Original Paper

Detection of Major Cardioembolic Sources in Real-World Patients with Ischemic Stroke or Transient Ischemic Attack of Undetermined Cause

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Abstract

Background/Aim: Current guidelines recommend transthoracic echocardiography (TTE) and ambulatory rhythm monitoring following ischemic stroke or transient ischemic attack (TIA) of undetermined cause for identifying cardioembolic sources (CES). Due to ongoing controversies about this routine strategy, we evaluated its yield in a real-world setting. ***Methods:*** In a tertiary medical center, we retrospectively evaluated consecutive patients with ischemic stroke or TIA of undetermined cause, who (after standard work-up) underwent TTE, ambulatory rhythm monitoring, or both. CES were classified as major if probably related to ischemic events and warranting a change of therapy. ***Results:*** Between January 2014 and December 2017, 674 patients had ischemic stroke or TIA of undetermined cause. Of all 484 patients (71.8%) who underwent TTE, 9 (1.9%) had a major CES. However, 7 of them had already been identified for cardiac evaluation due to new major electrocardiographic abnormalities or cardiac symptoms. Thus, only 2 patients (0.4%) truly benefitted from unselected TTE screening. Ambulatory rhythm monitoring was performed in 411 patients (61.0%) and revealed AF in 10 patients (2.4%). ***Conclusion:*** Detecting a major CES is essential because appropriate treatment lowers the risk of recurrent stroke. Nonetheless, in this real-world study that aimed at routine use of TTE and ambulatory rhythm monitoring in patients with ischemic stroke or TIA of undetermined cause, the prevalence of major CES was low. Most patients with major CES on TTE already had an indication for referral to a cardiologist, suggesting that major CES might also have been identified with a much more selective use of TTE.

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Introduction

Of all ischemic strokes, 20–30% are related to a cardioembolic source (CES) [1, 2], including atrial fibrillation (AF) and a variety of structural cardiac and ascending aortic pathologies [3]. Major CES have well-established pathophysiological relations to ischemic stroke and re-

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quire a change of therapy in order to reduce the risk of recurrent stroke, while minor CES might not necessarily be (directly) related to ischemic stroke and generally do not require changing therapy [3]. After standard in-hospital work-up of patients with ischemic stroke, the cause of the event remains unknown in 1 out of 4 patients [2]. In search of a major CES, these patients usually are referred for further cardiac assessment with echocardiography and ambulatory rhythm monitoring.

Echocardiography is the main imaging modality for detecting structural cardiac abnormalities [3], but its indication in patients with ischemic stroke remains a matter of debate [4, 5]. Most international guidelines advise routine echocardiographic evaluation in the setting of ischemic stroke or transient ischemic attack (TIA) of undetermined cause [3, 6–8]. However, the yield of transthoracic echocardiography (TTE) is uncertain. In previous studies it varied from 3 to 37%, but many of these studies assessed relatively small and inhomogeneous patient populations, and the used definitions of clinically relevant CES were dissimilar [5, 9–15]. In addition, current guidelines recommend rhythm monitoring for at least 24 h for detecting AF in patients with ischemic stroke. While these guidelines also consider more prolonged ambulatory rhythm monitoring to be reasonable, they specify neither the patient population to which this may apply nor the preferred method to be used [6, 8].

Aims

Our aim was to determine the rate of major CES detected by routine use of TTE and ambulatory rhythm monitoring in a consecutive series of patients with ischemic stroke or TIA of undetermined cause. For that purpose, the study applied a clear definition of clinically relevant findings, which was based on implications with a change of therapy.

Subjects and Methods

Study Design

At Medisch Spectrum Twente, a tertiary teaching hospital in the Netherlands, we assessed the clinical data on all patients aged 18 years or older from January 2014 to December 2017. Patients were included if they were diagnosed with ischemic stroke or TIA of undetermined cause after a standard work-up that consisted of medical history, physical examination, routine laboratory assessment, 12-lead electrocardiogram (ECG), continuous ECG monitoring for at least 24 h, brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) and carotid artery imaging with Doppler ultrasonography, CT angiography, or MR angiography. Ischemic stroke or TIA of undetermined cause due to

Table 1. Potential cardioembolic sources

	Therapy
Major cardioembolic sources	
Atrial fibrillation	OAC
Thrombus in the LA, LAA, or LV	OAC
LV aneurysm	OAC
Dilated cardiomyopathy with LVEF <35%	OAC
Mitral valve stenosis	OAC
Endocarditis	Antibiotics
Intracardiac tumor	Surgery
Minor cardioembolic sources	
Mitral valve prolapse	
Severe mitral annular calcification	
Moderate or severe aortic valve stenosis	
Aortic arch atheromatous plaques	
Patent foramen ovale	
Atrial septal aneurysm	

LA, left atrium; LAA, left atrial appendage; LV, left ventricle; LVEF, left ventricular ejection fraction; OAC, oral anticoagulation.

a negative evaluation was diagnosed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [16]. Patients were retrospectively identified from an electronic stroke database. Results from neurologic and cardiac investigations and therapeutic consequences were collected from original electronic patient files.

TTE Methods

The patients underwent TTE assessment by an experienced sonographer according to the European Association of Cardiovascular Imaging (EACVI) recommendations. They were imaged in the left lateral decubitus position, using commercially available TTE devices (EPIQ, iE33 or CX50 systems; Philips Medical Systems, The Netherlands). Images were obtained with a 5-MHz transducer in the parasternal and apical views (standard long-axis, short-axis, 2-chamber, and 4-chamber images). Standard two-dimensional, color Doppler, and both pulsed and continuous wave Doppler data were stored. All images were analyzed by board-certified cardiologists for left ventricular function, regional wall motion abnormalities, relevant valvular disease, atrial volume, and the presence of thrombi or tumors, using IntelliSpace Cardiovascular software (ISCV version 1.2; Philips Medical Systems Nederland B.V., Eindhoven, The Netherlands). Major CES were defined as findings that presumably were the CES of stroke and provided an indication for a change of therapy. Minor CES were defined as possible CES of stroke without therapeutic consequences [2, 3]. An overview of the major and minor CES and corresponding recommended therapy changes is provided in Table 1.

Ambulatory Rhythm Monitoring Methods

The patients were monitored with a 24-h 3-channel (5-lead) Philips DigiTrak XT Holter monitoring system (Philips Medical Systems Nederland B.V.), a 7-day 1-channel (2-lead) Vitaphone 3100BT event loop recorder (Vitaphone GmbH, Mannheim, Ger-
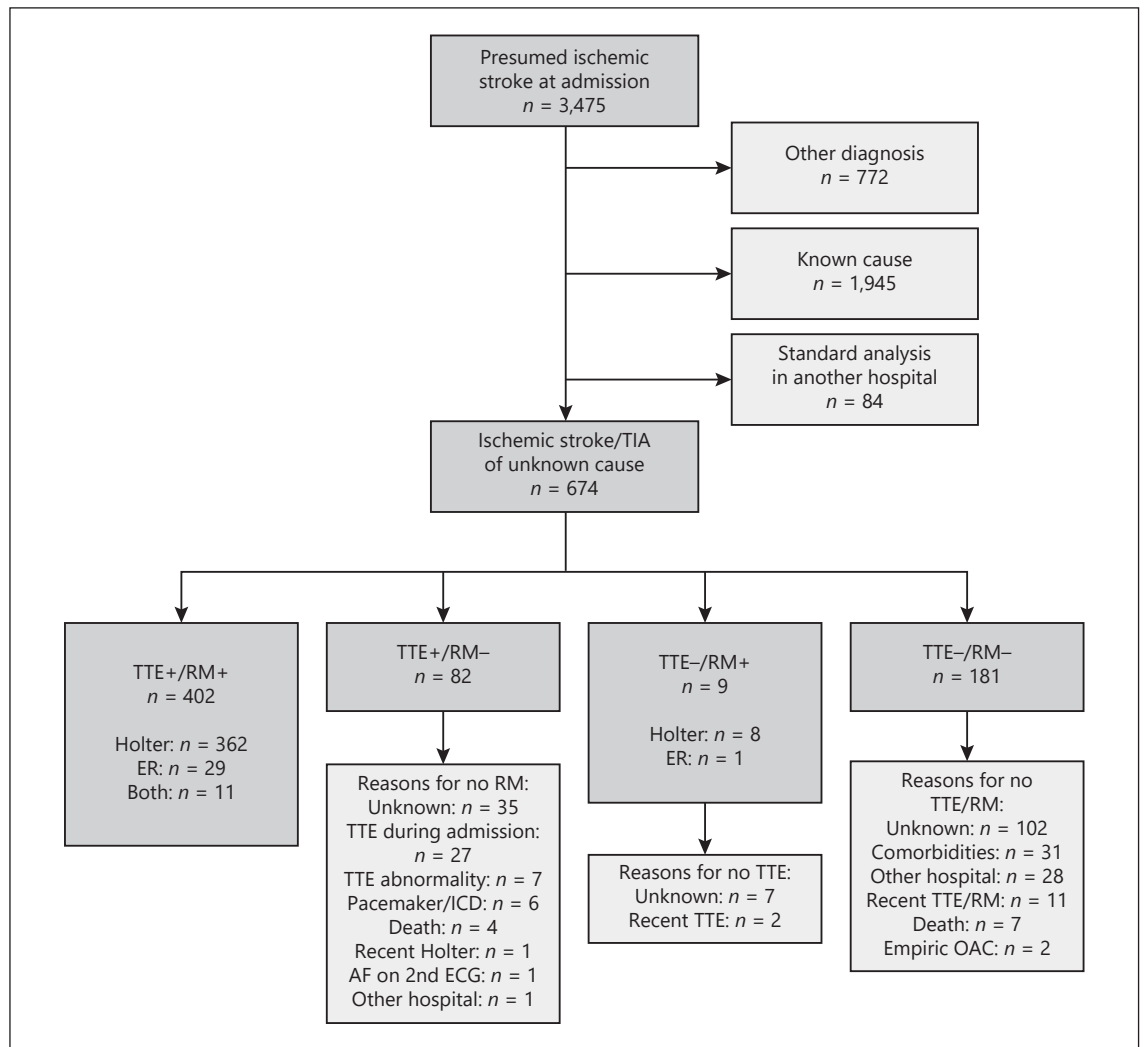
Fig. 1. Flowchart of patient inclusion. TTE, transthoracic echocardiography; RM, (ambulatory) rhythm monitoring; ER, event recorder; ICD, implantable cardioverter-defibrillator; AF, atrial fibrillation; OAC, oral anticoagulants.

many), or both, at the discretion of the treating cardiologist. The patients were asked to note when they had symptoms of chest pain, palpitations, or dyspnea. Patients with a Vitaphone event loop recorder could initiate recording when experiencing cardiac complaints. In addition, automatic AF detection was triggered based on R-R interval variability calculated by an integrated algorithm. All recorded episodes were analyzed by a board-certified cardiologist for AF or other arrhythmias, using Zymed analysis software (Philips Medical Systems Nederland B.V.) in case of Holter monitoring or the Vitaphone integrated software in case of event recording. AF was defined as a sequence of at least 30 s of irregular R-R intervals in the absence of distinct repeating P waves but presence of irregular atrial activity.

Outcome Measures and Statistical Analysis

The main study outcomes of interest were the rate of patients with a major or minor CES on TTE or ambulatory rhythm monitoring and the proportion of patients with a change of therapy. The data are presented as numbers and frequencies, mean ± SD, or median and interquartile range (IQR), as appropriate. All analyses were performed with SPSS, version 24 (IBM Corp., Armonk, NY, USA).

Results

From January 2014 until December 2017, 3,475 patients were admitted to the stroke unit of our medical center. A total of 674 patients had ischemic stroke or TIA of unknown cause; 484 (71.8%) of these patients underwent TTE, and 411 patients (61.0%) had an evaluation with ambulatory rhythm monitoring. In 181 (26.9%) of the el-

igible patients, no further cardiac investigation was performed (Fig. 1). Table 2 presents the characteristics of the included patients.

Yield of TTE

TTE revealed a major CES in 9/484 patients (1.9%) and a minor CES in 20/484 patients (4.1%). Further details are presented in Table 3. In 1 patient, mobile thrombi in the aortic arch were seen, which had not been classified as a major CES beforehand but were considered as such. Of all 9 patients with major CES on TTE, 6 had major ECG abnormalities that warranted echocardiographic assessment. Of the remaining 3 patients, 1 patient had severe exertional dyspnea that warranted further cardiac evaluation. Additional characteristics of these patients are shown in Table 4.

Yield of Ambulatory Rhythm Monitoring

Ambulatory rhythm monitoring revealed previously unknown AF in 10/411 patients (2.4%) of whom 370 patients underwent 24-h Holter monitoring, 30 had a 7-day event recorder, and 11 had both. Holter monitoring showed AF in 10 patients (2.6%), but 7-day event recording detected AF in none of the patients. The median duration between hospital admission and Holter monitoring was 40.5 (IQR 28.0–65.25) days, and the median duration between admission and 7-day event recording was 64.5 (IQR 40.5–110.0) days. Online supplementary Table 1 (see www.karger.com/doi/10.1159/000512743 for all online suppl. material) presents additional details of these patients.

Therapeutic Consequences

In all patients with a major CES there was a change of therapy. Further details are presented in Table 3.

Discussion

In this study on consecutive patients with ischemic stroke or TIA of undetermined cause, TTE revealed a major CES in 1.9% of the patients, and ambulatory rhythm monitoring detected AF in 2.4% of the assessed patients. Most patients with major CES on TTE (78%) already had an indication for further cardiac evaluation, based on symptoms or new ECG abnormalities. Therefore, it is fair to assume that the vast majority of these patients also would have been identified with a much more selective use of TTE.

Several earlier studies assessed the yield of echocardiography in patients with stroke [5, 9–15], but comparisons with the findings of the present study are hampered by several factors. Among the previous studies, the yield of echocardiography ranged from 3 to 37%, which is largely related to substantial differences in study populations. Most studies also included patients with a known cause of embolism, or nonischemic stroke [5, 9–14]. An additional factor with major impact on the yield is the evolution of which findings are classified as "therapy changers." For instance, some previous studies reported spontaneous echo contrast [11], or dilated cardiomyopathy or left ventricular wall dyskinesia regardless of the left ventricular ejection fraction [10, 13], as reasons for changing therapy. Current evidence does not suggest changing therapy based on these pathologies [3].

The findings of the present study suggest that routine screening with TTE in patients with ischemic stroke or TIA of undetermined cause is inefficient, since a major CES was found in 9 patients (1.9%). Furthermore, 7 of these 9 patients had new major ECG abnormalities or complaints of severe exertional dyspnea. Referring these

Table 2. Characteristics of the included patients

	TTE (n = 484)	Rhythm monitoring (n = 411)
Male sex	266 (54.8)	225 (54.7)
Age, years	65.7±13.8	66.0±13.3
Cardiovascular risk factors		
Hypertension	286 (59.1)	237 (57.7)
Diabetes	119 (24.6)	100 (24.3)
Dyslipidemia	391 (80.8)	338 (82.2)
Smoking	141 (29.1)	117 (28.5)
History of		
TIA	47 (9.7)	38 (9.2)
Ischemic stroke	51 (10.5)	42 (10.2)
Myocardial infarction	52 (10.7)	40 (9.7)
Type of event		
TIA	93 (19.2)	81 (19.7)
Ischemic stroke	391 (80.8)	330 (80.3)
Baseline NIHSS score	3 (2–5)	3 (2–5)
Localization		
Cortical	329 (68.0)	271 (65.9)
Subcortical	146 (30.2)	131 (31.9)
Lacunar	0	0
Border zone	1 (0.2)	2 (0.5)
Multiple locations	8 (1.7)	7 (1.7)

Data are presented as n (%) except for age (mean ± SD) and NIHSS (median [interquartile range]). TTE, transthoracic echocardiography; TIA, transient ischemic attack; NIHSS, National Institute of Health Stroke Scale.

Table 3. Potential cardioembolic sources found by TTE or rhythm monitoring, and therapeutic consequences

| | n (%) | Type of treatment | | |
		OAC	antibiotics	surgery
TTE (n = 484)				
Major risk sources	9 (1.9)	7	2	0
Thrombus in the LA, LAA, or LV	1 (0.2)	1	0	0
LV aneurysm	0	–	–	–
LV aneurysm and DCM with LVEF <35%	1 (0.2)	1	0	0
DCM with LVEF <35%	4 (0.8)	4	0	0
Mitral valve stenosis	0	–	–	–
Endocarditis	2 (0.4)	0	2	0
Intracardiac tumors	0	–	–	–
Mobile thrombi in the aortic arch[1]	1 (0.2)	1	0	0
Minor risk sources	20 (4.1)			
Mitral valve prolapse	3 (0.6)			
Severe mitral annular calcification	0			
Moderate aortic valve stenosis	3 (0.6)			
Severe aortic valve stenosis	0			
Aortic arch atheromatous plaques	1 (0.2)			
Patent foramen ovale	12 (2.5)			
Atrial septal aneurysm	1 (0.2)			
Ambulatory rhythm monitoring (n = 411)				
Atrial fibrillation	10 (2.4)	10	0	0

Data are presented as n (%). TTE, transthoracic echocardiography; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; OAC, oral anticoagulation. [1] Considered a major cardioembolic source with indication for oral anticoagulation although not classified beforehand.

Table 4. Characteristics of the patients with a major cardioembolic source on TTE

No.	Sex	Age, years	TTE findings	Complaints	ECG	Brain imaging
1.	M	48	DCM with LVEF <35%	Chest pain	Negative T in leads I, aVL, V4–V6	MRI: ischemia of the pons
2.	M	70	DCM with LVEF <35%	Palpitations	LBBB, ST elevation in leads V1–V3, ST depression in leads V5–V6	CT: no recent ischemia
3.	F	36	DCM with LVEF <35%	Exercise dyspnea	Normal	MRI: recent ischemia in the left MCA territory
4.	M	53	DCM with LVEF <35%	Exercise dyspnea	LBBB	CT: no recent ischemia
5.	M	57	DCM with LVEF <35% + LV aneurysm	No cardiac complaints	No R wave progression in anterior leads	CT: recent ischemia in the left MCA territory
6.	F	86	Endocarditis	Exercise dyspnea	Normal	CT: no recent ischemia
7.	M	66	Endocarditis	Fever chills, chest pain	Q waves in leads II, III, aVF, ST depression in leads V2–V5	MRI: diffuse bilateral spreading of areas of recent ischemia
8.	F	44	Left ventricular thrombus	No cardiac complaints	Q waves in leads V1–V3	MRI: recent ischemia in the right MCA territory
9.	F	78	Mobile aortic thrombi	No cardiac complaints	Normal	CT angiography: occlusion of the M3 segment indicating cortical ischemia

TTE, transthoracic echocardiography; ECG, electrocardiogram; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; LBBB, left bundle branch block; CT, computed tomography; MCA, middle cerebral artery.

patients to a cardiologist should be considered usual medical care. Thus, standard work-up would already have resulted in identifying CES in most of these patients, while in 2 patients, representing 0.4% of all patients who underwent TTE, a major CES would have been missed. Our results suggest that, with data from large prospective studies, the use of TTE in patients with ischemic stroke of undetermined cause could be optimized to reduce the number of futile examinations.

Intuitively, one may feel that transesophageal echocardiography (TEE) could be preferred for diagnosing CES, because it has a higher sensitivity for detecting left atrial appendage thrombi, complex aortic plaques, and vegetations. However, as an initial screening tool after ischemic stroke, TEE usually has no added value, because left atrial appendage thrombi are almost exclusively present in patients with AF [3], and oral anticoagulants do not lower the risk of recurrent stroke in patients with complex aortic plaques [17]. In addition, the diagnosis of infective endocarditis is based on the Duke criteria. When endocarditis is suspected, TTE is recommended as the first diagnostic modality, which has a sensitivity of approximately 60% for detecting a vegetation. However, if TTE results are negative and the clinical suspicion of endocarditis remains high, further evaluation with TEE, which has a sensitivity of 85–90% for detecting a vegetation, is necessary [3]. Nonetheless, patients with a high clinical suspicion of endocarditis were not considered to have ischemic stroke of undetermined cause and, thus, were not eligible for our study.

In the present study, ambulatory rhythm monitoring detected AF in 2.4% of the patients, and no more AF was detected in the small group of patients with 7-day event recording as compared to 24-h Holter monitoring. The longer period of time between the ischemic event and the initiation of the 7-day event recording might have played a role. A meta-analysis of Holter monitoring during 1–7 days showed a much higher detection rate of 10.7% [18]. Also, several other studies have demonstrated that AF is detected more frequently by prolonged and early-initiated monitoring [19, 20], suggesting approaches to improve AF detection.

Strengths and Limitations

The present study evaluated the results of both TTE and ambulatory rhythm monitoring in a relatively large group of patients with ischemic stroke of undetermined cause. In addition, we only classified cardiovascular pathologies as major CES if they were associated with a change of therapy.

Our study also has limitations. First, it is a single-center study with a retrospective design. This limits generalization of the findings. Second, 28% of the eligible patients did not undergo TTE and 39% had no additional ambulatory rhythm monitoring. Although cardiac assessment is part of clinical routine if standard work-up does not reveal the cause of ischemic stroke or TIA, physicians sometimes refrain from further analyses in individual patients, which may have resulted in over- or underrepresentation of findings. Third, the majority of patients underwent the shortest acceptable duration of ambulatory rhythm monitoring, and the time from ischemic event to initiation of ECG monitoring was relatively long. Fourth, the prevalence of patent foramen ovale (PFO) may be an underrepresentation, because patients that were not eligible for PFO closure at that time did not undergo agitated saline-enhanced echocardiography. PFO closure should only be considered in patients with cryptogenic embolism and a PFO with a high probability of a causal relationship, based on patient age, cardiovascular risk factors, and PFO characteristics [21, 22]. Evidence for this recommendation became available after publication of the results of the CLOSE, RESPECT, and Gore REDUCE trials, which was at the end of the inclusion period of our study [23–25].

Conclusions

Detecting a major CES is essential because it often leads to a change of therapy in order to reduce the risk of recurrent stroke. In this real-world study that aimed at routine use of TTE and ambulatory rhythm monitoring in patients with ischemic stroke or TIA of undetermined cause, the prevalence of major CES was low. Most patients with major CES detected by TTE already had an indication for referral to a cardiologist, which suggests that the majority of these pathologies would also have been identified with a much more selective use of TTE. These data call current cardiac screening into question. A large-scale, prospective multicenter study is warranted to provide data that may help develop a more efficient approach.

Statement of Ethics

This retrospective study is exempt from Ethics Committee approval. According to Dutch law, this study did not require a formal assessment by a medical Ethics Committee because the patients were not subjected to interventions other than in the context of standard medical care or imposed upon a particular course of conduct.

Conflict of Interest Statement

Funding Sources

Author Contributions

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