# Synchrony, Contractile Function and Benefit of CRT – Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy

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# Disclosure

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- **S.D. Solomon**: consulting fees from Boston Scientific

# Background

- While CRT has shown dramatic benefit in appropriate patients, up to 30% of the patients do not respond to CRT and there is no consensus on how to best identify patients who will respond
- LV mechanical dyssynchrony continues to be considered a potential predictor of response to CRT, yet the recent PROSPECT study suggested that echocardiographic and tissue-Doppler parameters have limited predictive accuracy
- The extent to which the benefit of CRT is secondary to improvement in synchrony remains unknown

Chung ES et al. Results of the Predictors of Response to CRT Trial (PROSPECT). Circulation. 2008;117: 2608-16

# CRT in Mildly Symptomatic Patients (NYHA I/II)

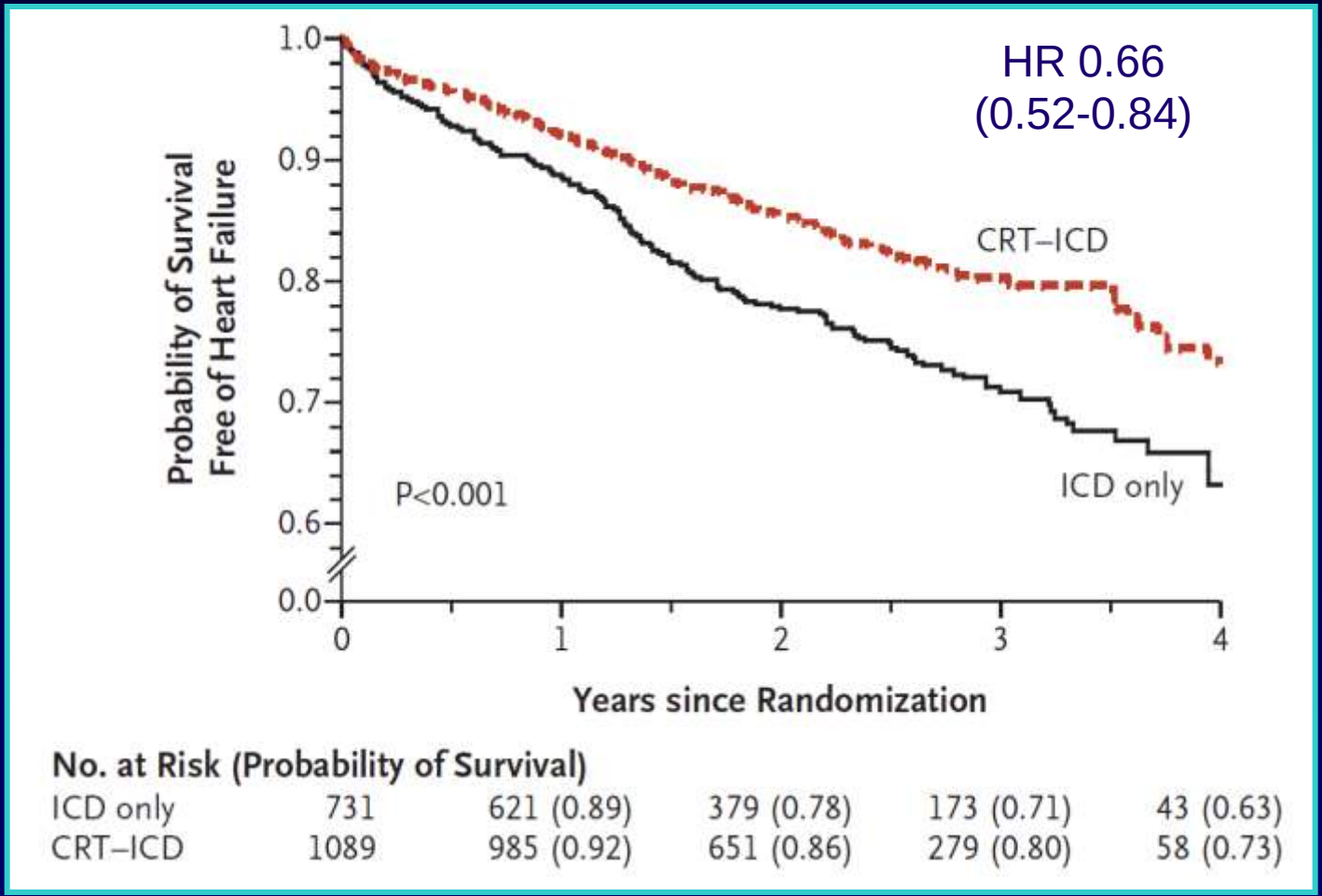
- Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) enrolled 1820 patients, randomized in 3:2 CRT-D vs. ICD

- Main inclusion criteria
  - Ischemic heart disease in NYHA class I or II

    *OR*
  - Non-ischemic heart disease NYHA class II

    *AND*
  - Stable optimal pharmacologic therapy for heart failure
  - LVEF ≤ 30%
  - QRS duration ≥130ms

# 34% Reduction in the Risk of Death or Nonfatal Heart Failure in patients receiving CRT-D compared with ICD-Only




**No. at Risk (Probability of Survival)**

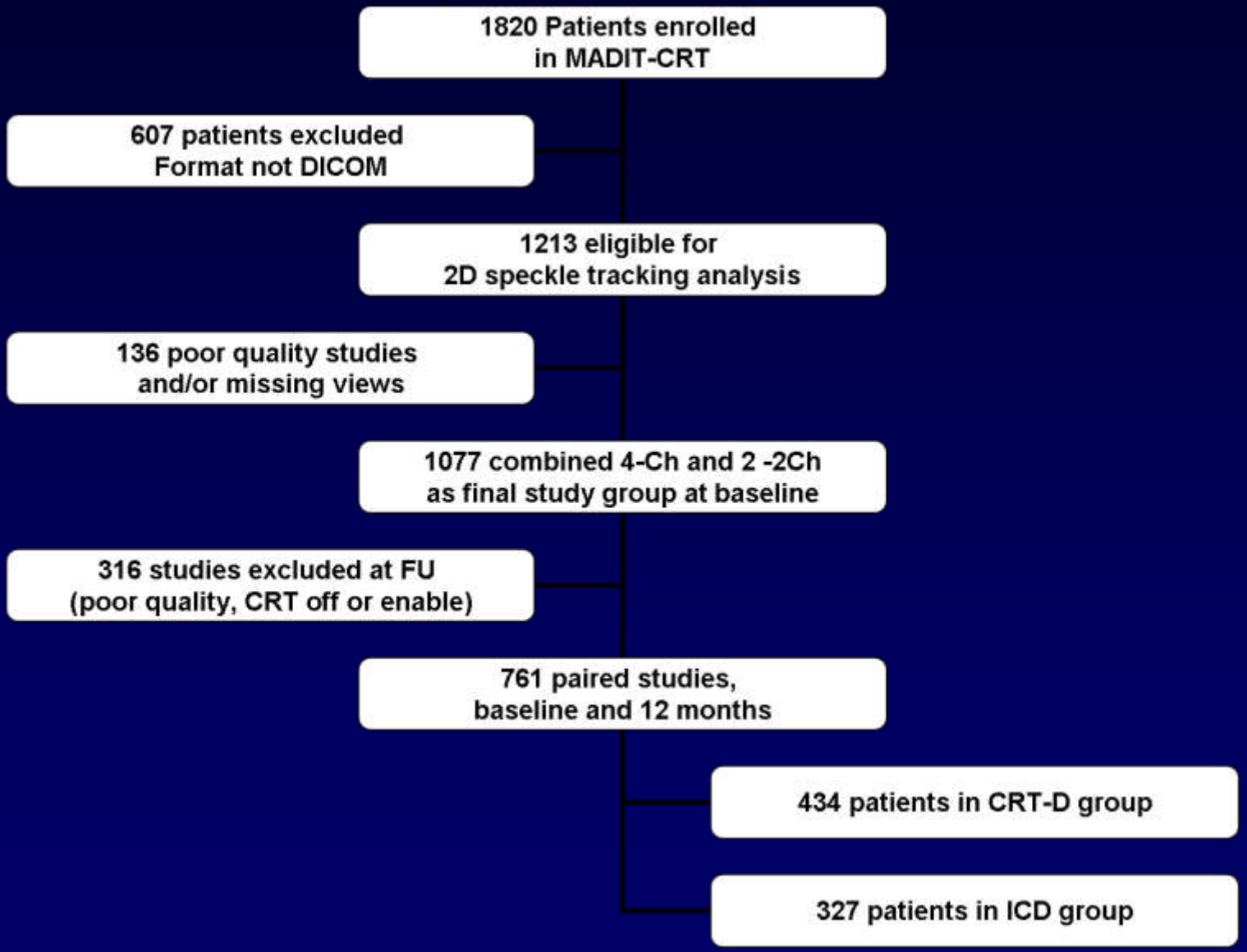
| | | | | | |
|---|---|---|---|---|---|
| ICD only | 731 | 621 (0.89) | 379 (0.78) | 173 (0.71) | 43 (0.63) |
| CRT–ICD | 1089 | 985 (0.92) | 651 (0.86) | 279 (0.80) | 58 (0.73) |

Moss AJ et al. N Engl J Med 2009; 361: 1329-38.

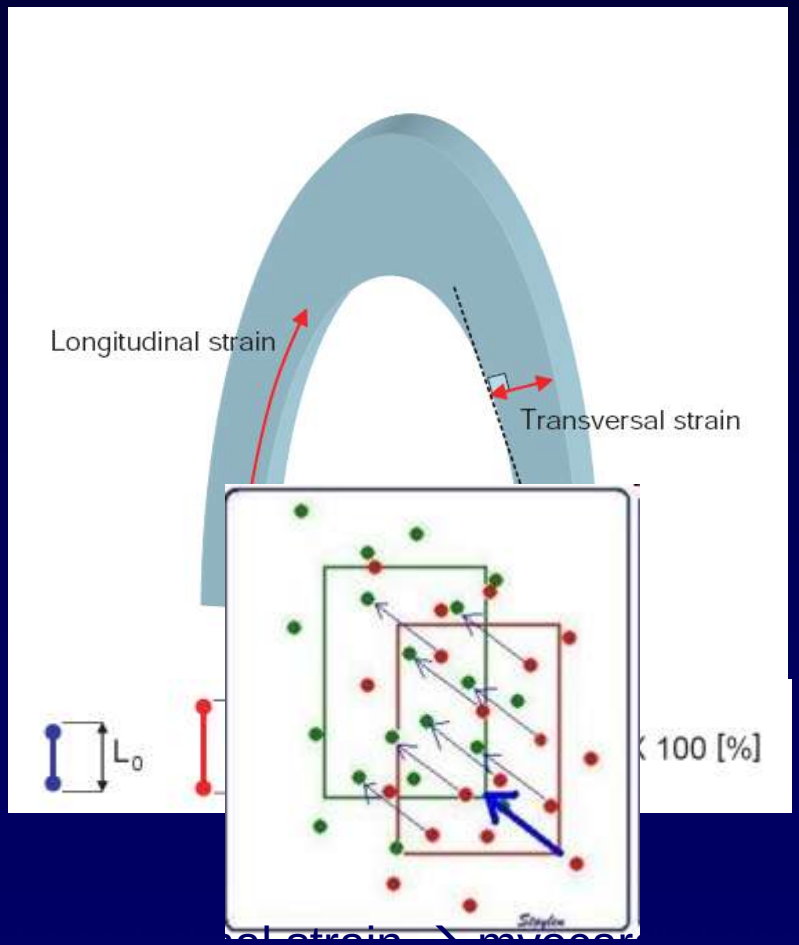
# Objectives

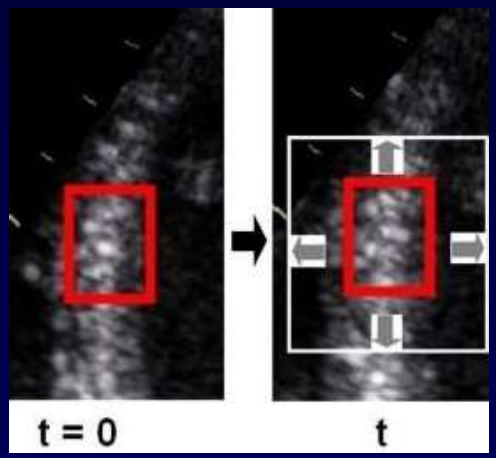
- To understand the relationship between baseline LV dyssynchrony, contractile function and response to CRT
- To assess the long-term effects of CRT on LV dyssynchrony and contractile function compared to ICD only
- To evaluate the relationship between these changes over the first year and subsequent outcomes (median post one year follow-up= 14.9 months).

# Study Population



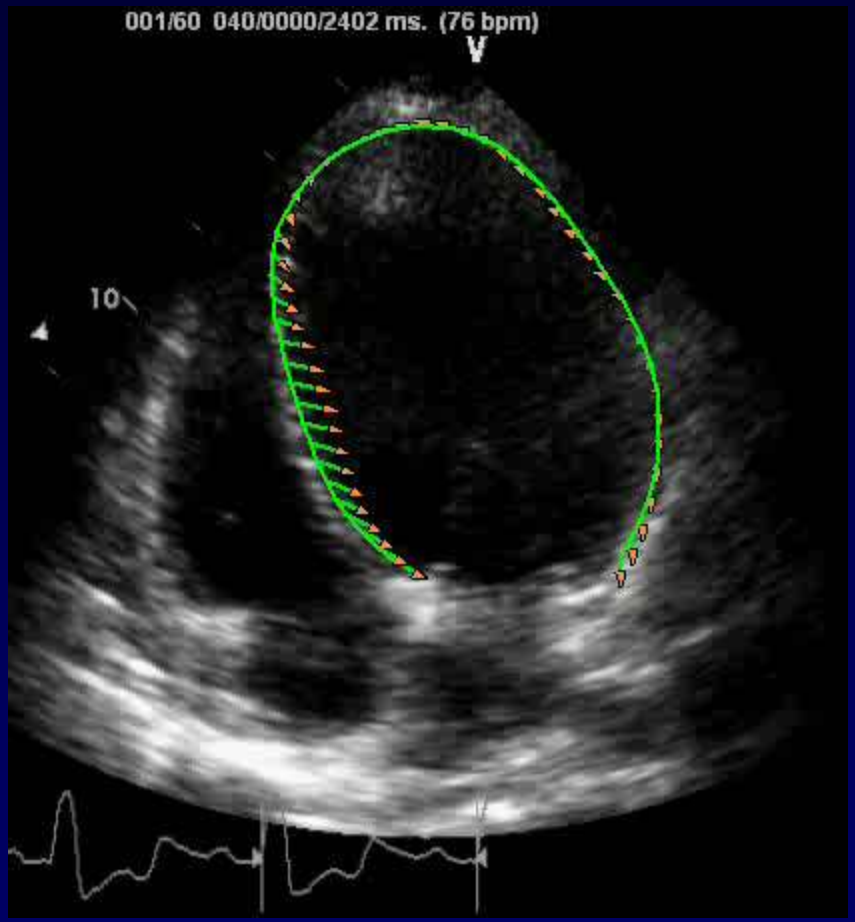
# Strain Measured by 2D-speckle Tracking Echocardiography



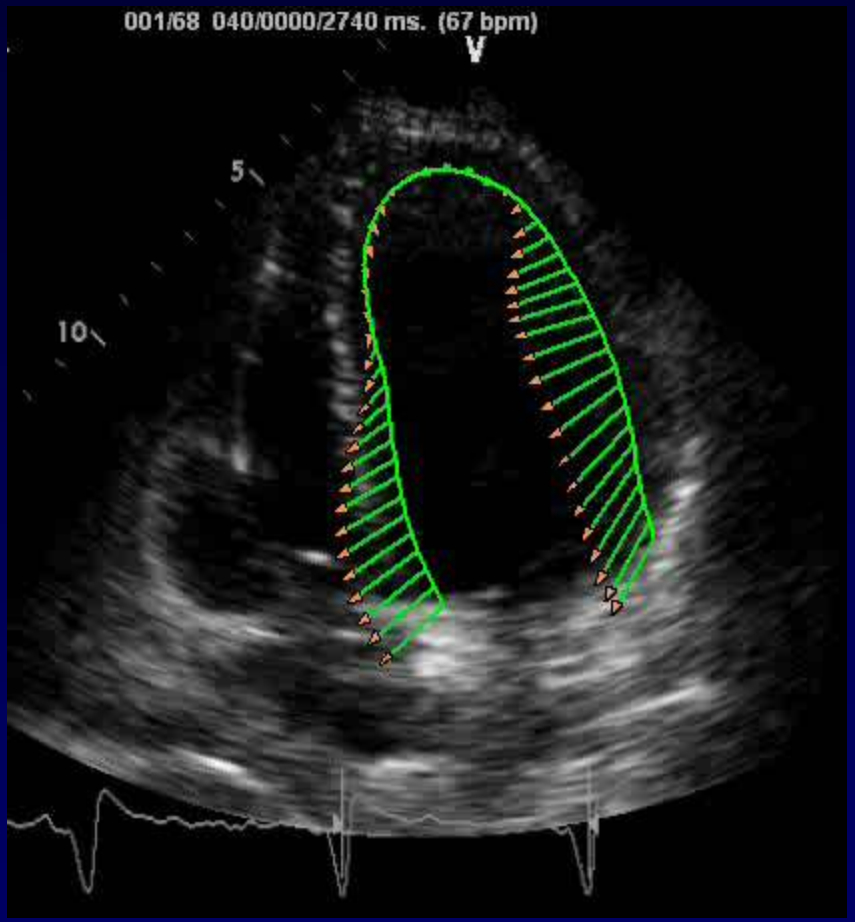




Speckle tracking analyzes the motion of the coherent “speckle” within the myocardium on ultrasound images to assess myocardial deformation and to distinguish passive motion from active contractile motion. This method is angle independent and can generate data in the longitudinal, circumferential, or radial/transverse direction.

# Example for speckle tracking strain imaging



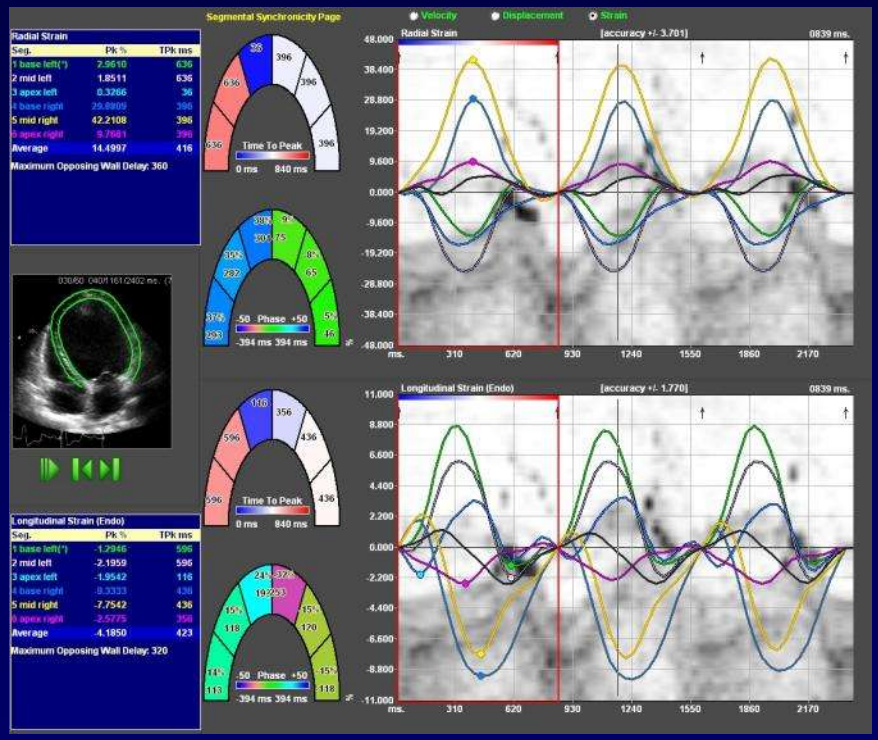

Baseline

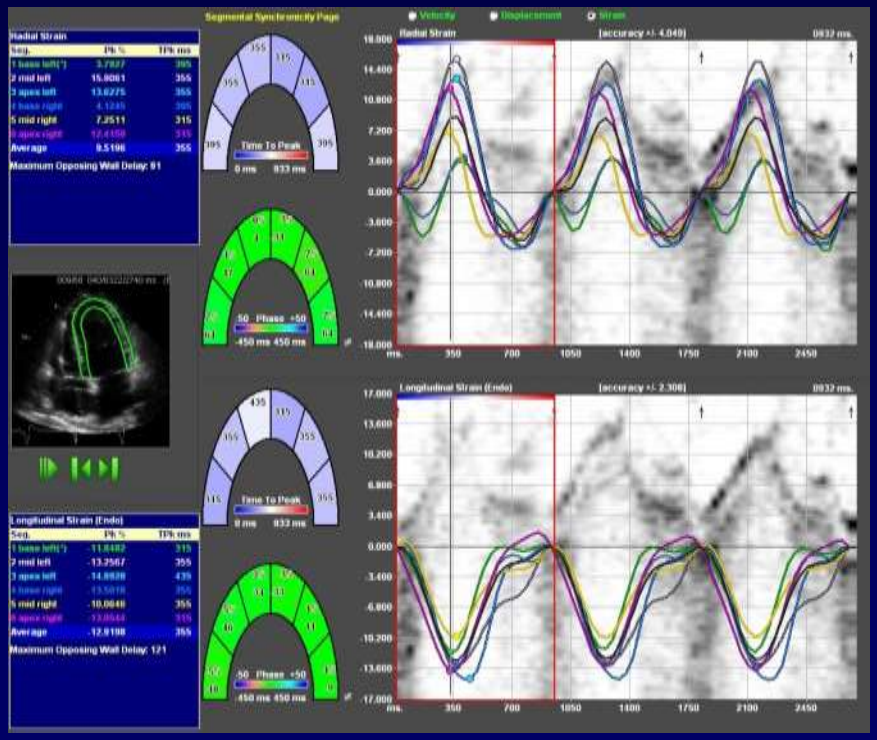



12 months CRT
ON

# Assessment of Dyssynchrony and Contractile Function

- Dyssynchrony defined as the standard deviation of time to peak radila/transverse strain out of 12 segments (SD-TTS)
- Contractile function was determined by averaging longitudinal strain



# Statistical Analyses

- We assessed the relationship between
  - dyssynchrony (12 segments) assessed by time to peak strain
  - Average peak longitudinal strain (12 segments)

  …and primary clinical outcome of death or non fatal HF events.

  Diagnosis of HF required signs and symptoms consistent with congestive heart failure that was responsive to intravenous decongestive therapy on an outpatient basis or an augmented decongestive regimen with oral or parenteral medications during an in-hospital stay.
- Investigators were blinded to treatment assignment, clinical covariates, and clinical outcomes
- Cox proportional hazards regression model. 10 strongest predictors of the primary outcome identified (age, gender, QRS duration, LBBB, LVEF, LVESV, eGFR, diuretic use, heart rate and ischemic status) using stepwise elimination and backward selection of a 30 covariate model

# Reproducibility

- Intra- and inter-observer variation for dyssynchrony and strain was assessed in a sample of 75 randomly selected patients with a broad range of LVEF.

- The coefficients of variation for intra- and inter-observer reproducibility were 13.8% and 15.4% for time-to-peak transverse strain and 7.7% and 8.0% for global longitudinal strain, respectively.

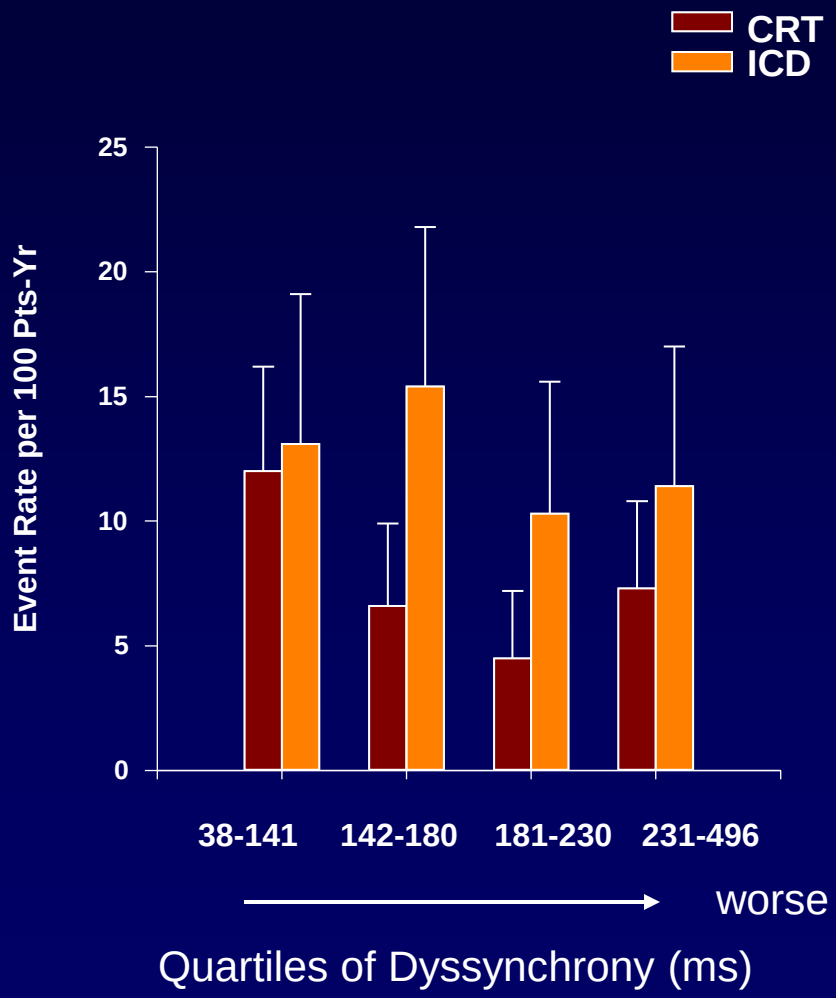
# Baseline Characteristics by Quartiles of Dyssynchrony

| | Quartiles of Dyssynchrony (ms) | | | | |
|---|---|---|---|---|---|
| | Less → | | | More | |
| | **38–141 (n=272)** | **142–180 (n=273)** | **181–230 (n=269)** | **231–496 (n=263)** | **p for trend** |
| Age, yrs | 65 ± 11 | 64 ± 11 | 63 ± 11 | 65 ± 11 | 0.92 |
| Female, n(%) | 46 (17%) | 77 (28%) | 69 (26%) | 76 (29%) | 0.005 |
| NYHA II, n(%) | 225 (83%) | 228 (84%) | 226 (84%) | 227 (86%) | 0.26 |
| Ischemic, n(%) | 170 (63%) | 150 (55%) | 133 (49%) | 148 (56%) | 0.071 |
| QRS (ms) | 152 ± 17 | 156 ± 19 | 160 ± 19 | 161 ± 20 | <0.0001 |
| LVEF (%) | 29.8 ± 3.4 | 29.4 ± 3.3 | 28.8 ± 3.4 | 29.0 ± 3.5 | 0.0004 |
| LVEDV (mL) | 237 ± 48 | 243 ± 58 | 253 ± 56 | 257 ± 67 | <0.0001 |
| LVESV (mL) | 167 ± 39 | 173 ± 47 | 181 ± 45 | 184 ± 55 | <0.0001 |

# Baseline Characteristics by Quartiles of Strain

| | Quartiles of Strain (%) | | | | |
|---|---|---|---|---|---|
| | Better → | | | Worse | |
| | **-19.0 to -10.6 (n=271)** | **-10.59 to -8.7 (n=269)** | **-8.69 to -6.94 (n=269)** | **-6.93 to -2.0 (n=268)** | **p for trend** |
| Age (yrs) | 65 ± 11 | 66 ± 11 | 64 ± 11 | 62 ± 11 | 0.0001 |
| Female, n(%) | 81 (30%) | 61 (23%) | 70 (26%) | 56 (21%) | 0.045 |
| NYHA II, n(%) | 222 (82%) | 231 (86%) | 217 (81%) | 236 (88%) | 0.19 |
| Ischemic, n(%) | 128 (47%) | 156 (58%) | 167 (62%) | 150 (56%) | 0.03 |
| QRS (ms) | 153 ±16 | 157 ± 19 | 165 ± 19 | 163 ± 21 | <0.0001 |
| LVEF (%) | 31.1 ± 3.3 | 29.4 ± 3.1 | 29.0 ± 2.9 | 27.5 ± 3.4 | <0.0001 |
| LVEDV (mL) | 219 ± 39 | 238 ± 43 | 249 ± 51 | 284 ± 74 | <0.0001 |
| LVESV (mL) | 151 ± 31 | 168 ± 34 | 178 ± 40 | 207 ± 60 | <0.0001 |

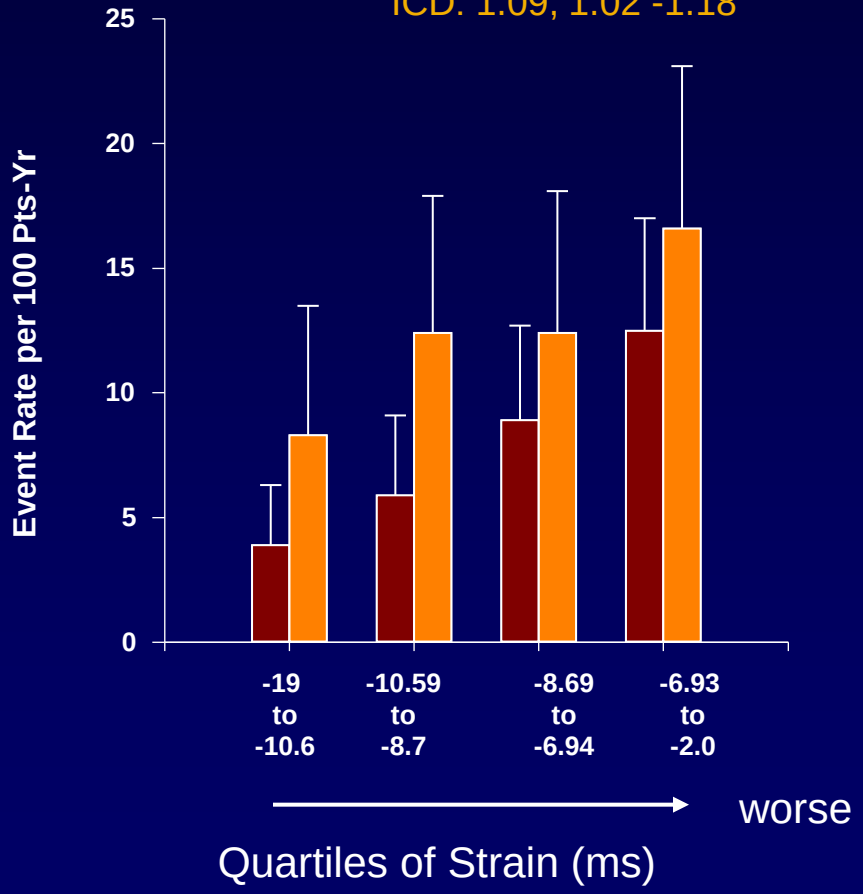
# Individual Relationship Between Synchrony, Strain and Primary Event Rate




HR per 1% increase strain for 1º Outcome:

CRT: 1.19, 1.10-1.28

ICD: 1.09, 1.02 -1.18

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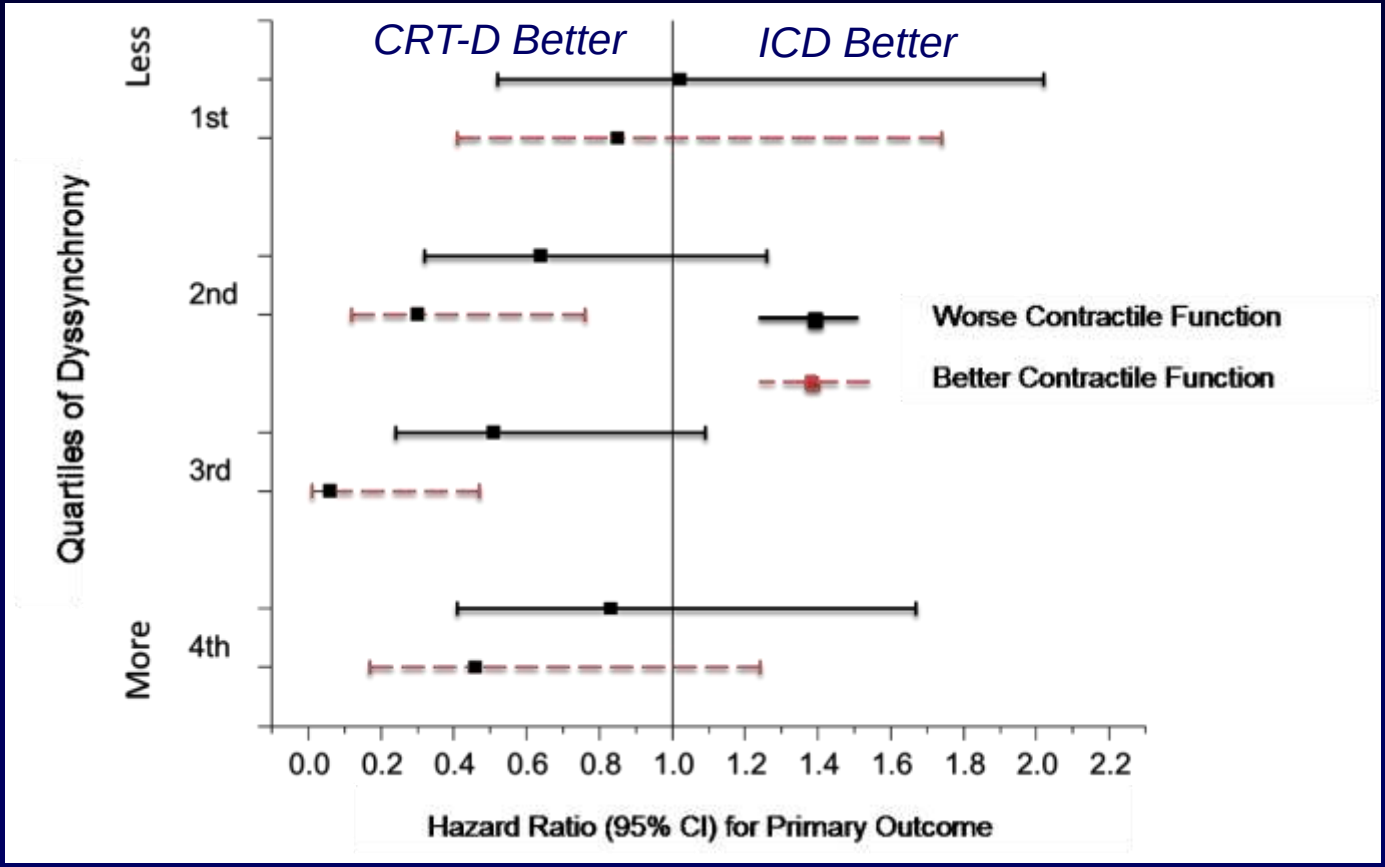
# Relationship between Synchrony, Contractile Function and Primary Outcome




# Adjusted for age, sex, QRS duration, LBBB, LA volume, LVEF, LVESV, eGFR, diuretic use, heart rate, and ischemic status at study enrollment

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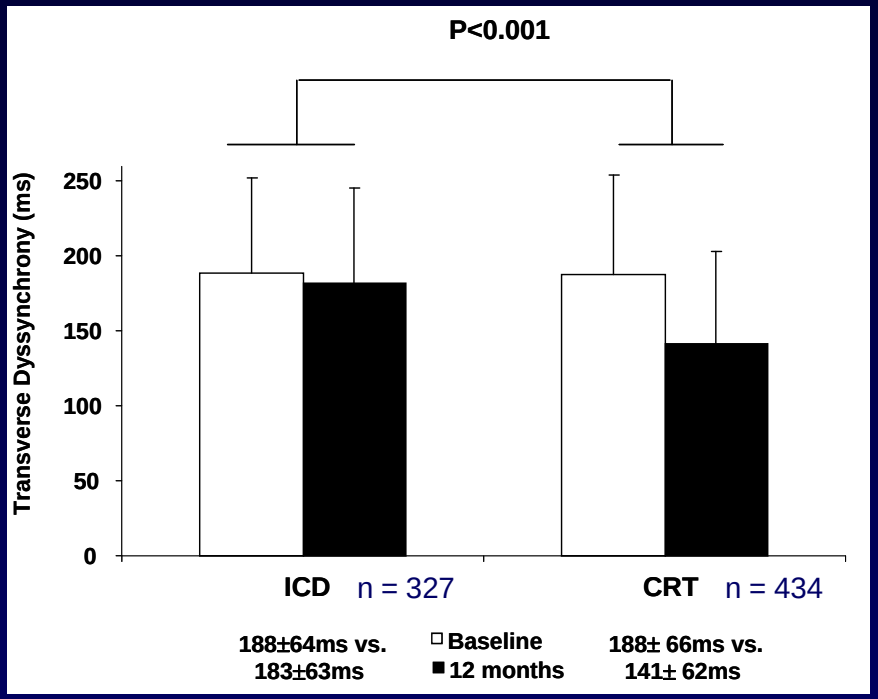
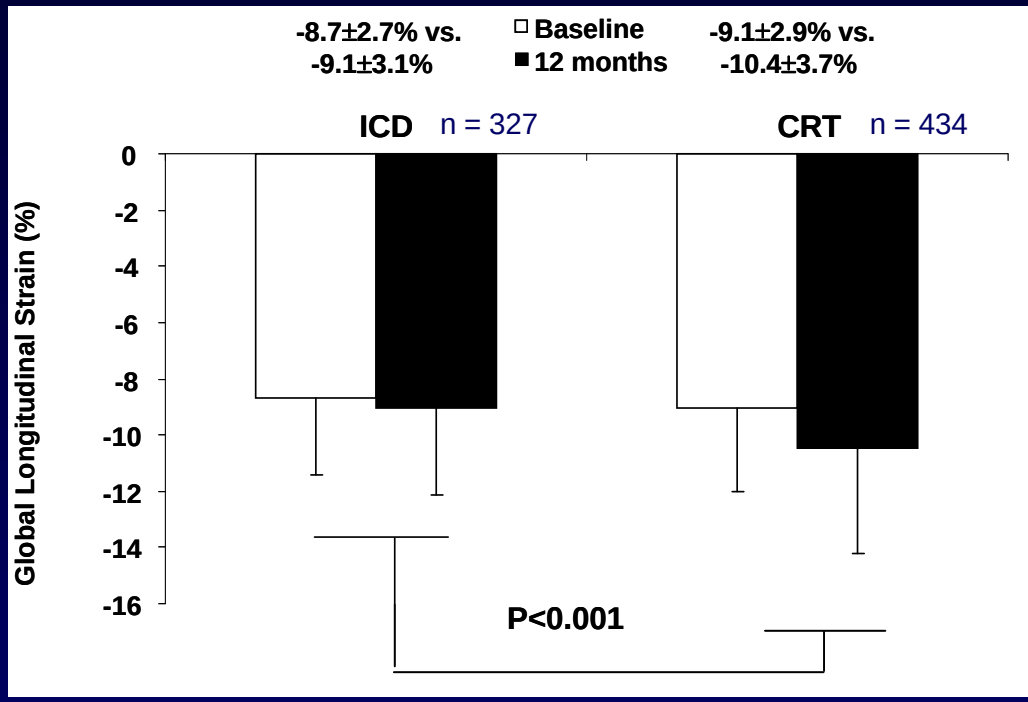
# Changes in LV Dyssynchrony and Contractile Function from Baseline to 1 Year in ICD only and CRT-D groups




Both dyssynchrony (-45±85 vs. -7±77ms, p< 0.001) and contractility (-1.4±3.1 vs. -0.3±2.5%, p<0.001) improved to a greater degree in CRT-D vs. ICD.

Between treatment groups differences in the change in LV dyssynchrony and LV contractile function measures from baseline to 12-months were assessed in analysis of covariance adjusting for treatment group, ischemic etiology and baseline measure of dyssynchrony or strain

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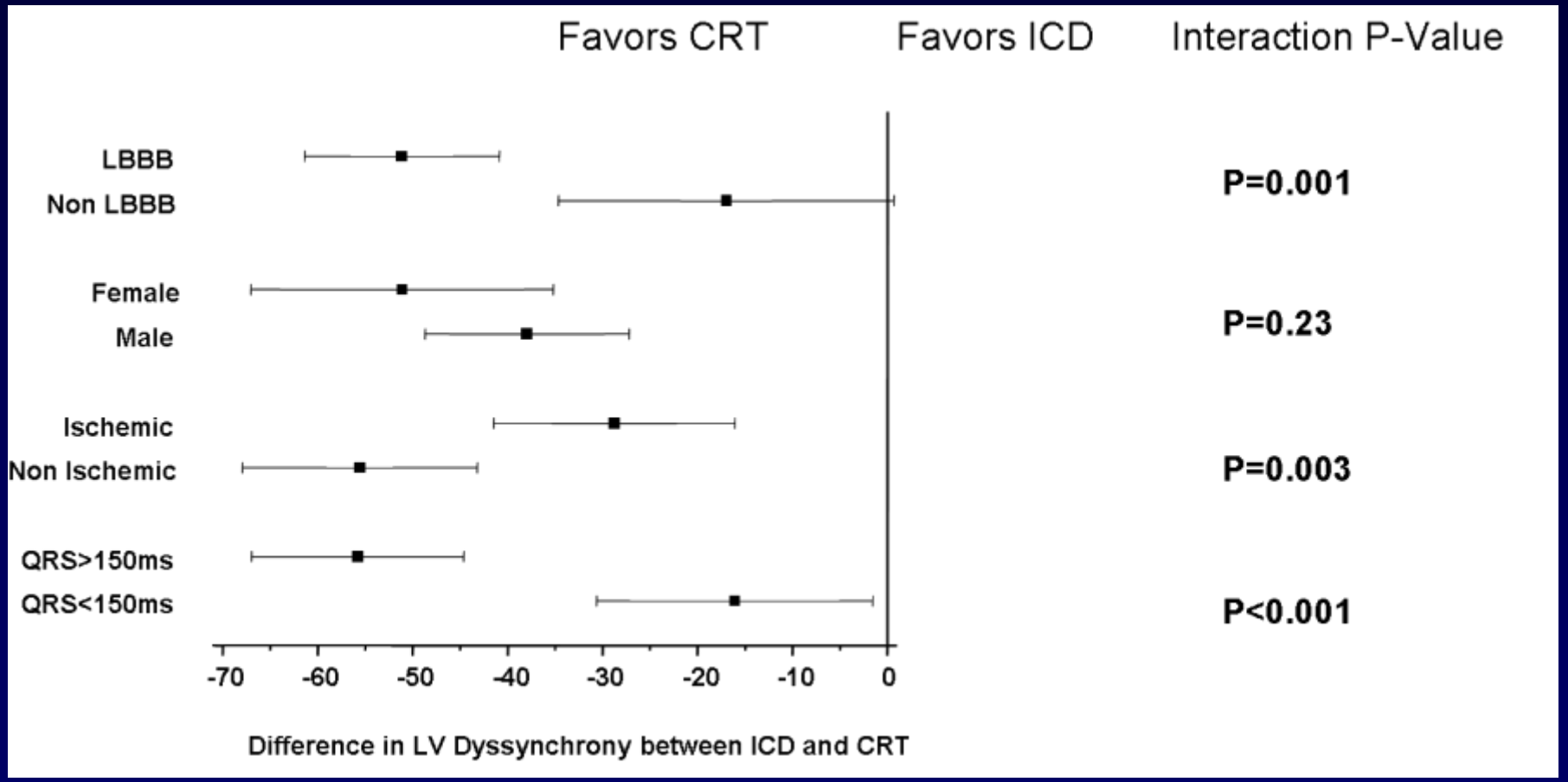
# Effect of Treatment on LV Dyssynchrony in Subgroups

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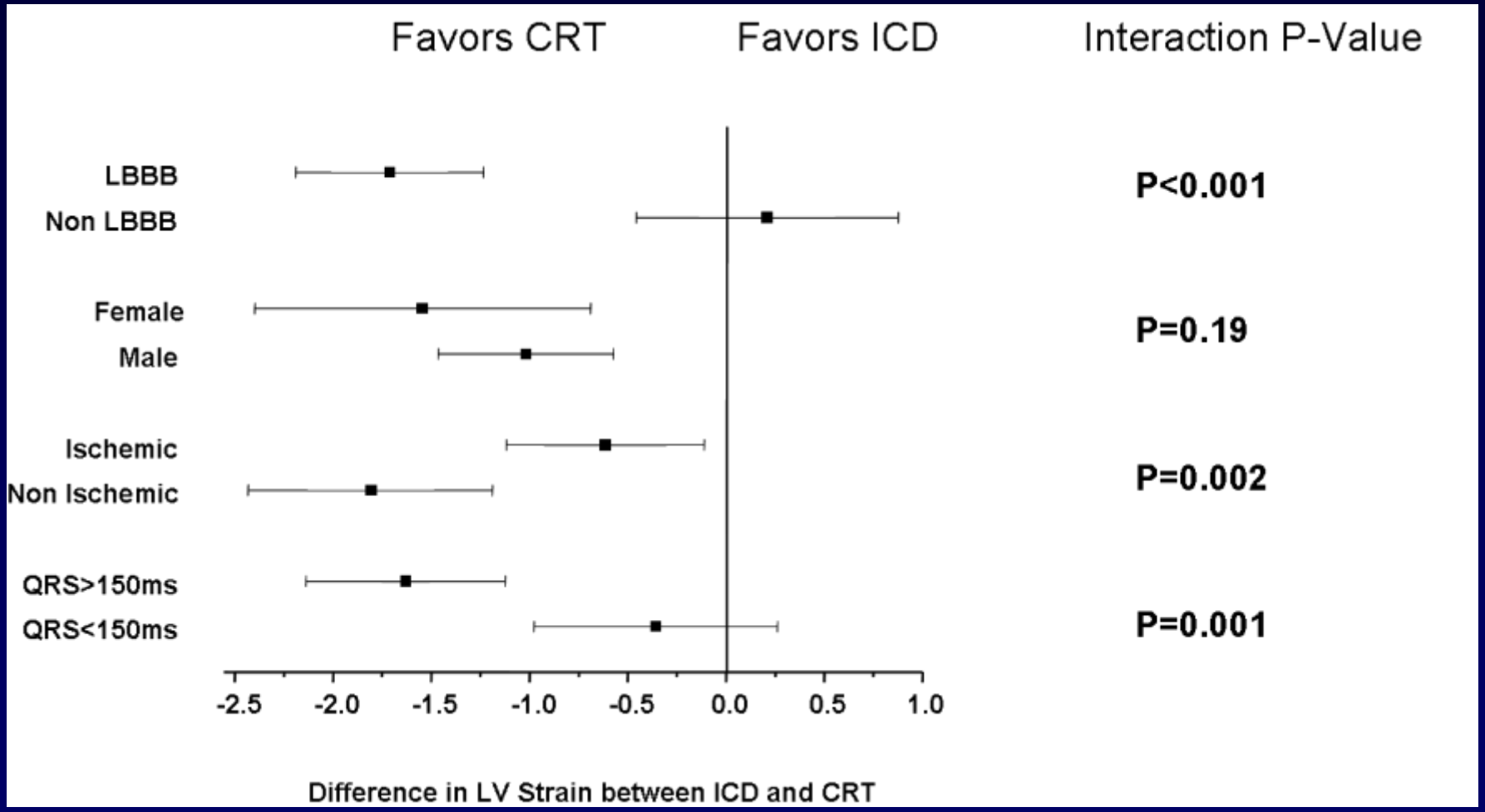
# Effect of Treatment on LV Contractile Function in Subgroups

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# Relationship between Changes in LV Dyssynchrony and Contractile Function measured by GLS and Primary Outcome. Landmark Analysis. N=715.

| | Unadjusted HR | Adjusted HR for Baseline, Treatment, Ischemic Status, Δ LVESV | Multivariable* |
|---|---|---|---|
| Improvement in Dyssynchrony (per 20ms decrease) | 0.93 (0.89-0.98) P=0.007 | 0.93 (0.87-0.99) P=0.047 | 0.95 (0.89-1.02) P=0.17 |
| Improvement in LV Contractility (per 1 percent point improvement) | 0.84 (0.78-0.91) P<0.001 | 0.76 (0.66-0.85) P<0.001 | 0.77 (0.68-0.86) P<0.001 |

* Adjusted for baseline LV dyssynchrony or global longitudinal strain, treatment, ischemic status, Δ LVESV, Δ LVEF, age, gender, QRS, LBBB

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# Limitations

- Patients with non-digital and poor quality images were excluded prior to analysis; however, no baseline differences between included and excluded patients
- Follow-up studies with device on availability in fewer patients than baseline
- Nevertheless, this remains the largest cohort of patients with these measures in a randomized trial with associated clinical outcomes

# Conclusions

- Both mechanical dyssynchrony and contractile function are important independent determinants of benefit from CRT
- These methods are more robust and reproducible than earlier Doppler techniques and may help to identify which patients would derive greater benefit from CRT
- CRT resulted in significant improvement in both LV dyssynchrony and contractile function measured by strain and these improvements were associated with better subsequent outcomes.
- Whether these methods should be used to select patients for CRT, or to monitor patients in this or other populations should be tested prospectively

# Dyssynchrony, Contractile Function, and Response to Cardiac Resynchronization Therapy

Dorit Knappe, MD*; Anne-Catherine Pouleur, MD*; Amil M. Shah, MD; Susan Cheng, MD; Hajime Uno, PhD; W. Jackson Hall, PhD; Mikhail Bourgoun, MD; Elyse Foster, MD; Wojciech Zareba, MD, PhD; Ilan Goldenberg, MD; Scott McNitt, MS; Marc A. Pfeffer, MD, PhD; Arthur J. Moss, MD; Scott D. Solomon, MD; for the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy Investigators

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# Relationship between improvement in left ventricular dyssynchrony and contractile function and clinical outcome with cardiac resynchronization therapy: the MADIT-CRT trial

Anne-Catherine Pouleur[1†], Dorit Knappe[1†], Amil M. Shah[1], Hajime Uno[1], Mikhail Bourgoun[1], Elyse Foster[2], Scott McNitt[3], W. Jackson Hall[3], Wojciech Zareba[3], Ilan Goldenberg[3], Arthur J. Moss[3], Marc A. Pfeffer[1], and Scott D. Solomon[1*] for the MADIT-CRT Investigators

Pouleur et al. Eur Heart J 2011