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REVIEW ARTICLE

Relationship between Ischemic Stroke and Atrial Fibrillation, Systematic Review

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ABSTRACT

Introduction: Atrial Fibrillation (AF) is not only one of the main causes of stroke, but it is also the most common sustained cardiac arrhythmia. As a result of population aging, an increase in the prevalence of AF and other associated chronic cardiovascular diseases, such as Systemic Arterial Hypertension (SAH) and Diabetes Mellitus (DM), is expected, contributing to a higher incidence of stroke. The magnitude of this fact reflects the reason why stroke is considered the second cause of death in the world, and the first cause of death in Brazil, in addition to being the second cause of cognitive losses. The main causes that favor the occurrence of ischemic stroke determine the situation of risk groups. Such factors can be classified as modifiable, non-modifiable and potential risk group.

Objective: The aim of this study was to systematically review the public health literature on the relationship between ischemic stroke and atrial Fibrillation.

Methods: Systematized literature review performed by searching the Web of Science database (Clarivates), Science Direct (Scopus), Wiley Online Library (John Wiley and Sons), Taylor and Francis (Taylor & Francis Group) and PubMed (NIH), using the descriptors Relationship between Ischemic Stroke and Atrial Fibrillation and other cardiovascular diseases in primary care, both in English and Portuguese. A total of 3860 articles were found, of which 64 were selected for the review by six evaluators independently. The articles surveyed are from the period 2015 to 2022.

Results: In addition to the epidemiological magnitude, AF is important for its clinical consequences, including thromboembolic occurrences, with an increase, on average, of 4 times the probability of a stroke, in addition to being correlated with the high risk of all-cause mortality and other circumstantial determinants, such as heart failure. Conclusion: The analyzed studies demonstrated that there may be an adjusted incidence of ischemic stroke associated with AF and other cardiovascular diseases by stroke age, being age dependent in men. Social factors may contribute to the late discovery of the association between stroke, AF and other cardiovascular diseases.

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Introduction

Cerebral Vascular Accident (CVA) is a common neurological syndrome among adults and the elderly, being the second cause of death in the world and one of the main reasons for hospitalization [1-3]. Together, stroke and coronary artery disease were responsible for 15.2 million deaths in 2015 [4,5], in addition to several motor and neurological sequelae [6].

Atrial Fibrillation (AF) is a supraventricular tachyarrhythmia identified by uncoordinated atrial activation, leading to worsening atrial mechanical function [7], which can affect up to 50% of adults and the number of patients is constantly growing [8].

There is a high risk of developing ischemic stroke after the diagnosis of AF, as there is a strong association between stroke and AF. AF is the most common cause of ischemic stroke, increasing the risk of stroke by five to eight times. Few circumstances in medicine are as significant as the finding of a risk factor, the probability of its repair and the improvements produced therefrom, and all of them must be conveniently addressed [9,10]. This event emphasizes the magnitude of a wide etiological investigation, aiming at an appropriate prevention of stroke in these patients who can take advantage of the precaution of anticoagulation [10].

Methods

This study constitutes a systematic review, classified as exploratory and descriptive. The elaboration of the research was bibliographical research in electronic databases on methods associated with RSL (Systematic Literature Review) and SMARTER applications (Simple Multi-Attribute Rating Technique using Exploiting Rankings). The work carried out is qualitative and quantitative. The qualitative analysis of the data is carried out intuitively and inductively during the survey of the theoretical framework. It is also quantitative by using the multicriteria method. In addition, there is also a numerical experimental study in order to simulate an article selection situation based on the observed criteria. From bibliographical research, located in the databases: Web of Science data (Clarivates), Science Direct (Scopus), Wiley Online Library (John Wiley and Sons), Taylor and Francis (Taylor & Francis Group), and PubMed (NIH).

The search in the databases was carried out using the terminologies registered in the Health Sciences

Descriptors created by the Virtual Health Library developed from the Medical Subject Headings of the US National Library of Medicine, which allows the use of common terminology in English and Portuguese. The keywords used in Portuguese for the search in the databases were: 3860. As a tool to support decision in the selection and prioritization of articles, were considered a set of criteria as essential to represent the state of the art of the subject object of the research. This method has the following characteristics: (i) rigorous logic allows acceptance of the method as a decision support tool; (ii) simple to understand and apply with easily interpreted results. After all, the result obtained totaled 64 articles that contemplated the desired characteristics for the study.

Theoretical Reference

Stroke is a medical emergency characterized as a neurological syndrome, of sudden onset, resulting in the interruption of cerebral blood flow. It can be classified as stroke or hemorrhagic stroke [11].

It is the second leading cause of mortality and one of the leading causes of morbidity worldwide. The high incidence of sequelae after stroke determines an important social and economic impact. As the population ages, its signs increase, particularly in low - and middle - income countries. Stroke incidence and mortality vary across countries, geographic regions and ethnicities, and especially in high-income countries, prevention, intensive care and neurorehabilitation programs have led to a substantial reduction in the burden of stroke over the last 30 years [12].

Stroke can be classified into Hemorrhagic (HS) and Ischemic (IS). HS occurs due to the rupture of cerebral blood vessels, causing blood leakage in the brain or between the brain and the meninges, affecting 15% of the cases [13,14]. It includes subarachnoid hemorrhage, which is usually caused by the rupture of a congenital saccular aneurysm located in the polygonal artery of Willis, and intraparenchymal hemorrhage, which has as its basic cause the hyaline degeneration of the intraparenchymal arteries, and the main disease is related to systemic arterial hypertension (SAH) [15].

IS caused by local vascular occlusion, which leads to interruption of oxygen and glucose supply to the brain tissue and subsequently affects the metabolic process of the area in question. It is responsible for approximately 87% of cases of stroke [16].

Furthermore, stroke can be subdivided into atherothrombotic, cardioembolic, lacunar, and undetermined or cryptogenic.

The atherothrombotic is characterized by atherosclerotic pathology of the intracranial and cervical arteries and is the factor with the highest recurrence of ischemic stroke, corresponding to approximately 48% of the cases [17]. Atherosclerosis is identified by loss of elasticity and thickening of the blood vessel wall and subsequent production of atheromas. Atherosclerotic lesions develop in response to inflammatory stimuli, reproduction of smooth muscle cells, release of several cytokines, synthesis of connective tissue matrix, calcification, concentration of lipids and macrophages [18].

The cardioembolic is the result of a cardiac embolism, being the second main cause of ischemic stroke, and responsible for approximately 15-30% of the cases [19]. A large number of heart diseases are considered potential sources of embolism. Among them, we can mention atrial fibrillation, recent myocardial infarction, artificial mechanical valves, mitral valve stenosis, atrial or left ventricular thrombosis and atrial myxoma, dilated cardiomyopathy, infectious and non-bacterial thrombotic endocarditis and ventricular aneurysm [20].

Stroke is characterized by small infarctions (2-20 mm in diameter) in the deep cerebral white matter, basal ganglia or pons, supposedly resulting from the occlusion of a single small perforating artery that irrigates the subcortical areas of the brain [21].

Lacunar stroke is caused by Cerebral Small Vessel Disease (cSVD), a term used for different pathological processes that affect the small vessels of the brain. Cerebral small vessels play a crucial role in cerebral lacunar infarction and deep or cortical hemorrhages. In addition to cognitive decline and dementia, gait problems are also frequently associated with cSVD [22].

Among all stroke events, 20-40% are identified as undetermined or cryptogenic [23,24]. This stroke subtype is defined as cerebral ischemia of unexplained or incomprehensible origin. The cause of this stroke subtype is still unknown for three reasons: [1] investigations may not address all known causes of stroke, [2] the case may be transient or reversible and the propaedeutic diagnosis may not be performed in a timely manner, and [3] there are some truly

unknown causes of stroke. Therefore, the incidence of cryptogenic stroke depends on the performance and speed of the test [25,26].

Atrial Fibrillation (AF) is the most common sustained arrhythmia, and is characterized by uncoordinated atrial activation, with impairment of atrial function [27]. Of a dynamic and progressive nature, AF is a disease with multifactorial causes of epidemic proportions, with severe complications and a considerable negative effect on public health [28]. This damage caused by AF to the atrial mechanical function increases the possibility of formation of an intratrial thrombus, which may suffer embolism in the arterial circulation and generate an IS. Patients with AF have an annual incidence of ischemic stroke of approximately 5%, estimated by the presence of additional risk factors [29,30].

AF is intrinsically related to cardiovascular aging, with a 33% increase in the worldwide prevalence of AF observed over the past 20 years [31,32], and the worldwide prevalence of AF is expected to triple by the year 2050 [33].

AF is considered the most common cause of cardioembolic stroke, increasing the risk of stroke by five to eight times [34]. However, there are determining factors in the current evidence regarding AF screening, such as those linked to the individual and the environment, which directly influence the screening [35].

The threat of stroke in patients with AF is immediately associated with age, with a risk of 1.5% per year between 50 and 59 years old; for patients between 80 and 90 years of age, the risk increases to 23.5% per year [36]. Several comorbidities, such as diabetes, peripheral vascular disease, systemic arterial hypertension, heart failure and previous stroke, significantly increase the risk of stroke. Preventive intervention with anticoagulation has advantages at any age [37].

Results

The database search found a total combination of 3860 articles, of which 184 were selected for full text reading. Of these, 64 were selected using the SMARTER method (Simple Multi-Attribute Rating Technique using Exploiting Rankings), which were included for descriptive data analysis. In figure 1, the stages and indicators used in the selection are described.

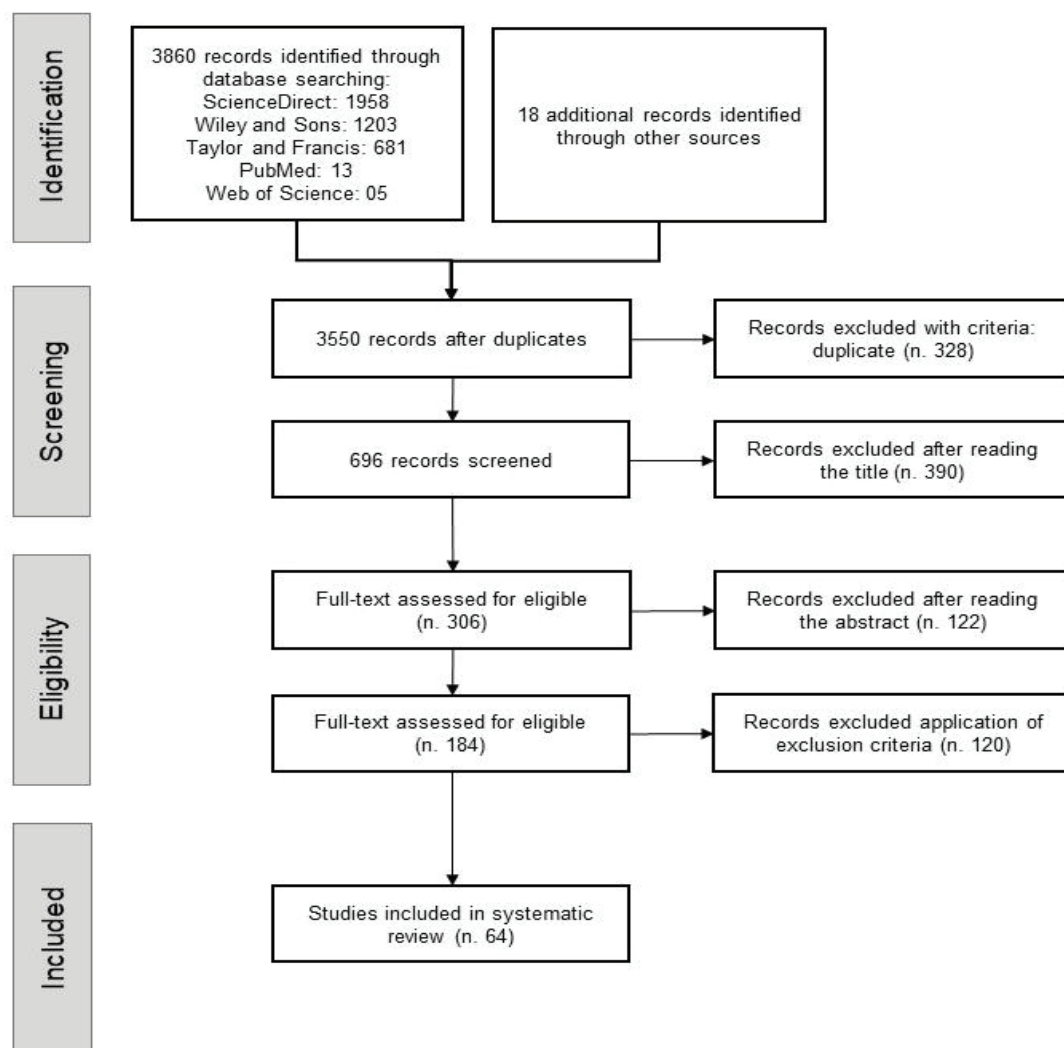


Figure 1 Number of articles identified as a possible relationship between ischemic stroke and atrial fibrillation and other cardiovascular diseases in primary care.

Discussion

Studies have shown an age-standardized reduction in strokes in many regions, but show an exception in East Asia and southern sub-Saharan Africa. Despite this, stroke is still prevalent and disabling, with over 80 million survivors worldwide and a growing absolute number of DALYs [38]. In Brazil, 80% of stroke cases are classified as CVA, demonstrating its epidemiological importance in the country, being the first cause of death, in addition to being the second cause of cognitive losses [39,40].

Although the age-adjusted incidence of stroke in men (mainly ischemic stroke is about 30% higher than in women) [41,42], a meta-analysis [43] from data stratified by age from 44 studies in 19 countries, demonstrated age heterogeneity, and the incidence of

males for females is 45% higher from 45 to 64 years old, 21% higher from 75 to 84 years old and only 9 % higher in ages over 85 years. Although no numerical estimates are provided, graphical representations of gender-specific incidence rates in the Framingham Heart Study (involving white participants only) [44] and the Northern Manhattan Stroke Study (involving whites, blacks and Hispanics) [45] show that there are more men up to 74 years of age than women, but the incidence is higher in women over 74 years of age.

In Brazil, epidemiological data indicate that there were more than 700,000 cases of strokes (2010), representing more than 141,000 deaths. Although there are multiple potential causes of stroke, it is estimated that approximately 20% of strokes are attributed to AF, and it is frequently associated with worse outcomes [46].

According to data from primary care in Brazil, the total prevalence of AF in the population was 1.8%, and it is estimated that among octogenarians (8.4%) and nonagenarians (11.0%) it is higher. The prevalence of AF was strongly associated with higher mean age, being higher in men compared to women in all age groups. Hypertension was the most commonly associated disease, and Chagas disease was the comorbidity with the strongest association with AF. The use of warfarin is associated with only 1.5% of patients [47].

While the prevalence of AF in Brazil is estimated at 2–3% of the population, consistent with the Brazilian age pyramid [47–49], there is a serious limitation of data on risk factors and access to diagnostic means [49,50]. According to a study by the Joinville Stroke Registry (JOINVASC), the diagnosis of AF in patients with ischemic stroke –CE was performed only after the ischemic stroke in 47% of patients. Among the patients with a previous diagnosis of AF, only 27% of the patients were using oral anticoagulation, and most of these were using the prescribed medication irregularly [9,51].

In addition to the epidemiological magnitude, AF is important for its clinical consequences, including thromboembolic occurrences, with an increase, on average, of 4 times the probability of a stroke, in addition to being correlated with the high risk of mortality from all causes and other determinants circumstances, such as heart failure [52,53]. The incidence determined for age and the prevalence of AF is lower in females compared to males, however, it does not occur with morbidity and mortality. AF is correlated with a high relative risk of all-cause mortality: stroke, cardiovascular mortality, cardiac events and heart failure in women [54].

According to the American Heart Association [55], the percentage of patients with AF reported in the United States of America (USA) benefiting from the government health insurance system (Medicare) in 2010 was 2% for those under 60 years of age and 9% for those over 65 years. The risk of developing AF after age 40 in individuals of European descent is 23% for women and 26% for men. Although risk factors for AF are more prevalent among African-Americans, a study in the USA demonstrated that the prevalence of AF is 32% lower in blacks than in whites [56].

In Australia, Europe and the US, the current estimated prevalence of AF is around 1–4%, with

lower prevalence evident in Asia (0.49%–1.9%). The prevalence of AF is higher among whites. In Western Europe, Australia and North America, 70% of people with AF are > 65 years old, while the average age of patients with AF in other geographic regions is generally lower [32].

Medicare data from 2019 showed that in-hospital mortality was 25.3% for patients with AF and 16.0% for patients without AF. One-year mortality was 48.3% in patients with AF and 32.7% in patients without AF. Patients with AF had a higher rate of fatal or sequelae strokes (3.1%) than patients hospitalized for other reasons [57].

According to the US Centers for Disease Control and Prevention, this condition affects 2.7 million to 6.1 million adults in the US each year and that number is expected to double in the coming years. It is a fact that is quite expected in developed countries, generating great concern as it adds costs to the health system. However, it has the same impact in low- and middle-income countries due to the increase in non-communicable heart diseases worldwide [58].

A great impact of morbidity and mortality is associated with AF, with higher risks of hospitalization due to thromboembolic events or hemodynamic changes. In the US, it is estimated that the cost of treating patients with AF is \$26 billion, adding about \$8,700 per year in additional costs for this patient compared to individuals without the disease (2004–2006 estimates). Of the total annual hospitalizations in the US, 467,000 people have AF as their primary diagnosis, in addition to approximately 99,000 deaths each year [56,59].

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According to data from primary care in Brazil, the total prevalence of AF in the population was 1.8%, and it is estimated that among octogenarians (8.4%) and nonagenarians (11.0%) it is higher. The prevalence of AF was strongly associated with higher mean age, being higher in men compared to women in all age groups. Hypertension was the most commonly associated disease, and Chagas disease was the comorbidity with the strongest association with AF.

The use of warfarin is associated with only 1.5% of patients [47].

It is estimated that approximately one third of hospitalizations due to arrhythmias in Brazil are due to AF [60]. According to data from DATASUS, 656,740 people were hospitalized in Brazil for "conduction disorders and arrhythmias" and 41,771 died for "Flutter and AF" between January 2008 and April 2019. In the same period, 1,497,681 hospitalizations were recorded by stroke and non-specific stroke (hemorrhagic or ischemic), and 960,830 deaths between 1996 and 2017. Based on these data, AF data may be underestimated, given the significant association of AF data with stroke, its prevalence in the population and the majority of asymptomatic patients [61].

Particularly in Brazil, which has one of the highest rates of cerebrovascular disease in Latin America, being proportional to the increase in AF cases, which results in increased long-term mortality, high rates of cerebrovascular risk factors and lower survival rates, particularly in those participants with AF who were not on anticoagulant therapy for at least six months after an acute event [62].

Final Considerations

The analyzed studies demonstrated that there may be an adjusted incidence of stroke associated with AF and other cardiovascular diseases by age of stroke, being predominant in men, being age dependent. In Brazil, it is estimated that the prevalence of AF corresponds to approximately 2–3% of the population, consistent with the Brazilian age pyramid, strongly associated with risk factors, and with social class, which interferes with access to information and consequently the means of diagnosis available in the public health network.

These factors contribute to the discovery of the late association between stroke, AF and other cardiovascular diseases, which are often neglected. Based on these data, AF data may be underestimated, given the significant association of AF data with stroke, its prevalence in the population and the majority of asymptomatic patients.

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