Κριτική προσέγγιση των νεότερων ενδείξεων για τον καρδιακό επανασυγχρονισμό

4ο Συνέδριο Επεμβατικής Καρδιολογίας και Ηλεκτροφυσιολογίας

Θεμιστοκλής Μαούνης
Ωνάσειο ΚΧΚ

Θεσσαλονίκη, 26.11.11

European Heart Journal (2010) 31, 2677–2687
doi:10.1093/eurheartj/ehq337

ESC GUIDELINES

2010 Focused Update of ESC Guidelines on device therapy in heart failure

An update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy

Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association

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ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) Developed in Collaboration With the American Association for Thoracic Surgery and Society of Thoracic Surgeons

Andrew E. Epstein, John P. DiMarco, Kenneth A. Ellenbogen, N.A. Mark Estes, III, Roger A. Freedman, Leonard S. Gettes, A. Marc Gillinov, Gabriel Gregoratos, Stephen C. Hammill, David L. Hayes, Mark A. Hlatky, L. Kristin Newby, Richard L. Page, Mark H. Schoenfeld, Michael J. Silka, Lynne Warner Stevenson, and Michael O. Sweeney

J. Am. Coll. Cardiol. 2008;51;e1-e62; originally published online May 15, 2008; doi:10.1016/j.jacc.2008.02.032

Recommendation in patients with heart failure in New York Heart Association function class III/IV

Recommendation	Patient population	Class[a]	Level[b]	Ref.[c]
CRT-P/CRT-D is recommended to reduce morbidity and mortality[d]	NYHA function class III/IV LVEF ≤35%, QRS ≥120 ms, SR Optimal medical therapy Class IV patients should be ambulatory[e]	I	A	5–19

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Reasonable expectation of survival with good functional status for >1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D.
[e]No admissions for HF during the last month and a reasonable expectation of survival >6 months.

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CLASS I

1. **For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, CRT with or without an ICD is indicated for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms with optimal recommended medical therapy. *(Level of Evidence: A)*** (222,224,225,231)

Table I Inclusion criteria in randomized clinical trials evaluating cardiac resynchronization therapy in heart failure

Trial	Patients	NYHA class	LVEF (%)	LVEDD (mm)	SR/AF	QRS (ms)	ICD
MUSTIC-SR[16]	58	III	≤35	≥60	SR	≥150	No
MIRACLE[5]	453	III, IV	≤35	≥55	SR	≥130	No
MUSTIC AF[35]	43	III	≤35	≥60	AF	≥200	No
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PATH CHF II[55]	89	III, IV	≤35	NA	SR	≥120	Yes/no
COMPANION[10]	1520	III, IV	≤35	NA	SR	≥120	Yes/no
CARE HF[11]	814	III, IV	≤35	≥30	SR	≥120	No
CARE HF[17]	813	III, IV	≤35	≥30	SR	≥120	No
REVERSE[21,22]	610	I, II	≤40	≥55	SR	≥120	Yes/no
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CRT-P/CRT-D

- Ασθενείς για CRT έχουν ένδειξη κατηγορίας I και για εμφύτευση απινιδωτή (MADIT-SCDHeFT)
- ? Αντιαρρυθμική-προοαρρυθμική επίδραση CRT
- Μείωση αιφνιδίου θανάτου από CRT (CARE-HF extension) κατά 46%
- Μειωμένος κίνδυνος αιφνιδίου θανάτου σε μη ισχαιμικούς σε σύγκριση με ισχαιμικούς εμφύτευση απινιδωτή ⇒ μικρότερο όφελος, εξάλλου μη ισχαιμικοί μεγαλύτερο όφελος από CRT (CARE-HF ⇓49%-32%)
- Πιο ηλικιωμένοι ασθενείς, βαρύτερη καρδιακή πάθηση, εκτίμηση κινδύνου επιπλοκών
- ❖ Κόστος

Recommendation in patients with heart failure in New York Heart Association function class III/IV

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Table 1. Characteristics of trials in heart failure patients with wide QRS.

Baseline characteristics	CARE HF [24]		COMPANION [23]		MIRACLE [20, 32]		MUSTIC [18]		MUSTIC AF [19]	
	Medical Rx	CRT	Medical Rx	CRT	Medical Rx	CRT	First study group	Second study group	UniRV–BiV	BiV–UniRV
Randomization	Yes		Yes		Yes		Yes		Yes	
Follow up	24.9 months		12 months		6 months		6 months		6 months	
Number	404	409	308	617	225	228	29	29	18	25
Mean QRS	160*	160*	158*	160*	165 ± 20	167 ± 21	172 ± 22	175 ± 19	209 ± 18	209 ± 21
Age	66*	67*	68*	67*	64 ± 11	64 ± 10.7	64 ± 11	64 ± 8	66 ± 9	65 ± 9
Men (%)	73	74	69	67	68	68	65.5	82.7	77	84
Ischemic (%)	40	36	59	54	58	50	37.3	37.3	143	13
NYHA III (%)	93	94	82	87	91	90	100	100	100	100
QoL	NA	NA	39	40	59 ± 21	59 ± 20	48 ± 19	46 ± 25	50 ± 20	40 ± 23
6 MWD	NA	NA	244*	274*	291 ± 101	305 ± 85	354 ± 110	346 ± 111	317 ± 71	338 ± 95
LVEF	25*	25*	22*	20*	21.6 ± 6.2	21.8 ± 6.3	23 ± 7	23 ± 7	30 ± 12	23 ± 7
Diuretics (%)	44	43	94	94	93	94	94	94	100	100
ACEI or ARB (%)	95	95	89	89	90	93	96	96	100	100
Beta-blockers (%)	74	70	66	68	55	62	28	28	23	23
Spirinolactone (%)	59	54	53	53	NA	NA	22	22	16	16
Digoxin (%)	45	40	NA	NA	79	78	48	48	58	58

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Spirinolactone (%)	59	54	53	53	NA	NA	22	22	16	16
Digoxin (%)	45	40	NA	NA	79	78	48	48	58	58

Stavrakis, et al. J CV EP 2011

- Μετανάλυση: 5 μελέτες- 6500 ασθενείς
- CRT μείωσε σημαντικά τον κίνδυνο θανάτου ή νοσηλείας μόνο σε ασθενείς με QRS>150msec σε όλες τις λειτουργικές κατηγορίες ασθενών

Τύπος διαταραχής της αγωγής

- CARE-HF (Gervais, Eur J Heart Fail 2009), πολύ κακός προγνωστικός δείκτης το RBBB και το παρατεταμένο PR
- Rickard, et al.PACE 2010: Μικρότερο όφελος από CRT σε ασθενείς με RBBB ή IVCD σε σύγκριση με LBBB

«Επανασυγχρονισμός” σε στενό QRS

- 40-50% ασθενών με καρδιακή ανεπάρκεια και στενό QRS έχουν «δυσυγχρονισμό».

Αρκετές μικρές μελέτες έχουν δείξει όφελος από CRT σε ασθενείς με στενό QRS και «δυσυγχρονισμό»

	Bleeker et al. [47]		Yu et al. [48]		Achilli et al. [46]		Gasparini et al. [49]	
	< 120 ms	> 120 ms	< 120 ms	> 120 ms	< 120 ms	> 120 ms	< 120 ms	> 120 ms
Reduction in NYHA	0.9 ± 0.6	1.1 ± 0.6	0.73 ± 0.49	0.81 ± 0.68	1.6 ± 0.1	1.7	NA	NA
Reduction in QoL	13 ± 16	17 ± 12	8 ± 19	18 ± 20	NA	NA	NA	NA
Improvement 6 MWD	89 ± 107	130 ± 95	46 ± 88	53 ± 61	93.5 ± 18.7	138.2 ± 27	182	128
Improvement in LVEF (%)	8 ± 8	9 ± 7	7.3 ± 6.3	8.3 ± 7.6	9 ± 0.9	10.6 ± 0.8	14	9
Reduction in LVEDV[1] (cc)/ /LVEDD[2] [mm]	26 ± 32[1]	35 ± 51[1]	8.6 ± 14[1]	16.1 ± 17.6[1]	65.6 ± 8.52[2]	71.6 ± 10.72[2]	NA	NA
Reduction in LVESV[1] (cc)/ /LVESD[2] [mm]	39 ± 34[1]	44 ± 46[1]	17.1 ± 18.6[1]	24.2 ± 21[1]	55.6 ± 8.22[2]	57.9 ± 112[2]	71.8	55.3
All cause mortality	9	14	NA	NA	3	7	3	51
Sudden death	0	2	NA	NA	1	4	1	5
Progressive HF	8	11	NA	NA	2	2	0	35

RethinQ

- CRT σε ασθενείς με QRS<120 και δυσυγχρονισμό
- Χωρίς βελτίωση σε VO2max, ούτε σε ποιότητα ζωής, ούτε σε 6MWD, ούτε όγκο LV
- Μόνο σε μερικούς βελτίωση NYHA
- f/up μόνο 6 μήνες

❖EchoCRT, CRT-narrow, EARTH

ΗΚΓ ή υπερηχοκαρδιογραφικός δυσυγχρονισμός;

- Πολλές μικρές μονοκεντρικές μελέτες είχαν δείξει υπεροχή υπερηχογραφικών κριτηρίων για επιλογή ασθενών για CRT.
- Μεγάλος αριθμός δεικτών «δυσυγχρονισμού»
- Πολυκεντρική μελέτη PROSPECT μελετήσε 12 δείκτες και απέτυχε να βρει ένα υπερηχογραφικό δείκτη με αξιόλογη προγνωστική αξία

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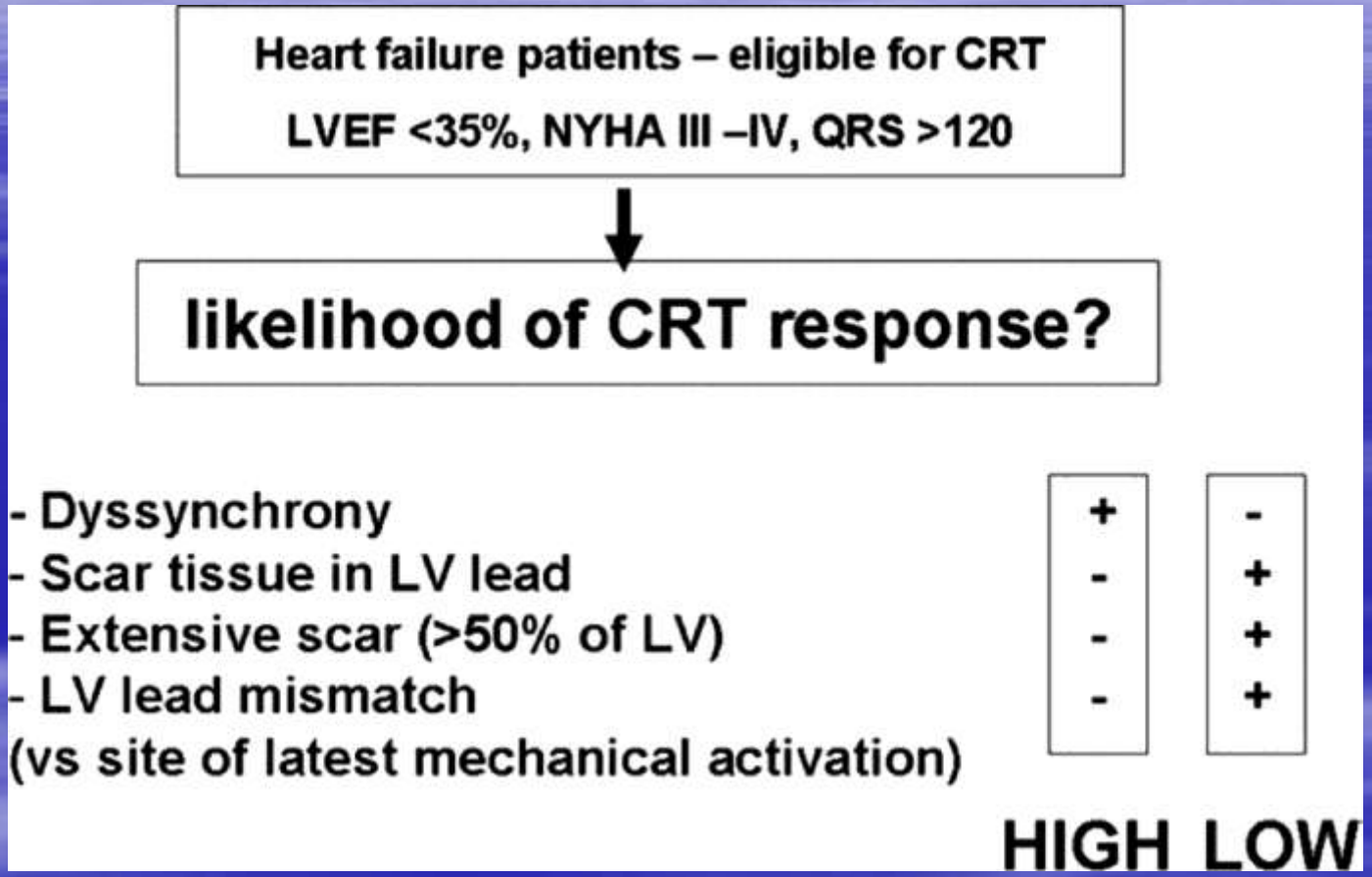
NYHA IV

- COMPANION: βελτίωση νοσηρότητας (μη σημαντική θνησιμότητας) σε περιπατητική (δίχως νοσηλεία > 1 μήνα) κατηγορία IV
- CARE-HF: μεγαλύτερη μείωση συμβαμάτων σε IV (50%-36%) σε σύγκριση με III, αλλά οριακή σημαντικότητα
- Ασθενείς IV σε ενδοφλέβια ινότροπα: κυρίως μεμονωμένες ανακοινώσεις με αντιφατικά αποτελέσματα

Παρά τη χρήση των κριτηρίων αυτών 30% των ασθενών δεν αποκρίνονται στη θεραπεία

Algorithm to Help Determine Whether the Patient Has a High or Low Likelihood of Response to CRT



Van Bommel, R. J. et al. J Am Coll Cardiol 2010;56:754-762

JACC Journal of the American College of Cardiology

Άλλοι παράγοντες που πιθανώς να έπρεπε να λαμβάνονται υπόψιν

- Ισχαιμική ή μη αιτιολογία
- Πολύ μεγάλη διάταση ΑΚ (>75mm)
- Βαριά ανεπάρκεια μιτροειδούς
- Βαριά δυσλειτουργία ΔΚ
- Πνευμονική υπέρταση
- ΧΑΠ
- Βαριά περιφερική αρτηριοπάθεια
- Τελικό στάδιο ΧΝΑ

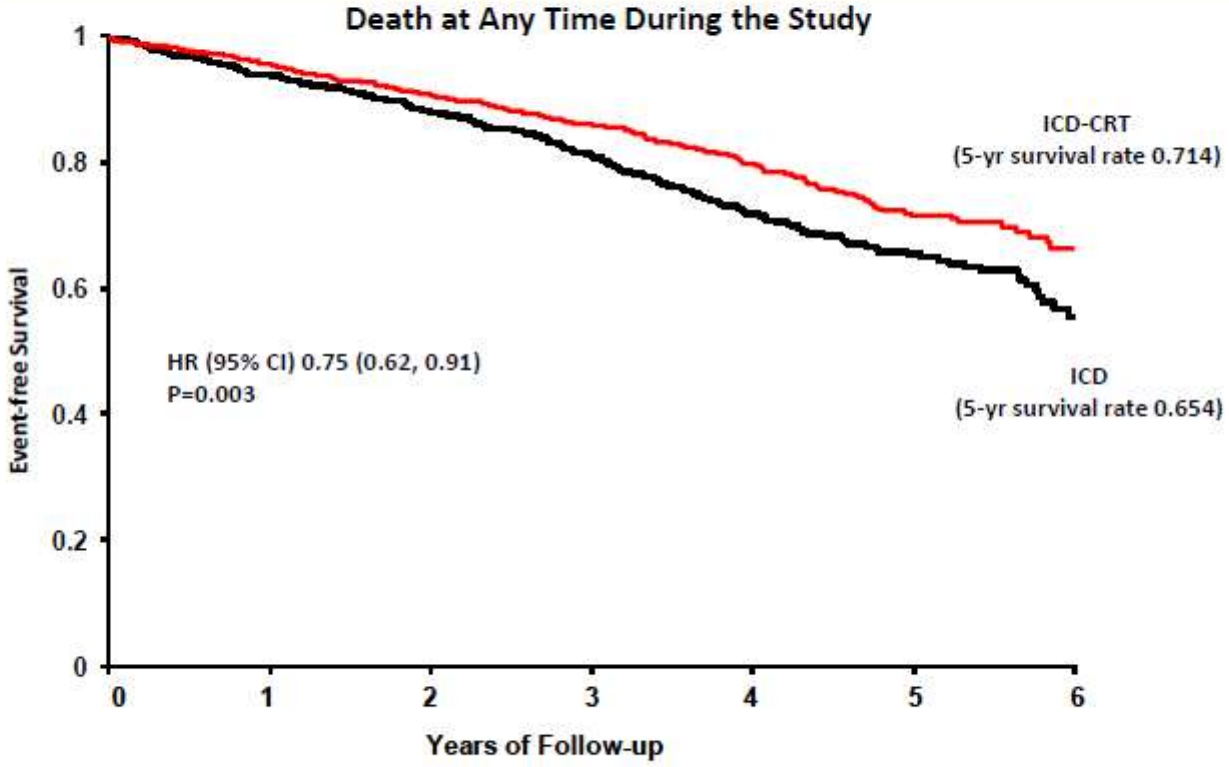
Recommendation in patients with heart failure in New York Heart Association function class II

Recommendation	Patient population	Class[a]	Level[b]	Ref.[c]
CRT preferentially by C T-D is recommended to rec e morbidity or to preven disease progression[d]	NYHA function class II LVEF ≤35%, QRS ≥150 ms, SR Optimal medical therapy	I	A	9, 20–22

ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American

MIRACLE ICD II, MADIT-CRT, REVERSE (+ European Extension), RAFT

Kaplan-Meier Estimates of All cause Mortality



No. at Risk							
ICD/CRT	894	849	685	502	333	167	53
ICD	904	841	670	482	289	149	35

Recommendation in patients with heart failure in New York Heart Association function class II

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Μελέτες CRT σε NYHA I-II

	ΕΕ	QRS	ΠΡ.ΣΤΟΧΟΣ	ΑΠΟΛΟΤΕΛ	Δ. ΣΤΟΧΟΣ
MIRACLE ICD II	<35	>130	VO2max	–	+/-
REVERSE	<40	>120	ΚΛΙΝΙΚΟ	–	+
REVERSE EE	«	«	«	+	+
MADIT-CRT	<30	>130	ΘΝΗΣ+ΚΑ	+	+
RAFT	<30	>120	ΘΝΗΣ+ΚΑ	+	+

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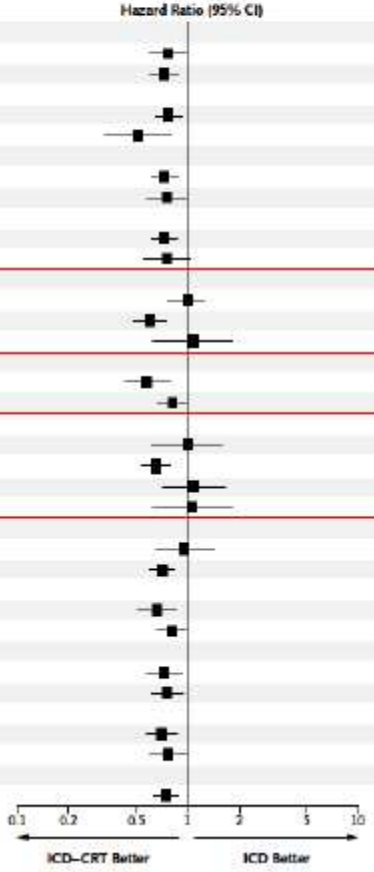
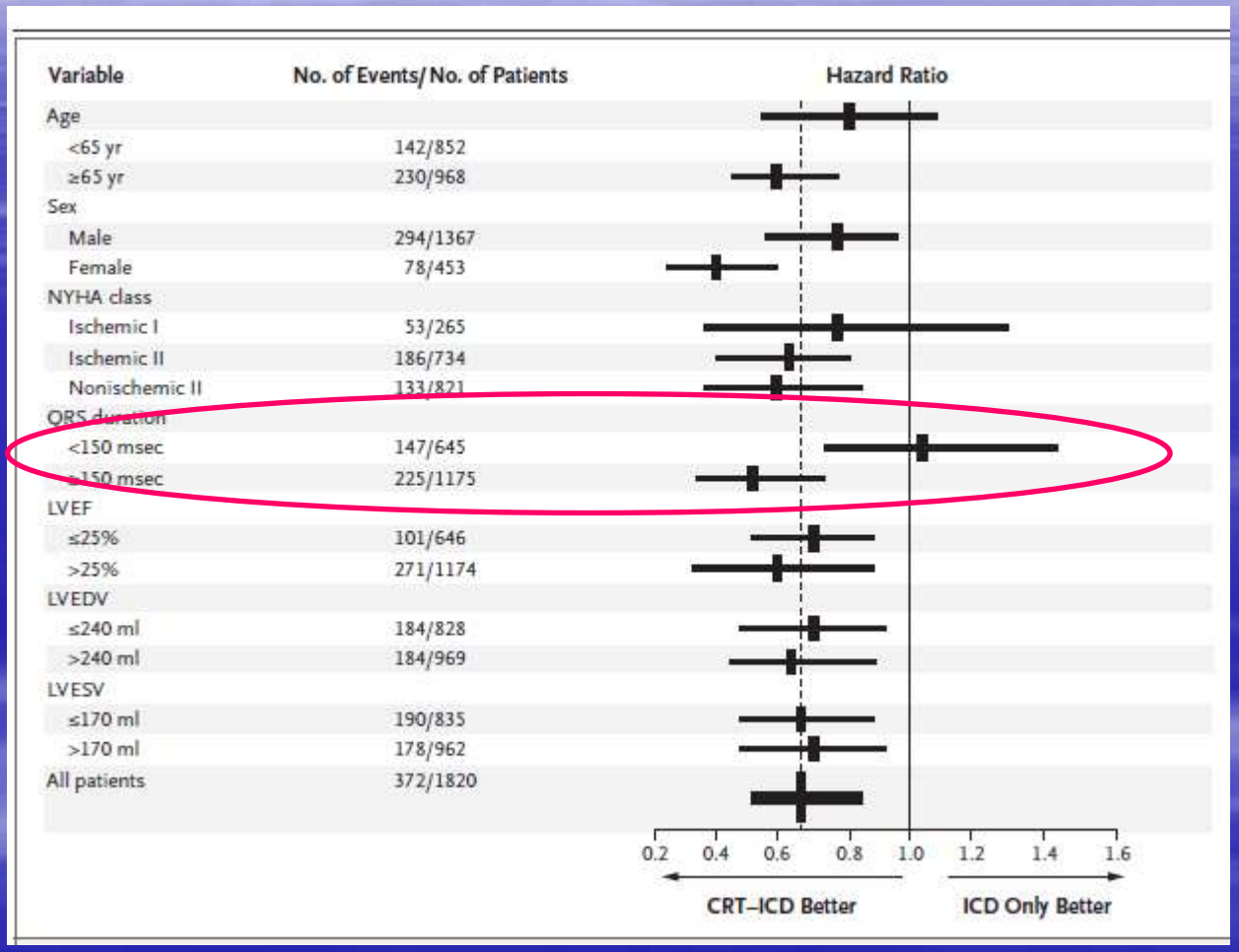
Μελέτες CRT σε NYHA I-II

	EF	QRS	ΠΡ.ΣΤΟΧΟΣ	ΑΠΟΛΟΤΕΛ	Δ. ΣΤΟΧΟΣ
MIRACLE ICD II	<35	>130	VO2max	_	+/-
REVERSE	<40	>120	ΚΛΙΝΙΚΟ	_	+
REVERSE EE	«	«	«	+	+
MADIT-CRT	<30	>130	ΘΝΗΣ+ΚΑ	+	+
RAFT	<30	>120	ΘΝΗΣ+ΚΑ	+	+

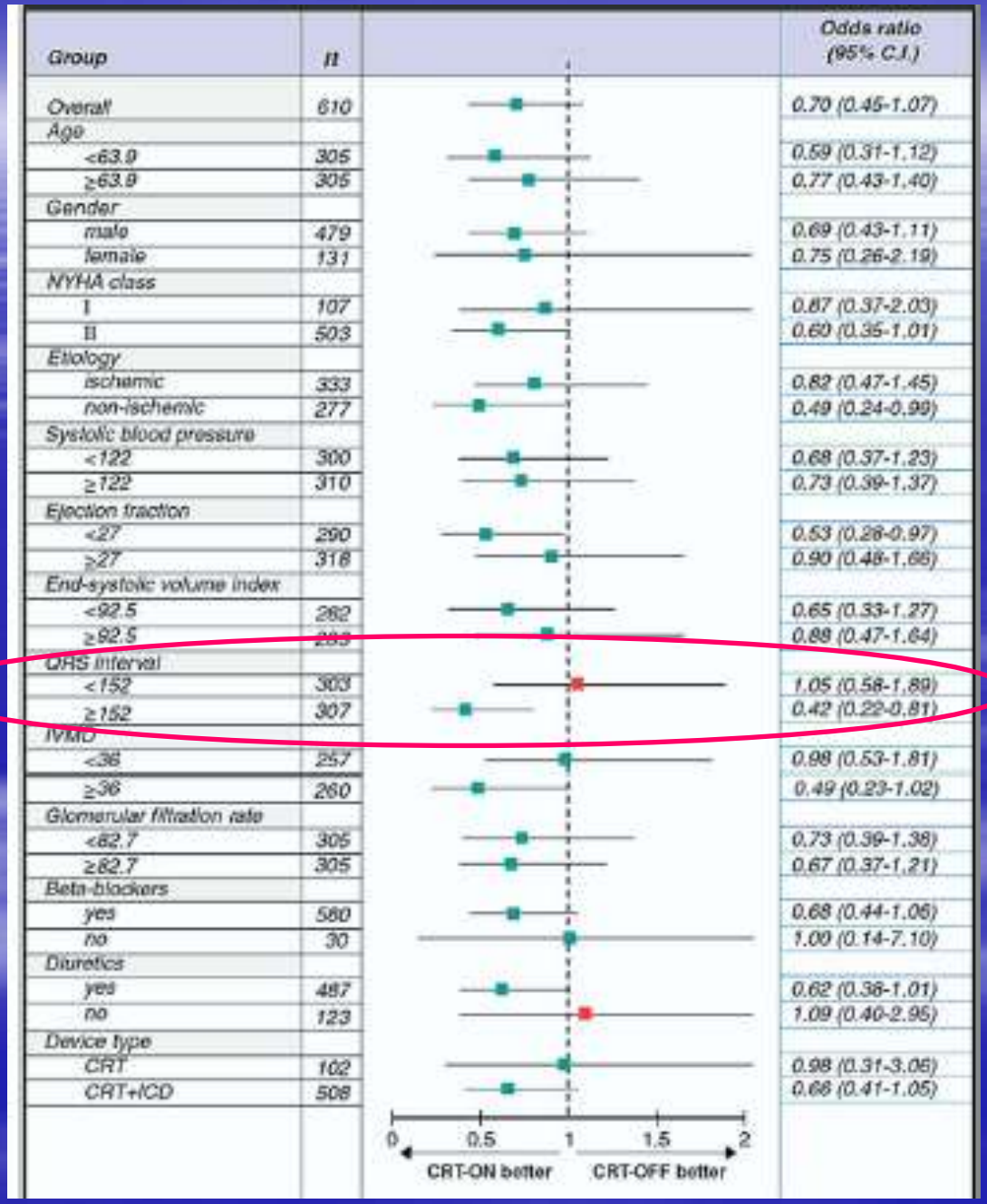
Primary Outcome: Subgroup Analysis

Subgroup	No./Total No.	P Value for Interaction
Age		0.75
< 65 yr	74/763	
≥ 65 yr	420/1035	
Sex		0.09
Male	373/1490	
Female	88/308	
NYHA class		0.91
II	446/1438	
III	215/360	
Underlying heart disease		0.90
Ischemic	488/1261	
Nonischemic	163/597	
QRS duration		0.003
Intrinsic QRS <150 msec	248/627	
Intrinsic QRS ≥150 msec	339/1036	
Paced QRS ≥ 200 msec	54/135	
Left ventricular ejection fraction		0.05
< 20%	175/431	
≥ 20%	486/1367	
QRS morphologic features		0.046
Right bundle-branch block	70/161	
Left bundle-branch block	449/1295	
NIVCD	88/207	
Paced	54/135	
Atrial rhythm		0.14
Permanent atrial fibrillation or flutter	104/229	
Sinus or atrial paced	557/1569	
Diabetes		0.22
Yes	258/606	
No	403/1192	
Hypertension		0.84
Yes	202/799	
No	369/999	
Estimated GFR		0.70
< 60 ml/min/1.73 m²	407/900	
≥ 60 ml/min/1.73 m²	250/882	
All patients		




Variable
No. of Events/ No. of Patients
Hazard Ratio
Age
<65 yr
142/852
≥65 yr
230/968
Sex
Male
294/1367
Female
78/453
NYHA class
Ischemic I
53/265
Ischemic II
186/734
Nonischemic II
133/821
QRS duration
<150 msec
147/645
≥150 msec
225/1175
LVEF
≤25%
101/646
>25%
271/1174
LVEDV
≤240 ml
184/828
>240 ml
184/969
LVESV
≤170 ml
190/835
>170 ml
178/962
All patients
372/1820
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
CRT–ICD Better
ICD Only Better

MADIT- CRT


Group
n
Odds ratio (95% C.I.)
Overall 610 0.70 (0.45-1.07)
Age
<63.9 305 0.59 (0.31-1.12)
≥63.9 305 0.77 (0.43-1.40)
Gender
male 479 0.69 (0.43-1.11)
female 131 0.75 (0.26-2.19)
NYHA class
I 107 0.87 (0.37-2.03)
II 503 0.60 (0.35-1.01)
Etiology
ischemic 333 0.82 (0.47-1.45)
non-ischemic 277 0.49 (0.24-0.99)
Systolic blood pressure
<122 300 0.68 (0.37-1.23)
≥122 310 0.73 (0.39-1.37)
Ejection fraction
<27 290 0.53 (0.28-0.97)
≥27 318 0.90 (0.48-1.66)
End-systolic volume index
<92.5 282 0.65 (0.33-1.27)
≥92.5 283 0.88 (0.47-1.64)
QRS interval
<152 303 1.05 (0.58-1.89)
≥152 307 0.42 (0.22-0.81)
IVMD
<36 257 0.98 (0.53-1.81)
≥36 260 0.49 (0.23-1.02)
Glomerular filtration rate
<82.7 305 0.73 (0.39-1.38)
≥82.7 305 0.67 (0.37-1.21)
Beta-blockers
yes 580 0.68 (0.44-1.06)
no 30 1.00 (0.14-7.10)
Diuretics
yes 487 0.62 (0.38-1.01)
no 123 1.09 (0.40-2.95)
Device type
CRT 102 0.98 (0.31-3.05)
CRT+ICD 508 0.66 (0.41-1.05)
0
0.5
1
1.5
2
CRT-ON better
CRT-OFF better

REVERSE

Recommendations in patients with heart failure and permanent atrial fibrillation

Recommendations	Patient population	Class[a]	Level[b]	Ref.[c]
CRT-P/CRT-D[d] should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS ≥130 ms Pacemaker dependency induced by AV nodal ablation	IIa	B	27–40
CRT-P/CRT-D[d] should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS ≥130 ms Slow ventricular rate and frequent pacing[e]	IIa	C	—

CLASS IIa

1. **For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy. *(Level of Evidence: B)*** (220,231)

Upadhyay, et al 2008 Μετανάλυση CRT σε AF/SR

- ΚΕ ⇑ περισσότερο σε ΚΜ
- NYHA: βελτίωση περισσότερο σε SR
- 6MWD: βελτίωση περισσότερο σε SR
- QoL: βελτίωση περισσότερο σε SR

- Gasparini, JACC 2006: Μόνο ασθενείς σε ΚΜ και Ablation κΚκ βελτιώθηκαν (συγκρίσιμα με SR)- φαρμακευτική μόνο αγωγή (Vp>85%) χωρίς βελτίωση

Recommendations in patients with heart failure and a concomitant class I pacemaker indication

Recommendations	Patient population	Class[a]	Level[b]	Ref.[c]
CRT-P/CRT-D[d] is recommended to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS ≥120 ms	I	B	41–48
CRT-P/CRT-D[d] should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS <120 ms	IIa	C	—
CRT-P/CRT-D[d] may be considered to reduce morbidity	NYHA function class II LVEF ≤35%, QRS <120 ms	IIb	C	—

CLASS IIa

2. **For patients with LVEF less than or equal to 35% with NYHA functional Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable.** ***(Level of Evidence: C)*** (231)

CLASS IIb

1. **For patients with LVEF less than or equal to 35% with NYHA functional Class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing, CRT may be considered.** ***(Level of Evidence: C)*** (231)