Online Data Supplement. Cardiac Resynchronization Therapy

Study/Aim	Type of Study	N (total)	n (Exp/ Interv CRT)	n (Placebo/ Comparator)	Follow-Up (Mo)	Baseline Treatment	NYHA Class	EF (%)	QRS Duration (ms)	Exclusion Criteria	QRS Subgroups by Duration (ms)	Composite Endpoint (for QRS Subgroups)	Results
CARE HF (1) Aim of trial was to analyze the effects of a CRT-P on the risk of complications and death among patients who were receiving standard medical therapy for moderate or severe HF and demonstrated cardiac dyssynchrony by echocardiography and/or intraventricular conduction delay.	RCT	813	409	Medical therapy*: 404	29.4	ACEI, beta-blockers, and spironolactone	III or IV	≤35	≥120	Patients who had a major cardiovascular event in the previous 6 wk, those who had conventional indications for a pacemaker or an ICD, and those with HF requiring continuous IV therapy and those with AF were excluded.	120 to 159 (n=290); >159 (n=505)	All-cause mortality or hospitalizations for major cardiovascular event including HF hospitalization	HR: 0.63; 95% CI: 0.51 to 0.77; (p<0.001), CRT primary and significant improvement NYHA, MLHF, euroqol.
COMPANION (2) Aim of trial was to compare optimal pharmacologic therapy plus a CRT-Pacemaker, optimal pharmacologic therapy plus a CRT-Defibrillator, and optimal pharmacologic therapy alone in a population with advanced HF and intraventricular conduction delays.	RCT	1,520	CRT-P: 617; CRT-D: 595	Medical therapy*: 308;	16.2 (CRT-P),15.7 (CRT-D) 11.9 (medical)	ACEI, beta-blockers, and spironolactone	III or IV	≤35	≥120	AF, clinical indication for a pacemaker or implantable defibrillator, a hospitalization for the treatment of HF or the equivalent in the preceding 12 mo.	120 to 147 (n=324); 148 to *168 (n=314); >168 (n=287)	All-cause mortality or hospitalizations.	HR: 0.81(p=0.014) for primary endpoint for CRT-P and HR: 0.80 (p=0.01) for CRT-D. HR: 0.76; 95% CI: 0.58 to 1.01for CRT-P reducing all-cause mortality (p=0.059). CRT-D by HR: 0.64; 95% CI: 0.48 to 0.86; (p=0.003). N/S between CRT-P and CRT-D, 6MW, MLHF, NYHA significantly improved with both.
MADIT-CRT (3) Aim of trial was to determine whether a CRT-D would reduce the risk of death or HF events in patients with mild NYHA functional class I-II cardiac symptoms (NYHA I or II	RCT	1,820	1,089	Medical therapy*: 731	28.8	ACEI, beta-blockers, and spironolactone .	1 or II	≤30	≥130	Patients were excluded from enrollment for a variety of reasons, including an existing indication for CRT; having an implanted pacemaker, ICD, or resynchronization device; NYHA class III or IV symptoms, previous CABG,	130 to 149 (n=645); >149 (n=1175)	All-cause mortality or HF event (HF hospitalization or outpatient intravenous diuretic therapy).	HR: 0.66; 95% CI: 0.52 to 0.84; (p=0.001), death 3% per y in both groups.

[ischemic cardiomyopathy] or NYHA II [nonischemic]), a reduced EF, and a wide QRS complex.										PCI, or an enzyme-positive MI within 3 mo before enrollment; AF within 1 mo before enrollment.			
MIRACLE (4) Aim of trial was to evaluate the therapeutic approach of CRT in patients with HF who have an intraventricular conduction delay.	RCT	453	228	225	6	Diuretic, ACEI or an ARB, and (usually) digitalis and a beta-blocker.	III or IV	≤35	≥130	Patients were excluded if they had a pacemaker, ICD, an indication for or a contraindication to cardiac pacing, a cardiac or cerebral ischemic event within the previous 3 mo, or if they had had an atrial arrhythmia within the previous mo. In addition, patients were not allowed to participate if they had a systolic blood pressure of >170 or <80 mm Hg, a heart rate of >140 bpm, a serum creatinine level of >3.0 mg per deciliter (265 μmol per liter), or serum aminotransferase levels > 3 times the upper limit of normal.		Primary endpoints were the NYHA functional class, quality of life, and the distance walked in 6 min.	Compared to the control group, patients in the CRT group experienced an improvement 6MW p=0.005, NYHA. (p<0.001), quality of life.
MIRACLE ICD (5) The trial examined the efficacy and safety of combined CRT and ICD therapy in patients with NYHA class III or IV congestive HF despite appropriate medical management.	RCT	369	187 - ICD activated, CRT on	182 - ICD activated, CRT off	6	Optimized medical treatment.	3 or 4	≤35	≥130	Estimated survival 6 mo, baseline 6 min, walk test 450 m. Bradycardia requiring pacemaker, unstable angina, MI, CABG, percutaneous transluminal coronary angioplasty, cerebral vascular accident, or transient ischemic attack within previous 3 mo, 2 infusions of inotropic drug per wk, SBP 80 mm Hg or 170 mm Hg, resting heart rate 140/min, serum creatinine 3 mg/dL (265 μmol/L) Hepatic enzymes			The primary double-blind study end points were changes between baseline and 6 mo in quality of life, functional class, and distance covered during a 6 min walk. At 6 mo, patients assigned to CRT had a greater improvement in median (95% CI) quality of life score (–17.5 [–21 to –14] vs. –11.0 [–16 to –7], p=0.02) and functional class (–1 [–1 to –1] vs. 0 [–1 to 0], p=0.007) than controls but were no different in the change in distance walked in 6 min (55 m [44-79] vs. 53 m [43-75], p=0.36).

										3-fold upper normal values, severe lung disease, chronic atrial arrhythmias, or cardioversion, or paroxysmal AF within previous 1 mo heart transplant recipient, severe VHD.			Peak oxygen consumption increased by 1.1 mL/kg per min (0.7-1.6) in the CRT group vs. 0.1 mL/kg per min (–0.1 to 0.8) in controls (p=0.04), although treadmill exercise duration increased by 56 sec (30-79) in the CRT group and decreased by 11 sec (–55 to 12) in controls (P=0.001). No significant differences were observed in changes in left ventricular size or function, overall HF status, survival, and rates of hospitalization. No proarrhythmia was observed and arrhythmia termination capabilities were not impaired.
RAFT (6) Aim of trial was to evaluate whether adding CRT to an ICD and optimal medical therapy might reduce mortality and morbidity among patients with EF<30%, class II, III HF, QRS >120, paced QRS ≥200 msec.	RCT	1,798	894	No CRT: 904	40	ACEI, beta-blockers, and spironolactone.	II or III	≤30	≥120	Patients with a major coexisting illness or a recent cardiovascular event such as ACS or use of IV inotropic therapy were excluded. Other exclusion criteria included uncorrected VHD, restrictive or HCM, cor pulmonale, prosthetic tricuspid valve, or preexisting ICD.	120 to 149 (n=627); >149 (n=1036)	All-cause mortality or HF hospitalization.	33% vs. 40% primary, HR: 0.75; 95%CI 0.64 to 0.87, p<0.001, death: HR: 0.75; 95% CI: 0.62 to 0.91, HF hospitalization: HR: 0.68; 95% CI: 0.56 to 0.83; (p<0.001), adverse events: 124 vs. 58. Benefit comparable in NYHA class II and III, No benefit if RBBB, IVCD, paced, or permanent AF, or QRS <150.
REVERSE (7) Aim of trial was to determine the effects of CRT in NYHA functional class II HF and NYHA functional class I (ACC/AHA stage C) patients with previous HF symptoms.	RCT	610	419	CRT-off: 191	12	ACEI, beta-blockers, and spironolactone.	1 or II	≤40	≥120	Patients were excluded if in the 3 mo before enrollment they were classified as NYHA functional class III or IV or had been hospitalized for HF. Those in need of cardiac pacing, those who had been paced from a previous device, or those with permanent or persistent atrial arrhythmias also were excluded.	120 to 151 (n=303); >151 (n=307)	HF clinical composite response, which scores patients as improved, unchanged, or worsened.	N/S primary worsened 16% vs. 21% off, p=0.10, secondary time to hospital, HR: 0.47, p=0.03, LVESV smaller -18 vs. -1, p<0.0001.

*Diuretics, ACE inhibitors, beta-blockers, and spironolactone.

6MW indicates distance walked in 6 minutes; ACC/AHA, American College of Cardiology/American Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; bpm, beats per minute; CABG, coronary-artery bypass grafting; CARE-HF, Cardiac resynchronization in heart failure; CI, confidence interval; COMPANION, Comparisons of medical therapy, pacing, and defibrillation in heart failure; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; EF, ejection fraction; euroqol, European Quality of Life -5 Dimensions instrument; HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; IVCD, intraventricular conduction delay; LVESV, left ventricular end-systolic volume; MADIT-CRT, Multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy; MI, myocardial infarction; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MIRACLE ICD, Multicenter InSync Implantable Cardioversion Defibrillation Randomized Clinical Evaluation; MLHF, Minnesota Living with Heart Failure questionnaire, range from 0 to 105, with higher scores reflecting a poorer quality of life; n, subgroup of N; N/S, not significant; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RAFT, Resynchronization-defibrillation for ambulatory heart failure trial; RBBB, right bundle-branch block; RCT, randomized controlled trial; REVERSE, Resynchronization reverses remodeling in systolic left ventricular dysfunction; SBP, systolic blood pressure; and VHD, valvular heart disease.

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