

Cardiac resynchronization

Responders, non-responders, hyper-responders

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The Benefit from CRT is well established

Clinical Studies Evaluating CRT in Heart Faillure

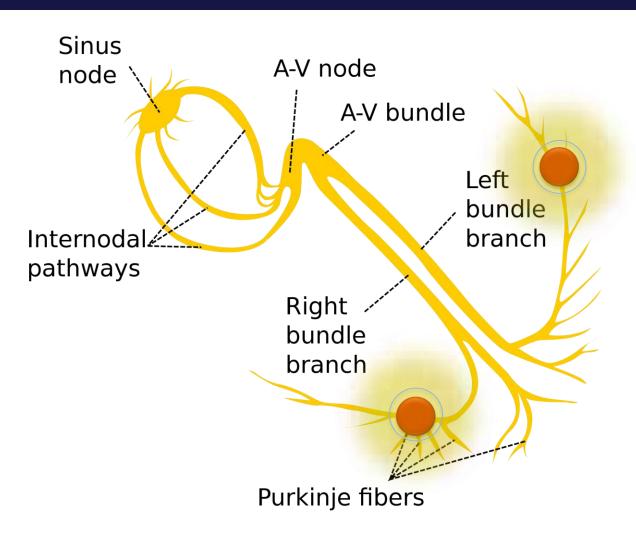
Trial (ref)	No.	Design	NYHA	LVEF	QRS	Primary endpoints	Secondary endpoints	Main Findings	Trial (ref)	No.	Design	NYHA				
MUSTIC-SR ⁵²	58	Single-blinded, crossover, randomized CRT vs. OMT, 6 months	Ш	<35%	≥150	6MWD	NYHA class, QoL, peak VO, LV volumes, MR hospitalizations, mortality	CRT-P improved 6MWD, NYHA class, QoL, peak VO ₂ , reduced LV volumes and MR and reduced hospitalizations	MR OMT		Double-blinded randomized OMT vs. CRT-P / or vs. CRT-D,	III-IV				
PATH-CHF ⁵¹	41	Single-blinded, crossover, randomized RV vs. LV vs. BiV, 12 months	III–IV	NA	≥150	Peak VO ₂ , 6MWD	NYHA class, QoL hospitalizations	CRT-P improved NYHA class, QoL and 6MWD and reduced hospitalizations	CARE-HF56	813	Double-blinded randomized OMT vs. CRT-P 29.4 months	III-IV				
MIRACLE ⁴⁹	453	Double-blinded, randomized CRT vs. OMT, 6 months	III-IV	≤35%	≥130	NYHA class, 6MWD , QoL	Peak VO ₂ LVEDD, LVEF, MR clinical composite response	CRT-P improved NYHA class, QoL and 6MWD and reduced LVEDD, MR and increased LVEF	REVERSE	610	randomized CRT-ON vs. CRT-OFF,	I-II				
MIRACLE-ICD ⁵⁴	369	Double-blinded, randomized CRT-D vs. ICD, 6 months	III-IV	≤35%	≥ 30	NYHA class, 6MWD , QoL	Peak VO ₂ LVEDD, LVEF, MR clinical composite response	CRT-D improved NYHA class, QoL, peak VO ₂	MADIT-CRT ⁵⁶ 1820	-CRT ⁵⁶ 1820	randomized CRT-D vs. ICD,	[-II				
CONTAK-CD ⁵³	490	Double-blinded randomized CRT-D vs. ICD, 6 months	II-III- IV	≤35%	≥120	NYHA class, 6MWD , QoL	LV volume, LVEF composite of mortality, VT/VF, hospitalizations	CRT-D improved 6MWD, NYHA class, QoL, reduced LV volume and increased LVEF	RAFT ⁶² 1798	FT*2 1798 Do		T ⁶² 1798 De		T ⁶² 1798 Double	Double-blinded,	11–111
MIRACLE-ICD II69	186	Double-blinded, randomized CRT-D vs. ICD, 6 months	JI.	≤35%	≥130	Peak VO ₂	VE/VCO ₂ , NYHA, QoL, 6MWD, LV volumes and EF, composite clinical	CRT-D improved NYHA, VE/CO ₂ and reduced LV volumes and improved LVEF			vs. ICD 40 months					

Trial (ref)	No.	Design	NYHA	LVEF	QRS	Primary endpoints	Secondary endpoints	Main Findings
COMPANION ⁵⁵	1520	Double-blinded randomized OMT vs. CRT-P / or vs. CRT-D, 15 months	III–IV	≤35%	≥120	All-cause mortality or hospitalization	All-cause mortality, cardiac mortality	CRT-P and CRT-D reduced all-cause mortality or hospitalization
CARE-HF ⁵⁶	813	Double-blinded randomized OMT vs. CRT-P 29.4 months	III-IV	≤35%	≥120	All-cause mortality or hospitalization	All-cause mortality, NYHA class, QoL	CRT-P reduced all-cause mortality and hospitalization and improved NYHA class and QoL
REVERSE ⁶⁸	610	Double-blinded, randomized CRT-ON vs. CRT-OFF, 12 months	⊢II	≤40%	≥120	% worsened by clinical composite endpoint	LVESV index, heart failure hospitalizations and all-cause mortality	CRT-P/CRT-D did not change the primary endpoint and did not reduce all-cause mortality but reduced LYESV index and heart failure hospitalizations.
MADIT-CRT ⁵⁶	1820	Single-blinded, randomized CRT-D vs. ICD, I2 months	I-II	≤30%	≥ 30	All-cause mortality or heart failure hospitalizations	All-cause mortality and LVESV	CRT-D reduced the endpoint heart failure hospitalizations or all-cause mortality and LYESV. CRT-D did not reduced all-cause mortality
RAFT ⁶²	1798	Double-blinded, randomized CRT-D vs. ICD 40 months	11–111	≤30%	≥120	All-cause mortality or heart failure hospitalizations	All-cause mortality and cardiovascular death	CRT-D reduced the endpoint all-cause mortality or heart failure hospitalizations. In NYHA III, CRT-D only reduced significantly all-cause mortality

More than 8000 patients included in randomized controlled trials

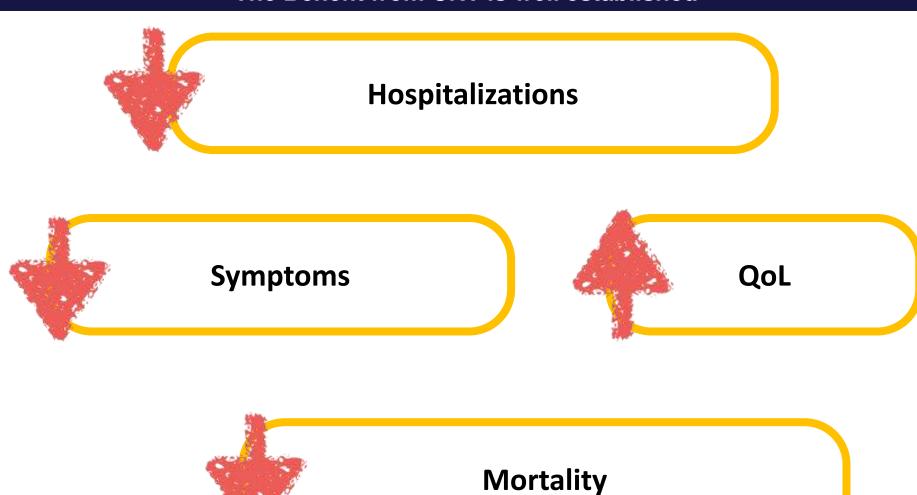


The Benefit from CRT is well established



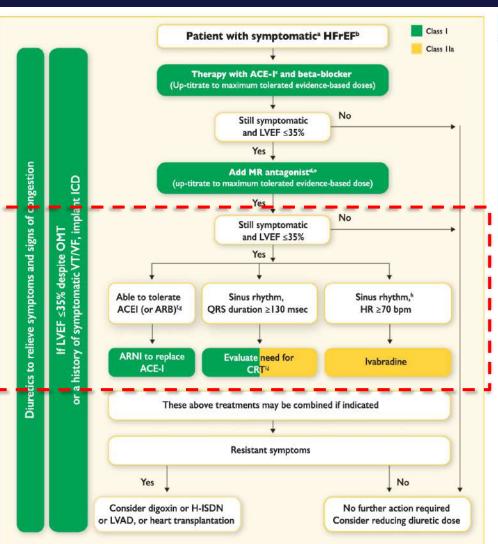


The Benefit from CRT is well established





The Benefit from CRT is well established



Recommendations for cardiac resynchronization therapy implantation in patients with heart failure Class* Level* CRT is recommended for symptomatic petients with HF in sinus rhythm with a QRS duration ≥150 msec and LB8B QRS 261-272 morphology and with LVEF <35% despite OMT in order to improve symptoms and reduce morbidity and mortality. CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB 261-272 QRS morphology and with LVEF <35% despite OMT in order to improve symptoms and reduce morbidity and mortality. CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130-149 msec and LBBB QRS 266,273 morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality. CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130-149 msec and non-LBBB IIb 266.273 QRS morphology and with LVEF <35% despite OMT in order to improve symptoms and reduce morbidity and mortality. CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular 274-277 pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1). CRT should be considered for patients with LVEF ≤35% in NYHA Class III-IV[®] despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular 278-281 capture is in place or the patient is expected to return to sinus rhythm. Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT 282 and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.



- HFrEF ≤ 35%, QRS ≥ 130ms
- HFrEF, RV pacing

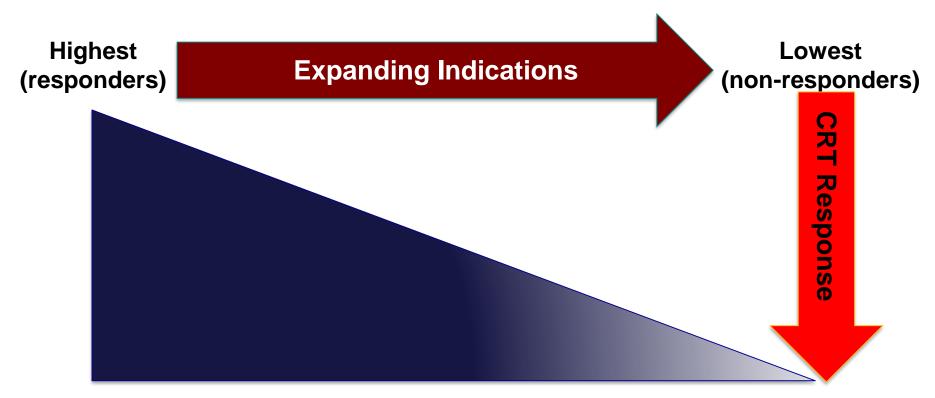
CRT is contra-indicated in patients with a ORS duration < 130 msec

283-285



Patient Selection

Magnitude of benefit from CRT



Wider QRS
Left Bundle Branch Block
Females
Non-ischaemic cardiopathy

Males Ischaemic cardiopathy Narrower QRS
Non-Left Bundle Branch
Block



Responders vs Non-responders

Responders

- Clinical measures (functional & QoL)
- LV reverse remodelling
- Event-based measures

Vs

Non-responders

- ø clinical improvement
- ø LV reverse remodelling
- ø Event-based measures



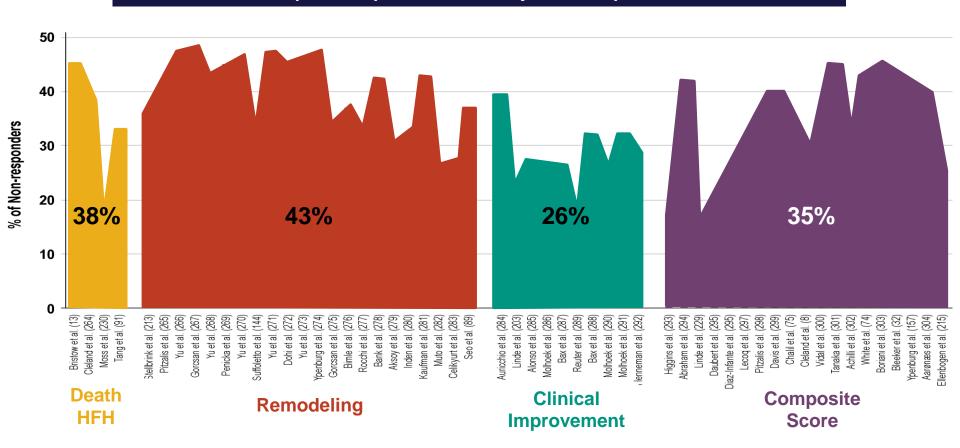
- LVEF ≥ 5% and/or LVESV ≤ 15%
- ↓ NYHA ≥ 1 class
- Ø HF hospit, deaths



Magnitude of Non Response to CRT

Globaly 30-40% Non Responders

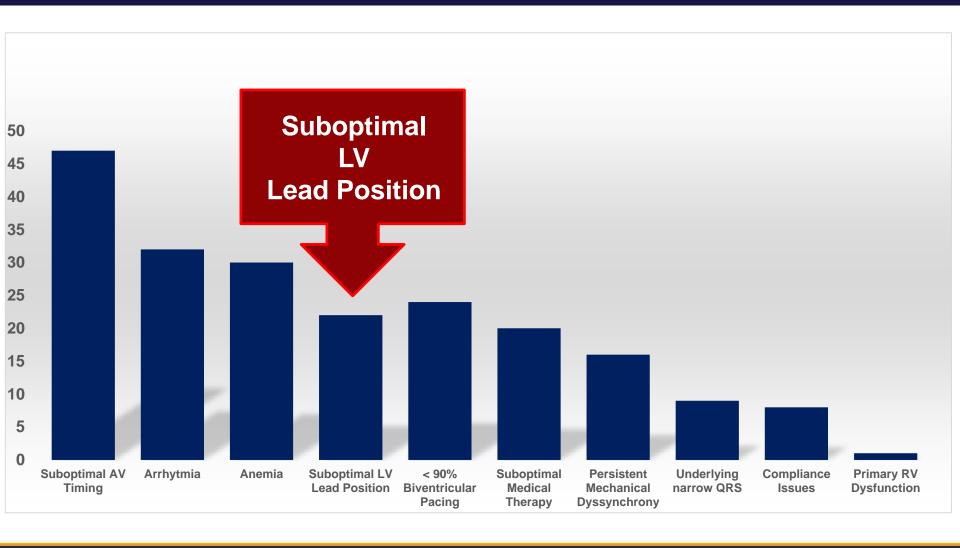
Non Responders per Clinical Study and Response Criteria





Follow up - Non Responders to CRT

Potential Reasons for Non Response





Implantation Failure

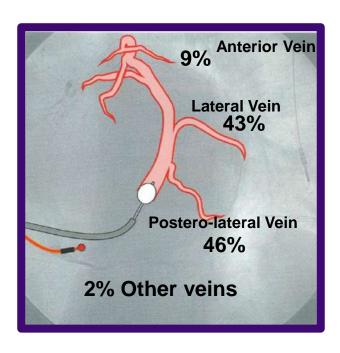
Inadequate LV Lead Position

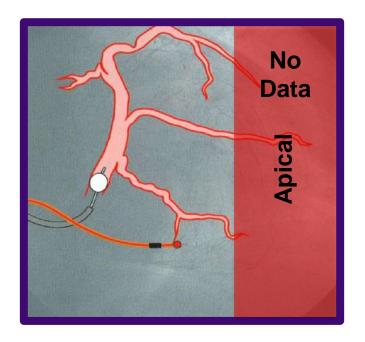
2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy

Preferred tools and techniques for implantation of cardiac electronic devices in Europe: results of the European Heart Rhythm Association survey



ESC GUIDELINE

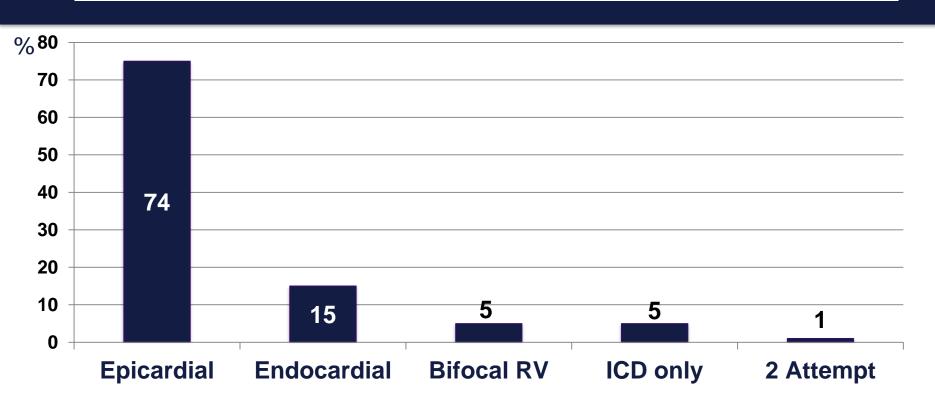




At least 11 % patients have suboptimal LV Lead Position

Second option for LV Lead Placement

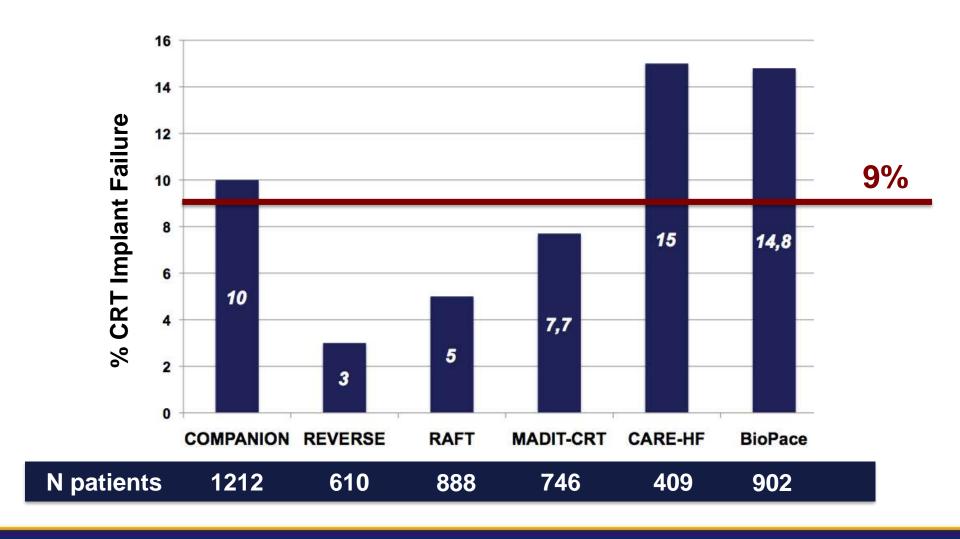
Preferred tools and techniques for implantation of cardiac electronic devices in Europe: results of the European Heart Rhythm Association survey





Implant Failure

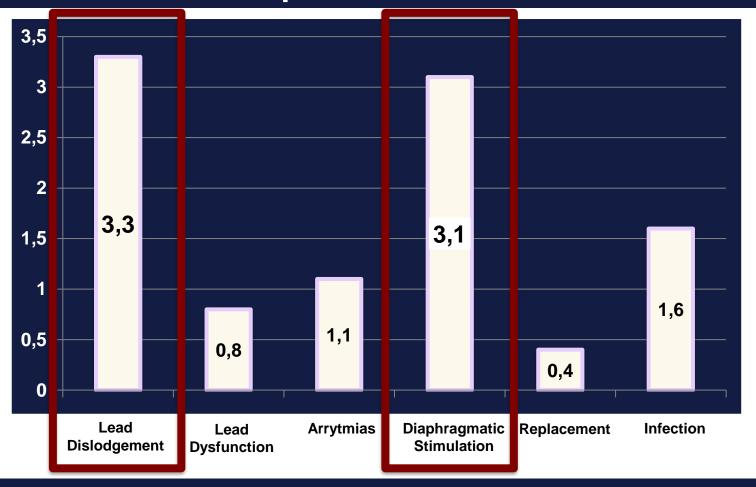
Implant Failure in Randomized Trials





Implantation Failure

Short-mid term complications 9-15 months follow-up



6% Complications due to implant difficulties



How to increase the rate of responders?



Improvement in patient selection

Optimization of medical therapy

Assessment of dyssynchrony

Assessment of latest activated areas and burden of myocardial scar



Improvement in patient selection

Optimization of medical therapy

Assessment of dyssynchrony

Assessment of latest activated areas and burden of myocardial scar



Improvement in patient selection

Optimization of medical therapy

Assessment of dyssynchrony

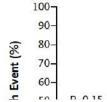
Assessment of latest activated areas and burden of myocardial scar



Assessment of dyssynchrony

- Evaluated pre-procedure?
- Large RCTs have failed to prove benefit evaluating dyssynchrony (EchoCRT, PROSPECT)

A Primary Composite Outcome



Conclusion—Given the modest sensitivity and specificity in this multicenter setting despite training and central analysis, no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT beyond current guidelines. Efforts aimed at reducing variability arising from technical and interpretative factors may improve the predictive power of these echocardiographic parameters in a broad clinical setting. (Circulation. 2008;117: 2608-2616.)

			Years	s since R	andomiz	ation		
No. at Risk								
CRT	404	297	223	155	103	65	42	19
Control	405	302	236	166	119	71	44	15

N Engl J Med 2013; 369:1395-1405

Circulation 2008; 117:2608-2616



Assessment of dyssynchrony

Assessment of latest activated areas and burden of myocardial scar



Assessment of latest activated areas and burden of myocardial scar

• Image-guided LV placement in latest activated areas (TARGET, STARTER)

	Target Group (n = 103)	Control Group (n = 104)	p Value		hoca iided
Latest site of activation, % (% basal/mid) Inferior Posterior Lateral	13 (13) [4/9] 38 (39) [14/24] 32 (33) [13/19]	14 (15) [5/9] 41 (43) [15/26] 31 (32) [11/20]	0.962	Distribution of LV lead location LAO projection Anterolateral	
Anterior Anteroseptal Inferoseptal	9 (9) [3/6] 4 (4) [1/3] 4 (4) [1/3]	7 (7) [3/4] 4 (4) [1/3] 3 (3) [0/3]		Lateral Posterolateral Posterior	
LV lead position, % (% basal/mid/apical) Inferior Posterior Lateral	12 (12) [4/7/1] 35 (36) [12/20/3] 46 (47) [16/29/1]	6 (6) [1/4/1] 38 (40) [14/22/2] 47 (49) [13/31/3]	0.442	RAO projection Basal Mid-ventricular	
Anterior	3 (3) [1/2]	6 (6) [2/4]		Apical	

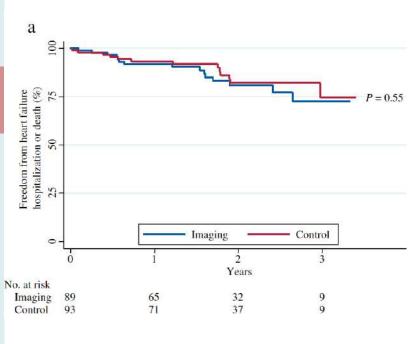
	Echocardiographic- Guided CRT (n=96)	Routine Control CRT (n=69)	<i>P</i> Value
Distribution of LV lead loc	eation		-
LAO projection			0.867
Anterolateral	17%	15%	
Lateral	40%	46%	
Posterolateral	36%	30%	
Posterior	7%	9%	
RAO projection			0.114
Basal	39%	17%	
Mid-ventricular	39%	43%	
Apical	23%	33%	



Assessment of latest activated areas and burden of myocardial scar

Multimodality imaging-guided LV lead placement

	Imaging group $(n=89)$	Control group $(n = 93)$	P
Optimal CS tributary			0.90
Anterior vein	1 (1)	1 (1)	
Left marginal vein	62 (70)	62 (67)	
Posterior vein	26 (29)	29 (31)	
Middle cardiac vein	0 (0)	1 (1)	
Optimal LV pacing site			0.75
Anterior	1 (1)	1 (1)	
Lateral	62 (70)	61 (66)	
Posterior	26 (29)	29 (31)	
Inferior	0 (0)	2 (2)	
Distribution of LV lead position by cardiac CT	P. 118078-11	1.17.4	0.11
LV short-axis			
Anterior	4 (5)	2 (2)	
Lateral	41 (47)	38 (42)	
Posterior	39 (44)	50 (56)	
Inferior	4 (5)	0 (0)	
LV long-axis			0.43
Basal	48 (55)	52 (58)	
Mid-LV	36 (41)	37 (41)	
Apical	4 (5)	1 (1)	
LV lead electrical delay, % of QRS	80 (72-85)	78 (68-84)	0.24
Relationship of LV lead to optimal CS branch			0.01
1. priority	74 (83)	60 (65)	
2. or 3. priority	15 (17)	32 (35)	
Relationship of LV lead to optimal pacing site			0.66
Concordant	43 (49)	39 (43)	
Adjacent	44 (50)	49 (54)	
Remote	1 (1)	2 (2)	
Scar at LV pacing site	3 (3)	2 (2)	0.68

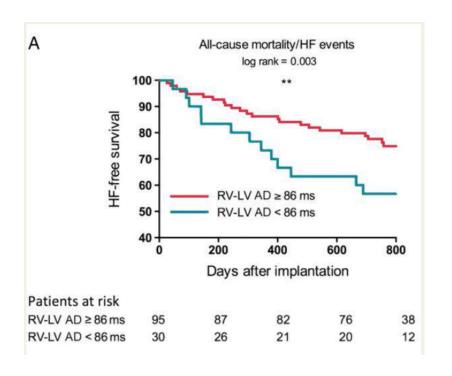


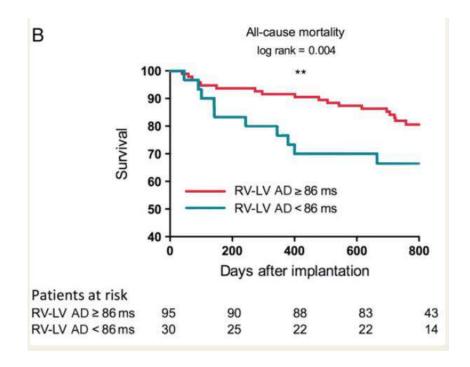


Assessment of latest activated areas and burden of myocardial scar

LV lead implantation in LAD

reduction of all-cause mortality and HF events

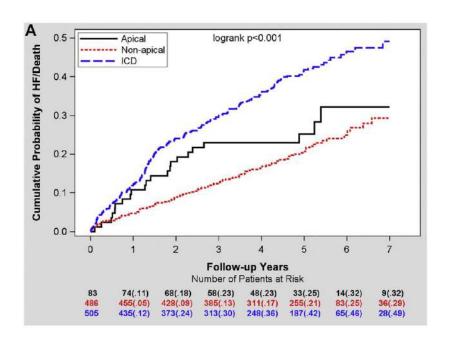






Assessment of latest activated areas and burden of myocardial scar

 LV lead implantation in lateral/posterior wall, non-apical is associated with reduction in death/HF events.



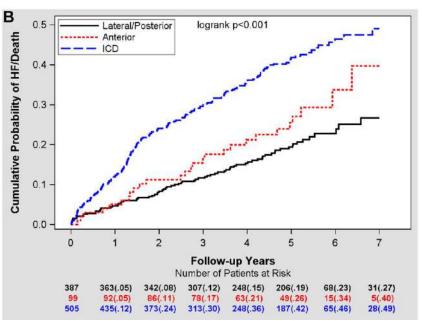


FIGURE 1 Cumulative Probability of Heart Failure or Death in Patients With LBBB ECG Pattern by LV Lead Location



Assessment of dyssynchrony

Assessment of latest activated areas and burden of myocardial scar

Yes, but...



Assessment of dyssynchrony

Assessment of latest activated areas and burden of myocardial scar



- Technical challenges of LV lead implantation
- Latest activated areas
- Multisite pacing
- Multipoint pacing



Venogram

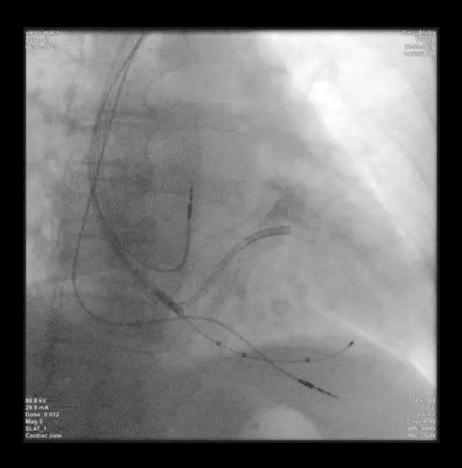




LAO view RAO view





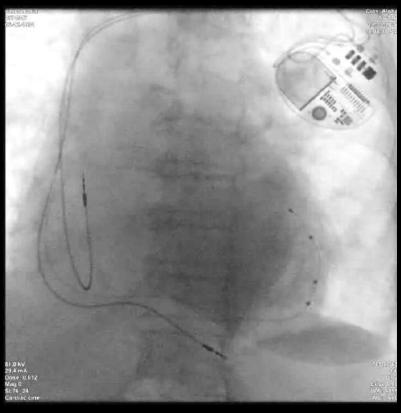


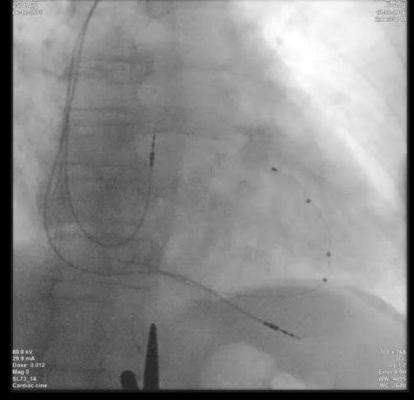
Snare

LV lead traction



Final Position

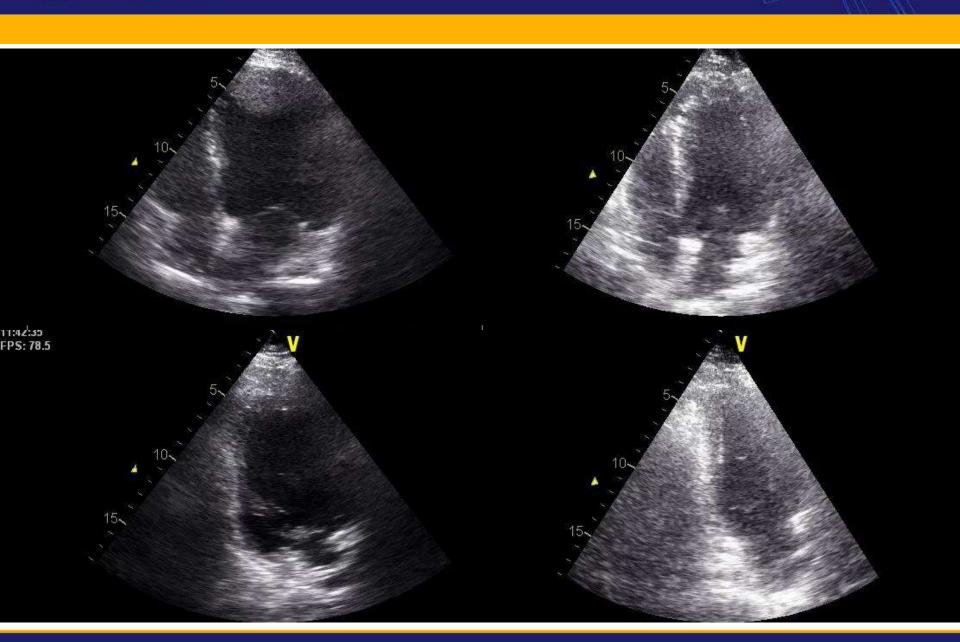




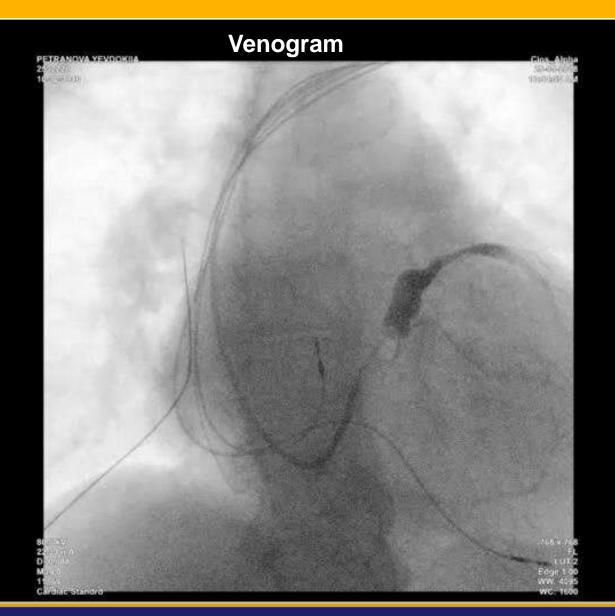
LAO view RAO view



Echo – Basal – 6 Months









Selective Venogram

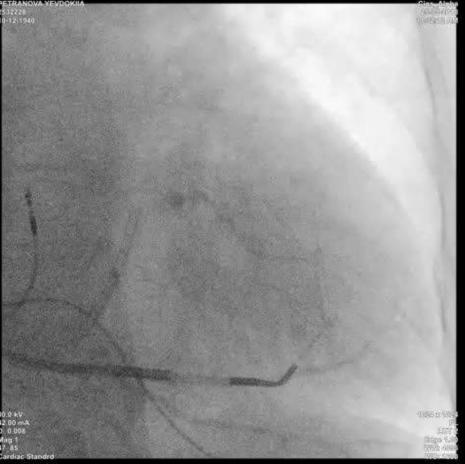






Selective Venogram





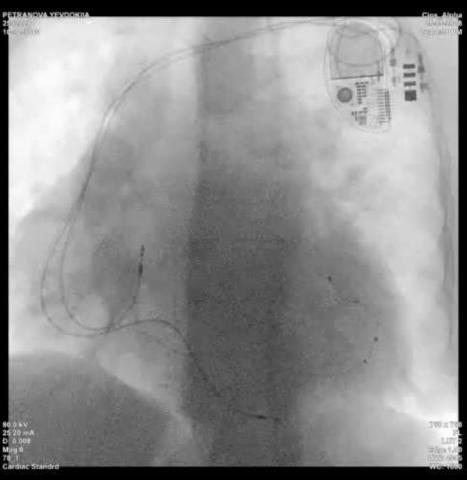


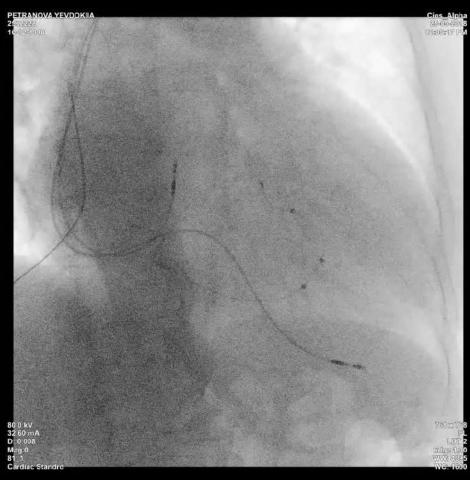






Final Position

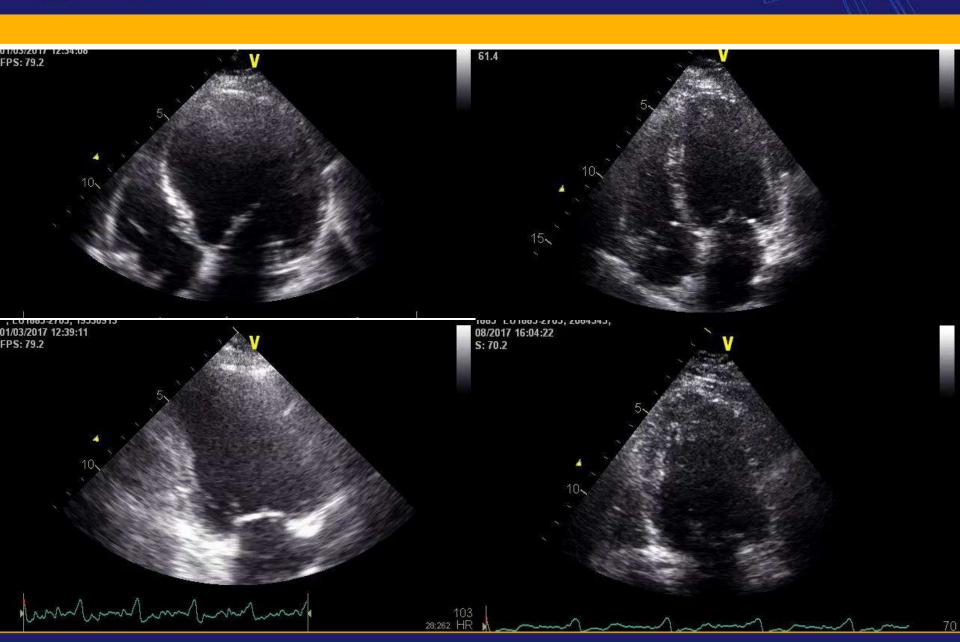




LAO view RAO view



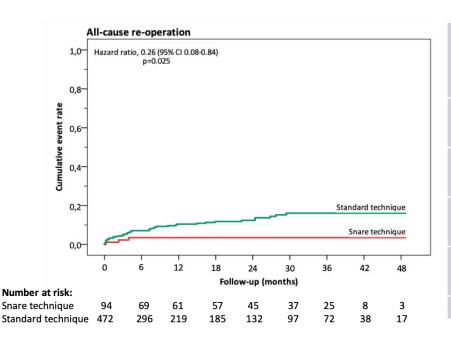
Echo – Basal – 6 Months





Snare technique after standard technique failure

- 566 CRTs implanted since 2015, 16.6% with snare (n=94).
- Snare technique \downarrow all-cause surgical revision with a NNT of 14

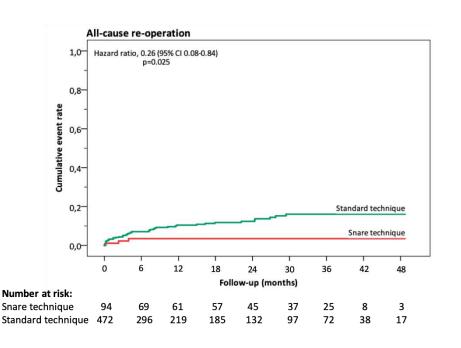


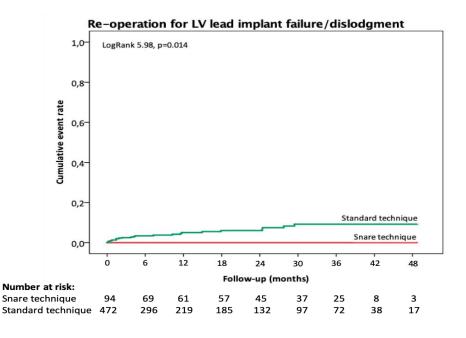
Causes of re-operation	Snare group [see] (N=3)	Standard group (N=50)	Total (N=53)
LV lead implant failure or dislodgment	0	25	25 (47.2%)
RV lead dislodgment	1	9	10 (18.9%)
RA lead dislodgment	1	6	7 (13.2%)
Infection	0	6	6 (11.3%)
Device extrusion	1	4	5 (9.4%)



Snare technique after standard technique failure

- 566 CRTs implanted since 2015, 16.6% with snare (n=94).
- Snare technique \downarrow all-cause surgical revision with a NNT of 14.
- ↓ surgical revision due to LV lead implant failure/dislodgement

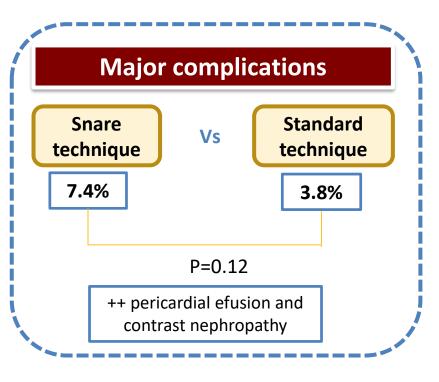


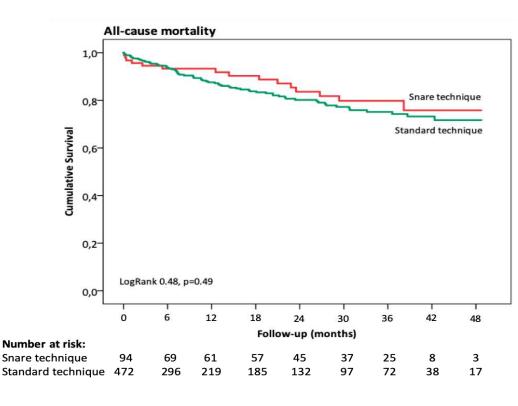




Snare technique after standard technique failure

• The rate of major complications, 30-day mortality and all-cause mortality (15.9% vs 15.5%, p = 0.49) were similar between groups.

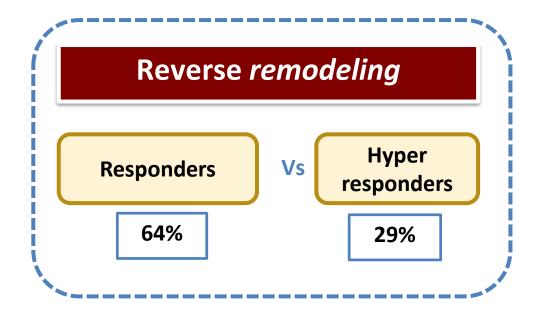






Snare technique after standard technique failure

 Response to CRT in 64% of patients who would not benefit from the therapy otherwise.

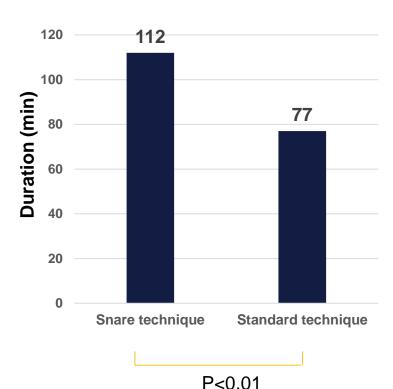




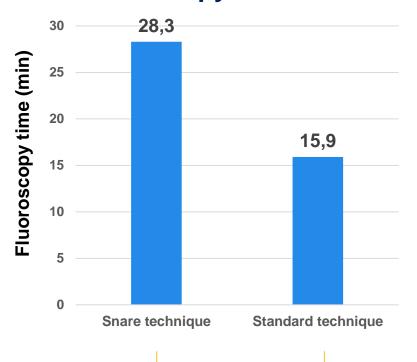
Snare technique after standard technique failure

Snare technique with longer procedure duration and fluoroscopy time.

Procedure duration



Fluoroscopy time





Assessment of dyssynchrony

Assessment of latest activated areas and burden of myocardial scar

Presence of suitable tributaries



- Technical challenges of LV lead implantation
- Latest activated areas
- Multisite pacing
- Multipoint pacing



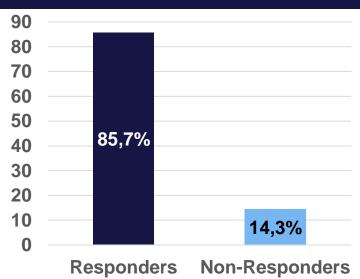
iBox-CRT: Can we do it better?



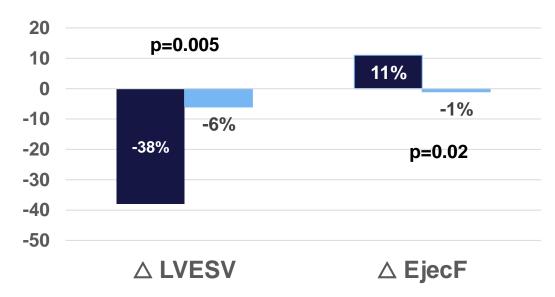
Automatically, <u>operator-independent</u>, assess the conduction <u>delay between RV pacing and the LV</u> available veins to select the LV pacing site. Evaluate the impact of LV site on clinical and remodeling outcomes.

Response Rate Overall population

Reduction LVESV > 15% Increase EF > 10%



LVESV and Ejection Fraction Variations 0-6 Months





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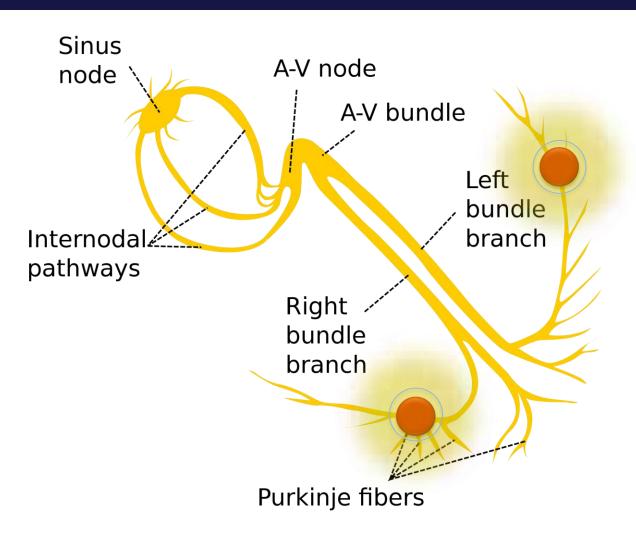


- Technical challenges of LV lead implantation
- Latest activated areas
- Multisite pacing
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CRT – Clinical Evidence

The Benefit from CRT is well established

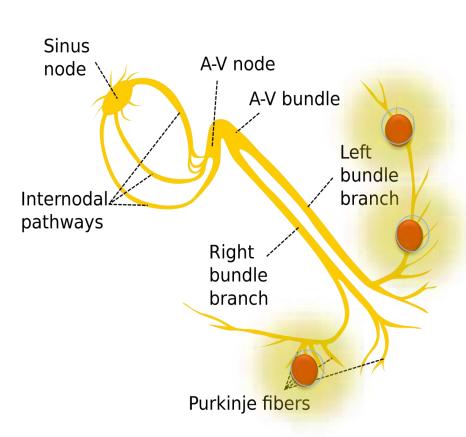




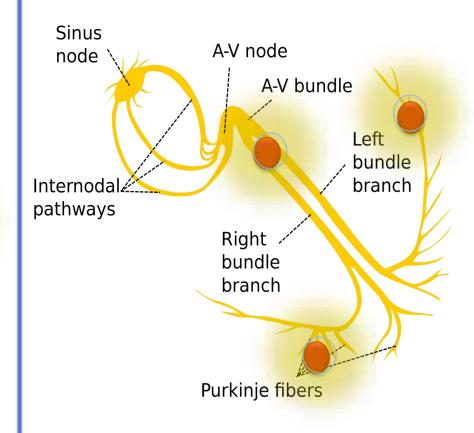
CRT – Clinical Evidence

Multisite pacing

• <u>1 RV lead + 2 LV leads</u>



• 2 RV leads + 1 LV lead





Multisite pacing

Multisite pacing improves symptoms, QoL, LVEF

Patient baseline characteristics Table I Global Tri-V Group Age (years, mean ± SD) 73 ± 11 72 ± 10 Male sex (N, %) 37 (97.5) 28 (85) Ischemic cardiomyopathy (N, %) 10 (25) 7 (21) NYHA I (N, %) 3 (7.5) 2(6) NYHA II (N, %) 14 (34) 12 (36) NYHA III (N, %) 24 (58.5) 19 (58) NYHA IV (N, %) 0(0)0(0) Angiotensin conversion enzyme inhibitor (N,%) 34 (85) 28 (85) Aldosterone receptor blocker (N,%) 3 (7.5) 3 (9) Mineralocorticoid receptor antagonist (N,%) 23 (57.5) 19 (57.5) Beta-blocker (N,%) 34 (85) 27 (82) Diuretic (N,%) 36 (90) 29 (88) Digoxin (N,%) 11 (27.5) 8 (245) Amiodarone (N,%) 7 (17.5) 6 (18) Antithrombotics (N,%) 6 (15) 4 (12) Vitamin K antagonist (N,%) 24 (60) 21 (64) Novel oral anticoagulant (N,%) 11 (27.5) 9 (27.5) Pre-implantation QRS (ms) 170 ± 25 169 ± 27 Left bundle branch block pattern (N, %) 34 (85) 29 (87.9) Pre-implantation ejection fraction (%,mean ± SD) 25 ± 8 26 ± 7 CRT-D (N, %) 26 (65) 26 (58) CRT-P (N, %) 14 (35) 14 (42) AV node ablation (N, %) 6 (17.5) 6 (18.2)



Figure 2 NYHA class distribution (%) at the various time points among all Tri-V patients.

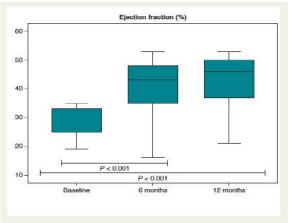


Figure 3 Mean ejection fraction during follow-up.

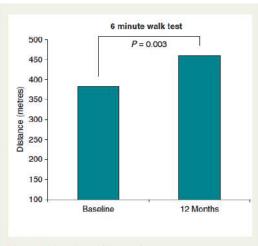


Figure 5 Six-minute walking test distance.

Marques P, et al. Europace (2018) 20, 986–992



Assessment of dyssynchrony

Assessment of latest activated areas and burden of myocardial scar

Presence of suitable tributaries

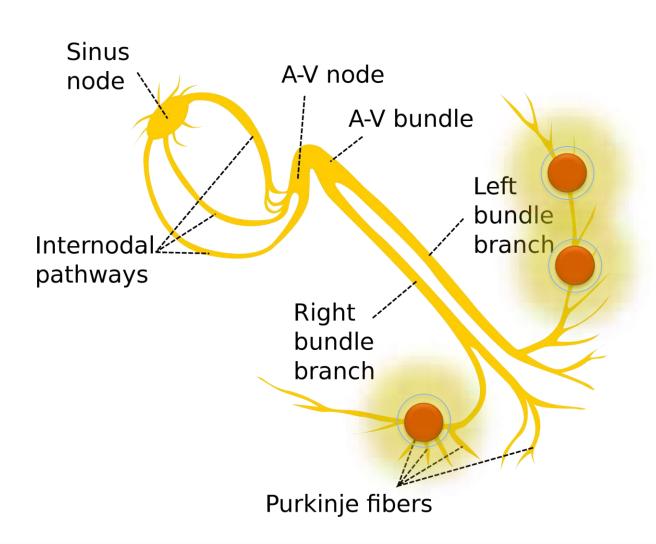


- Technical challenges of LV lead implantation
- Latest activated areas
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- Multipoint pacing



CRT – Clinical Evidence

Multipoint pacing

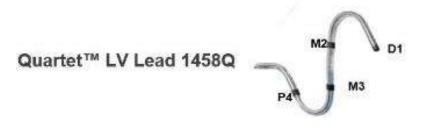


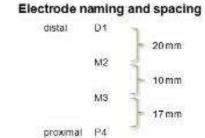


CRT – Clinical Evidence

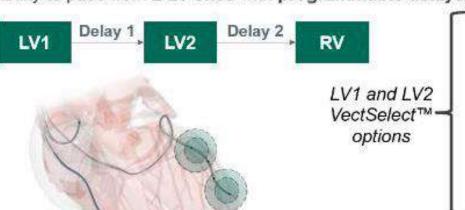
Quadripolar Pacing Technology MultiPoint™ Pacing







Ability to pace from 2 LV sites with programmable delays

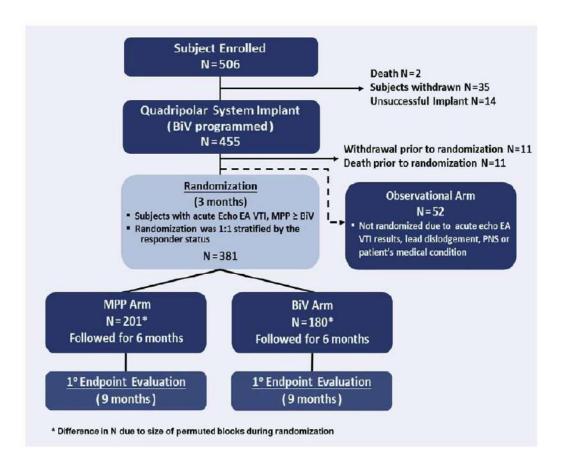


Vector	Cathode to Anode	
Vector 1	Distal 1 to Mid 2	
Vector 2	Distal 1 to Proximal 4	
Vector 3	Distal 1 to RV Coil	
Vector 4	Mid 2 to Proximal 4	
Vector 5	Mid 2 to RV Coil	
Vector 6	Mid 3 to Mid 2	
Vector 7	Mid 3 to Proximal 4	
Vector 8	Mid 3 to RV Coil	
Vector 9	Proximal 4 to Mid 2	
Vector 10	Proximal 4 to RV Coil	



MPP IDE trial

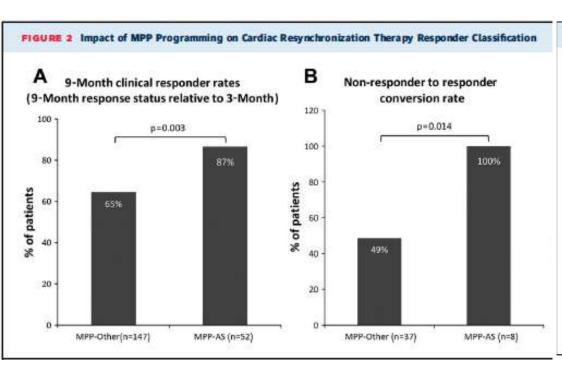
MPP-AS may improve response to CRT

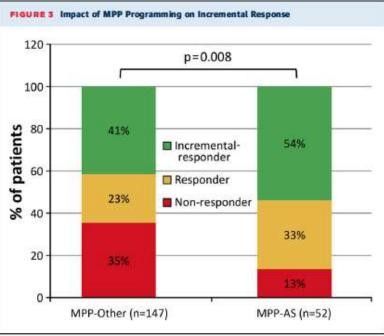




MPP IDE trial

MPP-AS may improve response to CRT

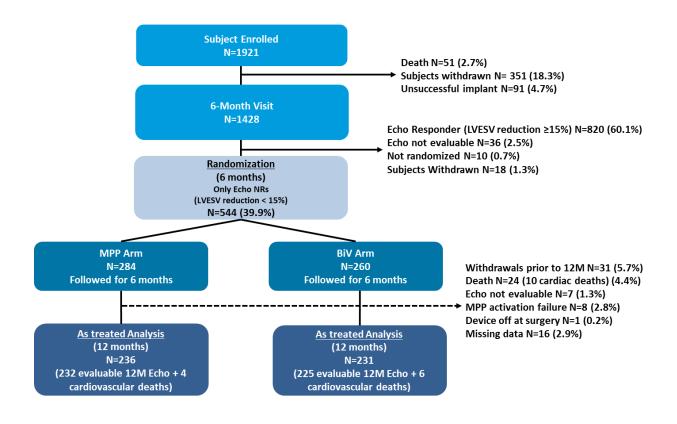






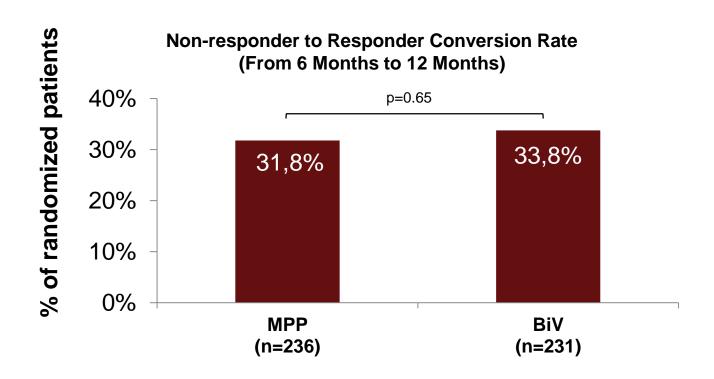
MORE CRT MPP trial

MPP-AS may improve response to CRT?



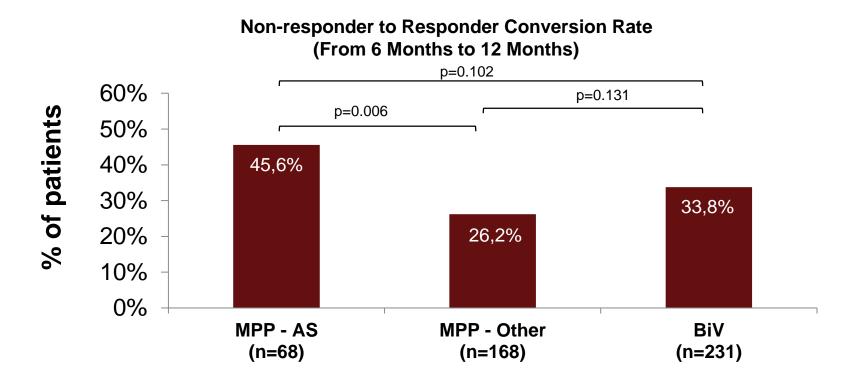
MORE CRT MPP trial

MPP-AS may improve response to CRT?



MORE CRT MPP trial

MPP-AS may improve response to CRT?





MultiPoint Pacing

Optimization of left ventricular pacing site plus multipoint pacing improves remodeling and clinical response to cardiac resynchronization therapy at 1 year

Francesco Zanon, MD, FESC, FHRS,* Lina Marcantoni, MD,* Enrico Baracca, MD,* Gianni Pastore, MD,* Daniela Lanza, MD,† Chiara Fraccaro, MD, PhD,† Claudio Picariello, Luca Conte, MD,† Silvio Aggio, MD,† Loris Roncon, MD,† Domenico Pacetta, Eng,‡ Nima Badie, PhD,§ Franco Noventa, MD, Frits W. Prinzen, PhD, FESC¶

Zannon F, et al. Heart Rhythm. 2016 Aug;13(8):1644-51

Single Center, non randomized 110 patients 1 year follow-up

Objective:

Compare Clinical and Echocardiographic response between standard Biv, Optimized Biv (Q-LV), Optimized + MPP

Response	STD	ОРТ	OPT + MPP
Ecocardiographic	55.6% (42.4-68.0)	72.2% (56.0-84.2)	90% (69.9-97.2)
Clinical	66.7% (46.0-71.3)	77.8% (61.9-88.3)	95% (76.4-99.1)

Combining MPP with optimal positioning of the LV lead on the basis of electrical delay and hemodynamics enhances reverse remodeling and improves clinical outcomes beyond the effect due to conventional CRT.



Responders vs Non-responders

Responders

- Clinical measures (functional & QoL)
- LV reverse remodelling
- Event-based measures







Responders vs Non-responders

Responders

- Clinical measures (functional & QoL)
- LV reverse remodelling
- Event-based measures

Hyper-responders

- Ø symptoms
- LVEF ≥ 50%; ↓ LVESV ≥ 30%





Conclusion

CRT improves prognostic and clinical outcomes

Patient selection:

, LBBB, wide QRS, NI cardiopathy

30-40% non-responders

Alternative techniques to implant LV lead

New technologies to assess latest activated areas LV lead



Lateral or postero-lateral wall of the LV, non-apical



Conclusion

CRT improves prognostic and clinical outcomes

Patient selection:

, LBBB, wide QRS, NI cardiopathy

30-40% non-responders

Alternative techniques to implant LV lead

New technologies to assess latest activated areas LV lead

Multisite pacing

Multipoint pacing



Cardiac resynchronization

Responders, non-responders, hyper-responders

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