

REVIEW ARTICLE

Expanding cardiac substrates in embolic stroke of undetermined source beyond atrial fibrillation

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Abstract

Embolic stroke of undetermined source (ESUS) represents a significant proportion of ischemic strokes in which a definite etiology cannot be identified despite comprehensive diagnostic evaluation. Traditionally, occult atrial fibrillation has been considered the primary underlying mechanism; however, emerging evidence suggests that a broader spectrum of cardiac abnormalities may contribute to embolic risk. The concept of atrial cardiopathy has expanded the understanding of thromboembolic stroke beyond overt atrial fibrillation, highlighting the role of structural, functional, and electrophysiological alterations of the left atrium. In addition to atrial pathology, other potential cardiac sources—including left atrial appendage dysfunction, ventricular thrombus, valvular abnormalities, patent foramen ovale, and heart failure—have been implicated in ESUS. Advances in cardiac imaging, prolonged rhythm monitoring, and biomarker assessment have improved the detection of these covert substrates. Despite these developments, optimal strategies for risk stratification and secondary prevention remain uncertain, as recent trials of empiric anticoagulation in ESUS have yielded neutral results. This review summarizes current evidence on diverse cardiac mechanisms underlying ESUS, outlines diagnostic approaches for identifying occult embolic sources, and discusses implications for targeted management. A more individualized evaluation of cardiac substrates may refine therapeutic decisions and improve the prevention of recurrent stroke in this heterogeneous population.

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1. Introduction

Ischemic stroke remains a major cause of morbidity and mortality worldwide, with cardioembolism accounting for a substantial proportion of cases. For decades, atrial fibrillation (AF) has been regarded as the dominant cardiac mechanism underlying embolic stroke. This traditional view has shaped diagnostic algorithms, risk stratification

models, and preventive strategies, placing AF at the center of cardioembolic stroke pathophysiology.¹ However, an increasing body of evidence suggests that this AF-centered paradigm is overly restrictive and fails to account for a significant proportion of ischemic strokes in which no arrhythmia is documented despite extensive rhythm monitoring.²

The concept of embolic stroke of undetermined source (ESUS) has further highlighted the limitations of the conventional framework. Many patients who present with embolic-appearing infarcts lack identifiable AF even after prolonged monitoring, yet demonstrate clinical and imaging features consistent with a cardiac source.³ These observations have prompted a reassessment of how cardiac contributions to stroke are conceptualized, shifting the focus from rhythm disorders alone toward underlying structural and functional abnormalities of the heart.

Emerging data indicate that the propensity for thromboembolism may reflect a broader spectrum of atrial disease rather than the presence of AF per se. Structural remodeling, mechanical dysfunction, endothelial changes, and prothrombotic alterations within the atrial myocardium can precede or even occur independently of clinically apparent arrhythmia.⁴ This has led to the introduction of the concept of atrial cardiopathy, which encompasses a range of atrial abnormalities that may contribute to thromboembolic risk without necessarily manifesting as AF.⁵

Beyond the atria, additional cardiac substrates have gained recognition as potential contributors to ischemic stroke. Ventricular dysfunction, valvular pathology, low-flow states, and paradoxical embolic pathways may all play roles in generating cerebral emboli in the absence of AF. These mechanisms challenge the notion that AF is a prerequisite for cardioembolism and underscore the need for a more comprehensive framework that integrates diverse cardiac substrates.⁶

In this context, ischemic stroke should increasingly be viewed not simply as a consequence of arrhythmia but as the downstream manifestation of a complex interplay between structural heart disease, hemodynamic disturbances, and prothrombotic states. Expanding the understanding of cardiac substrates beyond AF has important implications for diagnosis, monitoring, and preventive strategies. Identifying these hidden contributors may ultimately refine patient selection for anticoagulation and improve secondary stroke prevention.

A structured narrative review methodology was adopted for this review. A comprehensive literature search was conducted using PubMed to identify relevant

articles published up to January 2026. The search strategy included combinations of the following terms: “ischemic stroke,” “cardioembolic stroke,” “atrial fibrillation,” “atrial cardiopathy,” “left atrial appendage,” “ventricular thrombus,” “heart failure,” “patent foramen ovale,” and “autonomic dysfunction.” Priority was given to contemporary studies, large cohort analyses, mechanistic investigations, and major review articles addressing cardiac contributors to ischemic stroke beyond AF. Reference lists of selected articles were also screened to ensure completeness. Only peer-reviewed studies available in PubMed were included, and emphasis was placed on clinically relevant and pathophysiologically informative data to support the evolving concept of diverse cardiac substrates underlying ischemic stroke.

The aim of this review is to provide a comprehensive overview of the diverse cardiac substrates contributing to ESUS beyond overt AF. By integrating emerging evidence on structural, functional, hemodynamic, and autonomic cardiac abnormalities, this narrative review aims to move beyond the traditional AF-centered framework and highlight the broader spectrum of cardiac conditions that may predispose to cerebral embolism in patients with ESUS. In addition, this review emphasizes the clinical relevance of a substrate-oriented evaluation and discusses how recognition of these mechanisms may improve etiological assessment and support more individualized secondary prevention strategies.

2. Traditional paradigm: Atrial fibrillation as the prototype

Atrial fibrillation has long been considered the prototypical cardiac mechanism underlying ischemic stroke. The association between AF and thromboembolism is well established, with numerous epidemiological studies demonstrating an approximately five-fold increase in stroke risk among affected individuals.⁷ The pathophysiological link is primarily attributed to blood stasis within the left atrium, particularly the left atrial appendage, resulting from ineffective atrial contraction and altered hemodynamics.⁸ This prothrombotic environment is further amplified by endothelial dysfunction and systemic hypercoagulability, creating conditions consistent with Virchow’s triad.⁹

The left atrial appendage has been identified as the predominant site of thrombus formation in AF-related stroke, with transesophageal echocardiography studies revealing thrombi in this structure in the majority of cardioembolic events.¹⁰ Reduced appendage emptying velocity, spontaneous echo contrast, and atrial dilation are frequently observed in patients with AF and have been correlated with increased embolic risk.¹¹ These findings have historically reinforced the concept that rhythm

disturbance is the primary driver of thrombus formation.

Clinical risk stratification tools such as the CHA₂DS₂-VASc score further support the central role of AF by linking stroke risk to patient-specific characteristics in patients with AF.¹² Anticoagulation strategies have therefore been largely guided by the detection of AF, reflecting the assumption that arrhythmia is a necessary precursor to embolic events. Indeed, randomized trials of oral anticoagulation have consistently demonstrated substantial reductions in stroke risk among AF patients, solidifying its position as the dominant therapeutic target.¹³

Despite this strong association, several limitations of the AF-centered paradigm have become increasingly apparent. First, a considerable proportion of patients with embolic-appearing strokes do not have detectable AF even after prolonged monitoring.¹⁴ Second, the temporal relationship between AF episodes and stroke events is often inconsistent, with many strokes occurring in the absence of recent arrhythmic activity.¹⁵ Finally, AF burden does not always correlate with thromboembolic risk, suggesting that underlying atrial pathology rather than the arrhythmia itself may be the critical determinant.¹⁶

These observations challenge the notion that AF is a prerequisite for cardioembolism and suggest that additional mechanisms may be operative in the development of embolic stroke. Rather than serving solely as a causal factor, AF may instead represent a marker of an underlying pathological substrate that predisposes to thromboembolism. Recognition of the limitations of this traditional rhythm-centered framework has therefore prompted a shift toward a broader substrate-oriented perspective, encouraging investigation of structural, functional, and neurocardiac abnormalities that may contribute to embolic risk even in the absence of documented AF. This evolving concept provides the rationale for systematic evaluation of alternative cardiac sources, including atrial cardiopathy, left atrial appendage dysfunction, ventricular abnormalities, and other covert contributors that may underlie ESUS, and forms the conceptual basis for the substrate-based approach discussed in the following sections.

3. The concept of atrial cardiopathy

Growing evidence suggests that thromboembolic risk may arise from underlying atrial pathology even in the absence of overt AF. This has led to the development of the concept of atrial cardiopathy, which encompasses structural, functional, and electrophysiological abnormalities of the atrial myocardium that predispose to thrombogenesis independently of rhythm disturbance.¹⁷⁻¹⁹ In this

framework, AF is no longer viewed solely as the initiating mechanism of embolism but rather as one possible manifestation of a diseased atrial substrate.

Structural remodeling represents a central component of atrial cardiopathy. Left atrial enlargement and fibrosis have been associated with an increased risk of ischemic stroke even in patients without documented AF.²⁰ These changes may impair atrial contractility and promote localized blood stasis, creating conditions favorable for thrombus formation. Functional alterations, including reduced reservoir and conduit function of the left atrium, further contribute to hemodynamic inefficiency and prothrombotic flow patterns.²¹

Electrophysiological abnormalities also provide indirect evidence of atrial disease. Prolonged P-wave duration, increased P-wave terminal force in lead V1, and frequent atrial ectopy have all been linked to future stroke risk, suggesting that electrical remodeling may reflect an underlying pathological milieu capable of generating embolic events.²² These markers support the notion that atrial dysfunction may precede or occur independently of clinically detectable arrhythmia.

Biomarkers have further strengthened this concept. Elevated levels of natriuretic peptides, particularly N-terminal pro-B-type natriuretic peptide, have been associated with incident stroke in patients without AF, likely reflecting increased atrial wall stress and subclinical dysfunction.²³ Collectively, these findings suggest that atrial cardiopathy may represent a distinct and clinically relevant source of thromboembolism, expanding the understanding of cardiac contributions to ischemic stroke beyond AF alone. The principal diagnostic modalities used to detect covert cardiac sources of embolism are outlined in [Table 1](#).

4. Subclinical atrial dysfunction

Beyond overt structural remodeling, increasing attention has been directed toward subclinical atrial dysfunction as a potential contributor to ischemic stroke. This condition refers to impaired atrial mechanical performance that may exist in the absence of documented AF or significant chamber enlargement.²⁴ Such dysfunction may precede electrical instability and represent an early manifestation of atrial disease.

Mechanical abnormalities of the left atrium can promote localized blood stasis even when the sinus rhythm is maintained. Reduced atrial contractile function and diminished reservoir capacity have been associated with impaired forward flow dynamics and increased thrombogenic potential.²⁵ Importantly, these alterations

Table 1. Diagnostic modalities for detecting cardiac sources of embolism in embolic stroke of undetermined source

Modality	Target abnormality	Strengths	Limitations
Transthoracic echocardiography	LV thrombus, chamber size, function	Non-invasive, widely available	Limited LAA visualization
Transesophageal echocardiography	LAA thrombus, PFO, valvular lesions	High sensitivity for embolic sources	Semi-invasive
Cardiac MRI	LV thrombus, fibrosis	High tissue resolution	Limited availability
Prolonged rhythm monitoring	Subclinical AF	Detects paroxysmal arrhythmia	Requires long-term follow-up
Biomarkers (e.g., NT-proBNP, troponin)	Atrial dysfunction	Easy to obtain	Non-specific
HRV analysis	Autonomic dysfunction	Non-invasive, widely available, reflects neurocardiac regulation	Limited specificity, not yet part of routine ESUS diagnostic algorithms

Abbreviations: AF: Atrial fibrillation; ESUS: Embolic stroke of undetermined source; HRV: Heart rate variability; LAA: Left atrial appendage; LV: Left ventricle; MRI: Magnetic resonance imaging; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PFO: Patent foramen ovale.

may not be detectable through routine clinical evaluation, highlighting the limitations of relying solely on rhythm monitoring for stroke risk assessment.

The left atrial appendage may also exhibit functional impairment despite the absence of AF. Reduced appendage emptying velocities have been observed in patients in sinus rhythm and linked to an increased likelihood of spontaneous echo contrast, suggesting that mechanical failure rather than arrhythmia alone may drive thrombus formation.²⁶ These findings support the concept that atrial dysfunction represents a continuum in which mechanical abnormalities may precede or exist independently of electrical disturbances.

Collectively, these observations indicate that thromboembolic risk is not confined to patients with clinically detectable AF but instead reflects a broader spectrum of atrial structural, functional, and electrophysiological abnormalities. Subclinical atrial dysfunction may promote blood stasis, endothelial activation, and impaired atrial mechanical performance, thereby facilitating thrombus formation even in the absence of overt arrhythmia.²⁰⁻²² Within the framework of ESUS, these findings support the concept that atrial cardiopathy may represent an important covert substrate

underlying otherwise unexplained embolic events.

Recognition of atrial dysfunction as a potential embolic mechanism independent of documented AF has important implications for etiological classification and risk stratification, highlighting the need for a more comprehensive evaluation of atrial structure and function beyond conventional rhythm monitoring alone. This substrate-oriented perspective also provides a conceptual link to other atrial sources of embolism, particularly left atrial appendage dysfunction, which is discussed in the following section.

5. Left atrial appendage as an independent embolic source

The left atrial appendage has traditionally been regarded as the principal site of thrombus formation in patients with AF. However, accumulating evidence suggests that the appendage may serve as an independent embolic source even in the absence of documented arrhythmia.²⁷ This perspective aligns with the broader concept that structural and functional abnormalities within the atrium may predispose to thromboembolism independently of rhythm disturbances.

Anatomical variability of the left atrial appendage has been associated with differential thromboembolic risk. Certain morphologies, particularly those characterized by complex lobulation or narrow orifices, may promote localized flow stagnation and increase susceptibility to thrombus formation.²⁸ These features can exist irrespective of the presence of AF and may reflect underlying atrial pathology.

Functional impairment of the appendage further contributes to this risk. Reduced emptying velocity and diminished contractile activity have been observed in patients without AF and are associated with spontaneous echo contrast, indicating a prothrombotic milieu.^{27,29} Such findings suggest that mechanical dysfunction of the appendage may precede or occur independently of arrhythmia, reinforcing its potential role as a primary embolic source.

These observations highlight the importance of evaluating appendage structure and function when assessing stroke etiology. The left atrial appendage should therefore be considered not merely as a passive bystander in AF but as a dynamic structure capable of contributing to thromboembolic events across a broader spectrum of cardiac conditions.

6. Ventricular sources of cardioembolism

Although atrial pathology has received considerable attention in the context of ischemic stroke, ventricular abnormalities also represent important and sometimes underrecognized sources of embolism. Left ventricular systolic dysfunction, particularly in the setting of regional wall motion abnormalities, may promote intracavitary blood stasis and thrombus formation.³⁰ This risk is most pronounced following myocardial infarction, where akinetic or dyskinetic segments create localized zones of low flow that favor thrombus development.

Left ventricular thrombus remains a well-established complication after large anterior infarctions and is strongly associated with embolic events, including stroke.³¹ Even in the era of contemporary reperfusion therapy, residual ventricular remodeling and impaired contractility may sustain prothrombotic conditions. Importantly, thrombus formation may occur in the absence of overt clinical signs, underscoring the need for careful imaging evaluation in patients with otherwise unexplained embolic stroke.³⁰

Non-ischemic cardiomyopathies also contribute to embolic risk. Dilated cardiomyopathy, characterized by chamber enlargement and reduced systolic function, can create similar hemodynamic disturbances that facilitate

thrombus formation.³² Furthermore, inflammatory or infiltrative myocardial diseases may alter ventricular function and endothelial integrity, further enhancing thromboembolic potential.

These findings emphasize that ventricular pathology should be systematically considered when evaluating cardiac substrates of ischemic stroke. Thromboembolism originating from the ventricle represents a distinct mechanism that operates independently of AF, highlighting the broader spectrum of cardiac substrates contributing to cerebral embolism.^{30,32}

7. Valvular and structural cardiac disease

Valvular and structural cardiac abnormalities represent additional contributors to ischemic stroke that extend beyond AF-related mechanisms. Certain valvular pathologies create a prothrombotic environment through altered intracardiac flow patterns, endothelial injury, and localized turbulence. Mitral stenosis, for example, has long been associated with thromboembolic risk due to impaired atrial emptying and increased left atrial pressure, even in the absence of documented AF.³³

Degenerative valvular disease may also play a role. Calcific aortic and mitral valve changes have been linked to embolic phenomena through mechanisms that include microthrombus formation and endothelial disruption.³⁴ In addition, Lambl's excrescences, filiform structures located along valve closure lines, have been implicated as potential embolic sources in patients with otherwise unexplained ischemic stroke.³⁵

Infective endocarditis represents a more direct mechanism, where vegetations composed of fibrin, platelets, and microbial elements may embolize to the cerebral circulation.³⁶ While typically associated with overt clinical manifestations, subclinical or healed valvular lesions may still contribute to embolic risk.

Prosthetic valves further illustrate the complexity of structural cardiac contributions to stroke. Both mechanical and bioprosthetic valves can predispose to thrombus formation under certain hemodynamic conditions, particularly when flow disturbances or endothelialization abnormalities are present.³⁷

Collectively, these conditions underscore the importance of considering valvular and structural cardiac disease in the broader evaluation of stroke etiology. Their contribution to thromboembolism is mediated not by arrhythmia, but rather by mechanical and endothelial factors that promote thrombogenesis.

8. Patent foramen ovale and paradoxical embolism

Patent foramen ovale (PFO) has emerged as an important structural cardiac substrate in the evaluation of ischemic stroke, particularly in younger patients and those with otherwise unexplained embolic events. The presence of a right-to-left shunt creates a potential pathway for venous thrombi to bypass the pulmonary circulation and enter the systemic arterial system, resulting in paradoxical embolism.³⁸ This mechanism operates independently of AF and reflects a distinct pathway of cardioembolic stroke.

However, not all PFOs confer equal risk. Certain anatomical features, such as a large shunt size or the presence of an associated atrial septal aneurysm, have been linked to a higher likelihood of embolic events.³⁹ These structural characteristics may facilitate more efficient passage of embolic material into the arterial circulation, particularly during transient increases in right atrial pressure such as Valsalva maneuvers.

Recent clinical trials have reinforced the relevance of PFO as a stroke mechanism by demonstrating reduced recurrence rates following percutaneous closure in selected patients.⁴⁰ These findings support the concept that PFO is not merely an incidental finding but may represent a clinically meaningful contributor to embolic stroke in specific contexts.

Not all detected PFOs are clinically relevant. Distinguishing incidental findings from pathogenic PFO is essential when evaluating stroke etiology. Clinical tools such as the Risk of Paradoxical Embolism score may assist in identifying patients in whom PFO is more likely to represent a causal mechanism rather than an incidental anatomical variant.⁴¹

Recognition of paradoxical embolism expands the spectrum of cardiac substrates beyond arrhythmia and emphasizes the importance of structural evaluation in patients with ischemic stroke of unclear origin.

9. Heart failure and low-flow states

Heart failure represents another important cardiac condition associated with an increased risk of ischemic stroke, independent of AF. Reduced cardiac output and impaired ventricular function may create low-flow conditions that promote thrombus formation within the cardiac chambers.⁴² In such settings, sluggish intracardiac circulation facilitates blood stasis and contributes to a prothrombotic environment.

Beyond hemodynamic impairment, heart failure is characterized by systemic endothelial dysfunction and

activation of inflammatory and coagulation pathways. These alterations may enhance thrombin generation and platelet activation, further increasing the likelihood of thromboembolic events.⁴³ Importantly, this risk persists even in patients who remain in sinus rhythm, suggesting that ventricular dysfunction itself may be sufficient to predispose to embolism.

Neurohormonal activation also contributes to this process. Increased sympathetic activity and activation of the renin-angiotensin system may promote endothelial dysfunction, inflammation, and prothrombotic signaling, thereby enhancing vascular instability.^{32,44} These alterations can interact with impaired flow dynamics and ventricular dysfunction to create a hemodynamic and biological milieu that favors thrombus formation and subsequent embolization even in the absence of overt arrhythmia.

Recognizing heart failure as a potential source of embolic stroke broadens the conceptual framework of cardiac substrates and underscores the contribution of hemodynamic disturbance in addition to structural and electrical abnormalities. Reduced cardiac output, intracardiac stasis, and prothrombotic activation may create conditions that favor thrombus formation even in the absence of overt arrhythmia, reinforcing the need to consider ventricular dysfunction within the spectrum of embolic risk.^{32,33}

10. Autonomic dysfunction as an emerging mechanism

Beyond structural and hemodynamic abnormalities, autonomic nervous system dysfunction has emerged as an increasingly recognized contributor to ischemic stroke through its effects on cardiac electrophysiology, vascular regulation, endothelial integrity, and thrombogenic signaling pathways. Growing evidence suggests that disturbances in sympathetic-parasympathetic balance may influence embolic risk even in the absence of overt AF, supporting the concept that neurocardiac interactions represent an additional and potentially underrecognized component within the spectrum of cardiac substrates implicated in ESUS.⁴⁵⁻⁴⁷

10.1. Neurocardiac axis and central autonomic regulation

Cardiovascular homeostasis is tightly regulated by the central autonomic network, a distributed system involving cortical, subcortical, and brainstem structures that coordinate heart rate control, vascular tone modulation, and hemodynamic stability. Key regions such as the insular cortex, anterior cingulate cortex, hypothalamus, amygdala, and medullary autonomic centers contribute to

the integration of afferent and efferent autonomic signals that influence cardiac mechanical and electrophysiological function.⁴⁶

Disruption of these regulatory pathways may lead to sustained sympathetic predominance or impaired parasympathetic modulation, both of which are associated with increased cardiovascular instability.⁴⁶ Experimental studies have demonstrated that autonomic imbalance can alter atrial refractoriness, promote triggered activity, and increase susceptibility to atrial electrical remodeling, thereby facilitating conditions favorable for thromboembolism even in the absence of sustained arrhythmia.⁴⁸ These findings support the hypothesis that autonomic dysfunction may function as an upstream contributor to embolic risk rather than merely a secondary epiphenomenon of cardiovascular disease.

Furthermore, disturbances involving the insular cortex have been associated with alterations in cardiac autonomic tone and adverse cardiovascular outcomes, highlighting the bidirectional interaction between central autonomic regulation and peripheral cardiovascular function.⁴⁶ Such neurocardiac interactions may contribute to subclinical yet clinically relevant alterations in atrial mechanical performance and vascular stability that predispose to embolic events.

10.2. Sympathetic activation, endothelial dysfunction, and thrombogenic signaling

Autonomic imbalance characterized by sympathetic predominance has been linked to activation of inflammatory and prothrombotic pathways that contribute to vascular instability and embolic susceptibility.⁴⁸ Increased sympathetic tone promotes catecholamine-mediated platelet activation, enhances thrombin generation, and facilitates endothelial dysfunction, thereby creating a procoagulant environment that may increase the likelihood of intracardiac thrombus formation.⁴⁹

In addition to its effects on platelet activity, sympathetic overactivation has been associated with increased oxidative stress and reduced nitric oxide bioavailability, both of which impair endothelial function and contribute to vascular dysregulation.⁵⁰ These alterations may promote a thrombogenic milieu even in patients without detectable AF, suggesting that autonomic dysfunction may represent an independent pathway contributing to embolic risk. Importantly, these mechanisms may act synergistically with structural cardiac abnormalities such as atrial enlargement or ventricular dysfunction, amplifying thrombogenic potential and facilitating embolic events through combined neurohormonal and hemodynamic pathways.^{32,48}

10.3. Heart rate variability as a quantitative marker of autonomic dysfunction

Heart rate variability (HRV) represents one of the most widely used non-invasive indicators of autonomic nervous system activity and reflects the dynamic interplay between sympathetic and parasympathetic modulation of cardiac rhythm.⁴⁶ Reduced HRV has consistently been associated with increased cardiovascular morbidity and mortality across a wide range of clinical populations.⁵¹

Importantly, impaired HRV has also been linked to an increased risk of incident stroke and adverse cerebrovascular outcomes, supporting the hypothesis that autonomic dysregulation contributes to cerebrovascular vulnerability through mechanisms extending beyond conventional vascular risk factors.⁵² Reduced HRV reflects diminished parasympathetic modulation and relative sympathetic dominance, both of which are associated with impaired atrial contractile function, altered vascular tone regulation, and increased thrombogenic signaling.^{46,48} Within the ESUS population, HRV abnormalities may represent a surrogate marker of neurocardiac instability and may help identify patients in whom covert autonomic dysregulation contributes to embolic risk despite the absence of overt arrhythmia.

10.4. Interaction between autonomic dysfunction and atrial cardiopathy

Emerging evidence suggests that autonomic dysfunction may contribute directly to the development and progression of atrial cardiopathy through its effects on atrial structure, electrophysiological stability, and mechanical performance.⁵² Chronic sympathetic activation has been associated with atrial fibrosis, altered calcium handling, impaired atrial contractility, and conduction heterogeneity, all of which may promote localized blood stasis and thrombus formation independent of clinically detectable AF.⁵³

These observations support the concept that autonomic imbalance and atrial cardiopathy should be viewed as interconnected components of a broader pathophysiological continuum rather than independent mechanisms. Neurohormonal activation may accelerate atrial remodeling processes that increase embolic susceptibility even before the development of sustained atrial arrhythmia, thereby providing a mechanistic explanation for embolic stroke occurring in patients without documented AF. This interaction is particularly relevant in the context of ESUS, where covert atrial disease is increasingly recognized as an important contributor to embolic risk despite the absence of detectable rhythm disturbances.

10.5. Baroreflex dysfunction and hemodynamic variability

Baroreflex sensitivity represents another important component of autonomic cardiovascular regulation and plays a critical role in maintaining short-term blood pressure stability and cerebral perfusion homeostasis.⁵³ Impairment of baroreflex responsiveness has been associated with increased blood pressure variability, endothelial dysfunction, and vascular instability, all of which may contribute to cerebral embolic susceptibility.⁵⁴

Reduced baroreflex sensitivity may also reflect broader autonomic dysregulation affecting both cardiac and vascular compartments. These alterations may interact with structural cardiac abnormalities to create a hemodynamic environment favorable to thrombus formation, particularly in patients with otherwise unexplained embolic stroke.⁵⁴ Within the ESUS framework, subtle disturbances in autonomic-mediated blood pressure regulation may therefore represent an additional mechanism contributing to embolic risk beyond traditional structural cardiac substrates.

10.6. Integration of autonomic dysfunction within the embolic stroke of undetermined source substrate spectrum

Rather than acting as an isolated mechanism, autonomic dysfunction is more likely to interact with multiple cardiac and vascular pathways contributing to embolic stroke.⁴⁸ Neurohormonal activation associated with sympathetic predominance may exacerbate atrial remodeling, impair endothelial function, increase platelet activation, and amplify thrombogenic signaling, thereby creating a permissive environment for embolic events.⁵⁵

In this context, autonomic imbalance may represent a covert contributor within the heterogeneous spectrum of ESUS mechanisms. Its interaction with atrial cardiopathy, heart failure-related neurohormonal activation, and low-flow states supports the concept that embolic stroke may result from a complex interplay between structural abnormalities and neurocardiac regulatory disturbances rather than a single dominant etiological pathway.^{32,52} Recognition of autonomic dysfunction as part of the ESUS substrate spectrum therefore provides an additional conceptual framework for understanding embolic risk in patients without detectable AF.

10.7. Clinical implications and future directions

Increasing interest has been directed toward the potential role of autonomic biomarkers in refining stroke risk stratification beyond conventional rhythm-based approaches. Non-invasive assessment of autonomic

function, particularly HRV analysis, may represent a promising adjunctive tool for identifying individuals with neurocardiac dysregulation who could benefit from more comprehensive etiological evaluation and targeted preventive strategies.⁵⁶

Future investigations integrating autonomic biomarkers with advanced cardiac imaging, prolonged rhythm monitoring, and circulating markers of atrial cardiopathy may help clarify the clinical relevance of autonomic dysfunction in ESUS populations. Such multimodal approaches may improve identification of covert embolic substrates and contribute to the development of more individualized prevention strategies in patients with otherwise unexplained embolic stroke. Non-invasive assessment of autonomic function using HRV analysis may provide complementary information in selected ESUS patients. The spectrum of cardiac-related substrates potentially contributing to embolic risk in ESUS, including autonomic dysfunction, is summarized in [Table 2](#).

11. Therapeutic implications of cardiac substrate-oriented evaluation in embolic stroke of undetermined source

The recognition of diverse cardiac substrates has important therapeutic implications for the concept of ESUS, a term introduced to describe non-lacunar ischemic strokes with no definite cause identified despite standard diagnostic evaluation.⁵⁷ While initially presumed to represent occult AF in many cases, subsequent studies have demonstrated that a substantial proportion of ESUS patients do not develop AF even with extended monitoring.²

This has prompted reconsideration of the underlying mechanisms. Rather than reflecting undetected arrhythmia alone, ESUS may arise from a variety of structural and functional cardiac abnormalities that predispose to thromboembolism. Atrial cardiopathy, left atrial appendage dysfunction, ventricular impairment, and paradoxical embolic pathways may each contribute to embolic events without manifesting as AF.⁵⁸

The failure of large randomized trials to demonstrate superiority of empiric anticoagulation over antiplatelet therapy in unselected ESUS populations further underscores the heterogeneity of underlying mechanisms.⁵⁹ These findings suggest that a one-size-fits-all approach based on the assumption of occult AF may be insufficient. Instead, identifying specific cardiac substrates may be necessary to guide targeted preventive strategies.

This may explain the neutral results of major ESUS trials such as NAVIGATE-ESUS and RE-SPECT ESUS, which were based on the assumption that occult AF

Table 2. Major cardiac substrates in embolic stroke of undetermined source

Cardiac substrate	Pathophysiological mechanism	Diagnostic clues	Imaging/monitoring tools
Atrial cardiopathy	Structural/electrical atrial dysfunction without AF	LA enlargement, abnormal P-wave indices, elevated NT-proBNP	TTE, TEE, ECG markers, biomarkers
Subclinical AF	Intermittent arrhythmia causing embolism	Device-detected episodes	Holter, ILR
LAA dysfunction	Stasis and thrombus formation	Reduced LAA flow velocity, SEC	TEE
LV thrombus	Post-MI or LV dysfunction	Regional wall motion abnormalities	TTE, CMR
Valvular heart disease	Flow turbulence, endothelial injury	Prosthetic/native valve pathology	TTE, TEE
Patent foramen ovale	Paradoxical embolism	Right-to-left shunt	TEE, bubble study
Heart failure	Hypercoagulability, low flow states	Reduced LVEF	TTE
Autonomic dysfunction	Sympathetic–parasympathetic imbalance leading to endothelial dysfunction, atrial remodeling, platelet activation, and hemodynamic variability	Reduced HRV, impaired baroreflex sensitivity	HRV analysis, autonomic function testing

Abbreviations: AF: Atrial fibrillation; CMR: Cardiac magnetic resonance; ECG: Electrocardiography; HRV: Heart rate variability; ILR: Implantable loop recorder; LA: Left atrium; LAA: Left atrial appendage; LVEF: Left ventricular ejection fraction; LV: Left ventricle; MI: Myocardial infarction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SEC: Spontaneous echocardiographic contrast; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography.

was the dominant mechanism.^{6,59} In reality, ESUS likely represents a heterogeneous spectrum of cardiac substrates rather than a single pathophysiological entity, limiting the effectiveness of uniform anticoagulation strategies. Potential therapeutic implications based on the underlying cardiac substrate are summarized in Table 3. Ongoing trials evaluating anticoagulation strategies in patients with atrial cardiopathy, such as ARCADIA⁵ and ATTICUS,⁶⁰ may help clarify whether substrate-based treatment approaches improve outcomes in ESUS populations.

Reframing ESUS as a syndrome reflecting diverse cardiac and hemodynamic contributors aligns with the evolving understanding of ischemic stroke and underscores that mechanisms extend beyond overt AF, including atrial dysfunction, structural heart disease, and low-flow states.⁵² This perspective highlights the need for a more comprehensive and individualized etiological assessment integrating imaging, rhythm monitoring, and biomarkers to better identify underlying sources and guide targeted

prevention strategies.

From a practical perspective, evaluation of patients with ESUS should extend beyond the sole search for overt AF. In selected patients, a substrate-oriented diagnostic approach may include prolonged rhythm monitoring, detailed echocardiographic assessment of left atrial and left atrial appendage function, evaluation for ventricular thrombus or structural heart disease, and investigation for PFO when clinically appropriate.^{30,38,58} Circulating biomarkers such as N-terminal pro-B-type natriuretic peptide and selected autonomic markers may provide complementary information in identifying covert cardiac dysfunction, although their role remains supportive rather than definitive.^{23,56} Integration of these modalities may help improve etiological classification and support more individualized secondary prevention strategies in patients with ESUS.

In addition to cardiac substrates, emerging evidence

Table 3. Therapeutic implications according to the cardiac substrate

Cardiac substrate	Potential therapy	Evidence status
Subclinical AF	Oral anticoagulation	Established
Atrial cardiopathy	Anticoagulation (investigational)	Ongoing trials (ARCADIA, ATTICUS)
LV thrombus	Anticoagulation	Established
PFO	Closure in selected patients	Established
Valvular lesions	Surgical/interventional management	Established
Heart failure	Guideline-directed therapy	Supportive

Abbreviations: AF: Atrial fibrillation; LV: Left ventricle; PFO: Patent foramen ovale.

suggests that selected patients classified as ESUS may harbor competing vascular embolic sources that can influence etiological classification and secondary prevention strategies.⁶⁰ Recent studies have demonstrated that increased coronary atherosclerotic burden may reflect a broader systemic vascular substrate associated with embolic stroke risk.⁶¹ Similarly, advanced vascular imaging approaches such as CTA-based Plaque-RADS classification have identified high-risk nonstenotic carotid plaques as potential embolic sources in patients previously categorized as ESUS.⁶² These observations further support the importance of individualized substrate-oriented evaluation integrating both cardiac and extracardiac mechanisms when planning secondary prevention strategies. These findings suggest that ESUS should not be considered a purely cardiac entity but rather a heterogeneous syndrome requiring comprehensive multimodal evaluation.⁶³

12. Future directions

Advances in cardiac imaging and monitoring technologies are likely to play a central role in refining the understanding of ischemic stroke mechanisms. High-resolution echocardiographic techniques, cardiac magnetic resonance imaging, and strain analysis may improve the detection of subtle structural and functional abnormalities that precede overt arrhythmia.⁶⁴ These tools offer the potential to identify high-risk atrial or ventricular substrates that would otherwise remain unrecognized.

Biomarker-based risk stratification also represents a promising avenue. Circulating markers reflecting myocardial stress, inflammation, and endothelial dysfunction may help uncover underlying cardiac pathology in patients without detectable AF.^{65,66} Integrating such markers into clinical assessment could facilitate more precise identification of patients who may benefit from targeted preventive strategies.

Continuous rhythm monitoring remains important for detecting covert atrial arrhythmias; however, emerging strategies increasingly emphasize evaluation of the broader cardiac substrate rather than rhythm alone. Integrating structural imaging, functional assessment, and circulating biomarkers may provide a more comprehensive characterization of embolic risk and support a more individualized, mechanism-based approach to secondary prevention.⁶⁶

Several ongoing and recently completed clinical trials are evaluating substrate-oriented diagnostic and therapeutic strategies that may help refine etiological classification and secondary prevention approaches in patients with ESUS. In particular, randomized studies such as the ARCADIA⁵ and ATTICUS⁶⁰ trials are investigating whether anticoagulation provides benefit in patients with evidence of atrial cardiopathy in the absence of documented AF, representing a shift toward substrate-based treatment strategies rather than rhythm-based decision-making alone.

In parallel, studies focusing on intensified rhythm monitoring have explored the role of early detection of subclinical AF as a potential mechanism underlying otherwise unexplained embolic stroke. Trials such as LOOP⁶⁷ and STROKESTOP⁶⁸ evaluated systematic screening strategies for covert AF using prolonged rhythm monitoring approaches, while the NOAH-AFNET 6 trial⁶⁹ investigated whether anticoagulation may reduce thromboembolic risk in patients with atrial high-rate episodes without clinically documented AF.

Together, these investigations reflect an evolving transition from a purely arrhythmia-centered paradigm toward a broader substrate-oriented framework integrating atrial cardiopathy, autonomic dysfunction, and covert rhythm disturbances into ESUS risk stratification.^{70,71} Future studies combining advanced cardiac imaging, prolonged rhythm monitoring, and circulating biomarkers may further clarify the relative contribution of individual substrates and support more individualized prevention strategies in this heterogeneous patient population.

13. Limitations

This review has several limitations. First, this is a narrative review rather than a systematic review or meta-analysis; therefore, study selection was not based on a formal quantitative synthesis and may reflect the scope of the selected literature. Second, the available evidence supporting several proposed cardiac substrates, particularly autonomic dysfunction and some biomarker-based approaches, remains heterogeneous and is largely derived from observational and mechanistic studies rather than definitive randomized data. Third, ESUS represents a heterogeneous clinical construct, and the relative contribution of individual cardiac substrates may vary across patient populations. Finally, several diagnostic and therapeutic strategies discussed in this review remain investigational and require confirmation in prospective clinical trials.

14. Conclusion

The traditional view of ischemic stroke as predominantly driven by AF is increasingly being challenged by emerging evidence highlighting the role of broader cardiac substrates. Structural remodeling, mechanical dysfunction, ventricular impairment, valvular abnormalities, paradoxical embolic pathways, and autonomic imbalance all contribute to a complex network of mechanisms capable of promoting thromboembolism in the absence of overt arrhythmia.

This expanded perspective underscores the importance of moving beyond rhythm-based paradigms toward a more comprehensive evaluation of cardiac structure

and function. Recognizing these diverse contributors may help explain a substantial proportion of embolic strokes previously categorized as cryptogenic and offer an opportunity to refine diagnostic and preventive strategies.

Ultimately, ischemic stroke should be viewed not solely as a consequence of AF but as a manifestation of underlying cardiac disease in its various forms. Future advances in imaging, biomarkers, and individualized assessment are likely to further clarify these relationships and support more targeted secondary prevention strategies.

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Conflict of interest

The authors declare they have no competing interests.

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