# CHADS2 Score in Predicting Cerebrovascular Events – A Meta-Analysis

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## Abstract

The CHADS2 score aims to stratify the risk of cardiovascular events and is useful for the optimization of the therapeutic choices in patients with moderate / high risk. This meta-analysis aims to ascertain whether the CHADS2 score is effective in predicting cerebrovascular events in patients with atrial fibrillation (AF).

We performed a literature search in PubMed, Embase and Scielo, from March 2011 to April 2012. The studies were selected according to predetermined criteria.

Six cohort observational and prospective studies evaluating the predictive ability of CHADS2 score for cerebrovascular events and death were included in the meta-analysis. Defined endpoints (mortality and/or non-fatal stroke) were compared between patients with CHADS2 < 2 and patients with CHADS2 > 2, also considering the presence/absence of AF. With regard to the occurrence of cardiovascular events, for the combined outcome and death/non-fatal stroke individually, there was a greater risk in the group with CHADS2 score > 2, with an OR of 2.92 (CI: 2.08-4.10; p<0.00001), 2.85 (CI: 2.23-3.65; p<0.00001) and 3.23 (CI: 2.11-4.94; p<0.00001), respectively. This study also demonstrated that the risk of cardiovascular events was higher for individuals with CHADS2 > 2, regardless of the presence of AF: OR=2.93 (CI: 2.81-3.06; p<0.00001) in patients with AF; OR=2.94 (CI: 2.87-3.01; p<0.00001) in patients without AF.

The results clearly indicate the discriminative capacity of the CHADS2 score for cerebrovascular events, regardless of the presence or absence of AF. Therefore, the CHADS2 score allows the identification of patients at moderate/high risk and the selection of appropriate therapeutic strategies. (Arq Bras Cardiol. 2013;100(3):294-301)

## Introduction

Atrial fibrillation (AF) is a common arrhythmia that represents an important independent risk factor for the occurrence of systemic and particularly cerebrovascular thromboembolism[1-5]. The latter has deserved particular attention in recent times, either by its increasing prevalence, or by its association with potentially severe complications[5-13]. The main complications associated with AF are heart failure and systemic thromboembolism, which affects cerebral circulation in most cases (> 70%), and is a major cause of disability, resulting in severe impairment of quality of life and, depending on the severity, the death of some patients[12,14]. Therefore, AF is an important cause of stroke, which is the 2nd leading cause of death worldwide and the leading cause of neurological disability that requires rehabilitation care[1,2].

The CHADS2 score is a method used for assessing cardiovascular risk and its usefulness is based on the prediction of strokes through a scoring system that integrates a set of individual risk factors. The CHADS2 score is a scoring system that assigns 1 point for any of the following conditions: C - congestive heart failure, H - hypertension; A – Age ≥ 75 years; D - diabetes mellitus; S - previous stroke or transient ischemic attack (TIA), which receives 2 points. The greater the number of points detected in a given patient, the greater the likelihood of a thromboembolic complication[10,12,14,15]. A score of 2 or higher entails an increased stroke risk, and thus, the use of anticoagulant therapy is advisable, unless there are contraindications[5,11,12,14,15]. In this aspect, there has been an agreement on the adoption of warfarin when the stroke risk is high and aspirin when the stroke risk is low; therefore, the use of CHADS2 score may be an important tool for stroke risk stratification, allowing therapies to be better tailored to the patient's needs on an individual basis[5,7].

Thus, the objective of this study is to verify if the CHADS2 score is effective in predicting cerebrovascular events and to determine if this predictive ability depends on the presence of AF.

## Keywords

Stroke; risk factors; prognosis; atrial fibrillation; meta-analysis.

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## Methods

### Design of the study

We performed a systematic review and meta-analysis of the published literature, listing risk of death, cardiovascular events and hospitalization in patients without SAS and with untreated SAS. The methodology used was based on PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines[16].

### Inclusion criteria

To achieve the fundamental objective of the study and guide the search and selection of articles, we defined the final outcomes and the inclusion and exclusion criteria.

The following final outcomes were defined: total mortality, cardiovascular death (CV death); death from other causes; cardiovascular events (CV events); and duration of nonfatal hospitalizations. The inclusion and exclusion criteria were defined as described in Table 1.

### Research

After defining the inclusion and exclusion criteria and the final outcomes, we defined the search criteria. It was decided that Pubmed would be the main search engine for primary research, supplemented by EMBASE and Scielo, and by direct consultation of specialty journals such as The Journal of the American Medical Association, Journal of the American College of Cardiology, The New England Journal of Medicine and Lancet. An electronic search of articles was conducted from October 2011 to April 2012.

In the first approach, a keyword search was conducted without any restriction or filter, using the keywords CHADS2 score, stroke, and atrial fibrillation. Then we repeated the search with the following combinations of keywords: CHADS2 and/or atrial fibrillation; CHADS2 and/or mortality; CHADS2 and/or stroke; CHADS2 and/or cerebrovascular events; atrial fibrillation and/or stroke. After that, further research was carried out to verify the existence of any meta-analyses, which were not found until April 2012. Then the following filters were applied to previous searches: Humans, All Adult: 19+ years, Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, published in the last 15 years Sort by: Publication Date, which allowed reaching the final number of articles according to the predefined characteristics.

### Data extraction

Article selection was based on a standardized form shown in Figure 1, which was rated by two independent reviewers, in order to classify the articles according to title, abstract or full text. When the title and the abstract of the studies did not contain the necessary information to complete the form, they were referred to a comprehensive review of the articles. At the end of the independent review, the two reviewers met to resolve disagreements arising from the classification regarding the inclusion or exclusion of studies.

A total of 9665 resulting articles were analyzed from the initial electronic search. In the first analysis, we removed duplicate articles (n = 538), those with no useful content (n = 322), and those with a title that did not correspond (n = 8755) to the meta-analysis objective. A new electronic search was conducted to obtain the full text of the 50 final articles. For this search, we once again used Pubmed and other complementary databases to obtain the full articles. This research was conducted in a university network that had access permission to various scientific journals, which allowed access to articles from the Internet without any restriction. After obtaining all the full articles, we proceeded to a new critical assessment according to the criteria defined above. We evaluated the presence of the following endpoints: *mortality, nonfatal cerebrovascular events*. Of the 50 final articles, 28 were excluded because they had insufficient information, 7 had a non-prospective design, 7 had an unclear stratification by classes in the CHADS2 score, and 2 had no data referring to events. Finally, there were 6 articles that met all inclusion criteria for the meta-analysis. The selection process of the studies is shown in Figure 2.

### Statistical Analysis

The data were analyzed by the statistical software Review Manager Version 5.0 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2008), using fixed effects and random effects models. Heterogeneity was evaluated by the Cochrane Q test and complemented with $I^2$, which indicates the proportion of variability among studies, providing a measure of heterogeneity. The sample was considered homogeneous for a value of $p \geq 0.05$ and the value of $I^2 \leq 25\%$. The results were examined by comparing patients with low-risk CHADS2 score (score $<2$) with high-risk score (score$>2$) patients, with the endpoints defined dichotomously, for which we calculated the odds ratio (OR) and the 95% confidence intervals (CI). With respect to symmetrical or asymmetrical distribution of the sample, this was obtained through the funnel plot, with the weight of the study or the size of the sample on the y axis and the risk ratio on the x axis.

The statistical significance criterion used was a p-value less than or equal to 0.05, for a confidence interval of 95%.

**Table 1 - Inclusion and exclusion criteria used in the research**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Prospective studies | Duplicate studies |
| Studies carried out in adults | Studies carried out in children |
| Studies with information that allow good characterization | Non-prospective studies |
| Articles published preferentially in English | Studies with insufficient information |
| At least one predefined outcome | Case reports or review articles |
| | No predefined outcome |

**Study reference**: _____

**Selection level**:
Title: _____ Abstract: _____ Text: _____

**Selection criteria**
**Patients**
Study patients with AF? yes/no
Study patients without AF? yes/no

**Intervention**
Study patients with CHADS2 score > 2 points? yes/no

**Control**
Study patients with chads score <2 points? yes/no

**Events**
Does it include any of the following events as outcome variable, individually or combined:
Nonfatal stroke, cardiovascular mortality? yes/no

**Design**
Is it a cohort, observational and prospective study? yes/no

**Action** (include only if all the above answers are "yes"):
Include:_____ Exclude:_____ Doubtful:_____

**Figure 1 –** *Example from the selection table of articles for meta-analysis review.*

## Results

### Selected studies

The described selection criteria were applied to all the 9665 studies. The publications were studied, and only 6 studies were selected (Table 2) and more deeply and critically evaluated.

The meta-analysis included 6 cohorts, observational and prospective studies that evaluated the predictive ability of the CHADS2 score for cerebrovascular events and death. The defined endpoints (mortality and/or nonfatal stroke) were compared between patients with CHADS2 <2 (low risk) and patients with CHADS2> 2 (moderate/high risk), and also the presence/absence of AF.

The analysis was conducted in a combined sample of 473,584 patients, aged over 20 years, including 146,572 patients with chronic AF, and 327,012 patients with no AF.

## Meta-analysis

### CHADS2 and cardiovascular events

The occurrence of cardiovascular events (stroke and/or death) was reported in six studies[3-5,7,10,11] and, according to the analysis (Figure 3), was significantly higher in the group with CHADS 2 score greater than 2 (OR = 2.92; CI :2.08–4.10; p <0.00001), and there was heterogeneity in the global effect of the sample ($Chi^2$ = 764.17; p <0.00001). Although there was heterogeneity among studies, it was noted that all of them had effects in the same direction, individually indicating an association between a score greater than 2 and a greater risk of major cardiovascular events. The OR indicated an approximately 3-fold increase in the risk of cardiovascular events in patients with CHADS2 score> 2 points, compared to the group with CHADS2 score <2 points.

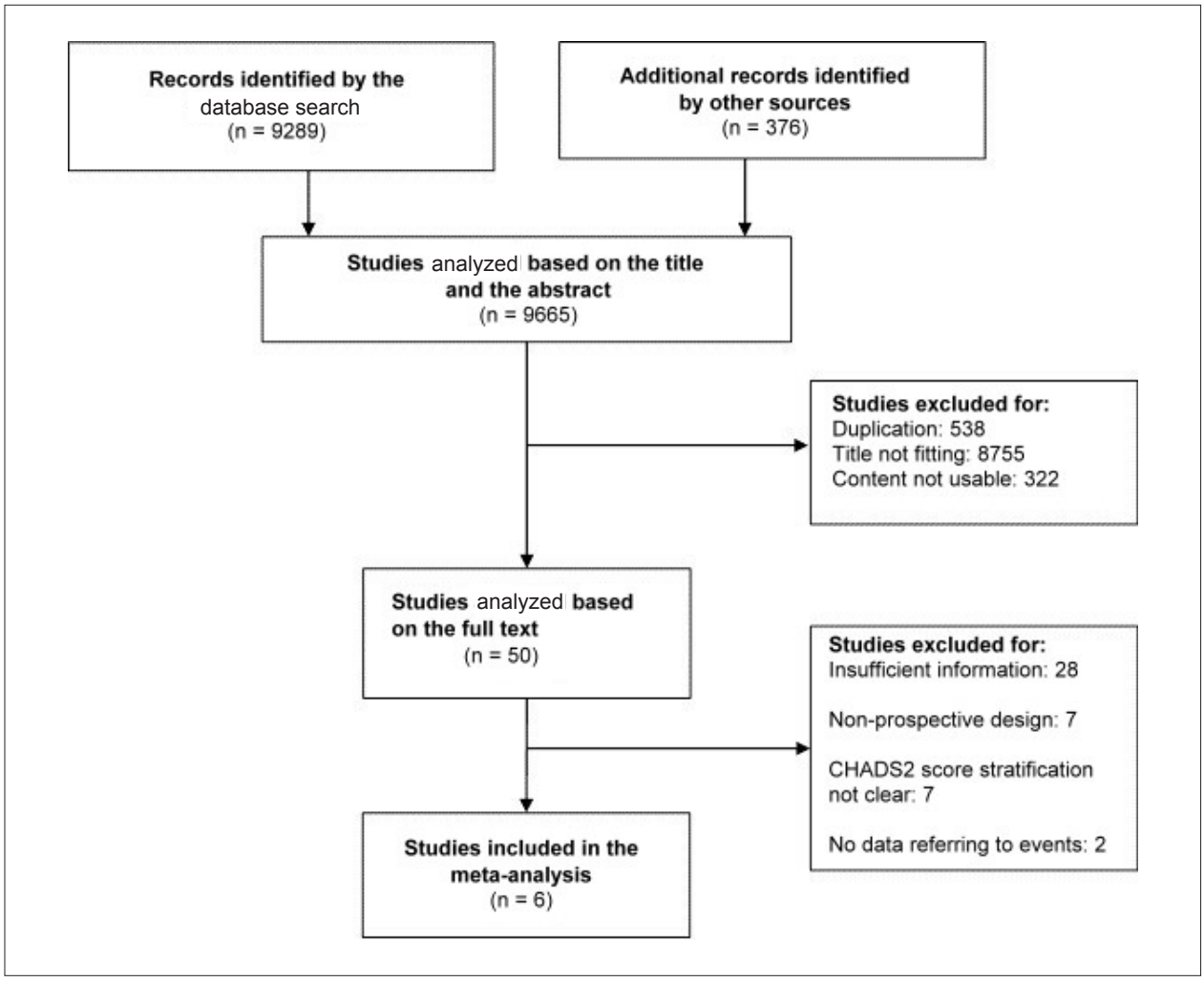


**Figure 2 –** *Selection process of the studies.*

### CHADS2 and stroke

The incidence of stroke was mentioned in five studies[3-5,7,11]. The analysis showed that the incidence was significantly higher in patients with a CHADS2 score greater than 2 points (OR = 3.23, CI: 2.11–4.94; p <0.00001; cf. Figure 4), and there was also heterogeneity in the global effect of the sample ($Chi^2$ = 89.18; p <0.00001), although all the studies indicated the same association. The OR showed an important stroke risk in the group with a CHADS2 score> 2, also indicating a 3-fold greater risk.

### CHADS2 and mortality

Mortality was reported in two studies[10,11] and the analysis demonstrated that there was a significant difference between the groups (see Figure 5), with an increased risk of death in the group with a CHADS2 score > 2 points (OR = 2.85; CI: 2.23–3.65; p <0.00001). As with the previous analysis, there was also heterogeneity in the global effect of the sample ($Chi^2$ = 13.69; p = 0.0002) without significant expression as to the documented association.

### CHADS2, AF and cardiovascular events

The occurrence of cardiovascular events (stroke and/or death) in individuals with and without AF was described in two studies[3,10] representing an aggregate number of 83.628 patients with AF, and 327.052 patients without AF. A meta-analysis with analysis of sub-groups (cf. Figure 6) showed that the risk of a cardiovascular event is higher for individuals with CHADS2 score > 2 points, regardless of the presence or absence of AF. In the group with AF, the risk of cardiovascular events was significantly higher for CHADS2 scores > 2 points (OR = 2.93; CI: 2.81–3.06; p <0.00001). In the group without AF, there was an increased risk, with a similar magnitude, of the occurrence of these events for CHADS2 scores > 2 points (OR = 2.94; CI: 2.87–3.01; p <0.00001). The meta-analysis showed that the risk of cardiovascular events is about 3 times greater for individuals with CHADS2 score > 2 points, regardless of the presence or absence of AF (OR = 2.94, CI: 2.88–3.00; p <0.0001).

**Table 2 - Characteristics of selected studies**

| Author (Year) | Sample (N) | Groups | Events | Type of study | Characteristics of patients |
|---|---|---|---|---|---|
| **Rietbrock, Stephan (2008)** | 305566 | Group with AF (51,807)<br>Group without AF (253,759) | Stroke | Prospective | Similar proportions of men and women; Mean age > 40 years; Parameters included: age, sex, body mass index, duration of AF diagnosis, ischemic heart failure, heart failure or cardiomyopathy, diabetes mellitus, cardioversion, hypertension, use of antiarrhythmics, warfarin, aspirin. |
| **Nobuyuki Masaki, (2009)** | 265 | Group with AF | Stroke | Prospective | Mean age 72 years, 65% men and 35% women; Exclusion of patients with severe valvular disease requiring intervention. Other conditions identified: hypertension, diabetes mellitus, and hyperlipidemia. |
| **Gage, Brian (2001)** | 1733 | Group with AF | Stroke | Prospective | Mean age 81 years; 42% men and 58% women. |
| **Sandhu, Roopinder (2011)** | 42 834 | Group with AF | Stroke and mortality | Prospective | Mean age 73 years; Exclusion of patients with aortic or mitral disease. |
| **Oldgren, Jonas (2011)** | 18 112 | Group with AF | Stroke | Prospective | Mean age 82 years; Other associated diseases: heart failure, diabetes mellitus, hypertension, coronary heart disease, myocardial infarction, medication with aspirin, beta-blockers, statins, amiodarone. |
| **Henriksson, Karin (2010)** | 105 074 | Group with AF (31821);<br>Group without AF (73253) | Mortality | Prospective | Mean age 80 years in the group with AF (46% men and 54% women), and 74 years in the group without AF (52% men and 48% women). |

*AF: Atrial fibrillation.*

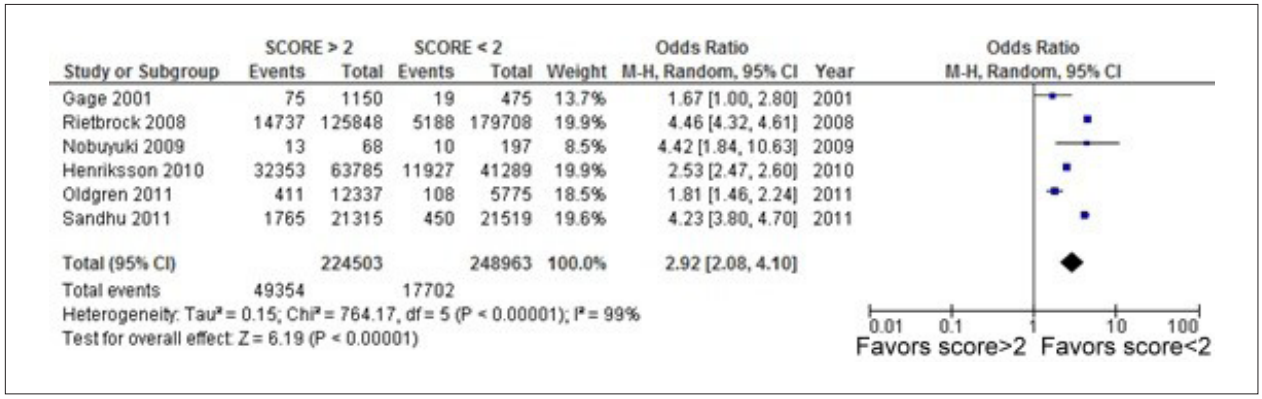


**Figure 3 -** *Forest plot for comparative analysis of the occurrence of cardiovascular events.*

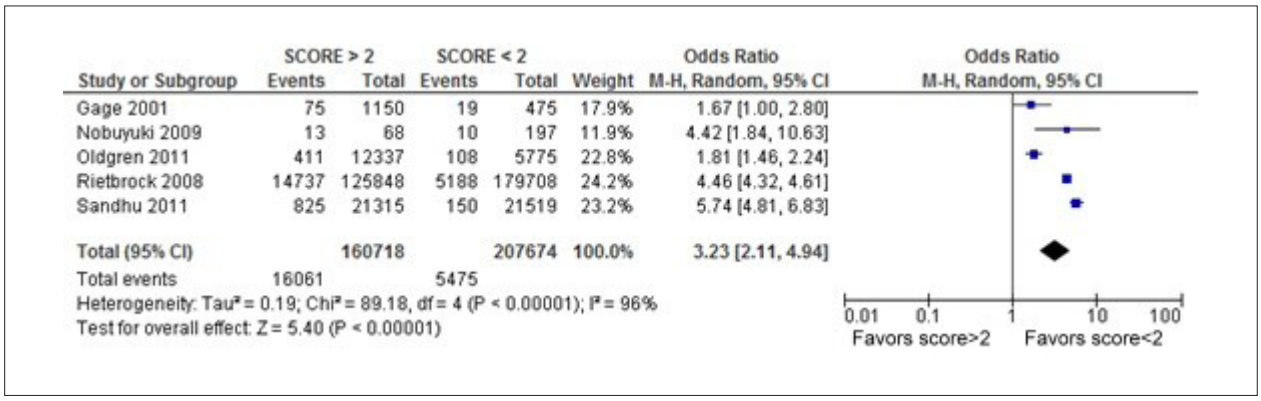


**Figure 4 -** *Forest plot for comparative analysis of the occurrence of stroke.*

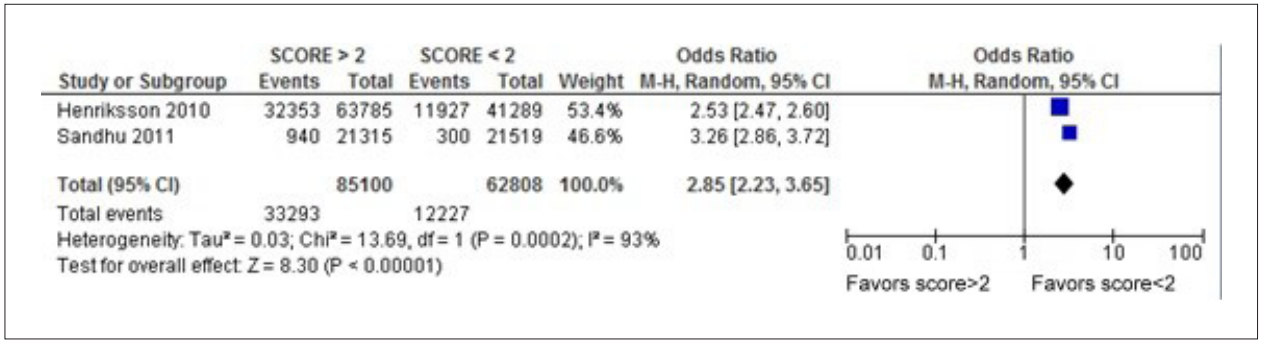


**Figure 5 -** *Forest plot for comparative analysis of mortality.*

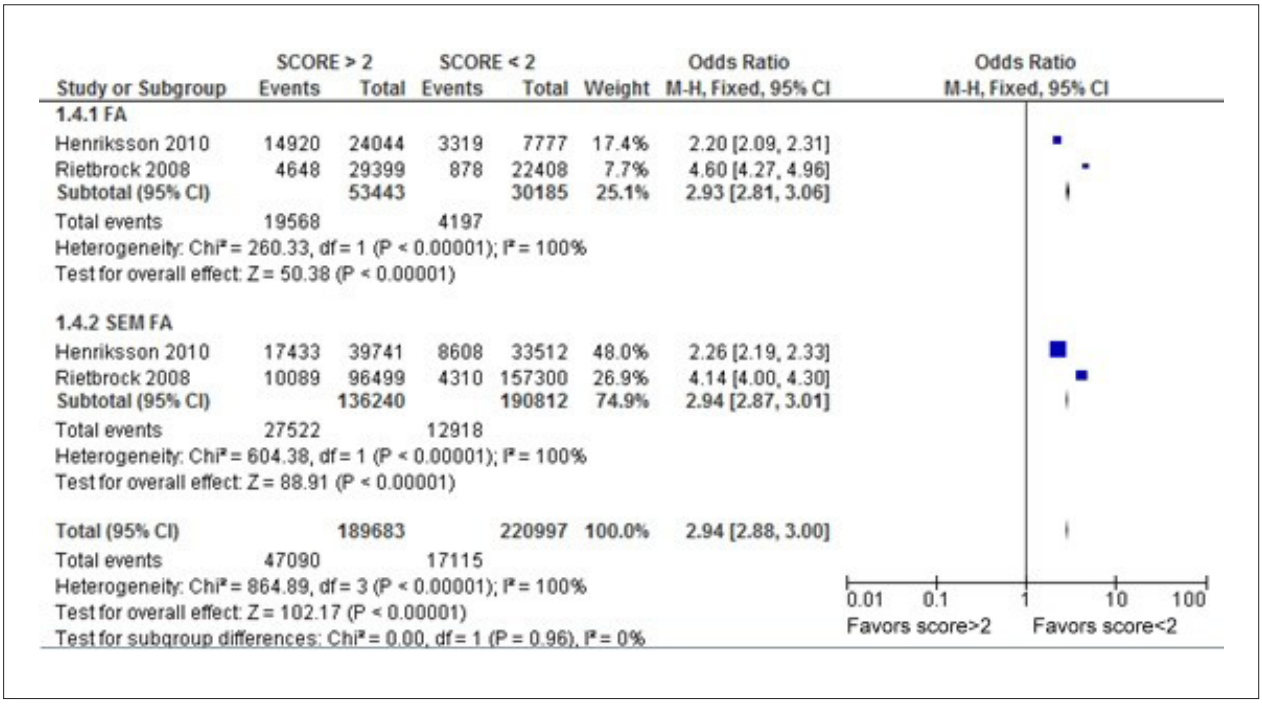


**Figure 6 -** *Forest plot for comparative analysis of the occurrence of cardiovascular events in individuals with and without AF.*

## Discussion

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and its prevalence increases with age. It is an important risk factor for thromboembolic stroke, and it affects up to 9% of the population aged around 80 years and is associated with significant morbidity and mortality[1]. Patients who suffer from this arrhythmia have a 3% to 4% risk of stroke per year, although this risk varies significantly when based on individual clinical characteristics[2,17].

The antithrombotic therapy with warfarin has proved highly effective in preventing stroke and improving survival, despite its association with the risk of bleeding, requiring intensive monitoring of blood coagulation and a systematic optimization of its titration[12].

In an attempt to avoid unnecessarily aggressive treatment regimens for low-risk patients, risk stratification schemes have been developed to optimize the therapeutic decision-making. Currently, several risk stratification systems have been validated and are clinically well established[6,7,14,17].

The CHADS2 score is the most widely used model, and it has been developed using stroke risk factors. This score uses a points system based on individual risk factors in the clinical setting, including congestive heart failure, hypertension, age, diabetes mellitus, and previous stroke or TIA, and it is a valuable tool for predicting cerebrovascular events in high risk patients. This score complements other tools that are also used in the clinical evaluation of patients, of which integration enables the use of the best strategies for anticoagulation therapy, especially in patients at moderate risk[13,15].

The association of a higher CHADS2 score in AF patients with stroke and death was well validated in the studies reported in the meta-analysis[2-5,7,10,11]. Therefore, the results indicate a 3-fold higher risk of stroke (OR = 3.23; CI: 2.11–4.94; p <0.00001), death (OR = 2.85; CI: 2.23–3.65; p <0.00001), and cardiovascular events (OR = 2.92; CI: 2:08–4:10, p <0.00001) for individuals with CHADS2 score greater than two points and chronic AF, i.e., with a profile of moderate/high thromboembolic risk .

As to the occurrence of cardiovascular events (stroke and/or death) in individuals with or without AF, the data from this study shows that the risk of a cardiovascular event is greater for individuals with CHADS2 score > 2 points regardless of the presence or absence of AF. In fact, in the AF group, the risk of cardiovascular events was significantly higher for CHADS2 scores > 2 points (OR = 2.93; CI: 2.81–3.06; p <0.00001), and with a magnitude similar to that seen in group without AF (OR = 2.94; CI: 2.87–3.01; p <0.00001). In this aspect, there is evidence confirming the efficacy of CHADS2 score in predicting cerebrovascular events, not only in individuals with AF, but also for those without it. In fact, although AF has been considered a risk factor for these adverse events, it remains unclear whether this is truly an independent risk factor or a risk marker of other diseases that do determine this risk, such as prolonged hypertension or congestive heart failure. This distinction is important, as it is not yet clear whether aggressive treatment of atrial fibrillation will improve or not the clinical outcomes in this specific context[2].

The CHADS2 score has been advocated as the means for determining the need for anticoagulation in patients with AF, and this study supports the CHADS2 score as a strong clinical prediction tool, useful in patients with cardiovascular disease, and valuable for preventive action.

In sum, AF is a prevalent and increasing problem, which significantly increases stroke risk, and the CHADS2 score is a good indicator of stroke risk.

The CHADS2 score, in addition to being a powerful predictor of stroke, is also a predictor of the occurrence of death. This study showed that individuals with CHADS2 score > 2 points and chronic AF have a 3-fold greater risk of stroke and/or death. This study clearly suggests the ability of the CHADS2 score in predicting cerebral thromboembolism and death in patients with AF. However, it is important to emphasize that the predictive ability of the CHADS2 score was independent from the presence of AF, extending the scope of its usefulness to other clinical settings, rendering it an effective method with great clinical importance to be used in preventing cerebrovascular events.

## Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Santos C, Pereira T, Conde J; Acquisition of data, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Santos C, Pereira T.

### Potential Conflict of Interest

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

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### Study Association

This study is not associated with any post-graduation program.

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