Stroke

AHA SCIENTIFIC STATEMENT

Cardiac Contributions to Brain Health: A Scientific Statement From the American Heart Association

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ABSTRACT: The burden of neurologic diseases, including stroke and dementia, is expected to grow substantially in the coming decades. Thus, achieving optimal brain health has been identified as a public health priority and a major challenge. Cardiovascular diseases are the leading cause of death and disability in the United States and around the world. Emerging evidence shows that the heart and the brain, once considered unrelated organ systems, are interdependent and linked through shared risk factors. More recently, studies designed to unravel the intricate pathogenic mechanisms underpinning this association show that people with various cardiac conditions may have covert brain microstructural changes and cognitive impairment. These findings have given rise to the idea that by addressing cardiovascular health earlier in life, it may be possible to reduce the risk of stroke and deter the onset or progression of cognitive impairment later in life. Previous scientific statements have addressed the association between cardiac diseases and stroke. This scientific statement discusses the pathogenic mechanisms that link 3 prevalent cardiac diseases of adults (heart failure, atrial fibrillation, and coronary heart disease) to cognitive impairment.

Key Words: AHA Scientific Statements ■ cognition ■ heart diseases ■ stroke

The heart and brain are reciprocally linked in a 2-way connection whereby the heart provides oxygen and nutrients to sustain the brain, and the brain in return provides autonomic nervous system control to the heart. This synergism is vital to the maintenance of brain and bodily health, and we must consider the potential for interdependency of major organ systems, once thought to be disparate, on the basis of shared phenotypic and genotypic expression.[1] Adverse changes in gray matter volumes, cortical thickness, white matter (WM) microstructure, and functional networks have been associated with cardiac phenotypes. For example, greater left cardiac ventricular wall thickness coexists with microstructural metrics of cerebral WM tracts, indicating a connection between abnormal heart characteristics and WM microstructure.[1] Furthermore, it is increasingly recognized that vascular risk factors (VRFs) and cardiovascular diseases (CVDs) may lead to brain injury and disrupt normal brain structure and function.[2,3] In relation to brain health, both congenital and acquired cardiac diseases have been associated with cognitive impairment and dementia.[4] Understanding the mechanisms whereby cardiac diseases lead to brain injury and impair brain health, the frequency of associated cognitive impairment, and management and prevention strategies are germane to those in general and specialty care practices.

This scientific statement examines the contributions of 3 prevalent cardiac diseases in adults (heart failure [HF], atrial fibrillation [AF], and coronary heart disease [CHD]) to brain health, with emphasis on the pathogenic processes that link these 3 disorders to cognitive impairment. The contribution of depression, a common concomitant of CVD, and congenital heart disease to brain health will be addressed in future scientific statements.

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SEARCH STRATEGY

For the HF section, we performed a PubMed search using the following search terms: cognitive impairment OR neuropsychological dysfunction OR dementia AND heart failure, HFpEF AND cognitive impairment OR neuropsychological dysfunction; HFrEF AND cognitive OR neuropsychological impairment; heart failure AND stroke; and heart failure AND depression. For the AF section, we performed a PubMed database search using the following key words: cognitive dysfunction OR cognitive impairment OR dementia AND atrial fibrillation; cognitive dysfunction OR cognitive impairment AND atrial fibrillation; and atrial fibrillation AND therapies OR treatment for cognitive impairment OR cognitive dysfunction. For the CHD section, we performed a PubMed database search using the following key words: cognitive dysfunction OR cognitive impairment OR dementia AND coronary artery/heart disease OR heart failure; cognitive dysfunction OR cognitive impairment AND atherosclerosis OR vascular disease; coronary artery/heart disease AND microvascular dysfunction OR cognitive impairment OR cognitive dysfunction; and coronary artery/heart disease AND therapies OR treatment for cognitive impairment OR cognitive dysfunction. We prioritized meta-analyses as well as large, population-based longitudinal studies published in the past 15 years and limited our search to studies written in English.

HEART FAILURE

Frequency of Cognitive Impairment in HF

HF is a complex clinical syndrome and a major public health burden secondary to various cardiac and noncardiac pathologies, resulting in functional or structural impairment of ventricular filling or ejection of blood. The most common underlying causes of HF include CHD, hypertension, obesity, diabetes, arrhythmias, and valvular heart disease. Rarer causes include autoimmune diseases, peripartum heart disease, and substance abuse.[5] The longstanding New York Heart Association classification system was based on symptom severity; a newer taxonomy emphasizes the continuum of this syndrome, with advanced stages linked to poorer survival. Guidelines recognize 3 different phenotypes: reduced (≤40%), midrange (41%–49%), and preserved (≥50%) left ventricular ejection fraction (EF).[5] The prevalence of HF was 27 per 1000 in 2014, with a lifetime risk of ≈1 in 4. Whereas the proportion of people with HF with reduced EF (HFrEF) is declining, the prevalence of HF with midrange or preserved EF (HFpEF) is increasing.[4,5] It is well established that HF is associated with cognitive decline, affecting self-care, medication compliance, disease management, and frailty in older adults.[6–8] In a large systematic review, the prevalence of cognitive impairment in HF cohorts was 43%.[9] Attention, language and verbal fluency, processing speed, working memory, and executive function are commonly affected cognitive domains.[7,10] We recognize that the different HF phenotypes are independently associated with brain injury; the frequency of cognitive dysfunction appears to be greater in HFrEF than in HFpEF in some studies, but not in others.[11,12] Most of the data on cognitive outcomes have been reported for HF as a global entity, and independently for HFpEF and HFrEF, with insufficient findings for HF with midrange EF.

Mechanisms Whereby HF May Cause Brain Injury and Cognitive Impairment

Structural and functional markers of brain injury and brain disease in people with HF may be due to shared underlying risk factors leading to adverse effects on both the heart and the brain, transient ischemic attack or stroke, or covert brain injury (eg, WM hyperintensities, silent brain infarction, cortical atrophy) mediated by pathophysiologic pathways, such as reduced blood flow.[13] Although the evidence in this area is limited, it has been observed that the changes in gray matter volume observed in patients with HF are not completely explained by coexisting VRF or reduced EF. In addition, increased hyperintensity burden has been described in individuals with left ventricular systolic and diastolic dysfunction.[14,15] Furthermore, data from the CARDIA study (Coronary Artery Risk Development in Young Adults) show that midlife diastolic dysfunction and abnormal cardiac structure, represented by increased left ventricular mass index and left atrial volume index over 25 years, but not decreased left ventricular EF, are associated with cognitive decline. These associations remained after accounting for confounders, such as VRFs, and history of AF, CHD, or stroke.[16] Thus, it is likely that other mechanisms, such as inflammation, neurohormonal activation, and genetic predisposition, contribute to the cognitive decline observed in people with HF.

Sympathetic Nervous System Activity, Inflammation, Hypoperfusion, and Brain Infarction

The different HF phenotypes share common characteristics, including increased sympathetic nerve activity (particularly at the hypothalamic paraventricular nucleus, the nuclei of the lamina terminalis that lack blood–brain barrier [BBB], and the rostral and caudal ventrolateral medulla nuclei), activated renin-angiotensin system, and systemic inflammation, all of which have been associated with cognitive impairment.[17] Circulating cytokines and inflammatory proteins can also cross the BBB and activate microglia to its proinflammatory form. Abnormal flow and blood constituents, along with abnormalities in cardiac and vessel walls, also predispose to thromboembolic stroke, with rates up to 2.23 events per 100

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person-years, compared with 1.17 (P<0.01) in patients without HF. Silent brain infarction is common in both ischemic and nonischemic cardiomyopathy, with a prevalence that appears much greater than for frank stroke.[18] Overall, cardioembolism is the most common stroke subtype in HF.[19] The epidemiology of stroke based on HF subtype, however, is incompletely characterized. Whereas stroke is commonly reported in patients with HFrEF independent of the presence of AF, less is known in patients with preserved or midrange EF.[20] Among individuals with coexisting AF, the frequency of stroke and systemic embolism may be greater in HFpEF than in HFrEF, and it has been hypothesized that this difference is related to comorbidities.[21]

Worsening cognition in HFrEF has been primarily associated with a reduction of cerebral blood flow, with the association being stronger in older adults.[22,23] Hypoperfusion leads to oxidative stress with overproduction of reactive oxygen species, inflammation (associated with elevated tumor necrosis factor–α, toll-like receptor 4, interleukin [IL]–6, and IL-1), glial activation, brain mitochondrial dysfunction, dendritic spine loss (synaptic dysfunction), and neuronal apoptosis.[24] Microglia-mediated neuroinflammation along with upregulation of the translocator protein are proposed as some of the mechanisms underlying cognitive impairment, as well as mood and anxiety disorders, in ischemia-induced HF models.[25] Neurohormonal activation, a process characterized by the increased secretion of molecules by the neuroendocrine system, is implicated in the pathophysiology of HFrEF.[26] Given that some of the molecules involved in this process, such as angiotensin II and catecholamines, have an active role in cognition, it is also possible that neurohormonal activation contributes to cognitive decline in these patients.[27,28] In addition, neuroanatomic areas commonly affected in neurodegenerative dementias, such as the hippocampus and cortical layers III and V, are particularly sensitive to hypoxic/ischemic injury, as occurs in patients with cardiac arrest or those with severely reduced cardiac output.[29,30] This correlates with data obtained in experimental models that indicate that hypoxia/ischemia and hypoperfusion can contribute to neurodegeneration through an enhancement in the amyloidogenic processing of the amyloid-β precursor protein and hyperphosphorylation of tau.[31–33]

Vascular and Related Factors

Patients with HFpEF may share common manifestations or risks with their reduced EF counterparts, including endothelial damage, atherosclerosis, fibrosis and stiffening, inflammation-induced hypercoagulability, diabetes, and hypertension. Although there is some reduction in cerebral blood flow in HFpEF from diastolic dysfunction, cognitive decline in this case appears more related to comorbid VRFs. Recent findings from the ARIC study (Atherosclerosis Risk in Communities) have also suggested that an elevated cardiac index in the setting of HFpEF is associated with poorer cognition.[11] Obesity and sleep-disordered breathing, both conditions commonly seen in patients with HF, are associated with cognitive decline. People with these conditions have an elevated prevalence of atrial cardiopathy, abnormal cardiac rhythms, such as AF, and systemic inflammation (adiposity and volume of epicardial adipose tissue serve as an amplifier of inflammation), which predispose to stroke. In addition, reduced brain volume and WM integrity are increasingly recognized in people with sleep-disordered breathing.[34]

Neurodegeneration and Genetic Factors

Serum levels of biomarkers of neurodegeneration, including phospho-tau, neurofilament light chain, amyloid-β_{40}, are associated with cardiac dysfunction.[35,36] In addition, HF has been associated with abnormal functional connectivity between the precuneus, an important association area in the brain commonly affected in Alzheimer disease (AD), and other brain regions.[37] Furthermore, data obtained in observational studies indicate that neurodegenerative diseases and HF may share genetic and protein profiles. For example, variations in *PSEN1* and *PSEN2*, both genes associated with AD, have been associated with HF.[38] Also, intramyocardial deposits of amyloid-β_{40} and β_{42}, both commonly seen in neurodegeneration, as well as diastolic dysfunction, have been observed in patients with AD.[39] Furthermore, elevated plasma levels of amyloid-β_{40} are associated with a higher risk of HF, but not with increased amyloid burden in the brain as assessed by amyloid PET imaging.[36,40] Studies done in preclinical models have shown that epigenetic mechanisms may regulate hippocampal function in HF.[41] These observations suggest commonalities in the pathogenesis of HF and neurodegeneration. Although provocative, the evidence in this area is emerging, and additional studies are needed to substantiate these observations.

Prospects for Prevention and Treatment of HF to Maintain Brain Health

Both stroke and decreased tissue perfusion are associated with cognitive decline and are prevalent in HFrEF. Therefore, it is expected that the implementation of evidence-based approaches to improve stroke volume and EF may improve brain health. Therapeutic interventions for HF are aimed at each stage to modify risk factors (stage A), avoid progression of asymptomatic disease (stage B), prevent or treat symptoms (stage C), and decrease mortality risk in advanced disease (stage D). Figure 1 summarizes the medical management of patients with HF.[5] The long-term effect of these treatments on brain health measures, particularly cognitive performance, however, has not been demonstrated

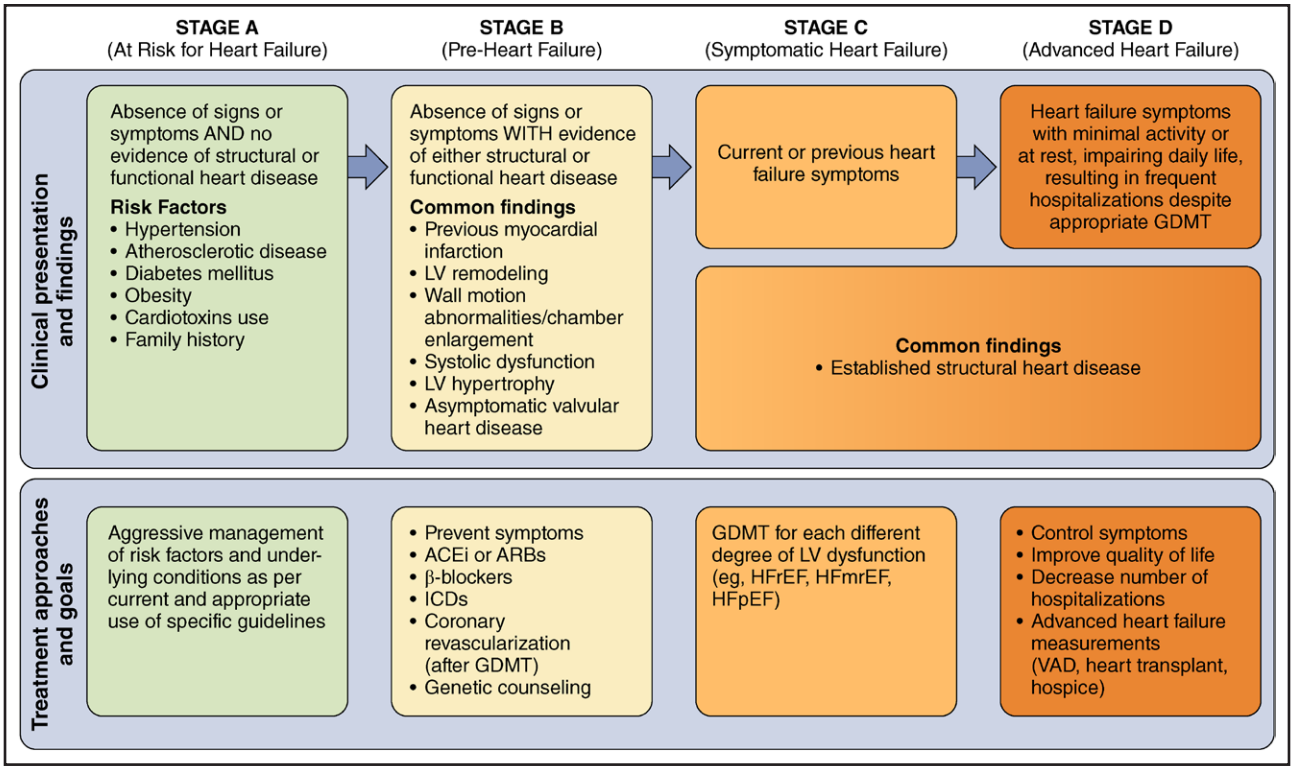

Figure 1. Heart failure stages and treatment approaches.[5]
Clinical findings and general treatment approaches and goals by HF stage. ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LV, left ventricular; and VAD, ventricular assist device.

completely. In addition, stroke, one of the most common causes of cognitive decline, is a relatively frequent complication of surgical interventions used in patients with severe HF, with an incidence of ≈10% at 1 year for both durable mechanical circulatory support and heart transplantation.[42,43] Thus, screening for cognitive impairment is recommended before surgical interventions.

ATRIAL FIBRILLATION

Frequency of Cognitive Impairment in AF

AF is the most common sustained clinical arrhythmia in adults. The overall prevalence and incidence of AF are projected to increase, with up to 15.9 million individuals expected to have AF in the United States by 2050.[4] Whereas the association between AF and stroke is well-established, the link between AF and cognition requires further clarification.[4] In a large meta-analysis, AF was associated with a 39% increased risk of cognitive impairment in the general population.[44] Although controversial, some studies have suggested that women may face a higher susceptibility to cognitive impairment compared with men.[45] This observation is noteworthy, especially considering that observational data suggest that women with AF may be undertreated with anticoagulation and have an increased risk of AF-associated stroke, which is typically more severe and clinically disabling than other types of stroke.[46]

The use of implantable devices also confirms that subclinical paroxysmal AF is particularly prevalent in the general population as well as in patients with silent (or covert) and cryptogenic stroke.[47] Thus, it is likely that current estimates do not accurately capture the contribution of AF to cognitive decline in the general population. Active research is underway to improve the accuracy and determine the beneficial effect of smartwatches and other wearables for the detection and monitoring of cardiac arrhythmias such as AF.[48] The improved detection of subclinical AF in the general population will provide valuable information on the contribution of this condition to brain health.

Mechanisms Whereby AF May Cause Cognitive Impairment

VRFs and Stroke

AF and dementia share several risk factors, such as hypertension, diabetes, HF, smoking, vascular disease, sleep-disordered breathing, and advanced age. These conditions also lead to structural and functional

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changes, including WM hyperintensity burden, silent brain infarction, decreased hippocampal and total gray matter volumes, and functional neural network abnormalities, that result in cognitive decline.[49] However, there is evidence that suggests that the association between AF and dementia is not completely accounted for by these risks.[50] Stroke is a strong predictor of cognitive impairment in these patients, and the CHA_2DS_2-VASc score, a validated stroke risk stratification tool in AF, is directly associated with risk of dementia. Furthermore, oral anticoagulation reduces the risk of dementia in patients with AF by ≈50%.[51,52] However, incident AF is associated with dementia even after censoring for stroke.[52,53] In a large meta-analysis, the odds of dementia among patients with AF was 2.0 in unselected patients and 2.4 in those with recent stroke compared with patients without AF.[54] In comparison, among individuals without a history of stroke, AF is associated with an ≈1.4- to 2.2-fold increase in the risk of dementia or cognitive impairment.[44,53] In addition, in BRAIN-AF (Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation), which included individuals with AF but no history of stroke or transient ischemic attack, lower Montreal Cognitive Assessment scores were observed among participants with permanent or persistent AF relative to those with paroxysmal AF.[55] Although the interpretation of these studies is confounded by heterogeneity, the collective evidence suggests that the relationship of AF with cognitive impairment is not completely explained by history of stroke, and other factors, including AF burden, may be at play.

Cerebral Microhemorrhages

Microhemorrhages, which are markers of cerebral microvascular pathology that typically occur in association with cerebral amyloid angiopathy or exposure to modifiable VRFs, particularly hypertension, are more commonly seen in patients with ischemic stroke and AF than in patients without AF.[56] Microhemorrhages are a risk factor for intracerebral hemorrhage, which is a stroke subtype that, compared with cerebral infarction, carries an elevated risk of morbidity and mortality.[57,58] In addition, evidence suggests that microhemorrhage burden has a direct relationship with cognitive decline as well as vascular and neurodegenerative dementias.[59] Whereas the mechanistic underpinnings of this association have not been elucidated, microhemorrhages have been observed more commonly in patients with AF treated with warfarin, particularly among patients with international normalized ratio variability.[56,60] The significance of these results is unclear because of possible selection bias, and further studies are needed to confirm whether these observations extend to direct oral anticoagulants.

Cardiac Output

Cognitive impairment in patients with AF may also be due to reduced cardiac output without overt clinical symptoms of HF, which can compromise cerebral blood flow specifically in areas involved in cognitive function, such as the temporal lobes. As such, one would not expect AF-related cognitive dysfunction to be responsive to systemic anticoagulation. People with small vessel disease may be susceptible to reduction of cardiac output, although there has been a general paucity of study in this area.

Inflammation and AD

In addition to the aforementioned mechanisms, inflammation may play a role in AF-associated brain injury. AF and AD are associated with systemic inflammation and similar profiles of proinflammatory (eg, IL-1β, IL-8, tumor necrosis factor–α) and anti-inflammatory (eg, IL-10, transforming growth factor–β) mediators have been described in both conditions.[61,62] Inflammation is associated with endothelial dysfunction, platelet activation, and upregulation of coagulation pathways, which lead to thrombosis and cerebrovascular injury.[63] In addition, proinflammatory pathways lead to atrial remodeling and can perpetuate AF. In the brain, amyloid-β aggregates induce glial cell activation and the production of proinflammatory cytokines that lead to neuronal cell dysfunction and death. Upregulation of inflammatory pathways can lead to upregulation of β-secretases, which generate amyloid-β. More research is needed to understand how AF and AD immune-mediated mechanisms influence each other; however, these observations illustrate the complex interaction that exists between the nervous and cardiovascular systems and identify the proinflammatory milieu in AF as a potential target for preventing cognitive impairment.

Prospects for Prevention and Treatment of AF to Maintain Brain Health

Based on the available evidence, it has been hypothesized that treatment of the hypercoagulable state associated with AF using anticoagulation or reducing AF burden by rhythm control or catheter ablation may decrease the risk of dementia. There is indirect evidence that effective treatment of AF, as summarized in Figure 2, reduces the risk of cognitive impairment, and future clinical trials will investigate this hypothesis.[64–66] Retrospective analysis of an American claims database and other evidence suggests that AF suppression with catheter ablation may result in a greater reduction in dementia risk compared with antiarrhythmic therapy alone, which might be explained by more effective suppression of AF with ablation.[67] However, these results should be interpreted with caution, because individuals with cognitive decline are less likely to be referred for catheter ablation, and the

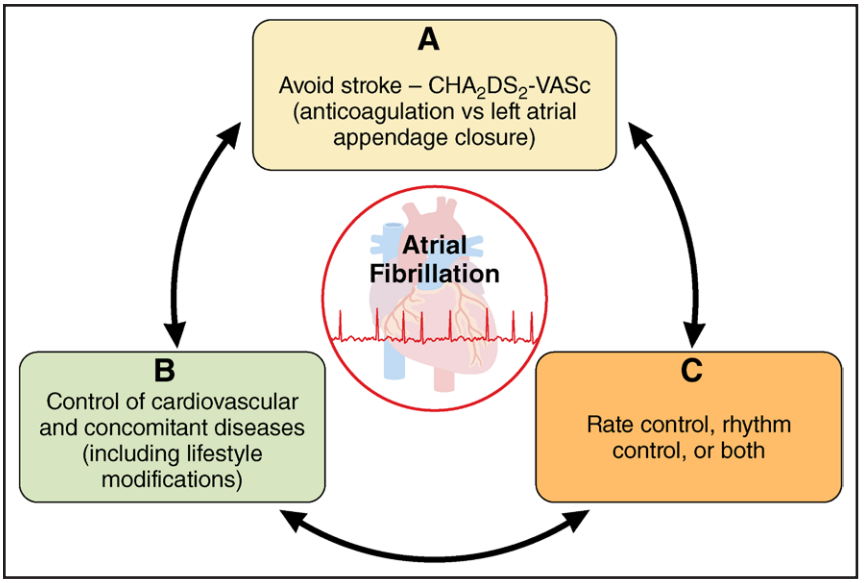

Figure 2. ABC pathway for management of atrial fibrillation.[64,65] A refers to avoiding stroke by using risk stratification tools (such as the CHA_2DS_2-VASc score) to identify individuals at high risk of stroke and systemic embolism who are candidates for anticoagulation or left atrial appendage closure. B refers to better rate and rhythm control by using pharmacologic or nonpharmacologic approaches (eg, ablation or electrical cardioversion), or both. C refers to optimal control of risk factors, including cardiovascular risk factors and other comorbidities, and lifestyle modifications.

quality of the evidence in this area is relatively weak. Several studies are underway to determine whether restoring regular sinus heart rhythm using catheter ablation for AF reduces cognitive dysfunction and brain abnormalities compared with medications alone.[68,69]

CORONARY HEART DISEASE

Frequency of Cognitive Impairment in CHD

In a large systematic review including >1 million participants, the relative risk of dementia among participants with a history of CHD was 1.27 (95% CI, 1.07–1.50) compared with those without CHD.[70] Data from registries show that cognitive decline is associated with myocardial infarction (MI), with rates ranging from 2% to nearly 50%.[71,72] Given that vascular risks compromise brain and cardiac health, it is possible that many patients with CHD have cognitive impairment preceding their acute coronary event. However, in 1 study, individuals with incident coronary events had cognitive decline after the event, but no steeper decline before the event.[73] In a study including data from 6 large US-based population cohort studies, there was no immediate decline in cognition after MI, but participants with incident MI showed a steeper decline in global cognition, memory, and executive function. Similar findings were obtained in the ELSA study (English Longitudinal Study of Ageing).[73,74] Data from several observational studies have consistently demonstrated an inverse relationship between subclinical CVD and poor brain health. In MESA (Multi-Ethnic Study of Atherosclerosis), for example, the presence of elevated coronary artery calcium was associated with a hazard ratio for dementia of 1.24 (for 1 SD higher $\log_2$ [coronary artery calcium+1]; 95% CI, 1.08, 1.41; P=0.002), and this association was not completely explained by underlying VRFs, *APOE4* genotype, or history of stroke.[75] Collectively, these observations suggest that the association between CHD and cognitive decline is not fully driven by shared risk factors.

Mechanisms Whereby CHD May Cause Cognitive Impairment

VRFs, Inflammation, BBB, and Related Factors

VRFs trigger systemic inflammation and possibly neuroinflammation, along with BBB dysfunction.[2] In addition, it is recognized that CHD and associated atherosclerosis contribute to inflammation, which can affect the cerebral macro- and microcirculations. For example, hypertension affects the cerebrovascular endothelium, leading to increases in BBB permeability, allowing potentially harmful substances to enter the brain tissue and cause neuroinflammation, particularly in the WM. Data obtained in preclinical models show that the BBB and other neurovascular elements have an active role in the removal of toxic bioproducts, including amyloid-β and tau.[2,76] Furthermore, VRFs, through neuroimmune mechanisms and oxidative stress, can increase the production of amyloid-β. Conversely, amyloid-β can promote vasoconstriction. In addition, reduced cerebral blood flow along with abnormal hemodynamic responses to neural activation have been described in AD.[77] These observations indicate that the pathogenesis of vascular injury and neurodegeneration, once considered distinct disease processes, are intimately intertwined. There may be shared risk between CHD and brain health on a genetic basis: a polygenic risk score for coronary pathology was associated with brain atrophy and cognitive ability.[78,79] Furthermore, internal (eg, racial, ethnic, genetic) and external (eg, traumatic injuries, toxins) factors may potentiate the development of atherosclerosis and influence cognitive outcomes.[2,80] There are other pathways related to CHD that may lead to damage to the cerebral microcirculation or

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neuroinflammation and, by extension, compromise brain health. These include but are not limited to alterations in cardiac output and arrhythmias, autonomic nervous system responses, angiotensin I and II activation, lipid deposition in smooth muscle cells, complement activation, and others.[81]

Microvascular Circulation and Cardiac Sequelae

Microvascular dysfunction is a pathologic process affecting the microcirculation of the brain and the heart. Coronary microvascular dysfunction is associated with cerebral small vessel disease and reduced cerebral blood flow. Data from C3 (Cerebral-Coronary Connection), a prospective study consisting of 73% women that evaluated the prevalence of coronary microvascular dysfunction in patients with CHD, showed that those with abnormal coronary flow reserve <2.0 had a higher burden of WM hyperintensities (43.2% versus 20.0%; P=0.044). Low coronary flow reserve was also associated with abnormal cerebral blood flow hemodynamics on transcranial Doppler and worse cognitive test scores.[82] Cardiac sequelae of CHD include the development of AF and wall motion abnormalities, which may increase the risk of left atrial thrombus, leading to embolism and changes in hemodynamics, such as impaired cardiac output from HF, symptomatic arrhythmias, or cardiogenic shock, leading to cerebral hypoperfusion and ischemia in border zone areas of the brain.[83] Silent cerebral infarcts are also more prevalent in patients with CHD (odds ratio, 2.83 [95% CI, 1.38, 5.82]). In addition, unrecognized MI in men was associated with an increase in WM disease volume and asymptomatic strokes, both conditions that lead to cognitive impairment.[84,85]

Prospects for Prevention and Treatment of CHD to Maintain Brain Health

The American College of Cardiology and American Heart Association published clinical practice guidelines for the management of patients with chronic CHD, which are summarized in Figure 3.[86] The beneficial effect of VRF control on cognitive performance in specific groups of individuals with CHD, however, has not been established conclusively. In some CHD populations, the results for VRF control have been promising. For example, in SPRINT-MIND (Systolic Blood Pressure Intervention Trial: Memory and Cognition in Decreased Hypertension), a systolic blood pressure goal of <120 mm Hg did not reduce the incidence of the primary outcome (probable dementia) compared with the more conservative goal of <140 mm Hg. However, intensive blood pressure control reduced the occurrence of mild cognitive impairment and the composite of mild cognitive impairment and probable dementia.[87] In a meta-analysis of randomized clinical trials that investigated the effect of blood pressure treatment on cognitive outcomes, blood pressure lowering reduced the risk of dementia and cognitive impairment from 7.5% in the control group to 7.0% in the active treatment group.[88] In an individual patient data meta-analysis that included ≈28 000 individuals, a blood pressure reduction of 10/4 mm Hg was associated with a reduced risk of incident dementia (odds ratio, 0.87 [95% CI, 0.75–0.99]).[89]

Studies that investigated the effect of diabetes control on cognition have provided mixed results.[90] Randomization to statins in adults without CHD did not alter cognitive outcomes in the HOPE-3 trial (Heart Outcomes Prevention Evaluation-3).[91] In the ASPREE study (Aspirin in Reducing Events in the Elderly), which evaluated 18 847 adults ≥65 years of age without CHD, statin therapy did not modify the risk of incident dementia, mild cognitive impairment, or cognitive decline; nor did the use of aspirin, which otherwise plays an important role in secondary prevention in patients with CHD.[92,93] In STABILITY (Standard ACL Reconstruction vs ACL+Lateral Extra-Articular Tenodesis Study), darapladib, a reversible inhibitor of lipoprotein phospholipase A_2 that reduces plaque vulnerability, was compared with placebo in 10 634 patients with CHD in 38 countries to determine its effect on the composite of cardiovascular death, MI, or stroke. In exploratory analysis, darapladib did not improve cognitive performance, but modifiable VRFs, such as exercise, diabetes, hypertension, and other factors, including education level and global region, were independent predictors of cognitive performance.[94] In a single-center, single-blind randomized clinical trial performed in elderly patients, more than one third of whom were hospitalized, primarily with cardiovascular conditions, an exercise intervention proved to be safe and effective to reverse the functional decline associated with acute hospitalization.[95]

Because VRFs can contribute to cognitive impairment through multiple pathways, it is believed that individual interventions may be insufficient to preserve cognitive vitality and multidomain interventions and precision medicine techniques may be needed. In PreDIVA (Prevention of Dementia by Intensive Vascular Care) and MAPT (Multidomain Alzheimer Preventive Trial), cognitive outcomes did not differ between the multidomain intervention and standard care.[96,97] In contrast, in FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability), there was a benefit in neurocognitive performance at 2 years in favor of multidomain intervention, which included diet, exercise, cognitive training, and VRF control.[98]

In relation to cardiac revascularization interventions, coronary artery bypass graft surgery has been believed to contribute to cognitive decline and dementia. However, subsequent studies identified that cognitive decline after coronary artery bypass grafting was primarily driven by the underlying VRFs that led to coronary artery bypass graft surgery rather than the

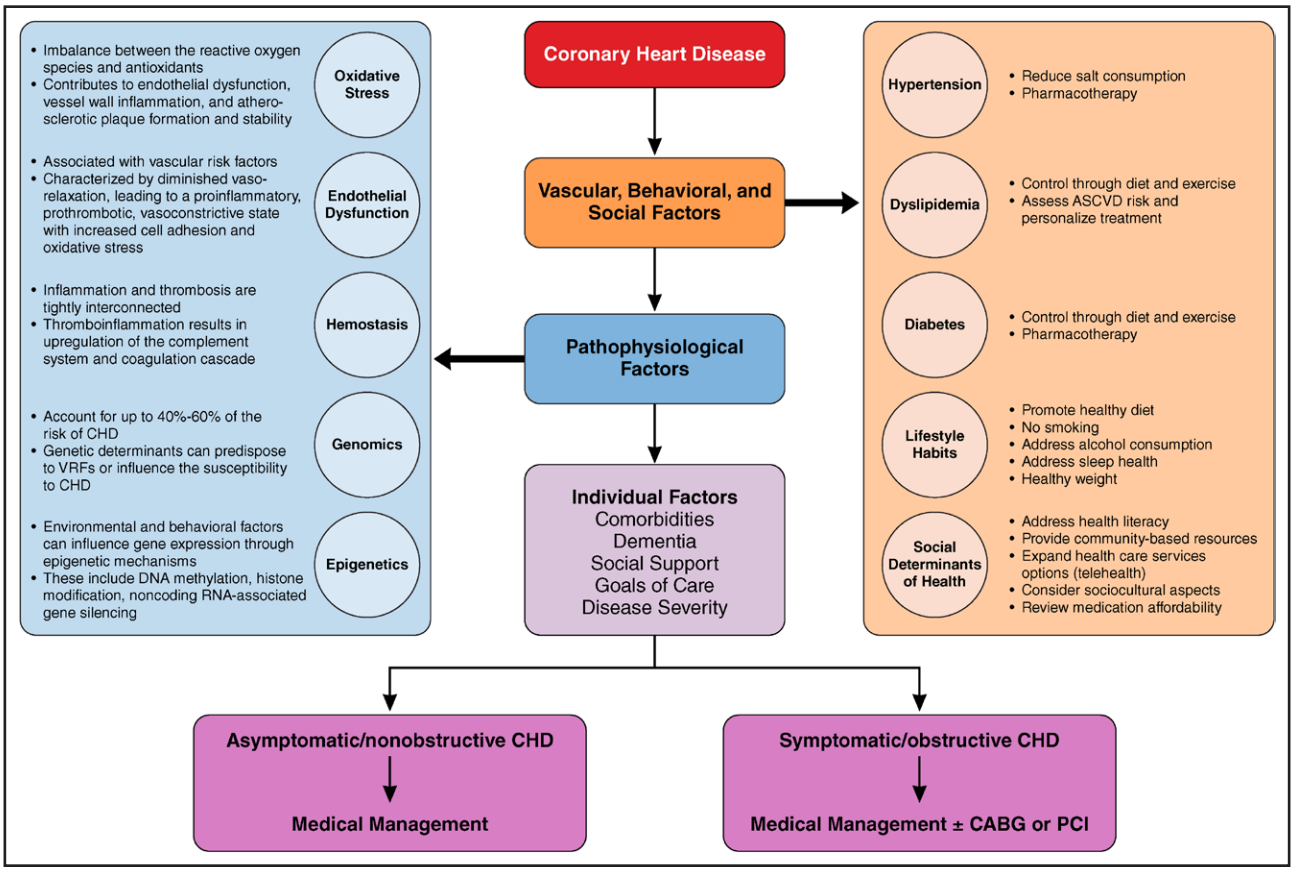

Figure 3. Coronary heart disease: pathogenic mechanisms, risk factors, and treatment considerations.[86]
ASCVD indicates atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CHD, coronary heart disease; PCI, percutaneous coronary intervention; and VRF, vascular risk factor.

surgical intervention.[99] The importance of the underlying disease, rather than the procedure itself, on cognitive decline is further emphasized by the fact that cognitive outcomes are comparable for patients receiving coronary artery bypass grafting or percutaneous coronary intervention.[100] However, the data in this area should be interpreted with caution, because a diagnosis of dementia in patients requiring acute coronary interventions may influence decision-making and result in selection bias.[101]

DISCUSSION AND FUTURE PERSPECTIVES

The cumulative evidence obtained in epidemiologic and basic science studies confirms that the trajectories of cardiac health and brain health are inextricably intertwined through modifiable and nonmodifiable factors (Figure 4). Observational data obtained in population studies and registries show that cerebral microstructural changes, covert brain infarction, stroke, and hypoperfusion are associated with the development of brain pathology in people with cardiac disease. Evidence obtained in preclinical models confirms that the upregulation of proinflammatory pathways, oxidative stress, BBB dysfunction, and microvascular dysregulation also contribute to cognitive impairment in these individuals. Furthermore, genetic links between heart and brain abnormalities are identifiable by Mendelian randomization.[1] Despite the multiple advances achieved in this area, however, our understanding of the contributions of cardiac disease to cognition remains fraught with inconsistencies and gaps.

The data presented herein have several important implications for research, public health, and clinical practice. From a research perspective, an important barrier to understanding the heart–brain connection is the lack of evidence demonstrating that the appropriate management of cardiac diseases has a beneficial effect on age-related cognitive changes. Several procedures used for patients with advanced CVDs, including coronary artery bypass graft, transplantation, and transcatheter aortic valve replacement, are associated with iatrogenic stroke, with a possible negative effect on cognitive performance.[42,43] Furthermore, although controversial, some of the medications typically used in patients with cardiac diseases, including statins and some antihypertensive drugs, may be associated with improved cognitive performance.[102,103] Understanding the ultimate effect of these and other

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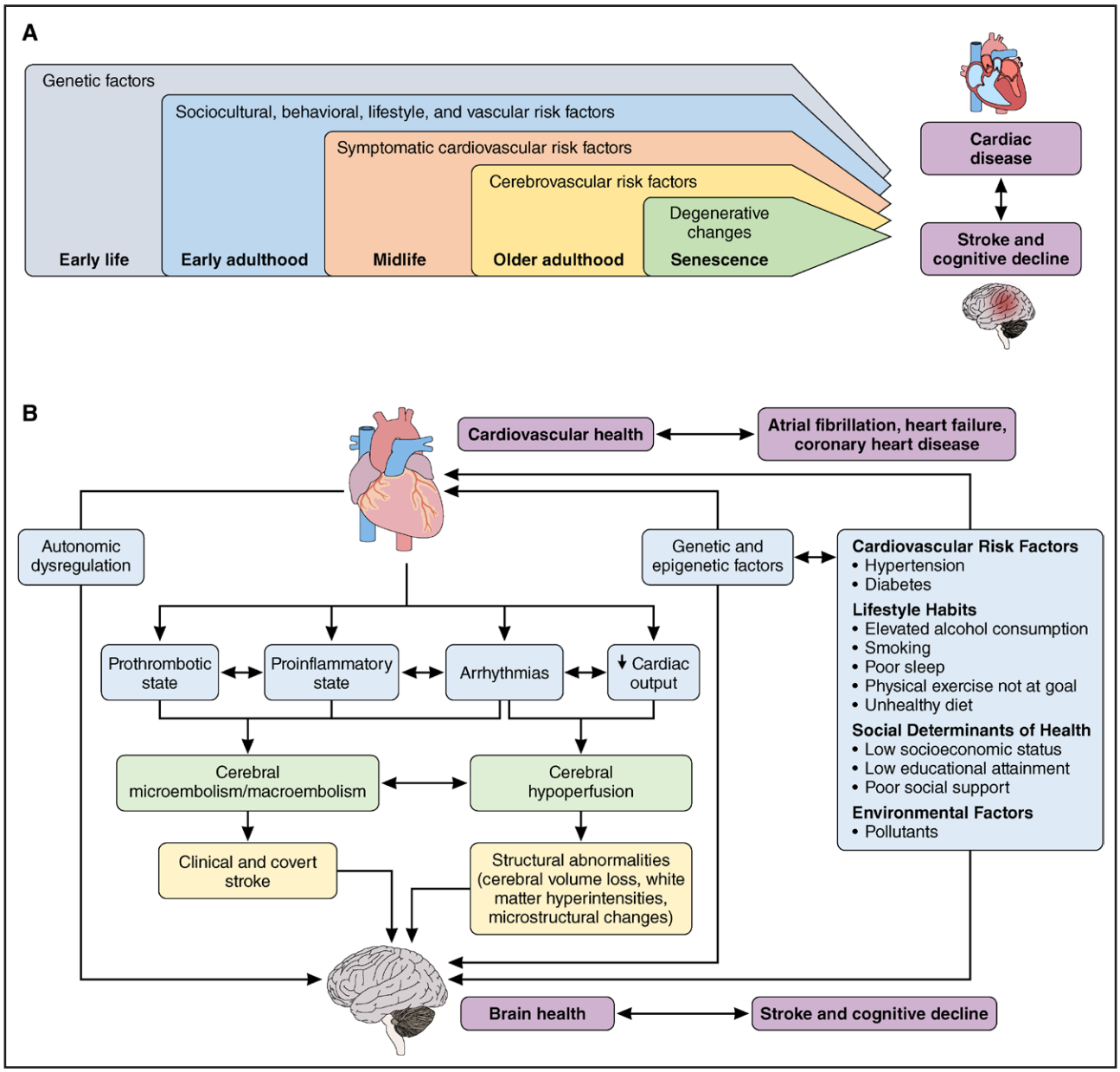

Figure 4. Heart–brain axis.
Progression of disease across the lifetime continuum and shared risks and mechanistic factors. Upper panel: Genetic, social and environmental factors, and lifestyle habits across the age continuum can promote or hinder cardiac and brain health. Neurologic damage can result in myocardial injury, and cardiac diseases can compromise brain health by causing stroke and dementia. Lower panel: Cardiovascular risk factors can lead to inflammation and a prothrombotic state as well as cardiovascular and cerebrovascular alterations, including structural abnormalities, which can lead to stroke and cognitive impairment.

treatments on brain health requires the acknowledgement of the need for and incorporation of standardized cognitive and functional outcomes in cardiovascular trials and the use of extended follow-up. In addition, although systemic and organ-specific inflammation are agreed to play an active role in the pathogenesis of cardiac disease and dementia, including AD, more research is needed to elucidate whether immunomodulation has a beneficial effect on cognitive trajectory.[61,62] Also, the participation of factors associated with disease development and resilience, including social determinants of health, epigenetic changes, extracellular vesicles, and the specific role of different constituents of the neurovasculome, such as the glymphatic system, on the heart–brain axis remains largely unknown.[2,76,80] Furthermore, the interpretation and generalizability of the studies described herein are confounded by disparate methodologies, including small sample sizes, cross-sectional designs, and underrepresentation of Black individuals, Hispanic individuals, and other underrepresented populations.

A large proportion of the general population, including children and young adults, have undiagnosed or partially controlled VRFs and CVD.[4] Several factors may explain this observation, including limited access to health care, social media messages promoting the use of alternative and often unproven preventatives or treatments, inertia to initiate or escalate treatment, and misconceptions and social constructs leading to acceptance of unhealthful states (such as obesity) and behaviors (such as sedentary lifestyle, unhealthful diet, and elevated consumption of alcohol, marijuana, and artificially sweetened beverages). Also, the prevailing view in the public and the medical community is that the most common type of dementia (ie, AD) cannot be prevented. Thus, the effect of VRF control in delaying the onset of cognitive decline and cardiac disease is often overlooked. Randomized trials that investigate the use of multimodal interventions for the prevention of cognitive decline have yielded conflicting results.[2] Because these studies target older populations, it has been proposed that preventative studies of longer duration including young adults may be necessary to assess the effect of VRFs on the development of dementia later in life. Performing such randomized trials might be challenging owing to the required extended follow-up period.

From a public health standpoint, however, consistent epidemiologic evidence supports the notion that prevention and early treatment of cardiac diseases are effective strategies to maintain age-dependent cognition. Thus, culturally and age-tailored education campaigns promoting early adoption of healthy lifestyles may reduce the burden of dementia in the general population. The development of humanized monoclonal antibodies that bind amyloid-β has renewed hopes for the discovery of a disease-modifying therapy for AD. However, the medical maxim *sublata causa tollitur effectus* ("upon removal of the cause, the effect is removed") reminds us that prevention is better than cure. Thus, from a clinical perspective, the early implementation of strategies to monitor and promote cardiovascular health, such as Life's Essential 8, and the adoption of evidence-based guidelines for the management of patients with CVDs constitute important steps to tackling the public health challenges associated with the expanding prevalence of cognitively impairing disorders and attaining our ultimate goal of ensuring brain health for all across the lifetime continuum.[2,104]

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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*Modest.

†Significant.

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