

Atrial Fibrillation and Cognitive Function: A Review

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Abstract:

A number of vascular risk factors and vascular diseases contribute to cognitive impairment and dementia. Many studies and registries show an association of atrial fibrillation (AF) with cognitive impairment, cognitive decline and dementia. This is true for vascular dementia and Alzheimer's disease. The assumed multifactorial mechanisms include ischemic stroke, both apparent and silent, cerebral micro-infarcts, cerebral hemorrhage and reduced cerebral blood flow. A number of retrospective observational and prospective studies support that anticoagulation in patients with AF may reduce the risk of cognitive decline and dementia. This holds for both vitamin-K antagonists (VKA, e.g. warfarin) and non-vitamin-K antagonist oral anticoagulants (NOACs). However, it still remains unproven, that anticoagulation reduces cognitive decline and dementia in AF patients, based on randomised trials.

Key words: atrial fibrillation - cognitive impairment - dementia - anticoagulation

Condensed Abstract: Studies and registries show an association of atrial fibrillation (AF) with cognitive impairment, cognitive decline and dementia. The assumed mechanisms include ischemic stroke, both overt and silent, cerebral micro-infarcts and reduced cerebral blood flow. Anticoagulation in patients with AF may reduce the risk of cognitive decline and dementia, however this remains unproven, based on randomised trials.

Abbreviations:

AD = Alzheimer's disease
AF = atrial fibrillation
CMB = cerebral micro-bleeds
HR = hazard ratio
ICH = intracerebral hemorrhage
INR = international normalized ratio
MMSE = Mini Mental State Examination
NOAC = non-vitamin-K oral anticoagulant
OAC = oral anticoagulant
OR = odds ratio
RR = relative risk
SD = senile dementia
TIA = transient ischemic attack
TTR = time in therapeutic range
VD = vascular dementia

Atrial fibrillation (AF) and dementia are predominantly diseases of elderly people. The incidence of AF and cognitive decline increases with advanced age, and the co-occurrence of these two frequent conditions might be explained by a common factor such as increasing age. A number of studies, however, indicate that vascular risk factors and vascular diseases not only contribute to vascular dementia but also to degenerative dementias such as Alzheimer's disease (1, 2). Importantly, AF increases the risk of stroke five-fold and stroke is an important risk factor and predictor of cognitive decline and dementia (3). Thus, a number of studies have indicated that the presence of AF might accelerate the risk of cognitive decline and dementia, even in patients without prior stroke.

This review article will provide an overview of the current knowledge on the relationship between AF, cognitive impairment and decline, and dementia and the possible role of anticoagulation for the prevention of dementia in patients with AF.

Is AF associated with cognitive impairment, cognitive decline, and dementia?

A number of prospective and retrospective studies have investigated the relationship between AF, cognitive decline and dementia (**Table 1**). The prospective Intermountain Heart Collaborative Study database evaluated 37,025 consecutive patients followed up them for a mean of 5 years for the development of AF and dementia (4). In this cohort 10,161 (27%) patients developed AF and 1,535 (4.1%) developed dementia - importantly AF was independently associated with all dementia types, with the highest risk in the younger group (<70 years). A posthoc-analysis of the ONTARGET and TRANSCEND studies showed that AF was associated with an increased risk of cognitive decline (hazard ratio [HR] 1.14, 95% confidence interval [CI] 1.03-1.26), new onset dementia (HR 1.30, 95% CI 1.14-1.49), loss of independence in performing activities of daily living (HR 1.35, 95% CI 1.19-1.54) and admission to long-term

care facilities (HR 1.53, 95% CI 1.31-1.79) (5).

The prospective Rotterdam study followed 6,514 dementia-free participants from 1989 to 2010 (6). and found that Prevalent AF increased the risk of dementia (HR 1.33; 95% CI 1.02-1.73). Among 6,196 participants without prevalent AF during 79,003 person-years of follow-up, 723 participants (11.7%) developed incident AF and 932 individuals (15.0%) developed dementia. As with other studies above, AF was associated with an increased risk of dementia in younger participants (<67 years). The Whitehall II study recruited 10,308 persons aged 33-45 years between 1985 and 1988 and followed them until 2013 (7). In this cohort incident dementia was more frequent in patients with AF compared to persons without AF (HR 1.87, 95% CI 1.37-2.55).

The relationship between AF and dementia is also evident from Asia. For example, a study from Taiwan identified 332,665 AF subjects without dementia from the "National Health Insurance Research Database". Found that patients with AF had a higher risk of dementia (HR 1.42, 95% CI 1.40-1.45) after adjustment for age, gender, baseline differences and medication use (8).

The relationship between AF, cognitive impairment and dementia was also shown in ameta-analysis. Kalantarian et al. (9) identified 21 studies with 89,907 participants and investigated the association of AF with cognitive decline and dementia. AF was significantly associated with a higher risk of cognitive impairment independent of a history of stroke (RR 1.34, 95% CI 1.13-1.58) (**Table 2**). The risk of dementia was also significantly increased (RR 1.38, 95% CI 1.22-1.56) (**Table 2**).

In summary, there is strong evidence from many prospective registries and studies that AF is associated with cognitive impairment, cognitive decline and dementia. This is also true for

patients without prior stroke. Such an association, however, does not necessarily imply a causal relationship, as there is very likely a multifactorial interaction with various cardiovascular risk factors involved, e.g. blood pressure control and renal function changes. The AF patient's risk profile is also dynamic and many risk factors change over time (10, 11); many of the reported associations are based on baseline risk and have not tracked temporal changes in risk.

Is AF associated with Alzheimer's disease or vascular dementia?

Alzheimer's disease and vascular dementia are by far the most common subtypes of dementia. Based on postmortem findings in relatively younger patients, Alzheimer's disease is characterized by neurodegenerative changes in the brain like amyloid depositions and neurofibrillary tangles. In the last decades accumulating evidence has established that stroke and cardiovascular disease are important risk factors not only of vascular dementia but also of Alzheimer's disease (4, 12-20).

Pre-clinical markers of cerebrovascular disease, which can be visualized with various imaging techniques, such as intima media thickness of the carotid artery and white matter lesions and lacunar infarcts in the brain, have likewise been related to Alzheimer's disease (17, 20-22). Besides cardiovascular disease, conventional vascular risk factors, such as hypertension, diabetes mellitus and smoking, have also been associated with an increased risk of Alzheimer's disease (23, 24). The similarity of the presumed underlying pathophysiology of vascular dementia and Alzheimer's disease is clinically relevant, as treatment of cardiovascular disease and vascular risk factors may potentially prevent a significant proportion of dementia cases, a disease for which no treatment is currently available (25).

The population-based Rotterdam Study previously showed that AF was more prevalent in participants with dementia (26) and a stronger association for Alzheimer's disease compared to

vascular dementia; however, the cross-sectional design of this study does not allow conclusions regarding a possible causal relationship. More recently, the Rotterdam Study explored the longitudinal relationship between AF and the risk of dementia, separately for prevalent and incident AF, and for all-cause dementia and Alzheimer's disease (6). In this cohort, Alzheimer's disease occurred in 787 of 994 (79%) participants with prevalent AF and in 741 of 932 (79%) with incident AF. For both prevalent and incident AF, associations were only slightly attenuated when Alzheimer's disease was separately investigated - in persons with prevalent AF, the HRs for all-cause dementia was 1.33 (95% CI 1.02-1.73) versus a non-significant 1.29 (95% CI 0.95-1.75) for Alzheimer's disease, and in those with incident AF, the HRs were non-significant for all-cause dementia 1.23 (95% CI 0.98-1.56) versus 1.18 (95% CI 0.91-1.54) for Alzheimer's disease.

Since dementia gradually develops over many years, AF probably needs to develop at a younger age to contribute to the neuropathology of underlying dementia, i.e. the typical Alzheimer changes or vascular lesions or both. Associations of other vascular risk factors of dementia, such as hypertension, hypercholesterolemia, and obesity also appear to differ with age; these elements are risk factors for dementia only when diagnosed earlier in life (27-29).

Similarly, if AF is a causal factor in the etiology of dementia, one would expect that the longer a person suffers from this condition, the higher the risk of dementia would be. Indeed, the Rotterdam Study demonstrated that the risk of either all-cause dementia or Alzheimer's disease was highest for people who suffered the longest duration of AF, although this dose-response relationship was only present in younger participants. In contrast, a Finnish study concluded that the presence of AF in mid-life was not a risk factor of subsequent dementia, whereas late-life AF was (30); however, survival bias might have influenced these results, because only persons who

survived until a late re-examination were included in the study.

In summary, AF probably increases the risk of both vascular dementia and Alzheimer's disease, however the relationship to dementia is most probably stronger when AF starts at middle age and with a longer-duration of AF.

What are the mechanisms leading to cognitive decline and dementia in patients with AF?

AF-associated cognitive decline occurs even in the absence of clinical strokes. Clinically recognized strokes are only the tip of the iceberg of AF-induced brain ischemia. Covert (i.e. silent) brain infarcts detected by neuroimaging in AF patients are more frequent than clinical strokes (31) and are associated with cognitive dysfunction (32) (Table 3). In addition to macroscopic covert brain infarcts, smaller cerebral micro-infarcts (beyond the resolution of conventional neuroimaging) are linked to cognitive impairment (33) and AF is an independent risk factor for such cerebral micro-infarcts (34). Indeed, the Atherosclerosis Risk in Communities Study observed that cognitive decline in patients with AF was only observed in those who had subclinical cerebral infarcts (35). Hence, unrecognized embolism is a plausible mechanism underlying AF-associated cognitive impairment and dementia.

Reduced cardiac output in the absence of clinical heart failure is associated with reduced cerebral blood flow in the elderly, particularly blood flow to the temporal lobes (36) and this has been associated with incident dementia, including Alzheimer's disease (37). AF is associated with reduced cardiac output and cerebral blood flow (38, 39), and chronic cerebral hypoperfusion could play a role (which is unresponsive to anticoagulation) in AF-associated cognitive decline. If so, then efforts to re-establish sinus rhythm could have a beneficial effect on cognition – at least theoretically. In the largest randomized trial so far, assignment to rhythm control had no benefit on cognition, but this was potentially confounded by unequal use of

anticoagulation (39). This is being further assessed in a large ongoing randomized controlled trial (EAST) (40). Other potential mechanisms also warrant consideration (**Table 4**).

On balance, subclinical embolic brain ischemia (covert brain infarcts, cerebral micro-infarcts) is likely to account for most of the cognitive deterioration associated with AF, but until further established by response to anticoagulants based on randomized trials, (for example, BRAIN-AF NCT02387229) this remains unproven.

How might treatment of AF decrease the risk of cognitive decline and dementia?

If we assume that dementia and AF are associated we can perhaps assume that anticoagulation might reduce the risk of cognitive decline and incident dementia in patients with AF.

There is some suggestive evidence from observational studies that anticoagulation of AF patients (and good time in therapeutic range (TTR) with warfarin anticoagulation) is associated with reduced cognitive decline (41), supporting the contribution of embolism to cognitive impairment. However, potential confounding in these observational studies limits confidence in a cause-effect relationship.

One randomized trial did not report a difference in cognition between AF patients treated with warfarin versus aspirin during 2.7 years of follow-up, but assessment of cognition was insensitive for decline (42). Another small prospective longitudinal cohort study in the UK did not find an effect of antithrombotic therapy in patients with AF on cognitive function (43).

A systematic review of 19 studies assessed the association between cognitive impairment and AF thromboprophylaxis (44). One randomized controlled trial, comparing anticoagulation against antiplatelet therapy and change in MMSE score from baseline to last follow-up (maximal duration: 5.9 years) suggested a nonsignificant difference perhaps favoring anticoagulation

(mean difference: 0.90, 95% CI: 0.29-1.51). Another randomized controlled trial found a mean difference in MMSE score of 0.80 (95% CI: -0.07 to 1.67) in favor of anticoagulation. The pooled odds ratio (OR) suggested no association with incident dementia, when comparing anticoagulant to antiplatelet therapy (two studies, Odds Ratio (OR): 1.23, 95% CI: 0.80-1.91) or no treatment (three studies, OR: 0.89, 95% CI: 0.47-1.69). Thus, there was no definitive evidence of cognitive benefit or harm from anticoagulation.

When VKAs are used as thromboprophylaxis, the efficacy and safety are closely related to the quality of anticoagulation control, as reflected by the average TTR(45). This is relevant to the impact on dementia. For example, decreasing categories of percentage TTR were associated with increased dementia risk (vs TTR>75%) as follows: <25%: HR 5.34, P < .0001; 26%-50%: HR 4.10, P < .0001; and 51%-75%: HR 2.57, P = .001(46).

The Olmsted County population-based study also investigated the association of TTR during warfarin therapy and risk of dementia in 2800 non-demented AF patients (41). Incident dementia diagnosis occurred in 357 patients (12.8%) over a mean follow-up of five years. After adjusting for confounders, warfarin therapy was associated with a reduced incidence of dementia (HR 0.80; 95% CI, 0.64-0.99); however, only those in the 2 highest quartiles of TTR were associated with lower risk of dementia. Overall, better quality of anticoagulation management represented as percentage TTR among AF patients without dementia seems to be associated with lower dementia incidence.

In recent years, the NOACs have changed the landscape of stroke prevention in AF, with their increasing use in many countries compared to warfarin (47). The question arises as to whether NOAC use may be associated with a lower risk of new-onset dementia compared to warfarin. In a propensity-matched analysis, patients taking NOAC were 43% less likely to develop

stroke/TIA/dementia than those taking warfarin but this difference was non-significant (HR 0.57; 95% CI 0.17 - 1.97; p = 0.38)(48).

Further, a retrospective registry study of all patients with hospital diagnosis of AF and no previous diagnosis of dementia in Sweden between 2006 and 2014 investigated the possible impact of anticoagulation on the incidence of dementia in patients with AF (49). Propensity score matching, falsification endpoints, and analyses according to intention-to-treat as well as on-treatment principles were used, and the study included 444,106 patients and over 1.5 million person years at risk. Patients without prior stroke on anticoagulant treatment at *baseline* had a 29% lower risk of dementia than patients without anticoagulant treatment (HR 0.71, 95% CI 0.68-0.74) with a 48% lower risk when analyzed on treatment (HR 0.52, 95% CI 0.50-0.55). Direct comparisons between NOACs and warfarin showed no significant difference.

A possible mechanism underlying the observed benefit of anticoagulation could be the prevention of cerebral micro-emboli and silent brain infarcts. The benefit of OAC treatment was more pronounced among patients in whom treatment had been initiated early after the first diagnosed AF episode suggesting that there could be a dose-response relationship between unprotected time in AF and development of dementia. There was also a trend towards more benefit from treatment in patients with higher CHA₂DS₂-VASc scores supporting the notion that micro-embolization might be a cause of dementia in AF patients.

In summary, we have only indirect evidence that effective anticoagulation in AF reduces the risk of cognitive impairment and dementia. Nevertheless, these observational results are supportive in arguing for the initiation of prospective clinical trials on the possible benefit of anticoagulation in AF for the prevention of cognitive decline and dementia.

Impact of rhythm control

Cardioversion or AF ablation may result in sinus rhythm and improve cardiac output and cerebral perfusion. In the Intermountain AF study, for example, Bunch et al (50) compared 4,212 consecutive patients who underwent AF ablation to 16,848 age/gender matched controls with AF (no ablation) and 16,848 age/gender matched controls without AF, who were followed up for at least 3 years. Of the 37,908 patients, Alzheimer's dementia occurred in 0.2% of the AF ablation patients compared to 0.9% of the AF non-ablation patients and 0.5% of the non-AF patients ($P < 0.0001$). Other forms of dementia were also reduced significantly in AF patients treated with ablation.

Prospective randomized trials investigating the potential benefit of rhythm control or cardioversion in AF would need to run for at least 10 years to show an impact on cognitive decline and dementia, and would require many thousands of patients. Therefore, it is unlikely that such trials will ever be funded.

Practical considerations

Elderly patients with AF and cognitive impairment can be difficult to treat with oral anticoagulation. Anticoagulation should only be initiated and maintained if a family member/carer or nurse supervises drug intake. In the case of VKAs, adequate INR control and continued adherence with therapy is required to avoid adverse outcomes (51, 52). With the NOACs, drug adherence is crucial given the relatively short half-life of these drugs (53).

Another unresolved practical issue is the question of whether anticoagulation should be introduced in AF patients with CHA₂DS₂-VASc score of 0-1 in males or 1-2 in females who have covert (i.e. silent) brain infarcts detected by neuroimaging performed due to various clinical indications or in patients with mild cognitive decline (no previous stroke or transient ischemic attack) or not. If silent infarcts show an “embolic” pattern (e.g. multiple infarcts in different vas-

cular territories) this appearance might justify anticoagulation use (35). Considering the relatively weak evidence that anticoagulation in AF prevents the progression from cognitive impairment to dementia, we would not recommend anticoagulation in these patients simply for the prevention of dementia at the present time.

Patients with cognitive impairment and dementia also have a higher risk of falls (54). While a very high risk of falls might constitute a contraindication for anticoagulation, it has been estimated that a patient would need to fall 295 times per year for the benefits of ischemic stroke reduction with anticoagulation to be outweighed by serious bleeding risks (55). The present availability of a specific reversal agent for dabigatran (Idaruzicumab) (54) and andexanet alfa for antiXa inhibitors (56) where available, makes the management of NOAC-induced major hemorrhage or injury much easier (57).

Conclusions

A number of recent epidemiological studies have reported an association of AF with cognitive impairment, cognitive decline, and dementia. The risk of dementia was increased both for total dementia and Alzheimer's disease with HRs ranging from 1.03 to 2.9, with the association between AF and dementia being strongest for patients aged <65 years. The increased risk of dementia was seen for vascular as well as Alzheimer's disease, but this is perhaps unsurprising since dementia and AF share a number of common vascular risk factors such as hypertension, heart failure, diabetes and lipid disorders. Other common risk factors include age, obesity and physical inactivity. Also, silent strokes and micro-bleeds are more common in patients with AF than in patients in sinus rhythm.

In our view, the data are sufficient to regard AF as an independent cardiovascular risk

factor for accelerated cognitive impairment and dementia. Clinical stroke is only part of the story of AF-associated brain ischemia; the most likely mechanism linking AF and cognitive impairment is covert embolism to the brain causing silent (macro) brain infarcts and cerebral micro-infarcts. Chronic cerebral hypoperfusion is also plausible. While it is tempting to justify initiation of anticoagulation, it remains unproven thus far that anticoagulation (which is so effective for reducing clinical stroke) also reduces cognitive decline and dementia in AF patients. This is currently being investigated in a number of ongoing clinical trials.

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Figure Legends

Figure 1: Relationship between atrial fibrillation, cognitive decline and dementia via different mechanisms. (adapted from Kalantarian & Ruskin, *Cardiol Clin* 2016)(58). Atrial fibrillation can lead by a number of mechanisms to thrombus formation in the left atrial appendage and cause clinical stroke or silent stroke. Both lead to morphological changes in the brain promoting cognitive decline or dementia. Genetic factors can contribute to both, dementia and atrial fibrillation. A number of vascular diseases and vascular risk factors have been associated with cognitive decline and dementia.

Table 1

Association of AF with cognitive impairment or dementia. Results from 5 prospective registries. Odds ratios and (95% confidence intervals)

Study	N	Follow-up (Years)	Cognitive Decline	Dementia
Bunch et al (4)	37025	5		1.06-1.73*
Marzona et al. (5)	31506	5	1.14 (1.03-1.26)	1.30 (1.14-1.54)
De Bruijn et al. (6)	6514	21		1.33 (1.02-1.73)
Sing-Manoux et al. (7)	10308	15	1.87 (1.37-2.55)	
Liao et al (8)	332665	15		1.42 (1.40-1.45)

*Odds ratios across 4 subgroups of dementia; 95% CI not provided

Table 2

Association of AF with cognitive impairment or dementia. Results from a meta-analysis of 14 studies with 31506 AF patients and controls (9). RR = relative risk

Parameter	N studies	RR	(95% CI)
Association between AF and cognitive impairment with or without stroke	14	1.40	1.19-1.64
Association between AF and dementia	8	1.38	1.22-1.56
Association between AF and cognitive impairment	9	1.50	1.18-1.91
AF and cognitive impairment independent of stroke	10	1.34	1.13-1.58
AF and cognitive impairment after stroke	7	2.70	1.82-4.00

Table 3. Association of AF and silent cerebral infarctions. Results from a meta-analysis of 11 studies with 5317 AF patients and controls (59) OR = Odds ratio

Parameter	N studies	OR	(95% CI)
Association of AF and silent cerebral infarction, MRI	5	2.30	1.44-3.68
Association of AF and silent cerebral infarction, CT	4	3.45	2.03-5.87
Prevalence of silent cerebral infarction in AF patients, MRI	9	0.40 (40%)	0.29-0.51
Prevalence of silent cerebral infarction in AF patients, CT	6	0.22 (22%)	0.12-0.32

Table 4. Potential mechanisms underlying atrial fibrillation (AF)-associated cognitive impairment

Association	Genetic predisposition common to both dementia and AF	
	Shared risk factors (e.g. age, hypertension, diabetes)	
Causation	Clinical stroke	
	Covert/silent (macro) brain infarcts detected by neuroimaging	
	Cerebral microinfarcts caused by:	Microembolism
		AF-associated prothrombotic state
		AF-induced neuroendocrine perturbations (e.g. BNP)
		Hypoperfusion
		Inflammation
	Reduced cerebral blood flow	
Epiphenomenon	Treatment for AF causes cognitive impairment (e.g. beta-blockers)	