Respond Study

The Contribution of SonR to Increasing Responder Rates

Francis Murgatroyd

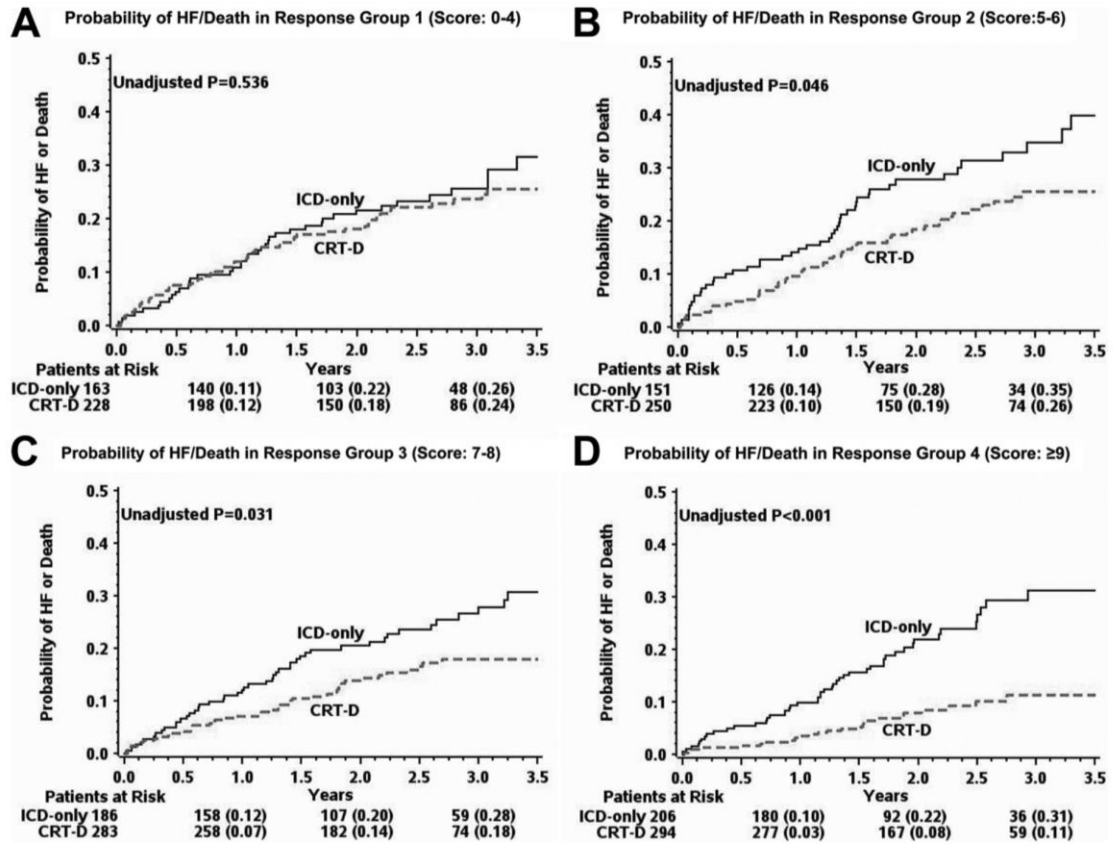
King's College Hospital, London

Francis Murgatroyd
Interests 2015-7

- Speaker
  - Boston Scientific, Livanova, Medtronic, St Jude
- Consultancy/Advisory Board
  - Boston Scientific, Medtronic, St Jude
- Research
  - Steering committee: Medtronic
  - Investigator: Livanova, Medtronic, St Jude
- Stock Ownership
  - None

CRT-D vs ICD
MADIT-CRT Subgroup Analysis

- 7 factors associated with response:-
  - Female
  - Nonischaemic
  - LBBB
  - QRS ≥150ms
  - Prior HFH
  - LVEDV ≥125ml/m^2
  - LA <40ml/m^2
- Weighted score (0-9) derived



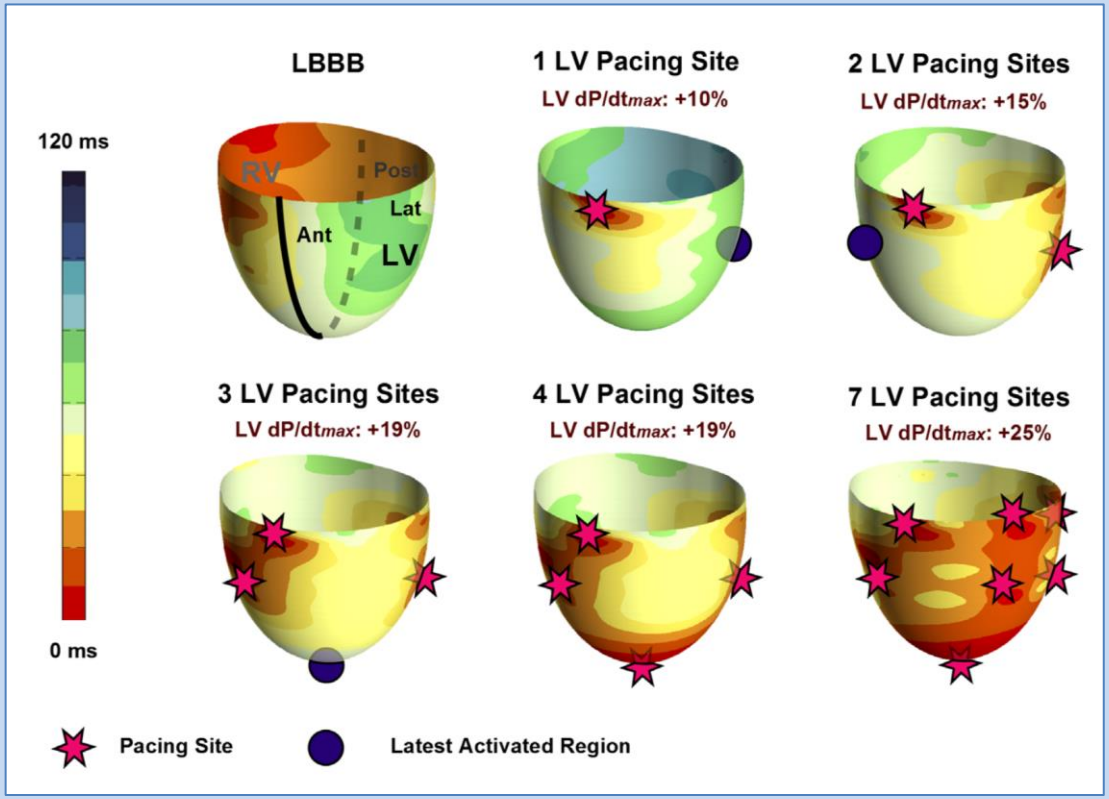
Goldenberg I et al Circulation 2011; 124:1527-36

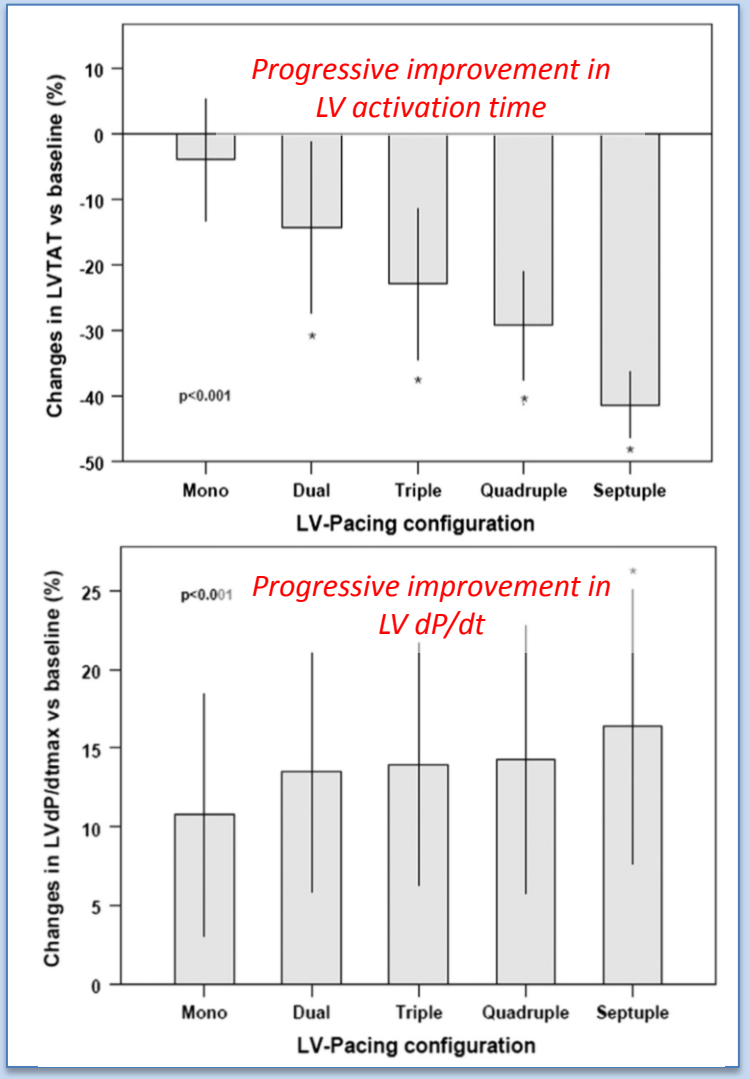
How to Optimize Response to CRT

- *Pre-implant*
  - Select and optimize patients carefully
- *At implant*
  - Consider multisite/multipoint pacing
  - Optimise LV lead location

Multisite LV pacing

Canine Chronic LBBB Model

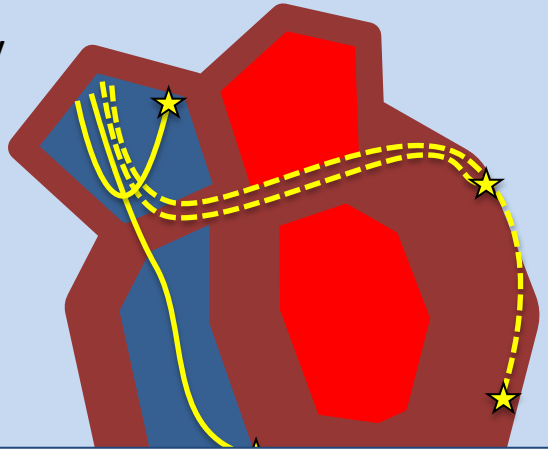




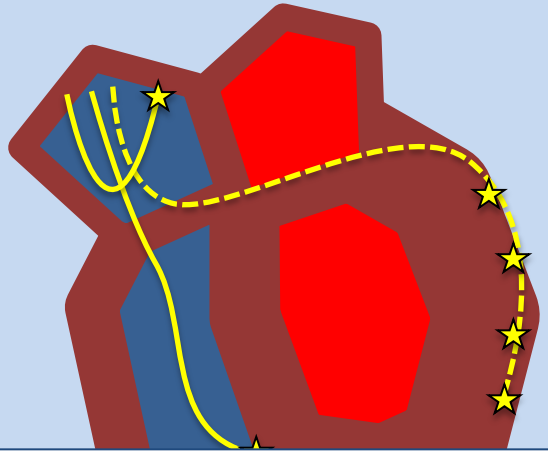
Ploux,S Heart Rhythm 2014;11:119-125

Multi-Site/Multi-Point Pacing

RV + 2LV



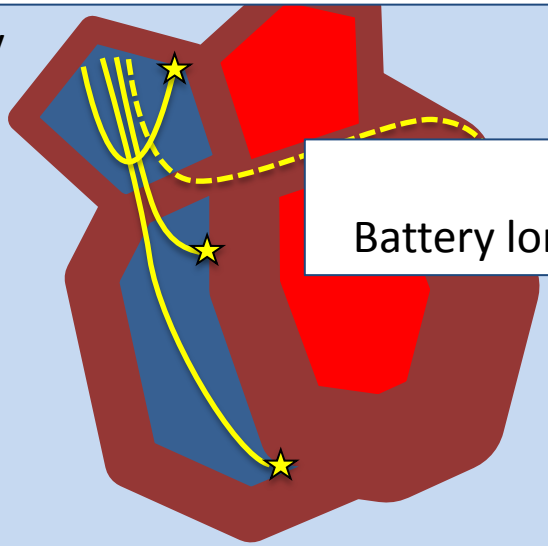
RV +
quad LV



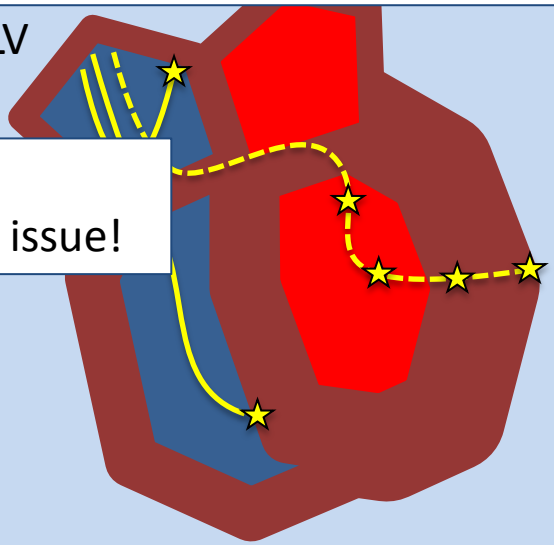
Tri-Ventricular Implants
4 Leads -more complications!
Primary implant or for non-responders?

Multipoint Pacing
Single CS branch
Limited choice of sites

2RV + LV



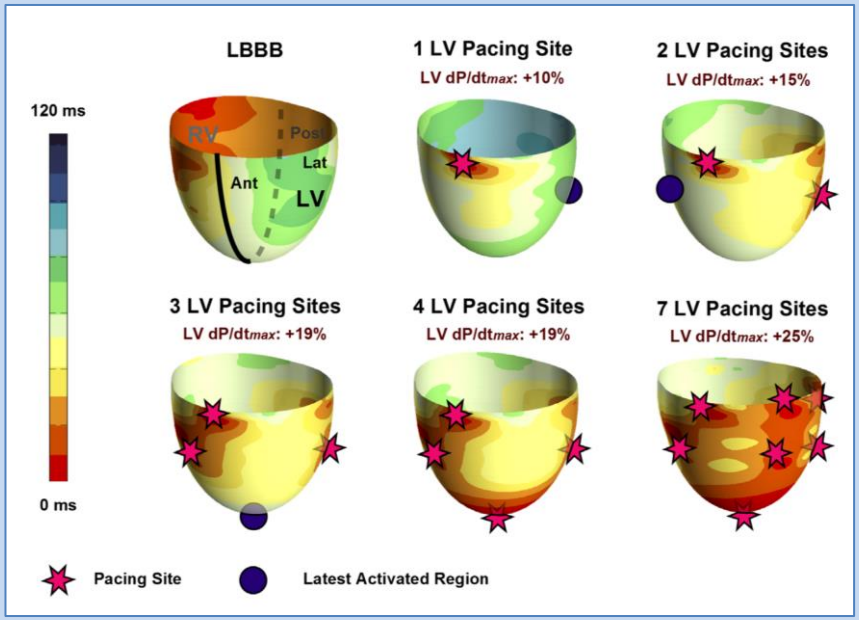
quad LV



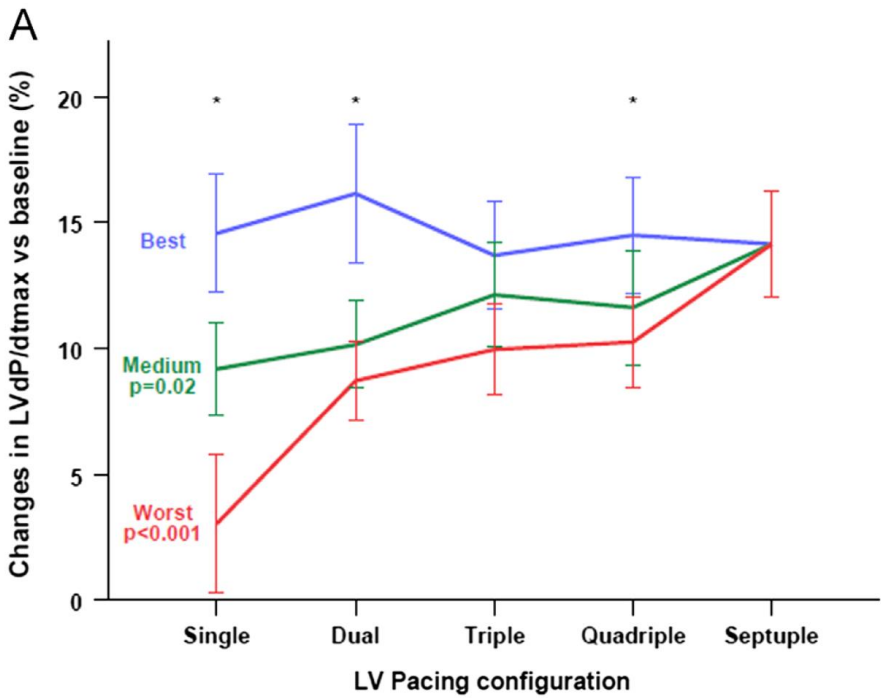
All Options
Battery longevity will be an issue!

Multisite LV pacing

Canine Chronic LBBB Model



But…



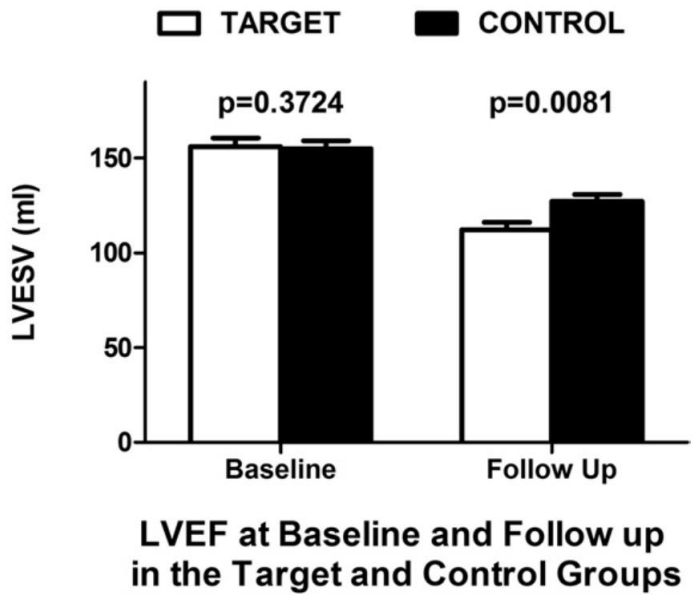
Just as good results with pacing at (single) best LV location.

Ploux,S Heart Rhythm 2014;11:119-125

Guiding LV Lead Placement
TARGET Study

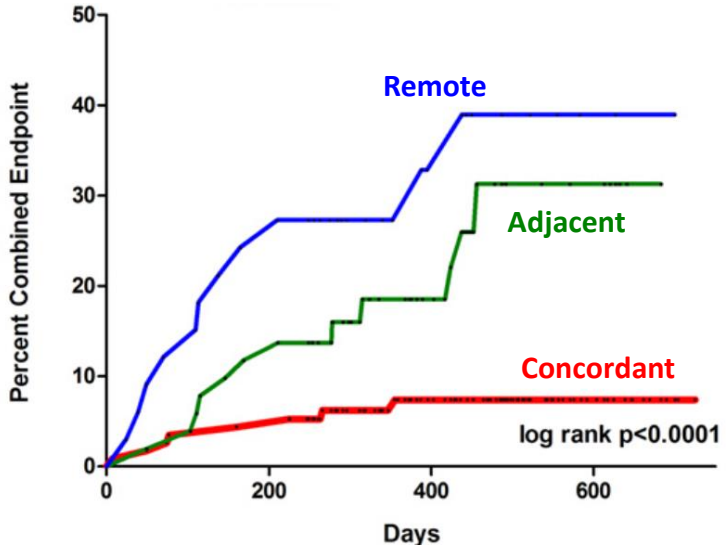
- N = 221, conventional CRT indication
- Speckle-tracking 2D radial strain analysis (basal and mid LV short axis)
- Randomized 1:1
  1. LV lead at site of latest activation (TARGET)
  2. Unguided implant (CONTROL)

1° endpoint: LVESV at 6 month



LVEF at Baseline and Follow up in the Target and Control Groups

Death + HFH according to LV lead site (all patients)



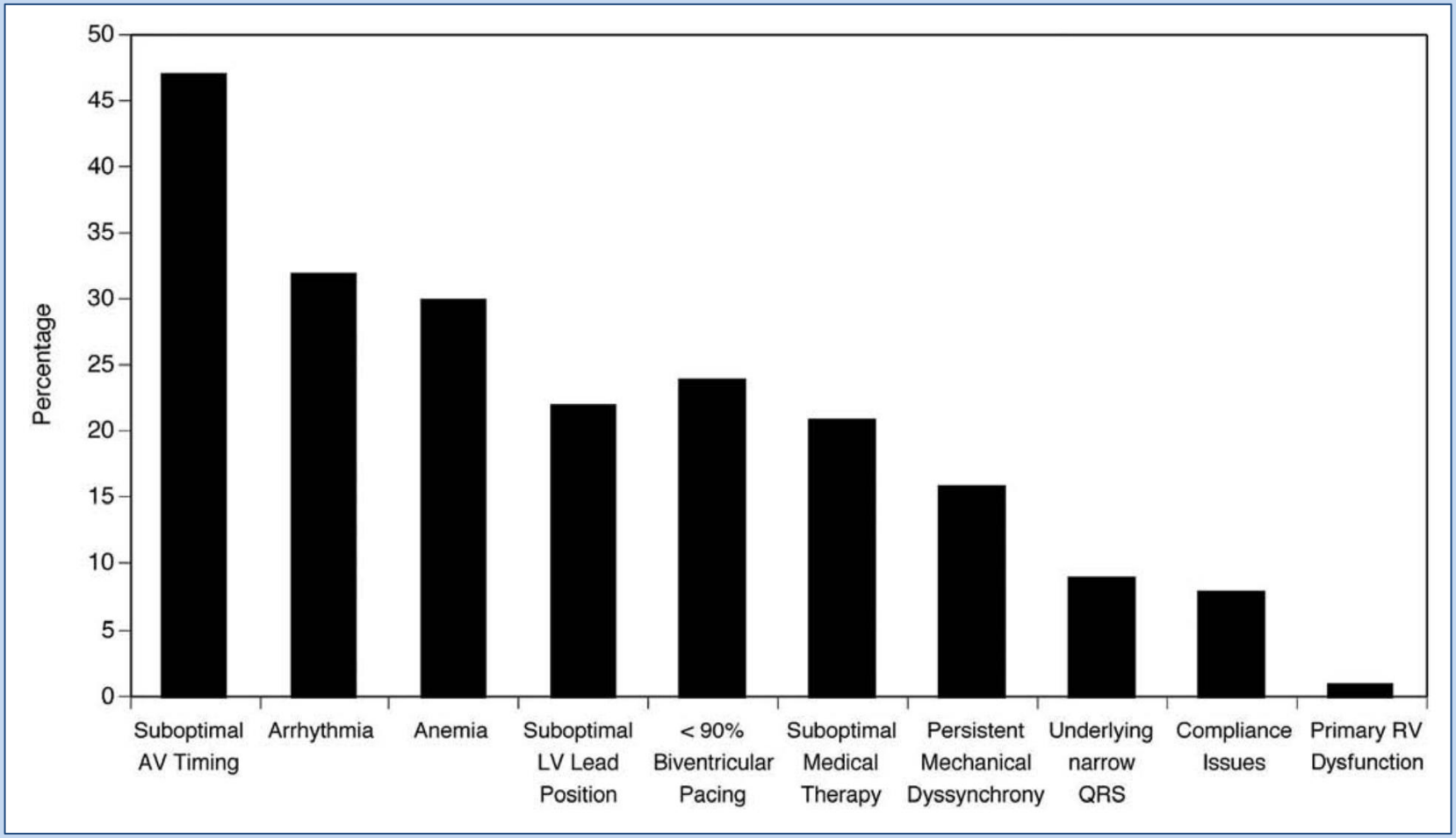
Khan,F et al JACC 2012;59:1509-18

How to Optimize Response to CRT

- *Pre-implant*
  - Select and optimize patients carefully
- *At implant*
  - Optimise LV lead location
  - Consider multisite/multipoint pacing
- *After implant*
  - Optimize medically, maximize % Vpacing
  - Optimize LV/RV *timing*

Supoptimal response to CRT

Identified Reasons (n = 75, 6mo post implant)

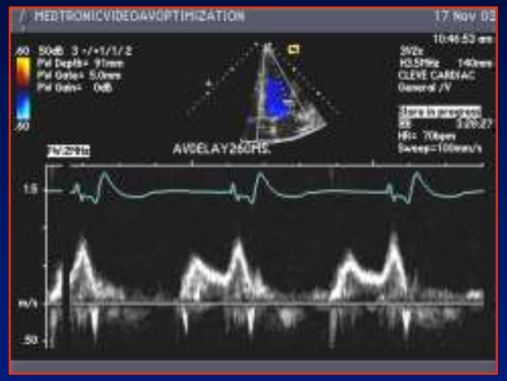


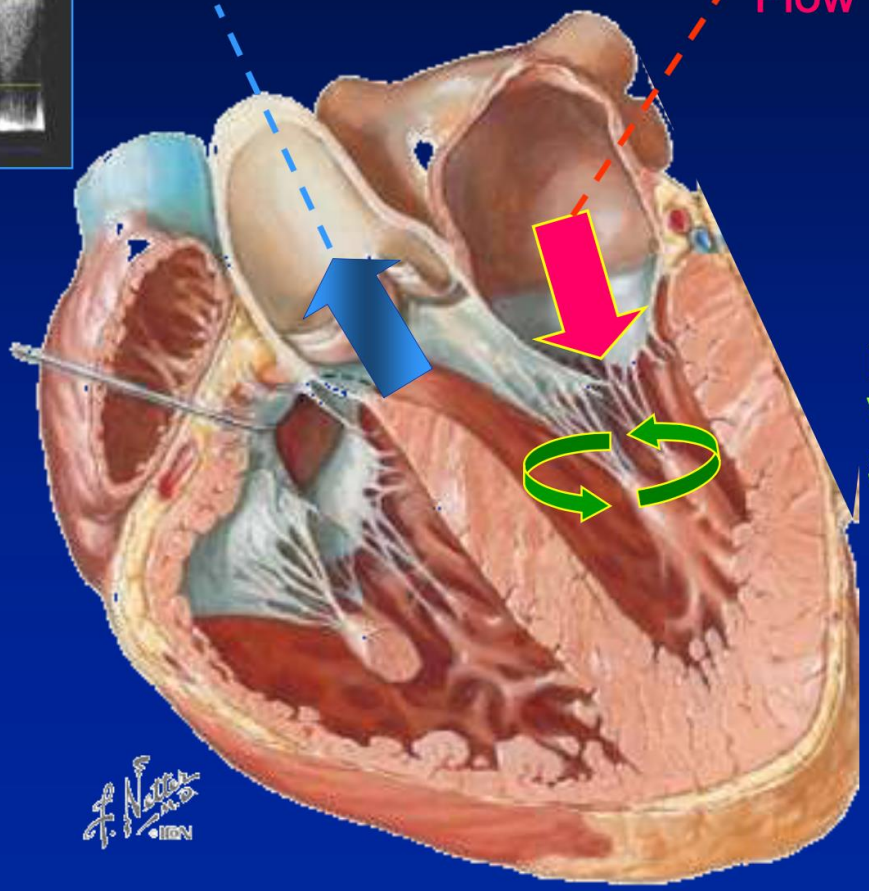
Mullens W et al JACC 2009; 53: 765-73

Echo Targets for CRT Optimization

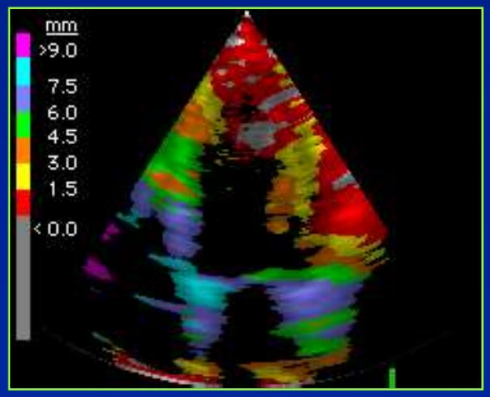
Stroke Volume
(Aortic VTI)

Trans-mitral
Flow





Intra-
Ventricular
Synchrony



Tomassoni G Heart Rhythm 2014

Techniques for Optimization of Timing Intervals

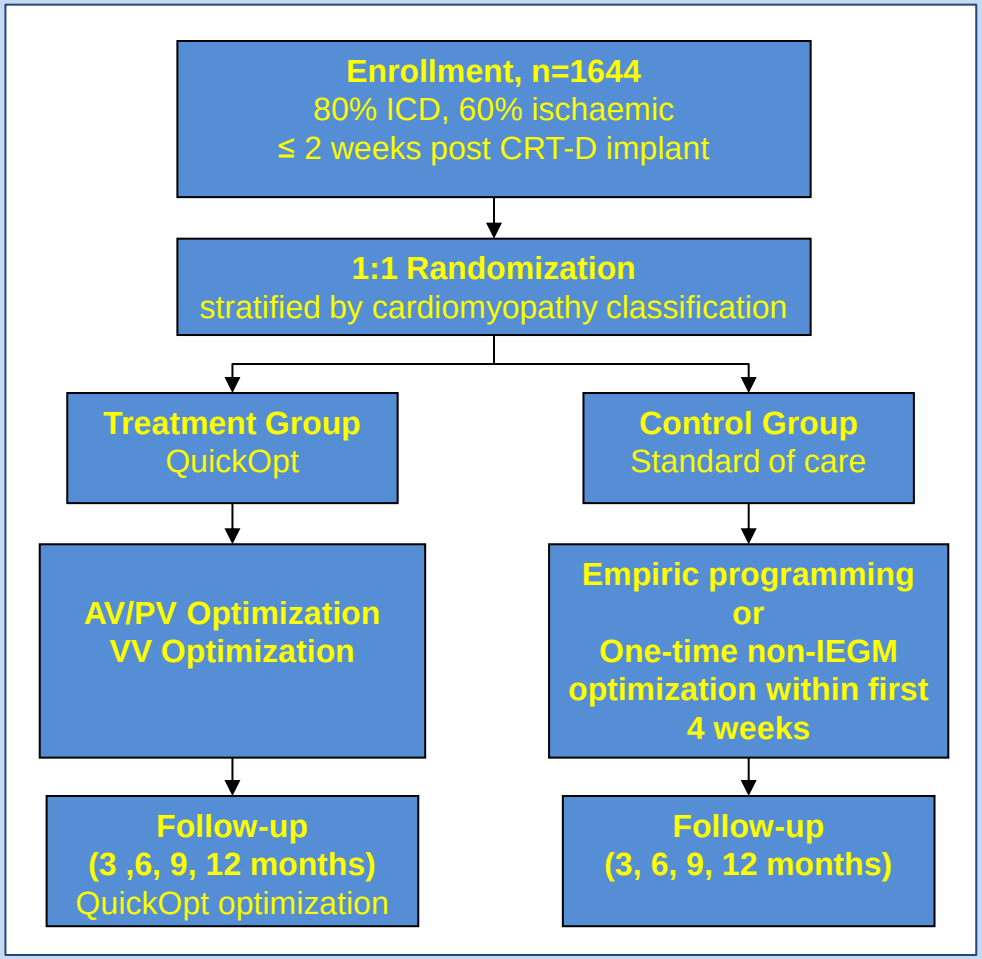
AV Optimization	VV Optimization
Echo methods	
• Mitral inflow (Ritter, iterative, VTI) • Aortic VTI • Other (MPI, 3D echo, ICD)	• Aortic VTI • Tissue Doppler Imaging • 3D echo
Device-Based Algorithms	
• Smart Delay ™ • QuickOpt ™ • SonR™	• QuickOpt ™ • SonR ™ • (Adaptive CRT™)
Other Methods	
• Surface ECG (QRS morphology) • Finger plethysmography • Accoustic	• Surface ECG (QRS morphology) • Finger plethysmography • Radionuclide imaging

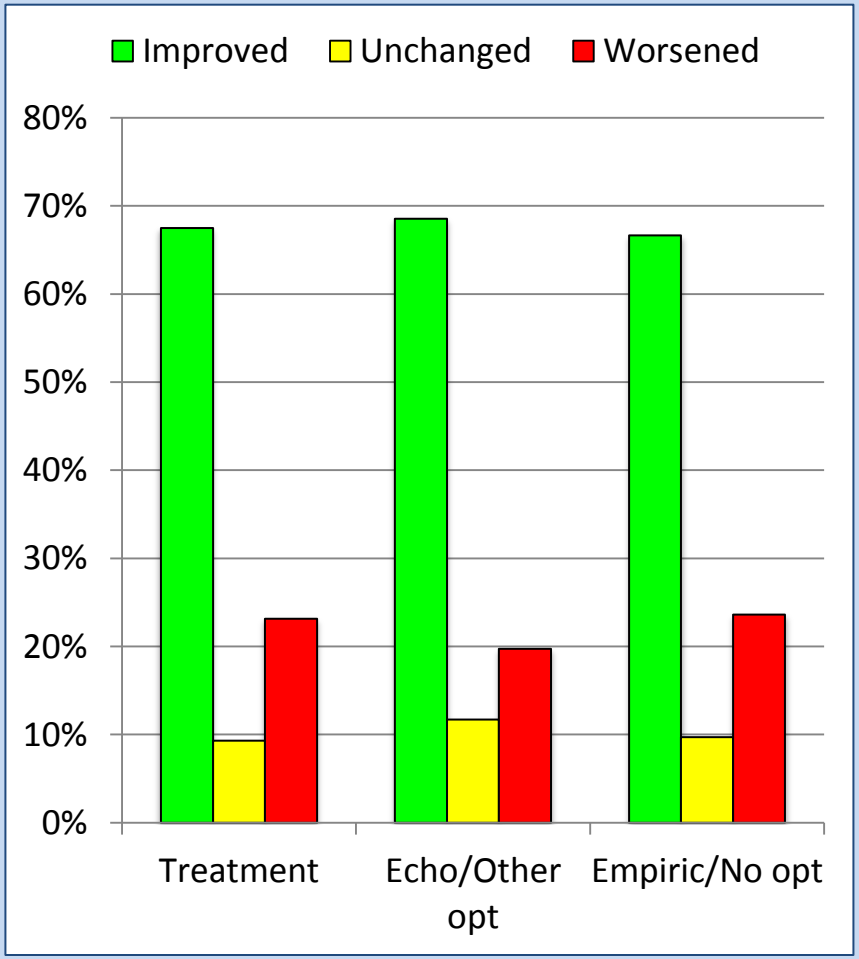
Adapted from Cuoco FA JCE 2012;23:110-8

Quick-Opt™ (SJM): FREEDOM Trial Results

Primary Endpoint (HF Clinical Composite Score)

- AV optimization based on AEGM width + adjustments
- VV optimization based on RV&LV timings in SR and RV/LV pacing

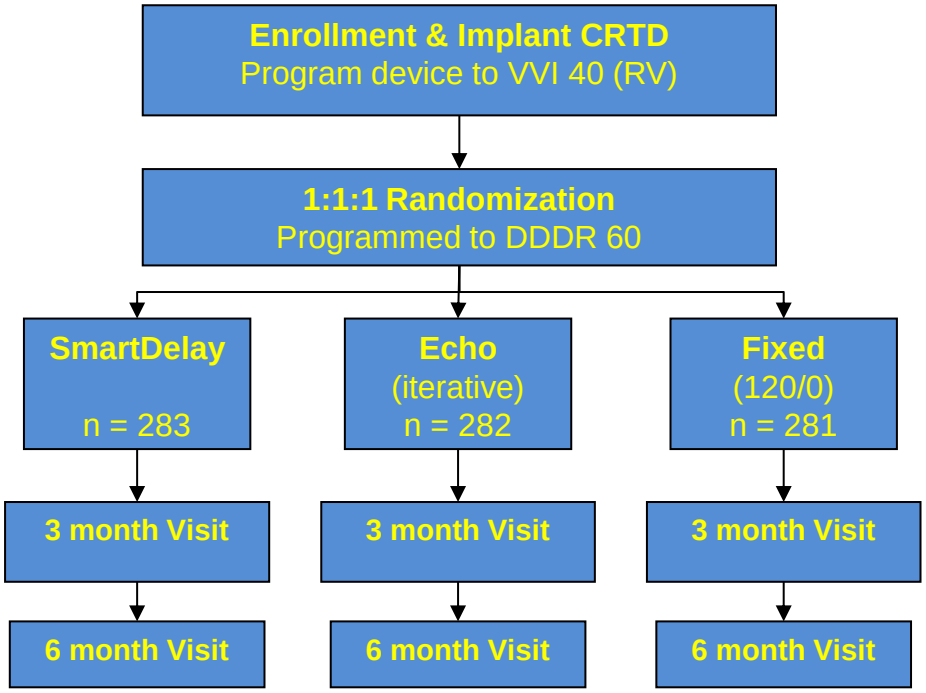




Abraham WT Heart Rhythm 2010

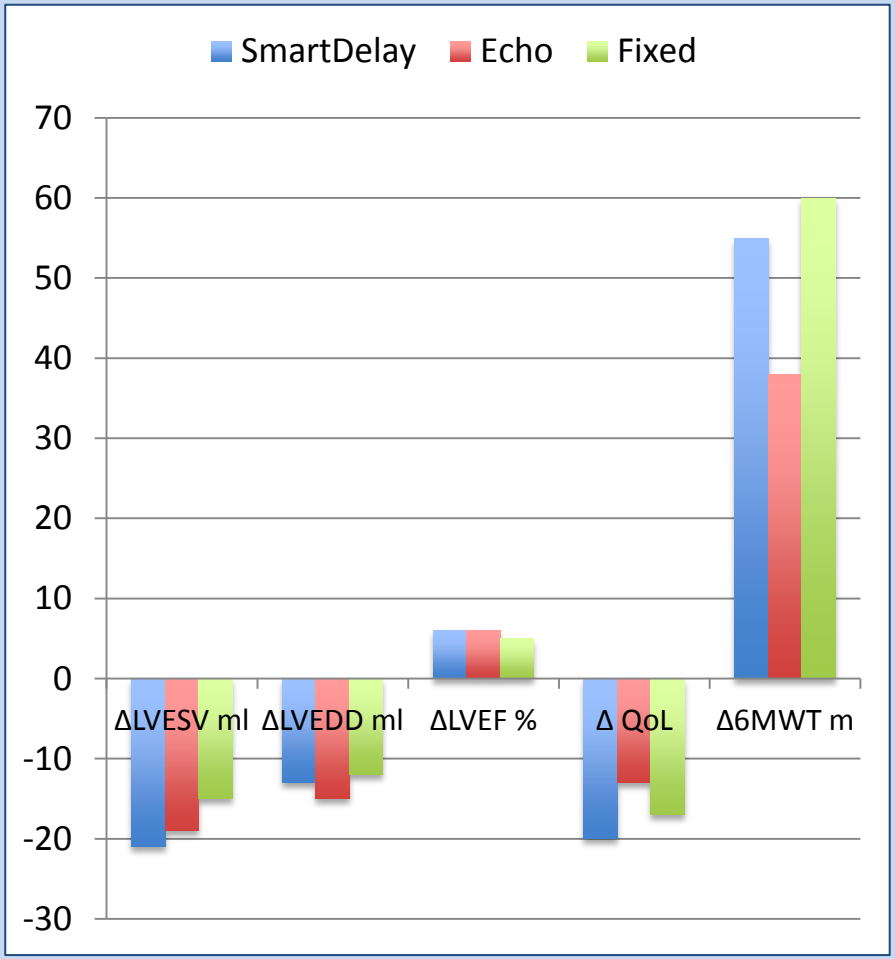
SmartDelay™ (BSC): SMART-AV Trial
Design and Results

- Algorithm derived from ExpertEase (developed during PATH-CHF I & II, & SAVE-R)
- AVD calculated from sensed and paced AVI, and QRSd



1° endpoint: LVESV

2° endpoints: LVEDV, LVEF, NYHA, 6MWT, QoL

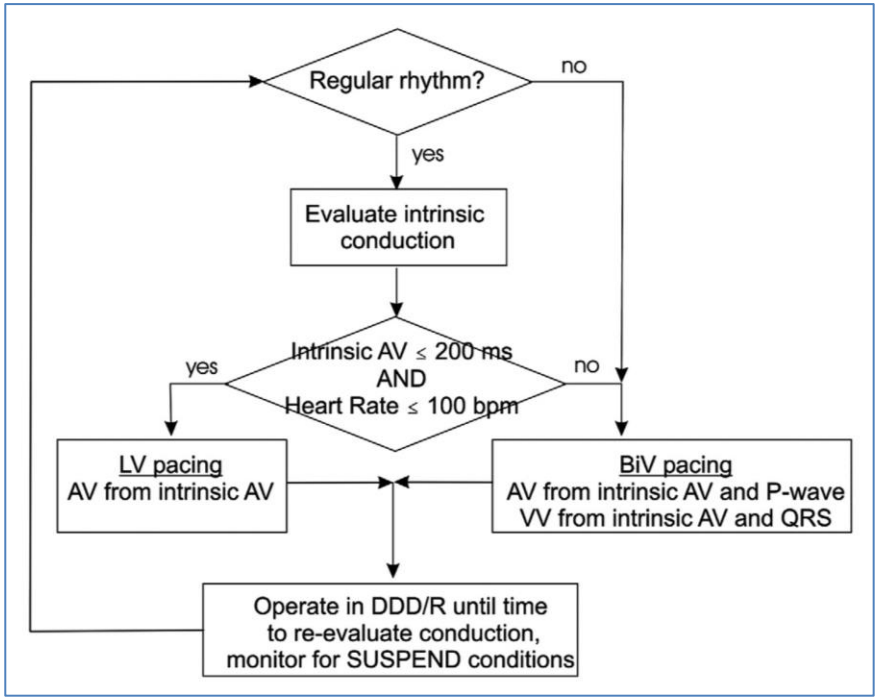


Stein KM et al PACE 2010;33:54-63; Ellenbogen K et al Circulation 2010;122:2660-8

Device-Based Algorithms
Adaptive CRT™ (MDT)

Aims to promote intrinsic conduction

- Dynamic measurements of
  - AVd
  - RA-Pend
  - RV-QRSend (from farfield)
- *If conduction good:*
  - LV only pacing to preempt R
- *If conduction poor:*
  - BiV pacing, AV and VV est. from measurements
- *If arrhythmia, etc*
  - BiV pacing at last determined settings

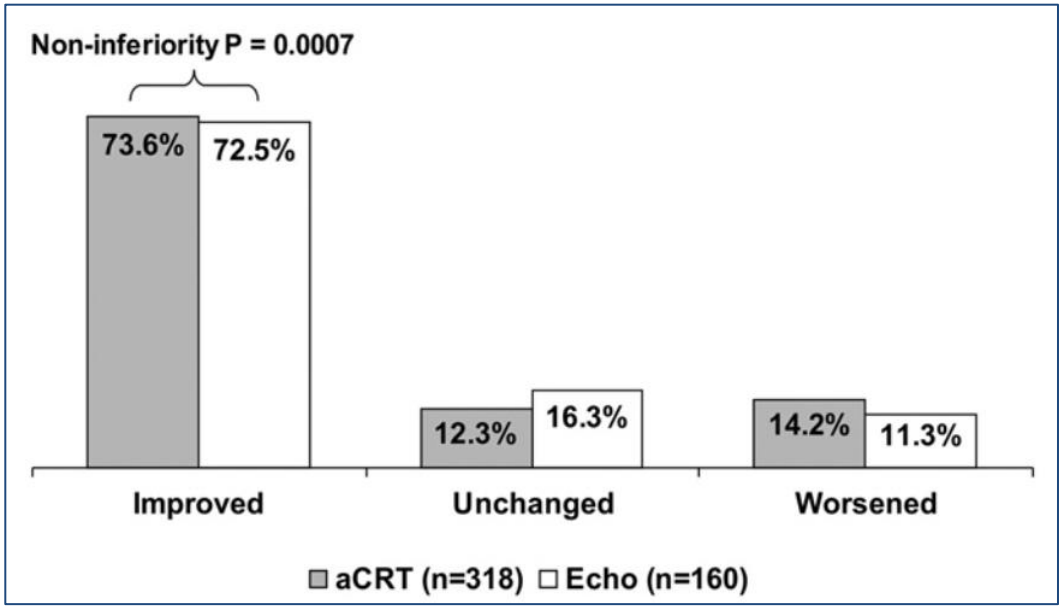


Krum H et al AHJ 2012;163: 747-752

Device-Based Algorithms
Adaptive CRT™ (MDT)

522 patients randomized (2:1) aCRT vs echo-opt. BiV

- *Noninferiority demonstrated:*[1]
  - Similar improvement in clinical composite score
  - Similar haemodynamic performance

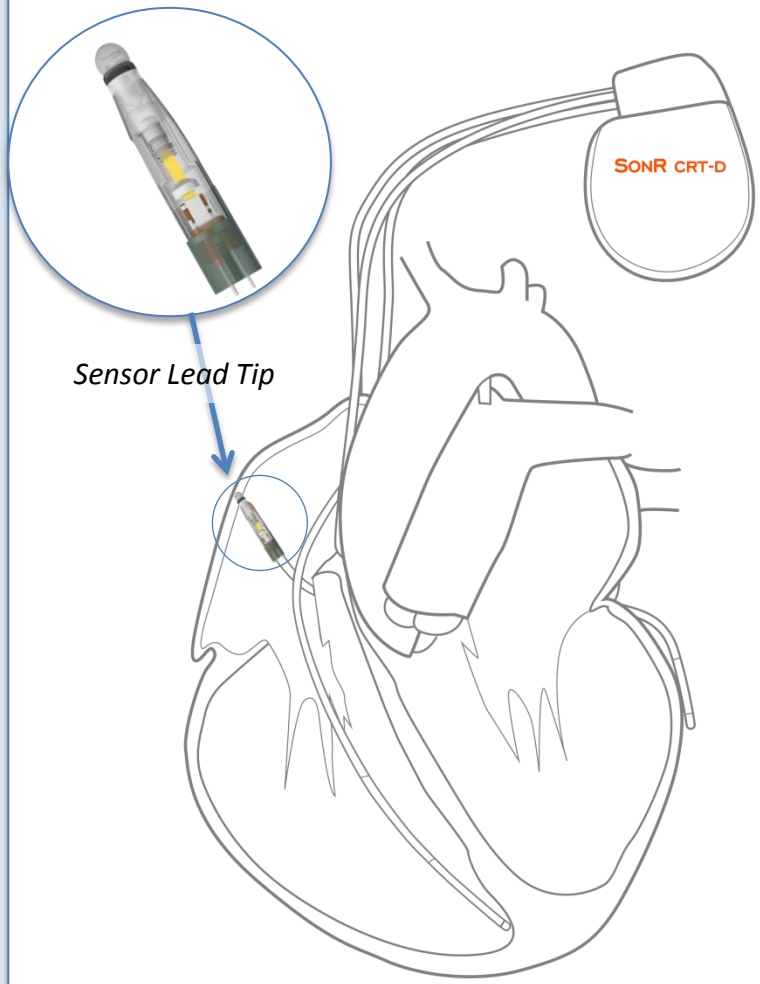


- Retrospective analysis
  - Improved outcomes in aCRT arm, in pts with >50% sLVP (1/3)
  - Improved outcomes with aCRT if AV conduction good, worse if poor

1. Martin D et al Heart Rhythm 2012; 9:1807-14

2: Birnie D et al Heart Rhythm 2013;10:1368-74

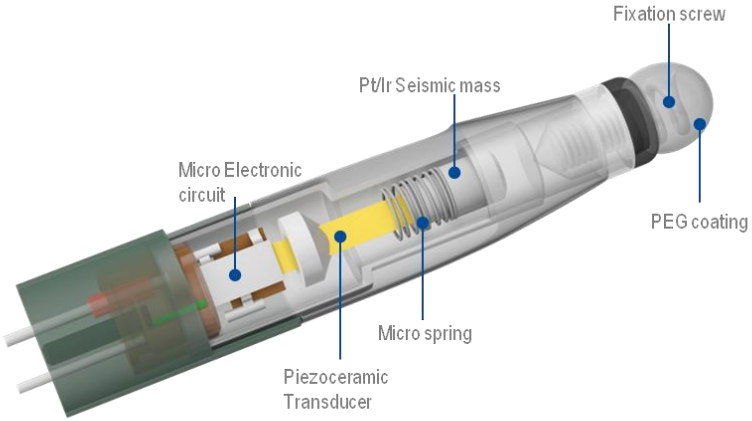
Peak Endocardial Acceleration (PEA)



*Brugada J, Brachmann J, Delnoy PP et al. Am Heart J , 2014 ; Vol 167 (4):429-435§

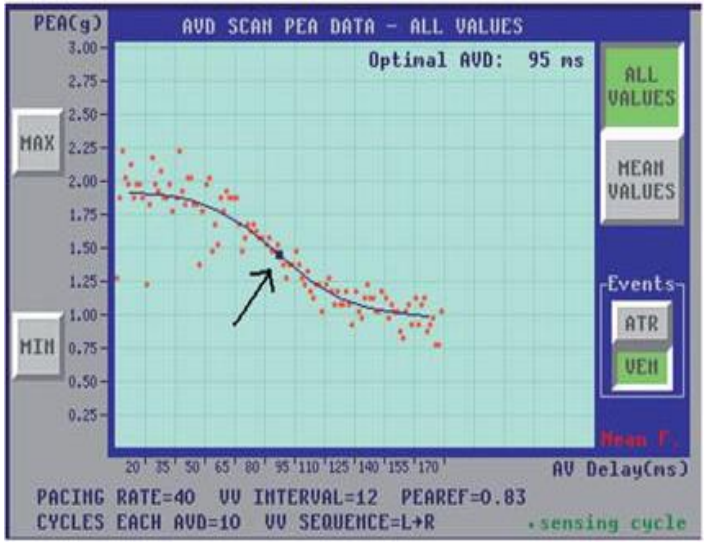
Device-Based Algorithms
SonR™ (Sorin)

- *Micro-accelerometer hermetically embedded at tip converts vibration to electrical signal*
- *Bipolar, 7.8F, silicone insulation/PU overlay*



- *First PEA signal (during isovol. contraction) correlates with contractility (LV dP/dt)*

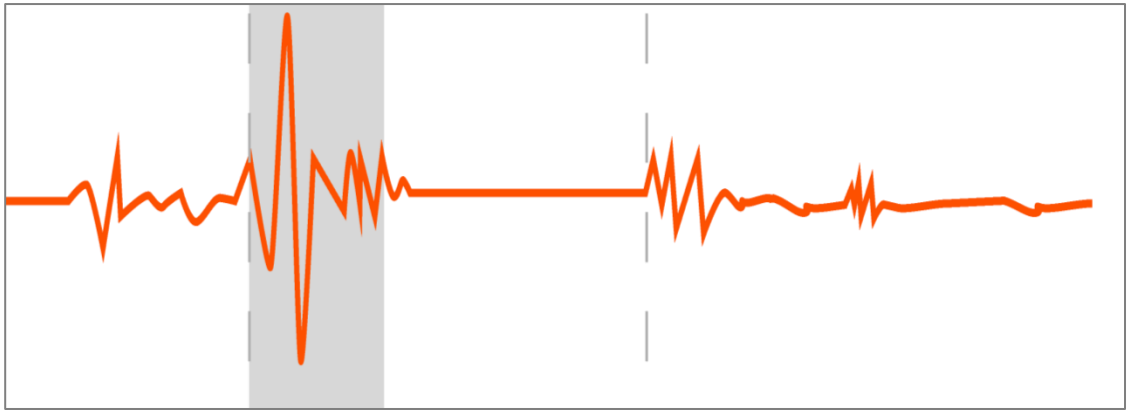
- Step 1: PEA vs VV delays (7) examined
- Step 2: PEA vs AV delays (11) examined
- Step 3: AUC of AV/VV matrix used to select optimal settings



FDM

Weekly AV and VV optimization by SonR is performed at rest and exercise

REAL-TIME
SONR SIGNAL



SonR performs automatic optimization on a weekly basis.

At rest
Evaluation of 64 AVD/VVD combinations

At exercise
Evaluation of 5 AVD/VVD combinations

VVD
Paced AVD
Sensed AVD

Optimized timings

Paced AVD
Sensed AVD

SonR™ V lead in CRT-P Device

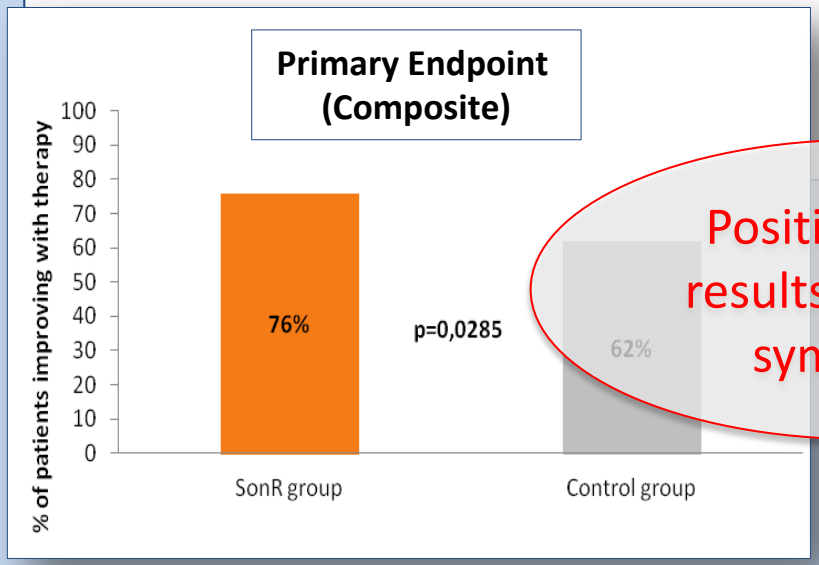
CLEAR Study

N = 238 randomized (CRT not indicated for ICD)

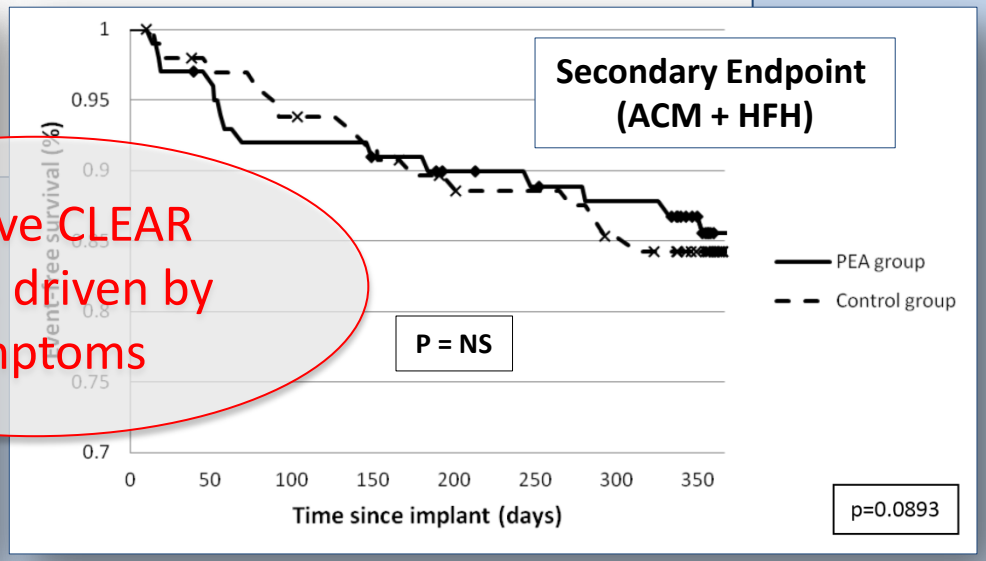
Primary endpoint

Proportion of patients who improved in each group at 1 year, based on a composite of:

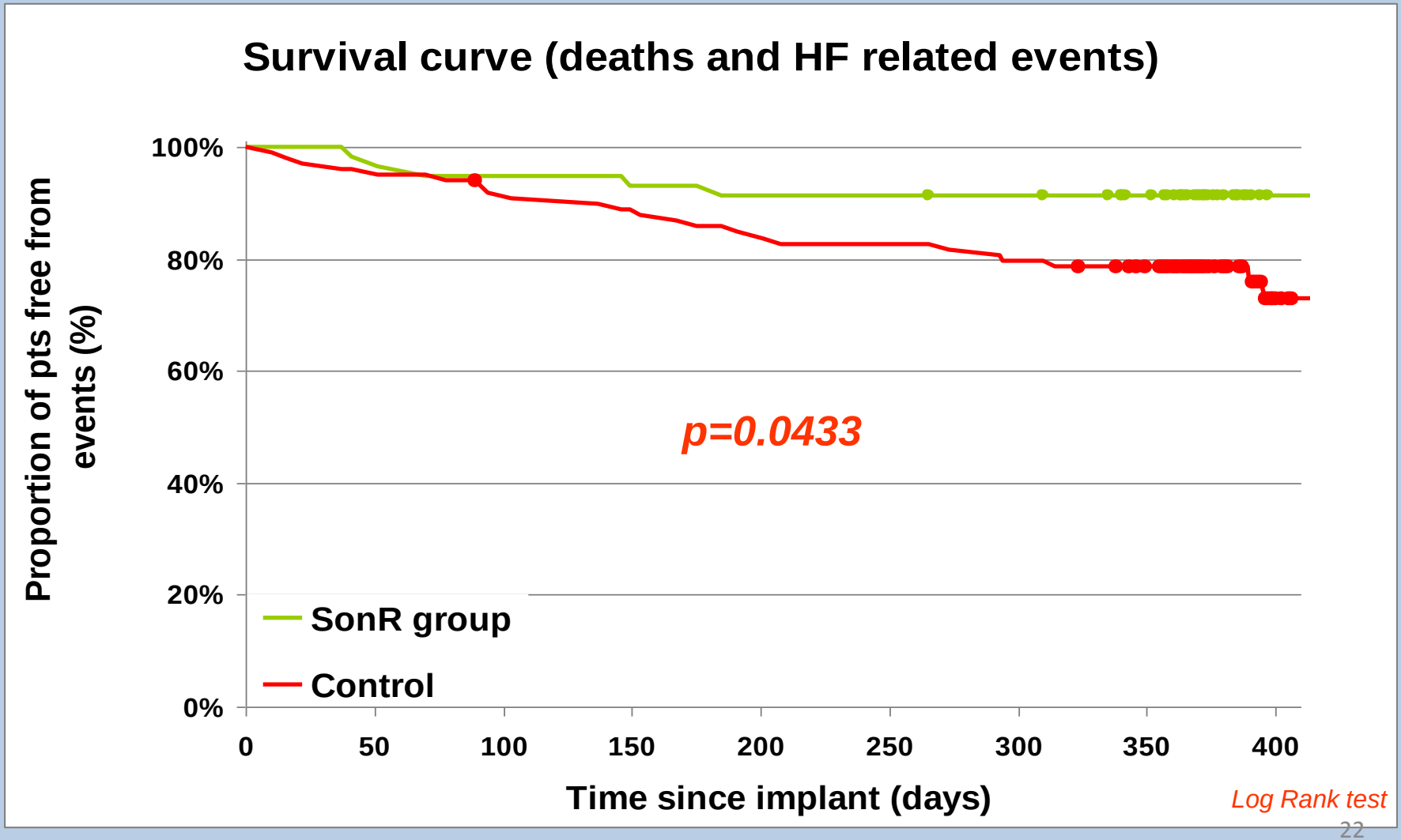
- All-cause mortality
- Heart failure hospitalization
- Functional class (NYHA)
- QOL (EQ5D)



Positive CLEAR results driven by symptoms



CLEAR Study results
Per protocol analysis



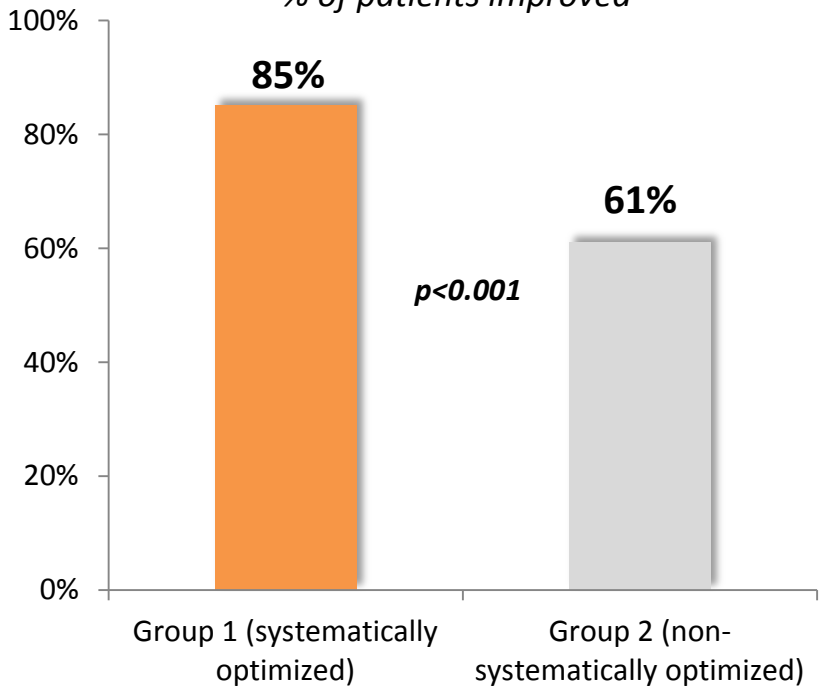
FDM

CLEAR Post-Hoc Results

Repeated Optimization is the Key

Primary (composite*) endpoint

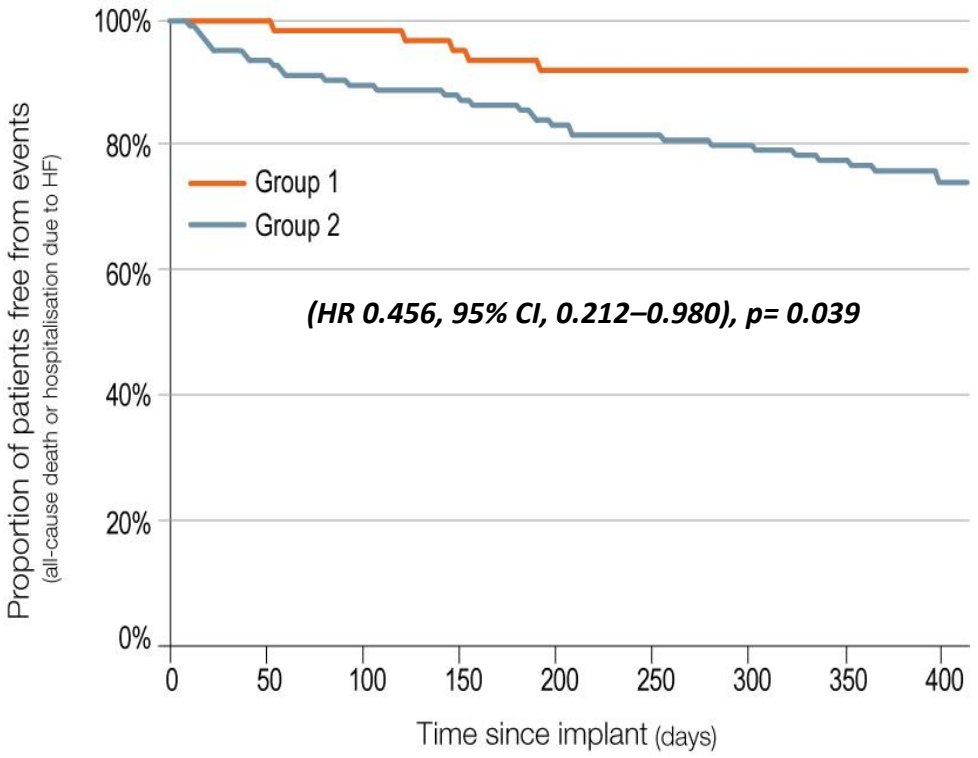
% of patients improved



*ACM, HFH, NYHA class and QoL

Secondary endpoint

All-cause mortality + HF hospitalization



RESPOND-CRT Study

Objectives

To demonstrate that

1. SonRtip atrial lead is safe

2. Auto-optimization with SonR is noninferior to echo AV+ VV to improve CRT response

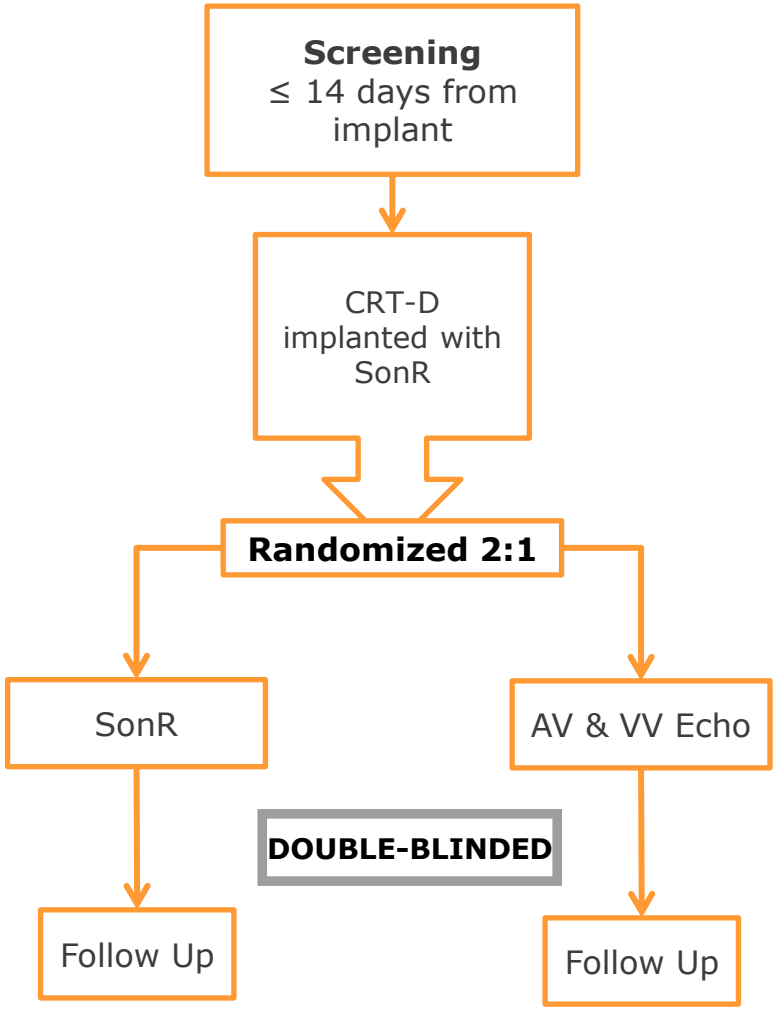
RESPOND-CRT

Study design

- International, Multicenter, trial (125 sites in Europe, USA, Australia)
- Randomized (2:1), Prospective, Double-blinded
- Enrolment Jan 2012 – Oct 2014
- 2 year followup, results published 2016

PATIENTS

- LVEF ≤ 35%
- NYHA III or IV
- LBBB: QRS ≥ 120 ms
- Non-LBBB: QRS ≥ 150 ms
- Not permanent AF



*Brugada J, Brachmann J, Delnoy PP et al. Am Heart J , 2014 ; Vol 167 (4):429-435§

RESPOND-CRT

Endpoints

RESPOND-CRT STUDY

PRIMARY SAFETY END POINT

Freedom from acute (0-3 months) and chronic (4-12 months) SonRtip complications

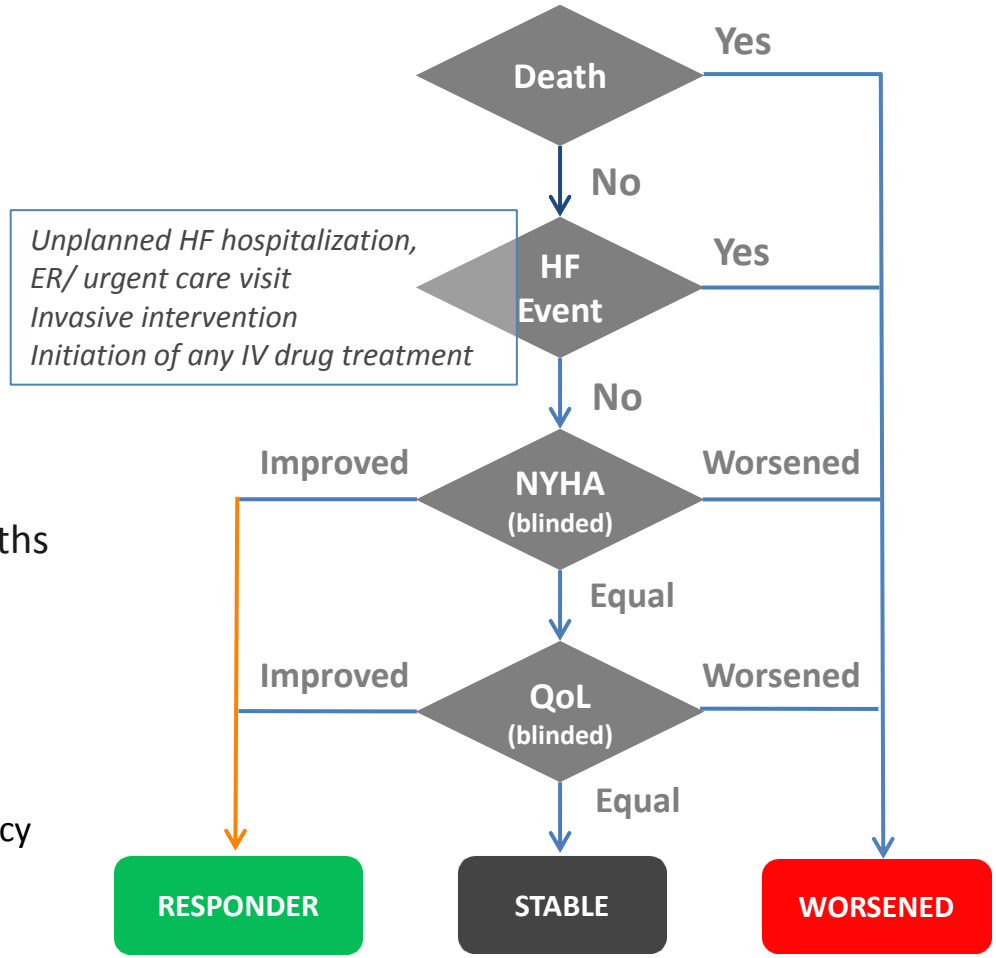
PRIMARY EFFICACY END POINT

Non-inferiority on the proportion of responders, based on a set of criteria (10% non-inferiority margin), at 12 months

SECONDARY END POINTS

- → All-cause death or HF hospitalization
- → Worsened patients
- → Subgroups analysis on the primary efficacy end point

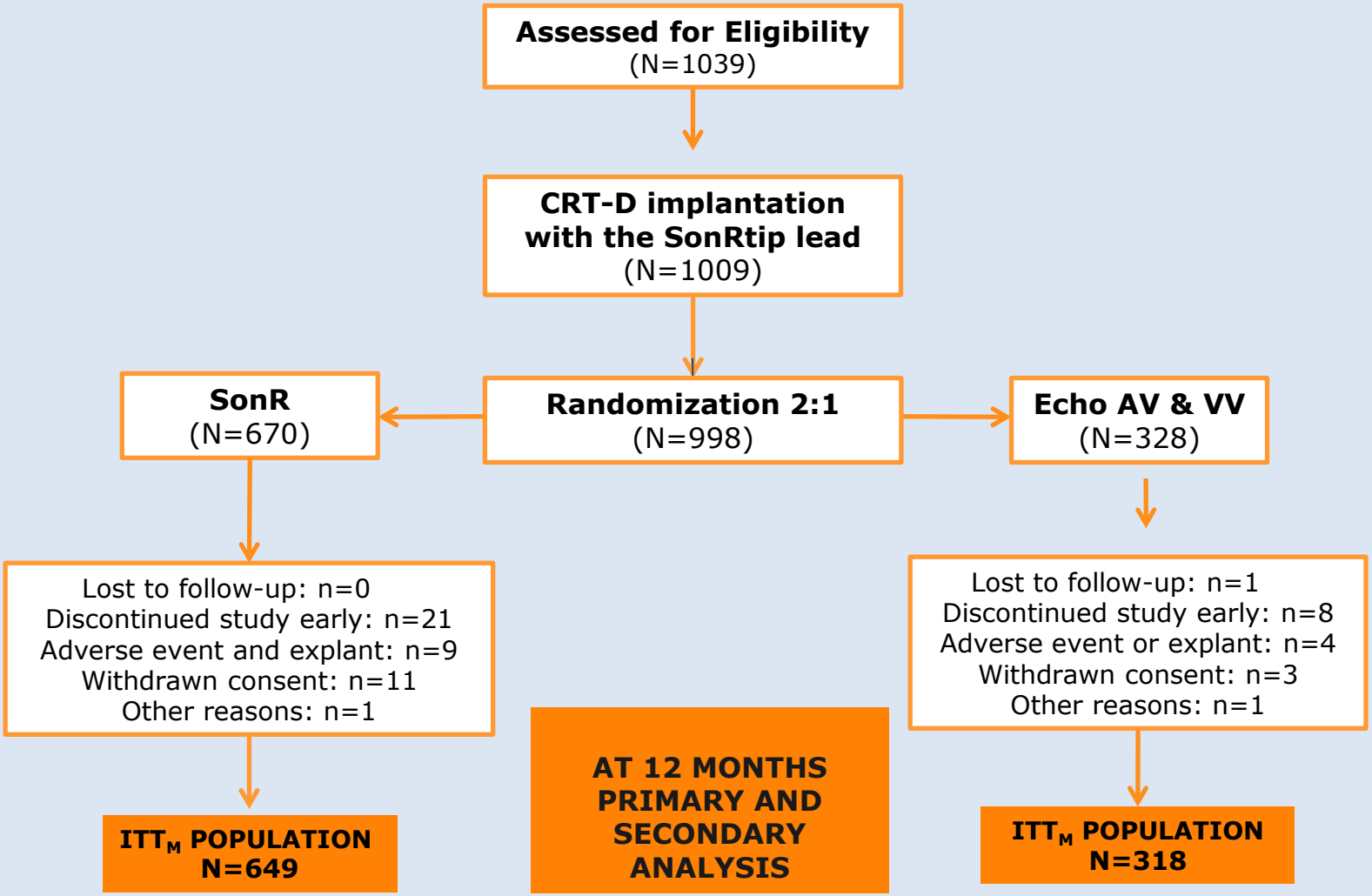
Response to CRT is based on a hierarchical set of clinical criteria



*Brugada J, Brachmann J, Delnoy PP et al. Am Heart J , 2014 ; Vol 167 (4):429-435§

Patient flow chart

RESPOND-CRT STUDY



Brugada J et al. Late-Breaking Clinical Trials I, Clinical Response to Cardiac Resynchronization Therapy with theSonR Hemodynamic Sensor: The RESPOND-CRT Randomized Trial, Presented at Heart Rhythm 2016 - 05/05/16.

Baseline demographics

RESPOND-CRT STUDY

PATIENT CHARACTERISTICS	SonR (n=670)	Echo AV & VV (n=328)	P value
Age (years)	**67.2 ±10.2**	**66.6 ±10.2**	0.34
Male	**70.4%**	**65.5%**	0.12
NYHA class III	**96.6%**	**95.4%**	0.027
LVEF %	**29.4 ±8.4%**	**29.6±8.0%**	0.78
QRS (ms)	**160.7 ±23.1 ms**	**160.0 ±21.9 ms**	0.65
LBBB	**84.0%**	**88.4%**	0.06
Ischemic	**45.5%**	**42.5%**	0.37
Beta-blockers	**89.4%**	**92.1%**	0.18
ACEI, substitutes or ARBs	**89.9%**	**88.7%**	0.58
History of atrial fibrillation	**15.6%**	**17.3%**	0.49
Diabetes	**37.3%**	**41.8%**	0.17
Renal dysfunction	**22.8%**	**24.7%**	0.51

Brugada J et al. Late-Breaking Clinical Trials I, Clinical Response to Cardiac Resynchronization Therapy with theSonR Hemodynamic Sensor: The RESPOND-CRT Randomized Trial, Presented at Heart Rhythm 2016 - 05/05/16.

Primary Safety End-Points

RESPOND-CRT STUDY

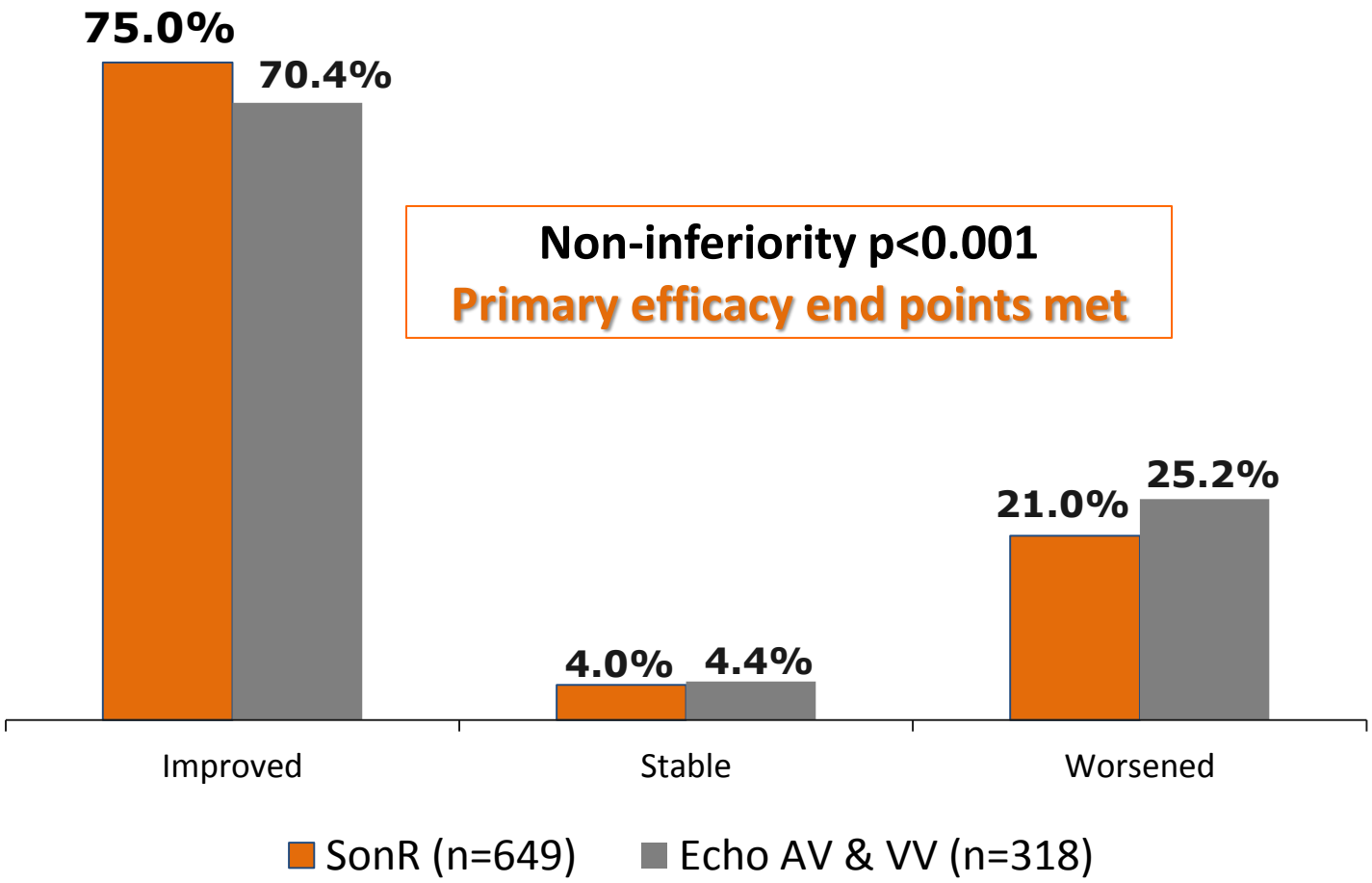
SonRtip **Implant** success rate	SonRtip Complication free rate **from 0 to 3 months**	SonRtip Complication free rate **from 4 to 12 months**
99,8%	**98,5%**	**99,8%**
	vs 91% (objective) p<0.001	vs 94% (objective) p<0.001

1st 3 month dislodgement rate = 1%

Primary Safety Endpoint Met

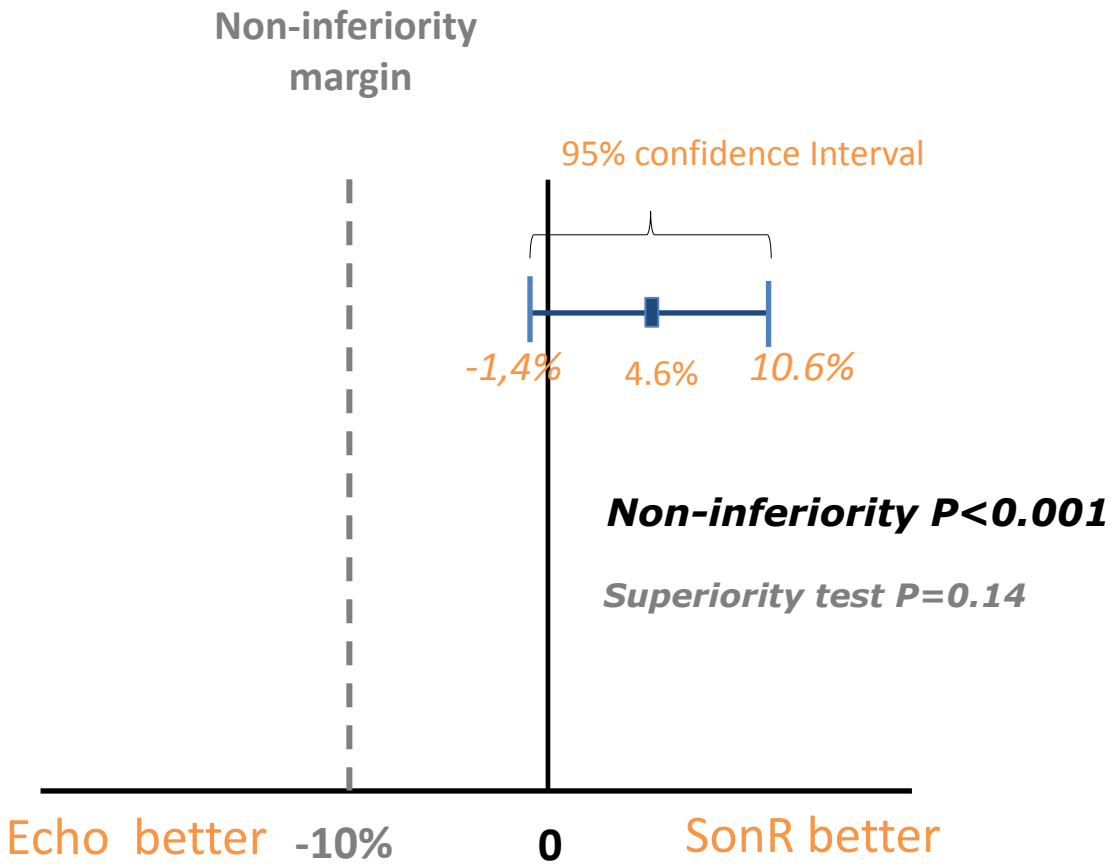
Brugada J et al. Late-Breaking Clinical Trials I, Clinical Response to Cardiac Resynchronization Therapy with theSonR Hemodynamic Sensor: The RESPOND-CRT Randomized Trial, Presented at Heart Rhythm 2016 - 05/05/16.

Primary Efficacy End-Points (12 months)



Brugada J et al. Late-Breaking Clinical Trials I, Clinical Response to Cardiac Resynchronization Therapy with theSonR Hemodynamic Sensor: The RESPOND-CRT Randomized Trial, Presented at Heart Rhythm 2016 - 05/05/16.

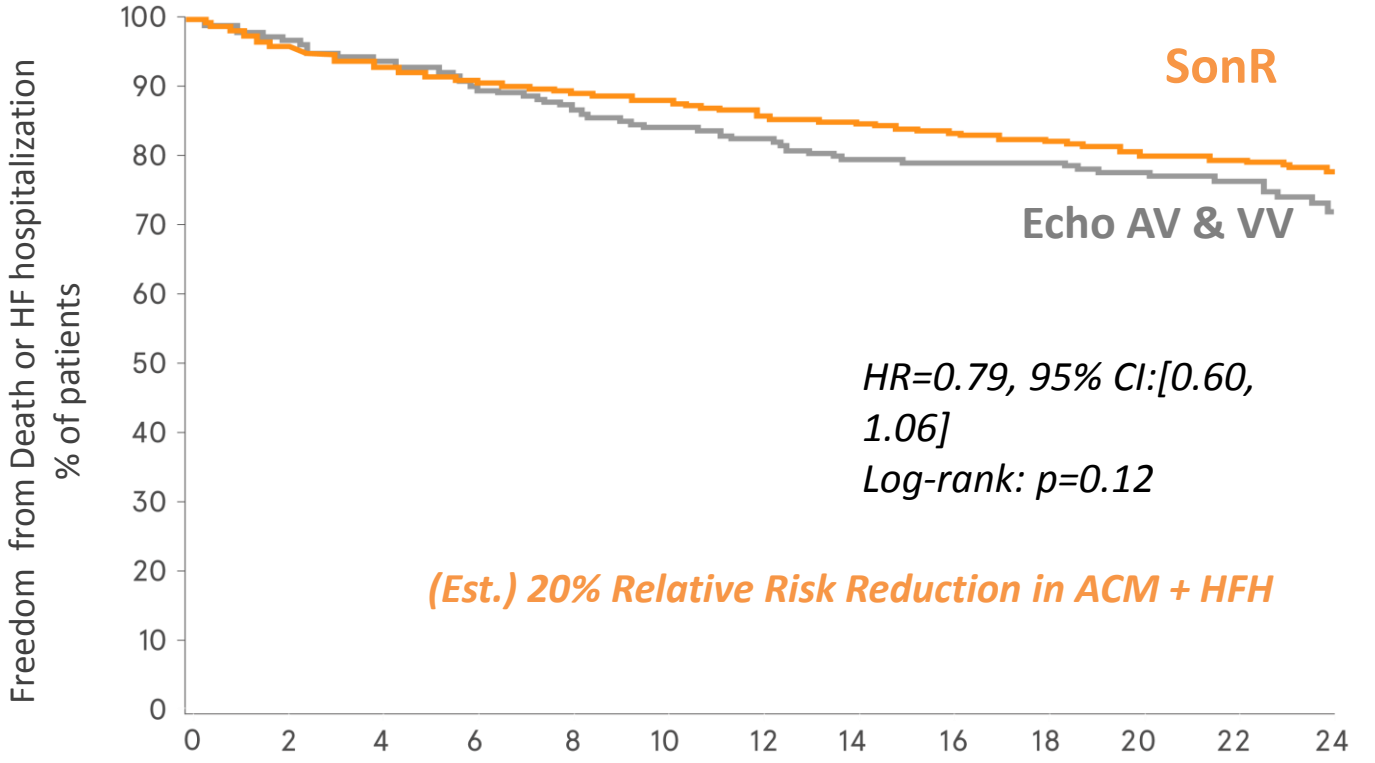
Difference in responder rate (12 months)



Non-inferiority one-sided test (margin of 10%), P-values <0.025 were considered statistically significant

RESPOND-CRT 2ary Endpoints

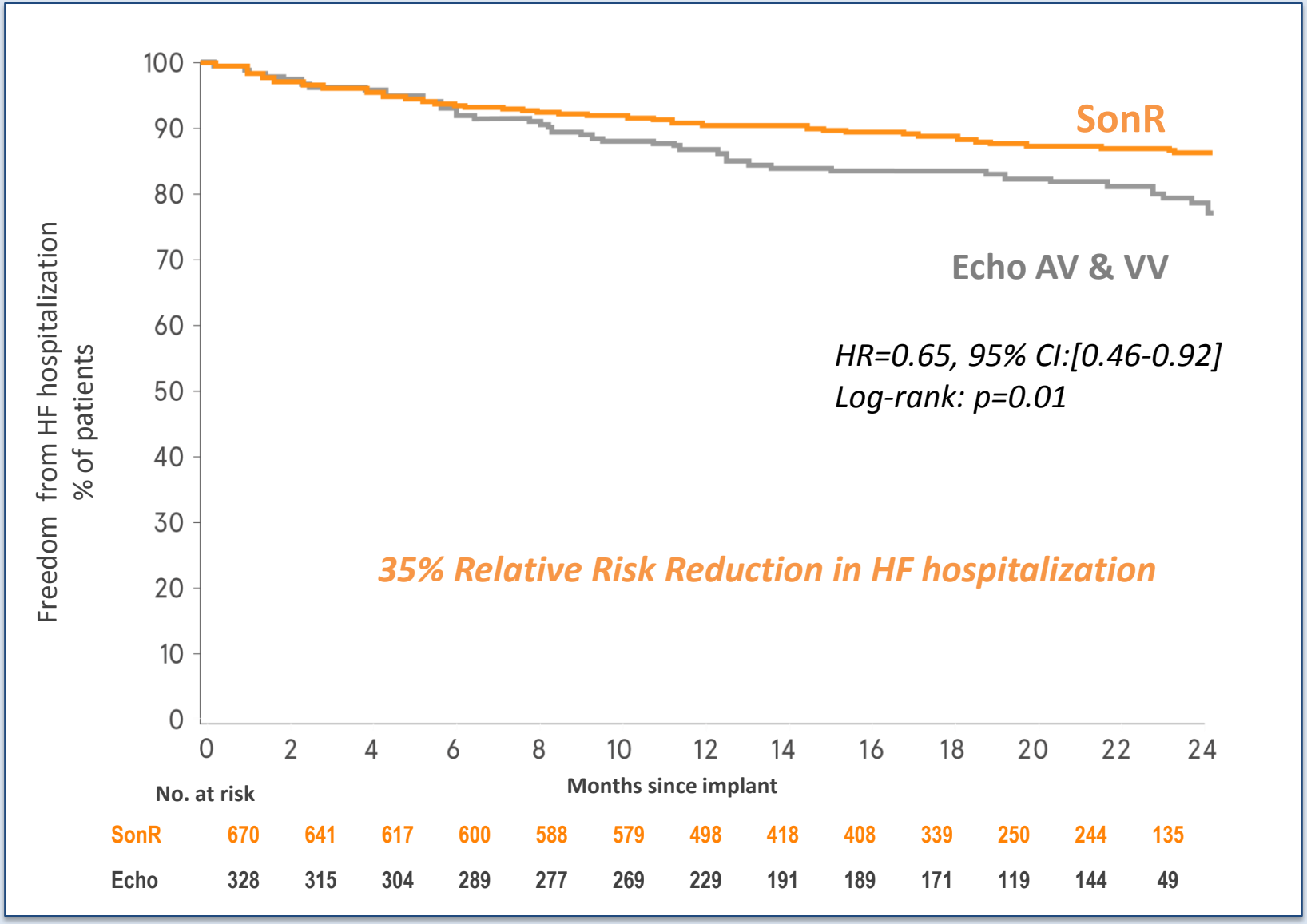
Freedom from All-Cause Death or HF Hospitalization



No. at risk													
SonR	670	641	617	600	588	579	498	418	408	339	250	244	135
Echo	328	315	304	289	277	269	229	191	189	171	119	144	49

Brugada J et al. Late-Breaking Clinical Trials I, Clinical Response to Cardiac Resynchronization Therapy with the SonR Hemodynamic Sensor: The RESPOND-CRT Randomized Trial, Presented at Heart Rhythm 2016 - 05/05/16.

Freedom from HF Hospitalization

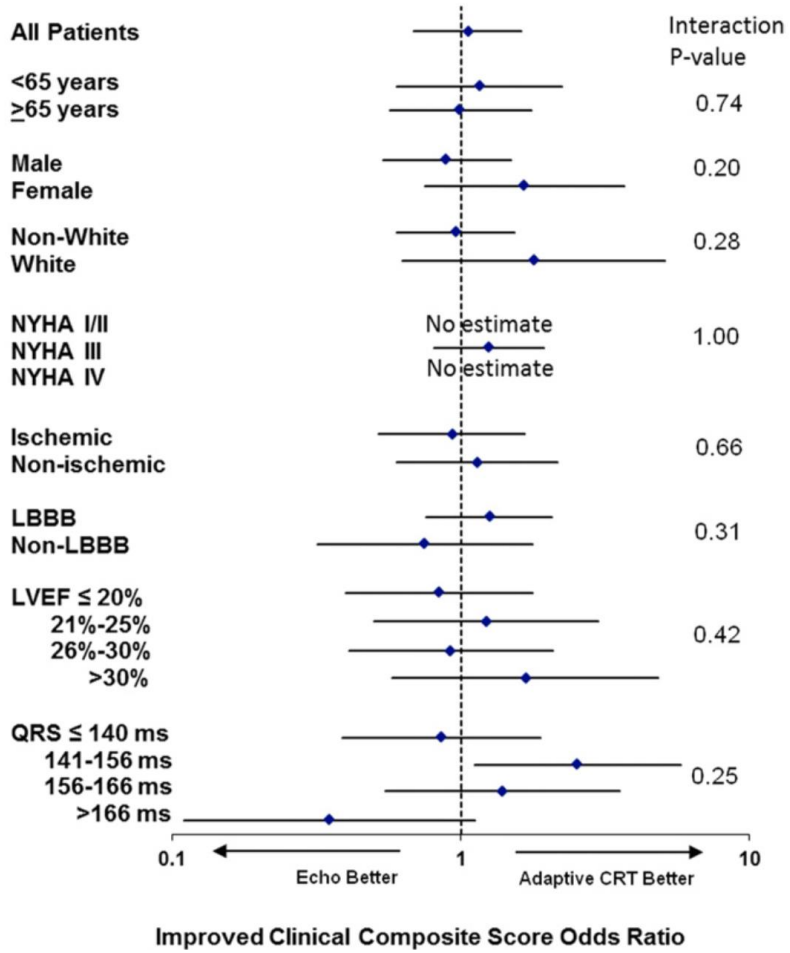


Brugada J et al. Late-Breaking Clinical Trials I, Clinical Response to Cardiac Resynchronization Therapy with the SonR Hemodynamic Sensor: The RESPOND-CRT Randomized Trial, Presented at Heart Rhythm 2016 - 05/05/16.

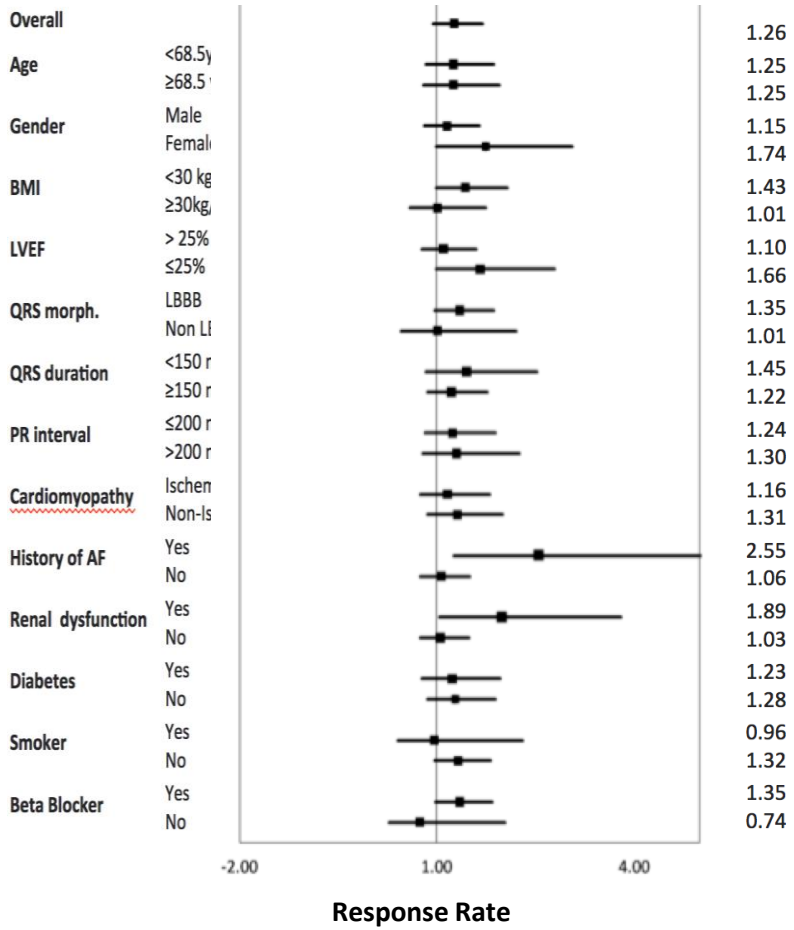
Auto Optimisation vs Echo

Subgroup Analysis

Adaptive CRT Study



RESPOND CRT Study



RESPOND-CRT

Conclusions – 12 & 18months

Primary Safety Endpoint

→ SonRtip atrial lead has good safety/dislodgement profile

Primary Efficacy Endpoint

→ SonR *at least* as effective as AV&VV echo-guided optimization to maximize CRT response

Prespecified Secondary Endpoints

→ SonR ass. With 35% reduction in HF hospitalization

Subgroup Analysis

→ SonR higher response rate in most subgroups, esp.

- → 48% reduction in CV death/HFH in pts with AF history
- → 41% reduction in CV death/HFH in pts with renal dysfunction