Transoesophageal echocardiography findings in young patients with cryptogenic ischemic stroke

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ESC European Society of Cardiology

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EACVI DOCUMENT

EACVI recommendations on cardiovascular imaging for the detection of embolic sources: endorsed by the Canadian Society of Echocardiography

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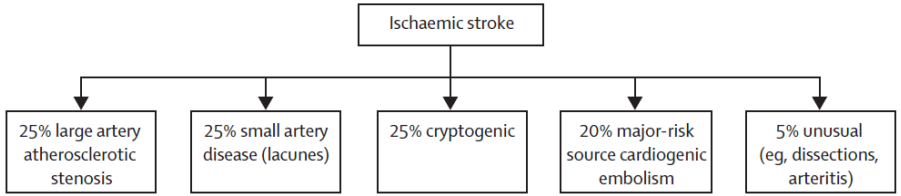
Background

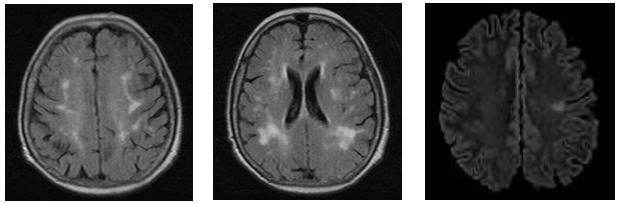
Ischemic stroke (IS) is one of the **leading causes of morbidity, mortality, and long-term disability** worldwide including the European Union.

Demographic data shows a trend toward **increasing numbers of patients** in the near future. Currently, the incidence of IS is estimated between 2.0 to 2.5 per 1000 inhabitants in Western countries. In the Czech Republic, more than 19 000 IS patients were admitted in specialized stroke centers in year 2016 *(Tomek et al., European Stroke Journal 2017).*

Cardioaortic embolism to the brain accounts for approximately 15–30% of ischaemic strokes and is often referred to as cardioembolic stroke, which is generally severe and prone to early and long-term recurrences. Identifying potential cardiac sources of embolism is a key objective, because treatment may vary according to the cardiac condition diagnosed.

The global **incidence of cardioembolic IS** is estimated about 20 to 25% of all IS, however other 30-40% of etiologically non-determined IS may represent **unrecognized cardioembolic IS**. Regarding this, the incidence of CE stroke may increase nearly to 50% *(Grau et al., Stroke 2001)*





Definitions

Cerebral infarction

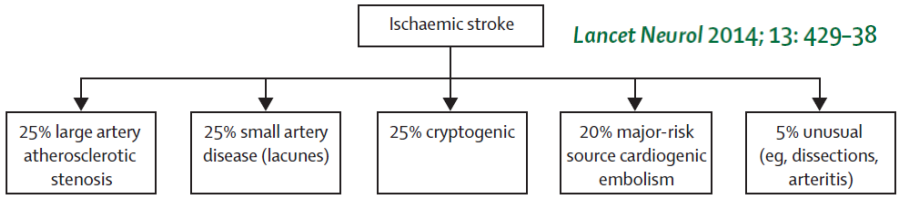
Cerebral infarction is defined as brain, spinal cord, or retinal cell death attributable to ischaemia, based on neuroimaging, neuropathological evidence, and/or clinical evidence of permanent injury.

Transient ischaemic attack

TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction.

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

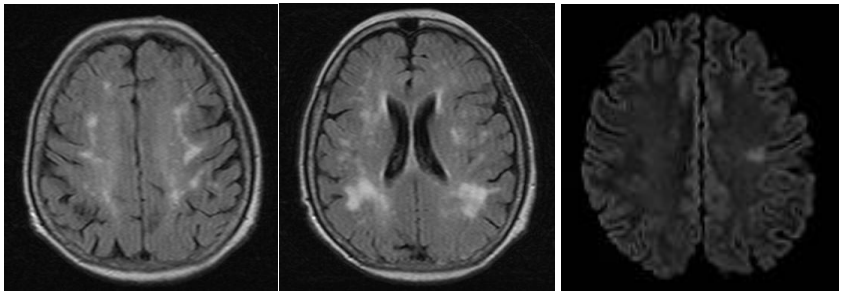
Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O'Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group



Lancet Neurol 2014; 13: 429–38

Schematic drawings of patterns of brain infarctions signalling different stroke mechanisms:

(A) Cardioembolic stroke is probable in cortical infarcts with territorial distribution;
(B) the same holds true for large striatocapsular infarcts;
(C) but not for lacunar infarctions, by definition located subcortically;
(D) low-flow infarct can be located subcortical or cortical (right panel), but their distribution is interterritorial not territorial.



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Cardiac sources of cerebral embolism

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Major sources of stroke risk	Minor or unclear sources of stroke risk
Atrial fibrillation	Mitral valve prolapse
Recent myocardial infarction	Mitral annulus calcification
Previous myocardial infarction (LV aneurysm)	Spontaneous echo contrast
All cardiomyopathies including non-compaction and takotsubo cardiomyopathies	Calcified aortic stenosis
Cardiac masses (except calcifications)	Valvular strands
Intracardiac thrombus	Atrial septal aneurysm without PFO
Intracardiac tumours	
Fibroelastoma	
Marantic vegetations	PFO
Rheumatic valve disease (mitral stenosis)	
Aortic arch atheromatous plaques	Atrial septal pouch
Endocarditis	Giant Lambl's excrescences
Prosthetic valve (mechanical especially)	

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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

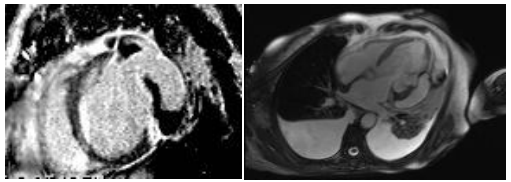
Paradoxical embolism
- Patent foramen ovale
- Atrial septal defect
- Pulmonary arteriovenous fistula

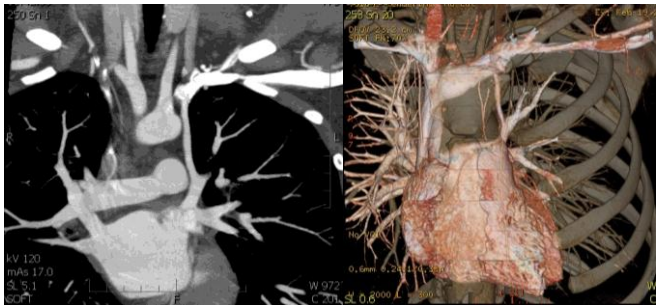
Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13:429-38.

Cardiovascular imaging tools

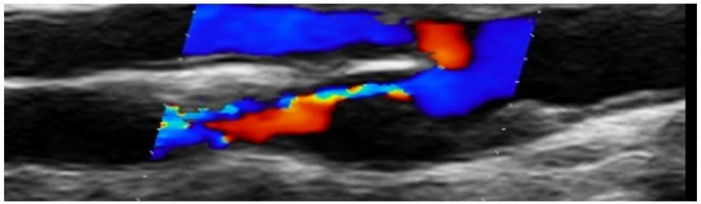
1. Transthoracic and transoesophageal echocardiography

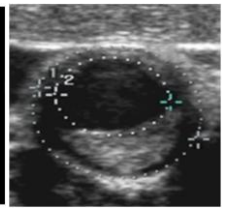
2. Computed tomography and magnetic resonance imaging





3. Vascular imaging





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Transthoracic and transoesophageal echocardiography

- Accurate **identification of the IS etiology** is substantial for adequate and effective secondary prevention.
- More than 30 cross-sectional studies have evaluated **the yield of TTE or TEE, in detecting cardiac sources of embolus** in patients with stroke. In consecutive patients, the yield of echocardiography for the detection of intracardiac masses ranged from 0% to 21%. Pooled data from these studies suggest an overall yield of 4% for TTE and 11% for TEE.
- In a retrospective study that included 1458 patients hospitalized for stroke with a suspected cardioembolic cause, **TEE changed the management** in approximately 16% of patients, leading to the introduction of anticoagulation and antibiotics, PFO closure and coil embolization.
- In a meta-analysis of 12 studies, the **pooled rate of reported anticoagulation therapy attributed to abnormal TEE findings** among 3562 patients with ischaemic stroke was 8.7%.

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Computed tomography and magnetic resonance imaging

- Both CT and MRI are highly accurate for detecting **LAA thrombosis** in patients with AF, with 100% sensitivity and specificity relative to TOE.
- CT also allows the identification of **valvular prosthesis thrombosis, aortic atheroma, PFO, atrial septal defect, and intracardiac tumours**.
- CMR is more sensitive and accurate than TTE for the detection of **intraventricular thrombi** after acute or chronic MI, and allows the detection of LV thrombi in patients with ESUS and a history of MI that may have been missed on TTE.

Table S2 CT and MRI in the diagnosis of cardiac source of embolism

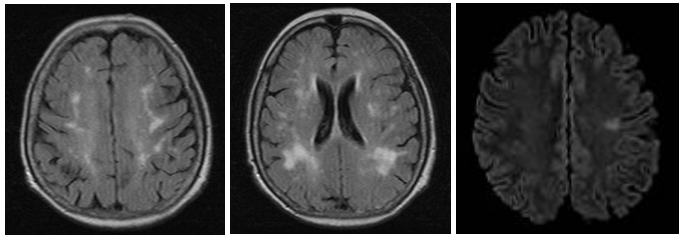
Reference	Patients	Techniques	Input of CT or MRI for the detection of for detection of cardiac sources of embolism
Boussel 2011[1]	46 patients with ischaemic stroke	CT vs. TOE	Sensitivity of CT was 72% and specificity was 95% for detection of CSE CT facilitated correct aetiologic classification for 83% of patients
Hur 2009[2]	137 patients with ischaemic stroke	CT vs. TOE	Sensitivity of CT was 89% and specificity was 100% for detection of cardiac source of embolism
Sipola 2013[3]	101 patients with ischaemic stroke	CT vs. TTE/TOE	CT + TTE/TOE vs. TTE/TOE for detection of cardiac source of embolism: sensitivity 91% vs. 41%, respectively, $P < 0.001$; specificity 98% vs. 99%
Haeusler 2017[4]	103 patients with acute ischaemic stroke of undetermined origin	MRI vs. TOE	Cardiac MRI identified stroke aetiology in an additional 6.1% of patients
Liberman 2017[5]	93 patients with ischaemic stroke, including 64 with cryptogenic stroke	MRI vs. TOE	Cardiac MRI reduced the percentage of patients with cryptogenic stroke by slightly more than 1%
Zahuranec 2012[6]	20 patients with ischaemic stroke	MRI vs. TOE	TEE identified more potential cardioembolic sources than CMR imaging
Baher 2014[7]	85 patients with ischaemic stroke and 21 with transient ischaemic attack	MRI vs. TOE	Cardiac MRI and delayed enhancement cardiac MRI resulted in a 26.1% reduction and a 39.1% reduction, respectively, of cryptogenic strokes

CSE, cardiac source of embolism; CMR, cardiac magnetic resonance; CT, computed tomography; ESUS, embolic strokes of undetermined source; MRI, magnetic resonance imaging; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Subjects and methods

The study set consisted of young acute IS patients <50 years enrolled in the prospective HISTORY (Heart and Ischemic STrOke Relationship studY) study, registered on ClinicalTrials.gov NCT01541163).

In all patients, the brain ischemia was confirmed on CT or MRI.

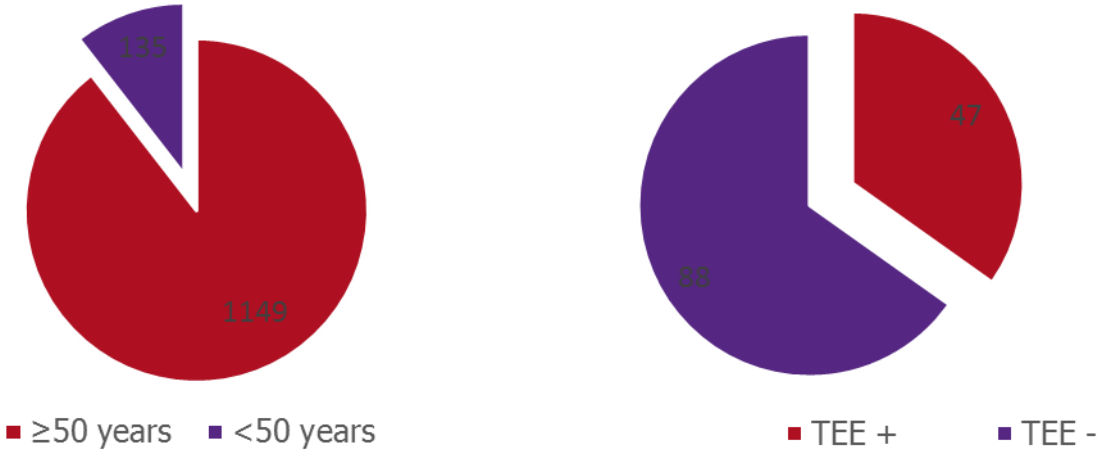


Admission ECG, serum specific cardiac markers, TEE, 24-hour and 3-week ECG-Holter were performed in all patients.

Results

Out of 1284 patients enrolled in the HISTORY study, 135 (73 males, mean age 40.2±8.1 years) were <50 years.

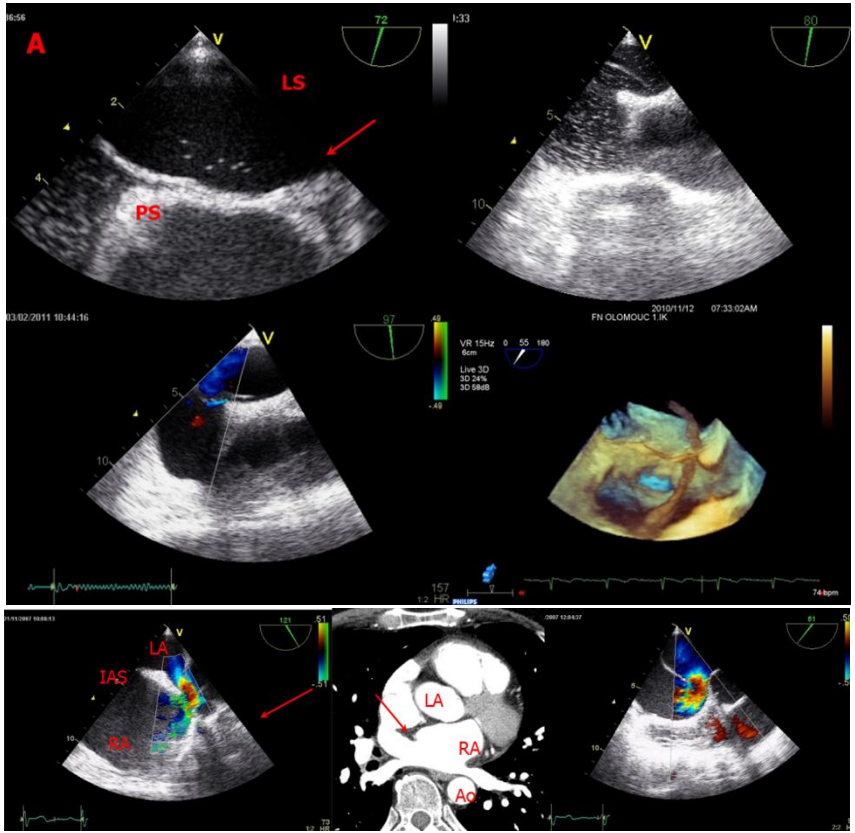
In total, the **relevant TEE abnormities were present in 47 (35%)** of these patients.



Results 1

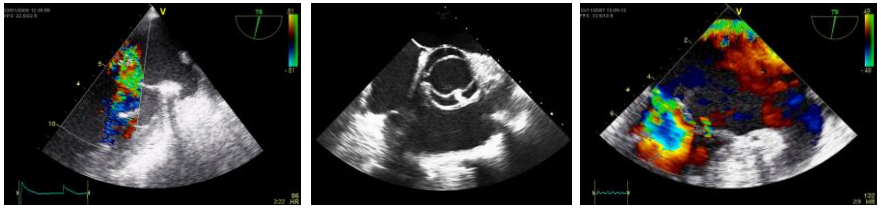
Patent foramen ovale (PFO) with evident left to right shunt was detected in 38 (28%) patients, with significant right to left shunt in 25 (19%) patients.

Other **atrial septal defect** with clinically significant bidirectional flow in 4 (3%) patients.



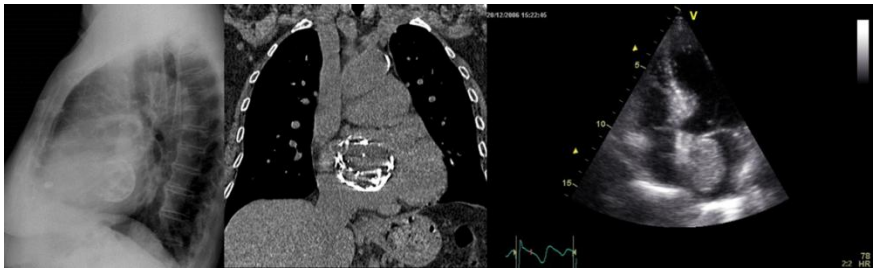
Results 2

Significant **valvular heart disease** was present in 2 (1%) patients (1 bicuspid aortic valve with moderate aortic regurgitation, 1 chronic severe mitral regurgitation).



In 4 (3%) patients severe **left ventricular systolic dysfunction** (left ventricular ejection fraction ≤35%) due to idiopathic dilated cardiomyopathy.

Left atrial myxoma was detected in 1 patient.



Diagnostic algorithm: proposal for a diagnostic approach based on the current evidence

Recommendations for cardiovascular imaging tools[45]

TTE, TOE, CMR

TTE should be performed systematically before TOE for evaluation of the cardiovascular source of embolus.

Contrast TTE, using intravenous injection of agitated saline, should be performed systematically at baseline and after provocative manoeuvres (Valsalva manoeuvre, coughing, both).

General indications in search of cardiac or aortic sources of embolism

Contrast TTE is the initial imaging modality of choice for evaluation of the cardiac and aortic sources of embolus.

Contrast TOE should be done in selected patients for evaluation of the cardiovascular sources of embolus if no identified source is found on TTE.

Contrast TOE should be performed according to the clinical context, but emergent indications are limited (e.g. fever, prosthesis).

Contrast TOE should be performed rapidly (ideally within 48 h) in case of ischaemic stroke, peripheral embolism, or previous heart valve replacement (percutaneous or surgical).

Contrast TOE is not indicated in ischaemic stroke patients with a previously identified source.

A comprehensive stroke CT protocol, including the intracranial and cervical arteries, aortic arch, cardiac chambers and walls, and coronary arteries, can be proposed in trained centres as an alternative initial imaging modality for evaluation of the cardiac and aortic sources of embolus.

CMR could be proposed in unselected patients with cryptogenic stroke who have a non-diagnostic cardiac evaluation including contrast TOE.

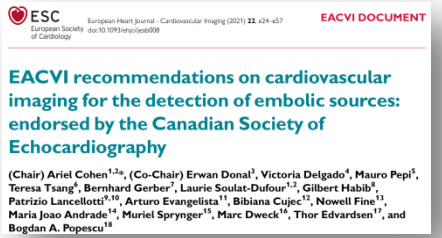
Vascular imaging

Doppler ultrasound (first-line), CTA, and/or MR angiography are recommended for evaluating carotid stenoses.

When carotid stenting is being considered, it is recommended that any Doppler ultrasound study be followed by either MR or CTA to evaluate the aortic arch, as well as the extra- and intracranial circulation.

When CEA is considered, it is recommended that Doppler ultrasound be corroborated by MR or CTA or repeat Doppler ultrasound performed by an expert.

CEA, carotid endarterectomy; CMR, cardiac magnetic resonance; CT, computed tomography; CTA, computed tomography angiography; MR, magnetic resonance; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.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Conclusions

1. Echocardiography constitutes the primary choice for cardiac imaging after acute ischaemic stroke, with **TTE and TEE** providing complementary information.
2. *The **relevant structural abnormities** with embolic potential were detected using TEE in 35% of young IS patients.*
3. Routine **use of TEE** to elucidate the causes of stroke, has a role especially in young patients who present with cryptogenic stroke and no cardiovascular risk factors, as well as in the setting of a PFO associated with a deep venous thrombosis.
4. Currently, **comprehensive cardiologic examination** should be a standard part of routine diagnostic management in most IS patients, moreover in cryptognic IS patients it should include TEE and long-term ECG-Holter monitoring
5. Cardiac **CT and MRI** are valuable alternatives in specific situations.
6. Atrial **septal anomalies** deserve careful examination to describe at-risk PFO and to discuss the indications of PFO closure in patients with cryptogenic stroke, after in-depth discussion and the ruling out of other possible causes, including occult AF (Holter or prolonged rhythm monitoring, insertable cardiac monitors).
7. Patients with cryptogenic IS constitute a heterogeneous group, leading to therapeutic implications based on the potential mechanism. The **concept of ESUS deserves further refinement**, because the results of the 2 studies are negative.

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