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ORIGINAL RESEARCH

Yield of Echocardiography in Ischemic Stroke and Patients With Transient Ischemic Attack With Established Indications for Long-Term Direct Oral Anticoagulant Therapy: A Cross-Sectional Diagnostic Cohort Study

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BACKGROUND: We aimed to determine the diagnostic yield of transthoracic (TTE) and transesophageal echocardiography (TEE) in patients with ischemic stroke and transient ischemic attack with established indications for direct oral anticoagulants before the index event.

METHODS AND RESULTS: This was a retrospective cohort study of consecutive patients with preceding established indications for long-term therapeutic direct oral anticoagulants presenting to a single comprehensive stroke center with ischemic stroke or transient ischemic attack. Choice of echocardiography modality was based on expert recommendations. The primary outcome was a composite of prespecified management-relevant high-risk findings adjudicated by an expert panel, based on TTE and TEE reports according to evidence-based recommendations. Explorative analyses were performed to identify biomarkers associated with the primary outcome. Of 424 patients included (median [interquartile range] age, 78 [70–84] years; 175 [41%] women; National Institutes of Health Stroke Scale, 4 [1–12]; 67% atrial fibrillation), 292 (69%) underwent echocardiography, while 132 (31%) did not. Modality was TTE in 191 (45%) and TEE in 101 (24%). Median time from index event to echocardiography was 2 (1–3) days. TTE identified 26 of 191 (14%) patients with 35 management-relevant pathologies. TEE identified 16 of 101(16%) patients with 20 management-relevant pathologies. Most management-relevant findings represented indicated coronary artery disease and valvular pathologies. In a further 3 of 191 (2%) patients with TTE and 4 of 101 (4%) patients with TEE, other relevant findings were identified. Variables associated with management-relevant high-risk pathologies included more severe stroke, diabetes, and laboratory biomarkers (NT-proBNP [N-terminal pro-B-type natriuretic peptide], C-reactive protein, D-dimer, and troponin levels).

CONCLUSIONS: In patients with established indications for long-term direct oral anticoagulant therapy and stroke who received echocardiography, both TTE and TEE identified a relevant and similar proportion of management-relevant high-risk pathologies and predictive biomarkers could help to guide diagnostic workup in such patients.

Key Words: anticoagulation ■ cardio-aortic pathology ■ diagnostic yield ■ direct oral anticoagulants ■ echocardiography

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CLINICAL PERSPECTIVE

What Is New?

- In patients with ischemic stroke with prior direct oral anticoagulation therapy, transthoracic and transesophageal echocardiography identified a relevant and similar proportion of management-relevant high-risk cardio-aortic pathologies when applying expert and guideline recommendations for choosing the echocardiography modality.
- Most management-relevant findings pointed toward coronary artery disease and valvular pathologies.
- Variables associated with management-relevant high-risk pathologies included more severe stroke, diabetes, and laboratory biomarkers (NT-proBNP [N-terminal pro-B-type natriuretic peptide], C-reactive protein, D-dimer, and troponin levels).

What Are the Clinical Implications?

- Echocardiography should also be performed in patients with ischemic stroke with preceding direct oral anticoagulant therapy, not only to understand the index event but also to pick up comorbid cardiovascular conditions.
- Laboratory and clinical features might help to decide in which patients to perform echocardiography if resources are limited.
- Prospective randomized studies of the available diagnostic modalities need to clarify the overall clinical impact of the diagnostic testing as well as the impact of an individualized secondary prevention strategy on meaningful clinical outcomes.

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
TTE	transthoracic echocardiography
TEE	transesophageal echocardiography

Cardioaortic embolism accounts for about a quarter of acute ischemic stroke (AIS).[1] Recent guidelines recommend echocardiography for the structural workup of cryptogenic and embolic stroke, but the efficacy of echocardiography to prevent recurrent cardiovascular events by optimizing secondary prevention is uncertain.[2] The number needed to screen to change management on an evidence-based principle is high.[3,4]

The most frequent and clinically significant management consequence of echocardiography findings is the initiation of oral anticoagulant treatment, usually after detection of atrial or ventricular thrombi.[5] However, as 15% of patients with AIS already have indications for long-term oral anticoagulants, these findings do not change management in this increasing group of patients.[6] In the past decades, there has been a rapid transition from vitamin K antagonist therapy to direct oral anticoagulants (DOACs) among patients with indications for oral anticoagulation. Consequently, the overall diagnostic yield of echocardiography for treatment change–relevant findings might be particularly low in this patient subgroup.

We therefore aimed to report on the diagnostic yield of transthoracic (TTE) and transesophageal echocardiography (TEE) for the composite yield of management-relevant high-risk findings triggering an evidence-based management change in patients with established indications for DOAC therapy before the index event. This included prespecified cardio-aortic sources of embolism, but also findings indicating coronary artery disease or valvular pathologies. Furthermore, we aimed to identify biomarkers associated with management-relevant findings.

METHODS

Data Availability Statement

Since the study structure has the characteristics of both an observational cohort and a diagnostic study, we followed the Strengthening the Reporting of Observational Studies in Epidemiology as well as the Standards for Reporting of Diagnostic Accuracy Studies guidelines (checklists attached in Data S1). We will share the data upon reasonable request from qualified investigators for the purposes of replicating or pooling results. The analysis and the registry were approved by the Ethics Committee Bern (KEK 2019-01010), and the requirement for active informed consent was waived according to Swiss law.

Eligibility Criteria

We retrospectively included all consecutive adult patients with confirmed ischemic or clinically confirmed transient ischemic events as final diagnosis in the medical report, who had indications for long-term therapeutic DOAC therapy (before the index event). Patients were identified from the prospective stroke registry of our comprehensive stroke center between January 2015 and December 2019. Indications for therapeutic-dose DOAC therapy included atrial fibrillation (AF) but also other indications such as recurrent thromboembolic events. The COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) regime (low-dose rivaroxaban plus aspirin) was not available in Switzerland during the study time frame; hence, such patients were

not included. For most indications such as AF and thromboembolic events, there are clear indications to prefer DOAC over vitamin K antagonist therapy.[7] Since vitamin K antagonist therapy remains first-line only for specific indications such as mechanical heart valves, we chose to restrict our analysis to patients on DOACs only. Patients with additional antiplatelet prescriptions were also included. In case of recurrence during the study period, only the first (index) stroke with preceding DOAC therapy was considered. Patients refusing the use of their data for research purposes were excluded (Swiss law). Otherwise, no exclusions were made and all AIS etiologies according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, including small-vessel occlusion, were considered. At our institution, we perform routine echocardiography in all patients with AIS, given that shared cardiovascular risk factors might result in relevant cardiac pathologies regardless of stroke subtypes, as it has been shown for AF.[8] The choice between TTE and TEE was based on expert recommendations[9,10] considering clinical symptoms and potential management consequences (see Figure for decision tree). We do not routinely consider other forms of diagnostic cardiac work, such as cardiac magnetic resonance imaging or cardiac computed tomography similar to the clinical practice worldwide.[11]

Echocardiography Technique

TTE and TEE were performed by sonographers and cardiologists in training, supervised by trained cardiologists with extensive experience in echocardiography according to institutional and international standards.[12] At our institution, TTE does not comprise a bubble test to screen for patent foramen ovale, since we perform TEE if closure would be considered. Because both tests were performed in routine clinical workup, clinical information and other results such as laboratory values were available to the performers/readers of the tests.

For the current study, documentation of prespecified pathologies in the echocardiography reports was retrospectively extracted by one investigator (K.B.) using a standardized extraction sheet. This included information on indeterminate test results for each pathology. Pathologies were defined according to echocardiography guidelines.[13-16]

Then, an expert panel of a board-certified stroke neurologist (T.R.M.) and a board-certified cardiologist and echocardiography fellow (E.B.) adjudicated the treatment relevance of the prespecified high-risk findings retrospectively using information of TTE and TEE reports as well as clinical information from electronic medical records.

Within the prospective registry, research fellows collected baseline variables such as information on vascular risk factors, laboratory values including cardiac biomarkers (Elecsys Troponin T-high sensitive, Roche), and outcomes using electronic case report forms.

Outcomes

The primary outcome was the composite yield of management-relevant high-risk findings triggering an evidence-based medication change, further diagnostic testing (eg, coronary angiography if coronary artery disease is suspected), or interventions/surgery as a direct consequence of it. Those high-risk findings included (1) pathologies of the left ventricle (thrombus, wall motion abnormalities, ejection fraction ≤35% or worsening of left ventricular ejection fraction ≥10% compared with prior echocardiography, dilated or other cardiomyopathy), (2) atrial (appendage) pathologies (thrombus, patent foramen ovale), (3) valvular pathologies (endocarditis, thrombosis, high-grade valvular disease), (4) nonthrombotic masses, and (5) aortic dissection. Prespecified high-risk pathologies with an evidence-based management change, but which were known before (eg, detection of a previously known regional wall motion abnormality) were also reported and classified as not having consequences. For adjudication of consequences, certain consequence was present if the evidence-based management change was not implemented anyway as a consequence of the stroke. Uncertain consequence was rated when a pathology was present but it was unclear whether it should have resulted in a management change (eg, whether it was known before). Secondary end points included the percentage of technically indeterminable findings by each modality and surrogate parameters associated with management-relevant high-risk findings.

Statistical Analysis

We use standard descriptive methods: medians (interquartile ranges) or means (with SD), as appropriate, as well as percentages to present the distribution of continuous, ordinal, and categorical variables, respectively. We compared variables between groups using Pearson's χ^2 or Fisher's exact test for categorical variables and the Wilcoxon rank-sum or Kruskal-Wallis test for continuous and ordinal variables. The 95% CI of the yield was calculated using the normal approximation to the binomial calculation. Because of the primarily descriptive purpose and missing information on relevant findings in patients with preceding oral anticoagulation, no sample size calculation was possible. STATA 16 (StataCorp, College Station, TX) including the *table 1_mc* was used. In addition to pathophysiologically plausible and established predictors from the literature, least absolute shrinkage and selection operator was used for to select the variables of a multiple logistic regression model.[17] Complete case analysis was done without imputation. A significance level of 0.05 was used without adjustment for multiple comparisons.

RESULTS

Of 5064 patients with ischemic stroke during the study time frame, 438 fulfilled the inclusion criteria. After exclusion of 10 patients with a second recurrent event and 4 patients who refused the use of their data for research purposes, the final cohort consisted of 424 patients with long-term indication for DOAC therapy (Figure S1). Median (interquartile range) age was 78 [70–84] years, 175 (41%) were women, median National Institutes of Health Stroke Scale was 4 [1–12]. A total of 352 (83%) had confirmed ischemic stroke and 72 (17%) suspected transient ischemic attack. AF was present in 67% of patients, 33% had recurrent or high-risk thromboembolic events such as pulmonary embolism or deep venous thrombosis as indication for long-term DOAC therapy.

Of those, 191 (45%) underwent TTE, 101 (24%) underwent TEE, and 132 (31%) did not receive echocardiography. Patients for whom no echocardiography was performed had more severe stroke, less often hyperlipidemia, shorter hospital duration, and a worse prognostic profile with markedly higher rates of death at 3 months. As compared with patients undergoing TTE and patients not receiving echocardiography, those who underwent TEE were younger, and less often had AF and arterial hypertension, reflecting a lower cardiovascular risk profile. Otherwise, no statistically significant differences were found. Most importantly, type of DOAC medication and history of heart valve replacement were similar across groups (Table 1). Rates of intravenous thrombolysis was overall 7% without differences between the groups (P=0.57).

Median time from index event to echocardiography was 2 [1–3] days. Frequencies of indeterminate results of each pathology according to the modality are shown in Table S1. In patients undergoing TTE, indeterminate results were highest for patent foramen ovale and regional wall motion abnormality as compared with ejection fraction. Patent foramen ovale and wall motion abnormality for TEE. There were no missing TTE or TEE reports and no serious adverse events attributable to echocardiography occurred.

Most common high- and moderate-risk pathologies are shown in Table 2 and Table 3. Overall, TTE identified 26 of 191 (14%; 95% CI, 9–18) patients with 35 certain management-relevant pathologies (see Table S2 for details on consequences). In a further 18 of 191 (9%) patients, high-risk pathologies were identified with uncertain treatment relevance. Another 91 pathologies were identified that had no management-relevant consequences. TEE, on the other hand, identified 16 of 101 (16%; 95% CI, 9–23%) patients with 20 certain management-relevant pathologies. In a further 8 of 101 (8%) patients, high-risk pathologies were identified with uncertain treatment relevance. Another 51 pathologies were identified that had no management-relevant consequences. Most management-relevant findings had no clear causal connection with the AIS but pointed toward coronary artery disease and valvular pathologies.

In a further 3 of 191 (2%) patients on TTE and 4 of 101 (4%) patients on TEE, other relevant findings (non–high-risk) were identified (see Table 3). However, most of the non–high-risk pathologies resulted in no change of management.

When TTE and TEE were combined, 42 of 292 (14%) patients with 55 certain management-relevant pathologies were found. In a further 26 (8.9%) patients, high-risk pathologies were identified with uncertain treatment relevance (Table S3).

Variables associated with certain management-relevant high-risk pathologies included more severe stroke, diabetes, and laboratory biomarkers (troponin levels, NT-proBNP [N-terminal pro-B-type natriuretic peptide], C-reactive protein, and D-dimer). There were no significant differences in distribution of high-risk and non–high-risk pathologies in patients with AF (see Table S4 and S5) for details. TOAST etiology was not significantly associated with presence of management-relevant high-risk pathologies. Age was also not a significant factor for this prediction (P=0.26). In the multiple regression analysis, diabetes (adjusted odds ratio, 3.2; 95% CI, 1.3–8.0), NT-proBNP (adjusted odds ratio per 1000 pg/mL, 1.22; 95% CI, 1.03–1.46), and D-dimer (adjusted odds ratio per 1000 µg/mL, 1.18; 95% CI, 1.06–1.31) were independently associated with a certain management-relevant high-risk pathology (Table S6). A total of 189 of 292 (65%) of patients could be included in this complete-case full model. Besides higher NT-proBNP there were no relevant differences between patients with and without missing data items (Table S7).

Fewer patients with transient ischemic attack had any high- or moderate-risk pathologies with uncertain or certain management-relevant consequences. Otherwise, variables associated with any high- or moderate-risk pathologies were identical to the above-mentioned variables (see Table S4). Also here, AF, age, and TOAST etiology were not significantly different between patients with and without any relevant pathology.

DISCUSSION

This single-center, retrospective cohort study on the yield of echocardiography in ischemic stroke and patients with transient ischemic attack with established indications for long-term direct oral anticoagulant therapy has the following main findings:

1. In the subgroup of patients in whom echocardiography was performed in the acute stroke setting,

Table 1. Baseline Characteristics According to Use and Modality of Echocardiography

	Entire cohort (n=424)	No. available	TTE (n=191)	No. available	TEE (n=101)	No. available	No echocardiography (n=132)	No. available	*P* value*
Epidemiology									
Age	77.5 (69.9–83.6)	424	78.8 (72–85)	191	71.9 (67–79.1)	101	79.4 (71.2–85.4)	132	<0.001
Female sex	175 (41.3)	424	80 (41.9)	191	34 (33.7)	101	61 (46.2)	132	0.15
NIHSS on admission	4 (1–12)	389	3 (1–9)	178	2.5 (1–7)	94	8 (3–18)	117	<0.001
Transient ischemic attack	72 (17.0)	424	31 (16.2)	191	18 (17.8)	101	23 (17.4)	132	0.93
Death at 3 mo	68 (16.5)	411	19 (10.2)	187	6 (6.2)	97	43 (33.9)	127	<0.001
Duration of hospitalization	3.0 (1.9–6.4)	396	2.9 (1.9–5.8)	181	4.7 (2.6–8.1)	100	2.7 (1.6–5.9)	115	<0.001
Medication									
Type of DOAC therapy		424		191		101		132	0.78
Rivaroxaban	286 (67.5)		129 (67.5)		64 (63.4)		93 (70.5)		
Apixaban	95 (22.4)		39 (20.4)		27 (26.7)		29 (22.0)		
Dabigatran	20 (4.7)		11 (5.8)		4 (4.0)		5 (3.8)		
Edoxaban	23 (5.4)		12 (6.3)		6 (5.9)		5 (3.8)		
Additional antiplatelet therapy	34 (8.2)	415	13 (7.0)		7 (7.0)		14 (10.9)		0.40
Medical history of cardiovascular risk factors									
Atrial fibrillation/flutter	282 (67.1)	420	133 (70.4)	189	53 (53.5)	99	96 (72.7)	132	0.004
Arterial hypertension	359 (85.5)	420	166 (87.8)	189	77 (77.8)	99	116 (87.9)	132	0.045
Coronary artery disease	100 (24.0)	416	42 (22.3)	188	31 (31.6)	98	27 (20.8)	130	0.13
Diabetes mellitus	108 (25.7)	420	49 (25.9)	189	32 (32.3)	99	27 (20.5)	132	0.12
Hyperlipidemia	321 (76.8)	418	155 (82.9)	187	84 (84.8)	99	82 (62.1)	132	<0.001
Smoking	59 (14.7)	401	22 (11.8)	186	20 (20.8)	96	17 (14.3)	119	0.13
History of stroke	134 (32.0)	419	59 (31.4)	188	34 (34.3)	99	41 (31.1)	132	0.85
Peripheral artery disease	40 (9.6)	416	15 (8.0)	188	8 (8.1)	99	17 (13.2)	129	0.26
History of heart valve replacement		415		187		99		129	0.43
Biological	14 (3.4)		4 (2.1)		5 (5.1)		5 (3.9)		
Mechanical	2 (0.5)		2 (1.1)		0 (0.0)		0 (0.0)		
None	399 (96.1)		181 (96.8)		94 (94.9)		124 (96.1)		
Echocardiography features									
Time from index event to echocardiography, days	2 (1–3)	288	2 (1–3)	187	2 (1–3)	101		/	0.11

(*Continued*)

Table 1. Continued

	Entire cohort (n=424)	No. available	TTE (n=191)	No. available	TEE (n=101)	No. available	No echocardiography (n=132)	No. available	*P* value*
Laboratory values									
NT-proBNP, pg/mL	702 (272–1887)	203	895 (391–2127)	131	460 (196–948)	69	800 (791–1553)	3	0.003
Creatinine kinase, U/L	81 (52–132)	307	81.5 (52–133.5)	176	86 (56–130)	95	73 (56.5–121)	36	1.00
C-reactive protein, mg/L	5 (2–13)	361	4 (2–11)	182	6 (2–13)	97	6 (3–23)	82	<0.001
D-dimer, µg/L	763 (354–1965)	326	636 (343–1369)	159	687 (276–1688)	87	1188 (596–3266)	80	<0.001
Troponin, ng/L	19 (11–35)	337	21 (12–32)	173	15 (9–33)	91	22 (13–57)	73	0.042
Estimated glomerular filtration rate, mL/min	86 (70.5–104)	416	84.5 (73–104.5)	188	88 (68–101)	99	86 (70–106)	129	0.97

Categorical data are expressed as real numbers (n) and percentages (%). Continuous data are presented as median (n) and interquartile range (Q1-Q3). DOAC indicates direct oral anticoagulant; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

This table includes 132 patients without echocardiography, which are not presented in the other tables.

*P stands for the comparison across the 3 groups (TTE vs TEE vs no echocardiography).

TTE and TEE were both feasible and interpretable in most patients.

2. When applying expert and guideline recommendations for choosing the echocardiography modality, TTE (14%) and TEE (16%) had a similar diagnostic yield to identify certain management-relevant pathologies.
3. Most management-relevant findings pointed toward coronary artery disease and valvular pathologies.
4. Variables associated with certain management-relevant high-risk pathologies included more severe stroke, diabetes, and laboratory biomarkers (NT-proBNP, C-reactive protein, D-dimer, and troponin levels).

Current guidelines advocate for TTE only in the setting of cryptogenic stroke and TEE in patients with embolic stroke of undetermined source or in cases in which patent foramen ovale occlusion would be considered.[18,19] Since a frequent management consequence of echocardiography is therapeutic oral anticoagulation,[5] we hypothesized that in the rapidly increasing subgroup of patients with an established indication for long-term anticoagulation, the diagnostic yield for management-relevant findings is low.

Contrary to our hypothesis, we found a similar proportion of management-relevant high-risk pathologies in 1 of 7 patients for both TTE and TEE. Given a relevant percentage of high-risk pathologies with uncertain management consequences and moderate-risk pathologies with certain management consequences, this number might even underestimate the true diagnostic yield of echocardiography in this patient population.

Prior studies showed that presence of left atrial dilatation—especially if severe—might help to estimate early stroke recurrence risk in patients with AF.[20] However, the management consequence is unclear since all patients qualify for anticoagulation and the prospective studies randomizing early versus later start of DOAC need to address whether the subgroup with left atrial dilatation or thrombus might be among those who benefit from earlier start of oral anticoagulation.[21] Herm et al reported that major cardiac sources of embolism were identified by echocardiography in 10% (n=18) of AF patients with AIS.[22] However, echocardiographic findings did not result in any therapeutic intervention other than immediate anticoagulation in this cohort. Similarly, Moores et al[23] reported that TTE identified potentially clinically relevant findings in 7 (5.9%) of 118 patients with preexisting AF. However, those findings did not result in a change of medical management (0%). However, in both studies, only severely reduced ejection fraction was considered as a relevant finding and new regional wall motion

Table 2. Diagnostic Yield for the Prespecified High-Risk Management-Relevant Findings According to the Modality of Echocardiography

Pathologies	TTE (n=191)			TEE (n=101)		
	No consequences	Consequences	Total	No consequences	Consequences	Total
Left ventricle						
Left ventricular thrombus	3	0	3	0	0	0
Regional wall motion abnormalities	26	8 certain 9 uncertain	43	13	1 certain 3 uncertain	17
Left ventricular ejection fraction (≤35%) or worsening of left ventricular ejection fraction ≥10% compared with prior echocardiography	9	9 certain 5 uncertain	23	4	2 certain 2 uncertain	8
Dilated cardiomyopathy	6	1 certain 4 uncertain	11	3	1 certain	4
Other cardiomyopathy	6	1 certain	7	1	0	1
Atrial						
Left atrial (appendage) thrombus	1	0	1	1	1 certain 3 uncertain	5
Patent foramen ovale	7	0 certain 1 uncertain	8	15	1 certain 2 uncertain	18
Valvular						
Signs of endocarditis	0	2 certain	2	0	6 certain	6
Valve thrombosis	0	2 certain	2	0	1 certain 1 uncertain	2
High-grade valvular disease						
Aortic stenosis	25	6 certain 9 uncertain	40	12	4 certain 1 uncertain	17
Mitral stenosis	4	0	4	1	0	1
Mitral regurgitation	1	3 certain 2 uncertain	6	0	2 uncertain	2
Tricuspid regurgitation	3	3 certain 1 uncertain	7	1	1 certain	2
Other						
Nonthrombotic masses, eg, tumor	0	0	0	0	2 certain	2
Aortic dissection	0	0	0	0	0	0
Overall pathologies	91 without consequence	35 certain 31 uncertain	157	51 without consequence	20 certain 14 uncertain	85
Patients, n (%)		26 (13.6) certain 18 (9.4) uncertain			16 (15.8) certain 8 (7.9) uncertain	

TEE indicates transesophageal echocardiography; and TTE, transthoracic echocardiography.

abnormality. Ejection fraction worsening or valvular pathologies were not considered.

Harris et al[4] found that in patients with known AF, TTE results were less likely to influence treatment changes (adjusted odds ratio, 0.12; 95% CI, 0.006–0.66). Douen et al[24] reported that in 31 patients with newly diagnosed or known AF, TTE identified 1 left ventricular thrombus and moderate to severe left ventricular dysfunction in 2 additional patients with a history of myocardial infarction, suggesting that TTE does not provide relevant results in this cohort. Importantly, all those studies were done exclusively in patients with AF and mostly before the transition from vitamin K antagonist to DOAC had happened. Since our study also included patients with other indications for long-term DOAC therapy, it expands these data. Interestingly, AF versus other indications for anticoagulation was not significantly associated with identification of relevant pathologies.

One important aspect of our work is that we took into consideration not only the presence, but also the actual evidence-based management consequence of the findings. Analyzing not only the frequency of the pathologies, but the whole clinical case including previous echocardiography reports is important because even high-risk sources (eg, ventricular thrombi) might have no management consequence when they are already known. The ratio of high-risk pathologies to pathologies triggering management consequences was about 3:1 for TTE and 2:1 for TEE (Table 2). Exemplary

Table 3. Diagnostic Yield for Other Management-Relevant Findings According to the Modality of Echocardiography

Pathologies	TTE (n=191)			TEE (n=101)		
	No consequences	Consequences	Total	No consequences	Consequences	Total
Left ventricle						
Left ventricular hypertrophy	137	1 certain 3 uncertain	141	64	0	64
Left ventricular noncompaction	2	0	2	0	0	0
Atrial						
Left atrial dilatation	127	4 uncertain	131	64	4 uncertain	68
Spontaneous echo contrast "smoke"	2	0	2	9	1 certain 5 uncertain	15
Atrial septal aneurysm	3	0	3	11	1 certain	12
Valvular						
Aortic valve calcifications	78	6 certain 11 uncertain	95	39	4 certain 3 uncertain	46
Aortic valve strands	1	0	1	3	0	3
Aortic valve stenosis, any	25	6 certain 9 uncertain	40	12	4 certain 1 uncertain	17
Mitral valve calcification	45	3 uncertain	48	34	1 certain 1 uncertain	36
Mitral valve prolapse	2	1 certain 1 uncertain	4	4	0	4
Mitral valve stenosis, any	4	0	4	1	0	1
Other						
Complex aortic plaques	0	1 uncertain	1	9	1 certain 6 uncertain	16
Aortic aneurysm ≥45mm	1	1 uncertain	2	1	0	1
Not prespecified						
Pulmonary Hypertension	0	4 certain	4	0	1 certain	1
Pericardial and pleural effusion	0	0	0	0	1 certain	1
Overall pathologies	427	22 certain 33 uncertain	482	251	14 certain 20 uncertain	285
Patients, n (%)		12 (6) certain, 3 (2) without other high-risk pathologies 22 (12) uncertain, 9 (5) without other high-risk pathologies			10 (10) certain, 4 (4) without high-risk pathologies 13 (13) uncertain, 8 (8) without high-risk pathologies	

cases include a patient hospitalized for heart failure and newly diagnosed with dilatative cardiomyopathy several months before the index event, or a patient with a clinical diagnosis of infective endocarditis shortly before the index event. For other pathologies (Table 3), the ratio was even higher, showing that most pathologies do not alter management on an evidence-based level. This has to be considered in the interpretation of prior studies reporting the mere diagnostic yield of such pathologies without looking into the clinical case in detail. This point also has to be considered in future studies on this topic.

Another take-home message is that studies addressing the role of echocardiography in stroke should not only report and analyze findings that are causally related to the (embolic) event. We showed here that because of the shared cardiovascular risk factors, the most frequent findings triggering management consequences are those pointing toward newly diagnosed or worsened coronary artery disease. Additionally, high-grade valvular pathologies were frequently found—possibly also because of their linked cardiovascular risk factors.[25]

Importantly, the decision regarding which test to choose at our center was dependent on clinical presentation, with echocardiography being performed in a high percentage of patients with AIS. Interestingly, the yield was nonsignificantly different according to the TOAST etiology, strengthening the hypothesis of shared cardiovascular risk factors regardless of stroke mechanism. Using several biomarkers, we identified stroke severity, diabetes, NT-proBNP, and D-dimer

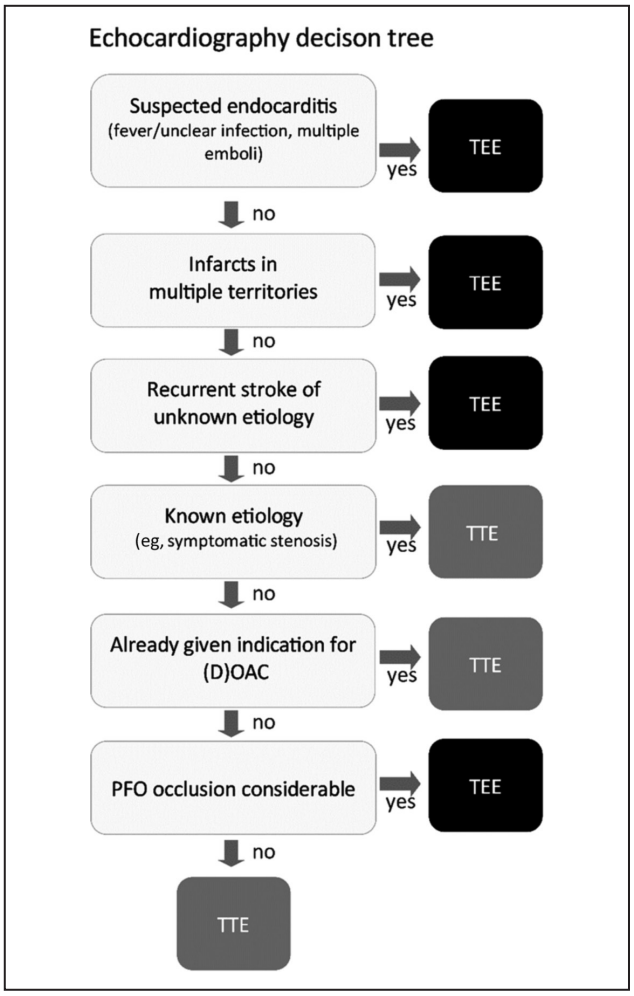

Figure. Decision tree TTE vs TEE during the study time frame.
Clinical decision tree of which modality of echocardiography to perform during the study time frame. (D)OAC indicates (direct) oral anticoagulant; PFO, patent foramen ovale; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

as independent predictors of certain management-relevant high-risk pathologies. These biomarkers are pathophysiologically plausible (eg, silent myocardial infarctions in patients with diabetes[26]) and might be helpful in selecting anticoagulated patients for echocardiography. However, they might not necessarily be causally related to the event and might simply be a surrogate of the underlying disease leading to the DOAC prescription in the first place. Importantly, other groups have identified troponin levels to be helpful in improving the yield of echocardiography, and this biomarker is more specific to cardiac injury than D-dimer levels.[27]

Strengths and Limitations

One strength of this study, besides its sample size, is that we performed echocardiography regardless of ischemic stroke subtype, allowing us to analyze the diagnostic yield in subgroups where guidelines do not routinely recommend echocardiography such as ischemic stroke caused by small-vessel occlusion. Another strength is the in-depth analysis of an evidence-based management consequence using expert adjudication incorporating information from the whole clinical case and prior echocardiography results. The choice of modality (TTE versus TEE) was based on clinical considerations incorporating available expert and guideline recommendations and hence might be generalizable to centers with similar selection approaches.

Obviously, its retrospective nature limits the study. Importantly, a third of the cohort did not undergo echocardiography because of an early transfer to other hospitals or early decision for palliative treatment, so our findings should not be extrapolated to this subset of patients. Unfortunately, in the patients transferred early to the spoke stroke units of our stroke network, findings of echocardiography could not be analyzed. Since echocardiography was performed as a part of the clinical workup, there was no blinding or central reading, and we could not analyze inter- as well as intrareader reliability. Also, the definition of high-risk pathologies is somewhat debatable. Another limitation is that we can only speculate about the value of the pathologies for stroke reclassification and impact of the management consequences on clinical outcomes, such as recurrent stroke or myocardial infarction. Although most key characteristics were balanced between patients with and without missing data items, the complete case analysis might have introduced bias.

CONCLUSIONS

Echocardiography revealed a relevant yield for identification of management-relevant high-risk findings in patients with stroke or transient ischemic attack and with established indications for long-term DOAC use. Using our decision algorithm, both TEE and TEE identified a similar proportion of management-relevant high-risk pathologies in 1 of 7 patients. Diabetes, NT-proBNP, and D-dimer were independent predictors of management-relevant high-risk findings. Further studies using randomization of the available diagnostic modalities and meaningful clinical outcomes need to clarify the overall clinical impact of the diagnostic testing.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Tables S1–S7
Figure S1

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Supplemental Material

Data S1.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Tables
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2/3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates	S Tables

		and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6 (NA)
	11	Rationale for choosing the reference standard (if alternatives exist)	Figure 1
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	6
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	NA, no comparison
	15	How indeterminate index test or reference standard results were handled	6, S Table 1
	16	How missing data on the index test and reference standard were handled	7
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	NA
	18	Intended sample size and how it was determined	7
RESULTS			
Participants	**19**	Flow of participants, using a diagram	NA, no comparison
	20	Baseline demographic and clinical characteristics of participants	Table 1
	21a	Distribution of severity of disease in those with the target condition	Table 1
	21b	Distribution of alternative diagnoses in those without the target condition	NA
	22	Time interval and any clinical interventions between index test and reference standard	Table 1
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	NA, no comparison
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	7
	25	Any adverse events from performing the index test or the reference standard	8
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	12
	27	Implications for practice, including the intended use and clinical role of the index test	13
OTHER INFORMATION			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	NA
	30	Sources of funding and other support; role of funders	13

Table S1. Frequencies of indeterminate results of the prespecified high-risk management-relevant findings according to the modality of echocardiography.

		TTE (N=191)	TEE (N=101)
Left Ventricle	Left ventricular thrombus	5 (2.6%)	1 (1.0%)
	Regional wall motion abnormalities	21 (11.0%)	7 (6.9%)
	Severely reduced ejection fraction (≤35%)	11 (5.8%)	16 (15.8%)
	Dilatative cardiomyopathy	5 (2.6%)	1 (1.0%)
	Other cardiomyopathy	5 (2.6%)	1 (1.0%)
Atrial	Left atrial (appendage) thrombus	8 (4.2%)	1 (1.0%)
	PFO and/or Atrial septal aneurysm	176 (92.1%)	12 (11.9%)
Valvular	Signs of endocarditis	5 (2.6%)	0 (0.0%)
	Valve thrombosis	5 (2.6%)	0 (0.0%)
	High-grade valvular disease		
	- Aortic stenosis	6 (3.1%)	0 (0.0%)
	- Mitral stenosis	5 (2.6%)	0 (0.0%)
	- Mitral regurgitation	5 (2.6%)	0 (0.0%)
	- Tricuspid regurgitation	5 (2.6%)	0 (0.0%)
Other	Non-thrombotic masses, e.g. tumor	4 (2.1%)	0 (0.0%)
	Aortic dissection	10 (5.2%)	0 (0.0%)

In this table, we present the rate of pathologies, were TEE or TEE was not able to rule in or rule out a specific pathology. In the case of PFO, on 92.1% of TTE exams, it was not able to determine whether a PFO was present or not (because we do TTE without agitated saline and always do TEE when PFO closure would be done). In 8% of exams, PFO could nevertheless be seen or ruled out by TTE

Table S2. Details on management consequences according to the modality of echocardiography.

	Pathologies	TTE (N=191)		TEE (N=101)	
		Consequences	**Consequences Detail**	**Consequences**	**Consequences Detail**
Left Ventricle	Left ventricular thrombus	0		0	
	Regional wall motion abnormalities	8 certain 9 uncertain	**Certain**: 6 CAD workup indicated (clearly new finding) 1 TakoTsubo 1 ICD evaluation **Uncertain**: 7 history of CAD, but unknown whether this regionality was known 2 CAD workup indicated, but patient declined (frail or palliative)	1 certain 3 uncertain	**Certain**: 1 CAD workup indicated (clearly new finding) **Uncertain**: 2 history of CAD, but unknown whether this regionality was known 1 CAD workup indicated, but patient declined (frail or palliative)
	Left ventricular ejection fraction (≤35%) or worsening of left ventricular ejection fraction ≥10% compared to prior echocardiography	9 certain 5 uncertain	**Certain:** 7 CAD workup indicated (clearly new finding) 1 TakoTsubo 1 medical therapy **Uncertain:** 2 history of CAD, but unknown whether low EF was known 3 best medical heart failure therapy, but unclear whether anyways indicated	2 certain 2 uncertain	**Certain:** 2 CAD workup indicated (clearly new finding) **Uncertain:** 1 history of CAD, but unknown whether low EF was known 1 best medical heart failure therapy, but unclear whether anyways indicated
	Dilated cardiomyopathy	1 certain 4 uncertain	**Certain:** 1 medical therapy **Uncertain:** 3 uncertain if known 1 best medical heart failure therapy, but unclear whether anyways indicated	1 certain	**Certain:** 1 medical therapy
	Other cardiomyopathy	1 certain	**Certain:** 1 new diagnosis of cardiac amyloidosis	0	
Atrial	Left atrial (appendage) thrombus	0		1 certain 3 uncertain	**Certain:** 1 Left atrial appendage occlusion in a patient with high-bleeding risk **Uncertain:** 3 might have influenced timepoint of anticoagulation start
	Patent foramen ovale	0 certain 1 uncertain	**Uncertain:** 1 PFO closure indicated, but patient declined (frail or palliative)	1 certain 2 uncertain	**Certain:** 1 PFO closure indicated **Uncertain:** 2 PFO closure indicated, but patient declined (frail or palliative)
Valvula	Signs of endocarditis	2 certain	**Certain:** 2 Infective endocarditis work-up and therapy (newly diagnosed)	6 certain	**Certain**: 2 Infective endocarditis work-up and therapy (newly diagnosed)

					2 suspicion of marantic endocarditis: tumor screening and low molecular weight heparin 1 dose adjustment anticoagulation 1 surgical therapy
	Valve thrombosis	2 certain	**Certain:** 2 rule out infective endocarditis and evaluation of valve replacement	1 certain 1 uncertain	**Certain:** 1 suspicion of marantic endocarditis: tumor screening and low molecular weight heparin **Uncertain:** 1 might have influenced timepoint of anticoagulation
	High-grade valvular disease				
	- Aortic stenosis	6 certain 9 uncertain	**Certain:** 6 replacement indicated (newly diagnosed, 2 urgent 4 scheduled for the following months) **Uncertain:** 8 replacement indicated, but patient declined (frail or palliative) 1 uncertain if known	4 certain 1 uncertain	**Certain:** 4 replacement indicated (newly diagnosed) **Uncertain:** 1 replacement indicated, but patient declined (frail or palliative)
	- Mitral stenosis	0		0	
	- Mitral regurgitation	3 certain 2 uncertain	**Certain:** 3 replacement indicated (newly diagnosed, 1 urgent 2 scheduled for the following months) **Uncertain:** 1 replacement indicated, but patient declined (frail or palliative) 1 uncertain if known	2 uncertain	**Uncertain:** 2 replacement indicated, but patient declined (frail or palliative)
	- Tricuspid regurgitation	3 certain 1 uncertain	**Certain:** 1 new, acute pathology, rule-out pulmonary embolism 2 progressive pathology, medical therapy adjusted **Uncertain:** 1 uncertain if known	1 certain	**Certain:** 1 new, acute pathology, rule-out pulmonary embolism
Other	Non-thrombotic masses, e.g. tumor	0		2 certain	**Certain:** 1 cardiac myxoma, surgery 1 newly diagnosed cardiac metastasis
	Aortic dissection	0		0	

Table S3. Diagnostic yield for the prespecified high-risk management-relevant findings for echocardiography overall (both TEE and TTE combined).

	Pathologies	Both modalities (N=292)		
		No Consequences	**Consequences**	**Total**
Left Ventricle	Left ventricular thrombus	3	0	3
	Regional wall motion abnormalities	39	9 certain 12 uncertain	60
	Left ventricular ejection fraction (≤35%) or worsening of left ventricular ejection fraction ≥10% compared to prior echocardiography	13	11 certain 7 uncertain	31
	Dilated cardiomyopathy	9	2 certain 4 uncertain	15
	Other cardiomyopathy	7	1 certain	8
Atrial	Left atrial (appendage) thrombus	2	1 certain 3 uncertain	6
	Patent foramen ovale	22	1 certain 3 uncertain	26
Valvular	Signs of endocarditis	0	8 certain	6
	Valve thrombosis	0	3 certain 1 uncertain	4
	High-grade valvular disease			
	- Aortic stenosis	37	10 certain 10 uncertain	57
	- Mitral stenosis	5	0	5
	- Mitral regurgitation	1	3 certain 4 uncertain	8
	- Tricuspid regurgitation	4	4 certain 1 uncertain	9
Other	Non-thrombotic masses, e.g. tumor	0	2 certain	2
	Aortic dissection	0	0	0
Overall pathologies		142	**55 certain** **31 uncertain**	240
Patients			**42 (14.4%) certain** **26 (8.9%) uncertain**	

Table S4. Association of biomarkers and clinical features with high-risk pathologies certainly leading to management consequences.

	No high-risk pathology (N=224)	N available	High-risk pathology (N=42)	N available	P
Epidemiology					
Age	76.2 (68.7-82.5)	224	79 (70.3-83.6)	42	0.26
Female sex	85 (37.9%)	224	17 (40.5%)	42	0.76
NIHSS on admission	3 (1-7)	209	4 (2-15)	39	0.047
TIA	43 (19.2%)	224	5 (11.9%)	42	0.26
TOAST etiology		218		40	0.22
Cardiac embolism	95 (43.6%)		23 (57.5%)		
Large artery atherosclerosis	28 (12.8%)		3 (7.5%)		
More than one possible etiology	32 (14.7%)		8 (20.0%)		
Other determined etiology	16 (7.3%)		5 (12.5%)		
PFO	2 (0.9%)		0 (0.0%)		
Small vessel disease	9 (4.1%)		0 (0.0%)		
Unknown etiology despite complete evaluation	23 (10.6%)		1 (2.5%)		
Unknown etiology with incomplete evaluation	13 (6.0%)		0 (0.0%)		
Medication					
Type of DOAC therapy		224		42	0.64
Rivaroxaban	145 (64.7%)		28 (66.7%)		
Apixaban	55 (24.6%)		8 (19.0%)		
Dabigatran	12 (5.4%)		2 (4.8%)		
Edoxaban	12 (5.4%)		4 (9.5%)		
Additional antiplatelet therapy					
Medical History of cardiovascular risk factors					
Atrial fibrillation/flutter	141 (63.8%)	221	25 (61.0%)	41	0.73
Hypertension	184 (83.3%)	221	35 (85.4%)	41	0.74
Coronary artery disease	55 (25.1%)	219	10 (24.4%)	41	0.92
Diabetes mellitus	56 (25.3%)	221	18 (43.9%)	41	0.015
Hyperlipidemia	184 (84.0%)	219	33 (80.5%)	41	0.58
Smoking	34 (15.7%)	216	5 (12.2%)	41	0.56
History of stroke	76 (34.4%)	221	9 (22.5%)	40	0.14
Peripheral artery disease	16 (7.3%)	220	5 (12.2%)	41	0.29
History of heart valve replacement		219		41	1.00
Biological	8 (3.7%)		1 (2.4%)		
Mechanical	2 (0.9%)		0 (0.0%)		
None	209 (95.4%)		40 (97.6%)		
Echocardiography features					
Time from index event to echocardiography, days	2 (1-3)	220	2 (1-3)	42	0.62
Laboratory values					

n-Terminal brain natriuretic peptide NT-proBNP, pg/mL	539 (197-1500)	148	1627 (648-3914)	33	<0.001
Creatinine Kinase CK, U/L	81 (52-132)	209	81 (57-135)	39	0.74
C-reactive protein CRP, mg/L	3 (2-10)	212	8.5 (2-21)	42	0.009
D-Dimer, µg/L	532 (315-1163)	189	1923 (544-3252)	35	<0.001
Troponin, ng/L	15 (9-28)	201	35.5 (16-63)	38	<0.001
Estimated glomerular filtration rate, ml/min	85 (71-101)	220	90 (69-107)	41	0.71
DOAC plasma levels, ng/ml	89 (43-177)	135	56 (28-147)	30	0.17

NIHSS: National Institutes of Health Stroke Scale; DOAC: direct oral anticoagulant; 26 patients with high-risk pathologies but uncertain management consequence not considered for this analysis

Table S5. Association of biomarkers and clinical features with any pathologies (high-risk and others) with (certain or uncertain) management consequences.

	No pathology (N=200)	N available	Any pathology (N=92)	N available	P
Epidemiology					
Age	76.1 (68.45-82.5)	200	78.85 (70.9-83.65)	92	0.096
Female sex	79 (39.5%)	200	35 (38.0%)	92	0.81
NIHSS on admission	3 (1-7)	185	4 (2-11)	87	0.019
TIA	40 (20.0%)	200	9 (9.8%)	92	0.030
TOAST etiology					0.078
Cardiac embolism	84 (43.3%)	194	52 (57.8%)	90	
Large artery atherosclerosis	23 (11.9%)		10 (11.1%)		
More than one possible etiology	29 (14.9%)		13 (14.4%)		
Other determined etiology	13 (6.7%)		8 (8.9%)		
PFO	2 (1.0%)		1 (1.1%)		
Small vessel disease	8 (4.1%)		1 (1.1%)		
Unknown etiology despite complete evaluation	22 (11.3%)		2 (2.2%)		
Unknown etiology with incomplete evaluation	13 (6.7%)		3 (3.3%)		
Medication					
Type of DOAC therapy		200		92	0.93
Rivaroxaban	130 (65.0%)		63 (68.5%)		
Apixaban	47 (23.5%)		19 (20.7%)		
Dabigatran	11 (5.5%)		4 (4.3%)		
Edoxaban	12 (6.0%)		6 (6.5%)		
Additional antiplatelet therapy					
Medical History of cardiovascular risk factors					
Atrial fibrillation/flutter	128 (64.3%)	199	58 (65.2%)	89	0.89
Hypertension	165 (83.3%)	198	78 (86.7%)	90	0.47
Coronary artery disease	51 (26.0%)	196	22 (24.4%)	90	0.78
Diabetes mellitus	48 (24.2%)	198	33 (36.7%)	90	0.030
Hyperlipidemia	164 (83.7%)	196	75 (83.3%)	90	0.94
Smoking	31 (16.1%)	193	11 (12.4%)	89	0.42
History of stroke	69 (34.8%)	198	24 (27.0%)	89	0.19
Peripheral artery disease	14 (7.1%)	197	9 (10.0%)	90	0.40
History of heart valve replacement		196		90	0.35
Biological	8 (4.1%)		1 (1.1%)		
Mechanical	2 (1.0%)		0 (0.0%)		
None	186 (94.9%)		89 (98.9%)		
Echocardiography features					
Time from index event to echocardiography, days	2 (1-3)	196	2 (1-3)	92	0.93
Laboratory values					

n-Terminal brain natriuretic peptide NT-proBNP, pg/mL	538 (198-1513)	135	1068 (573-2991)	65	<0.001
Creatinine Kinase CK, U/L	82 (52-132)	185	92 (56-148)	86	0.43
C-reactive protein CRP, mg/L	3 (2-10)	189	6 (2-16)	90	0.003
D-Dimer, µg/L	521 (307-1105)	169	956 (436-2530)	77	<0.001
Troponin, ng/L	15 (9-28)	179	27 (16-46)	85	<0.001
Estimated glomerular filtration rate, ml/min	84 (69-101)	196	87 (73-102)	91	0.66
DOAC plasma levels, ng/ml	89 (46-177)	122	56 (30-145)	60	0.052

NIHSS: National Institutes of Health Stroke Scale; DOAC: direct oral anticoagulant; PFO: persistent foramen ovale

Table S6. Logistic regression analysis for the association of features identified on LASSO with any high risk source.

	Odds Ratio	**Std. Err.**	**z**	**P>|z|**	**[95% Conf. Interval]**
Diabetes	3.237399	1.485663	2.56	0.010	1.316965 - 7.958258
N terminal pro brain natriuretic peptide (per 1 pg/mL)	1.000204	.0000893	2.28	0.022	1.000029 - 1.000379
C-reactive protein (per 1 mg/L)	1.002507	.0064764	0.39	0.698	.9898933 - 1.015281
D-dimer (per 1ug/L)	1.000165	.0000521	3.17	0.002	1.000063 - 1.000268
Constant term	.0505592	.0206208	-7.32	0.000	.0227318 - .112452
Logistic regression Number of obs = 189 LR chi2(4) = 28.98 Prob > chi2 = 0.0000 Log likelihood = -68.208076 Pseudo R2 = 0.1752					

Table S7. Key characteristics according to missing data for final model.

	No missing data (N=189)	N available	Missing data (N=103)	N available	P
Epidemiology					
Age	76.6 (69.7-82.6)	189	77.3 (68.4-82.5)	103	0.98
Female sex	72 (38.1%)	189	42 (40.8%)	103	0.65
NIHSS on admission	3 (1-8)	182	2.5 (1-10)	90	0.76
TIA	28 (14.8%)	189	21 (20.4%)	103	0.22
Death at three months	19 (10.3%)	184	6 (6.0%)	100	0.22
Medical History of cardiovascular risk factors					
Atrial fibrillation/flutter	122 (64.9%)	188	64 (64.0%)	100	0.88
Arterial hypertension	156 (82.5%)	189	87 (87.9%)	99	0.24
Coronary artery disease	48 (25.7%)	187	25 (25.3%)	99	0.94
Diabetes mellitus	60 (31.7%)	189	21 (21.2%)	99	0.059
Echocardiography features					
Time from index event to echocardiography, days	2 (1-3)	189	2 (1-3)	99	0.71
Laboratory values					
n-Terminal brain natriuretic peptide NT-proBNP, pg/mL	648 (245-1828)		1110 (777-2991)		0.024
C-reactive protein CRP, mg/L	4 (2-10)		5.5 (2-13)		0.24
D-Dimer, µg/L	687 (307-1774)		625 (389-956)		0.81
Troponin, ng/L	18 (10-32)		18.5 (11.5-33)		0.85

NIHSS: National Institutes of Health Stroke Scale; Categorical data are expressed as real numbers (n) and percentages (%). Continuous data are presented as median (n) and interquartile range [Q1-Q3].

This table does not include 132 patients without echocardiography.

Figure S1. Study flow chart.