Atrial fibrillation: A major risk factor for cognitive decline

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Atrial fibrillation is a common disease of the elderly, conferring considerable morbidity and mortality related to cardiovascular effects and thromboembolic risks. Anticoagulation, antiarrhythmic medications, and rate control are the cornerstone of contemporary management, whereas ablation and evolving surgical techniques continue to play important secondary roles. Growing evidence shows that atrial fibrillation is also a risk factor for significant cognitive decline through a multitude of pathways, further contributing to morbidity and mortality. At the same time, cognitive decline associated with cryptogenic strokes may be the first clue to previously undiagnosed atrial fibrillation. These overlapping associations support the concept of cognitive screening and rhythm monitoring in these populations. New research suggests modulating effects of currently accepted treatments for atrial fibrillation on cognition; however, there remains the need for large multicenter studies to examine the effects of novel oral anticoagulants, rhythm and rate control, and left atrial appendage occlusion on long-term cognitive function. (Am Heart J 2015;169:448-56.)

Background

Twenty-five percent of people >40 years of age will develop atrial fibrillation (AF).[1] Atrial fibrillation has been clearly established as a cause of embolic stroke from thrombus primarily originating in the atrial appendage.[2,3] Evidence is emerging to suggest that AF may also contribute to less dramatic but equally devastating neurologic decline. Treatment modalities for AF target various aspects, including control of heart rate, conversion of heart rhythm, and elimination of either the nidus for or propensity to form thrombus. The impact of these therapies on cognitive function is unknown. We conducted a systematic review of the literature to examine the current evidence and discuss the epidemiologic association between AF and cognitive function, pathophysiologic mechanisms, and the impact of current AF treatment on cognitive decline.

Methods

A systematic electronic literature search was conducted using Medline for studies published from January 1, 2004, to July 1, 2014, including the search phrases: atrial fibrillation, cognitive impairment, and cognitive decline. Articles not in the English language were excluded. Hand-selected references from articles were also reviewed. Studies were categorized into 3 categories based on topic: epidemiology, pathophysiology, and treatment (Figure 1). Further review of epidemiologic studies was restricted to systematic reviews and meta-analyses. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this review.

Epidemiology

Numerous studies have been conducted examining the association between AF and cognitive impairment, with diverse populations ranging from case series of acute stroke inpatients to community-dwelling population-based longitudinal studies. Because of the heterogeneity of populations, methods, and analysis of the literature, 4 reviews[4-7] and 3 meta-analyses[8-10] (Table I) were reviewed, whereas prospective cohort and cross-sectional studies were excluded. In general, studies support a positive association, with relative risk ranging from 1.4 to 2.8, depending on the presence of stroke. Significant heterogeneity was present, precluding a formal meta-analysis in several reviews. Two meta-analyses included studies of patients with strokes, finding significant heterogeneity among studies of broader patients and little heterogeneity when studies were limited to stroke patients[9] or dementia.[10] Only 1 meta-analysis examined studies of patients with normal cognitive function at baseline with no history of stroke,

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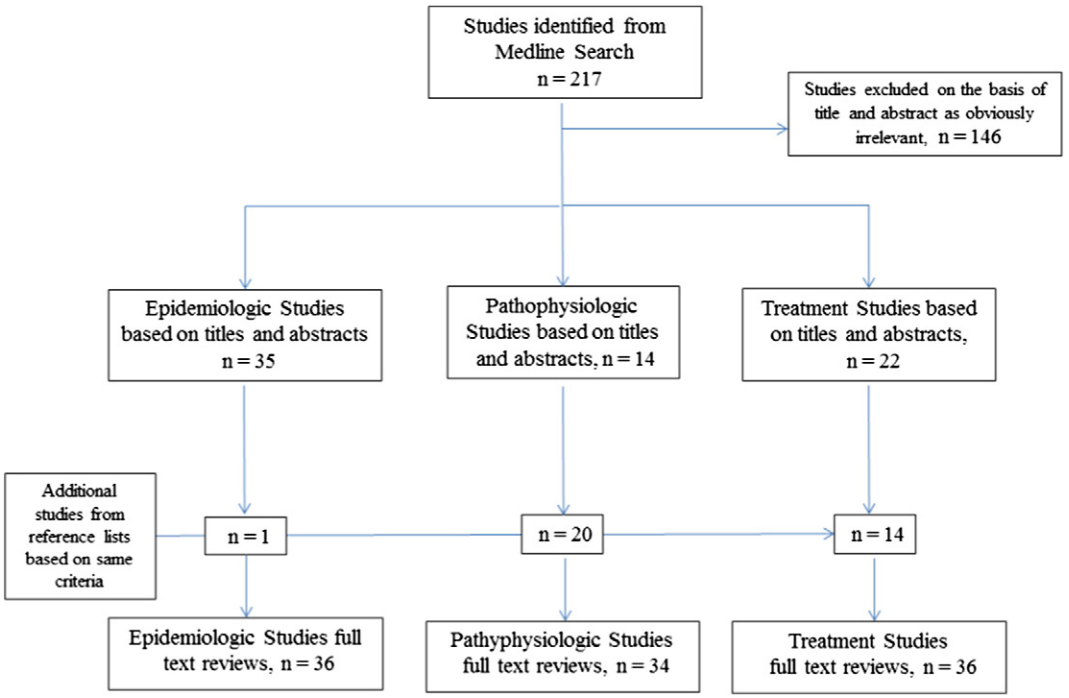
Figure 1



QUOROM diagram.

but the outcome examined was incident dementia and not cognitive decline.[8] Of note, the criteria for the diagnosis and classification of AF were noted by many authors to be poor[5,8,10]; 1 semisystematic review noted that 3 studies used a single electrocardiogram, software program, and diagnosis code as the basis for AF diagnosis.[5] New technologic advances with implantable loop recorders having higher sensitivity and specificity[11] may improve the diagnosis and classification in future AF studies.

Mechanistic insights

Hemodynamics

As noted in many of the epidemiologic studies, patients with AF often have concurrent diagnoses such as hypertension, previous stroke, and other cardiovascular diseases that confound the association and delineation of underlying mechanism. Atrial fibrillation decreases cardiac output secondarily to loss of atrioventricular synchrony and impairment of left ventricular filling.[12] As a result of this decreased cardiac output, cerebral hypoperfusion may occur, particularly in the elderly in whom compensatory autoregulation is impaired.[13] Regional cerebral blood flow in chronic AF patients without neurologic symptoms was lower than age-matched controls, with a differential from anterior to posterior but not between hemispheres. The magnitude of reduction differed by age, highest in younger patients (17.5% in aged 35-50 years vs 5.5% in age >66).[14] Transcranial Doppler studies of various cardiac dysfunctional states showed lower diastolic cerebral perfusion compared with controls; in AF patients, patients with presyncope had lower diastolic blood flow velocity compared with AF patients without neurologic symptoms.[15] The role of ventricular rates was examined in 1 study that found that, in the presence of AF, both rapid and slow ventricular rates were a major predictor of dementia, showing another theoretic mechanism linking reduced cardiac output to cognitive impairment; however, this study was underpowered and unadjusted.[16] Although the known hemodynamic consequences of AF have been quantified in these studies, no studies have clearly shown an association to cognitive impairment.

Role of inflammation and thrombosis biomarkers

Elevated levels of various inflammatory biomarkers have been associated with AF. Although inflammation is linked to a prothrombotic state, the mechanisms and associations with cognitive impairment remain unclear. Elevated C-reactive protein both independently and incrementally predicted AF in registry data after adjusting for coexisting cardiovascular disease.[17,18] The role of the proinflammatory cytokine interleukin (IL) 6 as a stimulant of C-reactive protein has been demonstrated in human hepatocytes,[19] and a review of studies showed correlation of various