ORIGINAL ARTICLE

Risk of Embolic Events in Patients with Chagasic Cardiomyopathy and Atrial Fibrillation Despite Antithrombotic Therapy: Is Anticoagulation Enough?

Riesgo de eventos embólicos en pacientes con miocardiopatía chagásica y fibrilación auricular a pesar de terapia antitrombótica: ¿es la anticoagulación suficiente?

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ABSTRACT

Background: Chagasic cardiomyopathy (CC) differs from other heart failure causes in multiple aspects, highlighting the risk of systemic embolisms. However, few studies have evaluated the risk of embolic events in anticoagulated patients with CC compared with other cardiomyopathies.
Objective: We aimed to analyze the incidence of systemic embolisms in a cohort of anticoagulated patients diagnosed with atrial fibrillation (AF) with and without CC.
Methods: A retrospective cohort study was carried out at a fourth level hospital in Colombia during the period 2014-2020. All patients diagnosed with cardiomyopathy of any etiology and AF, who were on an anticoagulation regimen were included. The primary outcome was the incidence of embolic events. A survival analysis was performed using adjusted Cox proportional hazard models. A p-value <0.05 was considered significant. All statistical tests were two-tailed.
Results: A total of 149 anticoagulated patients with cardiomyopathy were evaluated (median age: 71 years; women: 30.20%). The cumulative incidence of embolic events was significantly higher in patients with CC (17.50%) compared with those presenting other cardiomyopathies (4.95%), despite that the latter had a significantly higher CHA_2DS_2-VASc score (p=0.013). After multivariate analysis, patients with CC had a significantly higher risk of embolic events regardless of the CHA_2DS_2-VASc score and the type of anticoagulant prescribed (HR 5.65; 95% CI 1.46-21.83; p=0.012).
Conclusions: Chagasic cardiomyopathy was associated with a significantly higher risk of embolic events, despite anticoagulation therapy in both groups. More research is required to understand the origin of the risk observed in order to translate this knowledge into specific indications for anticoagulation in patients with CC.

Key words: Cardiomyopathy - Chagas disease - Embolic events - Oral anticoagulation

RESUMEN

Introducción: La miocardiopatía chagásica (MC) difiere de otras causas de insuficiencia cardíaca en múltiples aspectos, destacándose el riesgo de embolias sistémicas. Sin embargo, pocos estudios han evaluado el riesgo de eventos embólicos en pacientes anticoagulados con MC en comparación con otras miocardiopatías.
Objetivo: Nuestro objetivo fue analizar la incidencia de embolias sistémicas en una cohorte de pacientes anticoagulados con diagnóstico de fibrilación auricular (FA) con y sin MC.
Material y métodos: Se realizó un estudio de cohorte retrospectivo en hospital de cuarto nivel en Colombia durante el periodo 2014-2020. Se incluyeron todos los pacientes con diagnóstico de miocardiopatía de cualquier etiología y FA que estuvieran en régimen de anticoagulación. El resultado primario fue la incidencia de eventos embólicos. Se realizó un análisis de supervivencia mediante modelos de riesgos proporcionales de Cox ajustados. Un valor de p <0,05 se consideró significativo. Todas las pruebas estadísticas fueron de dos colas.

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Resultados: Se evaluaron 149 pacientes anticoagulados con miocardiopatía (mediana de edad: 71 años; mujeres: 30,20 %). La incidencia acumulada de eventos embólicos fue significativamente mayor en los pacientes con MC (17,50%) en comparación con aquellos con otras miocardiopatías (4,95 %), a pesar de que estos últimos tenían una puntuación CHA_2DS_2-VASc significativamente mayor (p=0,013). Tras el análisis multivariado, los pacientes con MC tuvieron un riesgo significativamente mayor de eventos embólicos independientemente de la puntuación CHA_2DS_2-VASc y del tipo de anticoagulante prescrito (HR 5,65; IC 95% 1,46-21,83; p=0,012). **Conclusiones:** La MC se asoció con un riesgo significativamente mayor de eventos embólicos, a pesar del tratamiento anticoagulante en ambos grupos. Se requiere más investigación para comprender el origen de este riesgo observado y traducir este conocimiento en indicaciones específicas de anticoagulación para pacientes con MC.

Palabras clave: Miocardiopatía - Enfermedad de Chagas-Eventos embólicos-Anticoagulación oral

INTRODUCTION

Chagas disease (CD) is endemic in American tropical and subtropical regions and has represented a public health problem in Latin America for decades. However, due to migration, it has become a global economic and health burden. (1) It is estimated that there are six million people infected with T. cruzi in Latin America, 300 000 in the United States, and 42 000 in Europe. (2) Chagas disease attributes a substantial burden to the patient and society regarding direct and indirect costs associated with medical care, early mortality, disability, and negative labor consequences such as loss of productivity due to absenteeism and tardiness. (3)

Chagas disease is known to have two forms: acute and chronic. (4) The acute phase of the disease is usually asymptomatic. After this phase, the patient enters a chronic phase, in which about 60-70% remain in the indeterminate form of the disease, characterized by positive serology for CD, but no evidence of structural cardiomyopathy or heart failure (HF) symptoms. (5) In this context, 30-40% of cases progress to clinical forms of the disease, with the cardiac form being the most frequent and severe manifestation. (6,7) Cardiac involvement is characterized by symptoms of HF, alterations of the conduction system, bradyarrhythmia and tachyarrhythmias, in addition to radiographic and echocardiographic alterations. (8,9) Besides, HF of chagasic origin is associated with higher mortality compared with other etiologies. (10)

During the chronic phase, multiple alterations in the structure and function of the myocardium lead not only to the development of HF symptoms but also to the appearance of prothrombotic conditions such as atrial fibrillation (AF) or even intraventricular clots, which are the product of the slow flow and structural alterations in the endocardium. (11,12) This association has been evidenced in some studies evaluating patients with cardiomyopathy of chagasic origin compared with cardiomyopathies of other etiologies. (13) This differential risk could be explained by some of the characteristics of chagasic cardiomyopathy (CC), such as a higher incidence of AF and apical aneurysms. Consequently, multiple studies have found a high incidence of ischemic stroke in patients with heart failure of chagasic etiology, highlighting the significant risk of embolic events with this condition. However, it is unknown whether there is benefit from anticoagulation in these patients despite not meeting the criteria for receiving anticoagulants by CHA_2DS_2-VASc scoring. Besides, few studies have compared the risk of embolic events exclusively in anticoagulated patients with CC versus other heart failure etiologies. Therefore, the objective of the present study was to evaluate the risk of embolic events and bleeding in anticoagulated patients with and without CC treated in a fourth-level specialized center in Colombia.

METHODS

Study population

A retrospective cohort study was conducted between 2014 and 2020 at the Heart Failure and Anticoagulation Clinic of a fourth-level hospital in Floridablanca, Colombia. The medical records of all patients assessed in the Anticoagulation Clinic were reviewed to assess their eligibility. Patients were included if they met the following criteria: a) age ≥18 years; b) having a diagnosis of cardiomyopathy of any etiology, and c) diagnosis of atrial fibrillation. The diagnosis of cardiomyopathy of other etiologies was based on the clinical records information, including hypertensive, ischaemic, and valvular etiologies in this group. On the other hand, we excluded patients with less than two follow-up appointments at the Anticoagulation Clinic and those with incomplete data in the electronic clinical records. A structured format was developed to extract information, which was collected retrospectively, covering sociodemographic, clinical, and laboratory variables.

Outcomes and main exposure

The outcomes of interest were time to first embolic event (including cerebrovascular events and systemic embolisms such as ischemic stroke, acute myocardial infarction of embolic origin, mesenteric ischemia of embolic origin, and other systemic embolisms of cardiogenic origin) and time to the first bleeding event (including minor or major skin, periodontal, other mucosae, intra-articular and central nervous system bleeding). Cardiomyopathy of chagasic origin was considered as the primary exposure, which was verified by registering a positive result of at least two different tests for Chagas Disease (Enzyme-Linked ImmunoSorbent Assay, haemagglutination-inhibition test, or indirect immunofluorescence test) and the presence of electrocardiographic abnormalities compatible with CC (left anterior fascicular block, right bundle branch block, atrioventricular blocks, ventricular premature beats, atrial fibrillation or flutter, heart rate ≤50 beats/min), or echocardiographic findings suggestive of myocardial involvement.

Statistical analysis

Categorical variables are presented as absolute numbers and proportions. The normality of the continuous variables was evaluated using histograms and the Shapiro-Wilk test. Variables with normal distribution are presented as means with their respective standard deviations and those with non-normal distribution are reported as medians with the corresponding interquartile range (IQR). A bivariate analysis comparing the sociodemographic and clinical characteristics according to the cardiomyopathy etiology was performed using the Chi-Square test, Fisher's exact test, Student´st test and the Mann-Whitney U test. The cumulative incidence of the events of interest was calculated with their respective 95% confidence intervals. Survival analysis was performed using the Kaplan-Meier method and adjusted Cox proportional hazard models. A value of $p < 0.05$ was considered significant. All statistical tests were two-tailed. The analyses were performed using the statistical software STATA version 16.

Ethical considerations

This research was carried out following Resolution No. 08430 of 1993 of the Colombian Ministry of Health, which establishes the scientific, technical, and administrative standards for health research. The research protocol was submitted and approved by the Scientific Technical Committee and Research Ethics Committee of the Hospital.

RESULTS

A total of 149 anticoagulated patients with cardiomyopathy were evaluated (Figure 1). Median age was 71 (63-78) years and 30.20% were women. Median left ventricular ejection fraction was 35% (25-46) and median international normalized ratio (INR), 2.5 (2.2-3.1). Among these patients, 56.38% were treated with direct oral anticoagulants (DOACs); 55.17% had coronary artery disease, 26.21% chronic kidney disease; 28.86% had a Chagas disease diagnosis; 26.21% had history of bleeding, and 19.31% had history of embolic events. In 33.10% of cases, patients had an implanted device (pacemaker, cardioverter defibrillator, and others). Median CHA_2DS_2-VASc score was 4 (3-5) points and the median HAS-BLED score was 2 (2-3) points (Table 1).

Coronary artery disease and chronic kidney disease were more frequent in patients with cardiomyopathy of other etiologies than in patients with CC. Patients with non-chagasic cardiomyopathies had an apparent higher risk of embolisms (higher CHA_2DS_2-VASc score) while patients with Chagas' cardiomyopathy had a greater number of devices implanted (Table 2).

The median follow-up time for embolism was 373

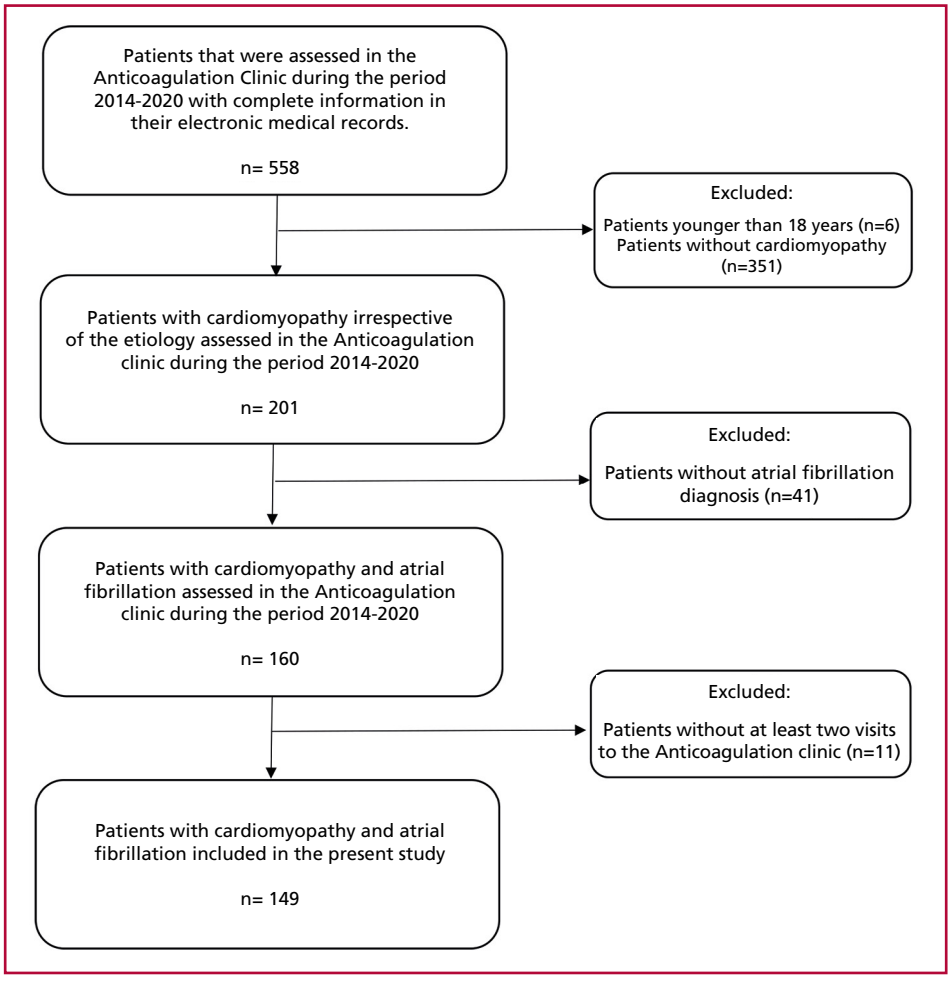

Fig. 1. Flow diagram summarizing the process of patient selection

(128-742) days, with a cumulative incidence of embolic events in the entire cohort of 8.05% (12/149; 95% CI 4.47-14.39%); 16.27% (7/43; 95% CI 7.34 -32.78%) in CC patients and 4.72% (5/106; 95% CI 1.63-11.17%) in other etiologies (p=0.013). Regarding bleeding, median follow-up time was 315 (117-691) days, with a cumulative incidence of 14.09% (21/149; 95% CI 9.19 - 21.28%) for the total cohort; 4.65% (2/43; 95% CI 0.58-16.16%) in CC patients and 17.92% (19/106; 95% CI 11.49-27.29%) in other etiologies (p=0.035).

Chagas disease was significantly associated with the presence of embolic events with a hazard ratio (HR) of 5.65 (95% CI 1.46-21.83; p = 0.012) in a multivariate regression model adjusted for the CHA_2DS_2-VASc score and the type of anticoagulant prescribed (Figure 2), but it was not associated with a higher bleeding risk: HR 0.24 (95% CI 0.05- 1.06; p = 0.059) in a model adjusted for the HAS-BLED score and the type of anticoagulant prescribed (Figure 3). For both models, the proportionality risk assumption was met.

There were no significant differences in embolic events, bleeding, and mortality according to the type of anticoagulant. (Table 3). These results were similar when analyzing only the CC population, but patients

Variable	n= 149
Age (years), median (IQR)	71 (63-78)
Females, n (%)	45 (30.20)
Coronary artery disease, n (%)	80 (55.17)
Chronic kidney disease, n (%)	38 (26.21)
Chagas disease, n (%)	43 (28.86)
History of LV thrombus, n (%)	8 (6.45)
History of bleeding, n (%)	38 (26.21)
History of embolic events, n (%)	28 (19.31)
Implanted devices, n (%)	48 (33.10)
LVEF (%), median (IQR)	35 (25-46)
DOAC use, n (%)	84 (56.38)
Creatinine, mg/dL, median (IQR)	1.0 (0.9-1.2)
INR, median (IQR)	2.5 (2.2-3.1)
CHA_2DS_2-VASc score, median (IQR)	4 (3-5)
HAS-BLED score, median (IQR)	2 (2-3)

DOAC: Direct Oral Anticoagulants; INR: international normalized ratio; IQR: interquartile range; LVEF: Left ventricular ejection fraction.

Table 1. Sociodemographic and clinical characteristics of patients with anticoagulated cardiomyopathy (n = 149).

Tabla 2. Sociodemographic and clinical characteristics according to the cardiomyopathy etiology (n = 149)

Variable	Chagasic Cardiomyopathy (n=43)	Cardiomyopathy of other etiologies (n=106)	p
Age (years), median (IQR)	68 (62-77)	73 (64-78)	0.108
Females, n (%)	15 (34.88)	30 (28.30)	0.428
Coronary artery disease, n (%)	17 (40.48)	63 (61.17)	0.023
Chronic kidney disease, n (%)	6 (14.29)	32 (31.07)	0.037
History of LV thrombus, n (%)	3 (8.11)	5 (5.75)	0.695
History of bleeding, n (%)	12 (28.57)	26 (25.24)	0.679
History of embolic events, n (%)	10 (23.81)	18 (17.48)	0.381
Implanted devices, n (%)	24 (57.14)	24 (23.30)	<0.001
LVEF (%), median (IQR)	35 (23-45)	38 (25-47)	0.510
DOAC use, n (%)	26 (60.47)	58 (54.72)	0.521
Creatinine, mg/dL, median (IQR)	1.0 (0.8-1.2)	1.0 (0.9-1.3)	0.307
INR, median (IQR)	2.4 (2.2-3.1)	2.5 (2.2-3.1)	0.905
CHA_2DS_2-VASc score, median (IQR)	3 (2-4)	4 (3-5)	0.013
HAS-BLED score, median (IQR)	2 (2-3)	3 (2-3)	0.345

DOAC: Direct Oral Anticoagulants; INR: international normalized ratio; IQR: interquartile range; LV: Left ventricular; LVEF: Left ventricular ejection fraction.

treated with warfarin in this group tended to present a higher risk of bleeding.

DISCUSSION

In the present cohort study, a significantly higher risk of embolic events was evidenced in patients with CC, despite receiving anticoagulant therapy and regardless of other clinical factors reflected by the CHA_2DS_2-VASc score and the type of anticoagulant prescribed. On the other hand, there was no significant difference in bleeding risk after adjusting for the HAS-BLED score and the type of anticoagulant received. These findings highlight the differential role of CC compared with other etiologies of heart failure.

Chagasic cardiomyopathy represents a unique model of thromboembolic risk due to its complex pathophysiology, which leads to a series of typical structural and functional alterations of the myocardium. (14) Some of the first evidence of the CC thromboembolic potential was reported in autopsy studies carried out almost 50 years ago, revealing that around 20% of the cases presented multiple cerebral infarcts, half of which were the cause of death. (15-17) Subsequently, several epidemiological studies have observed a significant association between CC and the development of symptomatic cerebrovascular disease, where the meta-analysis by Cardoso et al.¸ which evaluated eight studies that compared the risk of stroke in patients with CC in comparison to other etiologies stands out. This study concluded that patients diagnosed with CC had a risk almost two times higher for this outcome (OR 1.74, 95% CI 1.02-3.00), with a consistent result after sensitivity analysis. (13) Among the studies that compared the risk of cerebrovascular events in patients with CC versus other cardiomyopathy causes, only one corresponded to a cohort study, the majority being cross-sectional or case-control studies. (15,18-24)

Nevertheless, embolic events can occur even in the early stages of the disease, as reported in a cohort of patients with mild CC, in which a rate of 2.7 embolic events per 100 patient-years was estimated, being much higher than that observed in healthy patients. (25,26) However, there seems to be no difference regarding the risk of embolic events in patients in the indeterminate phase of the disease, even though a series of alterations in different coagulation factors have been documented in it, conditions which warrant further study. (25,27)

This observed high embolic risk derives not only from the development of congestive heart failure as a result of the chronic persistence of the parasite in the myocardium but also from the high frequency of severe conduction disorders (notably atrial fibrillation, intraventricular conduction defects, and even atrioventricular blocks), ventricular aneurysms, and mural thrombi, which have been significantly associated with sudden cardiac death and systemic thromboem-

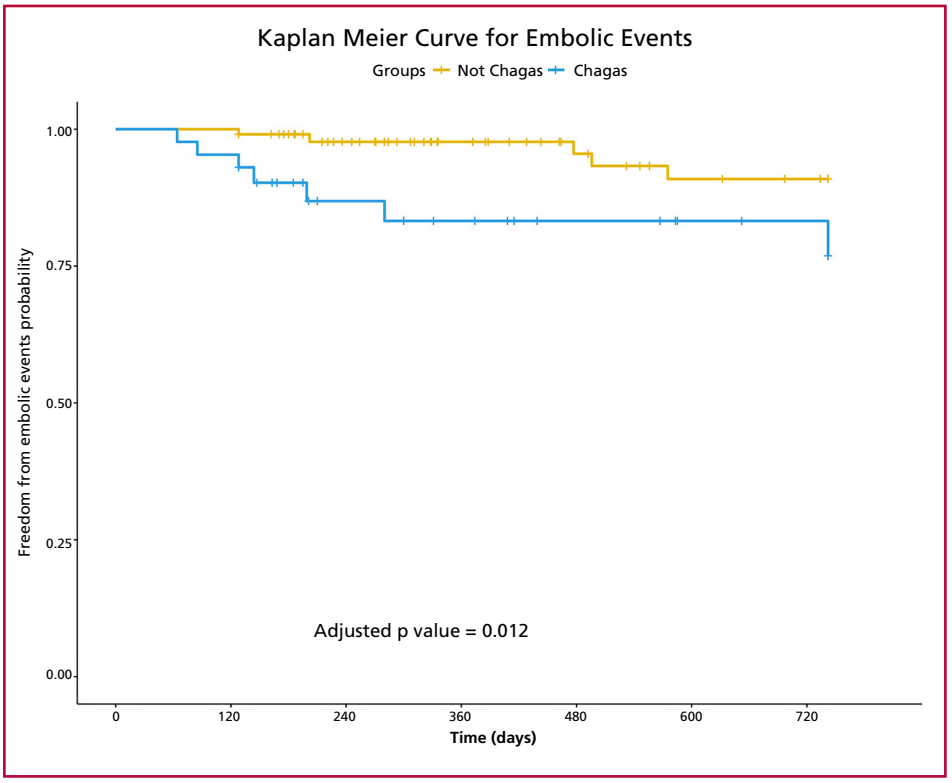

Fig. 2. Freedom from embolic events according to the cardiomyopathy etiology

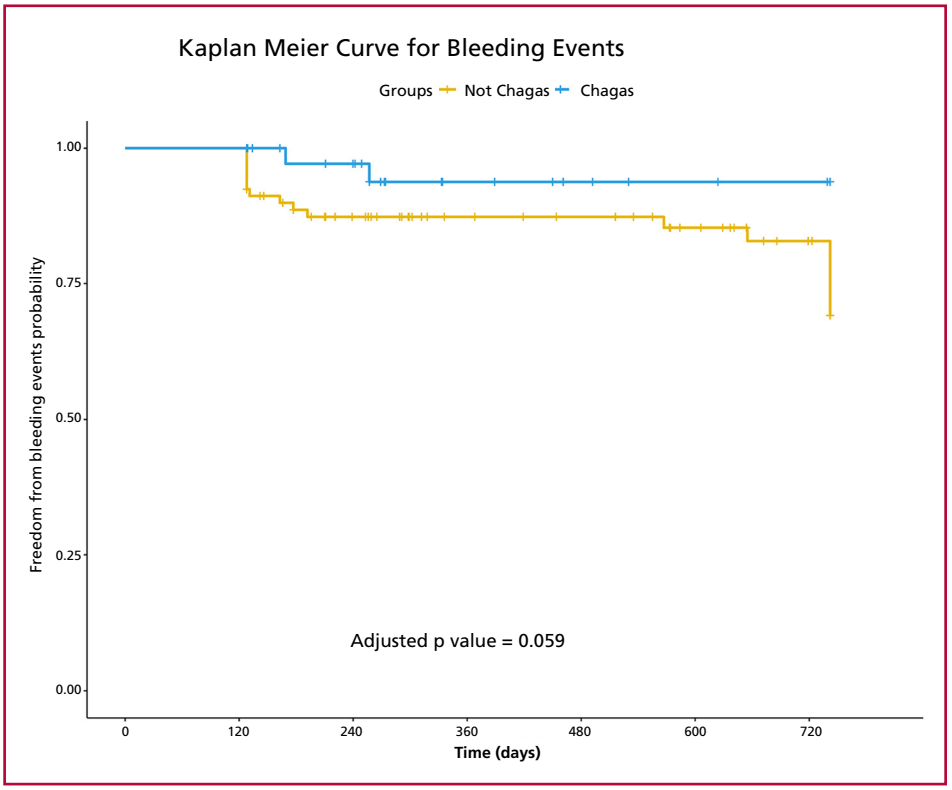

Fig. 3. Freedom from bleeding events according to the cardiomyopathy etiology

Anticoagulant	Embolic events	Bleeding events	Mortality
Warfarin (n= 65)	6 (9.23 %)	12 (18.46%)	2 (3.08%)
DOAC (n=82)	6 (7.31 %)	9 (10.97%)	1 (1.21%)
Total (n=147)	12 (8.16 %)	21 (14.28%)	3 (2.04 %)

Table 3. Outcomes according to the type of prescribed anticoagulant.

bolism in these patients. (2) However, other cardiovascular disorders observed in CC may also increase the risk of thromboembolic events, such as atherothrombosis of the great vessels and small vessel disease, which can be attributed to both typical cardiovascular risk factors and direct damage of T. cruzi to the vascular smooth muscle. (28) This may explain why about 25% of cerebrovascular events in patients with CC are classified as cryptogenic even after conducting additional studies such as echocardiography, 24-hour Holter monitoring, and carotid echo-Doppler. (29)

The present study adds relevant information to the current literature, revealing a significant difference between CC and other cardiomyopathies regarding embolic events incidence despite anticoagulation and after adjusting by relevant covariates. However, even when the potential pathophysiological mechanisms explaining these differences are well-known, there is still very poor awareness of the importance of initiating early prophylaxis in high-risk groups, although they do not fulfill the conventional criteria for anticoagulation used in other cardiomyopathies. (30-32) An important initiative in this aspect is being led by the Instituto de Pesquisa Evandro Chagas and the Fundação Oswaldo Cruz in Brazil. These two entities created the IPEC-FIOCRUZ score, which aims to propose prophylaxis strategies against cardioembolic ischemic stroke in Chagas disease based on clinical risk-benefit, achieving high precision in the identification of high-risk of embolic events groups (area under the ROC curve of this model was 0.90 [95% CI 0.86 - 0.94]). (33) However, the IPEC-FIOCRUZ was validated in a single center using a relatively small sample size, highlighting the need to perform additional studies to obtain an adequate external validation of this score and promote a more widespread use. This will potentially favor optimal anticoagulant prophylaxis among CC patients, further reducing the risk of embolic events in this population. (33)

Finally, not having observed differences in the risk of embolic events when comparing the types of anticoagulants used may reflect the limited statistical power of the present study derived from the relatively small sample. Currently, there is still a debate

in the literature regarding the usefulness of DOAC compared to warfarin for the management of conditions such as intraventricular thrombi and anticoagulation in prosthetic valves. (34,35) There are already studies comparing the types of anticoagulants in these contexts; however, we do not have a record of a study designed to evaluate the benefit of DOAC over warfarin as anticoagulant therapy in the specific context of CD. (36,37) Given their characteristic differences and high cardioembolic risk, it is necessary to carry out research aimed at clarifying both the type of optimal anticoagulant and the particular indications for its use in these patients.

Limitations

We must acknowledge the multiple limitations of the present study, highlighting the small sample size, which may have reduced the probability of identifying significant associations between the variables evaluated. The retrospective nature of the study may influence the quality of the information recorded. Finally, the group of cardiomyopathies of other etiologies represented a heterogeneous population, which may also interfere with the analyses performed. On the other hand, our study has a particular strength derived from the inclusion of patients only with a diagnosis of atrial fibrillation, which allowed us to demonstrate the role of other possible causes of embolism that justify the higher risk observed in the CC group.

CONCLUSION

Chronic CC represents a unique and characteristic myocardial involvement condition, associated with a significantly higher risk of embolic events than other cardiomyopathy etiologies, despite anticoagulation. This result was in accordance with what has been published so far in the scientific literature, with the added value of having evaluated only anticoagulated patients. It is necessary to carry out more studies that allow a clear understanding of the origin of this greater risk observed, in order to translate this knowledge into specific indications for anticoagulation in patients with CC, thus allowing an optimization in its management an improvement in its outcomes.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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