

## Prevention Strategies of Cardioembolic Ischemic Stroke in Chagas' Disease

Andréa Silvestre de Sousa<sup>1,2</sup>, Sérgio Salles Xavier<sup>1,2</sup>, Gabriel Rodriguez de Freitas<sup>2</sup>, Alejandro Hasslocher-Moreno<sup>1</sup>

Instituto de Pesquisa Clínica Evandro Chagas – FIOCRUZ/RJ<sup>1</sup>, Universidade Federal do Rio de Janeiro - UFRJ<sup>2</sup> - Rio de Janeiro, RJ - Brazil

### Summary

**Background:** The cardioembolic (CE) ischemic stroke is an important clinical manifestation of chronic chagasic cardiopathy; however, its incidence and the risk factors associated to this event have yet to be defined.

**Objective:** To determine prevention strategies for a common and devastating complication of Chagas' disease, the cardioembolic (CE) ischemic stroke.

**Methods:** 1,043 patients with Chagas' disease were prospectively evaluated from 03/1990 to 03/2002 and followed up to 03/2003. Cox regression was performed to create the CE risk score that was related with the annual incidence of this event: 4-5 points - >4%; 3 points - 2-4%; 2 points - 1-2%; 0-1 points - <1%. We evaluated the efficacy and safety of two treatment cohorts: (1) 52 patients who used warfarin (INR 2-3) for 14±14 months; (2) 104 patients who used acetylsalicylic acid (ASA) (200 mg/d) for 22±21 months.

**Results:** In group (1), the risk of a major bleeding that needed blood transfusion was 1.9% a year, without CE. Cox regression was used to identify 4 independent variables associated to the event (systolic dysfunction, apical aneurysm, primary alteration of ventricular repolarization and age > 48 years) and an CE risk score was developed, which was associated with the annual incidence of this event. In group (2) there were no bleeding complications and the annual incidence of CE was 3.2%, all of them in patients with 4-5 points.

**Conclusion:** Based on the risk-benefit analysis, warfarin prophylaxis for cardioembolic stroke in Chagas' disease is recommended for patients with a score of 4-5 points, in whom the risk of CE overweighs the risk of a major bleeding. With a 3-point score, the risks of bleeding and CE are the same, so the medical decision of using either warfarin or ASA has to be an individual one. In patients with a low risk of CE (2-point score) either ASA or no therapy can be chosen. The prophylaxis is not necessary in patients with 0-1 point scores, in whom the stroke incidence is near zero. (Arq Bras Cardiol 2008; 91(5) : 280-284)

**Key words:** Chagas' cardiomyopathy; cerebrovascular accident/complications; risk factors; prognosis.

### Introduction

Chagas' disease currently remains an important public health problem in Latin America, where there are around 16 to 18 million infected patients, of which 3 to 5 million are in Brazil<sup>1</sup>.

Around 30% of these patients will develop the chronic Chagasic cardiopathy, the most prevalent symptomatic clinical form and the most important determinant of its severity<sup>2,3</sup>, which has heart failure, tachy- and bradyarrhythmias and thromboembolic events as the main clinical manifestations<sup>4</sup>.

The actual incidence of the cardioembolic ischemic stroke (CE) in Chagas' disease has not been adequately defined. Although preliminary studies have suggested that these events can constitute relevant prognostic factors, their risk is not definitely known in chronic chagasic cardiopathy<sup>5</sup>.

Considering the clinical and socioeconomic importance of the cardioembolic ischemic stroke, studies that define its risk and propose preventive measures will always be very important. Within the model of cardioembolic stroke, the only subgroup with a well-established proposal of prophylaxis is the atrial fibrillation one<sup>6</sup>. Another model that has been described, the dilated cardiomyopathy model<sup>7-11</sup>, has not presented prospective studies capable of defining prevention strategies. In our country, the chronic chagasic cardiopathy can significantly contribute to the genesis of this lethal and certainly incapacitating event, maybe due to its highly emboligenic nature, justified by the innate characteristics of the cardiopathy<sup>12-15</sup>.

Considering such evidence, the present study was carried out aiming at proposing prevention strategies based on a risk-benefit analysis that are more adequate for this cardiopathy and its features.

### Methods

Consecutive patients admitted during the period of March 1990 to March 2002 who presented positive serology for Chagas' disease (direct immunofluorescence > 1:80 and ELISA

**Mailing address:** Andréa Silvestre de Sousa •

Fundação Oswaldo Cruz – IPEC – Av. Brasil, 4365 – Manguinhos – 21045-900 – Rio de Janeiro, RJ - Brazil

E-mail: asilvestre@cardiol.br

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> 1.2) were included in this prospective and observational cohort study. The patients were followed until March 2003, with a minimum follow-up period of 1 year.

The exclusion criteria were the evidence of another, non-chagasic cardiopathy or the patient's decision to withdraw from the study due to personal reasons or trip, with a follow-up period < 1 year.

All patients were submitted to the same clinic-epidemiological, electrocardiographic (12-lead electrocardiogram at rest with long DII derivation), radiographic (chest X-ray) and echocardiographic (using conventional cuts and their variations, aiming at the identification of segmental alterations that are specific for the chagasic cardiopathy, especially the apical aneurism) evaluation protocol.

The patients were followed on an outpatient basis, using specific medications directed at the symptoms or the presence of the cardiopathy: angiotensin-converting enzyme inhibitor, beta-blockers, diuretics, digitalis and anti-arrhythmic drugs.

Two specific treatment subpopulations were studied separately: patients using oral anticoagulation drugs according to the current guidelines (atrial fibrillation or flutter, intracavitary thrombus or previous cardioembolic event) and patients using acetylsalicylic acid (hypertensive patients, patients with diabetes and metabolic syndrome or those with apical aneurism associated to systolic dysfunction, the latter being a consensual indication of the researchers).

Events were defined as all the cases of ischemic stroke or transient ischemic attack defined as the cardioembolic type, according to the TOAST<sup>16</sup> classification. Computed tomography (CT) of the skull with and without contrast and Doppler of the carotid and vertebral arteries were performed whenever possible in the presence of the event.

All the cases classified by the group cardiologists were retrospectively evaluated by a neurologist blinded to the cases, applying the TOAST classification and establishing the inter-observer concordance. In case of discordance, the neurologist's evaluation was the one considered.

### Statistical analysis

A database with the variables studied was constructed using the SPSS software, version 11.0.

The degree of inter-observer concordance for the etiological diagnosis of the cardioembolic event according to the TOAST classification was evaluated by kappa statistics, with substantial concordance being defined when  $\kappa$  is between 0.61 and 0.8 and almost perfect concordance when  $\kappa$  is > 0.8.

Cox regression was used for the uni- and multivariate analysis of the risk predictors, allowing the construction of scores with specific risk subgroups. The accuracy of the constructed model was evaluated through the area under the ROC curve (Statistics C). The level of significance was set at 5% for all tests.

### Results

A total of 1,043 patients were followed during the period of March 1990 to March 2003, with complete follow-up in 84% of the cases (875 patients). The time of follow-up was  $65.6 \pm 44$  months (5.5 years). The mean age of the general cohort was  $45.8 \pm 11.7$  years, with a slight predominance of the female sex (53.4%).

Thirty-six evolution events were identified, with a diagnosis of cardioembolic stroke in 31 patients, resulting in an incidence of 3% or 0.56% per year. Skull CT was performed in 30 cases (83.3%) and Doppler of the carotid and vertebral arteries was performed in 21 patients (58.3%).

The concordance regarding the etiological diagnosis of ischemic stroke between the cardiologists and the neurologist was considered to be substantial, with a correlation coefficient of  $0.76 \pm 0.13$ .

Cox regression was used to construct a predictive model of CE ischemic stroke and a score of points was defined for each one of the independent variables selected, derived from the coefficients of regression of the multivariate analysis: 2 points for the systolic dysfunction and 1 point for the others (apical aneurism, primary alteration of the ventricular repolarization at the ECG and age > 48 years). A risk score was created, attributing to each patient 0 to 5 points, according to the presence or absence of each one of the identified risk factors. Table 1 describes the values of the coefficients of regression, score of points, standard error (SD), p and hazard ratio (HR) with a 95% confidence interval. The area under the ROC curve of this model was 0.90 (95%CI of 0.86 to 0.94). The incidence of CE ischemic stroke rises as the score of points increases, as shown in Figure 1.

### Treatment cohorts

A total of 52 patients used warfarin (20 cases of atrial fibrillation, 18 cases of CE stroke and 15 cases with intracavitary thrombi), aiming at keeping INR values between 2 and 3, with a follow-up time of  $13.99 \pm 14.12$  months. The higher incidence of bleeding, which necessitated blood transfusion, was 1.9% (n=1), with 100% efficacy in preventing the CE stroke.

**Table 1 - Predictive Model of CE ischemic stroke - Cox Regression**

	Coefficient	Score	SD	p	HR (95% CI)
Systolic Dysfunction	2.6	2	0.52	<0.001	13.21 (4.72-37)
Apical aneurysm	0.84	1	0.39	0.029	2.32 (1.09-4.95)
PAVR	0.96	1	0.40	0.016	2.62 (1.20-5.7)
Age>48 yrs	1.11	1	0.43	0.011	3.02 (1.29-7.09)

SD - standard deviation; HR - hazard ratio; 95% CI - confidence interval; PAVR - primary alteration of the ventricular repolarization.

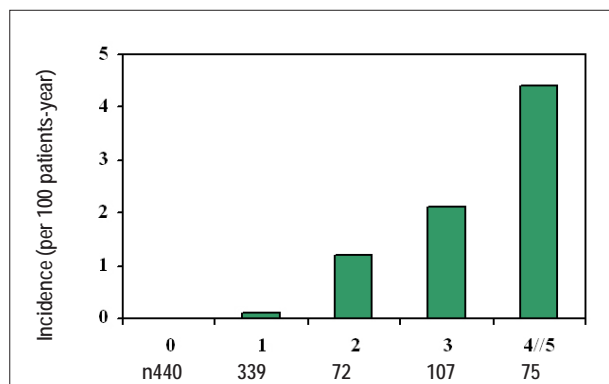


Figure 1 - Incidence-rate of CE ischemic stroke – Point Score

ASA was prescribed to 113 patients during the follow-up period, with a mean dose of 200 mg/dia. The mean follow-up period was  $22.8 \pm 22.6$  months, with no hemorrhagic complications. When the patients who initiated ASA use after the event were excluded, we identified 5 patients who evolved with CE ischemic stroke, all in the high-risk subgroup, with a score of 4-5 points. The incidence of CE ischemic stroke in all patients using ASA was 4.8% (3.2% a year) and 18% (13.3% a year) in the subgroup of patients with a score of 4-5 points.

#### Risk-benefit analysis

Considering the risk-benefit analysis, warfarin would be indicated to patients with a score of 4-5 points in whom the incidence of event (4.4% a year) outweighs the higher incidence of bleeding, which was approximately 2% a year in this cohort. In the subgroup with a score of 3 points, the incidence of the event and of bleeding with anticoagulant drugs is equivalent, with ASA or warfarin being indicated according to the individual risk of bleeding or embolization. Patients with a score of 2 points, with a low incidence of CE ischemic stroke (1.22% a year), should receive ASA or no prophylaxis. Patients with a score of 0-1 points, with a near-zero incidence of event, do not need prophylaxis. Table 2 summarizes prophylaxis recommendation, including the incidence of CE ischemic stroke in each risk subgroup.

## Discussion

The incidence of CE ischemic stroke in this cohort of patients with Chagas' disease was 0.56% a year, in a mean follow-up period of 5.5 years. This value seems to be lower than that described for ischemic cardiopathy, where the incidence of CE ischemic stroke was 1.1 to 1.8% a year<sup>7-11</sup>. However, these studies included only higher-risk patients, with moderate to severe systolic dysfunction. If this specific subgroup of the cohort is analyzed, it can be inferred that chagasic cardiopathy has a higher emboligenic potential, considering that the incidence of CE ischemic stroke in patients with moderate to severe dysfunction in this cardiopathy was 3.25% a year. In fact, the simple presence of systolic dysfunction in chagasic cardiopathy, regardless of the degree of myocardial involvement, was related to a high incidence of CE ischemic stroke (2.64% a year). Additionally, innate characteristics of this cardiopathy, such as the presence of specific segmental alterations, mainly the apical aneurism, would be an important risk factor for cardioembolic events<sup>14</sup>, even in the absence of systolic dysfunction, which makes us suggest that the conventional forms of prophylaxis in CE ischemic stroke cannot be simply extended to chagasic cardiopathy.

Not only the systolic dysfunction (of any degree), but also the presence of apical aneurism were selected as independent variables in CE ischemic stroke in this cohort of chagasic patients. The other selected variables were age > 48 years, which translates into a longer time of disease evolution and probability of event occurrence and the primary alteration of ventricular repolarization at the ECG, probably characterizing patients in whom the inflammatory process of the chagasic myocarditis is more active.

The model created with these four variables and transformed into a point score system allowed the characterization of subpopulations at increasing risk of CE stroke, as shown in Figure 1. Patients with a score of 4-5 points would have an incidence as high as 4.4% a year, in opposition to individuals with a score of 0-1 points and incidence close to zero.

When analyzing the treatment cohorts, we observed that there was no case of CE ischemic stroke during oral anticoagulation therapy, which allowed us to conclude that the efficacy of warfarin in preventing the event was 100%.

Table 2 - Prophylaxis Recommendation for CE ischemic stroke in Chagas' disease

Risk groups	n (%)	CE stroke Incidence <sup>†</sup>	Recommendation
4-5	75 (7.2%)	4.4	warfarin
3	107 (10.3%)	2.14	warfarin or ASA <sup>‡</sup>
2	72 (6.97%)	1.22	ASA or no prophylaxis
1	339 (32.8%)	0.1	No need for prophylaxis
0	440 (42.6%)	0	No need for prophylaxis

<sup>†</sup>Incidence expressed per 100 patients-year, <sup>‡</sup>Risk of CE stroke similar to that of bleeding – evaluate each case, considering the facilities in anticoagulation control.

However, this benefit involves a higher risk of bleeding, which is around 2% a year in this cohort and in the literature<sup>17</sup>. Thus, oral anticoagulation would be indicated as prophylaxis only in subgroups with high risk of cardioembolic events, characterized by patients with a score of 4-5 points. Patients using ASA did not present hemorrhagic complications; however, this drug is not as effective as the anticoagulant drug, considering that 5 events occurred with patients using antiplatelet drugs, all of them being high-risk patients (score of 4-5 points) and none of them with indication for anticoagulation therapy under the current guidelines<sup>18</sup>.

A total of 75 patients were characterized as being high-risk (4-5 points), which corresponds to 7.3% of the total cohort, where 14 CE ischemic strokes were diagnosed (45% of the events). Therefore, the anticoagulation therapy in 7.3% of the chagasic population would prevent around 45% of the CE ischemic strokes. If moderate to high-risk patients (3-5 points) received anticoagulation therapy, 80.6% of the events would be prevented (25 CE ischemic strokes), at the cost of a higher number of treatments: 17.6% of the population. Nevertheless, the anticoagulation of patients with a score of 3 points must be carefully deliberated, considering that the risk of bleeding is similar to that of the event incidence and it must be indicated only for patients with low risk of hemorrhagic complications and possibility of adequate INR control.

When taking into account the isolated general incidence of CE ischemic stroke in the cohort (0.56% a year), one could infer that a proposal for the prevention of this event would have a low impact on the population. However, as the prevalence of Chagas' disease remains elevated in our country, approximately 16,000 to 28,000 new cases of CE ischemic

stroke, related to this disease, would be expected every year. If we consider the specific risk subgroups, such as patients with moderate to severe dysfunction, which correspond to 15% of the total number of chagasic patients<sup>4</sup>, one could expect between 97,000 and 162,000 new cases of CE ischemic stroke a year in our country. Most of these cases would not be identified by the current anticoagulation guidelines; however, almost half of these cases could be prevented using the proposed score system.

Therefore, it is necessary to seek new prevention proposals for this very often incapacitating and high-risk event, the CE ischemic stroke, which are specifically directed at the innate characteristics of the chagasic cardiopathy, characterized by an elevated emboligenic potential. Based on this risk-benefit analysis, we suggest the use of warfarin (INR 2-3) for high-risk patients (4-5 points) and ASA or Warfarin for those with moderate risk (3 points).

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

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