Changing indications to CRT and current approaches to enhance response

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ESC GUIDELINES

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: John J.V. McMurray (Chairperson) (UK)*, Stamatis Adamopoulos (Greece), Stefan D. Anker (Germany), Angelo Auricchio (Switzerland), Michael Böhm (Germany), Kenneth Dickstein (Norway), Volkmar Falk (Switzerland), Gerasimos Filippatos (Greece), Cândida Fonseca (Portugal), Miguel Angel Gomez-Sanchez (Spain), Tiny Jaarsma (Sweden), Lars Køber (Denmark), Gregory Y.H. Lip (UK), Aldo Pietro Maggioni (Italy), Alexander Parkhomenko (Ukraine), Burkert M. Pieske (Austria), Bogdan A. Popescu (Romania), Per K. Rønnevik (Norway), Frans H. Rutten (The Netherlands), Juerg Schwitter (Switzerland), Petar Seferovic (Serbia), Janina Stepinska (Poland), Pedro T. Trindade (Switzerland), Adriaan A. Voors (The Netherlands), Faiez Zannad (France), Andreas Zeiher (Germany).

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ESC GUIDELINES

2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy

The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA).

Authors/Task Force Members: Michele Brignole (Chairperson) (Italy)*, Angelo Auricchio (Switzerland), Gonzalo Baron-Esquivias (Spain), Pierre Bordachar (France), Giuseppe Boriani (Italy), Ole-A Breithardt (Germany), John Cleland (UK), Jean-Claude Deharo (France), Victoria Delgado (Netherlands), Perry M. Elliott (UK), Bulent Gorenek (Turkey), Carsten W. Israel (Germany), Christophe Leclercq (France), Cecilia Linde (Sweden), Lluís Mont (Spain), Luigi Padeletti (Italy), Richard Sutton (UK), Panos E. Vardas (Greece)

Pazienti con insufficienza cardiaca in Classe NYHA II: Punti chiave

- Due recenti sperimentazioni prospettiche multicentriche randomizzate sull'insufficienza cardiaca lieve (MADIT-CRT e REVERSE) dimostrano una morbilità ridotta.
- Il 18% dei pazienti in REVERSE e il 15% dei pazienti in MADIT-CRT erano nella classe NYHA I alla baseline, sebbene la maggior parte di questi pazienti fosse stata precedentemente sintomatica.
- Il miglioramento si è osservato principalmente nei pazienti con QRS ≥ 150 ms e/**o LBBB tipico.**
- Nel MADIT-CRT, le donne con LBBB hanno mostrato una risposta particolarmente favorevole.
- Vantaggio in termini di sopravvivenza non stabilito.
- In MADIT-CRT l'estensione del rimodellamento inverso era concordante e predittiva del miglioramento nei risultati clinici.

2010 Focused Update of ESC guidelines on device therapy in Heart Failure, K.Dickstein et al., European Heart Journal doi:10.1093/eurheartj/ehq337

C. Linde: the REVERSE trial

2009

Europace (2009) **11**, v72–v76
doi:10.1093/europace/eup307

Cardiac resynchronization therapy in mild heart failure

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CRITERI D'INCLUSIONE E METODO

Classe NYHA I-II; LVEDD>55mm; FE: <40%; RS; QRS>120ms

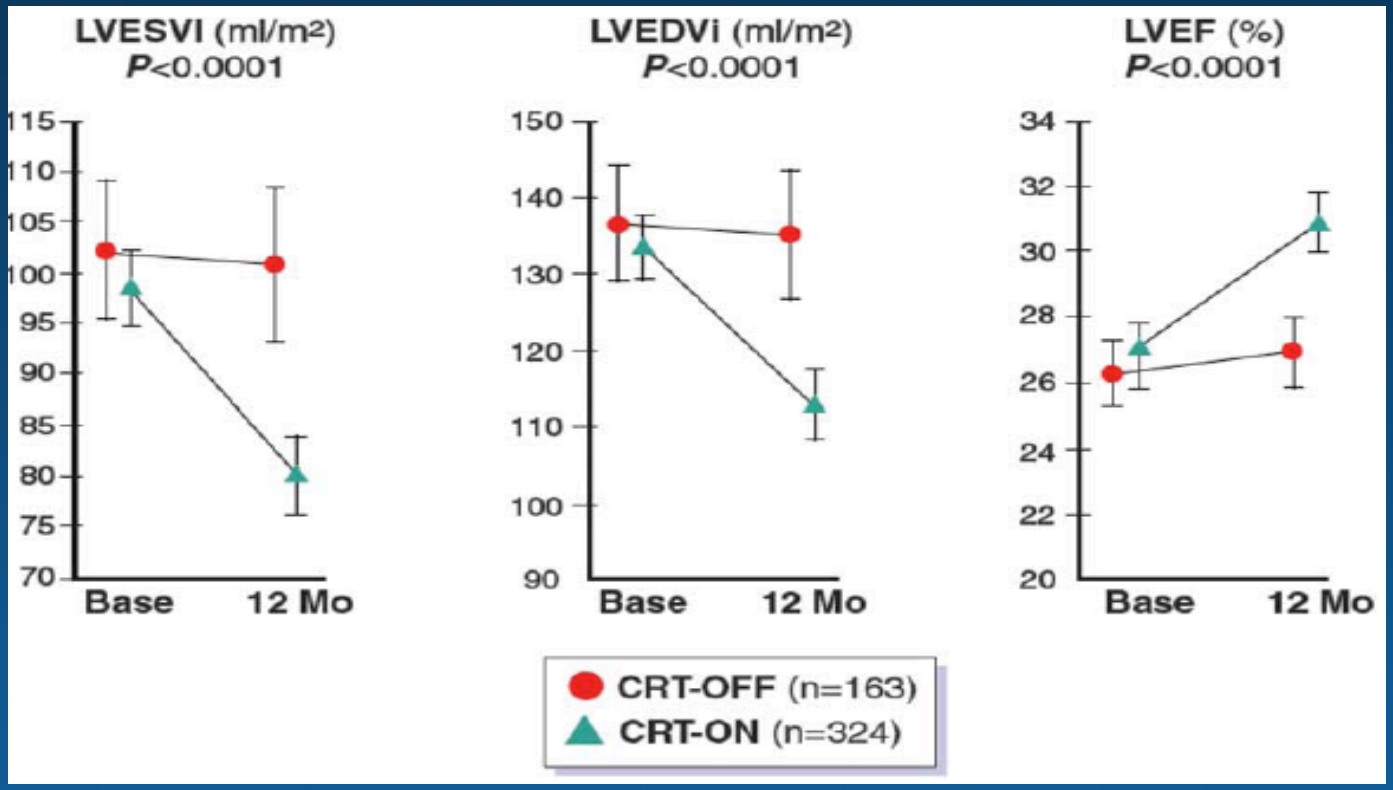
CRT on (con o senza ICD) vs CRT off (con o senza ICD)

It has been firmly established that cardiac resynchronization therapy (CRT) reduces symptoms and improves mortality in patients with moderate-to-severe chronic heart failure [New York Heart Association (NYHA) class III–IV], despite optimal heart failure medication and with wide QRS complex on the surface electrocardiogram as evidence of ventricular dyssynchrony, but not whether such treatment is efficacious in mildly symptomatic heart failure patients. In such patients, the treatment goal is to prevent disease progression rather than to improve symptoms. The REVERSE trial was the first randomized, controlled study of CRT in NYHA I–II patients. Cardiac resynchronization therapy in this study induced substantial reverse remodelling over 12–18–24 months of follow-up and was linked to a significant delay in the time to first heart failure hospitalization and eventually in the time to the combined endpoint of time to first heart failure hospitalization or death. The MADIT CRT designed as a morbidity–mortality study corroborated these findings with a significant reduction in heart failure events and significant reverse remodelling. These findings most likely will translate into a wider use of CRT in mildly symptomatic patients to prevent disease progression.

EUROPEAN SOCIETY OF CARDIOLOGY®

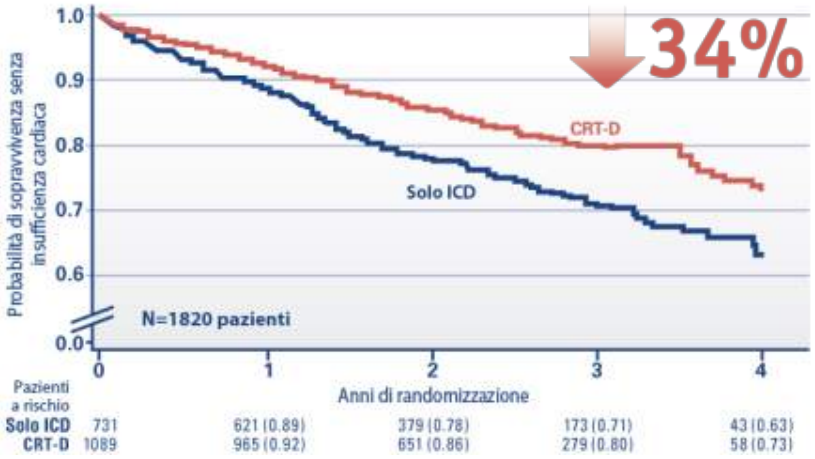
C. Linde

Europace (2009) **11**, v72–v76
doi:10.1093/europace/eup307



RISULTATI NEJM 2009[1]

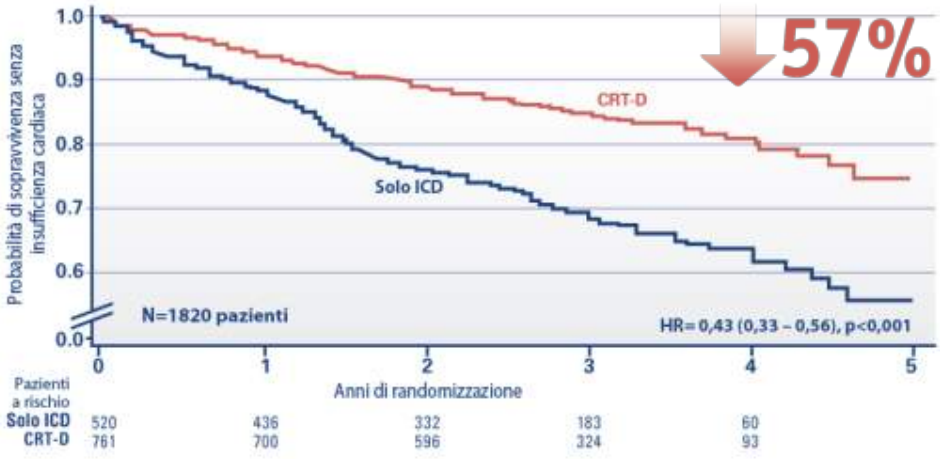
Risposta notevolmente precoce nel braccio CRT-D – a partire dai primi 2 mesi



ENDPOINT PRIMARIO PER TUTTI I PAZIENTI

Riduzione relativa del 34% della mortalità per tutte le cause o del primo evento di insufficienza cardiaca (p=0,001)

SOTTOANALISI LBBB* CON ULTERIORI 6 MESI DI FOLLOW-UP[2]



ENDPOINT PRIMARIO PER I PAZIENTI LBBB

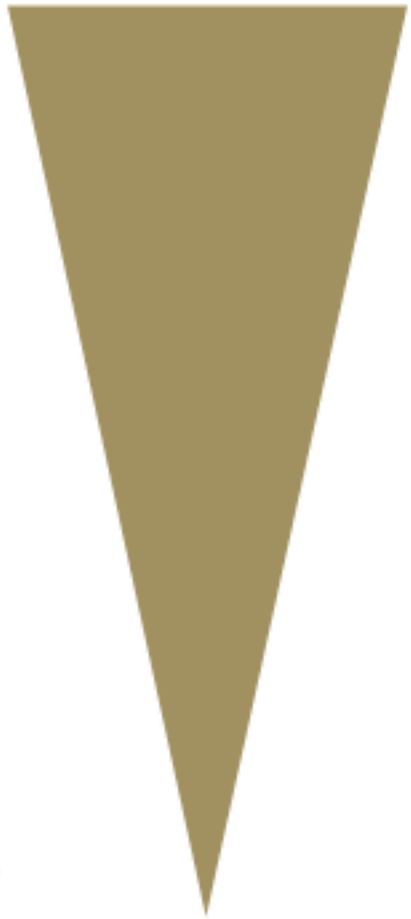
Riduzione del 57% della mortalità per tutte le cause o del primo evento di insufficienza cardiaca rispetto al solo ICD (p<0,001)

1. N Engl J Med. 2009 Oct 1;361(14):1329-38. Cardiac-resynchronization therapy for the prevention of heart-failure events. MADIT-CRT Trial Investigators.

2. Indicazione FDA 2010 per il sistema CRT-D COGNIS (solo USA).

*Il blocco di branca sinistro (LBBB) non era un parametro di inclusione per la sperimentazione MADIT-CRT. È stata tuttavia rilevata un'interazione significativa tra il trattamento e la morfologia del blocco di branca sinistro. Ulteriori analisi hanno evidenziato che il blocco di branca sinistro (LBBB) è una discriminante oggettiva del beneficio assicurato al paziente dalla CRT-D indipendentemente da altre caratteristiche alla baseline.

Magnitude of benefit from CRT



Highest (responders)

Wider QRS, left bundle branch block, females, non-ischaemic cardiomyopathy

Males, ischaemic cardiomyopathy

Lowest (non-responders)

Narrower QRS, non-left bundle branch block

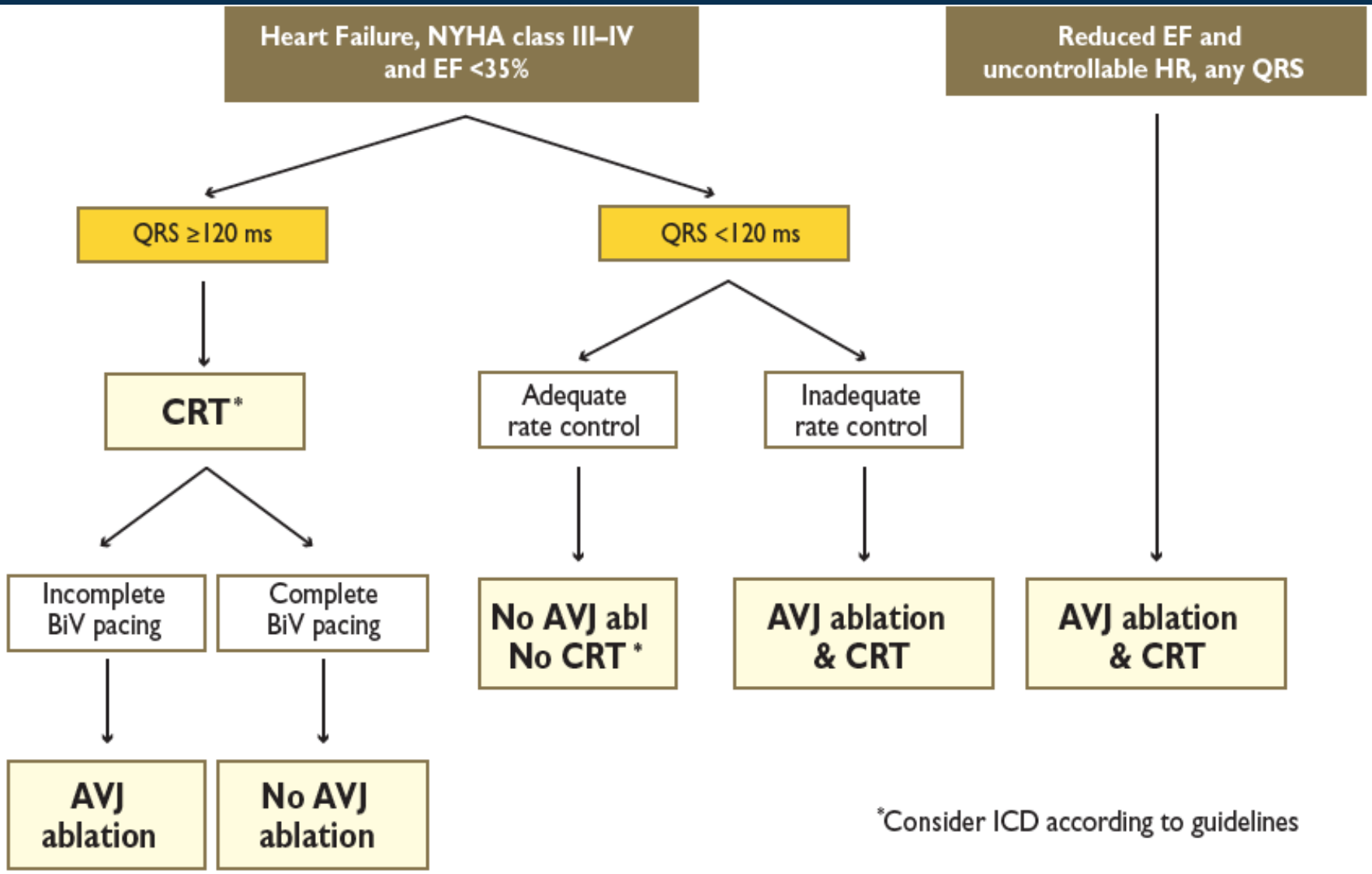
Indications for cardiac resynchronization therapy in patients in sinus rhythm

Recommendations	Class [a]	Level [b]	Ref. [c]
1) LBBB with QRS duration >150 ms. CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. [d]	I	A	48–64
2) LBBB with QRS duration 120–150 ms. CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. [d]	I	B	48–64
3) Non-LBBB with QRS duration >150 ms. CRT should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. [d]	IIa	B	48–64
4) Non-LBBB with QRS duration 120–150 ms. CRT may be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. [d]	IIb	B	48–64
5) CRT in patients with chronic HF with QRS duration <120 ms is not recommended.	III	B	65, 66

Indications for cardiac resynchronization therapy in patients with permanent atrial fibrillation

Recommendations	Class [a]	Level [b]	Ref. [c]
1) Patients with HF, wide QRS and reduced LVEF:			
1A) CRT should be considered in chronic HF patients, intrinsic QRS ≥120 ms and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment[d], provided that a BiV pacing as close to 100% as possible can be achieved.	**IIa**	**B**	62, 89–95
1B) AV junction ablation should be added in case of incomplete BiV pacing.	**IIa**	**B**	67–69, 90, 96–105
2) Patients with uncontrolled heart rate who are candidates for AV junction ablation. CRT should be considered in patients with reduced LVEF who are candidates for AV junction ablation for rate control.	**IIa**	**B**	89, 94, 105–107

Patients in atrial fibrillation



Patients with an indication for upgrading from conventional pacemaker or implantable cardioverter defibrillator to cardiac resynchronization therapy devices

De novo cardiac resynchronization therapy pacing in patients with conventional indication for anti-bradycardia pacing and moderate-to-severe LV dysfunction

Table 14 Summary of evidence for upgrading from conventional pacemaker or implantable cardioverter defibrillator to cardiac resynchronization therapy devices

Studies	No. of patients	Echo, ESD (%)	Echo, EF (%)	QoL scores (%)	NYHA class (%)	Clinical outcome
RCT, cross-over design, upgraded CRT vs RV						
Hoijer[110]	10	-2	-	Improved	-	Patient's preference: 90% CRT ($P = 0.01$)
Leclercq[108]	32	-4	0	-44	-16	Fewer hospitalizations (4 vs. 17, $P = 0.001$)
van Gerlop[111]	36	-9	+18	-10	-16	Responders, clinically relevant: 53%
Delnoy[109]	40	-31	+30	-19	-26	-
Total	***118***	***−6***	***+17***	***−22***	***−18***	-
Observational studies, post-CRT upgrading vs. pre-CRT						
Leon[115]	20	-8	+44	-33	-29	Fewer hospitalizations: −81%
Baker[112]	60	-	+26	-31	-29	-
Valls[117]	14	-8	+17	-	-24	-
Eldadah[113]	12	-	+16	-	-	-
Shimano[116]	18	-	+23	-	-35	Fewer hospitalizations: −81%
Laurenzi[114]	38	-5	+41	-68	-36	Responders, clinically relevant: 84%
Vatankulu[118]	26	-13	+18	-	-	-
Total	***188***	***−7***	***+28***	***−43***	***−31***	
Controlled studies, upgraded CRT vs. *de novo* CRT[a]						
Marai[121]	25 vs. 73	−1 vs. −1	+1 vs. +1	-	−0.3 vs. −0.7	NYHA ≥I class: 76 vs. 42% ($P = 0.01$)
Foley[119]	58 vs. 336	-	+10 vs. +4	Similar	Similar	Responders: 47 vs. 46% Mortality: 27 vs. 26%
Paparella[122]	39 vs. 43	-	+10 vs. +8	-	−1.2 v.s −1.1	Hospitalization: −81 vs. −77% Non-responders: 9 vs. 10%
Frohlich[120]	70 vs. 102	−7 vs. −6	+10 vs. +10	-	-	NYHA ≥I class: 53 vs. 51% Responders: 56 vs. 56%
EU survey[47]	692 vs. 1675	-	-	-	-1.0 vs. -1.0	At 1-year follow-up: similar mortality (8.6 vs. 7.9%), hospitalization (23 vs. 27%), improved quality of life (27 vs. 20%) and complications (11 vs. 10%)
Total	***884 vs. 2229***	-	-	-	-	

Table 15 Summary of evidence of RCTs of *de novo* CRT implantation compared with RV apical pacing in patients with conventional indication for anti-bradycardia pacing

Studies	No. of patients	Echo, ESV (%)	Echo, EF (%)	QoL scores (%)	NYHA class (%)	Clinical outcome
Patients with moderate/severe systolic dysfunction, CRT vs RV						
HOBIPACE[127]	30	-9	+22	-19	-24	Patient's preference: 67% CRT, 7% RV ($P = 0.0002$)
COMBAT[128]	60	-24	-21	-47	-24	Worsening HF or hospitalization: 3 vs. 8 patients
BLOCK HF[125, 126]	691	-	-	-	-	Significant 28% reduction in the combined primary endpoint of mortality, heart-failure related urgent care, and increase in LV end-systolic volume
Patients with preserved systolic function, CRT vs RV						
Albertsen123	50	-	+5	-	-17	-
PACE[124, 130]	177	-22	+13	No difference	-	Hospitalization for HF: 6 vs. 7% (ns)
PREVENT-HF[129]	108	-5	+7	-	-	Worsening of HF: 6 vs. 14% (ns)

Indication for upgraded or *de novo* cardiac resynchronization therapy in patients with conventional pacemaker indications and heart failure

Recommendations	Class [a]	Level [b]	Ref. [c]
1) Upgrade from conventional PM or ICD. CRT is indicated in HF patients with LVEF <35% and high percentage of ventricular pacing who remain in NYHA class III and ambulatory IV despite adequate medical treatment. [d]	I	B	47, 108–122
2) *De novo* cardiac resynchronization therapy. CRT should be considered in HF patients, reduced EF and expected high percentage of ventricular pacing in order to decrease the risk of worsening HF.	IIa	B	123–130

- how to achieve biventricular pacing as close to 100% as possible;
- how to select the best LV lead position;
- how to program the AV interval in order to achieve the maximum contribution of LA contraction to LV filling (AV resynchronization); and
- how to eliminate the residual LV dyssynchrony after simultaneous biventricular pacing by selecting the timing of RV and LV pacing by means of device interventricular (VV) interval optimization (including, at its extreme, LV pacing alone).

Parameter	Standard (current practice)	CRT optimization	Additional clinical benefit (compared to standard)	References
LV lead position	Posterolateral	• Avoid apical • Target latest activated area	Benefit likely (less hospitalization for HF) Benefit likely (one RCT more responders, less hospitalization for HF)	70–72 73
AV delay	Fixed empirical AV interval 120 ms (range 100–120 ms)	• Echo-Doppler: shortest AV delay without truncation of the A-wave (Ritter's method) or change in LV systolic function	• Uncertain or mild (one small RCT and several observational positive)	74
		• Device-based algorithms (SmartDelay, QuickOpt)	• Uncertain (two RCTs negative)	76, 79
VV delay	Simultaneous BiV	• Echo: residual LV dyssynchrony	• Uncertain or mild (one RCT showed mild benefit)	77
		• Echo-Doppler: largest stroke volume	• Uncertain (one RCT negative, one controlled positive)	78, 80
		• ECG: narrowest LV-paced QRS; difference between BiV and preimplantation QRS	• Unknown (no comparative study)	75
		• Device-based algorithms (Expert-Ease, Quick-Opt, Peak endocardial acceleration)	• Uncertain (three RCTs negative)	76, 82, 83
LV pacing alone	Simultaneous BiV	n.a.	Non-inferior	84–88

Loss of biventricular pacing

Sustained and effective biventricular pacing is crucial to achieving the best results from CRT.

In a recent trial involving 1812 HF pts treated with CRT, a percentage of biventricular pacing between 93–100% was associated with a 44% reduction in the composite end point (all-cause mortality and heart failure hospitalization), compared with a percentage of biventricular pacing between 0–92% (HR 0.56; P 1/4 0.00001).

In a cross-sectional analysis including 80 768 patients, a percentage of biventricular pacing > 98% was achieved in only 59% of pts. For pts with < 98% biventricular pacing, the most frequent cause of pacing loss was inappropriately programmed long AV delay (accounting for 34% of cases) followed by atrial tachycardia/AF (31% of cases) and premature ventricular complexes (17% of cases).

This evidence indicates that biventricular pacing has to be kept as close as possible to 100%

Biventricular pacing vs. left ventricular pacing alone

Several studies have demonstrated the non-inferiority of LV pacing alone.

The BELIEVE trial randomized, to biventricular- or LV pacing, 69 HF patients in NYHA functional class II–IV, QRS duration≥130 ms, LBBB and LVEF ≤35%.
After 12 months of follow-up, LV pacing induced similar improvements in clinical status, exercise capacity and LV dimensions and function, compared with biventricular pacing.

Recently B-LEFT HF trial, which randomized 176 CRT-D recipients to biventricular or LV pacing, confirmed these results.

A recent meta-analysis of five randomized trials for a total of 372 patients randomized to biventricular pacing and 258 to LV-only pacing showed that, in patients with moderate-to-severe HF, these two pacing modalities did not differ with regard to death/heart transplantation or need for hospitalizations.

LV pacing alone, in non-pacemaker-dependent patients,
seems to be non-inferior to biventricular pacing for improving soft endpoints (quality of life, exercise capacity and LV reverse remodelling) and might be considered, to lower the costs and complexity of the procedure and to increase the longevity of the device.

LV pacing alone seems particularly appealing in children and young adults

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

Giuseppe Boriani, MD, PhD,[a] Wolfgang Kranig, MD,[b] Erwan Donal, MD, PhD,[c] Leonardo Calo, MD,[d] Michela Casella, MD,[e] Nicolas Delarche, MD,[f] Ignacio Fernandez Lozano, MD,[g] Gerardo Ansalone, MD,[h] Mauro Biffi, MD,[a] Eric Boulogne, MSc,[i] and Christophe Leclercq, MD, PhD[c] for the B-LEFT HF study group

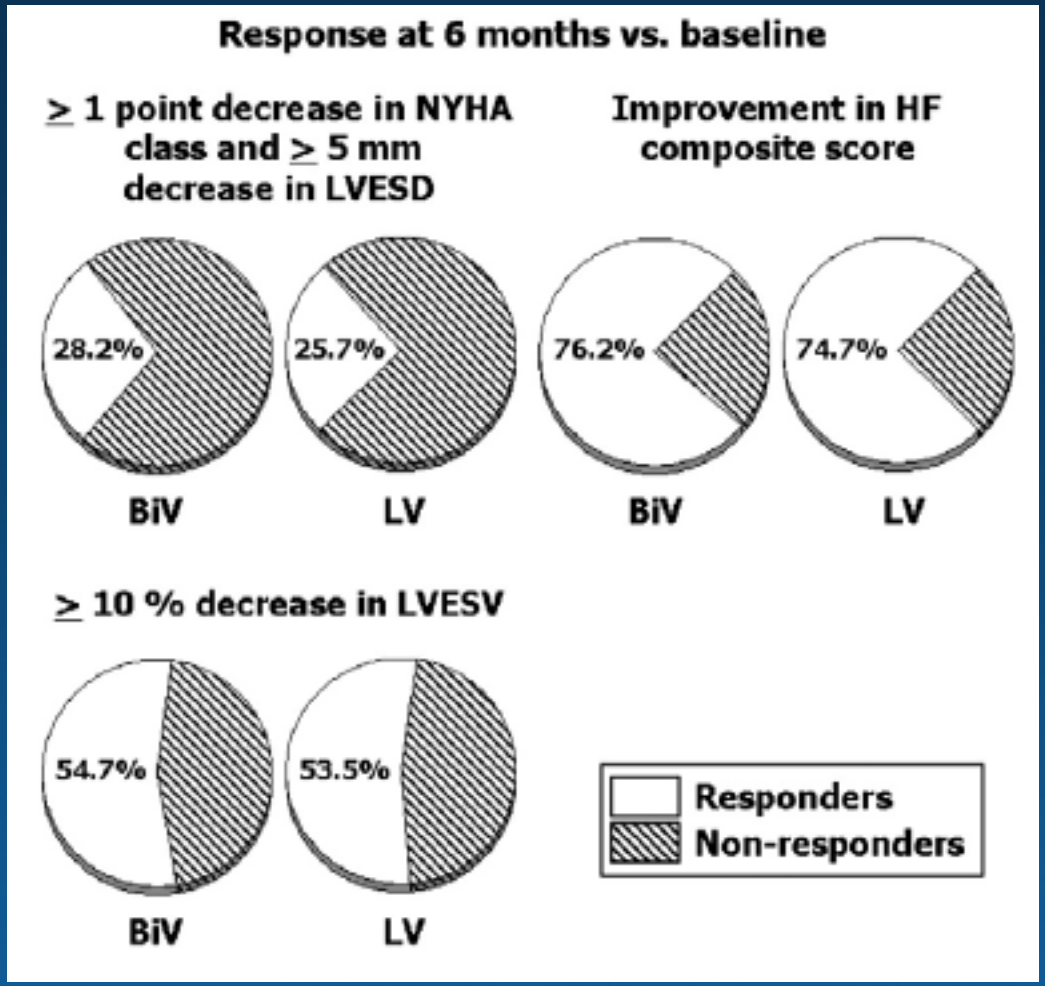
Bologna and Rome, Italy; Bad Rothenfelde, Germany; Rennes and Pau, France; Madrid, Spain; and Zaventem, Belgium

Background Biventricular (BiV) stimulation is the preferred means of delivering cardiac resynchronization therapy (CRT), although left ventricular (LV)–only stimulation might be as safe and effective. B-LEFT HF is a prospective, multicenter, randomized, double-blind study aimed to examine whether LV-only is noninferior to BiV pacing regarding clinical and echocardiographic responses.

Methods B-LEFT HF randomly assigned 176 CRT-D recipients, in New York Heart Association class III or IV, with an LV ejection fraction ≤35% and QRS ≥130 milliseconds, to a BiV (n = 90) versus LV (n = 86) stimulation group. Clinical status and echocardiograms were analyzed at baseline and 6 months after CRT-D implant to test the noninferiority of LV-only compared with BiV stimulation.

Results The proportion of responders was in line with current literature on CRT, with improvement in heart failure composite score in 76.2% and 74.7% of patients in BiV and LV groups, respectively. Comparing LV versus BiV pacing, the small differences in response rates and corresponding 95% CI indicated that LV pacing was noninferior to BiV pacing for a series of response criteria (combination of improvement in New York Heart Association and reverse remodeling, improvement in heart failure composite score, reduction in LV end-systolic volume of at least 10%), both at intention-to-treat and at per-protocol analysis.

Conclusions Left ventricular–only pacing is noninferior to BiV pacing in a 6-month follow-up with regard to clinical and echocardiographic responses. Left ventricular pacing may be considered as a clinical alternative option to BiV pacing. (Am Heart J 2010;159:1052-1058.e1.)


Response at 6 months vs. baseline
≥ 1 point decrease in NYHA class and ≥ 5 mm decrease in LVESD
Improvement in HF composite score
28.2%
25.7%
76.2%
74.7%
BiV
LV
BiV
LV
≥ 10 % decrease in LVESV
54.7%
53.5%
BiV
LV
Responders
Non-responders

Selection of left ventricular lead position

The largest delay in mechanical contraction in an HF patient with LBBB is most often located in the LV posterolateral region, which is therefore also the preferred location to place the LV lead.

A subanalysis of the COMPANION trial showed that anterior, lateral and posterior positions of the LV lead yielded similar clinical improvements and survival benefit.

The REVERSE study indicated that a lateral LV lead position was associated with superior results concerning reverse LV remodelling and time to death and/or first HF hospitalization.

Data collected from the MADIT-CRT trial have demonstrated that basal or mid-ventricular positions of the LV leadportended superior long-term outcomes compared with apical positions.

The TARGET trial randomized 220HFpatients to an LV non-apical lead position, coincident with the latest activated areas (as assessed with speckle tracking echocardiography) or to standard unguided LV lead position.
The group of patients with the LV lead positioned at the latest activated areas had a greater proportion of echocardiographic responders at 6 months follow-up (70 vs. 55%; P 1/4 0.031), more clinical responders and lower rates of all cause mortality and HF hospitalizations (log-rank P 1/4 0.0031).

Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy

The TARGET Study: A Randomized, Controlled Trial

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Cambridge, United Kingdom

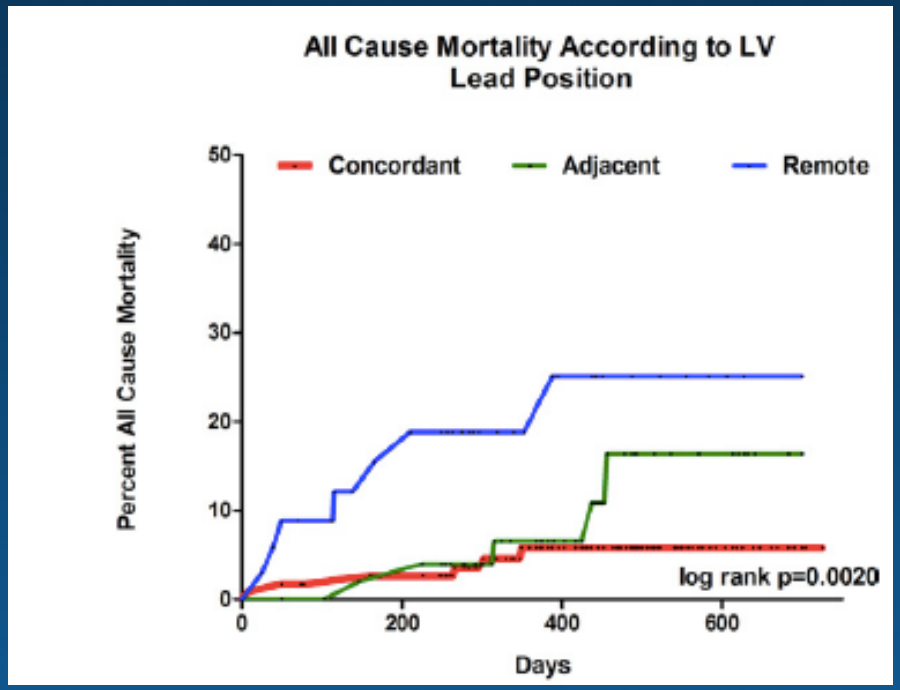
Objectives This study sought to assess the impact of targeted left ventricular (LV) lead placement on outcomes of cardiac resynchronization therapy (CRT).

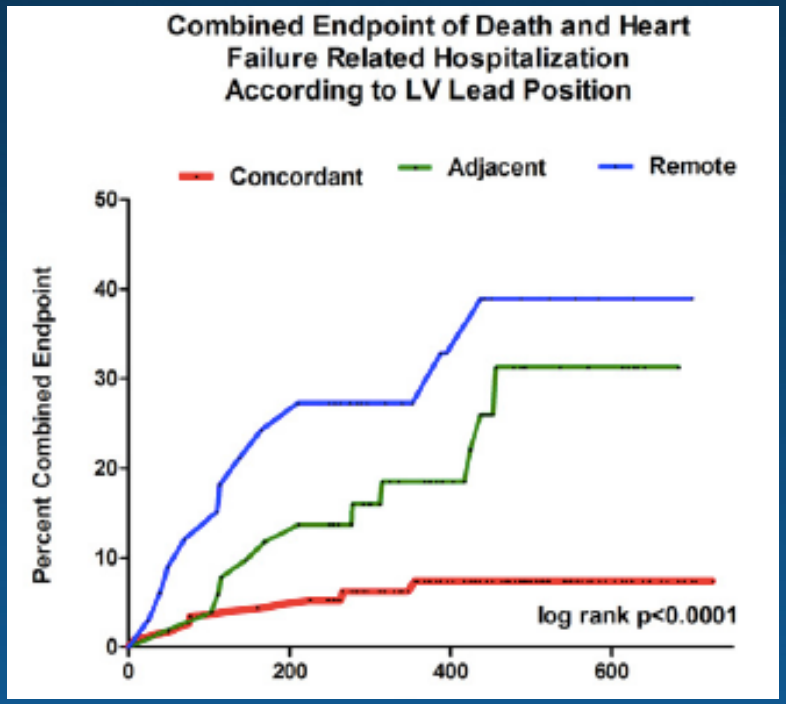
Background Placement of the LV lead to the latest sites of contraction and away from the scar confers the best response to CRT. We conducted a randomized, controlled trial to compare a targeted approach to LV lead placement with usual care.

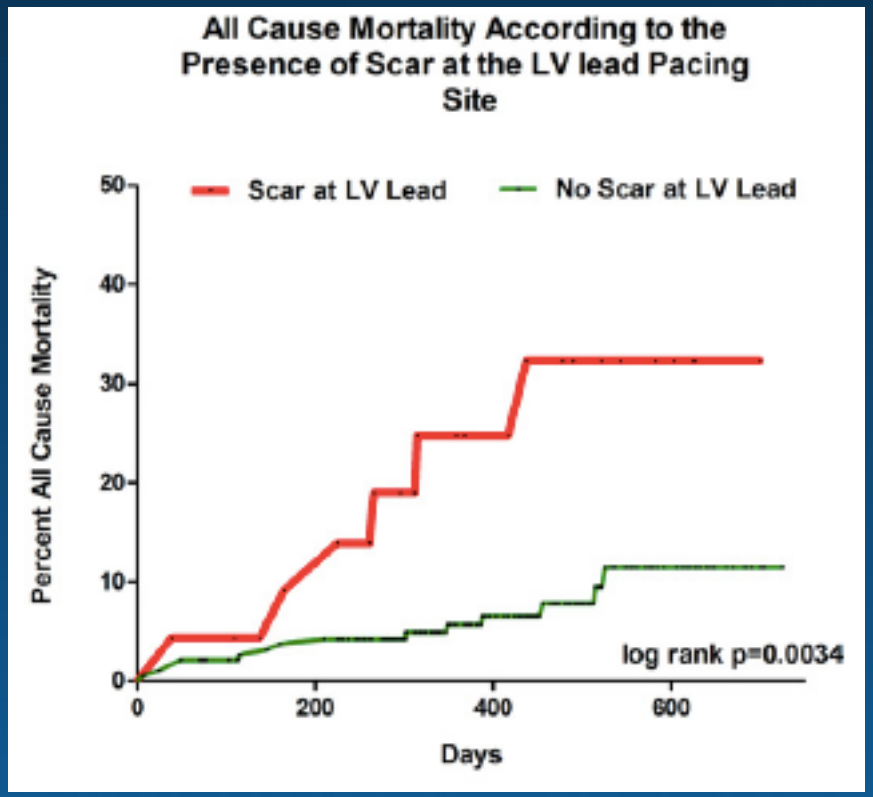
Methods A total of 220 patients scheduled for CRT underwent baseline echocardiographic speckle-tracking 2-dimensional radial strain imaging and were then randomized 1:1 into 2 groups. In group 1 (TARGET [Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy]), the LV lead 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.

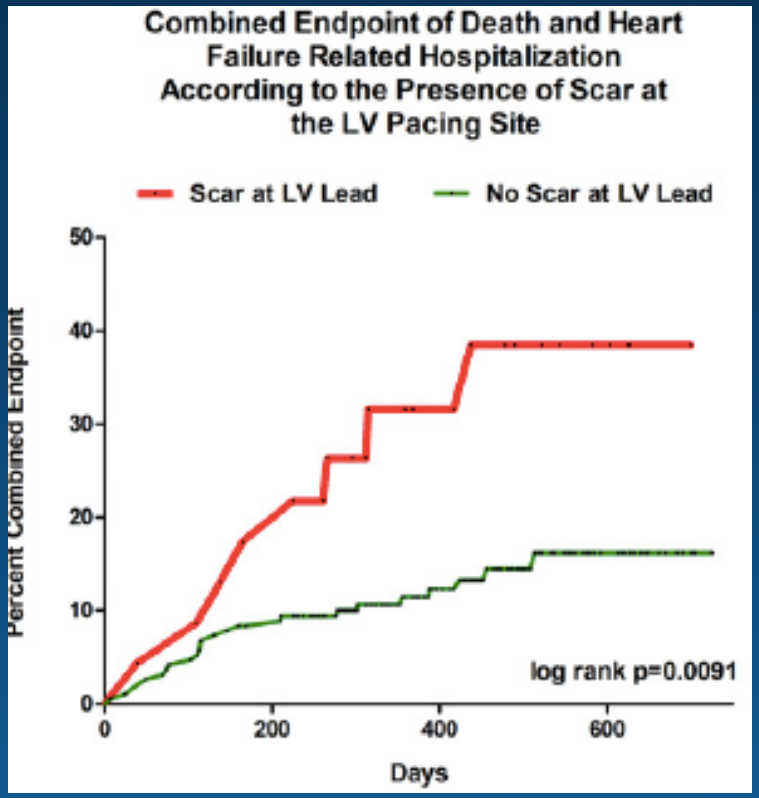
Results The groups were balanced at randomization. In the TARGET group, there was a greater proportion of responders at 6 months (70% vs. 55%, p = 0.031), giving an absolute difference in the primary endpoint of 15% (95% confidence interval: 2% to 28%). Compared with controls, TARGET patients had a higher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


All Cause Mortality According to LV Lead Position
Concordant
Adjacent
Remote
Percent All Cause Mortality
50
40
30
20
10
0
0
200
400
600
Days
log rank p=0.0020


Combined Endpoint of Death and Heart Failure Related Hospitalization According to LV Lead Position
Concordant
Adjacent
Remote
Percent Combined Endpoint
50
40
30
20
10
0
0
200
400
600
log rank p<0.0001


All Cause Mortality According to the Presence of Scar at the LV lead Pacing Site
Scar at LV Lead
No Scar at LV Lead
Percent All Cause Mortality
50
40
30
20
10
0
0
200
400
600
Days
log rank p=0.0034


Combined Endpoint of Death and Heart Failure Related Hospitalization According to the Presence of Scar at the LV Pacing Site
Scar at LV Lead
No Scar at LV Lead
Percent Combined Endpoint
50
40
30
20
10
0
0
200
400
600
Days
log rank p=0.0091

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

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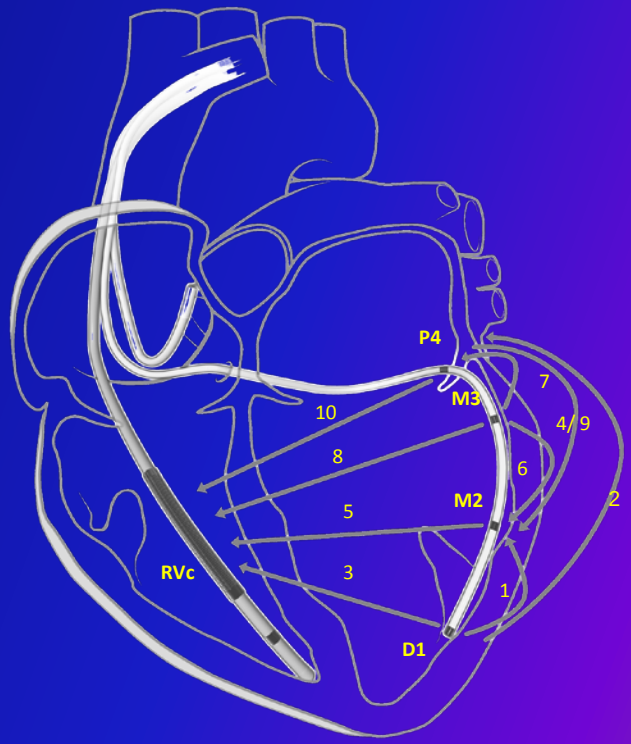
LV Lead Positioning Guided by ICE With Vector Velocity Imaging. ***Introduction*****: Intraoperative modality for "real-time" left ventricular (LV) dyssynchrony quantification and optimal resynchronization is not established. This study determined the feasibility, safety, and efficacy of intracardiac 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)*

	Pacing configurations	Cathode	Anode
1	**D1-M2**	Distal Tip	Medium 2
2	**D1-P4**	Distal Tip	Proximal 4
3	**D1-RVc**	Distal Tip	Rv coil
4	**M2-P4**	Mid 2	Proximal 4
5	**M2-RVc**	Mid 2	Rv coil
6	**M3-M2**	Mid 3	Medium 2
7	**M3-P4**	Mid 3	Proximal 4
8	**M3-RVc**	Mid 3	Rv coil
9	**P4-M2**	Mid 4	Medium 2
10	**P4-RVc**	Mid 4	Rv coil



Besides, thanks to 10 possible bipolar and unipolar pacing configurations, it may allow to avoid phrenic nerve stimulation

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Use of a quadripolar left ventricular lead to achieve successful implantation in patients with previous failed attempts at cardiac resynchronization therapy

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Aims Problems with implanting a left ventricular (LV) lead during cardiac resynchronization therapy (CRT) procedures are not uncommon and may occur for a variety of reasons including phrenic nerve stimulation (PNS) and high capture thresholds. We aimed to perform successful CRT in patients with previous LV lead problems using the multiple pacing configurations available with the St Jude Quartet model 1458Q quadripolar LV lead to overcome PNS or high capture thresholds.

Methods and results Four patients with previous failed attempts at LV lead implantation underwent a further attempt at CRT using a Quartet lead. In all four cases, successful CRT was achieved using a Quartet lead placed in a branch of the coronary sinus. Problems with PNS or high capture thresholds were seen in all four patients but were successfully overcome. Satisfactory lead parameters were seen at implant, pre-discharge, and at short-term follow-up (8.5 $\pm$ 5 weeks).

Conclusion The Quartet lead allows 10 different pacing vectors to be used and may overcome common pacing problems because of the multiple pacing configurations available. Problems with either PNS or unsatisfactory pacing parameters experienced during CRT may be resolved simply by changing the pacing configuration using this quadripolar lead system.

Single left ventricular vs. multiple site

Regarding multiple-site LV pacing, a small study including NYHA class III–IV HF patients in SR and LBBB demonstrated that dual-site LV pacing conferred larger acute haemodynamic improvements, compared with single-site LV pacing.

Two small controlled trials showed some functional benefit.

Additional larger randomized trials with long-term clinical follow-up are needed in order to determine the real value of this pacing modality.

Similarly, endocardial LV lead positioning has been shown to provide more homogeneous ventricular resynchronization and larger acute and mid-term improvements in LV function.

However, the associated thrombo-embolic and infection complications need to be resolvedbefore recommending this pacing modality.

Ongoing randomized trials using wireless leads will provide further evidence to this field.

Choice of pacing mode (and cardiac resynchronization therapy optimization)

Recommendations	Class [a]	Level [b]	Ref. [c]
1) The goal of CRT should be to achieve BiV pacing as close to 100% as possible since the survival benefit and reduction in hospitalization are strongly associated with an increasing percentage of BiV pacing.	IIa	B	67–69
2) Apical position of the LV lead should be avoided when possible.	IIa	B	70–72
3) LV lead placement may be targeted at the latest activated LV segment.	IIb	B	73

Criterio Elettrocardiografico:

QRS ≥ 120 msec

Reliability and Reproducibility of QRS Duration

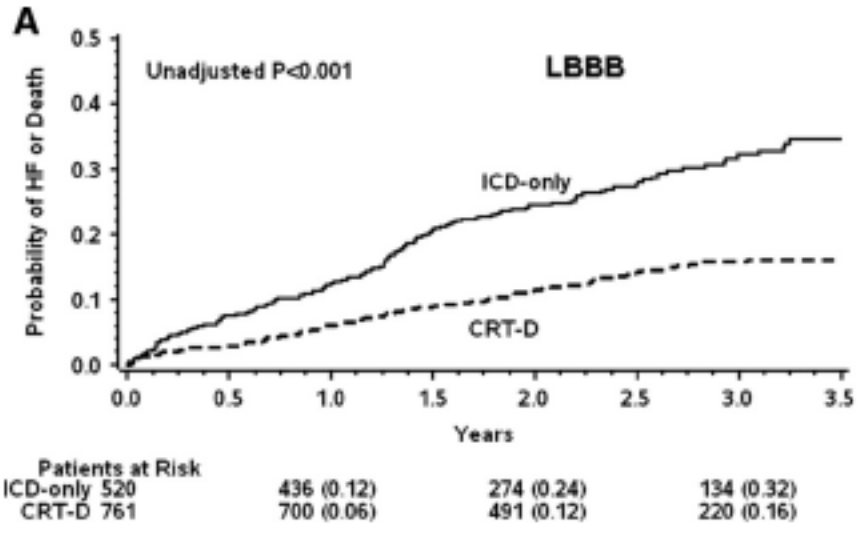
Significant interobserver differences *(P < 0.001) were found between each combination of* paired observers, with an up to 50-ms absolute variability between cardiologists and low concordance with computerized measurements. **Intraobserver absolute variability was also significant** (P < *0.01) for the 3* observers. These significant differences persisted (P < *0.01)* ***when focusing our interest on the ECGs in the*** **100–140 ms** ***range*** (defined as at least one out of the 4 measures in this range). Considering the 120 ms limit, 22 (27.5%) ECGs were differently classified by at least one of the cardiologists. We observed similar interobserver differences between each combination of paired observers with a 50 mm/s sweep speed.

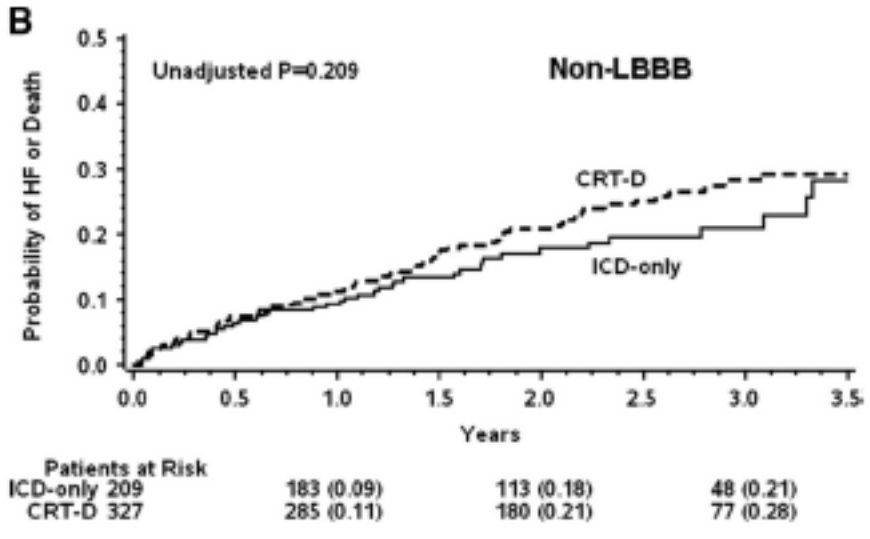
Guillebon et al. J Cardiovasc Electrophysiol, Vol. pp. 1-3, In press.

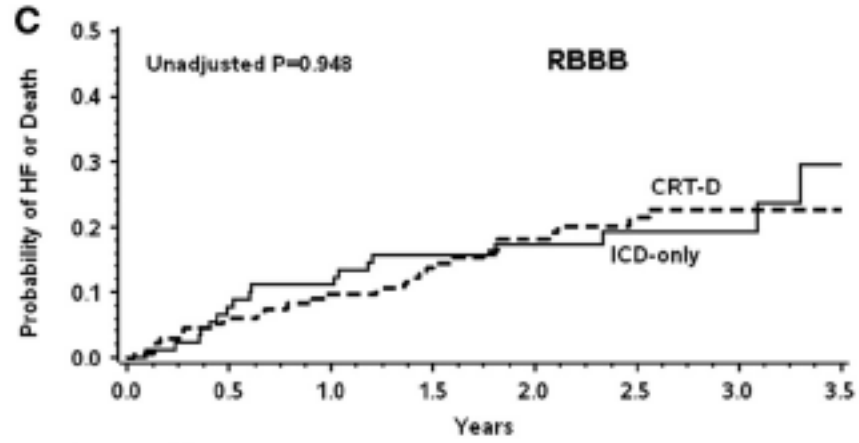
Evidences from randomized clinical trials

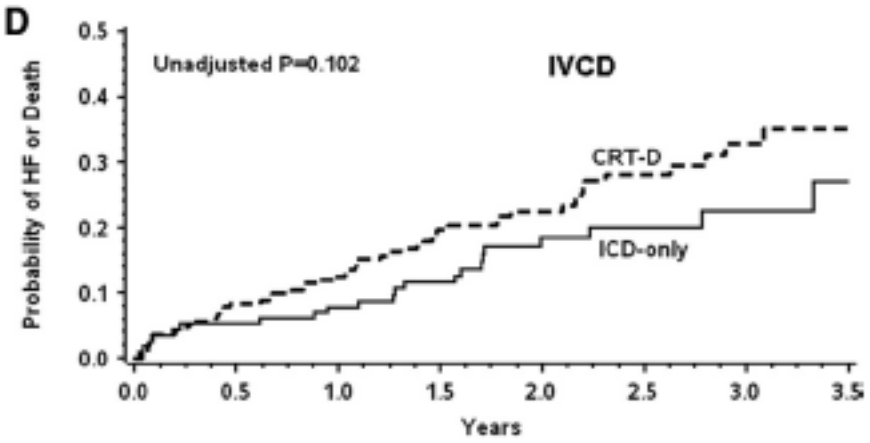
	QRS duration (msec)
COMPANION	≤ 147 NO advantage 148-168 No advantage in primary end-point > 168 CRT better
CARE-HF	< 160 NO advantage ≥ 160 CRT better
MUSTIC	Only ≥ 150 enrolled
MADIT-CRT	> 150 CRT better ≤ 150 No advantage
REVERSE	≥ 152 CRT better

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



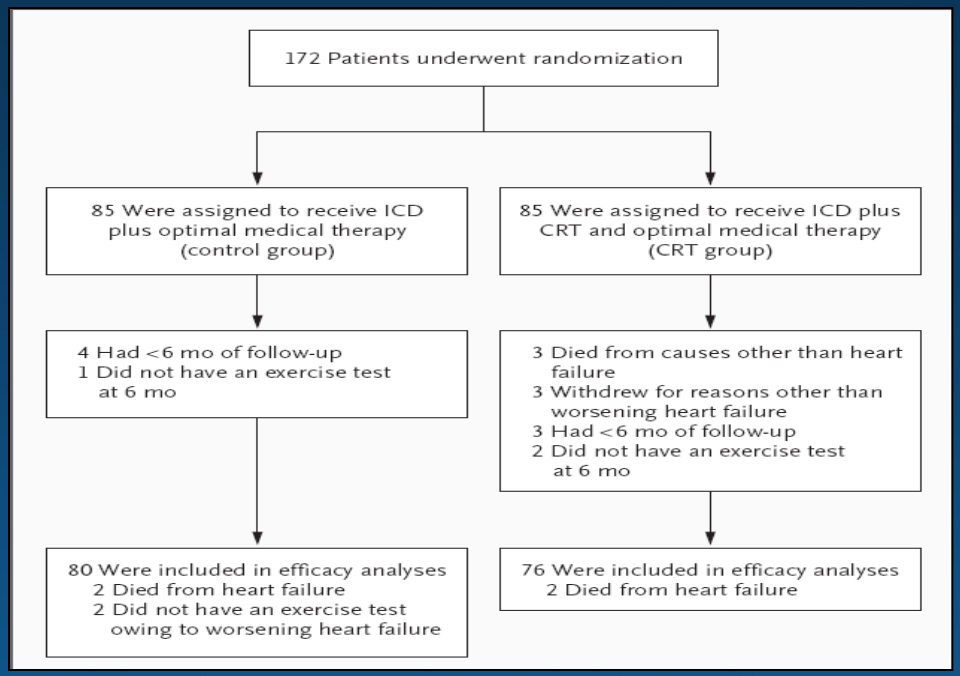






Circulation. 2011;123:1061-1072

CRT in Patients with HF and Narrow QRS (RethinQ) trial



Primary end point

Proportion of patients with an increase in peak oxygen consumption of at least 1.0 ml per kilogram of body weight per minute during cardiopulmonary exercise testing at 6 months.

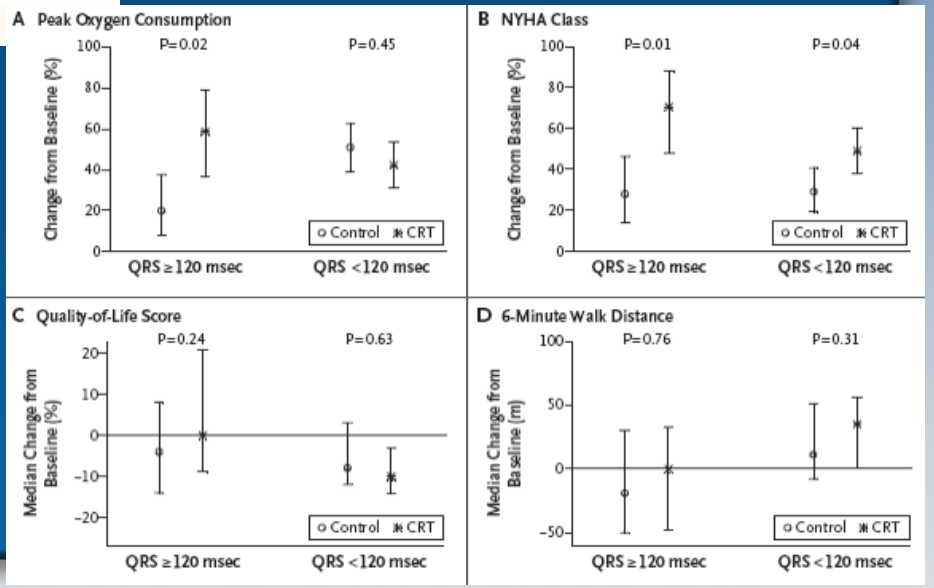
- Ischemic or nonischemic cardiomyopathy
- Ejection fraction ≤35%
- NHYA class III heart failure
- QRS interval <130 msec
- Mechanical dyssynchrony as measured on echocardiography.

CRT in Patients with HF and Narrow QRS (RethinQ) trial

Variable	Control Group	CRT Group	P Value
Primary end point			
Change in peak oxygen consumption			0.63
No. of patients	80	76	
Median change (95% CI) — ml/kg/min	0.5 (–0.3 to 1.1)	0.4 (-0.6 to 1.2)	
Increase of ≥1.0 ml/kg/min — no. (%)	33 (41)	35 (46)	
Secondary end points			
Change in quality-of-life score†			0.91
No. of patients	80	76	
Median change (95% CI)	–7 (–11 to 3)	–8 (–10 to –1)	
Change in NYHA class			0.006
No. of patients	80	76	
Improved by 1 class or more — no. (%)	23 (29)	41 (54)	
No change — no. (%)	51 (64)	31 (41)	
Worsened — no. (%)	6 (8)	4 (5)	

CRT did not improve peak oxygen consumption in patients with moderate-to-severe HF, providing evidence that patients with HF and narrow QRS intervals may not benefit from CRT.

Peak oxygen consumption and the NYHA class improved in patients in the CRT group with a QRS ≥120 msec. However, no difference was observed in the quality-of-life score and the 6-minute walking test in either stratum.



Criterio Clinico:

Classe NYHA

The limitations of the NYHA functional classification system

Table 4 Different criteria used to determine the New York Heart Association (NYHA) class of a patient

Criteria used to determine the NYHA class	% of cardiologists
Self-reported walking distance	70
Difficulty in climbing stairs	60
Ability to walk to local landmarks	30
Breathlessness interferes with daily activities	23
Breathless when walking around the house	23
No specific questions	13

Cardiologists could state multiple criteria for assessment.

Raphael et al. Heart 2007;93:476-482

The limitations of the NYHA functional classification system

Table 5 Results of the interoperator study

		NYHA class for assessor 2		
		I	II	III
NYHA class for assessor 1	I	1		
	II	1	18	10
	III		13	7

NYHA, New York Heart Association.

Raphael et al. Heart 2007;93:476-482

Terapia Medica Ottimale

Euro Heart Failure Survey 2003

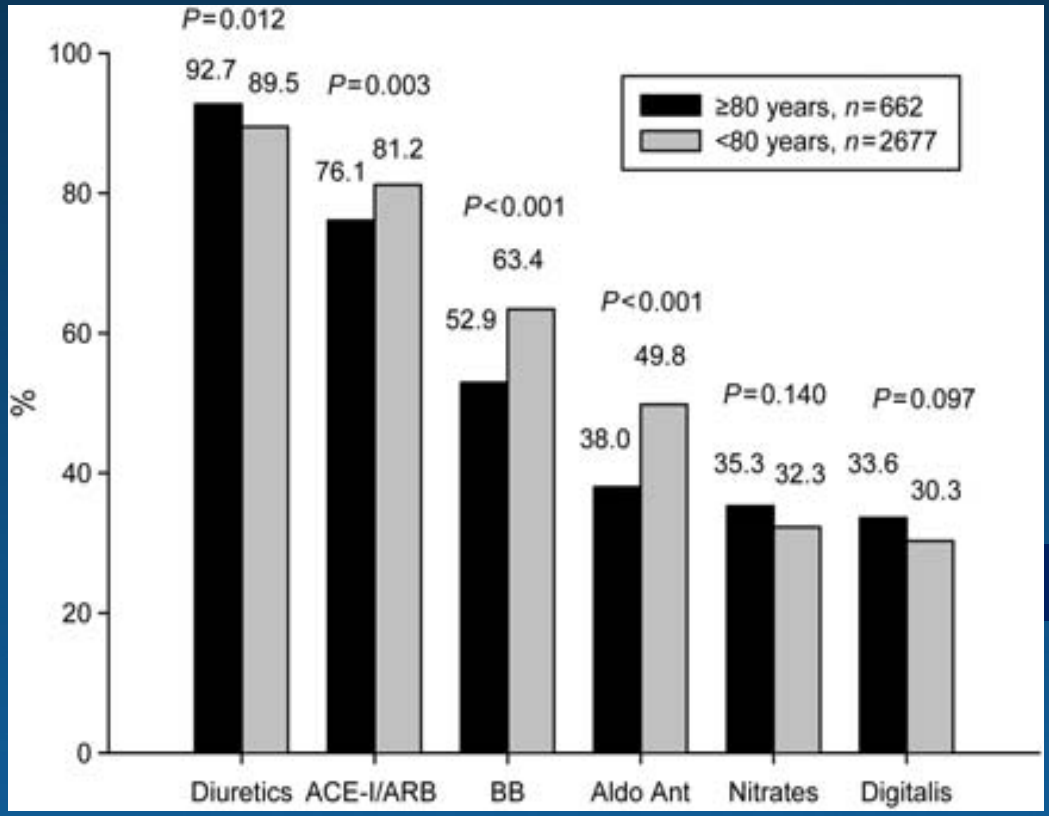
Table 1 Rate of prescription of the major heart failure medication in the overall population (n=11 016)

	(%)
ACE inhibitors	61.8 (40–85.1)
Angiotensin II receptor antagonists	4.5 (1.9–14)
Antithrombotic therapy (any)	77.6 (57.7–92.7)
Aspirin	29.1 (27.1–73)
Beta-Blockers	36.9 (10–65.8)
Calcium channel blockers	21.2 (9.8–33.4)
Cardiac glycosides	35.7 (17.3–53.5)
Diuretics	86.9 (64.2–96.4)
IV inotropic agents	7.2 (0.5–19.5)
Nitrates	32.1 (6.3–70.6)
Spironolactone	20.5 (5.7–58.5)

Only 17% of the population received the Recommended Triple Association: Diuretic, ACE- Inhibitor, Beta-blocker.

M. Komajda et al. European Heart Journal (2003)

Euro Heart Failure Survey II 2009



M. Komajda et al. European Heart Journal (2009)

Clinical Investigations

Beta-blocker Utilization and Outcomes in Patients Receiving Cardiac Resynchronization Therapy

Pennsylvania, USA…

Covariate	Hazard Ratio	95% CI	p value
Age (years)	1.01	0.97–1.05	NS
QRS Duration (ms)	0.98	0.96–0.99	0.025
Cr (mg/dL)	1.10	0.60–1.98	NS
LVEF	0.94	0.87–1.00	NS
Ischemic HF Etiology	0.42	0.13–1.37	NS
Statin Therapy	1.35	0.44–4.11	NS
Lack of BB Therapy and No Documented Justification	3.10	1.04–9.28	0.043

Abbreviations BB = beta-blocker; Cr = creatinine; HF = heart failure; NS = not significant.

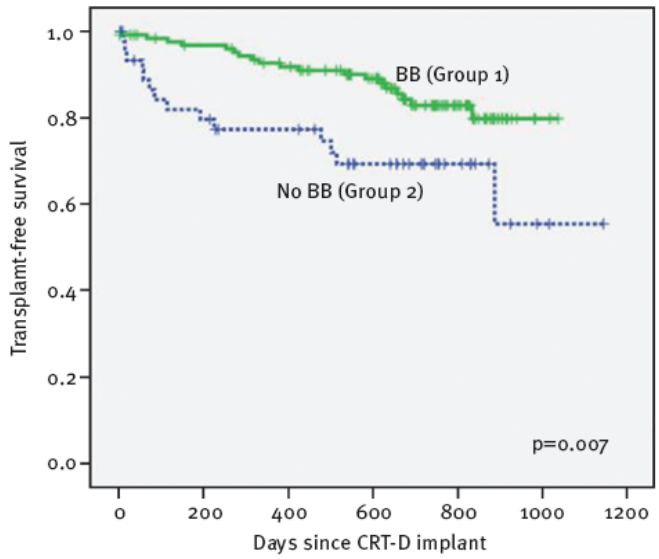


Figure 2. Kaplan-Meier estimates of the time to death or cardiac transplantation.

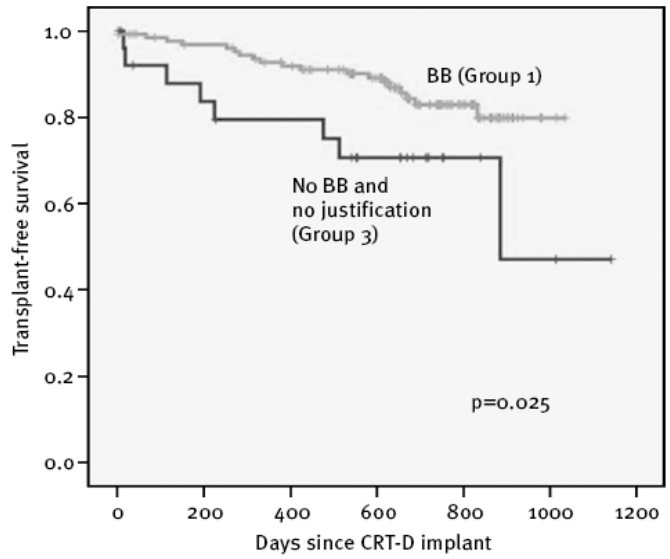


Figure 3. Kaplan-Meier estimates of the time to death or cardiac transplantation.

Voigt A. et al. *Clin Cardiol 2010*

Criterio Ecocardiografico:

FE ≤ 35%

Quantitative Assessment of Left Ventricular Size and Function

Side-by-Side Comparison of Real-Time Three-Dimensional Echocardiography and Computed Tomography With Magnetic Resonance Reference

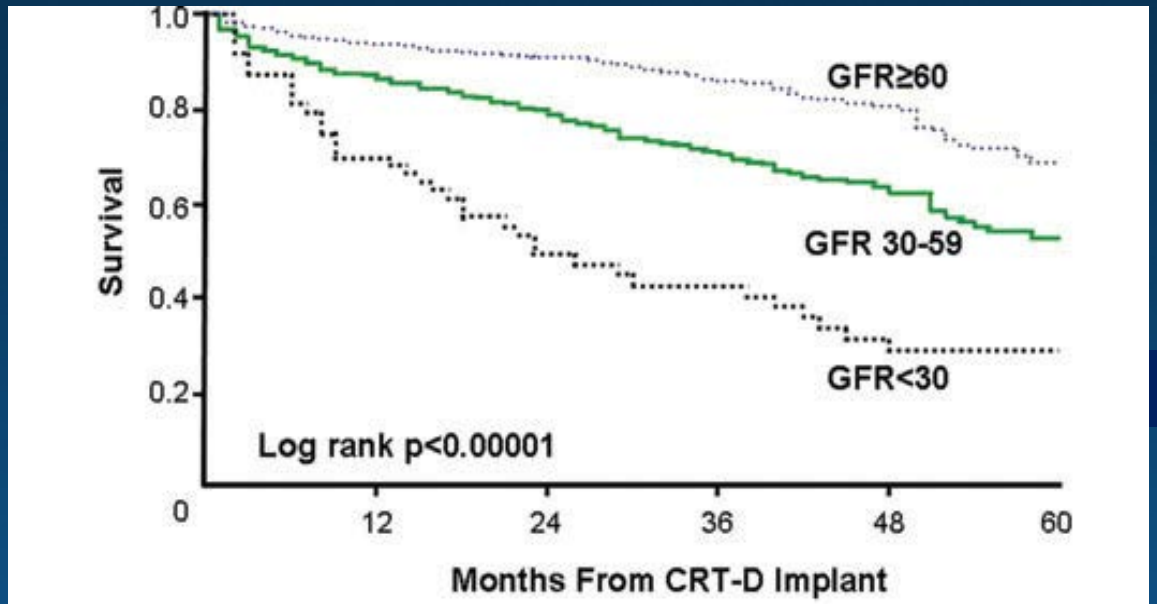
Interobserver and Intraobserver Variability of LV EDV and ESV and EF Obtained From Repeated Measurements by CMR, CCT, and RT3DE Images

	Interobserver Variability, %	Intraobserver Variability, %
EDV		
CCT	2.6±2.0	2.0±1.3
CMR	6.3±5.7	2.4±2.3
RT3DE	11.2±8.6	3.9±2.0
ESV		
CCT	5.7±5.2	2.2±3.1
CMR	7.7±6.6	6.3±4.6
RT3DE	14.2±11.8	5.6±3.9
EF		
CCT	6.5±4.9	2.1±3.4
CMR	8.5±9.7	6.2±6.2
RT3DE	10.5±8.3	5.6±3.4

Data are shown as mean±SD.

Sugeng L et al Circulation 2006;114:654

RENAL FUNCTION AND CRT

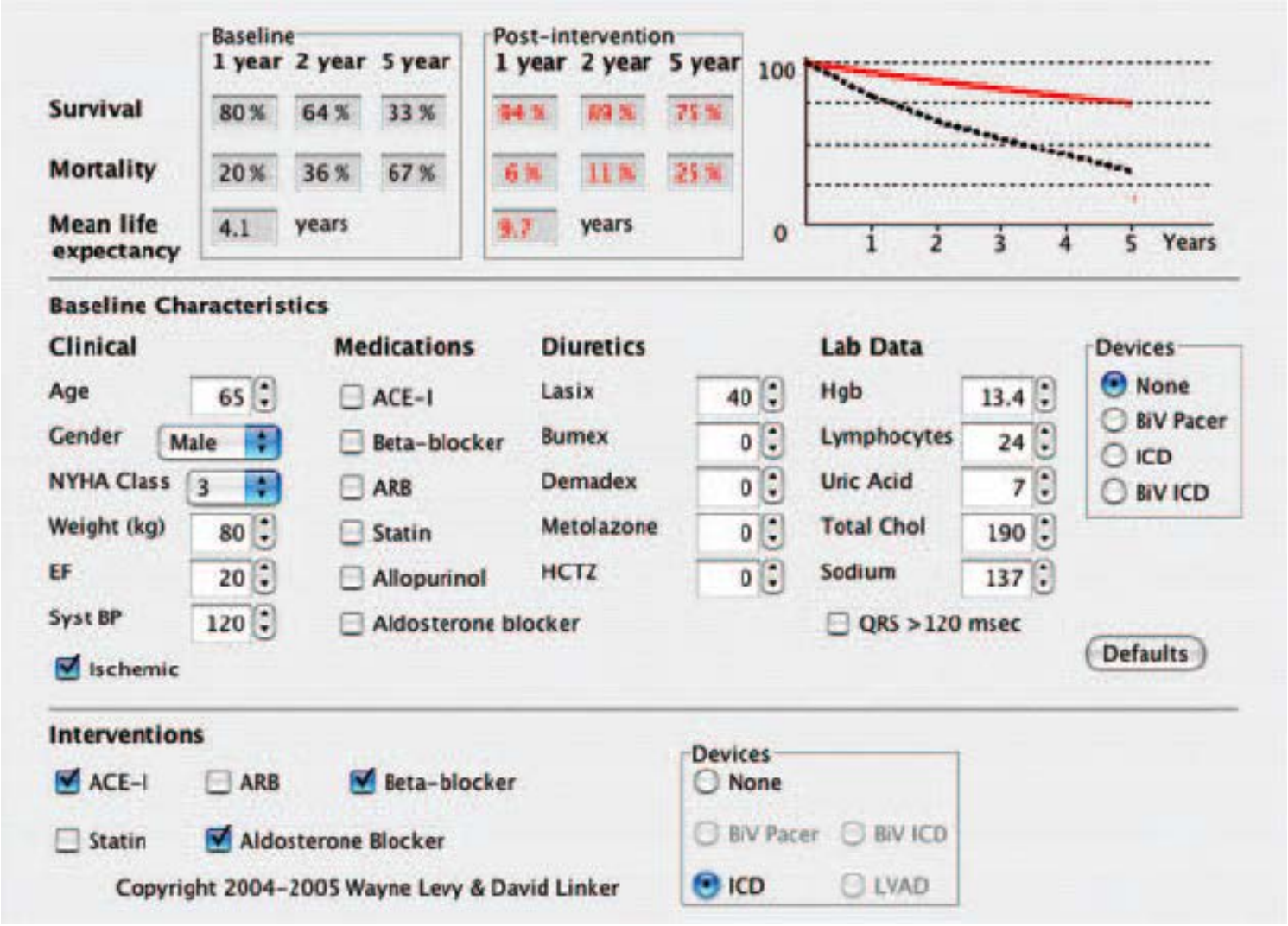


GFR≥60	376	326	255	181	98	42
GFR 30-59	347	283	220	152	91	32
GFR<30	64	42	23	19	11	3

Overall survival among CRT-D recipients stratified according to baseline GFR category

ADELSTEIN ET AL. PACE 2010; 1–10.

The Seattle Heart Failure Model: Prediction of Survival in Heart Failure



Circulation 2006;113;1424-1433

Tabella 3. L'indice CardioVascular Medicine-Heart Failure[17].

	Punteggio
Valutazione del rischio non cardiaco	
Età	1 per ogni decade >40
Anemia	1
Ipertensione 1	
BPCO	1
Diabete complicato	2
Insufficienza renale moderata/severa	2
Tumore metastatizzato/2 tumori	6
Valutazione del rischio cardiaco	
No betabloccanti	1
No ACE-inibitori	1
Classe NYHA III o IV	4
FE ≤20%	2
Valvulopatia severa	2
Fibrillazione atriale	1

ACE = enzima di conversione dell'angiotensina; BPCO = broncopneumopatia cronica ostruttiva; FE = frazione di eiezione.