Attualità in tema di ESUS

Carmelo Labate
SS Stroke Unit
SC Neurologia
AO Ordine Mauriziano
Torino

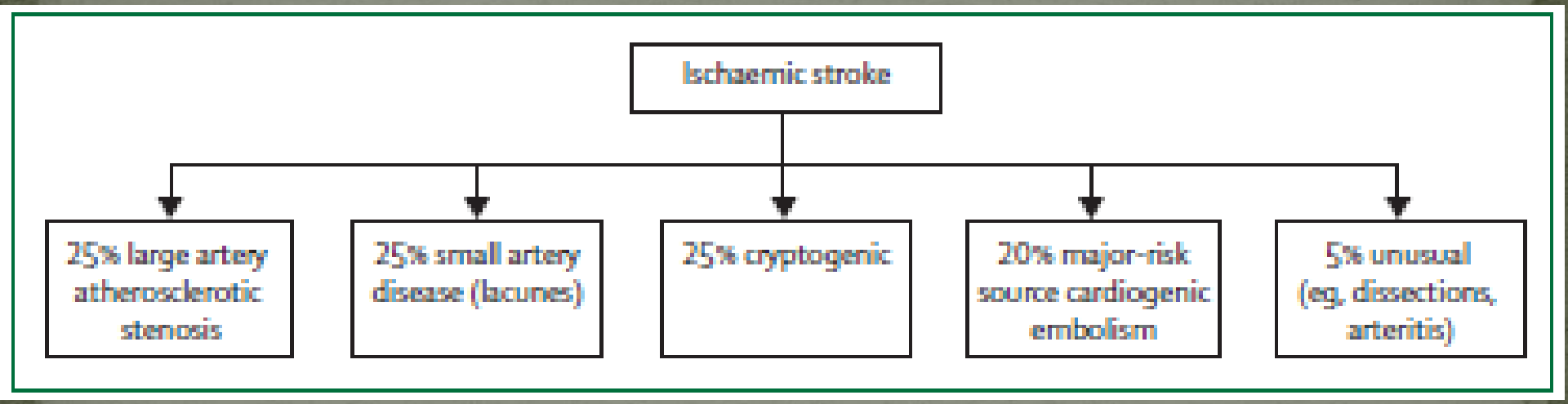
Personal View

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

Lancet Neurol 2014; 13: 429–38

ESUS


Ischaemic stroke
25% large artery atherosclerotic stenosis
25% small artery disease (lacunes)
25% cryptogenic
20% major-risk source cardiogenic embolism
5% unusual (eg, dissections, arteritis)

Un po' di storia…

- 1993: Trial of Org 10172 in Acute Stroke Treatment (TOAST)
- Ictus criptogenetico:
  - causa dello stroke non nota,
  - incompleto workup diagnostico,
  - più di una possibile causa

- Scarsamente utilizzato nei trials clinici
- Ictus criptogenetico 25%
- Non specifiche indicazioni terapeutiche derivate da studi randomizzati
- Terapia antiaggregante indicata da LG

Ictus criptogenetico: trials clinici

- WARSS (sottogruppo): ASA (325) versus TAO (INR 1,4-2,8)
  - Endpoint primario (Stroke o morte a 2 anni) nel 15% TAO e 16,5% in ASA
- ESPRIT : Arteriogenic ischemic stroke (non limitato ai criptogenetici); ASA versus TAO (INR 2,6)
  - Riduzione del 24% nel gruppo TAO (non statisticamente significativo)
- ARCH: Placche aortiche > 4 mm (ASA+ Clopid versus TAO (INR 2-3)
  - Non differenze significative tra i due gruppi
- WARCEF: ASA versus TAO in pazienti con riduzione della frazione cardiaca di eiezione

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- Definizione clinica pragmatica
- Ipotesi embolica
- Base per futuri trials randomizzati per individuare la migliore prevenzione secondaria

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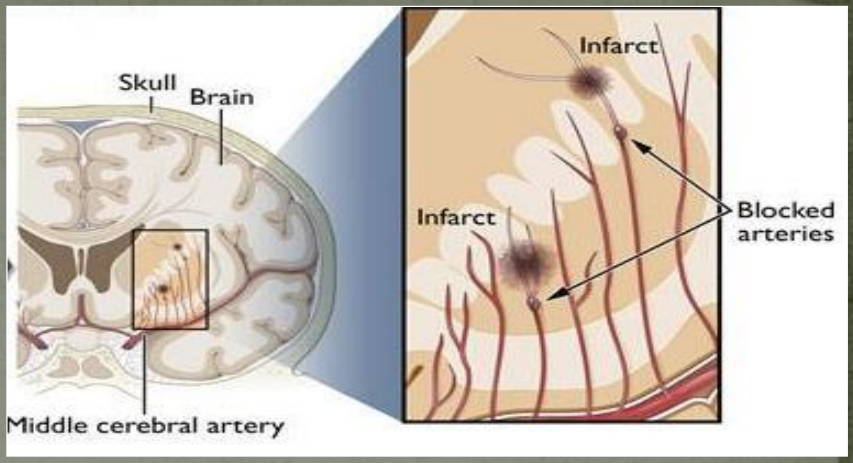
Panel 2: Criteria for diagnosis of embolic stroke of undetermined source*

- 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 ischaemia
- No major-risk cardioembolic source of embolism‡
- No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse)

*Requires minimum diagnostic assessment (panel 3). †Lacunar defined as a subcortical infarct smaller than or equal to 1·5 cm (≈2·0 cm on MRI diffusion images) in largest dimension, including on MRI diffusion-weighted images, and in the distribution of the small, penetrating cerebral arteries; visualisation by CT usually needs delayed imaging greater than 24–48 h after stroke onset. ‡Permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction less than 30%, valvular vegetations, or infective endocarditis.

ICTUS LACUNARE

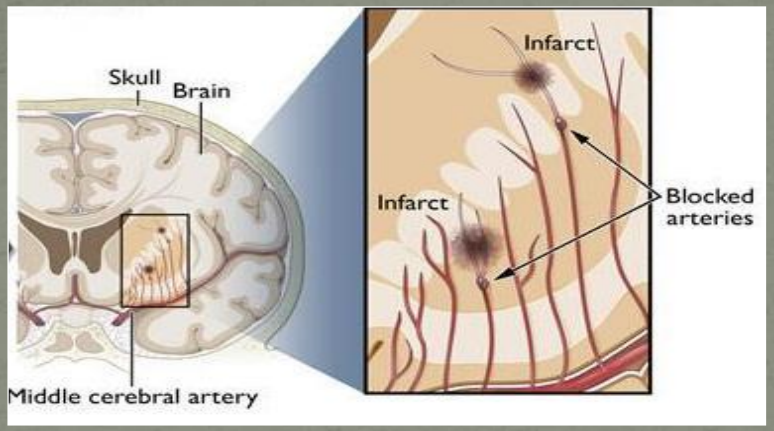


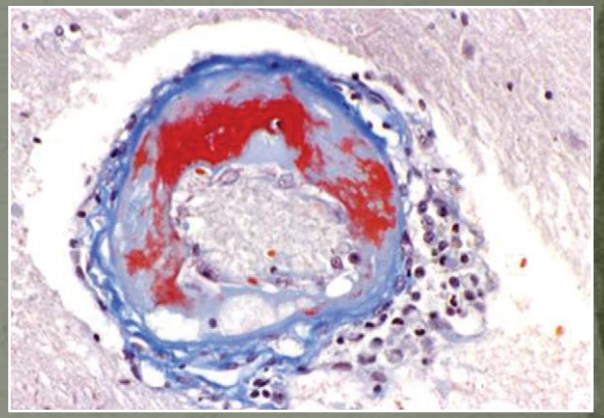
- 25% circa degli ictus ischemici
- Dal latino *lacuna,ae* “spazio vuoto”

  Infarto cerebrale sottocorticale profondo, di piccole dimensioni

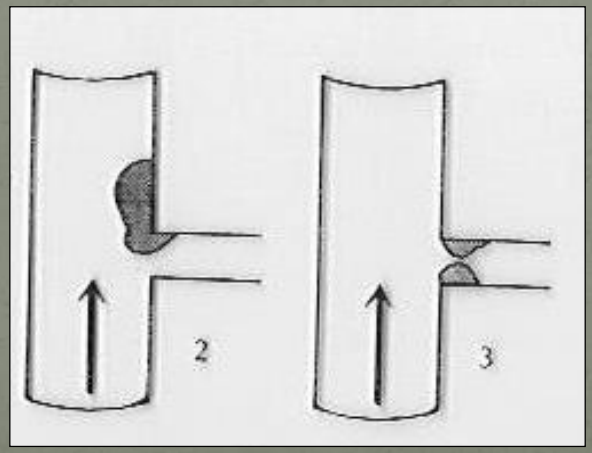
  (≤ 1.5 cm di diametro, 2 cm in diffusione RMN), localizzato prevalentemente a livello dei gangli della base, del talamo, capsula interna, corona radiata e del tronco encefalo e determinato dall’occlusione di un’arteria perforante
- Studi clinicopatologici di CM Fisher (1960-1980) sono stati fondamentali per le attuali conoscenze su questa patologia

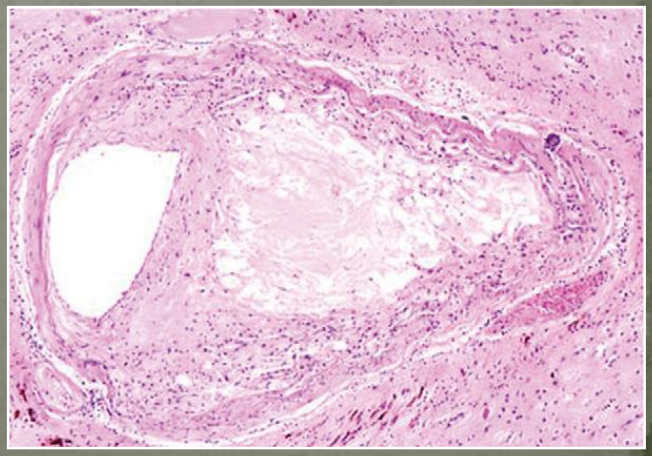
Lipoialinosi





Microateroma





views &reviews

NEUROLOGY 1989;39:1246-125

Intracranial branch atheromatous disease:

A neglected, understudied, and underused concept

Louis R. Caplan, MD

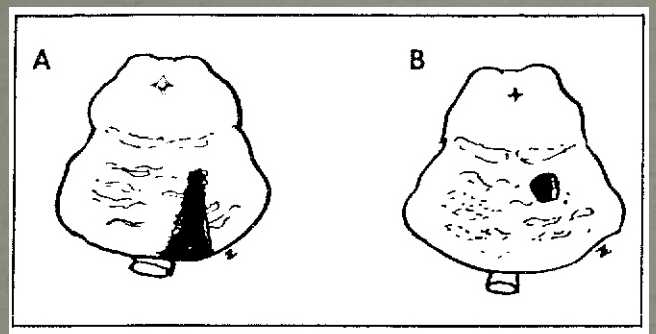
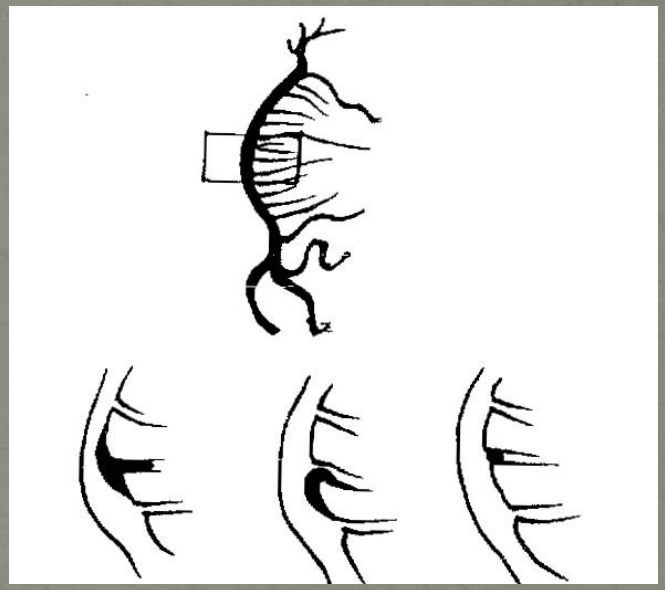


Figure 3. (A) Infarct of pons extending to basal surface due to atherosclerotic branch disease. (B) Lacune in pons due to lipohyalinosis.

A) infarto esteso alla superficie basale del ponte,conseguente a "branch atheromatous disease"

B) infarto distale caratterizzato da isola di tessuto ischemico nel parenchima cerebrale conseguente a lipoialinosi (B)



Ateroma murale

Ateroma giunzionale

Microateroma

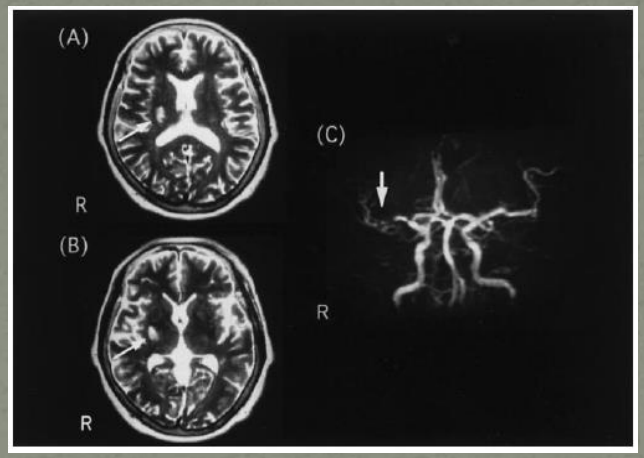
J Neurol (2000) 247 : 280–285

ORIGINAL COMMUNICATION

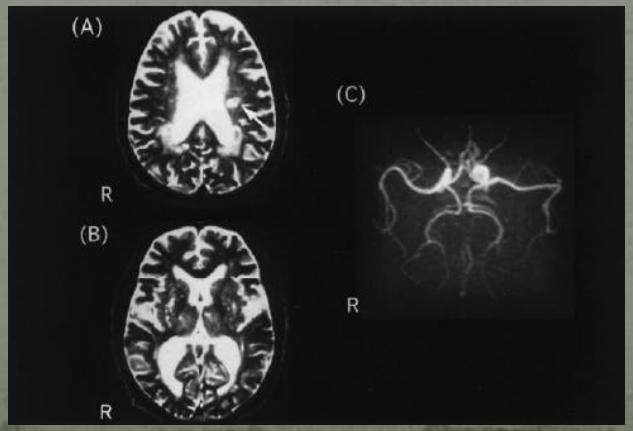
Tomohide Adachi
Shotai Kobayashi
Shuhei Yamaguchi
Kazunori Okada

MRI findings of small subcortical "lacunar-like" infarction resulting from large vessel disease

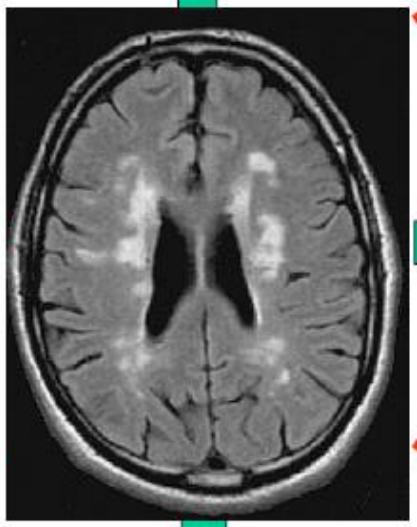
Infarto lacunar-like da stenosi MCA. Scarsi segni di malattia di piccoli vasi



Infarto lacunare puro, accompagnato da infarti lacunari silenti e iperintensità sostanza bianca, no stenosi MCA



Cause rare di infarto lacunare



- Sneddon
- Omocistinuria
- Vasculite
- Pseudoxantoma elasticum
- Mal di Fabry
- Sindrome da APS
- Altre …
- CADASIL

ESUS

Panel 2: Criteria for diagnosis of embolic stroke of undetermined source*

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ESUS

- Fonti cardioemboliche:
  - FA permanente o parossistica
  - Flutter atriale
  - Trombo intracardiaco
  - Valvole cardiache meccaniche
  - Mixoma atriale o altri tumori cardiaci
  - Stenosi mitralica
  - Recente (< 4 sett) infarto cardiaco
  - Frazione di eiezione ventricolo sn < 30%
  - Vegetazioni valvolari
  - Endocardite infettiva

ESUS

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Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source*

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

*Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder. †Cardiac telemetry is not sufficient.

ESUS: caratteristiche

Hart	Global Registry	Atene registry
30%	16-19% (14% non definito)	10% (13% non definito)
Età media 70	Età media 62	Età media 68
45% donne	43% donne	36% donne
66 % ipertesi	64 % ipertesi	64 % ipertesi
35% Diabetici	25% Diabetici	23,6% Diabetici
30% pregresso Stroke	17% Pregresso Stroke	10% pregresso TIA
Ricorrenza 3-6% per anno		5 % per anno

ESUS: frequenza e prognosi

- Tasso di Recidiva ictale del 11,3%
- Riscontro successiva di Fibrillazione atriale nel 29,1%

Panel 4: Comparison of cryptogenic stroke versus embolic stroke of undetermined source

Diagnostic criteria

*Cryptogenic ischaemic stroke**

- No arterial stenosis (>50%) or occlusion coupled with non-lacunar infarct on imaging
- No clinical lacunar syndrome if imaging shows no infarct or small (<1·5 cm) subcortical infarct
- No major-risk or medium-risk cardioembolic sources

Embolic stroke of undetermined source (ESUS)

- Non-lacunar brain infarct on imaging
- Open arteries (<50% stenosis) proximal to the infarct
- No major-risk cardioembolic source

Necessary diagnostic assessment

*Cryptogenic ischaemic stroke**

Not specified†

Embolic stroke of undetermined source (ESUS)

- Brain CT or MRI showing non-lacunar infarct
- Precordial echocardiography
- ECG and cardiac monitoring for ≥24 h
- Imaging of the extracranial and intracranial arteries supplying the area of the brain infarct

Limitations

*Cryptogenic ischaemic stroke**

- Inclusion of variable fraction of lacunar infarcts and intracranial arterial stenosis dependent on extent of diagnostic assessment (varies from study to study, and usually not described in detail)

Embolic stroke of undetermined source (ESUS)

- Transoesphageal echocardiography not recommended, and hence aortic arch atherosclerosis not characterised

ECG=electrocardiogram. *Criteria for cryptogenic stroke are not standardised; TOAST criteria for stroke of undetermined cause are considered here, excluding those with two or more potential causes.[28] †Some patients will have no likely cause established despite an extensive assessment. In others, no cause is found but the assessment was cursory.[28] In most studies of cryptogenic stroke, the extent of diagnostic imaging is not reported.

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.

ESUS

Panel 1: Causes of embolic strokes of undetermined source

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Covert paroxysmal atrial fibrillation

ESUS: FAP

- ECG
- Monitoraggio intraospedaliero
- ECG Holter
- Loop recorder esterno (fino a 30 gg)
- Mobile Cardiac Outpatient Telemetry (MCOT)
- Devices cardiaci elettronici impiantabili (pacemakers o defibrillatori)
- Loop recorder impiantabile

ESUS: FAP

- Clinical risk score

TABLE 3 | Clinical risk score.

STAF Score	Points
Suissa et al. (2009)	
Age >62 years	2
NIHSS Score ≥8	1
Left atrial dilatation	2
Absence of vascular etiology*	3
Interpretation	
Score ≥5 = sensitivity 89%, specificity 88%	
Fujii et al. (2013)	
Mitral valve disease	1
NIHSS Score ≥8	1
Left atrial dilatation (>3.8 cm)	1
BNP ≥ 144 pg/ml	2
Interpretation	
Score ≥3 = sensitivity 78%, specificity 83%	

ESUS: FAP

- Alterazioni ritmo all'ECG Holter (> 70 battiti atriali prematuri per 24 h)

- Durata della FA?

ESUS

Cancer-associated

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Arco aortico

Original Paper

Cerebrovascular Diseases

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Received: May 22, 2012
Accepted: January 2, 2013
Published online: April 9, 2013

Aging, Aortic Arch Calcification, and Multiple Brain Infarcts Are Associated with Aortogenic Brain Embolism

Yoshiaki Shimada[a] Yuji Ueno[a, b] Yasutaka Tanaka[a, b] Ayami Okuzumi[a]
Nobukazu Miyamoto[a] Kazuo Yamashiro[a] Ryota Tanaka[a] Nobutaka Hattori[a]
Takao Urabe[a, b]

[a]Department of Neurology, School of Medicine, and [b]Department of Neurology, Urayasu Hospital, Juntendo University, Tokyo, Japan

Arco aortico

Table 4. The CAM score criteria

Variables		Feature	Score
C	Calcification of aortic arch on chest X-ray	grade 0 grade 1 grade 2 grade 3	0 1 2 3
A	Age, years	<70 ≥70	0 1
M	MRI findings: number of infarcts and VTs	single lesion multiple lesions in 1 large vessel multiple lesions in 2 large vessels multiple lesions in more than 3 large vessels	0 1 2 3
The maximum total score is 7 points.			

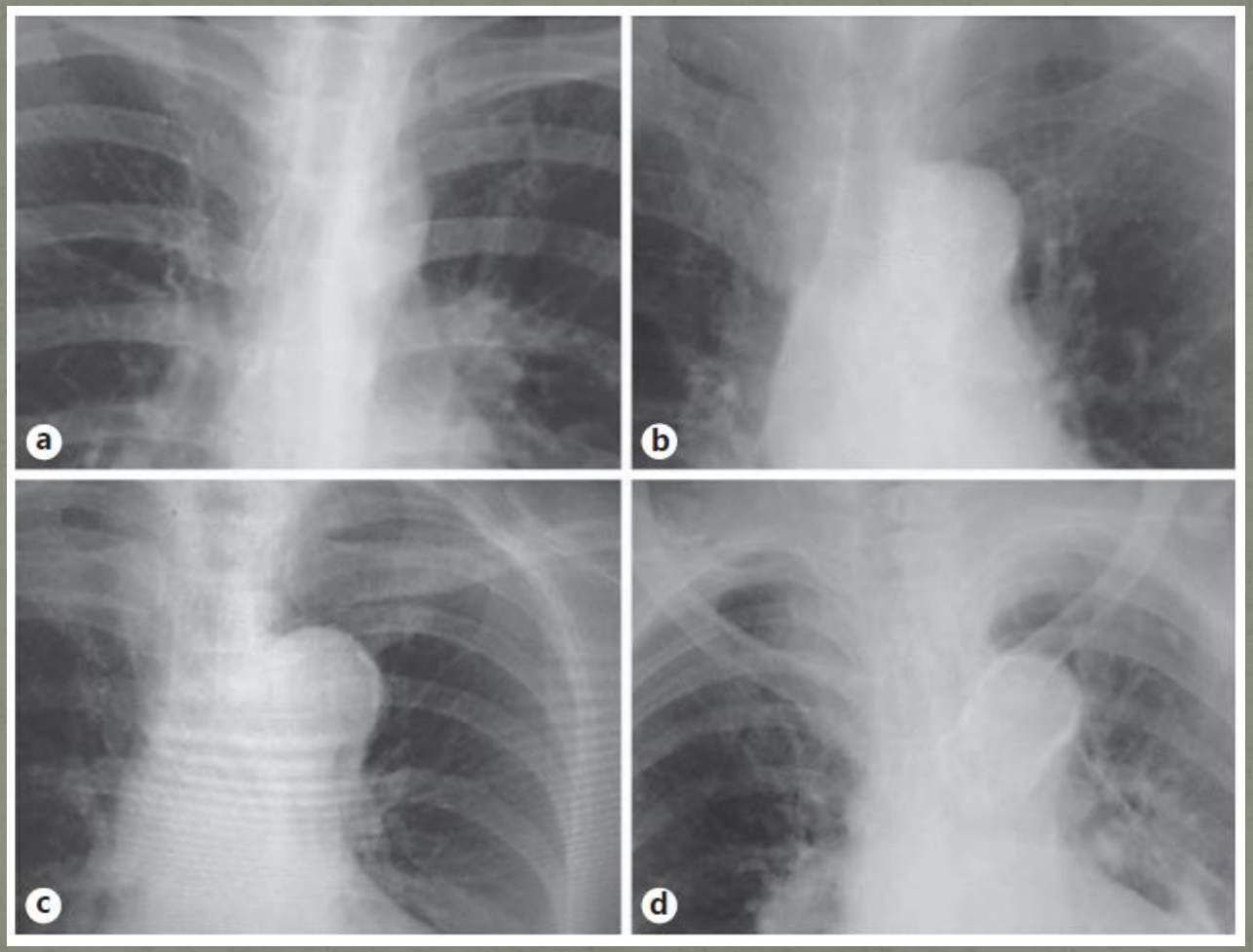
Arco aortico

Table 5. Adjusted ORs for MUAPs by their CAM score

CAM score	OR	95% CI	p
0	1 (reference)	1 (reference)	–
1–2, low risk	1.79	0.77–4.14	0.175
3–4, medium risk	7.68	2.89–20.44	<0.001
5–7, high risk	20.63	5.12–83.06	<0.001

Adjusted for vascular risk factors, laboratory findings, and MRI findings except for age, AoAC, and infarct patterns which are variables of the CAM score.

Arco aortico



ESUS

Cancer-associated

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Carotidopatia

Journal of Neurosurgery
Jan 2016 / Vol. 124 / No. 1 / Pages 27-42

Contemporary carotid imaging: from degree of stenosis to plaque vulnerability

Waleed Brinjikji, MD[1], John Huston III, MD[1], Alejandro A. Rabinstein, MD[2], Gyeong-Moon Kim, MD[3], Amir Lerman, MD[4], and Giuseppe Lanzino, MD[5]

Departments of [1]Radiology, [2]Neurology, [4]Cardiovascular Diseases, and [5]Neurosurgery, Mayo Clinic, Rochester, Minnesota; and [3]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Carotidopatia

- Dal grado di stenosi alla vulnerabilità di placca
  - Emorragia intraplacca
  - Ulcerazione
  - Neovascolarizzazione
  - Spessore cappuccio fibroso
  - Presenza di Core necrotico lipidico

Carotidopatia

- RMN (Ulcerazione, emorragia, core necrotico, infiammazione)
- CT (Ulcerazione, calcificazione)
- PET (infiammazione)
- Ultrasuoni (morfologia di placca)

- MES

Risk Factors Associated With Cerebrovascular Recurrence in Symptomatic Carotid Disease: A Comparative Study of Carotid Plaque Morphology, Microemboli Assessment and the European Carotid Surgery Trial Risk Model

Nishath Altaf, PhD, FRCS; Neghal Kandiyil, MRCS; Akram Hosseini, MRCP; Rajnikant Mehta, MSc; Shane MacSweeney, MChir, FRCS; Dorothee Auer, PhD

ORIGINAL ARTICLE

Carotid Plaque Hemorrhage on Magnetic Resonance Imaging Strongly Predicts Recurrent Ischemia and Stroke

Akram A. Hosseini, MRCP, MD,[1] Neghal Kandiyil, MRCS,[1,2] Shane T. S. MacSweeney, FRCS, MChir,[2] Nishath Altaf, FRCS, PhD,[1,2] and Dorothee P. Auer, FRCR, PhD[1]

Carotidopatia

- Identificazione placche a rischio in cui terapia medica non efficace
- Tipo di placca per indicazione a CAS versus CEA

Carotidopatia

- ECST 2:
  - Ipotesi: Best medical treatment (antiaggreganti Clopidogrel or ASA+ dypiradomole, statine, terapia antipertensiva, modifica fattori di rischio) è efficace quanto BMT + intervento di vascolarizzazione in pazienti con stenosi asintomatica o basso-medio rischio

ESUS

Cancer-associated

- Covert non-bacterial thrombotic endocarditis
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- Patent foramen ovale
- Atrial septal defect
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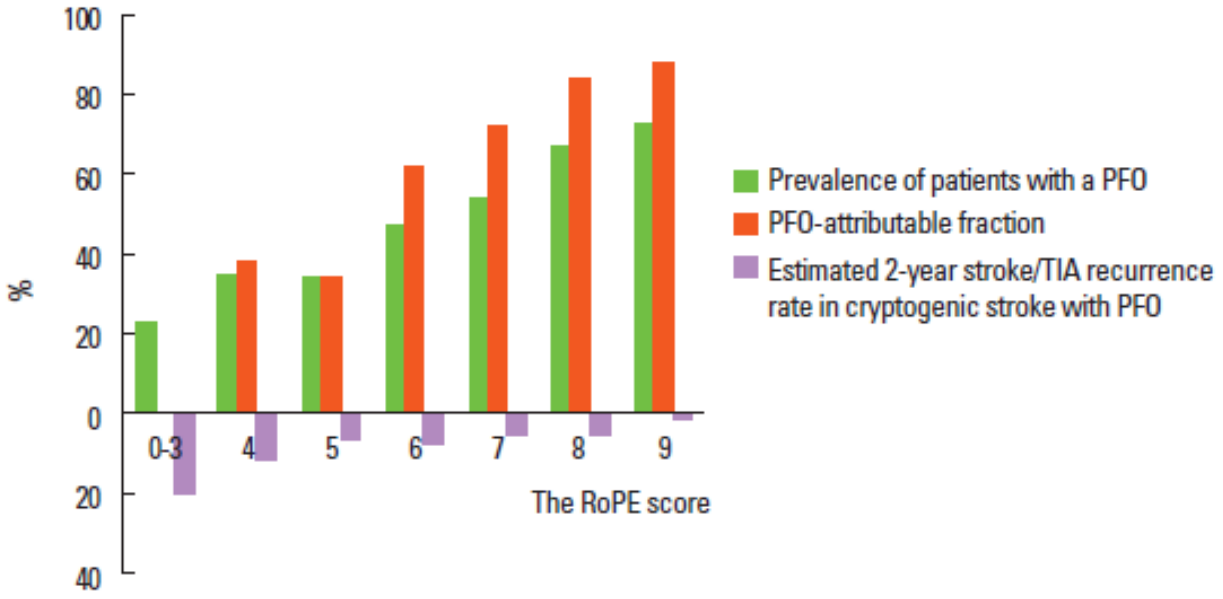
ESUS: PFO

- 25% popolazione generale
- Fattori associati a rischio di ricorrenza di stroke:
  - Shunt dx-sn evidenziabile in condizioni di riposo
  - Numero di microbolle durante Valsalva
  - Associazione tra PFO e aneurisma del setto interatriale
  - Aumentata mobilità del setto interatriale
- In 1/3 dei pazienti con ESUS incidentale/non patogenetica

PFO: RoPE score

Characteristics	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or TIA	1
Nonsmoker	1
Cortical infarct on imaging	1
Age (year)	
18-29	5
30-39	4
40-49	3
50-59	2
60-69	1
≥ 70	0
Maximum score	10



Neuroimaging Findings in Cryptogenic Stroke Patients With and Without Patent Foramen Ovale

David E. Thaler, MD, PhD; Robin Ruthazer, MPH; Emanuele Di Angelantonio, MD, MSc; Marco R. Di Tullio, MD; Jennifer S. Donovan, MS; Mitchell S.V. Elkind, MD, MS; John Griffith, PhD; Shunichi Homma, MD, FACC; Cheryl Jaigobin, MD, FRCP, MSc; Jean-Louis Mas, MD; Heinrich P. Mattle, MD; Patrik Michel, MD; Marie-Luise Mono, MD; Krassen Nedeltchev, MD, FESC; Federica Papetti, MD; Joaquín Serena, MD, PhD; Christian Weimar, MD; David M. Kent, MD, CM, MSc

(*Stroke*. 2013;44:675-680.)

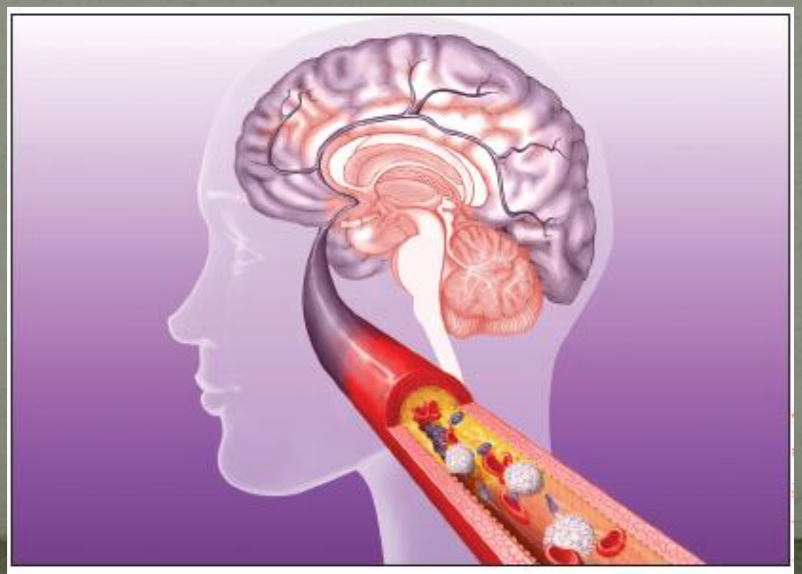
Table 4. PFO Prevalence by Presence or Absence of Radiological Variables

	All			
Variable	Total, n	% With PFO	Adjusted Odds Ratio	*P* Value
Index stroke large				
No	681	37		
Yes	1290	43	1.36	0.0025
Index stroke seen				
No	265	36		
Yes	2040	43	1.53	0.003
Superficial location				
No	779	37		
Yes	1018	48	1.54	<0.0001
Multiple index strokes				
No	1601	41		
Yes	278	43	1.21	0.1614
Prior stroke				
No	1547	43		
Yes	592	33	0.66	<0.0001

Odds ratios and *P* values are adjusted for site as a random effect.
PFO indicates patent foramen ovale.

ESUS critiche

- Non necessariamente embolico (trombosi in situ)
- Criteri diagnostici
- Denominazione “Stroke non lacunare senza causa definita”
- Fonte embolica arteriosa (esclusione stenosi > 50% non trattati chirurgicamente)



Trials in corso

Protocol

Design of Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS)

Hans-Christoph Diener[1*], J. Donald Easton[2], Christopher B. Granger[3], Lisa Cronin[4], Christine Duffy[5], Daniel Cotton[5], Martina Brueckmann[6,7], Ralph L. Sacco[8] on behalf of the RE-SPECT ESUS Investigators

Trials in corso

Protocol

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Rivaroxaban for secondary stroke prevention in patients with embolic strokes of undetermined source: Design of the NAVIGATE ESUS randomized trial

Robert G Hart[1], Mukul Sharma[1], Hardi Mundl[2], Ashkan Shoamanesh[1], Scott E Kasner[3], Scott D Berkowitz[4], Guillaume Pare[1], Bodo Kirsch[5], Janice Pogue[6], Calin Pater[7], Gary Peters[8], Antoni Davalos[9], Wilfried Lang[10], Yongjun Wang[11], Yilong Wang[11], Luis Cunha[12], Jens Eckstein[13], Turgut Tatlisumak[14], Nikolay Shamalov[15], Robert Mikulik[16], Pablo Lavados[17], Graeme J Hankey[18], Anna Czlonkowska[19], Danilo Toni[20], Sebastian F Ameriso[21], Rubens J Gagliardi[22], Pierre Amarenco[23], Daniel Bereczki[24], Shinichiro Uchiyama[25], Arne Lindgren[26], Matthias Endres[27], Raf Brouns[28], Byung-Woo Yoon[29], George Ntaios[30], Roland Veltkamp[31], Keith W Muir[32], Serefnur Ozturk[33], Antonio Arauz[34], Natan Bornstein[35], Alan Bryer[36], Martin J O'Donnell[37], Jeffrey Weitz[38], Frank Peacock[39], Ellison Themeles[40] and Stuart J Connolly[41]

Trials in corso

ClinicalTrials.gov

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

Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

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

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

Verified June 2016 by University Hospital Tuebingen

Sponsor:
University Hospital Tuebingen

Information provided by (Responsible Party):
University Hospital Tuebingen

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