Long-Term Survival with Cardiac Resynchronization Therapy in Mild Heart Failure Patients

MADIT-CRT Long Term Follow-Up

Adapted from the American College of Cardiology Late Breaking Presentation by Ilan Goldenberg, MD

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Washington, DC

The long-term follow-up of MADIT-CRT was supported by an unrestricted grant from Boston Scientific

Background: MADIT-CRT

1820 ICM/NICM pts:

- EF ≤ 30%
- QRS ≥ 130 msec
- NYHA I/II

Randomization:

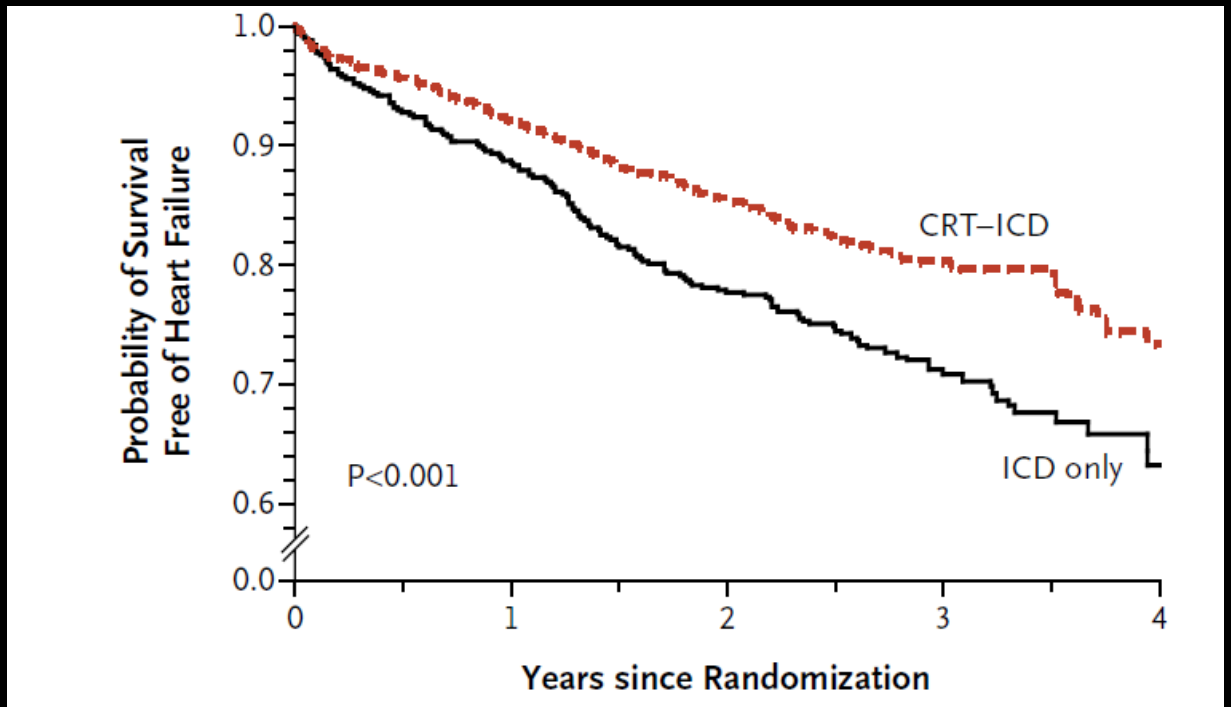
- CRT-D vs. ICD-only*
- 3:2 ratio

Mean Follow-Up:

- 2.4 yrs

Outcome:

- HR=0.66 (p=0.001)



No. at Risk (Probability of Survival)					
ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT–ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

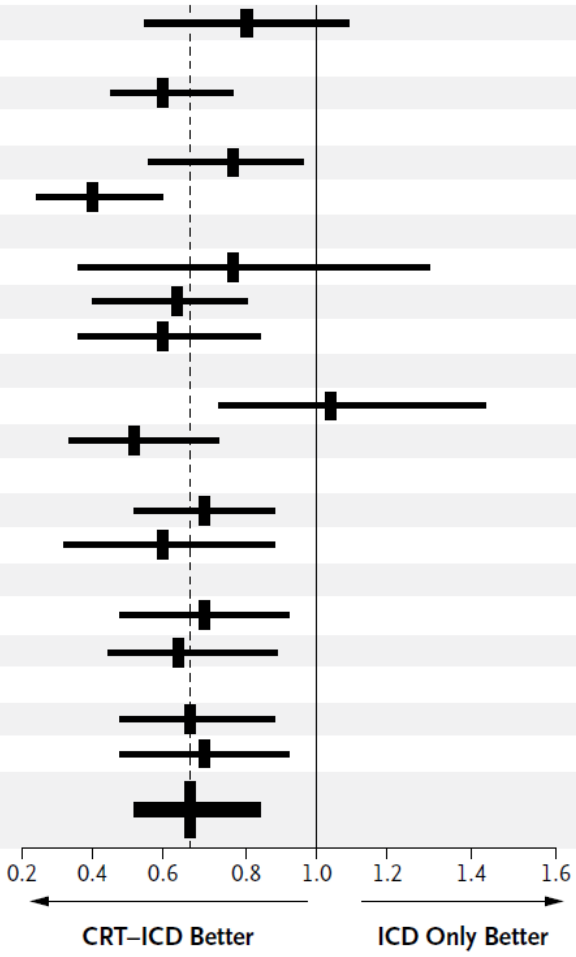
*Boston Scientific ICD and CRT-D devices

Moss A, et al. *NEJM*. 2009;361:1329-38

MADIT-CRT Subgroup Analysis

Differential clinical response: Gender, QRS duration

Variable	No. of Events/No. of Patients
Age	
<65 yr	142/852
≥65 yr	230/968
Sex	
Male	294/1367
Female	78/453
NYHA class	
Ischemic I	53/265
Ischemic II	186/734
Nonischemic II	133/821
QRS duration	
<150 msec	147/645
≥150 msec	225/1175
LVEF	
≤25%	101/646
>25%	271/1174
LVEDV	
≤240 ml	184/828
>240 ml	184/969
LVESV	
≤170 ml	190/835
>170 ml	178/962
All patients	372/1820



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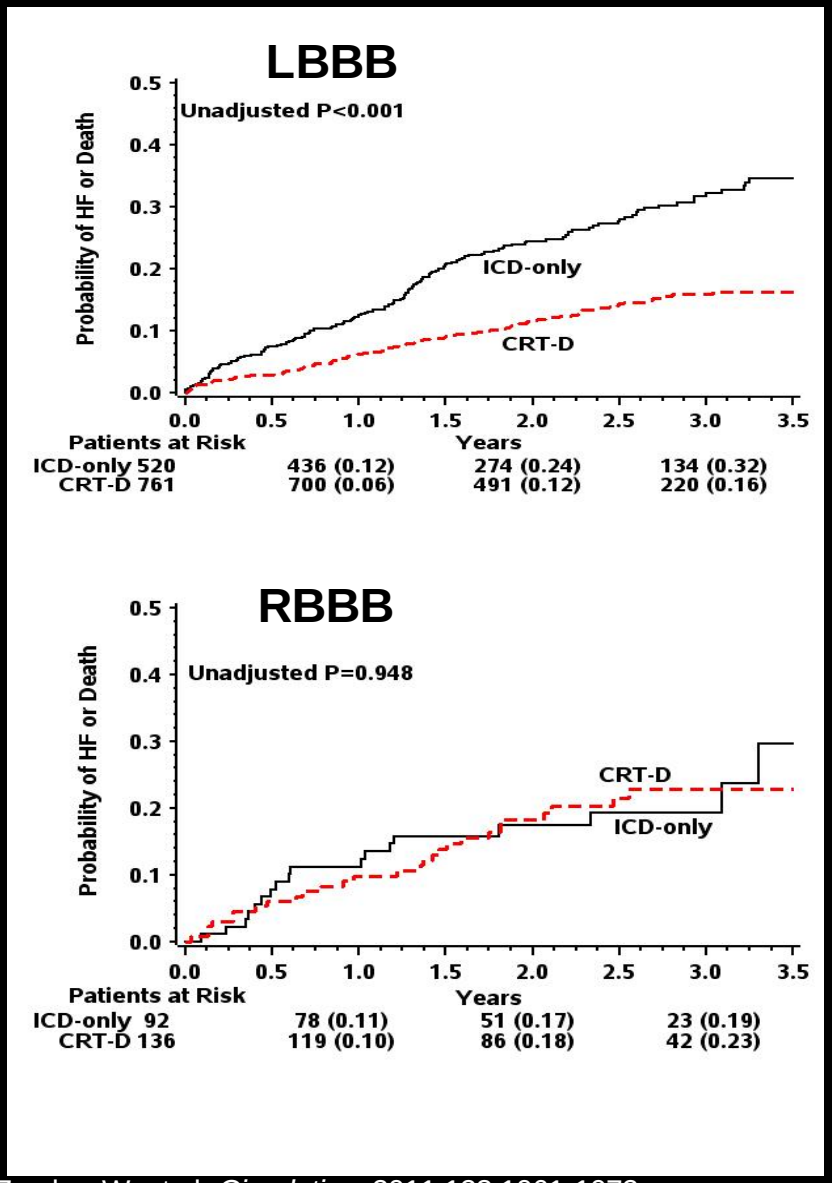
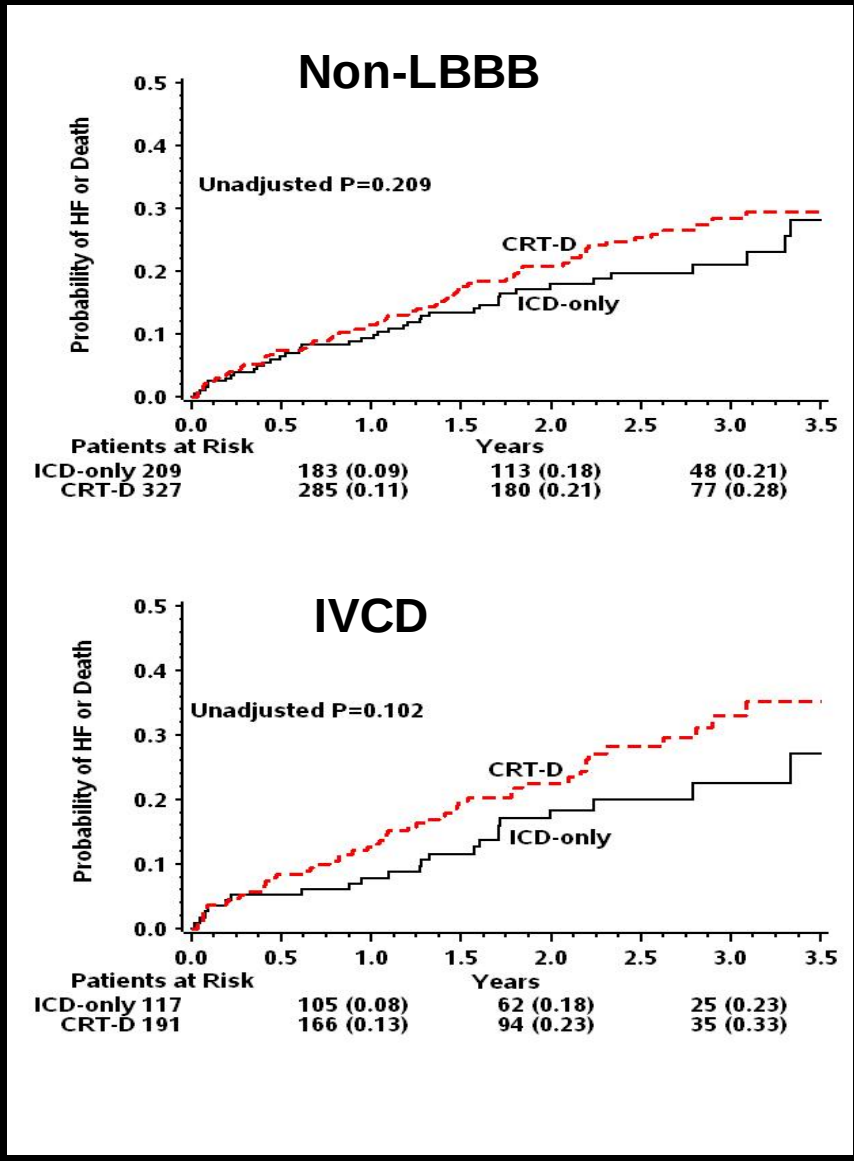
MADIT-CRT: QRS Morphology





Zareba, W, et al. *Circulation*. 2011;123:1061-1072

Slides adapted from those presented by Ilan Goldenberg, MD at ACC 2014, Washington, DC USA

MADIT-CRT Long-Term Follow-Up Study Purpose

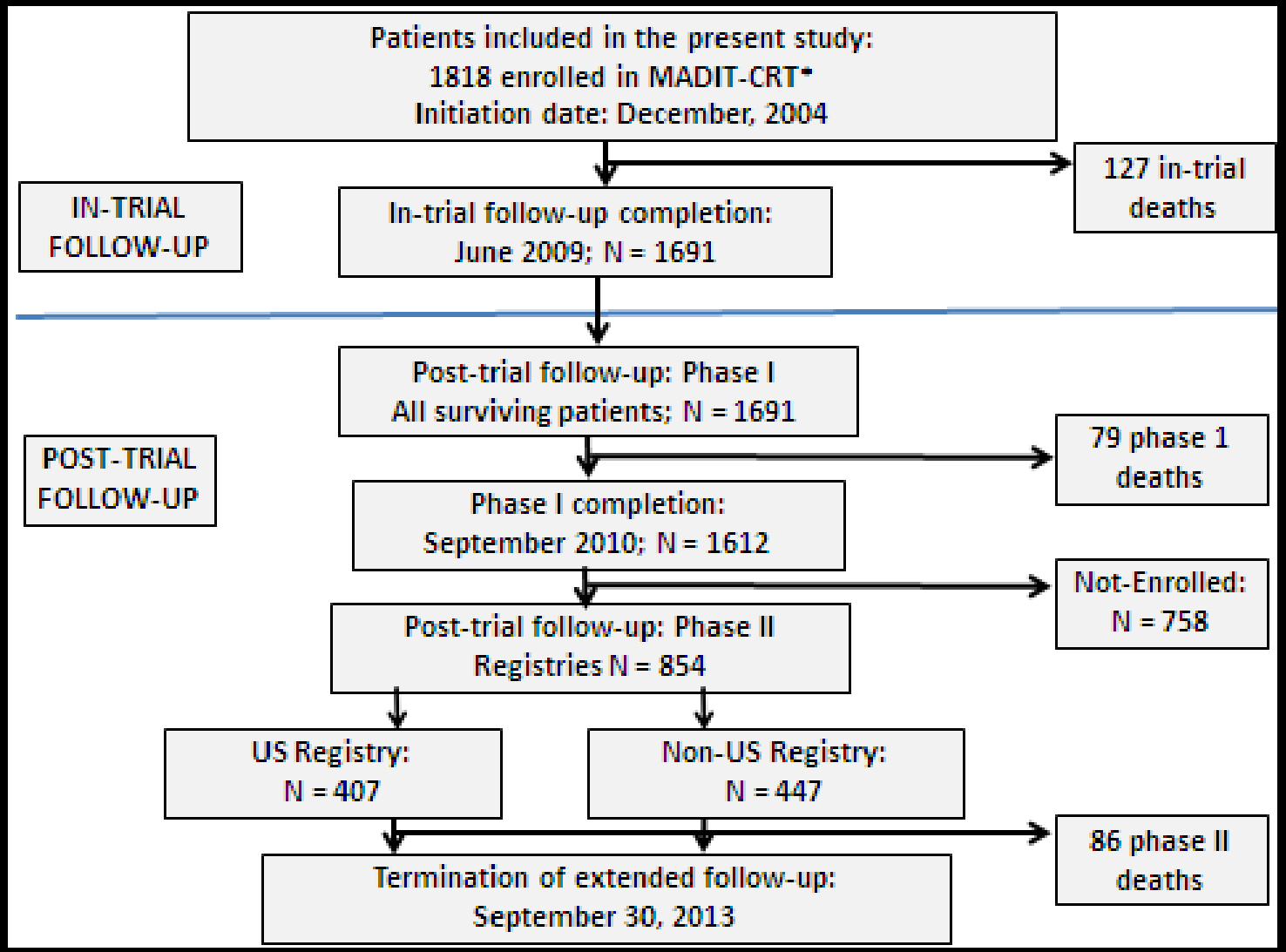
- Hypothesis: The pronounced reduction in heart failure events associated with CRT during the in-trial period of MADIT-CRT would translate into a long-term survival benefit

Population and Trial Periods

- MADIT-CRT study: In-trial period
  - 1820 patients:
    - 88 US centers; 1,271 pts (70%)
    - 24 Non-US Centers; 549 pts (30%)
  - In-trial period: December 22, 2004 – June 20, 2009

- MADIT-CRT Long Term Follow-up: Post-trial period
  - 1691 patients
  - Last in-trial follow-up visit – September 30, 2013

MADIT-CRT Long Term Follow-up: Study Design



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Outcome Measures

- Primary end point:
  - All-cause mortality from enrollment in MADIT-CRT through post-trial follow-up
- Secondary endpoints:
  - Separate occurrence of non-fatal HF events
  - Combined end point of non-fatal HF event or death

Statistical Analysis

- All analyses performed:
  - On an intention-to-treat basis by original treatment allocation regardless of in-trial and post-trial crossovers
  - By LBBB status at enrollment with interaction-term analysis

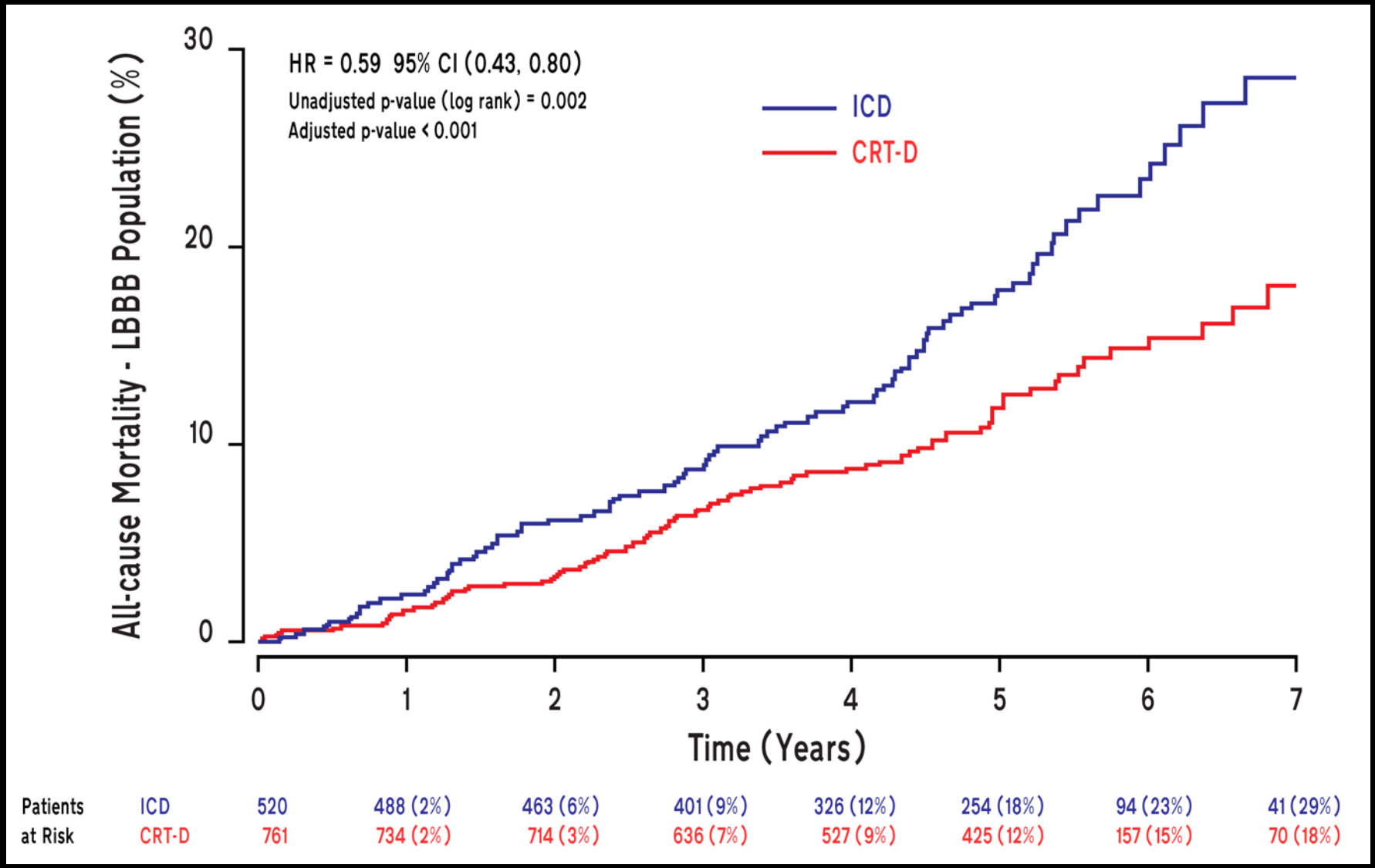
Results

Follow-Up Data

- Follow-up time:
  - In-trial: 2.4 yrs (IQR = 1.8 – 3.2)
  - Post-trial: 5.6 years (IQR = 5.1 – 6.4)
- Device change:
  - ICD to CRT-D: 9%
  - CRT-D to ICD: 5%
- Clinical events:
  - 292 pts died (16%)
  - 442 pts experienced a non-fatal HF event (24%)

LBBB: All-Cause Mortality

NNT = 9



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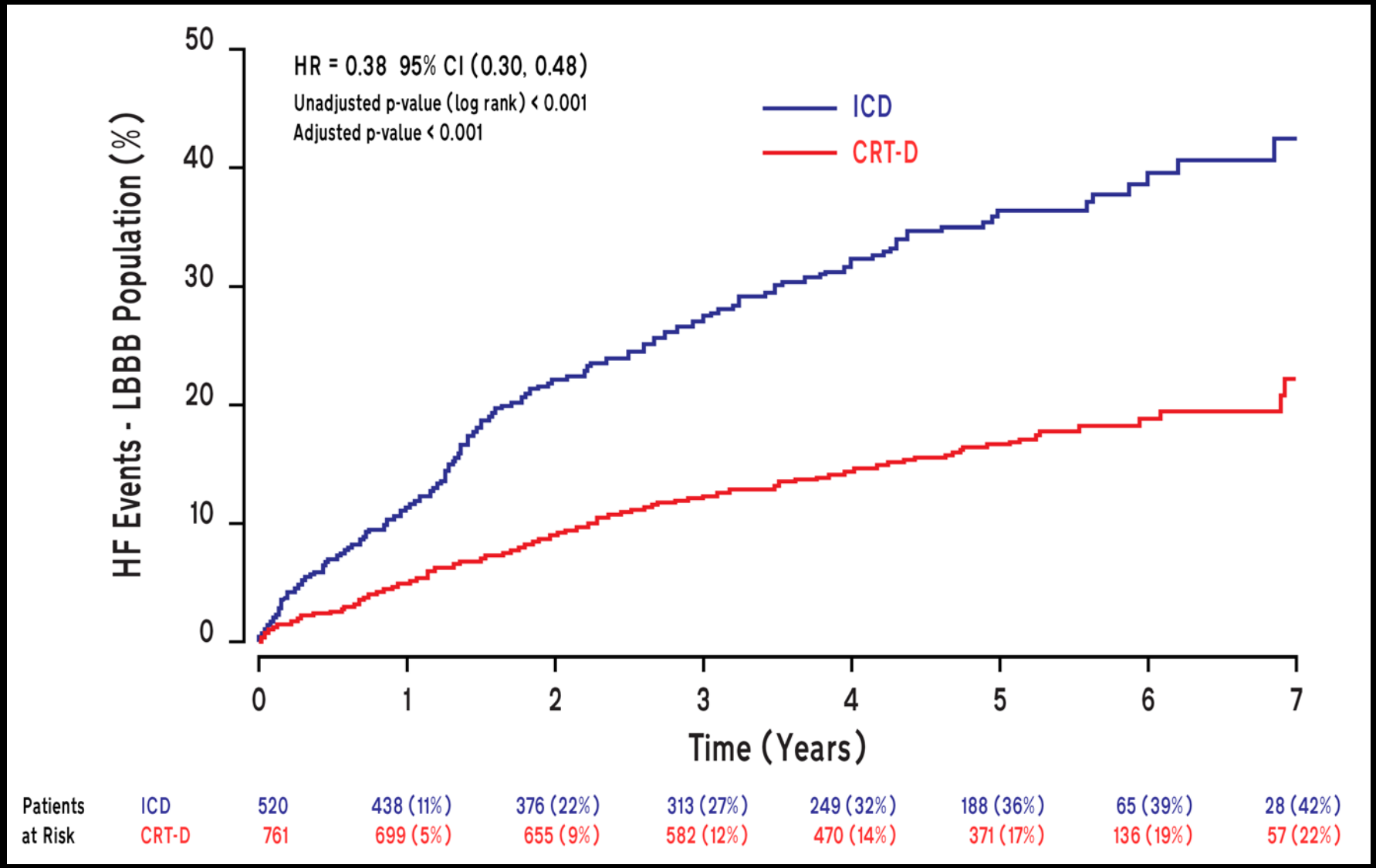
LBBB: Non-Fatal Heart Failure Events



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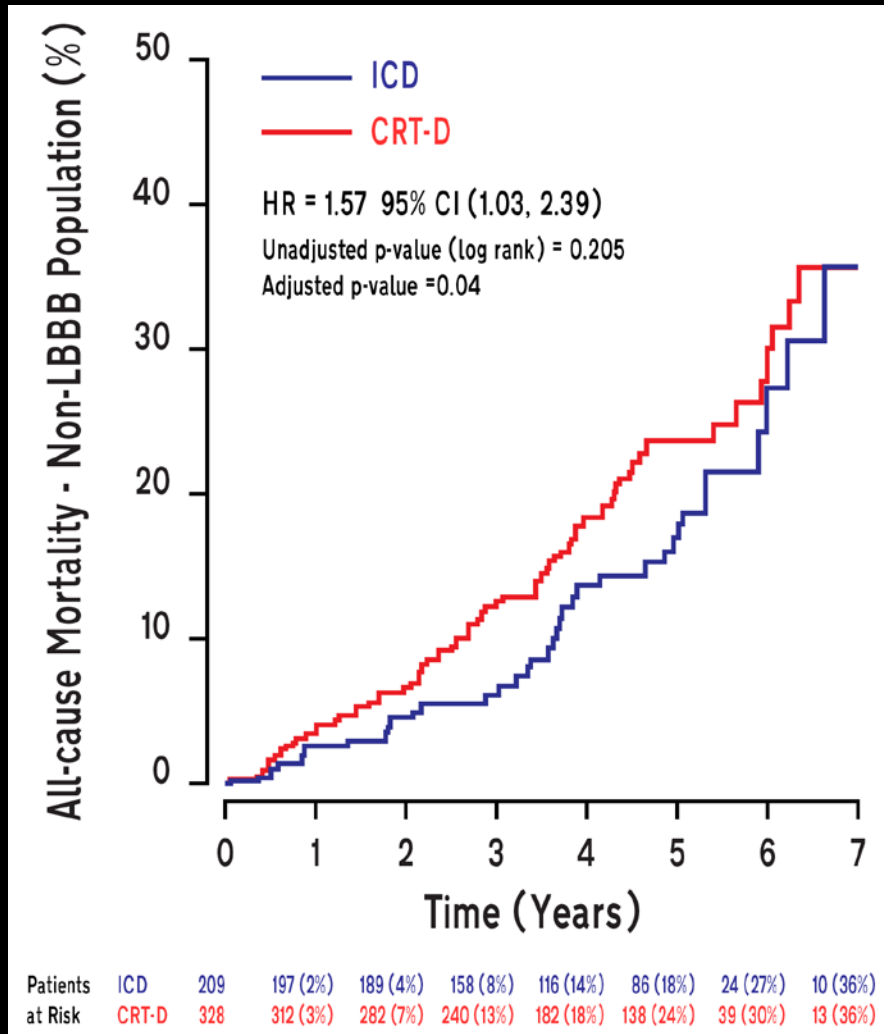
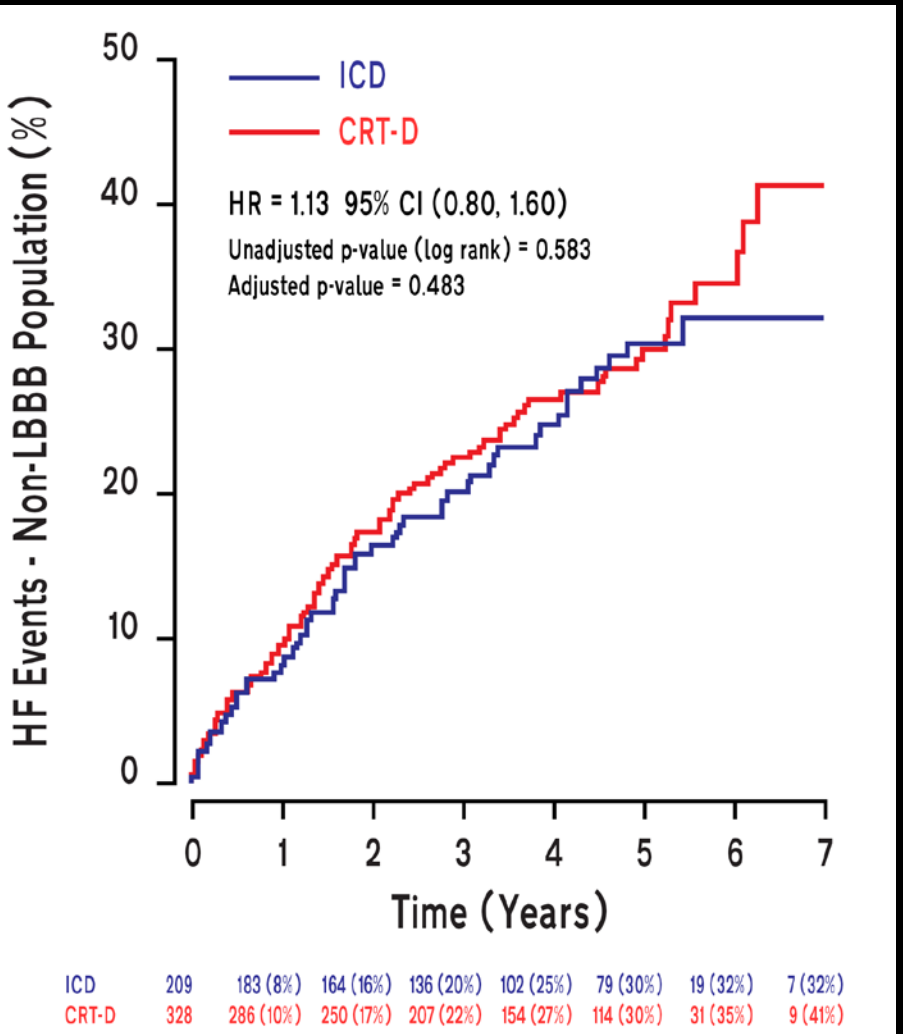
Non-LBBB

All-Cause Mortality



Non-Fatal Heart Failure Events



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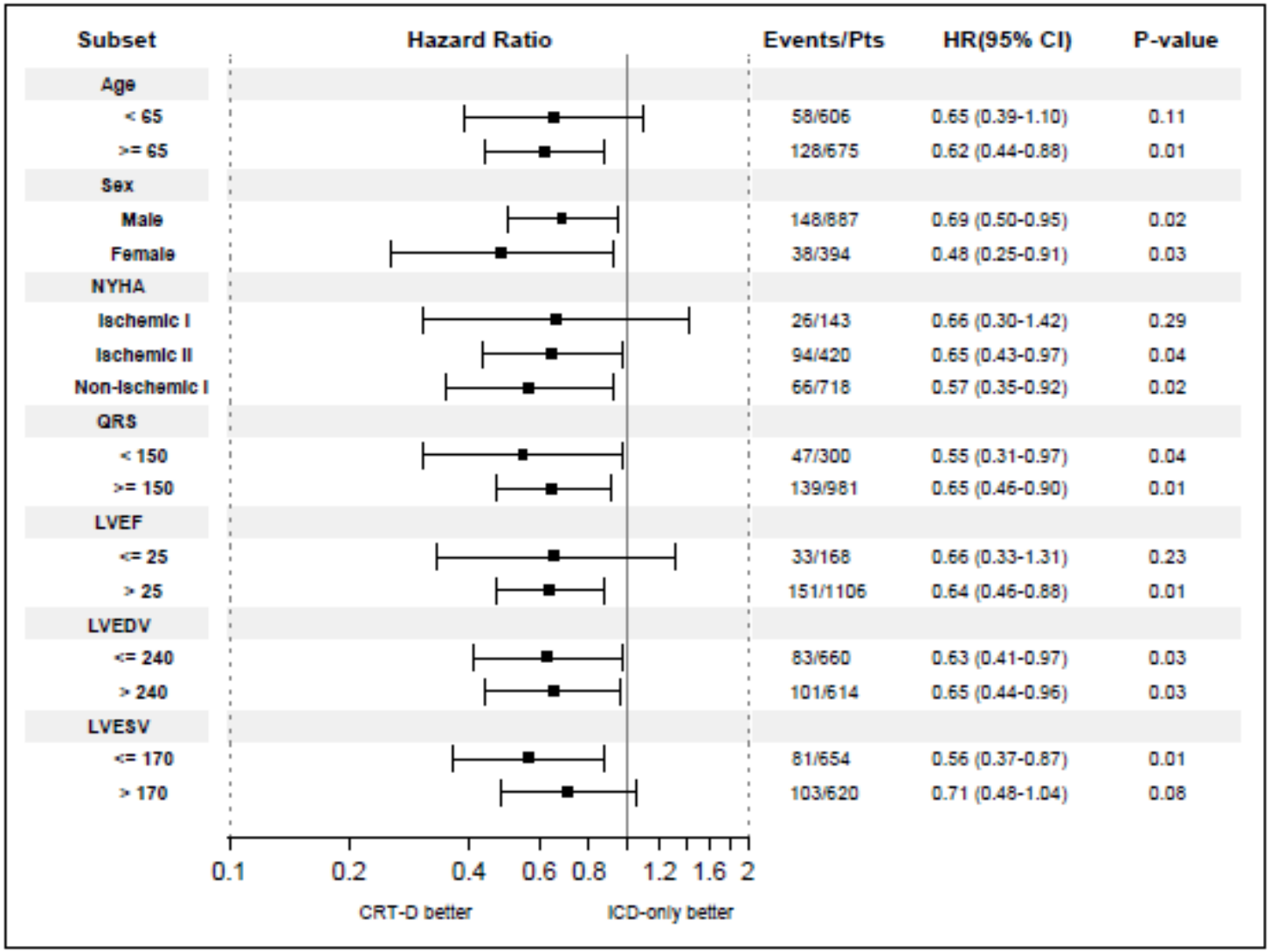
Multivariate Analysis
Survival Benefit of CRT-D by LBBB Status

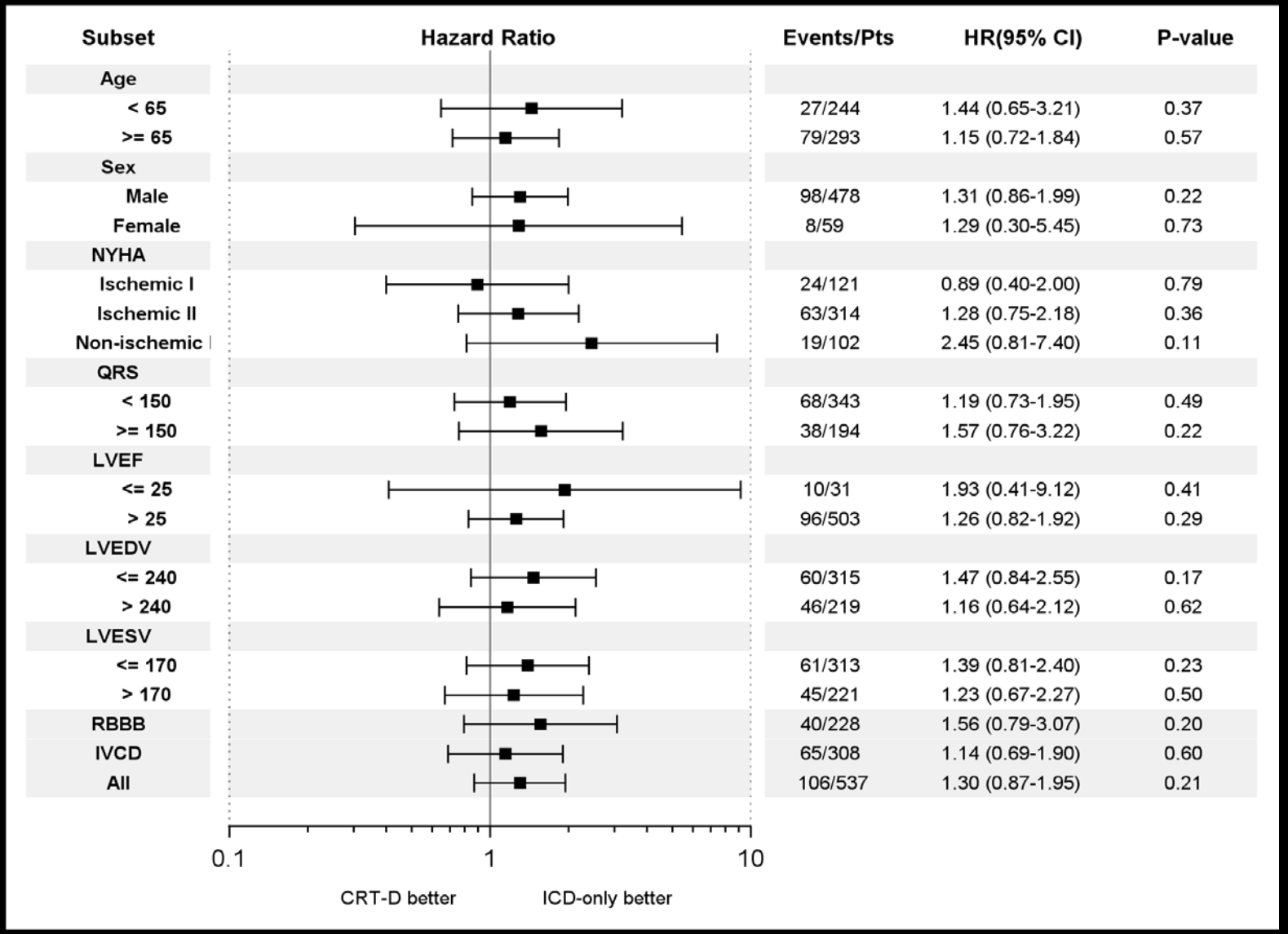
	LBBB		Non-LBBB		P-Interaction
End Point	HR (95% CI)	P-value	HR (95% CI)	P-value	
All-cause mortality	0.59 (0.43 – 0.80)	<0.001	1.57 (1.03 – 2.39)	0.04	<0.001
Non-fatal HF	0.38 (0.30 – 0.48)	<0.001	1.13 (0.80 – 1.60)	0.48	<0.001
HF or death	0.45 (0.37 – 0.56)	<0.001	1.27 (0.94 – 1.73)	0.12	<0.001

Findings are further adjusted for age at enrollment, serum creatinine ≥ 1.4 mg/dL, smoking status, diabetes mellitus, etiology of cardiomyopathy, LV end systolic volume, QRS duration ≥ 150 ms , NYHA class > II at 3 months prior to enrollment.

LBBB Subgroup Analysis



Non-LBBB Subgroup Analysis



Summary

- In patients with mild heart failure symptoms, left ventricular dysfunction, and LBBB, early intervention with CRT is associated with a significant long-term survival benefit

- No survival benefit found in mild heart failure patients without LBBB

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.
(Rev. Q)

Slides adapted from those presented by Ilan Goldenberg, MD at ACC 2014, Washington, DC USA

CRT-D Systems from Boston Scientific – PUNCTUA, ENERGEN, and INCEPTA

Indications 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

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 external 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.

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.

(Rev. A)

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.
(Rev. P)

Slides adapted from those presented by Ilan Goldenberg, MD at ACC 2014, Washington, DC USA

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.
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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

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(Rev. A)