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Cardiac imaging in ischemic stroke or transient ischemic attack of undetermined cause: Systematic review & meta-analysis

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ABSTRACT

Background: Patients with ischemic stroke or transient ischemic attack (TIA) of undetermined cause often undergo cardiac imaging in search of a cardioembolic source. As the choice of the most appropriate imaging approach is controversial and therapeutic implications have changed over time, we aimed to identify in patients with "cryptogenic stroke or TIA" the yield of transthoracic or transesophageal echocardiography (TTE or TEE) and cardiac computed tomography (CT).

Methods and results: We performed a systematic review and meta-analysis according to the PRISMA guidelines. Included were studies that assessed consecutive patients with ischemic stroke or TIA of undetermined cause to evaluate the yield of TTE, TEE, or cardiac CT for detecting cardioembolic sources. For each type of cardioembolic source the pooled prevalence was calculated. Only six out of 1458 studies fulfilled the inclusion criteria (1022 patients). One study reported the yield of TTE, four of TEE, and one of both TTE and TEE; no study assessed cardiac CT. Mean patient age ranged from 44.3–71.2 years, 49.2–59.7% were male. TTE detected 43 cardioembolic sources in 316 patients (4 (1.3%) major, 39 (12.3%) minor), and TEE 248 in 937 patients (55 (5.9%) major, 193 (20.6%) minor). The most prevalent major cardioembolic source was left atrial appendage thrombus, yet results were heterogeneous among studies.

Conclusions: TTE and TEE infrequently detect major cardioembolic sources that require a change of therapy. Findings should be interpreted with caution due to the limited number of studies. A large-sized prospective clinical trial is warranted to support evidence-based decision-making.

1. Introduction

After an ischemic stroke or transient ischemic attack (TIA), generally there is a diagnostic work-up in search of the cause of the event, as this information may guide treatment that aims at reducing the risk of recurrent ischemic events [1,2]. In 20–25% of patients, ischemic stroke can be attributed to cardiac embolism [3–5]. Cardiac emboli may not only result from atrial fibrillation (AF), but from a variety of structural abnormalities and conditions of the heart or the ascending aorta. Major cardioembolic sources are conditions that are considered presumable causes of an ischemic stroke and require a change of therapy, whereas for minor cardioembolic sources the causal relationship is uncertain and in most cases no change of therapy is required [5,6].

Despite a routine in-hospital diagnostic work-up that generally consists of imaging of the brain and carotid arteries, laboratory testing, electrocardiogram (ECG), and at least 24 h of cardiac rhythm monitoring, the underlying cause remains unknown in about 25% of patients [4]. In these patients, the event is referred to as "cryptogenic stroke" or "ischemic stroke of undetermined cause". The term "embolic stroke of undetermined source" (ESUS), which has been proposed as a more

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clearly defined concept, is confined to patients with an imaging-proven, non-lacunar cerebral infarction in the absence of a ≥ 50% ipsilateral extra- or intracranial arterial stenosis, and in the absence of a major cardioembolic source or other specific cause of stroke [4].

After negative routine work-up, most guidelines advise cardiac imaging [1,2,6,7], but it is much less defined how to examine the heart and what exactly to look for. Detecting a treatable, major cardioembolic source is of paramount importance, yet insights into the relation between cardiac conditions and ischemic stroke have shifted over the past years. Several cardioembolic sources, such as aortic atheroma or dilated cardiomyopathy, are no longer considered to have therapeutic implications in this context [8–10]. In addition, a causal relationship with stroke remains uncertain for spontaneous echo contrast, mitral valve prolapse, and mitral annular calcification. Furthermore, a patent foramen ovale (PFO), which is present in 20–30% of the general population, may often be a coincidental finding. Both, the risk of a PFO being causative and the risk of stroke recurrence due to PFO are related to several factors, such as patient age, cardiovascular risk factors, and characteristics of the PFO. Based on evidence from the CLOSE, RESPECT, and Gore REDUCE trials, PFO closure is recommended only in selected patients with estimated high probability that the PFO is causative [11–14]. Only in those patients considered eligible for closure, screening for PFO is required.

The choice of cardiac imaging technique is not a straightforward issue [15], as guidelines provide no consistent recommendations as to use transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) [1,2,6,7]. While TTE is non-invasive and easily accessible, both the left atrial appendage (LAA) and ascending aorta can be better visualized with TEE [6,15]. Furthermore, cardiac computed tomography (CT) has been suggested as an alternative to echocardiography [16].

Previous meta-analyses of cardiac imaging in patients with cryptogenic stroke assessed the yield of TEE only, and showed heterogeneous results [17,18], most likely due to differences in the extent of diagnostic work-up prior to echocardiography, dissimilar definitions of relevant echocardiographic findings, and selection bias (e.g., recruitment based on the referral for echocardiography). To the best of our knowledge, a systematic review of the existing evidence on the yield of TTE or cardiac CT has not yet been published. Hence, in the present systematic review and meta-analysis, we aimed at assessing the yield of imaging with TTE, TEE, or cardiac CT for detecting cardioembolic sources – in particular disorders with therapeutic consequences (i.e., major cardioembolic sources) – in patients with ischemic stroke or TIA of undetermined cause.

2. Methods

2.1. Study design and eligibility criteria

This review was performed according to the Preferred Reporting Items for Systematic Review an Meta-Analyses (PRISMA) 2009 checklist [19]. We searched for retrospective and prospective case-control and cross-sectional studies that were published in peer reviewed journals, written in English. Studies with cardiac imaging were included, if they reported the prevalence of major and minor cardioembolic sources in a consecutive population of patients with ischemic stroke or TIA of undetermined cause after routine in-hospital diagnostic work-up.

To minimize the risk of a selection bias, we excluded studies that selected patients based on referral for a certain cardiac imaging technique (e.g., echocardiography or cardiac CT). Studies were also excluded if <80% of patients underwent cardiac imaging or if the results for TTE and TEE were not separately reported.

Cardioembolic sources were classified based on current insights in possible relationships with ischemic stroke and treatment implications (supplemental Table I). Left-sided cardiac thrombi, mobile thrombi in the ascending aorta, mitral valve stenosis due to rheumatic valve disease, intracardiac tumors, and endocarditis were considered major cardioembolic sources because surgery or medical treatment (e.g., with oral anticoagulation and antibiotics) lower the risk of recurrent ischemic stroke [5,6,20–26]. Left ventricular (LV) aneurysm was classified as a major cardioembolic source. While an advantage of oral anticoagulation has not been proven for the overall population of patients with LV aneurysm [27], no results are available for the subpopulation of patients who recently experienced an ischemic stroke or TIA. Since LV thrombi are found in up to 48% of patients with LV aneurysm [28,29], prescription of oral anticoagulation may be justified in patients who also had an ischemic cerebral event and no evident alternative cause.

Moderate or severe aortic valve stenosis, complex atheromatous plaques in the aortic arch, and dilated cardiomyopathy with left ventricular ejection fraction <35% were considered as minor cardioembolic sources, as no benefit of treatment other than general secondary stroke prevention has been shown. Yet, these conditions are associated with higher risk of recurrent ischemic stroke [8–10,30]. A third category was reserved for patent foramen ovale (PFO), with or without atrial septal aneurysm (ASA), as a PFO may often be coincidental finding and only occasionally a potential source of cardioembolism.

2.2. Study search and selection

We identified studies by searching the CENTRAL, EMBASE, Pubmed, Scopus, and Web of Science databases using a combination of the following strings: ‘echocardiograph*’, ‘computed’, ‘CT’, ‘stroke undetermined’ and ‘cryptogenic stroke’. The last database search was performed on 27 July 2020. In addition, we screened the reference lists of all included articles and relevant reviews for potential eligible articles. Studies were evaluated for eligibility by two reviewers, SD and GM, and in case of disagreement by a third reviewer, HH. After reviewing the article titles, manuscripts were selected for reading abstracts, and subsequently for full-text review.

2.3. Data extraction and data items

The prevalence of pathologies defined as either major or minor cardioembolic source were independently obtained from the studies by both SD and GM. In addition, baseline characteristics of included patients, data on the diagnostic work-up prior to inclusion, and the application of either the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria [31] or ESUS definition [4] were obtained.

2.4. Risk of bias assessment

We used a quality assessment checklist based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist for cross-sectional studies [32] and the National Heart, Lung and Blood Institute (NIH) study quality assessment tool for observational cohort and cross-sectional studies [33], adjusted to meet study-specific criteria for quality assessment of the articles. Articles were assessed for bias on eight items: study setting, aim of study, outcome definitions, patient inclusion, patient consecutiveness, patient participation, description of data assessment methods, and blinded assessment of imaging results. The risk of publication bias was assessed by visual inspection of the funnel plots for each individual cardioembolic source, if appropriate.

2.5. Synthesis of results

We extracted the point prevalence and calculated the standard error and 95% confidence interval for each cardioembolic source in every study. When a cardioembolic source was reported by two or more studies, we used Review Manager ((RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to determine the weight assigned to each study in

order to calculate the pooled prevalence. A random effects model was used. Heterogeneity between studies was assessed with chi-squared statistics. For the interpretation of heterogeneity statistics, I^2 values of 50% or more were considered to represent substantial heterogeneity, whilst values of 75% or more were associated with considerable heterogeneity, according to the Cochrane Handbook for Systematic Reviews of Interventions [34]. Sensitivity analyses were performed when considered appropriate.

For each study we evaluated at which point in the stroke work-up patients were included and planned to perform subgroup analyses based on criteria for ischemic stroke of undetermined cause (i.e., according to TOAST criteria or ESUS definition) and age groups of patients below 50 years or 50 years and older.

3. Results

3.1. Study selection

A total of 3337 articles were identified by database search and another 25 from other sources, of which 1458 remained after removing duplicates (supplemental Fig. I). Search queries and results for each database are presented in supplemental Table II. After reviewing the titles, 540 articles were selected for reading abstracts, and subsequently 174 were selected for full-text review. Finally, six articles fulfilled the inclusion criteria and were included in both review and meta-analysis [35–40]. Supplemental Table III reports the reasons for excluding articles based on full-text analyses.

3.2. Study and patient characteristics

One study examined patients with TTE [36], four with TEE [37–40] and one with both TTE and TEE [35]. There was no study that assessed the yield of cardiac CT, meeting the inclusion criteria. The total number of included patients of all six included studies was 1022, and 49.2–59.7% were male. Patient characteristics at baseline are presented in supplemental Table IV; one study did not report this information [35].

3.3. Risk of bias

Supplemental Fig. II shows the risks of bias for each study. All six studies had a clearly defined aim, had a prospective design, and included patients in a prospective way. One included study did not report the enrollment period, and another one did not clearly define the various echocardiographic pathologies. Three of the included studies did not report whether patients with lacunar stroke were included, while one of these studies did use the TOAST criteria, which implies that such patients were excluded. In two studies, the proportion of the enrolled patients in respect to the total population of patients with stroke remained unclear. Three studies described the diagnostic tool in a limited way. Most studies did not report whether the analysts who performed the echocardiographic assessment were blinded to clinical patient data.

We considered the evaluation of publication bias by examination of funnel plots inappropriate, as cardioembolic sources were reported by five studies at most.

3.4. Results of individual studies and synthesis of results

3.4.1. Transthoracic echocardiography

Table 1 reports for each study the prevalence of cardioembolic sources identified by TTE. In a total of 316 patients from two studies, TTE detected 4 (1.3%) major and 39 (12.3%) minor cardioembolic sources, and 8 (2.5%) patients had PFO with or without ASA. No detailed clinical data was available to assess in individual cases the causality of PFO, which prevented us from determining the prevalence of PFO that could be considered a cardioembolic source. As one of both studies did not elaborate both valve disease and regional left ventricular dysfunction (e.g., a- or dyskinesia), these findings could not be assessed in the analysis. Forest plots of cardioembolic sources, reported by both studies, are displayed in Fig. 1. The major cardioembolic sources detected with TTE were LAA thrombus, LV thrombus, and LV aneurysm, which had a pooled prevalence of 0.4% (0.0–2.3), 0.5% (0.1–3.1), and 0.4% (0.0–2.3) of the examined patients, respectively. The most prevalent TTE-detected minor risk source was the presence of complex atheromatous plaques in the aortic arch with a pooled prevalence of 13.9% (9.5–19.8); yet considerable heterogeneity was present among the studies ($I^2 > 90\%$).

3.4.2. Transesophageal echocardiography

Table 2 presents the prevalence of cardioembolic sources as identified by TEE, which in a total of 937 patients detected 55 (5.9%) major and 193 (20,6%) minor cardioembolic sources. PFO was detected in 261 (27.9%) patient, of whom 73 (7.8%) also had ASA. Because of

Table 1
Prevalence of cardioembolic sources detected with TTE*†

CES	No of studies	Pts with CES	Total pts	Prev.	95% CI lower	95% CI upper	I2	p-value (heterogeneity)
Major risk sources		4	316					
LA thrombus [35,36]	2	0	316	0,00%	0,00	1,55	0%	$p = 1.00$
LAA thrombus [35]	1	1	231	0,43%	0,02	2,29		
LV thrombus [35,36]	2	2	316	0,54%	0,09	3,07	0%	$p = 0.43$
LV aneurysm [35]	1	1	231	0,43%	0,02	2,29		
Aortic thrombus [35]	1	0	231	0,00%	0,00	1,29		
Mitral valve stenosis [35]	1	0	231	0,00%	0,00	1,29		
Tumor [36]	1	0	85	0,00%	0,00	3,46		
Endocarditis	0	–	–	–	–	–		
Minor risk sources		39	316					
Aorta valve stenosis [35]	1	8	231	3,46%	1,62	6,47		
Complex aorta atheroma [35,36]	2	25	316	13,94%	9,46	19,79	97%	$p < 0.00001$
DCM LVEF <35% [35,36]	2	6	316	1,84%	0,55	5,04	0%	$p = 0.56$
Right-to-left shunt		8	316					
PFO [35]	1	3	231	1,30%	0,33	3,49		
PFO with ASA‡ [36]	1	5	85	5,88%	2,19	12,55		

TTE = transthoracic echocardiography, CES = cardioembolic source, LA = left atrial, LAA = left atrial appendage, LV = left ventricular, DCM = dilating cardiomyopathy, LVEF = left ventricular ejection fraction, MV = mitral valve, PFO = patent foramen ovale, ASA = atrial septal aneurysm.

* When a cardioembolic source is reported by one study, the point prevalence is presented, and when reported by two studies, the pooled prevalence is presented.

† Cardiac pathologies reported by studies but not included in table: De Bruijn 2006: mitral valve prolapse, mitral annular calcification, spontaneous echo contrast, atrial septal aneurysm, aortic aneurysm, false tendon, other (not specified). Santamarina 2012: dyskinesia/akinesia of the LV wall, spontaneous echo contrast, mitral valve stenosis/aortic stenosis (not separately reported).

‡ One study only reported the prevalence of PFO in combination with ASA, these results are not included in the prevalence of PFO alone.

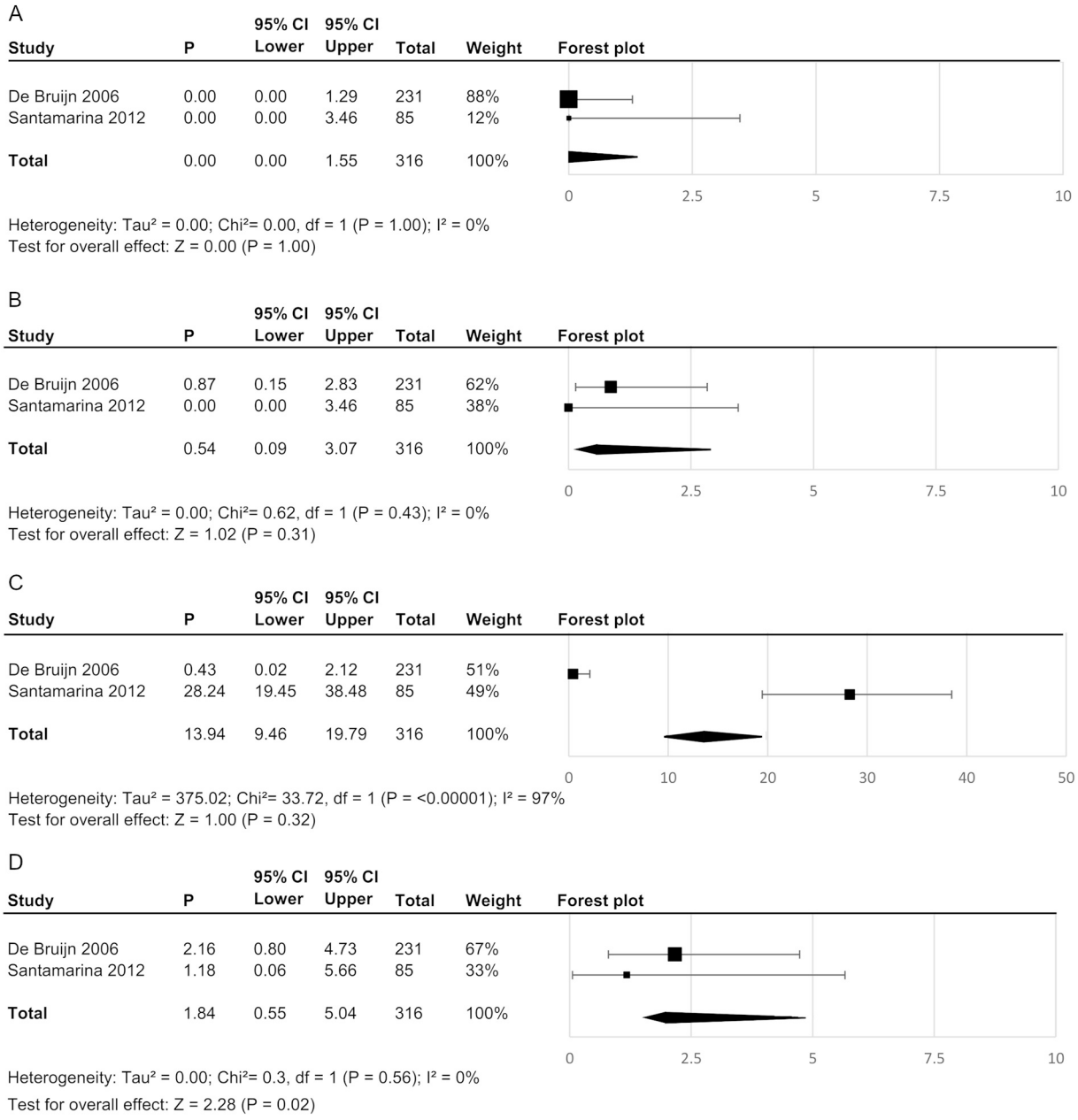

Fig. 1. Prevalence of cardioembolic sources detected with TTE, A: left atrial thrombus, B: left ventricular thrombus, C: complex aorta atheroma, D: dilated cardiomyopathy with left ventricular ejection fraction <35% (Santamarina et al. reported the prevalence of dilated cardiomyopathy with left ventricular ejection fraction <40%).

insufficient data on individual patient level, we could not determine the causality of PFO. As with TTE-based PFO detection, the rate of clinically relevant PFO, detected with TEE, remains unknown. Most cardioembolic sources were reported by only one or two of all five studies that reported TEE findings. Two studies reported a combined prevalence for left atrial (LA) and LAA thrombus, and thus these results are presented separately from data on the individual pathologies. Forest plots of pathologies that were described by at least two studies are shown in Fig. 2.

Two studies reported a high prevalence of LAA thrombus (15.2% (10.2–22.3)), but notably the findings of two other studies are not included in this rate, as these studies reported the presence of thrombi in the LA and/or LAA as a single combined rate (0.8% (0.2–2.3) that was considerably lower than the rate of LAA thrombi in the two aforementioned studies. Using TEE, all other individual major cardioembolic sources were found in less than 1%. A single study reported a higher prevalence of aortic thrombus (13/212(6.1%)); however, as the study's definition of this finding was 'a laminated deposition along the intimal surface with variable echogenicity', we categorized it as complex atheroma (i.e., no mobile aortic thrombus). The most common TEE-detected minor cardioembolic source was complex aortic atheroma with a pooled prevalence of 14.8% (11.1–21.5). Considerable heterogeneity was found for the detection of complex aortic atheroma and PFO ($I^2 > 90\%$).

3.5. Additional analyses

Supplemental Table V presents the diagnostic work-up for included patients for each study, including the use of TOAST criteria or ESUS definition for TTE and TEE respectively. Patients underwent prior 24-h rhythm monitoring for AF detection in one of two TTE studies, and two out of five TEE studies. In three TEE studies, patients underwent a TTE before TEE, and patients were not included in the study if the 24-h

Table 2
Prevalence of cardioembolic sources detected with TEE*†

CES	No of studies	Pts with CES	Total pts	Prev.	95% CI lower	95% CI upper	*I2*	*p*-value (heterogeneity)
Major risk sources		55	937					
LA thrombus [35,39]	2	2	292	0,51%	0,03	2,50	0%	$p = 0.55$
LAA thrombus [35,40]	2	41	261	15,18%	10,22	22,28	12%	$p = 0.29$
LA/LAA thrombus [37,38]	2	5	615	0,76%	0,18	2,34	0%	$p = 0.50$
LV thrombus [35,37]	2	3	634	0,35%	0,03	1,49	0%	$p = 0.40$
LV aneurysm [35]	1	1	231	0,43%	0,02	2,29		
Aortic thrombus [35]	1	0	231	0,00%	0,00	1,29		
Mitral valve stenosis [35]	1	0	231	0,00%	0,00	1,29		
Tumor [38,39]	2	1	273	0,05%	0,00	1,61	0%	p = 0.40
Endocarditis [38,39]	2	2	273	0,73%	0,12	3,41	42%	$p = 0.19$
Minor risk sources		193	937					
Aorta valve stenosis [35]	1	8	231	3,46%	1,62	6,47		
Complex aorta atheroma [36–40]	5	180	937	14,80%	11,11	21,55	95%	p < 0.00001
DCM LVEF <35% [35]	1	5	231	2,16%	0,80	4,73		
Right-to-left shunt		261	937					
PFO [35,37–40]	5	261	937	26,78%	19,63	35,48	98%	p < 0.00001
PFO with ASA‡ [37–40],	4	73	706	9,09%	5,57	15,46	63%	$p = 0.04$

TEE = transesophageal echocardiography, CES = cardioembolic source, LA = left atrial, LAA = left atrial appendage, LV = left ventricular, DCM = dilating cardiomyopathy, LVEF = left ventricular ejection fraction, MV = mitral valve, PFO = patent foramen ovale, ASA = atrial septal aneurysm.

* When a cardioembolic source is reported by one study, the point prevalence is presented, and when reported by two or more studies, the pooled prevalence is presented.

† Cardiac pathologies reported by studies but not included in table: De Bruijn 2006: mitral valve prolapse, mitral annular calcification, spontaneous echo contrast, atrial septal aneurysm, aortic aneurysm, false tendon, other (not specified). De Castro 2010: thrombogenic milieu (spontaneous echo contrast or atrial appendage flow <30 m/s), atrial septal aneurysm. Harloff 2006: spontaneous echo contrast, atrial appendage flow <30 m/s, aortic aneurysm, atrial septal aneurysm. Katsanos 2016: LA enlargement, atrial septal aneurysm, ventricular septum defect. Rauh 1996: atrial septal aneurysm.

‡ Four out of five studies reported the prevalence of PFO in combination with ASA as well as their individual prevalence. Results presented for the combination PFO and ASA are also included in the prevalence of PFO alone.

rhythm monitoring or the TTE detected a major cardioembolic source.

Due to the dissimilarity in prior diagnostic work-up prior to study inclusion and the use of TOAST criteria and ESUS definition among the limited number of available (and included) studies, a subgroup analysis based on the criteria for ischemic stroke of undetermined cause could not be performed. Furthermore, as none of the studies reported findings separately for patients <50 and ≥50 years of age, no data were available for an initially intended subgroup analysis to compare both age groups.

We performed sensitivity analyses for cardioembolic sources that were presented by all five studies that evaluated TEE. Sensitivity analyses based on the items used for bias assessment criteria did not have a substantial impact on heterogeneity for both complex aortic atheroma and PFO.

4. Discussion

For this systematic review and meta-analysis, we aimed at investigating in patients with ischemic stroke of undetermined cause the yield of echocardiography and cardiac CT for detecting (in particular major) cardioembolic sources. We found six studies [35–40] that described echocardiographic results in a total of 1022 patients, showing that TTE detected no more than 4 cardioembolic sources that warrant a change of therapy in 316 (1.3%) patients, and with TEE 55 of such cardioembolic sources were found in 937 (5.9%) patients. Yet, these prevalences may reflect an overestimation, as a single patient can have more than one cardioembolic source and, therefore, might have been counted more than once. Lastly, none of the studies that assessed the diagnostic value of cardiac CT fulfilled the prespecified inclusion criteria of this meta-analysis.

In the present analysis, TTE and TEE rarely detected a major cardioembolic source, with the exemption of TEE-detected LAA thrombus. De Bruijn et al. reported a remarkably high rate (16.4%) of TEE-detected LAA thrombus [35], while in the substantially smaller-sized study by Rauh et al. the prevalence was 10.0% [40]. In contrast, two other studies that reported the presence of thrombi in either LA or LAA altogether found a much lower prevalence of no more than 0.8% [37,38]. The most likely explanation for this discrepancy may be a substantial difference in rhythm monitoring prior to study inclusion, as LAA thrombi are almost exclusively found in patients with permanent or paroxysmal atrial fibrillation (AF) [6,41]. Thus, in most of the 41 patients with an LAA thrombus, covert AF is likely to be present, which might have been detected with appropriate (or extended) cardiac rhythm monitoring that generally puts less strain on patients than semi-invasive assessment with TEE.

Minor cardioembolic sources were detected more often, especially complex aortic atheroma. Interestingly, detection rates by TTE and TEE were quite similar. Lastly, PFO was reported in 26.8% of patients studied with TEE, which matches with the prevalence of PFO in the general population. However, as data on age and risk factors of these patients with PFO were unavailable, the rate of PFO that should be considered a cardioembolic source could not be determined. Although some studies described the prevalence of spontaneous echo contrast, unspecified left ventricular wall motion abnormalities, unspecified valvular disease, mitral valve prolapse, mitral annular calcification, and ASA in the absence of a PFO, we did not include these findings in the present meta-analysis, as its causal relevance in relation to ischemic stroke is uncertain [4–6,42].

In the present analysis, we only included studies that examined consecutive patients with ischemic stroke of undetermined cause, while we excluded studies that selected patients based on referral for TTE or TEE. This approach is in contrast with earlier meta-analyses [17,18]. It has the advantage that it reduces the risk of selection bias, as patients with higher suspicion of cardiac disease or younger patients might be more regularly referred for echocardiography. Furthermore, the question whether patients with ischemic stroke of undetermined cause are routinely referred for cardiac imaging can be determined by assessing hospital-wide practice. Yet, such data are scarce. Study results suggest that the referral practice may substantially differ, as we found considerable heterogeneity among study results for the detection of complex aortic atheroma and PFO. Sensitivity analyses based on items of the risk of bias assessment did not show any impact on the levels of heterogeneity. Differences in the definition and interpretation of imaging findings and differences between study populations (e.g., patient age, risk factors, and stroke severity) may also account for heterogeneity. In

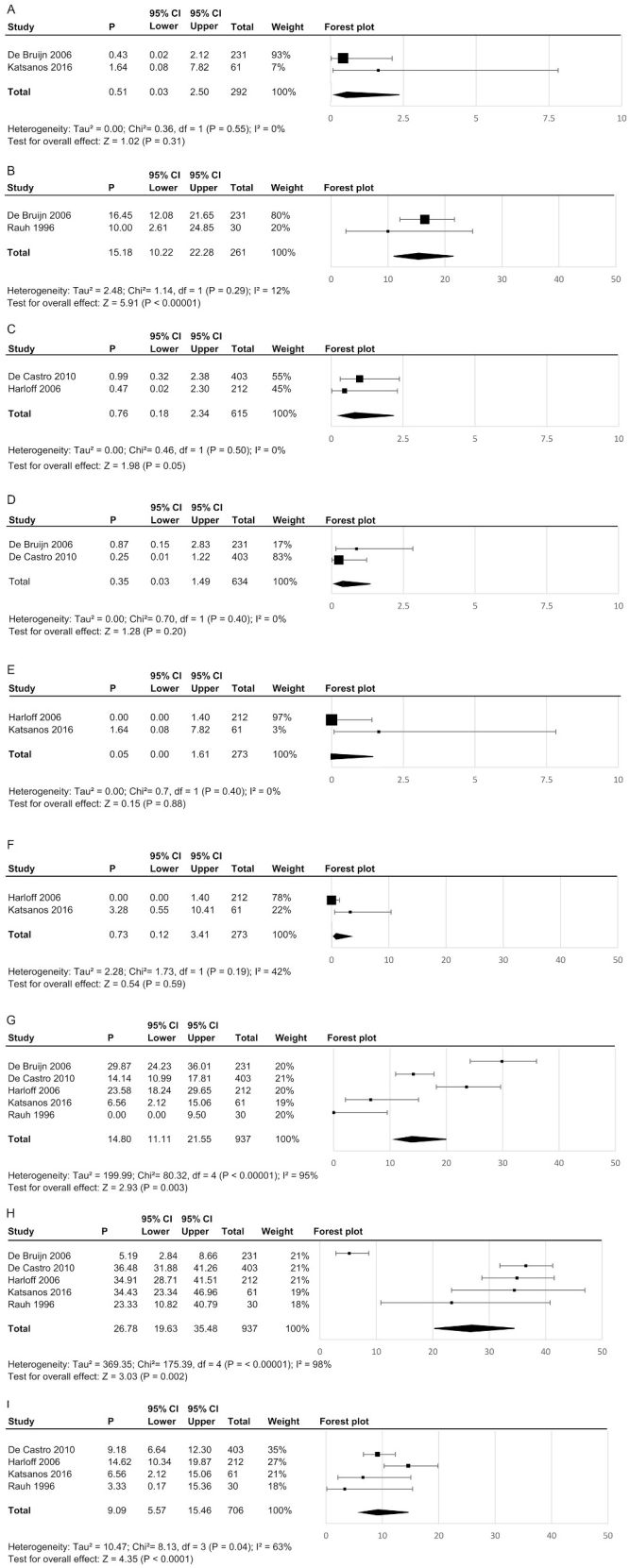

Fig. 2. Prevalence of cardioembolic sources detected with TEE, A: left atrial thrombus, B: left atrial appendage thrombus, C: left atrial and left atrial appendage thrombus, D: left ventricular thrombus, E: cardiac tumor, F: endocarditis, G: complex aorta atheroma, H: patent foramen ovale, I: patent foramen ovale with atrial septum aneurysm.

addition, considerable between-study differences in the extent of diagnostic work-up before patient inclusion may be important. Notably, three studies did not perform prior 24-h rhythm monitoring. In addition, three out of five studies that assessed TEE excluded patients who had a major cardioembolic source on prior TTE, which results in a more selected patient population and lowers the a priori likelihood of detecting clinically relevant pathologies with TEE.

4.1. Strengths and limitations

For this review and meta-analysis, we assessed the value of cardiac imaging in patients with ischemic stroke or TIA of undetermined cause. A strength of this study, in contrast with previous meta-analyses, is that we applied a highly stringent approach and included only studies that were not limited to the assessment of just one type of cardioembolic source or to minor cardioembolic sources only, but investigated and reported both major and minor cardioembolic sources. In addition, we considered all eligible patients with ischemic stroke of undetermined cause, instead of recruiting patients only because they were referred for echocardiographic assessment. This reduced the risk of selection bias.

Use of the stringent approach resulted in a limited number of no more than six included studies that examined a pooled patient population of almost 1000 patients. Most individual major cardioembolic sources were reported by just one or two studies, and we found substantial to considerable heterogeneity for analyses of cardioembolic sources that were reported by more than two studies. Consequently, the results should be interpreted with caution. Because of the relatively small number of studies in this meta-analysis, we could not examine potential publication bias, and we could not perform subgroup analyses based on criteria of ischemic stroke of undetermined cause and on age.

5. Summary

In patients with ischemic stroke of undetermined cause, several guidelines suggest a routine echocardiographic evaluation in order to detect treatable causes. Yet, the results of the present meta-analysis show that in such patients echocardiography infrequently detects major structural cardiac abnormalities. An exception is LAA thrombus, but the results of different studies are inconsistent, which may partly be related to differences in (or the absence of) cardiac rhythm monitoring prior to echocardiographic assessment. Due to the limited number of clinical studies, the results should be interpreted with caution. A large-sized prospective study is warranted to support evidence-based decision-making and guide future recommendations for clinical practice.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.06.047.

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