Ottimizzare la terapia di resincronizzazione per tutti i pazienti: sogno o realtà?

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Clinical response after CRT

Improvement >1 NYHA

Author(Ref.#)	Patients (n)	Follow-Up (Months)	Ischemic Etiology (%)	NYHA Functional Class	QRS Duration (ms)	LVEF (%)	Response Rate (%)
Bristow et al.(5) 2004	1,212	6	54	3.1+ / - 0.3	160	21	59
Higgins et al.(16) 2003	245	6	67	2.9 + / - 0.7	160 + / - 27	21 +/- 6	74
Pires et al.(17) 2006	537	6	21	3.1 + / - 0.3	168 +/- 19*	22 +/- 7*	62
Leon et al.(18) 2005	359	6	46	3.1 + / - 0.3	164 +/- 22	22 +/- 7	70
Abraham et al.(3) 2002	228	6	50	3.1 + / - 0.3	167 +/-21	22 +/- 6	68
Ypenburg et al.(19) 2006	191	6	56	2.9 + / - 0.5	163 +/- 30	21 +/- 7	76
Young et al.(4) 2003	187	6	64	3.1 + / - 0.3	165 +/- 22	24 +/- 7	70
Bleeker et al.(20) 2005	173	6	56	3.1 + / - 0.3	173 +/- 27	21 +/- 7	80
Bleeker et al.(21) 2005	170	6	55	3.2 + / - 0.4	173 +/- 27	21 +/- 8	78
Lellouche et al.(22) 2007	164	6	47	3.2 + / - 0.4	158 +/- 37	22 +/- 7	65
Bleeker et al.(14) 2006	144	3–6	53	3.1 + / - 0.4	157 +/- 26	21 +/- 8	70
Molhoek et al.(23) 2005	125	6	54	3.1 + / - 0.3	176 +/- 25	23 +/- 8	79
Boriani et al.(24) 2006	121	6	63	3.1 + / - 0.3	175 +/- 22	24 +/- 6	69
Gasparini et al.(25) 2003	104	9	55	3.0 + / - 0.7	165 +/- 37	27 +/- 7	69
Yeim et al.(26) 2007	100	6	46	3.1 + / - 0.2	158 +/- 28	27 +/- 6	71
Weighted mean		6	55.4	3.1	161.4	21.9	66.9

Bax and Gorcsan III, JACC 2009

Echocardiographic response after CRT

Reduction in LVESV

Author (years)	Pts (n)	FUP Months	Ischemic Etiology (%)	NYHA Functional Class	QRS Duration (ms)	LVEF (%)	Response Rate (%)
Yu et al. (2007)	265	3–10	56	3,1 +/- 0,4	NA	24 +/- 8	55*
Bleeker et al. (2006)	144	3–6	53	3,1 +/- 0,4	157 +/- 26	21 +/- 8	56†
Yu et al. (2005)	141	3–6	48	3,1 +/- 0,5	NA	27 +/- 7/24 +/- 11‡	62§
Yu et al. (2007)	107	3	NA	3,2 +/- 0,5	NA	27 +/- 8	58.
Fung et al. (2007)	85	3	47	3,2 +/- 0,7	NA	27 +/- 9	52.
Yu et al. (2006)	76	3	49	3,0 +/- 0,2	NA	28 +/- 10	55*
Jansen et al. (2006)	69	3	55	3,1 +/- 0,3	172 +/- 30	21 +/- 7	55†
Fung et al. (2007)	60	3	47	3,2 +/- 0,3	150 +/- 27/155 +/- 24‡	23 +/- 8/23 +/- 7‡	52.
Soliman et al. (2007)	60	12	42	3,0 +/- 0,3	170 +/- 27/171 +/- 31‡	19 +/- 4/17 +/- 3‡	78*
Jansen et al. (2008)	57	3	53	3,1 +/- 0,2	169 +/- 28	22 +/- 7	65§
Yu et al. (2005)	56	3	50	3,2 +/- 0,4	NA	26 +/- 9	54†
Yu et al. (2006)	55	3	51	3,2 +/- 0,4	NA	26 +/- 9	53†
Murphy et al. (2006)	54	6	54	3,0 +/- 0,3	157 +/- 34	27 +/- 8	44†
Yu et al. (2004)	54	3	41	3,2 +/- 0,4	147 +/- 25/155 +/- 33‡	25 +/- 10	57†
Zhang et al. (2006)	50	3	48	3,2 +/- 0,4	151 +/- 27	27 +/- 9	60§
Weighted mean		4,5	50,8	3,1	160	24,4	56,9

Bax and Gorcsan III, JACC 2009

CRT Optimization

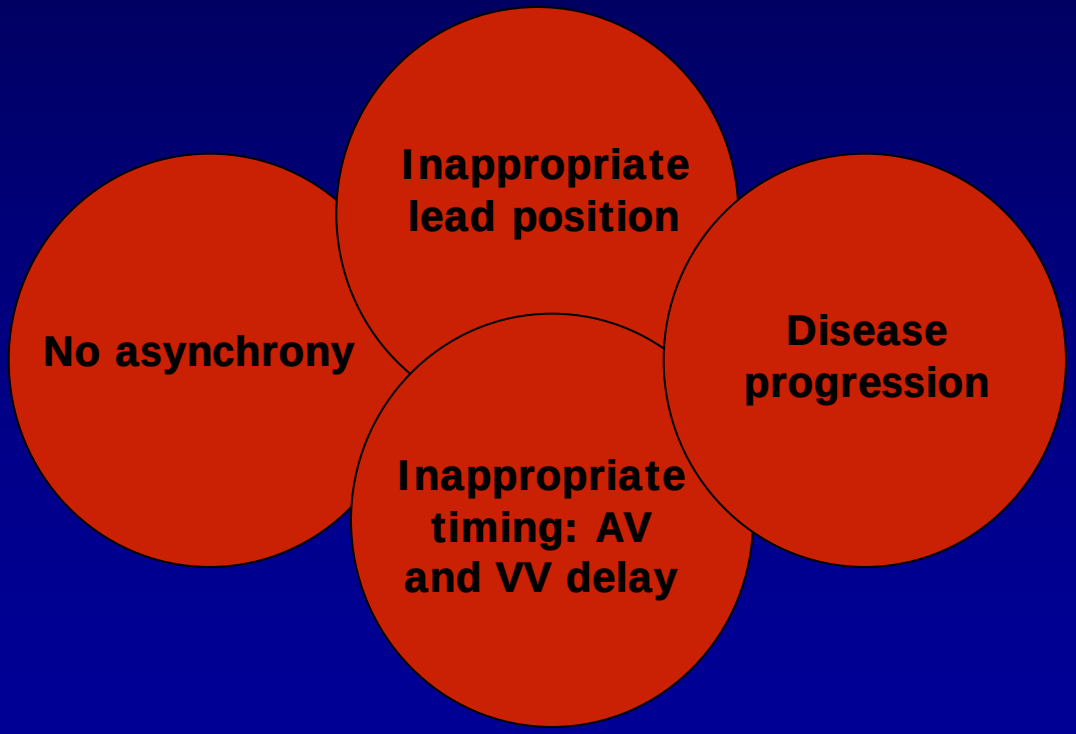
- ***Timing Cycles Were Optimized In Every Major Clinical Study***
- ***Existing CRT implant Guidelines are based on these trials***

Clinical Trial	AV delay	Optimization Frequency
PATH-CHF II	Optimized	Pre-discharge. Every follow-up
CARE HF	Optimized	Pre-discharge. Every follow-up.
MIRACLE	Optimized	Pre-discharge. Every follow-up
COMPANION	Optimized	Pre-discharge. Every follow-up

Non Responders

So …….. 30-40% of CRT patients do not have a positive response to Cardiac Resynchronization Therapy [1-3]

Reasons for CRT non-response



Abraham WT, CRT in chronic heart failure N Engl J Med 2002;346:1845-1853;
Cazeau S, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay N Engl J Med 2001;344:873-880
Young JB, Abraham WT et al. Combined CRT and implantable cardioversion defibrillation in advanced chronic heart failure JAMA 2003;289:2685-2694

CRT Optimization

- The theory behind CRT optimization is that CRT can be programmed specifically to meet the needs of an individual patient in such a way that a non-responder or suboptimal responder will derive more benefit (and even full benefit) of CRT

- Two main device-based approaches
  - Promoting CRT
  - Optimizing timing
    - AV timing
    - VV timing

Goal of CRT Optimization

Goal of AV Optimization

- Promote biventricular pacing
- Increase diastolic filling time
- Decrease diastolic mitral regurgitation
- Improve cardiac output
- Improve acute hemodynamics and early clinical response to CRT

Goal of VV Optimization

- Improve:
  - Ejection fraction
  - Cardiac output
  - Chamber efficiency
- Increase LV dP/dt, LV filling time

AV Optimization vs. “Out-of-the-box”

AV optimization improved clinical status vs. nominal settings

Data at 3 months	AV Optimization (n = 20)	120 ms (n = 20)	VTI vs. 120
NYHA improvement (≥ 1 class)	75%	40%	P < 0.03
QOL improvement	23 points	13 points	P < 0.03
EF improvement	7.8%	3.4%	P < 0.02
LVEDV change	–34 mL (P < .05 baseline)	–20 mL (P = NS)	P = NS

Sawhney NS, Waggoner AD, Garhwal S, et al. Randomized prospective trial of atrioventricular delayprogramming for cardiac resynchronization therapy. Heart Rhythm 2004;1(5):562-7

AV Optimization vs. “Out-of-the-box”

AV optimization improved clinical status vs. nominal settings

Data at 6 months	Echo (n = 23)	120 ms (n = 15)	Echo vs. 120
LVEF	32.1%	27.5%	P < 0.05
NYHA Class	2.1	3.0	P < 0.01

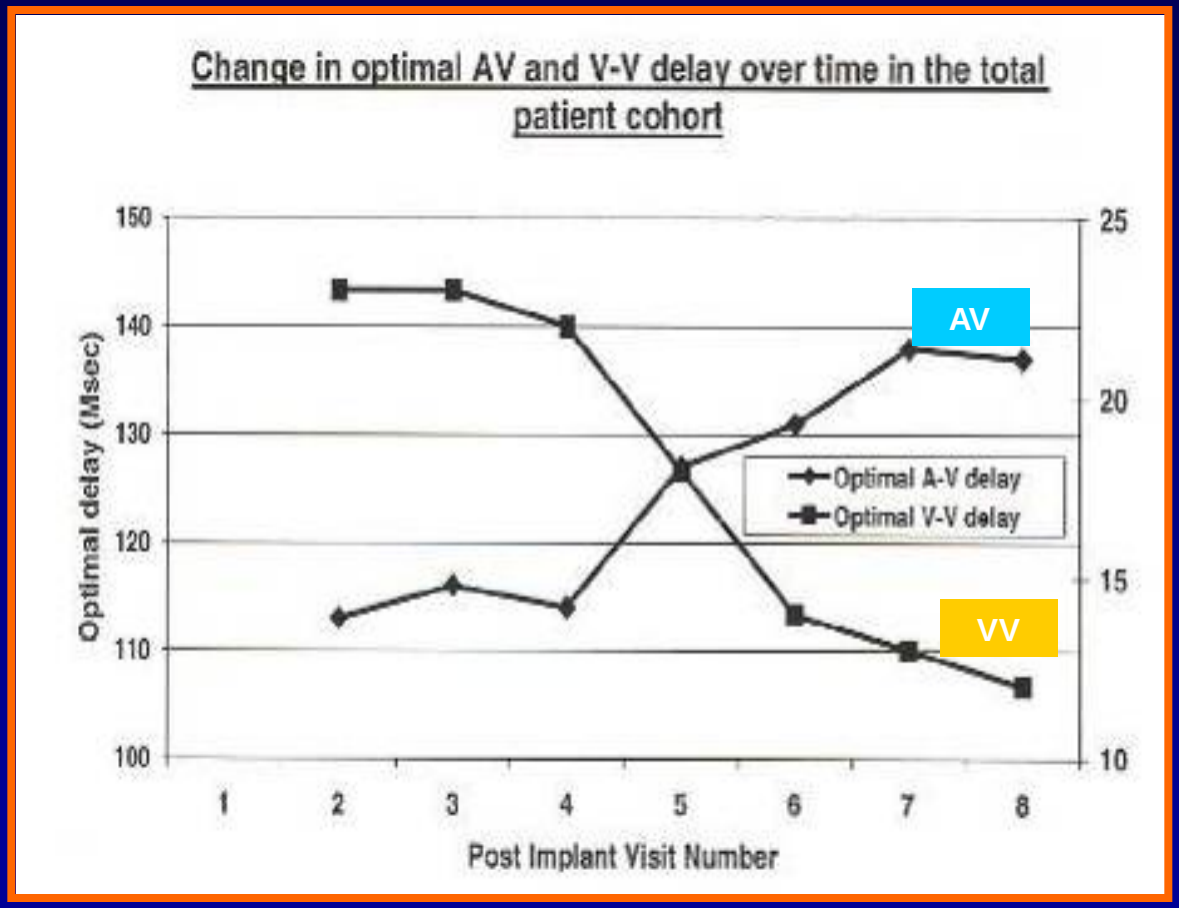
NYHA data at 6 months	Echo (n = 23)	120 ms (n = 15)
No Change	0	4
Improved 1 Class	16	11
Improved 2 Classes	7	0

Morales MA, Startari U, Panchetti L, et al. Atrioventricular delay optimizatoin by Doppler-derived left ventricular dP/dt improves 6-month outcome of resynchronized patients. PACE 2006;29:564-568

Optimal Delays change often over time

- 63 pts,
- EF < 35%
- NYHA ≥ II,
- QRS >150 ms
- LV Lead position: lateral vein or postero-lateral

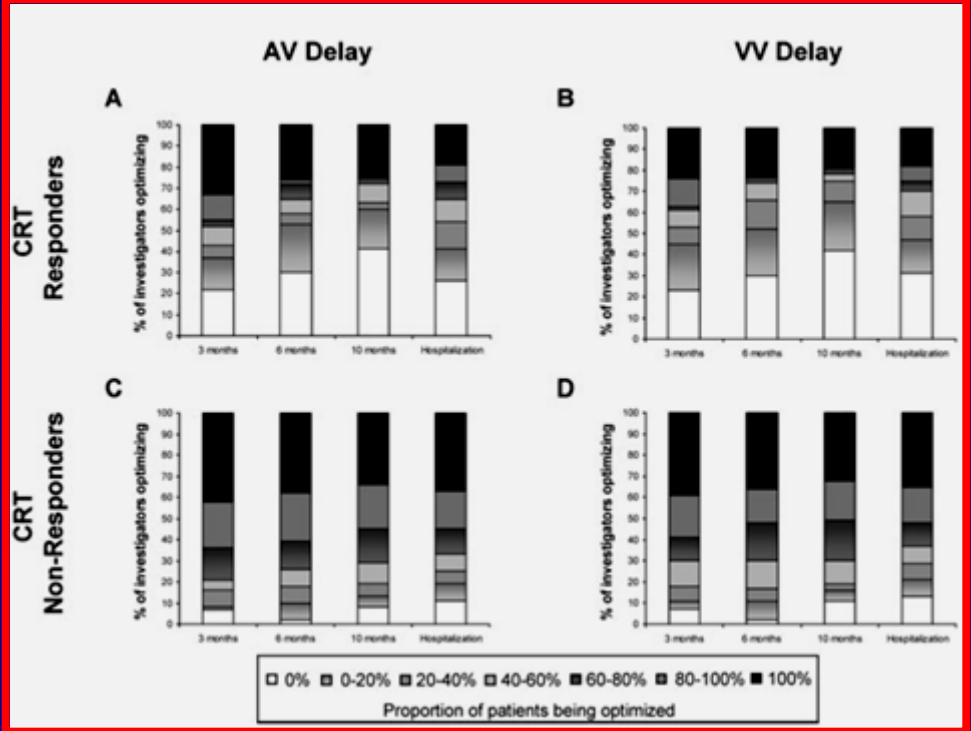
- Results:
  - Only 3 pts unchanged
  - 18 pts needed adjustments at each FU
  - VV 73 times in 27 pts
  - AV 43 times in 21 pts



O'Donnell et al., PACE 2005; 28:S24–S26)

Optimization of AV and VV Delays in the Real-World CRT Population: An International Survey

- 108 investigators from 16 countries
- To evaluate current standard of care for optimization of the A-V and V-V delays in CRT patients



13% of investigators systematically optimized the AV and VV delays

40 % of investigators did NOT optimize.

47% of investigators optimized selectively.

Non Resp. Optimized more frequently than Resp.

Factors Limiting the Use of Optimization

Fifty-six percent of investigators rated time availability as the most prominent factor limiting the optimization procedures. Lack of qualified staff was cited by 26% of investigators.

Gras et al., PACE 2009; 32:S236–S239

Echo Optimization

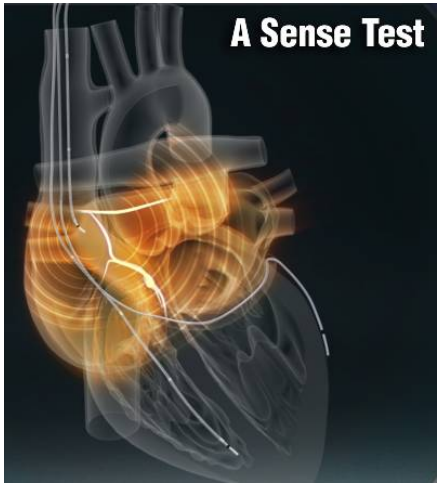
- Echocardiography is considered the "gold standard" of timing optimization
- Mitral velocity Doppler echo is used for AV timing optimization
  - CRT systems and conventional systems (ICDs, pacemakers)
  - Sensed and paced AV delays
- Aortic velocity time integral (VTI) echo is used for VV timing
  - RV and LV synchronization

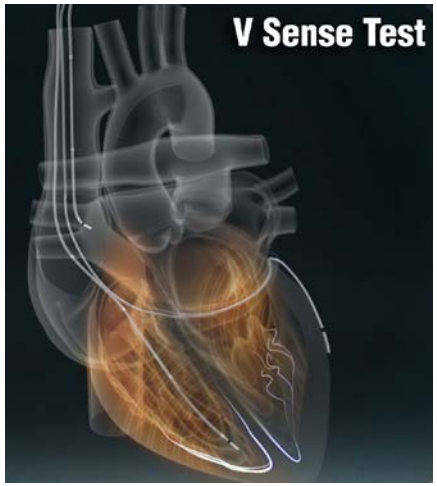
Metodi automatici device-based per l'ottimizzazione CRT

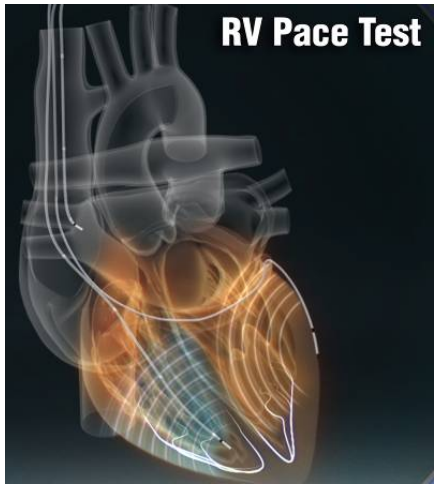
Metodi NON-emodinamici oggi disponibili		Metodi emodinamici
QuickOpt	**Smart Delay**	**Algoritmo SonR**
Basato su IEGM	Basato su IEGM	Basato su misure di **CONTRATTILITA'** cardiaca *(SonR, correlato LVdP/dt)*
Ottimizzazione eseguita solo con paziente a riposo	Ottimizzazione eseguita solo con paziente a riposo	Ottimizzazione con paz. **a riposo ed in esercizio**
Ottimizzazione eseguibile **solo** in ambulatorio **@ FU**	Ottimizzazione eseguibile **solo** in ambulatorio **@ FU**	Ottimizzazione @ FU (**manuale**) + ripetibile ogni settimana (**automatica**)
Lo studio FREEDOM dimostra che l'algoritmo **QuickOpt è NON INFERIORE** alla pratica clinica (echo)	SMART-AV dimostra che SmartDelay è **EQUIVALENTE** ad un'ottimizzazione **ecocardio oppure** ad una programmazione **empirica**	L'ottimizzazione settimanale con metodo **SonR** si è dimostrata **SUPERIORE** alla pratica clinica (studio CLEAR)

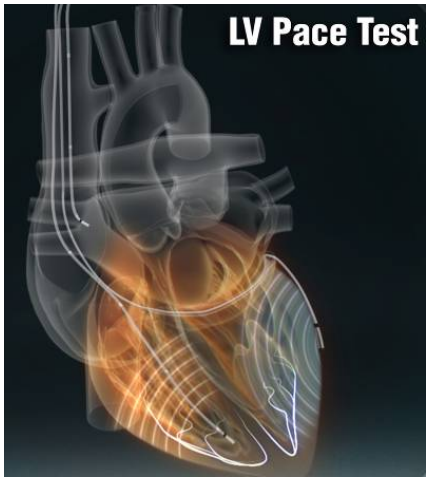
QuickOpt® - St.Jude Medical

- QuickOpt is an AV/VV optimization feature available on all St. Jude Medical High Power dual chamber and triple chamber devices. It is an IEGM programmer-based algorithm that recommends optimal AV, PV, and VV intervals for all CRT patients. QuickOpt electrically measures four conduction intervals, then calculates SAV, PAV (dual chamber and CRT-D), and VV delays (CRT-D only). Results are displayed on the programmer in about 90 seconds.
- This feature is an automatic***, in-office,*** programmer-based tool









FREEDOM trial

A total of 1647 pts (73.6% male, age 66.7 ± 11.2 years, 92.8% NYHA class III, 24.3 ± 7% LVEF, 152 ± 27.3 ms QRS duration) were enrolled

QuickOpt was shown to be equivalent to empiric programming which included echo optimization in only 32% of patients[1].

Results from the FREEDOM trial[2] demonstrated that there was a higher proportion of patients with low percent ventricular pacing (27%) in the QuickOpt arm compared to the empiric programming arm (22%).

FREEDOM failed to show superiority of QuickOpt to empiric programming.

CCS classification	OPT group (overall)		CON group (overall)		CON group (optimized)		CON group (not optimized /empiric programming)	
	N	%	N	%	N	%	n	%
Improved	520	66.58%	495	66.53%	187	68.25%	308	65.53%
Unchanged	63	8.07%	55	7.39%	23	8.39%	32	6.81%
Worsened	198	25.35%	194	26.08%	64	23.36%	130	27.66%
Total	781	100.00%	744	100.00%	274	100.00%	470	100.00%
p-value			0.86		0.80		0.53	

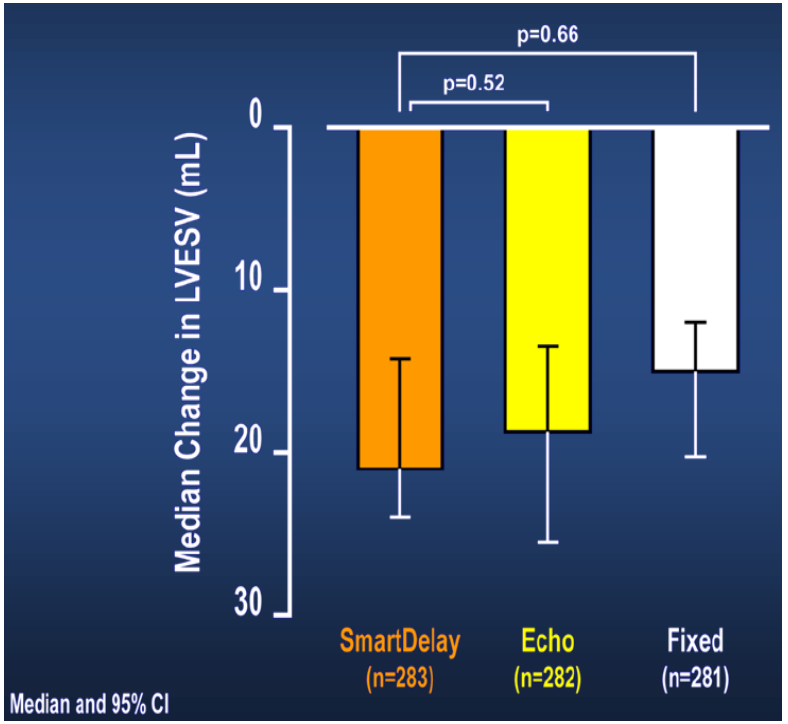
Abraham WT, Heart Rhythm 2010, Late Breaking Trial

SMART Delay – Boston Scientific

- This feature is an automatic, in-office, programmer-based tool to assess the intrinsic conduction times and recommend AV delays. It's similar to QuickOpt® from St. Jude Medical, in that it takes a few measurements and gives AV delay recommendations at one point in time based on electrical measurements of intrinsic AV interval and QRS duration.
- Designed to recommend an optimal paced and sensed AV delays to maximize LV dP/dtmax based on an individual's intrinsic conduction characteristics in 2.5 minutes or less
- No V-V optimization.

SMART-AV Trial

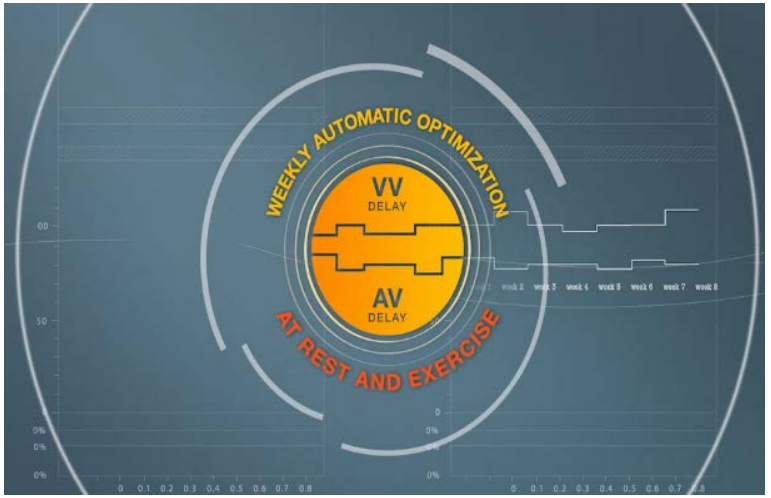
- SMART AV[1] is the first large scale trial to compare methods of optimizing AV delay, evaluate if more frequent re-optimization can improve clinical outcomes, and assess whether acute benefits translate into chronic benefits. It enrolled 1,014 patients in the US and in Europe. The change in LVESV for SmartDelay arm was no different than echocardiographic determined AV interval optimization as well as a Fixed AV delay of 120 ms.
- No difference in primary endpoint (LVESV change at 6 months)
- Smart-AV failed to show superiority of Smart-AV to nominal programming



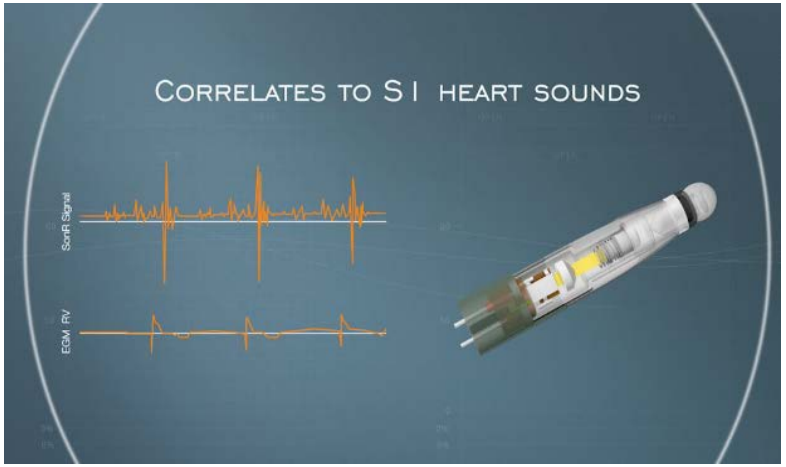
[1] Ellenbogen KA, Gold MR, Meyer TE, et al. Primary results from the SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial: a randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. *Circulation*. December 21, 2010;122(25):2660-2668.

Sorin: SonR®

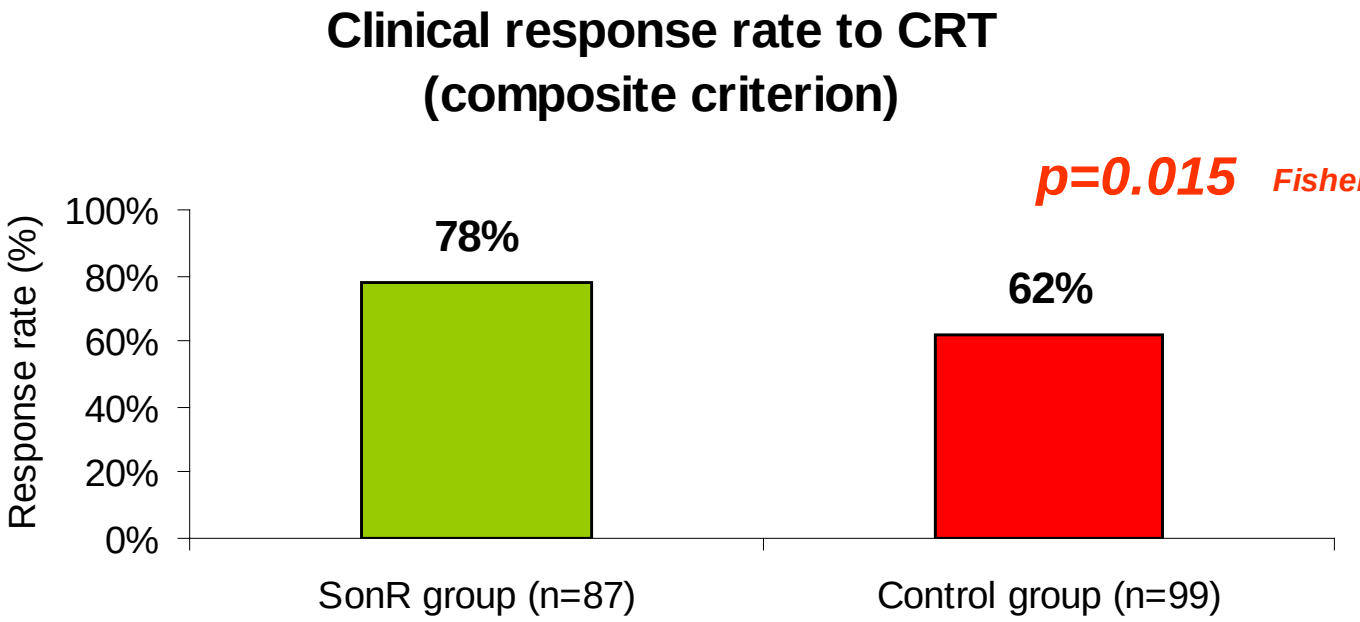
- SonR a weekly self-adjusting CRT optimization system providing optimized timing at rest and during exercise for improved CRT response



- SonR is a hemodynamic sensor embedded in the atrial pacing lead (called SonRTip) and the ParadymTMRF SonR CRT-D device. The sensor detects cardiac muscle vibrations that reflect the first heart sound and uses them to optimize AV and VV delays



CLEAR: Endpoint 1-ario (ITT)



Free from deaths / HF hospitalizations %	84%	75%	p=0.13
Riduzione NYHA %	81%	64%	p=0.0064
Aumento QOL score %	74%	65%	p=0.19

- CCC composto da: Mortalità da tutte le cause; Ospedalizzazioni da HF; Classe funzionale NYHA; Quality of Life (EuroQOL)

CLEAR: limiti & punti di forza

LIMITI

- Dispositivi CRT-P
- Elevato tasso di drop-out &/o non randomizzati
- Randomizzazione « Standard of care » (trattamento non controllato durante il FU) vs. SonR
- Classe NYHA non in doppio-cieco
- Endpoint 1-ario: significatività guidata prevalentemente dalla classe NYHA

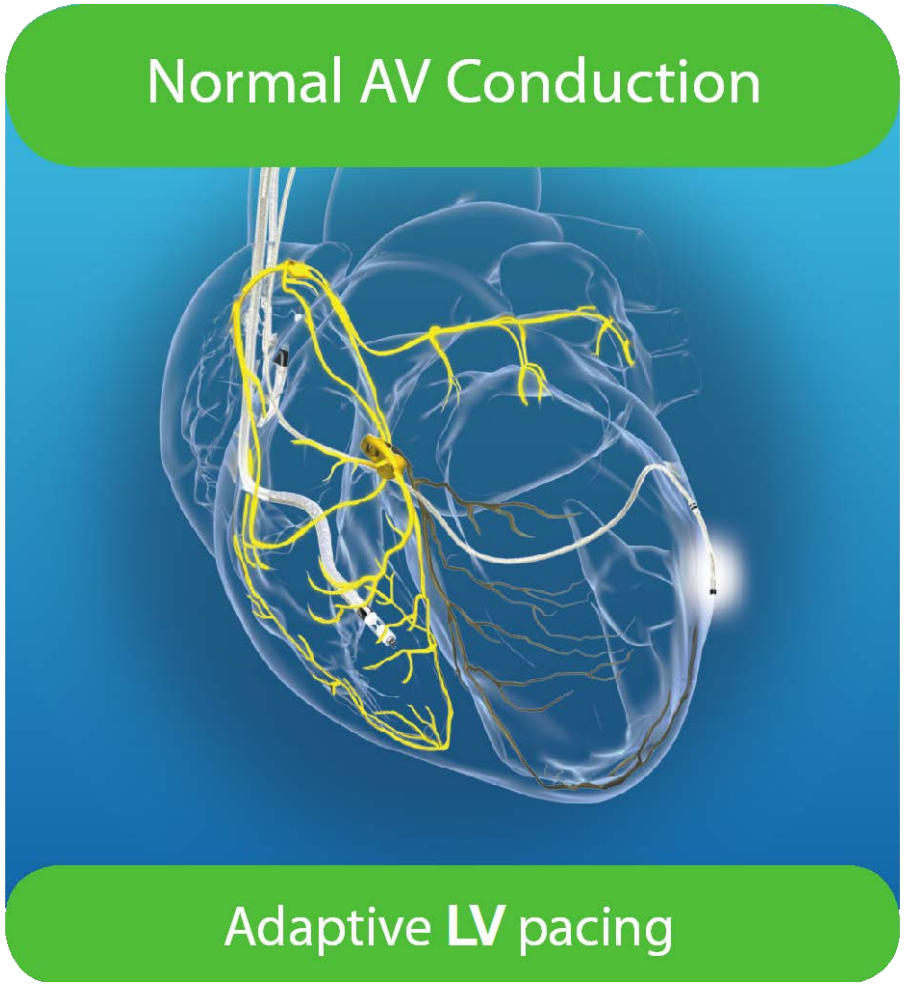
PUNTI di FORZA

- Endpoint 1-ario: significatività raggiunta vs trial IEGMs *(Smart-AV & Freedom)*
- Principio su base emodinamica (ottimizza contratt. & riempimento)
- Ripetibilità AUTOMATICA ottimizzazione

Adaptive CRT: Medtronic

- Adaptive CRT is a dynamic, physiologic pacing algorithm which enhances cardiac resynchronization therapy (CRT) by adjusting CRT parameters automatically with changes in patient activity levels and conduction status.
- Adaptive CRT means that every patient is optimized, every minute. It is a pacing algorithm that continuously and dynamically optimizes CRT pacing method and AV/VV delays according to conduction status and level of activity. It leverages a patient's intrinsic RV conduction when possible while still maintaining CRT. AdaptivCRT also provides continuous optimization of AV/VV timing settings.

Adaptive LV Pacing



Adaptive LV pacing leverages intrinsic RV conduction by pre-pacing the LV to synchronize with intrinsic RV activation[1]

- Adaptive LV promotes physiologic pacing by reducing RV pacing by 44%[2]
- Research shows that RV synchronized LV pacing is equivalent or superior to standard BiV pacing[3,4]
- In addition to the potential for an increase in CRT response, reducing RV pacing increases device longevity[1,2]

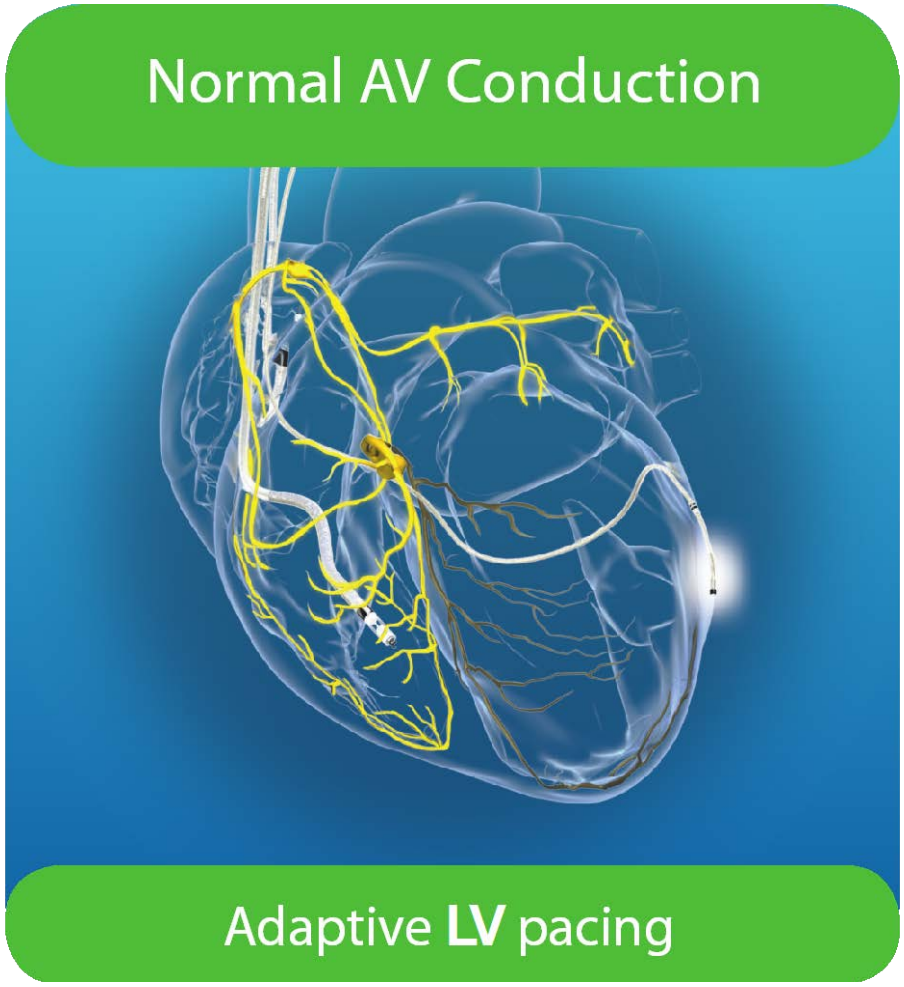
1 Medtronic Viva XT CRT-D manual.

2 Martin DO, et al. *Heart Rhythm.* Published online July 12, 2012.

3 van Gelder BM, et al. *J Am Coll Cardiol.* 2005;46:2305-2310.

4 Lee KL, et al. *J Cardiovasc Electrophysiol.* 2007;18:497-504.

Adaptive LV Pacing



Adaptive LV pacing leverages intrinsic RV conduction by pre-pacing the LV to synchronize with intrinsic RV activation

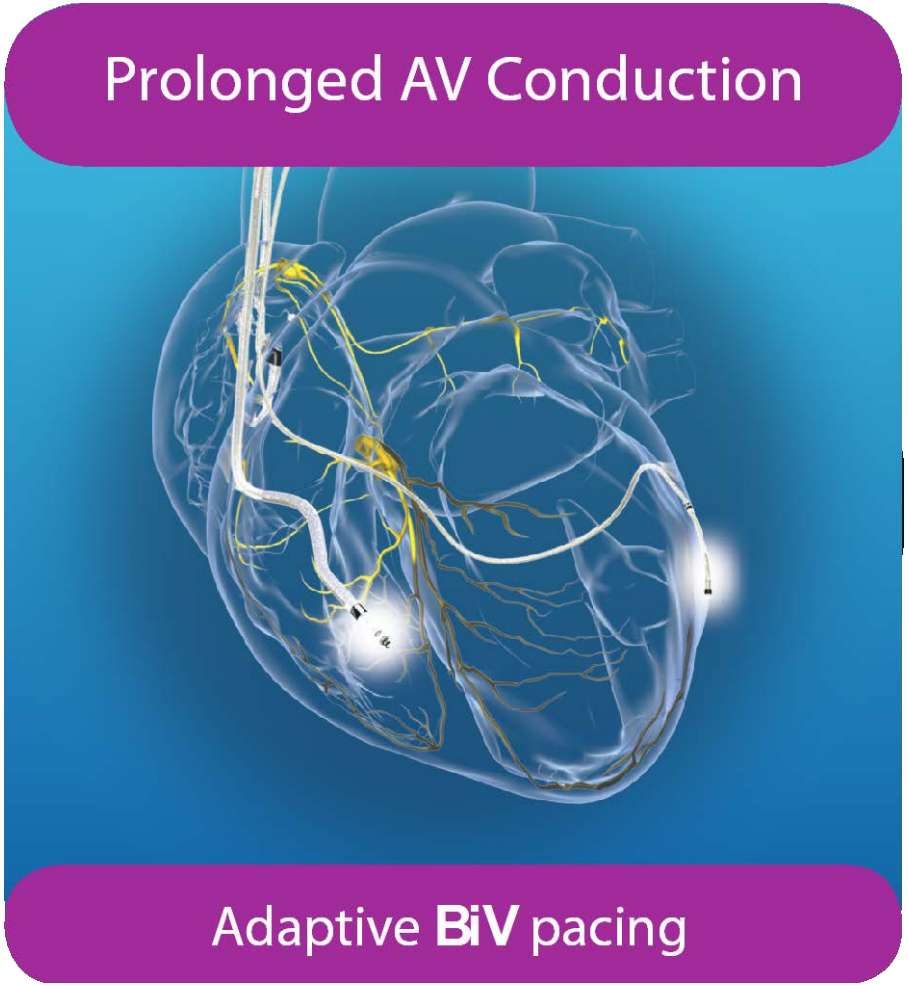
- The timing of the LV pace is automatically adjusted based on the atrial to intrinsic RV interval measurement to deliver an LV pace synchronized to the RV sense
- Adaptive LV pacing is available when 'Adaptive BiV and LV' is programmed[a,b]

[a] Adaptive LV pacing occurs if the patient's HR ≤ 100, AV conduction is normal, and LV capture is confirmed by the LVCM algorithm.

[b] Adaptive LV pacing is suspended if a tachyarrhythmia or incompatible device operation occurs.

Medtronic Viva XT CRT-D manual.

Adaptive BiV Pacing

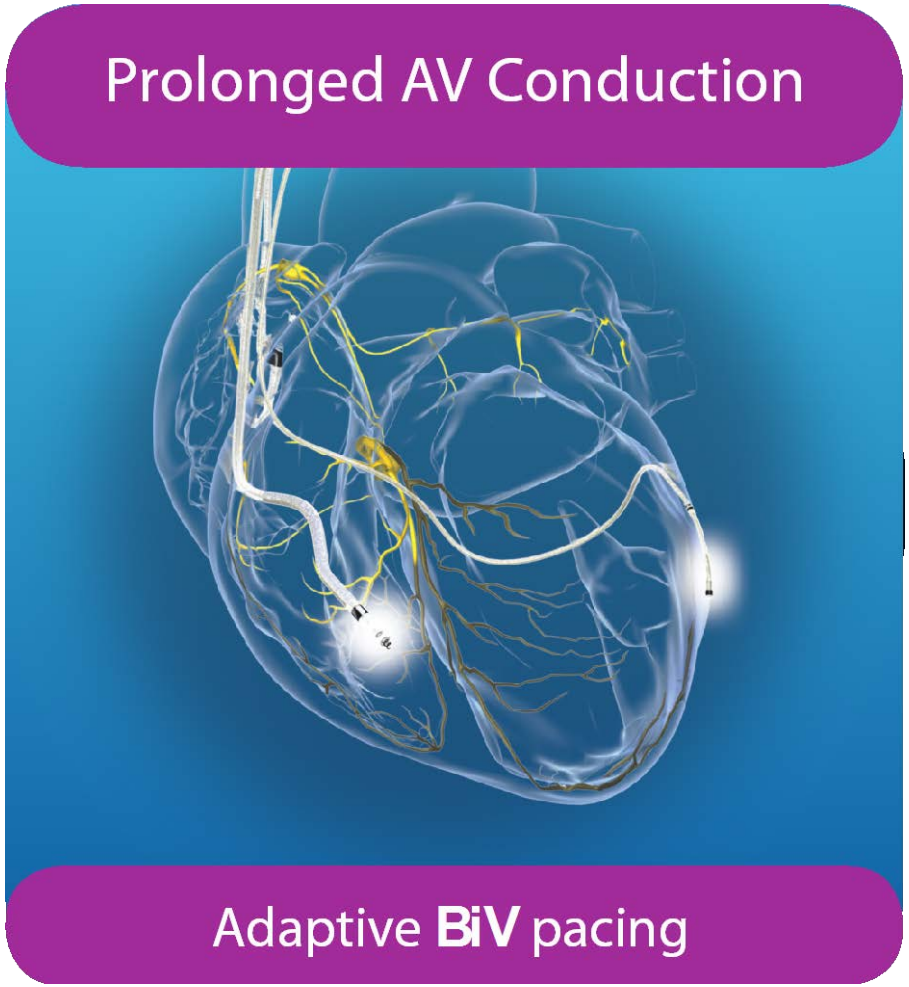


Adaptive BiV pacing automatically optimizes AV/VV delays based on changes in patient activity levels and conduction status

- Adaptive BiV provides automatic and continuous assessment of AV and VV delays
- Adaptive BiV maximizes CRT benefit by optimizing ventricular filling and ejection

Medtronic Viva XT CRT-D manual.

Adaptive BiV Pacing



Adaptive BiV pacing automatically optimizes AV/VV delays based on changes in patient activity levels and conduction status

- The AV delays are updated every minute based on AV interval and P-wave width measurements
- The ventricular pacing configuration (**RV->LV, LV->RV or LV**) and **V-V pace** delay are updated every minute based on AV interval and QRS width measurements
- Adaptive BiV pacing is available when 'Adaptive BiV and LV' or 'Adaptive BiV' is programmed*

*Adaptive BiV pacing is suspended if a tachyarrhythmia or incompatible device operation occurs.

Medtronic Viva XT CRT-D manual.

Adaptive CRT trial

OBJECTIVE:

Comparison between Adaptive CRT® algorithm and Echo optimization

METHODS:

522 patient, prospective, multicenter, randomized, double-blinded worldwide clinical trial

- NYHA Class III/IV
- QRS ≥ 120 ms
- LVEF ≤ 35%
- Randomized (2:1 ON vs. OFF)
- Rigorous & consistent echo protocol in control arm with optimizations at 1 & 6 months (AoVTI/iterative method)
- Follow-up at 6 months and 12 months

[1] Martin DO, Lemke B, Birnie D, et al. Investigation of a Novel Algorithm for Synchronized left ventricular pacing and Ambulatory Optimization of Cardiac Resynchronization Therapy. *Heart Rhythm*. October 2012 (in press). [6 mos data]

[2] Krum H, Lemke B, Birnie D,et al. A novel algorithm for individualized cardiac resynchronization therapy: rationale and design of the adaptive cardiac resynchronization therapy trial. *Am Heart J*. May 2012;163(5):747-752.e1.

Adaptive CRT trial

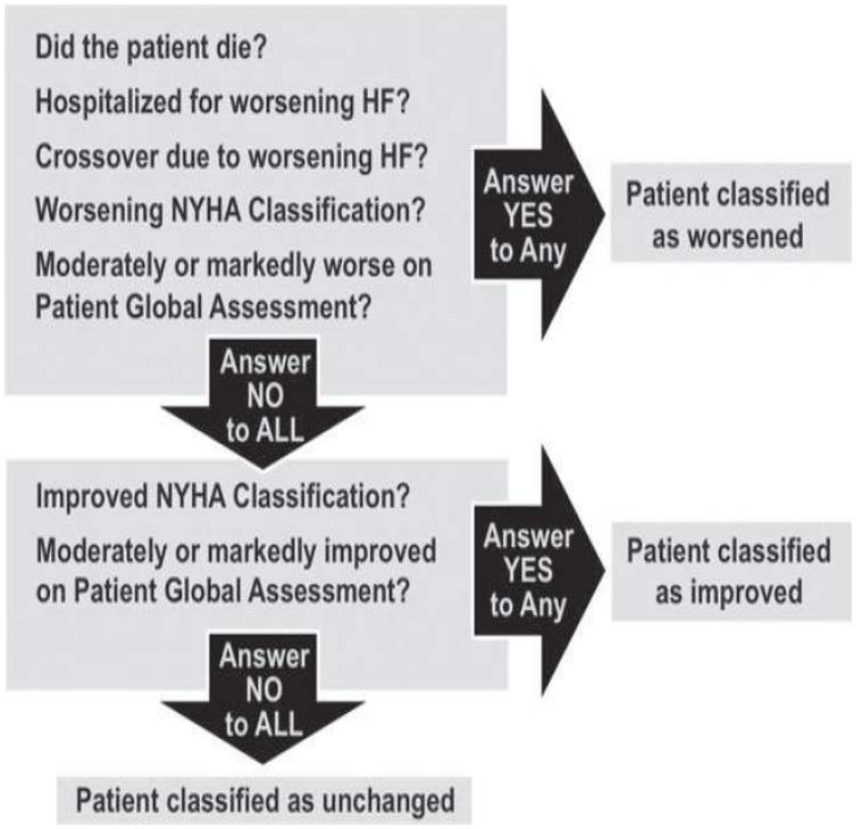


Figure 1 Clinical composite score definition. HF = heart failure; NYHA = New York Heart Association.

PRIMARY END POINT (6 Mos):

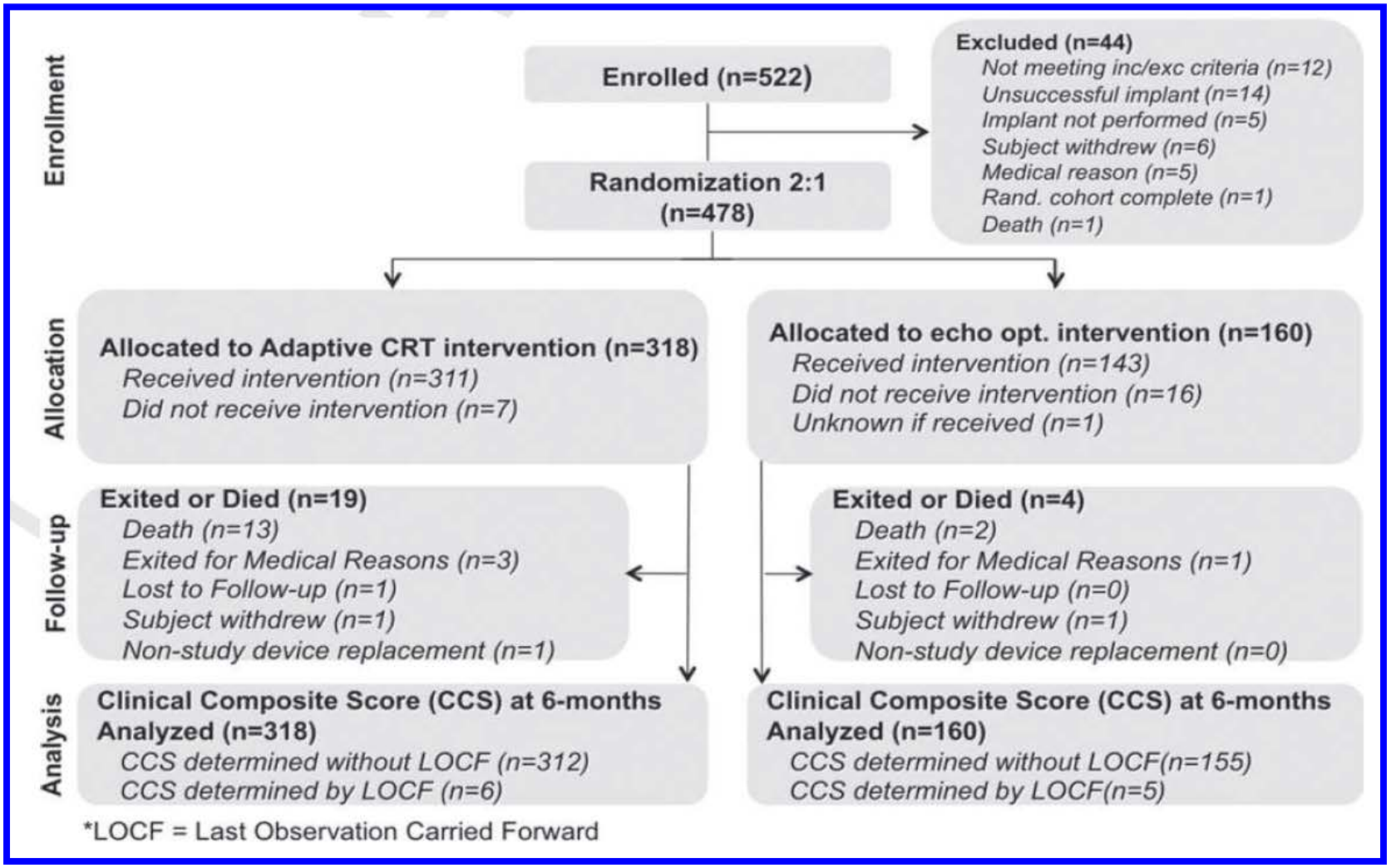
1. Clinical Composite Score (non-inferiority)
2. Cardiac Performance/Aortic VTI (non-inferiority)

RESULTS:

- AdaptivCRT algorithm was safe and at least as effective as BiV pacing with comprehensive echo optimisation across a variety of primary and secondary endpoints

Adaptive CRT trial

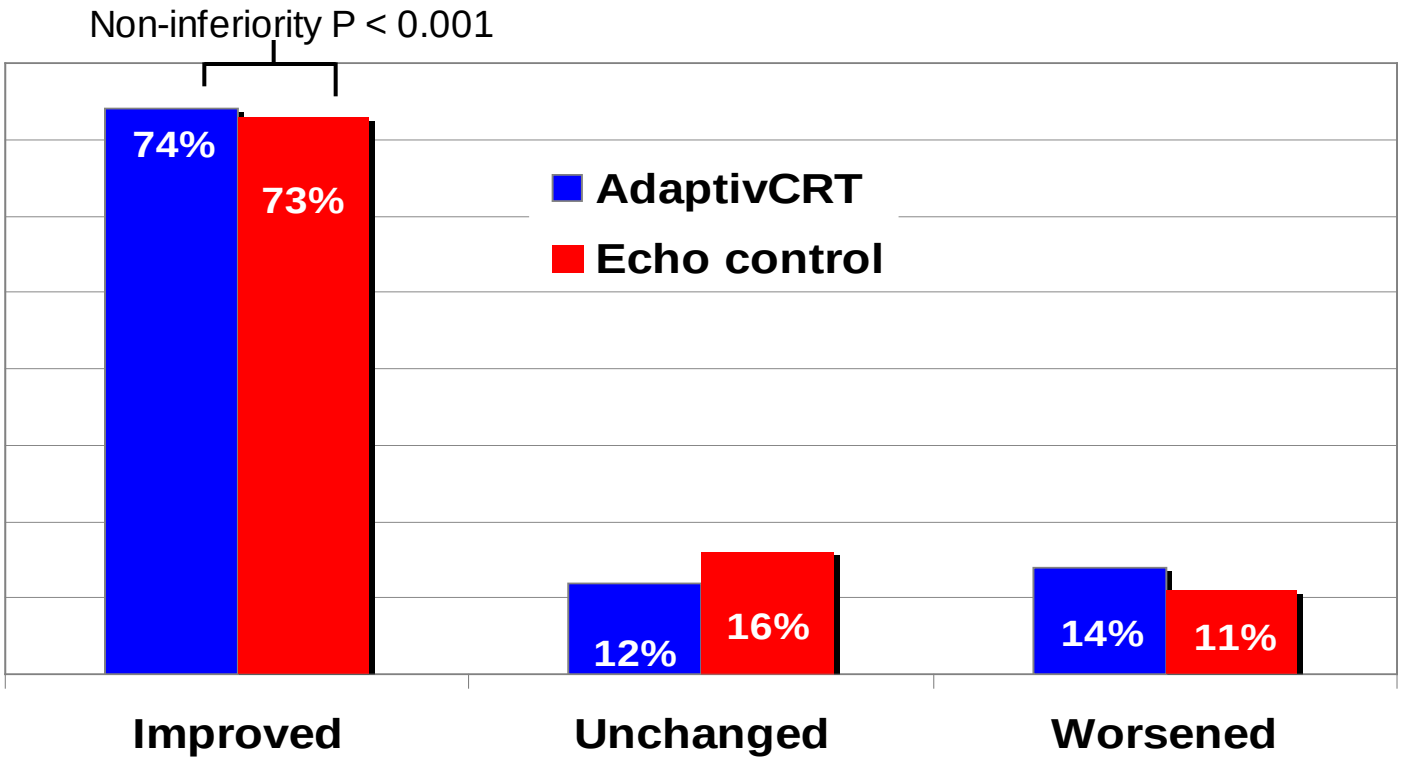
Flow diagram of clinical composite score



Adaptive CRT trial

Primary Endpoint 1(Clinical Composite Score):

AdaptivCRT® is Non-Inferior to Echo Optimization at 6 months

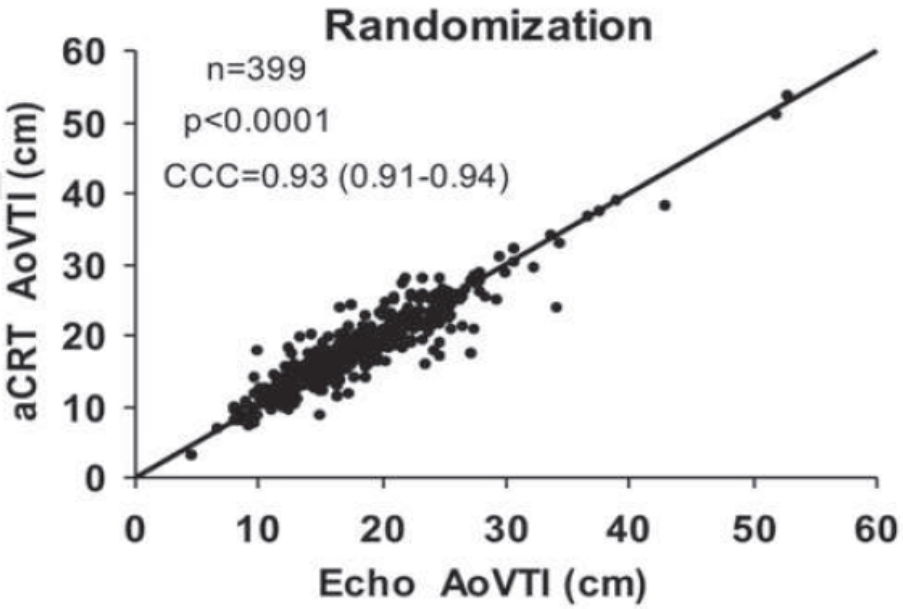


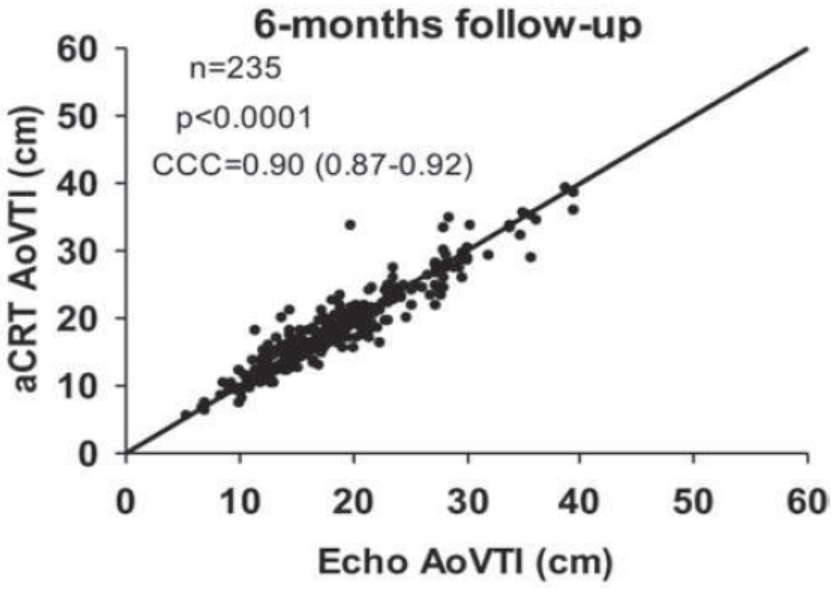
[1] Martin DO, et al. *Heart Rhythm*. Published online July 12, 2012.

Adaptive CRT trial

Primary Endpoint 2 (Cardiac Performance):

AdaptivCRT® is Non-Inferior to Echo Optimization at 6 months

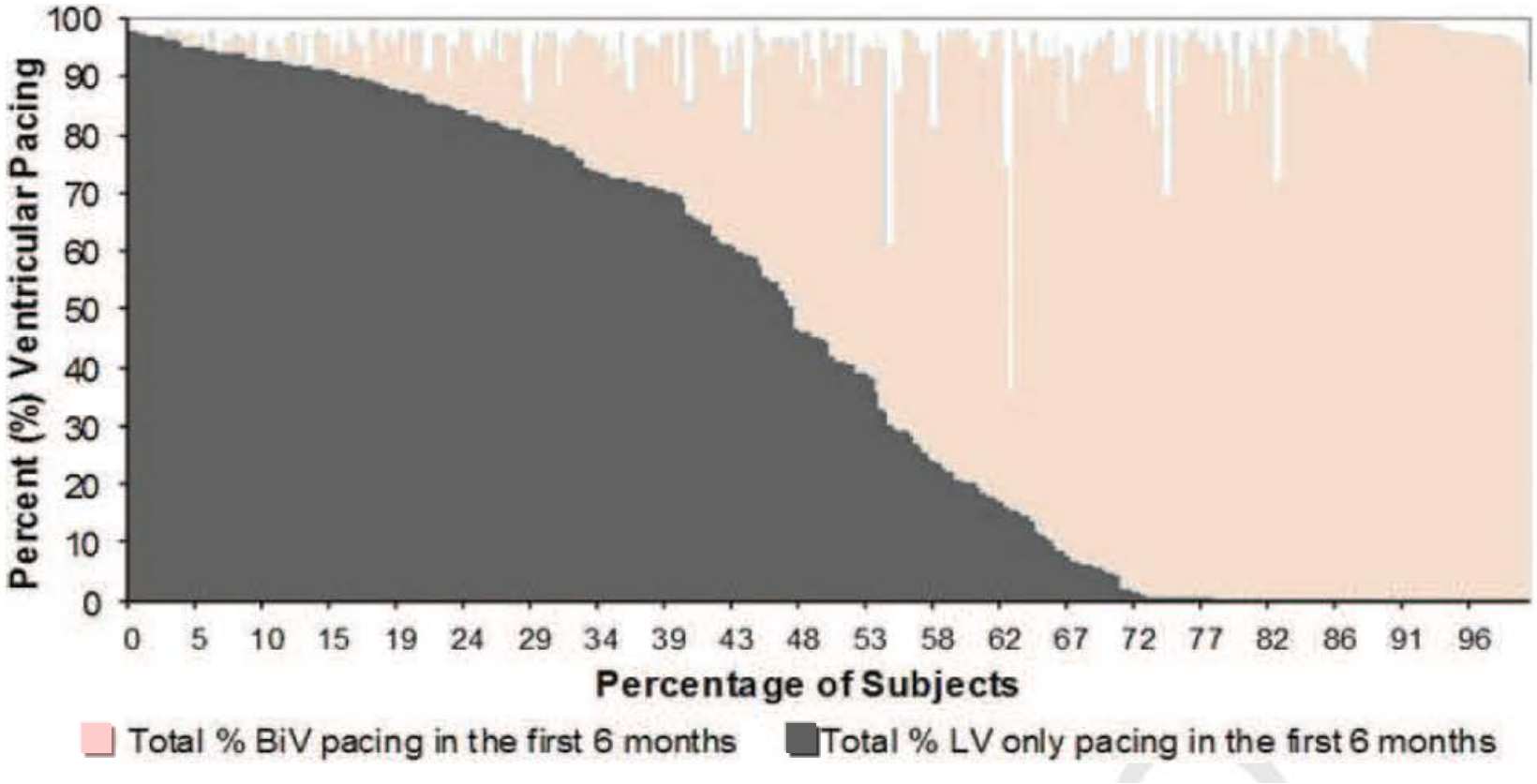




The second primary endpoint compared echocardiographic aortic velocity time integral (AoVTI) at the settings calculated by the aCRT algorithm and settings obtained using echocardiographic optimization protocol.

Adaptive CRT trial

Distribution of LV-only and biventricular pacing in the aCRT arm.



Adaptive CRT trial: Limitations

- The specific echocardiographic opti… r the treatment arm may h… s or no optimizati…
- … V … s … o
- … aCRT alg… 30 ms. It is possible that sm… adverse impact on clinical condition.
- Mi… interrogation data from aCRT patients (5.3% of the patients had at least 1 interrogation missing) could have had safety-related information.

Conclusions

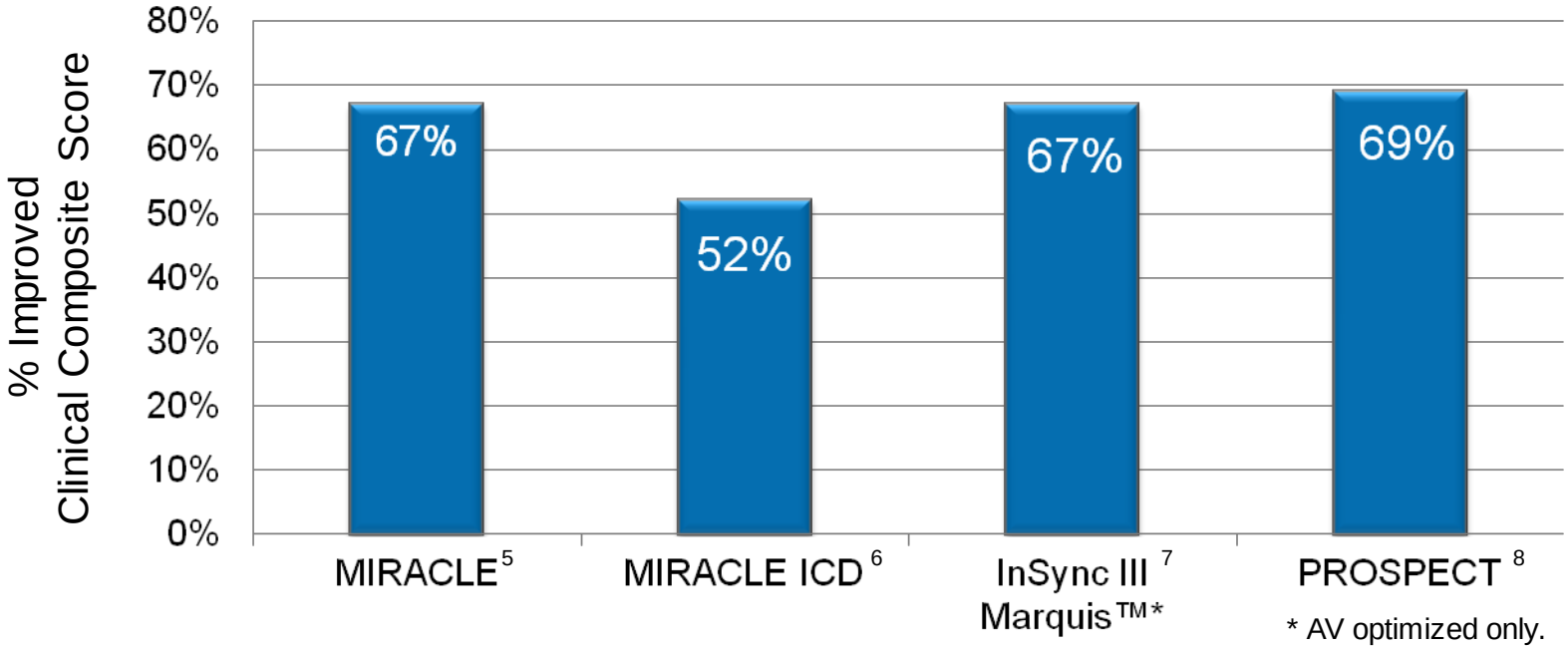
The aCRT algorithm is safe and at least as effective as BiV pacing with comprehensive echocardiographic optimization

AdaptivCRT® Response Analysis[4] Analysis of Clinical Response as Compared to Historical Trials

[4] Singh JP, Shen J, Chung ES. Clinical response with Adaptive CRT algorithm compared with echo guided AV optimization: a propensity score analysis of multi-center trials. Presentation at European Society of Cardiology Congress August 2012.

AdaptivCRT® Response Analysis[4]

Historical Cohort



Historical cohort comprised of MDT trials using Packer Clinical Composite score as end point

[4] Singh JP, Shen J, Chung ES. Clinical response with Adaptive CRT algorithm compared with echo guided AV optimization: a propensity score analysis of multi-center trials. Presentation at European Society of Cardiology Congress August 2012.

[5] Abraham WT, et al. *N Engl J Med*. 2002;346:1845-1853.

[6] Young JB, et al. *JAMA*. 2003;289:2685-2694.

[7] Abraham WT, et al. *Heart Rhythm*. 2005;2:S65.

[8] Chung ES, et al. *Circulation.* 2008;117:2608-2616.

AdaptivCRT® Response Analysis[4]

Methodology

Historical CRT cohort

n = 1,003 pts

Historical cohort includes MIRACLE, MIRACLE ICD, InSync III Marquis™*, and PROSPECT.

AdaptivCRT cohort

n = 318 pts

* AV optimised only.

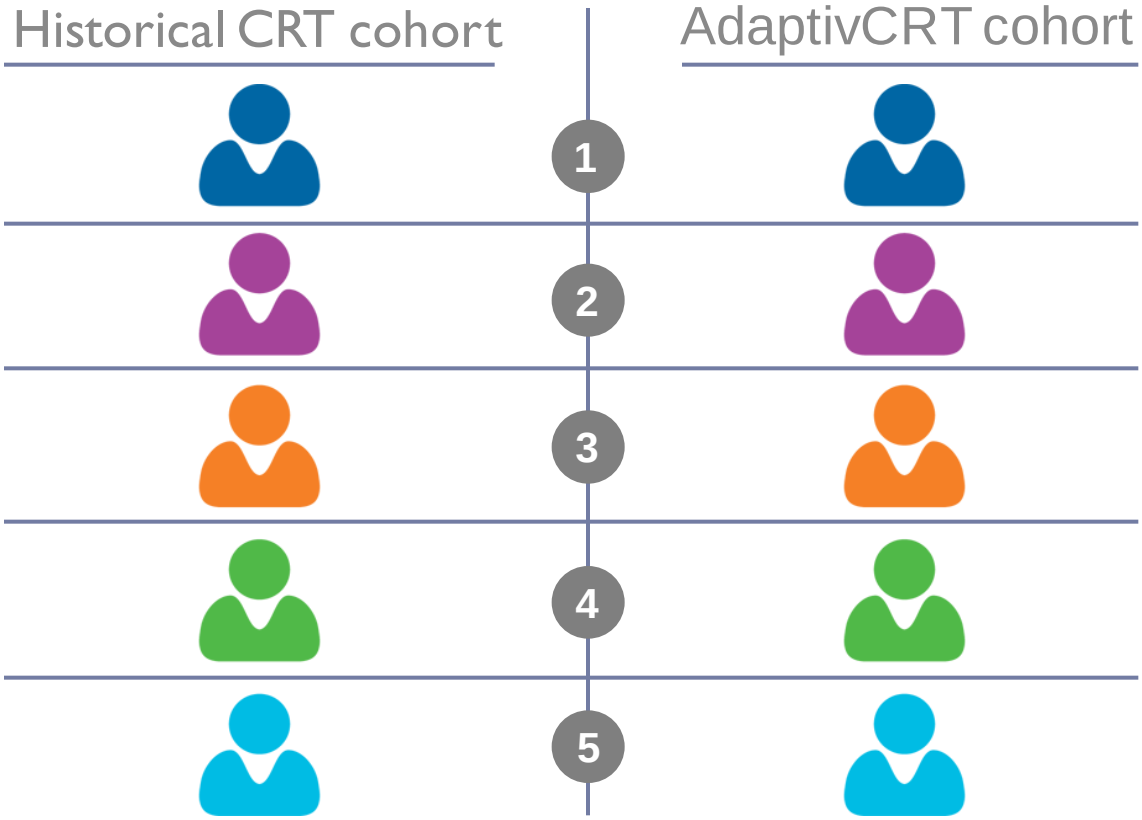
[4] Singh JP, Shen J, Chung ES. Clinical response with Adaptive CRT algorithm compared with echo guided AV optimization: a propensity score analysis of multi-center trials. Presentation at European Society of Cardiology Congress August 2012.

AdaptivCRT® Response Analysis[4]

Analysis:

1. Patients matched with similar baseline characteristics into 5 subgroups.
2. Patients without a match were discarded.

Methodology



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AdaptivCRT® Response Analysis[4]

Baseline Characteristics

22 Baseline Characteristics taken into account including:

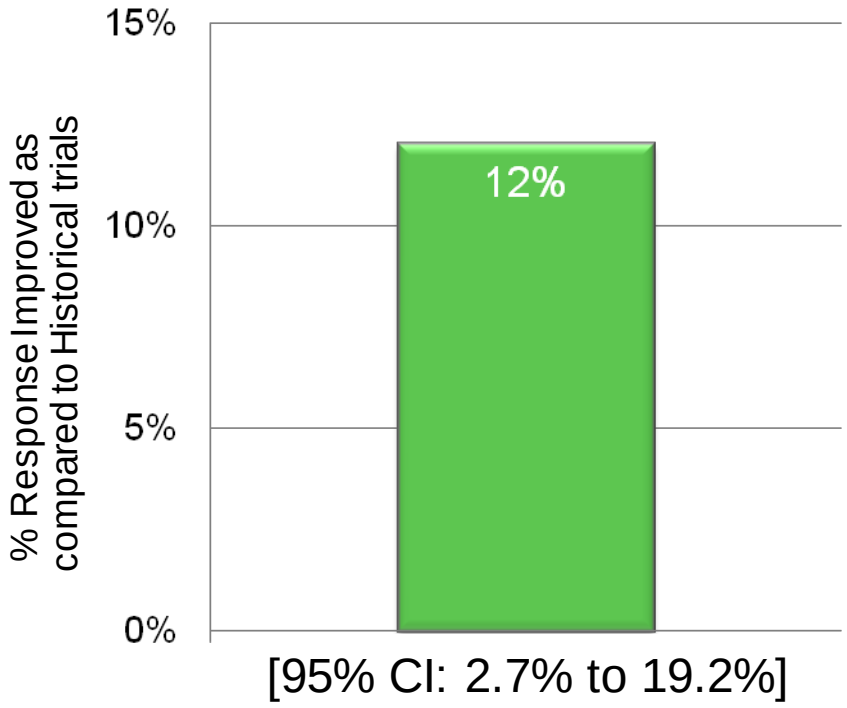
- Heart Dimension
  (LVEDD, LVEDV, LVESD, LVESV)
- LBBB
- QRS
- Ischemic vs. Non Ischemic Cardiomyopathy
- Beta Blocker Utilisation

[4] Singh JP, Shen J, Chung ES. Clinical response with Adaptive CRT algorithm compared with echo guided AV optimization: a propensity score analysis of multi-center trials. Presentation at European Society of Cardiology Congress August 2012.

AdaptivCRT® Response Analysis[4]

A 12% Absolute Higher Response Rate was Achieved with AdaptivCRT Compared to Historical CRT Trials

Differences between the clinical composite scores of the Historical and AdaptivCRT cohorts were averaged across the subgroups.



4 Singh JP, Shen J, Chung ES. Clinical response with Adaptive CRT algorithm compared with echo guided AV optimization: a propensity score analysis of multi-center trials. Presentation at European Society of Cardiology Congress August 2012.


Ottimizzare la terapia di resincronizzazione per tutti i pazienti: un po' meno sogno e un po' più realtà