

# Study Progress of the Influence of Atrial Fibrillation Treatment on Dementia

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To the Editor: In the clinic, atrial fibrillation (AF) is one of the most common types of arrhythmia encountered, and its burden and prevalence on the health-care system are still on the rise. Over the past 50 years, AF incidence has increased by roughly 350.0%.<sup>[1]</sup> In a review from the Global Burden of Disease study, it was estimated that the worldwide prevalence of AF is 596.2 or 373.1/100,000 men or women. The incidence of AF significantly increased with age.<sup>[2]</sup> Approximately 1% of AF patients are <60 years old, up to 12% of AF patients are in the 75–84 years age range and the AF prevalence is even higher in patients that are 80 years or older. Dementia is a disabling disease of the brain that characterized by impairments in memory and other cognitive functions. It can seriously affect human life. Worldwide, an estimated 33 million elderly individuals suffer from dementia, and this number is expected to reach 81.1 million by 2040. It is obvious that cognitive function deteriorates naturally with the aging of the body, but AF could accelerate the pace. According to some systematic reviews and meta-analysis, AF can increase the risk of dementia by 40%. For the elder individuals, who are more than 75 years old, their dementia usually resulting from cerebrovascular lesions and neurodegeneration. While for the middle age individuals who are 40–59 years old, the advent of dementia is derived from cardiovascular disease. AF increases the risk of stroke, heart failure, and mortality. However, AF may also increase the risk of dementia, given the mutual vascular risk factors, such as smoking, hypertension, high cholesterol, diabetes mellitus, advancing age, chronic kidney disease, vascular disease, heart failure, inactivity/low activity, genetics, sleep apnea, and alcohol consumption.<sup>[3,4]</sup> The term “cardiogenic dementia” was first introduced more than 40 years ago to support a possible link between AF and cognitive impairment. It was not until recently that demonstrated AF is an independent risk factor of cognitive impairment and may increase the risk of dementia through several mechanisms, including cerebral hypoperfusion, thromboembolism (including both stroke and subclinical cerebral infarcts), inflammation, anticoagulation cerebral micro-bleeds, and neuronal function impairment. Therefore, strategies that control the development of AF and promote cardiovascular health may help delay the onset of dementia. Traditional AF treatment involves anticoagulation, rhythm, and rate control. Thus, by understanding the potential relationship between AF and dementia, novel approaches may be proposed for future AF management.

One of the most severe complications of AF is embolic strokes, which increases the risk of stroke 5 folds. Evidence supporting the association

between AF and dementia in patients with stroke stems from both pathological and clinical studies. A history of strokes considerably increases the risk of dementia, with prevalence rates ranging from 13% to 32% from 3 months to 1 year after stroke. Moreover, incidence rates of new-onset dementia after stroke range from 24% within 3 years to 33% within 5 years. The size, severity, and the location of the stroke also affect the onset and severity of dementia. Apart from stroke, silent cerebral infarction is another potential link between AF and dementia. These infarctions tend to be small and are located deep in the white matter, which therefore often remains clinically unnoticed and can only be found through brain magnetic resonance. In a previous study that focused on brain magnetic resonance imaging (MRI), it was noted that roughly one-fourth of patients with AF suffered from silent cerebral infarctions. Moreover, previous studies demonstrated that anticoagulation therapy was effective in both stroke patients and silent cerebral infarction patients. Anticoagulant therapy can effectively inhibit the form of clot.

Bunch *et al.*<sup>[5]</sup> recently investigated the medical records of 10,537 patients who were on warfarin therapy (target international normalized ration, INR 2–3) within the Intermountain Healthcare system. The incident rates of dementia were roughly 2-fold higher in subjects with the poorest anticoagulation maintenance compared to patients with the highest anticoagulation time in a therapeutic range. Moreover, improved anticoagulation control was particularly effective in patients who already showed some cognitive impairment. In a recent study, the risk of dementia was compared between AF patients using warfarin or non-Vitamin K antagonist oral anticoagulants (NOACs). A lower risk of dementia was found among patients who received NOAC when compared to warfarin users.<sup>[6]</sup> In most individuals with AF, current guidelines recommend oral anticoagulation for stroke prevention, and the decrease in stroke risk will consequently lead to a reduced risk of adverse cognitive outcomes. However, it is not known whether anticoagulation always reduces the occurrence of dementia in AF patients? One study showed that long-term warfarin use decreased cognitive function

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through chronic cerebral injury from micro-bleeds, and increased the risk for major bleeds. The degree was dependent on the time spent in the therapeutic range (TTR).<sup>[7]</sup> Jacobs *et al.*<sup>[7]</sup> evaluated 992 warfarin-treated AF patients and showed that in more than 25% of cases, patients with an INR >3 were 2.40 folds more likely to develop dementia. Both microbleeds and microischemic events, though often subclinical, have been associated with a decrease in cognitive functioning. When patients with AF are put on anticoagulation therapy, the INR ratio should be monitored. According to the guidelines, the optimal range of warfarin was an INR of 2.0–3.0, and to achieve the best safety and efficacy endpoints, the average individual time in TTR should be >65%.<sup>[8]</sup> To reduce AF-associated dementia, we should not only focused on INR but on TTR. SAME-TT<sub>2</sub>R<sub>2</sub> (sex female, age <60 years, medical history more than 2 comorbidities, treatment [interacting medications, e.g., amiodarone], tobacco used [doubled], race [doubled]) is a recently developed rating scale for the prediction of patients who would do well on vitamin K antagonist with a high TTR of >70% (SAME-TT<sub>2</sub>R<sub>2</sub> score 0–1) and those who would do less well (SAME-TT<sub>2</sub>R<sub>2</sub> score ≥2). For individuals who received a high SAME-TT<sub>2</sub>R<sub>2</sub> score, NOACs may be a better treatment option. The RE-LY trial showed that for dabigatran at dose of 110 mg twice daily, the efficacy was generally similar to that of warfarin, except that for dabigatran, the risk of hemorrhagic stroke was lower. Dabigatran at a dose of 110 mg twice daily was safer than warfarin when risk of major bleeding was considered. The ROCKET AF trial showed that, when using rivaroxaban, the risk of hemorrhagic stroke was significantly lower compared to warfarin. In theory, reducing stroke can reduce dementia; however, studies that focused on the cognitive function of novel oral anticoagulant drugs on AF patients are limited. Brooy *et al.*<sup>[9]</sup> reported a case of an 89-year-old male skydiver with AF, who developed mild cognitive impairment shortly after commencing dabigatran. This medication was terminated and warfarin was used as an alternative anticoagulant. Marked cognitive and physical improvement was shown within 2 weeks of dabigatran cessation. Moreover, within 2 months, this patient returned to complete physical independence. Although the pathogenesis of this case is unclear, further evaluation of the role of thrombin in the brain is warranted.

Previous studies showed that, compared to men, women with AF had a higher relative risk of developing cerebrovascular events. This may be because antithrombotic drugs are more often prescribed to men since men are usually affected by several cardiovascular diseases. Therefore, antithrombotic therapy may be an effective treatment to reduce the incidence of stroke and slow down the process of dementia. However, in a Japanese trial, reduced risk of stroke was not observed when patients were using aspirin; however, the risk of bleeding was increased. In a recent Hong Kong cohort, aspirin showed a nonsignificant 18.7% reduction in ischemic strokes, compared with no therapy. Jacobs *et al.*<sup>[7]</sup> demonstrated that in AF patients who were given antiplatelet and anticoagulant therapies, the time exposed to overanticoagulation increased dementia risk. Thus, whether receiving antiplatelet and anticoagulant therapies is effective in the prevention of dementia is unclear.

In previous studies, biologically plausible mechanisms for the association between statin use and decreased stroke severity have been evaluated. Prestroke statin use increased collateral blood flow and reduced infarct size. Furthermore, statins can exert antithrombotic effects by inhibiting the coagulation pathway and platelet activation. Moreover, it was demonstrated a beneficial effect of baseline statins on the outcome of patients who had a stroke. The JUPITER trial demonstrated a significant reduction in venous thromboembolism with rosuvastatin. Statins may have beneficial effects in AF-related stroke. Ko *et al.*<sup>[10]</sup> demonstrated that prestroke statin use among individuals

who presented with ischemic stroke in AF associated with a 32% reduction in stroke risk. To reduce the risk of stroke among patients with ischemic stroke or transient ischemic attack, current guidelines strongly recommend statin therapy to intensively lower lipid levels.

The renin-angiotensin system (RAS) is involved in pathological mechanisms of target organ damage as well as the induction of hypertension. Thus, in addition to its antihypertensive effects, the RAS has been expected to prevent cardiovascular and cerebrovascular diseases. ACEI/ARBs are effective in the secondary prevention of AF, which has been proven in many large clinical trials. Furthermore, recent large clinical trials such as the LIFE study and the MOSES study indicated that blockade helped prevent first and recurrent strokes independently of its blood pressure-lowering effects. The Acute Candesartan Cilexetil Therapy in Stroke Survivors study showed that in the acute phase of stroke, RAS inhibition can lead to brain protection irrespective of its hypotensive effect. Brain RAS is involved in ischemic brain damage after stroke. Moreover, the activation of the human RAS exaggerates ischemic brain damage through stimulation of the angiotensin II Type 1 (AT<sub>1</sub>) receptor, whereas activation of the AT<sub>2</sub> receptor attenuated brain injury. Recent studies have raised the possibility that stimulation of AT<sub>2</sub> receptors may promote cell differentiation and regeneration of neuronal tissue. The renin-angiotensin-aldosterone system (RAAS) therapy is not only beneficial to prevent AF but is also beneficial to prevent dementia. Therefore, patients with a high risk of AF (heart failure and hypertension) as well as those who already suffered from AF are recommended to receive RAAS therapy.

During the past decade, catheter ablation of AF has rapidly developed from an experimental unproven approach to a common ablation procedure that is used around the globe. In recent years, several randomized trials have shown that in the prevention of recurrent and symptomatic AF, catheter ablation was superior to antiarrhythmic therapy. Since AF is an independent risk factor for dementia, catheter ablation should have beneficial effects in patients with dementia. AF patients treated with catheter ablation had significantly reduced rates of death, dementia, and stroke. However, catheter ablation can lead to the formation of microembolic. Herm *et al.*<sup>[11]</sup> used MRI to demonstrate several brain lesions in patients who underwent atrial catheter ablation for symptomatic AF. According to Herm, these brain lesions persisted to some extent but did not cause cognitive impairment. Kochhäuser *et al.*<sup>[12]</sup> suggested that no clinical overt cognitive deficit existed and no significant difference was found in cognitive function related to the ablation approach used. However, the number of microembolic signals correlated with a subtle, diffuse postprocedural impairment of neuropsychological function. Therefore, catheter ablation reduced the progression of dementia in AF patients, and the need to reduce microemboli during ablation is significant.

The association between AF and stroke is clear; however, some evidence indicates a link between AF and dementia that is independent of stroke. The following paragraphs include treatments targeting this mechanism.

AF, as shown to reduce cardiac output and this reduction, is greater at fast ventricular rates. The reduced cardiac output may lead to cerebral hypoperfusion, which may involve one of the mechanisms of AF patients to attain dementia. Especially in the elderly whose cerebral perfusion is already diminished, further cerebral blood flow reductions from heart-brain vascular related risk factors may lead to a “neuronal energy crisis” through reduced ATP synthesis, and lowered ATP production will trigger a series of metabolic events including hippocampal-glia activation, oxidative stress, aberrant protein synthesis, ionic membrane pump dysfunction, signal transduction impairment, and neurotransmitter failure. These events form the basis

of neurodegenerative changes. Early rhythm control attenuates the risk of developing dementia. Cacciatore *et al.*<sup>[13]</sup> evaluated the role of ventricular rate response on the incidence of dementia in elderly individuals with cognitive impairment and AF, and demonstrated that a low/high ventricular rate (<50/>90 beats per minutes [bpm]) is predictive of dementia in the presence but not in the absence of AF. Moreover, Efimova *et al.*<sup>[14]</sup> found a direct correlation between blood pressure and cognitive function. AF patients and rapid ventricular rates refractory to medical treatment have marked signs of brain hypoperfusion and impaired cognitive function. In the AFFIRM study, in which two groups have a similar heart rate, it was shown that disabling anoxic encephalopathy was similar between two groups.

Previously, adequate ventricular rate control was empirically defined as <80 bpm at rest. However, as the AFFIRM trial showed, strict rate-control therapy may result in symptomatic bradycardia in 7.3% of patients. Furthermore, the RACE study showed that a higher resting heart rates was not associated with adverse outcomes. Therefore, the guide recommended that a resting heart rate of <100 bpm should be the initial approach in AF patients. For individuals whose symptoms persisted or in which tachycardia-mediated cardiomyopathy occurred, a resting heart rate of <80 bpm was reasonable.<sup>[8]</sup> It remains unclear if this treatment is beneficial to slow down the process of dementia in AF patients.

Statin and RAAS therapy are important types of anti-inflammatory therapy. In our previous study, we focused on the association between cognitive impairment in stroke reduction. Recent studies have shown that in addition to reducing stroke, anti-inflammatory activities can delay the onset of dementia in AF patients via several mechanisms. AF increases highly sensitive C-reactive protein in a linear and independent manner in patients without and with coexistent cardiovascular diseases. AF is a pro-inflammatory condition that may be associated with the development of dementia. Elevated levels of inflammatory markers in both AF and dementia suggested a role of inflammatory pathways in the mediation of both diseases. The inflammatory mediators may accentuate vasculopathy and neuronal degeneration, thereby increasing the risk of dementia. Lappegard *et al.*<sup>[15]</sup> examined older patients with AF who underwent anti-inflammatory therapy and demonstrated that intensive lipid-lowering treatment can modify the deterioration of neurocognitive function and the loss of volume in certain cerebral areas. Chao *et al.*<sup>[16]</sup> found that compared with AF patients who were not treated with statins, statin users had a lower risk of nonvascular dementia. In a study in which over 4000 patients were enrolled, the association between inflammatory markers (CC-reactive protein and interleukin-6) and cognitive decline was modest but was much stronger in those with inherited risk. There is also evidence suggests that statins and extremely low cholesterol levels may increase the risk of intracranial hemorrhage after thrombolysis. Thus, additional studies are required to investigate that early targeted treatment of inflammation affects AF development, dementia, or a combination of both.

In conclusion, previous studies have shown that AF is associated with a higher risk of dementia. In this report, we discussed various treatments to reduce dementia in AF patients. These novel findings may be beneficial to thousands of patients and their families who already suffer from the devastating effects of AF and to all who have a higher probability to get demented, even if clinical symptoms of this dramatic pathology have not been observed.

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### Conflicts of interest

There are no conflicts of interest.

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