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Review article

Evaluation of the impact of anticoagulants on the incidence of dementia in patients whit atrial fibrillation: a narrative review

*Avaliação do impacto dos anticoagulantes na incidência de demência em pacientes com fibrilação atrial: uma revisão narrativa**

Caroline Fonseca Teixeira[1], Rodrigo Taranto de Reis[2], Larissa Rodrigues Perrenout Branca[3], Igor Dutra Braz[4]

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ABSTRACT: Atrial fibrillation (AF) is the most common type of cardiac arrhythmia and is associated with an increased risk of dementia. It is believed that the use of oral anticoagulant drugs is a protective factor for the development of dementia. Thus, this narrative review aimed to present and discuss the current evidence on the impact of anticoagulant use and cognitive impairment in people with AF. Selection was made using the MeSH terms: atrial fibrillation; dementia; treatment; anticoagulants. Inclusion criteria were randomized clinical trials and prospective cohorts published between 2015 and 2021, developed with human beings. 155 articles were identified, 10 of which met the inclusion criteria. Most of the studies analyzed observed a decrease in the risk of dementia whit the use of NOACs (new oral anticoagulants) in comparison to the use of warfarin. The study by Kim et al.[21] points out rivaroxaban as the most efficient drug to reduce the risk of dementia, among the NOACs. However, Søgaard et al.[15] showed a higher risk of dementia associated with the use of NOACs, when compared to warfarin. It is concluded that the NOACs and warfarin, decrease the risk of cognitive impairment and dementia in people with AF. However, it is not possible to say what is the best treatment currently offered.

KEYWORDS: Atrial fibrillation; Dementia; Anticoagulant.

RESUMO: A fibrilação atrial (FA) é o tipo mais comum de arritmia cardíaca e está associada a um maior risco de demência. Acredita-se que o uso de fármacos anticoagulantes orais seja um fator protetor para o desenvolvimento de demência. Assim, essa revisão narrativa teve o objetivo de apresentar e discutir a evidência atual sobre o impacto do uso de anticoagulantes e o comprometimento cognitivo em pessoas com fibrilação atrial. A seleção foi feita usando os MeSH terms: atrial fibrillation; dementia; treatment; anticoagulants. Foram incluídos ensaios clínicos randomizados ou coortes prospectivos publicados entre 2015 e 2021, desenvolvidos em seres humanos. Foram identificados 155 artigos, sendo que 10 cumpriam os critérios de inclusão. A maioria dos estudos analisados observaram uma diminuição no risco de demência com o uso dos NOACs (novos anticoagulantes orais) em relação ao uso da varfarina. O estudo de Kim et al.[21] aponta a rivaroxabana como droga mais eficiente para diminuição do risco de demência, dentre os NOACs. Contudo, Søgaard et al.[15] apresentaram um risco maior de demência associado ao uso dos NOACs, quando comparado à varfarina. Conclui-se, que os NOACs e a varfarina, diminuem o risco de quadro demencial em pessoas com FA. No entanto, ainda não é possível afirmar o melhor tratamento oferecido atualmente.

PALAVRAS-CHAVE: Fibrilação atrial; Demência; Anticoagulante.

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1. Centro Universitário de Volta Redonda (UniFOA); https://orcid.org/ 0000-0002-3028-3940; E-mail: caroline.fonsecat@gmail.com
2. Centro Universitário de Volta Redonda (UniFOA); https://orcid.org/0000-0003-0032-3013; E-mail: rtaranto.r@gmail.com
3. Universidade Nove de Julho; https://orcid.org/0000-0003-4296-912X; E-mail: larissarpbranca@gmail.com
4. Orientador, Centro Universitário de Volta Redonda (UniFOA); https://orcid.org/0000-0003-3362-7371; E-mail: igor.braz@foa.org.br
Correspondence: Alberto Cunha Rodrigues, 226. Apto 101. Volta Redonda, RJ; caroline.fonsecat@gmail.com

INTRODUCTION

Atrial fibrillation (AF) is characterized as a supraventricular tachyarrhythmia that presents low-amplitude electrocardiographic oscillations of the baseline (called F waves) with frequencies ranging from 300 to 600 beats per minute (bpm), associated with a disorganized ventricular rhythm between 100 and 160 bpm[1]. It is the most common type of cardiac arrhythmia, affecting about 0.51% of the world population[2]. AF is associated with high rates of morbidity and mortality, especially due to an increased risk of stroke and dementia[3]. It can be classified as First diagnosed, Paroxysmal, Persistent, Long-standing persistent, and Permanent[4]. The First diagnosed refers to the newly diagnosed AF episode. Paroxysmal refers to AF that has spontaneous resolution, requiring no intervention to cease. Persistent refers to AF lasting longer than seven days and only ceases after cardioversion. Long-standing persistent refers to AF lasting longer than 12 months in which a rhythm control strategy is adopted. "Permanent" refers to AF in which no attempt to restore/maintain sinus rhythm will be made. As seen, one of the therapeutic bases of AF is the evaluation between ensuring control of cardiac rhythm (CR) or heart rate (HR). It is important to note that HR control is as good as CR control for asymptomatic patients, especially in persistent[5] AF. CR control is more indicated for young and symptomatic patients. Regardless of the type of control, anticoagulation is the main strategy to prevent complications.[4]

Dementia, presented as a neurocognitive disorder by the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, is described as a complex group of symptoms related to cognitive and functional decline[6]. Dementia syndromes can present in various ways, with the most common forms including Alzheimer's disease (AD), vascular dementia (VaD), and dementia with Lewy bodies[7]. However, vascular dementia (VaD), considered the second most common form of dementia in the world, is responsible for approximately 15% of cases[8] and is the type of dementia most strongly associated with AF[9].

The proposed mechanisms for the association between AF and dementia are direct and indirect. A direct mechanism would be the formation of one or multiple arterial thrombi that compromise cerebral blood flow and contribute to the evolution of a demented state. However, according to the Rotterdam study from 1997[10], there is an association between atrial fibrillation and the risk of dementia independent of clinical stroke or aging. It is suggested that with the reduction of cardiac output caused by AF, a state of chronic cerebral tissue hypoperfusion develops. This, in association with the risks of chronic micro and macro thromboembolic events resulting from the pathophysiological processes of AF, may increase the predisposition to cognitive decline and the development of dementia. Moreover, AF and vascular and Alzheimer's dementia share risk factors such as hypertension, diabetes mellitus, smoking, and coronary artery disease, in addition to being associated with aging[11].

Besides the correlation between AF and cardioembolic events being well-known, AF is also an independent risk factor for the formation of cerebral embolic events. It leads to embolization of thrombi formed in the left atrial appendage, which are disseminated to various regions as they fall into the bloodstream, including the brain[12]. However, this arrhythmia is only capable of causing thromboembolic phenomena when associated with other risk factors, highlighting the multifactorial genesis of such events in AF, such as the presence of another cardiovascular disease, age, and sex[13]. Despite the multifactorial pathophysiology of thromboembolism, it is observed that the factors of Virchow's triad – blood stasis, endothelial injury, and alteration of blood constitution – are altered in patients with AF, suggesting that thromboembolic events are based on these alterations[12]. It is believed that AF itself is responsible for these variations in the triad components, leading to a state of hypercoagulability of the blood[13] and, therefore, it is an independent risk factor for such events.

Therefore, it is apparent that this pro-thrombotic state of AF increases the risk of developing thromboembolic incidents, including cerebral embolic events, the main and most serious consequence of this arrhythmia, which leads to cognitive damage such as dementia[3]. However, it is known that the pathophysiological mechanisms of vascular dementia in atrial fibrillation have not been fully elucidated and depend on the type, extent, and location of vascular lesions for determination of the clinical form.

Thus, given the pro-thrombotic state stimulated by AF, the use of oral anticoagulant drugs is believed to be a protective factor for the development or worsening of dementia, by maintaining adequate cerebral blood circulation. To assess the risk of developing thromboembolic events in people with AF, a risk score called CHA2DS2-VASc[14] was created, an acronym for Congestive heart failure, Hypertension, Age above 75 years, Diabetes, previous transient ischemic attack or Stroke, previous Vascular disease, Age between 65 and 74 years, and female Sex. With 0 points, there is no specific action. With 1 point, platelet anti-aggregation is recommended. With 2 or more points, full anticoagulation is indicated[14]. However, it is still unclear which anticoagulants have greater efficacy in preventing the development of dementia in patients with atrial fibrillation.

OBJECTIVE

This study aimed to present the current evidence on the impact of anticoagulant use and cognitive impairment

in people with permanent atrial fibrillation. In addition, it aimed to analyze studies comparing the use of different oral anticoagulants and their effects on reducing the risk of cognitive impairment and dementia in people with permanent AF, to discuss the evidence of the best currently available treatment.

METHODS

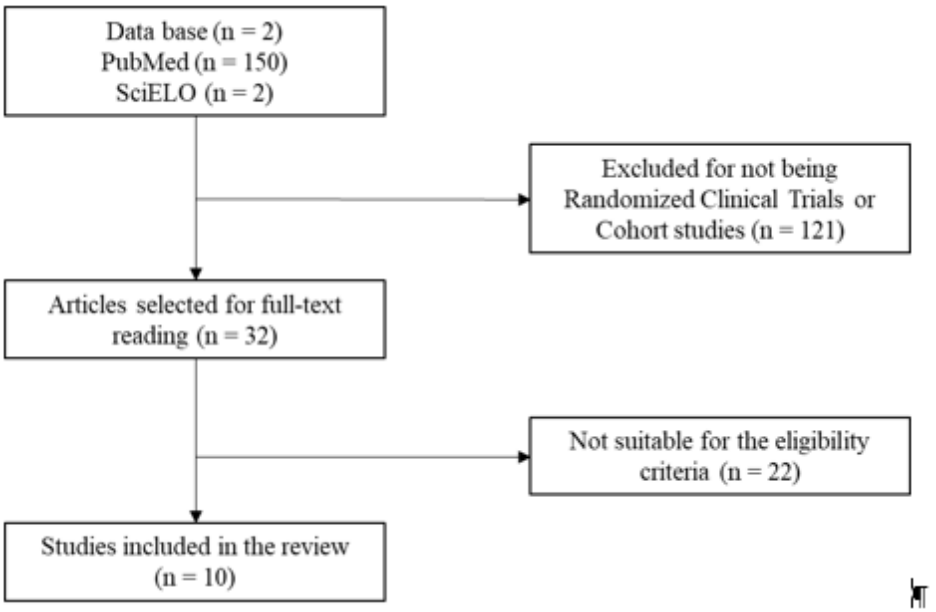
A narrative review was conducted based on articles from the Pubmed and SciELO platforms, using keywords and Health Sciences Descriptors (Decs), developed from the Medical Subject Headings (MeSH) of the US National Library of Medicine: "atrial fibrillation", "dementia", "treatment", "anticoagulants".

Randomized clinical trials and prospective cohorts published between 2015 and 2021, written in English, Spanish, or Portuguese, conducted in humans were selected. Articles that did not fit the theme or did not yet have preliminary results were excluded. The methodological analysis on scientific quality followed pre-established objective criteria of PRISMA guidelines - Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology.

In addition, a search was conducted on the ClinicalTrials.gov and Plataforma Brasil platforms to find ongoing randomized clinical trials that had already presented preliminary results. The terms "Atrial Fibrillation" and "Dementia" were used.

RESULTS

A total of 155 articles were identified, with 153 on the PubMed database and 2 on the SciELO platform. Initially, 121 articles were excluded based on abstracts that presented study designs not consistent with the search criteria. Thirty-two eligible articles were selected for full-text reading, and only 10 were related to the proposed topic and were included in the review (Figure 1).



Source: Authors.
Figure 1 - Flowchart of the article selection process

Among the ongoing studies, 22 were found on the ClinicalTrials.gov platform, of which only 3 were Randomized Clinical Trials related to the topic, but they have not presented preliminary results so far. Otherwise, no eligible studies were found on the Plataforma Brasil.

DISCUSSION

Søgaard et al.[15] analyzed the effect of treatment with non-vitamin K antagonist oral anticoagulants (NOACs) - apixaban, dabigatran, and rivaroxaban - or warfarin, on the risk of dementia. They analyzed a population of 33,617 new anticoagulant users with non-valvular AF and no previous neurological diagnosis of dementia, organized into 3 age groups. As a result, it was observed that among warfarin users, the rates of dementia were not significantly lower compared to NOAC users aged 60-69 years (hazard ratio, 0.92 [95% CI 0.48-1.72]) nor NOAC users aged 70-79 years (hazard ratio, 0.86 [95% CI 0.68-1.09]). However, in patients aged 80 years or older, NOACs were associated with significantly higher rates of dementia than warfarin (hazard ratio, 1.31 [95% CI 1.07-1.59]). According to the

authors, this may be due to confounding factors related to the lack of prior knowledge about comorbidities in patients over 80 years old, as well as the absence of information about adherence to treatment and target therapeutic range among warfarin users.

Mongkhon et al.[16] compared the risk of dementia or cognitive impairment in four groups of AF patients, including users of oral anticoagulation (OAC) versus non-users of OAC; OAC versus antiplatelet therapy; NOACs versus warfarin; and dual therapy (OAC plus one antiplatelet agent) versus no treatment. A population of 84,521 patients aged 18 years or older with newly diagnosed AF and no history of cognitive impairment was studied. As a result, treatment with oral anticoagulants was associated with a lower risk of dementia compared to no OAC treatment (hazard ratio [HR] 0.90 [95% CI 0.85-0.95] P<0.001) or antiplatelets (HR 0.84 [95% CI 0.79-0.90] P<0.001). No significant difference in the risk of dementia was observed for new oral anticoagulants (NOACs) versus warfarin (HR 0.89 [95% CI 0.70-1.14] P=0.373). Dual therapy was associated with a higher risk of dementia compared to no treatment (HR 1.17 [95% CI 1.05-1.31] P=0.006)[16], however, the study data doesn't indicate an explanation for this finding, and no hypothesis was suggested by the authors

Friberg and Rosenqvist[17] studied the incidence of dementia among AF patients on oral anticoagulants compared to those without anticoagulation, as well as analyzed the difference between NOACs and warfarin. They studied a population of 444,106 patients with hospital diagnosis of AF and no previous dementia diagnosis. As a result, patients on anticoagulation therapy were associated with a 48% lower risk of dementia compared to those without anticoagulation therapy (HR 0.52 [95% CI 0.50–0.55]). Additionally, the direct comparison between NOACs and warfarin showed no difference (HR 0.97 [95% CI 0.67–1.40])[17].

Ding et al.[18] examined the associations between AF and dementia and cognitive decline, as well as explored the cognitive benefit of anticoagulation therapy in AF patients. They studied a population of 2,685 patients over 60 years old without dementia. As a result, they found that AF was associated with a faster annual cognitive decline (β coefficient = -0.24 [95% CI -0.31 to -0.16]) and an increased all-cause dementia risk (HR = 1.40 [95% CI 1.11-1.77]). Among people with AF, the use of anticoagulant medication, but not antiplatelet therapy, was associated with a 60% reduction in dementia risk (HR = 0.40 [95% CI 0.18–0.92]). Therefore, they concluded that AF is associated with a faster global cognitive decline and an increased risk of dementia in people over 60 and the use of anticoagulant medication may reduce the risk of dementia in AF patients[18].

Field et al.[19] investigated the association between the incidence of AF, stroke, and dementia, and the potential modifying role of anticoagulation. A population of 91,372 individuals, divided into 2 groups of individuals with and without AF, was studied. Individuals with a prior neurological diagnosis were excluded. 2.3% of AF and 1.4% of non-AF individuals were recently diagnosed with dementia (HR 1.31 [95% CI 1.15-1.49]). The AF group had more comorbidities and higher rates of dementia, with and without anticoagulation, than the non-AF group. Individuals with AF not treated with anticoagulants had higher rates of dementia compared to non-AF (HR 1.39 [95% CI 1.18-1.64]). Individuals with AF treated with anticoagulants, compared to non-AF, had higher rates but declining rates of dementia (HR 1.23 [95% CI 1.03-1.46])[19].

Friberg et al.[20] analyzed if patients with low-risk AF who use oral anticoagulants are better protected from cerebral damage, whether it be dementia, ischemic stroke, or intracerebral bleeding, than patients who do not use OAC. The analyzed population was 91,254 individuals with hospital-diagnosed AF, of whom 43% used OAC at the beginning of the study. As a result, OAC treatment was associated with a lower risk of dementia (sHR 0.62 [95% CI 0.48-0.81]). This apparent benefit was restricted to patients over the age of 65, while OAC treatment for patients under 60 years of age without risk factors appeared to be harmful despite the possible benefits. Therefore, low-risk AF patients over the age of 65 who take OAC have a lower risk of dementia than those who do not use OAC[20].

Kim et al.[21] evaluated the association between the use of NOACs (dabigatran, rivaroxaban, and apixaban) and the risk of dementia, compared to warfarin. A population of 53,236 individuals with non-valvular AF and without dementia over 50 years old with recently prescribed NOACs were studied. They were initially divided into 2 groups, one receiving anticoagulation with warfarin and the other with anticoagulation with NOACs. Subsequently, each NOAC was individually compared to warfarin. The primary outcome assessed was the development of dementia. Patients on anticoagulation with any NOAC had a lower risk of dementia than those on warfarin (HR = 0.78 [95% CI 0.68-0.90]). Additionally, among the NOACs, rivaroxaban was associated with a greater reduction in the risk of dementia when compared to the other NOACs (HR = 0.83 [95% CI 0.74-0.92]). Therefore, the study indicates that NOACs were associated with a lower risk of dementia than warfarin in patients with non-valvular AF[21].

Wändell et al.[22] analyzed the correlation between the most used drugs in therapies for cardiovascular system pathologies and dementia, among men and women with AF. A population of 12,096 individuals was studied, divided into 9 major groups according to the medication each one was taking - warfarin, thiazides, beta-blockers, calcium channel blockers, digitalis, renin-angiotensin-aldosterone system blockers, statins, loop diuretics, and aldosterone antagonists. Individuals with a previous diagnosis of dementia were excluded. Considering only the variables

of sex and age, the group that was using warfarin was associated with a statistically significant lower risk of developing dementia when compared to the other groups (HR 0.79 [95% CI 0.68-0.92])[22].

Mailhot et al.[23] evaluated the influence of prescribed anticoagulants for patients with AF and high risk of cognitive impairment on their clinical management. A population of 1,244 individuals with AF and without dementia was studied and divided into four groups according to the outcome of frailty, cognitive impairment, both conditions, and none of the conditions. Patients with high CHA2DS2VASc score requiring anticoagulation were associated with a higher risk of cognitive impairment when untreated (OR = 1.35 [95% CI 1.13–1.62])[23].

Hyogo et al.[24] followed 2,113 participants with AF for one year to evaluate the primary outcomes (symptomatic cerebral infarction, including transient ischemic attack, systemic embolisms, and fatal hemorrhagic complications requiring hospitalization) and secondary outcomes (new signs of dementia, cardiac events causing hospitalizations and other causes of death, with dementia diagnosis determined by Mini-Mental State Examination and/or Hasegawa) in patients using NOACs and warfarin. As a result, it was concluded that the primary outcomes were found in nine (1.3%) NOAC users and 15 (2.2%) warfarin users. For the secondary outcomes, they were found in 24 (3.6%) NOAC users and 36 (5.4%) warfarin users. The incidence of new onset dementia did not differ between NOAC and warfarin users (1 [0.1%] vs. 3 [0.4%] out of 667 patients, $P = 0.32$)[24].

Overall, only Kim et al.[21] observed better performance of NOACs in reducing the risk of dementia compared to warfarin and the only one that could present rivaroxaban as the best drug for reducing the risk of dementia. However, Søgaard et al.[15] demonstrated that NOAC users over 80 years of age had an increased risk of dementia compared to warfarin users. Thus, there is a clear lack of consensus in the literature regarding the best protective medication against cognitive decline. These data were summarized in Chart 1.

Chart 1 - Presentation of studies comparing the risk of dementia of NOACs versus warfarin and the risk of dementia of anticoagulants versus no therapy.

Author HR		Dementia risk of NOACs versus Warfarin		Dementia risk of anticoagulants versus no therapy	
		95% IC	HR	95% IC	
Søgaard et al.[15]	60-69 years	0.92	0.48-1.76	-	-
	70-79 years	0.86	0.68-1.09	-	-
	80 years or more	1.31	1.07-1.59	-	-
Mongkhon et al.[16]		0.89	0.70-1.14	0.90	0.85-0.95
Friberg e Rosenqvist [17]		0.97	0.67–1.40	0.71	0.68-0.74
Ding et al. [18]		0.40	0.18–0.92	-	-
Friberg et al.[20]		0.62*	0.48–0.81	-	-
Kim et al. [21]		0.78	0,69-0,90	-	-

CI = Confidence interval; HR = Hazard Ratio; *sHR = subHazard Ratio.
Source: Authors

CONCLUSION

The evidence gathered in this study indicates that the use of new oral anticoagulants, such as apixaban, dabigatran, and rivaroxaban, or vitamin K antagonist anticoagulants, such as warfarin, reduces the risk of cognitive impairment and dementia in people with atrial fibrillation. However, it is not possible to determine the best treatment currently available, as there was no clinically significant difference in the development of dementia between users of new oral anticoagulants and warfarin.

Therefore, it is necessary to develop new studies to compare new oral anticoagulants and warfarin, in order to ensure the most effective treatment.

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