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EDITORIAL

Atrial Fibrillation and Cognitive Impairment

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ABSTRACT

Growing evidence suggests that atrial fibrillation (AF), in addition to its known thromboembolic risk, is a risk factor for significant cognitive impairment via several pathways, further contributing to morbidity and mortality. Whether anticoagulation, rhythm control strategies and other interventions aiming at preventing thromboembolic events and ameliorating the clinical outcome of AF patients, may also have a beneficial effect on long-term cognitive function remains to be seen in future studies. (*Rhythmoss* 2015;10(3):45-52)

Key Words: atrial fibrillation; stroke; cognitive function; silent cerebral infarcts; brain hypoperfusion; dementia

Abbreviations

AF = atrial fibrillation; MRI = magnetic resonance imaging; TEE = transesophageal echocardiography; TTR = time to therapeutic ratio; VKA = vitamin K antagonists

Introduction

Atrial fibrillation (AF) is the commonest arrhythmia (1-2%) in the general population, while due to its age-dependency its incidence may exceed 8-10% in the elderly, conferring considerable morbidity and mortality related to cardiovascular effects and thromboembolic

complications, notably stroke.^{1, 2} Oral anticoagulants for prevention of strokes and antiarrhythmic drugs for rate and/or rhythm control are the cornerstone of contemporary management, whereas evolving transcatheter ablation techniques play an increasingly important role.³

Mild cognitive impairment, initially defined as isolated memory deficit and later ascribed an expanded definition that includes different cognitive domains, can precede the development of dementia.⁴ Increasing evidence shows that AF is a risk factor for significant cognitive impairment in patients with and without a manifest stroke via a plethora of pathways (Table 1), further contributing to morbidity and mortality.⁵⁻⁸ Atrial fibrillation has also been associated with conversion of cognitive impairment to full dementia.⁴ Furthermore, previously undiagnosed AF should be suspected upon the emergence of cognitive decline associated with cryptogenic and/or silent strokes. Recent guidelines indicate that screening for AF should be undertaken with pulse taking and/or electrocardiography or rhythm monitoring in patients aged >65 years.⁹ The recently appreciated association of AF with cognitive decline should also lead to the concept of cognitive screening¹⁰ and rhythm monitoring in the aforementioned populations (Fig. 1).⁵ Although dementia and AF are common comorbidities in stroke patients, AF appears to have a potential role in cognitive impairment prior to a first stroke. Whether anticoagulation, rhythm control

strategies and other interventions aiming at preventing thromboembolic events and ameliorating the clinical outcome of AF patients, may also have a beneficial effect on long-term cognitive function remains to be seen in future studies.

Studies of Cognitive Impairment in Atrial Fibrillation

According with a cross-sectional Swedish study based on a cohort of 952 community-living men, aged 69 to 75 years, men with AF (n=44) had lower mean adjusted cognitive z scores than men without AF (P=0.0003).¹¹ The exclusion of stroke patients or adjustments for 24-hour diastolic blood pressure and heart rate, diabetes, and ejection fraction did not change this relationship. Men with AF who were treated with digoxin (n=27) performed markedly better than those without treatment (n=9; P=0.0005). Thus, this study demonstrated an association between AF and low cognitive function independent of stroke, high blood pressure, and diabetes.

A Framingham Study including 1011 men (mean age of 61 years) free of clinical stroke and dementia indicated that those with (n = 59) vs those without (n = 952) AF at 8 months after the AF surveillance period exhibited significantly lower mean levels of cognitive performance.¹²

In a cross-sectional evaluation of 122 stroke-free individuals with AF compared with 563 individuals aged 37-84 years without AF, stroke-free individuals with AF performed significantly worse in tasks of learning and memory (P < 0.01) as well as attention and executive functions (P < 0.01).¹³ There was also a trend (P = 0.062) towards worse performance in learning and memory tasks in patients with chronic as compared with paroxysmal AF. Corresponding to the memory impairment, hippocampal volume on magnetic resonance imaging (MRI) was reduced in patients with AF. The authors concluded that even in the absence of manifest stroke, AF is a risk factor for cognitive impairment and hippocampal atrophy.

A post-hoc analysis of 2 randomized controlled trials involving 31,506 patients (aged 66.5 years) and evaluating the efficacy of treatment with ramipril plus telmisartan (ONTARGET) or telmisartan alone (TRANSCEND) in reducing cardiovascular disease, indicated that AF was present at baseline in 1016 participants (3.3%) and developed during follow-up (median 56 months) in an additional 2052 participants (6.5%).¹⁴ Atrial fibrillation was associated with an increased risk of cognitive decline (hazard ratio - HR 1.14), new dementia (HR 1.30), loss of independence in performing activities of daily living (HR 1.35) and admission to long-term care facilities (HR 1.53), regardless of having a stroke or not, or receiving antihypertensive drugs. The authors concluded that

cognitive and functional decline are consequences of AF, even in the absence of overt stroke.

Among 270 individuals, 180 patients with AF (90 paroxysmal and 90 persistent) and 90 controls, at least 1 area of silent cerebral ischemia on MRI was present in 80 patients (89%) with paroxysmal AF, 83 (92%) with persistent AF, and 41 (46%) controls (p < 0.01).¹⁵ The number of areas of silent cerebral ischemia per subject was higher in patients with persistent AF than in those with paroxysmal AF (41.1±28.0 vs 33.2 ± 22.8, p = 0.04). Cognitive performance was significantly worse in patients with persistent and paroxysmal AF than in controls.

A recent prospective observational study evaluated the prevalence of prestroke cognitive impairment in 788 stroke patients (69.5% ischemic strokes, 21.3% transient ischemic attacks, and 9.1% hemorrhagic strokes), and examined whether AF was associated with prestroke cognitive impairment.¹⁶ Prestroke cognitive impairment was detected in 96 (12.5 %) patients. Of these, 33 patients (4.3 %) were demented before the actual stroke event. AF was independently associated with prestroke cognitive impairment. The authors concluded that patients with an acute stroke frequently show a history of cognitive impairment before the event; AF is independently associated with prestroke cognitive impairment.

According to a longitudinal analysis in the Cardiovascular Health Study, a community-based study of 5,150 men and women aged ≥65 years, who did not have AF or a history of stroke at baseline, 552 (10.7%) developed incident AF during a mean follow-up of 7 years.¹⁷ Cognitive function was tested with use of the Modified Mini-Mental State Examination (3MSE), which is a general screening tool assessing memory, orientation, calculation, and verbal fluency. Scores on the 3MSE range from zero (worst) to 100 (best) with a cutoff of <78 points for dementia screening. Mean 3MSE scores declined faster after incident AF compared with no prior AF, e.g. the predicted 5-year decline in mean 3MSE score from age 80 to age 85 was 26.4 points for individuals without a history of AF, but was 210.3 points for those experiencing incident AF at age 80, a 5-year difference of 23.9 points. The authors concluded that in the absence of prior stroke, people with incident AF are likely to reach thresholds of cognitive impairment or dementia at earlier ages than people with no history of AF.

A recent Australian prospective substudy of a multicenter randomized trial of an AF-specific disease management intervention (the Standard versus Atrial Fibrillation spEcific management studY; SAFETY) examined the incidence of mild cognitive impairment among 260 patients with chronic AF, aged 72±11 years (53% men, mean CHA2DS2-VASc score 4±2) and

sought to identify predictors of this cognitive dysfunction.¹⁸ A total of 169 patients (65%) were found to have mild cognitive impairment at baseline with multiple deficits in cognitive domains, most notably in executive functioning, visuospatial abilities and short-term memory. Predictors of impaired cognition were lower education level (odds ratio - OR 5-6), higher CHA2DS2-VASc score (OR 1.46) and prescribed digoxin (OR 2.19). The authors concluded that mild cognitive impairment is highly prevalent among older high-risk patients hospitalized with AF.

Even in patients with heart failure having their own reasons for cognitive decline, the occurrence of AF further exacerbates cognitive dysfunction. According to a recent study, among 187 patients with heart failure,¹⁹ those with AF (32.1%) exhibited worse global cognition, memory, and cerebral blood flow velocity of the middle cerebral artery relative to patients without AF, above and beyond the effects that could be ascribed to heart failure severity and other demographic and medical factors. Partial correlations controlling for possible confounds showed that decreased blood flow velocity of the middle cerebral artery predicted worse cognition in multiple domains in the overall sample ($r = 0.13$ to 0.15 , $P < 0.05$) and in the subgroup of heart failure patients with AF ($r = 0.26$ to $r = 0.28$, $P < 0.05$), but not among heart failure patients without AF. The authors concluded that AF exacerbates cognitive deficits in heart failure, possibly through its association with decreased cerebral perfusion.

A metaanalysis of 14 studies including 46,637 patients, aged 71.7 years, showed that AF was associated with a significant increase in dementia overall (odds ratio-OR 2.0, $p < 0.0001$), albeit with substantial heterogeneity.⁶ When stratified by participants, the association was significant (with little heterogeneity) in studies focusing solely on patients with stroke (7 studies, OR 2.4, $p < 0.001$), and of borderline significance (with substantial heterogeneity) for studies in broader populations (7 studies, OR 1.6, $p = 0.05$). For conversion of mild cognitive impairment to dementia, one study showed a significant association with AF (OR 4.6). The authors concluded that there is consistent evidence supporting an association between AF and increased incidence of dementia in patients with stroke, but there remains considerable uncertainty about any link in the broader population.

According to another metaanalysis of 8 studies with 77,668 elderly patients, aged 61-84 years, with normal cognitive function at baseline, of whom 11,700 (15%) had AF, 4773 of 73,321 (6.5%) patients developed dementia at a mean follow-up of 7.7 ± 9.1 years.²⁰ At pooled analysis adjusted for baseline confounders and covariates, AF was independently associated with increased risk of incident dementia (HR = 1.42, $P < .001$).

The authors concluded that AF is independently associated with increased risk of dementia.

In a recent review of studies comparing the incidence of cognitive impairment and/or dementia in patients with/without AF, 8 out of 11 studies (3 cross-sectional, 2 case-control and 3 prospective cohorts) reported an association between cognitive decline and AF, but the risk varied.⁷ Among cross-sectional studies, patients with AF had a 1.7 to 3.3 greater risk of cognitive impairment, and a 2.3-fold increased risk of dementia, compared to patients in sinus rhythm.

According with another meta-analysis of 21, albeit heterogeneous, studies, AF was significantly associated with a higher risk of cognitive impairment independent of stroke history (relative risk - RR = 1.34), in patients with first or recurrent stroke (RR = 2.7) and in a broader population of patients with or without a history of stroke (RR = 1.4).²¹ Limiting the analysis to prospective studies yielded similar results (RR = 1.36). Restricting the analysis to studies of dementia eliminated the significant heterogeneity (P value = 0.137) but did not alter the pooled estimate substantially (RR = 1.38). The authors concluded that evidence suggests that AF is associated with a higher risk of cognitive impairment and dementia, with or without a history of clinical stroke.

One should also keep in mind some conflicting results. According with prospective 9-year follow-up population-based study in Finland, among 553 subjects (92% of the total population) aged ≥ 85 years, AF was significantly associated with stroke at baseline; (32% vs 16.7%; $P < 0.001$).²² Dementia at baseline was significantly associated with age, clinical stroke, and the presence of apolipoprotein E epsilon4 allele, but not with sex, education, or vascular risk factors. The authors concluded that AF is a significant and preventable risk factor for stroke but not for dementia in the very old. Similarly in a prospective longitudinal cohort study of 362 men and women aged > 60 ,²³ there were no clinically important differences in cognitive function between baseline and follow-up at 1 and 3 years, between 174 AF cases and 188 controls in sinus rhythm, nor between subgroups on aspirin, warfarin or neither.

However, accumulating data linking AF to not just mild cognitive impairment but to more advanced cognitive dysfunction (dementia) remain worrisome. A large cohort study indicated that among 37,025 individuals from the Intermountain Heart Collaborative Study database (mean age 61 ± 18 years),²⁴ a total of 10,161 (27%) developed AF and 1,535 (4.1%) developed dementia (179 vascular dementia, 321 senile dementia, 347 Alzheimer's, 688 non-specified) during a 5-year follow-up. Patients with dementia were older with higher rates of hypertension, coronary artery disease, renal failure, heart failure, and prior strokes. In age-based

analysis, AF independently was associated with all dementia types, with the highest risk in the younger group (<70). More importantly, in patients with dementia, AF was associated with a marked increased risk of mortality (hazard ratio ~ 1.4; P < 0.0001).

Etiology

A plethora of etiologies of cognitive impairment and dementia have been implicated in a variety of clinical conditions, among which vascular contributions predominate,²⁵ but non-vascular causes are also important. Unfortunately, a 5-10% prevalence of dementia in affluent countries has been recognized in people ≥ 65 years of age.²⁵ Even more importantly, in 2002, an estimated 5.4 million people (22.2%) in the United States aged ≥ 71 years had cognitive impairment without dementia,²⁶ while both ends of the spectrum are associated with excess mortality.⁸ The most important cerebrovascular pathology that contributes to cognitive impairment is cerebral infarcts and AF is a common source and cause of cerebral thrombo-embolism. However, cognitive decline has also been noted even in the absence of a clinically manifest stroke.

Silent brain infarction is often found in patients with AF and has been proposed as possibly implicated in cognitive decline (Table 1). A group of 103 neurologically asymptomatic patients (76 men, aged 63 \pm 10 years) with nonvalvular AF were screened for silent brain infarction with MRI and also underwent transesophageal echocardiography (TEE) before transcatheter AF ablation (76 men; mean age 63 \pm 10 years).²⁷ A total of 31 (30%) patients showed silent brain infarction on brain MRI. Most lesions were multiple (61%) and small (<15 mm) in diameter (84%). Patients with silent brain infarction had a higher prevalence of left atrial abnormalities (45% vs 14%; P < .001) and complex aortic arch plaques (45% vs 7%; P < 0.001) compared with those without silent brain infarction. In multivariate analysis, left atrial abnormalities (odds ratio 4.13; P = 0.014) and complex aortic arch plaques (odds ratio 4.82; P = 0.024) were independent predictors of silent brain infarction, suggesting that microembolization of small thrombi derived from the fibrillating left atrium or advanced aortic atherosclerotic lesions may be important causes of silent brain infarction in patients with nonvalvular AF.

The prevalence of silent cerebral infarctions and their association with AF was estimated in a systematic review and meta-analysis of 11 studies including 5317 patients (aged 50 to 83.6 years) with AF and no clinical history of stroke or prosthetic valves.²⁸ When computed tomography and MRI studies were combined, AF was associated with silent cerebral infarctions (odds ratio - OR, 2.62). This association was independent of AF type (paroxysmal vs persistent). The overall prevalence of

silent cerebral infarction lesions, reported in 17 studies, among patients with AF was 40% on MRI and 22% on computed tomography. The authors concluded that AF is associated with more than a 2-fold increase in the odds for silent cerebral infarctions.

The association of incident AF with cognitive decline was examined in stroke-free individuals, stratified by subclinical cerebral infarcts on brain MRI scans in the Atherosclerosis Risk in Communities (ARIC) Study.²⁹ During follow-up, there were 48 incident AF events among 935 stroke-free individuals (aged 61.5 \pm 4.3 years; 62% women; 51% black). Incident AF was associated with greater annual average rate of cognitive decline tested by digit symbol substitution (-0.77; P=0.054) and word fluency (-0.80; P=0.048). Among participants without subclinical cerebral infarcts on brain MRI scans, incident AF was not associated with cognitive decline. The authors concluded that the association of incident AF with cognitive decline in stroke-free individuals can be explained by the presence or development of subclinical cerebral infarcts, raising the possibility that anticoagulation might prevent cognitive decline in AF.

The possibility of exposure to chronic microembolism or microbleeds resulting in repetitive cerebral injury that is manifest by cognitive decline, has been suggested by a study examining the association of low percentage of time in the therapeutic range (TTR) to higher risk for dementia due to under- or over-anticoagulation. Dementia was diagnosed in 109 patients (4.2%) (senile: 37 or 1.4%; vascular: 8 or 0.3%; Alzheimer: 64 or 2.5%) among 2605 AF patients (age 73.7 \pm 10.8 years, 54% male) anti-coagulated with warfarin.³⁰ The percent TTR averaged 63.1 \pm 21.3, with percent INR <2.0: 25.6% \pm 17.9% and percent INR >3.0: 16.2% \pm 13.6%. After adjustment, decreasing categories of percent TTR were associated with increased dementia risk (vs >75%): <25%: hazard ratio - HR 5.34, P < 0.0001; 26%-50%: HR 4.10, P < 0.0001; and 51%-75%: HR = 2.57, P=0.001. The authors concluded that quality of anticoagulation management represented as percent TTR among AF patients without dementia was associated with dementia incidence.

Thus, it is apparent that AF produces cognitive decline independent of stroke, suggesting additional effects of AF on the brain. In a cross-sectional analysis of 4251 non-demented participants (mean age, 76 \pm 5 years) in the population-based AGES-Reykjavik Study, 330 participants had AF.³¹ Participants with AF had lower total brain volume on MRI compared with those without AF (P<0.001). The association was stronger with persistent/permanent than paroxysmal AF and with increased time from the first diagnosis of the disease. Of the brain tissue volumes, AF was associated with lower volume of gray and white matter hyperintensities

($P < 0.001$ and $P = 0.008$, respectively), but not of white matter hyperintensities ($P = 0.49$). Participants with AF scored lower on tests of memory. The authors concluded that AF is associated with smaller brain volume, and the association is stronger with increasing burden of the arrhythmia. These findings suggest that AF has a cumulative negative effect on the brain independent of cerebral infarcts. The difference in total brain volume between individuals with and without AF equals a year and a half of normal loss of brain volume. In their discussion the authors consider the possible explanatory mechanisms for their findings. The association between AF and brain atrophy and lower performance on memory tests could be attributed to increased comorbidity and cerebral infarcts in the AF population. AF causes multiple microembolisms and microinfarcts to the brain and subsequent atrophy. Additionally, cerebral hypoperfusion, attributable to beat-to-beat variation in stroke volume, also may play a part. Patients with persistent/permanent AF may have more cerebral hypoperfusion than those with only paroxysmal AF, explaining the finding of greater brain atrophy encountered in patients with persistent/permanent AF.

The hypotheses that hemostatic function is altered in subjects with AF who develop dementia, and that long-term warfarin anticoagulation is protective against this complication were tested in an observational cohort study of 218 AF patients, of whom 145 (66%) were prescribed warfarin.³² Forty-nine (22%) met criteria for dementia after 3 years' follow-up. D-dimer, prothrombin fragment 1+2 and thrombin-antithrombin complexes levels were higher in AF subjects with dementia compared with those without ($P = 0.003-0.008$). These associations became of borderline statistical significance following adjustment for age. Logistic regression showed a trend towards warfarin use being independently associated with reduced prevalence of dementia (odds ratio 0.52, $P = 0.08$). The authors concluded that there is increased thrombin generation and fibrin turnover in subjects with AF and dementia compared with those without dementia. Long-term warfarin use may be protective against the development of dementia in subjects with AF.

The role of ventricular rate response on the incidence of dementia in elderly subjects with cognitive impairment and AF was examined in 358 cognitively impaired elderly subjects with and without AF, stratified in low/high (<50/>90) and moderate (>50/<90 bpm) ventricular rate response.³³ Over 10 years, among these cognitively impaired subjects, 135 (37.7%) progressed to dementia, 33 in the presence (75%) and 102 (32.5%) in the absence of AF ($p < 0.001$). Multivariate analysis showed that AF was a strong predictor of dementia (hazard ratio - HR = 4.10; $p < 0.001$). Importantly, low/high ventricular rate response (<50/>90 bpm) was

predictive of dementia in the presence (HR = 7.70, $p = 0.03$) but not in the absence (HR = 1.85; $p = 0.152$) of AF. The authors concluded that AF predicts dementia in elderly subjects with cognitive impairment, and ventricular rate response seems to play a key role in the incidence of dementia in cognitively impaired elderly subjects with AF.

Table 1. Mechanisms and Factors Implicated in Cognitive Impairment Associated With Nonvalvular Atrial Fibrillation (AF)

- *Silent (subclinical) brain infarction* due to microembolization of small thrombi emanating from the fibrillating left atrium in under-anticoagulated patients or from advanced aortic atherosclerotic lesions or
- *silent cerebral microbleeds* in over-anticoagulated patients
- *loss of brain volume (brain atrophy)* / lower volume of gray and white matter attributed to increased comorbidity and cerebral micro-infarcts or microembolisms with subsequent brain atrophy in the AF population
- *cerebral hypoperfusion*, attributable to beat-to-beat variation in stroke volume. Patients with persistent/permanent AF may have more cerebral hypoperfusion than those with only paroxysmal AF, explaining the finding of greater brain atrophy encountered in patients with persistent-permanent AF / low or high ventricular rate response (<50/>90 bpm) is predictive of dementia in the presence but not in the absence of AF.
- *altered hemostatic function* in patients with AF who develop dementia / higher D-dimer, prothrombin fragment 1+2 and thrombin-antithrombin complexes levels / increased thrombin generation and fibrin turnover in individuals with AF and dementia compared with those without dementia
- *? vitamin K deficiency* in patients on vitamin K antagonists contributing to cognitive dysfunction, due to the potential role of vitamin K in brain physiology and a suggestion that its deficiency may induce cognitive decline
- *systemic inflammatory mechanisms* as indicated by increased inflammatory markers correlating with neurocognitive functions and loss of volume

Experimental data indicate that vascular oxidative stress and inflammation are key pathogenic factors in neurovascular dysfunction,²⁵ and there is evidence that AF is associated with activated inflammatory mechanisms (reflected by an increase in various inflammatory markers), linked to the prothrombotic state of AF.³⁴ Finally, there is information that vitamin K is an important nutritional factor of cognitive health during

aging and animal data suggest that deficient vitamin K is a potential mechanism of cognitive impairment,³⁵ as lifetime consumption of a low-vitamin K diet is associated with higher levels of ceramides in the hippocampus, a key brain region in spatial memory and navigation; importantly, several studies have reported elevated levels of ceramides in neurodegenerative disease such as Alzheimer's disease. This information has raised concerns about the role of vitamin K antagonists in patients with AF and cognitive impairment, which contradicts the protective role of anticoagulants in thrombo-embolic complications and their presumed benefit in cognition that these agents are expected to confer in AF patients.

Interventions

Firstly, according to the AFFIRM functional status substudy, cognitive function was similar in rate-control and rhythm-control strategies.³⁶ Secondly, although one would have expected that oral anticoagulants would confer a protective effect in AF patients from cognitive decline, the data remain inconclusive.^{32,37} According to a randomized controlled trial, the BAFTA study, there is no evidence that anticoagulation confers clinically important protection over aspirin against cognitive decline in AF in the first 33 months of treatment other than that provided by preventing clinical stroke.³⁷ Indeed, among 973 patients with AF aged ≥ 75 years assigned to warfarin (n=488) or low-dose aspirin (n=485), there was no difference in cognitive function between the 2 groups at 9 or 21 months. At 33-month follow-up, there was a non-significant difference of 0.56 on adjusted analysis in favor of warfarin that decreased to 0.49 after multiple imputation.

A concern has been raised whether vitamin K antagonists (VKAs) may further contribute to cognitive dysfunction, due to the potential role of vitamin K in brain physiology, as already mentioned, and a suggestion that its deficiency may induce cognitive decline. A geriatric study comprising 267 older patients (aged 83.4 ± 8.1 years; 57% female) indicated that compared with participants without cognitive impairment (n = 70), those with compromised cognition used more frequently VKAs (p = 0.038).³⁸ The risk of cognitive impairment was 15% higher with VKAs; using VKAs was independently associated with cognitive impairment (adjusted odds ratio = 17.4, p = 0.028). Taking into consideration this latter caveat, it is bestowed upon future comparative trials to deduce any differential effect of the newer non-vitamin K anticoagulants on cognition in patients with AF.

A small group of 34 older patients with AF were treated with intensive lipid-lowering therapy with atorvastatin 40 mg and ezetimibe 10 mg (n=17), or placebo (n=17).³⁹ Significant reductions in inflammatory markers were recorded in the treatment group compared

to placebo. Reduction in plasma concentration of inflammatory markers correlated significantly with improvement in the neurocognitive functions memory and speed. Loss of volume in amygdala and hippocampus, as determined by MRI, was reduced in the treatment arm, statistically significant for left amygdala. The authors concluded that therapy with atorvastatin and ezetimibe can modify the decline of neurocognitive function, and the loss of volume in certain cerebral areas in older patients with AF.

The risk of non-vascular dementia was compared between statin (n = 51,253 AF patients aged ≥ 60 years who had received statin treatment) and control groups (n = 205,012 age- and gender-matched AF patients not on statin) (data from the National Health Insurance Research Database of Taiwan).⁴⁰ During follow-up, 17,201 patients experienced non-vascular dementia. The annual incidence of non-vascular dementia was lower in the statin group than in the control group (1.89% vs. 2.20%; p<0.001). Statin use exhibited a protective effect on the occurrence of non-vascular dementia, with an adjusted hazard ratio (HR) of 0.832. Among statin types, the use of rosuvastatin was associated with the largest risk reduction (adjusted HR=0.661). The authors concluded that statin use conferred a lower risk of non-vascular dementia in AF. Use of more potent statin and longer exposure duration may be associated with greater benefits.

According with an observational study, those (n=4,212) who underwent radiofrequency ablation therapy for AF, which currently offers a best available rhythm control strategy for AF, had significantly lower risk for dementia than age/gender matched AF patients who did not have an ablation (n=16,848) and similar to the risk of age/gender matched controls without AF (n=16,848).⁴¹ Of the 37,908 patients, aged 65 ± 13 years, 5,667 (14.9%) died, 1,296 (3.4%) had a stroke, and 1,096 (2.9%) were hospitalized for heart failure over >3 years of follow-up. AF ablation patients had a lower risk of death and stroke in comparison to AF patients without ablation. Alzheimer's dementia occurred in 0.2% of the AF ablation patients compared to 0.9% of the AF no ablation patients and 0.5% of the no AF patients (P < 0.0001). Other forms of dementia were also reduced significantly in those treated with ablation. Compared to patients with no AF, AF ablation patients had similar long-term rates of death, dementia, and stroke. The authors concluded that AF ablation patients have a significantly lower risk of death, stroke, and dementia in comparison to AF patients without ablation.

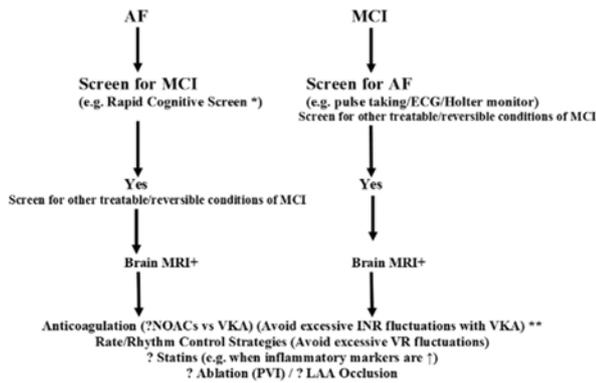


FIGURE 1. A suggested algorithm for screening for atrial fibrillation (AF) and/or mild cognitive impairment (MCI). ECG = electrocardiogram; LAA = left atrial appendage; MRI = magnetic resonance imaging; NOACs = non-vitamin K oral anticoagulants; PVI = pulmonary vein isolation (via radiofrequency or cryoballoon ablation); VKA = vitamin K antagonists; VR = ventricular rate

* Rapid Cognitive Screen (RCS) for Mild Cognitive Impairment (MCI) / (0-5 = dementia; 6-7 = MCI; 8-10 = normal).⁴⁴

● **Recall 5 objects** (Apple, Pen, Tie, House, Car) / Recall objects after clock drawing (5 points)

● **Clock Drawing** (Draw with time at 10 minutes to 11 o'clock) (4 points)

● **Insight:** Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had 3 children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after. What country did they live in? (1 point)

** Thromboembolic / hemorrhagic risk commensurate with CHA2DS2-VASc / HAS-BLED scores, respectively

The above results contrast with reports indicating that the ablation procedure itself may be associated with microinfarcts affecting patients' memory.^{42, 43} According to a small study, among 21 AF patients undergoing ablation, 3 (14%) developed new ischemic lesions detected on MRI shortly after intervention (clinically symptomatic in 1 and clinically silent in 2).⁴² In contrast to the control group (non-AF controls, n= 23) and in covariance of baseline performance, the ablation group showed worse neuropsychological outcome in verbal memory at 3 months post-procedurally. The authors concluded that adverse neuropsychological changes after AF ablation may represent cerebral complications of this procedure. In a larger study comprising 90 patients with AF undergoing ablation, post-operative neurocognitive dysfunction occurred in 13% - 20% at the 3-month follow-up compared with 0% in the non-ablation AF group.⁴³ No studies comparing different modes of AF

ablation (e.g. radiofrequency versus cryo-balloon ablation) and their effect on neurocognitive function have been conducted to date.

Finally, other modes of AF management, such as surgical or percutaneous closure of left atrial appendage, have not been explored whether they have an effect on cognition. However, the problem of cognitive impairment appears to be real and of utmost importance to consider in the AF patient population, and recommendations have been put forth advocating that all patients with AF be screened for cognitive decline and all patients with cognitive decline be screened for AF.⁵

Conclusion

There appears to be convincing evidence accumulated to date suggesting that AF, in addition to its known thromboembolic risk, is a risk factor for a whole spectrum of cognitive impairment by a variety of mechanisms, further contributing to morbidity and mortality. Screening for both conditions is strongly advisable (Figure 1).^{5, 10} Preliminary evidence indicates that anticoagulation, rhythm and rate control strategies may have a significant protective action, particularly at the early stages of the disease when mild cognitive impairment may still be a treatable condition,⁴⁴ although future randomized control studies are needed to further establish such claim.

REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837-847.
2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29-322.
3. Moukabayry T and Gonzalez MD. Management of Atrial Fibrillation. *Med Clin North Am*. 2015;99:781-794.
4. Forti P, Maioli F, Pisacane N, et al. Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment (MCI). *Arch Gerontol Geriatr*. 2007;44 Suppl 1:155-165.
5. Hui DS, Morley JE, Mikolajczak PC and Lee R. Atrial fibrillation: A major risk factor for cognitive decline. *Am Heart J* 2015;169:448-456.
6. Kwok CS, Loke YK, Hale R, Potter JF and Myint PK. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. *Neurology* 2011;76:914-922.
7. Udompanich S, Lip GY, Apostolakis S and Lane DA. Atrial fibrillation as a risk factor for cognitive impairment: a semi-systematic review. *Qjm* 2013;106:795-802.
8. Sachs GA, Carter R, Holtz LR, et al. Cognitive impairment: an independent predictor of excess mortality: a cohort study. *Ann Intern Med* 2011;155:300-308.
9. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;14:1385-1413.
10. Lin JS, O'Connor E, Rossom RC, Perdue LA and Eckstrom E. Screening for cognitive impairment in older adults: A systematic

- review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013;159:601-612.
11. Kilander L, Andren B, Nyman H, et al. Atrial fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men. *Stroke* 1998;29:1816-1820.
 12. Elias MF, Sullivan LM, Elias PK, et al. Atrial fibrillation is associated with lower cognitive performance in the Framingham offspring men. *J Stroke Cerebrovasc Dis* 2006;15:214-222.
 13. Knecht S, Oelschlager C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J* 2008;29:2125-2132.
 14. Marzona I, O'Donnell M, Teo K, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *Cmaj* 2012;184:E329-336.
 15. Gaita F, Corsinovi L, Anselmino M, et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol* 2013;62:1990-1997.
 16. Horstmann S, Rizos T, Rauch G, et al. Atrial fibrillation and prestroke cognitive impairment in stroke. *J Neurol* 2014;261:546-553.
 17. Thacker EL, McKnight B, Psaty BM, et al. Atrial fibrillation and cognitive decline: a longitudinal cohort study. *Neurology* 2013;81:119-125.
 18. Ball J, Carrington MJ and Stewart S. Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management? *Heart* 2013;99:542-547.
 19. Alosco ML, Spitznagel MB, Sweet LH, et al. Atrial fibrillation exacerbates cognitive dysfunction and cerebral perfusion in heart failure. *Pacing Clin Electrophysiol* 2015;38:178-186.
 20. Santangeli P, Di Biase L, Bai R, et al. Atrial fibrillation and the risk of incident dementia: a meta-analysis. *Heart Rhythm* 2012;9:1761-1768.
 21. Kalantarian S, Stern TA, Mansour M and Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann Intern Med* 2013;158:338-346.
 22. Rastas S, Verkkoniemi A, Polvikoski T, et al. Atrial fibrillation, stroke, and cognition: a longitudinal population-based study of people aged 85 and older. *Stroke* 2007;38:1454-1460.
 23. Park H, Hildreth A, Thomson R and O'Connell J. Non-valvular atrial fibrillation and cognitive decline: a longitudinal cohort study. *Age Ageing* 2007;36:157-163.
 24. Bunch TJ, Weiss JP, Crandall BG, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm* 2010;7:433-437.
 25. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American heart association/American stroke association. *Stroke* 2011;42:2672-2713.
 26. Plassman BL, Langa KM, McCammon RJ, et al. Incidence of dementia and cognitive impairment, not dementia in the United States. *Ann Neurol* 2011;70:418-426.
 27. Sugioka K, Takagi M, Sakamoto S, et al. Predictors of silent brain infarction on magnetic resonance imaging in patients with nonvalvular atrial fibrillation: A transesophageal echocardiographic study. *Am Heart J* 2015;169:783-790.
 28. Kalantarian S, Ay H, Gollub RL, et al. Association between atrial fibrillation and silent cerebral infarctions: a systematic review and meta-analysis. *Ann Intern Med* 2014;161:650-658.
 29. Chen LY, Lopez FL, Gottesman RF, et al. Atrial fibrillation and cognitive decline-the role of subclinical cerebral infarcts: the atherosclerosis risk in communities study. *Stroke* 2014;45:2568-2574.
 30. Jacobs V, Woller SC, Stevens S, et al. Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia. *Heart Rhythm* 2014;11:2206-2213.
 31. Stefansdottir H, Amar DO, Aspelund T, et al. Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. *Stroke* 2013;44:1020-1025.
 32. Barber M, Tait RC, Scott J, et al. Dementia in subjects with atrial fibrillation: hemostatic function and the role of anticoagulation. *J Thromb Haemost* 2004;2:1873-1878.
 33. Cacciatore F, Testa G, Langellotto A, et al. Role of ventricular rate response on dementia in cognitively impaired elderly subjects with atrial fibrillation: a 10-year study. *Dement Geriatr Cogn Disord* 2012;34:143-148.
 34. Guo Y, Lip GY and Apostolakis S. Inflammation in atrial fibrillation. *J Am Coll Cardiol* 2012;60:2263-2270.
 35. Carrie I, Belanger E, Portoukalian J, Rochford J and Ferland G. Lifelong low-phyloquinone intake is associated with cognitive impairments in old rats. *J Nutr* 2011;141:1495-1501.
 36. Chung MK, Shemanski L, Sherman DG, et al. Functional status in rate- versus rhythm-control strategies for atrial fibrillation: results of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Functional Status Substudy. *J Am Coll Cardiol* 2005;46:1891-1899.
 37. Mavaddat N, Roalfe A, Fletcher K, et al. Warfarin versus aspirin for prevention of cognitive decline in atrial fibrillation: randomized controlled trial (Birmingham Atrial Fibrillation Treatment of the Aged Study). *Stroke* 2014;45:1381-1386.
 38. Annweiler C, Ferland G, Barberger-Gateau P, et al. Vitamin K antagonists and cognitive impairment: results from a cross-sectional pilot study among geriatric patients. *J Gerontol A Biol Sci Med Sci* 2015;70:97-101.
 39. Lappegard KT, Pop-Purceleanu M, van Heerde W, et al. Improved neurocognitive functions correlate with reduced inflammatory burden in atrial fibrillation patients treated with intensive cholesterol lowering therapy. *J Neuroinflammation* 2013;10:78.
 40. Chao TF, Liu CJ, Chen SJ, et al. Statins and the risk of dementia in patients with atrial fibrillation: A nationwide population-based cohort study. *Int J Cardiol* 2015;196:91-97.
 41. Bunch TJ, Crandall BG, Weiss JP, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *J Cardiovasc Electrophysiol* 2011;22:839-845.
 42. Schwarz N, Kuniss M, Nedelmann M, et al. Neuropsychological decline after catheter ablation of atrial fibrillation. *Heart Rhythm* 2010;7:1761-1767.
 43. Medi C, Evered L, Silbert B, et al. Subtle post-procedural cognitive dysfunction after atrial fibrillation ablation. *J Am Coll Cardiol* 2013;62:531-539.
 44. Morley JE. Mild cognitive impairment-a treatable condition. *J Am Med Dir Assoc* 2014;15:1-5.