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Research Article

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The Contribution of Early Transesophageal Echocardiography to The Therapeutic Management of Patients with Embolic Stroke of Undetermined Source

(Short title: The impact of transesophageal echography in ESUS)

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Abstract

Background: *about 25% of ischemic strokes (IS) are of unknown origin. Because most of them are supposed to be cardio-embolic, the Embolic Stroke of Undetermined Source (ESUS) concept was proposed. Although transesophageal echocardiography (TEE) is more sensitive than transthoracic echocardiography (TTE) for the detection of potential cardiac sources of embolism and is widely available, its impact on the therapeutic management of ESUS patients remains controversial.*
Objectives: *To assess TEE's impact on therapeutic management and identify predictive factors associated with treatment modification (TM) in consecutive ESUS patients.*
Methods and Material: *Acute ESUS patients admitted to our stroke unit were prospectively included to undergo TEE. Demographic, laboratory, MRI, and echocardiographic data were recorded. The primary endpoint was the rate of TEE-induced TM other than simple antiplatelet therapy.*
Results: *Between October 2016 and May 2018, 154 ESUS patients were included. TEE induced a TM in 22 patients (14.3%). These patients were significantly older than those without treatment change (68.9 vs. 59.0 years, p<0.001), and they had more cardiovascular risk factors such as diabetes mellitus, hypertension, and hypercholesterolemia: 36.4% vs. 15.9% (p = 0.036), 68.2% vs. 43.9% (p=0.035) and 72.7% vs 28.8% (p<0.001) respectively. They also had higher CRP, hs Troponin I, and NT-pro-BNP: 63.6% vs. 33.3% (p=0.007), 50.0% vs. 22.7% (p=0.007), 31.8% vs. 9.8%, (p=0.011) respectively.*
Conclusion*: Abnormal TEE findings may decisively affect the treatment strategy in about 14% of ESUS patients. Early TEE should be performed in all ESUS patients with inconclusive TTE who have elevated cardiac biomarkers and/or cardiovascular risk factors.*

Keywords: *ESUS, transesophageal echocardiography, treatment modification, cardiac source of embolism.*

Key message: Abnormal TEE findings may decisively affect the treatment strategy in about 14% of ESUS patients, especially those with non-conclusive TTE, elevated cardiac biomarkers, and/or cardiovascular risk factors.

Abbreviations
AAA: aortic arch atheroma
AC: anticoagulation
AF: atrial fibrillation
ASA: atrial septal aneurysm
ASD: atrial septal defect
DAPT: dual antiplatelet therapy
DWI: Diffusion-Weighted imaging
EACVI: European Association of Cardiovascular Imaging
EAE: European Association of Echocardiography
ESUS: Embolic Strokes of Undetermined Source
FLAIR: Fluid Attenuated Inversion Recovery
IS: ischemic strokes
MAR: missing at random
MRI: Magnetic Resonance Imaging
NIHSS: National Institute of Health Stroke Score
PCSE: potential cardiac and aortic sources of embolism
PFO: patent foramen ovale
SCARF: subclinical atrial fibrillation
SWI: Susceptibility-Weighted Imaging
TEE: transesophageal echocardiography
TM: treatment modification
TTE: transthoracic echocardiography

Introduction

Despite significant advances in diagnostic capabilities, about 25% of ischemic strokes (IS) remain cryptogenic. As most of them are supposed to be cardio-embolic, the clinical ESUS concept was proposed, for Embolic Strokes of Undetermined Source[1]. An ESUS stroke is defined as a non-lacunar stroke, with no extra- or intra-cranial atherosclerosis resulting in more than 50% luminal stenosis in the arteries supplying the area of

ischemia, with no major cardiac source of embolism and no other specific cause of stroke.
Its assessment comprises Brain CT or MRI, 12-lead ECG, transthoracic echocardiography (TTE), cardiac monitoring for at least 24 hours with automated rhythm detection and imaging of both extracranial and intracranial arteries supplying the area of brain ischemia [1].

ESUS represents 9 to 25% of all ischemic strokes [2] and may be associated with a wide range of etiologies including covert atrial fibrillation (AF) [3-6]. Hence, routine detection of AF is mandatory in the diagnostic assessment of these patients. For the detection of the other potential cardiac and aortic sources of embolism (PCSE), transesophageal echocardiography (TEE) is the gold standard, superior to TTE [7]. However, it has been excluded from ESUS workup [1]. Furthermore, it is only considered as "reasonable" in this indication in the last American guidelines for the prevention of stroke in patients with stroke and transient ischemic attack [8]. Indeed, the therapeutic impact of TEE is still questioned.

Currently, in the absence of an identified PCSE after TTE, the therapeutic management of ESUS is based on antiplatelet therapy [9]. Two studies from the same team have reported 10% to 16% TEE-induced treatment modification (TM) other than simple antiplatelet therapy in ESUS patients [10,11].

In this prospective study, we aimed to further evaluate the TEE-induced TM rate other than simple antiplatelet therapy in acute ESUS patients and identify the predictive factors associated with those changes.

Methods

Patients

Consecutive patients with acute IS satisfying ESUS criteria[1] who were admitted to our stroke unit between October 2016 and May 2018 were prospectively included in the study. All had ECG, cardiac monitoring, TTE, brain MRI including Diffusion-Weighted imaging (DWI), Fluid Attenuated Inversion Recovery (FLAIR) and Susceptibility-Weighted Imaging (SWI) sequences, imaging of brain arteries and blood tests, and TEE. The impact of TEE on therapeutic management was recorded. As we aimed to include acute ESUS patients, only those having echocardiography less than 7 days after stroke entered the analyses.

Demographic, clinical, biological, and MRI data, echocardiographic investigations (both TTE and TEE), and TEE-induced TM were recorded. When AF was documented at admission or during hospitalization, even after TEE, patients were excluded from the study. The study was approved by the local ethics committee and informed consent was obtained from all the patients.

Echocardiography

TTE and TEE were performed by two experienced cardiologists and echocardiographic findings were classified according to the available guidelines in 2016 by the European Association of Echocardiography (EAE) and the European Association of Cardiovascular Imaging (EACVI) [12]. A uniform Case Report Form for TTE and TEE was fulfilled by the cardiologists. As a standard, TTE and TEE comprised a bubble study, unless this was impossible due to technical reasons or deemed unnecessary by the cardiologist.

TTE: all ESUS patients underwent standard TTE using a commercially available ultrasound system (EPIQ7, release 1.4.1, Philips Ultrasound) with a 1.3-4.2 MHz phased array transducer. PCSEs were classified according to the available guidelines [12], in major and minor or unclear risk sources.

TEE: was performed using the same ultrasound system, with a TEE X7-2t probe, under topical oropharyngeal anesthesia with lidocaine, unless contraindicated. In stable patients, intravenous midazolam was used (1-5 mg). PCSEs were classified according to the guidelines. Left atrial appendage area (LAA-A, cm^2), left atrial appendage emptying velocity (LAA-EV, cm/s) and patent foramen ovale (PFO) diameter were measured as described elsewhere [13-16]. Only patients with large shunt PFO, with or without atrial septal aneurysm (ASA), were classified in the PFO group. Large shunt associated with PFO was defined by the appearance of >30 microbubbles in the left atrium within the three cardiac cycles after right atrium opacification, at rest, or during provocation manoeuvers[16]. ASA was diagnosed on TEE when the basis of the aneurysm was ≥ 15mm and its excursion >10 mm [16]. Aortic arch atheroma was classified as complex when plaque thickness was ≥ 4 mm and/or in the presence of ulcerated plaques (depth and width ≥ 2 mm) and/or protrusive ones or in the presence of mobile debris [17,18].

Data collection

Demographic variables including age and National Institute of Health Stroke Score (NIHSS) at entry, and stroke risk factors were collected. These included diabetes, current smoking, hypertension, and hypercholesterolemia. Neurological factors such as previous stroke, artery occlusion, and multiple infarcts were collected. Biological data were collected including cholesterol levels, CRP which was dichotomized at 5mg/l, hs Troponin I which was dichotomized at 14pg/ml, and NT-pro-BNP which was dichotomized at 500pg/ml.

A few hours after TEE, the patients filled out a form about their understanding of TEE and how they experienced it.
A follow-up visit at 3 months was programmed, to address stroke recurrence, cardiovascular events, and Rankin score.

Statistical analysis

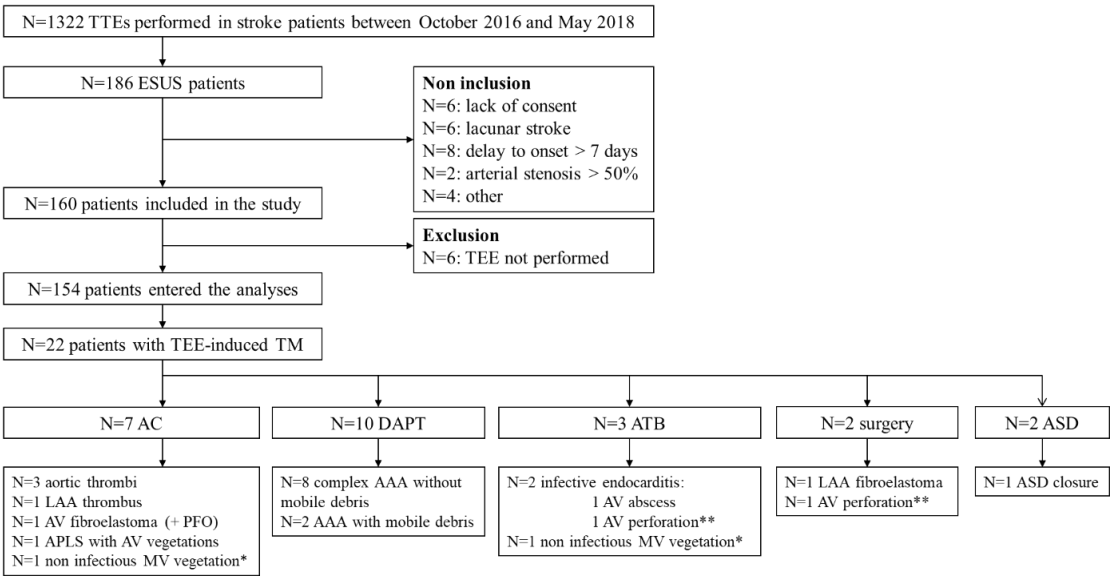
Statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna (2013)). The level of two-tailed significance was set at $p<0.05$ for all statistical procedures. Normal distribution in continuous variables was assessed using a Shapiro-Wilk test. Quantitative variables were presented as mean ± standard deviation or median and interquartile ranges as appropriate, categorical variables were presented by the number of observations and percentage. The rate of TEE-induced TM was calculated with a 95% confidence interval. After standard evaluation, baseline characteristics of ESUS patients were compared according to the presence (TM+ group) or the absence (TM- group) of TTE-induced TM. If variables were not normally distributed, a non-parametric Mann–Whitney test was applied. Otherwise, a t-test was used to evaluate differences between groups. Qualitative variables were analyzed using the X2 test or Fisher's exact test depending on the number of observations.

Results

General characteristics of the study population

A total of 1,322 TTEs were performed in patients with IS admitted to our Stroke Centre from October 2016 to May 2018 (Figure 1). Acute ESUS was diagnosed in 160 patients, 154 of whom underwent TEE. The mean delay between IS onset and TEE in ESUS patients was 3.2 days [95% CI: 0.6-5.8 days]. The study population was composed of 100 males and 54 females. Patients' characteristics are reported in Table 1.

Figure 1: Study flowchart diagram.



AAA: aortic arch atheroma; APLS: antiphospholipid syndrome; ATB: antibiotics; AC: anticoagulation; ASD: atrial septal defect; AV: aortic valve; DAPT: dual antiplatelet therapy; LAA: left atrial appendage; MV: mitral valve; TEE: transesophageal echocardiography; TM: treatment modification.
* Same patient (first treated with ATB)
** Same patient

Table 1: Demographic and Clinical baseline characteristics of the whole cohort.

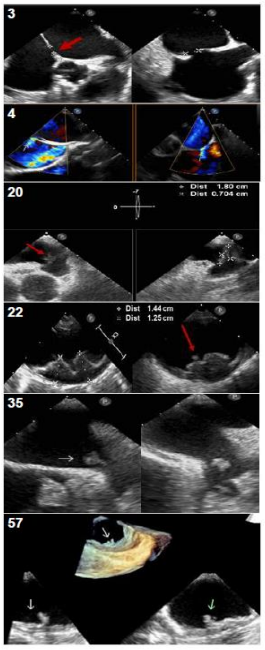
	Total N=154
Age (years), mean ± sd	60.5 ± 15.3
Male, n (%)	100/154 (64.9)
SBP (mmHg), mean ± sd	147 ± 23
DBP (mmHg), mean ± sd	85 ± 17
Hyperthermia >38 °C, n (%)	1 (0.7)
BMI (kg/m²), median [IQR]	25 [22-28]
NIHSS, median [IQR]	2 [1-5]
Hypertension, n (%)	73/154 (47.4)
Hypercholesterolemia, n (%)	54/153 (35.3)
Diabetes, n (%)	29/154 (18.8)
Cerebrovascular disease, n (%)	21/150 (14.0)
Antithrombotic therapy, n (%)	35/154 (22.7)
Smoking, n (%)	45/152 (29.6)
Ischemic Heart Disease, n (%)	11/150 (7.3)
LDL cholesterol (g/L), median [IQR]	1.13 [0.80-1.38]
SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BMI: Body Mass Index, NIHSS: National Institute of Health Stroke Score, sd: standard deviation, IQR: interquartile range.	

TEE findings and TEE-induced TM

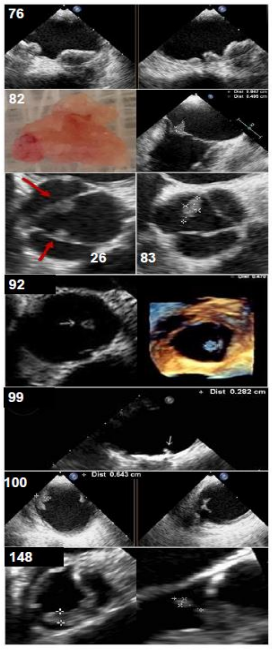
According to the classification of PSCE, TEE revealed 50 major and 118 minor PCSE compared to 40 and 82 using TTE, respectively. Among the major PCSE, 36 cases of complex aortic arch atheroma (AAA) were detected by TEE as compared to 6 suspected by TTE. Among the minor sources detected, 14 mitral valve prolapses and 77 Lambl's excrescences were detected by TEE as compared to 9 mitral valve prolapses and 1 Lambl's excrescence by TTE. Four patients had high-risk PCSE on both TTE and TEE. These patients were not included in the TM+ group. Finally, one patient had infectious aortic valve vegetations seen only on TEE. However, TEE was performed more than 7 days after the stroke onset. This patient was excluded from the study following the inclusion criteria.

Overall, as shown in Figure 2, 12 patients (7.8% [95% CI: 4.1-13.2%]) had consensual TEE-induced TM, including anticoagulation therapy (AC) in 6 patients, cardiac surgery in 1 patient, antibiotics (ATB) in 1 patient, ATB then AC in 1 patient, ATB, and surgery in 1 patient and dual antiplatelet therapy (DAPT) in 2 patients with mobile aortic debris which were not thrombi.

Figure 2: Impact of TEE on treatment change in ESUS patients.



Patient's nb	TEE diagnosis of PCSE	Treatment
2 (n°99, 100)	Mobile aortic arch debris	DAPT
8 (n°65, 71, 122, 130, 135, 142, 163, 174)	Aortic arch atheroma without mobile debris	DAPT
2 (n°22, 76)	Aortic arch thrombus	AC
1 (n°57)	Proximal descending aorta thrombus	AC
1 (n°35)	LAA thrombus	AC
1 (n°26)	Antiphospholipid syndrom with non infectious aortic vegetations	AC
1 (n°82)	Non infectious mitral vegetation (marastic)	AC
1 (n°92)	Aortic fibroelastoma (associated PFO)	AC
1 (n°20)	LAA fibroelastoma	Surgery
1 (n°148)	Infectious endocarditis	ATB, surgery
1 (n°83)	Aortic valve abcess	ATB (frailty)
1 (n°4)	Atrial septal defect	Closure
1 (n°3)	Atrial septal defect	No closure



ATB: antibiotics; AC: anticoagulation; DAPT: dual antiplatelet therapy; LAA: left atrial appendage; nb: number; PCSE: potential cardiac sources of embolism; TEE: transesophageal echocardiography.
Patient 82 underwent embolectomy: fibrino-cruoric thrombus without specificity. Pulmonary cancer was diagnosed later.

Additionally, 2 patients had TEE-documented atrial septal defects (ASD) which were not seen on TTE, and 8 had DAPT for complex aortic arch atheroma without mobile debris. These less consensual modifications are discussed in the dedicated section.

When considering these 10 patients (ASD closure and DAPT for complex AAA without mobile debris), TEE findings affected the therapeutic management in 22 out of the 154 patients (14.3%, 95% CI: 9.2-20.8%). Of note, patients with complex AAA had significantly more multiple infarcts on MRI (48.6 % vs 30.3%, p = 0.045).

Table 2: ESUS patients' characteristics according to the presence or the absence of TEE-induced treatment modifications.

N=154	TM- (N=132)	TM+ (N=22)	p
Age (years), mean ± sd	59.0 ± 15.5	69.2 ± 10.6	<0.001
Hypercholesterolemia, n (%)	38/131 (29.0%)	16/22 (72.7%)	<0.001
Diabetes mellitus, n (%)	21/132 (15.9%)	8/22 (36.4%)	0.04*
Hypertension	58/132 (43.9%)	15/22 (68.2%)	0.04
Smoking, n (%)	39/131 (29.8%)	6/21 (28.6%)	0.91
Multiple infarcts on DWI, n (%)	42/132 (31.8%)	11/22 (50.0%)	0.10
Artery occlusion, n (%)	42/132 (31.8%)	7/22 (31.8%)	1
Past Stroke on FLAIR, n (%)	30/132 (22.7%)	2/22 (9.1%)	0.25*
CRP > 5mg/l, n (%)	45/128 (35.2%)	14/22 (63.6%)	0.01
Hs Troponin I > 14 ng/ml, n (%)	30/128 (23.4%)	12/22 (54.5%)	0.003
NT-pro-BNP > 500 ng/ml, n (%)	14/125 (11.2%)	8/22 (36.4%)	0.01*
Thrombectomy, n (%)	14/132 (10.6%)	5/22 (22.7%)	0.15*
Thrombolysis, n (%)	22/132 (16.7%)	5/22 (22.7%)	0.54*
NIHSS, median [IQR]	2 [1.0-5.0]	2 [1.3-5.5]	0.91+

TM: Treatment Modification; DWI: Diffusion-Weighted Imaging; FLAIR: Fluid-Attenuated Inversion Recovery Imaging; NIHSS: National Institute of Health Stroke Score.
Continuous data were compared with t-test and categorical data using a χ^2 test unless noted.
* Fisher's Exact test
+ Mann-Whitney U test

Predictive factors associated with TEE-induced TM

When comparing TM+ and TM- groups, TM+ patients were significantly older, with significantly more frequent diabetes mellitus, hypercholesterolemia, and hypertension. They also had higher levels of CRP, has Troponin I, and NT-pro-BNP, as reported in Table 2. Neurological data were not significantly different in the two groups. After adjusting for age, CRP, hs Troponin I, and NT-pro-BNP remained significantly associated with TEE-induced TM, as shown in Table 3.

Table 3: Comparisons between groups.

	TM (reference TM -)		**PFO (reference PFO-)**
	OR* [95% CI], p	OR^{+} [95% CI], p	OR * [95% CI], p
CRP >5 mg/l	2.77 [1.04-7.35], 0.04	2.66 [0.96-7.41], 0.06	0.54 [0.23-1.25], 0.15
Hs Troponin I >14 ng/ml	2.71 [1.00-7.34], 0.049	2.74 [0.95-7.95], 0.06	0.51 [0.19-1.40], 0.19
NT-pro-BNP>500 ng/ml	3.11 [1.06-9.15], 0.04	2.00 [0.63-6.33], 0.24	0.18 [0.02-1.43], 0.11

TM: treatment modification; PFO: patent foramen ovale; OR: Odds Ratio; 95% CI: confidence interval.
*Adjustment for age
$^{+}$ Adjustment for age, diabetes, and hypercholesterolemia

Concerning PFO

A large shunt PFO on TEE was found in 38 patients (24.7% [95% CI: 18.1-32.3]). However, these large PFO shunts were also documented by TTE, which comprised a bubble study. Table 4 describes patients' characteristics according to the presence or the absence of large shunt PFO. As expected, patients with PFO were significantly younger. Hypercholesterolemia, diabetes mellitus, hypertension, and NT-pro-BNP elevation were significantly less prevalent in these patients.

Table 4: ESUS patients' characteristics according to the presence or the absence of PFO.

N=154	**PFO- (N=116)**	**PFO+ (N=38)**	**p**
Age (years), mean ± sd	62.4 ± 14.2	54.5 ± 17.2	0.01
Hypercholesterolemia, n (%)	47/115 (40.9%)	7/38 (18.4%)	0.01
Diabetes mellitus, n (%)	27/116 (23.3%)	2/38 (5.3%)	0.01
Hypertension, n (%)	63/116 (54.3%)	10/38 (26.3%)	0.003
Smoking, n (%)	36/114 (31.6%)	9/38 (23.7%)	0.36
Multiple infarcts on DWI, n (%)	43/116 (37.1%)	10/38 (26.3%)	0.23
Artery occlusion, n (%)	40/116 (34.5%)	9/38 (23.7%)	0.21
Past Stroke on FLAIR, n (%)	25/116 (21.6%)	7/38 (18.4%)	0.68
CRP > 5mg/l, n (%)	49/113 (43.4%)	10/37 (27.0%)	0.08
Hs Troponin I > 14 ng/ml, n (%)	36/112 (32.1%)	6/38 (15.8%)	0.052
NT-pro-BNP > 500 ng/ml, n (%)	21/111 (18.9%)	1/36 (2.8%)	0.02
Thrombectomy, n (%)	18/116 (15.5%)	1/38 (2.6%)	0.04*
Thrombolysis, n (%)	22/116 (19.0%)	5/38 (13.2%)	0.41
NIHSS, median [IQR]	2 [0-3]	2 [1-6.3]	0.01^{+}

PFO: patent foramen ovale; DWI: FLAIR: NIHSS: National Institute of Health Stroke Score; IQR: interquartile range.
Continuous data were compared with t-test and categorical data using a χ^2 test unless noted.
* Fisher's Exact test
$^{+}$ Mann-Whitney U test

Satisfaction survey

One hundred forty-eight patients were able to answer the survey after TEE. Among them, 39 (26.4%) described TEE as mildly unpleasant, 78 (52.7%) as moderately unpleasant, and 31 (20.9%) as very unpleasant. However, 100% were satisfied with their management concerning TEE.

Three months follow up

Follow-up information was available in 130 patients. Three patients died, 2 deaths in 58 and 66-year-old patients being cardiovascular. These patients had numerous cardiovascular risk factors. One of them was in the TM+ group.

Six patients had a recurrent stroke, 2 of which occurred in the TM+ group and 3 had cardiovascular events, 1 being in the TM+ group. Finally, 113 (86.9%) had a favorable outcome (modified Rankin Scale between 0 and 2).

Discussion

According to the guidelines [12], TEE revealed a major PSCE in approximately 32% of our acute ESUS patients, and complex AAA was the most common. Early TEE induced a treatment modification in 14.3% of these patients, which is in line with previous studies, reporting 10 % to 16% of TEE-induced TM [10,11]. Thirteen of the 22 TM+ patients had complex AAA. Among them, one had an aortic arch mobile thrombus, 2 had mobile aortic arch debris corresponding to ruptured plaques, and 1 had a mobile thrombus in the proximal descending aorta. The others had complex AAA without mobile debris. Indeed, most of them were missed by the initial TTE evaluation, which is not the gold standard for the diagnosis of AAA. Although the imaging of the aortic arch was not included in the diagnostic workup of ESUS as published in 2014 [1], complex AAA was

classified as a major PCSE by the EAE [12] and more recently by the EACVI[7]. Furthermore, complex AAA is an important independent risk factor for stroke, with 4 times greater odds of stroke in patients with severe AAA [19]. As suggested, it might impact the management of ESUS patients [20]. The optimal management of patients with aortic thrombi remains to be defined. However, AC and statins are a logical approach [12,21,22]. In patients with proximal descending aorta thrombus, the same treatment appears well-founded. Indeed, retrograde emboli to the brain have been hypothesized [23].

The concept of ESUS has been first introduced with the hope that anticoagulation may offer better secondary prevention than antiplatelet therapy in these selected patients. However, the trials so far have been negative [9,24,25]. The heterogeneity of stroke mechanisms in the ESUS population may be one of the explanations [26,27] since a subgroup of these patients will more benefit from antibiotics and surgery than anticoagulation.

Regarding complex AAA, the introduction of short-term DAPT in secondary prevention was accepted as feasible by the neurology community until the new guidelines were published in 2021 [8]. These latest guidelines do not address the issue of whether single or DAPT is appropriate in this setting.

Nevertheless, even after excluding complex AAA, which therapeutic management is debated, from the analyses, TEE still modifies the treatment in 14 of our 154 patients (9%). This is still in line with a recent retrospective study of 1284 patients with acute ischemic stroke who underwent TEE, in which TEE led to a TM in 10.5% of patients [28].

On another hand, while both TTE and TEE comprised PFO detection, we did not include PFO patients in the TM + subgroup. A large shunt PFO was found on TEE in 38 of our patients (24.7% [95% CI: 18.1-32.3]). Indeed, these large PFO shunts were also documented by TTE. Furthermore, positive studies about PFO closure in cryptogenic stroke were published after our study initiation [29-31].

Interestingly, the cardiovascular biomarkers and risk factors we investigated seem to be significantly more prevalent in TM+ patients. Cardiac hs Troponin elevation was reported to be more common in ESUS patients than in those with non-cardio-embolic strokes [32]. Hence, TEE could be a valuable tool in ESUS patients with has Troponin, BNP or NT-pro-BNP, and CRP elevation with normal TTE.

We suggest that although the ESUS concept as first constructed cannot alone guide treatment [26], it could be upgraded by TEE in selected patients, allowing an oriented treatment approach, on an individual basis.

One of the advantages of this study is the precocity of the TEE and hence of the TEE-induced TM, to limit as much as possible the risk of stroke recurrence.

Finally, although TEE is a semi-invasive diagnostic tool, only 20.9% of our patients described it as very unpleasant, and 100% were satisfied with their TEE examination. We did not encounter any complications. Hence, we believe that TEE is safe when performed according to the guidelines and when respecting the contraindications.

Study limitations

The main limitation is the lack of prolonged post-discharge rhythm monitoring in many patients since prolonged rhythm monitoring was not systematic at the time of writing the study protocol. However, all our patients had a 24-hours ECG Holter monitoring. Furthermore, it is not fully established that an AF detected after ESUS is always the cause of the preceding stroke [26,33].

Indeed, ESUS was thought to be caused by subclinical atrial fibrillation (SCARF). However, the temporal relationship between SCARF and embolic events in ESUS patients does not fully confirm this hypothesis [33]. ESUS population is heterogeneous, and other causes than SCARF may be responsible for the stroke. This led to the concept of atrial cardiomyopathy [34] which we did not address.

Furthermore, PFO was recorded as a minor or undetermined PCSE, the main studies regarding PFO closure and recurrent stroke being not yet published when the study was designed [30]. This study aimed to establish the yield of TEE in ESUS. However, PFO may be easily documented by TTE first and then confirmed by TEE.

Finally, we could not identify robust factors associated with TEE-induced TM, because of a lack of statistical power. However, this was a secondary exploratory endpoint.

Conclusion

ESUS patients with non-conclusive TTE, cardiovascular risk factors, and/or elevated biomarkers should benefit from TEE. Further studies are needed to confirm the yield of TEE in these selected ESUS patients.

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Conflicts of interest: None

Clinical trial registration: URL http://www.clinicaltrials.gov. Unique identifier NCT03107637.

Data availability statement: data may be obtained from Dr Amélie Yavchitz, ayavchitz@for.paris

Ethics approval statement: the study was approved by the local ethics committee.

Patient consent statement: informed consent was obtained from all the patients

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