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PERSPECTIVE ARTICLE

A hidden connection in neurocardiology between atrial fibrillation and ischemic periventricular leukoencephalopathy (leukoaraiosis): Current opinions and perspectives

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Abstract

Neurocardiology is a rapidly evolving multidisciplinary medical field at the intersection of cardiology and neurology. It examines the complex, mostly bidirectional relationships and physiological and pathophysiological interactions between the nervous and cardiovascular systems. The interconnections between atrial fibrillation and ischemic periventricular leukoencephalopathy (leukoaraiosis) are neither well known nor well studied. Nevertheless, the overall body of literature suggests a largely unidirectional relationship, in which long-standing atrial fibrillation causes central nervous system changes described as leukoaraiosis. Therefore, leukoaraiosis, often described as a surrogate for cerebral small vessel disease, is regarded in this article as a neuroanatomical aspect/consequence of previously detected arrhythmogenic disease—atrial fibrillation. It is no wonder that, despite many experimental and clinical investigations, an ancient term is still often used in the literature to describe a new spectrum of various clinical problems. However, previous global experience with the heart–brain axis suggests that this relationship is rarely unidirectional, since these two organs predominantly cooperate through reciprocal action and reaction, and the way leukoaraiosis affects the cardiovascular system remains unclear. In accordance with this, numerous pieces of research and a great deal of clinical practice in neurocardiology focus on mapping the unrevealed anatomical pathways of the cardiac neuraxis and on developing closed-loop neuromodulation therapies to treat various complex cardiovascular diseases, including neuromodulation therapies in the opposite direction along the cardiac neuraxis (for the treatment of neurological diseases). A thorough literature review of investigations and studies from PubMed/MEDLINE, Ovid, EMBASE, Scopus, Google Scholar, DOAJ, and the Cochrane Library databases was conducted to assess key data on the connection between atrial fibrillation and leukoaraiosis, along with its practical implications and future perspectives.

Keywords: Neurocardiology; Atrial fibrillation; Leukoaraiosis; Heart–brain axis; Fazekas scale

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1. Introduction

The field of neurocardiology has already discovered many ways in which the brain and the heart undeniably cooperate in what is sometimes called "the brain and cardiac axis." These discoveries have revealed pathophysiological pathways underlying many neurological and cardiovascular disorders (e.g., stress-related cardiomyopathy, Takotsubo syndrome, neurogenic stunned myocardium, Cushing's reflex/triad, vasomotor center reflex, baroreceptor reflex, the Bainbridge or atrial reflex, orthostatic intolerance, postural orthostatic tachycardia syndrome). However, the connection between atrial fibrillation and leukoaraiosis has not yet been broadly investigated or elucidated. Atrial fibrillation is statistically the most common arrhythmogenic disorder; its pathophysiology has been extensively investigated. On the other hand, leukoaraiosis has received less attention from the global scientific community. Logically, its pathophysiology is a more enigmatic mosaic. What is known, however, is that it represents a morphological change in brain white matter with characteristic manifestations on both magnetic resonance imaging (MRI) and computed tomography (CT) head scans. Common documented risk factors for ischemic periventricular leukoencephalopathy (leukoaraiosis) include aging, chronic arterial hypertension, diabetes mellitus, smoking, hyperhomocysteinemia, and cardiac diseases.[1-3] Aging, chronic arterial hypertension, and diabetes mellitus share a common molecular pathophysiological mechanism: these conditions induce similar alterations in the small penetrating arteries and arterioles of the brain's white matter, including replacement of the smooth muscle cells with fibro-hyaline material, thickening of the vascular wall, and consequent narrowing of the vascular lumen (arteriolosclerosis). Therefore, the association between microvascular damage, chronic arteriosclerosis, and leukoaraiosis is well established; however, the relationship between leukoaraiosis and atrial fibrillation remains far less understood. Broadly speaking, more than one-quarter of symptomatic ischemic infarctions are attributable to small vessel disease, which may manifest radiologically as lacunar infarcts or leukoaraiosis. These two pathophysiological mechanisms underlie cognitive dysfunction related to small vessel disease.

2. Discussion/Viewpoint synthesis

Leukoaraiosis is a neuroradiological concept referring to damage to the brain's white matter in the region surrounding the cerebral ventricles.[1,2] It is visually manifested as hypodensity of the periventricular white matter on CT scans or as signal hyperintensity in the same areas on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences. The histopathological basis of these subtle morphological changes consists of demyelination and loss of axons and oligodendrocytes, accompanied by the reparative process of gliosis. Leukoaraiosis develops practically only after prior damage to the brain's small vessels. More importantly, these morphological alterations have significant clinical implications. Individuals with leukoaraiosis are at an increased risk of future stroke and vascular dementia.[3,4] However, an important unresolved question concerns the relationship between the severity of leukoaraiosis, as assessed using the Fazekas scaling system (graded from 0–3), and the extent of neuropsychological dysfunction.[5] Notably, leukoaraiosis shares risk factors and underlying pathophysiological mechanisms with lacunar infarctions. As previously noted, the primary risk factors for both conditions are aging and chronic arterial hypertension.[1,2] In the general population, both a history of lacunar stroke and the presence of leukoaraiosis are associated with an increased risk of recurrent stroke and varying degrees of cognitive decline. Modern neuroradiological techniques (e.g., anatomical and functional imaging) have enabled us to detect morphological and functional changes that were previously difficult to identify. These advances made it possible to identify lacunar brain infarcts *in vivo*. Subsequently, in 1987, Canadian neurologist Vladimir Hachinski introduced the term leukoaraiosis.[4-7] Derived from Greek, the term describes patchy or diffuse white matter changes in the periventricular region or the centrum semiovale (rarefaction), which have since been described as leukoaraiosis. This term was first used purely descriptively for visible morphological brain alterations. With the introduction of MRI into clinical practice, white matter lesions, appearing as hyperintense areas on T2w/FLAIR sequences, were found in a large number of the elderly population, including those who were clinically asymptomatic. This observation raised questions about the clinical significance of these changes and their relationship with cognitive and other neurological function.[6] Subsequent foundational studies, beginning in 1992, established that these white matter changes—often associated with aging and vascular disease—are linked to cognitive impairment and mobility limitations.[1-3] Clinically, these findings highlight a substantial discrepancy between neuroimaging abnormalities and clinical manifestations. Although some individuals with leukoaraiosis remain clinically silent and asymptomatic, more severe forms are frequently associated with reduced processing speed, apathy, executive dysfunction, and verbal memory deficits.[1-4]

The Fazekas scale, a widely used grading system for white matter lesions, was proposed by Franz Fazekas *et al.*[7] in 1987. Fazekas, an Austrian neurologist, developed the classification to assess white matter changes on brain

imaging. The scale distinguishes between periventricular and deep white matter hyperintensities, with each region graded according to the extent and confluence of the lesions. Today, leukoaraiosis is commonly referred to as white matter hyperintensities (WMH) or white matter lesions for easier, practical routine communication.[7,8] Figures 1–10 and Table 1 illustrate the Fazekas grading system, including its tabular presentation and representative brain MRI images. Importantly, the etiology of periventricular and deep white matter lesions differs. Deep white matter lesions are commonly associated with chronic small vessel ischemia, whereas periventricular changes may involve a combination of pathological processes, including focal demyelination, myelin sheath disruption, ependymitis granularis, oligodendroglial swelling, spongiosis, disruption of the ependymal barrier between the cerebrospinal fluid and brain parenchyma, subependymal gliosis, and thickening and hyalinization of vessel walls with widening of perivascular spaces. Small vessel ischemia may also contribute, potentially resulting in localized ischemic necrosis and cavitation (lacunes) or diffuse white matter rarefaction (leukoaraiosis).[9] Therefore, this article focused not only on the morphological alterations in the heart and brain in patients with atrial fibrillation and leukoaraiosis but also on their clinical significance. In particular, it evaluates the relationship between these imaging findings and the patients' clinical, functional, and cognitive status.

Table 1. Fazekas scale of periventricular white matter lesions

Grade	Morphological alterations
0	Completely absent—no changes
1	"Caps" or pencil-thin lining changes
2	Smooth "halo" sign
3	Irregular periventricular signal extending into the deep white matter

The central focus of this article is the relationship between atrial fibrillation and leukoaraiosis. Although the available evidence remains limited in some respects and the nature of this relationship is still debated, the two conditions are thought to be closely associated. Both are linked to an increased risk of cognitive decline and stroke.[3,4,10] In the following sections, we summarize the current understanding of the relationship between leukoaraiosis and atrial fibrillation, with particular emphasis on their underlying pathophysiological mechanisms and clinical implications. We also discuss relevant illustrative studies to contextualize the available evidence.

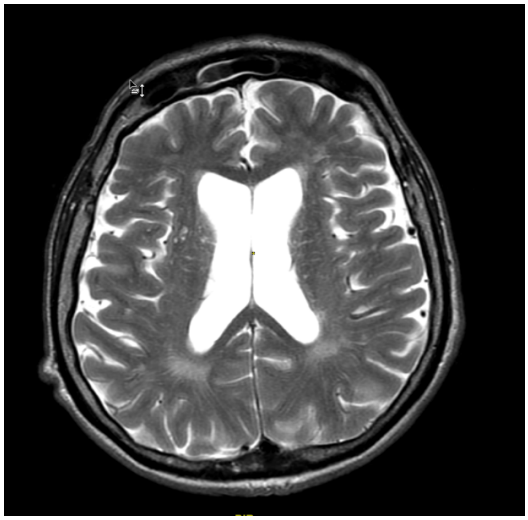


Figure 1. Axial T2-weighted endocranial magnetic resonance imaging image showing Fazekas grade I periventricular white matter, obtained on a Siemens 1.5 T scanner. Additionally, cortical reductive changes and some chronic microischemic/microangiopathic changes are also detectable.

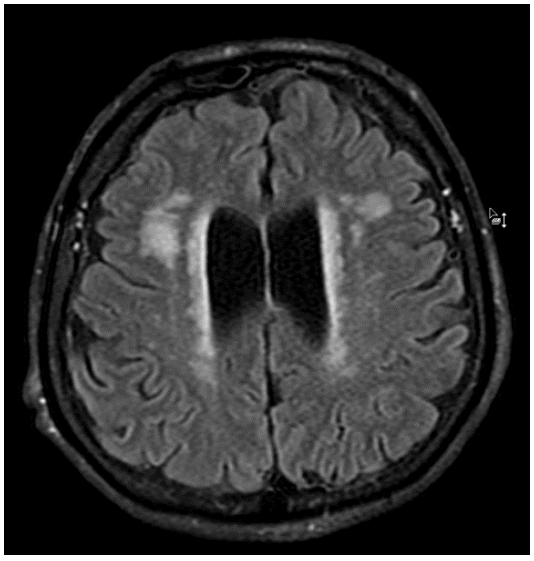


Figure 2. Axial fluid-attenuated inversion recovery endocranial magnetic resonance imaging image showing Fazekas grade I periventricular white matter, obtained on a Siemens 1.5 T scanner

2.1. Established interrelationship

Adults with previously diagnosed atrial fibrillation have a two- to threefold higher likelihood of concomitant leukoaraiosis than those without atrial fibrillation. Importantly, leukoaraiosis in these patients may exhibit a distinct distribution pattern, with a greater burden of white

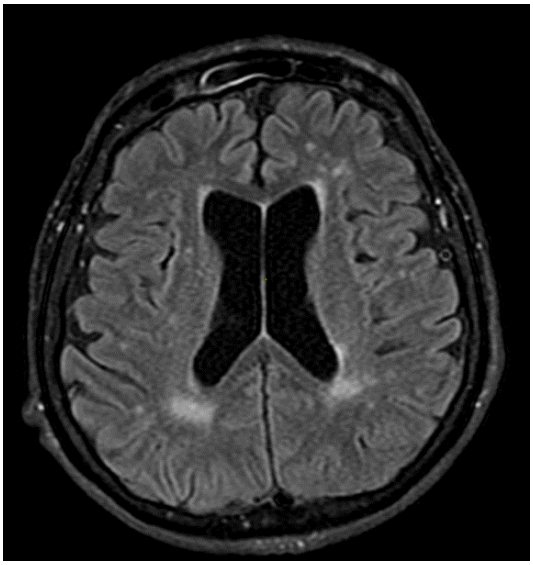


Figure 3. Axial fluid-attenuated inversion recovery endocranial magnetic resonance imaging image showing Fazekas grade I periventricular white matter, obtained on a Siemens 1.5 T scanner

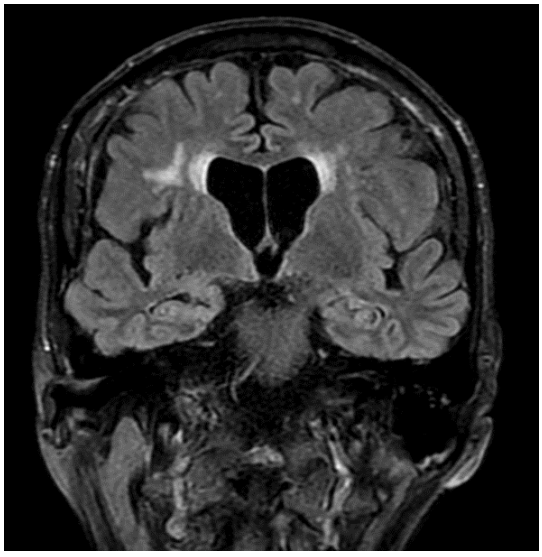


Figure 4. Coronal fluid-attenuated inversion recovery endocranial magnetic resonance imaging image showing Fazekas grade I periventricular white matter, obtained on a Siemens 1.5 T scanner

matter lesions in the deep and infracortical regions, as well as in the periventricular area.[7-11]

2.2. Primary developmental mechanisms

Several pathophysiological mechanisms may be responsible for the development of leukoaraiosis in patients with atrial fibrillation:

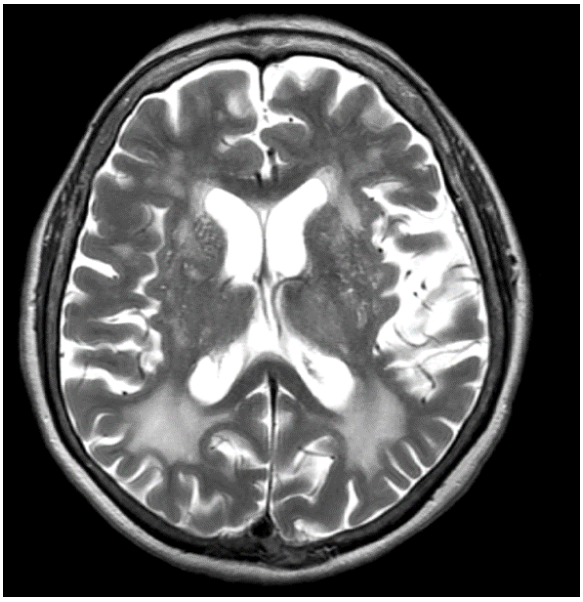


Figure 5. Axial T2-weighted endocranial magnetic resonance imaging image showing Fazekas grade II/III periventricular white matter, obtained on a Siemens 1.5 T scanner. Additionally, cortical reductive changes and numerous chronic microischemic/microangiopathic changes are detectable.

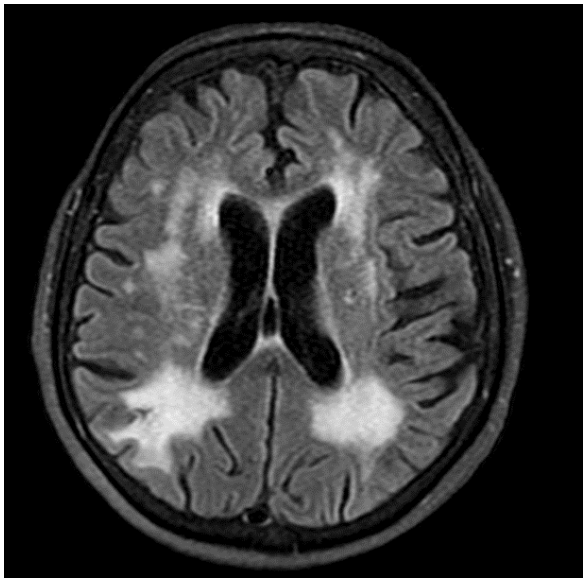


Figure 6. Axial fluid-attenuated inversion recovery endocranial magnetic resonance imaging image showing Fazekas grade II/III periventricular white matter, obtained on a Siemens 1.5 T scanner

- Chronic hypoperfusion state: The irregular and often rapid ventricular rate associated with atrial fibrillation

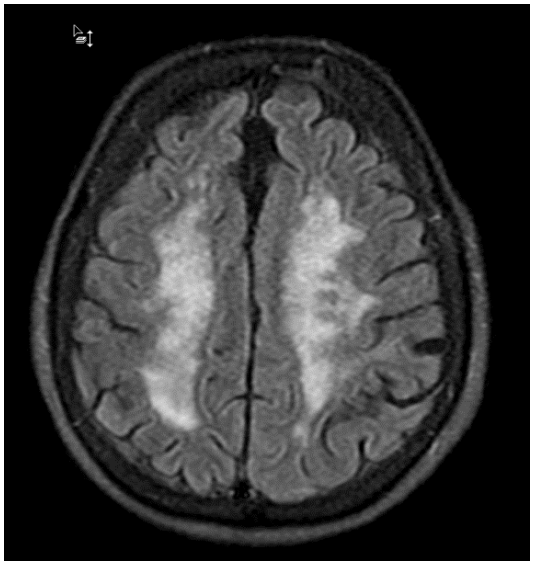


Figure 7. Axial fluid-attenuated inversion recovery endocranial magnetic resonance imaging image showing Fazekas grade II/III periventricular white matter, obtained on a Siemens 1.5 T scanner

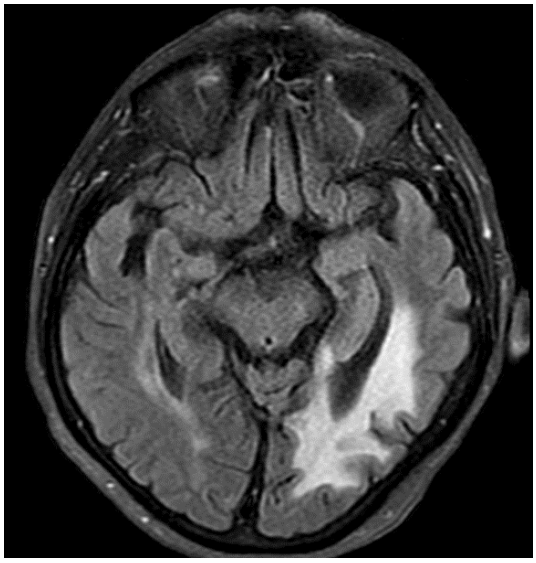


Figure 8. Axial fluid-attenuated inversion recovery endocranial magnetic resonance imaging image showing Fazekas grade II/III periventricular white matter, obtained on a Siemens 1.5 T scanner. The main focus is on its asymmetric temporal location.

may compromise cerebral hemodynamics by reducing the stability and efficiency of cerebral blood flow. Sustained or recurrent cerebral hypoperfusion may contribute to chronic microvascular injury and white matter damage.

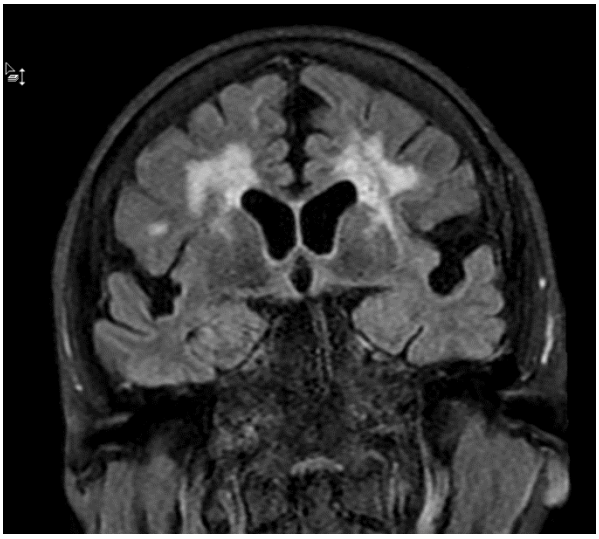


Figure 9. Coronal fluid-attenuated inversion recovery endocranial magnetic resonance imaging image showing Fazekas grade II/III periventricular white matter, obtained on a Siemens 1.5 T scanner

- Microemboli: Thrombi may form in the fibrillating atrium, particularly in patients with persistent or permanent atrial fibrillation. Small emboli may subsequently travel to the cerebral circulation, where they can obstruct small blood vessels and cause microscopic ischemic lesions and focal tissue injury. Repeated microembolic events may contribute to white matter damage and cognitive impairment.
- Shared risk factors: Both conditions share several risk factors and comorbidities, including chronic arterial hypertension, aging, diabetes mellitus, hyperhomocysteinemia, metabolic disorders, electrolyte disturbances, and numerous other vascular disorders.

2.3. Clinical implications/significance

The presence of moderate-to-severe leukoaraiosis (Fazekas grade II/III) may be associated with poorer functional outcomes and greater disability following an atrial fibrillation-related stroke. Leukoaraiosis has also been associated with an increased risk of recurrent stroke and myocardial infarction.[12]

Leukoaraiosis has been identified as an independent risk factor for intracranial hemorrhage (brain bleeding) in patients with atrial fibrillation receiving oral anticoagulants (blood thinners) for stroke prevention.[13,14] It is also a proven risk factor for hemorrhagic transformation following cardioembolic stroke in patients with atrial fibrillation.[13,14]

To provide a structured overview of the available

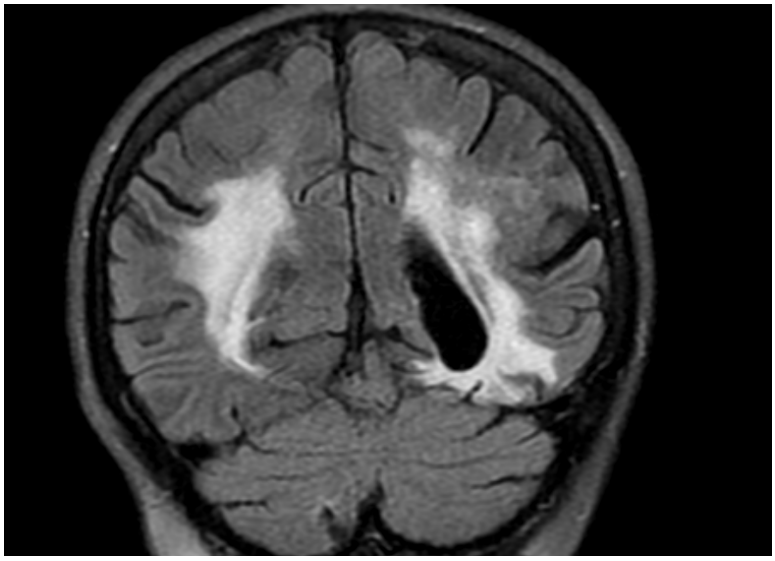


Figure 10. Coronal fluid-attenuated inversion recovery endocranial magnetic resonance imaging image showing Fazekas grade II/III periventricular white matter, obtained on a Siemens 1.5 T scanner

evidence, key clinical and neuroimaging studies investigating the relationship between atrial fibrillation and cerebral white matter abnormalities are summarized in Table 2. Particular emphasis is placed on population characteristics, atrial fibrillation phenotype, imaging methodology, WMH definition and grading, covariate adjustment, and principal outcomes. Overall, the available evidence suggests an association between atrial fibrillation and cerebral white matter abnormalities, although the relationship is heterogeneous and appears to depend on the population studied, vascular comorbidities, atrial fibrillation phenotypes, imaging methodologies, and WMH definitions. Early population-based studies predominantly implicated periventricular lesions, whereas subsequent studies identified increased deep/subcortical WMH burden and distinct anterior WMH distribution patterns. In contrast, the large Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS), a prospective epidemiological study conducted across four United States communities (each ARIC field center had a cohort sample of approximately 4,000 subjects between 45 and 64 years of age with follow-up), did not demonstrate an independent association between atrial fibrillation and WMH volume after extensive covariate adjustment. More recent findings from the Swiss Atrial Fibrillation Cohort Study (Swiss AF), a large multicenter prospective investigation involving 2,400 individuals aged 65 years or older recruited from clinical centers across Switzerland, have demonstrated a high prevalence of moderate-to-severe WMH among patients with atrial fibrillation and suggested a potentially distinct pattern of cerebral vascular injury in this population. Collectively, these findings indicate that the relationship between atrial fibrillation and WMH is multifactorial and may involve mechanisms beyond conventional cardioembolism.

In one of the early studies investigating the relationship between leukoaraiosis and clinical outcomes, Miyao *et al.*[15] examined 215 participants and demonstrated that, following a first lacunar infarct, dementia was more frequent among patients with leukoaraiosis. Additionally, life-table analysis revealed that the recurrent stroke rate was significantly higher in patients with leukoaraiosis than in those without this condition ($p = 0.004$). Overall survival following stroke was also significantly lower in patients with leukoaraiosis ($p = 0.012$). However, subsequent findings have not been entirely consistent. In a large study of 1,892 participants from the Athens Stroke Registry, Ntaios *et al.*[12] investigated the relationship between leukoaraiosis and recurrent stroke according to AF status. The study included 320 patients (16.9%) with leukoaraiosis and 670 (35.4%) with atrial fibrillation. Kaplan–Meier analysis demonstrated a significant difference in the cumulative probability of stroke recurrence between patients with and without leukoaraiosis in the non-atrial fibrillation group ($p < 0.01$), but not in the atrial fibrillation group ($p = 0.46$). Therefore, although both studies provide valuable evidence regarding the prognostic implications of leukoaraiosis, their findings differ, particularly regarding the relationship between leukoaraiosis and recurrent stroke. These discrepancies may reflect differences in study populations,

underlying vascular risk factors, stroke characteristics, and the presence or absence of atrial fibrillation. Several studies investigating cognitive function have also suggested that cognitive performance is significantly associated with factors such as the location of ischemic stroke lesions and the number of lacunar infarcts, with the latter emerging as a significant predictor of cognitive impairment. One possible explanation is that an acute lacunar infarction may unmask or exacerbate pre-existing cognitive dysfunction. In this scenario, the vascular event may act as a trigger, bringing to clinical attention the cumulative effects of pre-existing leukoaraiosis and additional ischemic injury on cognitive function.[16,17] In an earlier clinicopathological investigation in 1985 involving 17 cases, Dubas *et al.*[18] reported that 30% of subjects over the age of 65 years exhibited moderate-to-severe white matter changes. In a prospective investigation involving 251 subjects, Wei *et al.*[14] found, through univariate and multivariate analyses, that moderate-to-severe leukoaraiosis, especially in the periventricular and anterior/frontal regions, was associated with hemorrhagic transformation following cardioembolic stroke in patients with atrial fibrillation/rheumatic heart disease. These findings are clinically relevant because hemorrhagic transformation, particularly when it involves parenchymal hematoma or extensive bleeding, may adversely affect stroke outcomes and prognosis.

When considering the relationship between leukoaraiosis and cognitive function, the long-recognized influence of aging must also be taken into account.[19] As part of the natural aging process, leukoaraiosis may develop even in individuals without a history of cerebrovascular disease and may contribute to a decline in overall cognitive performance.[20] If leukoaraiosis is further exacerbated by vascular alterations, these pre-existing white matter changes may become more extensive, potentially exacerbating their effects on cognitive function. In a study by O'Sullivan [21], subcortical ischemic changes in the white and gray matter, together with lacunar infarctions, were identified as significant factors contributing to poorer cognitive performance. As previously noted, the mechanism and pathophysiology of leukoaraiosis remain incompletely clarified. Nevertheless, a prospective study by Wei *et al.*[22] involving 186 patients with ischemic stroke and atrial fibrillation, including 134 with leukoaraiosis, identified elevated fibrinogen levels (≥3.5 g/L) as a factor associated with the presence of leukoaraiosis. These findings suggest that fibrinogen may contribute to the development of leukoaraiosis and the overall burden of cerebral small vessel disease. Several potential mechanisms may explain this association. Elevated fibrinogen levels may promote neuroinflammation, increase blood viscosity, and impair microcirculatory blood flow, causing chronic cerebral hypoperfusion; they may also disrupt the blood–brain barrier and leak into brain tissue, triggering a toxic and inflammatory response that damages nerve fibers.[22] Clinically, elevated fibrinogen levels have been associated with more severe periventricular white matter changes and may be linked to an increased risk of cognitive impairment and vascular dementia. Further evidence supporting this association comes from a recent case-control study by Wu *et al.*[23], reporting that the odds of cognitive impairment increased with each unit increase in fibrinogen levels (adjusted odds ratio = 1.92, 95% CI = 1.06–3.48). Furthermore, subjects with fibrinogen levels greater than 4 g/L presented a significantly higher risk of cognitive impairment than those with levels between 2 and 4 g/L (adjusted odds ratio = 5.72, 95% CI = 1.22–26.82). Fibrinogen levels were also negatively correlated with global cognitive function (r_s = −0.235), visuospatial/executive function (r_s = −0.251), and normal-appearing white matter volume (r_s = −0.282).

Table 2. Key studies investigating the association between atrial fibrillation and cerebral white-matter abnormalities

Study	Population characteristics	AF subtype/ ascertainment	Imaging and WMH definition	Fazekas grade	Adjustment variables	Main outcome
de Leeuw *et al.* [24]	Population-based sample, *n*=1,077; older adults; 28 with AF	ECG-detected AF; previous ECGs available in a subgroup	1.5-T MRI; periventricular and subcortical white matter lesions rated separately	Not reported using modern Fazekas terminology	Age, sex, and vascular factors considered	AF associated with severe periventricular white matter lesions (RR 2.2, 95% CI: 1.0–5.2), but not subcortical lesions.
Kobayashi *et al.* [25]	71 NVAF patients + 71 age/sex-matched controls; mean age of NVAF group ~74 year	Non-valvular AF: 29 chronic + 42 paroxysmal	Brain MRI; silent cerebral infarcts, PVH, and DSWMH assessed	Semiquantitative PVH/DSWMH grading; not standard Fazekas	Stroke risk factors and $CHADS_2$ score; multivariable analysis	NVAF associated with more silent cerebral infarcts and higher DSWMH burden; NVAF independently predicted DSWMH and silent cerebral infarction.

(*Cont'd...*)

Table 2. (*Continued*)

Study	Population characteristics	AF subtype/ ascertainment	Imaging and WMH definition	Fazekas grade	Adjustment variables	Main outcome
Mayasi *et al.* [26]	234 embolic-stroke patients; 114 (49%) with AF; median age ~72 year	AF determined by clinical/cardiac evaluation; valvular and non-valvular AF represented	MRI/FLAIR; WMH classified by spatial lesion pattern	Fazekas score used for overall WMH burden	CHA_2DS_2-VASc, Fazekas score, embolic stroke pattern, infarct distribution, and interaction terms	AF independently associated with anterior subcortical WMH patches (OR: 3.65, 95% CI: 1.68–7.91; p=0.001).
Shao *et al.*[27] (ARIC-NCS)	1,899 participants; mean age 76 years; 133 (7%) with prevalent AF	AF identified by studying ECG or previous hospitalization codes	Brain MRI; quantitative WMH volume plus DTI (fractional anisotropy and mean diffusivity)	Not used as primary measure	Extensive demographic, vascular, metabolic, inflammatory, renal, APOE, stroke, and anticoagulant covariates	After extensive adjustment, AF was not independently associated with WMH volume or white matter microstructural integrity.
Aeschbacher *et al.*[28] (Swiss-AF)	1,738 patients with AF; mean age 73 year; 73% male	Established AF; contemporary multicentre AF cohort	Standardized brain MRI; white matter lesions, infarcts, and microbleeds	Fazekas ≥2 = moderate/severe white matter lesions	BP and major demographic/ vascular factors	Fazekas ≥II lesions in 54%; higher systolic BP strongly associated with white matter lesion burden; adjusted OR 2.54 for systolic BP ≥160 vs. <120 mmHg.
Pezel *et al.*[29]	MRI subgroup of Multi-Ethnic Study of Atherosclerosis; older adults with/ without AF	Prevalent/ Intermittent AF identified from studying ECG and clinical records	Brain MRI including WMH volume, white matter microstructural integrity, and cerebral microbleeds	Not a primary WMH measure	Extensive demographic, cardiovascular, metabolic, and socioeconomic covariates	AF associated particularly with abnormal white matter microstructural integrity and cerebral microbleeds, supporting a broader cerebral small vessel phenotype.
Srichawla *et al.*[30] (SAGE-AF)	86 participants with AF; older adults; 2-year prospective follow-up	AF cohort; AF duration recorded	Neuroimaging performed for clinical indications	Fazekas 0–III; grades II–III represented greater WMH burden	Age, sex, AF duration, anticoagulation, CHA_2DS_2-VASc, HAS-BLED, and major vascular/ comorbid conditions	Higher Fazekas burden associated with subsequent cognitive decline and frailty during follow-up.
Stegmann *et al.*[31] (Swiss-AF/ COMPASS MIND)	3,508 participants: 1,748 AF and 1,760 with atherosclerosis	Swiss-AF AF cohort vs. COMPASS-MIND atherosclerosis cohort	Standardized MRI; periventricular/ deep WMH, lacunes, non-lacunar infarcts, and microbleeds	Fazekas ≥II	Multivariable adjustment for demographic and vascular characteristics; sensitivity analysis excluding AF with clinical atherosclerosis	Severe periventricular WMH: 49% in AF vs. 37% in atherosclerosis; severe deep WMH: 35% vs. 31%; distinct cerebral lesion profile in AF.

Abbreviations: AF: Atrial fibrillation; APOE: Apolipoprotein E; BP: Blood pressure; CHA_2DS_2-VASc: Congestive heart failure: hypertension, age ≥75 years, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category; DSWMH: Deep and subcortical white matter hyperintensities; DTI: Diffusion tensor imaging; ECG: Electrocardiography; FLAIR: Fluid-attenuated inversion recovery; LVH: Left ventricular hypertrophy; MRI: Magnetic resonance imaging; NVAF: Non-valvular atrial fibrillation; OR: Odds ratio; PVH: Periventricular hyperintensity; RR: Relative risk; WMH: White matter hyperintensities.

2.4. Electrophysiological options in the treatment of atrial fibrillation

Electrophysiology, a rapidly expanding subfield of cardiology, is increasingly recognized worldwide in clinical practice. Although a direct effect of rhythm-control interventions on leukoaraiosis progression requires adequate prospective confirmation, comprehensive catheter-ablation strategies may be especially relevant in selected patients with advanced atrial substrate disease and recurrent atrial fibrillation after conventional pulmonary vein isolation (PVI).[32-34] This has particular importance for early and effective atrial fibrillation interventions, particularly in patients with persistent or advanced-stage persistent atrial fibrillation, in whom atrial remodeling, prolonged arrhythmia burden, impaired hemodynamics, and thromboembolic vulnerability may be greater.[32] Therefore, PVI remains the primary ablation strategy for atrial fibrillation.[32,34] However, additional interventions are often required in patients with persistent atrial fibrillation. Radiofrequency catheter ablation has recently emerged as a highly effective and valuable electrophysiological treatment option, particularly for atrial-origin arrhythmic disorders. Specifically, PVI is the cornerstone of most modern electrophysiological ablation approaches. Rapid technological evolution (e.g., cryoballoon ablation, the development of contact force-sensing catheters, high-power and short-duration radiofrequency ablation, pulse field ablation) and a widespread increase in operator experience with precision refinement have facilitated the effectiveness of catheter ablation to achieve successful PVIs with durable sinus rhythm restoration in single or multiple radiofrequency ablation procedures.[32-34] Despite these technical refinements, arrhythmia recurrence remains a major issue even after seemingly successful electrophysiological PVI at first sight. Documented official data on catheter ablation in this specific patient group are still scarce, and repeat radiofrequency ablation in this population remains, unfortunately, a reality even in the most experienced world clinics and is still considered a highly challenging procedure. Every radiofrequency ablation procedure also results in localized myocardial scarring, which may affect myocardial contractility and, depending on the extent and location of the scar tissue, potentially reduce left ventricular ejection fraction.

Point-by-point radiofrequency ablation and single-shot ablation, such as cryoballoon ablation, are established approaches for achieving complete PVI.[32,35] Despite continued advances in catheter ablation technology, the role of pulmonary vein (PV) reconnection in atrial fibrillation recurrence remains an important area of investigation. The precise in AF recurrence remains an important area of investigation. The precise proportion of patients who experience arrhythmia recurrence despite durable PVI remains uncertain, partly because non-invasive imaging techniques capable of reliably identifying PV reconnection are still limited. Although cardiac magnetic resonance (CMR) imaging is a rapidly evolving modality, evidence supporting its use in the assessment of PV reconnection remains limited.[32] Despite its initial promise, CMR-based assessment of PV reconnection has not yet become established in routine clinical practice and remains largely investigational.[36] In contrast, CMR is widely recognized as an important imaging modality for characterizing myocardial scar following ischemic injury, evaluating cardiomyopathies and cardiac tumors, and assessing ventricular volumes and ejection fraction. However, its role in cardiac electrophysiology, particularly in evaluating post-ablation PV reconnection, remains less established. One major limitation is the lack of standardized CMR sequences optimized specifically for post-PVI assessment. Furthermore, discrepancies between electroanatomical mapping and non-invasive CMR-based assessments of atrial tissue and lesion distribution complicate the interpretation of findings. Future advances in cardiac imaging may benefit from approaches analogous to magnetic resonance tractography and magnetic resonance elastography, which neuroradiology uses to characterize tissue architecture and mechanical properties. In neuro-oncology, magnetic resonance tractography helps visualize the relationship between brain tumors and surrounding white matter tracts, supporting preoperative surgical planning. Although its applications extend beyond neuro-oncology, this technique illustrates how advanced MRI methods can provide information about tissue organization and structural relationships that conventional imaging may not adequately capture. Similarly, further technical developments in CMR imaging could potentially improve the visualization and characterization of atrial tissue architecture and post-ablation lesions. Such advances may eventually help identify abnormal conduction pathways and improve the assessment of mechanisms underlying atrial fibrillation recurrence.

Based on the available evidence regarding catheter ablation in patients with recurrent arrhythmia following PVI, clear recommendations for the optimal ablation strategy remain lacking.[32] Some studies recommend estimating the mathematical probability of PV reconnection by considering the patient's clinical history, including previous ablation procedures and relevant clinical characteristics (e.g., age, comorbidities, particularly cardiovascular comorbidities, concomitant pharmacotherapy, left atrial chamber dimensions). Additional imaging modalities, including CMR, may

also help identify pre-existing left atrial lesions that could contribute to arrhythmic disorders. Decisions regarding repeat ablation should be individualized based on the type of arrhythmia recurrence, clinical symptoms, and other systemic comorbidities. Potential strategies for managing arrhythmia recurrence include atrial substrate modification guided by voltage mapping.

2.5. Catheter ablation strategies beyond pulmonary vein isolation

Several ablation strategies beyond PVI have been investigated as potential approaches for managing AF, both during initial ablation procedures and in patients with recurrent arrhythmia despite durable PVI. Growing evidence indicates that atrial fibrosis is a prevalent component of the left atrial substrate in patients with atrial fibrillation.[32,37] In addition to PV ostia, focal drivers and reentrant circuits (rotors) outside the PVs may contribute to atrial fibrillation maintenance. Targeting these sites through ablation may help maintain sinus rhythm in selected patients with persistent atrial fibrillation.[38] In patients with persistent atrial fibrillation, left atrial appendage ablation has been investigated as an adjunct to conventional ablation. Some studies have reported reduced recurrent atrial arrhythmias with this approach, without a significant increase in acute procedural complications.[39] Moreover, ablation of isoproterenol- or adenosine-induced non-PV triggers, including those originating from the superior vena cava and coronary sinus, may be considered in selected patients undergoing initial or repeat atrial fibrillation ablation.[40] Other approaches include ganglionated plexus ablation or modification, which has also been investigated as a means of reducing atrial fibrillation recurrence[41], and ablation of complex fractionated atrial electrograms in addition to PVI.[32] Epicardial and surgical ablation techniques, as well as renal denervation, have also been explored as potential strategies, particularly in patients with recurrent atrial fibrillation.[32]

Other important techniques for optimizing nonpharmacological treatment of atrial fibrillation include atrial fibrillation substrate modification, left atrial appendage isolation, non-PV trigger ablation, left atrial posterior wall isolation, superior vena cava isolation, ligament of Marshall and coronary sinus ablation, ganglionated plexus ablation, renal denervation, and surgical ablation.[32]

Ethanol infusion into the vein of Marshall provides access to epicardial arrhythmic circuits and has demonstrated incremental benefit in patients with persistent atrial fibrillation.[33,34] In a comprehensive meta-analysis, Hayıroğlu *et al.*[33] highlighted that adjunctive vein of Marshall ethanol infusion during atrial fibrillation ablation enhances procedural efficacy, albeit at the cost of increased procedural duration. Overall, vein of Marshall ethanol infusion combined with radiofrequency ablation represents a transformative approach that markedly improves procedural success rates and significantly reduces arrhythmia recurrence in patients undergoing ablation for atrial fibrillation.[33] In a retrospective analysis of 123 subjects, Çetin *et al.*[34] reported a lower observed recurrence rate with adjunctive vein of Marshall ethanol infusion and mitral isthmus ablation over a median follow-up of 12–15 months; however, no statistically significant improvement in long-term rhythm outcomes was observed.

The previously mentioned studies provide some context for how adjunctive ablation strategies, including posterior wall isolation, mitral isthmus ablation, and vein of Marshall ethanol infusion, could improve rhythm-control success in carefully selected populations with persistent atrial fibrillation. However, it is important to point out that any proposed neuroprotective benefits remain hypothesis-generating and should not be inferred solely from improved arrhythmia outcomes.

3. Future perspectives

In summary, several important points warrant particular emphasis. Atrial fibrillation is closely associated with the development and progression of leukoaraiosis, which can further exacerbate various post-stroke consequences. Given that therapies aimed at reducing ischemic changes in the central nervous system are not yet well established, optimal control of atrial fibrillation may represent one potential strategy for addressing these complications. The multidisciplinary management of atrial fibrillation requires an integrated, patient-centered approach that combines regular reassessment, stringent risk factor management, careful symptom control and, most importantly, stroke prevention. Although numerous antiarrhythmic drugs are currently available for the treatment of atrial fibrillation, their clinical pharmacology properties remain suboptimal. The effectiveness of many of these agents may decrease over time, and, more importantly, some have narrow therapeutic windows and can cause cardiovascular and systemic toxicity that may not follow a predictable dose–response relationship. Notably, certain antiarrhythmic agents are associated with substantial toxicity. Another important therapeutic option is electrophysiological intervention, which can provide durable rhythm control but is technically challenging and does not necessarily achieve long-term success after a single procedure in most patients with this disorder. Therefore, further experimental and clinical research in the fields of arrhythmology and electrophysiology is necessary. Beyond the established association between leukoaraiosis and lacunar infarction,

investigating their relationship with watershed infarctions as a specific stroke type would also be important, given the considerable overlap in their underlying characteristics. Post-radiation leukoencephalopathy, as a potentially accelerated form of white matter injury, also warrants more precise characterization. In addition to the previously discussed association between leukoaraiosis and fibrinogen, investigating its relationships with other inflammatory parameters (e.g., C-reactive protein [CRP], high-sensitivity CRP, D-dimer, neutrophils, leukocytes, neutrophil-to-platelet ratio, lymphocytes-to-platelet ratio) could provide clinically useful insights into the inflammatory component of leukoaraiosis. A more comprehensive characterization of the molecular pathways for structural and morphological changes in white matter using experimental models of moderate cerebral ischemia would be crucial to clarify unresolved questions and hypotheses regarding leukoencephalopathy and ischemia. Finally, the evidence reviewed herein highlights the need to consider leukoaraiosis as a potentially significant risk factor for intracranial hemorrhage, hemorrhagic transformation, and stroke recurrence when evaluating anticoagulation and thrombolysis therapy in these patients. In line with this, recent guidelines and recommendations regarding atrial fibrillation management (e.g., the American College of Cardiology/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society [ACC/AHA/ACCP/HRS] Guideline and the 2024 European Society of Cardiology [ESC] Guidelines) clearly highlight the importance of managing concomitant comorbidities and cardiovascular risk factors. Notably, the 2024 ESC Guidelines introduced the AF-CARE framework, representing a practical evolution from the previously used ABC pathway. Whether these changes will translate into better guideline implementation in clinical practice and, ultimately, improved patient outcomes remains to be determined.[42,43] Table 3 summarizes the most recent atrial fibrillation pharmacotherapy. Current knowledge of the barriers to guideline implementation in clinical practice should also be considered when discussing future perspectives. Although both recent guidelines provide comprehensive recommendations, certain areas remain insufficiently balanced, suggesting that further refinement and improvement are still needed.[44] In this regard, the recent Canadian Cardiovascular Society classification of atrial fibrillation, presented in Table 4 and based on

Table 3. Commonly used pharmacologic agents for treating atrial fibrillation

Variable	Atrial fibrillation pharmacological therapy
Heart rate control (to slow the heart rate)	Beta-blockers, calcium channel blockers, and digoxin
Rhythm control (to restore and, as much as possible, maintain the physiological sinus rhythm)	Class IC drugs, Class III drugs
Stroke prevention	NOACs/DOACs, Vitamin K antagonists
Downstream pharmacotherapies (to prevent atrial remodeling)	ACE Inhibitors or ARBs

Notes: This framework guides treatment decisions, including the choice between rate-control and rhythm-control strategies. The table was prepared in accordance with the latest American Heart Association recommendations and guidelines.[42]
Abbreviations: ACE: Angiotensin-converting enzyme; ARBs: Angiotensin receptor blockers; DOACs: Direct oral anticoagulants; NOACs: Non–vitamin K antagonist oral anticoagulants.

Table 4. Canadian Cardiovascular Society classification of atrial fibrillation based on episode duration (clinical pattern), pathophysiological triggers, and symptom severity

Atrial fibrillation classification	Clinical pattern
First detected or newly diagnosed atrial fibrillation	The initial detection of this arrhythmic disorder, regardless of its duration or the severity of symptoms.
Paroxysmal atrial fibrillation	Arrhythmic episodes that terminate spontaneously or with intervention within 7 days (usually lasting under 24 h).
Persistent atrial fibrillation	Continuous arrhythmic episodes that last longer than 7 days and require medical or electrical intervention to terminate.
Long-standing persistent atrial fibrillation	Continuous atrial fibrillation lasting for more than 12 months, where a rhythm-control strategy is still being pursued.
Permanent atrial fibrillation	Long-term continuous atrial fibrillation where both the patient and clinician have decided to accept the condition and abandon further attempts to restore normal physiological sinus rhythm.

Note: This framework guides treatment decisions, including the choice between rate-control and rhythm-control strategies.[45]

episode duration (clinical pattern), pathophysiological triggers, and symptom severity from the 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation, offers potentially more practical insights into this condition. Nevertheless, it does not resolve all existing challenges.[45] Figures 11 and 12 provide mechanistic diagrams summarizing the currently recognized heart–

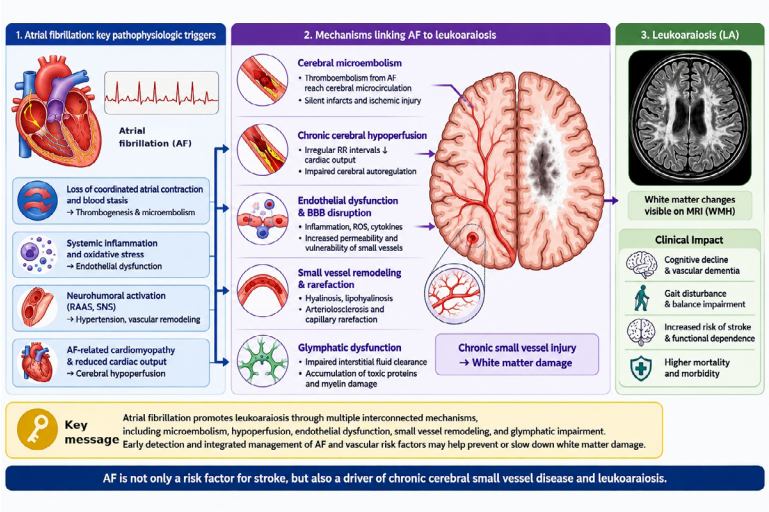


Figure 11. This mechanistic diagram highlights the connection between atrial fibrillation and leukoaraiosis, from cardiac arrhythmia to cerebral small vessel disease. As illustrated herein, atrial fibrillation (AF) can contribute to chronic cerebral small vessel injury through various pathophysiological mechanisms, including cerebral microembolism, chronic cerebral hypoperfusion, endothelial dysfunction and blood–brain barrier (BBB) disruption, small vessel remodeling and rarefaction, and glymphatic dysfunction. These processes can lead to white matter damage and leukoaraiosis, which may eventually result in substantial clinical manifestations and adverse consequences.
Abbreviations: MRI: Magnetic resonance imaging; RAAS: Renin–angiotensin–aldosterone system; ROS: Reactive oxygen species; SNS: Sympathetic nervous system; WMH: White matter hyperintensity.

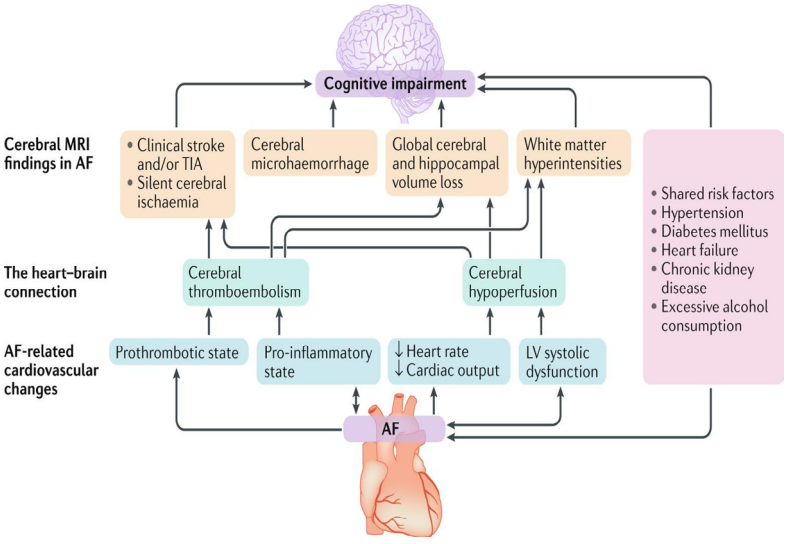


Figure 12. The main recognized and documented pathophysiological pathways contributing to cognitive impairment, one of the most serious consequences in patients with atrial fibrillation (AF), are illustrated here. As shown, cerebral thromboembolism and cerebral hypoperfusion are the two major triggers underlying the heart–brain axis, leading to central nervous system changes that may ultimately result in cognitive impairment.
Abbreviations: LV: Left ventricular; MRI: Magnetic resonance imaging; TIA: Transient ischemic attack.

brain interactions, predominant pathophysiological mechanisms, and pathways that may contribute to central nervous system deterioration and cognitive impairment associated with long-lasting atrial fibrillation.

4. Conclusion

The interrelationship between atrial fibrillation and leukoaraiosis is becoming increasingly important and attracting growing attention from the scientific community. Substantial evidence supports an association between leukoaraiosis and lacunar infarcts, as well as their impact on cognitive function. The presence of multiple bilateral subcortical lacunar infarcts alongside leukoaraiosis has been shown to be significantly associated with cognitive impairment. Further studies providing deeper insights into the pathophysiology of leukoaraiosis are essential to develop strategies to mitigate its impact on the onset of disease and mental disability. Finally, there is hope that novel pharmacological agents capable of directly targeting and reducing ischemic changes in the periventricular regions of the central nervous system will become available for widespread clinical use in the near future.

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