Published in final edited form as:

J Stroke Cerebrovasc Dis. 2011 November ; 20(6): 503–509. doi:10.1016/j.jstrokecerebrovasdis.2010.03.001.

Transesophageal Echocardiography Screening in Subjects with a First Cerebrovascular Ischemic Event

Kate C. Young, PhD MPH^{1,2} and Curtis G. Benesch, MD MPH^{1,3}

¹Department of Neurology, University of Rochester Medical Center

²Department of Surgery, University of Rochester Medical Center

³Department of Neurosurgery, University of Rochester Medical Center

Abstract

Our goal was to develop decision guides to predict the presence of a high risk source of embolus and to predict a change in management following transesophageal echocardiography (TEE) in subjects who present with a first cerebral ischemic event. We conducted a retrospective review of subjects ≥ 18 years who underwent TEE after a first ischemic event and were admitted to our stroke service from 2004–2007 ($n=287$). A high risk source of embolus and a change in clinical management (including medication changes or subsequent testing) were analyzed as separate endpoints using multivariate techniques and receiver-operator characteristic curves. 14.3% of subjects had a high risk source while an additional 61.3% had a potential (or low risk) source of embolus. Increasing age and no history of diabetes mellitus were independently associated with a high risk source of embolus. TEE would be recommended for non-diabetic individuals who are ≥ 66 years (sensitivity: 68%, specificity: 76%). The area under the curve (AUC) for detecting a high risk source was 0.773. TEE results changed medications or clinical management in 30.3% of patients. Current smokers were less likely to undergo a change in management. The AUC was uninformative (0.56) for predicting changes in management. Subjects presenting with a first ischemic event who are ≥ 66 years may benefit from TEE. While changes in management occurred in at least 30% of our cohort, no factors could be identified that predicted a change in management better than chance alone.

Keywords

Transesophageal echocardiography; cardioembolic sources; patient care management

Introduction

In subjects presenting with a cerebral ischemia, transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are diagnostic procedures that identify sources of embolism. TTE is a non-invasive bedside screening test for cardiac sources of emboli while TEE is an invasive test requiring sedation. However, TEE has a higher sensitivity than TTE for detecting left atrial thrombus.¹ The results of the TEE, positive or negative, ultimately

Corresponding Author: Kate C. Young, 575 Elmwood Ave, Box 681, Rochester, NY 14620, Phone: (585) 275-5091, Fax: (585) 273-1026, kate_young@urmc.rochester.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

guide clinical management. The frequency of high risk sources detected by TEE ranges from 8 to 10%.²⁻⁴ Moreover, prospective studies demonstrate that changes in clinical management based on the TEE results occurs in 7-12% of cases.³⁻⁵ A limitation to these studies is the inclusion of subjects with ischemic stroke who also had atrial fibrillation, a known risk factor for cardioembolic stroke that may require anti-coagulation irrespective of TTE or TEE findings.

Our study specifically looks at the association of demographic and clinical factors at presentation with the identification of high risk sources of emboli and the subsequent changes in clinical management following the TEE. Specific attention is given to the changes in management occurring as a direct result of the TEE (rather than the coincidental presence of atrial fibrillation). The purpose of this study is to develop a set of decision guides to improve patient selection for the use of TEE in those with a first ischemic event.

Methods

Study population

Records were identified by searching Strong Memorial Hospital (Rochester, NY) discharge information from 2004-2007 for stroke/TIA related ICD-9 codes 433-436, inclusive, and diagnostic related group (DRG) 88.72 (echocardiography). DRG 88.72 included both TTE and TEE. The inclusion criteria were age ≥ 18 years, TEE, no prior history of ischemic stroke/TIA and admission to our hospital's designated stroke service with an ischemic event. In total, 287 records met the inclusion criteria and were reviewed. The study was approved by our institutional RSRB/IRB.

Past medical history, current medications, suspected etiology at presentation (transient ischemic attack or stroke) and suspected subtype at presentation were obtained from the Neurology New Patient / Consult form. Events were coded as stroke when no information regarding the type of ischemic event was given. Also, the subtype was recorded as not specified/cryptogenic when no subtype was identified on the encounter form.

There are standardized methods for ultrasound assessment of carotid stenosis and ultrasound data were used, if available.⁶ Unilateral stenosis $\geq 50\%$ was considered relevant for studies of TEE.⁷ Standardized reporting techniques for magnetic resonance angiography (MRA) or CT angiography (CTA) were not routinely used. Thus, the determination of carotid artery stenosis was largely subjective for MRA and CTA during the time period studied.^{8, 9} The MRA or CTA report had to quantify stenosis as at least 70% or occluded (but not occluded with a thrombus) to be classified clinically significant carotid artery stenosis. The 70% or occluded threshold was a stringent, conservative criterion for a subjective assessment of stenosis.

Classification of embolic sources as high or low risk was pre-specified for the primary analysis. High risk sources of embolus included mobile aortic debris, aortic plaque $\geq 4\text{mm}$, left atrial thrombus, left atrial appendage thrombus, left ventricular thrombus, mitral valve thrombus and aortic valve thrombus.^{2, 4} Low risk or potential embolic sources included aortic aneurysm, aortic plaque $< 4\text{mm}$, aortic thrombus, atrial septal aneurysm (ASA), atrial myxoma, calcified aortic stenosis, dilated cardiomyopathy, false tendon, infective endocarditis, left atrial flow velocity $< 30\text{ cm/sec}$, left ventricular aneurysm, marantic endocarditis, mitral annular calcification, mitral or aortic valve filamentous strands, mitral valve prolapse, mitral valve stenosis, myxomatous mitral valve, patent foramen ovale (PFO), prosthetic valve, spontaneous echo contrast (SEC), ulcerated aortic plaque and vegetation.²⁻⁵ Low risk or potential embolic sources also found during the chart review included intra-

pulmonary shunt, pulmonary vein mass, fibrin excrescence and lipomatous hypertrophy of the intra-atrial septum.

Changes in management as a consequence of the TEE included medication changes, closure of a PFO, additional consult requests, and subsequent testing or procedures. Changes in medications included starting, stopping or dose changes for the following medication classes or specific agents: anti-coagulants, aspirin, antibiotics, statins, clopidogrel, and aspirin/extended-release dipyridamole. Subsequent testing or procedures included pelvic vein studies, lower extremity studies, hypercoagulable tests, blood cultures, trans-cranial Doppler, chest CT, cardiac studies, PFO closure and termination of a planned procedure. A change in management reflected a documented change in the post-stroke work-up or treatment with specific reference to the TEE results. During the time frame of the study, our institution participated in trials of PFO closure and medical management. Everyone who was referred to the trial had another change in management (e.g. lower extremity ultrasound), thus trial referral did not affect change in management as an outcome.

Data analysis

Data were presented as means $\pm$ SD for continuous variables and counts with absolute or relative frequency for categorical variables. Chi-squared tests were used to compare individual associations between patient characteristics and the presence of a high risk source of embolus on TEE. Patient characteristics included basic demographics, suspected etiology, suspected subtype, current medications, past medical history and coagulation panel values. A separate analysis was conducted with a change in management as the endpoint. Potential predictor variables that were components of the high risk source or low risk source categories were not included in the multivariate analysis for a change in management except where explicitly indicated (e.g. the identification of left atrial thrombus or PFO was not used to predict a change in management). A two-stage linear step-up procedure with the false discovery rate set to 0.05 was used to determine which subset of variables from the multivariate analyses were included in the final prediction model.¹⁰

Threshold values for the decision guides were derived using receiver-operator characteristic curves (ROC). The decision threshold was determined with the formula: (false positive cost / false negative cost) * [(1-prevalence)/prevalence].¹¹ The false positive cost / false negative cost ratio was pre-specified as 1.0. A secondary analysis evaluated a ratio of 0.25. Cost does not necessarily refer to the economic definition, rather it means a burden or undesirability. The final sample size of 287 provided power >90% for the ROC curve, assuming an alpha of 5% and an 8% event rate.

Results

Cohort characteristics

We identified individuals presenting with a first ischemic event who underwent TEE (Figure 1). The average age of this group was 59.8 years and 45% were female (Table 1). The median time from admission to TEE screening was 2 days (range 0 to 11 days).

Detecting sources of emboli

The prevalence of high risk embolic sources including left sided thrombus or severe aortic plaque was 14.3% (Table 2). Thrombus was identified in nine individuals while 32 had large, severe plaque or mobile plaque components. Five individuals had two high risk sources, all of which were mobile aortic plaque elements with severe aortic plaque. None of the individuals with high risk sources had PFO with ASA. However, PFO alone was

detected in 11 individuals from this high risk group. Low risk embolic sources, in the absence of any high risk source, were detected in 61.3% of the individuals.

Age, no history of diabetes, a positive history of valve disease, lower initial diastolic blood pressure and a positive history of peripheral vascular disease were identified by univariate analysis as variables associated with a high risk source of embolus detected by TEE, $p < 0.05$ (Table 3). Age was also presented as a categorical variable to illustrate the increased likelihood of detecting a high risk source of embolus per decade over the age of 50. Coagulation panel values, a history of atrial fibrillation and current atrial fibrillation were not associated with the detection of a high risk source of embolus. Of these factors, only age (OR: 1.05, 95% CI: 1.02-1.1) and no history of diabetes mellitus (OR: 8.26, 95% CI: 1.76-38.7) remained independently associated with a high risk source of embolus (Table 4).

ROC curves were used to create a decision guide for detecting a high risk source on TEE (Table 4, Figure 2). The area under the curve was 0.773. With a false positive/false negative cost ratio of 1.0, the sensitivity and specificity of the cut-off were 0.024 and 0.996, respectively. TEE would be recommended for non-diabetic individuals with a first ischemic event who were ≥ 88 years old. For a 14.3% prevalence of high risk sources at our institution, the positive predictive value (PPV) was 50% and the negative predictive values (NPV) was 86%. With a history of diabetes mellitus, the age cut-off increased beyond 100 years.

The age cut-off of 88 years had an extremely low sensitivity. To determine an operating point nearest the upper left of the ROC curve, the false positive / false negative cost ratio of 0.25 was also evaluated. This led to a sensitivity and specificity of 0.683 and 0.762, respectively. TEE would be recommended for non-diabetic individuals who were ≥ 66 years. The PPV and NPV were 32% and 93.5% for our cohort and practice patterns. The age cut-off for those with a history of diabetes was still greater than 100 years.

As a post-hoc secondary analysis, we looked at patient characteristics associated with the presence of left-sided thrombus (Table 3, $n=9$). Suspected cardioembolic subtype, a history of valve disease, a history of heart failure, a history of migraine and higher initial systolic blood pressures were associated with an increased likelihood of detecting thrombus on TEE. Suspected cryptogenic subtype lowered the likelihood of left-sided thrombus. Finally, a history of atrial fibrillation (but not current atrial fibrillation) increased the odds of thrombus. A multivariate analysis was not conducted because of the small sample size.

Changes in management

Changes to medications occurred in 15.3% of the individuals (Table 2). Additional testing, change to a planned procedure, additional consults or referrals occurred in 22.6% of the cases. Any subsequent change in management, either medications or practice, occurred in 30.3% of those who underwent TEE.

No history of hypertension, not taking lipid-lowering medications and lower initial diastolic blood pressure increased the likelihood of changes in patient management (Table 3, each $p < 0.05$ by univariate analyses). A history of atrial fibrillation and current atrial fibrillation were not associated with changes in management following TEE. Multivariate analysis for factors known prior to the TEE showed that nonsmokers/former smokers were more likely to undergo a change in management than current smokers (OR: 2.26, 95% CI: 1.05-4.89). The ROC curve for any change in management had an area under the curve of 0.56. Since this was little better than chance, the analysis was stopped.

Changes in management including the TEE findings

Physicians acted upon the TEE results. In addition to subject characteristics, univariate analyses showed that the presence of a high risk source, low risk source, or PFO increased the likelihood of a change in management (Table 3). The association between left atrial thrombus (OR: 7.1, 95% CI: 0.73-69.3) or SEC (OR: 1.7, 95% CI: 0.7-4.5) and changes in management did not reach statistical significance, likely due to lack of power.

Factors associated with a change in management including the results of the TEE were no history of hypertension, nonsmoker/former smoker, not currently in atrial fibrillation, initial diastolic blood pressure, low risk sources of embolus and an interaction term, age*low risk source (Table 4). PFO and SEC were not specifically included in the multivariate model because they were part of the low risk source category. A ROC curve was not completed because the goal of this analysis was to identify predictors of embolic sources and changes in management upon presentation (without knowing the results of the TEE).

Discussion

We detailed the use of TEE in patients with a first cerebral ischemic event at our institution. We identified high risk and potential (low-risk) sources of emboli and subsequent changes in medical management. Furthermore, these retrospective data were used to generate a decision guide which suggested that individuals ≥ 66 years with a first ischemic event may benefit from TEE screening.

Relying solely on subject characteristics, age and no history of diabetes mellitus predicted high risk sources of embolus (Supplementary Figure, I). Those subjects who were nonsmokers or former smokers were more likely to undergo a change in management (Supplementary Figure, II). Once sources of embolus were included as covariates in the model, nonsmokers/former smokers were still more likely to undergo a change in management (Supplementary Figure, III). While older age predicted high risk sources of emboli (I), once embolic sources were included, it was the younger individuals with a low risk embolic source who more likely to undergo a change in management (III). Older age was likely associated with complex aortic plaque as a high risk source, but this association did not translate to changes in management. Hyperlipidemia management for secondary prevention would have been started prior to the TEE, in which case the TEE results would confirm the need for aggressive cholesterol management. This retrospective study cannot determine whether TEE findings reaffirm management choices.

Almost one-third of this cohort underwent changes in medications or clinical management. Other studies reported a wide range of management changes based on TEE findings from 8% in patients with ischemic stroke to 22% of those referred for transient ischemic attack and 32% of patients with non-hemorrhagic ischemic stroke or peripheral embolism.(3-5) The prevalence of atrial fibrillation in these studies was as high as 14%. The strength of our analysis was that the changes in management specifically reflect the TEE findings.

While patients with atrial fibrillation were included in the analysis, any changes in management had to directly reference the TEE results. That is, if oral anti-coagulation was started for atrial fibrillation, it would only be counted as a change in management if the physician referenced the TEE results. We found no association between current atrial fibrillation or a history of atrial fibrillation and changes in management supporting the idea that changes in management following TEE in these subgroups were due to the TEE results. In fact, when TEE findings were included in the multivariate analysis, subjects not currently in atrial fibrillation underwent changes in management.

The association between age and high risk sources of embolus on TEE was consistent with the literature.¹² The low prevalence of diabetes mellitus in those with a high risk embolic source was a novel finding. Though diabetics may often present with lacunar strokes as first ischemic events, they should be no more or less likely to have high risk sources of embolus when presenting with possible cardioembolic events. Also, there was no association found between a history of diabetes mellitus and a change in management.

The prevalence of high risk sources was 14.3% and was higher than previous reports that ranged from 8-10%.^{3, 4} One limitation of our study was that selected patients were referred for TEE rather than TEE screening of consecutive individuals. There may be some degree of suspicion or need for confirmatory testing that leads to referral bias. Our cohort reflected a population of patients with a first ischemic stroke at a tertiary care center. The population may not reflect those with a second or third ischemic event or those seen at other hospitals. We categorized embolic sources as high or low risk based upon other studies of TEE. Different classification schemes may identify alternative predictive factors.

These evidence-based decision guides were designed help physicians determine who should undergo invasive TEE screening based on the potential to identify high risk sources or, alternatively, the likelihood of a change in management. Identifying individuals with high risk sources of emboli is necessary for secondary prevention of stroke. Also, selecting appropriate patients for TEE screening reduces overall disability from adverse events and guides appropriate utilization by limiting the number of TEEs that fail to identify an embolic source or change management. Patients with an ischemic event who are unlikely to have a change in management could undergo a less-invasive and less-expensive TTE screening.

The results of this study suggest that it is possible to identify a subset of individuals with a first ischemic event who should undergo TEE screening. Future studies include prospective validation of the decision guides and testing the applicability of the guides to those with recurrent ischemia. An evaluation of TTE would also be warranted since practice patterns are moving toward initial TTE screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

KCY was supported in part by National Institutes of Health (NIH) T32HL007937 (to Thomas A Pearson MD PhD MPH, Department of Community and Preventive Medicine, University of Rochester). Part of this project was supported by an American Heart Association Student Summer Scholarship in Cerebrovascular Disease and Stroke (KCY). CGB is supported in part by NIH RO1HL080107.

Reference List

1. Lin SL, Hsu TL, Liou JY, et al. Usefulness of transesophageal echocardiography for the detection of left atrial thrombi in patients with rheumatic heart disease. *Echocardiography*. 1992; 9:161–168. [PubMed: 10149880]
2. Albers GW, Comess KA, DeRook FA, et al. Transesophageal echocardiographic findings in stroke subtypes. *Stroke*. 1994; 25:23–28. [PubMed: 8266377]
3. Strandberg M, Marttila RJ, Helenius H, Hartiala J. Transoesophageal echocardiography in selecting patients for anticoagulation after ischaemic stroke or transient ischaemic attack. *J Neurol Neurosurg Psychiatry*. 2002; 73:29–33. [PubMed: 12082041]
4. Harloff A, Handke M, Reinhard M, et al. Therapeutic strategies after examination by transesophageal echocardiography in 503 patients with ischemic stroke. *Stroke*. 2006; 37:859–864. [PubMed: 16439702]

5. Dawn B, Hasnie AM, Calzada N, et al. Transesophageal echocardiography impacts management and evaluation of patients with stroke, transient ischemic attack, or peripheral embolism. *Echocardiography*. 2006; 23:202–207. [PubMed: 16524390]
6. Howard G, Baker WH, Chambless LE, et al. An approach for the use of Doppler ultrasound as a screening tool for hemodynamically significant stenosis (despite heterogeneity of Doppler performance). A multicenter experience. Asymptomatic Carotid Atherosclerosis Study Investigators. *Stroke*. 1996; 27:1951–1957. [PubMed: 8898797]
7. Harloff A, Handke M, Geibel A, et al. Do stroke patients with normal carotid arteries require TEE for exclusion of relevant aortic plaques? *J Neurol Neurosurg Psychiatry*. 2005; 76:1654–1658. [PubMed: 16291889]
8. Patel SG, Collie DA, Wardlaw JM, et al. Outcome, observer reliability, and patient preferences if CTA, MRA, or Doppler ultrasound were used, individually or together, instead of digital subtraction angiography before carotid endarterectomy. *J Neurol Neurosurg Psychiatry*. 2002; 73:21–28. [PubMed: 12082040]
9. Lell M, Fellner C, Baum U, et al. Evaluation of carotid artery stenosis with multisection CT and MR imaging: influence of imaging modality and postprocessing. *AJNR Am J Neuroradiol*. 2007; 28:104–110. [PubMed: 17213434]
10. Benjamini Y, Krieger AM, Yekutieli D. Adaptive linear step-up procedures that control the false discovery rate. *Biometrika*. 2006; 93:491–507.
11. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem*. 1993; 39:561–577. [PubMed: 8472349]
12. Stollberger C, Finsterer J. Transoesophageal echocardiography: which stroke patients benefit most from this investigation? *J Neurol Neurosurg Psychiatry*. 2003; 74:283–284. [PubMed: 12531977]

Figure 1.

Flow chart of TEE findings and changes in clinical management. LA/LAA: left atrial/left atrial appendage, LV: left ventricular, PFO: patent foramen ovale, ASA: atrial septal aneurysm, SEC: spontaneous echo contrast.

Figure 2.
Receiver-operator characteristic curve for the detection of a high risk embolic source.

Table 1

Cohort characteristics.

<u>Patient Characteristics</u>	
Age	59.8 ± 15.5
Gender, % female	45.3%
tPA given	8.7%
Systolic blood pressure	157 ± 31
Diastolic blood pressure	87 ± 19
<u>Suspected etiology at presentation</u>	<u>N (%)</u>
TIA	57 (19.9)
Stroke	226 (78.7)
Unknown	4 (2.1)
<u>Suspected subtype at presentation</u>	<u>N (%)</u>
Embolic/cardioembolic	59 (20.6)
Lacunar due to small artery disease	32 (11.2)
Carotid artery atherosclerosis	6 (2.1)
Dissection	2 (0.7)
Not specified or cryptogenic	188 (65.5)
<u>Time from admission to TEE</u>	<u>Days</u>
Range	0-11
Median	2
Average	2.4
<u>History (self-report)</u>	<u>N (%)</u>
Diabetes	72 (25.4)
Hypertension	173 (60.2)
Heart failure	22 (8.0)
Prosthetic valve	2 (0.7)
Valve disease	8 (2.8)
PVD	15 (5.2)
Hypercoagulable state	5 (1.7)
Migraine	28 (10.0)
Atrial fibrillation, history	23 (8.4)
Atrial fibrillation, current	21 (7.3)
<u>Medications (self-report)</u>	
Anti-hyperlipidemia	91 (31.5)
Anti-platelet	93 (33.0)
Anti-coagulant	10 (3.5)
Anti-hypertensive	166 (58.3)

Abbreviations: TIA: transient ischemic attack, tPA: tissue plasminogen activator, PVD: peripheral vascular disease, TEE: transesophageal echocardiography.

Table 2

Prevalence of TEE identified embolic sources and changes in management.

High risk sources	N (%)
Total	41 (14.3)
Thrombus (left sided)	9 (3.1)
Plaque (severe, ≥ 4 mm, or mobile)	32 (11.1)
Low risk/potential sources* (only)	N (% of 287)
Total	176 (61.3%)
Aortic plaque <4mm	117 (40.8)
PFO alone	51 (17.8)
PFO+ASA	16 (5.6)
MV/AV involvement [†]	16 (5.6)
SEC	12 (4.2)
ASA alone	7 (2.4)
Endocarditis	2 (0.7)
Other [‡]	14 (4.9)
Changes in management	N (%)
Any change	87 (30.3)
Medication change	44 (15.3)
Management change [§]	65 (22.6)
Both medication and management	22 (7.7)

* Data for those individuals with low risk/potential sources reflect those *without* a concomitant high risk source.

Abbreviations: PFO: patent foramen ovale, ASA: atrial septal aneurysm, SEC: spontaneous echo contrast, MV: mitral valve, AV: aortic valve.

[†] Includes filamentous strands (6), mitral annular calcification (6), valve prolapse (3), myxomatous valve (2), prosthetic valve (2), vegetation, and valve stenosis.

[‡] Includes dilated cardiomyopathy (3), intra-pulmonary shunt (3), fibrin excrescence, lipomatous hypertrophy of the intra-atrial septum (3), aortic aneurysm, pulmonary vein mass, aortic thrombus, and left ventricular aneurysm.

[§] Includes additional testing, consult requests, changes to planned procedures or PFO closure.

Table 3Univariate analyses where $p < 0.05$.

<i>For a high risk source of embolus</i>		
Variable	OR (95% CI)	p-value
Age, per year	1.06 (1.03-1.08)	<0.001
Age, categorical [*]		<0.002
50-59	2.2 (0.5-9.6)	
60-69	5.1 (1.35-19.6)	
70+	8.3 (2.4-29)	
No history of diabetes mellitus	7.5 (1.8-32)	0.006
History of valve disease	6.54 (1.57-27.3)	0.01
Diastolic blood pressure, initial, per mmHg	0.98 (0.96-0.997)	0.023
History of peripheral vascular disease	3.28 (1.06-10.1)	0.039
<i>For a thrombus (left sided)[†]</i>		
Variable	OR (95% CI)	p-value
Suspected cardioembolic subtype	5.31 (1.38-20.4)	0.019
History of valve disease	13 (2.21-75.8)	0.022
History of heart failure	6.82 (1.58-29.4)	0.024
History of atrial fibrillation [‡]	6.45 (1.5-27.7)	0.028
Suspected cryptogenic subtype	0.16 (0.03-0.8)	0.03
SBP initial, per mmHg	1.02 (1.00-1.03)	0.034
History of migraine	5.06 (1.19-21.5)	0.047
<i>For a change in management</i>		
Variable	OR (95% CI)	p-value
No history of hypertension	2.62 (1.54-4.46)	0.0004
Not taking lipid-lowering medications	2.03 (1.13-3.64)	0.018
Diastolic blood pressure, initial, per mmHg	0.98 (0.97-0.997)	0.02
<i>For a change in management, including TEE findings</i>		
Variable (those above plus the following)	OR (95% CI)	p-value
High risk source	3.22 (1.64-6.34)	<0.001
Low risk source	11.67 (4.11-33)	<0.001
PFO	18 (9.5-34.2)	<0.001

^{*} Age <50 years is the reference group

[†] P values <0.05 by fisher's exact test for categorical variables.

[‡] This refers specifically to history of atrial fibrillation. Current atrial fibrillation was analyzed separately and was not significantly associated with thrombus.

Table 4

Multivariate analyses and the two-stage linear step-up procedure.

Variable	OR (95% CI)	p-value
<i>For a high risk source</i>		
Age	1.05 (1.02-1.1)	0.006
No history of diabetes mellitus	8.26 (1.76-38.7)	0.007
<i>For a change in management</i>		
Nonsmoker/former smoker	2.26 (1.05-4.89)	0.037
<i>For a change in management, including TEE results</i>		
No history of hypertension	4.21 (1.6-11.1)	
Nonsmoker/former smoker	3.79 (1.35-10.6)	0.012
Not in atrial fibrillation	8.26 (1.29-52.9)	0.03
Diastolic blood pressure, initial	0.98 (0.95-1.00)	0.054
	Coefficient [†]	
Low risk source	4.6328	0.016
Age*low risk source	(-) 0.057	0.056
Age [‡]	0.0264	0.46

[†] Because of the interaction, coefficients are presented.

[‡] Age was not a variable identified after the two-stage linear step up procedure. It is presented because of the interaction term.