University Hospitals of North Midlands NHS
NHS Trust

Utilising CRT Algorithms-Can they improve CRT Response?

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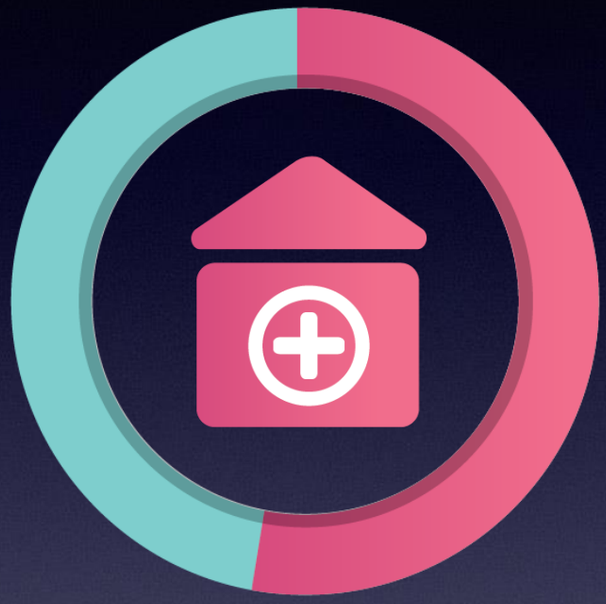
Heart Rhythm Congress
www.heartrhythmcongress.org

Cardiac Resynchronisation Therapy (CRT)

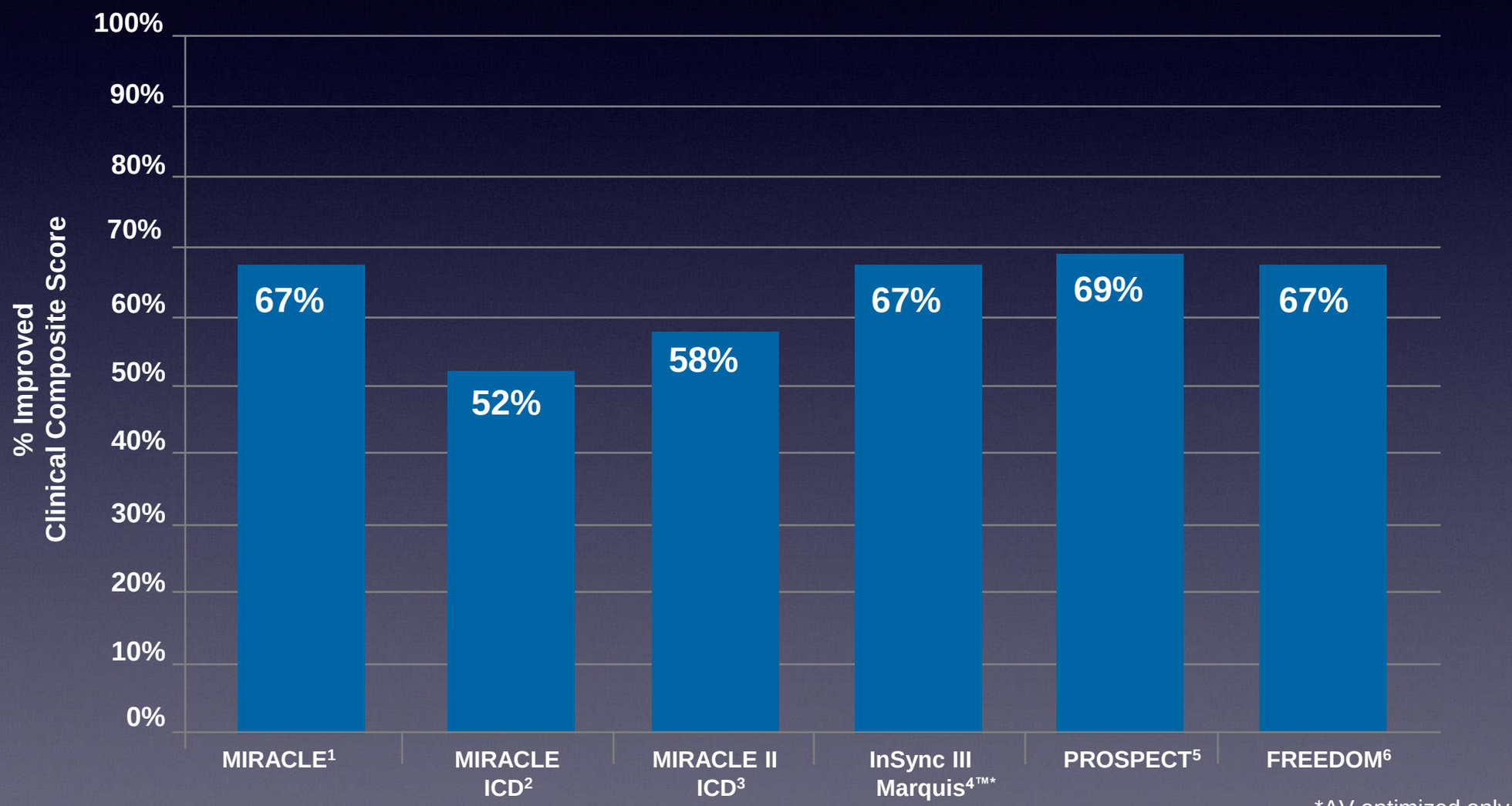
Reduces heart failure (HF) mortality by 40% on top of optimal medical therapy



Decreases HF-related hospitalisations by 52%

CRT Response Rate

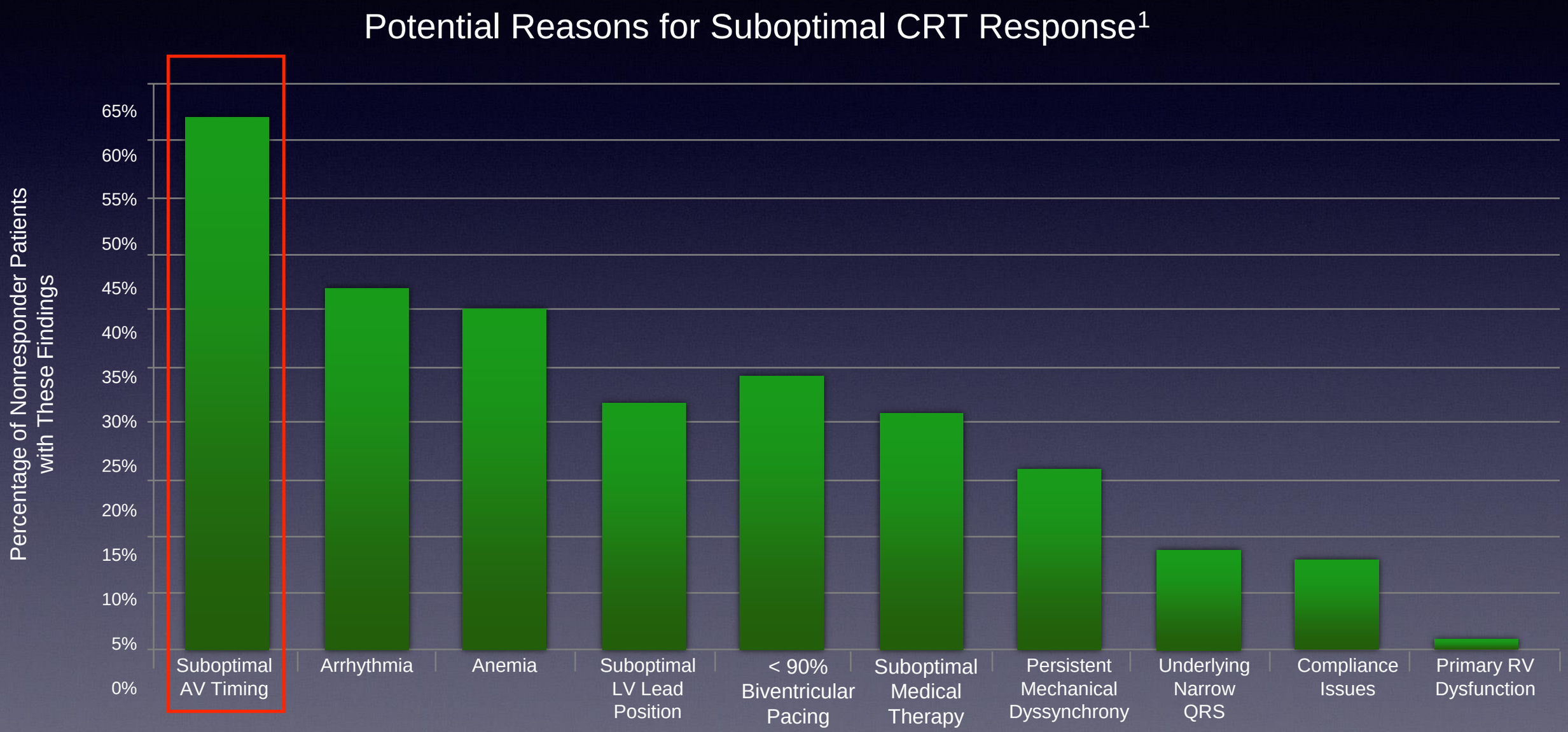
One-third of patients do not experience the full benefit of CRT[1-6]



*AV optimized only

[1] Abraham WT, et al. *N Engl J Med.* 2002;346:1845-1853.
[2] Young JB, et al. *JAMA*. 2003;289:2685-2694.
[3] Abraham WT, et al. *Circulation*. 2004;110:2864-2868.
[4] Chung ES, et al. *Circulation*. 2008;117:2608-2616.
[5] Abraham WT, et al. *Heart Rhythm*. 2005;2:S65.
[6] Abraham WT, et al. Late-Breaking Clinical Trials, HRS 2010. Denver, Colorado.

There are many drivers for CRT non responders



[1]Mullens W, et al. *JACC*. 2009;53:765-773.

Strategies to Improve CRT response

- Improve Patient Selection
- Device based optimisation

Table 1. Summary of Echocardiographic Predictors of Response to CRT

Echocardiographic Predictor	Description of Method	Echocardiography Method	Cutoff
SPWMD[10]	Septal-posterior wall motion delay; M mode measured by parasternal short-axis view	M mode	≥130 ms
IVMD[14]	Interventricular mechanical delay defined as the difference between left and right ventricular preejection intervals	Pulsed Doppler	≥40 ms
LVFT/RR[14]	Left ventricular filling time (LVFT) in relation to cardiac cycle length	Pulsed Doppler	≤40%

Table 3. Interobserver and Intraoperator Variability Summary

Echocardiographic Measure	Intraobserver CV, %	Interobserver CV, %	Interobserver κ Coefficient*
LVESV	3.8	14.5	NA
LPEI	3.7	6.5	0.67
SPWMD	24.3	72.1	0.35
Ts-SD	11.4	33.7	0.15
Ts-peak (basal)	15.8	31.9	0.25

LPEI indicates left ventricular preejection interval.

segments at basal level

Strategies to Improve CRT response

- Improve Patient Selection
- Device based optimisation

Device based optimisation

- More recently focus has been shifting to device based optimisation
- Potential benefits over echo:
  - Simpler to perform
  - No inter-observer variability
  - Can optimise more frequently

Device Companies

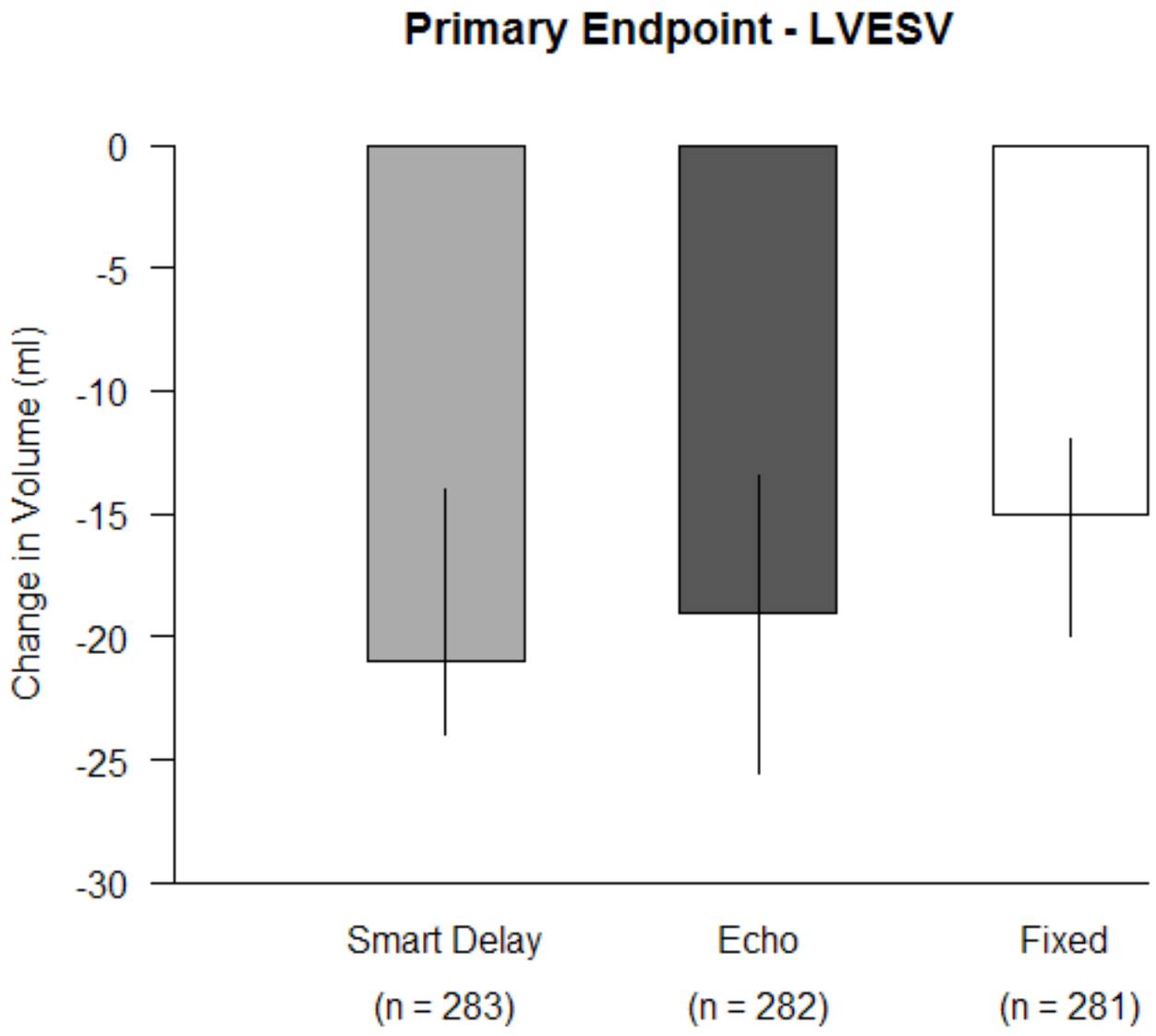
- Boston Scientific: Expert Ease for Heart Failure Smart Delay
- St Jude: Quick Opt, MPP
- Medtronic: Adaptive CRT, EffectivCRT, Multiple Point Pacing
- Sorin: SonR, Multiple Point Pacing

Boston Scientific-Smart Delay

- Smart Delay provides both paced and sensed recommendations by accounting for three inputs:
  - Intrinsic AV intervals (Sensed AV and Paced AV intervals),
  - Interventricular timing (surface QRS duration)
  - LV lead location

- Algorithm was developed from the results of several previous acute clinical studies (PATH CHF, PATH CHF II, and SAVER)

Boston Sci-Smart AV Trial



Primary Results From the SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) Trial

A Randomized Trial Comparing Empirical, Echocardiography-Guided, and Algorithmic Atrioventricular Delay Programming in Cardiac Resynchronization Therapy

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Background—One variable that may influence cardiac resynchronization therapy response is the programmed atrioventricular (AV) delay. The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) Trial prospectively randomized patients to a fixed empirical AV delay (120 milliseconds), echocardiographically optimized AV delay, or AV delay optimized with SmartDelay, an electrogram-based algorithm.

Methods and Results—A total of 1014 patients (68% men; mean age, 66±11 years; mean left ventricular ejection fraction, 25±7%) who met enrollment criteria received a cardiac resynchronization therapy defibrillator, and 980 patients were randomized in a 1:1:1 ratio. All patients were programmed (DDD-60 or DDDR-60) and evaluated after implantation and 3 and 6 months later. The primary end point was left ventricular end-systolic volume. Secondary end points included New York Heart Association class, quality-of-life score, 6-minute walk distance, left ventricular end-diastolic volume, and left ventricular ejection fraction. The medians (quartiles 1 and 3) for change in left ventricular end-systolic volume at 6 months for the SmartDelay, echocardiography, and fixed arms were −21 mL (−45 and 6 mL), −19 mL (−45 and 6 mL), and −15 mL (−41 and 6 mL), respectively. No difference in improvement in left ventricular end-systolic volume at 6 months was observed between the SmartDelay and echocardiography arms (P=0.52) or the SmartDelay and fixed arms (P=0.66). Secondary end points, including structural (left ventricular end-diastolic volume and left ventricular ejection fraction) and functional (6-minute walk, quality of life, and New York Heart Association classification) measures, were not significantly different between arms.

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.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00677014.

(*Circulation*. 2010;122:2660-2668.)

Key Words: clinical trials, randomized ■ echocardiography ■ electrophysiology ■ heart failure ■ implantable cardioverter-defibrillators

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.110.992552/DC1.

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St Jude - QuickOpt

AV Optimization:

- QuickOpt optimisation measures the total P-wave duration of eight IEGM events for the A-Sense test
- Measured P-wave durations are averaged
- The QuickOpt algorithm uses a proprietary formula to calculate the optimal AV delays

St Jude – QuickOpt VV

VV Optimization:

1. QuickOpt optimisation measures eight IEGM events for each of the V Sense, RV Pace and LV Pace tests.
   - V Sense—measures intrinsic interventricular delay
   - RV Pace—measures conduction speed from right to left
   - LV Pace—measures conduction speed from left to right

2. Measurements from each test are averaged

3. The QuickOpt algorithm uses a proprietary formula to calculate the optimal VV delay

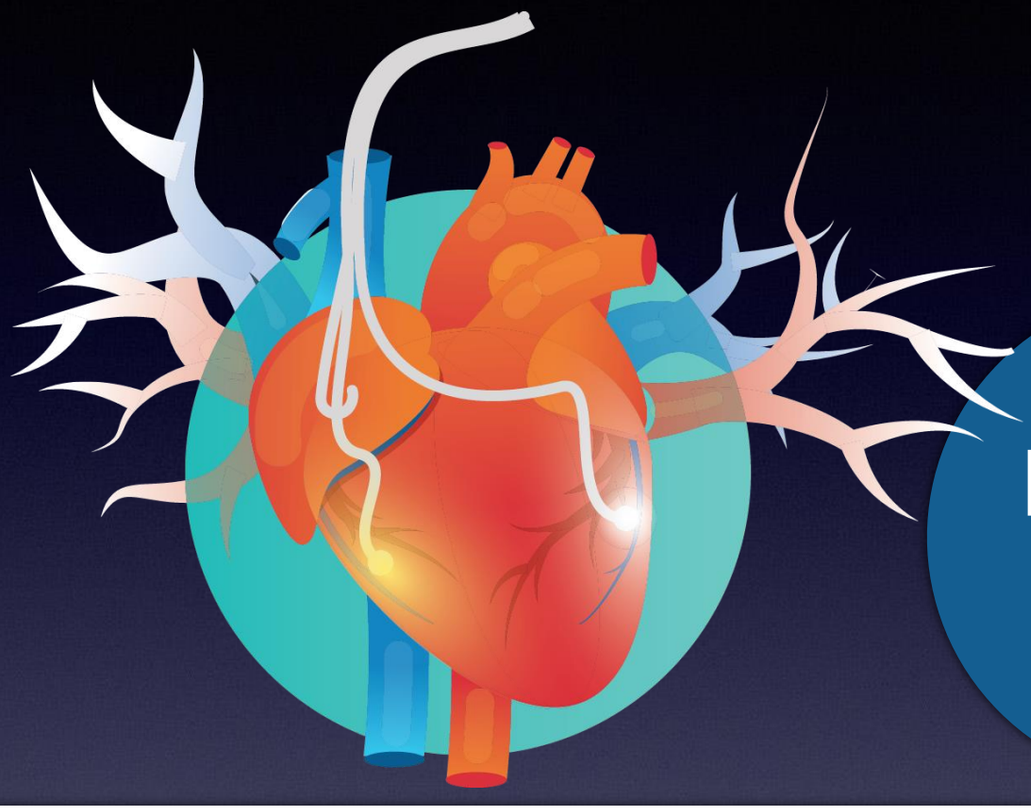
St Jude – Freedom Trial

- Randmised multicenter trial
- 1647 patients
- 1:1 randomisiation to QuickOpt vs Standard care

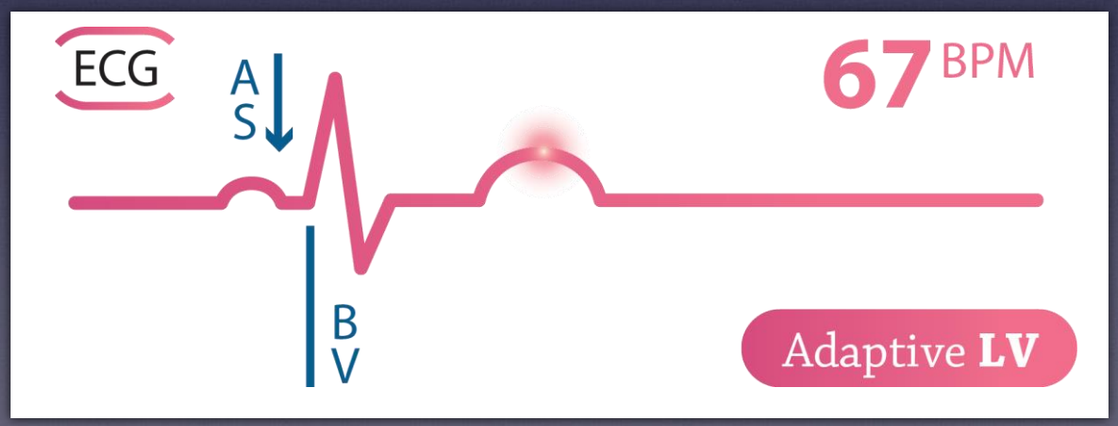
Intention-to-Treat					
	QuickOpt Optimization Treatment group		Control group		
Heart Failure Clinical Composite Score	n	%	n	%	p-value
Improved	551	**67.52%**	559	**67.51%**	0.50
Unchanged	76	9.31%	86	10.39%	
Worsened	189	23.16%	183	22.10%	
Total	816	100%	828	100%	

Medtronic AdaptivCRT

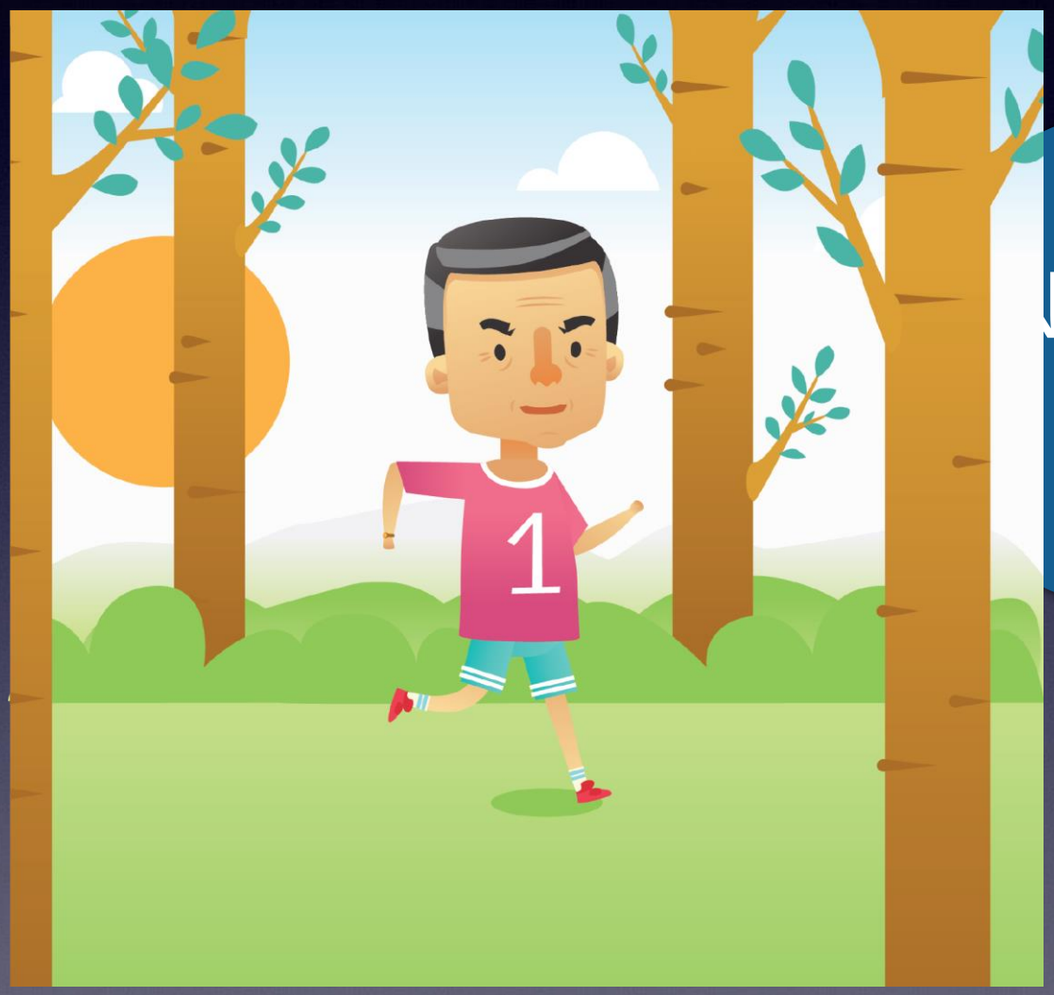
- Main goals are:
  - Achieve LV only pacing in patients with normal AV conduction
  - Achieve dynamic AV conduction to simulate normal AV function
  - To continually optimise AV and VV intervals to improve CRT response
- P and QRS width measurements occur every 16 hr
- AV Interval Measurements occur every minute



Normal
AV

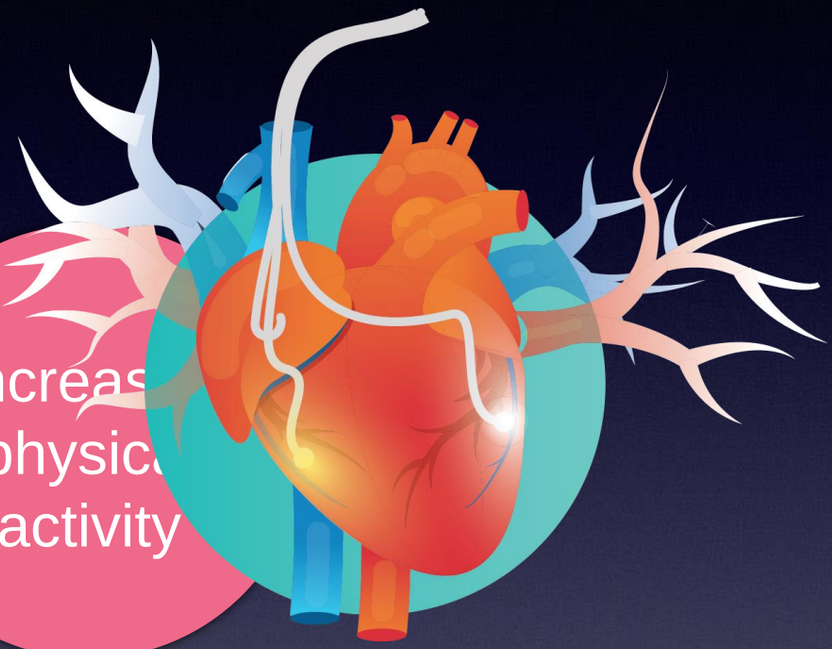


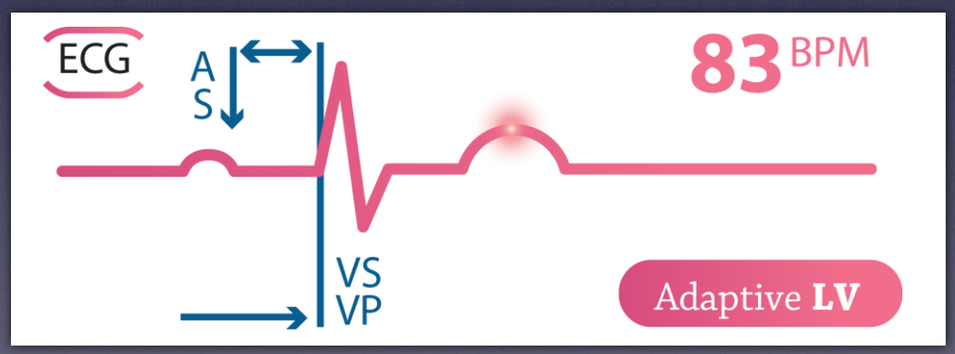
aCRT pre-paces LV &
reduces RV pacing



Normal AV

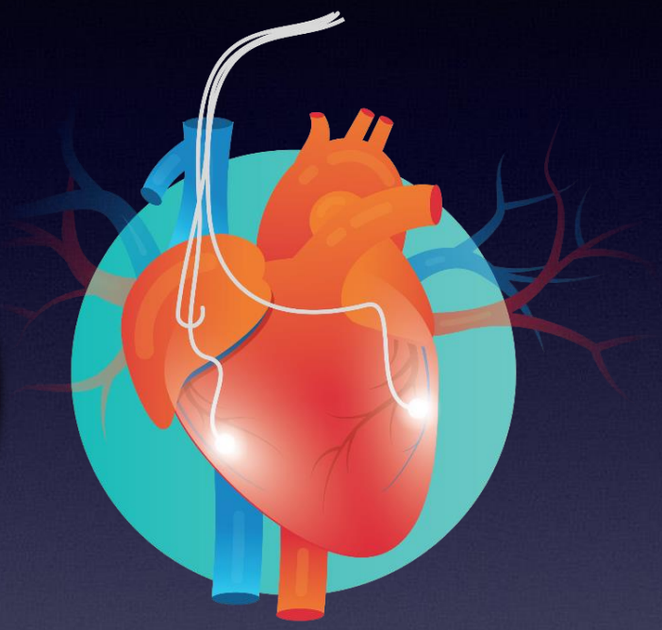
Increas physica activity

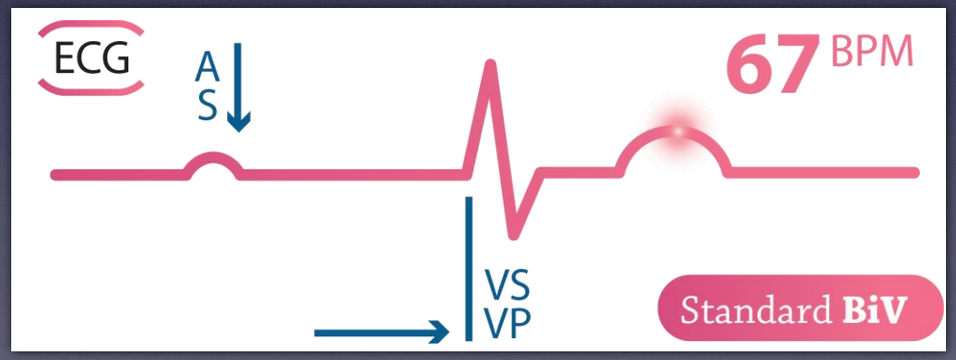




aCRT senses shortening in AV & optimises CRT

Prolonged AV





aCRT automatically switches to Biv pacing

Adaptive CRT Trial

- 522 patients, prospective, multi-center, randomised double-blinded study
- aCRT vs Echo optimised CRT

[1] Martin DO, et al. *Heart Rhythm*. 2012;9:1807-1814.
[2] Krum H, et al. *Am Heart J*. 2012;163:747-752.e1.

Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: Results of the adaptive CRT trial

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BACKGROUND In patients with sinus rhythm and normal atrioventricular conduction, pacing only the left ventricle with appropriate atrioventricular delays can result in superior left ventricular and right ventricular function compared with standard biventricular (BiV) pacing.

OBJECTIVE To evaluate a novel adaptive cardiac resynchronization therapy ((aCRT) algorithm for CRT pacing that provides automatic ambulatory selection between synchronized left ventricular or BiV pacing with dynamic optimization of atrioventricular and interventricular delays.

METHODS Patients (n = 522) indicated for a CRT-defibrillator were randomized to aCRT vs echo-optimized BiV pacing (Echo) in a 2:1 ratio and followed at 1-, 3-, and 6-month postrandomization.

RESULTS The study met all 3 noninferiority primary objectives: (1) the percentage of aCRT patients who improved in their clinical composite score at 6 months was at least as high in the aCRT arm as in the Echo arm (73.6% vs 72.5%, with a noninferiority margin of 12%; $P = .0007$); (2) aCRT and echo-optimized settings resulted in similar cardiac performance, as demonstrated by a high concordance correlation coefficient between aortic velocity time integrals at aCRT and Echo settings at randomization (concordance correlation coefficient = 0.93; 95% confidence interval 0.91–0.94) and at 6-month postrandomization (concordance correlation coefficient = 0.90; 95% confidence interval 0.87–0.92); and (3) aCRT did not result in inappropriate device settings. There were no significant differences between the arms with respect to heart failure events or ventricular arrhythmia episodes. Secondary end points showed similar benefit, and right-ventricular pacing was reduced by 44% in the aCRT arm.

CONCLUSIONS The aCRT algorithm is safe and at least as effective as BiV pacing with comprehensive echocardiographic optimization.

KEYWORDS Cardiac resynchronization therapy; Fusion pacing; Optimization; LV pacing; Heart failure

ABBREVIATIONS **aCRT** = adaptive CRT; **AoVTI** = aortic velocity time integral; **AV** = atrioventricular; **BiV** = biventricular; **CCS** = clinical composite score; **CRT** = cardiac resynchronization therapy; **HF** = heart failure; **LV** = left ventricular; **RV** = right ventricular; **VT/VF** = ventricular tachycardia/ventricular fibrillation

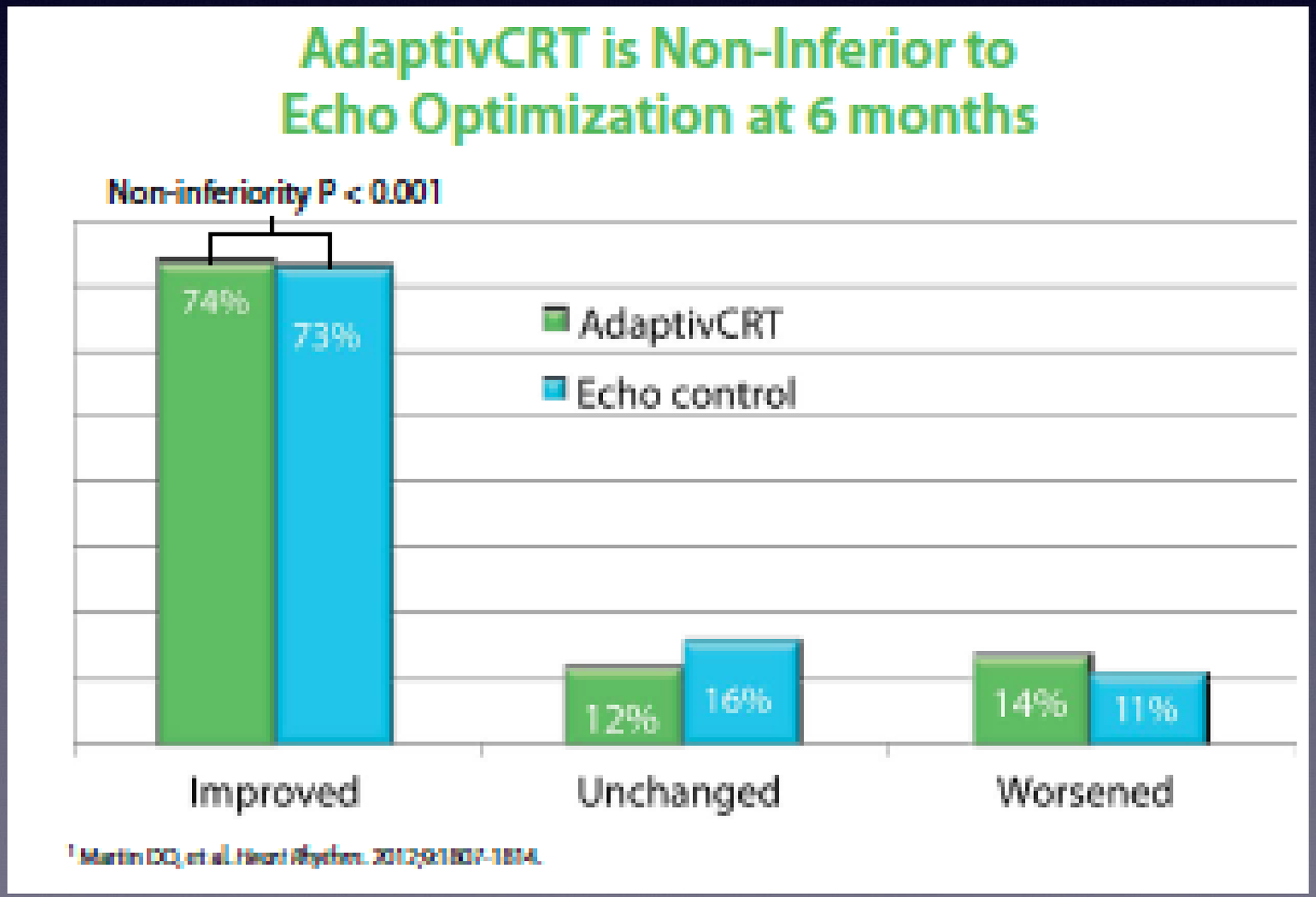
(Heart Rhythm 2012;9:1807–1814) © 2012 Heart Rhythm Society. All rights reserved.

The trial was sponsored by Medtronic, Mounds View, Minnesota. Dr Martin serves on a Medtronic advisory board. Dr Lemke has received honoraria and speaker's fees from Medtronic and Saint Jude Medical and speaker's fees from Boston Scientific. Dr Birnie has received honoraria and research grants from Medtronic. Dr Krum has received honoraria from Medtronic. Dr Lee has received research grants from Medtronic. Dr Aonuma has received honoraria, speaker's fees, and research grants from Medtronic. Dr Gasparini has received honoraria and served on advisory boards for Medtronic and Boston Scientific. Dr Starling has received honoraria from Novartis. Dr Milasinovic has received honoraria from Medtronic. Dr Gorcsan has consulted for or has received research grants from Biotronik, Medtronic, St Jude Medical, GE, and Toshiba Medical. T. Rogers is a statistician employed by Medtronic. A. Sambelashvili is a scientist employed by Medtronic. **Address for reprint requests and correspondence:** Dr David O. Martin, MD, MPH, The Cleveland Clinic Foundation, 9500 Euclid Avenue, J2-2, Cleveland, OH 44195. E-mail address: martind3@ccf.org.

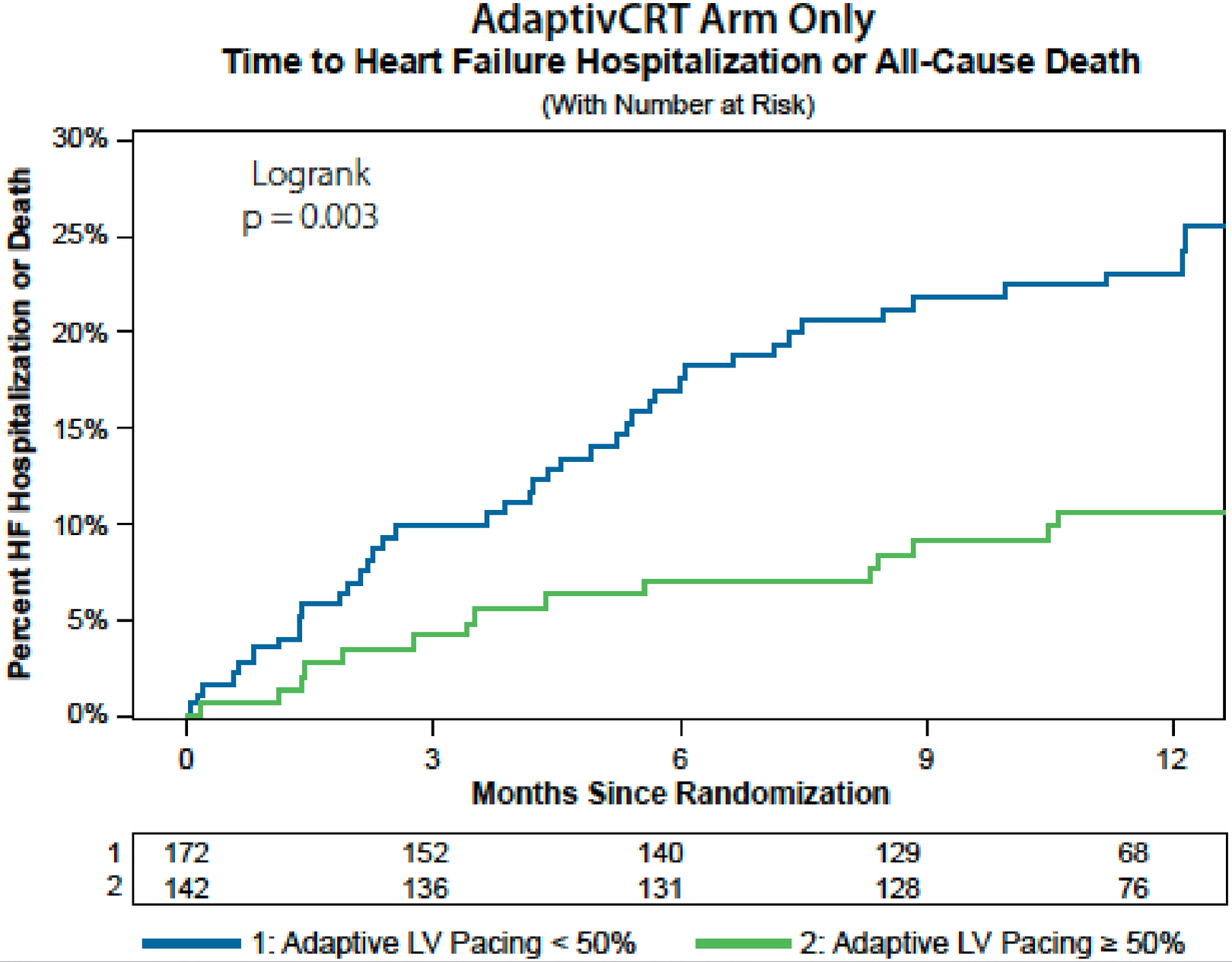
1547-5271/$ -see front matter © 2012 Heart Rhythm Society. All rights reserved. http://dx.doi.org/10.1016/j.hrthm.2012.07.009

Comparison to Echo optimisation

- Compared echo based optimisation (1 and 6 months) versus adaptive CRT.

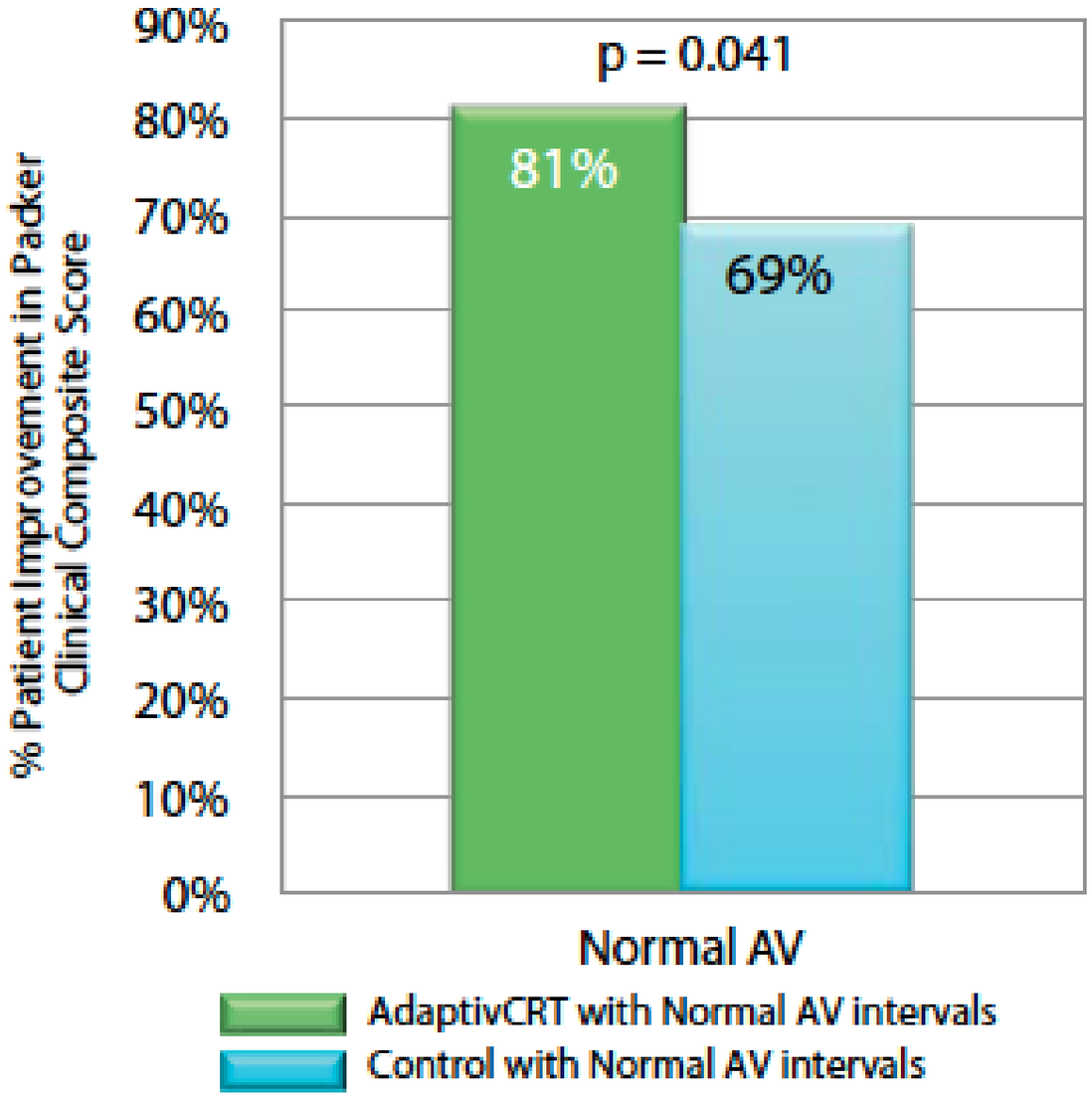


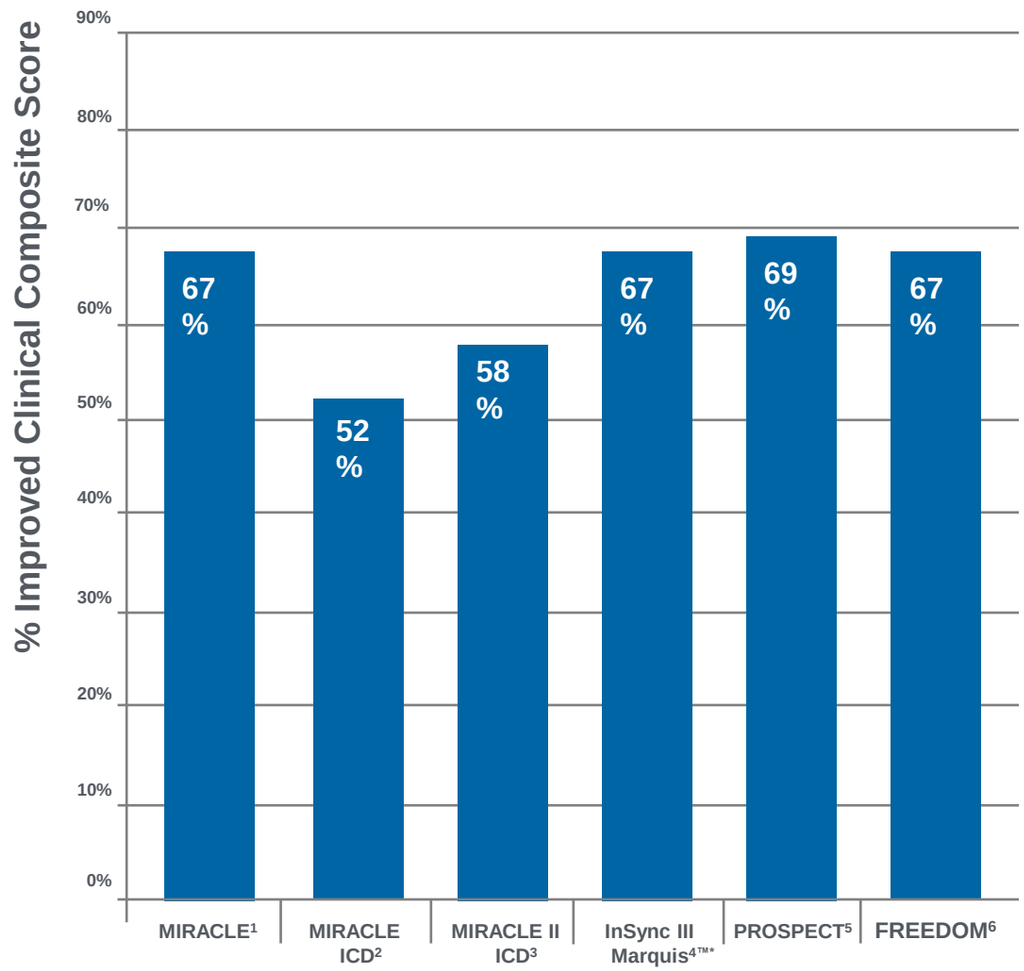
Higher percentage Synchronized LV Pacing in the aCRT Arm had a lower rate of death and HF hospitalizations



[1] Birnie D, Lemke B, Aonuma K, et al. Clinical outcomes with synchronized left ventricular pacing: Analysis of the adaptive CRT trial. *Heart Rhythm*. September 2013; 9 (10):1368-1374.

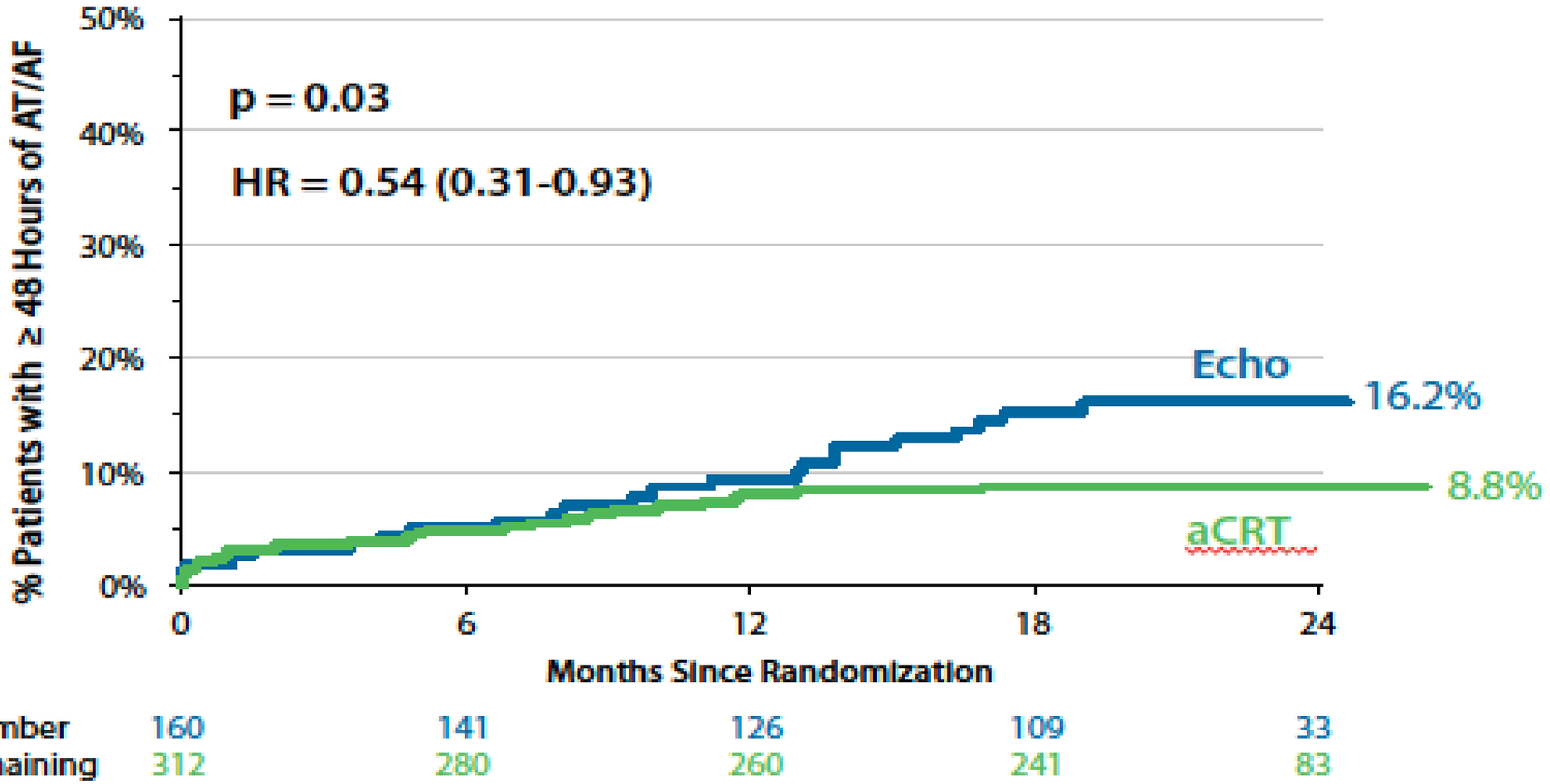
Improved clinical outcomes for patients with Normal AV Conduction





AdaptivCRT Reduced AF Risk

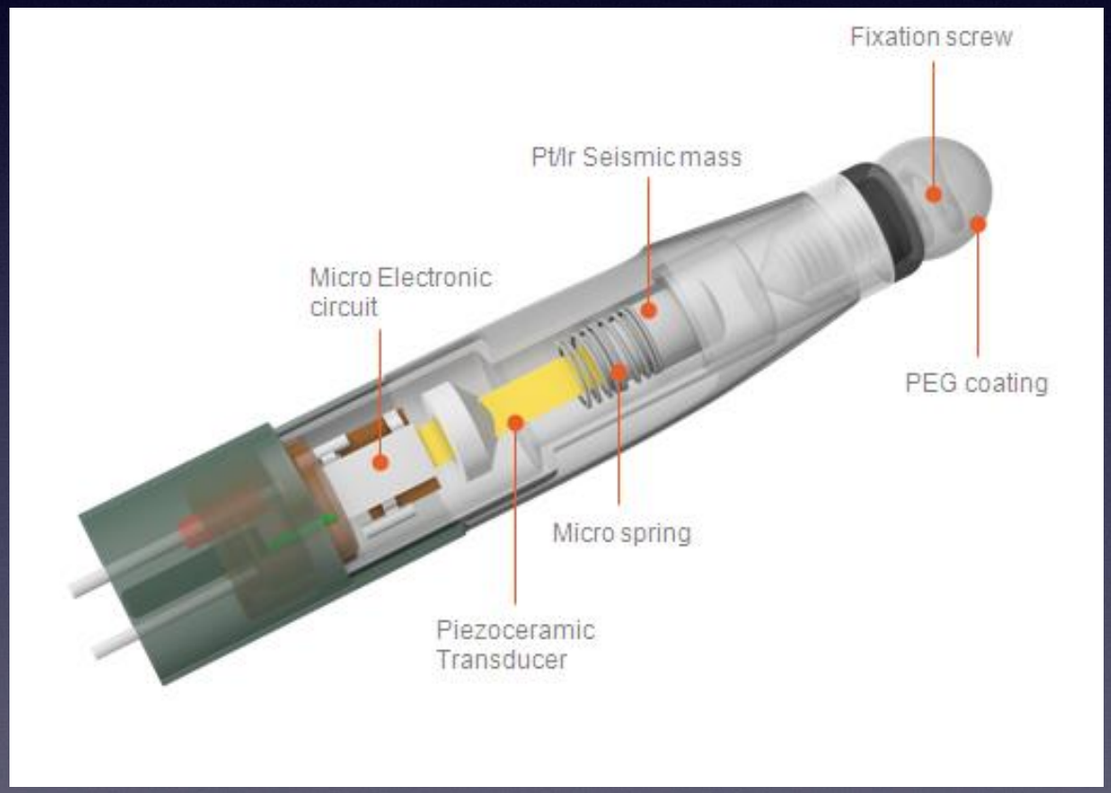
As compared to patients receiving echo optimized CRT



[1] Martin D, Lemke B, Aonuma K, et al. Clinical Outcomes with Adaptive Cardiac Resynchronization Therapy: Long-term Outcomes of the Adaptive CRT Trial. HFSA Late Breakers. September 23, 2013.

Sorin SonR

- Uses a hemodynamic sensor embedded in the atrial sense / pace lead, detects cardiac muscle vibrations that reflect the first heart sound
- The amplitude of the first heart sound reflects changes in contractility (LVdP/dtmax)



Sorin SonR

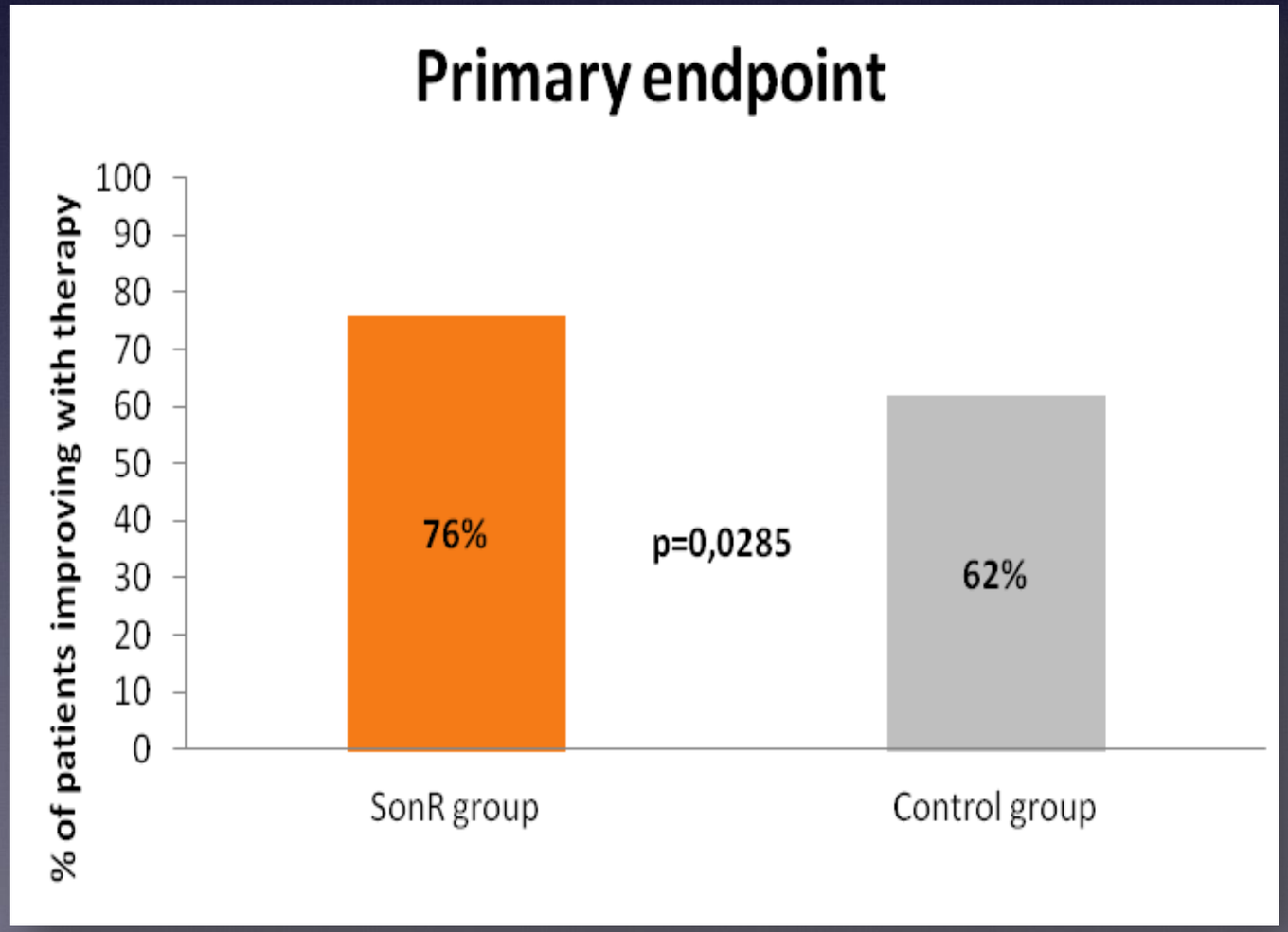
- Optimises VV & AV delays weekly

Every Monday:

- At 0:00am: search of the optimal VV configuration (7 VVd and 6 AVd)
- At 1:00am: search of the optimal sensed AV delay at rest (opt VVd and 11 AVd)
- At 2:00am: search of the optimal paced AV delay at rest (opt VVd and 11 AVd)
- At 12:00pm: search of the optimal AV delay at exercise (opt VVd and 5 Avd)

Sorin-CLEAR study

- Randomised Multicenter trial
- 238 patients 1:1 SonR vs standard practice



RESPOND CRT study design

DESIGN

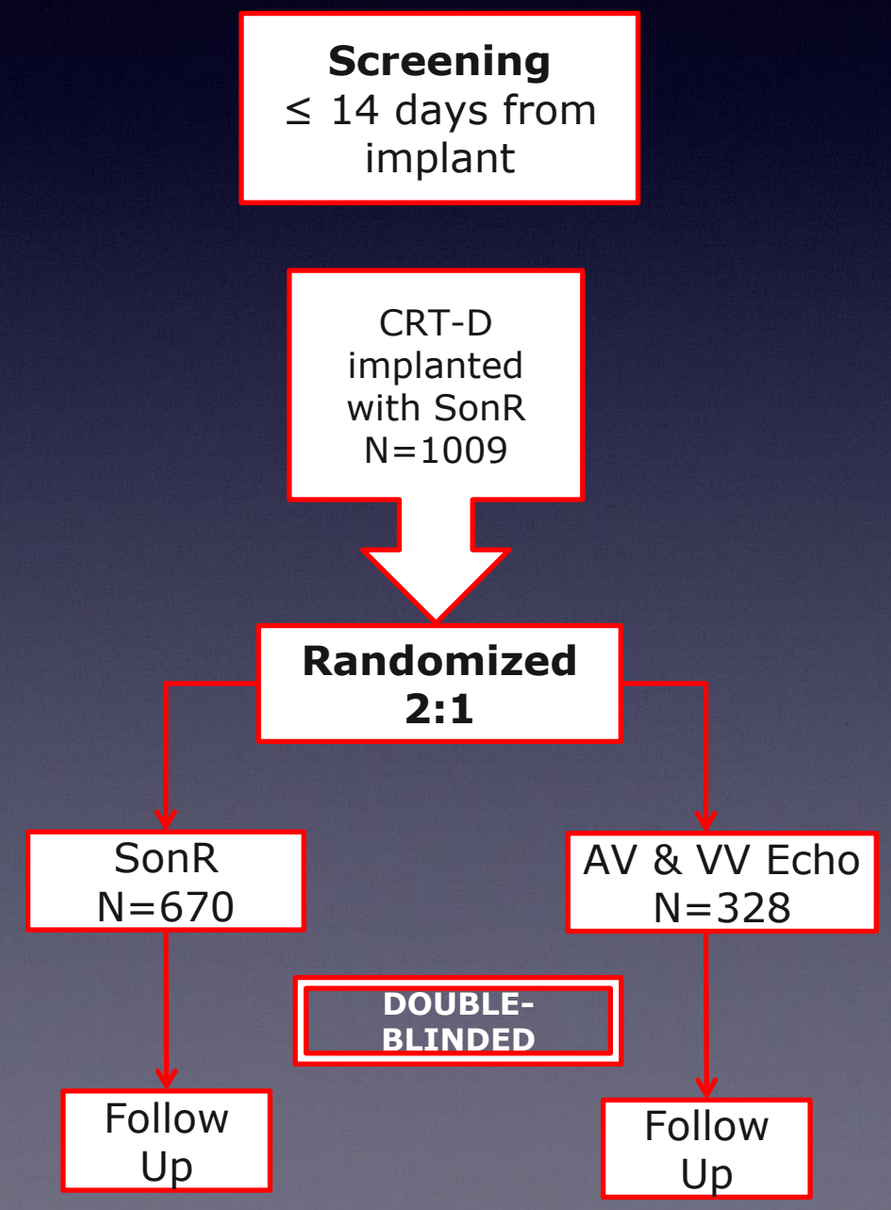
RESPOND-CRT is an International, Multicenter, Randomised (2:1), Prospective, Double-blinded trial

PATIENTS

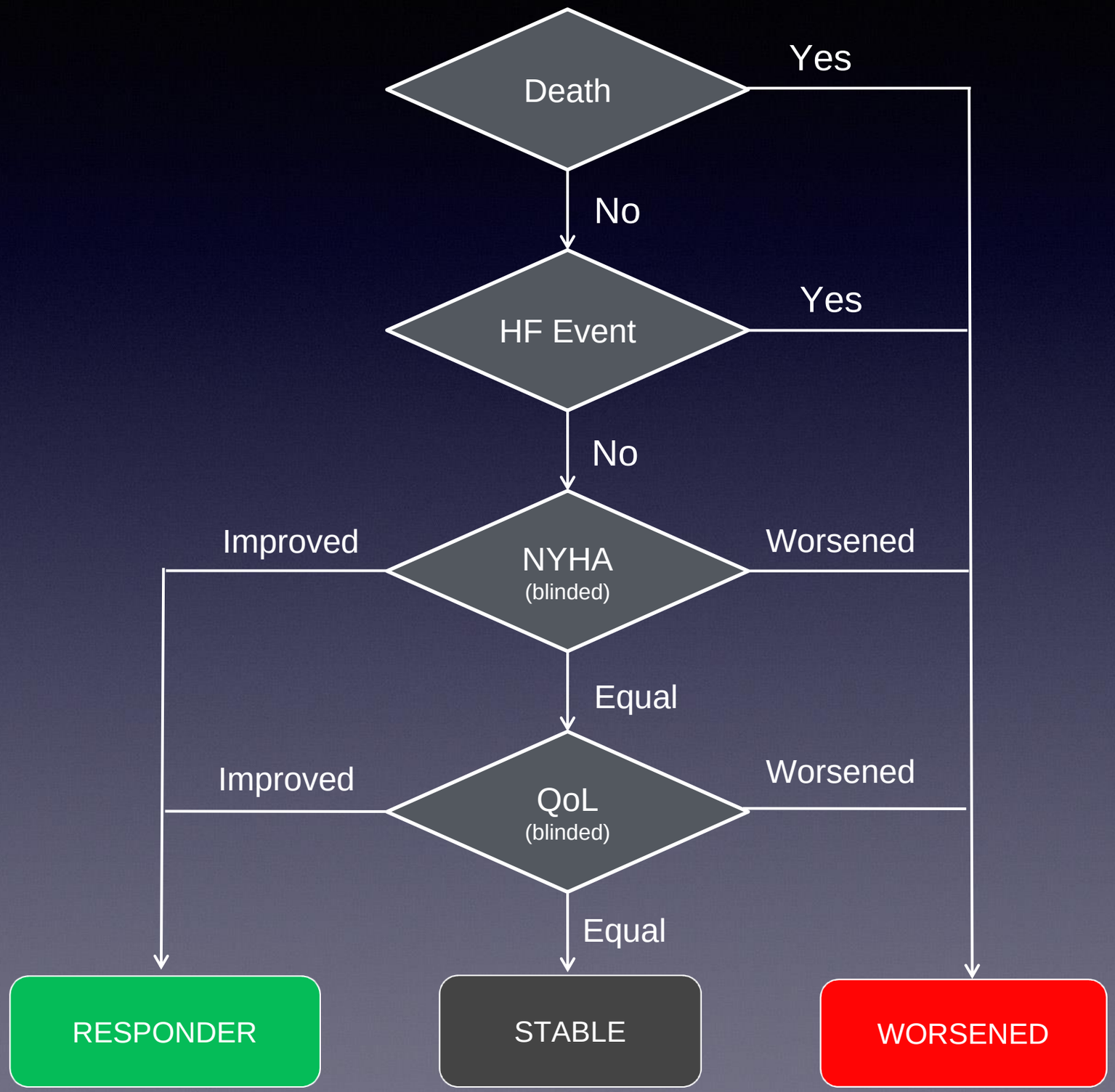
- → LVEF ≤ 35%
- → QRS ≥ 120 ms in LBBB or QRS ≥ 150 ms in non-LBBB
- → NYHA III or IV
- → Without permanent AF

ENROLLMENT

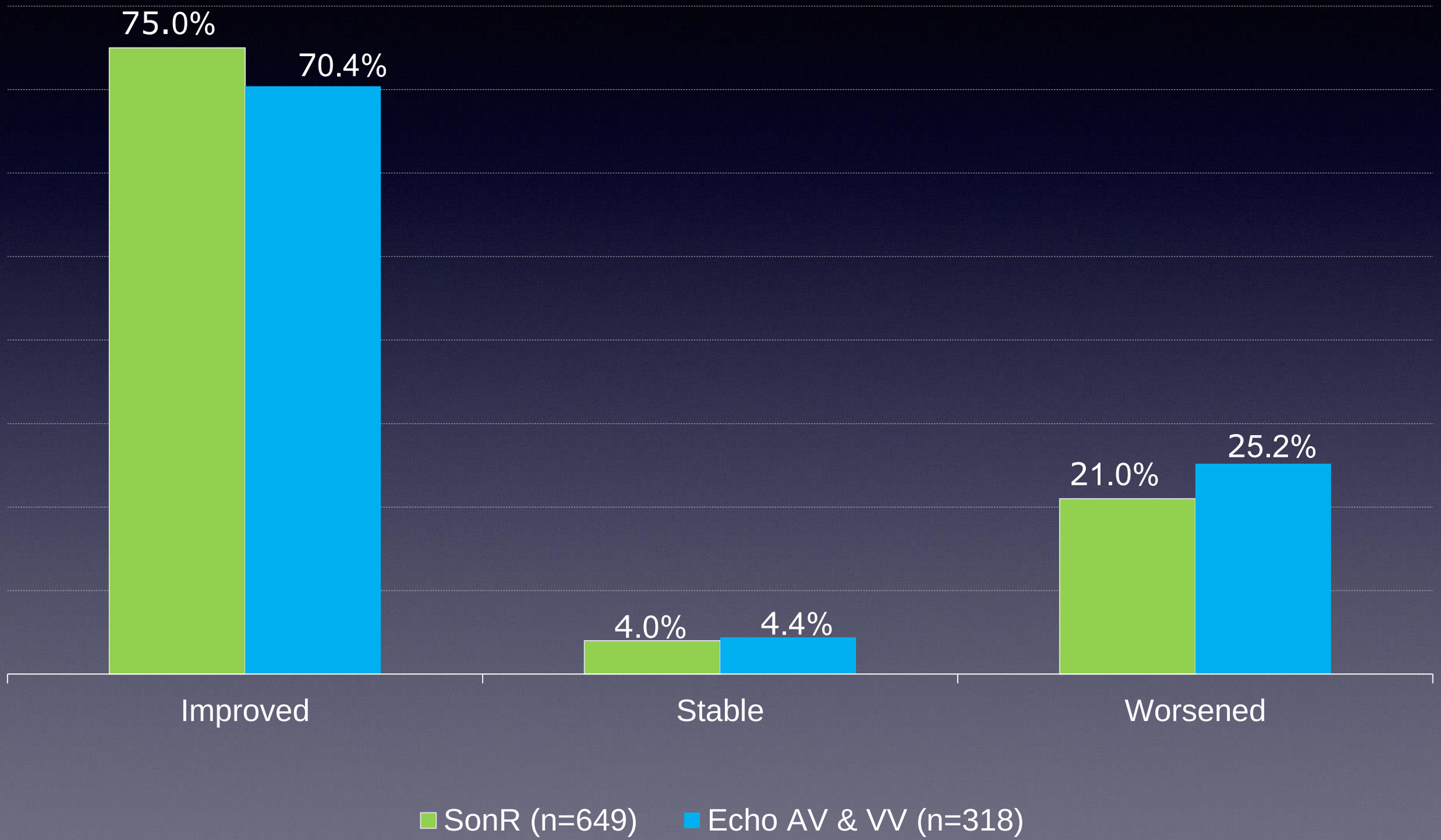
- → 125 sites in Europe, USA, Australia
- → Jan 2012 – Oct 2014
- → Long term follow up ongoing (2 years)



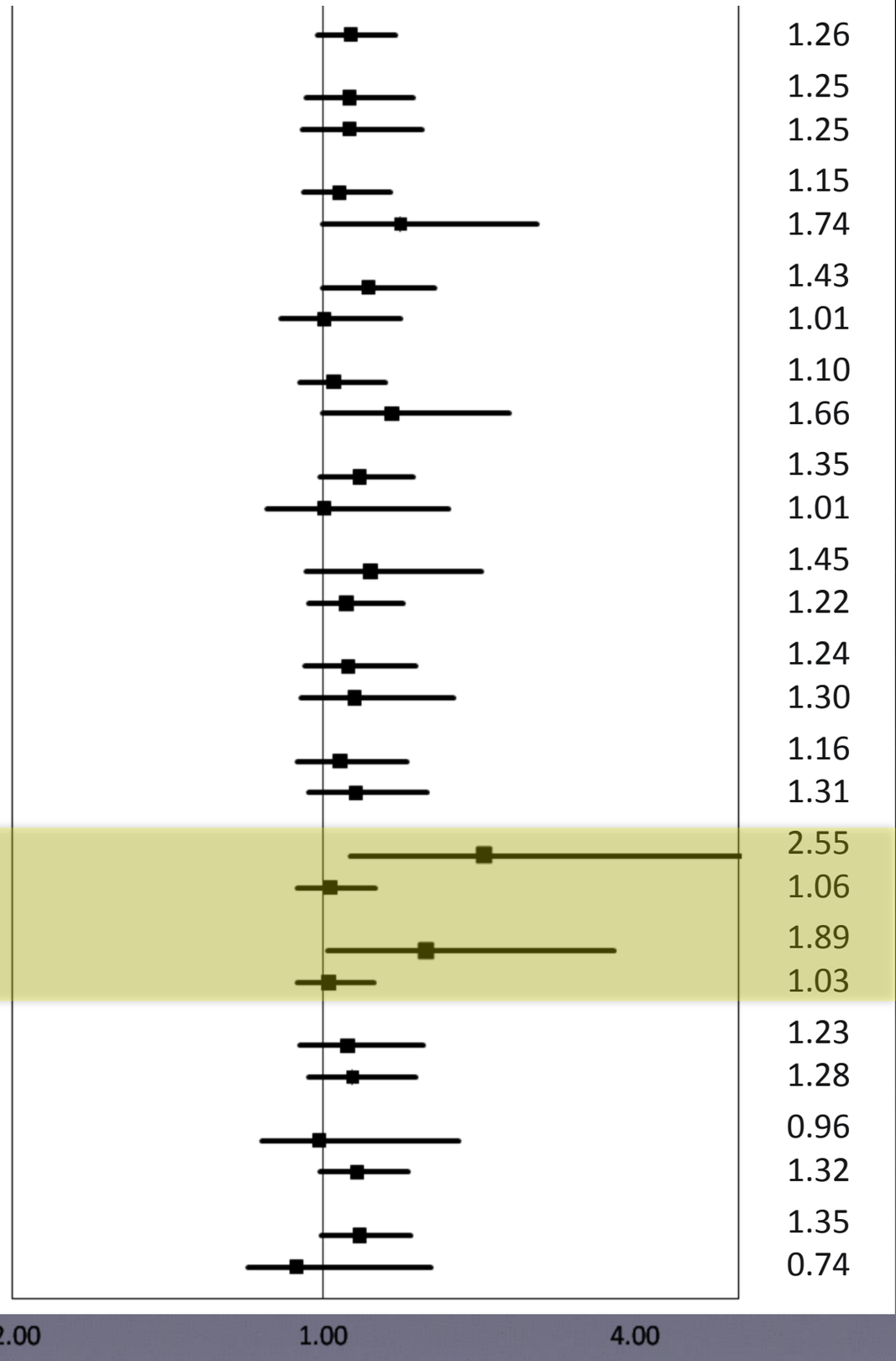
Response to CRT is based on a hierarchical set of clinical criteria



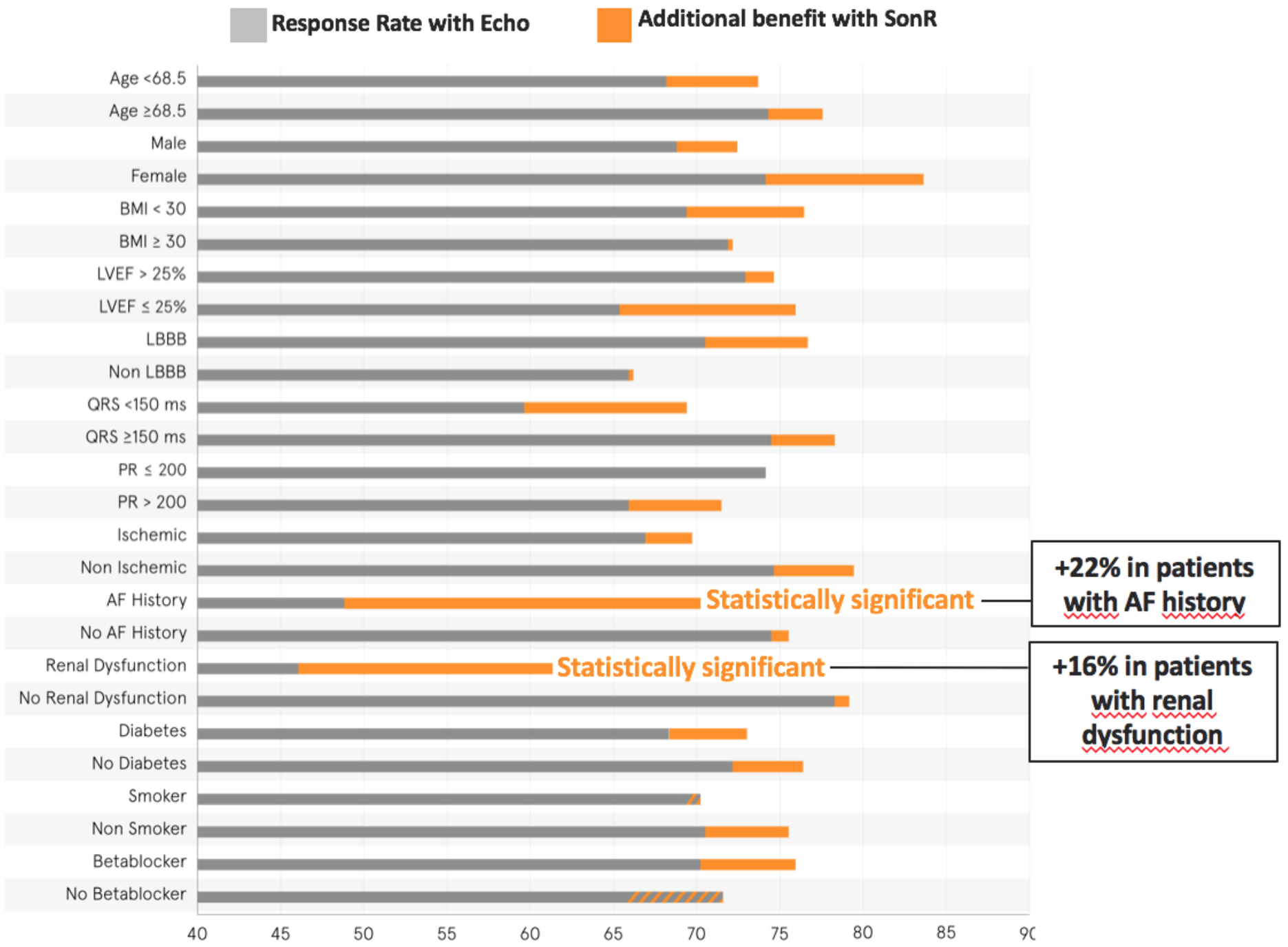
Primary efficacy end points at 12 months



VARIABLE		SonR (N=649)	Echo AV & VV (N=318)	P value	Odds Ratio
Overall		**75.0%**	**70.4%**		1.26
Age	<68.5years	**72.6%**	**68.1%**	**0.99**	1.25
	≥68.5 years	**77.3%**	**73.2%**		1.25
Gender	Male	**71.6%**	**68.6%**	**0.23**	1.15
	Female	**83.1%**	**73.9%**		1.74
BMI	<30 kg/m^2	**76.5%**	**69.5%**	**0.30**	1.43
	≥30kg/m^2	**72.2%**	**72.0%**		1.01
LVEF	> 25%	**74.7%**	**72.7%**	**0.21**	1.10
	≤25%	**75.8%**	**65.3%**		1.66
QRS morph.	LBBB	**76.8%**	**71.1%**	**0.51**	1.35
	Non LBBB	**66.0%**	**65.8%**		1.01
QRS duration	<150 ms	**68.0%**	**59.5%**	**0.62**	1.45
	≥150 ms	**77.9%**	**74.3%**		1.22
PR interval	≤200 ms	**78.0%**	**74.0%**	**0.89**	1.24
	>200 ms	**71.6%**	**65.9%**		1.30
Cardiomyopathy	Ischemic	**69.9%**	**66.7%**	**0.70**	1.16
	Non-Ischemic	**79.1%**	**74.3%**		1.31
History of AF	Yes	**70.2%**	**48.1%**	**0.03**	2.55
	No	**75.9%**	**74.8%**		1.06
Renal dysfunction	Yes	**61.9%**	**46.3%**	**0.07**	1.89
	No	**79.1%**	**78.6%**		1.03
Diabetes	Yes	**72.3%**	**67.9%**	**0.90**	1.23
	No	**76.8%**	**72.2%**		1.28
Smoker	Yes	**69.6%**	**70.6%**	**0.49**	0.96
	No	**75.9%**	**70.4%**		1.32
Beta Blocker	Yes	**76.1%**	**70.3%**	**0.27**	1.35
	No	**65.7%**	**72.0%**		0.74



Difference in responder rate for subgroups

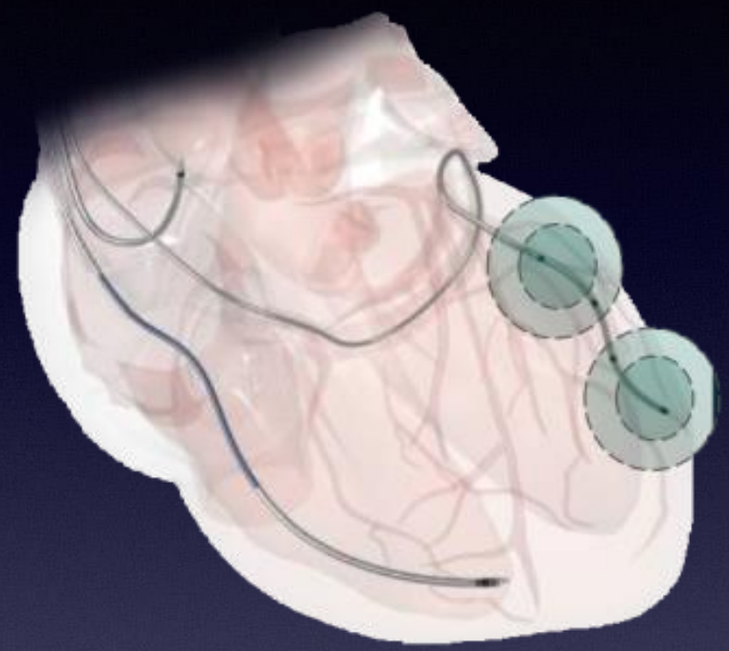


+22% in patients with AF history

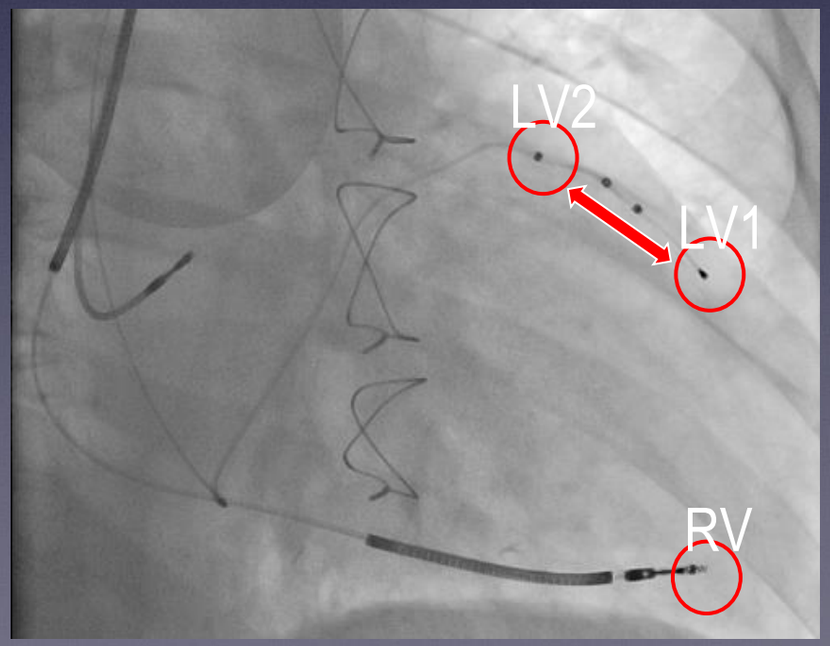
+16% in patients with renal dysfunction

Multi Point Pacing

- Pacing from **two** LV sites (“Multipoint LV stimulation”)
  and **one** RV
  - Capture a larger area
    - Engage areas around scar tissue
  - Improve pattern of depolarisation/repolarisation
  - Improve hemodynamics
  - Improve resynchronisation

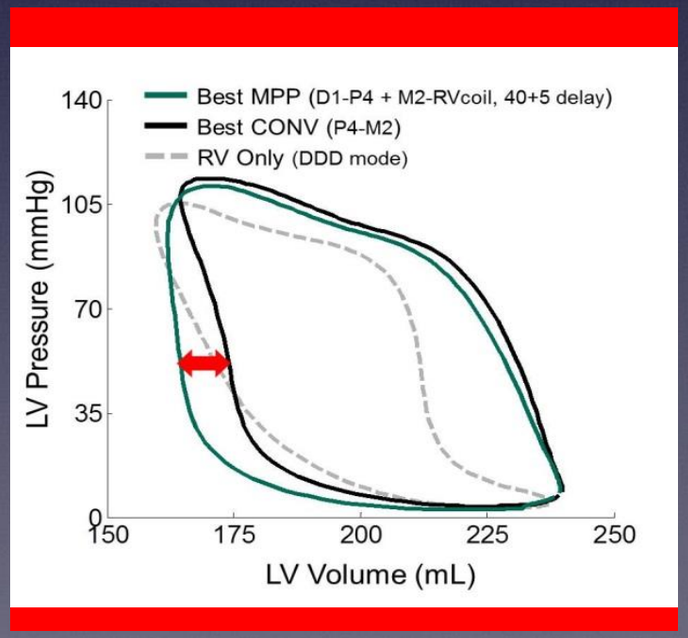


- Using MPP does appear to reduce battery life by around 6-12 months

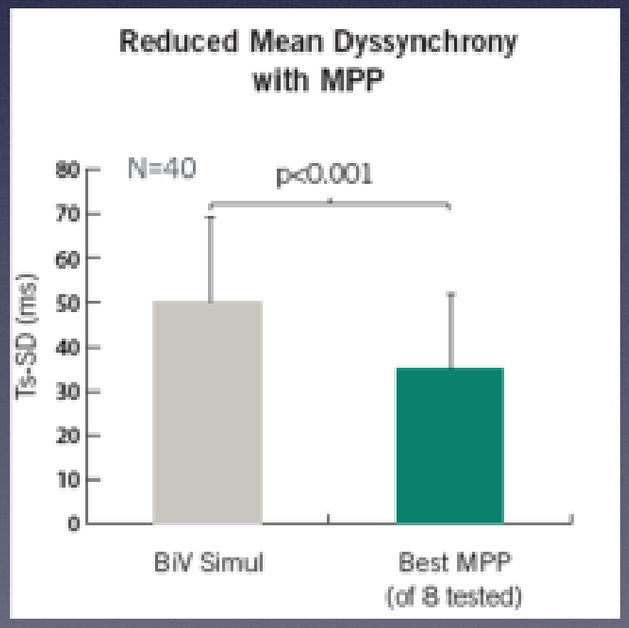


Acute data for MPP

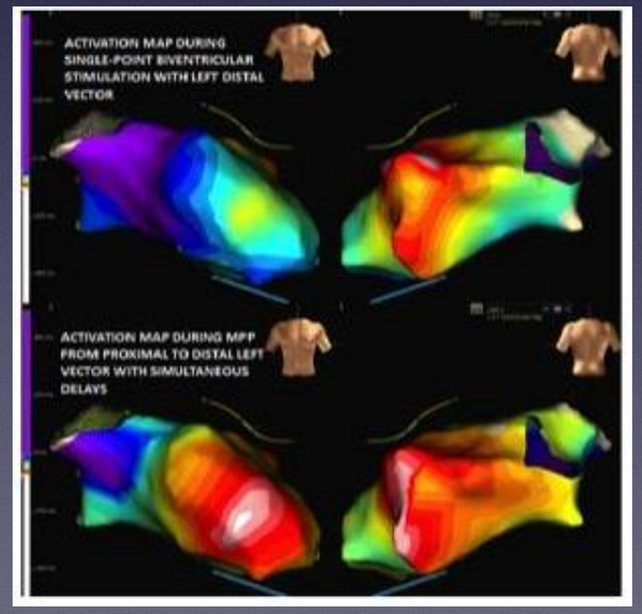
- Hemodynamic benefit:
  A study of 44 patients by Pappone et al. showed MultiPoint Pacing significantly improved acute LV hemodynamic parameters assessed with pressure-volume loop measurements.



- Mechanical benefit:
  Biventricular pacing with MultiPoint LV pacing reduced mechanical dyssynchrony measured with tissue Doppler in a multicenter study of 41 patients.

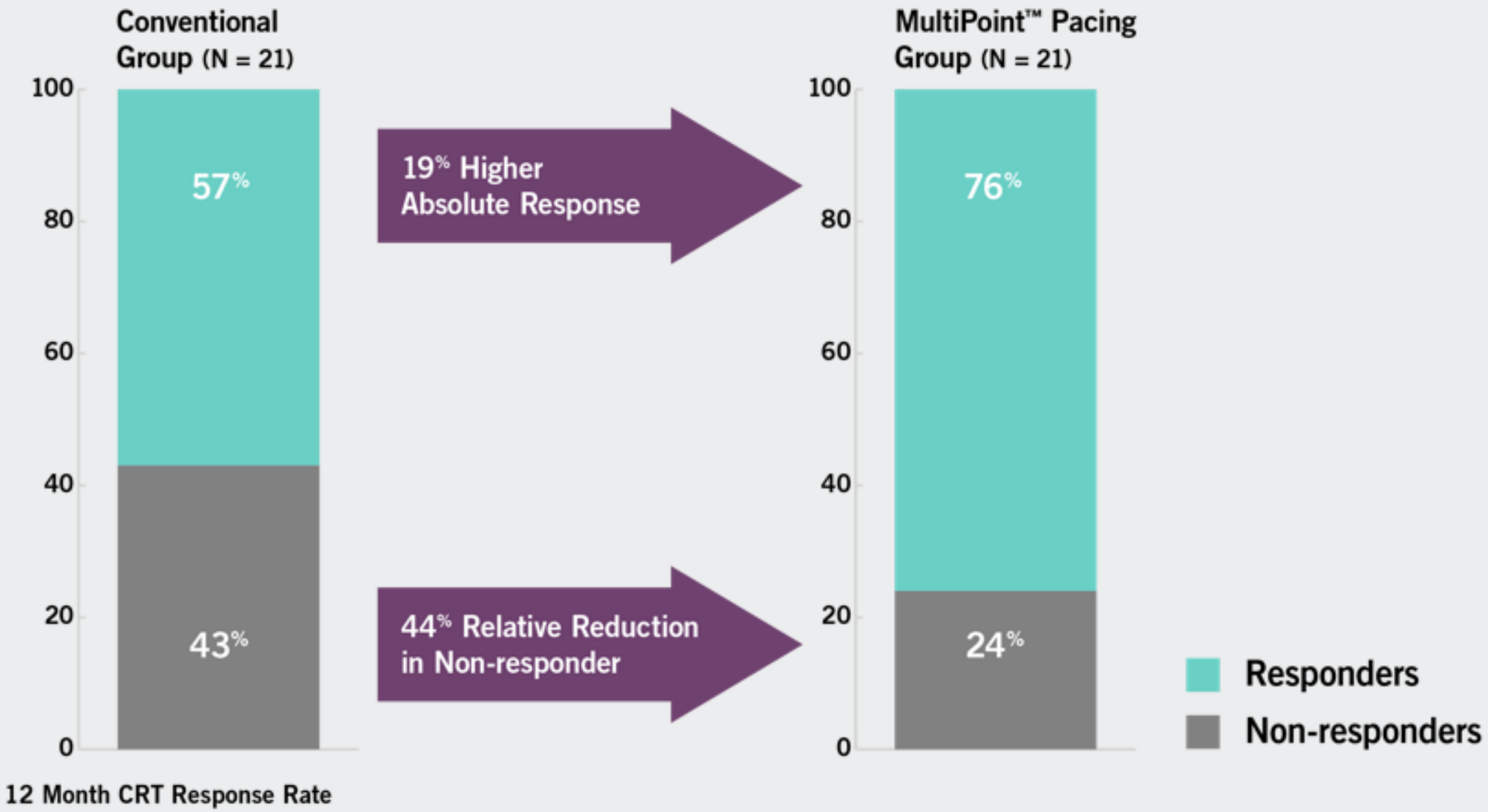


- Electrical benefit:
  MultiPoint pacing was able to recruit a greater portion of the LV than traditional biventricular pacing, resulting in reduced activation times and QRS duration.



12-MONTH CRT RESPONSE RATE[7]

Response definition:
ESV reduction ≥ 15% and Alive Status



MPP IDE Study

HRS

Safety and Efficacy of MultiPoint Pacing in Cardiac Resynchronization Therapy: The MultiPoint Pacing (MPP) IDE Trial

*Gery Tomassoni[1], James Baker II[2], Raffaele Corbisiero[3], Charles Love[4], David Martin[5], Robert Sheppard[6], Seth J. Worley[7], Niraj Varma[8], and Imran Niazi[9] on behalf of the MPP IDE Investigators

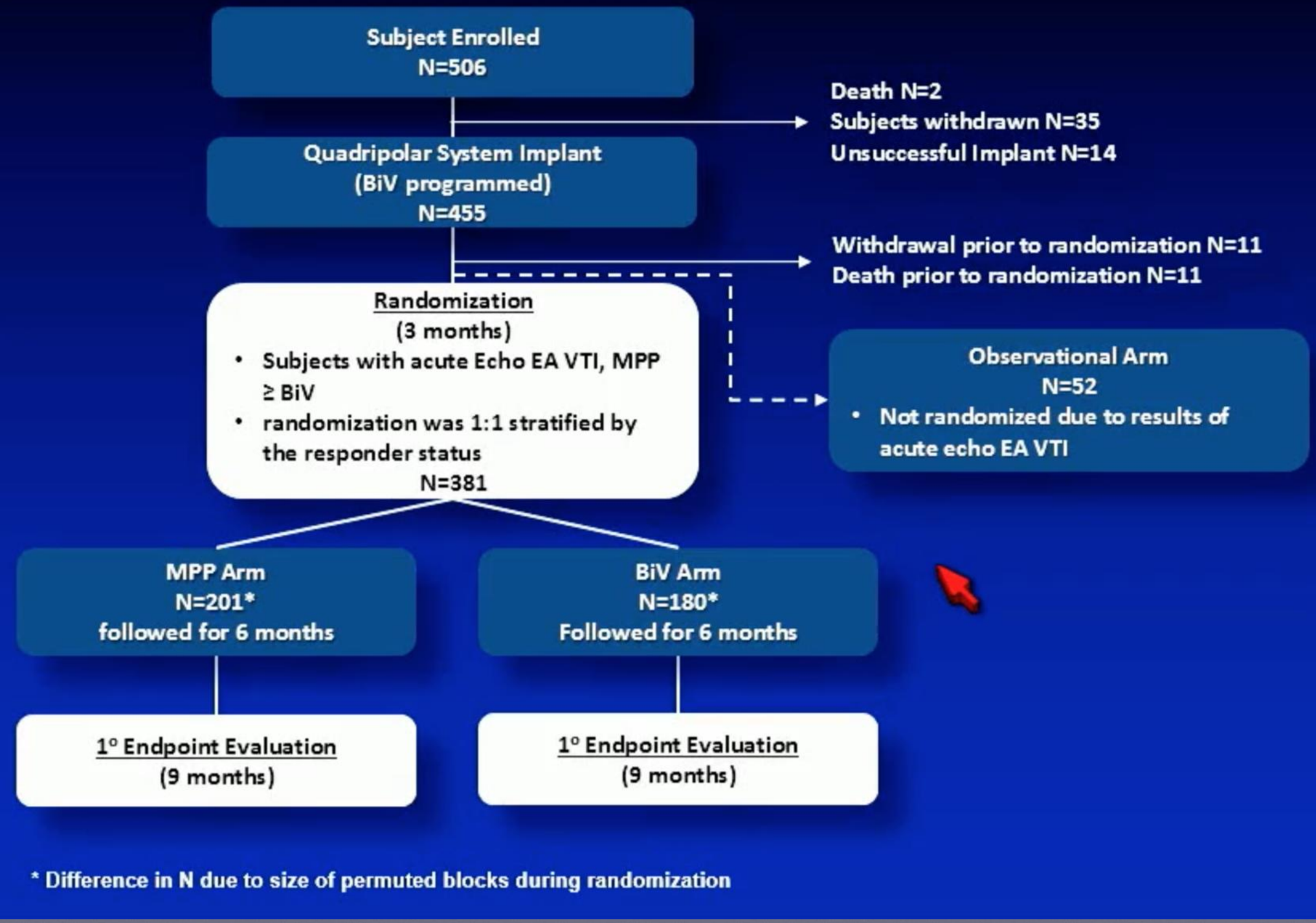
[1]Lexington Cardiology at Central Baptist, Lexington, KY, USA, [2]Saint Thomas Research Institute, Nashville, TN, USA, [3]Deborah Heart and Lung, Browns Mills, NJ, USA, [4]NYU Langone Medical Center, New York, NY, USA, [5]Lahey Clinic Medical Center - Cardiology, Burlington, MA, USA, [6]The Heart Institute, St. Petersburg, FL, USA, [7]Lancaster Heart Foundation, Lancaster, PA, USA, [8]Cleveland Clinic Foundation, Cleveland, OH, USA, [9]Aurora Cardiovascular Services, Milwaukee, WI, USA

*Advisor, Speaker, Medical Device Board: SJ Medical, Biosense Webster, Medtronic, Boston Scientific, Biotronics, Siemens, STXS, Topera, Atricure & Pfizer

HRS

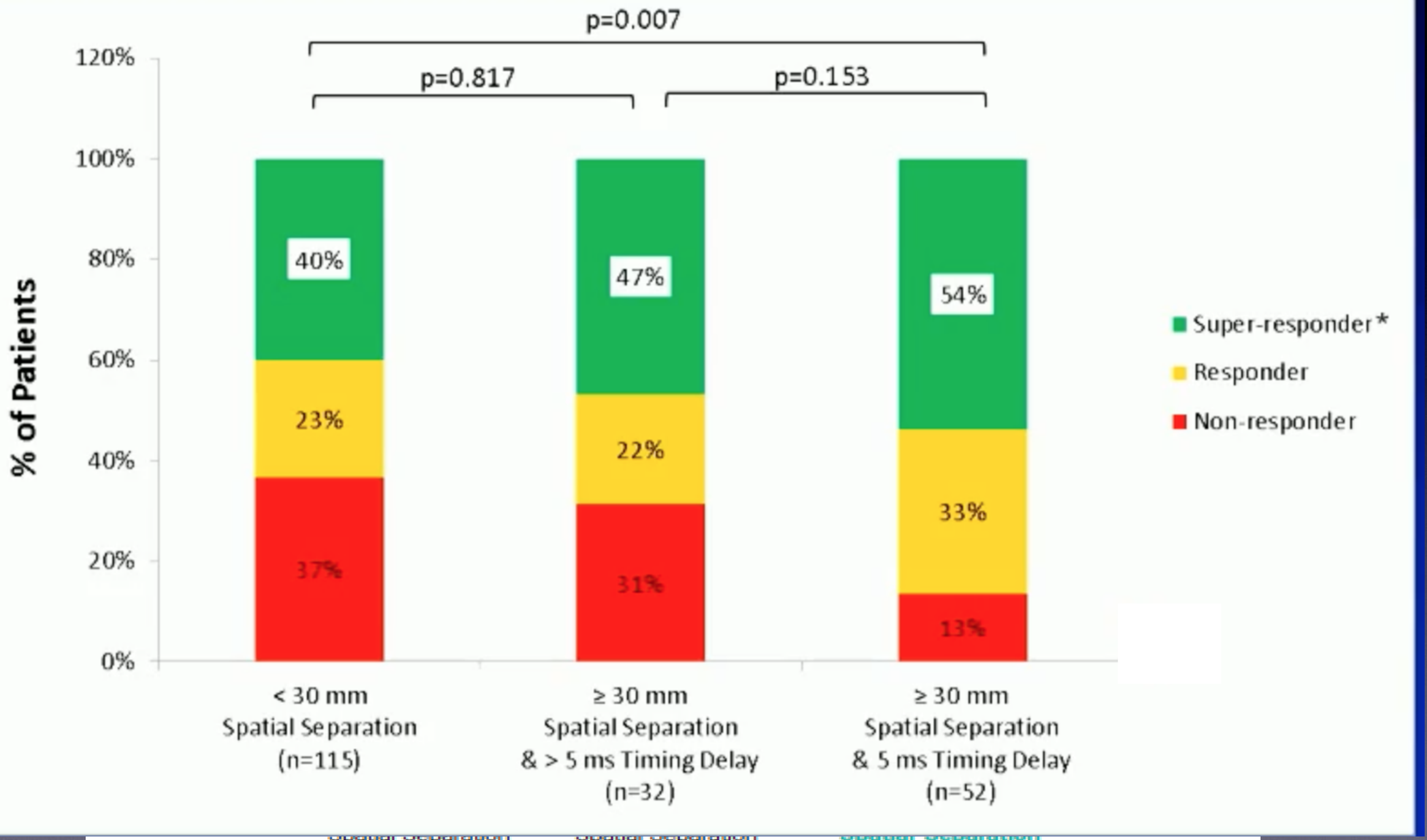
Study Flow and Disposition

Prospective, Multicenter, Randomized, Double Blind Controlled Trial



* Difference in N due to size of permuted blocks during randomization

Responder Rate



Spatial Separation
(n = 115)

Spatial Separation
& > 5 ms Timing Delay
(n = 32)

Spatial Separation
& 5 ms Timing Delay
(n = 52)

Conclusions

- Echo based optimisation has very little evidence base for routine clinical work
- Device based algorithms are becoming more common and in initial trials do appear to confer some increased benefit
- Multi point LV pacing may also improve response but does have effect on battery life
- No head to head data across the different companies

Thank You..