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CONTEMPORARY REVIEW

Secondary Stroke Prevention Following Embolic Stroke of Unknown Source in the Absence of Documented Atrial Fibrillation: A Clinical Review

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ABSTRACT: Approximately one-third of ischemic strokes are classified as cryptogenic strokes. The risk of stroke recurrence in these patients is significantly elevated with up to one-third of patients with cryptogenic stroke experiencing a further stroke within 10 years. While anticoagulation is the mainstay of treatment for secondary stroke prevention in the context of documented atrial fibrillation (AF), it is estimated that up to 25% of patients with cryptogenic stroke have undiagnosed AF. Furthermore, the historical acceptance of a causal relationship between AF and stroke has recently come under scrutiny, with evidence to suggest that embolic stroke risk may be elevated even in the absence of documented atrial fibrillation attributable to the presence of electrical and structural changes constituting an atrial cardiomyopathy. More recently, the term *embolic stroke of unknown source* has garnered increasing interest as a subset of patients with cryptogenic stroke in whom a minimum set of diagnostic investigations has been performed, and a nonlacunar infarct highly suspicious of embolic etiology is suspected but in the absence of an identifiable secondary cause of stroke. The ongoing ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) randomized trial and ATTICUS (Apixiban for Treatment of Embolic Stroke of Undetermined Source) study seek to further define this novel term. This review summarizes the relationship between AF, embolic stroke, and atrial cardiomyopathy and provides an overview of the clinical relevance of cardiac imaging, electrocardiographic, and serum biomarkers in the assessment of AF and secondary stroke risk. The implications of these findings on therapeutic considerations is considered and gaps in the literature identified as areas for future study in risk stratifying this cohort of patients.

Key Words: atrial cardiomyopathy ■ atrial fibrillation ■ cardiac magnetic resonance imaging ■ electrocardiogram ■ embolic stroke of unknown source ■ ischemic stroke

Ischemic stroke remains a leading cause of mortality and morbidity.[1] Atrial fibrillation (AF) is a well-recognized risk factor for stroke, accounting for up to 20% of ischemic events and AF-related strokes are associated with a significantly higher risk of disability or fatality compared with non-AF strokes.[1–3] While anticoagulation is effective in the secondary prevention of thromboembolic stroke, current guidelines recommend documentation of AF before initiation of anticoagulation therapy.[4] However, a diagnosis of AF can be elusive because of its paroxysmal and often asymptomatic nature, resulting in a proportion of thromboembolic strokes being erroneously classified as cryptogenic strokes.[5,6] There is no clear consensus on the appropriate length of investigation required for detecting AF or duration of AF

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Nonstandard Abbreviations and Acronyms

ARCADIA	Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke
ARIC	Atherosclerosis Risk in Communities
ARISTOTLE	Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation
ASSERT	Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing
ATTICUS	Apixiban for Treatment of Embolic Stroke of Undetermined Source
CRYSTAL-AF	Cryptogenic Stroke and Underlying Atrial Fibrillation
ESUS	embolic stroke of unknown source
IMPACT	Combined Use of Biotronik Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk
LAA	left atrial appendage
NAVIGATE ESUS	Rivaroxiban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source
$PTFV_1$	P-wave terminal force in lead V_1
RE-LY	Randomised Evaluation of Long-Term Anticoagulant Therapy
RE-SPECT ESUS	Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source
WARSS	Warfarin-Aspirin Recurrent Stroke Study

that is diagnostic, but recent trials have suggested that 30-day outpatient event-triggered monitoring or implantation of a loop recorder may increase the detection rate of AF after cryptogenic stroke by almost 30% over 3 years,[7–9] and 30 seconds is often used as an arbitrary cutoff for diagnosis.[4,10]

A more recent term, *embolic stroke of unknown source* (ESUS), describes a subset of cryptogenic stroke patients in whom a nonlacunar infarct highly suspicious of embolic etiology is suspected but in the absence of an identifiable secondary cause of stroke such as embolism, arteritis, dissection, and coagulopathy.[11] It has been hypothesized that anticoagulation therapy may benefit this group, particularly those with evidence of an atrial cardiomyopathy.[11,12]

Separately, there is growing evidence of a more complex interaction between AF and ischemic stroke than traditionally thought. Inconsistencies regarding temporal association and biological gradient between AF burden and ischemic stroke suggest that a conceptual shift may be required to understand the risk of stroke beyond traditional scoring methods.[13] Comorbidities or risk factors leading to underlying atrial disease may provide an atrial thromboembolic substrate (Figure 1).[13,14] Such models acknowledge that the risk of embolic stroke may be elevated even in the absence of diagnosed AF. A poststroke pathway consisting of clinical investigations aimed at detecting an atrial cardiomyopathy could potentially identify a cohort of patients at high risk for further cardioembolic strokes but without diagnosed AF and who may therefore arguably benefit from anticoagulation therapy.

Previous studies using noninvasive investigations such as atrial imaging, electrocardiography, and serum biomarkers have been highlighted as potential methods to identify and quantify structural and electrical atrial remodeling suggestive of an atrial cardiomyopathy. Atrial cardiac magnetic resonance imaging provides noninvasive characterization of atrial tissue and has been shown to identify changes in atrial geometry, contractile function, and fibrosis, which together constitute structural remodeling and may reflect a prothrombotic atrial cardiomyopathy.[16] Alternatively, electrocardiographic and implantable device parameters such as atrial high-rate episodes, atrial ectopy burden, P-wave terminal force in lead V_1 ($PTFV_1$), and PR interval have all been associated with increased ischemic stroke risk in the absence of diagnosed AF. Many of these markers have been further shown to independently correlate with structural atrial remodeling including fibrosis, hypertrophy, and dilatation and are thought to constitute electrical remodeling in the context of an atrial cardiomyopathy.[12]

This review will consider the relationship between AF, stroke, and atrial cardiomyopathy. Evidence pertaining to the clinical relevance of imaging, electrocardiographic, and serum biomarkers in the diagnosis of atrial cardiomyopathy and future stroke risk will be summarized. Impact on future therapeutic considerations will also be explored.

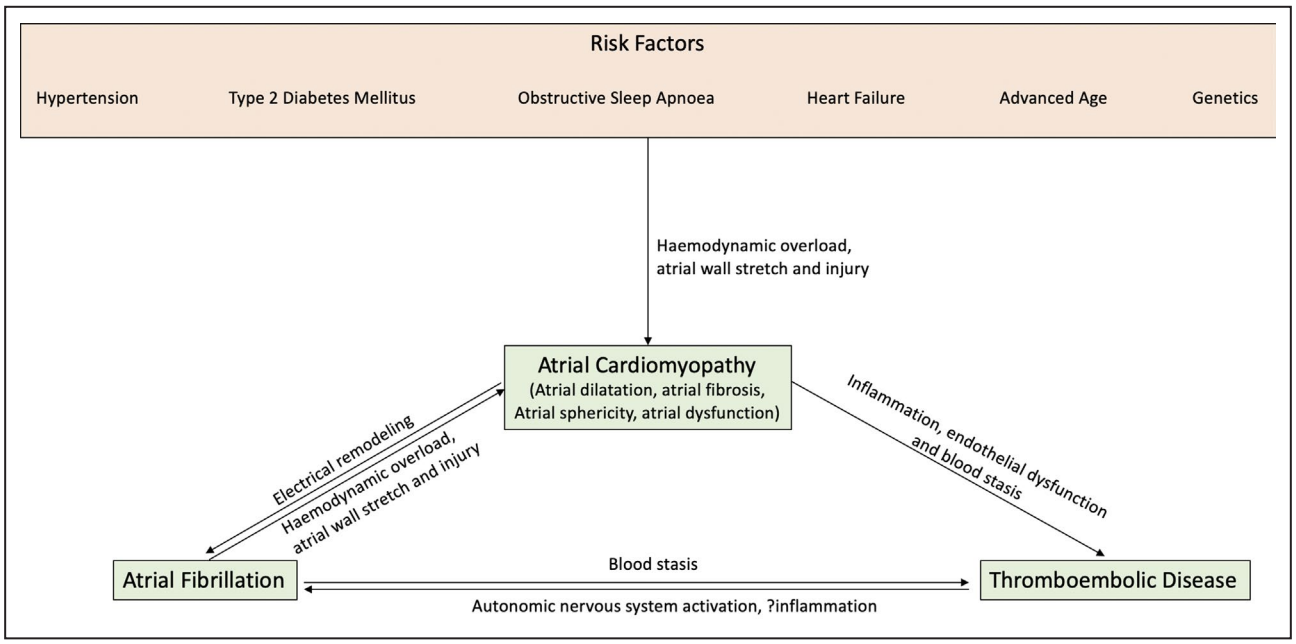

Figure 1. Schematic representation of the relationship between atrial cardiomyopathy, atrial fibrillation, and thromboembolic disease.[15]

ANTIPLATELET VERSUS ANTICOAGULATION THERAPY FOR SECONDARY STROKE PREVENTION

Anticoagulation in Cryptogenic Stroke

The WARSS (Warfarin-Aspirin Recurrent Stroke Study) was the first large randomized control study to perform a subgroup analysis that assessed the use of warfarin versus aspirin in secondary stroke prevention of patients with cryptogenic stroke. No change was found in the primary outcome of stroke or mortality between treatment groups. However, a significant limitation of the study was the wide range of diagnostic inclusion criteria in the cryptogenic stroke cohort including patients with ischemic stroke in whom >1 plausible cause was found or incomplete diagnostic assessment had been performed.[17–19] The breadth of underlying etiology of disease arguably resulted in limited clinical value of the study and reinforced the need for further subcategorization of patients with cryptogenic stroke.

Anticoagulation in Embolic Stroke of Unknown Source

The term embolic stroke of unknown source has since been defined as a separate entity that requires a minimum diagnostic assessment to be performed before categorization. Over 30% of patients with ischemic stroke are thought to meet this criterion.[11,20]

The importance of this subcategory stems from the recognition that a subgroup of patients with cryptogenic stroke in whom a primary embolic cause is suspected, despite an unidentified source, may arguably benefit from anticoagulation. Support for this hypothesis comes from data showing that clots extracted from patients with cryptogenic stroke were similar in histology and composition to those with cardioembolic stroke.[21] However, real-world data from 2 large randomized control studies recently conducted, NAVIGATE ESUS (Rivaroxiban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) trial and RE-SPECT ESUS (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source) trial failed to support this hypothesis.[22] The NAVIGATE ESUS trial was halted after an interim analysis of 7213 patients because of a higher risk of hemorrhage and no discernible difference in the primary outcome of secondary stroke or systemic embolism between patients randomly assigned to rivaroxaban or aspirin.[22] However, limitations of the study include the use of 15 mg of rivaroxaban rather than 20 mg as recommended for stroke prophylaxis. Furthermore, only 20 hours of cardiac rhythm monitoring was required for inclusion and >6 minutes of AF for diagnosis.[23] The RE-SPECT ESUS trial enrolled 5390 patients and also

found no difference between the treatment groups of dabigatran and aspirin.[24,25] However, a subgroup analysis suggested that dabigatran may be effective for patients >75 years of age, which may reflect the increasing incidence of undiagnosed AF within this subgroup.[25]

Postulated limitations of these studies explaining the neutral results include the breadth of the current ESUS definition.[25] Furthermore, although clot histology in atherosclerotic plaque rupture and thrombus formation is similar to that of cardioembolic strokes, current guidelines for secondary stroke prevention continue to advocate the use of antiplatelet agents over anticoagulation in this setting. The results of NAVIGATE-ESUS and RE-SPECT ESUS have both highlighted the need for further revision of the ESUS definition to identify those patients in whom anticoagulation would be of therapeutic benefit.

Anticoagulation in Embolic Stroke of Unknown Source With Evidence of Atrial Cardiomyopathy

Currently, there are 2 further ongoing trials: ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) randomized trial and ATTICUS (Apixiban for Treatment of Embolic Stroke of Undetermined Source), both of which are large randomized control studies assessing anticoagulation therapy and reduction in stroke recurrence in patients with ESUS. Both trials further subcategorize patients with ESUS into those with high-risk features suggestive of cardioembolism[12,26] (see Table 1). ARCADIA will recruit patients with specific biomarkers of atrial cardiomyopathy including elevated $PTFV_1$, serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) and left atrial diameter on echocardiogram. The inclusion criteria for ATTICUS are broader and include nonmajor risk factors for cardioembolism. As with NAVIGATE ESUS, a significant limitation of the ARCADIA study design is that the minimum period of cardiac rhythm monitoring required is 24 hours. Previous studies have suggested that longer periods of monitoring are required for detection of AF.[7,8] Although this study will likely include patients in whom AF would have been detected and therefore excluded following a longer period of monitoring, further analysis of this cohort may provide data regarding the impact of early anticoagulation, which as yet remains unknown. All patients in the ATTICUS study will have an implantable loop recorder inserted and cross over to the apixiban treatment arm should >2 minutes of AF be detected. Additionally, the primary end point will be new ischemic lesions identified on imaging rather than clinical stroke. The results of these studies will provide further evidence on the relevance of the ESUS subgroup in influencing treatment strategies.

Table 1. Studies Assessing Aspirin Versus Anticoagulation Therapy in Reducing Stroke Recurrence in Patients With Ischemic Stroke

Study Name	Study Design	Sample Size	Patient Cohort	Treatment Group	Primary Outcome Measure	Findings
WARSS (1993–2000)[18]	Multicenter, double-blind, randomized control study	2206	Cryptogenic stroke	Warfarin	Recurrent stroke or death	No difference between aspirin and warfarin in prevention of recurrent stroke/death or rate of major hemorrhage
NAVIGATE ESUS (2014–2018)[23]	Multicenter, double-blind, randomized control study	7213	ESUS	Rivaroxaban	Recurrent ischemic/hemorrhagic stroke or systemic embolism	Rivaroxaban was not superior to aspirin in prevention of recurrent stroke and was associated with a higher risk of bleeding
RE-SPECT ESUS (2014–2018)[24]	Multicenter, double-blind, randomized control study	5390	ESUS	Dabigatran	Recurrent stroke	Dabigatran was not superior to aspirin, but had a higher risk of nonmajor hemorrhage
ATTICUS (2015–2021)[26]	Multicenter, open-label, randomized control trial	≈500	ESUS and nonmajor risk factors for cardioembolic stroke	Apixaban	At least 1 new ischemic lesion identified on MRI imaging at 12 mo	Study in progress
ARCADIA (2018–2022)[12]	Multicenter, double-blind, randomized control study	≈1100	ESUS and biomarkers of atrial cardiomyopathy	Apixaban	Recurrent ischemic/hemorrhagic stroke	Study in progress

ARCADIA indicates Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke; ATTICUS, Apixiban for Treatment of Embolic Stroke of Undetermined Source; ESUS, embolic stroke of undetermined source; MRI, magnetic resonance imaging; NAVIGATE ESUS, Rivaroxiban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source; RE-SPECT ESUS, Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source; and WARSS, Warfarin-Aspirin Recurrent Stroke Study.

The study design of both the ARCADIA and ATTICUS trials suggests that noninvasive markers of atrial cardiomyopathy may be the key to identifying specific subgroups of patients with ischemic stroke that could benefit from early anticoagulation.[25] While many of these patients may go on to develop AF in the future, there may also be a cohort of individuals in whom biomarkers of atrial cardiomyopathy exists with elevated risk of stroke but in the absence of AF.

IS THERE A CAUSAL RELATIONSHIP BETWEEN AF AND STROKE?

The association between ischemic stroke and AF has been established in several studies, with patients with AF experiencing on average a 3- to 5-fold increased risk of stroke after adjustment for risk factors.[27–29] While there is clearly a strong association between the 2 with proven consistency among different cohorts, a true causal relationship has not been established as outlined below.[13]

Increased Duration of AF Does Not Increase Stroke Risk

Traditional theories suggest that during periods of AF, thromboembolic risk is increased because of ineffective atrial contraction leading to blood stasis and therefore, as per Virchow's triad, increased thromboembolic risk.[13] In the long-term, left atrial remodeling occurs in the context of long-standing AF leading to atrial dilatation, fibrosis, and increased blood stasis as a result of ineffective atrial contractility.[30–32]

It has been theorized that these remodeling changes contribute to an elevated stroke risk, and therefore patients with persistent AF are at higher risk of thromboembolic stroke. This was demonstrated in the ROCKET-AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) where the adjusted rates of stroke or systemic embolism were 2.18 in the persistent AF group, compared with 1.73 in the paroxysmal AF group. However, other studies including the RE-LY (Randomised Evaluation of Long Term Anticoagulant Therapy) trial found no significant change in thromboembolic risk between paroxysmal, persistent, and permanent AF.[33–37] Failure of trials to consistently demonstrate a clear relationship between AF duration and stroke risk suggests lack of causal effect between AF burden and ischemic stroke.[13]

Moreover, remodeling changes begin to occur after 1 week of AF and progress over time, whereas several studies have demonstrated increased stroke risk with AF episodes of shorter duration, suggesting that alternative/additional pathological processes increasing prothrombotic risk must be at play.[33,37,38]

Embolic Stroke Can Occur in Advance of Atrial Fibrillation

Inconsistencies in the temporal relationship between stroke and AF have also been demonstrated in previous studies (Figure 2). If AF alone increases the risk of thromboembolic disease, it stands to reason that AF should occur in advance of stroke. The ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing) trial assessed patients with a pacemaker or implantable cardiac defibrillator device and reported a 2.5-fold increase in the risk of stroke or systemic embolism in those in whom subclinical AF was detected. However, of those who had a stroke, only 8% had documented episodes of subclinical AF in the month preceding their stroke and as many as 16% had episodes of subclinical AF detected *after* the event.[39] This was further supported by the IMPACT (Combined Use of Biotronik Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk) trial, where strong association was once again demonstrated but in the absence of a temporal relationship.[40] These findings indicate that while there is a reproducible association between stroke and AF, a history of AF is not necessarily a prerequisite of a thromboembolic stroke.

Restoration of Sinus Rhythm Does Not Reduce the Risk of Ischemic Stroke

Finally, a causal relationship between AF and stroke would indicate that in the absence of the arrhythmia, a demonstrable reduction in thromboembolic stroke should be observed. A meta-analysis of rate versus rhythm control therapies in the management of AF showed the number of strokes to be unchanged regardless of strategy (odds ratio [OR], 0.99; 95% CI, 0.76–1.30), despite reasonable success at maintaining sinus rhythm (OR, 4.39; 95% CI, 2.84–6.78).[41] While these results were largely swayed by a single, large randomized control study, the AFFIRM trial (A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation, The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators), a further meta-analysis of 13 studies compared long-term stroke rates following catheter ablation with antiarrhythmic medication and found no evidence of reduced stroke risk.[42] This was evident despite improved effectiveness in maintaining sinus rhythm following catheter ablation compared with antiarrhythmic medication, with 445 of 855 patients crossing over from the medical to interventional arms of the studies because of drug failure or intolerance.[42]

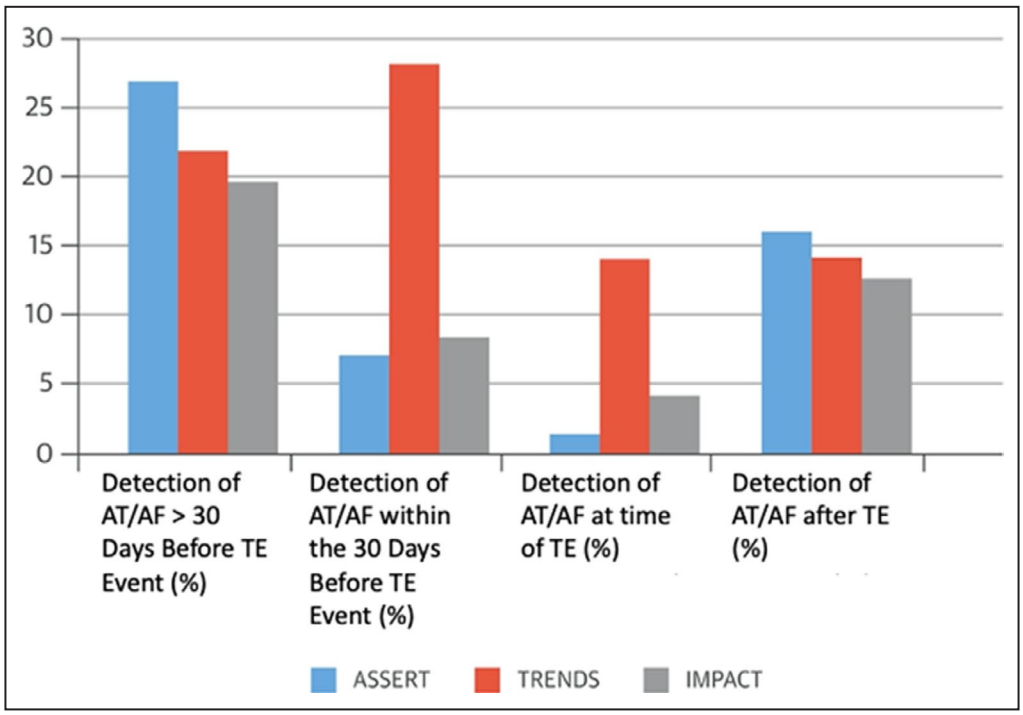

Figure 2. Graphical representation showing temporal dissociation between atrial tachycardia/atrial fibrillation (AT/AF) and thromboembolic stroke (TE) in ASSERT, TRENDS, and IMPACT studies.
ASSERT indicates Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing; IMPACT, Combined Use of Biotronik Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk; and TRENDS, The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk.
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These findings may be explained by atrial structural remodeling that exists even in the presence of adequate rhythm control; however, a previous large retrospective study suggests that risk factors for stroke may be different following catheter ablation, and alternative risk scores have been proposed that may improve stroke risk stratification after catheter ablation treatment.[43]

Can Ischemic Stroke Cause AF?

Although less commonly explored, stroke has been hypothesized to cause AF attributable to autonomic nervous system activation leading to changes in cardiac electrophysiology providing a substrate for atrial arrhythmias.[13,44] Previous clinical studies have observed a higher incidence of AF in the early poststroke period that may support this hypothesis.[8,45] However, patients in these studies had no prior heart rhythm monitoring for AF detection. Furthermore, the ASSERT trial observed a median time of 101 days before AF detection, suggesting that a proportion of patients within these studies may have had undiagnosed AF that preceded the stroke event.

The inconsistencies described above add further weight to the emerging concept that the relationship between AF and stroke may represent association rather than causation, and therefore consideration must be given to the implications of this on therapeutic considerations for stroke prevention.

LIMITATIONS OF CURRENT TREATMENT STRATEGIES

While the AF-stroke relationship remains incompletely understood, meta-analyses have rigorously proven anticoagulation therapy with vitamin K antagonists or direct oral anticoagulants in patients with AF significantly reduces the risk of stroke.[46,47] However, a delay in the detection of AF leads to further delays in initiation of anticoagulation therapy in a high-risk cohort. Previous studies show a reduction in thromboembolic stroke risk by as much as 60% following anticoagulation therapy, compared with 20% while on an antiplatelet agent, with the risk of stroke recurrence being highest in the initial 12 months following the event.[47,48] A large proportion of patients with ESUS are suspected

to have undiagnosed AF, yet do not receive anticoagulation.[7] With stroke recurrence rates as high as 30% in this cohort, it is conceivable that a proportion of these strokes are preventable with a change in treatment strategy tailored to the individual.

The limitations of the currently accepted AF-stroke model have several implications pertaining to therapy. First, it relies on an episode of AF being detected before initiation of anticoagulation therapy. The temporal dissociation described above suggests that the risk of stroke associated with AF may occur distant from the AF episode.[49] Even with an implantable loop recorder in situ, AF may be detected in only around 12% of patients with cryptogenic stroke over a 1-year period.[8] With historical studies demonstrating a reduction in secondary stroke risk from 12% to 4% per year (hazard ratio, 0.34; 95% CI, 0.36–0.79) in patients randomly assigned to receive anticoagulation or placebo following stroke, the risks of delaying anticoagulation in this cohort of patients are likely to be significant.[50] This observation was recently supported in the EAST-AFNET 4 (Early Rhythm Control Therapy in Patients with Atrial Fibrillation) study, where lower stroke rates were documented in patients receiving early rhythm control compared with usual care (treatment effect hazard ratio, 0.65; 95% CI, 0.44–0.97).[51]

Furthermore, a proportion of patients may never develop AF but remain at high risk of embolic stroke attributable to underlying atrial disease in keeping with an atrial cardiomyopathy. With current risk stratification models requiring a diagnosis of AF before initiation of anticoagulation therapy, this cohort does not currently meet the criteria for treatment.

ATRIAL BIOMARKERS FOR RISK STRATIFICATION OF PATIENTS WITH ESUS

The CHA_2DS_2VASc scoring system is unanimously the risk stratification tool of choice to identify main predictors of stroke in the context of AF.[52] Patients with AF with no identifiable risk factors are at only a marginally increased risk of stroke compared with patients without AF.[53] It is interesting to note that anticoagulation guidance has little focus on the clinical characteristics of atrial fibrillation such as arrhythmia duration, sustained rapid ventricular response or arrhythmia persistence, but rather on comorbidities associated with a cardiomyopathic state.

Recently, alternative biomarkers associated with an atrial cardiomyopathy have been associated with the risk of stroke independent of AF. Identification of such biomarkers, as outlined below, may represent a new approach for risk stratification in prevention of ischemic stroke, providing anticoagulation guidance in the absence of documented AF.

Cardiac Imaging Biomarkers

Atrial Fibrosis

Atrial fibrosis has been identified as a potential precursor leading to the initiation and perpetuation of AF. Fibrosis occurs as a result of excessive deposition of extracellular matrix predominantly containing collagen I, collagen III, and fibronectin.[54] Atrial structural remodeling at the tissue level comprises myocyte apoptosis, alterations in cellular metabolism, and accumulation of glycogen.[15,55] Together, these changes predispose to alterations in the orientation of cardiac myocytes, redistribution of gap junctions, and therefore velocity of electrical conduction, giving rise to electrical conduction delay and atrial substrate for sustaining AF. Furthermore, a thrombogenic substrate is generated because of increased inflammation, endothelial dysfunction, and blood stasis.[15] Together, these changes could lead to the development of a procoagulant state resulting in increased risk of thromboembolism and clinical stroke. Atrial structural remodeling could be caused by AF but may also be promoted by other factors such as age, hypertension, diabetes mellitus, inflammation, and heart failure, suggesting that stroke may be caused by AF or abnormal atrial substrate.[15,56] Atrial fibrosis may therefore precede AF, or be present even in the absence of AF.

To use the extent of left atrial fibrosis as a means of stroke risk stratification and a guide for anticoagulation therapy, a biological relationship in which severity of fibrosis is directly related to stroke risk needs to be demonstrated to prove causation. Indeed, accumulating evidence suggests that such a relationship may exist. An observational, case-control study of 111 patients detected a statistically significant increase in left atrial fibrosis of patients with cryptogenic stroke compared with stroke of other specific causes (excluding AF).[57,58] The left atrial phenotype of those with cryptogenic stroke appeared to be an intermediate between those with AF and other specific causes for stroke, possibly representing earlier detection of an atrial cardiomyopathy that may ultimately progress to AF with disease progression.[57,58] The process of disease progression is further supported in histological studies where greater fibrosis has been demonstrated in autopsies of patients with permanent AF compared with paroxysmal AF, although the extent of fibrosis was not found to correlate with the duration of AF history.[59]

Atrial cardiac magnetic resonance imaging is currently the gold standard tool for noninvasive atrial tissue characterization and has been used in the quantification of atrial fibrosis by identifying areas of late gadolinium enhancement in the atrial wall (Figure 3).[60] However, there are a number of

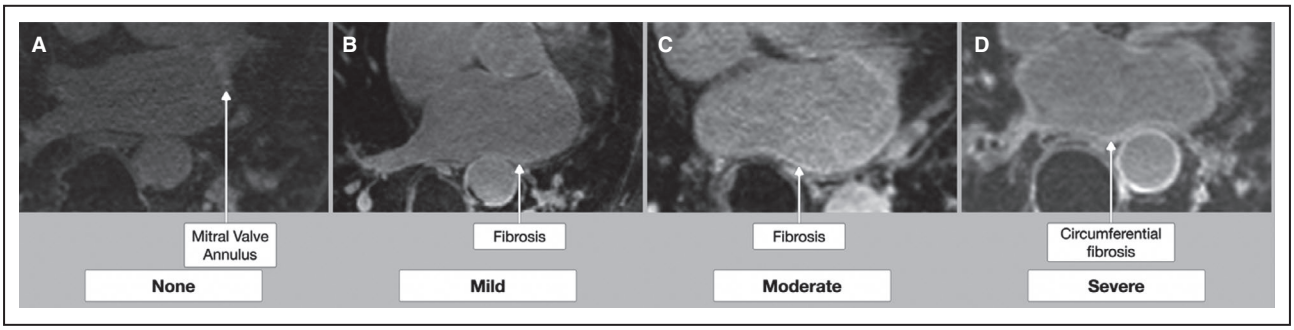

Figure 3. Representative left atrial cardiac magnetic resonance imaging showing various degrees of late gadolinium enhancement suggestive of a normal left atrium (A), focal area of fibrosis on the posterior wall of the left atrium (B)**, diffuse posterior wall fibrosis (C), and circumferential fibrosis (D).**

limitations of atrial late gadolinium enhancement assessment that could hinder its use as a risk assessment tool. First, cardiac magnetic resonance imaging is expensive and less readily available compared with alternative imaging techniques such as echocardiography. Second, accurate quantification of atrial fibrosis is dependent on the image quality acquired. There is currently a large variability in image acquisition parameters, image analysis, and postprocessing tools across different centers.[61]

Atrial Enlargement and Geometry

A susceptibility to atrial arrhythmias has been demonstrated during abnormal myocardial loading that results in atrial stretch and dilatation, playing an important role in the pathogenesis of AF.[38] During AF, uncontrolled ventricular rates can lead to increased hemodynamic overload and consequently cardiac failure, providing an underlying mechanism for atrial dilatation. However, comorbidities such as hypertension, heart failure, or mitral valve disease also contribute to atrial dilatation, increasing the vulnerability of the left atrium to AF. Ex vivo studies in guinea pig hearts demonstrated electrophysiological changes in atrial tissue following increased left atrial volume.[62] A further study in Langendorff-perfused rabbit hearts showed a graded increase in AF vulnerability that correlated with increasing atrial pressures.[63] Later, in vitro studies of atrial stretch have shown downstream effects of hypertrophy and apoptosis that feed into the structural and electrophysiological changes described above. Atrial dilatation is related to both the severity of the underlying disease as well as the AF burden and may therefore precede AF manifestation in the context of other risk factors.[38]

The relationship between atrial size and stroke risk has been controversial, in large part because of the significant limitations of studies that were conducted in patients with AF or mitral valve disease. A subgroup analysis of the Framingham Study assessed left atrial size and stroke risk in all patients >50 years of age.[64] After multivariable adjustment, left atrial size was found to be an independent predictor of stroke with every 10-mm increase in left atrial size, resulting in a relative risk ratio of 2.4 for men (95% CI, 1.6–3.7) and 1.4 for women (95% CI, 0.9–2.1).[64,65] Further population-based studies in the Northern Manhattan Stroke Study assessed the role of atrial enlargement as an independent risk factor for recurrent ischemic stroke in a multiethnic population.[65,66] Moderate to severe left atrial enlargement was demonstrated in patients with a recurrent cardioembolic or cryptogenic stroke with a hazard ratio of 2.83 after multivariable adjustment (95% CI, 1.03–7.81). These findings were attributed to reduced flow velocity in the LAA or left atrial enlargement representing a marker of end-organ damage from hypertension, which is a known risk factor for recurrent stroke.

Echocardiography is the most common modality of assessing atrial size and has dominated previous studies; however, a significant limitation is that it assumes a spherical left atrial shape, therefore frequently underestimating left atrial volume.[67–70] Improved image quality with cardiac magnetic resonance imaging has since increased our understanding of atrial shape.[71] The left atrium can often be asymmetrical, and AF disease progression frequently results in geometric changes such as sphericity, trapezoidal deformation, or alterations in roof shape.[72–74]

Left Atrial Appendage

The majority of left atrial thrombi have been reported to originate from the LAA.[75–77] Furthermore, trials of LAA closure were noninferior to warfarin in reducing the risk of ischemic stroke, highlighting the significance of LAA in stroke risk.[78,79]

Non–chicken wing LAA morphologies, including cactus, windsock, and cauliflower, have been shown

in some trials to increase stroke risk because of more extensive LAA trabeculations and smaller LAA orifice diameter.[80,81] However, a key limitation of these studies has often been interobserver reproducibility, with one study having found LAA morphology agreement to be 58.82%. To date, classification remains subjective, and there are no automated or semiautomated algorithms available between centers to ensure reproducibility.[80] In addition, LAA morphology has been investigated only in patients with AF, and the significance of morphology in the absence of AF remains unknown.

A cross-sectional study also demonstrated reduced LAA flow velocity on echocardiography between patients with AF and patients without AF, which may increase blood pooling and stasis, leading to clot formation.[82–84] While further studies are required to understand the relevance of LAA morphology in the absence of AF, there is some evidence that LAA flow may represent a biomarker of recurrent ischemic stroke risk.

Electrocardiographic Biomarkers

P-wave terminal force in lead V_1

$PTFV_1$ is defined as the duration (in seconds) of the negative terminal deflection of the P-wave in lead V_1 multiplied by the absolute value of its amplitude (in mm) and is considered a marker of left atrial abnormality.[85,86] Several studies have shown elevated $PTFV_1$ to be associated with atrial disease, including dilatation, hypertrophy, fibrosis, and abnormal interatrial conduction, all of which are consistent with structural and electrical remodeling changes that occur in atrial cardiomyopathy.[87] A 2-year study of 295 consecutive patients with ischemic stroke found $PTFV_1$ to be a strong predictor of paroxysmal AF in patients with ischemic stroke and noted a cutoff value of 0.04 mm/s for paroxysmal AF prediction (sensitivity, 80%; specificity, 72.2%.). $PTFV_1$ was argued to be a cheap and practical method for selecting patients that require more extensive electrocardiographic monitoring for the detection of AF in patients with ischemic stroke.[85] Abnormal $PTFV_1$ has also been shown to independently correlate with diffuse left ventricular fibrosis quantified on cardiac magnetic resonance imaging and measured as a surrogate for atrial fibrosis.[88]

Evidence of a correlation between $PTFV_1$ with ischemic stroke independent of AF dates back as far as 2005.[89] More recently, the ARIC (Atherosclerosis Risk in Communities) study provided further evidence of an association between P-wave terminal force in lead V_1 as both an AF predictor and incident ischemic stroke.[90] These findings have been further supported in the Multi-Ethnic Study of Atherosclerosis, ARIC study, and the Northern Manhattan Study, which showed an association between $PTFV_1$ and ischemic stroke independent of AF.[91,92]

Atrial Ectopy

High atrial ectopic burden has also been associated with an increased risk of developing AF,[93] and a recent single-center case-control study of 2800 patients found the mean premature atrial complex count on 24-hour monitoring to be 426 in the ischemic stroke group compared with 105 in the control group ($P<0.001$).[94] This was supported by the Copenhagen Holter Study cohort, in which excessive atrial ectopic activity (defined as either >30 atrial ectopics per hour daily or runs of >20 atrial ectopics) was associated with an increased stroke risk even in the absence of electrocardiographic evidence of AF.[95] A possible mechanism could be atrial ectopy occurring as a precursor to AF. Alternatively, atrial ectopy may be a marker of other risk factors such as hypertension, diabetes mellitus, or structural remodeling leading to atrial fibrosis and endothelial dysfunction, resulting in a hypercoagulable state.[95]

Prolongation of PR interval

Although the PR interval displays circadian variation,[96] population-based studies have shown prolongation of the electrocardiographic PR interval to be associated with a 2-fold increased risk of AF and up to 5-fold in those in the upper 95th centile after adjusting for risk factors.[97,98] PR prolongation could be a manifestation of initial conduction disease occurring as a result of structural cardiac abnormalities and therefore a further biomarker of atrial disease.[99,100] Alternatively, PR prolongation can be associated with other conduction abnormalities or a sign of slow intra- or interatrial conduction providing the atrial mechanism to sustain AF.[101] Both a large multicenter retrospective trial and the CRYSTAL-AF (Cryptogenic Stroke and Underlying Atrial Fibrillation) trial demonstrated a strong association between PR prolongation and increased AF incidence in cryptogenic stroke.[98,102]

$PTFV_1$, atrial ectopy, and PR prolongation have all demonstrated an association with ischemic stroke in the absence of AF and may be attributed to an underlying atrial cardiomyopathy. However, despite these associations, predictive models that have implemented these criteria, such as the Framingham AF Score, have displayed moderate or low predictive capacity.[98,103] These findings highlight the difficulty in application of large population trends on an individual patient level.

Serum Biomarkers

N-Terminal Pro-B-Type Natriuretic Peptide

NT-proBNP is a neurohormone released by the myocardium in response to increased wall tension. NT-proBNP can be elevated in a number of conditions, causing hemodynamic stress including heart failure, AF, and structural heart disease.[104] Previous studies have demonstrated elevated NT-proBNP in matched patients with AF compared with sinus rhythm as well as a rapid reduction in levels on restoration of sinus rhythm.[105,106] Furthermore, both the RE-LY substudy and later the ARISTOTLE study found the risk of stroke or systemic thromboembolism to be independently related to NT-proBNP in patients with AF and more than doubled in the highest compared with the lowest NT-proBNP quartile groups, suggesting there may be a role for inclusion of NT-proBNP in stratifying future stroke.[107,108] Additional studies advocate use of NT-proBNP levels in the detection of new AF following cryptogenic stroke; however, it may not add further diagnostic information over and above traditional noninvasive methods for AF detection.[109,110]

Troponin

Troponin is a cardiac enzyme most commonly used as a biomarker in the detection of myocardial infarction or injury but can also be serum detectable at low levels in patients with heart failure, structural heart disease, stable coronary artery disease, renal failure, and increasing age. The RE-LY substudy and ARISTOTLE studies demonstrated that rates of stroke were independently related to higher levels of troponin I. The RE-LY substudy results further indicated that addition of troponin I levels to a predictive model for stroke outcomes provided additional prognostic information.

Further studies are required to incorporate serum biomarkers in predictive models of future stroke risk following ESUS to determine their significance and implications on future anticoagulation.

ATRIAL CARDIOMYOPATHY

The term *atrial cardiomyopathy* has been defined as "any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations." Its clinical value may lie in its role as a precursor to AF, predicting those likely to develop AF as well as allowing substrate classification that may inform individualized patient care strategies. Furthermore, it may define a cohort of patients with hypercoagulability and at risk of thromboembolic disease (see Table 2). Several intra-atrial sampling studies assessing markers of hypercoagulability have shown a statistical difference in marker levels between patients with AF and patients without AF.[111,112] However, there are no studies as yet that have assessed whether a procoagulant state predates the onset of detectable AF. Furthermore, a limitation of these studies has been the inability to distinguish hypercoagulability secondary to concomitant comorbidities such as vascular disease or directly attributable to AF.[113,114]

The European Heart Rhythm Association/Heart Rhythm Society expert consensus on atrial cardiomyopathy proposes a histological classification of atrial cardiomyopathy (European Heart Rhythm Association Class I–IV), emphasizing it to be a descriptive classification rather than a pathway of disease progression.[115] The classification allows discrete cohorts of atrial cardiomyopathy to be studied further to validate the classification and understand its clinical relevance with regard to individualized therapy for patients with AF.

A cross-sectional pilot study of the NYCC SPOTRIAS (New York Columbia Collaborative Specialized Program of Translational Research in Acute Stroke) registry found that 63% of patients had at least 1 biomarker of left atrial cardiomyopathy (including severe left atrial enlargement, elevated NT-proBNP, or elevated $PTFV_1$). However, the sample size was too small to draw conclusions regarding clinical significance, as only 4 patients developed paroxysmal AF after their stroke, of which 2 had evidence of atrial cardiomyopathy as per the classification.

LIMITATIONS

Several limitations exist in the development of novel risk scores. First, there is significant overlap between several biomarkers, which can be difficult to separate.[57] For example, elevated B-type natriuretic peptide, a biomarker of atrial wall stress, has been found to be elevated in patients with atrial dilatation.[3] Similarly, $PTFV_1$ is a measure of left atrial activation and has historically been used as a marker of left atrial dysfunction. Other biomarkers such as left atrial size, geometry, or fibrosis may also affect the $PTFV_1$ and the risk score therefore compounded. Additionally, further studies are required to assess the comparable significance of each biomarker to understand its individual relevance within the risk score.[57] These limitations are significant in that the study design of recent and ongoing trials use variable definitions of atrial cardiomyopathy creating difficulty when comparing study outcomes.

A further limitation is the long-term follow-up required for AF detection in the ESUS group. It is well documented that the incidence of AF and atrial

Table 2. Features of Atrial Cardiomyopathy and Evidence of Association With AF and Stroke

	Study/Author	Sample Size	Association With AF	Association With Stroke	Limitations
Atrial fibrosis	Platonov et al[59]	30 patients	Patients with PsAF had greater fibrosis than those with PAF. 2 to 3× increase in fibrosis and fatty infiltration in patients with AF compared with sinus rhythm.	N/A	CMR imaging is expensive Accuracy of findings, in particular atrial fibrosis, is dependent on image quality acquired Large interobserver reproducibility of left atrial appendage morphology Large variability in image acquisition parameters, image analysis, and post-processing tools across different centers
	Boldt et al[55]	118 patients	Increased protein concentrations in patients with AF compared with those in sinus rhythm. No systematic difference in ECM expression between PAF and PsAF.	N/A	
	Fonseca et al[58]	111 patients	N/A	Cryptogenic stroke patients had a higher percentage of LA fibrosis compared with other stroke types (P=0.03). Patients with cryptogenic stroke had an intermediate LA phenotype compared with those with AF and other stroke causes.	
Atrial enlargement and geometry	Nazir et al[62]	12 guinea-pigs (ex vivo)	Increased LA volume and load changes resulted in increased arrhythmia occurrence or premature atrial beats.	N/A	
	Bode et al[63]	16 rabbits (ex vivo)	Acute atrial stretch significantly enhances vulnerability to AF.	N/A	
	Framingham Heart Study, Benjamin et al[64]	3099 patients (subgroup analysis)	N/A	After multivariable adjustment, for every 10 mm increase in LA size, the RR of stroke was 2.4 in men (95% CI, 1.0–1.5) and 1.4 in women (95% CI, 1.1–1.7).	
	Tullio et al[65]	721 patients (352 study group, 369 control group)	N/A	LA index was associated with ischemic stroke in the overall group (adjusted OR, 1.47 per 10 mm/1.7 m^2 of BSA; 95% CI, 1.03–2.11).	
	Cozma et al[72]	112 patients	LA dilatation is accompanied by changes in LA shape. Proportion of patients with trapezoidal LA shape was increased. LA dilatation and electrical remodeling are interrelated.	N/A	
	Bisbal et al[74]	106 patients	Left atrial sphericity is an independent predictor of recurrence of AF after AF ablation.	N/A	

(*Continued*)

Table 2. Continued

	Study/Author	Sample Size	Association With AF	Association With Stroke	Limitations
LAA	Belgaid et al[78]	407 patients	N/A	LAA occlusion is noninferior to warfarin in secondary stroke prevention in nonvalvular AF.	
	Holmes et al[79]	407 patients	N/A	LAA occlusion is noninferior to warfarin in secondary stroke prevention in nonvalvular AF.	
	Khurram et al[80]	65 patients	N/A	Extent of LAA trabeculations and smaller LAA orifice diameter are associated with stroke prevalence in AF patients. LAA morphologies were not associated with stroke risk.	
	Di Biase et al[81]	932 patients	N/A	Chicken wing morphology is 79% less likely to have a stroke/TIA history (OR, 0.21; 95% CI, 0.05–0.91; P=0.036) in patients with AF. Cauliflower morphology is 8 times (P=0.056) more likely to have had a stroke/TIA.	
	Lee et al[82]	218 patients (study group =67, control group=151)	N/A	In patients with flow velocity <37.0 cm/s, larger LAA orifice (>3.5 cm^2) was associated with a greater incidence of stroke in patients with AF.	
	SPAF-III study, Goldman et al[83].	721 patients	N/A	Patients in AF displayed lower peak antegrade (emptying) flow velocity than those in SR or with intermittent AF. AVp<20 cm/s was associated with appendage thrombus (P<0.01) and cardioembolic events (P<0.01).	
$PTFV_1$	Goda et al[85]	295 patients	$PTFV_1$ was significantly higher in patients with PAF than those without PAF (–0.051 vs 0.027 mm/s, P<0.001).	N/A	Despite strong association, predictive models have moderate or low predictive capacity.
	Northern Manhattan Study, Kamel et al[92]	1039 patients (study group=241, control group=798)	N/A	$PTFV_1$ was associated with cryptogenic or cardioembolic stroke (HR, 1.14; 95% CI, 1.08–1.58).	
	Atherosclerosis Risk in Communities study, Kamel et al[91]	14 552 patients	N/A	$PTFV_1$ >40 ms.mm was associated with incident ischemic stroke (HR, 1.33; 95% CI, 1.11–1.59) in the absence of AF.	
	ARIC study, Soliman et al[90]	15 429 patients	HR for incident AF associated with $PTFV_1$ was 1.22 (95% CI, 1.14–1.31) when corrected for demographic and clinical variables.	$PTFV_1$ was the strongest AF predictor for incident stroke. HR, 2.28 (95% CI, 1.79–2.90).	

(Continues)

Table 2. Continued

	Study/Author	Sample Size	Association With AF	Association With Stroke	Limitations
	Kohsaka et al[89]	341 patients (study group =146, control group=195 control)	N/A	$PTFV_1$ >40 ms.mm was associated with ischemic stroke after adjustment for other stroke risk factors (OR, 2.32; 95% CI, 1.29–1.48). Effect of $PTFV_1$ on stroke risk was strongly dependent on LV mass.	
Atrial ectopy	Koshy et al[94]	2800 patients	N/A	Mean premature atrial complex count on 24-hour monitoring 426 vs 105 (study group vs control group) with P-value <0.001.	
	Copenhagen Holter study cohort, Larsen et al[95]	678 patients	N/A	Excessive atrial ectopic activity (>30 ectopics/h or runs of over 20 ectopics) associated with an increased risk of stroke in absence of AF.	
	Dewland et al[93]	5201 patients	Atrial ectopy showed similar AF risk discrimination compared with AF Framingham Risk score. A 100% increase in hourly atrial ectopy was associated with a significant increase in AF risk (HR, 1.17; 95% CI, 1.13–1.22; P<0.001).		
Prolongation of PR interval	Framingham Heart Study, Cheng et al [97]	7575 patients	PR >200 ms associated with a 2-fold adjusted risk of AF (HR, 2.06; 95% CI, 1.36–3.12; P<0.001).	N/A	
	CRYSTAL AF, Thijis et al[8]	221 patients	PR prolongation was independently associated with an increased AF incidence in cryptogenic stroke patients (HR, 1.3 per 10 ms; 95% CI, 1.2–1.4; P<0.0001).	N/A	
	Montalvo et al[102]	687 patients		Mean PR interval was longer in patients with cryptogenic stroke compared with other known stroke etiology (175.4 vs 166.5). 23.2% of patients with cryptogenic stroke had a PR interval >200 ms compared with 13.8% of those with alternative stroke etiology (P=0.009).	

AF indicates atrial fibrillation; AVp, peak integrate (emptying) flow velocity; BSA, body surface area; CMR, cardiac magnetic resonance; CRYSTAL-AF, Cryptogenic Stroke and Underlying Atrial Fibrillation; ECM, extracellular matrix; HR, hazard ratio; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; N/A, not applicable; OR, odds ratio; PAF, paroxysmal atrial fibrillation; PsAF, persistent atrial fibrillation; $PTFV_1$, P-wave terminal force in lead V1; RR, relative risk; SPAF III, Stroke Prevention in Atrial Fibrillation III; and TIA, transient ischemic attack.

disease increases with advanced age presenting further challenges in differentiating patients with ESUS at increased risk of developing AF. Furthermore, AF detection following stroke is affected by a number of external noncardiac confounders, as yet unaccounted for in many of the risk scores, such as smoking, air pollution, and obesity. These factors likely have increased weighting over time, making it increasingly difficult to identify meaningful risk factors.

With this in mind, it is certainly worth considering recent technological advances and whether there may be a role for the use of machine learning in further defining risk factors. However, it is imperative that models are built using high-quality data and appropriate machine learning methodology to ensure reproducibility and clinical utility.

CONCLUSIONS

The relationship between AF and ischemic stroke is complex. Atrial cardiomyopathy may be an underlying mechanism for embolic stroke of unknown source but requires further research to create definitions of clinical significance. Imaging and electrocardiographic biomarkers of atrial cardiomyopathy in the absence of AF show promise in observational data (see Table 2), but studies implementing these biomarkers within risk stratification scores have, to date, lacked sensitivity and specificity, highlighting a need for improved risk stratification models. In addition, large randomized studies assessing anticoagulation in the ESUS group have not shown statistically significant benefit as yet, perhaps because of the further need to better identify patients at high risk of stroke recurrence. Ongoing studies, including ARCADIA and ATTICUS, will assess the clinical significance of ESUS in the context of underlying structural or electrical atrial disease. If positive, these studies could lead to the design of randomized trials where anticoagulation therapy is determined not by the presence or absence of AF but by the presence or absence of the underlying atrial cardiomyopathy. This development would result in a step change in the clinical management of patients with ESUS and should be an area of research priority over the coming years.

ARTICLE INFORMATION

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