LONG-TERM SURVIVAL WITH CARDIAC RESYNCHRONIZATION THERAPY IN MILD HEART FAILURE PATIENTS

Ilan Goldenberg, MD, Valentina Kutyifa, MD, PhD, Helmut Klein, MD, Scott McNitt, MA, Mary Brown, MA, Arthur J. Moss, MD; and the MADIT-CRT LTFU Executive Committee

From the Cardiology Division of the Department of Medicine (I.G., VK, HK, SM, AJ.M) University of Rochester Medical Center, Rochester, N.Y.; and Leviev Heart Center, Sheba Medical Center and Tel Aviv University, Israel (I.G.)

Presenter Disclosure Information

Ilan Goldenberg, MD

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

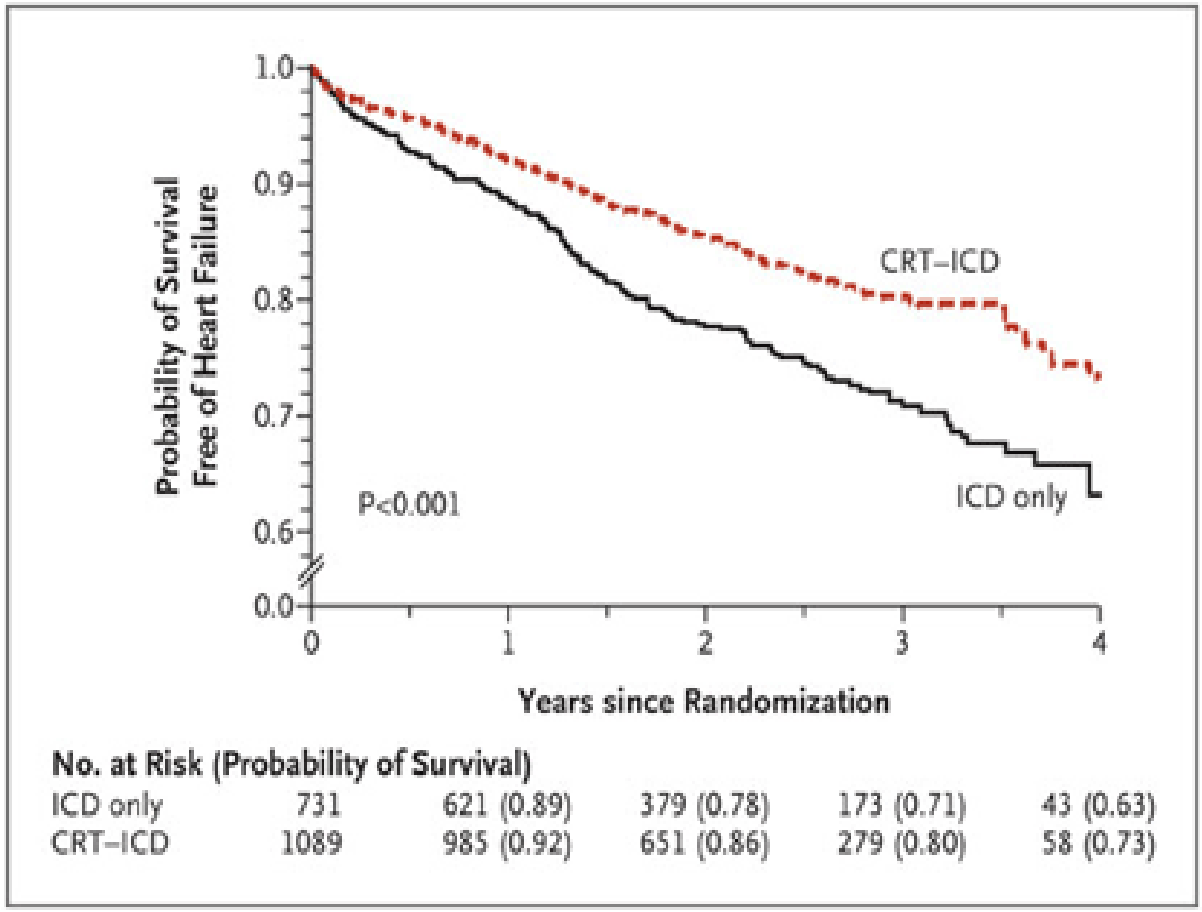
DISCLOSURE INFORMATION:

The following relationships exist related to this presentation:

The long-term follow-up of MADIT-CRT was supported by an unrestricted research grant from Boston Scientific to the University of Rochester Medical Center and to the Israeli Association for Cardiovascular Trials

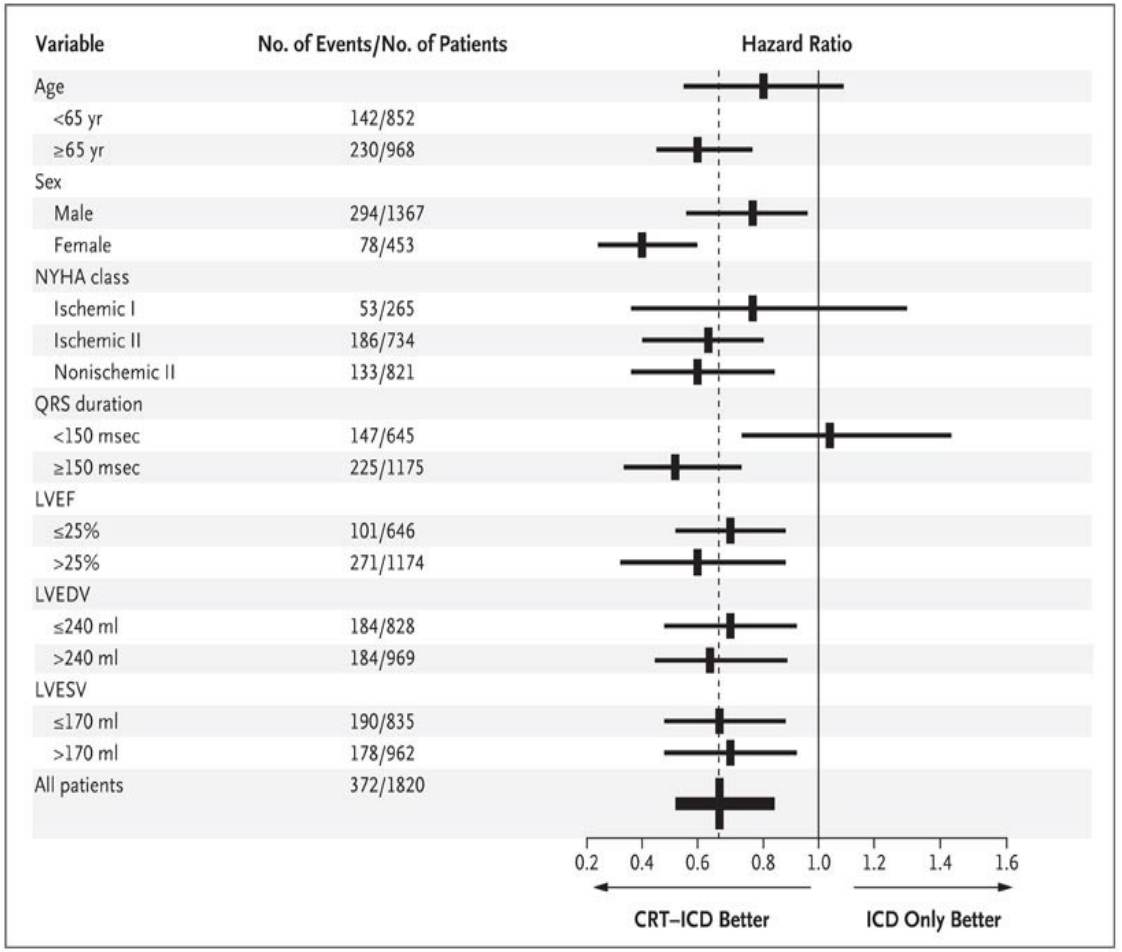
BACKGROUND: MADIT-CRT

- **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)



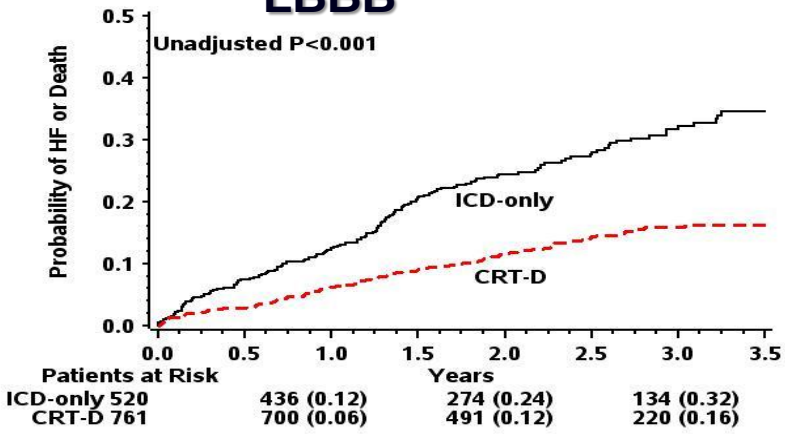
MADIT-CRT: SUBGROUP ANALYSIS
Moss et al. NEJM, 2009

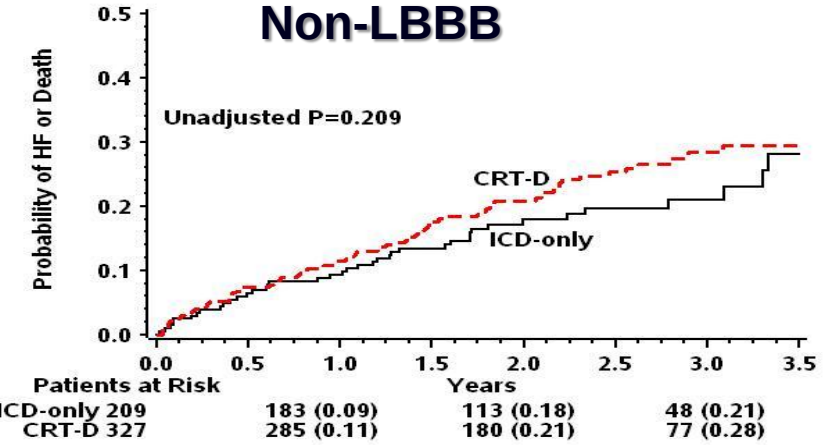
- **Differential clinical response:**
  - **Gender**
  - **QRS duration**

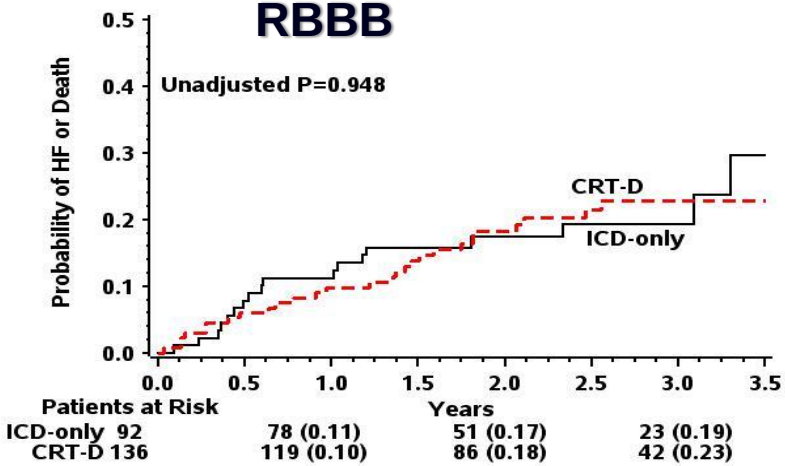


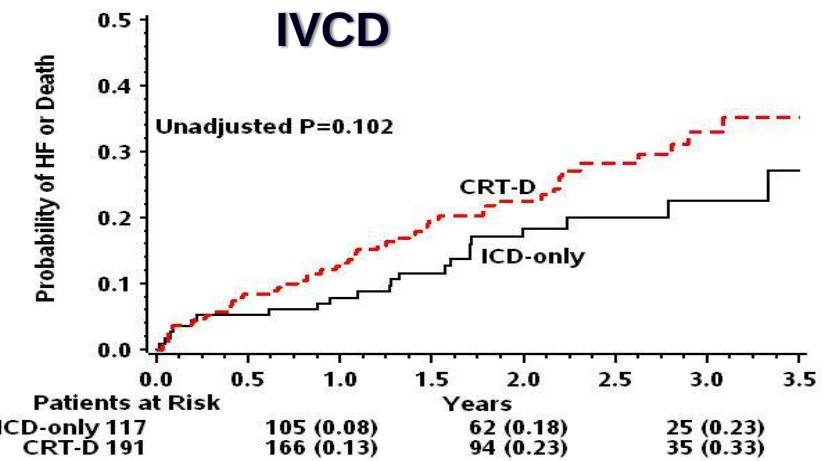
MADIT-CRT: QRS MORPHOLOGY

Zareba et al. Circulation , 2011









STUDY PURPOSE

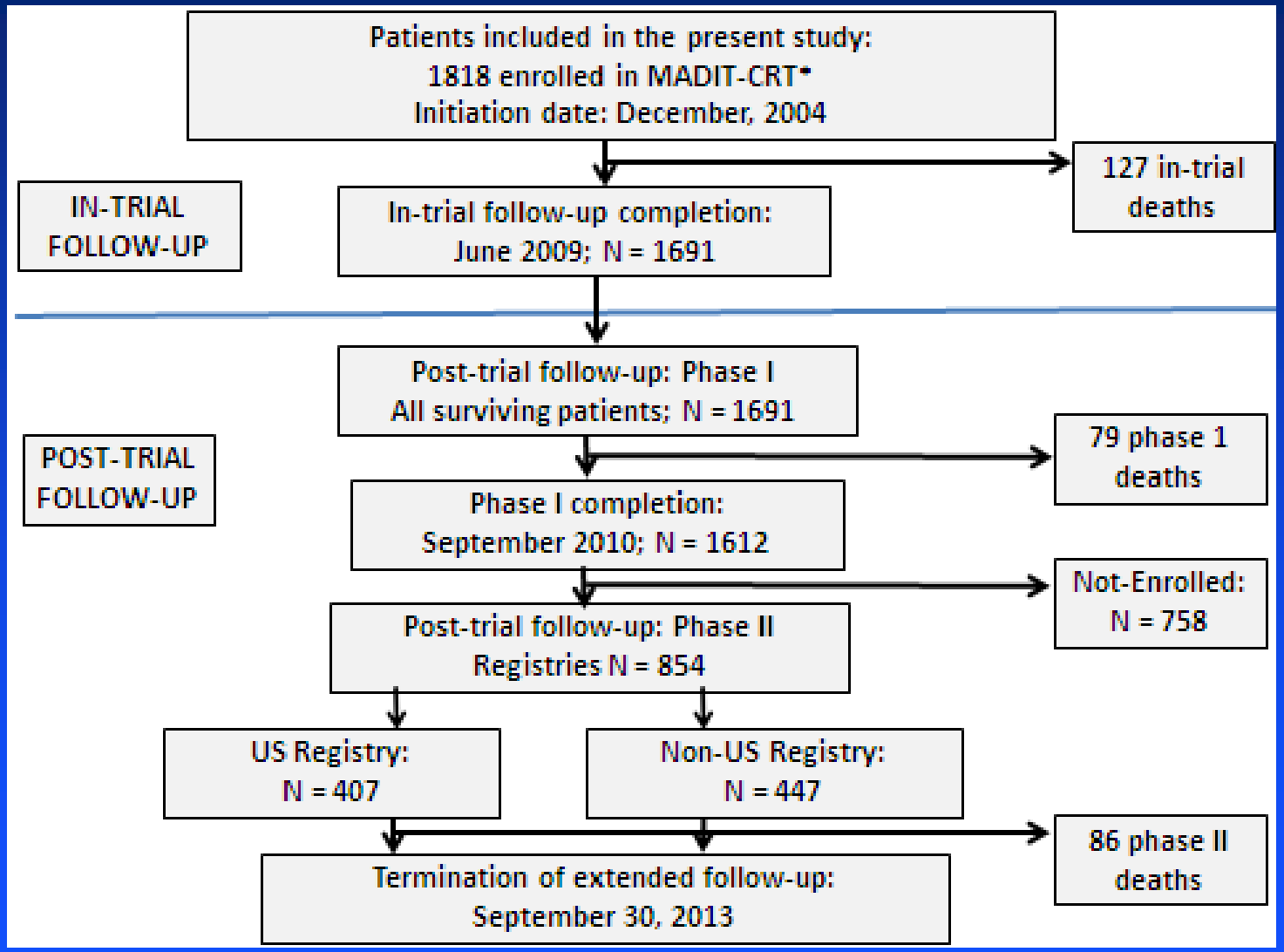
We hypothesized that the pronounced reduction in heart failure events associated with CRT during the in-trial period of MADIT-CRT would translate into a long-term survival benefit

METHODS

POPULATION AND TRIAL PERIODS

- 1820 MADIT-CRT patients:
  - 88 US Centers; 1,271 pts (70%)
  - 24 Non-US Centers; 549 pts (30%)
- MADIT-CRT: In-trial period
  - December 22, 2004 – June 20, 2009
- MADIT-CRT LTFU: Post-trial period
  - Last in-trial FU visit – September 30, 2013

MADIT-CRT LTFU: STUDY DESIGN



OUTCOME MEASURES

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

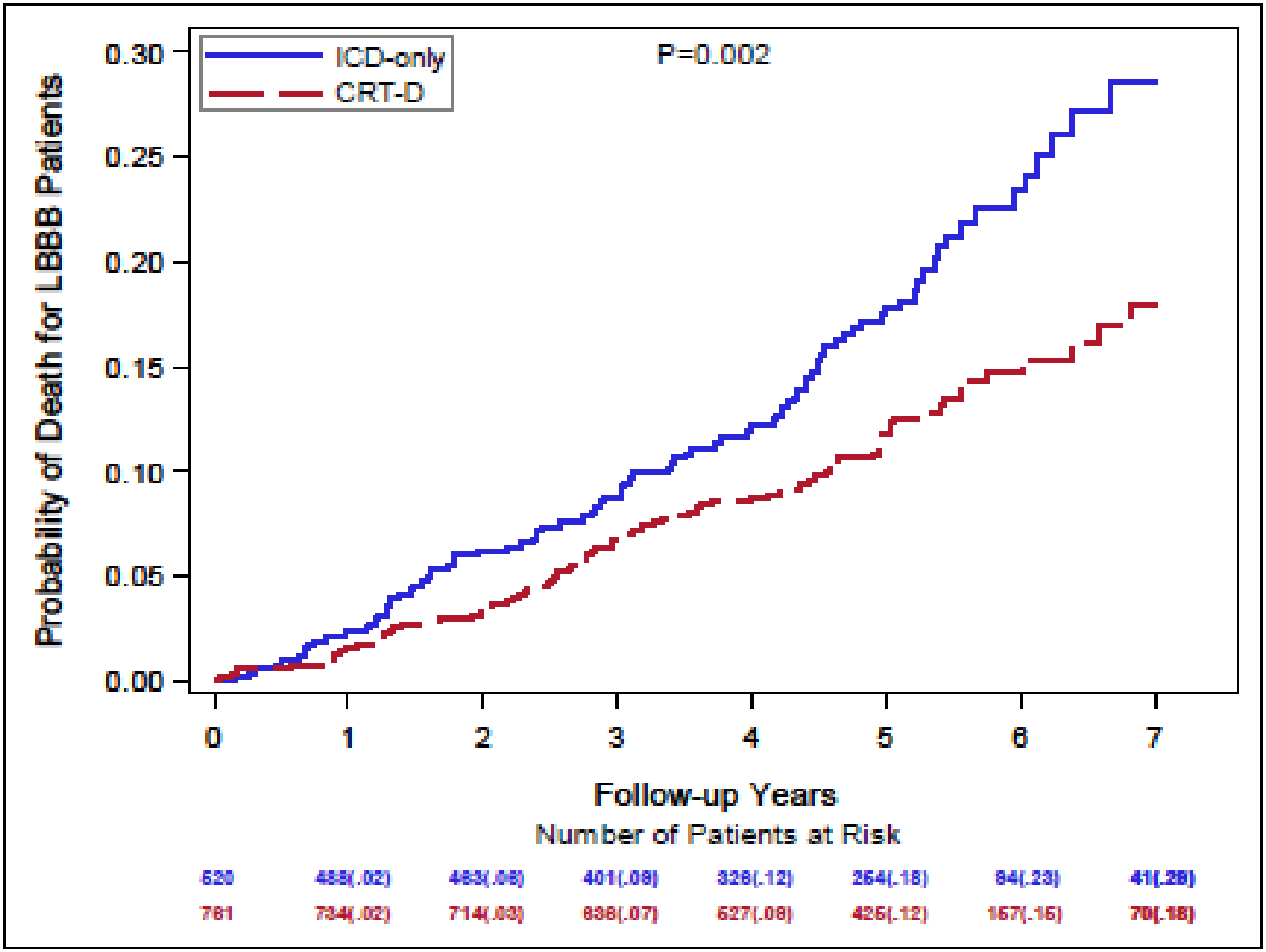
RESULTS

FOLLOW-UP DATA

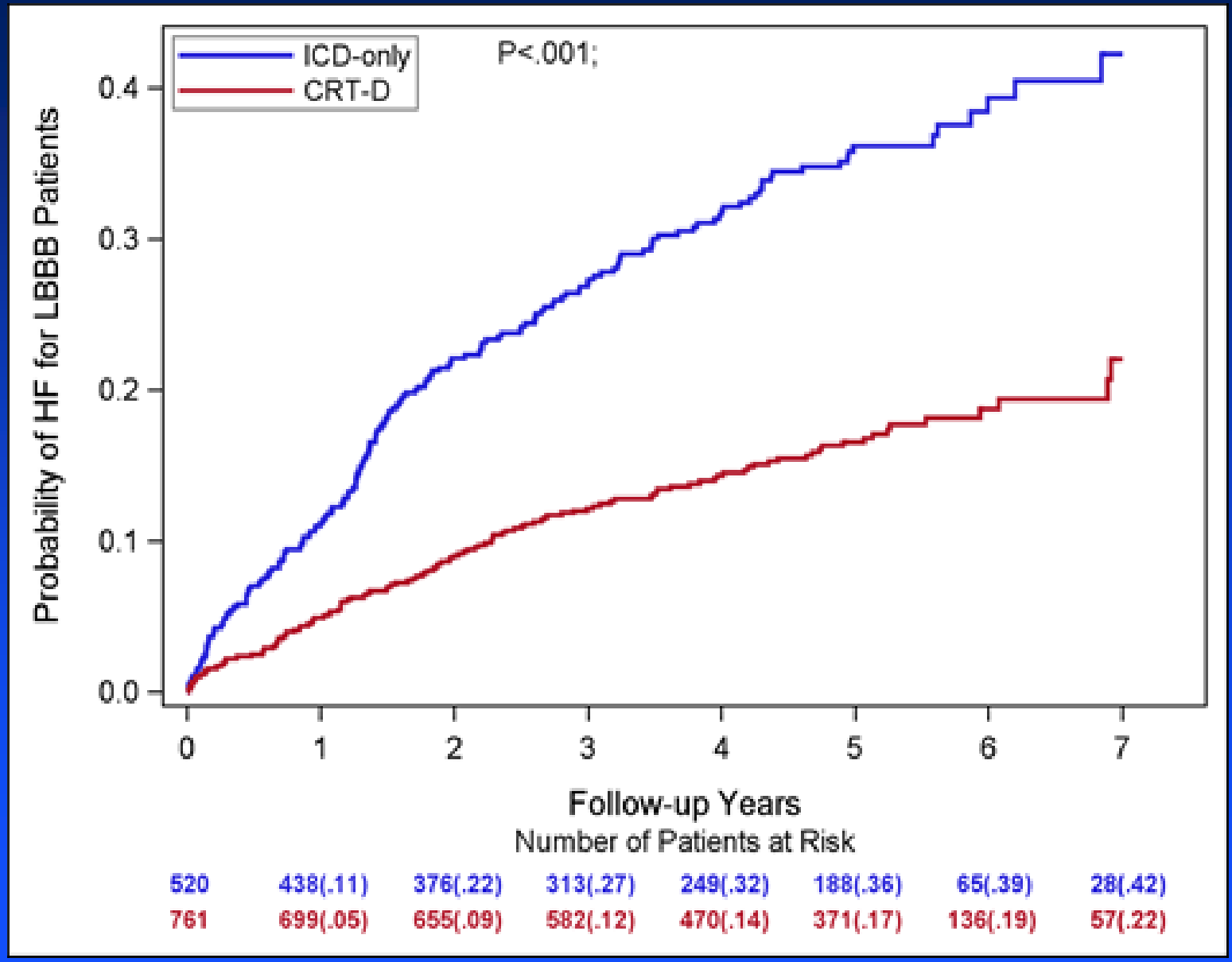
- **Follow-up time:**
  - In-trial: 2.4 yrs (IQR = 1.8 – 3.2)
  - Post-trial: 5.6 years (IQR = 5.1 – 6.4)
- **Device change:**
  - ICD to CRT-D: 9%
  - CRT-D to ICD: 5%
- **Clinical events:**
  - 292 pts died (16%)
  - 442 pts experienced a non-fatal HF event (24%)

LBBB: ALL-CAUSE MORTALITY

NNT = 9

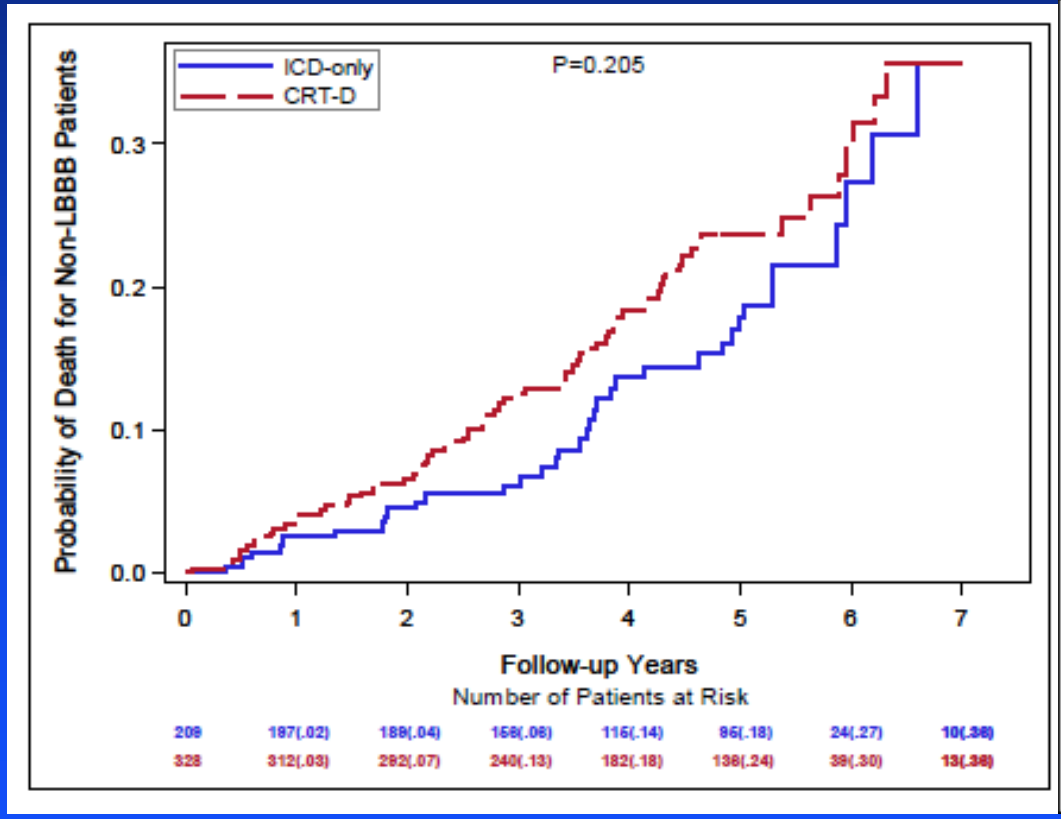


LBBB: NON-FATAL HF EVENTS

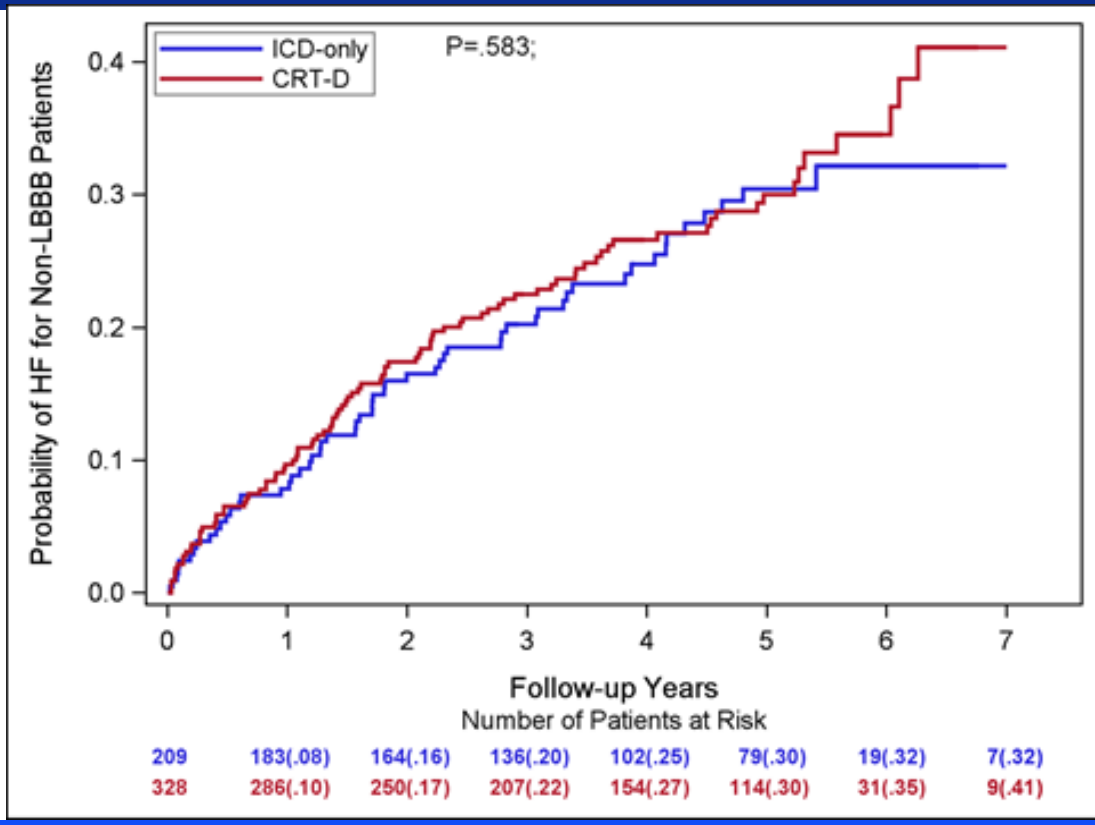


NLBBB

ALL-CAUSE MORTALITY



NON-FATAL HF EVENTS

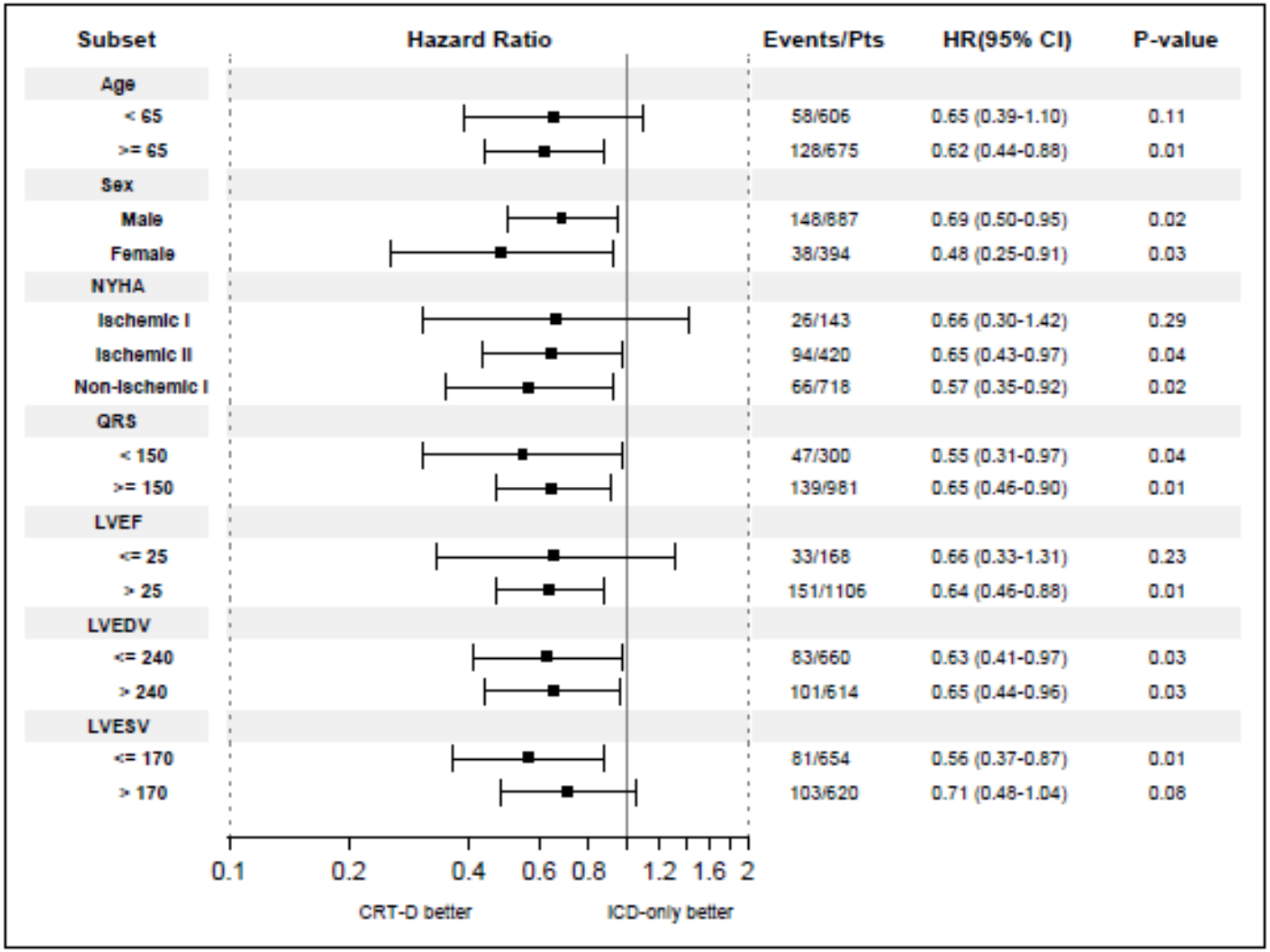


MULTIVARIATE ANALYSIS: SURVIVAL BENEFIT OF CRT-D BY LBBB STATUS

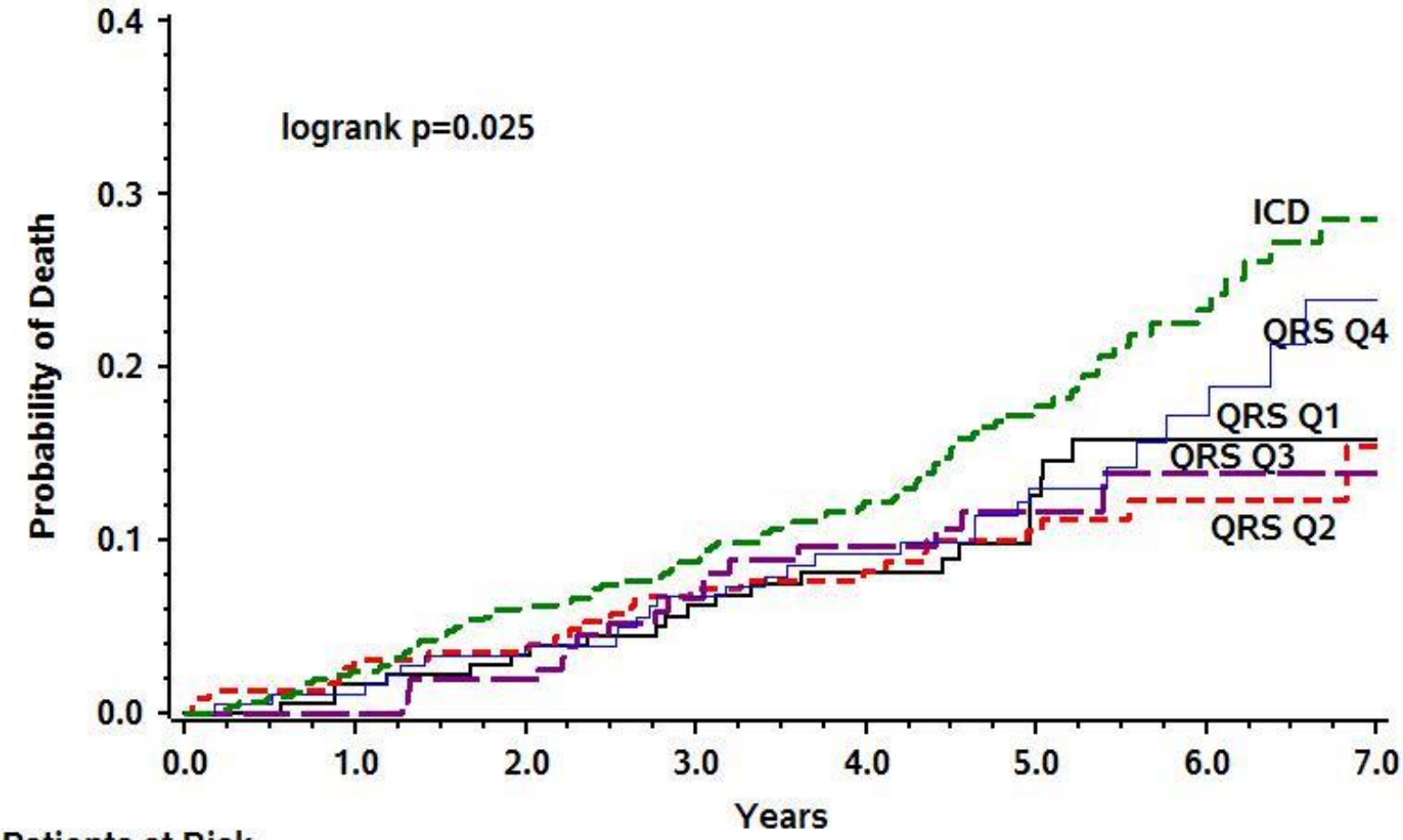
	LBBB		NLBBB		P-INT
END POINT	HR	P-value	HR	P-value	
All-cause mortality	0.59 (0.43 – 0.80)	<0.001	1.57 (1.03 – 2.39)	0.04	<0.001
Non-fatal HF	0.38 (0.30 – 0.48)	<0.001	1.13 (0.80 – 1.60)	0.48	<0.001
HF or death	0.45 (0.37 – 0.56)	<0.001	1.27 (0.94 – 1.73)	0.12	<0.001

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



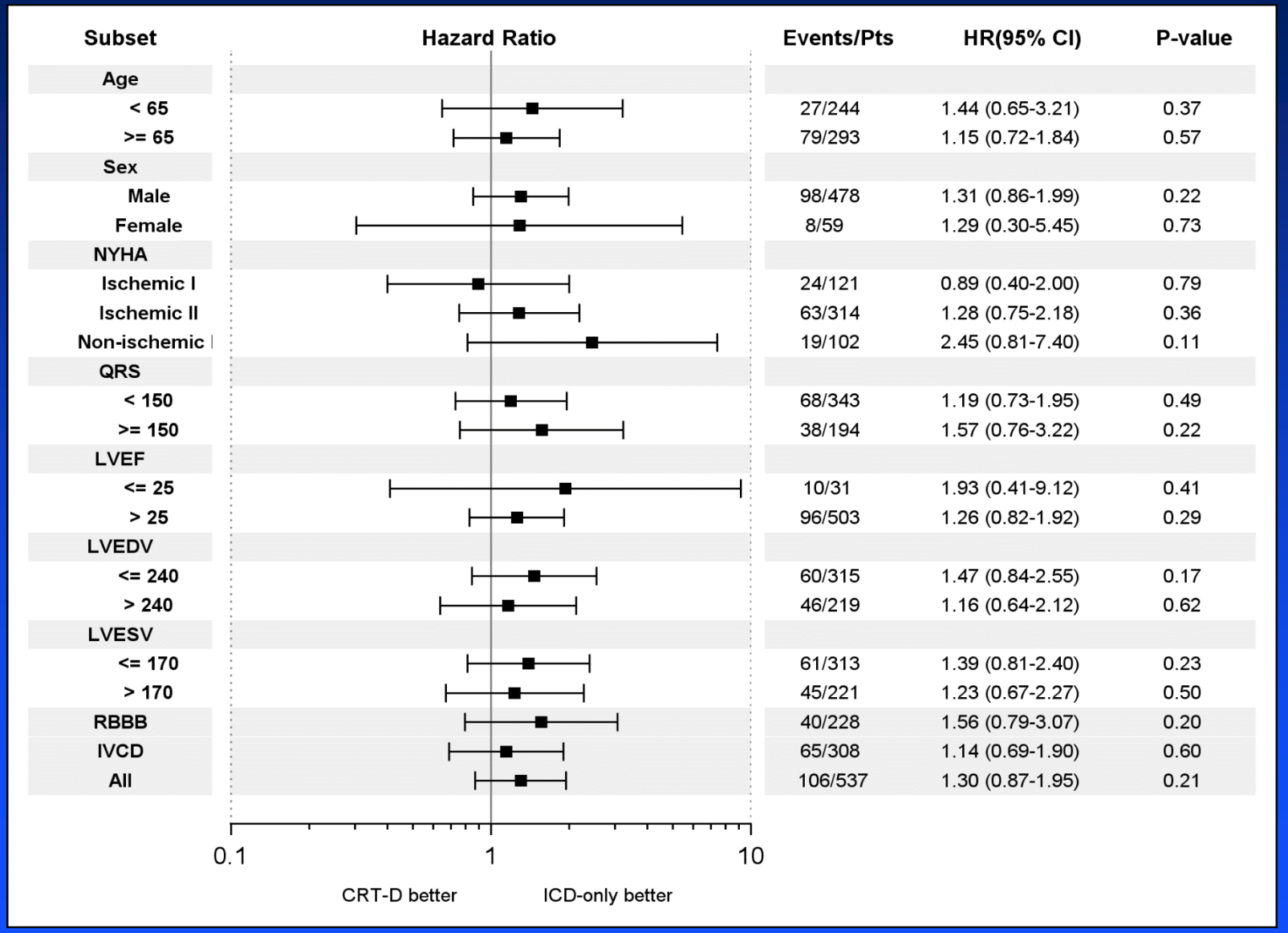
LBBB: EFFICACY IN QRS SUBGROUPS



Patients at Risk

QRS Q1	186	180 (0.02)	172 (0.04)	139 (0.07)	99 (0.10)	30 (0.16)	13 (0.16)
QRS Q2	232	219 (0.03)	209 (0.05)	173 (0.08)	142 (0.10)	60 (0.12)	19 (0.15)
QRS Q3	160	156 (0)	145 (0.05)	109 (0.09)	83 (0.12)	19 (0.14)	6 (0.14)
QRS Q4	183	176 (0.02)	171 (0.04)	146 (0.09)	117 (0.11)	48 (0.17)	16 (0.24)
ICD	520	485 (0.03)	447 (0.07)	351 (0.11)	260 (0.17)	95 (0.23)	35 (0.30)

NLBBB: SUBGROUP ANALYSIS



CONCLUSIONS

- 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 clinical benefit in mild heart failure patients without LBBB

MADIT-CRT LTFU EXECUTIVE COMMITTEE

Arthur J. Moss, MD (University of Rochester, Rochester NY, USA)
Ilan Goldenberg, MD (Sheba Medical Center, Israel and Rochester NY, USA)
Helmut Klein, MD (University of Rochester, Rochester NY, USA)
Valentina Kutyifa, MD (University of Rochester, Rochester NY, USA)
David S. Cannom, MD (Cedars-Sinai Heart Institute, USA)
Scott D. Solomon MD (WBH, Havard Medical School, USA)
Ariela Dan, PhD, (Sheba Medical Center, Israel)
Robert Klempfner, MD (Sheba Medical Center, Israel)
James P. Daubert, MD (Duke University Medical Center, Durham NC, USA)
Mark Estes III, MD (Tufts New England Medical Center, Boston, MA)
Mark A. Pfeffer MD, PhD (WBH, Havard Medical School, USA)
Elyse Foster, MD (University of California at SF, CA, USA)
Henry Greenberg, MD (St. Luke's Roosevelt Hospital, New York, NY, USA)
Aurelio Quesada MD (Hospital General de Valencia, Valencia, Spain);
Josef Kautzner MD (Institute for Clinical and Experimental Medicine, Prague, Czech Republic)
Bela Merkely, MD, PhD (Semmelweis University, Budapest, Hungary)
Malte Kuniss, MD (Kerchhoff Klinik, Bad Nauheim, Germany)
Sami Viskin MD (Tel Aviv Medical Center, Tel Aviv, Israel)
Mary W. Brown, MS (University of Rochester, Rochester NY, USA)
Wojciech Zareba, MD, PhD (University of Rochester, Rochester NY, USA)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Cardiac-Resynchronization Therapy in Mild Heart Failure

Ilan Goldenberg, M.D., Valentina Kutyifa, M.D., Ph.D., Helmut U. Klein, M.D., David S. Cannom, M.D., Mary W. Brown, M.S., Ariela Dan, Ph.D., James P. Daubert, M.D., N.A. Mark Estes III, M.D., Elyse Foster, M.D., Henry Greenberg, M.D., Josef Kautzner, M.D., Robert Klempfner, M.D., Malte Kuniss, M.D., Bela Merkely, M.D., Ph.D., Marc A. Pfeffer, M.D., Ph.D., Aurelio Quesada, M.D., Ph.D., Sami Viskin, M.D., Scott McNitt, M.S., Bronislava Polonsky, M.S., Ali Ghanem, M.D., Scott D. Solomon, M.D., David Wilber, M.D., Wojciech Zareba, M.D., Ph.D., and Arthur J. Moss, M.D.

ABSTRACT

BACKGROUND

The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) showed that early intervention with cardiac-resynchronization therapy with a defibrillator (CRT-D) in patients with an electrocardiographic pattern showing left bundle-branch block was associated with a significant reduction in heart-failure events over a median follow-up of 2.4 years, as compared with defibrillator therapy alone.

METHODS

We evaluated the effect of CRT-D on long-term survival in the MADIT-CRT population. Post-trial follow-up over a median period of 5.6 years was assessed among all 1691 surviving patients (phase 1) and subsequently among 854 patients who were enrolled in post-trial registries (phase 2). All reported analyses were performed on an intention-to-treat basis.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Goldenberg at Leviev Heart Center and Israeli Association for Cardiovascular Trials, Sheba Medical Center and Tel Aviv University, Tel Hashomer 5265601, Israel, or at ilan.goldenberg@sheba.health.gov.il; or to Dr. Moss at the Heart Research Follow-up Program, University of Rochester Medical Center, 265 Crittenden Blvd., CU 420653, Rochester, NY 14642-0653, or at heartajm@heart.rochester.edu.

Drs. Goldenberg, Kutyifa, Klein, and Moss contributed equally to this article.

This article was published on March 30, 2014, at NEJM.org.

THANK YOU