

Effectiveness of resynchronisation therapy in pharmacological treatment-resistant patients with NYHA class III-IV heart failure

ANTONIO ALBERTO LEÓN-MARTÍN¹, JUAN MANUEL BENEZET-PEÑARANDA²,
CRISTÓBAL MARTÍNEZ DELGADO, JOSÉ LUIS RODRÍGUEZ-MARTÍN⁴

¹Emergency Department. ²Arrhythmia Unit. ³Investigation Unit. Hospital General de Ciudad Real. Ciudad Real, Spain. ⁴Foundation for Healthcare Investigation in Castilla la Mancha. Toledo, Spain.

CORRESPONDENCE:

Dr. A. Alberto León Martín
C/ José María de la Fuente, nº 1,
portal 10, 3º B
13005 Ciudad Real, Spain
E-mail: aaleon@sescam.jccm.es

RECEIVED:

4-9-2007

ACCEPTED:

20-11-2007

CONFLICT OF INTEREST:

None

Objectives: To assess whether cardiac resynchronization therapy with single stimulation or associated with defibrillation has any effect on pharmacological treatment-resistant subjects with class III-IV heart failure, low ejection fraction (< 35%) and wide QRS (> 120 msec), using an systematic international review based on randomised clinical trials. **Method:** Systematic search and review of relevant literature on cardiac resynchronization in subjects with the above mentioned characteristics. Randomized controlled clinical trials assessing the effectiveness of cardiac resynchronization therapy versus conventional therapy were reviewed.

Results: Among 2417 references identified 2139 abstracts were selected; 896 being considered potentially relevant; 62 studies fulfilled our inclusion criteria; and 10 of them were included in the study.

Conclusions: Global mortality showed a relative reduction of risk of 29% (RR 0.71; 95% CI 0.59 to 0.85) when comparing resynchronization with only pharmacological treatment. On analysing mortality due to heart failure within the subanalysis of resynchronization versus only pharmacological treatment as control group, a significant reduction was found (37 mortality events in resynchronization group versus 66 in control group). This difference in specific mortality should be interpreted as clinically relevant (RR 0.55; 95% CI 0.38 to 0.81). In patients with advanced heart failure a significant improvement is observed in total, and specific mortality on comparing cardiac resynchronization with conventional pharmacological treatment. [Emergencias 2008;20:237-244]

Key words: Resynchronization. Heart failure. Biventricular stimulation.

Introduction

Heart failure (inefficacy of the heart muscle to maintain normal circulatory dynamism) is responsible for a high morbimortality in developed countries¹ and requires a high intake of the healthcare resources of a country. Half of the patients diagnosed with heart failure die within 4 years. Pharmacological therapy in heart failure has shown very important advances in recent years, improving the quality and life expectancy of these patients, although it is clearly inferior to that of persons without this disease. Despite full pharmacological treatment (diuretic + angiotensin convertor enzyme inhibitors II (ACEI-ARA2) + spironolactone + beta-blockers + digoxine) achieving a phase in the evolution of persistence of symp-

toms (dyspnoea, oedemas, oliguria, etc.) which incapacitates the patients and signals a fatal outcome, the only treatment is heart transplant or mechanical circulatory assistance².

A large part of these patients with treatments refractory to medical treatment present interventricular or intraventricular conduction disorders with complex wide QRS in the electrocardiogram (ECG) and express a lack of synchrony in the contraction of the ventricles or between the different areas of the same ventricle. In these cases, the implantation of a cardiac pacer able to synchronise the auricular contraction with the ventricular (optimisation of the AV interval) and at the same time achieve synchronic contraction of both ventricles (biventricular resynchronisation) improves

the quality of life of these patients, increases their life expectancy, delays the indication of heart transplantation and may even, in some cases, make it unnecessary³.

The guidelines of action of the American College of Cardiology and the American Heart Association⁴ consider indication type II with a level of evidence A as the therapy for cardiac resynchronisation (CRT) in patients with NYHA (New York Heart Association) grades III-IV heart failure refractory to full pharmacological treatment with an ejection fraction $\leq 35\%$ and a QRS duration of ≥ 120 ms.

To date, CRT has achieved an improvement in symptoms and functional capacity of patients with grades III-IV heart failure with a wide QRS, a reduction in the rate of hospitalisation, a reduction in ventricular filling pressure, an increase in the ejection fraction and cardiac load, a reduction in mitral insufficiency and a reduction in ventricular remodelling^{5,6}.

On comparing CRT versus placebo, the MIRACLE⁶, MUSTIC⁷ and PATH-CHF⁸ studies have reported a greater tolerance to exercise and an improvement in functional class. A recent metaanalysis⁸ of the clinical trials performed with cardiac resynchronisation up to 2002 confirmed a significant reduction in death by heart failure, although a significant reduction in terms of total mortality was not found. The COMPANION⁹ study showed that with stimulation only CRT reduced mortality by 19% versus patients under pharmacological treatment and by 20% with CRT with a defibrillator. The recent CARE-HF study¹⁰ demonstrated that CRT produces a significant reduction in total mortality as a single variable (OR 0.64) or combined with hospitalisation (OR 0.63).

The aim of this metaanalysis was to determine whether, after systematic review of the international literature based on randomised clinical trials, CRT both with isolated stimulation and with stimulation associated with defibrillation has any effect on the mortality of patients with full pharmacological treatment-resistant NYHA grades III-IV cardiac failure patients with a low ejection fraction ($< 35\%$) and a wide QRS (> 120 ms).

Methods

Reference search and identification of relevant studies

The reference search involved a process of documentation on the state of knowledge published with respect to treatment with CRT in rela-

tion to mortality from the perspective of controlled randomised clinical trials from their initiation up to now.

An electronic search of international databases such as Medline (Index Medicus), Embase (Excerpta Medica), Cochrane Library Registry of Clinical Trials was carried out. For national publications the IME (Índice Médico Español) and its electronic versions (KNOSYS and BASIS) were consulted using a search strategy specially adapted for the objectives of this study (Figure 1).

All the references of the articles identified through the previous search strategy were registered in a database created for this purpose. Once all the studies found had been registered, studies from this database fulfilling the determined inclusion criteria were selected for posterior review and statistical analysis.

Study eligibility criteria for inclusion in the analysis of this review

A) Type of studies: Controlled randomised clinical trials evaluating CRT therapy versus conventional therapy.

b) Type of patients: Full pharmacological treatment-resistant NYHA grades III-IV heart failure with a low ejection fraction ($< 35\%$) and a wide QRS (> 120 ms).

C) Type of interventions: The use of CRT compared with a reference standard or with conventional therapy.

D) Measures of results: Total and specific mortality.

Method of systematic review.

Data collection

Two reviewers (selected from among the investigator team and the technical personnel hired) independently selected the studies to be included in the review. On important discordance between the two evaluations a consensus was established with the participation, if required, of a third reviewer. The quality of the trials was assessed using the Jadad scale.

Statistical analysis of the data and interpretation

The effect of treatment was quantified using relative risk (RR). A $RR < 1$ indicated a beneficial therapeutic effect and an $RR > 1$ indicated a harmful effect. The results were combined using a fixed effect statistical model. The RevMan 4.2 programme was used for statistical calculations.

1. (biventricular adj (pacing or pacer\$ or stimulat\$)).mp.
2. resynchronization therapy.mp.
3. biv.mp.
4. (dual-chamber adj (pacing or pacer\$ or stimulat\$)).mp.
5. ((cardiac or heart) adj resynchronization).mp.
6. medtronic.mp.
7. Insync.mp.
8. "ela medical".mp.
9. exp cardiac pacing, artificial/
10. or/1-9
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. randomized controlled trials.sh.
14. random allocation.sh.
15. double blind method.sh.
16. single blind method.sh.
17. or/1-6
18. animal.sh. not human.sh.
19. 17 not 18
20. clinical trial.pt.
21. exp clinical trials.sh.
22. (clin\$ adj25 trial\$).ti,ab.
23. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
24. placebos.sh.
25. placebo\$.ti,ab.
26. random\$.ti,ab.
27. research design.sh.
28. or/20-27
29. 28 not 18
30. 29 not 19
31. 10 and 30

Figure 1. Medline search strategy.

Results

Of the 64 potentially relevant studies, which fulfilled the general inclusion criteria, 10 were finally included in the metaanalysis^{5-7,9-15} (see flow diagram; Figure 2).

The baseline characteristics of the patients included in the metaanalysis are shown in Tables 1 and 2.

Different subanalyses of these studies were performed based on the intervention and control group. Specifically, trials comparing resynchronisation versus full pharmacological treatment (Figures 3 and 4), resynchronisation versus implantable automatic defibrillators (IAD) (Figures 5 and 6), resynchronisation versus univentricular pacing were found (Figure 7).

Discussion

Since Cazeau described the spectacular improvement of a patient in whom anasarca was found after stimulation of the left ventricle in 1994, many authors have studied the effects of resynchronisation in heart failure.

In the 1990s many studies evaluating the acute haemodynamic benefits of resynchronisation (very short follow up period) were developed. These studies did not have a control group and the sample size was generally very small.

In the last 7 years, the number of randomised control studies evaluated long-term CRT has increased. To date, a large number of studies have been published, although most are clinical trials with a low number of patients. Only the CARE¹⁰ and COMPANION⁹ studies have included a significantly large number of patients. Cardiac resynchronisation has been evaluated in different clinical trials in terms of improvement of morbimortality. Most of these studies found benefits in chronic clinical parameters with resynchronisation. Few studies have been designed to assess mortality and the results of this objective vary greatly. In a metaanalysis, Bradley identified benefits only in terms of specific mortality.

Historically resynchronisation has been compared with optimised isolated medical treatment^{5,6,9,10}, univentricular pacing^{7,13-15} and IAD devices^{11,12}. The present metaanalysis makes a differential analysis of the effects of CRT on mortality versus isolated pharmacological treatment, univentricular pacing or IAD, respectively.

On comparing resynchronisation versus isolated full pharmacological treatment in the present study, total mortality by any cause showed a relative reduction in risk of 29% (RR 0.71 with a CI of 95% 0.59-0.85). However, in the previous metaanalysis by Bradley⁸ the reduction observed was of 23% which was not statistically significant (RR 0.77; CI 95% 0.51-1.18). This may be explained by the greater sample size in our study. It should be taken into account that on using mortality by any cause as the variable in contrast to when mortality by heart failure is used, the bias which may be introduced in the attribution of cause of death may be avoided, if the evaluation is not blind.

No statistically significant differences were found for the variable of total mortality on comparing resynchronisation with univentricular pacing (RR 10.4; CI 95% 0.32-3.37).

Neither was any difference found in mortality by any cause between resynchronisation + IAD

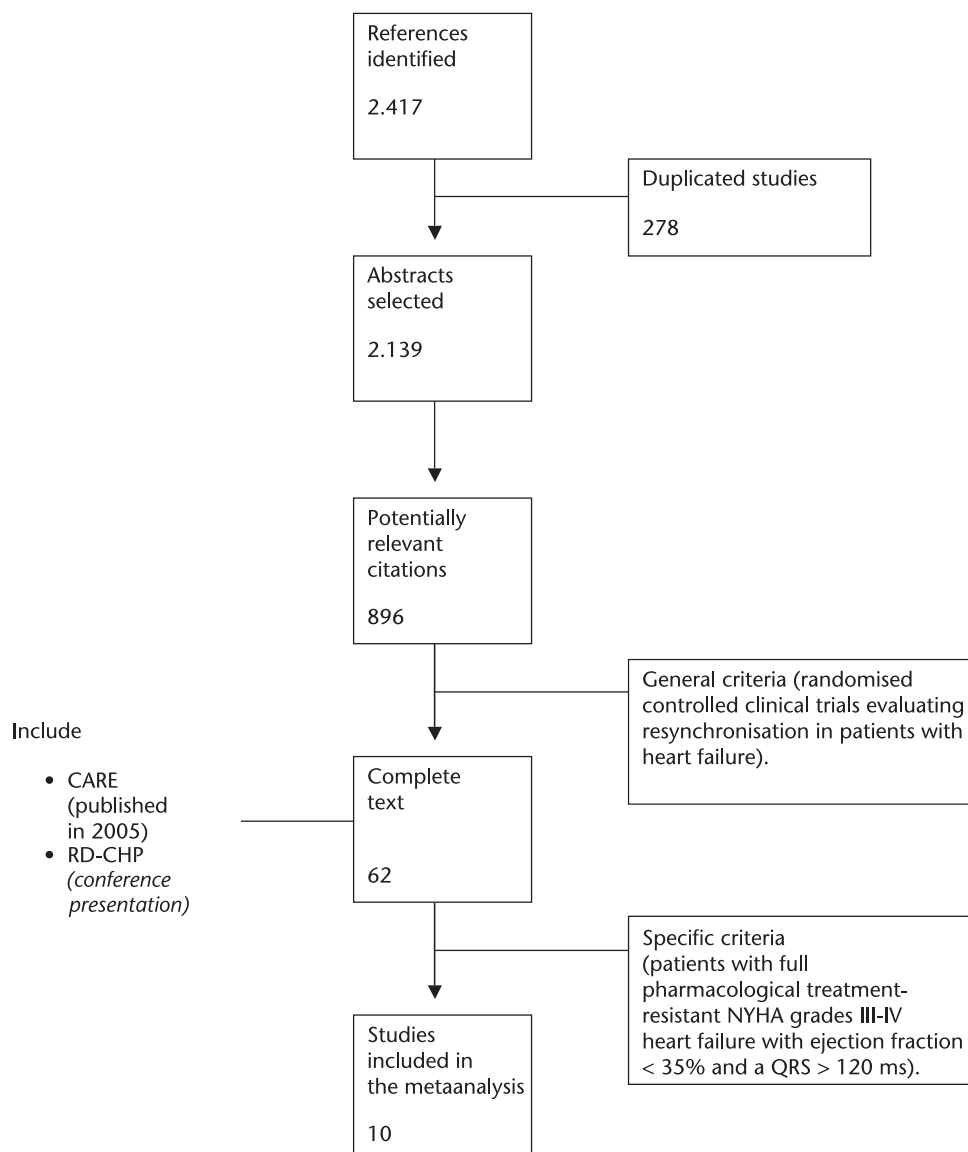


Figure 2. Study flow diagram.

versus IAD (RR 0.93; CI 95% 0.75-1.15). This lack of statistical significance is probably due to the death of these patients mainly being produced by the appearance of cardiac arrhythmias treated by defibrillator in the two groups. While non arrhythmic mortality derived from heart failure was produced in a low number of patients.

This study did not analyse the variable specific mortality comparing resynchronisation versus univentricular pacing since the studies found had a small sample size and were not designed with this objective.

The studies evaluating resynchronisation combined with IAD versus IAD devices (Higgins and Young^{11,12}) did not show significant differences in

specific mortality (52 events in the intervention groups versus 56 events in the control group). Again, these results suggest that the most frequent cause of mortality in these patients is arrhythmia.

In the present study specific mortality was only significantly reduced when the group compared was pharmacological treatment. Thus, if only the benefit of CRT in terms of a reduction in mortality is taken into account, the idealness of implanting simple monochamber devices with defibrillator (reduction in costs with the same objective) would have to be approached.

However, CRT versus IAD devices or unichamber effects has demonstrated benefits in both, improvement in the clinical NYHA class and in the

Table 1. Baseline characteristics of the patients included in the metaanalysis

		Men	Women	Age	NYHA-III	IHD	AF
Cazeau, 2001	TCR	66%	34%	64	100%		0%
	Control	83%	13%	64	100%		0%
Abraham, 2002	TCR	68%	32%	64	90%	50%	0%
	Control	68%	32%	64	91%	58%	0%
Cleland, 2005	TCR	74%	26%	67	94%	40%	
	Control	72%	28%	66	93%	35%	
Bristow, 2003	TCR	67%	33%	67	87%	54%	
	Control	69%	31%	68	82%	59%	
Bristow, 2003 (CD)	TCR	67%	33%	66	86%	55%	
	Control	69%	31%	68	82%	59%	
Young, 2003	TCR	75%	25%	66	88%	64%	
	Control	77%	23%	67	89%	75%	
Higgins, 2003	TCR	77%	23%	66	73%	65%	0%
	Control	78%	22%	66	71%	71%	0%
Leclercq, 2002	TCR	84%	16%	65	100%		100%
	Control	78%	22%	66	100%		100%
Auricchio, 2002	TCR	46%	54%	59	88%	42%	0%
	Control	59%	41%	60	82%	6%	0%
Garrigue, 2002	TCR						
	Control	100%		64			
Leclercq, 2003	TCR						
	Control			73			23%

IHD: ischaemic heart disease; AF: auricular fibrillation. NYHA: New York Heart Association. CRT: cardiac resynchronisation therapy.

perception of quality of life or the number of hospital admissions.

Future studies will answer questions of great interest such as: In which patients in whom resynchronisation is indicated should we combine a system with defibrillator?; Should we always use resynchronisation devices or would it be advisable to use other simpler, more efficient devices?

In conclusion, in patients with pharmacological treatment-resistant NYHA grades III-IV heart failure

with a low ejection fraction and a wide QRS, cardiac resynchronisation significantly improves mortality. In this study this improvement was confirmed for both total and specific mortality. These differences were not observed when the group of comparison was an IAD device of univentricular pacing (the variable of specific mortality was not analysed comparing resynchronisation versus univentricular pacing). These data indicate that the mortality in these patients seems to be a consequence of cardiac arrhythmias and the benefits of

Table 2. Baseline characteristics of the patients included in the metaanalysis

		PR (msec)	QRS (msec)	SBP	DBP	% ejection	TDV (mm)	MI (cm ²)
Cazeau, 2001	TCR		172					
	Control		175					
Abraham, 2002	TCR		167	114	69	22	70	7.6
	Control		165	115	68	22	69	6.2
Cleland, 2005	TCR		160	110	70	25	121	21
	Control		160	110	70	25	117	23
Bristow, 2003	TCR		160	110	68	20	68	
	Control		158	112	64	22	67	
Bristow, 2003 (CD)	TCR		160	112	68	22	67	
	Control		158	112	64	22	67	
Young, 2003	TCR		165	113	66	24	75	7.5
	Control		162	114	67	23	76	7.3
Higgins, 2003	TCR	204	164	116	68	21		
	Control	200	152	117	67	21		
Leclercq, 2002	TCR		209			23		
	Control		208			30		
Auricchio, 2002	TCR	190	174			21	71	
	Control	207	178			20	75	
Garrigue, 2002	TCR							
	Control		208			25		
Leclercq, 2003	TCR							
	Control					25		

SBP: systolic blood pressure; DBP: diastolic blood pressure. %ejection: left ventricular ejection fraction; TDV: telediastolic volume; MI: mitral insufficiency; CRT: cardiac resynchronisation therapy.

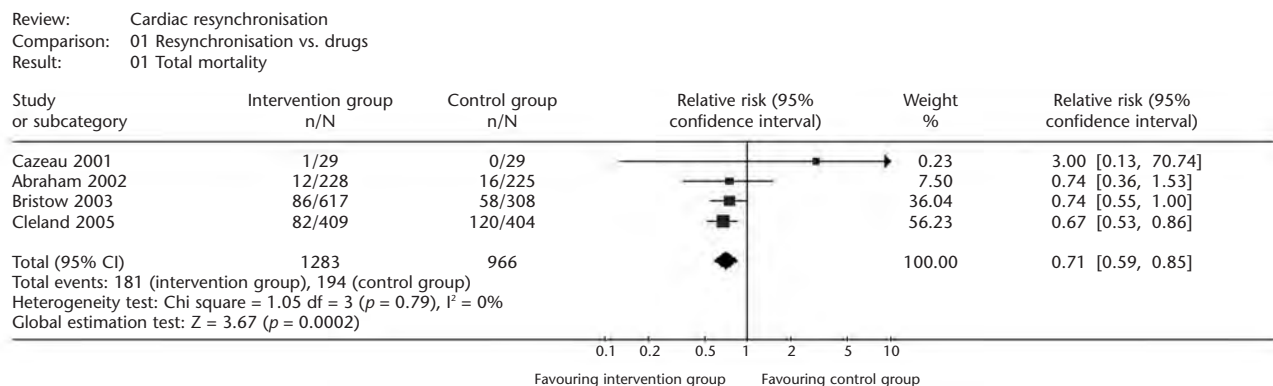


Figure 3. Metagraph for total mortality. Control group of isolated pharmacological treatment.

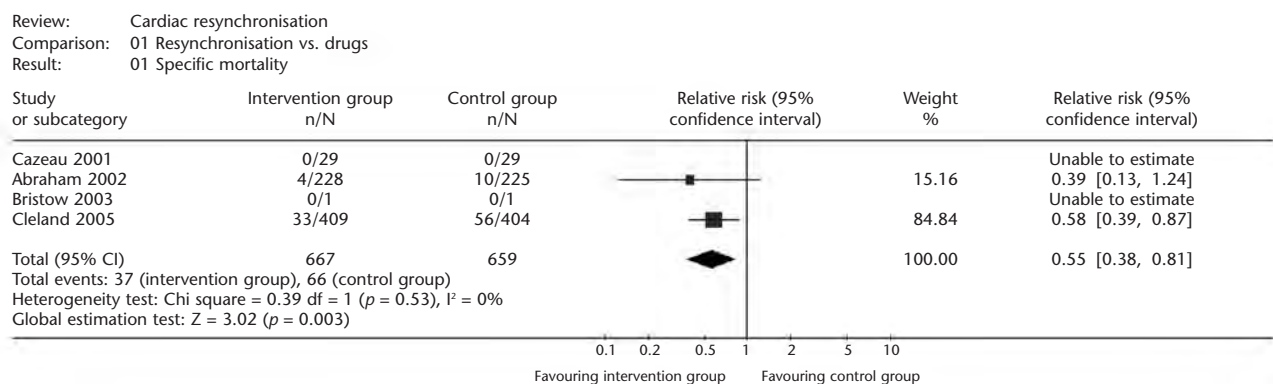


Figure 4. Metagraph for specific mortality. Control group of isolated pharmacological treatment.

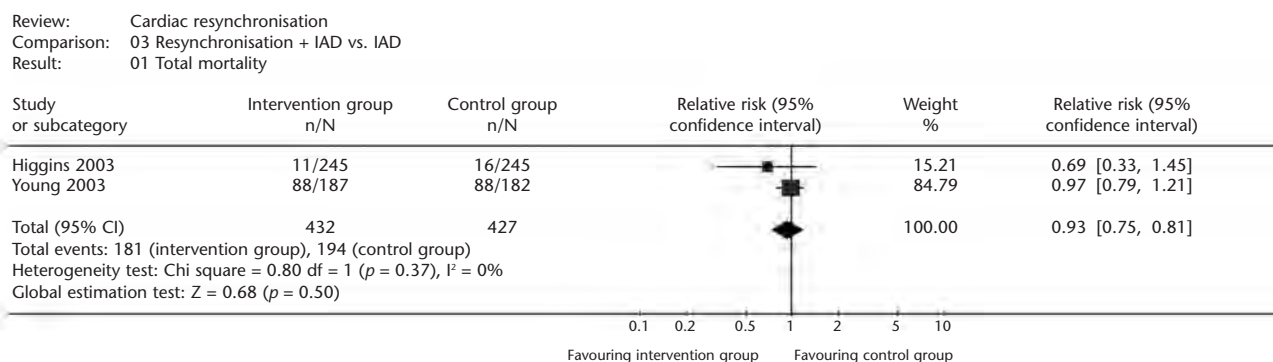


Figure 5. Metagraph for total mortality. Control group IAD.

resynchronisation lay in maintaining stable cardiac rhythm with optimised auriculoventricular synchronism.

References

- 1 Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.
- 2 Rose EA, Gelings AC. Long term use of a left ventricular assist device for end stage heart failure. *N Engl J Med* 2001;345:1435-43.
- 3 Kass DA, Chen-Husn CH. Improve left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation* 1999;99:1567-73.
- 4 Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WFC, Froelicher VF, et al. ACC/AHA Guidelines for Exercise Testing: A report of the American College of Cardiology/American Heart Association task force on practi-

Review: Cardiac resynchronisation
 Comparison: 03 Resynchronisation + IAD vs. IAD
 Result: 01 Specific mortality

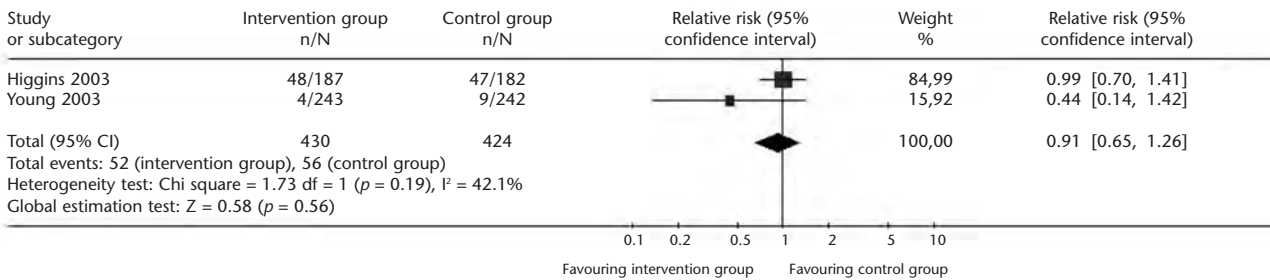


Figure 6. Metagraph for specific mortality. Control group IAD.

Review: Cardiac resynchronisation
 Comparison: 04 Resynchronisation vs. Univentricular pacing
 Result: 01 Total mortality

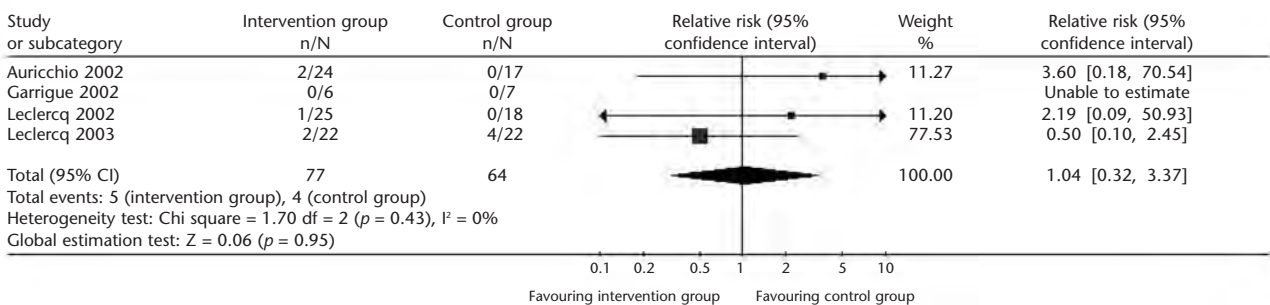


Figure 7. Metagraph for total mortality. Control group of univentricular pacing.

- ce guidelines (Committee on Exercise Testing). *J Am Coll Cardiol* 1997;30:260-311.
- Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C. Effect of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-80.
 - Abraham WT, Fisher WG, Smith AL, DeLurgio DB, Leon AR, Loh E. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-53.
 - Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;39:2026-33.
 - Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003;289:730-40.
 - Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-50.
 - Cleland JGF, Daubert J-C, Erdmann E. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-49.

- Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: The MIRACLE ICD Trial. *JAMA* 2003;289:2685-94.
- Higgins SL, Hummel J, Niazi I, Giudici MC, Worley SJ, Saxon LA. Cardiac resynchronization therapy for the treatment of heart failure in ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003;42:1454-9.
- Leclercq C, Cazeau S, Lellouche D. Upgrading from right ventricular pacing to biventricular pacing in previously paced patients with advanced heart failure: a randomized controlled study (the RD-CHF Trial). Presented at the European Society of Cardiology Congress. Vienna, Austria. 30 August-3 September 2003.
- Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002;23:1780-7.
- Garrigue S, Bordachar P, Reuter S, Jais P, Kobaeissy A, Gagnni G. Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation. prospective haemodynamic study. *Heart* 2002;87:529-34.

Eficacia de la terapia de resincronización en sujetos con insuficiencia cardiaca grados III-IV de la NYHA refractarios a tratamiento farmacológico

León-Martín AA, Benezet-Peñaranda JM, Martínez Delgado C, Rodríguez-Martín JL

Objetivos: Determinar, a partir de una revisión sistemática de ámbito internacional basada en ensayos clínicos con asignación aleatoria, si la terapia de resincronización cardiaca, tanto con estimulación aislada como estimulación asociada a desfibrilación, tiene algún efecto sobre la mortalidad en los pacientes en insuficiencia cardiaca grados III-IV refractaria al tratamiento farmacológico pleno, con una fracción de eyección baja (< 35%) y con un QRS ancho (> 120 ms).

Método: Revisión sistemática que evalúa terapia de resincronización cardiaca en pacientes descritos anteriormente. Para ello se han evaluado todos los ensayos clínicos controlados con asignación aleatoria que comparaban resincronización cardiaca frente a terapia convencional.

Resultados: Se identificaron 2.417 referencias. Se seleccionaron 2.139 resúmenes de los que 896 eran potencialmente relevantes. Cumplieron criterios generales de inclusión 62 estudios. Finalmente 10 cumplían estrictamente los criterios de selección.

Conclusiones: En nuestro estudio, cuando comparamos resincronización frente a tratamiento farmacológico aislado, constatamos que la mortalidad total presenta una reducción relativa de riesgo del 29% (RR 0,71 con IC al 95% 0,59 a 0,85). Cuando analizamos la mortalidad por insuficiencia cardiaca en el subanálisis de resincronización frente a tratamiento farmacológico aislado como grupo control, encontramos una reducción significativa (37 eventos en el grupo de resincronización frente a los 66 del grupo de tratamiento farmacológico). Destacamos que esta diferencia para la mortalidad específica debe interpretarse como clínicamente relevante (RR 0,55 con IC al 95% 0,38 a 0,81).

Conclusión: En pacientes con insuficiencia cardiaca avanzada, la resincronización cardiaca, respecto al tratamiento farmacológico convencional, mejora significativamente la mortalidad total y específica. [Emergencias 2008; 20: 237-244]

Palabras clave: Resincronización. Insuficiencia cardiaca. Estimulación biventricular.