Boston Scientific

CLINICAL SUMMARY

MADIT-RIT STUDY

CAUTION: Federal law restricts this device to sale by or on the order of a physician trained or experienced in device implant and follow-up procedures.

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CLINICAL STUDY - SUMMARY OF MADIT-RIT STUDY

The Multicenter Automatic Defibrillator Implantation Trial: Reduce Inappropriate Therapy (MADIT-RIT) study was designed to compare the occurrence of inappropriate therapy using high rate cutoff and/or long delay in primary prevention patients receiving an ICD or CRT-D device compared to standard programming.

STUDY DESIGN

The MADIT-RIT Study was a global, prospective, randomized, 3-arm trial using commercially available Boston Scientific ICDs or CRT-Ds.

Only Boston Scientific ICD (TELIGEN/ENERGEN) and CRT-D (COGNIS/ENERGEN) devices were used in this trial. Subjects were randomized to one of three treatment arms in a 1:1:1 ratio. The three study arms include:

- Arm A: Standard programming (with a 2.5-second delay at 170 to 199 beats per minute and a 1.0-second delay at ≥ 200 beats per minute)
- Arm B: High rate cutoff (with a 2.5-second delay before the initiation of therapy at a heart rate of ≥ 200 beats per minute)
- Arm C: Long delay + Rhythm ID (with a 60-second delay at 170 to 199 beats per minute, a 12-second delay at 200 to 249 beats per minute, and a 2.5-second delay at ≥ 250 beats per minute)

SUBJECT SELECTION

Subjects enrolled in the MADIT-RIT Study were selected from the investigators general patient population who met the current guidelines for dual-chamber ICD or CRT-D device implantation. The investigators were responsible for screening potential subjects and selecting those who met the eligibility criteria for the study.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Primary prevention patient with ischemic or nonischemic heart disease who met current guidelines for dual-chamber ICD or CRT-D device therapy.
- Patient in sinus rhythm at the time of the implant.
- Patient on stable optimal pharmacologic therapy for their cardiac condition.
- Patient ≥21 years of age, or legal representative, willing and capable of giving informed consent.

  If the indications for ICD/CRT-D implantation changed during the MADIT-RIT trial, patients who met the new criteria were eligible to participate. Please note that for the purposes of the MADIT-RIT trial, CRT-D patients with an NYHA Class IV indication were excluded.

Exclusion Criteria

- Patient with an implanted pacemaker or CRT-P
- Patient with an existing ICD or CRT-D device components
- Patient with a history of VT or VF
- Patient with permanent or chronic AF within the past three calendar months before enrollment
- Patient with coronary artery bypass graft surgery or percutaneous coronary intervention within the past three calendar months prior to enrollment
- Patient with enzyme-positive myocardial infarction within the past three calendar months prior to enrollment

- Patient with angiographic evidence of coronary disease who are candidates for coronary revascularization and are likely to undergo coronary artery bypass graft surgery or percutaneous coronary intervention in the foreseeable future
- Patient with second or third degree heart block
- Patient in NYHA Class IV
- Patient who is pregnant or plans to become pregnant during the course of the trial
- Patient with irreversible brain damage from preexisting cerebral disease
- Patient with presence of any disease, other than the patient's cardiac disease, associated with a reduced likelihood of survival for the duration of the trial, e.g., cancer, uremia, liver failure, etc.
- Patient with chronic renal disease with BUN ≥ 50 mg/dL or creatinine ≥2.5 mg/dL
- Patient participating in any other clinical trial
- Patient unwilling or unable to cooperate with the protocol
- Patient who lives at such a distance from the clinic that travel for follow-up visits would be unusually difficult
- Patient who does not anticipate being a resident of the area for the scheduled duration of the trial
- Patient unwilling to sign the consent for participation
- Patients whose physician does not allow participation

MADIT-RIT STUDY ENDPOINTS

Primary Endpoint

Time to first inappropriate therapy

Secondary Endpoint

All-cause mortality and syncope

RESULTS

Table 1 summarizes the baseline demographics for the MADIT-RIT subjects. Baseline characteristics were similar in the three groups.

Table 1. Baseline Demographic and Clinical Characteristics According to Treatment Group*

Variable	Conventional Therapy (N= 514)	High-Rate Therapy (N= 500)	Delayed Therapy (N= 486)
Age — yr	63±11	63±12	62±12
Male sex — no. (%)	357 (69.5)	354 (70.8)	353 (72.6)
Race — no./total no. (%)†			
White	393/509 (77.2)	371/493 (75.3)	355/483 (73.5)
Black	84/509 (16.5)	91/493 (18.5)	97/483 (20.1)
Asian	23/509 (4.5)	27/493 (5.5)	26/483 (5.4)
Other	9/509 (1.8)	4/493 (0.8)	5/483 (1.0)
Cardiac history — no./total no. (%)			
Ischemic heart disease	271/514 (52.7)	268/499 (53.7)	252/485 (52.0)
Nonischemic heart disease	243/514 (47.3)	231/499 (46.3)	233/485 (48.0)
Cardiac risk factors — no./total no. (%)			
Hypertension	346/513 (67.4)	359/497 (72.2)	324/485 (66.8)
Diabetes mellitus	166/510 (32.5)	159/491 (32.4)	160/482 (33.2)

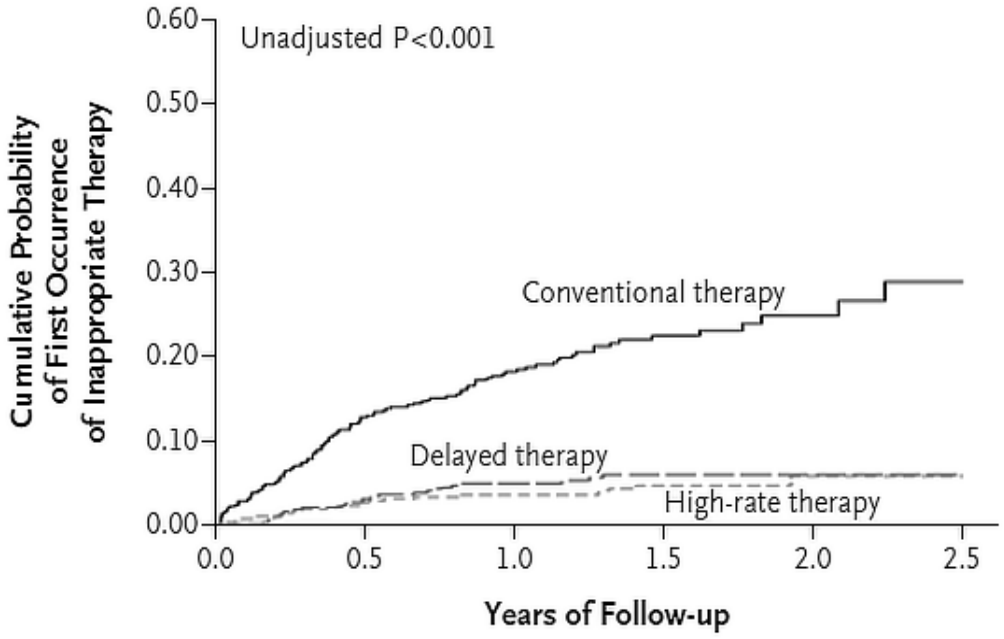
Variable	Conventional Therapy (N= 514)	High-Rate Therapy (N= 500)	Delayed Therapy (N= 486)
Current cigarette smoking	86/483 (17.8)	83/472 (17.6)	78/463 (16.8)
Atrial fibrillation	47/508 (9.3)	57/495 (11.5)	49/483 (10.1)
NYHA class II or III — no./ total no. (%)	495/507 (97.6)	482/495 (97.4)	474/484 (97.9)
Body-mass index‡	29.4±7.1	28.9±6.5	29.5±6.9
Cardiac findings at enrollment			
Blood pressure — mm Hg			
Systolic	124±20	123±19	124±19
Diastolic	73±11	73±12	73±12
Resting heart rate — beats/min	72±12	72±12	73±13
Ejection fraction — %	26±6	26±7	26±7
Defibrillator type — no./total no. (%)			
ICD	258/514 (50.2)	248/499 (49.7)	236/486 (48.6)
CRT-D	256/514 (49.8)	251/499 (50.3)	250/486 (51.4)
Medications — no./total no. (%)			
ACE inhibitor	348/514 (67.7)	339/499 (67.9)	327/485 (67.4)
Aldosterone antagonist	188/514 (36.6)	190/499 (38.1)	165/485 (34.0)
Aspirin	317/514 (61.7)	334/499 (66.9)	321/485 (66.2)
Beta-blocker	476/514 (92.6)	467/499 (93.6)	460/485 (94.8)
Digitalis	62/514 (12.1)	65/499 (13.0)	66/485 (13.6)
Diuretic	336/514 (65.4)	355/499 (71.1)	316/485 (65.2)
Lipid-lowering statin	295/514 (57.4)	308/499 (61.7)	275/485 (56.7)

* Plus–minus values are means ±SD. There were no significant differences at P<0.05 between treatment groups. Conventional therapy involved a 2.5-second delay before the initiation of device therapy (antitachycardia pacing or shock) at a heart rate of 170 to 199 beats per minute and a 1.0-second delay at 200 beats per minute or higher. High-rate therapy involved a 2.5-second delay at 200 beats per minute or higher. Delayed therapy involved a 60-second delay at 170 to 199 beats per minute, a 12-second delay at 200 to 249 beats per minute, and a 2.5-second delay at 250 beats per minute or higher. ACE denotes angiotensin-converting enzyme, CRT-D cardiac-resynchronization therapy with defibrillator, ICD implantable cardioverter–defibrillator, and NYHA New York Heart Association.
† Race was determined by self-report.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Primary Endpoint Results

When comparing Arm A (standard/conventional) vs. Arm B (high-rate cutoff) programming a 79% (HR 0.21, p < 0.001) reduction in the relative risk of first inappropriate therapy was seen. For Arm A vs. Arm C (Long-duration delay) programming a 76% (HR 0.24, p < 0.001) reduction was observed. Figure 1 represents the Kaplan-Meier (KM) curve for the primary endpoint. There is no clinically relevant difference in inappropriate therapy between Arms B and C.

Compared to the conventional therapy group, the high rate and delayed therapy groups had significantly fewer patients with a first occurrence of appropriate or inappropriate therapy. First occurrences of inappropriate antitachycardia pacing were most frequent with regular supraventricular tachyarrhythmia (in 73% of the patients) and atrial fibrillation (in 19%), and first occurrences of inappropriate shocks were also most frequent with these arrhythmias (in 55% and 36% of the patients, respectively).

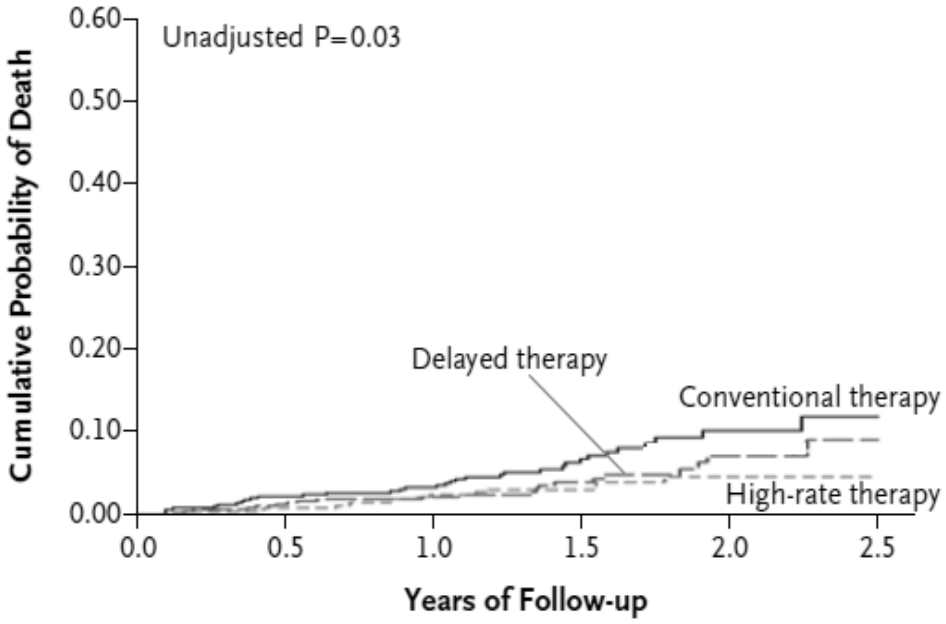


No. at Risk						
Conventional therapy	514	420 (0.13)	305 (0.18)	149 (0.22)	56 (0.25)	8 (0.29)
High-rate therapy	500	454 (0.03)	339 (0.04)	191 (0.05)	70 (0.06)	17 (0.06)
Delayed therapy	486	445 (0.03)	342 (0.05)	177 (0.06)	82 (0.06)	13 (0.06)

Figure 1. Cumulative Probability of First Occurrence of Inappropriate Therapy According to Treatment Group

Secondary Endpoint Results

During the trial mortality events for the randomized subjects were adjudicated by an independent committee of physicians. The results show that when comparing Arm A (standard/conventional) vs. Arm B (high-rate cutoff) programming a statistically significant 55% reduction in the relative risk of death was demonstrated (HR 0.45, p=0.001). For Arm A vs. Arm C (Long-duration delay) programming a non-statistically significant 44% reduction in the relative risk of death was shown (HR 0.56, p=0.06). Figure 2 represents the Kaplan-Meier curve for the secondary mortality endpoint.



No. at Risk

Conventional therapy	514	490 (0.02)	392 (0.03)	219 (0.07)	89 (0.10)	14 (0.12)
High-rate therapy	500	478 (0.01)	372 (0.02)	221 (0.03)	90 (0.05)	21 (0.05)
Delayed therapy	486	471 (0.01)	375 (0.02)	205 (0.04)	99 (0.07)	14 (0.09)

Figure 2. Cumulative Probability of Death According to Treatment Group

Syncope Endpoint Results

The study collected syncope events throughout the trial. These events were adjudicated by an Endpoint Committee of independent physicians. Table 2 shows the number of subjects that experienced a first syncope event along with the hazard ratios and p-values associated. The study showed that syncope was not increased based on any of the randomized programming arms within the study. There was no statistical difference noted for either Arm B vs. Arm A or Arm C vs. Arm A.

Table 2. MADIT-RIT Syncope Summary

	Arm A (Standard) N=514	Arm B (High-rate cutoff) N=500	Arm C (Long Duration delay) N=486	Arm B vs. Arm A HR; p-value	Arm C vs. Arm A HR; p-value
1st Syncope Event	23 subjects	22 subjects	22 subjects	1.32; 0.39	1.09; 0.80

ADVERSE EVENTS SUMMARY

There were 2878 adverse events in 1040 unique subjects. Of these, 632 Events were coded as Pulse Generator related events; 151 Lead related events; 1386 Patient Condition – Cardiovascular related events and 709 Patient Condition – Non-Cardiovascular related events. Table 3 below summarizes the number of adverse events by category that occurred in a given number of subjects.

Table 3. MADIT-RIT Adverse Event Summary

Category	Events*	Events per F/U Month	Subjects	% of Subjects
Pulse Generator Related	632	0.02	466	30.34
Lead Related	151	0.01	129	8.4
Patient condition – Cardiovascular Related	1386	0.05	682	44.4
Patient condition - Non Cardiovascular Related	709	0.03	424	27.6
Total	2878	0.11	1040	67.71

*Subjects may have AEs of more than one type; therefore the subject totals are not the sum of the individual totals.

DEATH SUMMARY

The Mortality Review Committee reviewed all deaths that occurred in MADIT-RIT. Their decisions were based on independent physician review of the data from device interrogation, adverse event case report forms and subject status case report forms. Every effort was made to classify cardiac deaths in terms of suddenness and arrhythmic mechanism by pre-specified Hinkle-Thaler criteria. There were a total of 74 deaths during the MADIT-RIT study. Table 4 provides the number of deaths and the cause of death classification from the enrolling center investigator.

Table 4. MADIT-RIT Mortality Events by Investigator Determined Category (N=1536)

Cause of Death	Total
Cardiac: Ischemic	4
Cardiac: Pump failure	21
Cardiac: Arrhythmic	4
Cardiac: Other	2
Non-Cardiac	25
Procedure: Implanted study device	0
Procedure: Other cardiac	0
Unknown	16
Not Classified By Investigator (died prior to randomization)	2
Total Deaths	74

CONCLUSION

The results of the MADIT-RIT trial show a reduction in both Arms B and C when compared to the standard programming in Arm A for both inappropriate therapy and all-cause mortality for primary prevention dual-chamber ICD and CRT-D subjects. The study also demonstrated that syncope was not increased based on any of the randomized programming arms within the study.

REFERENCE

Moss, A. J., Schuger, C., Beck, C. A., Brown, M. W., Cannom, D. S., Daubert, J. P., . . . for the MADIT-RIT Trial Investigators. (2012). Reduction in Inappropriate Therapy and Mortality through ICD Programming. New England Journal of Medicine, 367(24), 2275-2283.

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