ΟΜΑΔΑ ΕΡΓΑΣΙΑΣ ΑΟΡΤΗΣ ΚΑΙ ΠΕΡΙΦΕΡΙΚΩΝ ΑΓΓΕΙΩΝ

ΠΑΝΕΛΛΗΝΙΑ ΣΕΜΙΝΑΡΙΑ ΟΜΑΔΩΝ ΕΡΓΑΣΙΑΣ | 2019
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Β’ ΠΑΝΕΠΙΣΤΗΜΙΑΚΗ ΚΑΡΔΙΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΕΚΠΑ
ΠΓΝ ‘ΑΤΤΙΚΟΝ’
Embolic Stroke of Undetermined Source (ESUS) Criteria

• Non-lacunar ischemic stroke on CT or MRI

Lacunar = subcortical infarct ≤1.5 cm (≤2.0 cm on MRI diffusion images) in largest dimension, including on MRI diffusion-weighted images, and in distribution of small, penetrating cerebral arteries of cerebral hemispheres and pons

• Absence of atherosclerosis (extra- or intracranial) causing ≥50% luminal stenosis in arteries supplying the ischemic area

• No major risk cardioembolic source

Major risk source = Atrial Fibrillation (permanent or paroxysmal), sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, cardiac tumors (e.g. atrial myxoma), mitral stenosis, recent (<4 weeks) MI, left ventricular EF <30%, valvular vegetations, or infective endocarditis

• No other specific cause of stroke identified E.g. arteritis, dissection, migraine/vasospasm, drug abuse

Embolic Stroke of Undetermined Source (ESUS)

Strokes that meet ESUS criteria are thought to be due to sources of uncertain risk, including:

• Minor-risk potential cardioembolic sources.
• Occult paroxysmal atrial fibrillation.
• Undiagnosed malignancy.
• Arteriogenic emboli such as aortic arch atherosclerotic plaques or non-stenotic cerebral arteries.
• Paradoxical embolism through an atrial septal defect.
Embolic Stroke of Undetermined Source (ESUS)

MANAGEMENT (1):

• Depending on clinical suspicion, further evaluation may include any of the following:
  • Prolonged outpatient cardiac monitoring.
  • TEE.
  • Cardiac MRI.
  • Transcranial Doppler with monitoring for emboli.
  • Catheter angioplasty.
  • Workup for occult cancer.
  • Workup for non-embolic causes such as vasculitis.
Embolic Stroke of Undetermined Source (ESUS)

MANAGEMENT (2):

• Secondary prevention in all noncardioembolic ischemic strokes includes anti-platelet therapy, blood pressure control, anti-lipid therapy, and lifestyle modifications.

• The benefit of anticoagulation therapy in ESUS without proven atrial tachyarrhythmia is unclear and the subject of ongoing clinical trials.

• Certain patients aged ≤60 years with ESUS and patent foramen ovale (PFO) may benefit from percutaneous PFO closure in addition to antiplatelet therapy.

• In patients with recurrent ESUS, switching antiplatelet agents or starting empiric anticoagulation therapy is reasonable.
CONCLUSIONS

Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding. (Funded by Bayer and Janssen Research and Development; NAVIGATE ESUS ClinicalTrials.gov number, NCT02313909.)
Embolic Stroke of Undetermined Source (ESUS)

**RESPECT-ESUS is first randomized trial to investigate clinical profile of dabigatran vs ASA**

- 5,390-patient ESUS trial
- was designed to test whether dabigatran is superior to aspirin 100 mg a day for the prevention of **recurrent** stroke.
- Most patients in the dabigatran arm received 150 mg twice daily, but those 75 years and older and those with moderate renal impairment received the lower 110-mg dose
- Through a mean follow-up of 19 months, the rate of recurrent stroke (primary outcome) was 4.1% per year with dabigatran and 4.8% per year with aspirin, a **nonsignificant** difference (HR 0.85; P = 0.1)
- The **rate of major bleeding was similar in both arms**—1.7% per year with dabigatran and 1.4% per year with aspirin
- There were three fatal bleeds—all in the aspirin arm—during the trial.

*Results from RE-SPECT ESUS® trial presented at the 11th World Stroke Congress*
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

• ESUS comprises about 1 ischemic stroke in 6.
• Patients with ESUS were relatively young compared with other ischemic stroke subtypes.
• Patients with ESUS had minor strokes, consistent with small emboli.
• rate of stroke recurrence during (mostly) antiplatelet therapy → >4% per year (retrospectively)
• Need to define better antithrombotic prophylaxis for ESUS.

Stroke. 2017;48:867-872
Embolic Stroke of Undetermined Source (ESUS)

- **cardioembolism** has been postulated as a major underlying stroke mechanism in ESUS patients because **occult atrial fibrillation** has been frequently detected using prolonged cardiac monitoring.

The value of transesophageal echocardiography for embolic strokes of undetermined source.


Abstract

OBJECTIVE: Our aim was to evaluate the diagnostic yield of transesophageal echocardiography (TEE) in consecutive patients with ischemic stroke (IS) fulfilling the diagnostic criteria of embolic strokes of undetermined source (ESUS).

METHODS: We prospectively evaluated consecutive patients with acute IS satisfying ESUS criteria who underwent in-hospital TEE examination in 3 tertiary care stroke centers during a 12-month period. We also performed a systematic review and meta-analysis estimating the cumulative effect of TEE findings on therapeutic management for secondary stroke prevention among different IS subgroups.

RESULTS: We identified 61 patients with ESUS who underwent investigation with TEE (mean age 44 ± 12 years, 49% men, median NIH Stroke Scale score = 5 points [interquartile range: 3-8]). TEE revealed additional findings in 52% (95% confidence interval [CI]: 40%-65%) of the study population. TEE findings changed management (initiation of anticoagulation therapy, administration of IV antibiotic therapy, and patent foramen ovale closure) in 10 (16% [95% CI: 9%-28%]) patients. The pooled rate of reported anticoagulation therapy attributed to abnormal TEE findings among 3,562 acute IS patients included in the meta-analysis (12 studies) was 8.7% (95% CI: 7.3%-10.4%). In subgroup analysis, the rates of initiation of anticoagulation therapy on the basis of TEE investigation did not differ (p = 0.315) among patients with cryptogenic stroke (6.9% [95% CI: 4.9%-9.6%]), ESUS (8.1% [95% CI: 3.4%-18.1%]), and IS (9.4% [95% CI: 7.5%-11.8%]).

CONCLUSIONS: Abnormal TEE findings may decisively affect the selection of appropriate therapeutic strategy in approximately 1 of 7 patients with ESUS.
Conclusion

Among patients with a recent cryptogenic stroke or TIA who were 55 years of age or older, paroxysmal atrial fibrillation was common. Noninvasive ambulatory ECG monitoring for a target of 30 days significantly improved the detection of atrial fibrillation by a factor of more than five and nearly doubled the rate of anticoagulant treatment, as compared with the standard practice of short-duration ECG monitoring. (Funded by the Canadian Stroke Network and others; EMBRACE ClinicalTrials.gov number, NCT00846924.)

Conclusions

ECG monitoring with an ICM was superior to conventional follow-up for detecting atrial fibrillation after cryptogenic stroke. (Funded by Medtronic; CRYSTAL AF ClinicalTrials.gov number, NCT00924638.)
**Embolic Stroke of Undetermined Source (ESUS)**

**Noninvasive Cardiac Event Monitoring to Detect Atrial Fibrillation After Ischemic Stroke**

A Randomized, Controlled Trial

Peter Higgins, Peter W. MacFarlane, Jesse Dawso, Gordon T. McInnes, Peter Langhorne, and Kennedy R. Lees


**Conclusions**

*Routine noninvasive cardiac-event monitoring after acute stroke enhances detection of paroxysmal AF and early anticoagulation.* Extended monitoring should be offered to all eligible patients soon after acute stroke. Guidelines on investigation for AF in stroke patients could be strengthened.

*Stroke. 2013;44:2525–2531*

**Embolic Stroke of Undetermined Source and Detection of Atrial Fibrillation on Follow-Up: How Much Causality Is There?**

George Ntaios, MD,* Vasileios Papavasileiou, MD,†‡ Gregory Y.H. Lip, MD,‡ Haralamplos Milionis, MD,§ Konstantinos Makritsis, MD,* Anastasia Vemmou, MD,|| Eleni Koroboki, MD,|| Efstathios Manios, MD,|| Konstantinos Spengos, MD,¶ Patrik Michel, MD,# and Konstantinos Vemmos, MD||

**Conclusions**

*Stroke severity is similar between ESUS patients who were diagnosed with AF during follow-up and those who were not.* Given that AF-related strokes are more severe than strokes of other etiologies, this finding challenges the assumption that the association between ESUS and AF detected during follow-up is as frequently causal as regarded.

*J Stroke Cerebrovasc Dis. 2016;25(12):2975-2980*
Temporal Relationship between Subclinical Atrial Fibrillation and Embolic Events
Michela Brambatti, Stuart J. Connolly, Michael R. Gold, Carlos A. Morillo, Alessandro Capucci, Carmine Muto, Chu Lau, Isabelle C. Van Gelder, Stefan H. Hohnloser, Mark Carlson, Eric Fain, Juliet Nakamya, Georges H. Mairese, Marta Halytska, Wei Q. Deng, Carsten W. Israel and Jeff S. Healey
on behalf of the ASSERT Investigators

Circulation. published online March 14, 2014;

Conclusions—Although SCAF is associated with an increased risk of stroke and embolism, very few patients had SCAF in the month prior to their event.
Predictors of Finding Occult Atrial Fibrillation After Cryptogenic Stroke

Christopher G. Favilla, MD*; Erin Ingala, MD*; Jenny Jara, BA; Emily Fessler, BA; Brett Cucchiara, MD; Steven R. Messé, MD; Michael T. Mullen, MD; Allyson Prasad, CRNP; James Siegler, MD; Mathew D. Hutchinson, MD; Scott E. Kasner, MD

Results - Conclusions

Independent predictors of AF:

- **Age > 60 years** (odds ratio, 3.7; 95% confidence interval, 1.3–11) and
- **prior cortical or cerebellar infarction** seen on neuroimaging (odds ratio, 3.0; 95% confidence interval, 1.2–7.6).

- AF was detected in 33% of patients with both factors, but only 4% of patients with neither.
- No other clinical features (including demographics, CHA2DS2-VASc, echocardiographic findings or radiographic characteristics were associated with AF detection.

Stroke. 2015;46:1210-1215
Embolic Stroke of Undetermined Source (ESUS)

Other factors responsible for ESUS, apart from the detection of AF
Embolic Stroke of Undetermined Source (ESUS)

alternative mechanisms of cerebral ischemia in ESUS
• endothelial dysfunction
• atherosclerosis
• vulnerability of non-stenosing carotid or aortic plaques

• High prevalence of hypertension and hypercholesterolemia in ESUS patients suggest the presence of vascular dysfunction

Magnetic Resonance Angiography Detection of Abnormal Carotid Artery Plaque in Patients With Cryptogenic Stroke

Ajay Gupta, MD; Gino Gialdini, MD; Michael P. Lerario, MD; Hediye Baradaran, MD; Ashley Giambrone, PhD; Babak B. Navi, MD, MS; Randolph S. Marshall, MD, MS; Costantino Iadecola, MD; Hooman Kamel, MD

Conclusions
Our findings suggest that a proportion of strokes classified as cryptogenic may be mechanistically related to complicated, nonhemodynamically significant cervical carotid artery plaque that can easily be detected by routine magnetic resonance imaging/magnetic resonance angiography acute stroke protocols.
Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation

Hooman Kamel, Peter M Okin, WT Longstreth Jr, Mitchell SV Elkind, & Elsayed Z Soliman

ABSTRACT  Atrial fibrillation (AF) has long been associated with a heightened risk of ischemic stroke and systemic thromboembolism, but recent data require a re-evaluation of our understanding of the nature of this relationship. New findings about the temporal connection between AF and stroke, alongside evidence linking markers of left atrial abnormalities with stroke in the absence of apparent AF, suggest that left atrial thromboembolism may occur even without AF. These observations undermine the hypothesis that the dysrhythmia that defines AF is necessary and sufficient to cause thromboembolism. In this commentary, we instead suggest that the substrate for thromboembolism may often be the anatomic and physiological atrial derangements associated with AF. Therefore, our understanding of cardioembolic stroke may be more complete if we shift our representation of its origin from AF to the concept of atrial cardiopathy.
Atrial cardiopathy was defined as at least one of the following:

- serum NT-proBNP level > 250 pg/mL
- P-wave terminal force velocity in lead V1 (PTFV1) on electrocardiogram (ECG) greater than 5000 μV·ms
- severe left atrial enlargement (LAE) on echocardiogram.
Evaluating the Atrial Myopathy Underlying Atrial Fibrillation Identifying the Arrhythmogenic and Thrombogenic Substrate

Jeffrey J. Goldberger, MD, MBA; Rishi Arora, MD; David Green, MD, PhD; Philip Greenland, MD; Daniel C. Lee, MD, MSc; Donald M. Lloyd-Jones, MD, ScM; Michael Markl, PhD; Jason Ng, PhD; Sanjiv J. Shah, MD

- **Echocardiography →**
  1. *LA dimension/volume assessment*
  2. *LA chamber function* (eg, *LA ejection fraction, LA function index*); *tissue Doppler imaging* (*ie, a’ velocity*) for evaluation of the ability of LA contraction to affect the longitudinal velocity of the basal LV in late diastole; *speckle-tracking strain analysis* (for the evaluation of LA mechanics), and *3-dimensional echocardiography* (for the evaluation of LA size, shape, and function)

- **cardiac MRI →**
  1. *delayed enhancement MRI has been used to detect atrial fibrosis in vivo.*
  2. *Four-dimensional flow MRI is uniquely suited for the evaluation of LA flow velocities (an index of atrial function).*

- **ECG waveform analysis →** *significant electrical information in the f waves of the AF ECG*

- **Biomarker analyses →** *d-dimer, platelet factor-4, thrombin-antithrombin complexes and plasminogen activator inhibitor-1, natriuretic peptides, troponin, C-reactive protein, interleukin-6*)

*Circulation. 2015;132:278-291*
Conclusions:

• Subtle LA dysfunction, as assessed by LA reservoir strain with speckle-tracking echocardiography, is associated with CS independent of other cardiovascular risk factors.

• Subtle LA dysfunction, as assessed by LA reservoir strain is associated with the extend of aortic atherosclerosis in patients with ESUS.

Embolic Stroke of Undetermined Source (ESUS) & Cancer

Predictors of Occult Cancer in Acute Ischemic Stroke Patients

Dolores Cocho, MD, PhD, Jordi Gendre, MD, Anuncia Boltes, MD, Jordi Espinosa, MD, Ana C. Ricciardi, MD, Jordi Pons, MD, Marta Jimenez, MD, and Pilar Otermin, MD

Conclusions:
Occult malignancy was present in 2.1% of overall patients, and 5.3% of patients with stroke of undetermined cause.

Baseline levels of fibrinogen>600 mg/dL or CRP>20 mg/L in patients with ESUS might be good predictors of occult malignancy.


Ischemic stroke in patients with cancer: Is it different from usual strokes?

Eun-Jae Lee, Hyun-Wook Nah, Joo-Young Kwon, Dong-Wha Kang, Sun U. Kwon, Jong S. Kim

Results
Ischemic Stroke Cancer-active patients demonstrated:
• higher C-reactive protein (CRP) and D-dimer,
• more frequent cryptogenic stroke,
• patterns of multiple DWI lesions (in bilateral anterior or in anterior and posterior circulations),
• less prevalent conventional risk factors than non-ISCI patients,

Among Ischemic Stroke Cancer-active patients
• both elevated CRP and D-dimer levels were associated with cryptogenic mechanism and multiple lesion patterns.

Conclusions

Chronic inflammation and an activated coagulation system may contribute to the pathogenic mechanism of strokes, the extent of each depending on the activity and severity of cancer.

Impaired arterial elastic properties and endothelial glycocalyx in patients with embolic stroke of undetermined source
Ikonomidis I, Frogoudaki A, Vrettou AR, Andreou I, Palaiodimou L, Katogiannis K et al
(article in issue)

Background and Purpose:
Cardioembolism is a postulated mechanism of embolic stroke of undetermined source (ESUS). We investigated endothelial glycocalyx, aortic elastic properties, oxidative stress, and their association left atrial (LA) function in ESUS and healthy individuals.

Methods:
In 90 ESUS patients (age 50.4±13.2) and 90 controls with similar risk factors, we measured:

a) perfused boundary region (PBR) of the sublingual arterial microvessels (range 5-25 micrometers), a marker inversely related with glycocalyx thickness,
b) pulse wave velocity (PWV), central systolic blood pressure (cSBP) and augmentation index (Alx),
c) LA volume and strain using speckle-tracking imaging,
d) Malondialdehyde (MDA) and protein carbonyls (PC), as oxidative stress markers.
• **Results:**

1. Compared to controls, ESUS had higher PWV, PBR MDA, and PC levels as well as higher LA volume and reduced reservoir LA strain (p<0.05).

2. PBR>1.18 μm of microvessel ranging from 5-9μm and PWV>10.2m/s were associated with ESUS on multivariable analysis (odds ratio: 2.374 and 5.429, p<0.05 respectively) and increased the c-statistic of the initial model from 0.54 to 0.71.

3. In ESUS, glycocalyx damage (increased PBR) was related with increased PWV (p<0.01) which was linked with LA reservoir strain after controlling for age, sex, and risk factors [p=0.03].

4. Increased MDA and PC were related with glycocalyx damage, increased PWV (r=0.67 and r=0.52) AIx, central SBP and aortic atheroma (p<0.01).
Conclusions:
Arterial function and endothelial glycocalyx are severely impaired in ESUS likely on the grounds of increased oxidative stress and are linked to LA dysfunction suggesting their contribution to ESUS pathogenesis.
Take home messages

• TOE defines therapy, when pathology is detected
• Extended rhythm monitoring may reveal occult AF
• Endothelial dysfunction and arterial stiffening participate in pathways than promote cryptogenic stroke
• Results of antithrombotic treatment without a specific diagnosis are ambiguous
Thank you!
ΚΑΡΔΙΟΛΟΓΙΑ ΤΟΥ ΑΥΡΙΟ
ΣΑΧΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ ΚΑΙ ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ

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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.

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