ESUS (Embolic Stroke of Undetermined Source)

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Medicina Interna II

Ospedale San Giuseppe, Empoli

Eziopatogenesi stroke: criteri TOAST

- Malattia aterosclerotica dei grossi vasi extra-intracranici
- Malattia dei piccoli vasi (lacunare)
- Cardioembolica
- Altra determinata eziologia
- **Ad eziologia indeterminata**
  - Due o più cause plausibile (eziologia incerta)
  - **Criptogenetico**

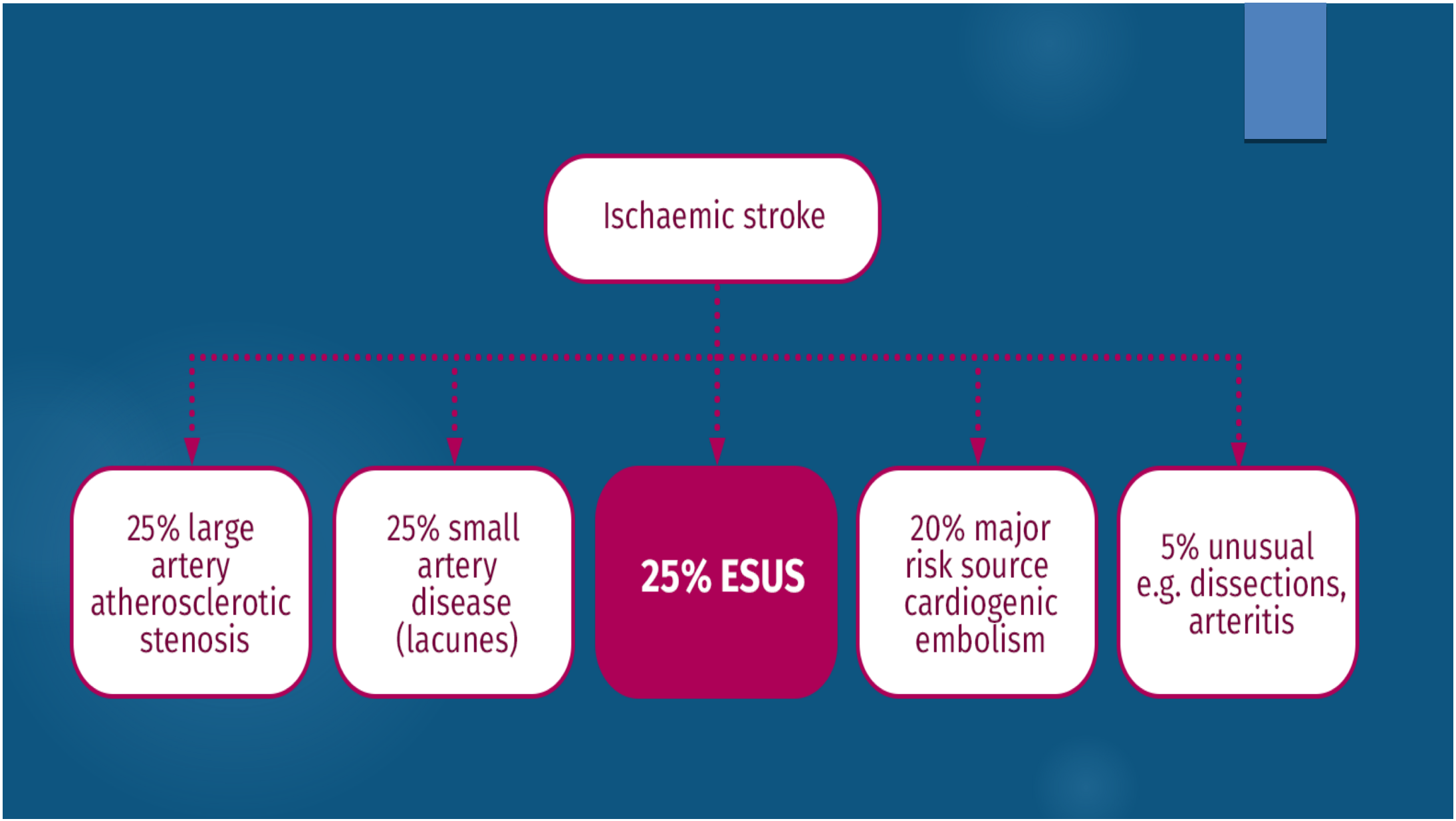
Lancet Neurol 2014; 13: 429–38

Personal View

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.


Ischaemic stroke
25% large artery atherosclerotic stenosis
25% small artery disease (lacunes)
25% ESUS
20% major risk source cardiogenic embolism
5% unusual e.g. dissections, arteritis

Panel 1: Causes of embolic strokes of undetermined source

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

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 sources are more often incidentally present than is the stroke cause when identified in an individual stroke patient, are associated with a low or uncertain rate of initial stroke, and consequently cause-effect relation and management implications are usually unclear.

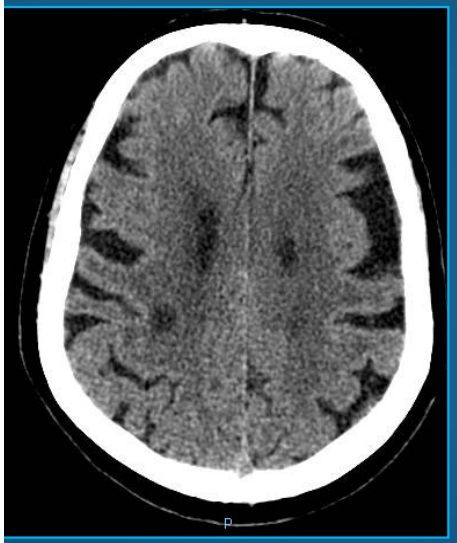
Si parte sempre dall'imaging

ORIGINAL ARTICLE

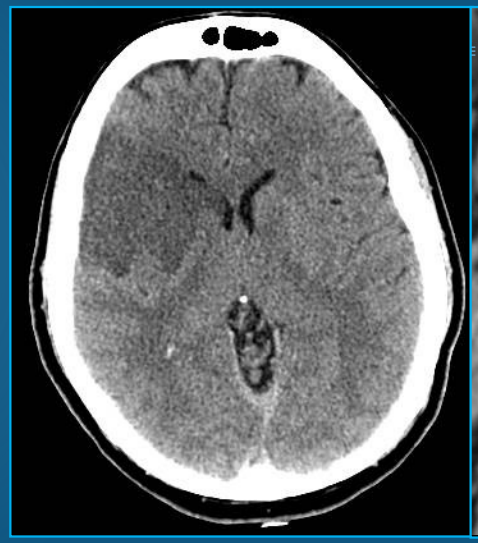
Annals of Medicine, 2015; 47: 406–413

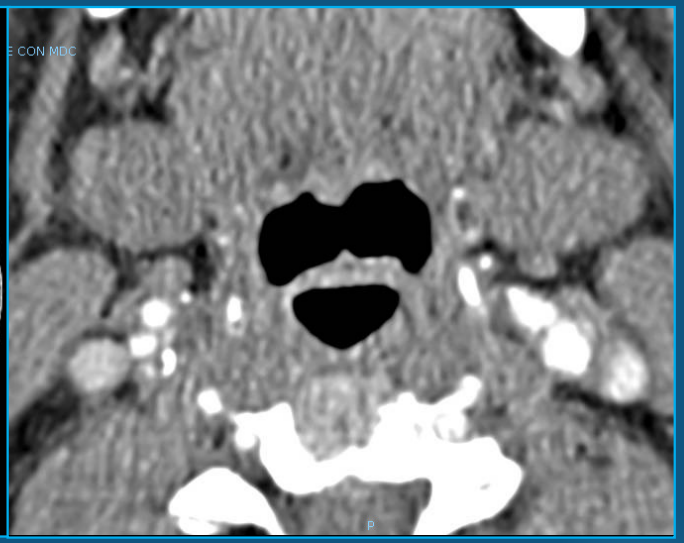
Undetermined stroke with an embolic pattern—a common phenotype with high early recurrence risk

Jukka Putaala[1], Tuomo Nieminen[2], Elena Haapaniemi[1], Atte Meretoja[1,3], Kirsi Rantanen[1], Noora Heikkinen[1], Janne Kinnunen[1], Daniel Strbian[1], Satu Mustanoja[1], Sami Curtze[1], Sami Pakarinen[2], Mika Lehto[2] & Turgut Tatlisumak[1,4,5]

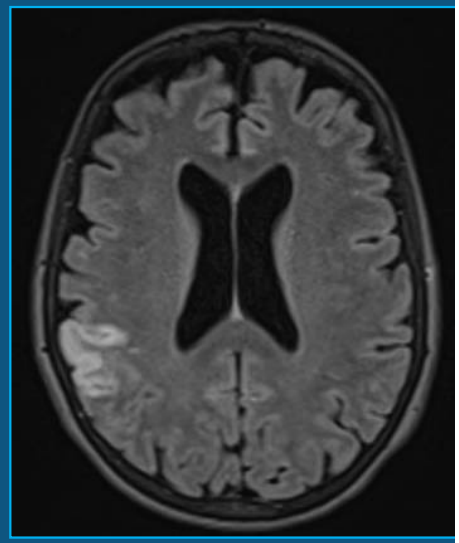


Lacunare





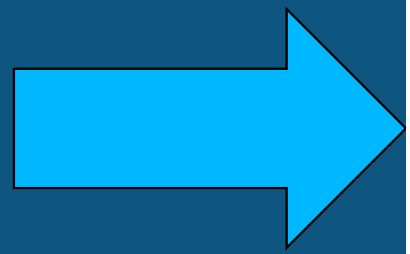
Stenosi serrata CI destra



Pattern embolico

Criteri diagnostici ESUS

- **Stroke non lacunare**
- **Assenza di stenosi dei grossi vasi extra o intracranici ≥ 50% nel territorio fornito dall'arteria stenotica**
- **Assenza di fonti maggiori di cardioembolismo:**
  - **FA/flutter atriale, protesi valvolari meccaniche, mixoma atriale o altri tumori, trombosi intracardiaca, stenosi mitralica, cardiomiopatia con FE < 30%, recente (< 4 settimane) IMA, vegetazioni valvolari/endocardite**
- **Assenza di altre cause specifiche (dissezioni, vasculiti, vasospasmo emicranico ecc)**



Diagnostica di minima ESUS

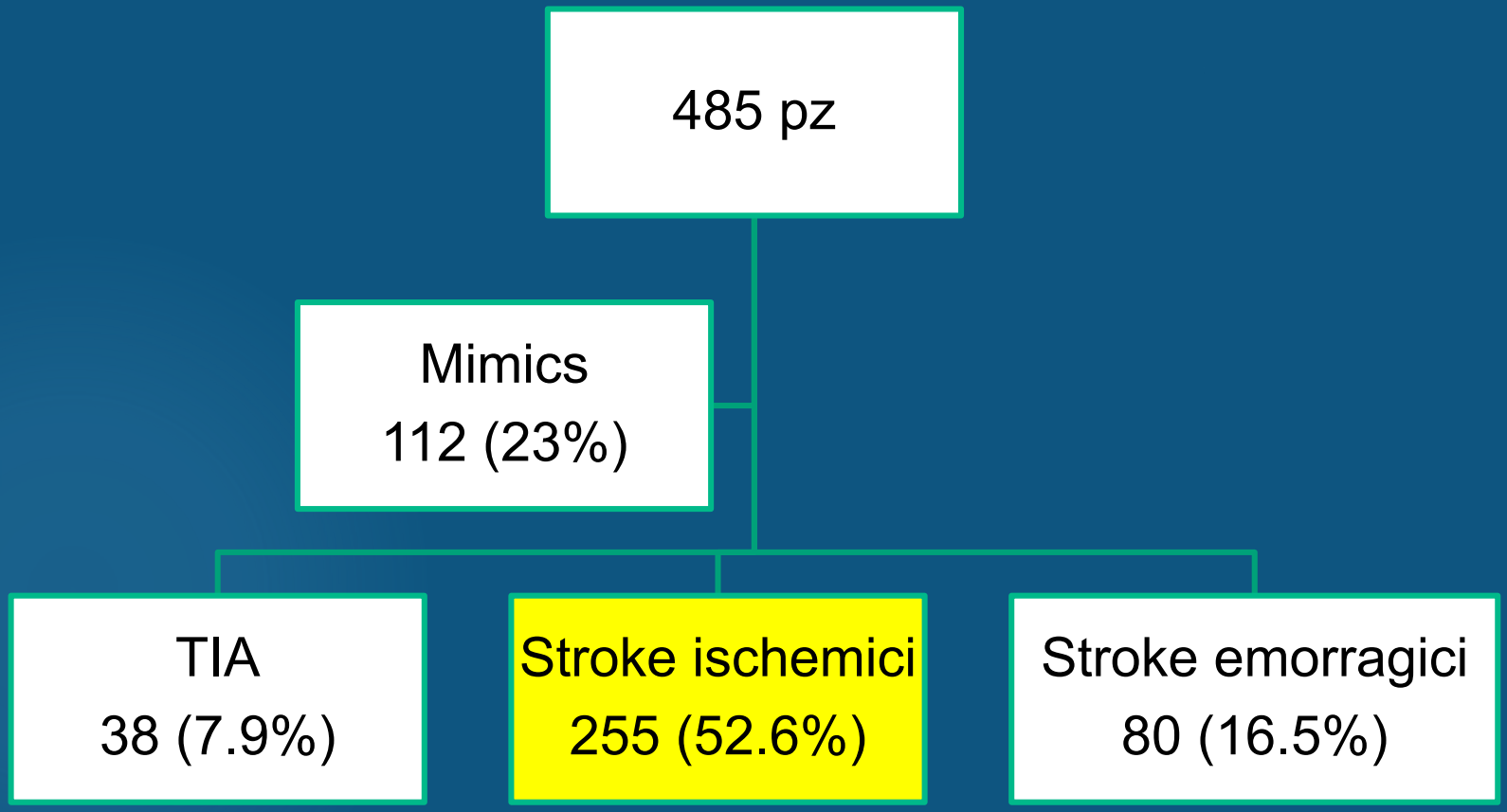
- TC o RM
- ECG 12 derivazioni
- Ecocardiografia TT
- Monitoraggio ECG ≥ 24 ore
- Imaging grossi vasi epi-aortici ed intracranici

Fare finta di niente

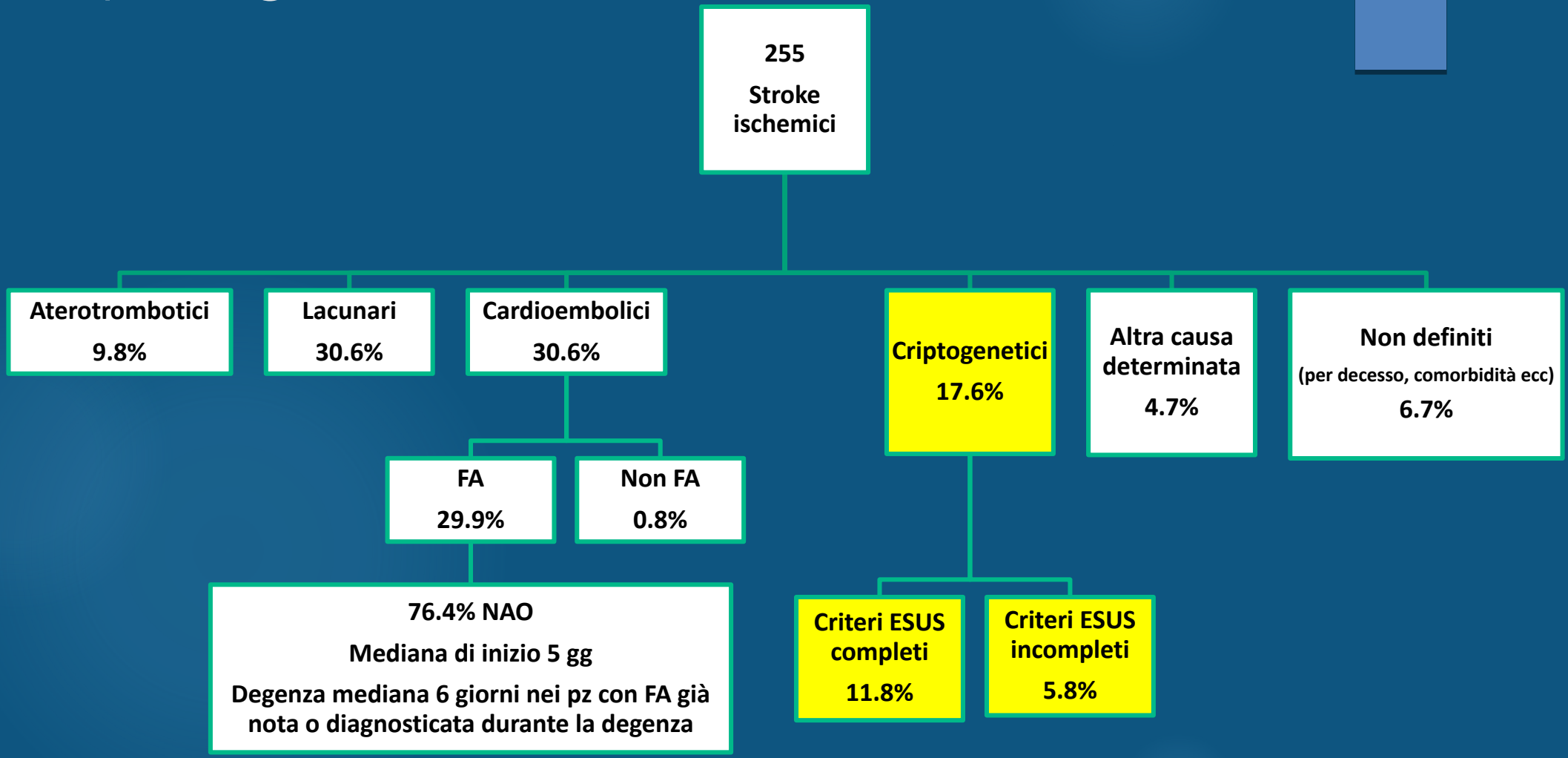
Fare tutto a tutti

Fare appropriatamente

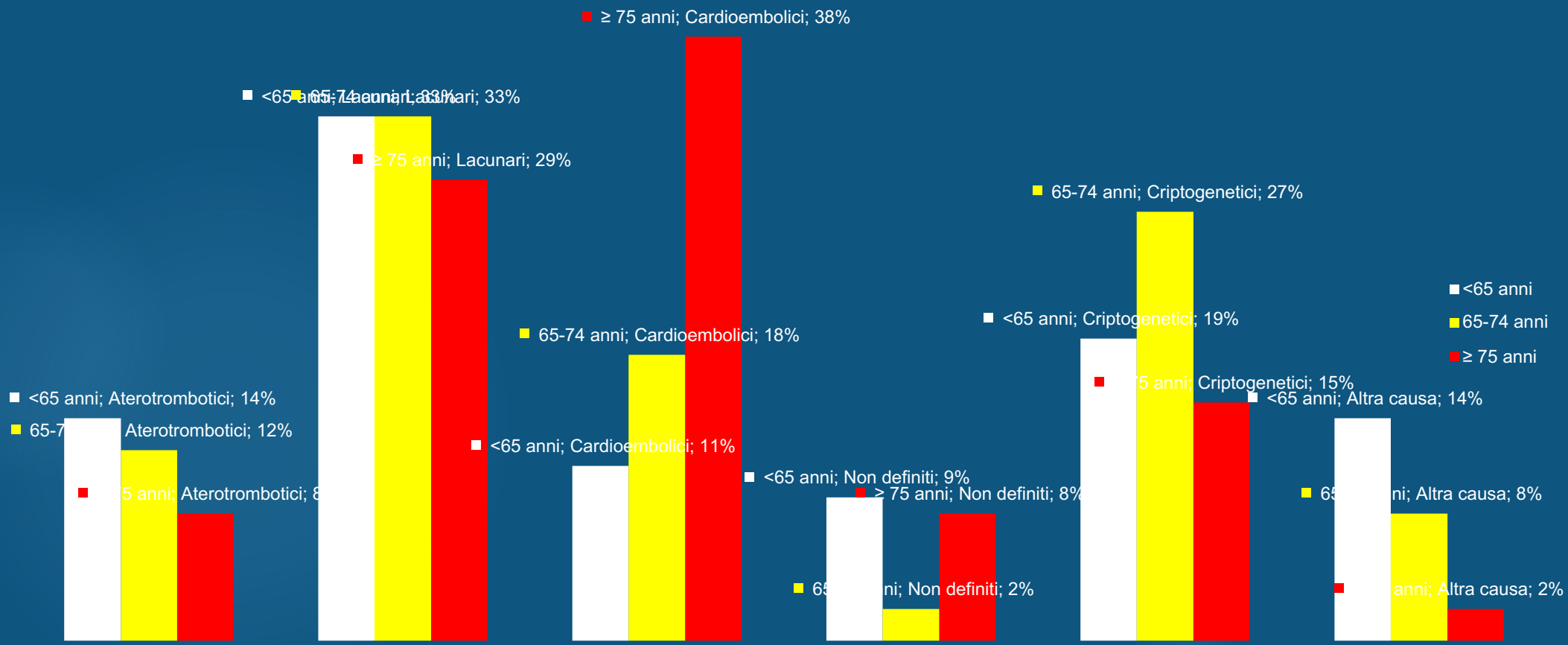
Area Stroke Empoli
Periodo 6 Nov 2017- 5 Set 2018: 10 mesi



Eziopatogenesi stroke ischemici



Eziopatogenesi stroke ischemici
Suddivisione per età



Stroke ischemico criptogenetico

Area Stroke Empoli (analisi su 10 mesi)

Numero	46
Età media ± DS	73 ± 13 anni
Criteri ESUS soddisfatti	30 (65%)
Dilatazione atriale sin	28.6%
CHA_2DS_2-VASC pre-stroke mediano (IQR)	4 (3-4)
CHA_2DS_2-VASC ≥ 4	54%
mRS alla dimissione mediana (IQR)	3 (2-3.75)

Burden e management FOP

Periodo 1 Aprile 2017- 30 Settembre 2018

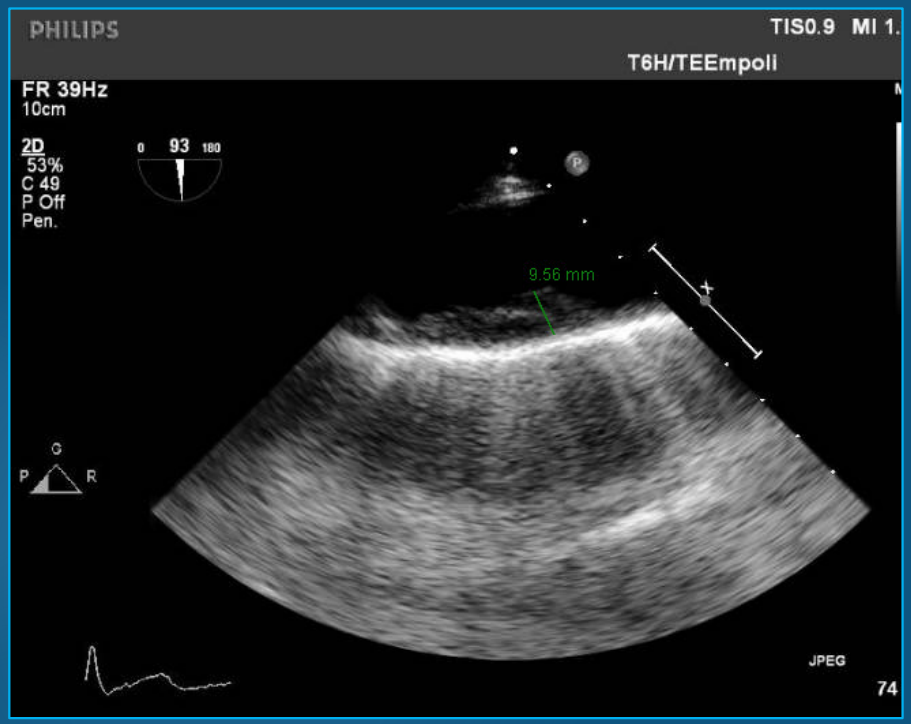
Numero	10 pazienti (5 F)
Età media ± DS	53± 14 anni
Età < 60 anni	80%
ROPE score Mediano (IQR)	6 (4.25-7)
Chiusura	5 (50%)
In fase di valutazione per chiusura	2 (20%)
Non chiusura	3 (30%)

1 FOP associato a protesi valvolare meccanica >> TAO+ASA

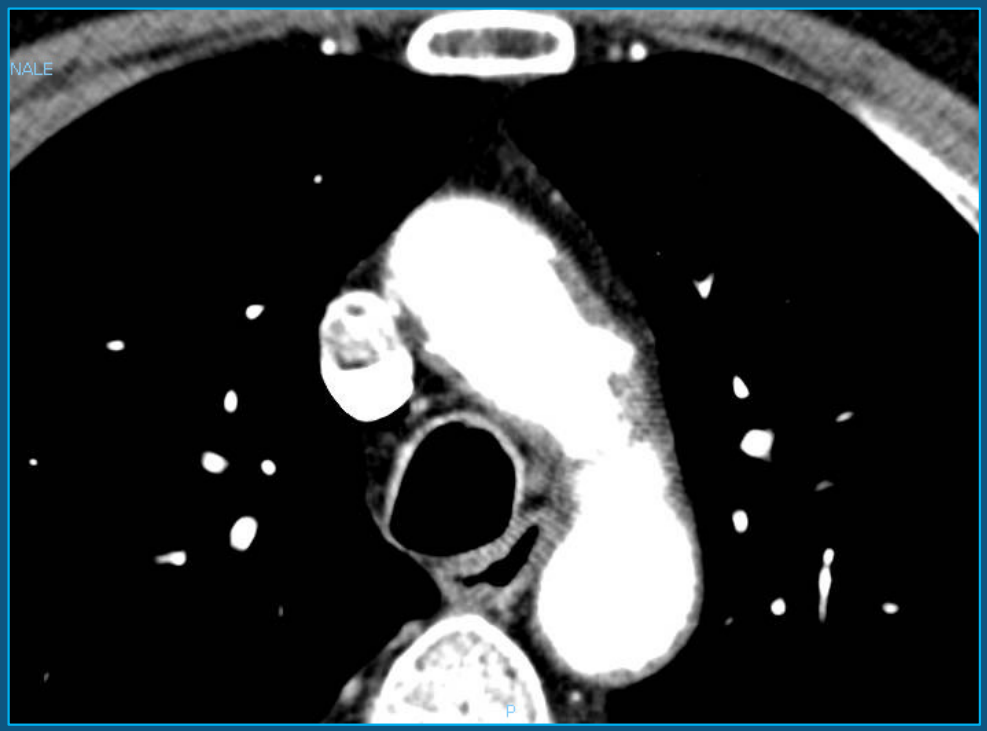
1 riscontro di FA >> NAO

1 pattern lacunare e dubbia SAA >> DAPT

Placche dell’arco aortico



Ecocardio TE



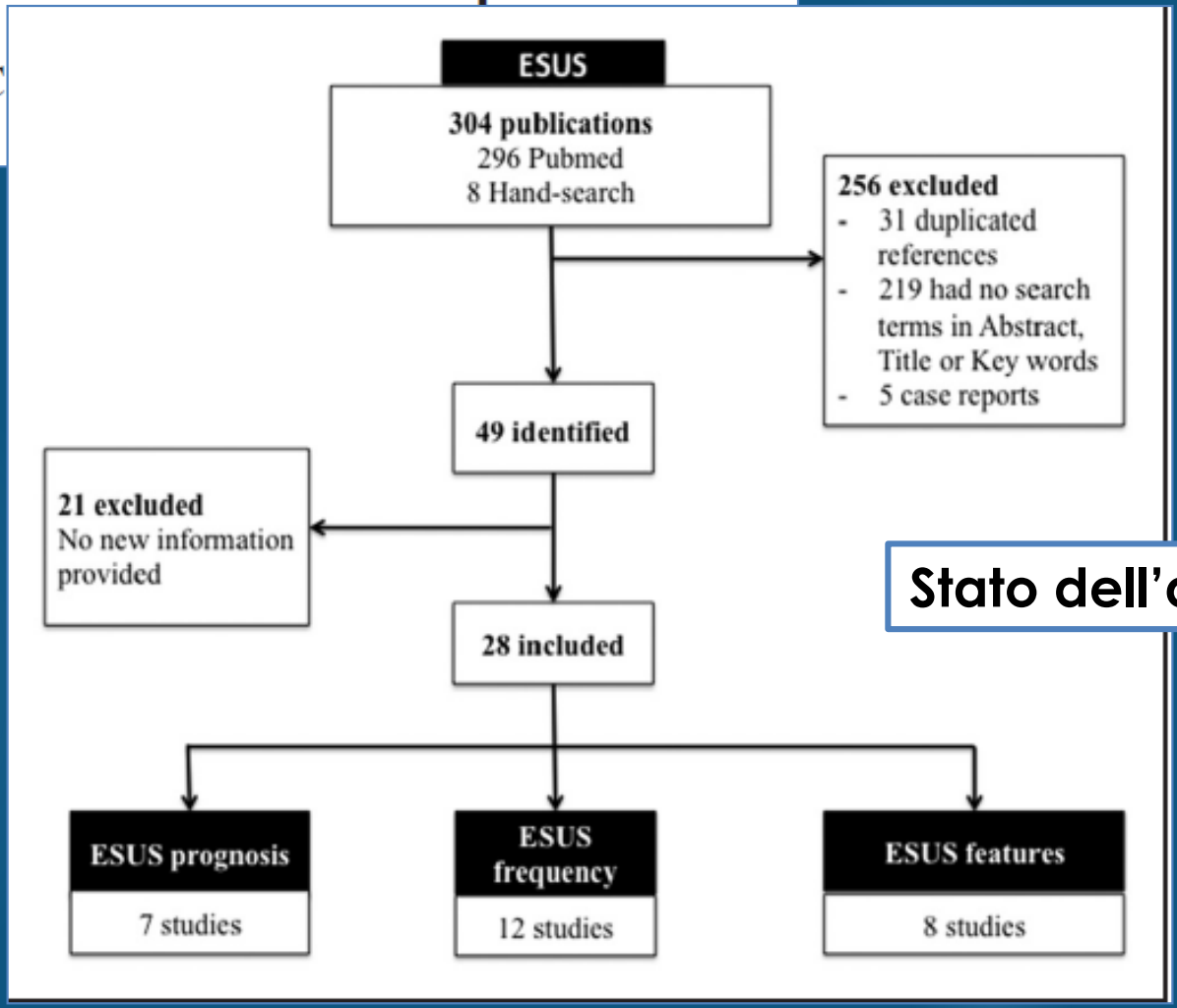
AngioTC

Embolic Stroke of Undetermined Source

A Systematic Review and Clinical Update

Robert G. Hart, MD; Luciana C
George Ntaios, MD,

Stroke. 2017;48:867-872



Stato dell'arte al 2016

Embolic Stroke of Undetermined Source

A Systematic Review and Clinical Update

Robert G. Hart, MD; Luciana Catanese, MD; Kanjana S. Perera, MBBS; George Ntaios, MD, PhD; Stuart J. Connolly, MD

Stroke. 2017;48:867-872.

Table 4. Prognosis of ESUS Patients*

Study	n/Mean Follow-Up (y)	Mean Age, y	Antithrombotic Therapy	AF During Follow-Up†	Stroke (Est Annualized Rate)†	Stroke, MI, Vascular Death (Est Annualized Rate)	Total Mortality (Est Annualized Rate)
Ntaios et al[13,26]‡	275 (3.2)	68	74% APT only, 22% OAC	80 (29%)	6.8%/y	9.0%/y§	8.2%/y
Li et al[15]	189 (1)	65	NR	NR	≈5%/y	NR	NR
Putaala et al[16]‡	46 (1.8)	62	85% APT, 11% OAC	NR	5.1%/y	NR	1.3%/y
Ntaios et al[24]‡	1095 (3.0)	68	87% APT only, 12% OAC	NR	4.8%/y‖	NR	4.5%/y
Masina et al[12]¶	84 (2.1)	73	99% APT	NR	2.3%/y	NR	NR
Ueno et al[22]#	177 (3.5)	64	72% APT, 29% OAC	NR	3.9%/y	5.0%/y**	1.3%/y
Arauz et al[23]††	149 (2.3)	44	91% APT, 5% OAC	NR	2.3%/y	NR	0%/y
Pooled – unweighted average‡,††	1545 (2.4)	68	87% APT, 12% OAC	…	4.0%/y	…	2.9%/y
Pooled – weighted average‡,††	1605 (2.7)	65	86% APT, 13% OAC	…	4.5%/y	…	3.9%/y

Rischio di stroke 5%/anno

Table 8 CHA_2DS_2VASc score and stroke rate

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

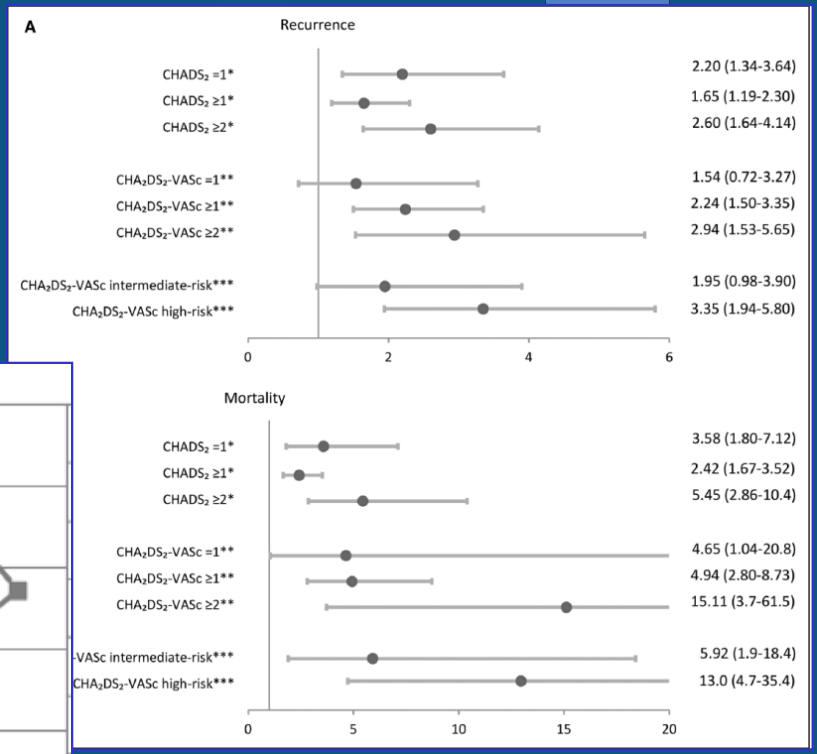
(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

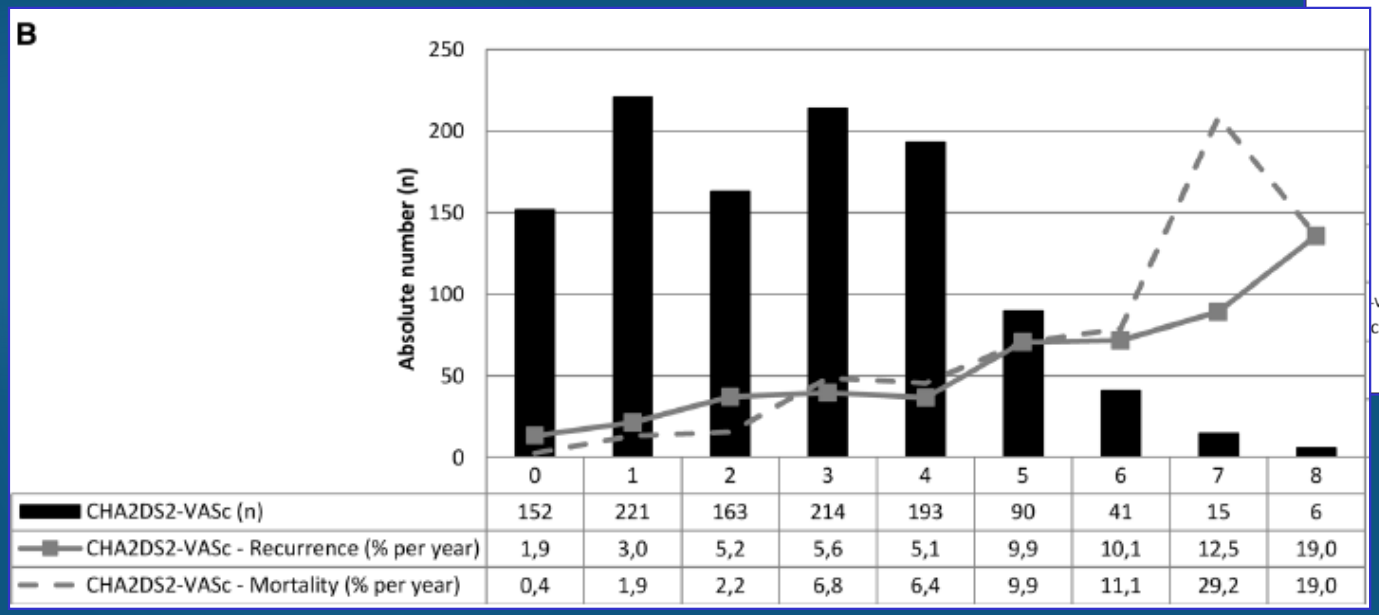
CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

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

George Ntaios, MD, PhD; Konstantinos Vemmos, MD; Gregory Y.H. Lip, MD; Eleni Koroboki, MD; Efstathios Manios, MD; Anastasia Vemmou, MD; Ana Rodríguez-Campello, MD; Elisa Cuadrado-Godia, MD; Eva Giralt-Steinhauer, MD; Valentina Arnao, MD; Valeria Caso, MD; Maurizio Paciaroni, MD; Exuperio Diez-Tejedor, MD, PhD; Blanca Fuentes, MD, PhD; Josefa Pérez Lucas, MD; Antonio Arauz, MD; Sebastian F. Ameriso, MD; Maximiliano A. Hawkes, MD; Lucía Pertierra, MD; Maia Gómez-Schneider, MD; Fabio Bandini, MD; Beatriz Chavarria Cano, MD; Ana Maria Iglesias Mohedano, MD; Andrés García Pastor, MD; Antonio Gil-Núñez, MD, PhD; Jukka Putaala, MD; Turgut Tatlisumak, MD; Miguel A. Barboza, MD; George Athanasakis, MD; Konstantinos Makaritsis, MD; Vasileios Papavasileiou, MD

Stroke. 2016;47:2278-2285.





	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

The NEW ENGLAND JOURNAL of MEDICINE

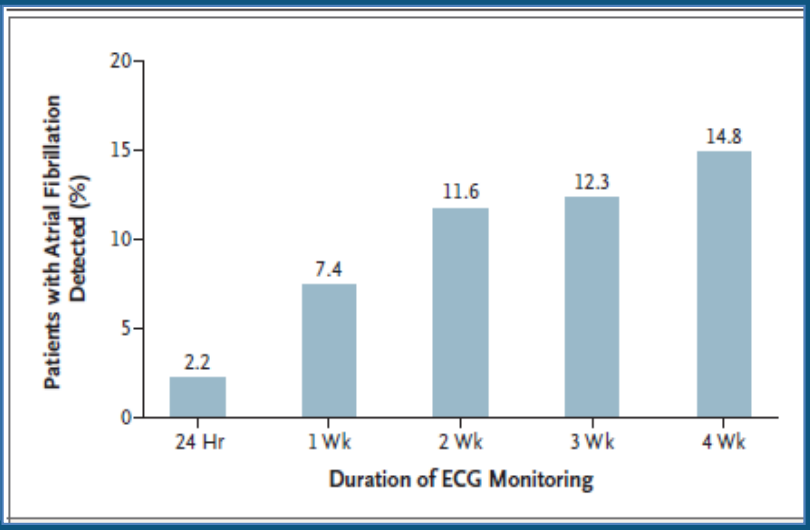
ESTABLISHED IN 1812 JUNE 26, 2014 VOL. 370 NO. 26

Atrial Fibrillation in Patients with Cryptogenic Stroke

EMBRACE

Table 2. Detection of Atrial Fibrillation in the Two Monitoring Groups.

Outcome	Intervention Group (N=286)	Control Group (N=285)	Absolute Difference (95% CI)	P Value	No. of Patients Needed to Screen (95% CI)*
	number/total number (percent)		*percentage points*		
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)

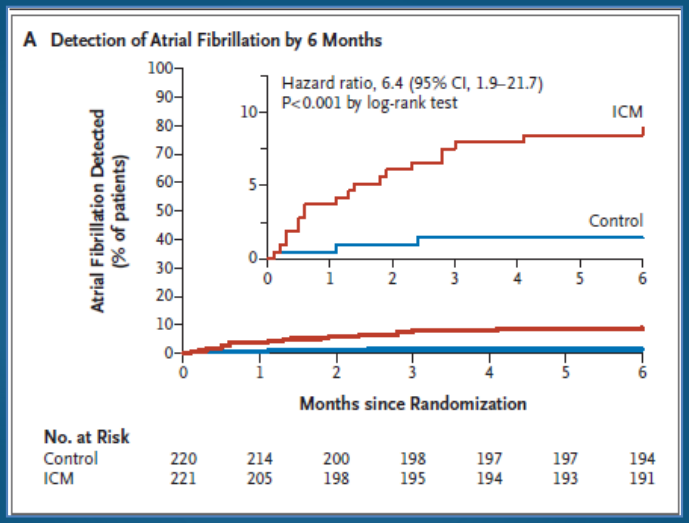


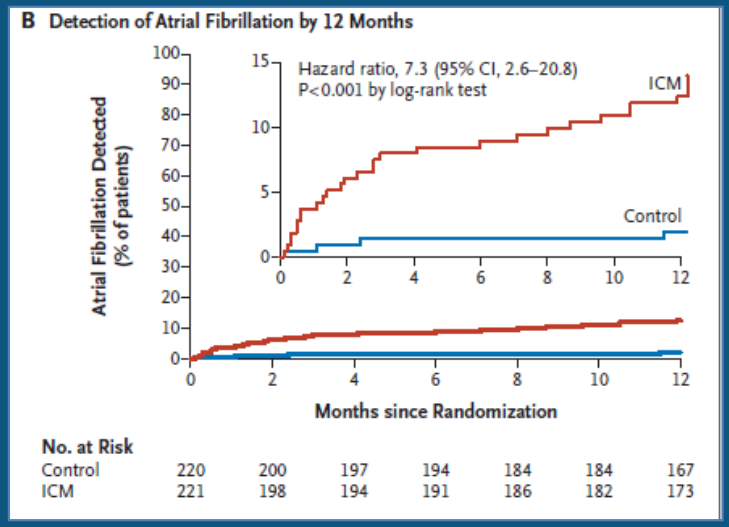
The NEW ENGLAND JOURNAL of MEDICINE

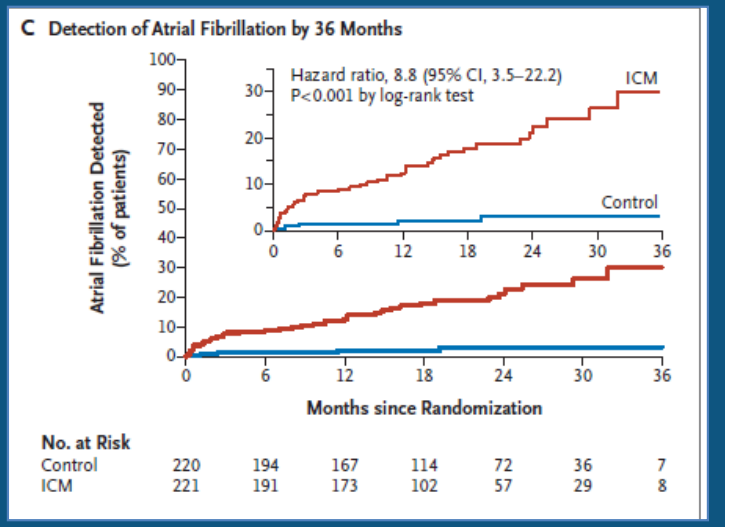
ORIGINAL ARTICLE

Cryptogenic Stroke and Underlying Atrial Fibrillation

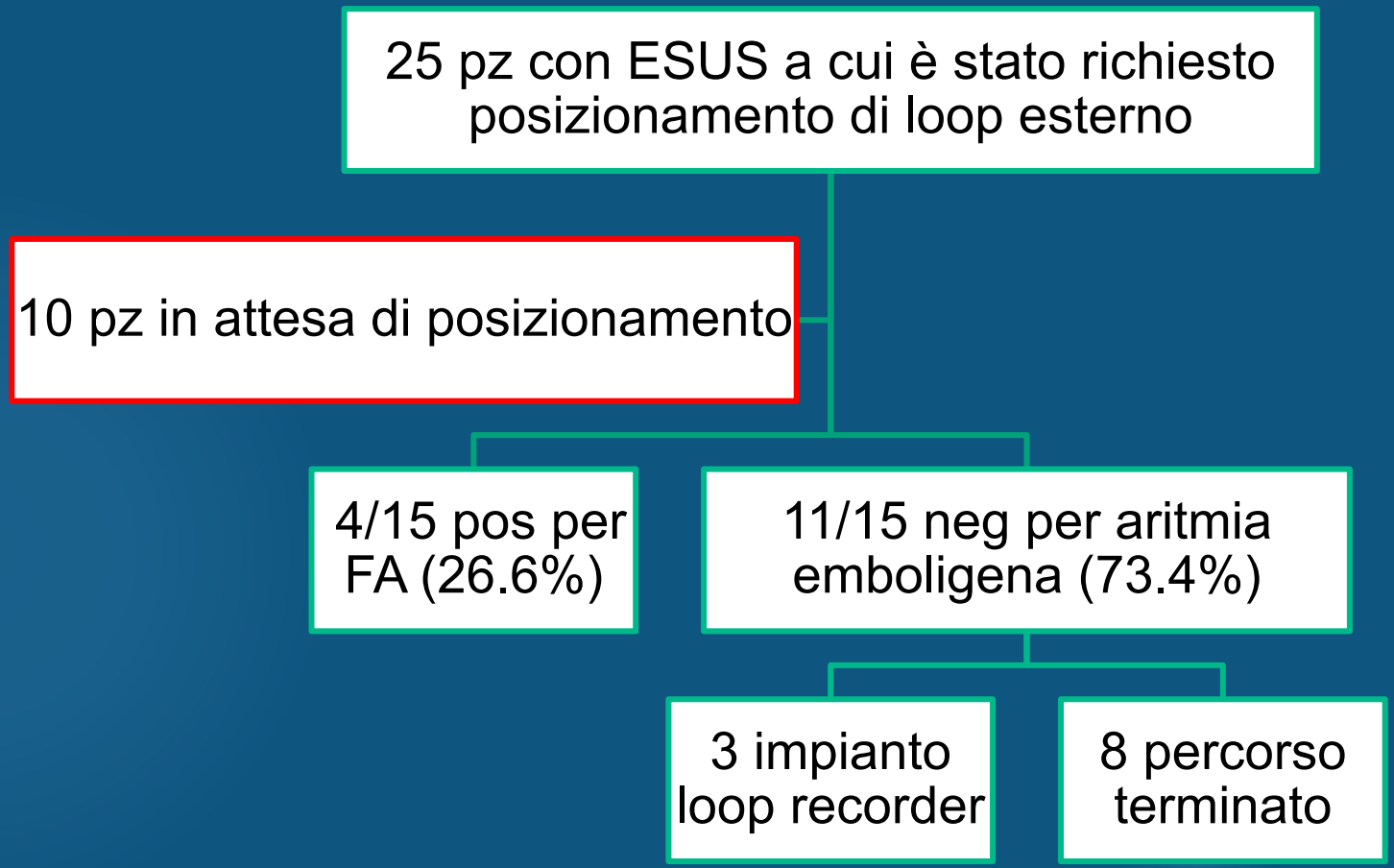
CRISTAL-AF







Monitorizzazione ECG protratta ambulatoriale Periodo 1 Aprile 2017-31 Agosto 2018



Direct oral anticoagulants in the early phase of non valvular atrial fibrillation-related acute ischemic stroke: focus on real life studies

15 Studi selezionati

2920 pz (47.8% F)

Outcome a 90 giorni:

- Recidiva di TIA/Stroke 2.25%
- Trasformazione emorragica/ sanguinamento intracranico 0.9%
- Mortalità per tutte le cause 1.5%

Masotti L et al. Submitted

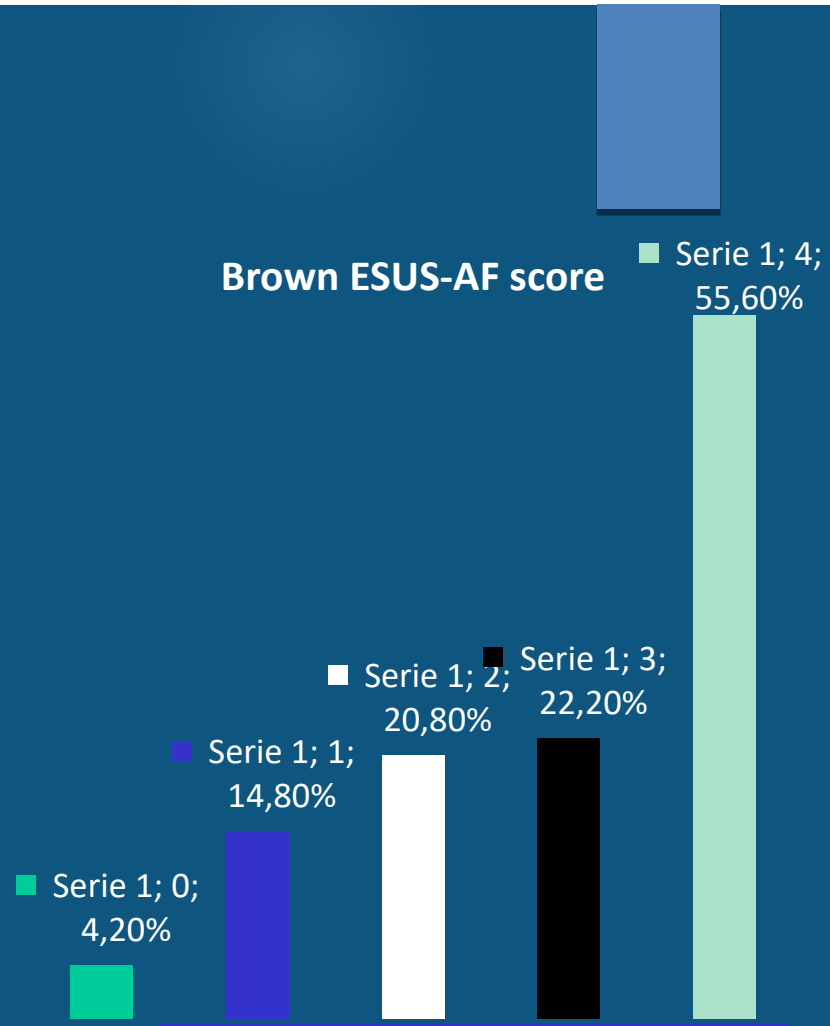
A Simple Score That Predicts Paroxysmal Atrial Fibrillation on Outpatient Cardiac Monitoring after Embolic Stroke of Unknown Source

Brittany Ricci, BS,* Andrew D. Chang, MS,* Morgan Hemendinger, MS,* Katarina Dakay, DO,* Shawna Cutting, MD,* Tina Burton, MD,* Brian MacGrory, MD,* Priya Narwal, MD,* Christopher Song, MD,† Antony Chu, MD,† Emile Mehanna, MD,† Ryan McTaggart, MD,‡§ Mahesh Jayaraman, MD,*‡§ Karen Furie, MD,* and Shadi Yaghi, MD*

Table 3. *Atrial fibrillation-risk scoring system and accuracy*

Age 65-74	+1
Age ≥ 75	+2
Moderate/Severe LAE	+2
AUC	.726

The accuracy of the model is provided as the area under the curve (AUC) of sensitivity plotted against the false-positive rate, using co-ordinates derived from thresholding each increment of score value (0-4).



63% della nostra casistica ha Brown ESUS-AF score ≥ 2; in questi CHA2DS2-VASC ≥ 4 72%

Episodi di FA si associano a rischio di stroke ma non c'è evidenza di relazione temporale tra FA e stroke

ASSERT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Subclinical Atrial Fibrillation and the Risk of Stroke

IMPACT

European Heart Journal (2015) 36, 1660–1668
doi:10.1093/eurheartj/ehv115

CLINI

Atrial fibrillation

Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices

Original Articles

The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk

The TRENDS Study

THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

J Am Coll Cardiol 2017;70:756–65

Atrial Cardiomyopathy

A Useful Notion in Cardiac Disease Management or a Passing Fad?

Jean-Baptiste Guichard, MD,[a,b] Stanley Nattel, MD[a,c,d]

EHRA/HRS/APHRS/SOLAECE expert consensus on Atrial cardiomyopathies: Definition, characterisation, and clinical implication☆,☆☆

Table 1
Definition of atrial cardiomyopathy.

Journal of Arrhythmia 32 (2016) 247–278

'Any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations'.

FIGURE 4 Potential Components of a Clinically Relevant Classification of Atrial Cardiomyopathies

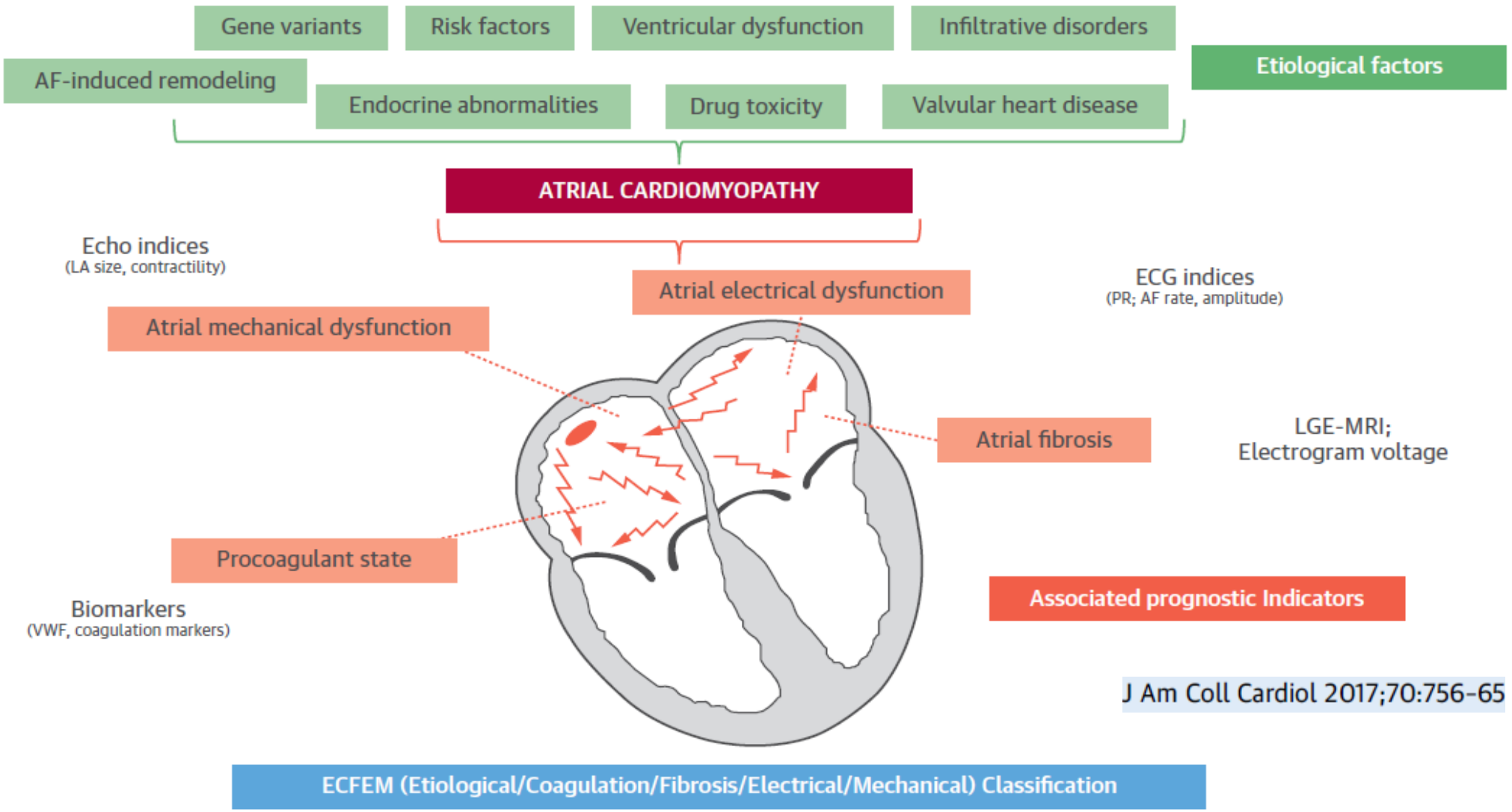
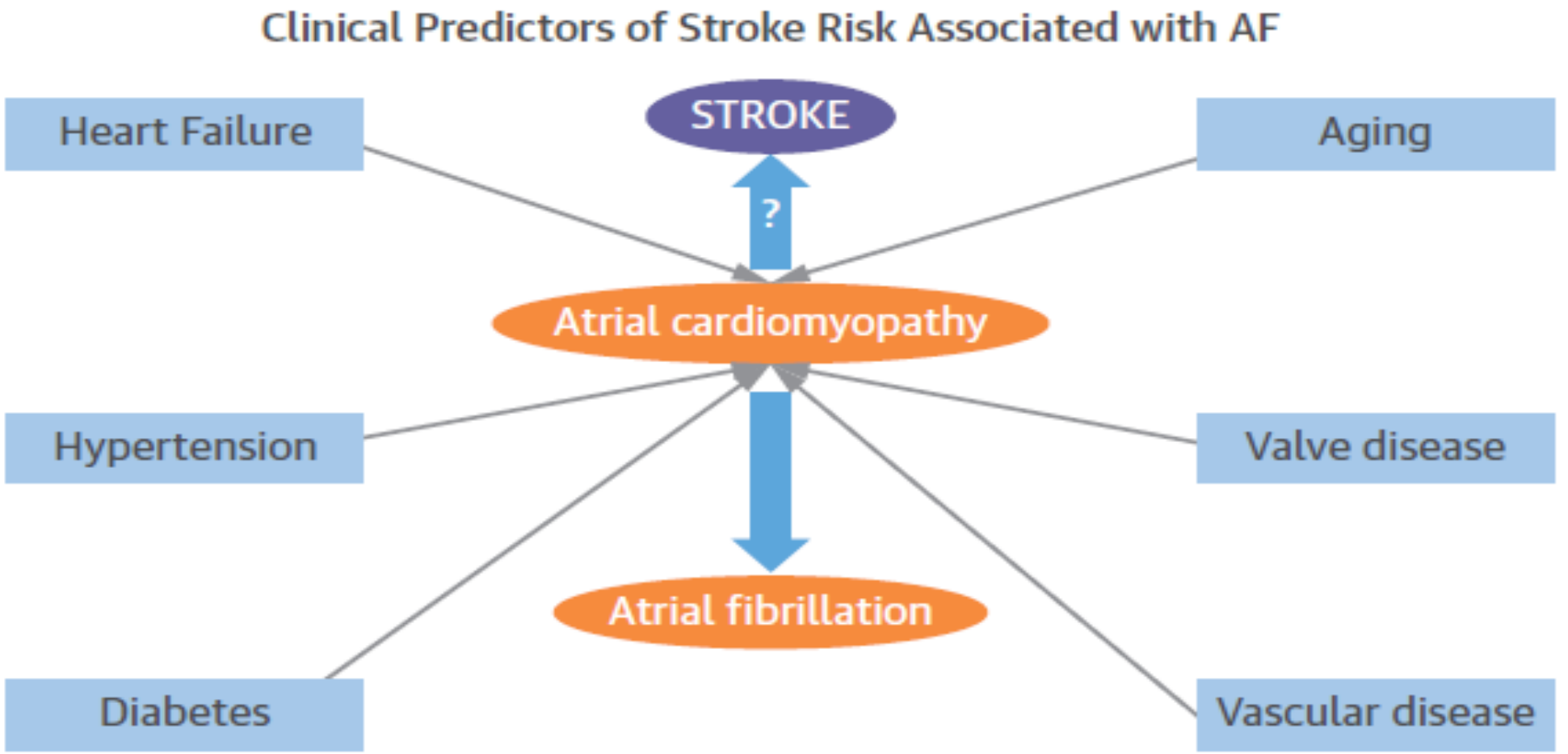
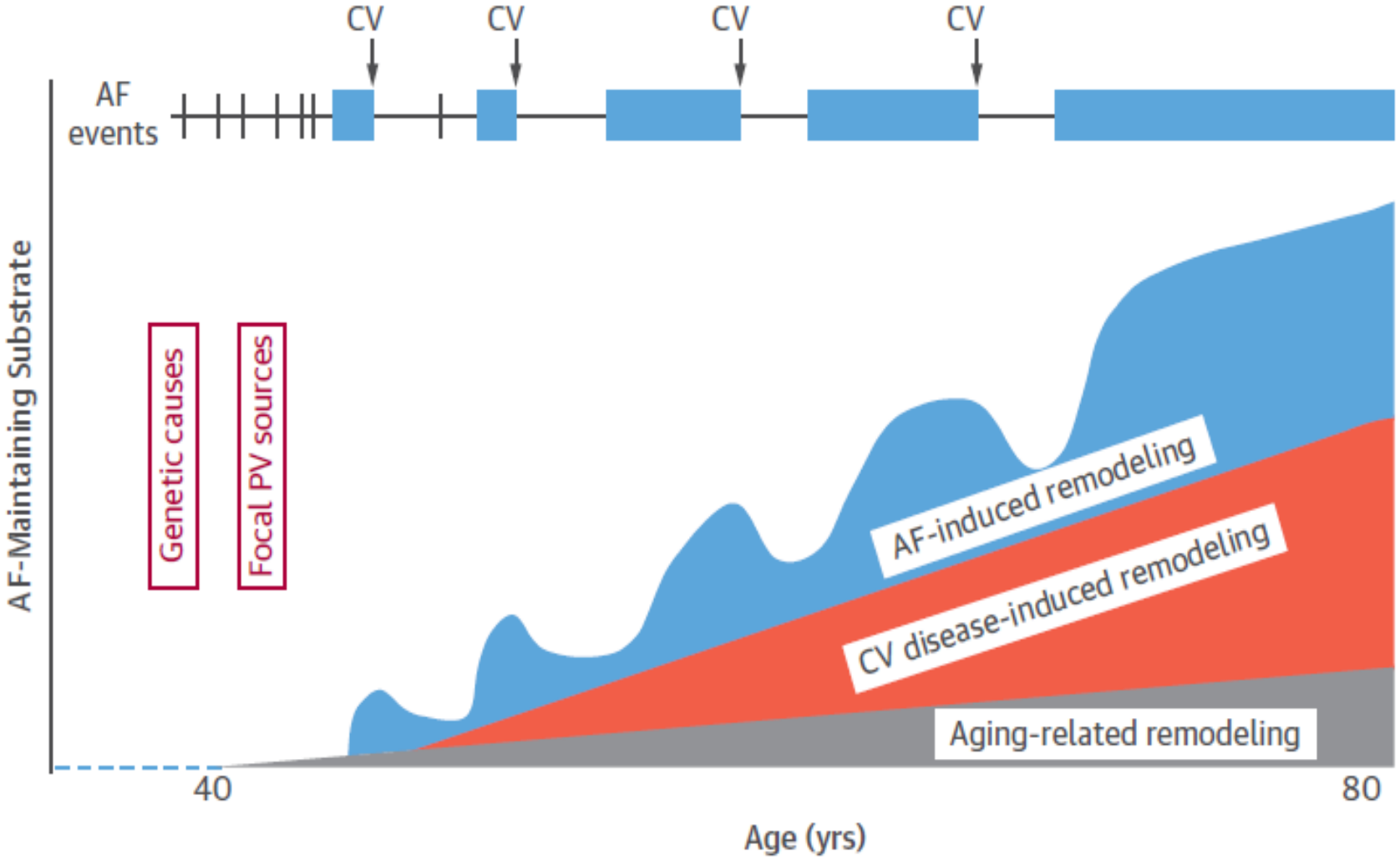


FIGURE 1 Clinical Predictors of Stroke Risk Incorporated in the $CHADS_2$ and CHA_2DS_2-VASc Schemes All-Cause Atrial Cardiomyopathy



J Am Coll Cardiol 2017;70:756-65

FIGURE 2 A Schematic Representation of the Natural History of AF



J Am Coll Cardiol 2017;70:756-65

Atrial cardiopathy: a mechanism of cryptogenic stroke

Shadi Yaghi, Hooman Kamel & Mitchell S.V. Elkind

Table: Atrial biomarkers and stroke

Cardiac biomarker	Association
Atrial Fibrillation	Associated with ischemic stroke and embolic infarcts
Atrial Cardiopathy Biomarkers	
Paroxysmal Supraventricular Tachycardia	Associated with ischemic stroke
Increase P-wave Terminal Force in V1	Associated with ischemic stroke, embolic stroke subtypes, and brain infarcts
Left Atrial Enlargement	Associated with ischemic stroke, embolic stroke subtypes, and brain infarcts
N-terminal pro b-type natriuretic peptide	Associated with ischemic stroke, cardioembolic stroke subtypes, and brain infarcts
High sensitivity cardiac troponin T	Associated with ischemic stroke and cardioembolic stroke subtypes
Left atrial appendage biomarkers in atrial fibrillation	
Left appendage morphology	Non-chicken wing morphology associated with ischemic stroke
Spontaneous echocardiographic contrast	Associated with ischemic stroke risk and embolic events
Reduced left atrial appendage flow velocity	Associated with ischemic stroke

Manuscript

P-Wave Terminal Force in Lead V_1 Predicts Paroxysmal Atrial Fibrillation in Acute Ischemic Stroke

Toshiaki Goda, MD, Yukio Sugiyama, MD, PhD, Nobuyu
Takeshi Ikegami, MD, Kotaro Watanabe, MD, Junya Kob
Daisuke Takahashi, MD

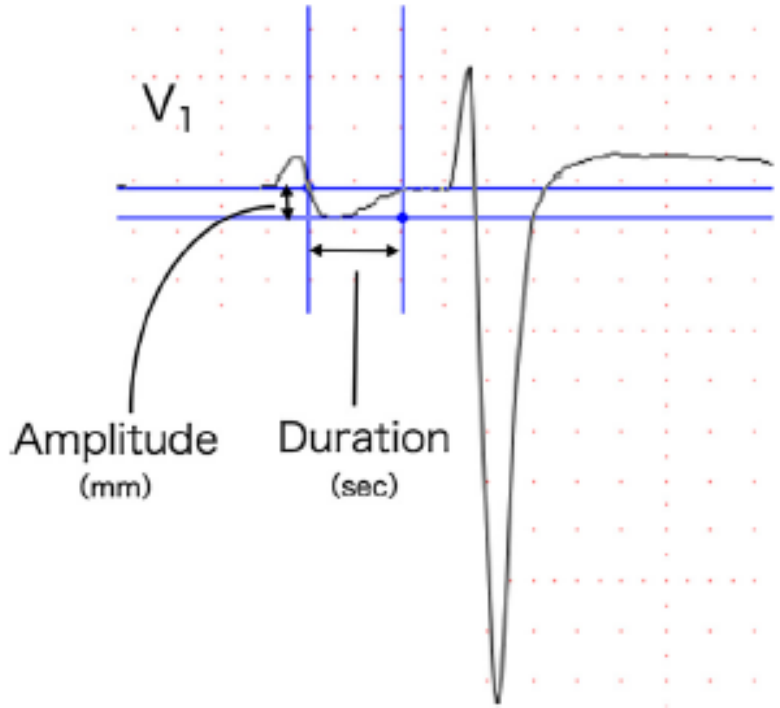


Figure 1. *Illustration of electrocardiogram parameters used to calculate P-wave terminal force in lead V_1 ($PTFV_1$). $PTFV_1$ is defined as the duration (in seconds) of the negative terminal deflection of the P-wave in lead V_1 multiplied by the absolute value of its amplitude (in millimeters).*

Journal of Stroke and Cerebrovascular Diseases, Vol. ■■, No. ■■ (■■), 2017

Atrial Cardiopathy and Cryptogenic Stroke: A Cross-sectional Pilot Study

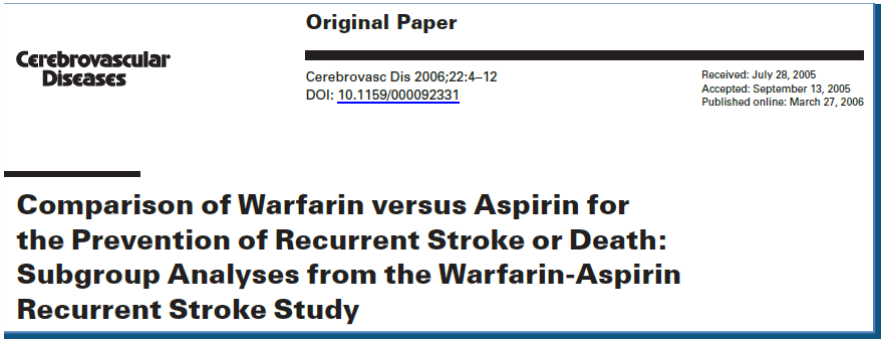
Shadi Yaghi, MD,* Amelia K. Boehme, PhD,†‡ Rebecca Hazan, MS,§
Eldad A. Hod, MD,‖ Alberto Canaan, BS,† Howard F. Andrews, PhD,‡
Hooman Kamel, MD,¶ Randolph S. Marshall, MD, MS,† and
Mitchell S. V. Elkind, MD, MS†

- 40 pazienti con stroke criptogenetico
  - 25 (63%) almeno un segno di cardiopatia atriale
    - 49% NT-proBNP elevato
    - 20% PTFV1 > 500 µVms
    - 5% severa dilatazione atriale

Journal of Stroke and Cerebrovascular Diseases, Vol. ■■, No. ■■ (■■), 2015:

- Profilassi secondaria specifica qualora si arrivi alla diagnosi eziopatogenetica
  - NAO/TAO se FA/flutter
  - Chiusura ± doppia o mono AP se FOP
  - DAPT nelle placche arco aortico
  - Ecc
- **Profilassi secondaria nei pazienti in cui non si abbia la diagnosi eziopatogenetica**
  - **AO vs AP?**

- Nessun RCT ha comparato:
  - AVK vs ASA
  - AVK vs DOAC
  - Doppia antiaggregazione vs mono-antiaggregazione



Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2006;22:4–12
DOI: 10.1159/000092331

Received: July 28, 2005
Accepted: September 13, 2005
Published online: March 27, 2006

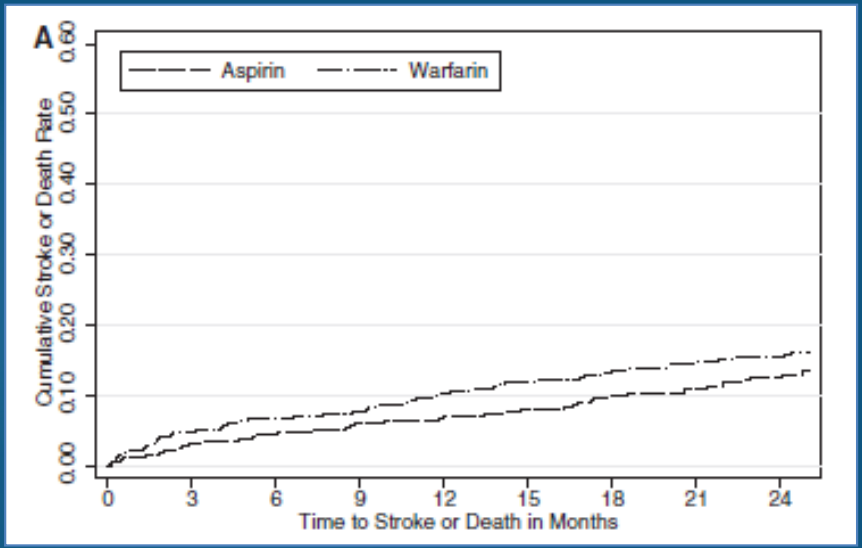
Comparison of Warfarin versus Aspirin for the Prevention of Recurrent Stroke or Death: Subgroup Analyses from the Warfarin-Aspirin Recurrent Stroke Study

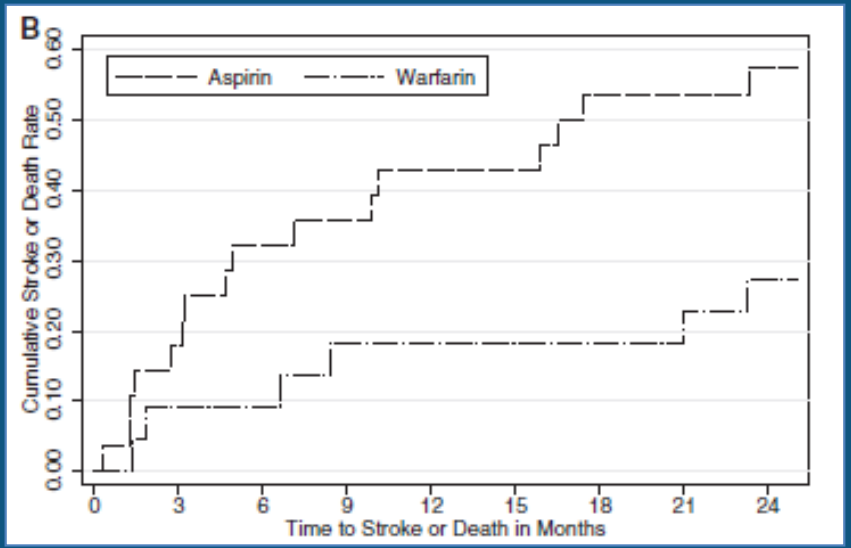
AVK INR 1.4-2.8
vs
ASA 325 mg

- 576 pz (26% del campione in studio) con stroke criptogenetico
  - **AVK meglio di ASA 325 mg:**
    - Stroke in pazienti senza storia di ipertensione arteriosa
  - **AVK peggio di ASA 325 mg**
    - Stroke di severità moderata
    - Stroke del circolo posteriore coinvolgenti il tronco-encefalo
  - **AVK=ASA**
    - Nel resto dei pazienti con stroke criptogenetico

Amino Terminal Pro–B-Type Natriuretic Peptide, Secondary Stroke Prevention, and Choice of Antithrombotic Therapy

W.T. Longstreth Jr, MD, MPH; Richard A. Kronmal, PhD; John L.P. Thompson, PhD; Robert H. Christenson, PhD; Steven R. Levine, MD; Rebecca Gross, BS; Robin L. Brey, MD; Richard Buchsbaum; Mitchell S.V. Elkind, MD, MS; David L. Tirschwell, MD, MSc; Stephen L. Seliger, MD, MS; J.P. Mohr, MD, MS; Christopher R. deFilippi, MD





Stroke. 2013;44:714-719.

Vitamin K antagonists versus antiplatelet therapy after transient ischaemic attack or minor ischaemic stroke of presumed arterial origin (Review)

Cochrane Database of Systematic Reviews 2012

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

Main results

We included eight trials with a total of 5762 participants. The data showed that anticoagulants (in any intensity) are not more efficacious in the prevention of recurrent ischaemic stroke than antiplatelet therapy (medium intensity anticoagulation: relative risk (RR) 0.80, 95% confidence interval (CI) 0.56 to 1.14; high intensity anticoagulation: RR 1.02, 95% CI 0.49 to 2.13).

There is no evidence that treatment with low intensity anticoagulation gives a higher bleeding risk than treatment with antiplatelet agents: RR 1.27 (95% CI 0.79 to 2.03). However, it was clear that medium and high intensity anticoagulation with vitamin K antagonists, with an INR of 2.0 to 4.5, were not safe because they yielded a higher risk of major bleeding complications (medium intensity anticoagulation: RR 1.93, 95% CI 1.27 to 2.94; high intensity anticoagulation: RR 9.0, 95% CI 3.9 to 21).

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

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

6.7. Antithrombotic Treatment

6.7. Antithrombotic Treatment	COR	LOE	New, Revised, or Unchanged
1. For patients with non-cardioembolic AIS, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events.	I	A	Recommendation reworded for clarity from 2014 Secondary Prevention. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.

Stroke. 2018;49:eXXX–eXXX. DOI: 10.1161/STR.0000000000000158.

REVIEW ARTICLE

Management of Embolic Stroke of Undetermined Sou

Tobias Geisler[1] · Annerose Mengel[2] · Ulf Ziemann[2] · Sven Poli[2]

Drugs 2018

NAVIGATE ESUS

terminated in October 2017 due to futility for the primary endpoint after enrolment of 7,214 patients

rivaroxaban 15 mg once daily

1:1 randomization, double-blinded

aspirin 100 mg once daily

primary endpoint: time to first recurrent stroke (ischemic, hemorrhagic, or unspecified), magnetic resonance imaging-positive transient ischemic attack, or systemic embolism

T. Geisler et al.

RE-SPECT ESUS

enrolment completed in December 2017 after randomization of 5,390 patients

dabigatran 150 mg twice daily

1:1 randomization, double-blinded

aspirin 100 mg once daily

primary endpoint: time to first recurrent stroke (ischemic, hemorrhagic, or unspecified)

ATTICUS

active, up to 600 patients with embolic stroke of undetermined source and additional risk factors for subclinical atrial fibrillation; continuous or daily ECG monitoring

apixaban 5 mg twice daily

1:1 randomization, open-label

aspirin 100 mg once daily

primary endpoint: new ischemic lesions on magnetic resonance imaging after 12 months

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

Rivaroxaban 15 mg vs ASA 100 mg

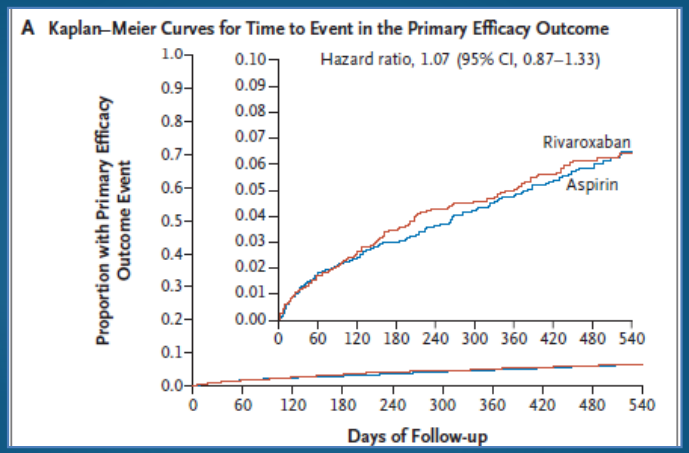


Table 2. Efficacy Outcomes.*

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)
Systemic embolism	1 (<0.1)	2 (0.1)	0.50 (0.05–5.51)
Any recurrent stroke, myocardial infarction, death from cardiovascular causes, or systemic embolism¶	207 (6.2)	195 (5.8)	1.06 (0.87–1.29)
Any disabling stroke	41 (1.2)	29 (0.8)	1.42 (0.88–2.28)
Myocardial infarction	17 (0.5)	23 (0.7)	0.74 (0.39–1.38)
Death from any cause	65 (1.9)	52 (1.5)	1.26 (0.87–1.81)
Death from cardiovascular causes¶	34 (1.0)	23 (0.7)	1.48 (0.87–2.52)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

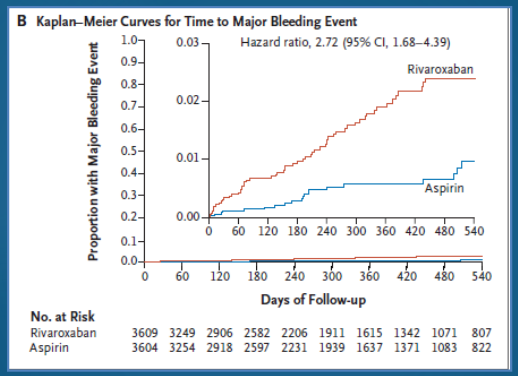


Table 3. Safety Outcomes.*

Outcome	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)	Hazard Ratio (95% CI)†	P Value
	no. of patients (annualized rate)			
Primary safety outcome: ISTH major bleeding‡	62 (1.8)	23 (0.7)	2.72 (1.68–4.39)	<0.001
Secondary safety outcomes				
Life-threatening or fatal bleeding	35 (1.0)	15 (0.4)	2.34 (1.28–4.29)	0.004
Clinically relevant nonmajor bleeding	118 (3.5)	79 (2.3)	1.51 (1.13–2.00)	0.004
Symptomatic intracranial hemorrhage§	20 (0.6)	5 (0.1)	4.02 (1.51–10.7)	0.003
Intracerebral hemorrhage	12 (0.3)	3 (0.1)	4.01 (1.13–14.2)	0.02
Subarachnoid hemorrhage¶	5 (0.1)	1 (0.0)	5.03 (0.59–43.0)	0.10
Subdural or epidural hematoma¶	3 (0.1)	2 (0.1)	1.51 (0.25–9.02)	0.65

Bienvenue / Welcome
11TH WORLD STROKE CONGRESS
MONTREAL, CANADA | OCTOBER 17-20, 2018
CME/CPD: Earn up to 27 Section 1 credits
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Abstract Details

Session title: OPENING: LATE-BREAKING TRIALS
Session type: PLENARY SESSION
Presentation number:

★ Abstract title:

RE-SPECT ESUS: DABIGATRAN VERSUS ACETYLSALICYLIC ACID FOR STROKE PREVENTION IN PATIENTS WITH EMBOLIC STROKE OF UNDETERMINED SOURCE

H. Diener[1], R. Sacco[2], J. Easton[3], C. Granger[4], L. Cronin[5], C. Grauer[6], D. Cotton[7], M. Brueckmann[8].

Table: Key Baseline Patient Characteristics:

Number of patients, n	5386
Mean age, yrs (SD)	66.2 (11.4)
Female, %	37
Median time to study entry, days	44
CHA_2DS_2-VASc scores, mean (SD)	4.3 (1.3)
TIA or stroke prior to index event, %	18
History of hypertension, %	74
Diabetes mellitus, %	23
Patent foramen ovale, %	13

SD, standard deviation; TIA, transient ischemic attack.

Embolic Stroke of Undetermined Source

A Systematic Review and Clinical Update

Robert G. Hart, MD; Luciana Catanese, MD; Kanjana S. Perera, MBBS; George Ntaios, MD, PhD; Stuart J. Connolly, MD

Stroke. 2017;48:867-872.

Table 4. Prognosis of ESUS Patients*

Study	n/Mean Follow-Up (y)	Mean Age, y	Antithrombotic Therapy	AF During Follow-Up†	Stroke (Est Annualized Rate)†	Stroke, MI, Vascular Death (Est Annualized Rate)	Total Mortality (Est Annualized Rate)
Ntaios et al[13,26]‡	275 (3.2)	68	74% APT only, 22% OAC	80 (29%)	6.8%/y	9.0%/y§	8.2%/y
Li et al[15]	189 (1)	65	NR	NR	≈5%/y	NR	NR
Putaala et al[16]‡	46 (1.8)	62	85% APT, 11% OAC	NR	5.1%/y	NR	1.3%/y
Ntaios et al[24]‡	1095 (3.0)	68	87% APT only, 12% OAC	NR	4.8%/y‖	NR	4.5%/y
Masina et al[12]¶	84 (2.1)	73	99% APT	NR	2.3%/y	NR	NR
Ueno et al[22]#	177 (3.5)	64	72% APT, 29% OAC	NR	3.9%/y	5.0%/y**	1.3%/y
Arauz et al[23]††	149 (2.3)	44	91% APT, 5% OAC	NR	2.3%/y	NR	0%/y
Pooled – unweighted average‡,††	1545 (2.4)	68	87% APT, 12% OAC	…	4.0%/y	…	2.9%/y
Pooled – weighted average‡,††	1605 (2.7)	65	86% APT, 13% OAC	…	4.5%/y	…	3.9%/y

Stroke ischemico criptogenetico
Area Stroke Empoli (analisi su 10 mesi)

Numero	46
Antiaggreganti	80.3%
Mono	69.5%
Doppia	10.8%
Anticoagulanti	19.7%
NAO	13%
TAO	4.5%
EBPM dosaggio anticoagulante	2.2%

Protocol

International Journal of Stroke WSO

The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: Rationale and methods

International Journal of Stroke
0(0) 1–8
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DOI: 10.1177/1747493018799981
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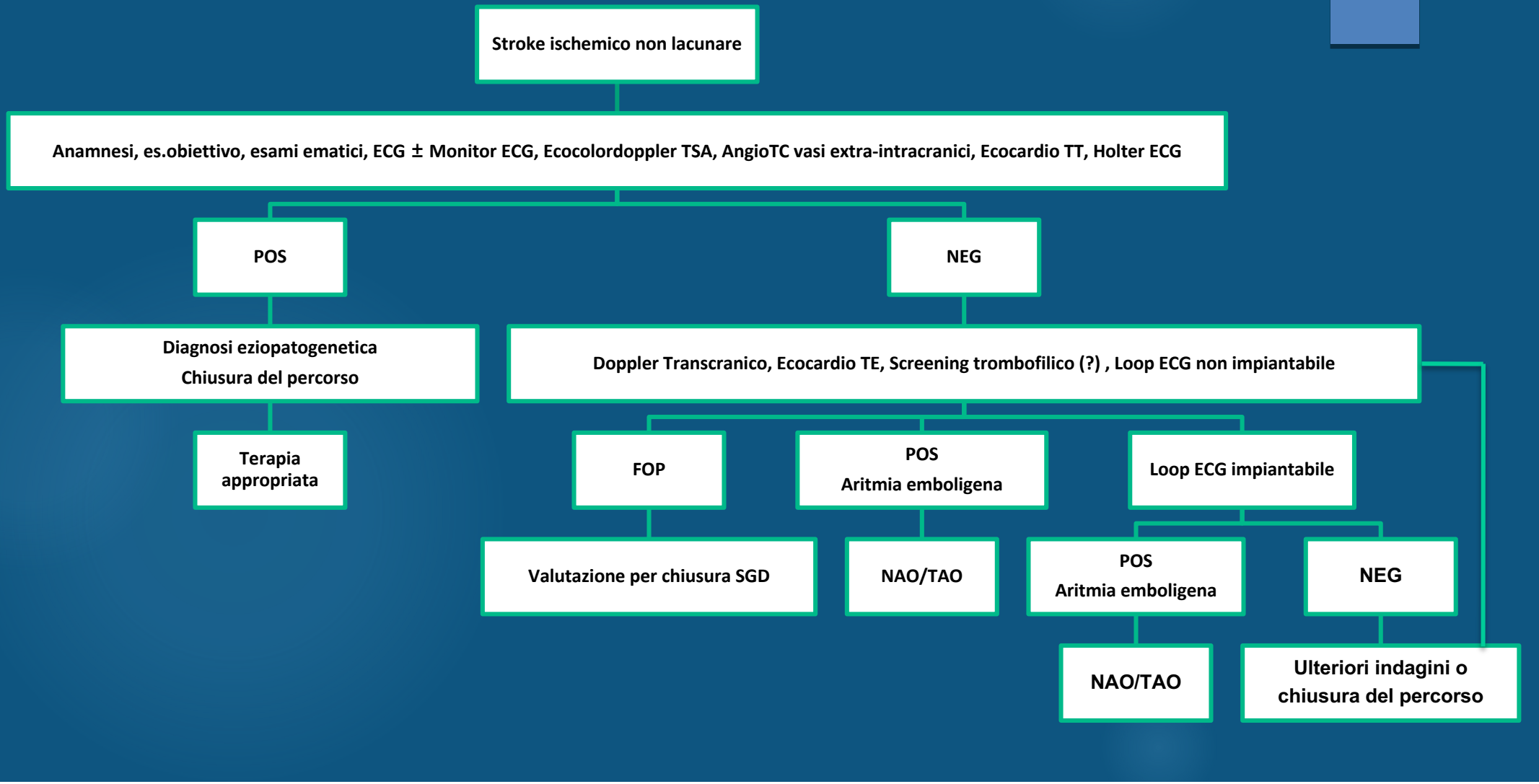
SAGE

Participants are randomly assigned to either active apixaban and placebo aspirin, or active aspirin and placebo apixaban. Those assigned to active apixaban receive a standard dose of apixaban 5 mg orally twice daily, except that participants who meet two or more of the standard dose-adjustment criteria (age $\geq$ 80 years, weight $\leq$ 60 kg, or creatinine $\geq$ 1.5 mg/dL) receive apixaban 2.5 mg orally twice daily. Those assigned to active aspirin receive a dose of 81 mg orally once daily. Both

- $PTFV_1 > 5000\,\mu V \times ms$ on 12-lead ECG;
- Serum NT-proBNP > 250 pg/mL;
- Left atrial diameter index $\geq 3\,cm/m^2$ on echocardiogram.

Percorso interno Ospedale San Giuseppe Empoli



Take home messages

- ESUS è una condizione frequente
- La gestione appropriata richiede uno sforzo organizzativo non indifferente che va oltre il percorso diagnostico effettuato durante la degenza ospedaliera e che implica necessariamente la presa in carico del paziente ed il suo follow-up
- Ad oggi non ci sono dimostrazioni di superiorità della terapia anticoagulante su quella antiaggregante
- Diventa fondamentale la personalizzazione della terapia sulla base delle caratteristiche del paziente
- In alcuni pazienti può essere ragionevole il trattamento anticoagulante (ad oggi AVK)
- I tempi per la realizzazione di un PDTA aziendale sono ormai maturi