Chagas disease is a serious health care problem in Latin America due to its high prevalence, morbidity and mortality. The migration from Latin American countries to the United States and Europe has disseminated a significant number of infected subjects. Most patients present the indeterminate form of the disease and remain without symptoms for decades. However, some groups believe that patients with the indeterminate form are at high risk for developing sudden death although no studies have been designed to investigate this issue.

We conducted a systematic review of follow-up studies in patients with asymptomatic Chagas disease, normal ECG and known cause of death. We found 15 articles including 9382 patients. Mortality rate in asymptomatic patients with normal ECG was very low (0.92%) and similar to that of controls without Chagas disease (p=0.38). This systematic review shows that sudden death is uncommon in the indeterminate form of the disease and that the risk of death is similar to that of the general population. Thus, these patients should be allowed to lead a normal working life and to practice physical activity, without alarming them unnecessarily about their condition or indicating sophisticated and expensive studies. Regular follow-up is necessary as the death risk increases considerably when the disease progresses to the cardiac form.

Chagas disease is the cause of more deaths in America than any other parasitic disease, and chagasic myocarditis is the most frequent form of chronic myocarditis worldwide. (1) Migration has disseminated chagasic patients worldwide, turning chagasic myocardiopathy into a problem of increasing magnitude in Europe (1) and the United States (2)

The disease has two phases 1) acute, with elevated parasitemia and indeterminate symptoms, and with 5% incidence of acute myocarditis and 2) chronic, which can also appear as indeterminate and has a long-term duration (a life-long disease in about 70% of the patients). The chronic phase is characterized by positive serology for antibodies against the parasite, but with no clinical signs and symptoms, normal electrocardiogram (ECG), and normal thorax and gastrointestinal tract radiographies. (3) It also presents cardiac (more frequently) and digestive forms (less frequently) which develop in 20-30% of the patients approximately 10-30 years after the primo-infection. The chronic phase constitutes a significant morbimortality burden, mainly due to heart failure (HF), sudden death (SD) and/or pulmonary or central nervous system embolism. (2, 4) Chronic chagasic cardiomyopathy (CCC) manifests with complex ventricular arrhythmias, bradiarrhythmias, atrioventricular blockade (AV), apical ventricular aneurisms, thromboembolism and ventricular dysfunction with HF. On the other hand, more than 2 out of 3 patients remain in the indeterminate form throughout their entire lifetime. (1) Similar to other groups, (3, 4) we have published (5) that the prognosis of the indeterminate form of the disease is good, and therefore, there is no need to generate needless worries neither in patients nor physicians, nor incur in unnecessary expenses to perform sophisticated

**Key words**

Chagas Disease - Death, Sudden, Cardiac

**Abbreviations**

<table>
<thead>
<tr>
<th>AV</th>
<th>Atrioventricular</th>
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</thead>
<tbody>
<tr>
<td>CCC</td>
<td>Chronic chagasic cardiomyopathy</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure</td>
</tr>
<tr>
<td>SD</td>
<td>Sudden death</td>
</tr>
</tbody>
</table>

**REV ARGENT CARDIOL. 2012;80:240-246.**
studies. Even so, there is certain concern regarding the possibility of increased risk of SD during the indeterminate form of the disease (6-9). However, there is scarce and confusing information on this topic. Many of the case series include both patients with the indeterminate form as well as with declared cardiomyopathies. (10-11). The Consensus of Chagas-Mazza Disease (12) recently published in this Journal, proposes a new classification with the purpose of eradicating the use of the “indeterminate form” due to the possible risk of SD in these patients, though it does not provide any supporting literature or evidence to sustain this statement. Accordingly, this consensus recommends an array of complementary studies, some of which are sophisticated and expensive, to analyze these patients, without any justifiable scientific basis.

SD was initially defined as death which occurs within the first hour after the onset of symptoms (13-15) and was then extended to include unobserved and unexpected deaths or those taking place during sleep without apparent cause. However, a definition based on the mechanism of death (arrhythmic SD) would be more desirable than a definition based on the time of death. (16) Another difference was made between “unexpected SD”, in patients with no known pathologies to explain the decease, and “expected SD”, occurring in patients having a pathology that might predict it. In the case of patients with Chagas disease, “unexpected” SD would correspond to patients suffering from the indeterminate form of the disease, whereas in those already presenting clinical signs of cardiomyopathy, SD would be “expected”. (17) Consequently, it is necessary to know the prevalence of SD in patients with the indeterminate form of the disease. (17)

The aim of this study was thus to systematically search, select and analyze death data published on chagasic patients to obtain reliable information on the risk of SD in patients with the indeterminate form of the disease.

**METHODS**

A bibliographic search in PubMed and Scielo was performed in March 2011 using the following keywords: “Chagas” and “follow-up studies [MeSH] or prognos*[Text Word] or predict*[Text Word] or course*[Text Word]”. Each article was surveyed to detect those where follow-up data of asymptomatic chagasic patients and their cause of death were reported. Studies reporting separately the follow-up of patients with the indeterminate form of the disease from those with CCC were considered eligible.

Articles were evaluated by two independent expert reviewers in the field of study and controversies were solved by consensus.

Careful examination of the studies revealed that many of the initially selected studies did not include a radiographic assessment of the patients, which would not allow their classification in the indeterminate form of the disease. Besides, some studies used other classification systems. It was therefore decided to perform the analysis on asymptomatic patients with normal ECG.

The hypothesis of similar mortality in asymptomatic chagasic patients with normal ECG and seronegative patients was statistically tested. Only seronegative patients with known ECG were used to build the null hypothesis. A contingency table was created to compare patient mortality with normal vs. abnormal ECG with Pearson’s chi square test. Statistical analysis was performed using Epidat 3.1 software.

### Statistical analysis

SPSS 11.0 software for Windows was used for statistical analysis. Results were expressed as mean ± standard deviation (SD). Student t test was used to compare means of independent samples. Results were considered to be statistically significant for p < 0.05. Higher levels of significance were considered for p < 0.01 and p < 0.001.

### RESULTS

The bibliographic search provided 1058 articles, 19 of which complied with the initial search criteria. Fifteen out of 19 studies contained sufficient data to constitute a group of asymptomatic chagasic patients with normal ECG (Figure 1). The four discarded articles did not report patient ECG and are briefly discussed next.

Acquatella et al. performed a prospective follow-up study in 5771 subjects with serologic analysis, in Poscio, Venezuela. Patients were classified according to the NYHA functional class, but were not categorized according to their ECG (18). On the other hand, Rodríguez Salas et al. (19) carried out a follow-up study of 283 chagasic patients separating symptomatic from asymptomatic ones, Heringer-Walther et al. (20) reported the prognostic value of the brain natriuretic peptide in chagasic patients and Pazin et al. (21) reported the prognostic value of the brain natriuretic peptide in chagasic patients.

![Flow diagram of included studies.](image-url)
Table 1. Summary of follow-up studies

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Inclusion criteria</th>
<th>Performed studies</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porto (22)</td>
<td>283</td>
<td>Ch. p.</td>
<td>ECG</td>
<td>6 y</td>
<td>17 deaths (6%) in the normal ECG group (5 SD [5/283; 1.8%], 9 HF y 3 non-cardiac causes). 131 deaths (37.9%) in the abnormal ECG group (64 SD, 62 HF y 5 non-cardiac causes)</td>
</tr>
<tr>
<td>Pinto Dias, et al. (23)</td>
<td>192</td>
<td>Ch. p. dead due to the disease</td>
<td>ECG</td>
<td>13.2 y</td>
<td>176 deaths, 37 in the normal ECG group; 81 (14%) out of the 566 ECGs performed on the dead patients were normal No causes of death were reported</td>
</tr>
<tr>
<td>Caeiro, et al. (24)</td>
<td>87</td>
<td>Ch. p.</td>
<td>CE, ECG, chest radiography</td>
<td>10 y</td>
<td>No deaths in groups Ech1 and Ech2A groups</td>
</tr>
<tr>
<td>Espinosa, et al. (25)</td>
<td>18</td>
<td>107 Ch p. and 22 seronegative p.</td>
<td>CE phonocardiography, ECG, chest radiography, Echo, 24 h Holter, ergometry, cine ventriculography</td>
<td>10 y</td>
<td>No deaths in groups IA and IB</td>
</tr>
<tr>
<td>Borges Pereira, et al.</td>
<td>76</td>
<td>192 Ch. p. and 188 control p.</td>
<td>CE, ECG, chest radiography</td>
<td>6 y</td>
<td>No deaths in group I</td>
</tr>
<tr>
<td>Rodrigues Coura, et al.</td>
<td>130</td>
<td>Ch. p. and control p</td>
<td>ECG</td>
<td>10 y</td>
<td>No deaths in patients with the indeterminate form of Chagasic disease</td>
</tr>
<tr>
<td>Carrasco, et al. (28)</td>
<td>110</td>
<td>Ch. p.</td>
<td>CE, ECG, ergometry, chest radiography, Echo, 24 h Holter, cine ventriculogram, coronariography, electrophysiology study</td>
<td>15 y</td>
<td>No deaths in groups IA and IB</td>
</tr>
<tr>
<td>Ianni, et al. (29)</td>
<td>160</td>
<td>Indeterminate form of Ch. disease p.</td>
<td>ECG and Echo</td>
<td>98 ± 30 m</td>
<td>No deaths</td>
</tr>
<tr>
<td>Viotti, et al. (30)</td>
<td>505</td>
<td>Ch. p.</td>
<td>ECG, chest radiography, Echo</td>
<td>9.9 y</td>
<td>No deaths in group 0</td>
</tr>
<tr>
<td>Benchimol Barbosa, (31)</td>
<td>14</td>
<td>Ch. p. with palpitations</td>
<td>ECG, Holter, AECG</td>
<td>84.2 ± 39.0 m</td>
<td>No deaths in group 1</td>
</tr>
<tr>
<td>Fabbro, et al. (32)</td>
<td>67</td>
<td>Ch. p.</td>
<td>Ch.p.</td>
<td>20 y</td>
<td>No deaths</td>
</tr>
<tr>
<td>Maguire, et al. (33)</td>
<td>243</td>
<td>PBS</td>
<td>Serology, ECG</td>
<td>7 y</td>
<td>Mortality in asymptomatic patients with normal ECG was similar to that in seronegative control patients</td>
</tr>
<tr>
<td>Mota, et al. (34)</td>
<td>252</td>
<td>PBS</td>
<td>Serology, ECG</td>
<td>10 y</td>
<td>Mortality in asymptomatic patients with normal ECG was similar to that in seronegative control patients</td>
</tr>
<tr>
<td>Storino, et al. (5)</td>
<td>103</td>
<td>Ch. p.</td>
<td>CE, ECG, chest radiography, Echo, Holter, ergometry, SPECT</td>
<td>12 y</td>
<td>No deaths in group I</td>
</tr>
<tr>
<td>Manzullo, et al. (35)</td>
<td>4335</td>
<td>Ch. p.</td>
<td>ECG</td>
<td>5 y</td>
<td>1 patient with normal ECG died (0.01%)</td>
</tr>
</tbody>
</table>

observed the prognostic value of minor abnormalities in the echocardiographic assessment of wall motility. However, none of these three studies analyzed patient ECG.

**Included studies (Table 1)**

Porto (22) performed a follow-up study in a cohort of 283 patients and observed 5 cases of SD over a 6 year period (0.3% per year). Of note, the group with normal ECG presented more deaths due to HF (9 deaths) than to SD (5 deaths).

Pinto Dias et al. (23) found a very high mortality rate in the group of patients with normal ECG (19.2% over the course of the study), but the causes of death were not reported. They also noted that only 81 out of the 566 dead patients (14%) had a normal ECG at the start of the study, so that most of them did not correspond to the indeterminate form of the disease. In a thorough follow-up study of 233 chagasic patients carried out during a period of 10 years, Caeiro et al. (24) did not report any death in the group of asymptomatic patients, either with normal or abnormal ECG.

Other studies (25-32) did not register deaths in asymptomatic patients with normal ECG. In a 6 year follow-up study, Maguire et al. (33) found no significant difference between the mortality of patients with positive serology and normal ECG and that of seronegative patients. However, patients with positive serology and ECG changes showed a considerably higher mortality rate than those with normal ECG. Similar results were obtained by Mota et al. (34) in a rural population. In a follow-up study published in this Journal, Storino et al. (5) analyzed 350 patients during 12 years to establish the rate of progression of CCC. None of the 103 patients with the indeterminate form of the disease died during the study, emphasizing the good prognosis of this clinical form of the disease. We have recently reassessed 270 patients belonging to the 5 year follow-up cohort, which were divided into three groups as in the original study: GI (indeterminate form), n = 78; GII (ECG abnormalities), n = 80; and GIII (HF), n = 112. Sixteen patients belonging to GI progressed to the other groups, 12 to GII due to ECG abnormalities and 4 to GIII for structural heart disease, but none of the GI patients died. Eight patients from group II worsened their ECG abnormalities and 16 progressed to GIII. There were no significant differences between patients that progressed from GI to GII and those that progressed from GII to GIII (Fisher’s exact test). In GIII, 19 patients died of “expected SD”. Apical aneurysms and severe arrhythmia were more frequent in GIII than in GI and GII (p<0.0001) (Figure 2).

The most extensive follow-up study was carried out by Manzullo et al. (35), in a population of 5170 chagasic patients, 4335 of whom had normal ECG. During the course of 5 years, 28 patients died, 14 due to SD, 1 of whom had a normal ECG. The annual death risk for patients with normal ECG was 0.01%, similar to that of the general population.

**Systematic analysis**

The 15 selected studies included 9382 chagasic patients, 6487 with normal and 2895 with abnormal ECG. Sixty patients with normal ECG (0.92%) and 529 (18.27%) with abnormal ECG died (OR 23.95 IC 95% 18.27-31.38; p < 0.0001). Four studies which included 1025 control non-chagasic patients reported 60 deaths (5.85%). However, the ECG was analyzed in only one of these studies where 8 out of 337 control patients with negative serology and normal ECG died (2.43%).

The log-lin (36) model was fitted to the data and the null hypothesis was tested. Results showed that: 1) the mortality of asymptomatic patients with normal ECG was not different from that in the control group with normal ECG (p = 0.38), and 2) patients with abnormal ECG (both chagasic as seronegative) exhibited increased mortality (p< 0.0001) compared with patients with normal ECG.

Regarding the risk of SD, five studies reported separately this type of death. Table 2 shows the relative risk of SD in patients with normal or abnormal ECG.

**DISCUSSION**

This systematic review shows that normal ECG implies a good prognosis in Chagas disease, since mortality rate in these patients (22-35) is similar to that of non-chagasic controls. (25, 26) The collective analysis of the data confirms the findings of individual studies. It is important to emphasize that the four discarded studies that did not include ECG presented comparable results. Both Hearing-Walther et al. (20) and Pazin Filho et al. (21) did no register deaths in asymptomatic patients, whereas Acquatella et al. (18) and Rodriguez Salas et al. (19) reported a small number of deaths in these patients, though in the study of Aquatella, the mortality rate was not different from that of non-chagasic controls. To reinforce our assertion, we carried out a search in PubMed of presumptive SD in chagasic patients. We found eight publications describing the mechanism of death, six
of which had autopsies. Mendoza et al. (37) analyzed 24 hour Holter recordings of 10 chagasic patients who suffered SD. All had complex ventricular arrhythmias, ruling out their classification in the indeterminate form of the disease. Sternick et al. (38) reviewed the history and ECG of chagasic patients who died suddenly, all of whom had normal ventricular function but, similar to the above study, complex ventricular arrhythmias. In a study carried out in 603 autopsies, 106 chagasic patients with SD were included. Chagasic patient hearts were bigger and heavier than those of control patients, indicative of a certain degree of previous cardiomyopathy, which excludes them from the indeterminate form of the disease. (39) Another small study in chagasic patients suffering SD was conducted by Andrade et al. (40) All these patients had enlarged hearts, presented signs of myocarditis and lesions in the conduction system. Bestetti et al. (41) reviewed the clinical history of 24 patients who died unexpectedly, only one of whom had a normal ECG. Baroldi et al. (42) reviewed the autopsies of 34 chagasic patients suffering SD, comparing them with those of 9 chagasic patients who died of HF, 38 AIDS patients and 26 healthy controls. The hearts of the SD group were the heaviest, eliminating them from the indeterminate form of the disease.

James et al. (43) performed autopsies in 3 chagasic patients who died of SD. Two hearts were extremely dilated and the third one presented an apical aneurism. Finally, in the autopsy of a chagasic patient who died of SD, Satoh et al. (44) reported that the heart weighed 450 g and had signs of HF.

The physician with limited experience in the management of chagasic patients should pay close attention to the patients included in the studies. As we have already shown in the preceding paragraphs, almost all the cases of SD described in the literature had an important degree of cardiomyopathy. Hiss et al. (10) have recently demonstrated that CCC progression is related with reversible perfusion disorders at rest. However, none of the patients included in the study suffered from the indeterminate form of the disease. All of them were in NYHA functional class ≥ II, had heart rate disorders (including 7 definitive pacemakers) and were under treatment for HF.

Regarding the importance of antimuscarinic antibodies referred to in the Consensus of Chagas-Mazza Disease (12), the same Sterin-Borda group demonstrated that the presence of these antibodies does not correlate with cardiomyopathy severity (45) and even in cardiomyopathy patients without dysautonomia, antibodies were only found in 4% of the cases. (46)

The main limitation in our work is the great heterogeneity of the included studies, especially in patient inclusion criteria and classification and in the follow-up periods. However, results are consistent, revealing very low or no mortality in asymptomatic patients with normal ECG. Large studies based on the chagasic population showed no significant differences compared to healthy controls.

Only one study (34) presented data of healthy control subjects with normal ECG. That is the reason a consistency analysis for joint estimation could not be performed, since other studies included in the control group patients with other types of cardiomyopathies. Table 2 shows that the RR of chagasic patients with normal ECG who died of SD vs. abnormal ECG was 0.21, whereas in non-chagasic patients with normal ECG it was 0.2. This finding suggests that the risk of SD in chagasic patients with normal ECG does not differ from that of the healthy population.

### CONCLUSIONS
Initial studies in asymptomatic chagasic patients should be an ECG, chest radiographies and an echocardiogram (47). In case the results are normal, death risk is similar to that of the general population and these patients can therefore lead a completely normal working and sporting life. It must be recalled, however, that these group of patients have to be controlled periodically due to the risk of disease progression, entailing risk of death. The optimal interval between these studies has not been established, though it seems reasonable to perform an annual ECG and the rest of the studies every 3-5 years, according to the shortest follow-up period corresponding to each of the analyzed studies. Similar recommendations can be found in the specific literature, as suggested by Rassi et al. (48) who postulate an algorithm to predict risk based on the ECG, the NYHA functional class, chest radiography and a 24 hour Holter. Concomitantly, Bestetti et al. (49) also suggested a risk stratification algorithm based on the ECG, an echocardiogram and a 24 hour Holter. None of these groups recommends the use of other studies. Furthermore, a recent guide published by the Sociedade Brasileira de Cardiologia suggests a routine ECG and chest radiography to

### Table 2. Clinical characteristics of the population

<table>
<thead>
<tr>
<th>Source</th>
<th>Chagasic patients</th>
<th>Seronegative patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal ECG</td>
<td>Abnormal ECG</td>
</tr>
<tr>
<td>Porto (22)</td>
<td>0.00925926</td>
<td>0.06666667</td>
</tr>
<tr>
<td>Pinto (23)</td>
<td>0.02375449</td>
<td>0.07346189</td>
</tr>
<tr>
<td>Maguire (33)</td>
<td>0.00312826</td>
<td>0.02380952</td>
</tr>
<tr>
<td>Mota (34)</td>
<td>0.00202429</td>
<td>0.01038462</td>
</tr>
<tr>
<td>Manzullo (35)</td>
<td>0.0000231</td>
<td>0.00094545</td>
</tr>
<tr>
<td>Total</td>
<td>0.00763788</td>
<td>0.03505363</td>
</tr>
</tbody>
</table>
RESUMEN
La muerte súbita es infrecuente en la forma indeterminada de la enfermedad de Chagas: una revisión sistemática

La enfermedad de Chagas es un problema sanitario de gran magnitud en América Latina debido a su alta prevalencia, morbilidad y mortalidad. A su vez, las migraciones desde los países latinoamericanos hacia los Estados Unidos y Europa han dispersado a una cantidad significativa de personas portadoras de la enfermedad. Es importante tener en cuenta que la mayoría de los pacientes permanecen en la forma indeterminada de la enfermedad por décadas, sin manifestar ningún síntoma ni signo de su afección. A pesar de ello, hay quienes sostienen que la forma indeterminada conlleva un aumento del riesgo de padecer muerte súbita, aunque no hay estudios que se hayan diseñado específicamente a fin de esclarecer esta cuestión.

En una revisión sistemática de los estudios con seguimiento de pacientes chagásicos asintomáticos con ECG normal y de causa conocida de muerte encontramos 15 artículos que incluyen el seguimiento de 9.382 pacientes. La mortalidad entre los asintomáticos con ECG normal fue muy baja (0,92%), que no resultó estadísticamente diferente de la de los controles no chagásicos (p = 0,38).

Esta revisión sistemática muestra que la muerte súbita es infrecuente en la forma indeterminada. Estos pacientes tienen el mismo riesgo que la población general y por lo tanto se les debe permitir que lleven una vida normal tanto en el aspecto laboral como en lo relativo a su actividad física, sin alarmarlos innecesariamente sobre su condición clínica ni abrumarlos con estudios sofisticados y costosos. Es necesario, sin embargo, el control periódico, ya que si el paciente progresa a la forma cardíaca el riesgo de muerte aumenta notablemente.

Palabras clave > Enfermedad de Chagas - Muerte súbita cardíaca

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Dedicated to:
Daniel Grana, indefatigable worker, selfless friend and outstanding researcher, who died suddenly at the age of 55 years, leaving us astounded and immersed in profound grief

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