ESC Heart & Brain Workshop

Secondary prevention after ESUS

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Supported by Bayer, Bristol-Myers Squibb and Pfizer Alliance, Boehringer Ingelheim, Daiichi Sankyo Europe GmbH and Medtronic in the form of educational grants. The scientific programme has not been influenced in any way by its sponsors.

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BAYER

Boehringer Ingelheim

Daiichi-Sankyo

Bristol-Myers Squibb

Pfizer

Medtronic
Further, Together

Declaration of Interest

Nothing to declare

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What is ESUS?

~85% of all strokes are ischaemic[1]

~25% of these have no known cause[2]

Previously termed 'cryptogenic':
~300,000 incident cases/year in North America and Europe

A subgroup of these are due to thromboembolism

New category proposed:

'Embolic stroke of undetermined source' (ESUS)[2]

1. Andersen K et al. Stroke 2009;40:2068–72
2. Hart RG et al. Lancet Neurol 2014;13:429–

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Hart RG et al. Lancet Neurol 2014;13:429–38

Advances in imaging and improved understanding of stroke pathophysiology

Reassessment of 'cryptogenic' stroke

Non-lacunar brain infarct without large artery stenosis or cardioembolic sources

International Working Group of experts proposes new definition

Step-wise approach to diagnosis

More clinically useful, positively defined entity than cryptogenic stroke

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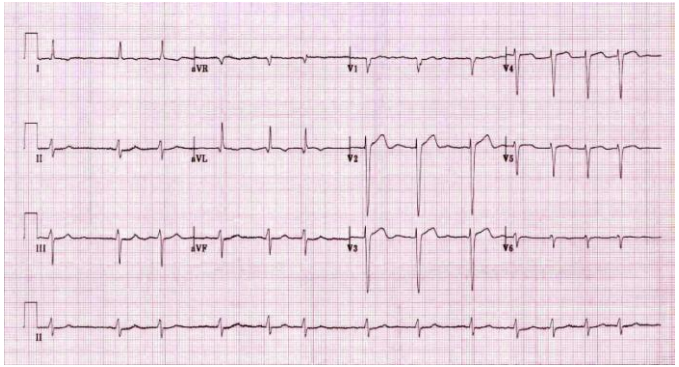
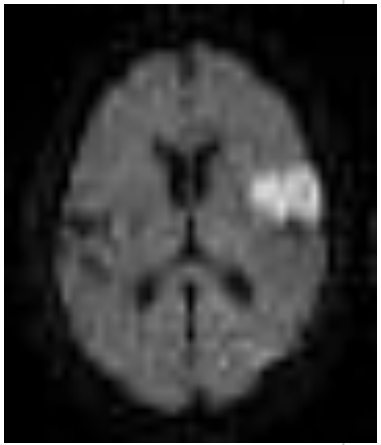
76 years-old male, with vascular risk factors, who presents with fluctuating right-hand paresia and mild aphasia…





Embolic ? **YES** ***Cryptogenic?*** **YES** ***ESUS ?*** **NO**

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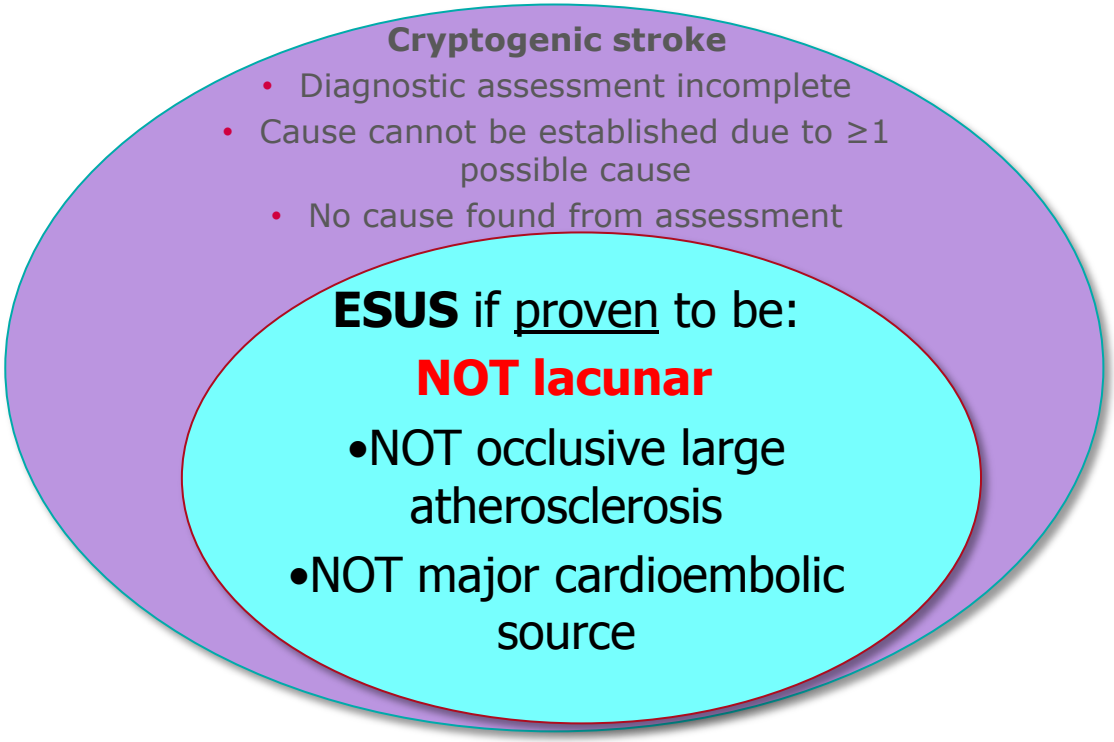
Definitions of cryptogenic stroke vs ESUS



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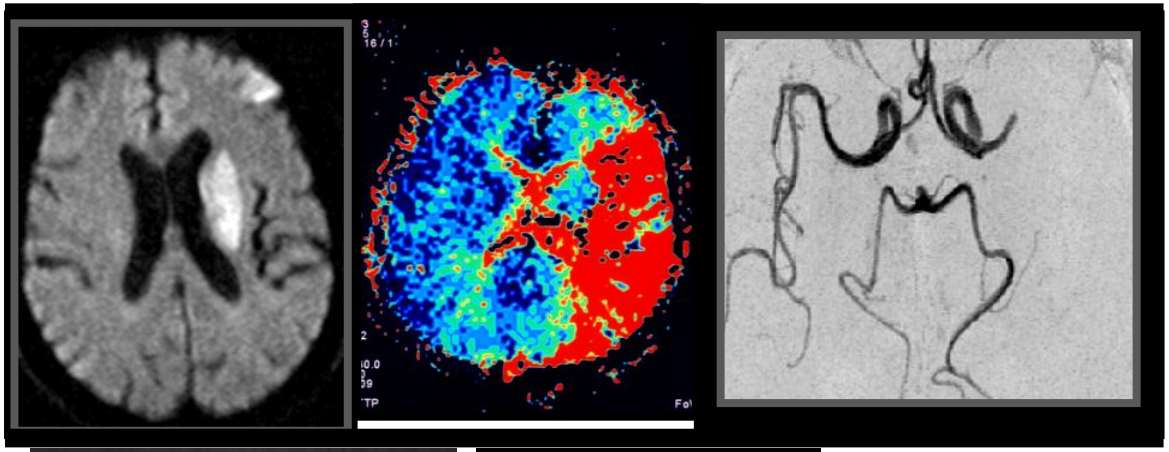
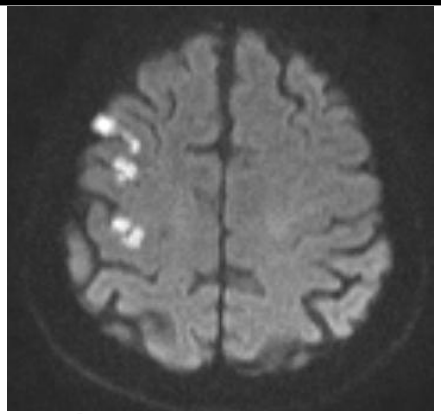
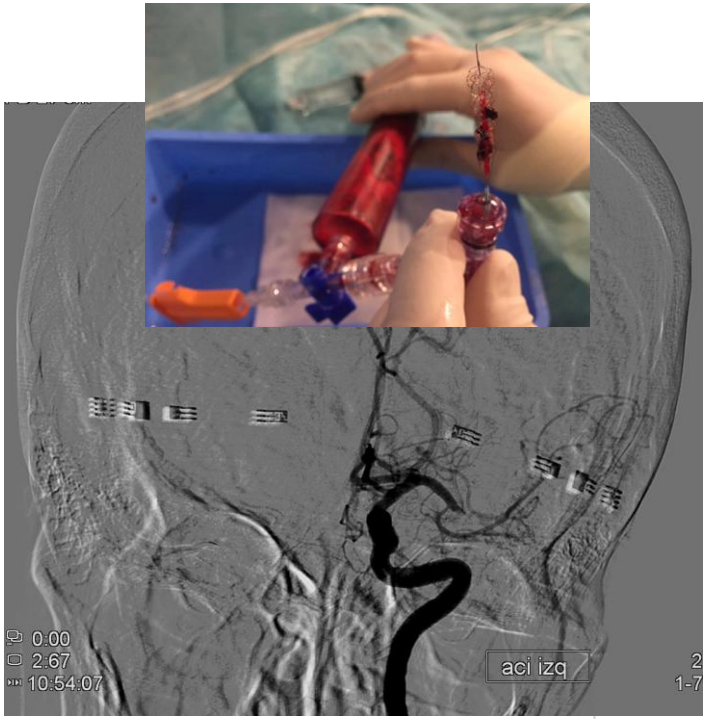




NOT lacunar*



* Subcortical infarct ≤1.5mm on CT or ≤2mm on MRI

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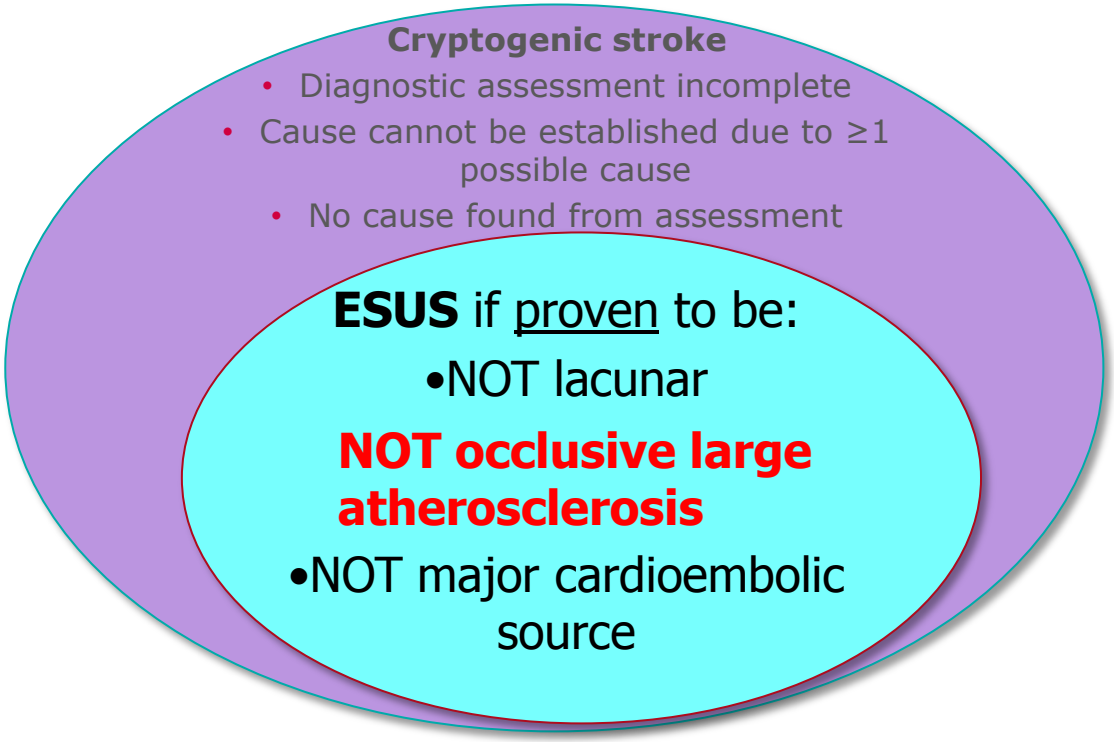
Definitions of cryptogenic stroke vs ESUS



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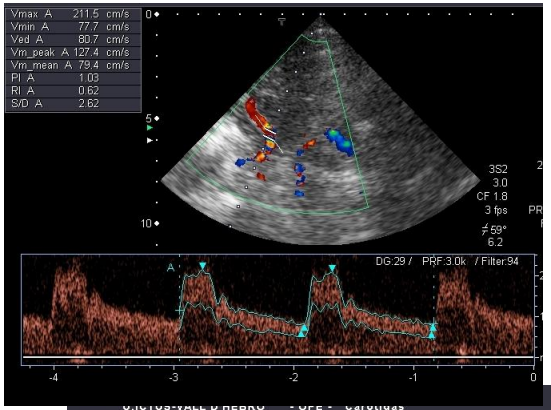

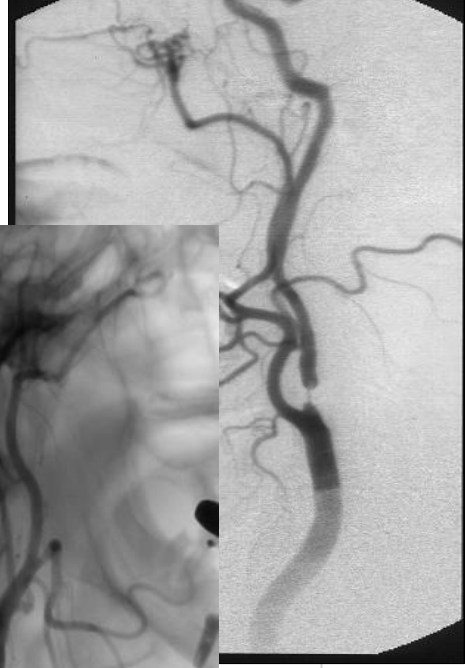

NOT occlusive large atherosclerosis

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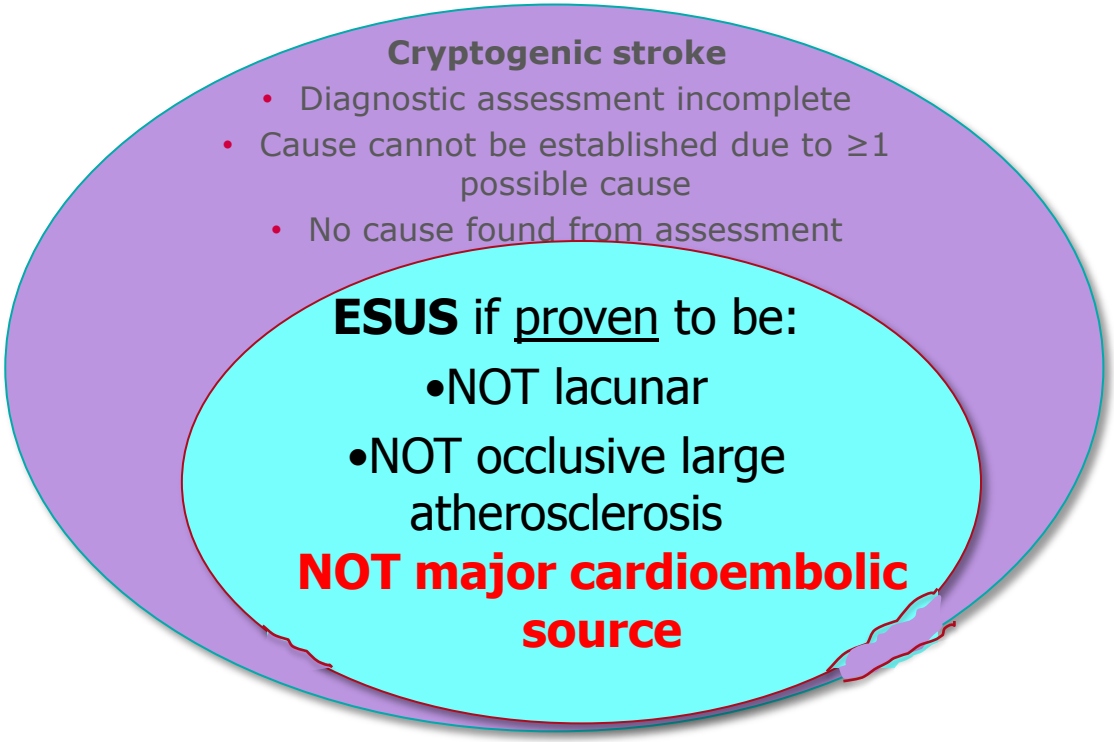
Definitions of cryptogenic stroke vs ESUS



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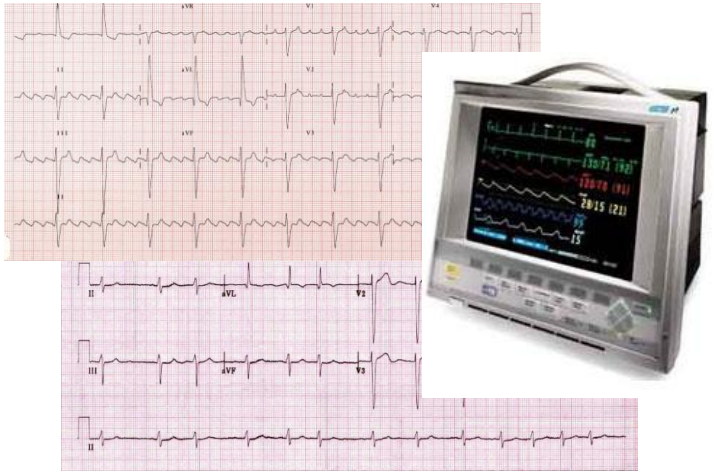
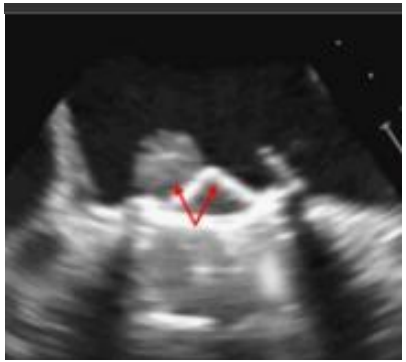
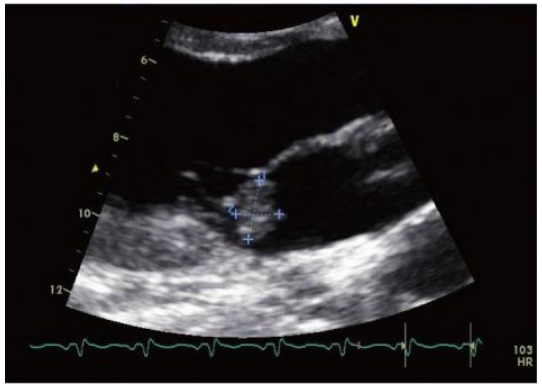
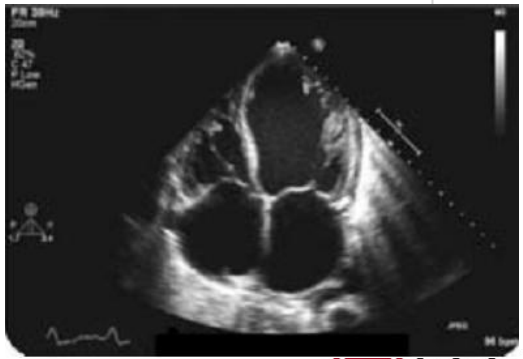






NOT major cardioembolic source



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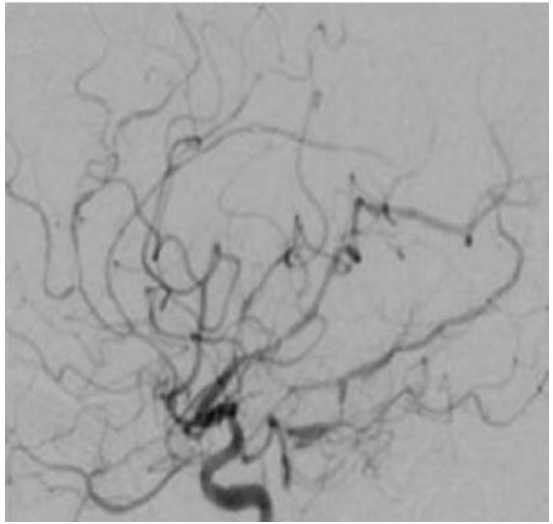
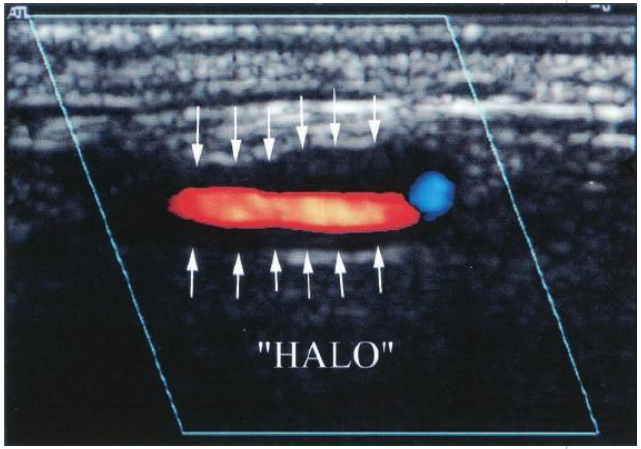
Infrequent stroke etiologies





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Brain CT/MRI showing only embolic infarct (more than 1.5 cm)

MRA/ CTA of extra and intracranial vessels supplying the area of infarct with less than 50% atherosclerosis

Negative Trans Thoracic Echocardiography (No intracardiac thrombus, prosthetic valve, , mitral stenosis, atrial myxoma or other cardiac tumors, recent (<4 weeks) myocardial infarction, LVEF < 30%, no valvular vegetations, no infective Endocarditis)

No other specific cause of stroke like arteritis, dissection, migraine/vasospasm, drug abuse identified

Cardiac monitoring for ≥24 h with automated rhythm detection and no history of Permanent or paroxysmal atrial fibrillation,

- Long term Cardiac monitoring (minimum 30 days)
  - Goal: Underlying surveillance of arrhythmias, in particular atrial fibrillation
- Consider Trans esophageal echocardiography
  - Goal: Aortic arch atheroma, atrial valvulopathy, aortic valvulopathy, atrial/ventricular septal pathology
- Consider coagulopathy work-up
  - D-Dimer, DVT screen, MRV of pelvic veins
  - Lab Evaluation of hypercoagulable states (younger patients)
  - Consideration of malignancy (older patients)
- Consider Metabolic or Genetic testing
  - e.g. Fabry disease, Mitochondrial disease work-up, CADASIL, CARASIL, HERNS, Migrainous infarction, etc.
- Consider Spinal Tap e.g. infection, vasculitis
- Consider further Imaging
  - CT Chest, Abdomen, Pelvis or PET scan (if malignancy suspected)
  - Cerebral Angiography (e.g. vasculitis, vasculopathy)

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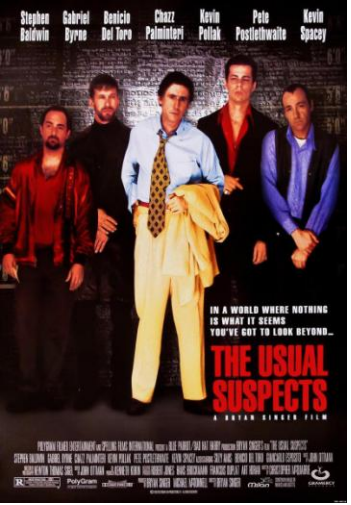

Covert AF

Non-AF auricular arrhythmias
Auricular dysfunction

Ventricular dysfunction CHF

Paradoxal embolism

Non-stenosant atherosclerosis

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Recurrent ischemic stroke

Study or subgroup	Anticoagulation n/N	Antiplatelet n/N
1 INR 2.0 - 3.6		
ESPRIT 2007	41/536	53/532
Garde 1983	7/114	6/127
Olsson 1980	1/68	3/67
Subtotal (95% CI)	**718**	**726**
Total events: 49 (Anticoagulation), 62 (Antiplatelet)		
Heterogeneity: Chi^2 = 1.46, df = 2 (P = 0.48); I^2 =0.0%		
Test for overall effect: Z = 1.25 (P = 0.21)		
2 INR 3.0 - 4.5		
SPIRIT 1997	14/651	14/665
Subtotal (95% CI)	**651**	**665**
Total events: 14 (Anticoagulation), 14 (Antiplatelet)		
Heterogeneity: not applicable		
Test for overall effect: Z = 0.06 (P = 0.95)		
Total (95% CI)	**1369**	**1391**
Total ev		
Heterog		
Test for		
Test for subgroup differences: Chi^2 = 0.36, df = 1 (P = 0.55), I^2 =0.0%		

0.1

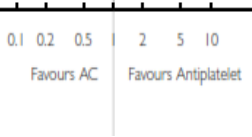
8 trials

Vitamin K antagonists versus antiplatelet th
transient ischaemic attack or minor ischaem
presumed arterial origin (Review)

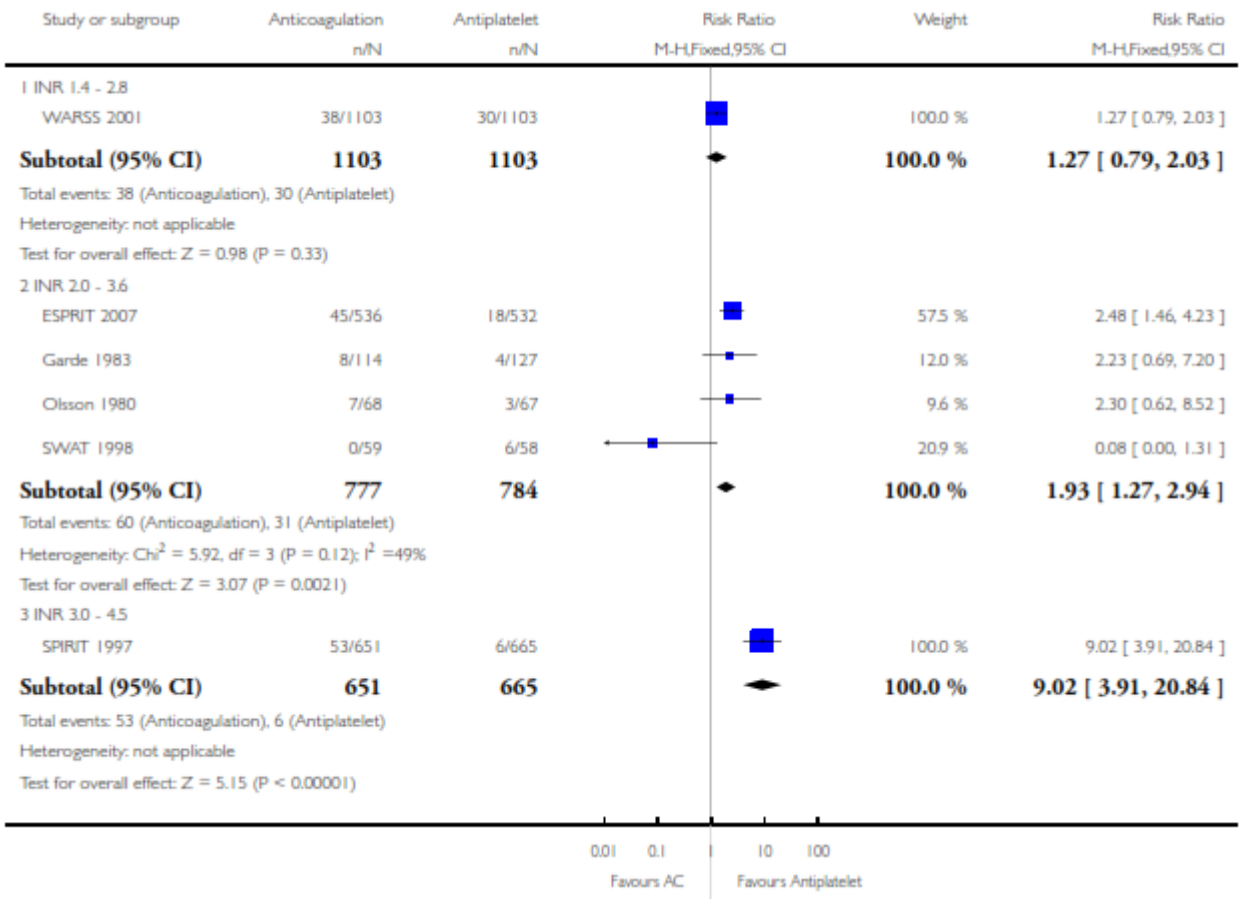
Vascular death, non fatal-stroke, non-fatal myocardial infarction or major bleeding complication

De Schryver ELLM, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ

Study or subgroup	Anticoagulation n/N	Antiplatelet n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 INR 2.0 - 3.6					
ESPRIT 2007	99/536	98/532		100.0 %	1.00 [0.78, 1.29]
Subtotal (95% CI)	**536**	**532**		**100.0 %**	**1.00 [0.78, 1.29]**
Total events: 99 (Anticoagulation), 98 (Antiplatelet)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
2 INR 3.0 - 4.5					
SPIRIT 1997	81/651	36/665		100.0 %	2.30 [1.58, 3.35]
Subtotal (95% CI)	**651**	**665**		**100.0 %**	**2.30 [1.58, 3.35]**
Total events: 81 (Anticoagulation), 36 (Antiplatelet)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.32 (P = 0.000015)					



Major bleeding complication



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Risk Stratification for Recurrence and Mortality in Embolic Stroke of Undetermined Source

Ntaios G et al. Stroke 2016;47:2278–85

Results—One hundred fifty-nine 5.6% r year) ischemic stroke/TIA recurrences and 148 5.2% r year) deaths occurred in 1095 patients (median age, 68 years) followed-up for a median of 31 months. Compared with CHADS, score 0,

	$CHADS_2$ (Maximum score, 6)	CHA_2DS_2-VASc (Maximum score, 9)
Risk Factor	**Points**	**Points**
Congestive heart failure	1	1
Hypertension	1	1
Diabetes	1	1
Vascular disease	N/A	1
Age 65-74	N/A	1
Age ≥75	1	2
Female sex	N/A	1
Previous stroke/TIA	2	2

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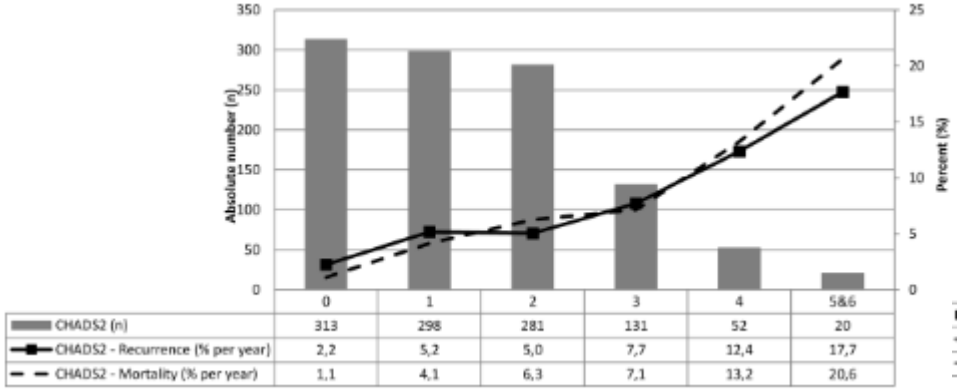
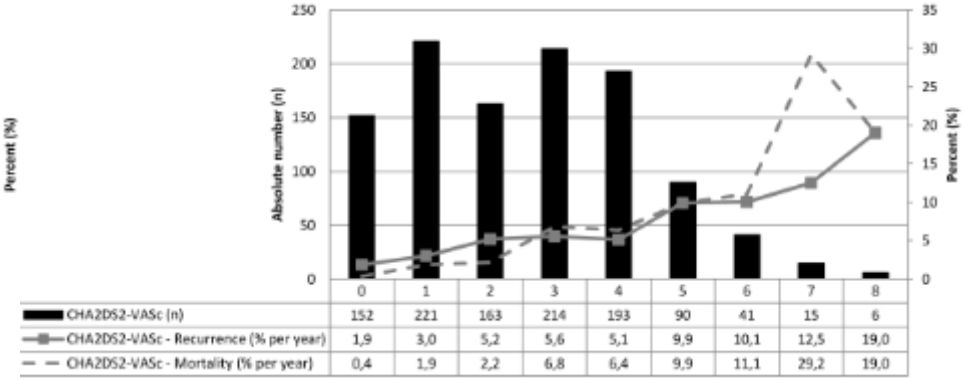
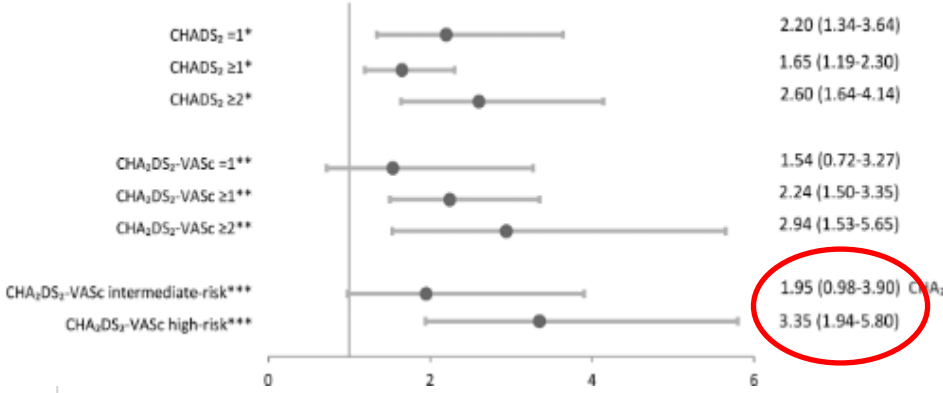


	0	1	2	3	4	5&6
CHADS2 (n)	313	298	281	131	52	20
CHADS2 - Recurrence (% per year)	2,2	5,2	5,0	7,7	12,4	17,7
CHADS2 - Mortality (% per year)	1,1	4,1	6,3	7,1	13,2	20,6

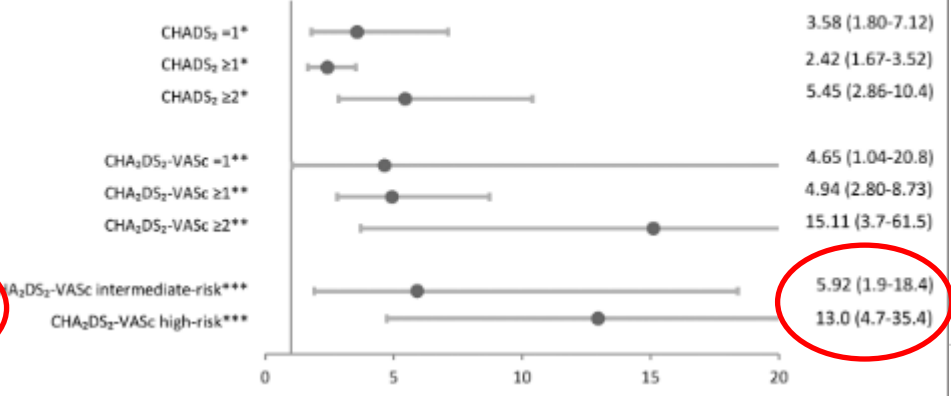


	0	1	2	3	4	5	6	7	8
CHA2DS2-VASc (n)	152	221	163	214	193	90	41	15	6
CHA2DS2-VASc - Recurrence (% per year)	1,9	3,0	5,2	5,6	5,1	9,9	10,1	12,5	19,0
CHA2DS2-VASc - Mortality (% per year)	0,4	1,9	2,2	6,8	6,4	9,9	11,1	29,2	19,0

Recurrence

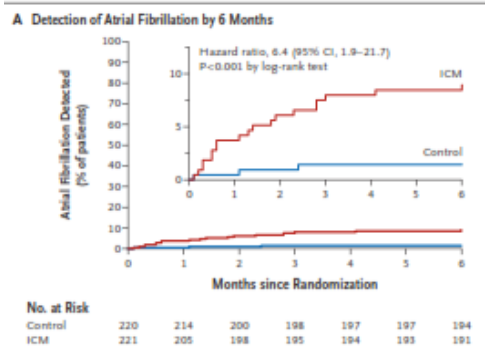


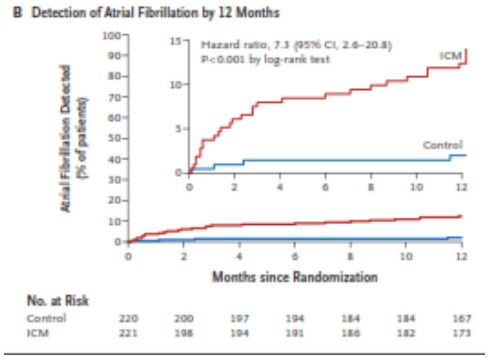
Mortality

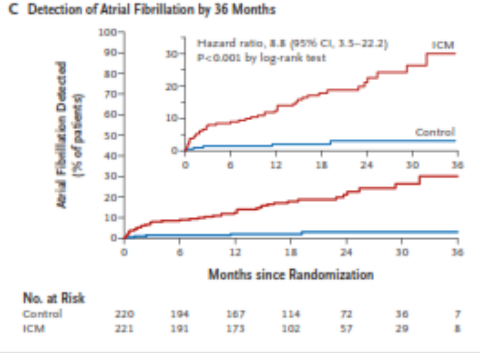


Covert AF and stroke risk

- 24h 3.8%
- 48% 6.4%
- 7 days 9 %
- 3 w- 6 mo 15%







Covert AF
Non-AF auricular arrhythmias
Auricular dysfunction

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treat then monitoring
OR
monitoring then treat

- **High clinical suspicion of cardioembolism**
- **Low risk of bleeding**
- **High recurrent risk (CHADS-VASC)**
- **High probalility of AF:**
  - Dilated atrium,
  - chicken wing apendage
  - BNP, troponin
  - Frequent extrasist

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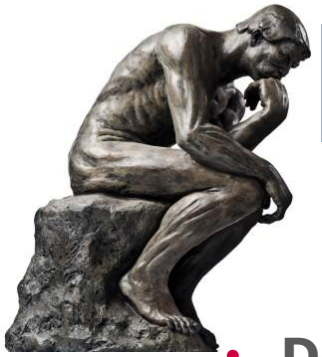

For how long?

- Depends on availability and type of long-term ECG monitoring
- 3 weeks to 3 months… to ≥ 1 year…
- If no AF detected…..switch to antiplatelet ?

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ESUS-RCT

- **NAVIGATE ESUS**
  - Rivaroxaban vs AAS
- **RE-SPECT ESUS**
  - Dabigatran vs AAS
- **ITTACUS**
  - Apixaban vs AAS

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NAVIGATE-ESUS: SECONDARY PREVENTION OF STROKE IN PATIENTS WITH A RECENT ESUS

ClinicalTrials.gov Identifier: NCT02313909

Recruitment Status : Terminated (Study halted early due to no efficacy improvement over aspirin at an interim analysis and very little chance of showing overall benefit if study were completed)

First Posted : December 10, 2014

Last Update Posted : October 23, 2017

Phase 3: Multicenter, randomized, double-blind study of secondary prevention of stroke & prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS)

Supported by BAYER

Principal Investigator at BMC: Viken Babikian, MD

Study duration: 18+ months

Study drugs: Rivaroxaban 15mg vs aspirin 100mg QD

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Thanks for you attention…