20 Years of Cardiac Resynchronization Therapy

A Revolution in Heart Failure Care

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

CARE-HF

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*

Last patient enrolled 2003 !

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*The CARE-HF Study investigators are listed in the Appendix.

This article was published at www.nejm.org on March 7, 2004.

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

CARE-HF

- Primary Publication: 6,547 citations as of August 2023
- Secondary Publications: 16 (2005-2022) – many cited >100 times
- Many editorials, reviews & meta-analyses

Eur J Echocardiography (2006) 7, 373–378

ELSEVIER

EUROPEAN

Baseline echocardiographic characteristics heart failure patients enrolled in a large European multicentre trial (CArdiac REsynchronisation Heart Failure study)

Stefano Ghio[a,*], Nick Freemantle[b], Alessandra Serio[a], Giulia Magrini[a], Laura Scelsi[a], Michele Pasotti[a], John G.F. Cleland[c], Luigi Tavazzi[a]

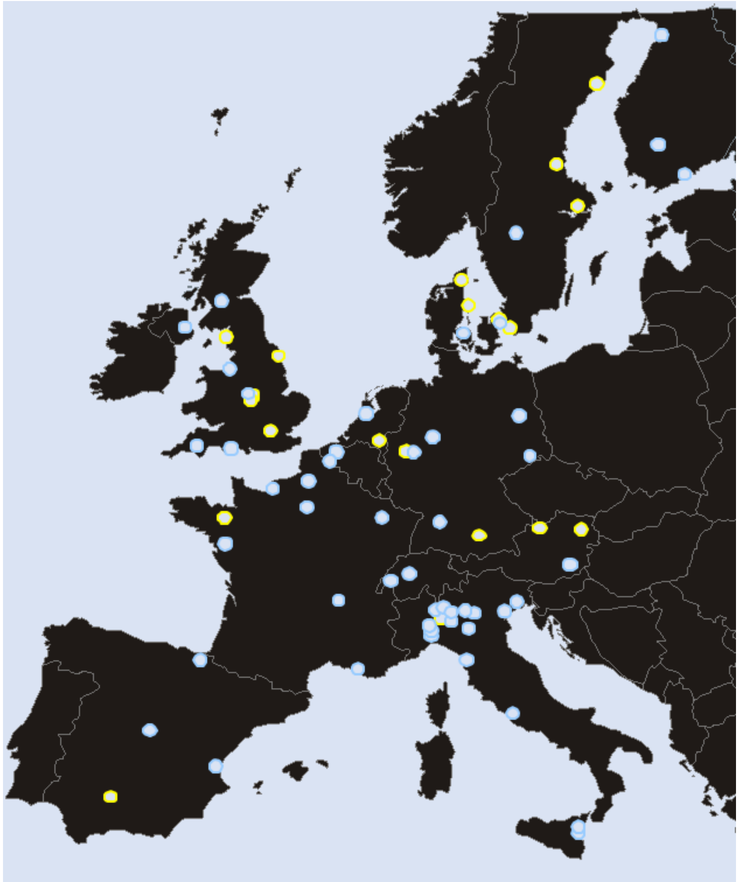
EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2009) **11**, 480–488
doi:10.1093/eurjhf/hfp034

Long-term left ventricular reverse remodelling with cardiac resynchronization therapy: results from the CARE-HF trial

Stefano Ghio[1]*, Nick Freemantle[2], Laura Scelsi[1], Alessandra Serio[1], Giulia Magrini[1], Michele Pasotti[1], Aparna Shankar[2], John G.F. Cleland[3], and Luigi Tavazzi[1]

[1]Division of Cardiology, Fondazione IRCCS Policlinico S. Matteo, University Hospital, Piazzale Golgi 1, 27100 Pavia, Italy; [2]Division of Primary Care, Public and Occupational Health, University of Birmingham, UK; and [3]Department of Cardiology, University of Hull, Kingston upon Hull, UK

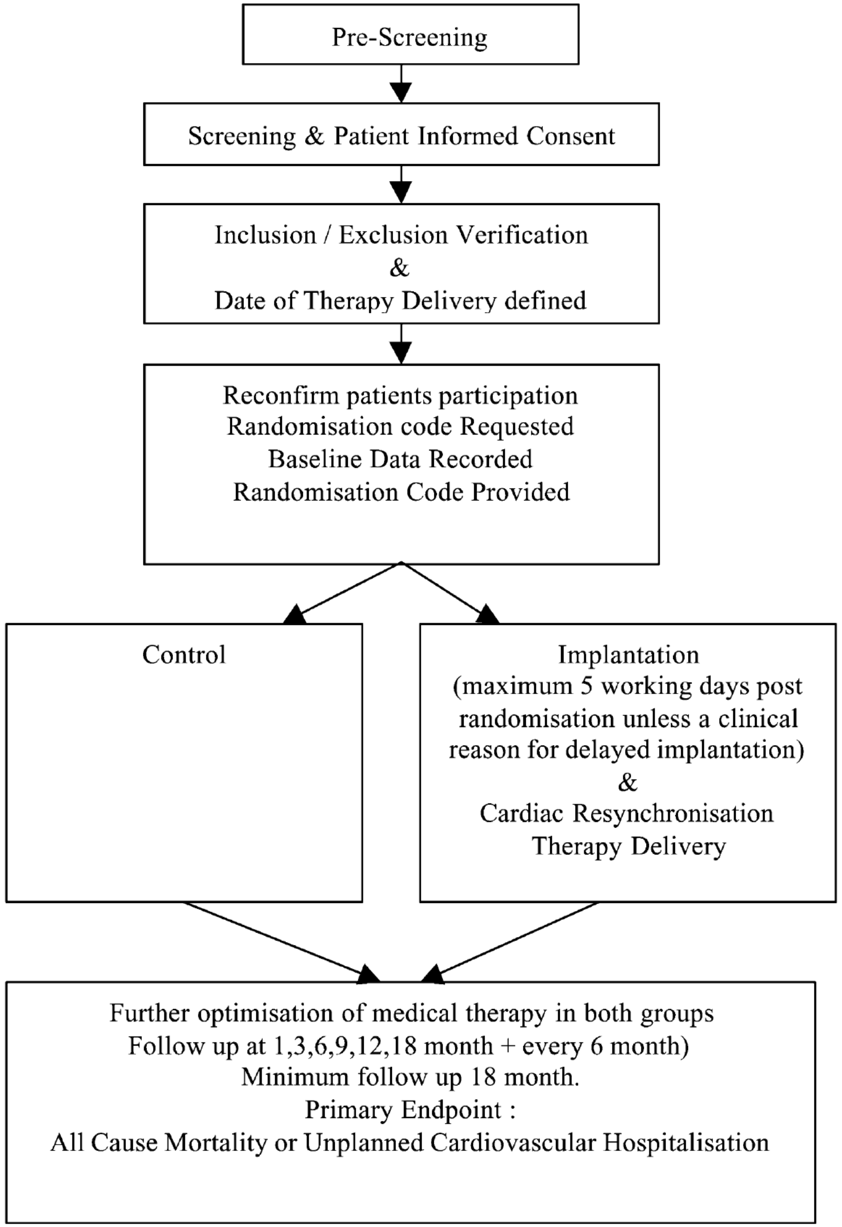


AV delay optimisation:
shortest AV-delay without compromising the left atrial contribution to LV filling.

Timelines

- MUSTIC: 2001 Single-Blind / X-over
  - N = 58; 3 months
- CARE-HF initiated enrolment in 2001
- MIRACLE: 2002 Double-Blind
  - N = 453; 6 months
- CARE-HF completed enrolment of 813 patients in 2003
- COMPANION: 2004 Not Blinded
  - N = 1,520; ~15 months
- CARE-HF published in 2005

J.G.F. Cleland et al. / European Journal of Heart Failure 3 (2001) 481–489



Main Inclusion & Exclusion Criteria

- Heart failure for at least 6 weeks requiring loop diuretics
- Currently in NYHA class III/IV
- A high standard of pharmacological therapy

- LV systolic dysfunction and dilation
  - EF ≤35%; EDD >30mm/height in metres

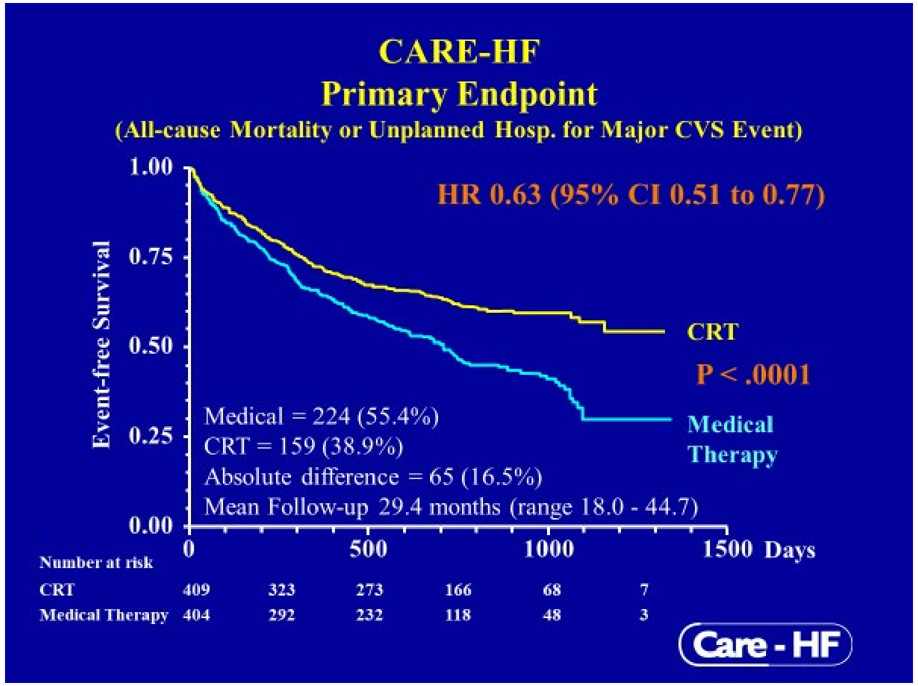
- QRS ≥120 ms
  - Dyssynchrony confirmed by echo if QRS 120-149 ms
    - Aortic pre-ejection delay >140ms
    - Interventricular mechanical delay >40 ms
    - Delayed activation of postero-lateral LV wall

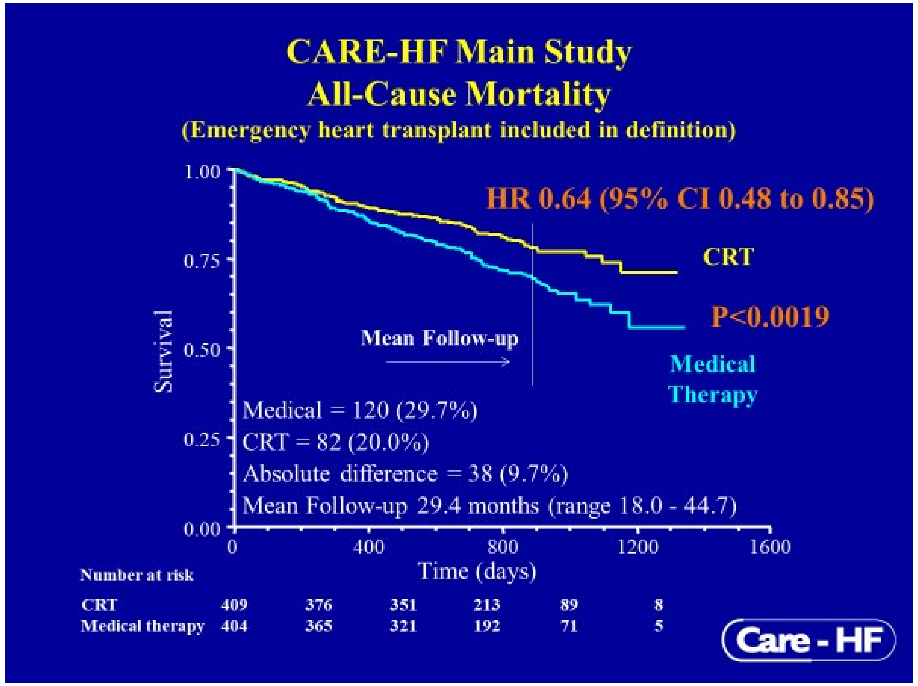
- Patients with AF or requiring pacing excluded

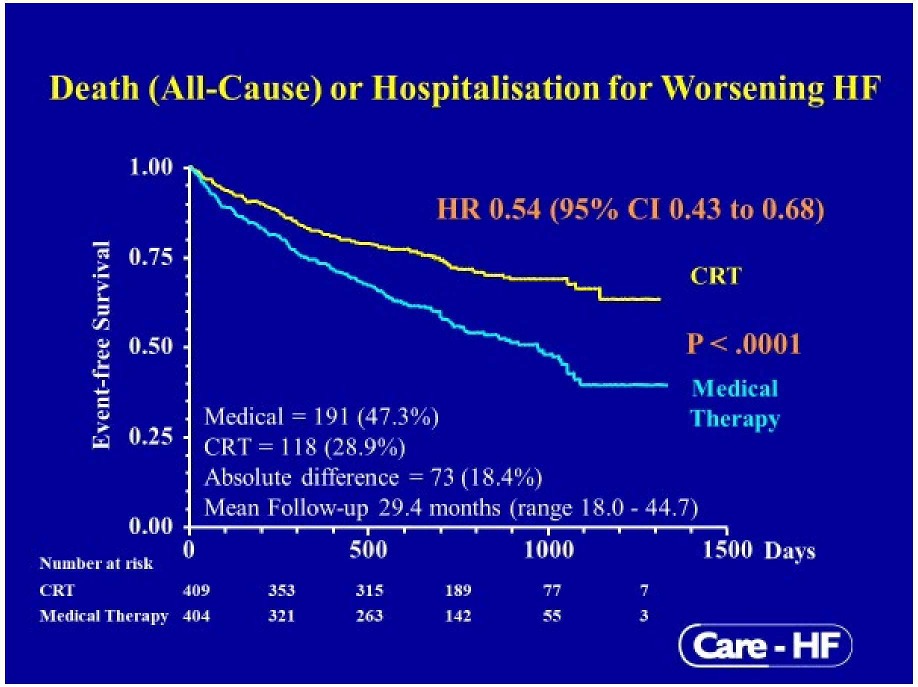
QRS ≥150ms
N = 721

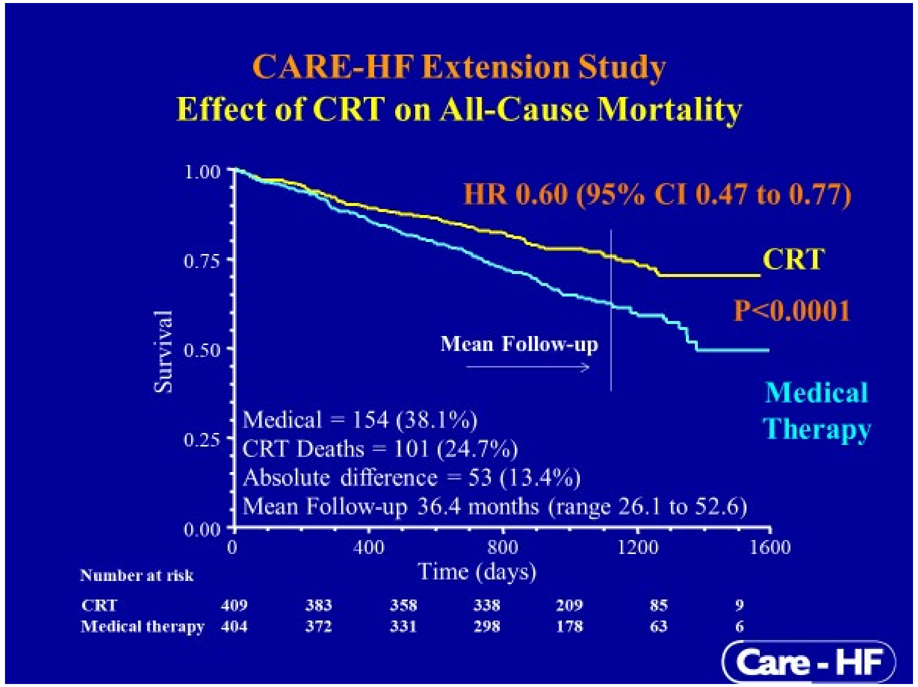
QRS 120-149ms
N = 92

Care - HF


CARE-HF
Primary Endpoint
(All-cause Mortality or Unplanned Hosp. for Major CVS Event)
HR 0.63 (95% CI 0.51 to 0.77)
Event-free Survival
1.00
0.75
0.50
0.25
0.00
CRT
P < .0001
Medical Therapy
Medical = 224 (55.4%)
CRT = 159 (38.9%)
Absolute difference = 65 (16.5%)
Mean Follow-up 29.4 months (range 18.0 - 44.7)
0
500
1000
1500 Days
Number at risk
CRT 409 323 273 166 68 7
Medical Therapy 404 292 232 118 48 3
Care - HF


CARE-HF Main Study
All-Cause Mortality
(Emergency heart transplant included in definition)
HR 0.64 (95% CI 0.48 to 0.85)
CRT
P<0.0019
Mean Follow-up
Medical Therapy
Survival
1.00
0.75
0.50
0.25
0.00
Medical = 120 (29.7%)
CRT = 82 (20.0%)
Absolute difference = 38 (9.7%)
Mean Follow-up 29.4 months (range 18.0 - 44.7)
0
400
800
1200
1600
Time (days)
Number at risk
CRT 409 376 351 213 89 8
Medical therapy 404 365 321 192 71 5
Care - HF


Death (All-Cause) or Hospitalisation for Worsening HF
HR 0.54 (95% CI 0.43 to 0.68)
Event-free Survival
1.00
0.75
0.50
0.25
0.00
CRT
P < .0001
Medical Therapy
Medical = 191 (47.3%)
CRT = 118 (28.9%)
Absolute difference = 73 (18.4%)
Mean Follow-up 29.4 months (range 18.0 - 44.7)
0
500
1000
1500 Days
Number at risk
CRT 409 353 315 189 77 7
Medical Therapy 404 321 263 142 55 3
Care - HF


CARE-HF Extension Study
Effect of CRT on All-Cause Mortality
HR 0.60 (95% CI 0.47 to 0.77)
CRT
P<0.0001
Mean Follow-up
Medical Therapy
Survival
1.00
0.75
0.50
0.25
0.00
Medical = 154 (38.1%)
CRT Deaths = 101 (24.7%)
Absolute difference = 53 (13.4%)
Mean Follow-up 36.4 months (range 26.1 to 52.6)
0
400
800
1200
1600
Time (days)
Number at risk
CRT 409 383 358 338 209 85 9
Medical therapy 404 372 331 298 178 63 6
Care - HF

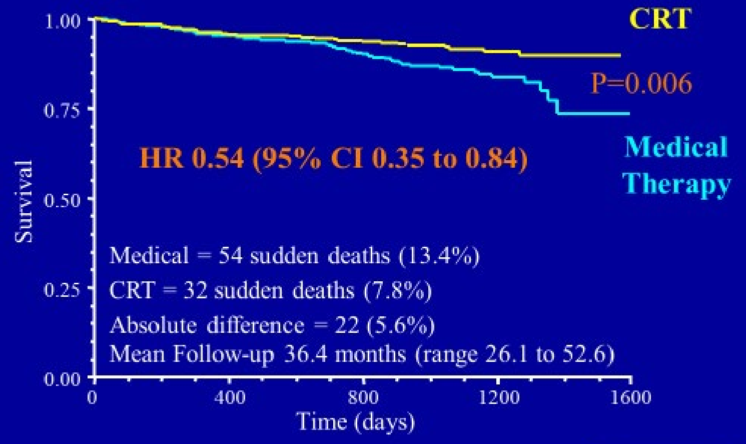
Mechanistic Outcomes

Outcome	Mean difference at 3 mth*	Mean difference at 18 mth*
Systolic BP (mm Hg)	+5.8 (P < 0.0001)	+6.3 (P < 0.0001)
LVEF (%)	+3.7 (P < 0.0001)	+6.9 (P < 0.0001)
Mitral regurgitation area (cm^2)	-5.1 (P < 0.0001)	-4.2 (P = 0.003)
NT Pro-BNP [pg mL^{-1}]	-225 (P = 0.36)	-1,122 (P = 0.0016)

* Positive values indicate higher value with CRT compared to control

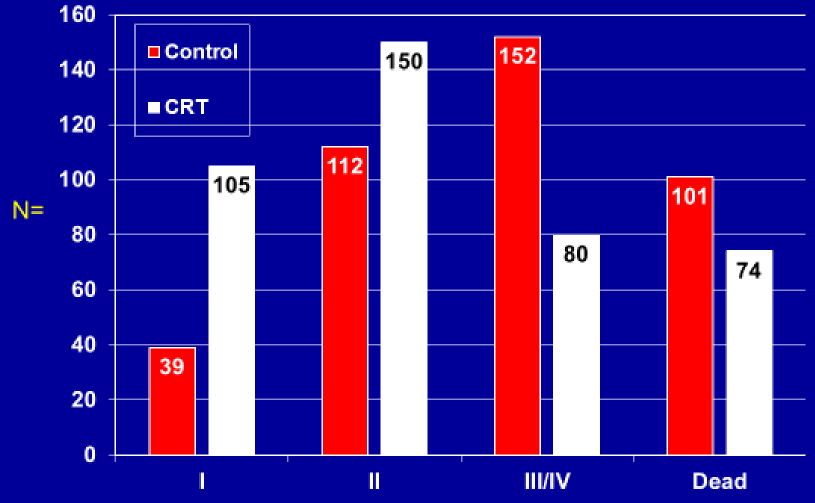
Care - HF

CARE-HF Extension Study
Time to Sudden Cardiac Death



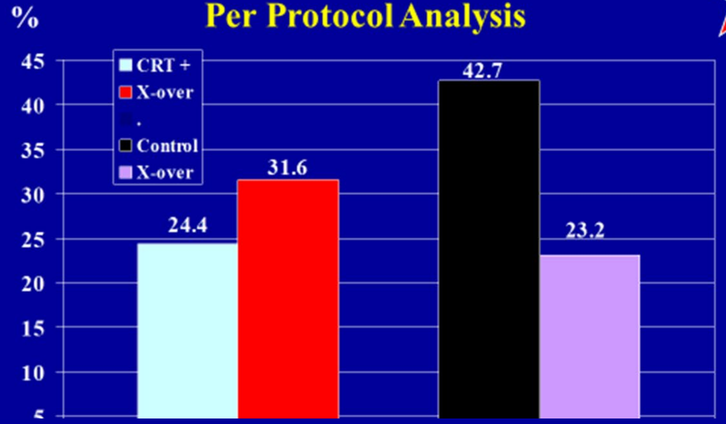
Care - HF

Outcome at 18 months



Care - HF

Mortality
Per Protocol Analysis



By ITT 24.7% 38.1%

Δ 13.4%

As treated 24.4% 42.7%

Δ 18.3%

Mean Follow-up 36.4 months

European Heart Journal (2013) **34**, 2281–2329
doi:10.1093/eurheartj/eht150

ESC GUIDELINES

2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy

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

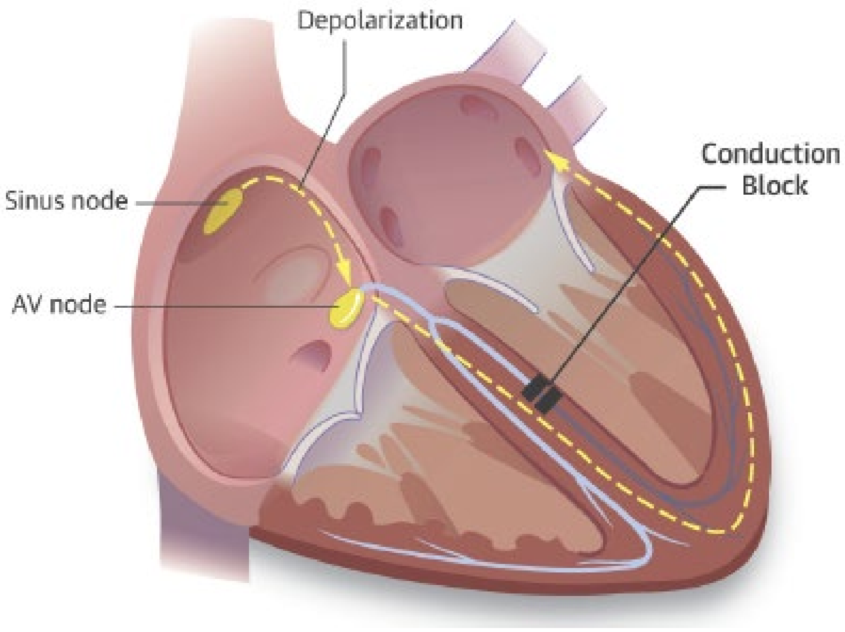
Areas of dissent from recommendations:

The recommendations given for indications for CRT (see below and Figure 8) represent a majority view of this Task Force but not all who contributed agreed. Several statements are based on subgroup analyses of RCTs that pose many problems with interpretation (interrelationship between QRS morphology and QRS duration, gender differences in response, prognostic benefit in ischaemic vs. non-ischaemic patients) or with areas of uncertainty that are still the objects of investigation (potential role of echocardiographic dyssynchrony in narrow QRS). Future studies might change our knowledge and recommendations.

Robust evidence for only one of these assertions !

Cardiac Resynchronization Therapy for HFrEF

- How does (might) it work?
- Compared to what?
- For whom?

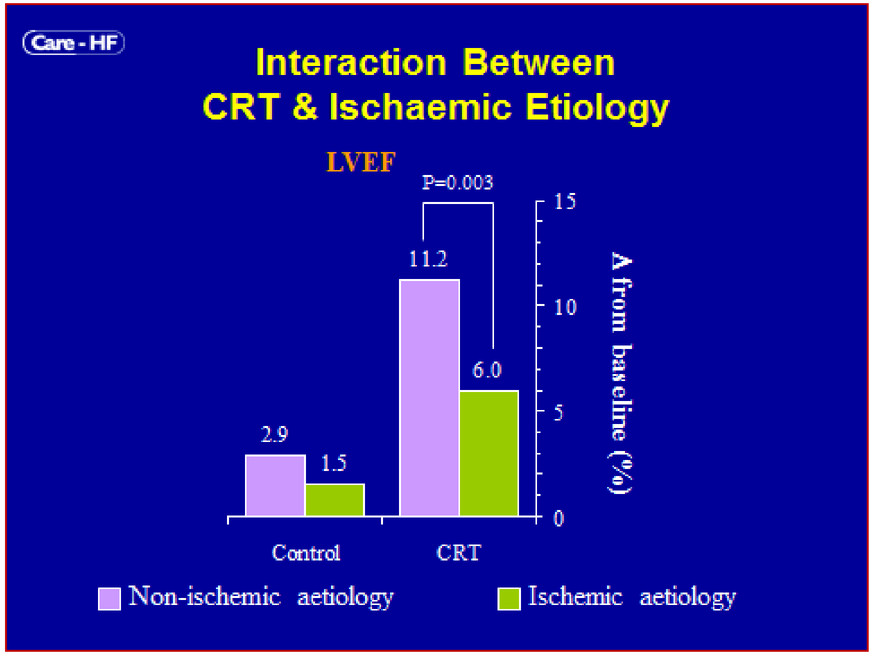


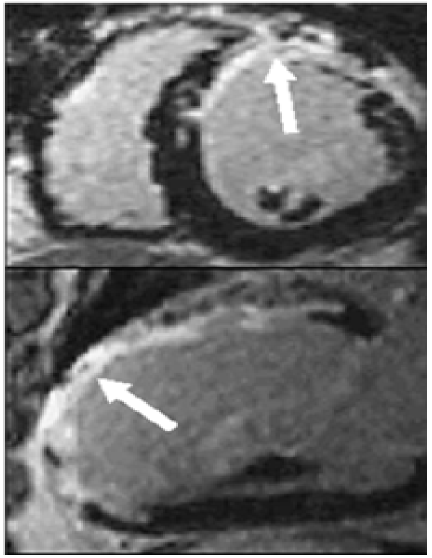
How Does CRT Work?

- Senses (and potentially paces) the RA
  - Prevents pauses / bradycardia (reducing sudden death)
- Shortens the AV interval (can't if in AF)
  - Pump-primes LV & RV
  - Reduces diastolic MR
- Ventricular Pacing
  - Tre
- Alters the timing of RV, LV free-wall & papillary muscle contraction
  - Stabilises the interventricular septum (reducing interventricular dyssynchrony)
  - Corrects delays in LV free-wall activation (reducing LV-dyssynchrony)
  - Reduce
- Raises systolic blood pressure (& improves haemodynamics)
  - By one or more
- Ventricular remodelling
  - Reduces risk of VT (and sudden death)

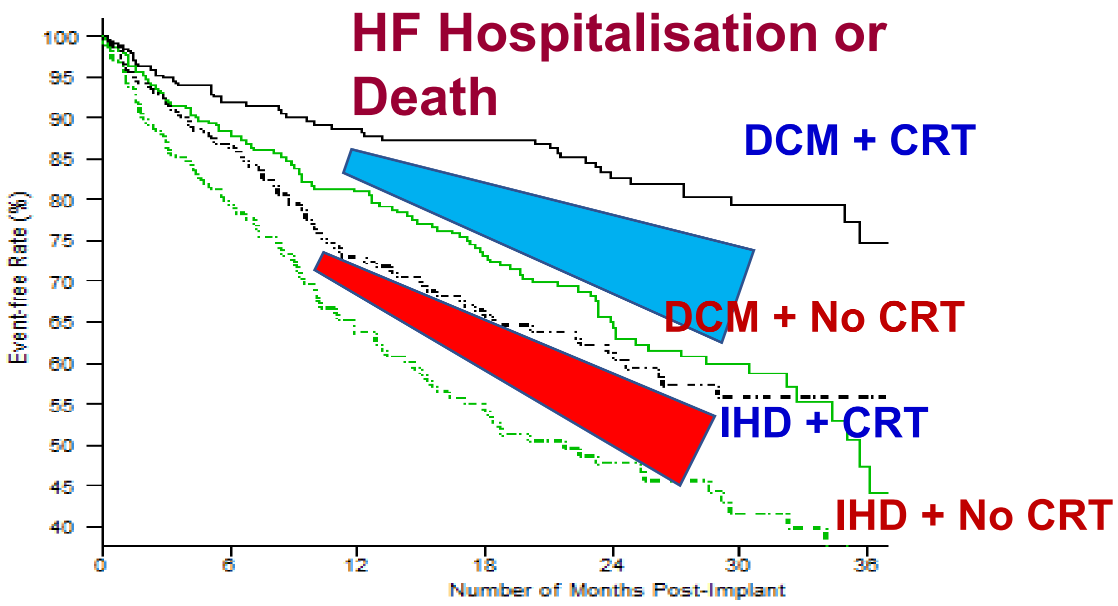
- Which of these mechanisms is most important?
- Does the importance of each mechanism vary from one patient to the next?
- Does the importance of each mechanism vary with physical activity?
- Does the importance of each mechanism vary over time?

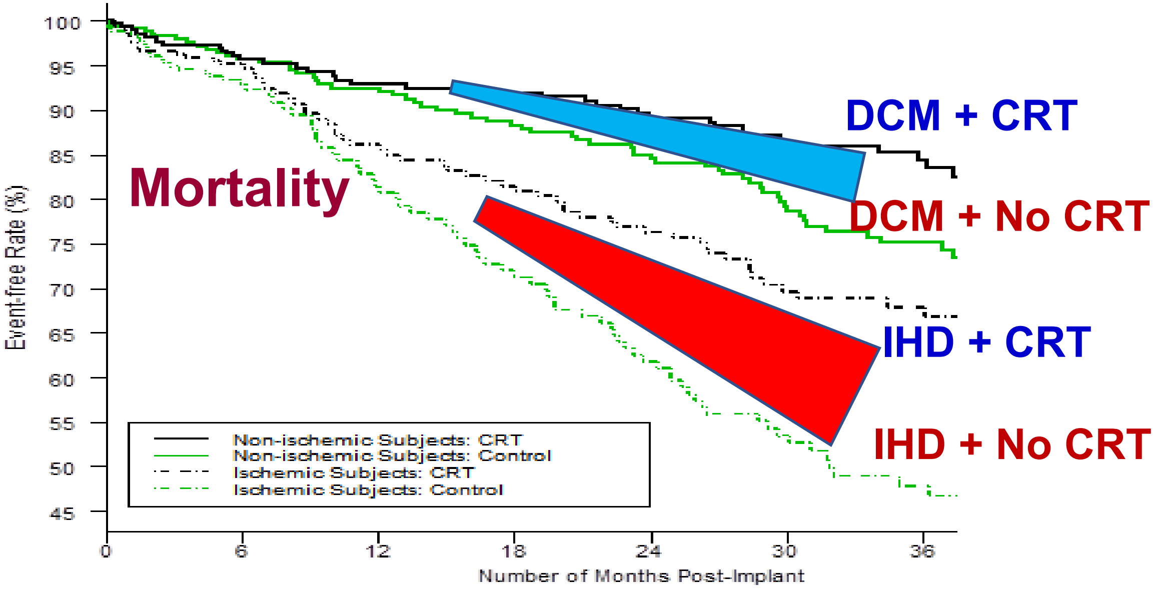
Meta-analysis of CRT Trials - Ischaemic Heart Disease





- Less benefit if IHD
  - Yes, for LVEF
  - Maybe for symptoms
  - Not true for mortality

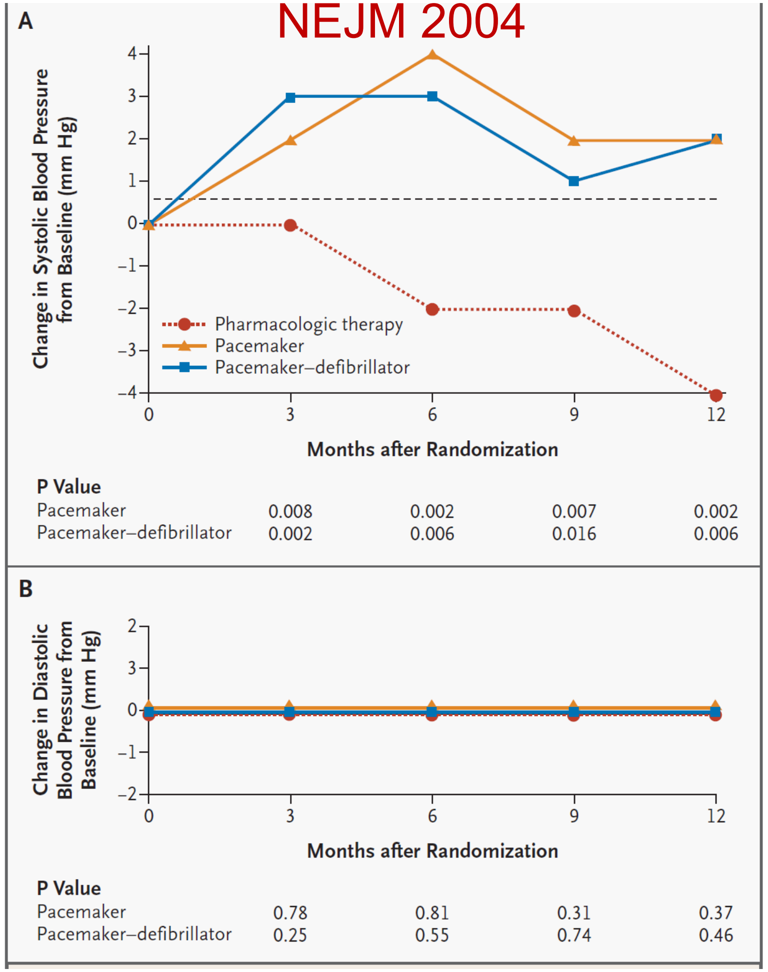




Effect of CRT on Blood Pressure

COMPANION

NEJM 2004



CARE-HF

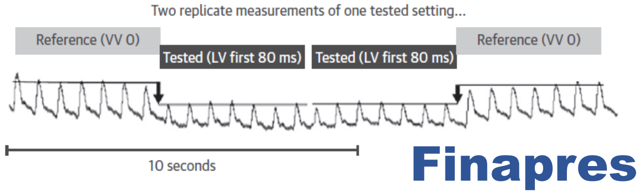
NEJM 2005

Table 3. Hemodynamic, Echocardiographic, and Biochemical Assessments.*

Variable	Difference in Means at 3 Mo (95% CI)	P Value	Difference in Means at 18 Mo (95% CI)	P Value
Heart rate (beats/min)	+1.1 (−1.2 to 3.4)	0.33	+1.0 (−1.5 to 3.6)	0.43
Systolic blood pressure (mm Hg)	+5.8 (3.5 to 8.2)	<0.001	+6.3 (3.6 to 8.9)	<0.001
Diastolic blood pressure (mm Hg)	+1.5 (0.1 to 2.9)	0.03	+1.3 (−1.8 to 4.4)	0.42
Interventricular mechanical delay (msec)	−21 (−25 to −18)	<0.001	−21 (−25 to −17)	<0.001
Left ventricular ejection fraction (%)	+3.7 (3.0 to 4.4)	<0.001	+6.9 (5.6 to 8.1)	<0.001
Left ventricular end-systolic volume index (ml/m²)	−18.2 (−21.2 to −15.1)	<0.001	−26.0 (−31.5 to −20.4)	<0.001
Mitral-regurgitation area†	−0.051 (−0.073 to −0.028)	<0.001	−0.042 (−0.070 to −0.014)	0.003
N-terminal pro–brain natriuretic peptide (pg/ml)‡	−225 (−705 to 255)	0.36	−1122 (−1815 to −429)	<0.002

FIGURE 2 Simplified Schematic of Hemodynamic Optimization Method

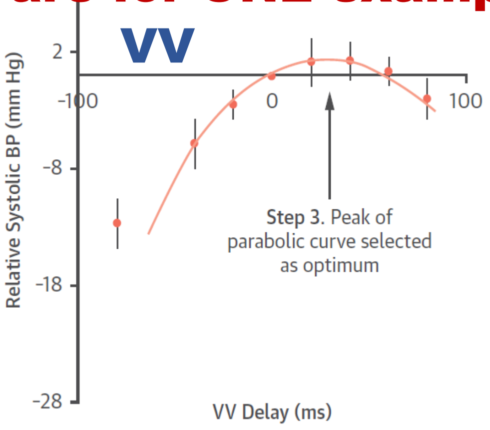
Step 1. Multiple replicate measurements of BP of tested setting against reference setting

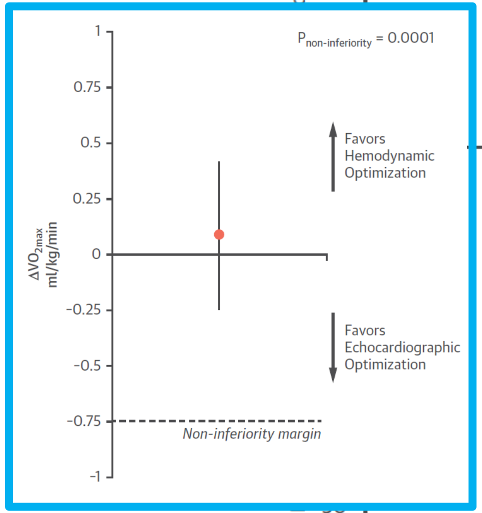


Finapres BP

Data are for ONE example only

Step 2. Average change in BP relative to reference setting plotted against VV delay

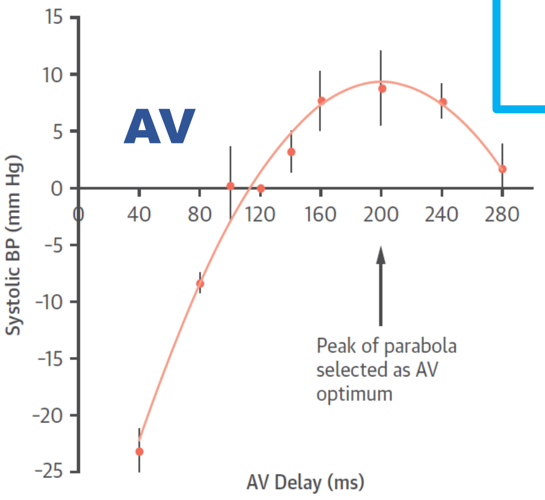


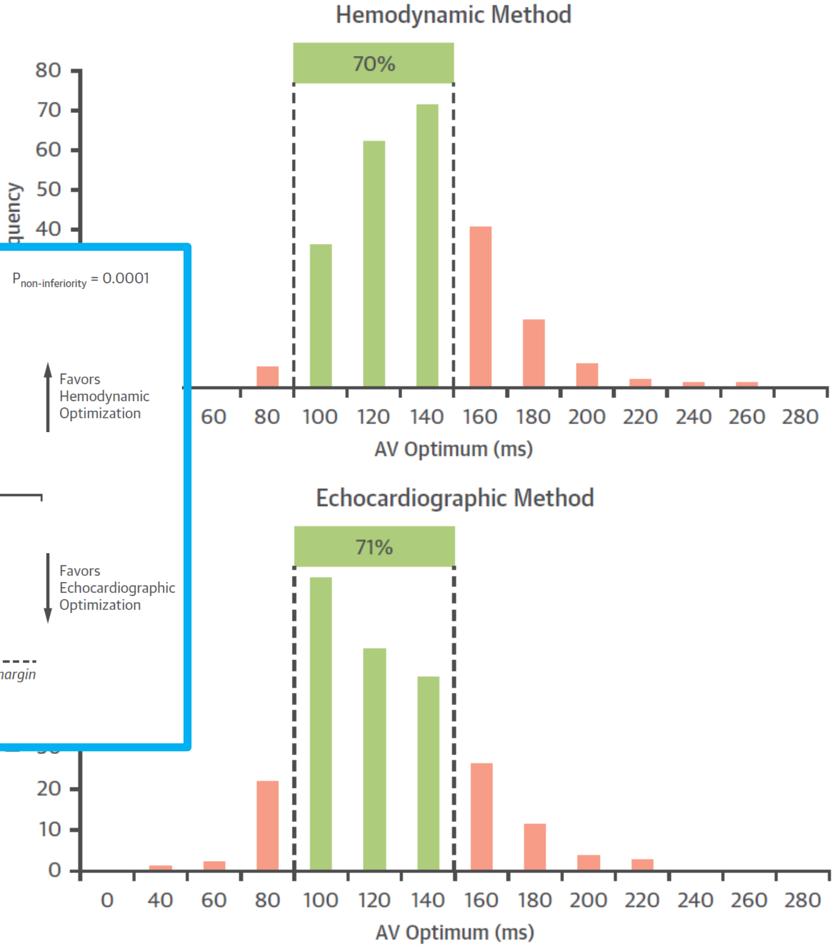


Multicenter Randomized Controlled Crossover Trial Comparing Hemodynamic Optimization Against Echocardiographic Optimization of AV and VV Delay of Cardiac Resynchronization Therapy

The BRAVO Trial

This same process is also performed with AV-delays to plot an AV optimization curve:





In approximately one-third of patients, the optimal atrioventricular (AV) delay was found to be more than 40 ms longer or shorter than the commonly used nominal setting of 120 ms. These patients are likely to have the most to gain from AV delay optimization.

(J Am Coll Cardiol Img 2019;12:1407–16)

Cardiac Resychronization Therapy

Compared to what?

CRT-P compared to Pharmacological Therapy	CRT-P compared to Back-up RV Pacing*	CRT-D compared to ICD + Back-up RV Pacing*
COMPANION	MIRACLE	MIRACLE-ICD
CARE-HF		MADIT-CRT
		RAFT
		REVERSE (mostly)

* A two-edged sword

Cardiac Resychronization Therapy

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* A two-edged sword

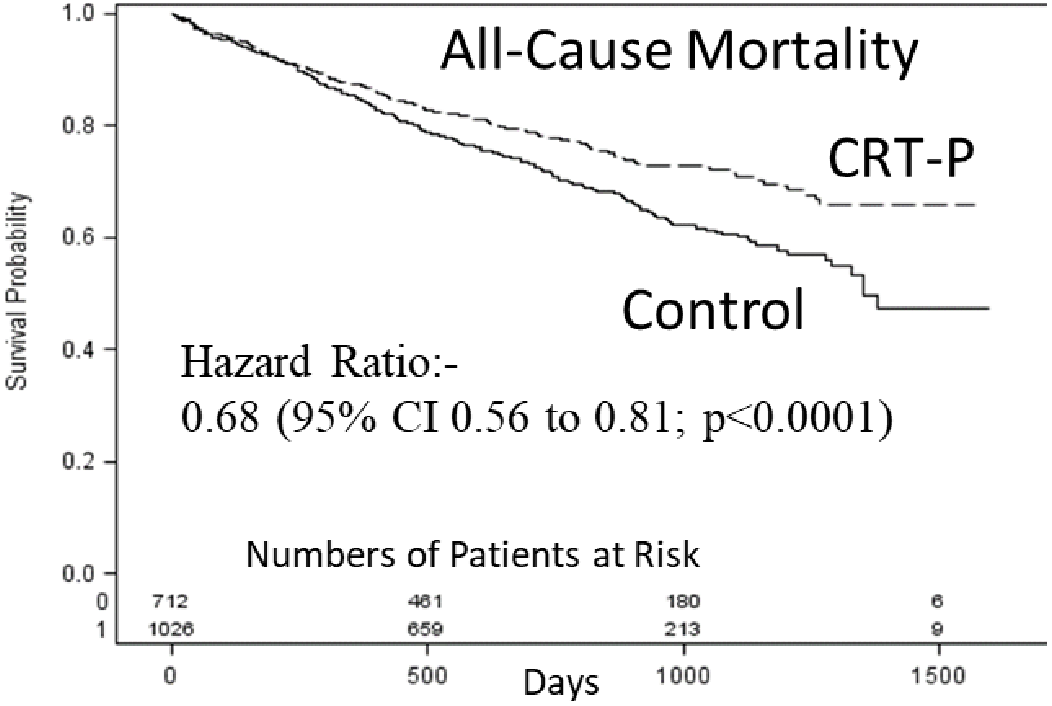
ESC European Society of Cardiology
European Journal of Heart Failure (2022) 24, 1080–1090
doi:10.1002/ejhf.2524
RESEARCH ARTICLE

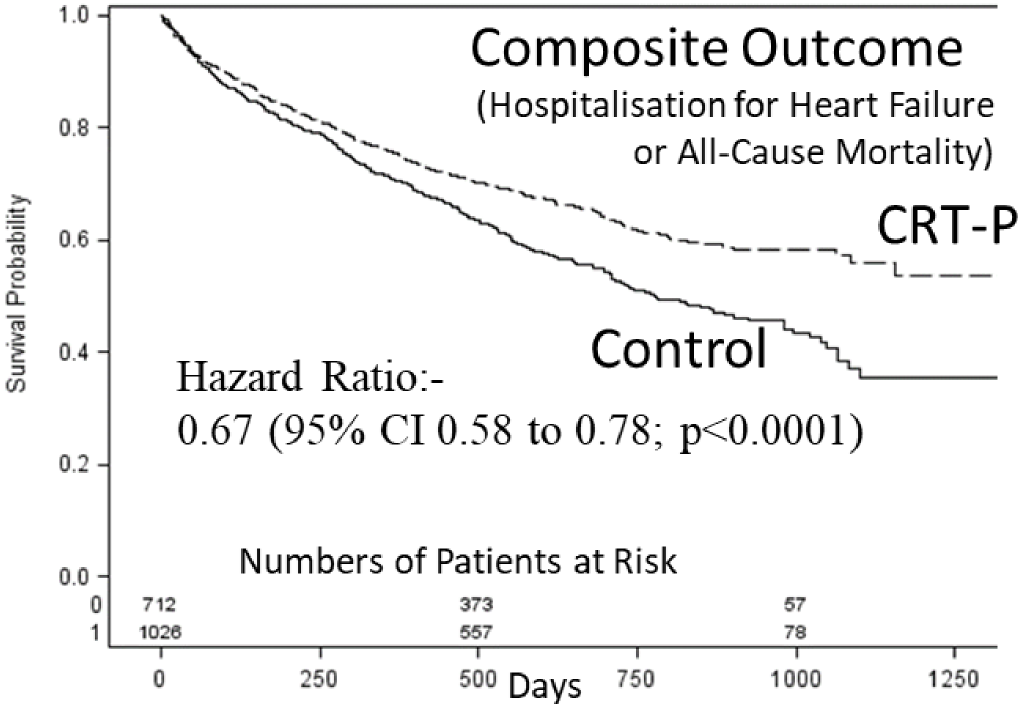
CRT-P compared to pharmacological therapy

The effect of cardiac resynchronization without a defibrillator on morbidity and mortality: an individual patient data meta-analysis of COMPANION and CARE-HF

2022

John G.F. Cleland[1]*, Michael R. Bristow[2], Nicholas Freemantle[3], Brian Olshansky[4], Daniel Gras[5], Leslie Saxon[6], Luigi Tavazzi[7], John Boehmer[8], Stefano Ghio[9], Arthur M. Feldman[10], Jean-Claude Daubert[11], and David de Mets[12]



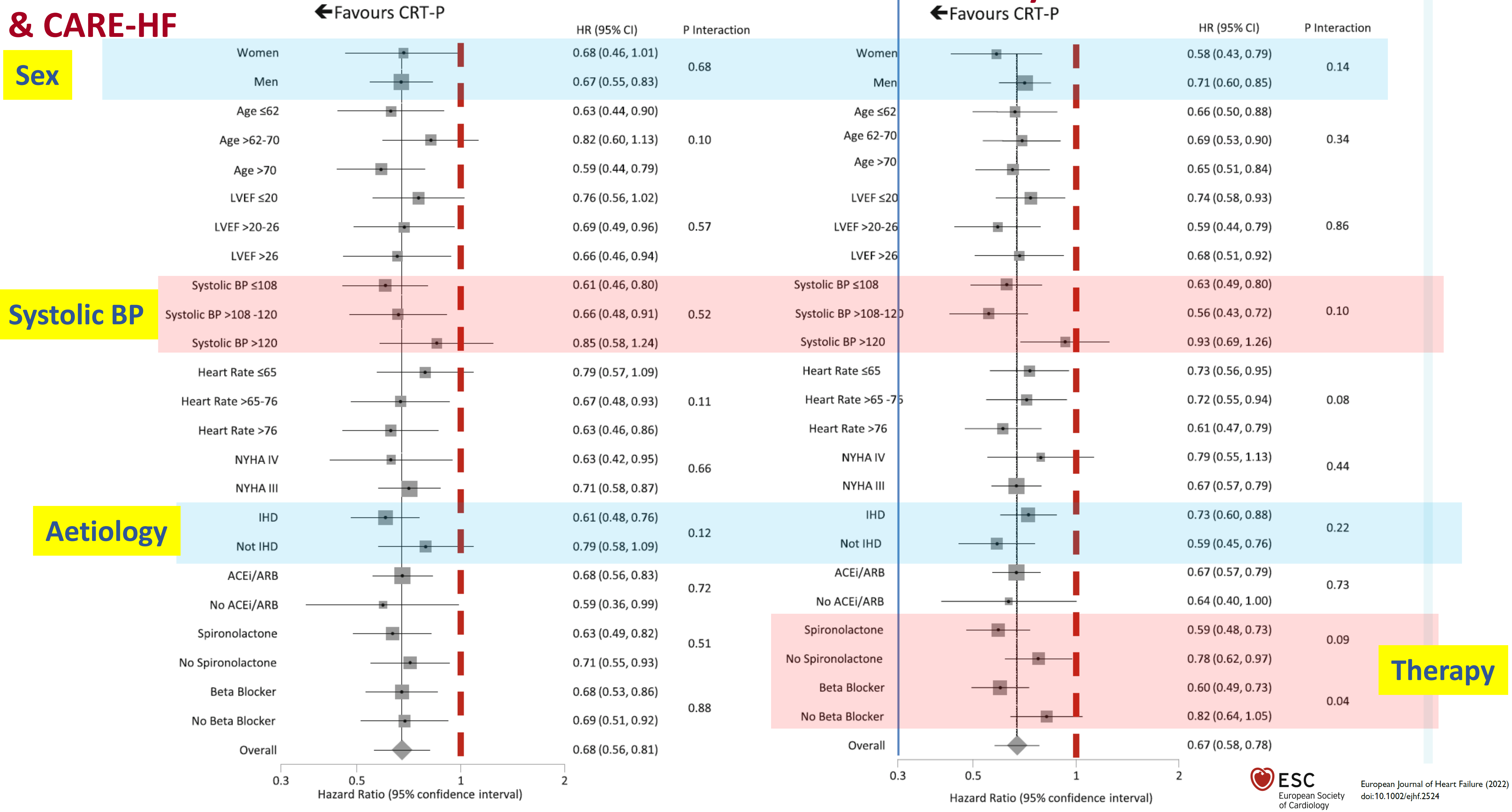


COMPANION & CARE-HF

Individual Patient Data Meta-analysis

A — Mortality

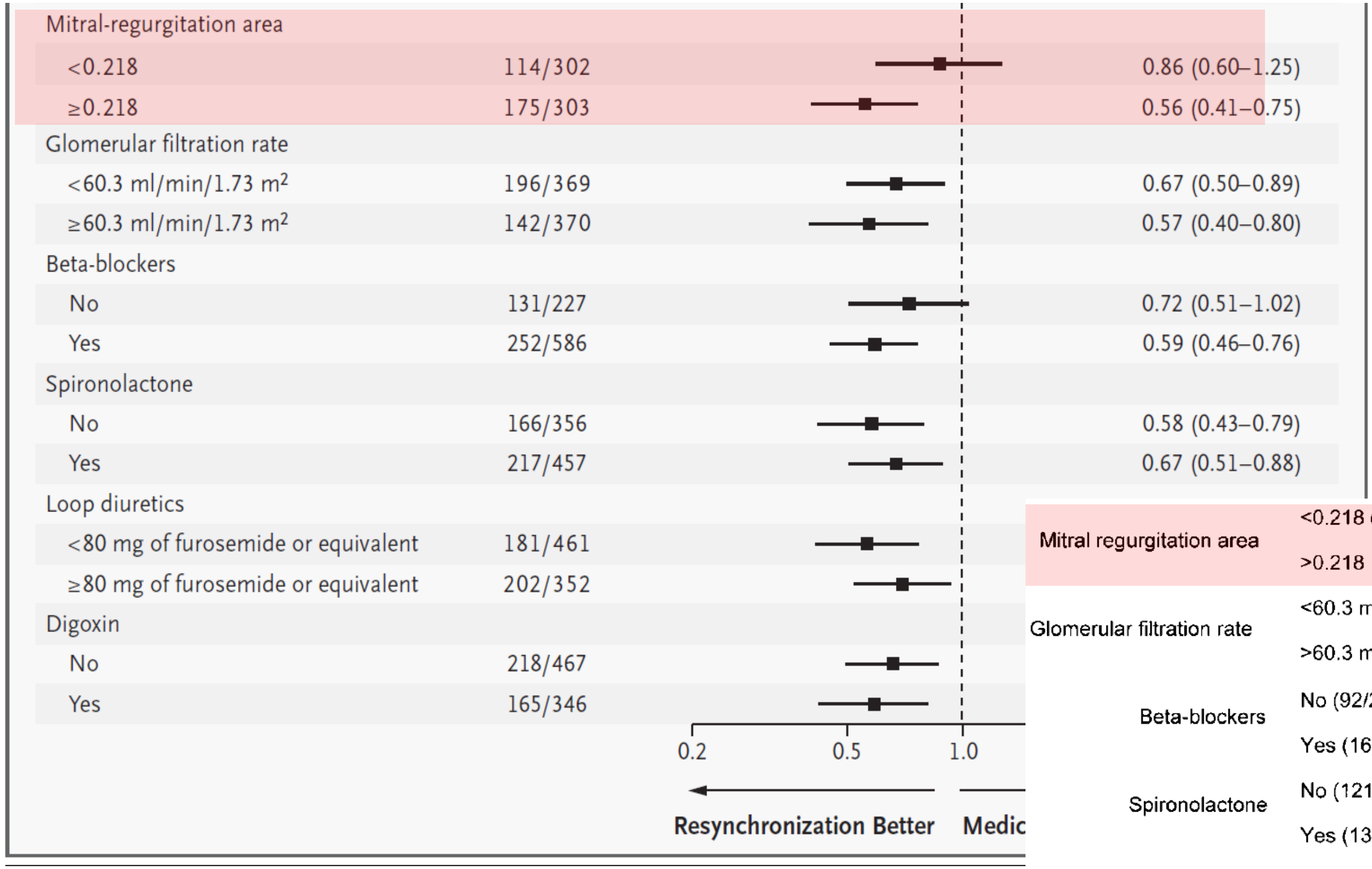
B — HF Hospitalisation or Mortality



ESC European Society of Cardiology

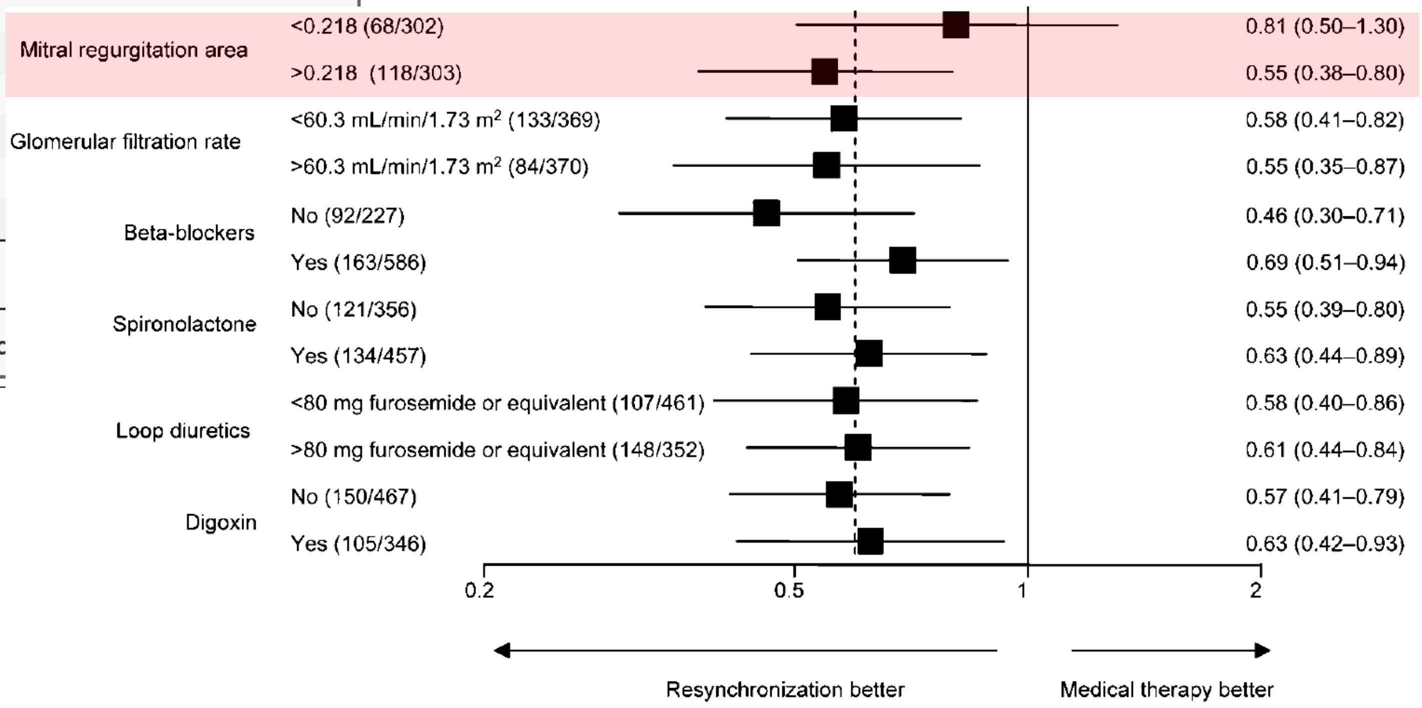
European Journal of Heart Failure (2022) **24**, 1080–1090
doi:10.1002/ejhf.2524

Primary Composite
(NEJM Main)

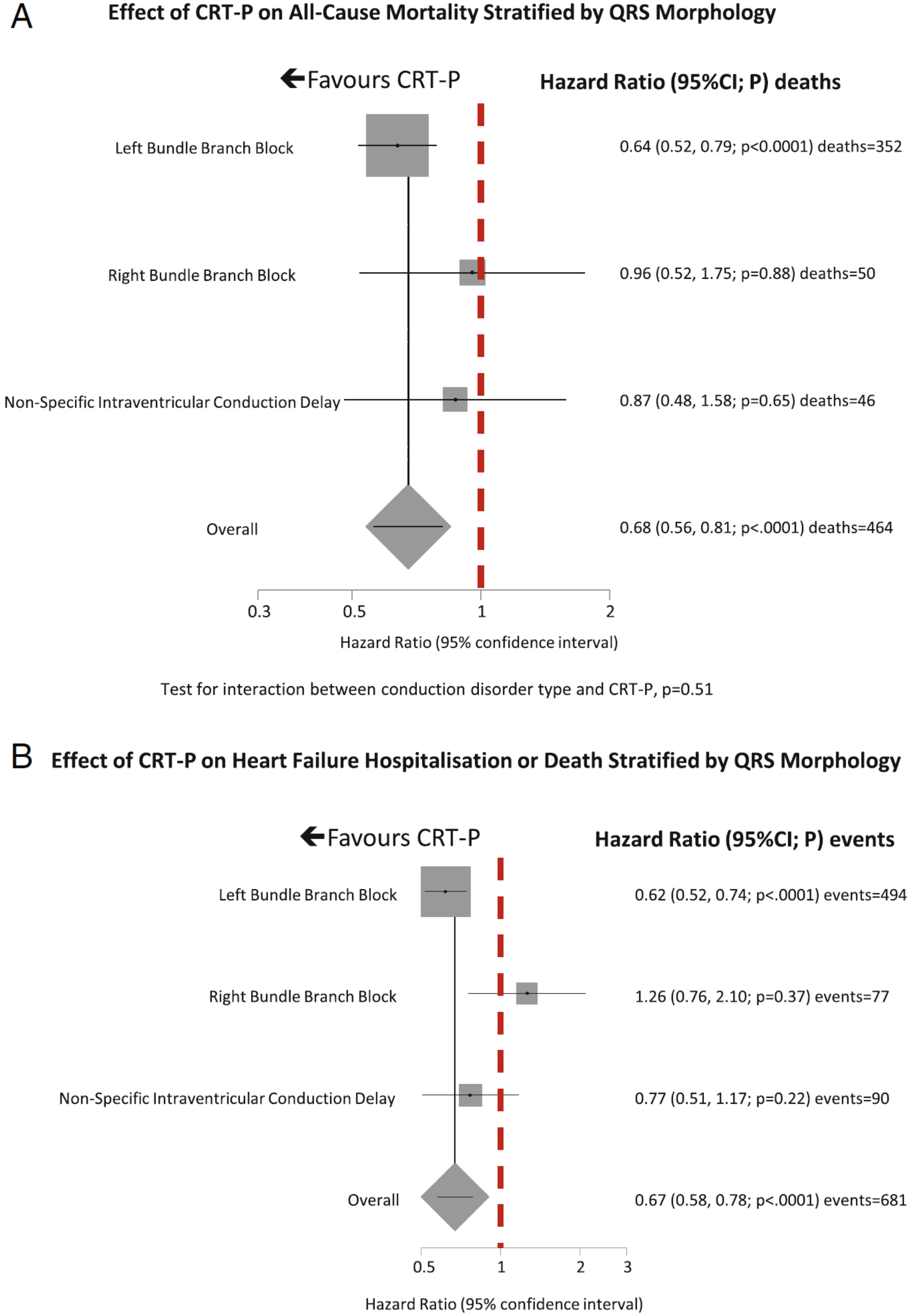


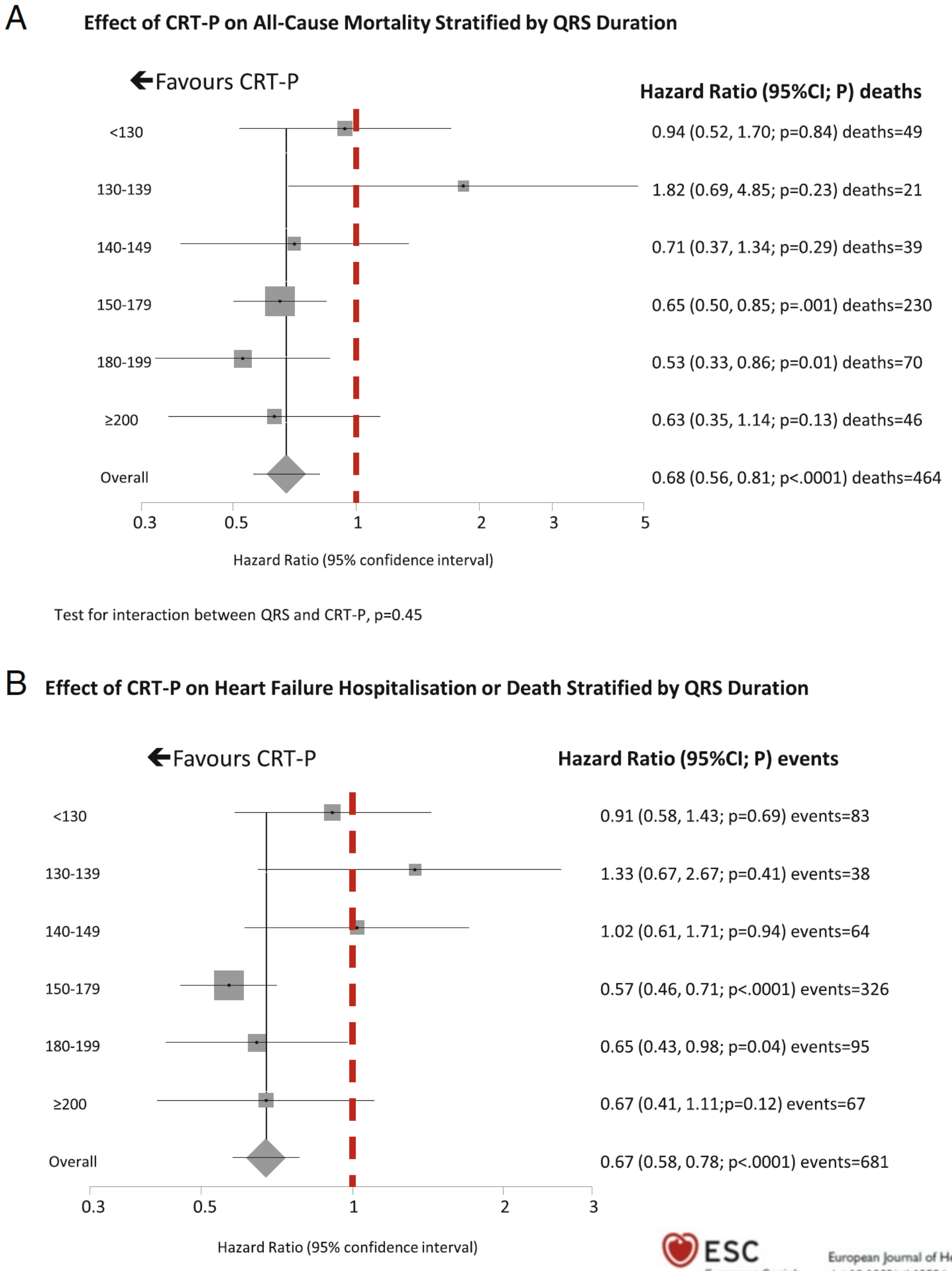
CARE-HF

All-Cause Mortality
(EHJ extension)



QRS Morphology COMPANION/CARE-HF QRS Duration



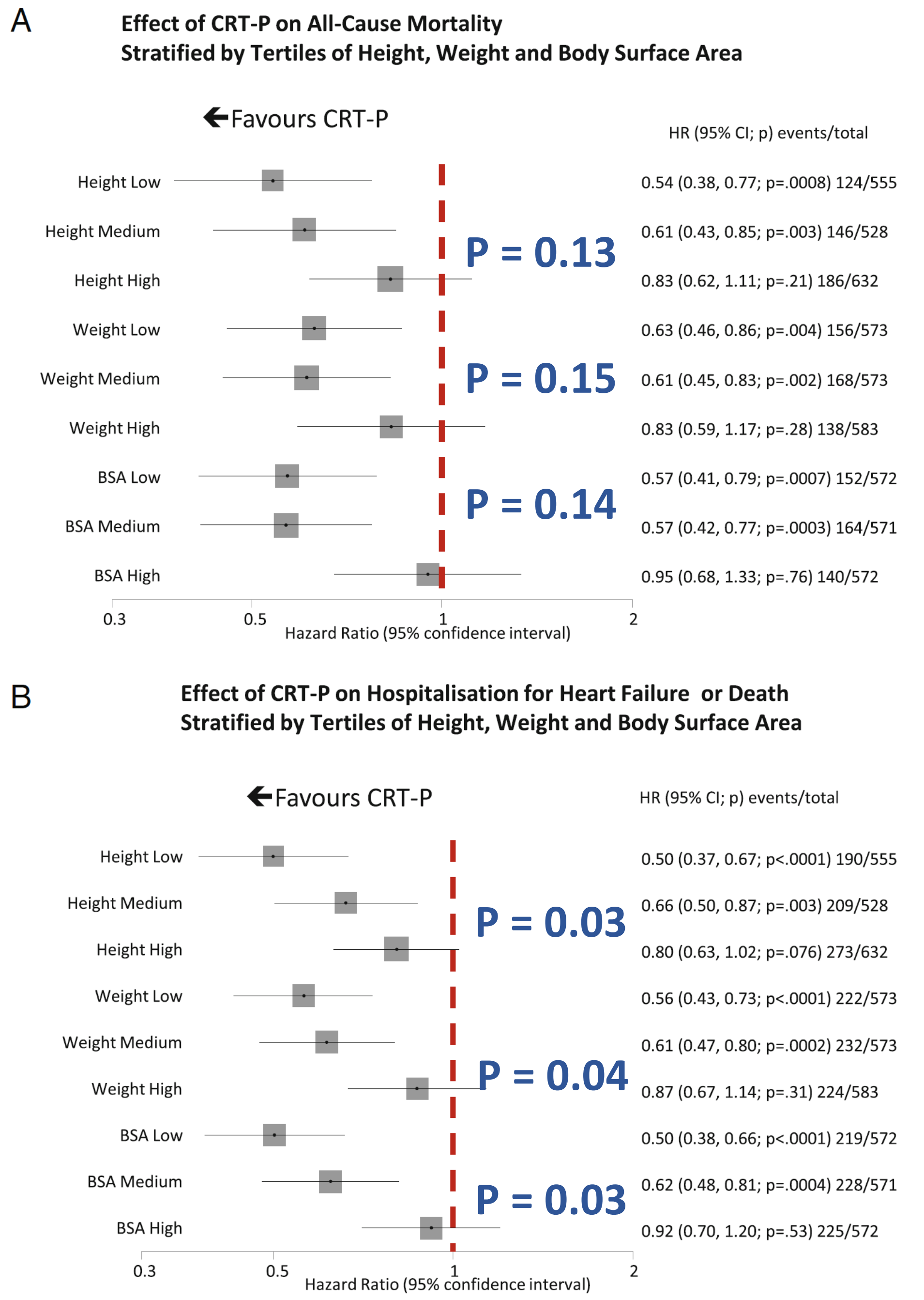


Test for interaction between QRS and CRT-P, p=0.27

ESC European Society of Cardiology
European Journal of Heart Failure (2022) 24, 1080–1090
doi:10.1002/ejhf.2524

COMPANION / CARE-HF
Individual Patient Data Meta-analysis

Eur J Heart Failure 2022

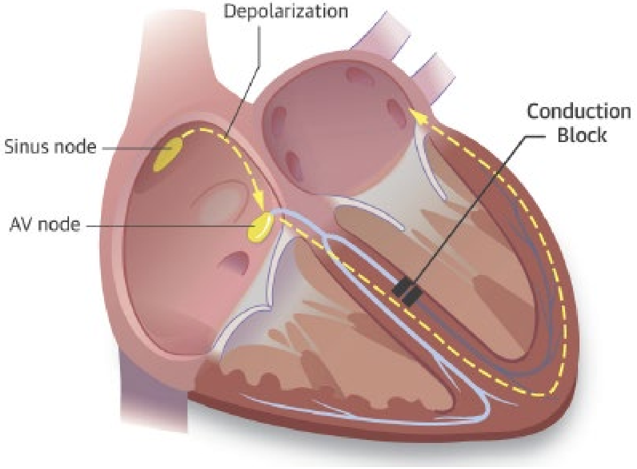


ESC European Society of Cardiology

European Journal of Heart Failure (2022) 24, 1080–1090
doi:10.1002/ejhf.2524

Cardiac Resynchronization Therapy for HFrEF

- Who has most to gain from CRT-P?
  - Sinus Rhythm
  - QRS >140 ms
  - Systolic BP ≤120 mmHg
  - Moderate Mitral Regurgitation
    - Super-responders



Cardiac Resychronization Therapy

Compared to what?

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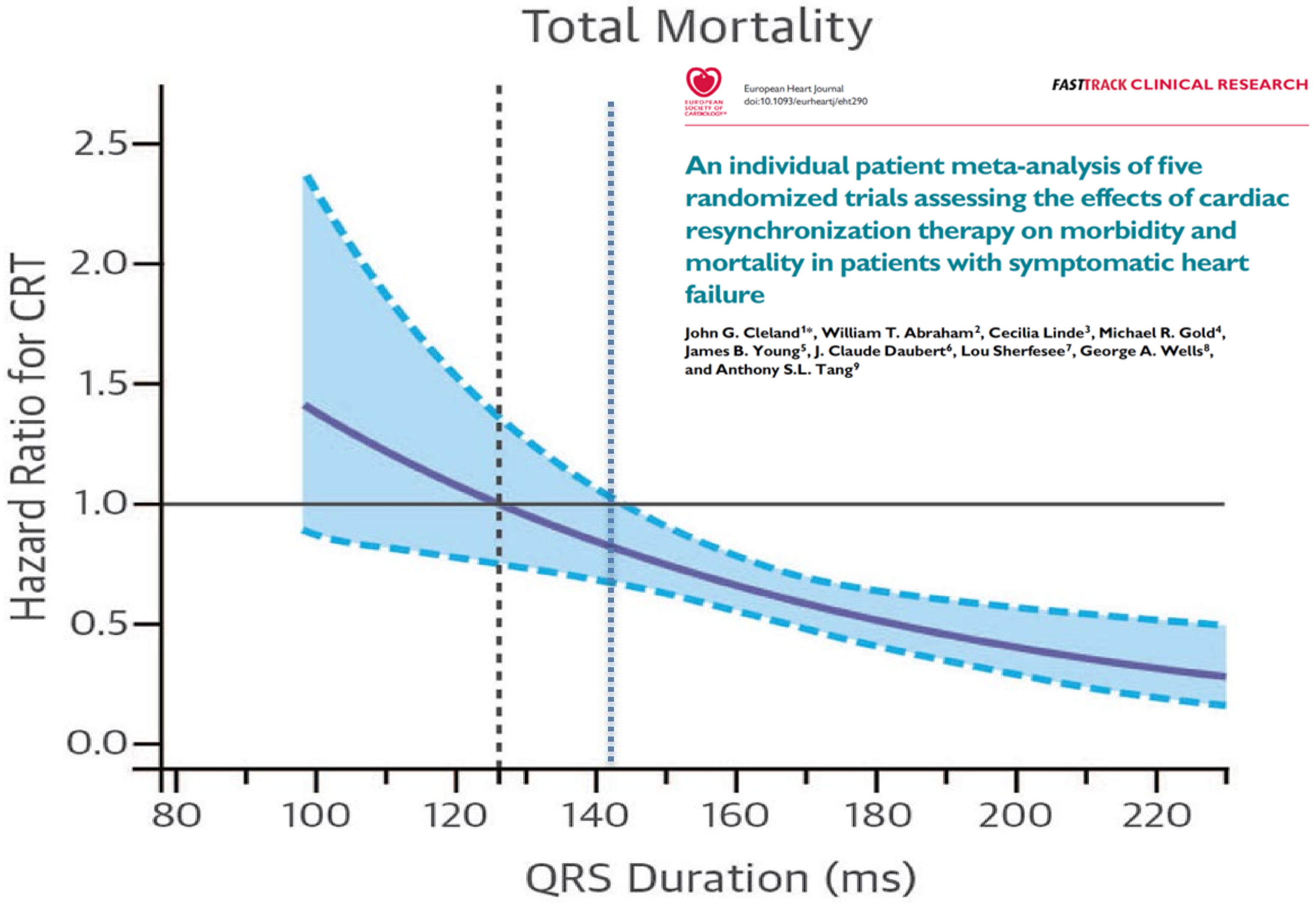
COMPANION	MIRACLE	MIRACLE-ICD
CARE-HF		MADIT-CRT
		RAFT
		REVERSE (mostly)

* A two-edged sword

Individual Patient Data Meta-Analyses
- predominantly CRT-D versus ICD

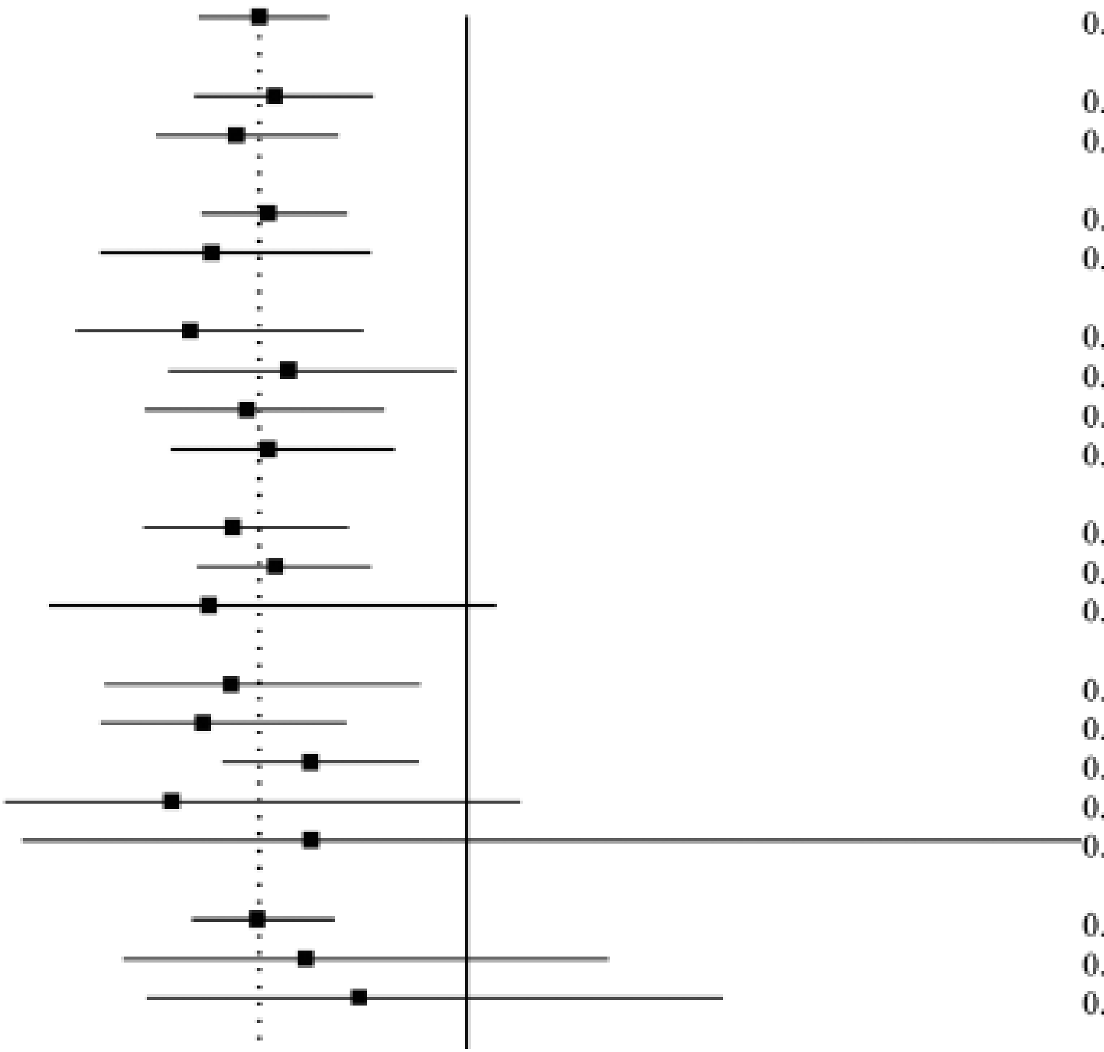
- **3,782 patients:**
- **QRS duration was the ONLY predictor of the effect of CRT on**
  - **Death or HF Hosp**
  - **Mortality**
- **Threshold ~130msec**



Individual Patient-Data Meta-analysis of Medtronic CRT Trials

Majority CRT-D versus ICD

Group	Deaths/total subjects	Hazard ratio (95% confidence intervals)
Overall	(662/3872)	0.66 (0.57, 0.77)
ICD subject	Yes (366/2437)	0.69 (0.56, 0.85)
	No (296/1435)	0.63 (0.5, 0.79)
Gender	Male (534/3004)	0.68 (0.57, 0.8)
	Female (128/868)	0.58 (0.41, 0.84)
Age	<58 (100/980)	0.55 (0.37, 0.83)
	58–66 (150/967)	0.71 (0.51, 0.98)
	66–72.5 (181/964)	0.64 (0.48, 0.86)
	>72.5 (231/961)	0.68 (0.52, 0.88)
NYHA	II (229/1877)	0.62 (0.48, 0.8)
	III (386/1849)	0.69 (0.56, 0.84)
	IV (47/146)	0.58 (0.32, 1.05)
LVEF	<15 (97/365)	0.62 (0.41, 0.92)
	16–20 (143/784)	0.57 (0.41, 0.8)
	21–30 (352/2162)	0.75 (0.6, 0.92)
	31–35 (32/318)	0.52 (0.25, 1.08)
	>35 (17/174)	0.75 (0.28, 2)
Morphology	LBBB (528/3036)	0.66 (0.55, 0.78)
	RBBB (65/346)	0.74 (0.44, 1.23)
	Neither (54/467)	0.82 (0.48, 1.41)



Cleland et al Eur Heart J 2013

MADIT-CRT

	LBBB	Not LBBB	RBBB	IVCD
N=	1281	536	228	308
Age (yrs)	64	65	66	64
Women (%)	31	11	8	13
IHD (%)	44	80	87	77
MI (%)	32	70	76	66
QRS (msec)	163	146	153	142

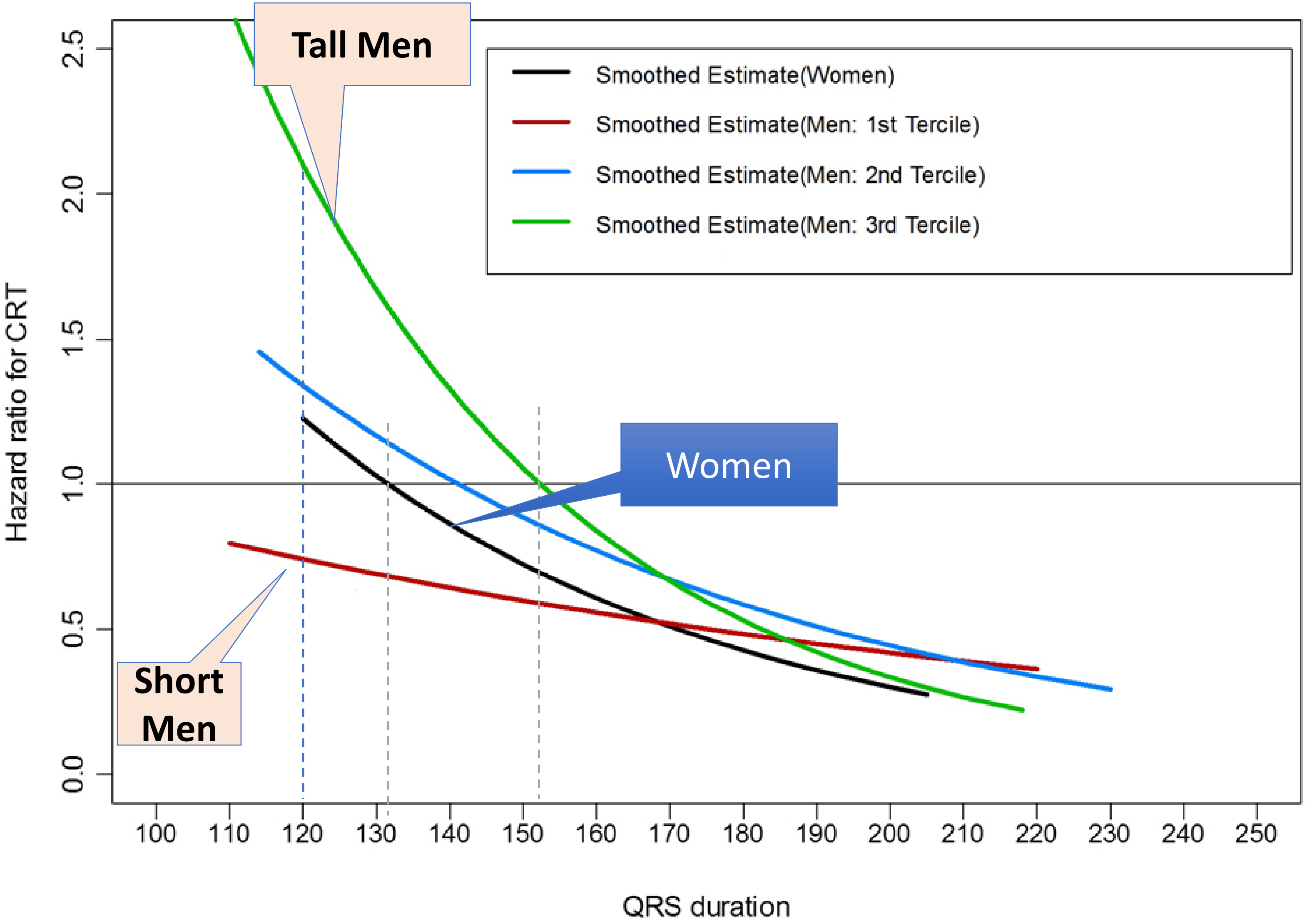
Zareba Circulation 2011

MADIT-CRT

	M/M ICD	M/M CRT-D	Death ICD	Death CRT-D
LBBB	32% of 520 = 166	16% of 761 = 122	7% of 520 = 36	8% of 761 = 61
RBBB	19% of 92 = 17	23% of 136 = 31	7% of 92 = 6	12% of 136 = 16
IVCD	23% of 117 = 27	33% of 191 = 63	4% of 117 = 5	15% of 191 = 29

Zareba et al Circ 2011

CRT IPD Meta-analysis

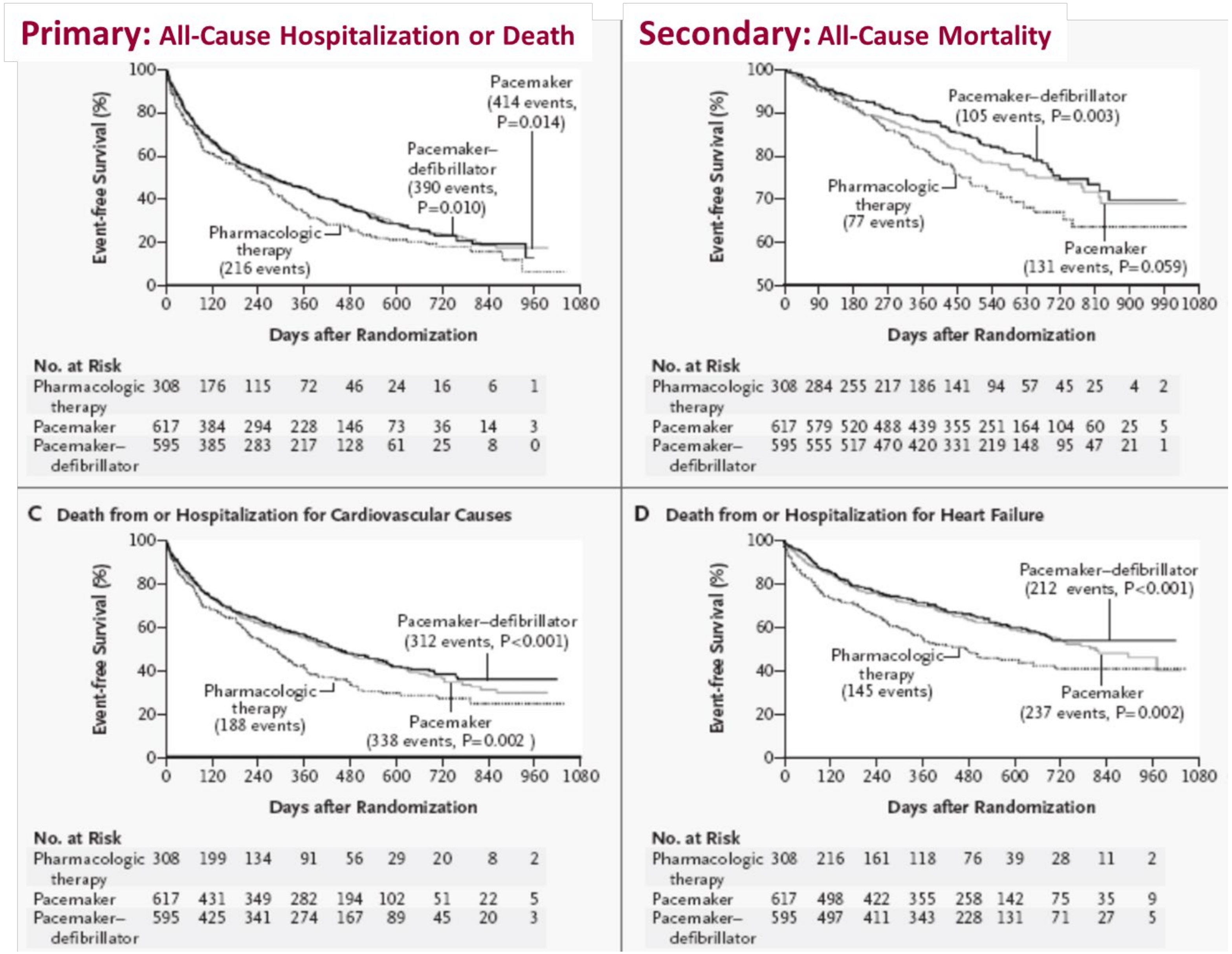


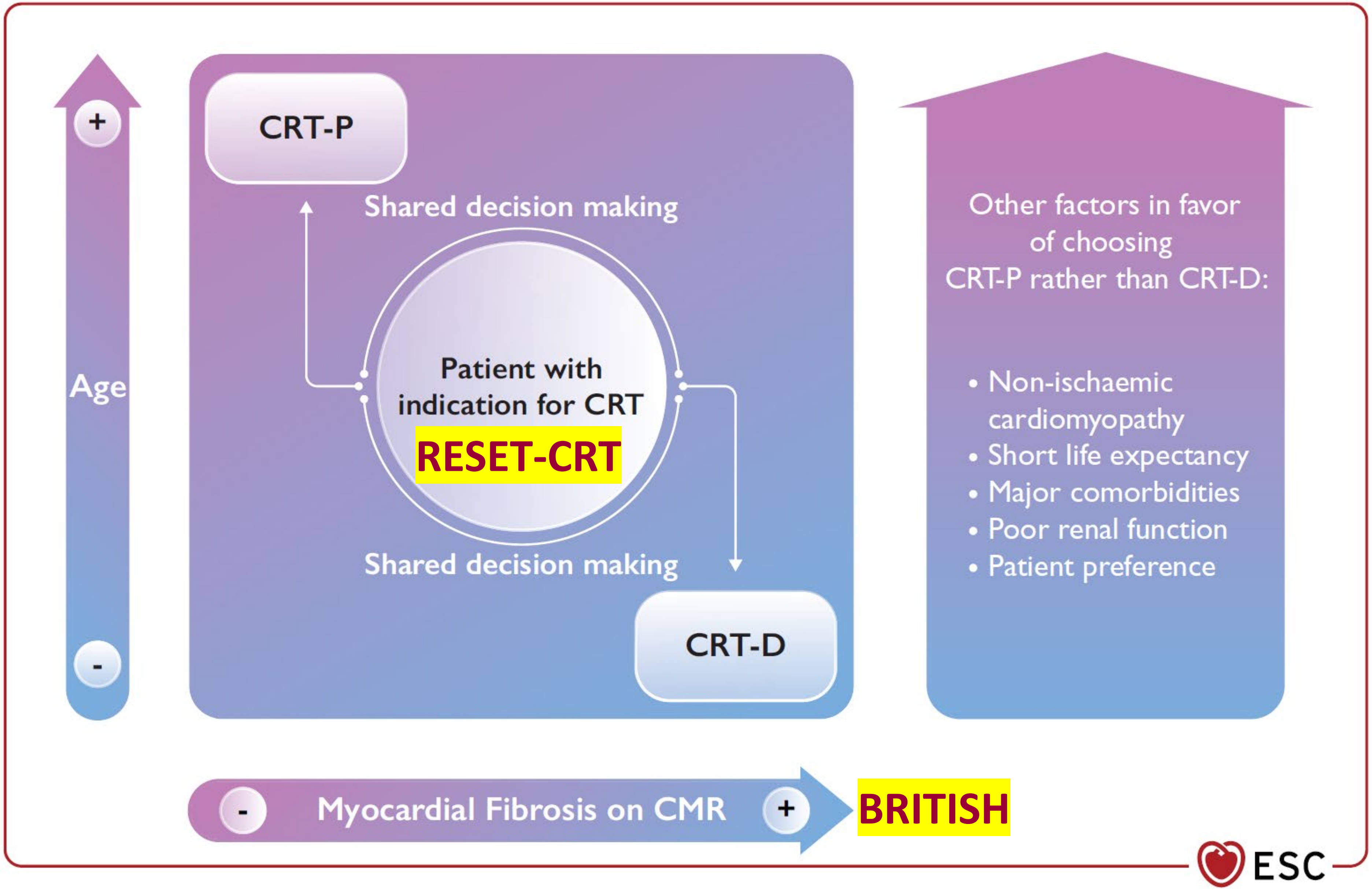
Subgroup	Height (cm) Median (IQR)
Women	160 (156 – 166)
Men: 1st tercile	168 (165 – 170)
Men: 2nd tercile	175 (173 – 177)
Men: 3rd tercile	183 (180 – 185)

Eur J Heart Fail. 2018 Apr;20(4):780-791.

CRT-P compared to CRT-D

COMPANION





CRT-P
Shared decision making
Age
+
-
Patient with
indication for CRT
RESET-CRT
Shared decision making
CRT-D
Other factors in favor
of choosing
CRT-P rather than CRT-D:
• Non-ischaemic
cardiomyopathy
• Short life expectancy
• Major comorbidities
• Poor renal function
• Patient preference
-
Myocardial Fibrosis on CMR
+
BRITISH
ESC

Cardiac Resynchronisation Therapy

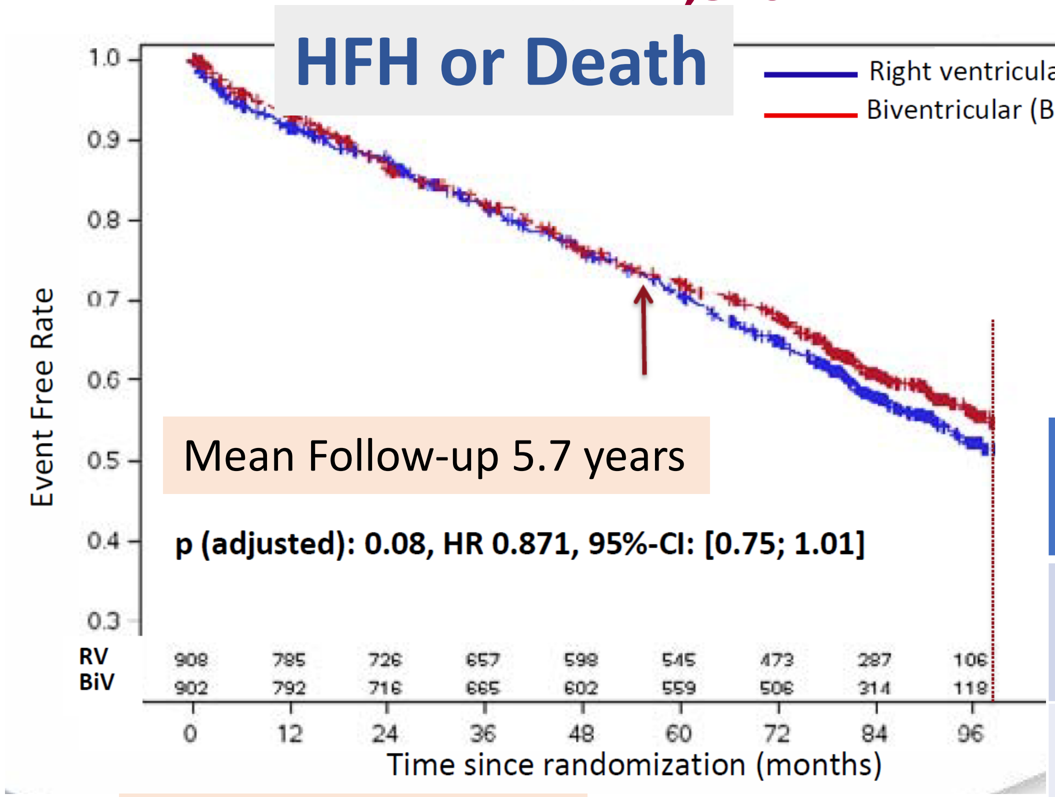
for patients with Atrial Fibrillation
Predominantly with reduced LVEF

Pulmonary Vein Ablation vs. OPT	Pulmonary Vein vs. AVN Node Ablation	AVN Ablation with BiV-P vs. RV-Pacing	AVN Ablation + BiV-P vs. OPT
CASTLE-AF Subgroup (n = 100)	PABA-HF (n = 81)	MUSTIC-AF (n = 37)	APAF-CRT (n = 133)
CASTLE-HTx Subgroup (n = 73)		PAVE (n = 184)	
		OPSITE (n = 56)	
		AVAIL (n = 108)	
		APAF (n = 186)	

BIOPACE – RV v BiV-Pacing

for patients with an indication for pacing

n = 1,810



LVEF ≤35%	152
LVEF 35-50%	419
LVEF >50%	1239
AF	450

ClinicalTrials.gov Identifier: NCT00187278

Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction

Anne B. Curtis, … . Adamson, Eugene S. Chu… Sherfesee, P… Timothy S… utton, M.D., for the Biventric… …g in Heart F… Patients with Atrioventricular Block (BLOCK HF) Trial Investig…

BLOCK-HF

LVEF Mean	40%
LVEF ≤35%	30%
LVEF >35-50%	70%
AF	53%

PROTECT-HF

Conduction System Pacing versus RV Pacing
For LVEF greater than 35%

	RV	Bi-V	Hazard Ratio	P-value
Mortality (co-primary)	307	305	0.926 (0.789 to 1.009)	0.350
HFH or Death (co-primary)	346	363	0.878 (0.756 to 1.020)	0.088
CV Death	106	107	0.97 (0.74 to 1.27)	0.813
6MW Distance	371	371	No difference	
Minnesota QoL	16	15	No difference	
Infection	76	118	Excess with Bi-V pacing	

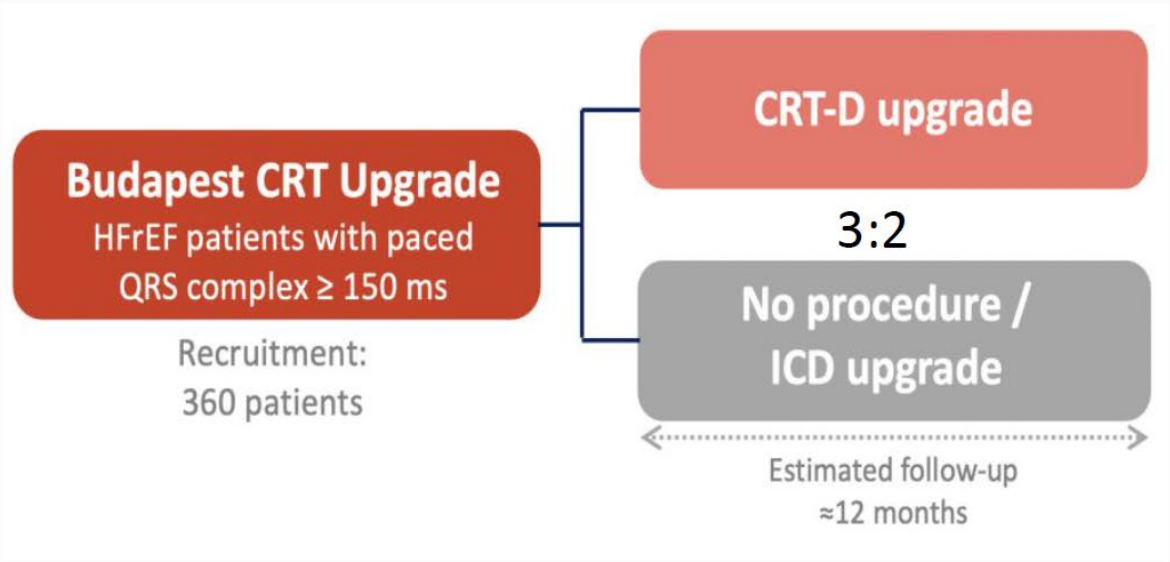
BUDAPEST CRT Upgrade - Study design

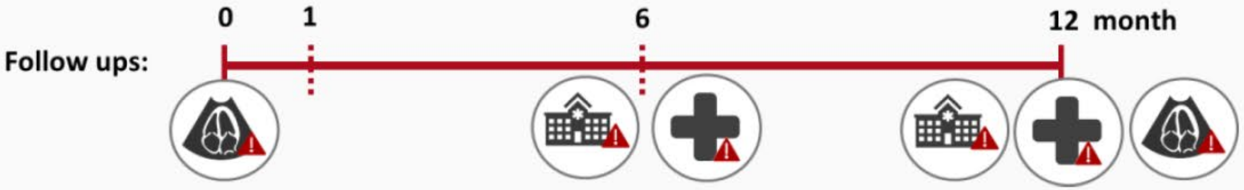
BP CRT

A Multicentre, Randomised, Controlled, Investigator-initiated Trial testing the hypothesis that CRT-D upgrade compared to ICD only would be associated with improved clinical outcomes

Key Inclusion Criteria: HFrEF patients with a prior pacemaker or ICD, RV pacing 20-100%, paced QRS complex ≥ 150 ms and GDMT

Key Exclusion Criteria: intrinsic QRS with LBBB morphology, severe renal dysfunction, severe RV dilatation, ACS events





COMPOSITE PRIMARY ENDPOINT

The first occurrence of

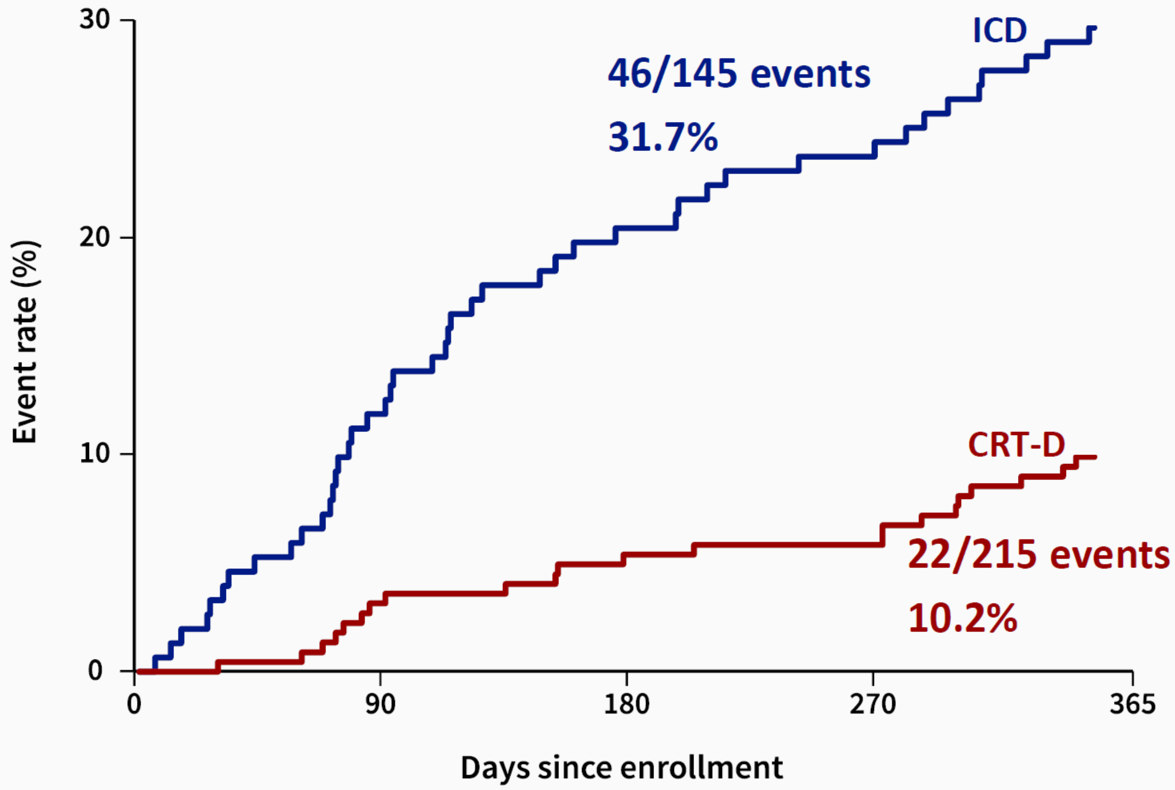
- HF hospitalisation,
- all-cause mortality,
- or < 15% reduction in LVESV from baseline to 12-month.

SECONDARY ENDPOINTS

1. Composite endpoint of HF hospitalisation and all-cause mortality
2. All-cause mortality
3. LVEDV and LVEF changes

Merkely et al, Eur J Heart Fail. 2022 Sep;24(9):1652-1661, doi: 10.1002/ejhf.2609.

Secondary Endpoint: All-cause mortality or HF hospitalisation



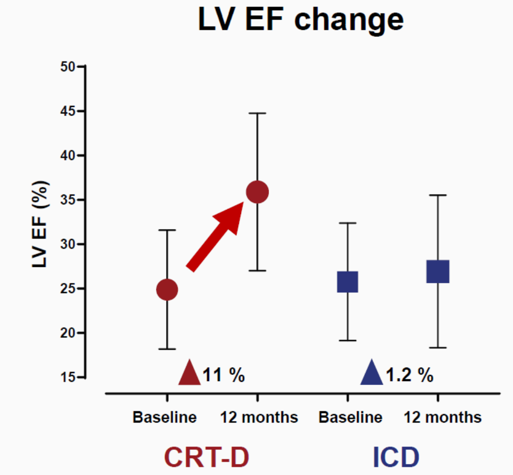
Number at risk, n

ICD	145	125	112	106	99
CRT-D	215	208	204	202	193

HR 0.28
95% CI 0.17-0.46

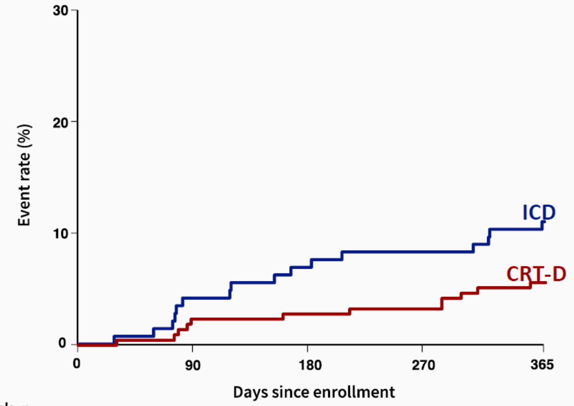
Adjusted HR 0.27
95% CI 0.16-0.47

NNT= 4.7



ESC Congress 2023
Amsterdam & Online

All-cause mortality



Number at risk, n

ICD	145	139	135	133	129
CRT-D	215	210	209	208	203

HR 0.49
95% CI 0.23-1.04

Safety Outcomes	CRT-D N = 215	ICD N = 145
VT or VF – no. / total no. (%)	1/215 (0.5)	21/145 (14.5)

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–94
doi:10.1093/eurheartj/ehab364
ESC GUIDELINES

2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy

Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC)

Some Predictions

- CRT-P implant rates will overtake CRT-D
  - ICD implantation rates will decline
- More Conduction System Pacing
- More Pulmonary Vein Ablation

Recommendations for cardiac resynchronization therapy in patients in sinus rhythm

Recommendations	Class[a]	Level[b]
LBBB QRS morphology		
CRT is recommended for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration ≥150 ms, and LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity and mortality.[37,39,40,254–266,283,284]	I	A
CRT should be considered for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration 130–149 ms, and LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity and mortality.[37,39,40,254–266,283,284]	IIa	B
Non-LBBB QRS morphology		
CRT should be considered for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration ≥150 ms, and non-LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity.[37,39,40,254–266,283,284]	IIa	B
CRT may be considered for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration 130–149 ms, and non-LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity.[273–278,281]	IIb	B
QRS duration		
CRT is not indicated in patients with HF and QRS duration <130 ms without an indication for RV pacing.[264,282]	III	A