Advances in Cardiac Arrhythmias and Great Innovations in Cardiology
XXVII Giornate Cardiologiche Torinesi
Turin, 23-24 October 2015

How to Select the Best Cardiac Resynchronization Therapy Candidate

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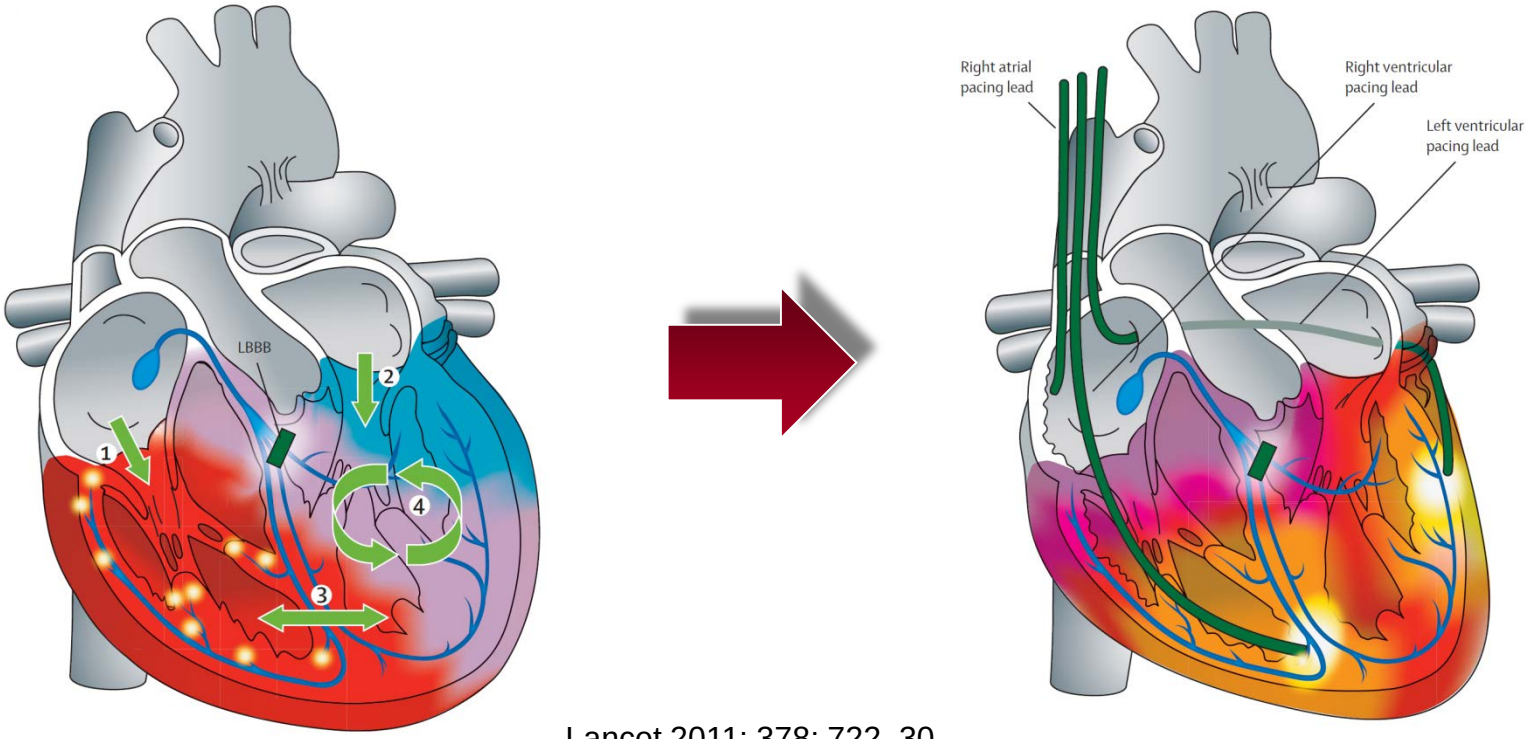
Disclosures

I do not have any conflict of interest to declare

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is an established treatment in symptomatic HF patients with reduced left ventricular EF and left bundle branch block (LBBB)



Lancet 2011; 378: 722–30

Cardiac Resynchronization Therapy

LBBB → **CRT**

Science Translational Medicine/AAAS.
Johns Hopkins Institute for Computational Medicine

- **Functional outcome**
  Cazeau S et al. NEJM 2001; 344:873-80
- **Survival outcome**
  Cleland J et al. NEJM 2005; 352:1539-49

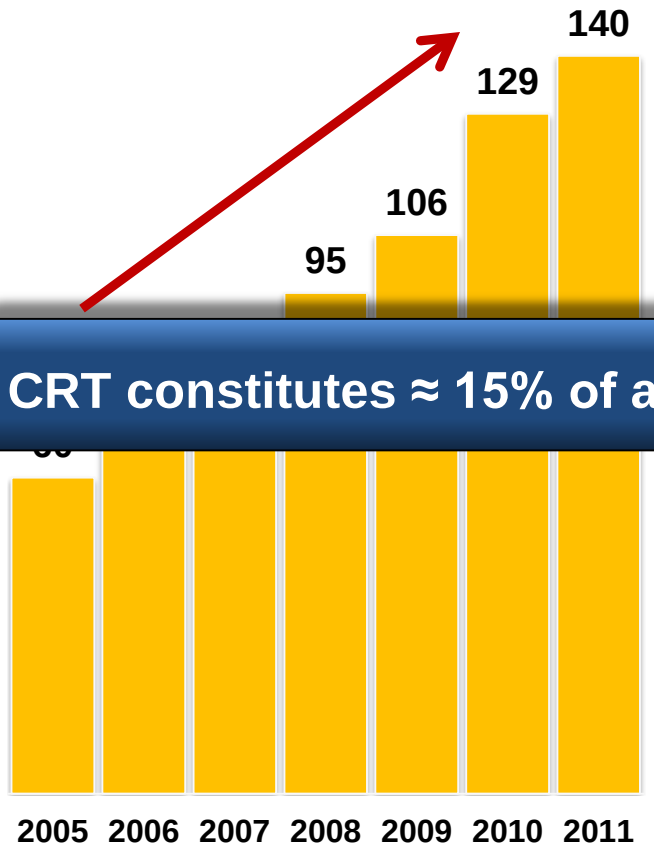
Evidence based GL

ESC HF GL EHJ 2012; 33:1787-847
ESC Pacing/CRT GL EHJ 2013; 34:2281-329

CRT Implementation in Europe

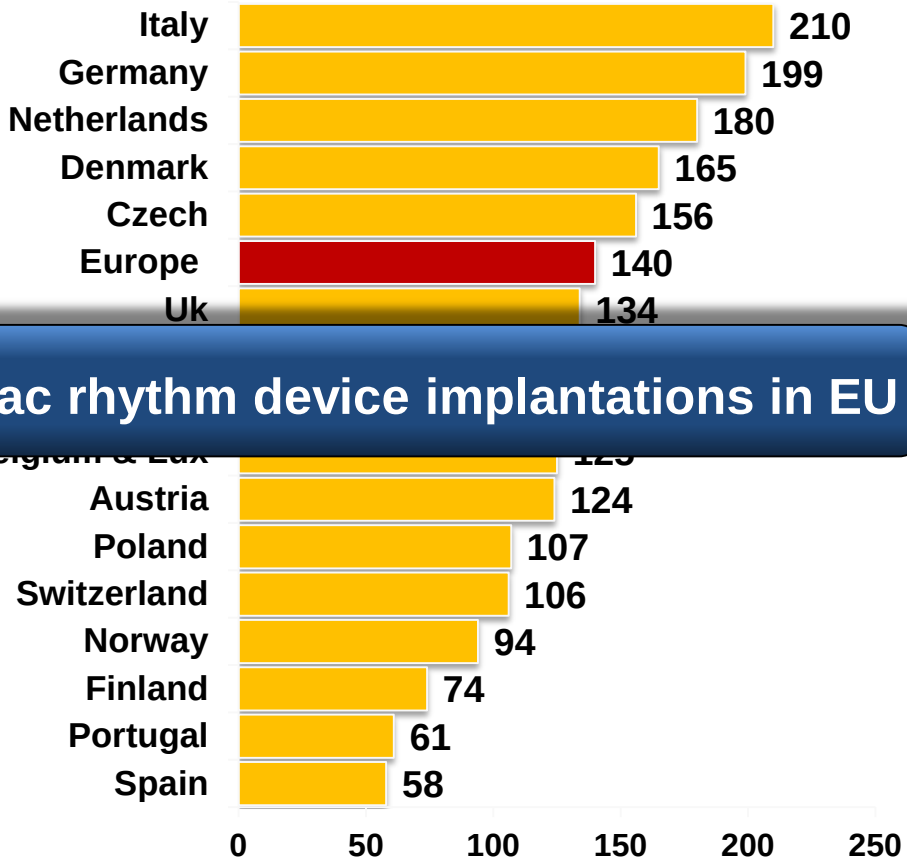
CRT Implantation - Trend

Units per million inhabitants



CRT in 2011 Implantation

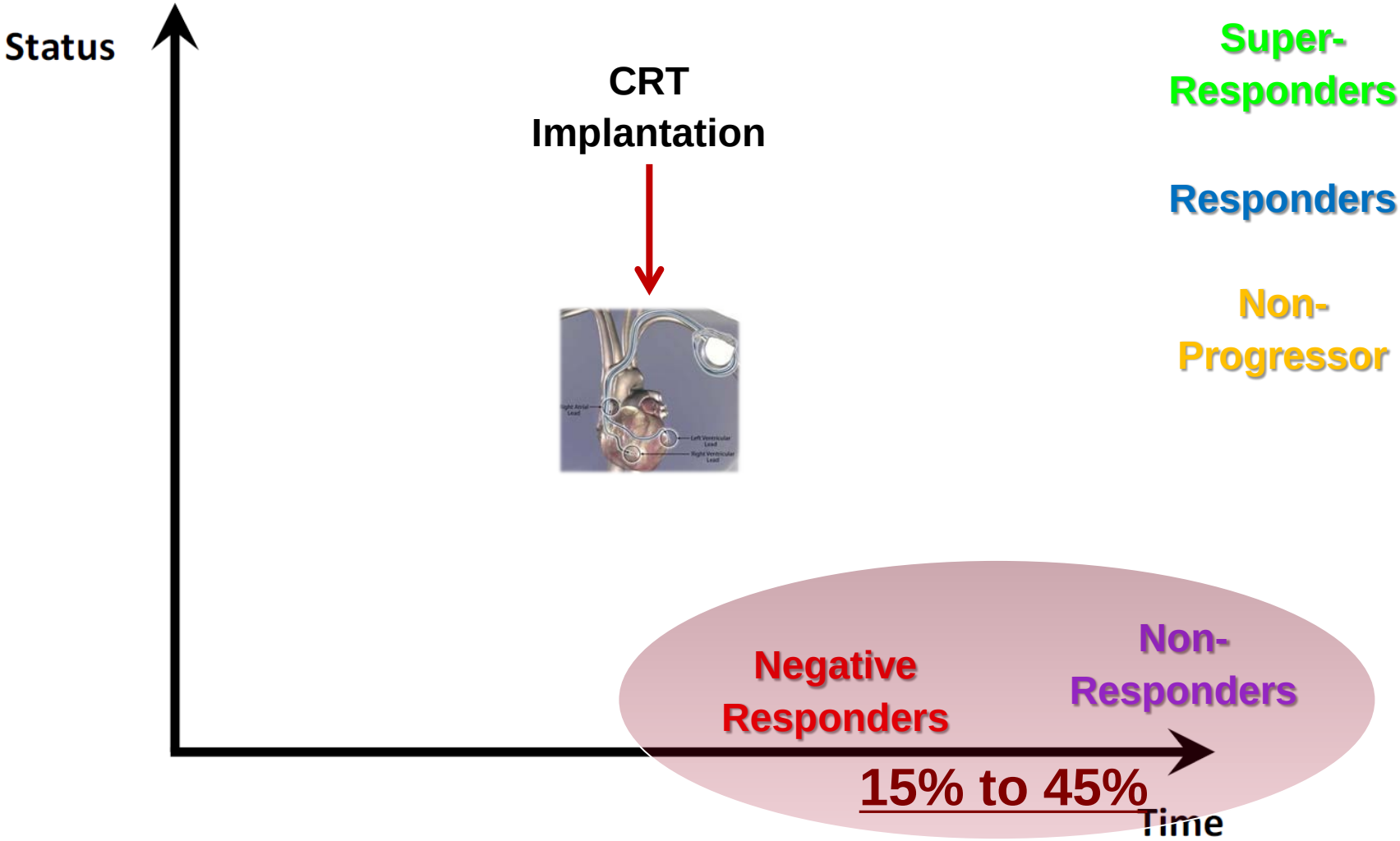
Units per million inhabitants



CRT constitutes ≈ 15% of all cardiac rhythm device implantations in EU

Source: eucomed (www.eucomed.org)

Possible Clinical Courses After CRT



Adapted from Steffel J, Ruschitzka F Circulation 2014; 130:87-90

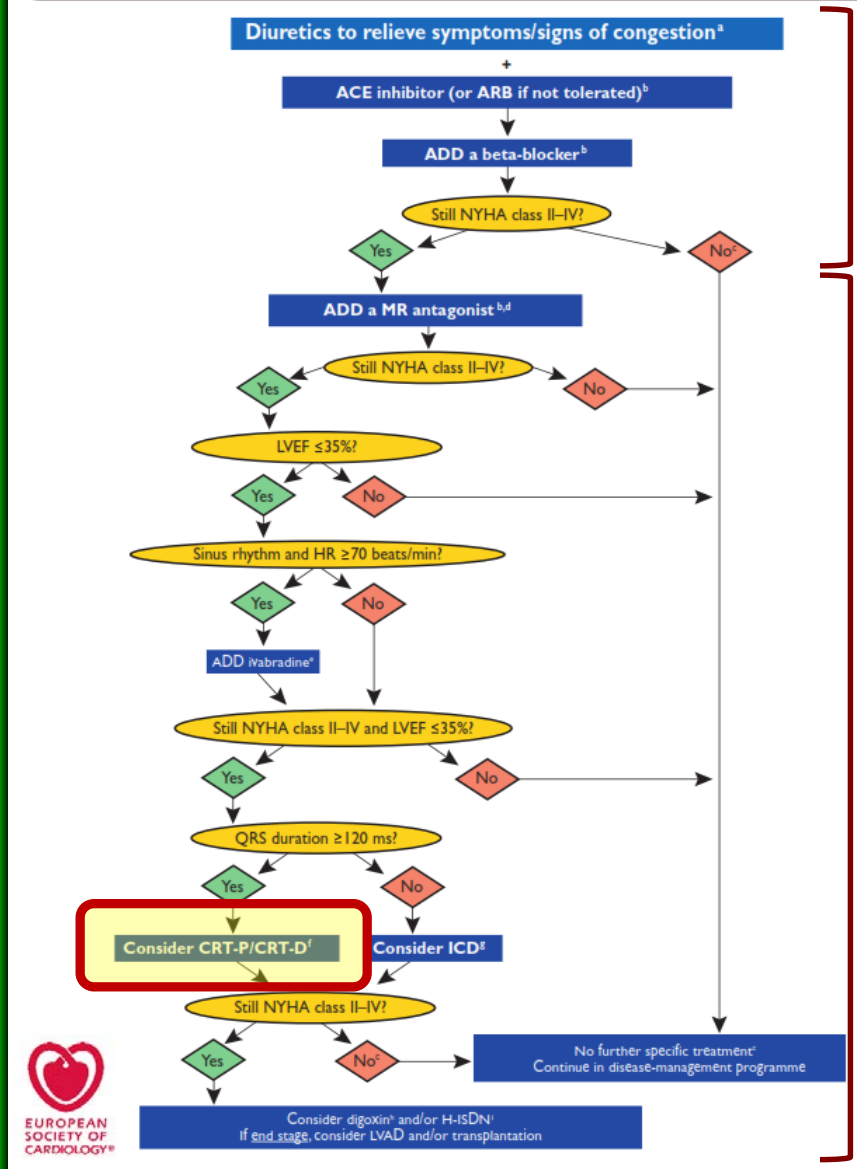
Avoiding Non-responders to CRT

1. Careful patient selection

2. Optimize pacing delivery

3. Optimize device programming

When should we consider CRT?



Reduced LVEF (≤40%) + Symptoms/signs

- ACE-I/ARBs or ARNI
- β-blockers
- Diuretics

Reduced LVEF (≤35%) + Symptoms/signs

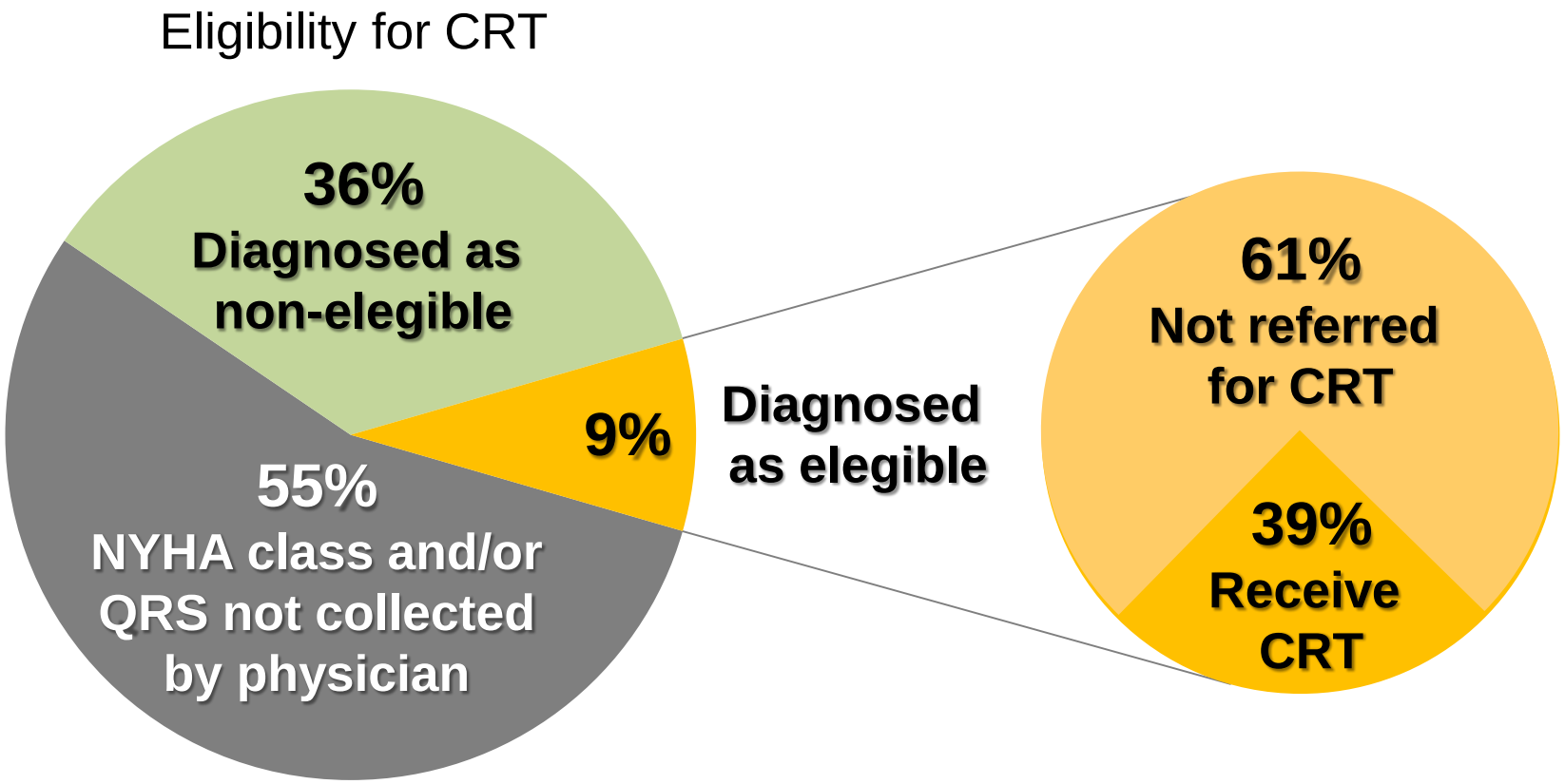
- Mineralcorticoid antag.
- Ivabradine
- Digoxin
- Hydralazine / ISDN
- Devices (ICD, CRT)
- VAD / Transplantation

Eur Heart J 2012; 33;1787–1847

Most indicated patients do not receive CRT

IMPROVE-HF Registry

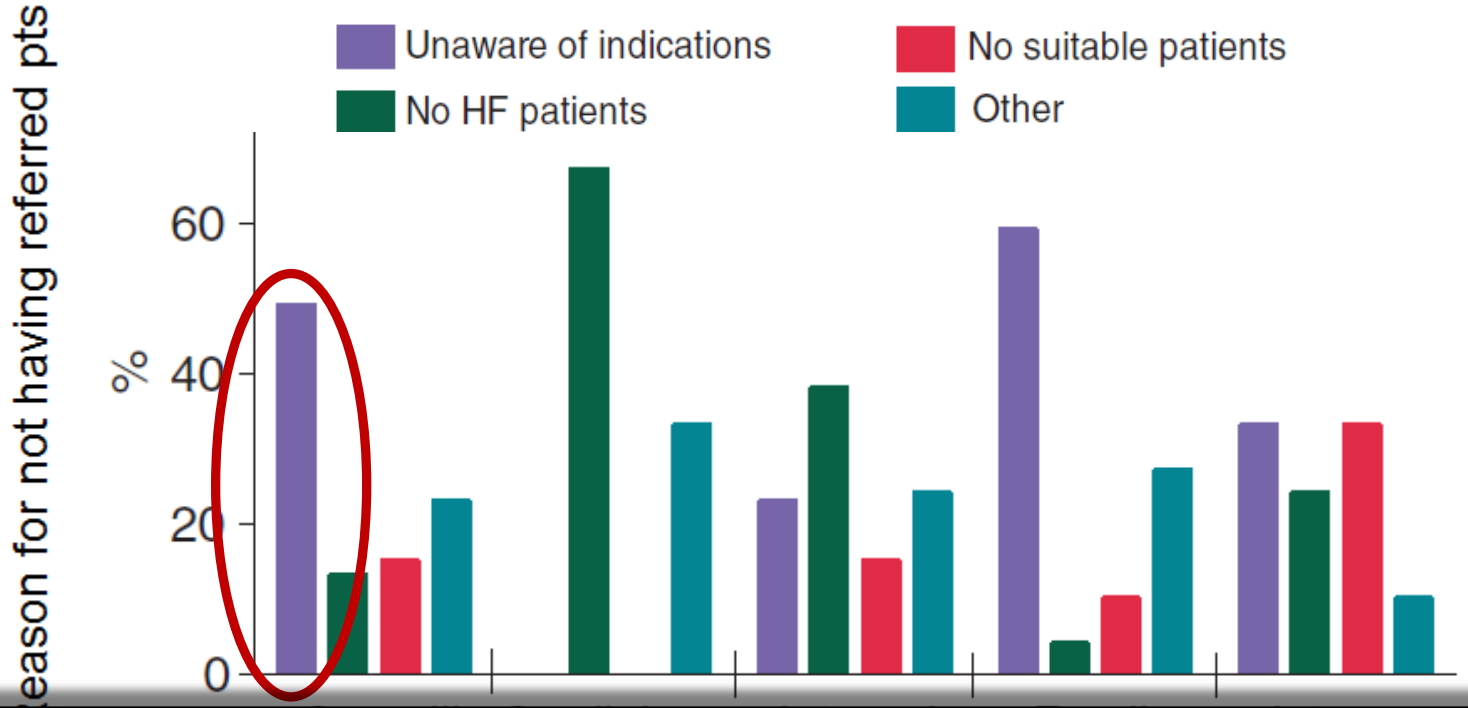
15381 outpatients pts with HF



Dickstein K HFA ESC 2012

Awarness gap in CRT indications

Survey among 519 Swedish Physicians
168 (37%) Responders



In 45% of cases, referall for CRT was denied because of unawareness

Hubinette et al. Europace 2014; 16;1580–1586

2013 ESC GL on Pacing and CRT Patients in Sinus Rhythm

Recommendations	Class [a]	Level [b]
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
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

Recommendations	Class [a]	Level [b]
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
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

Recommendations	Class [a]	Level [b]
5) CRT in patients with chronic HF with QRS duration <120 ms is not recommended.	III	B

Eur Heart J 2013; 34;2281–2329

Different Patterns of CRT Candidates

Optimal Medical Therapy

Optimal Medical Therapy (OMT) among CRT-D Candidates

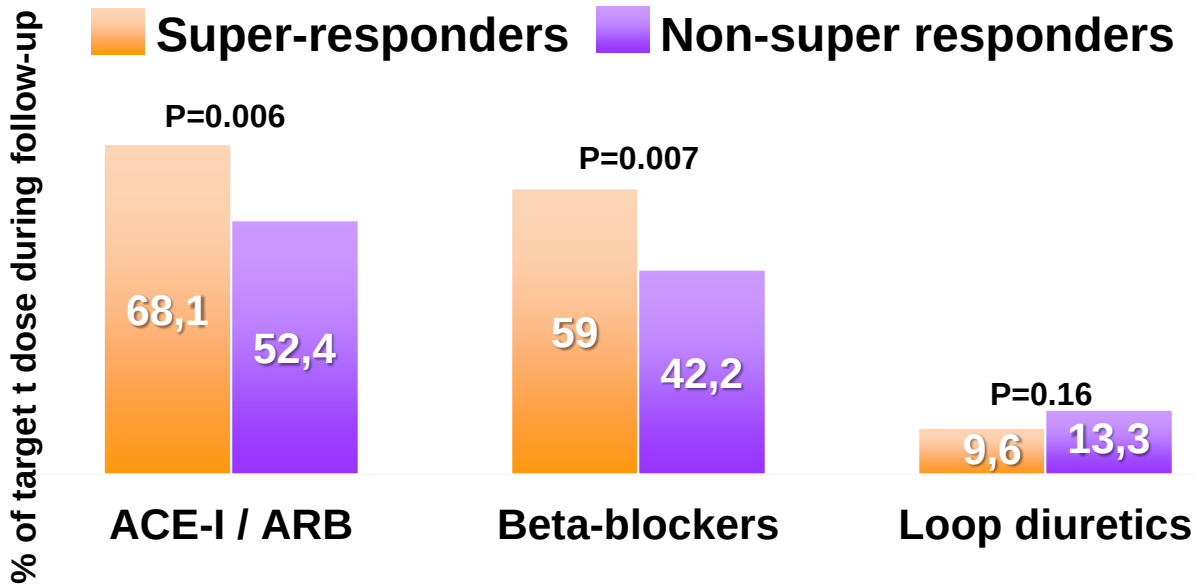
45392 Patients in the NCDR Registry undergoing CRT-D implantation between 2006-2008

Description	N (%)
Beta-blocker	39190 (87.4%)
Agiotensing converting enzyme inhibitor (ACE-I)	28029 (64.2%)
Angiotensin II receptor inhibitor (ARB)	8270 (18.6%)
Beta-blocker + ACE-I / ARB	31090 (70.3%)

Schneider PM et al. Am J Cardiol 2014; 113;2052–2056

Treatment with Higher Doses of EBM Therapy and CRT Outcome

N = 185
FU: 45 m

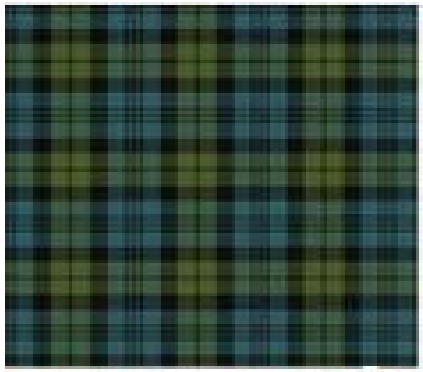


All-cause death / Transpl. / LVAD	HR (95% CI)	P-value
ACE-I / ARB	0.980 (0.969-0.992)	0.001
Beta-blocker	0.982 (0.971-0.994)	0.003
Loop diuretics	1.023 (1.005-1.041)	0.014

Adjusted for: QRS duration, bundle branch block, LVEF at baseline, Δ LVEF at follow-up, medications

Schmidt S et al. Eur Heart J 2014; 35;1051–1060

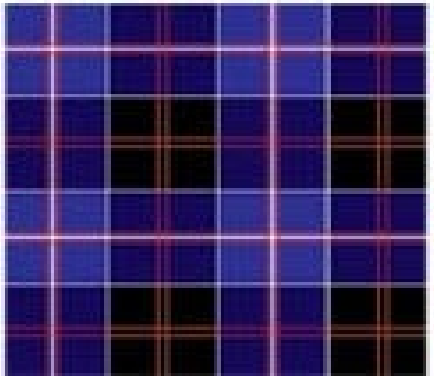
Different Patterns of CRT Candidates





NYHA Class

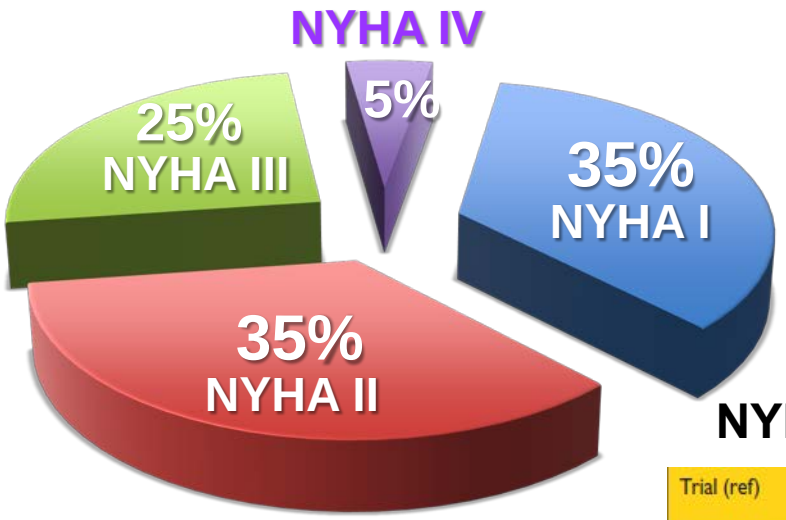


HF Population by NYHA Class

NYHA III or IV Ambulatory

Trial (ref)	No.	Design	NYHA
MUSTIC-SR[52]	58	Single-blinded, crossover, randomized CRT vs. OMT, 6 months	III
PATH-CHF[51]	41	Single-blinded, crossover, randomized RV vs. LV vs. BiV, 12 months	III–IV
MIRACLE[49]	453	Double-blinded, randomized CRT vs. OMT, 6 months	III–IV
MIRACLE-ICD[54]	369	Double-blinded, randomized CRT-D vs. ICD, 6 months	III–IV
CONTAK-CD[53]	490	Double-blinded randomized CRT-D vs. ICD, 6 months	II–III–IV
COMPANION[55]	1520	Double-blinded randomized OMT vs. CRT-P / or vs. CRT-D, 15 months	III–IV
CARE-HF[56]	813	Double-blinded randomized OMT vs. CRT-P 29.4 months	III–IV

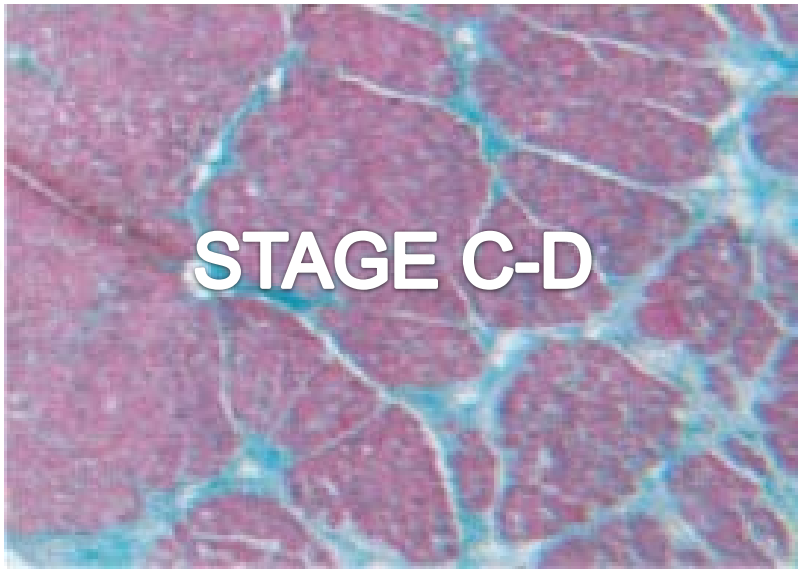


NYHA I or II (≈70%)

Trial (ref)	No.	Design	NYHA
MIRACLE-ICD II[60]	186	Double-blinded, randomized CRT-D vs. ICD, 6 months	II
REVERSE[61]	610	Double-blinded, randomized CRT-ON vs. CRT-OFF, 12 months	I–II
MADIT-CRT[50]	1820	Single-blinded, randomized CRT-D vs. ICD, 12 months	I–II
RAFT[62]	1798	Double-blinded, randomized CRT-D vs. ICD 40 months	II–III

How Long Should We Wait Before CRT?

NYHA I-II → **NYHA III-IV**



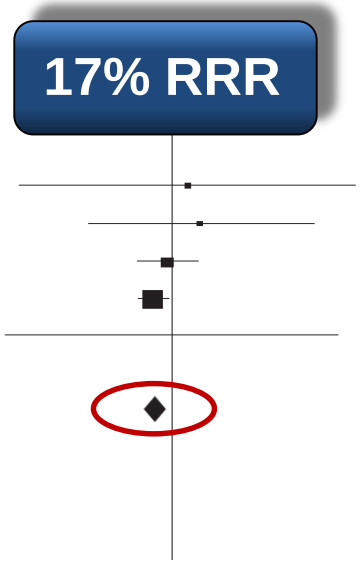
CRT in NYHA Class II Acts by Limiting Progression of HF Syndrome

CRT in Mild Heart Failure – Meta-analysis

All-cause mortality

Study, Year (Reference)	CRT Group, *n* Events	CRT Group, *n* Total	Control Group, *n* Events	Control Group, *n* Total	Weight, %	Risk Ratio (95% CI)
Predominantly NYHA class I/II						
MIRACLE ICD II, 2004 (36)	2	85	2	101	0.3	1.19 (0.17–8.26)
REVERSE, 2008 (11)	9	419	3	191	0.7	1.37 (0.37–4.99)
MADIT-CRT, 2009 (12)	74	1089	53	731	9.7	0.94 (0.67–1.32)
RAFT, 2010 (13)	186	894	236	904	39.6	0.80 (0.67–0.94)
Greater-EARTH, 2010 (27)	2	61	2	60	0.3	0.98 (0.14–6.76)
van Geldorp et al, 2010 (26)	0	19	0	18		Not estimable
Subtotal (95% CI)		2567		2005	50.5	0.83 (0.72–0.96)
Total events	273		296			
Heterogeneity: $Tau^2 = 0.00$; chi-square = 1.46; $P = 0.83$; $I^2 = 0\%$						
Test for overall effect: $Z = 2.43$; $P = 0.01$						

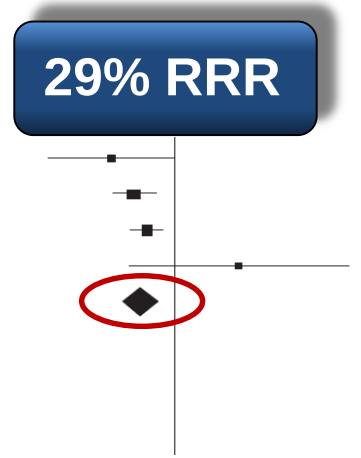
17% RRR



HF Hospitalization

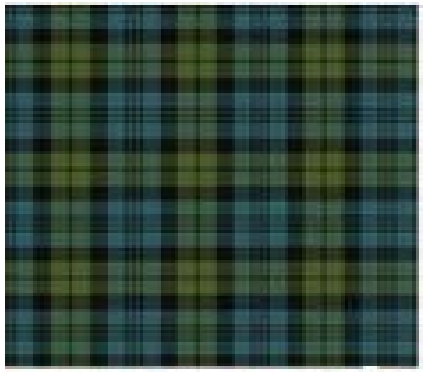
Study, Year (Reference)	CRT Group, *n* Events	CRT Group, *n* Total	Control Group, *n* Events	Control Group, *n* Total	Weight, %	Risk Ratio (95% CI)
Predominantly NYHA class I/II						
REVERSE, 2008 (11)	17	419	15	191	4.9	0.52 (0.26–1.01)
MADIT-CRT, 2009 (12)	136	1089	140	731	14.9	0.65 (0.53–0.81)
RAFT, 2010 (13)	174	894	236	904	16.3	0.75 (0.63–0.89)
Greater-EARTH, 2010 (27)	8	61	4	60	2.0	1.97 (0.63–6.19)
Subtotal (95% CI)		2463		1886	38.1	0.71 (0.57–0.87)
Total events	335		395			
Heterogeneity: $Tau^2 = 0.02$; chi-square = 4.79; $P = 0.19$; $I^2 = 37\%$						
Test for overall effect: $Z = 3.30$; $P = 0.001$						

29% RRR



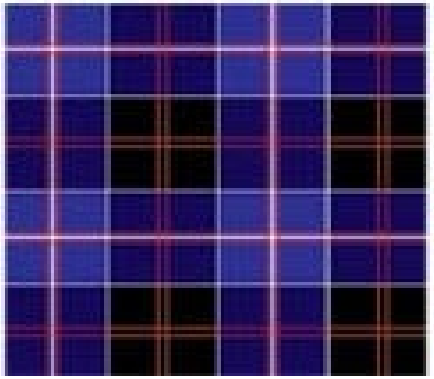
Al-Majed et a. Ann Intern Med 2011; 154: 401-412

Different Patterns of CRT Candidates

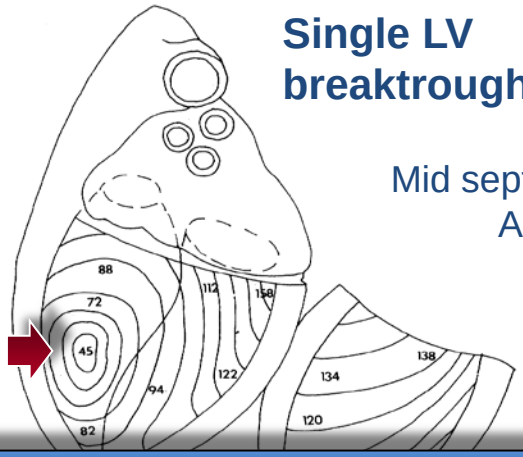


QRS

Morphology

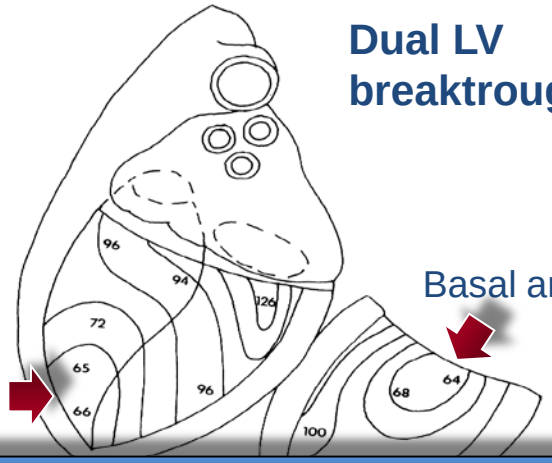


Electrical Activation in Left Bundle Branch Block



Single LV breaktrough point 67%

Mid septum: 9/12
Apex: 3/12

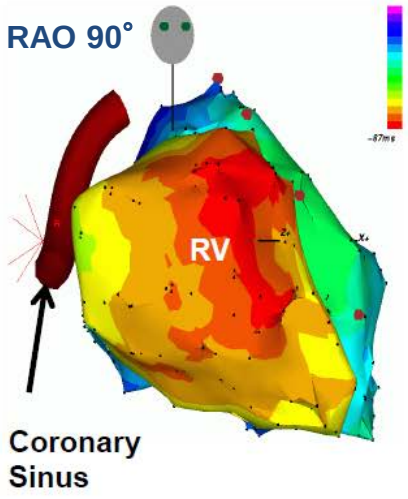


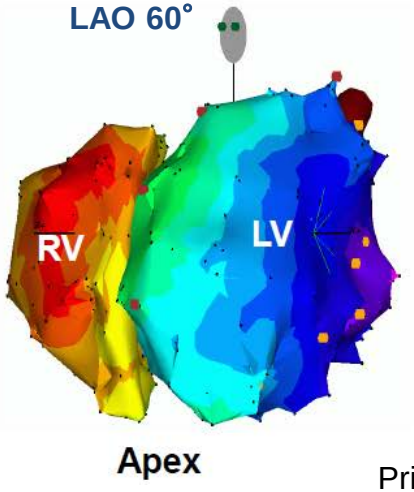
Dual LV breaktrough point 33%

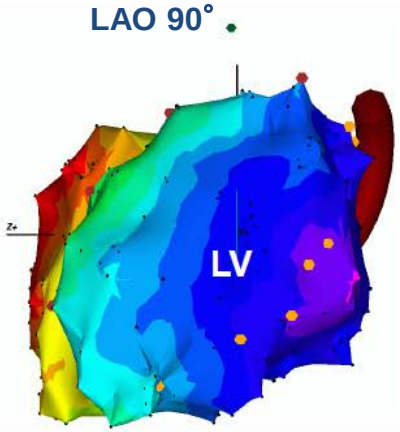
Mid septum: 5/6
Apex: 1/6

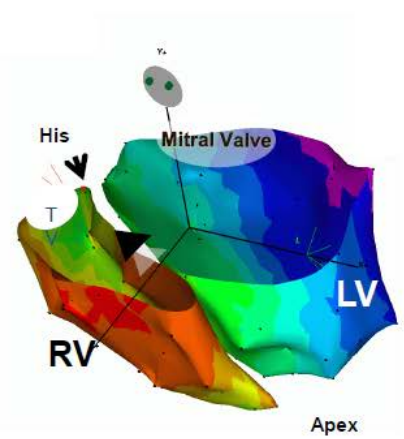
Basal anter free wall: 3/6
Apex: 2/6
Sup base: 1/6

In pts with LBBB there is significant delay between activation of the interventricular septum and activation of the left ventricular free wall



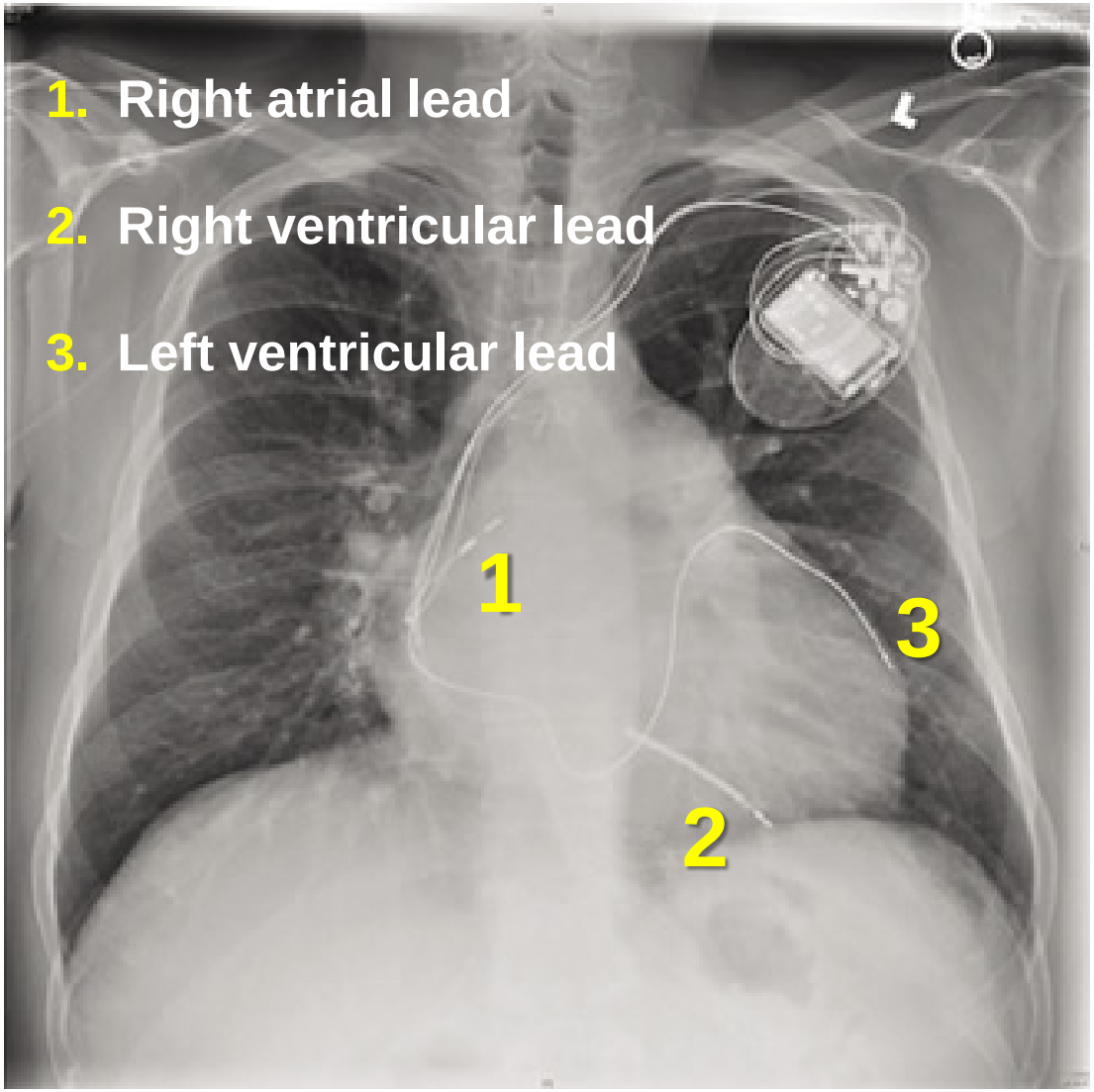




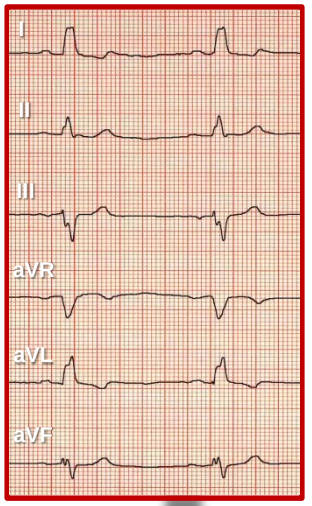


Prinzen FW, Auricchio A Circ Cardiovasc Imaging 2008; 1: 70-78

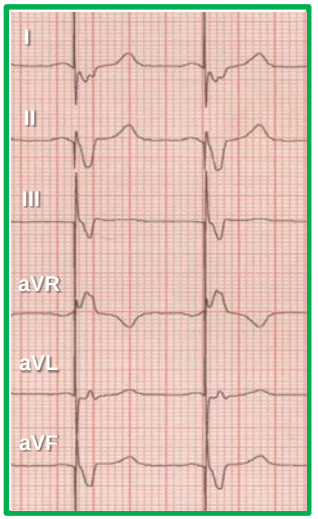
LBBB Is the Primary Target of CRT



LBBB

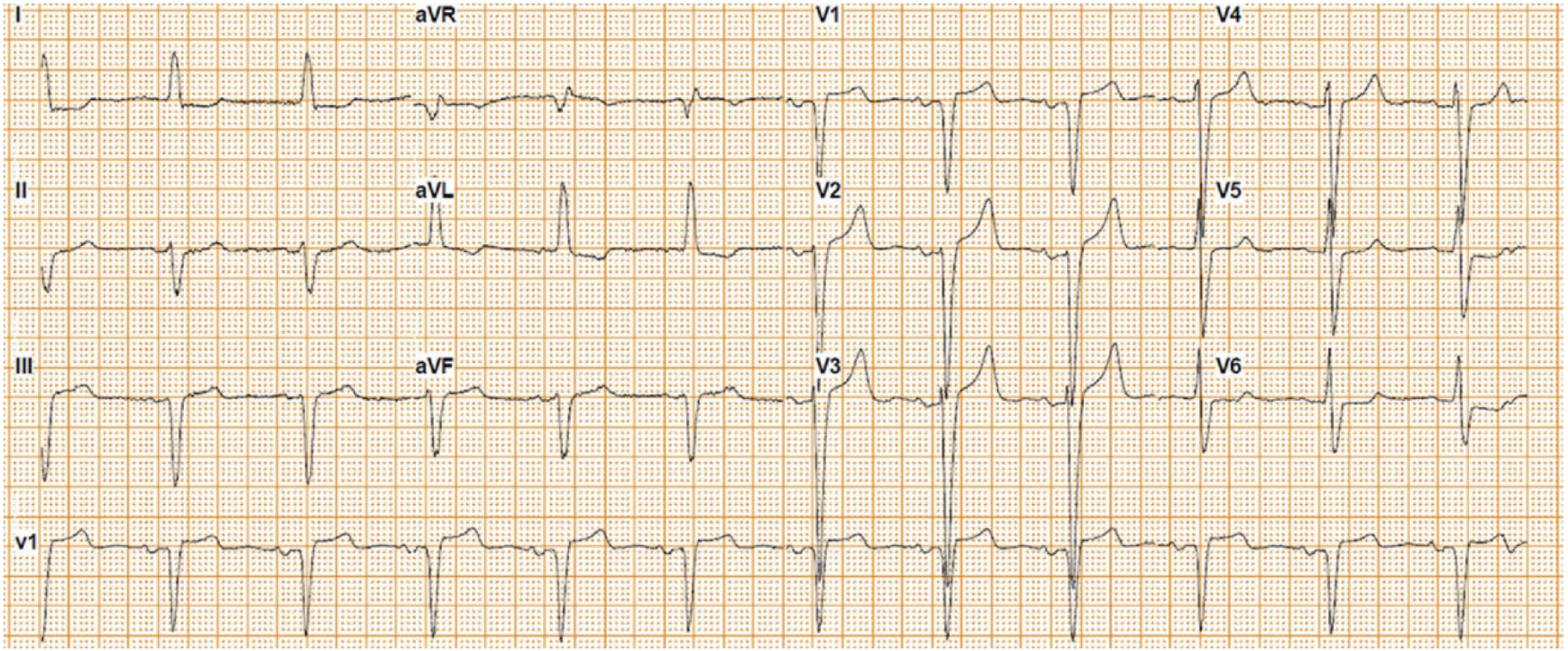


Biv Pacing



Is this Left Bundle Branch Block?

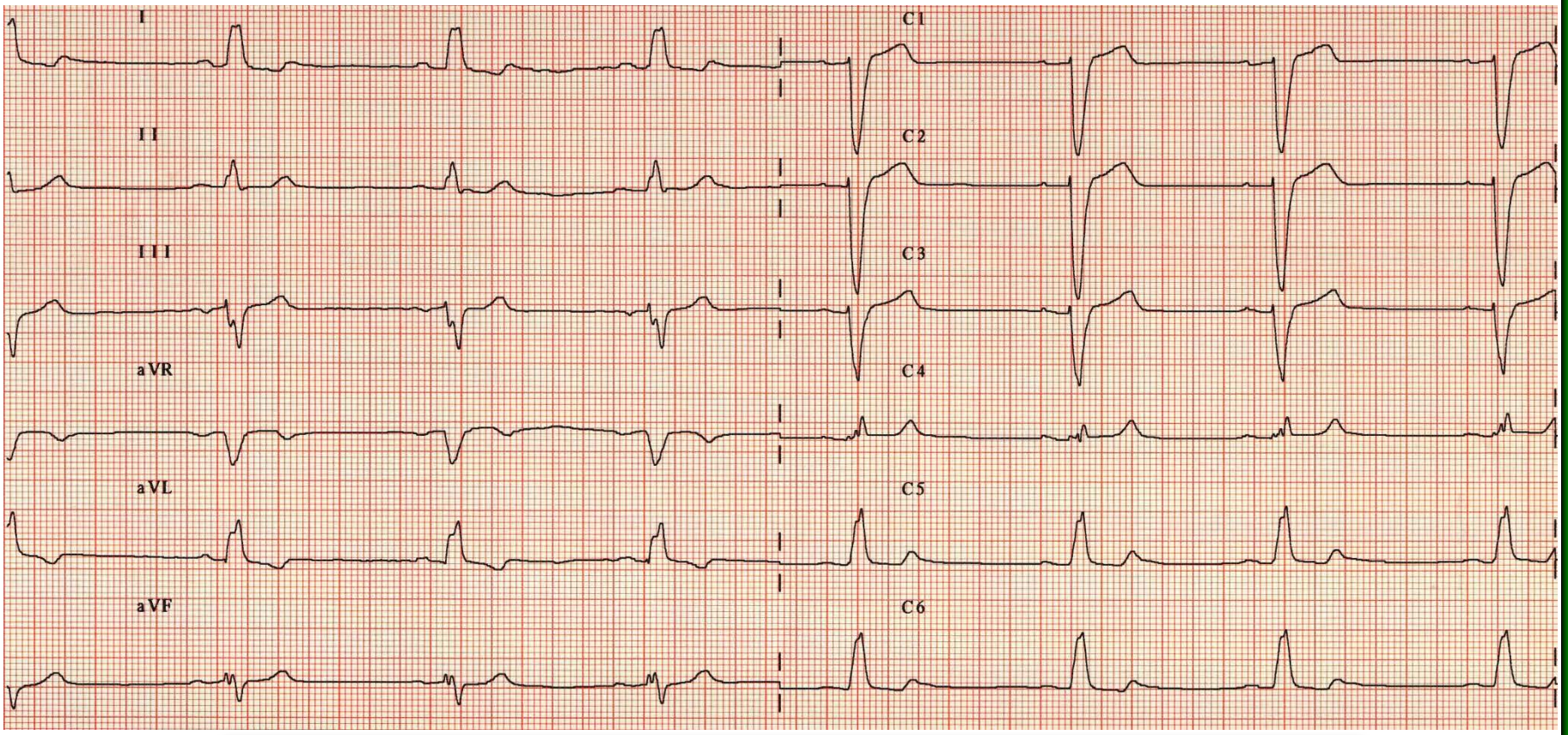
QRS Duration ≈ 120 msec



Left ventricular hypertrophy with left anterior hemiblock → No LBBB

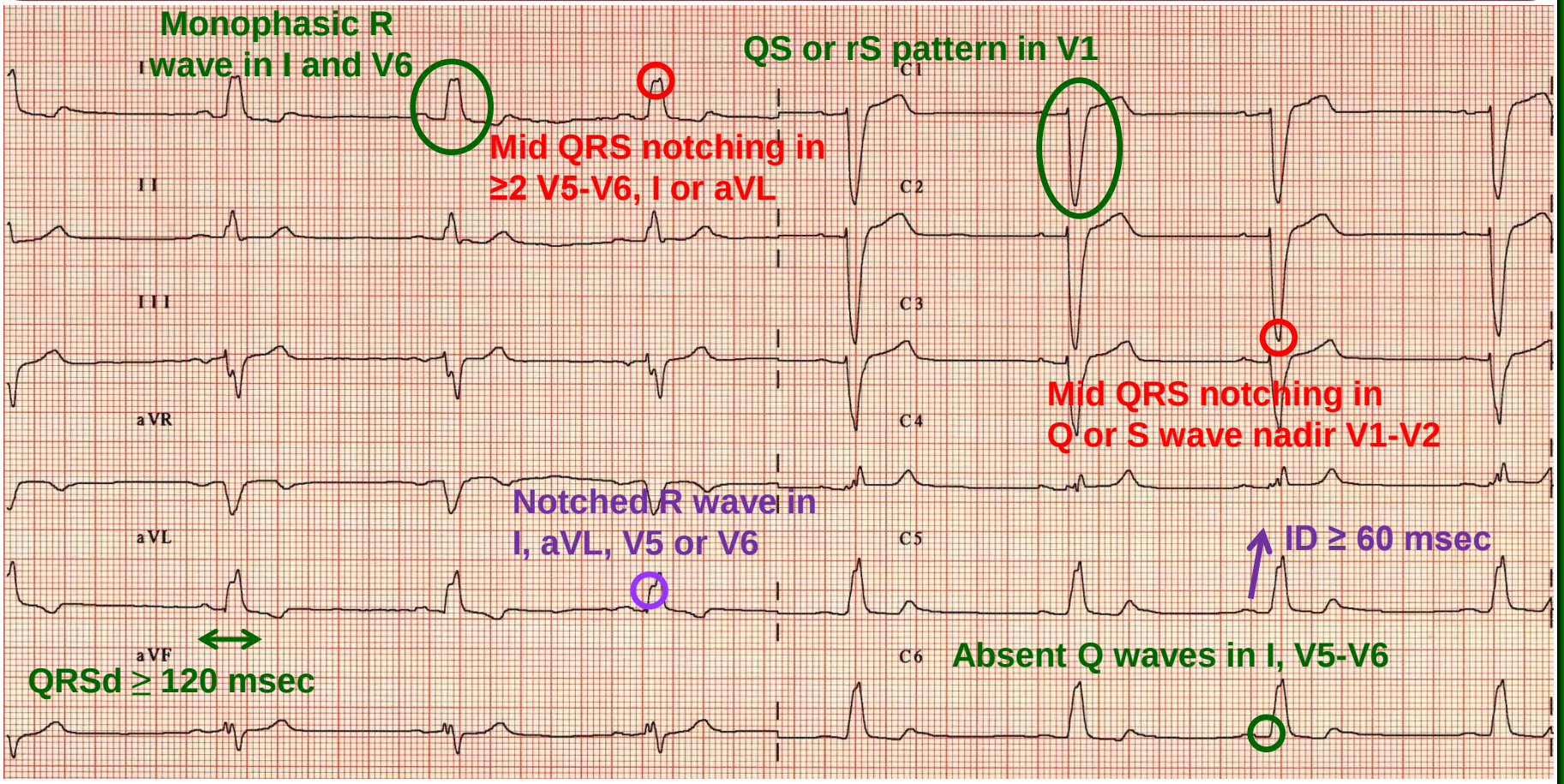
Is this Left Bundle Branch Block?

QRS Duration = 140 msec



Complete left bundle branch block → True LBBB

Redefining LBBB in the Era of CRT



Conventional criteria

Wagner GS. Marriott's Practical Electrocardiography Lippincott Williams & Wilkins 2008

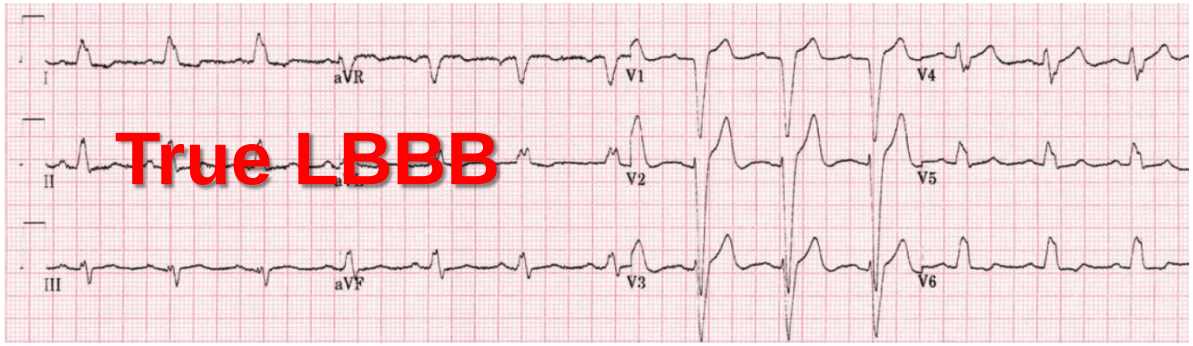
ESC/AHA criteria

Surawicz et al. JACC 2009; 53:976-981

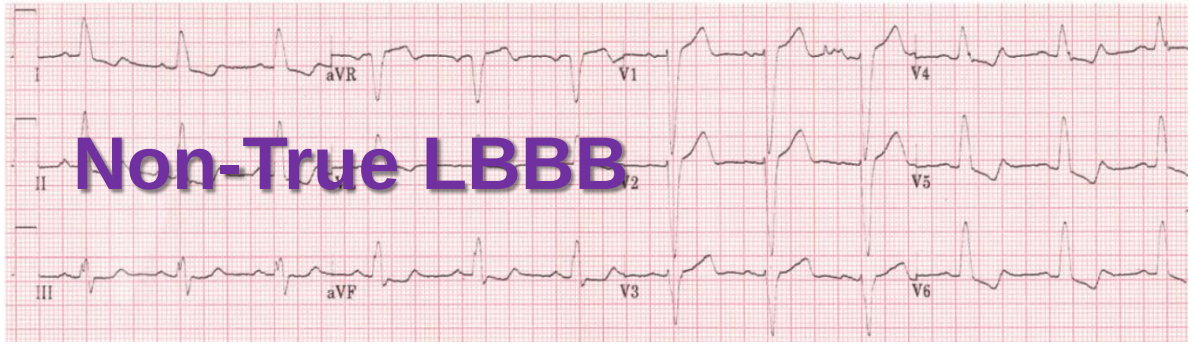
Strauss criteria

Strauss et al. Am J Cardiol 2011; 107: 927-934

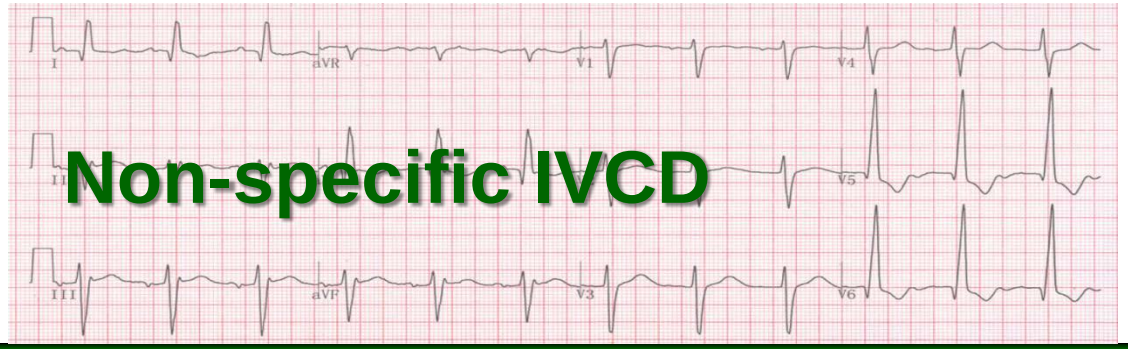
True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy



True LBBB **N=22**



Non-True LBBB **N=17**

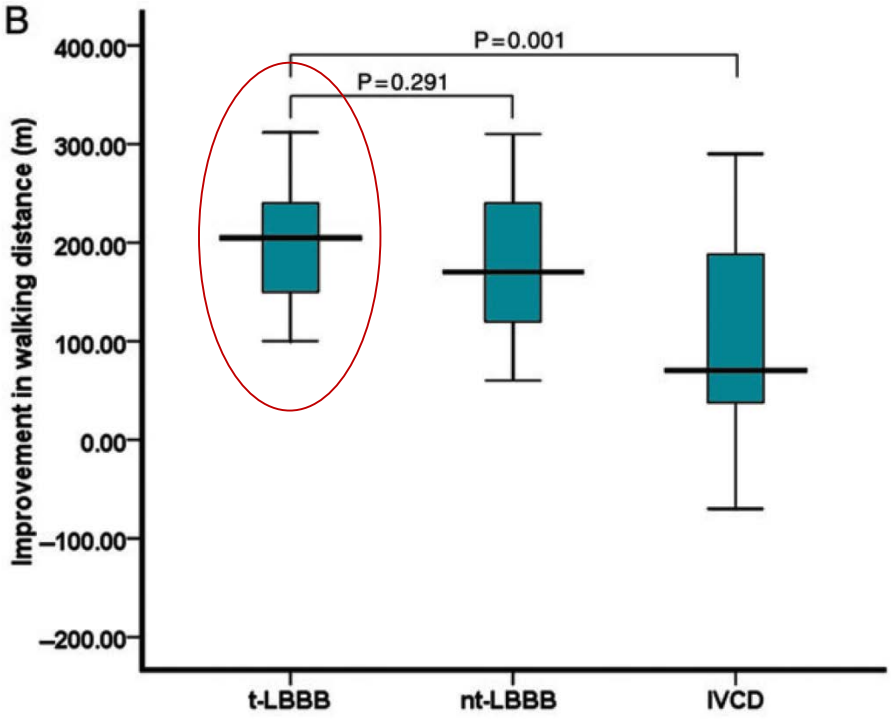


Non-specific IVCD **N=19**

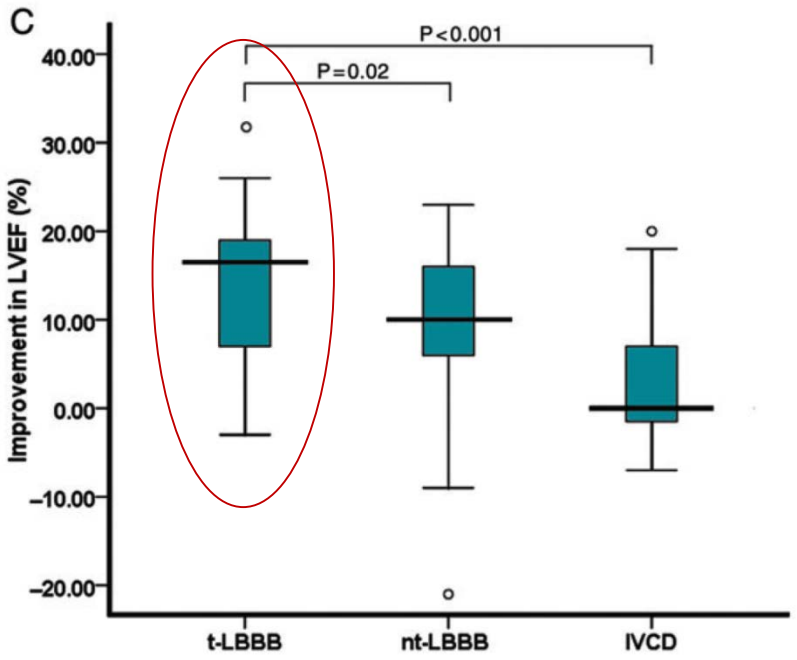
Tian Y et al.
Europace 2013; 15: 1499-1506

True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy

Walking Distance (m)



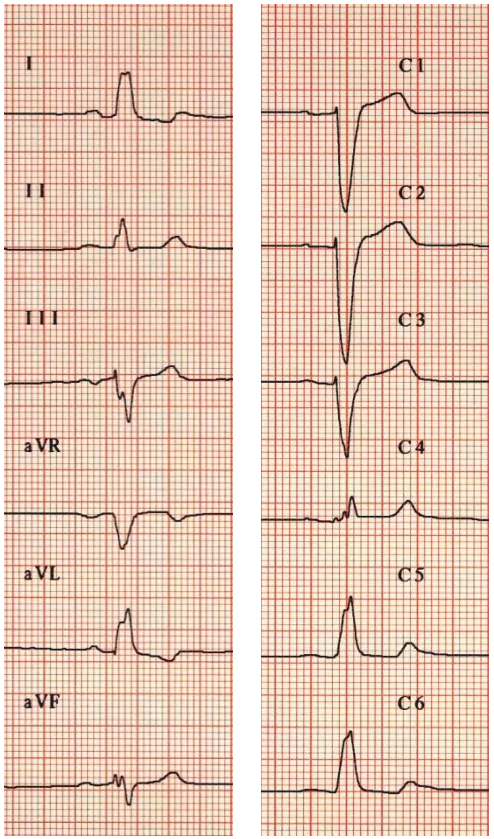
LVEF %

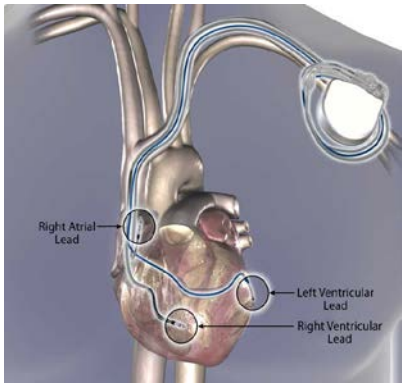


Tian Y et al. Europace 2013; 15: 1499-1506

Is the Effect of CRT similar in patients with wide QRS and non-LBBB pattern?

LBBB





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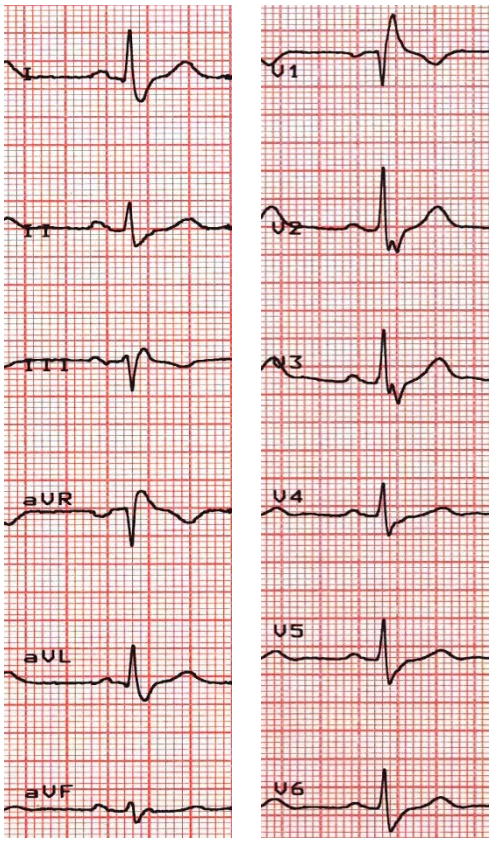
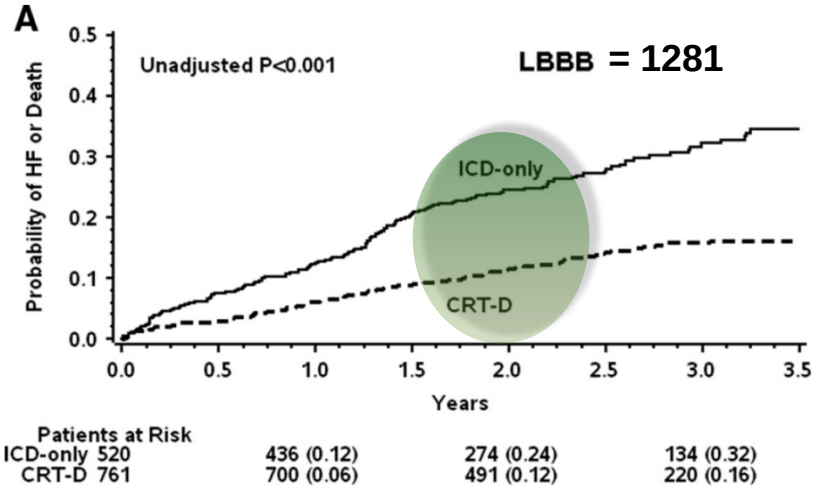
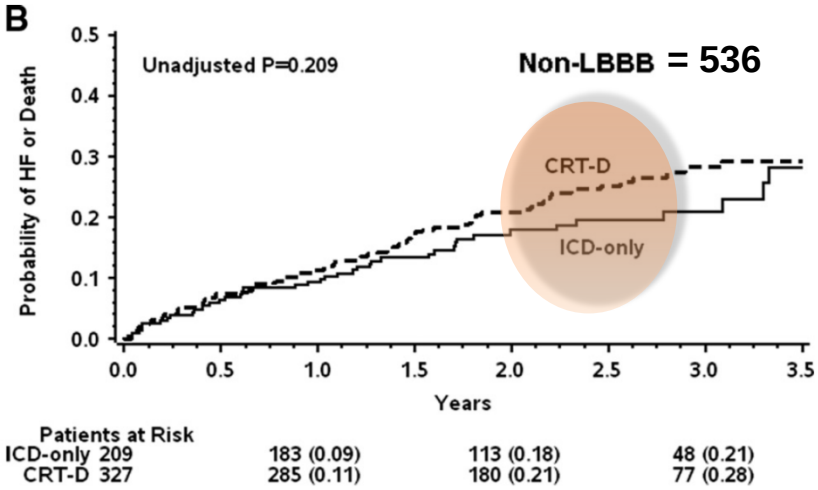
RBBB

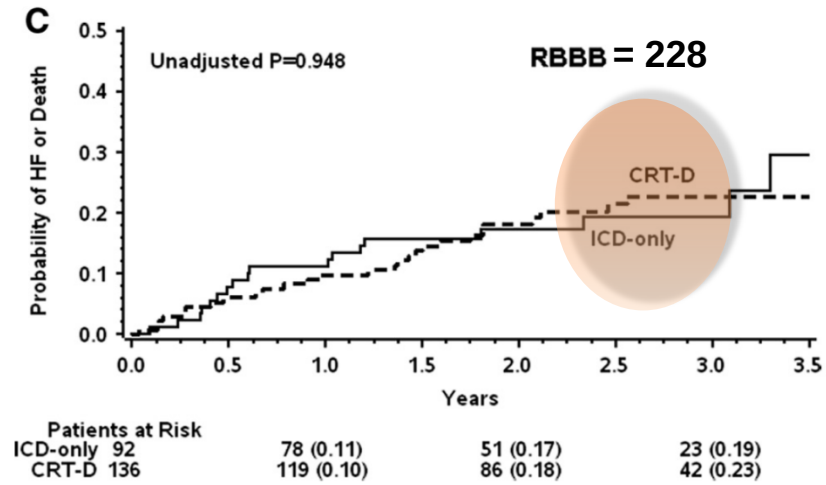


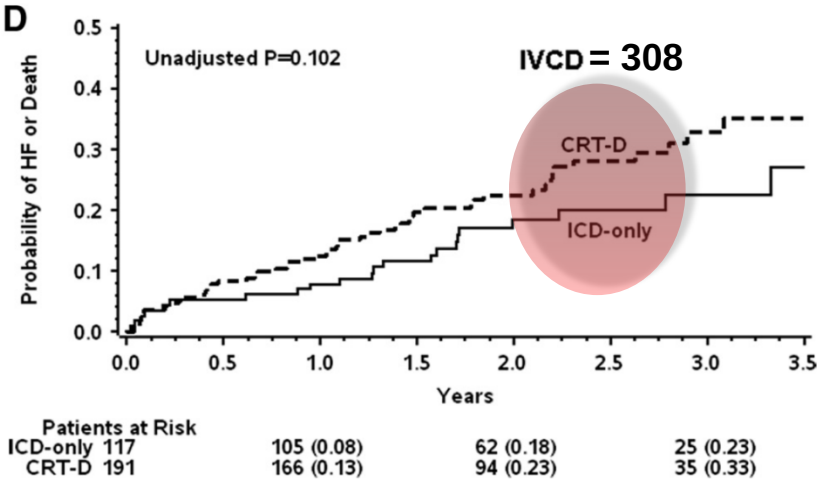
Non-left Bundle Branch Block and CRT

MADIT-CRT 1817 pts NYHA I-II, QRS≥130 msec, LVEF≤30%









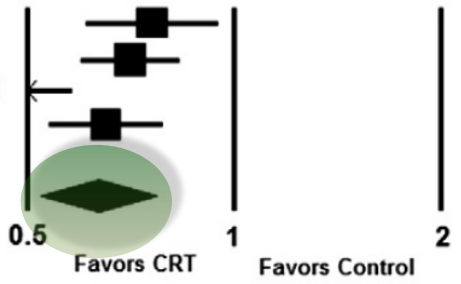
Zareba W et al. Circulation 2011; 123: 1061-1072

Non-LBBB and CRT – Meta-analysis

Total N=5356; 3009 CRT vs. 2347 controls

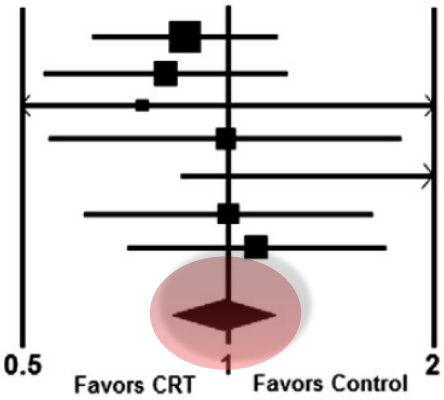
LBBB N=3947

Study name	Risk Ratio	Lower Limit	Upper limit	Z-Value	p-Value
COMPANION[10] - LBBB	0.76	0.61	0.95	-2.43	0.016
CARE-HF[11,32] - LBBB	0.70	0.60	0.83	-4.21	<0.0001
MADIT-CRT[12,13,15] - LBBB	0.45	0.35	0.58	-6.20	<0.00001
RAFT[14] - LBBB	0.65	0.54	0.79	-4.44	0.00001
Meta Analysis	**0.64**	**0.52**	**0.77**	**-4.55**	**0.00001**



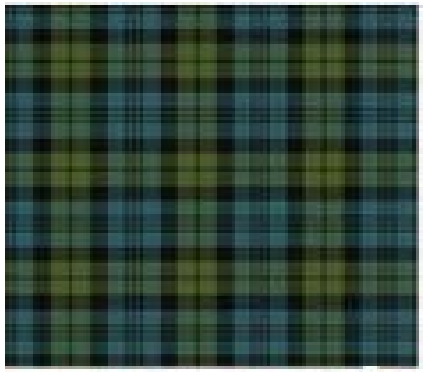
RBBB or IVCD N=1232

Study name	Risk Ratio	Lower Limit	Upper Limit	Z-Value	p-Value
COMPANION[10] - Non-LBBB	0.86	0.63	1.17	-0.96	0.34
CARE-HF[11,32] - RBBB	0.81	0.54	1.22	-0.99	0.32
CARE-HF[11,32] - IVCD	0.75	0.24	2.33	-0.50	0.62
MADIT-CRT[12,13,15] - RBBB	0.99	0.55	1.79	-0.03	0.97
MADIT-CRT[12,13,15] - IVCD	1.44	0.88	2.36	1.45	0.15
RAFT[14] - RBBB	1.00	0.62	1.62	0.00	1.00
RAFT[14] – IVCD	1.10	0.71	1.69	0.43	0.67
Meta Analysis	**0.97**	**0.82**	**1.15**	**-0.32**	**0.75**



Sipahi I et al. Am Heart J 2012;163:260-267

Different Patterns of CRT Candidates



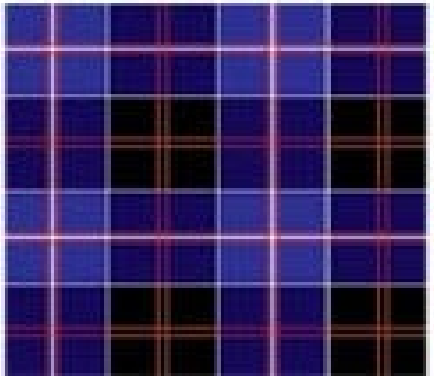

QRS

Duration

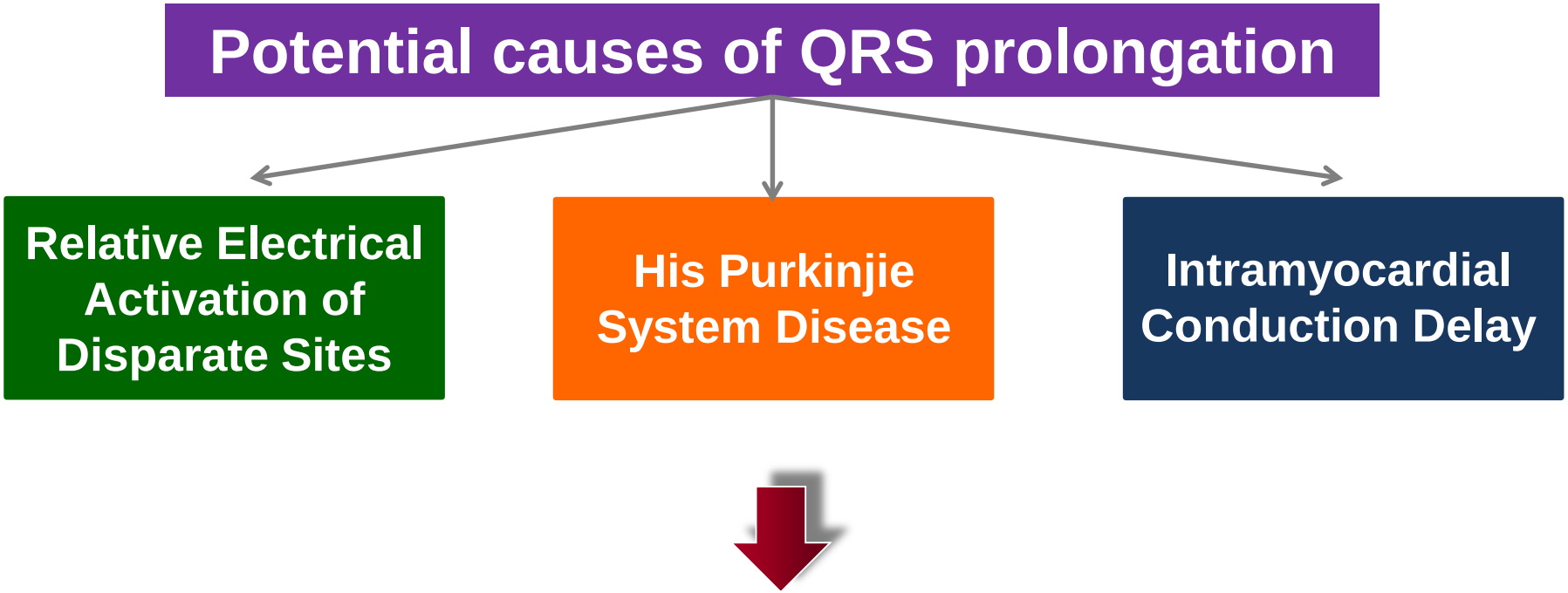








QRS Width and Response to CRT

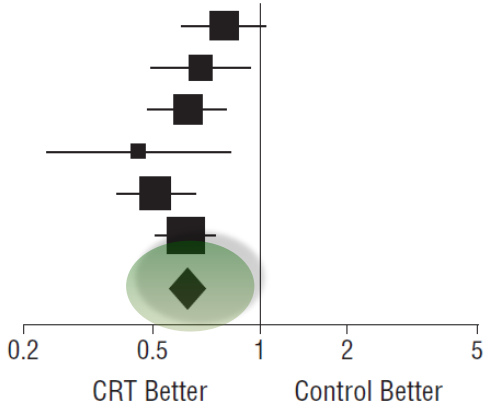


QRS duration is a simple and intuitive variable to guide patient selection and CRT optimization

Impact of QRS Duration on Clinical Event Reduction With Cardiac Resynchronization Therapy

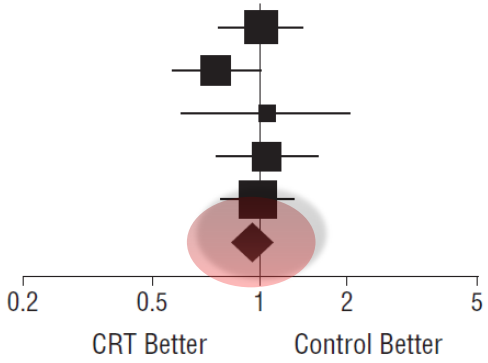
QRS ≥ 150 msec

	Statistics for each study		
	RR (95% CI)	*z* Value	*P* Value
COMPANION (QRS, 148-168 ms, n=314)	0.78 (0.59-1.04)	–1.70	.09
COMPANION (QRS, >168 ms, n=287)	0.66 (0.47-0.93)	–2.35	.02
CARE-HF (QRS, >159 ms, n=505)	0.60 (0.46-0.79)	–3.70	<.001
REVERSE (QRS, >151 ms, n=307)	0.42 (0.22-0.81)	–2.61	.009
MADIT-CRT (QRS, >149 ms, n=1175)	0.48 (0.37-0.63)	–5.41	<.001
RAFT (QRS, >149 ms, n=1036)	0.59 (0.48-0.73)	–4.93	<.001
Meta-analysis	**0.60 (0.53-0.67)**	**–8.67**	**<.001**



QRS < 150 msec

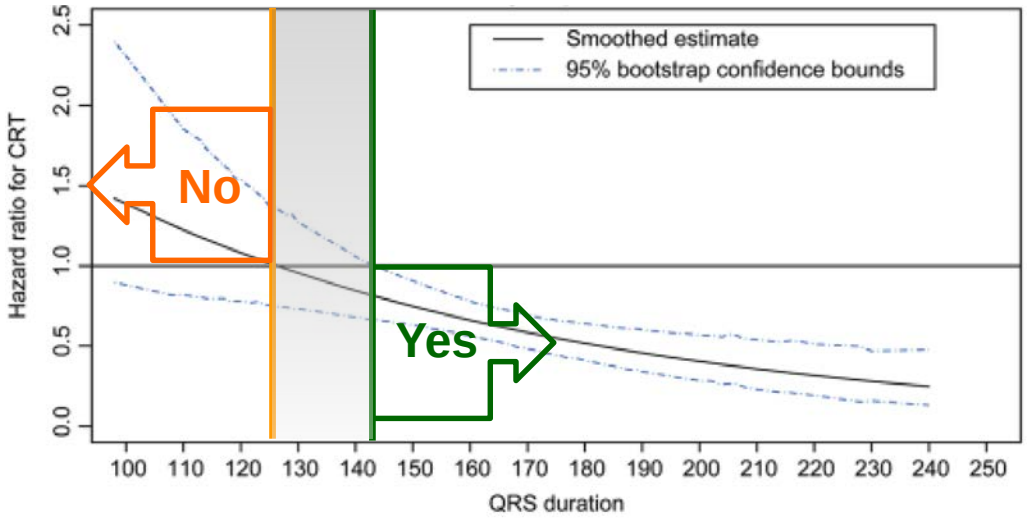
	Statistics for each study		
	RR (95% CI)	*z* Value	*P* Value
COMPANION (QRS, 120-147 ms, n=324)	1.01 (0.76-1.35)	0.07	.95
CARE-HF (QRS, 120-159 ms, n=290)	0.74 (0.54-1.02)	–1.86	.06
REVERSE (QRS, 120-151 ms, n=303)	1.05 (0.58-1.89)	0.16	.87
MADIT-CRT (QRS, 130-149 ms, n=645)	1.06 (0.74-1.52)	0.32	.75
RAFT (QRS, 120-149 ms, n=627)	0.99 (0.77-1.27)	–0.08	.94
Meta-analysis	**0.95 (0.82-1.10)**	**–0.68**	**.49**



Sipahi I et al. Arch Intern Med 2011; 171: 1454-1462

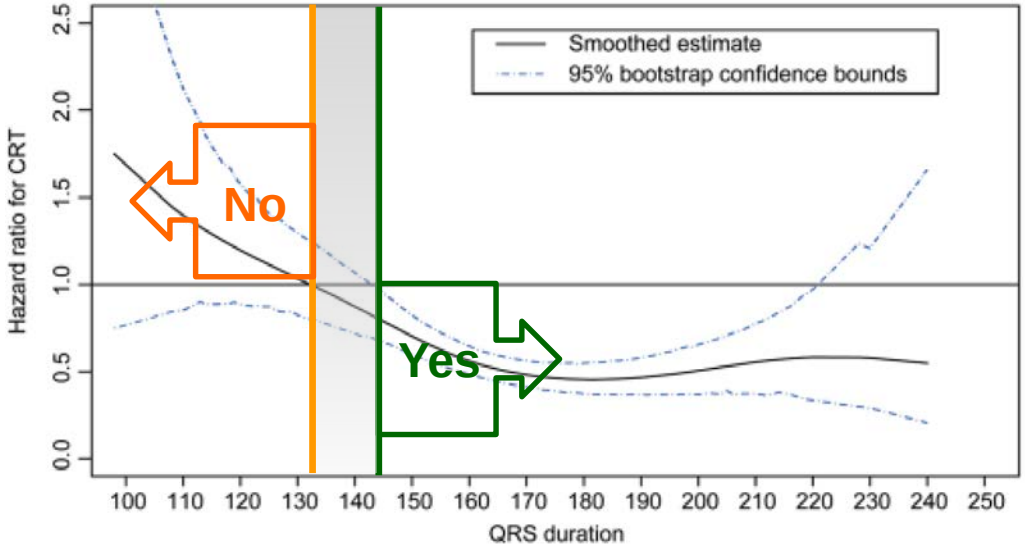
QRS Duration and Outcome After CRT

All-cause Mortality



Line of neutrality

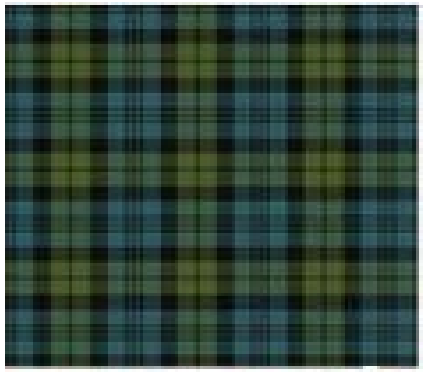
Composite Mortality/HF



Line of neutrality

Cleland J et al. Eur Heart J 2013; 34: 3547-3556

Different Patterns of CRT Candidates









Female Gender


Women in CRT Studies

Trials

Real World

Comparison between COMPANION, CARE-HF, REVERSE and CRT Survey cohorts

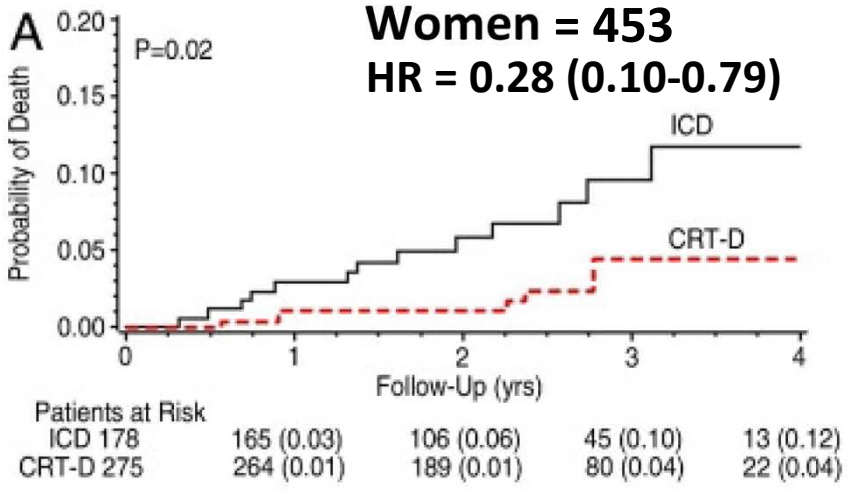
	COMPANION	CARE-HF	REVERSE	CRT Survey
Number of patients	1212	409	419	2438
Patients with a CRT-P (%)	51	100	18	27
Patients with a CRT-D (%)	49	NA	82	73
Previous device (PPM or ICD) (%)	0[a]	0[a]	0[a]	26
Mean age (years)	67	65	63	68
Women (%)	33	27	22	24
Ischaemic heart disease (%)	55	38	56	51
NYHA class III (%)	86	64	0[b]	70
LV ejection fraction (%)	22	26	27	26

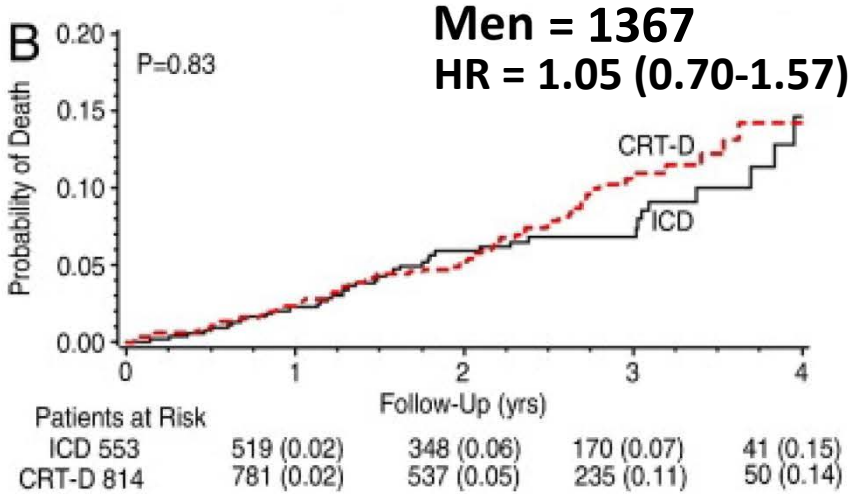
Women are underrepresented in CRT studies (24% of CRT in EU)

Dickstein K. et al. Eur Heart J 2009; 30: 2450-2460

MADIT-CRT – Outcome Men vs. Women

MADIT-CRT 1817 pts NYHA I-II, QRS≥130 msec, LVEF≤30%





Women in MADIT-CRT obtained greater reduction in death and HF

Arshad et al. JACC 2011; 57: 813-20

Sex Differences in QRS Duration

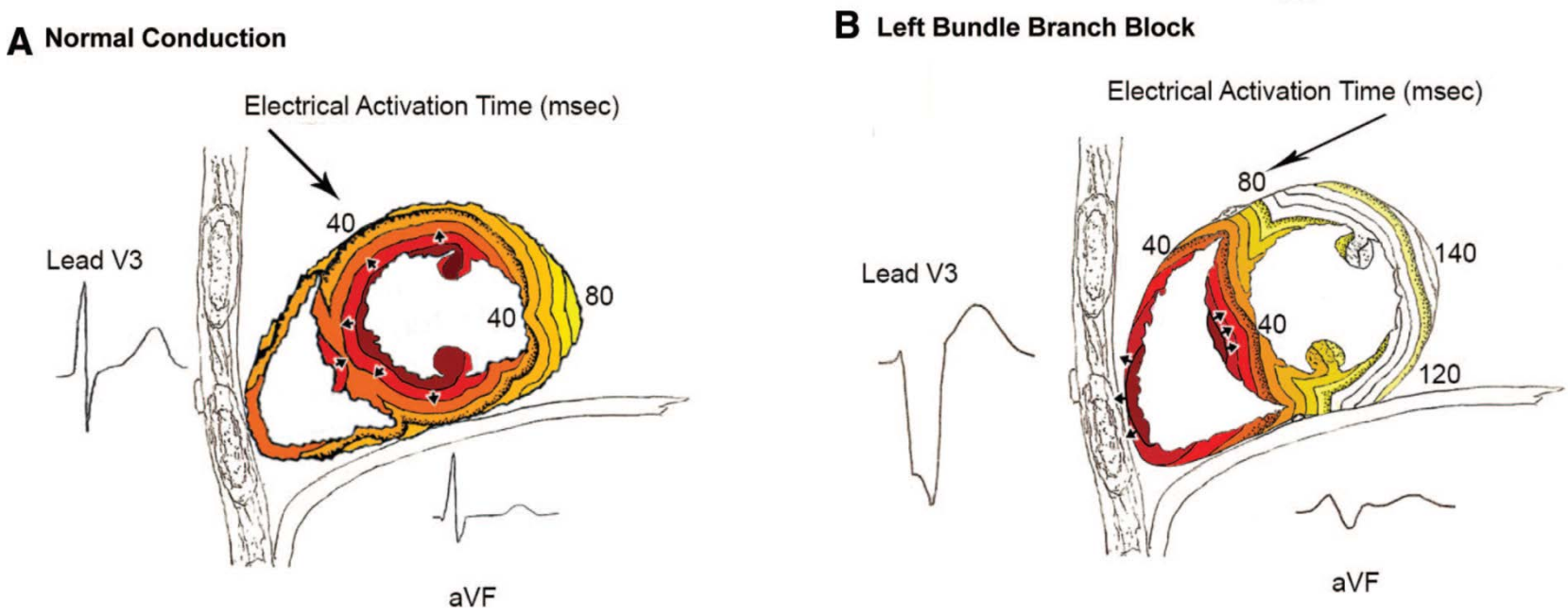
Table 4. Mean QRS Durations (±SD) in the Adult Male and Female White and Chinese Populations

	Men		Women	
Age (years)	White	Chinese	White	Chinese
18–29	94.6 ± 9.7	98.6 ± 10.8	85.1 ± 7.9	87.1 ± 7.6
30–39	94.3 ± 9.8	95.5 ± 11.9	86.7 ± 7.2	88.0 ± 10.1
40–49	93.3 ± 9.4	95.6 ± 11.0	85.7 ± 7.7	89.5 ± 10.1
50–59	92.7 ± 10.0	91.6 ± 12.6	85.3 ± 8.2	87.2 ± 10.5
≥60		93.4 ± 11.3		89.2 ± 10.6

Women have smaller hearts and narrower QRS duration *vs.* men
(≈10 msec difference in normal heart)

Macfarlane PW et al. J Electrocardiol 1994; 27 Suppl 14-9

Electrical Dyssynchrony in Women



"True LBBB" and dyssynchrony appear at narrower QRS duration in women

Strauss D et al. Circ Arrhythmia Electrophysiol. 2008;1:327-336

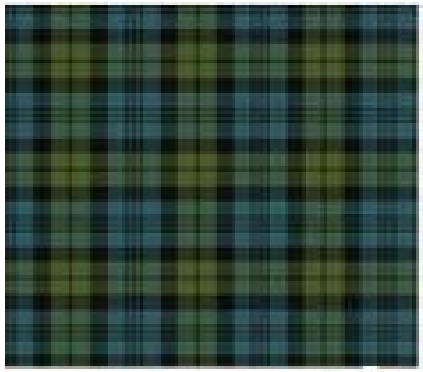
LBBB Definition in Men vs. Women

In summary, the need to identify patients for CRT has led us to reexamine the clinical definition of complete LBBB, because it is likely that only patients with complete LBBB receive significant benefit from CRT. We propose that criteria for complete LBBB should include QRS duration ≥140 ms (men) or 130 ms (women), QS or rS in leads V_1 and V_2, and mid-QRS notching or slurring in ≥2 of leads V_1, V_2, V_5, V_6, I, and aVL.

Gender Specific CRT Indications?

Strauss D et al. Am J Cardiol 2011; 107: 927-934

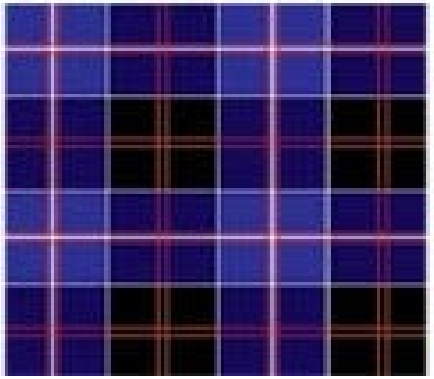
Different Patterns of CRT Candidates







Aetiology

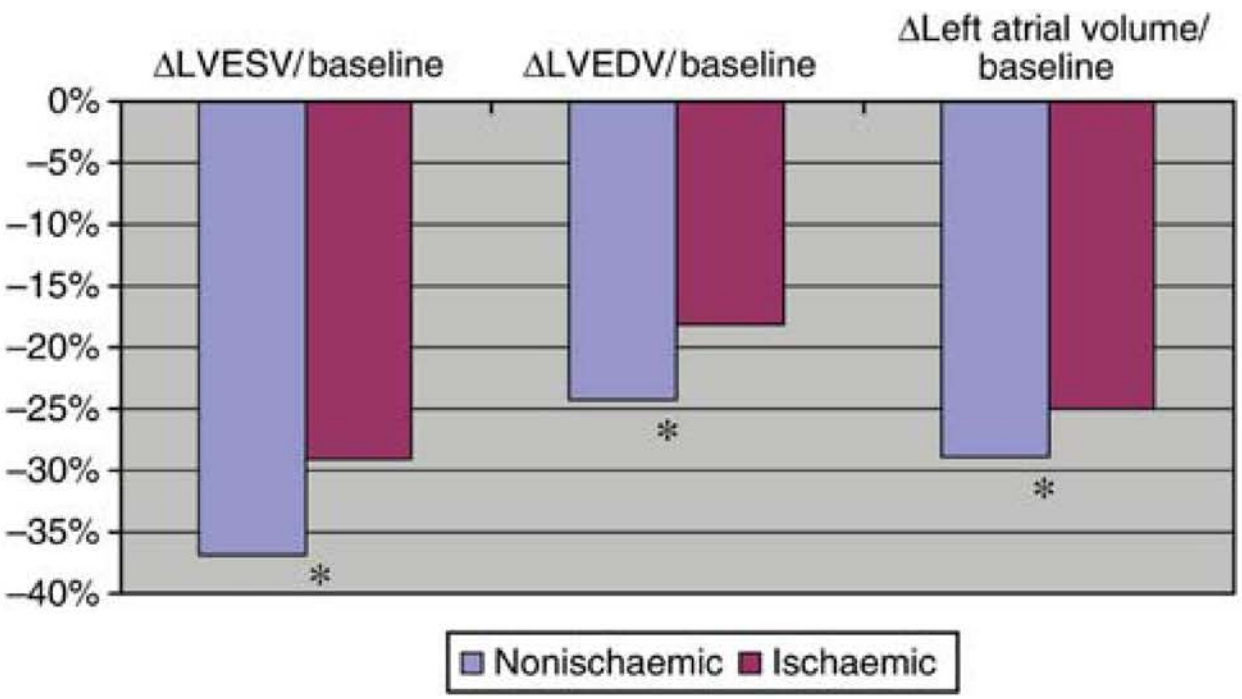



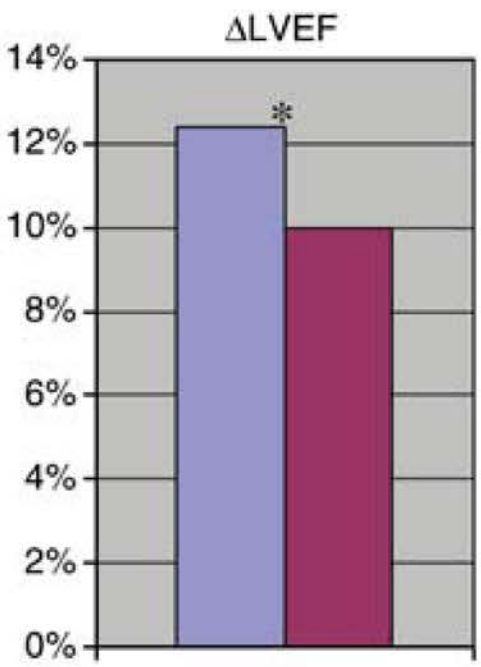
CRT and Heart Failure Aetiology

- ≈ 50% of CRT candidates have ischaemic CMP
- CRT response (particularly echo) less positive in ischaemic *vs.* non-ischaemic CMP

Pts with Ischaemic CMP	Pts with Non- ischaemic CMP
- Older	- More frequently female
- Lower LVEF	- More often OMT
- More comorbidites	- Greater QRS duration
- Lower prevalence of LBBB	- Higher prevalence of LBBB

MADIT-CRT
CMP Aetiology and CRT Response





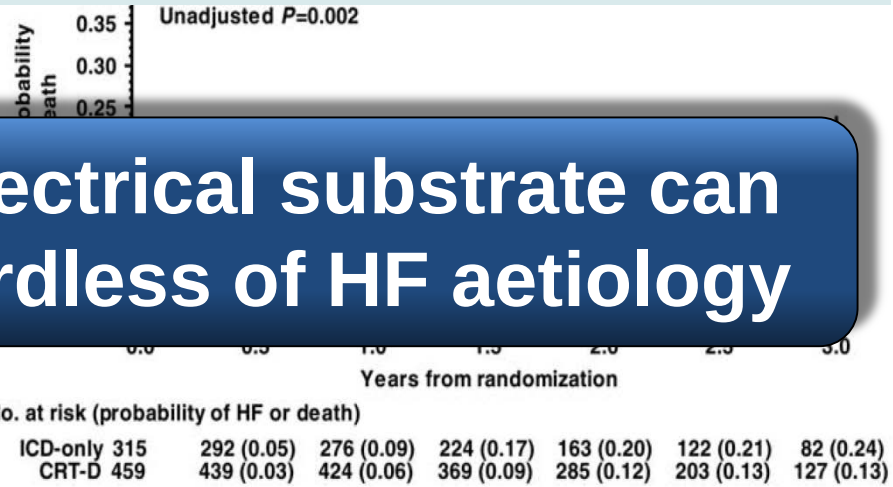
N=774 vs. N=1046

Barsheshet A. et al. Eur Heart J 2011; 32: 1622-1630

MADIT-CRT
CMP Aetiology and CRT Outcome

Clinical effect of cardiac resynchronization therapy with defibrillator vs. ICD by ischaemic aetiology

	All ischaemic (n = 1046)		Ischaemic NYHA II (n = 781)		Non-ischaemic (n = 774)		P for interaction*
	Adjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value	
HF or death	0.66 (0.52–0.85)	0.001	0.62 (0.47–0.83)	0.001	0.56 (0.39–0.80)	0.002	0.455
HF event	0.58 (0.45–0.77)	<0.001	0.57 (0.41–0.77)	<0.001	0.50 (0.35–0.75)	0.001	0.562
Death	0.99 (0.65–1.52)	0.984	0.96 (0.59–1.55)	0.854	0.87 (0.45–1.67)	0.669	0.728

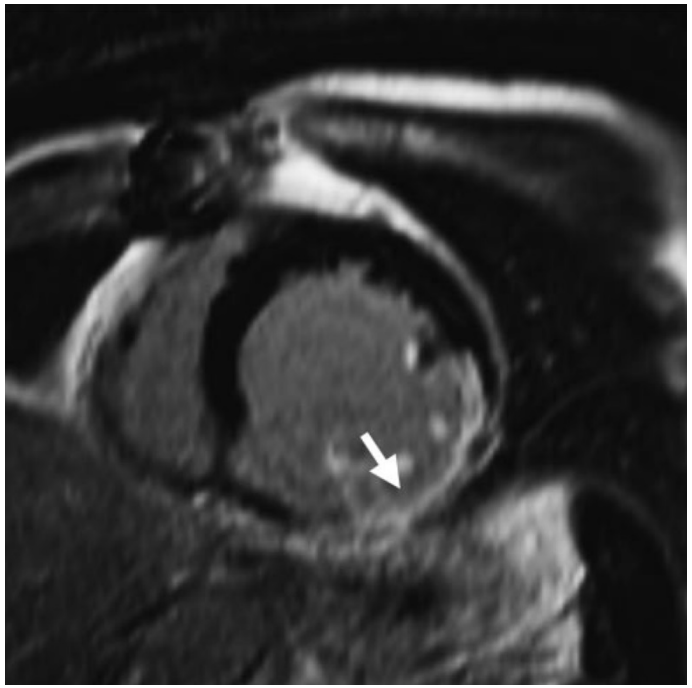


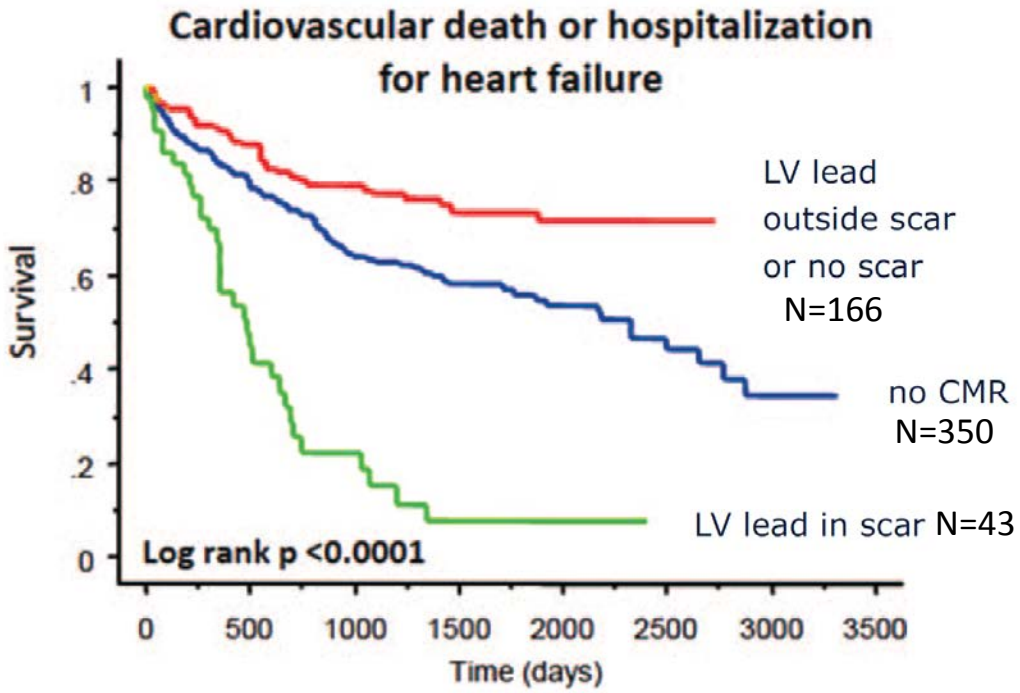
Patients with "true" electrical substrate can benefit from CRT regardless of HF aetiology

Barsheshet A. et al. Eur Heart J 2011; 32: 1622-1630

Localization and Magnitude of Scar

Viability of paced LV segment influences outcome (pacing scar = worse response)

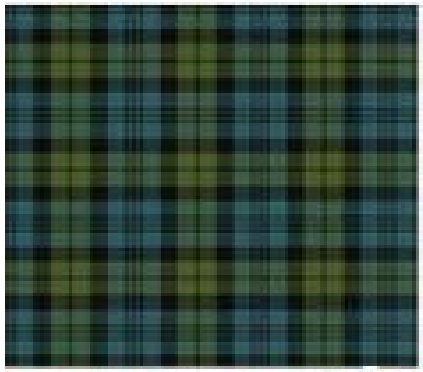




Bleeker GB et al. Circulation 2006; 113:969-76

Leyva F. et al. J Cardiovasc Magn Reson 2011; 13:29

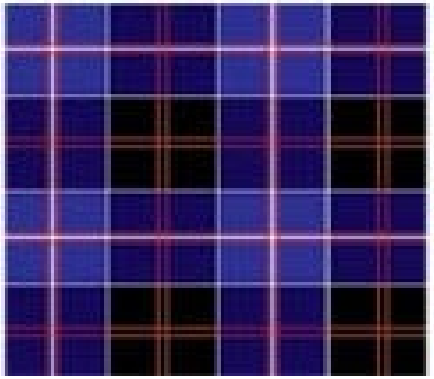
Different Patterns of CRT Candidates




Cardiac Rhythm



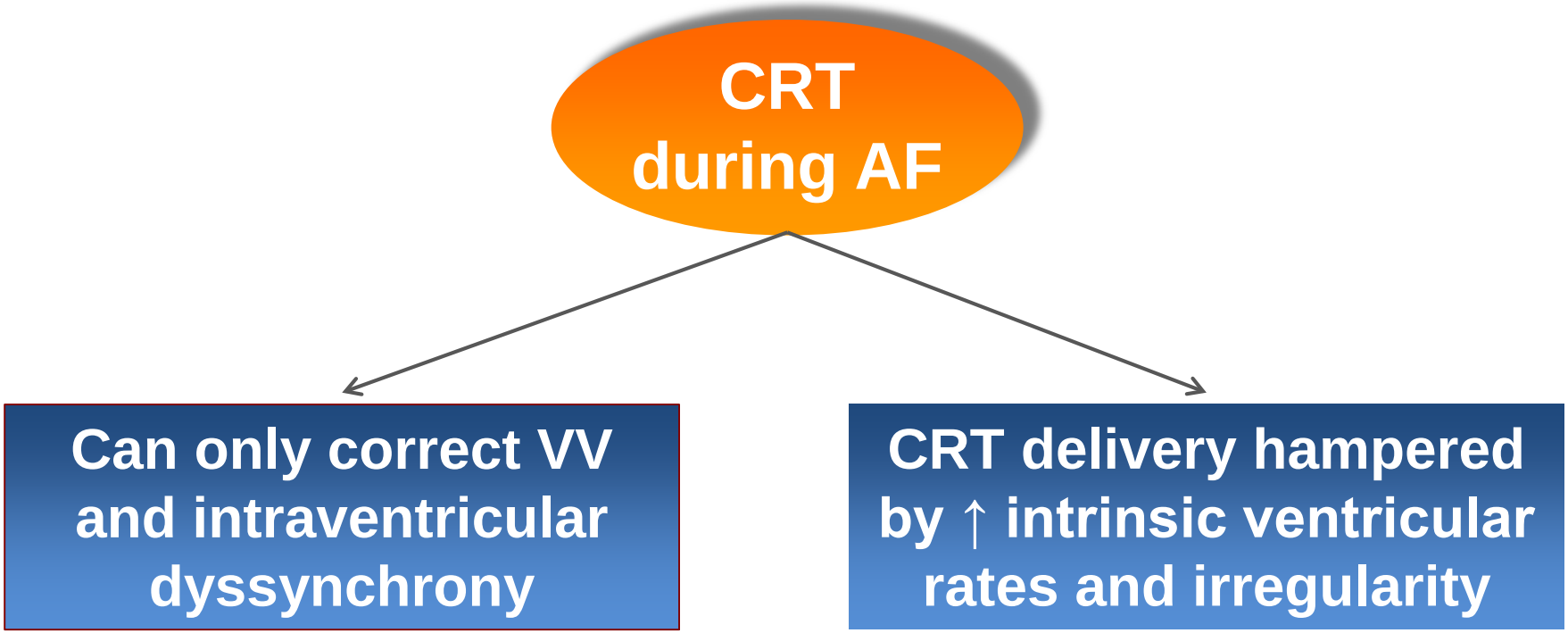




CRT in Atrial Fibrillation

- Atrial fibrillation (AF) occurs in ≈ 30% of HF pts
- Pts with AF represent ≈ 30% of CRT candidates
- CRT should be considered only in pts with permanent or long-standing persistent AF

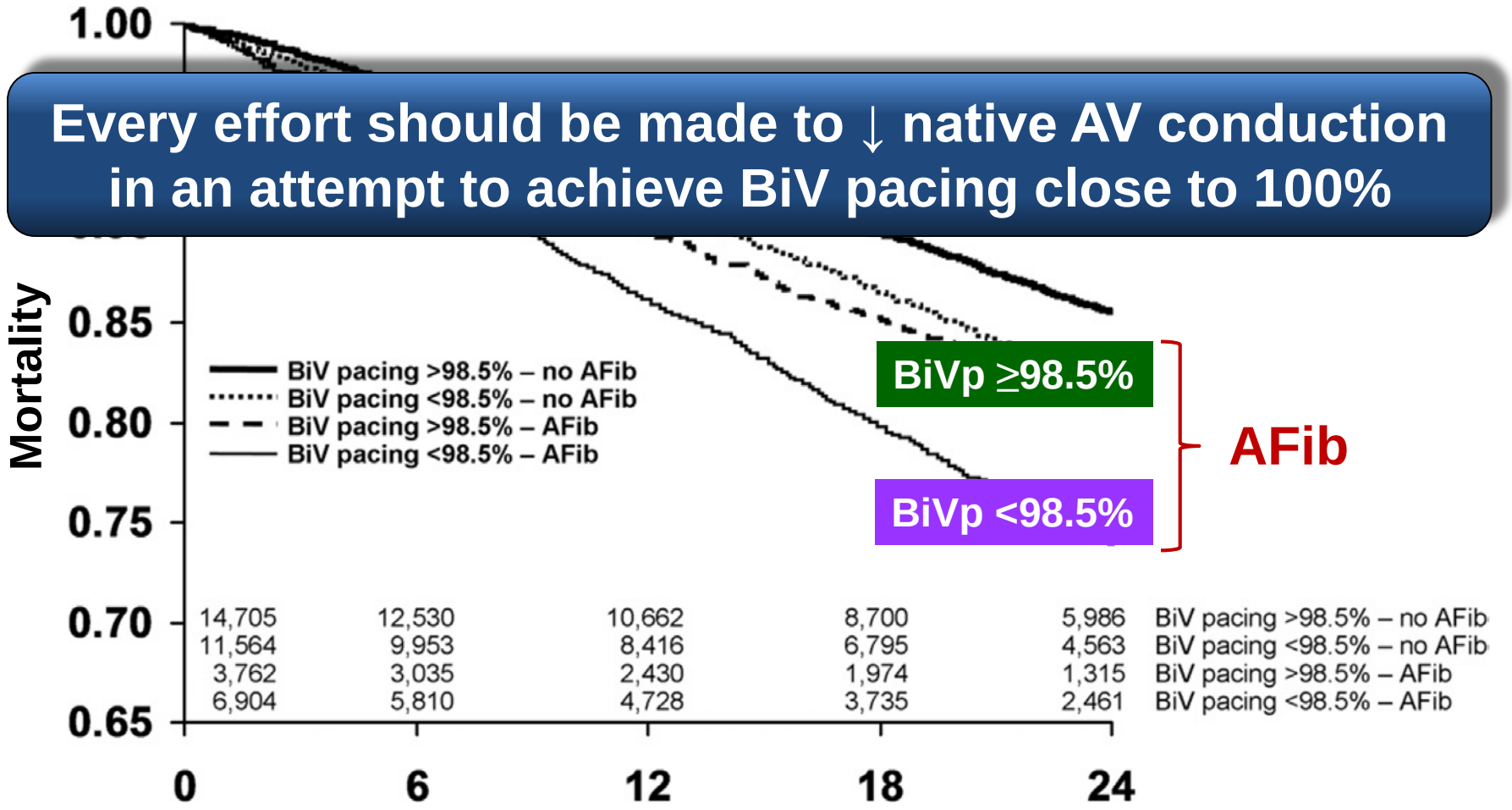
CRT in Atrial Fibrillation



Importance of Biventricular Pacing %

36,935 pts Followed-up in a Remote-monitoring Network

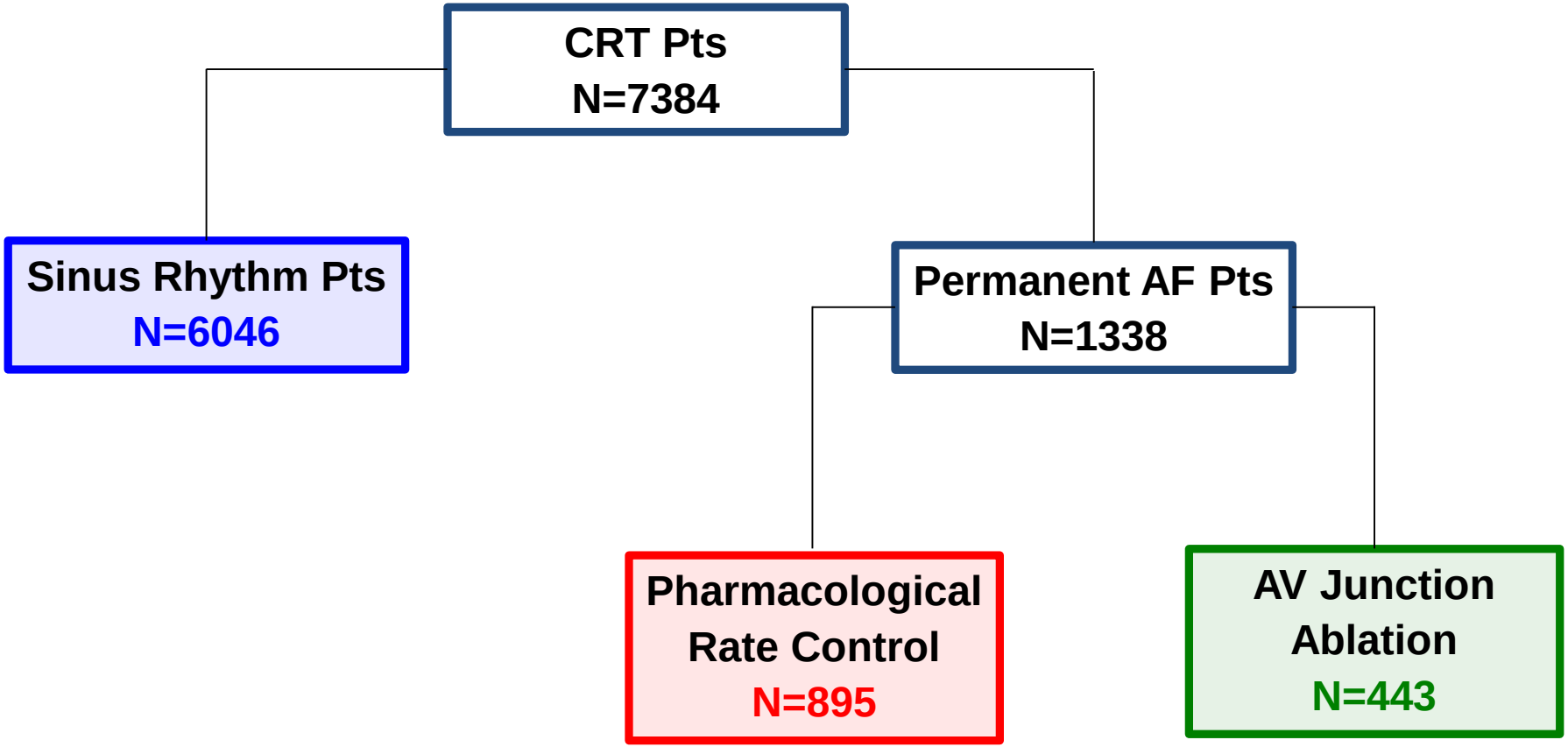
Every effort should be made to ↓ native AV conduction in an attempt to achieve BiV pacing close to 100%



Hayes D. et al. Heart Rhythm 2011; 8:1469-1475

Evidence for CRT in pts with AFib

Certify Multinational Registry – Median FU 37 months

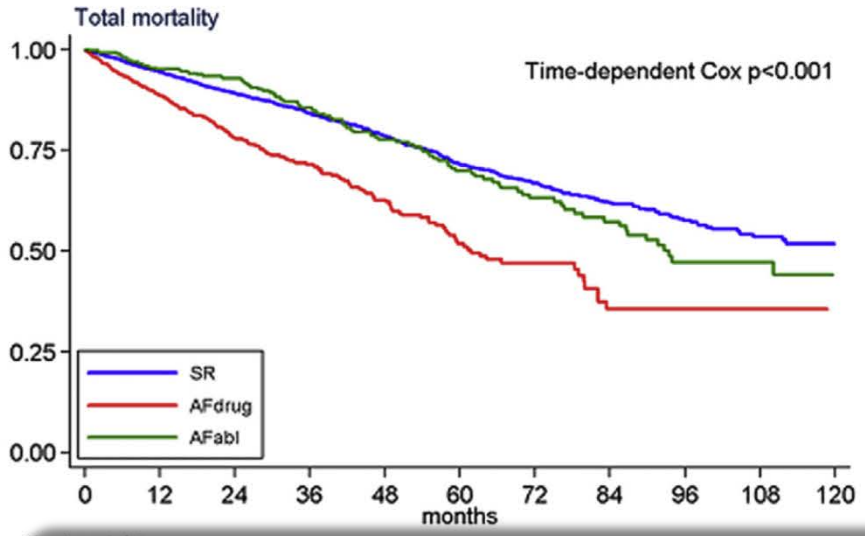


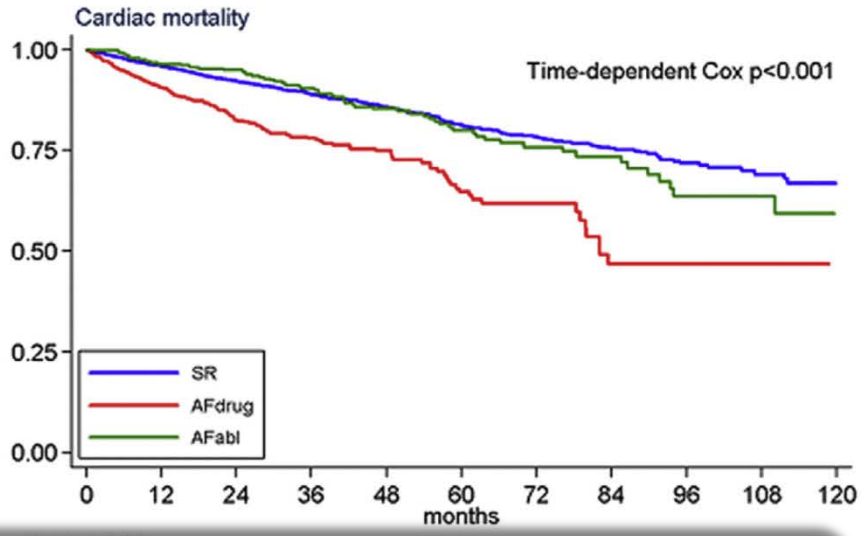
Gasparini M. et al. JACC Heart Fail 2013; 1:500-7.

Evidence for CRT in pts with AFib

Total mortality rates per 100 pys	
Sinus Rhythm	6.1
AV junction ablation	6.8
Pharmacological rate control	11.3

Cardiac mortality rates per 100 pys	
Sinus Rhythm	4.0
AV junction ablation	4.2
Pharmacological rate control	8.1





Pts receiving AV junction ablation had risk of total and cardiac mortality comparable to those in sinus rhythm

Gasparini M. et al. JACC Heart Fail 2013; 1:500-7.

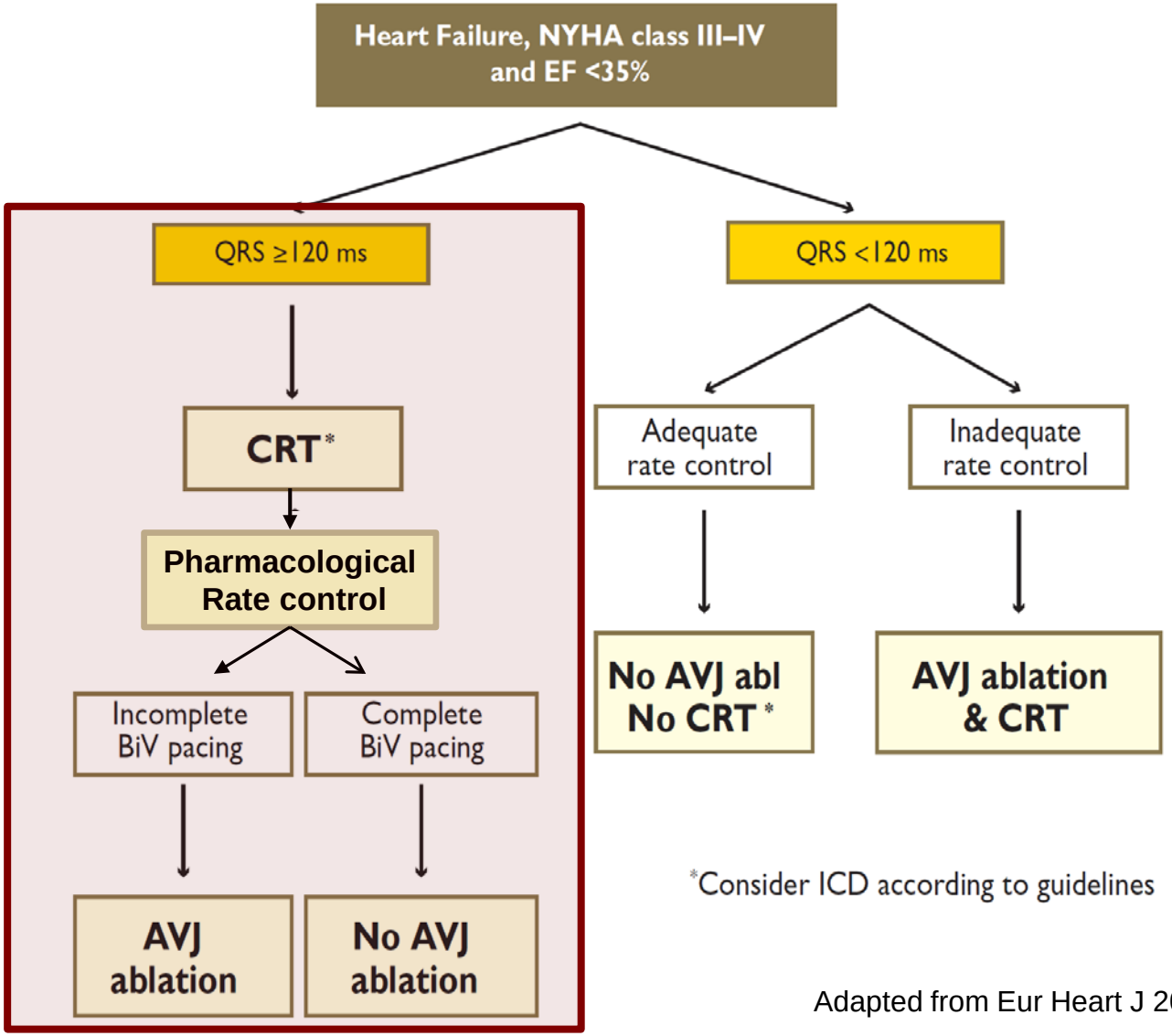
2013 ESC GL on Pacing and CRT
Pts with Permanent Atrial Fibrillation

Recommendations	Class [a]	Level [b]
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**
1B) AV junction ablation should be added in case of incomplete BiV pacing.	**IIa**	**B**

Recommendations	Class [a]	Level [b]
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**

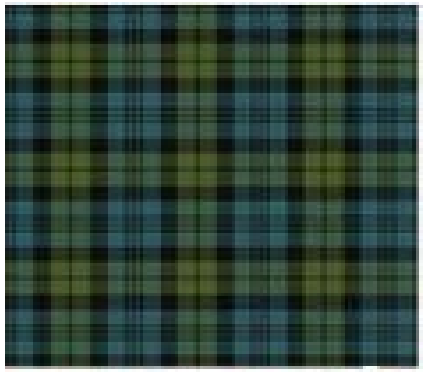
Eur Heart J 2013; 34;2281–2329

CRT in Atrial Fibrillation

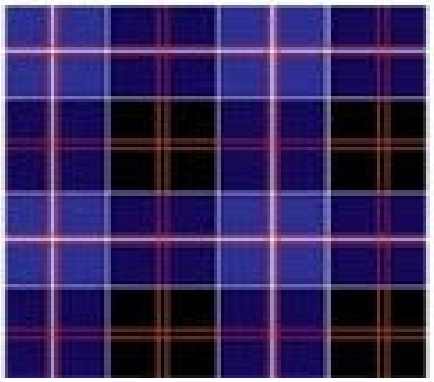


Adapted from Eur Heart J 2013; 34;2281–2329

Different Patterns of CRT Candidates




Take Home Messages

Take Home Messages

CRT has been proven effective in improving functional capacity, reducing hospitalizations and prolonging survival of patients with HF:

- **On top of optimal medical treatment**
- **Experiencing mild to moderate symptoms**
- **With documented LVEF reduction (≤35%)**
- **With left bundle branch block and/or wide QRS**
- **In sinus rhythm**

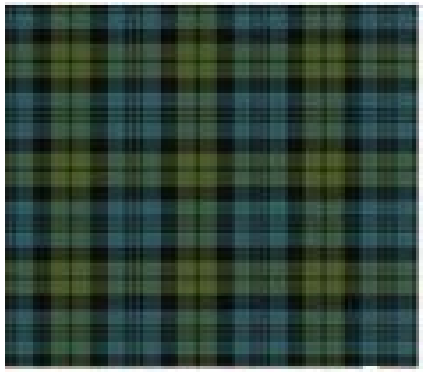
Take Home Messages

The use of CRT in patients with atrial fibrillation is reasonable but randomized data are lacking

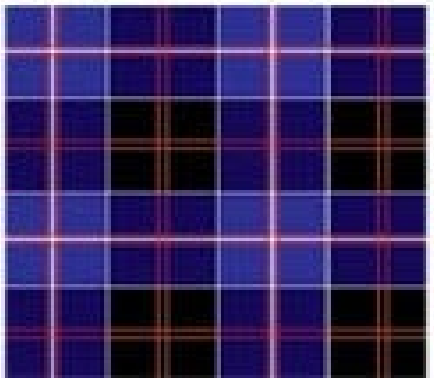
Currently no room for CRT in patients experiencing HF symptoms with QRS<120 msec


Thank you for your attention!

Different Patterns of CRT Candidates




Back-up Slides

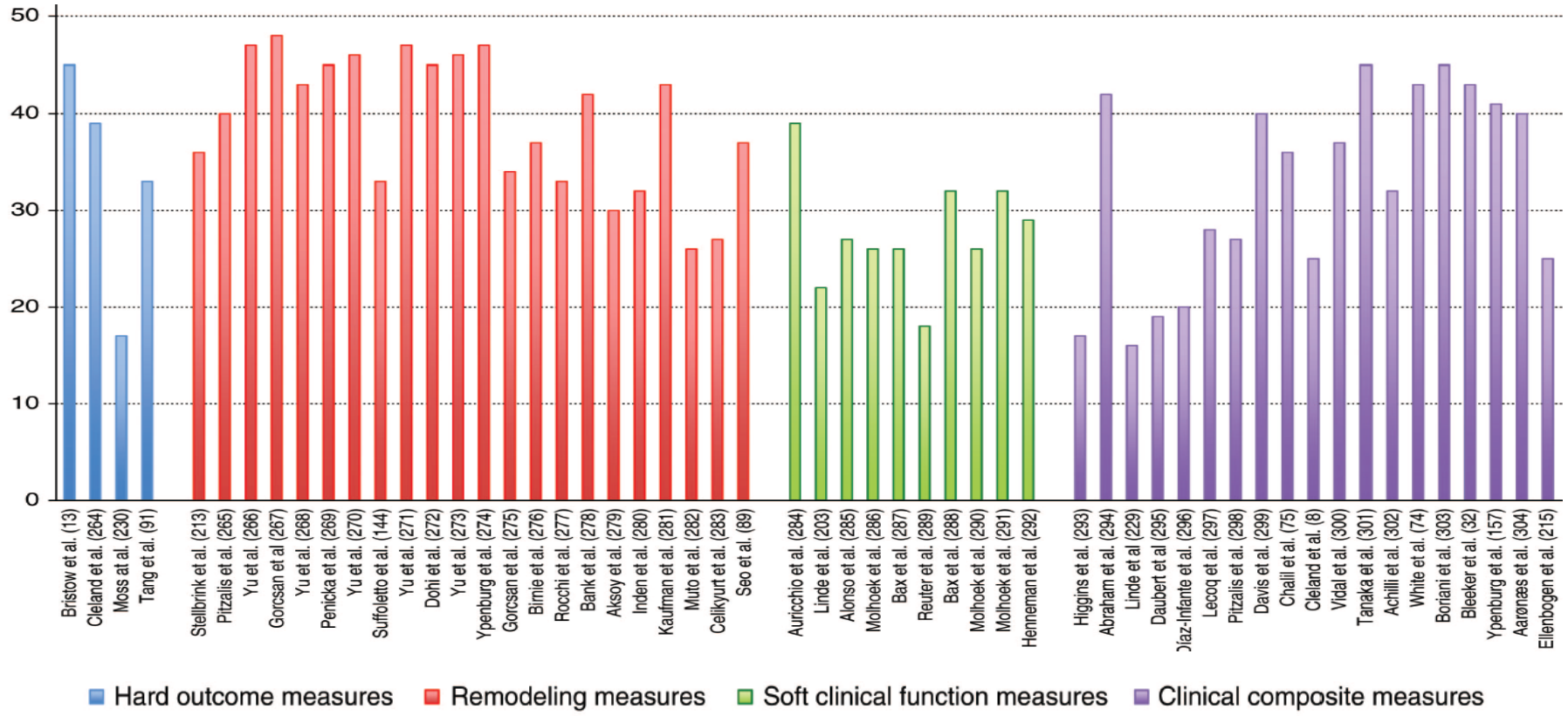



Non-responders Rate According to Measure of Response

CRT Non-responder

15% to 45%

- Measure of response
- HF severity (NYHA class I-II vs. NYHA class III-IV)
- Duration of follow-up
- More recent vs. older studies and technology



Daubert JC et al. Europace 2012; 14: 1236-1286

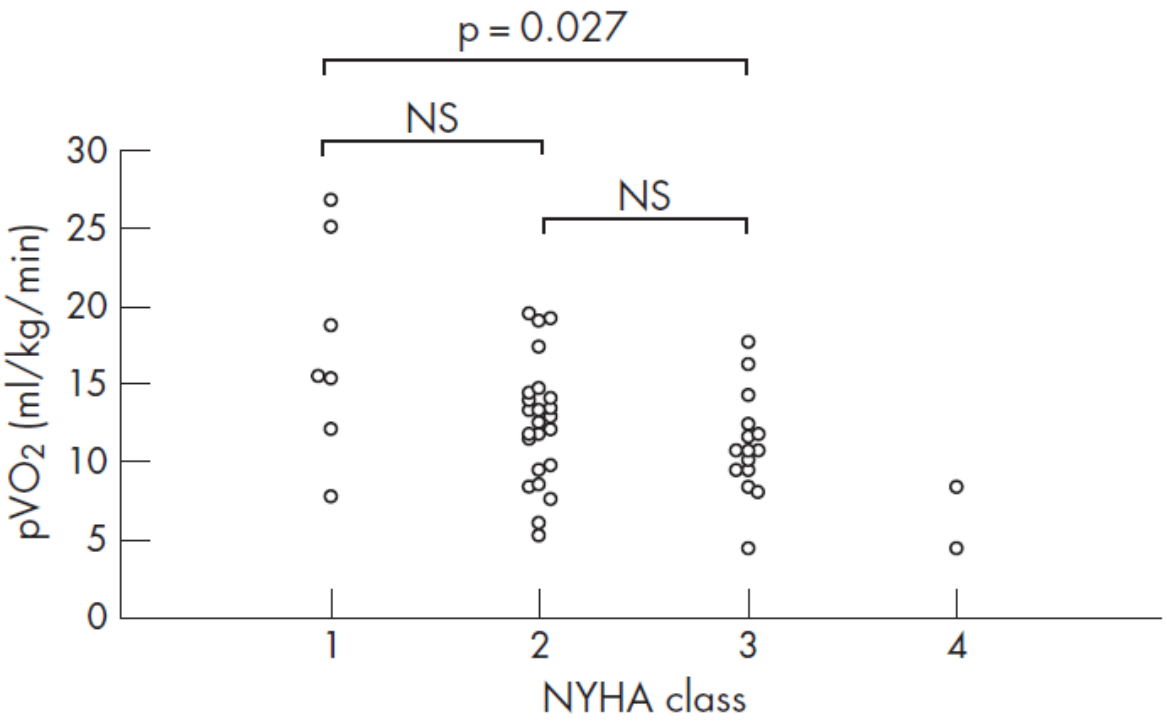
Optimal Medical Therapy (OMT) among CRT-D Candidates

45392 Patients in the NCDR Registry undergoing CRT-D implantation between 2006-2008

Description	N (%)
Beta-blocker	39190 (87.4%)
Agiotensing converting enzyme inhibitor (ACE-I)	28029 (64.2%)
Angiotensin II receptor inhibitor (ARB)	8270 (18.6%)
Beta-blocker + ACE-I / ARB	31090 (70.3%)
Patients receiving OMT + class I CRT indication	22276 (50.3%)

Schneider PM et al. Am J Cardiol 2014; 113;2052–2056

Fallacy of NYHA Functional Classification



Criteria used to determine the NYHA class	% of cardiologists
Breathlessness interferes with daily activities	25
Breathless when walking around the house	23

NYHA class for assessor 2		
III	13	7

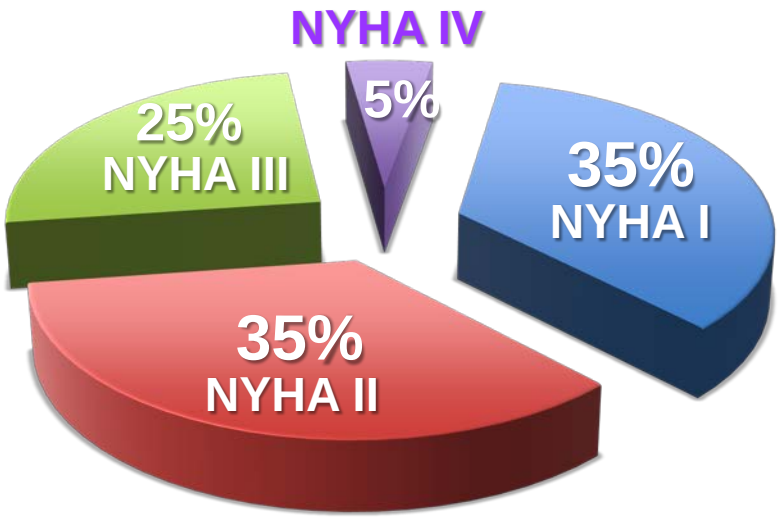
Only 54% of concordance between cardiologists in NYHA assessment

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

HF Population by NYHA Class

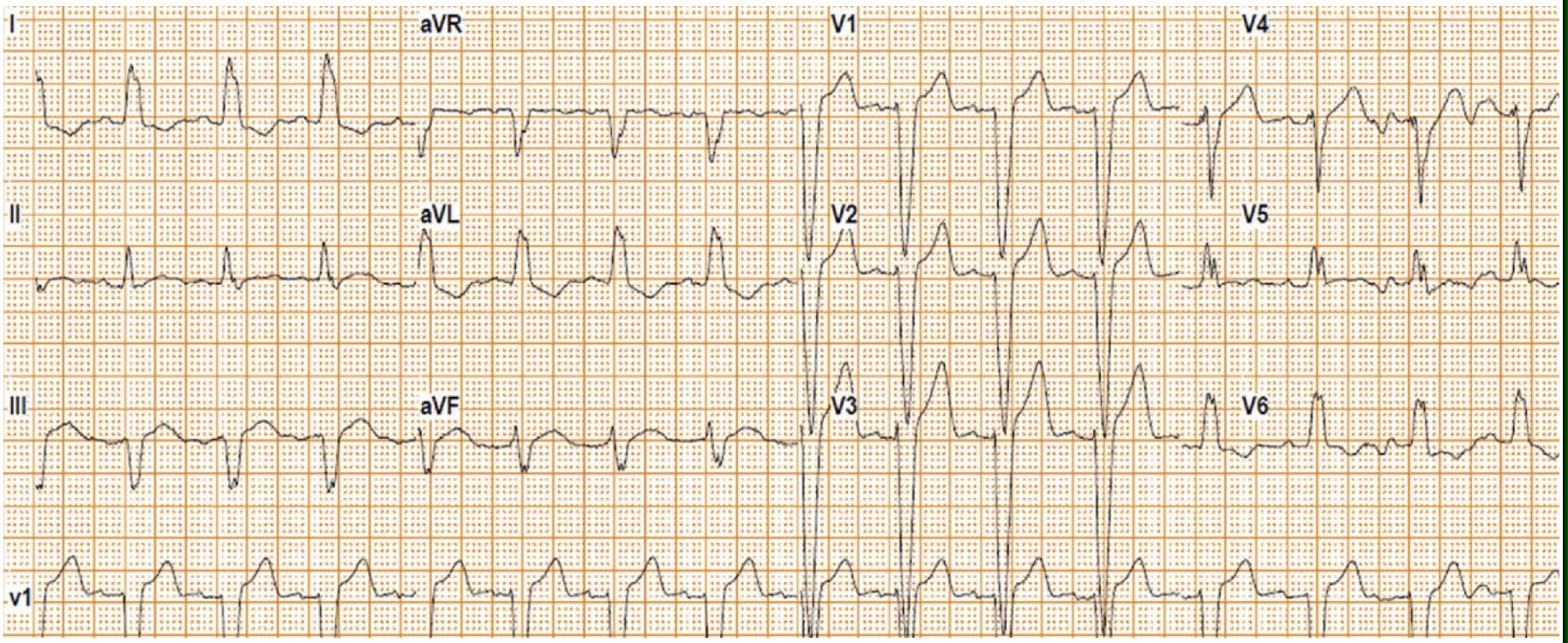
NYHA III or IV Ambulatory

Trial (ref)	No.	Design	NYHA
MUSTIC-SR[52]	58	Single-blinded, crossover, randomized CRT vs. OMT, 6 months	III
PATH-CHF[51]	41	Single-blinded, crossover, randomized RV vs. LV vs. BiV, 12 months	III–IV
MIRACLE[49]	453	Double-blinded, randomized CRT vs. OMT, 6 months	III–IV
MIRACLE-ICD[54]	369	Double-blinded, randomized CRT-D vs. ICD, 6 months	III–IV
CONTAK-CD[53]	490	Double-blinded randomized CRT-D vs. ICD, 6 months	II–III–IV
COMPANION[55]	1520	Double-blinded randomized OMT vs. CRT-P / or vs. CRT-D, 15 months	III–IV
CARE-HF[56]	813	Double-blinded randomized OMT vs. CRT-P 29.4 months	III–IV



Is this Left Bundle Branch Block?

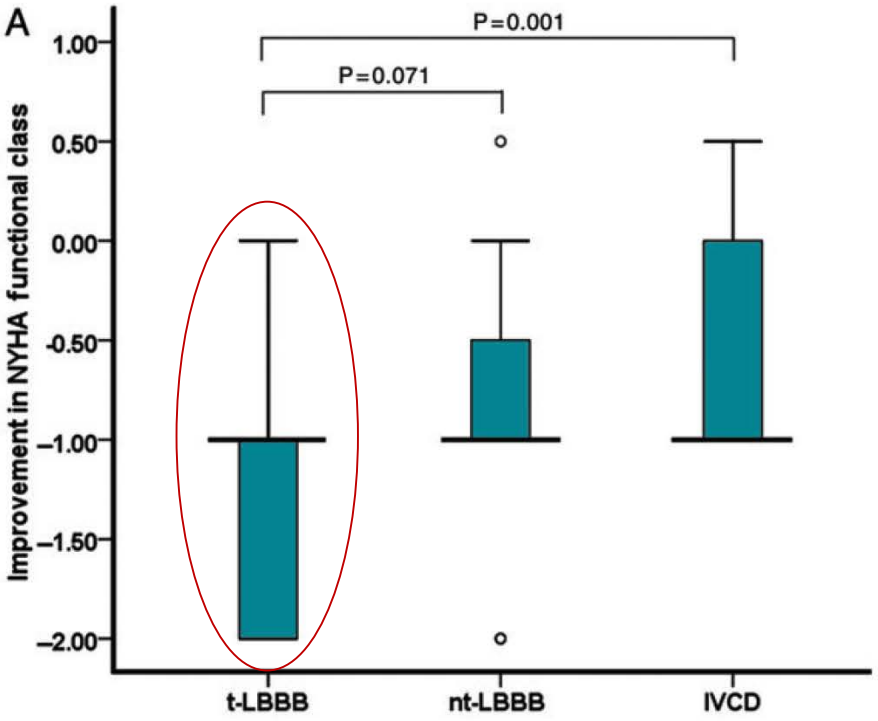
QRS Duration = 140 msec



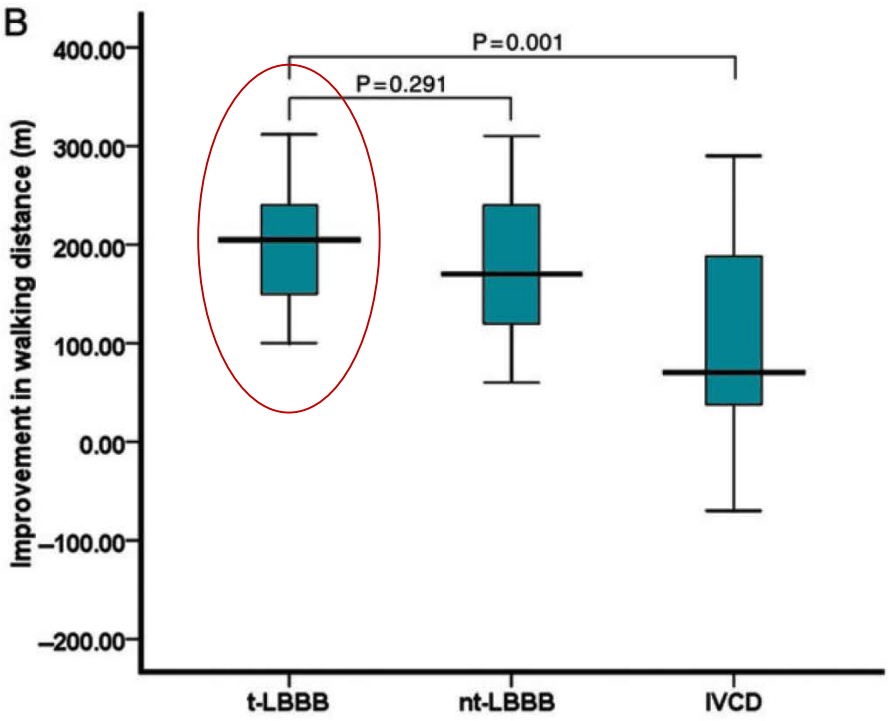
Complete left bundle branch block → True LBBB

True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy

NYHA Class



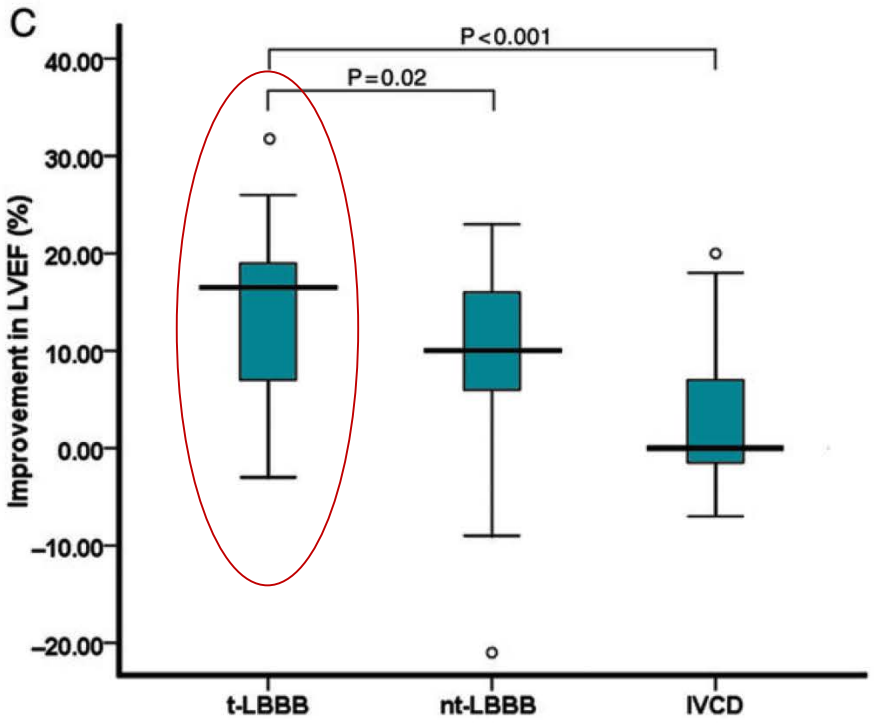
Walking Distance (m)



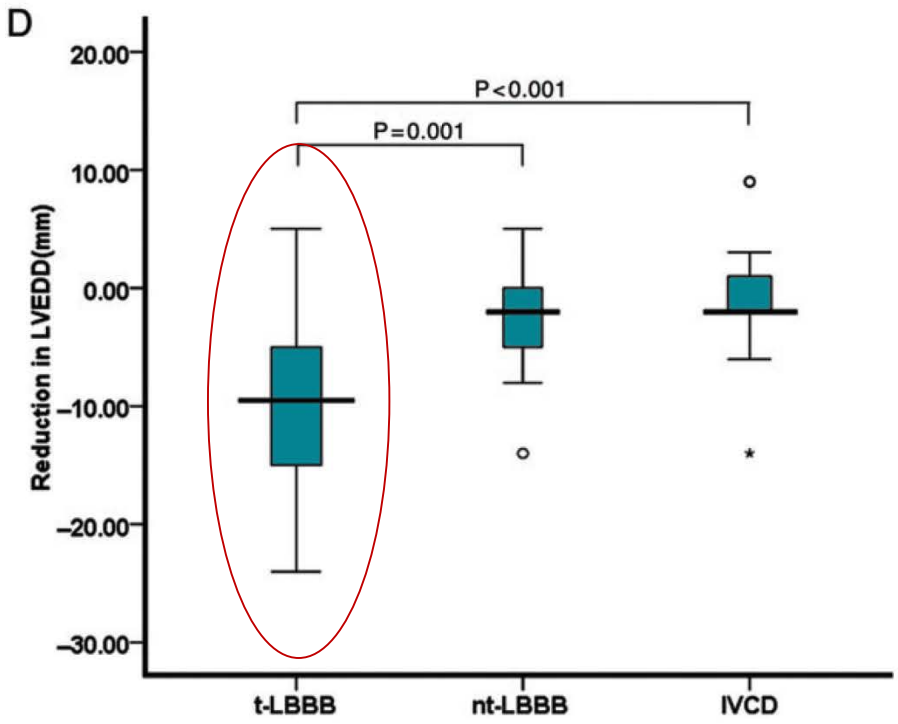
Tian Y et al. Europace 2013; 15: 1499-1506

True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy

LVEF %



LVED Diameter (mm)



Tian Y et al. Europace 2013; 15: 1499-1506

QRS Width and Response to CRT

Potential causes of QRS prolongation

- Relative Electrical Activation of Disparate Sites
- His Purkinjie System Disease
- Intramyocardial Conduction Delay

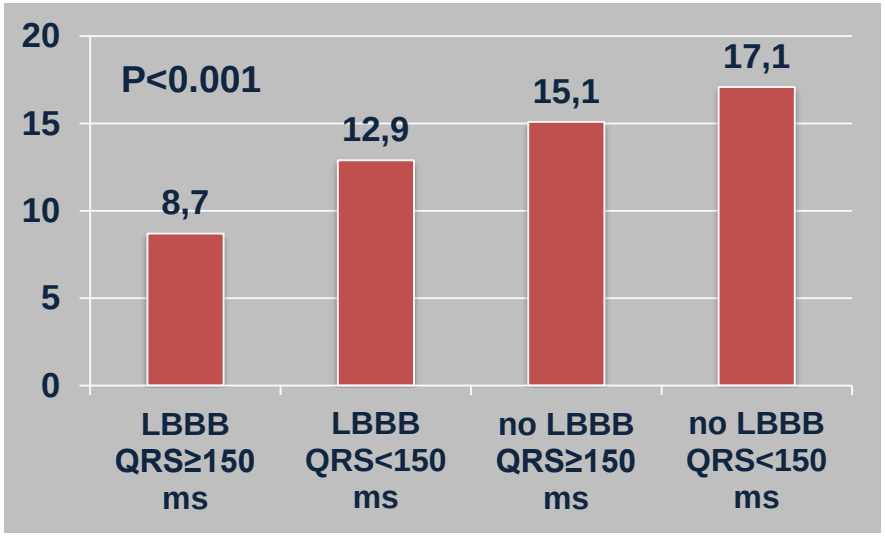
Major increase in QRS duration is associated with significant electropathy

QRS duration is a simple and intuitive variable to guide patient selection and CRT optimization

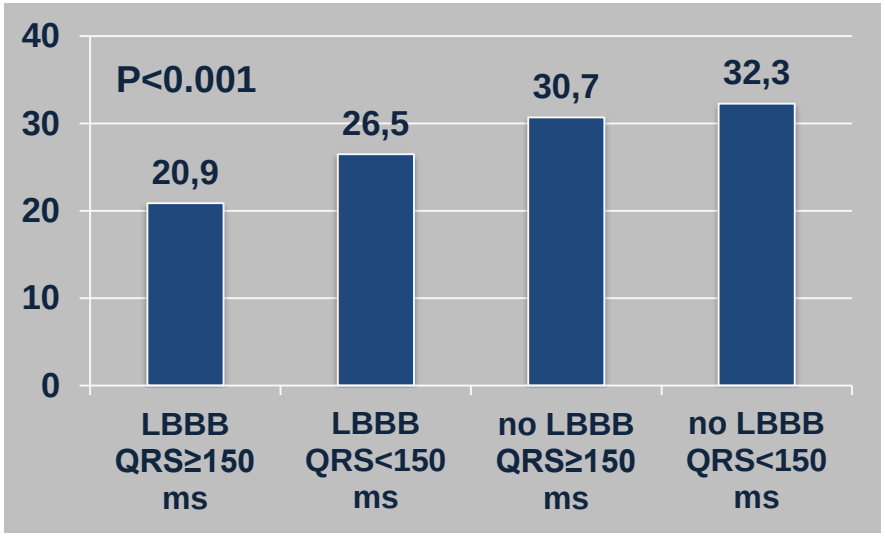
CRT and Outcome According to QRS Morphology in Real World

Medicare National CV Data ICD Registry CRT-D n=24169

% Heart failure readmission 1 year

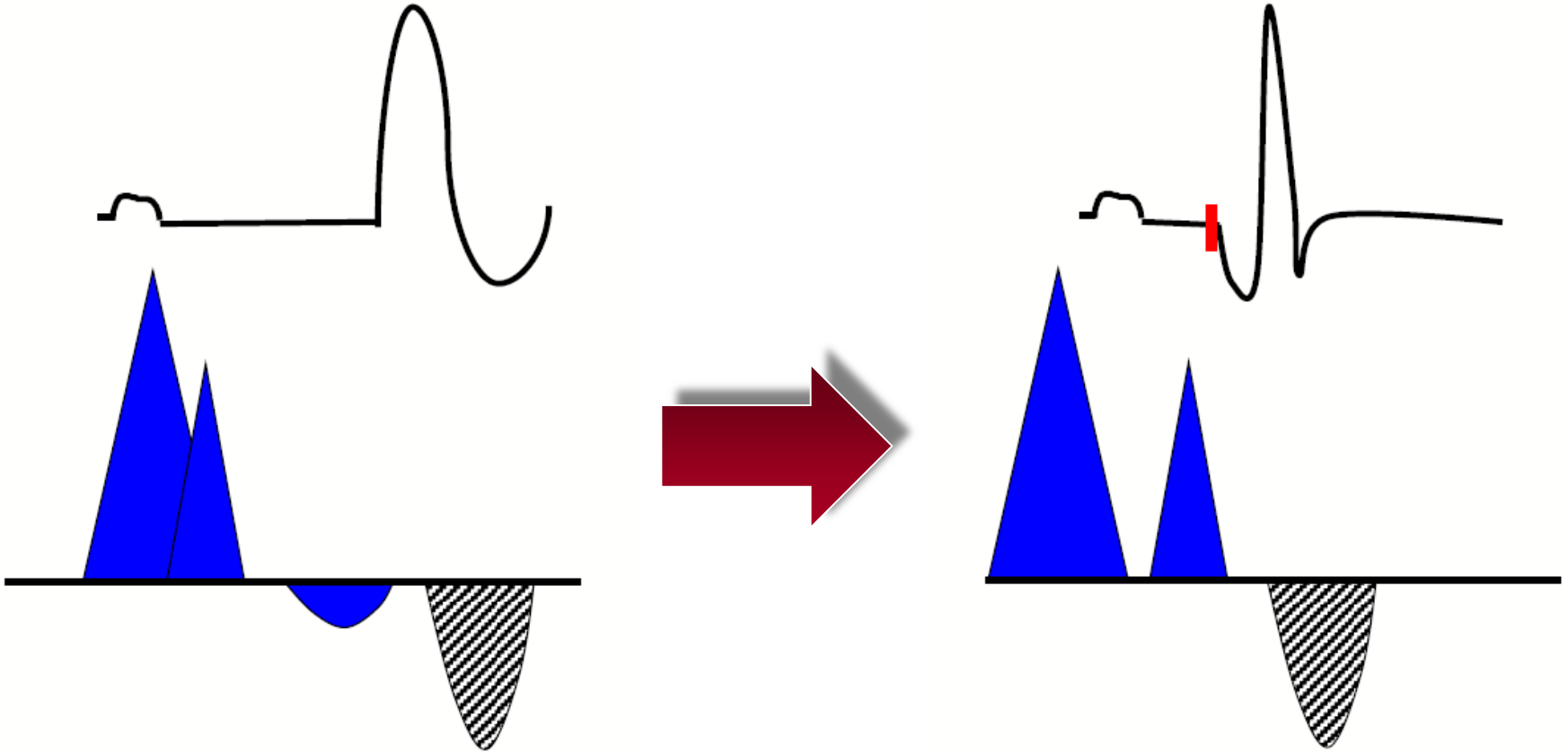


% All-cause mortality 3 years



Peterson PN et al. JAMA 2013; 310:617-626

Non-LBBB with Prolonged PR and CRT

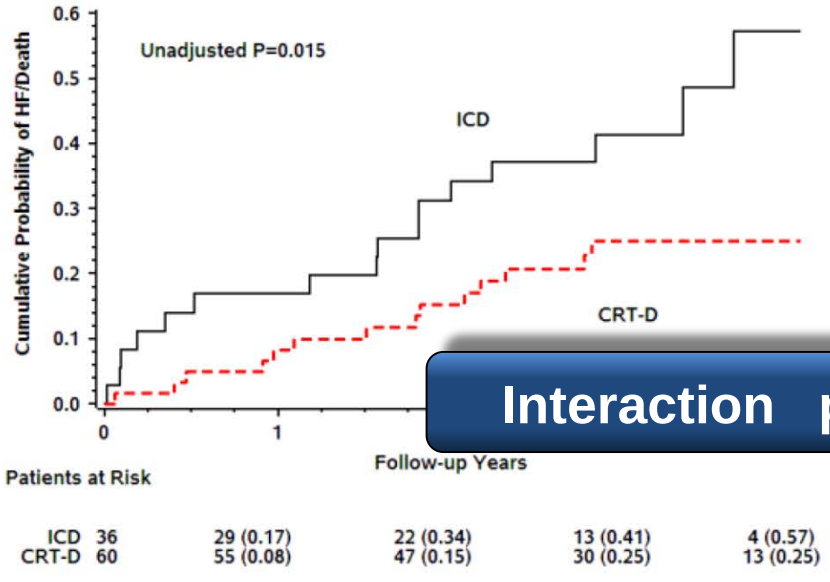


Original Article

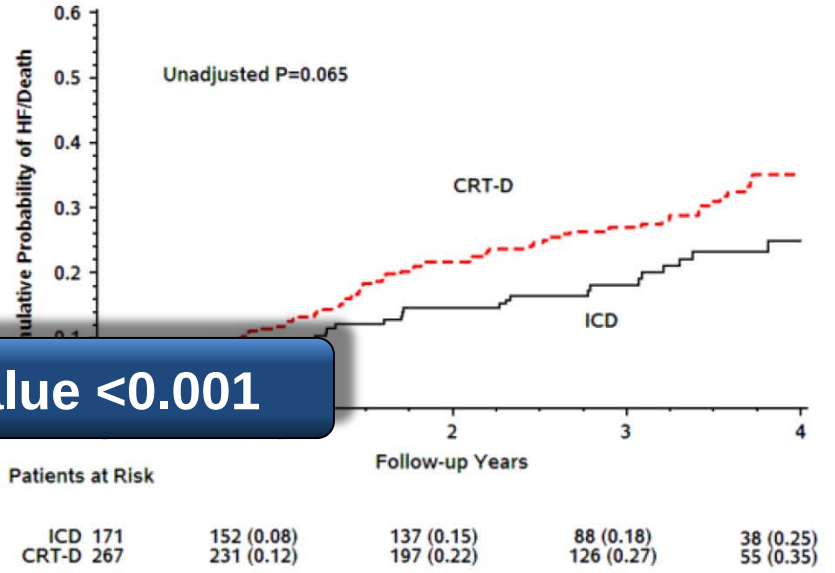
PR Interval Identifies Clinical Response in Patients With Non–Left Bundle Branch Block

A Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy Substudy

PR ≥230 msec



PR <230 msec



Interaction p-value <0.001

HR=0.27, CI: 0.13-0.57,. p<0.001

HR=1.45, CI: 0.95-2.19, p=0.078

Kutyifa et al. Circ Arrhythm Electrophysiol 2014; 7:645-651

Original Article

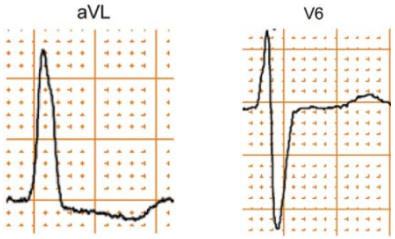
PR Interval Identifies Clinical Response in Patients With Non–Left Bundle Branch Block

A Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy Substudy

End point	HR	95% CI	p-value	Interaction
Heart Failure or Death (141 events)				
CRT-D: ICD in PR < 230 ms	1.45	0.96-2.19	0.078	**<0.001**
CRT-D: ICD in PR ≥ 230 ms	0.27	0.13-0.57	**<0.001**	
Heart Failure only (117 events)				
CRT-D: ICD in PR < 230 ms	1.31	0.84-2.05	0.235	**<0.001**
CRT-D: ICD in PR ≥ 230 ms	0.25	0.11-0.57	**<0.001**	
All-cause mortality (67 events)				
CRT-D: ICD in PR < 230 ms	2.14	1.12-4.09	**0.022**	**<0.001**
CRT-D: ICD in PR ≥ 230 ms	0.19	0.06-0.63	**<0.001**	

Kutyifa et al. Circ Arrhythm Electrophysiol 2014; 7:645-651

Narrow QRS and Mechanical Dyssynchrony



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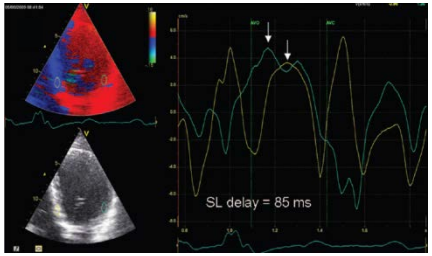


EchoCRT

Echocardiography guided Cardiac Resynchronization Therapy

809 Patients

CHF, NYHA III-IV, under OMT
LVEF ≤35%, LVEDD ≥55 mm
QRS <130 msec + Echo dyssynchrony

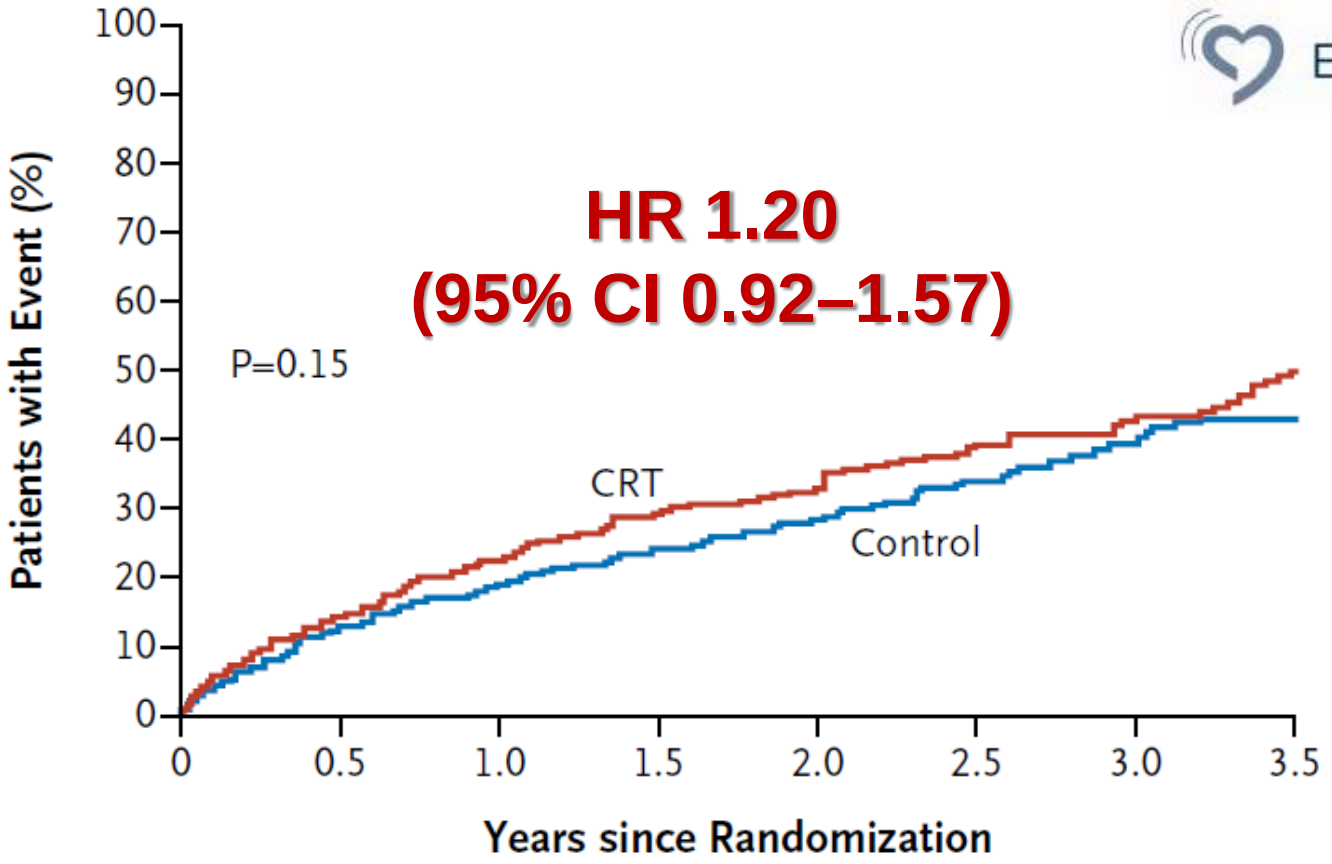
R

ICD
405

CRT-D
404

Ruschitzka F et al. NEJM 2013; 369:1395-405.

HF Hospitalization/All-cause mortality



No. at Risk								
CRT	404	297	223	155	103	65	42	19
Control	405	302	236	166	119	71	44	15

Ruschitzka F et al. NEJM 2013; 369:1395-405.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

ECG — Still the Best for Selecting Patients for CRT

Clyde W. Yancy, M.D., and John J.V. McMurray, M.D.

NEJM 2013; 369: 1463-1464

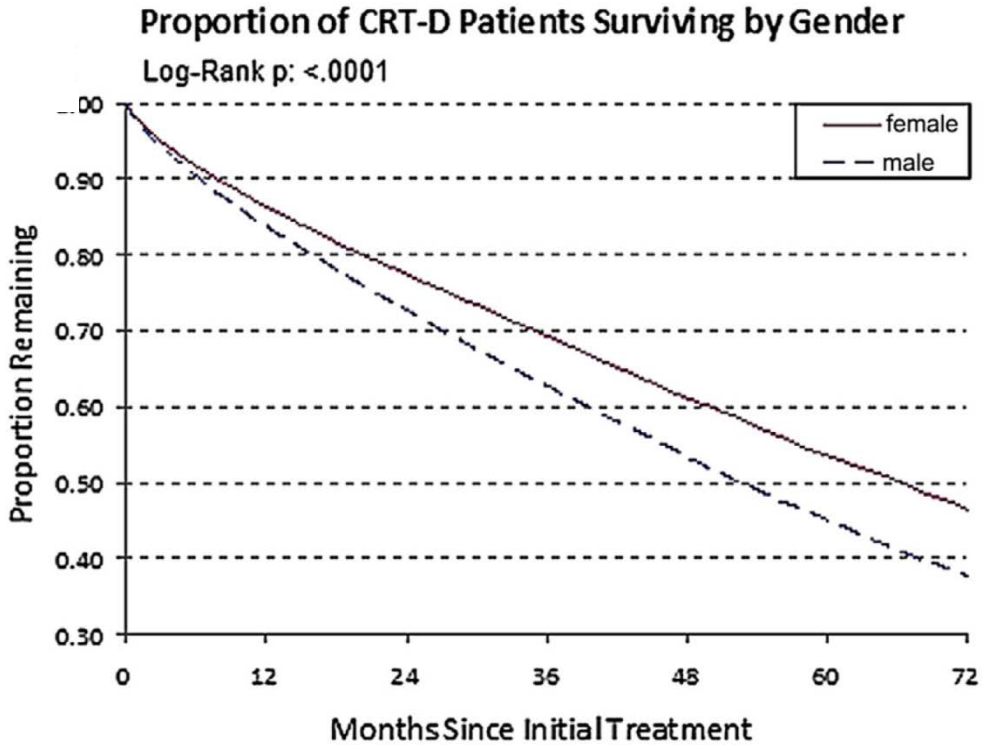
Differences between Men and Women in Cardiovascular Medicine

As compared with men, women:

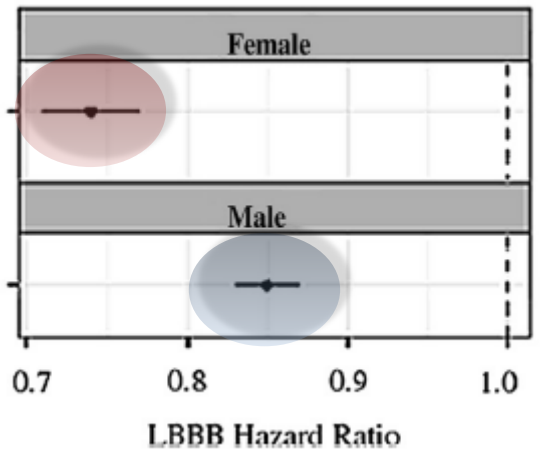
1. Lower prevalence of coronary artery disease
2. Higher prevalence of coronary μ-vascular dysfx
3. More likely to have HF with preserved LVEF
4. Higher prevalence of stress induced CMP
5. Greater susceptibility to QT prolonging drugs

Left Bundle Branch Block Predicts Better Survival in Women Than Men Receiving Cardiac Resynchronization Therapy

Long-Term Follow-Up of ~145,000 Patients



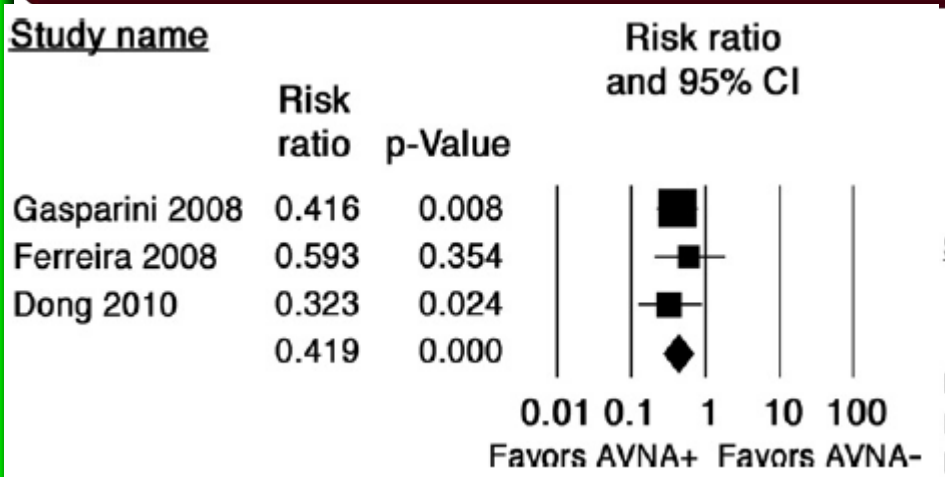
HR 0.74 (95% CI 0.71-0.77)



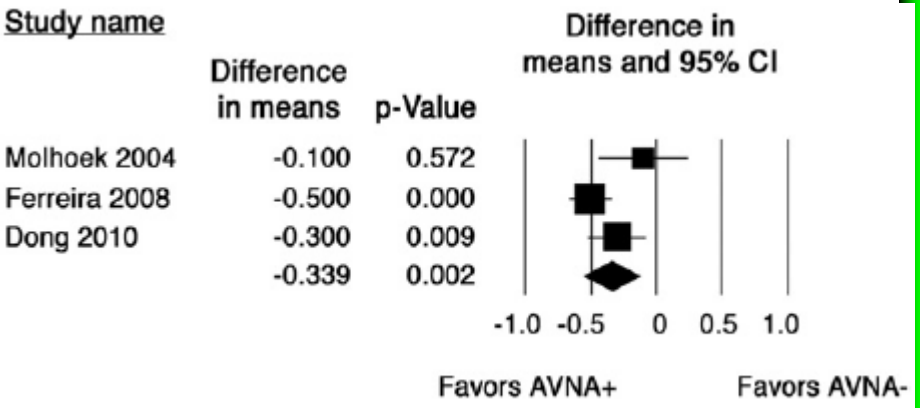
HR 0.85 (95% CI 0.83-0.87)

Loring Z et al. JACC Heart Fail 2013;1:237–44

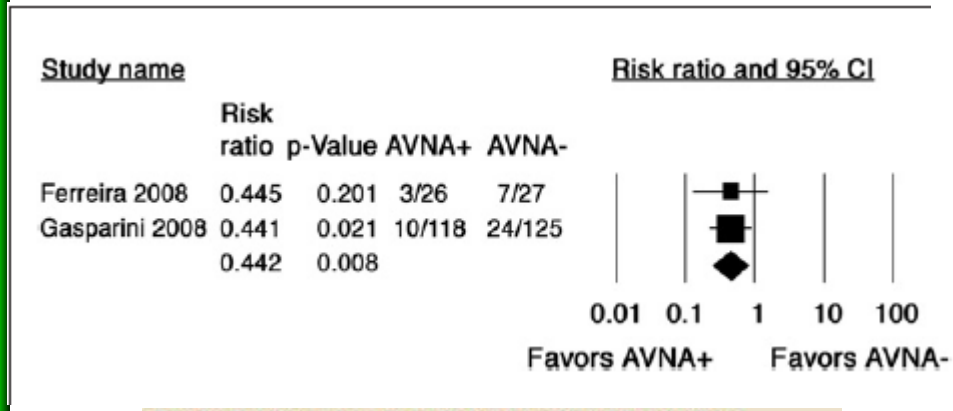
Evidence for CRT in pts with AFib



Risk Ratios for All-Cause Mortality in CRT-AF Patients Undergoing AVNA Versus Medical Therapy With Rate-Controlling Drugs

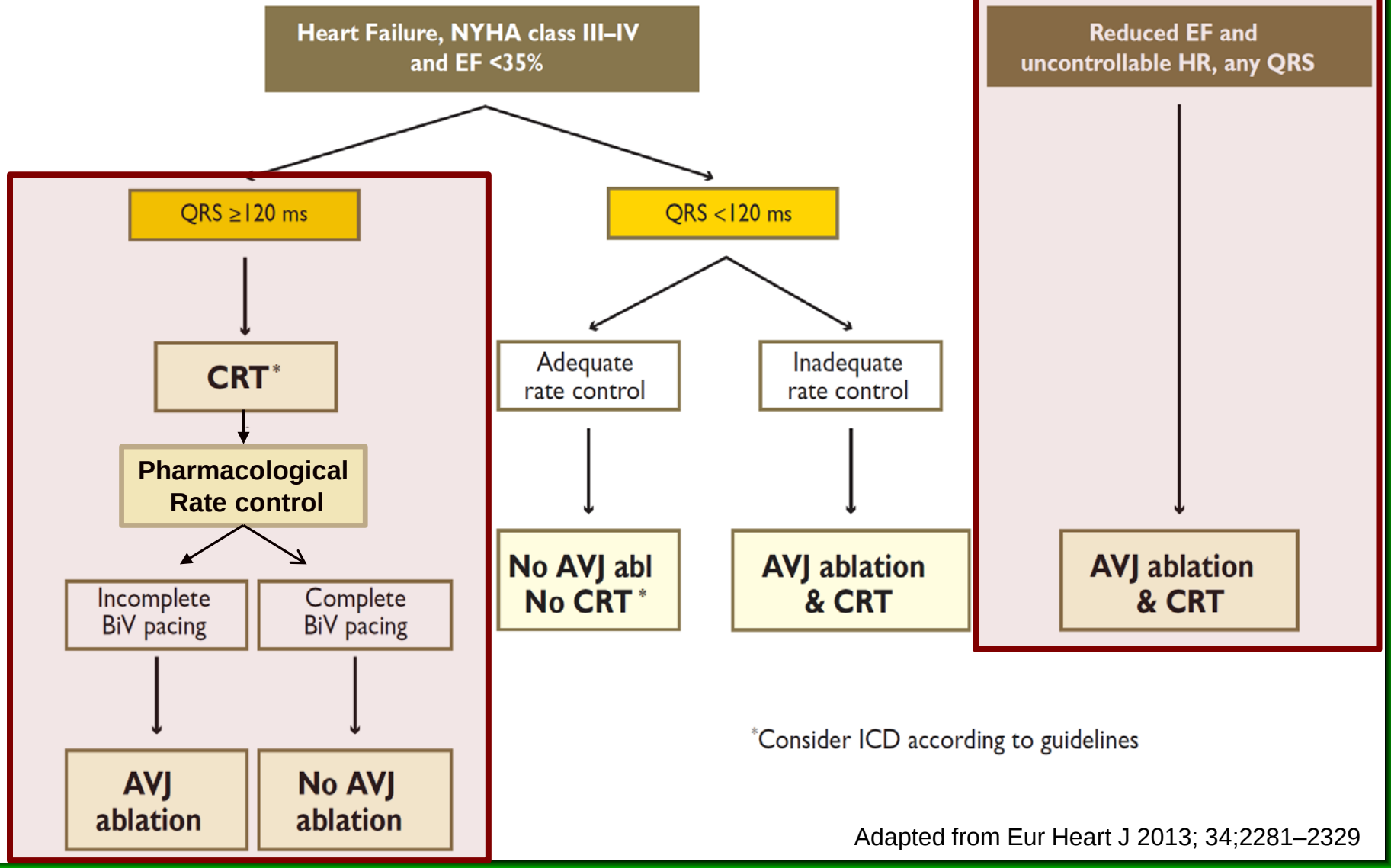


Mean Difference in NYHA Functional Class for CRT-AF Patients Undergoing AVNA Versus Medical Therapy With Rate-Controlling Drugs



Risk Ratios for Cardiovascular Mortality for CRT-AF Patients Undergoing AVNA Versus Medical Therapy With Rate-Controlling Drugs

CRT in Atrial Fibrillation



Adapted from Eur Heart J 2013; 34;2281–2329

Upgrading or de novo CRT in pts with conventional PM indication and HF

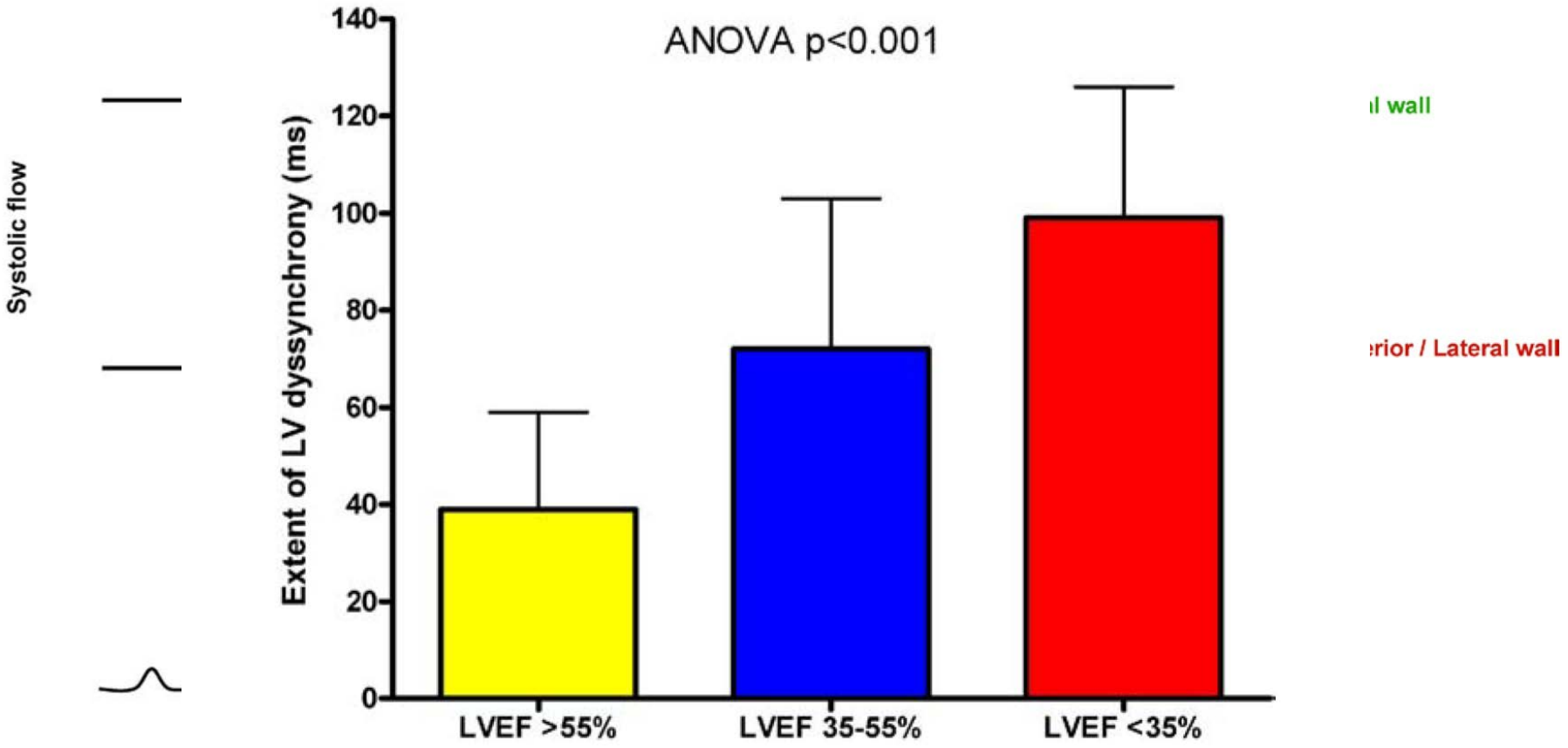
Recommendations	Class [a]	Level [b]	Ref. [c]
1) Upgrade from conventional PM or ICD. CRT is indicated in HF patients with LVEF <35% and high percentage of ventricular pacing who remain in NYHA class III and ambulatory IV despite adequate medical treatment. [d]	I	B	47, 108–122
2) *De novo* cardiac resynchronization 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

Eur Heart J 2013; 34;2281–2329

Dyssynchrony during RV pacing

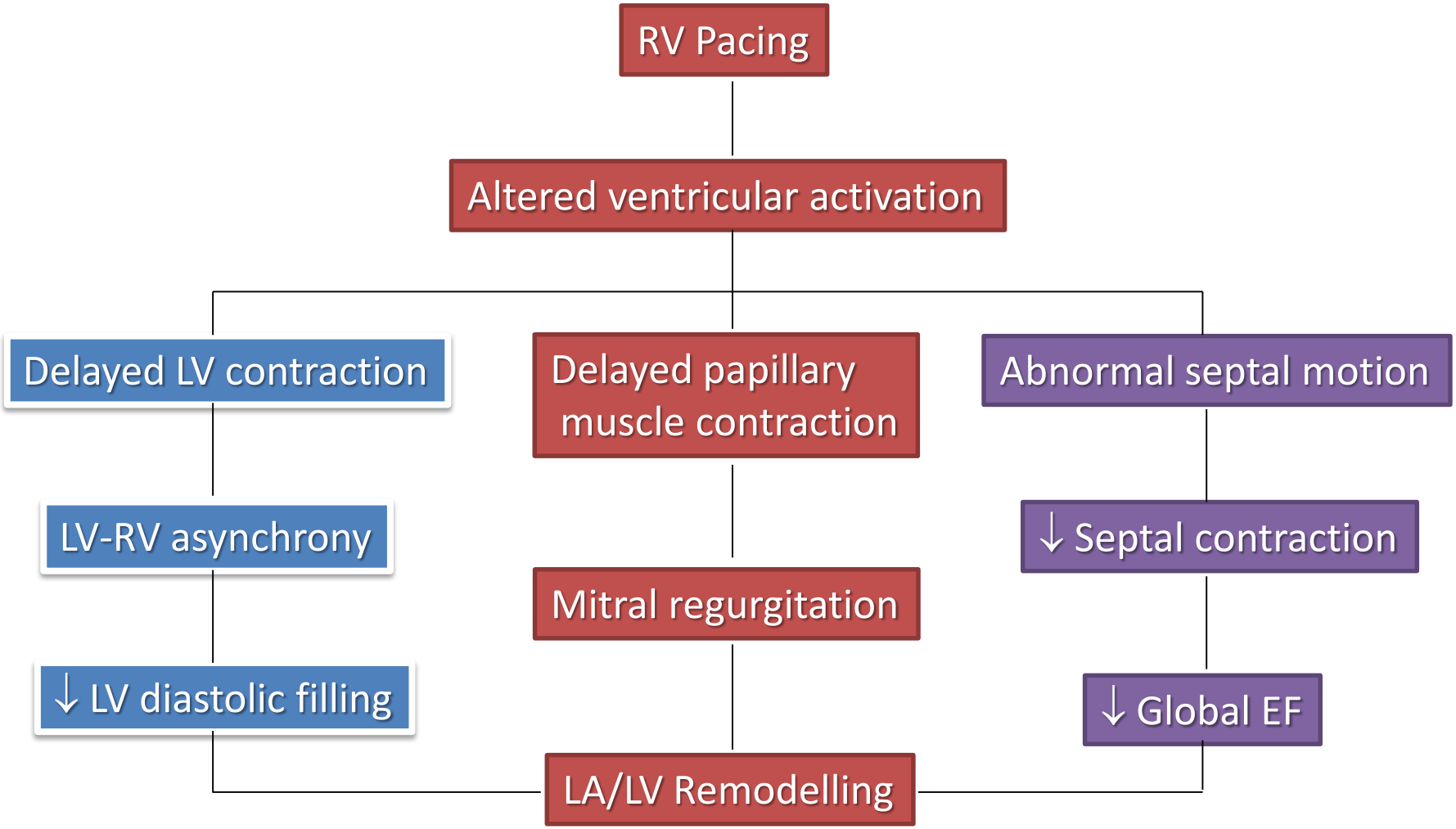
INTERVENTRICULAR DYSSYNCHRONY

INTRAVENTRICULAR DYSSYNCHRONY



JACC 2009; 54: 764-776

Detrimental effects of chronic RV pacing



Adapted from Curtis et al. US Cardiology 2008