

# Saving lives and reducing inappropriate device therapy: The MADIT family of implantable cardioverter-defibrillator and cardiac resynchronization therapy trials

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## Introduction

In 1980, Mirowski et al. [1] reported the first 3 patients treated with an automatic implantable defibrillator (AID). At that time, the AID was implanted with electrodes attached to the epicardium through a surgical thoracotomy with the battery portion of the unit placed under the skin in the abdominal wall. The AID detected the onset of ventricular fibrillation through a unique algorithm and the device was considered a “shock box” since shock was the only therapy delivered. The U.S. Food and Drug Administration (FDA) initially provided approval for use of the AID device in high-risk cardiac patients who had been resuscitated from a prior aborted cardiac arrest.

Around the same time frame, Medtronic developed a pacing approach (antitachycardia pacing [ATP]) to terminate rapid ventricular tachycardia (VT) by delivering a series of appropriately timed pacing stimuli in the interval between the QRS and T-wave complexes of the tachycardia (review article [2]). This pacing technique was effective in terminating VT in a majority of patients with ventricular tachyarrhythmias. However, this ATP approach produced acceleration of VT and even ventricular fibrillation and sudden death in a small percentage of patients, and ATP therapy was not approved by the FDA as a stand-alone therapy.

The AID was initially developed by Drs. Mirowski and Mower in association with Dr. M. Stephen Heilman at the Medrad/Intec Company

in Pittsburgh, Pennsylvania, and the implantable defibrillator was subsequently sold to CPI/Guidant Corporation in 1985. Although CPI/Guidant and Medtronic were competitors in the pacemaker field, both companies recognized the need for a device with tiered therapy that would include ATP and defibrillation. Through a cooperative agreement, CPI/Guidant and Medtronic jointly agreed on a device involving ATP and shock therapy, called the automatic implantable cardioverter defibrillator (AICD) for treating patients at risk for life-threatening VT and/or ventricular fibrillation.

## The first MADIT trial

Although the AICD was effective in terminating ventricular tachyarrhythmias, it was unclear how effective it really was in saving lives in the absence of a randomized clinical trial. This point was driven home by the Cardiac Arrhythmia Suppression Trial (CAST) that was initially reported in abstract form in 1989 [3] and published in 1991 [4]. This randomized trial included a number of antiarrhythmic drugs including flecainide and encainide that previously were shown to suppress ventricular ectopic beats. In the randomized antiarrhythmic drug trial, these medications were associated with an increased mortality when compared to conventional medical management, and the trial was stopped prematurely [4]. On the basis of the CAST trial, our multicenter group proposed to CPI/Guidant Corporation a randomized defibril-

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lator trial comparing the AICD to conventional drug therapy. The trial, called the Multicenter Automatic Defibrillator Implantation Trial (MADIT), was initiated in 1990 and involved 196 high-risk coronary patients with an ejection fraction  $\leq 30\%$ , documented asymptomatic non-sustained VT, and inducible, sustained, nonsuppressible ventricular tachyarrhythmia on electrophysiologic testing. These stringent, high-risk enrollment criteria were utilized since the AICD required a surgical thoracotomy and the randomized control group received conventional medical therapy and no thoracotomy. The results of this trial were reported in 1996 with a 54% reduction in mortality when comparing the AICD to conventional therapy (hazard ratio [HR] 0.46,  $p = 0.009$ ) [5]. The publication of this MADIT trial ushered in the AICD era.

### MADIT-II

The implantation of the AICD using transvenous electrodes became available in 1994, and we initiated the MADIT-II trial in 1997 to evaluate the survival benefit of prophylactic transvenous AICD in 1232 patients with a prior myocardial infarction and a left ventricular ejection fraction (LVEF)  $\leq 30\%$ . Patients were excluded from enrollment if they had coronary revascularization within the past 3 months or an acute myocardial infarction in the past month. This MADIT-II study, published in 2002, was associated with a 31% reduction in the risk of death in the AICD-treated patients as compared with patients in the conventional-therapy group (HR 0.69,  $p = 0.016$ ) [6]. Secondary analyses revealed that patients who experienced overt heart failure (HF) during the clinical trial were at the greatest risk for developing life-threatening ventricular tachyarrhythmias and achieved a greater benefit from the AICD [7].

### MADIT-CRT

Since HF contributed significantly to the risk of arrhythmic events, our MADIT Executive Committee decided to try and reduce the likelihood of developing HF with cardiac resynchronization therapy (CRT) in cardiac patients with mild-to-moderate HF. The randomized MADIT-CRT trial began in January 2003 and enrolled 1820 patients with NYHA Class I or II HF, LVEF  $\leq 30\%$ , and a QRS duration of  $\geq 130$  ms. MADIT-CRT was published in 2009 [8]. During an average follow-up of 2.4 years, CRT-D therapy was associated with a 34% reduction in death or HF, whichever came first, as compared to patients receiving implan-

table cardioverter-defibrillator (ICD)-only therapy (HR 0.66,  $p = 0.001$ ). The benefit associated with CRT-D was dominated by the reduction in HF events.

### MADIT-RIT

During the aforementioned MADIT trials and in a spectrum of device studies by other investigators, it was noted that inappropriate ICD or CRT-D therapies were frequent, with the potential for adverse effects. The definition of inappropriate therapy refers to ATP or shock therapy delivered for atrial tachyarrhythmias rather than for ventricular tachyarrhythmias. Beginning in 2009, we enrolled 1500 patients with a primary-prevention indication to receive an ICD or CRT-D devices with randomization to one of 3 programming configurations to determine which programming approach was most effective in reducing inappropriate therapy. This trial called MADIT-Reduce Inappropriate Therapy (MADIT-RIT) was published in 2012 and showed that device programming for therapy at a high tachycardia rate ( $\geq 200$  bpm) was associated with a significant 79% reduction in first occurrence of inappropriate therapy and a significant 55% reduction in death as compared to conventional programming group with therapy beginning at 170 bpm with 2.5 s delay [9]. Similar but less significant findings were observed when comparing inappropriate therapy in the delayed therapy group (60 s delay before firing at 170 bpm) to the conventional therapy group. In the overall trial, the improved programming was associated with a 6 to 8-fold reduction in inappropriate ATP and a 2 to 4-fold reduction in inappropriate shock therapy. More specifically, the total inappropriate shock energy delivered during the course of the trial was 3,714 joules in the conventional therapy group, 868 joules in the high-rate group, and 1,698 joules in the delayed therapy group.

### Clinical implications of MADIT-RIT

The clinical implications of the MADIT-RIT trial are that inappropriate ATP delivered for atrial tachycardias and unnecessary shock therapy for VTs in the 170 to 199 bpm range are risky, and elimination of these therapies is associated with reduced mortality. Clearly, the existing device algorithms for distinguishing between supraventricular tachycardia (sinus tachycardia, atrial tachyarrhythmias, atrial flutter/fibrillation) and ventricular tachyarrhythmias do not work well. In addition, ATP and shock therapy for non-sustained VT in the 170–199 bpm range is not needed and

can be considered unnecessary. It should be emphasized that this improved programming that was demonstrated in MADIT-RIT reduced mortality by 55% on top of the previously documented 31% reduction in mortality in ICD-treated patients that was shown in MADIT-II [6]. This improved ICD programming is already being accepted by leaders in field [10].

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