Cognitive Function: Is There More to Anticoagulation in Atrial Fibrillation Than Stroke?

Lin Cao*; Sean D. Pokorney, MD, MBA*; Kathleen Hayden, PhD; Kathleen Welsh-Bohmer, PhD; L. Kristin Newby, MD, MHS

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and those afflicted have reduced quality of life, functional status, and cardiac performance.1 Patients with AF have a higher risk of stroke, heart failure, and premature death relative to patients without AF.2 It is estimated that 2.5% of the population worldwide has AF, and the prevalence of AF increases substantially with age, especially after 50 years of age.3 AF is more common among white persons than black persons, and men are at 1.5 times greater risk for developing AF than women.3,4 In the United States, about 2.3 million people currently have AF, and the numbers are increasing rapidly. It is predicted that by 2050, 5.6 million people in the United States will have AF, with more than half of those patients aged >80 years.3 This represents a 2.5-fold increase over 50 years, reflecting both the growing proportion of elderly persons in the population3 and the increasing rates of comorbidities associated with AF, including coronary artery disease, hypertension, and congestive heart failure.2

Although the prevalence of AF is increasing, cognitive disorders are also on the rise in tandem with the aging of the population. Patients with mild cognitive impairment have increased morbidity and lower quality of life relative to patients with normal cognitive function,5,6 and compared with those with normal cognition, patients with dementia have increased mortality.7 The diagnosis of mild cognitive impairment is made based on cognitive testing scores that are lower than expected for a patient's age, typically due to memory, but these persons maintain independent functional status in terms of activities of daily living and instrumental activities of daily living.8 Patients are diagnosed with dementia when they have evidence of cognitive impairment on testing and this cognitive deficit affects their functional status.9

More than 20% of people aged >70 years have mild cognitive impairment.10 There are ≈800,000 cases of mild cognitive impairment and ≈560,000 cases of dementia annually in the United States, and patients who have progressed from mild cognitive impairment to dementia account for 75% of patients with dementia.11 The prevalence of dementia increases with age from about 5% of patients in their 70s to nearly 40% of patients in their 90s.12 The aging population is predicted to result in an increase in the prevalence of dementia such that >80 million people worldwide are expected to have dementia by 2040.13,14 Historically, patients were classified as having Alzheimer's disease if they had neurodegenerative disease and vascular dementia or if they had cerebral vascular lesions. This was an oversimplification because most patients have a combination of neurodegenerative and vascular lesions contributing to the clinical phenotype of dementia.15

This review is intended to review the literature and present the current findings on the association between AF and cognitive decline. The focus is on whether evidence shows that AF is associated with cognitive impairment beyond the relationship with stroke.

Literature Search Methods

Series of PubMed literature searches were conducted. The searches were limited to articles written in English and were performed January 7, 2015. The search terms included atrial fibrillation and hypoperfusion, atrial fibrillation and cognitive function, atrial fibrillation and silent stroke, atrial fibrillation and covert stroke, atrial fibrillation and cognitive impairment, atrial fibrillation and dementia, cardiovascular and dementia, and cognitive decline. The search yielded 3279 unique articles, and the titles and abstracts were screened for relevance. The citations in all relevant articles were examined for additional
studies. The principal findings from the search follow, presented by topic.

**Cardiovascular Disease and Cognitive Impairment**

The link between cardiovascular diseases and cognitive impairment has been well established. Coronary artery disease was associated with cognitive decline in a 6-year longitudinal study, and elevated risk scores for coronary heart disease, such as the Framingham Risk Score, were associated with cognitive decline in adults aged >50 years in both primarily white and primarily Hispanic populations. Blood pressure has been associated with cognitive decline, and this relationship includes hypertension, large variations in systolic blood pressure, and hypotension due to low cardiac output. A meta-analysis of 2937 heart failure patients and 14848 control patients found that heart failure was associated with cognitive impairment (hazard ratio [HR] 1.62, 95% CI 1.48 to 1.79).

**Cognitive Decline and Stroke**

Stroke is a major cause of cognitive impairment, and even mild to moderate strokes cause long-term decline in cognitive function. A study by Tatemichi et al was designed to determine the association between stroke and cognitive domains (memory, orientation, verbal skills, visuospatial ability, abstract reasoning, and attention to detail) affected by stroke. The study evaluated 227 patients 3 months after stroke and 240 control patients with no history of stroke. Impairment of memory, orientation, language, and attention were associated with stroke. Among a group of patients with cerebral small vessel disease, the number of lacunar infarcts at baseline was associated with cognitive impairment 3 to 5 years after presentation (HR 3.06, 95% CI 1.71 to 5.50).

**White Matter Lesions and Silent or Covert Cerebral Infarcts**

The mechanisms mediating cognitive disorder in cardiovascular diseases, including hypertension and atherosclerosis, are not entirely clear but appear to be related to central nervous system changes, including overt stroke events and covert cerebral infarcts. These covert cerebral infarcts are non-clinical events that are detected by magnetic resonance imaging of the brain, such as silent cerebral infarcts and white matter lesions. White matter lesions originate from demyelination, gliosis, cerebral infarct, and small vessel disease. White matter lesions on magnetic resonance imaging have been associated with cognitive decline, especially speed of cognitive processes. A meta-analysis showed that white matter lesions were associated with stroke (HR 3.3, 95% CI 2.6 to 4.4), dementia (HR 1.9, 95% CI 1.3 to 2.8), and death (HR 2.0, 95% CI 1.6 to 2.7). Furthermore, cardiovascular risk conditions of hypertension (odds ratio 1.73, 95% CI 1.23 to 2.42) and diabetes mellitus (odds ratio 3.68, 95% CI 1.89 to 7.19) have also been associated with covert or silent cerebral infarcts. Silent or covert cerebral infarcts appear meaningful, being associated with cognitive decline, increased risk of stroke, and dementia. The Rotterdam Scan Study of 1015 persons identified an HR of 2.26 (95% CI 1.09 to 4.70) for the association between silent cerebral infarcts and dementia. Similarly, data from the Atherosclerosis Risk in Communities study found that incident AF was associated with cognitive decline in patients with silent cerebral infarcts diagnosed by magnetic resonance imaging.

**Atrial Fibrillation and Risk of Embolic Events**

The extent to which AF is related to cognitive impairment is unclear. Although AF is associated with many cardiovascular conditions, it is also an established risk factor for ischemic stroke and systemic thromboembolism. AF is associated with an 3- to 5-fold increase in the risk of stroke. Stroke risk in AF patients increased with age, and up to 30% of strokes were in people aged >80 years. Among patients with coronary heart disease or heart failure, AF was associated with a 2-fold increase in stroke risk for men and a 3-fold increase for women. Strokes secondary to AF had worse prognoses than strokes in patients without AF.

**Overview of Anticoagulation for Atrial Fibrillation**

Risk stratification and stroke prevention are critical to the management of AF patients, and the current European and US guidelines for the management of AF are similar in their recommendations. Oral anticoagulation is important in patients at high risk for stroke because it decreases the stroke rate by nearly 80%, and patients at the highest risk for stroke derive the most benefit. One of the most commonly used anticoagulants is adjusted-dose warfarin, which reduces stroke risk by 64% relative to aspirin. Relative to aspirin, warfarin approximately doubles the risk of intracranial and major extracranial hemorrhage, but the absolute rate of intracranial hemorrhage with warfarin is low at 0.2% to 0.4% per year. A number of targeted non-vitamin K antagonist oral anticoagulants are now approved by the US Food and Drug Administration for stroke prevention in nonvalvular AF, including dabigatran (direct thrombin inhibitor), rivaroxaban (factor Xa inhibitor), apixaban (factor Xa inhibitor), and
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Table 1. Comparative Effectiveness Trials of Non–Vitamin K Oral Anticoagulants Versus Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (ARISTOTLE)</th>
<th>Dabigatran Low-Dose (RE-LY)</th>
<th>Dabigatran High-Dose (RE-LY)</th>
<th>Rivaroxaban (ROCKET)</th>
<th>Edoxaban Low-Dose (ENGAGE)</th>
<th>Edoxaban High-Dose (ENGAGE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>18 201</td>
<td>18 113</td>
<td>14 264</td>
<td>21 105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CHADS2 score</td>
<td>2.1±1.1</td>
<td>2.1±1.1</td>
<td>2.2±1.2</td>
<td>3.5±0.9</td>
<td>2.8±1.0</td>
<td>2.8±1.0</td>
</tr>
<tr>
<td>Medication dose</td>
<td>5 mg BID</td>
<td>110 mg BID</td>
<td>150 mg BID</td>
<td>20 mg daily</td>
<td>30 mg daily</td>
<td>60 mg daily</td>
</tr>
<tr>
<td>Stroke or systemic embolism, HR (95% CI)</td>
<td>0.79 (0.66 to 0.95)</td>
<td>0.91 (0.74 to 1.11)</td>
<td>0.66 (0.53 to 0.82)</td>
<td>0.79 (0.66 to 0.96)</td>
<td>1.07 (0.87 to 1.31)</td>
<td>0.79 (0.63 to 0.99)</td>
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<tr>
<td>Ischemic stroke, HR (95% CI)</td>
<td>0.92 (0.74 to 1.13)</td>
<td>1.11 (0.89 to 1.40)</td>
<td>0.76 (0.60 to 0.98)</td>
<td>0.91 (0.73 to 1.13)</td>
<td>1.41 (1.19 to 1.67)</td>
<td>1.00 (0.83 to 1.19)</td>
</tr>
<tr>
<td>Total mortality, HR (95% CI)</td>
<td>0.89 (0.80 to 0.998)</td>
<td>0.91 (0.80 to 1.03)</td>
<td>0.88 (0.77 to 1.00)</td>
<td>0.85 (0.70 to 1.02)</td>
<td>0.87 (0.79 to 0.96)</td>
<td>0.92 (0.83 to 1.01)</td>
</tr>
<tr>
<td>Intracranial hemorrhage, HR (95% CI)</td>
<td>0.42 (0.30 to 0.58)</td>
<td>0.31 (0.20 to 0.47)</td>
<td>0.40 (0.27 to 0.60)</td>
<td>0.67 (0.47 to 0.93)</td>
<td>0.30 (0.21 to 0.43)</td>
<td>0.47 (0.34 to 0.63)</td>
</tr>
<tr>
<td>Major bleeding, HR (95% CI)</td>
<td>0.69 (0.60 to 0.80)</td>
<td>0.80 (0.69 to 0.93)</td>
<td>0.93 (0.81 to 1.07)</td>
<td>1.04 (0.95 to 1.13)</td>
<td>0.47 (0.41 to 0.55)</td>
<td>0.80 (0.71 to 0.91)</td>
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</tbody>
</table>

HR indicates hazard ratio.

edoxaban (factor Xa inhibitor) (Table 1).55–58 The most important benefits that these newer drugs offer over warfarin are a >50% reduction in intracranial bleeding and a 10% reduction in all-cause mortality.54 In fact, the novel oral anticoagulants appear to have similar risk profiles to low-dose aspirin in terms of major bleeding and intracranial hemorrhage.59

Beyond Stroke: Atrial Fibrillation and Cognitive Decline

The role of AF in cognitive decline, independent of stroke, is uncertain. Many studies have found that AF is associated with cognitive decline,40,44,60,61 but it is less clear whether this association is directly related to AF itself or is a function of the population in which AF occurs, that is, an aging cohort with multiple comorbidities (Table 2).22,41,43,44,62–83 Cognitive impairment has been identified in as many as 69% of AF patients.84 In 1 study, AF was associated with increased risk of cognitive decline, new dementia, loss of independence in everyday life, and admission to long-term care facilities.22 Conversely, others have found no differences in cognitive decline between AF and non-AF patients.44

Multiple potential mechanisms explain the association between AF and cognitive decline. Cerebral microbleeds increase with age and anticoagulation,85 and microbleeds are associated with cognitive decline.86 Cerebral hypoperfusion during AF may contribute to cognitive impairment. Decreased diastolic cerebral perfusion has also been associated with AF,87 and irregularity of ventricular contraction during AF affects preload and cardiac output, which may result in a decreased mean cerebral flow.88 Inflammatory markers, including C-reactive protein, TNF-α, and IL-6, are associated with AF.89–91 Inflammatory markers such as C-reactive protein and IL-6 have been associated with cognitive decline and Alzheimer’s disease.92,93

Given the propensity to form thrombus (micro- and macrothrombi) in the left atrium and atrial appendage in the setting of AF, it is biologically plausible that AF could contribute to cognitive impairment through chronic ischemic–embolic insults, even without overt evidence of clinical stroke. Cognitive dysfunction in AF patients has been correlated with less effective anticoagulation, more vascular events, and more bleeding, likely related to decreased adherence to prescribed oral anticoagulation.46 In support of the hypothesis of chronic subclinical embolic contribution to cognitive decline in AF, silent infarcts are significantly more frequent among patients with AF than in those without AF (Table 3).39,41,43,73,94–97 The prevalence of silent cerebral infarcts among patients with AF varies widely in the literature but has been reported to be as high as 92%, which is twice the prevalence of silent cerebral infarcts among patients with normal sinus rhythm.39,73 Of the 92% of patients with silent cerebral infarcts, 61% had CHA2DS2-VASc scores ≤1, meaning they were not currently recommended to be treated with oral anticoagulation based on the AF guidelines in the United States.73 Furthermore, cognitive impairment rates are higher among AF patients than non-AF patients, even after excluding all patients with abnormalities on magnetic resonance imaging of the brain.50

Among AF patients with neurological imaging, the number of abnormal brain areas with tissue loss was significantly

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<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>AF Patients</th>
<th>Population</th>
<th>Follow-up</th>
<th>Cognitive Function Assessment</th>
<th>AF Association Cognitive Decline</th>
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<td>Farina62</td>
<td>1997</td>
<td>74</td>
<td>37</td>
<td>21 PAF, 16 persistent AF</td>
<td>Cross-section</td>
<td>MMSE*</td>
<td>Statistically significant for persistent, not significant for paroxysmal</td>
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<tr>
<td>Ott63</td>
<td>1997</td>
<td>6584</td>
<td>195</td>
<td>Mean age 69±9 years</td>
<td>Cross-section</td>
<td>MMSE and Geriatric Mental State Schedule</td>
<td>Adjusted OR 1.7 (1.2 to 2.5)</td>
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<tr>
<td>Kilander64</td>
<td>1998</td>
<td>952</td>
<td>44</td>
<td>Mean age 72±1 years</td>
<td>Cross-section</td>
<td>Trail Making Tests A and B, MMSE</td>
<td>Unadjusted, statistically significant</td>
</tr>
<tr>
<td>O’Connell65</td>
<td>1998</td>
<td>81</td>
<td>27</td>
<td>Mean age 72±1 years</td>
<td>Cross-section</td>
<td>Mini-Mental Status†</td>
<td>MMSE not statistically significant</td>
</tr>
<tr>
<td>Rozzini66</td>
<td>1999</td>
<td>269</td>
<td>55</td>
<td>13 PAF, 42 persistent AF</td>
<td>Cross-section</td>
<td>MMSE</td>
<td>Adjusted OR for paroxysmal AF 1.2 (0.3 to 4.8), OR for persistent AF 3.2 (1.5 to 6.6)</td>
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<tr>
<td>Elias67</td>
<td>2006</td>
<td>1011</td>
<td>59</td>
<td>Men, mean age 61 years</td>
<td>Cross-section</td>
<td>Wechsler Adult Intelligence Scale‡</td>
<td>Adjusted, statistically significant</td>
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<tr>
<td>Jozwiak68</td>
<td>2006</td>
<td>2314</td>
<td>547</td>
<td>Median age 80 years (75 to 86)</td>
<td>Cross-section</td>
<td>MMSE</td>
<td>OR 1.56 (1.27 to 1.92, (P=0.0001))</td>
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<tr>
<td>Debette69</td>
<td>2007</td>
<td>83</td>
<td>32</td>
<td>Mean age 62 years</td>
<td>Cross-section</td>
<td>MMSE</td>
<td>Adjusted OR 8.1 (1.9 to 34.6, (P=0.008))</td>
</tr>
<tr>
<td>Rastas70</td>
<td>2007</td>
<td>553</td>
<td>122</td>
<td>85 years and older</td>
<td>Cross-section</td>
<td>MMSE§</td>
<td>Unadjusted, not statistically significant</td>
</tr>
<tr>
<td>Knecht60</td>
<td>2008</td>
<td>533</td>
<td>87</td>
<td>Mean age 63±8 years</td>
<td>Cross-section</td>
<td>Composite†</td>
<td>Adjusted, statistically significant</td>
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<tr>
<td>Bilato71</td>
<td>2009</td>
<td>1576</td>
<td>135</td>
<td>Mean age 74 years</td>
<td>Cross-section</td>
<td>MMSE</td>
<td>Adjusted OR 1.14 (0.73 to 1.80)</td>
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<tr>
<td>Bellomo72</td>
<td>2012</td>
<td>57</td>
<td>26</td>
<td>Mean age 72±8 years</td>
<td>Cross-section</td>
<td>MMSE</td>
<td>Adjusted, statistically significant</td>
</tr>
<tr>
<td>Gaita73</td>
<td>2013</td>
<td>270</td>
<td>180</td>
<td>61% with CHA2-Ds2-VaSc &lt;2</td>
<td>Cross-section</td>
<td>Repeatable Battery for the Assessment of Neuropsychological Status</td>
<td>Unadjusted, statistically significant</td>
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<tr>
<td>Stefanadottir41</td>
<td>2013</td>
<td>4251</td>
<td>330</td>
<td>Mean age 76±5 years</td>
<td>Cross-section</td>
<td>Modified California Verbal Learning Test</td>
<td>Adjusted, statistically significant</td>
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<tr>
<td>Horstmann74</td>
<td>2014</td>
<td>788</td>
<td>165</td>
<td>Mean age 67±14 years</td>
<td>Cross-section</td>
<td>Informant questionnaire on cognitive decline in the elderly</td>
<td>OR of 2.97 (1.0 to 8.8, (P=0.05))</td>
</tr>
<tr>
<td>Tilvis75</td>
<td>2004</td>
<td>650</td>
<td>Mean 5 years</td>
<td>MMSE and Clinical Dementia Rating</td>
<td>RR 2.8</td>
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<tr>
<td>Fort76</td>
<td>2006</td>
<td>431</td>
<td>13</td>
<td>Mean age 75±5 years</td>
<td>Mean of 4 years</td>
<td>MMSE</td>
<td>Adjusted HR 1.10 (0.40 to 3.03)</td>
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<tr>
<td>Park44</td>
<td>2007</td>
<td>362</td>
<td>174</td>
<td>Mean age 76 years</td>
<td>Mean 3 years</td>
<td>MMSE</td>
<td>No significant association</td>
</tr>
<tr>
<td>Peters77</td>
<td>2009</td>
<td>3336</td>
<td>190</td>
<td>Mean age 53±6 years</td>
<td>Mean of 2 years</td>
<td>MMSE</td>
<td>HR 1.031 (0.619 to 1.718)</td>
</tr>
<tr>
<td>Bunch78</td>
<td>2010</td>
<td>37 025</td>
<td>10 161</td>
<td>Mean age 61±18 years</td>
<td>Mean of 5 years</td>
<td>ICD-9 code for dementia</td>
<td>Adjusted OR 1.73 ((P=0.001))</td>
</tr>
<tr>
<td>Dublin79</td>
<td>2011</td>
<td>3045</td>
<td>402</td>
<td>Median age 74 years</td>
<td>Mean of 7 years</td>
<td>Cognitive Abilities Screening Instrument</td>
<td>Adjusted HR 1.50 (1.16 to 1.94)</td>
</tr>
</tbody>
</table>

Continued
greater compared with non-AF patients.\textsuperscript{22,96} The areas with tissue loss were usually located in the cortex, but there was no difference in the size of the lesions between control and AF patients.\textsuperscript{96} Silent cerebral infarction was not a predictor of stroke in AF patients.\textsuperscript{39} AF has also been associated with smaller brain volumes than in patients without AF, and AF has been associated with lower total brain mass, gray matter, and white matter.\textsuperscript{41} The longer AF was present, the more brain volume decreased, and this was noted even without overt cerebral infarction. The memory domain appeared dispropor-

<table>
<thead>
<tr>
<th>Table 3. Data on Silent Cerebral Infarct in Atrial Fibrillation</th>
</tr>
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<tbody>
<tr>
<td><strong>Author</strong></td>
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<tr>
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<tr>
<td>Petersen\textsuperscript{96}</td>
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<td>Kempster\textsuperscript{97}</td>
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</tr>
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<td>Gaita\textsuperscript{73}</td>
</tr>
<tr>
<td>Stefansdottir\textsuperscript{41}</td>
</tr>
<tr>
<td>Chen\textsuperscript{43}</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CT, computed tomography; MRI, magnetic resonance imaging; RR, relative risk.
There were concerns that the MMSE was less sensitive to cognitive decline at 33 months within the warfarin group.\(^{110}\) In another study, the use of antithrombotic agents did not affect cognitive decline among AF patients.\(^{22}\) Similarly, Park and colleagues found no differences in cognitive decline among AF patients on aspirin, warfarin, or neither.\(^{44}\) An observational study, however, found a trend toward an association between warfarin use and lower rates of cognitive decline among patients with AF.\(^{109}\) The Birmingham Atrial Fibrillation Treatment of the Aged Study randomized 973 patients with CHA\(_2\)DS\(_2\)-VASc of at least 2 to warfarin versus aspirin and found a non-statistically significant trend toward decreased cognitive decline at 33 months within the warfarin group.\(^{110}\)

The clinical benefit of warfarin was seen only when a high frequency of time is in the therapeutic range.\(^{111}\) Data from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) found that among patients who had AF, who had a mean CHADS\(_2\) score of 2, and who were on warfarin, cognitive dysfunction was associated with lower time in the therapeutic range of anticoagulation, suggesting that maintaining therapeutic anticoagulation may decrease cognitive decline.\(^{45}\) Because non–vitamin K oral anticoagulants mitigate the challenges of time in the therapeutic range, there has been speculation that they may be able to slow or reverse cognitive decline among AF patients.

Additional prospective work is needed to quantify cognitive function and rates of cognitive decline among AF patients.
Compared with non-AF patients, especially by using more sensitive tools such as the MoCA. An ongoing clinical trial is the Aspirin in Reducing Events in the Elderly (ASPREE) study (ClinicalTrials.gov identifier NCT01038583), which is comparing aspirin and placebo for prevention of death, dementia, or disability in 19,000 patients. A neuroimaging substudy (ENVISION) will evaluate the effect of aspirin on the development of white matter hyperintense lesions, and results are expected in 2018. More data are also needed on the relationship between cognitive decline with AF and estimated vascular embolic risk, as well as how this may be affected by anticoagulation. These findings may be particularly important among subpopulations of AF patients for whom the US guidelines do not currently recommended anticoagulation therapy over aspirin or no antithrombotic therapy (CHA2DS2-VASC score of 0 or 1).

Conclusions
Most studies suggest that AF is independently associated with cognitive decline, even among patients with no clinical history of stroke. Cognitive decline is associated with stroke and silent cerebral infarcts, and patients with AF have higher rates of silent cerebral infarcts than patients without AF. The impact of anticoagulation on silent cerebral infarcts remains unknown. Cognitive decline is an important public health concern, and clinical trials are needed to evaluate the effect of oral anticoagulation on cognitive decline in patients with AF.

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