20 YEARS IN CRT THERAPY : WHAT'S MORE ?

Satellite Symposium: Advances in Cardiac Pacing and Arrhythmia Management

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The birth of CRT … in Europe, 20 years ago

1994, the first four-chamber cardiac resynchronization therapy implantation

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Cardiac resynchronization therapy implantation: a blend of skill and technology

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KEYWORDS
Cardiac resynchronization therapy;
Heart failure;
Implantable cardioverter defibrillator

This paper reviews the beginnings and the evolution of cardiac resynchronizat therapy (CRT), which required technological innovation and manual dexterity for application. The expectations of CRT and its problems today are analysed. The quent need for CRT with defibrillation capacity is discussed. Future developmen CRT is anticipated.

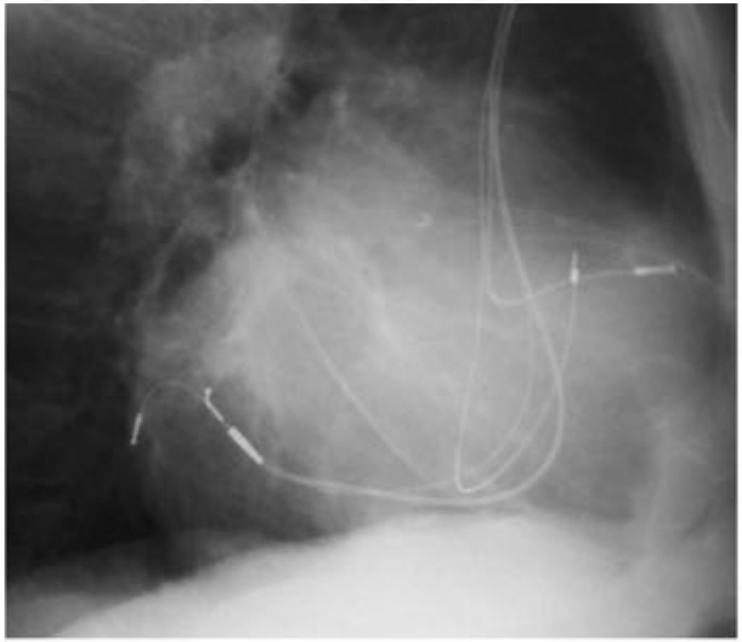


Figure 1 Lateral X-ray view of the first fully transvenous cardiac resynchronization therapy system (courtesy of D.G. and J.-C.D., University Hospital of Rennes, August 1994).

Introduction

Cardiac resynchronization therapy (CRT) was conceived in the mid-1990s. It offered not only atrioventricular (AV) synchronization as had previously been used in dual-chamber pacing but also synchronization of the two ventricles. By pacing the region of the left ventricle (LV) with the most delayed activation, it was possible both to improve interventricular synchrony and the synchrony of the LV itself.

At the outset of CRT, many pacing problems had already been overcome. For example, rate modulation in the absence of normal sinus node behaviour, mode switching from DDD to VVI or DDI for atrial tachyarrhythmias, and algorithms to avoid pacemaker-mediated tachycardia were all standard and well understood in the dual-chamber device of the mid-1990s.

Some inspired work anticipated the introduction of

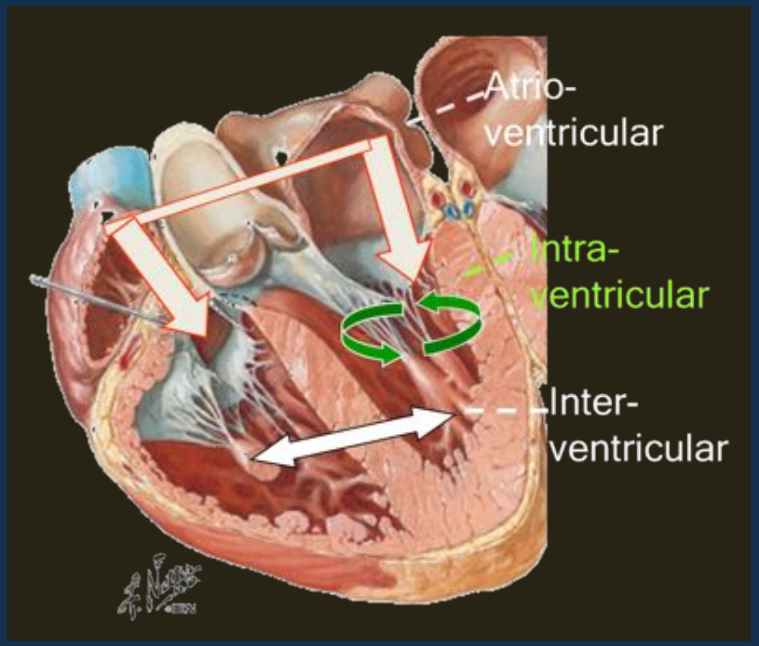
Dual-chamber pacing was initially thought to ben heart failure patients[3] but when more patients w studied, long-term improvement could not be cons ently demonstrated.[4–6]

The investigations of Prinzen's group served to und line the negative effects on coordination of LV contr tion imposed by RV apical stimulation.[7] The scene then set for the logical step of resynchronizing the ventri cles and in appropriate patients simultaneously resynchronizing the two atria at the same time.

1994, the first four-chamber cardiac resynchronization therapy implantation

The first published patient[8] was 54 years old: in New York Heart Association class IV, presenting non-ischaemic dilated cardiomyopathy, ejection fraction (EF) < 35%

In pts with refractory heart failure, left ventricular dysfunction, and intraventricular conduction abnormalities.



This should improve the hemodynamics of pts

CRT Objective:

Stimulate both ventricles more or less simultaneously

Approach

Transvenous

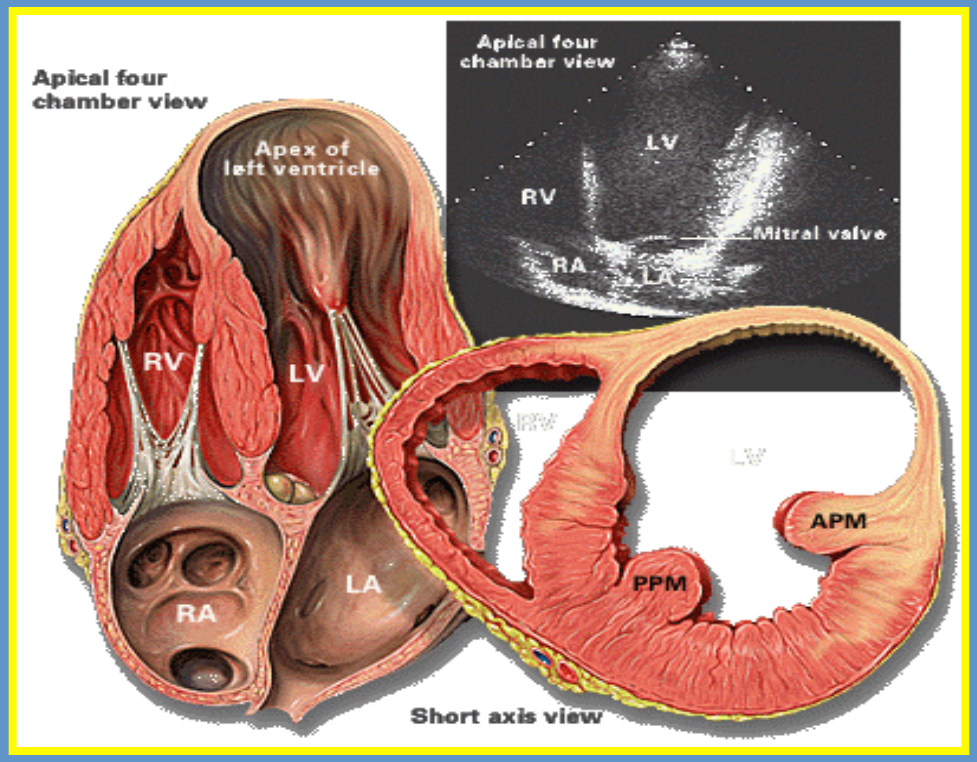
- Well-established technique
  (thousands of patients already treated)

- Possibility of using the catheter that best suits the patient's anatomy.

Failure of coronary sinus lead implantation: alternative approaches

- Epicardial Approach :
  - thoracotomy
  - Minithoracotomy
  - video-assisted thoracoscopic and robotic
- Transapical approach
- Transeptal approach (Inter-atrial puncture)

Ischemic



Idiopathic

Randomized Controlled Trials on CRT

Study						Results
MIRAC						+
MUSTIC						+
MUSTIC						+
PATH C						+
MIRACLE						+
CONTAK						+
COMPAN						+
PATH C						+
MIRACLE						+
CARE H						+

On Top of Optimal Drug Therapy

CRT Improves:

NYHA Class,
Quality of life score,
Exercise Capacity: 6 MW, Peak VO2
LV function: EF, MR
Reverse remodeling: LVEDV
Hospitalization

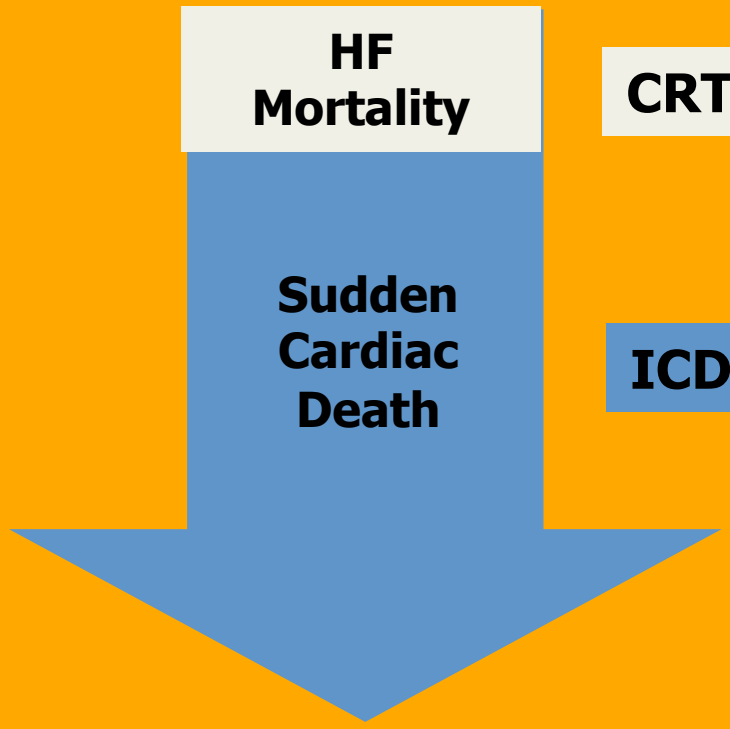
LVEF ≤ 35% for all trials

* RV paced QRS ¶ Primary endpoint not met; key secondary endpoints reached

Clinical Evidence: CRT Reduces Mortality & Hosp.

On Top of Optimal Drug Therapy

Further Reduction with CRT + ICD for Higher Risk Patients



TALITY

Singl

CAR (n=8

36%

40%

COM (n=1

% (n.s.)

36%

McAl (n=3

21%

Free (n=3

28%

Abdu (n=2

28%

Rive (n=2

29%

McAlister,

Freemant

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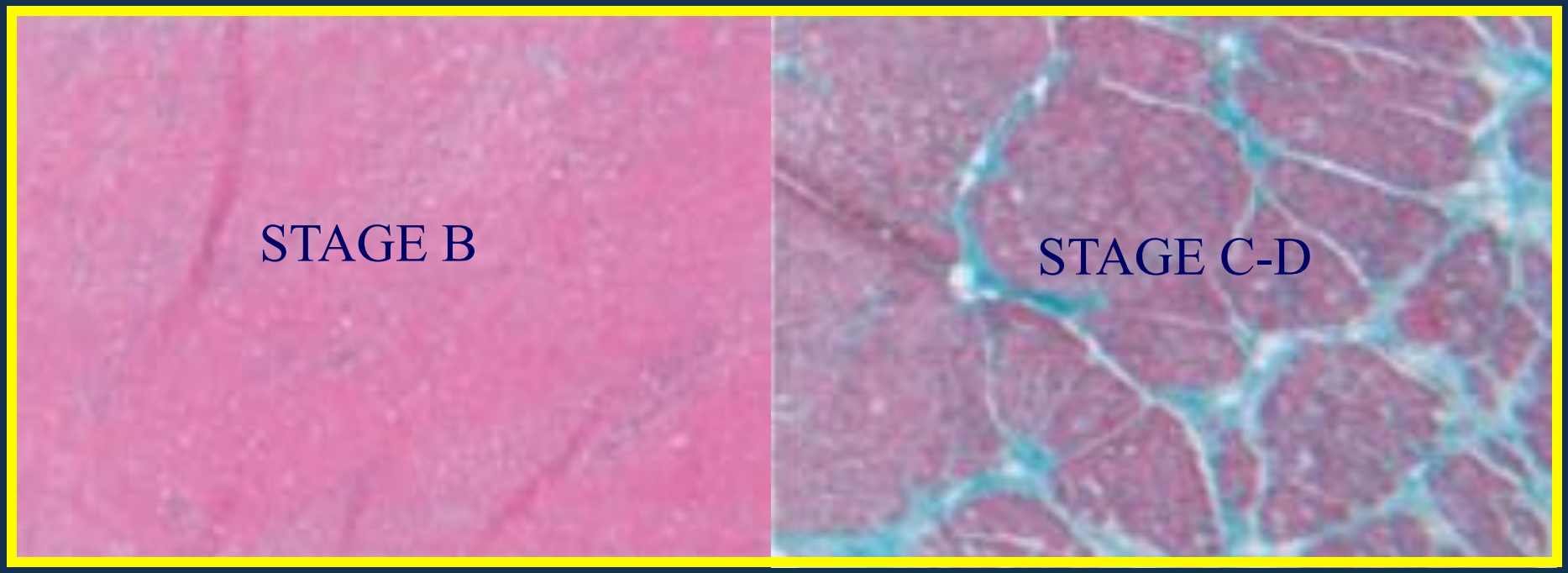
CRT :
Wait Untill NYHA III ?

NYHA I-II

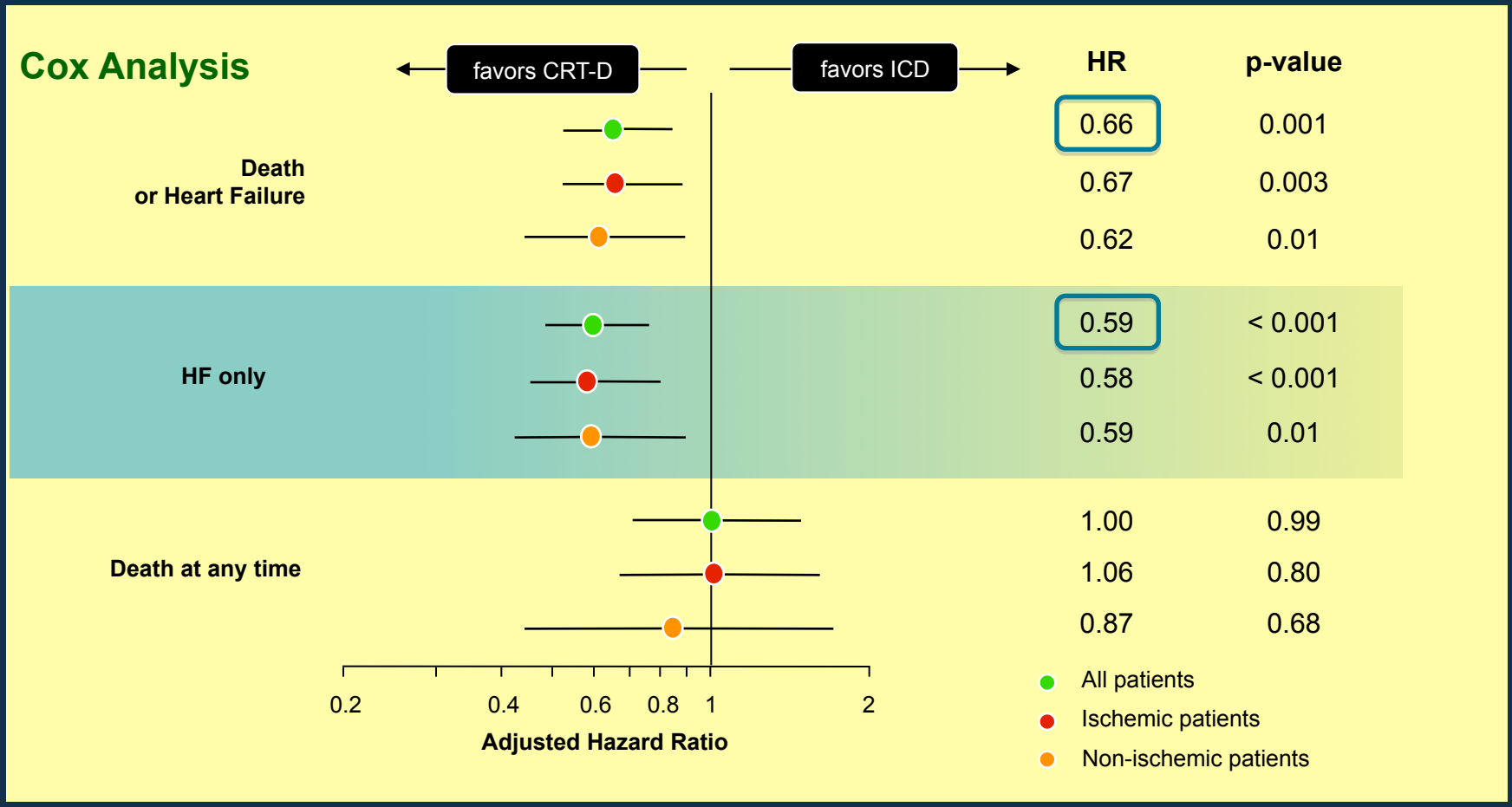
NYHA III-IV



MADIT-CRT – Results Primary Endpoint

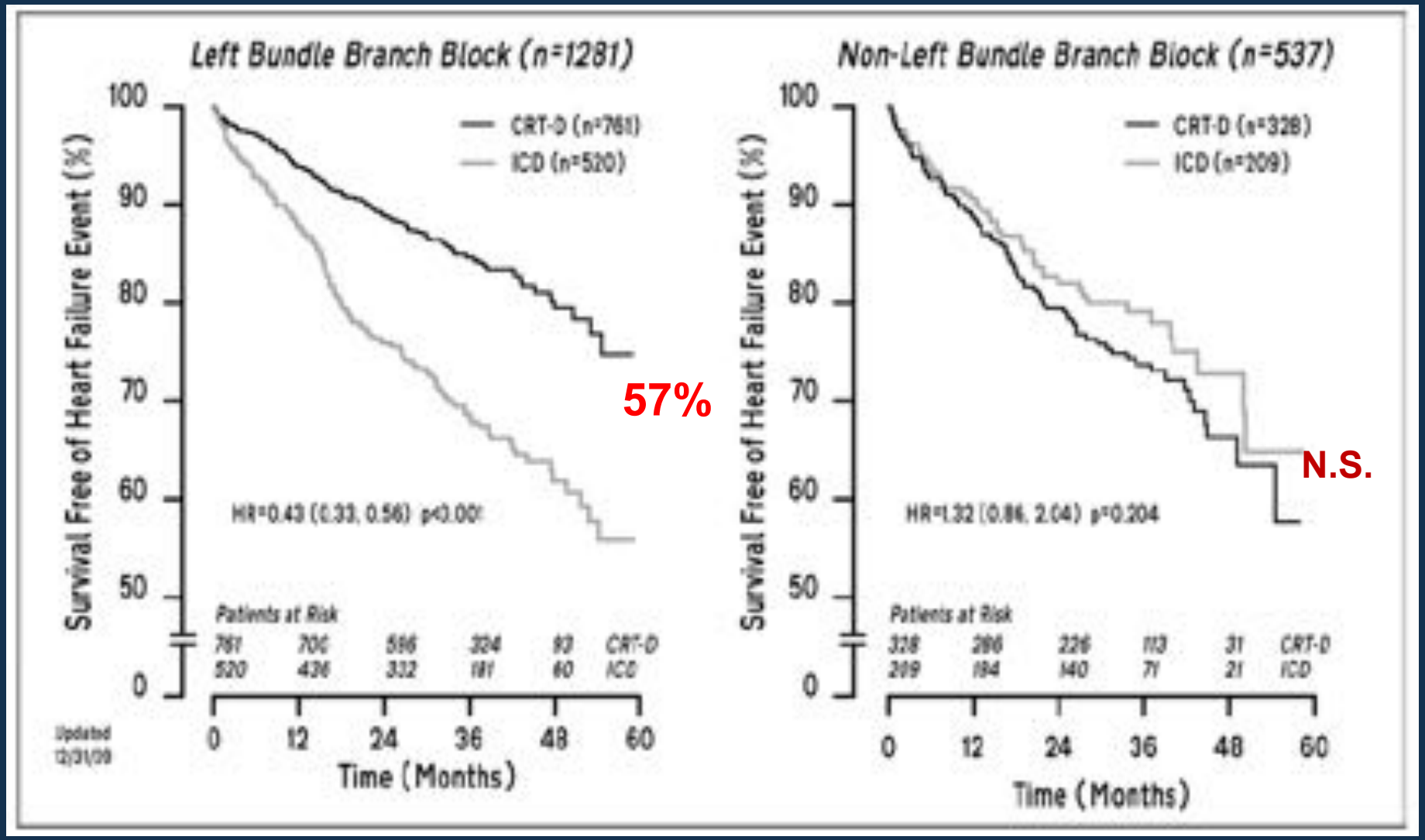
34% reduction in the risk of all-cause mortality or first HF event

- Benefit driven by **41% reduction** in the risk of heart failure events
- **Similar benefit** for ischemic and non-ischemic patient



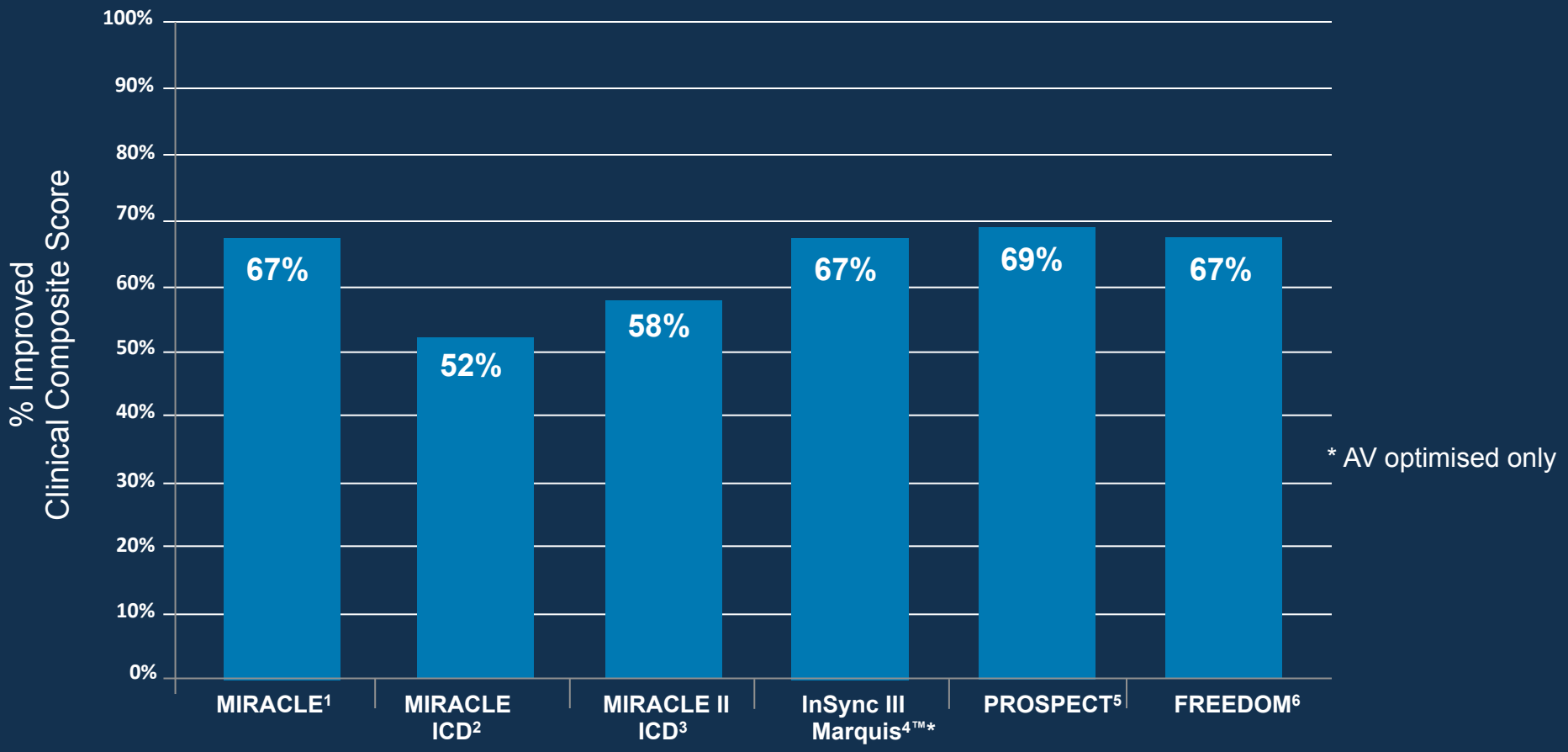
Moss AJ, Hall WJ, Cannom DS, et al. . NEJM. Sept 2009.

MADIT-CRT: Outcome by LBBB & Non-LBBB



The puzzle for CRT success

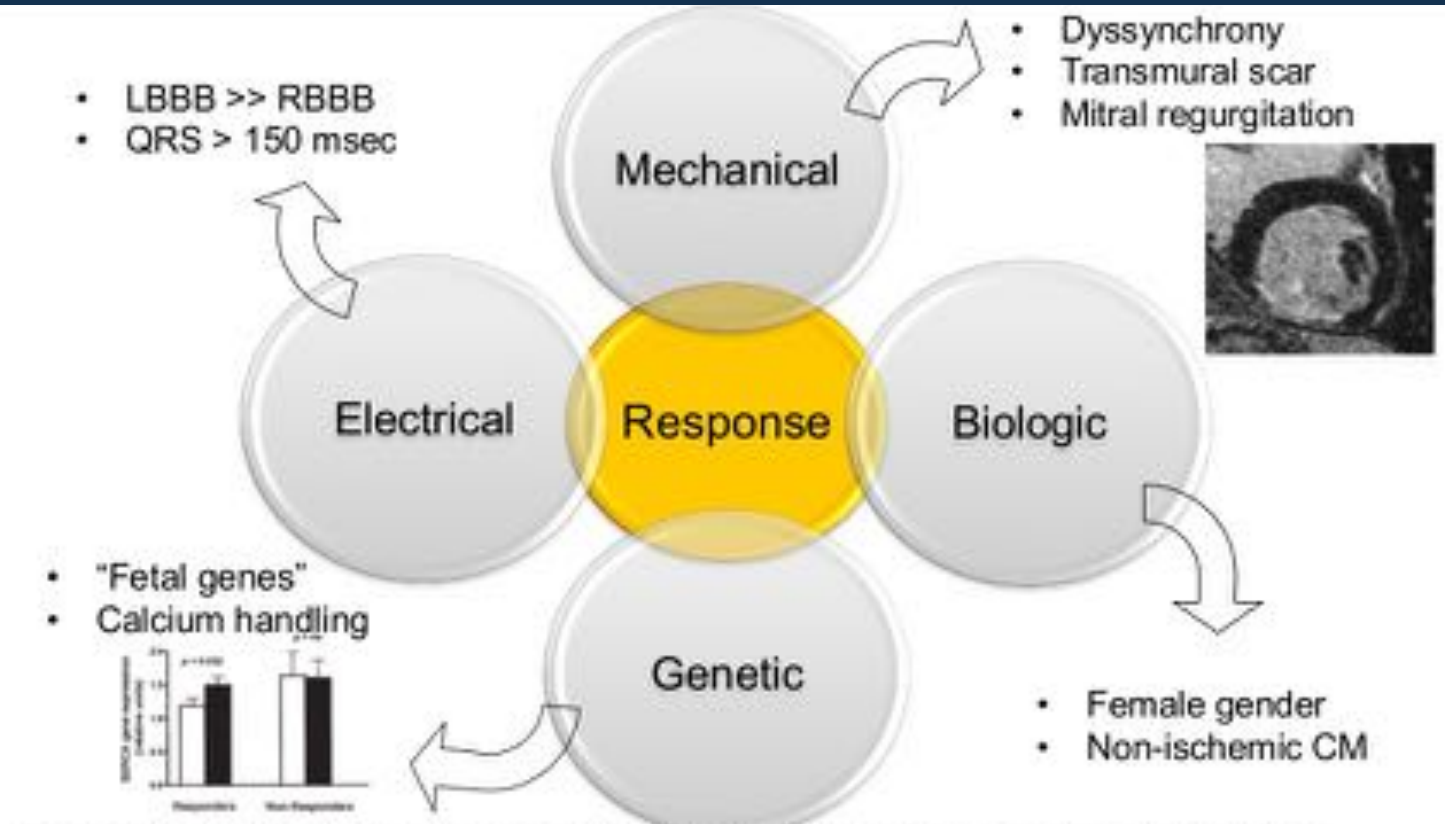
Left ventricular (LV) reverse remodelling is achieved in 60–70% of patients.



[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] Abraham WT, et al. *Heart Rhythm*. 2005;2:S65.
[5] Chung ES, et al. *Circulation.* 2008;117:2608-2616.
[6] Abraham WT, et al. *Late-Breaking Clinical Trials.* HRS 2010.


what have we learned?

Response to CRT is dependent upon multiple factors



Vanderheyden M, et al. J Am Coll Cardiol 2008;51:129–36; Moss AJ et. al. N Engl J Med. 2009;361:1329–1338.

How to Improve the CRT Success

- Selection of the pts
- Crt implant
- Follow up

Selection of the Pts

Imaging role

Value of Imaging in HF pts: useful for CRT also …

The selection of imaging modalities in HF pts depends on the information that's needed for the clinical management:

(1) underlying etiology (ischemic vs non-ischemic)

(2) in ischemic pts, evaluate need for revascularization

(myocardial ischemia / viability ?)

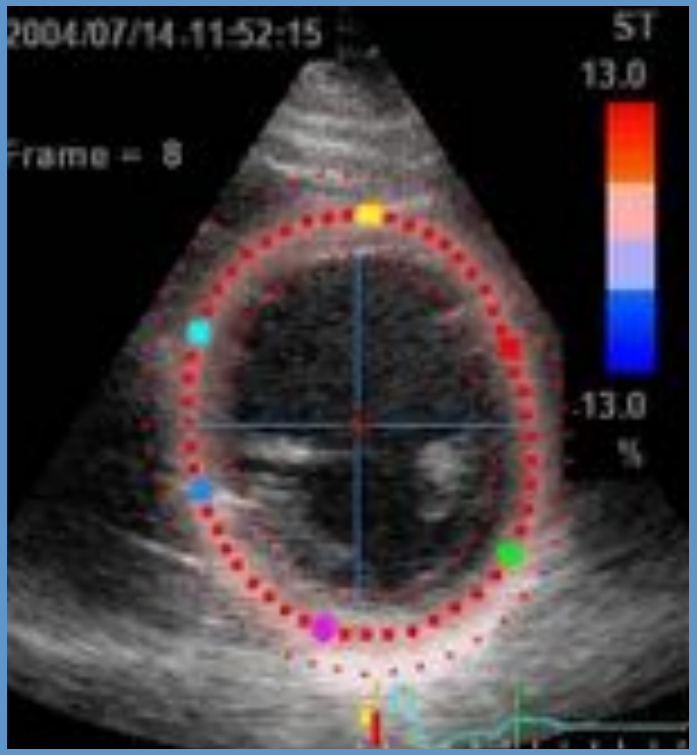
(3) LV function and shape assessment

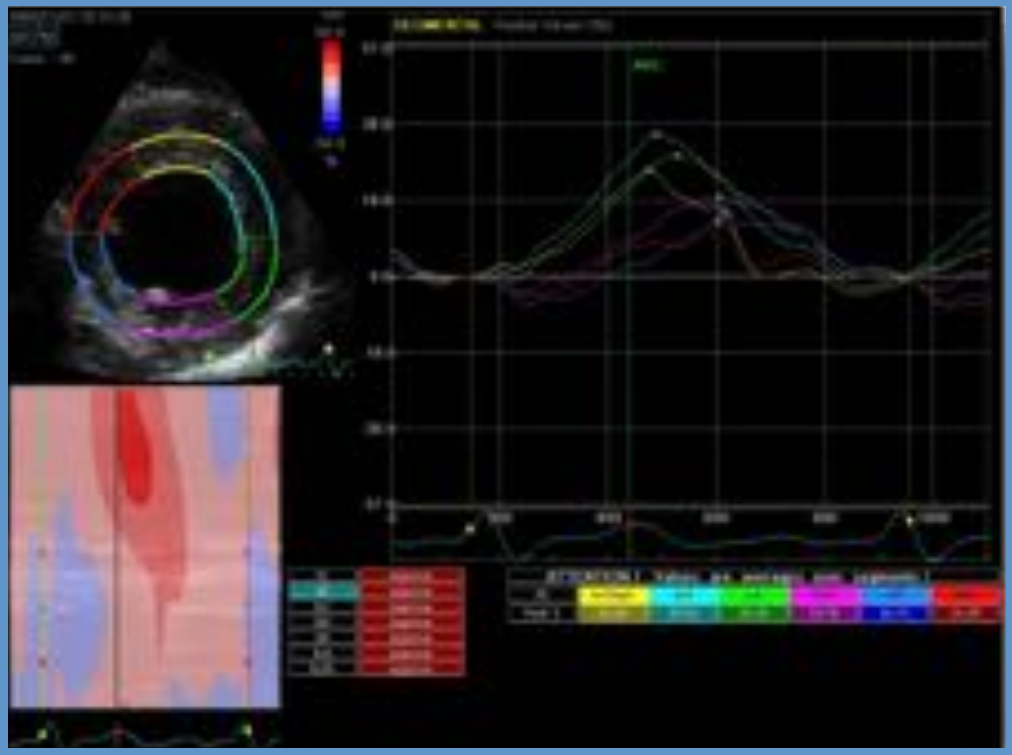
(4) presence of significant secondary mitral regurgitation

(5) device therapy with CRT and/or ICD (risk of SCD)

Bax JJ, Delgado V. *Myocardial viability as integral part of the diagnostic and therapeutic approach to ischemic HF*. J Nucl Cardiol 2015;22:229-45

Pre – CRT evaluation show the delay and to optimize response





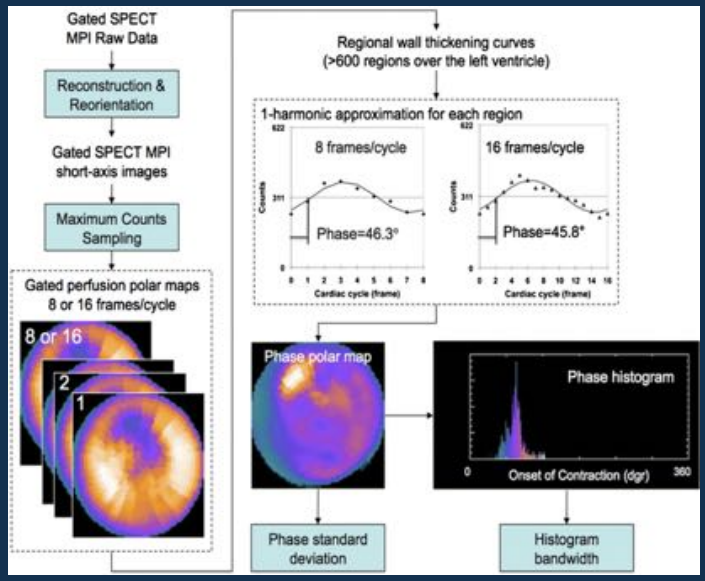
Echocardiographic speckle strain imaging can be used to identify the latest activated LV wall

Imaging to qualify candidates for CRT: SPECT

Imaging may help improve pts' selection.

Nuclear imaging techniques provide information on important pathophysiological determinants of response to CRT:

- Myocardial viability
- LV mechanical dyssynchrony
- Site of latest activation
- Extent and Location of LV scar tissue



*Phase analysis of ECG-gated **SPECT** myocardi*
perfusion imaging to assess LV dyssynchrony

Bax JJ, Delgado V. J Nucl Cardiol 2015;22:229-45

MRI

Cardiac resynchronization therapy in patients with postero-lateral scar by cardiac magnetic resonance: A systematic review and meta-analysis

Amin Daoulah, MD,[a,*] Alawi A. Alsheikh-Ali, MD, MSc,[b,c] Salem M. Al-Faifi, MD,[d] Sara R. Ochelbree, MD,[e] Ejazul Haq, MD,[a] Farhan M. Asrar, MD, MSc, MPH,[f,g] Adnan Fathey, MD,[a] Ali Ahmed Haneef, MD,[h] Faris Al Mousily, MD,[i] El-Sayed O, MD,[a] Amir Lotfi, MD[j]

MRI

Metanalysis of 11 prospective studies

(PubMed, EMBASE, Cochrane databases)

Conclusions:

The presence of transmural PL scar or significant scar within the LV pacing site detected by pre-implant MRI associates with a lower rate of clinical or echo response to CRT

Daoulah A & al. J of Electrocard 2015;48:783-90

Measurements of electrical and mechanical dyssynchrony are both essential to improve prediction of CRT response☆

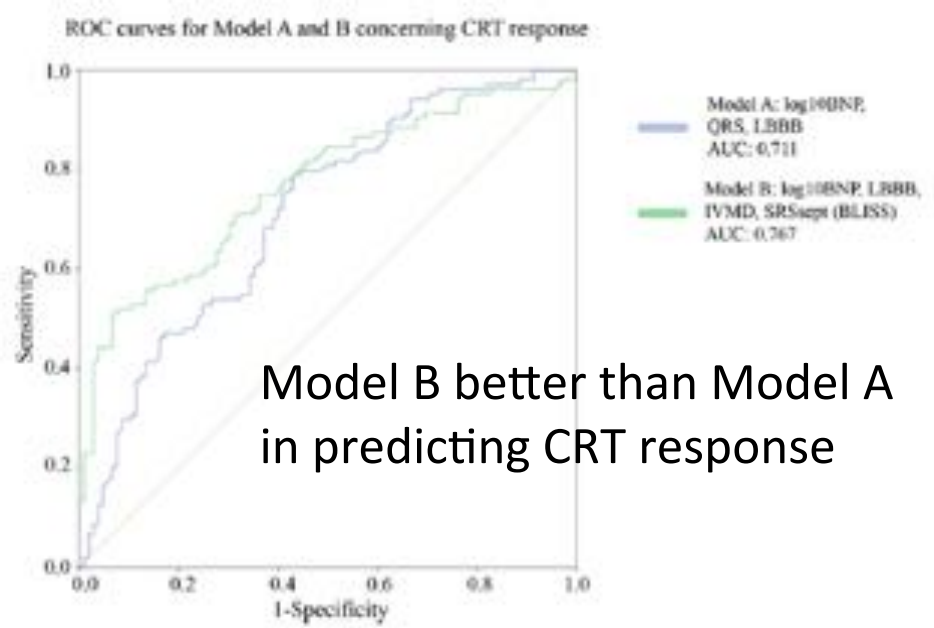
J. van't Sant, MD,* I.A.H. ter Horst, MD, S.C. Wijers, MD, T.P. Mast, MD, G.E. Leenders, MD, P.A. Doevendans, MD, PhD, M.J. Cramer, MD, PhD, M. Meine, MD, PhD

Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands

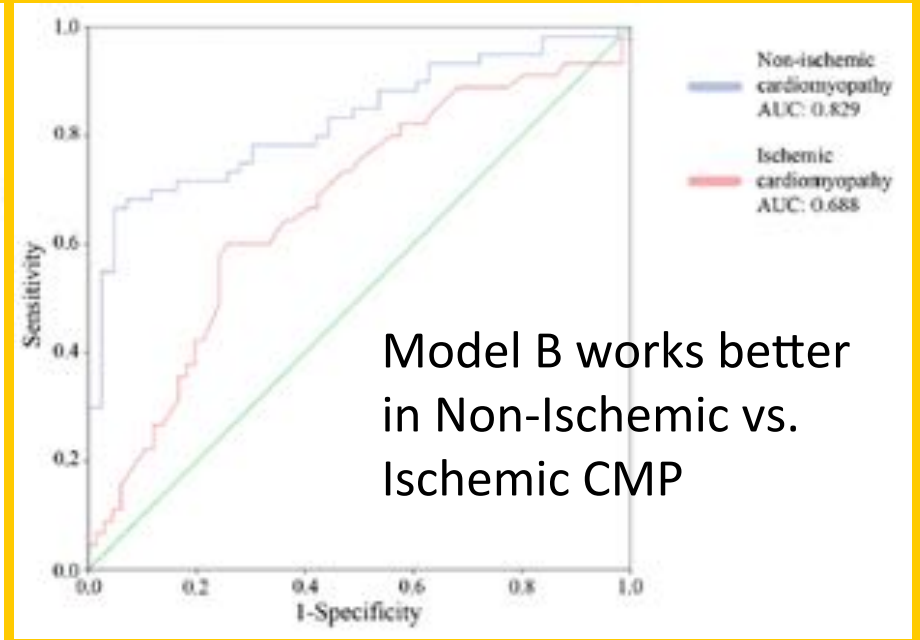
n = 227 CRT pts (51% ischemic)
Response was defined as "delta LVESV ≥ 15%" after 6M of CRT therapy.

Prediction models:

- Model A: clinical parameters and electrical dyssynchrony
- Model B: variables in model A + mechanical dyssynchrony (IVMD; SRS_{sept})



Model B better than Model A in predicting CRT response



Model B works better in Non-Ischemic vs. Ischemic CMP

van't Sant J & al. J of Electrocard 2015;48:601-8

Expanding populations

Expanding populations: pts who need V pacing

PRO: CRT may prevent pacing-induced CMP

Table 2
Randomized trials of biventricular versus right ventricular pacing

Acronym	Trial/Study	Better Outcomes with Bi-ventricular Pacing
BLOCK HF[38]	Biventricular vs right ventricular pacing in heart failure patients with AV block	Yes
PAVE[39]	Left ventricular-based cardiac stimulation after AV nodal ablation evaluation	Yes
ABLATE AND PACE[40]	Same	Yes
PACE[15,30,31]	Pacing to avoid cardiac enlargement	Yes
PREVENT- HF[41]	Preventing ventricular dysfunction in pacemaker patients without advanced heart failure	No
BIOPACE[42]	Biventricular pacing for atrioventricular block to prevent cardiac desynchronization	No
HOBIPACE[36]	Homburg biventricular pacing evaluation	Yes
COMBAT[37]	Conventional vs biventricular pacing in heart failure and bradyarrhythmias	Yes
Albertsen et al[43]	Conventional vs biventricular pacing in pacemaker patients with high-grade AV block	Yes

Herweg B & al. Card Electrophysiol Clin 2015;7:433-44

Expanding populations: pts who need V pacing

CONTRA: CRT is not appropriate for specific subgroups

CRT not appropriate for all pts requiring chronic RVp, mainly those **with preserved EF**.

No evidence that CRT reduces **mortality or symptoms** in pts with preserved LVEF.

Short FU reports show that CRT limits the decline of LVEF, but the absolute change in LVEF:

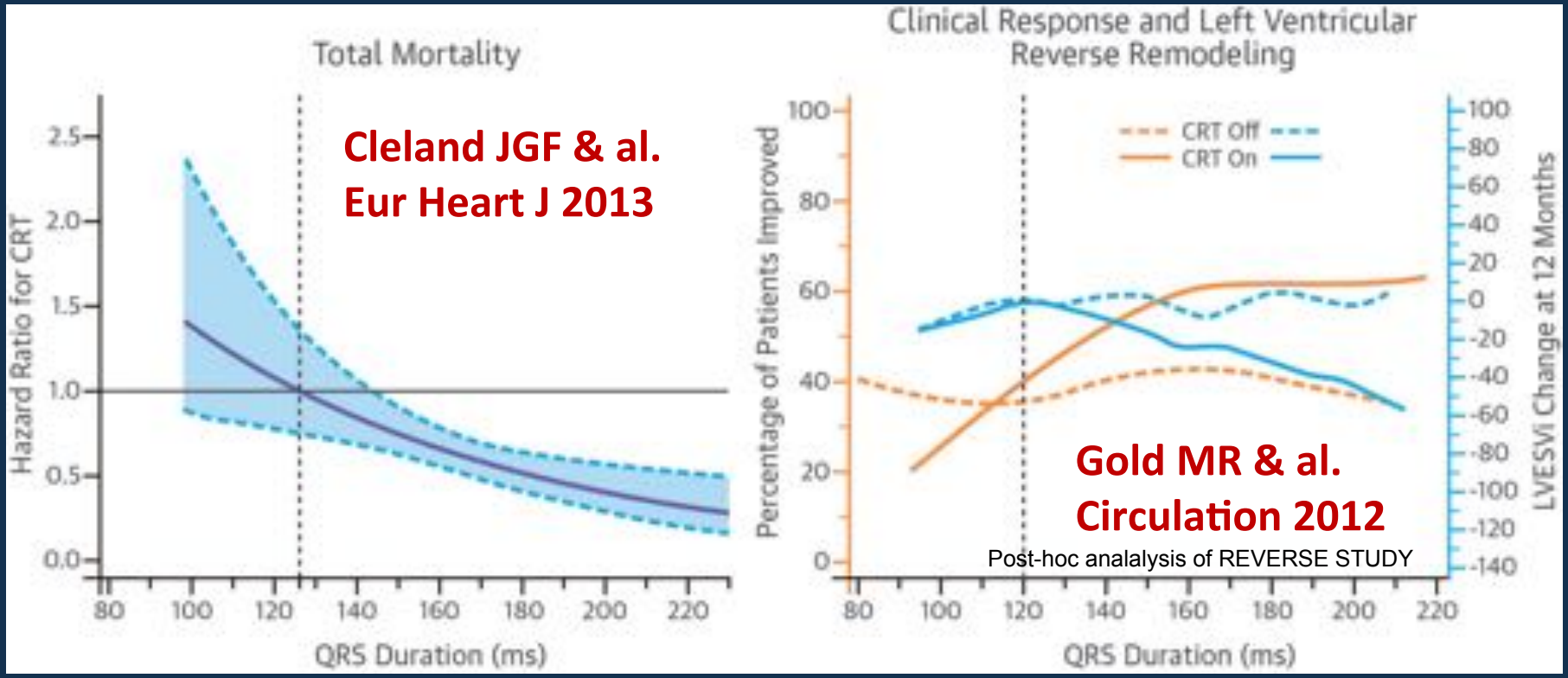
- is very limited
- does not associate with adverse clinical outcomes.

Implantation of a BiVp system is associated with:

- **longer procedure** time
- increased **fluoroscopy exposure**
- high rate of lead **complications and malfunction**

Expanding CRT populations: NARROW QRS ?

Several single-center studies showed a symptomatic benefit from CRT.



Leyva F & al. *20 Years of CRT.* JACC 2014;64(10):1047–58

CRT techniques: where we're going ...

alternatives pacing modes

Why to propose alternatives pacing modes?

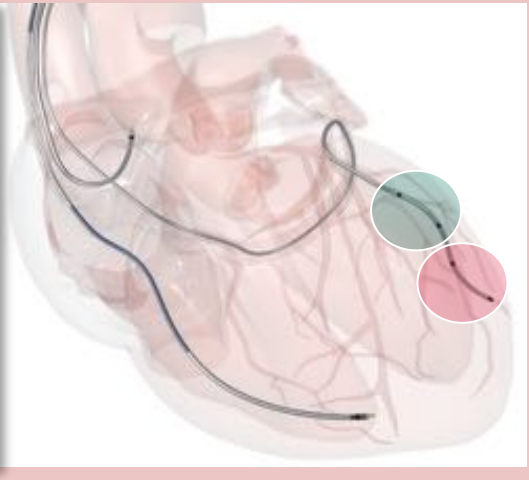
- *LV dyssynchrony is a complex process involving not only one LV spot but usually a large area*
- *Pacing in one spot at the epicardium level may not totally correct LV dyssynchrony and so may provide a sub-optimal resynchronization.*
- *With non optimal resynchronization the response to CRT may be sub-optimal or absent.*

Alternative Biventricular pacing

- Has been recently proposed as a safe and efficient method of resynchronization :
  - Dual site stimulation
  - Multi-area stimulation (RV + 2 LV // 2 RV + LV)
  - Multi site stimulation

Quadripolar Lead

- A quadripolar LV lead : with three ring electrodes located 20, 30, and 47 mm from the tip electrode.
- With compatible pacing system, it is possible to deliver independent pacing pulses to multiple electrodes of the lead, potentially capturing a larger area and engaging multiple zones in the long axis of the LV.



CRT delivery techniques: innovating approaches …

MULTISITE approach

- **Multi-Point-Pacing (MPP)**

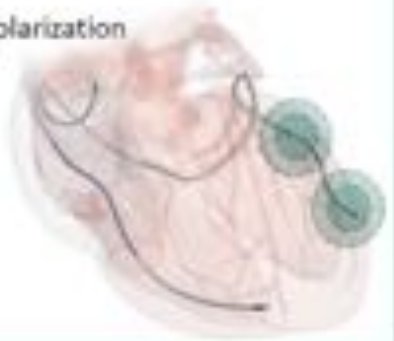
  Rinaldi CA, ***JICE 2014***

  Pappone C, ***Heart Rhythm 2014***

  Calò L, ***Am H J 2014***

  - Capture a larger area
  - Engage areas around scar tissue
  - Improve pattern of depolarization/repolarization
  - Improve hemodynamics
  - Improve resynchronization

  → **Improve CRT response**



- **Multi-Area-Pacing (MAP)**

Dual-site LV CRT:

Theoretical advantages in **faster and more physiological LV activation**.
Some clinical evidence supports dual LV pacing.
Sanoa & al. Europace 2009;11(Suppl-5):v29-31

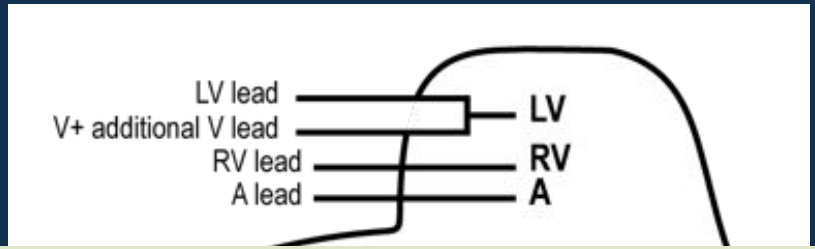
Triangle-V pacing (2RV+1LV):

Conventional BiV in pts with severe HF & dyss might not produce
A sufficient resynch. effect in the LV anterior free wall.
Tri-V may improve the resynchronization of the **LV anterior free wall**
(earlier depolarization benefiting from the additional RVOT pacing)
Yoshido & al. Eur Heart J. 2007;28(21):2610-9

CRT delivery techniques: innovating approaches …

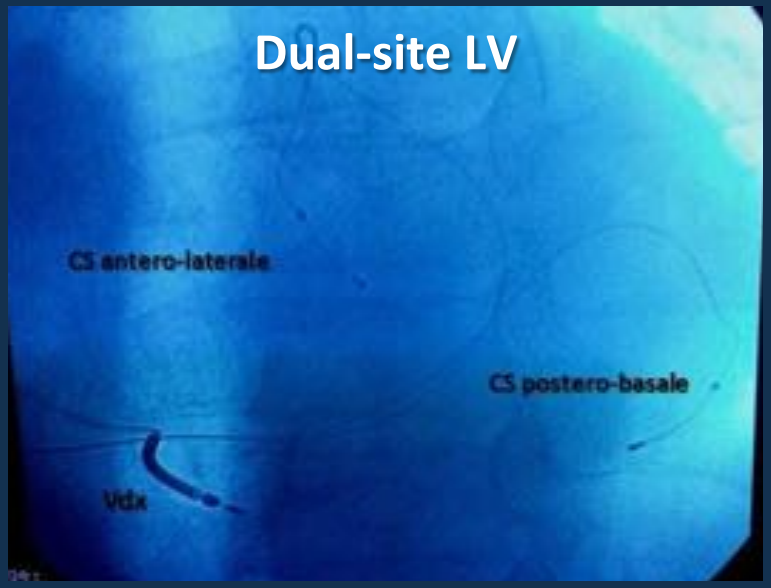
MULTI-AREA-PACING

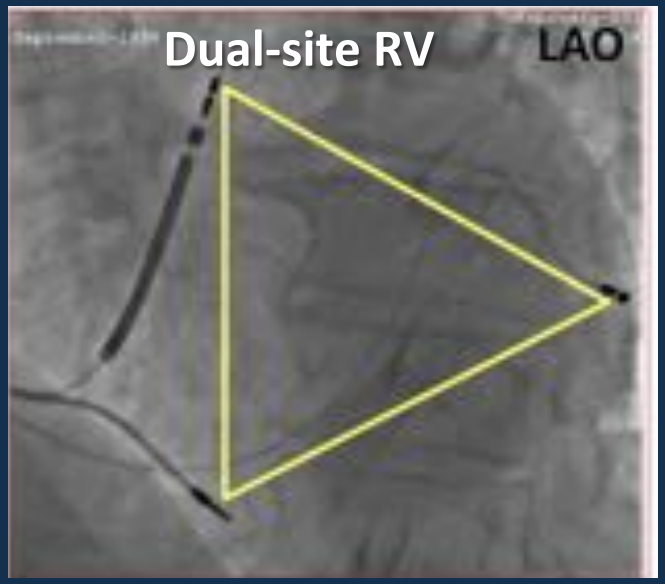
Dedicated TriV devices
modified header for
3 ventricular connections



No need for **Y-ADAPTOR**
Hypothetical **TriV configurations**:

- Dual-site RV
- Dual-site LV





CRT techniques: innovating approaches …
MULTI-AREA-PACING & Echo-optim @ implant

Intra-op echo-guided RV lead placement during CRT implant is **FEASIBLE** and acutely improves LV synchrony vs std BiV.

Most **optimized configurations** will require two RV leads, resulting in **TRIPLE-SITE V PACING**.

Long-term controlled studies needed to confirm whether a mechanically guided implant associates with better outcomes.

First experience of intraoperative echocardiography-guided optimization of cardiac resynchronization therapy delivery

Première expérience d'optimisation de la thérapie de resynchronisation cardiaque par une échocardiographie peropératoire

Ghassan Moubarak[a,*], Philippe Ritter[b], Jean-Claude Daubert[c], Serge Cazeau[a]

Moubarak G & al. Archives of CV Diseases 2014

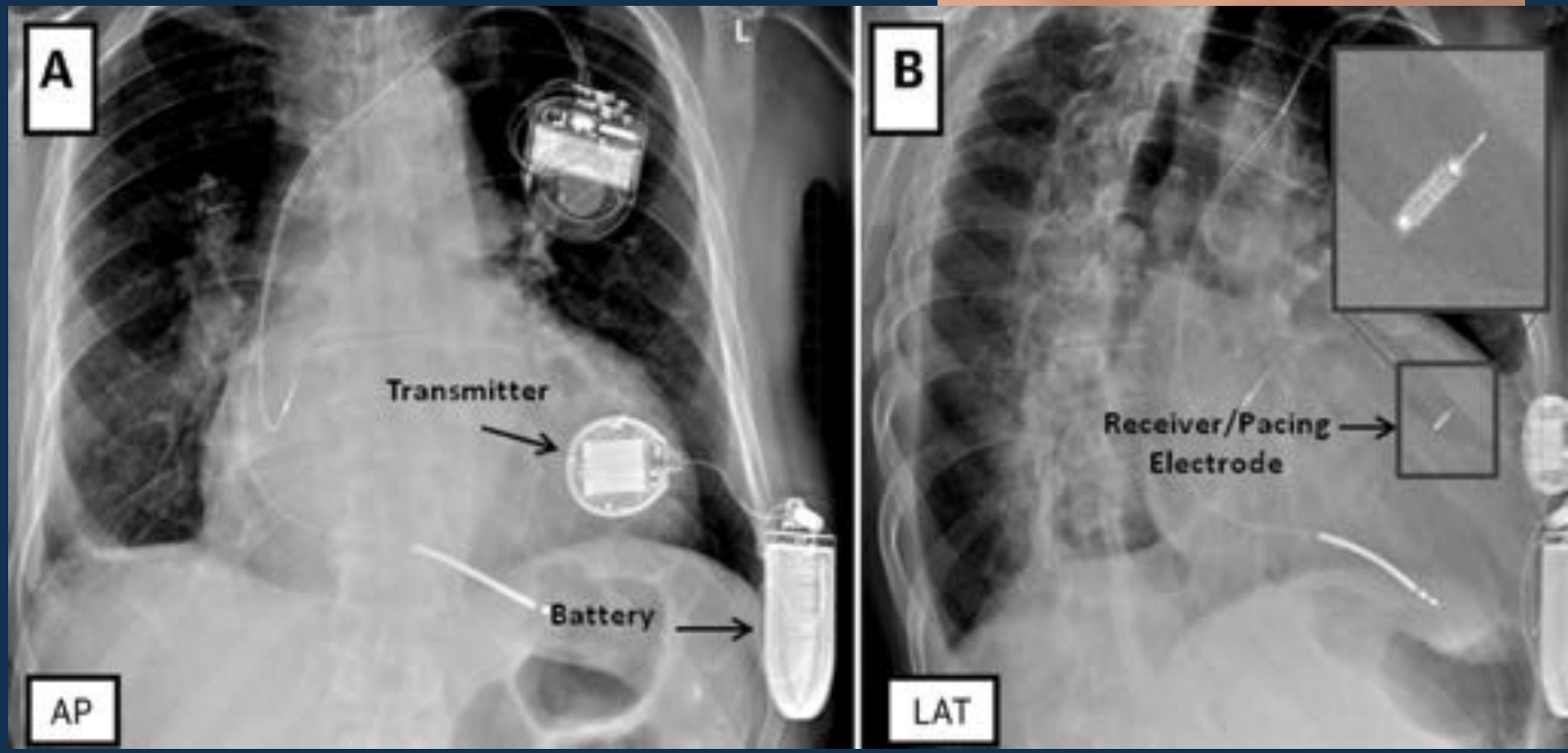
Table 1 Final pacing configuration.

	Final pacing configuration		
	Standard biventricular	Optimized biventricular	Triple-site ventricular
First implantation (n = 46)	5	16	25
Upgrade from dual-chamber pacemaker (n = 31)	10	6	15
Biventricular reoperation (n = 14)	0	0	14
Total (n = 91)	15 (17%)	22 (24%)	54 (59%)

CRT implant techniques: where we're going …

CRT delivery techniques: where we're going …

Leadless CRT …

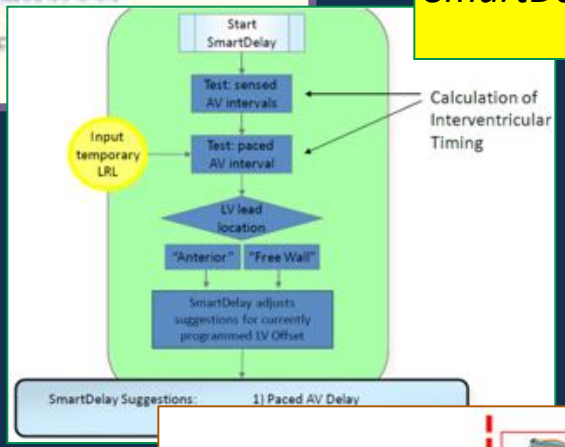


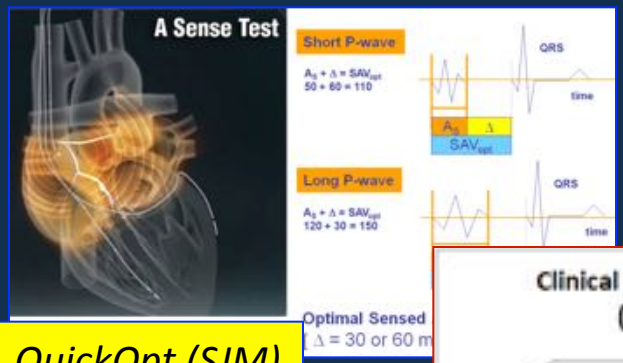
3) no instances of intra-procedural adverse events (15).

Miller MA & al. *Leadless Cardiac Pacemakers: Back to the Future.* JACC 2015:66(10):1179-89

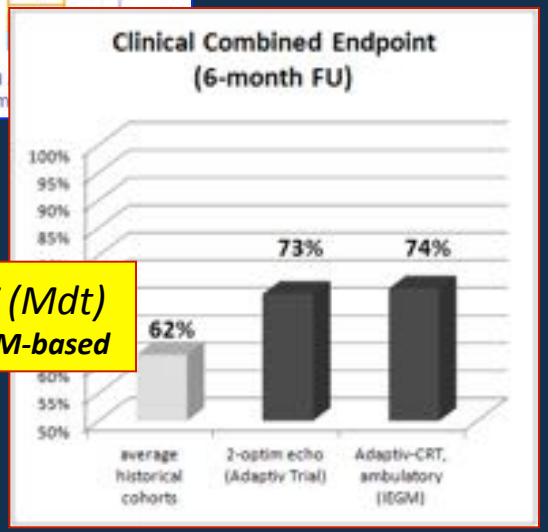
CRT post-implant care: Optimize, Optimize, Optimize …

SmartDelay (BSx)
IEGM-based

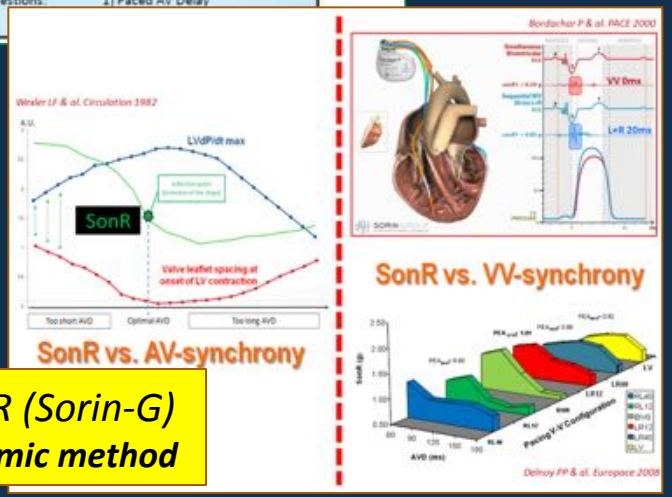




QuickOpt (SJM)
IEGM-based



Adaptive-CRT (Mdt)
IEGM-based

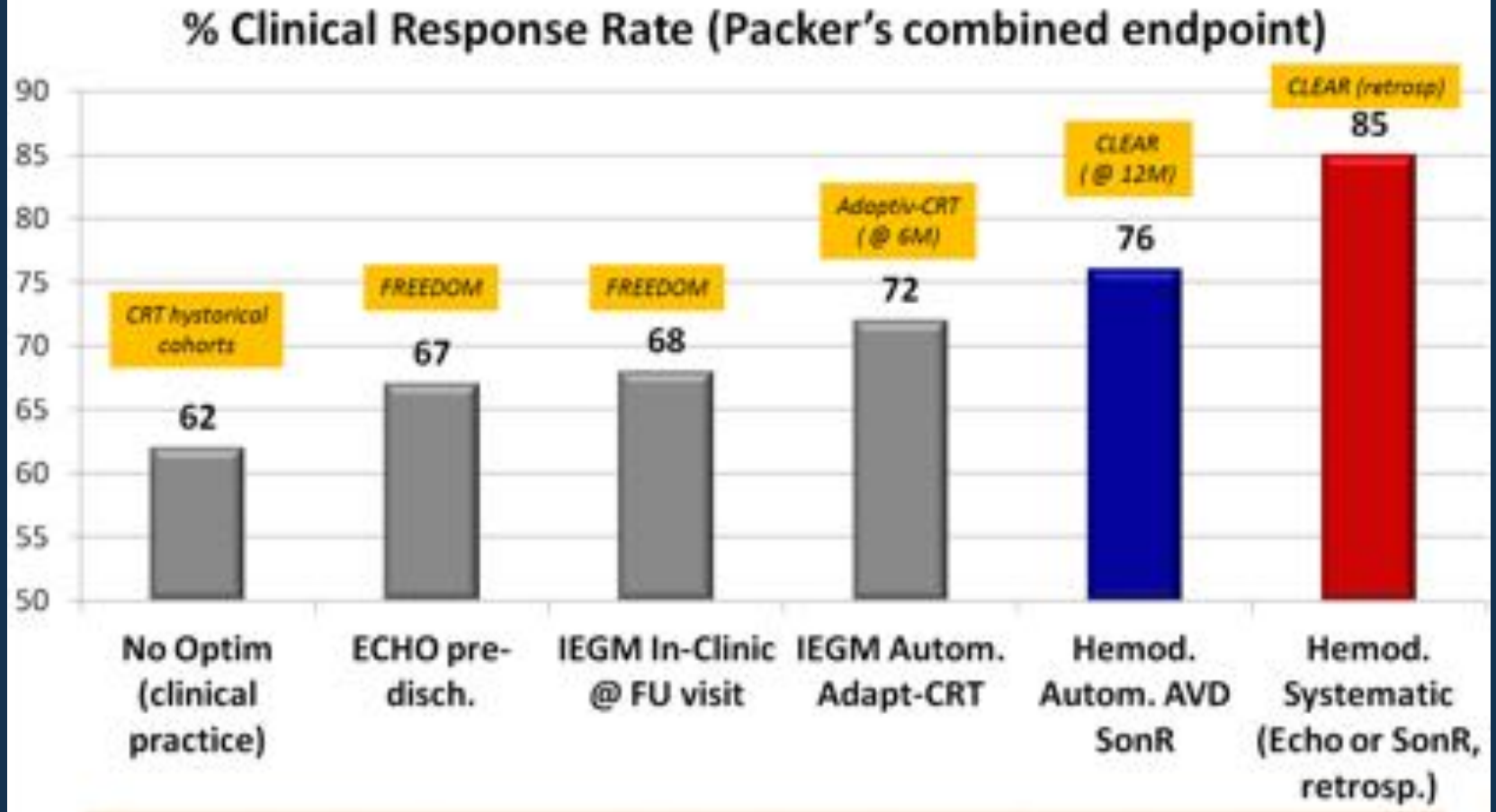


SonR (Sorin-G)
hemodynamic method

Lunati M & al.
JAFIB 2014;7(2)

CRT post-implant care: Optimize, Optimize, Optimize …

FU of CRT pts: the effects of optimization



*The combination of proper tools (**hemodynamic sensor**) together with a **frequent re-optimization** associates with a very high clinical response rate*

→ this relationship must be PROSPECTIVELY confirmed …

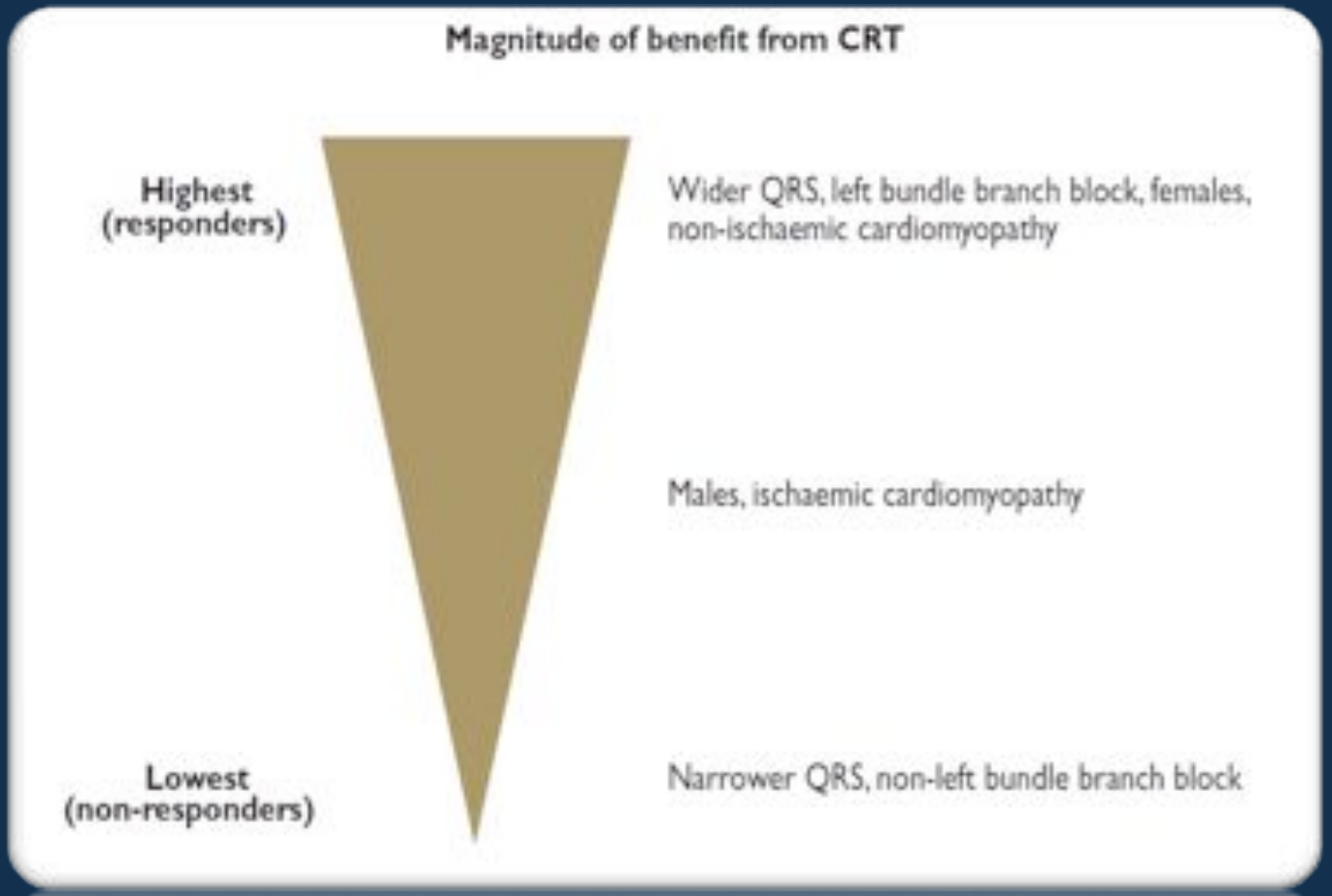
Lunati M & al. JAFIB 2014;7(2)

Conclusions open question

- **Areas for improvement in CRT**
  - Pts' Selection:
    - Imaging is promising
    - Subgroups (ongoing trials): AF, chronic RVp
  - CRT Technique:
    - Lead position optimization @ implant
    - Multi-Point / Multi-Area (ongoing trials)
    - LV endocardial (safety/efficacy?)
    - Leadless CRT (?)
  - Post-Implant Care:
    - Recommended a Pre-Hospital Discharge assessment
    - Systematic Optimization during FU (automatic tools, echo)

- **Underuse of CRT**
  - Awareness / cultural barriers: education / GL
  - Cost / Reimbursement issues (Country-dependant)
  - Eligibility criteria to be "fine tuned"

Clinical factors influencing the likelihood to respond to CRT.



European Heart Journal June 2013

CRT delivery techniques: where we're going …

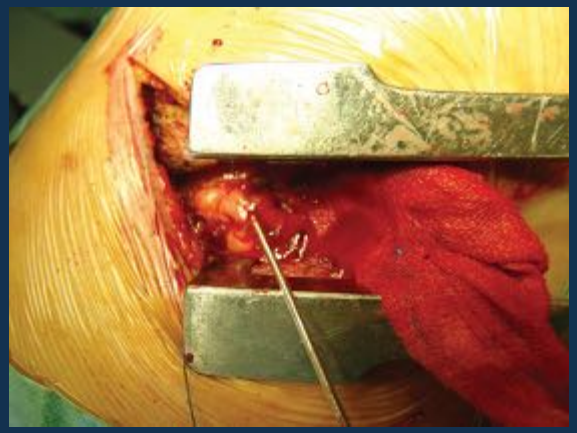
LV ENDOCARDIAL approach

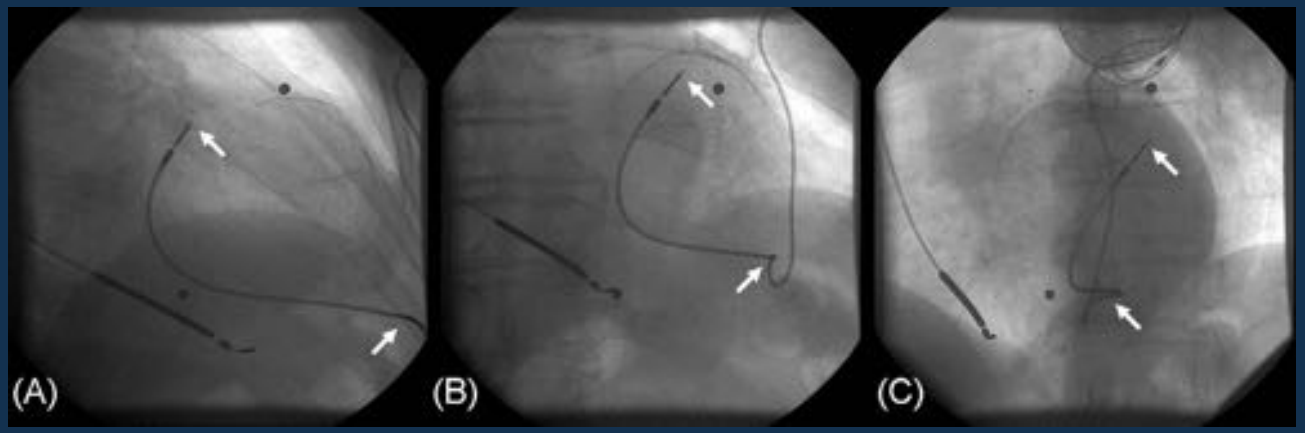
Trans-Septal approach

Known since late 90's, controversial outcomes in the beginnings
Still limited available clinical data (although positive) regarding efficacy and safety
Need for more long-term data

Trans-Apical approach

Same advantages than trans-septal, but less concerns about MR and extraction issues.
Case Reports only up to date …





Kassai I & al. *Transapical endocardial lead implantation for LV free wall pacing.* Europace 2008 (doi: 10.1093/europace/eun090)

CRT delivery techniques: where we're going …
LV ENDOCARDIAL TRANSAPICAL approach

della stimolazione endocardica
pia di resincronizzazione cardiaca
diante approccio transapicale

ito, Piersilvio Gerometta, Federica Michelotti, Bruno Passaretti, Antonino Piti

rdiovascolare, Cliniche Humanitas Gavazzeni, Bergamo

Mascioli G & al. Giornale Italiano di Cardiologia 2015;16(9):508-12 (two clinical cases of RE-DO CRT)

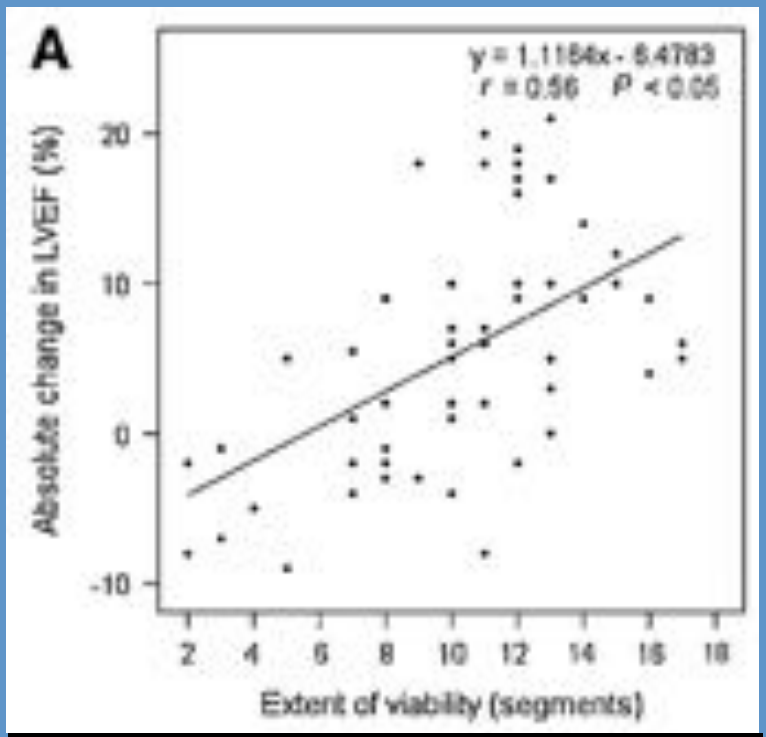
Extent of Viability to Predict Response to Cardiac Resynchronization Therapy in Ischemic Heart Failure Patients

J Nucl Med 2006; 47:1565–1570

Claudia Ypenburg[1], Martin J. Schalij[1], Gabe B. Bleeker[1,2], Paul Steendijk[1], Eric Boersma[3], Petra Dibbets-Schneider[4], Marcel P. Stokkel[4], Ernst E. van der Wall[1], and Jeroen J. Bax[1]

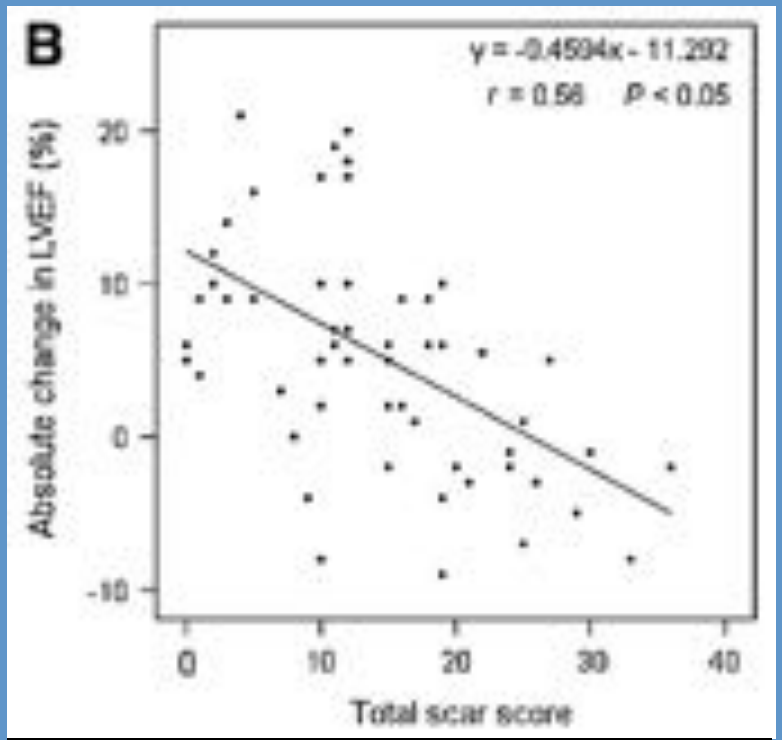
myocardial viability may be important for response to CRT.

all pts underwent nuclear imaging with 18F-FDG SPECT before implantation.



relation between the extent of viability and the absolute change in LVEF

after 6 mo of CRT.



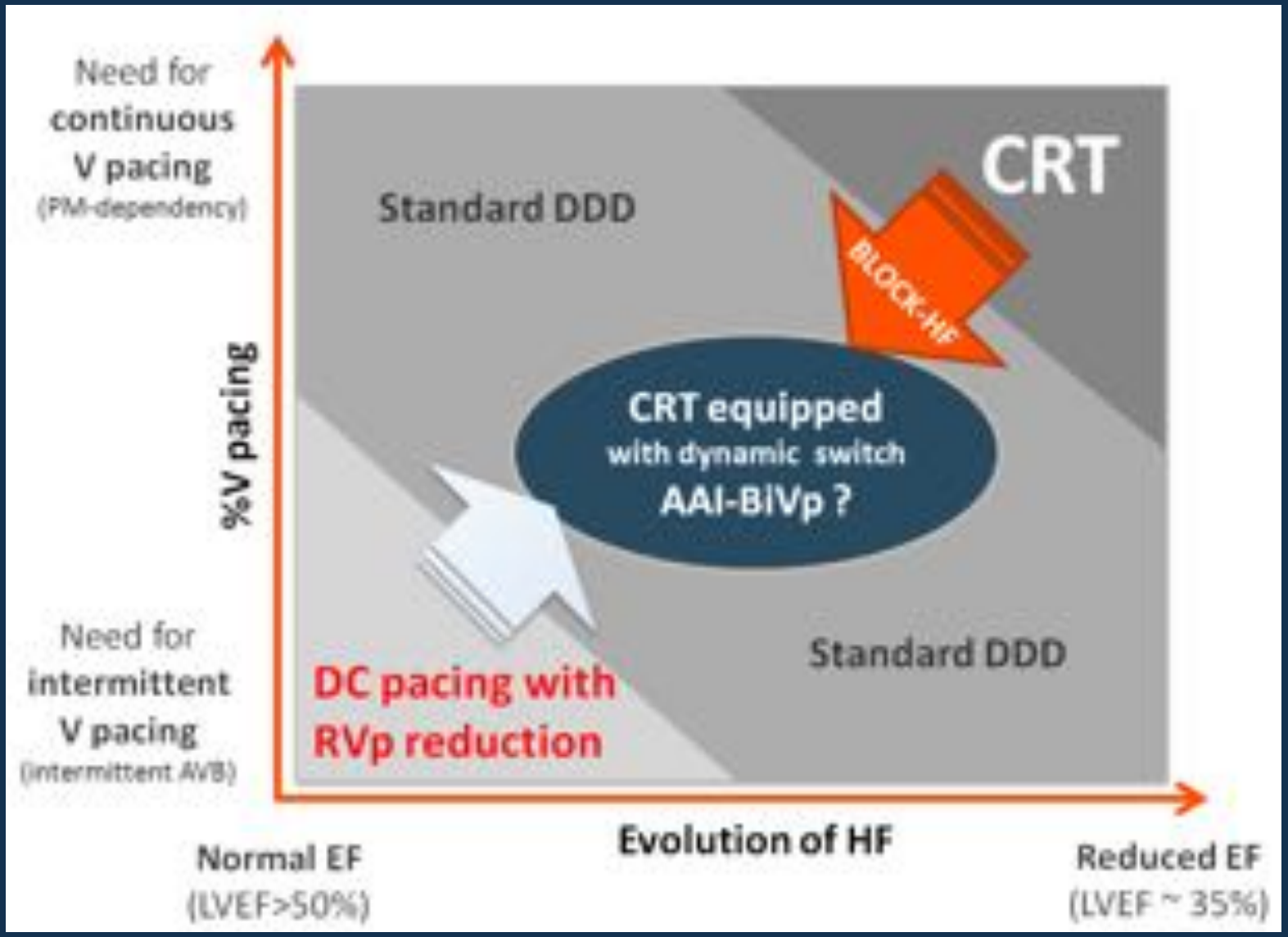
the total scar score was inversely related to the change in LVEF

Effects of CRT on left ventricular size and function in patients with average IC (NYHA Class II)

The CRT in class II acts by limiting the progression of the disease

LVESD, Left ventricular end-systolic diameter;
LVED volume, Left ventricular end-diastolic volume;
LVES volume, Left ventricular end-systolic volume;
Donal E et al. Eur Heart J (2006) 27;1018-1025

Expanding CRT populations: pts who need (continous/intermittent) Vp



Implantation Feasibility, Procedure-Related Adverse Events and Lead Performance During 1-Year Follow-Up in Patients Undergoing Triple-Site Cardiac Resynchronization Therapy: A Substudy of TRUST CRT Randomized Trial

- 100 PTS randomized in a 1:1 to conventional or triple-site CRT-D
- Fluoroscopic TIME TRIV system longer VS conventional
- Implantation success-rate similar
- Adverse events at 1 year FU were similar

12 months FU NYHA CLASS III/IV :

30% pz with conv CRT

12.5% TRIV CRT

Radoslaw L. et Coll. J. C. Electrophysiol 2012;23:1228-1236

1980

Abnormalities in intraventricular conduction, associated or not with delays in atrioventricular conduction, can adversely affect hemodynamic performance through the discoordination of cardiac contraction

Askenazi J.et al. Am J Cardiol.1984;53:99-104.

1984

Researchers have explored the extraordinarily simple original hypothesis that mechanical discoordination caused by delays in electrical conduction can be reverted by atrioventricular electrical stimulation