



MADIT-CRT Media Backgrounder

Trial Results

MADIT-CRT trial results were published in the *New England Journal of Medicine* and presented during a Hot Line session at the European Society of Cardiology (ESC) Congress in Barcelona, Spain on September 1st 2009.

The trial showed that Boston Scientific's cardiac resynchronization therapy defibrillators (CRT-Ds) were associated with a 34 percent relative reduction in the risk of all-cause mortality or first heart failure event in asymptomatic and mild (NYHA Class I and II¹) heart failure patients when compared to standard implantable cardioverter defibrillators (ICDs) ($p=0.001$).

In addition, MADIT-CRT data showed that:

- CRT-D therapy reduces the relative risk of heart failure intervention by 41 percent when compared to ICD therapy ($p < 0.001$).
- Patients treated with CRT-D therapy showed an improvement of 11 percent in left ventricular ejection fraction² as compared to a three percent improvement for ICD patients after one year.

Trial Overview:

The Multicenter Automatic Defibrillator Implantation Trial - Cardiac Resynchronization Therapy (MADIT-CRT), sponsored by Boston Scientific, is the largest randomized, NYHA Class I/II CRT-D trial to date, with more than 1800 patients enrolled at 110 centers in 14 countries.

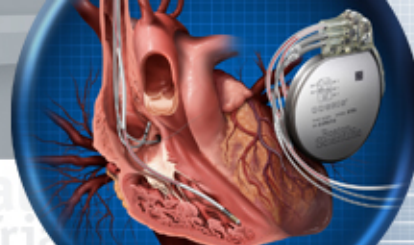
The Principal Investigator is Dr. Arthur Moss, University of Rochester, New York. Co-Principal Investigators are Dr. David Cannom and Dr. Helmut Klein.

Enrollment began in December 2004, and concluded April 24, 2008. MADIT-CRT was concluded in June 2009 when the primary endpoint was met.

MADIT-CRT was designed to assess whether early intervention with CRT-D for patients receiving optimal medical therapy can slow the progression of heart failure versus use of defibrillation therapy alone.

¹ MADIT-CRT patients are high risk (asymptomatic or mildly symptomatic, New York Heart Association Class I and II). High-risk is defined as QRS width ≥ 130 milliseconds and Left Ventricular Ejection Fraction $\leq 30\%$. The New York Heart Association clinical classifications of heart failure patients rank patients as Class I-II-III-IV, according to the degree of symptoms or functional limits, from asymptomatic to bed ridden.

² Left ventricular ejection fraction (LVEF) is a measurement of how well the heart is pumping. People with healthy hearts usually have an ejection fraction of 50% or greater. Patients who were candidates for the MADIT-CRT study had a LVEF of $\leq 30\%$



The primary endpoint will determine if CRT-D in high-risk, asymptomatic or mildly symptomatic patients will reduce the combination of death from any cause **or** first heart failure (HF) event, whichever comes first, when compared to ICD therapy alone.

The secondary endpoint will evaluate the effects of CRT-D, relative to ICD only, on the subject-specific rates of multiple HF events over the full study period.

In addition, there are 10 pre-specified sub-studies as well as a number of additional investigator-initiated sub-studies.

- Subjects are randomized to CRT-D or ICD-only. Randomization is stratified by clinical center and ischemic status.
- Approximately 60% of the subjects are randomly assigned to receive a CRT-D with biventricular pacing, and 40% to receive an ICD only.
- Optimal pharmacological therapy for heart failure is required in both treatment arms.
- Length of follow-up for each subject will depend on the date of entry into the study, since all subjects will be followed to a common study termination date.
- For more information visit www.clinicaltrials.gov

Patients who were candidates for the MADIT-CRT study met the following criteria:

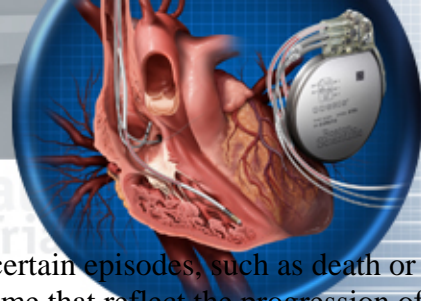
- NYHA Class I or II ischemic patients and NYHA Class II non-ischemic patients
- QRS duration \geq 130 ms
- Left ventricular ejection fraction \leq 30%
- Optimized on pharmacologic therapy for heart failure
- Sinus rhythm by ECG
- Men and women 21 years of age or older

Patients were excluded from the MADIT-CRT study if:

- Met general indications for CRT-D therapy
- Implanted pacemaker, ICD or CRT device
- NYHA Class I with non-ischemic cardiomyopathy
- NYHA Class III or IV in three calendar months prior to or at the time of enrollment
- CABG or percutaneous coronary intervention (balloon and/or stent angioplasty) within three months prior to enrollment
- MI within three months prior to enrollment
- Second or third degree heart block

The MADIT-CRT data are managed independent of the trial sponsor (Boston Scientific Corporation). The University of Rochester manages the MADIT-CRT data. All events are analyzed by an independent event committee.

MADIT-CRT is an event - driven trial in which patients are randomized to two treatments while events of clinical interest are counted until a pre-specified limit is reached. An event-driven trial is considered positive if statistical tests demonstrate that the new therapy significantly reduces the risk of events when compared to current medical practices. In the case



of MADIT-CRT, it was determined that the occurrence of certain episodes, such as death or heart failure events, are objective measures of patient outcome that reflect the progression of heart failure and would be superior to subjective measures, such as quality of life or symptoms, especially in a population that is asymptomatic or has mild symptoms at baseline. MADIT-CRT was designed to determine if the risk of events (death and heart failure events) is reduced with CRT-D devices when compared to ICDs.

In Europe 4 out of 10 patients die within one year of first hospitalization. In 2020 there will be 9 millions deaths due to heart failure each year. Boston Scientific estimates that 100,000-150,000 patients (in EU 5: France / Italy / Germany/ UK / Spain) could benefit from an expanded use of CRT-D based upon trial inclusion criteria and positive trial results.

Device Background

Cardiac resynchronization therapy with defibrillation (CRT-D)?

Is a therapy for heart failure where electrical stimulation pulses are delivered to the right and left ventricles to coordinate the contraction of the heart chambers for increased cardiac efficiency. The defibrillator backup monitors the heart for potentially fatal heart rhythms, and if detected, delivers a lifesaving shock.

CRT-D stands for *cardiac resynchronization therapy with defibrillator*. A CRT-D is a small, battery-powered device that holds a tiny computer. It is implanted in the body to provide special pacing therapy to treat heart failure. It can also detect and treat both fast and slow heart rhythms. Doctors program CRT-D devices to respond appropriately based on the heart's rhythm needs.

Treating dyssynchrony

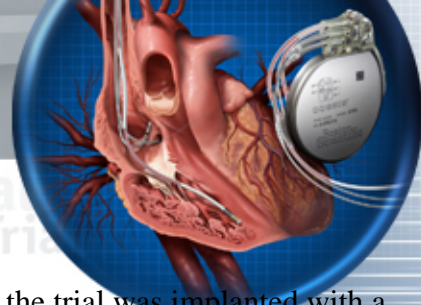
In heart failure, the chambers of the heart do not contract as they should. They are *dyssynchronous*, or *out of rhythm*. When that happens, the heart cannot provide the body with the energy it needs to function properly. CRT can help the heart pump better. It delivers specially timed electrical impulses to coordinate, or *resynchronize*, the timing of the heart's contractions. This therapy can help restore the heart's ability to fill with blood and work more efficiently.

Treating fast heart rhythms

If a dangerously fast ventricular heart rhythm occurs, the CRT-D device can deliver lifesaving therapy. Depending on the patient's condition, the CRT-D device may deliver small but rapid electrical signals called *antitachycardia pacing* (ATP) or it may deliver a full-energy shock. These therapies return the heart's rhythm to normal.

Treating slow heart rhythms

If an abnormally slow heart rhythm occurs, the CRT-D device can act like a pacemaker to deliver small electrical signals that help the heart beat more normally.



Device implantation

The patient randomized to either the CRT-D or ICD arm of the trial was implanted with a commercially available Boston Scientific device implanted by a qualified physician according to his/her or center's standard operating procedures.

For CRT-D programming, the goal is to maximize biventricular pacing and maximize tracking of intrinsic sinus rhythm.

For ICD programming, the goal is to minimize ventricular (and atrial if applicable) pacing unless the patient develops significant symptomatic bradycardia.

What is the difference between ICD therapy and CRT-D as currently indicated?

A: ICD therapy improves survival in high-risk cardiac patients by terminating potentially lethal ventricular tachyarrhythmias. CRT-D provides the same benefit of an ICD but also restores synchrony to improve left ventricular function in patients with advanced symptomatic heart failure. In this patient population, CRT has also been shown to improve exercise capacity, quality of life, and symptoms.

What devices were used in MADIT-CRT?

All market-approved Boston Scientific CRT-Ds within each particular geography were used in the trial including:

CRT-D: CONTAK RENEWAL, LIVIAN, COGNIS

ICD: VENTAK PRIZM, VENTAK PRIZM 2, VITALITY, CONFIENT

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