ANTIPLATELET THERAPY FOR SECONDARY PREVENTION OF CRYPTOGENIC STROKE

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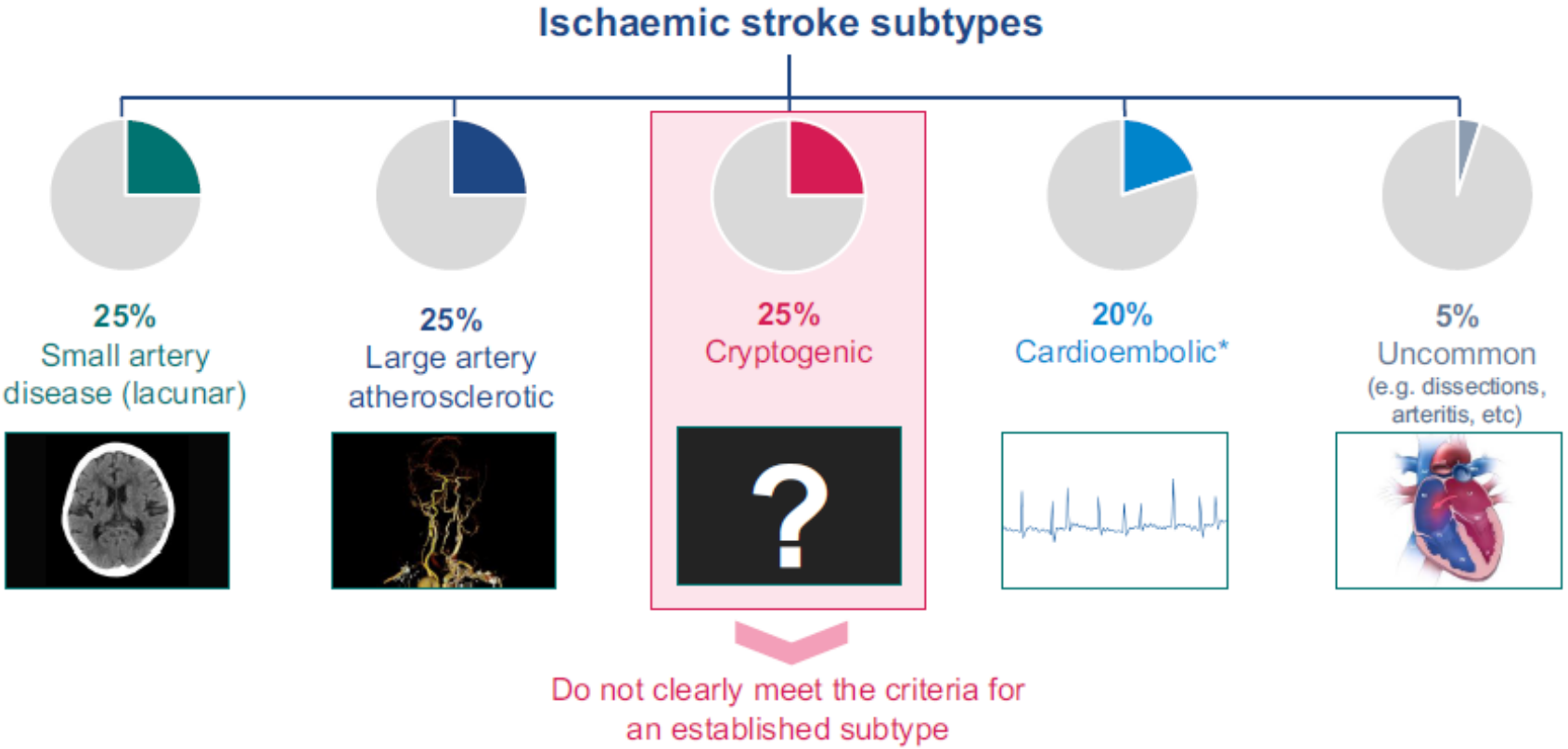
The TOAST classification system defines subtypes of ischemic stroke based on the cause



*Major-risk sources of cardioembolism (e.g. atrial fibrillation)
TOAST, Trial of ORG 10172 in Acute Stroke Treatment
Adams et al. Stroke 1993; Hart et al. Lancet Neurol 2014; Kamel, Healey. Circ Res 2017

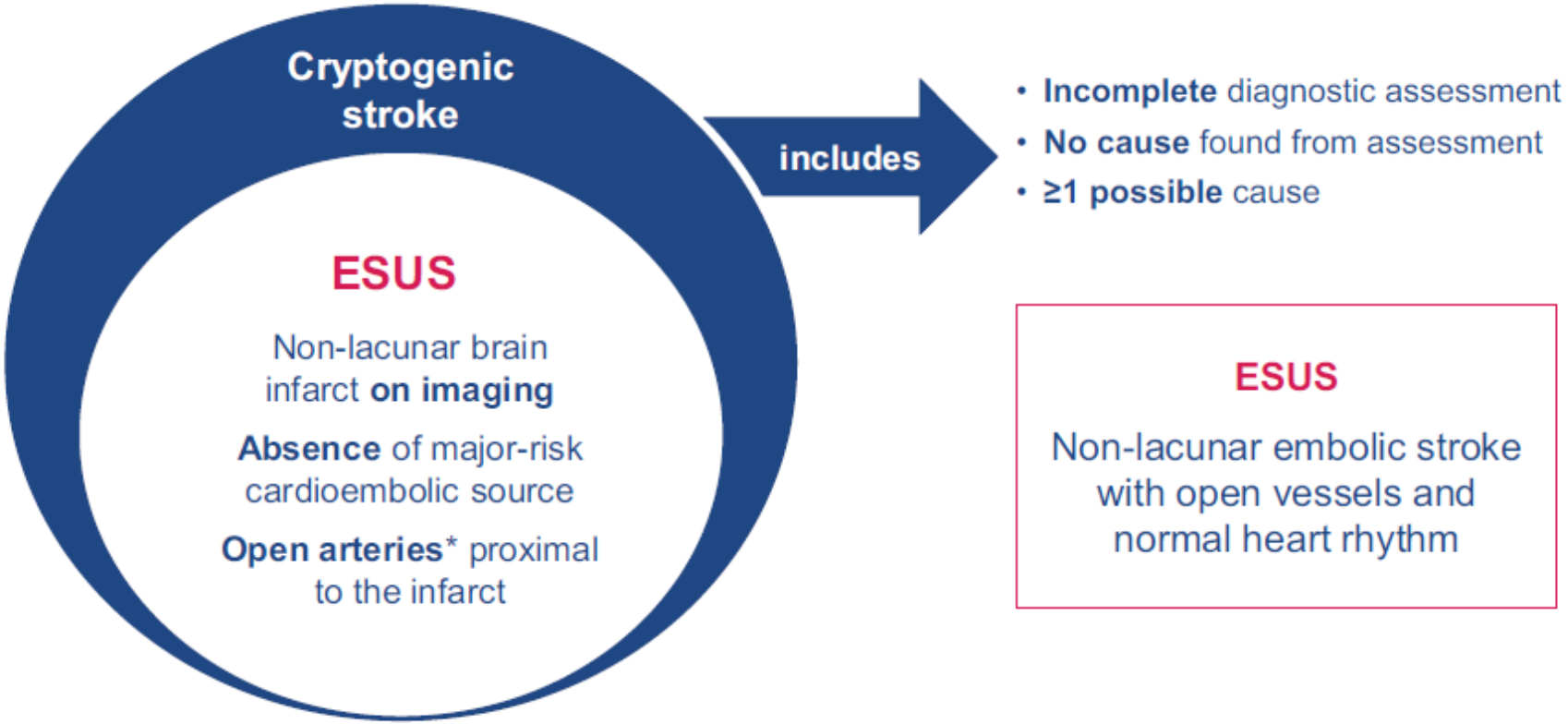
What is Cryptogenic Stroke (CS)? Definition

A cerebral infarct not attributed to a definite source of cardioembolism, large-vessel atherosclerosis, or small-vessel disease, despite:

- extensive cardiac, vascular, hematologic, and serological evaluation;
- evidence of >1 competing cause;
- incomplete diagnostic evaluation.

Circ Res. 2017;120:527-540.

ESUS is a defined subset of CS



*<50% stenosis

Modified from Hart et al. Lancet Neurol 2014

ESUS overview: what do we know?

ESUS accounts for around 1 in 6 ischaemic strokes

ESUS accounts for an average of 17% (9–25%) of ischaemic strokes

Patients with ESUS tend to be relatively young and experience mild strokes with high recurrence rates

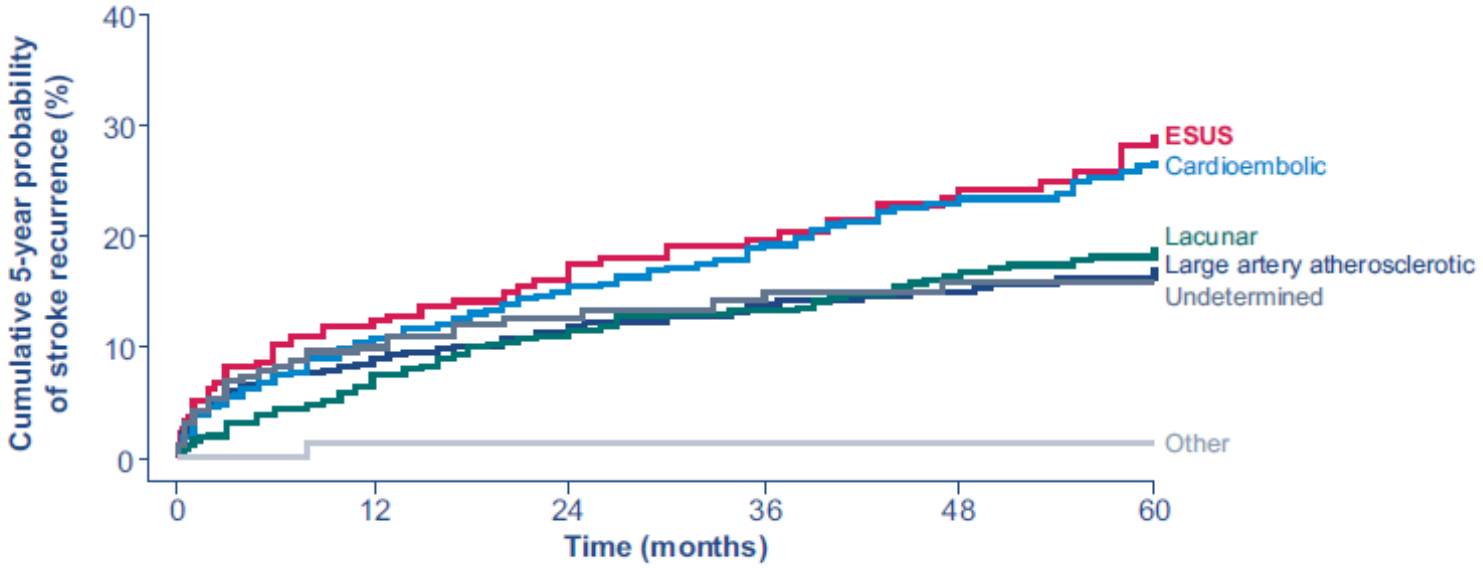
Mean age 65 years
Average annualized rate of recurrence of 4.5%

58% men
Mean NIHSS of 5 at stroke onset

Geisler T, Mengel A, Ziemann U, et al. Management of embolic stroke of undetermined source (ESUS). Drugs. 2018;78(8):823-831.
Hart RG, Catanese L, Perera KS, et al. Embolic stroke of undetermined source: a systematic review and clinical update. Stroke. 2017;48(4):867-872.

Stroke recurrence is high in patient with ESUS

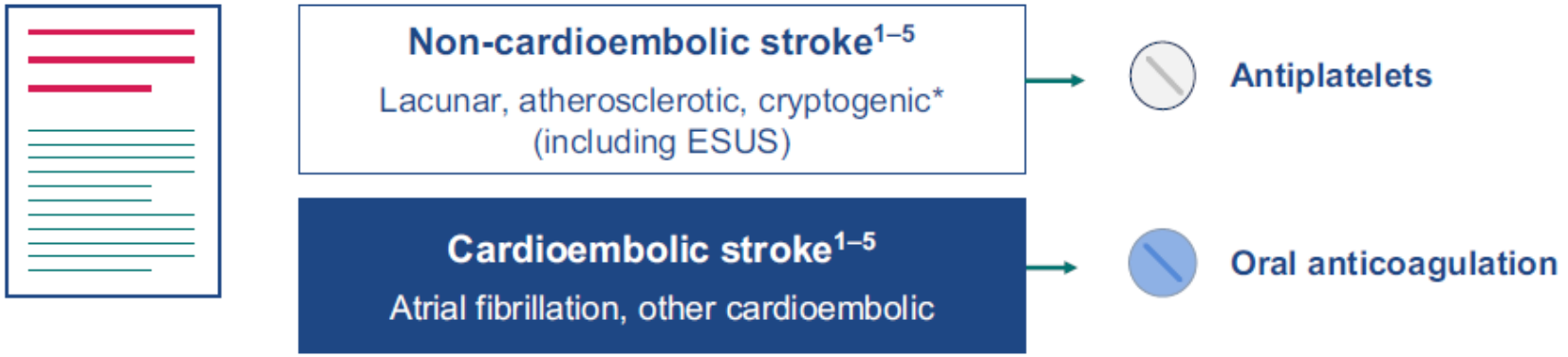
Athens Stroke Registry data



During a 5-year follow-up, **stroke recurrence was 29.0% in patients with ESUS**, similar to patients with cardioembolic stroke (26.8%), but significantly higher vs all types of non-cardioembolic stroke

N=2731; 10% of ischaemic strokes were classified as ESUS; covert AF was identified as the underlying aetiopathogenetic mechanism in ~44% of patients with ESUS
Ntaios et al. Stroke 2015a; Ntaios et al. Stroke 2015b

Guidelines currently recommend antithrombotic therapy for long-term secondary stroke prevention



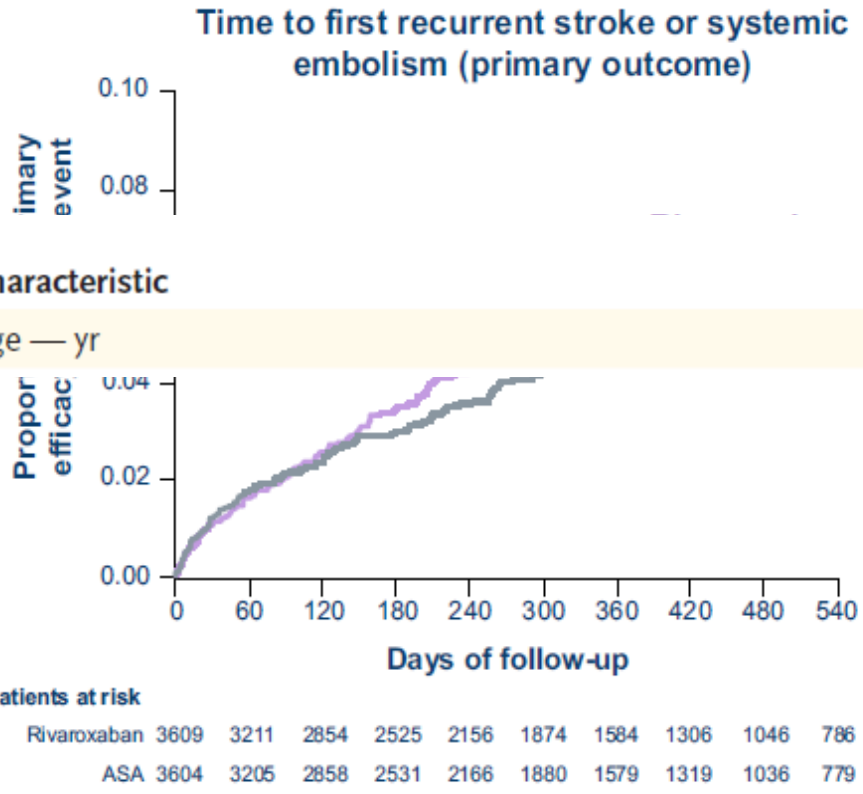
Clinical trials have investigated **whether oral anticoagulation is more effective** than antiplatelets in **preventing recurrence of ESUS**

*Only the ACCP 2008 guidelines make specific recommendations for cryptogenic stroke[5]

ACCP, American College of Chest Physicians

1. ESO Executive Committee. Cerebrovasc Dis 2008; 2. Lansberg. Chest 2012 Suppl.; 3. Kernan et al. Stroke 2014; 4. Powers et al. Stroke 2018; 5. Albers et al. Chest 2008

NAVIGATE ESUS: no benefit with rivaroxaban 15 mg OD vs ASA 100 mg OD



Rivaroxaban, n (%/yr)	ASA, n (%/yr)

Characteristic	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)
Age — yr	66.9±9.8	66.9±9.8

See Appendix II for patient baseline characteristics

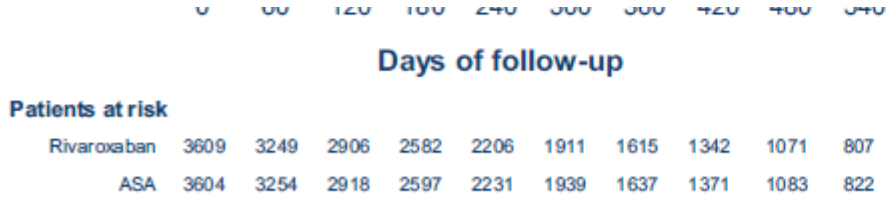
'Stroke' includes ischaemic, haemorrhagic, or undefined stroke

Hazard ratios and 95% CI were estimated on the basis of age group (<60 vs ≥60 years) in a stratified Cox proportional hazards model. ASA, acetylsalicylic acid

Hart et al. N Engl J Med 2018

NAVIGATE ESUS: rivaroxaban 15 mg OD associated with a higher risk of bleeding vs ASA 100 mg OD

Outcome	Rivaroxaban Group (N = 3609)	Aspirin Group (N = 3604)	Hazard Ratio (95% CI)†
	no. of patients (annualized rate)		
Primary efficacy outcome: any recurrent stroke or systemic embolism	172 (5.1)	160 (4.8)	1.07 (0.87–1.33)
Secondary efficacy outcomes			
Any recurrent stroke‡	171 (5.1)	158 (4.7)	1.08 (0.87–1.34)
Ischemic stroke‡	158 (4.7)	156 (4.7)	1.01 (0.81–1.26)
Hemorrhagic stroke§	13 (0.4)	2 (0.1)	6.50 (1.47–28.8)



*Major bleed at any site in the body according to the criteria of the International Society on Thrombosis and Haemostasis

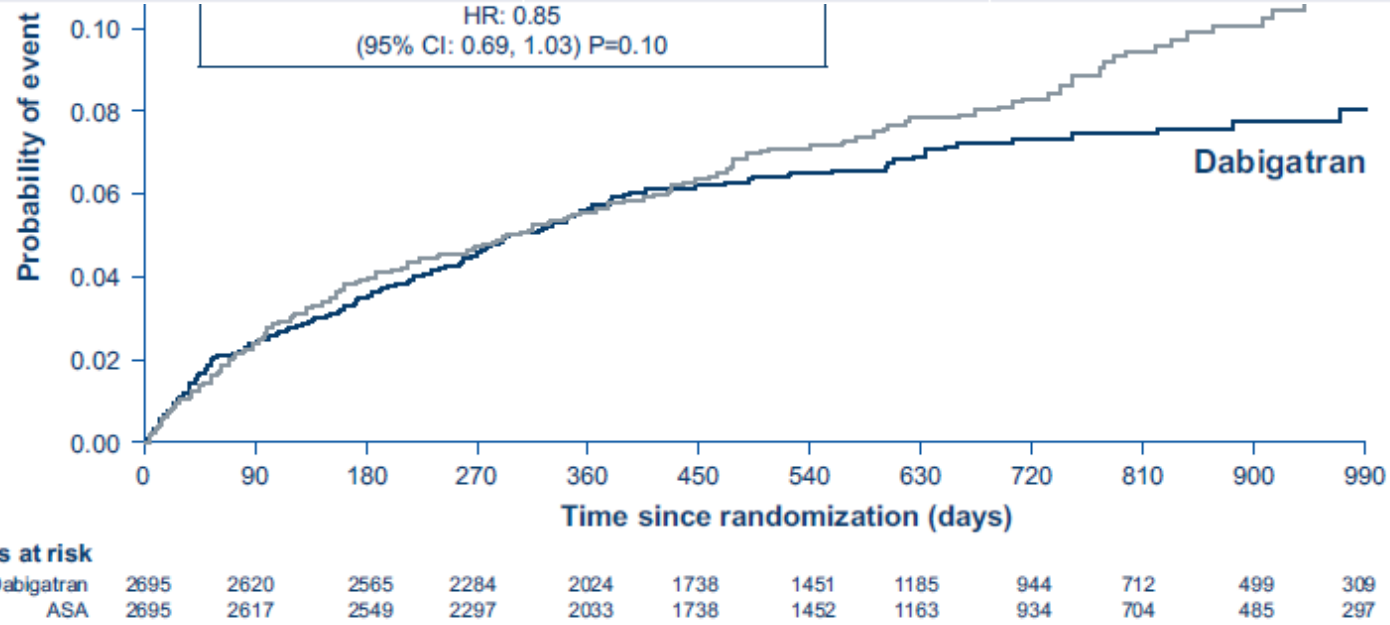
Hazard ratios and 95% CI were estimated on the basis of age group (<60 vs ≥60 years) in a stratified Cox proportional hazards model. ASA, acetylsalicylic acid

Hart et al. N Engl J Med 2018

RESPECT-ESUS: Time to first recurrent stroke

Time to first recurrent stroke

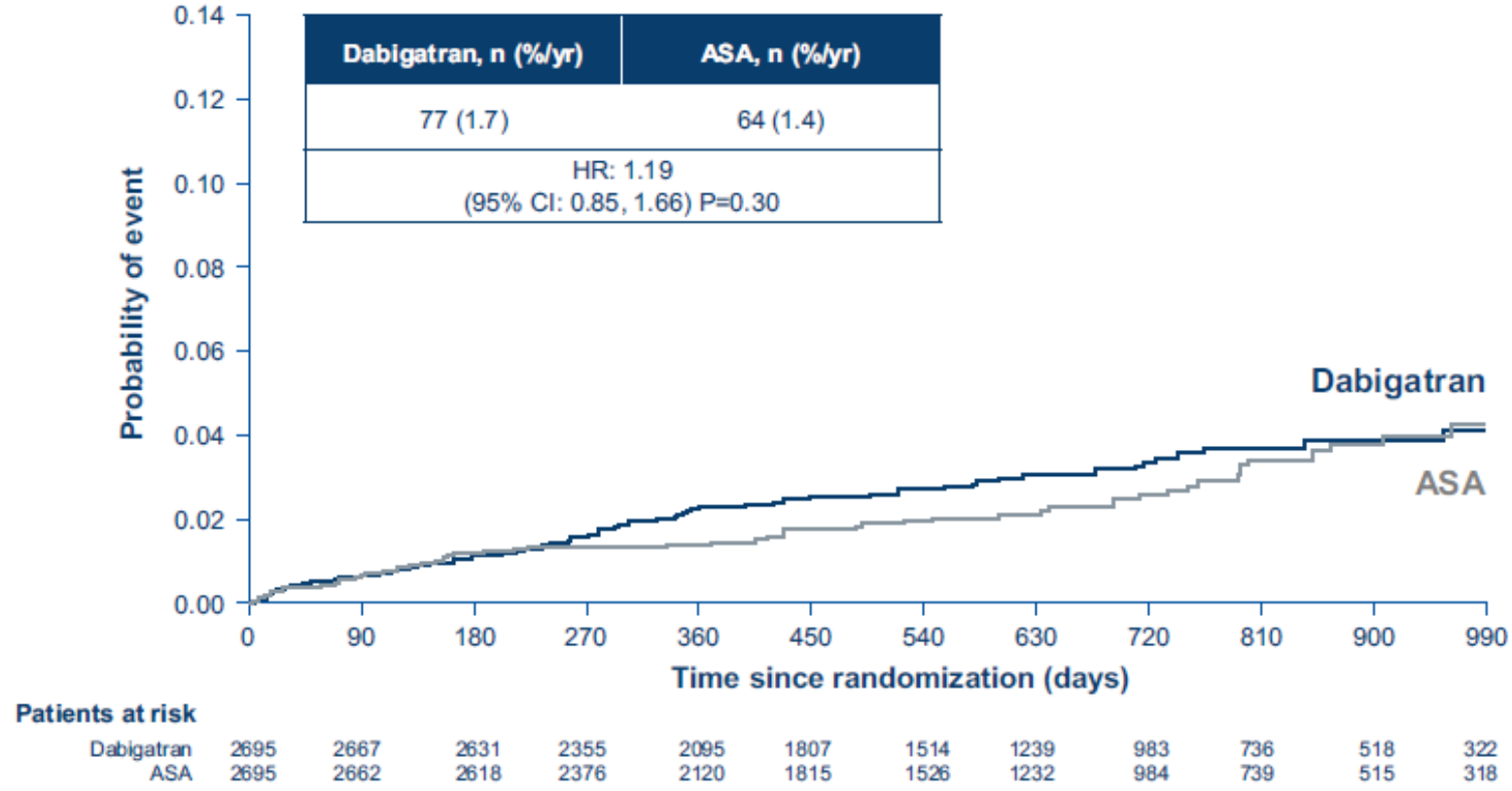
Characteristic	Dabigatran (N=2695)	ASA (N=2695)
Mean age, years (SD)	64.5 (11)	63.9 (11)



Patients at risk

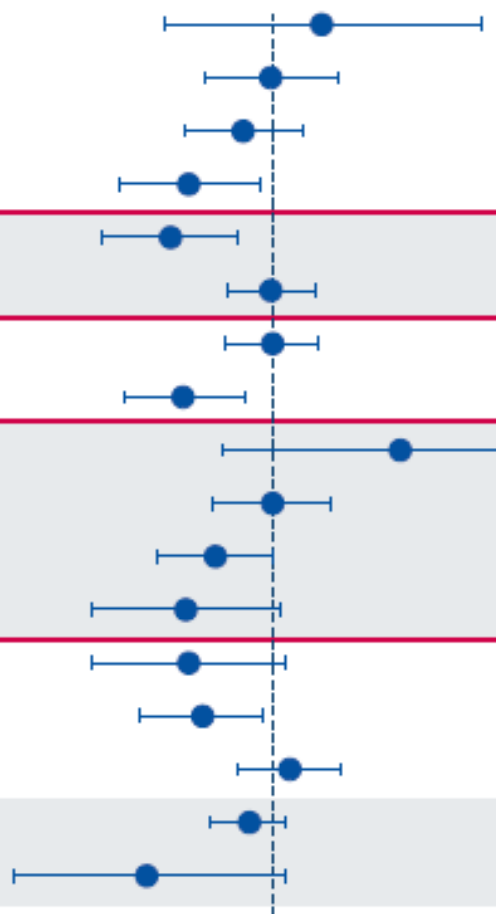
Dabigatran	2695	2620	2565	2284	2024	1738	1451	1185	944	712	499	309
ASA	2695	2617	2549	2297	2033	1738	1452	1163	934	704	485	297

RESPECT-ESUS: Time to first major bleed



RESPECT-ESUS: Recurrent stroke subgroup analyses

Subgroup		HR (95% CI)	HR (95% CI) dabigatran vs ASA	Interaction P value
Age classification	<50 years	1.31 (0.55, 3.15)		0.33*
	50–<65 years	0.99 (0.69, 1.43)		
	65–<75 years	0.85 (0.62, 1.19)		
	≥75 years	0.63 (0.43, 0.94)		
Dose assignment	110 mg	0.57 (0.39, 0.83)		0.01
	150 mg	0.99 (0.78, 1.26)		
Proton pump inhibitors	No	1.00 (0.77, 1.29)		0.03
	Yes	0.61 (0.44, 0.86)		
Time from index stroke to randomization	<8 days	2.02 (0.76, 5.38)		0.05
	8–30 days	1.00 (0.72, 1.38)		
	31–90 days	0.73 (0.53, 1.00)		
	≥91 days	0.62 (0.37, 1.04)		
Creatinine clearance at baseline	30–<50 mL/min	0.63 (0.37, 1.07)		0.11†
	50–<80 mL/min	0.68 (0.48, 0.95)		
	≥80 mL/min	1.10 (0.83, 1.46)		
Optional ASA at baseline	No	0.88 (0.71, 1.08)		0.16
	Yes	0.50 (0.24, 1.07)		

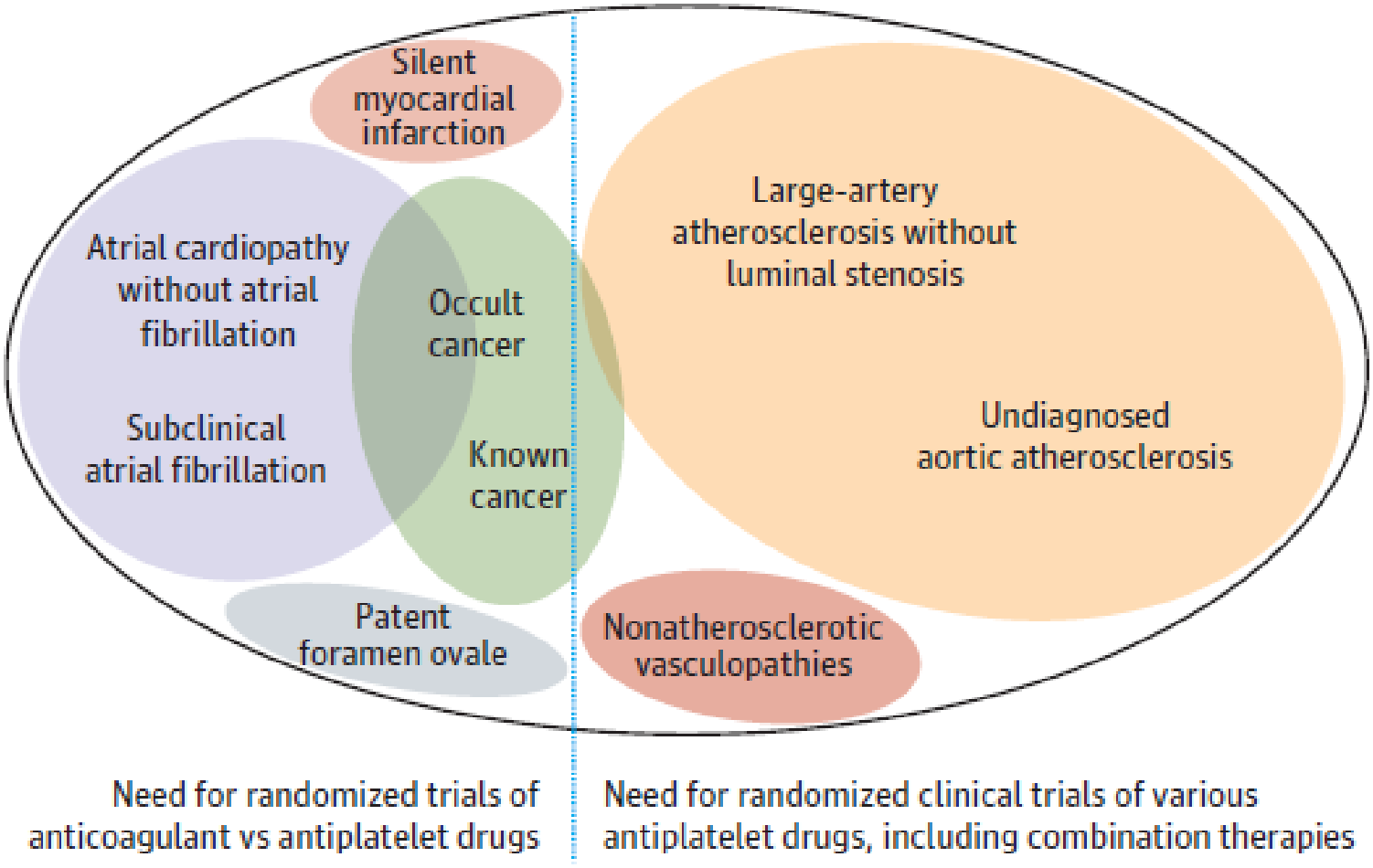


Causes of ESUS

- Causes of ESUS are heterogeneous.
- Mechanisms of stroke often do not occur in isolation.
- The *heterogeneity* of causal mechanisms leads to differences in stroke prevention strategies among ESUS patients.
- It is essential to determine the possible *culprit* in order to improve secondary stroke prevention strategies.

Circ Res. 2017;120:527-540
JAMA Neurology doi:10.1001/jamaneurol.2019.0591

Potential Occult Sources of Currently Unexplained Ischemic Stroke, Their Overlap, and Their Expected Response to Antithrombotic Drugs

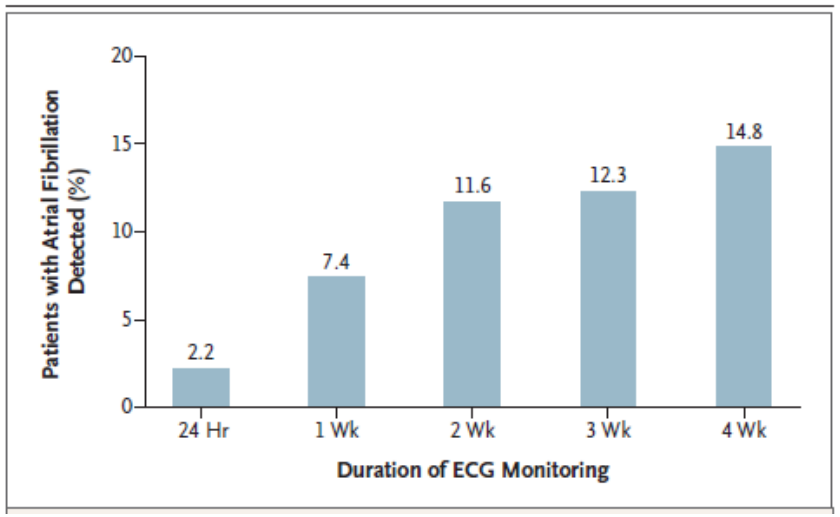


Occult Embolic Mechanisms Likely to Respond to Anticoagulant Therapy

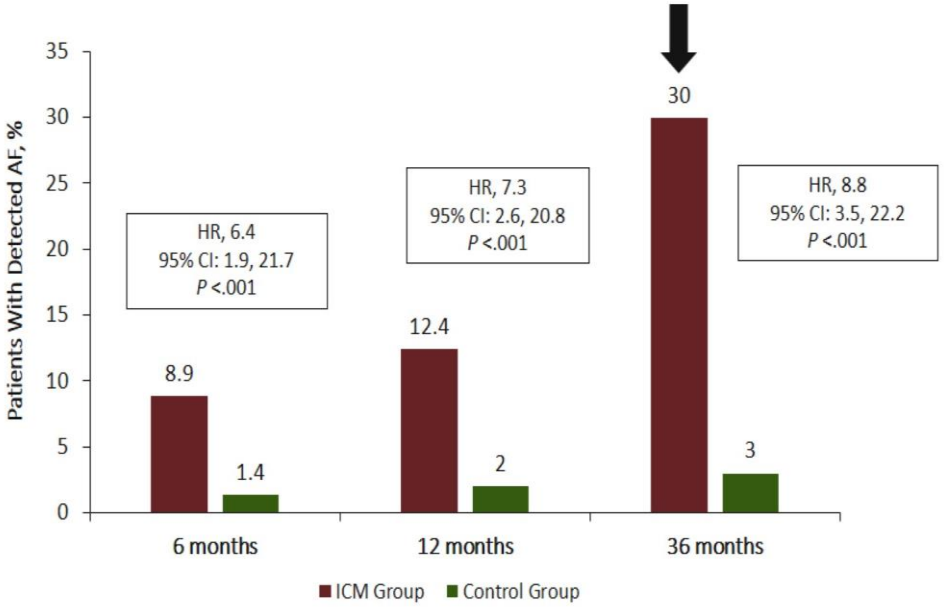
Subclinical Atrial Fibrillation

The more you look, the more you find…

EMBRACE



CRYSTAL AF



N Engl J Med 2014; 370:2478-2486
N Engl J Med 2014; 370:2467-2477

Occult Embolic Mechanisms Likely to Respond to Anticoagulant Therapy

Subclinical Atrial Fibrillation

- 70% of patients with ESUS have no AF, even after prolonged heart-rhythm monitoring.
- In many of these cases, AF occurs for the first time after the stroke.
- These findings undermine the notion of a direct, causal association between AF and stroke.

N Engl J Med. 2014;37 (26):2478-2486
N Engl J Med. 2012;366(2):120-129
Circulation. 2014;129(21):2094-2099

Occult Embolic Mechanisms Likely to Respond to Anticoagulant Therapy

Atrial Cardiopaty

- To date, anticoagulant therapy has not proven superior to antiplatelet therapy for preventing stroke recurrence in patients without known AF.

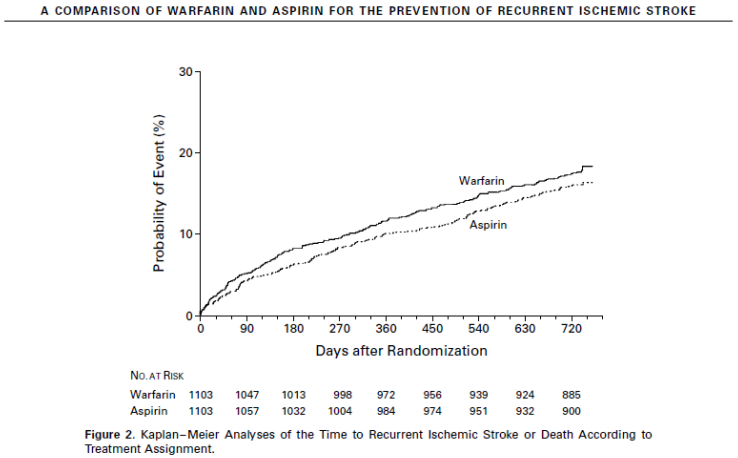


Figure 2. Kaplan–Meier Analyses of the Time to Recurrent Ischemic Stroke or Death According to Treatment Assignment.

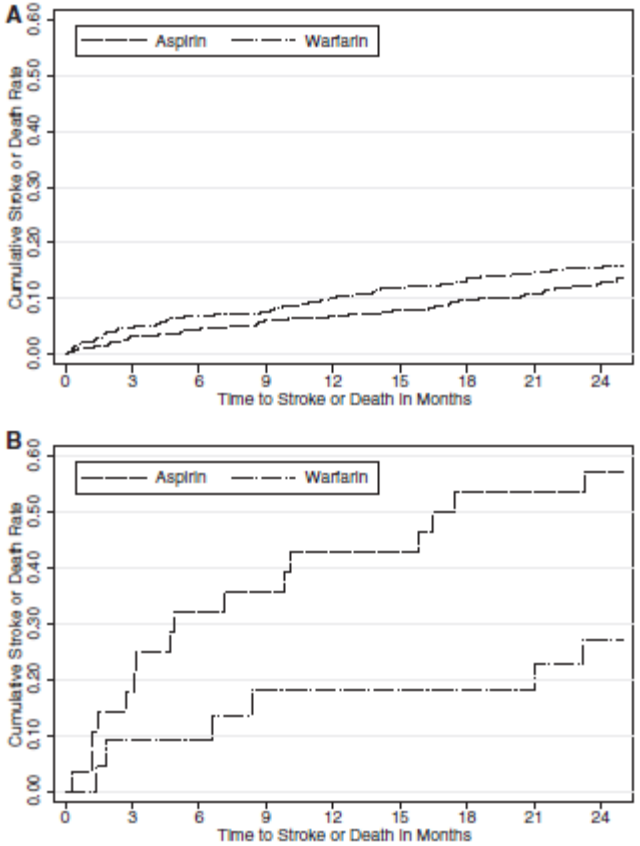
WARSS

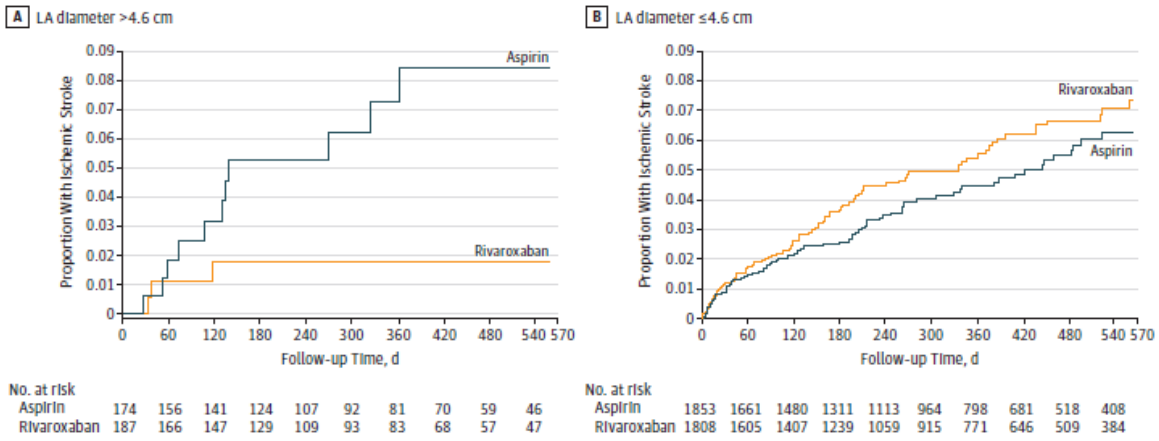
N Engl J Med. 2018;378(23):2191-2201
N Engl J Med. 2001;345(20):1444-1451.
Stroke. 2013;44(3):714-719.
JAMA Neurol. doi:10.1001/ jamaneurol.2019.0617

Occult Embolic Mechanisms Likely to Respond to Anticoagulant Therapy

Atrial Cardiopaty

- Post hoc analyses have found a benefit in the subset of patients with elevated N-terminal proB-type natriuretic peptide (5%) or an enlarged left atrium (9%).





1.7% vs 6.5% per year

N Engl J Med. 2018;378(23):2191-2201
N Engl J Med. 2001;345(20):1444-1451.
Stroke. 2013;44(3):714-719.
JAMA Neurol. doi:10.1001/ jamaneurol.2019.0617

Occult Embolic Mechanisms Likely to Respond to Anticoagulant Therapy

Patent foramen ovale (PFO)

Patient with cryptogenic stroke associated with PFO under the age of 60 years:

- Strong recommendation in favour of *PFO closure plus antiplatelet therapy* compared with antiplatelet alone;
- Weak recommendation in favour of PFO closure plus antiplatelet therapy compared with anticoagulants
- Weak recommendation in favour of anticoagulants compared with antiplatelet therapy

Mir H, *et al*. *BMJ Open,* 2018;8:e023761

Other possible causes of ESUS

- Cancer: *atherosclerosis* to be the most common cause of ischemic stroke in patients with malignancy.

Neurology.2014;83(1):26-33.
Stroke. 1994;25:1215–1218.
Archives of Medical Research 48 (2017) 12e26

- Cervical, intracranial and aortic atherosclerosis: Antiplatelet agents remain the mainstay of treatment in patients with CS and evidence of thick aortic arch plaque, intracranial or extracranial atherosclerosis.

JACC Cardiovasc Imaging. 2012;5(4):397-405.
Engl J Med. 2005;352(13):1305-1316.
Stroke. 2014;45 (5):1248-1257.
Stroke. 2014;45:2160–2236.
Lancet. 1991;337:1235–1243.

- Nonatherosclerotic Vasculopathies: cervical dissection, infectious nor inflammatory vasculopathies.

Lancet Neurol. 2015;14(4):361-367
Neurohospitalist. 2014;4(2):86-89

Conclusions

- ESUS accounts for 9 % to 25 % of ischemic stroke and is associated with a high recurrence rate.
- ESUS patients constitute a *heterogeneous* group of patients leading to therapeutic implications based on the potential mechanism of stroke.
- It is essential to determine the possible *culprit* because this will improve secondary stroke prevention strategies.
- Consider *long-term cardiac monitoring* in patient at high risk of AF (elderly, renal failure, atrial enlargement, high levels Pro-BNP).
- To date, antiplatelets represent the standard of care for patients with ESUS.

Grazie per l'attenzione

AHA/ASA Guideline

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

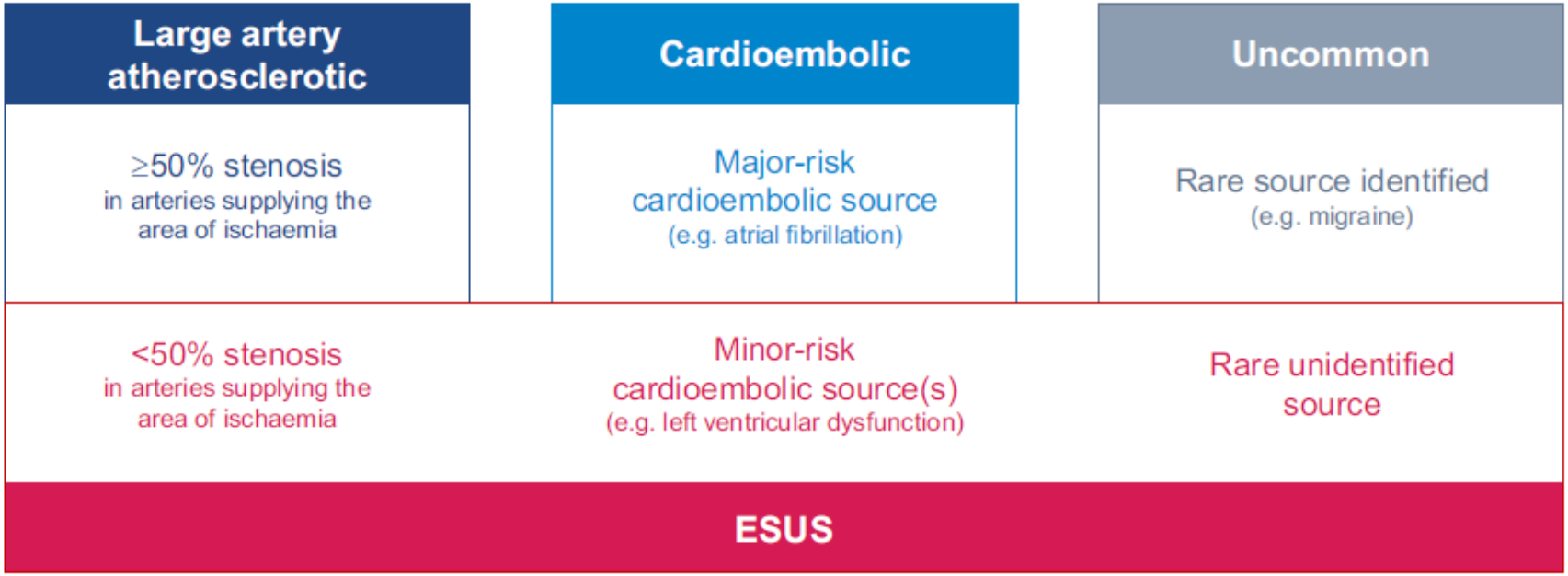
The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

- For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events *(Class I; Level of Evidence A)*.

- Vitamin K antagonist (VKA) therapy *(Class I; Level of Evidence A)*, apixaban *(Class I; Level of Evidence A)*, and dabigatran *(Class I; Level of Evidence B)* are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF *(Class IIa; Level of Evidence B)*. (New recommendation).

ESUS is an embolic stroke for which no probable cause is identified



Adapted from Hart et al. Lancet Neurol 2014

Occult Embolic Mechanisms Likely to Respond to Anticoagulant Therapy

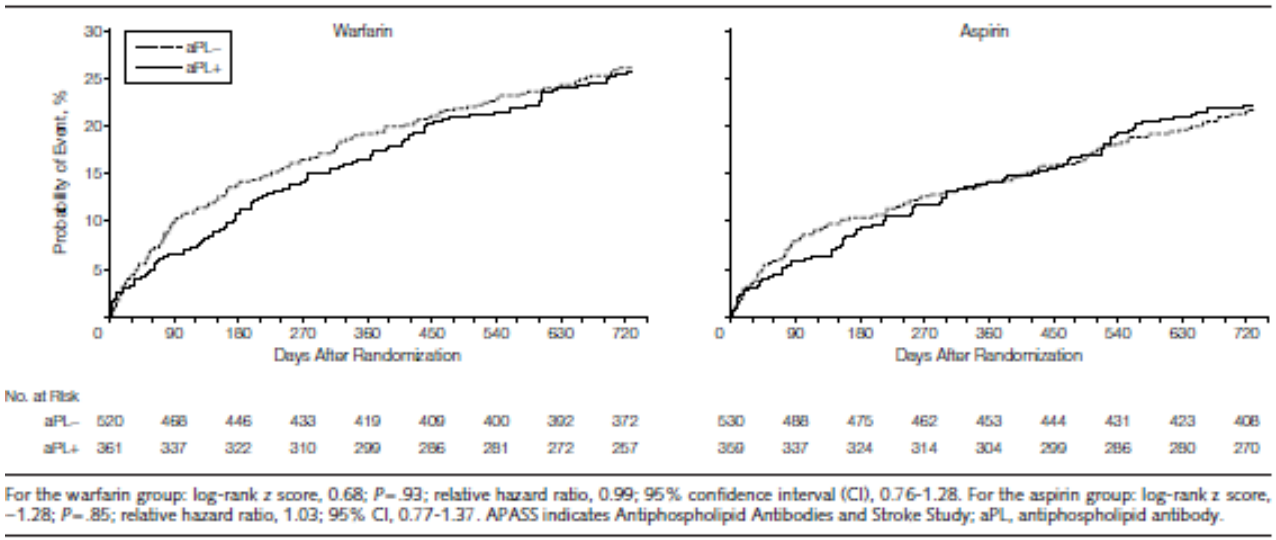
Patent foramen ovale (PFO)

- RESPECT trial do not support a protective effect of anticoagulation in patient with ESUS and PFO.
- PFO closure is superior to antithrombotic therapy to prevent stroke recurrence after cryptogenic stroke.
- PFO closure was associated with an increased risk of atrial fibrillation.

JAAC Journal. 2019; 73(3):278-87
J Am Heart Assoc. 2018;7: e008356
Lancet Neurol. 2018;17(12):1053-1060

Occult Embolic Mechanisms Likely to Respond to Anticoagulant Therapy

Antiphospholipid Antibodies



For the warfarin group: log-rank *z* score, 0.68; *P*=.93; relative hazard ratio, 0.99; 95% confidence interval (CI), 0.76-1.28. For the aspirin group: log-rank *z* score, −1.28; *P*=.85; relative hazard ratio, 1.03; 95% CI, 0.77-1.37. APASS indicates Antiphospholipid Antibodies and Stroke Study; aPL, antiphospholipid antibody.

APASS

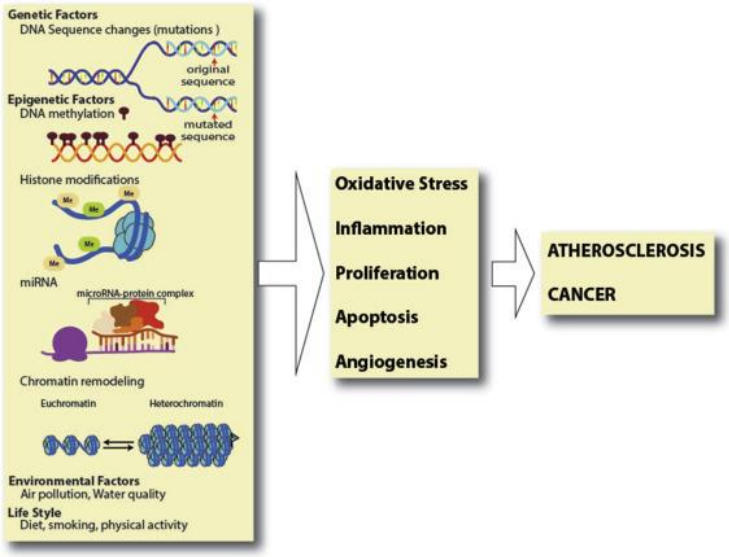
- Serum antiphospholipid antibodies are present in nearly 17% to 42% of patients with ischemic stroke.
- In patients with ischemic stroke and presence of antiphospholipid antibodies, clinical trials showed that anticoagulation therapy is as efficacious as antiplatelet therapy for secondary stroke.

Lancet Neurol. 2009;8:998–1005
JAMA. 2004;291:576–584.
Stroke. 2014;45:2160–2236

Occult Embolic Mechanisms Likely to Respond to Anticoagulant Therapy

Cancer

- About 50% of cancer-associated strokes are considered ESUS.
- *Hypercoagulability* is the most important stroke risk factor in cancer.
- The risks of anticoagulation in these patients is likely higher than in the general population with ESUS.
- Recent study found *atherosclerosis* to be the most common cause of ischemic stroke in patients with malignancy.

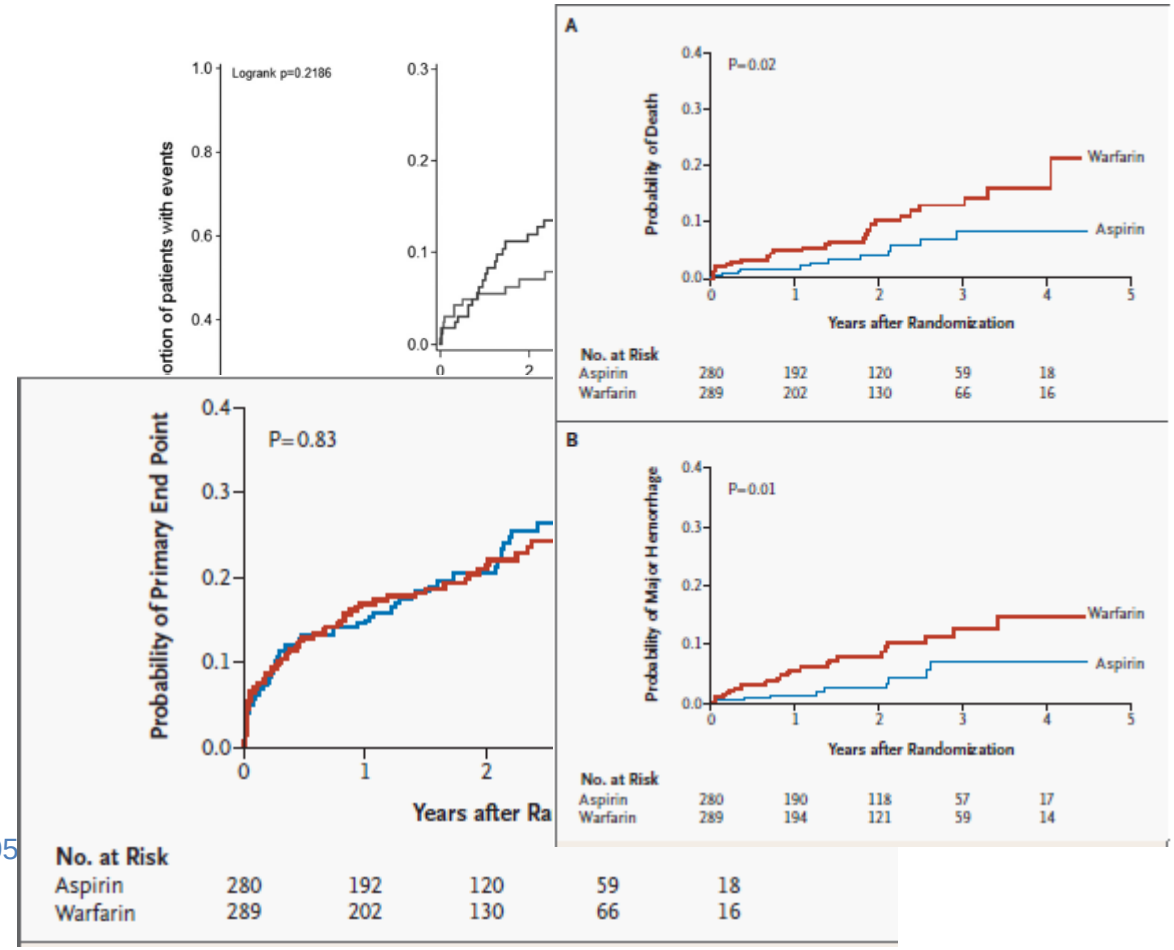


Neurology.2014;83(1):26-33.
Stroke. 1994;25:1215–1218.
Archives of Medical Research 48 (2017) 12e26

Occult Embolic Mechanisms Unlikely to Respond to Anticoagulant Therapy

Cervical, intracranial and aortic atherosclerosis

- A substantial proportion of ESUS cases may be the result of large-artery atherosclerotic disease.
- Antiplatelet agents remain the mainstay of treatment in patients with cryptogenic stroke and evidence of thick aortic arch plaque, intracranial or extracranial atherosclerosis.



JACC Cardiovasc Imaging. 2012;5(4):397-405
Engl J Med. 2005;352(13):1305-1316.
Stroke. 2014;45 (5):1248-1257.
Stroke. 2014;45:2160–2236.
Lancet. 1991;337:1235–1243.

Occult Embolic Mechanisms Unlikely to Respond to Anticoagulant Therapy

Nonatherosclerotic Vasculopathies

- Cervical Dissection: CADISS

	Intention-to-treat population				Per-protocol population			
	Antiplatelet group (n=126)	Anticoagulant group (n=124)	OR (95% CI)*	p value	Antiplatelet group (n=101)	Anticoagulant group (n=96)	OR (95% CI)*	p value
Ipsilateral stroke or death	3 (2%)	1 (1%)	0·335 (0·006–4·233)	0·63	3 (3%)	1 (1%)	0·346 (0·006–4·390)	0·66
Secondary endpoints								
Any stroke or death	3 (2%)	1 (1%)	0·335 (0·006–4·233)	0·63	3 (3%)	1 (1%)	0·346 (0·006–4·390)	0·66
Any stroke, death, or major bleed	3 (3%)	2 (2%)	0·673 (0·055–5·983)	1·00	3 (3%)	2 (2%)	0·696 (0·057–6·220)	1·00
Any stroke	3 (2%)	1 (1%)	0·335 (0·006–4·233)	0·63	3 (3%)	1 (1%)	0·346 (0·006–4·390)	0·66
Ipsilateral stroke, TIA, or death	4 (3%)	5 (4%)	1·280 (0·268–6·614)	0·98	4 (4%)	4 (4%)	1·054 (0·190–5·835)	1·00
Any stroke or TIA	5 (4%)	5 (4%)	1·017 (0·228–4·540)	1·00	5 (5%)	4 (4%)	0·836 (0·161–4·015)	1·00
Major bleeding	0 (0%)	1 (1%)	..	..	0 (0%)	1 (1%)	..	..
Death	0 (0%)	0 (0%)	..	..	0 (0%)	0 (0%)	..	..

Data for presence of residual stenosis (>50%) at 3 months have not yet been analysed. OR=odds ratio. TIA=transient ischaemic attack. *Tested with exact logistic regression.

Table 2: **Outcomes within 3 months**

- Neither infectious nor inflammatory vasculopathies would be expected to benefit from anticoagulant therapy.

Lancet Neurol. 2015;14(4):361-367
Neurohospitalist. 2014;4(2):86-89