplating the use of such a device for treatment.

## INDICATIONS FOR ICD THERAPY

The American College of Cardiology/American Heart Association and North American Society for Pacing and Electrophysiology (ACC/AHA/NASPE) recognises that there are a number of conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective (Class 1) (9). Table 1 lists the ACC/AHA/NASPE class 1 indications for ICD therapy. Further to this, ICD has also been commonly used in the prophylactic prevention of SCD for conditions such as long QT syndrome, Brugada syndrome, idiopathic VF, arrhythmogenic right ventricular dysplasia and hypertonic cardiomyopathy (1).

**Figure 1**

Table 1: 2002 ACC/AHA/NASPE class 1 indications for ICD therapy

1. Cardiac arrest due to ventricular fibrillation (VF) or VT not due to a transient or reversible cause.
2. Spontaneous sustained VT in association with structural heart disease.
3. Syncope of undetermined origin with clinically relevant, haemo-dynamically significant sustained VT or VF induced at electrophysiological study when drug therapy is ineffective, not tolerated, or not preferred.
4. Non-sustained VT in patients with coronary disease, prior myocardial infarction (MI), LV dysfunction, and inducible VF or sustained VT at electrophysiological study that is not suppressible by a Class I antiarrhythmic drug.
5. Spontaneous sustained VT in patients who do not have structural heart disease that is not amenable to other treatments.

## CLINICAL TRIALS

In the last decade also, a large amount of information has been available in the investigation of the uses of an ICD, particularly in regards to the prevention of sudden death from cardiac causes. Initial trials of this nature focused on patients at an increased risk of sudden cardiac death, based on a combination of low ejection fraction, and additional risk markers (5). While initial trials pertain exclusively to small numbers of patients due to restricted patient selection criteria, later trials used more simplified entry criteria and hence broadened the horizons for ICD indications.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) was the first completed randomised primary prevention trial which investigated whether prophylactic therapy with an ICD would improve survival rates in high-risk patients with coronary artery disease when compared with conventional medical therapy (10). A total of 196 patients were included in the two-sided sequential designed trial with death from any cause as the primary end point (10). MADIT reported that patients that were randomly assigned to ICD therapy with a previous myocardial infarction, a left ventricular ejection fraction < 0.35, a documented episode of asymptomatic unsustained ventricular tachycardia and inducible, non-suppressible ventricular tachyarrhythmia on electrophysiology study, were shown to have improved survival rates (54% reduction in mortality) when compared with medical therapy (10). The weakness of this study is that the study involved a small number of patients and there was a lack of treatment with beta-blockers and ACE inhibitors (5).

Investigators of the Multicenter Unsustained Tachycardia Trial (MUSTT) tested the hypothesis that antiarrhythmic therapy guided by electrophysiological testing reduces the risk of sudden cardiac death in a total of 704 patients with coronary artery disease and ejection fraction of < 0.4, with inducible, sustained ventricular tachycardia at

electrophysiology study (11). In this randomised trial, patients were assigned to receive either antiarrhythmic therapy, consisting of the administration of antiarrhythmic drugs or an ICD, or no antiarrhythmic therapy (11). The primary end point in this trial was cardiac arrest or death from arrhythmia. MUSTT verified the hypothesis that electrophysiological guided antiarrhythmic therapy reduces the risk of SCD in high-risk patients with coronary artery disease and concluded that therapy with an ICD was useful and superior to treatment with antiarrhythmic drugs in the primary prevention of SCD (11).

The effect of prophylactic implantation of an ICD on survival rates in patients with coronary heart disease, a depressed left ventricular ejection fraction and an abnormal signal-averaged electrocardiogram was assessed in the Coronary Artery Bypass Graft (CABG) Patch Trial, in which an ICD was randomised for implantation in 446 patients at the time of elective bypass surgery (12). The remainder of the 900 patients randomised for the trial (454 patients) was assigned to CABG surgery alone (CABG Patch 1997). The CABG Patch trial found no evidence of improved survival among the patients implanted with an ICD (12). While this study showed no added benefit of ICDs to surgical revascularisation, this may be due to the positive antiarrhythmic effect that CABG surgery has on patients at high-risk of ventricular arrhythmias (2, 3, 5, 11).

In the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II), 1,232 patients with a prior myocardial infarction and a left ventricular ejection fraction of < 0.3 were randomised to either implantation of an ICD (n = 742) or conventional medical therapy (n = 490) (3:2 ratio) to assess if the prophylactic implantation of a defibrillator would reduce all-cause mortality (12). Compared to previous primary prevention trials, MADIT II did not require invasive electrophysiological testing for risk stratification (3). Death from any cause was selected as the end point for the trial. The findings of MADIT II proved that the implantation of a defibrillator in patients with a previous MI and a reduced ejection fraction improves survival rates (12%, 28%, 28% relative reduction in mortality at 1, 2, and 3-years, respectively) and as a result recommends the use of an ICD in the primary prevention of SCD in this population subgroup (13).

A relatively recent trial, the defibrillator in acute myocardial infarction trial (DINAMIT), investigated the prophylactic use of an ICD after acute myocardial infarction to assess any

mortality benefit that may exist (<sub>13</sub>). A total of 674 patients was randomised to both the ICD or control group with 332 and 342 patients in each group; respectively. Of note was that 20 patients randomised to ICD therapy refused implantation, and exclusion of these patients from the study is suspected, however confirmation of this is not certain at this juncture (<sub>14</sub>). The patients enrolled in the study had a myocardial infarction documented as no less than 6 and no greater than 40 days with an average time from myocardial infarction to randomisation in the two groups of 18 days. A left ventricular ejection fraction  $\leq 0.35$  was also required for entry with a reported mean left ventricular ejection fraction of 0.28 (<sub>14</sub>).

The primary outcome in DINAMIT was death from any cause. Death due to cardiac arrhythmia was reported as being the secondary outcome. The results of this trial insinuates that while a statistically significant reduction in arrhythmia mortality occurred with implantation of an ICD when compared to control group (annual death rate, 1.5% and 3.5%, respectively), this is offset by the significantly increased rate in the ICD group from death from cardiac, nonarrhythmic causes when compared to the control. This led to the conclusion that prophylactic implantation does not reduce overall mortality in high-risk patients who have recently had a myocardial infarction (<sub>14</sub>). The reason given to the similar differences in magnitude in opposite directions for the two groups is concisely explained by Hohnloser et al (<sub>14</sub>) when they suggest that 'that the patients "saved" from an arrhythmia related death by ICD therapy are also at risk for death from other cardiac causes'. The authors, however, noted their uncertainty when explaining the unprecedented increase in mortality from nonarrhythmic causes of death (<sub>14</sub>).

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) remains one of the latest and largest randomised trials on the clinical effects of ICD therapy in the prevention of SCD. This largely awaited trial enrolled patients during the period from September 1997 to July 2001 and randomly assigned the 2,521 participants in relatively equal proportions to receive placebo (n = 847), amiodarone (n = 845), or a single-chamber ICD (n = 829) (<sub>15</sub>). In this trial, patients were followed every three months until October 2003 and death from any cause was the primary end point. Entry into the trial required the subject to be classified as having New York Heart Association (NYHA) class II or III heart failure and a left ventricular ejection fraction of  $\leq 0.35$ . The trial reported that placebo and amiodarone was

associated with a similar risk of death (hazard ratio, 1.06; 97.5 % confident interval, 0.86 to 1.30; P = 0.53) and further concluded that single-lead, shock-only ICD therapy resulted in a decreased risk of overall mortality of 23 % (hazard ratio, 0.77; 97.5 % CI, 0.62 to 0.96; P = 0.007) (<sub>15</sub>).

## CONCLUSIONS AND FUTURE PERSPECTIVES

ICDs reduce mortality and improves prognosis of patients susceptible to SCD. The use of an ICD has become a mainstay treatment option for the management of patients at an increased risk of sudden cardiac death. ICD implantation indications have broadened to include high-risk patients with coronary artery disease and reduced left ventricular ejection fraction in the primary prevention of SCD. Special mention should be given to the prophylactic implantation of an ICD at the time of a coronary artery bypass graft and in patients with a recent acute myocardial infarction, as implantation at this time doesn't appear to be warranted based on recent findings. Despite this, the growing trend of broadening indications for ICD implantation in the primary prophylaxis of SCD is necessary to move forward in the elusive task of reducing mortality from a condition that is accepted as one of the leading causes of death in the world today.

## CORRESPONDENCE TO

Lexin Wang, M.D., Ph.D., School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, NSW 2678, Australia. Tel: +61 2 69332905, Fax: +61 2 69 332587, E-mail: lwang@csu.edu.au

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**Author Information**

**Clinton G. Jarman, B.Sc.**

Central Coast Respiratory Services

**Lexin Wang, MD, PhD**

School of Biomedical Sciences, Charles Sturt University