MedCrave
Step into the World of Research

Journal of Neurology & Stroke

Review Article

Open Access

Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications

Abstract

Aging is the predominant risk factor for a wide spectrum of degenerative disorders that collectively affect millions worldwide, including Alzheimer's disease (AD), cerebrovascular disease, cardiac arrhythmias, cancer, and type 2 diabetes mellitus (DM2). In the United States alone, over six million individuals are affected by dementia—most commonly AD—while more than ten million live with atrial fibrillation (AFib), the most prevalent form of cardiac arrhythmia. Emerging epidemiological and clinical evidence indicates that AFib confers an increased risk of cognitive decline and dementia, particularly when diagnosed before the age of 65. Reported estimates suggest that AFib increases the risk of dementia in particular AD by 13% to over 65%, depending on age and other contributing factors. Conversely, individuals with AD exhibit a significantly higher prevalence of AFib (13.0%) compared with those without cognitive impairment (2.1%). The mechanistic underpinnings of this association remain incompletely understood. While cerebral microinfarcts and vascular injury have traditionally been implicated, several studies have demonstrated that the relationship persists even among individuals without overt stroke or cerebrovascular disease, implicating additional non-vascular pathways. Proposed mechanisms include systemic chronic inflammation, oxidative stress, and infectious processes. Notably, less attention has been directed toward shared aging-related mechanisms such as disruptions in proteostasis, cellular senescence, and common genetic susceptibilities. This review examines the converging biological pathways linking AD and AFib, with particular emphasis on their potential mechanistic intersections and translational relevance. We further discuss the therapeutic implications of these insights in the context of a rapidly evolving landscape-characterized by the advent of disease-modifying therapies for AD and innovative interventional strategies for AFib, including catheter ablation. Finally, we highlight the importance of considering the bidirectional dynamics of the brain–heart axis as a fundamental framework for understanding the pathophysiology and management of these interrelated disorders.

Volume 16 Issue 1 - 2026

Eliezer Masliah
Department of Neurosciences, University of California San Diego, USA

Correspondence: Eliezer Masliah, Retired

Received: December 26, 2025 | **Published:** January 12, 2026

Introduction

Aging is the primary risk factor for numerous degenerative disorders globally. As people age, they face a heightened risk for conditions such as Alzheimer's disease (AD), cerebrovascular and cardiovascular disease, cancer, and type 2 diabetes mellitus (DM2).[1] This relationship underscores the need for continued research into the mechanisms of aging to better understand and mitigate these widespread health challenges. In the United States alone, over six million individuals are affected by dementia, most commonly AD. Among cardiovascular conditions, atrial fibrillation (AFib), the commonest sustained cardiac arrhythmia in older adults affecting over 10 million in the US (Figure 1).[2]

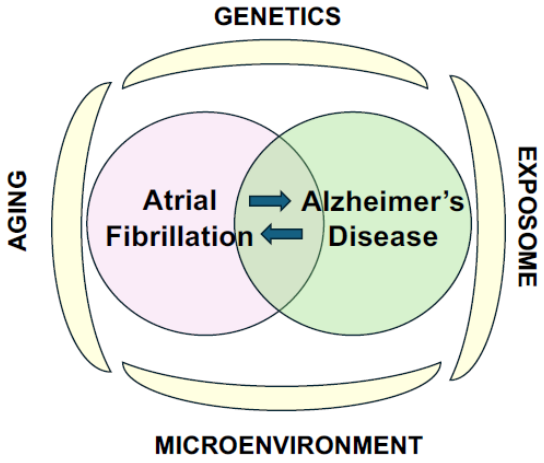

Figure 1 Conceptual depiction of the potential interactions aging, exposome, genetics, and the microenvironment in the interplay between AFib and AD. A complex set of interactions might regulate the mechanistic link between AFib and AD whereby similarities in genetics risk loci (eg: ApoE4, HSPG2, PLEC), exposome (eg: life style factors), aging mechanisms (eg: proteostasis, cell senescence) and microenvironment conditions (eg: amyloid formation, inflammation) might have roles in the converging pathogenesis.

In recent years it has been observed an increased association between AFib and cognitive decline and dementia, particularly when AFib is diagnosed before the age of 65 years.[3] This association is observed even among stroke free populations. The nature of this relationship is of clinical importance because if AFib contributes to AD (or dementia more broadly) via modifiable pathways that could open avenues for prevention. Importantly, since AFib is a well-known risk factor for ischemic stroke, and stroke is a major risk factor for dementia recent studies have adjusted for or exclude overt cerebrovascular disease.[4] In such studies AFib remained associated with dementia.[4] Indicating that the association between AFib and cognitive impairment was independent of shared risk factors such as hypertension and diabetes mellitus and persisted in patients without a history of stroke.[5]

While previous studies have focused on the contribution of vascular (eg: hypoperfusion, strokes, microinfarcts) and some non-vascular factors (eg: inflammation, genetics, life- style) in the pathogenesis of cognitive alterations in patients with AFib,[6] less is known about the role of shared aging molecular mechanisms such as proteostasis and cell senescence.[7] In this context the main objectives of this manuscript are to review some recent advancements and to discuss the unique role of emerging aging mechanisms in the relationship between dementia and AFib and it's therapeutical implications (Figure 1). Highlighting the importance of considering the bidirectional dynamics of the brain–heart axis as a fundamental framework for understanding the pathophysiology and management of these interrelated disorders.

Understanding whether AFib increases the risk of cognitive impairment and dementia may inform the management of AFib, in patient subgroups in whom treatment with rhythm modulation therapies, ablation and anticoagulation remains evolving.

Recent population based studies linking AFib and cognitive decline/dementia

Epidemiological and clinical studies indicates that AFib confers an increased risk of cognitive decline, mild cognitive impairment (MCI) and frank dementia, particularly when diagnosed before the age of 65 years.[8] Reported estimates suggest that AFib increases the risk of dementia and AD by 13% to over 65%, depending on age and other contributing factors.[9] Conversely, individuals with AD exhibit a significantly higher prevalence of AFib (13.0%) compared with those without cognitive impairment (2.1%)[10,11]

The nature and specific characteristics of this relationship are still under discussion. Here the influence of selected populations, varied lifestyle, environmental, genetics and aging mechanisms might contribute to both dementia and AFib heterogeneity such that when correlation studies are performed considerable variability might be observed (Figures 1).

For instance, in the past decade, several studies have confirmed that AFib is associated with cognitive impairment, MCI and dementia[11–13] even in the absence of clinically overt previous stroke.[3] However a few others have not shown a strong correlation.[9,14–17] For this reason, more extensive and larger analysis are needed. Recent meta-analysis studies have confirmed that AFib increases dementia risk (adjusted OR~1.6) and especially Alzheimer's disease (adjusted HR ~1.4) even in those without stroke[18]. Another recent meta-analysis focusing on AFib and risk of AD and vascular dementia (VaD) reported OR/RR of ~1.23 (95% CI: 1.13-1.34) for AD and ~1.80 (95% CI: 1.57-2.07) for VaD. These findings suggest that AFib may increase dementia risk by roughly 13-65 %, varying by sub-type and population.

Finally, a more recent meta-analysis that included 2.8 million persons confirmed that AFib was associated with 39% increased risk of cognitive impairment in the general population [n=15: 2 822 974 patients; hazard ratio=1.39; 95% Cl-) 1.25–1.53, I^2=90.3%; follow-up 3.8–25 years].[19]

This association appears to be observed even after correcting for known risk factors[12,20,21] and is more prominent in individuals under 65 compared with older patients with a higher burden of risk factors.[3] The report by the AF-SCREEN International collaboration is the most comprehensive and detailed analysis summarizing the evidence linking AFib and cognitive impairment and dementia and providing recommendations for the next steps[3]. They concluded that numerous observational studies have described an association between AFib and cognitive dysfunction ranging from mild impairment to overt dementia (including AD). The association is independent of manifest stroke as well as of the several risk factors common to both entities. However, the evidence for a direct causal relationship remains inconclusive.[3] Moreover they identified gap areas in the research such as: i) the need for confirmation in longer and larger prospective cohorts and adequately powered randomized controlled trials; ii) additional measures obtained by imaging and biomarkers may enhance the value of the CHA_2DS_2VASc score; iii) It is unknown whether there is a dose–response relation- ship between AFib burden and dementia: iv) Prospective randomized studies are required to confirm the beneficial effects of oral anticoagulant agents, rhythm control and atrial ablation and v) an integrated care approach to AFib management that includes treatment of related risk factors needs to be considered.[3] These might be required before screening for AF could be considered as a strategy to prevent or delay dementia.

More recent large population-based studies have yielded similar findings. For example, in a community study of nearly 200,000 adults, adjusted models showed that AFib was associated with a significantly increased risk of dementia (sub-distribution hazard ratio, 1.13 [95% CI, 1.09–1.16]). This association was more pronounced among younger adults and individuals with chronic kidney disease but did not differ by sex, race, or ethnicity.[9] Likewise, a community-based study from Spain including 2.5 million individuals found that AFib was independently associated with a modest increase in dementia risk, even after accounting for stroke (univariate HR, 3.39; P < .001). In that cohort, AFib was linked to a 4% overall increase in dementia risk, the association was strongest in patients younger than 70 years, who had a 21% higher risk of developing dementia. Remarkably, the risk of early-onset dementia (before age 65) was 36% higher among those diagnosed with AFib before 70 years of age.[22]

Pathogenesis of AD in the context of AFib and aging

Several vascular and non-vascular mechanisms have been recently proposed to explain the heightened risk of cognitive impartment and dementia in AFib patients (Figure 2).[3]

The most common vascular events includes: i) silent and overt strokes as AFib significantly increases the risk of blood clots forming in the heart that can travel to the brain, causing strokes, more commonly, it causes multiple "silent" cerebral infarcts (microembolism) that accumulate over time and lead to subtle but significant brain damage and cognitive decline; ii) cerebral hypoperfusion during AFib can lead to reduced cardiac output and irregular blood flow to the brain, a condition known as chronic cerebral hypoperfusion, the brain's autoregulation attempts to compensate, but over time, this can impair normal brain function, particularly in vulnerable areas like the

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke.* 2026;16(1):9–22. DOI: 10.15406/jnsk.2026.16.00646

hippocampus, a region critical for memory; iii) cerebral microbleeds resulting from Anticoagulation therapy, while crucial for preventing large strokes, can in some cases increase the risk of small cerebral microbleeds that might also contribute to cognitive dysfunction and iv) vascular dysfunction as AFib can lead to endothelial dysfunction, which impairs the function of blood vessels in the brain and the integrity of the blood- brain barrier, making brain tissue more vulnerable to damage.

Since the association between AFib and cognitive impartment and dementia is also, often observed among stroke free patients, other mechanisms has been proposed to be at play[11,23,24] including: i) inflammation as AFib is associated with a chronic systemic pro-inflammatory state, with elevated markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), this systemic inflammation may pass the compromised blood-brain barrier, leading to neuroinflammation that can accelerate AD pathology and ii) genetic factors and shared risk factors such as aging, hypertension, diabetes, and certain genetic predispositions like the APOE e4 genotype, which may increase vulnerability to both conditions (Figure 4).

Notably, AFib has been associated not only with an elevated risk of AD but also with increased susceptibility to other age-related neurodegenerative disorders, including vascular cognitive impairment and Lewy body–related conditions,[25–27] but not Fronto- Temporal dementia, supporting a role of selected aging related mechanisms (Figure 2).[6]

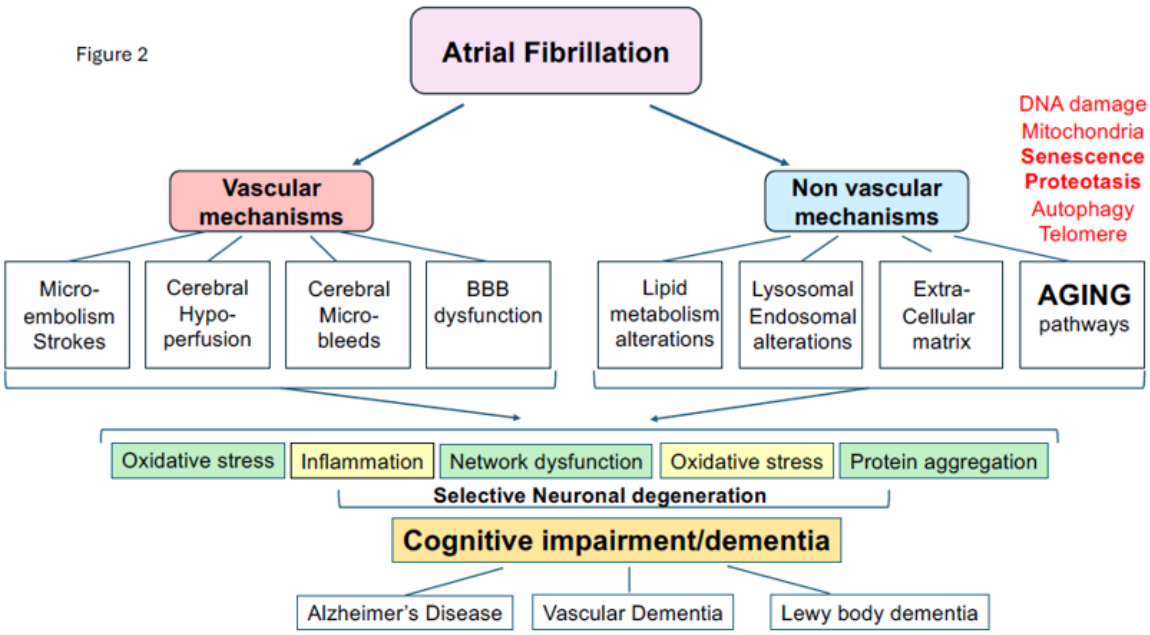

Figure 2 Diagrammatic representation of the potential vascular and non-vascular mechanisms involved in AFib that might lead to neurodegenerative disorders. In addition to the traditional vascular pathways involving strokes, hypoperfusion and neurovascular dysfunction, other non-vascular mechanisms also contribute in an important manner in heightening the risk of AD in patients with AFib. Among them alterations in aging pathways and regulation of lipids, extracellular matrix and lysosomal function, figure prominently leading to protein misfolding and aggregation, oxidative stress, inflammation and network dysfunction. This in turn could translate into increased risk for developing AD, LBD or Vascular dementia depending on the selective degeneration of vulnerable neuronal populations.

Common aging mechanisms shared by AFib and AD

The role of aging-related mechanisms in AFib and neurodegenerative disorders remains underexplored. Aging is proposed to involve a progressive and cumulative loss of homeostasis, characterized by alterations in nine fundamental cellular and molecular processes.[7] These include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (Figure 3).

Collectively, these "hallmarks of aging" are considered key determinants of the aging process and serve as a framework for guiding research and therapeutic strategies.[28–30] While all these factors might contribute to varying degrees - and are interconnected - for the purposes of this review we will specifically examine the potential roles of alterations in proteostasis and cellular senescence because of the mechanistic parallels between these two in the AFib and AD (Figure 2). Moreover, this manuscript focuses on AD, among the disorders with cognitive impairment associated with AFib because this condition is the most common of the neurodegenerative diseases of the aging population.

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke.* 2026;16(1):9–22.
DOI: 10.15406/jnsk.2026.16.00646

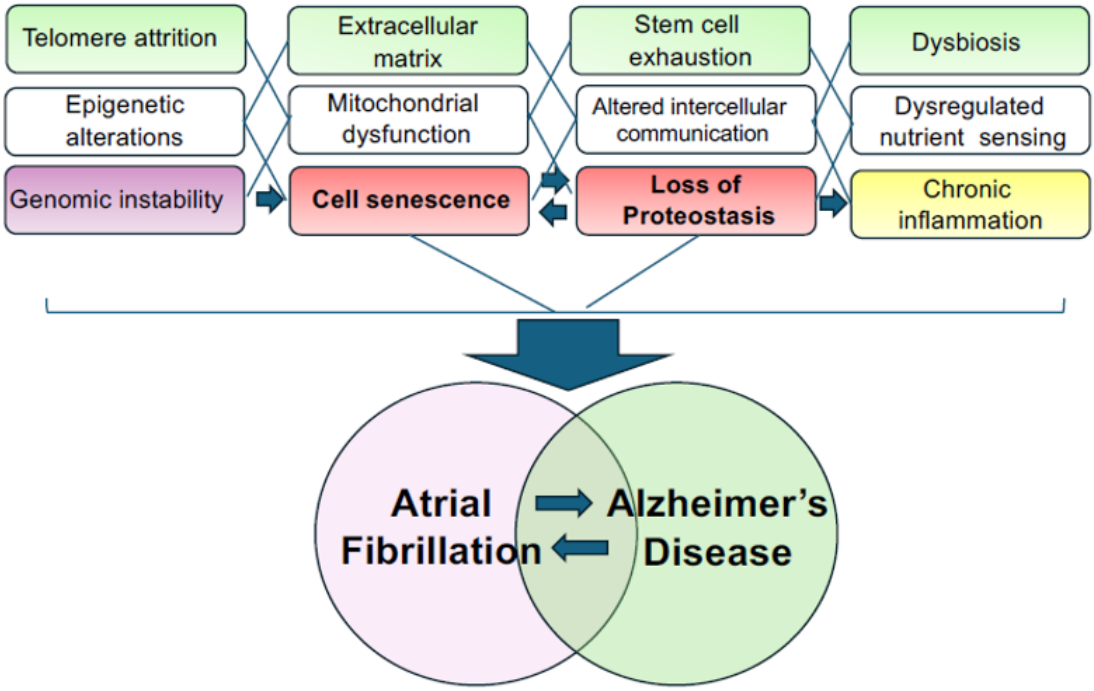

Figure 3 Hallmarks of aging in AFib and AD. Aging is proposed to involve a progressive and cumulative loss of homeostasis, characterized by increased genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. These alterations most likely act in conjunction as depicted by the lines joining the boxes. Among them, disruptions in proteostasis, and the accrual of senescent cellular populations are increasingly recognized as shared pathogenic features of both AD and AFib.

Alterations in proteostasis results in abnormal accumulation of intracellular and extracellular proteins that can result in a gain of toxic function or a loss of function[31,32] cell senescence refers to the process where a cell stops the cell cycle but does not die (Figure 4).[33–35] It is a response to cellular stress, such as DNA damage or shortened telomeres. Senescent cells accumulate during aging and display a senescent associated secretory phenotype (SASP) with the production of pro-inflammatory cytokines and chemokines (Figure 4).[36–38]

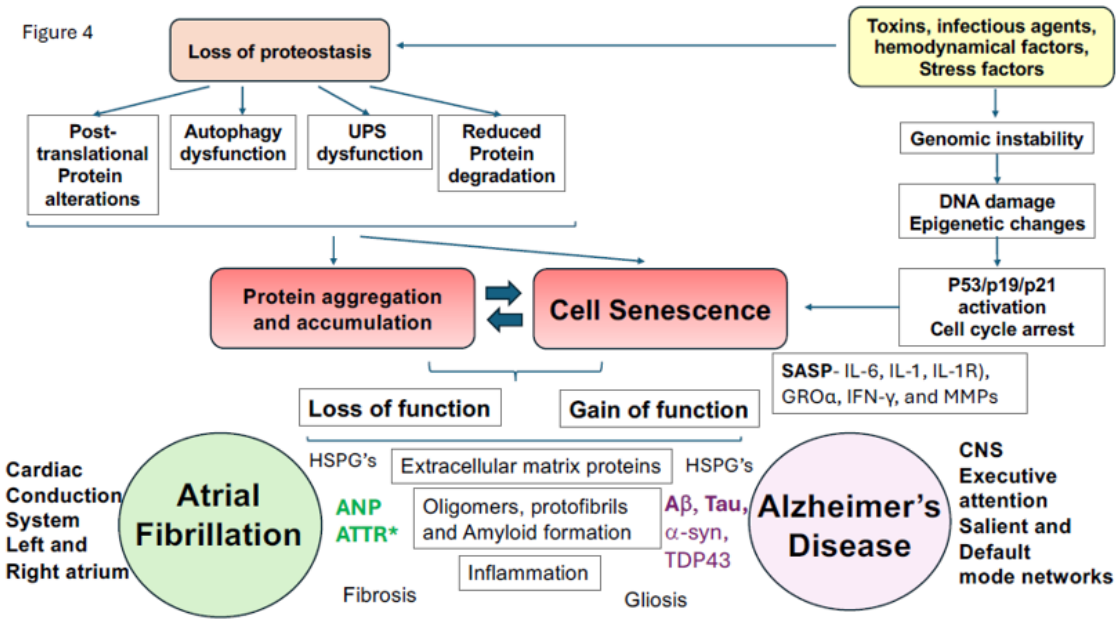

Figure 4 Diagrammatic representation of the potential aging pathways involved in AFib and AD. Chronic environmental stressors acting on a background of shared genetic susceptibility loci may converge on core pathways regulating proteostasis and cellular stress responses. Disruption of proteostasis promotes the misfolding, accumulation, and aggregation of specific proteins, including atrial natriuretic peptide (ANP) and extracellular matrix (ECM) components in AFib, leading to structural and functional remodeling of the atrial myocardium. In AD, analogous proteostatic failure results in the accumulation of amyloid-β

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke.* 2026;16(1):9–22.
DOI: 10.15406/jnsk.2026.16.00646

and tau, as well as α-synuclein and TDP-43, driving remodeling of neuronal networks linking the entorhinal cortex and hippocampus. In parallel, persistent DNA damage and dysregulation of cell-cycle checkpoint pathways involving p53, p19, and p21 induce stable cell-cycle arrest and promote the transition of cellular populations within the cardiac conduction system (CCS) and the central nervous system (CNS) into a senescent state. Senescent cells acquire a proinflammatory senescence-associated secretory phenotype (SASP), characterized by the secretion of cytokines, chemokines, and matrix-remodeling enzymes that amplify local tissue inflammation and remodeling. Together, protein aggregation–driven proteotoxic stress and SASP-mediated inflammatory signaling reshape cellular composition and intercellular communication, resulting in region-specific vulnerability of the posterior wall of the left atrium in AFib and the frontotemporal and parietal cortices in AD, thereby contributing to both shared and disease-specific pathological features.

The mechanisms of altered proteostasis in aging involve a decline in protein quality control, leading to the accumulation of misfolded proteins.[39–41] This is driven by: i) reduced protein degradation by extracellular enzymes; ii) altered ubiquitin proteosome system (UPS); iii) decreased autophagy-lysosomal system (ALS): iv) a decline in heat shock protein (HSP) function and v) increased oxidative stress and other post- translational modifications that damages proteins (Figure 4). These factors contribute to the formation of protein aggregates that impair cell function and are linked to age- related diseases. Remarkably, both in AD[42] and AFib[43] there is abnormal accumulation of proteins in the extracellular matrix of the myocardium and the neuropil of the CNS respectively accompanied by an inflammatory reaction.

In the following sections we will explore the pathological alterations in AD and AFib as well as the role of alterations in proteostasis and cell senesce that are common in these two disorders.

Degenerative pathology and proteinopathy in AD and AFib

Comparing AD and AFib, it is worth noting that both are progressive degenerative disorders of the aging population affecting conduction and electric activity in the brain and heart respectively (Figure 4) (Table 1). In AD, the degenerative process affects initially synaptic networks[44] between the entorhinal cortex and hippocampus in the temporal lobe and progress to affect executive networks among the fronto-parietal, the cholinergic forebrain and subcortical areas (Table 1).[45] This process is characterized by accumulation of aggregated proteins (eg: Aβ, Tau, α-synuclein, TDP43) that disseminate from cell to cell and trigger misfiring, neuroinflammation and eventually cell death of selected neuronal populations accompanied of astrocytosis and microgliosis (Table 1).[46–48] The extracellular deposits range from oligomers to protofibrils and frank amyloid fibers that results in the formation of neuritic plaques while the intraneuronal Tau aggregates to form neurofibrillary tangles (NFT's).[49–51] Heiko and Eva Braak proposed a six-stage hierarchical staging system based on the predictable spatiotemporal progression of these tau tangles through the brain (Table 1).[52] The stages correlate with the severity of the disease and follow specific anatomical pathways; with stages I and II to the transentorhinal region; stages III and IV with pathology increasing in the entorhinal cortex and hippocampus and begins to extend into the adjacent inferior temporal cortex and amygdala and stages V and VI where the NFT's are in all isocortical association areas, including the neocortex, frontal, and parietal lobes. These stages correlates with the clinical stages of the cognitive impairment (Table 1).[53]

Table 1 Comparison of clinical, anatomical, pathological, and molecular alterations in Atrial fibrillation and Alzheimer's Disease.

Characteristic	Atrial fibrillation	Alzheimer's disease
Clinical stages	Paroxysmal >persistent>long standing>permanent	Cognitive normal>subjective cognitive decline>mild cog decline>mild, moderate and severe dementia
Anatomical progression of pathology	Left atrium PV ostium>posterior wall>lateral>anterior>superior and septal> right atrium	Spreads along neural connections to the entorhinal cortex, hippocampus and amygdala > broadly to neocortex, including temporal, parietal, and frontal lobes, and finally to primary motor/sensory areas.
Cellular populations affected	Myocardial precursor cells?, myocytes, senescent myocytes?, myofibroblasts, sympathetic nervous system adrenergic fibers	Glutaminergic pyramidal neurons layers 2/3 and 5, GABA-anergic neurons, cholinergic neurons nucleus basalis, adrenergic neurons locus coeruleus
Ion Channels affected	Sodium channels (**Nav1.5**), Hyperpolarization-activated Cyclic Nucleotide-gated channels (**HCN**), L-type calcium channels (Cav1.1 and 1.3)	Potassium (K+) channels **(Kv1.1, Kv2.1, Kv7),** Calcium (Ca2+) channels **(L-type, NMDR high-voltage activated), and** Sodium (Na+) channels **(Nav1.1, Nav1.6)**
Gap junction proteins affected	Connexin 40 (Cx40) and Connexin 43 (Cx43)	Cx43 and Cx30 in astrocytes
Protein aggregates that form amyloids	Natriuretic peptides (ANP/BPN), desmin transthyretin (ATTR) and light-chain (AL)	Abeta and tau trough out the neocortex, hippocampus and subcortical regions and but also a-synuclein and TDP43 in the temporal regions and amygdala
Proteins accumulating	Extracellular matrix proteins (ECM) like proteoglycans, fibronectin, fibrillin-1, Collagen (Types I & III)	ECM proteins like Heparan Sulfate Proteoglycans (HSPGs), Chondroitin Sulfate Proteoglycans (CSPGs), Tenascin-C
Inflammatory components	IL6, IL8, Tumor Necrosis Factor- alpha (TNF-α), CRP, T cells, macrophages	IL-1β, IL6, TNF-α, chemokines, prostaglandins, T cells, microglia
Shared genetic risk loci	ApoE4, PLEC, HSPG2	ApoE4, PLEC, HSPG2

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke.* 2026;16(1):9–22. DOI: 10.15406/jnsk.2026.16.00646

Although the most prominent clinical manifestations of AD are progressive cognitive decline leading to MCI and dementia, these patients also exhibit at various stages of the disease, hyperactive network dysfunction affecting the temporal lobe that can be manifested as silent or overt seizure activity.[54–57]

Likewise, AFib is a progressive degenerative disorder that clinically spans a continuum—from paroxysmal to persistent, long-standing persistent, and ultimately permanent forms (Table 1).[58–60] The cellular and molecular basis of AFib remains under study, but research indicates that progressive changes in the atrial cardiac conduction system (CCS) can cause ectopic myocardial cells to gain abnormal electrical function (Table 1) (Figure 4).[61–63]

The CCS is a discrete, yet interconnected network of specialized cardiomyocytes embedded within the atrial and ventricular myocardium, organized to initiate, transmit, and coordinate electrical activation.[64,65] Although continuous with working myocardium, these cells differ in morphology, gap-junction density, and ion-channel expression, forming a functional syncytium optimized for rapid impulse propagation and hierarchical pacemaking.[65–67] The main components the sinoatrial (SA) node, which acts as the pacemaker that first trigger atrial contraction followed by the activation of the atrioventricular (AV) node, which in turn rapidly conduct the impulse throughout the ventricular walls via the His bundle, the bundle branches, and the Purkinje fibers.[68]

The SA node is a crescent-shaped structure located subepicardially at the junction of the superior vena cava and right atrial appendage, extending along the terminal groove. Histologically, it contains small, spindle-shaped pacemaker cells with sparse myofibrils and a rich autonomic innervation.[68] The node transitions into the surrounding atrial myocardium through paranodal and perinodal cells, which help distribute impulses into the right and left atria via preferential conduction pathways, including the crista terminalis, internodal tracts (anterior, middle, posterior), and Bachmann's bundle, the principal route to the left atrium.[68]

In AFib there is remodeling of the myocardial structure that creates a substrate where multiple, disorganized electrical impulses can arise and persist, often initiated by abnormal electrical activity around the left atrium posterior wall.[69] It is proposed that this remodeling process is progressive accounting for the various stages of severity of AFib. Remarkably, these ectopic focal triggers are frequently located around the pulmonary veins and the adjacent posterior wall of the left atrium.[70] From there, the disorganized electrical activity and the resulting fibrillatory process disseminate to the other walls of the left atrium, including the lateral, anterior, superior and septal (or medial) wall (Table 1).[71]

In severe or persistent cases, the condition becomes less dependent on the initial triggers and is maintained by a complex substrate often involving fibrosis, which causes slow conduction and allows for multiple re-entrant wavelets or stable rotors to persist throughout these various left atrial walls and potentially the right atrium as well.[72] The lateral wall is often the most severely affected by fibrosis as reveled by imaging techniques. Interestingly, the severity and distribution of the fibrosis correlate with the severity stage of the AFib.[72]

Histopathological studies have shown fibrosis myocyte hypertrophy, vacuolization and degenerative changes.[73] Other findings include inflammatory infiltrates and alterations to the sympathetic nerves. These changes, are known as atrial structural remodeling[74] and has been proposed to disrupt the normal electrical and structural integrity of the heart tissue, creating a substrate for the arrhythmia to persist.

It is worth noting that the fibrosis characterized by the excessive deposition of collagen types I, III, VI, and VIII might represent later stage alterations[75] and that at earlier phases other more subtle types of molecular or subcellular alterations in myocytes might occur, triggering the formation of ectopic cellular foci functioning as abnormal conduction cells[76]. Along these lines, it has been shown that at early stages of AFib, other specific extracellular matrix (ECM) proteins also accumulate in the atrial wall, including fibronectin-1, fibrillin-1, and fibromodulin (Table 1) (Figure 4).[76,77] In addition, at early stages of AFib it has been shown that abnormal deposits of atrial natriuretic peptides (ANP) that form oligomers and amyloid fibers might also involved (Table 1) (Figure 4).[78]

It has been proposed that a combination of hemodynamic, environmental, and genetic susceptibility factors contributes to the dysregulated secretion and accumulation of ANP and ECM proteins[79,80] in AFib (Table 1)(Figure 4). These alterations may facilitate the emergence of ectopic cardiac conduction cells around the pulmonary veins and other atrial regions. A central question is the identification of the molecular mechanisms by which atrial myocardial cells aberrantly acquire automaticity or conduction properties.

Current models proposed that the pathological accumulation of ANP, ECM proteins perturbs the local microenvironment, leading to cellular irritation, altered mechano- electrical signaling, and ultimately a shift in cellular functionality (Table 1) (Figure 4).[76–78]

Interestingly, in individuals with sporadic or hereditary cardiac amyloidosis there is also a high predisposition for AFi1.[81,82] The two most common types of amyloid proteins that misfold and accumulate in cardiac amyloidosis are transerethrin (ATTR) and light immunoglobulin light chains produced by plasma cells.[83] The prevalence of AFib with a prevalence ranging from 16% to 80%**,** depending on the cardiac amyloidosis subtype.[84] It is more common in ATTR, where up to 70% of patients may develop AFib (Table 1) (Figure 4).[84] AFib is considered a natural consequence of the disease due to amyloid fibril deposition in the heart, which leads to atrial dysfunction (Figure 4).

Similarly, in AD, the intracellular and extracellular accumulation of Aβ and tau oligomers, along with the propagation of protofibrillar assemblies, has been mechanistically linked to the selective degeneration of hippocampal circuits (Table 1) (Figure 4).[85,86] It is worth noting that in recent years accumulation of α-synuclein and TDP43 in specific brain regions in AD has also been described. Soluble Aβ oligomers impair synaptic transmission by disrupting N-methyl-D-aspartate receptor (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking, altering calcium homeostasis, and activating downstream kinases such as calcium/calmodulin-dependent protein kinase II (CaMKII) and glycogen synthase kinase-3 (GSK-3β).[45,87,88] Concurrently, tau oligomers destabilize axonal function and exacerbate synaptic dysfunction.[89] These combined effects promote network hyperexcitability via inhibitory interneuron dysfunction, reduced GABAergic tone, and increased excitatory drive. Aβ exposure reduces Kv3.1 and Nav1.1 channel expression in parvalbumin cells, impairing their high-frequency firing and disrupting network oscillatory precision (Table 1) (Figure 4).[45,90–92] Collectively, these processes contribute to progressive cognitive impairment and heighten susceptibility to subclinical epileptiform discharges and overt seizure activity (Figure 4).

However, considerable debate remains regarding the role of amyloid aggregates in AD - specifically, whether they are a primary driver of neurodegeneration or a secondary consequence of disrupted

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke*. 2026;16(1):9–22.
DOI: 10.15406/jnsk.2026.16.00646

neuronal function.[89,93] A similar question arises in AFib with respect to the deposition of ANP, ECM and ATTR aggregates: to what extent do these aggregates initiate abnormal electrical activity in the left atrium versus arise as a downstream effect of it? Although a discussion of this topic is beyond the scope of this manuscript, suffice to say that both in AD and AFib, the biology is more complex than a simple gain- or loss-of-function model. Early in the disease process, affected cells by the accumulation of aggregated proteins in combination with other hemodynamical and metabolic changes may exhibit aberrant *gain* of function before ultimately undergoing degeneration (Figure 4). This later accompanied by chronic inflammation and fibrosis (eg: fibroblast proliferation and collagen deposition) in the case of the heart and gliosis in the CNS (eg: astrocytosis and microglial activation) (Table 1) (Figure 4).

This suggests that, in addition to proteopathic mechanisms, other aging-related processes common to both AD[94,95] and AFib contribute to disease vulnerability.[96] Among these shared mechanisms, cellular senescence is of relevance, and its role is examined in detail in the following section (Figure 4).

Cellular senescence in AD and AFib

In the case of AD, it has been shown that one of the mechanisms involves Aβ and Tau pathology impairing interneuron excitability and synaptic GABAergic signaling, weakening both phasic and tonic inhibition, and simultaneously potentiating glutamatergic transmission and dendritic Ca^{2+} dynamics, leading to circuit disinhibition and pathologic hyperexcitability in hippocampal and cortical networks.[45,90,91] However, other mechanisms have been identified, including the potential role of inflammation, synaptic remodeling, neurogenesis alterations and cellular senescence in the hippocampus.[94]

In AFib the mechanisms through which ectopic, electrically hyperactive myocardial cells might emerge are under investigation[63] Some hypothetical mechanisms include: i) transdifferentiation or re-programming,[97,98] wherein terminally differentiated atrial cardiomyocytes aberrantly re-express ion channel subunits (e.g., HCN, Nav1.5) and connexins (Cx40, Cx43) in a pattern reminiscent of spindle-shaped specialized conduction cells; ii) alternatively, latent mesoderm-derived progenitor populations within the left atrium may undergo pathological differentiation into conduction system–like phenotypes in response to stressors such as fibrosis, oxidative stress, or neurohumoral activation and iii) aging-related cellular senescence in atrial myocytes may further contribute by initiating a pro-inflammatory SASP, which facilitates electrical remodeling and the acquisition of ectopic pacemaker-like properties, thereby promoting arrhythmogenic substrates (Table 1).[96]

Cellular senescence is present within CCS and is a significant contributor to age-related conduction abnormalities and arrhythmias, including sick sinus syndrome and AFib.[99] Senescence involves a transition to a stable cell-cycle–arrested phenotype accompanied by acquisition of a SASP, whereby cells secrete a broad repertoire of pro-inflammatory chemokines, cytokines, growth factors, and proteases. Key SASP components include IL-6, IL-1 receptor antagonist (IL-1RA), GROα, IFN-γ, and matrix metalloproteinases (MMPs), which together can disrupt extracellular matrix architecture, impair electromechanical coupling, and modulate tissue remodeling (Figure 4).[36,100,101]

Although SASP factors can exacerbate local inflammation and promote pathological remodeling, senescence also has context-dependent reparative functions. During tissue injury, transient senescent cell populations facilitate fibrosis, recruit immune effector cells, and coordinate the clearance of damaged or dysfunctional cells.[100–102] The net impact of senescence within the CCS therefore depends on the balance between its protective, short-lived roles in tissue repair and its detrimental effects when chronically sustained, which can destabilize conduction pathways and promote arrhythmogenesis.

This process is triggered by chronic injury, including oxidative stress and DNA damage, which leads to the upregulation of p53, p16^INK4a^ and p21, causing cell-cycle arrest and cessation of cell division[34] (Figure 4). In the heart, myocardial cells most prominently undergo senescence following chronic injury associated with myocardial ischemia and cardiomyopathy.[103] However, cardiac progenitor cells, myofibroblasts, endothelial cells, and fibroblasts can also undergo senescence during aging and under pathological conditions such as diabetes mellitus, chemotherapy, and arrhythmias.[103] In the cardiovascular system, cellular senescence can have a dual role depending on microenvironmental factors, genetic background, and cellular resilience—either promoting tissue repair or exacerbating inflammation and damage (Figure 4).[103]

In AFib, senescence of endothelial cells and fibroblasts has been linked to increased prevalence and severity of atrial fibrillation in the elderly,[103] although myocardial cells are also involved.[99] Senescent endothelial cells contribute to endothelial dysfunction, impaired nitric oxide signaling, and pro-thromboinflammatory activation, while senescent fibroblasts enhance extracellular matrix remodeling and fibrosis, creating a substrate that favors atrial conduction heterogeneity.[103] Moreover, senescent cardiomyocytes display reduced contractile reserve, mitochondrial dysfunction, impaired excitation– contraction coupling, and dysregulated calcium handling (including altered Ca^{2+} cycling and increased diastolic Ca^{2+} leak) (Table 1).[104] These changes compromise global myocardial performance and promote structural and electrical remodeling. Collectively, these senescence-associated alterations create a maladaptive microenvironment that can indirectly impair the CCS. The resultant increase in fibrosis, inflammatory cytokine load, oxidative stress, and disruption of intercellular coupling (e.g., via connexin downregulation) fosters conduction slowing, re-entry susceptibility, and arrhythmogenic instability, thereby further contributing to the initiation and maintenance of AFib.[105,106]

Likewise, chronic injury and cumulative DNA damage in the aging CNS can drive senescence or senescence-like states across multiple neural cell types including neurons, astrocytes, microglia, oligodendrocytes, and cerebrovascular endothelial cells - via conserved pathways involving activation of the p16^INK4a^/Rb and p21^CIP1^/p53 signaling axes (Figure 4).[107–109] Because neurons are terminally differentiated, permanently post-mitotic cells residing in G0, they cannot undergo classical replicative arrest. Instead, they acquire a "senescence-like phenotype" or neurescence[110,111] characterized by persistent DNA damage signaling, chromatin remodeling (e.g., H3K9me3 accumulation, formation of SAHF-like foci), mitochondrial dysfunction, metabolic reprogramming, and induction of a SASP-like secretory profile, despite the absence of canonical cell-cycle exit.[111] This neurescent state mirrors key molecular and functional elements of senescence in mitotically competent cells and is increasingly implicated in age-related neurodegenerative processes (Figure 4).[111]

In AD, multiple neural cell classes - including projection neurons, astroglia, and oligodendroglial lineage cells -exhibit molecular signatures consistent with bona fide cellular senescence.[94,112,113] Single-nucleus transcriptomic profiling of post-mortem AD cortex has demonstrated that >97% of senescence-enriched nuclei

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke*. 2026;16(1):9–22.
DOI: 10.15406/jnsk.2026.16.00646

correspond to excitatory glutamatergic neurons, with this population showing substantial overlap with tau-positive neuronal subtypes.[114] Within these datasets, cyclin-dependent kinase inhibitor 2D (CDKN2D/p19^INK4d^) emerged as the most discriminative marker loading onto the primary senescence eigengene, outperforming other canonical CDK inhibitors in identifying the senescence-associated transcriptional program.[114] Experimental AD models further support a causal relationship between proteopathic stress and neuronal senescence[115] both Aβ oligomers and pathological tau species induce DNA damage responses, chromatin remodeling (e.g., increased H3K9me3 and macroH2A deposition), and stable activation of the p16^INK4a^/p19^ARF^–Rb axis,[115,116] doi.org.[117,118] This is accompanied by the acquisition of a SASP enriched for proinflammatory cytokines, chemokines, and matrix-remodeling enzymes that propagate neuroinflammation and synaptic dysfunction. Importantly, pharmacological senolysis or genetic clearance of p16^INK4a^+/p19^INK4d^+ senescent cells in transgenic Aβ[118] or tau models[119] mitigates SASP signaling, reduces Aβ and tau accumulation, attenuates microglial activation, and rescues electrophysiological and cognitive impairments. These findings collectively implicate senescence of vulnerable neuronal subtypes as an active contributor to AD pathogenesis rather than a passive byproduct of neurodegeneration.

In summary, aging-related mechanisms, particularly disruptions in proteostasis, and the accrual of senescent cellular populations are increasingly recognized as shared pathogenic features of both AD and AFib (Figure 4). These convergent biological alterations support the hypothesis that parallel or mechanistically interlinked processes operating along a heart–CNS axis may underlie the elevated incidence of AD observed in individuals with AFib. Such processes could include systemic inflammatory coupling, impaired metabolic and vascular signaling, and cross-organ propagation of proteotoxic stress, collectively contributing to vulnerability in both neural and atrial CSS tissues.

Therapeutical implications

Given the epidemiological and mechanistic links between AFib, cognitive impairment, and AD, several clinically relevant questions arise. These include: i) how rhythm-control or rate-control interventions for AFib may modify long-term AD risk; ii) whether patients with AFib should undergo longitudinal monitoring with emerging AD biomarkers (e.g., plasma phosphorylated-tau species, Aβ42/40 ratios, neurofilament light); and iii) how current and future AFib therapies might interact with, or potentially modulate the efficacy of, disease-modifying AD therapeutics.

Over the past few years, AFib management has undergone rapid technological advancement. Innovations include high-resolution electroanatomical and digital mapping systems for CCS characterization, improved catheter-ablation strategies (e.g., pulsed-field ablation), next-generation oral anticoagulants with enhanced safety profiles, and procedural approaches such as left atrial appendage occlusion (LAAO) (e.g., the Watchman device) to reduce thromboembolic risk.[120–123] Similarly, AD patient care has advanced substantially with the recent FDA approval of anti-amyloid-β monoclonal antibodies (e.g., lecanemab, donanemab),[124,125] enabling disease- modifying treatment in early-stage patients. These therapies are complemented by the expansion of diagnostic tools- including amyloid and tau PET imaging as well as validated plasma biomarker panels—that facilitate earlier and more precise detection of AD pathology.[126–128]

For instance, a nationwide cohort study using the Korean National Health Insurance Service database comprising approximately 195,000 individuals demonstrated that AFib patients undergoing catheter ablation exhibited a significantly reduced risk of cognitive impairment and dementia.[129] Importantly, the association between ablation and decreased dementia incidence remained robust after adjustment for stroke as a time- dependent covariate (hazard ratio [HR] 0.76; 95% CI 0.61–0.95).

The protective effect was largely confined to patients in whom ablation successfully achieved durable rhythm control, whereas no significant reduction in dementia risk was observed in individuals with ablation failure. Catheter ablation was further associated with lower incidence rates of major dementia subtypes, including AD and vascular dementia.[129]

Converging evidence from other large population-based studies conducted in Europe,[130] Taiwan,[131] and the United States indicates that catheter ablation is associated with an approximate 30% reduction in dementia risk relative to standard medical management.[9] In a U.S. cohort, catheter ablation was linked to significantly lower dementia incidence (HR 0.52; 95% CI 0.45–0.61) as well as reduced all-cause mortality (HR 0.58; 95% CI 0.55–0.61).[132] Additionally, a separate comparative-effectiveness study reported that AFib patients treated with catheter ablation had a 41% lower dementia risk than those managed with antiarrhythmic drugs (AADs), with similar benefit observed in both men and women.[133] Moreover, several observational studies suggest that patients who undergo LAAO may have a lower incidence of composite dementia compared to those on long-term oral anticoagulation. One study reported a significantly lower risk of developing composite dementia (hazard ratio of 0.57) in the LAAO group.[134]

Collectively, these studies indicate that effective rhythm control in AFib - particularly via catheter ablation and LAAO may confer neuroprotective benefits by mitigating AFib- associated cerebral hypoperfusion inflammation and other aged-related alterations that contribute to cognitive decline. This emerging evidence raises an important translational question: should patients with AFib be systematically screened for AD–related circulating biomarkers, or conversely, should individuals with mild cognitive impairment or early dementia undergo proactive screening for subclinical or paroxysmal AFib? The issue is timely, given the rapid advancement of ultrasensitive plasma biomarkers for AD pathology (e.g., Aβ42/40 ratios, p-tau isoforms, NfL, GFAP) and the parallel development of more efficient, safer, and higher-resolution catheter ablation and LAAO technologies in conjunction with electronic wearable devises that can detect AFib early on.

In this context, the AF-SCREEN International Collaboration conducted an extensive evaluation of epidemiological, mechanistic, and clinical evidence linking AFib with cognitive impairment and dementia and subsequently issued a set of recommendations regarding diagnostic and therapeutic strategies.[3] Their consensus statement emphasized the need for rigorously designed, longitudinal clinical trials to delineate the causal pathways between AFib and neurodegeneration and to determine which interventional approaches - rhythm control, stroke-prevention strategies, or combined therapies - are most effective in preserving cognitive function and delaying the onset of dementia.

Additional therapeutic avenues relevant to the mechanistic overlap between AFib and AD relevant to aging mechanisms discussed in this review include emerging strategies aimed at enhancing proteostasis and mitigating cellular senescence. Interventions that improve protein quality control pathways - such as augmentation of chaperone activity, proteasomal or autophagic flux, protein folding stabilizers and

removal of protein aggregates and senescent cell populations - may theoretically attenuate both CCS and CNS degenerative pathology by reducing proteotoxic stress, chronic inflammation, and maladaptive remodeling.

A salient example is the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) with TTR tetramer stabilizers such as tafamidis, which have demonstrated significant improvements in cardiac structure and function[135] and favorable outcomes in patients with coexisting AFib.[136] Tafamidis acts by kinetically stabilizing the native TTR tetramer, thereby preventing its dissociation into misfolding-prone monomers that aggregate into amyloid fibrils. By slowing amyloid deposition, TTR stabilization mitigates diastolic dysfunction, atrial remodeling, and conduction abnormalities that predispose to AFib.[137]

Another pharmacologic class with putative geroprotective activity that may be relevant to the mechanistic intersection between AFib and AD comprises senolytic and senomorphic agents**.** Senolytics (e.g., the Dasatinib-plus-Quercetin combination) are compounds engineered to selectively eliminate senescent cells by exploiting their reliance on *senescence-associated anti-apoptotic pathways* (SCAPs).[138] These drugs target pro-survival nodes such as members of the BCL-2 family, or inhibit parallel pathways involving HSP90**,** p53, and other chaperone- or stress-response regulators.[139] By triggering apoptosis specifically in senescent cells, senolytics attenuate sterile, age- associated inflammation, remodel the inflammatory tissue microenvironment, and mitigate pathology across multiple chronic diseases.[140]

In contrast, senomorphic agents modulate - rather than eliminate - senescent cells by suppressing their SASP while maintaining cell viability. These compounds inhibit key SASP-generating signaling hubs, including NF-κB, mTOR, and related transcriptional programs.[141] By blocking the secretion of pro-inflammatory cytokines, chemokines, matrix-remodeling enzymes, and growth factors, senomorphics allow senescent cells to persist where they perform beneficial roles (e.g., in wound healing and tissue remodeling), while minimizing their detrimental paracrine effects.

Preclinical evidence in both AFib and AD models indicates that senolytic strategies may offer therapeutic benefit. In CCS and atrial remodeling models, senolytic treatment reduces AFib inducibility, atrial inflammation, and fibrosis.[142] In multiple AD mouse models, senolytics decrease Aβ and Tau burden, suppress neuroinflammation, and improve cognitive and behavioral phenotypes.[118,141–144]

Despite these encouraging findings, senolytic and senomorphic therapies remain early- stage investigational approaches for AFib and AD. Rigorous preclinical validation and controlled clinical trials are required to establish optimal dosing, long-term safety, tissue specificity, and therapeutic efficacy in humans.

Finally, an important emerging clinical intersection between AFib and dementia involves the management of AD patients receiving anti-amyloid monoclonal antibodies (e.g., lecanemab, donanemab). These immunotherapeutic agents have demonstrated efficacy in reducing fibrillar and soluble Aβ species within the brain and have been associated with modest but measurable slowing of cognitive decline.[124,125] However, amyloid clearance - particularly from cerebral vasculature—substantially increases the risk of amyloid-related imaging abnormalities (ARIA), including both vasogenic edema (ARIA- E) and microhemorrhages or macrohemorrhages (ARIA-H).[145] Because the risk and severity of ARIA-associated intracerebral bleeding are significantly amplified in individuals receiving oral anticoagulation (OAC), therapeutic anticoagulation is currently considered a major contraindication for anti-amyloid monoclonal antibody therapy.[146–148] A promising development to overcome this barrier is the increasing use of LAAO devices in AFib patients who are unsuitable for long-term anticoagulation.[149,150] By mechanically isolating the left atrial appendage and thereby reducing cardioembolic stroke risk without the need for chronic OAC, LAAO may enable a subset of AD patients with AFib to safely qualify for anti-amyloid antibody treatment. This emerging therapeutic pathway highlights a potentially important cardiology–neurology interface in the management of dual AFib–AD pathology.

Discussion and conclusions

Accumulating evidence from observational cohorts[3] and contemporary meta-analyses[18] indicates that AFib is mechanistically linked to cognitive impairment and dementia, even after adjustment for confounding variables, including clinical stroke and subclinical thromboembolism. Notably, the strength of this association is higher in adults younger than 65 years, suggesting contributory pathophysiological processes beyond conventional vascular risk.[8] Among late-life neurodegenerative disorders, AD exhibits the most consistent epidemiological association with AFib, although elevated risks have also been documented for vascular dementia and dementia with Lewy bodies.[25] Importantly, both AD and AFib represent progressive, degenerative conditions that propagate across distinct anatomical domains of the CNS and the CCS, respectively. While environmental, genetic, and vascular determinants exert substantial influence, the persistence of the AFib–cognitive impairment/dementia association in patients without overt cerebrovascular events underscores the potential involvement of shared, aging- related biological mechanisms (Table 1) (Figure 4). Accordingly, this review focused on convergent pathways of cellular senescence, impaired proteostasis, and other hallmarks of aging that may jointly contribute to the pathogenesis of AFib and AD (Figure 4).

In addition to cellular senescence and proteostasis decline, several other hallmarks of aging -including genomic instability (DNA damage), telomere attrition, epigenetic drift, deregulated nutrient-sensing pathways, mitochondrial dysfunction, stem-cell exhaustion, and altered intercellular communication-likely contribute to the shared pathobiology of AFib and neurodegenerative diseases (Figure 3). Perturbations in both senescence programs and protein-quality-control systems promote the accumulation of misfolded or aggregation-prone proteins,[151] leading to formation of amyloid deposits that trigger inflammation and tissue remodeling in AFib and AD. In the CNS, the dominant aggregation-prone proteins include Aβ and tau, although in recent years accumulation of α-synuclein, and TDP-43 have also been reported.[152,153] By contrast, in the heart, ANP accumulates,[78] and in selected cases TTR is the principal amyloid species that aggregates in AFib with ATTR[154] accompanied by fibrotic remodeling of the atrial tissue.[155] During early stages of aging related AFib there is accumulation of ANP, extracellular matrix proteins, these pathological processes promote structural and electrical remodeling, resulting in gain-of-function phenotypes in atrial cardiomyocytes that support ectopic firing, particularly near the pulmonary vein ostia, with subsequent propagation to additional atrial regions (Table 1) (Figure 4).[155,156] Analogously, in the prodromal and early stages of AD - driven by aging-related mechanisms and progressive buildup of amyloid and non-amyloid protein aggregates - neuronal networks exhibit functional dysregulation, including hyperexcitability arising from increased glutamatergic drive and impaired GABAergic inhibition (Table 1) (Figure 4).[157] At more advanced stages, both systems converge on degenerative outcomes: in the heart, progressive fibrosis,

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke.* 2026;16(1):9–22.
DOI: 10.15406/jnsk.2026.16.00646

collagen deposition, and deterioration of CCS architecture; and in the CNS, chronic reactive gliosis marked by astrocytic hypertrophy and elevated GFAP expression, along with microglial activation, synaptic degeneration, and neuronal loss (Table 1) (Figure 2).

Remarkably, observational evidence indicates that early identification and management of AFib, whether through catheter ablation, LAAO, or guideline-directed anticoagulation, reduces the risk of subsequent cognitive decline, including AD.[158,159] Nevertheless, adequately powered randomized controlled trials are still required to determine the optimal therapeutic strategy for specific AFib patient subgroups at elevated risk for AD. Emerging interventions relevant to both AFib and AD include senolytic and senomorphic agents aimed at selectively clearing senescent cells or SASP thereby reducing chronic inflammation; however, these modalities remain in early stages of clinical development.[138] In terms of protein accumulation, in ATTR, pharmacologic TTR tetramer stabilizers have demonstrated efficacy in preventing amyloid fibril formation and improving cardiac function, including reductions in AFib burden.[160,161] Similarly, two recently approved monoclonal antibodies for AD that enhance cerebral amyloid-β clearance have shown modest cognitive benefits in early-stage disease, their long-term effects and risk–benefit profiles continue to be evaluated.[124,125]

Another important dimension in the development of increasingly personalized therapies for patients with both AFib and AD is the integration of lifestyle factors and genetic background into clinical decision-making. Notably, AFib and AD share several genetic susceptibility loci. For example, variants in PLEC and HSPG2 have been implicated in both disorders, although their mechanistic contributions remain under investigation doi.[162,163] An intronic PLEC variant has been associated with elevated risk for both AD and AFib, potentially through its effects on cytoskeletal integrity and the organization of signaling complexes.[162–164] HSPG2 (perlecan), an extracellular matrix proteoglycan present within AD amyloid plaques, has also been linked to AFib, suggesting convergence at the level of extracellular matrix remodeling and vascular or neuroinflammatory pathways (Table 1) (Figure 1).[165]

Additional shared genetic risk factors, including genes involved in inflammatory regulation, lipid metabolism, and vascular homeostasis, further support the possibility of overlapping pathobiological mechanisms. Among these, the APOE ε4 allele confers increased susceptibility to both AD[166] and AFib.[167] Importantly, recent studies indicate that APOE ε4 may increase the risk of intracerebral hemorrhage in AFib patients treated with apixaban,[167] which is particularly relevant in AD, where anti-amyloid monoclonal antibodies also elevate the risk of ARIA and hemorrhagic complications.[124] These interactions raise potential contraindications or the need for heightened monitoring in APOE ε4 carriers. Consequently, alternative strategies for stroke prevention in AFib such as LAAO may require consideration in genetically high-risk individuals. Ultimately, case-by-case evaluation will be essential to balance therapeutic efficacy against bleeding risk as treatment approaches for AFib and AD continue to evolve.

Finally, it has long been recognized that the heart and CNS are closely interconnected through multiple genetic, vascular, hemodynamic, autonomic, and circadian rhythm pathways. These bidirectional brain–heart interactions involve continuous collection, integration, and interpretation of physiological signals, enabling coordinated regulation of homeostatic processes as well as cognitive functions. Recent studies indicate that cardiovascular aging is selectively associated with the aging of specific large-scale brain networks, including the salience, default mode, and somatomotor networks.[168] Lifestyle, genetic background, and environmental exposures contribute to the biological aging trajectories of both organs (Figure 1),[169,170] providing a mechanistic basis for the clinical adage that "what is good for the heart is good for the brain."

Although the heart and brain do not age at identical rates, their biological aging processes are tightly coupled.[168] Research shows that cardiac and neural biological age are correlated. That is when one organ exhibits accelerated aging relative to chronological age, the other is likely to do so as well networks.[168] Consistent with this, impaired cardiovascular health is associated with an older "brain age" phenotype and an increased rate of cognitive decline, whereas maintaining cardiovascular fitness supports healthier brain structure and function. In summary, understanding the links between genetics, lifestyle, vascular factors, and aging in AFib and AD will support improved treatments and prevention strategies.

Acknowledgements

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. Niccoli T, Partridge L. Ageing as a risk factor for disease. *Curr Biol.* 2012;22(17):R741–R752.
2. Andrade JG, Jackson LR 2nd, Diaz JC, et al. Atrial fibrillation in the Americas. *Lancet Reg Health Am*. 2025;47:101110.
3. Rivard L, Friberg L, Conen D, et al. Atrial fibrillation and dementia: a report from the AF–SCREEN International Collaboration. *Circulation*. 2022;145(5):392–409.
4. Saglietto A, Matta M, Gaita F, et al. Stroke–independent contribution of atrial fibrillation to dementia: a meta–analysis. *Open Heart.* 2019;6(1):e000984.
5. Madhavan M, Graff–Radford J, Piccini JP, et al. Cognitive dysfunction in atrial fibrillation. *Nat Rev Cardiol.* 2018;15(12):744–756.
6. Zhang W, Liang J, Li C, et al. Age at diagnosis of atrial fibrillation and incident dementia. *JAMA Netw Open*. 2023;6(11):e2342744.
7. Lopez–Otin C, Blasco MA, Partridge L, et al. Hallmarks of aging: an expanding universe. *Cell.* 2023;186(2):243–278.
8. Kogelschatz B, Zenger B, Steinberg BA, et al. Atrial fibrillation and the risk of early–onset dementia and cognitive decline: an updated review. *Trends Cardiovasc Med.* 2024;34(4):236–241.
9. Bansal N, Zelnick LR, An J, et al. Incident atrial fibrillation and risk of dementia in a diverse, community–based population. *J Am Heart Assoc.* 2023;12(6):e028290.
10. Alonso A, Arenas de Larriva AP. Atrial fibrillation, cognitive decline, and dementia. *Eur Cardiol*. 2016;11(1):49–53.
11. de Bruijn RF, Heeringa J, Wolters FJ, et al. Association between atrial fibrillation and dementia in the general population. *JAMA Neurol.* 2015;72(11):1288–1294.
12. Marzona I, O'Donnell M, Teo K, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *CMAJ*. 2012;184(6):E329–E336.
13. Rusanen M, Kivipelto M, Levalahti E, et al. Heart diseases and long–term risk of dementia and Alzheimer's disease: a population–based CAIDE study. *J Alzh*eimers Dis. 2014;42(1):183–191.
14. Marengoni A, Qiu C, Winblad B, et al. Atrial fibrillation, stroke and dementia in the very old: a population–based study. *Neurobiol Aging*. 2011;32(7):1336–1337.

15. Peters R, Poulter R, Beckett N, et al. Cardiovascular and biochemical risk factors for incident dementia in the Hypertension in the Very Elderly Trial. *J Hypertens*. 2009;27(10):2055–2062.
16. Rastas S, Verkkoniemi A, Polvikoski T, et al. Atrial fibrillation, stroke, and cognition: a longitudinal population–based study of people aged 85 and older. *Stroke.* 2007;38(5):1454–1460.
17. Piguet O, Grayson DA, Creasey H, et al. Vascular risk factors, cognition and dementia incidence over 6 years in the Sydney Older Persons Study. *Neuroepidemiology*. 2003;22(3):165–171.
18. Papanastasiou CA, Theochari CA, Zareifopoulos N, et al. Atrial fibrillation is associated with cognitive impairment, all–cause dementia, vascular dementia, and Alzheimer's disease: a systematic review and meta–analysis. *J Gen Intern Med*. 2021;36(10):3122–3135.
19. Koh YH, Lew LZW, Franke KB, et al. Predictive role of atrial fibrillation in cognitive decline: a systematic review and meta–analysis of 2.8 million individuals. *Europace.* 2022;24(8):1229–1239.
20. Chen LY, Norby FL, Gottesman RF, et al. Association of atrial fibrillation with cognitive decline and dementia over 20 years: the ARIC–NCS study. *J Am Heart Assoc*. 2018;7(6):e007301.
21. Chen LY, Agarwal SK, Norby FL, et al. Persistent but not paroxysmal atrial fibrillation is independently associated with lower cognitive function: the ARIC study. *J Am Coll Cardiol*. 2016;67(11):1379–1380.
22. Rodriguez–Garcia J, Ramos R, Ponjoan A, et al. Association between atrial fibrillation and dementia in a large population–based study in southern Europe. *Rev Esp Cardiol* (Engl Ed). 2025.
23. Li M, Jiang C, Lai Y, et al. Genetic evidence for causal association between atrial fibrillation and dementia: a Mendelian randomization study. *J Am Heart Assoc.* 2023;12(16):e029623.
24. Silva R, Miranda CM, Liu T, et al. Atrial fibrillation and risk of dementia: epidemiology, mechanisms, and effect of anticoagulation. *Front Neurosci.* 2019;13:18.
25. Javanshiri K, Siotis A, Heyman I, et al. High prevalence of atrial conduction abnormalities in Lewy body disease—a marker of cardiac complications? *Geroscience*. 2025;47(3):3169–3176.
26. Tabuas–Pereira M, Duraes J, Beato–Coelho J, et al. Lewy body dementia is associated with an increased risk of atrial fibrillation: a case–control study. *J Clin Neurosci.* 2022;99:62–65.
27. Demoniere F, Abdelli R, Rivard L, et al. Could the early detection of atrial fibrillation reduce the risk of developing dementia? *Biomedicines.* 2024;12(8):1931.
28. Lopez–Otin C, Blasco MA, Partridge L, et al. The hallmarks of aging. *Cell*. 2013;153(6):1194–1217.
29. Tenchov R, Sasso JM, Wang X, et al. Aging hallmarks and progression and age-related diseases: a landscape view of research advancement. *ACS Chem Neurosci.* 2024;15(1):1–30.
30. Keshavarz M, Xie K, Schaaf K, et al. Targeting the "hallmarks of aging" to slow aging and treat age-related disease: fact or fiction? *Mol Psychiatry*. 2023;28(1):242–255.
31. Cox D, Raeburn C, Sui X, et al. Protein aggregation in cell biology: an aggregomics perspective of health and disease. *Semin Cell Dev Biol.* 2020;99:40–54.
32. Shukla M, Narayan M. Proteostasis and its role in disease development. *Cell Biochem Biophys.* 2025;83(2):1725–1741.
33. Di Micco R, Krizhanovsky V, Baker D, et al. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat Rev Mol Cell Biol*. 2021;22(2):75–95.
34. Kumari R, Jat P. Mechanisms of cellular senescence: cell cycle arrest and senescence–associated secretory phenotype. *Front Cell Dev Biol.* 2021;9:645593.
35. Chaib S, Tchkonia T, Kirkland JL. Cellular senescence and senolytics: the path to the clinic. *Nat Med.* 2022;28:1556–1568.
36. Coppe JP, Desprez PY, Krtolica A, et al. The senescence–associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol.* 2010;5:99–118.
37. Zhang L, Pitcher LE, Yousefzadeh MJ, et al. Cellular senescence: a key therapeutic target in aging and diseases. *J Clin Invest.* 2022;132(15):e158450.
38. Song S, Lam EW, Tchkonia T, et al. Senescent cells: emerging targets for human aging and age–related diseases. *Trends Biochem Sci*. 2020;45(7):578–592.
39. Labbadia J, Morimoto RI. The biology of proteostasis in aging and disease. *Annu Rev Biochem.* 2015;84:435–464.
40. Hartl FU. Protein misfolding diseases. *Annu Rev Biochem.* 2017;86:21–26.
41. Hu C, Lin M, Wang C, et al. Current understanding of protein aggregation in neurodegenerative diseases. *Int J Mol Sci.* 2025;26(21):1042.
42. Selkoe DJ. Cell biology of protein misfolding: the examples of Alzheimer's and Parkinson's diseases. *Nat Cell Biol*. 2004;6:1054–1061.
43. Kishore P, Collinet ACT, Brundel B. Prevention of atrial fibrillation: putting proteostasis derailment back on track. *J Clin Med.* 2023;12(13):4971.
44. Masliah E, Crews L, Hansen L. Synaptic remodeling during aging and in Alzheimer's disease. *J Alzheimers* Dis. 2006;9(3 Suppl):91–99.
45. Palop JJ, Mucke L. Network abnormalities and interneuron dysfunction in Alzheimer disease. Nat Rev *Neurosci*. 2016;17(12):777–792.
46. Davis AA, Leyns CEG, Holtzman DM. Intercellular spread of protein aggregates in neurodegenerative disease. *Annu Rev Cell Dev* Biol. 2018;34:545–568.
47. Soto C, Pritzkow S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. *Nat Neurosci.* 2018;21(10):1332–1340.
48. Eisenberg D, Jucker M. The amyloid state of proteins in human diseases. *Cell.* 2012;148(6):1188–1203.
49. Nonaka T, Watanabe ST, Iwatsubo T, et al. Seeded aggregation and toxicity of alpha–synuclein and tau: cellular models of neurodegenerative diseases. *J Biol Chem*. 2010;285(45):34885–34898.
50. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta–peptide. *Nat Rev Mol Cell Biol.* 2007;8(2):101–112.
51. Sun KT, Mok SA. Inducers and modulators of protein aggregation in Alzheimer's disease- critical tools for understanding the foundations of aggregate structures. *Neurotherapeutics.* 2025;22:e00512.
52. Braak H, Braak E. Neuropathological staging of Alzheimer–related changes. *Acta Neuropathol.* 1991;82(4):239–259.
53. Grober E, Dickson D, Sliwinski MJ, et al. Memory and mental status correlates of modified Braak staging. *Neurobiol Aging*. 1999;20(6):573–579.
54. Targa Dias Anastacio H, Matosin N, Ooi L. Neuronal hyperexcitability in Alzheimer's disease: what are the drivers behind this aberrant phenotype? *Transl Psychiatry*. 2022;12(1):257.
55. Vossel KA, Tartaglia MC, Nygaard HB, et al. Epileptic activity in Alzheimer's disease: causes and clinical relevance. *Lancet Neurol.* 2017;16(4):311–322.
56. Kazim SF, Seo JH, Bianchi R, et al. Neuronal network excitability in Alzheimer's disease: the puzzle of similar versus divergent roles of amyloid beta and tau. *eNeuro.* 2021;8:e0507–20.2021.
57. Palop JJ, Mucke L. Amyloid–beta–induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. *Nat Neurosci.* 2010;13(7):812–818.

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke*. 2026;16(1):9–22.
DOI: 10.15406/jnsk.2026.16.00646

58. Shah AJ, Hocini M, Komatsu Y, et al. The progressive nature of atrial fibrillation: a rationale for early restoration and maintenance of sinus rhythm. *J Atr Fibrillation.* 2013;6(2):849.

59. Kato T, Yamashita T, Sagara K, et al. Progressive nature of paroxysmal atrial fibrillation: observations from a 14–year follow–up study. *Circ J.* 2004;68(6):568–572.

60. Wiggins BS, Cibotti-Sun M, Moore MM, et al. 2023 atrial fibrillation guideline–at–a–glance. *J Am Coll Cardiol.* 2024;83(1):280–284.

61. Schillinger KJ, Patel VV. Atrial fibrillation in the elderly: the potential contribution of reactive oxygen species. *J Geriatr Cardiol.* 2012;9(4):379–388.

62. Heijman J, Voigt N, Nattel S, et al. Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. *Circ Res.* 2014;114(9):1483–1499.

63. Markides V, Schilling RJ. Atrial fibrillation: classification, pathophysiology, mechanisms and drug treatment. *Heart.* 2003;89(8):939–943.

64. Veeraraghavan R, Gourdie RG, Poelzing S. Mechanisms of cardiac conduction: a history of revisions. Am J *Physiol Heart Circ Physiol.* 2014;306(5):H619–H627.

65. Vijayaraman P, Chelu MG, Curila K, et al. Cardiac conduction system pacing: a comprehensive update. *JACC Clin Electrophysiol.* 2023;9(11):2358–2387.

66. Christoffels VM, Moorman AF. Development of the cardiac conduction system: why are some regions of the heart more arrhythmogenic than others? *Circ Arrhythm Electrophysiol.* 2009;2:195–207.

67. Nattel S, Heijman J, Zhou L, et al. Molecular basis of atrial fibrillation pathophysiology and therapy: a translational perspective. *Circ Res.* 2020;127(1):51–72.

68. Tretter JT, Ponnusamy SS, Vijayaraman P, et al. The anatomy of atrial conduction: a review of anatomic landmarks integrated with computed tomographic virtual dissection to provide a road map for right atrial pacing. *Heart Rhythm*. 2026;23(1):131–142.

69. Al Ghamdi B, Hassan W. Atrial remodeling and atrial fibrillation: mechanistic interactions and clinical implications. *J Atr Fibrillation*. 2009;2(1):125.

70. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339(10):659–666.

71. Kurotobi T, Iwakura K, Inoue K, et al. Multiple arrhythmogenic foci associated with the development of perpetuation of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;3(1):39–45.

72. Chelu MG, King JB, Kholmovski EG, et al. Atrial fibrosis by late gadolinium enhancement magnetic resonance imaging and catheter ablation of atrial fibrillation: 5–year follow–up data. *J Am Heart Assoc.* 2018;7:e006313.

73. Chimenti C, Russo MA, Carpi A, et al. Histological substrate of human atrial fibrillation. *Biomed Pharmacother*. 2010;64(3):177–183.

74. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol.* 2014;63(22):2335–2345.

75. Boldt A, Wetzel U, Lauschke J, et al. Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease. *Heart*. 2004;90(4):400–405.

76. van den Berg NWE, Neefs J, Kawasaki M, et al. Extracellular matrix remodeling precedes atrial fibrillation: results of the PREDICT–AF trial. *Heart Rhythm*. 2021;18(12):2115–2125.

77. van Wijk SW, Su W, Wijdeveld L, et al. Cytoskeletal protein variants driving atrial fibrillation: potential mechanisms of action. *Cells*. 2022;11(3):2461.

78. Rahbar Kouibaran F, Sabatino M, Barozzi C, et al. Atrial natriuretic peptides as a bridge between atrial fibrillation, heart failure, and amyloidosis of the atria. *Int J Mol Sci*. 2023;24(7):15842.

79. Lozano–Velasco E, Franco D, Aranega A, et al. Genetics and epigenetics of atrial fibrillation. *Int J Mol Sci.* 2020;21(16):5717.

80. Ko D, Chung MK, Evans PT, et al. Atrial fibrillation: a review. *JAMA.* 2025;333(4):329–342.

81. Argiro A, Del Franco A, Mazzoni C, et al. Arrhythmic burden in cardiac amyloidosis: what we know and what we do not. *Biomedicines.* 2022;10(110:1810.

82. Wu R, Xia X, Niu Y, et al. Prevalence of atrial fibrillation and intervention therapy in cardiac amyloidosis. *Rev Cardiovasc Med.* 2025;26(5):37064.

83. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation.* 2012;126:1286–1300.

84. Romero CE, Correia EB, Siqueira Carvalho A, et al. Incidence and associated factors with atrial fibrillation in patients with transthyretin amyloidosis cardiomyopathy: insights from the multicenter REACT–SP registry. *Int J Cardiol Heart Vasc.* 2025;58:101658.

85. Gulisano W, Maugeri D, Baltrons MA, et al. Role of amyloid–beta and tau proteins in Alzheimer's disease: confuting the amyloid cascade. *J Alzheimers Dis.* 2018;64(s1):S611–S631.

86. Li S, Selkoe DJ. A mechanistic hypothesis for the impairment of synaptic plasticity by soluble Abeta oligomers from Alzheimer's brain. *J Neurochem.* 2020;154(6):583–597.

87. Zhang H, Jiang X, Ma L, et al. Role of Abeta in Alzheimer's–related synaptic dysfunction. *Front Cell Dev Biol.* 2022;10:964075.

88. Tu S, Okamoto S, Lipton SA, et al. Oligomeric Abeta–induced synaptic dysfunction in Alzheimer's disease. *Mol Neurodegener.* 2014;9:48.

89. Chang CW, Shao E, Mucke L. Tau: enabler of diverse brain disorders and target of rapidly evolving therapeutic strategies. *Science.* 2021;371(6352):eabb8255.

90. Hijazi S, Smit AB, van Kesteren RE. Fast–spiking parvalbumin–positive interneurons in brain physiology and Alzheimer's disease. *Mol Psychiatry.* 2023;28(12):4954–4967.

91. Hijazi S, Heistek TS, van der Loo R, et al. Hyperexcitable parvalbumin interneurons render hippocampal circuitry vulnerable to amyloid beta. *iScience.* 2020;23(7):101271.

92. Giorgio J, Adams JN, Maass A, et al. Amyloid–induced hyperexcitability in default mode network drives medial temporal hyperactivity and early tau accumulation. *Neuron.* 2024;112(4):676–686.e4.

93. Herrup K. The case for rejecting the amyloid cascade hypothesis. *Nat Neurosci.* 2015;18(6):794–799.

94. Sun L, Chen C. Senescence in aging and Alzheimer's disease. *Aging Dis*. 2025.

95. Saez–Atienzar S, Masliah E. Cellular senescence and Alzheimer disease: the egg and the chicken scenario. *Nat Rev Neurosci.* 2020;21(8):433–444.

96. Guo G, Watterson S, Zhang SD, et al. The role of senescence in the pathogenesis of atrial fibrillation: a target process for health improvement and drug development. *Ageing Res Rev*. 2021;69:101363.

97. Ausma J, Wijffels M, van Eys G, et al. Dedifferentiation of atrial cardiomyocytes as a result of chronic atrial fibrillation. *Am J Pathol.* 1997;151(4):985–997.

98. Barth AS, Merk S, Arnoldi E, et al. Reprogramming of the human atrial transcriptome in permanent atrial fibrillation: expression of a ventricular–like genomic signature. *Circ Res.* 2005;96:1022–1029.

99. Adili A, Zhu X, Cao H, et al. Atrial fibrillation underlies cardiomyocyte senescence and contributes to deleterious atrial remodeling during disease progression. *Aging Dis.* 2022;13(1):298–312.

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke*. 2026;16(1):9–22.
DOI: 10.15406/jnsk.2026.16.00646

100. Saito Y, Yamamoto S, Chikenji TS. Role of cellular senescence in inflammation and regeneration. *Inflamm Regen.* 2024;44(1):28.

101. Lecot P, Alimirah F, Desprez PY, et al. Context–dependent effects of cellular senescence in cancer development. *Br J Cancer.* 2016;114(11):1180–1184.

102. Serrano M. Senescence helps regeneration. *Dev Cell*. 2014;31(6):671–672.

103. Xu C, Qiu Z, Guo Q, et al. The role of cellular senescence in cardiovascular disease. *Cell Death Discov.* 2025;11(1):431.

104. Banerjee P, Kotla S, Reddy Velatooru L, et al. Senescence–associated secretory phenotype as a hinge between cardiovascular diseases and cancer. *Front Cardiovasc Med.* 2021;8:763930.

105. Jesel L, Abbas M, Park SH, et al. Atrial fibrillation progression is associated with cell senescence burden as determined by p53 and p16 expression. *J Clin Med*. 2019;9(1):36.

106. Staerk L, Sherer JA, Ko D, et al. Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. *Circ Res*. 2017;120(9):1501–1517.

107. Sikora E, Bielak–Zmijewska A, Dudkowska M, et al. Cellular senescence in brain aging. *Front Aging Neurosci.* 2021;13:646924.

108. Wang Y, Kuca K, You L, et al. The role of cellular senescence in neurodegenerative diseases. *Arch Toxicol.* 2024;98(8):2393–2408.

109. Shafqat A, Khan S, Omer MH, et al. Cellular senescence in brain aging and cognitive decline. *Front Aging Neurosci*. 2023;15:1281581.

110. Hudson HR, Riessland M, Orr ME. Defining and characterizing neuronal senescence, "neurescence," as G(X)–arrested cells. *Trends Neurosci*. 2024;47(12):971–984.

111. Herdy JR, Traxler L, Agarwal RK, et al. Increased post–mitotic senescence in aged human neurons is a pathological feature of Alzheimer's disease. *Cell Stem Cell.* 2022;29(12):1637–1652.e6.

112. Alshaebi F, Sciortino A, Kayed R. The role of glial cell senescence in Alzheimer's disease. *J Neurochem.* 2025;169(3):e70051.

113. Baker DJ, Petersen RC. Cellular senescence in brain aging and neurodegenerative diseases: evidence and perspectives. *J Clin Invest.* 2018;128(4):1208–1216.

114. Dehkordi SK, Walker J, Sah E, et al. Profiling senescent cells in human brains reveals neurons with CDKN2D/p19 and tau neuropathology. *Nat Aging.* 2021;1(12):1107–1116.

115. Dorigatti AO, Riordan R, Yu Z, et al. Brain cellular senescence in mouse models of Alzheimer's disease. *Geroscience.* 2022;44(2):1157–1168.

116. Fancy NN, Smith AM, Caramello A, et al. Characterisation of premature cell senescence in Alzheimer's disease using single–nuclear transcriptomics. *Acta Neuropathol*. 2024;147(1):78.

117. Lau V, Ramer L, Tremblay ME. An aging, pathology burden, and glial senescence build–up hypothesis for late–onset Alzheimer's disease. *Nat Commun*. 2023;14(1):1670.

118. Zhang P, Kishimoto Y, Grammatikakis I, et al. Senolytic therapy alleviates Abeta–associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. *Nat Neurosci.* 2019;22(5):719–728.

119. Bussian TJ, Aziz A, Meyer CF, et al. Clearance of senescent glial cells prevents tau–dependent pathology and cognitive decline. *Nature.* 2018;562(7728):578–582.

120. Kim JA, Khan K, Kherallah R, et al. Innovations in atrial fibrillation ablation. *J Interv Card Electrophysiol.* 2023;66(3):737–756.

121. Tzeis S, Gerstenfeld EP, Kalman J, et al. 2024 European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace.* 2024;26(4):euae043.

122. Nedios S, Sommer P, Bollmann A, et al. Advanced mapping systems to guide atrial fibrillation ablation: electrical information that matters. *J Atr Fibrillation*. 2016;8(6):1337.

123. Pham HN, Ibrahim R, Truong HH, et al. Advances in atrial fibrillation management: a guide for general internists. *J Clin Med*. 2024;13(24):2456.

124. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med.* 2023;388(1):9–21.

125. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *N Engl J Med.* 2021;384(18):1691–1704.

126. Zhang J, Zhang Y, Wang J, et al. Recent advances in Alzheimer's disease: mechanisms, clinical trials and new drug development strategies. *Signal Transduct Target Ther*. 2024;9(1):211.

127. Pahlke S, Kahale LA, Mahinrad S, et al. Blood–based biomarkers for detecting Alzheimer's disease pathology in cognitively impaired individuals within specialized care settings: a systematic review and meta–analysis. *Alzheimers Dement*. 2025;21(11):e70828.

128. Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement.* 2024;20(8):5143–5169.

129. Kim D, Yang PS, Sung JH, et al. Less dementia after catheter ablation for atrial fibrillation: a nationwide cohort study. *Eur Heart J*. 2020;41(47):4483–4493.

130. Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. *Eur Heart J.* 2016;37(31):2478–2487.

131. Li GY, Chen YY, Lin YJ, et al. Ablation of atrial fibrillation and dementia risk reduction during long–term follow–up: a nationwide population–based study. *Europace*. 2023;25(5):euad109.

132. Harrison SL, Buckley BJR, Austin P, et al. Catheter ablation and lower risk of incident dementia and mortality in older adults with atrial fibrillation. *J Am Geriatr Soc*. 2023;71(11):3357–3366.

133. Zeitler EP, Bunch TJ, Khanna R, et al. Comparative risk of dementia among patients with atrial fibrillation treated with catheter ablation versus antiarrhythmic drugs. *Am Heart J*. 2022;254:194–202.

134. Lu KH, Hsieh CY, Tsai HT, et al. Association between dementia and left atrial appendage occlusion in patients with atrial fibrillation: a TriNetX–based retrospective cohort study with target trial emulation. *Heart Rhythm O2*. 2025;6(2):151–158.

135. Shah SJ, Fine N, Garcia–Pavia P, et al. Effect of tafamidis on cardiac function in patients with transthyretin amyloid cardiomyopathy: a post hoc analysis of the ATTR–ACT randomized clinical trial. *JAMA Cardiol*. 2024;9(1):25–34.

136. Witteles R, Jefferies JL, Kapa S, et al. Atrial fibrillation as a prognostic factor for all–cause mortality in patients with transthyretin amyloid cardiomyopathy. *JACC CardioOncol*. 2024;6(4):592–598.

137. Jobbe–Duval A, Kharoubi M, Donal E, et al. Impact of tafamidis on survival in elderly patients: insights from the Healthcare European Amyloidosis Registry. *Int J Cardiol*. 2025;437:133522.

138. Hickson LJ, Langhi Prata LGP, Bobart SA, et al. Senolytics decrease senescent cells in humans: preliminary report from a clinical trial of dasatinib plus quercetin in individuals with diabetic kidney disease. *EBioMedicine*. 2019;47:446–456.

139. Aguado J, Amarilla AA, Taherian Fard A, et al. Senolytic therapy alleviates physiological human brain aging and COVID–19 neuropathology. *Nat Aging*. 2023;3:1561–1575.

140. Lelarge V, Capelle R, Oger F, et al. Senolytics: from pharmacological inhibitors to immunotherapies, a promising future for patients' treatment. *NPJ Aging*. 2024;10(1):12.

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke*. 2026;16(1):9–22. DOI: 10.15406/jnsk.2026.16.00646

141. Zhang L, Pitcher LE, Prahalad V, et al. Targeting cellular senescence with senotherapeutics: senolytics and senomorphics. *FEBS J*. 2023;290(5):1362–1383.

142. Mehdizadeh M, Naud P, Abu–Taha IH, et al. The role of cellular senescence in profibrillatory atrial remodelling associated with cardiac pathology. *Cardiovasc Res*. 2024;120(5):506–518.

143. Gonzales MM, Garbarino VR, Marques Zilli E, et al. Senolytic therapy to modulate the progression of Alzheimer's disease (SToMP–AD): a pilot clinical trial. *J Prev Alzheimers Dis*. 2022;9(1):22–29.

144. Yao M, Wei Z, Nielsen JS, et al. Senolytic therapy preserves blood–brain barrier integrity and promotes microglia homeostasis in a tauopathy model. *Neurobiol Dis*. 2024;202:106711.

145. Haeger A, Bottlaender M, Lagarde J, et al. What can 7T sodium MRI tell us about cellular energy depletion and neurotransmission in Alzheimer's disease? *Alzheimers Dement*. 2021;17(11):1843–1854.

146. Hampel H, Elhage A, Cho M, et al. Amyloid–related imaging abnormalities (ARIA): radiological, biological and clinical characteristics. *Brain*. 2023;146(11):4414–4424.

147. Ryan D, Feng W, Liu AJ. Cerebrovascular management considerations in patients on anti–amyloid therapies. *J Clin Med*. 2025;14(10):3420.

148. Doran SJ, Sawyer RP. Risk factors in developing amyloid–related imaging abnormalities (ARIA) and clinical implications. *Front Neurosci*. 2024;18:1326784.

149. Reddy VY, Holmes D, Doshi SK, et al. Safety of percutaneous left atrial appendage closure: results from the PROTECT AF trial and the Continued Access Registry. *Circulation*. 2011;123(4):417–424.

150. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long–term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014;64:1–12.

151. Tsoi PS, Quan MD, Ferreon JC, et al. Aggregation of disordered proteins associated with neurodegeneration. *Int J Mol Sci*. 2023;24(4):14862.

152. Spires–Jones TL, Attems J, Thal DR. Interactions of pathological proteins in neurodegenerative diseases. *Acta Neuropathol*. 2017;134(2):187–205.

153. Dhakal S, Wyant CE, George HE, et al. Prion–like C–terminal domain of TDP–43 and alpha–synuclein interact synergistically to generate neurotoxic hybrid fibrils. *J Mol Biol*. 2021;433(10):166953.

154. van den Berg MP, Mulder BA, Klaassen SHC, et al. Heart failure with preserved ejection fraction, atrial fibrillation, and the role of senile amyloidosis. *Eur Heart J*. 2019;40(16):1287–1293.

155. Zhao S, Johnston AM, Yiu CHK, et al. Aging–associated mechanisms of atrial fibrillation progression and their therapeutic potential. *J Cardiovasc Aging*. 2024;4.

156. Gyberg DJ, Patel RB, Zhang MJ. Time's imprint on the left atrium: aging and atrial myopathy. *J Cardiovasc Aging*. 2025;5.

157. Kim S, Nam Y, Kim HS, et al. Alteration of neural pathways and its implications in Alzheimer's disease. *Biomedicines*. 2022;10(4):1123.

158. Saglietto A, Ballatore A, Xhakupi H, et al. Association of catheter ablation and reduced incidence of dementia among patients with atrial fibrillation during long–term follow–up: a systematic review and meta–analysis of observational studies. *J Cardiovasc Dev Dis*. 2022;9(5):140.

159. Chen P, Chen Z, Pan D, et al. Catheter ablation and cognitive function in atrial fibrillation: a systematic review and meta–analysis. *Front Neurol*. 2022;13:934512.

160. Tschope C, Elsanhoury A, Kristen AV. Transthyretin amyloid cardiomyopathy—2025 update: current diagnostic approaches and emerging therapeutic options. *J Clin Med*. 2025;14(13):4785.

161. de Oliveira Ramos JV, Andrade Fernandes JV, de Abrantes Formiga YG, et al. Transthyretin stabilizer targeting for transthyretin amyloid cardiomyopathy: a systematic review and meta–analysis. *Med Clin (Barc)*. 2025;165(6):107200.

162. Koskeridis F, Fancy N, Tan PF, et al. Multi–trait association analysis reveals shared genetic loci between Alzheimer's disease and cardiovascular traits. *Nat Commun*. 2024;15(1):9827.

163. Thorolfsdottir RB, Sveinbjornsson G, Sulem P, et al. A missense variant in PLEC increases risk of atrial fibrillation. *J Am Coll Cardiol*. 2017;70(17):2157–2168.

164. Wiche G. Plectin in health and disease. *Cells*. 2022;11(9):1412.

165. Ariga T, Miyatake T, Yu RK. Role of proteoglycans and glycosaminoglycans in the pathogenesis of Alzheimer's disease and related disorders: amyloidogenesis and therapeutic strategies. *J Neurosci Res*. 2010;88(11):2303–2315.

166. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late–onset families. *Science*. 1993;261(5123):921–923.

167. Clocchiatti–Tuozzo S, Rivier CA, Renedo D, et al. APOE ε4 and risk of intracranial hemorrhage in patients with atrial fibrillation taking apixaban. *JAMA Neurol*. 2025;82(8):808–816.

168. Oh HS, Rutledge J, Nachun D, et al. Organ aging signatures in the plasma proteome track health and disease. *Nature*. 2023;624(7990):164–172.

169. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413–446.

170. Valls–Pedret C, Sala–Vila A, Serra–Mir M, et al. Mediterranean diet and age–related cognitive decline: a randomized clinical trial. *JAMA Intern Med*. 2015;175(7):1094–1103.

Citation: Masliah E. Aging mechanisms linking Alzheimer's disease and atrial fibrillation: therapeutical implications. *J Neurol Stroke*. 2026;16(1):9–22.
DOI: 10.15406/jnsk.2026.16.00646