CT angiography of the heart and aorta in TIA and ischaemic stroke: cardioembolic risk sources and clinical implications

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CT Angiography of the Heart and Aorta in TIA and Ischaemic Stroke: Cardioembolic Risk Sources and Clinical Implications

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Background: Cardiac emboli are important causes of (recurrent) ischaemic stroke. Aorta atherosclerosis might also be associated with an increased risk of stroke recurrence. This study aimed to evaluate the yield and clinical implications of CT-angiography (CTA) of the heart and aorta in the diagnostic workup of transient ischaemic attack (TIA) or ischaemic stroke. *Methods:* CTA of the heart and aortic arch was performed in TIA/ischaemic stroke patients, in addition to routine diagnostic workup. Occurrence of cardioembolic (CE) risk sources and complex aortic plaques were assessed. Implications of cardiac CTA for therapeutic management were evaluated *Results:* Sixty-seven patients were included (TIA n = 33, ischaemic stroke n = 34) with a mean age of 68 years (range 51−89) and median NIHSS of 0 (interquartile range 0−2). CE risk sources were detected in 29 (43%) patients. An intracardiac thrombus was present in 2 patients (3%; TIA 0%; ischaemic stroke 6%). Medium/low-risk CE sources included mitral annular calcification (9%), aortic valve calcification (18%) and patent foramen ovale (18%). Complex aortic plaque was identified in 16 patients (24%). In two patients with an intracardiac thrombus, therapeutic management changed from antiplatelet to oral anticoagulation. *Conclusions:* CTA of the heart and aorta has a high yield for detection of embolic risk sources in TIA/ischaemic stroke, with clinical consequences for 6% of ischaemic stroke patients. Implementation of CTA of the heart and aorta in the acute stroke setting seems valuable, but cost-effectiveness of this approach remains to be determined.

Key Words: Ischaemic Stroke—Transient Ischaemic Attack—Computed Tomography Angiography—Cardioembolism—Atherosclerosis

Introduction

Transient ischaemic attack (TIA) and ischaemic stroke (IS) patients are at high risk of recurrent stroke, in particular in the first week after the initial event.[1] Cardioembolic (CE) stroke accounts for 22% of all strokes[2] and is a severe stroke subtype with a high risk of recurrence and mortality.[3] In addition, presence of severe aorta atherosclerosis might be associated with an increased risk of recurrent stroke.[4] Especially thick (≥4 mm) or ulcerated atherosclerotic plaques in the thoracic aorta has been suggested to be a possible cause of TIA and IS.[5] For some CE sources and for aorta atherosclerosis, the optimal choice

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of therapy is unclear. However, identification of an intracardiac thrombus changes secondary prophylaxis from antiplatelets to anticoagulants which reduces stroke recurrence rate substantially.[6] Diagnostic evaluation in the acute to subacute phase of stroke is therefore important to initiate secondary prophylaxis to prevent recurrences.[7]

Current diagnostic workup for the identification of CE stroke includes electrocardiogram (ECG) recording, transthoracic echocardiography (TTE), and only when TTE shows no abnormalities in patients with a high suspicion of a CE source, transoesophageal echocardiography (TEE). There is no true gold standard for the identification of CE sources. Until now, TEE is often considered the best method for detection of left atrium (LA) and left atrial appendage (LAA) thrombi. However, TEE is relatively uncomfortable and carries a small risk of injury.[8] Moreover, guidelines recommend TTE because of its non-invasive nature and low costs.[9] Cardiac CTA has high sensitivity and specificity for identification of potential cardiac sources compared with TEE.[10–12] However, cardiac CTA is currently not recommended in guidelines for the identification of possible CE sources[9] and assessment of aorta atherosclerosis is generally not performed on a routine basis in clinical practice.

Early CTA screening could carry therapeutic implications by identifying a possible embolic source. Previous studies showed that implementation of CTA of the heart and aorta is a feasible alternative to TEE for identification of CE sources,[12] however, these studies either included patients with a high probability for having CE sources (e.g. suspected embolic stroke or AF),[4,10,13–17] or did not include patients with suspected TIA.[18–20] The objective of this study was therefore to investigate the yield and the therapeutic implications of CTA of the heart and aorta in patients presenting with TIA or IS without a specific high probability for CE sources.

Methods

This study was approved by the medical ethical committee of the Leiden University Medical Center and procedures were followed in accordance to institutional guidelines. All study procedures were performed after patients provided written informed consent.

Patients

Consecutive patients presenting for TIA evaluation were screened for inclusion at the Neurology Department of the Leiden University Medical Center (the Netherlands) from December 2011 until November 2014. After a pause (November 2014 until January 2017, because of lack of funding), consecutive TIA and IS patients were additionally screened for inclusion from January 2017 until February 2018. Hospital procedures for TIA patient evaluation were the same for both inclusion periods. TIA was defined as a temporary episode of focal neurological dysfunction (resolving within 24 h) resulting from brain or retinal ischaemia and without abnormalities on brain imaging, and IS as lasting focal neurological dysfunction (lasting more than 24 h, or resolving within 24 h but with ischaemic lesions on brain imaging).[21] Exclusion criteria were age below 50 years (because more stringent criteria with regard to radiation exposure are applicable to this age category),[22] known allergy to iodinated contrast agent, renal insufficiency indicated by Glomerular Filtration Rate (GFR) less than 50 mL/min, use of oral anticoagulants at the time of admission, and the inability to perform cardiac CTA within 1 week after symptom onset.

Standard diagnostic workup and study procedures

Standard diagnostic workup included single ECG recordings, unenhanced brain CT, and imaging of the carotid arteries (either CTA of the aortic arch to the vertex or cervical duplex ultrasound). Echocardiography (TTE and/or TEE) and prolonged ECG monitoring were performed when atrial fibrillation (AF) or another CE source was suspected on clinical grounds (i.e. no other cause identified, cortical symptoms or ischaemic events in different vascular territories). Specific study procedures included cardiac CTA in all patients and CTA of the aortic arch to the vertex when this was not performed according to standard workup. In more detail, for patients with suspected TIA standard diagnostic workup at our TIA clinic included duplex ultrasound, and CTA of the aortic arch until the vertex was performed as part of the research procedures. Since all diagnostic procedures were performed on the day of admission, CTA of the aortic arch to the vertex and cardiac CTA were performed immediately following standard diagnostic cervical duplex ultrasound and unenhanced brain CT examinations. For IS patients, the carotid arteries were generally assessed with CTA as part of standard diagnostic workup at the emergency room, so research procedures included only the additional cardiac CTA. Furthermore, in acute IS patients, rapid diagnostic workup is important because any delay in intravenous or intra-arterial recanalizing treatment will negatively influence patients' outcome. Informed consent was therefore not obtained in the acute phase, but postponed to the subacute phase, and cardiac CTA was performed within 2 days after standard diagnostic workup. When cardiac CTA indicated an intracardiac thrombus, TTE and/or TEE was performed to confirm this finding.

CT Image Acquisition

CT studies were obtained with a volumetric 320-detector row CT scanner (Aquilion-One from 2011–2018 or Aquilion-One Genesis from 2017–2018, Toshiba Medical Systems, Otawara, Japan). Patients received an unenhanced brain CT scan, followed by CTA of the aortic arch to the vertex. CTA was performed with injection of 50 mL of contrast agent (Ultravist 370 mg/mL, Bayer, Leverkusen, Germany) followed by a bolus of 35 mL saline, both

with a flow rate of 3.5 mL/s. Cardiac CTA was performed with a prospectively ECG-gated volumetric acquisition, after an additional bolus injection of 50 mL of contrast agent followed by 5 mL saline flush with a flow rate of 5.0 mL/s. Images were acquired during an inspiratory breath hold, without the use of beta-blockers.

Image Analysis

Unenhanced brain CT and CTA of the aortic arch to the vertex or cervical duplex ultrasound were evaluated according to standard clinical practice. Significant internal carotid artery stenosis was defined as symptomatic (ipsilateral) carotid stenosis of 50−99% observed on CTA according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.[23,24] On CTA, the thoracic aorta was assessed from the ascending aorta until 2 cm after the left subclavian artery of the proximal descending aorta.[5,25] We analysed the aorta for the presence of a complex aortic plaque, which was defined as ≥4 mm in thickness or presence of ulceration[4] (GH, 5 years of experience in CTA analysis, blinded to clinical aetiology). Evaluation of cardiac CTA was performed by a radiologist (LK, >20 years of experience, blinded to clinical aetiology) for occurrence of CE risk sources and categorized as high-risk versus medium/low-risk sources. High-risk CE sources included intracardiac thrombus in either LA, LAA or left ventricle (LV). These were defined as a filling defect with an oval or round shape in the LAA,[26] or with a lower attenuation than the papillary muscle in the LA or LV.[27] Medium/low-risk sources included mitral annular calcification, aortic valve calcification, patent foramen ovale,[11] atrial septal aneurysm, and presence of LV aneurysm without thrombus.[28] In addition, filling defects suspected to be an intracardiac thrombus, but lacking an oval shape or lower attenuation, were noted as a medium/low-risk source.[26,27]

Outcome assessments

Yield of CTA of the heart and aorta was assessed by descriptive statistics, reporting the proportion of high-risk, medium/low-risk CE findings and aortic plaques for all patients and for TIA or IS patients separately. Implications of cardiac CTA for therapeutic management were assessed by reporting the proportion of patients with a high-risk CE source resulting in a change in secondary preventive treatment from antiplatelet to oral anticoagulant therapy.

Results

In the periods December 2011− November 2014 and January 2017−February 2018, out of 802 screened patients, 163 patients (20%) were eligible for this study. (Fig. 1). Main reason for exclusion was an uncertain clinical diagnosis based on first assessment (symptoms likely not belonging to TIA or IS but indicating a possible other diagnosis) prior to standard diagnostic workup (n = 261). Other reasons for exclusion are shown in Fig. 1. Of the remaining 163 patients, cardiac CTA was not possible in 42 (26%) patients, due to logistics or technical problems (n = 9), early discharge (n = 7), not possible < 2 days after standard workup (n = 4), judged as too burdensome (mainly because of recent endovascular stroke treatment, n = 19), or other reasons (n = 3). A further 49 (30%) patients refused participation, resulting in the inclusion of 72 patients. Final diagnosis of a stroke mimic became evident after cardiac CTA in 5 patients with suspected TIA. In the final analysis, 67 patients were included. Although 47 patients presented with a suspicion of TIA, 14 of these 47 patients showed signs of recent ischaemia on diagnostic brain CT and diagnosis was therefore changed from TIA to IS. This resulted in the inclusion of 33 patients with TIA and 34 with IS. (Fig. 1). Baseline characteristics are shown in Table 1. Mean age of the patients was 68 years (range 51 to 89 years) and 69% were men. Median National Institutes of Health Stroke Scale (NIHSS) of all patients was 0 (interquartile range (IQR), 0−2); median NIHSS of the IS patients was 2 (IQR, 1−3.25). Two patients (3%) had a history of AF without being treated with oral anticoagulants.

Standard diagnostic evaluation

Results of standard diagnostic workup are shown in Table 2. ECG recordings of 9 patients were indicative of cardiac disease (e.g., arrhythmia, left ventricular hypertrophy or atrioventricular block). CTA identified 8 patients (12%; TIA 18%, IS 6%) with significant carotid artery stenosis and 3 patients (4%; TIA 0%, IS 9%) with an intracranial large vessel occlusion.

CTA of heart and aorta

Cardiac CTA was performed with a median of 2 days after symptom onset (IQR 1−2). On cardiac CTA, an intracardiac thrombus was present in 2 patients (3%; TIA 0%, IS 6%). Thirty-seven medium/low-risk CE sources were identified in 28 patients (42%) and included patent foramen ovale (n = 12, 18%), mitral annular calcification (n = 6, 9%) and aortic valve calcification (n = 12, 18%). Complex aortic plaques were identified in 16 patients (24%; TIA 30%, IS 19%); in 7 patients (10%) plaques were located proximal to the supra-aortic artery ipsilateral to the affected territory. Of these 7 patients, 3 patients also showed significant carotid artery stenosis. (Table 3).

TTE, TEE, Holter ECG

Both patients with an intracardiac thrombus were referred for further cardiology assessment 2 and 4 days

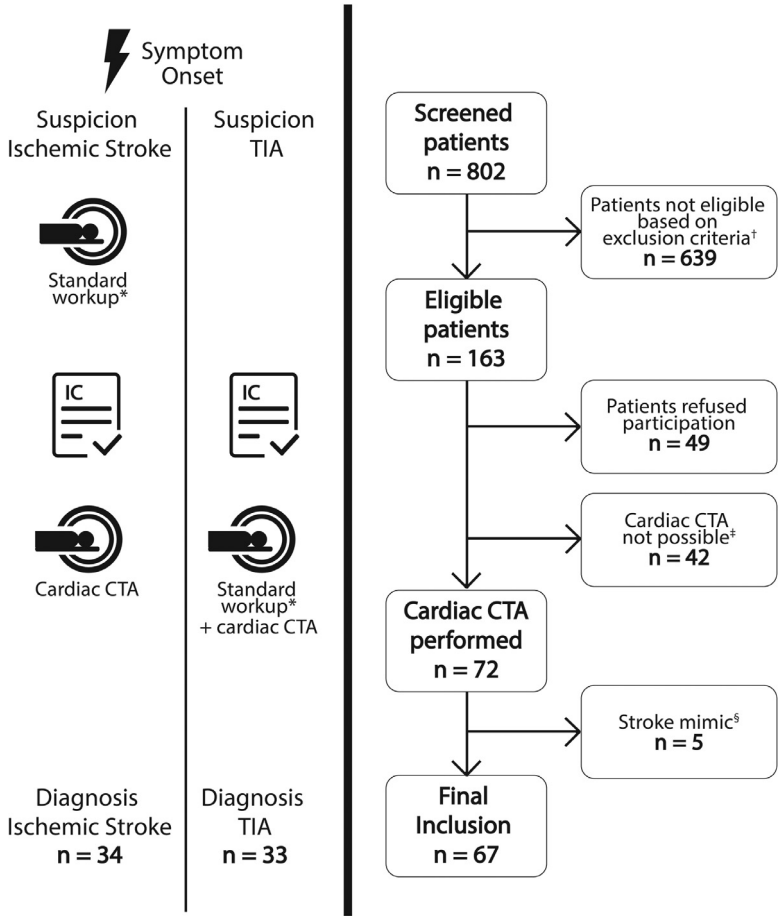

Fig. 1. *Flowchart of study procedures. CTA – Computed Tomography Angiography; IC – Informed Consent. * Standard workup: unenhanced brain CT, cervical duplex ultrasound and/or CTA of the aortic arch to the vertex, and single ECG recording. After cardiac CTA, echocardiography was performed in selected patients.* † *Patients were not eligible because of uncertain clinical diagnosis based on first assessment (n = 261), renal insufficiency (n = 120), allergy to iodinated contrast material (n = 10), symptom onset more than 7 days prior to admission (n = 94), age below 50 years (n = 92), unable to provide informed consent (n = 55), previous use of oral anticoagulants (n = 2), other known cause (n = 5).* ‡ *Cardiac CTA was not possible due to logistics or technical problems (n = 9), early discharge (n = 7), not possible < 2 days after standard workup (n = 4), judged as too burdensome (mainly because of recent endovascular stroke treatment, n = 19), or other reasons (n = 3).* § *Five patients were excluded after cardiac CTA due to diagnosis of stroke mimic (sporadic amyloid angiopathy, n = 1; subdural haemorrhage, n = 1; epilepsy, n = 1; orthostatic hypotension, n =1 ; transient tumour attack, n = 1).*

after cardiac CTA, respectively; both intracardiac thrombi were confirmed by TTE/TEE. Nineteen additional patients underwent routine cardiology assessment for clinical reasons (e.g. ECG findings, suspected CE aetiology). All patients received TTE, and 9/19 patients received TEE, after a median of 13.5 days (IQR 4.75–28.5). Holter ECG was performed in 19 patients (24-hour monitoring n = 11; 48 h n = 7; 1-week n = 1) but did not identify any AF.

Therapeutic implications

Cardiac CTA resulted in a change from antiplatelets to oral anticoagulants in the two patients who had an intracardiac thrombus. In these patients, there was no history of AF, nor was AF detected during cardiological assessment. The number needed to scan to change therapeutic management was 34.

Discussion

This study showed that prevalence of CE risk sources is substantial in patients with TIA and IS; a cardiac thrombus was identified in 3%, a medium/low-risk CE source in 42%. Also, a complex plaque in the aorta occurred often, i.e. in 24% of patients. Identification of an intracardiac thrombus on cardiac CTA changed therapeutic management from antiplatelet to oral anticoagulation treatment in two IS patients (6%).

The majority of CE risk sources identified were of medium/low risk that carry no direct therapeutic implications.[6] A large number of patients had atherosclerotic plaque in the aorta (48/67, 72%) of whom 16 (24%) had a complex plaque. These numbers are similar to previous studies reporting aorta atherosclerosis with CTA.[4,18,19] Although a newly diagnosed complex aortic plaque after TIA or IS can be suggestive of an atherosclerotic aetiology,

Table 1. *Baseline characteristics*

Clinical characteristics	Total N = 67	TIA N = 33	Ischaemic stroke N = 34
Age (Mean, range)	68 (51−89)	68 (51−89)	68 (52−83)
Men (n, %)	46 (69%)	23 (70%)	23 (68%)
Previous TIA/IS (n, %)	17 (25%)	6 (18%)	11 (32%)
Hypertension (n, %)	38 (57%)	12 (36%)	26 (76%)
Hyperlipidaemia (n, %)	22 (33%)	7 (21%)	15 (44%)
Diabetes mellitus (n, %)	12 (18%)	4 (12%)	8 (24%)
Myocardial infarction (n, %)	5 (7%)	2 (6%)	3 (9%)
Angina Pectoris (n, %)	7 (10%)	3 (9%)	4 (12%)
Atrial Fibrillation (n, %)	2 (3%)	0 (0%)	2 (6%)
Current smoking (n, %)	22 (33%)	9 (27%)	13 (38%)
Use of antiplatelets (n, %)	25 (37%)	11 (33%)	14 (41%)
Stroke characteristics			
Cortical symptoms*	19 (28%)	7 (21%)	12 (35%)
Retina involvement	12 (18%)	6 (18%)	6 (18%)
Lacunar syndrome	9 (13%)	4 (12%)	5 (15%)
Vertebrobasilar symptoms	10 (15%)	5 (15%)	5 (15%)
Other†	17 (25%)	11 (33%)	6 (18%)
Affected territory:			
Anterior circulation	53 (79%)	25 (76%)	28 (82%)
Posterior circulation	12 (18%)	6 (18%)	6 (18%)
Uncertain‡	2 (3%)	2 (6%)	0 (0%)
NIHSS (Median, IQR)	0 (0−2)	0 (0−0)	2 (1−3.25)

NIHSS − National Institutes of Health Stroke Scale; TIA − Transient Ischaemic Attack.
*Cortical symptoms included aphasia, higher mental function deficits and homonymous hemianopia.[40]
†Other symptoms included weakness or numbness.
‡Affected territory was uncertain when symptoms or imaging findings did not indicate either anterior or posterior circulation.

our population only had a limited number of complex plaques proximal to the supra-aortic arteries. Retrograde flow in the descending aorta could in theory allow emboli from plaques distal to the supra-aortic arteries to travel to the cranial circulation.[5,25,29] However, causality has yet to be proven and the most appropriate management in this setting remains undetermined. Previous studies on patients with aortic plaque indicated no added benefit in

Table 2. *Results of standard diagnostic workup*

	Total N = 67	TIA N = 33	Ischaemic stroke N = 34
ECG recordings			
Findings requiring cardiac investigation*	9 (14%)	4 (12%)	5 (15%)
Cardiac problems known from history†	6 (9%)	3 (9%)	3 (9%)
Unenhanced CT			
Early ischaemic changes	7 (10%)	0 (0%)	7 (21%)
Leukoaraiosis	24 (36%)	11 (33%)	13 (38%)
lacunar infarction	19 (28%)	10 (30%)	9 (27%)
Cervical CTA			
Significant carotid artery stenosis‡	6 (9%)	5 (15%)	1 (3%)
Carotid artery occlusion	1 (1%)	1 (3%)	0 (0%)
Carotid artery near occlusion§	1 (1%)	0 (0%)	1 (3%)
Cranial CTA			
Intracranial large vessel occlusion	3 (4%)	0 (0%)	3 (9%)

ECG − Electrocardiogram; CT − Computed Tomography; CTA − CT Angiography; TIA − Transient ischaemic attack.
Missing ECG recording in ischaemic stroke patient, n = 1.
*Findings on ECG requiring subsequent cardiac investigation include signs of arrhythmia, left ventricular hypertrophy, possible myocardial infarction, or atrioventricular block.
†Findings on ECG related to a known cardiac problem from patient history, including myocardial infarction, hypertrophic cardiomyopathy or left ventricular hypertrophy.
‡Significant carotid artery stenosis is defined according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria[23] as more than 50%.[24]
§Near total occlusion of the internal carotid artery is defined as NASCET grade of 99%.

Table 3. *Prevalence of CE risk sources and aorta atherosclerosis*

Cardiac CTA	Total N = 67	TIA N = 33	Ischaemic stroke N = 34
High-risk CE source (n, %)			
Intracardiac thrombus (LV/LA/LAA)	2 (3%)	0 (0%)	2 (6%)
Medium/low-risk CE source (n, %)			
Filling defects LA/LAA/LV*	2 (3%)	0 (0%)	2 (6%)
PFO	12 (18%)	4 (12%)	8 (24%)
Atrial septal aneurysm	2 (3%)	0 (0%)	2 (6%)
Mitral annular calcification	6 (9%)	2 (6%)	4 (12%)
Aortic valve calcification	12 (18%)	6 (18%)	6 (18%)
LV aneurysm without thrombus	3 (4%)	2 (6%)	1 (3%)
Total	28 (42%)	11 (33%)	17 (50%)
CTA of the aorta†			
Aortic plaque < 4 mm	32 (48%)	12 (36%)	20 (63%)
Complex aortic plaque	16 (24%)	10 (30%)	6 (19%)
Plaque > 4 mm	12 (18%)	7 (21%)	5 (16%)
Plaque with ulcer	4 (6%)	3 (9%)	1 (3%)

CE – Cardioembolic; CTA – CT Angiography; LV – Left ventricle; LA – Left atrium; LAA – Left atrial appendage; PFO – Patent foramen ovale; TIA – Transient ischaemic attack.

*Defined as a filling defect with an oval or round shape in the LAA[26] or a filling defect with a lower attenuation than the papillary muscle in the LA or LV.[27]

†Missing n = 2; in two ischaemic stroke patients the aorta was not included in the field of view of the CTA.

secondary prevention for warfarin compared with aspirin and clopidogrel.[30] However, effectiveness of oral anticoagulation versus the current reference standard of clopidogrel monotherapy[6] for treatment of complex aortic plaques, has not yet been investigated. The optimal treatment strategy for complex aortic plaques after TIA/IS could, therefore, still differ from current practice, especially with the novel anticoagulants with better safety profiles than warfarin.[31]

Two previous studies describing the use of CTA of the heart and aorta in patients with acute ischaemic stroke, reported an intracardiac thrombus prevalence of 10% (2/20 patients) and 5% (3/65 patients).[19,20] These proportions are somewhat higher than indicated by our study. All studies were small and therefore the differences in proportions might not be statistically significant. These studies included more severe stroke patients or had a higher proportion of patients with AF. Another study on patients with acute ischaemic stroke and TIA, reported a thrombus prevalence of 14% (3/21 patients), however, this study included patients with either AF or embolic stroke of undetermined source.[17] In our study, we excluded patients who were already treated with oral anticoagulants and our IS patients had relatively mild neurological deficits. Prevalence of high-risk CE sources might be higher in patients with severe stroke, since patients with CE related strokes have relatively more severe neurological deficits.[3]

Alternative strategies, compared with cardiac CTA, to increase the diagnostic yield for a CE risk source are either echocardiography or extended cardiac monitoring. A major limitation of TEE is patient discomfort; furthermore, TEE carries a small risk (<1%) of serious complications.[8] On the other hand, cardiac CTA also carries a small risk of kidney failure due to an increased contrast load (approximately 50 mL)[32] and a very small risk of cancer induction, especially in young patients, due to increased radiation exposure (approximately 1.5–2.5 mSv).[33] Whether the added benefit of identifying a CE risk source at an early stage with cardiac CTA outweighs the risk, especially for younger patients, remains to be determined.[33,34] The largest problem in clinical practice is the diagnostic delay that echocardiography may entail. Echocardiography is not always performed in the acute stage or in the first days after onset of symptoms.[20] Moreover, even when echocardiography is performed within a few days, this still gives a substantial delay compared with cardiac CTA that can be performed immediately on admission. Any delay inevitably increases the risk of recurrent events in patients with a cardioembolic stroke. Extended cardiac monitoring increases the rate of AF detection with resultant increased initiation of anticoagulants and a reduced risk of recurrent IS.[35] In addition, extended cardiac monitoring also enables identification of paroxysmal AF (PAF), which can be present in 24% of cryptogenic stroke patients[36] and has similar indication as persistent AF for anticoagulation treatment.[7,37] The yield of extended cardiac monitoring in detection of CE risk sources as compared to cardiac CTA is unknown at the moment and needs further evaluation, including cost effectiveness of each diagnostic strategy.

Our study has several limitations. First, this study included only patients above 50 years of age. However, for patients under the age of 50, yield of cardiac CTA might be substantially higher since cardioembolism is an important aetiology of stroke in younger people.[38] Second, CTA findings of medium/low-risk CE sources were

not confirmed by TTE or TEE. However, this study did not aim to compare TTE/TEE with cardiac CTA and previous studies already showed good test characteristics of cardiac CTA for CE risk sources.[11] Third, since we included patients with only mild deficits, we cannot extrapolate our results to patients with more severe strokes. Furthermore, the proposed cardiac CTA protocol requires an inspiratory breath hold that could be challenging for patients with more severe stroke and may affect image quality. However, the LA, LAA and LV have a relatively large size (in contrast to the coronary arteries, for example), and will therefore suffer little from respiratory artefacts. Even if no breath hold is possible, images will generally remain useful for detecting or excluding a high-risk CE source. Finally, cardiac CTA was performed with a median delay of 2 days after symptom onset, which might have negatively affected the yield since so-called 'wash-out' of thrombi may have occurred in this period.[39]

In conclusion, CTA of the heart and aorta has a high yield for detection of embolic risk sources in TIA/IS, with clinical consequences for 6% of IS patients. Cost-effectiveness of this approach, especially in comparison with long term cardiac monitoring, remains to be determined. However, from a patients' perspective, full diagnostic workup within one day might be the much-preferred option.

Declaration of Competing Interest

None.

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