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Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy (Review)

Martí-Carvajal AJ, Kwong JSW

Martí-Carvajal AJ, Kwong JSW.
Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy.
Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD009077.
DOI: 10.1002/14651858.CD009077.pub3.

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[Intervention Review]

Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy

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Editorial group: Cochrane Heart Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 7, 2016.

Citation: Martí-Carvajal AJ, Kwong JSW. Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy. *Cochrane Database of Systematic Reviews* 2016, Issue 7. Art. No.: CD009077. DOI: 10.1002/14651858.CD009077.pub3.

ABSTRACT

Background

Chagas disease-related cardiomyopathy is a major cause of morbidity and mortality in Latin America. Despite the substantial burden to the healthcare system, there is uncertainty regarding the efficacy and safety of pharmacological interventions for treating heart failure in people with Chagas disease. This is an update of a Cochrane review published in 2012.

Objectives

To assess the clinical benefits and harms of current pharmacological interventions for treating heart failure in people with Chagas cardiomyopathy.

Search methods

We updated the searches in the Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2016, Issue 1), MEDLINE (Ovid; 1946 to to February Week 1 2016), EMBASE (Ovid; 1947 to 2016 Week 07), LILACS (1982 to 15 February 2016), and Web of Science (Thomson Reuters; 1970 to 15 February 2016). We checked the reference lists of included papers. We applied no language restrictions.

Selection criteria

We included randomised clinical trials (RCTs) that assessed the effects of pharmacological interventions to treat heart failure in adult patients (18 years or older) with symptomatic heart failure (New York Heart Association classes II to IV), regardless of the left ventricular ejection fraction stage (reduced or preserved), with Chagas cardiomyopathy. We did not apply limits to the length of follow-up. Primary outcomes were all-cause mortality, cardiovascular mortality at 30 days, time-to-heart decompensation, disease-free period (at 30, 60, and 90 days), and adverse events.

Data collection and analysis

Two authors independently performed study selection, 'Risk of bias' assessment and data extraction. We estimated relative risk (RR) and 95% confidence intervals (CIs) for dichotomous outcomes. We measured statistical heterogeneity using the I^2 statistic. We used a fixed-effect model to synthesize the findings. We contacted authors for additional data. We developed 'Summary of findings' (SoF) tables and used GRADE methodology to assess the quality of the evidence.

Main results

In this update, we identified one new trial. Therefore, this version includes three trials (108 participants). Two trials compared carvedilol against placebo and another assessed rosuvastatin versus placebo. All trials had a high risk of bias.

Meta-analysis of two trials showed a lower proportion of all-cause mortality in the carvedilol groups compared with the placebo groups (RR 0.69; 95% CI 0.12 to 3.88, I^2 = 0%; 69 participants; very low-quality evidence). Neither of the trials reported on cardiovascular mortality, time-to-heart decompensation, or disease-free periods.

One trial (30 participants) found no difference in hospital readmissions (RR 1.00; 95% CI 0.31 to 3.28; very low-quality of evidence) or reported adverse events (RR 0.92; 95% CI 0.67 to 1.27; very low-quality of evidence) between the carvedilol and placebo groups.

There was very low-quality evidence from two trials of inconclusive effects on quality of life (QoL) between the carvedilol and placebo groups. One trial (30 participants) assessed QoL with the Minnesota Living With Heart Failure Questionnaire (21 items; item scores range from 0 to 5; a lower MLHFQ score is better). The MD was -14.74; 95% CI -24.75 to -4.73. The other trial (39 participants) measured QoL with the Medical Outcomes Study 36-item short-form health survey (SF-36; item scores range from 0 to 100; higher SF-36 score is better). Data were not provided.

One trial (39 participants) assessed the effect of rosuvastatin versus placebo. The trial did not report on any primary outcomes or adverse events. There was very low-quality evidence of uncertain effects on QoL (no data were provided).

Authors' conclusions

This first update of our review found very low-quality evidence for the effects of either carvedilol or rosuvastatin, compared with placebo, for treating heart failure in people with Chagas disease. The three included trials were underpowered and had a high risk of bias. There were no conclusive data to support or reject the use of either carvedilol or rosuvastatin for treating Chagas cardiomyopathy. Unless randomised clinical trials provide evidence of a treatment effect, and the trade-off between potential benefits and harms is established, policy-makers, clinicians, and academics should be cautious when recommending or administering either carvedilol or rosuvastatin to treat heart failure in people with Chagas disease. The efficacy and safety of other pharmacological interventions for treating heart failure in people with Chagas disease remains unknown.

PLAIN LANGUAGE SUMMARY

Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy

Review question
We reviewed pharmacological interventions for treating heart failure in people with Chagas cardiomyopathy.

Background
Named in honour of the Brazilian physician Carlos Chagas, Chagas disease is caused by the *Trypanosoma cruzi* parasite. It is common in Latin and Central America and leads to Chagas cardiomyopathy (heart muscle disease). It is an important cause of heart failure. The number of people infected with Chagas disease has been estimated to be about 10 to 12 million worldwide; around 20% to 30% of individuals infected with *Trypanosoma cruzi* will develop symptomatic heart disease at some point during their lives. In the Americas in 2005, there were estimated to be 7,694,500 people infected by *Trypanosoma cruzi* and 1,772,365 suffering from chagasic cardiomyopathy. Infected people from endemic countries in Latin America are migrating throughout the world. As a result, what was thought to be a health problem in the Americas is rapidly becoming a world health problem. It has been estimated that 300,167 individuals with *Trypanosoma cruzi* infection live in the United States, with 30,000 to 45,000 cardiomyopathy cases and 63 to 315 congenital infections annually. Standard treatment options for non-Chagas disease heart failure are used for treating Chagas disease-related heart failure. However, because of fundamental differences in the affected populations, it is important to assess the benefits and harms of pharmacological interventions for Chagas disease-related heart failure.

Study characteristics
We identified one new trial, so there are now three studies involving 108 participants. All studies were conducted in Brazil during 2004, 2007, and 2012. Two trials evaluated the effects of carvedilol versus placebo; one trial assessed rosuvastatin versus placebo.

Key results
The results were inconclusive that carvedilol reduced all-cause mortality or improved quality of life more than placebo. The safety profile of carvedilol for Chagas cardiomyopathy remains unclear. One study assessed the effect of rosuvastatin versus placebo, but did not show an effect size. Therefore, the results from available clinical trials neither support nor reject the use of carvedilol or rosuvastatin in treating this clinical entity. Further investigation is warranted to investigate the exact applicability of conventional heart failure treatment agents in Chagas cardiomyopathy.

Quality of evidence
Our confidence in the results of this review is very low because the included trials had a high risk of bias and were small. which generated imprecise results.

Date searched: 15 February 2016.

Summary of findings for the main comparison. Carvedilol compared with placebo for heart failure in patients with Chagas cardiomyopathy

Carvedilol compared with placebo for heart failure in patients with Chagas cardiomyopathy

Patient or population: heart failure in patients with Chagas cardiomyopathy
Settings: outpatients
Intervention: carvedilol
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Carvedilol				
All-cause mortality Follow-up: 4 to 6 months	**86 per 1000**	**59 per 1000** (10 to 333)	**RR 0.69** (0.12 to 3.88)	69 (2 studies)	⊕⊖⊖⊖ **very low** [1,2]	
Cardiac mortality at 30 days	See comment	See comment	Not estimable	69 (2 studies)	See comment	No trials reported this outcome
Time-to-heart decompensation	See comment	See comment	Not estimable	69 (2 studies)	See comment	No trials reported this outcome
Disease-free period (at 30, 60, and 90 days)	See comment	See comment	Not estimable	69 (2 studies)	See comment	No trials reported this outcome.
Overall survival	See comment	See comment	Not estimable	39 (1 study)	⊕⊖⊖⊖ **very low** [1,3]	Diniz 2004 only reported P = 0.525
Quality of life assessed with the Minnesota Living With Heart Failure Questionnaire (MLHFQ). The total score for the 21 items ranges between 0 and 105. A lower MLHFQ score indicates less effect of heart failure on a patient's quality of life. Follow-up: 6 months		The mean quality of life in the intervention group was **14.74 lower** (24.75 to 4.73 lower)		30 (1 study)	⊕⊖⊖⊖ **very low** [1,3]	

Adverse events Follow-up: 6 months	**867 per 1000**	**797 per 1000** (581 to 1000)	**RR 0.92** (0.67 to 1.27)	30 (1 study)	⊕⊖⊖⊖ **very low** [1,4]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded one level due to limitations in design and execution: random sequence generation, allocation concealment and blinding at any level: unclear risk of bias.
[2] Downgraded two levels due to imprecision. The sample size was very small (N = 69) and the number of events was very low (N = 5).
[3] Downgraded two levels due to imprecision. The sample size was very small (N = 30) with wide confidence interval for the QoL outcome.
[4] Downgraded two levels due to imprecision. The sample size was very small (N = 30) and the number of events was very low (N = 25).

Summary of findings 2. Rosuvastatin versus placebo for treating heart failure in patients with Chagas cardiomyopathy

Patient or population: chronic heart failure in Chagas cardiomyopathy patients
Settings: unknown
Intervention: rosuvastatin
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Rosuvastatin				
All-cause mortality	See comments	See comments	See comments	**39** **(1 study)**	See comments	Trial did not assess this outcome
Cardiac mortality at 30 days	See comments	See comments	See comments	**39** **(1 study)**	See comments	Trial did not assess this outcome
Time to heart decompensation	See comments	See comments	See comments	**39**	See comments	Trial did not assess this outcome

				(1 study)		
Disease-free period at 30, 60 and 90 days	See comments	See comments	See comments	**39** **(1 study)**	See comments	trial did not assess this outcome
Quality of life	See comments	See comments	See comments	**39** **(1 study)**	⊕⊖⊖⊖ **very low** [1,2]	Trial did not state effect size
Adverse events	See comments	See comments	See comments	**39** **(1 study)**	See comments	Trial did not assess this outcome
Hospital readmissions (heart failure- or adverse event-related)	See comments	See comments	See comments	**39** **(1 study)**	See comments	Trial did not assess this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded one level due to limitations in design and execution: random sequence generation, allocation concealment, and blinding at any level: unclear risk of bias.
[2] Downgraded two levels due to imprecision. The sample size was very small (N = 39).

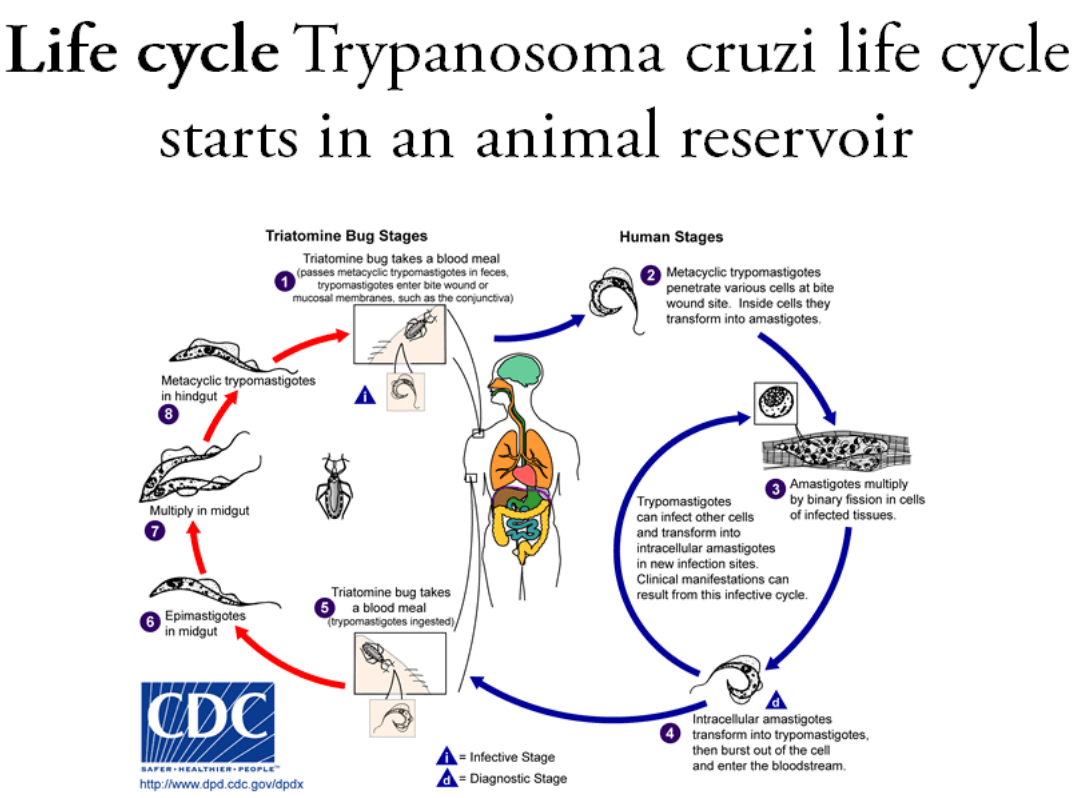
BACKGROUND

Description of the condition

Definition and epidemiology

The pathogen and clinical manifestations of Chagas disease, named after Carlos Chagas, a Brazilian physician, were first discovered in 1909 (Labarthe 1998; Moncayo 2010). Chagas disease is also known as human American trypanosomiasis, and is endemic in the American continent (Moncayo 2006; Moncayo 2009). It is caused by the parasite *Trypanosoma cruzi (T. cruzi)* and is the major cause of infectious myocarditis worldwide (Andrade 2011; Figure 1).

Figure 1. Trypanozoma cruzi life cycle. Reproduced with permission from CDC.



One of the clinical forms of Chagas disease is "Chagas disease (chronic) with heart involvement" (Labarthe 1998). Chagas disease is still a major cause of heart failure in South America (Khatibzadeh 2013; Mendez 2001; Malik 2015a) and thus remains an important health problem (Rassi 2006). The number of people infected with Chagas disease has been estimated to be about 10 to 12 million worldwide, and it is estimated that 20% to 30% of individuals infected with *T. cruzi* will develop symptomatic heart disease at some point during their lives (Gascón 2007). Furthermore, there are an estimated 200,000 new cases per year in 15 Latin American countries (Costa 2012). Table 1 shows the burden of the infected population in America, where in 2005, there were 7,694,500 people infected by *Trypanosoma cruzi* and 1,772,365 suffering from Chagasic cardiopathy (OPS 2006). Table 2 shows the epidemiology of infected people from endemic countries in Latin America migrating throughout the world. This shows how an issue that was considered an American health problem is rapidly becoming a world health problem (Schmunis 2010). Bern 2009 has estimated that 300,167 individuals with *T. cruzi* infection live in the United States. With 30,000 to 45,000 cardiomyopathy cases and 63 to 315 congenital infections annually, *T.cruzi* causes a substantial burden of disease in the United States (Bern 2009; Malik 2015b; Melton 2015; Traina 2015). Preventive approaches, such as control of the Triatomine bug and ecological niche studies, are key to reducing the incidence of Chagas disease (Carrasco 2012; Cruz-Pacheco 2012; Gurgel-Goncalves 2012; Yamagata 2006). The economic burden of Chagas disease could be higher than diseases such as, rotavirus, cervical cancer, and Lyme disease (Lee 2013).

Etiology of Chagas disease

Chagas disease is an acquired inflammatory cardiomyopathy characterized by chronic fibrosing myocarditis (varying from focal or multifocal to diffuse; Rassi Jr 2009; Rossi 1991). The etiology of Chagas disease is multifactorial (Marin-Neto 2007). Parasite

persistence has been hypothesized as a cause (Dávila 2002b; Zhang 1999); however, controversy exists about it (Elias 2003). Autoimmunity is another pathogenic mechanism (Dávila 2002b; Tanowitz 2009). Chagas disease has been considered to be a paradigm of infection-induced autoimmune disease (Gironès 2005; Gironès 2007). Autoimmune reactions seem to be mediated by a *T. cruzi* protein, *Trypanosoma cruzi calreticulin* (Ribeiro 2009). The role of autoantibodies in the physiopathology of Chagas disease has been described (Medei 2008). Recently, the immunopathology and genetics aspects of Chagas disease cardiomyopathy were extensively reviewed, and it was concluded that Th1 t-cell-rich myocarditis, with cardiomyocyte hypertrophy and prominent fibrosis are prominent findings in this disease (Cunha-Neto 2014). There is strong evidence that it develops as a result of additive and even synergistic effects of several distinct mechanisms, rather than from one factor (Bonney 2008).

The pathogenesis of Chagas disease is not completely understood, but the evidence suggests that it could be explained by four pathogenetic mechanisms: direct parasite damage to the myocardium, immunologic mechanisms, dysautonomia, and microvascular disturbances (Biolo 2010; Dávila 2004; Dávila 2005). The complexity of the immune response generated during *T. cruzi* infection strengthens the concept that the host immune response is critical for disease control and evolution (Dutra 2008; Esper 2015).

Pathophysiology and cardiovascular clinical manifestations

Pathophysiology of Chagas disease has been reviewed widely by Rassi Jr 2009 and Higuchi 2003. The cardiac clinical form is caused by an inflammatory reaction in the heart tissue, leading to a spectrum of debilitating and morbid cardiac diseases (Dutra 2008). The diagnostic triad suggestive of Chagas disease includes: a) epidemiological history; b) positive serology (antibodies against *T. cruzi*) in at least two tests; and c) clinical findings such as: heart failure; syncope; complex arrhythmias; embolisms; electrocardiographic findings, such as right bundle block, left anterior hemiblock, or a combination of the latter two conditions; ventricular extrasystoles; ST-T segment anomalies; and apical aneurysm of the left ventricle, among others (Acquatella 2008; Machado 2012; Ribeiro 2012b). These syndromes are caused by inflammatory lesions and an immune response, particularly mediated by either CD4-positive T-lymphocytes, CD8-positive T-lymphocytes, interleukin-2 or interleukin-4 with cell and neuron destruction and fibrosis (Coura 2010). Congestive heart failure is more commonly expressed by prominent signs of systemic congestion, with less intense pulmonary congestion. This peculiar feature of Chagas disease is linked to early severe damage of the right ventricle, a chamber frequently neglected in investigations of cardiac function (Marin-Neto 1998). Patients with congestive heart failure secondary to Chagas cardiomyopathy have a poorer prognosis than those with congestive heart failure secondary to hypertension (Bestetti 2013), which could be explained by malignant ventricular arrhythmias, which lead to sudden cardiac death (Veloso 2014). However, it is controversial (Betestti 2014).

In the acute phase, death is mostly caused by myocarditis, and in the chronic phase, by irreversible cardiomyopathy (Punukollu 2007). It has been suggested that inflammatory cardiomyopathy of Chagas' disease is a genetically driven autoimmune disease (Teixeira 2011).

Mortality during the acute phase of cardiac Chagas is around 5%, while five-year mortality of chronic Chagas disease with cardiac dysfunction is above 50% (Punukollu 2007). Pathological findings in the heart include mononuclear inflammatory infiltrate, focal myocarditis, epicarditis and neuroganglionitis, associated with variable focal fibrosis and widely variable autonomic dysfunction (Ribeiro 2012a). The immune-inflammatory response has been considered to be the cause of the autonomic dysfunction, which may trigger life-threatening arrhythmias and sudden death (Ribeiro 2012a).

The risk of mortality in patients affected by Chagas disease includes three stages: low (total mortality: 2% and 10% at five years and 10 years, respectively), intermediate (total mortality: 18% and 44% at five years and 10 years, respectively), and high (total mortality: 63% and 84% at five years and 10 years, respectively; Rassi Jr 2010). This stratification of risk of death has led to the following recommended approaches, which are based on expert opinion rather than evidence of benefit (Rassi Jr 2010):

1. Low stage without New York Heart Association (NYHA) class III or IV, left ventricular systolic dysfunction (echocardiography), cardiomegaly (chest radiography), or both, and non-sustained ventricular tachycardia (24-hour Holter monitoring) - possibly treat with antiparasitic drug.
2. Intermediate stage without NYHA class III or IV, left ventricular systolic dysfunction (echocardiography), cardiomegaly (chest radiography), or both, but with non-sustained ventricular tachycardia (24-hour Holter monitoring) - possibly treat with amiodarone and an antiparasitic drug.
3. Intermediate stage without NYHA class III or IV, with left ventricular systolic dysfunction (echocardiography), cardiomegaly (chest radiography), or both, but absence of non-sustained ventricular tachycardia (24-hour Holter monitoring) - treat with angiotensin-converting enzyme inhibitors, beta-blockers, diuretics (for selected patients), and possibly treat with an antiparasitic drug.
4. High stage without NYHA class III or IV, with left ventricular systolic dysfunction (echocardiography), cardiomegaly (chest radiography), or both, and with non-sustained ventricular tachycardia (24-h Holter monitoring) - treat with angiotensin-converting enzyme inhibitors, amiodarone, diuretics (for selected patients), beta-blockers (if clinically tolerated), and possibly treat with an implantable cardioverter defibrillator.
5. High stage with NYHA class III or IV, with left ventricular systolic dysfunction (echocardiography), cardiomegaly (chest radiography), or both, and with non-sustained ventricular tachycardia (24-hour Holter monitoring) - treat with angiotensin-converting enzyme inhibitors, spironolactone, amiodarone, diuretics, digitalis, beta-blockers (if clinically tolerated), heart transplantation (if clinically tolerated), and possibly treat with an implantable cardioverter defibrillator.

Description of the intervention

In Chagas disease, the haemodynamic and neurohormonal responses are similar to those in other cardiomyopathies. This common pathophysiology suggests that therapies effective in usual heart failure cases should also be beneficial in Chagas disease (Botoni 2007). Pharmacological agents such as angiotensin-converting enzyme inhibitors and beta-blockers are likely to be as important in Chagas disease as in other heart failure syndromes

(Biolo 2010). Serious adverse events have been observed with these medications in chronic heart failure. See Appendix 1 for adverse events from pharmacological therapy to treat heart failure.

Pharmacological interventions for treating heart failure include many different families of drugs (Adorisio 2006; Hamad 2007; Mills 2001):

1. Angiotensin-converting enzyme inhibitors: captopril, lisinopril, fosinopril sodium, enalapril maleate, benazepril, quinapril, ramipril;
2. Angiotensin II receptor antagonists: losartan, candesartan, valsartan, irbesartan;
3. Aldosterone receptor antagonists: spironolactone, eplerenone;
4. Inotropes: milrinone, dobutamine;
5. Digitalis: digoxin;
6. Diuretics: furosemide;
7. Vasodilators: isosorbide dinitrate, hydralazine, nitroprusside, nesiritide (recombinant human B-type natriuretic peptide);
8. Beta-adrenoceptor antagonists: carvedilol, metoprolol, bisoprolol;
9. Calcium sensitizers: pimobendan, levosimendan.

There is insufficient evidence to support the efficacy of nitrofurans or imidazolic drugs for treating overt Chagas disease (Reyes 2005). The existing evidence on its prevention indicates a need to test these and newer agents in more and larger RCTs that include clinical outcomes for chronic asymptomatic*T. cruzi* infection (Villar 2002).

Trypanocidal efficacy of posaconazole and ravuconazole is being tested (Buckner 2010; Diniz 2010; Olivieri 2010). Recently, the relevance and current limitations of, and new approaches to, specific chemotherapy for Chagas disease have been reviewed (Urbina 2010).

How the intervention might work

The above-mentioned pharmacological interventions work through many different mechanisms (Hamad 2007).

1. Angiotensin-converting enzyme inhibitors reduce angiotensin II production by blocking the plasma and pulmonary endothelial angiotensin-converting enzyme. Angiotensin II produces deleterious cardiovascular effects including direct vasoconstriction, increased sympathetic discharge, release of catecholamines, increased sodium reabsorption in the proximal tubule, and the release of aldosterone.
2. Angiotensin II receptor antagonists block the effects of the angiotensin II, which generates the activation of two types of receptors on the cell surface: angiotensin II type 1 and angiotensin II type 2. Angiotensin II receptor antagonists type1 mediate vasoconstriction and stimulate aldosterone and vasopressin secretion, which cause sodium and water retention.
3. Aldosterone receptor antagonists reduce the action of aldosterone, a hormone produced by the adrenal glands. Aldosterone causes vasoconstriction, increases salt and water retention, and stimulates the growth of fibroblasts and the synthesis of collagen.
4. Inotropes cause increased inotropic effects and vasodilation independent of the stimulation of beta-receptors (milrinone), or through the stimulation of the of beta-receptors of the heart.
5. Digitalis leads to increased myocardial contractility through the increase of intracellular calcium.
6. Diuretics increase the excretion of sodium and water, which reduces fluid retention.
7. Vasodilators reduce afterload and preload by dilating both arterial and venous blood vessels.
8. Beta-adrenoceptor antagonists reduce the sympathetic nervous system and renin-angiotensin system.
9. Calcium sensitisers increase myocardial contractility.

Why it is important to do this review

A review of the evidence for treating heart failure associated with Chagas disease is required for the following reasons:

First, Chagas disease is a major cause of morbidity and mortality in Latin America (Rassi 2000; Schmunis 2010). Second, treatment of Chagas' cardiomyopathy during acute decompensated heart failure is very expensive (Abuhab 2013). Third, although there are published systematic reviews of the effect of trypanocidal drugs for the different stages of Chagas disease, no systematic review of the pharmacological interventions commonly used in chronic heart failure has been conducted for Chagas disease (Reyes 2005; Villar 2002). Fourth, the management of Chagas disease may be even more difficult than that of other dilated cardiomyopathies (Dobarro 2008). This worse prognosis may be due to a greater degree of cardiac impairment (lower ejection fraction) and haemodynamic instability (lower systolic blood pressure and heart rate), increased activation of the renin-angiotensin system, and increased cytokine levels (Silva 2008), and reduces the quality of life (Sousa 2015). Therefore, there are uncertainties about the benefits of using pharmacological interventions, and the rates of their adverse effects. Drugs for treating heart failure are associated with severe adverse events, which in patients with Chagas disease, could be life-threatening. Fifth, the increasing number of people affected by Chagas disease emigrating from the Americas to developed countries may cause a radical increase in the incidence of this disease over the coming years, however, European cardiologists are unfamiliar with this chronic cardiomyopathy (Bimbi 2014; Dobarro 2008; Gascón 2010; Gascón 2007; Muñoz 2009; Soriano 2009; Strasen 2014; Table 2). Therefore, a review is needed to improve patient care through therapeutic decision making, based on the best evidence-based treatment.

This is an update of a Cochrane review previously published in 2012, which sought to answer the research question: "What are the benefits and harms of pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy?" (Hidalgo 2012).

Appendix 2 provides a medical glossary.

OBJECTIVES

To assess the clinical benefits and harms of current pharmacological interventions for treating heart failure in people with Chagas cardiomyopathy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials, regardless of publication status (trials may be unpublished or published as an article, an abstract, or a letter). We applied no language, country, or sample size limitations. We included trials conducted in either a hospital or community setting, or both. We applied no limits on the length of follow-up.

Types of participants

Adults (18 years or older) with symptomatic heart failure (New York Heart Association class II to IV; Table 3), regardless of whether the left ventricular ejection fraction stage was reduced or preserved, in patients with Chagas cardiomyopathy. We considered trials that evaluated pharmacotherapies in a general heart failure population that included participants affected by Chagas cardiomyopathy.

Types of interventions

Interventions

1. Angiotensin converting enzyme inhibitors (ACE inhibitors): captopril, lisinopril, fosinopril sodium, enalapril maleate, benazepril, quinapril, ramipril;
2. Angiotensin II receptor antagonists: losartan, candesartan, valsartan, irbesartan;
3. Aldosterone receptor antagonists: spironolactone, eplerenone;
4. Inotropes: milrinone, dobutamine;
5. Digitalis: digoxin;
6. Diuretics: furosemide;
7. Vasodilators: isosorbide dinitrate, hydralazine, nitroprusside, nesiritide (recombinant human B-type natriuretic peptide);
8. Beta-adrenoceptor antagonists: carvedilol, metoprolol, bisoprolol;
9. Calcium sensitisers: pimobendan, levosimendan.

Comparisons

1. Placebo;
2. Standard care (low-salt diet, rest);
3. Any head-to-head comparisons.

Types of outcome measures

Primary outcomes

1. All-cause mortality;
2. Cardiac mortality at 30 days;
3. Time-to-heart decompensation;
4. Disease-free period (at 30, 60, and 90 days).

Secondary outcomes

1. Overall survival, defined as "the proportion of persons in a specified group, alive at the beginning of the time interval, who survive to the end of the interval" (Porta 2008);
2. Quality of life, measured with any validated scale;
3. Hospital readmissions (heart failure- or adverse event-related);
4. Adherence grade, which will be measured as the proportion of time patients took more than 80% of study medication (Granger 2009);
5. Adverse events, classified as "any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment" (Nebeker 2004);
6. Digoxin toxicity: extra-cardiac, or cardiac, or both, signs and symptoms attributed to digoxin. These clinical manifestation are more common above 2.5 nmol/L (2.0 µg/L). Extra-cardiac manifestation include visual disturbances, anorexia, nausea, or vomiting. Cardiac manifestations include rhythm disturbances (Bauman 2006).

Search methods for identification of studies

Electronic searches

We updated the searches run in 2011 (Appendix 3), on 16 February 2016 (Appendix 4).

The following databases were searched:

- Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2016, Issue 1),
- MEDLINE (Ovid; 1946 to February Week 1 2016),
- EMBASE (Ovid; 1947 to 2016 Week 07),
- LILACS (1986 to 15 February 2016), and
- Web of Science (Thomson Reuters, 1970 to 15 February 2016).

We used the Cochrane sensitive-maximising RCT filters to search MEDLINE and EMBASE (Lefebvre 2011).

We imposed no language restrictions.

Searching other resources

We updated the searches of the Clinical Trials Search Portal of the World Health Organization for ongoing and unpublished trials, and Clinicaltrials.gov/ for ongoing and other relevant trials on 15 February 2016 (Appendix 4). We also checked the reference lists of all the trials identified by the above methods.

We contacted the main author of NCT00323973 to obtain further details about the potentially published trial.

Data collection and analysis

We conducted data collection and analysis of data according to methods set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two authors (AMC, JK) independently assessed each reference to see whether it met the inclusion criteria. Any disagreements were resolved through consensus.

Data extraction and management

Two authors (AMC, JK) independently extracted data from the selected trials using a standardised data extraction form. Any disagreements were resolved through consensus. For the first version of this Cochrane review, Dr Viana Zuza Diniz was contacted, and sent us the full text of her PhD thesis (Diniz 2004).

Assessment of risk of bias in included studies

All review authors independently assessed the risk of bias of the trials according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We assessed the following domains, using the following definitions.

Generation of the allocation sequence

- Low risk if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice was considered adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear risk if the trial was described as randomised, but the method used for the generation of allocation sequence was not described.
- High risk if a system involving dates, names, or admittance numbers was used for the allocation of participants.

Allocation concealment

- Low risk if the allocation of participants involved a central independent unit, on-site locked computer, identical looking, numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear risk if the trial was described as randomised, but the method used to conceal the allocation was not described.
- High risk if the allocation sequence was known to the investigators who assigned participants, or if the study was quasi-randomised.

Blinding (or masking)

We assessed each trial (as low, unclear, or high risk) with regard to the following types of blinding:

- blinding of clinician (person delivering treatment) to treatment allocation;
- blinding of participant to treatment allocation;
- blinding of outcome assessor to treatment allocation.

Incomplete outcome data

- Low risk if the numbers and reasons for dropouts and withdrawals in all intervention groups were described, or it was specified that there were no dropouts or withdrawals.
- Unclear risk if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- High risk if the number or reasons for dropouts and withdrawals were not described.

We further examined the overall percentages of dropouts in each trial, per randomised arm, and evaluated whether intention-to-treat analysis was performed, or could be performed from the published information. We measured outcomes against all participants randomised. We did not impute values.

Selective outcome reporting

- Low risk if pre-defined or clinically relevant and reasonably expected outcomes were reported.
- Unclear risk if not all pre-defined or clinically relevant and reasonably expected outcomes were reported, or were not fully reported, or it was unclear whether data on these outcomes were recorded or not.
- High risk if one or more clinically relevant and reasonably expected outcomes were not reported; data on these outcomes would be expected to have been recorded.

Other bias:

- Low risk if the trial appears to be free of other components that could put it at risk of bias.
- Unclear risk if the trial may or may not be free of other components that could put it at risk of bias.
- High risk if there are other factors in the trial that could put it at risk of bias, e.g., early stopping, industry involvement, or an extreme baseline imbalance.

We considered trials at low risk of bias to be those that adequately generated their allocation sequence; had adequate allocation concealment, blinding, and handling of incomplete outcome data; were free of selective outcome reporting; and were free of other bias.

We considered trials in which we assessed at least one of the domains as having a high risk of bias or unclear risk of bias, to be trials with high risk of bias.

Measures of treatment effect

We calculated the relative risk (RR) with 95% confidence intervals (CI) for binary outcomes of all-cause mortality and safety.

Dealing with missing data

We assessed the percentages of overall dropouts for each included trial and each randomised arm and evaluated whether an intention-to-treat analysis had been performed or could be performed with the available published information. We contacted Dr Viana Zuza Diniz who sent us the full text of her PhD thesis (Diniz 2004).

We conducted an intention-to-treat analysis. We measured outcomes against all participants randomised. We did not impute values.

Assessment of heterogeneity

We quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). When heterogeneity was detected ($I^2 > 50\%$), we attempted to identify the possible causes of heterogeneity (Higgins 2011).

Assessment of reporting biases

We did not assess publication bias with a funnel plot because we only included three trials. For future updates, we will attempt to assess whether the review is subject to publication bias by using a funnel plot, if at least 10 trials are included.

Data synthesis

We pooled the results from the trials using Review Manager software (RevMan 2014). We summarized findings using a fixed-

effect model, according to the *Cochrane Handbook of Systematic Reviews for Interventions* (Higgins 2011).

Summary of findings

We used the principles of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess the quality of the body of evidence associated with up to seven outcomes (Balshem 2011; Brozek 2011; Guyatt 2008; Guyatt 2011h). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence takes into consideration within study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias (Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g).

This updated Cochrane review assessed the quality of the body of evidence associated with these seven specific outcomes: all-cause mortality, cardiac mortality at 30 days, time-to-heart decompensation, disease-free period (at 30 days, 60 days, and 90 days), quality of life, adverse events.

Subgroup analysis and investigation of heterogeneity

In subsequent updates of this review, when sufficient data are available, we plan to carry out the following subgroup analyses:

1. Intervention;
2. New York Heart Association stage;
3. Conduction system disturbances;
4. Atrial and ventricular arrhythmias;
5. Chronic versus acute heart failure;
6. Heart failure with preserved ejection fraction: ≤ 40% versus > 40%.

We will only perform subgroup analysis for primary outcomes.

Sources of heterogeneity in the assessment of the primary outcome measure will be explored by subgroup analyses and meta-regression analyses. The meta-regression analyses will assess route of administration (intramuscular versus intravenous) and participants' characteristics. We will only conduct meta-regression if at least 10 trials are included.

Sensitivity analysis

For future updates, we plan to conduct a sensitivity analysis comparing the results from all trials as follows:

1. Those trials with high methodological quality (studies classified as having a 'low risk of bias' versus those identified as having a 'high risk of bias') (Higgins 2011);
2. Those trials that performed intention-to treat versus per-protocol analyses.

We will also evaluate the risk of attrition bias, as estimated by the percentage of participants lost. Trials with a total attrition of more than 30%, or where differences between the groups exceed 10%, or both, will be excluded from meta-analysis but will be included in the review.

RESULTS

Description of studies

Results of the search

The initial search in 2011 identified 1125 unique records; we assessed six of these in full text. A seventh study was ongoing (NCT00323973). We excluded four studies (see Excluded studies).

The search in February 2016 identified 1041 new records, which resulted in 879 unique references after duplicates were removed, which we screened. After examining the titles and abstracts (857 references) and ongoing trials (22 registered studies), we excluded 878 references. We obtained full reprints of the remaining reference for a more detailed examination. Ultimately, we were able to find and include one new randomised clinical trial (Andrade 2012).

In total, this updated review includes three trials (four references) conducted in Brazil, and published between 2004 and 2012 (Andrade 2012; Botoni 2007; Diniz 2004). These trials involved 108 randomised participants. See Figure 2 for details.

Figure 2. Study flow diagram first update 16 February 2016

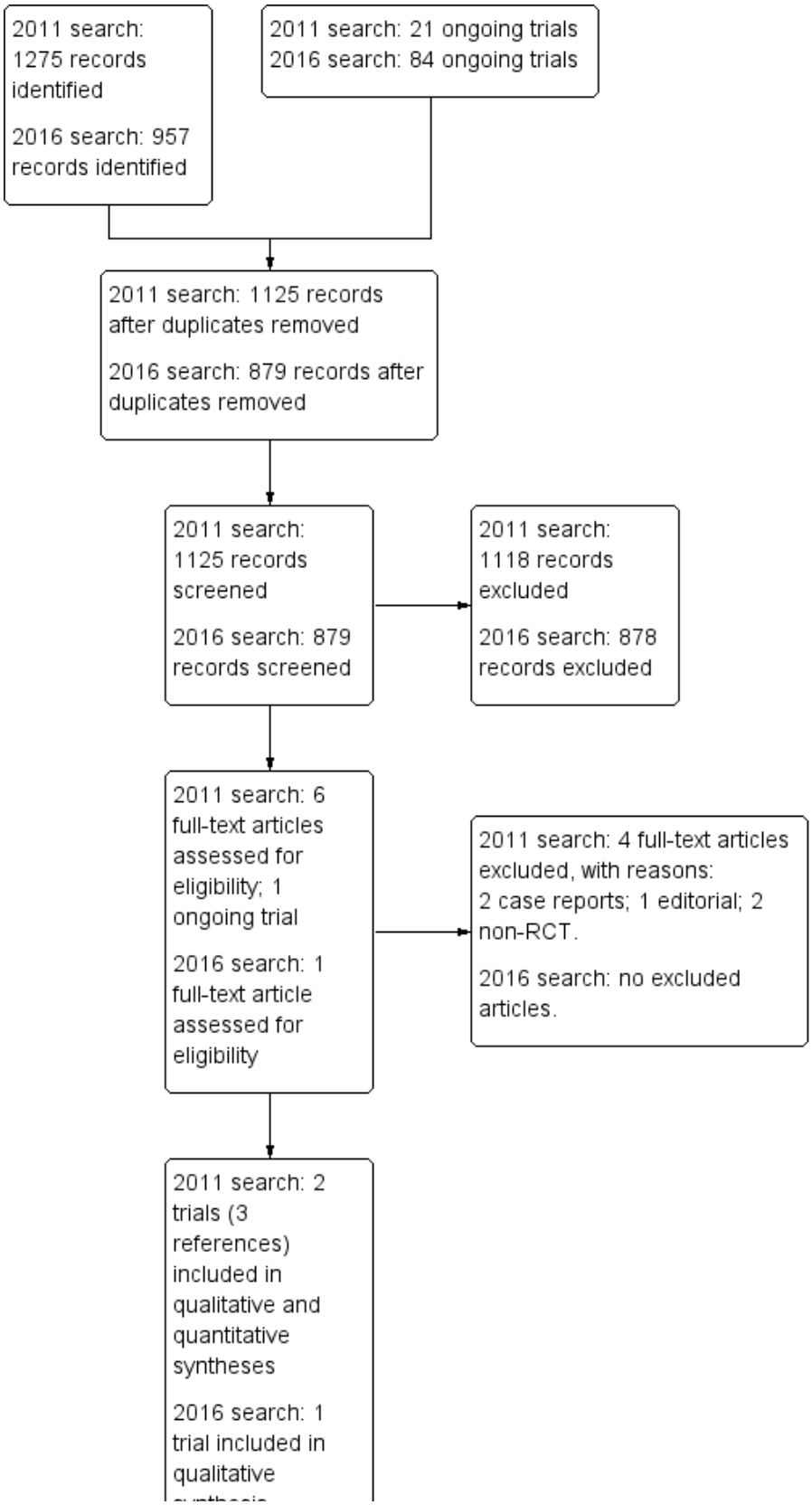


Figure 2. (Continued)

qualitative synthesis.

Total: 3 trials (4 references)

Included studies

We provide a detailed description of the included trials in the Characteristics of included studies.

One trial reported no demographics, baseline, inclusion or exclusion criteria data (Andrade 2012). This trial involving 39 participants assessed rosuvastatin versus placebo. Information was obtained from a conference abstract. We contacted the trial author for details.

The following information came from Botoni 2007 and Diniz 2004. Overall, the mean age of the participants was 48.3 years (standard deviation (SD) 0.42). The percentage of male participants was 74.2% (SD 3.96). Botoni 2007 described New York Heart Association (NYHA) classes across both comparison groups. Fifty percent of the participants had NYHA class II/III. No participants had NYHA class IV (Botoni 2007). On the contrary, Diniz 2004 described NYHA class by comparison group. Fifteen participants in the carvedilol group had NYHA class between II to IV and the control group had NYHA class between II and III (Diniz 2004). The mean (SD) left ventricular ejection fraction (LVEF) for the carvedilol group in Botoni 2007 was 43.2 (19.9) versus 47.9 (15.3) for the control group. The mean (SD) LVEF for the carvedilol group was 0.26 (0.07) versus 0.24 (0.06) for control group in Diniz 2004.

Both trials assessed carvedilol by oral administration as the experimental intervention and placebo as the control group. Both were conducted using a parallel design with two arms, and both were conducted with out-patients. The mean sample size was 34.5 (SD 6.36; range 30 to 39). One trial was reported in two publications (Diniz 2004). One trial reported that the sample size was calculated a priori (Botoni 2007), while the other did not (Diniz 2004). The included studies had follow–up periods ranging from four months to 29 weeks (Botoni 2007; Diniz 2004). One study was sponsored by drug company (Botoni 2007).

See Characteristics of included studies table for details.

Excluded studies

We excluded four references. Two were case reports (Bestetti 2011; Dávila 2002a), one reference was an editorial (Dávila 2008), and one was a non-randomised controlled trial (Issa 2010). See the Characteristics of excluded studies table.

Ongoing studies

We identified one ongoing study (NCT00323973). We contacted the lead author who advised us on three separate occasions that the publication of this trial was held up in the editorial phase due to missing data. See Characteristics of ongoing studies for details.

Risk of bias in included studies

Overall, all trials had a high risk of bias. See Figure 3 and Figure 4 for risk of bias graph and summary.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

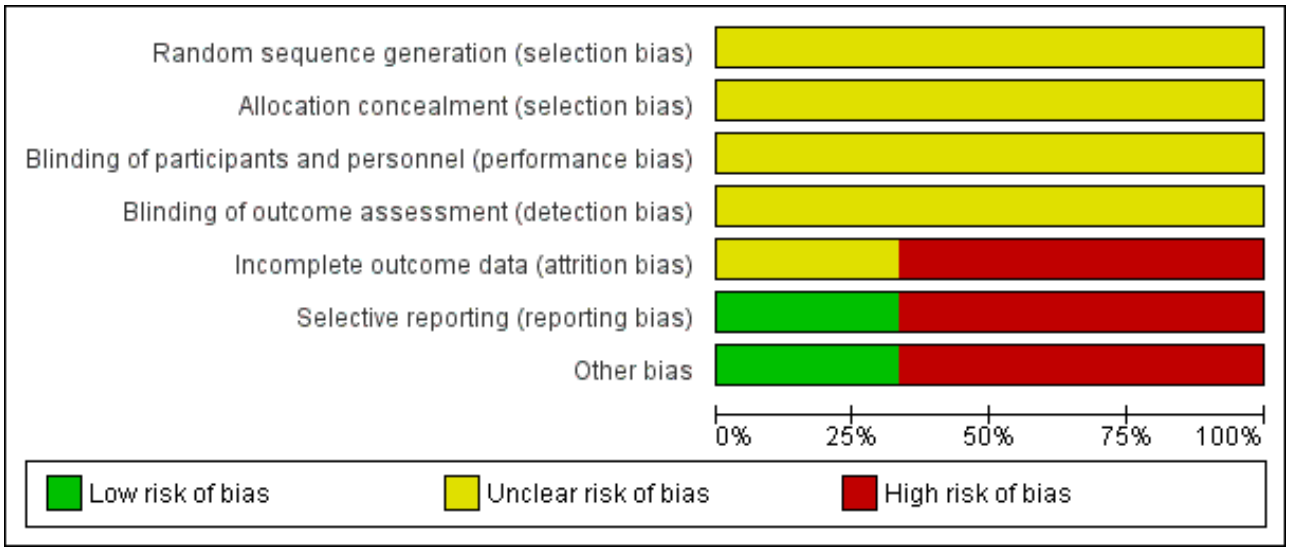
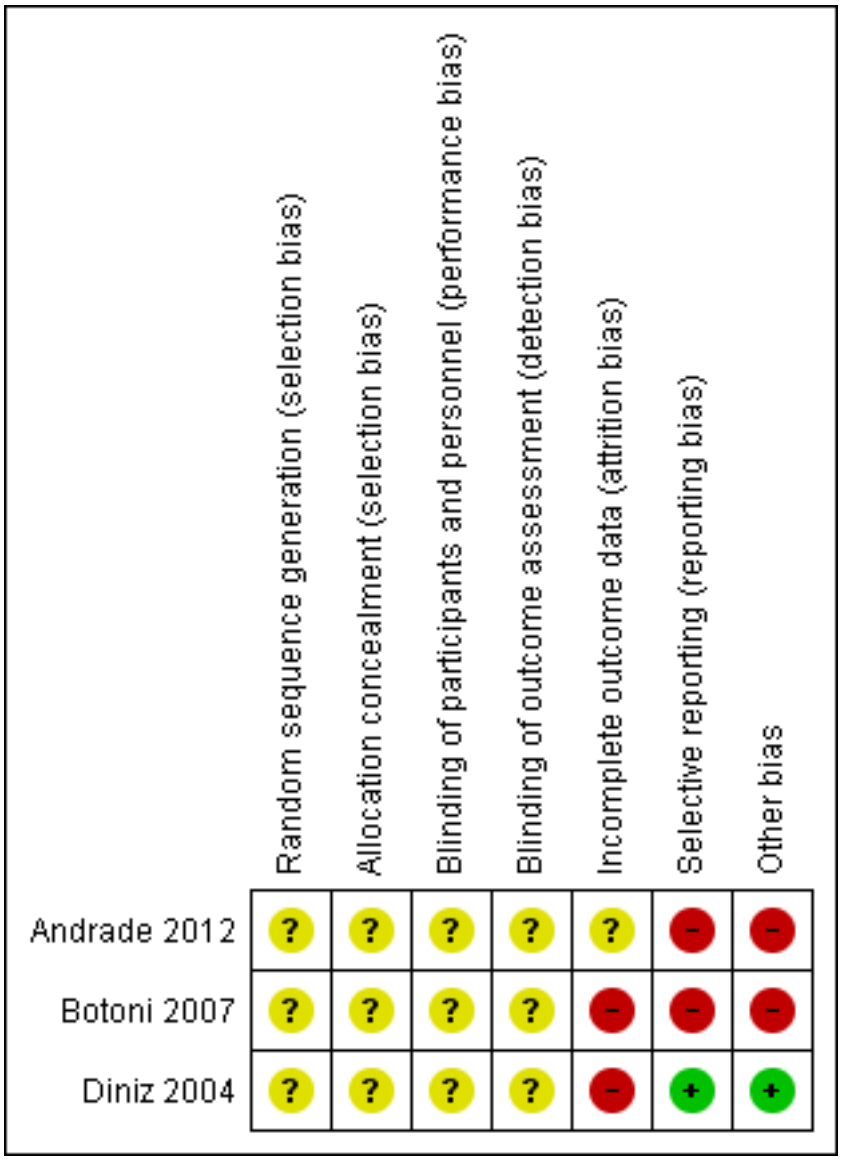


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias domain for each included study.



Allocation

All trials were at unclear risk of bias for random sequence generation and allocation concealment domains.

Blinding

All trials were at unclear risk of bias for blinding of participants, personnel, and outcome assessors.

Incomplete outcome data

Andrade 2012 and was rated as having unclear risk of bias for this domain, while Diniz 2004 and Botoni 2007 were at a high risk of bias for this domain.

Selective reporting

One trial had a low risk of bias (Diniz 2004). Two trials were rated as having high risk of reporting bias (Andrade 2012; Botoni 2007).

Other potential sources of bias

One trial had a low risk of bias (Diniz 2004). Andrade 2012 and Botoni 2007 had bias in the presentation of data. Botoni 2007 received sponsorship from a drug company, therefore it was rated as having high risk of industry bias.

Effects of interventions

See: **Summary of findings for the main comparison** Carvedilol compared with placebo for heart failure in patients with Chagas cardiomyopathy; **Summary of findings 2** Rosuvastatin versus placebo for treating heart failure in patients with Chagas cardiomyopathy

The results were based on three trials involving 108 participants (Andrade 2012; Botoni 2007; Diniz 2004). See Summary of findings for the main comparison and Summary of findings 2.

Primary outcomes

The two trials (69 participants) that assessed carvedilol versus placebo reported only one of our primary outcomes of interest (Botoni 2007; Diniz 2004). No data were available on the other outcomes (30-day cardiovascular mortality, time-to-heart decompensation, disease-free period at 30, 60, and 90 days). Andrade 2012 assessed none of our primary outcomes.

All-cause mortality

Carvedilol versus placebo

Meta-analysis of two trials (69 participants) found a lower proportion of all-cause mortality in the carvedilol group than the placebo group (2/34 (5.88%) versus 3/35 (8.57%); RR 0.69; 95% CI 0.12 to 3.88; I^2 = 0%; Analysis 1.1; very low-quality evidence; Botoni 2007; Diniz 2004).

Secondary outcomes

Overall survival

Carvedilol versus placebo

One trial (30 participants) found similar overall survival results between the carvedilol and placebo groups (P = 0.525; very low-quality evidence; Diniz 2004).

Hospital readmissions

One trial (30 participants) found similar hospital readmission results between the carvedilol and placebo groups (4/15 (26.66%) versus 4/15 (26.66%); RR 1.00; 95% CI 0.31 to 3.28; P = 1.0; Analysis 1.2; very low-quality evidence; Diniz 2004).

Quality of life

Carvedilol versus placebo

Due to inconsistency in measurement units between the two trials assessing this outcome, we were unable to combine the results from these trials.

Botoni 2007 (39 participants) assessed this outcome with the Medical Outcomes Study 36-item short-form health survey (SF-36). This scale includes one multi-item scale that assesses eight health concepts and 36 items (Ware 1992). Each item is quantified from 0 (worst) to 100 (better). Botoni 2007 found inconclusive differences between the carvedilol and placebo groups for functional capacity, physical limitation, pain, general state, vitality, social aspects, mental health, and emotional aspects.

Diniz 2004 assessed quality of life with the Minnesota Living With Heart Failure Questionnaire (MLHFQ). There are 21 items; each item is scored from 0 to 5, with a total range between 0 and 105. A lower MLHFQ score indicates less effect of heart failure on a patient's quality of life (Pietri 2004). There is very low-quality evidence that the effects on quality of life are inconclusive when carvedilol is compared with placebo (MD -14.74; 95% IC -24.75 to -4.73; 30 participants; Analysis 1.3).

Rosuvastatin versus placebo

Andrade 2012 (39 participants) reported no improvement in terms of quality of life. Trial authors provided no effect size.

Adverse events

Carvedilol versus placebo

One trial found a 'significant' reduction in systolic and diastolic blood pressure, and changes in renal function and serum electrolytes in both groups, but provided but no data. It also reported reductions in heart rate in both the carvedilol and placebo groups, but there was no recorded episode of symptomatic bradycardia (Botoni 2007). On the other hand, Diniz 2004 found uncertainty in the difference in adverse events between the carvedilol and placebo groups (12/15 (80%) and 13/15 (86.7%); RR 0.92; 95% CI 0.67 to 1.27; Analysis 1.4; very low-quality evidence).

DISCUSSION

Summary of main results

This updated Cochrane review of pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy included a total of three trials (108 participants), all of which were conducted in Brazil. Two of the trials compared carvedilol with placebo (69 participants; Botoni 2007; Diniz 2004), and one compared rosuvastatin with placebo (39 participants; Andrade 2012). Our GRADE assessment found very low-quality evidence on the effects of either carvedilol or rosuvastatin for treating heart failure in Chagas cardiomyopathy. All of the trials were small and had a high risk of bias. A drug company sponsored one trial (Botoni 2007).

We combined data from two trials, and found that carvedilol reduced all-cause mortality over placebo, but the confidence intervals were wide and crossed the line of significance (Botoni 2007; Diniz 2004). It was not possible to pool data from Botoni 2007 and Diniz 2004 for overall survival or adverse events. Taking each trial separately, we found inconclusive results between the carvedilol and placebo groups regarding these outcomes. The trial comparing rosuvastatin and placebo reported no information. We found no conclusive results between carvedilol and placebo on hospital readmissions (Diniz 2004).

It was also not possible to pool quality of life (QoL) results; the effects across individual trials were inconclusive. One trial used the Minnesota Living With Heart Failure Questionnaire (MLHFQ) and reported that carvedilol significantly improved QoL more than placebo (Diniz 2004). On the contrary, Botoni 2007 found no conclusive results for QoL between the carvedilol with placebo groups when measured with the Medical Outcomes Study 36-item short-form health survey (SF-36). Andrade 2012 did not report an effect size for QoL when rosuvastatin was compared with placebo.

None of the trials evaluated main clinical outcomes, such as cardiac mortality at 30 days, time-to-heart decompensation, disease-free period (at 30, 60, and 90 days), adherence grade, or digoxin toxicity.

All evidence was graded as very low-quality. See Summary of findings for the main comparison; Summary of findings 2 for details.

Overall completeness and applicability of evidence

This updated Cochrane review includes three small trials, which found inconclusive results between the effects of either carvedilol or rosuvastatin compared with placebo. All these issues yielded very low-quality evidence (Ioannidis 2008a).

Only one meta-analysis combined the data from two trials with very small sample sizes and a very low number of events. It has been shown that meta-analyses that include a limited number of participants and events are prone to overestimate the estimate of effect (Ioannidis 2008a; Ioannidis 2008b; Thorlund 2011).

When dealing with such neutral results, we need to keep in mind that 'absence of evidence' is not 'evidence of absence' (Altman 1995; Fermi Paradox). The fact that this review did not detect conclusive results between the two intervention groups does not imply that placebo and carvedilol have the same mortality risk. The first possible explanation is failure to determine an appropriate sample size (Green 2002; Schulz 1995). In Freiman 1978, the authors suggested that "many of the therapies labelled as 'no different from control' in trials using inadequate samples, have not received a fair test" and that "concern for the probability of missing an important therapeutic improvement because of small sample sizes deserves more attention in the planning of clinical trials". In 1998, Moher, et al emphasized that "most trials with negative results did not have large enough sample sizes to detect a 25% or a 50% relative difference" (Moher 1998). Moreover, it has been suggested that the most important therapies adopted in clinical practice have shown more modest benefits (Kirby 2002).

Quality of the evidence

The GRADE approach was employed to interpret result findings and the GRADE profiler (GRADEPRO) allowed us to import data from Review Manager to create 'Summary of findings' tables (Summary of findings for the main comparison and Summary of findings 2). The main source of bias in the included trials was the lack of detail in describing the generation of randomisation sequences and the concealment of allocation (Andrade 2012; Botoni 2007; Diniz 2004). Trials also lacked detail on their blinding processes. Our assessment of the risk of bias of the included studies has been previously described, and a summary can be found in Figure 3 and Figure 4. Included trials were generally considered to be at a high risk of bias. Uncertainty remains about possible harms from the interventions, due to a lack of detail in presenting safety data. All trials had very small sample sizes and a very low number of events, which reduced the precision and create wide confidence intervals. One trial is susceptible to high risk of industry bias (Botoni 2007).

Potential biases in the review process

In the process of performing a systematic review, there is a group of biases called significance-chasing biases (Ioannidis 2010). This group includes publication bias, selective outcome reporting bias, selective analysis reporting bias, and fabrication bias (Ioannidis 2010). Publication bias represents a major threat to the validity of systematic reviews, particularly in reviews that include small trials. This Cochrane review has a low risk of publication bias due to the thorough trial search process, through which we detected the primary source of Diniz 2004. Selective outcome reporting bias operates through suppression of information on specific outcomes and has similarities to study publication bias, in that 'negative' results remain unpublished (Ioannidis 2010). This Cochrane review found that included trials had a high risk of selective outcome reporting (Andrade 2012; Botoni 2007).

This update has two limitations. First, data from Andrade 2012 were gathered from a conference abstract. Second, we were not able to get information on the results of NCT00323973, which is completed, and compared bisoprolol versus placebo. However, we tried to reduce the negative impact of both limitations by contacting the main authors of Andrade 2012 and NCT00323973.

AUTHORS' CONCLUSIONS

Implications for practice

This first update of the Cochrane review found very low-quality evidence for the effects of either carvedilol or rosuvastatin, both compared with placebo, for treating heart failure in people with Chagas disease. The results were based on three trials with a high risk of bias, involving 108 participants.

Therefore, current evidence neither supports nor refutes prescription of these medications for people suffering from heart failure associated with Chagas cardiomyopathy. Until randomised clinical trials provide evidence of a treatment effect, and the trade-off between potential benefits and harms is established, policy-makers, clinicians, and academics should be cautious when recommending or administering either carvedilol or rosuvastatin for the treatment of heart failure in people with Chagas disease.

This updated Cochrane review does not provide evidence for other conventional pharmacological interventions for treating heart failure in people with Chagas cardiomyopathy.

Implications for research

This updated Cochrane review has highlighted a need for large, well-designed, high-quality randomised trials to assess the benefits and harms of pharmacological interventions for treating heart failure in people with Chagas cardiomyopathy. The potential trials should include main clinical outcomes (patient-oriented outcomes) such as all-cause mortality, quality of life, overall survival, cardiac mortality at 30 days, time-to-heart decompensation, disease-free period (at 30 days, 60 days, and 90 days), hospital readmissions (heart failure- or adverse event-related), adherence grade, adverse events, and digoxin toxicity.

The trials should be conducted by independent researchers and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement to improve the quality of reporting of efficacy, and obtain better reports of harms in clinical research (Ioannidis 2004; Moher 2010; Turner 2012). Future trials should be planned in accordance with the recommendations of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT; Chan 2013a; Chan 2013b) and the Foundation of Patient-Centered Outcomes Research (Basch 2012; Gabriel 2012).

ACKNOWLEDGEMENTS

We thank the Center of Disease Control (Atlanta, USA) for permission to reproduce Figure 1.

For this update, we thank Verônica Abdala, Gerente de Servicios de Información y Producción de Fuentes de Información from BIREME/OPS/OMS, who sent us the full text of the PhD thesis Diniz 2004. We want to express our gratitude to Ricardo Hidalgo, Daniel Simancas and Susana Nicola for their contributions in the first version of this Cochrane review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Andrade 2012

Methods	1. Design: parallel (2 arms) 2. Country: Brazil 3. Multicenter: unclear 4. International: no 5. Follow-up period: unknown 6. Treatment duration: 4 weeks
Participants	Randomised: 39 1. Rosuvastatin: 23 2. Placebo: 16 Trial authors did not report information on: age, gender, inclusion or exclusion criteria, or New York Heart Association stage.
Interventions	1. Rosuvastatin: 20 mg/day. Manufacturer: not given. 2. Placebo (physical and chemical properties): not reported. 3. Treatment duration: four weeks. Cointervention: not given.
Outcomes	1. Serum markers of inflammation (C Reactive Protein) 2. Quality of life Trial authors did not classify their outcomes as primary or secondary.
Notes	1. All information was gathered from an abstract. 2. Date of trial: not reported. 3. Trial register number: not reported. 4. Sample size estimation a priori: not reported. 5. Sponsor: not reported. 6. Role of sponsor: does not apply. We sent an e-mail to the trial author on 23 January 2015.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "... we randomized..." (Page 90).

Andrade 2012 *(Continued)*

		Insufficient information to permit judgment of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote "...double-blind, placebo-controlled..." (page 90) Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote "...double-blind, placebo-controlled..." (page 90) Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	High risk	The study report failed to include results for a key outcome that would be expected to have been reported for such a study
Other bias	High risk	Bias in the presentation of the data.

Botoni 2007

Methods	1. Design: parallel (2 arms) 2. Country: Brazil 3. Multicenter: no 4. International: no 5. Follow-up period: 4 months
Participants	• Enrolled: 42 • Lost participants before randomisation: 7.1% (3/42) • Randomized: 39 1. Carvedilol group: 19 2. Placebo group: 20 • Receiving drug: 39 1. Carvedilol group: 19 (48.7%) 2. Placebo group: 20 (51.3%) • Lost post randomisation: 24% (3/39) 1. Carvedilol group: 5.2% (1/19) 2. Placebo group: 10% (2/20) 3. Imbalance between comparison groups: 4.8% • Analysed: 1. Carvedilol group: 18 (95%) 2. Placebo group: 18 (90%) • Age (years SD): 1. Overall group: Baseline: 47.8 (10.4) 2. Overall group: After RAS inhibition: 48.2 (10.4) • Gender (male): 1. Overall group: baseline: 71.4% (30/42) 2. Overall group: after RAS inhibition: 69.2% (27/39) • Inclusion criteria:

Botoni 2007 *(Continued)*

	1. Positive for *T. cruzi* as confirmed by 2 or more serological tests (indirect immunofluorescence, ELISA, indirect hemagglutination); 2. Cardiomyopathy when at least 3 of the following criteria were fulfilled: Left ventricular end diastolic diameter (LVDD) N55 mm; LVDD/body surface area N2.7cm/m^2; left ventricular ejection fraction (LVEF) b55%; QRS interval N120 ms; echocardiographic evidence of diffuse or segmental systolic wall motion abnormalities. • Exclusion criteria: 1. Pregnant; 2. Using any beta-blocker; 3. Hypertension, diabetes mellitus, thyroid dysfunction, chronic obstructive pulmonary disease, asthma, renal or hepatic failure.
Interventions	1. Experimental: carvedilol 3.125 mg and up-titrated every 15 days to 25 mg twice a day. Duration: 4 months 2. Control: placebo. Details not stated. Nature of placebo: not stated. 3. Co-intervention: enalapril was started at 5 mg and up-titrated weekly to 20 mg twice a day. Spironolactone was given at a dose of 25 mg once a day. In cases of intolerance, characterized by cough or angioedema, enalapril was replaced with losartan 50 mg once a day. (page 544.e2)
Outcomes	• Primary: 1. Change in left ventricular ejection fraction. • Secondary: 1. Changes in other echocardiographic parameters; 2. Framingham score; 3. Quality of life (36-item Short-Form Health Survey); 4. New York Heart Association class; 5. Radiographic indices; 6. Brain natriuretic peptide levels, chemokines; 7. Safety.
Notes	1. ClinicalTrials.gov Identifier: NCT01557140 2. Sample size estimation a priori: yes 3. Date of Trial: May 2003 and March 2004. 4. Sponsor: Baldacci Pharmaceutical Laboratory and FUNED (Fundacao Ezequiel Dias) 5. Rol of sponsor: carvedilol and placebo were supplied by Baldacci Pharmaceutical Laboratory and FUNED (Fundacao Ezequiel Dias), respectively 6. Conflict of interest: none stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was achieved by each patient selecting an envelope that contained a number. The number was sent to the pharmacist, who provided the appropriate medication box to each patient. The medication container was identified only by each patient's name." (page 544e2)
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was achieved by each patient selecting an envelope that contained a number. The number was sent to the pharmacist, who provided the appropriate medication box to each patient. The medication container was identified only by each patient's name." (page 544e2)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "…the patients were assigned in a double blind fashion to receive either placebo or carvedilol... each patient selecting an envelope that contained a number. The number was sent to the pharmacist, who provided the appro-

Botoni 2007 *(Continued)*

		priate medication box to each patient. The medication container was identified only by each patient's name." (page 544e2)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss of participants before randomisation: 7.1% (3/42) Lost post-randomisation: 24% (3/39) Carvedilol group: 5.2% (1/19) Placebo group: 10% (2/20) Imbalance between comparison groups: 4.8% Quote: “Three patients were lost in phase 1, each because of sudden death, poorly controlled ventricular tachycardia, and noncompliance. Of the 39 patients who entered phase II, 20 were randomised to receive placebo and 19 were randomised to receive carvedilol. Two patients from the placebo group were lost, each because of death caused by intractable HF and intolerable symptoms. One patient from the carvedilol group died suddenly." (page 544e5-544e6)
Selective reporting (reporting bias)	High risk	The study report failed to include results for a key outcome that would be expected to have been reported for such a study.
Other bias	High risk	Industry bias

Diniz 2004

Methods	1. Design: parallel (2 arms) 2. Country: Brazil 3. Multicenter: 4. International: no 5. Intention-to-treat for mortality from any cause: yes. 6. Follow-up period: 6 months
Participants	• Enrolled: 63 • Randomized: 30 1. Carvedilol group: 15 2. Placebo group: 15 • Participants receiving drug: 30 1. Carvedilol group: 15 2. Placebo group: 15 • Lost post-randomisation: 10% (3/30) 1. Carvedilol group: 6.6% (1/15) 2. Placebo group: 13.2% (2/15) 3. Imbalance between comparison groups: 6.6% • Analysed: 1. Carvedilol group: 80% (12/15) 2. Placebo group: 86.6% (13/15) 3. Differences between comparison groups: 6.6% • Age (years, mean (SD)):

Diniz 2004 *(Continued)*

1. Carvedilol group: 46.2 (7.62)
2. Placebo group: 51.06 (6.11)

- Follow up (weeks, mean (SD)):

1. Carvedilol group: 28.78 (1.48)
2. Placebo group: 29.5 (1.79)

- Gender (male):

1. Carvedilol group: 83.3% (12/15)
2. Placebo group: 73.3% (11/15)

- Inclusion criteria:

1. Age 18 to 65 years;
2. New York Heart Association: II to IV;
3. Ejection fraction and left ventricular fraction using isotopic ventriculography: ≤ 35%;
4. All of the participants were already using digitalis, diuretics, angiotensin converting enzyme inhibitors and spironolactone, and may or may not have been using amiodarone and anticoagulant.

- Exclusion criteria:

1. Functional class IV requiring use of vasoactive drugs;
2. Severe bradycardia ≤ 50 beats per minute;
3. Atrioventricular blocks 2nd or 3rd degree, without permanent pacemaker;
4. Systolic blood pressure ≤ 60 mm Hg;
5. Comorbidities, such as renal insufficiency (creatinine ≥ 3.0), or hepatic disease, serious bronchial asthma, or chronic obstructive pulmonary disease;
6. Pregnant or not using contraception.

Interventions	1. Carvedilol group: 3.125 mg/day and up-titrated every 8 days to 50 mg/day. Duration: 4 months 2. Placebo: details not stated 3. Nature of placebo: not stated
Outcomes	• Outcomes were not explicitly described as primary or secondary: 1. Functional class; 2. Overall survival; 3. Quality of life (Minnesota Living with Heart Failure questionnaire (MLHFQ)); 4. Blood pressure; 5. Heart rate; 6. Electrocardiogram parameters; 7. Ventricular remodeling; 8. Change in left ventricular ejection fraction; 9. Change in noradrenaline and brain natriuretic peptide levels; 10. Adverse events.
Notes	1. Clinical trial number: not applicable 2. Sample size estimation a priori: not given 3. Trial conduction date: not given 4. Sponsor: not stated 5. Conflict of interest: not stated 6. Data were gathered from PhD thesis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'

Diniz 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss post-randomisation: 16.6%. Comment: this trial had a small sample size; therefore, 16.6% could be considered a high loss of participants.
Selective reporting (reporting bias)	Low risk	This trial included four important outcomes: mortality, adverse events, quality of life, and safety.
Other bias	Low risk	-

SD = standard deviation
≥ = greater than or equal to
≤ = less than or equal to

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bestetti 2011	Case report.
Dávila 2002a	Case report.
Dávila 2008	Editorial.
Issa 2010	Non-randomised clinical trial.

Characteristics of ongoing studies *[ordered by study ID]*

NCT00323973

Trial name or title	1. Scientific title: A randomized double-blind placebo force-titration controlled study with bisoprolol in patients with chronic heart failure secondary to Chagas cardiomyopathy. 2. Public title: Chagas cardiomyopathy bisoprolol intervention study: Charity.
Methods	• Randomised, placebo controlled trial, parallel design (2 arms). • Double blind (Subject, caregiver, investigator, outcomes assessor). • Primary purpose: treatment • Inclusion criteria: 1. Males or females aged 18 to 70 years; 2. Heart failure symptoms NYHA functional class II to IV; 3. Left ventricular ejection fraction < 40%, determined by bi-dimensional echocardiography using modified Simpson's rule for ventricular volumes;

NCT00323973 *(Continued)*

4. Subjects must be on standard and stable outpatient doses of ACEIs or angiotensin II receptor antagonist for at least four weeks;
5. Subjects receiving diuretics must be on a stable dose for at least two weeks;
6. Clinical Euvolemia: as evidenced by absence of rales, no pleural effusion or ascites and no more than minimal peripheric edema.

- Exclusion criteria:

1. CHF due to ischaemic heart disease, valvular disease or any other etiology different than CD;
2. Severe aortic insufficiency;
3. Baseline advanced AV block defined as Mobitz type 2 or third degree AV block;
4. Serum creatinine > 2.5 mg/dl;
5. Resting heart rate < 45 beats per minute;
6. Known malignancy and other severe disease which shorten life expectancy < 6 months;
7. Subjects with contraindications for beta-blockers: severe obstructive chronic pulmonary disease, asthma, severe pulmonary hypertension, type 1 diabetes mellitus, or history of hypoglycaemia;
8. Suspected or confirmed chronic infectious disease including HIV and hepatitis B;
9. History of active substance or alcohol abuse within the last year;
10. Clinically significant psychiatric illness, which can negatively affect subject compliance and participation in the trial;
11. Pregnancy or lactation;
12. Organic disease or gastrointestinal surgery, which can affect the oral absorption and pharmacodynamics of the medication under study;
13. Enrollment and participation in another active treatment trial within the previous month;
14. Failure to provide written informed consent.

Participants	1. Age minimum: 18 years 2. Age maximum: 70 years 3. Gender: Both 4. Chagas cardiomyopathy and chronic heart failure
Interventions	1. Experimental: bisoprolol: 5 mg (Quiros 2006). 2. Control: placebo.
Outcomes	• Primary: 1. Bradycardia requiring pacemaker implantation; 2. Clinically significant sustained monomorphic ventricular tachycardia causing syncope: sustained ventricular tachycardia or ventricular fibrillation; 3. Hospital admission caused by heart failure; 4. Major adverse cardiovascular events: stroke, systemic embolism, resuscitated sudden death. • Secondary: 1. Heart failure worsening or mortality related with chronic heart failure; 2. Need for Implantable cardioverter-defibrillator, cardiac resynchronisation therapy or pacemaker therapy; 3. New AV block; 4. Non-cardiovascular death; 5. Perceived quality of life worsening.
Starting date	July 2003.
Contact information	Carlos A Morillo, MD, FRCPC. Fundación Cardiovascular de Colombia.
Notes	1. Date of registration: 05/05/2006. 2. Sponsor: Fundación Cardiovascular de Colombia. 3. Target sample: 500. 4. Recruitment status: completed.

NCT00323973 *(Continued)*

5. Study drug and placebo provided by Merck Colombia (Quiros 2006).

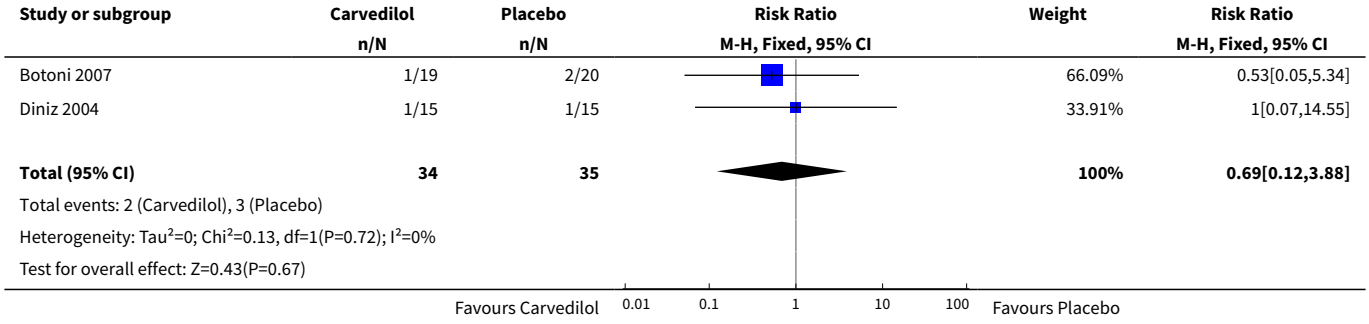
We contacted the lead author on 19 November 2014.

DATA AND ANALYSES

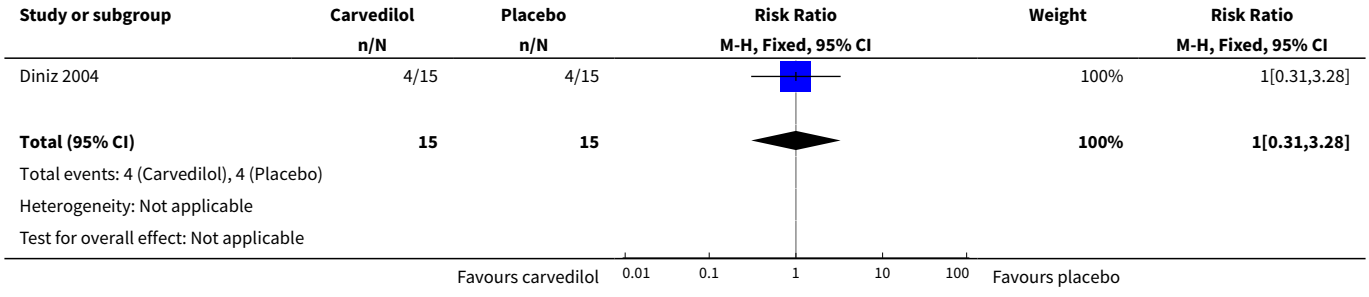
Comparison 1. Carvedilol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	69	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.12, 3.88]
2 Hospital readmissions	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.31, 3.28]
3 Quality of life	1	30	Mean Difference (IV, Fixed, 95% CI)	-14.74 [-24.75, -4.73]
4 Adverse events	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.67, 1.27]

Analysis 1.1. Comparison 1 Carvedilol versus placebo, Outcome 1 All-cause mortality.

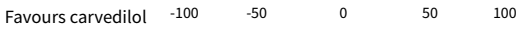


Analysis 1.2. Comparison 1 Carvedilol versus placebo, Outcome 2 Hospital readmissions.



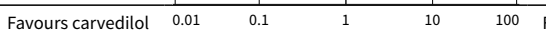
Analysis 1.3. Comparison 1 Carvedilol versus placebo, Outcome 3 Quality of life.

Study or subgroup	Carvedilol N	Carvedilol Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Diniz 2004	15	23.5 (8.7)	15	38.3 (17.8)		100%	-14.74[-24.75,-4.73]
Total ***	**15**		**15**			**100%**	**-14.74[-24.75,-4.73]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.89(P=0)							



Analysis 1.4. Comparison 1 Carvedilol versus placebo, Outcome 4 Adverse events.

Study or subgroup	Carvedilol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Diniz 2004	12/15	13/15		100%	0.92[0.67,1.27]
Total (95% CI)	**15**	**15**		**100%**	**0.92[0.67,1.27]**
Total events: 12 (Carvedilol), 13 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.63)					



ADDITIONAL TABLES

Table 1. Burden of infected population in the Americas and by region

Variable (2005)	The Americas	Southern Cone	Andean Community	Centroamerican region and Belize	French Guayana, Guyana, Suriname	Mexico	USA
Population	531,432,850	259,805,650	113,545,000	39,656,200	1,397,000	107,029,000	-
Infected	7,694,500	4,451,900	1,168,000	806,600	18,000	1,100,000	100,000 to 200,000 people from endemic countries.
Congenital Chagas (annual)	14,385	9,365	2,600	1,300	20	1,100	-
Chagas cardiopathy	1,772,365	1,180,990	361,954	129,345	933	99,143	-

Data from OPS 2006.

Table 2. Epidemiology of infected immigrants from Latin America endemic countries to the world

Destination country	Year	Infected Immigrants from Latin American endemic countries	Immigrants with chronic Chagas disease
Australia	2006	3.8% of 80,522	Not described.
Canada	2006	3.5% of 156,960	Not described.
Japan	2007	80,912 immigrants from Brazil, 15,281 from Peru, and 19,413 from other South American countries whose country of origin was not identified. Information about infected people was not supplied.	Not described.
Europe (15 countries excluding Spain)	2005	2.9% of 483,074 legal Latin American immigrants.	Not described.
Spain	2007	5.2% of 1,678,711. 24 to 92 newborns born to South American *T. cruzi* infected mothers in Spain may have been congenitally infected with *T. cruzi* in 2007	17,390
USA	2000	1.9% of approximately 13 million Latin American immigrants.	49,157
	2007	2% of 17 million.	65,133

Data from Schmunis 2010.

Table 3. New York Heart Association (NYHA) Classification System

NYHA class I (mild)	NYHA class II (mild)	NYHA class III (moderate)	NYHA class IV (severe)
No limitation of physical activity - ordinary physical activity does not cause tiredness, heart palpitations, or shortness of breath.	Slight limitation of physical activity - comfortable at rest, but ordinary physical activity results in tiredness, heart palpitations, or shortness of breath.	Marked or noticeable limitations of physical activity - comfortable at rest, but less than ordinary physical activity causes tiredness, heart palpitations, or shortness of breath.	Severe limitation of physical activity - unable to carry out any physical activity without discomfort. Symptoms also present at rest. If any physical activity is undertaken, discomfort increases.

APPENDICES

Appendix 1. Adverse events commonly associated with drugs used for treatment of heart-failure

Angiotensin converting enzyme inhibitors (ACE inhibitors).(Adorisio 2006)(Hamad 2007)	**Angiotensin II receptor antagonists**(Adorisio 2006)	**Aldosterone receptor antagonists** (Hamad 2007)	**Inotropes** (Hamad 2007)	**Digitalis** (Adorisio 2006)	**Diuretics** (Hamad 2007)(Adorisio 2006)	**Vasodilators** (Adorisio 2006)	**Beta-adrenoceptor antagonists**(Adorisio 2006)	**Calcium antagonists**(Adorisio 2006)
1. By bradykinin potentiation (Dry cough (5% of patients), and Angioedema (0.1–0.2% of patients)). 2. Related to angiotensin suppression (hypotension, increase in serum creatinine and potassium). 3. Others are hypotension & electrolyte imbalance.	1. Hypotension. 2. Worsening renal function and hyperkalaemia.	1. Hyperkalemia. 2. Gynecomastia by spironolactone.	1. Arrhythmic events (atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation). 2. Severe hypotension.	1. Cardiac arrhythmias (e.g., ectopic and reentrant cardiac rhythms and heart block). 2. Gastrointestinal symptoms (e.g., anorexia, nausea, and vomiting). 3. Neurologic complaints (e.g., visual disturbances, disorientation, and confusion).	1. Metabolic abnormalities: 1.1. Contraction alkalosis. 1.2. Hyponatremia. 1.3. Hypokalemia. 1.4. Increased blood urea nitrogen and creatinine. 1.5. Hypomagnesemia. 2. Hemodynamic: 2.1. Hypotension and/or diminished renal perfusion.	1. Headache. 2. Dizziness.	1. Fatigue and weakness. 2. Symptomatic bradycardia. 3. Hypotension. 4. "Administration of β-blockers is contraindicated in patients with severe bronchospasm, symptomatic bradycardia, or advanced heart block in the absence of a pacemaker". 5. Bronchospam in patients with chronic obstructive pulmonary disease.	1. Negative inotropic effect and reflex neurohormonal activation. 2. Peripheral and pulmonary oedema.

Appendix 2. Medical glossary

TERM	DEFINITION	SOURCE
Chagas Disease	Infection with the protozoan parasite *Trypanosoma cruzi*, a form of trypanosomiasis endemic in Central and South America. It is named after the Brazilian physician Carlos Chagas, who discovered the parasite. Infection by the parasite (positive serologic result only) is distinguished from the clinical manifestations that develop years later, such as destruction of parasympathetic ganglia; Chagas cardiomyopathy; and dysfunction of the oesophagus or colon.	MeSH Database PubMed
Carvedilol	Antioxidant with alpha as well as beta blocking activity; structure in first source	MeSH Database PubMed
Chagas cardiomyopathy	A disease of the cardiac muscle developed subsequent to the initial protozoan infection by *Trypanosoma cruzi*. Fewer than 10% of those infected develop acute illness such as myocarditis (mostly in children). The disease then enters a latent phase without clinical symptoms until about 20 years later. Myocardial symptoms of advanced Chagas disease include conduction defects (heart block) and cardiomegaly	MeSH Database PubMed
Digoxin	A cardiotonic glycoside obtained mainly from Digitalis lanata; it consists of three sugars and the aglycone digoxigenin. Digoxin has positive inotropic and negative chronotropic activity. It is used to control ventricular rate in atrial fibrillation and in the management of congestive heart failure with atrial fibrillation. Its use in congestive heart failure and sinus rhythm is less certain. The margin between toxic and therapeutic doses is small.	MeSH Database PubMed
Dilated cardiomyopathy	A form of cardiac muscle disease that is characterized by ventricular dilation, ventricular dysfunction, and heart failure. Risk factors include smoking, alcohol consumption, hypertension, infection, pregnancy, and mutations in the LMNA gene encoding Lamin type A, a nuclear lamina protein.	MeSH Database PubMed
Heart failure	A heterogeneous condition in which the heart is unable to pump out sufficient blood to meet the metabolic need of the body. Heart failure can be caused by structural defects, functional abnormalities (ventricular dysfunction), or a sudden overload beyond its capacity. Chronic heart failure is more common than acute heart failure which results from sudden insult to cardiac function, such as myocardial infarction.	MeSH Database PubMed
Left ventricular ejection fraction	Ejection fraction is a measurement of the percentage of blood leaving your heart each time it contracts.	http://www.mayoclinic.com/health/ejection-fraction/AN00360 (accessed on 21 November 2011)
Renin-Angiotensin-System	A blood pressure regulating system of interacting components that include renin, angiotensinogen, angiotensin converting enzyme, angiotensin I, angiotensin II, and angiotensinase. Renin, an enzyme produced in the kidney, acts on angiotensinogen, an alpha-2 globulin produced by the liver, forming angiotensin I. Angiotensin-converting enzyme, contained in the lung, acts on angiotensin I in the plasma converting it to angiotensin II, an extremely powerful vasoconstrictor. Angiotensin II causes contraction of the arteriolar and renal vascular smooth muscle, leading to retention of salt and water in the kidneys and increased arterial blood pressure. In addition, angiotensin II stimulates the release of aldosterone from the adrenal cortex, which in turn also increases salt and water retention in the kidney. Angiotensin-converting enzyme	MeSH Database PubMed

(Continued)

	also breaks down bradykinin, a powerful vasodilator and component of the Kallikrein-Kinin system.	
Trypanosoma Cruzi	The agent of South American trypanosomiasis or Chagas disease. Its vertebrate hosts are man and various domestic and wild animals. Insects of several species are vectors.	MeSH Database PubMed

Appendix 3. Search strategies 2011

CENTRAL

#1 MeSH descriptor Chagas Disease explode all trees
#2 chagas*
#3 trypanosom*
#4 MeSH descriptor Trypanosomiasis, this term only
#5 cruzi
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Heart Failure explode all trees
#8 heart next failure*
#9 cardiac next failure*
#10 myocardial next failure*
#11 heart next incompet*
#12 cardi* next incompet*
#13 myocard* next incompet*
#14 heart next insufficien*
#15 cardi* next insufficien*
#16 myocard* next insufficien*
#17 cardi* next shock
#18 myocard* next shock
#19 heart next arrest*
#20 cardi* next arrest*
#21 myocard* next arrest*
#22 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#23 (#16 OR #17 OR #18 OR #19 OR #20 OR #21)
#24 (#22 OR #23)
#25 (#6 AND #24)

MEDLINE

1. exp Chagas Disease/
2. chagas*.tw.
3. cruzi*.tw.
4. trypanosom*.tw.
5. Trypanosomiasis/
6. or/1-5
7. exp Heart Failure/
8. ((cardi* or heart* or myocard*) adj2 (failure* or incompet* or insufficien* or shock or arrest*)).tw.
9. 7 or 8
10. 6 and 9
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. randomized.ab.
14. placebo.ab.
15. drug therapy.fs.
16. randomly.ab.
17. trial.ab.
18. groups.ab.
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp animals/ not humans.sh.

21. 19 not 20
22. 10 and 21

EMBASE

1. Chagas disease/
2. cardiomyopathy/
3. chagas*.tw.
4. cruzi*.tw.
5. trypanosomiasis/
6. trypanosom*.tw.
7. or/1-6
8. exp heart failure/
9. ((cardi* or heart* or myocard*) adj2 (failure* or incompet* or insufficien* or shock or arrest*)).tw.
10. 8 or 9
11. 7 and 10
12. random$.tw.
13. factorial$.tw.
14. crossover$.tw.
15. cross over$.tw.
16. cross-over$.tw.
17. placebo$.tw.
18. (doubl$ adj blind$).tw.
19. (singl$ adj blind$).tw.
20. assign$.tw.
21. allocat$.tw.
22. volunteer$.tw.
23. crossover procedure/
24. double blind procedure/
25. randomized controlled trial/
26. single blind procedure/
27. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. (animal/ or nonhuman/) not human/
29. 27 not 28
30. 11 and 29
31. limit 30 to embase

Web of Science

1. TS=chagas*
2. TS=cruzi*
3. TS=trypanosom*
4. 3 OR 2 OR 1
5. TS=((cardi* or heart* or myocard*) SAME (failure* or incompet* or insufficien* or shock or arrest*))
6. 4 AND 5

LILACS

(heart or cardiac) and failure [Words] or "HEART FAILURE" [Subject descriptor] and chagas$ or cruzi$ or trypanosom$ [Words]

WHO ICTRP

chagas* and heart or chagas* and cardi*

clinicaltrials.gov

chagas and (heart or cardiac)

Appendix 4. Search strategies 2016

CENTRAL

#1 MeSH descriptor Chagas Disease explode all trees

#2 chagas*

#3 trypanosom*

#4 MeSH descriptor Trypanosomiasis, this term only

#5 cruzi

#6 (#1 OR #2 OR #3 OR #4 OR #5)

#7 MeSH descriptor Heart Failure explode all trees

#8 heart next failure*

#9 cardiac next failure*

#10 myocardial next failure*

#11 heart next incompet*

#12 cardi* next incompet*

#13 myocard* next incompet*

#14 heart next insufficien*

#15 cardi* next insufficien*

#16 myocard* next insufficien*

#17 cardi* next shock

#18 myocard* next shock

#19 heart next arrest*

#20 cardi* next arrest*

#21 myocard* next arrest*

#22 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)

#23 (#16 OR #17 OR #18 OR #19 OR #20 OR #21)

#24 (#22 OR #23)

#25 (#6 AND #24)

MEDLINE OVID

The Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format has been applied (Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org)

1. exp Chagas Disease/

2. chagas*.tw.

3. cruzi*.tw.

4. trypanosom*.tw.

5. Trypanosomiasis/

6. or/1-5

7. exp Heart Failure/

8. ((cardi* or heart* or myocard*) adj2 (failure* or incompet* or insufficien* or shock or arrest*)).tw.

9. 7 or 8

10. 6 and 9

11. randomized controlled trial.pt.

12. controlled clinical trial.pt.

13. randomized.ab.

14. placebo.ab.

15. drug therapy.fs.

16. randomly.ab.

17. trial.ab.

18. groups.ab.

19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. exp animals/ not humans.sh.

21. 19 not 20

22. 10 and 21

EMBASE OVID

The Cochrane RCT filter for OVID EMBASE has been applied (Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org)

1. Chagas disease/

2. cardiomyopathy/

3. chagas*.tw.

4. cruzi*.tw.

5. trypanosomiasis/

6. trypanosom*.tw.

7. or/1-6

8. exp heart failure/

9. ((cardi* or heart* or myocard*) adj2 (failure* or incompet* or insufficien* or shock or arrest*)).tw.

10. 8 or 9

11. 7 and 10

12. random$.tw.

13. factorial$.tw.

14. crossover$.tw.

15. cross over$.tw.

16. cross-over$.tw.

17. placebo$.tw.

18. (doubl$ adj blind$).tw.

19. (singl$ adj blind$).tw.

20. assign$.tw.

21. allocat$.tw.

22. volunteer$.tw.

23. crossover procedure/

24. double blind procedure/

25. randomized controlled trial/

26. single blind procedure/

27. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. (animal/ or nonhuman/) not human/

29. 27 not 28

30. 11 and 29

31. limit 30 to embase

ISI Web of Science

No RCT filter has been applied to this search. The reasonably low number of hits does not justify the risk of missing relevant papers by applying a RCT filter which has not been reliably tested and verified in its sensitivity and precision.

6 #5 AND #4

5 TS=((cardi* or heart* or myocard*) SAME (failure* or incompet* or insufficien* or shock or arrest*))

4 #3 OR #2 OR #1

3 TS=trypanosom*

2 TS=cruzi*

1 TS=chagas*

LILACS

(heart or cardiac) and failure [Words] or "HEART FAILURE" [Subject descriptor] and chagas$ or cruzi$ or trypanosom$ [Words]

WHO ICTRP Search Portal

Search string: chagas* and heart or chagas* and cardi*

Clinicaltrials.gov

Search string: chagas and (heart or cardiac)

WHAT'S NEW

Date	Event	Description
23 March 2016	New citation required but conclusions have not changed	One new trial identified for inclusion.
15 February 2016	New search has been performed	Searches have been re-run and are up-to-date to February 2016.

CONTRIBUTIONS OF AUTHORS

AMC took the lead in writing up the Cochrane Review.

JK: revised the Cochrane Review.

DECLARATIONS OF INTEREST

In 2004 Arturo Martí-Carvajal was employed by Eli Lilly to run a four-hour workshop on 'how to critically appraise clinical trials on osteoporosis and how to teach this'. This activity was not related to his work with The Cochrane Collaboration or any Cochrane review.

In 2007 Arturo Martí-Carvajal was employed by Merck to run a four-hour workshop on 'how to critically appraise clinical trials and how to teach this'. This activity was not related to his work with The Cochrane Collaboration or any Cochrane review.

Joey Kwong has no known conflict of interest

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Iberoamerican Cochrane Network, Spain.

  Academic
- Cochrane Heart Group, UK.

  Academic.

INDEX TERMS

Medical Subject Headings (MeSH)

Carbazoles [*therapeutic use]; Cardiotonic Agents [adverse effects] [*therapeutic use]; Carvedilol; Chagas Cardiomyopathy [*complications]; Heart Failure [*drug therapy] [etiology]; Propanolamines [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Rosuvastatin Calcium [*therapeutic use]; Survival Analysis

MeSH check words

Adult; Humans; Middle Aged