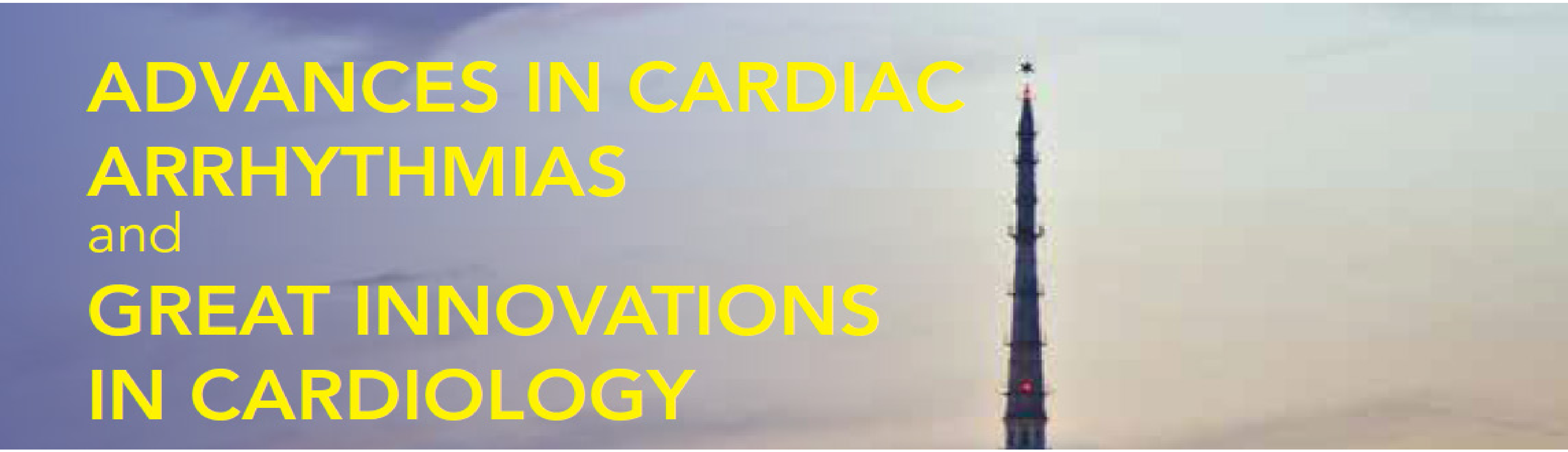
Adaptive-ness and effective-ness: the two primary goals to achieve in CRT



Roberto Rordorf

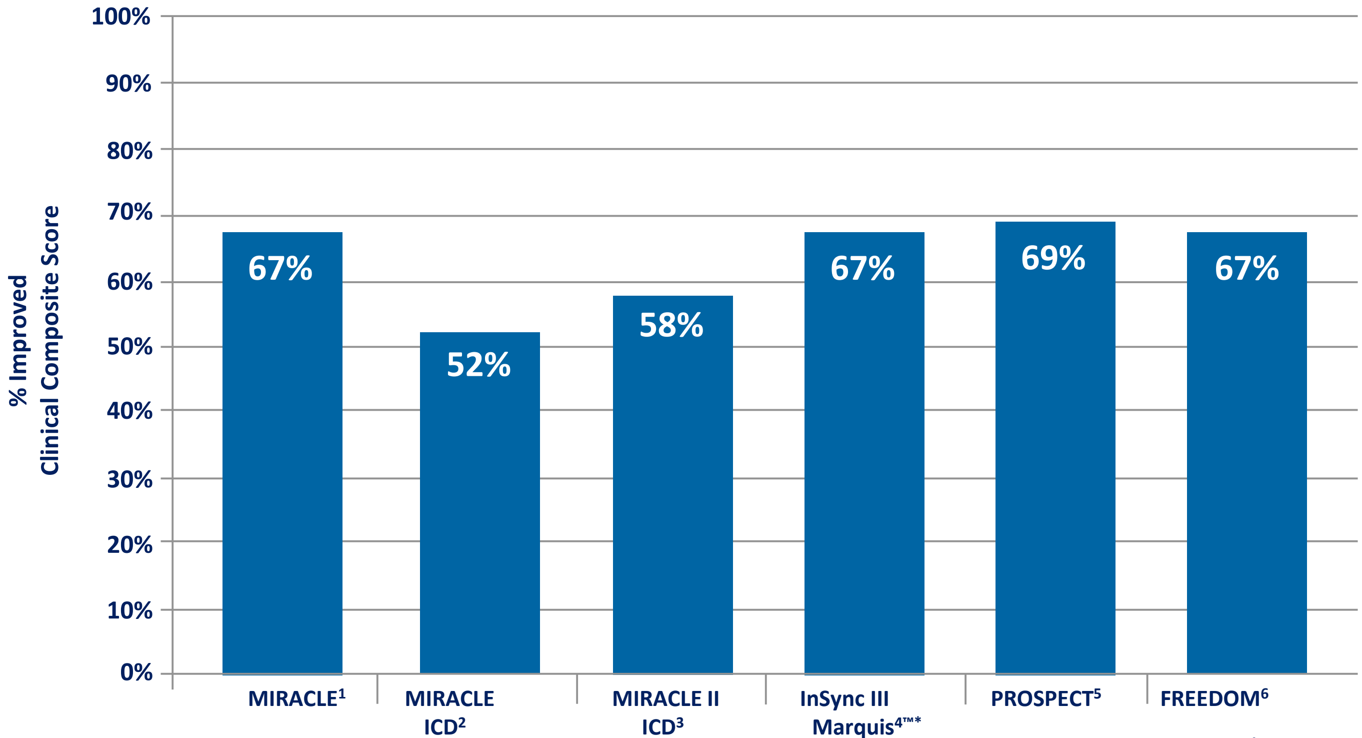
Unità di Elettrofisiologia, Divisione di Cardiologia

IRCCS Policlinico S. Matteo, Pavia

Torino, October 14th 2016

CRT Response Rates

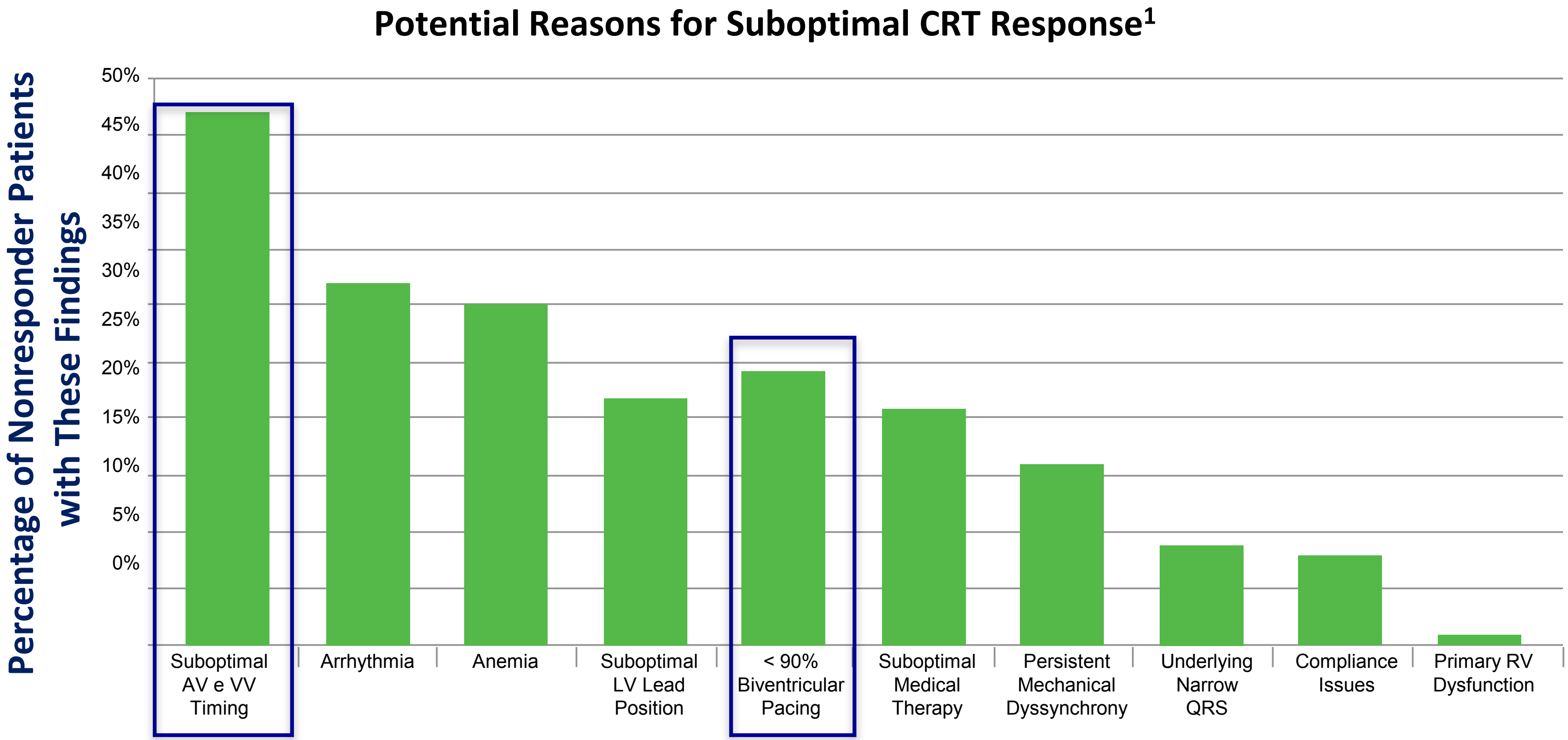
One-third of patients do not experience the full benefit of CRT[1-6]



*AV optimised 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.

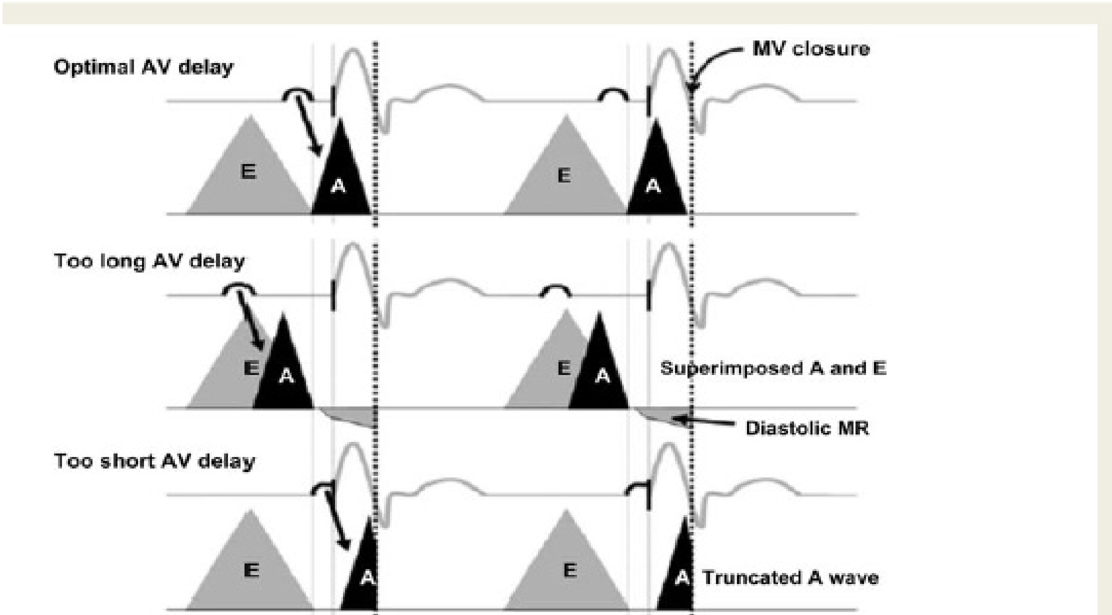
There are Many Drivers for CRT Non-Response



Achieving maximum CRT response requires a multi-disciplinary approach.

Mullens W, et al. JACC. 2009;53:765-773.

Rational for AV e VV optimization

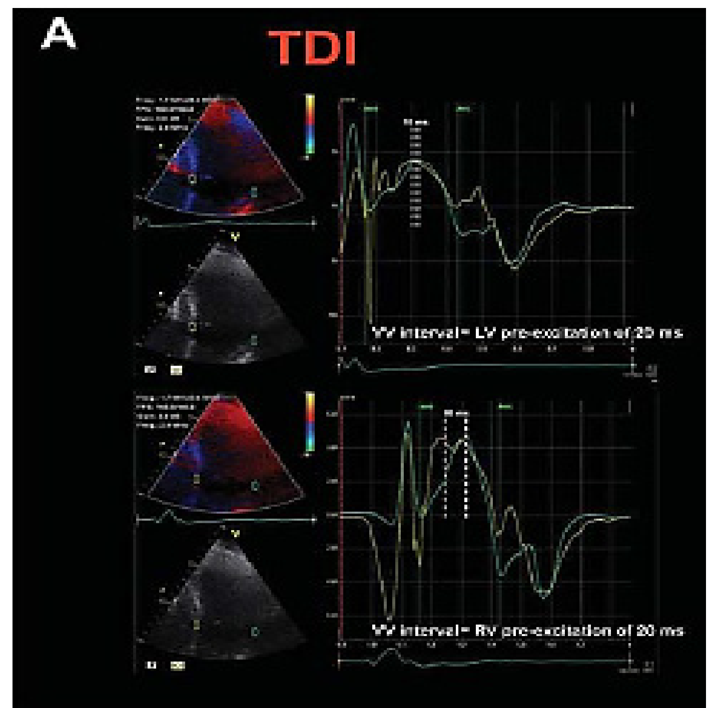


Optimal AV
✓ Maximization of LV filling before MV closure

Optimal VV

✓ Compensate for LV delays:

- suboptimal LV lead position,
- abnormal global activation,
- regional conduction delays across infarcted myocardium

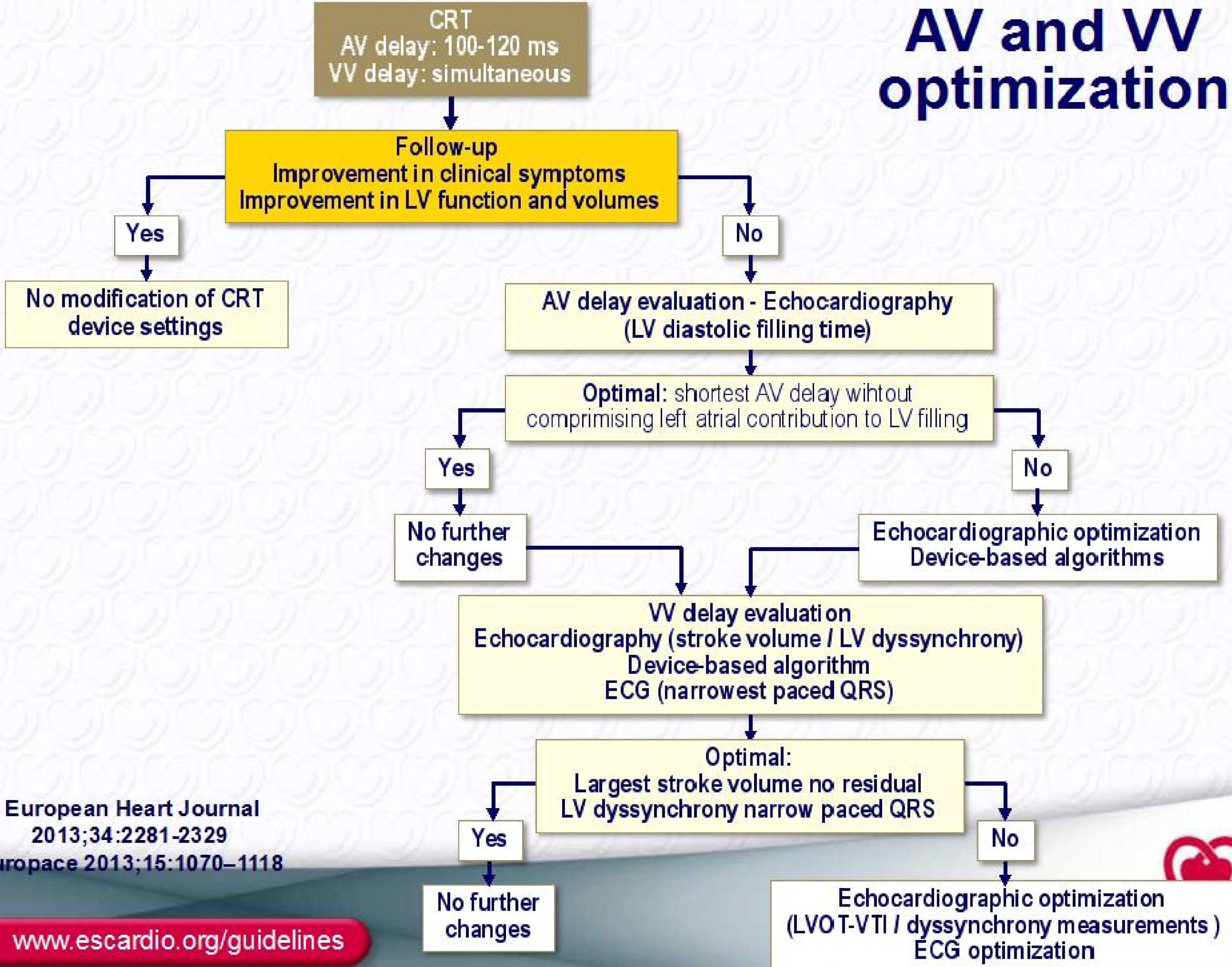


Summary of evidence for AV e VV optimization

Parameter	Standard (current practice)	CRT optimization	Additional clinical benefit (compared to standard)
LV lead position	Posterolateral	• Avoid apical • Target latest activated area	• Benefit likely (less hospitalization for HF) • Benefit likely (one RCT more responders, less hospitalization for HF)
AV delay	Fixed empirical AV interval 120 ms (range 100–120 ms)	• Echo-Doppler: shortest AV delay without truncation of the A-wave (Ritter's method) or change in LV systolic function	• Uncertain or mild (one small RCT and several observational positive)
		• Device-based algorithms (SmartDelay, QuickOpt)	• Uncertain (two RCTs negative)
VV delay	Simultaneous BiV	• Echo: residual LV dyssynchrony	• Uncertain or mild (one RCT showed mit benefit)
		• Echo-Doppler: largest stroke volume	• Uncertain (one RCT negative, one controlled positive)
		• ECG: narrowest LV-paced QRS; difference between BiV and preimplantation QRS	• Unknown (no comparative study)
		• Device-based algorithms (Expert-Ease, Quick-Opt, Peak endocardial acceleration)	• Uncertain or mild (three RCTs)
LV pacing alone	Simultaneous BiV	n.a.	Non-inferior

2013 ESC guidelines on pacing and CRT

AV and VV optimization



European Heart Journal 2013;34:2281-2329
Europace 2013;15:1070–1118

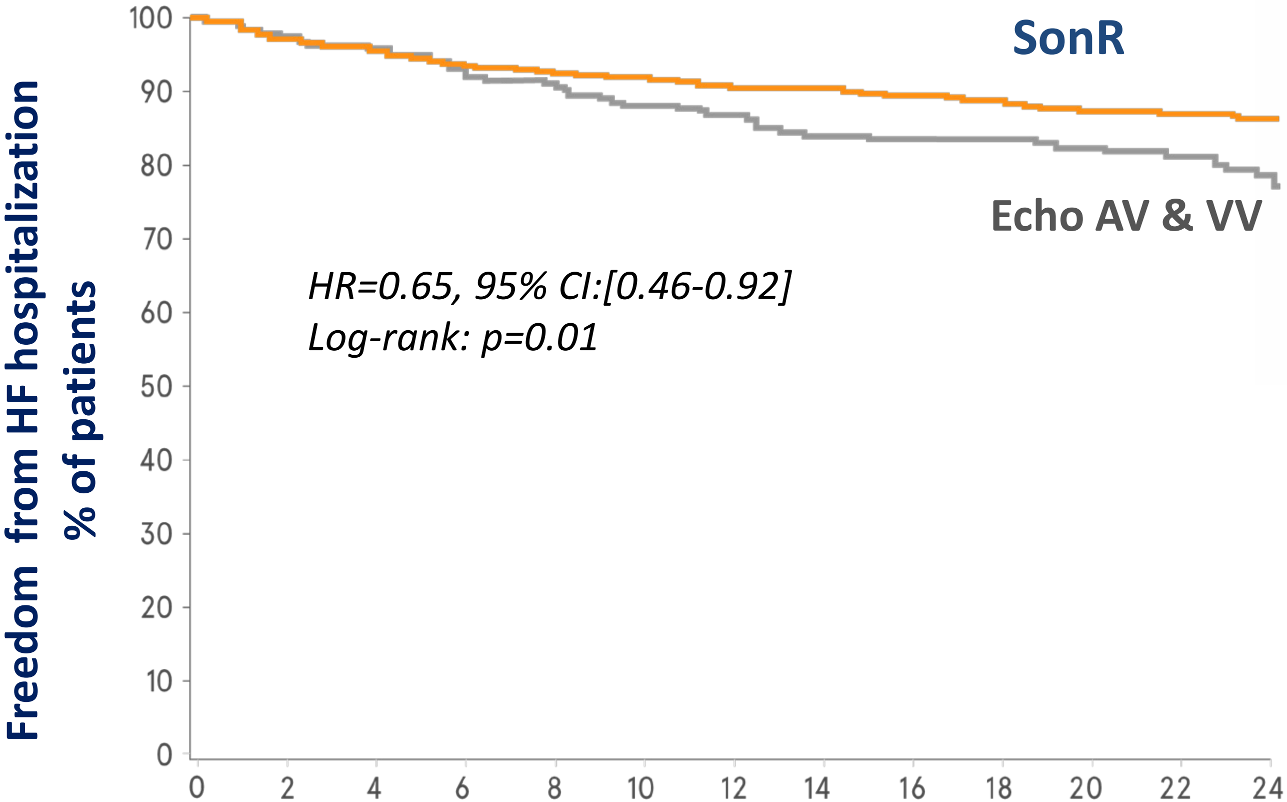
Reasons for lack of efficacy Of AV & VV optimization in clinical practice

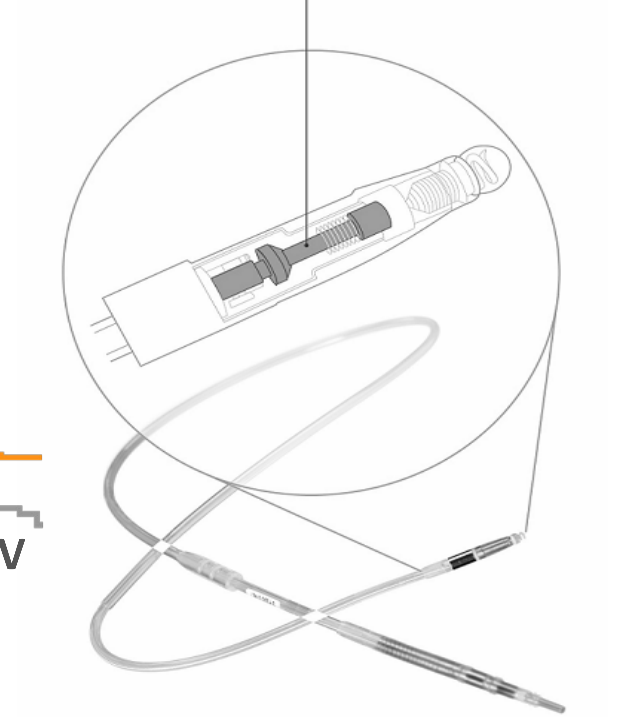
- ✓ Time consuming (usually performed just once)
- ✓ Usually performed at rest (variation over time, exercise)
- ✓ Limited evidence in favour of one method (ECG, ECHO)

Device algorithms for AV and VV optimization

- ✓ Quick Opt (St.Jude Medical)
- ✓ Smart AV (BSC)
- ✓ SonR (Livanova-Sorin)
- ✓ Adaptiv CRT (Medtronic)

Respond CRT Trial





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. Heart Rhythm 2016, Late Breaking Clinical trials

BIV vs. LV only pacing

block: The Bi vs Left Ventricular Pacing: An International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias (BELIEVE) multicenter prospective randomized pilot study

Gasparini M et al. Am. Heart J 2006

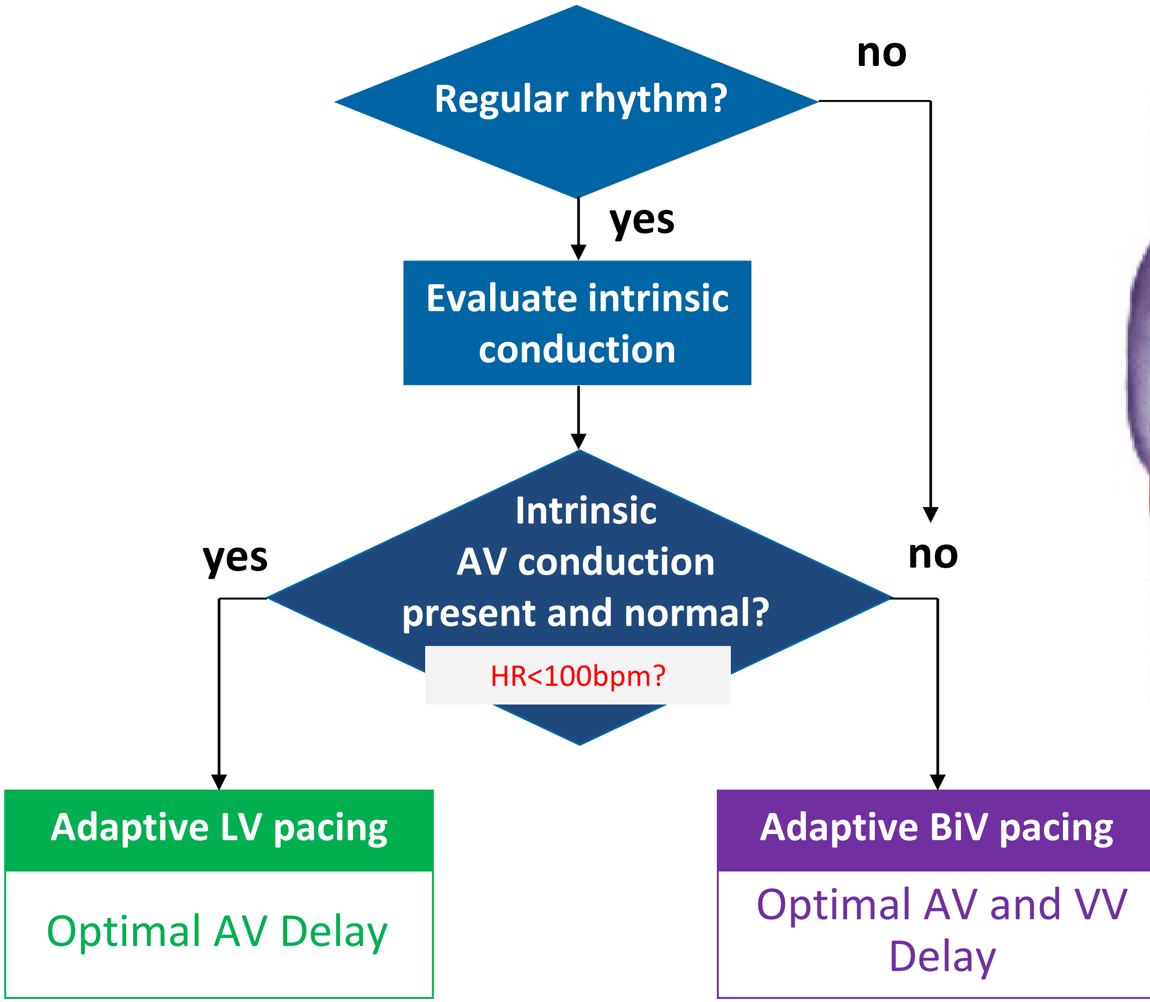
A randomized double-blind comparison of biventricular versus left ventricular stimulation for cardiac resynchronization therapy: The Biventricular versus Left Univentricular Pacing with ICD Back-up in Heart Failure Patients (B-LEFT HF) trial

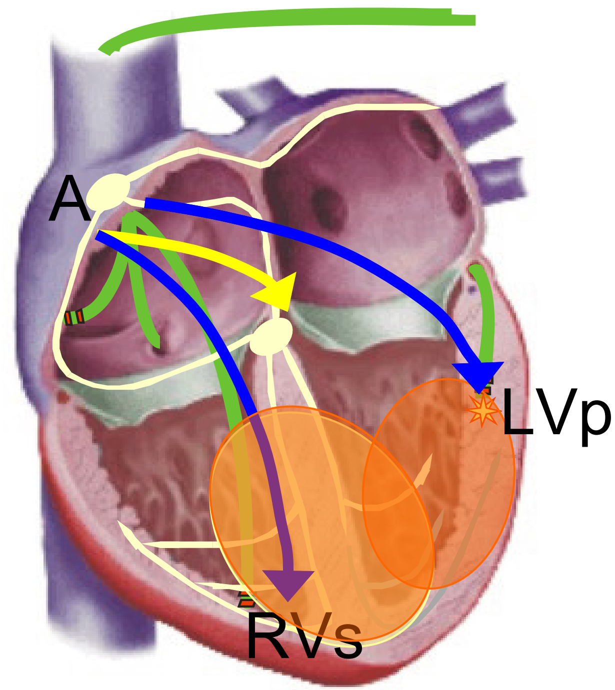
Boriani G et al. Am. Heart J 2010

Left Ventricular Versus Simultaneous Biventricular Pacing in Patients With Heart Failure and a QRS Complex ≥120 Milliseconds

Thibault B et al. Circulation 2011

AdaptivCRT Algorithm





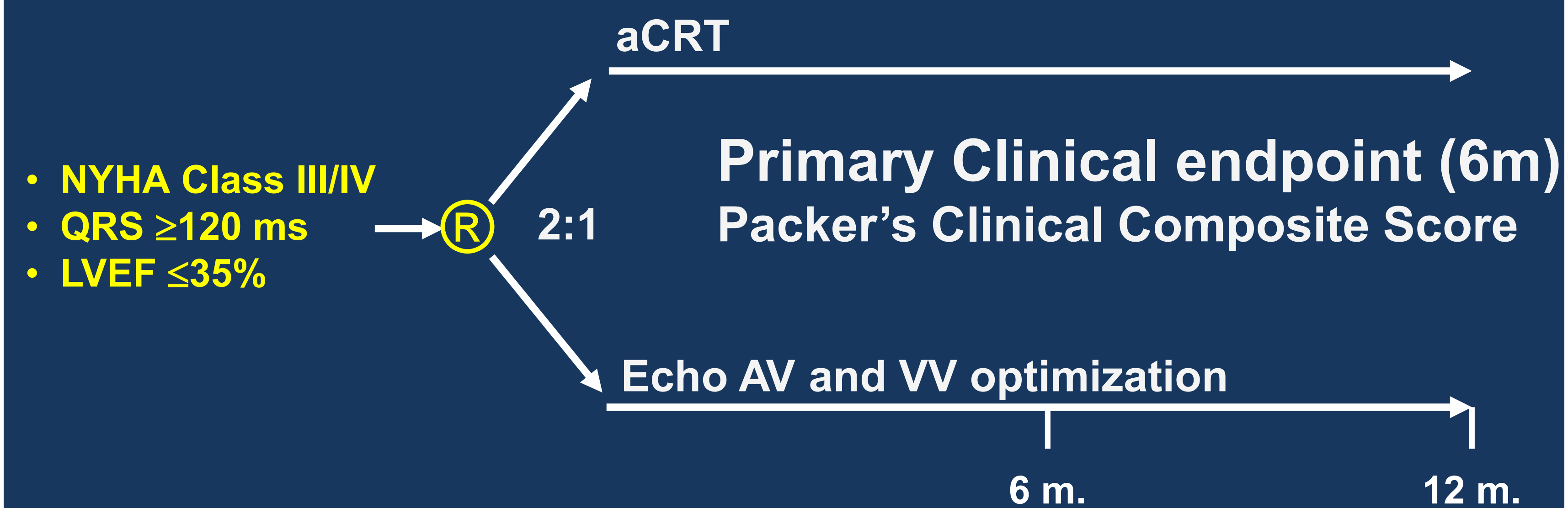
Adaptive CRT Study

Comparison between aCRT and Echo-optimized BiV pacing

Randomized
n=478

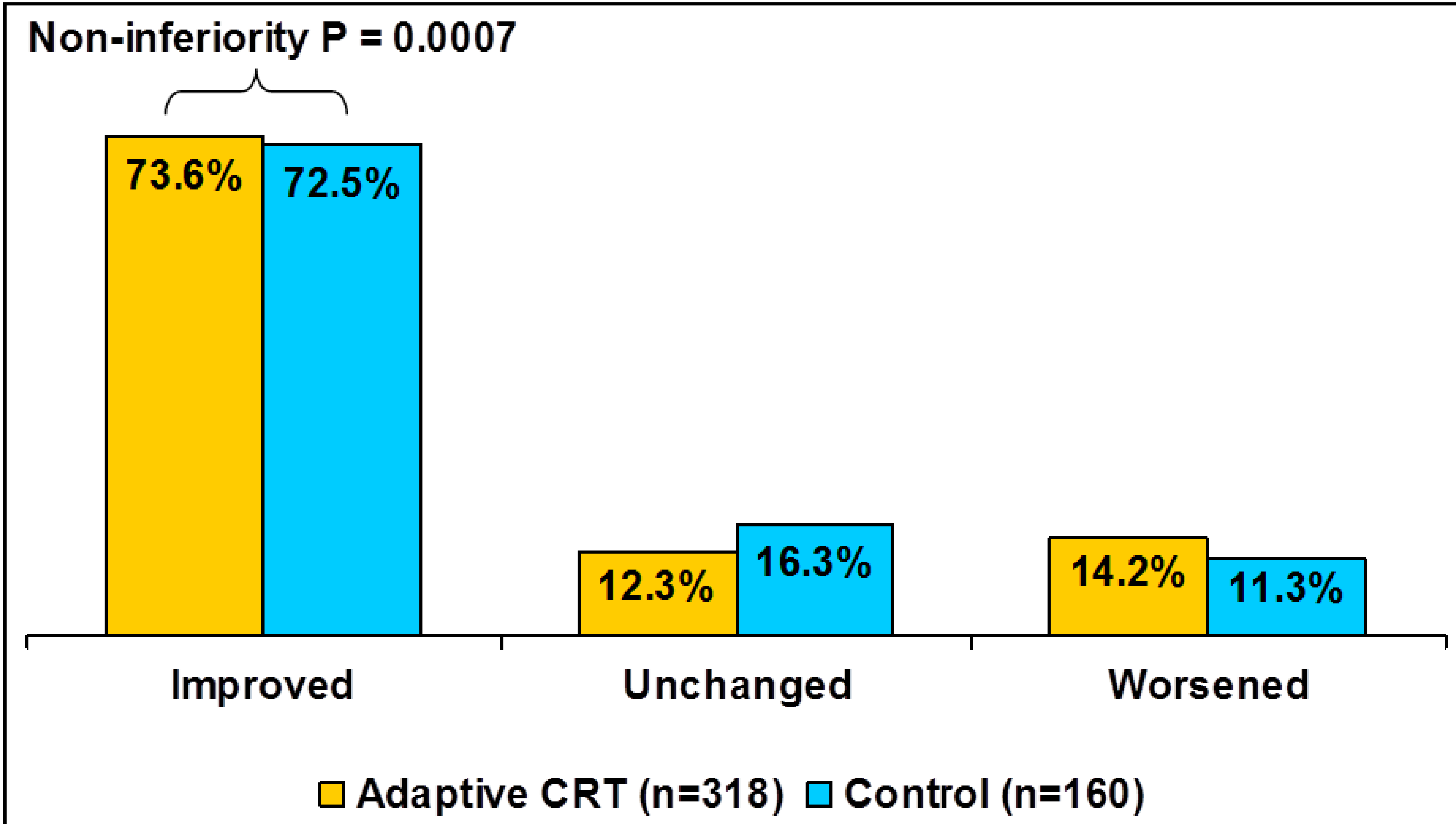
Randomization
Double-blinded

Follow-up



Krum H et al. Am Heart J 2012 ; 163: 747-752

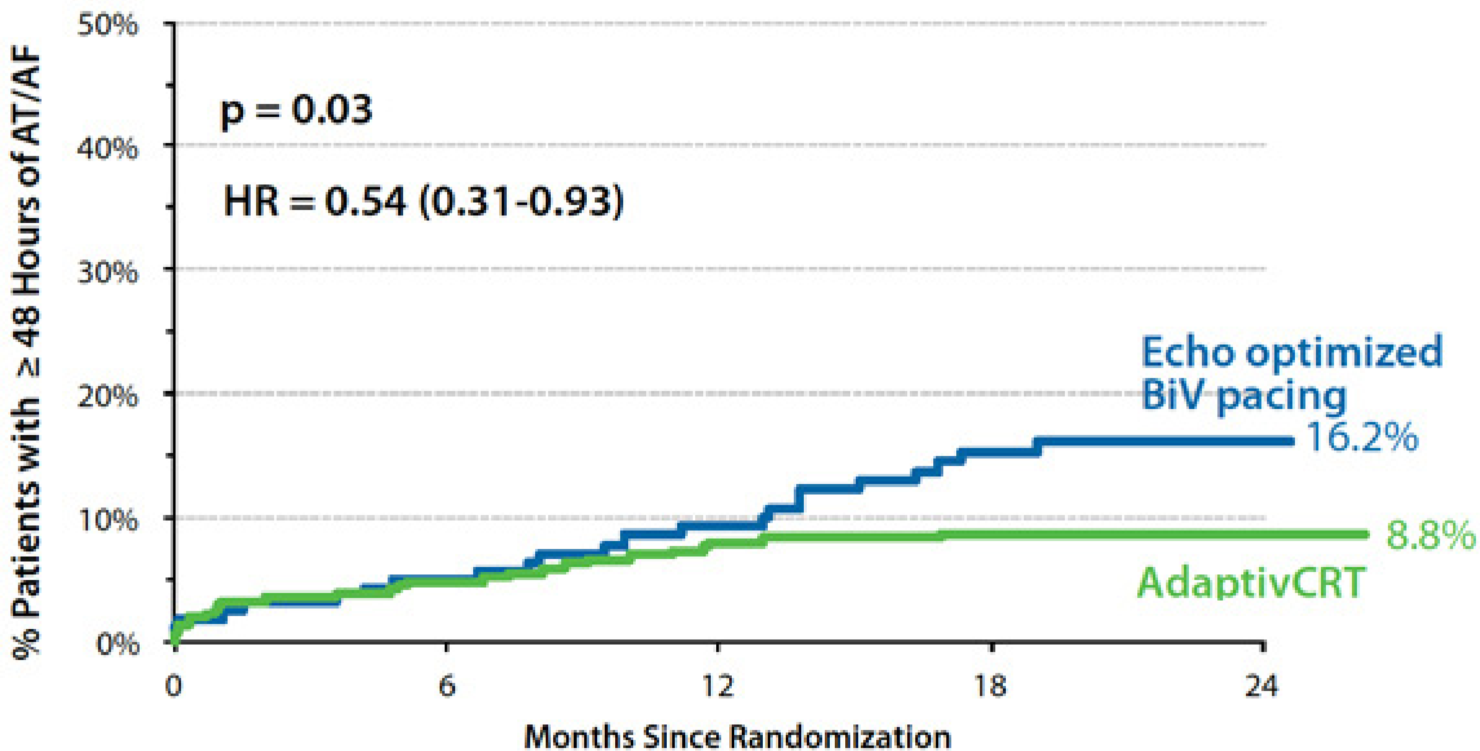
Adaptive CRT: main findings



Martin DO. Heart Rhythm 2012;9: 1807-1814

Adaptive CRT: main findings

46% reduction in AF risk



Number	160	141	126	109	33
remaining	312	280	260	241	83

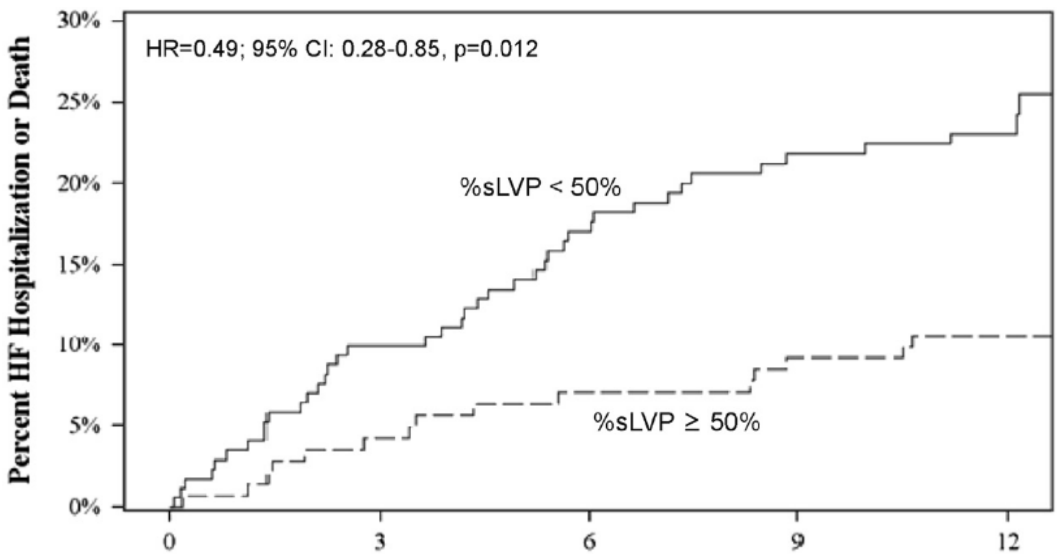
Martin D, et al. Can Adaptive Cardiac Resynchronization Therapy Reduce Atrial Fibrillation Risk? Circulation. 2013;128(22S):A17740.

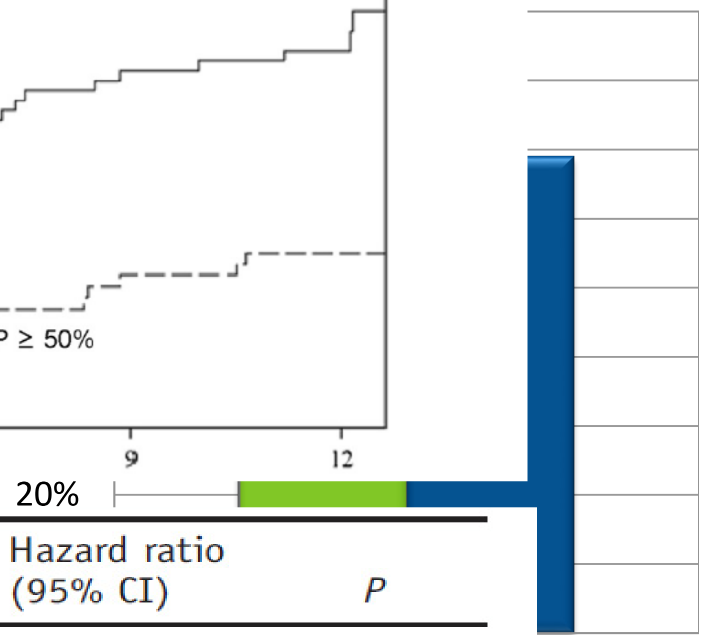
Martin D, et al. Clinical Outcomes with Adaptive Cardiac Resynchronization Therapy: Long-term Outcomes of the Adaptive CRT Trial. HFSA Late Breakers. September 23, 2013.

Adaptive CRT in pts with normal AV conduction

Patients with normal AV conduction

p = 0.041

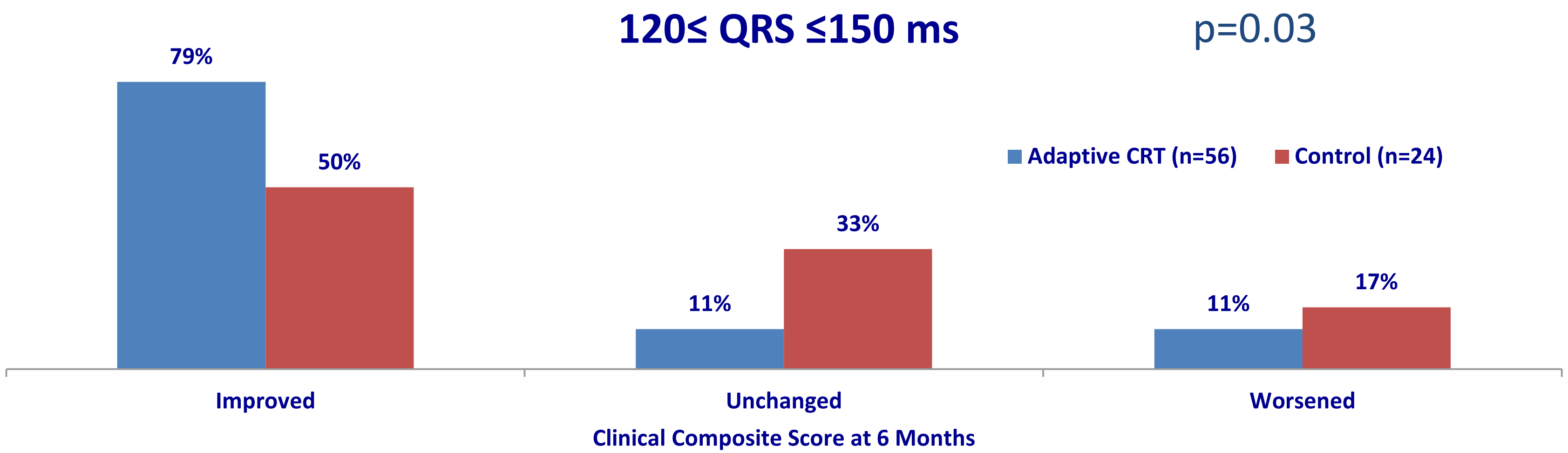


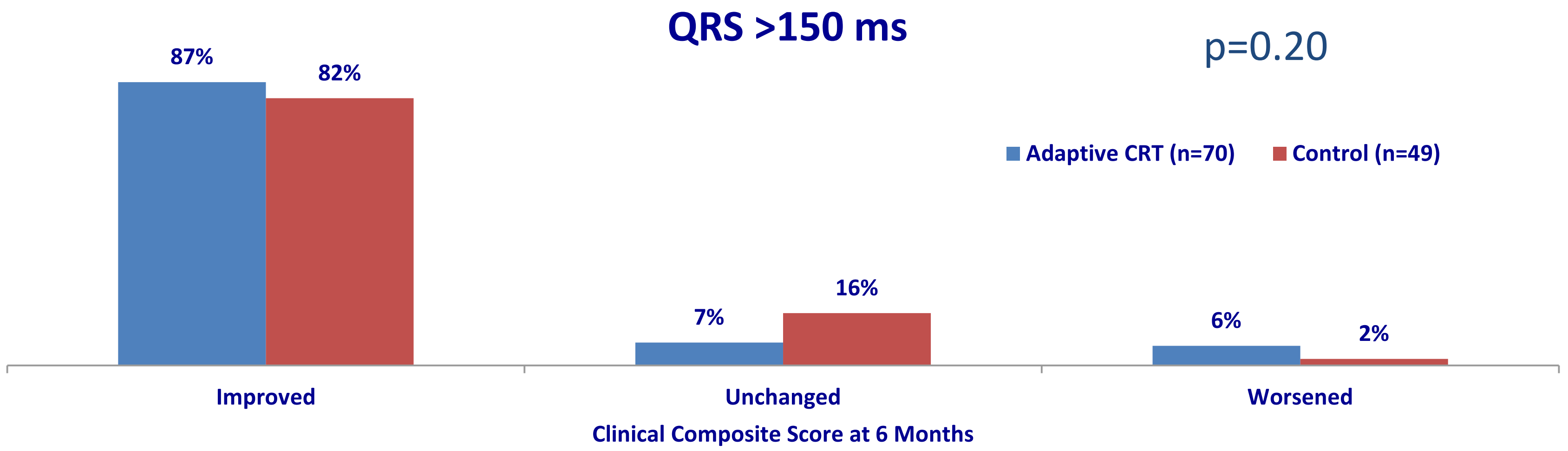


Covariate	Value	Hazard ratio (95% CI)	*P*
Renal dysfunction	Yes	2.22 (1.30–3.81)	.004
LVEF (%)	Per 1% increase	0.93 (0.90–0.97)	<.001
QRS duration (ms)	≤156	2.34 (1.33–4.10)	.003
%sLVP	≥50%	0.49 (0.28–0.85)	.012

Birnie D, et al. Heart Rhythm. 2013;10:1368-1374.

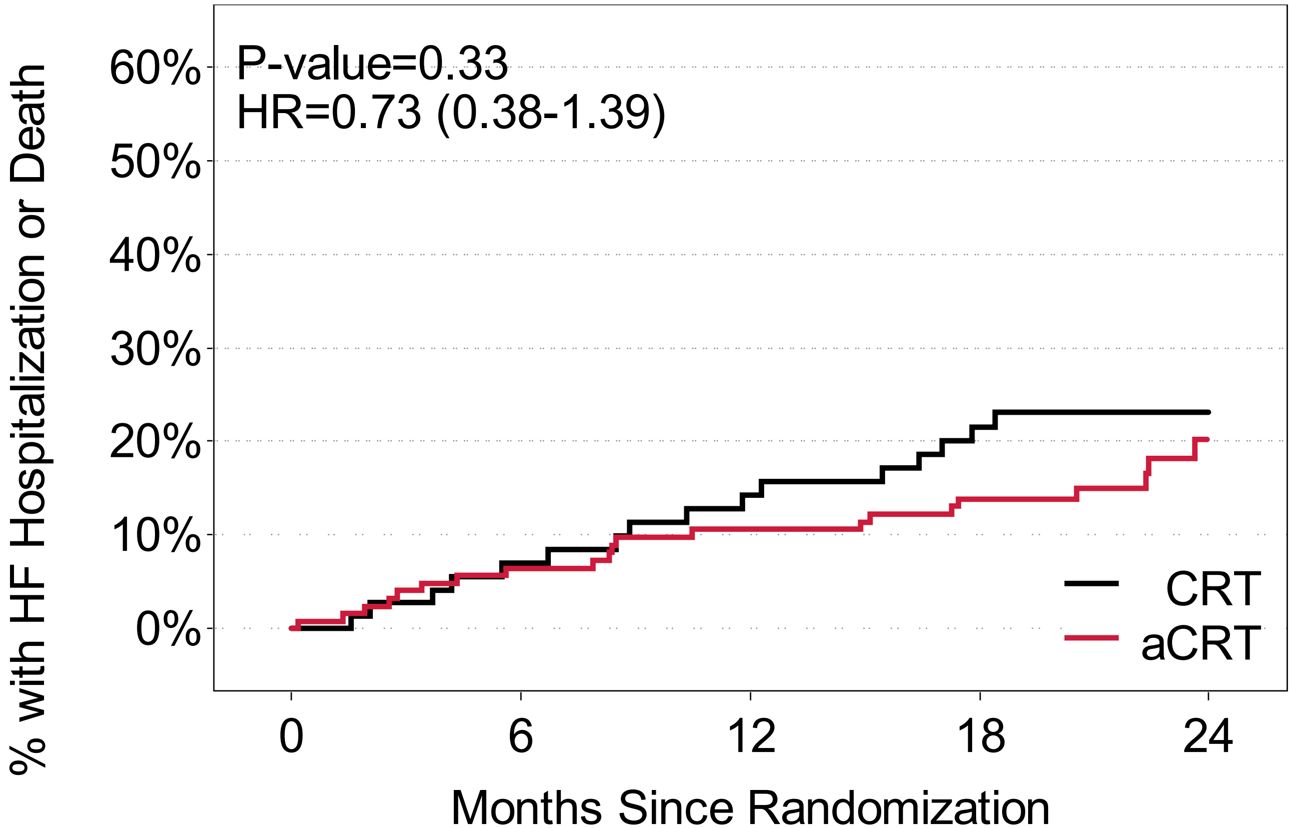
Adaptive CRT in Patients with Normal AV Conduction and Left Bundle Branch Block: Does QRS Duration Matter?





Aonuma K, et al. HRS 2015 Scientific Session

Results: all-cause death+HF hospitalization

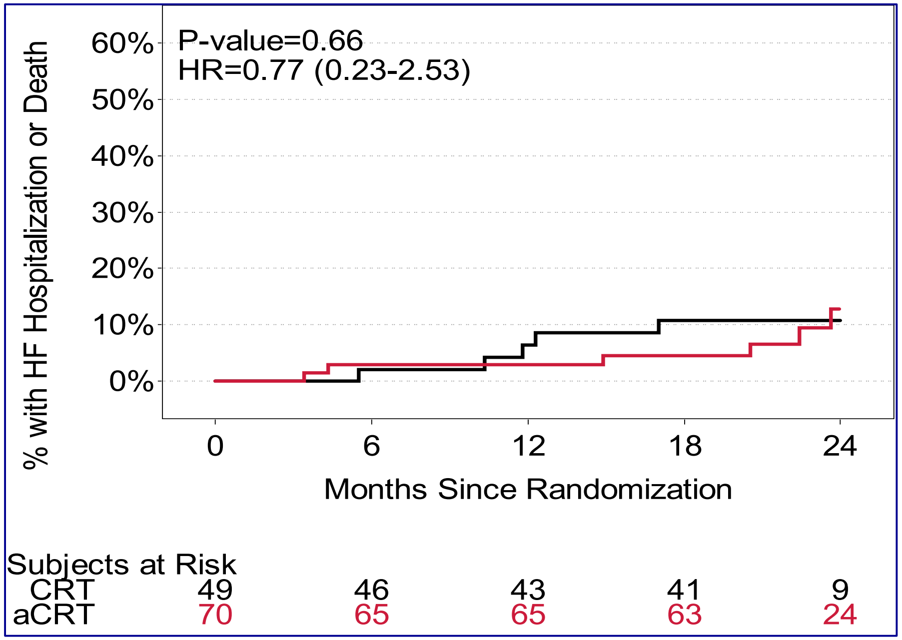


Subjects at Risk					
CRT	73	65	59	53	17
aCRT	126	115	109	103	38

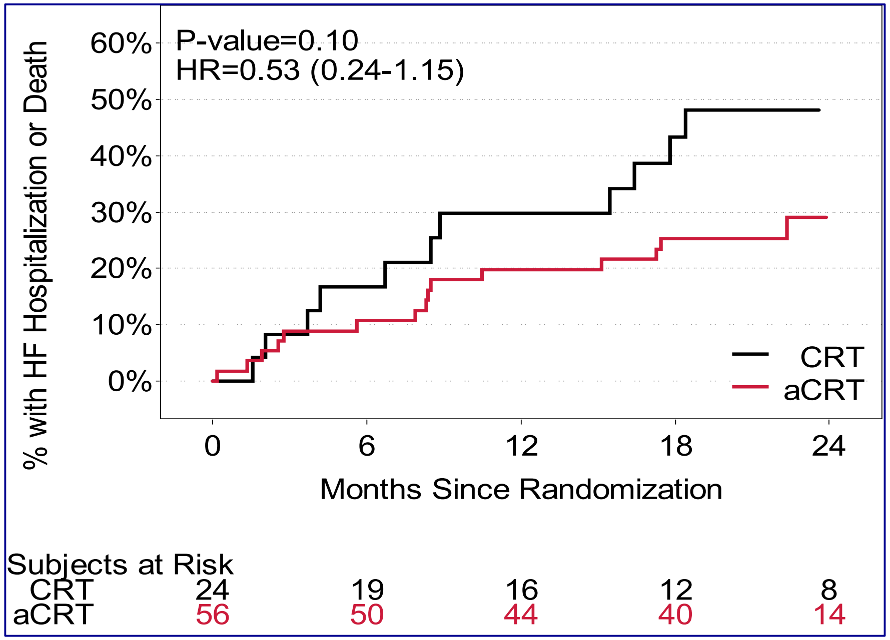
Aonuma K, et al. HRS 2015 Scientific Session

Results: all-cause death+HF hospitalization

QRS>150 msec



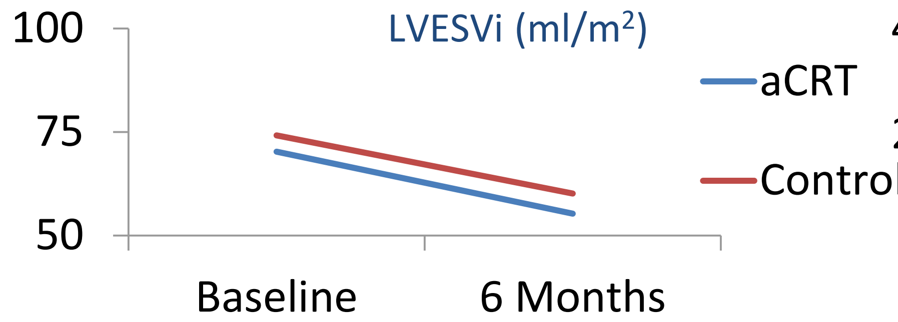
QRS:120-150 msec

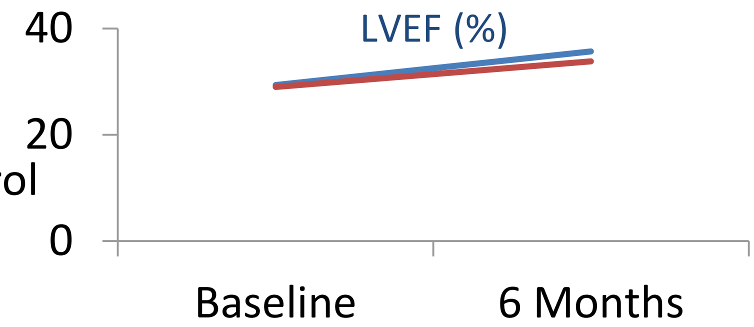


Aonuma K, et al. HRS 2015 Scientific Session

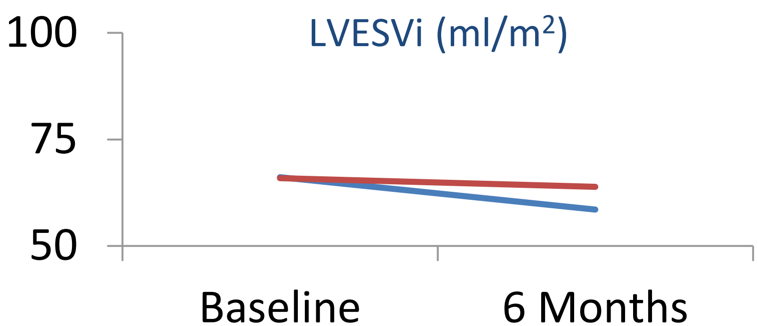
Results: LV reverse remodelling

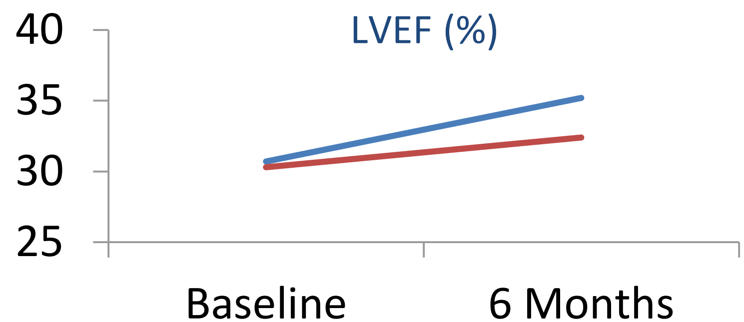
All Patients



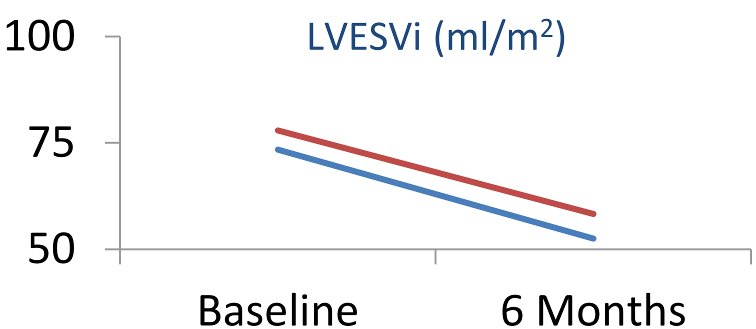


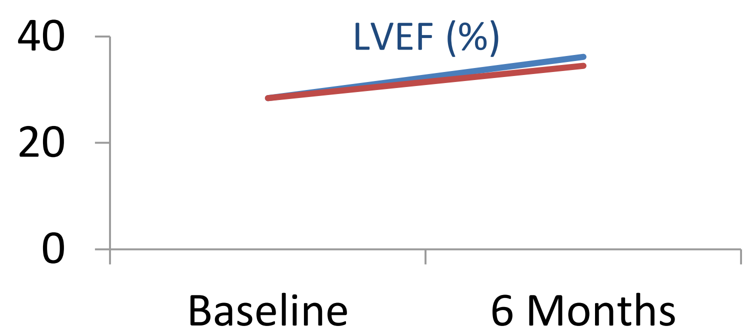
QRS: 120-150





QRS: >150





Aonuma K, et al. HRS 2015 Scientific Session

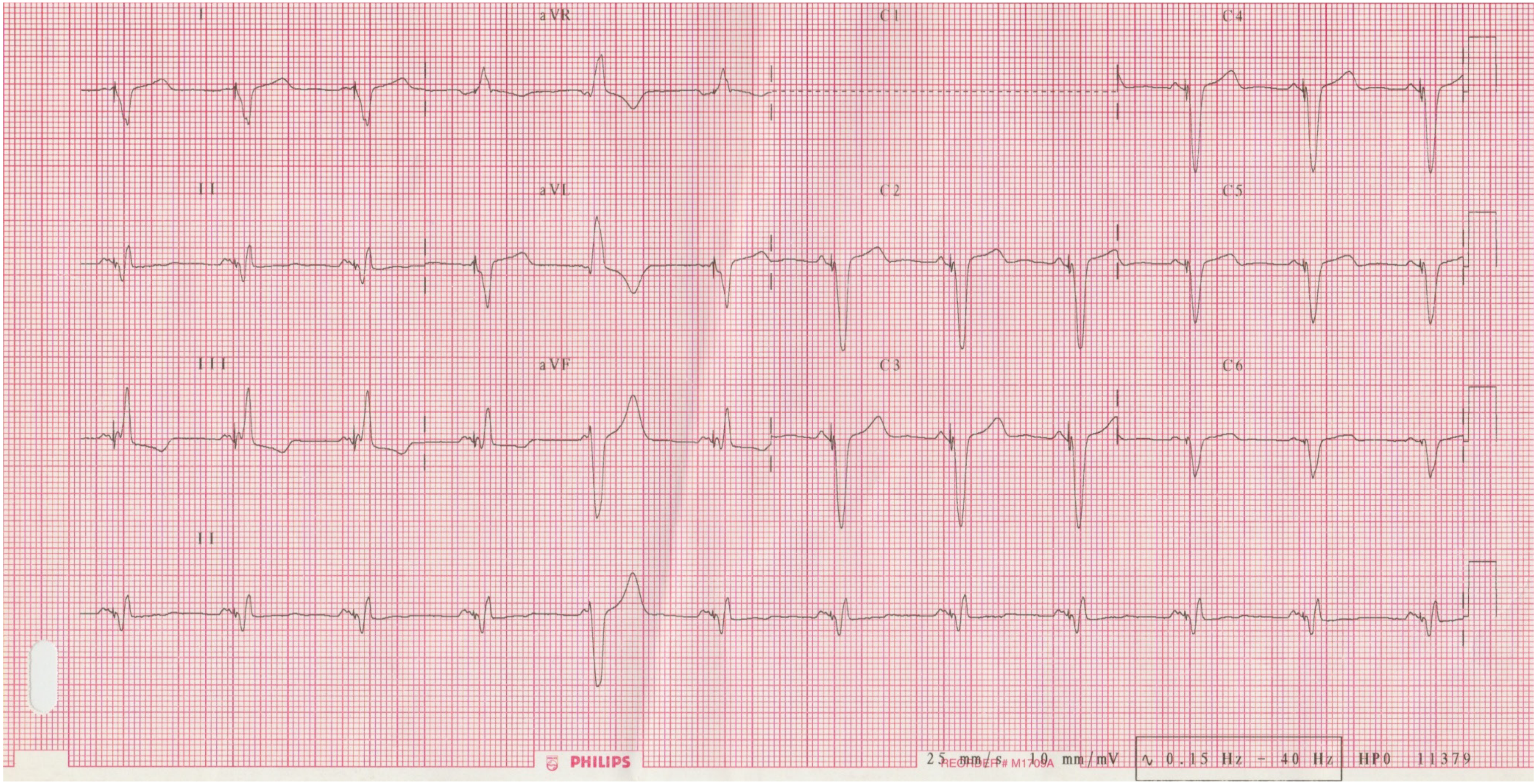
Clinical Case

- A 57 year old man with post-MI dilated cardiomiopathy

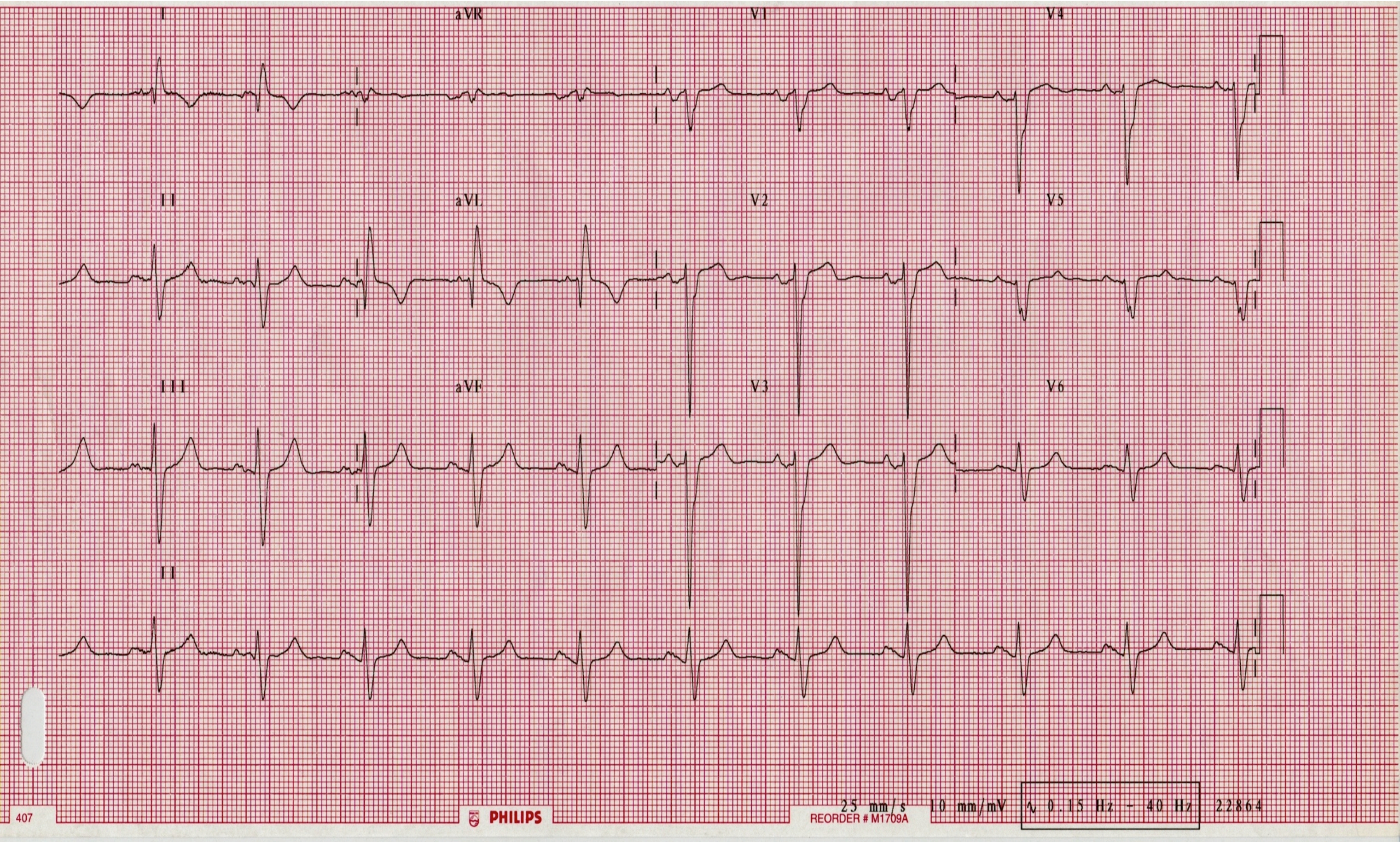
- Cardiovascular disease risk factors: smoking, dyslipidemia
- Comorbidities: COPD, HCV-related chronic liver disease

- Cardiovascular history
  - Acute myocardial infarction (1992), CABG+ventriculoplasty
  - Biventricular ICD implantation (November 2014)
  - No response to CRT (echo in June 2015 LVEF 25%)
  - In December 2015 pocket and leads infection by S. Aureus and Corynebacterium Amycolatum; in January 2016 extraction of 3 leads and ICD removal

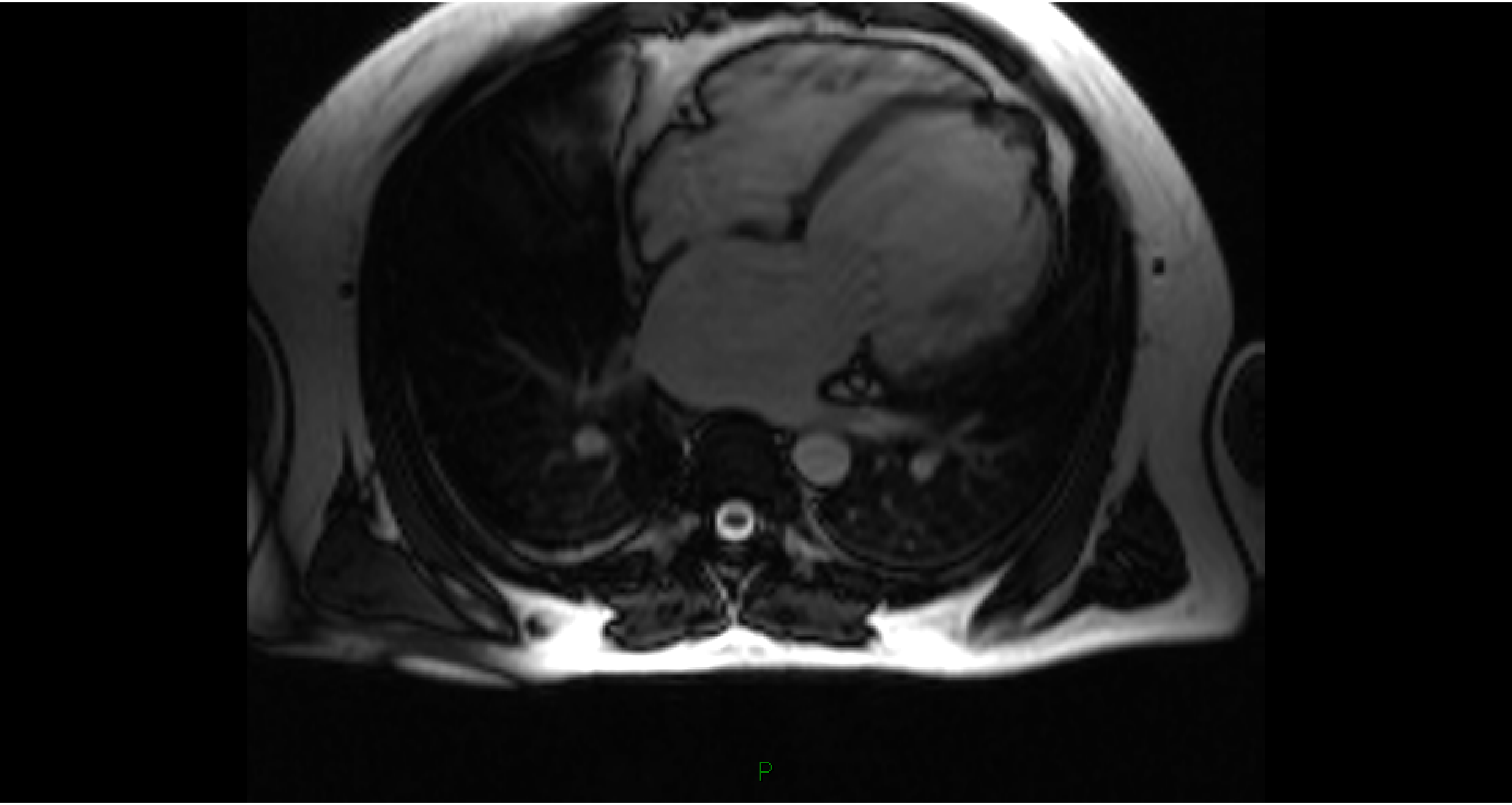
Baseline ECG



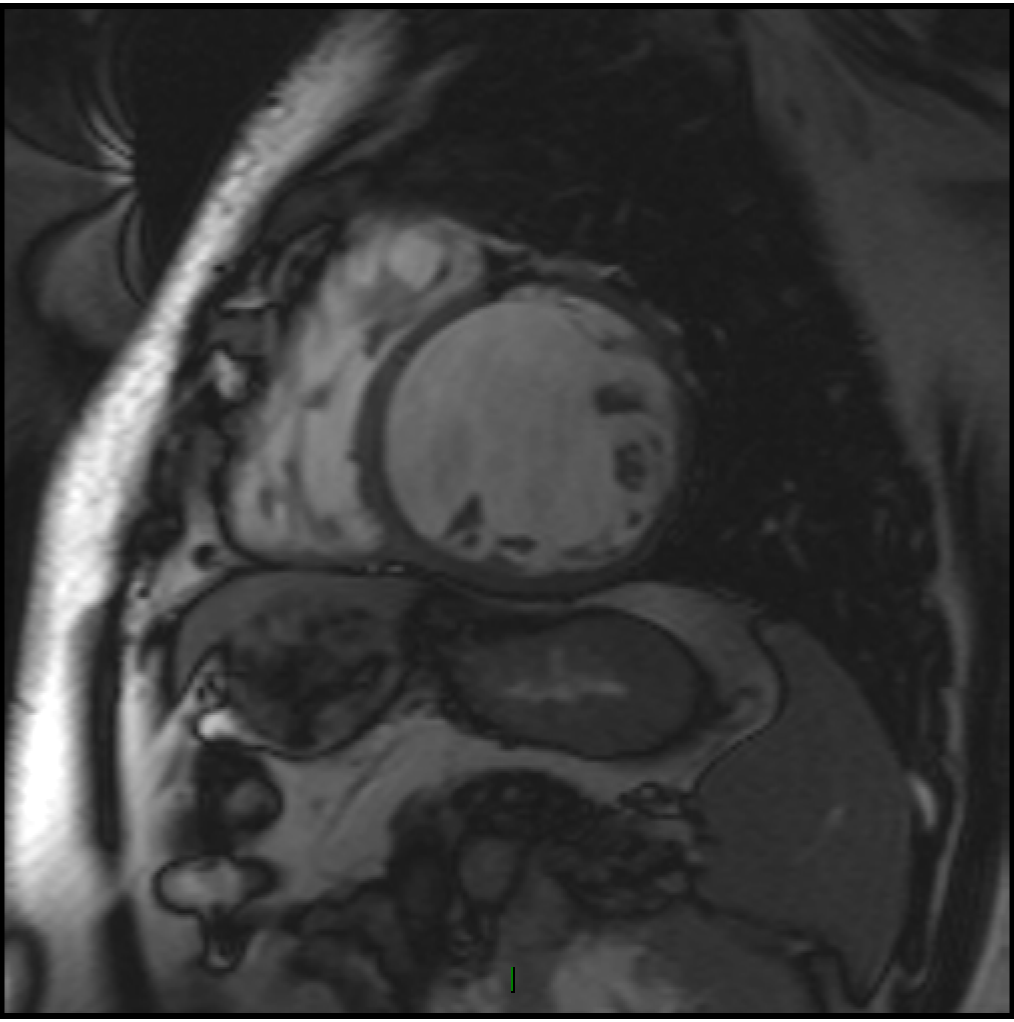
ECG after ICD removal and lead extraction

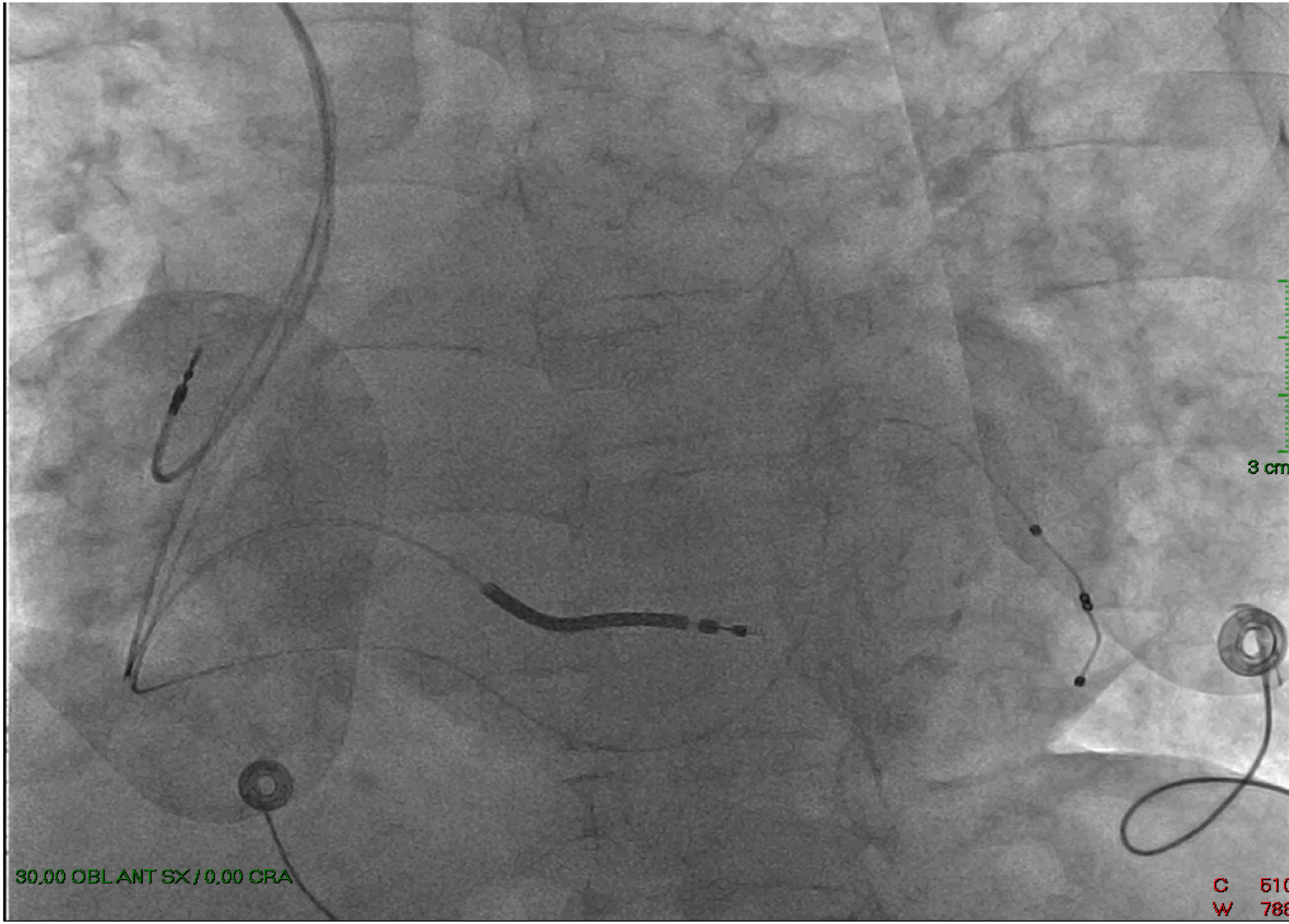


Case Presentation: MRI



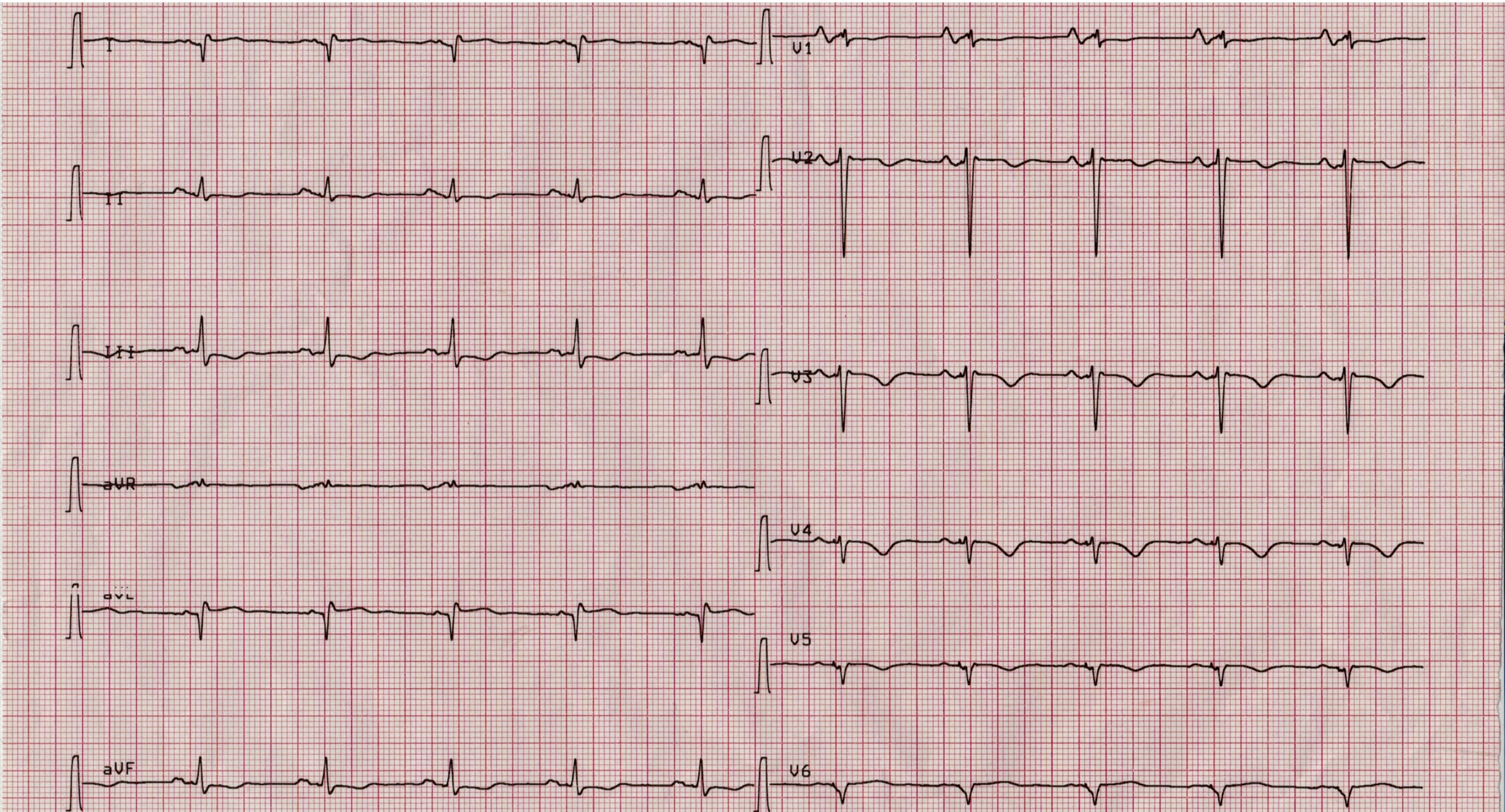
Case Presentation: MRI




3 cm
30,00 OBL ANT SX / 0,00 CRA
C 510
W 788

Case Presentation: post-implantation ECG

- After about 2 weeks of combined antibiotic therapy (vancomycin, cefazolin) minocycline), biventricular ICD has been implanted.

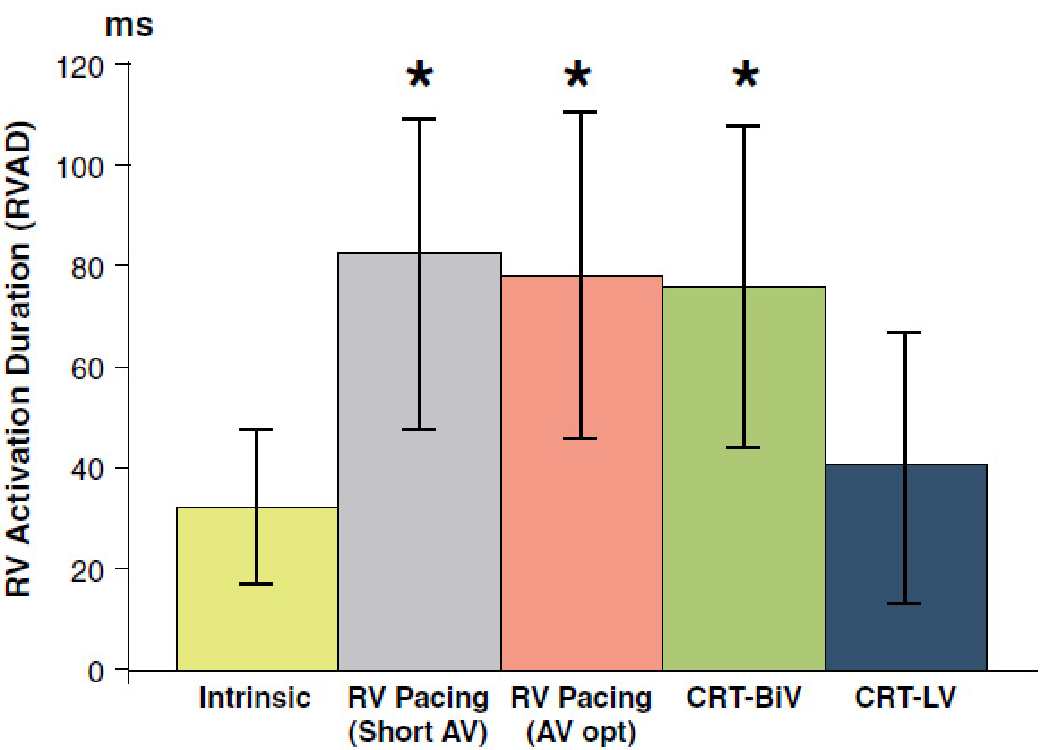


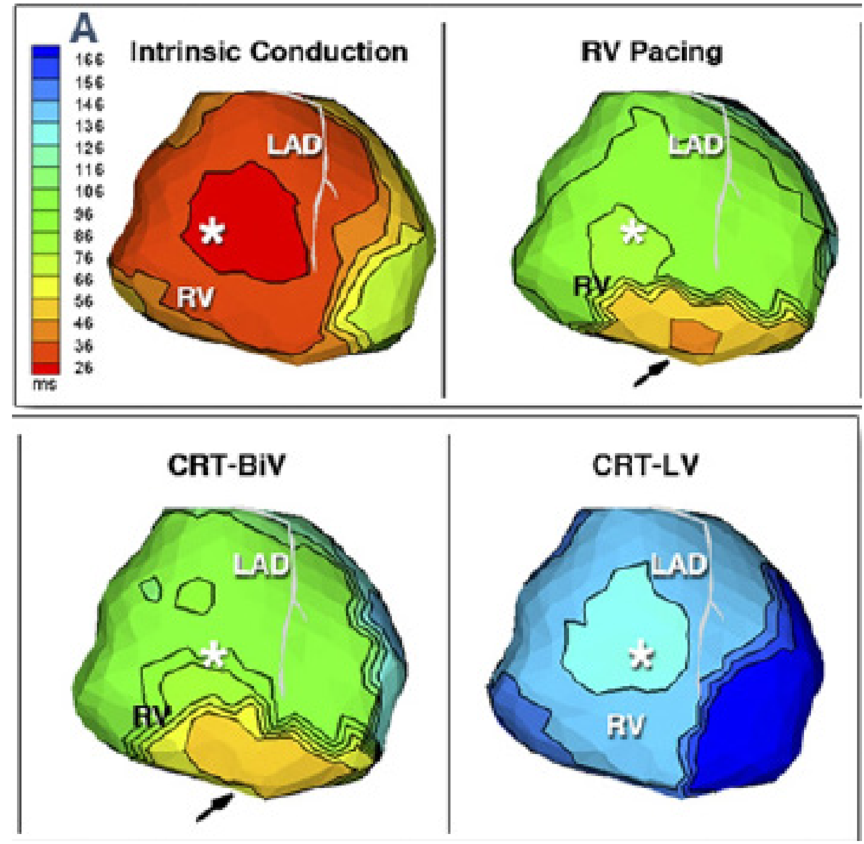
Rational for synchronized LV Pacing

In patients with sinus rhythm, LBBB and normal atrio-ventricular conduction LV only pacing synchronized to fuse with intrinsic conduction could lead to:

- ✓ Better LV function than BiV pacing (++ in pts with intermediate QRS duration)
- ✓ Better RV function than BiV pacing
- ✓ Extended device longevity

RV pacing and RV electrical activation





Varma N, et al. JACC Cardiovasc Imaging 2010;3:567-575

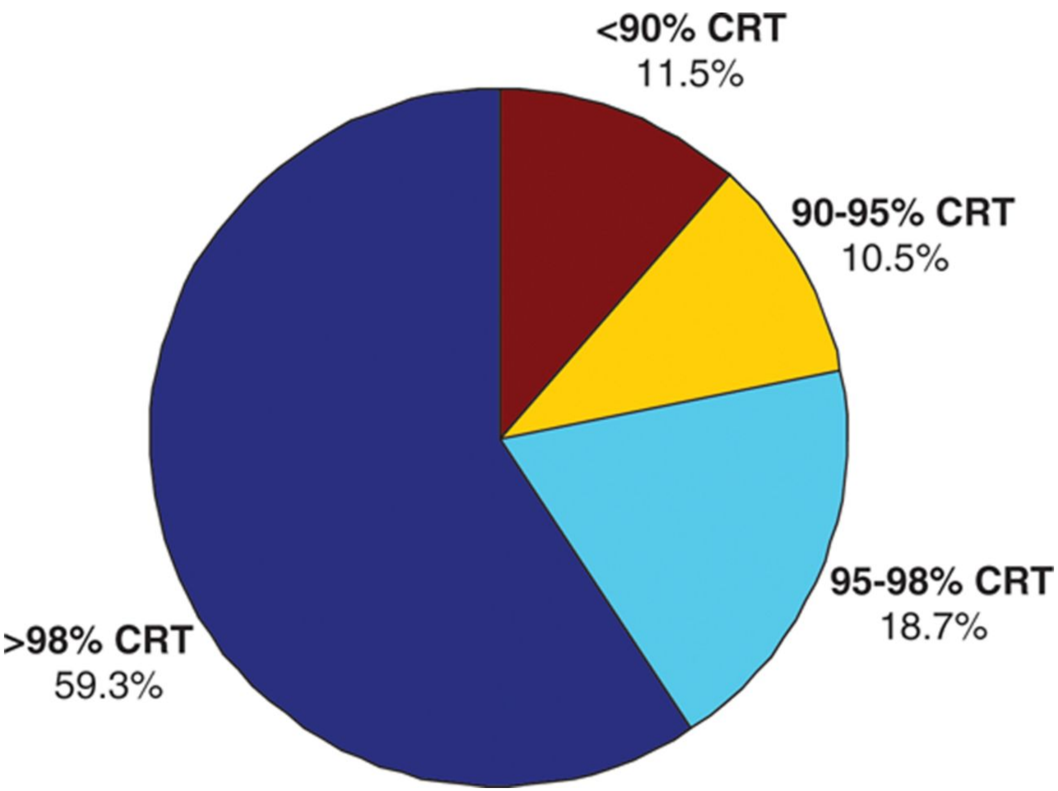
AdaptResponse Clinical Study

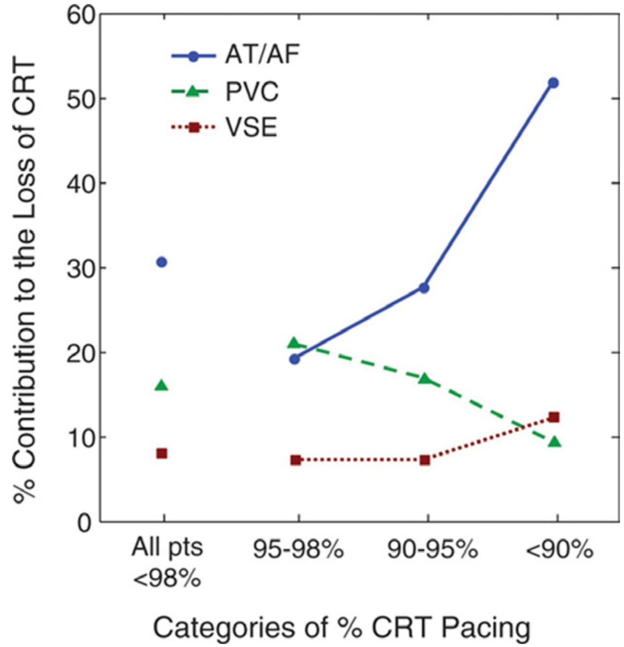
- Prospective, randomized, controlled, interventional, single-blinded, global multi-center, post market clinical study
- Event driven, minimum of two years Follow Up

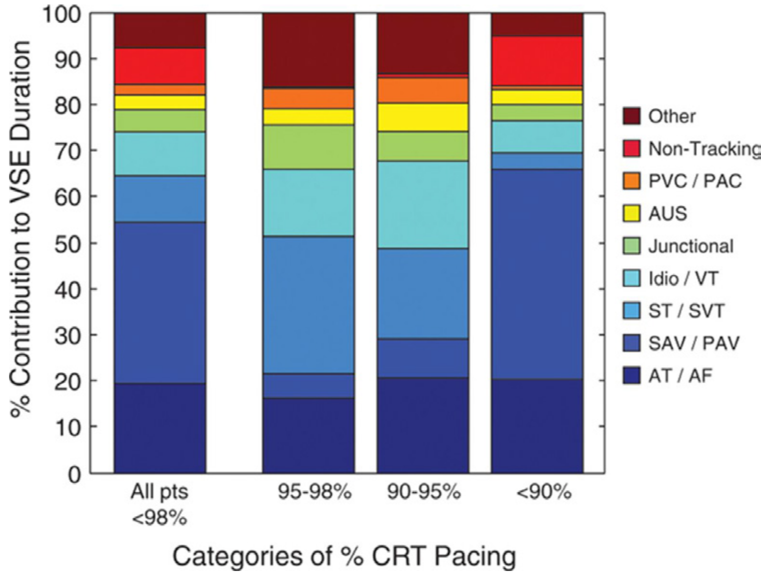
  (3,6,12,18,24M visits)
- 3000 subjects in up to 200 centers WW
- Subjects are randomized 1:1 to aCRT ON vs. aCRT OFF
  - Control group: optimized per physician discretion
- Subjects with LBBB, normal AV conduction, EF≤ 35%,

  NYHA II, III, or IV
- Subjects implanted with CRT-P/D containing the aCRT algorithm
- Primary Endpoint
  - **Time to first HF event + Mortality**

Loss of CRT pacing



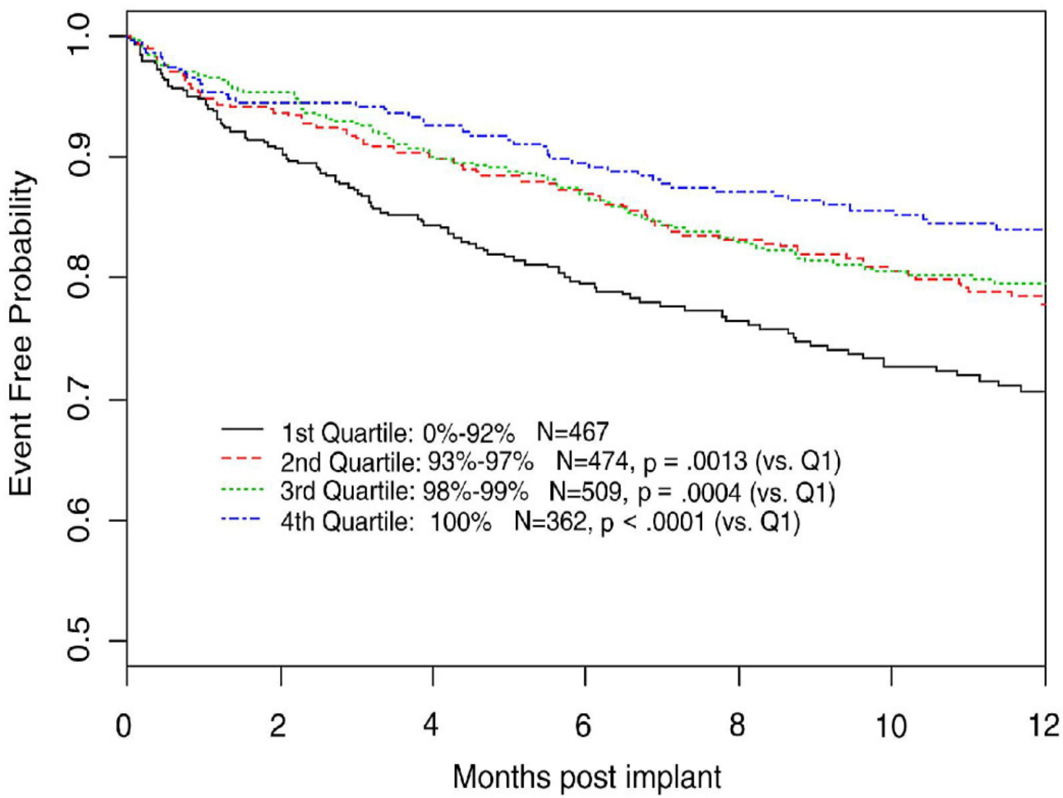




Alan Cheng et al. Circ Arrhythm Electrophysiol. 2012;5:884-888

Role of percentage BIV pacing

N=1812
(CRT RENEWAL and REFLEX trials)



Koplan et al. JACC 2009; 53 (4): 355-360.

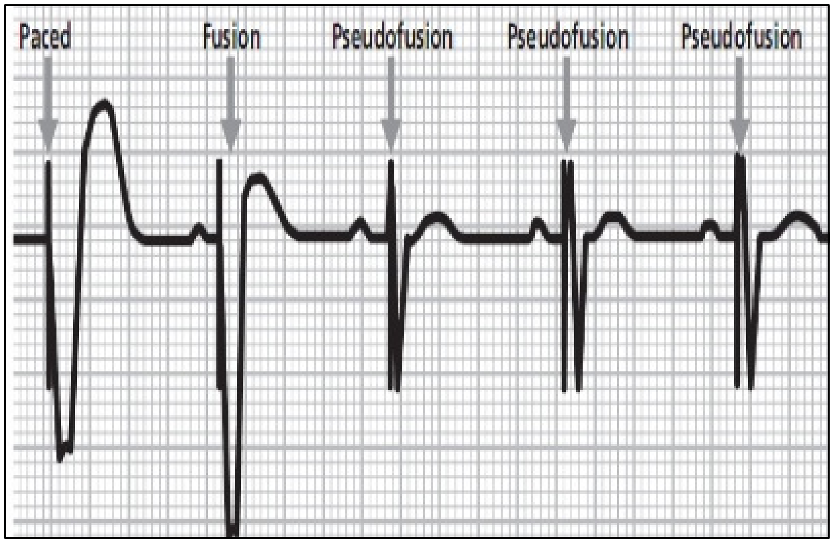
%BIV pacing should be>95% (ideally near 100%)

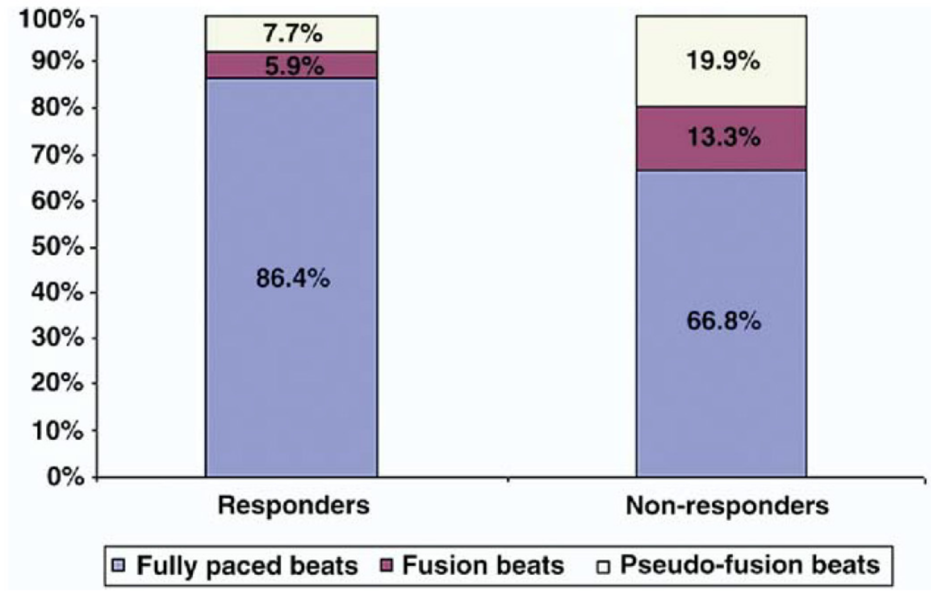
2012 EHRA/HRS consensus document on CRT

Recommendations	Class [a]	Level [b]
1) The goal of CRT should be to achieve BiV pacing as close to 100% as possible since the survival benefit and reduction in hospitalization are strongly associated with an increasing percentage of BiV pacing.	IIa	B

2013 ESC guidelines on pacing and CRT

100% BIV pacing is not 100% effective pacing



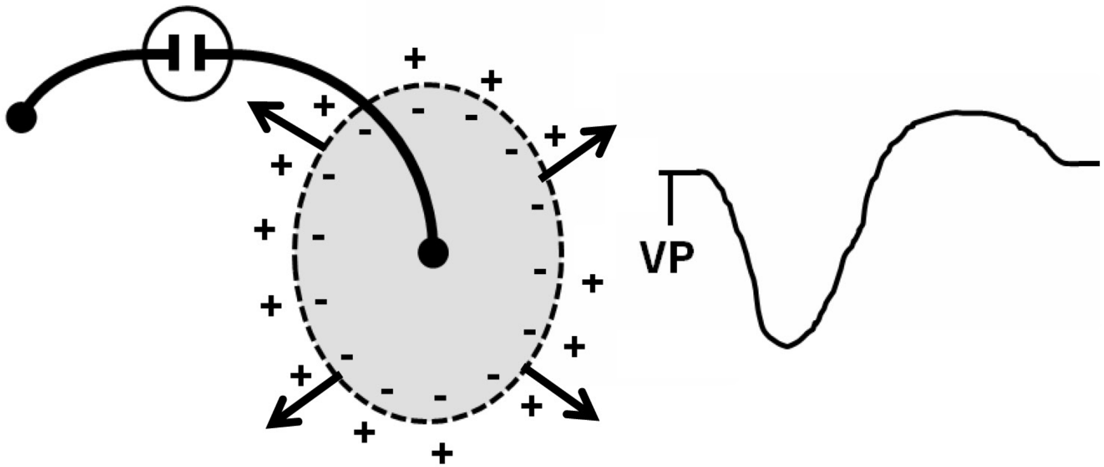


Pacing counters includes fully captured, fusion and pseudo-fusion beats

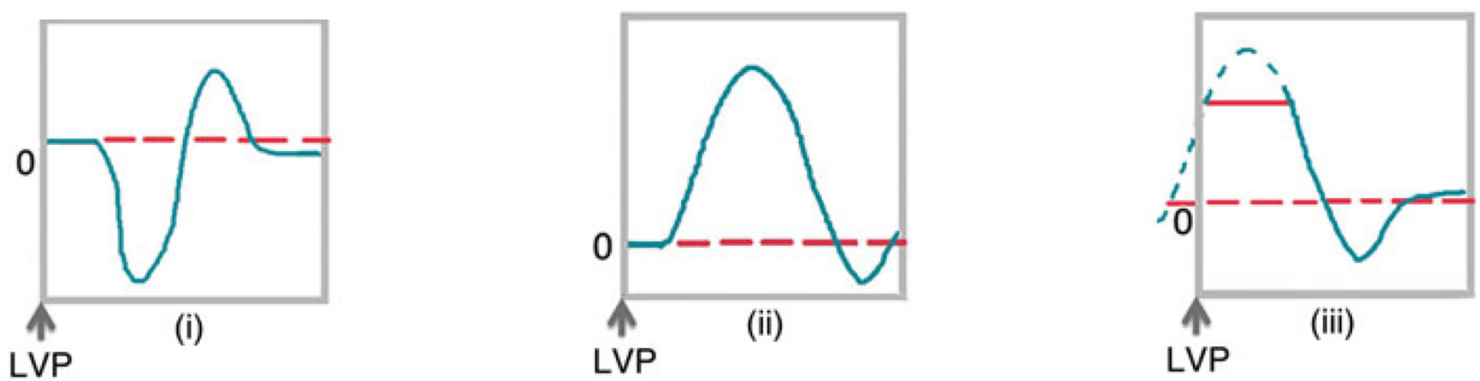
Kamath GS et al. JACC 2009;53:1050-1055

Automated detection of effective left-ventricular pacing: going beyond percentage pacing counters

Subham Ghosh[1], Robert W. Stadler[1], and Suneet Mittal[2*]



QS/QS-r Morphology Of Unipolar LV EGM is reflective of Effective Pacing



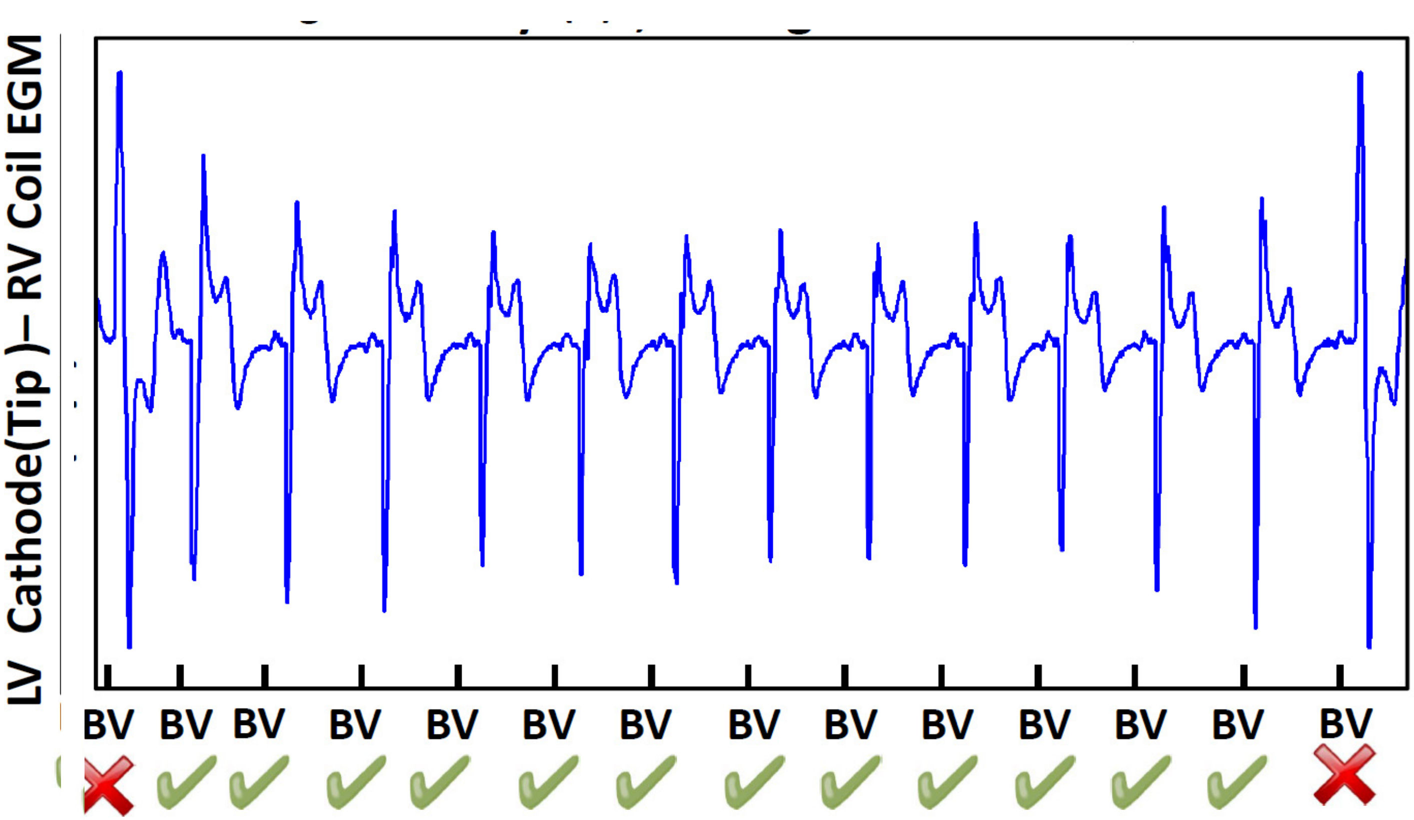
Effective LV pacing

Loss of capture

Pseudo-fusion

Europace 2015;17:1555-62

EffectivCRT™ algorithm

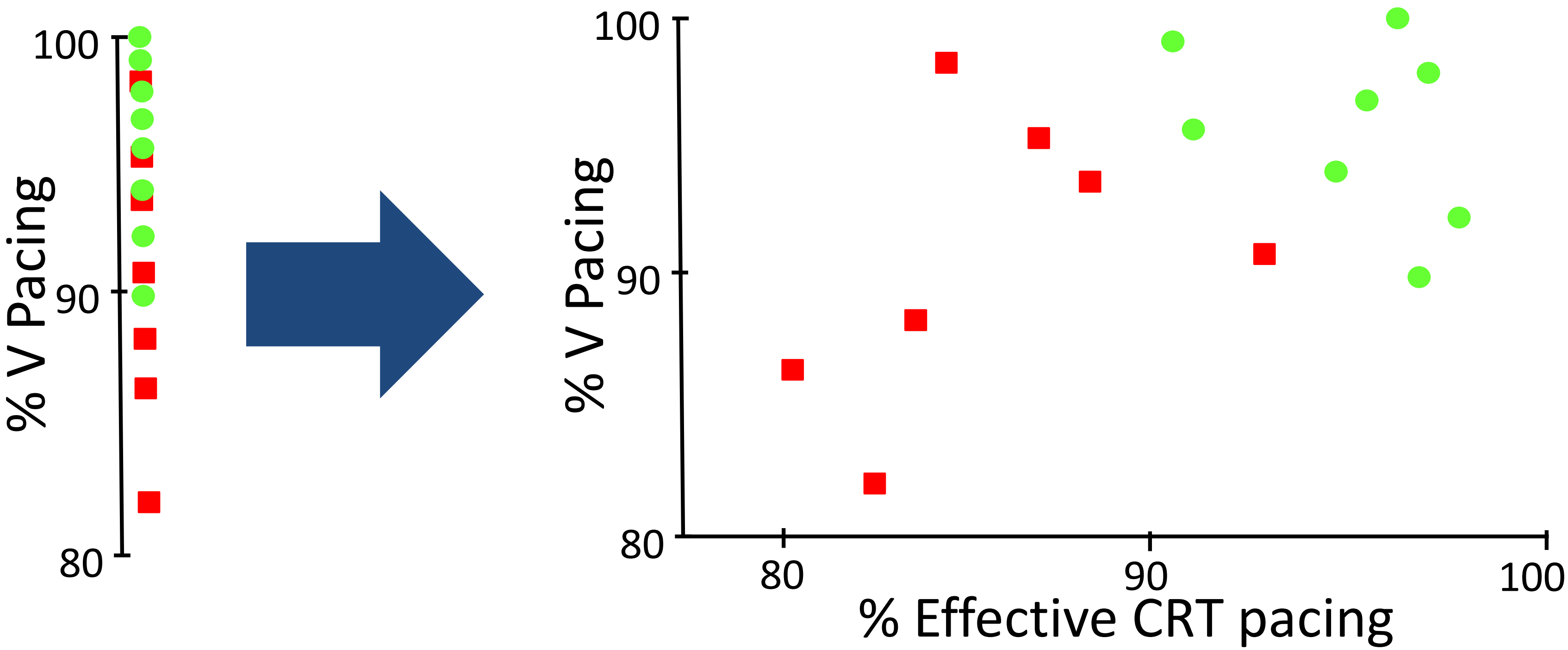


Europace 2015;17:1555-62

EffectivCRT™ Diagnostics

Before the EffectivCRT™ Diagnostic:
Only see the <u>quantity</u> of pacing

With the EffectivCRT™ Diagnostic:
Also see the <u>quality</u> of pacing



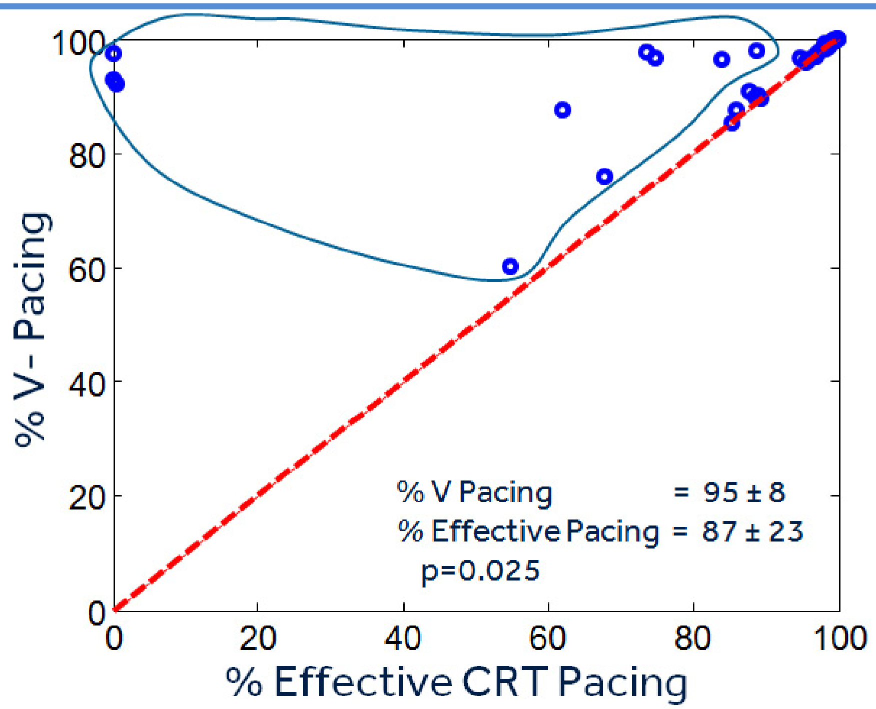
EffectivCRT: clinical evidence

- **Method:** 40 CRT patients post-implant with standard of care device programming; Ambulatory device data collected by Holters over 24 hours.

- **Conclusion:** In 25% of patients, device-reported % V Pacing overestimated effective CRT

▪ Causes of ineffective CRT included pseudo-fusion, complete or intermittent lack of LV capture.

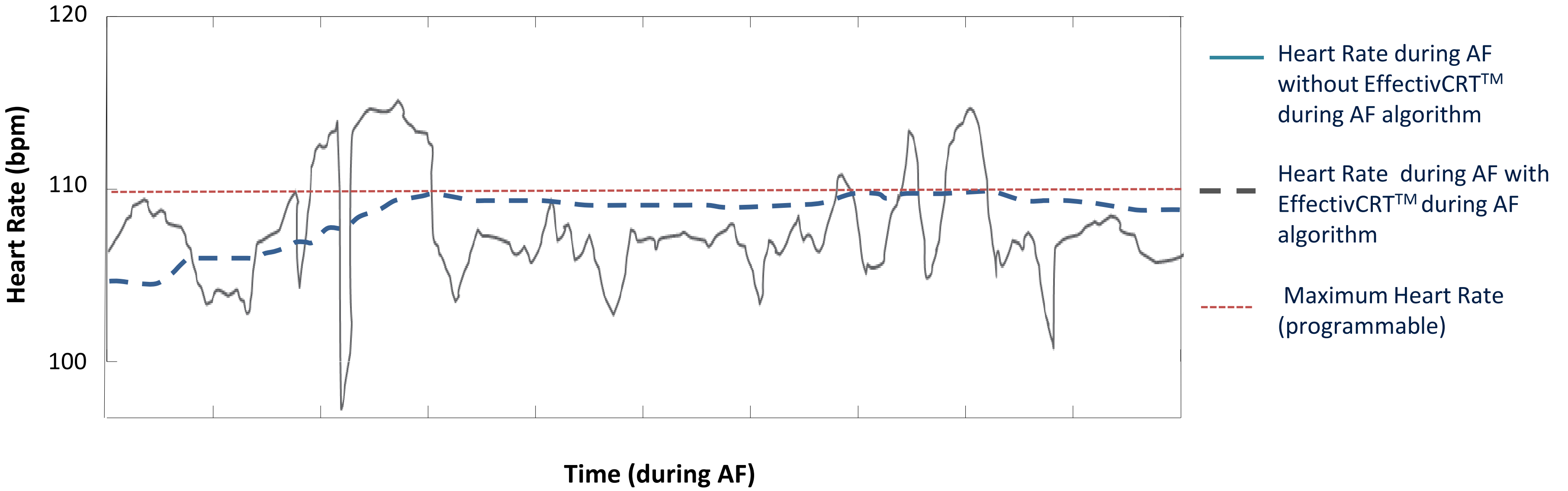
▪ 3/40 pts had NO Effective pacing, whereas the %V pacing was >90%
- Possible scar (poor pacing substrate)



[1] Ghosh S, et al. Heart Rhythm 2015. Abstract 17-04.

EffectivCRT during AF

- The "Effective CRT during AF" algorithm:
  - Improves the percentage of time the patients receives effective CRT by changing the pacing rate without substantially increasing the average heart rate
    - If it detects too much ineffective pacing or sensed events, it increases the pacing rate
    - If it detects enough effective pacing, it decreases the pacing rate
  - The maximum heart rate is programmable.
- Compatible with AdaptivCRT™



CRTee study

Study Overview:

Prospective, randomized, multicenter crossover study in 22 centers

54 CRT pts with paired data

Aim

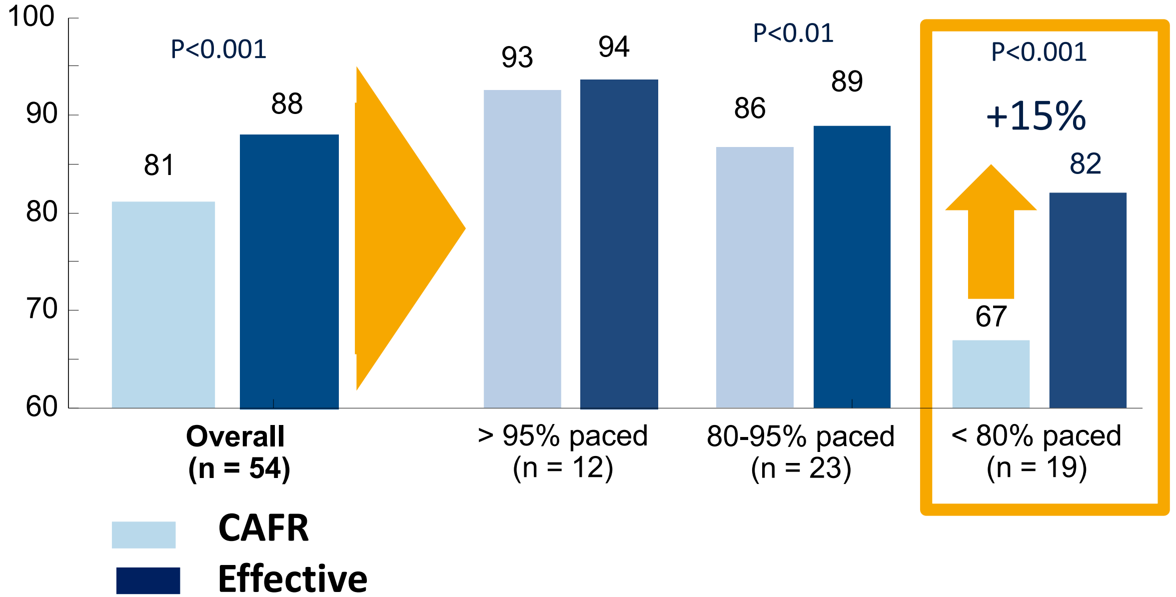
% effective pacing with EffectivCRT during AF is superior to % effective pacing with CAFR.

Inclusion criteria:

- ≥ 6 days with ≥ 4 hours of AF each day, during a 4 week period
- % V. pacing during AF ≤ 97%

Exclusion criteria:

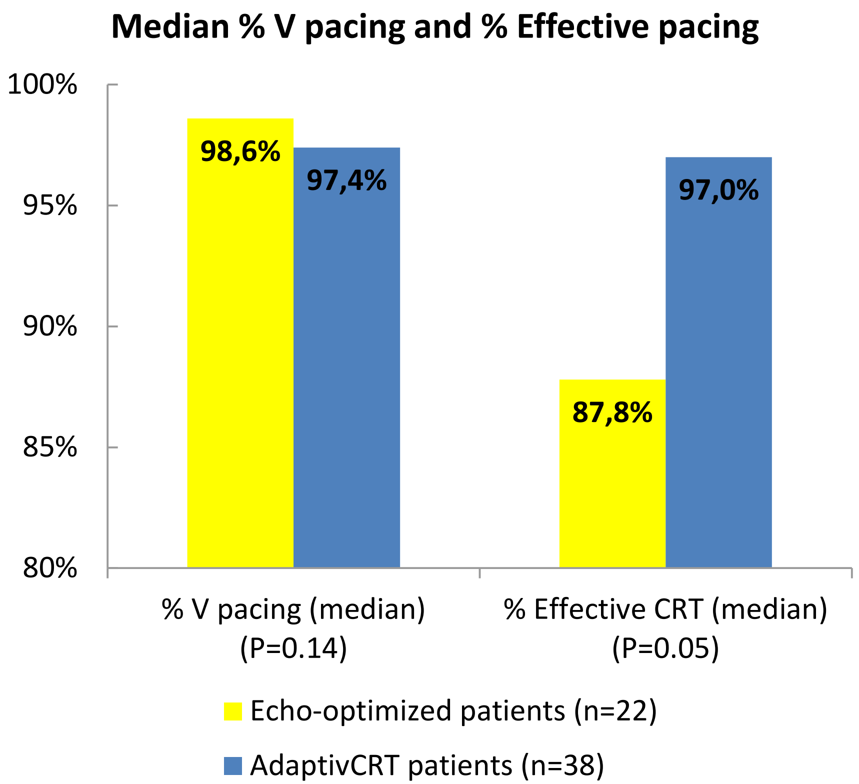
- AV node ablation
- 3rd degree or complete heart block

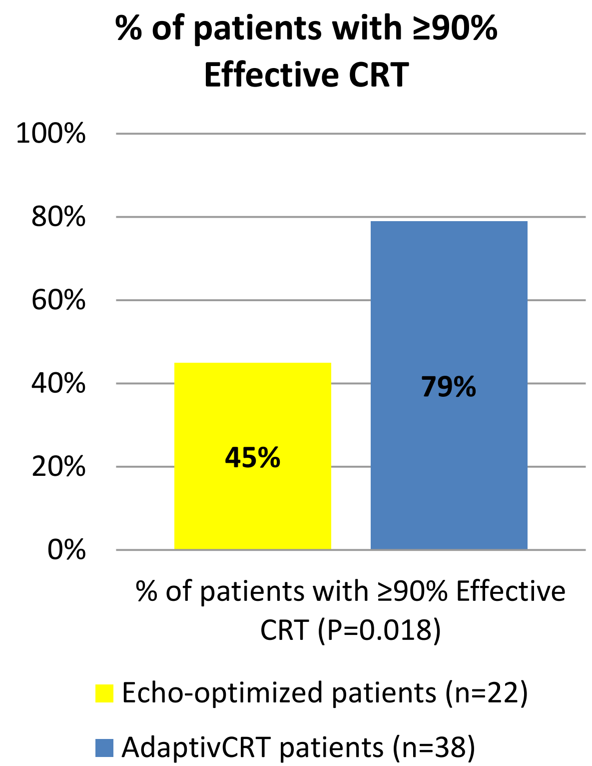


Average heart rate increased by only 3 beats-per-minute, from 77 to 80 bpm, p<0.001.

AdaptivCRT and Effective CRT

SUB-ANALYSIS FROM THE ADAPTIVCRT TRIAL





[1] AdaptivCRT™ Algorithm Increases Effective LV Pacing Compared with Echo-Optimized CRT
Robert W. Stadler, Subham Ghosh, Axel Kloppe , Poster at HRS 2015.

Conclusions

- ✓ CRT is not a “one fits all” therapy.
- ✓ Frequent optimization and reprogramming are time consuming in clinical practice.
- ✓ Device algorithms are likely to favour more “adaptiv-ness” of CRT therapy to the single patient.
- ✓ Although more data are required it is very likely that the use of device algorithms will turn into a greater “effectiv-ness”.

Grazie