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ANTITHROMBOTIC TREATMENT AND EMBOLIC STROKES OF UNDETERMINED SOURCE

Abstract

Purpose – Embolic Stroke of Undermined Source (ESUS) refers to patients with non-lacunar cryptogenic embolic stroke, despite recommended diagnostic work-up. Embolism is the most possible underlying mechanism. It has been stated as a hypothesis that anticoagulation could be the most appropriate treatment selection as a secondary stroke prevention strategy for these patients. Available information has been reviewed about ESUS and antithrombotic treatment.

Methods – A systematic literature review was conducted to assess the frequency of ESUS, patients' features, recurrence, outcomes and antithrombotic treatment using PubMed and Google Scholar mainly from 2014 to the present. English language studies were only included.

Results – 2 large randomized control trials the NAVIGATE ESUS (Rivaroxaban vs Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients with Recent Embolic Stroke of Undetermined Source) and the RE-SPECT ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients with Embolic Stroke of Undetermined Source) tested oral anticoagulation efficacy in secondary stroke prevention in ESUS patients with neutral results. This review examines the findings of anticoagulation trials in patients with ESUS, suggests possible reasons for their neutral results, and indicates the ongoing and future research in this group of patients aiming to reduce stroke recurrence.

Conclusions – Although ESUS can occur at any age, patients fulfilling ESUS criteria have been mainly observed in younger patients. The average of annual recurrence rate is estimated to be around 4.5-5%. Stroke severity is usually minor, and in some cases with even no traditional vascular risk factors. ESUS comprises a heterogeneous group of patients, with a very high possibility of an undetected source of embolism. There is a need to update ESUS definition and criteria in which thorough investigations and more comprehensive diagnostic work-up will be required, assisting clinicians to detect the source of cerebral embolism and individualizing treatment approaches.

Key words: ESUS, cryptogenic, stroke, embolism, secondary prevention

Context table **Page**

Chapter 1

1.1 Introduction

An ischemic stroke may be the consequence of many vascular diseases. Establishing the most likely cause is important because the cause of stoke influences both short-term and long-term prognosis and it affects treatment decisions, especially those related to the prevention of recurrent events. [1]

According to TOAST classification, there are the following sub-types of ischemic stroke comprised of

Large artery atherosclerosis 25%, Small artery occlusion (lacunae) 25%, Cardio-embolism 20%, Other demonstrated cause 5% (non-atherosclerotic vasculopathies, prothrmbotic disorders) and those of undetermined cause (cryptogenic) 25%. [1,2]

ESUS as a nosological entity (Embolic Stroke of Undetermined Source) was introduced in 2014 for the subset of patients with cryptogenic ischemic stroke in whom embolism was the most probable stroke mechanism and cardioembolic sources, occlusive atherosclerosis, and lacunar stroke were definitely excluded. [2,3]

Terms ESUS and cryptogenic are not the same, as the latter is referring to patients with multiple stroke etiologies or incomplete diagnostic work-up. [4]

With the introduction of the ESUS entity, many ischemic strokes are more properly separated from the cryptogenic ones as the latter refers to patients with unfinished testing or other etiology. The diagnostic definition of ESUS includes non-lacunar infarction (small vessel occlusion), no 50% large artery atherosclerotic stenosis supplying the ischemic area, no major risk cardioembolic sources, and no other specific causes of stroke. [2,5]

Accordingly, ESUS diagnosis requires a basic set of assessments, abbreviated as '**HEAD'**: **H**ead imaging by computerized tomography (CT) or magnetic resonance imaging (MRI) to rule out lacunar infarcts (less than 1.5 cm in diameter by CT or 2 cm by MRI); (2) **E**lectrocardiogram (ECG) and Echocardiography: 12-lead ECG, 24-hr Holter monitor and transthoracic echocardiography to rule out major risk cardioembolic sources, including atrial fibrillation (AF), atrial flutter, intracardiac thrombus, valvular heart diseases, etc.; **A**rterial

imaging of cervico-cephalic large arteries using Doppler ultrasound, CT or MR angiography to rule out large artery stenosis (>50%); and **D**ifferential diagnosis of other specific causes, such as vasculitis, dissection, migraine/vasospasm, etc. [2,5]

The ESUS concept is based on the assumption that the main mechanism of cryptogenic stroke is thromboembolic. That gave rise to the idea that there is an indication for oral anticoagulants (non-vitamin K agonists and NOACs) with the ultimate goal of reducing stroke recurrence. [6]

Based on this assumption clinical trials were set up testing the safety and efficacy of rivaroxaban and dabigatran versus aspirin in patients with ESUS, while the ESUS construct was immediately spread among clinicians. [6]

Chapter 2

2.1 Methods

2.1.1 Aim

A systematic review of published articles was conducted about the embolic strokes of unknown source and their therapeutic strategies.

2.1.2 Study selection

All included articles were in English. The major eligibility criterion was the reference to ESUS. The selected articles were mainly published since 2014. Abstract eligibility screening was performed to see if they meet any criteria. The inclusion of duplicate publications of the same data was avoided by examining data for any similarities. One abstract is included.

2.1.3 Search strategy

Literature was electronically searched. Pubmed and Google Scholar were used as the main and secondary database source respectively. The P.I.C.O. (patient; intervention; comparison; outcome) model (Table 1) was used for formulating the search strategy for the article

identification process. All the associated studies were primarily selected based on the title and abstract with further selections being made taking into account the full text of the published articles. All articles of the search strategy were evaluated by one author under the supervision of a senior physician.

P	Patient, Population or Problem	Patients with an ESUS.
I	Intervention	Patients treated with anticoagulants for a stroke of an ESUS as embolism is presumed to be its main mechanism.
C	Comparison	Compared to non-anticoagulant therapies.
O	Outcome you would like to measure or achieve	Secondary treatment effectiveness concerning ESUS recurrence.

Table 1 P.I.C.O model.

2.1.4 Extraction of data

Data were extracted from the text and tables. Demographics (age, sex), patient risk factors for an ischemic stroke (e.g. diabetes mellitus, hypertension, obesity, high cholesterol levels etc), frequency, stroke phenotype, potential physiological mechanisms, recurrence rates, outcomes and clinical trials about ESUS were included.

A PRISMA-guided search strategy of PubMed and Google Scholar, was performed. Terms "embolic stroke of unknown source OR ESUS" and "embolic stroke OR cryptogenic stroke OR embolism" are used for articles identification. Results used were mainly published since 2014.

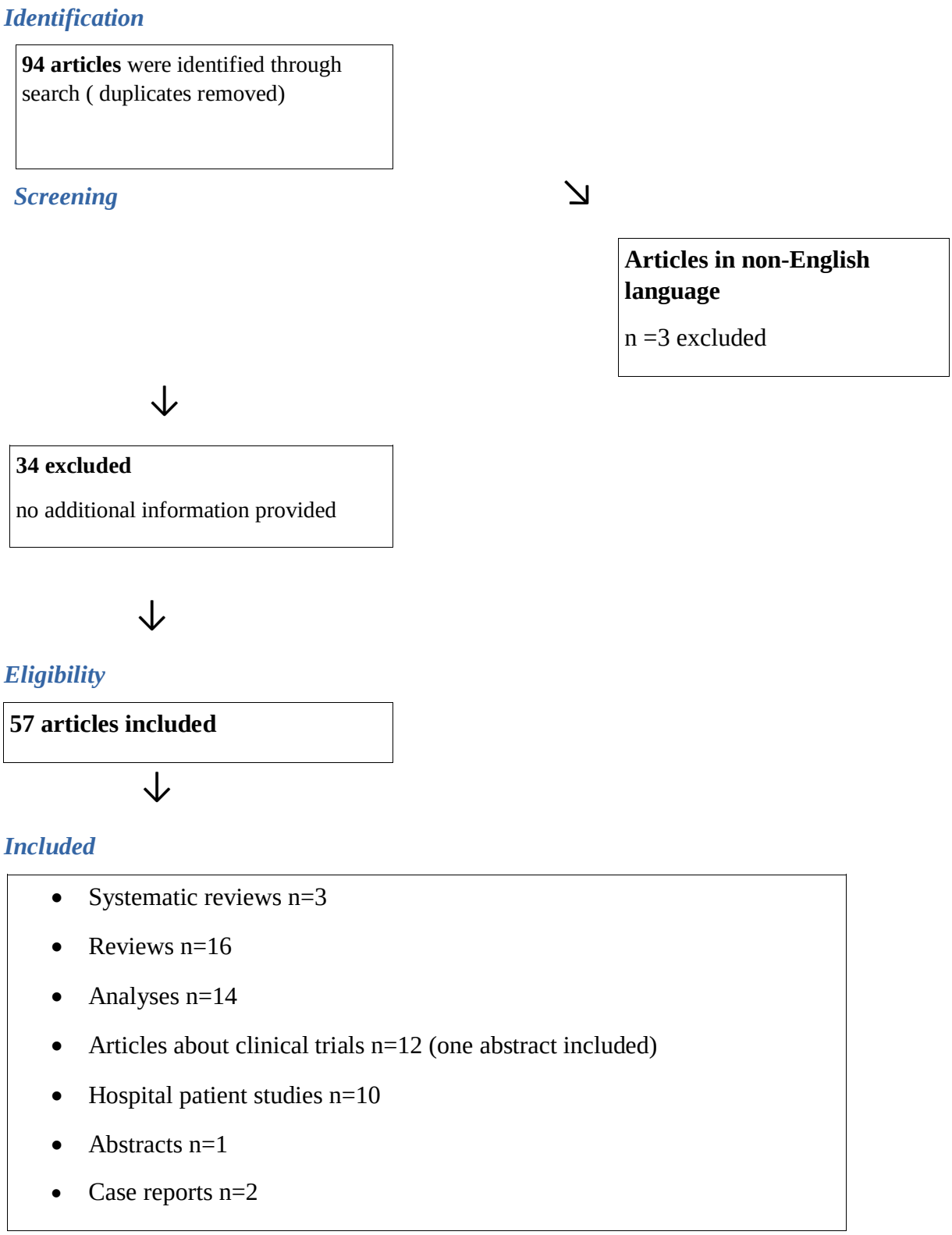

Figure 1 Flow chart presenting the selection of studies.

2.1.5 Definitions

Stroke: Sudden occurrence of a focal non-epileptic neurologic deficit.

ESUS: Embolic stroke of undetermined source, a clinical construct proposed in 2014 to characterize patients with non-lacunar cryptogenic ischemic strokes in whom embolism was the most possible stroke mechanism. [2]

2.1.6 Statistical analysis

Only descriptive data were presented in this systematic review.

Chapter 3

3.1 Results

The results that emerge from this systematic review are the following

Frequency

The frequency of ESUS in ischemic strokes is estimated at an average of about 17% (7 - 42%). ESUS patients are typically younger with minor strokes. Frequency is not affected by geographic differences. [3,4]

Phenotype and age groups

ESUS is a usual stroke etiology and may happen at any age. [7] So far this type of stroke has been mainly observed in patients who are typically younger (less than 65 years old), with a lower frequency of classical vascular risk factors and with milder strokes compared to other types of ischemic strokes (mean initial NIHSS score of 5). [3,4,5]

Potential mechanisms and Diagnostic work-up

Paroxysmal Atrial Fibrillation (AF)

The detection of paroxysmal AF is quite difficult. It can be easily overlooked when brief cardiac monitoring is used. There is a significant raising of risk for stroke even with short-lasting events of AF [8] and clinical trials (CRYSTAL-AF [9], EMBRACE [10], FIND-$AF_{RANDOMISED}$[11]) have been conducted on this topic to clarify the value of prolonged cardiac monitoring in AF detection.

Left ventricular disease, Left Atrial Cardiopathy and blood biomarkers

Any dysfunction of the left ventricle could be associated with ESUS by several pathophysiological factors in the context of heart failure like low cardiac output, dilated chambers, poor contractility and endothelial dysfunction. [4]

Left atrial abnormalities can be a possible cause of an embolic stroke. These can act either as precursors of AF or as independent factors for left atrial thrombus formation. Thrombus formation can happen even without the presence of AF. It is defined by the presence of specific biomarkers which are P wave terminal force velocity in V1 on ECG > 5000μVms, severe left atrial enlargement on echocardiogram ($\geq$3cm/m^2), or serum levels of N terminal pro-brain natriuretic peptide (NT – proBNP) > 250 pg/mL. Risk factors such as aging, obesity, diabetes mellitus, hypertension, and sleep apnea can lead to left atrium extracellular progressive matrix remodeling with subsequent atrial fibrosis. Dilatation and dysfunction of the left atrium may further cause atrial blood stasis and subsequent stroke. [5,12] Left atrial cardiopathy detection is important due to its association with AF (AF worsens cardiopathy and vice versa). [8]

BNP is secreted by the myocardium and the left atrium is its main source. Elevated levels are correlated with increased cardiac chamber stress and/or atrial disease, and has been found in patients with AF and thromboembolism or when systolic or diastolic dysfunction exists. These data can associate BNP as a stoke marker with cardioembolic causes. Other blood biomarkers that can be related to ischemic stroke are those of myocardial lesion such as CK-MB, troponin and myoglobin. Although higher levels of all these biomarkers were found in embolic strokes, only BNP and CK-MB are independently related to embolic abnormalities, associating them with an embolic stroke during its acute phase. [13,14]

Occult structural cardiac lesion

There are cases such as aortic atheroma, papillary fibroelastoma, left atrial appendage thrombi, or atrial myxoma that can cause a stroke with ESUS characteristics and cannot be detected by transthoracic ultrasound. In such cases a transesophageal echocardiogram (TEE), cardiac computed tomography (CT) or cardiac magnetic resonance imaging (CMR) should be considered as an option for further diagnostic work-up. In this way a better resolution of the aortic arch (particularly if the thickness of atherosclerotic plaque is more than 4mm [5]) and the heart valves can be ensured, since they can act as a potential source of thrombi that may be missed in a transthoracic study. [8]

Patent foramen ovale (PFO)

PFO can cause an embolic stroke. This can occur with the formation of a clot in the foramen or by paradoxical embolism from the venous system to the cerebral arteries. Transthoracic echocardiogram with microbubble test and transesophageal echocardiogram studies can diagnose PFO and determine its size assessing also a possible interatrial septal aneurysm in order to decide for further intervention. [8]

Atherosclerosis

Aortic arch atheromas and substenotic atheroslerosis (less than 50%) of the extracranial carotid arteries are also very likely to be a source of emboli. The types of stenosis with the highest risk are considered to be those with a thickness greater of 4mm in the aorta and those with vulnerable plaque characteristics, in the carotid artery ipsilateral to the stroke side, that can cause stroke due to artery–to–artery embolization. [8]

Hypercoagulability

Conditions causing arterial or venous hypercoagulability should be ruled out especially in patients younger than 50 years old. These conditions may be the consequence of conditions such as antiphospholipid antibody syndrome, protein C / protein S / antithrombin III deficiency, Factor V Leiden mutation, hyperhomocysteinemia, prothrombin gene mutation. [8]

Malignancy

Occult cancer is also a very likely cause of ESUS. Patients with an indicative clinical history, advanced age or family cancers should be screened for malignancy. In cancer patients, there is a 15% chance of having an ischemic stroke. However, only 50% of those are diagnosed with the underlying malignancy. The risk for a subsequent stroke depends on the underlying malignancy (e.g. lung cancer or gastrointestinal cancer are considered to be the most embolic ones [4,14]). The most probable mechanisms of ischemic stroke related to cancer are hypercoagulopathy, tumor embolism, mechanical compression of the vessels, marantic endocarditis, anemia, radiotherapy and antineoplastic treatment adverse effects among others. An imaging pattern of these strokes has been observed (multiple territory infractions) however there is no specific imaging approach. [4,14]

Carotid web

It is about a type of focal fibromuscular dysplasia presented as a non-atheromatous tissue in the lumen of the carotid artery. This tissue can cause an ischemic stroke without a significant stenosis. In this case, the preferred screening method is the computed tomography (CTA). This allows a clear view of the vessel, calcium deposition, atherosclerotic plaque, and thrombus formation. This strand of tissue causes altered hemodynamics leading to stasis in the vessel. Carotid webs usually cause less than 50% stenosis. [8]

Diagnostic Work-up

The diagnostic testing recommended for patients with ESUS should include Brain CT/MRI showing only embolic infarct, MRA/CTA of extracranial and intracranial vessels supplying the zone of stroke with less than 50% atherosclerosis, negative transthoracic echocardiography (e.g. no recent less than 4 weeks myocardial infarction, no infective endocarditis, LVEF<30%), no other specific cause of stroke like arteritis, dissection, migraine/vasospasm, drug abuse. [14]

A complete physical examination is mandatory as well as a meticulous assessment of personal and family history are also essential. In case that there are no traditional risk factors, additional tests should be made. These are prolonged cardiac monitoring, transesophageal echocardiography and CMRI for cardiac imaging. PFO patients should undergo an ultrasonography of the lower limbs and/or MRV of the pelvis. Sub-stenotic arterial lesions (of

less than 50%) demand a meticulous assessment including MRA, T1 fat saturation (if dissection is suspected), or conventional catheter angiography if subtle or multifocal irregularities are found, especially in younger patients. In case there are systemic manifestations indicating infectious or inflammatory diseases a CSF examination is required. The possibility of hypercoagulable state, especially in younger patients, should be confirmed, especially for those with recurrent thrombosis or family history. If elderly patients are found with a multi-vessel territory infarct this is suggestive for further investigation for malignancy (e.g. with a total body CT or a PET scan). Finally, metabolic and genetic testing for rare ischemic stroke causes, such as Fabry disease, CADASIL, Mitochondrial disease etc., should be considered. [14]

Recurrence rates

The risk is highest initially (at least 10% in the first few weeks) and reduces within 12 months. [15] The average of annual recurrence rate is estimated to be around 4.5-5%[2,3,4] with higher recurrence rates compared to non-ESUS patients.[3] Typically stroke recurrence in ESUS patients is considered high. Prior stroke or transient ischemic attack (TIA), current tobacco user, age, diabetes, multiple acute infarcts on neuroimaging, and prior aspirin use are the most significant predictive factors for recurrence. [16] ESUS patients who develop AF have a greater risk for a new stroke than those who do not develop AF. [17] Compared to all other types of strokes the stroke recurrence in ESUS patients is higher, excluding the cardioembolic ones. [18,19]

Potential embolic sources

The possibility of ESUS embolic sources; In AF-ESUS study 65% of patients had >1 potential embolic source, 31.1% ≥3 potential sources, 29.7% a single source and 4.8% had none. On average each patient had 2 potential embolic sources. [4]

Outcome – Prognosis

ESUS mortality is not as severe as in cardioembolic events. It resembles most to a lacunar or a large–artery atherosclerotic stroke. The prognosis in ESUS patients is close to large-artery atherosclerotic strokes and better than in patients with cardioembolic ones. Recurrent stroke risk is higher in ESUS than in non-cardioembolic strokes. The probability of a cardiovascular event is similar to all other stroke types excluding patients with lacunar stroke who have significantly lower risk. [18]

ESUS Treatment and Secondary prevention

Two clinical trials have been conducted comparing anticoagulants with aspirin as the most suitable treatment option in patients with ESUS.

The NAVIGATE ESUS trial tested 7,213 patients to either rivaroxaban 15mgr daily (3609 patients) or aspirin 100mgr (3604 patients). [20] The main assumption in the NAVIGATE ESUS trial was that rivaroxaban would have a lower stroke recurrence without the increase of bleeding risk relative to aspirin. [21] The primary efficacy outcome was the first recurrence of ischemic or hemorrhagic stroke or systemic embolism in a time-to-event analysis; the primary safety outcome was the rate of major bleeding. There was an early termination of the trial because of an increased bleeding rate without corresponding to an offset benefit in the rivaroxaban group of patients after a follow-up of 11 months. The endpoint of first recurrent stroke or systemic embolism occurred in 172 patients (4.8%) on rivaroxaban and 160 patients (4.4%) on aspirin. The rate of major bleeding was greater for rivaroxaban compared with aspirin. [22]

The RE-SPECT ESUS trial tested 5,390 patients to either dabigatran 150 mg (2695 patients) or 110 mg twice daily (depending on age and kidney function) (2695 patients) or aspirin 100 mg daily (2695 patients). The primary outcome was recurrent stroke. The primary safety outcome was major hemorrhage. During a mean follow up of 19 months recurrent stroke occurred in 117 patients (6.6%) on dabigatran and 207 patients (7.7%) on aspirin. The rate of major bleeding was similar in both groups (1.7% vs 1.4%). [22,23]

In conclusion oral anticoagulation has not been superior to aspirin for stroke prevention in patients with ESUS.

Overview on the results of the included studies	
Frequency of ESUS	About 17% (7-42%)
Phenotype and age groups	Less severe strokes, patients usually younger (< 65 years old)
Potential mechanisms of ESUS	Paroxysmal AF, Left ventircular disease, Left atrial cardiopathy, occult structural cardiac lesion, PFO, Carotid/aortic arch atherosclerosis, Hypercoagulability, Malignancy, Carotid web
Diagnostic work-up	**"HEAD"** assessement **H**ead imaging (CT or MRI), **E**CG (12 lead ECG and 24 hr Holter monitoring) and (transthoracic) echocardiography, cervico-cephalic **A**rterial imaging (Doppler ultrasound, CTA or MRA), **D**ifferential diagnosis of other stroke causes
Recurrence rates	4.5-5% average annual rate
Number of potential embolic sources per patient	2 potential sources on average
Outcome and Prognosis	Outcome and mortality similar to large-artery stroke, better compared to cardioembolic strokes
ESUS treatment and secondary prevention	Clinical trials with neutral results (oral anticoagulation vs aspirin)

Table 2 Results overview

Chapter 4

4.1 Discussion

The ESUS construct was introduced due to the hypothesis of Hart et al. that anticoagulants would be the best option for this sub-type of stroke [24], considering that a cardioembolic mechanism in the context of (covert) AF is the most potential cause.

However, this systematic review shows that AF is not always the reason and the main cause of an ESUS. AF appeared to affect a large proportion of patients with ESUS [25] but in recent studies seems that it comprises only a fraction of possible causes. It can be estimated that roughly 1/3 of patients [26] suffer from AF related stroke. Definitely, further discussion is required regarding the topic and more research is needed to demonstrate more clearly and accurately the actual number of these patients. So far, it is obvious from the reviewed articles that certain methods and ways of determining this percentage of AF related strokes have been used.

The first of these methods is related to the assessment of the clinical severity of stroke according to the NIHSS scale. It has been found that cardioembolic strokes present with a sudden onset and with maximal severity from the outset, giving the patient a high score on the NIHSS scale (due to their severe clinical picture). Thus, considering that an ESUS is cardioembolic due to AF, it should normally have a similar clinical picture as a non-ESUS cardioembolic stroke. On the contrary, is has been found that ESUS severity was less compared with cardiombolic ones (median NIHSS of an ESUS was 5 and median NIHSS of a cordioembolic stroke was 13) [26]. It is worth mentioning that the stroke severity of ESUS patients in the Athens Stroke Registry was significantly lower compared with those suffering from a cardioembolic stroke. Additionally, in the NAVIGATE ESUS and RE-SPECT ESUS trials the stroke severity of ESUS patients was even lower. [4] A possible explanation for this is that these events provoked by bursts of paroxysmal AF were less severe in comparison to those having as etiology persistent or permanent AF. As a consequence, many patients with ESUS may be eligible for long-term ECG monitoring either with an insertable device or in a non-invasive way [26], a topic that is being discussed a lot recently.

Attempts were made to find a possible link between AF and ESUS by its detection during follow-up. Since strokes caused by AF have a more severe clinical picture, it is assumed that

stroke severity would be greater in ESUS patients who were detected with AF during follow-up (supposing that AF found during follow-up was linked to an ESUS). This assumption was never proved and there are doubts if there is any link between ESUS and AF noticed in follow-up. This is because it is very likely that the ischemic stroke is caused by another embolic source (e.g. from artery-to-artery, from the aortic arch or even from < 50% stenosis of the internal carotid supplying the stroke zone) and the recording of AF in the follow-up is only a coincidental event. This may also be a possible explanation why strokes are equally severe among the AF and the non-AF ESUS patients. However, no link was found between detected AF during follow-up in ESUS patients and the causative stroke mechanism, leading to further diagnostic and therapeutic implications. Consequently, attributing the etiology of stroke to AF recorded in follow-up patients may not be treated properly if the stroke is actually caused by another embolic source (e.g. a substenotic carotid plaque). [27]

Besides, it is was shown that the identification of the predictors of the AF associated ESUS among the general ESUS population could influence any decisions concerning the antithrombotic treatment. These can be advanced age, moderate-to-severe left atrial enlargement on echocardiography as well as all the classical vascular risk factors (obesity, congestive heart failure, hypertension, coronary artery disease, peripheral vascular disease, valvular disease). All of these conditions may play a significant role in the assessment of AF risk in patients with cryptogenic cerebral embolism. Covert AF is a very possible etiology of embolism in certain ESUS subgroups like the elderly. RE-SPECT ESUS trial showed that patients over 75 years old had a notable benefit of lower-dose dabigatran over aspirin, which may lead to the conclusion of a new developed or covert AF. [4]

Finally, regarding the detection of AF as a causative ESUS factor the use of prolonged cardiac rhythm monitoring (PCM) by an insertable cardiac monitor (ICM) is also reported. It is found that different types of cardiac rhythm monitoring influence the frequency of detection of covert paroxysmal AF. In general, the longer patients are monitored, the more likely they are to be found with AF. This duration can be from at least 24 hours with external monitoring as far as several years with an implanted one (with the latter having a prohibited widespread use due to cost and invasiveness). [5] Randomized controlled trials of PCM like the CRYSTAL-AF [9] , EMBRACE [10], Find-$AF_{RANDOMISED}$ [11] , observational studies and meta-analyses showed that AF may be found in 30% of patients with an ESUS in long term follow-up. Nevertheless, the etiological relationship between AF and the index stroke is still under

discussion, especially for those events of AF which are subclinical, with a short duration or they are detected long after stroke. [4] Moreover, despite the fact that the definition of AF duration > 30 seconds is consistent across all included studies there is substantial disagreement between stroke physicians and cardiologists in the management of patients with stroke and AF duration < 30 seconds, with the former being more likely to accept AF bursts of < 30 seconds as sufficient for the diagnosis of AF and anticoagulation initiation.[28] Nevertheless, there is a lot of uncertainty concerning this topic, particularly among the pathophysiological relationship between late detection of brief episodes of AF and ESUS [3] and how PCM could play a potential role in secondary stroke prevention of cryptogenic ischemic stroke and TIA. [26] This uncertainty is enhanced by the results of ASSERT [29] and TRENDS [30] trials. These studies showed that events of embolism causing stroke or systematic embolism did not occur close to an episode of subclinical AF. [4]

Due to the increasing spending pressure on health care systems and adverse effects of invasiveness, several patient selection system stratification of AF risk prediction were developed. The purpose of these systems is to determine in which patients the use of ICM will be most beneficial and cost-effective. A study was conducted on patients from the CRYSTAL–AF study who had an insertable cardiac monitor. In this study the HAVOC score appeared to be the most suitable, especially compared to the $CHADS_2$ and $CHAD_2DS_2VAS_C$ scores. The HAVOC score seemed to be a successful tool in the stratification of AF risk detection in patients with an ICM from the CRYSTAL-AF cohort. It was found that patients with moderate to high HAVOC scores were likely to benefit more from long-term continuous ICM monitoring than patients with low scores.[31] Recently, another study developed a scoring system called the AF-ESUS score. This system aims to spot patients with low probability of new diagnosis of AF, thus helping physicians to differentiate who is in the need of long term cardiac monitoring. It is a multivariate scoring system assigning points for age, arterial hypertension, left ventricular hypertrophy signs on ECG, left atrial diameter > 40mm, left ventricular ejection fraction <35%, supraventricular extrasystoles, presence of subcortical infarct, and non-stenotic carotid plaque (either ipsilateral or contralateral to the ischemic territory); patients with higher scores may be better candidates for PCM compared to those with ≤ 0 (AF-ESUS score ≤0 is correlated with low incidence of AF detection corresponding to 94.9% sensitivity and 98.1% negative predictive value for distinguishing those cases who will not present with AF on follow-up). However,

there is a need to further confirm the validity of this scoring system before it can be widely applied in clinical practice. [32,33]

This systematic review also showed that transesophageal echocardiogram (TEE) should probably be considered as an essential part in the baseline diagnostic work-up. Still, it is not mandated neither by ESUS criteria nor by the randomized clinical trials NAVIGATE ESUS and RE-SPECT ESUS. TEE can detect the possible cause of stroke and indicate the right treatment in a significant percentage of cases. In ESUS patients TEE examination revealed abnormal findings in a great percentage (more than half) with a significant impact in the management other than anticoagulant initiation (closure of patent foramen ovale, antibiotic administration due to infective endocarditis etc). [8]

PFO was detected in almost 1/3 of patients with ESUS. Both younger and older patients with cryptogenic stroke have a higher prevalence of PFO. [34] Both NAVIGATE and RE-SPECT ESUS trials stated that neither rivaroxaban nor dabigatran were superior to aspirin in patients with ESUS and PFO. So far, PFO closure is the best choice of treatment for ESUS patients < 60 years as long as they do not present any other possible cause of ischemic stroke. [35] However, PFO closure seems to be effective in younger patients. Elderly patients may be at greater danger for venous thromboembolism (due to less physical exercise and comorbidity) and consequent paradoxical embolism through PFO. Therefore, in this case, anticoagulants may be a better option for patients over 60 years old. [36,37]

Non-stenotic (≤ 50%) carotid atherosclerotic plaques with ≥ 3mm thickness are presented with a greater prevalence ipsilaterally to an ESUS. [38] The results of the NAVIGATE trial showed that patients who had carotid plaques ipsilaterally to the stroke were up to 40%. The imaging findings of non-stenotic carotid arteries in ESUS patients were analyzed by several studies. One of these studies found that 37.5% of carotid arteries ipsilateral to stroke had American Heart Association (AHA) lesion type VI vs zero AHA type VI contralateral to stroke. This type of plaques have as its most common feature intraplaque hemorrhage (75%), followed by fibrous plaque rupture (50%) and luminal thrombus (33%). [39]These patients appeared to be more likely to have a greater incidence for a new stroke compared with the patients who did not have carotid plaques at all. [6] This fact shows that an arterio-arterial embolism is possible even if lumen stenosis is less than 50%, indicating another possible mechanism of ESUS that is not effectively managed with oral anticoagulants. [40] At this point, it should be mentioned that an association was found between carotid atherosclerosis, PFO,

and AF in patients with ESUS. There is an inverse correlation between PFO and non-stenotic carotid atherosclerosis. Patients with PFO are less likely to have atherosclerosis of the carotid arteries. [41,42] Also, in patients with ESUS and ipsilateral plaque of the carotid artery the AF detection is less common. [4,42]

Aortic arch atheroma (AAA) is a usually detected in ESUS patients (if they are screened with TEE) [6] and it is also a significant and commonly ignored cause of embolism. Mobile, complex and large (4mm) AAAs especially in older patients have a great risk of an embolic stroke. Additionally, these AAAs are associated with a greater risk for coronary artery disease. In neuroimaging AAAs embolic strokes are shown as multi-territorial infarcts. AAA provoked strokes have a high risk for recurrence. [6] Complex AAA tend to cause left sided embolic strokes more frequently than right sided strokes. The most likely explanation is that aortic plaques are located distally to innominate artery which supplies the right sided cerebral circulation. Complex AAA tend to cause multiterritorial strokes more frequently compared to patients without complex AAA. This can be explained by the underlying pathology of stroke, as the thrombus that is superimposed upon an aortic plaque may break into several fragments, which may embolize into different arterial segments of the cerebral circulation. [43] Regarding the treatment of non-stenotic carotid artery and AAA, vitamin K antagonists and NOACs did not appear to have an advantage in the secondary prevention of ischemic strokes while at the same time they increase the risk of major bleeding. [6]

The intracranial atherosclerotic plaques as a cause of an ESUS are the least studied, due to the limitations of the available screening techniques. Although not histologically validated, with the development and the use of high resolution MRI in clinical practice it is has been possible the direct in vivo analysis of a plaque, concerning its morphology, composition and remodeling pattern. This finding is particularly important for large plaques with positive remodeling and therefore a higher risk of stroke. Still, the best preventive approaches in these patients have not been clearly defined. [44]

Cancer related stroke could be another possible underlying etiology of an ESUS. Data from the NAVIGATE trial showed cancer cases in 7.5% of the included patients. [6] The recurrence stroke rate in those patients was higher compared to patients without cancer and with a tendency for major bleeds with rivaroxaban. Malignancy related strokes do not have a good prognosis and they are associated with high mortality at follow-up. [6] For this reason the identification and management of the occult malignancy very important. Therefore, an

appropriate management for such cases seems to have not been precisely determined. Therefore, additional tests including D-dimer for possible underlying malignancy and TEE that excludes non-bacterial thrombotic endocarditis should be considered. [6] To date, there is no clear evidence if there is any indication of anticoagulants in cancer-related ESUS. [4]

Patients' age was at an average 65 years old with man to women ratio close to 1:1, while men cases were presented with a slightly greater frequency than women (42% were women) [3]. ESUS occur mainly at a younger age (≤ 50 years old) with fewer or even no classical risk factors for ischemic stroke. ESUS have the same prognosis in all age groups. Stroke severity were usually minor and in some cases no traditional vascular risk factors for ischemic stroke were found. [45] ESUS comprises a non-homogeneous type of stroke cases, in which there is a very high possibility for an occult source for embolism. [46]

The annual recurrent ESUS rates are averaged at 4.5% (3-6%) [2,3]. ESUS patients presented with greater possibility for a new stroke than non-ESUS patients. So far, it is not obvious if the stroke recurrence risk is greater in the first weeks following an ESUS as the assumed ESUS origin may differ (i.e. PFO associated ESUS vs aortic arch plaque-associated ESUS). [3] In the NAVIGATE ESUS trial, the most important factors in the first recurrent ischemic stroke were identified. These are prior stroke or TIA, current tobacco user, age, diabetes, multiple acute infarcts on neuroimaging and prior aspirin use. Prior stroke or TIA found to be the strongest predictor factor for ESUS. All the emerging potential risk factors for recurrence were related to atherosclerosis. [16]

In an attempt for finding additional risk factors and for better understudying of the mechanisms of ESUS and their pathophysiology, some supplementary studies have been performed. In the context of this effort, the level of visceral adipose tissue (VAT) was studied as a probable risk factor in patients with ESUS. High levels of VAT were often detected than any other ordinary vascular risk factor for stroke. [13] The risk of heart disease is greater in patients with central obesity than in those with peripheral obesity. This could be explained by the fact that VAT has a greater metabolic activity than subcutaneous adipose tissue. It is found that it secretes several factors that are related to the damage of the endothelium by regulating the inflammatory and procoagulant response via increased secretion of procoagulant mediators (e.g. PLASMINOGEN ACTIVATOR INHIBITOR-1, tissue factor, enhanced platelet activity). [4] VAT is also directly related to the increase in epicardial fat which is closely related to the cause of venous thrombosis. There is also a predisposition of

patients with increased VAT to atherosclerosis and consequently to the development of AF. Therefore all these facts suggest that high levels of VAT may act as a substrate for thrombosis and a subsequent stroke. [14,47]

Finally, it has to be noted that there is a brief reference of another possible predisposing risk factor. It is about a case report concerning the role of extreme Lipoprotein(a) (Lpa) levels in ESUS recurrence in a 46 year old woman who was found with an ischemic stroke and an extremely elevated plasma Lp(a) level. Since it is stated that cerebral vascular disease, peripheral vascular disease and carotid atherosclerosis could be related to increased Lp(a), the article concluded that high Lp(a) could cause a carotid vulnerable plaque. However, there was not a meticulous approach on the subject and further studies are needed. [48]

The two the trials (NAVIGATE ESUS & RE-SPECT ESUS) of oral anticoagulation in patients with ESUS are recently completed. The outcome of these clinical trials shows that anticoagulants are not related to lower rates of stroke recurrence in comparison to aspirin. [4] In the NAVIGATE ESUS trial, there was a notable dissimilarity concerning hemorrhagic events between rivaroxaban and aspirin assigned patients. In the RE-SPECT ESUS trial the rates of these outcomes between dabigatran and aspirin assigned patients were with no difference. [4] The rates of major bleeding were the same among rivaroxaban and dabigatran assigned patients, while the rates of major bleeding in patients assigned to aspirin in the NAVIGATE ESUS were lower compared with patients assigned to aspirin in RE-SPECT ESUS trial. [4]

The ESUS trials' neutral results could be explained by the overlap of possible sources of embolism maybe as a result of several possible different entities condensation of a non-homogenous group of causes into one diagnosis. This fact may justify the inability of ESUS trials to distinguish those patients who benefit from oral anticoagulant therapy for secondary stroke prevention. [4,46] It should also be noted that finding a possible source of embolism should not be considered as the main reason for an ESUS but rather as a mere coincidence . [4] There are still no clear answers about how to treat these strokes. The two large trials (NAVIGATE ESUS and RE-SPECT ESUS) despite their neutral results could show the way on how to treat these patients. They come to the conclusion for a more targeted treatment. [4]

Consequently, the general view that many different nosological entities of a very heterogeneous group of patients (ranging from some very young patients without any

traditional risk factors to middle-aged patients with many cardiovascular risk factors [46]) could fit in a single causative factor as well as that cardioembolism due to subclinical paroxysmal AF is the main underlying mechanism of ESUS are still under discussion.

There was a proposal of phenotype clinical differentiation that could be classified as "atherosclerotic" and "non-atherosclerotic" with the latter referring to younger patients who do not have classical vascular risk factors or evidence of usual stroke etiologies. In these cases arterial dissection or paradoxical embolism due to PFO may be the cause of the embolism. [49]

Ongoing trials results may give crucial information about secondary prevention. ARCADIA[50] and ATTICUS[51] trials which test the efficacy of apixaban compared with aspirin for the secondary stroke prevention in ESUS patients with concomitant atrial cardiopathy, as well as the discussion about reducing ESUS recurrence in patients with aortic arch, cervical or intracranial atherosclerosis when low dose oral anticoagulation and aspirin are combined are taking place at this time. The COMPASS [52] clinical trial gave significant information about combining anticoagulants in a low dose and aspirin in coronary and peripheral artery disease compared with aspirin monotherapy, having a significant clinical benefit despite the increased bleeding risk.[4] A similar future clinical trial assessing the hypothesis of anticoagulants in a low dose and aspirin combination would be well-advised as it could suggest several facts about stroke recurrence in ESUS patients and aortic arch, cervical, or intracranial atherosclerosis. [4]

All evidence so far show that the high prevalence of patients with ESUS, the significant risk for stroke, the available diagnostic tools and the creation of new therapeutic approaches (eg combining anticoagulants in low doses and aspirin) accentuate the need of further future research. [4]

Limitations

This systematic review was conducted by only one author. Additionally, the limitations of this systematic review relate to the fact that since ESUS is a new nosological concept there is no extensive relevant literature as well as published studies covering this topic. Available data are incomplete and there is strong evidence that they are needed to be revised. The neutral results of the two major studies of NAVIGATE ESUS and RE-SPECT ESUS did not help to give clear answers about secondary prevention. Ongoing studies may provide new data on secondary prevention options; however, there is still a long way to reach safe conclusions to such an extent that effective treatment criteria for ESUS patients could be established.

Chapter 5

5.1 Conclusion

ESUS still represents a heterogeneous [53,54] group of patients with different causes of cerebral embolism. Existing data show that there is 1 ESUS in every 6 ischemic strokes. ESUS tend to occur in younger age groups with a significant risk of stroke recurrence.[3] The concept that the majority of the cryptogenic strokes are caused by embolism is not a new idea [3] which has been suggested more than 20 years ago. [55] Still, there has been little improvement concerning the secondary prevention in cryptogenic ischemic stroke. [3] Apart from young patients with PFO there are no any data concerning new proposed therapeutic options. [56] Maybe PFO patients less than 60 years old with no other possible etiology of embolism should be removed from ESUS category as there is strong evidence of the large benefit of the PFO closure and causal association with stroke recurrence. [4] Finding the source of embolism is crucial for creating the best treatment plan, especially among patients with cardioembolic stroke [57]. New definitions and more suitable guidelines of ESUS are needed to be introduced, individualizing patient's treatment and avoiding indiscriminate anticoagulation. With the exception of undetected paroxysmal AF other potential embolic mechanisms could be involved (PFO, aortic plaque, non-stenotic unstable carotid plaque, cardiac valvulopathies,

coagulation disorders and undetected malignancy) requiring specific treatments, which is not always the case of oral anticoagulation. The most suitable secondary prevention for ESUS still remains unclear with unselective anticoagulant treatment (with VKAs or NOACs) being neither effective nor safe. Taking into account the above ESUS patients should undergo thorough and personalized investigation (i.e. high resolution vessel imaging, TEE investigation and long term cardiac monitoring to identify paroxysmal AF) in such manner that clinicians may be assisted to decide the ideal treatment approaches in secondary prevention.

Summary

The ESUS concept was proposed in 2014 to characterize patients with a non-lacunar stroke and no convincing etiology. Terms ESUS and cryptogenic are not the same as the latter also comprises patients with multiple stroke etiologies and incomplete diagnostic work up. [4] ESUS patients are typically younger with mild strokes. The stroke recurrence is 4-5%. Oral anticoagulants were thought to be effective by reducing the risk of stoke recurrence as it was assumed that the main mechanism was cardioembolic. This hypothesis was tested in two large randomized trials (the NAVIGATE ESUS and the RE-SPECT ESUS) but the results were neutral. So far there are no clear therapeutic data. The treatment strategy should be individualized avoiding indiscriminate anticoagulation.

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