Reducing the Risk of Dementia in Atrial Fibrillation and Multiple Sclerosis

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Introduction

Atrial Fibrillation (AF) is the most commonly encountered sustained dysrhythmia in clinical practice [1]. According to a meta-analysis that included patients from 8 Asian countries, AF prevalence ranges from 0.37% to 3.56% in community settings and from 2.8% to 15.8% in hospitals [2]. The most devastating neurological complications of AF include stroke and cognitive impairment. Dementia is a relentlessly progressive condition characterized by impaired memory, judgment, and executive functioning. Among the various 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 contributors [3,4]. Dysrhythmias like AF have been identified as significant risk factors for dementia [5]. It has been observed that dementia can occur in patients with AF even in the absence of stroke.

A study from the Intermountain Healthcare registry demonstrated that AF increases the risk of all types of dementia, with younger individuals (<70 years) showing the highest risk [6]. The association between arrhythmias and impaired cognition was noted over 40 years ago, with "cardiogenic dementia" used to describe the decline in cerebral function attributed to cardiac dysrhythmias. Cardiogenic dementia may result from bradyarrhythmias, tachyarrhythmias, and extrasystoles. Reduced blood pressure or variability in ventricular filling during arrhythmias or premature complexes may precipitate cognitive decline [7]. The aging brain may be more susceptible to these conditions, and prolonged episodes of these arrhythmias may eventually impair 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 AF patients is multifactorial and complex. Nevertheless, a procoagulant state leading to thromboembolism is believed to be a unifying mechanism of brain injury [4]. With a procoagulant state being the dominant mechanism of dementia, anticoagulation emerges as a potential therapy to prevent brain injury. In recent years, Direct Oral Anticoagulant Agents (DOACs) have become preferred over Vitamin K Antagonists (VKAs) in managing patients with non-valvular AF [9].

The meta-analysis conducted by Fong *et al.* recently published in JACC: Asia, represents a significant advancement in the study of Atrial Fibrillation (AF) and its association with dementia, particularly focusing on the impact of Direct Oral Anticoagulants (DOACs) in Asian populations [10]. This study contributes valuable insights into the effectiveness of DOACs compared to Vitamin K Antagonists (VKAs) in preventing dementia among AF patients.

In their analysis of 10 studies, Fong *et al.* found that DOAC use was associated with a reduced risk of dementia when compared to VKAs (HR: 0.88) [10]. The study population had a mean age ranging from 70.4 years to 75.7 years and included participants from diverse geographical regions.

Interestingly, the meta-analysis highlighted a statistically significant benefit of DOACs in relatively younger patients (aged 65 years-75 years), while the protective effect was less evident in older patients (>75 years). Moreover, the study compared the efficacy of DOACs across different continents, revealing a significant advantage in Asian patients (HR: 0.81; 95% CI: 0.68%-0.86%), with less pronounced benefits observed in European populations. Data from American patients were limited but also indicated a beneficial effect of DOACs.

While previous research has extensively documented the efficacy of DOACs in reducing stroke risk across global populations, including in landmark studies conducted in Europe, the meta-analysis did not find a clear benefit in preventing dementia. This observation is not fully explained, but the study suggests that Asian populations, who have a heightened sensitivity to VKAs and are more susceptible to intracranial bleeding due to lower

body weight and supratherapeutic effects with DOACs, may derive greater benefit from DOAC therapy.

These findings are consistent with previous meta-analyses that have shown DOACs to be more effective and safer than VKAs in Asian populations, particularly in the context of stroke prevention [9]. The study's results underscore the significant role of DOACs in stroke and dementia prevention among Asians, with a favorable bleeding risk profile. Notably, no significant differences were observed among the four DOACs included in the analysis.

Future studies could explore the differential effects of DOACs on various types of dementia, as this meta-analysis did not consistently report hazard ratios by dementia subtype. For a more comprehensive understanding of these findings, please refer to the original article by Fong *et al.* available in JACC: Asia [10-13].

Dementia arises from various pathological processes, including genetic factors, neurodegenerative conditions, and vascular disorders. While multi-infarct or vascular dementia is directly linked to thromboembolic events, the pathogenesis of Alzheimer's Disease or frontotemporal dementia is considerably complex. Although AF is a recognized risk factor for AD, the pathologic mechanisms involve neurodegeneration with amyloid deposition and metabolic processes. Emerging evidence suggests that AD may also be associated with neuronal loss due to cerebral hypoperfusion [11].

Cerebral hypoperfusion can result from a decline in mean arterial pressure due to inadequate ventricular filling, loss of atrioventricular synchrony, and variability in RR intervals. The precise mechanism of cerebral hypoperfusion-induced neuronal damage caused by mild hypotension due to dysrhythmias requires further evaluation. Cerebral autoregulation, which preserves cerebral perfusion until the mean pressure reaches 60 mm Hg, plays a crucial role in these processes [12]. In older adults with cardiovascular risk factors, dysfunction in these autoregulatory mechanisms may render individuals vulnerable to neuronal injury.

Direct Oral Anticoagulants (DOACs) have been shown to reduce thrombin formation, which can be proinflammatory and lead to amyloid deposition [13]. However, further randomized studies are needed to fully understand the role of anticoagulation in preventing and managing AD, given its complex pathophysiology. Preventing AD may require strategies targeting cerebral hypoperfusion in addition to anticoagulation and therapies aimed at preventing the breakdown of acetylcholine.

For more comprehensive information on this topic, further studies are warranted to elucidate the intricate relationships between AF, cerebral hypoperfusion, and the development of AD.

Current evidence identifies two pivotal mechanisms of dementia that can be targeted: thromboembolism and hypoperfusion [14]. Catheter-based therapies designed to address these mechanisms include left atrial appendage occlusion and Atrial Fibrillation. The role of AF ablation in dementia prevention is currently under evaluation in ongoing studies. An observational study has suggested a lower incidence of dementia in patients who underwent ablation during a 3-year follow-up period [15]. However, some studies have shown a mild cognitive decline post-ablation as well [16]. Other therapeutic strategies that may prevent hypoperfusion include cardioversion, rate control, and anti-inflammatory therapy using statin agents. Lee et al. have indicated that smoking cessation following a new diagnosis of AF may reduce the risk of dementia [17].

The recent study by Fong et al. offers interesting insights into the potential of Direct Oral Anticoagulants (DOACs) to prevent dementia [10]. However, there are several limitations that need to be acknowledged, notably the scarcity of randomized controlled trials. Additionally, the lack of specific data on dementia subtypes and AF burden, as well as variability in the use of cognitive decline assessment tests, are significant limitations. Addressing these constraints will be crucial in future research to fill gaps in our understanding. Future studies should focus on topics such as the value of AF screening for dementia prevention, adjustments to the CHADS-VASC2 score or development of new scores to predict dementia risk, and the role of anticoagulation therapy in patients with silent AF and those at low risk for stroke [18].

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

For further insights, continued research is necessary to refine our understanding of the interplay between AF, dementia, and therapeutic interventions.

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