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Atrial fibrillation and dementia

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ABSTRACT

Emerging evidence has shown a consistent association between AF and risk of dementia, including Alzheimer's disease. It is likely that a constellation of various mechanisms combine to cause dementia in AF patients. Both AF and dementia share multiple common risk factors, and as such these may be targets of early prevention strategies to reduce risk. In patients with AF, choices regarding type and duration of anticoagulation as well as rhythm- and rate-control strategies can influence dementia risk.

Atrial fibrillation

Atrial fibrillation (AF) is an emerging disease epidemic and is currently affecting approximately 2.3 million people in the United States. This rhythm disorder is predicted to extend its reach to 5.6 million people in the United States by the year 2050 due to the "Baby Boom" (people born between 1946 and 1964) population reaching 85 years and older [1].

Factors that often drive progression of AF are related to age and coexistent cardiovascular disease state. All forms of AF, including paroxysmal AF, can negatively alter left atrial size, substrate, and function. These changes are often characterized by dilatation and contractile dysfunction, which develop very early after arrhythmia diagnosis, and can significantly impact response to therapeutic interventions [2]. These maladaptive changes over time often increase arrhythmia burden and severity and may be responsible for the morbidity and mortality associated with the disease state. They can also specifically impact contractile function of the atrium of left atrial appendage and as a consequence increase risk of macro- and micro-cerebral ischemic events.

Dementia

Dementia is a condition describing a constellation of symptoms that cause alterations in memory, social functions, and cognitive abilities. Alzheimer's disease is the most common form of dementia in the United States, accounting for 60–80% of dementia occurrences, while 10–20% are attributable to vascular dementia [3]. Alzheimer's disease afflicts 5.4 million in the United States, with the vast majority of these people being 65 years and older [4]. Similar to AF, the dementia burden is increasing as the "Baby Boom" generation reaches the ages of 65 and older. The number of people affected by Alzheimer's dementia is projected to triple by the year 2050 in the United States [4].

Despite general declines in stroke and cardiovascular mortality and morbidity, the prevalence of dementia has remained relatively stable. The decline in stroke and cardiovascular mortality has been attributed to early recognition, smoking reduction, and early and/or more aggressive treatment of diabetes, hypertension, and dyslipidemia [5]. The lack of simultaneous impact on dementia, despite lower rates of stroke and vascular disease that were felt to increase risk of dementia, suggest that we need to think broadly about risk factors and expand research into novel strategies for disease prevention and treatment.

Atrial fibrillation and dementia

There is significant evidence that confirms the association between AF and dementia, including idiopathic or Alzheimer's

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dementia (Table). Our group has explored the relationship between AF and dementia in a study of 37,025 patients from the Intermountain Heart Collaborative Study [3]. We included patients with no history of dementia and at least 5 years of follow-up data. Given the large nature of this study, we used ICD-9 codes to define dementia. To minimize risk of misclassification, we used ICD-9 codes that were entered by neurology only. Our results showed that AF contributed to the development of all types of dementia. The prevalence of both diseases advances with increasing age and predisposes patients to a rise in the incidence of mortality. Interestingly, in our study the younger group studied (patients <70 years) had the highest relative risk of developing Alzheimer's dementia (odd ratio = 2.30, $p = 0.001$). This highest relative risk of dementia in the younger AF patients suggests that the association is more than an epiphenomena stemming from disease states that share advancing age as a common risk. However, the Table does highlight some inherent challenges in these types of studies. They are observational and look at dementia that has broad manifestations in presentation and progression. Those with serial cognitive testing are going to be more accurate than those that rely on other methods for dementia diagnosis. Those that are not designed upfront to look at the influence of AF on cognition will have accuracy limitations in diagnosis and understanding of the arrhythmia and the influence of arrhythmia treatment on outcomes.

Each disease state shares many common risk factors with the other, many of which are potentially modifiable if disease-based preventative lifestyle changes are started early in life (Fig. 1). Although a common thought is that AF resulted in cognition impairment due to stroke, all forms of dementia, including idiopathic variants, are increased in AF patients (Table).

The association between AF and dementia is complex. Both disease states share many common risk factors (Fig. 1), and understanding these risk factors may provide clues into the key mechanisms of both disease states. More importantly, many of the shared risk factors are modifiable, and if early preventative lifestyle changes are adopted, the disease states may be avoided altogether. However, given the complexity and variability of both disease states, it is likely that multiple potential mechanisms underlie the association between AF and dementia.

Understanding the mechanisms of disease association and then discovering avenues to reduce risk are paramount. In patients with AF, there is also a significant association between dementia onset and total mortality [3]. In our prior study, we found that in patients with AF that develop dementia of any subtype, mortality is significantly increased (HR = 1.46–2.14). Similar to the general association data, the greatest risk of death in those patients with AF and dementia was found in the youngest cohort studied (<70 years, HR across multiple subtypes = 1.55–2.07).

Potential mechanisms underlying dementia in AF patients

Repetitive injury from microemboli and/or microbleeds

One of the most feared complications of AF is disabling stroke. The majority of strokes in patients with AF are

Table – Longitudinal studies that examine the association of incident dementia and atrial fibrillation.

References	Population	Follow-up	Dementia diagnosis	Dementia risk
Rusanen et al. [33]	4 Populations >midlife $n = 1510$	>25 Years	Mini-Mental Status Exam Self-Administered Questionnaire	TD: HR = 2.61 (95% CI: 1.01–6.47) Increased risk if APOE positive
Marzona et al. [34]	Mean age = 67 $n = 31,506$	56 Months (mean)	Mini-Mental Status Exam Independent living Assessment	TD: HR = 1.30 (95% CI: 1.14–1.49)
Dublin et al. [35]	Median age = 74 $n = 3045$	6.8 Years (mean)	Cognitive Abilities Screening Instrument Neuropsychological and clinical assessment	TD: HR = 1.38 (95% CI: 1.10–1.73) AD: HR = 1.50 (95% CI: 1.16–1.94)
Bunch et al. [3]	Mean age = 61 $n = 37,025$	5 Years	ICD-9 Codes entered by neurologists	TD: HR = 1.44 (95% CI: 1.23–1.69) AD: HR = 1.06 (95% CI: 0.85–1.33)
Marengoni (2011) [36]	>78 Years $n = 685$	4.0 Years (mean)	Cognitive test battery Clinical Examination	TD: HR = 0.9 (95% CI: 0.5–1.7) AD: HR = 0.8 (95% CI: 0.4–1.5)
Peters et al. [37]	Mean age = 84 $n = 3336$	2.2 Years (mean)	Mini-Mental Status Exam Clinical Examination if MMSE abnormal	TD: HR = 1.03 (95% CI: 0.62–1.72)
Rastas et al. [38]	Mean age = 88 $n = 553$	3.5 Years (mean)	Mini-Mental Status Exam Clinical Dementia Rating Medical history	TD: 16.4% (AF) vs. 18.6% (no AF)
Tilvis et al. [39]	Mean age = 80 $n = 650$	1, 5, and 10 Years	Mini-Mental Status Exam Clinical Dementia Rating	TD: HR = 2.9 (95% CI: 1.3–6.1) Association only at 5-year follow-up
Piguet et al. [40]	Mean age = 81 $n = 377$	6 Years	Clinical and Neuropsychological Examinations	TD: 35% (AF) vs. 30% (no AF) AD: 13% (AF) vs. 11% (no AF)

TD, total dementia; AD, alzheimer dementia; HR, hazard ratio; OR, odds ratio.