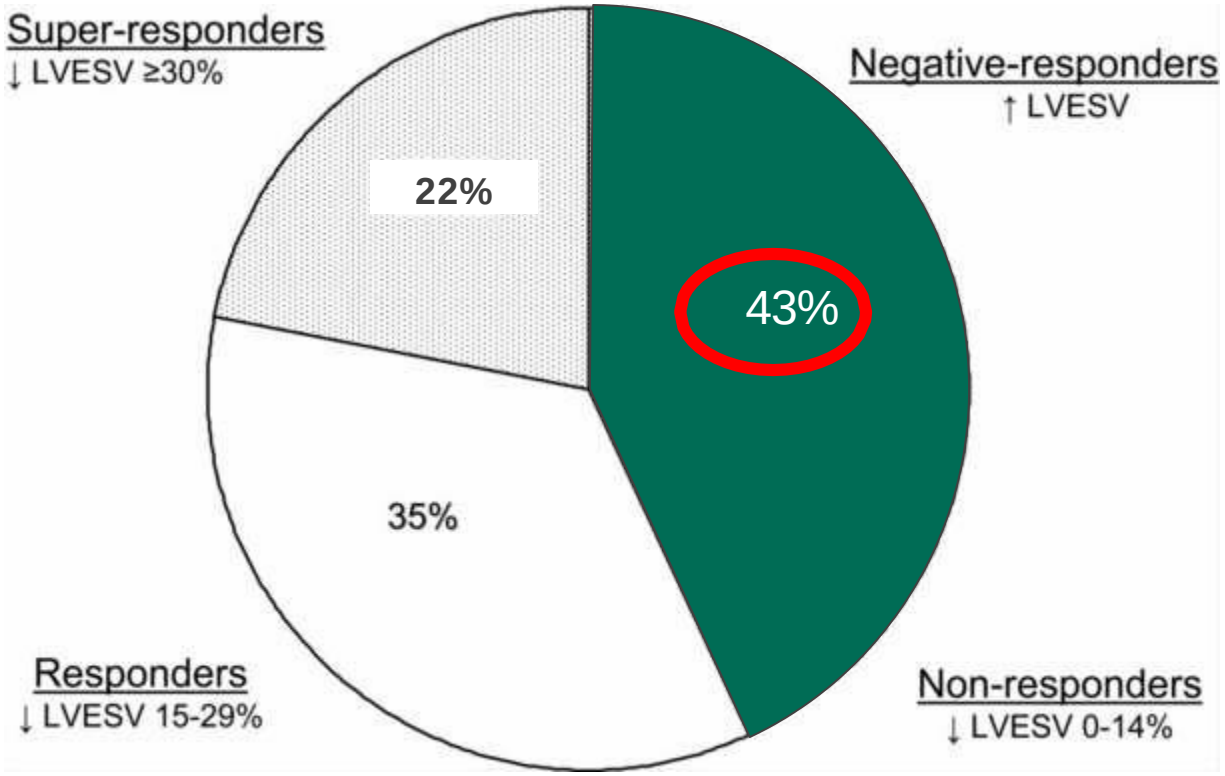
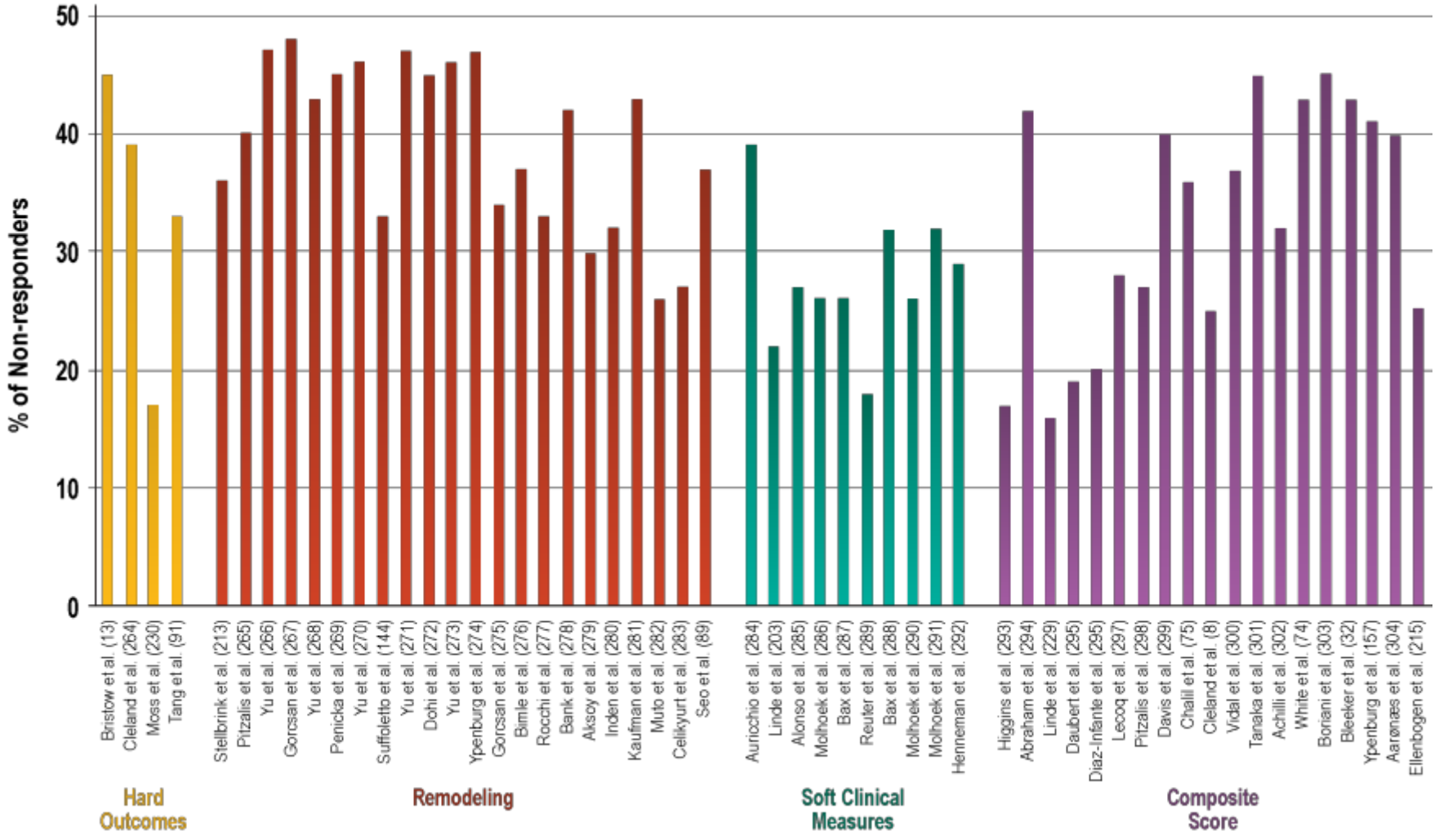
CRT Challenge



43% of CRT patients classified as negative or non-responders after 6 months

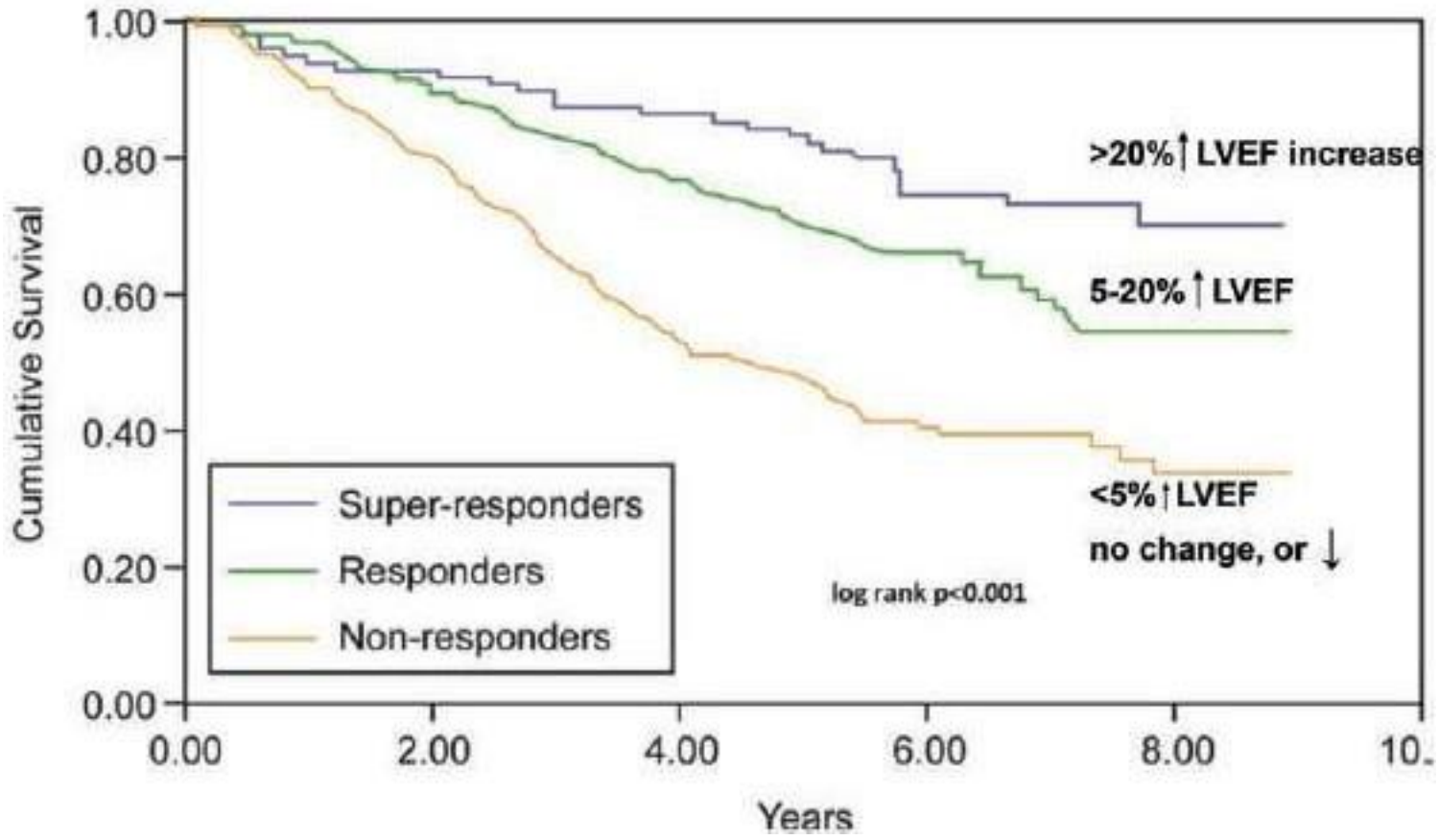
Ypenburg, C., et al. Journal of the American College of Cardiology 2009

CRT Response: Inadequate and unpredictable



Daubert, J.C., et al. Europace, 2012

Survival Effect of CRT of Super-Responders, Responders, and Non-Responders



Rickard et al. Heart Rhythm 2014

Who is CRT responder? Different definition

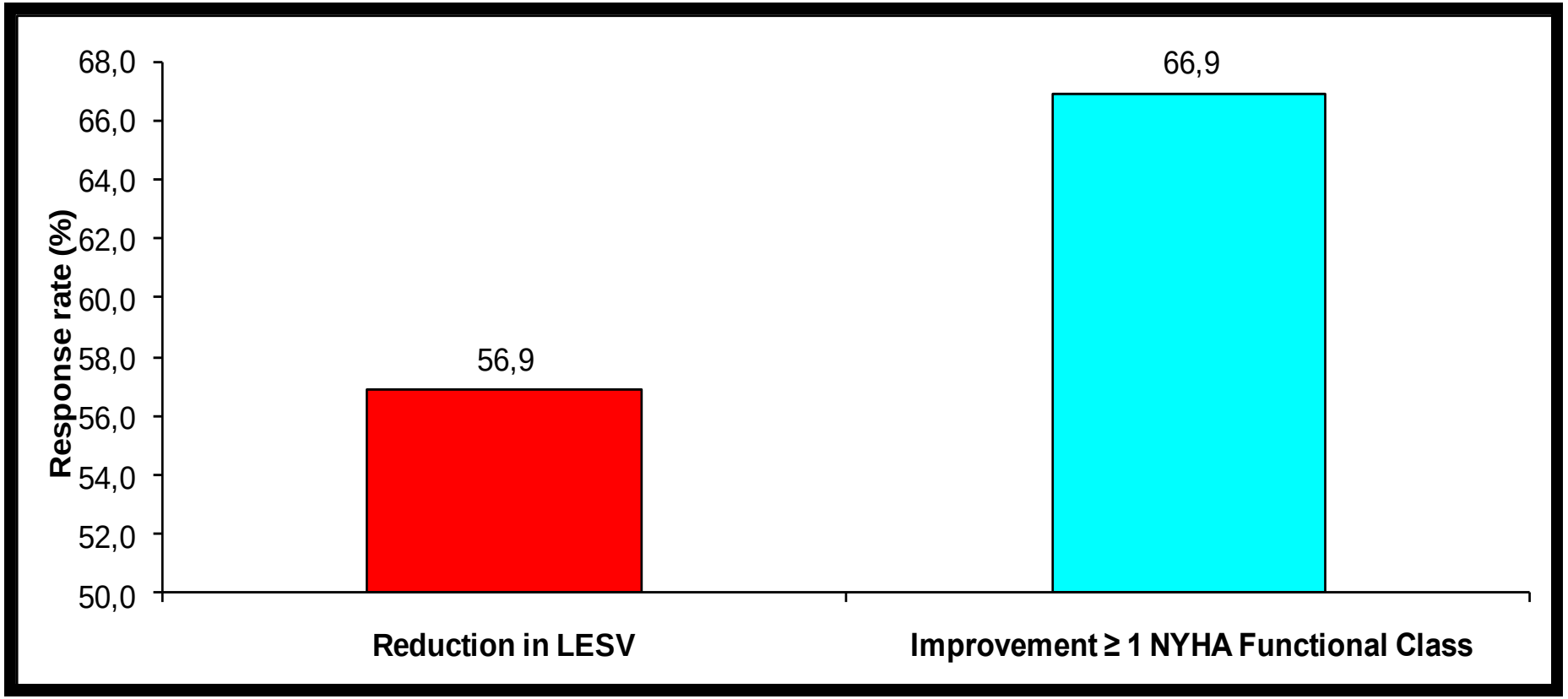
Table 1. Recent trials with the reports of nonresponder rate to cardiac resynchronization therapy

No.	References	Patient no.	Inclusion criteria	Parameters of response	Follow-up time	Response (nonresponse) rate
01	Goldstein *et al.* [12]	1820	EF ≤ 30%, QRS ≥ 130 ms, 55% ischemic	≥30% reduction in LVESV	1 year	58% (42%)
02	Hoogslag *et al.* [13]	170	EF 27 ± 7%, QRS 154 ± 23 ms, 65% ischemic	Improvement by ≥1 NYHA classes; ≥15% reduction in LVESV; ≥15% decrease in NT-proBNP	6 months	66% (34%) 58% (42%) 54% (46%)
03	Delnoy *et al.* [14]	199	NYHA III/IV, EF ≤ 35%, LVEDD ≥ 30 mm/m^2, QRS > 120 ms, 39% ischemic	Improvement by ≥1 NYHA classes or ≥10% increase in EuroQol-Visual Analogue Scale score	6 months	61% (39%)
04	Khan *et al.* [15]	220	NYHA III/IV, EF ≤ 35%, QRS ≥ 120 ms, 56% ischemic	≥15% reduction in LVESV; improvement by ≥1 NYHA classes	6 months	70% (30%) 83% (17%)
05	Ritter *et al.* [16]	238	NYHA III/IV, EF < 35%, QRS > 150 ms or >120 ms with mechanical dyssynchrony, 39% ischemic	Free from death or hospitalization and improvement by ≥1 NYHA classes or ≥10% decrease in QOL score	1 year	63% (37%)
06	Gold *et al.* [17]	426	EF 26 ± 7%, QRS 151 ± 19 ms, 59% ischemic	>15% reduction in LVESV; >10 points decrease in QOL score	6 months	68% (32%) 72% (28%)
07	Khan *et al.* [18]	131	NYHA III/IV, EF ≤ 35%, QRS ≥ 120 ms, 57.3% ischemic	≥15% reduction in LVESV	6 months	58% (42%)
08	Leyva *et al.* [19]	322	EF 24.2 ± 10.2%, QRS 157.4 ± 28.7 ms, 65% ischemic	Improvement by ≥1 NYHA classes or ≥25% increase in 6-min hall-walk distance	1 year	78% (22%)
09	Muto *et al.* [20]	231	EF < 35%, QRS ≥ 120 ms, NYHA III/IV, LVEDD ≥ 55 mm, 43% ischemic	≥10% reduction in LVESV	6 months	74% (26%)
10	Boriani *et al.* [21]	176	NYHA III/IV, EF ≤ 35%, QRS ≥ 130 ms, LVEDD ≥ 55 mm, 52% ischemic	NYHA functional change and ≥5 mm decrease in LVESD or improvement in heart failure composite score or ≥10% decrease in LVESV	6 months	76% (24%)

- The% of non-responders depends on the parameter that you chose to measure and the cut-off value to define the response.
- Expect 100% responder is not realistic.

Curr Opin Cardiol 2015;30:40-9

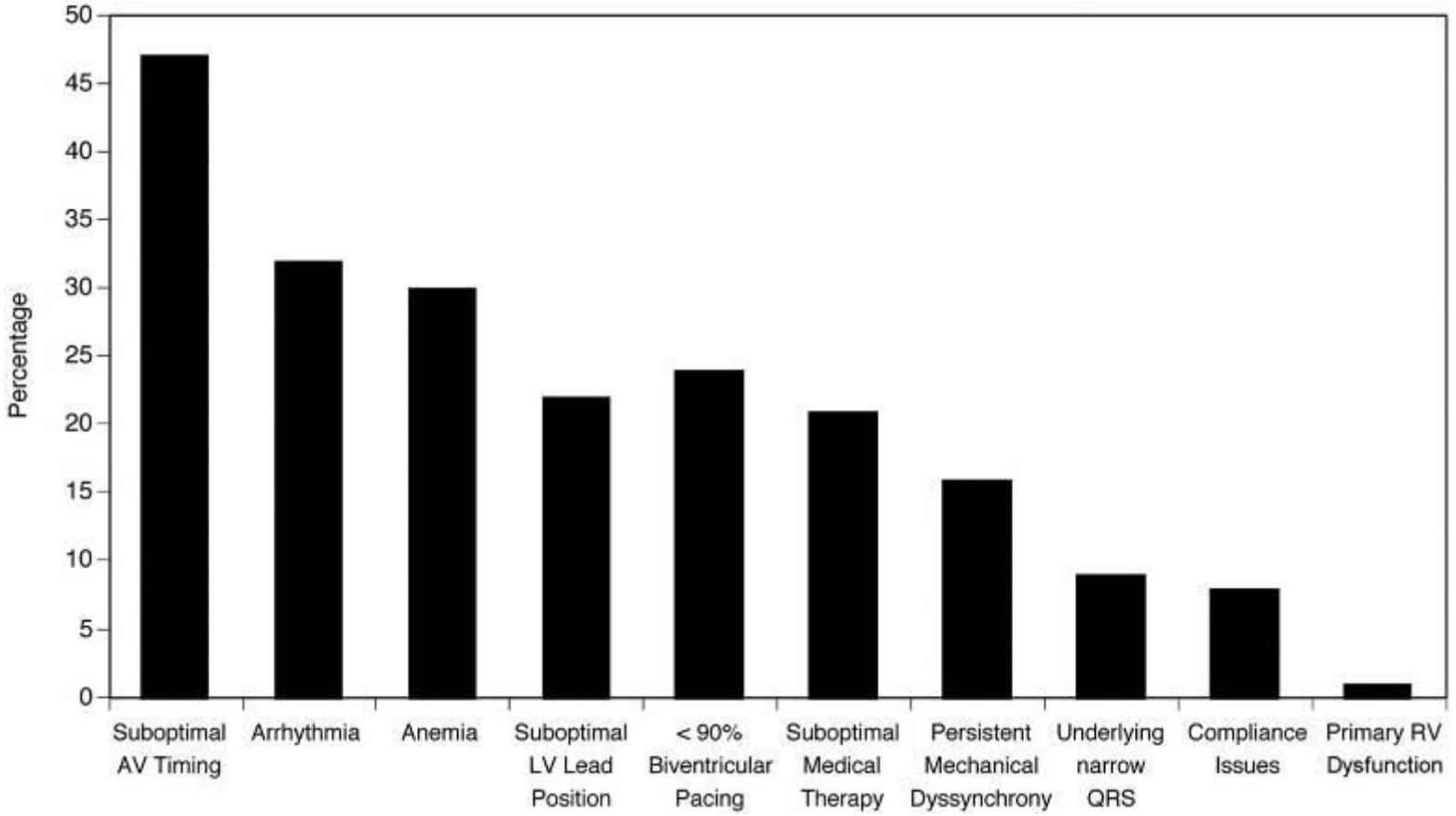
Response to CRT



- Non – response rate remained almost the same in the last decade
- Non-responders cannot be always identified at the time of implant.

Bax and Gorcsan III, JACC 2009

Potential Reasons for Suboptimal Response



Mullens, W. et al. J Am Coll Cardiol 2009;53:765-773

LV Pacing and Location:
Anatomical Specific LV Lead placement

LBBB

Conventional: LV Site of electrical & mechanical delay = lateral and PL wall

Target Lateral or PL branch of the CS Issues

30-40% Non-responder rate

8-10% of eligible pts do not receive CRT due to anatomical constraints

LV Pacing and Location:
Patient Specific LV Lead placement

Need to "personalize" LV final site

How to determine "best" LV site

- **Site of latest electrical activation**
  - **Guided by QLV, Electrical mapping**
- **Site of latest mechanical activation**
  - **Guided by hemodynamic data**
  - **Guided by imaging (ICE/3 D Echo/Tissue speckle tracking, MRI, CT scan, SPECT Nuclear)**

How to arrive at "best" LV site

- **Transvenous vs Epicardial vs Endocardial**

LV Pacing and Location

Non-apical LV lead location better than apical

Target the site of maximal electrical delay:

QLV >95 ms,Body surface mapping

Target the site of maximal mechanical delay:

Tissue speckle tracking (TARGET Trial), Cardiac MRI, SPECT (Guide-CRT)

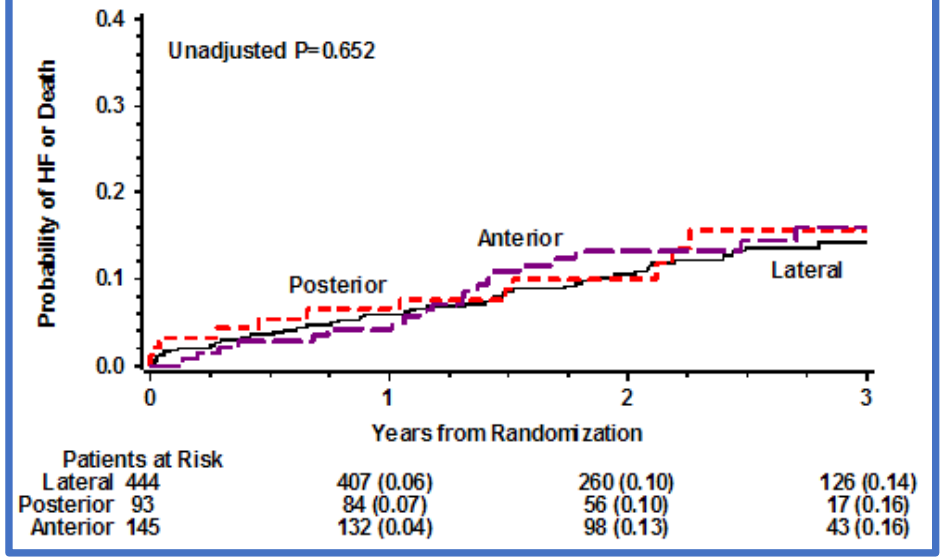
Quadripolar LV leads better than bipolar leads

Multisite (MPP) LV lead pacing maybe better than single site

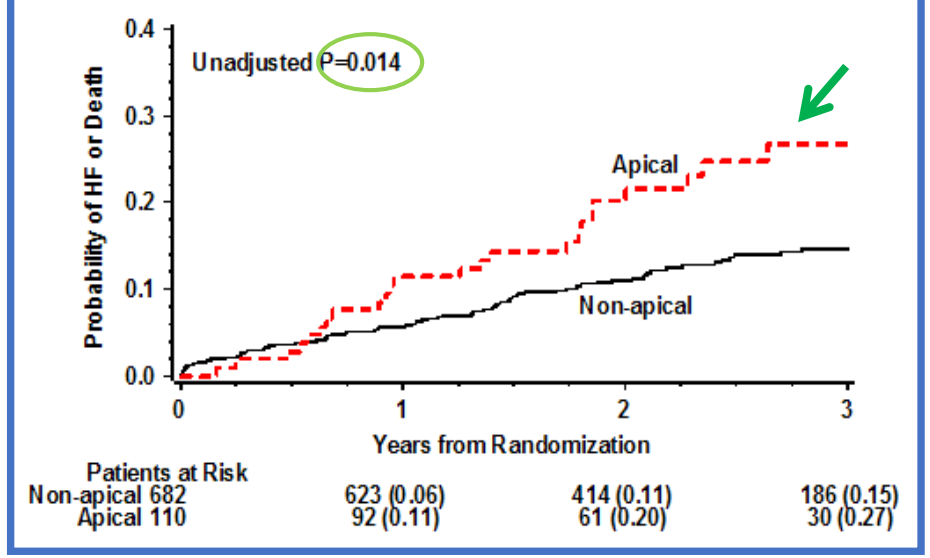
LV endocardial pacing may be better than epicardial pacing

Death &/or Heart Failure

Anterior, posterior and lateral position



Apical versus Non-apical position



- No difference amongst Anterior, Posterior and Lateral lead positions
- Apical lead positions associated with significantly worse clinical outcome
- Differences maintained even after non-apical leads sub-stratified to mid-ventricular & basal

Imaging

Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy

The TARGET Study: A Randomized, Controlled Trial

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Cambridge, United Kingdom

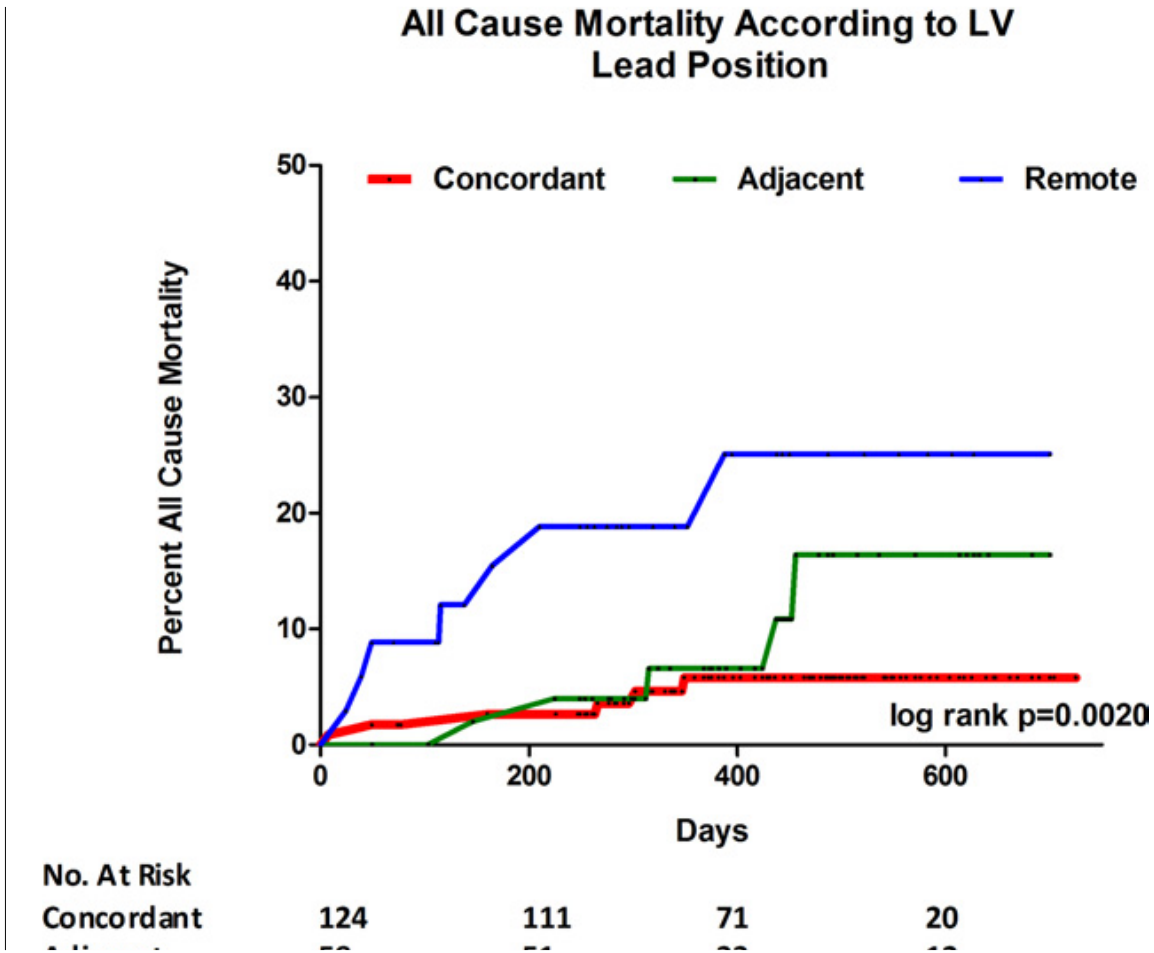
Objectives This study sought to assess the impact of targeted left ventricular (LV) lead placement on outcomes of cardiac resynchronization therapy (CRT).

Background Placement of the LV lead to the latest sites of contraction and away from the scar confers the best response to CRT. We conducted a randomized, controlled trial to compare a targeted approach to LV lead placement with usual care.

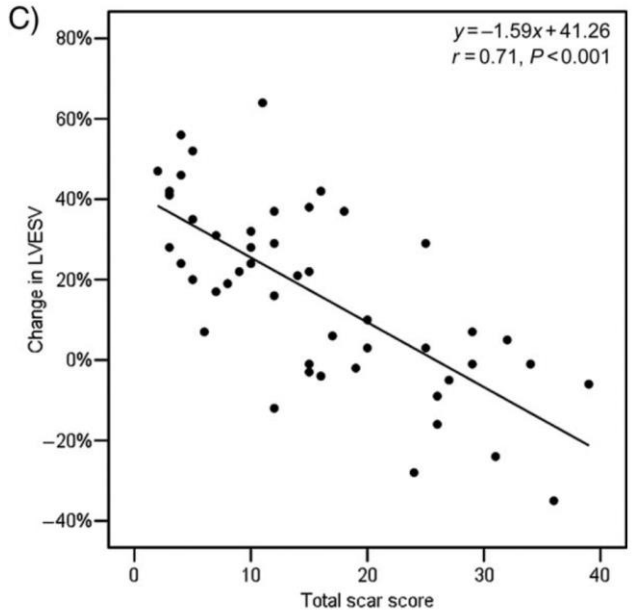
Methods A total of 220 patients scheduled for CRT underwent baseline echocardiographic speckle-tracking 2-dimensional radial strain imaging and were then randomized 1:1 into 2 groups. In group 1 (TARGET [Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy]), the LV lead was positioned at the latest site of peak contraction with an amplitude of >10% to signify freedom from scar. In group 2 (control) patients underwent standard unguided CRT. Patients were classified by the relationship of the LV lead to the optimal site as concordant (at optimal site), adjacent (within 1 segment), or remote (≥2 segments away). The primary endpoint was a ≥15% reduction in LV end-systolic volume at 6 months. Secondary endpoints were clinical response (≥1 improvement in New York Heart Association functional class), all-cause mortality, and combined all-cause mortality and heart failure–related hospitalization.

Results The groups were balanced at randomization. In the TARGET group, there was a greater proportion of responders at 6 months (70% vs. 55%, p = 0.031), giving an absolute difference in the primary endpoint of 15% (95% confidence interval: 2% to 28%). Compared with controls, TARGET patients had a higher clinical response (83% vs. 65%, p = 0.003) and lower rates of the combined endpoint (log-rank test, p = 0.031).

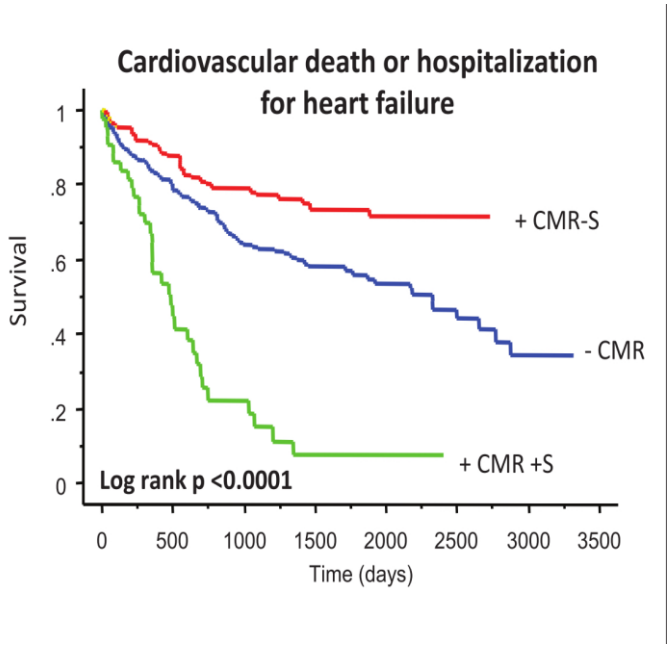
Conclusions Compared with standard CRT treatment, the use of speckle-tracking echocardiography to the target LV lead placement yields significantly improved response and clinical status and lower rates of combined death and heart failure–related hospitalization. (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy [TARGET] study); ISRCTN19717943) (J Am Coll Cardiol 2012;59:1509–18) © 2012 by the



Avoiding myocardial scar



Less LV remodelling with ↑ scar burden



X6 fold ↑ CV death if LV tip in scar (using CMR)

Positioning of Left Ventricular Pacing Lead Guided by Intracardiac Echocardiography with Vector Velocity Imaging During Cardiac Resynchronization Therapy Procedure

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From the *Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, Texas, USA; †Electrophysiology Division, Central Baptist Hospital, Lexington, Kentucky, USA; ‡UOC Cardiologia, Policlinico Casilino ASL/RMB, Rome, Italy; §Division of Cardiovascular Medicine, Gill Heart Institute, University of Kentucky, Lexington, Kentucky, USA; ‖Department of Internal Medicine, Tong-Ji Hospital, Tong-Ji Medical College, Huazhong University of Science and Technology, Wuhan, China; ¶Department of Cardiology, University of Foggia, Foggia, Italy; #Division of Cardiology, Stanford University, Palo Alto, California, USA; ††Department of Biomedical Engineering, University of Texas, Austin, Texas, USA; ‡‡School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

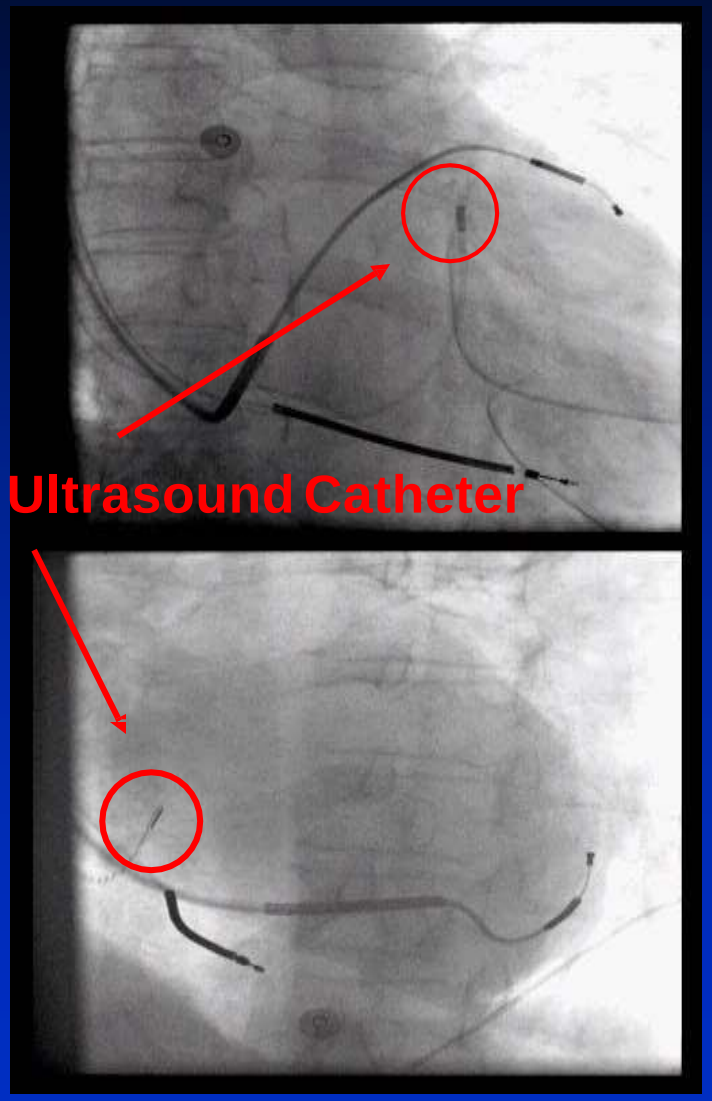
LV Lead Positioning Guided by ICE With Vector Velocity Imaging. ***Introduction*: Intraoperative modality for "real-time" left ventricular (LV) dyssynchrony quantification and optimal resynchronization is not established. This study determined the feasibility, safety, and efficacy of intracardiac echocardiography (ICE), coupled with vector velocity imaging (VVI), to evaluate LV dyssynchrony and to guide LV lead placement at the time of cardiac resynchronization therapy (CRT) implant.**

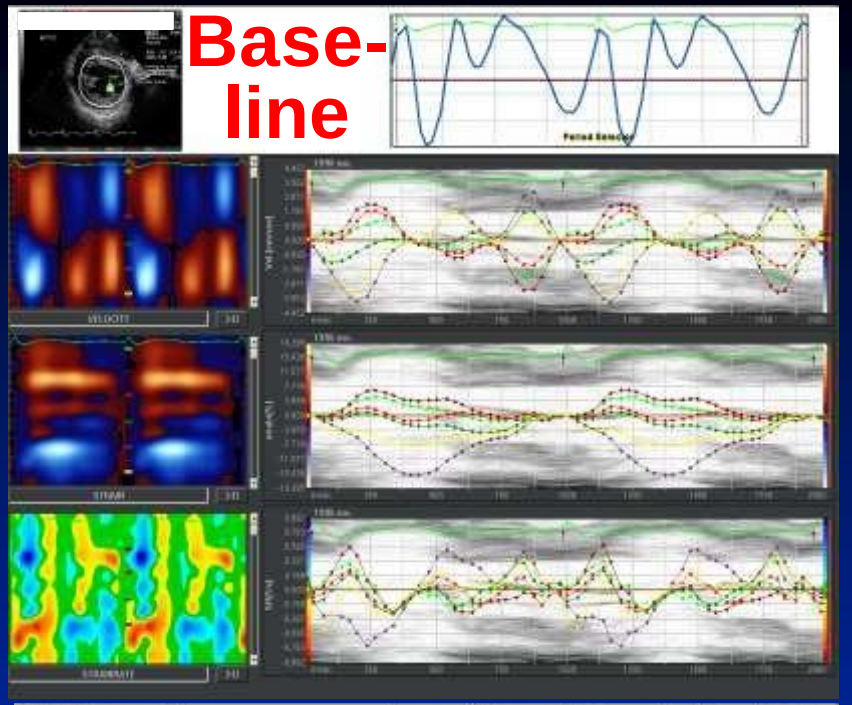
***Methods*: One hundred and four consecutive heart failure patients undergoing ICE-guided (Group 1, N = 50) or conventional (Group 2, N = 54) CRT implant were included in the study. For Group 1 patients, LV dyssynchrony and resynchronization were evaluated by VVI including visual algorithms and the maximum differences in time-to-peak (MD-TTP) radial strain. Based on the findings, the final LV lead site was determined and optimal resynchronization was achieved. CRT responders were defined using standard criteria 6 months after implantation.**

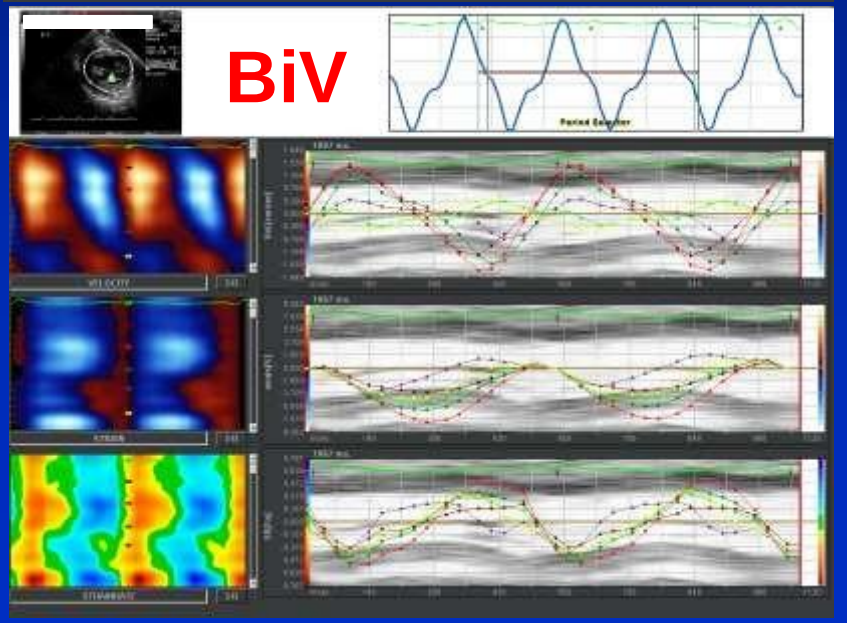
***Results*: Both groups underwent CRT implant with no complications. In Group 1, intraprocedural optimal resynchronization by VVI including visual algorithms and MD-TTP was a predictor discriminating CRT response with a sensitivity of 95% and specificity of 89%. Use of ICE/VVI increased number of and predicted CRT responders (82% in Group 1 vs 63% in Group 2; OR = 2.68, 95% CI 1.08–6.65, P = 0.03).**

***Conclusion*: ICE can be safely performed during CRT implantation. "Real-time" VVI appears to be helpful in determining the final LV lead position and pacing mode that allow better intraprocedural resynchronization. VVI-optimized acute resynchronization predicts CRT response and this approach is associated with higher number of CRT responders.** *(J Cardiovasc Electrophysiol, Vol. 22, pp. 1034-1041, September 2011)*

Intracardiac ultrasound guided LV lead implant







Positioning of left ventricular pacing lead guided by intracardiac echocardiography with vector velocity imaging during cardiac resynchronization therapy procedure. Bai R, et al. J Cardiovasc Electrophysiol. 2011 Sep;22(9):1034-41

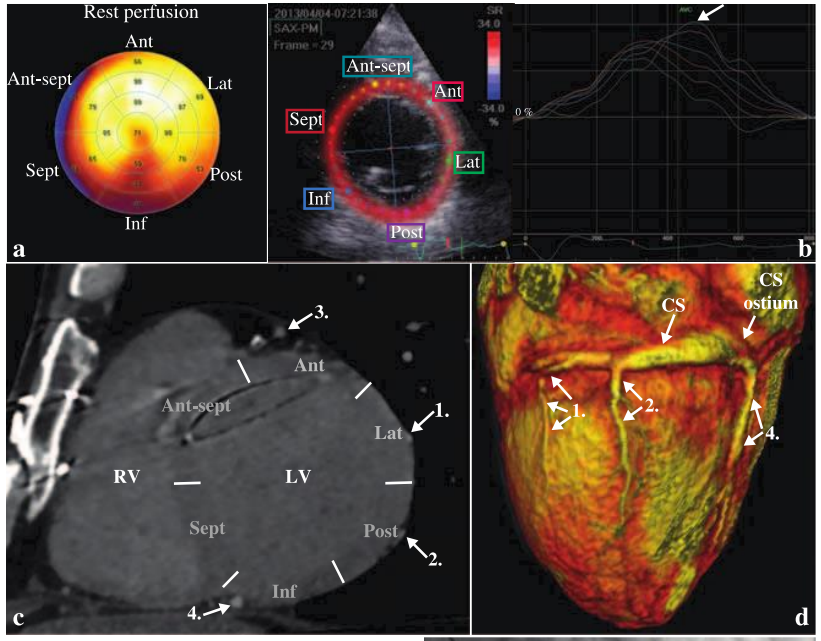
Multimodality imaging-guided left ventricular lead placement in cardiac resynchronization therapy: a randomized controlled trial

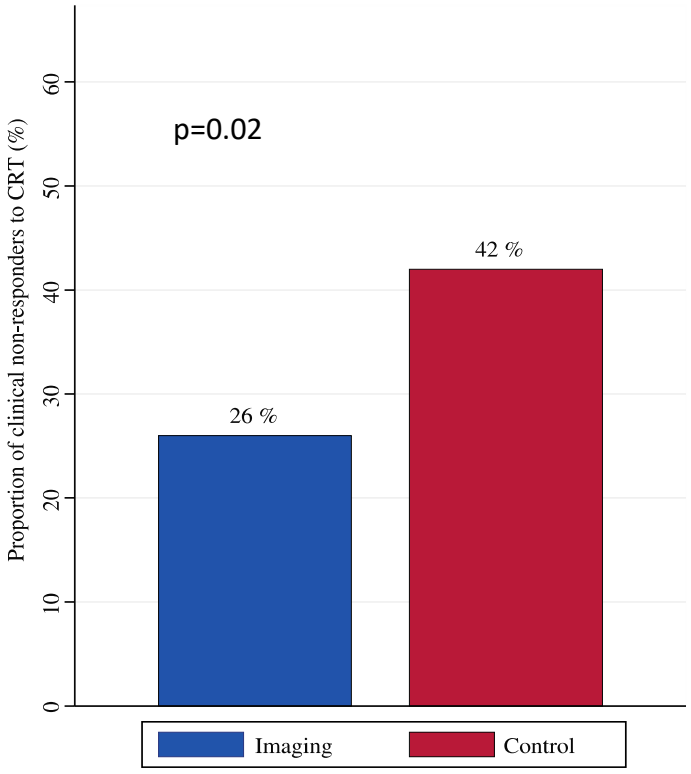
Anders Sommer[1]*, Mads Brix Kronborg[1], Bjarne Linde Nørgaard[1], Steen Hvitfeldt Poulsen[1], Kirsten Bouchelouche[2], Morten Böttcher[3], Henrik Kjærulf Jensen[1], Jesper Møller Jensen[1], Jens Kristensen[1], Christian Gerdes[1], Peter Thomas Mortensen[1], and Jens Cosedis Nielsen[1]

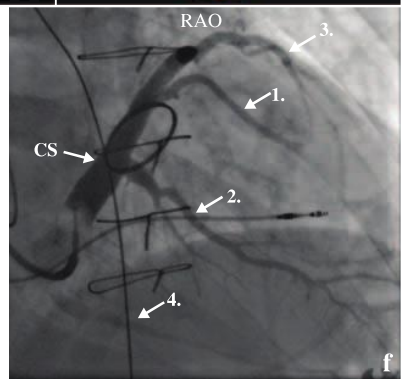
Aim Left ventricular (LV) lead position at the latest mechanically activated non-scarred myocardial LV region confers improved response to cardiac resynchronization therapy (CRT). We conducted a double-blind, randomized controlled trial to evaluate the clinical benef t of multimodality imaging-guided LV lead placement in CRT.

Methods and results Patients were allocated (1:1) to imaging-guided LV lead placement using cardiac computed tomography (CT) venography, ^{99m}Technetium myocardial perfusion imaging, and speckle-tracking echocardiography radial strain to target the optimal coronary sinus (CS) branch closest to the non-scarred myocardial segment with latest mechanical activation (imaging group, $n = 89$) or to routine LV lead implantation in a posterolateral region with late electrical activation (control group, $n = 93$). The primary endpoint was clinical non-response to CRT [≥1 of the following after 6 months: (1) death, (2) heart failure hospitalization, or (3) no improvement in New York Heart Association class and <10% increase in 6-min walk distance]. Secondary outcomes included LV remodelling and the combination of all-cause mortality and hospitalization owing to heart failure during 1.8 ± 0.9 years. Analysis was intention-to-treat. In the imaging group, fewer patients reached the primary endpoint (26% vs. 42%, $P = 0.02$). More patients in the imaging group had the LV lead placed in the optimal CS branch (83% vs. 65%, $P = 0.01$). There were no between-group differences in reverse LV remodelling or the combined endpoint of death or hospitalizations for failure.

Conclusions Multimodality imaging-guided LV lead placement towards the CS branch closest to latest mechanically activated non-scarred myocardial LV segment reduces the proportion of clinical non-responders to CRT. Larger long-term multicentre studies are needed.



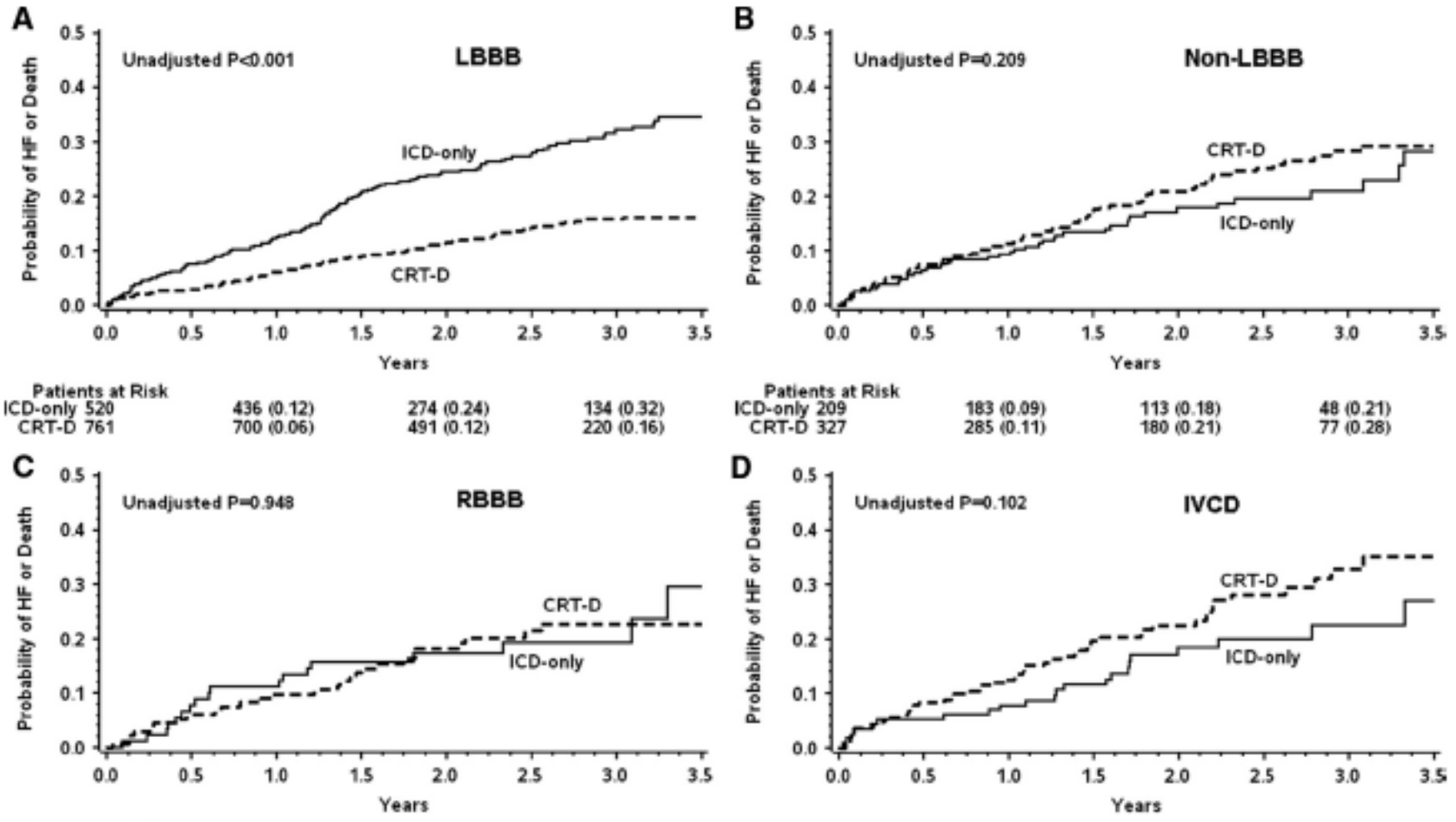




Sommer A et al. Eur J Heart Fail. 2016 Nov;18(11):1365-1374

QRS morphology

Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic DefibrillatorImplantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT)



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Patients with left bundle branch block and left axis deviation show a specific left ventricular asynchrony pattern: Implications for left ventricular lead placement during CRT implantation☆,☆☆

Luigi Sciarra, MD,[a] Paolo Golia, MD,[a] Zefferino Palamà, MD,[a,*] Antonio Scarà, MD,[a] Ermenegildo De Ruvo, MD,[a] Alessio Borrelli, MD,[a] Anna Maria Martino, MD,[a] Monia Minati, MD,[a] Alessandro Fagagnini, MD,[a] Claudia Tota, MD,[a] Lucia De Luca, MD,[a] Domenico Grieco, PhD,[a] Pietro Delise, MD,[b] Leonardo Calò, FESC[a]

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[b] *Division of Cardiology, Hospital of Conegliano, Veneto, Italy*

Abstract

Background: Left bundle branch block (LBBB) and left axis deviation (LAD) patients may have poor response to resynchronization therapy (CRT). We sought to assess if LBBB and LAD patients show a specific pattern of mechanical asynchrony.

Methods: CRT candidates with non-ischemic cardiomyopathy and LBBB were categorized as having normal QRS axis (within −30° and +90°) or LAD (within −30° and −90°). Patients underwent tissue Doppler imaging (TDI) to measure time interval between onset of QRS complex and peak systolic velocity in ejection period (Q-peak) at basal segments of septal, inferior, lateral and anterior walls, as expression of local timing of mechanical activation.

Results: Thirty patients (mean age 70.6 years; 19 males) were included. Mean left ventricular ejection fraction was 0.28 ± 0.06. Mean QRS duration was 172.5 ± 13.9 ms. Fifteen patients showed LBBB with LAD (QRS duration 173 ± 14; EF 0.27 ± 0.06). The other 15 patients had LBBB with a normal QRS axis (QRS duration 172 ± 14; EF 0.29 ± 0.05).

Among patients with LAD, Q-peak interval was significantly longer at the anterior wall in comparison to each other walls (septal 201 ± 46 ms, inferior 242 ± 58 ms, lateral 267 ± 45 ms, anterior 302 ± 50 ms; $p < 0.0001$). Conversely, in patients without LAD Q-peak interval was longer at lateral wall, when compared to each other (septal 228 ± 65 ms, inferior 250 ± 64 ms, lateral 328 ± 98 ms, anterior 291 ± 86 ms; $p < 0.0001$).

Conclusions: Patients with heart failure, presenting LBBB and LAD, show a specific pattern of ventricular asynchrony, with latest activation at anterior wall. This finding could affect target vessel selection during CRT procedures in these patients.

Keywords: CRT; left blunde block; left axis deviation; Tissue doppler

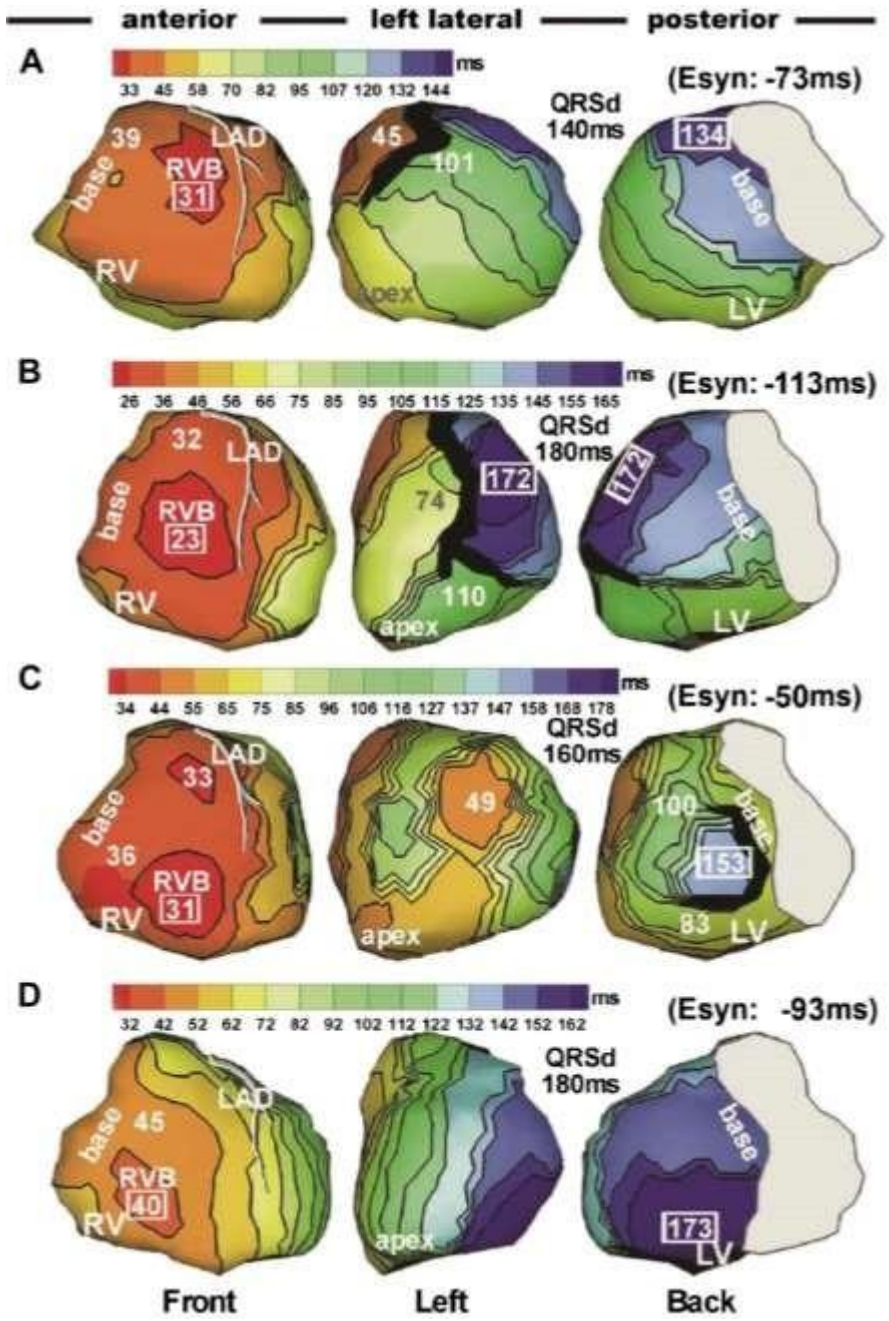
Issue: QRS Duration & LBBB

12 lead surface QRS duration limited information

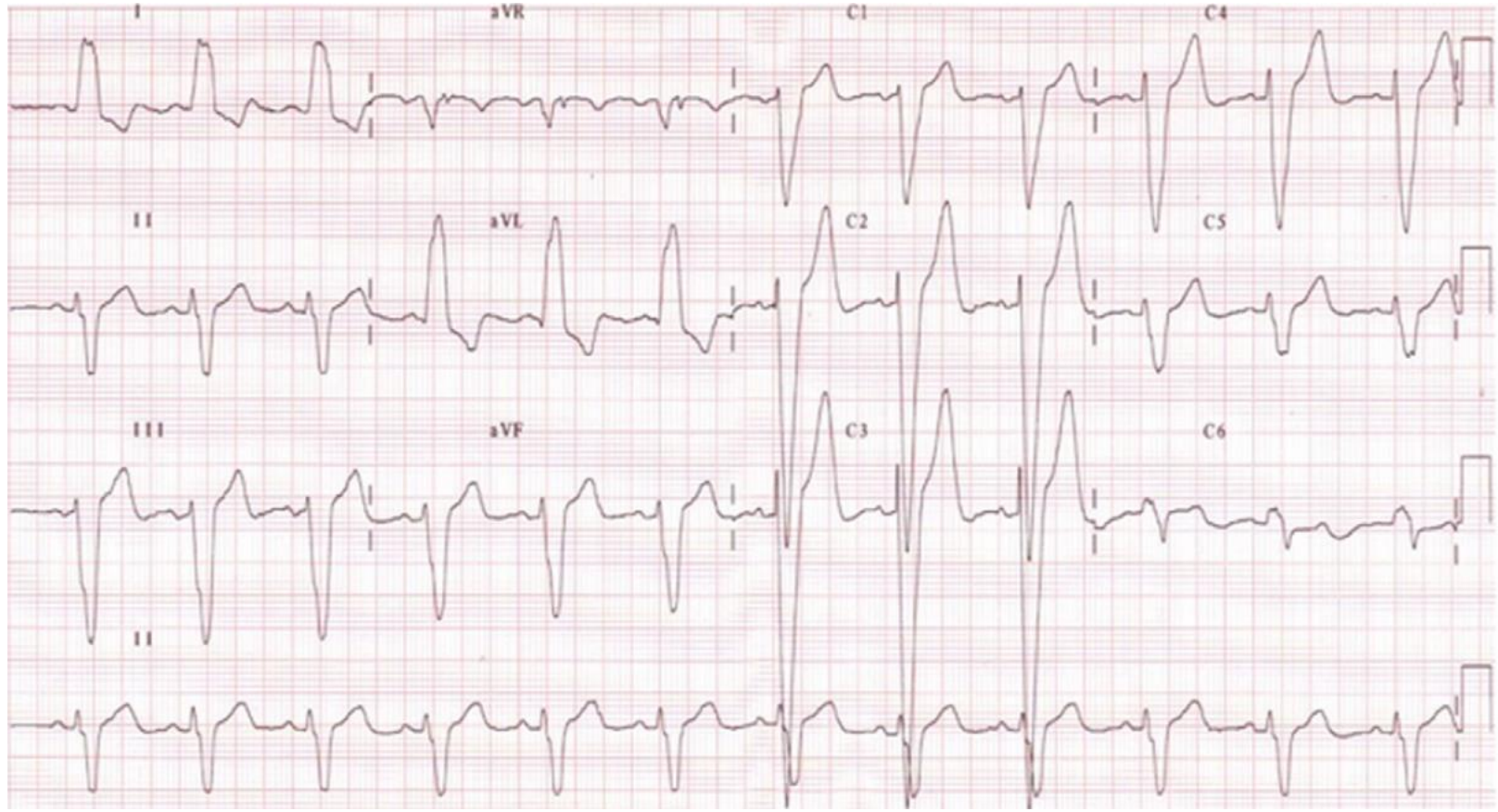
Reflection of total duration of ventricular activation but not a reliable marker of LV activation

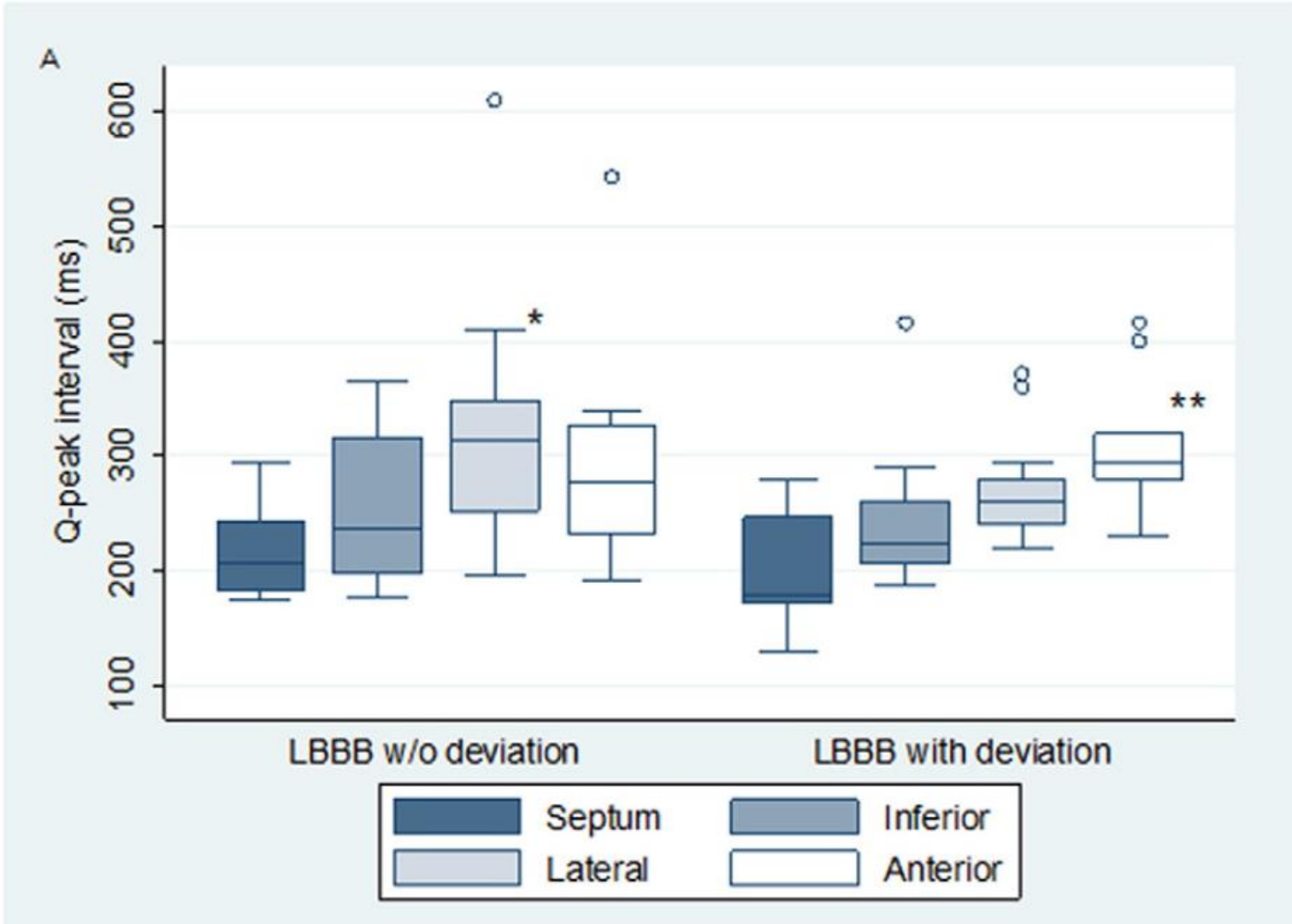
Significant variations of LV activation with typical LBBB can be be seen

Important factor to determine CRT response and lead location position at implant



Varma N et al. Card Electrophysiolo Clin 2015.

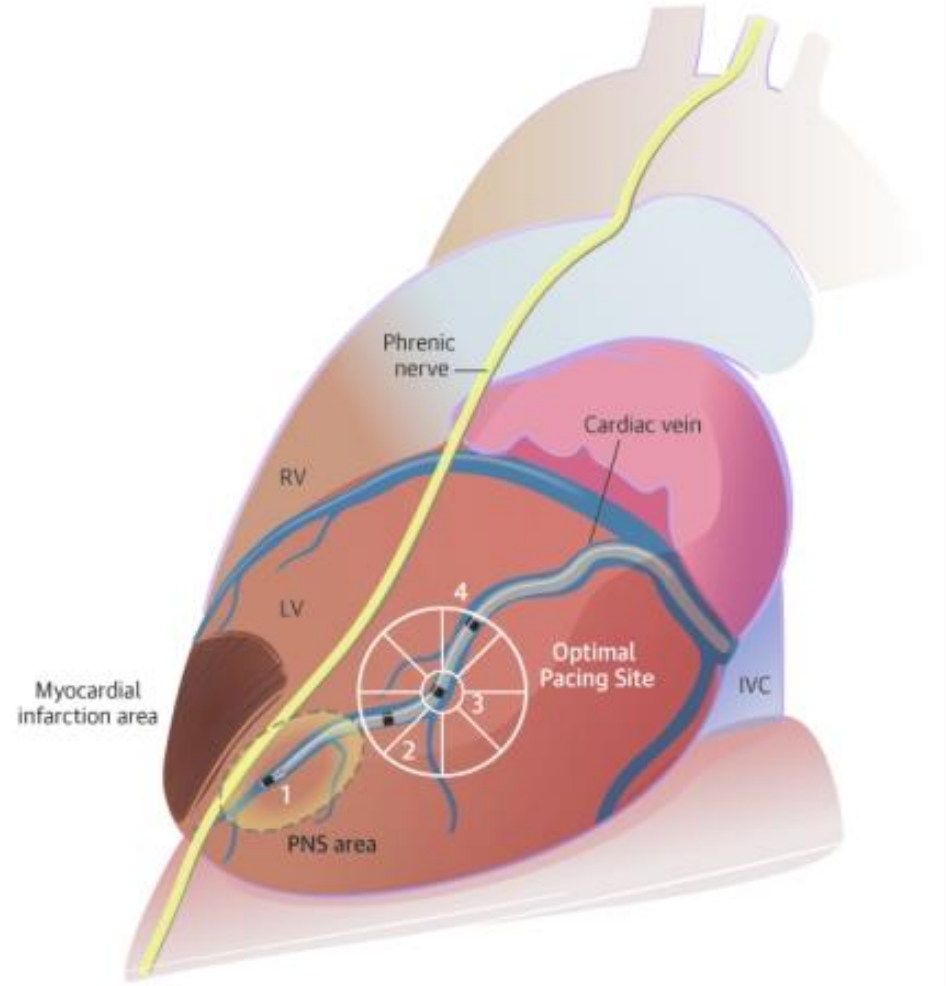

I
aVR
C1
C4
II
aVL
C2
C5
III
aVF
C3
C6
II

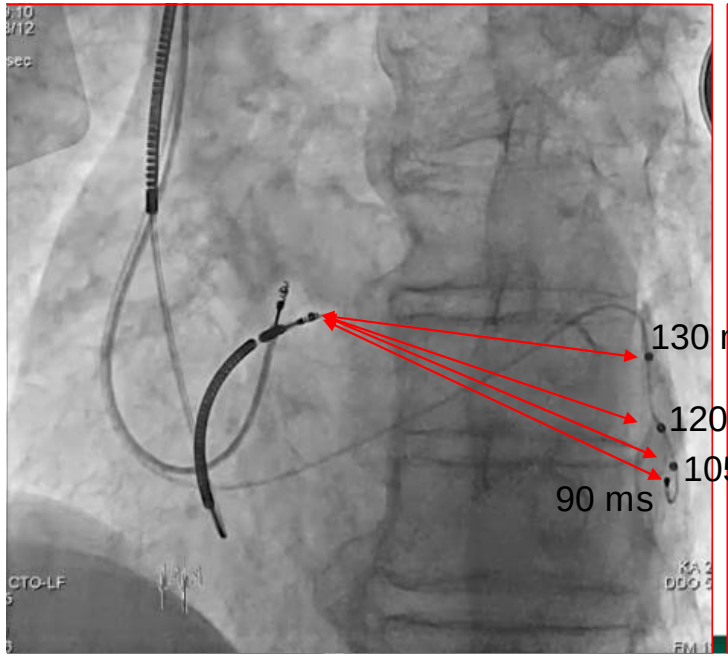

A
Q-peak interval (ms)
100
200
300
400
500
600
*
**
LBBB w/o deviation
LBBB with deviation
Septum
Lateral
Inferior
Anterior

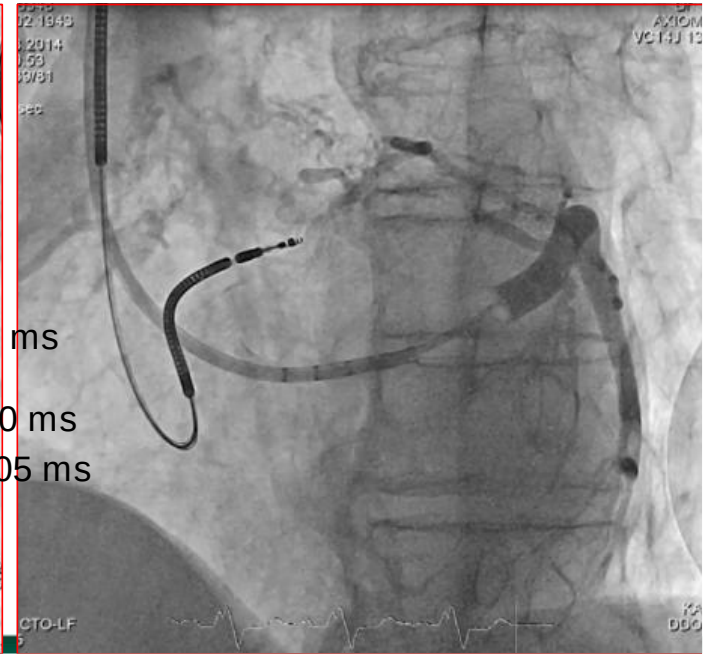
LV lead

LV lead

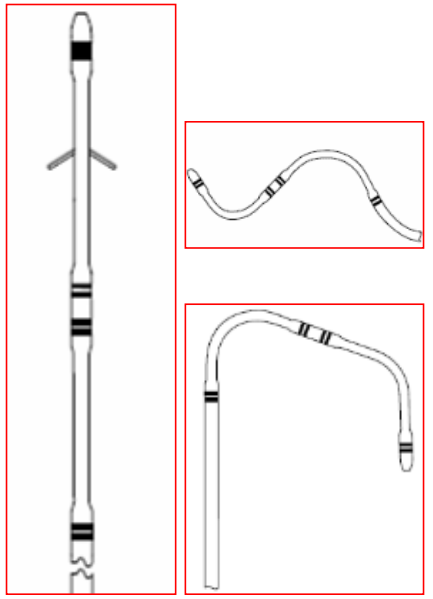
- multipoint stimulation -



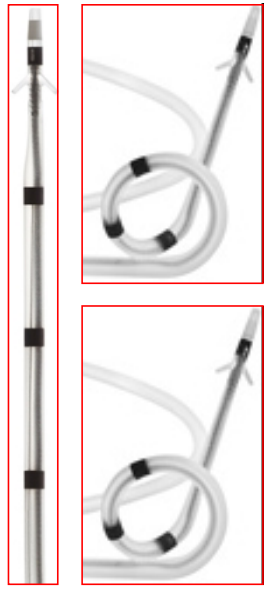




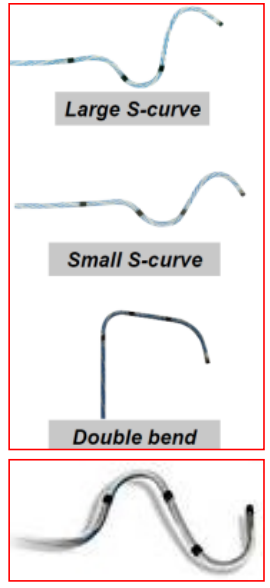
Biotronik Sentus



Medtronic Attain Performa



Boston-Scientific Acuity X4



SJM Quartet

Acute echocardiographic optimization of multiple stimulation configurations of cardiac resynchronization therapy through quadripolar left ventricular pacing: A tailored approach

Leonardo Calò, MD, FESC, Annamaria Martino, MD, Ermenegildo de Ruvo, MD, Monia Minati, MD, Simona Fratini, MD, PhD, Marco Rebecchi, MD, Chiara Lanzillo, MD, PhD, Alessandro Fagagnini, MD, Alessio Borrelli, MD, Lucia De Luca, MD, PhD, and Luigi Sciarra *Rome, Italy*

Background Cardiac resynchronization therapy (CRT) is ineffective in approximately 30% of recipients, in part due to sub-optimal left ventricular (LV) pacing location. The Quartet LV lead, with 2 additional electrodes proximal to conventional bipolar lead electrodes, enables 10 different pacing configurations at four independent LV locations. In a CRT patient cohort, we sought to evaluate the spectrum of echocardiographic and electrocardiographic response over these 10 configurations, to select the optimal one in each patient. Moreover, we sought to evaluate the 6-months clinical and echocardiographic response to a "tailored approach" in which the optimal LV pacing configuration for CRT was determined by echocardiographic measures, QRSd and pacing capture thresholds.

Methods Twenty-two consecutive CRT indicated patients were implanted with a quadripolar CRT system (St. Jude Medical). Optimal LV pacing configuration was determined by echocardiographic measures, including velocity time integral (VTI), myocardial performance index (MPI) and mitral regurgitation (MR), and an electrocardiographic measure (QRS duration) during pacing from each of the configurations at pre-discharge. The optimal LV pacing vector was chosen for every patient. Clinical and echocardiographic assessment was repeated after 6 months.

Results Various configurations provided different VTI, MPI, MR and QRSd values. Conventional bipolar vectors (ie, D1-M2, D1-RVc, M2-RVc) were rarely associated with the best echocardiographic improvements and provided significantly worse VTI, MR, MPI, and QRSd values than the best configuration for every patient ($P = .005$, $P = .05$ and $P = .03$ for VTI; $P = .01$, $P = .005$ and $P = .001$ for MPI; $P = .003$, $P = .01$ and $P = .005$ for MR, $P > .5$, $P = .01$ and $P = .05$ for QRSd) Conversely, "unconventional" proximal configurations (ie, making use of P4 and M3 electrodes) were generally characterized by higher acute VTI, MR and MPI improvements. CRT devices were reprogrammed with an "unconventional" LV pacing configuration in 50% of patients. A significant improvement in New York Heart Association class (81%), LV ejection fraction (76%), end-diastolic and end-systolic volumes was observed after 6 months ($P = .02$, $P < .001$, $P = .02$ and $P = .003$, respectively).

Conclusions In this study, conventional bipolar vectors of quadripolar-CRT were rarely associated with the best echocardiographic improvements. Quadripolar CRT utilizing optimal LV pacing configuration was associated with a significant improvement in New York Heart Association class and LV ejection fraction after 6 months. (Am Heart J 2014;0:1-9.)

A Meta-Analysis Of Quadripolar Versus Bipolar Left Ventricular Leads On Post-Procedural Outcomes

Mohit K. Turagam, MD[1], Muhammad R. Afzal, MD[2], Sandia Iskander, MD[2], Madhu Reddy, MD[2], Luigi Di Biase, MD[3], Andrea Natale, MD[4], Dhanunjaya Lakkireddy, MD, FHRS[2]

Abstract

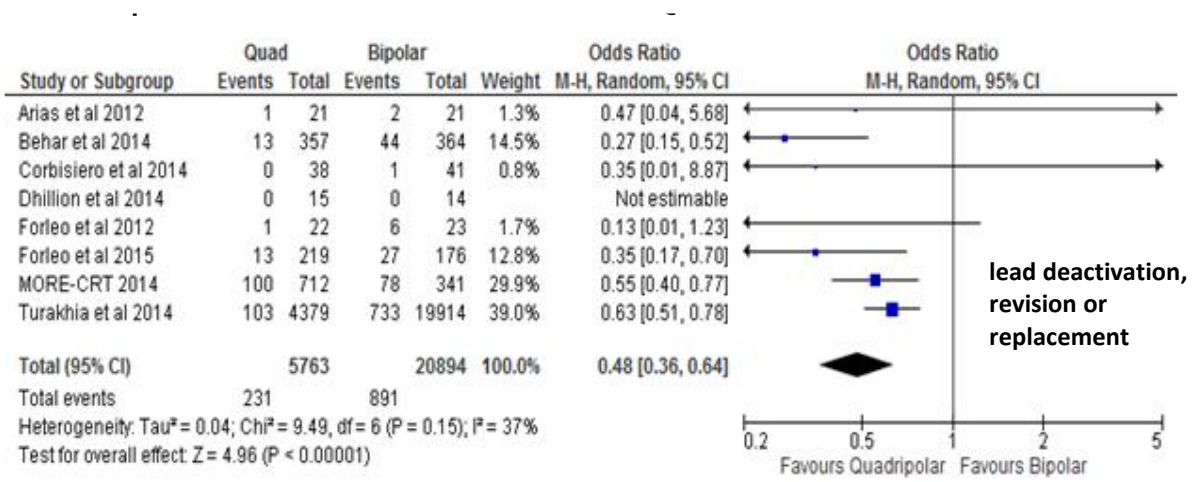
Objective: We aimed to perform a meta-analysis from eligible studies to analyze the true impact of QL when compared with BL with regard to post-procedural outcomes including lead deactivation, revision or replacement.

Background: Many observational and retrospective studies showed that quadripolar left ventricular leads (QL) are associated with better outcomes and fewer complications when compared with bipolar leads (BL).

Methods: We performed a comprehensive literature search through June 30, 2015 using: quadripolar, bipolar, left ventricular lead and CRT in Pubmed, Ebsco and google scholar databases.

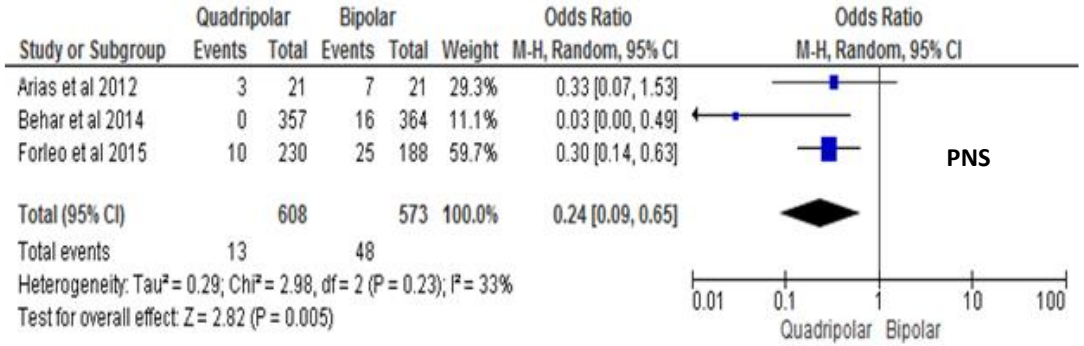
Results: The analysis included 8 studies comparing QL and BL implantation. Post-procedural outcomes such as lead deactivation, revision or replacement were used as primary outcome and assessed with Mantel–Haenszel risk ratio (RR). Secondary outcomes included total fluoroscopy/procedure time, occurrence of phrenic nerve stimulation (PNS) and all-cause mortality on follow up. Follow-up duration for the studies ranged from 3 to 60 months. Compared with BL, the use of QL is associated with 52 % reduction (relative risk 0.48; 95% CI: 0.36-0.64, p=0.00001) in the risk of deactivation, revision or replacement of the LV lead. QL had significantly lower fluoroscopy/procedure time, PNS and all-cause mortality when compared with BL.

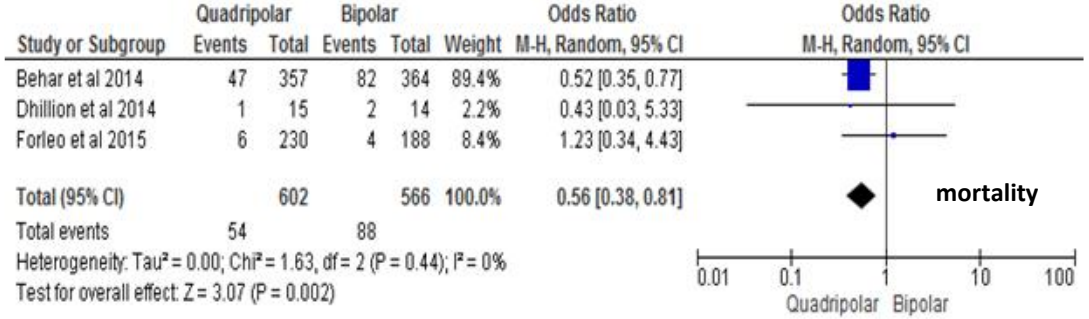
Conclusion: Our meta-analysis shows that QL implantation was associated with decreased risk of LV lead deactivation, revision or replacement when compared with BL.



Cost-Effectiveness Analysis of Quadripolar Versus Bipolar Left Ventricular Leads for Cardiac Resynchronization Defibrillator Therapy in a Large, Multicenter UK Registry

	Quadripolar (n = 319)		Bipolar (n = 287)		
	n	Cost (£)	n	Cost (£)	p Value
ACS	35	115,029	21	67,544	0.13
Arrhythmia	59	51,218	65	55,557	0.23
Heart failure	51	137,695	75	195,841	0.003
System explantation and reimplantation	5	121,122	6	136,788	0.76
Generator replacement	9	142,026	19	273,276	0.03
RA/RV lead revision	27	88,918	24	69,840	0.21
LV lead revision	5	16,466	15	43,650	0.02
Total episodes/cost	191	672,474	225	842,484	<0.001





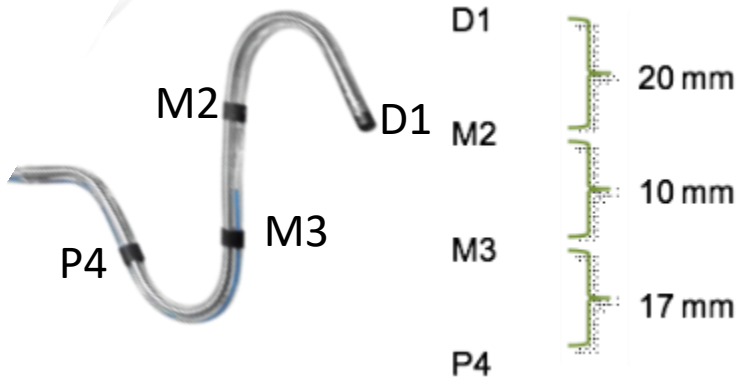
Turagam MK et al. J Atr Fibrillation. 2016 Aug-Sep; 9(2): 1472
Behar JM et al. JACC Clin Electrophysiol. 2017 Feb;3(2):107-116

Multipoint pacing

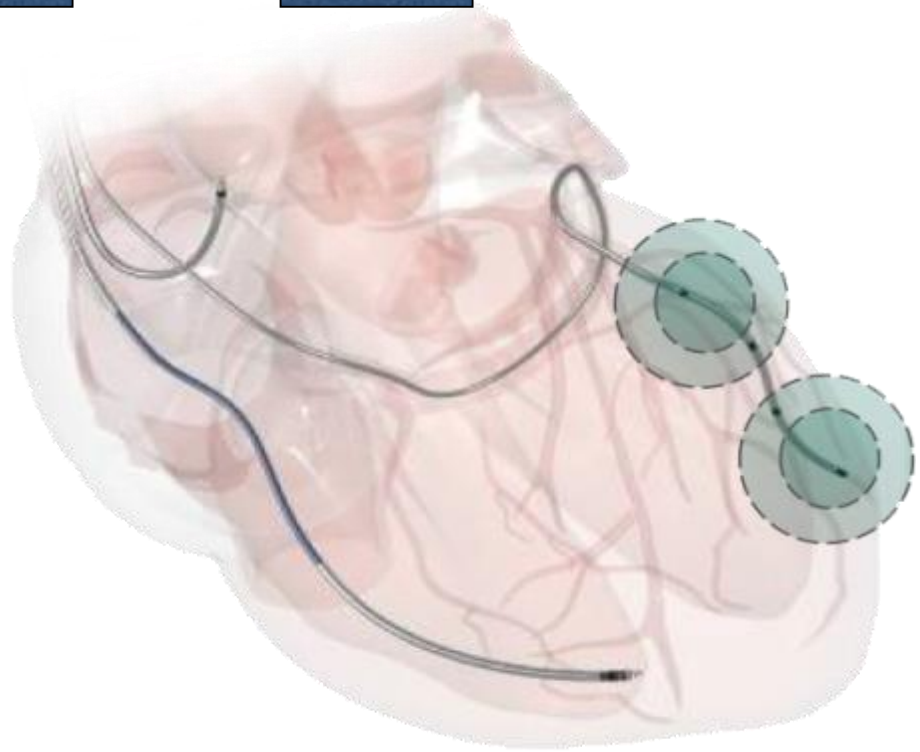
Quadripolar Pacing Technology … a consolidate base for a new CRT era: the MultiPoint Pacing

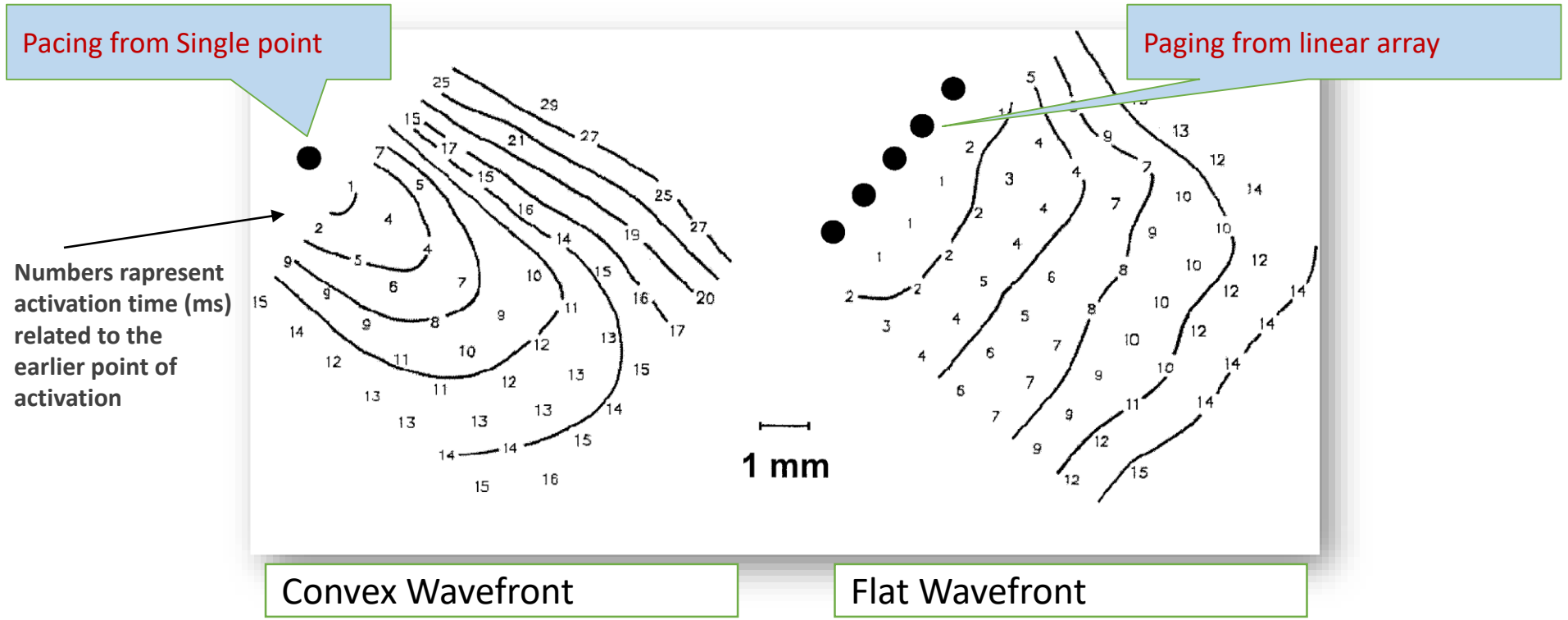
What is MultiPoint pacing (MPP)?

Ability to pace from **2 LV sites** with a **single LV lead** with **programmable delays**



Quartet™ LV Lead 1458Q





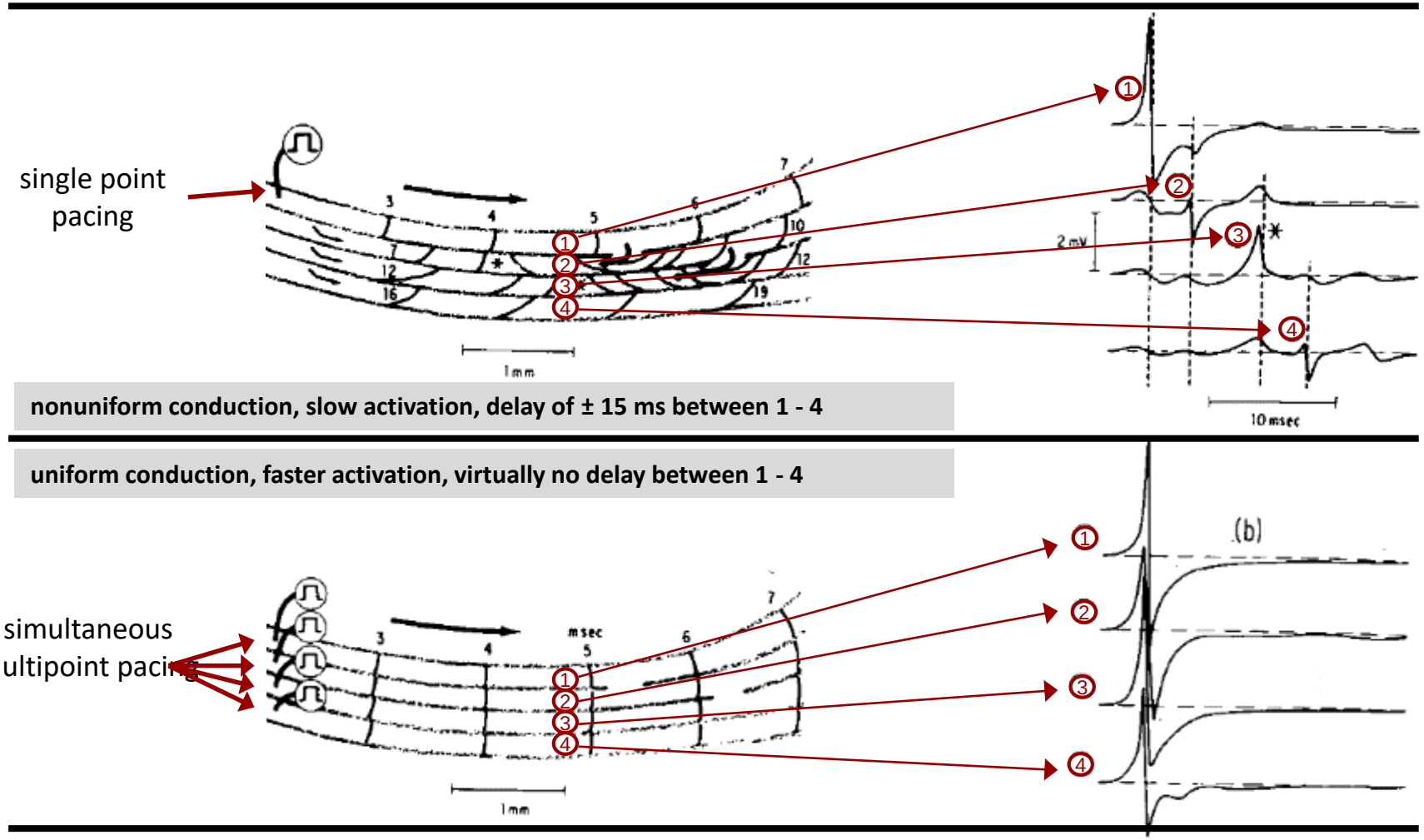
Results:

- Optical activation maps obtained with laser scanning
- Demonstrate that stimulation by single electrode generates a more elliptical wavefront , while the stimulation from linear array generates a flatter wavefront
- The greater curvature of the more elliptical wavefront causes a lower conduction velocity of 15%.

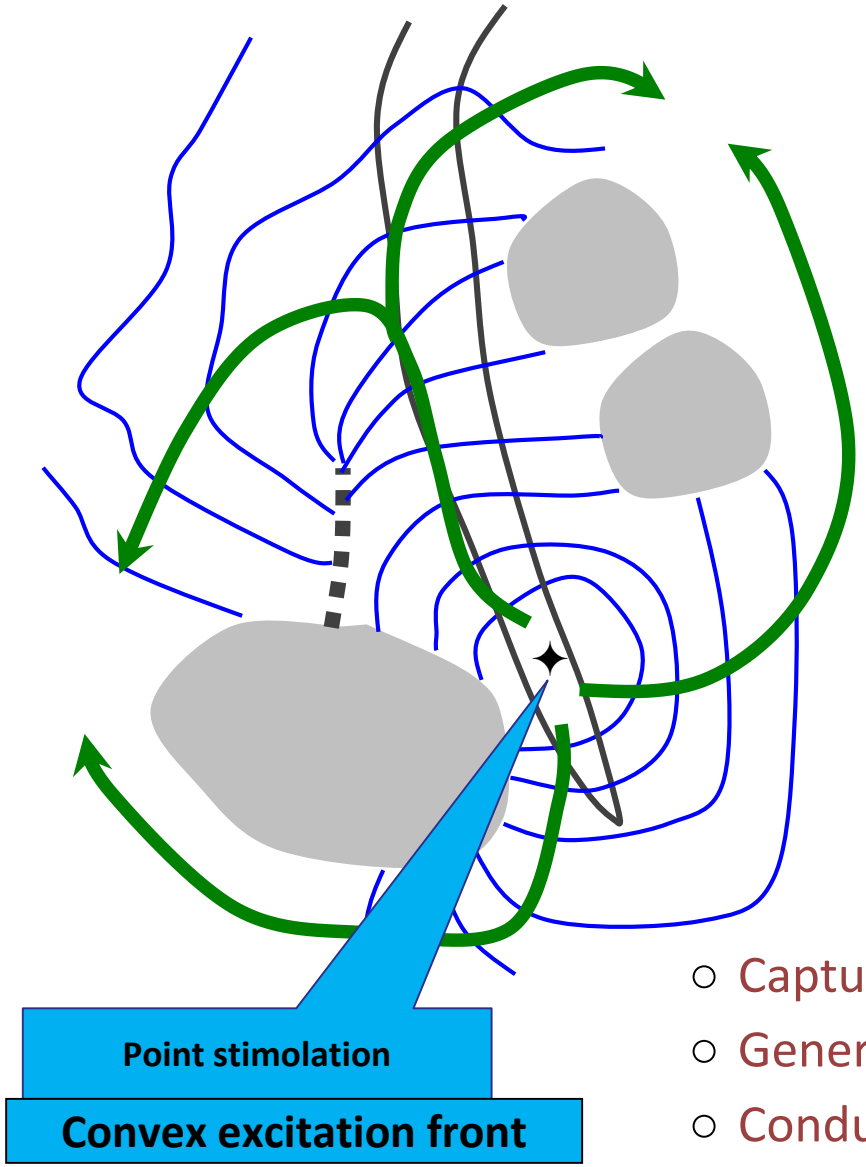
Fast et al., Cardiovascular Research 1997; 33: 258–271

Concept of Multipoint Pacing: Early Experimental Evidence

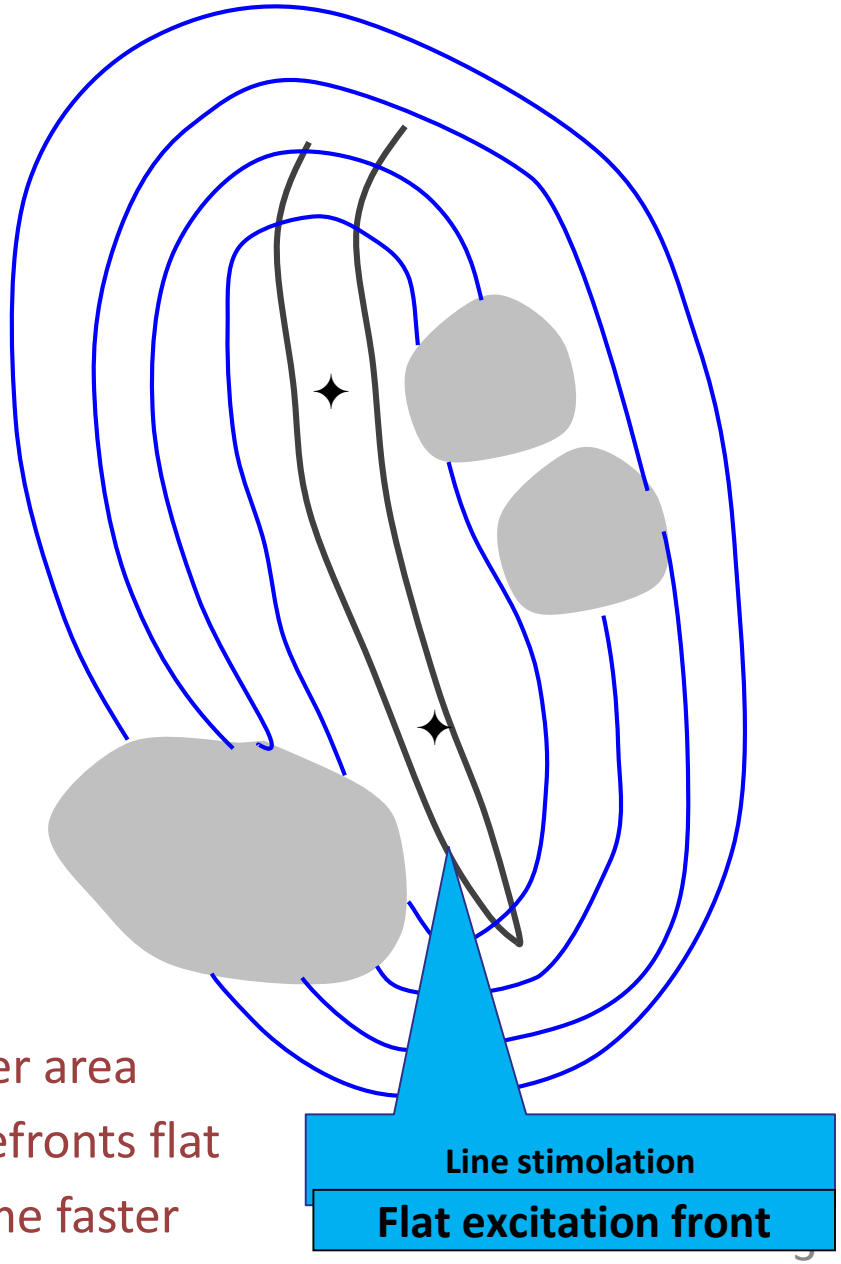
Muscle bundle with horizontal fiber orientation



Spach MS, et al. Circ Res. 1982;50:175 -191



- Capture a larger area
- Generate wavefronts flat
- Conduction time faster



Benefits	AUTHOR	PARAMETER	RESULTS
Electrical activation	Menardi et al. Heart Rhythm 2015	QRS lenght activation time of the LV	12% relative reduction of QRS 15% relative reduction of the total activation time
	Forleo et al. Europace 2016	QRS lenght	Significant reduction of the QRS accompamied by a LVEF increase
Mechanical	Rinaldi et al. Journal of Cardiac Failure 2013	Dyssynchrony (TDI)	Significant reduction in echocardiographic dyssynchrony in 63% pts
	Osca et al. Europace 2015	Dyssynchrony (Radial Strain)	Dyssynchrony reduction
	Rinaldi C.A et al., J Interv Card Electrophysiol 2014	Dyssynchrony (TDI) VTI LVOT	Dyssynchrony reduction in 64% of patients Increase of VTI LVOT (evaluated in 13 patients)
Hemodynamic	Thibault et al. Europace 2013	Variation of dp/dt	dp/dt improvement in 72% of patients
	Pappone et al. Heart Rhythm 2014	Pressure/Volume loops	Improvement of the hemodynamic parameters
Pacing site	Zanon et al. Heart Rhythm 2015	Q-LV e dP/dt	Correlation between most delayed Q-LV and increased dP/dt

ESC European Society of Cardiology
European Heart Journal (2019) **40**, 2979–2987
doi:10.1093/eurheartj/ehz109

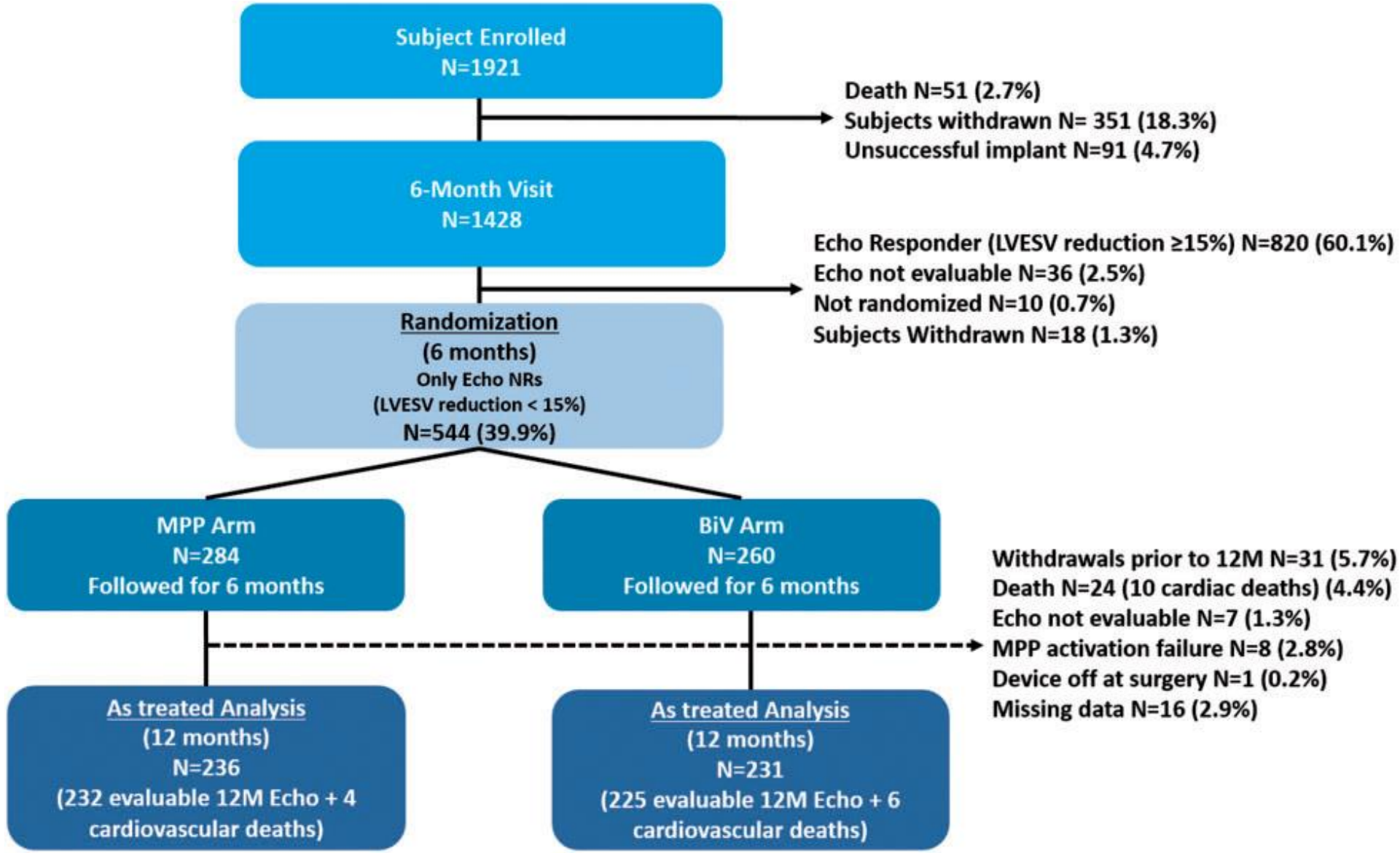
CLINICAL RESEARCH
Arrhythmia/electrophysiology

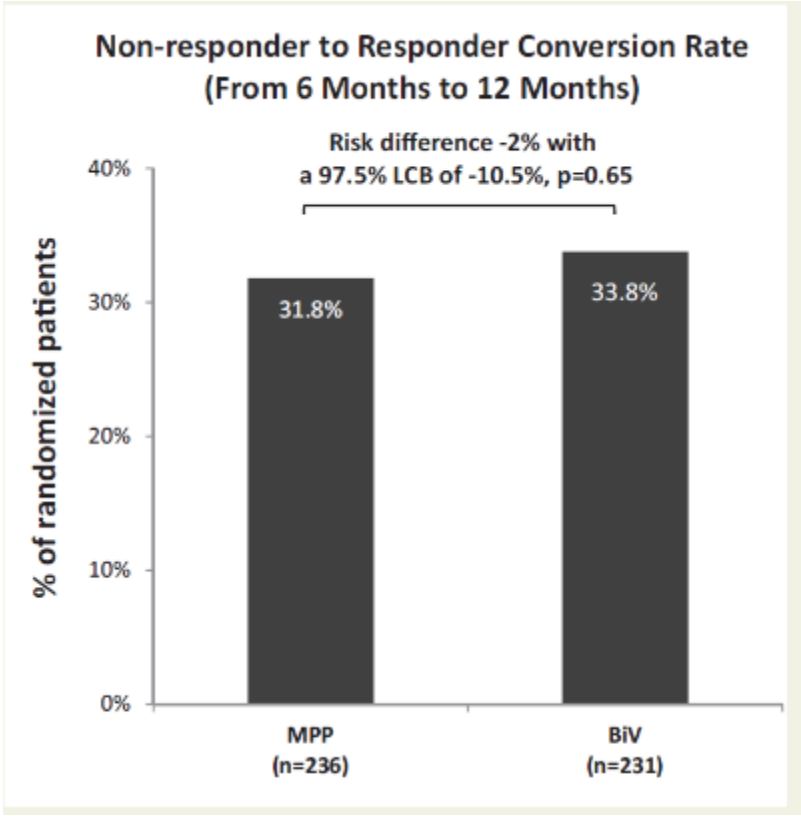
Cardiac resynchronization therapy non-responder to responder conversion rate in the more response to cardiac resynchronization therapy with MultiPoint Pacing (MORE-CRT MPP) study: results from Phase I

Christophe Leclercq[1]*, Haran Burri[2], Antonio Curnis[3], Peter Paul Delnoy[4], Christopher A. Rinaldi[5], Johannes Sperzel[6], Kwangdeok Lee[7], Leonardo Calò[8], Alfredo Vicentini[9], Joaquin Fernandez Concha[10], and Bernard Thibault[11]; on behalf of the MORE-CRT MPP Investigators

[1]Université de Rennes I, CICIT 804, Rennes, CHU Pontchaillou, Rennes, France; [2]University of Geneva, Geneva, Switzerland; [3]Università degli Studi di Brescia, Brescia, Italy; [4]Isala Klinieken, Zwolle, The Netherlands; [5]King's College, London, UK; [6]Kerckhoff Klinik, Bad Nauheim, Germany; [7]Abbott, Plano, TX, USA; [8]Policlinico Casilino, Italy; [9]Casa di Cura Dott, Pederzoli, Italy; [10]Hospital Universitario Infanta Cristina, Spain; and [11]Université de Montréal, Montreal, Canada

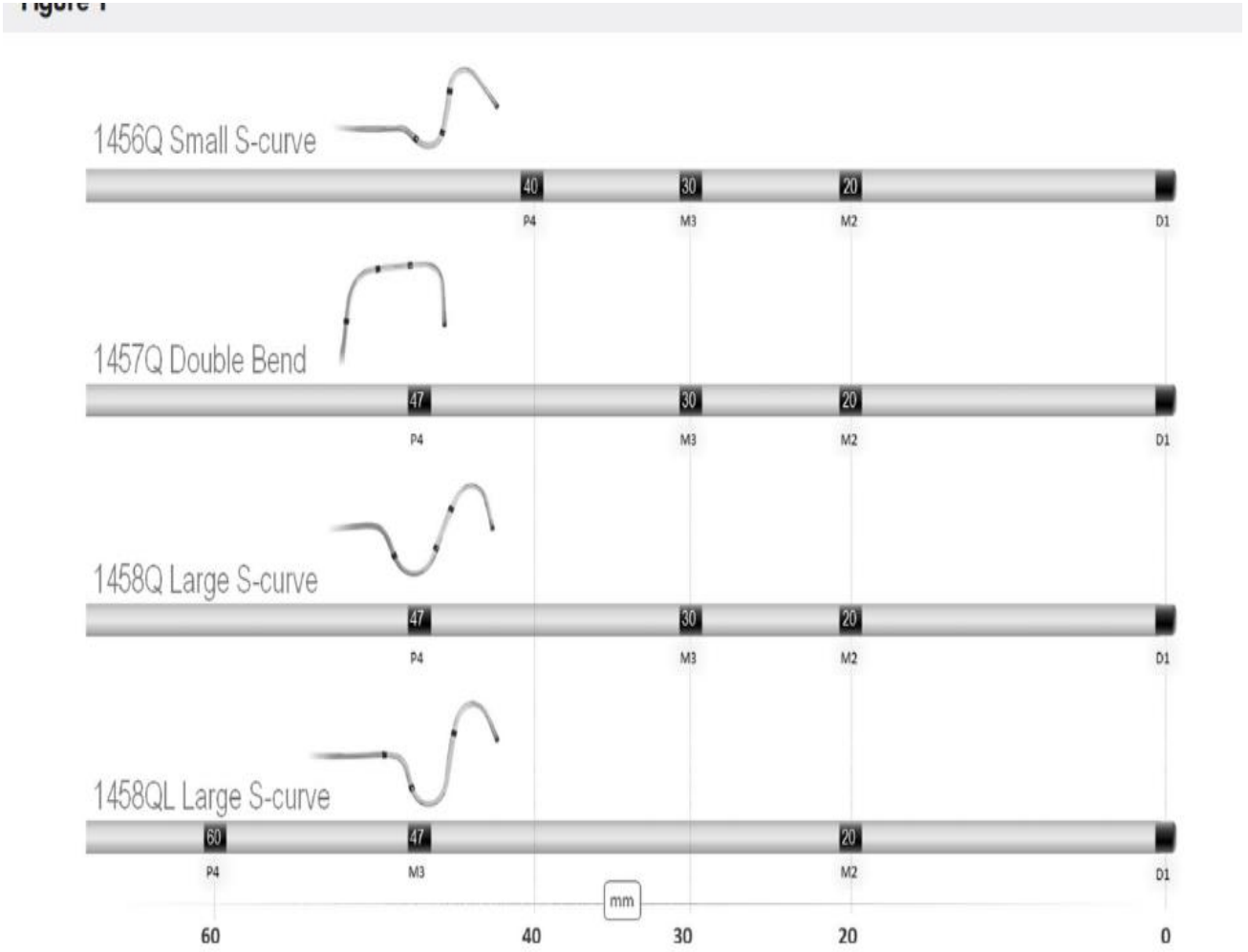
- Prospective, randomized, multi-centre study, designed to assess the impact of MPP to treat echocardiographic nonresponders to standard biventricular pacing after 6 months
- This is the Phase I of the study which allows physicians to programme MPP according to their discretion ('no mandated MPP programming')
- Pts with an LVESV reduction of at least 15% classified as responders exited the study. Pts non-responders were randomized in a 1:1 ratio to receive either MPP or continued biventricular pacing for an additional 6 months.


Subject Enrolled
N=1921
Death N=51 (2.7%)
Subjects withdrawn N= 351 (18.3%)
Unsuccessful implant N=91 (4.7%)
6-Month Visit
N=1428
Echo Responder (LVESV reduction ≥15%) N=820 (60.1%)
Echo not evaluable N=36 (2.5%)
Not randomized N=10 (0.7%)
Subjects Withdrawn N=18 (1.3%)
Randomization
(6 months)
Only Echo NRs
(LVESV reduction < 15%)
N=544 (39.9%)
MPP Arm
N=284
Followed for 6 months
BiV Arm
N=260
Followed for 6 months
Withdrawals prior to 12M N=31 (5.7%)
Death N=24 (10 cardiac deaths) (4.4%)
Echo not evaluable N=7 (1.3%)
MPP activation failure N=8 (2.8%)
Device off at surgery N=1 (0.2%)
Missing data N=16 (2.9%)
As treated Analysis
(12 months)
N=236
(232 evaluable 12M Echo + 4 cardiovascular deaths)
As treated Analysis
(12 months)
N=231
(225 evaluable 12M Echo + 6 cardiovascular deaths)

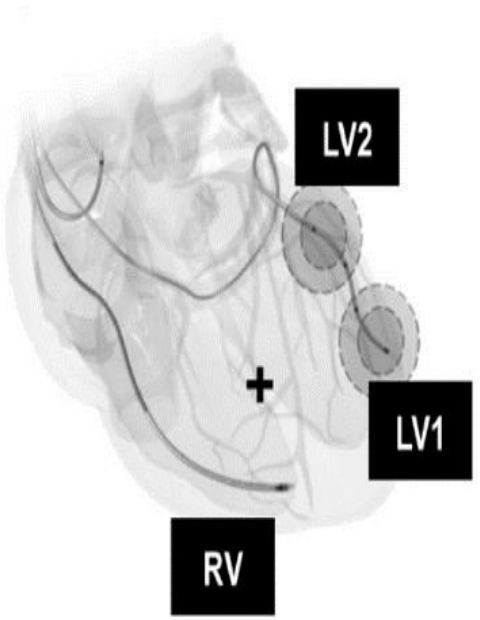


The study results demonstrated no difference in non-responder to responder conversion rate between the MPP and BiV arms

Spaziatura elettrocateteri

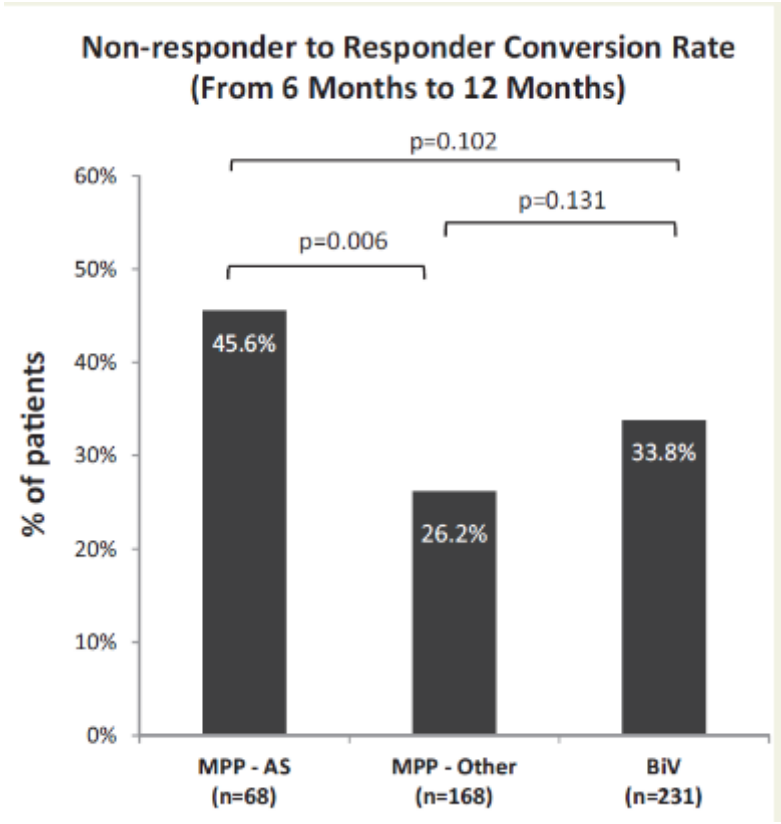


Vettori disponibili



Vector	Cathode to Anode
1	D1 → M2
2	D1 → P4
3	D1 → RV Coil
4	M2 → P4
5	M2 → RV Coil
6	M3 → M2
7	M3 → P4
8	M3 → RV Coil
9	P4 → M2
10	P4 → RV Coil
11	D1 → Can
12	M2 → Can
13	M3 → Can
14	P4 → Can

MultiPoint Pacing programming subgroup analysis



The study assessed non-responder to responder conversion rates with MPP programmed to a wide anatomical separation [i.e. distance between cathodal LV electrodes >_30mm—either D1–P4/P4–D1 (47 mm) or D1–M3/M3–D1 (30 mm) cathodal combination for LV1 and LV2] and the shortest intraventricular and interventricular timing delays of 5ms (MPP-AS)

MPP-AS provided a significantly higher non-responder to responder conversion rate compared to MPP-Other and a non-significant trend in higher conversion rate compared to biventricular pacing

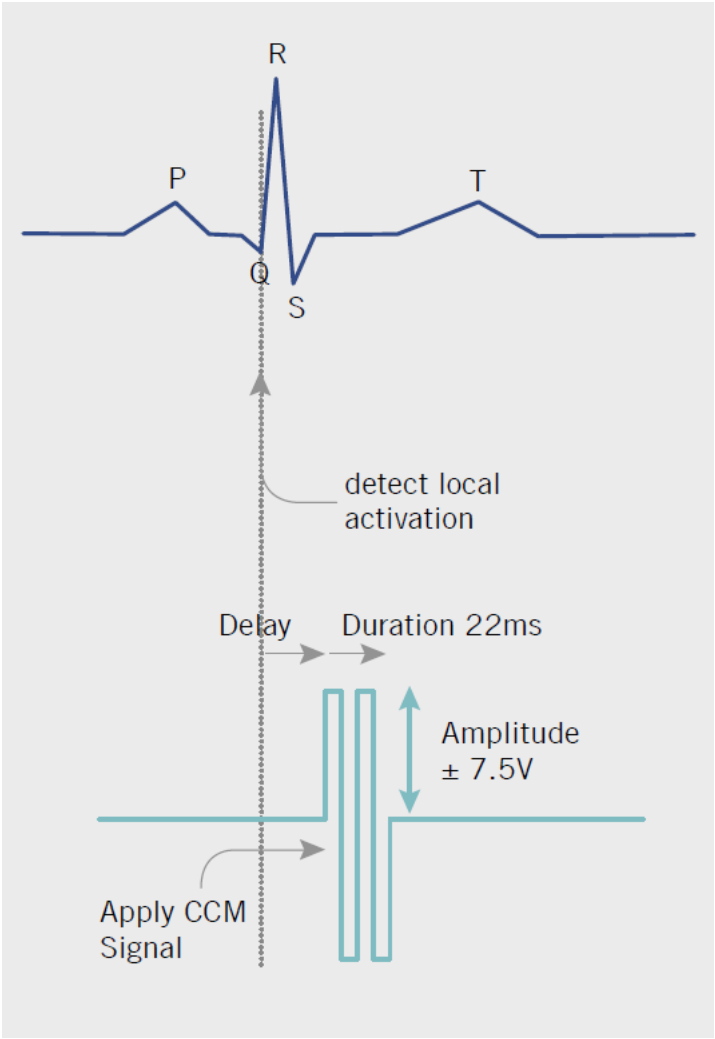
MORE-CRT MPP–PHASE II trial

- prospective, randomized, multicenter study
- to assess the 6M impact of MPP programmed to mandated MPP-AS settings in subjects who do not respond to 6 months of BiV pacing (MPP OFF).
- Approximately 5,000 subjects with a standard CRT indication will be enrolled and implanted with a quadripolar CRT system (Abbott) capable of delivering MPP.
- Only BiV pacing is activated at implant.
- At 6M, subjects classified as CRT nonresponders (15% reduction in LV end-systolic volume) are randomized (1:1) to MPP or continued BiV pacing.
- The mandated MPP parameters (eg, MPP-AS) are programmed to subjects randomized to the MPP arm.
- At 12M, the 2 groups will be compared to determine if there is a difference in CRT response rate.

Cardiac Contractility Modulation

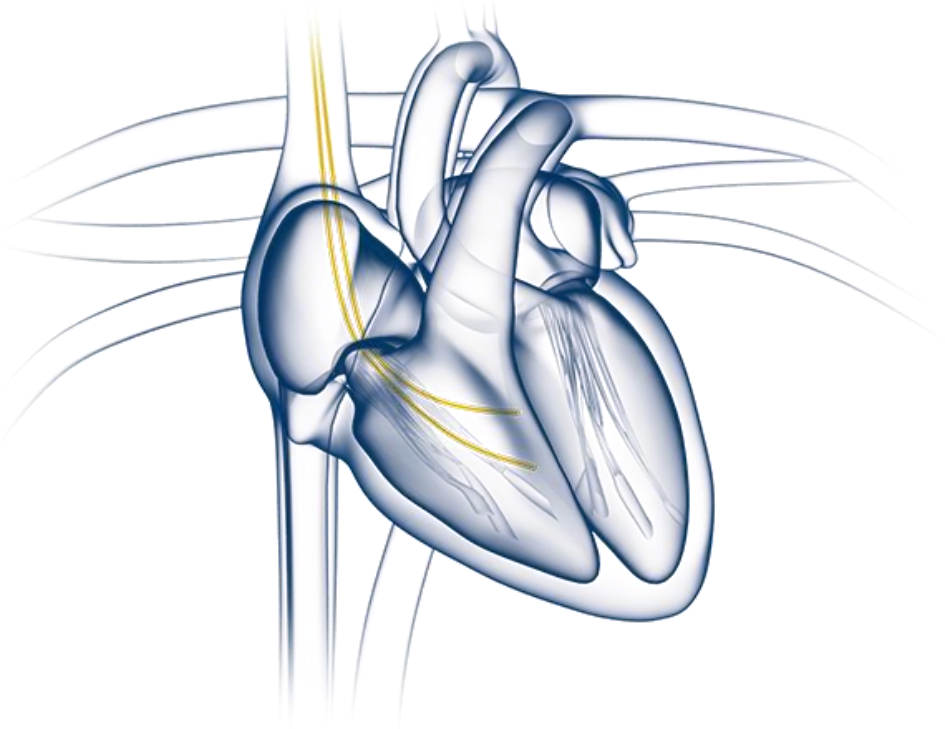
OPTIMIZER Smart and CCM™ signal

- **Cardiac Contractility Modulation** is a unique and innovative **therapy for patients with reduced and moderately reduced left ventricular systolic function and normal QRS duration**.
- CCM therapy is delivered by the Optimizer® Smart, an implantable pulse generator, that delivers the **non-excitatory impulses to the right ventricular septum during the absolute refractory period**

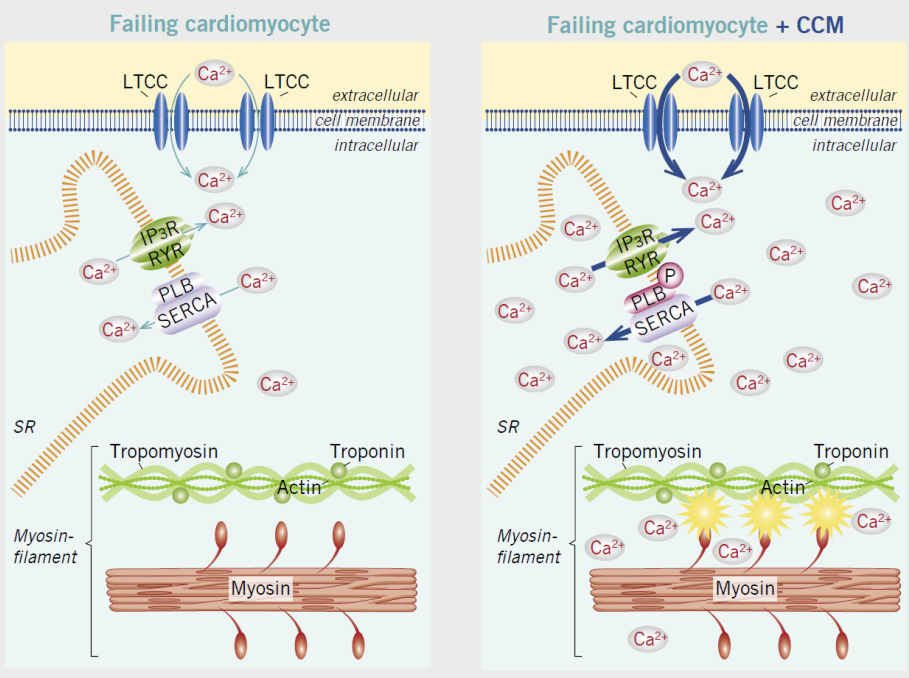


OPTIMIZER Smart system details

- **Implant with 2 usual pacemaker screw-in leads in right ventricle** (atrium not necessary with the latest algorithm)
- Rechargeable battery: **expected life 15 years**
- **Charging suggested once per week / ~ 60-90 min**



Mechanism of Action

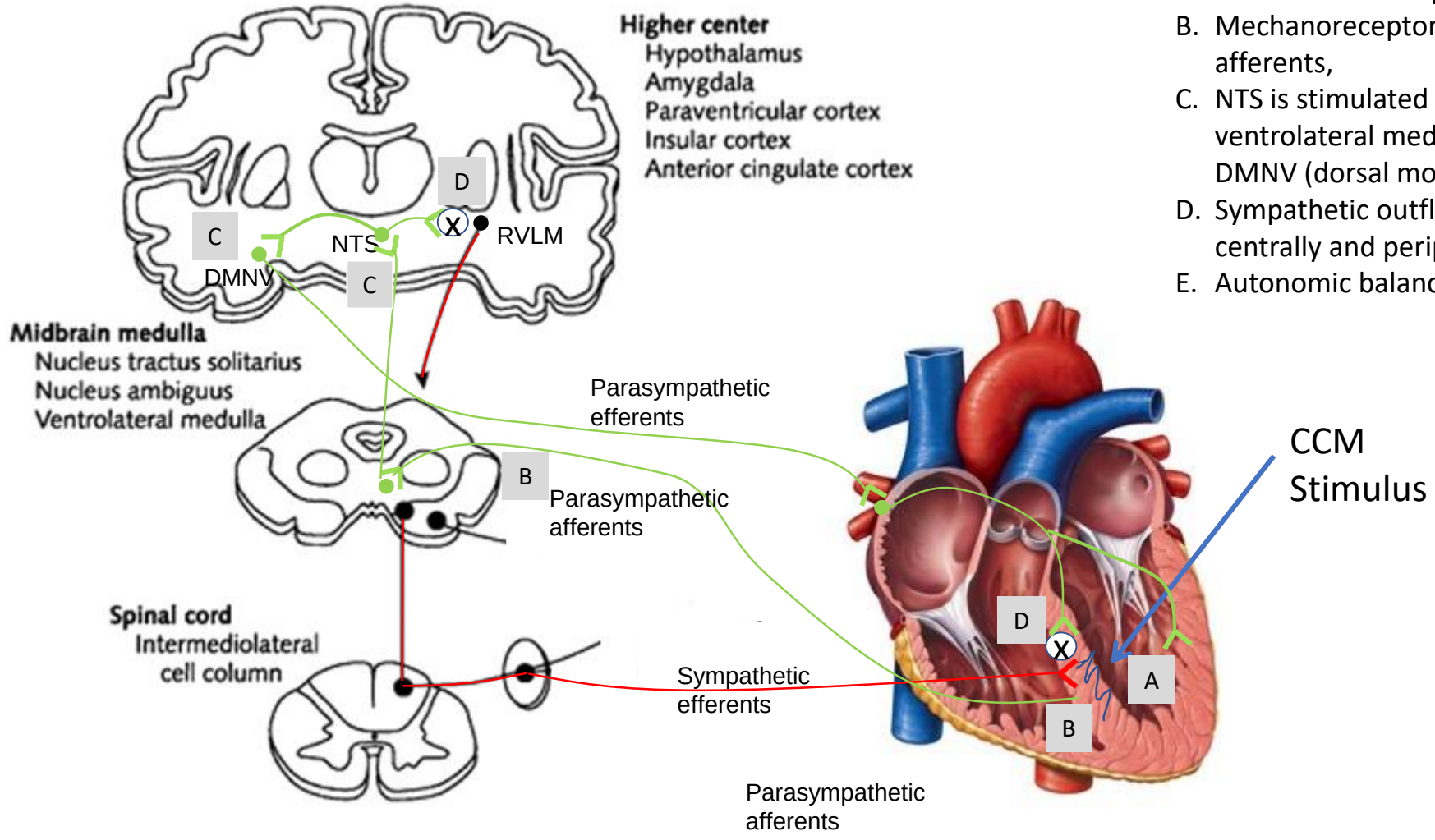


- CCM non-excitatory electrical signal results in acute changes in calcium handling.
- It enhances the efficiency of cytoplasmic-sarcoplasmic reticulum calcium transfer and elicits a rapid positive inotropic effect without increasing myocardial oxygen consumption, by strengthening the contractility of the myosin filament.

Seconds — ***Hours*** — ***Months***

Normalization of Key Regulatory Proteins Activity → **Reversal of the Fetal Gene Program** → **Demonstrated Reverse Remodeling**

Rebalancing Cardiac Autonomic Tone



CCM: Restoring vagal cardiac tone

A. CCM increases septal contraction
B. Mechanoreceptors activate vagal afferents,
C. NTS is stimulated to inhibit RVLM (rostral ventrolateral medulla) and activate DMNV (dorsal motor nucleus of vagus)
D. Sympathetic outflow is inhibited centrally and peripherally
E. Autonomic balance is restored

Optimizer®: Randomized Clinical Trial History

Study Name	Comments	Rand.	Device	Countries	Total patients
FIX-HF-1	Acute study		Opt I	Italy	40
FIX-HF-2	First chronic study		Opt I	Italy	6
FIX HF-3	CE study (EU)		Opt II	Italy, Germany, Austria	22
FIX-CHF-4	Crossover double-blind, 6 months	Yes	Opt II	Italy, Austria, Germany, France, The Netherlands and Czech	164
FIX-HF-5 Phase I	CCM vs OMT, 6 months	Yes	Opt II	USA	49
FIX-HF-5 Phase II	CCM vs. OMT	Yes	Opt III	USA	428
FIX-HF-9	CCM vs. OMT	Yes	Opt III	Hong Kong	42
FIX-CHF-12	CRT non-responder study		Opt III	Germany	19
FIX-CHF-13	CCM dosage (5 vs. 12 hours)		Opt III	Germany	20
CCM HF	CCM Registry		Opt III	Germany	143
FIX-CHF-18	Comparison 1 vs 2 leads		Opt III, Opt IVs	Germany	48
Fix-5c	CCM vs. OMT confirmatory	Yes	Opt IVs	USA, Germany, Czech	160
CCM-REG	CCM Registry		Opt IVs, Smart	Germany, Russia, France, Italy	370
Total					**1511**

- All randomized studies showed significant impact on exercise tolerance and quality of life
- Peak VO2 endpoint consistently positive across all trials
- Subgroup analyses (whether or not pre-specified) demonstrated greatest benefits in HF patients with moderately reduced ejection fractions ranging from 35% to 45%

Clinical evidence: from latest publications to patient selection

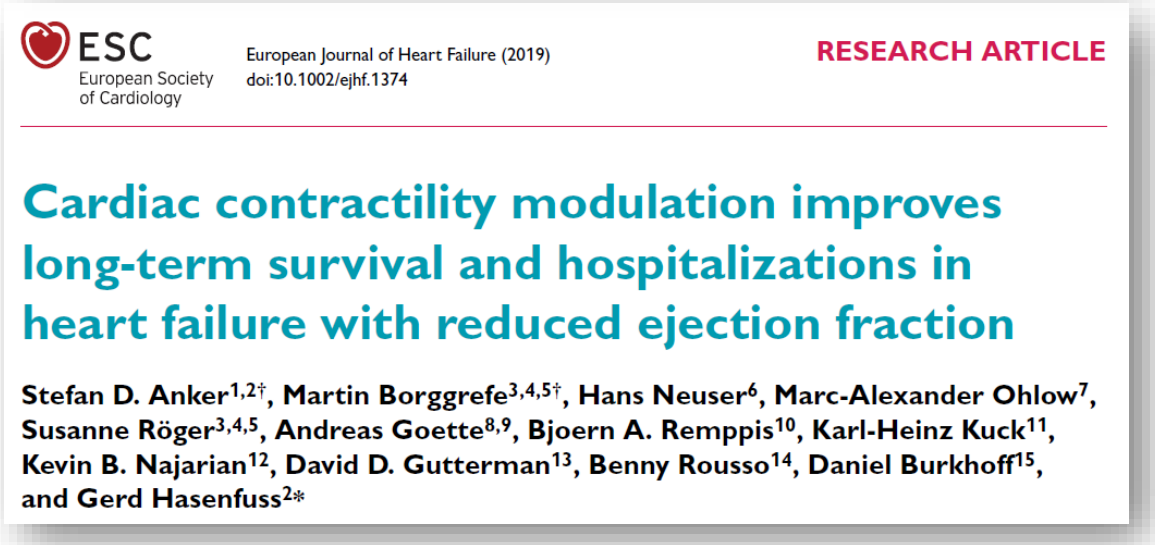
The FIX-HF-5C Study

JACC: HEART FAILURE VOL. ■, NO. ■, 2018

A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation

William T. Abraham, MD,[a] Karl-Heinz Kuck, MD,[b] Rochelle L. Goldsmith, PHD,[c] JoAnn Lindenfeld, MD,[d] Vivek Y. Reddy, MD,[e] Peter E. Carson, MD,[f] Douglas L. Mann, MD,[g] Benjamin Saville, PHD,[h] Helen Parise, SCD,[i] Rodrigo Chan, MD,[j] Phi Wiegn, MD,[k] Jeffrey L. Hastings, MD,[k] Andrew J. Kaplan, MD,[l] Frank Edelmann, MD,[m] Lars Luthje, MD,[m] Rami Kahwash, MD,[n] Gery F. Tomassoni, MD,[o] David D. Gutterman, MD,[p] Angela Stagg, BS,[q] Daniel Burkhoff, MD, PHD,[r] Gerd Hasenfuß, MD[s]

“Real World Registry”: CCM-REG



ESC European Society of Cardiology

European Journal of Heart Failure (2019) doi:10.1002/ejhf.1374

RESEARCH ARTICLE

Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction

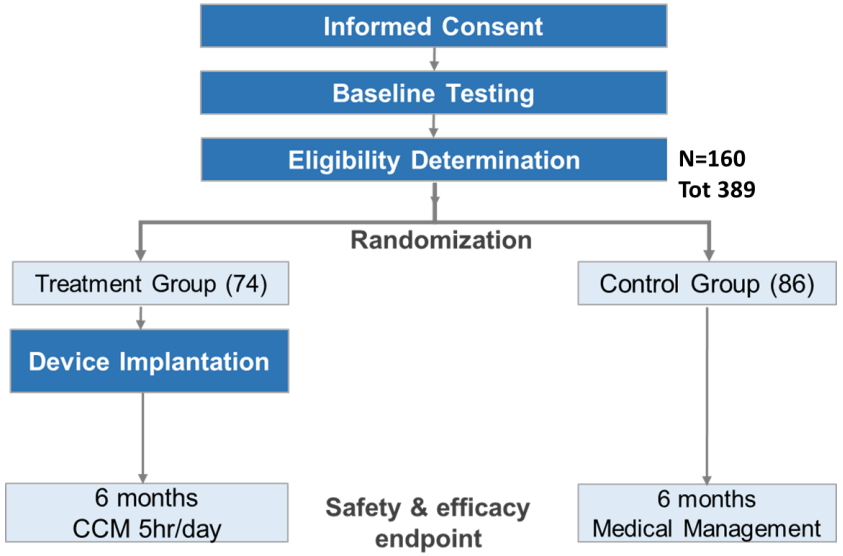
Stefan D. Anker[1,2†], Martin Borggrefe[3,4,5†], Hans Neuser[6], Marc-Alexander Ohlow[7], Susanne Röger[3,4,5], Andreas Goette[8,9], Bjoern A. Remppis[10], Karl-Heinz Kuck[11], Kevin B. Najarian[12], David D. Gutterman[13], Benny Rousso[14], Daniel Burkhoff[15], and Gerd Hasenfuss[2*]

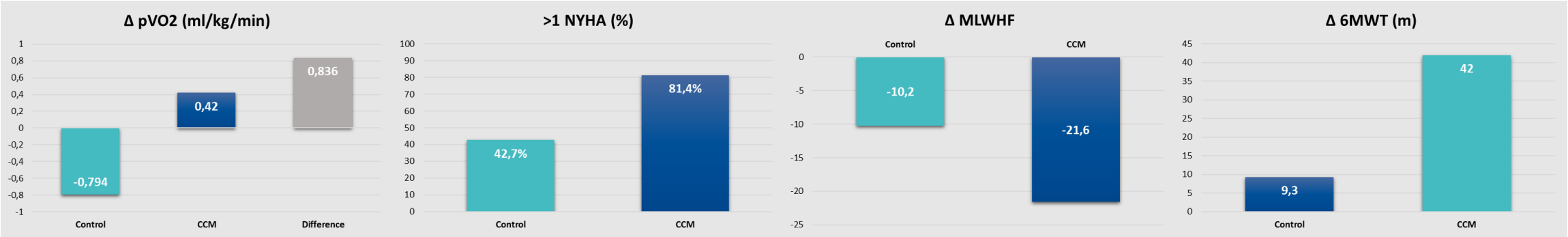
Abraham et al, JACC Heart Failure 2018
G. Hasenfuss, European Journal of Heart Failure (2019) doi:10.1002/ejhf.137

FIX-HF-5C Study

- Prospective, randomized study of optimal medical therapy (OMT) alone versus OMT+ CCM
- **NYHA III or IV, QRS <130 ms and EF 25%-45**
- 160 + 229 = 389 pts

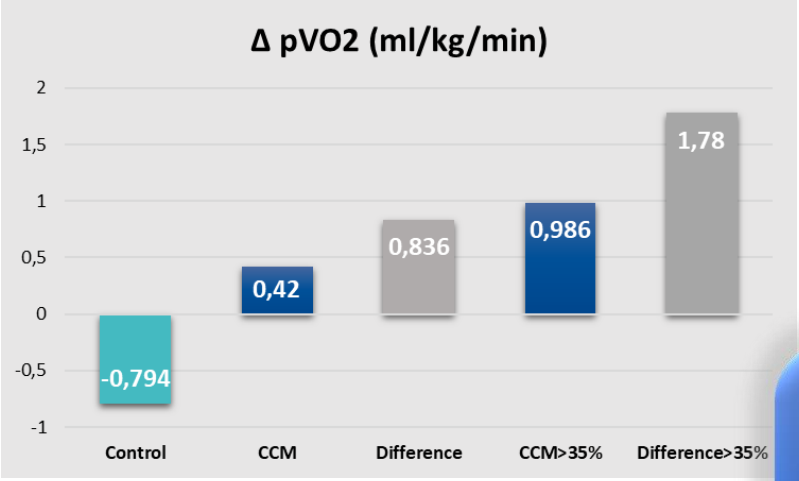
- **Study met all specified endpoints:**
  - Peak VO2, MLWHFQ, NYHA, 6MWT better with treatment
  - Even stronger effects noted in patients with EF 35-45%

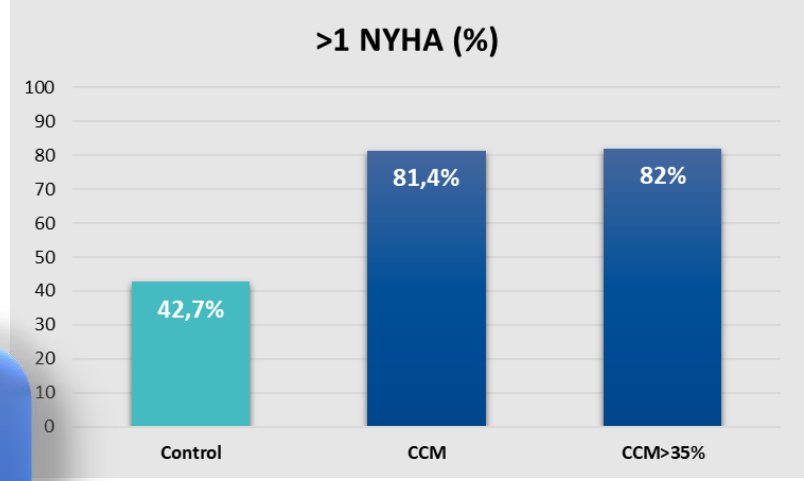




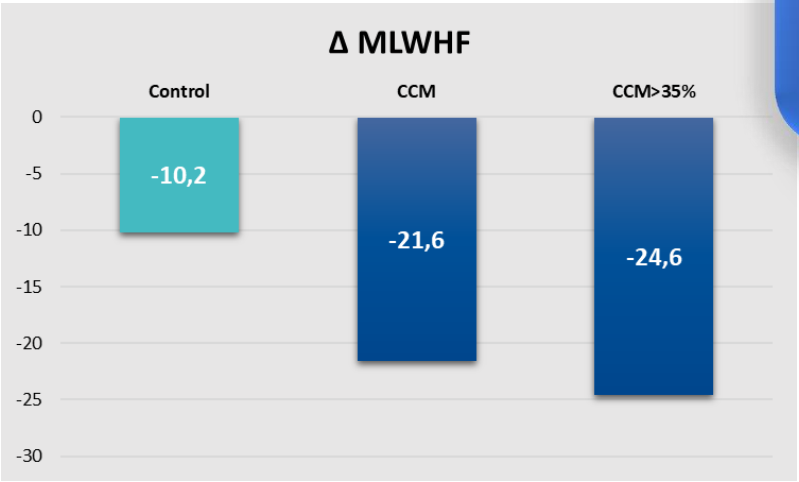
JACC: Heart Failure 2018: ISSN 2213-1779

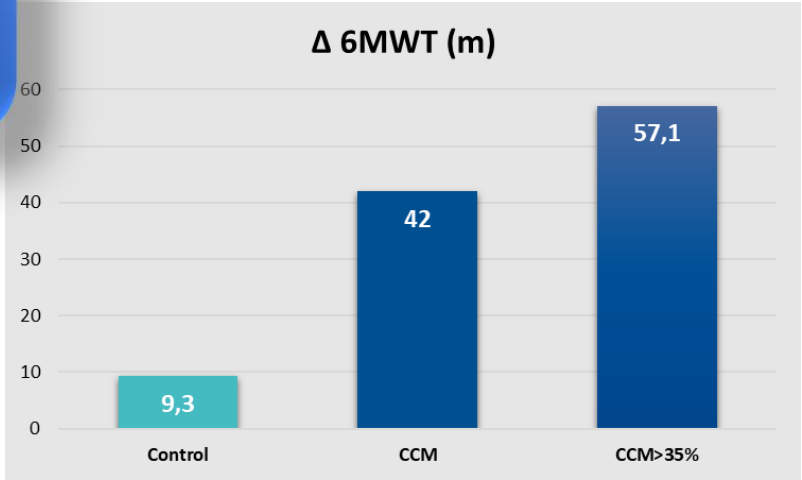
FIX-HF-5C Study





Even stronger effects in patients with EF 35-45%





Abraham et al, JACC Heart Failure 2018

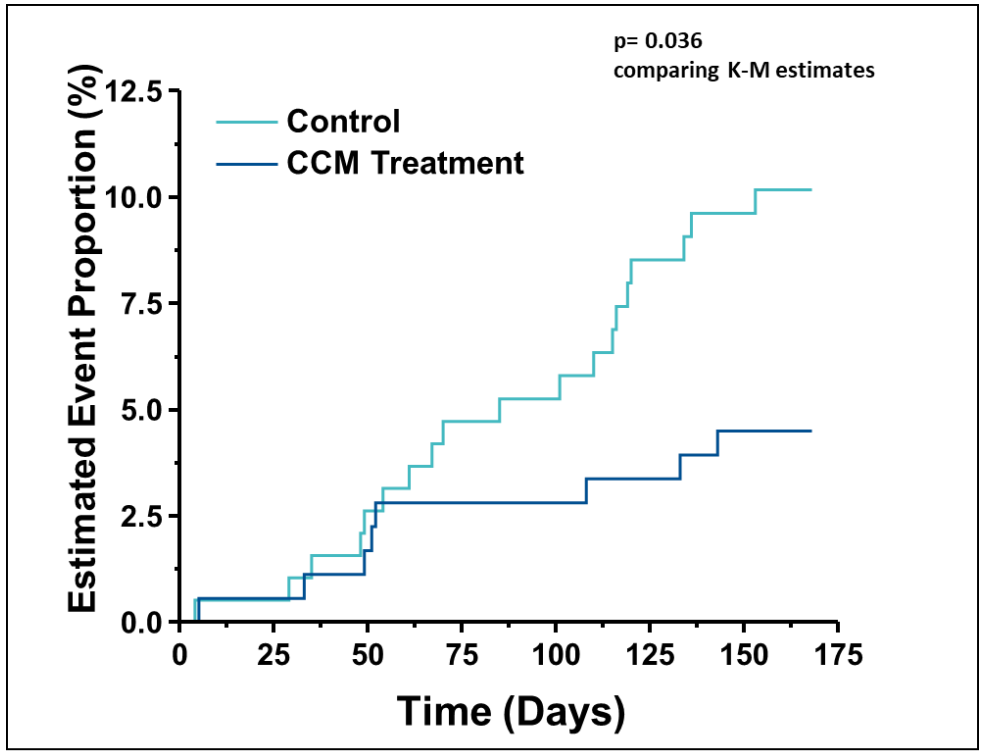
FIX-HF-5C Study

- Significant improvement in survival free of cardiac death and heart failure hospitalization (**97.1%** in treatment vs. **89.2%** in control; $p < 0.07$)

73% reduction in event rates

from 10.8% in the control to 2.9% in the treatment group

- Subgroup analysis showed that this improvement was mainly driven by a significant reduction in events for the EF 25% to 35% cohort ($p < 0.009$).



JACC: Heart Failure 2018: ISSN 2213-1779

Summary for the FIX-HF-5C Study

- **Study met all specified endpoints:**
  - Peak VO2, MLWHFQ, NYHA better with treatment
  - Acceptable rate of device/procedure-related complications
  - Reduced Cardiovascular Death/HF Hospitalizations
  - Even stronger effects noted in patients with EF 35-45%

- **In patients with EF 25%-45%, QRS<130ms, on Guideline Directed Medical Therapy with persistent NYHA III/IVa symptoms, CCM is safe and effective in improving exercise tolerance and QoL and reduces HF hospitalizations**

Abraham et al, JACC Heart Failure 2018

“Real World Registry”: CCM-REG

- European prospective registry study @ 31 sites aimed to assess longer-term impact of **CCM on hospitalizations and mortality** in a real-world experience with the **same population as FIX-HF-5C** (25≤EF≤45%)
- 400 pts in total, 140 patients with EF 25% - 45% receiving CCM therapy for clinical indication
- **2 Year Follow-up**: Minnesota Living with Heart Failure Questionnaire (MLWHFQ), LVEF, Cardiovascular and HF hospitalizations (compared to hospitalizations during the year prior to CCM)
- **3 year Follow-up**: Mortality (compared to predicted mortality by the Seattle Heart Failure Model, SHFM; MAGGIC)

G. Hasenfuss, EHF, Vienna 2018
European Journal of Heart Failure (2019) doi:10.1002/ejhf.1374

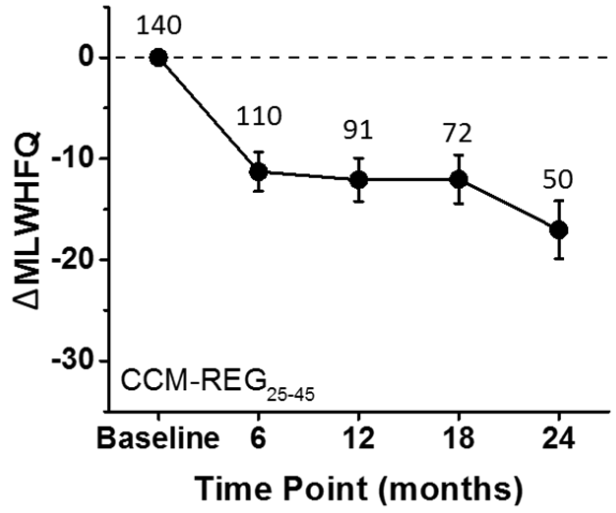
“Real World Registry”: CCM-REG

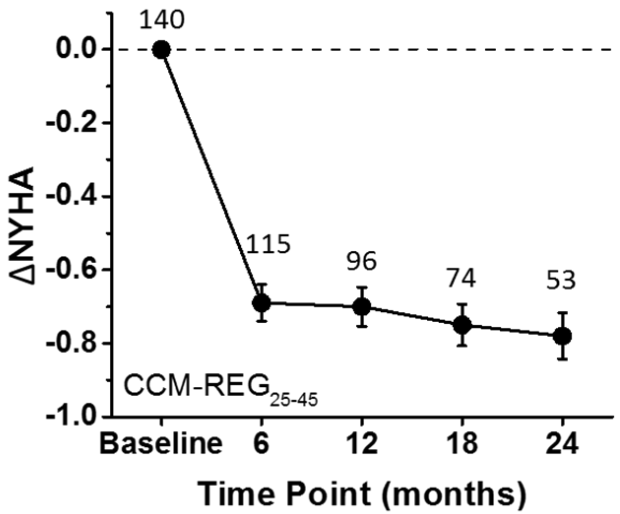
ESC European Society of Cardiology
European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1374
RESEARCH ARTICLE

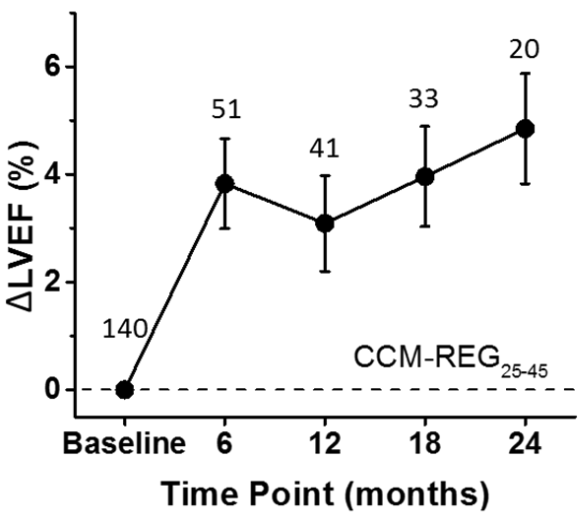
Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction

Stefan D. Anker[1,2†], Martin Borggrefe[3,4,5†], Hans Neuser[6], Marc-Alexander Ohlow[7], Susanne Röger[3,4,5], Andreas Goette[8,9], Bjoern A. Remppis[10], Karl-Heinz Kuck[11], Kevin B. Najarian[12], David D. Gutterman[13], Benny Rousso[14], Daniel Burkhoff[15], and Gerd Hasenfuss[2*]

Symptoms and quality of life (NYHA class, MLHFQ) showed sustainable improvement and of **similar magnitude to the ones observed in the randomized studies**. LVEF also improved during the early follow-up period, as in prior studies.







G. Hasenfuss, EHF, Vienna 2018
European Journal of Heart Failure (2019) doi:10.1002/ejhf.1374

“Real World Registry”: CCM-REG

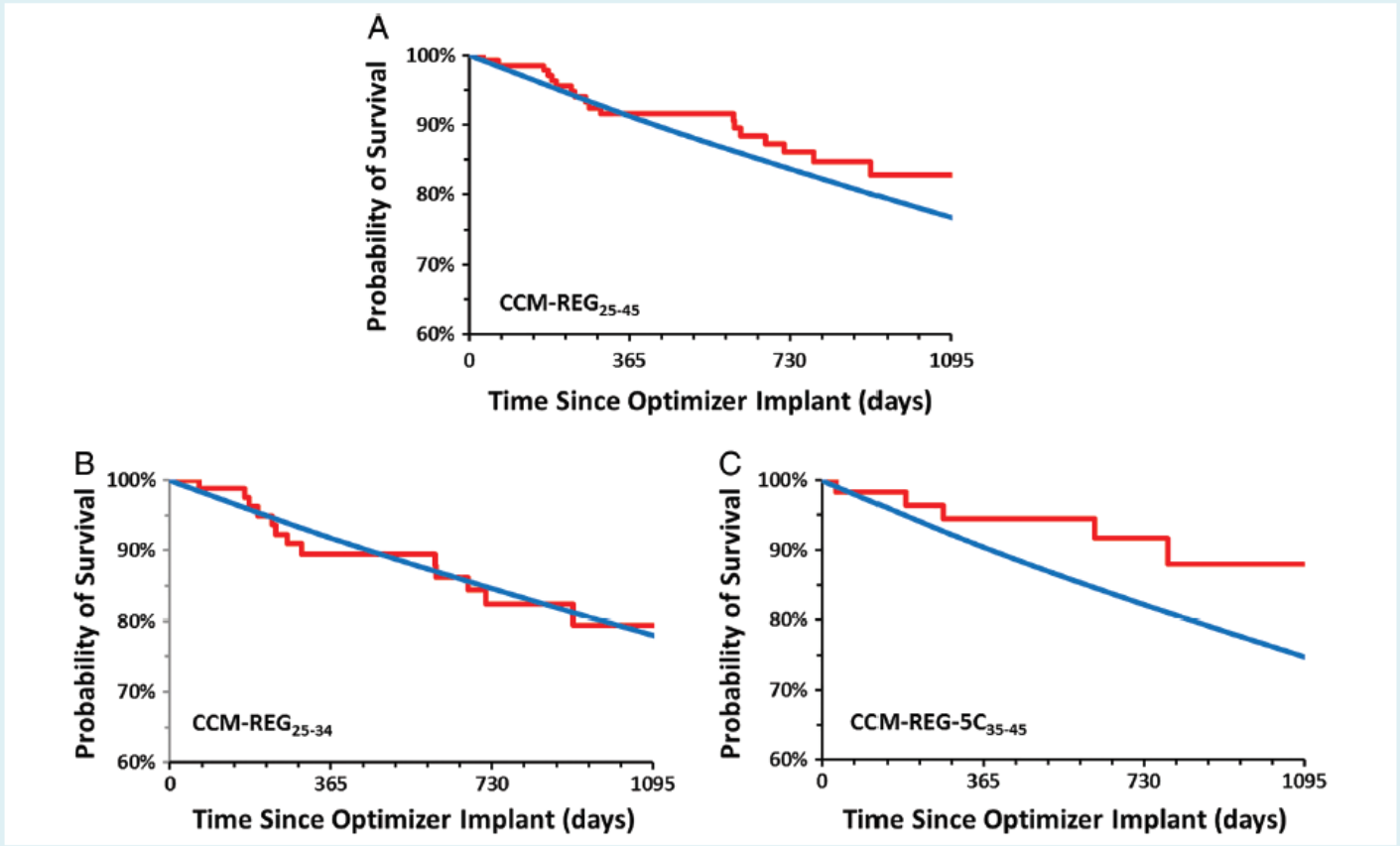


Figure 1 Kaplan–Meier survival curves over 3 years of follow-up. (*A*) Survival rates of the CCM-REG$_{25\text{-}45}$ cohort (red) which were comparable to the values predicted by the Seattle Heart Failure Model (blue). (*B*) In the CCM-REG$_{25\text{-}34}$ cohort with LVEF $< 35\%$, survival was similar to that predicted by the Seattle Heart Failure Model. (*C*) For the CCM-REG-5C$_{35\text{-}45}$ cohort with LVEF $\geq 35\%$, observed survival was greater than predicted by the model.

3-year survival was comparable to that predicted by SHFM in the overall group and the CCM-REG$_{25\text{-}34}$ group, whereas in the subset of patients with 35%≤LVEF≤45%, survival was significantly better than predicted by SHFM.

Collectively, these data both confirm and extend the evidence for the safety and efficacy of CCM.

G. Hasenfuss, EHF, Vienna 2018
European Journal of Heart Failure (2019) doi:10.1002/ejhf.1374

CCM in the ESC consensus HF 2019

European Journal of Heart Failure

Research Article | Free Access

Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology

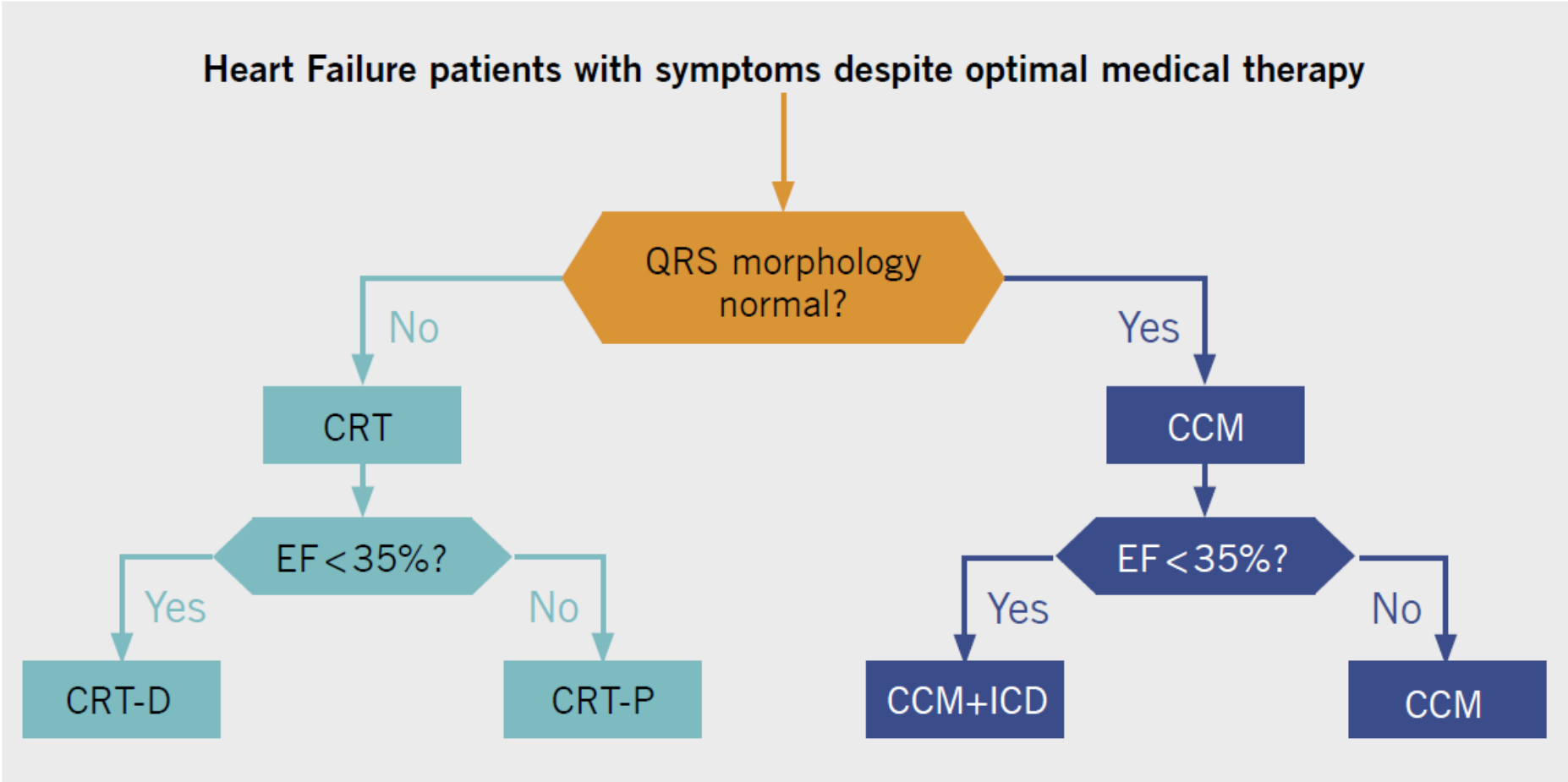
15. Cardiac contractility modulation

Consensus recommendation. CCM **may be considered** in patients with HFrEF (LVEF between 25-45%) and a narrow QRS complex (<130 ms) in order to improve exercise capacity, quality of life and alleviate HF symptoms.

Practical comments. CCM is now approved in the US and Europe. CCM may be used to improve symptoms and exercise capacity in selected HFrEF patients with troublesome symptoms despite pharmacological therapy who have a QRS duration of <130msec and are therefore not indicated for CRT.

EUROPEAN SOCIETY OF CARDIOLOGY

CCM: Position in the Treatment Paradigm



Common CCM™ patient profile

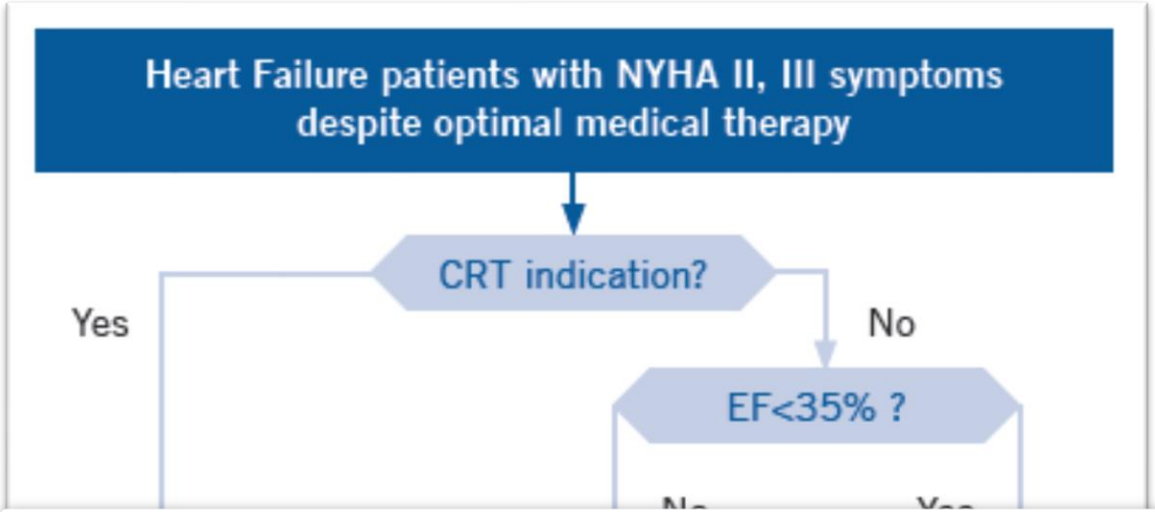
- *NYHA III/IV*
- *Normal QRS duration*
- *EF 25–45%*
- *Peak VO_2 ≥9ml/kg/min*

Common contraindications

- *Mechanical tricuspid*
- *No venous access*

CCM tomorrow

Smart Mini **Integra**



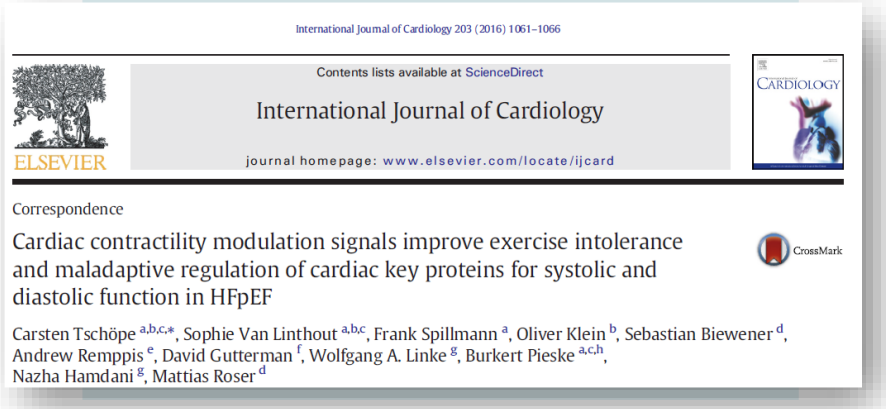
Open invetigations:

- **CRT non responder**
- **Diastolic HF**

CCM HFpEF Study

Table 1 Data from registries or subgroup analyses showing that treatments able to improve clinical outcome in heart failure with reduced ejection fraction seem to be beneficial in heart failure with mid-range ejection fraction, but not in heart failure with preserved ejection fraction too

	HFrEF	HFmrEF	HFpEF
ACEI	+	NA	–
ARB	+	(+)	–
BB	+	(+)	–
Ivabradine	+	NA	–
MRA	+	(+)	–
Digitalis	+	NA	–
ARNI	+	NA	NA
Diuretics	+c	+c	+c
Defibrillator	+	+*	+*
CRT	+	+c	NA
CCM	+c	+c	Case reports



International Journal of Cardiology 203 (2016) 1061–1066

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journal homepage: www.elsevier.com/locate/ijcard

Correspondence

Cardiac contractility modulation signals improve exercise intolerance and maladaptive regulation of cardiac key proteins for systolic and diastolic function in HFpEF

Carsten Tschöpe [a,b,c,*], Sophie Van Linthout [a,b,c], Frank Spillmann [a], Oliver Klein [b], Sebastian Biewener [d], Andrew Remppis [e], David Gutterman [f], Wolfgang A. Linke [g], Burkert Pieske [a,c,h], Nazha Hamdani [g], Mattias Roser [d]

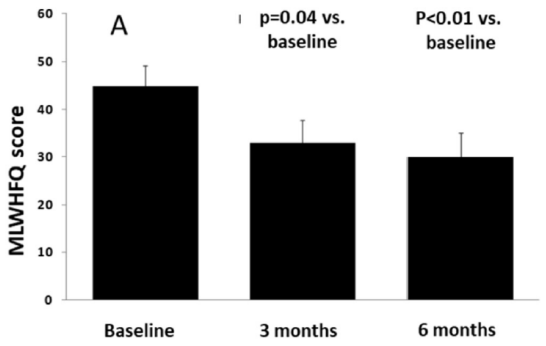
CCM -HFpEF study

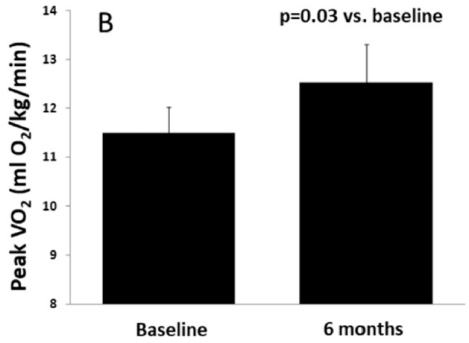
- Ongoing pilot study to evaluate the efficacy and safety of CCM therapy in heart failure patients with baseline EF ≥ 50%
- Prospective, multicentre, single arm open label, exploratory study
- Expansion of CE mark for therapy in patients with HFpEF
- 60 patients will be enrolled from up to 30 sites
- Follow up period 24 weeks

Tschope et al., EJHF (2019) 21, 14–22

Thschope et al., International Journal of Cardiology 203 (2016) 1061–1066

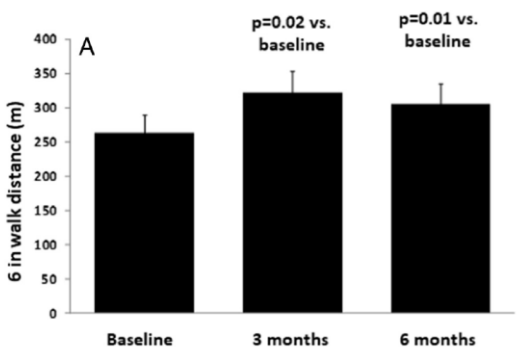
FIX-CHF-12: CCM in CRT non responders

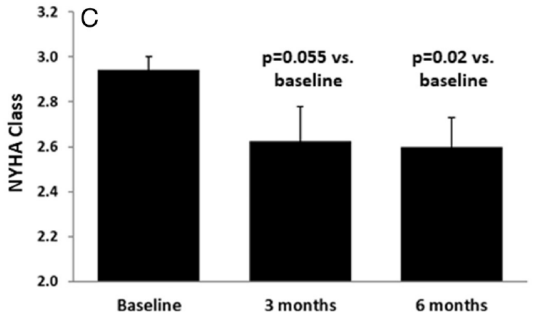


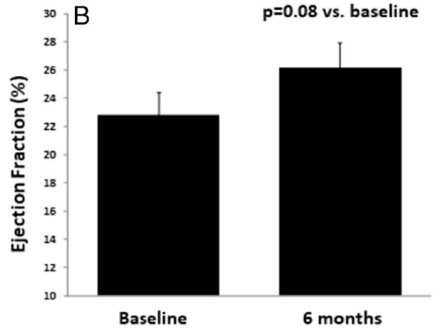


CCM is efficacious and safe in patients with moderate-to-severe heart failure on OMT, who do not respond to CRT.

Following 3–6 months of CCM added to OMT and CRT, patients showed **improvements in exercise tolerance (peak VO2), and quality of life (MLWHFQ), as well as 6 minute walk distance, and NYHA classification, with a trend toward improvement in LVEF.**







J. Kuschyk et al. / International Journal of Cardiology 277 (2019) 173–177

CCM tomorrow

- ~23cc IPG with “physiological” tear-drop-shaped enclosure.
- Delivers CCM signals using algorithms that are substantially equivalent to those of the OPTIMIZER Smart IPG.
- Auto-setup of CCM delivery algorithm
- RF-based communications for high-speed telemetry
- >15 years longevity

Smart Mini CCM

- Integrates CCM™ therapy with a rescue ICD in a two-lead IPG
- CCM™ and telemetry features same as OPTIMIZER SMART-Mini
- Rescue ICD capable of delivering ATP, 36J defibrillation shocks, and post-shock brady pacing
- 15 year minimum longevity
- Uses rechargeable Li-ion cell for CCM™ and ICD sensing
- Hybrid Li-SVO/CFx battery used only for antitachy therapy (and sensing if Li-ion cell is discharged)

Integra CCM-D

CRT Response
Current Issues

Multiple different factors between individual pts can affect response:

Genetic & gender differences

Stage & CHF etiology

LV lead location

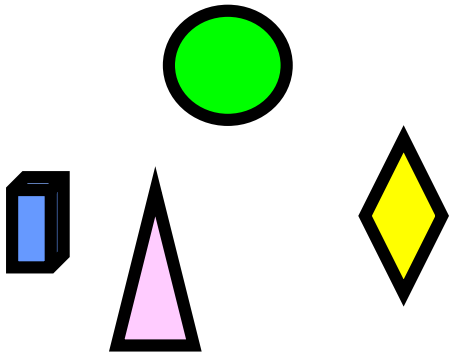
QRS morphology &width

Presence of co-morbidities, LV scar, & AF/PVC's

Coronary sinus valves/stenosis/limited target vessels

Device management: AV & VV optimization, ensuring BiV pacing

caratteristiche del modello medico positivista

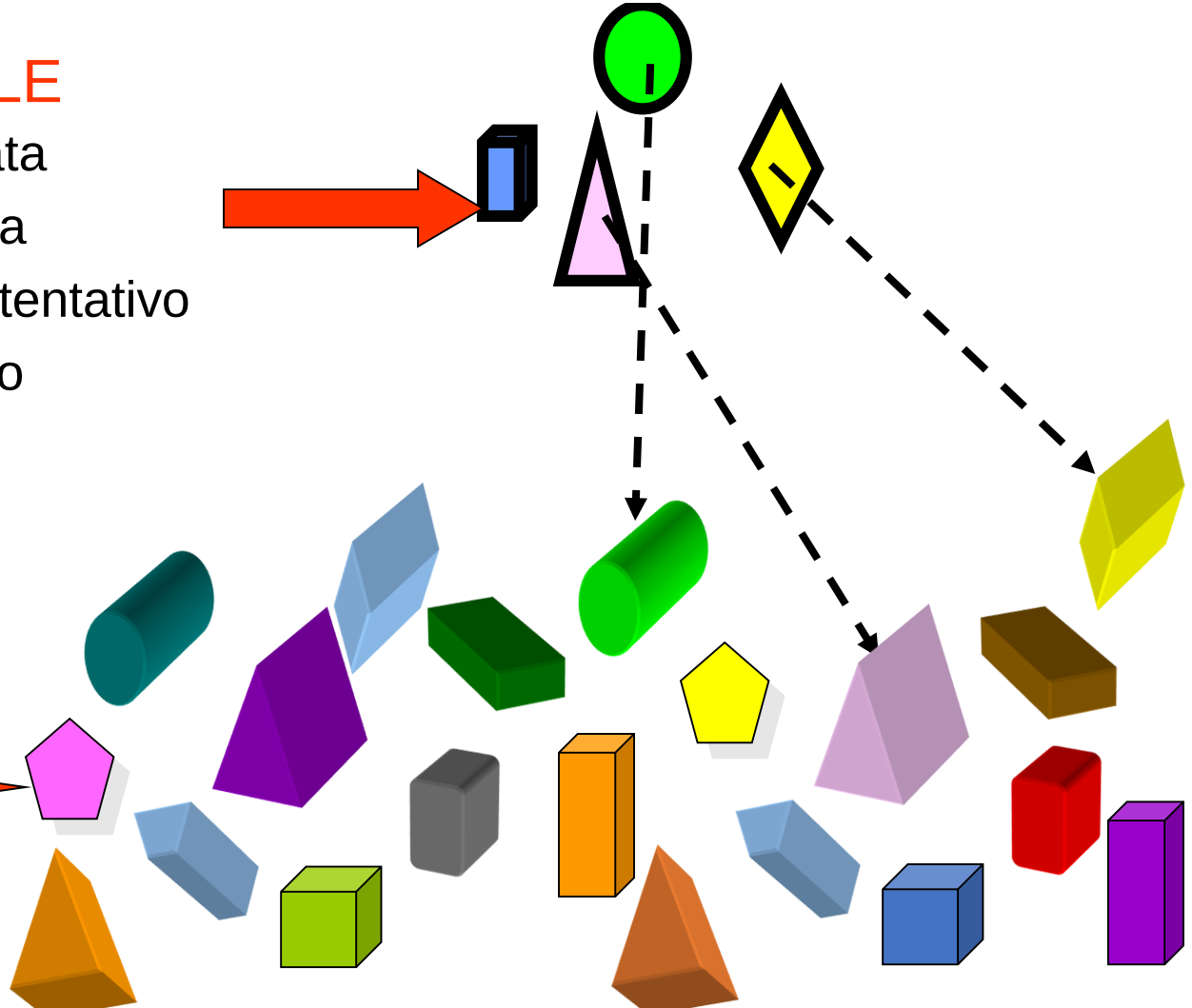


- divinizzazione della tecnica
- riduzione della complessità socioculturale della persona ai modelli biologici
- individuo come oggetto genetico e non soggetto esistenziale
- economicismo (*tutti i malati dovrebbero essere X, quindi tutti loro dovrebbero avere le necessità Y perché tutti loro dovrebbero costare Z*)

NARRAZIONE DEL PROFESSIONISTA

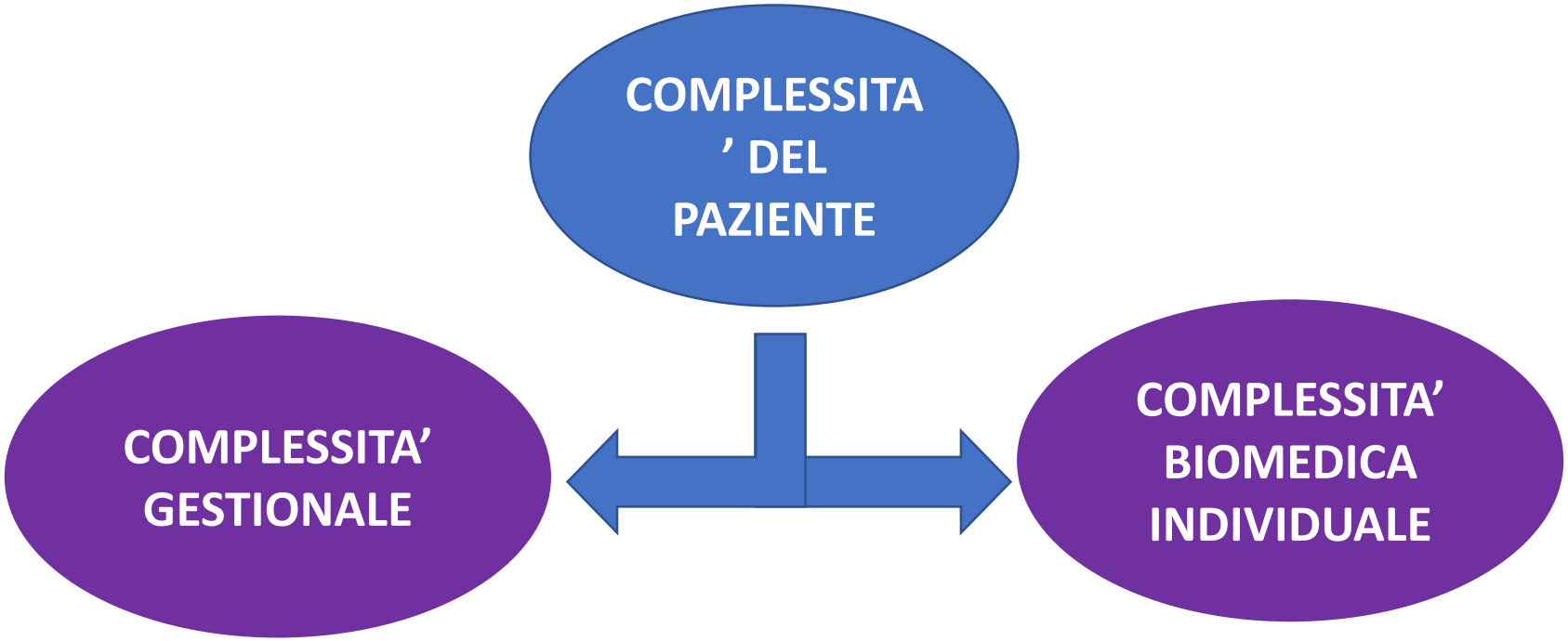
MODELLO MENTALE

è una visione semplificata della realtà che ci aiuta a risparmiare energie nel tentativo di comprendere il mondo



NARRAZIONE DEL PAZIENTE

PERSONALIZZARE SIGNIFICA RISPONDERE ALLA COMPLESSITA’



SOUNDING BOARD

Precision Medicine — Personalized, Problematic, and Promising

J. Larry Jameson, M.D., Ph.D., and Dan L. Longo, M.D.

This article was published on May 27, 2015, at NEJM.org.

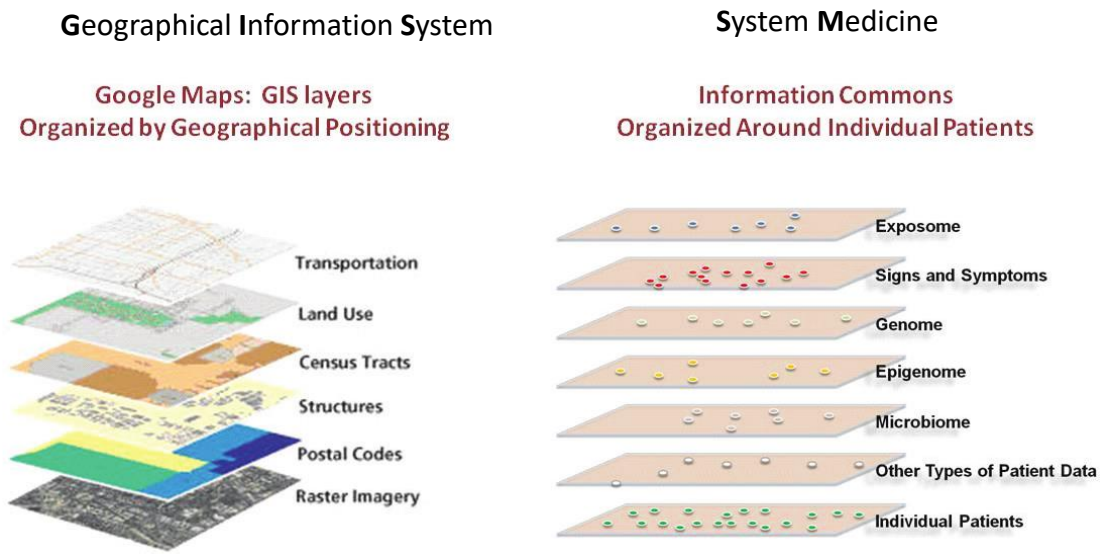
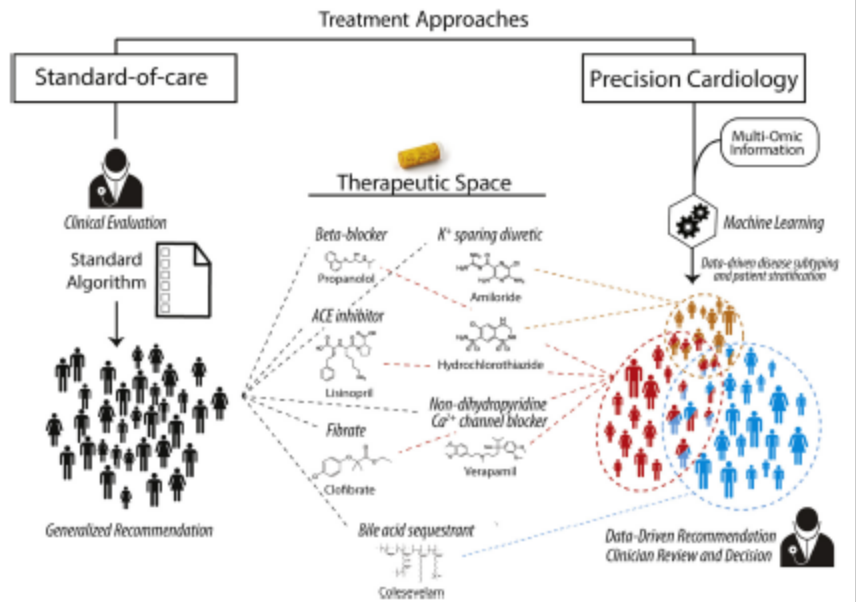


FIGURE 1-2 An Information Commons might use a GIS-type structure.
The proposed, individual-centric Information Commons (right panel) is somewhat analogous to a layered GIS (left panel). In both cases, the bottom layer defines the organization of all the overlays. However, in a GIS, any vertical line through the layers connects related snippets of information since all the layers are organized by geographical position. In contrast, data in each of the higher layers of the Information Commons will overlay on the patient layer in complex ways (e.g., patients with similar microbiomes and symptoms may have very different genome sequences).
SOURCE: FPA 2011 (left panel).

FIGURE 2 Conceptualization of a Personalized Medicine Approach to Cardiology Contrasted With the Current Standard of Care



In the precision approach to cardiology, multi-omic information is incorporated to identify subtle strata of patients which can be differentially treated within the existing therapeutic space. ACE = angiotensin-converting enzyme.