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Cardiovascular computed tomography versus transoesophageal echocardiography after cryptogenic ischaemic stroke – a pilot study of 12 patients

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Abstract

Objective: Transoesophageal echocardiography (TEE) is the gold standard for the detection of cardiac emboli sources in ischaemic stroke patients, but new computed tomography (CT) scanners are able to visualize the heart. This pilot study aimed to compare findings on TEE with combined cardiovascular scan and cerebral CT angiography in cryptogenic ischaemic stroke patients.

Methods: This pilot study enrolled patients with cryptogenic ischaemic stroke who underwent a combined cardiovascular and cerebral CT angiography scan and a TEE examination, which were interpreted in a blinded manner.

Results: Twelve patients with cryptogenic ischaemic stroke were included (mean age 56 years). Of these, 10 patients underwent both a combined cardiovascular and cerebral CT angiography and a TEE examination. All cardiovascular CT scans were readable at sinus rhythm. None of the

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simultaneous cerebral angiograms were compromised. Thrombi were not detected in any patients. Patent foramen ovale was visualized in five patients by TEE, while cardiovascular CT only identified three. Cardiovascular CT revealed in addition an X-ray negative pulmonary metastasis in one patient, aortic coarctation in another and significant coronary stenosis in four patients.

Conclusion: The sensitivity for detecting patent foramen ovale was considerably lower for cardiovascular CT than for TEE, however the cardiovascular CT revealed several other very important clinical findings.

Keywords

Stroke, computed tomography, cardiovascular, transoesophageal echocardiography

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Introduction

In 20–40% of all strokes, no cause can be established and these strokes are often referred to as cryptogenic.[1] It is argued that many of these strokes are embolic and originate in the heart, aortic arch or the proximal cerebral arteries,[2] which underlines the need for feasible diagnostic tools to visualize these structures. Cardioembolic stroke accounts for 14–30% of ischaemic strokes.[3] Currently, European guidelines recommend that selected stroke patients are examined with echocardiography to look for cardiac sources of embolism.[4]

Echocardiography can be undertaken as a transthoracic examination (TTE) or as a transoesophageal examination (TEE). TTE is performed with an ultrasound transducer placed on the chest and images are obtained through the chest wall, while a TEE is undertaken by introducing a small ultrasound probe through the oesophagus and placing it behind the heart. TEE is considered the gold standard method and it is superior to TTE for the detection of cardiac emboli sources in stroke patients,[5] although TEE is semi-invasive and uncomfortable for the patient. Cardiovascular magnetic resonance imaging has been used for the detection of cardiac emboli sources, but it is relatively expensive and often unavailable.[6] Compared with magnetic resonance imaging, computed tomography (CT) is better at visualizing the coronary arteries.[7] CT techniques have evolved significantly during the last decade. As the scanners become faster, they improve the visualization of dynamic structures such as the heart, whilst exposing the patient to a much lower radiation dose. The high-pitch spiral technique used with the new dual source scanners can freeze the whole heart in diastole using a very low X-ray dose (<1 mSv) and it is feasible to extend the cardiovascular scan to cover the thoracic cavity, neck and cerebral vessels in the same scan.[8]

A cardiovascular CT scan is noninvasive and has until now been used for the detection of aortic plaques,[9] measuring the left atrial wall thickness and density, detection of patent foramen ovale (PFO),[10] detection of coronary stenosis[11] and detection of left atrial appendage thrombus in patients with atrial fibrillation.[12,13] In 2010, investigators assessed the CT technique for visualizing the aorta, the four chambers of the heart and the coronary arteries and found it to be consistently adequate.[14] The aim of this pilot study was to compare findings on a cardiovascular CT angiogram with conventional TEE in stroke patients, and to investigate the feasibility of a combined cardiovascular and cerebral CT angiogram in stroke patients in order to be able to do a larger scale study on this subject.

Patients and methods

Patient population

This pilot study enrolled consecutive patients in the Stroke Unit, Herlev Hospital, University Hospital of Copenhagen, Herlev, Denmark between 1 January 2014 and 1 December 2014. The patients were above the age of 18 years and suffered from a nondisabling ischaemic stroke within 14 days prior to enrolment. The stroke was visualized with a magnetic resonance imaging scan. No obvious cause of the stroke was detected after a routine work-up (2-day electrocardiogram event recording, ultrasound of carotid arteries or CT angiogram and blood tests). Exclusion criteria were as follows: atrial fibrillation, patients on anticoagulant treatment, patients who received intravenous thrombolysis, patients unable to cooperate during the TEE (e.g. not being able to swallow the probe) and patients with contraindications to either use of CT contrast or to TEE. Since the aim of the study was to compare the two methods (cardiovascular CT and TEE), it needed to detect the possible load and incidence of thrombus material in nonanticoagulated patients. Patients who were treated with intravenous thrombolysis or anticoagulation medication were likely to have a lower incidence of vascular occlusive material and were thus excluded.

Patients were invited to participate in the study. The scanning techniques were not part of an institutional work-up of stroke. The trial was approved by The Danish Ethical Committee (H-4-2013-120) and the Data Monitoring Committee (HEH-2014-005, I-Suite nr: 02602). All patients provided written informed consent.

Stroke site classification

The site of the stroke was recorded according to the Bamford classification[15] and symptoms were rated by the National Institutes of Health Stroke Scale (NIHSS).[16] After study inclusion, all patients were examined as soon as possible by both TEE and a combined cardiovascular and cerebral CT angiogram.

Transoesophageal echocardiography examination

The TEE was performed according to standard European guidelines with injection of agitated salt water and Valsalva manoeuvre to visualize a potential PFO.[17] Patients fasted for 6 h before the examination and for 2 h after the local anaesthesia in the pharynx to avoid aspiration. The TEE was performed under conscious sedation. The equipment used for TEE was a Philips iE33 ultrasound system (Philips Healthcare, Best, the Netherlands).

Combined cardiovascular and cerebral CT angiogram

The combined electrocardiogram (ECG)-gated cardiovascular and carotid CT was done without beta blocker agents on a scanner with a second generation dual-source CT system (SOMATOM Definition Flash; Siemens Healthcare, Erlangen, Germany), using the fast double-spiral FLASH technique with a high pitch of 3.2. Iomeron 350 mg iodine/ml was used as contrast media with an injection speed of 5 ml/sec. The first 90 ml of pure contrast media was injected intravenously and this was followed by 40 ml of 50% saline and 50 ml of pure saline tracer. A region of interest (ROI) was set in the left atrium. The scan started with a delay of 8 s when the bolus tracker registered a Hounsfield Unit-value of 100. ECG-triggering allowed initialization of the scan at the bottom of the heart in early diastole and the primary scan ended at the vertex. To avoid possible ‘pseudo clot’ configuration in the left atrium due to insufficient blood/contrast mix, a late scan in the venous phase over the heart was performed. The kV-setting and mAs were set according to Siemens care-kV software protocol. Safire iterative reconstruction level two was used.

Interpretation of the TEE and CT scans

When interpreting both the cardiovascular CT scans and the TEEs, investigators noted whether there were signs of PFO or other atrial septal defects, thrombus mass, aortic plaques $\geq$4 mm, pulmonary vein abnormalities, or aortic, mitral or pulmonal valve disease. For the cardiovascular CT scans, the investigators also noted if the scanned segment showed signs of coronary artery disease or other obvious pathologies.

Both the cardiovascular and cerebral CT and the TEE were interpreted by investigators who were blind to the result of the other investigation. The cardiovascular CT was interpreted blind by two senior radiologists (P.S.U. & Hanne Heebøl) and the cerebral parts of the scans were interpreted blind by two senior neuroradiologists (M. O.K. & Emil Andonov Smilkov). All scans were rated for their quality. In nine of the cases, one senior cardiologist (B.N.) performed and interpreted the TEE scans. In two cases, the TEE examination was done by another senior cardiologist (A.M. B.S.). All the TEE scans were examined blind by another experienced cardiologist.

Results

During the inclusion period, this pilot study screened 216 patients and 12 patients were included. All patients underwent the planned cardiovascular and cerebral CT angiography. Only 10 of the 12 included patients had both TEE and CT angiogram data. Eleven patients had the planned TEE, but one patient did not have the TEE examination done because the cardiovascular CT revealed a pulmonary metastasis that required immediate transfer to another hospital. The TEE of one patient was not done with agitated salt water. These two patients were excluded from the comparison between the TEE and the cardiovascular CT.

Demographic and clinical information on the 12 patients is presented in Table 1. According to the Bamford classification,[15] five had cortical strokes in the anterior

Table 1. Demographic and clinical characteristics of patients ($n = 12$) with cryptogenic stroke who were enrolled in this pilot study to compare findings on a cardiovascular and cerebral computed tomography angiogram with those of a transoesophageal echocardiography examination.

Characteristic	Study cohort $n = 12$
Sex, male/female	10/2
Age, years	56
Blood pressure, mmHg	140/87
Smoker	6
Non-smoker/previous smoker	6
Alcohol use beyond recommendations	1
NIHSS	1
Time from stroke to transoesophageal echocardiography, days	6.5
Time from stroke to cardiovascular computed tomography angiogram, days	5.3

Data presented as mean or *n* of patients.
NIHSS, National Institutes of Health Stroke Scale.

circulation and six had cortical strokes in the posterior circulation. One patient had new strokes in both the anterior and the posterior circulations. Seven patients had more than one new ischaemic lesion. The mean time from stroke to TEE was 6.5 days, while the mean time from stroke to cardiovascular CT was 5.3 days. The mean interval between TEE and CT scan was 1.2 days (i.e. 6.5–5.3 days).

The results of the TEE compared with the cardiovascular CT in the 10 patients who received both examinations are presented in Table 2. No thrombi were detected with any of the scans. PFO was found in five patients, two of these were only found with TEE. Figure 1a shows CT findings in a patient with PFO. Figure 1b (close-up of Figure 1a) shows a distinct left atrial flap in the expected location of the septum primum (black arrow) and a definite jet of contrast material into the unopacified right atrium (white arrow). Significant coronary stenosis (>50%) was found in four patients on the cardiovascular CT. In one patient, coarctation of the aorta was documented on the cardiovascular CT but not on the TEE. None of the patients had significant aortic plaques (≥4 mm). No significant aorta, mitral or pulmonal valve diseases or lung vein malformations were found.

The results of the cardiovascular and cerebral CT scans showed that in nine (75%) of the scans, the coronary arteries were visualized with sufficient resolution to determine the presence of coronary plaques. Three patients (25%) had too high heart rate for such an evaluation. All other cardiac structures were well defined in all 12 examinations. All of the neck and cerebral arteries were readable. Five out of 12 scans were acceptable and seven out of 12 scans were very well defined. The two neuroradiologists agreed in 10 of the 12 cases. In two cases, they disagreed on the grade of the stenosis detected. The mean

Table 2. Findings from the 10 patients who underwent both a transoesophageal echocardiography (TEE) examination and a cardiovascular and cerebral computed tomography (CT) angiogram[a].

Findings	Transoesophageal echocardiography	Cardiovascular CT angiography	
		First read	Second read
Patent foramen ovale	5	3	3
Aorta valve thickened	1	3	1
Aorta valve insufficiency	1	0	0
Mitral valve thickened	2	3	2
Mitral valve insufficiency	3	0	0
Aorta ascendens plaque	1	0	0
Aorta descendens plaque or calcification	1	1	1
Aorta thoracalis calcification		0	1
LAD artery stenosis		2	4
RCA stenosis		1	1
Coarctation of the aorta		1	1
Annuloaortic ectasia		2	1
Chronic obstructive pulmonary disease		1	1

Data presented as *n* of patients.

[a]One patient did not have a TEE and one patient's TEE examination was excluded for technical reasons. Their data are not included in the table. Cardiovascular CT on these patients revealed a pulmonary metastasis in one patient and a patent foramen ovale together with a right coronary artery stenosis in the other patient.

LAD, left anterior descending artery; RCA, right coronary artery.

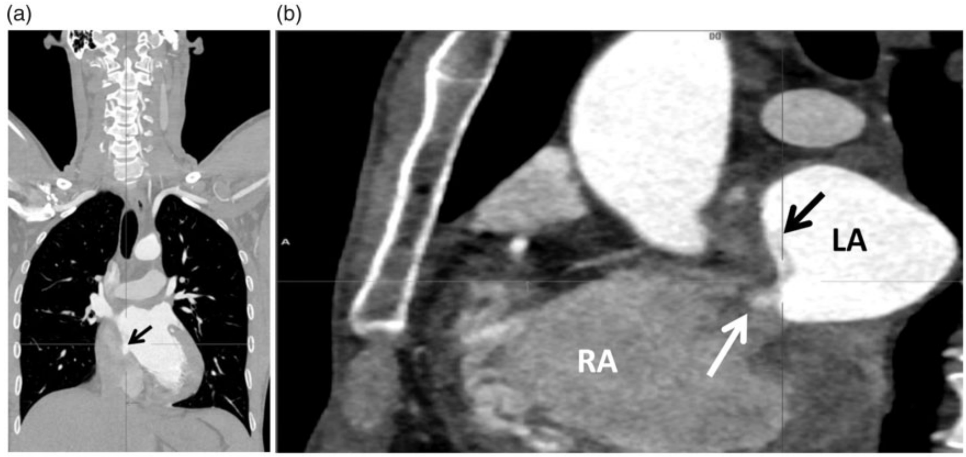

Figure 1. Cardiovascular computed tomography angiogram findings in a patient with patent foramen ovale (black arrow) (a). A close-up image of A shows a distinct left atrial flap in the expected location of the septum primum (LA, black arrow) and a definite jet of contrast material into the unopacified right atrium (RA, white arrow) (b).

agreement between the two senior radiologists regarding the cardiovascular CT was 77% in 13 different evaluated features (in eight of the 13 features there was a 100% agreement, in the remaining five features there was between 0% and 66.7% agreement, thus in total a mean agreement of 77% in the 13 features; Table 2).

The image quality of both the cerebral parts and the cardiovascular parts of the CT scan was evaluated systematically by two senior radiologists. The image quality was not graded, but was evaluated by answering 'yes' or 'no' to whether the quality was satisfactory or not. All the cerebral scans were rated by the two neuroradiologists to be of good quality. Three of the 12 cardiovascular parts of the CT scans were rated suboptimal for evaluation of the coronary arteries by both radiologists, the main reason being an increased heart rate.

Discussion

This present pilot study demonstrated that it was possible to perform the combined cardiovascular and cerebral CT scan on all included patients. The present study did not find any thrombi or emboli originating in the heart or in the arteries supplying the brain. Occurrences of such thrombi or emboli are relatively rare, and it would not be possible to visualize emboli already propagated to small arteries in the brain thereby causing the index stroke. More PFOs were detected with TEE than with cardiovascular CT. Considering TEE is the gold standard, in this present study the sensitivity of the cardiovascular CT for detection of PFO was 60% while the specificity was 100%. Previously, other investigators compared cardiovascular CT with TEE and found a sensitivity of 73.1% and a specificity of 98.4%.[10] Combined cardiovascular and cerebral angiograms may perform comparably with TEE regarding some aspects of the search for a cardiac source of embolus. However, considering TEE as the gold standard for PFO detection, the cardiovascular CT had a substantially lower sensitivity for PFO than TEE, which indicates that the currently applied cardiovascular CT should not be used alone in the stroke work-up.

A meta-analysis from 2015 did not support PFO closure for prevention of stroke.[18] However, in the light of the results of the REDUCE study,[19] patients with PFO closure combined with antiplatelet therapy had a reduced risk of subsequent ischaemic stroke compared with patients assigned to antiplatelet therapy alone. But PFO closure was associated with higher rates of device complications and atrial fibrillation.[19] The RESPECT study showed that PFO closure was associated with a lower rate of recurrent ischaemic strokes than medical therapy alone during an extended follow-up period.[20] Currently, European guidelines do not yet recommend any specific treatment when detecting a PFO in stroke patients.[4] If this practice is changed in the future, it may influence the choice of method for the investigation of cardiac emboli sources.

Significant coronary stenoses were found in four patients (40%) corresponding to previous studies in stroke patients with frequencies of 18–48%.[11,21–23] The detection of these stenoses led to further investigations and in two cases followed by specific treatment. The patients with a detected coronary stenosis had not complained of chest pain before, but when questioned thoroughly, they did have corresponding symptoms. These observations may extend to the general stroke population. If cardiovascular CT scans become more widely used to improve current treatments, a better understanding of the most optimal treatment of incidentally found coronary stenoses is required.

One patient was diagnosed with coarctation of the aorta and it is possible that this finding was significant for the aetiology of the index stroke, since stroke is one of the long-term complications of coarctation of the aorta.[24]

The TEE requires 6 hours of fasting before the examination. It is a semi-invasive procedure that is uncomfortable and distressing for the patient and severe complications have been reported.[25] Dysphagia, a common symptom in stroke patients, can pose problems in performing the TEE procedure. When a stroke patient is admitted to our hospital, a brain CT scan, a chest X-ray and an ultrasound examination of the carotid arteries are routinely performed. If a brain CT scan could be extended to a combined cardiovascular and cerebral CT with angiogram it would save the chest X-ray and ultrasound of the carotid arteries and at the same time save the need for a later TEE. For the patient, this could save time, money and reduce discomfort. A cerebral angiography exposes a patient to radiation of 5 mSv, adding a cardiovascular scan would increase the estimated X-ray dose to 6–7 mSV in total. Addition of a cardiovascular CT would provide less than 0.1% life attributable risk of cancer.[26]

Standard cardiac CT is limited to identifying large pato-anatomic features of a PFO and only occasionally a reverse contrast leak from the left to right atrium is visualized (white arrow, Figure 1b). However, it is possible that significant anterograde shunting of blood from the right to left side of the heart can be visualized indirectly with an early dynamic CT scan. If near simultaneous contrast arrival in the two atria is detected it will confirm an interatrial communication. This technique has been applied in a non-ionising magnetic resonance imaging protocol.[27] To the best of our knowledge, a similar radiation dose-neutral approach in cardiac CT has not been published, but by simple alternative placing of the standard dynamic bolus tracking in, or at the level of the atria, simultaneous atrial signal intensity curves could be performed (Figure 2). No antegrade contrast shunting to the left atrium

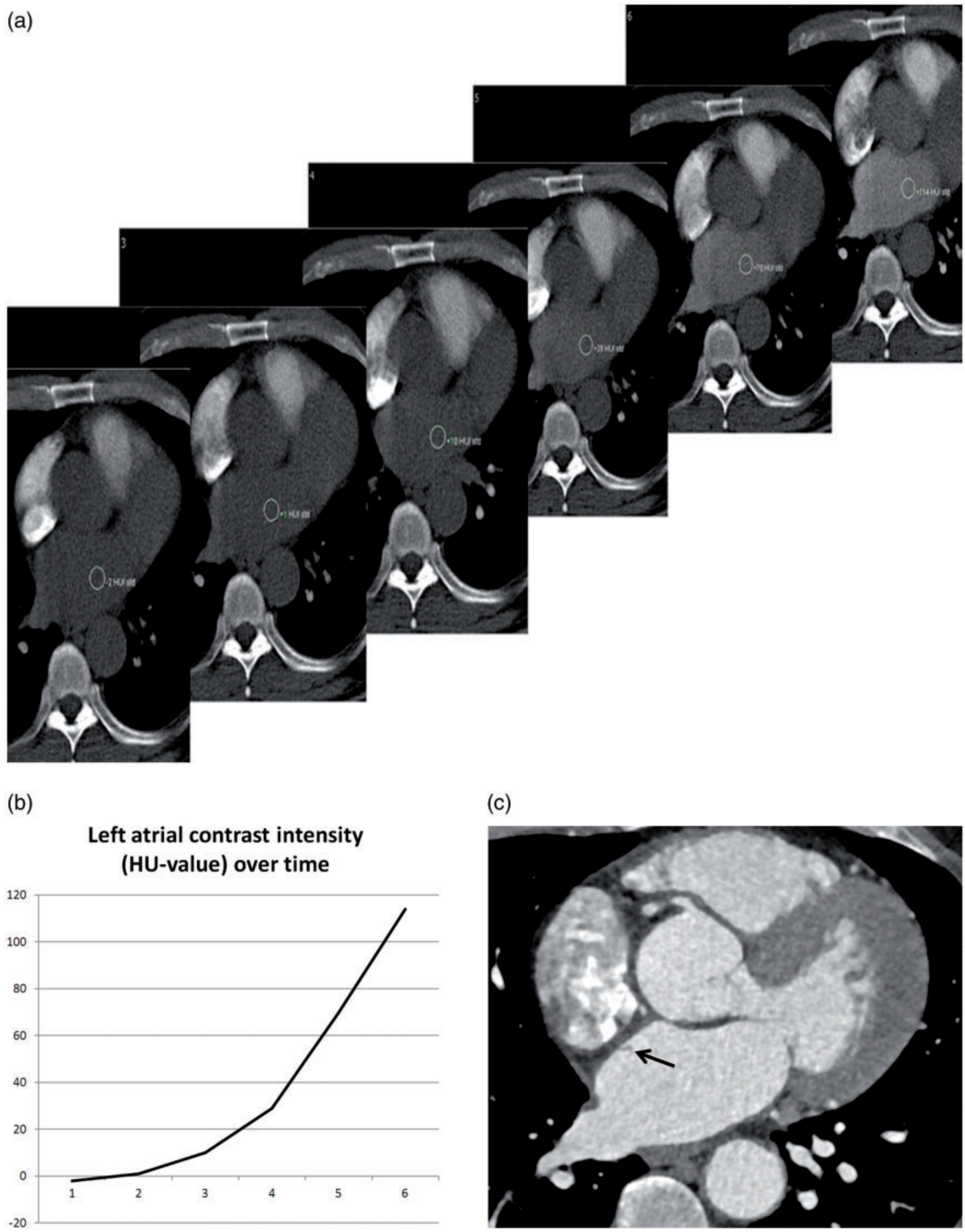

Figure 2. Cardiovascular computed tomography images showing alternative placement of pre-scan contrast intensity measurement region of interest (ROI) in the left atrium and simultaneous measurement of the potential right to left contrast shunt. (a) Bolus track ROI in the left atrium. (b) Left atrial contrast intensity curve. (c) Patent foramen ovale indicated by discrete septum primum prominence into the left atrium. The black arrow shows a discrete flap, but no retrograde contrast shunt.

was observed in any of the patients in the current study, but this could have been the case if the right atrial pressure had been raised during this pre-scan by voluntary Valsalva manoeuvre.[28]

This present study had a number of limitations. First, the study population was small and highly selected, consisting of cryptogenic stroke patients that were relatively young, who had few comorbidities and low NIHSS scores, so the actual findings cannot be applied to the general stroke population. Future studies must explore whether cardiovascular CT is feasible in the general stroke population. The low number of included patients was due to practical issues, since both protocols for the TEE and cardiac CT examinations could only be performed during office hours. There was limited access to the TEE equipment and manpower to undertake the examinations. Secondly, as this was a pilot study, only a small standardized assessment of inter-observer agreement was undertaken. An inter-observer variability analysis should be done as part of a large-scale study. Thirdly, the study did not measure serum D-dimer levels or undertake lower extremity ultrasonography. These measures could have suggested an embolic source for the stroke, especially in PFO patients.

An advantage of this study was the close timing of the TEE and cardiovascular CT examinations, thereby providing a solid basis for comparing the two methods. The mean time from the stroke to the cardiovascular CT was almost 1 day less than the mean time from stroke to TEE. As a 6-hour fast was required prior to TEE, time delays in the work-up only applied to TEE rather than to the cardiac CT scan.

In conclusion, this pilot study demonstrated that the sensitivity for detecting PFOs was considerably lower for cardiovascular CT than for TEE. However, these data suggest that a combined cardiovascular and cerebral CT examination might be feasible and could provide supplementary information with assumed positive implications for stroke patients. It is possible that new CT scanning techniques will be better at detecting PFO, thus making CT useful in the diagnostic work-up of stroke aetiology.

Declaration of conflicting interests

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References

1. Fonseca AC and Ferro JM. Cryptogenic stroke. *Eur J Neurol* 2015; 22: 618–623.
2. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014; 13: 429–438.
3. Arboix A and Alio J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev* 2010; 6: 150–161.
4. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; 25: 457–507.
5. de Bruijn SF, Agema WR, Lammers GJ, et al. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. *Stroke* 2006; 37: 2531–2534.
6. Baher A, Mowla A, Kodali S, et al. Cardiac MRI improves identification of etiology of acute ischemic stroke. *Cerebrovasc Dis* 2014; 37: 277–284.
7. Schuijf JD, Bax JJ, Shaw LJ, et al. Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and

multislice computed tomography for noninvasive coronary angiography. *Am Heart J* 2006; 151: 404–411.
8. Wang Z, Chen Y, Wang Y, et al. Feasibility of low-dose contrast medium high pitch CT angiography for the combined evaluation of coronary, head and neck arteries. *PLoS One* 2014; 9: e90268.
9. Chatzikonstantinou A, Krissak R, Fluchter S, et al. CT angiography of the aorta is superior to transesophageal echocardiography for determining stroke subtypes in patients with cryptogenic ischemic stroke. *Cerebrovasc Dis* 2012; 33: 322–328.
10. Kim YJ, Hur J, Shim CY, et al. Patent foramen ovale: diagnosis with multidetector CT – comparison with transesophageal echocardiography. *Radiology* 2009; 250: 61–67.
11. Hur J, Lee KH, Hong SR, et al. Prognostic value of coronary computed tomography angiography in stroke patients. *Atherosclerosis* 2015; 238: 271–277.
12. Romero J, Husain SA, Kelesidis I, et al. Detection of left atrial appendage thrombus by cardiac computed tomography in patients with atrial fibrillation: a meta-analysis. *Circ Cardiovasc Imaging* 2013; 6: 185–194.
13. Wu X, Wang C, Zhang C, et al. Computed tomography for detecting left atrial thrombus: a meta-analysis. *Arch Med Sci* 2012; 8: 943–951.
14. Furtado AD, Adraktas DD, Brasic N, et al. The triple rule-out for acute ischemic stroke: imaging the brain, carotid arteries, aorta, and heart. *AJNR Am J Neuroradiol* 2010; 31: 1290–1296.
15. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991; 337: 1521–1526.
16. Goldstein LB, Bertels C and Davis JN. Interrater reliability of the NIH stroke scale *Arch Neurol* 1989; 46: 660–662.
17. Flachskampf FA, Badano L, Daniel WG, et al. Recommendations for transoesophageal echocardiography: update 2010. *Eur J Echocardiogr* 2010; 11: 557–576.
18. Li J, Liu J, Liu M, et al. Closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and a history of cryptogenic stroke or transient ischemic attack. *Cochrane Database Syst Rev* 2015; 9: CD009938.
19. Sondergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017; 377: 1033–1042.
20. Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017; 377: 1022–1032.
21. Amarenco P, Lavallee PC, Labreuche J, et al. Prevalence of coronary atherosclerosis in patients with cerebral infarction. *Stroke* 2011; 42: 22–29.
22. Calvet D, Touze E, Varenne O, et al. Prevalence of asymptomatic coronary artery disease in ischemic stroke patients: the PRECORIS study. *Circulation* 2010; 121: 1623–1629.
23. Yoo J, Yang JH, Choi BW, et al. The frequency and risk of preclinical coronary artery disease detected using multichannel cardiac computed tomography in patients with ischemic stroke. *Cerebrovasc Dis* 2012; 33: 286–294.
24. Suradi H and Hijazi ZM. Current management of coarctation of the aorta. *Glob Cardiol Sci Pract* 2015; 2015: 44.
25. Hilberath JN, Oakes DA, Shernan SK, et al. Safety of transesophageal echocardiography. *J Am Soc Echocardiogr* 2010; 23: 1115–1127.
26. Faletra FF, D'Angeli I, Klersy C, et al. Estimates of lifetime attributable risk of cancer after a single radiation exposure from 64-slice computed tomographic coronary angiography. *Heart* 2010; 96: 927–932.
27. Mohrs OK, Petersen SE, Erkapic D, et al. Diagnosis of patent foramen ovale using contrast-enhanced dynamic MRI: a pilot study. *AJR Am J Roentgenol* 2005; 184: 234–240.
28. Williamson EE, Kirsch J, Araoz PA, et al. ECG-gated cardiac CT angiography using 64-MDCT for detection of patent foramen ovale. *AJR Am J Roentgenol* 2008; 190: 929–933.