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EDITORIAL COMMENT

Reducing the Risk of Dementia in Atrial Fibrillation*

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Atrial fibrillation (AF) is the most common sustained dysrhythmia encountered in clinical practice.[1] A meta-analysis that included patients from 8 Asian countries showed an AF prevalence of 0.37% to 3.56% in the community setting and 2.8% to 15.8% in hospitals.[2] The most devastating neurologic complications of AF include stroke and cognitive impairment. Dementia is a relentlessly progressive condition characterized by impaired memory, judgment, and executive functioning. Among the numerous causes of dementia, the most common are Alzheimer's disease (AD), which accounts for most cases, and vascular dementia. Numerous cardiovascular risk factors, such as hypertension, diabetes, smoking, and vascular disease, have been recognized as risk factors.[3,4] Dysrhythmias such as AF have been recognized as important risk factors for dementia.[5] It has been observed that dementia occurs in patients with AF even without stroke. A study from the Intermountain Healthcare registry showed that AF increased the risk for all types of dementia, and the highest risk was observed in younger individuals (aged <70 years).[6] This association between arrhythmias and impaired cognition was observed more than 40 years ago, when the term *cardiogenic dementia* was used to describe the decline in cerebral function attributed to cardiac dysrhythmias. Cardiogenic dementia may result from bradyarrhythmias, tachyarrhythmias, and extrasystoles. The reduction in blood pressure or the variability in ventricular filling during arrhythmias or premature complexes may precipitate a cognitive decline.[7] The aging brain may be more sensitive to these conditions; and prolonged episodes of these arrhythmias may eventually be deleterious to brain function. In patients with AF, dementia may be caused by ischemic stroke, cerebral microembolism, cerebral hypoperfusion, neuroendocrine perturbations, and vascular inflammation.[8] The precise mechanism of dementia in patients with AF is multifactorial and may be difficult to ascertain. Nevertheless, it is conceivable that a procoagulant state resulting in thromboembolism could be the unifying mechanism of brain injury.[4] With a procoagulant state being the dominant mechanism of dementia, anticoagulation emerges as a possible therapy to prevent this insult to the brain. In recent years, direct oral anticoagulant agents (DOACs) have superseded vitamin K antagonists (VKAs) in the management of patients with nonvalvular AF.[9]

The meta-analysis by Fong et al,[10] published in this issue of *JACC: Asia,* is an important contribution to this field of AF and dementia because it addresses the value of DOACs in Asian patients.[10] In this meta-analysis of 10 studies, DOAC use was associated with a lower risk of dementia when compared with VKAs (HR: 0.88). The mean age of the patients in this analysis ranged from 70.4 to 75.7 years, and the study included patients from different continents. In the analysis based on various regions, Fong et al,[10] observed a statistically significant benefit of DOACs in relatively younger patients (aged 65-75 years) but not in older patients (>75 years). The most intriguing analysis of the study compared the benefits of DOACs across Asian, European, and American populations. The study found a significant benefit of DOACs in Asian patients (HR: 0.81; 95% CI: 0.68-0.86) and not in European patients. The analysis included only 1 study with American patients, and it showed a significant benefit of DOACs. The benefit of DOACs in reducing stroke have been well documented in landmark studies across all populations, including

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those in Europe. The observation of lack of benefit of DOACs in preventing dementia observed in this meta-analysis is not well explained. The significant benefit in Asian patients has been ascribed to the heightened sensitivity of Asian populations to VKAs that makes Asians susceptible to intracranial bleeding and lower body weight and gives them a supratherapeutic effect with DOACs. This benefit of DOACs in Asian populations was observed in a meta-analysis of landmark studies of DOACs in stroke prevention.[9] The study showed that DOACs have greater efficacy and safety than VKAs in Asians as compared with non-Asian patients.[9] The results of these 2 meta-analyses suggest that DOACs have a significant role in stroke and dementia prevention in Asians and are accompanied by a lower bleeding risk. There was no difference among the 4 DOACs in the included studies. It would have been interesting to see the effect of DOACs on various types of dementia, but as Fong et al[10] observe, studies have not been consistent in reporting HRs according to the type of dementia.

Dementia is the result of different pathologic processes such as genetic, neurodegenerative, and vascular disorders. Although multi-infarct or vascular dementia is clearly linked to thromboembolic events, the pathogenesis of AD or frontotemporal dementia is very complex. Indeed, AF is a recognized risk factor for AD, but neurodegeneration with amyloid deposition and metabolic processes are well recognized pathologic entities. Emerging data suggest that AD may be related to neuronal loss secondary to cerebral hypoperfusion.[11] Cerebral hypoperfusion could be the result of a decline in mean arterial pressure as a result of inadequate ventricular filling, loss of atrioventricular synchrony, and variability in RR intervals. The precise mechanism of cerebral hypoperfusion-induced neuronal damage resulting from mild hypotension caused by dysrhythmias needs further evaluation. Cerebral autoregulation is a mechanism that preserves cerebral perfusion until the mean pressure reaches 60 mm Hg.[12] In older adults with cardiovascular risk factors, these autoregulatory mechanisms may be malfunctional, thus making these individuals vulnerable to neuronal injury. DOACs have been shown to reduce thrombin formation that can be proinflammatory and lead to amyloid deposition.[13] Further randomized studies are required to address this complex issue of anticoagulation in preventing and managing AD. Given the complex pathophysiology, prevention of AD may require targeting cerebral hypoperfusion in addition to anticoagulation and therapies that prevent breakdown of acetylcholine.

Current evidence reveals 2 pivotal mechanisms of dementia to be targeted: thromboembolism and hypoperfusion.[14] The catheter therapies that target these mechanisms are left atrial appendage occlusion and AF ablation. The role of AF ablation in the prevention of dementia is also not clear and is being evaluated in ongoing studies. An observational study showed a lower incidence of dementia in patients undergoing ablation at 3 years of follow-up.[15] On the contrary, a mild cognitive decline has been demonstrated post-ablation.[16] Other therapies that may prevent hypoperfusion are cardioversion, rate control, and anti-inflammatory therapy with statin agents. Lee et al[17] have shown that smoking cessation after a new diagnosis of AF may reduce the risk of dementia.

The present study by Fong et al[10] makes some interesting observations on the value of DOACs to prevent dementia. However, some limitations need to be highlighted, the most important being the paucity of randomized studies. The lack of data specific to dementia subtypes and AF burden and the variability in the use of tests for cognitive decline are other significant limitations. Given these constraints, future studies will address the gaps in our knowledge, such as the value of screening for AF to prevent dementia, amending the CHADS-VASC2 score or developing scores to predict dementia, and anticoagulation therapy for silent AF and in patients with a low risk for stroke.[18]

In conclusion, the present meta-analysis demonstrates that DOACs are effective in preventing dementia in patients with AF, especially Asians. Therapies that target hypoperfusion and other risk factors in addition to anticoagulation therapy may prove to be more effective in preventing dementia in patients with AF.

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