

**RE**synchronization re**VE**rses **R**emodeling in  
**S**ystolic left v**E**ntricular dysfunction:  
Results of the REVERSE Trial

Cecilia Linde, Stockholm, Sweden  
William T. Abraham, Columbus, U.S.  
Michael R. Gold, Charleston, U.S.  
Jean-Claude Daubert, Rennes, France

On Behalf of the **REVERSE**  
Investigators and Coordinators

# Acknowledgments

## Steering Committee

W. T. Abraham, J-C. Daubert (study initiator), C. Linde (coordinating clinical Investigator), M. Gold

## Echo Core Labs

Ghio, S, St. John Sutton, MG

## Adverse Events Advisory Committee

D. Böcker, J. P. Boehmer, J. G. F. Cleland, M. Gold, J. T. Heywood, A. Miller (chair)

## Data Monitoring Committee

J. Aranda, J. Cohn (chair), P. Grambsch; M. Komajda

## Investigators

**Austria:** H. Mayr, A. Teubl; **Belgium:** R. Willems; **Canada:** C. Simpson; **Czech Republic:** J. Lukl; **Denmark:** H. Eiskjær, C. Hassager, M. Møller, T. Vesterlund; **France:** E. Aliot, P. Chevalier, J-C. Daubert, J-M. Davy, P. Djiane, H. Le Marec; **Germany:** G. Groth, G. Klein, T. Lawo, C. Reithmann; **Hungary:** T. Forster, T. Szili-Török; **Ireland:** R. Sheahan; **Italy:** S. Lombroso, M. Lunati, L. Padeletti, M. Santini; **Netherlands:** B. Dijkman; **Norway:** S. Færestrand, F. T. Gjestvang; **Spain:** I. Fernandez Lozano, R. Muñoz Aguilera, A. Quesada Dorador; **Sweden:** C. Linde, F. Maru, K. Säfström; **United Kingdom:** G. Goode; **United States:** U. Birgersdotter-Green, J. Boehmer, E. Chung, S. Compton, J. Dinerman, D. Feldman, R. Fishel, G. J. Gallinghouse, M. Gold, S. Hankins, J. Herre, M. Hess, E. Horn, S. Hsu, S. Hustead, S. Jennison, E. Johnson, W. B. Johnson, G. Jones, R. Malik, A. Merliss, S. Mester, S. Moore, N. Nasir, F. Pelosi, Jr., D. Renlund, K. Rist, R. Sangrigoli, R. Silverman, D. Smull, K. Stein, L. Stevenson, J. Stone, N. Sweitzer, D. Venesy, L. Zaman.

## Sponsor

Medtronic Inc.

# ***Presenter Disclosure Information***

Cecilia Linde, MD, PhD

**The following relationships exist related to this presentation:**

- *Consulting Fees, Medtronic and St. Jude, moderate level*
- *Research Grants, Medtronic and the Sweden Heart and Lung Foundation, significant level*

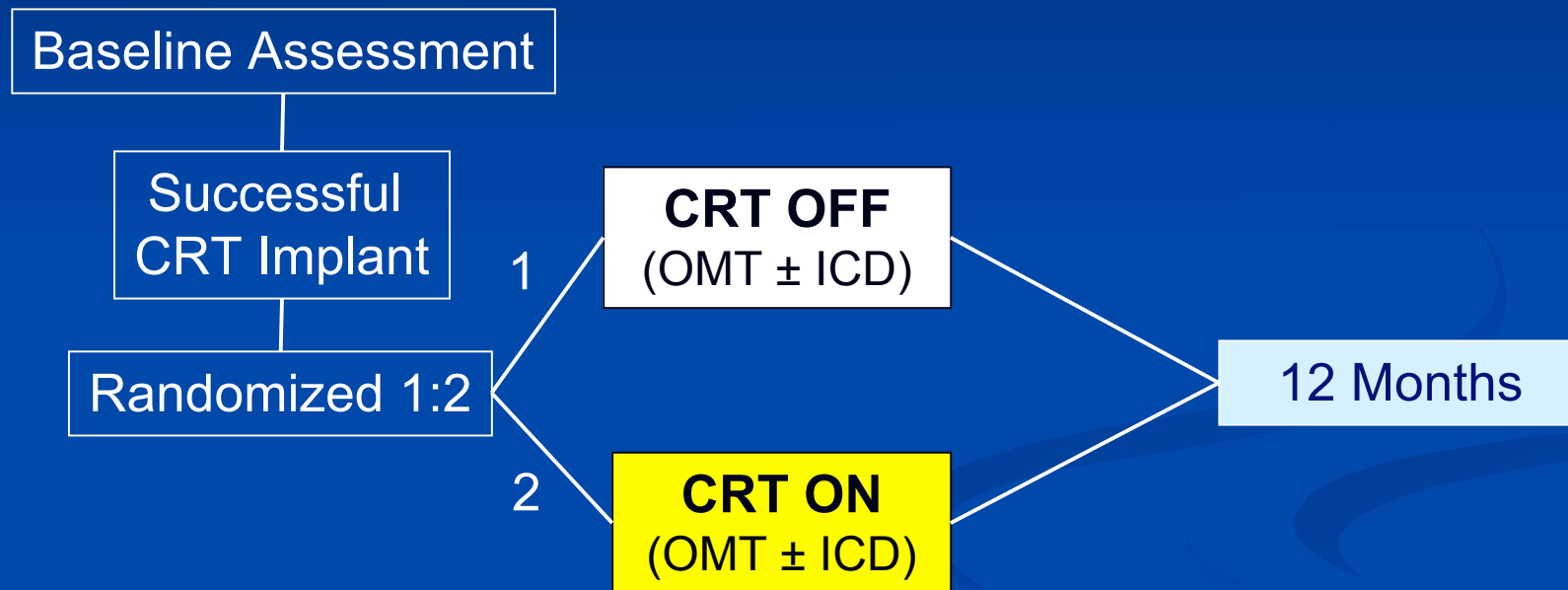
## ***Purpose and Design***

- To determine the effects of CRT with or without an ICD on disease progression over 12 months in patients with asymptomatic and mildly symptomatic heart failure and ventricular dysynchrony
- Randomized, double-blind, parallel-controlled clinical trial

## *Inclusion Criteria*

- NYHA Class II or I (previously symptomatic)
- QRS  $\geq$  120 ms; LVEF  $\leq$  40%; LVEDD  $\geq$  55 mm
- Optimal medical therapy (OMT)
- Without permanent cardiac pacing
- With or without an ICD indication

# Study Schematic



U.S., Canada: at 12 Months, all patients recommended CRT ON  
Europe: at 24 Months, all patients recommended CRT ON

## ***End Points***

- **Primary:** HF Clinical Composite Response, comparing the proportion of patients worsened in CRT OFF vs. CRT ON groups
  - Composite includes: all-cause mortality, HF hospitalizations, crossover due to worsening HF, NYHA class, and the patient global assessment assessed in double blind manner
- **Prospectively Powered Secondary:** Left Ventricular End Systolic Volume Index (LVESVi) comparing CRT OFF vs. CRT ON subjects
  - LVESVi is assessed by two core labs (1 in Europe, 1 in U.S)

# Enrollment and Randomization

684 Enrolled (2004-2006)

----- -42 ineligible or withdrew

642 Implant Attempts

----- -21 unsuccessful implant

621 Successful CRT Implants

**(97%)**

----- -11 exits after successful implant

610 Patients Randomized

U.S. 343 (56%); Europe 262 (43%); Canada 5 (<1%)

**CRT OFF 191 Patients**

**CRT ON 419 Patients**

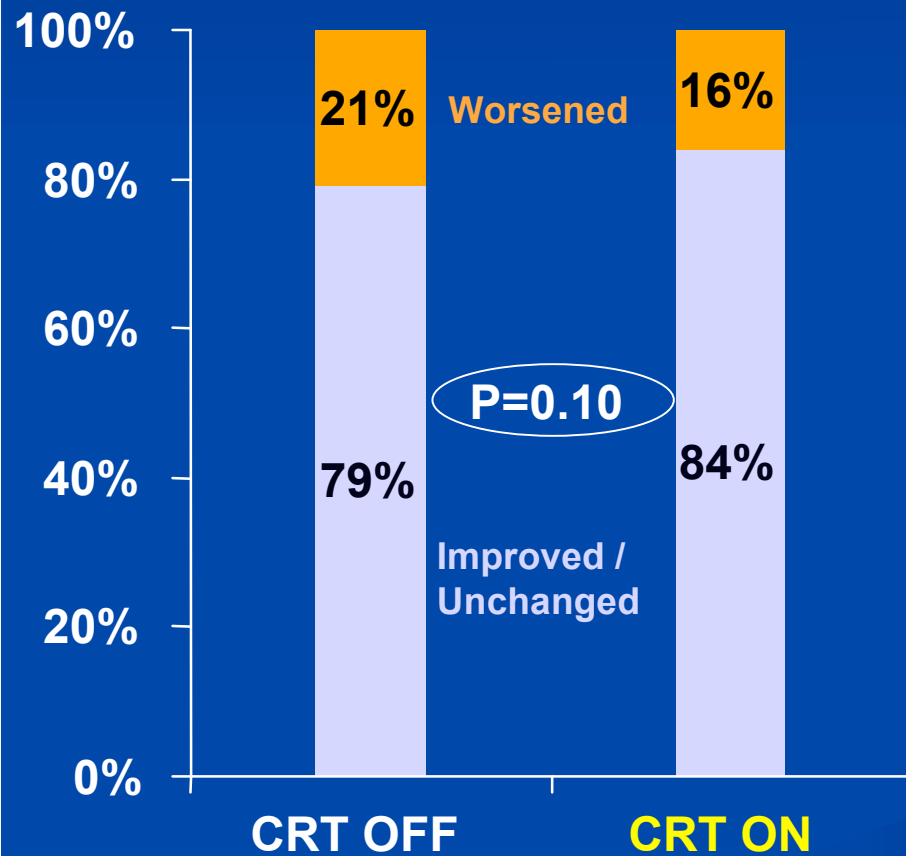
- 594/598 completed 12 month follow-up
- 12 deaths **(2%)**
- 0 lost to follow-up, 0 exits

## **Baseline Characteristics of Randomized Cohort (n=610)**

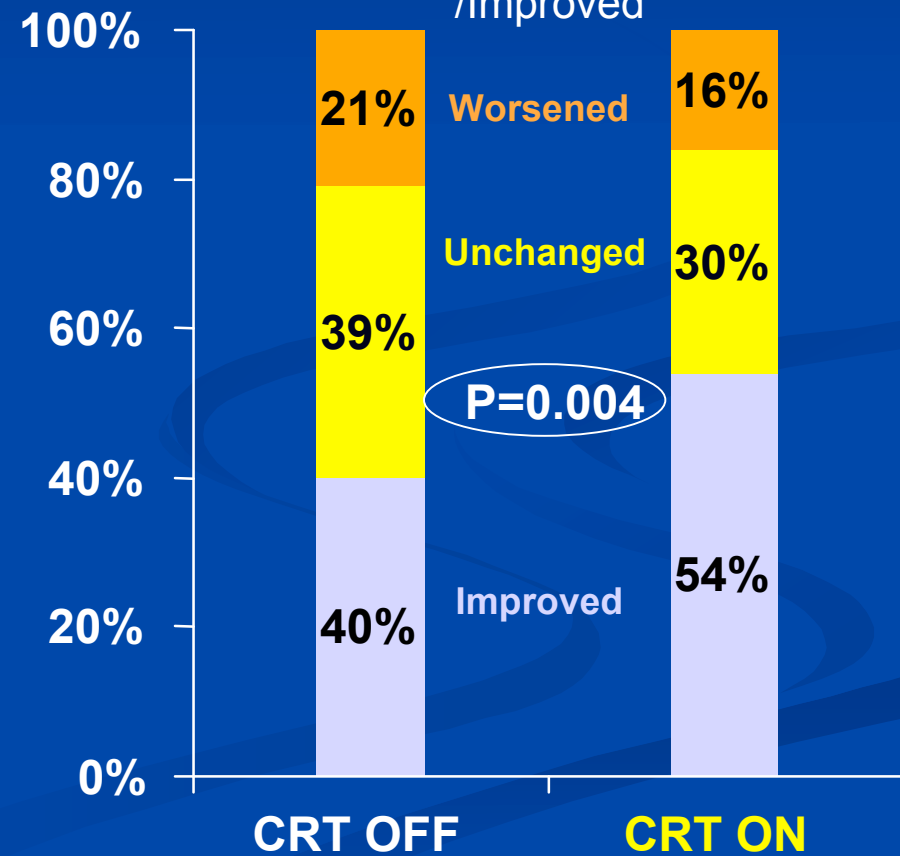
	<b>CRT OFF N=191</b>	<b>CRT ON N=419</b>	<b>P-value</b>
Age (mean) yrs	61.8 ± 11.6	62.9 ± 10.6	0.26
NYHA II	83%	82%	0.82
ICD	85%	82%	0.41
Beta-blockers	94%	96%	0.32
ACE-i/ ARB	97%	96%	0.63
Diuretics	77%	81%	0.33
EF	26.4 ± 7.0	26.8 ± 7.0	0.50
LVEDD (mm)	70 ± 9	69 ± 9	0.34
QRS (ms)	154.4 ± 24.1	152.8 ± 21.0	0.41
Ischemic	51%	56%	0.22

# Primary End Point: Clinical Composite Response

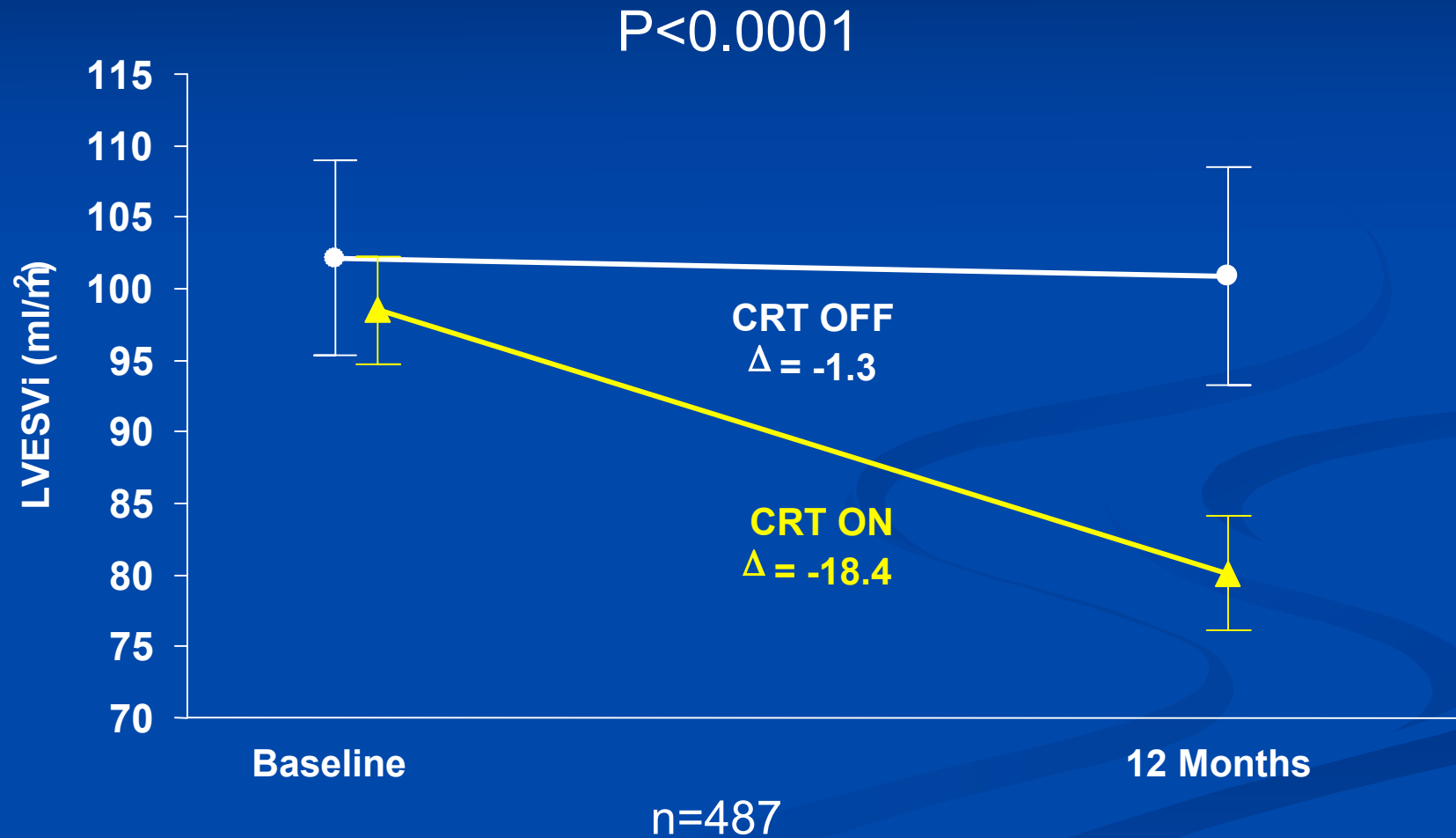
Pre-Specified Analysis  
Proportion Worsened



Conventional Analysis  
Distribution Worsened/Unchanged / Improved

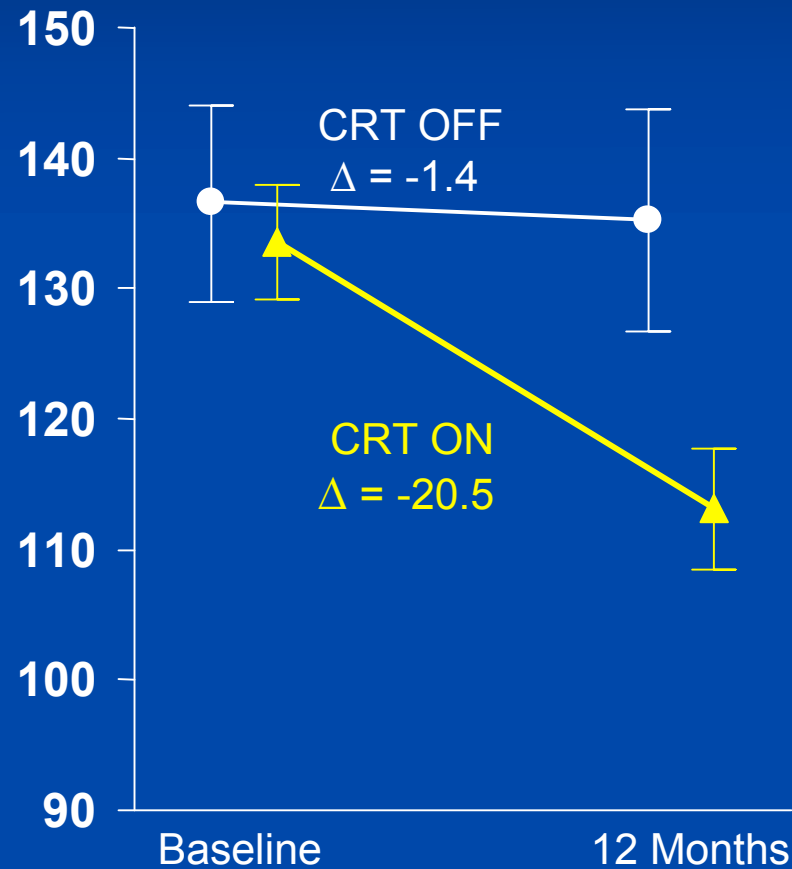


# Powered Secondary End Point: LVESVi (ml/m<sup>2</sup>)

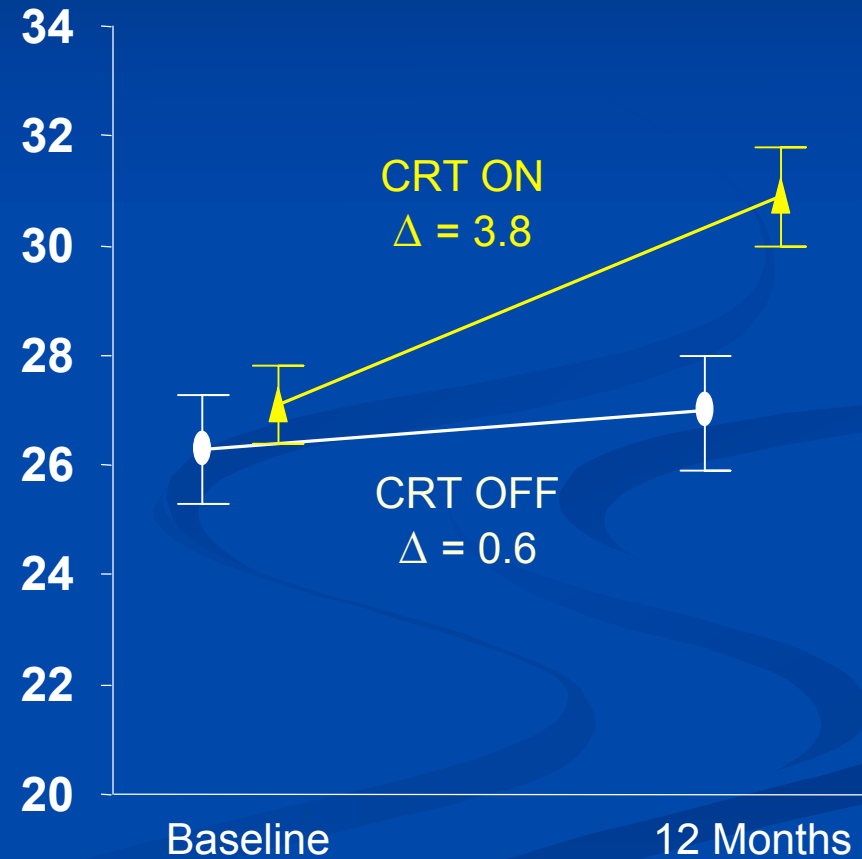


# Other Remodeling Parameters

LVEDVi (ml/m<sup>2</sup>)  
P<0.0001

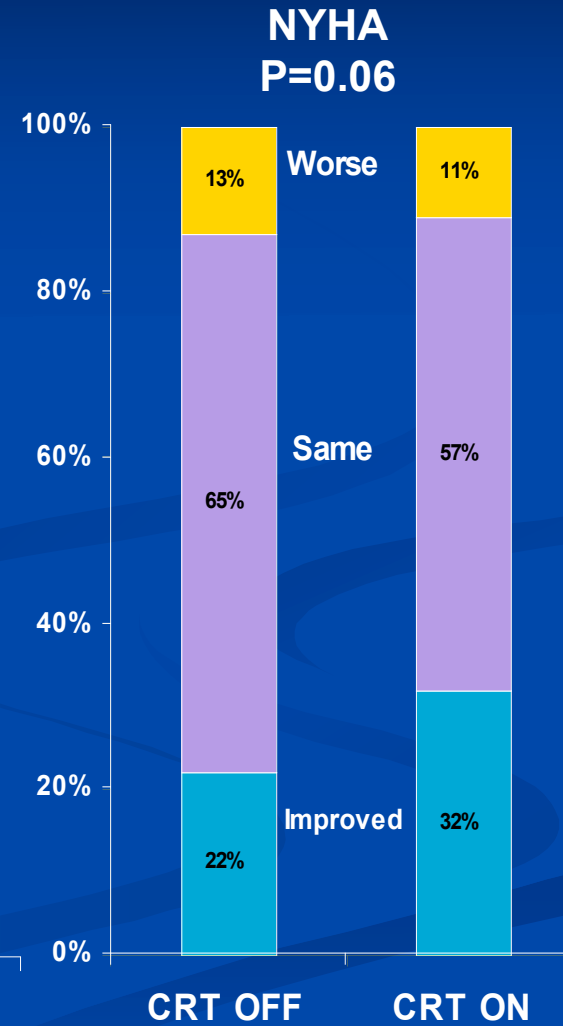
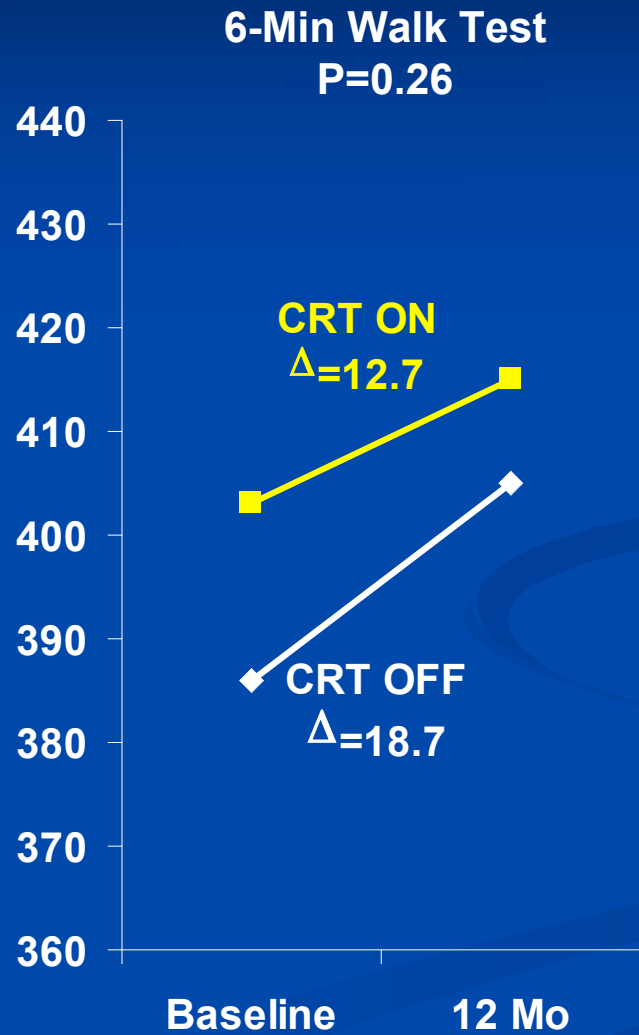
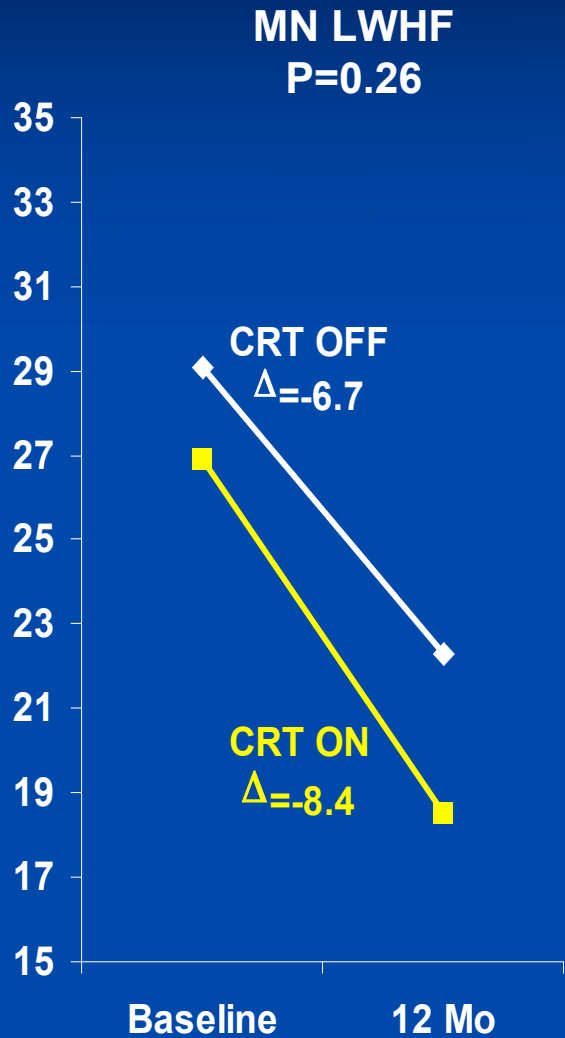


LVEF (%)  
P<0.0001

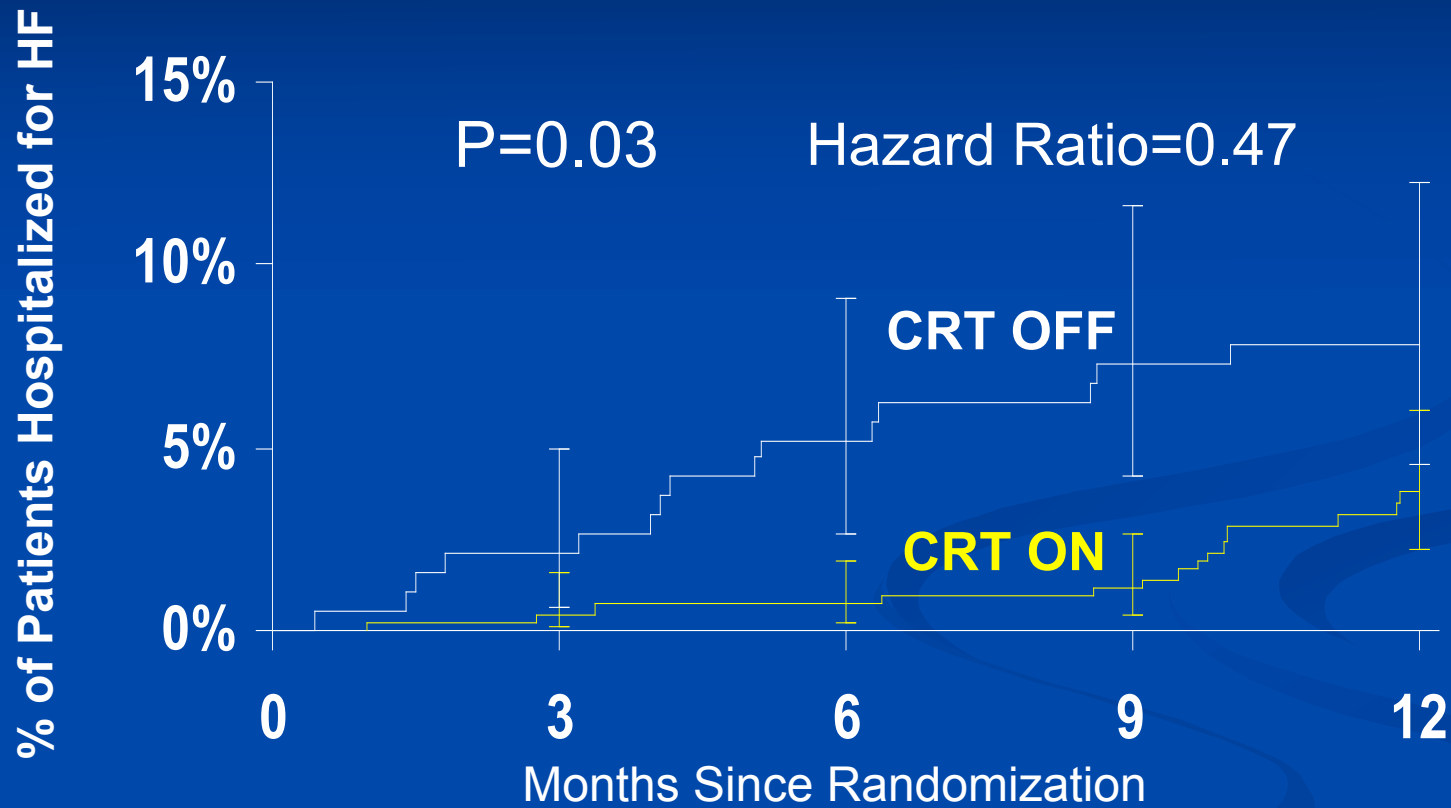


n=487

# Other Secondary Endpoints



# Time to First HF Hospitalization



Number at Risk

CRT OFF	191	187	181	176	119
CRT ON	419	415	411	409	251

# *Safety*

- 97% implant success rate
- 9.5 % LV-lead related complications
  - 66 in 59 / 621 successfully implanted patients
  - LV lead dislodgements, diaphragmatic stimulation, subclavian vein thrombosis, etc.

## ***Conclusion***

REVERSE is the first large, randomized, double-blind study to show that CRT in asymptomatic and mildly symptomatic heart failure patients on optimal medical therapy:

- Reverses LV remodeling
- Reduces the risk of heart failure hospitalization
- May improve clinical outcome as assessed by the clinical composite response measure

Note: FDA has not yet reviewed the clinical data to determine whether or not CRT systems are safe and effective in this patient population.