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

Hidalgo R, Martí-Carvajal AJ, Kwong JSW, Simancas-Racines D, Nicola S

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Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy

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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 patients with Chagas disease.

Objectives

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

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library) Issue 1, 2011, MEDLINE (Ovid), EMBASE (Ovid), LILACS and ISI Web of Science to April 2011. We checked the reference lists of included papers. No language restrictions were applied.

Selection criteria

We included randomized clinical trials assessing the effects of pharmacological interventions for treating heart failure in adult patients (≥18 years) with symptomatic heart failure (New York Heart Association class II to IV), irrespective of the left ventricular ejection fraction stage, reduced or preserved, with Chagas cardiomyopathy. No limits were applied with respect to the follow-up duration. Primary outcomes were all-cause mortality, cardiovascular mortality at 30 days, time to heart decompensation and 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 risks (RR) and the respective 95% confidence intervals (CIs) for dichotomous outcomes. We measured statistical heterogeneity using the I² statistic. We used a fixed-effect model to synthesize the findings. We contacted authors for additional data.
Main results

We included two randomized clinical trials involving 69 participants. Both trials compared carvedilol against placebo, and had a high risk of bias. Carvedilol compared with placebo did not significantly affect all-cause mortality (2/34 (5.88%) versus 3/35 (5.87%); pooled RR 0.69, 95% CI 0.12 to 3.88, I² = 0%). None of the trials reported on cardiovascular mortality, time to heart decompensation or disease-free period. Evidence on the adverse effects of carvedilol is inconclusive.

Authors’ conclusions

This Cochrane review has found a lack of evidence on the effects of carvedilol for treating heart failure in patients with Chagas disease. The two included trials were underpowered and had a high risk of bias. There are no conclusive data to support the use of carvedilol for treating Chagas cardiomyopathy. Unless randomized 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 and administering carvedilol for treating heart failure in patients with Chagas disease. The efficacy and safety of other pharmacological interventions for treating heart failure in patients with Chagas disease is unknown.

Plain Language Summary

Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy

Named in honor of the Brazilian physician Carlos Chagas, Chagas disease is caused by the Trypanosoma cruzi parasite which needs humans for the start of its life cycle. It is common in Latin and Central America and leads to Chagas cardiomyopathy (heart muscle disease), and 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, and 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 cardiopathy. Furthermore, infected people from endemic countries in Latin America are migrating throughout the world. As a result, what was thought to be an American health problem 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. There is a need to assess the benefits and harms of pharmacological interventions for Chagas disease-related heart failure, due to fundamental differences in the affected populations. This Cochrane review identified two randomized clinical trials of these interventions, involving 69 participants. These trials evaluated the use of carvedilol against placebo in the treatment of heart failure in people with Chagas cardiomyopathy. We found no significant difference between carvedilol and placebo in reducing all-cause mortality. The safety profile of carvedilol for Chagas cardiomyopathy remains unclear. These results are based on trials at high risk of bias. The existing evidence from available clinical trials does not support the use of carvedilol in treating heart failure in patients with Chagas cardiomyopathy. Further investigation is warranted to investigate the exact applicability of conventional heart failure treatment agents in Chagas cardiomyopathy. Preventive approaches such as control of the Triatome bug and ecological niche studies are key to reducing the incidence of Chagas disease.
**SUMMARY OF FINDINGS FOR THE MAIN COMPARISON**

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
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<td>Assumed risk</td>
<td>Corresponding risk</td>
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<td>Placebo</td>
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<td>Carvedilol</td>
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<tr>
<td><strong>Overall mortality</strong></td>
<td>Study population</td>
<td>RR 0.69 (0.12 to 3.88)</td>
<td>69 (2 studies)</td>
<td>⊘☺☺☺ very low</td>
<td>2,3,4</td>
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<td>Follow-up: mean 5 months</td>
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<td></td>
<td>86 per 1000</td>
<td>59 per 1000 (10 to 333)</td>
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<td>Moderate</td>
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<td>30 day cardiovascular mortality</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td></td>
<td>Time to heart decompensation</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
<td>Disease-free period at 30, 60 and 90 days</td>
<td>NA</td>
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*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;
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<th>GRADE Working Group grades of evidence</th>
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<tr>
<td><strong>High quality:</strong> Further research is very unlikely to change our confidence in the estimate of effect.</td>
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<tr>
<td><strong>Moderate quality:</strong> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td><strong>Low quality:</strong> 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.</td>
</tr>
<tr>
<td><strong>Very low quality:</strong> We are very uncertain about the estimate.</td>
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1. Two Brazilian randomized clinical trials.
2. Random sequence generation, allocation concealment and blinding at any level: unclear risk of bias.
3. I²: 0%
4. 69 participants with 5 events.
5. Not available.
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) (Figure 1) and is the major cause of infectious myocarditis worldwide (Andrade 2011).

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

Life cycle Trypanosoma cruzi life cycle starts in an animal reservoir

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 (Mendez 2001) 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 (Gascón 2007) 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 what was thought to be 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; therefore, T. cruzi causes a substantial disease burden in the United States (Bern 2009). Preventive approaches such as control of the Triatominus bug and ecological niche studies are key to reducing the incidence of Chagas disease (Carrasco 2012; Cruz-Pacheco 2012; Gurgel-Goncalves 2012; Yamagata 2006).

**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 as a paradigm of infection-induced autoimmune disease (Gironés 2005; Gironés 2007). Autoimmune reactions seem to be mediated by a T. cruzi protein, Trypanosoma cruzi calreticulin (Ribeiro 2009). Recently, the role of autoantibodies in the physiopathology of Chagas disease has been described (Medei 2008). However, there is strong evidence that it develops as a result of additive and even synergistic effects of several distinct mechanisms, rather than of one factor (Bonney 2008). In conclusion, 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 (Biolol 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).

**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). These syndromes are caused by inflammatory lesions and an immune response, particularly mediated by CD4(+), CD8(+), IL2 and IL4, 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).

In the acute phase, death is mostly caused by myocarditis, and in the chronic phase, by irreversible cardiomyopathy (Punukollu 2007). 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 2012). 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 2012).

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 death has led to the following recommended approaches (Rassi Jr 2010):

1. Possibly antiparasitic drug for low stage without New York Heart Association (NYHA) class III or IV, left ventricular systolic dysfunction (echocardiography) or cardiomegaly (chest radiography), or both, and non-sustained ventricular tachycardia (24-h Holter monitoring).

2. Possibly treat with amiodarone and an antiparasitic drug for intermediate stage without NYHA class III or IV, left ventricular systolic dysfunction (echocardiography) or cardiomegaly (chest radiography), or both; but, with non-sustained ventricular tachycardia (24-h Holter monitoring).

3. Angiotensin-converting enzyme inhibitors, beta-blockers, diuretics (for selected patients), possibly treat with an antiparasitic drug for intermediate stage without NYHA class III or IV, with left ventricular systolic dysfunction (echocardiography) or cardiomegaly (chest radiography), or...
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both; and absent non-sustained ventricular tachycardia (24-h Holter monitoring).

4. Angiotensin-converting enzyme inhibitors, amiodarone, diuretics (for selected patients), beta-blockers (if clinically tolerated), possibly treat with an implantable cardioverter defibrillator for high stage without NYHA class III or IV, with left ventricular systolic dysfunction (echocardiography) or cardiomegaly (chest radiography), or both; and with non-sustained ventricular tachycardia (24-h Holter monitoring).

5. Angiotensin-converting enzyme inhibitors, spironolactone, amiodarone, diuretics, digitalis, beta-blockers (if clinically tolerated), heart transplantation (if clinically tolerated), possibly treat with an implantable cardioverter defibrillator for high stage with NYHA class III or IV, with left ventricular systolic dysfunction (echocardiography) or cardiomegaly (chest radiography), or both; and with non-sustained ventricular tachycardia (24-h Holter monitoring).

All of the above pharmacological approaches are based on expert opinion rather than evidence of benefit.

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 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 overt Chagas disease (Reyes 2005) and the existing evidence on its prevention indicates a need to test these or 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 of 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 activation of two types of receptors on the cell surface: angiotensin II type 1 and angiotensin II type 2. Angiotensin II receptor antagonists type 1 mediates vasoconstriction and stimulates aldosterone and vasopressin secretion which causes 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 vasodilatation 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 the 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 sensitizers 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:

1. Chagas disease is a major cause of morbidity and mortality in Latin America (Rassi 2000; Schmunis 2010).
2. Although there are published systematic reviews of the effect of trypanocidal drugs for the different stages of Chagas disease (Reyes 2005; Villar 2002), no systematic review of the pharmacological interventions commonly used in chronic heart failure has been conducted for Chagas disease.

3. 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). Therefore, there are uncertainties in 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.

4. 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 (Dobarro 2008; Gascón 2010; Gascón 2007; Muñoz 2009; Soriano 2009; Table 2).

5. A review is needed to improve patient care through the therapeutic decision making based on the best evidence-based treatment.

This Cochrane review updates current knowledge and resolve any uncertainties. Our research question was: "What is the benefit and harm of pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy?" Appendix 2 provides a medical glossary.

**OBJECTIVES**

To assess the benefits and harms of current pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy disease, mainly on the clinical end points such as: all-cause mortality, overall survival, quality of life, adverse events.

**METHODS**

Criteria for considering studies for this review

**Types of studies**

Randomized clinical trials irrespective of publication status (trials may be unpublished or published as an article, an abstract, or a letter). No language, country and sample size limitations were applied. We included trials conducted in either a hospital or community setting, or both. No limits were applied with respect to period of follow-up.

**Types of participants**

Adults (≥18 years) with symptomatic heart failure (New York Heart Association class II to IV) (Table 3) irrespective of the left ventricular ejection fraction stage, reduced or preserved, in patients with Chagas cardiomyopathy. We considered trials evaluating pharmacotherapies in a general heart failure population including 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.
  7. Vasodilators: isosorbide dinitrate, hydralazine, nitroprusside, nesiritide (recombinant human B-type natriuretic peptide)
  9. Calcium sensitizers: 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 manifestations are clearly more common above 2.5 nmol/L (2.0 µg/L). Extra-cardiac manifestation including visual disturbances, anorexia, nausea, vomiting. Cardiac manifestations include rhythm disturbances (Bauman 2006)

Data extraction and management

Two authors (SN, DS) independently extracted data from the selected trials using a standardized data extraction form. Any disagreements were resolved through discussion with the other authors (RH, AM-C). We also contacted Dr Viana Zuza Diniz who sent us the full text of her PhD thesis (Diniz 2004).

Assessment of risk of bias in included studies

Three authors (RH, AM-C, and DS) independently assessed the risk of bias of each trial using a simple form following the domain-based evaluation as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). This section was checked by Joey Kwong. We assessed the following domains:
1. Generation of the allocation sequence.
2. Concealment of allocation.
3. Blinding (of participants, personnel and outcome assessors).
4. Incomplete outcome data.
5. Selective outcome reporting.
6. Other bias (baseline imbalance, early stopping, drug company involvement) (Gurusamy 2009; Ioannidis 2008a; Ioannidis 2008b).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library) (Issue 1 of 4, 2011), MEDLINE (Ovid) (1948 to March Week 5 2011), EMBASE (Ovid) (1947 to 2011 Week 14), LILACS (1986 to April 2011) and ISI Web of Science (1970 to April 2011) using the search strategies as reported in (Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7). We used RCT filters recommended by the Cochrane Collaboration to search MEDLINE and EMBASE (Lefebvre 2011).

Searching other resources

We searched the Clinical Trials Search Portal of the World Health Organization (http://apps.who.int/trialsearch/) for ongoing and unpublished trials (Appendix 8). We also searched Clinicaltrials.gov for ongoing and other relevant trials (Appendix 9). We also checked the reference lists of all the trials identified by the above methods.

Data collection and analysis

Selection of studies

Two authors (SD, DS) independently assessed each reference to see whether it met the inclusion criteria. Any disagreements were resolved through discussion with other co-authors (RH, AM-C).
High risk, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomized.

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

We further examined the percentages of dropouts overall in each trial and per randomization arm and we evaluated whether intention-to-treat analysis was performed or could be performed from the published information.

**Selective outcome reporting**
- Low risk, if pre-defined or clinically relevant and reasonably expected outcomes were reported on.
- Unclear risk, if not all pre-defined or clinically relevant and reasonably expected outcomes were reported on or were not reported on fully, 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 on; data on these outcomes were likely to have been recorded.

**Other bias (Baseline imbalance, early stopping, drug company involvement):**
- Low risk, the trial appears to be free of other components that could put it at risk of bias.
- Unclear risk, the trial may or may not be free of other components that could put it at risk of bias.
- High risk, 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 low-risk of bias trials to be those that adequately generated their allocation sequence; had adequate allocation concealment, adequate blinding, adequate 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 with 95% confidence intervals for the following binary outcomes: all-cause mortality and safety.

**Dealing with missing data**
We assessed the percentages of dropouts overall for each included trial and per each randomization arm and we 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.

**Assessment of heterogeneity**
We quantified statistical heterogeneity using the I² 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 (I² > 50%) we attempted to identify the possible causes of heterogeneity (Higgins 2011).

**Assessment of reporting biases**
We did not assess publication bias by a funnel plot because we included only two trials. For future updates, we will attempt to assess whether the review is subject to publication bias by using a funnel plot if ≥10 trials are included.

**Data synthesis**
We pooled the results from the trials using Review Manager software (RevMan 2011). We summarized findings using a fixed-effect model according 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) system to assess the quality of the body of evidence associated with specific outcomes (all-cause mortality) in our review (Balshem 2011; Brozek...
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).

For future updates, we will also assess the quality of the body of evidence associated with specific outcomes (all-cause mortality, quality of life, overall survival, cardiac mortality at 30 days, time to heart decompensation, disease-free period (at 30 days, at 60 days and 90 days), hospital readmissions (heart failure- or adverse event-related), adherence grade, adverse events and digoxin toxicity).

**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. By 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: \( \leq 40\% \) 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 the effect of methodological quality (high versus low), route of administration (intramuscular versus intravenous), and patients’ characteristics. We will only conduct meta-regression if \( \geq 10 \) RCTs are included.

**Sensitivity analysis**

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

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**

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

**Results of the search**

We identified 1125 references using our search strategies, and assessed 6 of these in full text. A seventh study is ongoing (NCT00323973). We excluded four studies (see Excluded studies). We included two studies (Botoni 2007; Diniz 2004). These trials involved 69 randomized participants. They were both conducted in Brazil and published between 2004 and 2007 (see Figure 2).
Figure 2. Study flow diagram

1275 records identified through database searching
- CENTRAL Issue 1 of 4, 2011 (The Cochrane Library); B
- MEDLINE (Ovid) 1946 to March Week 5 2011: 126
- OVID EMBASE Classis + EMBASE 1947 to 2011 Week 14: 578
- ISI Web of Science: 397
- LILACS: 168

21 ongoing trials

1125 records after duplicates removed

1125 records screened

1119 records excluded

6 full-text articles assessed for eligibility, 1 ongoing trial

2 studies included in qualitative and quantitative syntheses

4 full-text articles excluded, with reasons: 2 case reports; 1 editorial, 2 non-RCT.
Included studies

We provide a detailed description of the included trials in the Characteristics of included studies. Overall, the mean age of the participants was 48.3 years (standard deviation (SD) 0.42). The percentage of included male participants was 74.2% (SD 3.96). Botoni 2007 described NYHA classes across both comparison groups. Fifty percent of the patients had NYHA class II/III (Botoni 2007). No patients had NYHA class IV (Botoni 2007). On the contrary, Diniz 2004 described NYHA class by comparison group. Fifteen patients 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 RCTs 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, in Brazil. The mean sample size was 34.5 ± 6.36 (minimum 30, maximum 39). One RCT was associated with one duplicate publication (Diniz 2004). One RCT reported if 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 4 months (Botoni 2007) to 29 weeks (Diniz 2004). One study reported sponsorship (Botoni 2007).

See Characteristics of included studies table for details.

Excluded studies

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

Ongoing studies

We identified one ongoing study (NCT00323973). See Characteristics of ongoing studies for details.

Risk of bias in included studies

Both trials were of low methodological quality overall. 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.

![Risk of bias graph](Image)
Figure 4. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

**Allocation**

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

**Blinding**

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

**Incomplete outcome data**

Botoni 2007 was at unclear risk for this domain, while Diniz 2004 was at a high risk of bias for this domain.

**Selective reporting**

Both studies were at high risk of bias for this domain.

**Other potential sources of bias**
Both trials had sampling bias (Botoni 2007; Diniz 2004). Diniz 2004 had bias in the presentation of data.

**Effects of interventions**

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

The results are based on two trials involving 69 participants (Botoni 2007; Diniz 2004). See Summary of findings for the main comparison.

**Primary outcomes**

The two trials reported on only one of our outcomes of interest. No data were available on the other outcomes (30day cardiovascular mortality, time to heart decompensation, disease-free period at 30, 60 and 90 days).

**All-cause mortality**

Meta-analysis of two trials (69 participants, 5 events) showed carvedilol was associated with a non-statistically significant reduction in all-cause mortality compared with placebo (pooled RR 0.69, 95% CI 0.12 to 3.88, I² = 0%; P = 0.67) (Botoni 2007; Diniz 2004) (Analysis 1.1).

**Secondary outcomes**

**Overall survival**

One trial found no significant difference between the carvedilol group and placebo group (P = 0.525) for overall survival (Diniz 2004).

**Quality of life**

Botoni 2007 found no significant change between the carvedilol group and the control group in quality of life as assessed by SF-36. Diniz 2004 used the Minnesota Living With Heart Failure Questionnaire and reported a statistically significant difference in the carvedilol group before and after treatment (55 ± 15.22 (pre-treatment) versus 23.54 ± 8.66 (post-treatment), P < 0.001), whereas the placebo group showed no significant benefit in improving quality of life (44.26 ± 15.22 (pre-treatment) versus 8.28 ± 17.78 (post-treatment), P < 0.001).

**Adverse events**

One trial found a significant reduction in systolic and diastolic blood pressure (Botoni 2007). This trial reported changes in renal function and serum electrolytes in both groups (Botoni 2007). Botoni 2007 reported reductions in heart rate in the carvedilol and placebo groups, but there was no recorded episode of symptomatic bradycardia. Diniz 2004 found no significant differences in the adverse events assessed, namely NYHA functional class deterioration, abdominal pain, heart beats and dizziness.

**DISCUSSION**

**Summary of main results**

This review of pharmacological interventions for treating heart failure in people with Chagas cardiomyopathy included two trials (69 participants) which assessed carvedilol (Botoni 2007; Diniz 2004). Their critical appraisal shows weak evidence for the use of carvedilol in treating heart failure in Chagas cardiomyopathy. We did not find significant differences for reducing all-cause mortality, overall survival, quality of life, and adverse events in patients with Chagas cardiomyopathy complicated by heart failure treated with carvedilol versus placebo. The studies did not evaluate main clinical outcomes such as cardiac mortality at 30 days, time to heart decompensation, disease-free period (at 30, 60 and 90 days), hospital readmissions (heart failure- or adverse event-related), adherence grade and digoxin toxicity (Botoni 2007; Diniz 2004). The benefits and harms of carvedilol versus placebo for treating heart failure in people with Chagas cardiomyopathy remain unclear. See the Summary of findings for the main comparison for details of all-cause mortality.

**Overall completeness and applicability of evidence**

Only two trials were found by this review and they failed to detect statistically significant differences between the groups. It has been pointed out that meta-analyses including a limited number of patients and events are prone to yield overestimated intervention effect estimates (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 any differences 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 (Schulz 1995; Green 2002). In a remarkable paper from 28
years ago, Freiman et al 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” (Freiman 1978). 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 main source of bias in the included trials was the lack of detail in describing the generation of randomization sequences and the concealment of allocation (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 described previously 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. See the Summary of findings for the main comparison shows details for all-cause mortality.

Both trials (Botoni 2007; Diniz 2004) had two additional biases: sampling bias and bias in the presentation of data (Porta 2008). See Characteristics of included studies for details.

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 have high risk of selective outcome reporting (Botoni 2007; Diniz 2004).

Authors’ conclusions

Implications for practice

This Cochrane review provides evidence that carvedilol does not seem to reduce all-cause mortality in patients suffering from heart failure associated with Chagas cardiomyopathy. Furthermore, carvedilol does not seem to improve overall survival and quality of life, or to reduce adverse events. The results are based on two trials with high risk of bias involving 69 patients that assessed carvedilol compared with placebo. Therefore, prescription of this intervention for patients suffering from heart failure associated with Chagas cardiomyopathy can neither be supported nor rejected, unless new evidence from a large high-quality trial alters this conclusion. Consequently, policy-makers, clinicians, and academics should not yet recommend this drug for use in those patients. This Cochrane review does not provide evidence about other pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy.

Implications for research

This systematic review has highlighted a need for well-designed, high-quality randomized trial to assess the benefits and harms of pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy. The trial should include main clinical outcomes (patients-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. Future trials should be conducted by independent researchers and reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Ioannidis 2004; Moher 2010) and using the Foundation of Patient-Centered Outcomes Research recommendations (Anonymous 2012 Gabriel 2012).

Acknowledgements

We thank Center of Disease Control (Atlanta, USA) for permission to reproduce Figure 1. We express our gratitude to Rosiane Viana Zuza Diniz who sent us the full text of her PhD thesis (Diniz 2004). We thank Maria Cristina Rockenbach and Claudia Verônica Guerra for helping us with the Diniz 2004 translation.

We are grateful to peer reviewers for improving the quality of this Cochrane review.
**REFERENCES**

**References to studies included in this review**

Botoni 2007  

Dávila 2008  

**References to studies excluded from this review**

Bestetti 2010  

Dávila 2002a  

Dávila 2008  

Issa 2010  

**References to ongoing studies**

NCT00323973  

**Additional references**

Acquatella 2008  

Adoriso 2006  

Altman 1995  

Andrade 2011  

Anonymous 2012  

Balshem 2011  

Bauman 2006  

Bern 2009  

Biolo 2010  
Bonney 2008

Brozek 2011

Buckner 2010

Carrasco 2012

Costa 2012
Costa J, Peterson AT. Ecological niche modeling as a tool for understanding distributions and interactions of vectors, hosts, and etiologic agents of Chagas disease. Advances in Experimental Medicine and Biology 2012;710:59–70. [PUBMED: 22127886]

Coura 2010

Cruz-Pacheco 2012

Diniz 2010

Dobarro 2008

Dutra 2008

Dávila 2002b

Dávila 2004

Dávila 2005

Elias 2003

Fermi Paradox

Freiman 1978

Gabriel 2012

Gascón 2007

Gascón 2010

Gironès 2005

Gironès 2007
Gironès N, Carrasco-Marin E, Cuervo H, Guerrero NA, Sanoja C, John S, et al. Role of Trypanosoma cruzi...
Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy (Review)

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Guyatt 2010g

Guyatt 2011b

Guyatt 2011c

Guyatt 2011d

Guyatt 2011e

Guyatt 2011f

Guyatt 2011g

Hamad 2007

Higgins 2003

Higgins 2011

Higuchi 2003
Higuchi ML, Benvenuti LA, Reis MM, Metzger M. Pathophysiology of the heart in Chagas' disease: current status and new developments. *Cardiovascular Research* 2003;60(1):96–107. [MEDLINE: 14522411]

Higuchi 2004

Ioannidis 2008a

Ioannidis 2008b

Ioannidis 2010

Kirby 2002
Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy (Review)

Moncayo 2010

Muñoz 2009

Nebeker 2004

Oliveiri 2010

OPS 2006

Porta 2008

Punukollu 2007

Quiros 2006

Rassi 2000

Rassi 2006

Rassi Jr 2009

Rassi Jr 2010

RevMan 2011

Reyes 2005

Ribeiro 2009

Ribeiro 2012

Rossi 1991

Schmunis 2010

Schulz 1995

Silva 2008

Soriano 2009

Tanowitz 2009

Thorlund 2011

Urbina 2010

Villar 2002

Yamagata 2006

Zhang 1999

* Indicates the major publication for the study
### Characteristics of included studies  
*Botoni 2007*

| Methods | Randomized, double-blind, placebo-controlled trial, parallel design (2 arms)  
Country: Brazil  
Intention to treat for the primary end point: per protocol.  
Intention to treat for mortality per protocol.  
Follow-up period: 4 months  
Unit of randomization: patients  
Unit of analysis: patients |
|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Participants | 1) Enrolled: 42  
Lost patients before randomization: 7.1% (3/42)  
2) Randomized: 39  
Carvedilol group: 19  
Placebo group: 20  
3) Patients receiving drug: 39  
Carvedilol group: 19 (48.7%)  
Placebo group: 20 (51.3%)  
4) Lost post randomisation: 24% (3/39)  
Carvedilol group: 5.2% (1/19)  
Placebo group: 10% (2/20)  
Imbalance between comparison groups: 4.8%  
5) Analyzed patients:  
Carvedilol group: 18 (95%)  
Placebo group: 18 (90%)  
6) Age (years SD)  
Overall group: Baseline: 47.8 (10.4)  
Overall group: After RAS inhibition: 48.2 (10.4)  
7) Sex (male):  
Overall group: baseline: 71.4% (30/42)  
Overall group: after RAS inhibition: 69.2% (27/39)  
8) Inclusion criteria:  
• Positivity for *T. cruzi* as confirmed by 2 or more serological tests (indirect immunofluorescence, ELISA, and/or indirect hemagglutination)  
• Cardiomyopathy when at least 3 of the following criteria were fulfilled: LV end diastolic diameter (LVDD) N55 mm; LVDD/body surface area N2.7cm/m2; LV ejection fraction (LVEF) b55%; QRS interval N120 ms; and/or echocardiographic evidence of diffuse or segmental systolic wall motion abnormalities.  
9) Exclusion criteria:  
• Pregnant |
• Using any beta-blocker
• Hypertension
• Diabetes mellitus
• Thyroid dysfunction
• Chronic obstructive pulmonary disease
• Asthma
• Renal failure
• Hepatic failure

| Interventions | Carvedilol group: 3.125 mg and up-titrated every 15 days to 25 mg twice a day. Duration: 4 months
Placebo: details not stated.
Nature of placebo: not stated.
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 | Outcomes were not described explicitly.
Primary:
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 | A priori sample size estimation: yes
Quote “The sample size of 42 patients was chosen to provide the study with 80% power to detect a positive difference in LVEF of at least 5%, with a 2-sided statistical significance level set at 0.05% and assuming a 15% loss to follow-up.” (page 544.e5).
Sponsor: Baldacci Pharmaceutical Laboratory and FUNED (Fundacao Ezequiel Dias)
Roll of sponsor: carvedilol and placebo were supplied for Baldacci Pharmaceutical Laboratory and FUNED (Fundacao Ezequiel Dias), respectively |

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>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</td>
</tr>
</tbody>
</table>
### 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)

**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 appropriate medication box to each patient. The medication container was identified only by each patient’s name." (page 544e2)

### Blinding of outcome assessment (detection bias)

**Unclear risk**

Insufficient information to permit judgment of 'low risk' or 'high risk'

### Incomplete outcome data (attrition bias)

**Unclear risk**

Loss of patients before randomisation: 7.1% (3/42)

Lost post randomization: 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 non-compliance. 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 fails to include results for a key outcome that would be expected to have been reported for such a study.
### Other bias

<table>
<thead>
<tr>
<th></th>
<th>High risk</th>
<th>Sampling bias defined as &quot;Systematic error due to the methods or procedures used to sample or select the study subjects, specimens, or items (e.g., scientific papers), including errors due to the study of a nonrandom sample of a population.&quot; (Porta 2008).</th>
</tr>
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</table>

### Diniz 2004

#### Methods

<table>
<thead>
<tr>
<th></th>
<th>Randomized, double-blind, placebo-controlled trial, parallel design (2 arms)</th>
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<tbody>
<tr>
<td>Country: Brazil</td>
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<tr>
<td>Intention to treat for mortality from any cause: yes.</td>
<td></td>
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<tr>
<td>Follow-up period: 6 months</td>
<td></td>
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<tr>
<td>Unit of randomization: patients</td>
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<tr>
<td>Unit of analysis: patients</td>
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</table>

#### Participants

<table>
<thead>
<tr>
<th></th>
<th>1) Enrolled: 63</th>
<th>2) Randomized: 30</th>
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<tbody>
<tr>
<td>Carvedilol group: 15</td>
<td>Placebo group: 15</td>
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<tr>
<td>3) Patients receiving drug: 30</td>
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<td></td>
</tr>
<tr>
<td>Carvedilol group: 15</td>
<td>Placebo group: 15</td>
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<tr>
<td>4) Lost post randomization: 10% (3/30)</td>
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<tr>
<td>Carvedilol group: 6.6% (1/15)</td>
<td>Placebo group: 13.2% (2/15)</td>
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<tr>
<td>5) Analyzed patients:</td>
<td></td>
<td></td>
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<tr>
<td>Carvedilol group: 80% (12/15)</td>
<td>Placebo group: 86.6% (13/15)</td>
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<tr>
<td>6) Age (years SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol group: 46.2 ± 7.62</td>
<td>Placebo group: 51.06 ± 6.11</td>
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<tr>
<td>7) Follow up (weeks):</td>
<td></td>
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<tr>
<td>Carvedilol group: 28.78 ± 1.48</td>
<td>Placebo group: 29.5 ± 1.79</td>
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<tr>
<td>8) Sex (male):</td>
<td></td>
<td></td>
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<tr>
<td>Overall group: 77% (23/30)</td>
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<tr>
<td>9) Inclusion criteria:</td>
<td></td>
<td></td>
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<tr>
<td>● Age 18 to 65 years</td>
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<tr>
<td>● NYHA: II to IV</td>
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<tr>
<td>● Ejection fraction and left ventricular fraction using isotopic ventriculography: ≤ 35%</td>
<td></td>
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<tr>
<td>● All of the patients already using digitalis, diuretics, angiotensin converting</td>
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</table>
enzyme inhibitors and spironolactone, and may or may not be using amiodarone and anticoagulant

10) Exclusion criteria:
- Functional class IV requiring use of vasoactive drugs
- Severe bradycardia smaller or equal to 50 beats per minute
- Blocks atrioventricular the second or third degree, without permanent pacemaker
- Systolic blood pressure less than or equal to 60 mmHg
- Comorbidities such as renal insufficiency (creatinine greater than or equal to 3.0) or hepatic serious bronchial asthma or chronic obstructive pulmonary disease
- Pregnant or not using contraception.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Carvedilol group: 3.125 mg/day and up-titrated every 8 days to 50 mg/day. Duration: 4 months Placebo: details not stated Nature of placebo: not stated</th>
</tr>
</thead>
</table>

| Outcomes | Outcomes were not described as primary or secondary explicitly:  
- Functional class  
- Overall survival  
- Quality of life (Minnesota -LIhFE - Living with Heart Failure)  
- Blood pressure  
- Heart rate  
- Electrocardiogram parameters  
- Ventricular remodeling  
- Change in left ventricular ejection fraction (LVEF)  
- Change in noradrenaline and brain natriuretic peptide levels  
- Adverse events |

| Notes | A priori sample size estimation: not given  
Sponsor: not given  
Data were gathered from PhD thesis. |

<table>
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</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgment of ’low risk’ or ’high risk’</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgment of ’low risk’ or ’high risk’</td>
</tr>
</tbody>
</table>
Incomplete outcome data (attrition bias)
All outcomes | High risk | Loss post randomization: 16.6%.
Comment: this trial is small sample size; therefore, 16.6% could be considered as a high loss of participants

Selective reporting (reporting bias) | High risk | This RCT include three important outcomes: mortality as adverse event, quality of life and safety
However, this trial reported quality of life data inappropriately

Other bias | High risk | Bias in the presentation of data defined as “Error due to irregularities produced by digit preference, incomplete data, poor techniques of measurement, technically poor laboratory procedures, or intentional attempts to mislead.” (Porta 2008). Sampling bias defined as “Systematic error due to the methods or procedures used to sample or select the study subjects, specimens, or items (e.g., scientific papers), including errors due to the study of a non-random sample of a population.” (Porta 2008).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bestetti 2010</td>
<td>Case report.</td>
</tr>
<tr>
<td>Dávila 2002a</td>
<td>Case report.</td>
</tr>
<tr>
<td>Dávila 2008</td>
<td>Editorial.</td>
</tr>
<tr>
<td>Issa 2010</td>
<td>Non-randomized clinical trial.</td>
</tr>
</tbody>
</table>
### Characteristics of ongoing studies  
*ordered by study ID*

**NCT00323973**  
**Trial name or title**  
A Randomized Double-blind Placebo Force-titration Controlled Study With Bisoprolol in Patients With Chronic Heart Failure Secondary to Chagas Cardiomyopathy (Scientific title)  
Chagas Cardiomyopathy Bisoprolol Intervention Study: Charity (Public title)

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, Placebo controlled trial, parallel design (2 arms). Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor). Primary Purpose: treatment</td>
</tr>
<tr>
<td><strong>Inclusion Criteria:</strong></td>
</tr>
<tr>
<td>1. Males or females aged 18 to 70 years.</td>
</tr>
<tr>
<td>2. Heart failure symptoms NYHA functional class II to IV.</td>
</tr>
<tr>
<td>3. Left ventricular ejection fraction &lt;40% determined by bi-dimensional echocardiography using modified Simpson’s rule for ventricular volumes.</td>
</tr>
<tr>
<td>4. Subjects must be on standard and stable outpatient doses of ACEIs or angiotensin II receptor antagonist for at least four weeks.</td>
</tr>
<tr>
<td>5. Subjects receiving diuretics must be on a stable dose for at least two weeks.</td>
</tr>
<tr>
<td>6. Clinical Euvolemia: as evidenced by absence of rales, no pleural effusion or ascitis and no more than minimal peripheric edema.</td>
</tr>
<tr>
<td><strong>Exclusion Criteria:</strong></td>
</tr>
<tr>
<td>1. CHF due to ischemic heart disease, valvular disease or any other etiology different than CD</td>
</tr>
<tr>
<td>2. Severe aortic insufficiency</td>
</tr>
<tr>
<td>3. Baseline advanced AV block defined as Mobitz type 2 or third degree AV block</td>
</tr>
<tr>
<td>4. Serum creatinine &gt; 2.5 mg/dl.</td>
</tr>
<tr>
<td>5. Resting heart rate &lt; 45 beats per minute</td>
</tr>
<tr>
<td>6. Known malignancy and other severe disease which shorten life expectancy &lt; 6 months.</td>
</tr>
<tr>
<td>7. Subjects with contraindications for beta-blockers: severe obstructive chronic pulmonary disease, asthma, severe pulmonary hypertension, type 1 diabetes mellitus or history of hypoglycaemia.</td>
</tr>
<tr>
<td>8. Suspected or confirmed chronic infectious disease including HIV and hepatitis B.</td>
</tr>
<tr>
<td>9. History of active substance or alcohol abuse within the last year.</td>
</tr>
<tr>
<td>10. Clinically significant psychiatric illness which can negatively affect the subject compliance and participation in the trial.</td>
</tr>
<tr>
<td>11. Pregnancy or lactation.</td>
</tr>
<tr>
<td>12. Organic disease or gastrointestinal surgery which can affect the oral absorption and pharmacodynamics of the medication under study.</td>
</tr>
<tr>
<td>13. Enrollment and participation in other active treatment trial within the previous month.</td>
</tr>
<tr>
<td>14. Failure to provide written informed consent.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age minimum: 18 years</td>
</tr>
<tr>
<td>Age maximum: 70 years</td>
</tr>
<tr>
<td>Gender: Both</td>
</tr>
<tr>
<td>Chagas cardiomyopathy and chronic heart failure.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol: 5 mg (<a href="#">Quiros 2006</a>).</td>
</tr>
<tr>
<td>Control: placebo.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary:</strong></td>
</tr>
<tr>
<td>1. Bradycardia requiring pacemaker implantation. [Time Frame: 2 years].</td>
</tr>
<tr>
<td>2. Clinically significant sustained monomorphic ventricular tachycardia causing syncope: sustained</td>
</tr>
</tbody>
</table>
### NCT00323973 (Continued)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Description</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Ventricular tachycardia or ventricular fibrillation. [Time Frame: 2 years]</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Hospital admission caused by heart failure. [Time Frame: 2 years]</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>[Time Frame: 2 years]</td>
<td></td>
</tr>
<tr>
<td>Secondary:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Heart failure worsening or mortality related with CHF. [Time Frame: 2 years]</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Need for Implantable cardioverter-defibrillator (ICD), Cardiac resynchronization Therapy (CRT) or Pacemaker therapy (PM). [Time Frame: 2 years]</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>New AV block. [Time Frame: 2 years]</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Perceived quality of life worsening. [Time Frame: 2 years]</td>
<td></td>
</tr>
</tbody>
</table>

**Starting date**: July 2003.

**Contact information**: Carlos A Morillo, MD, FRCPC. Fundación Cardiovascular de Colombia

**Notes**: Date of registration: 05/05/2006.  
Sponsor: Fundación Cardiovascular de Colombia.  
Target sample: 500.  
Recruitment status: completed.  
Study drug and placebo provided by Merck Colombia (Quiros 2006).
DATA AND ANALYSES

Comparison 1. Carvedilol versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 All-cause mortality</td>
<td>2</td>
<td>69</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.69 [0.12, 3.88]</td>
</tr>
</tbody>
</table>

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

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

Comparison: 1 Carvedilol versus placebo

Outcome: 1 All-cause mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Carvedilol n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botoni 2007</td>
<td>1/19</td>
<td>2/20</td>
<td>66.1 % 0.53 [0.05, 5.34]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diniz 2004</td>
<td>1/15</td>
<td>1/15</td>
<td>33.9 % 1.00 [0.07, 14.55]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>34</td>
<td>35</td>
<td>100.0 % 0.69 [0.12, 3.88]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 2 (Carvedilol), 3 (Placebo)
Heterogeneity: Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable

ADDITIONAL TABLES

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

<table>
<thead>
<tr>
<th>Variable (2005)</th>
<th>The Americas</th>
<th>Southern Cone</th>
<th>Andean Community</th>
<th>Centroamerican region and Belize</th>
<th>French Guayana, Guyana, Suriname</th>
<th>Mexico</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>531,432,850</td>
<td>259,805,650</td>
<td>113,545,000</td>
<td>39,656,200</td>
<td>1,397,000</td>
<td>107,029,000</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 1. Burden of infected population in the Americas and by region  
(Continued)

<table>
<thead>
<tr>
<th>Infected</th>
<th>7,694,500</th>
<th>4,451,900</th>
<th>1,168,000</th>
<th>806,600</th>
<th>18,000</th>
<th>1,100,000</th>
<th>100,000 to 200,000 people from endemic countries.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Chagas</td>
<td>14,385</td>
<td>9,365</td>
<td>2,600</td>
<td>1,300</td>
<td>20</td>
<td>1,100</td>
<td>-</td>
</tr>
<tr>
<td>cardiology</td>
<td>1,772,365</td>
<td>1,180,990</td>
<td>361,954</td>
<td>129,345</td>
<td>933</td>
<td>99,143</td>
<td>-</td>
</tr>
</tbody>
</table>

Data from OPS 2006.

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

<table>
<thead>
<tr>
<th>Destination country</th>
<th>Year</th>
<th>Infected Immigrants from Latin American endemic countries</th>
<th>Immigrants with developed chronic Chagas disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>2006</td>
<td>3.8% of 80,522</td>
<td>Not described.</td>
</tr>
<tr>
<td>Canada</td>
<td>2006</td>
<td>3.5% of 156,960</td>
<td>Not described.</td>
</tr>
<tr>
<td>Japan</td>
<td>2007</td>
<td>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.</td>
<td>Not described.</td>
</tr>
<tr>
<td>Europe (15 countries excluding Spain)</td>
<td>2005</td>
<td>2.9% of 483,074 legal Latin American immigrants.</td>
<td>Not described.</td>
</tr>
<tr>
<td>Spain</td>
<td>2007</td>
<td>5.2% of 1,678,711. 24 to 92 newborns delivered by South American T. cruzi infected mothers in Spain may have been congenitally infected with T. cruzi in 2007</td>
<td>17,390</td>
</tr>
<tr>
<td>USA</td>
<td>2000</td>
<td>1.9% of approximately 13 million Latin American immigrants.</td>
<td>49,157</td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>2% of 17 million.</td>
<td>65,133</td>
</tr>
</tbody>
</table>

Data from Schmunis 2010.
Table 3. New York Heart Association (NYHA) Classification System

<table>
<thead>
<tr>
<th>NYHA class I (mild)</th>
<th>NYHA class II (mild)</th>
<th>NYHA class III (moderate)</th>
<th>NYHA class IV (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No limitation of physical activity - ordinary physical activity does not cause tiredness, heart palpitations, or shortness of breath</td>
<td>Slight limitation of physical activity - comfortable at rest, but ordinary physical activity results in tiredness, heart palpitations, or shortness of breath</td>
<td>Marked or noticeable limitation of physical activity - comfortable at rest, but less than ordinary physical activity causes tiredness, heart palpitations, or shortness of breath</td>
<td>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</td>
</tr>
</tbody>
</table>

**APPENDICES**

Appendix 1. Adverse events commonly associated with the following list of drug used for heart-failure treatment.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. - By bradykinin potentiation (Dry cough (5% of patients), and Angioedema (0.1-0.2% of patients)). 2. - Related to angiotensin suppression (hypotension, worsening renal function and hyperkalaemia).</td>
<td>1. - Hypotension. 2. - Hyperkalaemia. 3. - Gynecomastia by spironolactone.</td>
<td>1. - Hypotension. 2. - Severe hypotension.</td>
<td>1. - Arrhythmic events (atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation). 2. - Severe hypotension.</td>
<td>1. - Cardiac arrhythmias (e.g., ectopic and reentrant cardiac rhythms and heart block). 2. - Gastrointestinal symptoms (e.g., anorexia, nausea, weight loss).</td>
<td>1. - Metabolic abnormalities: 1. - Contracted blood pressure. 2. - Hyponatremia. 3. - Hypokalemia.</td>
<td>Headache. Dizziness.</td>
<td>1. - Fatigue and weakness. 2. - Symptomatic bradycardia. 3. - Hypotension. 4. - Administration of β-blockers is contraindicated.</td>
<td>1. - Negative inotropic effect and reflex neurohormonal activation. 2. - Peripheral and pulmonary oedema.</td>
</tr>
</tbody>
</table>
potension, increase in serum creatinine and potassium). Others are hypoten-
sion & electrolyte imbalance.

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chagas Disease</td>
<td>Infection with the protozoan parasite <em>Trypanosoma cruzi</em>, 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 esophagus or colon.</td>
<td>MeSH Database PubMed</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Antioxidant with alpha as well as beta blocking activity; structure in first source</td>
<td>MeSH Database PubMed</td>
</tr>
<tr>
<td>Chagas cardiomyopathy</td>
<td>A disease of the cardiac muscle developed subsequent to the initial protozoan infection by <em>Trypanosoma cruzi</em>. After infection, less than 10% develop acute illness such as myocarditis (mostly in children). The disease then enters a latent phase without clinical symptoms un-</td>
<td>MeSH Database PubMed</td>
</tr>
</tbody>
</table>
til about 20 years later. Myocardial symptoms of advanced Chagas disease include conduction defects (heart block) and cardiomegaly

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digoxin</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Dilated cardiomyopathy</strong></td>
<td>A form of cardiac muscle disease that is characterized by ventricular dilation, ventricular dysfunction, and heart failure. Risk factors include smoking, alcohol drinking, hypertension, infection, pregnancy, and mutations in the LMNA gene encoding Lamin type A, a nuclear lamina protein.</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Left ventricular ejection fraction</strong></td>
<td>Ejection fraction is a measurement of the percentage of blood leaving your heart each time it contracts. <a href="http://www.mayoclinic.com/health/ejection-fraction/AN00360">http://www.mayoclinic.com/health/ejection-fraction/AN00360</a> (accessed on 21 November 2011)</td>
</tr>
<tr>
<td><strong>Renin-Angiotensin-System</strong></td>
<td>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</td>
</tr>
</tbody>
</table>
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 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 strategy for CENTRAL Issue 1, 2011** *(The Cochrane Library)*

```
#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)
```
Appendix 4. Search strategy for MEDLINE (Ovid)

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

Appendix 5. Search strategy for EMBASE (Ovid)

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.
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

Appendix 6. Search strategy for ISL 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

Appendix 7. Search strategy for LILACS
(heart or cardiac) and failure [Words] or "HEART FAILURE" [Subject descriptor] and chagas$ or cruzi$ or trypanosom$ [Words]

Appendix 8. Search strategy for WHO ICTRP search portal
chagas* and heart or chagas* and cardi*

Appendix 9. Search strategy for Clinicaltrials.gov
chagas and (heart or cardiac)

HISTORY
Protocol first published: Issue 4, 2011
Review first published: Issue 11, 2012

CONTRIBUTIONS OF AUTHORS
Arturo Martí-Carvajal conceived and drafted the review with Ricardo Hidalgo, Joey Kwong, Daniel Simancas and Susana Nicola. Arturo Martí-Carvajal acts as contact author for the 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.

Ricardo Hidalgo, Joey Kwong, Daniel Simancas and Susana Nicola: none known.

SOURCES OF SUPPORT

Internal sources


External sources

- Iberoamerican Cochrane Network, Spain. Academic
- Cochrane Heart Group, UK. Academic.