MADIT Randomized Trial to Reduce Inappropriate Therapy (MADIT-RIT)

Adapted from AHA Late Breaking Trial Results Presented by

Arthur J. Moss, MD

Professor of Medicine
University of Rochester Medical Center

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Slides adapted from those presented by Arthur J Moss, MD at AHA 2012, Los Angeles, CA USA

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Background

- ICD is highly effective in reducing mortality in high-risk cardiac pts.[1-3]
- Despite sophisticated device-detection algorithms, 8-40% of ICD therapies are inappropriate with adverse side effects[4-14]
- Question: can ICD devices be reprogrammed to reduce inappropriate therapies?

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Study Overview

Study Hypothesis: Dual-chamber ICD or CRT-D devices with high-rate cutoff (>200bpm), or duration-delay (initial 60sec monitoring delay @>170bpm) plus Rhythm ID® detection will be associated with fewer 1st inappropriate therapies than standard/conventional programming (2.5sec delay @ >170bpm) without increase in mortality

Study Design: Randomized, 3-arm study of patients randomized 1:1:1 to either conventional, high-rate cutoff, or duration-delay programming

Primary Endpoint: First episode of inappropriate therapy (defined as shock or ATP)

B arm vs. A arm
C arm vs. A arm

Secondary Endpoints: All-cause mortality
Syncope

Number of Patients: 1500 from 98 centers
US, Canada, Europe, Israel and Japan

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Three Treatment Arms (abbreviated)*

Arm A (Conventional)	Arm B (High-rate)	Arm C (Duration-delay)
Zone 1:	Zone 1:	Zone 1:
≥170 bpm, 2.5s delay	170 bpm	≥170 bpm, 60s delay
Onset/Stability Detection Enhancements ON	Monitor only	Rhythm ID® Detection Enhancements ON
ATP + Shock		ATP + Shock
SRD 3 min initial		SRD Off
Zone 2:	Zone 2:	Zone 2:
≥200 bpm, 1s delay	≥200 bpm, 2.5s delay	≥200 bpm, 12s delay
Quick Convert™ ATP Shock	Quick Convert™ ATP Shock	Rhythm ID® Detection Enhancements ON ATP + Shock
		SRD Off
		Zone 3 :
		≥250 bpm, 2.5s delay
		Quick Convert™ ATP + Shock

For a complete listing of all programming parameters, please contact Boston Scientific at 1-800-CARDIAC

*All programming is within approved labeling. Rhythm ID® and Quick Convert™ are trademarks of Boston Scientific Corporation

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Eligibility

Inclusion Criteria

- Primary prevention patients with no Hx of VT/VF
- Sinus rhythm at enrollment; Hx PAF ok
- Pt. on stable, optimal pharmacologic therapy
- Age >21 yrs; informed consent

Exclusion Criteria

- Pt. with pacemaker, ICD or CRT-D device
- CABG or PTCA in past 3 months
- MI (enzyme +) or AF in past 3 months
- 2nd or 3rd degree heart block
- NYHA IV
- Chronic AF
- Renal disease: BUN>50mg/dlor Creatinine>2.5mg/dL

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Pre-specified End Points

Primary (90% power for hazard ratio 0.5 at $p<0.05$)

- First episode of inappropriate therapy (defined as shock or ATP)
  - B arm vs. A arm
  - C arm vs. A arm
- Rationale for first inappropriate therapy (IT)
  - Expect reprogramming to be common after IT
  - Protocol allows reprogramming after IT

Secondary

- All-cause mortality
- Syncope

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Baseline Demographic and Clinical Characteristics

	Therapy Group		
	A Conventional ≥170bpm n=514	B High-rate ≥200bpm n=500	C Duration-Delay ≥170bpm n=486
Age, yrs	64	63	62
Male, %	70	71	72
Ischemic, %	53	54	52
EF, %	26	26	26

No significant differences in 22 variables among the 3 Rx groups

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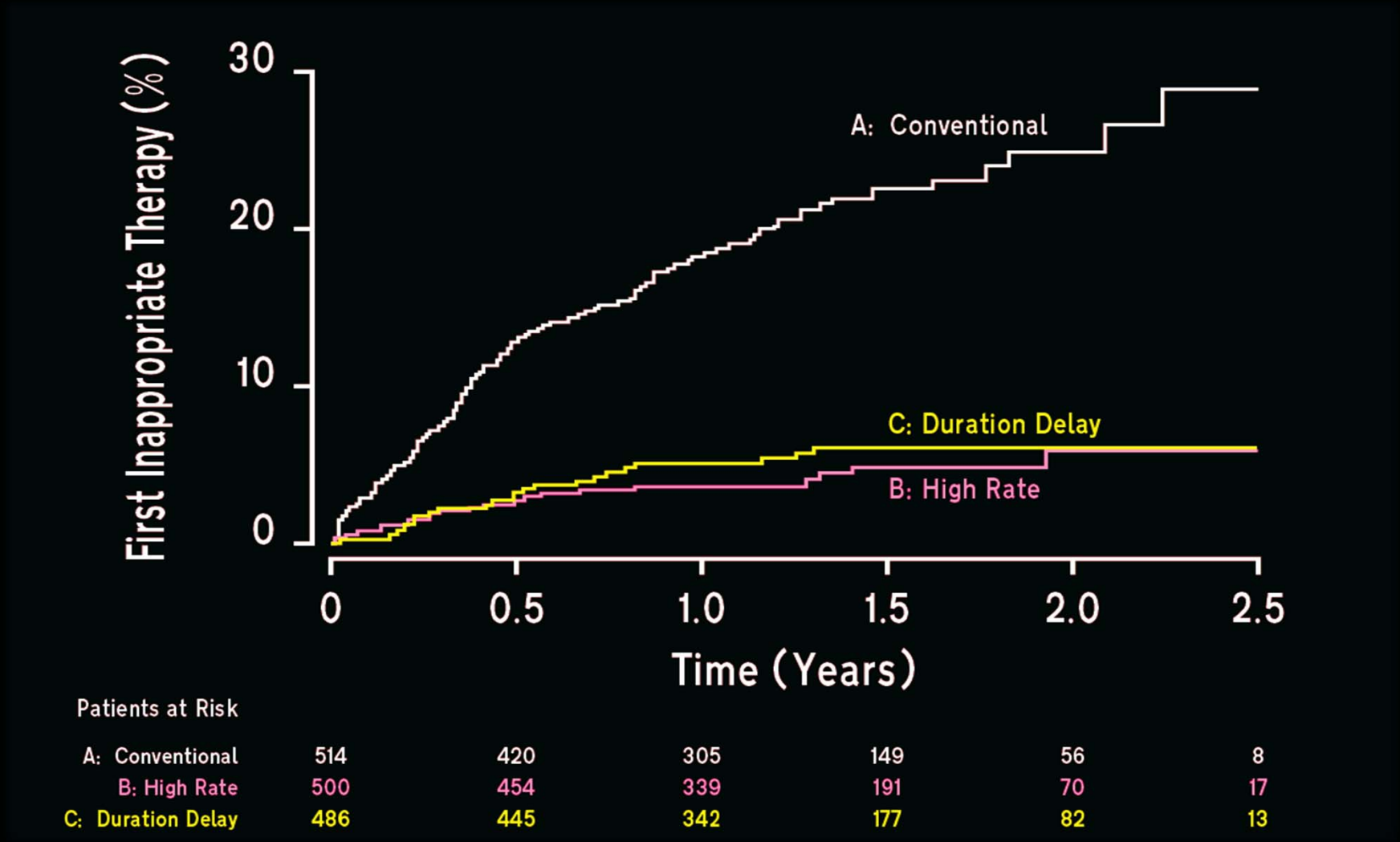
Cumulative Probability of First Inappropriate Therapy by Treatment Group



Patients at Risk						
A: Conventional	514	420	305	149	56	8
B: High Rate	500	454	339	191	70	17
C: Duration Delay	486	445	342	177	82	13

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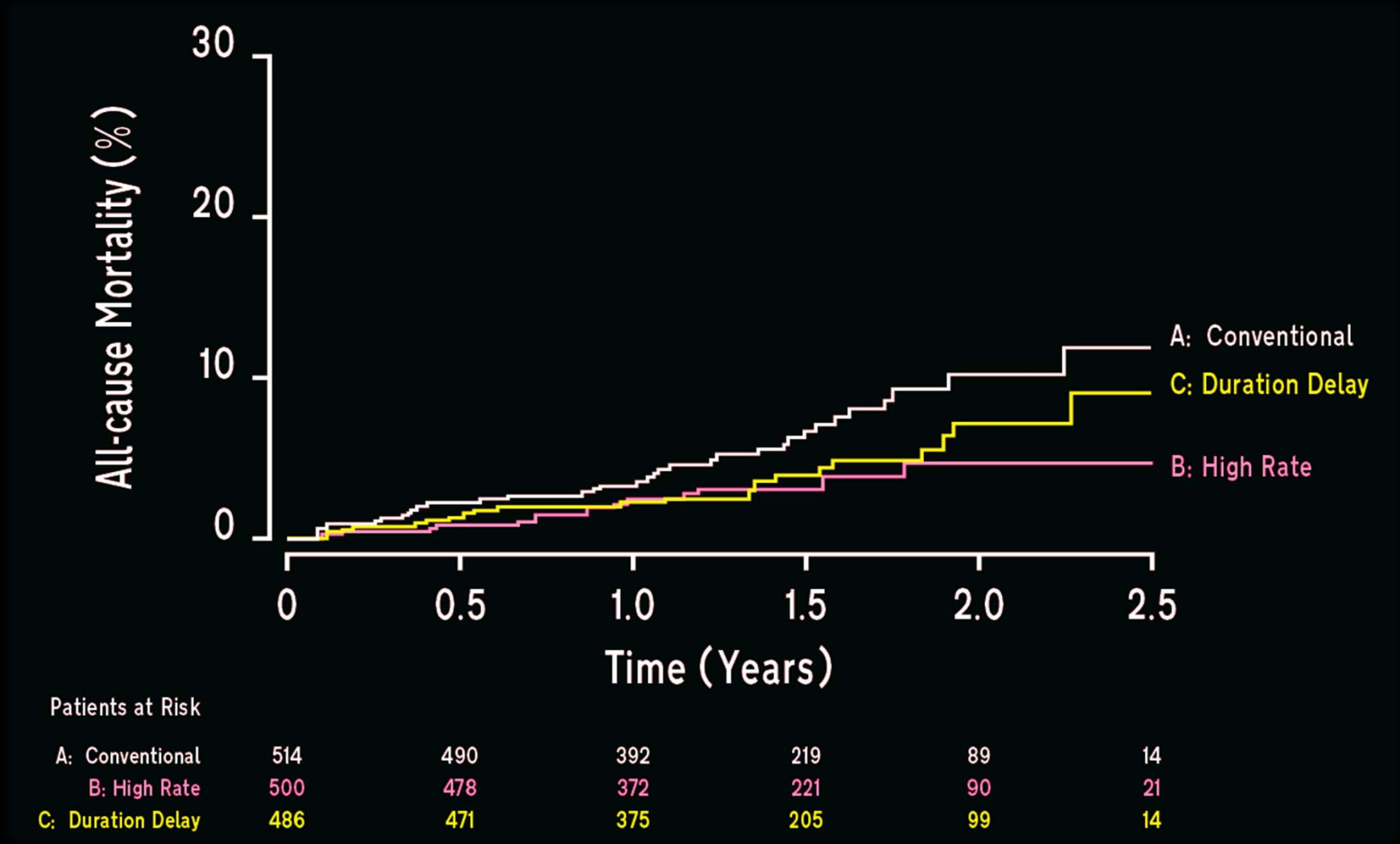
Cumulative Probability of Death by Treatment Group



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Frequency and Hazard Ratios for Inappropriate Therapy, Death, and Syncope by Treatment Group

	Treatment Groups			Treatment Group Comparisons			
	# of patients			B vs A		C vs A	
Events	A n=514	B n=500	C n=486	Hazard Ratio	P-value	Hazard Ratio	P-value
1st Inapp Therapy	105	21	26	0.21	<0.001	0.24	<0.001
Death	34	16	21	0.45	0.01	0.56	0.06
1st Syncope	23	22	23	1.32	0.39	1.09	0.80

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Arrhythmias Triggering First Inappropriate Therapies

	Treatment Group		
	A	B	C
Arrhythmias	# Patients 1st Inappropriate Therapies		
At Fib/Flut	24	11	5
Regular SVT	78	9	17
Other	3	1	4

Note: marked reduction in patients with1st inappropriate therapies in High-rate (B) and Duration-delay (C) groups for At Fib/Flut and Regular SVT when compared to Conventional therapy (A).

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Any Appropriate and Inappropriate Therapy by Treatment Group

	Treatment Groups # of Patients (% of Rx Group)			P-Value	
	A n=514	B n=500	C n=486	B vs A	C vs A
Any Appropriate Therapy					
Shock	28 (5)	26 (5)	19 (4)	0.86	0.25
ATP	111 (22)	38 (8)	20 (4)	<0.001	<0.001
Any Inappropriate Therapy					
Shock	31 (6)	14 (3)	15 (3)	0.01	0.03
ATP	104 (20)	20 (4)	25 (5)	<0.001	<0.001

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Summary

Improved ICD programming to high-rate (>200 bpm) or 60sec duration-delay is associated with:

1) ~75% reduction in 1st inappropriate therapy;
2) ~50% reduction in all-cause mortality

Dr. Moss and his co-authors speculated that the decrease in mortality in this trial could have been related to the reduction in inappropriate shock and ATP therapies

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CRT-D Systems from Boston Scientific

Indications and Usage

These Boston Scientific Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with heart failure who receive stable optimal pharmacologic therapy (OPT) for heart failure and who meet any one of the following classifications:

- Moderate to severe heart failure (NYHA Class III-IV) with EF ≤ 35% and QRS duration ≥ 120 ms
- Left bundle branch block (LBBB) with QRS ≥ 130 ms, EF ≤ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure

Contraindications

There are no contraindications for this device.

Warnings

Read the product labeling thoroughly before implanting the pulse generator to avoid damage to the system. For single patient use only. Do not reuse, reprocess, or resterilize. Program the pulse generator Tachy Mode to Off during implant, explant or postmortem procedures. Always have sterile external and internal defibrillator protection available during implant. Ensure that an external defibrillator and medical personnel skilled in CPR are present during post-implant device testing. Advise patients to seek medical guidance before entering environments that could adversely affect the operation of the active implantable medical device, including areas protected by a warning notice that prevents entry by patients who have a pulse generator. Do not expose a patient to MRI device scanning. Do not subject a patient with an implanted pulse generator to diathermy, Do not use atrial-tracking modes in patients with chronic refractory atrial tachyarrhythmias. Do not use atrial-only modes in patients with heart failure. LV lead dislodgment to a position near the atria can result in atrial oversensing and LV pacing inhibition. Physicians should use medical discretion when implanting this device in patients who present with slow VT. Do not kink, twist or braid the lead with other leads. Do not use defibrillation patch leads with the CRT-D system. Do not use this pulse generator with another pulse generator.

Precautions

For specific information on precautions, refer to the following sections of the product labeling: clinical considerations; sterilization, storage and handling; implant and device programming; follow-up testing; explant and disposal; environmental and medical therapy hazards; hospital and medical environments; home and occupational environments. Advise patients to avoid sources of electromagnetic interference (EMI) because EMI may cause the pulse generator to deliver inappropriate therapy or inhibit appropriate therapy.

Potential Adverse Events

Potential adverse events from implantation of the CRT-D system include, but are not limited to, the following: allergic/physical/physiologic reaction, death, erosion/migration, fibrillation or other arrhythmias, lead or accessory breakage (fracture/insulation/lead tip), hematoma/seroma, inappropriate or inability to provide therapy (shocks/pacing/sensing), infection, procedure related, and component failure. Patients may develop psychological intolerance to a pulse generator system and may experience fear of shocking, fear of device failure, or imagined shocking. In rare cases severe complications or device failures can occur.

Refer to the product labeling for specific indications, contraindications, warnings/precautions and adverse events. Rx only.
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CRT-D Systems from Boston Scientific – PUNCTUA, ENERGEN, and INCEPTA

IIndications and Usage

The PUNCTUA™, ENERGEN™, and INCEPTA™ Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with heart failure who receive stable optimal pharmacologic therapy (OPT) for heart failure and who meet any one of the following classifications:

- Moderate to severe heart failure (NYHA Class III-IV) with EF ≤ 35% and QRS duration ≥ 120 ms
- Left bundle branch block (LBBB) with QRS ≥ 130 ms, EF ≤ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure

Contraindications

There are no contraindications for this device.

Warnings

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For DF4-LLHH or DF4-LLHO leads, use caution handling the lead terminal when the Connector Tool is not present on the lead and do not directly contact the lead terminal with any surgical instruments or electrical connections such as PSA (alligator) clips, ECG connections, forceps, hemostats, and clamps. Do not contact any other portion of the DF4-LLHH or DF4-LLHO lead terminal, other than the terminal pin even when the lead cap is in place.

Precautions

For specific information on precautions, refer to the following sections of the product labeling: clinical considerations; sterilization and storage; implantation; device programming; follow-up testing; explant and disposal; environmental and medical therapy hazards; hospital and medical environments; home and occupational environments; and supplemental precautionary information. Advise patients to avoid sources of electromagnetic interference (EMI) because EMI may cause the pulse generator to deliver inappropriate therapy or inhibit appropriate therapy.

Potential Adverse Events

Potential adverse events from implantation of the CRT-D system include, but are not limited to, the following: allergic/physical/physiologic reaction, death, erosion/migration, fibrillation or other arrhythmias, lead or accessory breakage (fracture/insulation/lead tip), hematoma/seroma, inappropriate or inability to provide therapy (shocks/pacing/sensing), infection, procedure related, and component failure. Patients may develop psychological intolerance to a pulse generator system and may experience fear of shocking, fear of device failure, or imagined shocking. In rare cases severe complications or device failures can occur.

Refer to the product labeling for specific indications, contraindications, warnings/precautions and adverse events. Rx only.

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ICD Systems from Boston Scientific

ICD Indications and Usage

ICDs are intended to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias. ICDs (i.e. Vitality AVT) with atrial therapies are also intended to provide atrial antitachycardia pacing and atrial defibrillation treatment in patients who have or are at risk of developing atrial tachyarrhythmias.

Contraindications

Use of ICD systems are contraindicated in: Patients whose ventricular tachyarrhythmias may have reversible cause, such as 1) digitalis intoxication, 2) electrolyte imbalance, 3) hypoxia, or 4) sepsis, or whose ventricular tachyarrhythmias have a transient cause, such as 1) acute myocardial infarction, 2) electrocution, or 3) drowning. Patients who have a unipolar pacemaker.

Warnings

Read the product labeling thoroughly before implanting the pulse generator to avoid damage to the ICD system. For single patient use only, Do not reuse, reprocess, or resterilize. Program the pulse generator ventricular Tachy Mode to Off during implant, explant or post-mortem procedures. Always have external defibrillator protection available during implant. Ensure that an external defibrillator and medical personnel skilled in cardiopulmonary resuscitation (CPR) are present during post-implant device testing. Patients should seek medical guidance before entering environments that could adversely affect the operation of the active implantable medical device, including areas protected by a warning notice that prevents entry by patients who have a pulse generator. Do not expose a patient to MRI device scanning. Do not subject a patient with an implanted pulse generator to diathermy. Do not use atrial tracking modes (or an AVT device) in patients with chronic refractory atrial tachyarrhythmias. Do not use this pulse generator with another pulse generator. Do not kink, twist or braid lead with other leads..

Precautions

For specific information on precautions, refer to the following sections of the product labeling: clinical considerations; sterilization and storage; implantation; device programming; environmental and medical therapy hazards; hospital and medical environments; home and occupational environments follow-up testing; explant and disposal; supplemental precautionary information. Advise patients to avoid sources of electromagnetic interference (EMI).

Potential Adverse Events

Potential adverse events from implantation of the ICD system include, but are not limited to, the following: allergic/physical/physiologic reaction, death, erosion/migration, fibrillation or other arrhythmias, lead or accessory breakage (fracture/insulation/lead tip), hematoma/seroma, inappropriate or inability to provide therapy (shocks/pacing/sensing), infection, procedure related, psychologic intolerance to an ICD system – patients susceptible to frequent shocks despite antiarrhythmic medical management/imagined shocking, and component failure. In rare cases severe complications or device failures can occur.

Refer to the product labeling for specific indications, contraindications, warnings/ precautions and adverse events. Rx only.
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ICD Systems from Boston Scientific – PUNCTUA, ENERGEN, and INCEPTA

ICD Indications and Usage

PUNCTUA™, ENERGEN™, and INCEPTA™ ICDs are intended to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias.

Contraindications

Use of these ICD systems are contraindicated in: Patients whose ventricular tachyarrhythmias may have reversible cause, such as 1) digitalis intoxication, 2) electrolyte imbalance, 3) hypoxia, or 4) sepsis, or whose ventricular tachyarrhythmias have a transient cause, such as 1) acute myocardial infarction, 2) electrocution, or 3) drowning. Patients who have a unipolar pacemaker.

Warnings

Read the product labeling thoroughly before implanting the pulse generator to avoid damage to the ICD system. For single patient use only. Do not reuse, reprocess, or resterilize. Program the pulse generator ventricular Tachy Mode to Off during implant, explant or post-mortem procedures. Always have external defibrillator protection available during implant. Ensure that an external defibrillator and medical personnel skilled in cardiopulmonary resuscitation (CPR) are present during post-implant device testing. Patients should seek medical guidance before entering environments that could adversely affect the operation of the active implantable medical device, including areas protected by a warning notice that prevents entry by patients who have a pulse generator. Do not expose a patient to MRI device scanning. Do not subject a patient with an implanted pulse generator to diathermy. Do not use atrial tracking modes in patients with chronic refractory atrial tachyarrhythmias. Do not use this pulse generator with another pulse generator. Do not kink, twist or braid lead with other leads.
For DF4-LLHH or DF4-LLHO leads, use caution handling the lead terminal when the Connector Tool is not present on the lead and do not directly contact the lead terminal with any surgical instruments or electrical connections such as PSA (alligator) clips, ECG connections, forceps, hemostats, and clamps. Do not contact any other portion of the DF4-LLHH or DF4-LLHO lead terminal, other than the terminal pin even when the lead cap is in place.

Precautions

For specific information on precautions, refer to the following sections of the product labeling: clinical considerations; sterilization and storage; implantation; device programming; environmental and medical therapy hazards; hospital and medical environments; home and occupational environments follow-up testing; explant and disposal; supplemental precautionary information. Advise patients to avoid sources of electromagnetic interference (EMI).

Potential Adverse Events

Potential adverse events from implantation of the ICD system include, but are not limited to, the following: allergic/physical/physiologic reaction, death, erosion/migration, fibrillation or other arrhythmias, lead or accessory breakage (fracture/insulation/lead tip), hematoma/seroma, inappropriate or inability to provide therapy (shocks/pacing/sensing), infection, procedure related, psychologic intolerance to an ICD system – patients susceptible to frequent shocks despite antiarrhythmic medical management/imagined shocking, and component failure. In rare cases severe complications or device failures can occur.

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