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Original article

# Factors influencing the use of direct oral anticoagulants among patients with chronic chagas cardiomyopathy

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## ABSTRACT

**Objective.** Chronic Chagas Cardiomyopathy (CCC) carries a high risk of embolic events due to structural changes in the left ventricle and frequent conduction disorders. However, there is limited data on anticoagulant prescription patterns and factors influencing the use of direct oral anticoagulants (DOACs) in these patients. This study aims to characterize CCC patients based on the anticoagulant therapy received and identify factors associated with DOACs use. **Materials and methods.** A cross-sectional study was conducted at a tertiary-level hospital in Colombia between 2019-2022. Multivariate logistic regression models were used to assess factors associated with anticoagulant therapy and DOACs use. **Results.** Among 224 CCC patients, 65.7% (n=153) were on anticoagulants, with DOACs being the most prescribed (53%). Notably, 35% of patients at high risk of stroke (CHA2DS2-VASc) were not receiving anticoagulants. Atrial fibrillation (OR 256.08; 95% CI 61.94-1058.72), ventricular aneurysms (OR 4.82; 95% CI 1.54-15.09), and reduced interventricular septal thickness (OR 0.75; 95% CI 0.60-0.92) were associated with anticoagulant use. DOACs were mainly prescribed for patients with atrial fibrillation (OR 13.29; 95% CI 2.47-71.56) and high bleeding risk (HAS-BLED ≥3, OR 11.36; 95% CI 1.15-112.11). **Conclusions.** A significant proportion of CCC patients were not receiving anticoagulants despite their high risk of stroke and embolic events. The use of anticoagulation was significantly associated with atrial fibrillation, the presence of ventricular aneurysms and reduced interventricular septal thickness. It is crucial to raise awareness among healthcare professionals in endemic areas to improve treatment.

**Keywords:** Chagas Disease; Chagas Cardiomyopathy; Anticoagulants (Source: MeSH-NLM).

## RESUMEN

### Factores que influyen en el uso de anticoagulantes orales directos en pacientes con cardiomiopatía chagásica crónica

**Objetivo.** La cardiomiopatía chagásica crónica (CCC) conlleva un alto riesgo de eventos embólicos debido a cambios estructurales en el ventrículo izquierdo y trastornos de conducción frecuentes. Sin embargo, existen datos limitados sobre los patrones de prescripción de anticoagulantes y los factores que influyen en el uso de anticoagulantes orales directos (DOACs) en estos pacientes. Este estudio busca caracterizar a los pacientes con CCC según la terapia anticoagulante recibida e identificar los factores asociados con el uso de DOACs. **Materiales y métodos.** Se realizó un estudio transversal en un hospital de cuarto nivel en Colombia entre 2019-2022. Se utilizaron modelos de regresión logística multivariada para evaluar los factores asociados con la terapia anticoagulante y el uso de DOACs. **Resultados.** Entre los 224 pacientes con CCC, el 65,7% (n=153) recibía anticoagulantes, donde los DOACs fueron los más prescritos (53%). El 35% de los pacientes con alto riesgo de accidente cerebrovascular (CHA2DS2-VASc) no recibía anticoagulantes. La fibrilación auricular (OR 256,08; IC 95% 61,94-1058,72), los aneurismas ventriculares (OR 4,82; IC 95% 1,54-15,09) y el grosor reducido del tabique interventricular (OR 0,75; IC 95% 0,60-0,92) se asociaron con el uso de anticoagulantes. Los DOACs se prescribieron principalmente en casos de fibrilación auricular (OR 13,29; IC 95% 2,47-71,56) y alto riesgo de sangrado (HAS-BLED ≥3, OR 11,36; IC 95% 1,15-112,11). **Conclusiones.** Una proporción significativa de pacientes con CCC no recibía anticoagulantes a pesar de su alto riesgo de accidentes cerebrovasculares y eventos embólicos. El uso de anticoagulación se asoció significativamente con la fibrilación auricular, la presencia de aneurismas ventriculares y la reducción del espesor del tabique interventricular. Es crucial sensibilizar a los profesionales en áreas endémicas para mejorar el tratamiento.

**Palabras clave:** Enfermedad de Chagas; Cardiomiopatía Chagásica; Anticoagulantes (Fuente: DeCS-BIREME).

## Introduction

Chagas disease (CD) is a tropical neglected infectious disease caused by the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*). According to recent estimates from the World Health Organization, *T. cruzi* infection currently affects 8-10 million individuals worldwide, most of them located in Latin America. [1] Nevertheless, current estimates indicate that more than 300,000 individuals with CD currently live in the United States of America, while several studies have suggested that more than 50,000 individuals infected by *T. cruzi* are living in Europe.[2] In addition to its remarkable prevalence, CD is characterized by severe organ involvement, which develops in about 20% of infected individuals after the acute phase. [3] When the heart is the target organ affected, the condition is known as Chronic Chagas Cardiomyopathy (CCC), which represents one of the most prevalent causes of heart failure in Latin America.[1] CCC is a severe and complex cardiomyopathy, characterized by focal replacement of the myocardium by fibrosis, especially in the inferolateral segments and the cardiac apex. [3] This involvement is associated with a rapid deterioration of systolic and diastolic function, in addition to the development of cardiac arrhythmias, especially atrial fibrillation, and structural disorders such as left ventricular aneurysms, among others. [4] All these characteristics have positioned CCC as one of the etiologies of heart failure with the highest morbidity and mortality, in addition to placing CD as the parasitic disease with the highest burden of disease worldwide. [1,5]

Embolic events stand out among the most relevant complications observed in CCC patients. [6] The high prevalence of atrial fibrillation and ventricular aneurysms, which are associated with slow blood flow favoring the development of thrombi in their interior, along with the presence of a proinflammatory and prothrombotic disease state is reflected in a high incidence of stroke and systemic embolisms. [7] Furthermore, recent studies have suggested that CD represents an independent predictor of stroke and mortality in Heart Failure (HF) patients, highlighting the relevance of embolic events in the pathophysiology of CD and CCC. [7-9] Despite this, there is currently no evidence to support the use of anticoagulants in patients with CCC beyond the guideline recommendations for conditions such as atrial fibrillation, significantly limiting the possibility of reducing the incidence and mitigating the impact of embolic complications in this population. The present study aims to characterize a population of patients with CCC according to the type of anticoagulant therapy received and to assess the factors potentially associated with the use of direct oral anticoagulants (DOACs).

## Materials and methods

### Study design and population

This analytical cross-sectional study was conducted between 2019 and 2022 at the Heart Failure and Heart Transplant Clinic of the Fundación Cardiovascular de Colombia in Floridablanca, Colombia. Adult outpatients (> 18 years old) with a positive serological diagnosis of *T. cruzi* infection (positive IgG antibodies), patients with or without atrial fibrillation, and echocardiographic or electrocardiographic abnormalities consistent with chronic Chagas cardiomyopathy were consecutively included during their follow-up evaluations at the clinic. We excluded individuals with neurological or cognitive alterations and people with no access to a telephone line.

### Data collection and variables

Information regarding sociodemographic, clinical, echocardiographic, and laboratory variables was registered at baseline by using a standard form. Sociodemographic data included the age, sex, civil status, residence area, socioeconomic stratum, and healthcare provider. Regarding clinical variables, HF severity was assessed using the New York Heart Association (NYHA) classification and the American College of Cardiology/American Heart Association classification for patients with CCC. The following comorbidities were assessed: type 2 Diabetes Mellitus, chronic kidney disease, arterial hypertension, atrial fibrillation, chronic obstructive pulmonary disease (COPD), peripheral artery disease, cancer, liver disease, and hypercholesterolemia. Furthermore, echocardiographic variables included conventional cardiac dimensions, Doppler measurements, and longitudinal strain by speckle tracking measurements. Finally, laboratory variables included N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitive cardiac troponin T (hs-cTnT), Neutrophil gelatinase-associated lipocalin (NGAL), C-reactive protein (CRP), and Cystatin-C (Cys-C) levels.

### Data collection and variable selection

Clinical and sociodemographic characteristics were extracted from the electronic medical record and recorded in a Microsoft Excel database. Variables that could act as confounders were included: age, sex, history of cardiovascular disease (CVD), socioeconomic status (6-level classification, with level 1 being the lowest and level 6 the highest), diabetes mellitus, smoking, chronic kidney disease, atrial fibrillation, and history of heart failure. CVD was defined as previous coronary revascularization (surgical or percutaneous), stroke, peripheral arterial disease, or documentation of coronary disease through invasive or non-invasive tests. Upon admission, the GRACE score was calculated and cognitive status was assessed with the Mini-Cog tool (score from 0 to 5, where <3 points indicates possible cognitive impairment). LDL cholesterol, creatinine, and hemoglobin values were recorded at admission, and the glomerular filtration rate (GFR) was estimated using the 2009 CKD-EPI equation. During coronary arteriography, the type of vascular access, culprit

vessel, and number of compromised vessels were considered. All patients underwent a transthoracic echocardiogram.

### Procedures

#### Stroke and bleeding risk stratification

The CHA2DS2-VASc score was used to assess the risk of stroke in the evaluated patients as follows: one point was assigned to females, individuals having an age between 65 and 74 years, and those diagnosed with hypertension, type 2 diabetes mellitus, congestive heart failure, and vascular disease. Furthermore, two points were assigned if a history of stroke/transient ischemic attack/thromboembolism was reported and if the age was ≥ 75 years. Patients were classified as having a high risk of stroke when the CHA2DS2-VASc score was ≥ 2 for males and ≥ 3 for females, according to the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation. [10]

On the other hand, the HAS-BLED score was used to evaluate the risk of bleeding by assigning one point per condition: age > 65 years, hypertension, abnormal liver function, abnormal renal function, stroke history, prior major bleeding or predisposition to bleeding, labile International normalized ratio (INR), medication usage predisposing to bleeding, and alcohol use. A score of ≥ 3 defined a high risk of bleeding, as recommended by the 2020 ESC guideline. [10]

#### Study outcome

The primary outcome was anticoagulant therapy use, defined as whether the patients received any anticoagulant drug. The secondary outcome was direct oral anticoagulant (DOAC) use, which was defined as the use of any of the currently available DOACs in Colombia (Apixaban, Rivaroxaban, and Dabigatran).

#### Ethical aspects

The Institutional Committee on Research Ethics approved the research protocol of the study, CEI-2019-00001. All patients provided written informed consent for their participation in the study.

#### Statistical analysis

Categorical variables were presented as numbers and proportions, while continuous variables were reported as medians and interquartile ranges (IQR). The Chi-square and Fischer exact tests were used to assess differences in categorical variables. In contrast, the Mann-Whitney U test and the Kruskal-Wallis test were used for continuous variables. Variables with a p-value < 0.10 in the univariate analysis were included in multivariate logistic regression models adjusted by age and sex to assess the independent predictors of anticoagulant therapy prescription and DOAC use. The results of these models were reported using odds ratios (ORs) and 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant for all tests. All analyses were performed using Statistical Package STATA version 15 (Station College, Texas, USA).

## Results

A total of 224 patients with CCC diagnosis were included, highlighting a majority of males (n=123; 54.9%) and a median age of 67 years (IQR: 60–74). Among the included individuals, most had a NYHA functional class of II (55.4%), 13.4% had a history of stroke, and 62.1% were diagnosed with atrial fibrillation. Most of the patients were receiving anticoagulant therapy (n=144; 64.3%), with most of the patients receiving DOACs, mostly apixaban (n=56; 25%), followed by rivaroxaban (n=47; 20.9%), and dabigatran (n=15; 6.7%). Finally, a total of 26 patients were receiving warfarin (n=26; 11.6%). **Table 1** and **Table 2** summarize the baseline characteristics of the evaluated patients according to the anticoagulant therapy prescribed.

### Stroke and bleeding risk

Regarding stroke risk, the median CHA2DS2-VASc score was 3 (IQR: 2–4), with 143 patients (63.8%) having a high risk of stroke (Males ≥3; females ≥2). Of these high-risk patients, 59.4% were on DOACs, 5.6% were receiving warfarin, and 35.0% were not receiving anticoagulant therapy **(Table 3)**. Moreover, within the DOACs group, 72% had a high risk of stroke, while for patients receiving warfarin, this value was 30.8%. Interestingly, 62.5% of the patients not receiving anticoagulant therapy had a high risk of stroke according to the CHA2DS2-VASc score. Among these patients, 18 (36%) had a previous diagnosis of atrial fibrillation and 16 (32%) were receiving aspirin, with only three patients with an atrial fibrillation (AF) diagnosis receiving aspirin-only treatment.

On the other hand, the median HAS-BLED score was 2 (IQR: 1–2), with 53 patients (23.7%) having a high risk of bleeding. Among patients with high risk of bleeding, 60.4% were on DOACs, 3.8% were receiving warfarin, and 35.8% were not receiving anticoagulant therapy **(Table 3)**. Furthermore, 32% of the patients receiving DOACs had a high risk of bleeding, being this proportion lower for patients receiving warfarin (7.7%) and those not under anticoagulant therapy (23.8%).

### Factors associated with anticoagulant prescription

We identified in the univariate analysis several variables potentially associated with anticoagulant prescription, highlighting stroke history, atrial fibrillation, hypercholesterolemia, diuretics use, implantable cardioverter-defibrillator use, the presence of diastolic dysfunction, the systolic thickness of the interventricular septum (IVS), and the area of the right atrium. Nevertheless, only atrial fibrillation diagnosis (adjusted Odds Ratio (aOR) =256.08; Confidence Interval (CI) 95% 61.94 to 1058.72), the presence of a ventricular aneurysm (aOR=4.82; CI 95% 1.54 to 15.09), and the IVS thickness (aOR=0.75; CI 95% 0.60 to 0.92) were independently associated with anticoagulant prescription in this population **(Table 4)**.

**Table 1.** Baseline demographic, clinical, and laboratory characteristics of the included patients according to the anticoagulation status.

| | DOAC (N=118) | Warfarin (N=26) | No anticoagulant (N=80) | Total (N=224) | p-value |
|---|---|---|---|---|---|
| **Sociodemographic parameters** | | | | | |
| Age (years), median (Q1-Q3) | 70 (63 –76) | 62 (59 – 68.5) | 65 (60–71.3) | 67 (60–74) | < 0.001 |
| Men, n (%) | 61 (51.7) | 22 (84.6) | 40 (50.0) | 123 (54.9) | 0.005 |
| BMI kg/m$^2$, median (Q1-Q3) | 24.5 (21.9 –26.8) | 24.8 (22.5 –27.9) | 24.3 (21.6– 27.4) | 24.5 (21.9–27.2) | 0.984 |
| Residence Area, n (%) | | | | | |
| Urban | 80 (67.8) | 18 (69.2) | 51 (63.8) | 149 (66.5) | 0.799 |
| Rural | 38 (32.2) | 8 (30.8) | 29 (36.2) | 75 (33.5) | |
| Socioeconomic level, n (%) | | | | | |
| Low (1-2) | 94 (79.7) | 23 (88.5) | 65 (81.3) | 182 (81.3) | |
| Middle (3-4) | 22 (18.6) | 3 (11.5) | 14 (17.5) | 39 (17.4) | 0.344 |
| High (5-6) | 2 (1.7) | 0 (0) | 1 (1.2) | 3 (1.3) | |
| Health affiliation, n (%) | | | | | |
| Contributive | 17 (14.4) | 3 (11.5) | 11 (13.8) | 31 (13.8) | |
| Particular | 12 (10.2) | 3 (11.5) | 14 (17.5) | 29 (12.9) | 0.673 |
| Subsidized | 54 (45.8) | 14 (53.8) | 30 (37.5) | 98 (43.8) | |
| Others | 35 (29.7) | 6 (23.1) | 25 (31.2) | 66 (29.5) | |
| **Past medical history and clinical parameters** | | | | | |
| Stroke, n (%) | 23 (19.5%) | 3 (11.5%) | 4 (5.0%) | 30 (13.4%) | 0.013 |
| DM2, n (%) | 20 (16.9%) | 4 (15.4%) | 14 (17.5%) | 38 (17.0%) | 0.969 |
| COPD, n (%) | 16 (13.6%) | 1 (3.8%) | 12 (15.0%) | 29 (12.9%) | 0.325 |
| PAD, n (%) | 1 (0.8%) | 1 (3.8%) | 2 (2.5%) | 4 (1.8%) | 0.483 |
| CKD, n (%) | 24 (20.3%) | 3 (11.5%) | 13 (16.2%) | 40 (17.9%) | 0.511 |
| HBP, n (%) | 58 (49.2%) | 8 (30.8%) | 39 (48.8%) | 105 (46.9%) | 0.216 |
| Bleeding history, n (%) | 15 (12.7%) | 2 (7.7%) | 8 (10.0%) | 25 (11.2%) | 0.701 |
| Labile INR, n (%) | 7 (5.9%) | 2 (7.7%) | 0 (0.0%) | 9 (4.0%) | 0.068 |
| Atherosclerosis, n (%) | 3 (2.5%) | 1 (3.8%) | 1 (1.2%) | 5 (2.2%) | 0.699 |
| CAD, n (%) | 9 (7.6%) | 0 (0.0%) | 10 (12.5%) | 19 (8.5%) | 0.123 |
| Atrial Fibrillation, n (%) | 112 (94.9%) | 17 (65.4%) | 10 (12.5%) | 139 (62.1%) | < 0.001 |
| Valvular disease, n (%) | 34 (28.8%) | 8 (30.8%) | 19 (23.8%) | 61 (27.2%) | 0.669 |
| Hypercholesterolemia, n (%) | 14 (11.9%) | 7 (26.9%) | 13 (16.2%) | 34 (15.2%) | 0.145 |
| Pulmonary Embolism | 2 (1.7%) | 0 (0.0%) | 0 (0.0%) | 2 (0.9%) | 0.404 |
| CCC Stage (ACC/AHA) | | | | | |
| B | 54 (45.8%) | 9 (34.6%) | 31 (38.8%) | 94 (42.0%) | |
| C | 62 (52.5%) | 15 (57.7%) | 49 (61.2%) | 126 (56.2%) | 0.088 |
| D | 2 (1.7%) | 2 (7.7%) | 0 (0.0%) | 4 (1.8%) | |
| NYHA Classification | | | | | |
| I | 23 (19.5%) | 6 (23.1%) | 13 (16.2%) | 42 (18.8%) | |
| II | 65 (55.1%) | 11 (42.3%) | 48 (60.0%) | 124 (55.4%) | 0.589 |
| III | 27 (22.9%) | 8 (30.8%) | 19 (23.8%) | 54 (24.1%) | |
| IV | 3 (2.5%) | 1 (3.8%) | 0 (0.0%) | 4 (1.8%) | |
| ACEI | 39 (33.1%) | 10 (38.5%) | 25 (31.2%) | 74 (33.0%) | 0.794 |
| ARB | 38 (32.2%) | 9 (34.6%) | 23 (28.8%) | 70 (31.2%) | 0.811 |
| Beta-blockers | 111 (94.1%) | 25 (96.2%) | 71 (88.8%) | 207 (92.4%) | 0.285 |
| MRAs | 97 (82.2%) | 22 (84.6%) | 56 (70.0%) | 175 (78.1%) | 0.087 |
| Diuretics | 62 (52.5%) | 17 (65.4%) | 28 (35%) | 107 (47.8%) | 0.008 |
| Digoxin | 9 (7.6%) | 6 (23.1%) | 3 (3.8%) | 18 (8.0%) | 0.007 |
| Antiarrhythmics | 49 (41.5%) | 13 (50.0%) | 24 (30.0%) | 86 (38.4%) | 0.113 |
| ARNIs | 33 (28.0%) | 7 (26.9%) | 17 (21.2%) | 57 (25.4%) | 0.558 |
| ICD use | 50 (42.4%) | 10 (38.5%) | 26 (32.9%) | 86 (38.6%) | 0.111 |
| Pacemaker use | 21 (17.8%) | 2 (7.7%) | 11 (13.9%) | 34 (15.2%) | 0.389 |
| SBP | 110 (1-127.5) | 103 (91-125.3) | 116 (1.8-138.3) | 110.5 (99-130) | 0.080 |
| DBP | 64 (55-75.5) | 64 (57-74.5) | 69.5 (59-78.3) | 66 (56-77) | 0.376 |
| SPMSQ Score | 9 (7-10) | 9.5 (8.8-10) | 8 (7- 9) | 9 (7-10) | 0.008 |
| **Biomarkers** | | | | | |
| Cystatin-C (mg/L) | 1.4 (1.1-1.9) | 1.3 (1.0-1.6) | 1.3 (1.1-1.7) | 1.355 (1.1-1.7) | 0.149 |
| NGAL (ng/mL) | 14.8 (4.4-31.3) | 12.3 (10.8-23.8) | 12.6 (4.9-37.8) | 13.7 (4.9-32.9) | 0.972 |
| NT-proBNP (pg/mL) | 1589 (555.9-3560.3) | 1560 (263.3-4051.5) | 1113 (269-3744.5) | 1349.5 (438.1-3759.3) | 0.464 |
| CRP | 1.9 (1.4-5.1) | 2.4 (1.1-7.7) | 2.3 (1.4-4.1) | 2.2 (1.4-5.0) | 0.980 |
| Hs-cTnT (ng/L) | 15 (7.6-21) | 12 (7.6-23.8) | 11.9 (6.7-19.2) | 14 (7.3-21) | 0.756 |

ACEI: Angiotensin-Converting Enzyme Inhibitors. ARB: Angiotensin II Receptor Blockers. ARNI: Angiotensin Receptor-Neprilysin Inhibitors. BMI: Body Mass Index. CAD: Coronary Artery Disease. CKD: Chronic Kidney Disease. CCC: Chronic Chagas Cardiomyopathy. COPD: Chronic obstructive pulmonary disease. CRP: C-reactive Protein. DBP: Diastolic Blood Pressure. DM2: Diabetes Mellitus type 2. DOAC: Direct oral anticoagulants. HBP: High Blood Pressure. Hs-cTnT: High-Sensitivity Cardiac Troponin T. ICD: Implantable Cardioverter Defibrillator. INR: International Normalized Ratio. MRA: Mineralocorticoid Receptor Antagonists. NGAL: Neutrophil Gelatinase-Associated Lipocalin. NYHA: New York Heart Association. NT-proBNP: N-terminal pro B-type Natriuretic Peptide. SPMSQ: Short Portable Mental State Questionnaire.

### Factors associated with DOACs prescription

On the other hand, regarding the factors associated with DOACs prescription over warfarin, the univariate analysis revealed that age, sex, atrial fibrillation diagnosis, peripheral artery disease diagnosis, a history of bleeding, digoxin use, the left ventricular ejection fraction, and a HAS-BLED score ≥3 were significantly associated with DOACs prescription. **Table 5** summarizes the result of the multivariate logistic regression analysis, including only the variables independently associated with DOACs prescription.

## Discussion

Chagas disease represents an independent risk factor for stroke and systemic embolisms, independently of the severity of the cardiomyopathy; nevertheless, there are currently no specific recommendations for anticoagulant therapy in this special population. In the present study, we assessed the use of anticoagulants in a real-world cohort of patients with chronic Chagas Cardiomyopathy in an endemic region. We observed a significant proportion of patients with CCC and high risk of stroke, according to their CHA2DS2-VASc score, that are currently not receiving anticoagulant therapy. Furthermore, we identified several sociodemographic, clinical and echocardiographic factors significantly associated with anticoagulant prescription and type of anticoagulant prescribed in this population.

The association between the diagnosis of CD and a higher risk of stroke was discovered more than 20 years ago, as several autopsy and clinical studies started revealing a significantly higher incidence of cardioembolic events (0.56 to 2.67 per 100 person-years) in CD and CCC patients compared to the general population. [11-16] Moreover, it has been estimated that about 20% of stroke patients in endemic areas are seropositive for *T. cruzi*, highlighting the critical role of this entity in the pathophysiology of stroke in these regions. [7] Factors associated with this outcome include the high incidence of AF in this population, which has been estimated at between 10% and 20%, and structural alterations such as ventricular aneurysms, which result in the development of intracardiac thrombi. [4,17,18] The high incidence of AF reported in our study coincides with the profile of the population evaluated. This is due to the fact that our cohort corresponds to a group of patients with established cardiomyopathy referred to a fourth-level cardiovascular center. In addition, the inclusion of patients with previous cardiovascular conditions favored the selection of individuals at high risk of AF.

Nevertheless, cardioembolic events are not the only mechanism behind the development of stroke in CCC, as other pathophysiological processes present in CD also promote the development of this complication, highlighting small vessel disease and large vessel atherosclerosis. [6,19] Furthermore, the proinflammatory status characteristic of CD and CCC has been recently associated with a hypercoagulable state characterized by a higher level of molecules such as prothrombin fragments 1 + 2 (F1+2), PAI-1, and P-selectin. Higher levels of these factors favor fibrin synthesis, in addition to reducing its degradation through inhibition of plasminogen activation. [20]

Considering the multifactorial origin of embolic events observed in patients with CCC, it is crucial to use criteria specific to this condition to determine the eligibility of patients to receive anticoagulation therapy. With this objective in mind, the study by *Sousa et al.*, published in 2007, evaluated the risk factors for stroke in patients with CD and developed a scoring system to guide the decision of anticoagulation in this population.[12] This study included 1043 patients, who were followed for a median of 5.5 years, highlighting a stroke incidence of 3% or 0.56% per year. The score was based on four variables: systolic dysfunction (two points), apical aneurysm (one point), ventricular repolarization disorder (one point), and age over 48 years (one point). From this study, it was recommended that anticoagulant therapy be initiated in patients with a score of more than two points, while in those with less than two points, the recommendation indicated individualized management based on the risk of bleeding and embolic events in each particular patient.[12] Although this study and its recommendations are included in the Brazilian consensus on Chagas disease, the lack of validation of its results, as well as the low incidence of the outcome, have significantly limited the application of this scale. [6]

Therefore, at present, the decision to initiate anticoagulant therapy in patients with CCC is individualized and mostly based on extrapolations of recommendations made for other conditions such as atrial fibrillation. [6] In this context, the results of the present study acquire relevance by highlighting the trends in the use of anticoagulants in this population. Firstly, suboptimal use of anticoagulant therapy in patients with a potential indication for anticoagulant therapy given by the CHA2DS2-VASC score was observed, with around one-third of these patients reporting the use of aspirin. This highlights the potential lack of routine stroke risk assessment in this population, which may derive from a limited knowledge of CCC-related cardioembolic complications.[21,22] We highlight in this regard the need to improve awareness in health care professionals about the risk of embolic events in these patients to optimize the stroke risk assessment during clinical consultations and increase the use of anticoagulant therapy when indicated. [21,22]

Furthermore, the multivariate logistic regression analysis indicated that patients with atrial fibrillation, and at least one aneurysm of the left ventricle had a significantly higher probability of receiving anticoagulant therapy, while the thickness of the interventricular septum in systole was negatively associated with anticoagulants use. As expected, patients with atrial fibrillation were more frequently anticoagulated due to

**Table 2.** Echocardiographic parameters of the included patients.

| | DOAC (N=118) | Warfarin (N=26) | No Anticoagulant (N=80) | Total (N=224) | p-value |
|---|---|---|---|---|---|
| **Echocardiographic parameters** | | | | | |
| Interventricular Septum in Diastole (mm)* | 10 (8–12) | 10 (8– 10.8) | 10 (8– 12) | 10 (8– 12) | 0.787 |
| Posterior Wall Thickness in Diastole (mm)* | 7 (6– 8) | 7 (6–8) | 7 (6– 8) | 7 (6– 8) | 0.135 |
| Interventricular Septum in Systole (mm)* | 13 (11–15) | 12 (10–14.750) | 13 (12–15) | 13 (11– 15) | 0.345 |
| Posterior Wall Thickness in Systole (mm)* | 9 (8–10) | 8 (7– 9) | 9 (7– 11) | 9 (7.3–11) | 0.208 |
| LV Indexed Mass (g/m$^2$)* | 117 (86 –151) | 129.5 (111.3–161.8) | 122 (82– 167) | 119 (86 – 158) | 0.465 |
| LVEF (%)* | 39 (30–49) | 40 (28.5 – 46) | 41 (27.5 – 50.5) | 40 (28.3 – 49) | 0.738 |
| ESV (mL)* | 67 (49 – 115) | 118 (62.8 –147.8) | 83 (49–147) | 77 (49.3–128.5) | 0.153 |
| EDV (mL)* | 116 (89 –175) | 182 (112– 201.750) | 135 (97.5 –206) | 127.5 (93–189.8) | 0.047 |
| RA area (cm$^2$)* | 21 (16– 27) | 22.5 (18–31) | 17 (14–22) | 19 (16–25) | 0.002 |
| LA area (cm$^2$)* | 27 (21–31) | 29.5 (25– 32) | 22 (18–27.3) | 25.5 (20– 31) | < 0.001 |
| Left atrial area (cm$^2$)* | 53 (42.750–72) | 57 (47–83) | 45 (30–57) | 51 (39–69.3) | 0.001 |
| Mitral E wave velocity (cm/s)* | 78 (62–95) | 91 (74–96) | 68.5 (55.3– 84.8) | 74.5 (59.8–94) | 0.001 |
| Mitral annulus velocity (cm/s)* | 53 (30– 77) | 60 (37.5– 83.5) | 75.5 (58–89.8) | 68.5 (41.3–80.8) | 0.004 |
| MAPSE (mm)* | 10 (8– 12) | 10.5 (8– 12.3) | 11 (8–13) | 10 (8–12) | 0.468 |
| TAPSE (mm)* | 16.5 (12 –19) | 15 (14–19.8) | 17 (15– 21) | 17 (13– 20) | 0.054 |
| Lateral S' velocity (cm/s)* | 5 (4.250- 8) | 5 (4.5- 7) | 6 (4- 8) | 6 (4- 8) | 0.749 |
| Lateral E' velocity (cm/s)* | 9 (6– 12) | 10 (7– 11) | 7 (5–11) | 8 (5.250– 11) | 0.050 |
| Lateral A' velocity (cm/s)* | 6.5 (4– 10) | 9 (3.5–10.5) | 9 (7–12) | 8 (5–11) | 0.006 |
| Septal S' velocity (cm/s)* | 5 (4– 6) | 5 (3.5– 5.5) | 5 (4–7) | 5 (4–6) | 0.200 |
| Septal E' velocity (cm/s)* | 5.5 (4.3- 8) | 6 (4- 7) | 5 (3-7) | 5 (4- 7) | 0.163 |
| Septal A' velocity (cm/s)* | 6 (3– 9) | 6 (2–8.5) | 8 (6–10) | 7 (4–9.3) | 0.002 |
| LV Aneurism | 56 (49.12%) | 8 (32%) | 22 (27.85%) | 86 (39.45%) | 0.197 |
| Diastolic dysfunction | | | | | |
| I | 63 (54.8%) | 13 (52.0%) | 29 (37.2%) | 105 (48.2%) | 0.001 |
| II | 23 (20.0%) | 1 (4.0%) | 33 (42.3%) | 57 (26.1%) | |
| III | 12 (10.4%) | 5 (20.0%) | 8 (10.3%) | 25 (11.5%) | |
| IV | 17 (14.8%) | 6 (24.0%) | 8 (10.3%) | 31 (14.2%) | |
| GLS (%)* | -10 (-13.5 – -6.9) | -8.9 (-11.2– -4.7) | -9.3 (-12.8 – -6.4) | -9.7 (-13 – -6.6) | 0.211 |
| Mechanical Dispersion (ms)* | 71 (50– 109) | 78 (45.3– 110) | 73 (55– 105.5) | 73 (51– 108.3) | 0.911 |
| Apical-Septal | -10.5 (-16 – -2.8) | -7 (-12.3 – -1.3) | -9 (-15 – -4.3) | -9 (-15 – -3) | 0.249 |
| Apical-Anterior | -9 (-15– -3.8) | -6 (-8– -3.3) | -7.5 (-11.8 – -2) | -8 (-14 – -3) | 0.264 |
| Apical-Lateral | -7.5 (-13 – -2.8) | -5 (-8 – -2) | -7 (-11.8 – -0.3) | -7 (-13 – -2) | 0.326 |
| Apical-Inferior | -10 (-18 – -3.8) | -6 (-12.3– 0) | -8.5 (-15 – -1.3) | -9 (-16 – -2) | 0.268 |
| Mid-Anteroseptal | -12.5 (-16 – -8) | -11.5 (-14 – -8.3) | -11.5 (-17 – -6) | -12 (-16 – -7) | 0.652 |
| Mid-Anterior | -10 (-14 – -6) | -9 (-13.250– -4) | -11 (-14 – -5) | -10 (-14 – -6) | 0.632 |
| Mid-Anterolateral | -8 (-13 – -3) | -7.5 (-11.3 – -1.8) | -7 (-12.5– -3) | -7 (-13– -3) | 0.799 |
| Mid-Inferolateral | -9 (-14– -2) | -8 (-13– -2.8) | -6 (-12– 1.5) | -7.5 (-13– -2) | 0.314 |
| Mid-Inferior | -9 (-14– -4) | -8.5 (-14– -4.5) | -8 (-12.750– -4) | -9 (-14– -4) | 0.687 |
| Mid-Inferoseptal | -12 (-16– -7) | -8.5 (-12.3– -7) | -10.5 (-15.8– -7) | -11 (-16– -7) | 0.752 |
| Basal-Anteroseptal | -10.5 (-15– -7) | -7.5 (-10– -5.5) | -10.5 (-15– -5) | -10 (-15– -6) | 0.217 |
| Basal-Anterior | -11 (-14– -8) | -7.5 (-13– -2) | -11.5 (-15– -6) | -11 (-14– -7) | 0.279 |
| Basal-Anterolateral | -8 (-14– 2.3) | -4.5 (-9.3– 3.3) | -7.5 (-15– 2) | -8 (-14– 2.8) | 0.347 |
| Basal-InferoLateral | -7 (-14– 3) | -6.5 (-11– 0) | -5 (-15– 3) | -6.5 (-13– 3) | 0.779 |
| Basal-Inferior | -10 (-14– -4.8) | -8.5 (-13– -5.8) | -8.5 (-13.8– -6) | -9 (-14– -5) | 0.986 |
| Basal-Inferoseptal | -8 (-11.250– -5) | -7.5 (-10.5– -4) | -9 (-13– -5) | -8 (-12– -5) | 0.578 |
| PSAP | 47 (44 – 51.5) | 54 (47–58) | 51 (48–58.3) | 49 (45– 55.3) | 0.084 |

EDV: End-Diastolic Volume. ESV: End-Systolic Volume. GLS: Global Longitudinal Strain. LA: Left Atrium. LVEF: Left Ventricular Ejection Fraction. MAPSE: Mitral Annular Plane Systolic Excursion. RA: Right Atrium. PAD: Peripheral Artery Disease. PSAP: Pulmonary Artery Systolic Pressure. SBP: Systolic Blood Pressure. TAPSE: Tricuspid Annular Plane Systolic Excursion.

**Table 3.** Anticoagulant therapy among patients with Chronic Chagas Cardiomyopathy according to the risk level of stroke and bleeding.

| | DOAC N (%) | Warfarin N (%) | No Anticoagulant N (%) | p-value |
|---|---|---|---|---|
| CHA2DS2-VASc | | | | < 0.001 |
| Low risk (Male: 0-2; female: 0-1) | 33 (27.97) | 18 (69.23) | 30 (37.50) | |
| High Risk (Male ≥3; female ≥2) | 85 (72.03) | 8 (30.77) | 50 (62.50) | |
| HAS-BLED | | | | 0.108 |
| Low risk (<3) | 86 (72.88) | 24 (92.31) | 61 (76.25) | |
| High Risk (≥ 3) | 32 (27.12) | 2 (7.69) | 19 (23.75) | |

DOAC: Direct oral anticoagulants.

the routine stroke risk assessment performed in these patients, while anticoagulation in patients with a left ventricular aneurysm may be explained by the presence of a thrombus inside the aneurysm defect. [6,23] On the other hand, the thickness of the IVS may reflect the degree of ventricular dilatation observed in advanced stages of the disease, which correlates with the presence of aneurysms but also with the risk of embolic events as evidenced in multiple studies. [7,9]

Similarly, the multivariate analysis evaluating the factors associated with the prescription of DOACs suggested the diagnosis of atrial fibrillation as the variable most strongly associated with the use of these drugs. This result may potentially derive from greater use of warfarin in scenarios other than AF in which there is little evidence regarding DOACs benefit, such as the presence of intracavitary thrombus. [24,25] However, the presence of left ventricular aneurysms was not associated with the type of anticoagulant prescribed, potentially due to the limited sample size in our study. Moreover, patients prescribed with DOACs presented a significantly higher risk of bleeding according to the HAS-BLED score; therefore, DOACs selection may have been influenced by the lower bleeding risk attributable to their use compared to warfarin in some scenarios. [26,27] On the other hand, male patients were significantly less prescribed with DOACs, which is consistent with a previous study performed in patients with atrial fibrillation in Spain. [28] Similarly, peripheral artery disease was associated with significantly lower odds of DOACs prescription, which may be potentially explained by the conflicting evidence regarding the benefit of DOACs use in this condition compared to warfarin and antiplatelet therapy.[29,30] Finally, higher values of the left ventricle ejection fraction were associated with lower odds of DOACs prescription, which may reflect the preference for these medications in patients with more advanced heart failure.

The present study suffers from multiple limitations, most notably its small sample size, which limited the possibility of evaluating additional relevant factors associated with anticoagulant prescription due to lack of statistical power and risk of model overfitting. On the other hand, relevant psychosocial factors that could have influenced the prescription of anticoagulants were not considered. Finally, there was no information on the history of intraventricular thrombi, arrhythmic load, or clinically relevant arrhythmia events in this population.

In conclusion, a significant proportion of patients with chronic Chagas cardiomyopathy were not receiving anticoagulant therapy, despite their high risk of stroke and embolic events. The use of anticoagulation was significantly associated with atrial fibrillation, the presence of ventricular aneurysms, and reduced interventricular septal thickness. In addition, DOACs were preferred over warfarin in the female sex, in patients with atrial fibrillation, and in those with a

**Table 4.** Factors independently associated with anticoagulant therapy in patients with chronic Chagas cardiomyopathy.

| | OR (95% CI) | p-value |
|---|---|---|
| Atrial Fibrillation | 256.08 (61.94-1058.72) | <0.001 |
| Ventricular Aneurysm | 4.82 (1.54-15.09) | 0.007 |
| IVS-Systole | 0.75 (0.60-0.92) | 0.006 |

All differences adjusted by age and sex.
OR: Odds Ratio. IVS-Systole: Interventricular Septum-Systole

**Table 5.** Factors independently associated with direct oral anticoagulant use compared with warfarin use in patients with chronic Chagas cardiomyopathy.

| | OR (95% CI) | p-value |
|---|---|---|
| Male sex | 0.13 (0.02-0.72) | 0.019 |
| Peripheral Artery Disease | 0.02 (0.01-0.62) | 0.025 |
| Atrial Fibrillation | 13.29 (2.47-71.56) | 0.003 |
| LVEF (%) | 0.89 (0.82-0.97) | 0.009 |
| HAS-BLED, score ≥ 3 | 11.36 (1.15-112.11) | 0.038 |

All differences adjusted by age and sex.
OR: Odds Ratio. IVS-Systole: Interventricular Septum-Systole

high risk of bleeding, whereas the use of these drugs was lower in patients with peripheral artery disease and in those with higher left ventricular ejection fraction values. Future studies evaluating the potential benefit of DOACs compared to warfarin with respect to the risk of embolic and bleeding events in this population will allow the generation of specific recommendations for patients with CCC considering their particular risk profile. Until then, awareness about the use of anticoagulants in these patients needs to be increased through education campaigns aimed at health professionals about the factors associated with embolic events in this population.

### Author's Contributions

**SAGO:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing-Original Draft. **LZR:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - Review & Editing, Supervision, Project administration. **LJAM:** Investigation, Writing - Review & Editing. **MAQS:** Investigation, Writing - Review & Editing. **LPBM:** Investigation, Writing - Review & Editing. **AYSG:** Writing - Review & Editing, Visualization. **LEE:** Conceptualization, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

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