Predictors of Long-Term Mortality in Patients With Ischemic Stroke Referred for Transesophageal Echocardiography

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Background and Purpose—Findings on transesophageal echocardiography (TEE) after ischemic stroke predict recurrent embolic events and prompt therapy; however, the additive predictive power of TEE findings on long-term mortality is unknown. Our goal was to study the impact of TEE findings on all cause mortality in ischemic stroke patients referred for TEE.

Methods—We reviewed 245 consecutive patients who underwent TEE for ischemic stroke of undetermined origin (2000 to 2003). Long-term survival was assessed using the Social Security Death Index.

Results—In a mean follow-up period of 3.0 (1.4 to 4.8) years, death occurred in 19.2% of patients. TEE findings included patent foramen ovale (18.8%), left atrium/left ventricle thrombus (2.4%), spontaneous echo contrast (3.7%), atrial septal aneurysm (3.3%), valve vegetation/mass/tumor (7.8%), complex aortic atheroma (CAA; 14.7%), and the composite of any cardiac source of embolus (39.2%). A total atherosclerotic burden (TAB) score was also recorded. On Cox hazard regression analysis, measures of aortic atherosclerosis (CAA [hazard ratio (HR), 2.7; 95% CI, 1.4 to 5.3] or TAB score [HR, 1.4; 95% CI, 1.2 to 1.6]) were independent predictors of death, whereas other TEE findings were not.

Conclusion—In patients with ischemic stroke of undetermined origin referred for TEE, measures of aortic atherosclerosis, including CAA, represent the only TEE findings that predict long-term mortality after all other clinical factors are considered. Further study is needed to determine whether treatments for CAA effect long-term survival in patients with ischemic stroke. (Stroke. 2006;37:204-208.)

Key Words: atherosclerosis ■ echocardiography, transesophageal ■ stroke

Patients who have experienced an ischemic stroke have an increased risk for mortality. Five-year survival after any ischemic stroke has been reported to be as low as 40%, and patients with a history of stroke have a 10-fold increase in all-cause mortality.1–3 Pre-existing cardiovascular conditions such as atrial fibrillation and left ventricular dysfunction are established risk factors for ischemic stroke and are associated with increased mortality.4,5 In patients with ischemic stroke without pre-existing high-risk conditions, the clinical factors associated with long-term mortality have not been widely studied.

Over the past decade, echocardiography has become instrumental in the workup of patients with ischemic stroke for the identification of potential cardiac sources of embolism. Transesophageal echocardiography (TEE) is useful for detection of findings such as spontaneous echo contrast, left atrial/ventricular thrombus, atrial septal aneurysm, patent foramen ovale (PFO), and complex aortic atheroma (CAA).6,7 Several studies have demonstrated associations between these findings and recurrent stroke.7–12 However, there are limited data on the predictive power of these findings on mortality after ischemic stroke and no mortality studies that adjust for other clinical risk factors and modern treatments of ischemic stroke patients.

Thus, our goal was to study the relationship between TEE findings and long-term mortality in patients presenting with stroke of unexplained origin who are referred for TEE. We sought to determine which TEE findings provided incremental predictive information on mortality after known clinical risk factors for death after ischemic stroke are accounted for.

Methods

We performed a retrospective study of 245 consecutive patients referred for TEE after documented ischemic stroke for the indication of exclusion of cardiovascular source of embolus at the University of Chicago between January 2000 and June 2003. Patients were identified by searching a database of all TEE studies performed at this institution. All patients were required to have a brain imaging study (computed topographic [CT], MRI, or magnetic resonance angiography) to confirm acute ischemic stroke. Patients in whom a diagnosis of ischemic stroke was not confirmed and patients with known pre-existing high-risk cardioembolic conditions (atrial fibrillation or flutter, left ventricular ejection fraction <30%, left ventricular aneurysm, aortic or mitral stenosis, known valvular vegetation or mass, any congenital heart disease, any prosthetic valve, or previous valve surgery) or carotid stenosis or previous carotid endarterectomy were excluded.

Medical records and radiology reports were reviewed by investigators blinded to TEE results. Patient characteristics included: age, sex, hypertension, hyperlipidemia, diabetes, current tobacco use,
renal insufficiency (creatinine $>1.5$ mg/dL), previous stroke, and history of coronary artery disease (CAD; defined by history of myocardial infarction, or a positive stress test or documented coronary stenosis $>50\%$ on coronary angiogram), hospital discharge medications, and stroke disability as assessed using the modified Rankin scale at hospital discharge.

Long-term survival was assessed using hospital records and the Social Security Death Index (SSDI). Patients were considered to be alive if the hospital medical records did not document death and the patient was not listed in the SSDI.

Cerebrovascular Events
Stroke subtypes were determined based on results of brain imaging studies. Cortical strokes were defined as those described on final head CT or MRI report as acute cortical, embolic, or cerebral or carotid artery distribution infarctions. Subcortical strokes were defined as those described on MRI as exclusively lacunar, subcortical, basal ganglia, or deep white matter infarctions. A CT scan alone was not considered diagnostic of a subcortical stroke unless the CT findings were supported by a documented neurologist diagnosis based on a clinical syndrome consistent this diagnosis. Strokes of either type with hemorrhagic conversion were noted.

Transesophageal Echocardiography
TEE images were acquired on Hewlett-Packard Sonos 5500 cardiac ultrasound machines using omni-plane transducers. Findings on TEE were identified from final TEE reports from a digital Enconcert database (Philips Medial Systems) at our institution. TEEs were performed and interpreted by expert echocardiographers in our laboratory.

TEE findings known or suggested to be associated with ischemic stroke were recorded, including left atrial thrombus, left ventricular thrombus, intracardiac tumors, spontaneous echo contrast, valvular vegetation or mass, valve strands/tumor, atrial septal aneurysm, PFO, and CAA (defined as a plaque in the ascending aorta/aortic arch or descending aorta that protrudes $\geq 4$ mm into the aortic lumen, or that is associated with ulceration or mobile features). Any potential cardioembolic source (CES) of embolus was defined as the composite of any finding described above.

Aortic atheroma was graded in all patients in the descending aorta and ascending aorta/arch on a scale from 1 through 5 (grade 1 = $<1$ mm intimal thickness; grade 2 = discrete plaques between 1 and 2 mm; grade 3 = plaques 2 and 4 mm; grade 4 = plaques $\geq 4$ mm; and grade 5 = mobile or ulcerated atheroma). A total atherosclerotic burden (TAB) score was calculated by summing the grade of the atheroma in the ascending aorta/arch and descending aorta. For the purposes of the TAB score calculation, all CAA (grades 4 and 5) were given a score of 4, thus TAB scores could range from 2 to 8. Atrial septal aneurysms were defined as a septal segment that undergoes phasic maximal excursion $\geq 15$ mm or that protrudes $\geq 10$ mm from midline into either atrium. Spontaneous echo contrast was defined as dynamic swirling of echodense material in the left atrium or left atrial appendage at standard gain settings. All patients referred for TEE for stroke undergo agitated saline contrast injection, and valsalva and cough maneuvers were used routinely to increase sensitivity of detection of PFOs.

Statistical Analysis
Cox proportional hazard regression analysis was performed to determine the effect of baseline characteristics and TEE findings on long-term survival in the total study population and the subgroup of patients with cortical stroke type. A multivariate model was constructed for each TEE finding found to be a univariate predictor of mortality to a $P<0.1$. Age, gender, and all baseline patient characteristics found to be univariate predictors of mortality ($P<0.1$) were entered in the multivariate models for CAA, TAB score, and CES in the total study group and CAA and TAB score in the cortical stroke only subgroup. Final multivariate models were chosen by the stepwise removal of variables beyond the significance level of $P<0.05$ to determine independent risk factors for mortality. Interaction testing involving variables in the final models was performed but did not reach statistical significance. Kaplan–Meier survival curves were generated to demonstrate the unadjusted effect of CAA on long-term survival.

Results
In a mean follow-up period of 3.0 (1.4 to 4.8) years (a total of 739 person years of follow-up), death occurred in 19.2% of patients (6.4 deaths per 100 person years). Baseline comorbidities and cardiac risk factors, medications, and stroke subtypes of the study populations are listed in Table 1. Study patients were found to have a high prevalence of cardiovascular risk factors including hypertension (76.7%), and diabetes (31.4%), and 18.4% had documented CAD. Patient characteristics of those patients who died and those who survived and the baseline characteristics as univariate predictors of mortality are also included in Table 1. Age, diabetes, CAD, absence of statin use, and a higher modified Rankin score were found to be significant univariate predictors ($P<0.05$) of death in the follow-up period, with a trend for cortical stroke type ($P=0.09$).

TEE findings are listed in Table 2. PFOs (18.8%) and CAA (14.7%) were the most prevalent potential cardiovascular sources of emboli identified on TEE, with any CES present in 39.2% of patients. Markers of aortic atherosclerosis (CAA and TAB score) were the only TEE findings found to be significant univariate predictors of death, with a trend for any CES (Figure; Table 2). The incidence of death in the follow-up period was 14.0 and 5.1 per 100 patient years of follow-up for patients with CAA and without CAA, respectively.

On multivariate Cox hazard regression analysis considering age, gender, diabetes, CAD, cortical stroke type, modified Rankin score, and absence of statin use, measures of aortic atherosclerosis (CAA [hazard ratio (HR), 2.7; 95% CI, 1.4 to 5.3; $P<0.01$] or TAB score [HR, 1.4; 95% CI, 1.2 to 1.6; $P<0.001$]) were strong independent predictors of death, whereas other TEE findings, including the composite of any CES, were not. In the final model including CAA, the only other independent predictors of death were absence of statin use (HR, 2.7; 95% CI, 1.2 to 6.0; $P=0.02$) and age (HR, 1.0; 95% CI, 1.0 to 1.1; $P=0.02$). In final model, including TAB score, absence of statin use (HR, 3.1; 95% CI, 1.4 to 7.0; $P<0.01$) and a higher modified Rankin score (HR, 1.30; 95% CI, 1.02 to 1.66; $P=0.04$) were the only other independent predictors of death.

Additional analysis was performed in the subgroup of patients with cortical strokes (subcortical strokes excluded). TEE findings identified to be significant univariate predictors of death in this subgroup again included CAA (HR, 3.5; 95% CI, 1.7 to 7.2; $P<0.001$) and TAB score (HR, 1.3; 95% CI, 1.1 to 1.5; $P<0.01$). The composite of any CES and other individual TEE findings were not significant univariate predictors of death in this subgroup. On multivariate Cox hazard regression analysis considering age, gender, diabetes, CAD, modified Rankin score, and absence of statin use, measures of aortic atherosclerosis (CAA [HR, 4.1; 95% CI, 1.9 to 8.5; $P<0.001$] or TAB score [HR, 1.4; 95% CI, 1.1 to 1.6; $P=0.001$]) were strong independent predictors of death among patients with cortical stroke referred for TEE.
Discussion

In this study of patients with ischemic stroke of undetermined origin referred for TEE for exclusion of cardiovascular source of embolus, markers of aortic atherosclerosis (CAA or total aortic atherosclerotic burden) were the only TEE findings identified to be independent predictors for long-term mortality after all other clinical factors were considered. Other individual cardioembolic findings and the composite of any potential CES were not independent predictors of long-term mortality.

Aortic atherosclerosis is a marker for systemic atherosclerotic disease and has accordingly been associated with vascular risk factors such as hypertension, diabetes, hypercholesterolemia, and increasing age. Recently, the prognostic significance of aortic atherosclerosis in unselected patients referred for TEE has been called into question. In a large prospective cohort study of randomly selected patients, the presence of any aortic atherosclerosis on TEE was associated with future cardiovascular events, but was not an independent predictor of future cardiovascular events after other patient risk factors were considered.\textsuperscript{13} The patients included were relatively low risk, with only 3.8% with previous strokes, 8.9% with diabetes, 8.5% with hyperlipidemia, and only 7.6% with CAA.\textsuperscript{13} Although the primary implications of this study are for primary prevention of ischemic...

| TABLE 1. Baseline Characteristics of the Total Study Group, Those Who Died and Survived the Follow-Up Period, and Cox Proportional Hazard Regression Univariate HR (95% CI) for All-Cause Mortality |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Baseline Characteristics        | Total Study Group (n=245) | Dead (n=47) | Alive (n=198) | HR (95% CI) | P Value |
| Age* (60.3–91)                  | 60.3             | 67.1           | 58.7           | 1.0 (1.0–1.1) | 0.001   |
| Male* (45.3%)                   | 45.3%            | 38.3%          | 47.0%          | 0.8 (0.4–1.4) | NS      |
| Hypertension (76.7%)            | 76.7%            | 83.0%          | 75.3%          | 1.4 (0.7–3.1) | NS      |
| Diabetes mellitus* (31.4%)      | 31.4%            | 44.7%          | 28.3%          | 1.8 (1.0–3.2) | 0.04    |
| Hyperlipidemia (33.5%)          | 33.5%            | 29.8%          | 34.3%          | 0.8 (0.4–1.5) | NS      |
| Tobacco use (30.2%)             | 30.2%            | 29.8%          | 30.3%          | 0.9 (0.5–1.7) | NS      |
| CAD* (18.4%)                    | 18.4%            | 29.8%          | 15.7%          | 1.9 (1.0–3.5) | 0.04    |
| Renal insufficiency<\textsuperscript{\textdagger} (16.3%) | 16.3%   | 23.4%          | 14.6%          | 1.6 (0.8–3.1) | NS      |
| Stroke type                     |                  |                |                |              |
| Cortical* (62.9%)               | 62.9%            | 72.3%          | 60.6%          | 1.7 (0.9–3.3) | 0.09    |
| Subcortical (37.1%)             | 37.1%            | 27.7%          | 39.4%          | 0.6 (0.3–1.1) | 0.09    |
| Hemorrhagic (8.2%)              | 8.2%             | 8.5%           | 8.1%           | 0.9 (0.3–2.5) | NS      |
| Modified Rankin score (mean)*   | 2.59             | 2.98           | 2.50           | 1.40 (1.1–1.79) | 0.01 |
| Medications                     |                  |                |                |              |
| Antiplatelet agents (76.7%)     | 76.7%            | 72.3%          | 77.8%          | 0.6 (0.3–1.2) | NS      |
| Warfarin (16.3%)                | 16.3%            | 19.1%          | 15.7%          | 1.2 (0.6–2.5) | NS      |
| Statin* (27.3%)                 | 27.3%            | 14.9%          | 30.3%          | 0.4 (0.2–0.9) | 0.03    |
| β-blocker (27.8%)               | 27.8%            | 31.9%          | 26.8%          | 1.2 (0.7–2.2) | NS      |
| ACE/ARB (35.9%)                 | 35.9%            | 31.9%          | 36.9%          | 0.9 (0.5–1.6) | NS      |

<sup>*</sup> Included in multivariate models; <sup>\textdagger</sup>creatinine >1.5 mg/dL. ACE/ARB indicates angiotensin-converting enzyme/angiotensin receptor blocker; NS, nonsignificant (P<0.01).

| TABLE 2. TEE Findings of the Total Study Group, Those Who Died and Survived the Follow-Up Period, and Cox Proportional Hazard Regression Univariate and Multivariate HR (95% CI) for All-Cause Mortality |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| TEE Findings                    | Total Study Group (n=245) | Dead (n=47) | Alive (n=198) | Univariate HR (95% CI) | P Value | Adjusted HR (95% CI) | P Value |
| SEC (3.7%)                      | 3.7%            | 4.3%           | 3.5%           | 1.1 (0.3–4.4) | NS      | ...                | ... |
| PFO (18.8%)                     | 18.8%           | 19.2%          | 18.7%          | 1.1 (0.5–2.2) | NS      | ...                | ... |
| Atrial septal aneurysm (3.3%)   | 3.3%            | 2.1%           | 3.5%           | 0.7 (0.1–5.0) | NS      | ...                | ... |
| LA/LV thrombus (2.4%)           | 2.4%            | 4.3%           | 2.0%           | 2.9 (0.7–12)  | NS      | ...                | ... |
| Any vegetation/mass/tumor (7.8%)| 7.8%            | 10.6%          | 7.1%           | 1.6 (0.7–4.1) | NS      | ...                | ... |
| CAA (14.7%)                     | 14.7%           | 31.9%          | 10.6%          | 3.2 (1.7–5.9) < 0.001  | 2.7 (1.4–5.3) < 0.01 |
| TAB (3.8%)                      | 3.8%            | 4.7            | 3.6            | 1.3 (1.1–1.5) < 0.001  | 1.4 (1.2–1.6) < 0.001 |
| Any CES (39.2%)                 | 39.2%           | 48.9%          | 36.9%          | 1.6 (0.9–2.9) 0.097   | 1.5 (0.8–2.7) NS     |

SEC indicates spontaneous echo contrast; LA/LV, left atrium/left ventricle.
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neurological events, it has prompted suggestions for a reassessment of the prognostic implications of aortic atherosclerosis on TEE.\textsuperscript{14}

In ischemic stroke patients, CAA has been shown to be a predictor of recurrent embolic events and combined cardiovascular end points,\textsuperscript{9,15–19} although the adjustment for patient risk factors in these analyses has been limited. Previous studies reporting an increased mortality risk associated with CAA have not adjusted for cardiovascular risk factors and comorbidities that would be expected to impact survival.\textsuperscript{16} No study has established aortic atherosclerosis on TEE as an independent predictor of mortality. Furthermore, previous studies have generally included unselected ischemic stroke patients, in whom other cardioembolic conditions known to be risk factors for mortality (left ventricular dysfunction, atrial fibrillation) and conditions with known associations to aortic atherosclerosis (atrial fibrillation, carotid stenosis) are prevalent, making assessment of the true prognostic implications of aortic atherosclerosis on TEE problematic.\textsuperscript{9,15–19} Our findings suggest that markers of aortic atherosclerosis, including CAA, found on TEE after ischemic stroke of undetermined origin are potent predictors of long-term mortality.

We chose to study all ischemic stroke patients without high-risk embolic conditions who had been referred for TEE, and thus all patients in whom the clinician felt TEE was indicated for exclusion of cardiovascular source of embolus. This represents the most clinically relevant population to establish for the first time the impact of TEE findings on mortality after ischemic stroke. However, because some may debate the utility of referral for TEE after strokes ultimately classified as subcortical or lacunar, we performed additional analysis on only patients categorized by head CT or MRI as cortical strokes, thus those with classic embolic features on neuroimaging studies. We found in this subgroup that aortic atherosclerosis (CAA or total aortic atherosclerotic burden) remained the only independent predictors of death after all other clinical factors were considered.

It is well established that ischemic stroke patients have a higher mortality compared with matched controls and have a high prevalence of vascular risk factors.\textsuperscript{1–3} Older age at presentation with first stroke has been shown previously to be one of the strongest predictors of future morbidity and mortality.\textsuperscript{2} We find that age remains an independent predictor of long-term mortality when the presence or absence of severe aortic athero-

ma (CAA) on TEE is considered, but it loses its predictive power when considered with a global continuous measure of aortic atherosclerosis (total atheroma burden). Other traditional risk factors for atherosclerosis and mortality, such as hypertension and diabetes, were not independent predictors of death in our study. Although these findings may be surprising at first, the inclusion of documented systemic atherosclerosis, the ultimate downstream consequence of these traditional risk factors, in our analysis not surprisingly diminished their relative risk.

We did not find that other cardiovascular sources of embolus found on TEE or the composite of all cardiovascular sources of emboli were independent predictors of all-cause mortality. Previously, in a prospective series of 40 unexplained stroke patients, O’Brien et al found that TEE allowed identification of a high-risk group and predicted cardiovascular mortality in a mean follow-up period of 14 months.\textsuperscript{15} However, individual TEE findings did not predict all-cause mortality in their study, and their study did not have the power to control for other clinical variables. Our findings confirm the ability of TEE to predict mortality after unexplained ischemic stroke but suggest markers of aortic atherosclerosis are the only individual TEE predictors of future death.

The only other consistent independent predictor of all cause mortality in this study was absence of postischemic stroke statin therapy. This finding is in concert with data from a number of large randomized controlled trials that demonstrated a potent mortality benefit of statin therapy in patients after ischemic stroke.\textsuperscript{20–22} In addition, our results establish the prognostic implications of aortic atherosclerosis on TEE in unexplained stroke patients even when postischemic stroke medical therapy, including statin therapy, is considered.

The limitations of this study are those expected from a retrospective observational study. We cannot be sure that aortic atherosclerosis plays a causative role in mortality after stroke, and because the SSDI was used to determine mortality, we cannot report detailed cause of death. However, it should be noted that multiple previous studies have established the relationship between aortic atheroma and future individual and combined vascular events.\textsuperscript{9,15–19} Additionally, all-cause mortality is the most unbiased mortality measure and thus is an appropriate end point to first establish the impact of TEE findings and the independent predictive power aortic atherosclerosis on mortality after stroke. Finally, we did not have the ability to include measures of baseline stroke severity, although
the modified Rankin scale was included, allowing us to control for overall disability after ischemic stroke. It remains unknown whether treatment of CAA will alter the long-term mortality of ischemic stroke patients. Previous studies have demonstrated that statin therapy and warfarin therapy are associated with fewer recurrent embolic events and combined cardiovascular events.\(^{17,23}\) Statins have been shown to be associated with fewer recurrent cardiovascular events in unselected TEE patients found to have CAA.\(^{23}\) Although the number of patients with CAA on statin therapy in the present study was too small to confirm a treatment benefit, our findings are consistent with these observations and further support the treatment of stroke patients with statin therapy. The role of warfarin therapy is less clear. Dressler et al demonstrated in a small cohort in patients presenting with systemic emboli and found to have mobile atheroma that warfarin therapy was associated with fewer recurrent vascular events but did not have the power to address mortality.\(^{24}\) In unselected patients found to have CAA on TEE, there is conflicting data on the protective benefit of warfarin therapy on prevention of combined vascular events.\(^{17,23}\) Although future studies are needed to establish the effect of medical therapy on long-term mortality in ischemic stroke patients found to have CAA on TEE, our results clearly identify for the first time the independent mortality risk associated with aortic atheroma in this population. Thus, an aggressive approach to risk factor modification in these patients is appropriate.

References

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