



OPEN ACCESS

EDITED BY
Abdallah Fayssol,
Hôpital Raymond-Poincaré, France

REVIEWED BY
Benjamin Y. Q. Tan,
National University Hospital, Singapore
Danesh Soltani,
University of California, Los Angeles,
United States

*CORRESPONDENCE
Federico Vancheri
✉ federico.vancheri@gmail.com

RECEIVED 07 August 2025
REVISED 01 April 2026
ACCEPTED 06 April 2026
PUBLISHED 22 April 2026

CITATION
Vancheri F, Vancheri S, Longo G,
Vancheri E and Henein MY (2026) Heart-
brain axis pathophysiological
understanding and clinical impact.
Front. Cardiovasc. Med. 13:1681715.
doi: 10.3389/fcvm.2026.1681715

COPYRIGHT
© 2026 Vancheri, Vancheri, Longo,
Vancheri and Henein. This is an open-
access article distributed under the
terms of the [Creative Commons
Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use,
distribution or reproduction in other
forums is permitted, provided the
original author(s) and the copyright
owner(s) are credited and that the
original publication in this journal is
cited, in accordance with accepted
academic practice. No use, distribution
or reproduction is permitted which does
not comply with these terms.

Heart-brain axis pathophysiological understanding and clinical impact

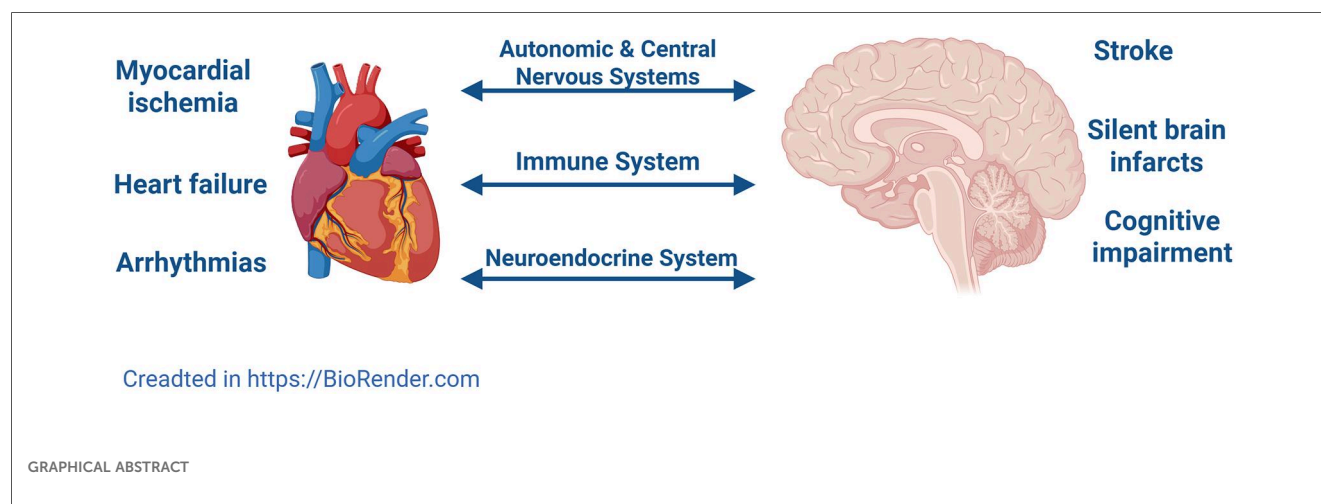
Federico Vancheri^{1*}, Sergio Vancheri², Giovanni Longo³,
Edoardo Vancheri⁴ and Michael Y. Henein⁵

¹Department of Internal Medicine, S. Elia Hospital, Caltanissetta, Italy, ²Interventional Neuroradiology Department, Besançon University Hospital, Besançon, France, ³Cardiovascular and Interventional Department, S. Elia Hospital, Caltanissetta, Italy, ⁴Department of Neurology, Hôpital Lariboisière, Paris, France, ⁵National Heart and Lung Institute, Imperial College, London, United Kingdom

The heart and brain are anatomically and functionally interconnected through nervous and humoral feedback mechanisms. Under physiological conditions, the heart-brain axis helps maintain cardiovascular and cerebral homeostasis. Pathology affecting one organ can profoundly impact the other, significantly worsening prognosis. The term *stroke-heart syndrome* refers to cardiovascular complications following acute ischemic stroke, including myocardial injury, infarction, ventricular dysfunction, arrhythmias (e.g., atrial fibrillation), heart failure, takotsubo syndrome, and sudden cardiac death. Brain damage-induced cardiac injury arises from a complex interplay of neuroinflammation, systemic immune activation, sympathetic-immune interactions, catecholamine toxicity, endothelial dysfunction, and gut-brain-heart axis involvement. Conversely, cardiac conditions, including myocardial ischemia, heart failure, and atrial fibrillation, are associated with an increased risk of stroke and cognitive decline. Myocardial ischemia can initiate systemic inflammation and neuroinflammation through sympathetic overdrive and platelet activation. Heart failure causes cerebral hypoperfusion and high thromboembolic risk, and atrial fibrillation promotes thrombus formation due to blood stasis. Atrial dysfunction and prothrombotic states may also occur independently of arrhythmia. This review summarises current evidence on the pathological interactions within the heart-brain axis, in the context of stroke, mental stress, ischemic heart disease, heart failure, and atrial fibrillation.

KEYWORDS

heart-brain axis, myocardial infarction, stroke, stroke-heart syndrome, takotsubo (stress) cardiomyopathy



1 Introduction

The diagnosis and treatment of cardiovascular disease (CVD) have traditionally focused on the primary clinical syndrome, such as stroke, myocardial infarction (MI), heart failure (HF), or arrhythmias, treating them as isolated disorders affecting either the heart or the brain. Although cardiac and cerebrovascular diseases share many underlying risk factors, including hypertension, diabetes, smoking, and dyslipidaemia, recent evidence suggests that pathological conditions involving both the heart and brain are not merely coincidental occurrences of separate diseases. Rather, they frequently arise from reciprocal and dynamic interactions between the cardiovascular (CV) and the nervous systems (1–4).

The heart and the brain are anatomically and functionally interconnected through complex neural and humoral pathways characterized by bidirectional feedback mechanisms mediated by the autonomic nervous system, hormones, and the immune responses. Under physiological conditions, this integrated network enables both systems to adapt to internal demands and external stimuli. However, pathological alterations in one organ can significantly impair the function of the other, often leading to adverse clinical outcomes.

Both ischemic and hemorrhagic stroke, as well as psychiatric disorders, such as depression and dementia, can disrupt cardiac neural regulation, resulting in myocardial ischaemia, left ventricular (LV) dysfunction and arrhythmias (5–10). Conversely, acute and chronic coronary artery disease (CAD), HF, atrial fibrillation (AF) and invasive cardiac interventions are associated with an increased risk of stroke and vascular dementia (11–15).

Despite this growing body of evidence, current risk stratification models do not incorporate neurocardiac parameters. Contemporary cardiovascular and stroke guidelines rely primarily on traditional clinical risk factors and organ-specific biomarkers. Consequently, no validated framework currently exists for integrating heart–brain interactions into routine prognostic assessment.

In this review, we synthesise contemporary evidence on the anatomical substrates, molecular mechanisms, and clinical

manifestations of the heart–brain axis across major pathological conditions, including stroke, psychological stress, myocardial ischaemia, HF, AF, and invasive cardiac procedures. The novelty of this review lies in its comprehensive, bidirectional perspective, emphasizing shared inflammatory, autonomic, and microvascular mechanisms that unify cardiovascular and neurological diseases within a single pathophysiological paradigm.

By integrating anatomical, molecular, and clinical evidence, this review aims to support the development of more comprehensive prognostic frameworks. Shared pathophysiological pathways provide a basis for novel biomarker panels and risk models that go beyond organ-specific assessments. Incorporating neurocardiac parameters such as heart rate variability, troponin dynamics, and combined cardiac and cerebral imaging markers into composite scores may improve early identification of patients at risk for heart–brain complications. This bidirectional paradigm also has implications for trial design and guideline development. Cardiovascular and neurological trials are largely conducted in parallel, with few shared endpoints. Future studies should include both cardiac and neurological outcomes, such as cognitive function, silent brain infarctions, and arrhythmia burden, to better reflect heart–brain interactions. Guideline should likewise consider integrated management pathways for high-risk groups, such as patients with stroke–heart syndrome, heart failure with cognitive impairment, or atrial fibrillation with silent brain ischaemia, as a practical step toward bridging cardiology and neurology in clinical care.

2 Functional anatomy of the heart–brain axis

2.1 Brain-to-heart pathways

The brain and the heart are interconnected through the central nervous system (CNS), the autonomic nervous system (ANS), and immune system. Efferent pathways from the brain to the heart originate within the central autonomic network (CAN), an

anatomically and functionally defined network comprising cortical, subcortical, brainstem, and spinal regions that integrates central and peripheral nervous system input (16–19). The CAN coordinates autonomic output by processing afferent sensory input and generating efferent responses that regulate CV function, transmitting signals to the heart and vasculature via the ANS while receiving sensory feedback through afferent pathways. The sympathetic and parasympathetic branches of the ANS exert direct effects on cardiac electrophysiology, myocardial contractility, vascular tone, and immune response [Figure 1, (20)]. Dysregulation within these pathways can contribute to cardiac dysfunction and adverse clinical outcomes.

2.1.1 Anatomy and clinical relevance of the CAN

2.1.1.1 Cortical structures

The cortical component of the CAN play a fundamental role in modulating autonomic activity during emotional and cognitive processes (2, 18, 21). The principal cortical regions involved include the insular cortex, the medial prefrontal cortex, the orbitofrontal cortex, the anterior cingulate cortex, and the posterior cingulate cortex.

The insular cortex (insula) is a key CAN component functionally linked to the limbic system, located within the lateral sulcus beneath the frontal, parietal, and temporal lobes. Ischemic lesions involving this region have been associated with an increased risk of cardiac complications (9, 22). Due to its vascular supply from the middle cerebral artery, the insula is frequently affected in ischemic stroke. Functional lateralisation has been observed in autonomic control, with the right insula predominantly associated with sympathetic activity and the left insula more closely linked to parasympathetic regulation (23).

Beyond autonomic regulation, the insula integrates autonomic, neuroendocrine, and inflammatory viscerosensory feedback into subjective emotional states (interoception) (24). Acute emotional stress may alter insular modulation of sympathetic and parasympathetic tone, leading to increased plasma catecholamine concentrations and a heightened risk of arrhythmias, including AF, complex ventricular and supraventricular arrhythmias, sudden cardiac death, and direct myocardial injury, such as myocytolysis and stress-induced (Takotsubo) cardiomyopathy (25, 26).

The medial prefrontal cortex, located in the medial frontal lobe, and orbitofrontal cortex, situated on the ventral surface of the frontal lobes, are involved in the cognitive appraisal and regulation of emotional responses. These regions exert inhibitory control over excessive sympathetic activation and facilitate parasympathetic recovery following stress.

The anterior cingulate cortex (ACC) located on the medial surface of the frontal lobes superior to the corpus callosum, integrates emotional, cognitive, and interoceptive information to modulate autonomic outflow. Through connections with limbic structures, the hypothalamus, and brainstem nuclei, it regulates sympatho-vagal balance during stress. Dysfunction in this region may promote autonomic imbalance and increase susceptibility to stress-related CV disease.

The posterior cingulate cortex located in the medial parietal lobe, integrates interoceptive, sensory, and cognitive inputs and contributes to autonomic modulation.

2.1.1.2 Subcortical structures

Subcortical structures, including the amygdala, hypothalamus, and thalamus, integrate emotional and sensory information with autonomic and neuroendocrine responses to maintain cardiovascular homeostasis (27).

The Amygdala, a paired limbic structure in the medial temporal lobe, mediates the relationship between psychological stress and CV disease by processing emotional and environmental stimuli (28). Through its connections with the insula and hypothalamus, the amygdala modulates CAN activity and influences autonomic control of CV system. Neuroimaging studies have shown that increased amygdala activity is associated with early markers of atherosclerosis, including carotid intima-media thickness, heightened blood pressure reactivity, enhanced inflammatory response to psychological stress, and increased all-cause mortality (29–31). Moreover, elevated resting amygdala activity in individuals without established CV disease has been linked to a higher incidence of future CV events. This association appears to be mediated by increased bone marrow activity and leukocyte mobilisation, which promote arterial inflammation and accelerate atherogenesis (32).

The Hypothalamus is located at the base of the diencephalon, flanking the third ventricle. It integrates limbic, cortical, and visceral inputs to coordinate autonomic and neuroendocrine output to the heart.

Within the hypothalamus, the paraventricular nucleus (PVN) has a central role in integrating afferent and efferent CV signals and modulating the baroreflex sensitivity and cardiovagal responses. The PVN is also a central component of the hypothalamic–pituitary–adrenal (HPA) axis. In response to stress, it releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary gland to secrete adrenocorticotrophic hormone (ACTH). ACTH, in turn, activates the adrenal cortex, leading to the release of cortisol, the primary stress hormone (33). While acute elevations in cortisol serve adaptive functions during stress, chronic hypercortisolemia may contribute to both myocardial and cerebral injury (34). In addition to its well-established anti-inflammatory effects, evidence suggests that sustained cortisol exposure may exert paradoxical pro-inflammatory and pro-atherogenic effects, contributing to CAD, vascular dysfunction, and microglial dysregulation (35–37). Dysregulation of hypothalamic function may promote sustained sympathetic activation, impaired parasympathetic tone, and chronic neuroendocrine imbalance, thereby contributing to the development and progression of cardiovascular disease.

The Thalamus, below the cerebral cortex and above the brainstem, on either side of the third ventricle, is an integrative relay between peripheral cardiovascular signals and higher brain centres involved in autonomic, emotional, and cognitive regulation (38). Through its extensive connections with the brainstem, hypothalamus, and cerebral cortex, the thalamus receives afferent input related to heart rate, blood pressure, and visceral sensations and transmits these information to key regions of the CAN, including the insula and ACC. Thalamic neuronal activity is closely modulated by cardiac and respiratory rhythms, supporting the synchronisation of cardiovascular and respiratory function. By integrating sensory, autonomic, and limbic inputs, the thalamus contributes to the regulation of

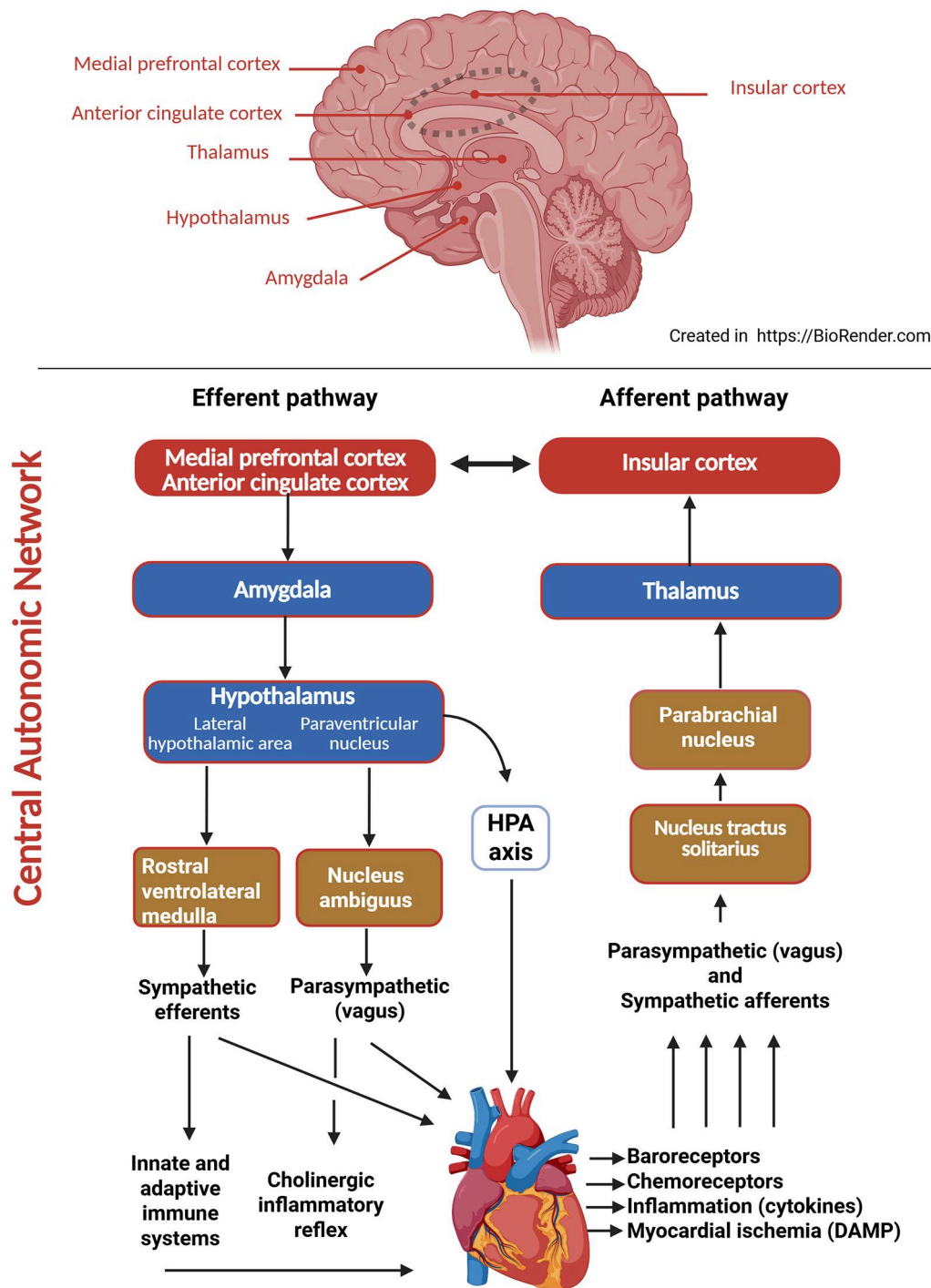


FIGURE 1

Bidirectional neural, immune, and neuroendocrine network of the heart-brain axis. The upper panel illustrates the principal cortical (red box) subcortical (blue box), and brainstem (brown box) structures forming the CAN involved in cardiovascular regulation. The lower panel depicts the bidirectional efferent and afferent pathways linking the brain and heart. Along the **efferent pathway** (left), cortical regions, including the medial prefrontal cortex and anterior cingulate cortex, process emotional and cognitive input and project via the amygdala to the hypothalamus. The paraventricular nucleus of the hypothalamus activates the HPA axis and coordinates descending autonomic output. Sympathetic efferents originate from the RVLM, while parasympathetic efferents arise from the nucleus ambiguus via the vagus nerve. Both limbs of the ANS converge on the heart, modulating cardiac electrophysiology, myocardial contractility, and coronary tone. Sympathetic signalling also activates the innate and adaptive immune systems through lymphoid organ innervation, linking neurogenic stress to systemic inflammation. Parasympathetic activity exerts an anti-inflammatory effect, known as cholinergic inflammatory reflex. Along the **afferent pathway** (right), baroreceptors, chemoreceptors, inflammatory mediators (cytokines), and DAMP released during myocardial ischaemia transmit sensory signals from the heart to the NTS. These signals are relayed sequentially through the parabrachial nucleus and thalamus to the insular cortex, enabling integrated haemodynamic regulation and closing the brain-heart feedback loop. CAN, central autonomic network; HPA, hypothalamic-pituitary-adrenal axis; RVLM, rostral ventrolateral medulla; ANS, autonomic nervous system; DAMP, damage-associated molecular patterns; NTS: nucleus tractus solitarius.

sympathetic and parasympathetic activity and links emotional and stress-related states to adaptive cardiovascular responses (39).

2.1.1.3 Brainstem structures

The brainstem, comprising the midbrain, pons, and medulla oblongata, contains critical sensory and motor nuclei and serves as the principal integrative and regulatory centre of the heart-brain axis (2, 4, 21, 27, 40). It integrates peripheral cardiovascular signals with autonomic, emotional, and neurohumoral processes through specialised nuclei; the upper brainstem mediates responses to stress, pain, and arousal, whereas the lower brainstem governs circulation and respiration.

Afferent information from arterial baroreceptors, peripheral and central chemoreceptors, cardiac mechanoreceptors, and visceral pathways converges primarily in the nucleus tractus solitarius (NTS), located in the dorsomedial medulla. NTS is the primary sensory integration centre for CV signals processing haemodynamic and metabolic inputs to regulate heart rate, blood pressure, and ventilation, and coordinating the baroreflex and chemoreflex.

In the midbrain, the periaqueductal grey (PAG) integrates cortical, limbic, and cardiac nociceptive inputs and modulates cardiovascular responses during stress and pain. Increased PAG activity has been associated with reduced baroreflex sensitivity and enhanced sympathetic tone, thereby facilitating adaptive responses to cognitive and emotional challenges.

The medulla contains several key autonomic nuclei, including the vasomotor centre and rostral ventrolateral medulla (RVLM), which regulate sympathetic outflow and peripheral vascular resistance. It also contains the dorsal vagal complex, comprising the NTS, nucleus ambiguus, dorsal motor nucleus of the vagus, and area postrema. The nucleus ambiguus provides the main parasympathetic efferent control to the heart, contributing to cardiac rhythm stabilisation. The NTS receives input from cardiac and vascular chemoreceptors and mechanoreceptors, as well as pulmonary and central pathways, and relays this information to respiratory centres such as the pre-Bötzinger complex, considered a key respiratory rhythm generator, as well as to the parabrachial nucleus, and locus coeruleus, thereby promoting physiological coordinated cardiovascular and respiratory function.

Within the pons, the locus coeruleus represents the primary source of central noradrenaline. During states of arousal, increased noradrenergic activity enhances sympathetic tone and facilitates cognitive processing. Through its direct connections with the amygdala and hypothalamus, the locus coeruleus plays a central role in modulating stress responses.

Through its connections with the hypothalamus and limbic system, the brainstem also influences neuroendocrine and immune pathways, including the HPA axis and inflammatory signaling. Following neurological injury, dysregulation of these networks leads to sympathetic overactivation and catecholamine excess, predisposing patients to arrhythmias, stress-induced cardiomyopathy, and sudden cardiac death.

2.1.2 Sympathetic and parasympathetic systems

The ANS, comprising sympathetic and parasympathetic branches, together with neuroendocrine mechanisms mediated by the HPA axis,

collectively regulate heart rate, myocardial contractility, vascular resistance, and systemic haemodynamics (33, 41).

Forebrain regions project to autonomic nuclei within the medulla and spinal cord, forming part of the extrinsic cardiac nervous system. This system integrates sympathetic and parasympathetic inputs that regulate the intrinsic cardiac nervous system, composed of cardiac ganglia distributed within the atrial and ventricular walls (27). Sympathetic activation originates from neurons in the RVLM, which project to the preganglionic neurons located bilaterally in the intermediolateral column of the thoracic spinal cord. These preganglionic fibres synapse with postganglionic sympathetic neurons in the intrathoracic ganglia, including the stellate ganglion. Postganglionic fibres subsequently project to the heart, where they modulate sinoatrial and atrioventricular nodal activity, myocardial contractility, and coronary vasomotor tone (42).

Sympathetic activation also stimulates adrenal medullary release of adrenaline and noradrenaline, which regulate myocardial perfusion and vascular tone, and activates the renin-angiotensin-aldosterone system (RAAS), promoting vasoconstriction and sodium retention.

The ANS is closely integrated with the immune system (43). Autonomic fibres densely innervate lymphoid organs such as the spleen and lymph nodes, as well as hematopoietic stem cells within the bone marrow, all of which express β -adrenergic receptors (44). Through these pathways, sympathetic signaling modulates leukocyte mobilization, inflammatory responses, and vascular inflammation, linking neurogenic stress responses to atherosclerotic progression.

Parasympathetic innervation of the heart arises from preganglionic neurons in the nucleus ambiguus in the brainstem. These fibres travel along the vagus nerve (cranial nerve X), and synapse with postganglionic neurons in the ganglia of the intracardiac nervous system (45).

Sympathetic and parasympathetic efferent neurons converge within atrial and ventricular cardiac ganglia, where they interact to finely regulate cardiac electrical and mechanical activity. The dynamic balance between these two systems is essential for cardiovascular homeostasis, and its disruption contributes to arrhythmogenesis, myocardial dysfunction, and adverse cardiovascular outcomes.

2.1.3 The intrinsic cardiac nervous system (ICNS)

Is organised into multiple interconnected ganglia, located within the epicardial fat surrounding the atria, atrioventricular junction, ventricles, the origin of coronary arteries, and pulmonary veins. These ganglia are linked by a dense network of nerve fibres forming intracardiac plexuses that innervate the myocardium, conduction system, and coronary vasculature (46).

The neuronal population of the ICNS includes efferent, afferent, and interneural elements. Efferent neurons mediate parasympathetic and sympathetic influences on cardiac tissues, regulating pacemaker function, conduction velocity, cardiomyocyte contractility, and myocardial perfusion. In contrast, afferent neurons convey sensory information related to mechanical, chemical, and metabolic stimuli (47, 48). The distribution of left- and right-sided sympathetic fibres over the ventricles is asymmetrical and exhibits considerable

interindividual variability. In conditions of sympathetic overactivity, such asymmetrical distribution may lead to regional differences in action potential duration and myocardial repolarization, thereby creating an electrophysiological substrate for ventricular arrhythmias (49).

Structural and functional ICNS alterations are implicated in atrial and ventricular arrhythmias, heart failure, and sudden cardiac death. Abnormal ganglionic activity may promote electrical instability and autonomic imbalance, establishing the ICNS as a therapeutic target for neuromodulation and ganglionated plexus ablation (50).

2.2 Heart-to-brain pathways

Afferent pathways from the heart to the brain originate from chemoreceptors and baroreceptors in the atria, ventricles, the aortic arch, carotid sinus and coronary and pulmonary arteries (51). Signals from these receptors are transmitted through spinal nerves and cardiac vagal afferents to the NTS in the brainstem. The NTS serves as the primary sensory integration center for cardiovascular input, generating autonomic reflexes and relaying information to higher brain regions, including the locus coeruleus, thalamus, PAG, amygdala, and hypothalamus. These signals are subsequently projected to cortical structures such as the insular cortex and ACC, enabling integrated hemodynamic regulation through descending efferent pathways (40).

Emerging evidence also suggests that the brain can both perceive and influence the progression of atherosclerotic lesions. The adventitia of atherosclerotic arteries is innervated by sensory and sympathetic fibres and contains clusters of immune cells, forming the *neuroimmune CV interfaces* (52). The development of atherosclerotic plaques has been associated with activation of hypothalamic nuclei involved in sympathetic regulation, supporting a role for central neural mechanisms in modulating plaque progression and vascular inflammation (53).

2.3 Mechanisms of heart-brain interactions

2.3.1 Neuroinflammation and systemic immune response

Both ischemic and hemorrhagic stroke induce neuronal cells necrosis, leading to increased blood-brain barrier (BBB) permeability and disruption of the structure and function of the neurovascular unit (NVU) (3, 54). This impairment compromises the brain's ability to autoregulate vascular tone, a phenomenon referred to as neurovascular uncoupling (Figure 2).

Cerebral ischemia activates microglia and astrocytes in response to damage-associated molecular patterns (DAMP), released by necrotic cells. While this inflammatory response initially serves a protective function, aiming at limiting further injury, prolonged or severe ischemia may exceed the compensatory capacity of glial cells, resulting in secondary cellular damage and progressive neurological dysfunction.

Under pathological conditions, glial cells may shift from an anti-inflammatory, reparative (M2) phenotype, to a pro-inflammatory (M1) phenotype. This phenotypic transition

promotes the release of pro-inflammatory cytokines and activation of cerebral endothelial cells, further compromising BBB integrity (55–58). Over time, sustained neuroinflammation contributes to structural and functional dysregulation of the central autonomic network (CAN) (59). These alterations may result in increased sympathetic tone and/or withdrawal of parasympathetic tone, impairing autonomic control of the heart, and activating the HPA axis (58, 60).

Persistent neuroinflammation may also promote the leakage of pro-inflammatory cytokines into the systemic circulation, transforming a localized central nervous system response into a generalised systemic inflammatory state (61, 62). Although these processes are most prominent in the acute phase of stroke, they may persist for months, contributing to long-term cardiovascular and neurological complications.

2.3.2 Direct catecholamine-mediated myocardial overstimulation

The autonomic and inflammatory consequences of neuroinflammation converge on the myocardium through a second, overlapping mechanism: direct catecholamine-mediated cardiac injury. Prolonged sympathetic overactivity may result in excessive catecholaminergic stimulation of the myocardium, leading to intracellular calcium overload in cardiomyocytes, mitochondrial dysfunction, contraction band necrosis, and coronary microvascular endothelial impairment (60, 63). Activation of β -adrenergic receptors by catecholamines enhances myocardial contractility and heart rate, thereby increasing myocardial oxygen demand. When oxygen demand exceeds supply, particularly in the presence of subclinical CAD, coronary demand ischemia may occur, potentially resulting in type 2 myocardial infarction (64, 65).

Sympathetic overdrive may destabilize atherosclerotic plaques, making them more prone to rupture. Excessive catecholamine release from sympathetic nerve endings also promotes inflammatory cell infiltration and fibrotic remodelling around the ganglionated plexi in the left atrium and pulmonary veins, creating a substrate for neurogenic atrial fibrillation (66, 67).

In addition, heightened sympathetic activity can induce life-threatening ventricular tachyarrhythmias, particularly in patients with inherited arrhythmogenic disorders such as long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, which are characterised by myocardial ion channel dysfunction (68).

2.3.3 Sympathetic effects on the immune system

Beyond its direct toxic effects on cardiomyocytes, sympathetic overactivation also shapes the inflammatory environment through its influence on immune cell activity. Increased sympathetic tone promotes the mobilisation of monocytes and neutrophils from the spleen and stimulates the proliferation of hematopoietic stem cells in the bone marrow, raising circulating leukocytes levels (69–71). These immune cells play a central role in the pathogenesis of atherosclerosis, MI, HF, and arrhythmias (43, 72–75).

Under physiological conditions, parasympathetic (vagal) activity exerts an anti-inflammatory effect. Acetylcholine, released from vagal efferent fibres inhibits the production of

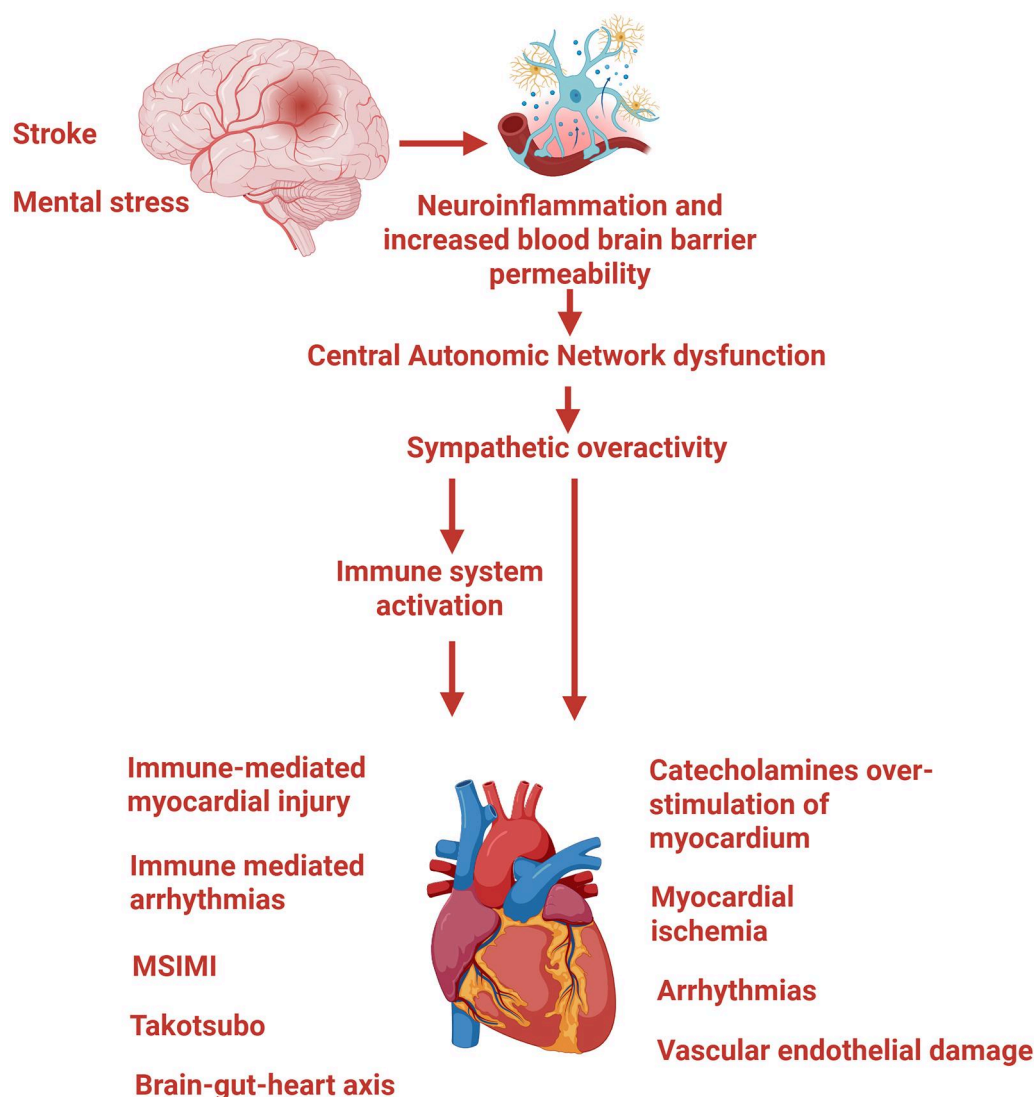


FIGURE 2

Effects of cerebral ischaemia on the heart. Stroke and mental stress initiate neuroinflammation and increased BBB permeability, disrupting the neurovascular unit and impairing the brain's ability to autoregulate vascular tone. The resulting structural and functional dysregulation of the CAN leads to sustained sympathetic overactivity, which propagates cardiac injury through two converging pathways. Through immune system activation, sympathetic overdrive promotes mobilisation of monocytes, neutrophils, and haematopoietic stem cells, generating a systemic pro-inflammatory state. This drives immune-mediated myocardial injury, including macrophage infiltration, fibrotic remodelling, and coronary microvascular dysfunction, as well as immune-mediated arrhythmias, MSIMI, Takotsubo cardiomyopathy, and gut-brain-heart axis dysregulation through increased gut permeability and translocation of pro-inflammatory microbial products. Through direct catecholaminergic overstimulation of the myocardium, excessive catecholamine release activates β -adrenergic receptors, increasing myocardial oxygen demand and promoting calcium overload, mitochondrial dysfunction, and contraction band necrosis. This pathway contributes to myocardial ischaemia, arrhythmias, including neurogenic atrial fibrillation and ventricular tachyarrhythmias, and vascular endothelial damage through platelet activation and impaired microvascular function. BBB, blood brain barrier; CAN, Central autonomic network; MSIMI, mental stress-induced myocardial ischaemia.

pro-inflammatory cytokines, including IL-1, IL-2, IL-6, and tumour necrosis factor- α (TNF- α), by tissue macrophages. This neuroimmune mechanism, known as the *cholinergic inflammatory reflex*, has a critical role in regulating immune and inflammatory responses (76, 77).

In the context of stroke, autonomic imbalance, characterised by increased sympathetic activity and reduced parasympathetic tone, impairs this protective reflex. The resulting loss of cholinergic inhibition allows inflammatory cytokine production to persist and amplify, sustaining systemic inflammation (78).

2.3.4 Immune-mediated myocardial injury

The systemic inflammatory state generated through these neuro-immune pathways exerts direct pathological effects on the heart, through immune-mediated mechanisms that compromise myocardial structure and function. The normal heart contains a large population of resident macrophages distributed around the coronary arteries, within the endothelium, in the pericardial space, and near the conduction system. These resident immune cells interact closely with the

cardiomyocytes, fibroblast and endothelial cells to maintain myocardial homeostasis (73, 79).

In conditions of chronic systemic inflammation, circulating cytokines activate tissue-resident cardiac macrophages, inducing a pro-inflammatory phenotype. Once activated, macrophages infiltrate the myocardium and stimulate microvascular endothelial cells, contributing to coronary microvascular dysfunction. This process may impair myocardial perfusion, promote LV dysfunction and the development of arrhythmias (80–82).

Moreover, pro-inflammatory cytokines drive conversion of cardiac fibroblast into myofibroblast, promoting extracellular matrix deposition and myocardial fibrosis (83, 84). Fibrotic remodeling alters electrical conduction and mechanical function, creating a substrate for arrhythmogenesis and progressive HF.

Cardiac macrophages also play a key role in the destabilisation of atherosclerotic plaques. They migrate into plaques and secrete proteolytic enzymes that degrade the fibrous cap, thereby increasing the risk of rupture and subsequent acute coronary events (85).

2.3.5 Immune-mediated arrhythmias

In addition to the structural and perfusion consequences described above, immune activation has direct electrophysiological effects, establishing a clear mechanistic link between inflammation and cardiac rhythm disturbances. Several studies have demonstrated a direct relationship between elevated pro-inflammatory cytokines in the heart and the development of rhythm disorders, particularly AF (86–88). The myocardium and the conduction system contain a substantial population of leukocytes, primarily macrophages, which are electrically coupled to cardiomyocytes through gap junctions. These macrophages depolarise in synchrony with adjacent cardiomyocytes, thereby modulating membrane potentials and contributing to normal electrophysiological function (73, 89, 90).

Systemic immune activation, such as that occurring after stroke, can disrupt this finely regulated cellular communication, increasing the risk of arrhythmias. Immune response may also generate autoantibodies that interfere with cardiac ion channels, further destabilising electrical activity (91, 92). Atrial remodelling caused by myocardial fibrosis further promotes AF by inducing slowed and heterogeneous conduction within the atrial myocardium. Notably, the relationship between inflammation and AF is bidirectional: AF itself sustains and amplifies inflammation, which in turn accelerates structural and electrical remodelling, creating a self-perpetuating arrhythmogenic substrate (88).

2.3.6 Vascular endothelial damage

Systemic inflammation and heightened sympathetic activity contribute to vascular endothelial injury by promoting platelet activation and leukocyte recruitment to the endothelial surface. These interactions induce a prothrombotic state, enhancing adhesion of leukocytes and platelets to the vessel wall and facilitating the development of arterial thrombus (93).

At the microvascular level, circulating pro-inflammatory cytokines directly impair endothelial function, leading to

coronary microvascular dysfunction (94, 95). Endothelial injury following stroke has also been associated with reduced levels of endothelial micro-RNA-126, a short sequence of noncoding RNA which regulate vascular integrity and angiogenesis (96).

2.3.7 Brain-gut-heart axis

A further dimension of heart-brain crosstalk involves the gastrointestinal tract. Through the brain-gut-heart axis, autonomic dysfunction and systemic inflammation trigger a cascade of gut-derived signals that amplify cardiovascular and neurological injury. Sympathetic overactivation and systemic inflammation can impair gastrointestinal function, leading to intestinal paralysis and increased gut permeability. These changes allow the translocation of bacteria and microbiota-derived endotoxins into the bloodstream (94, 97–99).

The entry of these microbial products into the circulation amplifies inflammatory cytokine levels, perpetuating systemic inflammation. The gut microbiota also contribute to inflammation metabolising dietary components such as choline, lecithin, and L-carnitine into trimethylamine-N-oxide (TMAO), a pro-atherogenic metabolite that activates macrophages and platelets, increasing the risk of thrombosis (100, 101). Systemic inflammation driven by gut-derived pathogens may compromise BBB integrity, exacerbating neuroinflammation and contributing to neural injury and dysfunction (102).

2.4 Clinical conditions of the heart-brain interaction

2.4.1 Clinical impact of stroke on the heart

Cardiac complications occur in approximately 20% of patients following acute stroke, and account for nearly 20% of deaths within the first three months. They represent the second leading cause of mortality after neurologic complications [Table 1, (60, 103, 104)]. Cardiac abnormalities typically peak during the early days after stroke; approximately one-third can occur within four weeks and one-fifth within three months (103, 105).

Stroke heart syndrome (SHS) is defined as the development of new CV complications or the exacerbation of pre-existing CAD, within 30 days of an acute ischemic stroke or other acute neurological conditions, including hemorrhagic stroke, subarachnoid hemorrhage, traumatic brain injury, and seizures (16, 65, 105, 106).

SHS encompasses a broad spectrum of cardiac manifestations, including myocardial injury, acute MI, LV systolic dysfunction, HF, and stress-induced cardiomyopathy (Takotsubo syndrome). Additional manifestations include electrocardiographic (ECG) abnormalities, atrial and ventricular arrhythmias (including AF) and sudden cardiac death [(107), Figure 2].

Although SHS may occur in individuals without previous cardiac disease, the severity of cardiac involvement is influenced by the presence of CV risk factors, advanced age, and underlying CAD (108, 109). Notably, more than half of patients with acute ischemic stroke and no history of cardiac disease, show evidence of subclinical coronary atherosclerosis, and approximately one-third have coronary stenosis >50% (110, 111).

TABLE 1 Incidence of neurogenic heart disease.

Clinical manifestations	Incidence
Myocardial injury: elevated hs-cTn	30–60% (118)
Chronic myocardial injury: persistently elevated hs-cTn, without clinical evidence of MI	11–40% (119, 312)
Acute myocardial injury: elevated cTn with a rising and/or falling pattern >20%, without clinical evidence of MI	15–25% (119, 312)
LV dysfunction: ejection fraction <50% or clinical HF	8–30% (16, 132, 134)
Acute myocardial infarction	~1.6% (313, 314)
	~50% in stroke patients with very high hs-cTn (121)
Concomitant acute ischemic stroke and STEMI	0.3–15% (116, 315)
ECG changes: QT interval prolongation, ST segment elevation or depression, deeply inverted T waves, atrio-ventricular and bundle branch blocks	20–65% (94, 146, 148)
Post-stroke AF: patients without known AF	24% on long-term Monitoring (16)
MSIMI:	20–70% of patients with stable CAD (166, 169)
Takotsubo cardiomyopathy:	~1% (176, 177)

hs-cTn, high-sensitivity cardiac troponin; MI, myocardial infarction; HF, heart failure; AF, atrial fibrillation; MSIMI, mental stress-induced myocardial ischemia; CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction.

The extent of cardiac involvement correlates with the severity and anatomical location of cerebral ischaemia, particularly in cases involving the insular cortex, underscoring the role of autonomic dysregulation in the pathogenesis of SHS (112–114). The clinical presentation varies widely, ranging from asymptomatic laboratory or ECG abnormalities to severe conditions requiring immediate intervention.

Acute ischemic stroke may occur simultaneously with MI [(115), Figures 3–8]. Although this presentation is uncommon, it is associated with a high in-hospital mortality rate, approaching 25% (116, 117). In such cases, the clinical presentation of MI may be atypical, particularly in older patients with neurological deficits, such as impaired consciousness or aphasia, which may obscure classical ischemic symptoms.

2.4.1.1 Myocardial injury

More than 50% of patients with acute ischemic stroke show evidence of myocardial injury, defined by elevated high-sensitive cardiac troponin (hs-cTn) levels in the absence of clinical features of myocardial infarction (MI) (16). These troponin elevations are typically transient and resolve within a few days. Serial troponin measurements are essential to distinguish *chronic myocardial injury*, characterised by persistently elevated or minimally fluctuating troponin levels, from *acute myocardial injury*, which is defined by a dynamic change exceeding 20% [(118, 119), Figure 9]. Acute myocardial injury may represent an

early stage in the progression towards MI, which is defined as myocardial injury with clinical evidence of acute myocardial ischemia.

Approximately 50% of patients with markedly elevated hs-cTn, either exceeding the diagnostic threshold for non-ST-segment-elevation MI (NSTEMI) or showing a significant dynamic rise and/or fall, may fulfil criteria for MI (120–122).

A substantial proportion of stroke patients with MI may have type 2 MI, resulting from an imbalance between myocardial oxygen supply and demand, often in the context of tachyarrhythmias, hypertensive emergencies, or respiratory failure (123).

Elevated cTn levels in patients with stroke, including those with minor stroke and transient ischemic attack (TIA), are strongly associated with an increased risk of cognitive impairment, recurrent vascular events, and both short and long-term mortality (110, 118, 124, 125). In a prospective cohort study, the long-term risk of major cardiovascular events (MACE) following stroke or (TIA) was approximately 13% within 1 year after discharge and 35% after a median follow-up of 4.4 years (126).

Brain natriuretic peptide (BNP) levels are frequently elevated during the first days following stroke and are associated with a higher risk of paroxysmal AF, worse functional outcomes, and increased mortality (127–129). BNP concentrations typically decline after the acute phase.

Current stroke management guidelines recommend early measurement of cardiac troponin to identify patients at high risk of adverse outcomes; however, they provide limited guidance regarding the subsequent diagnostic evaluation and management strategy (130). The coexistence of acute stroke and MI, especially ST-segment elevation MI (STEMI) poses significant diagnostic and therapeutic challenges due to narrow therapeutic windows and competing treatment priorities (131).

2.4.1.2 LV dysfunction and heart failure

Reduced LV ejection fraction (EF <50%), or clinically significant HF, accompanied by elevated BNP levels, may occur in approximately one-third of patients within the first few days after a stroke, and is associated with unfavourable functional outcomes (16, 132–134).

Systemic inflammation and immune activation may contribute to the development or progression of HF by exacerbating neurohumoral and autonomic dysregulation (135). In particular, brain injury involving the right insular cortex has been associated with impaired global LV longitudinal strain, even in patients without previous cardiac dysfunction (136). These cardiac abnormalities are associated with worse prognosis due to hemodynamic impairment and reduced systemic perfusion. However, since LV function prior to strokes is often unknown, accurately estimating the true prevalence of post-stroke cardiac dysfunction remains uncertain.

2.4.1.3 Arrhythmias

Continuous cardiac monitoring during the acute phase of stroke reveals that approximately 25% of patients experience clinically relevant arrhythmias, predominantly tachyarrhythmias (137). AF identified first identified after a stroke is termed AF detected after stroke (AFDAS) (65, 138, 139). AFDAS may arise from a combination of neurogenic mechanisms, secondary to

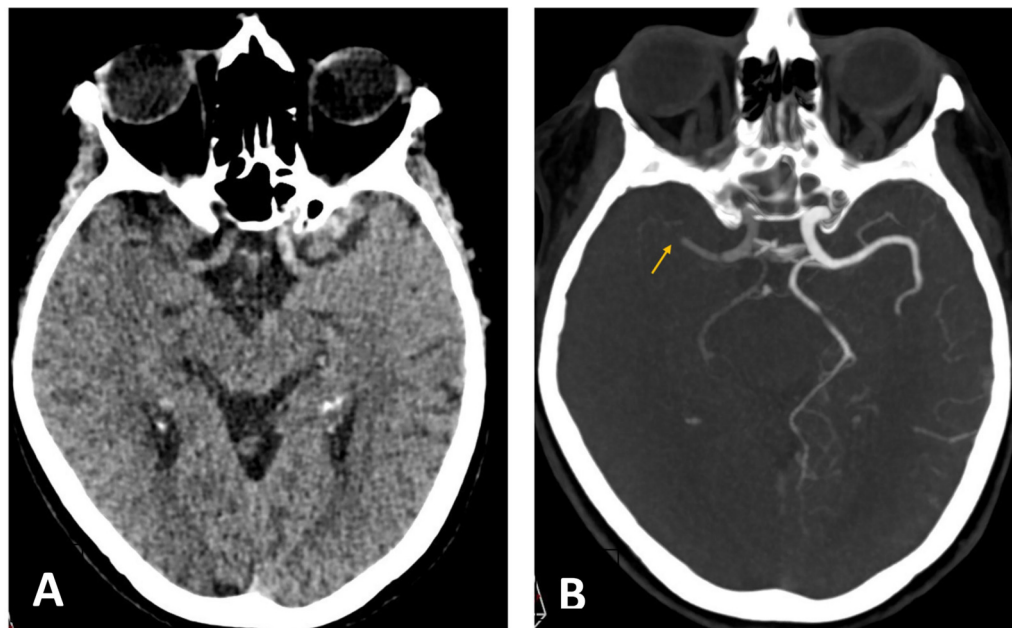


FIGURE 3

A 76-year-old woman was admitted to hospital with a right hemispheric stroke. Her National Institutes of Health Stroke Scale (NIHSS) score was 18. Non-contrast CT (A) showed no signs of established cerebral infarction. CT angiography (B) revealed an occlusion of the M1 segment of the right middle cerebral artery (MCA) (arrow).

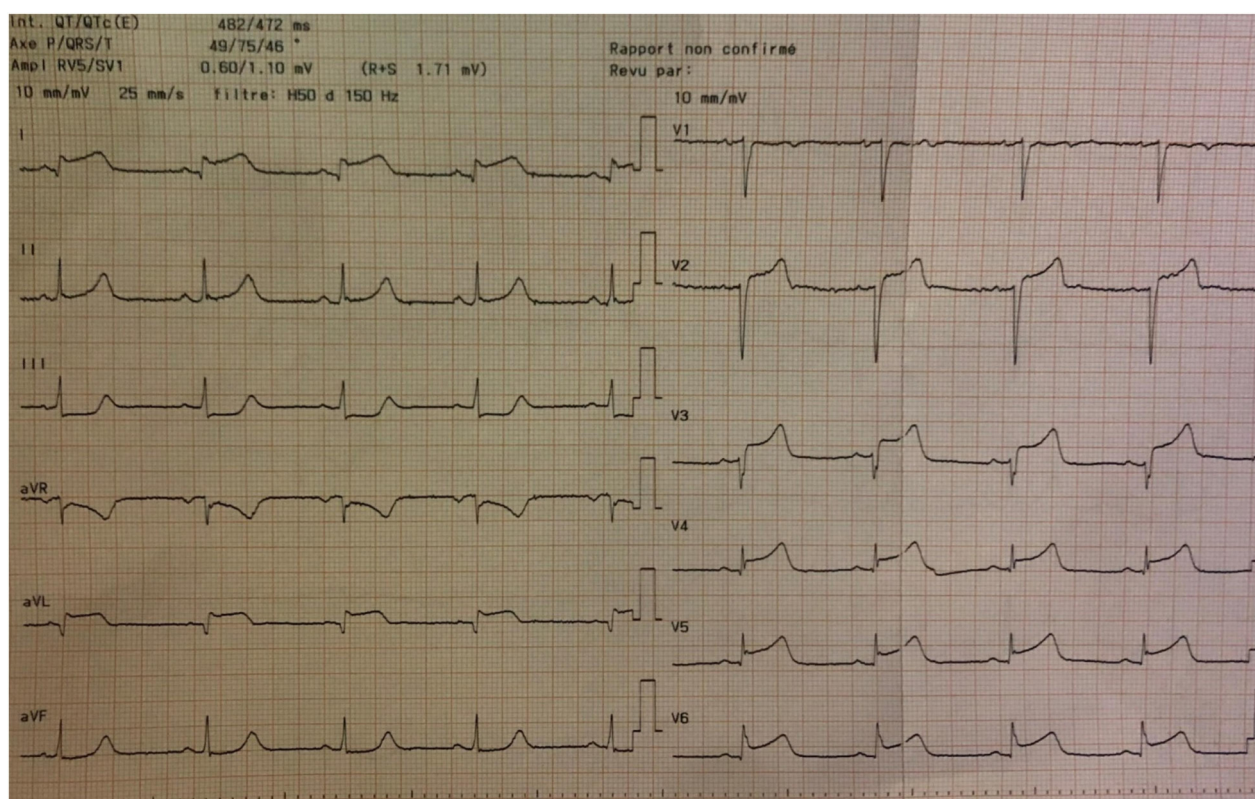


FIGURE 4

An acute myocardial infarction is also detected, which occurred without symptoms because of the unconscious state induced by the stroke. The ECG is consistent with a ST-segment elevation myocardial infarction (STEMI). Troponin 85 ng/L. Transthoracic echocardiogram in the emergency department demonstrated a reduced left ventricular ejection fraction (LVEF) of 30% and apical and septal hypokinesia, and no evidence of intracardiac thrombus. Urgent cerebral artery thrombectomy is planned, immediately followed by coronary angiography and myocardial revascularisation.

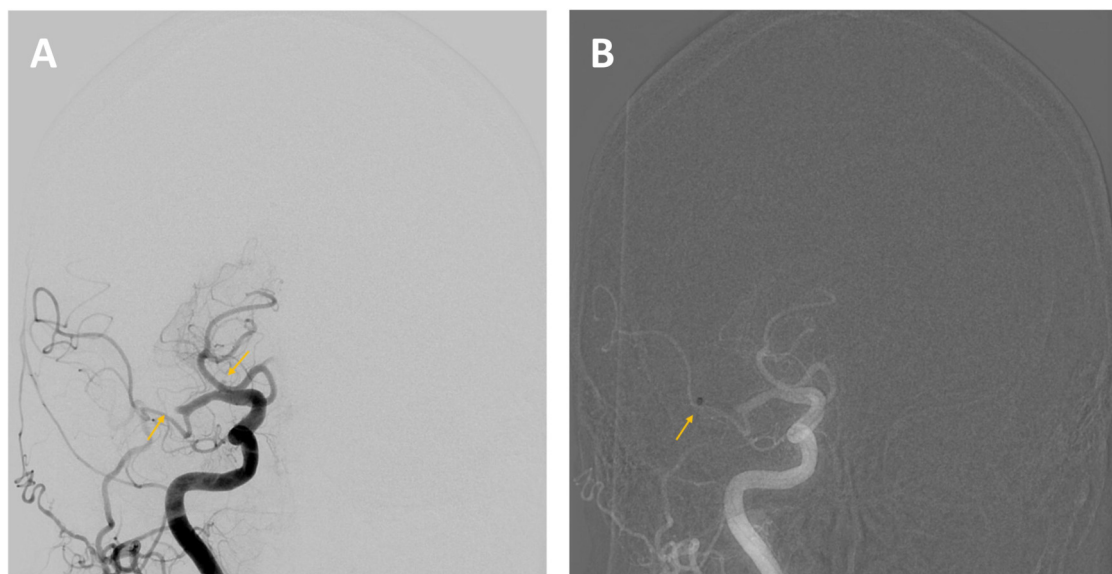


FIGURE 5

(A) An angiographic run of the right carotid axis confirmed occlusion of the M1 segment of the right middle cerebral artery (MCA) and demonstrated an additional occlusion at the origin of the A1 segment of the anterior cerebral artery (ACA). (B) Mechanical thrombectomy was performed using a contact aspiration catheter (the radiopaque catheter tip is indicated by the yellow arrow), resulting in successful reperfusion with a Thrombolysis in Cerebral Infarction (TICI) grade of 2c, indicating near-complete restoration of distal blood flow with minimal residual occlusion.

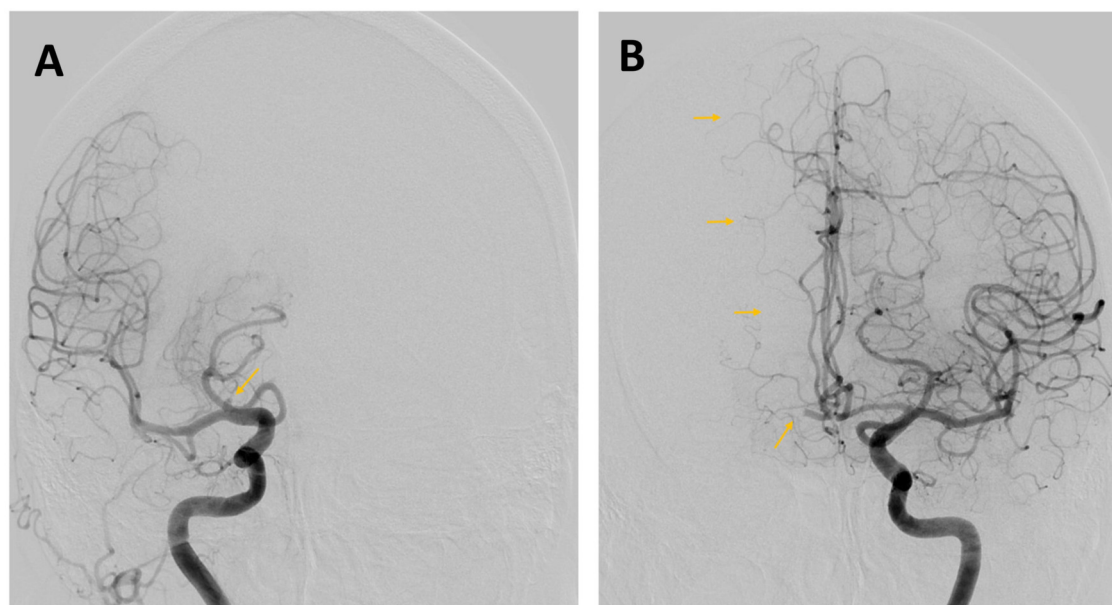


FIGURE 6

Results of the thrombectomy. (A) An angiographic run of the right carotid axis shows complete revascularisation of the right MCA territory, with persistent occlusion at the origin of the A1 segment of the right ACA (arrow). (B) An angiographic run of the left carotid axis demonstrates contralateral compensation of the ACA territory via the anterior communicating artery (arrow).

acute cerebral injury (neurogenic AFDAS), and underlying atrial vulnerability (cardiogenic AFDAS). It is frequently associated with strokes involving the insular cortex and other limbic structures that regulate autonomic control of cardiac rhythm (140, 141). Emerging evidence suggests that AFDAS may represent a distinct clinical entity compared with previously diagnosed AF and may be associated with a lower risk of stroke

recurrence (142, 143). Regardless of the differences, current recommendations support the initiation of oral anticoagulation therapy in all patients with AFDAS for secondary stroke prevention (144).

Electrocardiographic (ECG) abnormalities, including QT interval prolongation, ST segment elevation or depression, deeply inverted T waves (so called “cerebral T waves”), and

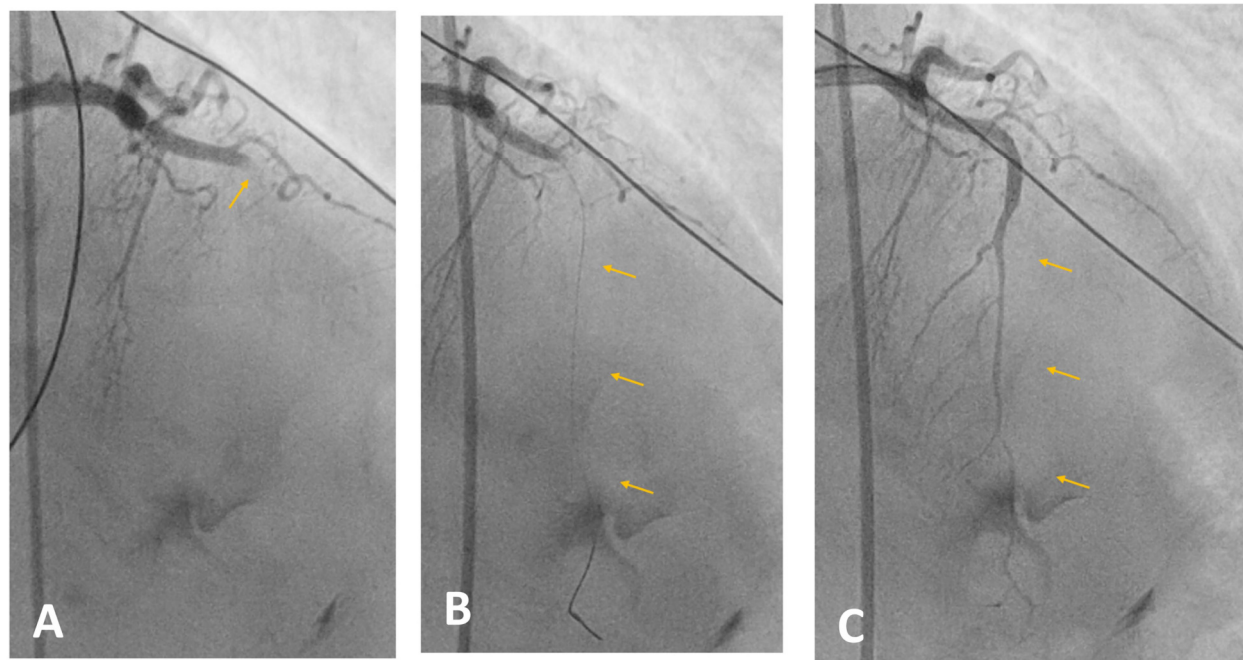


FIGURE 7

Coronary angiography. (A) Occlusion of the left anterior descending artery due to an intraluminal thrombus. (B) Mechanical thrombectomy with successful recanalisation of the artery. (C) Final angiographic result showing restored coronary flow.

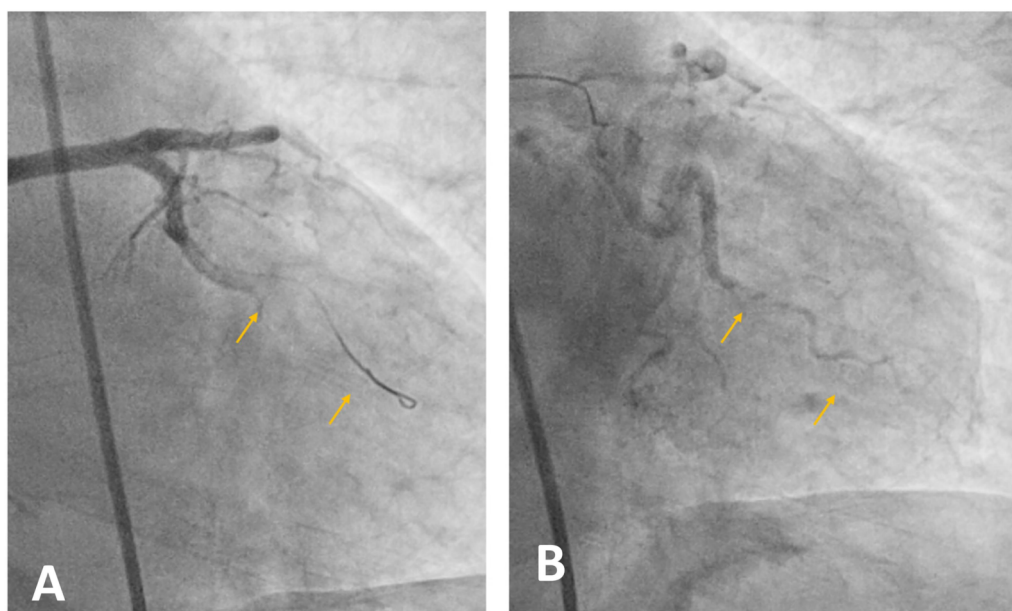


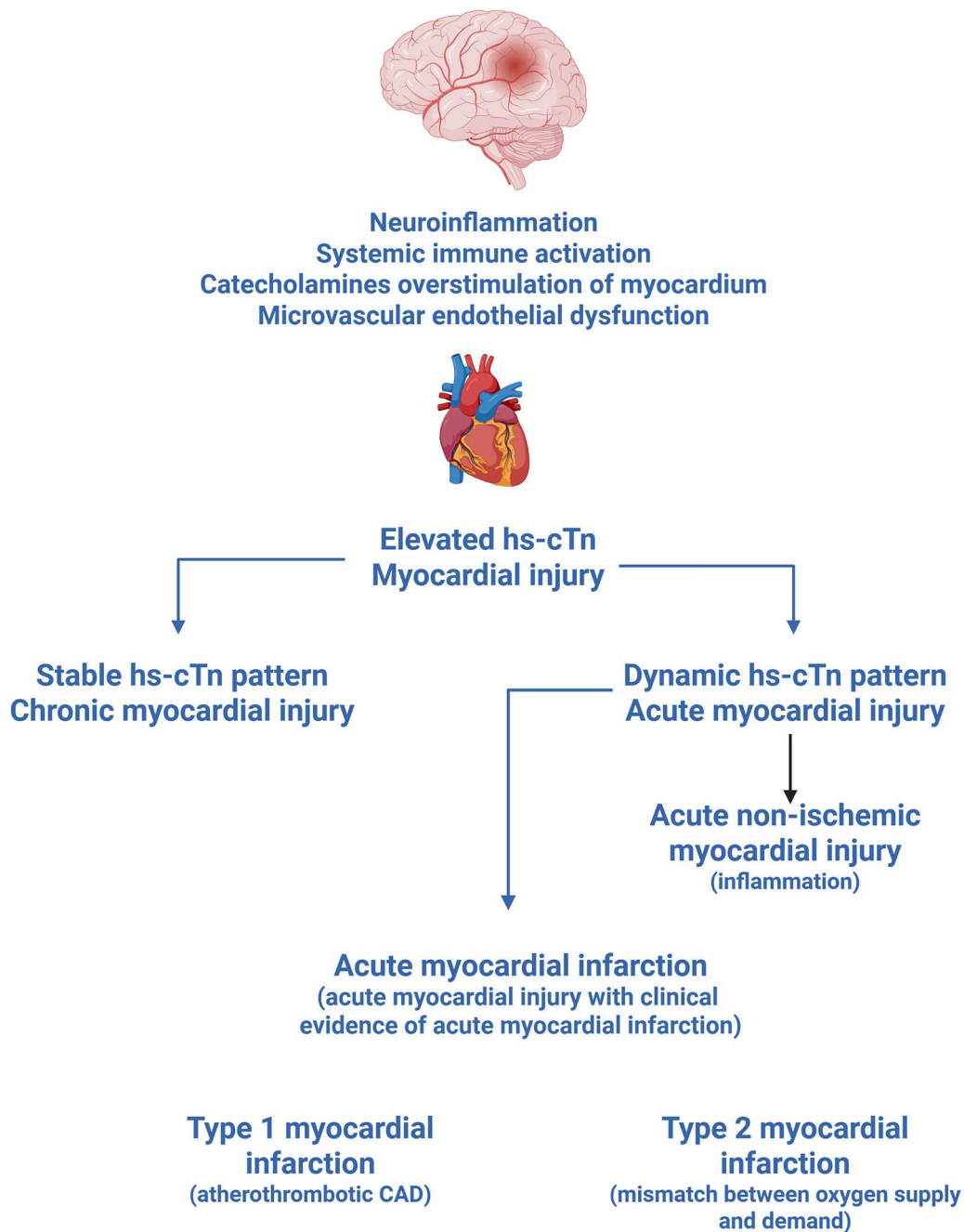
FIGURE 8

Coronary angiography. (A) The first marginal branch shows a short acute occlusion (<10 mm), classified as type B1, with an intraluminal thrombus at this site. (B) Recanalisation of the artery by thrombectomy followed by coronary stent placement.

atrio-ventricular or bundle branch blocks, are frequently observed during the first days following a stroke (145). These changes are often transient and are particularly common in patients with elevated cTn or pre-existing heart disease. However, their presence has been associated with poorer clinical outcomes (146–148).

2.4.2 Clinical impact of psychological stress on the heart

Acute and chronic psychological stress can trigger a wide range of CV abnormalities (149). Perceived threats are processed by the CNS, which evaluates environmental stimuli and initiates

**FIGURE 9**

Neurogenic myocardial injury following acute ischaemic stroke. Stroke-induced neuroinflammation, systemic immune activation, catecholamine overstimulation of the myocardium, and microvascular endothelial dysfunction all contribute to cardiomyocyte injury, reflected by elevated hs-cTn levels. Serial troponin measurements are essential to classify the pattern of injury. A stable hs-cTn pattern indicates chronic myocardial injury, characterised by persistently elevated or minimally fluctuating levels. A dynamic hs-cTn pattern, defined by a rise and/or fall exceeding 20%, indicates acute myocardial injury, which may represent either acute non-ischaemic injury driven by inflammation, or progression to acute MI when accompanied by clinical evidence of myocardial ischaemia. Approximately 50% of stroke patients with markedly elevated hs-cTn fulfil criteria for MI. When MI criteria are met, two subtypes are distinguished: Type 1 MI, caused by atherothrombotic coronary artery disease, and Type 2 MI, resulting from an oxygen supply-demand mismatch in the context of tachyarrhythmias, hypertensive emergencies, or respiratory failure. hs-cTn, high-sensitivity cardiac troponin; CAD, coronary artery disease; MI, myocardial infarction.

physiological responses aimed at adaptation. Stress arises when psychological demands exceed an individual's capacity to make adaptive changes (150). In such circumstances, the brain activates hemodynamic, neuroendocrine, and immune changes through mechanisms that partially overlap with those observed in ischemic brain injury. Elevated levels of stress-induced

noradrenaline may further influence microglial function via β -adrenergic receptors, thereby promoting neuroinflammatory signalling (151).

Acute mental stress refers to short-term exposure to intense stressors such as anger, fear, acute occupational strain, natural disasters, or emotionally charged sporting events (152–154).

Epidemiological studies have also documented increased rates of cardiovascular events on the first workday of the week and during the Christmas and New Year holiday period (155, 156).

Chronic psychological stress involves prolonged or repetitive exposure to stress, as occurs in conditions such as depression and anxiety (157, 158). Unlike acute stress responses, chronic mental stress is characterized by sustained sympathetic activation and systemic low-grade inflammation. These processes contribute to the progression of atherosclerosis and destabilization of coronary plaque, thereby increasing the risk of myocardial ischemia (159, 160).

2.4.2.1 Three major clinical entities are recognised

Mental stress-induced myocardial ischemia (MSIMI), is defined as transient myocardial ischemic response triggered by psychological stress rather than physical exertion (5, 161). In addition to MSIMI, ischemia with non-obstructive coronary arteries (INOCA), and myocardial infarction with non-obstructive coronary arteries (MINOCA), represent distinct but partially overlapping clinical entities characterised by complex interactions between central neural regulation and coronary pathophysiology.

INOCA refers to chronic or recurrent myocardial ischemia in patients with angiographically non-obstructive (<50%) coronary arteries and is primarily driven by coronary microvascular dysfunction, impaired vasodilatory reserve, and epicardial or microvascular vasospasm, irrespective of the precipitating trigger (162). In contrast, MINOCA denotes an acute myocardial infarction that fulfils universal diagnostic criteria in the absence of obstructive coronary stenoses (163).

MSIMI may manifest as angina, MI, arrhythmias, LV dysfunction, and stress-induced cardiomyopathy (Takotsubo syndrome) (155, 164–166). Its occurrence is influenced by an individual's CV risk profile (167). MSIMI is associated with a twofold increase in the incidence of major adverse cardiac events (MACE), even after adjustment for established CV risk factors (168). Among patients with stable CAD, the reported prevalence of MSIMI ranges from 20% to 70%, reflecting variability in the type of psychological stress applied, diagnostic methodologies used, and patient psychological characteristics (169). In these patients, ischemic responses may be triggered not only by acute emotional stress but also by everyday environmental stressors (170).

MSIMI may occur more frequently than exercise-induced myocardial ischemia and can be present in individuals who do not exhibit ischemia during exercise testing. Furthermore, it is not consistently associated with the angiographic severity of CAD (171). Angiographic and physiological studies suggest that MSIMI is largely related to impaired coronary microcirculatory function secondary to endothelial dysfunction (172, 173). MSIMI is often under-recognised because it may occur in the absence of chest pain. Holter monitoring studies have shown that more than two-thirds of ischemic episodes occur during daily activities, without anginal symptoms (174). Moreover, strong evidence indicates that mental stress-induced myocardial ischemia is independently associated with an increased risk of future cardiac events and mortality in patients with stable CAD (166).

Stress cardiomyopathy (Takotsubo syndrome, TTS) typically presents as congestive HF, clinically mimics STEMI. It is usually triggered by intense emotional or physical stress (175). The

condition is characterised by reversible balloon-like LV wall motion abnormalities, most commonly involving the apical segments, although mid-ventricular or focal patterns may also occur, in the absence of significant coronary artery obstruction (65). In the context of acute stroke, this condition is often referred to as “neurogenic stress cardiomyopathy” emphasizing the neurological trigger underlying the cardiac dysfunction.

TTS accounts for approximately 1%–3% of patients initially presenting with suspected STEMI, and occurs in about 1% of patients with acute stroke (176, 177). It predominantly affects postmenopausal women, likely due to reduced oestrogen levels which may enhance sympathetic vasoconstriction and impair endothelial function. TTS may also be triggered by intense, positive emotional experiences, a phenomenon described as “Happy heart syndrome” (178). Although LV systolic function typically recovers over time, long-term prognosis is comparable to that of patients with myocardial infarction (179). Contrary to earlier assumptions that TTS is a transient and benign condition, it is now recognized to carry substantial rates of acute complications, similar to those observed in acute coronary syndromes (179).

The underlying pathophysiology is thought to involve overstimulation of the sympathetic nervous system, in response to acute stress. Histopathological findings are consistent with catecholamine-mediated myocardial toxicity and include focal infiltration of mononuclear inflammatory cells, increased extracellular matrix protein deposition, and contraction band necrosis (myocytolysis).

Neuroimaging studies have shown structural alterations in limbic regions and impaired functional connectivity within the cortico-limbic network in patients with TTS (180). Affected regions include the prefrontal cortex, right insula, amygdala, hypothalamus, cingulate cortex, and thalamus, all of which regulate the autonomic function and cardiovascular responses to stress. Abnormal functional connectivity patterns may persist for weeks after the acute cardiac event, even following recovery of LV function (181). Furthermore, reduced functional brain connectivity may precede the development of TTS by several years. Retrospective analyses have shown increased amygdalar activity in individuals who later developed TTS, suggesting that heightened limbic reactivity may predispose susceptible individuals by amplifying autonomic and neurohormonal responses to future stressors (182–184).

2.4.2.2 Stress-induced arrhythmias

Both acute and chronic stress increase the risk of arrhythmias and sudden cardiac death (SCD). The incidence of ventricular arrhythmia is fivefold higher during periods of intense anger compared to control periods (185, 186). Moreover, anger and negative emotions are associated with the onset and progression of AF, even after adjustment for traditional CV risk factors and previous CAD (187). Negative emotional states activate the sympathetic nervous system while suppressing parasympathetic output (188). Catecholamine excess may increase the risk of arrhythmias by inducing electrical heterogeneity of ventricular depolarisation and repolarisation (189, 190). Another proposed mechanism is the “brain-heart laterality”, which suggests that lateralised imbalances in autonomic neural control may result in

asymmetrical sympathetic stimulation of the heart, thereby increasing the risk of arrhythmias (191–193).

Conversely, positive emotional states have been shown to decrease CV reactivity to stress, reducing heart rate and blood pressure responses, arrhythmia development, thrombogenesis, and the risk of CAD (194).

2.4.3 Clinical impact of cardiac disorders on the brain

Cardiac disease, such as MI, HF, AF, and invasive cardiac interventions, can induce brain injury through thromboembolic and inflammatory mechanisms (1, 11, 195). These processes may result in cerebral hypoperfusion, embolic events, and systemic immune activation, all of which contribute to neural damage. Secondary neuroinflammation arising from these mechanisms has been implicated in the development of ischemic stroke, cognitive impairment, depression, and vascular dementia. The bidirectional interaction between cardiac dysfunction and cerebral injury underscores the importance of considering cardiovascular disease as a major determinant of long-term neurological outcomes [Figure 10, (195–198)].

2.4.3.1 Myocardial ischemia

Both acute and chronic CAD are associated with brain injury and accelerated cognitive decline (11, 14, 199, 200). A history of CAD has been associated with a 27% increased risk of dementia (201). In patients with chronic CAD, brain magnetic resonance imaging (MRI) studies have shown an estimated “brain age” approximately 2.3 years older than chronological age, suggesting accelerated cerebral aging (202). Moreover, CAD is frequently complicated by HF and AF which are strongly associated with cognitive impairment and an increased risk of dementia (13, 201).

Approximately one third of patients who experience acute MI develop cognitive impairment and behavioural disorders, including anxiety and depression (203–208). Besides impairing long-term quality of life, these neuropsychiatric conditions are associated with a significantly increased risk of MI and MACE (209, 210).

Patients with acute MI have an increased risk of stroke, particularly within the first four weeks following the acute event and over the long term. Population-based studies have reported an incidence of ischemic stroke of 2.0% within the first month and 3.8% within one year after acute MI (211–213). Stroke occurring after MI is associated with significantly higher mortality, exceeding 30% at one year, compared to 18% in those without prior MI (214, 215).

Overall, the risk of stroke is higher in patients with ST-segment elevation MI (STEMI) compared to those with non-STEMI MI. Anterior MI is particularly associated with an increased risk of aneurysm formation, regional hypokinesis, and mural thrombus development, thereby increasing the risk of embolisation. However, stroke may occur following MI involving any coronary territory and is also observed in patients with non-ischemic dilated cardiomyopathy (3).

Clinically unrecognised MI, which accounts for one-third to one-half of all MI, is also linked to a higher risk of subsequent stroke (216, 217). Unrecognised MI may result in LV scarring, regional wall motion abnormalities and LV thrombus formation.

These conditions may account for a significant proportion of non-lacunar cryptogenic strokes, often classified as thromboembolic stroke of undetermined source (ESUS) (218, 219).

The incidence of LV thrombus varies widely, although it has declined in recent years due to early reperfusion therapies. Reported rates range from 4% to 39%, depending on the study population, imaging modalities, and timing of assessment (220–222). The incidence of acute ischemic stroke in patients with LV thrombus may exceed 10% (223).

The majority of ischemic stroke following MI are cardioembolic in origin and may be either clinically evident or silent, detectable only by brain MRI using diffusion-weighted imaging (DW-MRI) to identify ischemic lesions (217, 224–226). The combination of blood stasis due to LV wall motion abnormalities, endothelial ischemic injury, and hypercoagulability associated with the acute pro-inflammatory state, creates a highly thrombogenic myocardial environment favouring thrombus formation (227).

Furthermore, ischemic myocardium releases damage-associated molecular patterns (DAMPs) which activate immune cells and initiate a robust inflammatory response (228). This response is mediated by the release of cytokines, including tumour necrosis factor- α (TNF- α) and interleukins (e.g., IL-1, IL-16). Although this inflammatory cascade is essential for cardiac remodelling and scar formation to preserve and restore adequate myocardial function, prolonged activation may lead to a systemic inflammatory state characterized by persistent low-grade inflammation for weeks after MI (73, 229, 230).

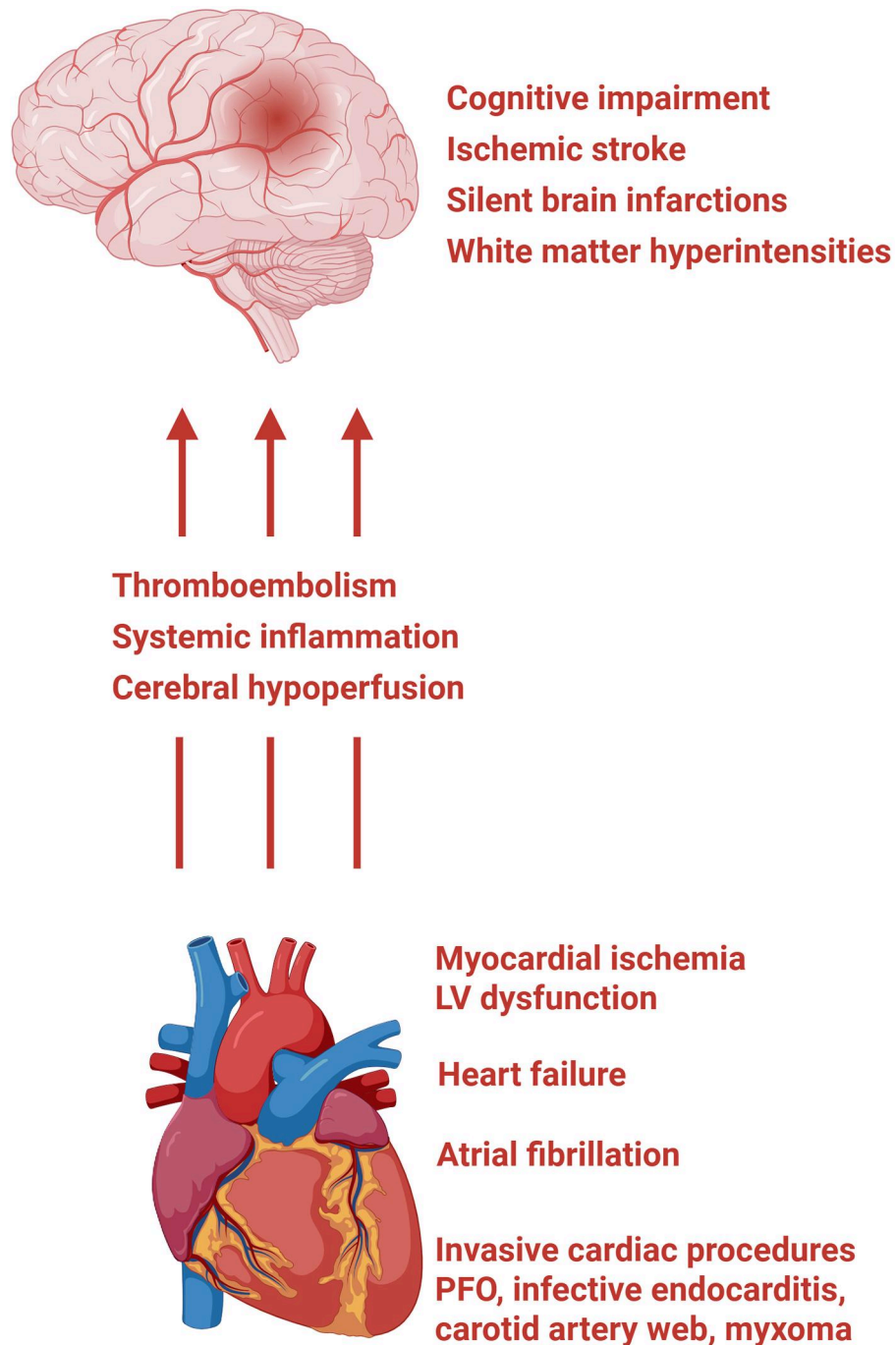
Imaging studies have shown that myocardial inflammation can promote activation of glial cells in the brain and disrupt the integrity of the BBB, contributing to neuroinflammation and subsequent neural dysfunction (195, 231). Circulating cytokines further induce a prothrombotic state by activating endothelial cells and platelets, increasing the risk of thrombus formation within the cerebral vasculature. This may result in small brain infarcts, that contribute to cognitive impairment (232).

Furthermore, thrombi rich in activated platelets release beta-amyloid. Recurrent microthrombotic events may promote beta-amyloid aggregation within and around cerebral vessels, particularly in memory-related regions, such as the hippocampus and amygdala, leading to cerebral amyloid angiopathy. This process contributes to cognitive decline and the formation of plaques characteristic of Alzheimer's disease (233, 234).

The inflammatory response following MI also triggers coronary microvascular endothelial dysfunction, impairing vasodilation in response to increased oxygen demand and potentially leading to coronary microvascular spasm and inadequate myocardial perfusion (235). Coronary microvascular dysfunction, as part of a systemic small-vessel disease, is associated with structural alterations in the cerebral microvasculature, particularly within subcortical regions, manifesting as white matter hyperintensities on brain MRI (236–238). Clinically, cerebral small-vessel disease may present as cognitive impairment or lacunar ischemic stroke (239).

2.4.3.2 Strategies to control neuroinflammation after MI

Although no therapies currently target post-MI neuroinflammation directly, several established clinical strategies may indirectly modulate neuroimmune activation by limiting

**FIGURE 10**

Effects of cardiac disorders on the brain. Cardiac conditions, including myocardial ischaemia and LV dysfunction, HF, AF, invasive cardiac procedures, and less common sources such as PFO, infective endocarditis, cardiac myxoma, and carotid artery web, cause cerebral injury through three converging mechanisms: thromboembolism, systemic inflammation, and cerebral hypoperfusion. Thromboembolism arises from blood stasis due to LV wall motion abnormalities and ventricular dilatation, atrial thrombus formation promoted by blood stasis within the left atrial appendage in AF, and periprocedural embolisation of thrombus, calcific debris, or atherosclerotic plaque fragments during cardiac interventions. Systemic inflammation, driven by DAMP-mediated immune activation following myocardial injury, generates a prothrombotic state, activates glial cells, and disrupts blood-brain barrier integrity, thereby amplifying neuroinflammation. Cerebral hypoperfusion results from reduced cardiac output in heart failure and from the irregular cardiac rhythm of AF, which causes repeated fluctuations in cerebral blood flow that may overwhelm autoregulatory mechanisms over time. Together, these pathways produce a spectrum of neurological consequences, ranging from clinically overt ischaemic stroke to subclinical injury detectable only on neuroimaging, including silent brain infarctions and white matter hyperintensities, as well as cognitive impairment and vascular dementia. LV, left ventricle; HF, heart failure; AF, atrial fibrillation; PFO, patent foramen ovale; DAMP, damage-associated molecular patterns.

myocardial injury and systemic inflammation (228). Early and effective reperfusion with primary percutaneous coronary intervention remains the cornerstone of infarct size reduction and is associated with attenuation of the inflammatory response. Smaller infarcts generate lower levels of DAMPs and pro-inflammatory cytokines, thereby reducing peripheral immune activation and subsequent neuroinflammatory signalling.

In addition, statins exert anti-inflammatory effects, suppress innate immune activation, and reduce circulating levels of C-reactive protein and interleukin-6. Antithrombotic therapies may further limit microvascular obstruction and reperfusion injury, indirectly mitigating inflammatory amplification.

Emerging evidence from anti-inflammatory cardiovascular trials, such as those evaluating colchicine (COLCOT) (240) and interleukin-1 β inhibition (CANTOS) (241), suggests that systemic modulation of inflammation can improve cardiovascular outcomes and may secondarily influence neuroinflammatory pathways. However, the clinical application of these therapies is limited by an increased incidence of infections and non-CV mortality. Hence, there is the need to select high-risk patients who could benefit from a potentially harmful treatment. A further improvement will be the use of nanotechnology to produce nanoparticle drug formulations designed to selectively deliver anti-inflammatory agents to specific tissues or immune cell populations (242).

Heart failure is associated with a broad spectrum of cerebral complications, including stroke, cognitive decline, dementia, and depressive disorders (196, 243–245). Depending on the applied criteria applied, 25%–70% patients with HF exhibit cognitive impairment or dementia (201, 246, 247). The prevalence of clinically evident stroke in patients with HF ranges between 4% to 11%, with higher rates in older patients (248–250). Even in patients with preserved left ventricular ejection fraction (LVEF), subclinical LV systolic or diastolic dysfunction is associated with an increased risk of silent brain infarctions (SBI), cerebral white matter hyperintensities (WMH), and brain atrophy on MRI (251). These findings reflect underlying small-vessel disease and may represent early precursors of clinically manifest stroke (252–254).

The pathophysiological mechanisms underlying cerebral dysfunction in HF include cardiac thromboembolism and cerebral hypoperfusion secondary to reduced cardiac output. Similar to myocardial ischemia, which often precedes the development of HF, it is characterised by low-flow state promoting blood stasis, due to impaired contractility and ventricular dilatation, a prothrombotic condition driven by low-grade inflammation, and endothelial dysfunction (248, 255). Together, these conditions create a thrombogenicity cardiac environment that accounts for cardioembolic stroke in patients with HF (227, 248, 256).

Impaired LV contractile function reduces cardiac output and directly compromises cerebral perfusion, particularly when cerebral autoregulation is impaired and cerebral blood flow becomes increasingly dependent on systemic hemodynamic (257). The brain receives approximately 15% of total cardiac output and has high metabolic demand but limited energy reserves. Therefore, cerebral function is highly dependent on adequate cardiac performance. Markedly reduced LV systolic function, reflected by a decreased LVEF, is strongly associated with an increased risk of stroke (258). Conversely, chronic

cerebral hypoperfusion may contribute to ANS dysfunction, further exacerbating cardiac decompensation, and initiating a self-perpetuating maladaptive neurocardiac feedback loop (259).

Prevention of cerebral injury in patients with heart failure is based on guideline-directed medical therapy (GDMT) combined with careful haemodynamic management and prevention of thromboembolic complications (245). Anticoagulation treatment is the cornerstone for prevention of cardioembolic stroke in HF with AF. Conversely, the prevention with direct oral anticoagulants (DOACs) or vitamin-k antagonists in patients with HF who remain in sinus rhythm is not well established, as potential benefits may be offset by an increased risk of major bleeding (260, 261). Neurological assessment in patients with chronic heart failure can improve early detection of cognitive impairment and silent cerebral infarction. Periodic cognitive screening and selective neuroimaging in high-risk individuals may promote timely intervention and improve strategies for secondary prevention.

Atrial fibrillation is associated with an approximately 20% lifetime risk of ischemic stroke, regardless of whether it is paroxysmal or permanent, and with a 40% increased risk of cognitive impairment, potentially related to both clinically evident and silent brain ischemia (144, 262–264). AF is also detected in up to 30% of cryptogenic strokes when prolonged cardiac rhythm monitoring is performed (265).

Traditionally, the prothrombotic risk associated with AF has been attributed to blood stasis, particularly within the left atrial appendage, which promotes thrombus formation and increases the risk of cerebral embolism. However, recent evidence suggests that the arrhythmia itself is not the sole determinant of thromboembolic risk (266). AF may arise from, or coexist with, an underlying atrial myopathy, which can contribute to stroke development independently of the arrhythmia.

Studies examining left atrial volume and strain have shown that ageing and systemic vascular risk factors, such as hypertension, pressure and volume overload, and ischemia, induce structural and functional alterations collectively termed atrial cardiomyopathy (267–269). This condition is characterised by fibrotic tissue remodelling, impaired atrial contractility, and electrophysiological disturbances. These changes result in atrial mechanical dysfunction and promote a prothrombotic state, thereby increasing the risk of cardioembolic stroke independently of manifest AF (270–273).

Other arrhythmias including premature atrial contractions, paroxysmal supraventricular tachycardia, and premature ventricular contractions, have also been associated with atrial cardiomyopathy and the development of cognitive impairment and stroke (274–276). Furthermore, atrial remodelling in AF stimulates the release of DAMPs, which trigger low-grade inflammatory responses that further contribute to thrombogenesis (88, 273).

In addition to cerebral embolism as a possible mechanism underlying cognitive decline, AF may also lead to transient or chronic cerebral hypoperfusion (277). The irregular rhythm characteristic of AF leads to variability in diastolic filling times and cardiac output, resulting in repeated episodes of relative hypo- and hyper-perfusion within the cerebral microvasculature. Although cerebral autoregulation generally maintains stable cerebral blood flow across a wide range of systemic blood

pressures, rapid fluctuations in cardiac stroke volume may overwhelm this compensatory mechanism. This disruption can impair normal flow-mediated vasodilation, compromise microvascular integrity, and contribute to cumulative cerebral injury over time (278).

2.4.3.3 Strategies for stroke prevention

Oral anticoagulation remains the cornerstone of stroke prevention in patients with AF and is associated with significant reductions in both overt and subclinical cerebral events (144). Restoration and maintenance of sinus rhythm may further improve cerebral perfusion, reduce atrial thrombus formation, and limit microembolisation, thereby potentially attenuating subclinical brain injury. Although early randomised trials did not demonstrate a significant difference in stroke risk between rhythm-control vs. rate-control strategies, more recent evidence suggests that early rhythm-control therapy, using antiarrhythmic drugs and/or catheter ablation, may reduce the risk of stroke in patients with recently diagnosed atrial fibrillation and cardiovascular comorbidities (279). Accordingly, rhythm-control strategies may offer additional neuroprotective benefit in selected patients, whereas rate control remains an appropriate approach in clinically stable, adequately anticoagulated individuals.

2.4.3.4 Invasive procedure-related thromboembolic brain ischemia

Cardiac procedures, including transcatheter and surgical valvular replacement, percutaneous and surgical coronary interventions, left atrial appendage occlusion, patent foramen ovale (PFO) closure, and AF catheter ablation, are associated with an increased risk of periprocedural cerebral ischemic injury [Table 2, (197, 280, 281)]. The extent of neurologic damage ranges from asymptomatic lesions detected only on neuroimaging to clinically disabling stroke. This risk is influenced by both procedural characteristics and patient-related comorbidities.

Neurological complications are primarily caused by acute cerebral embolisation occurring during the intervention. Embolic material may consist of thrombus, calcific debris from valvular leaflets, or fragments of atherosclerotic plaque dislodged during catheter manipulation. Mechanical disruption of vascular or valvular structures may also cause endothelial injury and plaque rupture, resulting in platelet activation and thrombus formation (225, 282, 283).

An inflammatory response may also arise secondary to myocardial ischemia-reperfusion injury, which can occur following restoration of coronary flow during primary percutaneous coronary intervention or fibrinolytic therapies (284, 285). Moreover, up to three-quarters of patients undergoing transcatheter valvular procedures develop systemic inflammatory response syndrome (SIRS) which may further promote cerebral thromboembolism and device-related thrombosis (283, 286).

Although the risk of periprocedural stroke is relatively uncommon, ranging from <1% after percutaneous coronary intervention (PCI), to 18% in patients receiving a LV assist device (LVAD), SBIs are frequently detected by DW-MRI, following invasive cardiac procedures, with reported rates of up to 90% in LVAD recipients (225). The long term clinical

TABLE 2 Risk of thromboembolic stroke caused by invasive cardiac procedures.

Procedure	30-day ischemic stroke	Silent brain infarctions
Transcatheter aortic valve implantation (TAVI)	2.3–7% (290, 316–318)	~70% (288, 289)
Surgical aortic valve replacement	5.1% (318)	58% (319)
Transcatheter mitral valve interventions	<1–2.6% (291, 320)	~85% (321)
Mitral valve surgical interventions	3.4% (322)	n.a.
PCI	<1% (197, 323)	10% (324)
CABG	1–5% (197, 281)	n.a.
Left atrial appendage closure	0.2–1.2% (320)	52% (280)
Patent foramen ovale closure	<1% (325)	
Atrial fibrillation catheter ablation	<1 (326)	~60% (327–329)
Left ventricular assist device (LVAD)	6–18% (197, 330)	>90%
Carotid artery revascularization	~2% (331)	n.a.

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

significance of these SBIs remains uncertain, and their contribution to subsequent cognitive decline has yet to be fully elucidated (287, 288).

Strategies to reduce the risk of procedure-related cerebral injury focus on minimising embolic burden, attenuating inflammatory responses, and optimising periprocedural management. The use of cerebral embolic protection devices (CEPD) in left-sided structural heart intervention has been shown to reduce the volume of SBI but not their overall incidence (287, 289–291). Careful patient selection and comprehensive preprocedural assessment, including evaluation of atherosclerotic burden and thromboembolic risk and comorbidities, are essential to identify individuals at increased vulnerability (292).

2.4.3.5 Less common sources of thromboembolic brain ischemia

Paradoxical embolism resulting from right to left shunt through PFO may account for approximately 4% of all ischemic strokes and up to 25% of embolic strokes of undetermined source, particularly in younger patients (293). The most widely accepted pathophysiological mechanism involves venous emboli bypassing pulmonary filtration by crossing the PFO into the left atrium and subsequently entering the systemic circulation. However, recent studies using high-resolution optical coherence tomography suggest that microthrombi may also arise within the PFO itself, especially in patients with a large PFO or an associated atrial septal aneurysm. These microthrombi have been described as small, irregular thrombi adherent to the

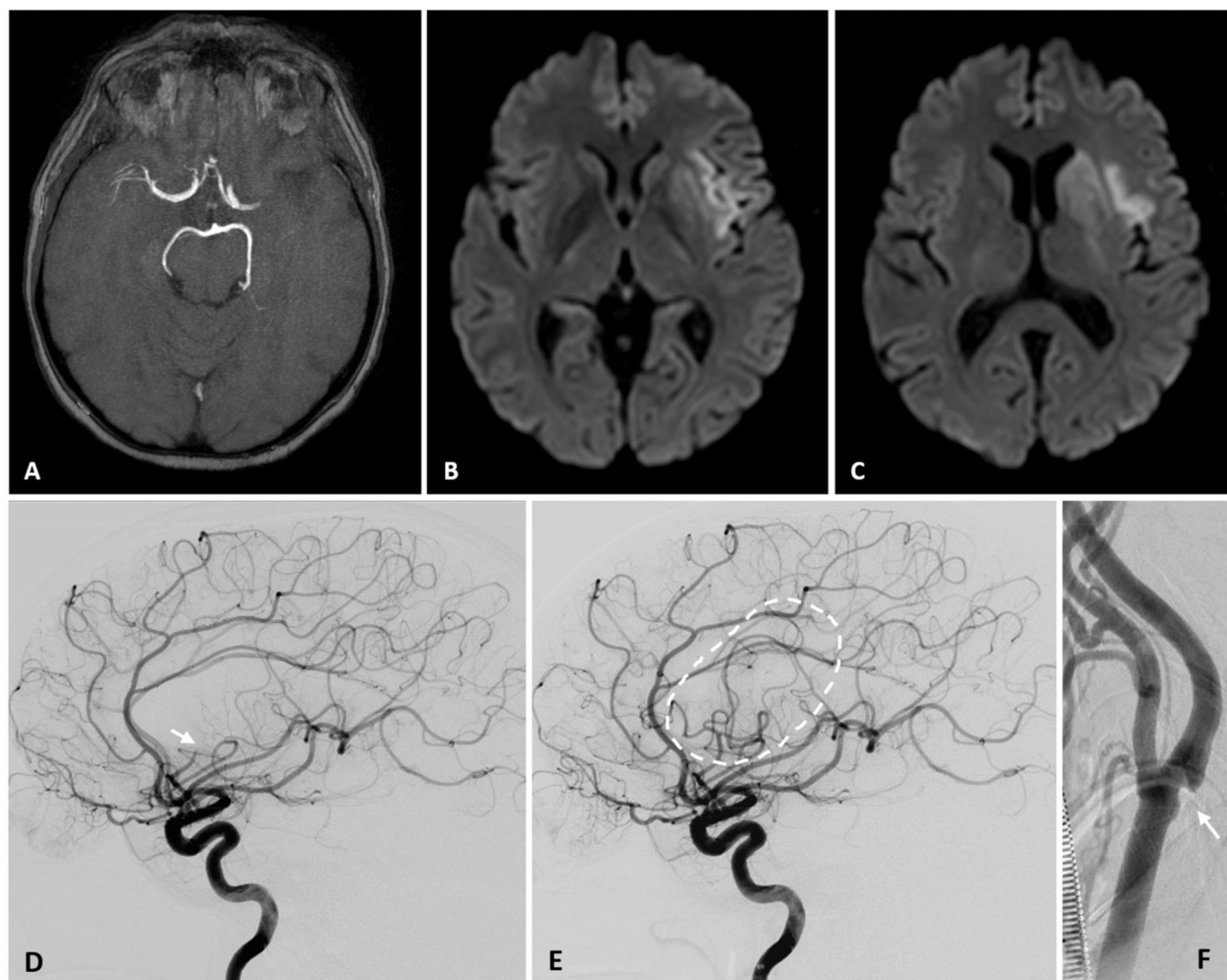


FIGURE 11

A 54-year-old woman with no cardiovascular risk factors presented with sudden-onset right-sided hemiplegia and aphasia. Emergency cerebral MR angiography revealed an occlusion of the M1 segment of the left middle cerebral artery (A), resulting in a deep MCA territory infarction (B, C). Intravenous thrombolysis was initiated during transfer from a peripheral hospital to the comprehensive stroke centre for thrombectomy. On arrival, initial angiographic assessment (D) demonstrated an occlusion of a left M2 branch (arrow). (E) Post-thrombectomy angiogram following a single pass with a stent retriever showed successful recanalisation and reperfusion of the downstream territory (dashed line). Final angiographic images at the left carotid bifurcation (F) revealed a carotid web (arrow). After excluding haemorrhagic transformation on CT at 24 h post-stroke, antiplatelet therapy with aspirin 160 mg/day was initiated for secondary prevention.

endocardial surface, free-floating thrombi formed *in situ*, or localized endocardial surface irregularities (294).

Thromboembolic neurological complications may also occur in the context of infective endocarditis. Clinically overt stroke develops in approximately 25% of patients, while subclinical cerebral infarctions, detectable only by MRI, have been reported in 48%–80% of cases (295, 296). Cardiac myxoma is likewise associated with a high incidence of embolic events, with stroke reported in 26%–45% of affected individuals (297, 298).

Carotid artery web is an under-recognised cause of cryptogenic stroke in young patients, accounting for an estimated 9%–37% of such cases (299, 300). It represents a non-atherosclerotic variant of fibromuscular dysplasia, consisting of a thin, shelf-like membranous projection into the lumen of the internal carotid artery, typically at its origin (301, 302). This anatomical abnormality disrupts local hemodynamic and promotes blood stasis, facilitating thrombus formation and subsequent embolic stroke [Figures 11, 12, (303)].

3 Knowledge gaps and future directions

Despite substantial progress in understanding the bidirectional relationship between the heart and the brain, important knowledge gaps remain, limiting a comprehensive understanding of heart-brain interactions and their clinical implications.

Research on heart-brain axis has mainly focused on signals from the brain to the heart, while the communication from the heart to the brain has received less attention. This reverse pathway, seen in conditions such as depression and cognitive decline associated with heart failure and CAD, is not yet completely understood and requires further clinical investigation.

Another major unresolved issue concerns the limited understanding of how neurocardiac and neuroimmune interactions change across the lifespan. Age-associated alterations in autonomic regulation and immune function, together with sex-related differences, may substantially modify disease progression



FIGURE 12

Several weeks after the ischaemic stroke, the patient underwent left carotid artery stenting. (A) Angiographic visualisation of the carotid web. (B) Contrast stagnation confirming haemodynamic disturbance caused by the web. (C) The stent flattens and flattens the web against the vessel wall, isolating the pouch from the bloodstream at the carotid bulb. In the following weeks, endothelialisation of the stent occurs, leading to complete exclusion and thrombosis of the pouch. (D) CT angiography at three-month follow-up demonstrates stent patency and complete thrombosis of the pouch.

and treatment responsiveness, yet these factors remain insufficiently explored. Furthermore, most studies on the heart-brain axis has focused on the relationship between clinical cardiac diseases and brain disorders, while the effects of subclinical abnormalities on neurological health need to be further studied (304). Research has shown that subtle age-related changes in cardiac hemodynamic, even in the absence of CV disease, may result in impaired neurovascular coupling, brain atrophy and microvascular damage (305). In population-based settings, subclinical cardiac impairment was associated with silent lacunar infarcts and an increased risk of future stroke and dementia (306).

The autonomic imbalance in heart-brain axis dysfunction may be evidenced by reduced heart rate variability (HRV), which is strongly associated with systemic inflammation. In addition, the analysis of low-frequency oscillations in ECG recordings, termed periodic repolarization dynamics, is associated with arrhythmic events (42). However, clinical evidences are not sufficient to support their inclusion in clinical guidelines.

Identifying reliable biomarkers is essential for patient stratification and monitoring therapeutic efficacy in disorders of heart-brain axis. Currently, troponin and natriuretic peptides represent the main biomarker used in clinical practice. However, they lack specificity in distinguish between neurogenic from primary cardiac injury. Moreover, there are insufficient data to determine the proportion of stroke patients with cTn elevation that may benefit from cardiac invasive diagnostic and therapeutic measures.

New potential biomarkers whose blood levels are altered by stroke, include macrovesicles (MVs), which are a group of lipid membrane-enclosed vesicles released by cells into the extracellular space, and microRNA, a short sequence of noncoding RNA

which regulates some biological processes including responses to hypoxia, angiogenesis and inflammation, by affecting gene expression (3, 11, 58). Circulating endothelial and leukocyte-derived MVs may influence heart-brain interactions and are considered a potential biomarker for CV risk stratification (307). Circulating microRNA are being considered as diagnostic and prognostic marker in patients with stroke (308).

Therapeutic strategies targeting heart-brain pathways have not been clearly established. Modulation of the autonomic nervous system is an attractive therapeutic strategy, given the increased sympathetic activity and reduced parasympathetic tone observed in dysfunction of the heart-brain axis. Several clinical trials have investigated device-based stimulation of the vagus nerve, spinal cord, and baroreceptors, in patients with heart failure or CAD, however, with inconsistent results (309, 310). Likewise, targeting cytokines pathways which represents a central mechanism linking heart and brain pathology remain uncertain. Only low-dose colchicine has been included in the guidelines for secondary prevention when patients with chronic coronary disease or post-MI who remain at high risk despite optimal therapy, while canakinumab is not routinely recommended (311). A further improvement will be the use of nanotechnologies to produce nanoparticle drug formulation which can be delivered to specific tissue or cell populations (242).

4 Conclusions

The heart and the brain share complex anatomical and functional bidirectional connections. Under physiological

conditions, their interplay is crucial for adapting to external stimuli and regulating internal homeostasis. In pathological conditions, damage to one of these organs causes significant pathophysiological disturbances in the other, thereby considerably worsening the prognosis.

Neuroinflammation and systemic immune activation are key mechanisms linking brain and heart disease. Stroke-related disruption of central autonomic network leads to sympathetic overactivation and persistent systemic inflammation, which contribute to myocardial injury, arrhythmogenesis, and heightened cardiovascular risk.

Conversely, cardiac disorders, such as myocardial infarction, heart failure, and atrial fibrillation can adversely impact brain structure and function. These effects are mediated through shared mechanisms, including systemic inflammation, cerebral hypoperfusion, thromboembolism, and microvascular dysfunction, resulting in neurological complications such as ischemic stroke and cognitive decline.

Recognition of this bidirectional relationship may improve risk stratification, prevention strategies, and therapeutic interventions across both brain and heart disease. However, despite growing evidence, the clinical implications of heart–brain interactions remain limited in clinical practice. By synthesizing this evidence, this review aims to highlight the need for more comprehensive prognostic frameworks, integrated biomarker panels, and future trials that incorporate both cardiac and neurological outcomes.

Author contributions

FV: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. SV: Conceptualization, Data curation, Supervision, Writing – review & editing. GL: Conceptualization, Writing – review & editing. EV: Conceptualization, Data curation, Supervision, Writing – review

& editing. MH: Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Testai FD, Gorelick PB, Chuang P-Y, Dai X, Furie KL, Gottesman RF, et al. Cardiac contributions to brain health: a scientific statement from the American Heart Association. *Stroke*. (2024) 55(12):e425–38. doi: 10.1161/STR.0000000000000476
- Valenza G, Matic Z, Catrambone V. The brain–heart axis: integrative cooperation of neural, mechanical and biochemical pathways. *Nat Rev Cardiol*. (2025) 22(8):537–50. doi: 10.1038/s41569-025-01140-3
- Hu J-R, Abdullah A, Nanna MG, Soufer R. The brain–heart axis: neuroinflammatory interactions in cardiovascular disease. *Curr Cardiol Rep*. (2023) 25:1745–58. doi: 10.1007/s11886-023-01990-8
- Goh FQ, Tan BYQ, Yeo LLL, Sia C-H. The heart–brain axis: key concepts in neurocardiology. *Cardiology Discovery*. (2025) 5(2):162–77. doi: 10.1097/CD9.0000000000000156
- Steptoe A, Kivimäki M. Stress and cardiovascular disease. *Nat Rev Cardiol*. (2012) 9(6):360–70. doi: 10.1038/nrcardio.2012.45
- Strike PC, Steptoe A. Behavioral and emotional triggers of acute coronary syndromes: a systematic review and critique. *Psychosom Med*. (2005) 67(2):179–86. doi: 10.1097/01.psy.0000155663.93160.d2
- Lampert R, Jain D, Burg MM, Batsford WP, McPherson CA. Destabilizing effects of mental stress on ventricular arrhythmias in patients with implantable cardioverter-defibrillators. *Circulation*. (2000) 101(2):158–64. doi: 10.1161/01.CIR.101.2.158
- Sun JL, Boyle SH, Samad Z, Babyak MA, Wilson JL, Kuhn C, et al. Mental stress-induced left ventricular dysfunction and adverse outcome in ischemic heart disease patients. *Eur J Prev Cardiol*. (2017) 24(6):591–9. doi: 10.1177/2047487316686435
- Sörös P, Hachinski V. Cardiovascular and neurological causes of sudden death after ischaemic stroke. *Lancet Neurol*. (2012) 11(2):179–88. doi: 10.1016/S1474-4422(11)70291-5
- Méloux A, Béjot Y, Rochette L, Cottin Y, Vergely C. Brain–heart interactions during ischemic processes: clinical and experimental evidences. *Stroke*. (2020) 51(2):679–86. doi: 10.1161/STROKEAHA.119.027732
- Gelosa P, Castiglioni L, Rzemieniec J, Muluhie M, Camera M, Sironi L. Cerebral derailment after myocardial infarct: mechanisms and effects of the signaling from the ischemic heart to brain. *J Mol Med*. (2022) 100(1):23–41. doi: 10.1007/s00109-021-02154-3
- Rusanen M, Kivipelto M, Levälähti E, Laatikainen T, Tuomilehto J, Soininen H, et al. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. *J Alzheimer's Dis*. (2014) 42:183–91. doi: 10.3233/JAD-132363
- Justin BN, Turek M, Hakim AM. Heart disease as a risk factor for dementia. *Clin Epidemiol*. (2013) 5:135–45. doi: 10.2147/CLEP.S30621
- Deckers K, Schievink SHJ, Rodriguez MMF, van Oostenbrugge RJ, van Boxtel MPJ, Verhey FRJ, et al. Coronary heart disease and risk for cognitive impairment or dementia: systematic review and meta-analysis. *PLoS One*. (2017) 12(9):e0184244. doi: 10.1371/journal.pone.0184244
- Doehner W, Ural D, Haeusler KG, Čelutkienė J, Bestetti R, Cavusoglu Y, et al. Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy. A position paper from the Study Group on Heart and Brain

Interaction of the Heart Failure Association. *Eur J Heart Fail.* (2018) 20(2):199–215. doi: 10.1002/ehf.1100

16. Scheitz JF, Nolte CH, Doeber W, Hachinski V, Endres M. Stroke–heart syndrome: clinical presentation and underlying mechanisms. *Lancet Neurol.* (2018) 17(12):1109–20. doi: 10.1016/S1474-4422(18)30336-3

17. Valenza G, Sclocco R, Duggento A, Passamonti L, Napadow V, Barbieri R, et al. The central autonomic network at rest: uncovering functional MRI correlates of time-varying autonomic outflow. *NeuroImage.* (2019) 197:383–90. doi: 10.1016/j.neuroimage.2019.04.075

18. Sklerov M, Dayan E, Browner N. Functional neuroimaging of the central autonomic network: recent developments and clinical implications. *Clin Auton Res.* (2019) 29(6):555–66. doi: 10.1007/s10286-018-0577-0

19. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin Proc.* (1993) 68(10):988–1001. doi: 10.1016/S0025-6196(12)62272-1

20. Mohanta SK, Yin C, Weber C, Godinho-Silva C, Veiga-Fernandes H, Xu QJ, et al. Cardiovascular brain circuits. *Circ Res.* (2023) 132(11):1546–65. doi: 10.1161/CIRCRESAHA.123.322791

21. Haque S, Dutta P. The heart-brain axis in the context of cardiovascular disease. *Physiology.* (2026) 41(2):147–58. doi: 10.1152/physiol.00020.2025

22. Oppenheimer S, Cechetto D. The insular cortex and the regulation of cardiac function. *Compr Physiol.* (2011) 6(2):1081–133. doi: 10.1002/cphy.c140076

23. Sposato LA, Fridman S, Whitehead SN, Lopes RD. Linking stroke-induced heart injury and neurogenic atrial fibrillation: a hypothesis to be proven. *J Electrocardiol.* (2018) 51(3):430–2. doi: 10.1016/j.jelectrocard.2018.02.006

24. Hugo D C, Neil A H. Visceral influences on brain and behavior. *Neuron.* (2013) 77(4):624–38. doi: 10.1016/j.neuron.2013.02.008

25. Marafioti V, Turri G, Carbone V, Monaco S. Association of prolonged QTc interval with takotsubo cardiomyopathy: a neurocardiac syndrome inside the mystery of the insula of reil. *Clin Cardiol.* (2018) 41(4):551–5. doi: 10.1002/clc.22910

26. Chouchou F, Mauguère F, Vallayer O, Catenio H, Isnard J, Montavont A, et al. How the insula speaks to the heart: cardiac responses to insular stimulation in humans. *Hum Brain Mapp.* (2019) 40(9):2611–22. doi: 10.1002/hbm.24548

27. Palma J-A, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. *Neurology.* (2014) 83(3):261–71. doi: 10.1212/WNL.0000000000000605

28. LeDoux J. The emotional brain, fear, and the amygdala. *Cell Mol Neurobiol.* (2003) 23:727–38. doi: 10.1023/A:1025048802629

29. Gianaros PJ, Sheu LK. A review of neuroimaging studies of stressor-evoked blood pressure reactivity: emerging evidence for a brain-body pathway to coronary heart disease risk. *NeuroImage.* (2009) 47(3):922–36. doi: 10.1016/j.neuroimage.2009.04.073

30. Muscatell KA, Dedovic K, Slavich GM, Jarcho MR, Breen EC, Bower JE, et al. Greater amygdala activity and dorsomedial prefrontal-amygdala coupling are associated with enhanced inflammatory responses to stress. *Brain Behav Immun.* (2015) 43:46–53. doi: 10.1016/j.bbi.2014.06.201

31. Mikail N, Sager DF, Gebert P, Haider A, Todorov A, Bengs S, et al. Imaging of the brain–heart axis: prognostic value in a European setting. *Eur Heart J.* (2024) 45(18):1613–30. doi: 10.1093/eurheartj/ehae162

32. Tawakol A, Ishai A, Takx RAP, Figueroa AL, Ali A, Kaiser Y, et al. Relation between resting amygdala activity and cardiovascular events: a longitudinal and cohort study. *Lancet.* (2017) 389(10071):834–45. doi: 10.1016/S0140-6736(16)31714-7

33. Herman JP, Ulrich-Lai YM. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci.* (2009) 10(6):397–409. doi: 10.1038/nrn2647

34. MacLeod C, Hadoke PWF, Nixon M. Glucocorticoids: fuelling the fire of atherosclerosis or therapeutic extinguishers? *Int J Mol Sci.* (2021) 22(14):7622. doi: 10.3390/ijms22147622

35. Chen X, Gu J, Zhang X. Brain-heart axis and the inflammatory response: connecting stroke and cardiac dysfunction. *Cardiology.* (2024) 149:369–82. doi: 10.1159/000538409

36. Bellavance M-A, Rivest S. The HPA - immune axis and the immunomodulatory actions of glucocorticoids in the brain. *Front Immunol.* (2014) 5:136. doi: 10.3389/fimmu.2014.00136

37. van den Akker ELT, Koper JW, van Rossum EFC, Dekker MJ, Russcher H, de Jong FH, et al. Glucocorticoid receptor gene and risk of cardiovascular disease. *Arch Intern Med.* (2008) 168(1):33–9. doi: 10.1001/archinternmed.2007.41

38. Shine JM, Lewis LD, Garrett DD, Hwang K. The impact of the human thalamus on brain-wide information processing. *Nat Rev Neurosci.* (2023) 24(7):416–30. doi: 10.1038/s41583-023-00701-0

39. Carrillo-Franco L, González-García M, Morales-Luque C, Dawid-Milner MS, López-González MV. Hypothalamic regulation of cardiorespiratory functions: insights into the dorsomedial and perifornical pathways. *Biology (Basel).* (2024) 13(11):933. doi: 10.3390/biology13110933

40. Pereira VH, Cerqueira JJ, Palha JA, Sousa N. Stressed brain, diseased heart: a review on the pathophysiological mechanisms of neurocardiology. *Int J Cardiol.* (2013) 166(1):30–7. doi: 10.1016/j.ijcard.2012.03.165

41. Ruiz Vargas E, Sörös P, Shoemaker JK, Hachinski V. Human cerebral circuitry related to cardiac control: a neuroimaging meta-analysis. *Ann Neurol.* (2016) 79(5):709–16. doi: 10.1002/ana.24642

42. Ziegler KA, Engelhardt S, Carnevale D, McAlpine CS, Guzik TJ, Dimmeler S, et al. Neural mechanisms in cardiovascular health and disease. *Circ Res.* (2025) 136(11):1233–61. doi: 10.1161/CIRCRESAHA.125.325580

43. Carnevale D, Lembo G. Neuroimmune interactions in cardiovascular diseases. *Cardiovasc Res.* (2021) 117(2):402–10. doi: 10.1093/cvr/cvaa151

44. Scanzano A, Cosentino M. Adrenergic regulation of innate immunity: a review. *Front Pharmacol.* (2015) 6:171. doi: 10.3389/fphar.2015.00171

45. Ardell JL, Armour JA, Terjung R. Neurocardiology: structure-based function. *Compr Physiol.* (2016) 6(4):1635–53. doi: 10.1002/cphy.c150046

46. Wake E, Brack K. Characterization of the intrinsic cardiac nervous system. *Auton Neurosci.* (2016) 199:3–16. doi: 10.1016/j.autneu.2016.08.006

47. Armour JA, Murphy DA, Yuan BX, MacDonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anat Rec.* (1997) 247(2):289–98.

48. Kapa S, Venkatachalam KL, Asirvatham SJ. The autonomic nervous system in cardiac electrophysiology: an elegant interaction and emerging concepts. *Cardiol Rev.* (2010) 18(6):275–84. doi: 10.1097/CRD.0b013e3181ebb152

49. Taggart P, Boyett MR, Logantha SJRJ, Lambiase PD. Anger, emotion and mental stress: from brain to heart. *Front Physiol.* (2011) 2:67. doi: 10.3389/fphys.2011.00067

50. Rackley J, Nudy M, Gonzalez MD, Naccarelli G, Maheshwari A. Pulmonary vein isolation with adjunctive left atrial ganglionic plexus ablation for treatment of atrial fibrillation: a meta-analysis of randomized controlled trials. *J Interv Card Electrophysiol.* (2023) 66(2):333–42. doi: 10.1007/s10840-022-01212-1

51. Hainsworth R. Cardiovascular control from cardiac and pulmonary vascular receptors. *Exp Physiol.* (2014) 99(2):312–9. doi: 10.1113/expphysiol.2013.072637

52. Mohanta SK, Peng L, Li Y, Lu S, Sun T, Carnevale L, et al. Neuroimmune cardiovascular interfaces control atherosclerosis. *Nature.* (2022) 605(7908):152–9. doi: 10.1038/s41586-022-04673-6

53. Vergallo R, Liuzzo G. The role of the neuroimmune axis as a new frontier in atherosclerosis. *Eur Heart J.* (2022) 43:2829–30. doi: 10.1093/eurheartj/ehac315

54. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron.* (2017) 96(1):17–42. doi: 10.1016/j.neuron.2017.07.030

55. Iadecola C, Buckwalter MS, Anrather J. Immune responses to stroke: mechanisms, modulation, and therapeutic potential. *J Clin Invest.* (2020) 130(6):2777–88. doi: 10.1172/JCI135530

56. Ziqing Z, Yunpeng L, Yiqi L, Yang W. Friends or foes: the mononuclear phagocyte system in ischemic stroke. *Brain Pathol.* (2023) 33(2):e13151. doi: 10.1111/bpa.13151

57. Maida CD, Norrito RL, Daidone M, Tuttolomondo A, Pinto A. Neuroinflammatory mechanisms in ischemic stroke: focus on cardioembolic stroke, background, and therapeutic approaches. *Int J Mol Sci.* (2020) 21(18):6454. doi: 10.3390/ijms21186454

58. Wang L, Ma L, Ren C, Zhao W, Ji X, Liu Z, et al. Stroke–heart syndrome: current progress and future outlook. *J Neurol.* (2024) 271(8):4813–25. doi: 10.1007/s00415-024-12480-4

59. Xue S, Zhou X, Yang Z-H, Si X-K, Sun X. Stroke-induced damage on the blood–brain barrier. *Front Neurol.* (2023) 14:1248970. doi: 10.3389/fneur.2023.1248970

60. Scheitz JF, Sposato LA, Schulz-Menger J, Nolte CH, Backs J, Endres M. Stroke–heart syndrome: recent advances and challenges. *J Am Heart Assoc.* (2022) 11(17):e026528. doi: 10.1161/JAHA.122.026528

61. Wang M, Peng Y. Advances in brain–heart syndrome: attention to cardiac complications after ischemic stroke. *Front Mol Neurosci.* (2022) 15:1053478. doi: 10.3389/fnmol.2022.1053478

62. Jayaraj RL, Azimullah S, Beiram R, Jalal FY, Rosenberg GA. Neuroinflammation: friend and foe for ischemic stroke. *J Neuroinflammation.* (2019) 16(1):142. doi: 10.1186/s12974-019-1516-2

63. Du Y, Demillard LJ, Ren J. Catecholamine-induced cardiotoxicity: a critical element in the pathophysiology of stroke-induced heart injury. *Life Sci.* (2021) 287:120106. doi: 10.1016/j.lfs.2021.120106

64. Bieber M, Werner RA, Tanai E, Hofmann U, Higuchi T, Schuh K, et al. Stroke-induced chronic systolic dysfunction driven by sympathetic overactivity. *Ann Neurol.* (2017) 82(5):729–43. doi: 10.1002/ana.25073

65. Sposato LA, Hilz MJ, Asperg S, Murthy SB, Bahit MC, Hsieh C-Y, et al. Post-Stroke cardiovascular complications and neurogenic cardiac injury: JACC state-of-the-art review. *J Am Coll Cardiol.* (2020) 76(23):2768–85. doi: 10.1016/j.jacc.2020.10.009

66. Sposato LA, Riccio PM, Hachinski V. Poststroke atrial fibrillation: cause or consequence? Critical review of current views. *Neurology.* (2014) 82(13):1180–6. doi: 10.1212/WNL.0000000000000265

67. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev.* (2000) 52(4):595–638. doi: 10.1016/S0031-6997(24)01470-4
68. Winbo A, Paterson DJ. The brain-heart connection in sympathetically triggered inherited arrhythmia syndromes. *Heart Lung Circ.* (2020) 29(4):529–37. doi: 10.1016/j.hlc.2019.11.002
69. Kenney MJ, Ganta CK. Autonomic nervous system and immune system interactions. *Compr Physiol.* (2014) 4(3):1177–200. doi: 10.1002/cphy.c130051
70. Sundman E, Olofsson PS. Neural control of the immune system. *Adv Physiol Educ.* (2014) 38(2):135–9. doi: 10.1152/advan.00094.2013
71. Simats A, Sager HB, Liesz A. Heart–brain axis in health and disease: role of innate and adaptive immunity. *Cardiovasc Res.* (2025) 120(18):2325–35. doi: 10.1093/cvr/cvae185
72. Swirski FK, Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. *Science.* (2013) 339(6116):161–6. doi: 10.1126/science.1230719
73. Swirski FK, Nahrendorf M. Cardioimmunology: the immune system in cardiac homeostasis and disease. *Nat Rev Immunol.* (2018) 18(12):733–44. doi: 10.1038/s41577-018-0065-8
74. Libby P, Nahrendorf M, Swirski FK. Leukocytes link local and systemic inflammation in ischemic cardiovascular disease: an expanded “cardiovascular Continuum”. *J Am Coll Cardiol.* (2016) 67(9):1091–103. doi: 10.1016/j.jacc.2015.12.048
75. Aksu T, Gopinathannair R, Gupta D, Pauza DH. Intrinsic cardiac autonomic nervous system: what do clinical electrophysiologists need to know about the “heart brain”? *J Cardiovasc Electrophysiol.* (2021) 32(6):1737–47. doi: 10.1111/jce.15058
76. Tracey KJ. The inflammatory reflex. *Nature.* (2002) 420(6917):853–9. doi: 10.1038/nature01321
77. Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex—linking immunity and metabolism. *Nat Rev Endocrinol.* (2012) 8(12):743–54. doi: 10.1038/nrendo.2012.189
78. Olshansky B. Vagus nerve modulation of inflammation: cardiovascular implications. *Trends Cardiovasc Med.* (2016) 26(1):1–11. doi: 10.1016/j.tcm.2015.03.016
79. Nicolás-Ávila JA, Hidalgo A, Ballesteros I. Specialized functions of resident macrophages in brain and heart. *J Leukocyte Biol.* (2018) 104(4):743–56. doi: 10.1002/JLB.6MR0118-041R
80. Zou L, Han R. Inflammatory response and immune regulation in brain-heart interaction after stroke. *Cardiovasc Ther.* (2022) 2022:2406122–7. doi: 10.1155/2022/2406122
81. Wang H, Zhang S, Xie L, Zhong Z, Yan F. Neuroinflammation and peripheral immunity: focus on ischemic stroke. *Int Immunopharmacol.* (2023) 120:110332. doi: 10.1016/j.intimp.2023.110332
82. Yan T, Chen Z, Chopp M, Venkat P, Zacharek A, Shen Y, et al. Inflammatory responses mediate brain–heart interaction after ischemic stroke in adult mice. *J Cereb Blood Flow Metab.* (2020) 40(6):1213–29. doi: 10.1177/0271678X18813317
83. Ma F, Li Y, Jia L, Han Y, Cheng J, Qi Y. Macrophage-Stimulated cardiac fibroblast production of IL-6 is essential for TGF β /smad activation and cardiac fibrosis induced by angiotensin II. *PLoS One.* (2012) 7(5):e35144. doi: 10.1371/journal.pone.0035144
84. Travers JG, Kamal FA, Robbins J, Yutzey KE, Blaxall BC. Cardiac fibrosis: the fibroblast awakens. *Circ Res.* (2016) 118(6):1021–40. doi: 10.1161/CIRCRESAHA.115.306565
85. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med.* (2013) 368(21):2004–13. doi: 10.1056/NEJMra1216063
86. Hegemann N, Barth L, Döring Y, Voigt N, Grune J. Implications for neutrophils in cardiac arrhythmias. *American Am J Physiol Heart Circ Physiol.* (2024) 326(3):H441–58. doi: 10.1152/ajpheart.00590.2023
87. Lappegård KT, Hovland A, Pop GAM, Mollnes TE. Atrial fibrillation: inflammation in disguise? *Scand J Immunol.* (2013) 78(2):112–9. doi: 10.1111/sji.12061
88. Hu Y-F, Chen Y-J, Lin Y-J, Chen S-A. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol.* (2015) 12(4):230–43. doi: 10.1038/nrcardio.2015.2
89. Grune J, Yamazoe M, Nahrendorf M. Electroimmunology and cardiac arrhythmia. *Nat Rev Cardiol.* (2021) 18(8):547–64. doi: 10.1038/s41569-021-00520-9
90. Hulsmans M, Clauss S, Xiao L, Aguirre AD, King KR, Hanley A, et al. Macrophages facilitate electrical conduction in the heart. *Cell.* (2017) 169(3):510–22. doi: 10.1016/j.cell.2017.03.050
91. Lazzarini PE, Laghi-Pasini F, Boutjdir M, Capocchi PL. Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. *Nat Rev Immunol.* (2019) 19(1):63–4. doi: 10.1038/s41577-018-0098-z
92. Maguy A, Mahendran Y, Tardif J-C, Busseuil D, Li J. Autoimmune atrial fibrillation. *Circulation.* (2023) 148(6):487–98. doi: 10.1161/CIRCULATIONAHA.122.062776
93. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med.* (2005) 352(16):1685–95. doi: 10.1056/NEJMra043430
94. Chen Z, Venkat P, Seyfried D, Chopp M, Yan T, Chen J. Brain–heart interaction: cardiac complications after stroke. *Circ Res.* (2017) 121(4):451–68. doi: 10.1161/CIRCRESAHA.117.311170
95. Zhang C. The role of inflammatory cytokines in endothelial dysfunction. *Basic Res Cardiol.* (2008) 103(5):398–406. doi: 10.1007/s00395-008-0733-0
96. Long G, Wang F, Li H, Yin Z, Sandip C, Lou Y, et al. Circulating miR-30a, miR-126 and let-7b as biomarker for ischemic stroke in humans. *BMC Neurol.* (2013) 13(1):178. doi: 10.1186/1471-2377-13-178
97. Prame Kumar K, McKay LD, Nguyen H, Kaur J, Wilson JL, Suthya AR, et al. Sympathetic-mediated intestinal cell death contributes to gut barrier impairment after stroke. *Transl Stroke Res.* (2023) 16:280–98. doi: 10.1007/s12975-023-01211-y
98. Yin J, Liao S-X, He Y, Wang S, Xia G, Liu F, et al. Dysbiosis of gut Microbiota with reduced trimethylamine-N-oxide level in patients with large-artery atherosclerotic stroke or transient ischemic attack. *J Am Heart Assoc.* (2015) 4(11):e002699. doi: 10.1161/JAHA.115.002699
99. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol.* (2015) 28(2):203–9.
100. Naghipour S, Cox AJ, Peart JN, Du Toit EF, Headrick JP. Trimethylamine N-oxide: heart of the microbiota–CVD nexus? *Nutr Res Rev.* (2021) 34(1):125–46. doi: 10.1017/S0954422420000177
101. Yang S, Li X, Yang F, Zhao R, Pan X, Liang J, et al. Gut Microbiota-dependent marker TMAO in promoting cardiovascular disease: inflammation mechanism, clinical prognosis, and potential as a therapeutic target. *Front Pharmacol.* (2019) 10:1360. doi: 10.3389/fphar.2019.01360
102. Huang Q, Xia J. Influence of the gut microbiome on inflammatory and immune response after stroke. *Neurol Sci.* (2021) 42(12):4937–51. doi: 10.1007/s10072-021-05603-6
103. Prosser J, Macgregor L, Lees KR, Diener H-C, Hacke W, Davis S. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke.* (2007) 38(8):2295–302. doi: 10.1161/STROKEAHA.106.471813
104. Tahsili-Fahadan P, Geocadin RG. Heart–brain axis: effects of neurologic injury on cardiovascular function. *Circ Res.* (2017) 120(3):559–72. doi: 10.1161/CIRCRESAHA.116.308446
105. Buckley BJR, Harrison SL, Lane DA, Hill A, Lip GYH. Stroke-heart syndrome: mechanisms, risk factors, and adverse cardiovascular events. *Eur J Prev Cardiol.* (2024) 31:e23–6. doi: 10.1093/eurjpc/zwad211
106. Stengl H, Poller WC, Di Vecce D, Templin C, Endres M, Nolte CH, et al. How the brain impacts the heart: lessons from ischaemic stroke and other neurological disorders. *Heart.* (2025) 111:99–108. doi: 10.1136/heartjnl-2024-324173
107. Sposato LA, Hilz MJ, Aspberg S, Murthy SB, Bahit MC, Hsieh C-Y, et al. Post-stroke cardiovascular complications and neurogenic cardiac injury JACC state-of-the-art review. *J Am Coll Cardiol.* (2020) 76(23):2768–85. doi: 10.1016/j.jacc.2020.10.009
108. Kim W-JMD, Nah H-WMD, Kim D-HMDP, Cha J-KMDP. Association between left ventricular dysfunction and functional outcomes at three months in acute ischemic stroke. *J Stroke Cerebrovasc Dis.* (2016) 25(9):2247–52. doi: 10.1016/j.jstrokecerebrovasdis.2016.05.004
109. Faiz KW, Thommessen B, Einvik G, Brekke PH, Omeland T, Rønning OM. Determinants of high sensitivity cardiac troponin T elevation in acute ischemic stroke. *BMC Neurol.* (2014) 14(1):96. doi: 10.1186/1471-2377-14-96
110. Gunnoo T, Hasan N, Khan MS, Slark J, Bentley P, Sharma P. Quantifying the risk of heart disease following acute ischaemic stroke: a meta-analysis of over 50000 participants. *BMJ Open.* (2016) 6(1):e009535. doi: 10.1136/bmjopen-2015-009535
111. Amarenco P, Lavallee PC, Ratani S, Ducrocq G, Juliard JM, Feldman L, et al. Prevalence of coronary atherosclerosis in patients with cerebral infarction. *Stroke.* (2011) 42(1):22–9. doi: 10.1161/STROKEAHA.110.584086
112. Krause T, Werner K, Fiebach JB, Villringer K, Piper SK, Haeusler KG, et al. Stroke in right dorsal anterior insular cortex is related to myocardial injury. *Ann Neurol.* (2017) 81(4):502–11. doi: 10.1002/ana.24906
113. Hermanns N, Wroblewski V, Bascuñana P, Wolf B, Polyak A, Ross TL, et al. Molecular imaging of the brain–heart axis provides insights into cardiac dysfunction after cerebral ischemia. *Basic Res Cardiol.* (2022) 117(1):52. doi: 10.1007/s00395-022-00961-4
114. von Rennenberg R, Siegerink B, Ganeshan R, Villringer K, Doehner W, Audebert HJ, et al. High-sensitivity cardiac troponin T and severity of cerebral white matter lesions in patients with acute ischemic stroke. *J Neurol.* (2019) 266(1):37–45. doi: 10.1007/s00415-018-9085-3
115. Ng TP, Wong C, Leong ELE, Chan MY-Y, Yeo LL, Yeo T-C, et al. Simultaneous cardio-cerebral infarction: a meta-analysis. *QJM.* (2022) 115(6):374–80. doi: 10.1093/qjmed/hcab158
116. Mehta S, Kakouros N, Mir T, Loree S, Qureshi W. Prevalence and outcomes of patients with acute ischemic stroke with concomitant ST-segment-elevation

- myocardial infarction (results from national inpatient sample 2016–2019). *Stroke*. (2024) 55(5):1245–53. doi: 10.1161/STROKEAHA.123.044550
117. Ho JS-Y, Zheng H, Tan BY-Q, Foo D, Foo L-L, Lim PZ-Y, et al. Incidence and outcomes of cardiocerebral infarction: a cohort study of 2 national population-based registries. *Stroke*. (2024) 55(9):2221–30. doi: 10.1161/STROKEAHA.123.044530
118. Scheitz JF, Stengl H, Nolte CH, Landmesser U, Endres M. Neurological update: use of cardiac troponin in patients with stroke. *J Neurol*. (2021) 268(6):2284–92. doi: 10.1007/s00415-020-10349-w
119. Stengl H, Ganeshan R, Hellwig S, Klammer MG, von Rennenberg R, Böhme S, et al. Frequency, associated variables, and outcomes of acute myocardial injury according to the fourth universal definition of myocardial infarction in patients with acute ischemic stroke. *Eur Stroke J*. (2022) 7(4):413–20. doi: 10.1177/23969873221120159
120. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J*. (2023) 44(38):3720–826. doi: 10.1093/eurheartj/ehad191
121. Nolte CH, von Rennenberg R, Litmeier S, Leistner DM, Szabo K, Baumann S, et al. Type 1 myocardial infarction in patients with acute ischemic stroke. *JAMA Neurol*. (2024) 81(7):703. doi: 10.1001/jamaneurol.2024.1552
122. Mochmann H-C, Scheitz JF, Petzold GC, Haeusler KG, Audebert HJ, Laufs U, et al. Coronary angiographic findings in acute ischemic stroke patients with elevated cardiac troponin: the troponin elevation in acute ischemic stroke (TRELAS) study. *Circulation*. (2016) 133(13):1264–71. doi: 10.1161/CIRCULATIONAHA.115.018547
123. Scheitz JF, Nolte CH, Laufs U, Endres M. Application and interpretation of high-sensitivity cardiac troponin assays in patients with acute ischemic stroke. *Stroke*. (2015) 46(4):1132–40. doi: 10.1161/STROKEAHA.114.007858
124. Scheitz JF, Mochmann H-C, Erdur H, Tütüncü S, Haeusler KG, Grittner U, et al. Prognostic relevance of cardiac troponin T levels and their dynamic changes measured with a high-sensitivity assay in acute ischaemic stroke: analyses from the TRELAS cohort. *Int J Cardiol*. (2014) 177(3):886–93. doi: 10.1016/j.ijcard.2014.10.036
125. Mahmood A, Ang SP, Qadeer YK, Hassan Virk HU, Tangsrivimol JA, Riaz I, et al. Incidence and outcomes of hospitalized acute ischemic stroke patients with subsequent ST-segment-elevation myocardial infarction. *Front Cardiovasc Med*. (2025) 12:1630805. doi: 10.3389/fcvm.2025.1630805
126. Carlsson A, Irewall A-L, Graipe A, Ulvenstam A, Moee T, Ögren J. Long-term risk of major adverse cardiovascular events following ischemic stroke or TIA. *Sci Rep*. (2023) 13(1):8333. doi: 10.1038/s41598-023-35601-x
127. Rost NS, Biffi A, Cloonan L, Chorba J, Kelly P, Greer D, et al. Brain natriuretic peptide predicts functional outcome in ischemic stroke. *Stroke*. (2012) 43(2):441–5. doi: 10.1161/STROKEAHA.111.629212
128. Shiroto H, Hagii J. Biomarkers for the detection of covert atrial fibrillation after ischemic stroke: NT-proBNP or BNP? *J Stroke Cerebrovasc Dis*. (2025) 34(6):108239. doi: 10.1016/j.jstrokecerebrovasdis.2025.108239
129. Jensen JK, Mickley H, Bak S, Korsholm L, Kristensen SR. Serial measurements of N-terminal pro-brain natriuretic peptide after acute ischemic stroke. *Cerebrovasc Dis*. (2006) 22(5–6):439–44. doi: 10.1159/000094997
130. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2019) 50(12):e344–418. doi: 10.1161/STR.0000000000000211
131. Akinseye OA, Shahreyar M, Heckle MR, Khouzam RN. Simultaneous acute cardio-cerebral infarction: is there a consensus for management? *Ann Transl Med*. (2017) 6(1):7. doi: 10.21037/atm.2017.11.06
132. Siedler G, Sommer K, Macha K, Marsch A, Breuer L, Stoll S, et al. Heart failure in ischemic stroke: relevance for acute care and outcome. *Stroke*. (2019) 50(11):3051–6. doi: 10.1161/STROKEAHA.119.026139
133. Min J, Young G, Umar A, Kampfschulte A, Ahrar A, Miller M, et al. Neurogenic cardiac outcome in patients after acute ischemic stroke: the brain and heart connection. *J Stroke Cerebrovasc Dis*. (2022) 31(12):106859. doi: 10.1016/j.jstrokecerebrovasdis.2022.106859
134. Heuschmann PU, Montellano FA, Ungethüm K, Rücker V, Wiedmann S, Mackenrodt D, et al. Prevalence and determinants of systolic and diastolic cardiac dysfunction and heart failure in acute ischemic stroke patients: the SICFAIL study. *ESC Heart Fail*. (2021) 8(2):1117–29. doi: 10.1002/ehf2.13145
135. Liori S, Arfaras-Melainis A, Bistola V, Parissis J. Heart and brain interactions in heart failure: pathophysiological mechanisms and clinical perspectives. *Heart Fail Rev*. (2025) 30:791–800. doi: 10.1007/s10741-025-10505-2
136. Chung D, Hong S-W, Lee J, Bang OY, Kim G, Seo W, et al. Topographical association between left ventricular strain and brain lesions in patients with acute ischemic stroke and normal cardiac function. *J Am Heart Assoc*. (2023) 12(15):e029604. doi: 10.1161/JAHA.123.029604
137. Kallmünzer B, Breuer L, Kahl N, Bobinger T, Raaz-Schrauder D, Huttner HB, et al. Serious cardiac arrhythmias after stroke: incidence, time course, and predictors—a systematic, prospective analysis. *Stroke*. (2012) 43(11):2892–7. doi: 10.1161/STROKEAHA.112.664318
138. Cerasuolo JO, Cipriano LE, Sposato LA. The complexity of atrial fibrillation newly diagnosed after ischemic stroke and transient ischemic attack: advances and uncertainties. *Curr Opin Neurol*. (2017) 30(1):28–37. doi: 10.1097/WCO.0000000000000410
139. Sposato LA, Chaturvedi S, Hsieh C-Y, Morillo CA, Kamel H. Atrial fibrillation detected after stroke and transient ischemic attack: a novel clinical concept challenging current views. *Stroke*. (2022) 53(3):e94–103. doi: 10.1161/STROKEAHA.121.034777
140. Scheitz JF, Erdur H, Haeusler KG, Audebert HJ, Roser M, Laufs U, et al. Insular Cortex lesions, cardiac troponin, and detection of previously unknown atrial fibrillation in acute ischemic stroke: insights from the troponin elevation in acute ischemic stroke study. *Stroke*. (2015) 46(5):1196–201. doi: 10.1161/STROKEAHA.115.008681
141. Tokunaga K, Toyoda K, Kimura S, Minematsu K, Yasaka M, Okada Y, et al. Association of the timing of atrial fibrillation detection and insular involvement with the risk of embolic events after acute ischemic stroke. *Ann Neurol*. (2024) 95(2):338–46. doi: 10.1002/ana.26815
142. Sposato LA, Field TS, Schnabel RB, Wachter R, Andrade JG, Hill MD. Towards a new classification of atrial fibrillation detected after a stroke or a transient ischaemic attack. *Lancet Neurol*. (2024) 23(1):110–22. doi: 10.1016/S1474-4422(23)00326-5
143. Induruwa I, Bhakta S, Herlekar R, Sur Roy A, Hajiev S, Warburton EA, et al. Recurrent vascular events and mortality outcomes in patients with known atrial fibrillation, compared to atrial fibrillation detected early after stroke. *Eur Stroke J*. (2025) 10(1):145–52. doi: 10.1177/23969873241272631
144. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM, et al. 2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): developed by the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC), with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Endorsed by the European Stroke Organisation (ESO). *Eur Heart J*. (2024) 45(36):3314–414. doi: 10.1093/eurheartj/ehae176
145. Olma MC, Tütüncü S, Fiessler C, Kunze C, Krämer M, Steindorf-Sabath L, et al. In-hospital ECG findings, changes in medical management, and cardiovascular outcomes in patients with acute stroke or transient ischemic attack. *J Am Heart Assoc*. (2023) 12(2):e027149. doi: 10.1161/JAHA.122.027149
146. Jensen JK, Bak S, Flemming Høiland-Carlsen P, Mickley H. Prevalence of electrocardiographic ST-T changes during acute ischemic stroke in patients without known ischemic heart disease. *Int J Cardiol*. (2008) 128(1):137–8. doi: 10.1016/j.ijcard.2007.05.055
147. Khechinashvili G, Asplund K. Electrocardiographic changes in patients with acute stroke: a systematic review. *Cerebrovasc Dis*. (2002) 14(2):67–76. doi: 10.1159/000064733
148. Dogan A, Tunc E, Ozturk M, Kerman M, Akhan G. Electrocardiographic changes in patients with ischaemic stroke and their prognostic importance: electrocardiographic changes in ischaemic stroke. *Int J Clin Pract*. (2004) 58(5):436–40. doi: 10.1111/j.1368-5031.2004.00010.x
149. Raggi P, Quyyumi AA, Henein MY, Vaccarino V. Psychosocial stress and cardiovascular disease. *Am J Prev Cardiol*. (2025) 22:100968. doi: 10.1016/j.ajpc.2025.100968
150. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet*. (2007) 370(9592):1089–100. doi: 10.1016/S0140-6736(07)61305-1
151. Gyoneva S, Traynelis SF. Norepinephrine modulates the motility of resting and activated microglia via different adrenergic receptors. *J Biol Chem*. (2013) 288(21):15291–302. doi: 10.1074/jbc.M113.458901
152. Jiao Z, Kakoulides SV, Moscona J, Whittier J, Srivastav S, Delafontaine P, et al. Effect of hurricane Katrina on incidence of acute myocardial infarction in New Orleans three years after the storm. *Am J Cardiol*. (2012) 109(4):502–5. doi: 10.1016/j.amjcard.2011.09.045
153. Wilbert-Lampen U, Leistner D, Greven S, Pohl T, Sper S, Völcker C, et al. Cardiovascular events during World Cup soccer. *N Engl J Med*. (2008) 358(5):475–83. doi: 10.1056/NEJMoa0707427
154. Kivimäki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol*. (2018) 15(4):215–29. doi: 10.1038/nrcardio.2017.189
155. Bodis J, Boncz I, Kriszbacher I. Permanent stress may be the trigger of an acute myocardial infarction on the first work-day of the week. *Int J Cardiol*. (2010) 144(3):423–5. doi: 10.1016/j.ijcard.2009.03.051
156. Mohammad MA, Karlsson S, Haddad J, Cederberg B, Jernberg T, Lindahl B, et al. Christmas, national holidays, sport events, and time factors as triggers of acute myocardial infarction: SWEDEHEART observational study 1998–2013. *Br Med J*. (2018) 363:k4811. doi: 10.1136/bmj.k4811
157. Carney RM, Freedland KE. Depression and coronary heart disease. *Nat Rev Cardiol*. (2017) 14(3):145–55. doi: 10.1038/nrcardio.2016.181

158. Allgulander C. Anxiety as a risk factor in cardiovascular disease. *Curr Opin Psychiatry*. (2016) 29(1):13–7. doi: 10.1097/YCO.0000000000000217
159. Liu M, Liu J, Zhang L, Xu W, Wei W, Ge Y, et al. An evidence of brain-heart disorder: mental stress-induced myocardial ischemia regulated by inflammatory cytokines. *Neurol Res*. (2020) 42(8):670–5. doi: 10.1080/01616412.2020.1783879
160. Rohleder N. Stimulation of systemic low-grade inflammation by psychosocial stress. *Psychosom Med*. (2014) 76(3):181–9. doi: 10.1097/PSY.0000000000000049
161. Strike PC, Steptoe A. Systematic review of mental stress-induced myocardial ischemia. *Eur Heart J*. (2003) 24(8):690–703. doi: 10.1016/s0195-668x(02)00615-2
162. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, et al. An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J*. (2020) 41(37):3504–20. doi: 10.1093/eurheartj/ehaa503
163. Parwani P, Kang N, Safaeipour M, Mamas MA, Wei J, Gulati M, et al. Contemporary diagnosis and management of patients with MINOCA. *Curr Cardiol Rep*. (2023) 25(6):561–70. doi: 10.1007/s11886-023-01874-x
164. Arri SS, Ryan M, Redwood SR, Marber MS. Mental stress-induced myocardial ischemia. *Heart*. (2016) 102(6):472–80. doi: 10.1136/heartjnl-2014-307306
165. Taggart P, Critchley H, Lambiase PD. Heart-brain interactions in cardiac arrhythmia. *Heart*. (2011) 97(9):698–708. doi: 10.1136/hrt.2010.209304
166. Vaccarino V, Almuwaqqat Z, Kim JH, Hammadah M, Shah AJ, Ko Y-A, et al. Association of mental stress-induced myocardial ischemia with cardiovascular events in patients with coronary heart disease. *JAMA*. (2021) 326(18):1818–28. doi: 10.1001/jama.2021.17649
167. Ramadan R, Sheps D, Esteves F, Maziar Zafari A, Douglas Bremner J, Vaccarino V, et al. Myocardial ischemia during mental stress: role of coronary artery disease burden and vasomotion. *J Am Heart Assoc*. (2013) 2(5):e000321. doi: 10.1161/JAHA.113.000321
168. Wei J, Rooks C, Ramadan R, Shah AJ, Bremner JD, Quyyumi AA, et al. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. *Am J Cardiol*. (2014) 114(2):187–92. doi: 10.1016/j.amjcard.2014.04.022
169. Zhang L, Bao Y, Wang X, Zhou Y, Tao S, Xu W, et al. A meta-analysis on the prevalence, associated factors and diagnostic methods of mental stress induced myocardial ischemia. *J Transl Med*. (2020) 18(1):218. doi: 10.1186/s12967-020-02383-z
170. Soufer R, Arrighi JA, Burg MM. Brain, behavior, mental stress, and the neurocardiac interaction. *J Nucl Cardiol*. (2002) 9(6):650–62. doi: 10.1067/mnc.2002.129884
171. Jiang W, Samad Z, Boyle S, Becker RC, Williams R, Kuhn C, et al. Prevalence and clinical characteristics of mental stress-induced myocardial ischemia in patients with coronary heart disease. *J Am Coll Cardiol*. (2013) 61(7):714–22. doi: 10.1016/j.jacc.2012.11.037
172. Padro T, Manfrini O, Bugiardini R, Canty J, Cenko E, De Luca G, et al. ESC working group on coronary pathophysiology and microcirculation position paper on 'coronary microvascular dysfunction in cardiovascular disease'. *Cardiovasc Res*. (2020) 116:741–55. doi: 10.1093/cvr/cvaa003
173. Ma H, Guo L, Huang D, Wang L, Geng Q, Zhang M. The role of the myocardial microvasculature in mental stress-induced myocardial ischemia. *Clin Cardiol*. (2016) 39(4):234–9. doi: 10.1002/clc.22522
174. Legault SE, Freeman MR, Langer A, Armstrong PW. Pathophysiology and time course of silent myocardial ischemia during mental stress: clinical, anatomical, and physiological correlates. *Br Heart J*. (1995) 73(3):242–9. doi: 10.1136/hrt.73.3.242
175. Ghadri J-R, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International expert consensus document on takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J*. (2018) 39(22):2032–46. doi: 10.1093/eurheartj/ehy076
176. Patel U, Desai R, Faisaluddin M, Fong HK, Singh S, Kumar G, et al. Prevalence and impact of takotsubo syndrome in hospitalizations for acute ischemic stroke. *Proc (Bayl Univ Med Cent)*. (2022) 35(2):156–61. doi: 10.1080/08998280.2021.1995932
177. Yoshimura S, Toyoda K, Ohara T, Nagasawa H, Ohtani N, Kuwashiro T, et al. Takotsubo cardiomyopathy in acute ischemic stroke. *Ann Neurol*. (2008) 64(5):547–54. doi: 10.1002/ana.21459
178. Ghadri JR, Sarcon A, Diekmann J, Bataiosu DR, Cammann VL, Jurisic S, et al. Happy heart syndrome: role of positive emotional stress in takotsubo syndrome. *Eur Heart J*. (2016) 37(37):2823–9. doi: 10.1093/eurheartj/ehv757
179. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N Engl J Med*. (2015) 373(10):929–38. doi: 10.1056/NEJMoa1406761
180. Templin C, Hänggi J, Klein C, Topka MS, Hiestand T, Levinson RA, et al. Altered limbic and autonomic processing supports brain-heart axis in takotsubo syndrome. *Eur Heart J*. (2019) 40(15):1183–7. doi: 10.1093/eurheartj/ehz068
181. Sciagrà R, Parodi G, Del Pace S, Genovese S, Zampini L, Bellandi B, et al. Abnormal response to mental stress in patients with takotsubo cardiomyopathy detected by gated single photon emission computed tomography. *Eur J Nucl Med Mol Imaging*. (2010) 37(4):765–72. doi: 10.1007/s00259-009-1362-z
182. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of takotsubo syndrome. *Circulation*. (2017) 135(24):2426–41. doi: 10.1161/CIRCULATIONAHA.116.027121
183. Silva AR, Magalhães R, Arantes C, Moreira PS, Rodrigues M, Marques P, et al. Brain functional connectivity is altered in patients with takotsubo syndrome. *Sci Rep*. (2019) 9(1):4187. doi: 10.1038/s41598-019-40695-3
184. Radfar A, Abohashem S, Osborne MT, Wang Y, Dar T, Hassan MZO, et al. Stress-associated neurobiological activity associates with the risk for and timing of subsequent takotsubo syndrome. *Eur Heart J*. (2021) 42(19):1898–907. doi: 10.1093/eurheartj/ehab029
185. Lampert R. Mental stress and ventricular arrhythmias. *Curr Cardiol Rep*. (2016) 18(12):118. doi: 10.1007/s11886-016-0798-6
186. Lampert R, Joska T, Burg MM, Batsford WP, McPherson CA, Jain D. Emotional and physical precipitants of ventricular arrhythmia. *Circulation*. (2002) 106(14):1800–5. doi: 10.1161/01.CIR.0000031733.51374.C1
187. Rosman L, Lampert R, Ramsey CM, Dziura J, Chui PW, Brandt C, et al. Posttraumatic stress disorder and risk for early incident atrial fibrillation: a prospective cohort study of 1.1 million young adults. *J Am Heart Assoc*. (2019) 8(19):e013741. doi: 10.1161/JAHA.119.013741
188. Hering D, Lachowska K, Schlaich M. Role of the sympathetic nervous system in stress-mediated cardiovascular disease. *Curr Hypertens Rep*. (2015) 17:80. doi: 10.1007/s11906-015-0594-5
189. Finlay MCM, Lambiase PDPF, Ben-Simon RMDF, Taggart PDF. Effect of mental stress on dynamic electrophysiological properties of the endocardium and epicardium in humans. *Heart Rhythm*. (2016) 13(1):175–82. doi: 10.1016/j.hrthm.2015.08.011
190. Herring N, Kalla M, Paterson DJ. The autonomic nervous system and cardiac arrhythmias: current concepts and emerging therapies. *Nat Rev Cardiol*. (2019) 16(12):707–26. doi: 10.1038/s41569-019-0221-2
191. Lambiase PD, Garfinkel SN, Taggart P. Psychological stress, the central nervous system and arrhythmias. *QJM*. (2023) 116(12):977–82. doi: 10.1093/qjmed/hcad144
192. Donato GL, Ozdemir H, Lane DA, Lip GYH, Keller SS, Proietti R. At the heart of the matter: how mental stress and negative emotions affect atrial fibrillation. *Front Cardiovasc Med*. (2023) 10:1171647. doi: 10.3389/fcvm.2023.1171647
193. Critchley HD, Taggart P, Sutton PM, Holdright DR, Batchvarov V, Hnatkova K, et al. Mental stress and sudden cardiac death: asymmetric midbrain activity as a linking mechanism. *Brain*. (2005) 128(1):75–85. doi: 10.1093/brain/awh324
194. Lampert R. Put on a happy face—it's a lot better than coumadin. *J Am Heart Assoc*. (2012) 1(3):e002444. doi: 10.1161/JAHA.112.002444
195. Thackeray JT, Hupe HC, Wang Y, Bankstahl JP, Berding G, Ross TL, et al. Myocardial inflammation predicts remodeling and neuroinflammation after myocardial infarction. *J Am Coll Cardiol*. (2018) 71(3):263–75. doi: 10.1016/j.jacc.2017.11.024
196. Havakuk OMD, King KSMD, Grazette LMD, Yoon AJ, Fong M, Bregman N, et al. Heart failure-induced brain injury. *J Am Coll Cardiol*. (2017) 69(12):1609–16. doi: 10.1016/j.jacc.2017.01.022
197. Shaban A, Leira EC. Neurological complications of cardiologic interventions. *Curr Neurol Neurosci Rep*. (2019) 19(2):6–9. doi: 10.1007/s11910-019-0923-1
198. Traub J, Frey A, Störk S. Chronic neuroinflammation and cognitive decline in patients with cardiac disease: evidence, relevance, and therapeutic implications. *Life*. (2023) 13(2):329. doi: 10.3390/life13020329
199. Xie W, Zheng F, Yan L, Zhong B. Cognitive decline before and after incident coronary events. *J Am Coll Cardiol*. (2019) 73(24):3041–50. doi: 10.1016/j.jacc.2019.04.019
200. Johansen MC, Ye W, Gross A, Gottesman RF, Whitney R, Briceño EM, et al. Association between acute myocardial infarction and cognition. *JAMA Neurol*. (2023) 80(7):723–31. doi: 10.1001/jamaneurol.2023.1331
201. Wolters FJ, Segufa RA, Darweesh SKL, Bos D, Ikram MA, Sabayan B, et al. Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis. *Alzheimers Dement*. (2018) 14(11):1493–504. doi: 10.1016/j.jalz.2018.01.007
202. Rauseo E, Salih A, Raisi-Estabragh Z, Aung N, Khandera N, Slabaugh GG, et al. Ischemic heart disease and vascular risk factors are associated with accelerated brain aging. *JACC Cardiovasc Imaging*. (2023) 16(7):905–15. doi: 10.1016/j.jcmg.2023.01.016
203. Feng L, Li L, Liu W, Yang J, Wang Q, Shi L, et al. Prevalence of depression in myocardial infarction: a PRISMA-compliant meta-analysis. *Medicine (Baltimore)*. (2019) 98(8):e14596. doi: 10.1097/MD.00000000000014596
204. Hui LIU, Luiten PGM, Eisel ULM, Dejongste MJL, Schoemaker RG. Depression after myocardial infarction: tNF- α -induced alterations of the blood-brain barrier and

- its putative therapeutic implications. *Neurosci Biobehav Rev.* (2013) 37(4):561–72. doi: 10.1016/j.neubiorev.2013.02.004
205. Kasprzak D, Kaczmarek-Majer K, Rzeźniczak J, Rzeźniczak J, Klamecka-Pohl K, Ganowicz-Kaatz T, et al. Cognitive impairment in cardiovascular patients after myocardial infarction: prospective clinical study. *J Clin Med.* (2023) 12(15):4954. doi: 10.3390/jcm12154954
206. Bernard C, Catheline G, Dilharreguy B, Couffignal T, Ledure S, Lassalle-Lagadec S, et al. Cerebral changes and cognitive impairment after an ischemic heart disease: a multimodal MRI study. *Brain Imaging Behav.* (2016) 10(3):893–900. doi: 10.1007/s11682-015-9483-4
207. Thong EHE, Quek EJW, Loo JH, Yun C-Y, Teo YN, Teo YH, et al. Acute myocardial infarction and risk of cognitive impairment and dementia: a review. *Biology.* (2023) 12(8):1154. doi: 10.3390/biology12081154
208. Karami N, Kazemian M, Karami A, Salimi Y, Ziapour A, Janjani P. Global prevalence of depression, anxiety, and stress in cardiac patients: a systematic review and meta-analysis. *J Affect Disord.* (2023) 324:175–89. doi: 10.1016/j.jad.2022.12.055
209. van Melle JP, de Jonge P, Spijkerman TA, Tijssen JGP, Ormel J, van Veldhuisen DJ, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med.* (2004) 66(6):814–22. doi: 10.1097/01.psy.0000146294.82810.9c
210. Wu Q, Kling JM. Depression and the risk of myocardial infarction and coronary death: a meta-analysis of prospective cohort studies. *Medicine (Baltimore).* (2016) 95(6):e2815. doi: 10.1097/MD.0000000000002815
211. Merkle AE, Diaz I, Wu X, Murthy SB, Gialdini G, Navi BB, et al. Duration of heightened ischemic stroke risk after acute myocardial infarction. *J Am Heart Assoc.* (2018) 7(22):e010782. doi: 10.1161/JAHA.118.010782
212. Kajermo U, Ulvenstam A, Modica A, Jernberg T, Moos T. Incidence, trends, and predictors of ischemic stroke 30 days after an acute myocardial infarction. *Stroke.* (2014) 45(5):1324–30. doi: 10.1161/STROKEAHA.113.001963
213. Ulvenstam A, Kajermo U, Modica A, Jernberg T, Söderström L, Moos T. Incidence, trends, and predictors of ischemic stroke 1 year after an acute myocardial infarction. *Stroke.* (2014) 45(11):3263–8. doi: 10.1161/STROKEAHA.114.005770
214. Budaj A, Flasińska K, Gore JM, Anderson FA, Dabbous OH, Spencer FA, et al. Magnitude of and risk factors for in-hospital and postdischarge stroke in patients with acute coronary syndromes: findings from a global registry of acute coronary events. *Circulation.* (2005) 111(24):3242–7. doi: 10.1161/CIRCULATIONAHA.104.512806
215. Brammas A, Jakobsson S, Ulvenstam A, Moos T. Mortality after ischemic stroke in patients with acute myocardial infarction: predictors and trends over time in Sweden. *Stroke.* (2013) 44(11):3050–5. doi: 10.1161/STROKEAHA.113.001434
216. Merkle AE, Bartz TM, Kamel H, Soliman EZ, Howard V, Psaty BM, et al. Silent myocardial infarction and subsequent ischemic stroke in the cardiovascular health study. *Neurology.* (2021) 97(5):e436–43. doi: 10.1212/WNL.00000000000012249
217. Merkle AE, Sigurdsson S, Eiriksdottir G, Safford MM, Phillips CL, Iadecola C, et al. Association between unrecognized myocardial infarction and cerebral infarction on magnetic resonance imaging. *JAMA Neurol.* (2019) 76(8):956–61. doi: 10.1001/jamaneurol.2019.1226
218. Fonseca AC. Stroke and recent myocardial infarction, reduced left ventricular ejection fraction, left ventricular thrombus, and wall motion abnormalities. *Curr Cardiol Rep.* (2023) 25(12):1687–97. doi: 10.1007/s11886-023-02009-y
219. Takasugi J, Yamagami H, Noguchi T, Morita Y, Tanaka T, Okuno Y, et al. Detection of left ventricular thrombus by cardiac magnetic resonance in embolic stroke of undetermined source. *Stroke.* (2017) 48(9):2434–40. doi: 10.1161/STROKEAHA.117.018263
220. Levine GN, McEvoy JW, Fang JC, Ibeh C, McCarthy CP, Misra A, et al. Management of patients at risk for and with left ventricular thrombus: a scientific statement from the American Heart Association. *Circulation.* (2022) 146(15):e205–23. doi: 10.1161/CIR.0000000000001092
221. Camaj A, Fuster V, Giustino G, Bienstock SW, Sternheim D, Mehran R, et al. Left ventricular thrombus following acute myocardial infarction: JACC state-of-the-art review. *J Am Coll Cardiol.* (2022) 79(10):1010–22. doi: 10.1016/j.jacc.2022.01.011
222. Boivin-Proulx L-A, Ieronig C, Demers S-P, Nozza A, Soltani M, Ghersi I, et al. Contemporary incidence and predictors of left ventricular thrombus in patients with anterior acute myocardial infarction. *Clin Res Cardiol.* (2023) 112(4):558–65. doi: 10.1007/s00392-023-02158-8
223. Leow AS-T, Sia C-H, Tan BY-Q, Kaur R, Yeo T-C, Chan MY-Y, et al. Characterisation of acute ischemic stroke in patients with left ventricular thrombi after myocardial infarction. *J Thromb Thrombolysis.* (2019) 48(1):158–66. doi: 10.1007/s12399-019-01829-6
224. Gaita FMD, Corsinovi LMDP, Anselmino MMDP, Raimondo C, Pianelli M, Toso E, et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol.* (2013) 62(21):1990–7. doi: 10.1016/j.jacc.2013.05.074
225. Lenarczyk R, Proietti M, Scheitz JF, Shah D, Siebert E, Gorog DA, et al. Clinical and subclinical acute brain injury caused by invasive cardiovascular procedures. *Nat Rev Cardiol.* (2025) 22(4):273–303. doi: 10.1038/s41569-024-01076-0
226. Witt BJ, Ballman KV, Brown RD, Mevenden RA, Jacobsen SJ, Roger VL. The incidence of stroke after myocardial infarction: a meta-analysis. *Am J Med.* (2006) 119(4):354. doi: 10.1016/j.amjmed.2005.10.058
227. Bäck M, Doehner W. Cardiac thrombogenicity in stroke: mechanisms and evaluation. *Eur J Vasc Endovasc Surg.* (2022) 64(2-3):150–2. doi: 10.1016/j.ejvs.2022.09.004
228. Matter MA, Paneni F, Libby P, Frantz S, Stähli BE, Templin C, et al. Inflammation in acute myocardial infarction: the good, the bad and the ugly. *Eur Heart J.* (2023) 45(2):89–103. doi: 10.1093/eurheartj/ehad486
229. Nahrendorf MMD, Frantz SMD, Swirski FKP, Mulder WJM, Randolph G, Ertl G, et al. Imaging systemic inflammatory networks in ischemic heart disease. *J Am Coll Cardiol.* (2015) 65(15):1583–91. doi: 10.1016/j.jacc.2015.02.034
230. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodeling. *Nat Rev Cardiol.* (2014) 11(5):255–65. doi: 10.1038/nrcardio.2014.28
231. Bascañana P, Hess A, Borchert T, Wang Y, Wollert KC, Bengel FM, et al. 11C-methionine PET identifies astroglia involvement in heart-brain inflammation networking after acute myocardial infarction. *J Nucl Med.* (2020) 61(7):977–80. doi: 10.2967/jnumed.119.236885
232. Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2011) 42(9):2672–713. doi: 10.1161/STR.0b013e3182299496
233. Kucheryavikh LY, Dávila-Rodríguez J, Rivera-Aponte DE, Zueva LV, Washington AV, Sanabria P, et al. Platelets are responsible for the accumulation of β -amyloid in blood clots inside and around blood vessels in mouse brain after thrombosis. *Brain Res Bull.* (2017) 128:98–105. doi: 10.1016/j.brainresbull.2016.11.008
234. Cermakova P, Eriksdottir M, Lund LH, Winblad B, Religa P, Religa D. Heart failure and Alzheimer's disease. *J Intern Med.* (2015) 277(4):406–25. doi: 10.1111/joim.12287
235. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med.* (2007) 356(8):830–40. doi: 10.1056/NEJMra061889
236. Mejia-Renteria H, Travieso A, Matías-Guio JA, Yus M, Espejo-Paeres C, Finocchiaro F, et al. Coronary microvascular dysfunction is associated with impaired cognitive function: the cerebral-coronary connection study (C3 study). *Eur Heart J.* (2023) 44(2):113–25. doi: 10.1093/eurheartj/ehac521
237. Bradley CP, Berry C. Microvascular arterial disease of the brain and the heart: a shared pathogenesis. *QJM.* (2023) 116(10):829–34. doi: 10.1093/qjmed/hcad158
238. Moroni F, Ammirati E, Hainsworth AH, Camici PG. Association of white matter hyperintensities and cardiovascular disease: the importance of microcirculatory disease. *Circ Cardiovasc Imaging.* (2020) 13(8):e010460. doi: 10.1161/CIRCIMAGING.120.010460
239. Koton S, Schneider ALC, Windham BG, Mosley TH, Gottesman RF, Coresh J. Microvascular brain disease progression and risk of stroke: the ARIC study. *Stroke.* (2020) 51(11):3264–70. doi: 10.1161/STROKEAHA.120.030063
240. Tardif J-C, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med.* (2019) 381(26):2497–505. doi: 10.1056/NEJMoa1912388
241. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med.* (2017) 377(12):1119–31. doi: 10.1056/NEJMoa1707914
242. Duivenvoorden R, Senders ML, van Leent MMT, Pérez-Medina C, Nahrendorf M, Fayad ZA, et al. Nanoimmunotherapy to treat ischaemic heart disease. *Nat Rev Cardiol.* (2019) 16(1):21–32. doi: 10.1038/s41569-018-0073-1
243. Rashid S, Qureshi AG, Noor TA, Yaseen K, Sheikh MAA, Malik M, et al. Anxiety and depression in heart failure: an updated review. *Curr Probl Cardiol.* (2023) 48(11):101987. doi: 10.1016/j.cpcardiol.2023.101987
244. Critchley HD, Yarova E, Howell S, Rosen SD. Appreciating the links between heart failure and depression. *QJM.* (2024) 117(1):3–8. doi: 10.1093/qjmed/hcad213
245. Doehner W, Böhm M, Boriani G, Christersson C, Coats AJS, Haessler KG, et al. Interaction of heart failure and stroke: a clinical consensus statement of the ESC Council on Stroke, the Heart Failure Association (HFA) and the ESC Working Group on Thrombosis. *Eur J Heart Fail.* (2023) 25(12):2107–29. doi: 10.1002/ehf.3071
246. Cannon JAMM, Moffitt PB, Perez-Moreno ACMDP, Walters MR, Broomfield NM, McMurray JVV, et al. Cognitive impairment and heart failure: systematic review and meta-analysis. *J Card Fail.* (2017) 23(6):464–75. doi: 10.1016/j.cardfail.2017.04.007
247. Witt LS, Rotter J, Stearns SC, Gottesman RF, Kucharska-Newton AM, Richey Sharrett A, et al. Heart failure and cognitive impairment in the atherosclerosis risk in communities (ARIC) study. *J Gen Intern Med.* (2018) 33(10):1721–8. doi: 10.1007/s11606-018-4556-x
248. Doehner W, Čelutkienė J, Yilmaz MB, Coats AJS. Heart failure and the heart-brain axis. *QJM.* (2023) 116(11):897–902. doi: 10.1093/qjmed/hcad179

249. Adelborg K, Szépligeti S, Sundbøll J, Horváth-Puhó E, Henderson VW, Ording A, et al. Risk of stroke in patients with heart failure: a population-based 30-year cohort study. *Stroke*. (2017) 48(5):1161–8. doi: 10.1161/STROKEAHA.116.016022
250. Witt BJMD, Gami ASMD, Ballman KVP, Brown RD, Meverden RA, Jacobsen SJ, et al. The incidence of ischemic stroke in chronic heart failure: a meta-analysis. *J Card Fail*. (2007) 13(6):489–96. doi: 10.1016/j.cardfail.2007.01.009
251. Yaqub A, Bis JC, Frenzel S, Koini M, Mbangadji D, Peloso GM, et al. Clinical and imaging markers of cardiac function and brain health. *Neurology*. (2025) 104(8):e213421. doi: 10.1212/WNL.00000000000213421
252. Yoshida Y, Jin Z, Russo C, Homma S, Nakanishi K, Ito K, et al. Subclinical left ventricular systolic dysfunction and incident stroke in the elderly: long-term findings from cardiovascular abnormalities and brain lesions. *Eur Heart J Cardiovasc Imaging*. (2023) 24(4):522–31. doi: 10.1093/ehjci/jeac145
253. Russo C, Jin Z, Homma S, Elkind MSV, Rundek T, Yoshita M, et al. Subclinical left ventricular dysfunction and silent cerebrovascular disease: the cardiovascular abnormalities and brain lesions (CABL) study. *Circulation*. (2013) 128(10):1105–11. doi: 10.1161/CIRCULATIONAHA.113.001984
254. Tan S, Ho CESM, Teo YN, Chan MY-Y, Lee C-H, Evangelista LKM, et al. Prevalence and incidence of stroke, white matter hyperintensities, and silent brain infarcts in patients with chronic heart failure: a systematic review, meta-analysis, and meta-regression. *Front Cardiovasc Med*. (2022) 9:967197. doi: 10.3389/fcvm.2022.967197
255. Chong A-Y, Lip GYH. Viewpoint: the prothrombotic state in heart failure: a maladaptive inflammatory response? *Eur J Heart Fail*. (2007) 9(2):124–8. doi: 10.1016/j.ejheart.2006.05.009
256. Scherbakov N, Doehner W. Heart-brain interactions in heart failure. *Card Fail Rev*. (2018) 4(2):87–91. doi: 10.15420/cfr.2018.14.2
257. Ovsenik A, Podbregar M, Fabjan A. Cerebral blood flow impairment and cognitive decline in heart failure. *Brain Behav*. (2021) 11(6):e02176. doi: 10.1002/brb3.2176
258. Di Tullio MR, Qian M, Thompson JLP, Labovitz AJ, Mann DL, Sacco RL, et al. Left ventricular ejection fraction and risk of stroke and cardiac events in heart failure: data from the warfarin versus aspirin in reduced ejection fraction trial. *Stroke*. (2016) 47(8):2031–7. doi: 10.1161/STROKEAHA.116.013679
259. Roy B, Woo MA, Wang DJJ, Fonarow GC, Harper RM, Kumar R. Reduced regional cerebral blood flow in patients with heart failure. *Eur J Heart Fail*. (2017) 19(10):1294–302. doi: 10.1002/ehf.874
260. Li W, Seo J, Kokkinidis DG, Palaodimos L, Nagraj S, Korompoki E, et al. Efficacy and safety of vitamin-K antagonists and direct oral anticoagulants for stroke prevention in patients with heart failure and sinus rhythm: an updated systematic review and meta-analysis of randomized clinical trials. *Int J Stroke*. (2023) 18(4):392–9. doi: 10.1177/17474930221109149
261. Lip GY, Gibbs CR. Anticoagulation for heart failure in sinus rhythm. *Cochrane Database Syst Rev*. (2001) 4:CD003336. doi: 10.1002/14651858.cd003336
262. Koh YH, Lew LZW, Franke KB, Elliott AD, Lau DH, Thiagarajah A, 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):1229–39. doi: 10.1093/eurpace/eurac003
263. Conen D, Rodondi N, Müller A, Beer JH, Ammann P, Moschovitis G, et al. Relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation. *J Am Coll Cardiol*. (2019) 73(9):989–99. doi: 10.1016/j.jacc.2018.12.039
264. Rivard L, Friberg L, Conen D, Healey JS, Berge T, Boriani G, et al. Atrial fibrillation and dementia: a report from the AF-SCREEN international collaboration. *Circulation*. (2022) 145(5):392–409. doi: 10.1161/CIRCULATIONAHA.121.055018
265. Sanna T, Diener H-C, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. (2014) 370(26):2478–86. doi: 10.1056/NEJMoa1313600
266. Kamel H, Okin PM, Elkind MSV, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke*. (2016) 47(3):895–900. doi: 10.1161/STROKEAHA.115.012004
267. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRSA/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Heart Rhythm*. (2017) 14(1):e3–40. doi: 10.1016/j.hrthm.2016.05.028
268. Mannina C, Ito K, Jin Z, Yoshida Y, Matsumoto K, Shames S, et al. Association of left atrial strain with ischemic stroke risk in older adults. *JAMA Cardiol*. (2023) 8(4):317–25. doi: 10.1001/jamacardio.2022.5449
269. Maheshwari A, Norby FL, Inciardi RM, Wang W, Zhang MJ, Soliman EZ, et al. Left atrial mechanical dysfunction and the risk for ischemic stroke in people without prevalent atrial fibrillation or stroke: a prospective cohort study. *Ann Intern Med*. (2023) 176(1):39–48. doi: 10.7326/M22-1638
270. Sonaglioni A, Vincenti A, Baravelli M, Rigamonti E, Tagliabue E, Bassi P, et al. Prognostic value of global left atrial peak strain in patients with acute ischemic stroke and no evidence of atrial fibrillation. *Int J Cardiovasc Imaging*. (2019) 35(4):603–13. doi: 10.1007/s10554-018-1485-z
271. Edwards JD, Healey JS, Fang J, Yip K, Gladstone DJ. Atrial cardiopathy in the absence of atrial fibrillation increases risk of ischemic stroke, incident atrial fibrillation, and mortality and improves stroke risk prediction. *J Am Heart Assoc*. (2020) 9(11):e013227. doi: 10.1161/JAHA.119.013227
272. Kamel H, Bartz TM, Elkind MSV, Okin PM, Thacker EL, Patton KK, et al. Atrial cardiopathy and the risk of ischemic stroke in the CHS (cardiovascular health study). *Stroke*. (2018) 49(4):980–6. doi: 10.1161/STROKEAHA.117.020059
273. Watson T, Shantsila E, Lip GYH. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet*. (2009) 373(9658):155–66. doi: 10.1016/S0140-6736(09)60040-4
274. Himmelreich JCL, Lucassen WAM, Heugens M, Bossuyt PMM, Tan HL, Harskamp RE, et al. Frequent premature atrial contractions are associated with atrial fibrillation, brain ischaemia, and mortality: a systematic review and meta-analysis. *Europace*. (2019) 21(5):698–707. doi: 10.1093/eurpace/euy276
275. Larsen BSBS, Kumarathurai PMD, Falkenberg JBS, Nielsen OWMDPD, Sajadieh AMDD. Excessive atrial ectopy and short atrial runs increase the risk of stroke beyond incident atrial fibrillation. *J Am Coll Cardiol*. (2015) 66(3):232–41. doi: 10.1016/j.jacc.2015.05.018
276. Farinha JM, Gupta D, Lip GYH. Frequent premature atrial contractions as a signalling marker of atrial cardiomyopathy, incident atrial fibrillation, and stroke. *Cardiovasc Res*. (2022) 119:429–39. doi: 10.1093/cvr/cvac054
277. Zenger B, Rizzi S, Steinberg BA, Ranjan R, Bunch TJ. This is your brain, and this is your brain on atrial fibrillation: the roles of cardiac malperfusion events and vascular dysfunction in cognitive impairment. *Arrhythm Electrophysiol Rev*. (2023) 12:e01. doi: 10.15420/aer.2022.29
278. Madhavan M, Graff-Radford J, Piccini JP, Gersh BJ. Cognitive dysfunction in atrial fibrillation. *Nat Rev Cardiol*. (2018) 15(12):744–56. doi: 10.1038/s41569-018-0075-z
279. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. (2020) 383(14):1305–16. doi: 10.1056/NEJMoa2019422
280. Rillig A, Bellmann B, Skurk C, Leistner DM, Haeusler KG, Lin T, et al. Left atrial appendage angiography is associated with the incidence and number of magnetic resonance imaging-detected brain lesions after percutaneous catheter-based left atrial appendage closure. *Heart Rhythm*. (2018) 15(1):3–8. doi: 10.1016/j.hrthm.2017.11.015
281. Kandimalla J, Hussain Z, Piriyaat P, Rodriguez G, Maud A, Khatir R, et al. Stroke rates following surgical versus percutaneous revascularization for ischemic heart disease. *Curr Cardiol Rep*. (2021) 23(5):45. doi: 10.1007/s11886-021-01471-w
282. Schmidt T, Schlüter M, Alessandrini H, Akdag O, Schewel D, Schewel J, et al. Histology of debris captured by a cerebral protection system during transcatheter valve-in-valve implantation. *Heart*. (2016) 102(19):1573–80. doi: 10.1136/heartjnl-2016-309597
283. Mannina C, Sharma A, Carbone A, Bossone E, Tuttolomondo A, Argulian E, et al. Association of systemic inflammatory response syndrome with cardiovascular events after mitral transcatheter edge-to-edge repair. *J Am Heart Assoc*. (2024) 13(22):e036539. doi: 10.1161/JAHA.124.036539
284. Apaijai N, Moises DM, Palee S, McSweeney CM, Saiyasit N, Maneechote C, et al. Pretreatment with PCSK9 inhibitor protects the brain against cardiac ischemia/reperfusion injury through a reduction of neuronal inflammation and amyloid beta aggregation. *J Am Heart Assoc*. (2019) 8(2):e010838. doi: 10.1161/JAHA.118.010838
285. Surinkaew P, Sawaddiruk P, Apaijai N, Chattipakorn N, Chattipakorn SC. Role of microglia under cardiac and cerebral ischemia/reperfusion (I/R) injury. *Metab Brain Dis*. (2018) 33(4):1019–30. doi: 10.1007/s11011-018-0232-4
286. Gorla R, Erbel R, Eagle KA, Bossone E. Systemic inflammatory response syndromes in the era of interventional cardiology. *Vasc Pharmacol*. (2018) 107:53–66. doi: 10.1016/j.vph.2018.04.003
287. Pérez-Camargo D, Travieso A, Carnero-Alcázar M, Taramasso M, Cobiella-Carnicer J, Maroto-Castellanos LC. Neurological outcomes of transcatheter aortic valve implantation with or without cerebral embolic protection devices: a meta-analysis. *J Stroke Cerebrovasc Dis*. (2022) 31(9):106605. doi: 10.1016/j.jstrokecerebrovasdis.2022.106605
288. Musa TA, Uddin A, Loveday C, Dobson LE, Igra M, Richards F, et al. Silent cerebral infarction and cognitive function following TAVI: an observational two-centre UK comparison of the first-generation CoreValve and second-generation Lotus valve. *BMJ open*. (2019) 9(1):e022329. doi: 10.1136/bmjopen-2018-022329
289. Woldendorp K, Indja B, Bannon PG, Fanning JP, Plunkett BT, Grieve SM. Silent brain infarcts and early cognitive outcomes after transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J*. (2021) 42(10):1004–15. doi: 10.1093/eurheartj/ehab002
290. Ng S, Cunningham T, Vavalle JP. Cerebral embolic protection devices for transcatheter aortic valve replacement: review of the literature and future perspectives. *Curr Cardiol Rep*. (2024) 26(5):339–47. doi: 10.1007/s11886-024-02035-4
291. Pagnesi M, Regazzoli D, Ancona MB, Mangieri A, Lanzillo G, Giannini F, et al. Cerebral embolic risk during transcatheter mitral valve interventions: an unaddressed

- and unmet clinical need? *ACC Cardiovasc Interv.* (2018) 11(6):517–28. doi: 10.1016/j.jcin.2017.12.018
292. Praz F, Borger MA, Lanz J, Marin-Cuartas M, Abreu A, Adamo M, et al. 2025 ESC/EACTS guidelines for the management of valvular heart disease: developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* (2025) 46(44):4635–736. doi: 10.1093/eurheartj/ehaf194
293. Sposato LA, Albin CSW, Elkind MSV, Kamel H, Saver JL. Patent foramen Ovale management for secondary stroke prevention: state-of-the-art appraisal of current evidence. *Stroke.* (2024) 55(1):236–47. doi: 10.1161/STROKEAHA.123.040546
294. Yan C, Li H, Wang C, Yu H, Guo T, Yundan P, et al. Frequency and size of *in situ* thrombus within patent foramen ovale. *Stroke.* (2023) 54(5):1205–13. doi: 10.1161/STROKEAHA.122.041524
295. Cooper HA, Thompson EC, Laureno R, Fuisz A, Mark AS, Goldstein SA. Subclinical brain embolization in left-sided infective endocarditis: results from the evaluation by MRI of the brains of patients with left-sided intracardiac solid masses (EMBOLISM) pilot study. *Circulation.* (2009) 120(7):585–91. doi: 10.1161/CIRCULATIONAHA.108.834432
296. Yanagawa B, Pettersson GB, Habib G, Ruel M, Saposnik G, Latter DA, et al. Surgical management of infective endocarditis complicated by embolic stroke: practical recommendations for clinicians. *Circulation.* (2016) 134(17):1280–92. doi: 10.1161/CIRCULATIONAHA.116.024156
297. Lee VH, Connolly HM, Brown RD. Central nervous system manifestations of cardiac myxoma. *Arch Neurol.* (2007) 64(8):1115–20. doi: 10.1001/archneur.64.8.1115
298. Litmathe J, Dafotakis M, Sucker C, Schulz JB. Cardiovascular causes of emergency neurology presenting to an ICU. *Perfusion.* (2016) 31:271–80. doi: 10.1177/0267659115613429
299. Sajedi PI, Gonzalez JN, Cronin CA, Kouo T, Steven A, Zhuo J, et al. Carotid bulb webs as a cause of “cryptogenic” ischemic stroke. *AJNR Am J Neuroradiol.* (2017) 38(7):1399–404. doi: 10.3174/ajnr.A5208
300. Choi PMC, Singh D, Trivedi A, Qazi E, George D, Wong J, et al. Carotid webs and recurrent ischemic strokes in the era of CT angiography. *AJNR Am J Neuroradiol.* (2015) 36(11):2134–9. doi: 10.3174/ajnr.A4431
301. Coutinho JM, Derkatch S, Potvin ARJ, Tomlinson G, Casaubon LK, Silver FL, et al. Carotid artery web and ischemic stroke: a case-control study. *Neurology.* (2017) 88(1):65–9. doi: 10.1212/WNL.0000000000003464
302. Kim SJ, Nogueira RG, Haussen DC. Current understanding and gaps in research of carotid webs in ischemic strokes: a review. *JAMA Neurol.* (2019) 76(3):355–61. doi: 10.1001/jamaneurol.2018.3366
303. Grory B M, Emmer BJ, Roosendaal SD, Zagzag D, Yaghi S, Nossek E. Carotid web: an occult mechanism of embolic stroke. *J Neurol Neurosurg Psychiatry.* (2020) 91(12):1283–9. doi: 10.1136/jnnp-2020-323938
304. Habibi P, Chen LY, Sorond FA, Shroff GR, Sabayan B. Heart-brain axis: subclinical cardiovascular changes and brain health. *J Am Heart Assoc.* (2026) 15:e047458. doi: 10.1161/JAHA.125.047458
305. Moore EE, Jefferson AL. Impact of cardiovascular hemodynamics on cognitive aging. *Arterioscler Thromb Vasc Biol.* (2021) 41(4):1255–64. doi: 10.1161/ATVBAHA.120.311909
306. de Bruijn RF, Portegies ML, Leening MJ, Bos MJ, Hofman A, van der Lugt A, et al. Subclinical cardiac dysfunction increases the risk of stroke and dementia: the Rotterdam study. *Neurology.* (2015) 84(8):833–40. doi: 10.1212/WNL.0000000000001289
307. Huo S, Kränkel N, Nave AH, Sperber PS, Rohmann JL, Piper SK, et al. Endothelial and leukocyte-derived microvesicles and cardiovascular risk after stroke: PROSCIS-B. *Neurology.* (2021) 96(6):e937–946. doi: 10.1212/WNL.00000000000011223
308. Bulygin KV, Beeraka NM, Saitgareeva AR, Nikolenko VN, Beylerli O, Akhmadeeva LR, et al. Can miRNAs be considered as diagnostic and therapeutic molecules in ischemic stroke pathogenesis? —Current Status. *Int J Mol Sci.* (2020) 21(18):6728. doi: 10.3390/ijms21186728
309. Pahuja M, Akhtar KH, Krishan S, Nasir YM, Génereux P, Stavrakis S, et al. Neuromodulation therapies in heart failure: a state-of-the-art review. *J Soc Cardiovasc Angiogr Interv.* (2023) 2(6):101199. doi: 10.1016/j.jscv.2023.101199
310. van Weperen VYH, Vaseghi M. The brain-heart axis: effects of cardiovascular disease on the CNS and opportunities for central neuromodulation. *Nat Rev Neurosci.* (2025) 27:159–77. doi: 10.1038/s41583-025-01000-6
311. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC guidelines for the management of chronic coronary syndromes: developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* (2024) 45(36):3415–537. doi: 10.1093/eurheartj/ehae177
312. Mihalovic M, Mikulenska P, Linková H, Neuberger M, Štětkářová I, Peisker T, et al. Prevalence of myocardial injury in patients after acute ischaemic stroke according to standard criteria. *Eur Heart J Suppl.* (2023) 25(Supplement_E):E3–9. doi: 10.1093/eurheartjsupp/suad104
313. Gattringer T, Niederkorn K, Seyfang L, Seifert-Held T, Simmet N, Ferrari J, et al. Myocardial infarction as a complication in acute stroke: results from the Austrian stroke unit registry. *Cerebrovasc Dis.* (2014) 37(2):147–52. doi: 10.1159/000357799
314. Alqahtani F, Aljohani S, Tarabishy A, Busu T, Adcock A, Alkhouli M. Incidence and outcomes of myocardial infarction in patients admitted with acute ischemic stroke. *Stroke.* (2017) 48(11):2931–8. doi: 10.1161/STROKEAHA.117.018408
315. Mishra J, Kumar A, Kumar S, Singh S, Kumar Nayan S, Dev A. Incidence of acute myocardial infarction in patients presenting with cerebrovascular accident in a tertiary care centre in Eastern India. *Cureus.* (2022) 14(9):e29005. doi: 10.7759/cureus.29005
316. Huded CP, Tuzcu EM, Krishnaswamy A, Mick SL, Kleiman NS, Svensson LG, et al. Association between transcatheter aortic valve replacement and early postprocedural stroke. *JAMA.* (2019) 321(23):2306–15. doi: 10.1001/jama.2019.7525
317. Carroll JDMD, Mack MJMD, Vemulapalli SMD, Herrmann HC, Gleason TG, Hanzel G, et al. STS-ACC TVT registry of transcatheter aortic valve replacement. *J Am Coll Cardiol.* (2020) 76(21):2492–516. doi: 10.1016/j.jacc.2020.09.595
318. Kapadia SRMD, Huded CPMDM, Kodali SKMD, Svensson LG, Tuzcu EM, Baron SJ, et al. Stroke after surgical versus transfemoral transcatheter aortic valve replacement in the PARTNER trial. *J Am Coll Cardiol.* (2018) 72(20):2415–26. doi: 10.1016/j.jacc.2018.08.2172
319. Indja B, Woldendorp K, Vallely MP, Grieve SM. Silent brain infarcts following cardiac procedures: a systematic review and meta-analysis. *J Am Heart Assoc.* (2019) 8(9):e010920. doi: 10.1161/JAHA.118.010920
320. Besir B, Kapadia SR. Cerebral embolic protection: is there a benefit for left atrial and mitral valve procedures? *Curr Cardiol Rep.* (2024) 26(12):1341–6. doi: 10.1007/s11886-024-02132-4
321. Braemswig TB, Kusserow M, Kruppa J, Reinthaler M, Erdur H, Fritsch M, et al. Cerebral embolisation during transcatheter edge-to-edge repair of the mitral valve with the MitraClip system: a prospective, observational study. *EuroIntervention.* (2022) 18(2):e160–168. doi: 10.4244/eij-d-21-00646
322. Udesch R, Solanki P, Mehta A, Gleason T, Wechsler L, Thirumala PD. Carotid artery stenosis as an independent risk factor for perioperative strokes following mitral valve surgical intervention. *J Neurol Sci.* (2017) 382:170–84. doi: 10.1016/j.jns.2017.10.004
323. Hamon M, Baron J-C, Viader F, Hamon M. Periprocedural stroke and cardiac catheterization. *Circulation.* (2008) 118(6):678–83. doi: 10.1161/CIRCULATIONAHA.108.784504
324. Yamaji K, Iwanaga Y, Takechi K, Fujita K, Kawamura T, Hirase C, et al. Prognostic significance of asymptomatic cerebral infarction in patients after cardiac catheterization. *Int Heart J.* (2024) 65(1):13–20. doi: 10.1536/ihj.23-382
325. Mas J-L, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med.* (2017) 377(11):1011–21. doi: 10.1056/NEJMoa1705915
326. Loring Z, Holmes DN, Matsouka RA, Curtis AB, Day JD, Desai N, et al. Procedural patterns and safety of atrial fibrillation ablation: findings from get with the guidelines-atrial fibrillation. *Circ Arrhythm Electrophysiol.* (2020) 13(9):e007944. doi: 10.1161/CIRCEP.119.007944
327. Zhang J, Li S, Sang C, Ma C. Atrial fibrillation catheter ablation associated silent cerebral emboli: a narrative review. *Pacing Clin Electrophysiol.* (2023) 46(9):1124–33. doi: 10.1111/pace.14779
328. Yu Y, Wang X, Li X, Zhou X, Liao S, Yang W, et al. Higher incidence of asymptomatic cerebral emboli after atrial fibrillation ablation found with high-resolution diffusion-weighted magnetic resonance imaging. *Circ Arrhythm Electrophysiol.* (2020) 13(1):e007548. doi: 10.1161/CIRCEP.119.007548
329. Calvert P, Kollias G, Pürerfellner H, Narasimhan C, Osorio J, Lip GYH, et al. Silent cerebral lesions following catheter ablation for atrial fibrillation: a state-of-the-art review. *Europace* (2023) 25(6):eua151.
330. Gallone G, Lewin D, Rojas Hernandez S, Rojas Hernandez S, Bernhardt A, Billion M, et al. Stroke outcomes following durable left ventricular assist device implant in patients bridged with micro-axial flow pump: insights from a large registry. *Artif Organs.* (2024) 48(10):1168–79. doi: 10.1111/aor.14775
331. Halliday A, Peto R, Farrell B, Bulbulia R, Bonati LH, Chester J, et al. Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. *Lancet.* (2021) 398(10305):1065–73. doi: 10.1016/S0140-6736(21)01910-3