

Ischaemic stroke in the absence of documented atrial fibrillation: is there who could benefit from anticoagulant therapy?

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About 25% of ischaemic strokes are of cryptogenic origin and a significant proportion of them has a certain embolic nature, and for these patients the term embolic stroke of undetermined source (ESUS) has been coined. In the absence of subclinical atrial fibrillation (AF) identifiable through prolonged electrocardiogram monitoring, atrial cardiomyopathy, demonstrable through non-invasive cardiac imaging, aortic plaques and heart failure with preserved sinus rhythm, have been recognized among the potential causes of ESUS. In patients with ESUS, randomized clinical trials performed so far have failed to demonstrate a benefit of therapy with direct oral anticoagulants (DOACs). However, it is possible that in patients in whom the presence of atrial cardiomyopathy is ascertained there may be a benefit of anticoagulant therapy in secondary prevention after ESUS. In patients with aortic plaques associated with a thrombotic component and in those with heart failure and preserved sinus rhythm in the absence of AF but with a high congestive heart failure, hypertension age, diabetes, stroke, vascular disease (CHA₂DS₂-VASc) score, the decision on anticoagulant therapy with DOACs could be made in the individual patient even in the absence of evidence from clinical trials.

Introduction

Ischaemic stroke represents a widespread and disabling disease in the Western world caused by the occlusion of a cerebral arterial vessel, the origin of which can be traced back to different conditions, mainly to a significant arterial disease of the large (25%) or small vessels (25%—determining lacunar stroke), to cardio-embolic sources [20%—primarily atrial fibrillation (AF) but also other less frequent causes such as left endoventricular thrombosis or infective endocarditis] or to more rare causes (5%—such as aortic dissection or arteritis). However, a significant proportion of these patients, equal to approximately 25% of total ischaemic strokes, does not actually receive a certain etiological diagnosis and remains labeled with the generic term of cryptogenic stroke. This category, in

addition to including patients without any risk factor, also groups subjects in whom an incomplete diagnostic work-up has been performed or in which more than one possible cause has been found without being able to reach a sure etiopathogenetic conclusion.

The group of patients with cryptogenic stroke includes patients with a definitely embolic etiology of stroke of undetermined source (ESUS).¹

Occult atrial fibrillation

There are several evidences that underline how an electrocardiogram (ECG) monitoring longer than the usual 24 hours can reveal a significantly higher number of paroxysmal AF. The Cryptogenic Stroke and Underlying AF (CRYSTAL-AF) study² was conducted on 441 patients (mean age 61 years) with a recent cryptogenic cerebral ischaemic event and negative 24-hour ECG-Holter, randomized to receive

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conventional monitoring or an implantable cardiac monitor (ICM). One year later, the AF diagnosis rate was significantly higher in the ICM group (12.4% vs. 2%— $P < 0.001$), with mostly asymptomatic episodes.

In order to identify possible predicting factors of occult AF in patients with ESUS, Ntaios *et al.*³ analyzed the data of 839 consecutive patients with recent cerebral ischaemic event, highlighting that age >60 years represented the main risk factor [odds ratio (OR) 5.55], followed by left atrial dilatation (OR 2.59), hypertension (OR 2.47) and the detection of supraventricular ectopic beats (OR 1.89). These data can allow to optimize the selection of subjects for prolonged ECG monitoring to search for the presence of occult AF.

Atrial cardiomyopathy

The existence of a close association between AF and ischaemic stroke has been demonstrated, traditionally considered a consequence of blood stasis secondary to ineffective contraction of the left atrium and left atrial appendage. In recent years, however, doubts have emerged on the actual causal relationship between the two conditions, supported by the evidence of a poor temporal correlation between AF episodes and cerebral ischaemic events found in trials conducted in patients with implanted cardiac devices that ensured continuous heart rhythm monitoring. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing (ASSERT) study⁴ looked for evidence of episodes of subclinical AF in 51 patients with recent stroke by interrogating the cardiac devices (pacemaker or defibrillator) of which they were carriers. AF was detected in half of the patients but surprisingly only in one case was it recorded close to the ischaemic event and only four subjects (8%) had had AF in the previous month; on the contrary, most of the subjects showed AF episodes long before or only after the ischaemic event.

These findings have led to suspect the existence of a structural/contractile remodeling condition of the atrium responsible in itself for the increased risk of stroke, defined as atrial cardiomyopathy and of which AF could be both a cause and an epiphenomenon. The pathogenesis of atrial cardiomyopathy can indeed be varied. In an Expert Consensus of the EHRA and other arrhythmological scientific societies of 2016,⁵ atrial cardiomyopathy is histologically divided into four main categories, which correspond to distinct underlying pathogenetic factors:

- Class I: primary damage to cardio-myocytes (AF, genetic pathologies, diabetes mellitus);
- Class II: increase in fibroblasts (age, cigarette smoking);
- Class III: intermediate forms (heart failure, valve diseases)
- Class IV: secondary forms to interstitial deposits (amyloidosis, granulomatosis, inflammatory infiltrates, glycosphingolipids).

These alterations are responsible for electrical and/or mechanical dysfunction of the atrium, resulting in a

state of increased coagulability, which can be evaluated using multi-modal imaging methods. The transthoracic echocardiogram represents classically the main method for the study of the left atrium, since it is able to easily evaluate its dimensions, better expressed as volume measured in biplane or more precisely with the 3D technique, and the contractile function, both through sampling of the atrial emptying speed with pulsed Doppler (A wave) which, more recently, through the methods of assessing the entity and speed of the parietal deformation of the atrium (strain and strain rate), proved to be highly sensitive in detecting early the existence of functional changes before the onset of atrial dilatation. Other diagnostic methods, although highly sensitive and specific, have limited availability in clinical practice. Cardiac computed tomography (CTC) shows high accuracy in assessing not only the volume of the atria but also morphological elements, such as a flattening or curvature of the roof of the left atrium indicative of advanced atrial disease or the presence of endocavitary thrombi.

Cardiac magnetic resonance (CMR) imaging represents the gold standard in quantifying cardiac chamber volumes and, through the evaluation of late gadolinium enhancement (LGE) and T1 mapping sequences, can detect the presence and extent of atrial fibrosis, an expression of advanced atrial disease and inverse predictor of procedural efficacy in patients undergoing AF ablation. Electro-anatomical mapping is a method that allows to reproduce 3D images of the atrial anatomy, sometimes optimized by superimposing previously acquired CTC/CMR images, on which the colorimetric map of the atrial electrical activity recorded point by point is built, highlighting the presence of pathological areas (low voltage, electrical silence or signal fractionation) related to the presence of fibrosis and indicative of the presence of a pro-arrhythmic substrate, sometimes with a higher sensitivity than the CMR. However, the invasiveness of the method inevitably limits its routine use in patients with suspected atrial cardiomyopathy.

Recently, the value of the 12-lead ECG in suspecting the presence of atrial cardiomyopathy in a simple and sensitive way has been emphasized. In a large retrospective observational study Maheshwari *et al.*⁶ examined the characteristics of the P wave in 2,229 patients with a diagnosis of AF and a previous ECG in sinus rhythm. In the subsequent follow-up, the detection of an anomaly in the P wave axis was found to be an element associated with an increase in cerebral ischaemic risk (HR 1.84) regardless of the variables identified with the CHA2DS2-VASc. The authors therefore suggested a modification of this score, naming it P2-CHA2DS2-VASc, with the addition of the P wave axis anomaly detected on ECG tracings in sinus rhythm to which 2 points in the thromboembolic risk score are attributed.

In 2020, the BAYES registry⁷ was published, a registry study that sought a correlation between inter-atrial block (IAB) and the incidence of AF and stroke in a population of 556 patients aged >70 years with structural heart disease but without a previous diagnosis of AF. Patients were divided into three groups based on the

duration and morphology of the *P* wave: IAB absent: normal duration of the *P* wave (<120 ms) (40.1%); Partial IAB: *P* wave \geq 120 ms and positive in the lower leads (35.3%); Advanced IAB: *P* wave \geq 120 ms and biphasic in the lower leads (24.6%). In the follow-up of approximately 2 years, the presence of advanced IAB was significantly correlated with the onset of AF [hazard ratio (HR) 2.9], stroke (HR 3.8) or both (HR 3.8). The authors suggested that the electrocardiographic survey of advanced IAB could represent a useful element to identify subjects at greater risk of stroke even in the absence of a previous diagnosis of AF.

Although atrial cardiomyopathy has been shown to have a significant impact in reducing atrial function, increasing the risk of AF and, independently of this, increasing the risk of stroke, there is currently no evidence for it, derived from prospective randomized clinical trials, to justifying the prescription of oral anticoagulant therapy in subjects with atrial cardiomyopathy in the absence of a diagnosis of AF.

Cardiac amyloidosis represents an important cause of atrial cardiomyopathy since amyloid deposits can involve the atria, affecting left atrial dysfunction and possible thromboembolic complications even in the absence of AF. In fact, in patients with cardiac amyloidosis, a non-negligible prevalence of intracardiac thrombi has been documented by CMR despite the absence of AF and in a recent Italian multi-center retrospective study, which included 406 patients with cardiac amyloidosis with a median follow-up of 19 months, arterial thromboembolic events have been reported in 10 patients in sinus rhythm and with no history of AF.⁸ With these premises, in patients with cardiac amyloidosis in the presence of AF, the indication for oral anticoagulant therapy appears reasonable regardless of the CHA2DS2-VASc score, while there is not yet sufficient evidence to recommend its initiation in all patients in absence of AF.

Antithrombotic therapy in patients with cryptogenic stroke and with ESUS

While in the presence of diagnosed AF, oral anticoagulant drugs represent the therapy of choice over antiplatelet drugs, uncertainties remain about the most suitable antithrombotic therapy in patients with ischaemic stroke when a precise etiological diagnosis is not reached.

The Warfarin-Aspirin Recurrent Stroke Study (WARSS) study published in 2001 is the first study that evaluated the usefulness of anticoagulant therapy in patients with cryptogenic ischaemic stroke.⁹ Conducted from 1993 to 2000, enrolled 2206 patients with ischaemic stroke <30 days randomized to receive warfarin [international normalized ratio (INR) ratio 1.4-2.8; median 1.9] vs. aspirin 325 mg and followed up for an average of 2 years. The results of the study were neutral, as the cumulative incidence of death and ischaemic stroke (warfarin 17.8% vs. aspirin 16%— $P=0.25$) and bleeding events (warfarin 2.2%/year vs. aspirin 1.49%/year) were comparable in both groups.

However, the analysis of data relating only to cryptogenic stroke patients enrolled in WARSS has provided significant insights for further research. In the 576 patients with cryptogenic stroke enrolled in the WARSS study at 2 years, a cumulative incidence of death or ischaemic stroke of 15% in the warfarin group and 16.5% in the aspirin group (HR 0.92) was observed. Considering the incidence of events only in 338 patients with brain imaging features suggestive of an embolic origin, the benefit rate associated with anticoagulant therapy appears significantly increased (death or ischaemic stroke equal to 12% in the warfarin group and 18% in the aspirin group—HR 0.66), as well as a significant benefit of warfarin therapy was observed in patients with elevated N-terminal-pro type B natriuretic peptide (NT-proBNP) compared to aspirin-treated patients (HR 0.3). Since the plasma levels of NT-proBNP are related to the degree of atrial overload, this laboratory parameter could represent a marker of possible cardio-embolic genesis in patients with cryptogenic ischaemic stroke.

The data emerging from the WARSS study led to hypothesize a possible beneficial effect of anticoagulant therapy compared to simple antiplatelet therapy in patients with non-lacunar cryptogenic ischaemic stroke. To identify those patients with cryptogenic non-lacunar ischaemic stroke in whom embolism is the most likely pathogenetic mechanism and to facilitate the conduct of randomized controlled clinical trials in this population, the term ESUS was introduced in 2014.¹ To meet this definition, patients must have had an ischaemic stroke and have undergone sufficient diagnostic work-up to exclude lacunar stroke, occlusive atherosclerosis and higher risk cardio-embolic sources, including brain CT/MRI, ECG 12 leads, transthoracic echocardiogram, 24-hour ECG-Holter and imaging investigation of extra and intracranial epiaortic vessels.

ESUS includes the majority of patients with cryptogenic stroke, involving approximately 17% of all patients with ischaemic stroke and typically affects younger individuals with milder strokes and an annual recurrence rate of around 4-5%, for most of them in the course of antiplatelet therapy. The potential causes of ESUS can be multiple (*Table 1*) and often represent minor causes of cardio-embolic risk.

The hypothesis that oral anticoagulant therapy can reduce the risk of stroke recurrence in ESUS, which emerged from the analysis of the WARSS study, was tested in four randomized controlled clinical trials.

The New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial vs. ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) study¹⁰ evaluated stroke recurrence in 7,213 patients with recent ESUS randomized to receive rivaroxaban 15 mg (regardless of renal function) or aspirin 100 mg. The study was stopped early due to an excess of bleeding events in the absence of benefit in reducing ischaemic events. In the median follow-up of 11 months, the recurrence of ischaemic stroke was comparable (4.7%/year in both groups) compared with a significant increase in major bleeding events (1.8%/year in the rivaroxaban and 0.7%/year in the aspirin group— $P<0.001$).

Table 1 Potential causes of ESUS

Subclinical atrial fibrillation		
Potential lower risk cardioembolic sources	Mitral valve	Myxomatous valve disease with prolapse Mitral annular calcification
	Aortic valve	Aortic valve stenosis Calcific aortic valve
	Non-AF arrhythmias and atrial stasis	Atrial asystole and sinus node disease High-frequency atrial episodes Stasis of the left auricle with reduced flow rates or spontaneous ecodensities
	Structural atrial abnormalities	Atrial septal aneurysm Chiari network
	Left ventricle	Moderate systolic or diastolic dysfunction (global or regional) Endomyocardial fibrosis Left ventricular non compaction
Cancer-related factors	Abacterial thrombotic endocarditis Tumor emboli from occult cancer	
Atherogenic emboli	Aortic arch atherosclerotic plaques Non-stenotic plaques of the cerebral artery with ulceration	
Paradoxical embolism	Patent foramen ovale	
	Atrial septal defect	
	Pulmonary arteriovenous fistula	

The Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etxilate Versus Acetylsalicylic Acid in Patients With ESUS (RE-SPECT ESUS) study¹¹ enrolled 5390 patients with recent ESUS randomized to receive dabigatran (150 mg or 110 mg x 2) or aspirin 100 mg. During the median follow-up of 19 months, the recurrence of ischaemic stroke (dabigatran 4.0%/year, aspirin 4.7%/year) and major bleeding (dabigatran 1.7%/year, aspirin 1.4%/year) it was substantially similar in the two groups.

Overall, in neither of the two trials was it possible to demonstrate an advantage of oral anticoagulant therapy over antiplatelet therapy in patients with ESUS, even in the presence of a favourable trend of reduction of cerebral ischaemic events highlighted in the RE-SPECT ESUS study after 12 months of therapy. The subgroup analysis of the RE-SPECT ESUS study showed a lower incidence of cerebral ischaemic events in patients > 75 years treated with dabigatran, probably the effect of a higher incidence of undiagnosed AF in this group of patients.

Two other large randomized trials are currently being completed that investigate the usefulness of oral anticoagulant therapy in patients with ESUS in association with major cardio-embolic risk factors.

The Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS) study aimed to enroll approximately 500 patients ≥ 18 years of age with ESUS and at least one additional risk factor (left atrium dilation > 45 mm in parasternal, presence of spontaneous echo contrast in left atrial appendage, velocity measured in left atrial appendage ≤ 20 cm/sec, episodes of high-frequency atrial activity, patent foramen ovale or CHA2DS2-VASc ≥ 4) already carrying or submitted to ICM implant. Patients were randomized within 7 days to

apixaban 5 mg x 2 (or reduced dose if applicable) or aspirin 100 mg but the detection of an AF episode lasting at least 2 minutes in patients on aspirin resulted in a switch to anticoagulant therapy. The primary endpoint was new ischaemic lesions on brain MRI over a 12-month follow-up. Patient enrollment was discontinued for futility after an interim analysis in 200 patients.

The Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke (ARCADIA) study¹² plans to recruit 1100 patients aged ≥ 45 years with ESUS associated with at least one suggestion for the diagnosis of atrial cardiomyopathy (amount of negative deflection of the P wave in V1 on the ECG, expressed as the product of the duration for amplitude, equal to > 0.05 mV per millisecond, NT-proBNP > 250 pg/mL and left atrial diameter ≥ 3 cm/m² on echocardiogram) by randomizing them to receive apixaban 5 mg x 2 (or reduced dose if applicable) or aspirin 81 mg, evaluating the incidence of cerebral ischaemic events and major hemorrhages in the follow-up. The result of this ongoing study will allow us to evaluate the role of non-invasive and therefore easy-to-use atrial cardiomyopathy biomarkers in supporting the choice of anticoagulant therapy in secondary prevention in patients with ESUS.

Table 2 summarizes the characteristics of the comparative studies between anticoagulants and antiplatelet agents in patients with ESUS.

Aortic plaques and stroke

Severe atherosclerosis of the aortic arch is a condition associated with an increased incidence and recurrence of ischaemic stroke, even during antiplatelet therapy. However, anticoagulation with warfarin has shown

Table 2 Clinical trials of comparison between anticoagulants and antiplatelet agents in patients with ESUS

	Trial Design	Number of patients	Characteristics	Comparison		Results
				therapy	Outcome	
WARSS (9) (1993-2000)	Multicentric, double-blind, randomized controlled	2206	Cryptogenic stroke	Warfarin vs. ASA	Stroke recurrence or death	Equivalence
NAVIGATE ESUS (10) (2014-18)	Multicentric, double-blind, randomized controlled	7213	ESUS	Rivaroxaban vs. ASA	Recurrent ischaemic or haemorrhagic stroke or systemic embolism	Equivalent efficacy but greater bleeding risk
RE-SPECT ESUS (11) (2014-18)	Multicentric, double-blind, randomized controlled	5390	ESUS	Dabigatran vs. ASA	Stroke recurrence	Equivalent efficacy but dabigatran increases minor bleeding
ATTICUS (2015-21)	Multicentric, open-label, randomized controlled	200	ESUS + minor cardioembolic risk factors	Apixaban vs. ASA	New ischaemic lesions on brain MRI	Study discontinued for futility after interim analysis
ARCADIA (12) (2018-22)	Multicentric, double-blind, randomized controlled	1100	ESUS + biomarker of atrial cardiomyopathy	Apixaban vs. ASA	Stroke recurrence	In progress

limited benefit in only a few retrospective studies. Ferrari *et al.*¹³ analyzed the incidence of embolic events and mortality in 129 patients with thoracic aortic atherosclerosis found on trans-esophageal echocardiography (plaques >1 mm). These events were significantly more frequent in subjects with complicated atherosclerosis (plaques >4 mm) treated with antiplatelet therapy than in those on warfarin, and this significance was even more pronounced in the presence of mobile aortic plaques (debris).

The only randomized clinical trial that attempted to define the antithrombotic therapy of choice in secondary prevention in patients with severe atherosclerosis of the aortic arch is the Aortic Arch Related Cerebral Hazard (ARCH) trial,¹⁴ unfortunately interrupted early before reaching a sufficient number to draw statistically significant conclusions. This trial enrolled 349 patients with a cerebral or systemic ischaemic event and severe aortic arch atherosclerosis (plaques >4 mm) as the sole embolic risk factor, randomizing them open label to receive warfarin (INR 2.0-3.0), or double antiplatelet therapy (aspirin 75/150 mg and clopidogrel 75 mg). After a median follow-up of 3.4 years, the incidence of the composite endpoint (ischaemic stroke, myocardial infarction, peripheral embolism, vascular death and intracranial hemorrhage) was comparable in the two groups (warfarin 11.3% vs. double antiplatelet therapy 7.6%; $P=0.5$), while vascular mortality alone was significantly more frequent in patients treated with anticoagulant (warfarin 3.4% vs. double antiplatelet therapy 0% $P=0.013$).

To date, therefore, there is insufficient evidence to recommend oral anticoagulant therapy in patients with cerebral ischaemic event in the presence of severe

atherosclerosis of the aortic arch. Future studies could compare the effectiveness of new direct oral anticoagulant (DOAC) drugs with antiplatelet therapy, which to date continues to remain the first choice in this category of patients.

Heart failure and stroke

In patients with heart failure in sinus rhythm, the risk of stroke is estimated at around 1% per year in mild-moderate forms of heart failure and can reach 4% in severe decompensation, although patients with more advanced heart failure are at increased risk of developing AF.

A prospective cohort study conducted through the Danish registries included 42 987 patients with heart failure (22% with concomitant AF) who were not anticoagulated. In a follow-up of 1 year from the diagnosis of heart failure, the risk of ischaemic stroke, systemic embolism and death was associated with the CHA2DS2-VASc score. The absolute risk of thromboembolic complications was shown to be high in these patients regardless of whether or not AF was present (8.2% vs. 9.7% in patients with or without AF, respectively).¹⁵

At the beginning of the new millennium, 4 studies were started comparing warfarin and aspirin in [patients with heart failure and sinus rhythm (Warfarin/Aspirin Study in Heart Failure, Heart Failure Long-Term Antithrombotic Study, The Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial, Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction) and the results of these studies were the subject of a subsequent meta-analysis which revealed a

41% reduction in the risk of stroke in primary prevention with warfarin compared to aspirin at the expense of a double risk of major bleeding and an overall lack of benefit on mortality.¹⁶

Real world data comes from the Spanish Red de Investigación en Insuficiencia Cardíaca multicenter registry which included 902 patients with heart failure, ejection fraction (EF) $\leq 35\%$ and sinus rhythm, of which 237 (26%) treated with oral anticoagulation. Multivariate analysis adjusted by propensity score demonstrated a reduction in the combined endpoint including cardiac death, heart transplant, coronary revascularization and hospitalization for cardiovascular causes (HR 0.74; 95% confidence interval, 0.56-0.97; $P=0.03$) in anticoagulated patients.¹⁷

Based on data from randomized clinical trials, the guidelines do not recommend oral anticoagulant therapy in patients with heart failure in sinus rhythm for primary prevention of stroke. Since DOACs are characterized by a better safety profile than warfarin, the possibility remains open that this category of drugs may be of benefit in patients with heart failure in sinus rhythm. The only data available so far in this regard come from the Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary artery Disease Following an Episode of Decompensated Heart Failure in which rivaroxaban at a dose of 2.5 mg x2 compared to placebo did not document a significant reduction in the combined endpoint of death, myocardial infarction or stroke in patients with heart failure and reduced left ventricular EF, coronary heart disease and absence of AF.¹⁸ In this study, rivaroxaban reduced the incidence of stroke but since it was not the primary endpoint, there remains the doubt that the use of a higher dose of DOAC, such as that used in AF, could produce more favourable results.

Left ventricular non compaction and stroke

Left ventricular non-compaction is a rare pathology of the heart muscle characterized by a marked parietal hyperbocolature due to the arrest of the myocardial maturation process during fetal development. Thromboembolic phenomena are described in 4-7% of patients in relation to AF (present in 25-30% of patients) and left ventricular thrombosis, conditions for which oral anticoagulation is mandatory. However, there is a moderate embolic risk even in patients with left ventricular non compaction and left ventricular dysfunction (EF $\leq 40\%$) in sinus rhythm. For these patients there is a broad consensus for the use of oral anticoagulant therapy after ischaemic stroke and also in primary prevention.¹⁹

Conclusions

At present, there is insufficient evidence to support the routine use of anticoagulant therapy in patients with ESUS. Since occult AF is still present in a substantial

number of these patients, efforts must be increased to reveal episodes of subclinical AF, particularly in elderly patients. The growing knowledge on the existence of atrial cardiomyopathy and the possibility of diagnosing it also with non-invasive methods is the object of evaluation in ongoing trials and will be able to better define the existence of a category of patients without AF who could still benefit from anticoagulant therapy in secondary prevention after ESUS.

In secondary prevention after ischaemic stroke, in patients with aortic plaques, particularly if mobile or with thrombotic component, or heart failure in sinus rhythm, the decision on anticoagulant therapy could be considered in the individual patient after careful evaluation of the risk/benefit ratio.

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References

- Hart RG, Diener HC, Coutts SB *et al.* Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;**13**:429-438.
- Sanna T, Diener HC, Passman RS *et al.* Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478-2486.
- Ntaios G, Perlepe K, Lambrou D *et al.* Identification of patients with embolic stroke of undetermined source and low risk of new incident atrial fibrillation: the AF-ESUS score. *Int J Stroke* 2021;**16**:29-38.
- Brambatti M, Connolly SJ, Gold MR *et al.* Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014;**129**:2094-2099.
- Goette A, Kalman JM, Aguinaga L *et al.* EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455-1490.
- Maheshwari A, Norby FL, Roetker NS *et al.* Refining prediction of atrial fibrillation-related stroke using the P₂-CHA₂DS₂-VASC score. *Circulation* 2019;**139**:180-191.
- Martinez-Selle M, Elosua R, Ibarrola M *et al.* Advanced inter-atrial block and P-wave duration are associated with atrial fibrillation and stroke in older adults with heart disease: the BAYES registry. *Europace* 2020;**22**:1001-1008.
- Cappelli F, Tini G, Russo D *et al.* Arterial thromboembolic events in cardiac amyloidosis: a look beyond atrial fibrillation. *Amyloid* 2021;**28**:12-18.
- Mohr JP, Thompson JLP, Lazar RM *et al.*; The Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;**345**:1444-1451.
- Hart RG, Sharma M, Mundl H *et al.* Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;**378**:2191-2201.
- Diener HC, Sacco RL, Easton JD *et al.* Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;**380**:1906-1917.
- Kamel H, Longstreth WT, Tirschwell DL *et al.* The Atrial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke randomized trial: rationale and methods. *Int J Stroke* 2019;**14**:207-214.
- Ferrari E, Vidal R, Chevallier T, Baodouy M. Atherosclerosis of the thoracic aorta and aortic debris as a marker of poor prognosis: benefit of oral anticoagulants. *J Am Coll Cardiol* 1999;**33**:1317-1322.
- Amarencu P, Davis S, Jones EF *et al.* The aortic arch related cerebral hazard trial investigators. Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. *Stroke* 2014;**45**:1248-1257.
- Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GYH. Assessment of the CHA₂DS₂-VASC score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *JAMA* 2015;**314**:1030-1038.

16. Hopper I, Skiba M, Krum H. Updated meta-analysis on antithrombotic therapy in patients with heart failure and sinus rhythm. *Eur J Heart Fail* 2013;**15**:69-78.
17. Avellana P, Segovia J, Ferrero A *et al.* Tratamiento anticoagulante en pacientes con insuficiencia cardíaca por disfunción sistólica y ritmo sinusal: análisis del registro REDINSCOR. *Rev Esp Cardiol* 2012;**65**:705-712.
18. Zannad F, Anker SD, Byra WM *et al.* for the COMMANDER HF Investigators. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med* 2018; **379**:1332-1334.
19. Chimenti C, Lavalle C, Magnocavallo M *et al.* A proposed strategy for anticoagulation therapy in noncompaction cardiomyopathy. *ESC Heart Failure* 2022;**9**:241-250.