Non-responders to CRT: what is wrong in this patients ?

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President European Heart Rhythm Association

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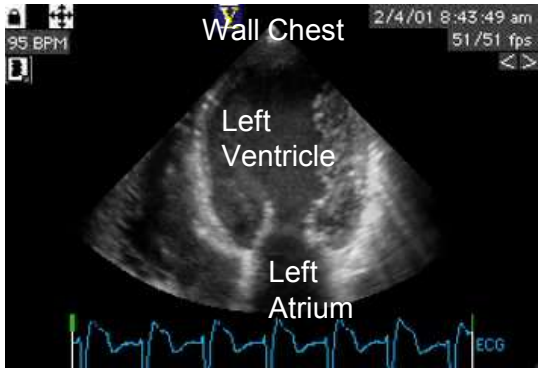
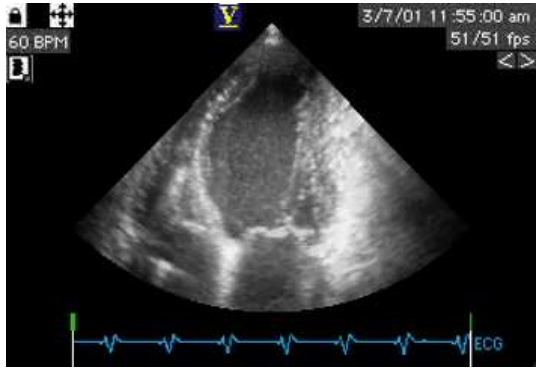
In the era of CRT, heart failure is a curable disease !



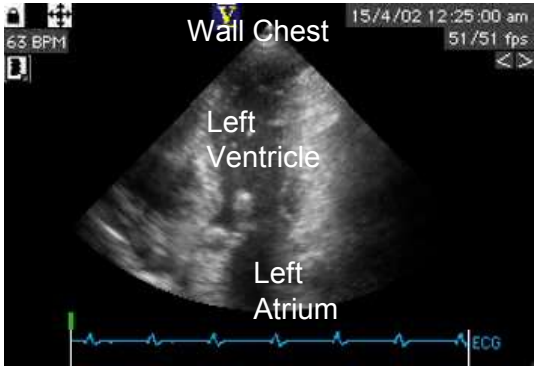


History

72 yrs old lady
Parox atrial fibrillation, LBBB, QRS 175 ms
Moderate hypertension
Sleep apnea
Moderate renal failure

- 1st diagnosis HF in 1995
  - No coronary artery disease
  - Optimal drug therapy
- Recurrent episodes of HF decompensation
  - Progressive intolerance to heart failure medication
- CRT-D implantation in 2001

2012: NYHA Class I
Follow-up by home doctor and remotely
No episode of atrial fibrillation since 2001



June 2012

The phenotype of CRT super-responder

Hypo-responders: Δ LVEF <7.9% (25%)

Responders: Δ LVEF 8% – 14.4% (49%)

Super-responders: Δ LVEF >14.4% (25%)

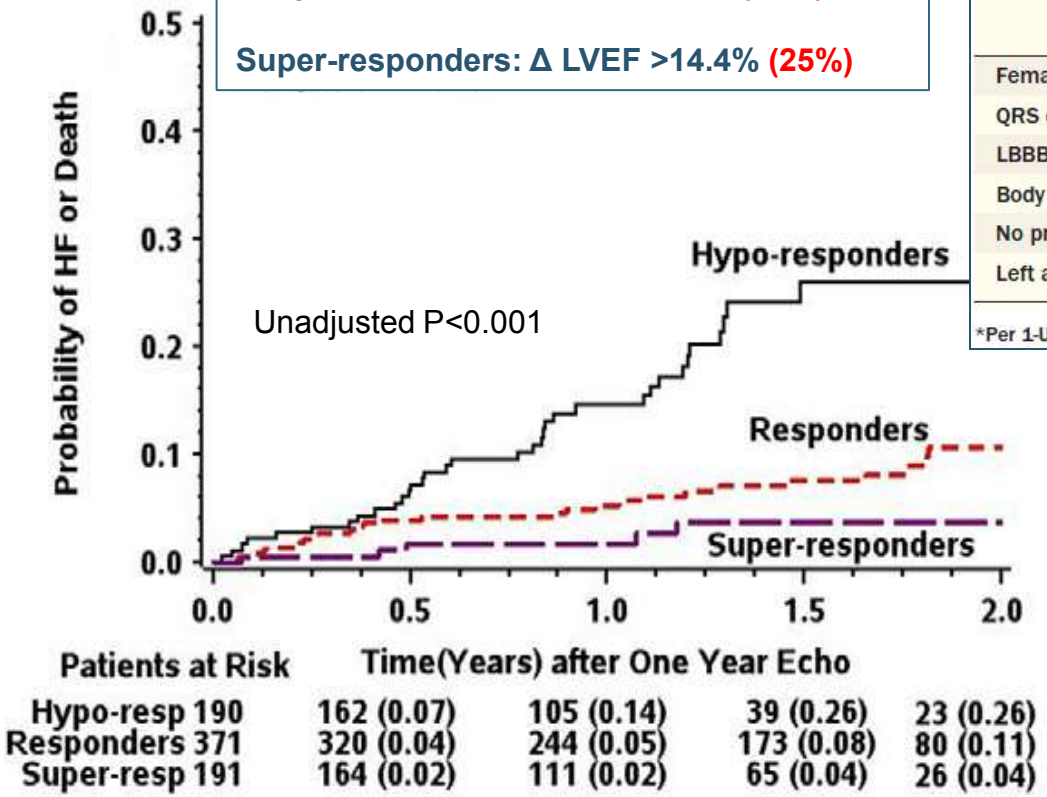
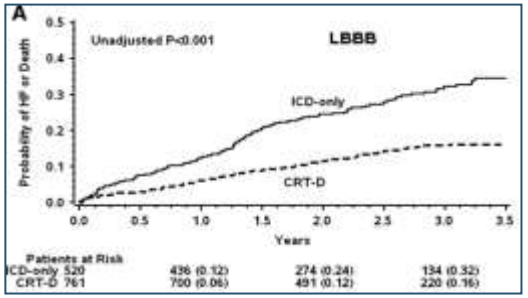


Table 3 Multivariate Analysis of Predictors of LVEF Super-Response

Variable	Odds Ratio	95% Confidence Interval	p Value
Female	1.96	1.32–2.90	0.001
QRS duration ≥150 ms	1.79	1.17–2.73	0.007
LBBB	2.05	1.24–3.40	0.006
Body mass index <30 kg/m^2	1.51	1.03–2.20	0.035
No prior myocardial infarction	1.80	1.20–2.71	0.005
Left atrial volume index, SD*	1.47	1.21–1.79	<0.001

*Per 1-U SD below mean.



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Hsu et al JACC 2012

ESC Clinical Practice Guidelines - 2012

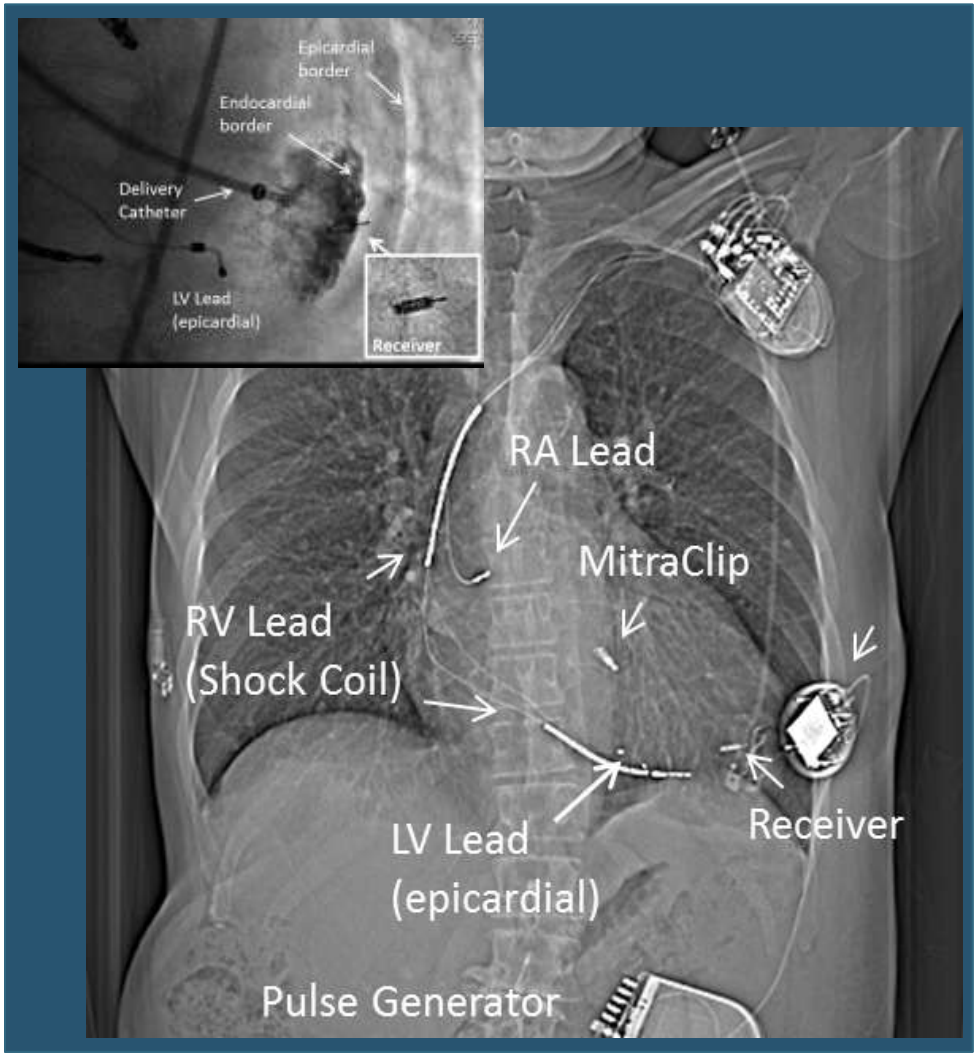
NYHA Class III-IV

Recommendations	Class[a]	Level[b]	Ref[c]
LBBB QRS morphology CRT-P/CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥120 ms, LBBB QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death.	I	A	156, 157
Non-LBBB QRS morphology CRT-P/CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death.	IIa	A	156, 157

NYHA Class II

Recommendations	Class[a]	Level[b]	Ref[c]
LBBB QRS morphology CRT, preferably CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥130 ms, LBBB QRS morphology, and an EF ≤30%, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death.	I	A	154, 155
Non-LBBB QRS morphology CRT, preferably CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤30%, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death.	IIa	A	154, 155

In the era of CRT, heart failure is still a challenging disease !



History

56 yrs old gentlman
Parox atrial fibrillation, IVCD, QRS 140 ms
Sleep apnea
Moderate renal failure

- **1st diagnosis HF in 2001**
  - PTCA LAD
  - Optimal drug therapy
  - Reduced ejection fraction (LVEF 25%)
  - ICD implantation for primary prevention of SCD in 2002
- **Recurrent episodes of HF decompensation**
  - Upgrade of ICD to CRT-D in 2005
  - Ablation of paroxysmal atrial fibrillation in 2007
- **Frequent hospitalization due to HF decompensation**
  - Implantation of MitraClip in 2010
- **Persistent symptoms of HF (NYHA class III)**
  - Implantation of WiCS system in 2011

NYHA Class II, HF out-patient clinic

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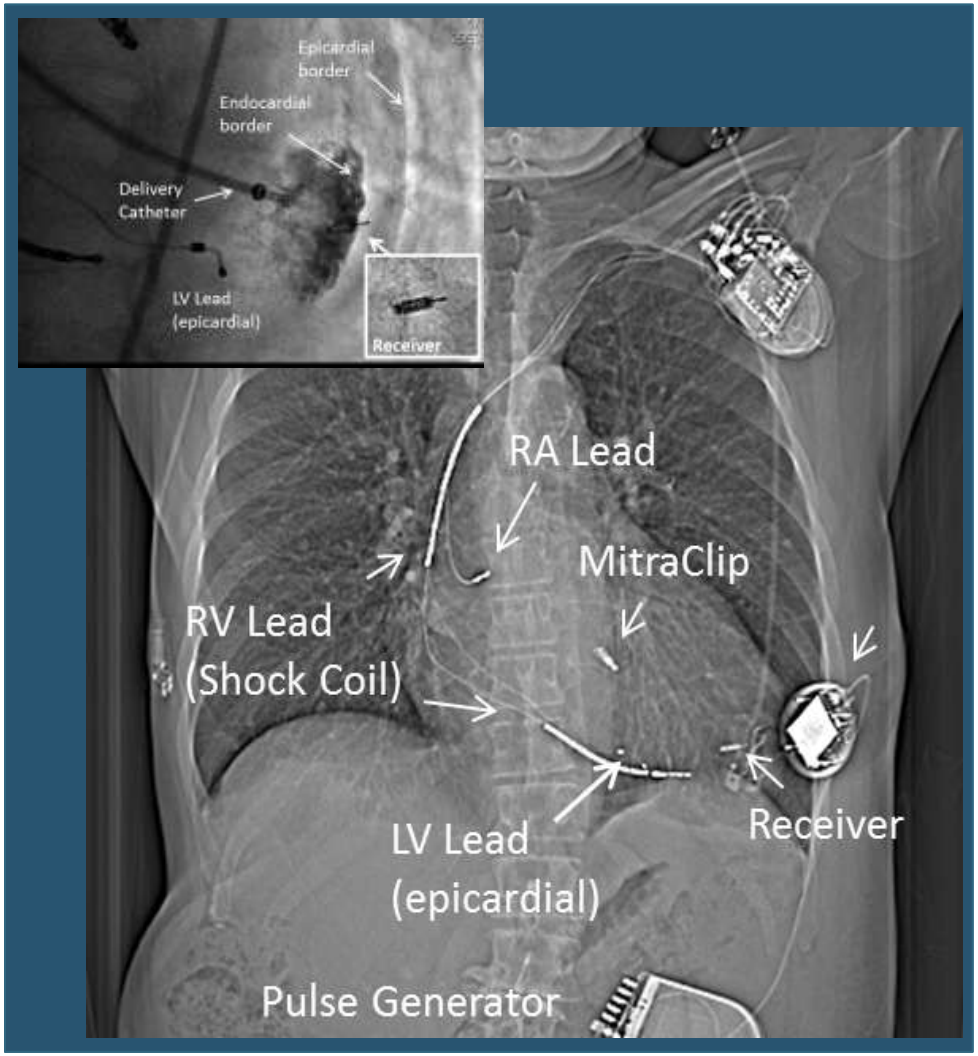
In the era of CRT, heart failure is still a challenging disease !



What was wrong in this case?

1) Disease progression
2) Suboptimal therapy delivery
3) Inability to match proper therapy with substrate / disease
4) Multiple mechanisms contributing to heart failure

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The puzzle of response (or non-response) to CRT




Strategies to recompose the puzzle

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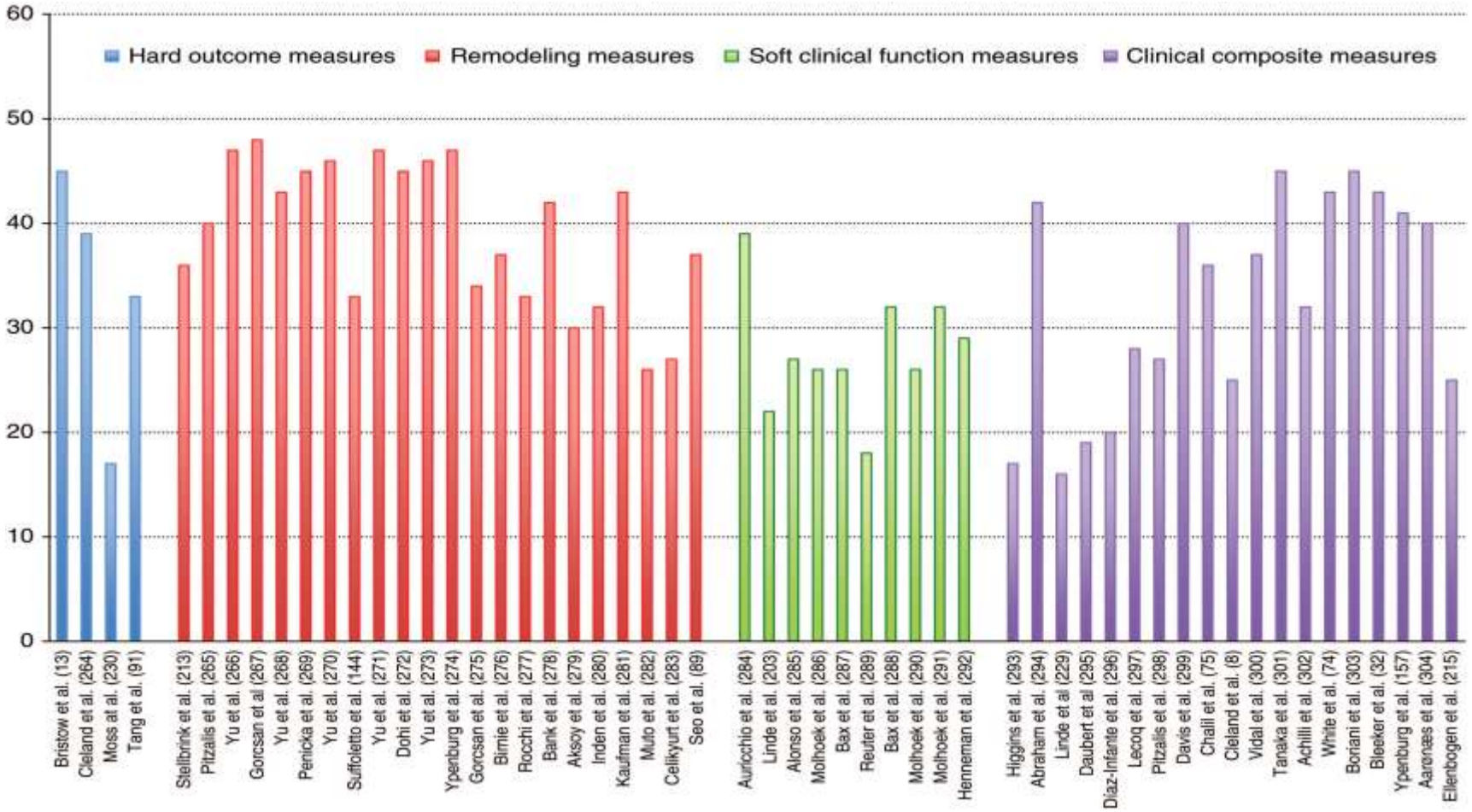
The binary category approach: Outcome varies according to measurement method



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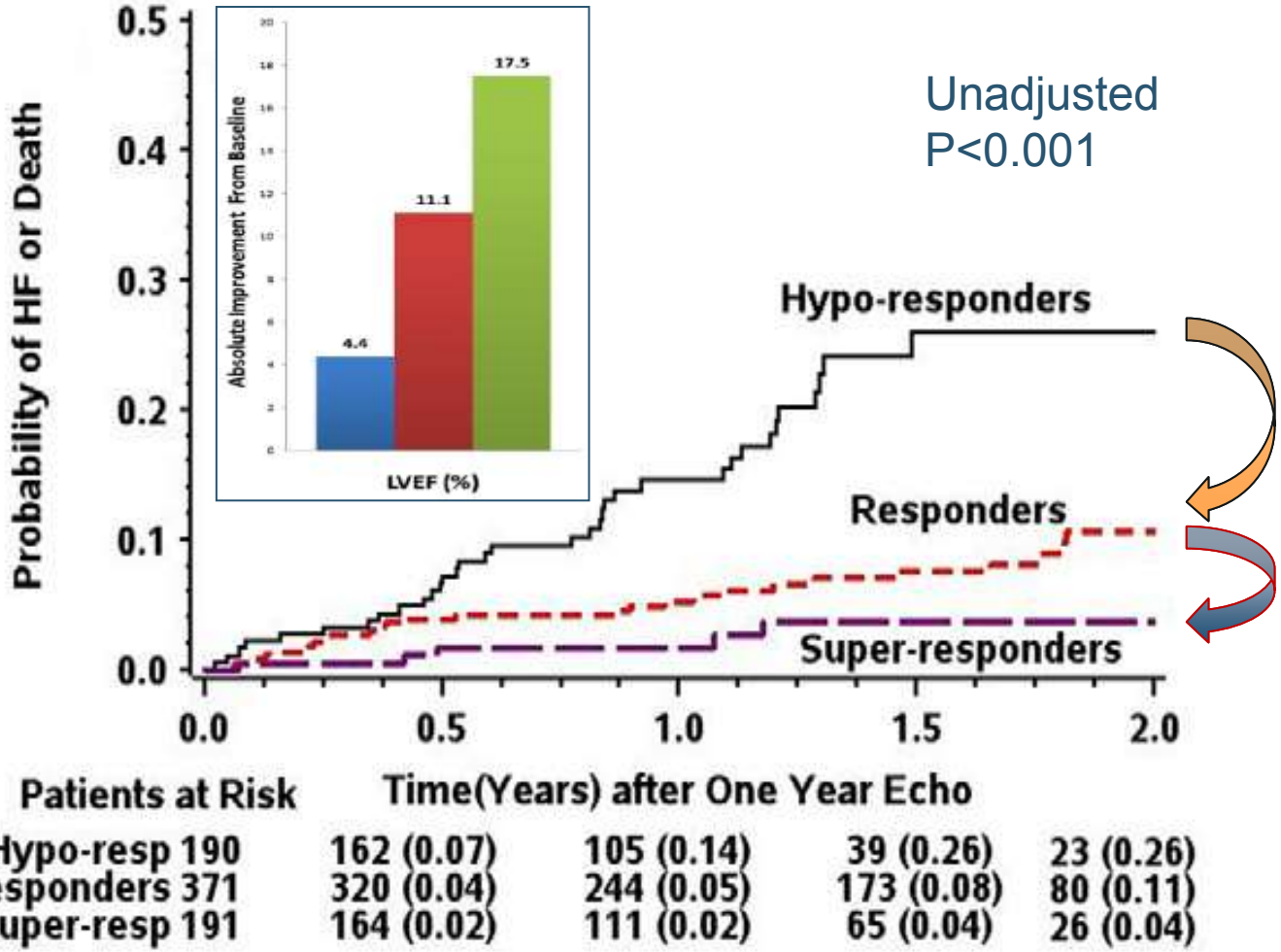
Daubert JC et al Europace 2012

The multiple categories of response are indicating different treatment strategy goals post-CRT



Unadjusted
P<0.001

Convert a hypo-responder into a responder

Maximize the response

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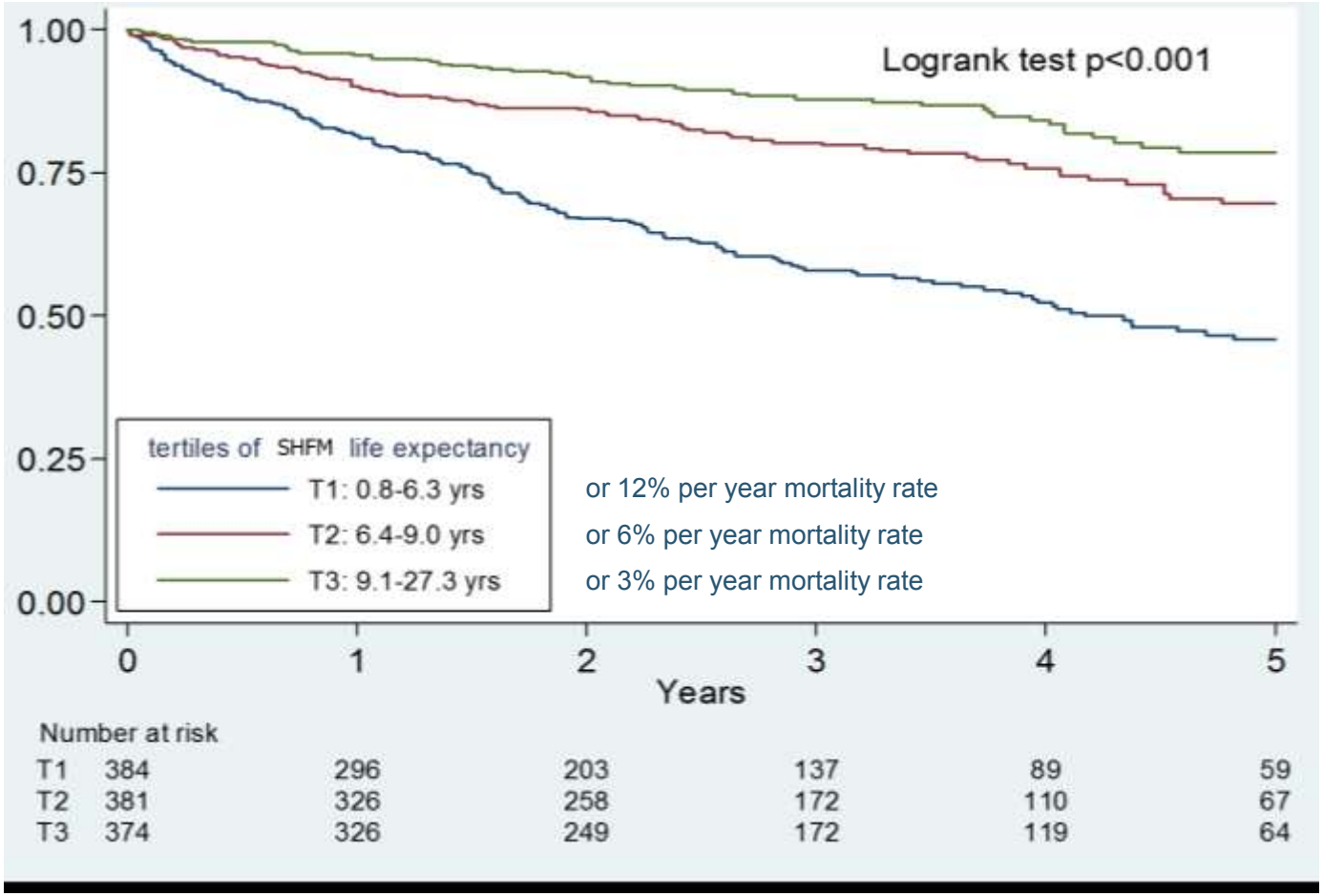
Hsu et al JACC 2012

The multiple categories of response by Seattle Heart Failure Score



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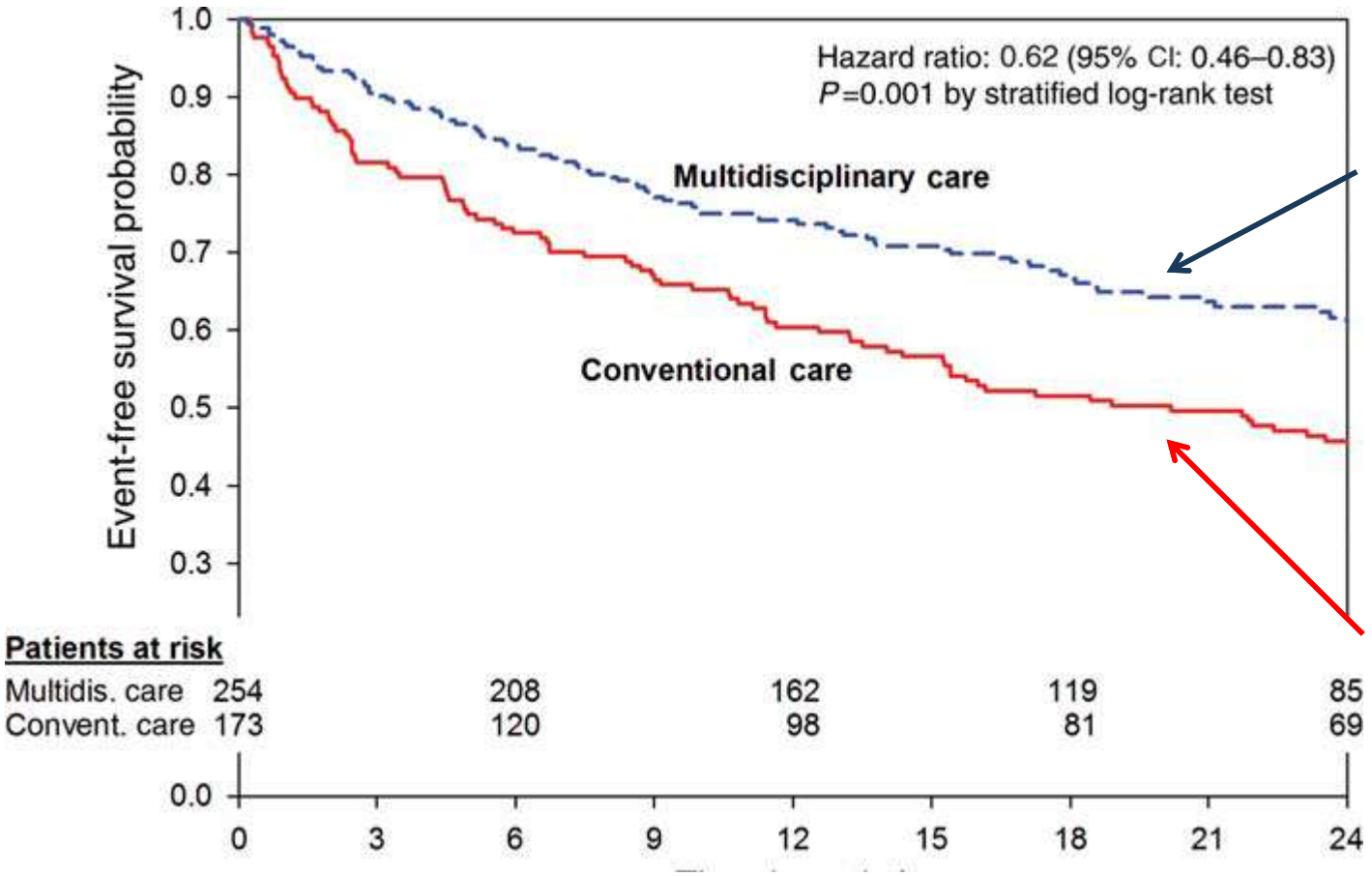
Regoli et al. Eur Heart J 2012

Multidisciplinary management



Integrated clinic setting by a team of subspecialists from the
- heart failure
- electrophysiology, and
- echocardiography service
- at 1-, 3-, and 6-months post-implant

Conventional care setting, patients were seen as needed by each subspecialist and in EP device clinic in separate visits at varying intervals. Echocardiogram-guided optimizations were dictated by physician discretion and not performed routinely.

Using binary category of response to CRT w/out consideration on remote device/arrhythmia management

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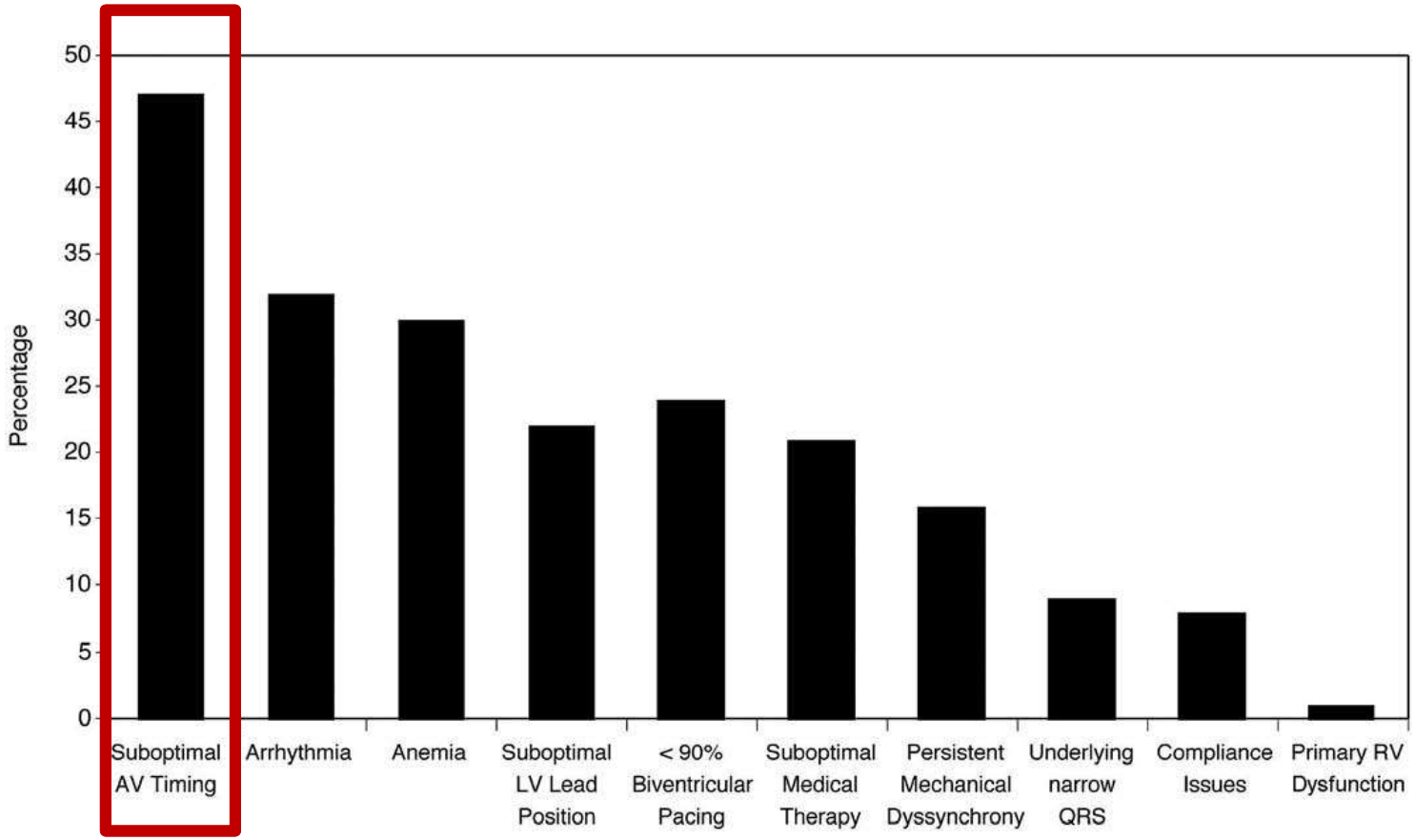
Altman et al. Eur Heart J 2012

Causes of no-response to CRT in the era of binary category assessment



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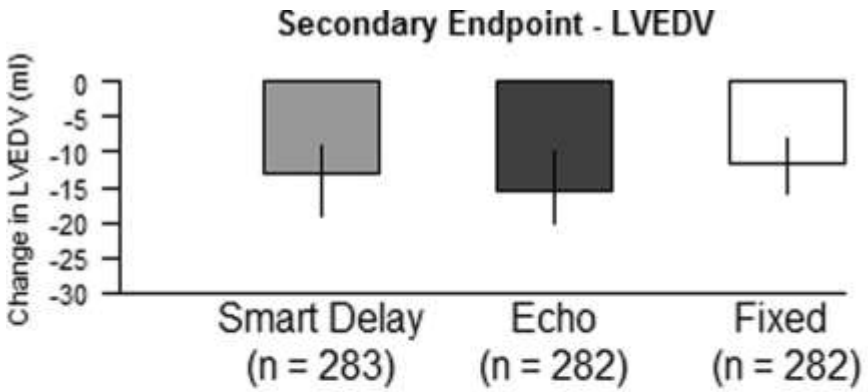
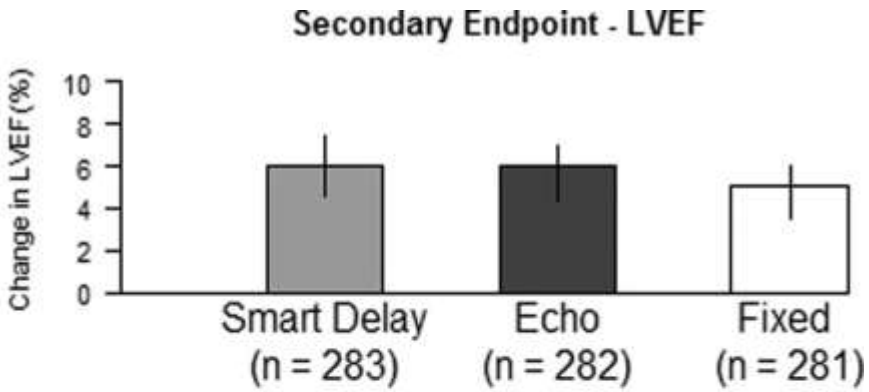
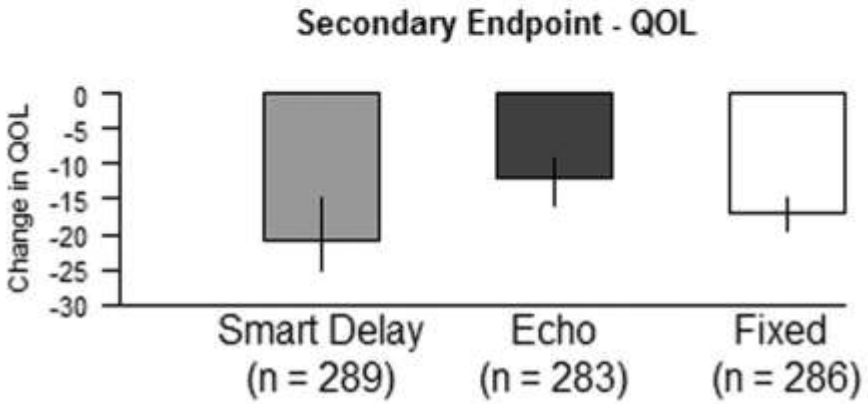
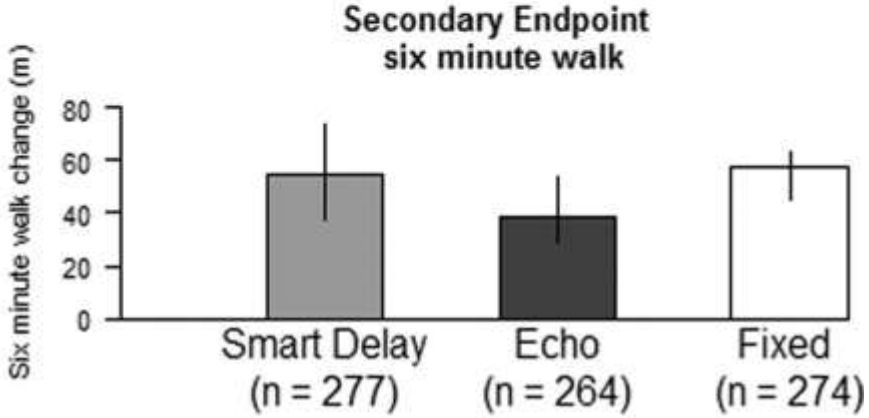
Mullens W et al. JACC 2009;53:765–73

AV delay optimization in CRT patients









Conclusions—Neither SmartDelay nor echocardiography was superior to a fixed AV delay of 120 milliseconds. The routine use of AV optimization techniques assessed in this trial is not warranted. **However, these data do not exclude possible utility in selected patients who do not respond to cardiac resynchronization therapy.**

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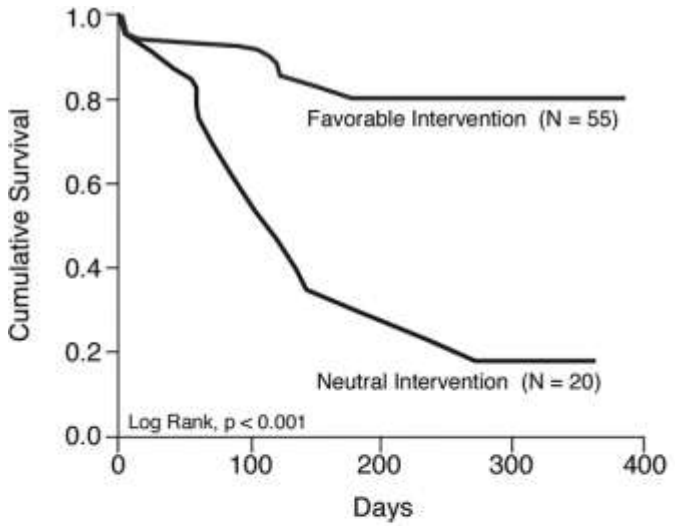
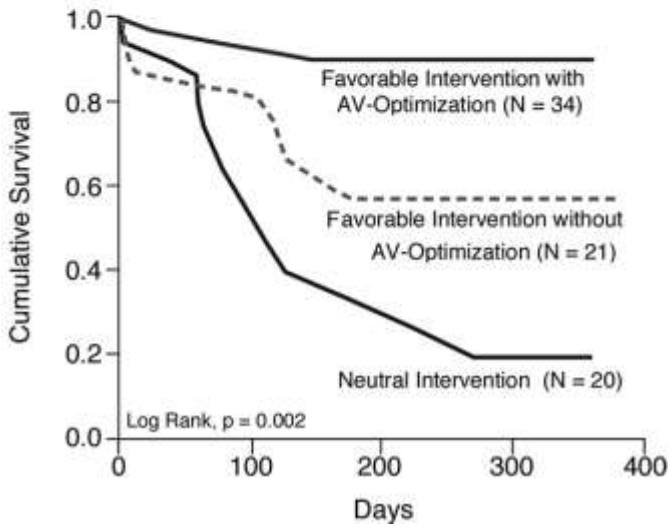
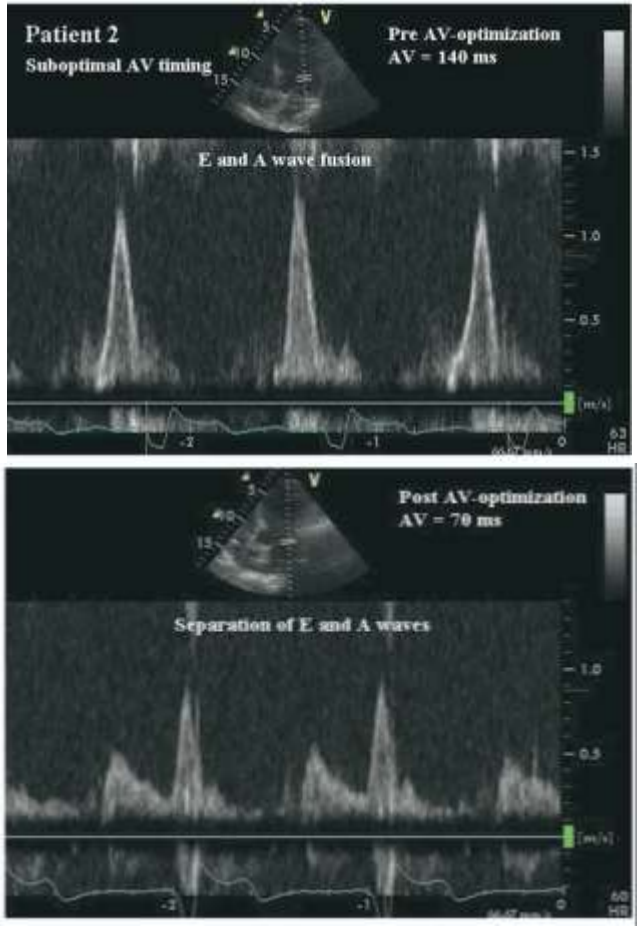
Ellenbogen et al. Circulation 2010

Suboptimal AV Delay as cause of no-response to CRT







Mullens W et al. JACC 2009;53:765–73

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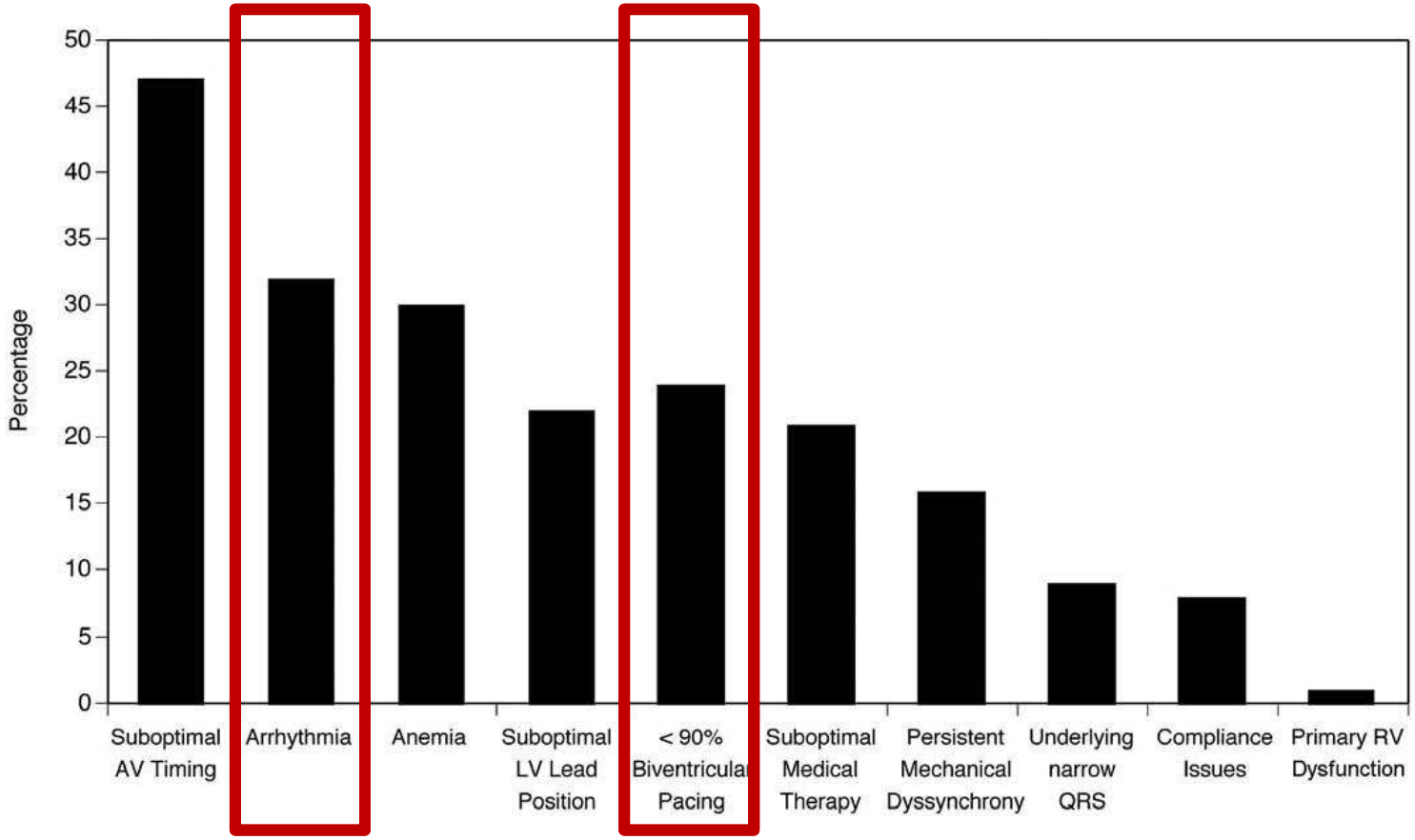
Causes of no-response to CRT



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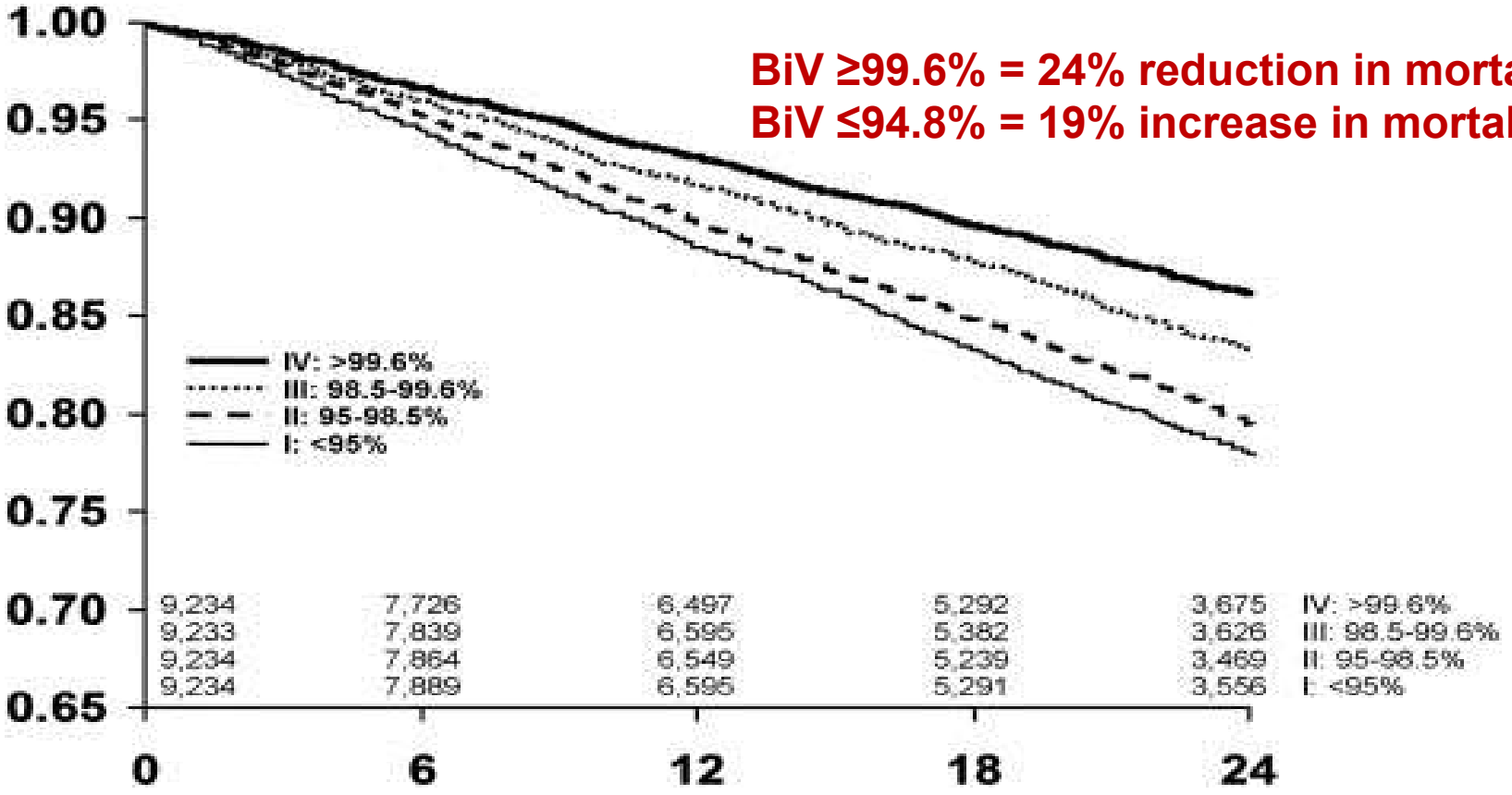
Mullens W et al. JACC 2009;53:765–73

CRT and the relationship of percent BiV pacing to symptoms and survival

36,935 pts followed up in the LATITUDE RM network



BiV ≥99.6% = 24% reduction in mortality
BiV ≤94.8% = 19% increase in mortality

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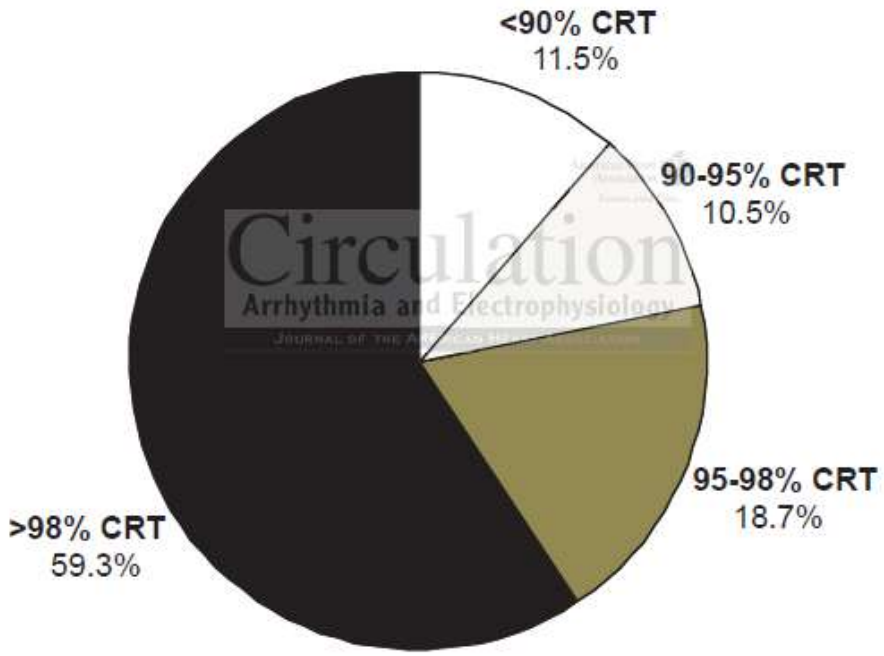
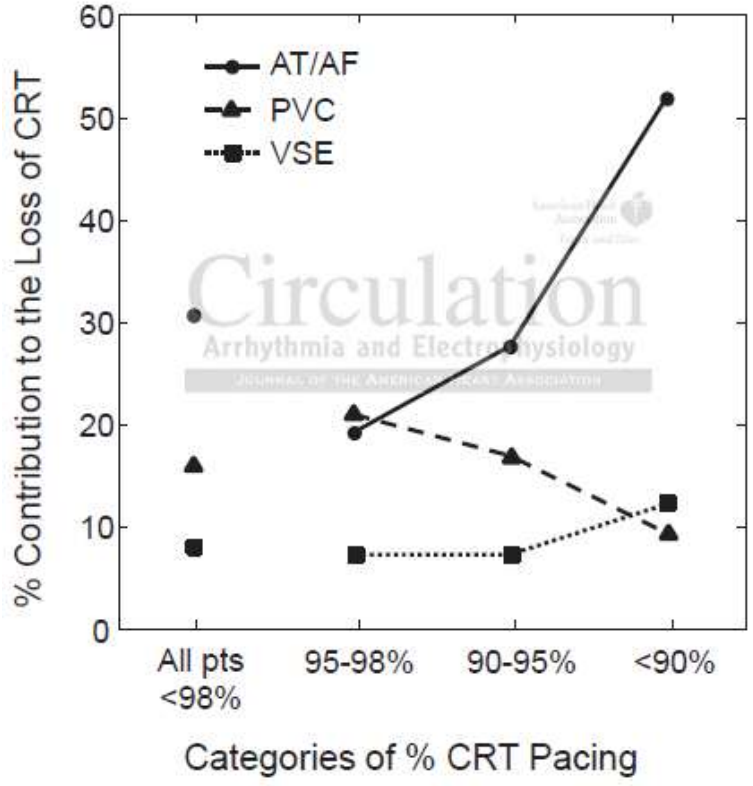
Hayes et al., Heart Rhythm 2011, 8, 1469 - 1475

Reasons for loss of CRT





32,844 Patients

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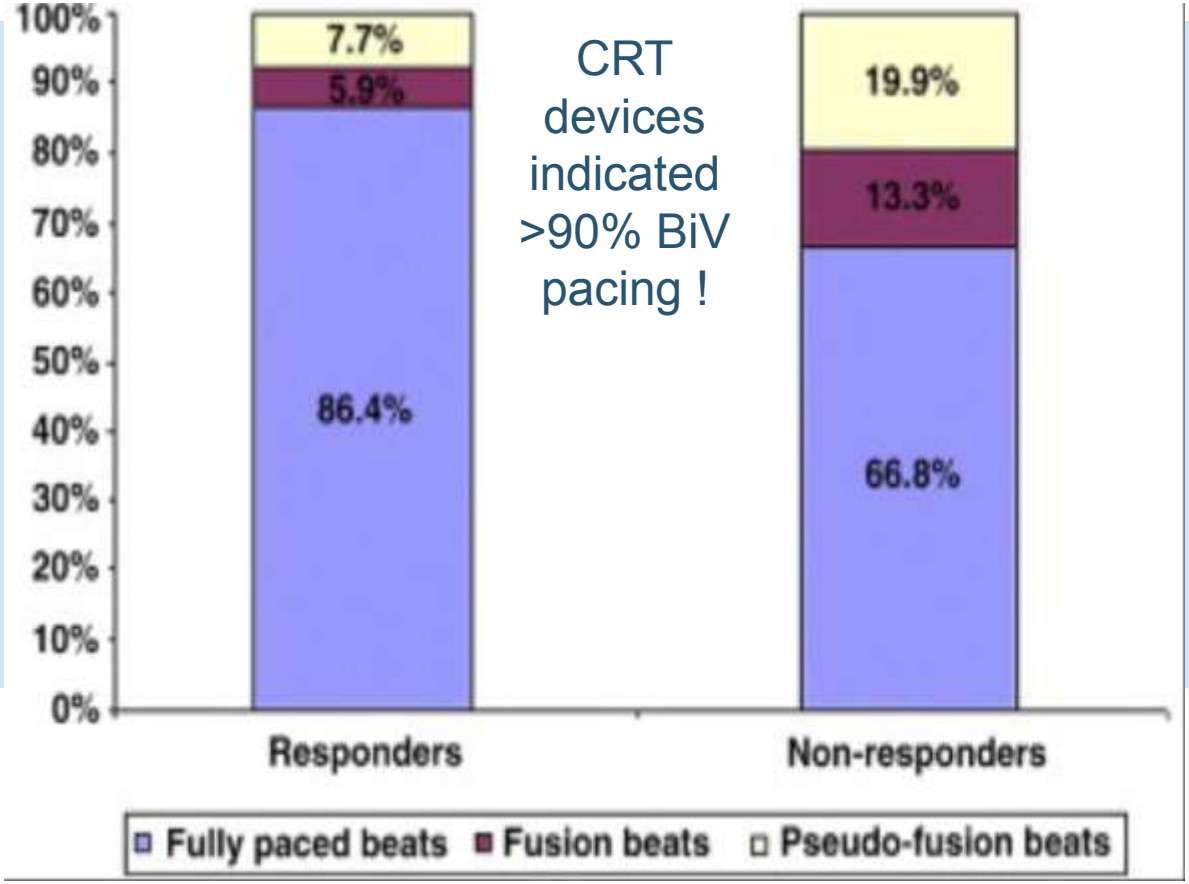
Cheng et al. Circ A & E 2012

The Utility of 12-Lead Holter Monitoring in Patients With Permanent AF for the Identification of Nonresponders After CRT



CRT devices indicated >90% BiV pacing !

In pts with permanent AF and HF, using data from CRT counters alone to estimate percentage of BiV stimulation time may be MISLEADING, because counters likely overestimate the degree of BiV pacing

Kamath et al., J Am Coll Cardiol. 2009;53(12):1050-1055

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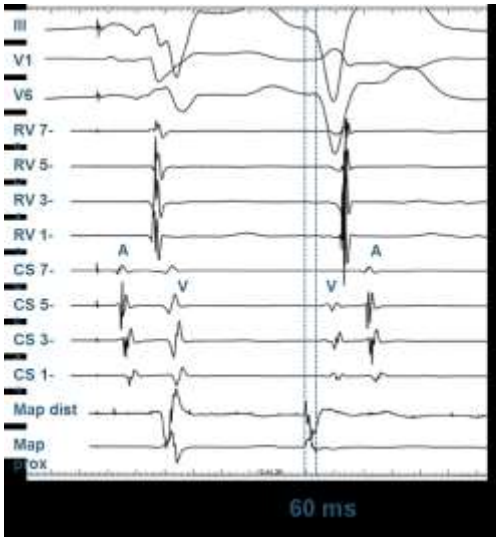
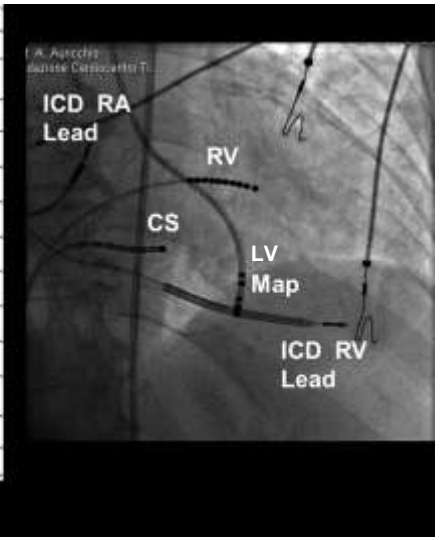
Frequent VES as cause of no-response to CRT





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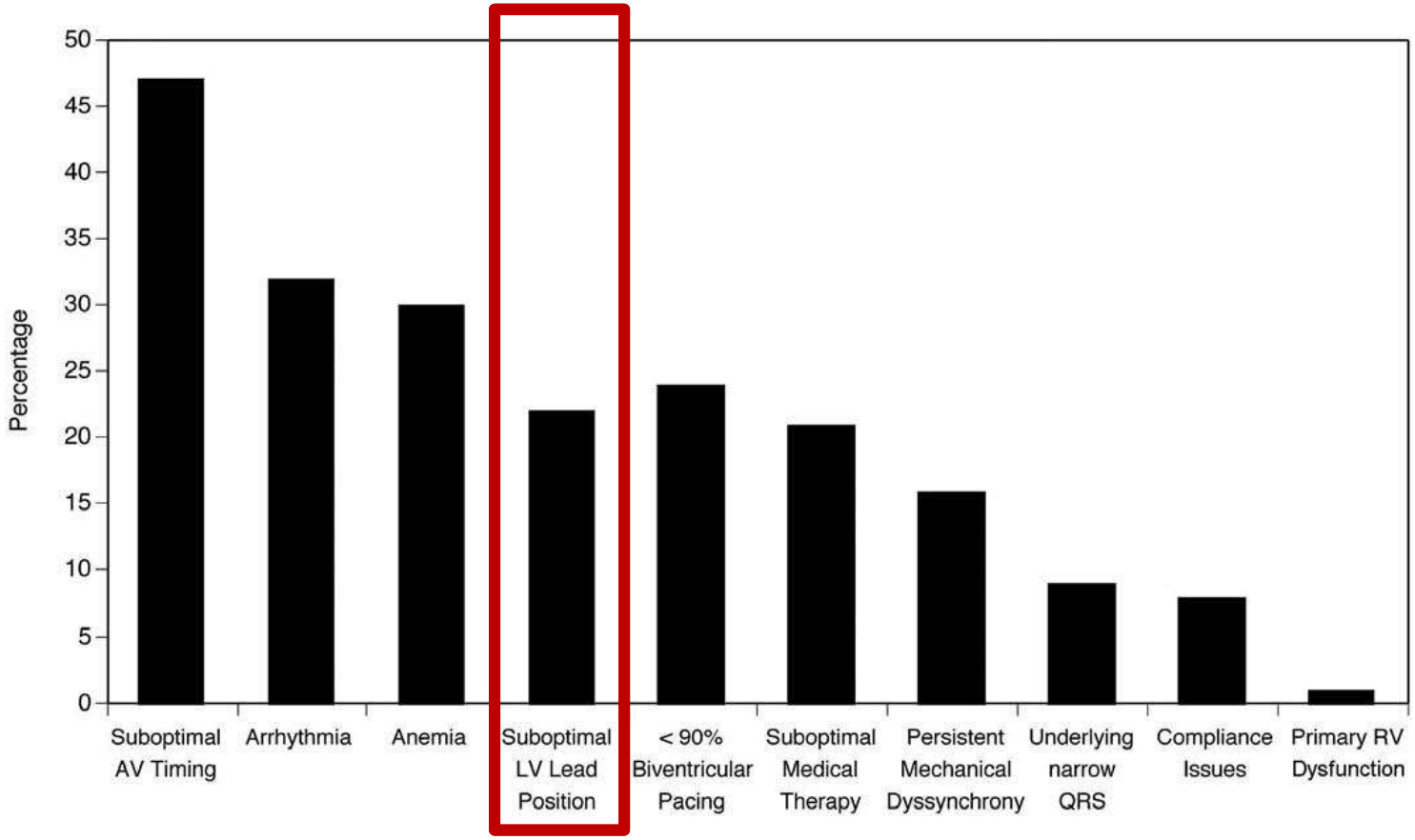
Causes of no-response to CRT



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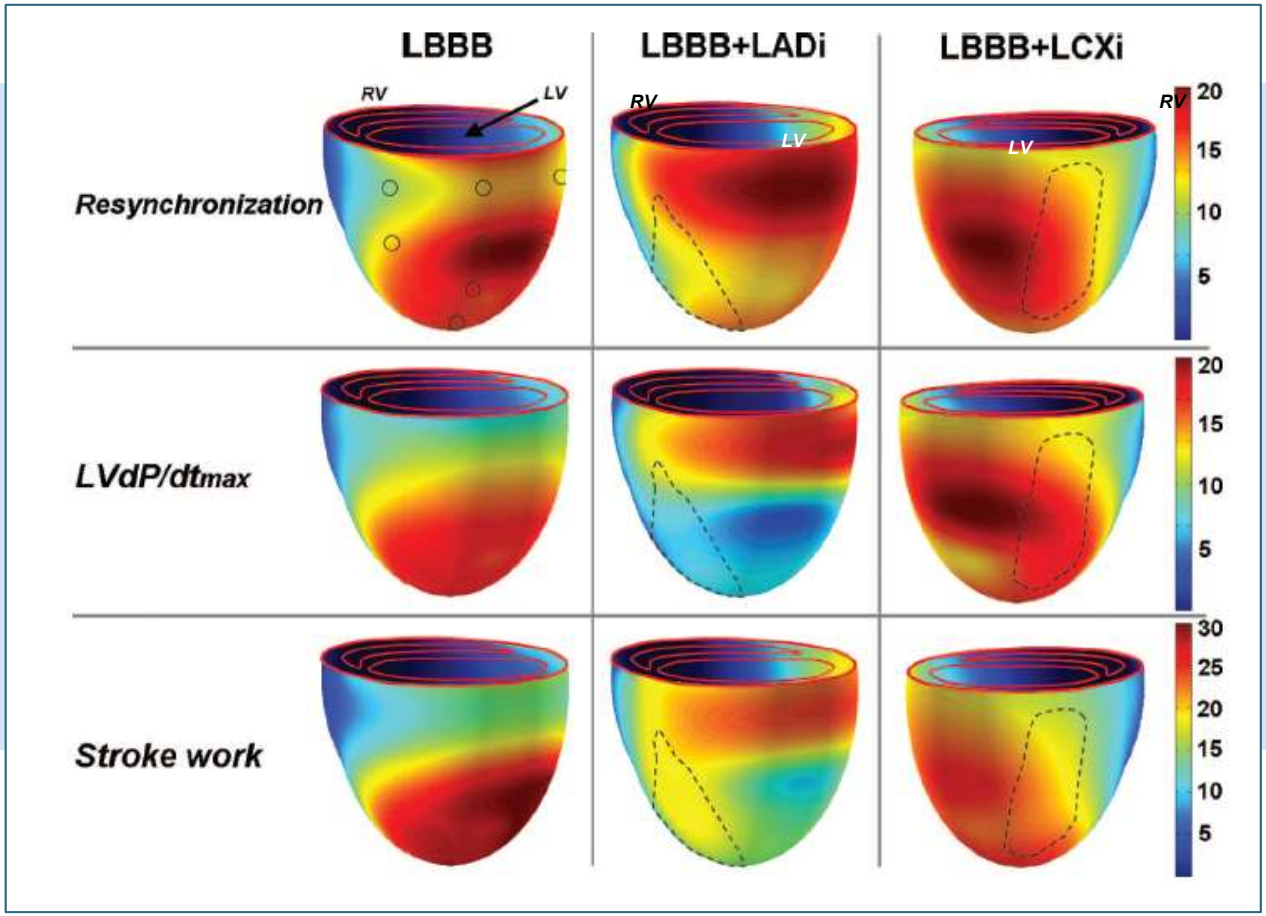
Mullens W et al. JACC 2009;53:765–73

Importance of LV lead location in chronic canine model of myocardial infarction



Rademakers et al. Circ A & E 2010

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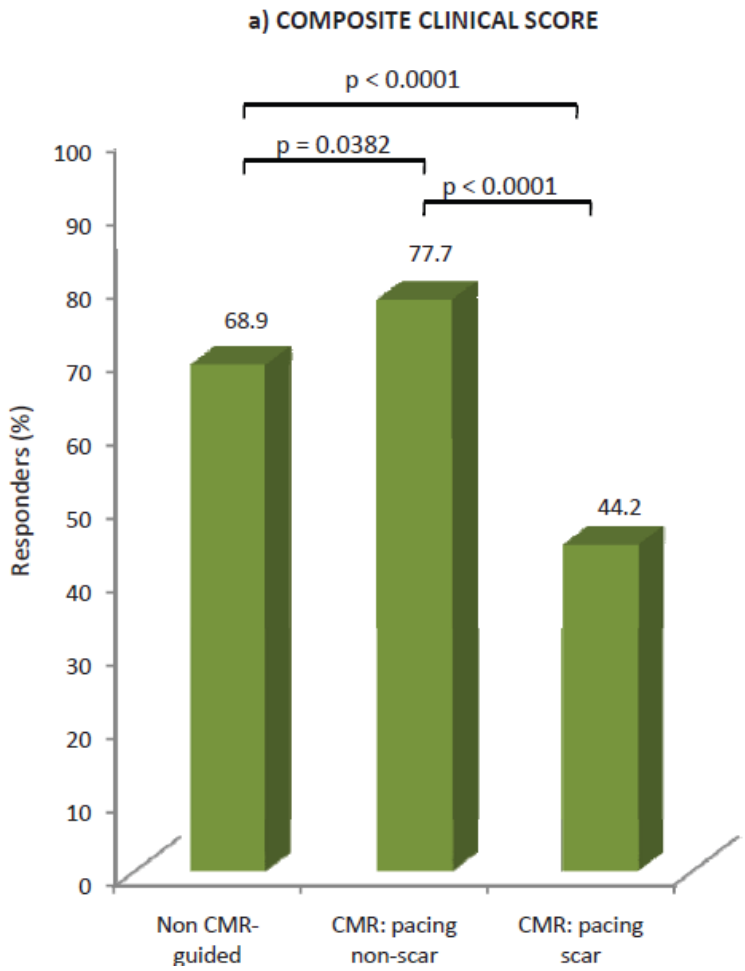
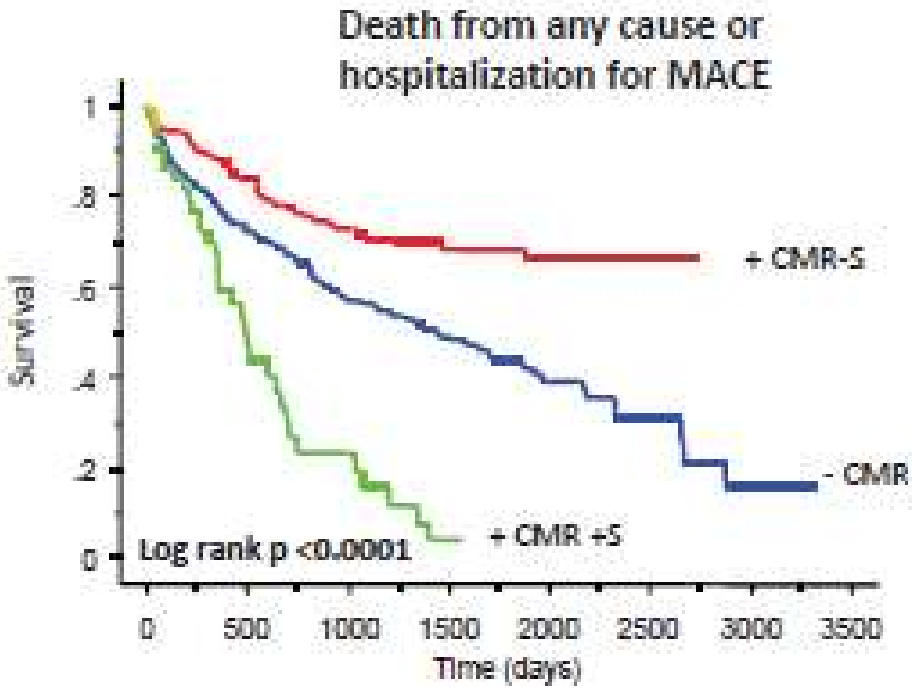
Outcome: pacing in scar vs. outside scar





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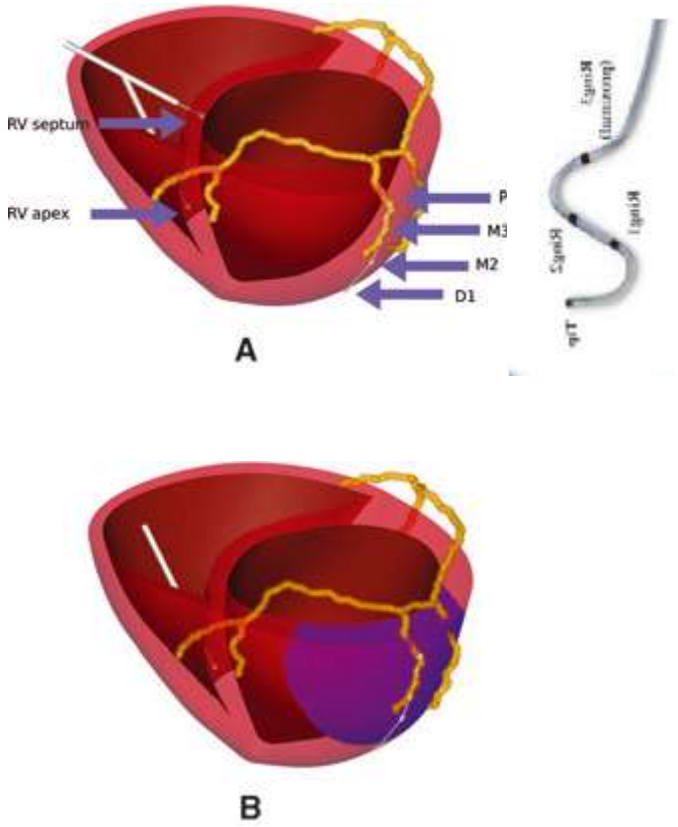
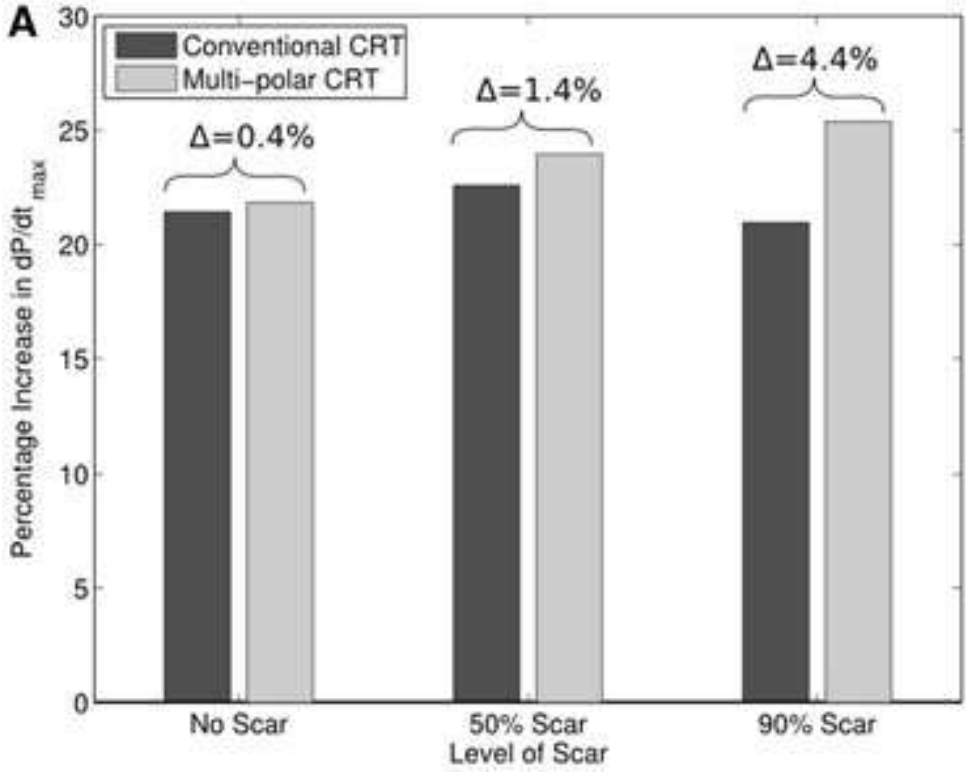
Leyva et al. J Cardiovasc Magn Resonance 2011

Biophysical Modeling to Simulate the Response to Multisite Left Ventricular Stimulation Using a Quadripolar Pacing Lead





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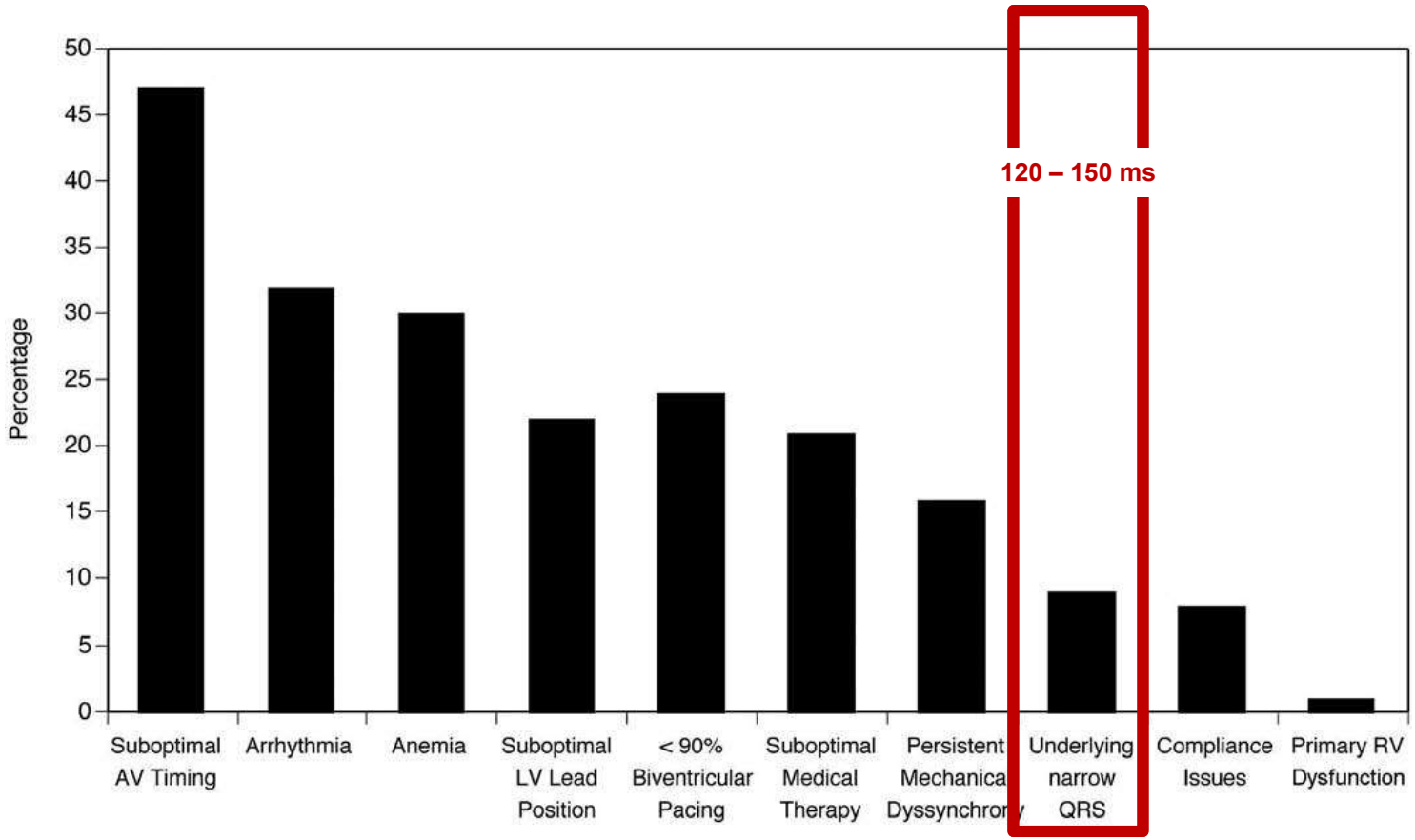
Niederer et al. PACE 2012

Causes of no-response to CRT



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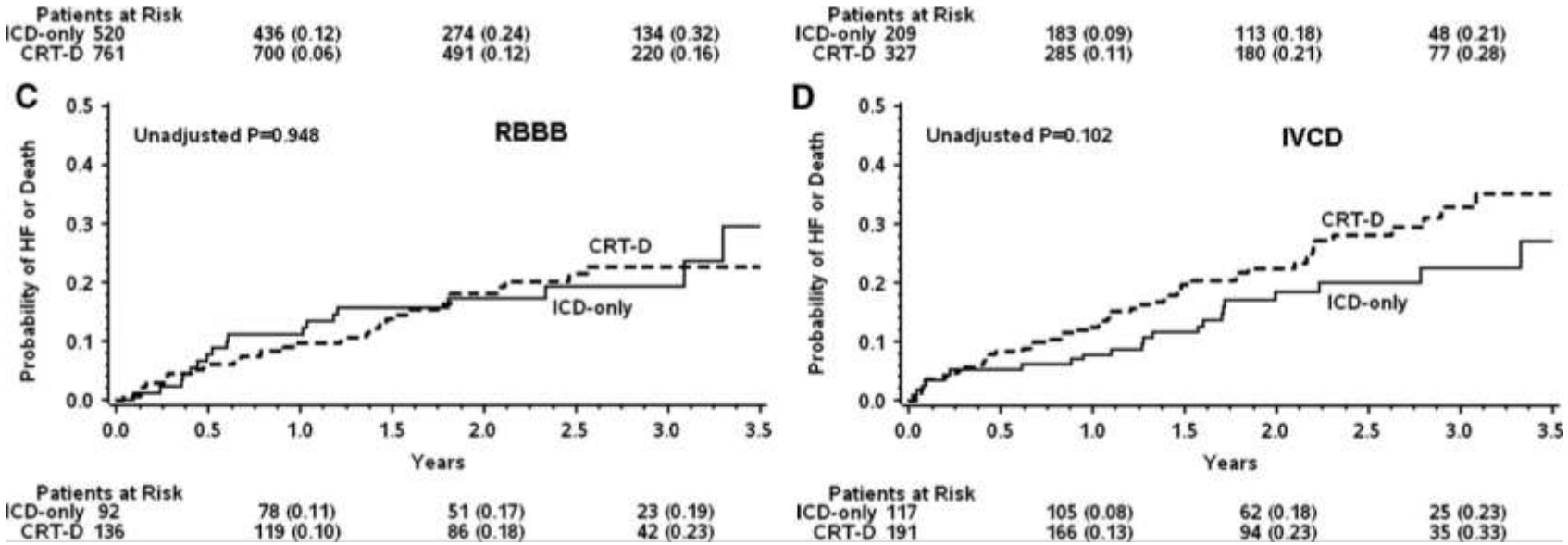
Mullens W et al. JACC 2009;53:765–73

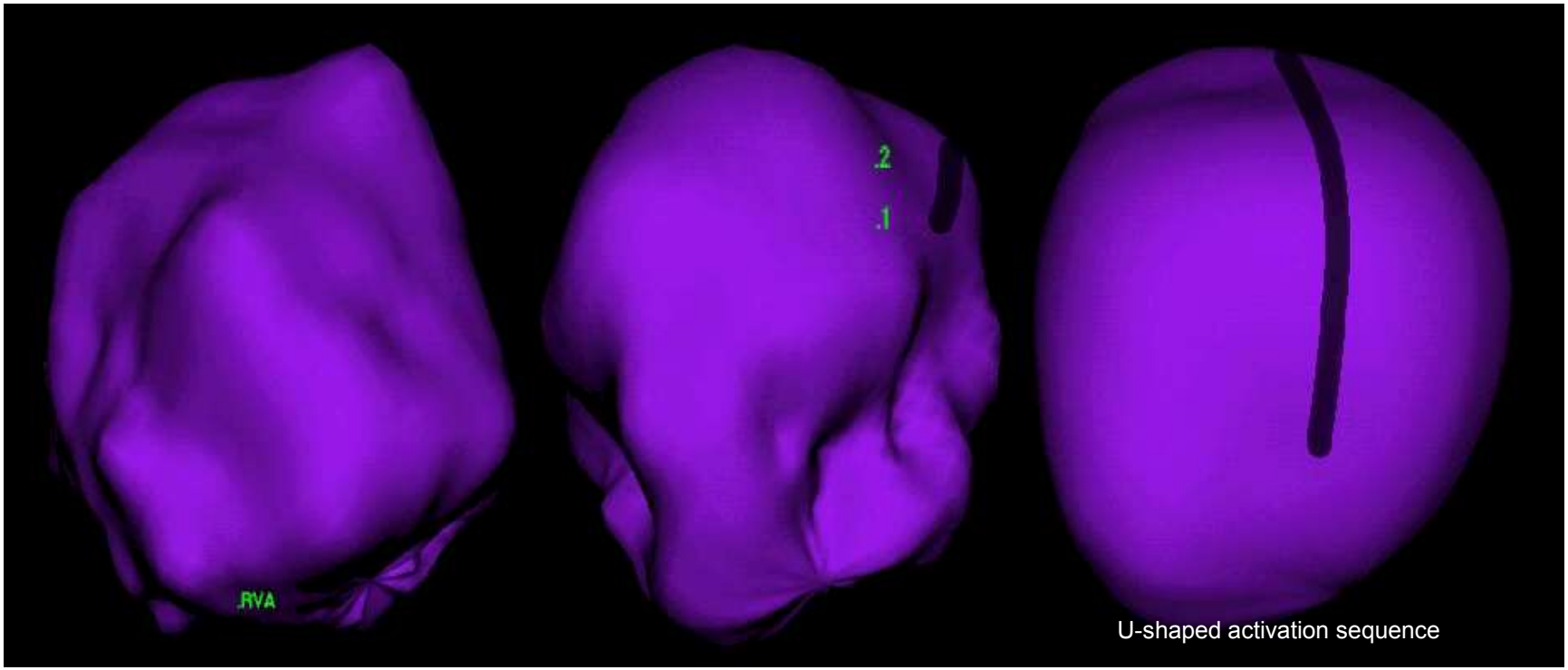
CRT-D has neutral effect in pts with RBBB, but in those with ICVD ……



CARDIOCENTROTICINO

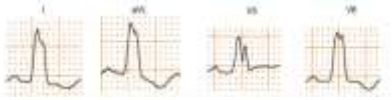
Zareba et al Circulation 2011

LV activation sequence (U-shaped) in dilated cardiomyopathy and heart failure



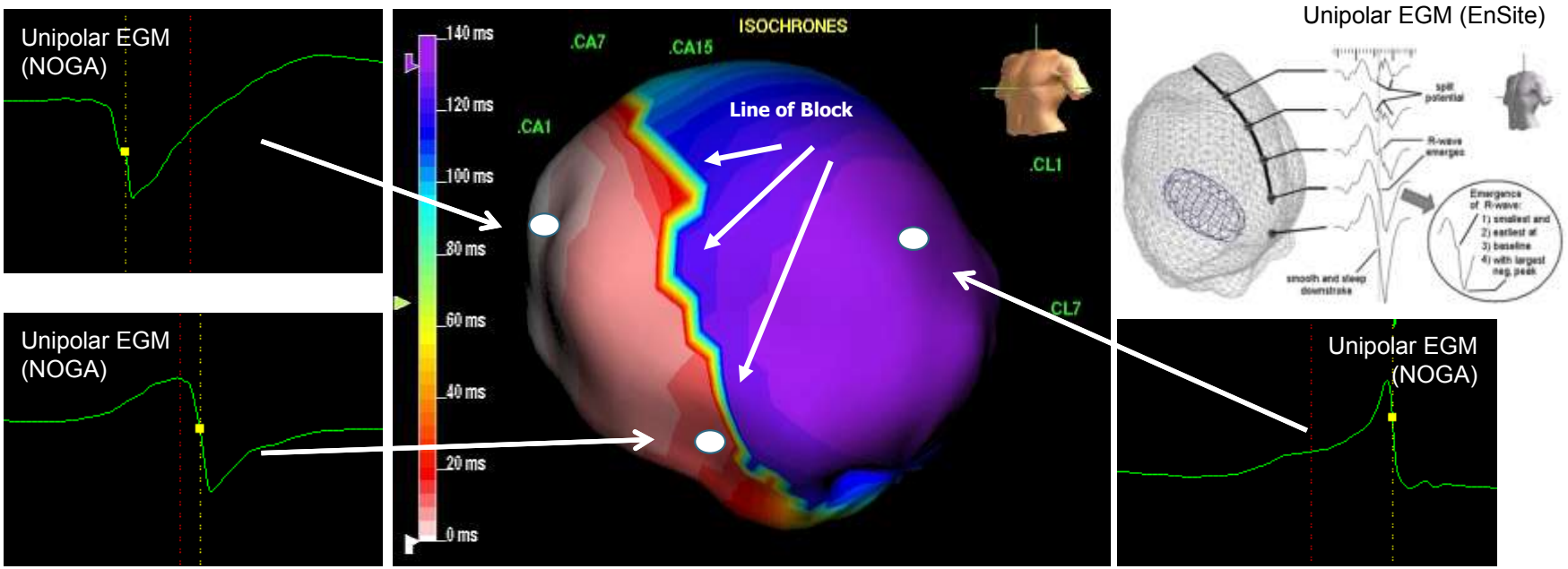
Normal QRS Morphology and Duration

QRS Duration: 125 ms



QRS Duration: 158 ms

Local EGMs in complete LBBB



Auricchio et al. Circulation 2004

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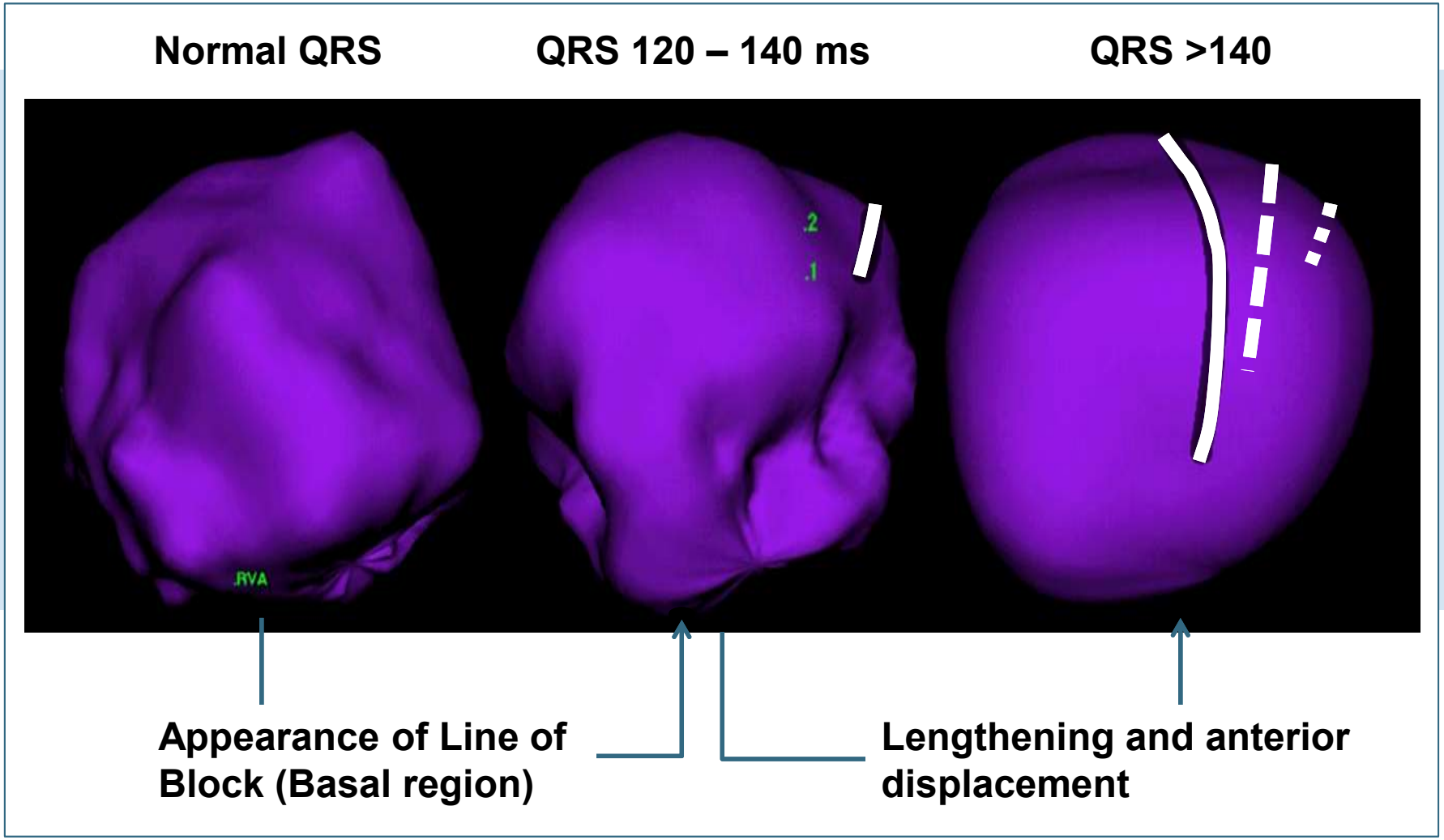
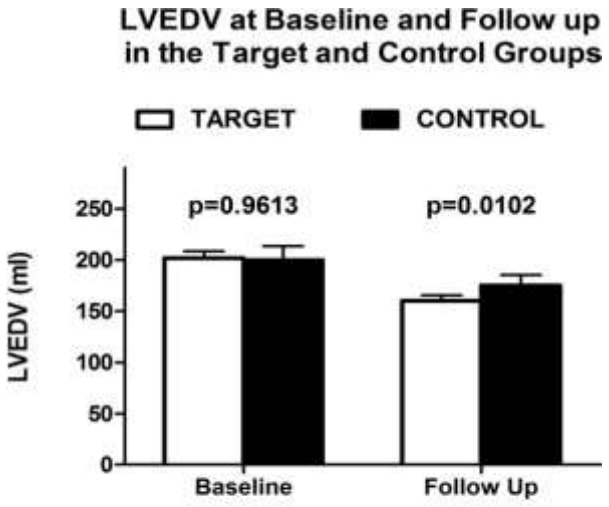
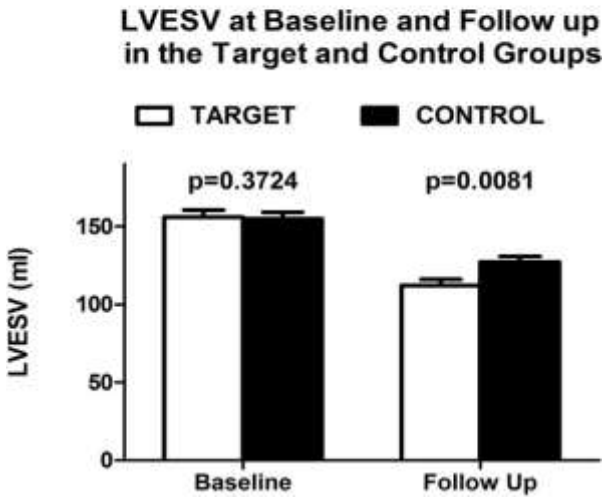
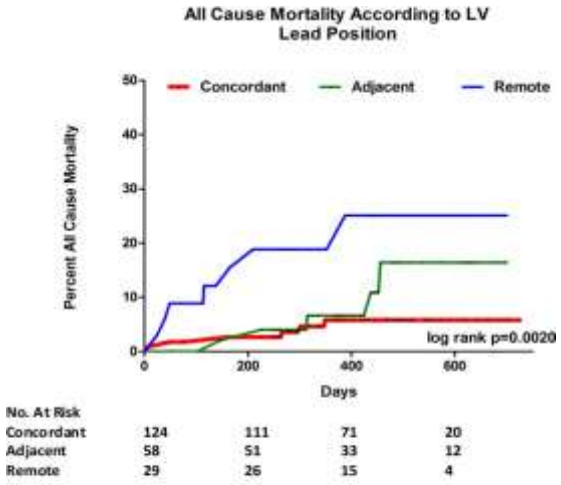
Changes of line of block position and length with QRS change in LBBB patients

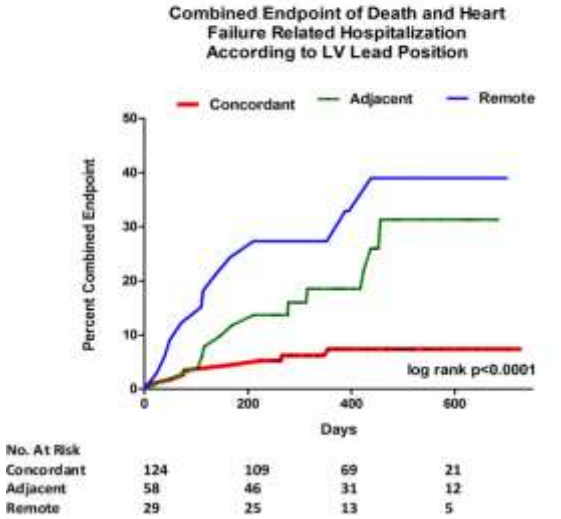


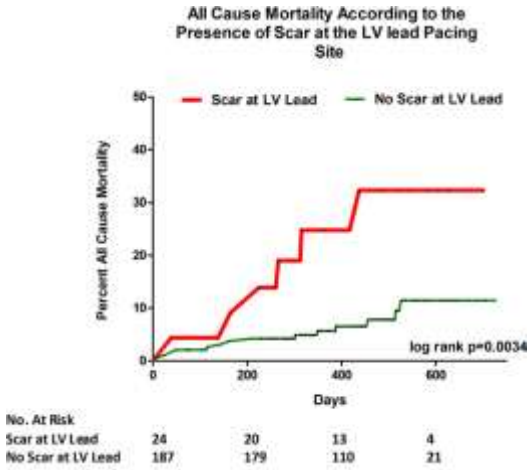
Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy (TARGET)











The use of speckle-tracking echocardiography to the target LV lead placement yields significantly improved response and clinical status and lower rates of combined death and heart failure–related hospitalization.

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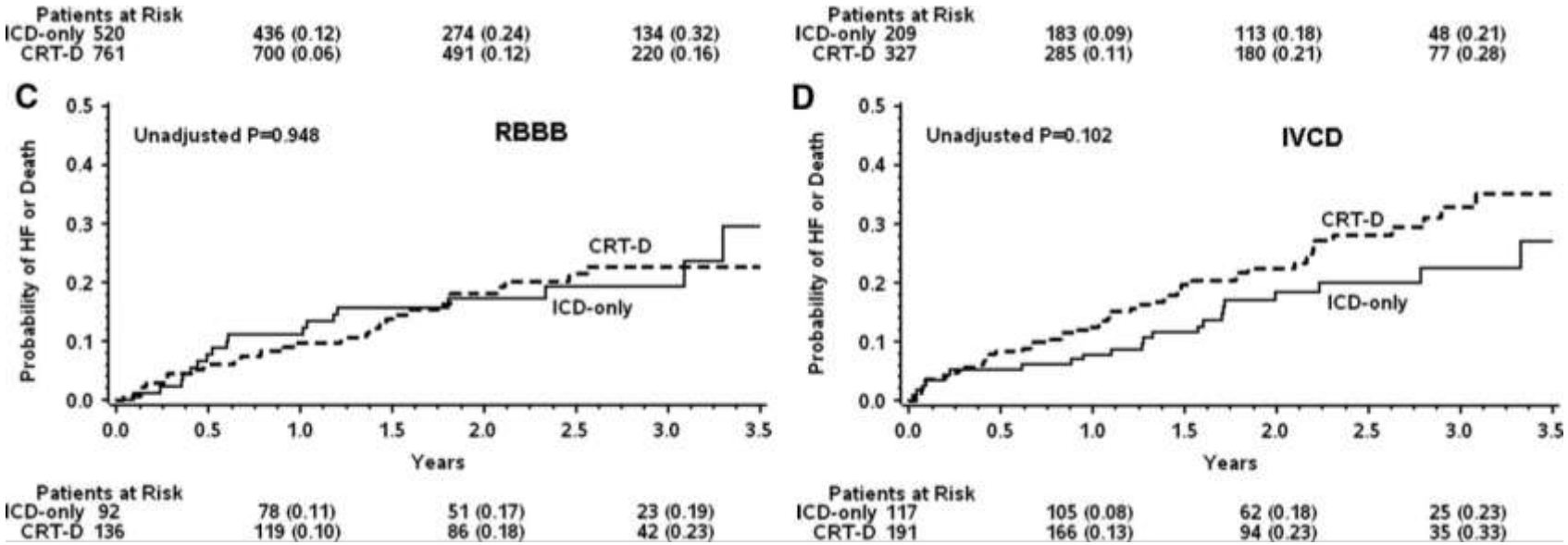
Khan FK et al. JACC 2012; 59:1509–18

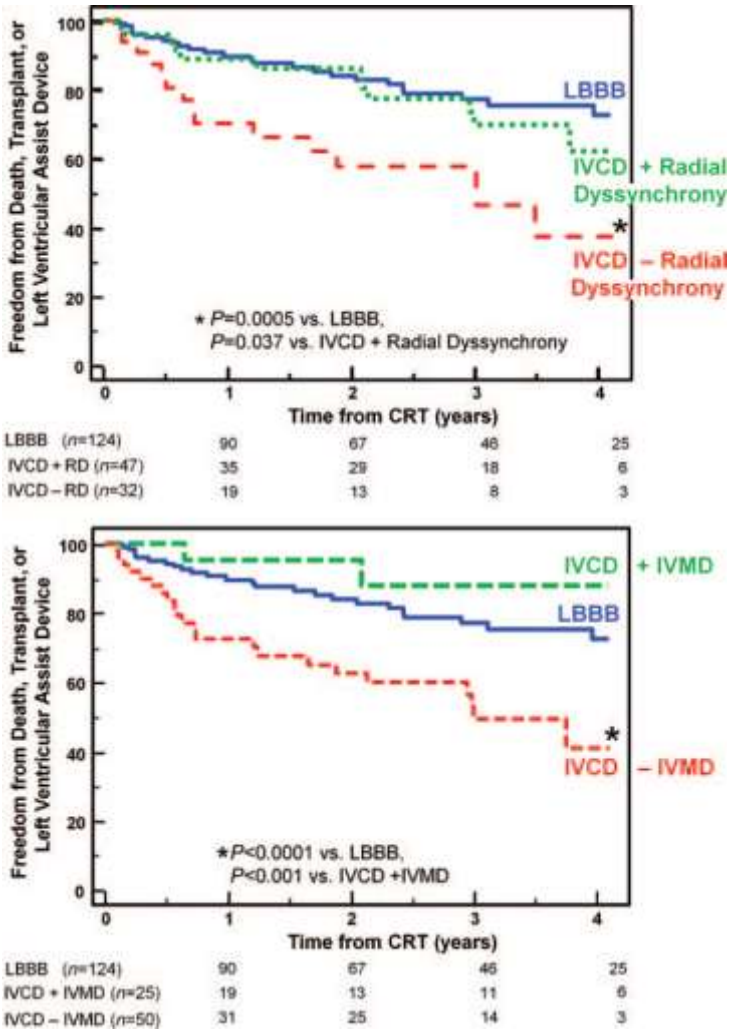
CRT-D has neutral effect in pts with RBBB, but why so ?

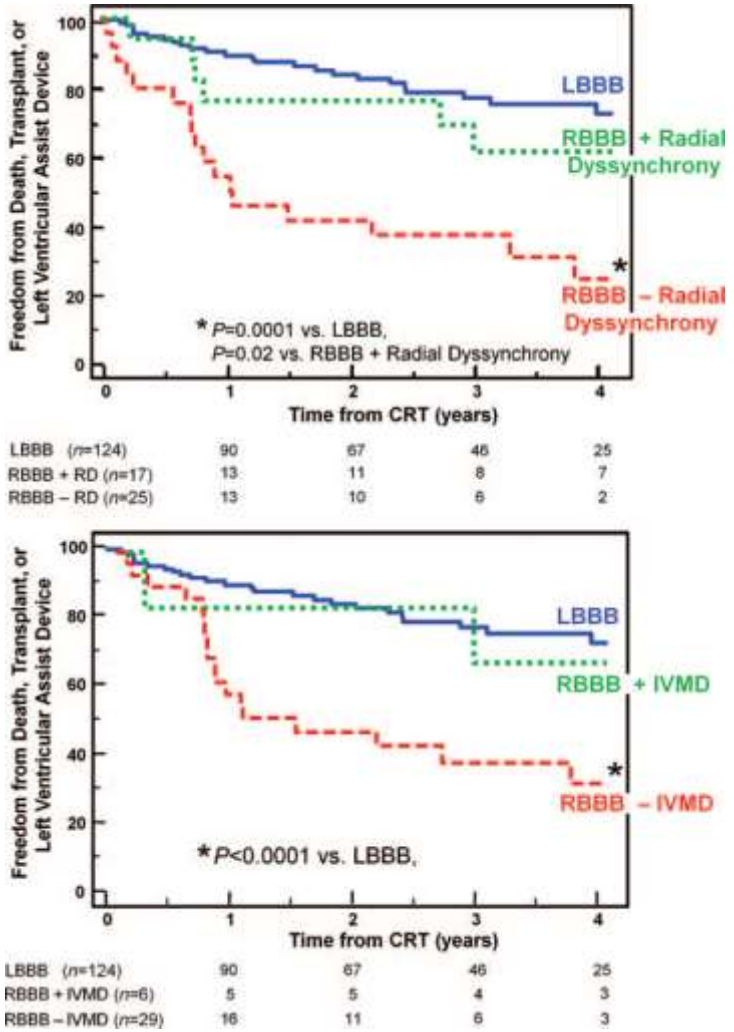


CARDIOCENTROTICINO

Zareba et al Circulation 2011

Importance of radial dyssynchrony on outcome

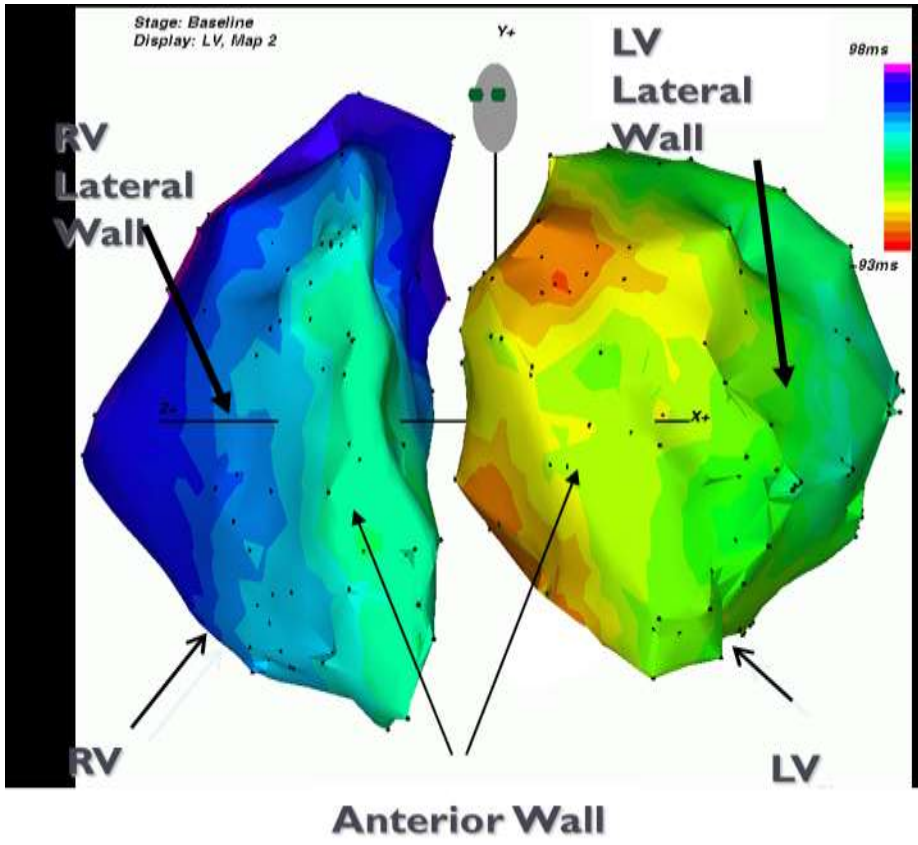




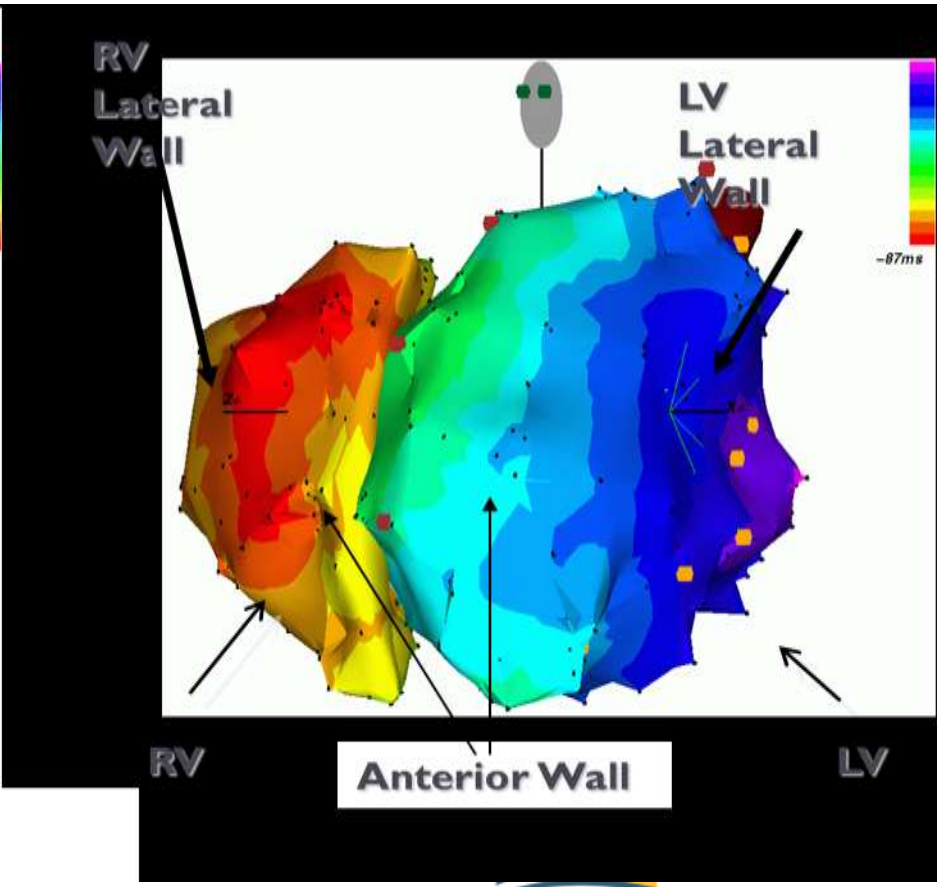
Hara et al. Eur Heart J 2012

Is CRT delivery suboptimal in RBBB patients ?

Right Bundle Branch Block



Left Bundle Branch Block



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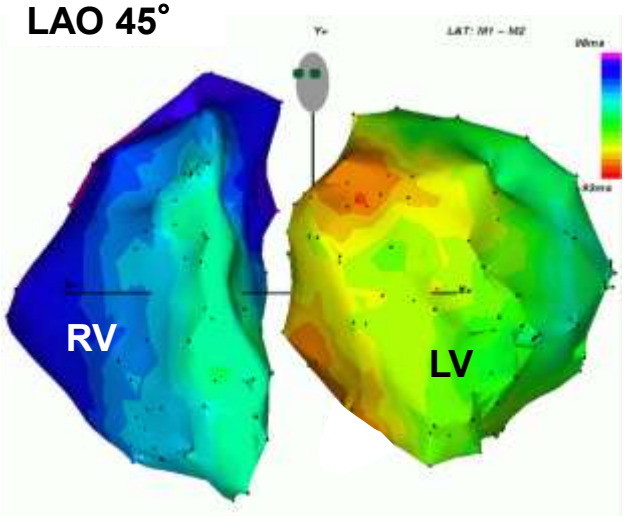
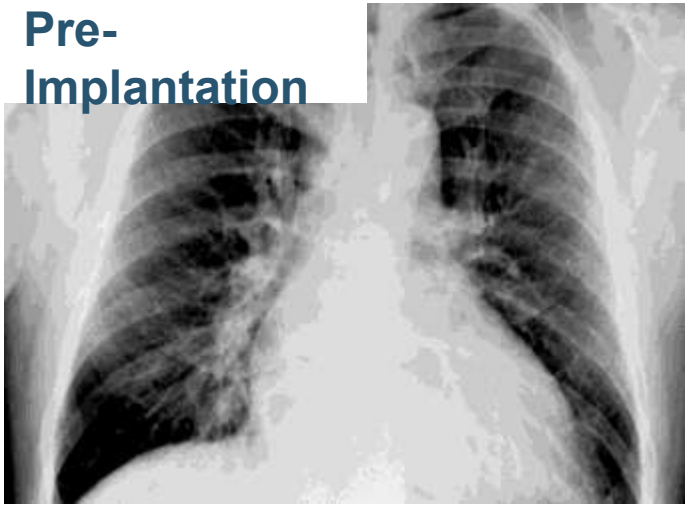
Fantoni et al. JCE 2005

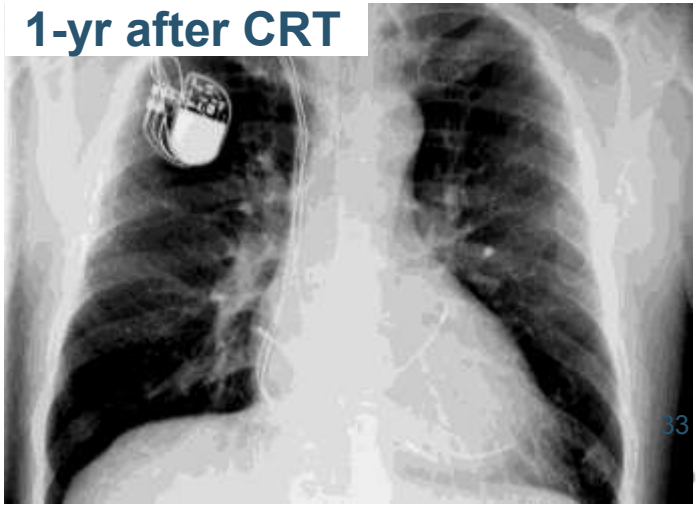
CRT in a RBBB Patient



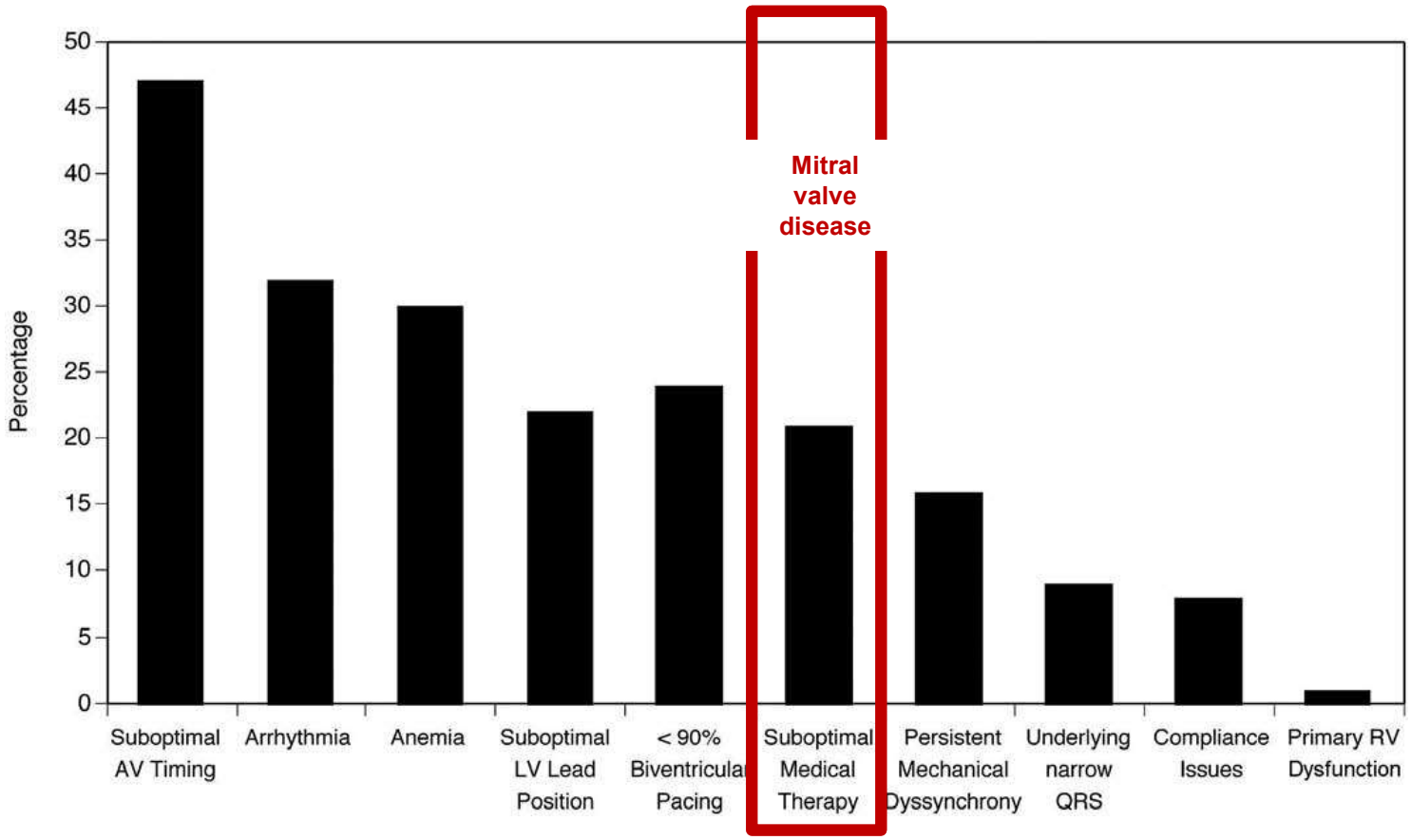
Pre-Implantation



1-yr after CRT



Causes of no-response to CRT



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Mullens W et al. JACC 2009;53:765–73

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 58, No. 21, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.06.061

FOCUS ISSUE: STRUCTURAL HEART DISEASE

Clinical Research

Correction of Mitral Regurgitation in Nonresponders to Cardiac Resynchronization Therapy by MitraClip Improves Symptoms and Promotes Reverse Remodeling

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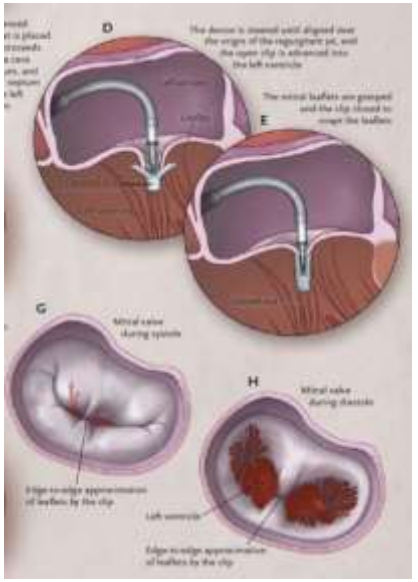
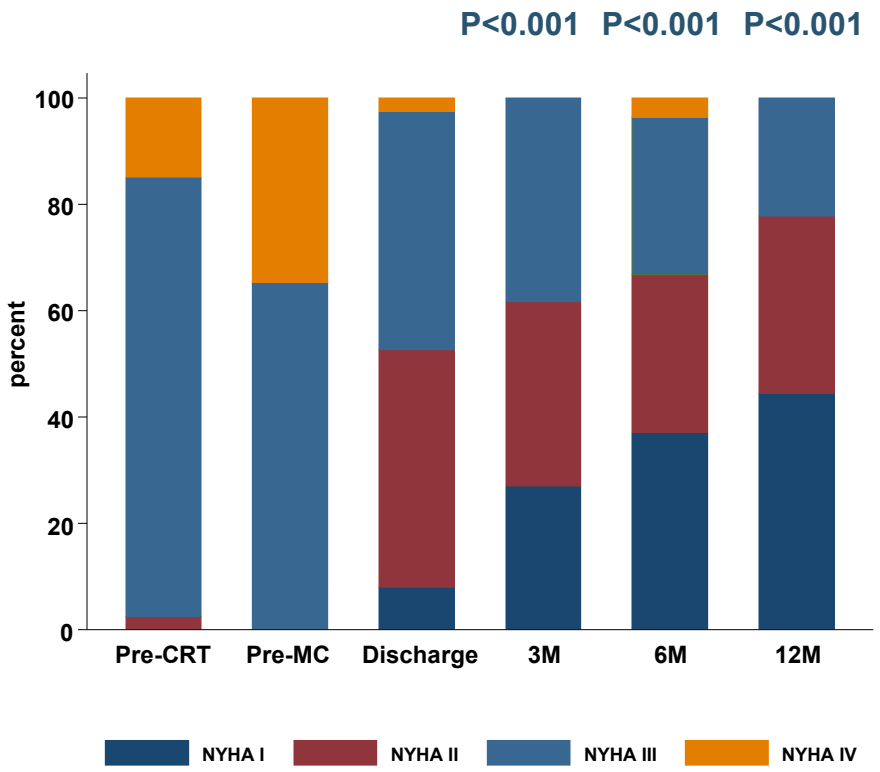
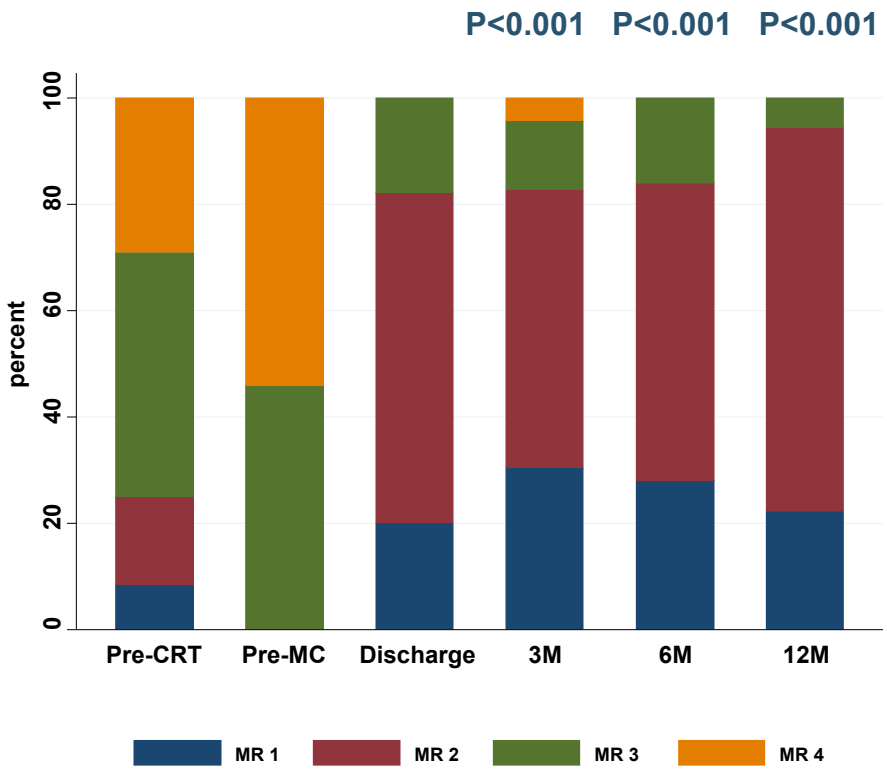
Francesco Maisano, MD,§ Rainer Hoffmann, MD,‖ Gian Paolo Ussia, MD,¶
Giovanni B. Pedrazzini, MD,* Jan van der Heyden, MD,# Simona Fratini, MD, PHD,**
Catherine Klersy, MD, MSC,†† Jan Komtebedde, DVM,* Olaf Franzen, MD,‡
on behalf of the PERMIT-CARE Investigators



Age	70.3 ± 9.2 yrs
Male Gender	44 (86%)
Ischemic cardiomyopathy	37 (73%)
Previous interventions (%)	
CABG or PCI	24 (47%)
Valve surgery	4 (8%)
Functional New York Heart Association Class	
III	32 (63%)
IV	17 (35%)
CRT-D (%)	47 (92%)
Month since CRT	32.9 ± 25.7

Change in NYHA class and MR after MitraClip in 51 CRT non-responders





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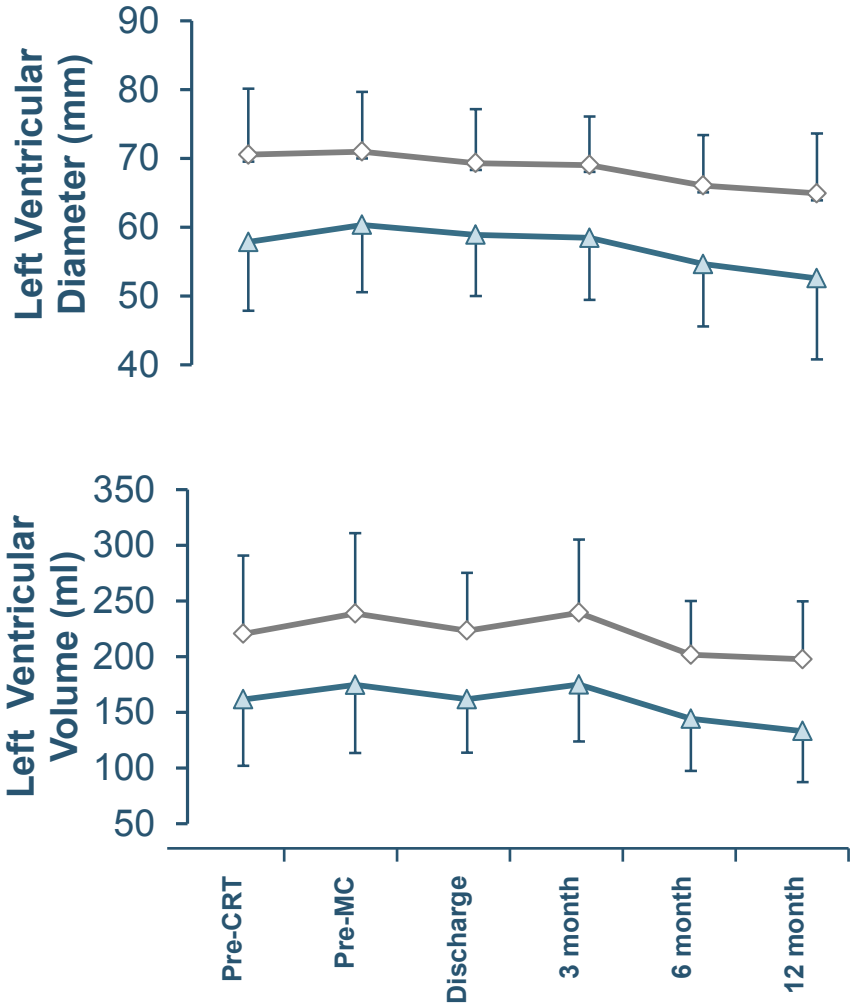
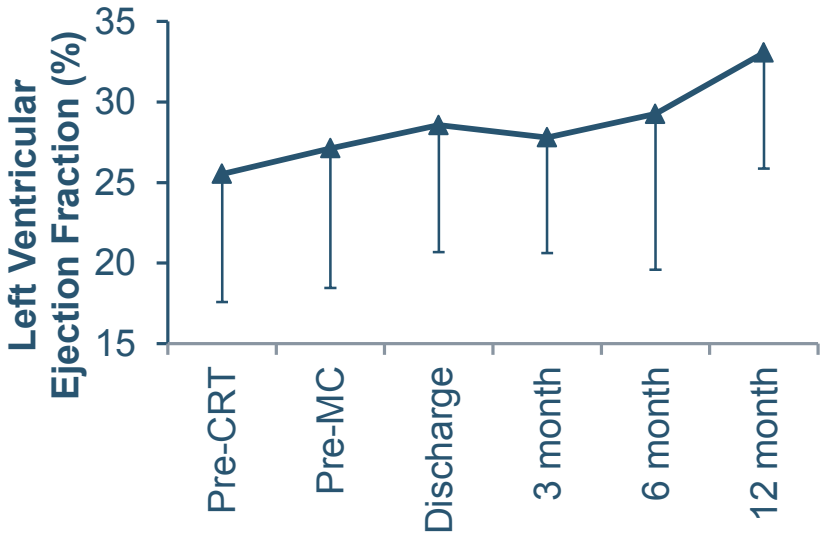
A. Auricchio et al. JACC 2011; 58: 2183-9

Reverse remodeling in CRT non-responders treated by MitraClip





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A. Auricchio et al. JACC 2011; 58: 2183-9

Conclusions

A multidisciplinary protocol-driven approach to ambulatory CRT patients who did not exhibit a positive response long after implant may uncover potential contributors to a suboptimal response such as

- **Suboptimal AV Delay**
- **Frequent atrial and/or ventricular arrhythmias**
- **Major valvular abnormalities**
- **Pacing in scar dense areas**
- **Mismatch between pacing and electrical / mechanical abnormality**

may potentially maximize the potential of CRT, and

may be associated with a reduction in adverse events.