Issues in clinical trials devices

CRT

Cecilia Linde

Stockholm 13th december, 2019

Disclosures

Cecilia Linde receives

Research grants to institution from Astra Zeneca, Swedish Heart-Lung-foundation and Stockholm County Council

Speaker honoraria from Medtronic, Abbot, Liva Nova, Novartis, Vifor , Microport, Boston Scientific, Impulse Dynamics, Bayer

Defibrillators and CRT save lives

Prim prof ICDs are indicated in

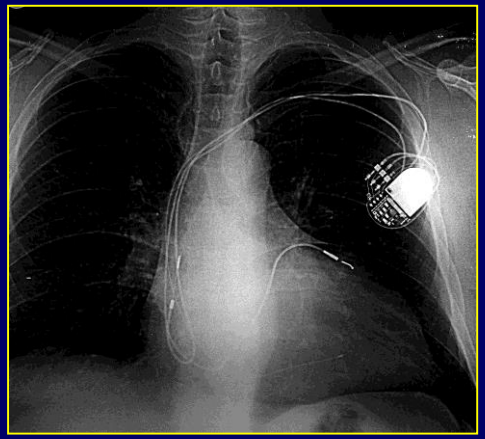
50% of HF patients (HFrEF) and in 10% after myocardial infarction

But ony in HFrEF

CRTs are indicated in 30% of HF patients (RiksSvikt registry)

NYHA class, LVEF, QRS width/LBBB are the gate-keepers

But ony in HFrEF



What the 2016 ESC HF guidelines say

HFA Heart Failure Association

European Heart Journal
doi:10.1093/eurheartj/ehw128

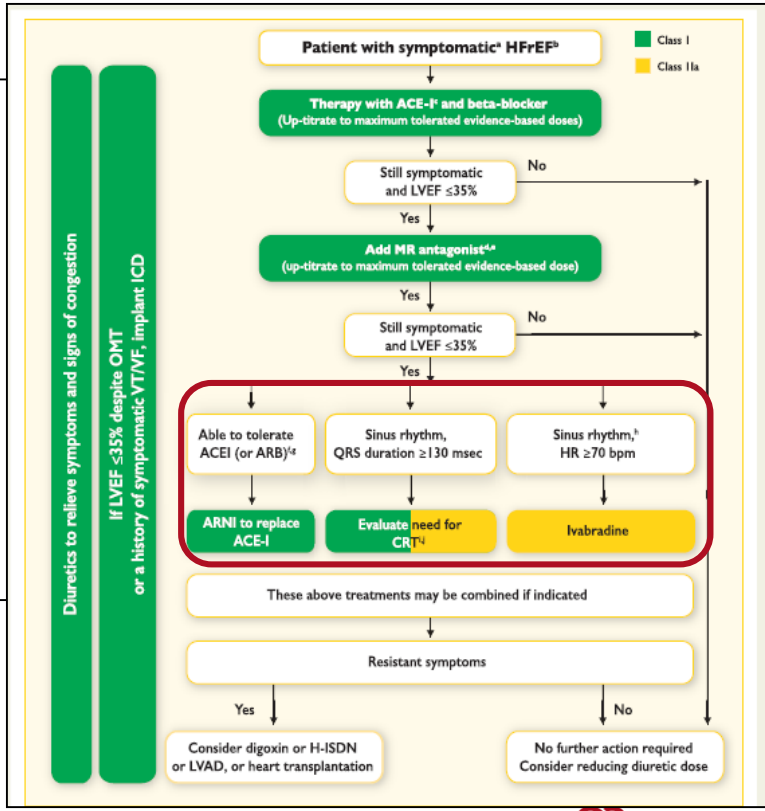
ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)



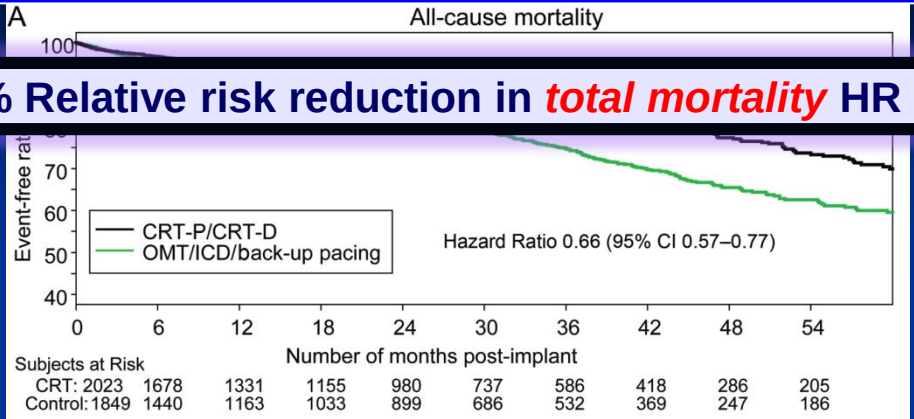
Consider CRT+/-ICD
In symptomatic HFrEF
Provided QRS ≥ 130 ms

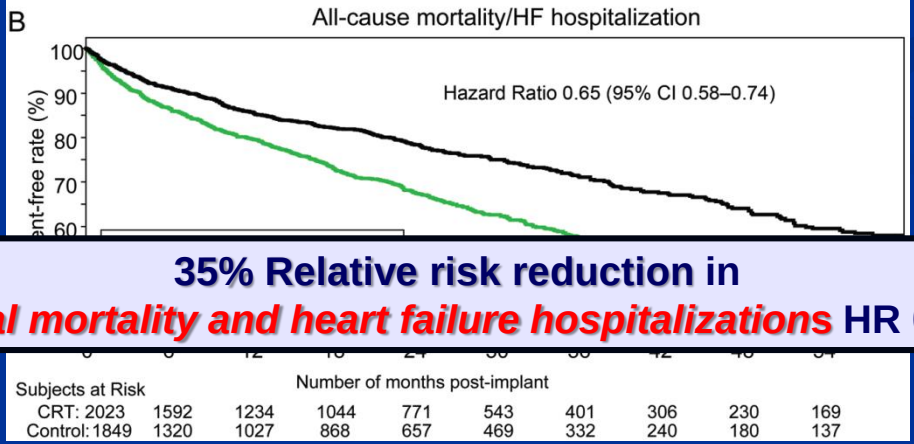
ESC

Results from a case-based meta-analysis:5 RCT (NYHA II-III) In pts on optimal medical treatment

34% Relative risk reduction in *total mortality* HR 0.66

N=3872 pts





35% Relative risk reduction in *Total mortality and heart failure hospitalizations* HR 0.65

Cleland J et al Eur Heart J 2013: 46:3547

CRT – a 20 year success story

What is different about device **studies**

Challenges

Patient safety / perioperative long term device related complications
Risk benefit calculation

Expert implanter needed

High up front cost of therapy

Lack of reimbursement

Non belief from the medical society

Common order of device trials

HFA Heart Failure Association

Smaller studies
Highly specialized centers
Sicker patients

1. **Observational studies**
2. **Crossover RCT studies**
   - Tight control of inclusion criteria
   - Core lab echo
   - Long run in with OMT

Followed by
3.**Parallell RCT** with hard endpoints

4. Moving to Mild HF RCT with hard endpoints

ESC

NYHA III-IV patients

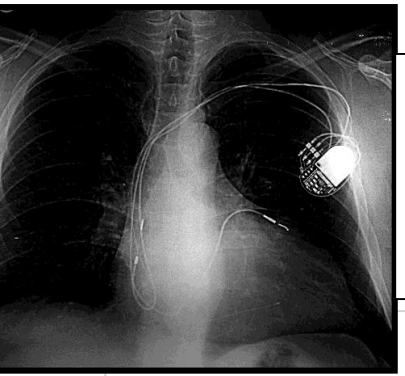
Cardiac resynchronisation therapy
a French invention

Permanent Left Ventricular Pacing With Transvenous Leads Inserted Into The Coronary Veins

J. CLAUDE DAUBERT[1], PHILIPPE RITTER[2], HERVÉ LE BRETON[1], DANIEL GRAS[1,2], CHRISTOPHE LECLERCQ[1], ARNAUD LAZARUS[2], JACQUES MUGICA[2], PHILIPPE MABO[1] and SERGE CAZEAU[2]

From the [1]Service de Cardiologie A, Hotel Dieu/CHRU 35033 Rennes Cedex, [2]Département de Stimulation Cardiaque, Centre Chirurgical du Val d'Or, Saint-Cloud France

PACE 1998;21:239-245



N Engl J Med 2001;344:873-80.

EFFECTS OF MULTISITE BIVENTRICULAR PACING IN PATIENTS WITH HEART FAILURE AND INTRAVENTRICULAR CONDUCTION DELAY

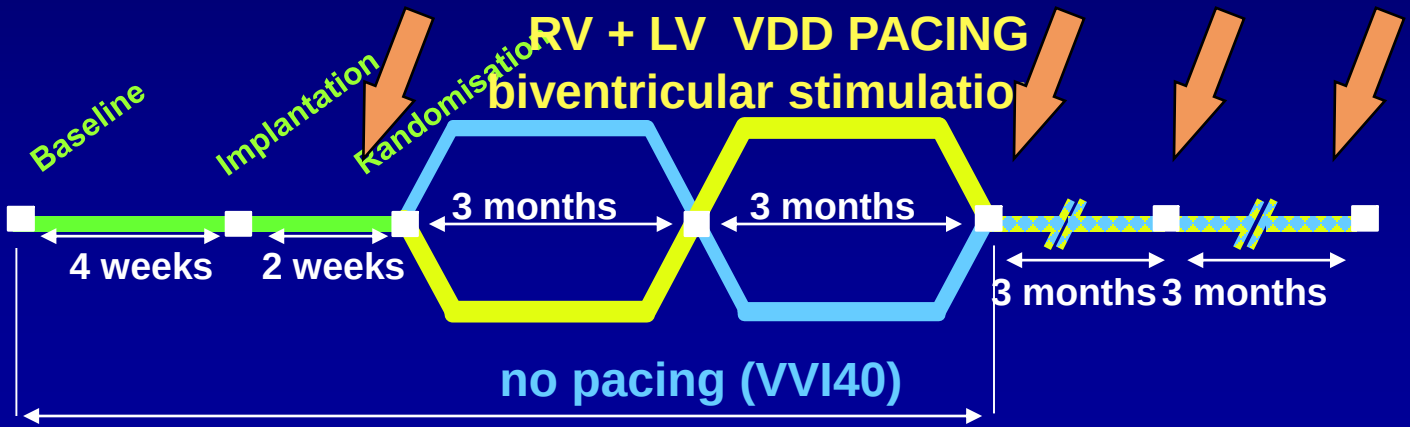
SERGE CAZEAU, M.D., CHRISTOPHE LECLERCQ, M.D., THOMAS LAVERGNE, M.D., STUART WALKER, M.D., CHETAN VARMA, M.D., CECILIA LINDE, M.D., STÉPHANE GARRIGUE, M.D., LUKAS KAPPENBERGER, M.D., GUY A. HAYWOOD, M.D., MASSIMO SANTINI, M.D., CHRISTOPHE BAILLEUL, PH.D., AND JEAN-CLAUDE DAUBERT, M.D., FOR THE MULTISITE STIMULATION IN CARDIOMYOPATHIES (MUSTIC) STUDY INVESTIGATORS*

ESC

Mustic
Study

Study design SR Group

- **Randomised single blind comparison of**
  - * Biventricular VDD pacing with optimal AV delay
  - * Inactive VVI pacing (40 bpm)



MUSTIC study results : CRT vs VVI in severe HF sévere – NYHA III et QRS > 150 ms

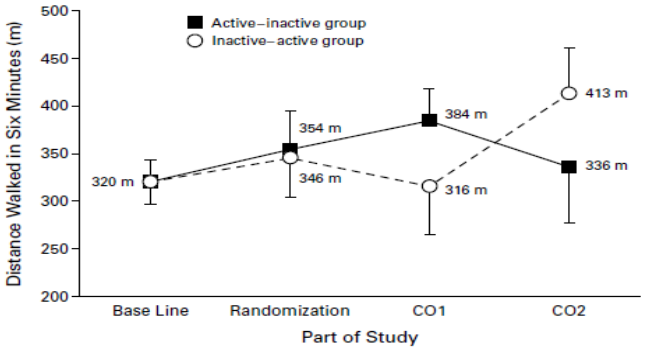


Figure 2. Distance Walked in Six Minutes at Specified Times during the Study.
The mean (±SD) values are given for each part of the study. CO1 denotes the end of crossover period 1, and CO2 the end of crossover period 2.

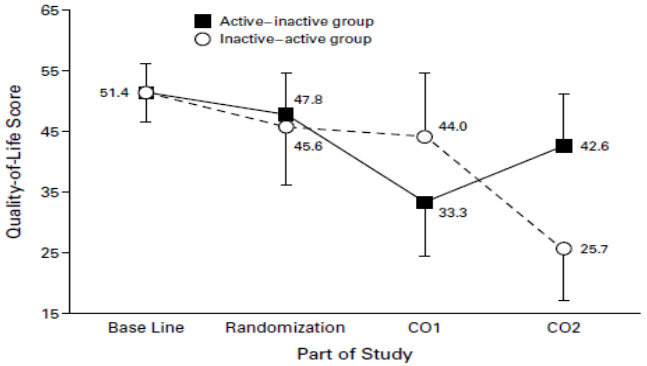


Figure 3. Quality-of-Life Score (Assessed with the Minnesota Living with Heart Failure Questionnaire) at Specified Times during the Study.
The mean (±SD) values are given for each phase of the study. CO1 denotes the end of crossover period 1, and CO2 the end of crossover period 2. A higher score indicates a poorer quality of life (range, 0 to 105).

Six minute walk
Improved 23%
In BiV arm

Quality of life
Improved 32%
In BiV arm

Cazeau S et al NEJM 2001

ORIGINAL ARTICLE

N Engl J Med 2005;352:1539-49.

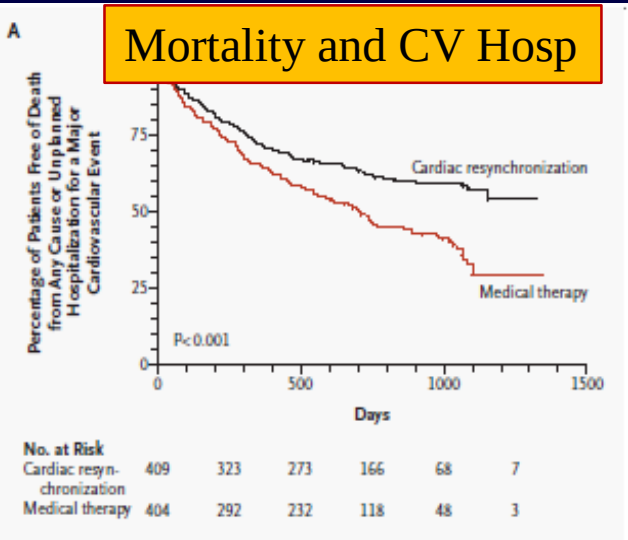
The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure

John G.F. Cleland, M.D., Jean-Claude Daubert, M.D.,
Erland Erdmann, M.D., Nick Freemantle, Ph.D., Daniel Gras, M.D.,
Lukas Kappenberger, M.D., and Luigi Tavazzi, M.D.,
for the Cardiac Resynchronization — Heart Failure (CARE-HF) Study Investigators

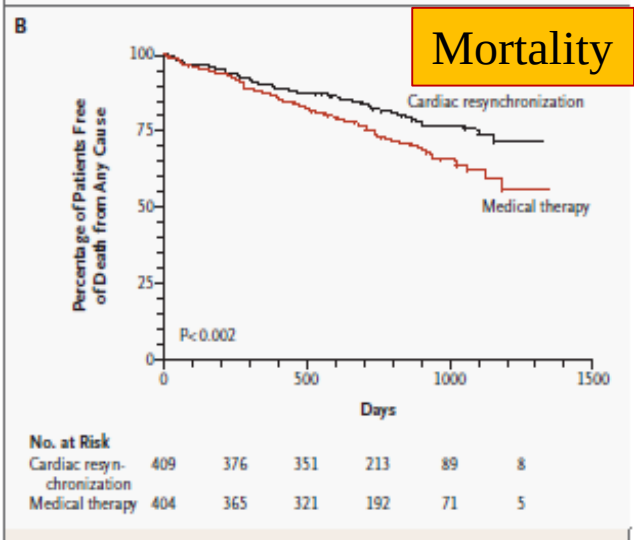
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Medical Therapy Alone (N=404)	Medical Therapy plus Cardiac Resynchronization (N=409)
Age (yr)		
Median	66	67
Interquartile range	59–72	60–73
Male sex (%)	293 (73)	304 (74)
NYHA class IV (%)	27 (7)	23 (6)
Dilated cardiomyopathy (%)	193 (48)	177 (43)
Ischemic heart disease (%)	144 (36)	165 (40)
QRS duration (msec)		
Median	160	160
Interquartile range	152–180	152–180

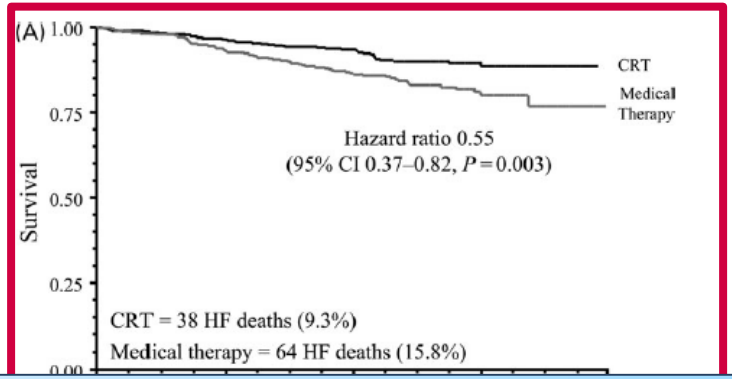
Mortality and CV Hosp



Mortality

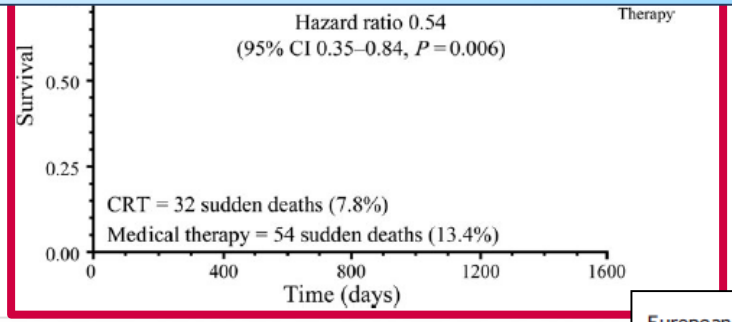


Long term outcome results in CARE-HF



HF mortality

It took more than 2 years with CRT compared to optimal medical treatment to reduce
The risk of sudden cardiac death in the CARE HF trial



European Heart Journal (2006) 27, 1928–1932
doi:10.1093/eurheartj/ehl099

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Michael R. Bristow, M
Steven Krueger, M.D.
Peter Carson, M.D.,
Bill G. White, Ph.D., Dale W
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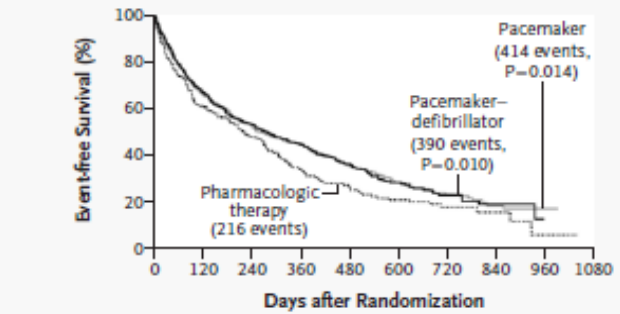
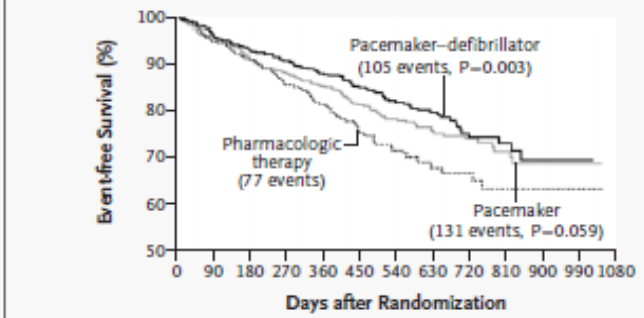
Table 1. Clinical Characteristics of the 1520 Patients.*

Characteristic	Optimal Pharmacologic Therapy (N=308)	Cardiac-Resynchronization Therapy	
		Pacemaker (N=617)	Pacemaker–Defibrillator (N=595)
Age (yr)	68	67	66
Male sex (%)	69	67	67
NYHA class III (%)	82	87	86
Duration of heart failure (yr)	3.6	3.7	3.5





NYHA class II/I

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ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.08.027

Cardiac Resynchronization

Randomized Trial of Cardiac Resynchronization in Mildly Symptomatic Heart Asymptomatic Patients W Dysfunction and Previous

Cecilia Linde, MD, PHD,* William T. Abrah
Martin St. John Sutton, MD,§ Stefano Ghio,
(REsynchronization reVErses Remodeling in
*Stockholm, Sweden; Columbus, Ohio; Charlest
Pavia, Italy; and Rennes, France*

European Heart Journal (2013) **34**, 2592–2599
doi:10.1093/eurheartj/eht160

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study

Cecilia Linde[1]*, Michael R. Gold[2], William T. Abraham[3], Martin St John Sutton[4], Stefano Ghio[5], Jeff Cerkvenik[6], and Claude Daubert[7], on behalf of the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) Study Group

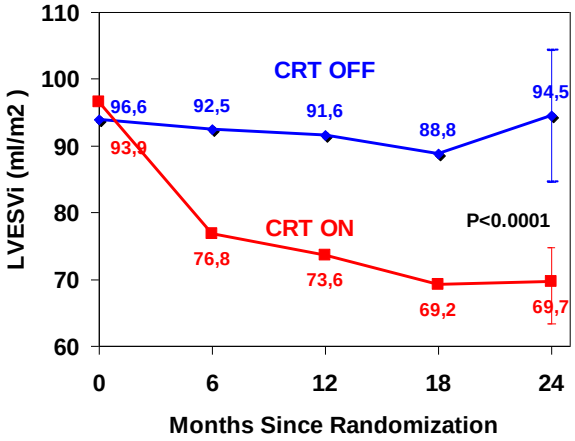
[1]Department of Cardiology, Karolinska University Hospital, S- 17176, Stockholm, Sweden; [2]Division of Cardiology, Medical University of South Carolina, Charleston, SC, USA; [3]Division of Cardiovascular Medicine and the Davis Heart and Lung Research Institute, The Ohio State University, Columbus, OH, USA; [4]University of Pennsylvania Medical Center, Philadelphia, PA, USA; [5]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [6]Medtronic, Inc, Minneapolis, MN, USA; and [7]Département de Cardiologie, CHU, INCERM, CIC_IT 804 Rennes, France

Received 23 January 2013; revised 12 March 2013; accepted 16 April 2013; online publish-ahead-of-print 2 May 2013

See page 2582 for the editorial comment on this article (doi:10.1093/eurheartj/eht238)

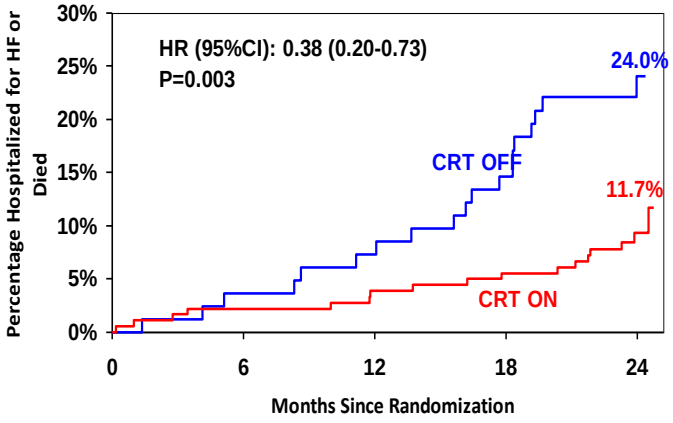
REVERSE: CRT in HF Classe NYHA I-II

Powered Secondary End Point: LVESVi



73 centres (EU et Etats Unis)
674 patients

Time to First HF Hospitalization or Death



C Daubert et Al, J Am Coll Cardiol 2009; 54: 1837-1846

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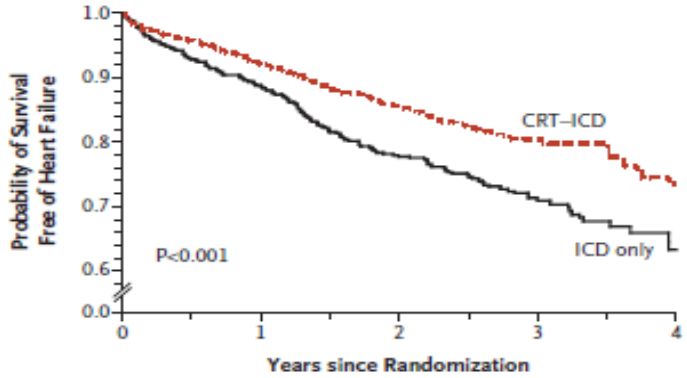
ESTABLISHED IN 1812

Cardiac-Resyn

Arthur J. Moss, M.D., W. Jackson
James P. Daubert, M.D.
Steven L. Higgins, M.D., I
and Wojciech

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Variable	ICD-Only Group (N=731)	CRT-ICD Group (N=1089)
Age — yr	64±11	65±11
Male sex — no. (%)		
Race — no./total no. (%)†		
White		
Black		
Other		
Cardiac history — no. (%)		
Ischemic heart disease		
NYHA class I		
NYHA class II		
Nonischemic heart disease		
NYHA class II		
NYHA class III or IV >3 mo bef		
Cardiac risk factors — no./tota		
Treatment for hypertension		
Atrial fibrillation >1 mo bef		
Diabetes mellitus		
Cigarette smoking		
Body-mass index ≥30‡		
Coronary-bypass surgery		
Cardiac findings at enrollment		
Blood pressure — mm Hg		
Systolic		
Diastolic		
Blood urea nitrogen ≥26 mg		
Creatinine — mg/dl	1.2±0.4	1.2±0.4
Left bundle-branch block — no./total no. (%)	520/729 (71.3)	761/1088 (69.9)
Right bundle-branch block — no./total no. (%)	92/729 (12.6)	136/1088 (12.5)
QRS duration ≥150 msec — no. (%)	476 (65.1)	699 (64.2)
Left ventricular ejection fraction	0.24±0.05	0.24±0.05
Six-minute walk distance — m	363±108	359±107



No. at Risk (Probability of Survival)

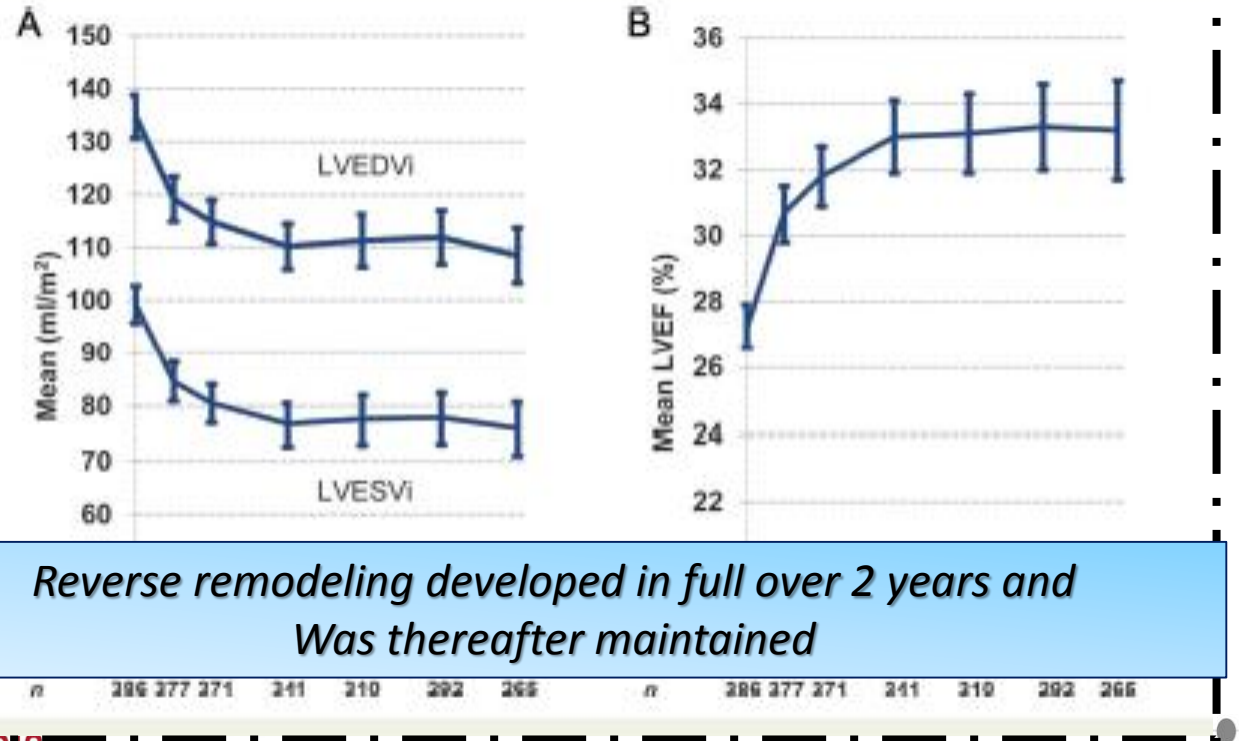
ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT–ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

Figure 2. Kaplan–Meier Estimates of the Probability of Survival Free of Heart Failure.

There was a significant difference in the estimate of survival free of heart failure between the group that received cardiac-resynchronization therapy plus an implantable cardioverter–defibrillator (CRT–ICD) and the group that received an ICD only (unadjusted P<0.001 by the log-rank test).

Mechanism of action

Time course of of reverse remodeling over 5 yrs in the REVERSE trial



Reverse remodeling developed in full over 2 years and Was thereafter maintained

Reverse remodeling by drugs and CRT

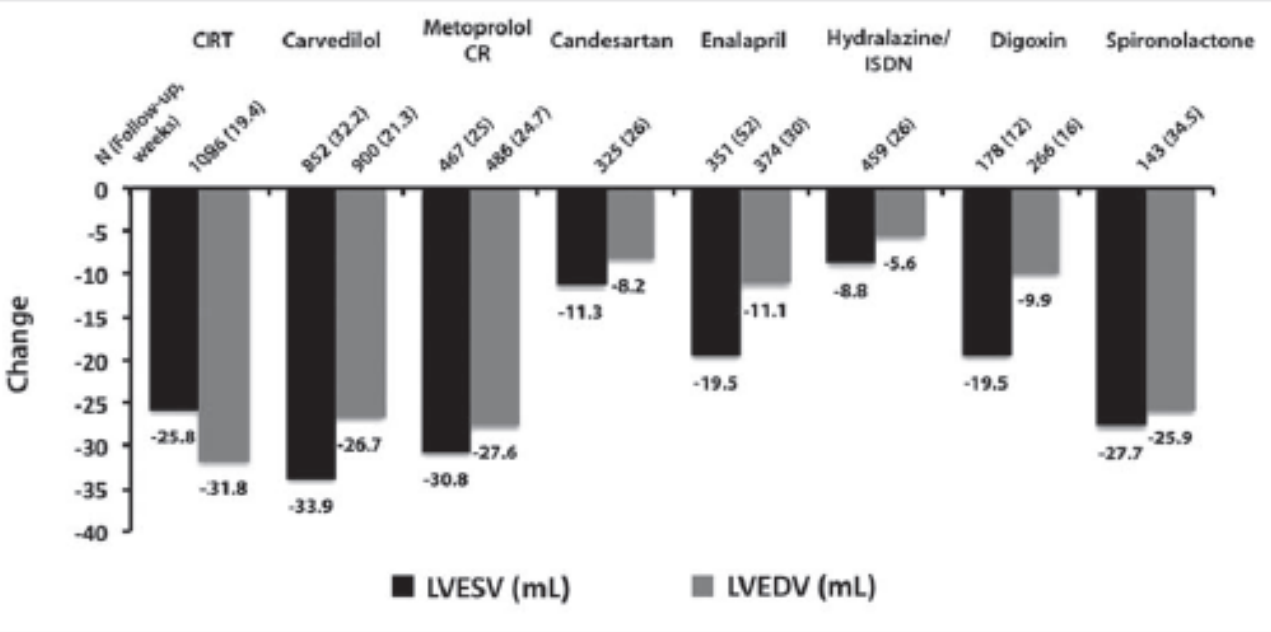


Figure 4 LV remodelling: CRT vs. medical therapy in heart failure. ISDN, isosorbide dinitrate; ESV, end systolic volume, EDV, end-diastolic volume. Adapted from Kramer *et al.*[43] References: CRT,[6,8,44,45] carvedilol,[46–56] metoprolol CR,[57–59] Candesartan,[60] Enalapril,[61–63] Hydralazine/ISDN,[64] Digoxin,[65,66] Spironolactone.[67,68]

Kramer DG JACC 2010;56:392

Trial	N Pts	NYHA	LVEF %	SR/AF	QRS ms	BBB	Morb/ Mort
MUSTIC-SR	58	III	<35%	SR	>150	NS	no
MIRACLE	453	III,IV	<35%	SR	>130	NS	no
MUSTIC AF	43	III	<35%	**AF**	>200	NS	no
PATH CHF	41	III,IV	<35%	SR	> 120	NS	no
MIRACLE ICD	369	III,IV	<35%	SR	>130	NS	no
CONTAK CD	227	II,IV	<35%	SR	>120	NS	no
MIRACLE ICD II	186	II	<35%	SR	>130	NS	no
MADIT CRT	1800	I,II	<30%	SR	>130	NS	Yes
RAFT	1800	II,III	<30%	SR/**AF**	>120	NS	yes
BLOCK HF	920/680	I-III	<50%	SR/AVB	NA	NS	yes
ECHO CRT	810	III-IV	<35%	SR	<130	NS	yes
BIOPACE	1820	Any	Any	AVB	NA	NA	Yes

12,000 pts included in >20 RCT
including six morbidity mortality trials
None had LBBB as inclusion criterium
Few (262) had AF as inclusion criterium

How sub group analysis may lead to new research questions

- The QRS width and the morphology
- Aetiology
- Female sex
- Left ventricular ejection fraction

Companion and **CARE HF** Sub group analysis

Variable	No. of Patient	
	Pharmacologic therapy (n=308)	Pacemaker (n=617)
Age		
≤65 yr	123	272
>65 yr	185	345
Sex		
Male	211	415
Female	97	202
Cardiomyopathy		
Ischemic	181	331
Nonischemic	127	285
NYHA class		
III	253	537
IV	55	80
LVEF		
≤20%	143	324
>20%	165	293
LVEDD		
≤67 mm	133	257
[illegible]	[illegible]	[illegible]
QRS interval width		
≤147 msec	115	209
148–168 msec	111	203
>168 msec	82	205
[illegible] block		
Left	215	426
Other	93	190

Group	Patients with Event/Total No. of Patients	Hazard Ratio (95% CI)
Overall	383/813	0.63 (0.51–0.77)
Age		
<66.4 yr	163/406	0.55 (0.40–0.75)
≥66.4 yr	220/407	0.68 (0.52–0.89)
Sex		
Male	290/597	0.62 (0.49–0.79)
Female	93/215	0.64 (0.42–0.97)
NYHA class		
III	349/763	0.64 (0.52–0.80)
IV	34/50	0.50 (0.25–1.01)
Dilated cardiomyopathy		
No	238/443	0.68 (0.53–0.88)
Yes	145/370	0.51 (0.36–0.73)
Systolic blood pressure		
<117 mm Hg	208/401	0.60 (0.46–0.80)
≥117 mm Hg	170/402	0.66 (0.48–0.89)
NT-BNP		
<214.5 pg/ml	122/366	0.53 (0.36–0.76)
≥214.5 pg/ml	224/366	0.70 (0.54–0.91)
Ejection fraction		
<24.7%	205/372	0.65 (0.49–0.86)
≥24.7%	152/373	0.62 (0.44–0.85)
End-systolic volume index		
<119.2 ml/m^2	156/366	0.71 (0.52–0.98)
≥119.2 ml/m^2	193/366	0.54 (0.40–0.73)
QRS interval		
<160 msec	152/290	0.74 (0.54–1.02)
≥160 msec	222/505	0.60 (0.46–0.79)

Benefit from CRT in women and men by QRS widths in MADIT CRT inclusion criteria QRS ≥ 130 ms

Table 3. Hazard Ratios for CRT-D vs ICD-Only for Primary End Point by QRS Morphology and Duration for Each Sex

	Males			Females		
	n	HR (95% CI)	*P*	n	HR (95% CI)	*P*
QRS duration						
<140 ms	240	1.69 (0.97–2.95)	0.063	61	0.20 (0.06–0.66)	0.008
140–159 ms	465	0.77 (0.52–1.12)	0.164	178	0.31 (0.15–0.63	0.001
160–179 ms	417	0.51 (0.33–0.79)	0.003	153	0.42 (0.19–0.94)	0.036
≥180 ms	242	0.50 (0.28–0.89)	0.019	61	0.33 (0.09–1.23)	0.100
QRS morphology						
LBBB*	887	0.56 (0.42–0.75)	<0.001	394	0.25 (0.15–0.41)	<0.001
Non-LBBB	477	1.25 (0.84–1.85)	0.273	59	1.55 (0.41–5.88)	0.516
RBBB	210	0.94 (0.52–1.72)	0.841	18	NA	
IVCD	267	1.49 (0.89–2.52)	0.133	41	1.31 (0.33–5.26)	0.701

In this sub-study of MADIT CRT only LBBB pts benefited

Zareba W et al Circulation 2011;123:1061

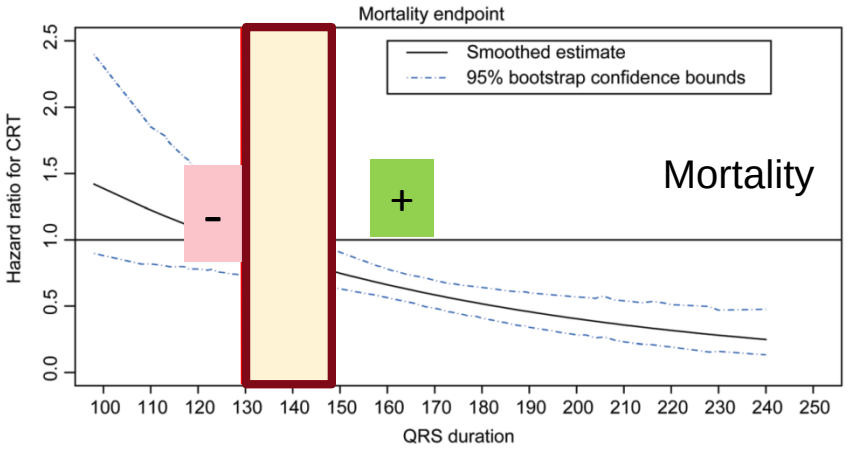
European Heart Journal (2013) 34, 3547–3556
doi:10.1093/eurheartj/eht290

FASTTRACK CLINICAL RESEARCH

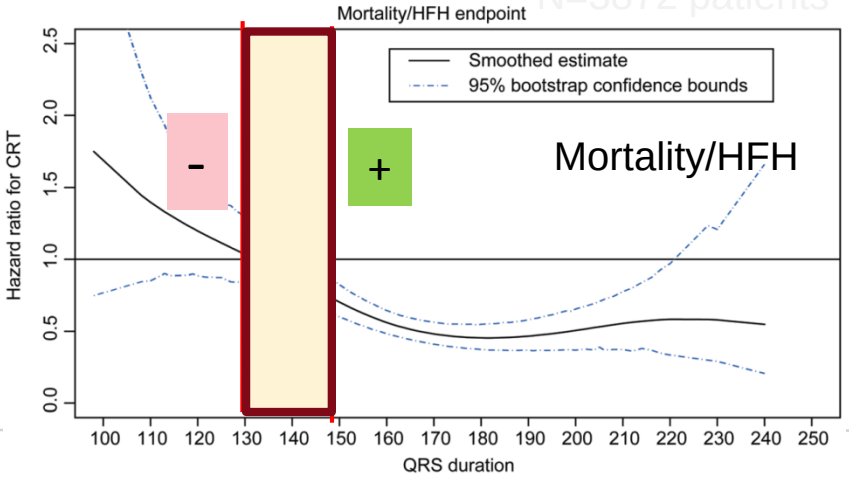
An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure

John G. Cleland[1]*, William T. Abraham[2], Cecilia Linde[3], Michael R. Gold[4], James B. Young[5], J. Claude Daubert[6], Lou Sherfesee[7], George A. Wells[8], and Anthony S.L. Tang[9]

Hazard ratios and 95% CI of benefit of CRT with regard to QRS width



N=3872 patients



Cleland J et al Eur Heart J 2013

HF guidelines and CRT indication in patients **with LBBB**

Recommendations	Class[a]	Level[b]
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B

CRT *is recommended in patients with LBBB*

Level of evidence depends on QRS width

HF guidelines and CRT indication in patients **with non-LBBB?**

CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B

CRT should or may be considered in with non- LBBB

Level of evidence depends on QRS width

Results of the EchoCRT study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiac-Resynchronization Therapy in Heart Failure with a Narrow QRS Complex

Frank Ruschitzka, M.D., William T. Abraham, M.D., Jagmeet P. Singh, M.D., Ph.D., Jeroen J. Bax, M.D., Ph.D., Jeffrey S. Borer, M.D., Josep Brugada, M.D., Ph.D., Kenneth Dickstein, M.D., Ph.D., Ian Ford, M.D., Ph.D., John Gorcsan III, M.D., Daniel Gras, M.D., Henry Krum, M.B., B.S., Ph.D., Peter Sogaard, M.D., D.M.Sc., and Johannes Holzmeister, M.D., for the EchoCRT Study Group*

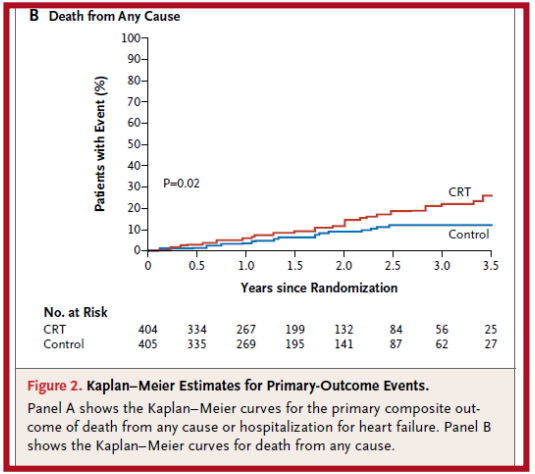


Figure 2. Kaplan–Meier Estimates for Primary-Outcome Events.
Panel A shows the Kaplan–Meier curves for the primary composite outcome of death from any cause or hospitalization for heart failure. Panel B shows the Kaplan–Meier curves for death from any cause.

As a consequence….

CRT is contra-indicated in patients with a QRS duration < 130 msec.	III	A

How sub group analysis may lead to new research questions

- The QRS width and the morphology
- Aetiology
- **Female sex**
- Left ventricular ejection fraction

Benefit from CRT in women and men by QRS widths in MADIT CRT inclusion criteria QRS ≥ 130 ms

Table 3. Hazard Ratios for CRT-D vs ICD-Only for Primary End Point by QRS Morphology and Duration for Each Sex

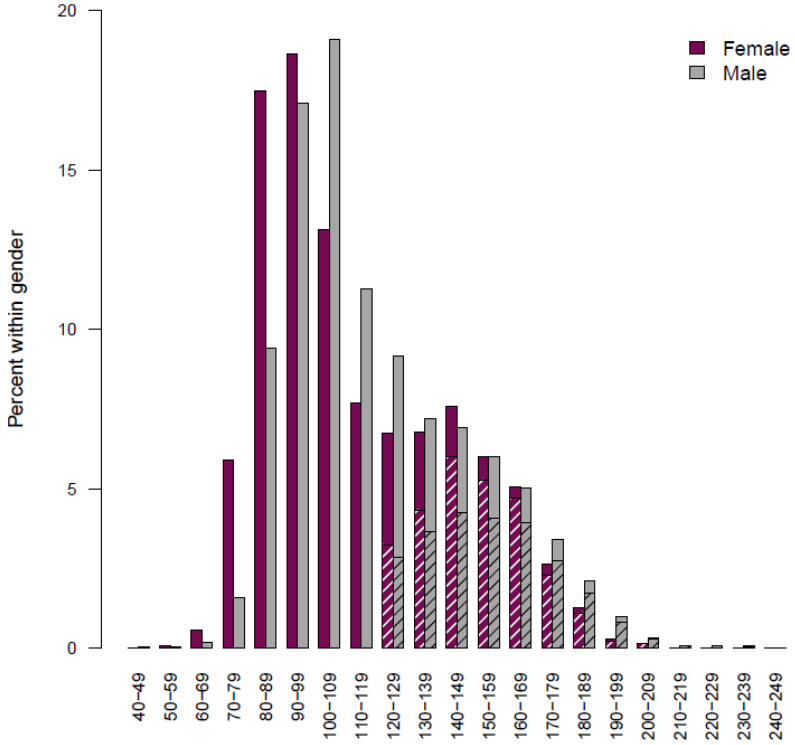
	Males			Females		
	n	HR (95% CI)	*P*	n	HR (95% CI)	*P*
QRS duration						
<140 ms	240	1.69 (0.97–2.95)	0.063	61	0.20 (0.06–0.66)	0.008
140–159 ms	465	0.77 (0.52–1.12)	0.164	178	0.31 (0.15–0.63	0.001
160–179 ms	417	0.51 (0.33–0.79)	0.003	153	0.42 (0.19–0.94)	0.036
≥180 ms	242	0.50 (0.28–0.89)	0.019	61	0.33 (0.09–1.23)	0.100
QRS morphology						
LBBB*	887	0.56 (0.42–0.75)	<0.001	394	0.25 (0.15–0.41)	<0.001
Non-LBBB	477	1.25 (0.84–1.85)	0.273	59	1.55 (0.41–5.88)	0.516
RBBB	210	0.94 (0.52–1.72)	0.841	18	NA	
IVCD	267	1.49 (0.89–2.52)	0.133	41	1.31 (0.33–5.26)	0.701

In this sub-study of MADIT CRT women benefited at lower QRS widths

ESC

Zareba W et al Circulation 2011;123:1061

QRS width and LBBB (hatched) in women and men in Swedish heart failure registry RiksSvikt 13.782 pts



LBBB in HFpts
27% in women
24% in men

Women with heart failure have smaller QRS than men and women had LBBB at smaller widths

European Journal of Heart Failure (2018) 20, 780–791
doi:10.1002/ejhf.1133

RESEARCH ARTICLE

The interaction of sex, height, and QRS duration on the effects of cardiac resynchronization therapy on morbidity and mortality: an individual-patient data meta-analysis

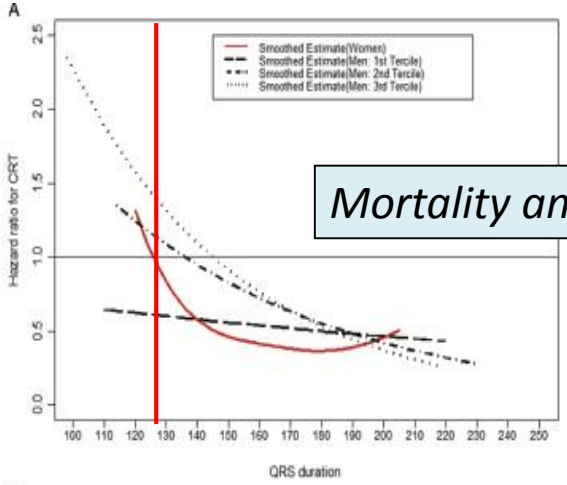
Cecilia Linde[1]*, John G.F. Cleland[2], Michael R. Gold[3], J. Claude Daubert[4], Anthony S.L. Tang[5], James B. Young[6], Lou Sherfesee[7], and William T. Abraham[8]

Women per se and men by terciles of height

Table 2 Patient characteristics by height tercile for men

	Women ($n = 794$)	Men (tercile 1) ($n = 886$)	Men (tercile 2) ($n = 935$)	Men (tercile 3) ($n = 881$)
Study				
MIRACLE	154 (19.4%)	92 (10.4%)	110 (11.8%)	123 (14.0%)
MIRACLE ICD	103 (13.0%)	95 (10.7%)	158 (16.9%)	193 (21.9%)
CARE-HF	190 (23.9%)	221 (24.9%)	170 (18.2%)	135 (15.3%)
REVERSE	112 (14.1%)	101 (11.4%)	138 (14.8%)	151 (17.1%)
RAFT	235 (29.6%)	377 (42.6%)	359 (38.4%)	279 (31.7%)
Age (years)				
Mean ± SD	64.3 ± 10.8	66.3 ± 9.6	64.7 ± 10.5	63.6 ± 10.3
Median (IQR)	65.9 (57.6–72.5)	67.7 (59.6–73.3)	65.7 (57.7–72.8)	64.6 (57.1–71.1)
Range	23.0–89.0	32.6–87.5	20.4–87.8	25.5–93.8
QRS duration (ms)				
Mean ± SD	161.8 ± 20.4	160.5 ± 22.8	159.6 ± 23.1	162.1 ± 23.8
Median (IQR)	160 (150–175)	160 (144–176)	160.0 (140.0–175.0)	160 (144–180)
Range	94–263	93 - 228	80 - 240	96–250
Height (cm)				
Mean ± SD	161 ± 8	166.3 ± 4.6	174.8 ± 2.0	182.9 ± 4.0
Median (IQR)	160 (156–166)	167.6 (165.1–169.9)	175.0 (173.0–176.8)	182.9 (180.1–185.4)
Range	121–186	132.1–171.5	172.0–177.8	178.1–200.7

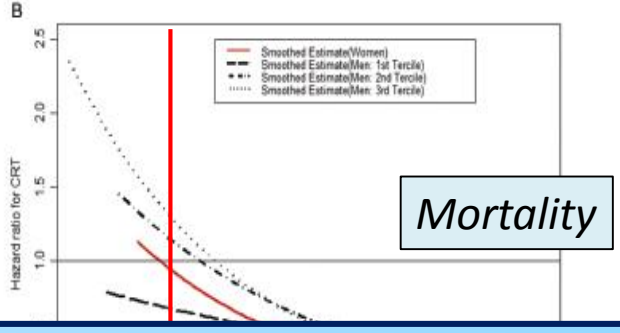
Height and response to CRT in women and men by height tertiles



Mortality and HFH

women

Shortest tertile of men



Mortality

Female sex was not independent predictor of CRT benefit and short men (< 165 cm) benefited over a wide range of QRS widths

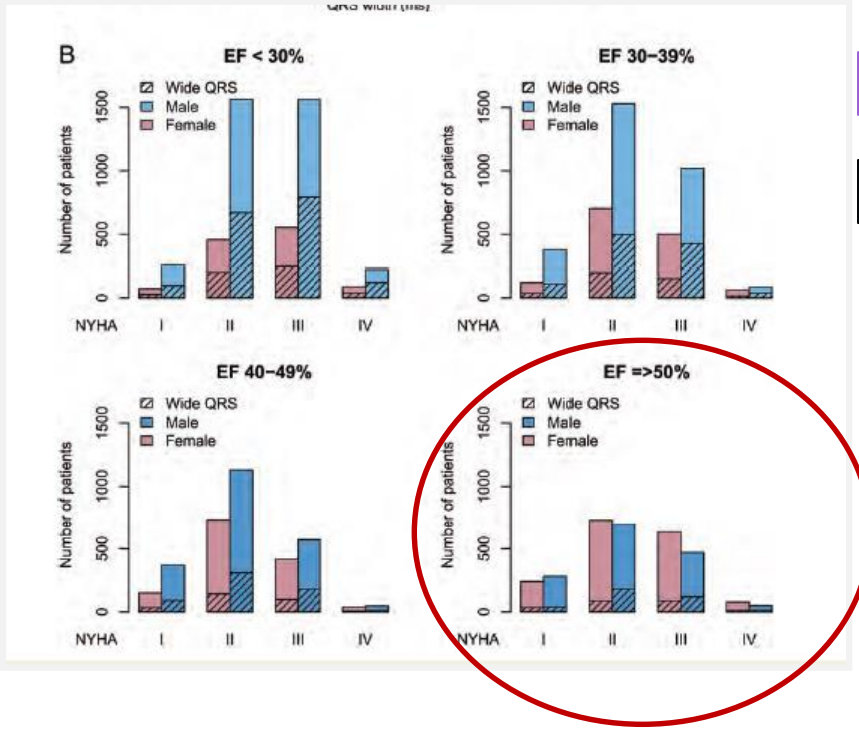
QRS duration

How sub group analysis may lead to new research questions

- The QRS width and the morphology
- Aetiology
- Female sex
- **Left ventricular ejection fraction**

LVEF and QRS width distribution by gender in the Swedish HF registry in 25.171 pts

Lund LH et al Eur Heart J 2013; 34:529



Women

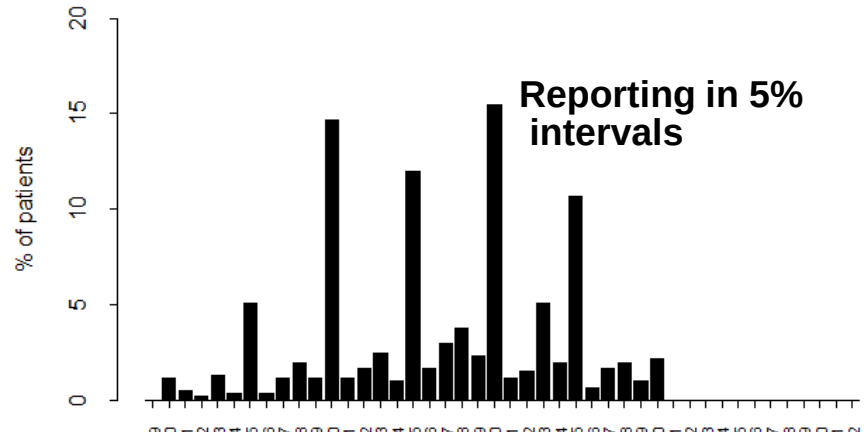
Men

Less women had HFrEF and more LVEF > 40%

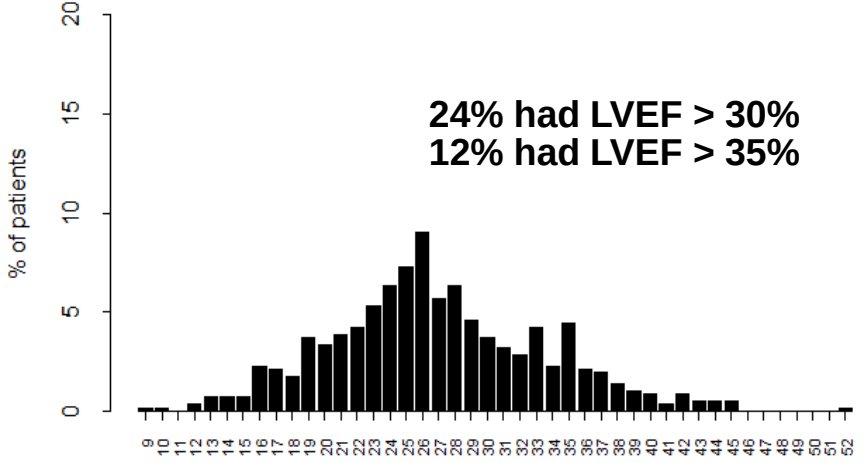
REVERSE a RCT in NYHA I/II HF n=610

distribof baseline LVEF (Inclusion criteria LVEF ≤ 40%) mean LVEF 28%

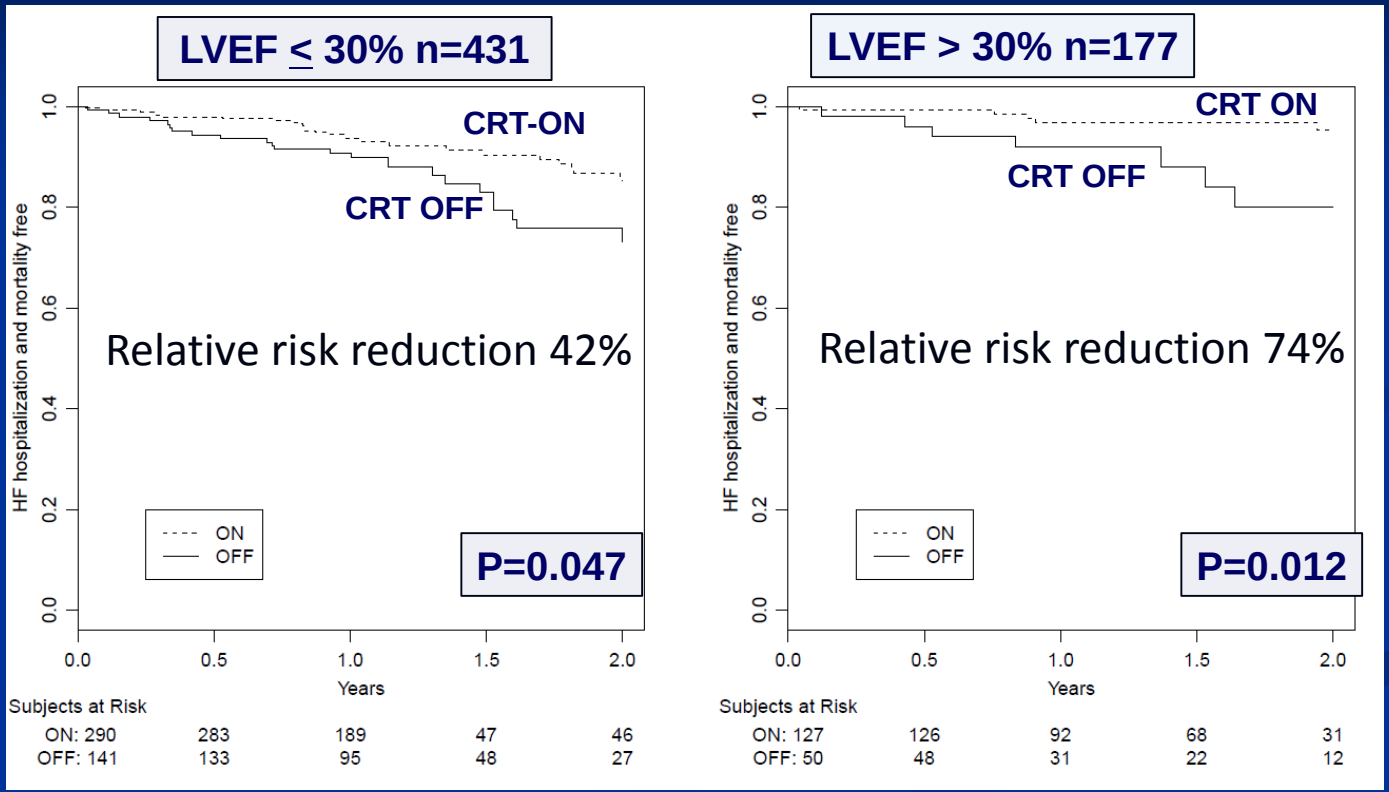
LVEF by Center



LVEF by Core Lab

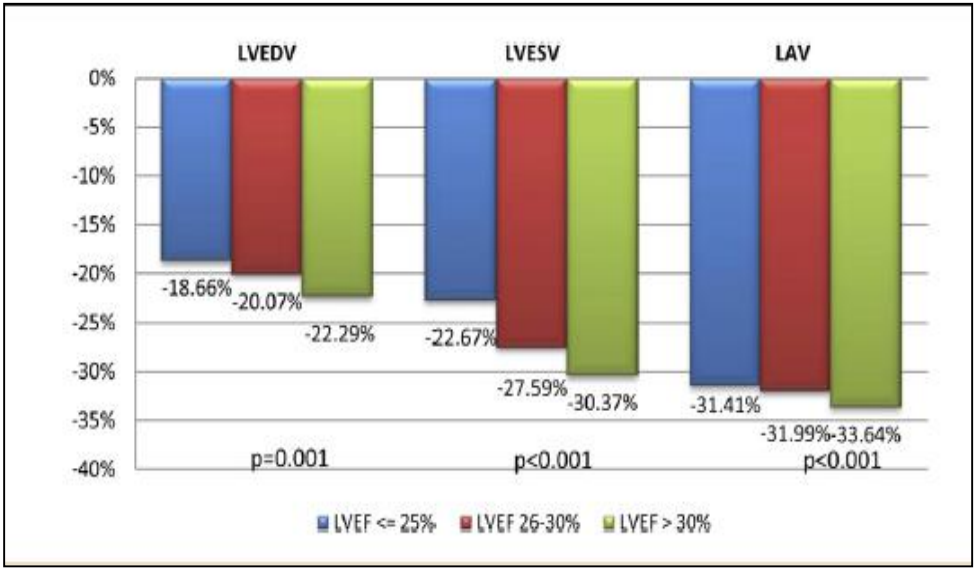


Time to HF hosp or death in REVERSE patients with LVEF ≤ 30% or > 30%



Linde et al Circ HF 2013;6:1180

Results of MADIT CRT in CRT vs control as regards reverse remodeling by LVEF



Kutfyia V et al JACC 2013

ESC

International Journal of Cardiology 202 (2016) 349–355

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HFA Heart Failure Association

Cardiac resynchronization therapy in chronic heart failure with moderately reduced left ventricular ejection fraction: Lessons from the Multicenter InSync Randomized Clinical Evaluation MIRACLE EF study

Cecilia Linde [a,*], Anne B
Francisco Levya [g], Shin-

Table 1
Inclusion and exclusion criteria in the MIRACLE EF study.

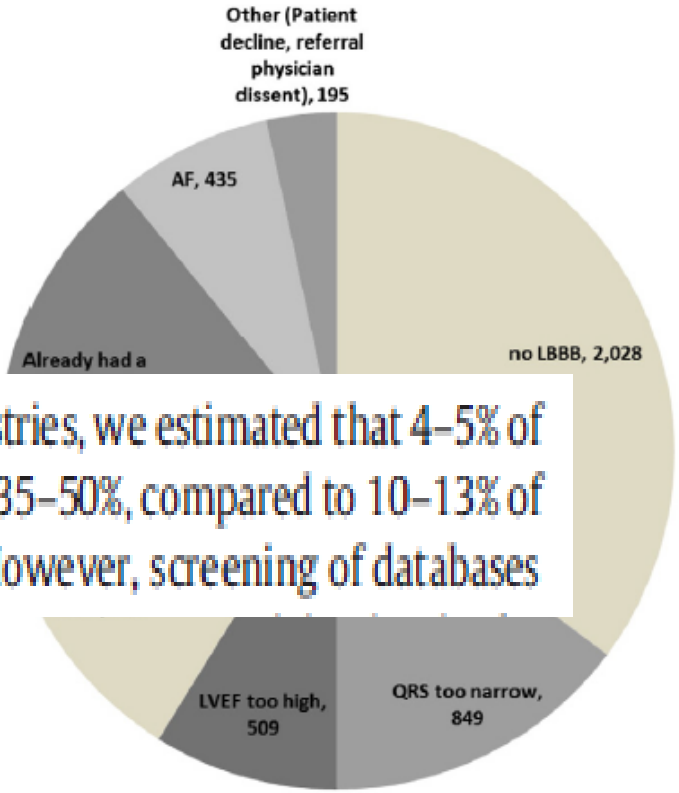
Inclusion criteria
Chronic heart failure > 90 days in duration
LVEF between 36% to 50%
LBBB with QRS ≥ 130 ms
Patient is either
A. NYHA Class III OR
B. NYHA Class II, with hospitalization for HF in the last 12 months OR
C. NYHA Class II, without hospitalization for HF, but with BNP ≥ 250 pg/ml or NT-proBNP > 1000 pg/ml
Sinus rhythm at time of enrollment
Sinus rhythm at time of enrollment
Optimal medical therapy per guidelines for Heart Failure, Ischemic Heart Disease (IHD), Hypertension and Atrial Fibrillation, as applicable
No change in non-diuretic heart failure medical therapy within prior 30 days
Able to receive pectoral implant
Able to receive pectoral implant
Signed and dated informed consent
Expected to remain available for follow-up visits
Willing and able to comply with the Clinical Investigation Plan

ESC

Powered Study Objectives

- Primary Efficacy: Time to first event defined as:
  - **All-cause mortality**, or
  - **HF Event**, defined as either:
    - Inpatient hospitalization for HF, or
    - Outpatient event requiring invasive clinical intervention and management for HF (i.e. IV diuretics, ultrafiltration, or equivalent) and overnight stay
- Primary Safety: System-related Complication-free at 6 months > 80%

MIRACLE EF terminated due to Low recruitment



Based on available national HF registries, we estimated that 4–5% of HF patients have both LBBB and an EF 35–50%, compared to 10–13% of HF patients with LVEF <35% [10,11]. However, screening of databases

25 centers searched records of 60,372 HF patients. Filtering by QRS, LVEF or both, yielded 5,754 potential candidates (average of 230 per site) who were then screened manually.

HFA
Heart Failure
Association

Conclusion

More benefit from CRT with LBBB and with longer QRS duration *but the two go togehter*

Women may benefit more but reason unclear
Size or sex?

CRT may be benefical across a wider range of low LVEFs in HFrFEF

Conclusion

Sub group analysis never give the truth

Meta-analysis are helpful

But Randomised studies are s needed
Or at least studies powered to answer the question
e.g. women vs men