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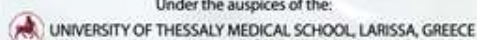
DEPARTMENT OF MEDICINE
& RESEARCH LABORATORY OF INTERNAL MEDICINE
UNIVERSITY OF THESSALY MEDICAL SCHOOL,
LARISSA, GREECE
Director: Professor G.N. Dalekos

In cooperation with:



† HSO HELLENIC STROKE ORGANIZATION

Under the auspices of the:



8th Larissa International Congress of Internal Medicine

March **17-19**, 2016
Larissa Imperial Hotel
LARISSA, GREECE

<http://www.internalmedicine-uth.gr>

The Congress has been accredited
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Direct oral anticoagulants for Embolic Strokes of Undetermined Source?

George Ntaios

University of Thessaly, Larissa/Greece

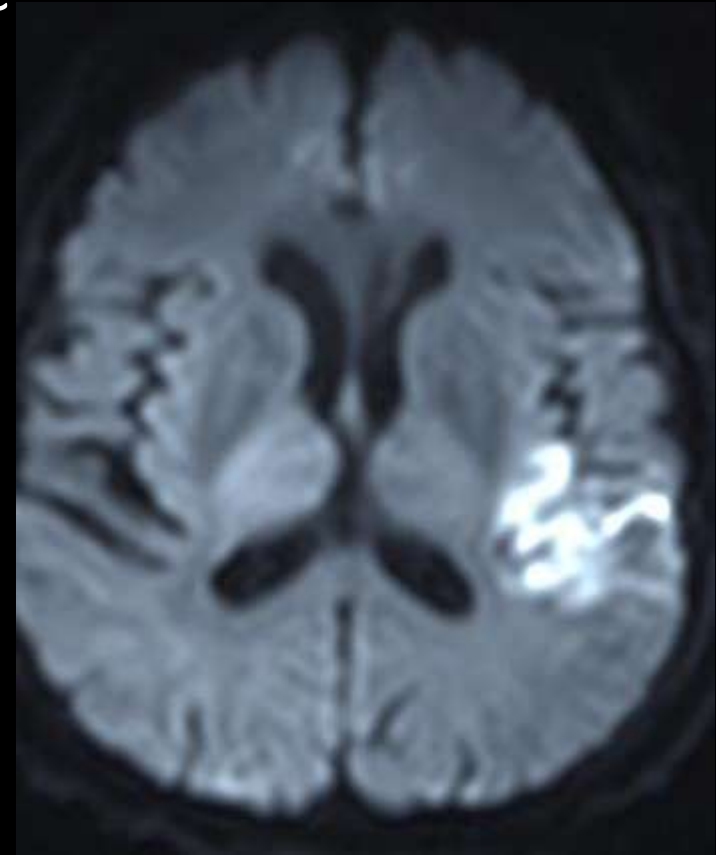


Disclosures

- Scholarships: European Stroke Organization; Hellenic Society of Atherosclerosis.
- Honoraria: Medtronic; Quintiles; Boehringer-Ingelheim.
- Speaker fees: Sanofi; Boehringer-Ingelheim; Galenica; Elpen; Bayer
- Support to attend conferences: Bayer; Sanofi-Aventis; Pfizer; Lundbeck; Boehringer-Ingelheim; Galenica; Elpen; BMS
- Participation in trials:
 - NAVIGATE-ESUS / National Coordinator (Greece)
 - PRECIOUS / National Coordinator (Greece).
 - ENOS / National Coordinator (Greece).
 - FOURIER / Principal investigator (Larissa).
 - EBBINGHAUS / Principal Investigator (Larissa).
 - BIOSIGNAL / Principal Investigator (Larissa).
 - PREVISE / Principal investigator (Larissa).
 - GLORIA-AF / Sub-investigator (Larissa).

Our patient

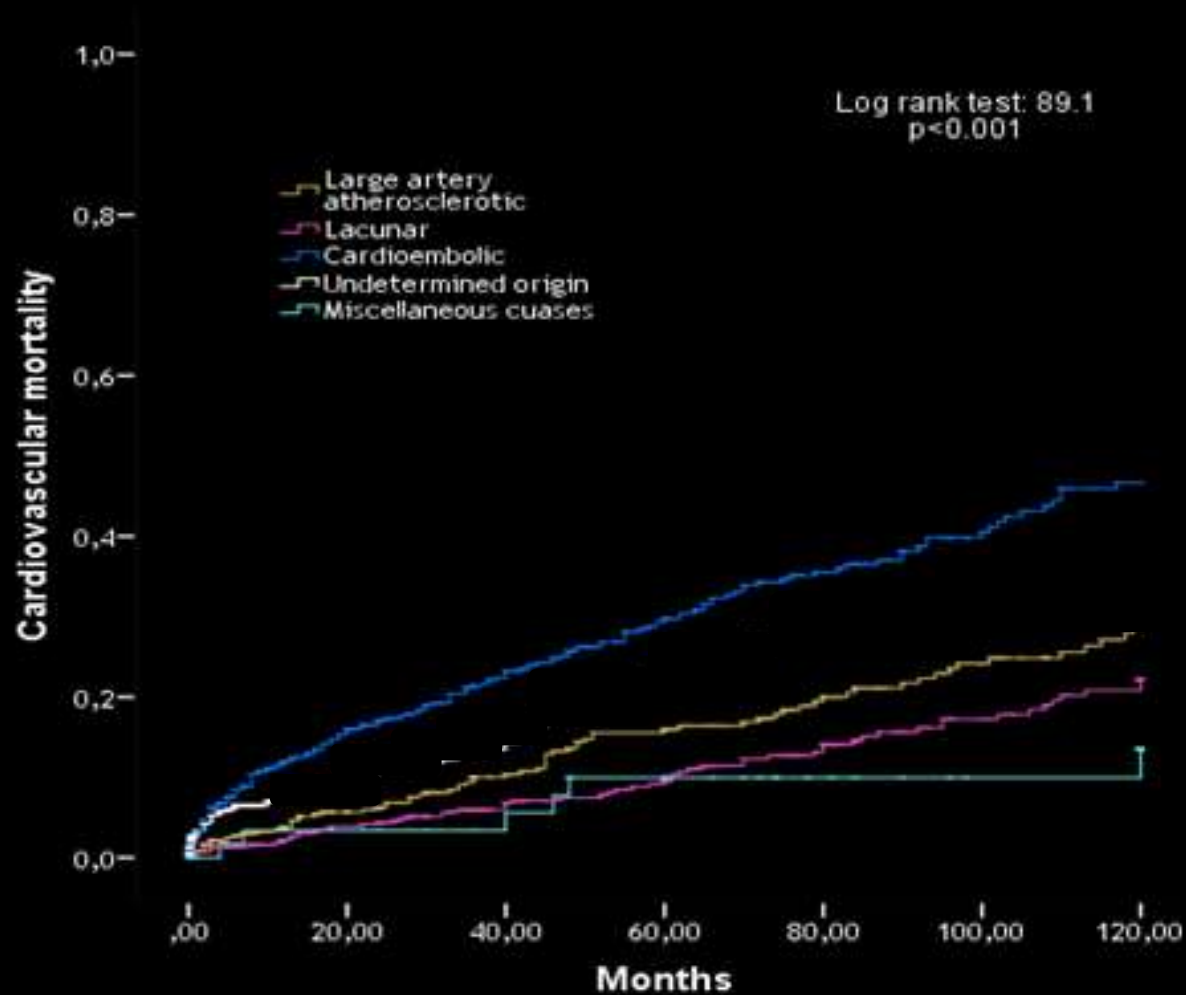
- ✓ 81yrs
- ✓ Fully dependent at 3months
- ✓ Hypertensive, Non-smoker, non-diabetic
- ✓ LDL: 104mg/dl
- ✓ LA diameter: 42mm
- ✓ Triplex: 30% LICA stenosis
- ✓ 24hrs ECG: -
- ✓ Echocardiograph: -



Cryptogenic stroke: not rare

	Population	N	Mean age (years)	Criteria for cryptogenic stroke	Frequency
Besancon Stroke Registry (2000) ⁹¹	Prospective registry	1776	71	Study specific	18%†
Athens Stroke Registry (2000) ⁹²	Prospective registry of first-ever strokes	885	70	Not specified	21%
German Stroke Data Bank (2001) ⁹³	Prospective registry	5017	66	Modified TOAST criteria	23%
WARSS (2001) ⁹⁴	Randomised trial	2206	63	TOAST criteria	26%
Erlangen Study (2001) ⁹⁵	Population-based	583	73	TOAST criteria	32%
Ankara (2002) ⁹⁶	Prospective registry	264	66	TOAST criteria	33%
Suwon (2003) ⁹⁷	Prospective registry	204	62	TOAST criteria	18%
TULIPS (Japan) (2004) ⁹⁸	Prospective registry	831	72	NINDS SDB	23%
Perugia (2006) ⁹⁹	Prospective stroke unit	358	NR	TOAST criteria	17%
PRoFESS (2008) ¹⁰⁰	Randomised trial	20 332	66	TOAST criteria	16%‡
Bern (2008) ¹⁰¹	Prospective registry	1288	NR	TOAST criteria	39%
Buenos Aires (2010) ⁵⁰	Retrospective case series of stroke and TIA	155	67	TOAST criteria	27%
ASTRAL (2010) ¹⁰²	Prospective inpatient registry	1633	73	Modified TOAST criteria	12%§
North Dublin (2010) ¹⁰³	Population-based registry	381	NR	Causative Classification System ¹⁰⁴	26%
VITATOPS (2010) ¹⁰⁵	Randomised trial	8164	63	Study specific ¹⁰⁶	14%
PERFORM (2011) ¹⁰⁷	Randomised trial	19 100	67	Study specific ¹⁰⁸	22%
Mannheim Stroke Center (2012) ¹⁰⁹	Prospective case series	103	69	TOAST criteria	30%
Hebi, China (2012) ¹¹⁰	Retrospective case series	425	65	TOAST criteria	16%
South Korea (2012) ¹¹¹	Prospective hospital-based registry	3278	64	TOAST criteria	21%
Miami/Mexico City (2012) ¹¹²	Prospective registry of Hispanics	671	NR	Modified TOAST criteria	17%
Santiago, Chile (2012) ¹¹³	Prospective stroke unit	380	66	TOAST criteria	20%
Barcelona (2012) ⁸	Prospective stroke unit	274	NR	TOAST criteria	32%
Santiago de Compostela (2013) ¹¹⁴	Prospective case series	1050	NR	TOAST criteria	35%
Bavaria (2013) ⁵¹	Prospective stroke unit	..	NR	TOAST criteria	17%

Cryptogenic stroke: **not innocent**



Cryptogenic stroke: **what actually do you mean?**

Cryptogenic

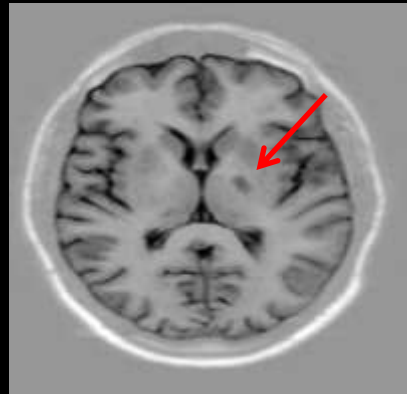
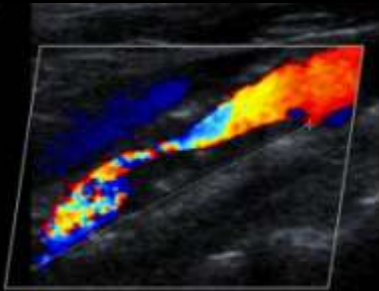
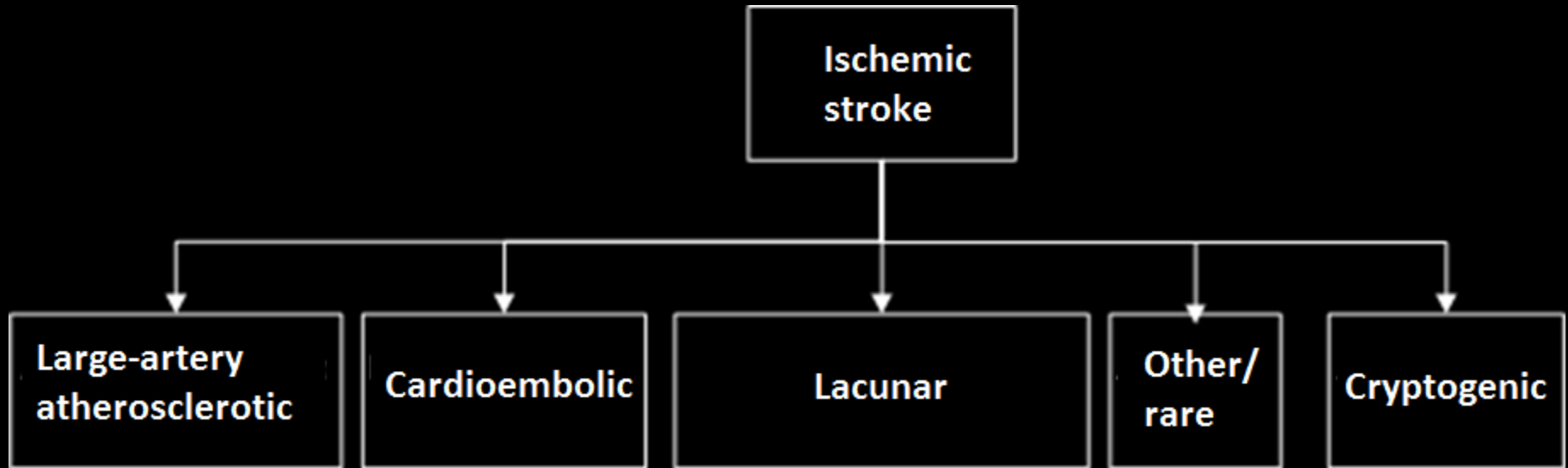
```
graph TD; A[Cryptogenic] --> B[Not investigated]; A --> C[Multiple causes]; A --> D[Really cryptogenic];
```

Not investigated

Multiple causes

Really cryptogenic

TOAST classification



ESUS: Embolic Strokes of Undetermined Source

Embolic strokes of undetermined source: the case for a new clinical construct

Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O'Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

Cryptogenic (of unknown cause) ischaemic strokes are now thought to comprise about 25% of all ischaemic strokes. Advances in imaging techniques and improved understanding of stroke pathophysiology have prompted a reassessment of cryptogenic stroke. There is persuasive evidence that most cryptogenic strokes are thromboembolic. The thrombus is thought to originate from any of several well established potential embolic sources, including minor-risk or covert cardiac sources, veins via paradoxical embolism, and non-occlusive atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries. Accordingly, we propose that embolic strokes of undetermined source are a therapeutically relevant entity, which are defined as a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources, with a clear indication for anticoagulation. Because emboli consist mainly of thrombus, anticoagulants are likely to reduce recurrent brain ischaemia more effectively than are antiplatelet drugs. Randomised trials testing direct-acting oral anticoagulants for secondary prevention of embolic strokes of undetermined source are warranted.

ESUS: diagnostic criteria

- ✓ **Stroke** detected by CT or MRI that **is not lacunar**.
- ✓ **Absence** of extracranial or intracranial atherosclerosis causing **>50% luminal stenosis** in arteries supplying the area of ischemia.
- ✓ **No major-risk cardioembolic source of embolism** (*permanent or paroxysmal AF, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent (<4 weeks) MI, LVEF<30%, valvular vegetations, or infective endocarditis*).
- ✓ **No other specific cause** of stroke identified.

ESUS: potential causes

Covert paroxysmal atrial fibrillation

Cancer-associated

- Covert non-bacterial thrombotic endocarditis
- Tumour emboli from occult cancer

Arteriogenic emboli

- Aortic arch atherosclerotic plaques
- Cerebral artery non-stenotic plaques with ulceration

Paradoxical embolism

- Patent foramen ovale
- Atrial septal defect
- Pulmonary arteriovenous fistula

Minor-risk potential cardioembolic sources*

Mitral valve

- Myxomatous valvulopathy with prolapse
- Mitral annular calcification

Aortic valve

- Aortic valve stenosis
- Calcific aortic valve

Non-atrial fibrillation atrial dysrhythmias and stasis

- Atrial asystole and sick-sinus syndrome
- Atrial high-rate episodes
- Atrial appendage stasis with reduced flow velocities or spontaneous echodensities

Atrial structural abnormalities

- Atrial septal aneurysm
- Chiari network

Left ventricle

- Moderate systolic or diastolic dysfunction (global or regional)
- Ventricular non-compaction
- Endomyocardial fibrosis

ESUS: diagnostic algorithm

- ✓ Brain CT or MRI
- ✓ 12-lead ECG
- ✓ Precordial echocardiography
- ✓ Imaging of both extra- and intracranial arteries supplying the area of brain ischemia
- ✓ Cardiac monitoring for ≥ 24 hours with automated rhythm detection

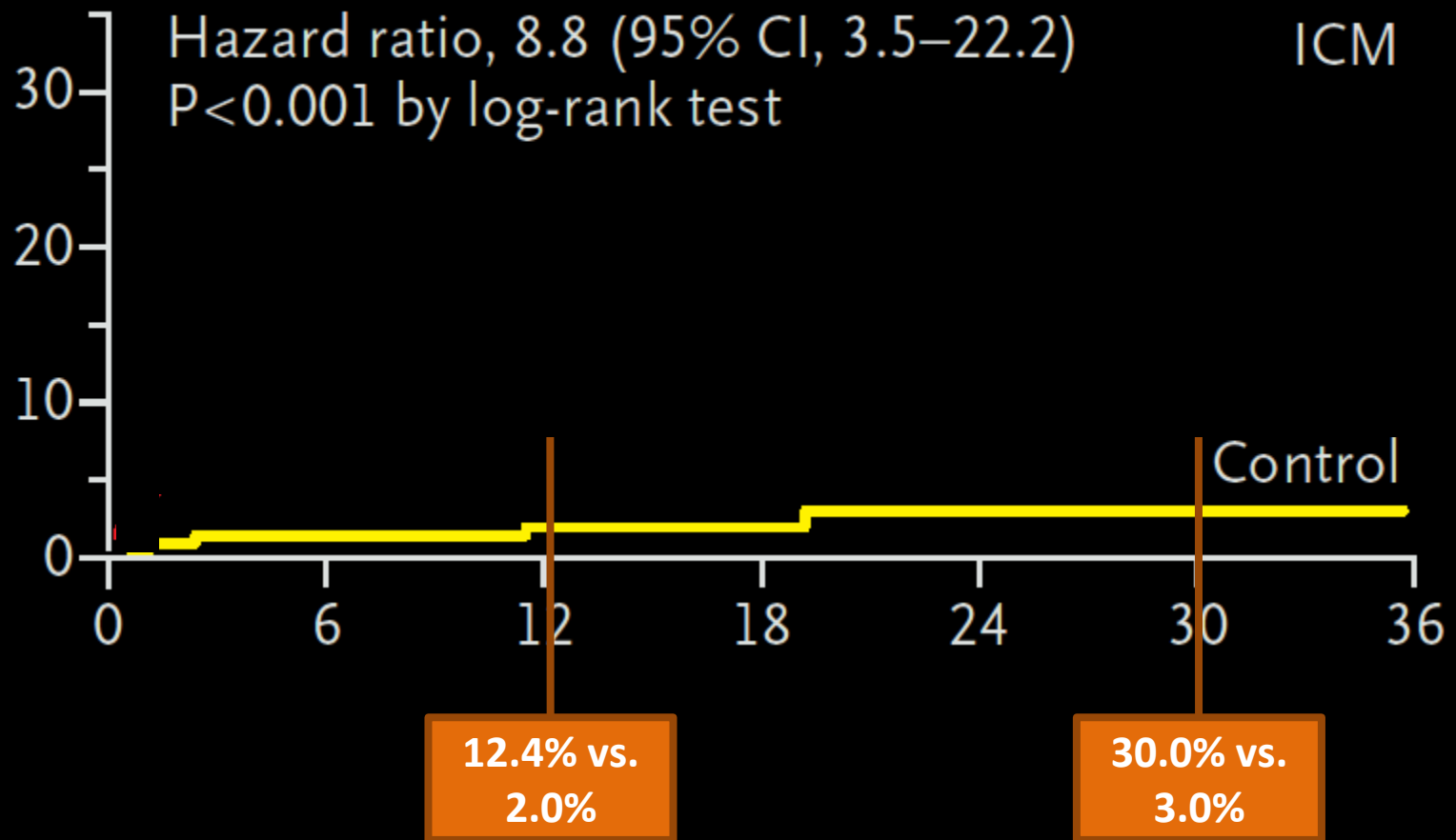
The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Cryptogenic Stroke and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, M.D., Ph.D.,
Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, M.D.,
Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D.,
Marilyn Mollman Rymer, M.D., Vincent Thijs, M.D., Ph.D.,
Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D.,
and Johannes Brachmann, M.D., for the CRYSTAL AF Investigators*

CRYSTAL-AF: the more you look, the more you find



EMBRACE: the more you look, the more you find

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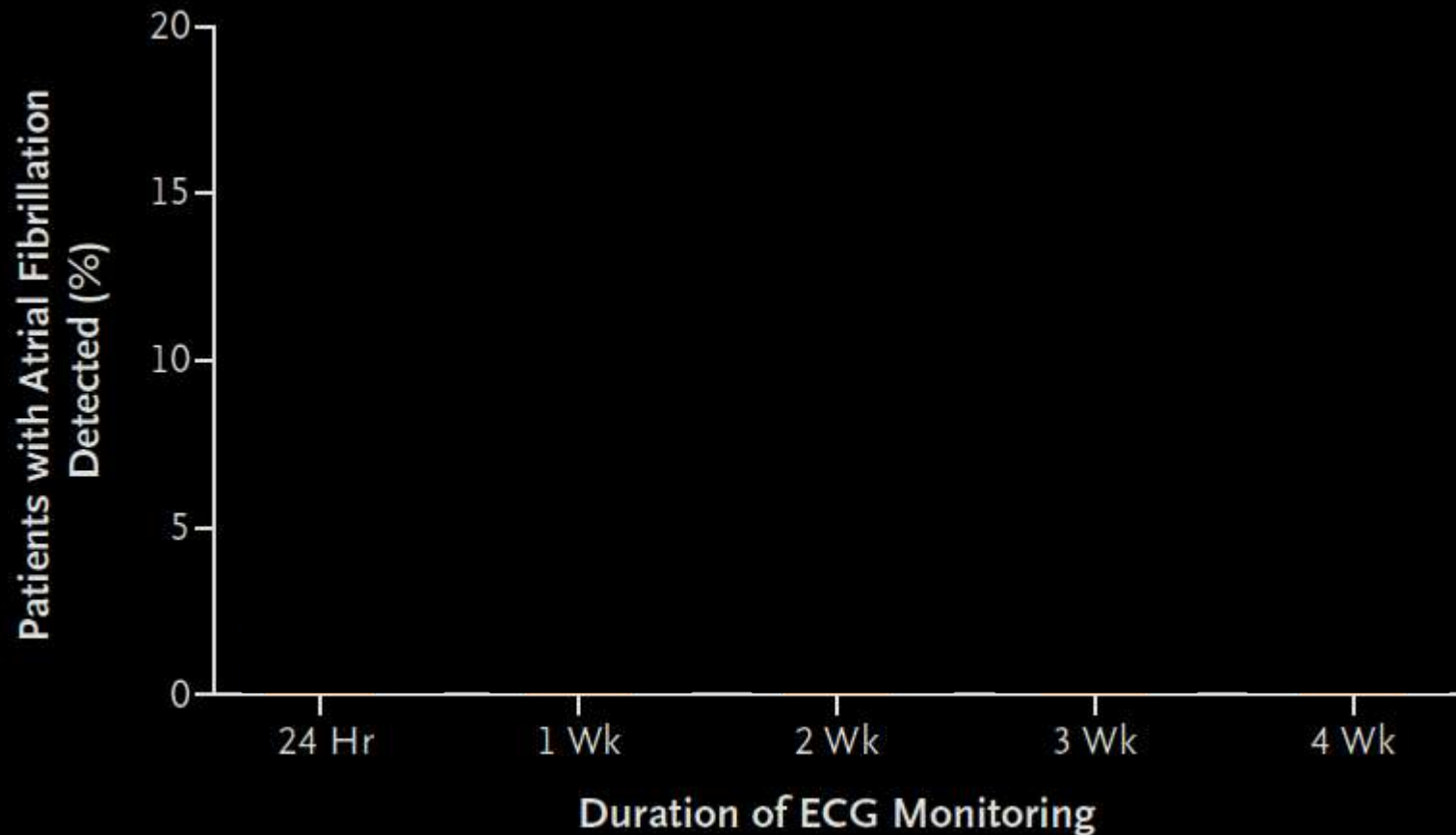
Atrial Fibrillation in Patients with Cryptogenic Stroke

David J. Gladstone, M.D., Ph.D., Melanie Spring, M.D., Paul Dorian, M.D., Val Panzov, M.D., Kevin E. Thorpe, M.Math., Judith Hall, M.Sc., Haris Vaid, B.Sc., Martin O'Donnell, M.B., Ph.D., Andreas Laupacis, M.D., Robert Côté, M.D., Mukul Sharma, M.D., John A. Blakely, M.D., Ashfaq Shuaib, M.D., Vladimir Hachinski, M.D., D.Sc., Shelagh B. Coutts, M.B., Ch.B., M.D., Demetrios J. Sahlas, M.D., Phil Teal, M.D., Samuel Yip, M.D., J. David Spence, M.D., Brian Buck, M.D., Steve Verreault, M.D., Leanne K. Casaubon, M.D., Andrew Penn, M.D., Daniel Selchen, M.D., Albert Jin, M.D., David Howse, M.D., Manu Mehdiratta, M.D., Karl Boyle, M.B., B.Ch., Richard Aviv, M.B., Ch.B., Moira K. Kapral, M.D., and Muhammad Mamdani, Pharm.D., M.P.H., for the EMBRACE Investigators and Coordinators*

EMBRACE: the more you look, the more you find

Outcome	Intervention Group (N= 286)	Control Group (N= 285)	Absolute Difference (95% CI)	P Value	No. of Patients Needed to Screen (95% CI)*
	<i>number/total number (percent)</i>	<i>number/total number (percent)</i>	<i>percentage points</i>		
Primary outcome: detection of atrial fibrillation with duration ≥ 30 sec within 90 days†	45/280 (16.1)	9/277 (3.2)	12.9 (8.0–17.6)	<0.001	8 (5.7–12.5)
Secondary outcomes‡					
Detection of atrial fibrillation with duration ≥ 30 sec	44/284 (15.5)	7/277 (2.5)	13.0 (8.4–17.6)	<0.001	8 (5.7–11.9)
Detection of atrial fibrillation with duration ≥ 2.5 min	28/284 (9.9)	7/277 (2.5)	7.4 (3.4–11.3)	<0.001	14 (8.8–29.4)
Detection of atrial fibrillation of any duration	56/284 (19.7)	13/277 (4.7)	15.0 (9.8–20.3)	<0.001	7 (4.9–10.2)

EMBRACE: the more you look, the more you find



ESUS: Embolic Strokes of Undetermined Source

Embolic strokes of undetermined source: the case for a new clinical construct

Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O'Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

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ESUS in the Athens Stroke Registry

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

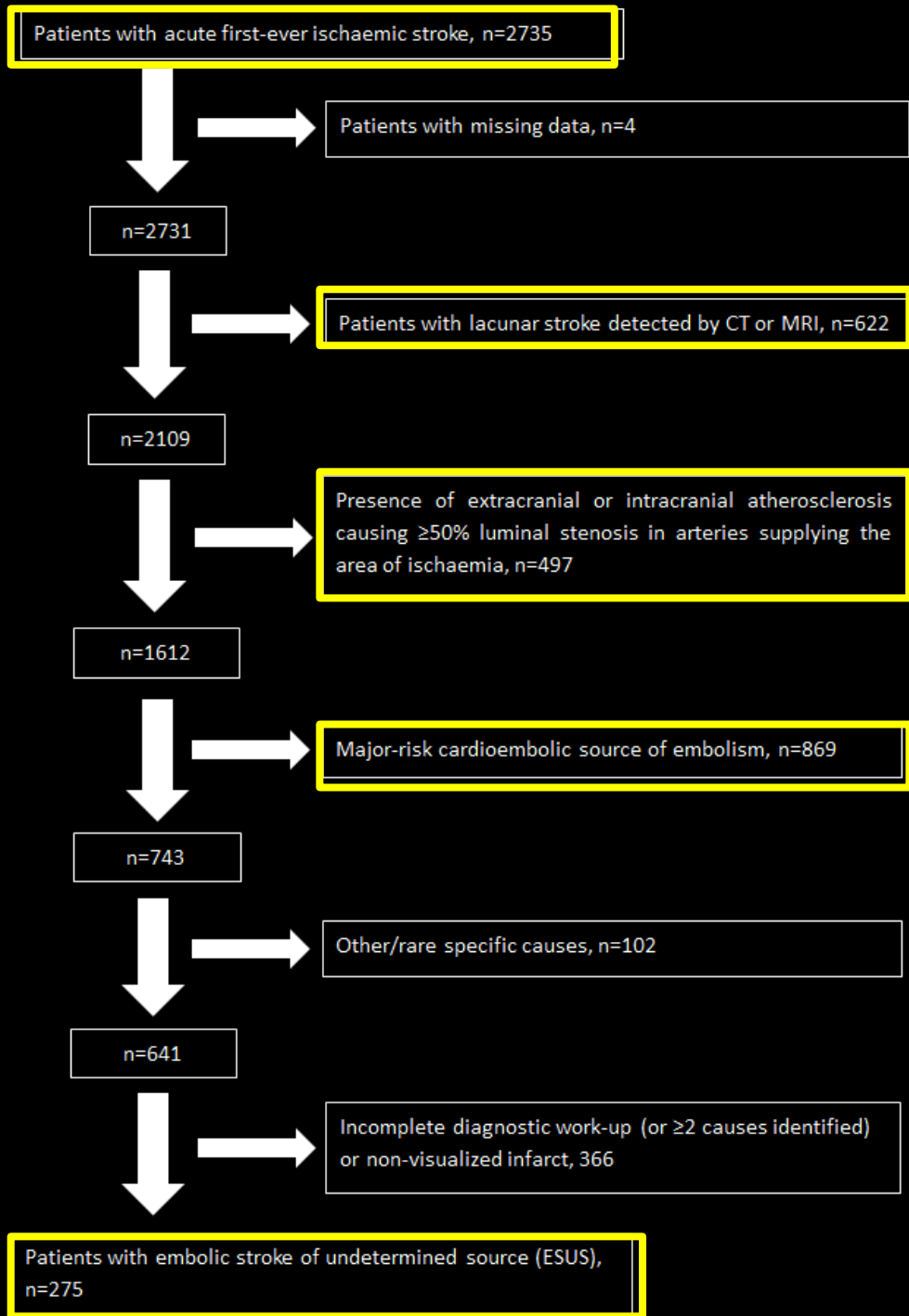


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Embolic Strokes of Undetermined Source in the Athens Stroke Registry: A Descriptive Analysis

George Ntaios, Vasileios Papavasileiou, Haralambos Milionis, Konstantinos Makaritsis, Efstathios Manios, Konstantinos Spengos, Patrik Michel and Konstantinos Vemmos

Stroke. 2015;46:176-181; originally published online November 6, 2014;



ESUS: patient characteristics

	ESUS (n=275)	Large-Artery Atherosclerotic (n=497)	Cardioembolic (n=869)	Lacunar (n=622)	Undetermined Other Than ESUS* (n=366)	Other Determined (n=102)
Demographics						
Female sex	99 (36.0%)	114 (22.9%)	461 (53.0%)	173 (27.8%)	166 (45.4%)	49 (48.0%)
Age, y	68.0 (58.0–76.0)	67.0 (60.0–73.0)	76.0 (70.0–82.0)	69.0 (60.0–75.0)	74.0 (67.0–81.0)	56.0 (43.0–74.0)
Comorbidities—risk factors						
Hypertension	178 (64.7%)	382 (76.9%)	631 (72.6%)	518 (83.3%)	259 (70.8%)	50 (49.0%)
Diabetes mellitus	65 (23.6%)	163 (32.8%)	192 (22.1%)	181 (29.1%)	115 (31.4%)	17 (16.7%)
Smoking	83 (30.2%)	251 (50.5%)	157 (18.1%)	235 (37.8%)	111 (30.3%)	39 (38.2%)
Previous TIA	27 (9.8%)	102 (20.5%)	53 (6.1%)	59 (9.5%)	39 (10.7%)	17 (16.7%)
Heart failure	22 (8.0%)	23 (4.6%)	139 (16.0%)	15 (2.4%)	31 (8.5%)	10 (9.8%)
Dyslipidemia	140 (50.9%)	273 (55.3%)	266 (30.7%)	306 (49.4%)	159 (43.6%)	40 (39.2%)
Coronary artery disease	65 (23.7%)	132 (26.8%)	169 (19.5%)	84 (13.6%)	86 (23.7%)	16 (15.7%)
Atrial fibrillation	0 (0.0%)	21 (4.2%)	774 (89.1%)	36 (5.8%)	41 (11.2%)	0 (0.0%)

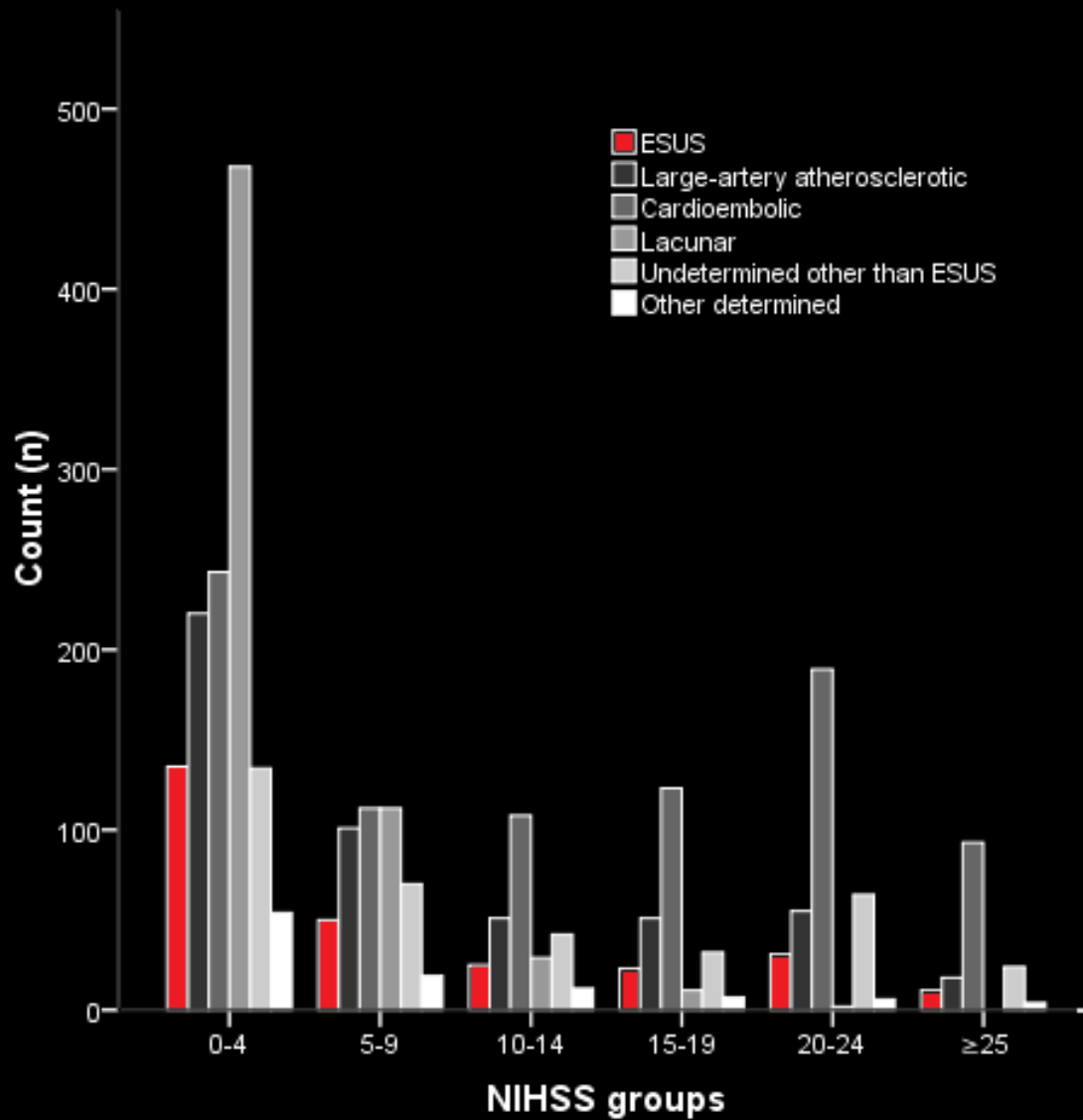
ESUS: patient characteristics

	ESUS (n=275)	Large-Artery Atherosclerotic (n=497)	Cardioembolic (n=869)	Lacunar (n=622)	Undetermined Other Than ESUS* (n=366)	Other Determined (n=102)
Mode of onset						
Maximal at onset	204 (74.2%)	255 (51.3%)	713 (82.1%)	290 (46.6%)	219 (59.8%)	58 (56.9%)
Gradual worsening	37 (13.5%)	112 (22.5%)	82 (9.4%)	99 (16.0%)	62 (16.9%)	15 (14.7%)
Shuttering/stepwise	15 (5.5%)	66 (13.3%)	24 (2.8%)	132 (21.3%)	25 (6.8%)	9 (8.8%)
Fluctuating	4 (1.5%)	23 (4.6%)	10 (1.2%)	40 (6.5%)	11 (3.0%)	8 (7.8%)
Unknown or missing data	15 (5.5%)	41 (8.2%)	39 (4.5%)	59 (9.5%)	49 (13.4%)	12 (11.8%)

ESUS: patient characteristics

	ESUS (n=275)	Large-Artery Atherosclerotic (n=497)	Cardioembolic (n=869)	Lacunar (n=622)	Undetermined Other Than ESUS* (n=366)	Other Determined (n=102)
Clinical and laboratory values						
Systolic blood pressure, mm Hg	150 (130–160)	150 (140–170)	150 (130–170)	160 (140–180)	150 (135–170)	140 (120–150)
Diastolic blood pressure, mm Hg	85 (80–90)	90 (80–90)	85 (80–90)	90 (80–100)	84 (80–90)	80 (70–90)
Glucose, mg/dL	109 (93–141)	111 (95–154)	118 (98–153)	105 (92–139)	116 (98–163)	100 (90–125)
NIHSS score	5 (2–14)	5 (2–15)	13 (4–22)	2 (1–4)	8 (3–18)	4 (1–12)

ESUS: stroke severity



Mitral valve

Myxomatous valvulopathy with prolapse 5 (1.8%)

Mitral annular calcification 8 (2.9%)

Aortic valve

Aortic valve stenosis 3 (1.1%)

Calcific aortic valve 12 (4.4%)

Non-atrial fibrillation atrial dysrhythmias and stasis

Atrial asystole and sick-sinus syndrome 3 (1.1%)

Atrial high-rate episodes 7 (2.6%)

Atrial appendage stasis with reduced flow velocities or spontaneous echodensities 6 (2.2%)

Atrial structural abnormalities

Atrial septal aneurysm 10 (3.6%)

Chiari network 0

Left ventricle

Moderate systolic or diastolic dysfunction (global or regional) 42 (15.4%)

Ventricular non-compaction 12 (4.4%)

Endomyocardial fibrosis 1 (0.4%)

Covert paroxysmal atrial fibrillation (detected during follow-up)

Atrial fibrillation detected on stroke recurrence 30 (11.0%)

Atrial fibrillation detected on monitoring during follow-up 50 (18.3%)

Atrial fibrillation not confirmed but strongly suspected 38 (13.9%)

Cancer-associated

Covert non-bacterial thrombotic endocarditis 1 (0.4%)

Tumor emboli from occult cancer 2 (0.8%)

Arteriogenic emboli

Aortic arch atherosclerotic plaques 9 (3.3%)

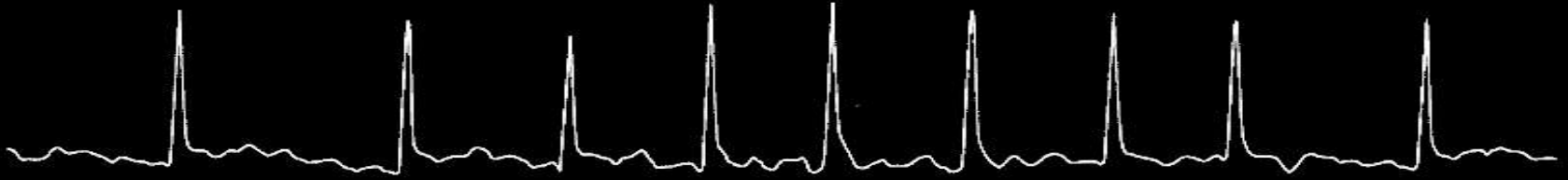
Cerebral artery non-stenotic plaques with ulceration 29 (10.6%)

Paradoxical embolism

Patent foramen ovale 11 (4.0%)

Atrial septal defect 3 (1.1%)

ESUS & AF at follow-up: how much causality is there?



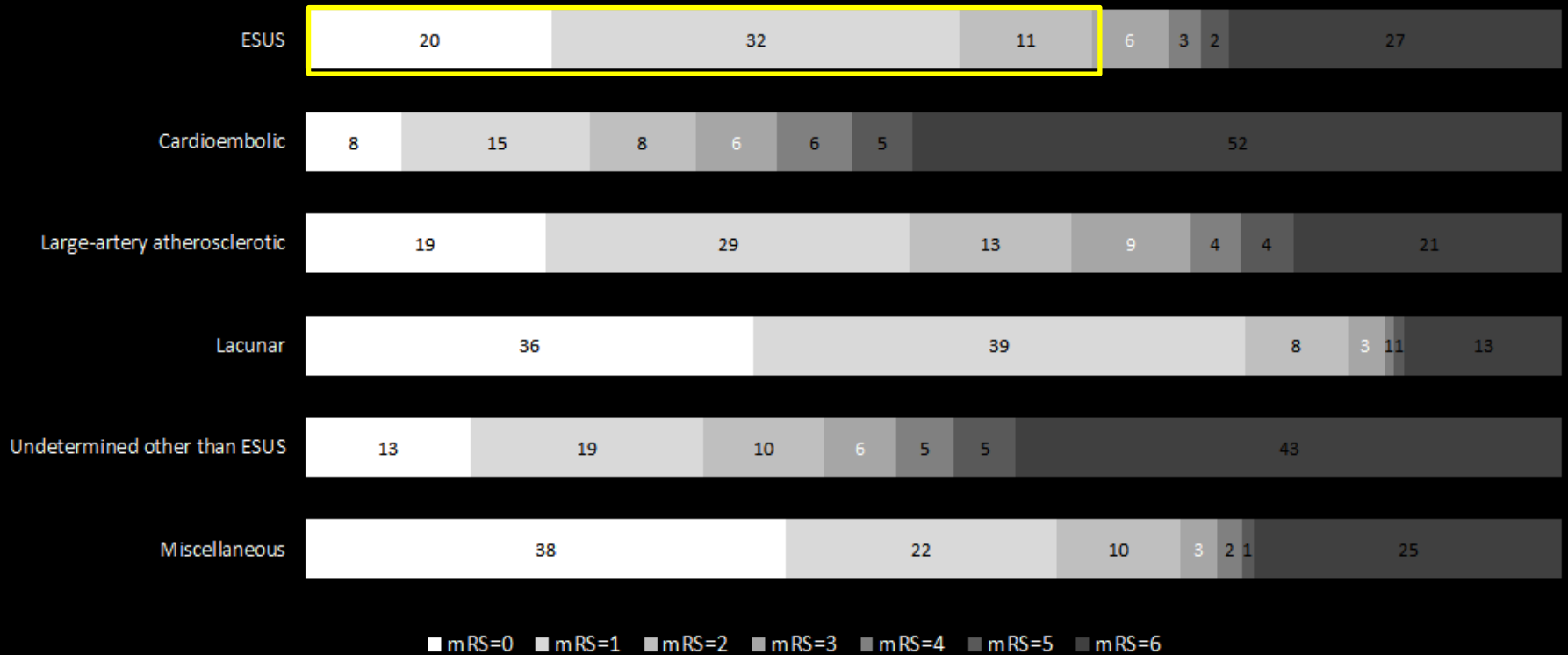
AF-related strokes are more severe

Patient characteristics	Large-artery atherosclerotic stroke n=496	Cardioembolic stroke n=993	Lacunar stroke n=647	Stroke of undetermined origin n=533	Stroke of miscellaneous causes n=61
NIHSS on admission	9	13	4	9	8

ESUS & AF: how much of a causality?

	AF ESUS (n=80)	Non-AF ESUS (n=195)	p-value
NIHSS score	5 (2-13)	5 (2-14)	0.998

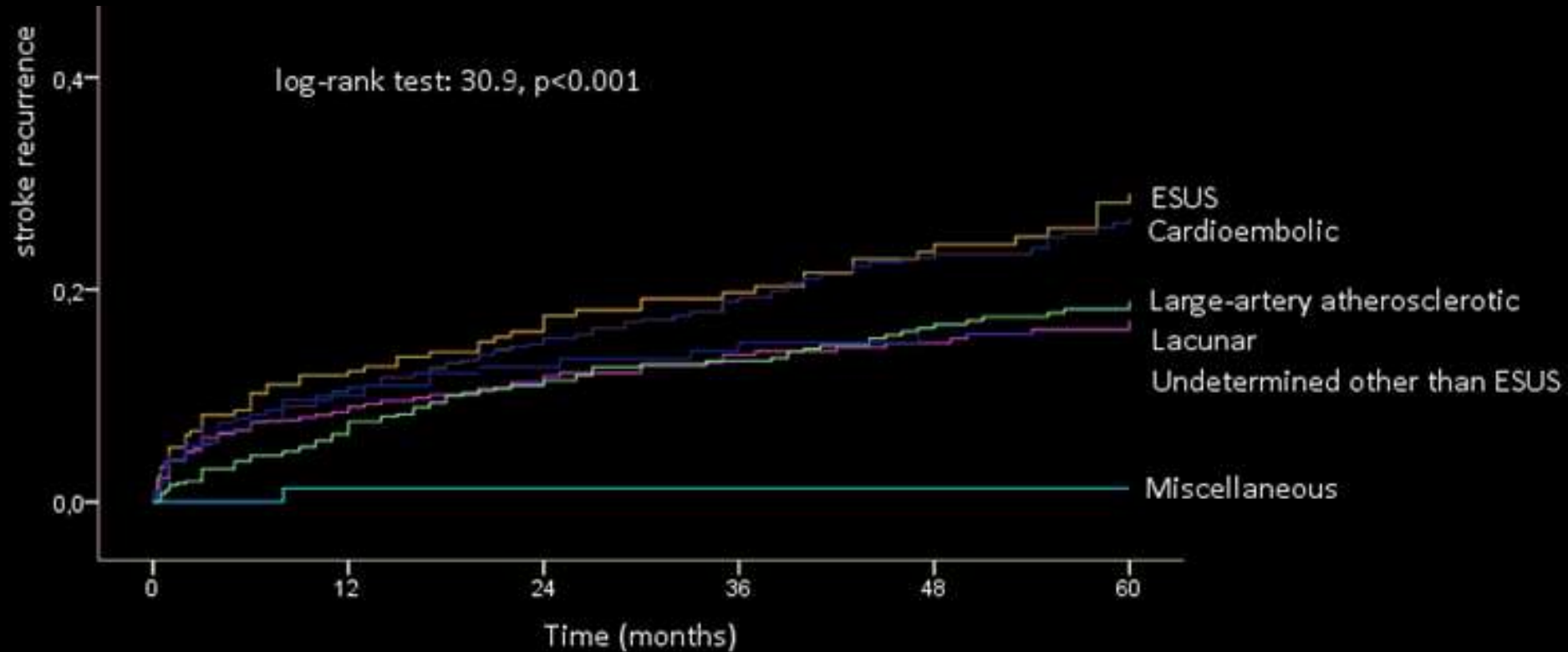
ESUS: 5-yrs functional outcome



ESUS: what is the risk for recurrence?

1. Minimal risk.
2. Low risk.
3. Medium risk.
4. High risk.

ESUS: 5-yrs stroke recurrence



So, how to treat my ESUS patient?



Recommendations for Antithrombotic Therapy for Noncardioembolic Stroke or TIA (Oral Anticoagulant and Antiplatelet Therapies)

Recommendations

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

Aspirin (50 mg/d to 325 mg/d) monotherapy (*Class I; Level of Evidence A*), the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (*Class I; Level of Evidence B*), and clopidogrel 75 mg monotherapy (*Class IIa; Level of Evidence B*) are all acceptable options for initial therapy. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics.

The addition of aspirin to clopidogrel increases risk of hemorrhage and is not recommended for routine secondary prevention after ischemic stroke or TIA (*Class III; Level of Evidence A*).

For patients allergic to aspirin, clopidogrel is reasonable (*Class IIa; Level of Evidence C*).

For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been studied in patients who have had an event while receiving aspirin (*Class IIb; Level of Evidence C*).

So, how to treat my ESUS patient?

Approach 2



So, how to treat my ESUS patient?



NAVIGATE- ESUS

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (ESUS) (NAVIGATE ESUS)

This study is currently recruiting participants. (see [Contacts and Locations](#))

Verified January 2015 by Bayer

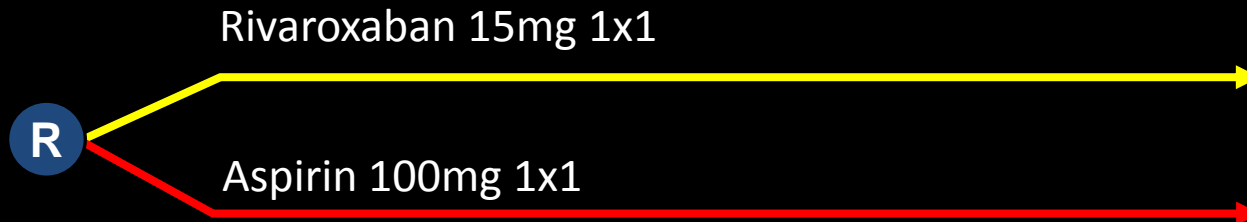
Sponsor:
Bayer

Collaborators:
Janssen, LP
Hamilton Health Sciences Cooperation, Population Health Research Institute

Information provided by (Responsible Party):
Bayer

ClinicalTrials.gov Identifier:
NCT02313909

First received: December 8, 2014
Last updated: January 28, 2015
Last verified: January 2015
[History of Changes](#)



RESPECT - ESUS

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source (RE-SPECT ESUS)

This study is currently recruiting participants. (see [Contacts and Locations](#))

Verified January 2015 by Boehringer Ingelheim

Sponsor:

Boehringer Ingelheim

Information provided by (Responsible Party):

Boehringer Ingelheim

ClinicalTrials.gov Identifier:

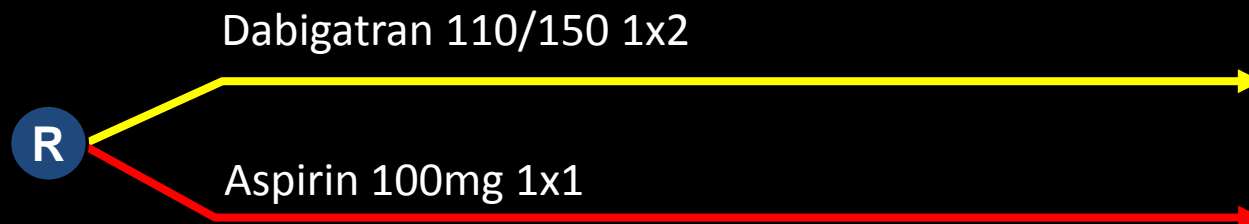
NCT02239120

First received: September 10, 2014

Last updated: January 22, 2015

Last verified: January 2015

[History of Changes](#)



ATTICUS

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS)

This study is not yet open for participant recruitment. (see [Contacts and Locations](#))

Verified April 2015 by University Hospital Tuebingen

Sponsor:

University Hospital Tuebingen

Information provided by (Responsible Party):

University Hospital Tuebingen

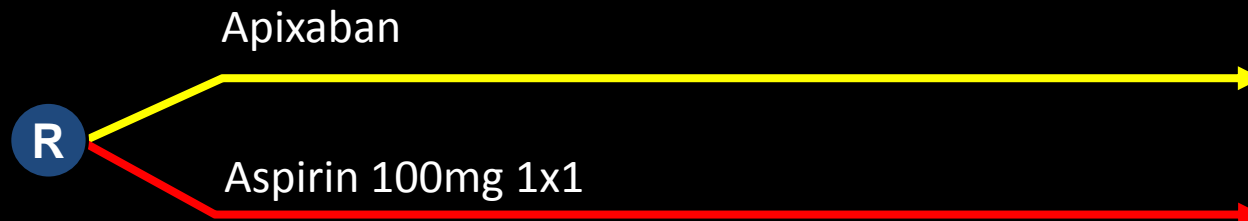
ClinicalTrials.gov Identifier:
NCT02427126

First received: March 20, 2015

Last updated: May 7, 2015


Last verified: April 2015

[History of Changes](#)



What if?

- Everybody gets happy!
- Almost half stroke patients get an anticoagulant!



*So, how would you treat
your ESUS patient?*

1. An antiplatelet?
2. An anticoagulant?
3. Implant a Loop Recorder to detect AF?
4. Randomize in NAVIGATE?
5. I don't know, will ask Charlotte Cordonnier.

Take-home messages

- ✓ Cryptogenic → ESUS
- ✓ ~10% of all stroke patients
- ✓ ESUS needs a complete (?) diagnostic work-up
- ✓ Covert AF is frequently detected in ESUS
- ✓ Perhaps AF is over-estimated as a stroke cause
- ✓ High recurrence rate
- ✓ NOACs to replace antiplatelets?

