Atrial fibrillation as a risk factor for cognitive impairment: a semi-systematic review

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Summary

It is unclear if atrial fibrillation (AF) is an independent risk factor for cognitive impairment. This review evaluates the available evidence and provides an overview of the association between AF and cognitive function. Electronic database searches, January 1990 to December 2012, identified 271 studies comparing the incidence of cognitive impairment and/or dementia in patients with/without AF. Cognitive function was diagnosed by a physician using the mini-mental state examination (MMSE) or other established diagnostic criteria. Studies with <20 participants and without direct comparison to controls in sinus rhythm were excluded. There were no restrictions on the basis of age, language or study design. Full texts of 11 studies were obtained. Eight studies (three cross-sectional, two case-control and three prospective cohorts) reported an association between cognitive decline and AF. Among cross-sectional studies, patients with AF had a 1.7 (95% CI 1.2–2.5) to 3.3 (95% CI 1.6–6.5) greater risk of cognitive impairment, and a 2.3-fold (95% CI 1.4–3.7) increased risk of dementia, compared to patients in sinus rhythm. There was marked heterogeneity in the design, size and quality of studies and reporting of the data which precluded formal meta-analysis. Eight studies reported an association between AF and cognitive impairment and/or dementia, but the magnitude of risk varied. Further large-scale prospective studies are needed to establish whether AF is a risk factor for cognitive decline, utilizing objective measures of cognitive function and neuropsychological testing, and to investigate the potential benefit of anticoagulation on reducing cognitive impairment and development of dementia.

Introduction

Atrial fibrillation (AF) is associated with impaired cognitive function, but given the common association of AF with various co-morbidities and the greater prevalence and incidence of AF with increasing age,1 the precise causal (and independent) relationship of AF to cognitive impairment has not been quantified nor proven. Various mechanisms may be implicated in which AF can increase the risk of cognitive impairment. One is the increased risk of asymptomatic or silent cerebral infarction as a result of embolization,2,3 a mechanism similar to that of an ischaemic stroke. An increase in silent brain infarction on magnetic resonance imaging (MRI) more than doubles the
risk of dementia on neuropsychological testing. Other studies have lacked detailed neuro-imaging, and there was less certainty that AF causes cognitive impairment due to silent brain infarction. Another potential mechanism is that during AF, cardiac output is impaired, leading to under-perfusion of the brain and progressive cognitive impairment, however, ejection fraction quantified by echocardiography was not significantly correlated with cognitive impairment. Thus, the available evidence for the proposed pathophysiological mechanisms linking AF to cognitive impairment is equivocal.

Known risk factors for cognitive impairment include age, sex, educational level, family history, along with risk factors for cerebrovascular disease such as hypertension and diabetes. Thus, the impairment in cognitive function may simply reflect these co-morbidities rather than AF per se. Since the ageing population is expected to increase in the future, in addition to a continued rise in the prevalence of AF, it is important to gain insights into the relationship(s) between AF and cognitive impairment so that preventative measures, e.g. earlier and holistic treatment of AF, can be initiated to reduce or remove the associated burden of cognitive impairment.

Two previous systemic reviews have examined the relationship between AF and cognitive impairment and AF and dementia. Mead and Keir concluded that the association between AF and cognitive decline was inconclusive given the possible biases in the included studies whereas Kwok et al. suggested that the association between dementia and AF existed in those AF patients with stroke but the relationship between cognitive impairment and AF per se was not certain in the broader AF population.

This semi-systemic review re-evaluates the available evidence and provides an overview of the association between AF and cognitive function.

Methods

Electronic literature searches of Medline and EMBASE between 1 January 1990 and 31 December 2012 were performed. The search terms included each of the following individually and in combination: ‘atrial fibrillation’, ‘cognitive impairment’, ‘cognitive decline’ and ‘dementia’, and returned 271 citations (Figure 1).

The inclusion criteria were studies that reported comparisons of patients with and without AF regarding their cognitive function. There were no restrictions on the type of study design. Studies were included only where the diagnosis of cognitive impairment and/or dementia was made by an attending physician, with the use of the mini-mental state examination (MMSE) or other established diagnostic criteria, such as the DSM IV or ICD-9 codes for the diagnosis of dementia.

Studies with <20 participants and those without direct comparison of AF patients to controls in sinus rhythm were excluded. The 271 articles retrieved from the searches were firstly screened based on the title and abstract, by one reviewer, leading to the exclusion of 260 articles that were obviously irrelevant to the review (Figure 1). The full papers of the remaining 11 studies were retrieved and the following information was obtained: study design, participant information (number of AF patients and controls, mean age, percentage of men, etc.), diagnostic methods for cognitive impairment/dementia/AF, incidence/prevalence of cognitive impairment and/or dementia. The references of all included studies were examined to identify any other potentially relevant articles.

Results

Searches identified 11 studies that examined the relationship between AF and cognitive impairment: three cross-sectional studies (Table 1), three case-control studies (Table 2) and five prospective longitudinal or cohort studies (Table 3). Of these, eight studies reported an association between AF and cognitive impairment whereas three other studies failed to establish this link.

The number of participants ranged considerably from 74 to 37 025 and there was a wide range of follow-up periods, ranging from 3.5 to 30 years. In addition, the age of the participants also varied; the youngest patients had a mean age of 58 years, whereas the oldest were on average 88.4 years.

Three studies did not find a relationship between AF and cognitive decline. However, the cohort study by Park et al. had a very high rate of lost to follow up compared to others (attrition rate of 59%) and thus there was a possibility of healthy survivor effect contributing towards the negative result in this study. The small study (n=27 with AF) by O’Connell et al. lacked information on co-existent dementia and cerebrovascular disease, and found no significant difference in MMSE between patients with AF and controls, although some differences were seen for verbal and non-verbal memory and some attention tests. The study by Rastas et al. found that AF was a significant and preventable risk factor for stroke but not for dementia in the very old, and therefore it is possible the AF contribution to the
## Table 1  Cross-sectional studies investigating atrial fibrillation and cognitive function

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Diagnosis of AF/cognitive impairment or dementia</th>
<th>Findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kilander et al. \textsuperscript{11} 1998</td>
<td>Cross-sectional study, community based, in Uppsala, Sweden</td>
<td>952 men, mean age 72.4</td>
<td>AF assessed by ECG. Cognitive function assessed by MMSE and the Trail Making Tests</td>
<td>Cognitive score in men with AF was 0.41 SD lower than men without AF</td>
<td>Women excluded</td>
</tr>
<tr>
<td>Ott et al. \textsuperscript{12} 1997</td>
<td>Cross-sectional study from Rotterdam Study</td>
<td>6584 participants (60.8% male, mean age 69.2)</td>
<td>AF assessed by ECG. Dementia assessed by neuropsychological tests including MMSE</td>
<td>Dementia more than twice as likely in patients with AF than those without AF (OR 2.3, 95% CI 1.4–3.7)</td>
<td>Patients excluded based on incomplete data; possible healthy survivor effect</td>
</tr>
<tr>
<td>Rozzini et al. \textsuperscript{13} 1999</td>
<td>Cross-sectional study in an elderly care unit</td>
<td>269 elderly patients (31% male, mean age 80.4)</td>
<td>AF assessed by ECG. Cognitive function assessed by MMSE</td>
<td>Chronic AF patients had a 3.3-fold higher risk of cognitive impairment than those in sinus rhythm</td>
<td>Lack of detail on how confounders were controlled for</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CI, confidence intervals; ECG, electrocardiogram; MMSE, mini-mental state examination; OR, odds ratio, SD, standard deviation.
<table>
<thead>
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<tr>
<td>Farina et al.</td>
<td>Case-control, hospital of Milan, Italy</td>
<td>16 chronic AF (81% male, mean age 65.3); 21 paroxysmal AF (76% male, mean age 58.3); controls matched for age, education and presence of hypertension</td>
<td>AF assessed by medical records</td>
<td>MMSE median of 29 in chronic AF and paroxysmal AF and median of 30 in controls, P-value &lt; 0.05; chronic AF patients showed a poorer performance on MMSE on tasks exploring attention and verbal memory whereas paroxysmal AF patients were significantly impaired in the long-term memory task</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Knecht et al.</td>
<td>Case-control, community based, Munster, Germany</td>
<td>87 AF (83% male, mean age 60), 446 controls (43% male, mean age 64)</td>
<td>AF assessed by medical records</td>
<td>Significant lower score in tasks of learning and memory (P &lt; 0.01); worse in chronic AF than paroxysmal AF patients; hippocampal atrophy in patients with AF</td>
<td>Controls not matched, patients with AF were younger</td>
</tr>
<tr>
<td>O’Connell et al.</td>
<td>Case-control, community based, Tyne and Wear, England</td>
<td>27 AF age and sex matched to 54 controls (48 men, mean age 71.96)</td>
<td>AF assessed by medical records</td>
<td>No significant difference for MMSE (mean 26.3 in AF, 27.2 in control) and pre-morbid intelligence; significant difference for verbal memory tasks</td>
<td>Lack of information on co-existent dementia and cerebrovascular disease; small sample size</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CI, confidence intervals; ECG, electrocardiogram; MMSE, mini-mental state examination; SD, standard deviation.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Follow-up period</th>
<th>Diagnosis of AF/cognitive impairment or dementia</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Bunch et al.15 2010</td>
<td>Prospective observational study; patients from Intermountain Heart Collaborative Study database</td>
<td>N=37,025 (60% male, mean age 60.6)</td>
<td>Mean 5 years</td>
<td>Both AF and dementia assessed by medical records and discharge summary</td>
<td>Significantly higher prevalence of dementia in patients with AF compared to non-AF (e.g., 3.3% vs. 1.3%, respectively, for non-specific dementia P&lt;0.0001)</td>
<td>Use of medical record to identify AF and dementia may not be accurate</td>
</tr>
<tr>
<td>Elias et al.16 2006</td>
<td>Prospective observational study; Framingham offspring men</td>
<td>N=1011 (mean age 61)</td>
<td>Maximum 30 years</td>
<td>AF assessed by various sources including Framingham study examination Cognitive function assessed by neuropsychological tests</td>
<td>AF patients scored significantly lower on the global cognitive test. The difference in performance between the non-AF and the AF cohorts was approximately 0.5 SD. Sample bias towards healthier participants, cognitive function was assessed only once</td>
<td>Excluded women</td>
</tr>
<tr>
<td>Marzona et al.5 2012</td>
<td>Post-hoc analysis of the ONTARGET and TRANSCEND RCTs</td>
<td>N=31,506 (70.4% men, mean age 66.5)</td>
<td>Mean 56 months</td>
<td>AF diagnosed by ECG and past medical history from trial data Cognitive function assessed by MMSE</td>
<td>AF significantly associated with cognitive decline (HR 1.14, 95% CI 1.03–1.26)</td>
<td>Sub-group analysis of two RCTs; patients with multiple risk factors which are known to be correlated with functional and cognitive decline</td>
</tr>
<tr>
<td>Park et al.17 2007</td>
<td>Prospective cohort study, community based, England</td>
<td>74 new AF (43% male) and 86 controls (61% male). Mean age 75.6</td>
<td>12 and 36 months</td>
<td>AF assessed by ECG. Cognitive impairment assessed by neuropsychological tests including MMSE</td>
<td>In 18 of the 19 cognitive function tests there was no significant effect by group; most of the mean scores were similar</td>
<td>High loss to follow up with attrition rate of 59%; healthy survivor effect may contribute towards negative result; recent diagnosis of AF means that no cognitive decline may have been apparent at 3 year follow up</td>
</tr>
<tr>
<td>Rastas et al.18 2007</td>
<td>Prospective cohort study, population based in Vantaa, Finland</td>
<td>All residents aged over 85 living in Vantaa (553 individuals, 20% male, mean age 88.4)</td>
<td>Mean 3.5 years</td>
<td>AF assessed by ECG and medical records Dementia assessed by neuropsychological tests including MMSE/neurologist’s clinical examination</td>
<td>New dementia in subjects with AF was 16.4% and 18.6% in subjects without AF. AF is not an independent risk factor for dementia</td>
<td>Very elderly subjects, and the development of dementia in this age group may be multifactorial Duration of AF was unknown in most subjects</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CI, confidence intervals; ECG, electrocardiogram; HR, hazard ratio; MMSE, mini-mental state examination; RCT, randomized controlled trial; SD, standard deviation.
development of dementia is smaller in extremely old patients.

Eight studies,\textsuperscript{5,6,11–16} three cross-sectional,\textsuperscript{11–13} two case-control,\textsuperscript{6,14} and three prospective cohort studies\textsuperscript{5,15,16} reported an association between cognitive decline and AF. Among the cross-sectional studies patients with AF had an odds ratio (OR) of 1.7 (95% CI 1.2–2.5)\textsuperscript{12} to 3.3 (95% CI 1.6–6.5)\textsuperscript{13} greater risk of cognitive impairment, and a 2.3-fold (95% CI 1.4–3.7) increased risk of dementia,\textsuperscript{12} compared to patients in sinus rhythm. In the post-hoc analysis of the ONTARGET and TRANSCEND patients, those with AF at baseline had an increased risk of cognitive decline (HR 1.14, 95% CI 1.03–1.26) compared to patients without AF.\textsuperscript{5}

**Diagnosis of AF**

Among those studies reporting an association between cognitive function and AF, the diagnosis of AF was made using either ECG alone,\textsuperscript{11–13,17} medical record/hospital discharge summary alone\textsuperscript{6,14,15} or both.\textsuperscript{4,5,16,18} Two studies may have been prone to under-diagnosis of AF (especially paroxysmal AF) as they only used a single one-off ECG\textsuperscript{12,17} and in one study,\textsuperscript{12} a software programme was used to detect the presence of AF on the ECGs. Bunch et al.\textsuperscript{15} used the hospital discharge summary from the large Intermountain Heart Collaborative study, where the diagnosis of AF was dependent on the accuracy of disease coding.

Three studies\textsuperscript{6,13,14} divided AF patients into those with paroxysmal AF and those with chronic AF, and their results showed a trend for a decline in cognitive function with paroxysmal AF patients scoring lower than patients in sinus rhythm, but higher than patients with chronic AF.

**Gender differences**

Two studies\textsuperscript{11,16} excluded women and only one study found that the association between AF and dementia was restricted to women\textsuperscript{12} whereas the other studies did not report significant gender differences.

**Prior stroke**

Five studies excluded patients with previous history of stroke or transient ischaemic attack\textsuperscript{4,6,13,14,16} whereas two cross-sectional studies evaluated the relationship between AF and cognitive function in patients with and without stroke.\textsuperscript{11,12} The mean cognitive score of men with AF was still significantly lower than control patients in sinus rhythm after exclusion of stroke patients (\(-0.24 \pm 0.12\) vs. \(0.17 \pm 0.03\), respectively; \(P=0.0004\)).\textsuperscript{11}

**Diagnosis of cognitive impairment/dementia**

All studies used a battery of neuropsychological tests to determine the participant’s cognitive function with an exception of one study\textsuperscript{15} that used medical records and ICD-9 codes to diagnose dementia. The tests revealed different aspects of cognitive function, with those most commonly used being: MMSE, trail making tests, Wechsler adult intelligence scale and the Wechsler memory scale. Most studies also involved a neurologist’s examination and questionnaires. The ONTARGET/TRANSCEND ancillary analyses\textsuperscript{5} included other primary endpoints such as inability to perform daily living activities independently to monitor functional decline of the patients.

MMSE was used in eight studies.\textsuperscript{4–6,11–13,17,18} The score allows a direct comparison between groups although the analysis and cut-off points differed between studies: a cut-off of <26 was used in the Rotterdam study,\textsuperscript{12} whereas Rozzini et al.\textsuperscript{13} used a cut-off of <24. The remaining studies compared the mean MMSE scores between patients with AF and controls.

Among the studies showing evidence of AF and cognitive impairment, the significant methodological differences and disparity in the reporting of the results: \(z\)-score,\textsuperscript{11,14,16} relative risk,\textsuperscript{13} odd ratio,\textsuperscript{12} hazard ratio,\textsuperscript{17} median scores of the cognitive test(s) and rates of dementia in each group, made it difficult to pool together the results and quantify the risk of developing cognitive impairment/dementia in AF patients, or to assess the independent relationship of AF to cognitive impairment.

**Effect of treatment**

Marzona et al.\textsuperscript{5} found that the use of antithrombotic therapy did not modify the association between AF and cognitive decline, with HR 1.12 (95% CI 1.04–1.21) in patients taking an antithrombotic agent and 1.04 (95% CI 0.65–1.66) in patients receiving no treatment. Park et al.\textsuperscript{17} found no statistically significant differences between neuropsychological test scores between AF patients taking aspirin, or warfarin or no therapy.

**Other investigations to confirm cognitive function**

In one study patients underwent CT head and/or MRI scans, and hypo-dense lesions were seen in
31.3% of chronic AF and 9.5% with paroxysmal AF patients, but no imaging was performed in the controls. Knecht et al. also performed MRI in AF patients and reported a reduction in hippocampal volume, which corresponded to memory impairment. Another study performed autopsy in 306 patients and found that the number of multiple large ischaemic lesions was much higher in patients with AF (14%) than controls (4.3%, P = 0.005).

Discussion

Although the evidence thus far supports an association between AF and cognitive impairment and suggests a 2- to 3-fold increased risk, further prospective large-scale cohort studies need to be established to investigate the causal (and independent) relationship between AF and the cognitive decline and/or dementia, with objective measurements of cognitive function, and to examine the potential benefit, if any, from anticoagulant treatment in reducing cognitive impairment and/or dementia.

Cross-sectional studies and case-control studies can only show an association between AF and cognitive impairment and not a causal relationship as the two variables were measured concurrently. Most cohort studies excluded patients with pre-existing dementia or cognitive impairment in an attempt to prove that AF precedes the event. Confounding variables including hypertension, myocardial infarction, diabetes mellitus, educational status and the use of antithrombotic agents were statistically adjusted for in almost all of the studies; however, residual confounding is likely as statistical adjustment cannot account for all biological processes.

Three studies showed a trend for increasing cognitive impairment between sinus rhythm, paroxysmal AF and chronic AF, and this partly supports the cause-effect hypothesis. However, the data are still limited, but are consistent with cerebral imaging data showing increasing silent strokes in chronic (or permanent) AF compared to patients with paroxysmal AF.

Previous stroke is a strong driver for cognitive impairment. A recent systemic review found a strong correlation between stroke and dementia, which doubled the risk in older population. Cognitive impairment in AF patients compared to sinus rhythm was still evident even after exclusion of stroke patients.

The time at which AF was diagnosed was uncertain in most studies, with one exception and it is possible that a patient had been suffering with AF for years before being included in a particular study. There was a wide range of follow-up periods between studies, and studies with short follow-up period may have suffered from lead-time ascertainment bias (patients may have developed cognitive impairment or the impairment may have worsened if they had been followed up for longer). Further, in studies with a longer follow up, participants were more likely to be exposed to confounders, as they developed co-morbidities which are risk factors of cognitive impairment. The risk factors for AF and cognitive impairment overlap, increasing with old age and co-morbidities such as diabetes and hypertension, which are also more prevalent in older people. Hence, age alone may increase the risk of cognitive impairment and the mean age of the patients in each study is an important factor to take into consideration when interpreting the results. It is also possible that the cognitive decline started before the AF was evident. Antithrombotic treatment did not appear to influence cognitive impairment, and if the latter was the sequela of silent strokes, this may have been prevented by appropriate anticoagulant therapy.

Although not included in our semi-systematic review due to lack of a comparative control group, a community-based study in Minnesota provides some support for a link between AF and cognitive impairment. Miyasaka et al. measured the rate of dementia in stroke-free patients with newly diagnosed AF and found a cumulative rate of dementia of 10.5% at 5 years follow up. The occurrence of post-AF dementia was associated with significantly increased mortality risk (HR 2.9, 95% CI 2.5–3.3), even after adjustment for multiple co-morbidities, and did not vary with age (P = 0.75) or sex (P = 0.33). Bunch et al. compared the rate of Alzheimer’s disease in AF patients who underwent catheter ablation for AF and found significantly less Alzheimer’s disease in ablated patients (0.2% vs. 0.9% P < 0.0001). Again, treatment of AF may potentially reduce the risk of cognitive decline. Further, a study by Barber found that long-term warfarin use may reduce the risk of dementia in AF patients.

Limitations

There was marked heterogeneity in the design, sample size, quality of the studies and reporting of the data which precluded a formal meta-analysis. Also, many associated co-morbidities which may have contributed to the association of AF with cognitive impairment were not measured or analysed. Although many studies assessed cognitive function using the MMSE, this has many limitations and may be too crude to detect subtle declines in function.
which are common in vascular cognitive impairment.  

**Conclusions**

In this semi-systemic review, 8 out of 11 studies reported an association between AF and cognitive impairment and/or dementia, but the magnitude of risk varied. Further large-scale prospective cohort studies are needed to establish whether AF is a risk factor for cognitive decline, utilizing objective measures of cognitive function and neuropsychological testing, and to investigate the potential benefit of anticoagulation on reducing cognitive impairment and development of dementia.

**Conflict of interest:** None declared.

**References**