Cognitive dysfunction in atrial fibrillation

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Abstract | Atrial fibrillation (AF) is the most common arrhythmia in adults, and its incidence and prevalence increase with age. The risk of cognitive impairment and dementia also increases with age, and both AF and cognitive impairment or dementia share important risk factors. In meta-analyses of published studies, AF is associated with a 2.4-fold and 1.4-fold increase in the risk of dementia in patients with or without a history of stroke, respectively. This association is independent of shared risk factors such as hypertension and diabetes mellitus. Neuroimaging has illustrated several potential mechanisms of cognitive decline in patients with AF. AF is associated with increased prevalence of silent cerebral infarcts, and more recent data also suggest an increased prevalence of cerebral microbleeds with AF. AF is also associated with a pro-inflammatory state, and the relationship between AF-induced systemic inflammation and dementia remains to be investigated. Preliminary reports indicate that anticoagulation medication including warfarin can reduce the risk of cognitive impairment in patients with AF. Catheter ablation, increasingly used to maintain sinus rhythm in patients with AF, is associated with the formation of new silent cerebral lesions. The majority of these lesions are not detectable after 1 year, and insufficient data are available to evaluate their effect on cognition. Large prospective studies are urgently needed to confirm the association between AF and dementia, to elucidate the associated mechanisms, and to investigate the effect of anticoagulation and rhythm control on cognition.

Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population, affecting 6.8 million individuals in the USA in 2015 (REF.[1]). Worldwide, >33 million individuals have AF[2], the majority of whom are elderly. By the year 2050, 88% and 53% of individuals with AF are projected to be aged >65 years and >80 years, respectively[3]. Advanced stages of cognitive impairment or dementia, affecting 5.1 million individuals aged >65 years in the USA, are another major cause of morbidity and mortality in elderly individuals[4]. The evolving demographics of an ageing population in the USA are anticipated to result in a 2.5–3.0-fold increase in the prevalence of both AF and dementia by 2050 (REFS[1,3,4]). These important epidemiological trends are expected to cause a major increase in health-care expenditure[5,6].

AF and dementia share important risk factors, including age and cardiovascular risk factors such as hypertension and diabetes mellitus[7–9]. AF is associated with an increased risk of stroke, which in turn can increase the risk of cognitive impairment and dementia[10,11]. Other AF-related adverse cerebrovascular effects include hypoperfusion[12] and microembolism[13], which might increase the risk of dementia, independently of clinical stroke. The influence of factors other than stroke on dementia has been the subject of investigation for a long time. An independent association between AF and dementia could translate into a substantial increase in the morbidity, mortality, health-care utilization, and cost associated with both conditions. In this Review, we explore the evidence for cognitive impairment in AF and the related mechanisms. We also discuss the potential therapeutic opportunities that this association might represent to prevent cognitive impairment in individuals with AF, and we highlight the research areas that will require future investigation.

Is AF associated with cognitive impairment?

Individual studies into the association between AF and dementia or cognitive impairment have substantial heterogeneity in both their design and conclusions. Consequently, a review of the factors that make the interpretation of these studies challenging is warranted before discussing the individual studies. The definitions and tools used to diagnose cognitive impairment vary in clinical practice and across the published literature. For instance, studies have used either systematic cognitive function testing or clinical

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Key points

- Atrial fibrillation is associated with increased risks of dementia and cognitive impairment, independent of history of stroke and other shared risk factors.
- Proposed mechanisms of cognitive impairment in atrial fibrillation include cerebral thromboembolism, cerebral hypoperfusion, and cerebral microbleeds.
- Anticoagulation might be protective against cognitive impairment in atrial fibrillation, but further prospective studies are needed.
- Catheter ablation of atrial fibrillation is associated with new silent cerebral lesions, but the effect on cognitive function is unknown.

diagnoses with International Classification of Disease (ICD) codes to diagnose cognitive impairment. The use of ICD codes relies on clinical recognition of cognitive impairment by a treating physician, a setting that can lead to substantial underdiagnosis[14,15]. The tools for systematic screening of cognitive impairment vary from comprehensive batteries of neuropsychometric tests to single-screening instruments, which can lead to underdiagnosis or overdiagnosis. Other considerations can affect the estimated prevalence of cognitive dysfunction in the general population, including varying diagnostic criteria for dementia, severity of cognitive impairment (for instance, mild cognitive impairment (MCI) versus dementia), and the specific cognitive domains tested[16]. Given the substantial variability in the terminology and diagnostic criteria found in the literature, the broad term 'cognitive impairment' is used in this Review. Despite a standardized electrocardiogram (ECG)-based method to diagnose AF, considerable variability in the prevalence of AF can be observed between studies depending on the frequency of the screening and the tools used[17]. Study design and length of follow-up are also important considerations. Cross-sectional studies can inform on the association between AF and cognitive impairment, but the lack of information on the temporal sequence of the onset of the diseases limits their value. For this reason, in this Review, we concentrate on prospective longitudinal studies on the evolution of cognitive function in AF, which have established that dementia occurs after the diagnosis of AF. These largely epidemiological studies might also be biased by competing diagnoses that affect the risk of AF and dementia, which might not be adequately adjusted for by statistical methods. These studies also do not account for any effect that the treatment of AF and anticoagulation might have on the risk of dementia. Given that the majority of the data are derived from Western populations, their applicability to non-Western countries needs to be verified. We provide an overview of the literature with these caveats in mind.

Cognitive impairment in AF after stroke. AF is associated with a fivefold increase in the risk of stroke, and the risk increases with age[11]. Stroke in patients with AF is also more severe and more likely to lead to clinically significant disability than stroke in patients without AF[18]. AF-related stroke also has a higher 1-year recurrence rate and 1-year mortality than non-AF-related stroke[19]. Stroke itself is a powerful cause of cognitive decline. In the general population, 10% of patients develop dementia after a first stroke[10]. Several individual studies have reported a significant association between AF and dementia in patients with prior stroke[20–23]. In a meta-analysis, Kwok and colleagues reported a 2.4-fold increase in the risk of dementia after stroke (95% CI 1.7–3.5) in patients with AF compared with patients without a history of AF[24]. The increased risk might be due to greater prevalence and severity of comorbidities such as hypertension and diabetes in patients who develop both AF and stroke. As discussed later, another plausible explanation is that AF provides a favourable milieu for the development of dementia after stroke owing to additional insults to the brain from cerebral hypoperfusion and silent strokes. Neurological deficits make routine neuropsychometric testing more difficult and can challenge the diagnosis of dementia after stroke[25]. Cognitive domains other than memory can also be preferentially affected. Therefore, the management of stroke in patients with AF should include longitudinal assessment of multiple domains of cognitive function.

Cognitive impairment in AF in the general population. Emerging evidence suggests that AF is associated with an increased risk of dementia in individuals without a history of stroke, independent of shared risk factors. An overview of important studies on the association between AF and dementia, including their design and outcomes, is provided (TABLE 1). A careful analysis revealed substantial heterogeneity in the designs and findings of the individual studies[24]. Some studies, including the Intermountain Health Collaborative Study[26] and the Rotterdam Study[27], reported a significant association between AF and future risk of dementia, whereas other studies did not[28–31]. Two independent meta-analyses of prospective longitudinal studies by Kalantarian and colleagues[32] (relative risk (RR) 1.40, 95% CI 1.19–1.64) and Santangeli and colleagues[33] (HR 1.42, 95% CI 1.17–1.72) reported a higher risk of dementia or cognitive dysfunction in patients with AF without a history of stroke than in individuals without AF. The risk of Alzheimer dementia and the risk of vascular dementia are both increased in patients with AF[26]. As in the general population, Alzheimer dementia is the dominant subtype of dementia diagnosed in patients with AF[26]. However, these data must be interpreted with caution given that epidemiological studies are limited in their capacity to distinguish between subtypes of dementia.

Study design and power as well as length of follow-up might account for some of the discrepancy in outcomes between observational studies, but the intriguing possibility of the influence of age and sex needs to be considered. Studies that found an increased risk of dementia in patients with AF tended to enrol younger individuals than the studies that did not. Bunch and colleagues reported that AF significantly increased the risk of dementia in individuals aged <70 years but not in individuals aged >80 years[26]. In the Rotterdam Study[27], the association between AF and dementia was stronger in patients aged <75 years than in older individuals. In a subsequent update of the longitudinal Rotterdam Study[34], the investigators reported

Table 1 | **Studies on the association between atrial fibrillation and cognitive impairment**

Study (year)	Design	Number of patients, age (years), % male, mean follow-up (years)	Ascertainment of AF	Neurocognitive assessment and outcome	Outcome measure	Results	Refs
Bunch et al. (2010)	Prospective longitudinal study; individuals enrolled in the Intermountain Health Collaborative Study	• 37,025 • 60.6 (±17.9) • 60.1 • 5	ICD-9 codes or ECG documentation; incident and prevalent AF were included	ICD-9 codes for dementia; no systematic assessment of cognition	Dementia	Significant association between AF and dementia (OR 1.56, 95% CI 1.40–1.74)	26
Dublin et al. (2011)	Prospective longitudinal, community-based study	• 3,045 • 74.3 (70.3–79.5) • 40 • 6.8	ICD codes for AF; incident and prevalent AF were included	Screening with Cognitive Abilities Screening Instrument; diagnosis with neuropsychological assessment	Dementia	Significant association between AF and dementia (HR 1.38, 95% CI 1.10–1.73)	142
Marzona et al. (2012)	Prospective longitudinal study; participants enrolled in two randomized trials of antihypertensive therapy (ONTARGET and TRANSCEND)	• 31,506 • 66.5 (±7.2) • 70 • 4.7	Incident and prevalent AF were included	MMSE	Decline in cognitive function score; dementia diagnosed by a physician or MMSE score ≤23	AF was associated with new dementia (HR 1.30, 95% CI 1.14–1.49) and with cognitive decline (HR 1.14, 95% CI 1.03–1.26)	31
Thacker et al. (2013)	Prospective longitudinal study; community-based cohort	• 5,888 • 73.0 (±5.4) • 41 • 7	ICD codes and annual ECG; only incident AF was included	Modified MMSE	Decline in cognitive function score	Significant increase in the rate of decline in cognitive function score with ageing in AF	38
Tilvis et al. (2004)	Prospective longitudinal study; population-based Helsinki Ageing Study	• 650 • 75 (37%), 80 (33%), and 85 (30%) at time of enrolment • 60 • 5 and 10	NR	MMSE and CDR	Cognitive decline defined as an increase in CDR class or a decrease of ≥4 points in MMSE score	AF was associated with cognitive decline at 5 years (RR 2.88, 95% CI 1.26–6.06)	39
Elias et al. (2006)	Prospective cross-sectional study; community-based cohort of Framingham Offspring Study	• 1,011 • 61 (37–89) • 100 • NA	ECG diagnosis	Neuropsychological assessment battery	Cognitive function scores	AF was associated with worse performance in multiple cognitive domains	143
Forti et al. (2007)	Prospective longitudinal study of individuals with MCI and normal cognition	• 611 • 75.2 (±9.0) • 37 • 3 in MCI group and 4 in normal cognition group	Participant-reported history, medical charts	MMSE and neuropsychiatric battery	Dementia is defined by a deficit in ≥2 cognitive domains that is severe enough to affect functional abilities	AF was associated with dementia in individuals with MCI (HR 4.63, 95% CI 1.72–12.46) but not in individuals with normal cognition at baseline (HR 1.10, 95% CI 0.40–3.03)	36
Park et al. (2007)	Prospective longitudinal community-based study with matched cohorts of individuals with or without AF	• 423 • 75.6 • 52.5 • 1 and 3	ECG documentation	Neuropsychological assessment battery	Decline in cognitive test scores	No significant difference in cognitive function scores between cohorts with or without AF	144
Rastas et al. (2007)	Prospective longitudinal community-based study of community of individuals aged >85 years	• 553 • 88.4 (±2.9) • 20 • 3.5 and 8.0	ECG or Holter documentation	Neuropsychological assessment battery and neurologist examination	Dementia per DSM-III criteria	AF was not associated with incident dementia in the very elderly individuals	145
Marengoni et al. (2011)	Prospective longitudinal, population-based study of individuals aged >75 years	• 685 • >75 • NR • 6	Clinical diagnosis identified using ICD-9 codes	MMSE	Dementia per DSM-III criteria	AF was not associated with incident dementia (HR 0.9, 95% CI 0.5–1.7)	28

Table 1 (cont.) | **Studies on the association between atrial fibrillation and cognitive impairment**

Study (year)	Design	Number of patients, age (years), % male, mean follow-up (years)	Ascertainment of AF	Neurocognitive assessment and outcome	Outcome measure	Results	Refs
Haring et al. (2013)	Prospective longitudinal study of women enrolled in the Women's Health Initiative Memory Study	• 6,455 • 65–79 • 0 • 8.4	Participant-reported history	Modified MMSE and neurocognitive and neuropsychiatric examinations	MCI or probable dementia	No significant association between AF and MCI or probable dementia ($P = 0.24$)	29
Di Carlo et al. (2007)	Prospective Italian longitudinal study on ageing	• 2,830 • 73.7 (±5.6) • 53.7 • 3.9 (±0.7)	Clinical documentation of AF	Neuropsychiatric battery	Progression of normal cognition and MCI to dementia	No significant association between AF and progression to dementia in individuals with MCI or normal cognition	37
Ott et al. (1997)	Cross-sectional population-based Rotterdam Study	• 6,583 • 69.2 (±9.1) • 41.8 • NA	ECG documentation	MMSE followed by neuropsychiatric battery	Dementia per DSM-III; cognitive impairment defined by MMSE score <26	AF was associated with dementia (HR 2.3, 95% CI 1.4–3.7) and cognitive impairment (HR 1.7, 95% CI 1.2–2.5)	27
Li et al. (2011)	Prospective longitudinal study of individuals with MCI	• 837 • 66.5 (±7.1) • 41.7 • 5	ICD-9 codes	MMSE for screening; neuropsychiatric battery testing for the individuals who screened positive	Conversion of MCI to dementia defined by DSM-IV criteria	AF was not associated with progression of MCI to dementia (HR 1.09, 95% CI 0.54–2.20)	146
Peters et al. (2009)	Prospective longitudinal study of individuals with hypertension aged ≥80 years; Hypertension in the Very Elderly Trial	• 3,336 • ≥80 • 39.6 • 2	ECG documentation	MMSE for screening; neuropsychiatric testing for the individuals who screened positive	Dementia defined by DSM-IV criteria; cognitive decline defined by MMSE score <24 or an annual decline of ≥3 points in score	AF was not associated with dementia (HR 1.03, 95% CI 0.62–1.72) and cognitive decline (HR 1.08, 95% CI 0.80–1.46)	30
Jozwiak et al. (2006)	Cross-sectional study of hospitalized patients aged ≥65 years	• 2,314 • 76 (71–81) • 34.9 • NA	ECG diagnosis	MMSE	Impaired cognitive function defined by MMSE score <24	Significant association between AF and impaired cognitive function (OR 1.56, 95% CI 1.27–1.92)	147
Alonso et al. (2017)	Cross-sectional community-based study in the Atherosclerosis Risk in Communities Neurocognitive Study	• 6,432 • 79 (±5) with AF; 76 (±5) without AF • 41 • NA	ECG documentation or ICD-9 codes	Neurocognitive battery and neurological examination	Dementia and MCI using the National Institute on Ageing–Alzheimer's Association definition	Significant association between AF and dementia (OR 2.25, 95% CI 1.64–3.10) and between AF and MCI (OR 1.28, 95% CI 1.04–1.56)	148
Nishtala et al. (2018)	Longitudinal community-based Framingham Heart Study	• 2,682 • 72 (±9) with AF • 45 • 1–3 in AF group 2; 2–3 in non-AF group 3	Patient-reported diagnosis verified using medical records	Battery of neurocognitive tests	Score in individual tests of neurocognitive function that assess different domains	Greater decline in score of executive function in AF during follow-up	149
de Bruijn et al. (2015)	Longitudinal population-based Rotterdam Study	• 6,514 • 75.7 (±8.1) with AF; 68.3 (±8.5) without AF • 41 • 20	Routine ECG screening and patients' medical records	Screening using MMSE and Geriatric Mental State Schedule organic level; individuals with abnormal scores had neuropsychological testing to diagnose dementia	Dementia defined using DSM-III criteria	Higher incidence of dementia in patients with prevalent AF (HR 1.34, 95% CI 1.03–1.74) and with incident AF (HR 1.23, 95% CI 0.98–1.56)	34

AF, atrial fibrillation; CDR, Clinical Dementia Rating; DSM, *Diagnostic and Statistical Manual of Mental Disorders*, third (DSM-III) and fourth (DSM-IV) editions; ECG, electrocardiogram; ICD, International Classification of Diseases; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NA, not applicable; NR, not reported; RR, relative risk.

that incident AF was associated with an increased risk of dementia in patients aged <67 years but not in older patients. The risk of dementia was also associated with the length of AF history in younger patients, which is suggestive of a dose–response relationship[34]. Therefore, AF might be an important risk factor for dementia in the less elderly individuals given that other risk factors that trigger neurodegeneration become more important in the very elderly population. Patients with AF might also be at risk of more rapid progression of cognitive dysfunction at a younger age. MCI is a precursor of dementia and is associated with an increased probability of progression to dementia[35]. Forti and colleagues reported that AF was associated with an increased risk of conversion from MCI to dementia[36]. Even if this finding was not confirmed by a large Italian cohort study[37], other studies have reported a greater decline in cognitive function scores in patients with AF than in individuals without AF[38,39]. Therefore, future studies investigating methods to preserve cognition in patients with AF should particularly focus on the relatively younger elderly individuals, such as those aged <70 years.

Preliminary studies suggest that women are at greater risk of cognitive impairment than men. This finding is interesting given that women are also at higher risk of AF-related stroke. The Rotterdam Study[27] reported a stronger association between AF and dementia in women than in men. The Mayo Clinic Study of Aging[35] also reported a stronger association between cardiac diseases (including AF) and non-amnestic MCI in women than in men. However, in the Women's Health Initiative Memory Study[29], AF was not associated with MCI or dementia in women aged 65–79 years. Therefore, sex-specific differences in the risk of cognitive impairment warrant further investigation.

Subclinical AF, which is detected by devices that provide prolonged monitoring of cardiac rhythm, has been shown to be associated with a higher risk of stroke. For example, a study using cardiac implanted electronic devices showed that atrial tachyarrhythmias lasting >6 min were associated with a 2.5-fold increase in the risk of stroke[40]. Whether oral anticoagulation is effective in preventing strokes in patients with subclinical AF is the subject of the ongoing ARTESiA trial[41]. To date, the effect of subclinical AF on cognitive function has not been studied.

Neuroimaging in AF

Neuroimaging has contributed to our understanding of the mechanisms by which AF can lead to cognitive impairment. CT of the brain is widely used to image patients with AF, particularly in acute stroke to rule out intracerebral haemorrhage. Given its lack of sensitivity to detect old ischaemic events, CT has been mostly replaced by MRI for non-urgent brain imaging[42]. Brain MRI can reveal a number of asymptomatic findings, including silent cerebral infarction (SCI), white matter hyperintensities, and cerebral microbleeds. An introduction to the findings from brain MRI in AF is provided below, followed by a detailed assessment of their implications for the understanding of the pathophysiological mechanisms of cognitive decline in AF. Examples of important findings from brain MRI in AF are shown (FIG. 1). The terminology that we use is based on the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE)[43], but note that these definitions are not standardized across the literature.

Silent cerebral infarction. SCI refers to the presence of focal cerebral ischaemia in the absence of clinical signs and symptoms. Population-based studies suggest that the frequency of SCI detected on brain MRI is 21%

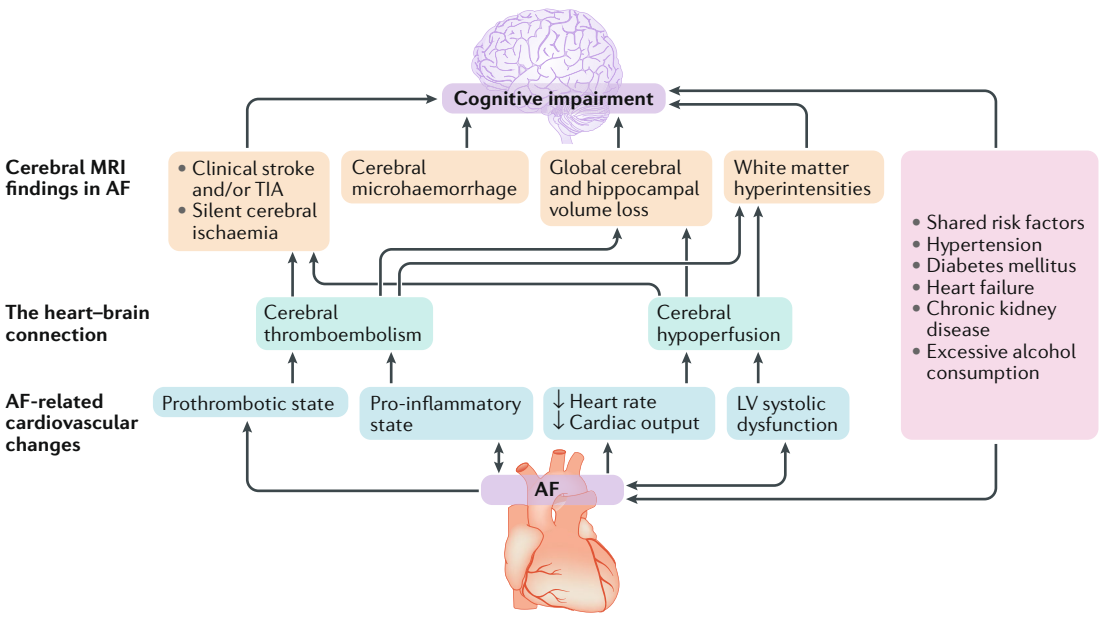

Fig. 1 | **Proposed pathophysiology of cognitive impairment in atrial fibrillation.** Atrial fibrillation (AF) has a number of effects that predispose to cognitive impairment, including a prothrombotic state, a pro-inflammatory state, and reduced cardiac output. Final pathways leading to cognitive impairment potentially include cerebral embolism, haemorrhage, and volume loss. LV, left ventricular; TIA, transient ischaemic attack.

in the general population at a mean age of 72 years and that the presence of these silent infarcts increases the risk of future stroke and dementia[44,45]. Cross-sectional studies utilizing CT or MRI have revealed a higher prevalence of SCI in individuals with AF than in individuals without AF in the absence of a clinical history of stroke[46–52]. In a meta-analysis of 17 studies, AF was associated with a higher prevalence of SCI (OR 2.6, 95% CI 1.8–3.8)[32]. The reported prevalence of SCI in AF varies, probably owing to differences in the study population, imaging techniques, and the definition of SCI. In the pooled analysis of studies, the prevalence of SCI in patients with AF was 40% (95% CI 29–51%) on MRI and 22% (95% CI 13–32%) on CT[32]. The prevalence of SCI was similar in patients with paroxysmal AF or with persistent AF, although patients with persistent AF had a greater number of lesions per person[32,49]. Subclinical AF was associated with SCI in patients with diabetes[52]. Therefore, the risk of SCI-associated dementia in AF might be present regardless of the symptoms and the duration of AF. The number of SCIs also correlates with the $CHADS_2$ score[50]. The pathophysiology of SCI in AF includes thromboembolism, but the role of anticoagulation in preventing SCI and its effect on cognition are not well studied.

Brain atrophy. Small cohort studies have provided information on global and regional brain volumes in patients with AF. In a cross-sectional study of stroke-free individuals, AF was associated with smaller hippocampal volumes and correspondingly worse memory performance, whereas no association was observed between AF and total brain volume or white matter hyperintensity volume[53]. By contrast, in the population-based Mayo Clinic Study of Aging[13], AF was associated with a lower total grey matter volume but was not associated with changes in hippocampal volume.

Cerebral microbleeds. Cerebral microbleeds are small areas of signal void (generally 2–5 mm in diameter, but sometimes up to 10 mm) with associated blooming, which can be seen on T2-weighted MRI or other sequences that are sensitive to susceptibility effects, as defined by the STRIVE terminology[43]. Cerebral microbleeds are common in the general population and have been reported in 15% of the participants in the Rotterdam Scan Study[44], a population-based prospective study conducted in a general community setting. In this study, the presence of cerebral microbleeds increased the risk of dementia by twofold. Cerebral microbleeds are markers of cerebral small-vessel disease, and deep cerebral and lobar microbleeds are associated with hypertensive small-vessel disease and amyloid angiopathy, respectively. Cerebral microbleeds predict future intracerebral haemorrhage and cognitive decline in the general population[54–58]. Cerebral microbleeds found in patients with a history of ischaemic stroke or transient ischaemic attack are associated with a twofold increased risk of future ischaemic stroke and an eightfold increased risk of future intracerebral haemorrhage[59].

Cerebral microbleeds have been reported in patients with AF and stroke, although a direct pathophysiological role for AF has not been established. In a small cohort of patients with AF and ischaemic stroke, cerebral microbleeds were noted in 27% of patients and were associated with future stroke events[60]. In another cohort, cerebral microbleeds were seen in 30% of 507 patients with AF and ischaemic stroke[61]. The burden of microbleeds correlated with ischaemic stroke-related mortality during a median follow-up of 2.5 years, and the presence of lobar microbleeds was also associated with future intracerebral haemorrhage[61]. Coexisting vascular risk factors such as age and hypertension are likely to explain any association between AF and cerebral microbleeds. Oral anticoagulation with warfarin has been associated with increased incidence of cerebral microbleeds; conversely, the presence of cerebral microbleeds (in particular lobar microbleeds) has been associated with increased risk of warfarin-associated intracerebral haemorrhage[57,58,61]. In a cohort of patients with nonvalvular AF, the $CHADS_2$ and CHA_2DS_2-VASc scores correlated with the presence and number of cerebral microbleeds. In addition, cerebral microbleeds, but not the $CHADS_2$ or CHA_2DS_2-VASc scores, were predictive of future occurrence of intracerebral haemorrhage[62].

Transcranial Doppler. Microembolic signals were detected using transcranial Doppler in 21% of patients with AF compared with 5% of controls without known AF[63], but whether microemboli contribute to cognitive decline in AF requires further investigation.

Can neuroimaging be used to guide AF treatment? Emerging data on the role of SCI and cerebral microbleeds in AF raise the question of whether neuroimaging can be used to fine-tune the treatment for AF and mitigate the effect of AF on the brain[64]. Despite being promising, the available evidence is still insufficient to allow the clinical use of this tool. Potential areas of research in neuroimaging to guide the individualization of treatment for AF include: the utility of MRI-detected SCI to refine risk stratification for future stroke and cognitive impairment; the predictive value of the presence, distribution, and burden of cerebral microbleeds or superficial siderosis for future intracerebral haemorrhage; and the utility of the findings from MRI in guiding therapy, including the choice of anticoagulants (vitamin K antagonist or direct oral anticoagulants (DOACs)), for patients.

Role of other imaging techniques in predicting neurocognitive outcomes. The utility of several measures of vascular and cardiac health in predicting neurocognitive outcomes in the general population is an area of active investigation, although data specific for AF are currently not forthcoming. Arterial stiffness measured by tonometry has been shown to correlate positively with the progression of cognitive decline[65]. Cardiac index assessed using ECG has been shown to correlate with cerebral blood flow in the temporal region[66], and lower cerebral blood flow is a potential cause of cognitive decline. Additionally, a nonlinear relationship was found between left ventricular ejection fraction and accelerated cognitive decline[67]. Whether these correlations extend to patients with AF and whether they can be effective therapeutic targets require further investigation.

Pathophysiology of cognitive decline in AF

The mechanisms of cognitive impairment in AF are likely to be multifactorial, and several plausible biological mechanisms have been proposed. The complex interactions between AF-related vascular phenomena and neuroimaging evaluation of dementia are summarized (FIG. 2) and discussed below.

Shared risk factors. AF and dementia share a number of risk factors. Advancing age is the most important risk factor for dementia, and the incidence and prevalence of AF also dramatically increase with age[1,4]. Comorbid illnesses including hypertension, diabetes mellitus, coronary artery disease, and heart failure are known risk factors for both dementia and AF[7–9,68–71]. Other shared risk factors include chronic kidney disease[72,73], excessive alcohol consumption[74,75], and sleep apnoea[76,77]. These comorbidities can accumulate with age, thereby contributing to a parallel increase in the incidence of AF and dementia. However, the existence of shared risk factors is unlikely to be the only explanation for the association between AF and dementia that is seen in epidemiological studies. Indeed, several studies have demonstrated an association between AF and dementia after adjustment for the risk factors mentioned above. However, in observational studies, a residual confounding effect due to unidentified shared risk factors or to the lack of adjustment for the severity of the comorbidities cannot definitely be ruled out. Nevertheless, the observation that the association between the two conditions is stronger in younger individuals and becomes nonsignificant in very elderly individuals argues against a singular role of the accumulation of shared risk factors with age in the pathogenesis of dementia in AF[26].

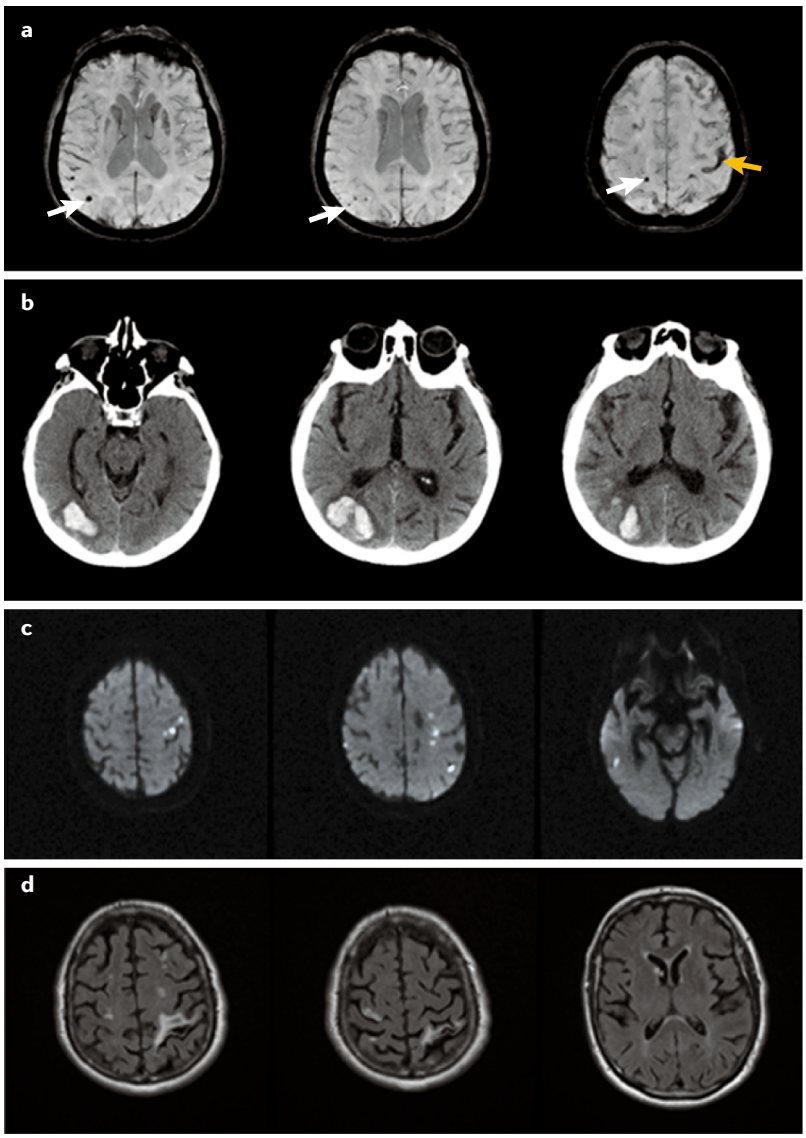

Fig. 2 | **Neuroimaging findings in patients with atrial fibrillation. a** | Axial T2 star-weighted angiography MRI sequence demonstrating multiple lobar cerebral microbleeds (white arrows) and superficial siderosis (yellow arrow) consistent with amyloid angiopathy. **b** | Axial CT of the head demonstrating a lobar intracerebral haemorrhage in a patient with atrial fibrillation (AF) who previously had cerebral microbleeds. **c** | Axial diffusion-weighted MRI demonstrating multiple acute ischaemic strokes in different vascular territories consistent with embolism in a patient with AF. **d** | T2-weighted fluid attenuated inversion recovery (FLAIR) MRI demonstrating multiple areas of chronic ischaemic infarction in a patient with AF.

Cerebral infarction. Cerebral infarction is likely to be one of the major factors that contribute to cognitive decline in AF. AF induces a prothrombotic state and pro-inflammatory state, both of which increase the risk of cerebral infarction[78]. Barber and colleagues reported the expression of serum markers of increased thrombin generation and fibrin turnover in patients with AF who developed dementia, which suggests a predisposition to thrombosis[79]. Clinical stroke increases the risk of dementia in AF, but SCI is far more common and is an important putative link in the pathway leading to dementia. Despite SCI being associated with dementia in the general population, this association is not well studied in patients with AF[45]. In the population-based Mayo Clinic Study of Aging[13], patients with both AF and SCI were threefold more likely to develop MCI than patients with either AF or SCI only (FIG. 3). Two other studies reported lower scores in certain domains of cognitive function, including visuo-spatial ability, in patients with AF and SCI[47,49]. However, the larger prospective epidemiological studies on cognition in AF did not perform neuroimaging. Therefore, the temporal association between the incidence of AF and the development of SCI and dementia should be a focus of future studies.

Cerebral hypoperfusion. Cerebral hypoperfusion has been associated with the development of both vascular and Alzheimer dementia[80], and chronic cerebral hypoperfusion in systolic and diastolic heart failure has been associated with dementia[67,81]. Similarly, AF can result in reduced cardiac output secondary to increased heart rate, R–R interval variability, and reduced left ventricular systolic function[82]. In patients with heart failure, the presence of AF exacerbated cerebral hypoperfusion (detected by transcranial Doppler) and cognitive deficits[12]. Persistent AF has also been associated with reduced total cerebral blood flow compared with that in individuals in sinus rhythm at the time of imaging[83]. Whether AF causes a critical degree of cerebral hypoperfusion sufficient to cause cognitive decline in cohorts without heart failure has not been

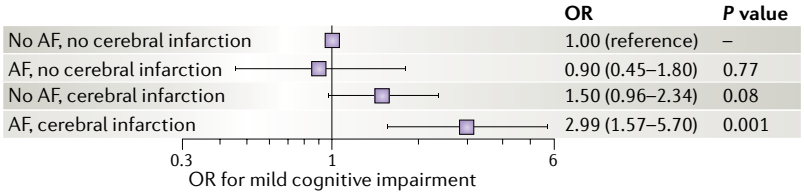

Fig. 3 | **Interaction between atrial fibrillation, cerebral infarction, and mild cognitive impairment.** The presence of cerebral infarction on cerebral MRI in patients with atrial fibrillation (AF) is associated with mild cognitive impairment: results from the Mayo Clinic Study of Aging. Reproduced with permission from REF.[13], Elsevier.

investigated. Although white matter hyperintensities — a marker of small-vessel disease — are strongly associated with cerebral hypoperfusion, a cause–effect relationship has not been established[84]. Whether AF is associated with a higher incidence of white matter hyperintensities is controversial[64]. Prospective longitudinal studies to assess regional and global cerebral blood flow in AF and their correlation with changes in cognitive function are needed. These studies should use advanced neuroimaging techniques such as PET and arterial spin labelling MRI[84]. Restoration of sinus rhythm in AF using antiarrhythmic drug therapy or catheter ablation might have the potential to improve cerebral perfusion and mitigate cognitive decline. The effect of rhythm control on cognition in AF requires further study.

Intracerebral haemorrhage and cerebral microbleeds. Intracerebral haemorrhage is a feared complication of the use of oral anticoagulation in AF, with a reported annual rate of 0.1–2.5%[85]. Intracerebral haemorrhage has been associated with cognitive decline but has a low overall incidence even among patients receiving anticoagulation therapy[86,87]. Among patients with acute ischaemic stroke, cerebral microbleeds are more common in individuals with AF than in individuals without AF[88], are more prevalent among patients taking anticoagulants[89], and are associated with an increased risk of dementia in the general population[90]. However, the incidence of cerebral microbleeds in patients with AF and without stroke is not well defined[91]. Whether cerebral microbleeds have a direct pathogenic role in the development of dementia is controversial[58]. However, they are likely to be a marker of the pathogenic mechanisms underlying dementia, including hypertensive small-vessel disease and cerebral amyloid angiopathy, which is seen in patients with Alzheimer dementia. Microbleeds that are positioned in critical regions of the brain might also directly affect cognition, but current evidence is limited[58]. Although the role of intracerebral microhaemorrhage and macrohaemorrhage in causing dementia in AF is likely to be limited, further studies are required.

Inflammation. AF is associated with the expression of cardiac and systemic inflammatory markers involved in the onset of AF. In addition, AF itself might activate inflammatory pathways leading to the electrical and structural remodelling of the atria that perpetuates AF[78]. The pro-inflammatory state in AF might result in cognitive impairment through the induction of a prothrombotic state that promotes cerebral infarcts or through other putative mechanisms such as the direct effects of inflammatory markers on the brain.

A number of inflammatory markers have been associated with stroke in AF, including C-reactive protein (CRP), IL-6, von Willebrand factor, and asymmetric dimethylarginine[92–95]. The mechanisms of inflammation-mediated thrombosis include endothelial dysfunction, activation of the coagulation pathways, and platelet activation[78]. Dementia, including Alzheimer dementia, is associated with a cerebral neuroinflammatory process[96]. The inflammatory processes in AF and Alzheimer dementia share a number of common pathways, including CRP, tumour necrosis factor, IL-1, IL-4, IL-10, and transforming growth factor-β[78,96]. In an in vitro model of rapidly paced atrial myocytes mimicking AF, oxidative stress was shown to produce γ-ketoaldehydes, which are highly reactive lipid-derived mediators that can produce pre-amyloid oligomers from proteins. Pre-amyloid oligomers produced in atrial myocytes through this mechanism might perpetuate AF[97]. γ-Ketoaldehydes have also been implicated in the production of pre-amyloid oligomers from amyloid-β1, which are implicated in Alzheimer dementia, providing a potential link between the two disease processes[98]. Whether the cardiac and systemic pro-inflammatory markers in AF directly lead to cerebrovascular or neural dysfunction is currently unknown, and the association between hypothetical mechanisms and disease causation remains unproven. Answers will not be forthcoming unless the trials that investigate anti-inflammatory mechanisms and therapies in atherosclerosis include prospective data on cognitive function and testing.

Effect of AF treatment on cognition

Patients with AF are frequently treated with anticoagulants, medications to control the heart rate, antiarrhythmic agents, and catheter ablation. Although the efficacy of these therapies to control AF-related symptoms and reduce the risk of stroke has been the subject of large randomized, controlled trials, their effect on cognition is not well understood. The important pathophysiological pathways by which AF therapies might affect cognition are summarized (FIG. 4).

Anticoagulation. Anticoagulation with warfarin or a DOAC has been shown to reduce the incidence of stroke in AF and is recommended for individuals at moderate-to-high risk of stroke[99]. Oral anticoagulants might also reduce the risk of dementia by reducing systemic embolism. Conversely, oral anticoagulation is associated with an increased risk of intracerebral haemorrhage and cerebral microbleed, two events that might be associated with a higher risk of dementia. Despite these competing issues, most patients treated with oral anticoagulants have a net clinical benefit from stroke reduction. Whether this net benefit of neural preservation also induces a reduction in cognitive dysfunction is the subject of active investigation[100]. In a population-based cohort of incident AF, Madhavan

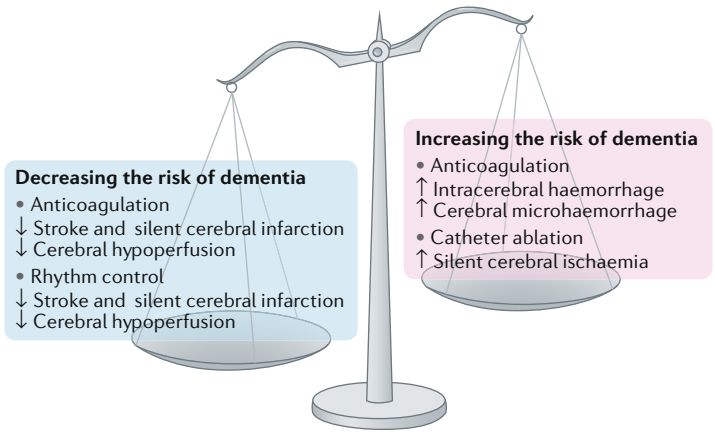

Fig. 4 | **Potential effects of treatment for atrial fibrillation on the risk of future dementia.** Treatment of atrial fibrillation can exert competing effects on the risk of dementia. For example, anticoagulation can decrease the risk of thromboembolism and increase the risk of cerebral haemorrhages at the same time.

and colleagues found a significant reduction in the incidence of dementia in warfarin-treated patients during a mean follow-up of 5 years[101]. The BAFTA study[102], a randomized, controlled trial that compared Mini-Mental State Examination (MMSE) scores in patients with AF treated with warfarin versus aspirin, showed no significant difference between the two groups during a mean follow-up of 2.7 years. However, after 33 months of follow-up, MMSE scores showed a trend in favour of warfarin[102]. Barber and colleagues also reported a trend towards reduced incidence of dementia in patients with AF treated with warfarin compared with untreated patients after 3 years of follow-up, although statistical significance was not reached[79]. Both studies were limited by their small sample size and their fairly short durations of follow-up. Current evidence on the effect of anticoagulation on cognitive impairment in AF, therefore, remains inconclusive[103].

Several observational studies have reported an inverse correlation between cognitive decline and the time in the therapeutic range when taking warfarin, which measures its anticoagulation efficacy[101,104,105]. Interestingly, Madhavan and colleagues reported a higher risk of dementia in patients with either subtherapeutic or supratherapeutic anticoagulation than in patients in the therapeutic range of warfarin[101]. The combination of supratherapeutic anticoagulation with warfarin and an antiplatelet agent has been reported to increase the incidence of dementia in patients with AF[106]. These findings suggest that increased systemic thromboembolism with subtherapeutic international normalized ratio (INR) and increased risk of cerebral haemorrhage with supratherapeutic INR predispose to cognitive decline[107]. These studies did not perform neuroimaging, and a cause–effect relationship cannot be inferred. Nevertheless, these findings emphasize the importance of maintaining the INR in the therapeutic range in patients treated with warfarin.

DOACs might provide a more steady state of anticoagulation, are equally effective in preventing stroke, and are associated with lower risks of intracerebral bleeding and cerebral microhaemorrhages than warfarin[108–111]. In an observational cohort study, patients treated with DOACs had a lower incidence of a combined end point of stroke and dementia than patients receiving warfarin[112]. The different effects of DOACs and warfarin or antiplatelet therapy on cognition in patients with AF and at high risk of stroke need to be compared in future prospective trials. Two such trials are ongoing and will help to shed light on DOACs: BRAIN-AF[113], which compares rivaroxaban with aspirin, and the GIRAF study[114], which compares dabigatran with warfarin. Left atrial appendage closure using a percutaneously delivered device has been shown to be noninferior to anticoagulation with warfarin to prevent stroke[115]. However, whether this option translates into a reduced incidence of cognitive dysfunction is not known.

Rate versus rhythm control. Controlling the rhythm in patients with AF through the use of antiarrhythmic drugs is frequently pursued to attenuate symptoms related to AF. The effect of rhythm control on cognitive outcomes is currently unknown. The randomized, controlled AFFIRM trial[116] showed no significant difference in mortality in patients treated with rate versus rhythm control. A subset of patients in the AFFIRM trial underwent cognitive testing. No significant difference was seen in the MMSE scores of patients treated with rate control and those treated with an antiarrhythmic drug to control the rhythm[117]. Investigators in the ongoing EAST trial[118] are randomly assigning patients with AF to evaluate the effects of catheter ablation and an antiarrhythmic drug on the control of heart rate and rhythm, with cognitive dysfunction as a secondary end point.

Catheter ablation. The risk of dementia following catheter ablation of AF can be affected by the competing factors of increased risk of cerebral emboli during the procedure and potential reduction in the risk of stroke or hypoperfusion due to long-term rhythm control. Catheter ablation carries a <1% risk of clinically overt stroke or transient ischaemic attack[119]. However, new silent cerebral lesions (SCLs) detected on cerebral MRI after catheter ablation are a common occurrence and are reported in 4.3–38.9% of patients[120–123]. The reported incidence varies depending on procedural factors, imaging characteristics, and the definitions used. Although much remains to be studied regarding the aetiology and risk factors for SCLs related to ablation, the risk factors associated with the procedure seem to be most relevant. The use of phased duty-cycled radiofrequency catheter, lower intensity of intravenous heparin anticoagulation, and electrical cardioversion during the procedure are associated with a higher risk of SCL[122–125]. No significant difference was noted between cryoablation and radiofrequency ablation with irrigated catheter[126]. Conversely, continuation of therapeutic anticoagulation with warfarin during ablation was associated with a lower risk of SCL[127]. In one study, 2% of patients undergoing ablation of AF while receiving therapeutic anticoagulation with warfarin experienced an SCL, whereas 14% of patients who stopped taking warfarin before the ablation with heparin bridging had

an SCL[127]. DOACs have also been shown to be effective in preventing clinical thromboembolism after catheter ablation compared with uninterrupted warfarin[128]. The timing of administration of heparin during the ablation is also relevant. Heparinization before trans-septal puncture is associated with lower incidence of SCL than heparinization after trans-septal puncture[127]. The ongoing AXAFA trial[129] is investigating the effect of different anticoagulation regimens on the formation of SCL and will provide further guidance on the management of periprocedural anticoagulation. Patient-related risk factors include advanced age, persistent AF, lower left ventricular ejection fraction, and spontaneous echo contrast on transoesophageal echocardiography[124,126,130]. An overview of the proposed pathophysiology of SCL related to ablation is provided[131] (FIG. 5).

The effect of new SCL after catheter ablation on cognition is not known. SCLs have been demonstrated to resolve on follow-up MRI performed 1 year after the ablation in >90% of patients[132,133]. However, canine studies have revealed proliferation and activation of cerebral glial cells in association with the cerebral lesions produced by particulate debris or gaseous embolism, raising concern about potential effects on cognition in the long term[134]. Neuropsychological testing 90 days after catheter ablation showed a decline in cognitive function in 13% of patients with AF undergoing ablation compared with 0% of controls without ablation[135]. In another study, neuropsychological testing 1 month after catheter ablation did not show a difference in cognitive function[136]. However, a follow-up period of several years after ablation is critical given that the long-term risk of dementia in patients after stroke is still twice the risk compared with that in the healthy population, even in the absence of dementia within the first year of stroke[137]. In the only published study with long-term follow-up, the rates of stroke and dementia in patients with AF undergoing ablation were reported to be lower than in patients with AF without ablation and similar to those in individuals without AF[138]. However, this study is limited by its observational design and by the lack of systematic cognitive testing, emphasizing the need for systematic, prospective, long-term studies of cognition after catheter ablation. Microinfarcts have emerged as an important pathological substrate of dementia[139]. Whether new SCLs lead to a significant increase in microinfarct burden requires confirmation.

Anti-inflammatory therapy. The pro-inflammatory milieu in AF provides a potential therapeutic target for the prevention of cognitive decline. Statins have anti-inflammatory properties, and small prospective studies have evaluated their effect on inflammatory markers, cognitive function, and brain volume in AF. In a cohort of 34 patients with AF, combination therapy with atorvastatin and ezetimibe resulted in a significant reduction in the levels of CRP, IL-1, IL-9, IL-13, IL-17, and IFNγ compared with placebo[140]. In this study, warfarin therapy was associated with persistent thrombin potential, which was reduced by the addition of statin

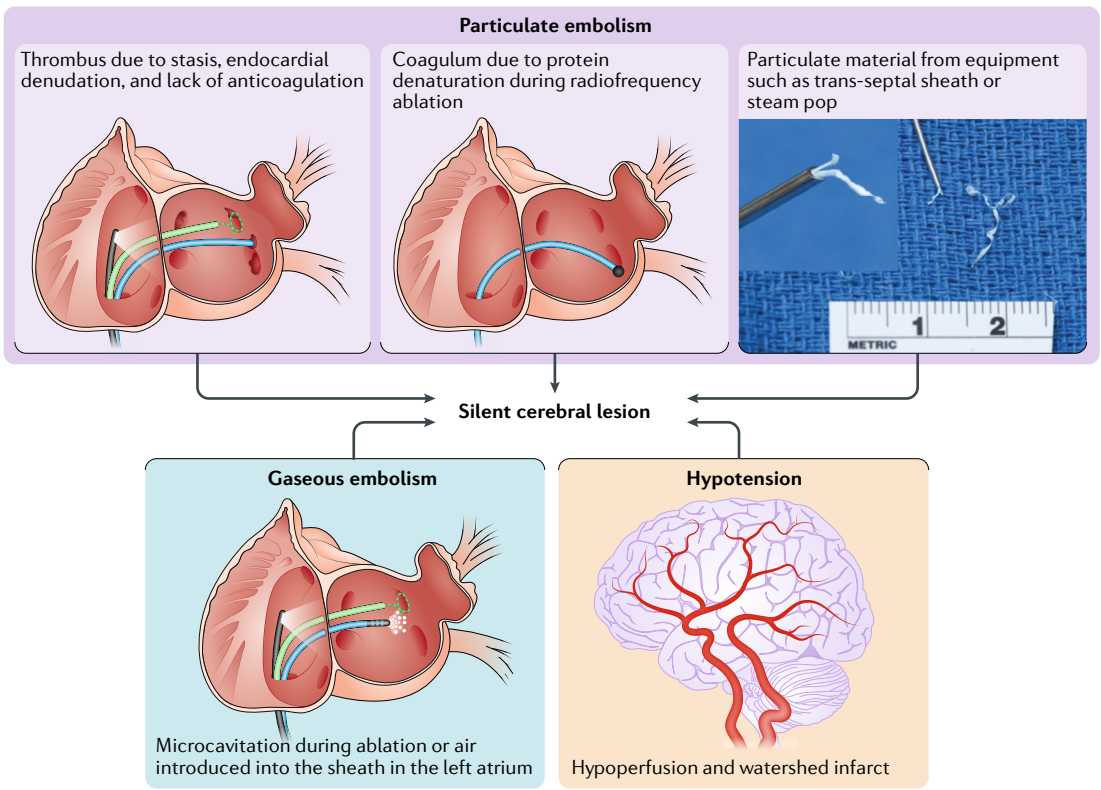

Fig. 5 | **Proposed aetiology of silent cerebral lesions after catheter ablation of atrial fibrillation.** Catheter ablation of atrial fibrillation is associated with an increased risk of silent cerebral lesions. The proposed mechanisms of these new lesions include particulate embolism (thrombus or coagulum), gaseous embolism, and cerebral hypoperfusion.

Box 1 | **Future directions of investigations**

Our current state of knowledge leaves several unanswered questions regarding the epidemiology, risk factors, pathophysiology, treatment, and prevention of cognitive impairment in patients with atrial fibrillation (AF). Areas in need of investigation include:

Risk factors
Identification of the risk factors for dementia in patients with AF.

Prevention
Assessment of the predictive value of neuroimaging to fine-tune AF management and prevent stroke, intracranial haemorrhage, and dementia.

Pathophysiology
Assessment of the temporal relationship between the occurrence of asymptomatic findings on neuroimaging, such as silent ischaemia and cerebral microbleeds, and future cognitive impairment.

Treatment
Evaluation of the effect of anticoagulation on the risk of dementia, with subsequent assessment of the differential effect of individual oral anticoagulants on cognitive impairment in AF. Evaluation of the effect on cognition of rate control versus rhythm control and of specific treatments for AF, such as catheter ablation and antiarrhythmic drugs.

therapy. Therefore, the anti-inflammatory effect of statin therapy might have an incremental benefit in reducing the prothrombotic state in patients treated with warfarin. In another report from the same investigators, atorvastatin and ezetimibe therapy for 1 year was associated with improvement in neurocognitive testing scores and reduction of volume loss in the amygdala and left hippocampus[141]. These results need to be reproduced in a larger cohort with longer follow-up.

Conclusions

AF and dementia are responsible for increased morbidity, mortality, and health-care expenditure in elderly individuals. Emerging evidence shows that AF is associated with cognitive impairment independently of the occurrence of stroke and of a number of shared risk factors. AF leads to a high prevalence of SCI, which might be an important mechanism by which AF affects cognition. AF-induced systemic inflammation might also have a role. The pathophysiology of dementia in AF and the therapeutic strategies to reduce dementia warrant further investigation (BOX 1). Systematic trials on the effect on cognition of AF treatments such as anticoagulation, catheter ablation, and eventually anti-inflammatory therapies are also required to reduce the major influence of AF and dementia on the longevity and quality of life of our expanding older population.

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Author contributions

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