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# Atrial Fibrillation and Dementia: A Report From the AF-SCREEN International Collaboration

Léna Rivard, MD, MSc; Leif Friberg, MD, PhD; David Conen, MD, MPH; Jeffrey S. Healey, MD, MSc*; Trygve Berge, MD, PhD; Giuseppe Boriani, MD, PhD; Axel Brandes, MD, DMSc; Hugh Calkins, MD*; A. John Camm, MD*; Lin Yee Chen, MD; Josep Lluis Clua Espuny, MD, PhD; Ronan Collins, MD; Stuart Connolly, MD; Nikolaos Dagres, MD; Mitchell S.V. Elkind, MD, MSc; Johan Engdahl, MD, PhD; Thalia S. Field, MD, MHSc; Bernard J. Gersh, MB, ChB, DPhil; Taya V. Glotzer, MD; Graeme J. Hankey, MD; Joseph A. Harbison, MD, FD; Karl Georg Haeusler, MD; Mellanie T. Hills, BSc; Linda S.B. Johnson, MD, PhD; Boyoung Joung, MD, PhD; Paul Khairy, MD, PhD; Paulus Kirchhof, MD; Derk Krieger, MD, PhD; Gregory Y.H. Lip, MD; Maja-Lisa Løchen, MD, PhD; Malini Madhavan, MBBS; Georges H. Mairesse, MD; Joan Montaner, MD, PhD; George Ntaios, MD, MSc; Terence J. Quinn, MD; Michiel Rienstra, MD, PhD; Mårten Rosenqvist, MD, PhD*; Roopinder K. Sandhu, MD, MPH; Breda Smyth, MD; Renate B. Schnabel, MD, MSc*; Stavros Stavrakis, MD, PhD; Sakis Themistoclakis, MD; Isabelle C. Van Gelder, MD, PhD; Ji-Guang Wang, MD, PhD*; Ben Freedman, MBBS, PhD*

**ABSTRACT:** Growing evidence suggests a consistent association between atrial fibrillation (AF) and cognitive impairment and dementia that is independent of clinical stroke. This report from the AF-SCREEN International Collaboration summarizes the evidence linking AF to cognitive impairment and dementia. It provides guidance on the investigation and management of dementia in patients with AF on the basis of best available evidence. The document also addresses suspected pathophysiologic mechanisms and identifies knowledge gaps for future research. Whereas AF and dementia share numerous risk factors, the association appears to be independent of these variables. Nevertheless, the evidence remains inconclusive regarding a direct causal effect. Several pathophysiologic mechanisms have been proposed, some of which are potentially amenable to early intervention, including cerebral microinfarction, AF-related cerebral hypoperfusion, inflammation, microhemorrhage, brain atrophy, and systemic atherosclerotic vascular disease. The mitigating role of oral anticoagulation in specific subgroups (eg, low stroke risk, short duration or silent AF, after successful AF ablation, or atrial cardiopathy) and the effect of rhythm versus rate control strategies remain unknown. Likewise, screening for AF (in cognitively normal or cognitively impaired patients) and screening for cognitive impairment in patients with AF are debated. The pathophysiology of dementia and therapeutic strategies to reduce cognitive impairment warrant further investigation in individuals with AF. Cognition should be evaluated in future AF studies and integrated with patient-specific outcome priorities and patient preferences. Further large-scale prospective studies and randomized trials are needed to establish whether AF is a risk factor for cognitive impairment, to investigate strategies to prevent dementia, and to determine whether screening for unknown AF followed by targeted therapy might prevent or reduce cognitive impairment and dementia.

**Key Words:** atrial fibrillation ■ cognitive dysfunction ■ dementia



Individuals with atrial fibrillation (AF) are at increased risk of cognitive impairment and dementia.[1–10] Whether the link is causal is an unanswered question. The prevalence of both dementia and AF is expected to increase with population aging worldwide. Projections indicate that the number of individuals with AF will increase by 150%

Correspondence to: Léna Rivard, MD, MSc, Montreal Heart Institute, Université de Montréal, 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada. Email lena.rivard@umontreal.ca

*AF-SCREEN International Collaboration Steering Committee member.

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## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AF** | atrial fibrillation |
| **ARIC** | Atherosclerosis Risk in Communities |
| **$CHADS_2$ score** | congestive heart failure (1 point), hypertension (1 point), age ≥75 (2 points), diabetes (1 point), previous stroke or TIA (2 points) |
| **$CHA_2DS_2VASc$ score** | congestive heart failure (1 point), hypertension (1 point), age ≥75 (2 points), diabetes (1 point), previous stroke or TIA (2 points), vascular disease (1 point), age 65 to 74 (1 point), and sex (female; 1 point) |
| **CSVD** | cerebral small vessel disease |
| **DOAC** | direct oral anticoagulant |
| **MoCA** | Montreal Cognitive Assessment |
| **MRI** | magnetic resonance imaging |
| **NT-proBNP** | N-terminal pro–B-type natriuretic peptide |
| **OAC** | oral anticoagulation |
| **TIA** | transient ischemic attack |
| **VKA** | vitamin K antagonist |

in the next 4 decades and that the incidence of dementia will double with every 5.9-year increase in age, reaching >75 million people worldwide by 2030 and >135 million by 2050.[11,12] AF and dementia will therefore exert an increasing health and economic toll.

The AF-SCREEN International Collaboration was founded in 2015 with the purpose of promoting discussion and research about screening for unknown or undertreated AF to reduce stroke and death and to advocate for implementation of country-specific AF screening programs (www.afscreen.org). The collaboration includes >170 physicians (cardiologists, electrophysiologists, primary care physicians, stroke neurologists, and geriatricians), nurses, allied health professionals, epidemiologists, health economists, and patient group representatives from 37 countries. Between 2020 and 2021, 46 expert members of the AF-SCREEN International Collaboration prepared a document outlining the current knowledge of AF and dementia. In September 2020, 90 members (including the 46 members of the writing committee) discussed the draft document and critical gaps at the Virtual AF-SCREEN International Collaboration Meeting. Key points were determined using a Delphi process and retained if agreement was >85%. Complete details of the online survey results from 115 members are provided in Supplemental Material 1.

Numerous observational studies over the past 10 years, including several meta-analyses, provide growing evidence that AF is associated with cognitive impairment and dementia, even in the absence of clinically overt previous stroke[2–10,13] (Table S1). However, many studies included in the meta-analyses are small, are cross-sectional, have short follow-up, or were conducted in highly selected populations (eg, primarily the White population or hospitalized patients). Other important issues pertain to the tools used to assess both cognition and AF and the variability of risk factors over time. Several observational studies have considered the presence of risk factors at baseline without considering the emergence of or change in risk factors during follow-up in a time-dependent fashion. Therefore, direct comparison between studies is difficult. Furthermore, the relationship between AF and dementia is complex, because they share epidemiologic similarities and several risk factors such as advanced age, arterial hypertension, diabetes, hyperlipidemia, sleep apnea, coronary artery disease, heart failure, chronic kidney disease, obesity, physical inactivity, and excessive alcohol consumption.[14,15] It is therefore pertinent to question whether the association between AF and cognitive impairment/dementia could be explained by shared pathophysiology or whether AF is implicated in the causal pathway (Table 1). The association between AF and cognitive impairment/dementia seems to persist even after adjusting for known risk factors[6,10,16,17] and is stronger in younger patients compared with older patients with a higher burden of shared risk factors, which would not be expected if the association was purely attributable to confounding.[7] Two other factors favoring causality are temporality (ie, AF preceding cognitive decline) and a biological gradient between AF burden (ie, time since diagnosis and proportion of time spent in AF, discussed later) and cognitive impairment.[7,8,16,18] The objective of this report is to review the current understanding of the relationship between AF and cognitive impairment/dementia, treatment, and potential value of early AF detection by screening. Our aim is to identify knowledge gaps to focus research efforts to prevent or delay the onset of cognitive impairment/dementia associated with AF.

**Table 1. Factors Favoring Causality or Not**

| Factors favoring causality | Shared, potentially confounding risk factors |
|---|---|
| Association stronger in younger patients | Age |
| Association persists after adjustment with known risk factors | Arterial hypertension |
| Increased risk of dementia with longer time in AF (time since diagnosis and type of AF) | Diabetes |
| | Coronary artery disease |
| Temporality | Excessive alcohol consumption |
| | Heart failure |
| | Hyperlipidemia |

AF indicates atrial fibrillation.

## PROPOSED MECHANISMS UNDERLYING ASSOCIATION OF AF AND COGNITIVE DYSFUNCTION

The association between AF and cognitive dysfunction (Figure 1) is likely multifactorial, and several mechanisms have been proposed. Whereas the primary driver of AF-induced cognitive impairment appears to be cerebral infarction, other proposed mechanisms include AF-related cerebral hypoperfusion, inflammation, microhemorrhage, and brain atrophy or systemic atherosclerotic vascular disease.[19]

### Clinically Manifest Ischemic Stroke and Silent Cerebral Infarcts

By definition, stroke refers to a clinically overt and persistent focal neurologic deficit. AF is associated with a 4- to 5-fold increased risk of ischemic stroke, and ≈30% to 35% of ischemic strokes may be related to AF.[20] Stroke-related cognitive impairment may be the result of single strategic infarcts, multiple territorial or small infarcts, or secondary neurodegeneration.[14] Stroke considerably increases the risk of dementia, with incidence rates of new-onset dementia reported from 24% within 3 years after stroke to 33% within 5 years.[21] A meta-analysis of 7 studies showed that the presence of AF more than doubled the risk of developing dementia after stroke (odds ratio 2.4).[2]

In addition to manifest ischemic stroke, silent or covert brain cardioembolism may contribute to cognitive decline. In a meta-analysis, AF was associated with a 2.6-fold increased risk of silent cerebral infarcts.[13] Cross-sectional and longitudinal studies have shown that silent cerebral infarcts are associated with future stroke and dementia. In an observational study that assessed the prevalence of silent cerebral infarcts by magnetic resonance imaging (MRI) and its association with cognitive impairment,[22] patients with AF had lower cognitive function scores across all tested domains when compared with controls in sinus rhythm. In studies using systematic brain imaging, 15% to 50% of patients with AF have a brain infarct[23] and silent cerebral infarcts at the time of diagnosis of AF are up to 5 times as common as symptomatic infarcts.[24] Although they may not cause overt neurologic deficits at onset, they are associated with both concurrent cognitive performance as well as future risk of cognitive decline.[25,26] However, the prospective SWISS-AF study found that potentially embolic silent large noncortical or cortical infarcts, but not small infarcts, had a similar association with lower cognitive scores as previous clinical ischemic events in patients with AF.[27]

In addition, microembolization and hypoperfusion associated with AF may precipitate ischemic demyelination similar to that seen in cerebral small vessel disease (CSVD), furthering cognitive decline. AF is often associated with an increased prevalence of CSVD that may be a marker for adverse cognitive and clinical outcomes.[28] Recent studies found that the manifestation of cognitive and other neurologic deficits in the context of small

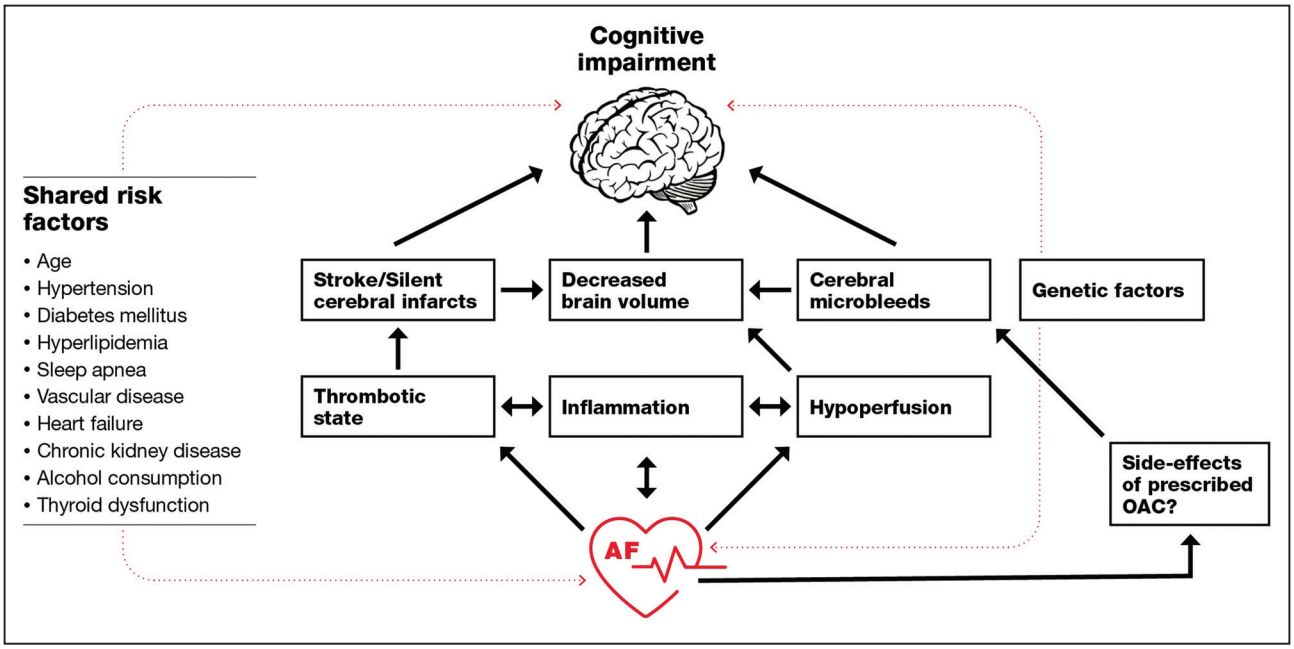


**Figure 1. Suspected mechanisms of cognitive impairment in atrial fibrillation.**
Suspected mechanisms linking atrial fibrillation (AF) and cognitive impairment are depicted by solid black arrows. AF could lead to cognitive impairment through different mechanisms: cerebral infarcts, decreased brain volume, and cerebral microbleeds. Hypothesized mechanisms of decreased brain volume include hypoperfusion of gray matter, silent cerebral infarcts, microbleeds, and inflammation. Inflammation is also thought to enhance hypercoagulability and the formation of thrombi. Oral anticoagulants (OAC) are suspected to increase the risk of cerebral microbleeds. Genetic factors and shared risk factors (red dotted lines) could contribute to both AF and cognitive impairment.

infarcts may be a function, in part, of burden of white matter disease, both in AF-specific[29] and general post-stroke cohorts.[30] In a longitudinal population-based study, 1044 participants underwent serial cognitive assessment and brain MRI or positron emission tomography. Participants with both AF and infarction were more likely to have mild cognitive impairment than those with AF alone.[31] A similar observation was made in the study with the longest follow-up: the ARIC study (Atherosclerosis Risk in Communities).[32] During 20 years of follow-up, 2106 participants developed AF and 1157 participants developed dementia. After accounting for cardiovascular risk factors, including clinically overt ischemic stroke, the average decline in cognitive function was greater in participants with AF than in those without AF; among 935 stroke-free patients, a decline in executive function and verbal fluency was associated with incident AF only in the subgroup with silent cerebral infarcts. This finding and the reduction of cognitive impairment/dementia with oral anticoagulation (OAC) in observational studies[18,33,34] suggest that the vascular insult is likely the cause of cognitive deterioration. Taken together, the evidence points to silent cerebral infarcts as being an intermediate factor in the association between AF and cognitive impairment.

## Cerebral Microbleeds

Some reports showed an association between burden of cerebral microbleeds, particularly in lobar locations, and poorer cognition. This relation persists even after adjustment for vascular risk factors and additional imaging markers of CSVD. However, in a large cohort of patients with AF, cerebral microbleeds were not associated with cognitive function.[27] Although an increased burden of microbleeds attributable to OAC has been proposed as a mechanism for cognitive impairment in AF, it is uncertain whether OAC causes microbleeds. A small prospective MRI study found that warfarin, but not direct oral anticoagulants (DOACs) or antiplatelet use, was associated with the development of new microbleeds at 1 year in individuals with AF.[35] However, in a retrospective study, supratherapeutic ranges during warfarin therapy were associated with an increased risk of dementia.[33]

## Cerebral Hypoperfusion

In addition to cerebral microemboli and microbleeds as putative mechanisms linking AF to cognitive impairment, it has been suggested that AF can result in transient or chronic cerebral hypoperfusion. AF decreases cardiac output secondarily to loss of atrioventricular synchrony, resulting in reduction in stroke volume, cardiac output, and blood pressure.[19] Beat-to-beat variability may also contribute to impaired cerebral perfusion through decreased cardiac performance.[36] Although cerebral autoregulation is expected to maintain cerebral blood flow during a wide blood pressure range, several studies have reported a decrease of cerebral perfusion in patients with AF. A reduction in cerebral perfusion was noted by noninvasive hemispheric blood flow measurements in 31 patients with permanent AF when compared with expected age-matched values.[37] In 358 patients >65 years of age with cognitive impairment (Mini-Mental State Examination score <24), excluding those with a history of transient ischemic attack (TIA), stroke, or dementia, AF was associated with a 4-fold increased risk of dementia after a mean follow-up of 10 years.[38] Pertinent to the cerebral hypoperfusion hypothesis, those with low (<50 bpm) or high (>90 bpm) ventricular response rates on 24-hour Holter monitoring had a 7-fold increased risk of dementia when compared with patients with a moderate ventricular response rate. These results are supported by computational data showing that higher ventricular rates are related to a progressive decrease in cerebral perfusion and hypotensive events downstream to the middle cerebral artery.[39] Moreover, in a cross-sectional study, patients with persistent AF had reduced flow to the brain and hypoperfused brain tissue when compared with those with paroxysmal AF and sinus rhythm.[40] In addition, the high prevalence of cognitive impairment and dementia in patients with AF and concomitant heart failure further supports the potential effect of cerebral hypoperfusion. In cross-sectional studies, cerebral blood flow was lower in patients with more white matter hyperintensity, but the link between hypoperfusion and cerebral white matter hyperintensities is debated.[41]

## Inflammation and Atherosclerotic Vascular Disease

Several studies have suggested that inflammation is an important component of the pathophysiologic process that leads to AF and, in turn, AF aggravates the inflammatory response.[42,43] Inflammation is thought to enhance hypercoagulability and the formation of thrombi, potentially increasing the risk for stroke and for malfunction of cerebrovascular regulation, which has been associated with Alzheimer and vascular dementia.[44,45] Indeed, increased markers of inflammation have been linked to cognitive impairment in patients with AF. Studies have also shown that hemostatic function is altered in those who develop dementia, with an association between hemostasis and vascular dementia, including increased levels of thrombin generation markers (D-dimer and prothrombin fragment 1+2) and endothelial dysfunction (von Willebrand factor and plasminogen activator inhibitor).[46] In rodent models of Alzheimer disease, in the absence of AF, dabigatran (a direct antithrombin) was shown to reduce pathologic changes and inflammation and to slow deterioration in cognitive function.[47] Inflammation may be a nonspecific marker of atherosclerotic vascular disease that has been associated with both cognitive impairment

and AF.[48] Preclinical markers of cardiovascular disease (such as subclinical atherosclerosis, aortic stiffness, and intima-media thickness of the carotid artery) have been linked to both an increased risk of AF and cognitive impairment.[15,48,49] Likewise, there is a link between $CHADS_2$ (congestive heart failure [1 point], hypertension [1 point], age ≥75 [2 points], diabetes [1 point], previous stroke or TIA [2 points]) and $CHA_2DS_2VASc$ (congestive heart failure [1 point], hypertension [1 point], age ≥75 [2 points], diabetes [1 point], previous stroke or TIA [2 points], vascular disease [1 point], age 65 to 74 [1 point], and sex [female; 1 point]) scores and the risk of dementia in patients with AF, with higher scores associated with an increased risk of dementia.[50]

### Brain Volume

The nature of the association between smaller brain volumes, AF, and cognition is debated. Hypothesized mechanisms include hypoperfusion of gray matter, microinfarctions, microbleeds, and inflammation. In a cross-sectional analysis of 4252 participants without dementia, AF was associated with a lower volume of gray and white matter.[51] The association was stronger in patients with persistent compared with paroxysmal AF. A smaller hippocampal volume, as measured by structural MRI, has been associated with cognitive decline and progression toward Alzheimer disease in patients with mild cognitive impairment. In the ARIC Neurocognitive Study, AF was also associated with smaller brain volumes (especially deep gray matter and hippocampal volumes), and the association was stronger among older individuals.[52] Whether AF is independently associated with a smaller hippocampal volume remains controversial. In a series of 87 patients with AF compared with 446 controls in sinus rhythm, AF was significantly and independently associated with a smaller hippocampal volume and lower performance metrics in learning, memory, and executive functions, but not overall brain volume or extent of white matter hyperintensity.[53] These results were not corroborated in a cross-sectional analysis of 1044 participants with multimodality neuroimaging, which found that AF was associated with lower total gray matter volume and presence of infarctions, but not with hippocampal volumes.[31] A recent study reported that preexisting cognitive impairment in patients with AF with ischemic stroke or TIA is common and associated with imaging markers of CSVD and neurodegeneration (ie, lacunes, increased periventricular and deep white matter hyperintensity, and medial temporal atrophy).[54]

Key point 1: There is a consistent association between AF and dementia, but it is uncertain whether, and to what extent, the association is causal or confounded by shared risk factors.

Key point 2: There are several potentially treatable pathophysiologic mechanisms that might underpin the association between AF and cognitive impairment, including strategically located or multiple brain infarcts (cardiac emboli), low blood flow to the brain (systemic hypotension), and multiple brain hemorrhages. These could be explored in controlled trials to determine whether part or all of the relationships between AF and dementia are preventable.

## ROLE OF CEREBRAL IMAGING IN PATIENTS WITH AF

Patients with AF have a high burden of clinically unrecognized brain damage. The clinical significance of these findings remains largely unknown and the role of routine neuroimaging in patients with AF is not well defined.[55] In patients with AF, cerebral findings such as white matter hyperintensities and other cardinal features of CSVD and microbleeds may be associated with current and future cognitive performance.[56] More research is required to define the significance of brain MRI findings in patients with AF and the role of initial cerebral imaging screening and repeat neuroimaging studies.

### What Modalities Are Appropriate?

MRI is the gold standard of brain imaging because of its unique potential to provide detailed information about existing cerebrovascular disease. MRI is the modality of choice for the evaluation of CSVD (fluid-attenuated inversion recovery shows white matter changes and lacunar infarcts, T2-weighted images show infarcts, and susceptibility-weighted images reveal microbleeds) and amyloid angiopathy that may be highly relevant for cognitive decline and further management.[57,58] It is also more informative than computed tomography in detecting patterns of focal atrophy, which may help to differentiate coexisting dementia pathologies such as Alzheimer dementia.[59] Advanced metabolic and functional neuroimaging modalities, such as single-photon emission computed tomography, fluorodeoxyglucose–positron emission tomography, and blood oxygenation level–dependent MRI, can identify impaired brain physiology before the onset of obvious atrophy and may be used in the investigation and phenotyping of dementia.[60] These modalities require expert interpretation and should be used only by specialists with expertise in dementia.[61,62] An overview of commonly used imaging modalities in cognitive impairment/dementia is provided in Figure 2.

### Who Should Be Imaged and When?

The role of cerebral imaging in patients with AF, outside of new or worsening cognitive complaints or other neurologic events (ie, new focal neurologic deficits, encephalopathy, or seizures), is not well defined. In an asymptomatic patient with AF, cerebral imaging could identify

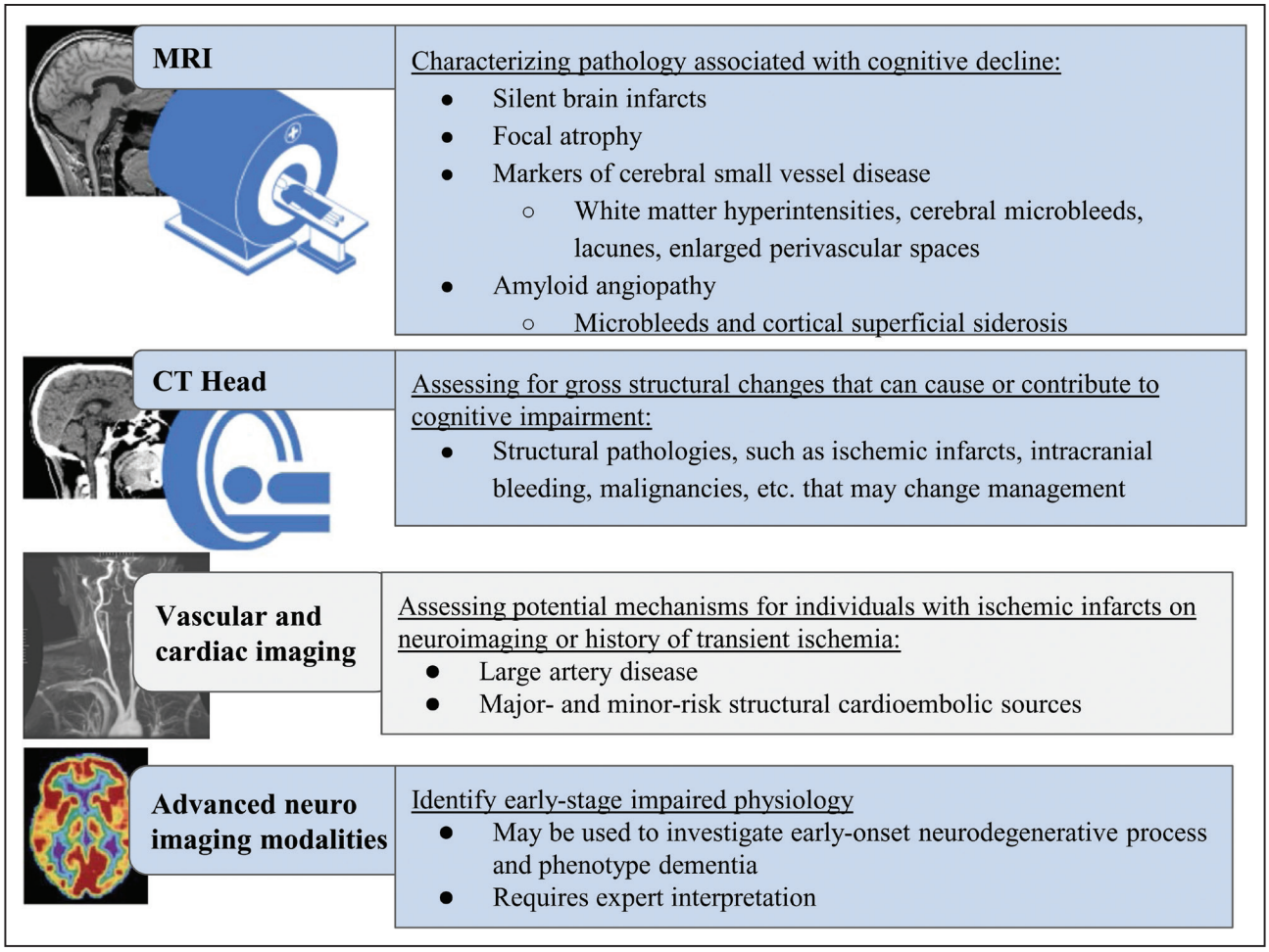


**Figure 2. Imaging modalities in cognitive impairment/dementia.**
CT indicates computed tomography; and MRI, magnetic resonance imaging.

markers of CSVD and neurodegeneration that are linked to an increased risk of cognitive impairment in the general population.[56] In the future, if interventions to prevent dementia in AF are identified, early detection of cognitive decline by routine cognitive testing in patients with AF should prompt cerebral imaging, but until then, the role of routine imaging in patients without evidence of cognitive dysfunction remains undetermined.

## Implication of Incidental Findings

Covert brain infarcts are defined as lesions detected on neuroimaging in the absence of clinical history of symptomatic stroke. Presence of ≥3 infarcts supports the diagnosis of vascular cognitive impairment.[63] It is not clear whether silent cerebral infarct in patients with AF should lead to an increase in the patient's $CHA_2DS_2$-VASc score and thus prompt OAC therapy in otherwise low-risk patients.[64] Although practice patterns among neurologists are heterogeneous, many would consider it reasonable to initiate OAC for silent cerebral infarcts thought to be cardioembolic. Whereas an intracranial hemorrhage is an indication to withhold OAC, intracranial microbleed, which is a risk factor for intracranial hemorrhage, is not a contraindication for OAC. The presence of microbleeds concomitant with an acute stroke increases the risk for recurrent ischemic stroke. With DOACs, the risk of intracranial bleeding is lower than with warfarin. In a substudy of AVERROES (A Phase III Study of Apixaban in Patients With Atrial Fibrillation), in which 931 patients with AF underwent serial cerebral MRI, DOACs did not increase the incidence of microbleeds compared with acetylsalicylic acid.[65]

## What Is the Role of Follow-Up Imaging?

There is no high-quality evidence to guide recommendations for repeat brain imaging in patients with AF, with or without cognitive impairment. AF is, however, associated with an increased risk of adverse brain imaging changes over time. A recent longitudinal community-based neuroimaging study of 963 individuals, 3% of whom developed new AF, found that the AF cohort had independently higher odds of new silent cerebral infarcts (41% versus 18%) and worsening ventricular and sulcal grades (brain architectural features associated

with increased risk of dementia) on MRI over 11 years of follow-up.[28] In an older community-based longitudinal study in which 1433 individuals received baseline and follow-up brain MRIs over 5 years, incident cortical infarcts, but not incident infarcts overall, were associated with AF.[66] A randomized clinical trial comparing warfarin with placebo in 525 individuals with AF found a 1% annual incidence of silent cerebral infarct on computed tomography in the warfarin group versus 1.6% in the placebo group over 3 years of follow-up (NS).[67] New neurologic issues should prompt urgent repeat neuroimaging and cognitive decline should trigger cerebral imaging. At what interval cognitive testing and cerebral imaging should be repeated remains unknown.

Key point 3: Cerebral imaging, with MRI preferred over computed tomography, should be performed in the workup of cognitive impairment in patients with AF. The role of routine baseline and follow-up cerebral imaging in AF without cognitive impairment is uncertain.

## DEFINITION AND ASSESSMENT OF COGNITIVE FUNCTION

Although a recent consensus statement has suggested that all individuals with AF should be assessed for cognitive impairment,[68] assessment for mild cognitive impairment is recommended in people who express concerns (or for whom close relatives express concerns) about memory or impaired cognition.[69] Given the association between AF and cognitive impairment/dementia, even a moderate degree of suspicion for cognitive impairment in patients with AF should trigger a formal cognitive assessment.

Cognitive testing in people with AF can be considered a staged process, with the first stage being a form of cognitive triage. This can be performed by any clinician and is suited to even the busiest outpatient or ward setting. This could consist of a validated screening question, such as "Have you had problems with memory or thinking in the past 12 months and is this affecting your day-to-day activities?" The question can also be posed to family members in attendance. Questionnaires such as the IQCODE (Informant Questionnaire for Cognitive Decline in the Elderly) can help structure this assessment. Collateral information from an independent source is vital because insight into cognitive difficulty may not always be maintained. If no concerns are raised, testing can stop but the question can be asked again in the future. This easy to perform but blunt form of testing could be considered the cognitive equivalent of a manual pulse check.

If the person or his or her family expresses concern around cognition, the next step could consist of a multidomain cognitive screening tool, such as The Montreal Cognitive Assessment (MoCA) or the Folstein Mini-Mental State Examination, as described in Table 2. The purpose of this screening is not to establish a diagnosis but to stratify risk and inform the need for referral to specialist memory services. Such screening requires more time and training than a single question. It could be considered the cognitive equivalent of a 12-lead ECG.

In AF, all domains are generally affected (including attention, executive function [including social recognition], language, memory, and visual-spatial capacities; described in Table 3 and Supplemental Material 2), such that a screening tool that covers each domain is preferred.[22] Many assessment tools have been described in the literature and a wide variety are used in practice.[70] Tools used to assess cognition vary between trials and therefore direct comparisons are not possible. Choice of test will be influenced by familiarity with the tool, likeli-

**Table 2. Comparison of Commonly Used Cognitive Screening Tools[74]**

| Variables | ACE-III | AMT-10 | GP-Cog | 6 CIT | MMSE | MoCA | OCS |
|---|---|---|---|---|---|---|---|
| Administration time, min | 15 to 20 | <5 | <5 | <5 | 10 | 10 | 15 |
| Copyright | Free to use | Free to use | Free to use | Free to use | Pay per use | Pay to train | Free to use |
| Validated in AF | No | No | No | No | Yes | Yes | No |
| Non-English versions | Yes | Yes | Yes | No | Yes | Yes | Yes |
| Short form available | Yes | Yes | NA | NA | No | Yes | No |
| Training available | Yes | No | Yes | No | Yes | Yes | Yes |
| Recommended setting | Hospital | Hospital (acute) | Primary care | Various | Various | Various | Hospital |
| Attention | Yes | Yes | No | Yes | Yes | Yes | Yes |
| Executive function | No | No | Yes | No | No | Yes | Yes |
| Language | No | No | No | No | Yes | Yes | Yes |
| Memory | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Perceptual-motor | No | No | Yes | No | Yes | Yes | Yes |
| Social cognition | No | No | No | No | No | No | No |

6-CIT indicates 6-item Cognitive Impairment Test; ACE, Addenbrooke's Cognitive Examination–III; AF, atrial fibrillation; AMT-10, 10-item Abbreviated Mental Test; GP-Cog, General Practitioner Assessment of Cognition; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; and OCS, Oxford Cognitive Screen.

**Table 3. Definitions and Assessment of Cognitive Function**

| Domains | Assessment |
|---|---|
| Cognitive domains | Attention |
| | Memory |
| | Executive function, which is a set of mental skills that includes working memory, flexible thinking, and self-control (eg, skills to plan, organize, shift from 1 activity to another, pay attention) |
| | Language |
| | Visuospatial processing |
| Cognitive decline | Change in cognitive function that is greater than expected from normal aging |
| | Can be diagnosed through changes in standardized cognitive test scores over time |
| Mild cognitive impairment | Characterized by cognitive decline that is greater than expected from normal aging, but without affecting activities of daily living |
| Amnestic | Characterized by memory complaints |
| | High risk of progression toward Alzheimer disease |
| Single domain amnestic | Isolated memory impairment |
| Multiple domain amnesic | Memory impairments and deficits in one or more cognitive domains |
| Dementia | Defined as deficits in at least 2 cognitive domains that represent a decline from a previous level of functioning and that are sufficiently severe to affect activities of daily living |

Components of cognitive domains are described in Supplemental Material 2.

hood of the test identifying impairment, and the resources or time needed to administer testing. The MoCA and the Mini-Mental State Examination are the most used screening tools to detect mild cognitive impairment. The MoCA[71] is considered a sensitive screening test for vascular dementia; the Mini-Mental State Examination is less sensitive but more specific.[72,73] The MoCA has been used to detect cognitive decline over time: a 3-point decline has been shown to be associated with a meaningful clinical reduction in cognitive function, as assessed by trained research psychologists. These tests may be insensitive for detecting subtle impairments in executive function, which is preferentially affected in vascular cognitive impairment. The pattern of cognitive impairment varies between dementia subtypes and certain tests were designed for specific diagnoses (see Table 3).[74]

For a minority of people, referral for comprehensive neuropsychological assessment may be required. This is a highly specialized activity usually performed in a memory clinic or neurology setting. This detailed testing considers multiple aspects of cognition and allows for a diagnostic formulation that can be used for treatment planning. It could be considered the cognitive equivalent of an electrophysiologic cardiac assessment. If cognitive impairment is confirmed, reversible causes including side effects from medications, sleep apnea, depression, and other medical conditions should be ruled out. Impairing medications should generally be discontinued or replaced and coexisting vascular comorbidities should be addressed, such as hypertension, diabetes, and unhealthy lifestyle factors (eg, reducing alcohol intake and implementing regular exercise).[69]

Key point 4: Screening for unknown AF should be considered in patients with cognitive impairment.

Key point 5: There is a need for standardized cognitive testing in patients with AF.

## KNOWLEDGE GAPS

### Is There a Causal Link Between AF and Impaired Cognition?

The role of AF in cognitive impairment and dementia requires confirmation in longer and larger prospective cohorts and well-designed adequately powered randomized controlled trials (Tables 4 and 5).[75,76] Candidate mechanisms for cognitive decline in patients with AF can be untangled in larger cohorts with longer follow-ups, but controlled clinical trials of AF therapies with cognition or dementia as outcomes are required to determine a causal relation between AF and cognitive decline. In 6514 dementia-free participants in the prospective population-based Rotterdam Study, new-onset dementia was strongly associated with duration of exposure to AF in younger participants.[8] Furthermore, in 325 participants in the ARIC study, persistent AF but not paroxysmal AF (assessed by a 14-day ECG patch monitoring) was associated with lower cognitive function scores.[16] This biological gradient between AF burden and cognitive impairment favors causality but could nevertheless be mediated by unmeasured or imperfectly quantified upstream factors. The role of AF screening in prevention of cognitive decline is contingent on results of studies demonstrating that directed interventions after AF diagnosis result in a reduction in cognitive decline and dementia. This is analogous to the situation with stroke, in which evidence of effectiveness of OAC in prevention of AF-related stroke preceded studies of the effectiveness of strategies of screening for AF to prevent stroke.[77] Ideally, studies of population screening for AF should include cognitive decline or dementia as an end point in addition to stroke. Even if OAC is found effective in reducing cognitive decline in AF, as in stroke, there will be no certainty whether AF is more a villain than bystander in the process.[78]

### Development of Scores to Predict Cognitive Decline

The identification of specific risk factors to stratify patients with AF most likely to develop dementia or cognitive impairment could come from the prospective cohort studies described previously. A variation on the

**Table 4. Knowledge Gaps and Questions to Address**

| Knowledge gaps | Questions to address | Importance* |
|---|---|---|
| Pathophysiology | | |
| Association between AF and cognitive dysfunction | Is there a direct causal association between AF and cognitive dysfunction? | +++ |
| | Is the strength of association modified by other risk factors? | |
| Mechanisms | Do microemboli, hypoperfusion, and inflammation play important roles in the pathophysiology of cognitive dysfunction in AF? | ++ |
| | What is the role of genetics? | |
| | How can the observed increased incidence of Alzheimer disease and other nonvascular types of dementia in AF be explained? | |
| Prevention | | |
| Oral anticoagulation | | |
| Role of anticoagulation on the prevention of cognitive decline and dementia | Should OACs be extended to low-risk patients? | +++ |
| | What is the minimum atrial burden associated with cognitive decline/dementia? | |
| | How does progression of AF burden affect cognitive function? | |
| | Are safety and efficacy similar between VKA and DOACs and among the various DOACs? | |
| | Should atrial cardiomyopathy be considered an indication for OAC? | |
| | What is the role of left atrial appendage occlusion? | |
| | When should OAC treatment be initiated for dementia prevention? Is it advisable to think about a specific risk threshold for OAC initiation considering that cognitive decline is not a discrete event but a gradual process? | |
| Rhythm control | | |
| Role of AF ablation and cardioversion | Does AF ablation prevent cognitive decline? | + |
| | If so, should indications for AF ablation be extended to asymptomatic patients? | |
| | Is there a difference between energy sources (radiofrequency versus cryoablation)? | |
| | What is the effect of multiple electric cardioversions and AF ablation? Should there be a threshold limit per patient? | |
| Role of AADs | Do AADs have an effect on cognitive dysfunction and, if so, is there a difference among the agents? | + |
| | Do rhythm control interventions have an effect on cognition? | |
| Role of irregularity of rhythm | Does irregularity of rhythm (premature atrial beats, short atrial runs) play a role in cognition? If so, should treatment be more aggressive? | + |
| | Should patients with extensive supraventricular activity (apart from AF) also receive OAC treatment? | |
| | Is there a difference in risk of cognitive decline in patients with AF with regular rhythm (ie, pacing) or irregular rhythm? | |
| Rate control | | |
| | What is the optimal rate control target for cognitive outcomes? | + |
| | What is the optimal pacing rate in patients with AV node ablation? | |
| | Is there a difference between rate control drugs? | |
| Drug therapy | | |
| | What is the role of anti-inflammatory drugs to prevent cognitive dysfunction in patients with AF? | + |
| | Role of statins? | |
| Multidisciplinary approaches | | |
| | Is a systematic multidisciplinary approach effective in preventing cognitive dysfunction in patients with AF? | ++ |
| Biomarkers | | |
| | Can biomarkers be developed and validated to predict cognitive dysfunction in patients with AF? | ++ |
| | What is the role of such biomarkers in screening, treatment, and follow-up of patients with AF? | |
| Brain MRI | | |
| | What is the role of brain MRIs in the screening and follow-up of patients with AF? | ++ |

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; AV, atrioventricular; DOAC, direct oral anticoagulant; MRI, magnetic resonance imaging; OAC, oral anticoagulant; and VKA, vitamin K antagonist.

*The importance of knowledge gaps was put to a vote at the 2020 Virtual AF-SCREEN International Collaboration Meeting.

**Table 5. Ongoing Trials That Include Cognitive Function or Dementia as End Points**

| Questions to be addressed | Study name | Methods |
|---|---|---|
| Oral anticoagulation | | |
| Are safety and efficacy similar between VKA and DOACs? | ARISTA | Main inclusion criteria: NVAF and $CHA_2DS_2VASC$ score ≥2 |
| | | Primary end point: change in cognitive function (using standardized neurocognitive assessment) and new silent cerebral infarcts on MRI |
| | | Randomized, single-blinded |
| | | Groups: apixaban and warfarin |
| | | Follow-up 24 months, n=280 |
| | CAF[75] | Main inclusion criteria: NVAF, $CHA_2DS_2VASC$ score ≥2, >65 years of age |
| | | Primary end point: incident dementia determined by a formal diagnosis of dementia by a neurologist |
| | | Randomized open-label |
| | | Groups: dabigatran and warfarin |
| | | Follow-up 24 months, n=120 |
| What is the minimal amount of atrial burden associated with cognitive decline/dementia? Should OAC be extended to silent AF in high-risk patients? | ARTESiA Neurocognitive Substudy | Main inclusion criteria: SCAF ≥6 minutes but <24 hours and a high $CHA_2DS_2VASC$ score |
| | | Primary end point: change of cognitive functions (MoCA) |
| | | RCT |
| | | Groups: apixaban versus ASA 81 mg |
| | | n=1000 |
| | NOAH | Main inclusion criteria: SCAF ≥6 minutes and $CHA_2DS_2VASC$ score ≥2 |
| | | RCT |
| | | Primary end point: all-cause death |
| | | Secondary outcome: change of cognitive functions (MoCA) |
| Should OACs be extended to low-risk patients? | BRAIN-AF[76] | Main inclusion criteria: NVAF with low $CHA_2DS_2VASC$ score |
| | | Primary end point: cognitive decline (MoCA decreased ≥3 points from baseline) and/or stroke/TIA |
| | | RCT |
| | | Groups: rivaroxaban 15 versus standard of care (placebo or ASA 100 mg) |
| | | Mean follow-up 5 years; n=2280 |
| Should OAC be continued after a successful AF ablation? | OCEAN | Main inclusion criteria: absence of AF recurrence ≥12 months after AF ablation procedure |
| | | Primary end point: composite of stroke, systemic embolism, and covert embolic stroke as detected by brain MRI |
| | | Secondary end points: differences on neuropsychological testing (MoCA and MMSE) |
| | | Randomized open-label |
| | | Groups: rivaroxaban 15 versus ASA 81 mg |
| | | n=1572 |
| Rhythm control | AFCOG | Main inclusion criteria: NVAF and rhythm control strategy |
| | | Primary end point: difference in cognitive score (CANTAB) |
| | | Cohort |
| | | Groups: standard of care interventions to convert patient from AF to normal rhythm |
| | | n=600 |
| | Comparison of Brain Perfusion in Rhythm Control and Rate Control of Persistent Atrial Fibrillation* | Main inclusion criteria: persistent NVAF |
| | | Primary end point: cognitive functions (K-MoCA) and brain perfusion (CT) |
| | | Groups |
| | | Randomized open-label |
| | | Follow-up 3 months; n=200 |
| AF ablation | | |
| Does AF ablation prevent cognitive decline? | DIAL-F | Main inclusion criteria: AF and ≥50 years of age |

(*Continued*)

**Table 5. Continued**

| Questions to be addressed | Study name | Methods |
|---|---|---|
| | | Primary end point: improvement or no worsening in MoCA score |
| | | Case–control |
| | | Groups = AAD versus AF ablation |
| | | Follow-up 2 years; n=888 |
| AF screening | | |
| Does AF screening prevent cognitive decline? | UK SAFER | Main inclusion criteria: ≥65 years and no known AF |
| | | Primary end point: reduction in the number of strokes, heart attacks, and deaths |
| | | Cognition is a secondary end point |
| | | RCT |
| | | Groups = AF screening versus no AF screening |
| | | Follow-up 5 years; n=120 000 |
| Other approaches | | |
| What is the role of left atrial appendage occlusion? | PLUG Dementia | Main inclusion criterion: left appendage closure for AF |
| | | Primary end point: cognitive decline (11-item ADAS-Cog and DAD) |
| | | Cohort |
| | | Follow-up 24 months; n=60 |

AAD indicates antiarrhythmic drug; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; AF, atrial fibrillation; AFCOG, Acute Cognitive Changes During Atrial Fibrillation Episodes (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04033510); ARISTA, Trial of Apixaban Versus Warfarin in Reducing Rate of Cognitive Decline, Silent Cerebral Ischemia and Cerebral Microbleeds in Patients With Atrial Fibrillation (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03839355); ARTESiA, Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (URL: https://www.clinicaltrials.gov; Unique identifier: NCT01938248); ASA, acetylsalicylic acid; BRAIN-AF, Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02387229); CAF, Cognitive Decline and Dementia in Atrial Fibrillation Patients (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03061006); CANTAB, Cambridge Neuropsychological Test Automated Battery; $CHA_2DS_2VASc$ score, congestive heart failure (1 point), hypertension (1 point), age ≥75 (2 points), diabetes (1 point), previous stroke or transient ischemic attack (2 points), vascular disease (1 point), age 65 to 74 (1 point), and sex (female; 1 point); CT, computed tomography; DAD, Disability Assessment for Dementia; DIAL-F, Cognitive Impairment in Atrial Fibrillation (URL: https://www.clinicaltrials.gov; Unique identifier: NCT01816308); DOAC, direct oral anticoagulant; K-MoCA, Korean version of the Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NOAH, Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02618577); NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; OCEAN, Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02168829); PLUG Dementia, Overall and MRI-Based Impact of Percutaneous Left Atrial Appendage Closure on the Cognitive Decline and Dementia in Patients With Atrial Fibrillation (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03091855); RCT, randomized controlled trial; SCAF, subclinical atrial fibrillation; TIA, transient ischemic attack; UK SAFER, Screening for Atrial Fibrillation with ECG to Reduce Stroke; and VKA, vitamin K antagonist.

*Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02633774.



$CHAD_2DS_2VASc$ score that predicts cognitive decline could identify patients who would benefit most from screening for cognitive impairment and possibly in the future aid in selection of appropriate candidates for interventions to prevent dementia. Additional measures obtained by imaging and biomarkers may enhance the value of the $CHA_2DS_2VASc$ score but this remains to be determined.

## Role of Anticoagulation

### *Role of Anticoagulation in Low-Risk Patients*

It is plausible that recurrent subclinical microemboli may play a role in the association between AF and dementia. OAC could reduce this risk. Several observational studies suggest a protective effect of OAC therapy on cognitive outcomes in patients with AF (Table S2).[18,33,34,79–81] Therefore, the question of OAC is highly pertinent for patients with AF who do not have a clear indication for anticoagulation. BRAIN-AF (Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation; URL: https://www.clinicaltrials.gov; Unique identifier: NCT02387229) is a prospective, multicenter, double-blind, randomized controlled trial that is assessing whether rivaroxaban 15 mg daily reduces the composite outcome of stroke/TIA or neurocognitive decline (defined by a decrease in the MoCA score ≥3) in patients with AF considered to be at a low risk for stroke.[76] The comparator arm is standard of care, as defined by placebo in patients without vascular disease and acetylsalicylic acid in patients with vascular disease.

Should certain clinical features such as left atrial dilatation, mild left ventricular systolic dysfunction, serum biomarkers (eg, brain natriuretic peptide, C-reactive protein, troponin, D-dimers) or silent cerebral infarcts detected by MRI trigger OAC in patients with AF and a low $CHA_2DS_2VASc$ score with the aim of preventing cognitive decline? Should the presence of an underlying atrial cardiomyopathy, in the absence of AF, be a trigger

for anticoagulation with the aim of preventing cardioembolism dependent on a pathologic atrial substrate without overt AF and thereby reduce dementia? In the ARIC-PET study (Atherosclerosis Risk in Communities–Positron Emission Tomography), atrial cardiopathy (defined as left atrial enlargement, increased P-wave terminal force, or serum NT-proBNP [N-terminal pro–B-type natriuretic peptide]) was associated with elevated brain amyloid assessed by positron emission tomography.[82] Alternatively, should OAC be routinely prescribed to patients with AF regardless of the $CHA_2DS_2VASc$ score with the objective of improving long-term cognitive outcomes? Randomized controlled trials are required to address these critical questions. Risk to benefit ratios need to be established considering that OAC is associated with adverse events, including bleeding. In a large retrospective registry study, a lower risk for dementia was observed with OAC in patients >65 years, whereas OAC in patients <60 years appeared to be harmful owing to excess risk of a composite of ischemic stroke, intracerebral hemorrhage, and dementia, with no excess risk of dementia alone.[34]

### Role of Anticoagulation in Silent AF

It is unknown whether there is a dose–response relationship between AF burden and dementia. Some reports suggest that persistent AF is more deleterious than paroxysmal AF.[16] In TRENDS (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics) and ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial), in patients with an implanted cardiac electronic device, a higher AF burden was associated with an increased risk of stroke.[83,84] How much AF should prompt OAC to prevent stroke remains a topic of debate. Just as important is whether OAC therapy might prevent cognitive decline or dementia and whether AF burden is an important determinant. ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; URL: https://www.clinicaltrials.gov; Unique identifier: NCT01938248) is a prospective, multicenter, double-blind, randomized controlled trial that is enrolling 4000 patients with subclinical AF <24 hours in duration (detected by an implanted pacemaker, defibrillator, or cardiac monitor) who have additional risk factors for stroke.[85] More than 3000 patients have thus far been randomized to receive apixaban (according to standard AF dosing) or acetylsalicylic acid 81 mg daily. The primary outcome is the composite of stroke, TIA with diffusion-weighted MRI evidence of cerebral infarction, or systemic embolism. A neurocognitive substudy is incorporated in the ARTESiA trial in which participants are subjected to serial MoCA tests. Likewise, the NOAH trial (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; URL: https://www.clinicaltrials.gov; Unique identifier: NCT02618577) is currently enrolling patients with subclinical AF and a $CHA_2DS_2VASc$ score ≥2. Participants are randomized to edoxaban or acetylsalicylic acid. The primary end point is the first occurrence of stroke/TIA or systemic embolism. Cognitive function changes (assessed by MoCA) is a secondary outcome. Those substudies should shed light on the effect of OAC in preventing cognitive decline in patients with subclinical AF who have additional risk factors for stroke. An important issue in patients with device-detected asymptomatic AF (subclinical AF) is the proportion who develop clinical AF and the time course of the transition. This is complicated by the dynamic nature of subclinical AF, with transitions within patients from lower to higher AF burden categories depending on the AF burden at first detection and $CHADS_2$ score.[86]

### Type of Anticoagulation

Another knowledge gap regarding OAC for the prevention of cognitive decline in patients with AF is the selection of agent. Several reports have suggested that a DOAC is associated with a lower risk of dementia than a vitamin K antagonist (VKA).[34,79] In contrast, Danish registries found no clinically meaningful difference in the development of dementia between users of DOACs or warfarin apart from a higher risk in DOAC users 80 years and older.[87] Compared with a VKA, DOAC therapy may also reduce the incidence of cerebral microhemorrhage (suspected to be associated with cognitive dysfunction).[88] In patients with a current indication for anticoagulation, it is not ethically feasible to conduct a trial that would randomize patients to OAC versus placebo to assess cognitive outcomes. However, observational studies suggest a protective effect of OAC therapy on cognitive outcomes in patients with AF.[79,80] Several studies comparing DOACs and warfarin on the rate of cognitive decline are ongoing (apixaban in ARISTA [Trial of Apixaban Versus Warfarin in Reducing Rate of Cognitive Decline, Silent Cerebral Ischemia and Cerebral Microbleeds in Patients With Atrial Fibrillation; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03839355], dabigatran in CAF[75] [Cognitive Decline and Dementia in Atrial Fibrillation Patients; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03061006)], rivaroxaban in ACCOG [Anticoagulants and Cognition; URL: https://www.clinicaltrials.gov; Unique identifier: NCT04073316]; see Table 4). Cited studies are described in Table S3.

### Role of AF Screening

The target population to screen has yet to be established and will depend, in part, on the results of ongoing trials, particularly with regards to the effect of OAC on cognitive outcomes. It is unknown whether AF screening should be extended to all asymptomatic people with risk factors for stroke to detect subclinical AF and to prevent not just stroke but also dementia and whether this also should also be extended to patients with a low $CHA_2DS_2VASc$

score.[76,85] It is pertinent to question whether AF screening should be extended to all patients with cognitive impairment or only those with cognitive impairment and cerebral imaging anomalies. Ideal strategies to screen for AF remain to be defined and would require more intensive screening than a single time point, either by multiple ECG snapshots over a 2- to 4-week period or by continuous external/wearable or implanted devices (loop recorders or other devices) for variable durations.

### Role of AF Ablation

Periprocedural ischemic strokes are a known complication of catheter ablation for AF, with silent cerebral infarcts observed in up to 40% of patients.[89] Ablation technologies have been compared in small studies; mode of periprocedural and intraprocedural anticoagulation has been repetitively identified as major predictor for occurrence of silent cerebral infarcts.[82] The effect of catheter ablation on neurocognitive function is less well understood. One study assessed 150 patients who underwent radiofrequency catheter ablation for paroxysmal AF, persistent AF, and supraventricular tachycardia, as well as controls on the waiting list for AF ablation.[90] At 2 days after ablation, 28% of patients with paroxysmal AF, 27% with persistent AF, and 13% with supraventricular tachycardia had a decline in cognitive performance compared with the preablation state. In multivariable analyses, time spent in the left atrium was the only factor associated with a decline in cognitive performance. Regarding long-term outcomes, an observational study assessed 4212 patients who underwent AF ablation and 16848 age- and sex-matched controls with AF and no ablation.[91] After 3 years of follow-up, AF ablation was associated with a lower risk of dementia (0.2% versus 0.9%), but allocation to ablation was not randomized, so residual confounding could account for the observed differences. In a recent large nationwide cohort of patients with AF, ablation was associated with decrease dementia risk after propensity score matching to account for baseline difeerences.[92] The recently published EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) demonstrated a 21% lower risk of adverse cardiovascular outcomes in 1395 patients randomized to early rhythm control therapy compared with 1394 patients randomized to usual care.[93] The change in cognitive function, assessed by MoCA at 2 years, was not different between groups. Further studies are required to confirm the effect of AF ablation on long-term cognitive function.

The ongoing DIAL-F case–control study (Cognitive Impairment in Atrial Fibrillation; URL: https://www.clinicaltrials.gov; Unique identifier: NCT01816308) is comparing the incidence of cognitive impairment (assessed by MoCA) associated with catheter ablation for AF versus antiarrhythmic drugs. The effect of multiple procedures on cognitive outcomes remains unknown. Whether OAC is required after a successful ablation is being investigated in OCEAN (Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial; URL: https://www.clinicaltrials.gov; Unique identifier: NCT02168829), in which cognition is a secondary end point (assessed by the MoCA score). Cited studies are described in Table S3.

### Role of Electric Cardioversion

In recent small studies, successful electric cardioversion to sinus rhythm improved cerebral blood flow measured by MRI and cerebral tissue oxygen saturation measured by bedside near-infrared spectroscopy.[94] Conversely, electric cardioversion may increase the risk of cerebral microemboli. The effect of multiple cardioversions on cerebral microemboli and cognitive outcomes is unknown. Studies are ongoing to assess cognitive function and the incidence of new-onset silent cerebral infarcts after programmed direct-current cardioversion as assessed by diffusion-weighted sequences in brain MRI (NOR-FIB2 [Fibrosis, Inflammation and Brain Health in Atrial Fibrillation: The Norwegian Atrial Fibrillation and Stroke Study; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03816865]).

### Role of Rate Control

The optimal rate control management strategy and the effect of rate control drugs (eg, digoxin, β-blockers, nondihydropyridine calcium channel blockers) on cognitive outcomes in AF remain unknown.

### Role of Inflammation

Inflammation could be responsible for damaging the blood–brain barrier and causing cerebral microstructural changes. Further studies are required to elucidate the role of inflammation in the development of cognitive dysfunction in patients with AF, as well as the role of anti-inflammatory drugs. Statin therapy appears to positively affect cognitive outcomes in patients with AF (study described in Table S3).[95] Such findings require confirmation in randomized trials before widespread adoption.

### Role of Genetics and Biomarkers

Whether there are shared genetic factors for AF and dementia is an area of ongoing research. A recent Mendelian randomization study found no evidence to support a causal association between AF and Alzheimer disease.[96] Studies are required to confirm these results and clarify the role of genetic factors that may interact with AF in influencing neurocognitive outcomes.

If the link between AF and dementia is confirmed, there will likely be an increased interest in assessing biologic (cerebrospinal fluid or plasma) and imaging biomarkers associated with cognitive impairment in the AF population. Over the past decade, much progress has been made toward detecting biomarkers of diagnostic and prognostic value for dementia.[97] Identifying specific biomarkers that predict cognitive decline in patients with AF could potentially inform screening and management strategies. Biomarkers may potentially

refine risk stratification in patients deemed clinically at low risk.[98] Nonetheless, the limitations of biomarkers for everyday clinical use must balance predictive ability against practicality.[97]

### *Role of an Integrated Approach*

In a Korean nationwide registry, incident AF was associated with an increased risk of dementia, independent of clinical stroke, in an elderly population; OAC and good blood pressure control were linked to a decreased incidence of dementia.[99] An integrated care approach to AF management that includes treatment of related risk factors was associated with a lower risk of dementia.[100]

Key point 6: Several studies indicate that OAC is associated with reduced development of cognitive dysfunction. Prospective randomized studies are required to confirm these findings.

Key point 7: Cognition/cognitive decline using reliable measures of cognitive function should be included as a primary or secondary end point in future prevention trials in AF and in large registries or cohort studies.

Key point 8: Studies of screening for unrecognized AF followed by treatment are required to determine whether this strategy could reduce cognitive dysfunction in subgroups of patients, such as those at risk of cognitive decline or with preexisting mild cognitive impairment.

## PATIENT PERSPECTIVE

Contemporary data from population surveys have indicated that the general public's knowledge regarding the potential for dementia risk reduction and treatment of symptoms remains poor. It is increasingly recognized that incorporating the patient's perspective into the measurement of outcomes is an integral part of evaluating effect of disease and treatment and improving health services and care. A recent systematic review evaluated which outcomes were most important to patients with mild cognitive impairment or Alzheimer dementia, their caregivers, and health care professionals.[101] A total of 34 studies conducted in 13 countries were included, involving between 4 and 1116 participants. These studies identified 32 outcomes across 7 domains (cognition; functioning and dependency; behavioral and neuropsychiatric; patient length and quality of life; caregiver-oriented outcomes; health, social care, and treatment-related outcomes; and social issues). Of these outcomes, 8 were relevant to all stakeholders: memory decline; activities of daily living; loss of functioning, independence, and autonomy; mental health; quality of life; maintaining identity and personality; caregiver burden; and health services and disease information. There were 2 outcomes that only patients identified as important: length of life and executive function.

The literature regarding patient-reported outcomes and patient preferences among participants reflecting the dementia spectrum is sparse. Patient-reported outcomes and patient preferences have not been routinely incorporated into clinical trials or research registries of patients with cognitive dysfunction.[70] Instead, surrogates for patient-reported outcomes are typically used, such as activities of daily living and cognition; patient preferences are often ascertained indirectly from health-related outcome measures or health-utility indices. The use of proxy measures is limited by being too generic, reliance on the caregiver rather than the patient perspective, lack of comprehensiveness across the entire dementia spectrum, preference for ease of measurement rather than patient perspective, and lack of validity.[70]

Important knowledge and research gaps exist regarding the lived experience of the individual across the dementia spectrum. It is critical that future research of dementia and cognitive impairment in AF involves increasing public awareness of early detection and prevention, identification of patient-specific outcome priorities and patient preferences, and development of patient-reported outcomes that are easily measured and statistically robust to allow for routine use.

Key point 9: Patient perspectives regarding AF-related cognitive impairment should be integrated into outcome measurements and possible treatments for AF-related cognitive decline.

## CONCLUSIONS

AF and cognitive impairment are major health issues that are expected to increase exponentially in the future. Patients place a high degree of importance on cognitive dysfunction and dementia as outcome measures. Numerous observational studies have described an association between AF and cognitive dysfunction ranging from mild impairment to overt dementia. The association is independent of manifest stroke as well as of the several risk factors common to both entities. Several pathophysiologic mechanisms have been proposed, some of which are potentially amenable to early intervention. Prospective and randomized clinical trials are required to understand links between AF and cognitive decline and to determine which interventions could effectively prevent decline in cognitive function and avert or delay the onset of dementia. These are required before screening for AF could be considered as a strategy to prevent or delay dementia.

## ARTICLE INFORMATION

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### Affiliations

Montreal Heart Institute, Université de Montréal, Canada (L.R., P. Khairy). Karolinska Institute, Stockholm, Sweden (L.F., M.R.). Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada (D.C., J.S.H., S.C.). Vestre Viken Hospital Trust, Norway (T.B.). Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Italy (G.B.). Odense University Hospital, Denmark (A.B.). Johns Hop-

kins University, Baltimore, MD (H.C.). Cardiovascular Clinical Academic Group, St Georges Hospital, London, UK (A.J.C.). University of Minnesota, Minneapolis (L.Y.C.). Catalonian Health Institute, Spain (J.L.C.E.). Tallaght Hospital, Dublin, Ireland (R.C.). Department of Electrophysiology, Heart Center Leipzig at University of Leipzig, Germany (N.D.). Columbia University, New York (M.S.V.E.). Karolinska Institutet, Department of Clinical Sciences, Danderyds Hospital, Stockholm, Sweden (J.E.). University of British Columbia, Vancouver Stroke Program, Canada (T.S.F.). Mayo Clinic, Rochester, MN (B.J.G.). Hackensack University Medical Centre, NJ (T.V.G.). Medical School, Faculty of Health and Medical Sciences, The University of Western Australia (G.J.H.). Trinity College, Dublin, Ireland (J.H.). Department of Neurology, Universitätsklinikum Würzburg, Germany (K.G.H.). StopAfib.org, Decatur, TX (M.T.H.). Lund University, Sweden (L.J.). Yonsei University College of Medicine, Seoul, South Korea (B.J.). University Heart and Vascular Center UKE Hamburg, Germany (P. Kirchhof). German Center for Cardiovascular Research (DZHK), partner site Hamburg/Kiel/Lübeck, Germany (P. Kirchhof). Institute of Cardiovascular Sciences, University of Birmingham, UK, and AFNET, Münster, Germany (P. Kirchhof). University Hospital of Zurich, Switzerland (D.K.). Aalborg University, Denmark (G.Y.H.L.). Department of Community Medicine, UiT The Arctic University of Norway, Tromsø (M.L.L.). Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN (M.M.). Cliniques du Sud Luxembourg, Arlon, Belgium (G.H.M.). Neurovascular Research Laboratory, Vall d'Hebron Institute of Research (VHIR), Barcelona, Spain (J.M.). Stroke Research Program, Institute of Biomedicine of Seville, Spain (J.M.). IBiS/Hospital Universitario Virgen del Rocío/CSIC/University of Seville, Spain (J.M.). Department of Neurology, Hospital Universitario Virgen Macarena, Seville, Spain (J.M.). University of Thessaly, Greece (G.N.). University of Glasgow, Glasgow Royal Infirmary, UK (T.J.Q.). University of Groningen, University Medical Center Groningen, the Netherlands (M.R., I.C.V.G.). Cedars-Sinai, Los Angeles, CA (R.K.S.). Department of Public Health, Health Service Executive West, Galway, Ireland (B.S.). University Heart Centre, Hamburg, Germany (R.B.S.). University of Oklahoma Health Sciences Center, Oklahoma City (S.S.). Ospedale dell'Angelo Venice-Mestre, Venice, Italy (S.T.). Jiaotong University School of Medicine, China (J.G.W.). Heart Research Institute for Charles Perkins Centre Heart Research Institute, and Concord Hospital Cardiology, the University of Sydney, Australia (B.F.).

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## Supplemental Material

Supplemental Material 1 and 2
Tables S1–S3

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