Therapeutic Strategies After Examination by Transesophageal Echocardiography in 503 Patients With Ischemic Stroke

Andreas Harloff, MD; Michael Handke, MD; Matthias Reinhard, MD; Annette Geibel, MD; Andreas Hetzel, MD

Background and Purpose—Transesophageal echocardiography (TEE) is the gold standard in detecting high-risk (ie, aortic thrombi) and potential sources (ie, patent foramen ovale [PFO]) of cerebral embolism. We sought to evaluate the additional information and therapeutic impact provided by TEE in stroke patients and to characterize patients in whom TEE is indispensable.

Methods—We included 503 consecutive patients (mean age 62.2 years) with acute brain ischemia. Each patient received TEE and the following routine diagnostics: ultrasound of brain supplying arteries, ECG or Holter-ECG, transthoracic echocardiography, and brain imaging (computed tomography or MRI). Stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. High-risk sources in TEE were: aortic thrombi or plaques ≥4 mm, thrombi in left atrial cavity/left atrial appendage, spontaneous echo contrast, and left atrial flow velocity <30 cm/s. Potential sources in TEE were PFO, atrial septal aneurysm, and aortic plaques <4 mm.

Results—Stroke etiology was determined by routine diagnostics in 276 of 503 patients (54.9%). Of the remaining 227 patients (undetermined etiology), 212 (93.4%) were candidates for oral anticoagulation (OA). TEE revealed a high-risk source, with indication for OA in 17 of them (8.0%). A potential source leading to OA was found in an additional 48 patients (22.6%). The remaining 147 patients (69.3%) were treated by platelet inhibitors or statins.

Conclusions—TEE strongly influenced secondary prevention and led to OA in one third of our patients with stroke of undetermined etiology. TEE is indispensable in all patients being candidates for OA when routine diagnostics cannot clarify stroke etiology. (Stroke. 2006;37:859-864.)

Key Words: echocardiography, transesophageal ■ stroke, acute ■ stroke management

Transesophageal echocardiography (TEE) is superior to transthoracic echocardiography (TTE) in detecting high-risk sources and potential sources of cerebral embolism.1-4 Complication rate in TEE is low,5 but the procedure is semi-invasive, time consuming, and often not readily available everywhere. Therefore, it might be applied primarily to patients with stroke of undetermined etiology (ie, patients showing normal results in ECG, carotid ultrasound, and TTE, who are candidates for oral anticoagulation [OA]).

However, recommendations of TEE in stroke patients are controversial: in a systematic review, TEE was recommended only for younger patients to exclude rare sources of cerebral embolism such as atrial thrombi despite sinus rhythm.6 Leung et al7 recommended TEE for patients with abnormal TTE and for younger patients when finding of patent foramen ovale (PFO) may contribute to patient management. Warner et al8 pointed out that routine TEE is not cost-effective; patients with atrial fibrillation would receive OA anyway, and those in sinus rhythm would usually have findings for which only aspirin is indicated. However, others showed that TEE changed secondary prevention toward OA in 10% of the patients with stroke of undetermined etiology.9,10 In 441 unselected stroke patients, TEE revealed a cardiac abnormality leading to OA in 8% of the patients who were in sinus rhythm and had no clinical evidence of a cardiac disease. TEE was therefore recommended for all patients without contra-indication against anticoagulation.3

Because of these conflicting data, our aim was to identify the therapeutic impact of TEE in stroke patients and to compile an algorithm of TEE indication based on our findings and the current treatment guidelines for different stroke causes to characterize patients in whom TEE is indispensable.

Subjects and Methods

Study Population
A total of 596 consecutive patients admitted to our stroke unit fulfilled the inclusion criteria (18 to 85 years of age and acute brain ischemia). Twenty-four patients declined to undergo TEE examina-
tion. All others were prospectively enrolled after approval by the local ethics committee. Written informed consent was obtained after detailed information. In 37 patients, TEE could not be performed for the following reasons: 10 were in a too bad clinical condition (ie, massive brain stem infarction in basilary artery thrombosis, large brain infarction with herniation); 10 were transferred to another clinic or died before TEE could be performed; in 14, TEE could not be accomplished because of an uncontrollable gag reflex or gastrointestinal tract obstruction; and in 3, TEE was done previously in another clinic, but data acquisition was inconsistent with our protocol. Thirty-two additional patients were excluded because diagnosis on discharge was another than brain ischemia. Finally, we included a consecutive series of 503 patients.

Within a median of 2 days after stroke onset, all patients received TEE. Furthermore, the following examinations (routine diagnostics) were performed in the same period: cranial computed tomography, MRI of the brain, or both, duplex sonography of extracranial and intracranial arteries with a 4- to 7-MHz linear array scanner (ATL; HDI 5000/3500); degree of internal carotid artery (ICA) stenosis was defined according to the European Carotid Surgery Trial protocol.11 Furthermore, each patient received TTE and ECG. In patients with assumed atrial fibrillation or unproductive routine diagnostics, we additionally performed 24-hour ECG Holter monitoring. In patients ≤60 years of age, we screened blood for factor V Leiden mutation, decreased antithrombin III, protein C and S, and increased antiphospholipid antibody titer.

Without usage of TEE data, we retrospectively classified infarct etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.12 Patients were divided into group 1 if stroke etiology could be classified based on routine diagnostic information only. The remaining patients were defined as “undetermined etiology” and formed group 2. Group 3 contained all patients with contraindications against OA (ie, severe cerebral small-vessel disease, uncontrollable hypertension, incompliance of intake of phenprocoumon, severe alcohol abuse, danger of recurrent falls, and gastrointestinal ulcers) who were excluded from group 2 because TEE findings would not lead to another treatment than platelet inhibitors (Figure 1).

**TTE and TEE**

The ultrasound system ATL HDI 3500 was used for transthoracic (2 MHz transducer) and transesophageal (5 MHz transducer) echocardiographic examinations. A routine TTE examination of the heart was first done in each patient. Precise quantification of the left ventricular ejection fraction was made according to the recommendations in cases of reduced left ventricular function.13 TEE was performed on average 3±2 days (median 2 days) after admission. The left atrium was examined thoroughly with respect to spontaneous echo contrast (SEC) and thrombi. SEC was defined as a pattern of slowly swirling intracavitary densities imaged with gain settings adjusted to distinguish background noise and classified as dense.

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**Figure 1.** Flow chart for identification of stroke patients with the need of TEE performance.
when continuously present at standard gain. A thrombus was diagnosed when a fixed or mobile echo-dense mass could be clearly differentiated from the wall of the left atrial cavity/left atrial appendage (LA/LAA). For measurement of end-diastolic peak flow velocity, the Doppler sample volume was positioned in the proximal third of the appendage and the average taken of the values of 5 cycles. Atrial septal aneurysm (ASA) was diagnosed when the excursion of an abnormally redundant and mobile atrial septum was ≥ 10 mm. Injections of an agitated contrast agent (gelifundol) were performed at rest and during Valsalva maneuver. A right-to-left shunt was diagnosed when microbubbles were detected in the left atrium within 4 cardiac cycles after right atrial opacification. The ascending aorta and the aortic arch including the outlet of the left subclavian artery were examined with respect to aortic plaques defined as irregular intimal thickening with increased echogenicity. The thickest plaque was considered for classification. Atheroma were divided into lower risk (ie, < 4 mm) and into higher risk (ie, ≥ 4 mm), and presence of ulcerations or mobile components/thrombi was recorded. Aortic thrombus was defined as laminated deposition along the intimal surface, with variable echogenicity, and which may be associated with mobile lesions.

Statistical Analysis

All analyses were performed by SAS statistical package (version 6.12). Results are expressed as absolute frequencies and percentages where appropriate. We used 2-tailed t tests and χ² tests to compare proportions. A 2-tailed P < 0.05 was considered to indicate statistical significance.

Basic Findings

The baseline characteristics of the 503 study participants are shown in Table 1. Coagulation disorders in the 108 patients of group 2 ≥ 60 years of age were: heterozygote factor V Leiden mutation in 5 (4.8%), decreased antithrombin III in 0 (0.0%), decreased protein C and S in 2 (2.2%) and 9 patients (9.9%), respectively, and increased antiphospholipid antibody titer in 1 patient (1.1%).

Stroke etiology could be classified by routine diagnostic data (ie, without TEE data) in 276 (54.9%) patients (group 1) according to the TOAST classification (Figure 1). In the remaining 227 (45.1%) patients, we found contraindications against OA in 15: severe cerebral small-vessel disease (n = 7), severe alcohol abuse or incompliance (n = 2), ataxia with recurrent falls (n = 2), uncontrollable hypertension (n = 1), and...

Figure 2. TEE-guided therapeutic management of patients with stroke of undetermined etiology. The finding of multiple high and potential risk sources in some patients is the reason for the discrepancy between the number of TEE parameters and patients.
multiple contraindications (n = 3). Therefore, TEE data were further evaluated in 212 patients (93.4%) of group 2.

**TEE Findings in Group 1**

In group 1, TEE detected 168 cardiac high-risk sources that were most frequent in the cardioembolic group (136 of 168; 81.0%), less frequent in the large-artery atherosclerosis group (28 of 168; 16.7%) and in patients with small-vessel disease (4 of 168; 2.4%), and absent in other stroke subtypes (Table 2). Of 124 patients in the cardioembolic group, 104 (83.9%) showed intermittent or chronic atrial fibrillation, and TEE found LA/LAA thrombi in 13 (12.8%), SEC in 44 (43.1%), and reduced LAA flow in 34 (32.7%) of them. However, these findings were not mutually exclusive; in 12 of 13 (92.3%) patients with LA cavity/appendage thrombus, TEE additionally showed SEC, and in 9 of 13 patients (69.0%), additional LAA flow <30 cm/s was found. Furthermore, in 2 patients, TEE detected both aortic thrombi and SEC.

**TEE Findings in Group 2 and Therapeutic Management**

TEE revealed cardiac high-risk sources for cerebral embolism in 42 patients (19.8%) leading to OA in 17 (8.0%). A potential source was found in the remaining 170 patients (80.2%) of group 2 (Figure 2).

After exclusion of patients with high-risk sources, PFO, ASA, or both were found in 71 patients (33.5%). With regard to stroke morphology in brain imaging, existence of a Valsalva maneuver preceding onset of symptoms, detection of deep venous thrombosis by ultrasound, and underlying coagulation disorders, respectively, 48 of them were discharged with OA (22.6%). The rate of OA was 25 of 39 (64.1%) in patients with PFO, 2 of 6 (33.3%) in ASA, and 21 of 26 (80.8%) when PFO and ASA were detected. The remaining 122 patients (ie, absence of cardiac high-risk sources and PFO/ASA with indication for OA) received optimization of cardiovascular risk factors or were treated by platelet inhibitors or statins.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of Patients in Group 1 (determined stroke etiology) and Group 2 (undetermined etiology)</th>
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<tr>
<td><strong>Characteristic</strong></td>
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<td>Age, y</td>
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<tr>
<td>Female sex, no. (%)</td>
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<tr>
<td>Hypertension, no. (%)</td>
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<tr>
<td>Diabetes, no. (%)</td>
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<td>Hyperlipidemia, no. (%)</td>
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<td>Smoking, no. (%)</td>
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<td>CHD, no. (%)</td>
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<td>Stroke/TIA, no. (%)</td>
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<td>PAD, no. (%)</td>
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Values are means ±SD.

CHD indicates coronary heart disease; Stroke/TIA, history of brain ischemia; PAD, peripheral artery disease.

<table>
<thead>
<tr>
<th><strong>TABLE 2. TEE Findings in Group 1 (determined stroke etiology) and in Group 2 (undetermined etiology)</strong></th>
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<tr>
<td><strong>Distribution of Patients</strong></td>
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<tr>
<td>Group 1</td>
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<tr>
<td>Large-artery atherosclerosis (n=83, 30.4%)</td>
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<tr>
<td>Small-vessel disease (n=59, 21.6%)</td>
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<tr>
<td>Other determined etiology (n=10, 3.7%)</td>
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<tr>
<td>All patients (n=276)</td>
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<tr>
<td>Group 2</td>
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<tr>
<td>Group 3</td>
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Statistical analyses were not performed in group 3 because of the small number of patients.

AT indicates aortic thrombus; LAAT, left atrial cavity/appendage thrombus; AA, aortic atheroma.
Comparison of TEE Results in Both Groups
Aortic thrombi were more frequent in group 2, whereas occurrence of plaques ≥4 mm was comparable. The frequency of LA/LAA thrombus, SEC, and LAA flow <30 cm/s was much higher in patients of group 1 (Table 2). Compared with group 1, the frequency of PFO + ASA was ≈3 × higher and the frequency of isolated PFO ≈2 × higher in patients of group 2. There was no significant difference concerning the incidence of isolated ASA (Table 2).

Discussion
By use of routine diagnostic procedures, stroke etiology could be classified according to the TOAST criteria in more than half of our patients. However, without TEE data, a high proportion of patients remained with “stroke of undetermined etiology.” In this stroke subgroup, the therapeutic impact of TEE was high; only because of TEE findings, 65 of 212 patients (30.6%) were treated with OA on discharge instead of aspirin or statin treatment alone. In contrast to Warner et al,8 several of our patients had an indication for OA, although they were in sinus rhythm. The percentage of patients treated with OA in the subgroup “stroke of undetermined etiology” was ≈3 × higher in our population than described previously.3,9,10 Rauh et al10 treated only patients with cardiac high-risk sources with OA, and Strandberg et al3 did not precise which kind of TEE results led to OA. Also, different algorithms in preselecting patients for TEE may have led to different percentages of OA,7 whereas the present study performed TEE consecutively in all patients.

Clinical Implications of Cardiac High-Risk Sources in TEE
Aortic Thrombi and Plaques ≥4-mm Thickness
The detection of aortic thrombi in TEE changed secondary prevention to OA for at least 4 to 6 weeks in our patients, and this therapy was also chosen in other studies.19,20 However, there is no evidence based treatment for this situation so far. With disappearance of aortic thrombi in TEE control 4 weeks later, medication was changed to platelet inhibitors plus statins for plaque stabilization in our patients.

Aortic plaques ≥4 mm are an independent predictor of recurrent stroke.15 However, the proper therapy for this condition is unknown so far. In smaller, nonrandomized studies, oral anticoagulants were superior to aspirin,20,21 whereas in a larger retrospective, nonrandomized analysis, only statins showed a significant benefit.22 The ongoing Aortic arch Related Cerebral Hazard (ARCH) trial comparing clopidogrel plus aspirin versus warfarin will contribute substantial information for the optimal treatment and might increase the diagnostic impact of TEE. Furthermore, knowledge of high-risk aortic atherosclerosis (ie, plaques ≥4 mm) will also lead to intensified treatment of cardiovascular risk factors in these patients.

Reduced LAA Flow, SEC, and LA Cavity/Appendage Thrombi
Atrial fibrillation, mitral stenosis, LA enlargement, and left ventricular dysfunction predispose to reduced LAA emptying velocity, stasis of blood, SEC, and thrombus formation in LA cavity/appendage, all of which can be detected by TEE.21,23–25 SEC was present in ≈45% of our patients with atrial fibrillation, which is slightly lower than described previously.23,26 This can be explained by the inclusion of patients with intermittent atrial fibrillation in this subgroup. The high rate of SEC in our patients with LA cavity/appendage thrombus in group 1 strongly supports the linkage between SEC, thrombus formation, and cerebral embolism. Because of the fact that cardioembolic strokes and thrombus formation are significantly reduced under OA in patients with SEC or atrial fibrillation,21,26,27 we treated patients accordingly.

Safety of Omitting TEE in Stroke Patients
In group 1, TEE revealed 5 cardiac high-risk sources with indicated OA in 5 patients of the large-artery atherosclerosis group but in no patient of the other subgroups (Table 2). Therefore, without TEE performance, a possible indication for OA theoretically could have been missed in 1.8% of the 276 patients of group 1. However, in ≈50%, ICA stenosis screening for additional cardiac high-risk sources seems only reasonable when distribution of brain ischemia is not in concordance with the side of the stenosis. Therefore, we believe that TEE can be omitted in patients of group 1 without loss of safety when stroke etiology can be classified definitely on the basis of routine diagnostics. The additional detection of potential cardiac sources in TEE in patients of group 1 did not influence therapy as long as other causes for stroke such as cardioembolism or small-vessel disease were more probable and guided secondary prevention.

Clinical Implications of Potential Risk Sources in TEE
Most of our patients with PFO + ASA received OA, whereas this treatment was chosen for fewer patients with isolated PFO or ASA. PFO and ASA have been implicated as risk factors for stroke,28 but therapeutic recommendations for PFO and ASA are still controversial. Recently, Homma et al29 reported in a large prospective study no significant difference of stroke recurrence rate among those with no, small, or large PFO. They neither found any difference among those with PFO and PFO + ASA nor in patients with PFO when they were treated with aspirin or warfarin. This is in contrast to a previous study of Mas et al,30 who found a multiplicative risk of PFO + ASA for stroke recurrence rates. A meta-analysis found warfarin superior to aspirin therapy in preventing recurrent ischemic events and the success rate in stroke prevention of surgical PFO closure comparable to anticoagulation.31 The increased incidence of isolated PFO and especially of PFO + ASA in our patients of group 2 is in concordance with a meta-analysis that found in patients <55 years of age a 3 × higher prevalence of PFO and 6 × greater prevalence of ASA in patients with stroke of undetermined etiology than in the general population.32 These findings suggest a potential role of PFO and ASA as a cause of cardioembolic stroke.

The indication for OA or closure of PFO or ASA is individually made depending on clinical circumstances and patients’ personal attitude until prospective randomized data become available. Therefore, even in isolated PFO or ASA,
closure of PFO or OA should be discussed in case of recurrent cerebral embolism. TEE is not only valuable in acute diagnostics; the impact of this procedure is augmented by the importance for the planning, performance, and follow-up of surgical or percutaneous closure of PFO and ASA.

Summary
Because of TEE examination, secondary prevention was significantly influenced toward OA in one third of our patients with stroke of undetermined etiology after routine diagnostics. We propose to define stroke etiology and consecutive secondary prevention by routine diagnostics first because this procedure has proven to be safe in our stroke population. Patients with ≥50% ICA stenosis have an increased risk of aortic thrombi and should be examined by TEE when stroke symptoms are discordant to the side of stenosis. We strongly recommend additional TEE in all other patients without contraindication against anticoagulation when routine diagnostics cannot clarify stroke etiology. Our algorithm for TEE indication (Figure 1) helps saving TEE in >50% of all stroke patients and reveals significant findings in the remaining patients. It needs to be emphasized that our TEE-guided therapeutic strategies are not evidence based but presumably in agreement with most clinicians. Therefore, therapeutic impact of TEE might alter by new clinical evidence derived from ongoing or future trials establishing optimal treatment of cardiac high or potential risk sources of cerebral embolism.

References
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*Stroke*. 2006;37:859-864; originally published online January 26, 2006; doi: 10.1161/01.STR.0000202592.87021.b7

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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