Journal of the Neurological Sciences 399 (2019) 172–181

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Neuropsychological and neuroimaging evidences of cerebral dysfunction in stroke-free patients with atrial fibrillation: A review

Silva D.S.[a,c], Coan A.C.[b,c], Avelar W.M.[a,c,*]

[a] Stroke Center, Department of Neurology, State University of Campinas, Campinas, SP, Brazil
[b] Neuroimaging Laboratory, Department of Neurology, State University of Campinas, Campinas, SP, Brazil
[c] Brazilian Institute of Neuroscience and Neurotechnology, BRAINN, at UNICAMP, Campinas, SP, Brazil

ARTICLE INFO

Keywords:
Cardiac arrhythmia
Cognition
Executive function
Brain volume

ABSTRACT

Atrial fibrillation (AF) is the most common heart arrhythmia, with the highest prevalence in the elderly. AF has been correlated with silent lesions and cognitive impairment, even in the absence of stroke. The cognitive impairment in AF represents a risk of functional decline, morbidity, mortality and high costs, constituting a public health problem due to the increasing prevalence of this arrhythmia. Cognitive analysis of patients with AF without stroke has shown poor performance in executive, memory and learning functions. The greater loss occurs in speed processing and performance of instrumental tasks leading to functional dependence. Neuroimaging studies have shown both structural and functional abnormalities in individuals with AF even in the absence of cognitive impairment. The mechanisms related to cognitive impairment and cerebral abnormalities in the AF are still a matter of discussion in the literature and, therefore, how to stop its progression is unknown. We reviewed the recent evidence about AF and dementia in patients without stroke, with special emphasis to the reported profile of cognitive dysfunction and the neuroimaging evidence of brain abnormalities.

1. Background

Atrial fibrillation (AF) is the most common arrhythmia in the general population [1,2] and a well-accepted independent risk factor for stroke [3,4]. It is characterized by irregularity of heart rate and "*f*" wave at the baseline of the electrocardiogram. Advancing age is considered the most prominent risk factor for AF development and the number of individuals with this arrhythmia is likely to increase in the next decades [5,6]. Indeed, cognitive dysfunction can occur in patients with AF when a history of clinical embolic stroke is evident, but in recent years, a robust range of evidence has emerged to support AF as a risk factor for cognitive impairment and dementia even in the absence of cardioembolic stroke.

The full comprehension of the mechanisms by which AF may lead to cognitive impairment in patients without any evidence of stroke are not completely understood [7]. Currently, there is no knowledge on how to prevent cognitive dysfunction in stroke-free patients with AF; therefore, clarifying the underlying mechanisms of cognitive impairment in AF without stroke is considered critical [7].

In this review, we aimed to address the recent literature evidence about the association between AF and dementia in patients without stroke, with special emphasis to the reported profile of cognitive dysfunction and the neuroimaging evidence of brain abnormalities. We also discuss the main proposed mechanisms involved with the possible cerebral damage and cognitive abnormalities in stroke-free individuals with AF.

2. AF beyond the traditional risk for embolic stroke: an independent risk factor for cognitive impairment

Cognitive impairment in older patients is considered a multifactorial disorder [8]. In the past ten years, however, emergent evidence has appointed AF as an independent risk factor for structural brain damage and dementia even in patients with no history of stroke. The mark zero for the recent advance in this field was the large cross-sectional, population-based study by Alewijn Ott et al., published in 1997 [9]. The authors investigated the association of AF with dementia and cognitive impairment in the elderly (The Rotterdam Study) and found significant association of AF with impaired cognitive function and dementia [9]. At the beginning of the current decade, two meta-analyses highlighted that AF is an independent risk factor for cognitive impairment and dementia [10,11]. These meta-analysis, including large

* Corresponding author at: Departamento de Neurologia, Faculdade de Ciências Médicas – UNICAMP, Cidade Universitária Zeferino Vaz, Campinas, SP CEP 13083-970, Brazil.
E-mail addresses: wagner.avelar@hc.unicamp.br, wagner.avelar@gmail.com (W.M. Avelar).

https://doi.org/10.1016/j.jns.2019.02.027
Received 31 July 2018; Received in revised form 18 January 2019; Accepted 18 February 2019
Available online 18 February 2019

samples of patients, found a greater risk of cognitive decline among patients with AF even after adjustments for the impacts of possible confounding factors [10,11]. Also, recently, prospective evidences suggesting that AF increases the risk of cognitive decline and dementia independently of stroke emerged from a *post hoc* analysis of two randomized controlled trials [12].

More recently, especially in the last five years, longitudinal studies have added up to the knowledge of cognitive impairment and AF. Chen et al. [13] published a long-term follow-up study in a community-based cohort to assess the association between AF and cognitive performance. With [20] years of follow-up, the authors found that AF was associated with greater cognitive decline and increased risk of dementia, independently of ischemic stroke (global cognitive Z score = 0.115, 95% confidence interval, 0.014–0.215) [13]. Another recent long-term follow-up study by de Bruijn et al. [14], with a similar time of evaluation, presented similar results. By analyzing the younger participants, Bruijn et al. [14] also showed a dose-response association between AF and dementia [14]. This observation may appoint to a critical role of the relationship between time of exposure to AF and risk of dementia. Younger patients with AF may stay for a long time over the influence of this arrhythmia and its consequences, such as chronic cerebral hypoperfusion and cerebral silent infarcts.

Therefore, AF duration appears to be important in the development of cognitive impairment among patients with this arrhythmia. This is supported by a recent prospective study over 15 years of follow-up, which evaluated the potential dose-response association of duration of exposure to AF with cognitive decline [15]. However, this observation was not found in the O'Connell et al [16] and, in their study, AF time of exposure did not show influence on cognitive performance.

In addition, populations with high prevalence of AF also have a higher prevalence of degenerative neurological disease and dementia, such as Alzheimer's disease. However, as highlighted by Jacobs et al. [17], the presence of a higher relative risk of Alzheimer dementia among younger patients (< 70 years) with AF suggests that the presence of this arrhythmia is more than an epiphenomenon [17]. In the Bunch et al. [18] study, AF was associated to all types of dementia. Despite the strong association between advanced age and dementia, the highest risk of Alzheimer's dementia was found, again, in the younger AF group [18]. Whether AF may accelerate Alzheimer's dementia through white matter changes or silent strokes remains not absolutely understood. Indeed, despite of advanced age among patients with AF, even after adjustments in study design and analysis for possible confounding factors common in elderly people, several studies continue to appoint the association between AF and cognitive impairment as highlighted in Table 1 (see study characteristics column).

Therefore, in the last decade, strong evidence arose to support the association between AF and dementia. At this point, stroke appears to be just the tip of the iceberg in the relationship between AF and cognition.

Stroke risk scores commonly used in clinical practice in neurology may predict risk for dementia in AF patients [19–22]. A large-scale population-based study by Liao et al. [19] with 332,665 AF subjects found that CHA_2DS_2-VASc score could be used as a tool to estimate the risk of dementia in AF patients. This result is supported by other large-scale population-based cohort study using $CHADS_2$ score to predict risk of vascular and Alzheimer's dementia in an AF sample [20]. High $CHADS_2$ score was associated to major risk of developing dementia. Higher CHA2DS2-VASc score was predictor of mild cognitive impairment in a randomized trial with 260 AF participants as well [21]. Interestingly in the Graves et al. study [22] with 6030 patients, all participants were under anticoagulation and history of stroke was not statistically different between no-AF and AF group. The authors conclude that dementia risk increased with increasing CHADS2 scores, supporting this tool as a predictor of dementia even in a sample under chronic anticoagulation. Despite of that, AF was itself associated with higher rates of dementia across all CHADS2 score strata [22].

3. Assessing the cognitive impairment profile in patients with AF without stroke

One barrier to the better understanding of the cognitive profile of patients with AF is the lack of standardized tests used for cognitive evaluation in the main studies in this field. One of the most commonly used tests is the Mini-Mental Status Examination (MMSE), but this tool has critical limitations in the evaluation of the executive functions and it can have low sensitivity to detect subtle changes in cognition, particularly among patients with higher education [23].

Since MMSE is considered as a poor screening tool for executive function, some studies in this field had used complementary tests to add frontal lobe function information such as the digit symbol substitution test, which is useful to assess attention and cognitive speed process. A longitudinal analysis by Thacker et al [24], with an average of 7 years of follow-up, used a modified version of the MMSE and the digit symbol substitution test. This study included 5150 patients, of whom 552 developed new AF. Patients with incidental AF, even without clinical stroke, achieved scores for cognitive impairment or dementia at an earlier age than patients without AF [24].

More recently, studies have used a wide battery of cognitive assessment in order to evaluate different cognitive domains in patients with AF [15,16,23,25–27]. Nishtala et al. [23] found that AF without stroke was associated with a vascular profile of changes in cognitive function after accounting for vascular risk factor burden and APOE4 [23]. In this cross-sectional and longitudinal study, the participants underwent a neuropsychological assessment that included different cognitive domains such as attention, executive function, and visual memory.

In another cross-sectional study with 87 patients with AF without stroke, Knecht et al. [25] performed an extensive neuropsychological assessment. This study deserves to be highlighted due to the robustness of its cognitive analysis. The authors evaluated several cognitive domains possibly affected in cases of AF without stroke using tools such as the Stroop test and Trail-making test for inhibition capacity, attention and cognitive flexibility in the scope of executive functions, digit span for working memory, symbol digit to cognitive speed process, test of reproduction of the complex figure of Rey to evaluate visuoconstructive skills and visual memory, as well as verbal learning test sequence of words [25]. Compared to controls without AF, patients with AF without stroke had worse performance in executive function and attention, besides disorders of memory and learning. Furthermore, subjects with AF performed significantly worse in tasks of learning and memory compared with controls. There was also a tendency to a worse performance in learning and memory functions among those with chronic AF compared with those with the paroxysmal patter of this arrhythmia [25].

As many studies have used different methodologies for assessing cognitive functions, establishing an accurate profile of cognitive dysfunction in AF may be difficult as conflicting results are reported across different studies (Table 1) [7,9,12–16,18,23–25,27–36]. However, these studies show predominant executive dysfunction, including loss of attention and processing speed impairment, low cognitive flexibility as well as poor cognitive performance in others domains, especially memory, abstract reasoning and visual-spatial abilities.

Results regarding memory impairment are especially conflicting in the literature. Some studies focus only in tests traditionally implicated with evaluation of the executive function, such as digit substitution test (processing speed, attention and cognitive flexibility, executive function) and verbal fluency (executive function and lexical access) [7,13]. The larger longitudinal study with more than 2000 patients with AF by Chen et al. [13] recently found no significant memory decline. In this study, AF was associated with poor performance in digit substitution and word fluency tests, appointing to executive dysfunction, mainly cognitive flexibility and ability to use strategies as well as self-monitor skill impairment [13]. This observation in a long time community

Table 1
Cognitive assessment in patients with AF along several different studies and its main results.

Study and author	Number of subjects with AF/study design	Cognitive assessment design/cognitive ability tested	Main cognitive profile findings/main results
Atrial Fibrillation and Dementia in a Population-Based Study The Rotterdam Study. Ott et al. [9]	195 AF subjects of the 6584 participants. Cross-sectional analysis. Include participants with dementia and with impaired cognitive function without dementia. Association between AF and cognitive disorders in the absence of clinical strokes was evaluated using multiple regression analyses.	MMSE test and Geriatric Mental State Schedule as screening evaluation. Some participants were submitted to 2-h neuropsychological testing [a] according clinical indication.	Positive associations of AF with dementia and impaired cognitive function. Exclusion of subjects with a history of stroke did not reduced the associations observed.
Atrial fibrillation and cognitive function: case-control study. O'Connell et al. [16]	27 patients with non-valvular AF. Prospective community based case controlled study. No history of stroke, transient ischemic attack, dementia, and thyrotoxicosis. Controls matched for age and sex, without AF.	MMSE test Wechsler logical memory test, verbal long term memory, Rey complex figure test, non-verbal memory, digit span, short term memory, PASAT, test of everyday attention, selective attention, divided attention.	AF was associated with poorer cognitive performances. No association observed between time to exposure to AF and cognitive performance.
Atrial Fibrillation Is an Independent Determinant of Low Cognitive Function: A Cross-Sectional Study in Elderly Men Kilander et al. [33]	44 AF participants Cross-sectional study based on a cohort of a community-living men in Sweden. Analyses were adjusted for age, education, and occupational level. Relation between AF and cognitive *z* score was analyzed, with stroke and other vascular risk factors taken into account.	MMSE test Trail Making Tests A and B Global cognitive function and executive function (speed and shifting capacity, subcortical function).	AF participants had lower adjusted cognitive score compared to subjects without AF and this finding remains after exclusion of patients with stroke.
Atrial fibrillation and cognitive disorders in older people. Sabatini et al. [34]	42 patients with AF Exclude patients with AF and < 70 yd., critical stenosis, stroke or TIA, dementia, MMES < 20 or other clinical conditions.	MMSE test	Poor MMES performance in AF compared to normal sinus rhythm subjects.
Atrial Fibrillation Is Associated With Lower Cognitive Performance in the Framingham Offspring Men. Elias et al. [28]	59 AF participants free of clinical stroke and dementia. Include middle-aged participants with AF Authors performed covariation analysis for age, education, cardiovascular risk factors, and prevalent cardiovascular disease.	Wechsler adult intelligence and memory scale, Trail making test (A and B), Hooper visual organization test. Abstract reasoning, new learning and memory, immediate and delayed recall visual/spatial stimuli and verbal passages, executive function, attention, concentration, visual scanning, and speed of tracking.	Significant lower mean levels of cognitive performance among patients with AF compared with subjects in normal sinus rhythm: impairment in global cognition and abstract reasoning, visual reproductions-immediate recall, visual reproductions-delayed recall, visual organization, logical memory-delayed recall and executive functioning.
Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment (MCI). Forti et al. [29]	24 participants with AF Prospective study involving subjects with mild cognitive impairment and normal cognitive participants with AF. Analysis was adjusted for sociodemographic and medical variables. Neuroimaging not available in that sample (silent stroke was not exclude formally in all subjects).	Italian version of the MMSE. Wide neurophysiological battery with evaluation of several cognitive domains such as: memory (Rey test to recall words), attention, language, executive functions using phonological word fluency, abstract reasoning and visuospatial skills (Raven's 47 progressive colored matrices and copy of drawings.	Authors conclude that AF is a predictor of conversion to dementia among patients with mild cognitive impairment.
Atrial Fibrillation, Stroke, and Cognition. A Longitudinal Population-Based Study of People Aged 85 and Older Rastas et al. [31]	122 AF participants (83 without stroke). Prospective 9-year follow-up population based study (Southern Finland). Neuroimaging was lacking in most subjects enrolled in this study.	MMES Diagnostic and Statistical Manual of Mental Disorders (Third edition-revised)	AF were not linked to dementia.
Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Knecht et al. [25]	87 patients with AF. Cross-sectional analysis. Exclude participants with chronic neurologic and psychiatric disorders such as Parkinson diseases, dementia and history of ischemic stroke.	Auditory verbal learning Test (German version), Stroop test, DSS test, Trail-making test, verbal (category and letter) fluency, Rey-Osterrieth complex figure test. Learning and memory abilities, executive function and attention, working memory and visuospatial abilities.	AF was associated with poor performance in attention and executive functions as well as memory and learning compared with controls without AF, even after controlling for other vascular risk factors.

(*continued on next page*)

Table 1 (*continued*)

Study and author	Number of subjects with AF/study design	Cognitive assessment design/cognitive ability tested	Main cognitive profile findings/main results
Cardiovascular and biochemical risk factors for incident dementia in the Hypertension in the Very Elderly Trial. Peters et al. [35]	190 AF participants Prospective observational study that includes patients with past stroke.	MMES and clock drawing tests Diagnostic and Statistical Manual of Mental Disorders IV edition.	No relationship between AF and cognitive decline or dementia.
Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Bunch et al. [18]	10,161 AF patients Prospective study (based in a large health care database, the Intermountain Heart Collaborative Study) mean of follow-up of 5 years.	International Classification of Diseases (ninth revision) used for dementia identification. No neuropsychological assessment battery reported in published article.	Authors found that AF was independently associated with all forms of dementia (vascular, Alzheimer, senile and no specified).
Atrial fibrillation, stroke and dementia in the very old: A population-based study. Marengoni et al. [30]	68 participants with AF dementia- and stroke-free Follow-up (6-year) study of a large-scale community cohort (derived from the Kungsholmen Project) of very old adults.	MMES test	No association between AF and Dementia
Atrial Fibrillation and Risk of Dementia: A Prospective Cohort study. Dublin et al. [36]	132 participants with AF A prospective cohort study (population-based sample of adults age 65 and older without dementia or clinical stroke) Analysis covariates from education, sex, diabetes, hypertension, systolic and diastolic blood pressure, coronary diseases, incident stroke, and congestive heart failure	Tests performed for attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction, list-generating fluency, abstraction, and judgment (The Cognitive Abilities Screening Instrument –CASI).	AF was associated with higher risk of dementia independent of stroke.
Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. Marzona et al. [12]	3068 participants had AF Prospective study with post-hoc analysis of two randomized controlled trials (ONTARGET and TRANSCEND), median follow-up of 56 months. Exclude patients with heart failure, valvular disease and uncontrolled hypertension. Analysis was adjusted for several confounders such as previous stroke or TIA, age, level of education, sex and baseline MMSE score.	MMSE test	Authors found that AF was associated with an increased risk of cognitive loss, new dementia, loss of independence in performing activities of daily living as well as admission to a long-term care facility on the multivariable analysis.
Atrial fibrillation (AF) and cognitive impairment in the elderly: A case–control study. Bellomo et al. [59]	26 AF participants Case–control study No medical history of past stroke	MMSE test	AF had significantly lower cognitive scores than those with sinus rhythm.
Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. Stefansdottir et al. [27]	330 AF participants Cross-sectional analysis (non-demented participants) population-based AGES-Reykjavik Study. Analysis was adjusted for demographic, cardiovascular risk factors and cerebral infarcts.	Cognitive test battery include The California Verbal Learning Test, DSS Test, Figure Comparison Test, Stroop Test (part 1, 2 and 3), Digits Backward test, a shortened version of the Spatial Working Memory subtest of the Cambridge Neuropsychological Test Automated Battery. Main domains evaluated were memory, processing speed and executive function	AF patients scored lower on tests of all three cognitive domains: memory, processing speed and executive function. AF time of exposure was associated with worst scores in memory (cumulative effect). Results remained even after adjusting for the higher prevalence of cardiovascular risk factors and cerebral infarcts in AF population.
Prevalence of Silent Cerebral Ischemia in Paroxysmal and Persistent Atrial Fibrillation and Correlation With Cognitive Function. Gaita et al. [60]	180 AF participants Exclusion of participants with previous history of stroke or TIA as well as others organ severe dysfunctions or clinical disorders. The study rule out patients with dementia or depression. Patients were underwent to clinical assessment, including medical history and thromboembolic risk assessment using CHA2DS2-VASc score.	MMES test Repeatable Battery for the Assessment of Neuropsychological Status. Immediate memory, visuospatial abilities, language, attention, and delayed memory.	AF patients had worse cognitive performance in all domains of cognition evaluated compared with controls. Visual-spatial abilities were worse in patients with persistent AF patter.

(*continued on next page*)

Table 1 (*continued*)

Study and author	Number of subjects with AF/study design	Cognitive assessment design/cognitive ability tested	Main cognitive profile findings/main results
Atrial fibrillation and cognitive decline: A longitudinal cohort study. Thacker et al. [24]	552 AF participants Longitudinal prospective analysis in the Cardiovascular Health Study (community-based study) - mean of 7 years of follow-up. Exclude participants with clinical stroke	100-point Modified Mini-Mental State Examination and the DSS Test. Telephone Interview for Cognitive Status and Informant Questionnaire on Cognitive Decline in the Elderly for some participants who did not have in-person cognitive assessments 23. Processing speed, visuomotor coordination, attention	Cognitive performance declined faster in participants after incident AF was identified than before it was identified in the curse of study follow-up compared with controls.
Atrial Fibrillation and Cognitive Decline–The Role of Subclinical Cerebral Infarcts: The ARIC Study. Chen et al. [7]	48 AF patients Community-based prospective cohort study (Atherosclerosis Risk in Communities – ARIC study).	Cognitive evaluation consisted of DSS, DWR and the WF test. Executive functions, memory and cognitive flexibility	Poor cognitive performance was observed regard DSS and WF test in patients who develop incident AF compared with subjects who not develop AF but incident AF was not associated with a greater rate of decline in DWR.
Atrial Fibrillation Exacerbates Cognitive Dysfunction and Cerebral Perfusion in Heart Failure. Alosco et al. [32]	60 AF participants. Cross-sectional study (participants with heart failure that were enrolled in an National Institutes of Health (NIH) study examining neurocognitive outcomes in older adults with heart failure). Exclusion criteria: history of significant neurological disorder (dementia, stroke, multiple sclerosis, *etc.*), head injury, severe psychiatric disorder, past or current substance abuse and severe kidney disease.	MMES – modified version (3MS) Trail Making Test A and B, DSS and Frontal Assessment Battery, California Verbal Learning Test-II long delay free recall and total recognition hits, Boston Naming Test and Animal Fluency test. Memory, executive functions and language skills.	Poor cognitive performance was observed main in memory. No significant differences between groups for attention/executive function or language. Data showed that AF was associated with additive deficits in global cognitive status and memory in patients with heart failure compared with controls with heart failure without AF.
Association Between Atrial Fibrillation and Dementia in the General Population. de Bruijn et al. [14]	318 AF participants. Longitudinal study (population-based, Rotterdam Study) with long time follow-up ([20] years). Analysis censored for stroke and adjusted for age, sex, and cardiovascular risk factors.	Cognitive screening with the MMES and the Geriatric Mental State Schedule organic level. An informant interview with the Cambridge Examination for Mental Disorders of the Elderly was done if patient had poor performance in the screening protocol. In some cases (if necessary) neuropsychological testing was done[a]	Prevalent AF was related to an increased risk of dementia. Burden (longest duration) of AF of exposure was associated with increased risk of dementia, independent of clinical stroke, especially among younger patients with AF.
Atrial fibrillation as a risk factor for cognitive decline and dementia. Singh-Manoux A et al. [15]	414 AF participants. Prospective study (long time follow-up) with covariation analysis including stroke and other medical chronic disorders such as heart failure and coronary diseases.	Alice Heim 4-I test. Memory, reasoning, verbal fluency (phonemic and semantic).	Poor cognitive performance was found across all age groups, in analysis adjusted for all confounders and was greater in those with longer exposure to AF. Results showed greater cognitive decline (reasoning and verbal fluency performances) in those with AF, but there were no associations between AF and memory decline.
Atrial fibrillation and cognitive decline in the Framingham Heart Study. Nishtala et al. [23]	122 AF patients Cross-sectional and longitudinal analysis (Framingham Heart Study Original and Offspring cohorts). Adjusted models for age and sex, and then for vascular risk factors and *APOE4*. Participants with history of clinical stroke were excluded	Trail Making Test A and B, Visual Reproductions: Immediate and Delayed Recall, Hooper Visual Organization, Wechsler Adult Intelligence Test Similarities, Visual memory, abstract reasoning, executive functions, visuospatial organization and attention.	Authors reported vascular profile of change in the cognitive function among patients with AF. AF was significantly associated with poorer attention and executive function.

(*continued on next page*)

Table 1 (*continued*)

Study and author	Number of subjects with AF/study design	Cognitive assessment design/cognitive ability tested	Main cognitive profile findings/main results
Association of Atrial Fibrillation With Cognitive Decline and Dementia Over 20 Years: The ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study).	2106 AF participants Community-based cohort (Atherosclerosis Risk in Communities study), with long follow-up.	DWR, DSS and WF tests. Verbal learning, short-term memory, executive function, expressive language and processing speed.	linear models for global cognitive, DWRT, DSST, and WFT Z scores found that AF was associated with greater decline in the scores of all tests except the DWR test.
Chen et al. [13]	Analysis accounting for cardiovascular risk factors, including ischemic stroke.		Incident AF was associated with higher risk of dementia even after adjustment for prevalent and incident ischemic stroke.
Atrial fibrillation, antithrombotic treatment, and cognitive aging. A population-based study.	522 AF participants	MMSE	AF was associated with a faster decline in global cognitive function and an increased risk of dementia, (vascular and mixed dementia).
Ding M et al. [58]	Population-based study of people aged 60 years and older. 9-year follow-up.		

AF: atrial fibrillation; **MMSE**: mini mental state examination (measure orientation to time, orientation to place, registration, attention and calculation, recall, naming and repetition, comprehension, reading ability, writing ability and design copy- ability to visual construction); **PASAT**: paced auditory serial addition test; **DWR**: Delayed Word Recall test; **DSS**: Digit Symbol Substitution test; **WF**: Word Fluency test; **TIA:**transient ischemic attack; **CHA2DS2-VASc score**: congestive heart failure or left ventricular dysfunction, hypertension, age, diabetes, stroke or transient ischemic attack, thromboembolism, and vascular disease;

[a] Not specified in the published article.

based-study with analysis accounting for cardiovascular risk factors, including ischemic stroke, supports the evidence of predominant executive function impairment (vascular profile of cognitive dysfunction) among patients with AF [7, 15, 23]. The main results on cognitive profile found in several different studies in this field are summarized in Table 1.

4. Neuropsychiatric manifestations in AF without stroke

Beyond cognitive impairment, it is possible that patients with AF without stroke may present other neuropsychiatric problems, such as depression and anxiety. However, there is lack of data in the literature addressing this issue. Some authors have reported the presence of depression and anxiety among AF patients but, in general, literature contains just few studies and evidence is somewhat small. In a study with 101 patients with AF without stroke compared with normal sinus rhythm controls during six months follow-up, Thrall et al. [37] found elevated levels of depression and anxiety in almost one-third of patients in the AF group compared to no AF group. Another study with a small sample reported that AF patients are more likely to develop anxiety [38].

5. AF and Neuroimaging: evidence of cerebral atrophy and brain network disruption

Patients with AF, even without cerebral infarcts, have lower brain volume compared to controls [27]. AF was also associated with loss of total cerebral gray matter, which was correlated with disease duration [27]. Knecht S et al. [25] found hippocampal atrophy in patients with AF without stroke, which was correlated with memory deficits.

The results of a cross-sectional study with 330 patients with AF without dementia showed a cumulative negative association between brain volume and the pattern of AF, which was stronger for patients with earlier diagnoses and the persistent pattern of this arrhythmia [27]. This indicates that the type of AF (persistent/permanent *versus* paroxysmal AF) and duration of the disease (time of exposure) may influence not only the cognitive performance but also contribute to brain structural changes. [14,15,25].

A recent resting-state functional MRI study showed disruption in a paramount brain network, the default mode network, in patients with AF and no evidence of stroke [39]. The result adds evidence to the occurrence of cerebral dysfunction among patients with AF even in the absence of stroke. Moreover, the abnormal connectivity in this important cognitive brain network may help to explain how AF works to produce cognitive impairment in these patients.

The Swiss Atrial Fibrillation (Swiss-AF) cohort is a prospective multicenter observational cohort study across 13 centers in Switzerland with the aim to establish a large interdisciplinary platform to study the interrelationships of AF and the possible progression of structural and functional brain damage over time [40]. It enrolled 2133 patients up to 7 April 2017 [40]. However, at the moment the present manuscript was written, the SwissAF study investigators had only published results of prevalence of silent vascular brain lesions among patients with AF and no history of stroke. They reported a high burden of silent vascular brain lesions on the structural neuroimaging study in a sample of 1388 subjects with AF (41% of patients had silent vascular brain lesions)[41].

6. Possible mechanisms of cognitive impairment in AF

6.1. Microbleeds and white matter disease

Microbleeds are small hypointense foci on MRI T2*-weighted gradient-recalled echo associated with histopathological evidence of previous hemorrhage in the brain tissue [42]. It is related to bleeding-prone microangiopathy (hypertensive vasculopathy/fibrohyalinosis and cerebral amyloid angiopathy) [43]. Microbleeds are associated with cognitive impairment [44,45].

In a study with 500 nondemented elderly patients with small vessel disease, the presence, number and location of microbleeds in the gradient echo T2*-weighted MRI was analyzed after adjustment for age, sex, education, depressive symptoms, total brain volume, white matter lesion volume, and lacunar and territorial infarcts [46]. Microbleeds in frontal and temporal lobe were correlated with cognitive performance independently of coexisting white matter lesions and lacunar infarcts [46], and a correlation between deep microbleeds and cognitive performance was also observed. In a previous study by Werring et al. [45], microbleeds were associated with executive dysfunction and its effect on cognition appears to be independent of coexisting ischemic cerebrovascular disease and the severity of ischemic small vessel disease.

Many patients with AF use anticoagulation therapy, what favors the occurrence of microbleeds. Since the microbleeds has been associated to poor cognitive performance [44,46],at least in part, its occurrence could explain part of the process leading to the cognitive impairment observed in AF. However, to date, there is a lack of studies about microbleeds and cognitive function in stroke-free patients with AF. Furthermore, the underlying mechanisms leading to this association are unknown [46]. One possibility is that microbleeds could cause cognitive dysfunction if they disrupt strategically important white matter tracts or eloquent cortical areas [45].

In fact, brain white matter hyperintensity detected in MRI exams are associated with AF and with poor cognitive performance [47,48,49]. Its occurrence may be associated to cerebral hypoperfusion [49], and some authors have considered that white matter hyperintensity in AF patients may be linked to a cardiovasculopathy that affects the brain. However, the pathogenesis of white matter hyperintensity remains not completely clear. At least in part, cerebral white matter diseases may explain AF cognitive decline. This reasoning is supported by two groups of evidences. First, there are studies demonstrating that in patients with AF and embolic stroke, the arrhythmia was associated with more anterior/frontal white matter hyperintensity [47]. Second, there are evidences that patients with large white matter hyperintensity volume, as compared with patients with smaller or no white matter hyperintensity, have poor cognitive performance in cognitive domains associated with frontal lobe systems [48].

6.2. Hemodynamic repercussion

Another possible mechanism associated with cognitive impairment in patients with AF is hemodynamic changes secondary to the cardiac arrhythmia. Studies using transcranial doppler support the relation between AF and lower cerebral blood flow even without evident ischemia [50,51]. Totaro et al· [51] assessed cerebral blood flow during and after an attack of paroxysmal AF in a small sample. During the attack and after conversion to sinus rhythm, the mean flow velocity decreased significantly in middle cerebral artery [51]. The result indicates that the decrease in cardiac output causes a decrease in the perfusion pressure and in the velocity of cerebral blood flow [51]. Other recent study evaluated the cerebral blood flow and brain perfusion in a large cohort of elderly individuals with AF using MRI. The authors found that persistent AF, but not paroxysmal AF, was associated with decreased total cerebral blood flow, and estimated whole brain perfusion [52]. Also, there is evidence of significant increase in cerebral blood flow after conversion of AF to sinus rhythm [53]. These results support the hypothesis that hemodynamic changes in patients with AF may play a role in cerebral dysfunction and perhaps it may explain in part the association between AF and cognitive impairment.

A recent systematic review and meta-analysis [54] assessing the effect of AF on cognitive function in patients with heart failure found that patients with both heart failure and AF are more likely to have cognitive impairment in comparison to their AF-free counterparts (OR, 1.94; 95% CI, 1.30–2.87) [54]. The study conducted by Alosco et al [32] showed that AF was associated with poor cognitive performance in patients with heart failure when compared with subjects with heart failure and no AF (Table 1). Exploring cerebral blood flow using transcranial doppler ultrasonography in patients with AF and heart failure, that study showed an association between AF and additive deficits in global cognitive status and memory abilities in older adults with heart failure [32]. The authors believe that these findings may support reduced cerebral blood flow as one possible mechanism by which AF contributes to cognitive dysfunction in patients with concomitant heart failure [32]. They observed that decreased in the cerebral blood flow velocities in the middle cerebral artery in patients with heart failure and AF was associated with poor performance in attention/executive function, memory and language abilities. However, among participants without AF, there was no significant association between cerebral blood flow velocities and any of the cognitive domains evaluated [32].

6.3. Microembolizations and silent cerebral infarctions

Due to the well-known propensity of patients with AF to have intracavitary thrombus with potential cerebral embolization, it is plausible that subclinical microstructural damage to the brain parenchyma can exist in these patients. Corroborating this hypothesis is the observation that AF is associated with silent cerebral infarctions in patients with no history of symptomatic stroke, independently of AF type [55]. Around 30% of patients may have silent infarcts as demonstrated by a recent neuroimaging study [26].

Silent cerebral ischemia appears to be implicated with cognitive dysfunction in patients with AF. However, studies have found a significantly lower performance on cognitive tests in patients with AF even after adjusting for the higher prevalence of cardiovascular risk factors and cerebral infarcts [27], Chen et al. [7] suggest that the association between incident AF and cognitive decline is mediated by the presence or development of subclinical cerebral infarctions [7].

6.4. Cumulative risk factors

It is well known that AF and dementia share some of the same risk factors such as advanced age, hypertension and cardiac failure [6]. Therefore, the population predisposed to develop AF is also more prone to have chronic hypertension, diabetes, heart failure, and other risk factors for stroke and brain damage. However, in a recent study with 15 years follow-up, the association between AF with accelerated cognitive decline and higher risk of dementia was explained, in part, by incident cardiovascular disease in patients with that arrhythmia. The result shows that AF may predispose to cerebral dysfunction when associated to major cardiovascular disorders [15]. However, this issue is not completely understood and contradictory results are shown in the literature. In the Chen et al. [13] study, which also had a long time of follow-up, AF was again significantly associated with poor performance in cognitive tests, even when additional adjustments were made to prevalence of coronary heart diseases, heart failure, diabetes mellitus, systolic and diastolic blood pressure or use of hypertensive medication for example.

Therefore, there is some uncertainty about the real contribution of cardiovascular risk factors in AF related dementia despite the robust analysis presented by Chen et al. [13]. Although heart failure, hypertension, diabetes and other common disorders in elderly may contribute to cognitive impairment, the presence of these risk factors without AF appears to be not enough to completely explain the higher risk of cognitive impairment found in some studies in elderly with this arrhythmia. A longitudinal study performed just with patients with isolated AF (not associated with other cardiovascular risk factors, such as heart failure or hypertension) may provide a definitive answer to this question but, for the moment, evidence for independent association between AF and dementia appears to be strong.

6.5. Neuroinflammation

Some authors consider neuroinflammation a possibility to explain at least part of the complex process by which cognitive impairment occurs in patients with AF. Several inflammatory markers are elevated in patients with AF [56]. For Lappegard and coworkers, the inflammatory processes related with AF may trigger thrombotic microinfarctions. This process may be a possible explanation for the development of dementia in AF despite an adequate anticoagulation [56]. This is corroborated by the findings of the same authors who had shown persistent prothrombotic state in a small sample of anticoagulated patients with AF in a previous study [57]. Analysis of a small sample using an intensive

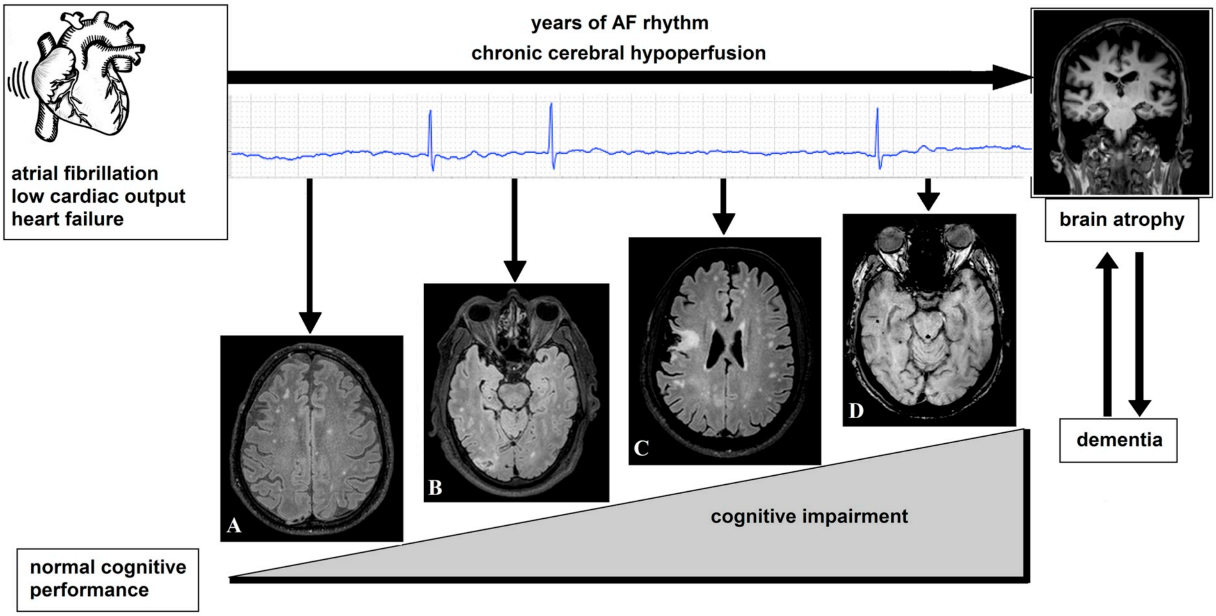

Fig. 1. Possible different mechanisms involved with cognitive impairment in patients with atrial fibrillation. Low cardiac output may conduce to cerebral chronic hypoperfusion and brain atrophy. In addition, ischemic embolic process with large and small vessels involved can produce histologic brain damage. The result of these different ways to brain injury could be cognitive dysfunction with limitations in activities of daily living. A: small microangiopathic lesions. B: a small silent infarct (right occipital lobe). C: a major cerebral infarct (cardioembolic stroke in right frontal lobe). D: microbleeds in lobar (temporal) region. AF: Atrial Fibrillation.

lipid-lowering treatment showed a statistically significant correlation between the reduction of inflammatory markers and delayed neurocognitive decline in older patients with AF [56]. This type of data supports the hypothesis that inflammatory processes may play an important role in cognitive performance in patients with AF. Fig. 1 shows some of the possible mechanisms by which AF may lead to cerebral damage and cognitive impairment.

7. Prevention of cognitive decline in patients with AF

Despite the current knowledge about stroke prevention, whether anticoagulation is effective for prevention of dementia in AF is not completely known [15]. However, a recent study reported that anticoagulant drugs was associated with 60% decreased risk of dementia in a sample of stroke-free AF patients [58]. A large study is currently underway to evaluate the efficacy and safety of a new oral anticoagulant compared to acetylsalicylic acid in reducing stroke, transient ischemic attack and neurocognitive decline in patients with AF. The Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in AF (BRAIN-AF, ClinicalTrials.gov identifier-NCT number: NCT02387229) is a phase 3 clinical trial estimated to enroll 6396 participants. It may shed light on the impact of anticoagulation on the neurocognitive performance in patients with AF under thromboprophylaxis.

8. Conclusions

AF is considered an independent risk factor for cognitive impairment and dementia. The profile of cognitive dysfunction found in stroke-free AF patients points to poor executive performance, but studies with methodological differences show conflicting results. So far the best method to stop the progression of cognitive dysfunction associated with AF in patients without history of stroke is not known. Some of the main theories that aim to explain the cognitive impairment seen in AF without stroke include the influence of this arrhythmia in cerebral hemodynamics, microembolizations and microbleeds, but these mechanisms are still a matter of intense discussion. To date, there is a lack of studies of brain functional images in patients with AF and no dementia, as well studies evaluating the effect of the reversal of this arrhythmia over brain structure and cognition, especially prospective studies. New researches focused on how AF can influence brain physiology and function may help to clarify the role of this arrhythmia in the development of cognitive impairment between cognitively normal patients. In the future, this field will probably be better explored through noninvasive real-time examination techniques of regional cerebral blood flow, such as transcranial doppler, near-infrared spectroscopy monitoring the real-time cerebral hemodynamic state and different MRI sequences. Cognitive impairment should be screened in patients with AF, even without a history of stroke, preferably using a battery of sensitive neuropsychological tests to detect mild cognitive impairment, validated for culture, age and educational level.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was funded by FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo), grants # 2013/07559-3 and # 2013/00099-7.

Authors' contributions

Silva DS wrote the manuscript. Coan AC assisted with drafting and reviewing the manuscript. Avelar WM assisted with manuscript review.

Acknowledgements

This study was funded by FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo), grants # 2013/07559-3 and # 2013/00099-7.

References

[1] B.P. Krijthe, A. Kunst, E.J. Benjamin, G.Y. Lip, O.H. Franco, A. Hofman, et al., Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060, Eur. Heart J. 35 (2013) 2746–2751, https://doi.org/10.1093/eurheartj/eht280 (PubMed).

[2] D.M. Lloyd-Jones, T.J. Wang, E.P. Leip, M.G. Larson, D. Levy, R.S. Vasan, et al., Lifetime risk for development of atrial fibrillation: the Framingham Heart Study, Circulation 110 (9) (2004) 1042–1046, https://doi.org/10.1161/01.CIR.0000140263.20897.42.
[3] P.A. Wolf, R.D. Abbott, W.B. Kannel, Atrial fibrillation as an independent risk factor for stroke: the Framingham Study, Stroke 22 (1991) 983–988.
[4] C. Marini, F. De Santis, S. Sacco, T. Russo, L. Olivieri, R. Totaro, A. Carolei, Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study, Stroke 36 (2005) 1115–1119.
[5] R.B. Schnabel, X. Yin, P. Gona, M.G. Larson, A.S. Beiser, D.D. McManus, C. Newton-Cheh, S.A. Lubitz, J.W. Magnani, P.T. Ellinor, S. Seshadri, P.A. Wolf, R.S. Vasan, E.J. Benjamin, D. Levy, 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study, Lancet 386 (2015) 154–162, https://doi.org/10.1016/S0140-6736(14)61774-8.
[6] L. Staerk, J.A. Sherer, D. Ko, E.J. Benjamin, R.H. Helm, Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes, Circ. Res. 120 (2017) 1501–1517, https://doi.org/10.1161/circresaha.117.309732.
[7] L.Y. Chen, F.L. Lopes, R.F. Gottesman, et al., Atrial fibrillation and cognitive decline–the role of subclinical cerebral infarcts: the ARIC study, Stroke 45 (9) (2014) 2568–2574, https://doi.org/10.1161/STROKEAHA.114.005243.
[8] B. Wozakowska-Kaplon, G. Opolski, D. Kosior, E. Jaskulska-Niedziela, E. Maroszynska-Dmoch, M. Wlosowicz, Cognitive disorders in elderly patients with permanent atrial fibrillation, Kardiol. Pol. 67 (2009) 487–493.
[9] A. Ott, M.M. Breteler, M.C. de Bruyne, et al., Atrial fibrillation and dementia in a population-based study. The Rotterdam study, Stroke 28 (1997) 316–321.
[10] S. Kalantarian, T.A. Stern, M. Mansour, J.N. Ruskin, Cognitive impairment associated with atrial fibrillation: a meta-analysis, Ann. Intern. Med. 158 (5) (2013) 338–346, https://doi.org/10.7326/0003-4819-158-5-201303050-00007 Pt 1.
[11] P. Santangeli, L. Di Biase, R. Bai, et al., Atrial fibrillation and the risk of incident dementia: a meta-analysis, Heart Rhythm. 9 (2012) 1761–1768.
[12] I. Marzona, M. O'Donnell, K. Teo, P. Gao, C. Anderson, J. Bosch, et al., Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies, CMAJ 184 (6) (2012) E329–E336 (PubMed: 22371515).
[13] L.Y. Chen, F.L. Norby, R.F. Gottesman, et al., Association of atrial fibrillation with cognitive decline and dementia over 20 years: the ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study), J. Am. Heart Assoc. 7 (2018) e007301, https://doi.org/10.1161/JAHA.117.007301.
[14] R.F.A.G. de Bruijn, J. Heeringa, F.J. Wolters, et al., Association between atrial fibrillation and dementia in the general population, JAMA Neurol. 72 (11) (2015) 1288–1294, https://doi.org/10.1001/jamaneurol.2015.2161.
[15] A. Singh-Manoux, A. Fayosse, S. Sabia, M. Canonico, M. Bobak, A. Elbaz, et al., Atrial fibrillation as a risk factor for cognitive decline and dementia, Eur. Heart J. (2017), https://doi.org/10.1093/eurheartj/ehx208.
[16] J.E. O'Connell, C.S. Gray, J.M. French, et al., Atrial fibrillation and cognitive function: case-control study, J. Neurol. Neurosurg. Psychiatry 65 (1998) 386–389.
[17] V. Jacobs, S.C. Woller, S. Stevens, Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia, Heart Rhythm. 11 (12) (2014) 2206–2213, https://doi.org/10.1016/j.hrthm.2014.08.013.
[18] T.J. Bunch, et al., Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia, Heart Rhythm. 7 (4) (2010) 433–437, https://doi.org/10.1016/j.hrthm.2009.12.004 (Epub 2009 Dec 11).
[19] Liao, et al., Risk and prediction of dementia in patients with atrial fibrillation — a nationwide population-based cohort study, Int. J. Cardiol. 199 (2015) 25–30.
[20] R.-H. Chou, et al., Prediction of vascular dementia and Alzheimer's disease in patients with atrial fibrillation or atrial flutter using CHADS2 score, J. Chin. Med. Assoc. 79 (2016) 470e476.
[21] J. Ball, M.J. Carrington, S. Stewart, et al., Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management? Heart 99 (2013) 542–547.
[22] K.G. Graves, et al., Atrial fibrillation incrementally increases dementia risk across all $CHADS_2$ and CHA_2DS_2VASc strata in patients receiving long-term warfarin, Am. Heart J. 188 (2017) 93–98, https://doi.org/10.1016/j.ahj.2017.02.026.
[23] A. Nishtala, R.J. Piers, J.J. Himali, A.S. Beiser, K.L. Davis-Plourde, J.S. Saczynski, D.D. McManus, E.J. enjamin, R. Au, Atrial fibrillation and cognitive decline in the Framingham Heart Study, Heart Rhythm. 15 (2) (2018) 166–172, https://doi.org/10.1016/j.hrthm.2017.09.036.
[24] E.L. Thacker, B. McKnight, B.M. Psaty, et al., Atrial fibrillation and cognitive decline: a longitudinal cohort study, Neurology 81 (2013) 119–125.
[25] S. Knecht, C. Oelschlager, T. Duning, H. Lohmann, J. Albers, C. Stehling, et al., Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy, Eur. Heart J. 29 (2008) 2125–2132.
[26] J. Graff-Radford, M. Madhavan, P. Vemuri, A.A. Rabinstein, R.H. Cha, M.M. Mielke, K. Kantarci, V. Lowe, M.L. Senjem, J.L. Gunter, D.S. Knopman, R.C. Petersen, C.R. Jack Jr., R.O. Roberts, Atrial fibrillation, cognitive impairment, and neuroimaging, Alzheimers Dement. 12 (2016) 391–398.
[27] H. Stefansdottir, D.O. Arnar, T. Aspelund, S. Sigurdsson, M.K. Jonsdottir, H. Hjaltason, L.J. Launer, V. Gudnason, Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts, Stroke 44 (2013) 1020–1025.
[28] M.F. Elias, L.M. Sullivan, P.K. Elias, et al., Atrial fibrillation is associated with lower cognitive performance in the Framingham offspring men, J. Stroke Cerebrovasc. Dis. 15 (2006) 214–222 (PubMed: 17904078).
[29] P. Forti, et al., Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment (MCI), Arch. Gerontol. Geriatr. 44 (Suppl. 1) (2007) 155–165, https://doi.org/10.1016/j.archger.2007.01.023.
[30] A. Marengoni, et al., Atrial fibrillation, stroke and dementia in the very old: a population-based study, Neurobiol. Aging 32 (7) (2011) 1336–1337, https://doi.org/10.1016/j.neurobiolaging.2009.08.002 (Epub 2009 Sep 4).
[31] S. Rastas, A. Verkkoniemi, T. Polvikoski, et al., Atrial fibrillation, stroke, and cognition: a longitudinal population-based study of people aged 85 and older, Stroke 38 (2007) 1454–1460.
[32] Alosco, et al., Atrial fibrillation exacerbates cognitive dysfunction and cerebral perfusion in heart failure, Pacing Clin. Electrophysiol. 38 (2) (2015) 178–186, https://doi.org/10.1111/pace.12543.
[33] L. Kilander, B. Andren, H. Nyman, et al., Atrial fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men, Stroke 29 (1998) 1816–1820.
[34] T. Sabatini, G.B. Frisoni, P. Barbisoni, et al., Atrial fibrillation and cognitive disorders in older people, J. Am. Geriatr. Soc. Apr 48 (4) (2000) 387–390.
[35] R. Peters Peters, R. Poulter, N. Beckett, et al., Cardiovascular and biochemical risk factors for incident dementia in the Hypertension in the Very Elderly Trial, J. Hypertens. 27 (2009) 2055–2062.
[36] S. Dublin, M.L. Anderson, S.J. Haneuse, et al., Atrial fibrillation and risk of dementia: a prospective cohort study, J. Am. Geriatr. Soc. 59 (2011) 1369–1375.
[37] G. Thrall, G.Y.W. Lip, D. Carroll, D. Lane, Depression, anxiety, and quality of life in patients with atrial fibrillation, Chest 132 (4) (2007) 1259–1264.
[38] R. Serpytis, A. Navickaite, E. Serpytiene, et al., Impact of atrial fibrillation on cognitive function, psychological distress, quality of life, and impulsiveness, Am. J. Med. 131 (6) (2018) 703.e1–703.e5, https://doi.org/10.1016/j.amjmed.2017.12.044.
[39] D.S. Silva, W.M. Avelar, B.M. de Campos, A.P.B.L. Lino, M.L.F. Balthazar, M.J.O. Figueiredo, F. Cendes, A.C. Coan, Default mode network disruption in stroke-free patients with atrial fibrillation, Cerebrovasc. Dis. 45 (2018) 78–84, https://doi.org/10.1159/000486689.
[40] C. David, et al., Design of the Swiss Atrial Fibrillation Cohort Study (Swiss-AF): structural brain damage and cognitive decline among patients with atrial fibrillation, Swiss Med. Wkly. 147 (2017) w14467.
[41] S. Blum, M. Kuehne, N. Rodondi, et al., Prevalence of Silent Vascular Brain Lesions among Patients with Atrial Fibrillation and no Known History of Stroke. Abstract, 1358 ESC Congress, Munich, 2018, p. 2018.
[42] A. Shoamanesh, C.S. Kwok, O. Benavente, Cerebral microbleeds: histopathological correlation of neuroimaging, Cerebrovasc. Dis. 32 (2011) 528–534.
[43] F. Fazekas, R. Kleinert, G. Roob, et al., Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds, AJNR Am. J. Neuroradiol. 20 (1999) 637–642.
[44] M.M. Poels, M.A. Ikram, A. van der Lugt, A. Hofman, W.J. Niessen, G.P. Krestin, M.M. Breteler, M.W. Vernooij, Cerebral microbleeds are associated with worse cognitive function: the Rotterdam scan study, Neurology 78 (2012) 326–333.
[45] D.J. Werring, D.W. Frazer, L.J. Coward, N.A. Losseff, H. Watt, L. Cipolotti, M.M. Brown, H.R. Jäger, Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI, Brain 127 (10) (2004) 2265–2275, https://doi.org/10.1093/brain/awh253 1 October.
[46] A.G. van Norden, H.A. van den Berg, K.F. de Laat, A.R. Gons, E.J. van Dijk, F.E. de Leeuw, Frontal and temporal microbleeds are related to cognitive function: the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) Study, Stroke (12) (2011) 3382–3386, https://doi.org/10.1161/STROKEAHA.111.629634.
[47] Y. Mayasi, et al., Atrial fibrillation is associated with anterior predominant white matter lesions in patients presenting with embolic stroke, J. Neurol. Neurosurg. Psychiatry 0 (2017) 1–8, https://doi.org/10.1136/jnnp-2016-315457.
[48] R. Au, et al., Association of white matter hyperintensity volume with decreased cognitive functioning, Arch. Neurol. 63 (2006) 246–250.
[49] F.-E. De Leeuw, J.C. De Groot, M. Oudkerk, et al., Atrial fibrillation and the risk of cerebral white matter lesions, Neurology 54 (2000) 1795–1801, https://doi.org/10.1212/WNL.54.9.1795.
[50] Y.-C. Su, et al., Evaluation of cerebral blood flow in acute ischemic stroke patients with atrial fibrillation: a sonographic study, J. Formos. Med. Assoc. 116 (2017) 287e294, https://doi.org/10.1016/j.jfma.2016.05.009.
[51] R. Totaro, C. Corridoni, C. Marini, R. Marsili, M. Prencipe, Transcranial Doppler evaluation of cerebral blood flow in patients with paroxysmal atrial fibrillation, Ital. J. Neurol. Sci. 14 (1993) 451–454.
[52] M. Gardarsdottir, S. Sigurdsson, T. Aspelund, et al., Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion, Europace 0 (2017) 1–7, https://doi.org/10.1093/europace/eux220.
[53] M. Gardarsdottir, S. Sigurdsson, T. Aspelund, V.A. Gardarsdottir, V. Gudnason, D.O. Arnar, Cerebral blood flow is improved after cardioversion of atrial fibrillation. Oral abstract session: atrial fibrillation: risk factors, fibrosis and outcomes, EP Europace 17 (Suppl. 3) (2015) iii11–iii13, https://doi.org/10.1093/europace/euv152 1 June 2015.
[54] P.G. Myserlis, A. Malli, D.K. Kalaitzoglou, G. Kalaitzidis, M. Miligkos, D.G. Kokkinidis, A.P. Kalogeropoulos, Atrial fibrillation and cognitive function in patients with heart failure: a systematic review and meta-analysis, Heart Fail. Rev. 22 (1) (2017) 1–11, https://doi.org/10.1007/s10741-016-9587-y.
[55] S. Kalantarian, H. Ay, R.L. Gollub, H. Lee, K. Retzepi, M. Mansour, J.N. Ruskin, Association between atrial fibrillation and silent cerebral infarctions: a systematic review and meta-analysis, Ann. Intern. Med. 161 (9) (2014) 650–658, https://doi.org/10.7326/M14-0538.
[56] K.T. Lappegård, M. Pop-Purceleanu, W. van Heerde, J. Sexton, I. Tendolkar, G. Pop, Improved neurocognitive functions correlate with reduced inflammatory burden in

atrial fibrillation patients treated with intensive cholesterol lowering therapy, J. Neuroinflammation 10 (2013) 78, https://doi.org/10.1186/1742-2094-10-78.
[57] J. van Kuilenburg, K.T. Lappegård, J. Sexton, I. Plesiewicz, P. Lap, L. Bouwels, T. Sprong, T.E. Mollnes, F. Verheugt, W.L. van Heerde, G.A. Pop, Persisting thrombin activity in elderly patients with atrial fibrillation on oral anticoagulation is decreased by anti-inflammatory therapy with intensive cholesterol-lowering treatment, J. Clin. Lipidol. 5 (4) (2011) 273–280, https://doi.org/10.1016/j.jacl.2011.05.003.
[58] M. Ding, L. Fratiglioni, K. Johnell, Atrial fibrillation, antithrombotic treatment, and cognitive aging, Neurology 91 (19) (2018) e1732–e1740, https://doi.org/10.1212/WNL.0000000000006456.
[59] A. Bellomo, et al., Atrial fibrillation (AF) and cognitive impairment in the elderly: a case–control study, Arch. Gerontol. Geriatr. 55 (2012) 247–250, https://doi.org/10.1016/j.archger.2011.07.017.
[60] Gaita, et al., Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function, J. Am. Coll. Cardiol. 62 (2013) 1990–1997.