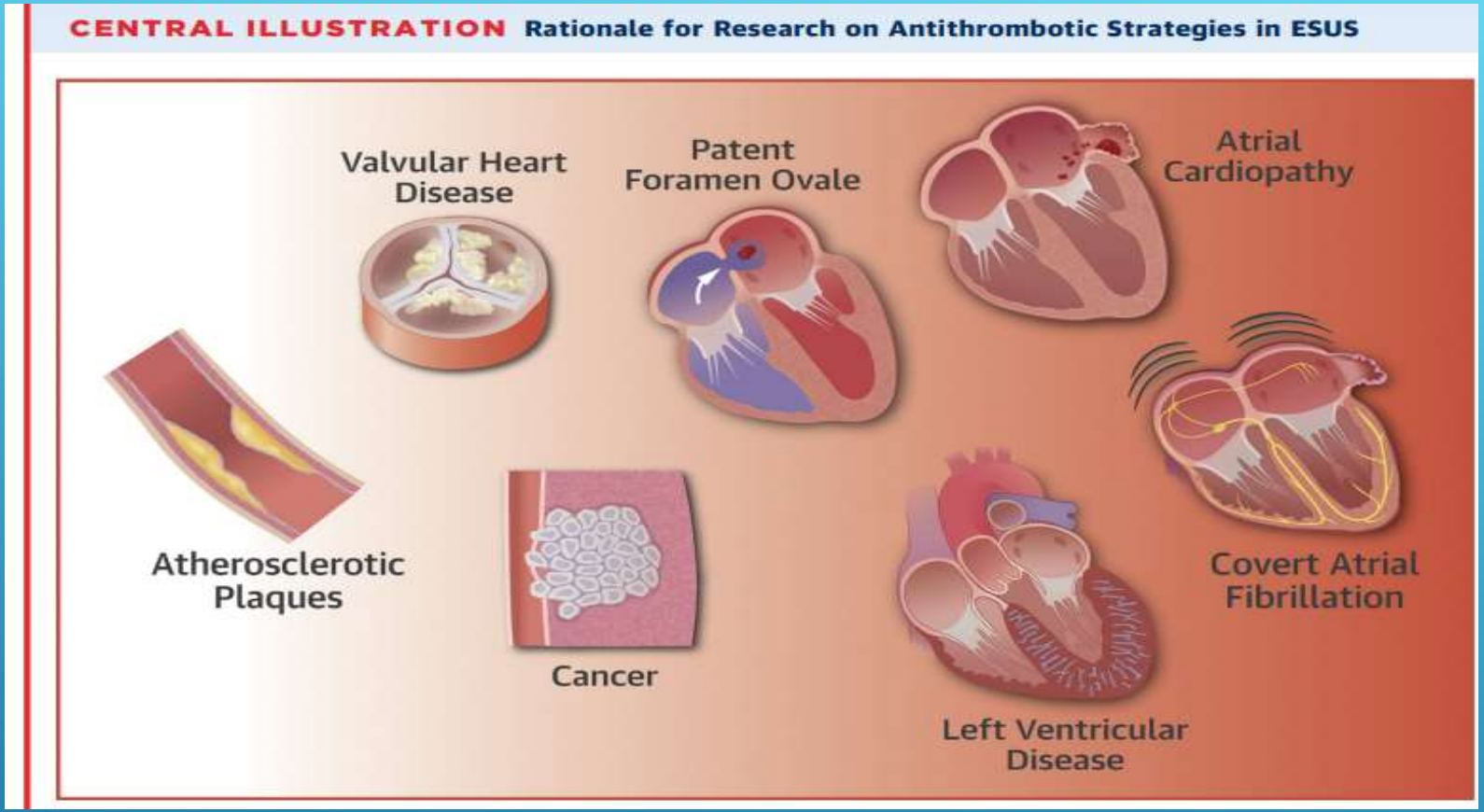
EMBOLIC STROKE OF UNDETERMINED SOURCE

- was introduced in 2014 to describe patients with a nonlacunar ischemic stroke and no convincing etiology (1). The terms ESUS and cryptogenic stroke are not synonyms, as the latter also includes patients with multiple stroke etiologies or incomplete diagnost

ESUS

JACC VOL. 75, NO. 3, 2020

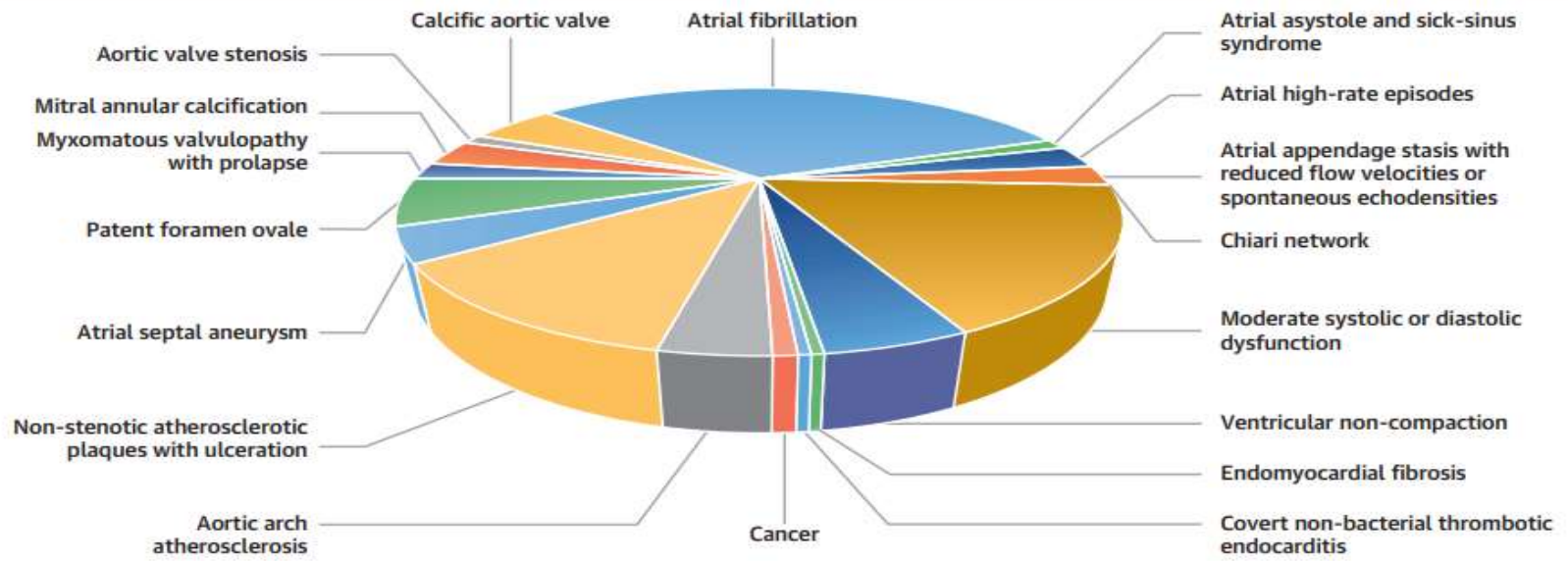


THE MAIN PATHOLOGIES

JACC VOL. 75, NO. 3, 2020

JACC VOL. 75, NO. 3, 2020
JANUARY 28, 2020:333–40

FIGURE 1 Distribution of Potential Etiologies of ESUS in the Athens Stroke Registry



Adapted from Ntaios et al. (2). ESUS = embolic stroke of undetermined source.

JACC VOL. 75, NO. 3, 2020

- ESUS represents a large patient group as it involves approximately 17% of all ischemic stroke patients, who are typically younger patients with mild strokes. In addition, these patients have a considerable rate of stroke recurrence of 4% to 5%/year
- nearly 90% of ESUS patients had been treated with antiplatelet
- NAVIGATE ESU (RIVAROXABAN)
- RE-SPECT ESUS (DABIGATRAN)
- ATTICUS(APIXABAN)

JACC VOL. 75, NO. 3, 2020

- Covert atrial fibrillation seems to be less important as an ESUS etiology than was initially conceived.
- d meta-analyses , showed that AF may be detected in 30% of ESUS patients during long-term follow-up;

AF IN ESUS:

JACC VOL. 75, NO. 3, 2020

AF IN ESUS:

- The rate of AF detection during follow-up in ESUS patients is similar to other non-ESUS stroke patients, as shown in the Find-AF-RANDOMISED study
- ESUS patients are phenotypically different compared with stroke patients with AF, with the former being younger with milder strokes, as shown across registries and trials
- The majority of embolic events (stroke or systemic embolism) does not occur proximal to recent episodes of atrial tachycardia or AF, as shown in patients with implantable cardiac monitoring devices in the ASSERT

- left ventricular disease(, low cardiac output, dilated chambers, poor contractility, endothelial dysfunction, and others)
- arterial disease,
- atrial cardiopathy

3 MOST PREVALENT POTENTIAL EMBOLIC

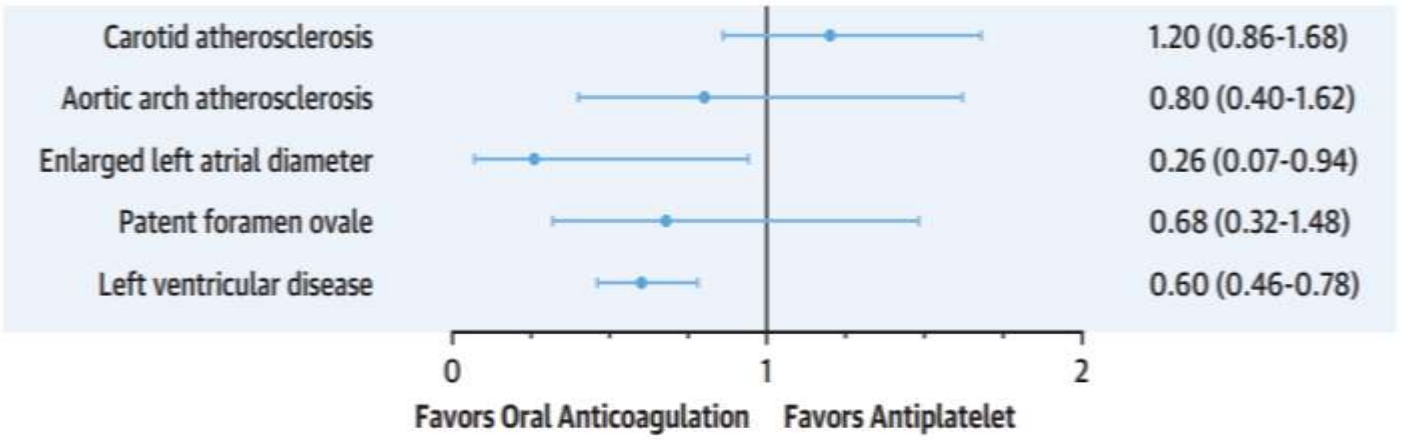
- atherosclerotic plaques in the aortic arch, cerebral, and intracranial arteries (drawn towards the white-colored end of the spectrum in the illustration), the main pathophysiological trigger is plaque rupture and subsequent local platelet activation and aggregation leading to formation of white thrombi, which may respond better to antiplatelets

CAROTID ATHEROSCLEROTIC PLAQUES

- white thrombi
- red thrombi

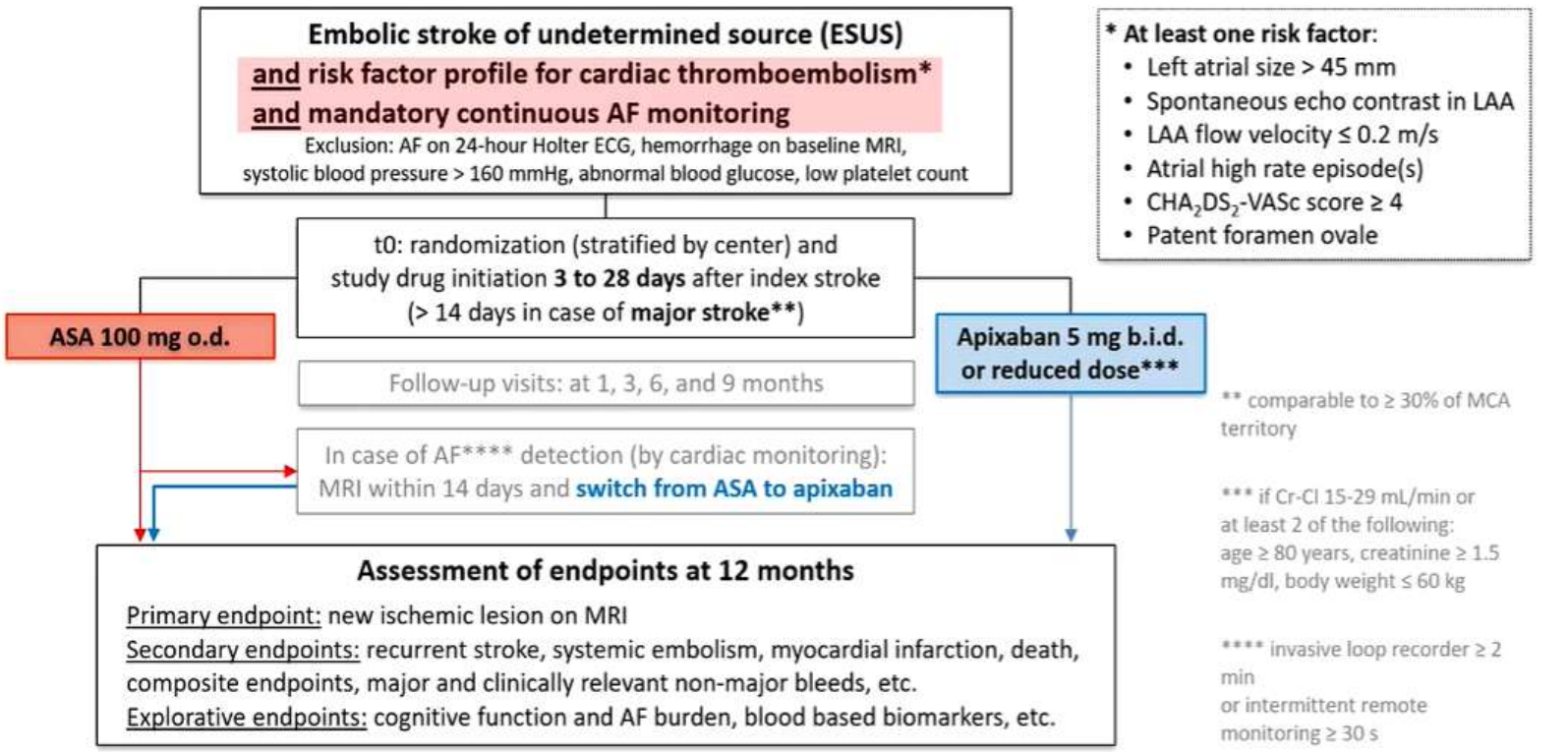
WHY WERE THE ESUS TRIALS NEUTRAL?

FIGURE 3 Comparison Between Oral Anticoagulation and Antiplatelet Treatment in Patients With ESUC/Cryptogenic Stroke and Underlying Potential Embolic Source



ATTICUS: Apixaban for TreatmenT of embolIC stroke of Undetermined Source

S Poli[1]*, T Keller[2], P Martus[3], K Poli[1], U Ziemann[1], and T Geisler[2]* (*contributed equally)
on behalf of the Steering Committee and ATTICUS investigators


Embolic stroke of undetermined source (ESUS)
and risk factor profile for cardiac thromboembolism*
and mandatory continuous AF monitoring
Exclusion: AF on 24-hour Holter ECG, hemorrhage on baseline MRI, systolic blood pressure > 160 mmHg, abnormal blood glucose, low platelet count
t0: randomization (stratified by center) and study drug initiation 3 to 28 days after index stroke (> 14 days in case of major stroke**)
ASA 100 mg o.d.
Apixaban 5 mg b.i.d. or reduced dose***
Follow-up visits: at 1, 3, 6, and 9 months
In case of AF**** detection (by cardiac monitoring): MRI within 14 days and switch from ASA to apixaban
Assessment of endpoints at 12 months
Primary endpoint: new ischemic lesion on MRI
Secondary endpoints: recurrent stroke, systemic embolism, myocardial infarction, death, composite endpoints, major and clinically relevant non-major bleeds, etc.
Explorative endpoints: cognitive function and AF burden, blood based biomarkers, etc.
* At least one risk factor:
• Left atrial size > 45 mm
• Spontaneous echo contrast in LAA
• LAA flow velocity ≤ 0.2 m/s
• Atrial high rate episode(s)
• CHA2DS2-VASc score ≥ 4
• Patent foramen ovale
** comparable to ≥ 30% of MCA territory
*** if Cr-Cl 15-29 mL/min or at least 2 of the following: age ≥ 80 years, creatinine ≥ 1.5 mg/dl, body weight ≤ 60 kg
**** invasive loop recorder ≥ 2 min
or intermittent remote monitoring ≥ 30 s
ESOC 2022
The Voice of Stroke in Europe
ATTICUS
Apixaban is not indicated for stroke prevention after ESUS
eso-conference.org

Further secondary efficacy outcomes

	ALL (N=352)	Apixaban (n=178)	ASA (n=174)	P value
Ischemic stroke and TIA	28 (8.0 %)	13 (7.3 %)	15 (8.6 %)	0.63
Systemic embolism*	1 (0.3 %)	0 (0 %)	1 (0.6 %)	0.49
Pulmonary embolism*	1 (0.3 %)	0 (0 %)	1 (0.6 %)	0.49
Myocardial infarction	4 (1.1 %)	1 (0.6 %)	3 (1.7 %)	0.31
All cause death	7 (2.0 %)	3 (1.7 %)	4 (2.3 %)	0.83
Composite endpoint (recurrent stroke, systemic embolism, pulmonary embolism, myocardial infarction, all cause death)	30 (8.5 %)	13 (7.3 %)	17 (9.8 %)	0.41

Log rank except *Fisher's exact

Bleeding complications

	ALL (N=352)	Apixaban (n=178)	ASA (n=174)	P value
Major bleed	3	2	1	
Intracranial hemorrhage	0	0	0	
Gastrointestinal bleed	1	1	0	
Fatal bleed	0	0	0	
Major and clinically relevant non-major bleed	13	5	8	
Gastrointestinal bleed	3	1	2	
Minor bleed	54	36	18	
Patients with minor bleed	41 (11.6 %)	27 (15.2 %)	14 (8.0 %)	
Patients with any bleed	48 (13.6 %)	30 (16.9 %)	18 (10.3 %)	0.075

Chi-square

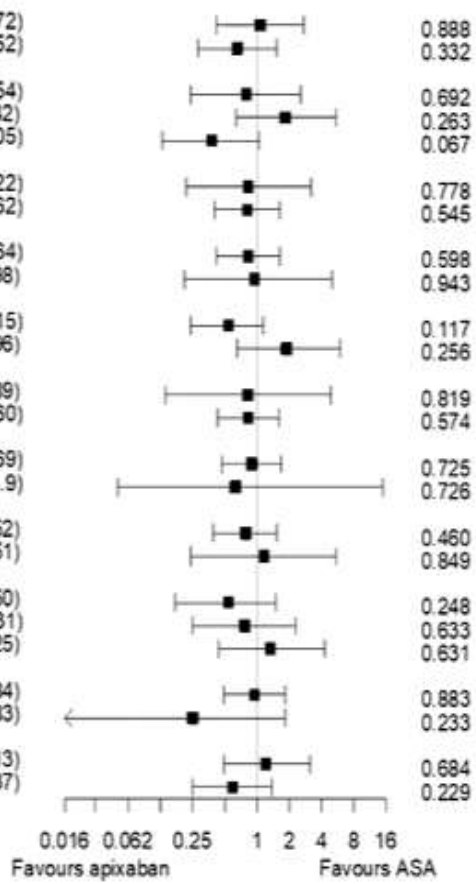
ESOC 2022 The Voice of Stroke in Europe

ATTICUS

Apixaban is not indicated for stroke prevention after ESUS

eso-conference.org

Subgroup		Apixaban group (n = 169)	ASA group (n = 156)	Odds Ratios (95% CI)	P value
Sex	Female	11 (81)	10 (78)	1.07 (0.42 - 2.72)	0.888
	Male	12 (88)	15 (78)	0.65 (0.28 - 1.52)	0.332
Age	< 65 years	6 (58)	7 (55)	0.79 (0.24 - 2.54)	0.692
	65 to < 75 years	10 (50)	7 (58)	1.82 (0.64 - 5.42)	0.263
	75+ years	7 (61)	11 (43)	0.38 (0.13 - 1.05)	0.067
GFR (Cockroft-Gault)	< 60 ml/min/m2	6 (35)	5 (25)	0.83 (0.22 - 3.22)	0.778
	60+ ml/min/m2	17 (134)	20 (131)	0.81 (0.40 - 1.62)	0.545
PFO	No	18 (126)	22 (132)	0.83 (0.42 - 1.64)	0.598
	Yes	5 (42)	3 (24)	0.95 (0.21 - 4.98)	0.943
Diabetes	No	12 (120)	19 (111)	0.54 (0.24 - 1.15)	0.117
	Yes	11 (48)	6 (44)	1.88 (0.65 - 5.96)	0.256
Hypertension	No	3 (25)	3 (21)	0.82 (0.14 - 4.89)	0.819
	Yes	20 (144)	22 (135)	0.83 (0.43 - 1.60)	0.574
History of cancer	No	21 (148)	23 (147)	0.89 (0.47 - 1.69)	0.725
	Yes	2 (21)	1 (7)	0.63 (0.05 - 14.9)	0.726
Previous Stroke/TIA	No	19 (146)	21 (130)	0.78 (0.39 - 1.52)	0.460
	Yes	4 (23)	4 (26)	1.16 (0.24 - 5.51)	0.849
CHA2DS2-VASc	2 to 4	6 (66)	11 (70)	0.54 (0.17 - 1.50)	0.248
	5	7 (55)	8 (50)	0.77 (0.25 - 2.31)	0.633
	6+	10 (48)	6 (36)	1.32 (0.44 - 4.25)	0.631
CAD/MI/CHF	No	22 (156)	20 (136)	0.95 (0.49 - 1.84)	0.883
	Yes	1 (13)	5 (20)	0.25 (0.01 - 1.83)	0.233
Time index stroke to randomization	< 8 days	13 (81)	9 (66)	1.21 (0.49 - 3.13)	0.684
	8+ days	10 (88)	16 (90)	0.59 (0.25 - 1.37)	0.229



ESOC 2022 The Voice of Stroke in Europe

ATTICUS

Apixaban is not indicated for stroke prevention after ESUS

eso-conference.o

Summary

- ATTICUS was the first trial testing the concept of DOAC vs. ASA in an enriched ESUS population with additional risk factors for cardiac thromboembolism **including clinical, echocardiographic and electrocardiographic AF predicting factors**
- Apixaban was not superior to 'ASA with **switch to apixaban in case of AF detection by mandatory cardiac monitoring'** in preventing new ischemic lesions during 12 months of follow up
- AF is common (28 %) in the our enriched ESUS population
- In this study, **early initiation of apixaban after ESUS (median 8 days)** appeared safe with only number of minor bleeds being increased versus ASA

ESOC 2022 The Voice of Stroke in Europe

ATTICUS

Apixaban is not indicated for stroke prevention after ESUS

eso-conference.org