APPENDIX

Description of characteristics of studies

1. CRT versus OMT, sinusal rhythm

	Methods	Population	Intervention	Outcomes	Notes
Abraham 2002 MIRACLE	USA, 45 centers. From November 1998 to December 2000. Not blinded (open label). Randomization after implantation.	N = 453 patients with moderate / severe symptomatic heart failure NYHA III (91 %) - IV with LVEF < = 35 % (21.6 +/- 6) and QRS > = 130 ms (167 +/- 20). Ischemic cardiomyopathy (54 %) or nonischemic, sinus rhythm. Men 68 %, 65 +/- 11 years. Exclusion criteria: pacemaker of ICD previous implants, no indication or contraindication of PM, cardiac or cerebral ischemic events in the last three months, atrial arrhythmia in the previous month.	Two branches: CRT (PM with transvenous RA and biventricular implant), versus OMT. Evaluation at 6 months.	Primary: NYHA functional class, quality of life scale as Minnesota, distance walked in 6 minutes	Financial support by MEDTRONIC In the 2 groups (225 and 228 patients), there were few complications (2) related to the device. Only 5 to 13 losses to follow. 3-11 % patients admitted to reposition the electrode.
Saxon 2002 VIGOR	USA, 19 centers. From October 1996 to April 1998. No mention blinding. Randomization after implantation. Cross-over.	N = 53 patients with symptomatic heart failure NYHA II- IV, LVEF < = 30 %, QRS > 0.12 s , sinus rhythm , 80 % nonischemic / 20 % ischemic . Men 57 %, 58 +/- 14 years, 63 % LBBB, 3% RBBB, 34 % inespecific blocking pattern. Exclusion criteria: VT / VF associated with AMI, ICD implantation or indication, indication of permanent PM, etc.	Two branches: randomization to active biventricular VDD PM or " off" for 6 weeks , followed by another 6 + 6 weeks of active PM. Epicardial device. Follow-up at 6 weeks in the period after randomization.	Primary: peak O2 consumption during maximum exercise	Support in the echocardiographic analysis by GUIDANT. Early discontinuation of this work for patient inclusion rate too low.
Auricchio 2003 PATH-CHF	Multicenter (Germany, Netherlands and USA). From September 1998 to January 2001. Single blind. Randomization after implantation. Cross-over.	N = 89 patients with dilated cardiomyopathy of any cause (ischemic 38 %), LVEF <= 30 %, sinus rhythm, NYHA II- III (33 %) / IV (67 %) and no hospitalization in the last month for heart failure. QRS 155 +/- 20 ms, Men 66 %, 60 +/- 9 years, LBBB 88 %. 73 % beta blockers. Exclusion criteria: AF / atrial flutter, stenosis or reconstruction - replacement	Two branches: 2 successive periods (3 months each) in crossover trial: 1st PM active, followed by inactive ; 2nd MP inactive followed by active MP. Added ICD functionality according to clinical guidelines. Transvenous implant, implant the LV epicardial	Primary: peak O2 consumption , distance walked in 6 minutes, Minnesota score for quality of life	MEDTRONIC and GUIDANT implanted devices. No financial support for these pharmaceutical companies mentioned. Epicardial (71 %) or transvenous (29 %) LV electrode implant. 40 % ICD devices function. Losses in the follow-up 22 %

		mitroaortic surgery, coronary revascularization, ACS previous 3 months.	or transvenous. Follow-up at 6 months.		
Bristow 2004 COMPANION	USA, 28 centers. From January 2000 to December 2002. Open (not blinded). Implantation of the device after randomization.	N = 1520 patients with symptomatic(3.5-3.7 years) advanced in the last 6-12 months heart failure NYHA III (82-87 %) - IV, ischemic cardiomyopathy (54-59 %) or not, LVEF <= 35 %, QRS >= 0.12 s, PR > 0.15 s, sinus rhythm , with no indication of PM or ICD. Men 67-69 %, 66-68 years, 69-73 % LBBB / RBBB 9-12 %. Beta-blockers 66-68 %. Exclusion criteria: hospitalization caused by heart failure or need for iv inotropic therapy in the previous month, unstable angina, myocardial infarction, recent bypass surgery) , obstructive hypertrophic cardiomyopathy, ischemic heart disease.	Three branches: OMT, CRT and CRT combined with defibrillation capability (CRT + ICD). Transvenous devices. Follow-up at 12 months of the main outcome.	Primary: combination of all cause mortality and hospitalization at 12 months. Cardiovascular death data are collected in a 2.6 years follow- up (from 11.9 to 16.2 months median follow-up)	Financial support by GUIDANT. Success in the implant 87 % CRT and 91 % CRT+ICD. Moderate - severe adverse events in relation to the implant in 10 % and 8 % patients. As an open study, there is a much higher rate of drop-outs in the OMT group (26 %) compared to the other 2 groups (6 and 7%); if patients agreed after informed consent, underwent implantation of a CRT / CRT + ICD device; the data of these patients with " elective implant " were excluded from the analysis, although these patients were followed mainly to the end. A decrease in mortality from all causes is statistically significant different in the CRT + ICD branch (RRR 36 %, p = 0.003) , without reaching the level of significance in the branch CRT (RRR 24 %, p = 0.059), the authors attributed this to the follow too short.
Cleland 2005 CARE-HF	Europe, 82 centers. From January 2001 to March 2003. Single blind . Implant after randomization.	N = 813 patients with symptomatic heart failure NYHA III systolic dysfunction (93 %) - IV despite adequate OMT, with EF <= 35% - 25(21-29)%-, QRS>= 150 ms (or between 120 and 149 ms with echocardiographic dyssynchrony criteria), 72% beta blockers, sinus rhythm. 73% men, 66 (59-73) years, LBBB. Exclusion criteria: supraventricular arrhythmias, major cardiovascular events in the past 6 weeks, MP or standard indication for ICD , or HF	Two branches: OMT versus CRT atrio-biventricular transvenous device. Mortality data at 3 years (mean 37.4 months follow-up).	Primary outcome:death from any cause or hospitalization for major cardiovascular unplanned event	MEDTRONIC economic support. 5% of patients assigned to CRT never received this device, and 23.5% of patients assigned to OMT received CRT. Adverse events in the CRT group: 6% displacement of the electrocatheter, 2.4% coronary sinus dissection, 1.5% pouch erosion, etc."Significant" percentage of cross -over: 19 patients in the CRT branch (4.6%) never received such treatment, and 95 pacients in OMT branch

		requiring treatment iv			(23.5 %) received a CRT device.
Piepoli 2008	Italy, 2 centers. It does not describe the period of inclusion of patients (must be before the date of dispatch of the article, February 2008. Implant after randomization. No clear blinding.	N = 89 patients with advanced symptomatic heart failure with stable NYHA III (89 %) - IV (11%, with LBBB and QRS >150 ms (160-164 +/- 3 ms) and OMT. 58% ischemic heart disease. LVEF 23 to 24 +/- 1 %, sinus rhythm. 72 % male, 71-73 +/- 1 years. Exclusion criteria: permanent AF or previous MP definitive implant.	Two branches: CRT (43% with ICD function associated) versus OMT. Transvenous implantation of the device.	Stress tests index, BNP concentration and NYHA class. Follow-up to 12 months.	Financial support by GUIDANT. Two patients with complications in implant: 1 electrode dislocation, 1 increased depolarization threshold requiring reposition. Lower hospitalization, but not reduced mortality.
Goscinska 2008	Poland, 1 center. From September 2005 to October 2006. Single blind, cross-over. Implant after randomization.	N = 23 patients scheduled for coronary artery bypass surgery NYHA III- IV, LVEF <= 35% (30 +/- 2.6%), sinus rhythm and intraventricular echocardiographic dyssynchrony (QRS 138 +/- 32 ms). NYHA III. 87 % male, 64.7 +/- 7 years, LBBB 78 %. Exclusion criteria: AF chronic, heart problem that requires surgery CABG, PM or ICD indication.	Two branches: active versus inactive CRT (defensive PM VVI 40 /min) in 2 periods cross-over of three months duration each other. Posterior system programming as patient preferences for 6 months.	Primary outcomes: NYHA class, distance walked in 6 minutes, quality of life.	No mention of financial support. Small population. Quality of life results better than in other jobs. After 1 exitus in the early postoperative period, in the 2 branches no loss or cross-over occurs, all patients completed all 3 treatment periods .
Pokushalov 2010	Multicenter, Slovenia. It does not describe inclusion period (should be before the presentation at a conference in February 2009). Simple blind. Implant the device after randomization.	N = 164 consecutive patients with advanced symptomatic heart failure NYHA III- IV, ischemic cardiomyopathy, LVEF <= 35% (28-30 +/- 2), QRS >= 120 ms (139 +/- 29), echocardiographic dyssynchrony, sinus rhythm. 89 % men, 62.4 +/- 8 years, LBBB 79.4 %. Exclusion criteria: previous heart surgery	Two branches: coronary artery bypass surgery versus coronary artery bypass surgery with CRT.	Primary outcomes: Global mortality. 29.4 to 31.4 months median follow.	Not described funding. More frequent reoperation for perioperative bleeding in the group without CRT (4 versus 2). Readmissions for heart failure much more frequent in the group without CRT (2 versus 9) There are no randomized studies comparing epicardial versus transvenous implant; implantation in the "right" area can be achieved in a smaller percentage (including 70%), and chronic stimulation threshold is much higher with trasnvenous implant.
Foley 2011 RESPOND	UK, 1 center. From August 2007 to September 2009. Open, not double-blind. PM implantation after randomization.	N = 60 patients with moderate to severe symptomatic HF NYHA III- IV with normal QRS <0.12 s, ischemic cardiomyopathy (83 %), LVEF <35%, sinus rhythm, with no indication MP. Men 82%, 67-	CRT transvenous device versus OMT. MR suppor for the LV electrode not rests on scar tissue.	Primary outcome: change in distance walked in 6 minutes. Follow up to six months.	Sponsored by Medtronic. No incidences / complications related to implantation of the device. Despite not having enough power (small sample size), a difference in mortality

		69+/- 8-10 years. Exclusion criteria: acute ischemic heart disease (1 month), structural valve disease, comorbidities.			between the two groups, especially mortality due to LV failure, is detected.

2. CRT versus OMT, definitive pacemaker

	Methods	Population	Intervention	Outcomes	Notes
Cazeau 2001 MUSTIC-SR	Europe (France, Germany, UK, Sweden, Switzerland and Italy), multicentric. Since March 1998 to 1 year later. Simple blind cross-over. Randomization after implantation of atriobiventricular device.	N = 48 patients with severe heart failure due to systolic LV dysfunction (idiopathic or ischemic), NYHA III in at least 1 month, sinus rhythm, LVEF <35 % (23 +/- 7 %), QRS > 150 ms (176 + / -19 ms. No standard indication of definitive MP. Men 75 %, 63 +/- 10 years, 87 % LBBB. Exclusion criteria: hypertrophic or restrictive cardiomyopathy, suspected acute myocarditis, ACS or coronary surgery last three months.	Two branches: active versus inactive PM in a cross-over design, in 2 periods of 12 weeks each. Transvenous implant.	Primary outcome: distance walked in 6 minutes	Financial support by ELA. High percentage of losses. Few hospitalizations and low mortality, probably due to little follow-up period (24 weeks). Of the initial 64 patients, there were 5 failures of electrocatheter placement in LV (success 92%), premature displacement of electrode in 8 patients, that was solved in 5 with relocation. Globally 88 % functional electrode.
Leclerq 2002 MUSTIC-AF	Europe (France, Germany, UK, Sweden, Switzerland and Italy), 15 centers. From March 1998 to June 1999. Single blind, crossover. Randomization after implantation of atriobiventricular device.	N = 43 patients with severe heart failure due to systolic LV dysfunction (idiopathic or ischemic), NYHA III in at least 1 month, permanent AF (> 3 mo), LVEF <35 % (25 +/- 10 %), QRS > 150 ms (207 +/- 17 ms. 51 % patients with previous definite PM. Men 82 %, 66 +/- 9 years. 64 % of patients with node AV ablation. 30 % ischemic heart disease, 70 % idiopathic. 23 % treated with beta-blockers. Exclusion criteria: hypertrophic or restrictive cardiomyopathy, suspected acute myocarditis, ACS or coronary surgery in last three months.	At the time of inclusion biventricular PM is implanted, node AV ablation will be made when required. Two branches: conventional RV and biventricular pacing for a period of three months, followed soon after by a second cross-over period with biventricular and RV pacing, respectively, for 3 months.	Primary outcome: distance walked in 6 minutes. Measures at the end of the first cross-over period. The mortality data after 2 cross-over periods.	ELA PM implant. Success implant of biventricular device 92 %, with 87 % of patients with fully functional at the end of the 2 cross-over periods. 5 early electrode dislocations corrected later. Much greater preference for biventricular pacing (N = 33) than RV pacing (N = 4).
Martinelli 2002	Brazil, one center. From	N = 24 patients with advanced	Following implantation of	Measures of LVEF and	No financial support given.

	January 1997 to October 2000. No cited blinding. Cross-over. Randomization after implantation.	symptomatic heart failure NYHA III (33 %) - IV (67 %) stable in the past two weeks, irreversible cardiomyopathy (Chagas 29 %, ischemic 38 %, idiopathic 21%) and LBBB. LVEF 19 +/- 5 %, sinus rhythm 96 %, 96 % male, 55 years, LBBB. 27 % taking beta-blockers. Exclusion criteria: 2nd - 3rd degree AV block, acute myocarditis, acute or ischemic heart bypass pending.	the device, there is randomized to biventricular versus RV pacing, 2 cross-over periods of six months. Median follow-up 2 years. LV lead implant by mini - thoracotomy.	NYHA class.	Implanted devices are Medtronic. No disaggregated data in each treatment arm. Short series, apparently with no significant losses in monitoring patients.
Doshi 2005 PAVE-VecToR	Multicenter, USA and Canada. From August 2000 to August 2003. Single blind (patient) , implant after randomization	N = 252 patients with AF of > 30 days, indication of node AV ablation and definitive PM to treat a rapid ventricular rate and limitation of deambulation (< 450 m in 6 minutes). Advanced symptomatic heart failure NYHA I- III, 30-38 % ischemic cardiomyopathy, valvular 16-19 %, 14-16% nonischemic. Men 64 %, 67-70 +/- 10 years. 54 % taking beta-blockers. Exclusion criteria: NYHA IV, ICD or need for cardiac surgery, valvular prosthesis	Two branches: biventricular versus RV pacing. Transvenous implants. Follow-up at 6 months.	Primary outcome: change in the distance at 6 minutes at 6 months.	Financial support by St Jude Medical. There is no intention-to - treat analysis (exclusion of 21 patients initially randomized to CRT without successful PM implantation). In the subgroup analysis performed, the measured results are better in patients with LVEF <=45 %. Mechanical complications during implantation are more frequent in the biventricular PM (15 versus 6%). Patients with biventricular PM with LVEF < = 45 % or symptoms of heart failure NYHA II- III have an improvement in the distance walked in 6 minutes higher than in patients without these data.
Brignole 2005 OPSITE	Multicenter -not indicates number of centers, major authors are 10 different centers, Europe (Italy, UK, Greece, Sweden) - .	N = 56 patients with permanent AF in which it was decided to perform ablation AV node followed by definitive PM implantation for symptomatic AF with very high ventricular rate ; or	Transvenous implantation of biventricular pacing device with electrode in RV (apex) and LV (through the coronary sinus). Two successive stages with	Quality of life (Minnesota scale) and exercise capacity (6-minute walk test). Measures after finishing the 2nd active period	Independent work from the pharmaceutical industry, but with financial support by VITRATRON and St Jude Medical. From the initial 56 patients, 2 mini-

	From July 2001 to January 2003. Single blind, cross-over. Randomization after implantation.	permanent AF and heart failure resistant to drug treatment, with depressed LV function and / or LBBB with decission to implant CRT device. NYHA 2.5 +/- 0.5. Ischemic cardiomyopathy 30 %, other 70%. AF of 6.6 +/- 4.2 years duration. LVEF 38 +/- 14 %. Men 61 %, 70 +/- 8 years. Take 52 % beta blockers. Exclusion criteria: NYHA IV despite OMT, AMI in the previous 3 months, sustained VT or VF, after implantation of a permanent PM.	cross-over: them : 1st phase LV versus RV pacing, and 2nd phase with RV versus biventricular pacing (3 months each period , 12 months period total)	(CRT versus VD pacing) of 6 months, the outcomes in the first active treatment period are not evaluated.	thoracotomy for epicardial implantation was needed. There are 15 lost to follow up (including 6 deaths. 25% patients prefered pacing from the RV compared to CRT.
Höijer 2006	Sweden, one center. From September 2002 to August 2003. Double - blind, cross-over . Randomization after implantation.	N = 10 patients with advanced symptomatic heart failure NYHA III (80 %)- IV (20 %) without LBBB on ECG preimplantation final MP. MP dominant rhythm. 40 % by slow FA in VVIR, DDDR and 60 % high grade AV Block -40 % - -20% and sinus dysfunction - . MP definitive implant +/- 74.7 43 months ago. Not describe cardiomyopathy, or basal QRS LVEF, or beta blockers taking %. 80 % men, 66.9 +/- 8 years, LBBB. No exclusion criteria described	In patients with chronic PM, is implanted an electrode in LV transvenously (90 %, and in 1 case thoracotomy for superior vena cava occlusion). Two branches: biventricular versus RV pacing, with 2 consecutive periods and cross -over of two months each.	Distance traveled in 6 minutes, symptom index, echocardiographic measurements and pacing mode preferred by the patient.	Small population N = 10. 9 preferred biventricular pacing , and 1 was indecisive.
Kindermann 2006 HOBIPACE	Germany, one center. It does not specify the period of incorporation. Single blind (patient), cross-over. Implant after randomization.	N = 30 patients with symptomatic bradycardia and AV conduction disorder requiring final PM. Symptomatic heart failure (NYHA 3 +/- 0.6) , 57 % ischemic cardiomyopathy , LVEF 26 +/- 8 %, 174 +/- 42 ms QRS, sinus rhythm 70 % / 30 % permanent AF. Men 77 %, 70 +/- 8 years, 63 %. Taking beta-blockers by 100 % patients at the time of inclusion. No exclusion criteria specified.	Two branches: biventricular versus RV pacing. Transvenous electrodes. Cross-over study , follow up of three months each period.	Echocardiographic values (LVEF), peak O2 consumption , Minnesota scale.	Without support from the pharmaceutical industry.3 reoperations for dislocations generator electrode and dysfunction.
Res 2007 BRIGHT	Netherlands 9 centers. Late 2002 to mid 2005.	N = 42 patients with advanced symptomatic heart failure NYHA	Two branches: RV bifocal resynchronization therapy	Primary outcome: LVEF (at 6 months, after 2	19% losses. Complications: 1/42

	Single Blind (patients). Randomization after PM implantation. Cross-over .	III- IV (3 +/- 0.2), 52 % ischemic cardiomyopathy (CABG prior 19%), LVEF <35 %, QRS > = 0.12 s, sinus rhythm. Men 73.8 %, 69 +/- 9 years , LBBB 100 %, 76 % with beta-blockers. No specific exclusion criteria.	(apex and outflow tract RV) versus control (OMT, PM inhibited at a frequency of 40/ min).	periods of treatment of 3 months each).	persistent problems with an electrode which requires replacement of LV electrode; 1 patient required electric cardioversion (AF); 8 patients do not tolerate mode change from bifocal PM with atrial sensing to PM VVI at 40 beats/ min .
Leclerq 2007 RD-CHF	France and Germany, 11 centers. From August 2000 to July 2002. Single blind (patients), implant after randomization, cross-over.	N = 44 patients with advanced symptomatic heart failure NYHA III- IV with > = 1 month of OMT, LVEF <35 %, PM definitively implanted previously (49 +/- 34 months) according to accepted indications requiring generator replacemento. Sinus rhythm 54 %, men 91 %, 73 +/- 8 years, QRS 207 +/- 25 ms. 50 % ischemic cardiomyopathy, 43% idiopathic dilated. Exclusion criteria: hypertrophic obstructive cardiomyopathy , suspected acute myocarditis, acute ischemic heart disease	After the "improvement" of a PM with biventricular pacing, patients are randomized during a first period of 3 months with biventricular versus RV pacing, and a second period of three months are RV and biventricular pacing. Transvenous device. The results are described at the end of the cross-over period (3 months of treatment).	Primary outcomes: NYHA class, distance walked in 6 minutes, quality of life (Minnesota scale) after cross -over periods.	Of the 56 eligible patients, 10 are excluded after failing to place the electrode in LV (17.8 %). These high losses (the previous 10 , and 2 more for improper selection of the generator) limit their conclusions. ELA implant devices. No mentioned financial support to the company in the performance of work.
Albertsen 2008	Denmark, one center. From September 2003 to June 2005, consecutive patients. No specific blinding. Randomization after implantation.	N = 50 patients with varying heart failure NYHA I- IV (90 % I- II), hypertensive/ischemic (94 %) cardiomyopathy and valvular heart disease (10%), LVEF 24 ± 6%, QRS 117 ms (RV group)/143 (biventricular pacing), sinus rhythm, indicated implant of definitive PM (for high degree paroxysmal or persistent AV Block). Men 68%, 76 years (67-81), LBBB 8%, 16% received beta-blockers. Exclusion criteria : other conduction disorders including AV block grade I or AMI in 3 months prior cardiac surgery, iatrogenic AV block , etc.	Two branches: control (bicameral definitive PM definitive bicameral, with electrodes in RA and outflow tract RV) and CRT (already described 2 electrodes and one third by transvenous coronary sinus. Follow-up 1 year (initially planned) and 3 years.	Primary outcome: LVEF measured at 12 months.	Financial support by the Danish Heart Foundation. Implant success 100 %. 5 reoperations for dislocation of the electrode. 3 patients with phrenic nerve stimulation
Yu 2009 PACE	Hong Kong and	N = 177 patients with normal	After intravenous	Primary:	Medtronic support.

	Malaysia, 4 centers. From March 2005 to July 2008. Double blind. Randomization after implantation	systolic function (45 %) with standard PM definitive indication (sinusal disfunction -41 % - or advanced AV block -59 %-). 12% patients with a history of heart failure, 22% chronic ischemic heart disease. LVEF 61-62 +/- 7 %, QRS 107 +/- 30 ms, men 54 % , 68-69 +/- 11 years. 28 % taking beta-blockers. Exclusion criteria: persistent AF , ACS, coronary intervention/ CABG in the previous 3 months, life expectancy < 6 months , etc.	pacemaker implantation atrio- biventricular, it randomizes these 2 programmable modes: RD versus biventricular pacing	echocardiographic measurements of LVEF and LVEDV at 12 months. There is a further evaluation of results at 2 years (work published in 2011).	Success rate of CRT device implantation 92%. There are 14 patients with high threshold depolarization from LV, and 2 patients with coronary sinus dissection without consequences. 7 patients with diaphragmatic stimulation, which requires a reschedulings and 2 cross -over to RV pacing described. Small population, underpowered.
Martinelli 2010 COMBAT	Brazil 4 centers. January 2004 to June 2006. Double -blind, double cross-over. Randomization after implantation	N = 60 patients with heart failure NYHA II- IV (17 , 52 and 32%) , LVEF <40% , cardiomyopathy, ischemic (17%) and idiopathic (28%) of Chagas disease (52%), with a indication of permanent PM (AV block 32% 2nd degree type II, 18% advanced, 50 % complete). 65 % male, 57.4 to 59.3 years, sinus rhythm 100 %, mean QRS 154 and 148 ms. Exclusion criteria: isolated sinus node dysfunction, unstable angina / IAM / bypass surgery in the previous 3 months, recent stroke, prior pacemaker implant, chronic AF / atrial flutter.	Randomization 2 sequences of 3 successive periods of three months with function DDD biventricular - RV. Subsequently the patient is assigned to the stimulation mode with better performance (follow-up 24 months). Mean follow-up 17.5 +/- 10.5 months.	Primary outcomes: NYHA functional class, Minnesota quality of life scale, distance walked in 6 minutes, peak O2 consumption. Immediately after completion of 3 cross-over periods (9 months) .	Partial financial support from Medtronic. Of the 68 initially valued patients, 4 not included for failure of implant system, and 4 losses to follow-up. At follow-up there were AF, 4 early crosses from RV to biventricular branch, 2 patients with increased threshold of the LV electrode, 2 patients need to reposition the LV electrode.
Orlov 2010 AVAIL CLS/CRT	USA , 22 centers . December 2004 to May 2008. Single blind (only the patient), randomization after implantation.	N = 127 patients with symptomatic persistent or permanent AF with poor control of ventricular rate to undergoing ablation of AV node and subsequent implantation of a definitive MP, with symptomatic heart failure NYHA II (49 %) - III (59%) , 19-24% valvular heart disease, ischemic heart disease 10-49; % 6-20 % patients with LVEF	Three branches: biventricular pacing algorithm with closed loop stimulation , ventricular pacing with another algorithm (accelerometer) and RV pacing. Transvenous devices. Follow-up data at 6 months.	Echocardiographic measurements, quality of life scale and distance travelled in 6 minutes (6 minutes).	Placement electrocatheter failures 7.2%. No mention funding. BIOTRONIK implanted devices.

		< = 45 %. Men 36-65 %, 70-74 years. Take beta-blockers 11-15%. Exclusion criteria: life expectancy < 6 months, planned cardiac transplantation, non-threatening heart condition for life, ICD implantation, etc.			
van Geldorp 2010	Holland, one center. From October 2004 to October 2006. Single Blind (patients). Randomization after implantation. Cross-over.	N = 36 p atients with permanent definitive MP, with stimulation > 95% beats, with echocardiographic evidence of remodeling (LVEDV > 55 mm or LVEF <40 %) without evaluating data of heart failure. Ischemic 36 %, 53% permanent AF, LVEF 36 +/- 10 %, QRS with active pacemakers 195 +/- 26 ms, chronic RV PM (10 +/- 7 years), 77.8 % men , 65+ / -10 years, AV block spontaneous 47 %, 8% post-surgical, 31% ablation of the His bundle in permanent AF. Exclusion criteria : LVEF <35 % with NYHA III- IV (strict indication CRT), AMI/ cardiac surgery 6 months, extracardiac factors that may limit ability effort or life expectancy.	An update from RV to biventricular PM was performed, with implantation of a transvenous electrode (in patients where indicated was also updated with ICD function). After a period of 2-4 weeks, 2 cross-over periods of 6 months each, RV or biventricular activation occurred; after them , all patients were left with biventricular activation.	LVEF and other echocardiographic measurements , NYHA functional class	Economic support by BOSTON company.Two pacients with failed implant before randomization. 1 epicardial PM. 3 reoperations (electrode dislocation, diaphragmatic stimulation).
Stockburger2011 PREVENT-HF	Germany, Spain and Italy, 14 centers. Approximate inclusion period patients: September 2007 (previous publication in Europace) - November 2010 (job submission with results, to another journal). Implant after randomization. Unclear blinding.	N = 108 patients with an I or IIA indication of permanent PM, expected ventricular pacing > 80 %. LVEF 55-57 +/- 12 %, QRS 124-121+/- 30 ms, 10% AF, men 76-68 %, 69-72 +/- 9 years, 32 % ischemic cardiopathy, patients received beta-blockers. Exclusion criteria: NYHA III- IV, AMI or cardiac surgery in the previous 3 months.	Two branches: RV apical pacing (DDD) versus biventricular . Transvenous implant.	Primary outcomes: echocardiographic assessments (LVEDV). Follow-up to 12 months.	Financial support by MEDTRONIC. 12 lost to follow –up. 16 and 12 % of patients with crossing from the planned branch to the other (biventricular to RV, and RV to biventricular, respectively). Adverse events (including electrode implant problems and heart failure) in 18/58 and 21/50 patients.
Brignole 2011 APAF	Italy, Spain and Greece, 19 centers. From July 2005 to December 2009.	N = 186 patients with permanent AF (17-24 months) and indication of node AV ablation (to control	AV node ablation is performed, and subsequent implantation of CRT device	Primary outcomes: composite of death or heart failure,	Financial support by Medtronic, with no intervention in the design or

	Blinded patients and members of the evaluation committee of clinical events. Randomization after CRT device implantation.	ventricular rate), heart failure refractory to treatment, depressed LV function and wide QRS. 64 % with prior hospitalization for AF or heart failure, 49 % pacients with NYHA III- IV, chronic ischemic heart disease 28.5 %, 42.5 % dilated cardiomyopathy, LVEF 37-38 +/- 14 %, 50 % patients with QRS > = 0.12 s. Men 70 %, 72 +/- 9 years. 58% taking beta-blockers. Exclusion criteria: NYHA IV and SBP < = 80 mmHg despite OMT, severe noncardiac disease, AMI in previous 3 months, severe valvular disease, implantation or ICD.	(strategy "ablate and pace"). Two branches: CRT (ultrasound guided) versus RV apical pacing. Transvenous implant. Devices implanted with ICD function as decided by your doctor (39 % patients).	hospitalization for heart failure, or worsening of heart failure. Median follow-up 20 months.	statistical data handling. Success LV lead implantation in 91-92 % patients. In 4 patients is not achieved LV pacing, in 2 (CRT group) stimulation is lost, and the bag and/or system was revised in 3 patients (all in the RV group). Significant improvement in combined endpoint, without significant difference in overall mortality.
Curtis 2013 BLOCK HF	150 centers worldwide. Double -blind randomization after CRT device implantation function.	N = 691 patients with indication of PM implant because of AV block grade 3, AV block 2nd grade symptomatic or asymptomatic, AV block 1st with similar symptoms to pacemaker syndrome and documented phenomenon of Wenckebach or PR> 0.30 s stimulating at 100 beats/ min. Mild to moderate heart failure (NYHA I- III in the pre-implantation month. 39-61 % ischemic cardiomyopathy, LVEF > = 50 % in the previous month (33-43 %), LBBB 33 %. No sex or age described. Exclusion criteria: classical indication for CRT, severe acute ischemic or valvular heart disease, NYHA IV.	2 groups: biventricular versus RV pacing. In 30% cases the implantation of a CRT+ICD device were allowed (poorer LVEF, higher percentage of myocardial infarction and more advanced NYHA class)	Primary outcome: death from any cause or hospitalization for heart failure; improved systolic volume index of LV. Mean follow-up 37 +/- 23 months.	MEDTRONIC funding. Successful implantation of the device in 93.7% of cases, with low percentages of impossibility of cannulation of the coronary sinus or dislocation of the electrode with increase in pacing threshold. In the first 30 days after implantation 113 (14 %) severe adverse events, 83 in relation to the CRT system -dislocations (3%), atrial fibrillation (1.1%), complications related to LV electrode (6.4%). Described 14.7 % losses , and 14% cross-over (more common from the RV to the biventricular pacing group).

3. CRT+ICD versus ICD

	Methods	Population	Intervention	Outcomes	Notes
Lozano2000 VENTAK/CONTAK	Multicenter (USA, Europe, Australia).	N = 490 patients with symptomatic heart failure NYHA II (35%) - III	ICD implantation with PM biventricular function. LV	All-cause mortality. Analysis at the time of	Short duration. It did not evaluate the symptomatic

	Patients enrolled prior to the date of publication of the work (2000). No specific blinding. Randomization after implantation. Cross-over.	(57%) - IV (8%), ischemic cardiomyopathy (68%) or not, LVEF <= 35% (22 +/- 7), QRS > 120 ms, sinus rhythm with ventricular tachycardia or ventricular fibrillation and indication for ICD implantation. Men 83 %, 65 +/- 10 years. Taking beta-blockers 38 %. Exclusion criteria: PM indication, chronic atrial tachycardia resistant to drug treatment.	electrode via thoracotomy. Two cross -over periods of three months each in which randomizes TRC (biventricular pacing) versus OMT and the reverse in the following period.	cross-over, after the first active period of three months.	benefit of CRT. These devices appear to decrease the need for antiarritmias therapies. No describes losses, cross - over or complications related to the implant.
Young 2003 MIRACLE ICD	USA, multicentre. From October 1999 to August 2001. Double blind. Randomization after successful implantation.	N = 369 patients with advanced symptomatic heart failure NYHA III (89 %) - IV (11 %), ischemic cardiomyopathy (70 %) or not, LVEF <= 35 % (24 +/- 6), QRS >= 130 ms (162-165 +/- 22), sinus rhythm, with high risk of life - threatening arrhythmias (cardiac arrest due to ventricular fibrillation/tachycardia, or ventricular sustained spontaneous or inducible tachyarrhythmia) and indication of ICD (primary or secondary). Men 77 %, 68 +/- 11 years, 13 % RBBB. Taking beta-blockers 60 %. Exclusion criteria: bradycardia that requires definitive PM, unstable ischemic heart disease, chronic atrial arrhythmias.	Two branches : CRT "on" and controls (CRT "off"). Transvenous devices. Follow up to six months.	Changes in quality of life, functional class and distance walked in 6 minutes.	Financial support by MEDTRONIC. 8% CRT implant attempts without success. Following implantation, 3% losses to follow-up, 11% relocations of LV,and low rates of cross-over (8 and 5 %), more frequently for worsening heart failure and impaired LV stimulation. Follow up until 6 months may be too short to show beneficial effects of CRT.
Higgins 2003 CONTAK-CD	USA, 47 centers. From February 1998 to December 2000. Double blind. Randomization after implantation.	N = 490 patients with heart failure NYHA II (13 %) - III (72 %) - IV (15 %), 68 % ischemic heart disease, LVEF <= 35 %, QRS > = 120 ms (152-164 +/- 27) with conventional indication for ICD. Men 77 %, 66 +/- 11 years, 53 % LBBB/ 15 % RBBB. 43 % taking beta-blockers. Exclusion criteria: atrial tachyarrhythmias, definitive indication of PM.	Implant CRT + ICD device, patients randomized to treatment with CRT ("on") versus OMT (TRC "off"). Transvenous device. Follow up to 6 months.	Primary outcome: progression of heart failure, defined as all-cause mortality, hospitalization for worsening heart failure and ventricular tachycardia requiring electrical therapy.	Financial support for GUIDANT. In 11.6% of patients there could not be implanted transvenous LV lead in the coronary sinus. In the remaining patients, the device was implanted transvenously (N = 448) and transthoracic (N=53).2% periprocedural mortality implant: 1% pump failure, incessant VT, pulseless

					electrical activity, etc.
Abraham2004 MIRACLEICDII	Several centers, USA. Until July 2002. Randomization after implantation. Double blind. Randomization after implantation.	N = 186 patients with less advanced chronic heart failure NYHA II, ischemic cardiomyopathy (57 %) or not, LVEF <= 35 % (24.4 +/- 6.7), QRS >= 130 ms (166 +/- 25), sinus rhythm, indicated ICD implantation. Men 89 %, 63 +/- 13 years, LBBB. Taking beta-blockers 63 %. Exclusion criteria: indication or contraindication to PM.	Transvenous implant of a device with 3 electrodes (RA, RV and LV). Subsequently allocation into 2 branches: CRT + ICD versus ICD (CRT "off"). Follow up to 6 months.	Peak O2 consumption, NYHA class, quality of life (Minnesota score) and distance walked in 6 minutes	MEDTRONIC financial support. 9% unsuccessfully attempts to implant. 4 (2%) of dislocations of LV electrocatheter, unsolvable. 2 patients in the CRT + ICD received only ICD, and 5 of the ICD group received CRT + ICD. Improving physical ability, despite the short follow. Without differences in mortality.
RHYTHM ICD 2004	50 hospitals, probably from the US. From July 2002 to Obtubre 2003. Double blind. Randomization after implantation.	N = 187 patients with advanced symptomatic heart failure NYHA III (87%) -IV (13%), ischemic cardiomyopathy (74%) or not, LVEF <= 35% (24.8 +/- 7.7), QRS >= 150 ms (168 +/- 15), sinus rhythm, and indication for ICD implantation. Men 72 %, 69, LBBB 78 %. 24% taking beta blockers. Exclusion criteria: standard indication for PM, chronic AF, distance > 400m walked in 6 minutes, recent ischemic heart disease.	Following implantation, randomization to 2 branches: CRT "on" versus control (TRC "off") . Follow up to 6 months. Transvenous implant.	Peak O2 consumption, defibrillation efficacy, NYHA class, quality of life and traveled distance at 6 minutes.	Funded by St Jude Medical. 23 patients (11 %) with difficulty or technical problems in device implantation (coronary sinus cannulation failure, high thresholds, etc). High losses - 40 (22.5 %) - counting both branches .
Piccirillo 2006	Italy 1 center. Before June 2005 (submitted paper to the journal), with 1 year follow-up. Case-control study, in which patients with stable heart failure were randomized to the two branches: CRT + ICD and ICD. No clear blinding.	N = 31 patients with stable symptomatic heart failure without worsening or hospitalization in the previous 3 months, NYHA III (32 %) - IV (68 %), LVEF <= 35% (22 to 23 +/- 8%), QRS >120 ms (159 +/- 8 ms), sinus rhythm. Men 81%, 65 +/- 8 years. 90% taking beta-blockers. Exclusion criteria: primary valve disease, frequent extrasystoles, AF and other arrhythmias that require PM or ICD, coronary revascularization in the previous 3 months.	Randomization to 2 branches: ICD+CRT versus ICD. Evaluation at 12 months. No clear whether the devices are transvenous.	Ventricular arrhythmias, NYHA class, LVEF.	The main objective of the study was to assess whether the spectral analysis of heart rate variability predicts the occurrence of ventricular arrhythmias. No serious complications were cited after implants Selected outpatients.
Beshai 2007 RethinQ	USA, 34 centers. From August 2005 to	N = 172 patients with moderate symptomatic NYHA III heart	Following implantation of the device with CRT +	Primary outcome: increased peak O2	In 4 patients (1.6 %) can not implement the system.7

	January 2007. Double blind. Randomization after implantation.	failure, ischemic (52%) and nonischemic cardiomyopathy, LVEF <= 35% (25 +/- 6), QRS <130 ms (107 +/- 13), sinus rhythm, indication for ICD implantation (primary 86% and secondary) and echocardiographic dyssynchrony data. Taking beta-blockers 95 %, men 65 %,58-60 +/- 14 years. Exclusion criteria: standard indication to PM, after CRT.	ICD function, randomization to CRT "on" versus TRC "off". Transvenous implant. Evaluation at 6 months.	consumption of at least 1 ml/kg in the 6 minutes walk test.	incomplete baseline monitoring are described, 6 deaths or withdrawals from non-cardiac causes, 4 (2 and 2) deaths from heart failure, and some complications: 13 electrode displacements , 6 bag infections- hematomas, 2 losses of capture, 3 stimulation of the phrenic nerve, 1 drilling coronary sinus , etc. Financial support by St Jude Medical.
Linde 2008 REVERSE	USA, Canada and Europe, 73 centers. From September 2004 to September 2006. Randomization after implantation. Double blind.	N = 610 patients with less advanced heart failure NYHA I (82 %) - II (18 %) in the previous 3 months, 79% ischemic cardiomyopathy, LVEF <= 40% (26.4 +/- 7 %), QRS >= 120 ms (154 +/- 24). Sinus rhythm. Men 79 %, from 61.8 to 62.9 +/- 11 years. Taking beta-blockers 95 %. Exclusion criteria: heart failure NYHA III- IV in the last three months, need to implant or previous PM implant, persistent - permanent atrial arrhythmias.	Transvenous implant devices with CRT + ICD function and randomization to CRT ("on") versus OMT (TRC "off"). Follow-up to 12 months.	Combined endpoint of heart failure, with 3 categories: worsening, no change or improvement. Hospitalizations for heart failure, rupture of blinding for worsening heart failure, or worsening NYHA stage worsening are assessed.	Implant device with CRT + ICD function in 87% cases, and CRT function in the remaining 13 %. No funding specifically cites the work. Peri - implant complications (26; 4%) are described by progressive heart failure, arrhythmia, digestive bleeding, etc; and late complications (111; 18 %) by dislocations of electrodes (66, the most frequent LV), diaphragmatic irritation, AF / atrial flutter, hematoma, etc. 20 patients crossover: 6 from CRT to CRT “off” (worsening heart failure, diaphragmatic stimulation) and 14 passed to TRC "on" (especially for worsening heart failure).
Moss 2009 MADIT-CRT	USA, Canada and Europe , 110 centers. From December 2004 to April 2008. Implant after randomization. Probably not blind	N = 1820 patients with mild heart failure symptoms -NYHA I (15%) - II (85 %) - ischemic (55 %) and non-ischemic cardiomyopathy, LVEF <= 30%, QRS >= 130 ms, indicating for ICD as clinical guidelines. Sinus rhythm or PM. Men 75%, 64-65 +/- 11 years, 70% LBBB/13% RBBB. Taking beta-	Randomization to receive trasnvenous device CRT+ICD versus ICD. Transvenous devices. Mean follow-up of 2.4 years.	Composite endpoint of death from any cause or nonfatal cardiac event.	Financial support by BOSTON. "Defensive" mode device in oligosymptomatic patients. The device implanted in 14 + 5 patients es withdrawn. There are 91 patients (12 %) in the ICD group receiving CRT + ICD device, and 82 (8 %) in the

		blockers 93 %. Exclusion criteria: indication for CRT, previous implantation of PM, CRT or ICD; MI or coronary intervention or coronary artery bypass surgery in the previous 3 months; AF in the previous month.			ICD-CRT branch where there is difficulty in implementing the LV catheter and end up getting one ICD device.
Pinter 2009	Canada, 7 centers. It does not specify the inclusion period (before publication in 2009). Single blind (patients). Randomization after implantation.	Prophylactic study of CRT in patients with mild to moderate heart failure and relatively short follow-up. N = 72 patients at high risk of sudden death, irreversible structural heart disease, LVEF <= 35%, sinus rhythm , symptoms of mild to moderate heart failure, QRS > 120 ms. Patients met standard criteria for ICD but not TRC. LVEF 21 to 24 +/- 8 %, 89 % sinus rhythm. Men 79 %, 66 +/- 9 years. Exclusion criteria: need of MP for bradycardia, ACS in the past 6 weeks, CABG surgery in the past 4 weeks, RBBB, angina CCS class 3-4.	Implant device with 3 electrodes (RA, RV and LV) and ICD function; randomization in 2 branches: CRT "on" versus CRT "off".	Principal: variation of systolic left ventricular volume as scintigraphy. Measures 6 months.	Financial support for GUIDANT 17% of implant failures system, representing exclusions before randomization. 7% loss to follow up to 6 months
Tang 2010 RAFT	Canada, Europe, Turkey and Australia, 34 centers. From January 2003 to February 2009. Double blind. Implant after randomization.	N = 1798 patients with symptomatic moderate heart failure NYHA II (80 %) - III (20 %) with ischemic cardiomyopathy (67 %) or not, LVEF <= 30 % (22.6 +/- 5.4%), QRS >= 120 ms (158 +/- 24 ms) with sinus rhythm or PM (87 %) or with supraventricular arrhythmias, with controlled ventricular rate. Predicted implantation of ICD for primary or secondary prevention of sudden death. 83 % men, 66.2 +/- 9.4 years, LBBB (72 %) / RBBB (9%). Taking beta-blockers 90 %. Exclusion criteria: significant comorbidity, recent cardiovascular event.	Two branches: ICDs and CRT + ICD. Followed for 40 +/- 20 months. Transvenous devices.	Primary: principal: all-cause mortality or hospitalization for heart failure	Funding by the Canadian Institute of Health, and by MEDTRONIC. Protocol change with the ongoing study to include only patients NYHA II. Ostensible crossover rate: 93 (11 %) from ICD to ICD + CRT, and 53 (6 %) from ICD to ICD + CRT (for failure to implant or malfunction of the LV lead). The frequency of complications related to the device or implant are 7% (ICD group) and 13 % (CRT + ICD group)
Diab 2011	UK, one center. From	N = 44 patients with advanced	Patients with	NYHA class, quality	No funding specified by

	2007 to 2009. Double blind. Implant after randomization. Consecutive patients.	symptomatic heart failure NYHA III (92 %) - IV (8 %), ischemic cardiomyopathy (80 %) or not, LVEF <35 % (22-26 +/- 7), QRS > 120 ms (138 +/- 18), 81 % sinus rhythm, with need for ICD implantation. Men 89 %, 66 +/- 11 years, LBBB. Taking beta-blockers 76 %. Exclusion criteria are not specified.	echocardiographic evidence of dyssynchrony were assigned to CRT + ICD. Patients without dyssynchrony were randomized to ICD versus CRT + ICD. Included in the analyses data from these past 2 randomized groups. Transvenous devices. Follow-up at 6 months.	Minnesota scale of life, hospitalizations and LVEF.	pharmaceutical companies. 2% CRT + ICD implants without success (1 epicardial implantation). 5% of readmissions need recolococación electrode (1 electrocatheter in CRT group, and 1 electrocatheter in the DAI group). The presence of dyssynchrony can better predict response to CRT
Thibault 2013LESSER-EARTH	Canada, 12 centers. From 2003 to 2011. Double blind. Randomization after implantation.	N = 85 patients with symptomatic heart failure (NYHA III - IV 34 %) with distance walked in six minutes test <= 400 meters, with ischemic cardiomyopathy (69 %) or not, LVEF <= 30 % (28-31 + / -9%) in the last 6 months, QRS <120 ms (105 +/- 10 ms) with sinus rhythm (history of AF 9%). Clinical indication for ICD implantation. Men 71 %, 60-62 +/- 12 years. Taking 96% beta-blockers. No prerequisites, nor the presence of LV dyssynchrony, nor a minimum value of QRS duration. Exclusion criteria: permanent AF, AMI or heart surgery in the past 6 weeks, and other limiting factors (angina, intermittent claudication, arthritis, valvulopathy)	After a "run -in" randomization to two branches: active CRT (CRT + ICD) and inactive CRT (ICD). Follow-up to 12 months. Transvenous devices.	Principal: duration of submaximal treadmill.	Funding by the Canadian Institute of Health Research and St Jude. Early termination of the trial for futility (inability to demonstrate benefit, or even possibility of harm associated with the intervention). Problems relating to the CRT system that prevent proper performance and subsequent randomization, 34/159 (21.4 %). Comprehensive monitoring, with 5/44 (11.4%) and 2/41 (5%) of losses withdrawal of consent or loss to follow.

4. ICD versus OMT

	Methods	Population	Intervention	Outcomes	Notes
Moss 1996 MADIT	30 USA hospitals and 2 Europe. From December 1990 to September 1993. Not clarified blinding. Implant after randomization.	N = 196 patients with AMI previous >= 3 weeks, no current indication of coronary intervention or bypass surgery, EF <= 35 %, and non-sustained ventricular tachycardia unrelated to the previous AMI and inducible ventricular tachycardia at electrophysiologic study could not be	OMT versus defibrillator implant, 1st transthoracic (until August 1993), and then transvenous. Mean follow-up 27 months (37 for transthoracic, 16 for transvenous).	Death from any cause.	Financial support by GUIDANT. 11% of patients assigned to OMT received ICD, and 5% in ICD group received OMT. More frequent adverse effects in the ICD group (19 vs 12%) , mainly due to problems with ICD electrocatheter. Very slow rate of inclusion,

		suppressed with procainamide. Advanced symptomatic heart failure NYHA II or III 65 %, LVEF 25 - 27 +/- 7 %, sinus rhythm. Men 92 %, 62-64 +/- 9 years. 17 % taking beta-blockers. Exclusion criteria: previous cardiac arrest or ventricular tachycardia unrelated to heart attack, bypass surgery in previous 2 months, or coronary intervention in previous 3 months.			possible selection bias
Bigger 1997 CABGPatch	USA and Germany, 37 centers. From 1990 to 1996. Open. Implant after randomization.	N = 900 patients <80 years with ischemic heart disease (55 % 3-vessel disease) undergoing elective CABG surgery with high risk of sudden death (LVEF <36 %) and alterations in signal-averaged ECG. NYHA II or III 74%, LVEF 27 +/- 6 %, 72% QRS > 100 ms. Men 84 %, 63-64 +/- 9 years, LBBB 11%. 21 % taking beta-blockers. Exclusion criteria: sustained ventricular tachycardia or ventricular fibrillation, mitral- aortic prior or concomitant surgery, CABG emergency surgery.	Prophylactic implantation of epicardial GUIDANT ICD at the time of CABG surgery versus control (OMT).	Overall mortality. Mean follow-up 32 +/- 16 months.	Financial support by GUIDANT. Cross-over rate: 18 (4%) of those assigned to OMT received ICD, and 12 (2.7%) of those assigned to ICD received OMT. More frequent infectious postoperative complications in the ICD group, and more frequent AMI in the control group.
Buxton 1999 MUSTT	USA and Canada, 85 centers. From November 1990 to October 1996. Randomization after implantation. Open.	N = 704 patients with ischemic heart disease (previous AMI <= 1 year 40 %, > 3 years 50 %), LVEF <= 40 % (median 29-30) and asymptomatic nonsustained ventricular tachycardia, which can induce ventricular tachycardia in electrophysiological studies. (The real objective is to assess whether the therapy guided by electrophysiologic study, can reduce mortality in these patients). NYHA I (37%)/II (39%)/III (24%). Men 90 %, 66-67 years (median). Taking beta-blockers 29-51 %. Exclusion criteria: history of syncope or sustained / ventricular fibrillation over 48 hours, ventricular tachycardia after the onset of AMI, non-sustained ventricular	Two branches: randomization to no antiarrhythmic therapy and treatment as the result of the electrophysiological study. In this second branch, there is a first subgroup assigned to antiarrhythmic medication, and another assigned to ICD.	Primary outcome: cardiac arrest or arrhythmic death. Median follow-up 39 months. Mortality at 5 years.	Pharmaceutical support by St Jude Medical and GUIDANT. Combined results of the initial randomization versus treatment guided by electrophisiologic study, with no blind later election between ICD and antiarrhythmic therapy in the 2nd branch. The results of mortality in the ICD group compared to the group with antiarrhythmic therapy may be magnified by not being randomized groups. 17% patients assigned to the guided therapy group electrophysiologic study changed treatment option, and 12% changed antiarrhythmic medication to ICD.

		tachycardia in the context of acute ischemia, metabolic disorders, etc.			
Moss 2002 MADIT II	Multicenter, 71 USA hospitals and 5 in Europe. From 1997 to late 2001. Open. Implantation after randomization	N = 1232 patients after AMI (>= 1 month) with LVEF <= 30% increased risk of lethal arrhythmias with symptomatic heart failure NYHA I (36%) / II (34%)/ III (24%) / IV (5%), 23 +/- 6 % LVEF, QRS > 0.12 s 50 %, 8% AF. Men 84 %, 65 +/- 10 years, 19 % LBBB / RBBB 8%. Previous bypass surgery 57 %, 44 % after PTCA. 70 % taking beta-blockers. Exclusion criteria: ICD indication, bypass surgery in the previous 3 months or AMI in the previous month , severe cerebrovascular disease, NYHA IV at the time of inclusion.	Transvenous ICD device versus OMT. 7.6 years median follow.	Death from any cause.	Financial support for GUIDANT. 15 problems in the ICD group with 5 non-fatal infections requiring surgery. ICD survival benefit begins to be seen from 9 months after implantation. Low rate of crossover: 22 patients received ICD in the OMT group, and 21 patients in the ICD group are not implanted the device, and in 9 retired, also there were 9 cardiac transplants. In a follow up to 8 years survival benefit remains the DAI (HR 0.66, 0.56 to 0.78) branch.
Bänsch 2002 CAT	Germany, 15 centers. From May 1991 to March 1997. No mention blinding. Implant after randomization.	N = 104 patients < 70 years with newly diagnosed dilated cardiomyopathy (<9 months) and LVEF <= 30 %, NYHA II (65 %) - III (35 %) without symptomatic ventricular tachycardia documented. LVEF 24 +/- 7 %, 83 % sinus rhythm / atrial flutter AF- 35 % / final PM 1%. Normal QRS 64 %, 30 % LBBB. Men 80 %, 52 +/- 11 years. 4% taking beta-blockers. Exclusion criteria: previous AMI, coronary stenosis >70 % for coronary angiography , myocarditis , ventricular tachycardia/ fibrillation, other cardiomyopathies	Two branches : ICD (transvenous implant) versus OMT. Mean follow-up 23 +/- 4 months.	Principal: all-cause mortality at 1 year.	Financial support by GUIDANT. 15 problems in the ICD group with 5 nonfatal infections requiring surgery. ICD survival benefit begins to be seen from nine months after implantation. Low rate of cross-over : 22 patients received BMT group ICD, and 21 patients in the ICD group are not implanted the device , and in 9 retired , also there were 9 cardiac transplants. In a follow up to 8 years survival benefit remains in the ICD branch(HR 0.66, 0.56 to 0.78).
Strickberger2003 AMIOVIRT	USA, 10 centers. From August 1996 to September 2000. Not described blinding. Implant after randomization.	N = 103 patients with nonischemic dilated cardiomyopathy, lasting 3.5-4 +/- 4 years , with LVEF <= 35 % and asymptomatic nonsustained ventricular tachycardia. No electrophysiological study was performed. NYHA I (16%) / II (64%) / III (19%). LVEF 23 +/- 10%. Men 70%, 60 +/- 12 years, 48% LBBB /	Two branches: ICD versus OMT including taking amiodarone.	Death from any cause. Follow-up at 1 and 3 years	Partial funding by GUIDANT. Study discontinuation due to futility, observed rates lower than expected. Amiodarone is discontinued in 48 % of patients receiving treatment for adverse effects (18 +/- 13 months). Rates of cross -over: 16 % of the amiodarone group received

		12% RBBB. Exclusion criteria: syncope, pregnancy, contraindications to amiodarone or ICD, current treatment with antiarrhythmic drug class I.			an ICD, and 22% of the ICD group received amiodarone.
Kadish 2004 DEFINITE	Multicenter, USA. From July 1998 to June 2002. Blinding unclear. Implant after randomization.	N = 458 patients with nonischemic dilated cardiomyopathy, LVEF <= 35 % (mean 21.4%) and premature ventricular complexes or nonsustained ventricular tachycardia. Clinical heart failure in the last 3.3 - 2.4 years. NYHA I (22 %) / II (57 %) / III (21 %), mean QRS 115 ms, sinus rhythm 25 %. 71 % men, mean age 58.3 years, 20 % LBBB / 3.3% RBBB. Taking beta-blockers 85 %. Exclusion criteria: NYHA IV, not candidates for ICD, definitive PM carriers, acute myocarditis, familiar cardiomyopathy associated with sudden death.	Single chamber ICD (RV) versus OMT. Discouraged antiarrhythmic.	All-cause mortality. Mean follow-up 29 +/- 14 months	Funded by St Jude Medical, but with a separate numeric data management. 3 nonfatal complications in implant (hemothorax, pneumothorax and cardiac tamponade)and 10 in the following weeks: dislocations, thrombosis and infection of the device. There were 23 patients (10%) of OMT group who received ICD in the follow-up for unexplained syncope or cardiac arrest.
Hohnloser 2004 DINAMIT	Multicenter multinational (12 countries: Canada, Germany, UK, Slovakia, Poland, etc; and 73 centers). From April 1998 to September 2003. Open. Implant after randomization.	N = 674 patients with myocardial infarction 6-40 days (average 18 days), and LVEF <= 35% (28 +/- 5%) and impaired autonomic function (low heart rate variability). In 2/3 of the patients there was reperfusion therapy (thrombolysis and/or coronary angioplasty). 97% sinus rhythm. Anterior AMI 72%. Men 76%, 62 +/- 11 years, QRS 107 +/- 24 ms, 87% taking beta-blockers. They received amiodarone in 8% ICD and 14% OMT patients. Exclusion criteria: severe heart failure NYHA IV, current bypass surgery, coronary intervention on 3 vessels, prior ICD, waiting list for a heart transplant.	Two branches: single chamber ICD (RV) versus OMT. Mean follow-up 30 +/- 13 months.	All-cause mortality.	Financial support for St Jude Medical. 25 patients with complications related to ICD: electrode dislocation, pneumothorax, and inappropriate shocks. Describe protocol few outlets: 20 patients refused ICD implants.
Bardy 2005 SCD-HeFT	Multicenter, USA. From September 1997 to July 2001, with follow-up until October 2003. No	N = 2521 outpatients with heart failure NYHA II (70 %) -III (30 %), stable ischemic (52%) and nonischemic, LVEF <= 35 % (24-25%), AF / atrial flutter 15 %. Men	Implantation of single chamber ICD, OMT or OMT + amiodarone.	Death from any cause. Follow-up 45.5 months.	Financial support by MEDTRONIC and Wyeth. 27 % of losses in drug treatment groups (22 % and 32 % placebo amiodarone). 7% of patients in the

	blinding. Implant after randomization.	77 %, 60 years (median). 69 % taking beta-blockers. No additional data on exclusion criteria			drug treatment groups broken blinding and passed openly amiodarone (n = 44 in amiodarone group, n = 81 in placebo group). In patients randomized to ICD implantation, 2 % did not agree to the implant, 1 implant not successfully achieved, 4% retired along the follow-up, complications 5% patients at implant, and 9% at follow-up.
Steinbeck 2009 IRIS	Multicenter, Germany. From June 1999 to October 2007. Open, unblinded. Implant after randomization.	N = 898 patients with recent myocardial infarction (5-31 days, 86% still in the hospital) with risk of sudden death: LVEF <= 40% and FC >= 90/min, and/or non-sustained ventricular tachycardia (> 150/min) on Holter monitoring. Men 77 %, 63 +/- 11 years, ST elevation AMI 77 %, 90 % reperfusion with PCI or bypass, 45 % heart failure at admission, LBBB 8%, 13.5 % AF, LVEF 35 +/- 9%, 88% taking beta-blockers. Exclusion criteria: severe arrhythmias prior MI or >48 hours later, NYHA IV refractory to treatment, indicating bypass surgery, etc.	Two branches: OMT or ICD (81% single chamber, only RV). Mean follow-up 37 months.	Overall mortality from any cause.	Financial support by MEDTRONIC and Astra Zeneca, without participating in the performance of work. Up to 15.7 % (65 patients) developed complications related to ICD, with surgical revision of the electrocatheter in 10 patients.

Abbreviations: NYHA New York Heart Association; LVEF Left Ventricular Ejection Fraction; ICD implantable cardioverter defibrillator; PM pacemaker; CRT cardiac resynchronization therapy; OMT optimal medical treatment; LBBB / RBBB left / righ bundle branch block; VT / VF ventricular tachycardia / fibrillation; AMI acute myocardial infarction; LV /RV / RA left / right ventricle / atrial; BNP brain natriuretic peptide; CABG coronary aortic bypass graft; HF heart failure; MR magnetic resonance; AF atrial fibrillation; AV auriculo-ventricular; ACS acute coronary syndrome; LVEDV left ventricule end diastolic volume; SBP systolic blood pressure.

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REASON FOR THE EXCLUDED CLINICAL TRIALS

1. Abraham 2012: optimized sequential versus simultaneous stimulation.
2. Auricchio 1999 and 2002 PATH- CHF: crossover trial , patients randomized to univentricular versus biventricular stimulation -mostly LV. No separates data from patients stimulated solely from RV.
3. Bänsch 2004 "1 + 1": randomized trial comparing single-chamber versus bicameral ICD.
4. Boriani 2010 B- LEFT -HF (Leclercq 2006 Material and methods): clinical trial comparing 2 types of CRT (LV versus biventricular).
5. Botto 2011 TRADE HF: implant of a device with functionalities CRT + ICD + power capacity therapies headphones; compare medical management versus electrical treatment of atrial arrhythmias
6. Brignole 1994: small clinical trial (N = 23) with symptomatic paroxysmal atrial fibrillation, which are randomized to ablation of the AV node with VVI pacemaker implantation versus medical therapy and implantation of VVI.
7. Brignole 1997: clinical trial with randomization to AV node ablation and implantation of dual chamber pacemaker DDDR mode -change versus medical therapy in patients with paroxysmal atrial fibrillation poor clinical tolerance. Implanting CRT device is not cited
8. Brignole 1998: This seems to be an extension of previous work, with greater number of patients and mean follow-up.
9. Brignole 1999 PAF: clinical trial similar to the previous approach, with fewer patients and shorter follow-up the similar work of 1998. Is it the same work?
10. Carlsson 2003: clinical trial on the efficacy of 2 safety margins of discharge energy in ICDs implanted via subpectoral
11. Conolly 2001 CIDS: efficacy study of ICD versus amiodarone in patients recovered from tachycardia / ventricular fibrillation, or with unmonitored syncope but presumably arrhythmogenic
12. Deisenhofer 2001: randomized comparison of RV versus bicameral ICD.
13. Domanski 1999 AVID: treatment with antiarrhythmic medication versus ICD for secondary prevention of serious ventricular arrhythmias.
14. Dorian 2004 ASTRID: comparison of 2 detection algorithms / differential diagnosis of ventricular versus supraventricular tachycardia.
15. Eberhardt 2009: Early postoperative coronary artery bypass surgery (first 96 hours), randomization to pacing biventricular DDD, DDD with electrode on outflow tract RV, or AAI.
16. Ellenbogen , 2010 , 2010 Stein SMART AV: comparison work different types of AV delay optimization in CRT patients (fixed AV delay, AV delay optimized by echocardiography , and the AV delay as algoritmo SmartDelay).
17. Evonich 2012: randomized, N = 40, atrio- ventricular or biventricular patients in patients undergoing cardiac surgery during the intraoperative period; echocardiographic measures variables.
18. Friedman 2006: comparison of RV versus bicameral ICDensayo clínico de comparación de DAI monocameral versus bicameral
19. Garrigue 2002, 2003: small crossover trial (N = 13) of biventricular versus LV pacing in patients with chronic atrial fibrillation.
20. Gasparini 2006 BELIEVE: comparison of devices with CRT +ICD function with electrodes in LV versus biventricular.
21. Gasparini 2009 RELEVANT: in this trial 2 types of CRT with ICD functionality with 2 anti tachycardia schedules were compared.
22. Gasparini 2010 ADVANCE CRT-D: 2 forms of release/setting antitachycardia pacemaker (biventricular versus RV)

23. Gold 2010: small randomized study (N = 28) in which are implanted 2 types of CRT (LV and biventricular) device and assesses the effect of auricular overstimulation and optimization of the AV interval.
24. Gold 2013 SMART AV: substudy of this work, to assess whether the VLK interval is associated with atrioventricular optimization.
25. Hamdan 2006 AVERT-AF: clinical trial that randomizes patients with symptomatic AF and LVEF <= 35 % receiving optimal medical therapy versus AV node ablation and implantation of a CRT + ICD device. This publication is in material and methods. We don´t found the results of this work on the web (scheduled for completion in 2008).
26. Khan 2012 TARGET: randomized to electrode LV placement "blind" versus imaging optimization.
27. Kolb 2010 OPTION: randomization to ICD implantation of RV versus RV+RA -the latter with possibility of atrial antitachycardia algorithms-, and evaluate inappropriate shocks and a combined cardiovascular morbidity and overall mortality.
28. Kristiansen 2012: randomized trial of consecutive patients who were implanted a CRT device with an electrode on RV apex versus high posterior septal face (with a second electrode implanted in the last VI activated zone as echocardiography) .
29. Kuck 2000 CASH: ICD versus medical treatment in secondary prevention after cardiac arrest.
30. Leclerq 2008 TRIP-HF: comparison of 2 types of CRT, biventricular (LV and RV) versus three ventricular electrodes (2 in LV and 1 RV).
31. Lenarczyk 2009 TRUST CRT: randomized, single-center comparison of two types of TRC prospective trial (conventional biventricular and "triple site" with 2 electrodes LV and 1 in RV).
32. Levy 2001: clinical trial of patients with atrial fibrillation with mixed fast / slow ventricular response, randomized to VVIR pacemaker implantation with ablation of His bundle versus the same pacemaker implant + drug treatment. Implanting CRT device is not cited.
33. Marshall 1999: clinical trial in patients with symptomatic paroxysmal atrial fibrillation who are randomized to AV node ablation and implantation of dual chamber pacemaker algorithm "fast" or " slow" versus management with medical treatment. Implantation of a CRT device is not cited.
34. Martin 2007 PEGASUS CRT: in all patients CRT is implanted, and it is randomized to different modes of atrial pacing
35. Martin 2012 Adaptative CRT (aCRT): 2 types of CRT (+ICD) devices are compared: CRT functionality according to a new automatic selection algorithm outpatient, and optimized by echocardiography.
36. Mihalcz 2010: prospective randomized comparison of 2 types of surgical access TRC (transapical versus epicardial).
37. Moss 2012 MADIT RIT: clinical trial of 3 different configurations of programming in patients with ICD indicated for primary prevention.
38. Ng 2007: cohort study of patients with narrow QRS and different NYHA functional class, with CRT implant and evaluation of LV remodeling and clinical events.
39. Padeletti 2008 MASCOT: trial where 2 types of CRT compared with and without anti atrial fibrillation algorithm.
40. Rao 2007 DECREASE Compare 3 types of CRT : LV pacing, biventricular simultaneous and sequential biventricular .
41. Raviele 2005: patients who have suffered an AMI were randomized to receive drug treatment or ICD guided by electrophysiologic study.
42. Rogers 2012: randomized, double blind comparison of 2 types of CRT: triventricular (apex RV, coronary sinus and posterolateral branch of the coronary sinus) versus biventricular.
43. Sawhney 2004: randomized study in patients undergoing CRT implantation, with 2 different ways to program the AV delay.
44. Sedlacek 2010: clinical trial comparing 2 types of CRT (biventricular versus LV pacing).

45. Sirker 2007 LOLA ROSE: small crossover trial (N = 18) comparing LV versus biventricular pacing.
46. Stein 2010 SMART -AV: clinical trial comparing CRT with different types of AV delay optimization.
47. Theuns 2004: randomized trial of 2 ICD schedules, RV versus bicameral.
48. Thibault 2011 GREATER EARTH (2 cites): comparing 2 types of CRT.
49. Touiza 2001: cohort study of patients with implantation of a biventricular versus LV CRT device at the discretion of their physician.
50. Valzania 2008: patients with chronic heart failure and LBBB and CRT device implantation, are randomized to biventricular versus LV pacing (comparison of two types of TRC), results (echocardiographic parameters) to 3 months.
51. Walter 2000: part of a randomized crossover trial with valuation of biventricular pacing in patients with sinus rhythm and chronic atrial fibrillation undergoing AV node ablation. This work values antiarrhythmic effect of biventricular pacing, and not measures mortality or other clinical or echocardiographic data.
52. Wang 2011 BIPACS: biventricular pacing after cardiac surgery (CABG and / or valve surgery). Only intraoperative stimulation, echocardiographic measurements after the end of bypass surgery.
53. Weerasooriya 2003 (AIRCRAFT): clinical trial that evaluated in patients with heart failure and atrial fibrillation the effectiveness of AV node ablation versus pharmacotherapy, it doesn´t cites the implant CRT devices.
54. Wever 1995: randomized study of survivors of sudden cardiac death, N = 60, ICD versus conventional medical treatment, with a mean of 24 months (secundary prevention ICD).
55. Wilkoff 2002 DAVID: clinical trial with dual chamber ICD implantation and subsequent randomization to DDDR pacemaker function 70 beats / minute depending VVI versus 40 beats / minute.
56. Wilkoff 2006 EMPIRIC: clinical trial comparing standard programming versus empirical adjustments to your cardiologist, in patients with ICD implantation.
57. Wilkoff 2009 DAVID –II: clinical trial with ICD implantation bicameral and comparison of atrial pacing (70 beats / min) versus ventricular pacing minimum (40 / min).
58. Zabel 2013 CONNECT -OptiVol: randomized study of patients with CRT and ICD devices, and a system of patient's fluid monitoring. This work values the reduction of the number of hospital readmissions for cardiac decompensation.

To consult the incompleted trials registered in ClinicalTrials.gov, go to the citation #13.