Review Article

Cognitive Function in Atrial Fibrillation: A Narrative Review of Evidence and Mechanisms

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Abstract

Atrial fibrillation (AF) is associated with cognitive impairment, with or without history of stroke. The risk of developing cognitive impairment is increased after clinical stroke. Prospective registries confirm the increased risk of both vascular and Alzheimer's dementia in patients with AF. The purported mechanistic links between AF and cognitive impairment are clinical stroke, subclinical cerebral small-vessel disease, autonomic dysfunction, and systemic and neuroinflammation. Several shared risk factors and genetics also contribute to this interplay. In this review, we explore the evidence bridging cognitive impairment with AF and review the mechanisms and therapeutic targets.

Keywords: Atrial fibrillation, cognitive impairment, dementia, neurocognitive disorder, subclinical infarction

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia with an estimated lifetime risk of 1 in 3 for white people and 1 in 5 for people of colour.[1,2] The risk of AF increases with age and burden of clinical risk factors. The prevalence increases from 0.12% to 0.16% in patients younger than 50 years to 13.5%–17.8% in those over 80 years of age.[3] The worldwide prevalence of AF is approximately 60 million, affecting 1%–3% of the population and has increased over 3-fold in the last five decades.[4] It is further expected to increase by >60% by 2050, leading to considerable morbidity, mortality, and disability.[1,5]

The epidemiology of dementia appears similar with an estimated 55 million individuals currently living with this neurodegenerative condition.[6] It is estimated to more than double by 2050 exerting a massive health burden on the growing population.[6,7]

Large population-based studies have shown that AF is associated with a risk of developing vascular and Alzheimer's dementia even in stroke-free individuals.[8-13] This risk was noted to be higher in the individuals younger than 70 years in population-based studies.[8,14] AF increases the risk of Alzheimer's disease by 30%–50% and doubles the risk of developing vascular dementia.[12,13] In the SAFETY study, mild cognitive impairment (MCI) as defined by Montreal Cognitive Assessment (MoCA) <26 was found in 65% of elderly hospitalized patients with AF across three tertiary care hospitals in Australia.[15] The *post hoc* analysis of ONTARGET and TRANSCEND, two large randomized controlled trials, showed a 40% greater risk of severe cognitive impairment in participants with AF.[16] Multiple meta-analyses confirmed a similar increased risk of severe cognitive impairment with AF in population studies even in the absence of clinical stroke [Table 1].[17-23] However, in the poststroke cohort, AF was associated with a 2.70-fold increased risk of cognitive impairment.[17] The population living with both AF and cognitive impairment is expected to become a major public health challenge with aging of the general population [Figure 1].

The etiology of cognitive impairment in patients with AF is multifactorial. We aim to summarize the evidence linking

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Table 1: Meta-analyses evaluating the association between atrial fibrillation and cognitive impairment

Meta-analyses	Number of included studies	Number of participants	Inference
Koh *et al*., 2022	61	822,794	39% increased risk of cognitive impairment in general population with AF 2.7 times increased risk in poststroke cohort AF associated with SCI, SVD, and white matter hyperintensities even in absence of clinical stroke
Papanastasious *et al*., 2021	43	231,564 poststroke 352,494 stroke-free	AF had significant association with dementia (OR = 1.6, 95% CI = 1.3–2.1), vascular dementia (OR = 1.7; 95% CI = 1.2–2.3), and Alzheimer's dementia (HR = 1.4; 95% CI = 1.2–1.6)
Kokkinidis *et al*., 2020	14	14,360 patients with prior history of stroke	AF associated with increased risk of composite endpoint of cognitive impairment or dementia in patients with prior history of stroke (OR = 2.26, 95% CI = 1.611–3.19)
Stefanidis *et al*., 2018	5	-	AF associated with significantly increased risk for cognitive decline (HR = 1.26, 95% CI = 1.12–1.43)
Myserlis *et al*., 2017	5	1,670 patients with heart failure	In patients with heart failure, AF is significantly associated with the risk of cognitive impairment (OR = 1.94; 95% CI = 1.30–2.87)
Kalantarian *et al*., 2013	21	89,907	AF significantly associated with cognitive impairment In patients with first-ever or recurrent stroke (RR = 2.70, 95% CI = 1.82–4.00) In all comers (RR = 1.40, 95% CI = 1.19–1.64) In patients without stroke history (RR = 1.34, 95% CI = 1.13–1.58)

OR=Odds ratio, CI=Confidence interval, AF=Atrial fibrillation, HR=Heart rate, SCI=Subclinical cerebral infarction, SVD= Small vessel disease, RR=Relative risk

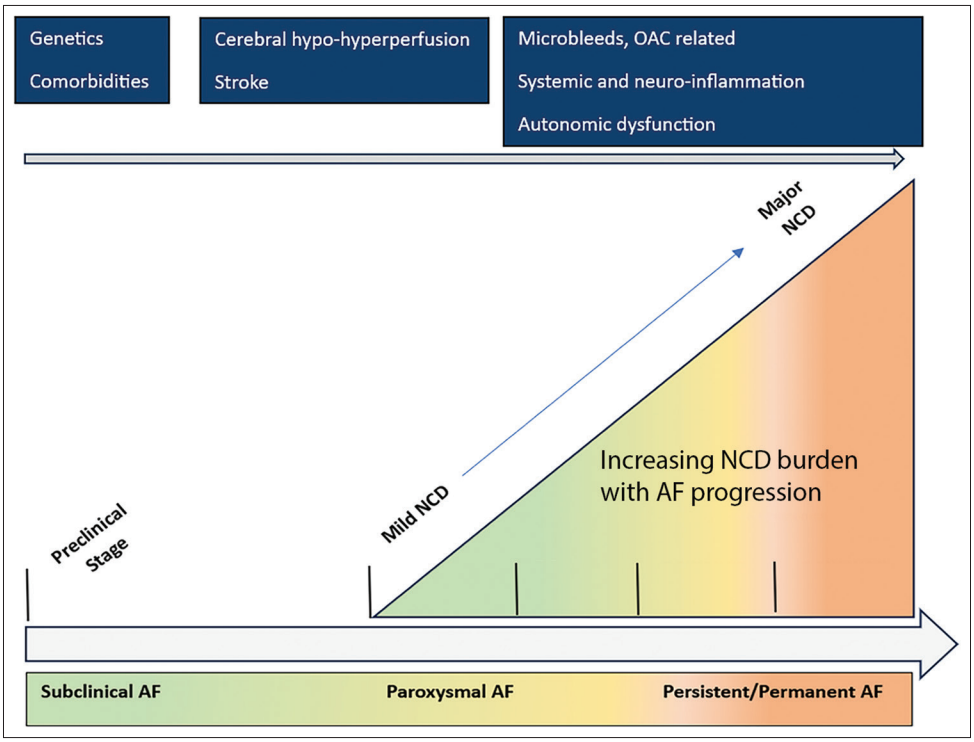

Figure 1: Progression of atrial fibrillation and neurocognitive disorders. OAC = Oral anticoagulant, NCD = Neurocognitive disorder, AF = Atrial fibrillation

AF with cognitive impairment and their mechanistic links. We further review the current literature to explore potential therapeutic options including early detection, follow-up, and treatment.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition categorizes dementia as "Neurocognitive Disorder" (NCD) and classifies it into MCI or Prodromal Disease and Major NCD. MCI refers to decline in cognitive performance without impairment of independence or activities of daily living. Major NCD is related to substantial cognitive impairment that interferes activities of daily living.[24,25] For the purpose of this review, we use the terms "cognitive decline," "cognitive impairment," and "cognitive dysfunction" and "dementia" interchangeably as they have been used in clinical studies and trials and they refer to the broad spectrum of NCD.

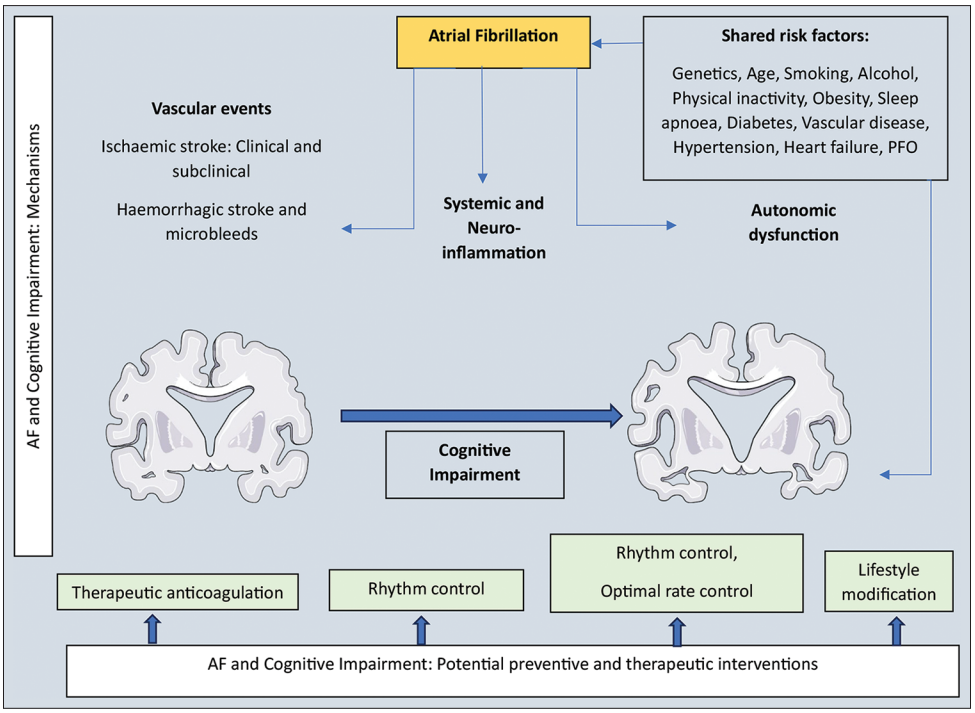

Figure 2: Mechanistic links between atrial fibrillation and neurocognitive disorders and proposed strategies. AF = Atrial fibrillation, PFO = Patent foramen ovale

Atrial Fibrillation Burden and Neurocognitive Disorders

AF burden may be directly related to the risk of NCDs. A small study comparing cognitive function among patients with paroxysmal AF (AF burden 1%–6%) and persistent AF (AF burden 100%) as assessed by Zio Patch found that only persistent AF was associated with cognitive dysfunction.[26] However, the study had profound limitations with respect to sample size and short duration of monitoring. Larger studies using the Zio Patch have shown that AF burden predicts MoCA score even after multivariable adjustment.[27,28]

Using the comprehensive Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test for cognition assessment, Gaita *et al*. provided the evidence for increased risk of subclinical cerebral infarction (SCI) as well as cognitive dysfunction in patients with paroxysmal and persistent AF compared to controls.[29] The risk appeared to be related to AF burden with persistent AF demonstrating greater cognitive decline compared to paroxysmal.

Subclinical AF (SCAF) refers to atrial high-rate episodes detected by continuous monitoring on implanted cardiac devices. A secondary analysis of the large LOOP study revealed no effect of SCAF on cognitive function assessed by MoCA.[30] However, the defined cutoff for SCAF was 6 min. It has been previously shown that SCAF has been associated with stroke only if episodes last longer than 24 h.[31] A previous meta-analysis has demonstrated that SCAF leads to a high risk of progression to clinical AF as well as stroke.[32] Furthermore, the patients in LOOP study were treated by oral anticoagulants (OACs) that could have mitigated any ischemic stroke risk in these participants. Regardless, there is currently no evidence that SCAF can lead to cognitive decline.

Assessment of Cognitive Function in Patients with Atrial Fibrillation

The AF-SCREEN collaboration that comprises >170 physicians and allied professionals from over 37 countries recommends using a simple screening question to assess the risk of NCD in AF patients as a baseline. This entails asking if the patient has had any memory or thinking problems in the preceding 1 year and if this affects daily activities.[33] While this simple assessment may serve as a basic screen, a more detailed assessment of cognition may be needed using tests that evaluate specific domains.

An early neuropsychological assessment can help in defining subsets at risk of further decline and promote better monitoring of cognitive function. Both cortical and vascular dementia has been reported in AF and it appears that all domains of cognitive function are affected.[29,33] These domains include attention, learning and memory (immediate, recent, and long term), executive function, language, visuospatial abilities, processing speed, and social cognition.[25]

The commonly used instruments used for assessing cognitive function in participants with AF in clinical studies are summarized in Table 2. Simple screening tests can include, apart from the question above, clock-draw-test and mini-cog.

Table 2: Commonly used cognitive assessment instruments in participants with atrial fibrillation in clinical studies

Short cognitive tests	Intermediate cognitive tests	Longer cognitive tests
Basic question	MMSE	CERAD
Clock-draw-test	MoCA	RBANS
Mini-cog		
Useful as screening tool	Domain-specific information available	Longer time to administer (>15 min)
Insensitive to subtle dysfunction	Less data on follow-up assessment	Ability to assess subtle impairment
Insensitive to assess changes	MoCA: Less useful in moderate to severe dementia due to difficulty in completion. More useful for early cognitive decline	More useful to assess disease progression
	MMSE: Better suited to monitor decline in cognitive function	

MMSE=Mini Mental Status Examination, MoCA=Montreal Cognitive Assessment, CERAD=Consortium to Establish a Registry for Alzheimer's disease, RBANS=Repeatable Battery for the Assessment of Neuropsychological Status

These tests have limited ability to detect subtle dysfunction and cannot be used to monitor progress of disease.[34,35] Commonly used tests in studies have been the Mini Mental State Examination (MMSE) and MoCA. They may be more sensitive to detect MCI and domain-specific function. However, their utility on assessing disease progression is limited and considerable biases exist with regard to age, socioeconomic background, and education of participants.[36] Longer length tests include the Consortium to Establish a Registry for Alzheimer's Disease and the RBANS.[37-39] While these tests provide more comprehensive information about domain-specific cognitive function and are more sensitive to assess changes and disease progression, a formal neuropsychological assessment remains the gold standard supplemented by brain imaging if dementia is suspected.

Atrial Fibrillation and Neurocognitive Disorders: Mechanistic Links

Shared risk factors

Both AF and NCD are complex disease entities with multiple shared and independent genetic and environmental risk factors. These include nonmodifiable (age and genetics) and modifiable risk factors (lifestyle factors like obesity and physical inactivity) as well as cardiovascular risk factors (diabetes, hypertension, and obstructive sleep apnea). Acquired risk factors may play a role in the modulation of genetic risk to cause neurocognitive decline [Figure 2].[40,41]

The genetic susceptibility to cognitive impairment in patients with AF may explain the paradoxically higher risk seen in younger patients.[42] There is preliminary evidence that genetically mediated AF may be associated with increased risk of overall dementia as well as vascular dementia but not Alzheimer's or Lewy body dementia. This risk appears to be primarily mediated through stroke and low cardiac output.[41] However, in patients with genetic risk of AF but no clinical AF, this does not translate into increased risk of dementia, providing strong implication for AF in dementia causation.[43] The PITX2 loci have been associated with incident AF, and among patients with AF, it strongly correlates with incident dementia.[44]

Several environmental and modifiable risk factors are common between AF and cognitive decline and include lifestyle variables (diet, smoking, alcohol intake, and physical inactivity) as well as cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, and obesity).[45] Accumulation of risk factors is known to increase the risk for both AF and dementia.[46] The role of patent foramen ovale in brain health is investigational due to the association with paradoxical embolism.

Despite prior research utilizing extensive multivariate adjustment, the effect of confounding factors interlinking AF and dementia remains a major concern. However, several findings point toward a causative role of AF independent of the common risk factors shared with dementia. These include an absence of cognitive decline in phenotypically negative AF but carrying AF-related genes, greater cognitive decline in patients with persistent AF compared to paroxysmal AF, and improvement in cognitive function with AF ablation.[14,29,43]

Stroke, atrial fibrillation, and cognitive function

Stroke is an independent risk factor for new-onset cognitive impairment in patients with AF.[47] It doubles the lifetime risk of developing dementia with the risk apparent as early as 3 months poststroke.[48-50] In addition, in patients with AF-related ischemic stroke/transient ischemic attack, up to a quarter have preexisting cognitive decline.[51,52] Cognitive impairment after stroke is associated with worse functional outcomes, dependency, disability, depression, and poor quality of life.[50] Similarly, cognitive impairment before a stroke event may predict poorer functional outcomes in these populations.[51]

The mechanisms of poststroke cognitive decline have been postulated to be immunological as well as inflammatory with white matter changes, amyloid deposition in cerebral vasculature, and hypertension acting in unison.[48,53,54]

In patients with AF, up to two-thirds have silent strokes also known as silent cerebral ischemia.[55] While the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65–74 years and sex category [female]) score predicts the risk of clinical stroke, its utility in determining the risk of SCI has not been well studied. In the Swiss-AF cohort, CHA_2DS_2-VASc score did appear to correlate with the risk of silent strokes as determined by magnetic resonance imaging (MRI).[56,57] The impact of silent cerebral infarcts on cognitive decline has been studied in several clinical

studies. The Swiss-AF cohort showed that despite high rates of anticoagulant use, silent cerebral infarcts were common in patients with AF, and these had similar cognitive decline as overt brain infarcts.[55] Meta-analyses of studies using both MMSE and MoCA have shown a positive correlation between SCI and cognitive decline.[58,59]

Silent cerebral infarcts may lead to ischemic demyelination with consequent small-vessel disease. The presence of small-vessel disease on brain imaging has been shown to correlate with acute cognitive dysfunction and failure to improve cognitive scores at 1 year. In the ARIC study, participants with AF and silent infarcts experienced cognitive decline in executive function, while those with incident AF without silent infarcts did not, providing evidence for vascular mechanisms as being responsible at least partly for neurocognitive dysfunction.[60]

Another vascular aspect of dementia causation in AF is occurrence of cerebral microbleeds (CMBs). Patients with CMBs are also paradoxically at higher risk of ischemic stroke. CMBs result from cerebral microangiopathy with minor bleeding and consequent hemosiderin deposits into the brain. It has been postulated that CMBs result from OAC use among AF patients, with higher incidence in patients on warfarin therapy compared to novel OAC (NOAC) use. Supratherapeutic international normalized ratio (INR) has been shown to be a risk factor for NCD. Previous meta-analyses have shown twice the risk of dementia or MCI in patients with CMBs compared to those without.[61] The presence of CMBs is an independent risk factor for recurrent ischemic strokes, intracerebral hemorrhage, and future mortality, even among patients on OAC.[62]

Autonomic dysfunction in atrial fibrillation

In the Swiss-AF cohort, cardiac autonomic function and cognitive function were studied in participants with AF. Impaired heart rate (HR) variability and higher mean HR were independently associated with poorer cognitive scores in AF patients.[63] Each 10-unit change of HR variability triangular index led to 0.7 MoCA points change.[63] Both higher (>100 bpm) and lower (<60 bpm) average HRs have been associated with incident dementia. However, data assessing the treatment outcomes of HR control on neuropsychological manifestations of AF are lacking.[47]

Cerebral blood flow (CBF) as well as cerebrovascular reserve has been found to be impaired in patients with AF.[64] AF leads to beat-to-beat variability in HR and cardiac output and this may impact both short-term and long-term cerebral autoregulation and blood–brain barrier.[42] With varying systole and diastole, ventricular filling periods are altered with consequent alterations in CBF. This series of irregular hypo-hyperperfusion leads to compensatory microvascular changes that eventually become maladaptive and lead to fulminant vascular pathology.[65] Among heart failure patients with AF, reduced CBF velocity in middle cerebral artery has been observed and this has been linked to cognitive dysfunction.[66] Computational modeling has shown that AF leads to periods of hyperperfusion as well as hypoperfusion in CBF, with the greatest effect seen distally at the arteriolar and capillary ends. Altered pulsatile hemodynamics of CBF may, in part, contribute to cognitive dysfunction seen with AF.[67] Greater small-vessel disease and white matter hyperintensities with consequent cognitive decline appear to play a role in these patients.[68,69]

Systemic inflammation

AF and systemic inflammation have a bidirectional, cyclical relationship where one begets, and potentially exacerbates, the other. Inflammatory cytokines including interleukin-6 (IL-6) and C-reactive protein (CRP) are elevated in patients with AF compared to controls, with greater elevations in patients with persistent AF as compared to paroxysmal AF.[70] Complement activation has also been well described in AF subsets and C3 and C4 levels modulate effects of CRP on AF occurrence.[71] Serum YKL-40, a myocardial inflammatory marker, correlates with the risk of AF.[72]

Apart from stroke, other mechanisms underlie systemic inflammation-induced cognitive decline. IL-6 has been shown to lead to endothelial dysfunction and vascular inflammation.[65,73] Ensuing neuroinflammation can lead to endothelial dysfunction and oxidative stress, ultimately leading to cerebral microstructure disintegration, neuronal, and neuroglial cell death.[65,74,75]

Using near-infrared spectroscopy, Yoshihisa *et al*. have been able to demonstrate decreased frontal and temporal lobe activity in AF patients and a decrease in MMSE scores in these subsets.[76]

Atrial Fibrillation and Neurocognitive Disorders: Therapeutic Strategies

Lifestyle changes

Lifestyle interventions provide an easy-to-apply, feasible, and cost-effective way to address these complex subsets [Table 3]. Lifestyle changes have been known to impact burden of AF as well as its complications.[18,77,78] However, their role in preventing cognitive decline in AF is not well systematically evaluated. It would be prudent to assume that with their effect on AF burden and cardiac remodeling, lifestyle interventions would eventually lead to better cognitive outcomes. In unselected elderly populations at risk, multidomain interventions targeted at promoting healthy lifestyle changes have been shown to improve or maintain cognitive function in blinded randomized trials.[79] These include interventions targeted at weight, diet, social activities, stress, anxiety and depression, physical activity, alcohol and smoking, and education about self-management.[79-81]

In a Korean population study, the risk of incident dementia was 13% lower among patients who started on exercise and 34% in those who maintained exercise. This risk reduction was greatest in those who exercised at 5–6 times per week with moderate-to-vigorous exercise.[82] Cerebral perfusion increases in proportion to an increase in cardiac output.[82]

Both Mediterranean and Dietary Approach to Systolic Hypertension (DASH) diets have been shown to positively affect

cognitive function. Specifically, the Mediterranean-DASH diet intervention for neurodegenerative delay diet has been studied extensively for prevention of Alzheimer's disease/cognitive dysfunction in the general population.[83] Similarly, weight loss has been shown to lead to improvement in memory, language, and attention in randomized controlled trials, but the magnitude of weight loss required, and the impact of confounding factors remain undetermined.[84] The role of yoga and meditation is also investigational in people with cognitive impairment.[85] However, its role is limited by lack of randomized controlled trials, and absence of homogeneity in the frequency, duration, and components of the intervention.[85,86]

Oral anticoagulation

The benefits of anticoagulation in preventing new-onset dementia remain unclear. The BAPTA study randomized patients to aspirin or warfarin (targeted to INR 2–3) but found no difference in cognitive outcomes at 33 months. However, patients who developed stroke were censored in the final analysis, which points to the predominant stroke prevention role of OAC in cognitive function preservation of these drugs.[87]

Among patients with a higher ischemic risk assessed by CHA_2DS_2-VASc score but no history of stroke or cognitive dysfunction, OAC has been shown to reduce the risk of developing new-onset dementia compared to aspirin or no therapy. The benefit may be greater for warfarin if time in therapeutic range (TTR) ≥65%.[88]

In a large meta-analysis including 8 studies with over 470,000 participants with AF, OAC significantly reduced the risk of cognitive impairment with newer OACs (NOACs: edoxaban,

Table 3: Suggested management strategy to prevent or delay cognitive impairment in patients with atrial fibrillation

Lifestyle changes	Managing comorbidities
Weight reduction (≥10% or BMI <27 kg/m^2 in AF suggested, impact on cognitive function unclear) Physical activity: At least 150 min of moderate physical activity per week Alcohol: Limiting alcohol intake Smoking and tobacco: Abstention Sleep: Poor sleep related to NCD. Impact of pharmacological interventions currently unclear Anxiety: Cognitive behavior therapy, mindfulness Social: Social engagement and community support	Diabetes (target <7%) Hypertension (target ≤130/80 mmHg) Dyslipidemia: Guideline recommended lifestyle and pharmacological treatment Obstructive sleep apnea: Continuous positive airway pressure
NCD	**AF management**
Assess early (simple screening tools can help) Early referral to a neuropsychologist for evaluation and management	Mitigate stroke risk: OAC for high stroke risk; NOACs preferred OAC If using warfarin, TTR important Rate control Rhythm control

BMI=Body mass index, NCD=Neurocognitive disorder, OAC=Oral anticoagulant, NOAC=Novel oral anticoagulants, TTR=Time in therapeutic range, AF=Atrial fibrillation

Table 4: Meta-analyses evaluating the impact of oral anticoagulation on cognitive impairment in patients with atrial fibrillation

Meta-analyses	Number of included studies	Number of participants	Inference
Lee *et al*., 2021	9	611,069	NOAC use associated with lower composite risk of dementia compared to warfarin group (OR = 0.56, 95% CI = 0.34–0.94) Apixaban and Rivaroxaban (vs. warfarin) associated with lower risk of composite dementia outcomes but not dabigatran
Zeng *et al*., 2019	8	454,273	Anticoagulation associated with lower risk of cognitive impairment compared to no anticoagulation in patients with AF (RR = 0.72, 95% CI = 0.69–0.75) independent of stroke/TIA
Mongkhon *et al*., 2019	6	452,878	OAC use was protective against dementia (RR = 0.79, 95% CI = 0.67–0.93) High percentage of TTR associated with reduced risk of dementia in warfarin users (RR = 0.38, 95% CI = 0.22–0.64)
Cheng *et al*., 2018	8	471,057	OAC associated with lower cognitive impairment risk compared to no OAC in AF patients (HR = 0.71, 95% CI = 0.69–0.74) NOACs associated with lower cognitive impairment risk compared to warfarin (HR = 0.51, 95% CI = 0.37–0.71) Subtherapeutic TTR associated with greater cognitive impairment risk versus therapeutic TTR

NOAC=Novel oral anticoagulants, TTR=Time in therapeutic range, OAC=Oral anticoagulant, AF=Atrial fibrillation, HR=Heart rate, OR=Odds ratio, CI=Confidence interval, TIA=Transient ischemic attack, RR= Relative risk

apixaban, rivaroxaban, and dabigatran) having a greater protective effect compared to warfarin.[89] This has also been observed in another recently conducted meta-analysis with NOACs associated with significant reduction of cognitive impairment compared to warfarin.[90] Other systematic reviews and meta-analyses have reiterated these results [Table 4].[91-93] However, these results have been reported with low confidence due to observational nature of the included studies.[89,90]

NOACs appear to offer advantages specific to cognitive preservation. CMBs have been reported only among patients on warfarin and not on direct OACs. The exact reason for this is not understood but might relate to periods of supratherapeutic INR. Thrombin is known to promote vascular neuroinflammation and plays an important role in Alzheimer's dementia by supporting the formation of Abeta-containing fibrin clots resistant to degradation.[94] These clots can lead to cerebral amyloid angiopathy, blood–brain barrier dysfunction, and neuronal and neuroglial cell death. By either inhibiting thrombin activity or production, NOACs are expected to offer advantages in early-stage dementia.[94,95]

Warfarin use among nonvalvular AF (NVAF) patients has been shown to be associated with 20% decreased risk of cognitive dysfunction. This risk reduction appears to be linear with the time spent in therapeutic range. Both subtherapeutic and supratherapeutic INRs can lead to worse neuropsychological outcomes among warfarin recipients.[47,93,96] In a secondary analysis of the ACTIVE trial, among participants with AF on oral anticoagulation, low MMSE scores correlated with a TTR below mean (65%).[97] Ten percentage decrease in time spent in subtherapeutic INR translates to 30% reduction in risk of dementia.[96]

There are, however, inherent difficulties using Vitamin K antagonists (VKA) in elderly patients with AF. Vitamin K is known to participate in neuronal survival through Vitamin K-dependent protein activation. It is also required for sphingolipid synthesis that forms an essential constituent of neuron membranes and myelin sheaths.[98] There have been concerns that VKA use might lead to worse cognitive outcomes even after adjusting for the heightened risk associated with AF. Small studies have shown that VKA use might lead to worse outcomes in the executive domains even though overall MMSE scores are not impacted.[98,99]

Patients with AF and cognitive impairment are less likely to receive anticoagulation despite indications and having worse outcomes and higher mortality.[100-103] At the same time, older patients with longer disease duration or institutionalization are more likely to receive warfarin rather than NOACs.[104] Over half of these patients receive inadequate warfarin or improper monitoring leading to suboptimal INR ranges.[105] NOACs remain underused in the elderly NVAF population with chronic AF, the group that is most likely to benefit from OAC. However, a stable warfarin strategy may perhaps be safer than switching to NOACs in a frail population in view of adverse events with NOACs.[106]

Rate and rhythm control in atrial fibrillation

A pilot longitudinal study reports that rhythm control may lead to a lower risk of new-onset dementia as compared to rate control.[107] This underlies the fact that rhythm control offers added advantages over rate control, and traditionally, rate control groups have more severe comorbidities and are more advanced into their disease. The impact of pharmacological rhythm control versus catheter ablation on cognitive outcomes has yielded conflicting data, but new-onset dementia has been reported to be lower (HR = 0.60; 95% confidential interval = 0.42–0.88, $P < 0.05$) in catheter ablation arm in a systematic review.[107] Some studies have shown that catheter ablation for AF is associated with initial worsening of cognitive scores, others have not. The postablation cognitive dysfunction appears transient with recovery in all patients. Longer procedure time is an independent predictor of cognitive impairment after ablation.[108] The initial worsening of cognitive function may be due to microembolism during the procedure. As many as 27%–87.5% of patients have been reported to have silent microembolic infarction, detected by brain MRI after catheter ablation for AF.[109] These lesions may subsequently evolve into microbleeds but resolve in most patients. While ablation appears to increase the risk of microemboli, this does not correlate with future risk of cognitive decline.[110,111]

Several studies have shown that AF ablation might lead to improved cognitive function despite incidental subclinical cerebral emboli.[109] In the AXAFA-AFNET4 dataset, catheter ablation for AF led to improvement in patients with at least mild cognitive decline (defined by MoCA <26, 30.3% at baseline to 21.8% at 3 months).[112] Among patients on uninterrupted anticoagulation, MoCA has been reported to improve by a median of 1 unit at 3 months after the procedure. The choice of OAC does not appear to influence this outcome.[113] The type of ablation strategy does not seem to influence neurocognitive function.[114,115] Pulsed-field ablation (PFA) is a newer modality to treat AF and employs electrical impulses to cause irreversible cell electroporation and death. Currently, data on impact of PFA on cognitive function in AF patients are under investigation.

Furthermore, it appears that both cerebral activity and neurocognitive function improve after catheter ablation.[76] A recent clinical trial demonstrated improvement of CBF by 13.7% after ablation with no changes in hippocampal volumes.[77] Beneficial mechanisms of ablation on brain function are postulated as autonomic recovery of both extrinsic and intrinsic cerebral centers, decreased inflammation, as well as decreased risk of subsequent stroke.[116]

Similar results have been reported among patients undergoing percutaneous left atrial appendage closure (LAAC). Over half develop acute brain lesions within 24 h of LAAC with a higher risk among those who receive a greater number of LAA angiographies. However, the effect on cognitive function remains unclear with most studies reporting no effect.[117] In patients receiving LAAC after catheter ablation for AF,

cognitive scores have been shown to be better as compared to OAC alone.[118] This is consistent with the high risk of microemboli despite OAC therapy as shown in Swiss-AF trial.[55]

Impact of Cognitive Impairment in Patient with Atrial Fibrillation

Cognitive decline can have significant impacts on treatment-seeking behavior and AF symptomatology. Severe AF symptoms (European Heart Rhythm Association [EHRA] IV) were reported in 23% of AF patients with normal MMSE, but only 14% of patients with mild cognitive dysfunction (MMSE <24). However, none of the patients with MMSE <24 reported EHRA IV symptoms. At the same time, those with severe cognitive decline were more likely to be admitted for severe heart failure symptoms, likely related to the poor care-seeking behavior in this population.[119] Elderly patients with cognitive dysfunction have significantly higher risk for both cardiovascular and all-cause death and need to be identified early.[120]

Knowledge Gaps and Potential Avenues for Research

Global management of dementia syndromes has been recently set as a public health priority. NCDs and AF often coexist in the aging population. The understanding of cognitive impairment in AF is evolving and there are several knowledge gaps and avenues for further research.

1. Role of AF burden in cognitive decline: What is the minimum AF burden that leads to neurocognitive impairment?
2. Does SCAF affect brain health?
3. Are there specific genetic risk factors that predict cognitive impairment in patients with AF?
4. Does optimal rate control in AF delay or prevent the onset of cognitive impairment?
5. Does aggressive risk factor management in AF delay or prevent the onset of cognitive impairment?

Conclusions

AF is associated with NCDs through a complex multifactorial mechanism. This includes clinical stroke and subclinical microembolic brain infarction, autonomic dysfunction, and systemic and neuroinflammation. There is preliminary evidence to suggest that targeted risk management and treatment can prevent or delay the onset of cognitive decline in AF patients. Despite multiple observational studies confirming NCDs in AF, strategies for prevention in patients with AF remain predominantly focused on oral anticoagulation and catheter ablation for AF. Further research is warranted to develop strategies to delay or prevent cognitive impairment in this population.

Author contributions

Rakesh Agarwal (RA) and Rajiv Mahajan (RM) defined the sections and figures for the current review and wrote the first draft. Phillip J. Tully (PJT) and RM provided critical review of the manuscript. RM provided the supervision for completion of the current review. All authors gave final approval for the current version to be published.

Ethical statement

Ethical statement is not applicable for this article.

Data availability statement

All data generated or analyze during this study are included in this published article [and its supplementary information files].

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Phillip J. Tully is an Editorial Board Member of *Heart and Mind*. The article was subject to the journal's standard procedures, with peer review handled independently of Dr. Phillip J. Tully and the research groups. There are no conflicts of interest. Dr. Mahajan has served on the advisory board of Abbott. The University of Adelaide reports receiving on behalf of Dr. Mahajan lecture and/or consulting fees from Abbott, Bayer, Biotronik, Medtronic, and Pfizer. The University of Adelaide reports receiving on behalf of Dr. Mahajan research funding from Abbott, Bayer, and Medtronic. The remaining authors do not report any conflicts of interest.

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