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Echocardiography in Patients with Symptomatic Intracranial Stenosis

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Abstract

Background and Purpose—Echocardiography is often performed in stroke patients, even when alterative stroke etiologies are identified. We evaluated the utility of echocardiography in patients with TIA or stroke due to stenosis of a major intracranial artery.

Methods—The Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial was an NIH-funded randomized, double-blinded, multicenter clinical trial in which 569 patients with TIA or ischemic stroke attributed to angiographically-proven 50–99% stenosis of a major intracranial artery were randomly assigned to warfarin or aspirin. Patients with unequivocal cardiac sources of embolism were excluded. The risk of ischemic stroke, myocardial infarction (MI), and vascular death was compared among patients who had or did not have echocardiography performed prior to enrollment, and Cox proportional hazards models were employed to determine whether echocardiographic abnormalities present in >5% of subjects were associated with these outcomes.

Results—264 of 569 patients in WASID had echocardiograms; 37% were transesophageal. Of these 264 patients, 69 suffered subsequent ischemic stroke, MI, or vascular death. Patients who underwent echocardiography had similar event rates to those who did not (p=0.18). Common abnormalities identified on echocardiography were not associated with subsequent risk in this population.

Conclusions—Among patients with TIA or stroke due to intracranial arterial stenosis, echocardiography appears to offer limited diagnostic and prognostic value.

Ischemic strokes are often classified by etiology as either due to large vessel atherosclerosis, cardioembolism, small vessel occlusion, other determined etiology, or undetermined (cryptogenic) etiology.[1] Distinction of these mechanisms is critically important for secondary stroke prevention, is useful for determining prognosis, and may be relevant to acute therapy as well.[2, 3] Given the importance of stroke subtype, many if not the majority of stroke patients undergo an assessment of cardiac function and structure with electrocardiography and echocardiography, though it remains unclear whether this is warranted for all patients.[4, 5] In addition to identifying high-risk potential sources of cardioembolism such as intracardiac

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thrombus or severe cardiomyopathy, echocardiography is a sensitive tool that often detects a number of otherwise occult abnormalities. Several of these cardiac abnormalities are the subject of ongoing studies, including patent foramen ovale (PFO) and aortic arch atheroma, though their roles are likely most relevant for patients without an alternative well-defined cause of stroke.[6–8] We investigated whether echocardiography provided clinically relevant information about diagnosis and prognosis in patients with TIA or stroke due to atherosclerotic stenosis of a major intracranial artery.

Methods

The Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial was an NIH-funded randomized, double-blinded, multicenter clinical trial in which 569 patients with TIA or ischemic stroke attributed to angiographically-proven 50–99% stenosis of a major intracranial artery were randomly assigned to warfarin or aspirin.[9] Patients with unequivocal cardiac sources of embolism were excluded, but no specific algorithm for cardiac evaluation was dictated. Therefore, investigators could use any combination of medical history, physical examination, electrocardiography (ECG), echocardiography, and/or other diagnostic test. If echocardiography was performed prior to enrollment, the findings were recorded on a case report form. Timing of echocardiography was also determined relative to the first identification of the symptomatic intracranial arterial stenosis by any vascular imaging study, since the decision to perform this test might be related to prior knowledge of an alternative stroke etiology. In WASID, patients were followed until a stroke, death, or the end of the trial. Myocardial infarction (MI) was a secondary endpoint and patients continued in the study, so a patient could have an MI and then a stroke. Patients were followed for a mean of 1.8 yrs. Patients lost to follow-up were censored at the last contact date.

Logistic regression was performed to compare groups (echocardiography done vs. not done) at baseline. For this analysis, Cox proportional hazards models and the log-rank test were employed to determine whether the use of echocardiography or whether echocardiographic abnormalities present in >5% of subjects and implicated in stroke pathogenesis were associated with the combined outcome of ischemic stroke, MI, and/or vascular death. All reported p-values are two-sided; p values <0.05 were considered statistically significant. Because of the exploratory nature of the analyses, we did not adjust the p-values for multiple testing.

Results

In WASID, 264 (46%) of 569 patients had echocardiograms, 37% of which were transesophageal. Table 1 summarizes the baseline characteristics of the WASID study population based on whether or not echocardiography was performed. Although the groups were similar with respect to most baseline characteristics, in multivariable logistic regression analysis those subjects who underwent echocardiography were more likely to be have stroke rather than TIA as the qualifying event (OR=1.7; 95%CI:1.2–2.5; p=0.0005) and to be enrolled earlier (less than the median of 17 days from the qualifying event) than later in the study (OR=1.6; 95%CI:1.2–2.3; p=0.005), but were less likely to be on antithrombotic therapy at the time of the qualifying event (OR=0.6; 95%CI:0.4–0.9; p=0.018)

Of the 264 patients with echocardiography, 69 (26%) suffered subsequent ischemic stroke (55), MI (8), or other vascular death (12). Table 2 summarizes outcome events for the patients based on whether or not echocardiography was performed. There were no significant differences in the rates of stroke (in or out of the territory of the symptomatic stenotic artery), MI, and/or vascular death between these groups. Adjustment for the baseline differences between the two groups did not alter these results. Further, after stratification of subjects according to baseline severity of stenosis (<70% vs. ≥70%), there were again no differences in event rates between

patients with or without echocardiography, nor statistical interactions between severity of stenosis and performance of echocardiography (data not shown).

A secondary analysis was performed wherein patients were divided into 3 groups: 119 (21%) who underwent echocardiography prior to or on the same day as the identification of the intracranial stenosis, 89 (16%) with echocardiography afterward, and those without echocardiography (305, 54%) (there were an additional 56 patients (10%) who had echocardiography but the timing with respect to vascular imaging was unknown). As in the primary analysis, there were no differences in event rates among these three groups.

The prevalent echocardiographic abnormalities in the patients who had echocardiograms were left atrial size>5cm (7%), patent foramen ovale (7%), mitral annular calcification (13%), calcific aortic valve (12%), left ventricular hypertrophy (42%), global hypokinesis (6%), and aortic arch atherosclerosis (11%). There were no significant associations of any of these echocardiographic findings with the combined outcome, as shown in Table 3.

Discussion

Patients with symptomatic intracranial atherosclerotic disease who underwent echocardiography had similar outcomes to those without this diagnostic test. Therefore, echocardiography appears to offer limited prognostic and diagnostic value in such patients. These patients have a well-defined etiology of their cerebrovascular event, and the major source of their future risk is in the territory of the stenotic artery.[9, 10] Patients who had echocardiography differed in some respects from those who did not, though only early enrollment after the qualifying event among these factors has been associated with an increased risk of subsequent events.[10] A substantial proportion of patients had one or more cardiac abnormalities identified on echocardiography, but none of these were associated with an increased risk of major vascular events. The role of many of these abnormalities is of uncertain prognostic significance in general after stroke, [6–8] but they seem particularly irrelevant in this population.

A drawback of this study relates to generalizability. Patients were excluded from the WASID study if they had an unequivocal source of cardioembolism, with the following specified in the protocol: atrial fibrillation, mitral stenosis, mechanical valve, endocarditis, intracardiac clot or vegetation, myocardial infarction within 3 months, severe dilated cardiomyopathy, or left atrial spontaneous echo contrast.[9] Atrial fibrillation accounts for about half of cardiogenic emboli and would be detected by ECG.[11] The other relatively common cardioembolic sources, such as recent myocardial infarction, mechanical valve, and severe dilated cardiomyopathy would also be clinically evident without echocardiography in the vast majority of such cases. Therefore, echocardiography would effectively have excluded from this analysis only patients with the uncommon and otherwise undetected findings of asymptomatic mitral stenosis, vegetation, or spontaneous echo contrast, which would account for less than 10% of cardioembolic strokes and an even smaller proportion of all strokes. The number of patients excluded from the trial because of these findings is unknown, but likely there were relatively few. The sample of patients with each individual cardiac abnormality was relatively small, limiting the power to detect differences. For example, the risk of events appeared numerically greater in patients with enlarged left atria or with aortic atheroma, but this was not statistically significant. Finally, we were unable to compare the utility of transthoracic vs. transesophageal echocardiography in this population because of the limited sample size.

Ultimately, there was no difference in major outcomes between patients who had echocardiography and those who did not. If a sizeable number of patients without echocardiography had undetected high-risk cardioembolic sources, this would likely have been

reflected by higher event rates in that group. Thus, the role of echocardiography in patients with known symptomatic intracranial stenosis may be limited to those patients for whom there is a high index of suspicion for an otherwise undiagnosed high-risk source of cardioembolism.

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References

1. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE. the TOAST Investigators. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Stroke 1993;24:35–41. [PubMed: 7678184]
2. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: A population-based study of functional outcome, survival, and recurrence. Stroke 2000;31:1062–1068. [PubMed: 10797166]
3. Kasner SE, Kimmel SE. Accuracy of initial stroke subtype diagnosis. A decision analysis. Cerebrovascular Diseases 2000;10:18–24. [PubMed: 10629342]
4. McNamara RL, Lima JA, Whelton PK, Powe NR. Echocardiographic identification of cardiovascular sources of emboli to guide clinical management of stroke: A cost-effectiveness analysis. Annals of Internal Medicine 1997;127:775–787. [PubMed: 9382398]
5. Otto, CM. Clinical indications for echocardiography (chapter 5). In: Otto, CM., editor. Textbook of clinical echocardiography. Philadelphia: Elsevier Saunders; 2004.
6. Messe SR, Silverman IE, Kizer JR, Homma S, Zahn C, Gronseth G, Kasner SE. Practice parameter: Recurrent stroke with patent foramen ovale and atrial septal aneurysm: Report of the quality standards subcommittee of the american academy of neurology. Neurology 2004;62:1042–1050. [PubMed: 15078999]
7. Macleod MR, Amarenco P, Davis SM, Donnan GA. Atheroma of the aortic arch: An important and poorly recognised factor in the aetiology of stroke. Lancet Neurol 2004;3:408–414. [PubMed: 15207797]
8. Fujimoto S, Yasaka M, Otsubo R, Oe H, Nagatsuka K, Minematsu K. Aortic arch atherosclerotic lesions and the recurrence of ischemic stroke. Stroke 2004;35:1426–1429. [PubMed: 15118179]
9. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Kasner SE, Benesch CG, Sila CA, Jovin TG, Romano JG. for the WASID investigators. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. NEJM 2005;352:1305–1316. [PubMed: 15800226]
10. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Benesch CG, Sila CA, Jovin TG, Romano JG, Cloft HJ. for the WASID investigators. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation 2006;113:555–563. [PubMed: 16432056]
11. Cerebral Embolism Task Force. Cardiogenic brain embolism. Arch Neurol 1986;43:71–84. [PubMed: 3510609]

Table 1

Baseline characteristics of patient groups with and without echocardiography

Baseline Characteristic	Echocardiogram Groups*	
	Not Done (n = 305)	Done (n = 264)
Randomized to warfarin	49%	53%
Male gender	62%	61%
White race	64%	51%
Age (yrs)	63.7 (11.2)	63.4 (11.7)
Systolic BP (mmHg)	139.7 (16.8)	140.0 (17.4)
Diastolic BP (mmHg)	76.9 (11.0)	76.8 (9.5)
BMI	28.4 (4.9)	29.0 (5.5)
On antithrombotic agent at QE	59%	45%
Drinks Alcohol	42%	38%
Sedentary	25%	27%
Ever Smoked	66%	63%
Hx of Ischemic Stroke	26%	23%
Hx of TIA	29%	20%
Hx of Hypertension	85%	84%
Hx of Diabetes	40%	36%
Hx of Lipid Disorder	72%	69%
Hx of Coronary Artery Disease	30%	24%
Qualifying Event (% Stroke)	54%	69%
Stenotic Artery		
Internal Carotid	22%	21%
Middle Cerebral	27%	39%
Vertebral	19%	20%
Basilar	25%	15%
Multiple Arteries	7%	5%
Percent Stenosis (%)	63.9 (15.4)	63.2 (17.1)
Severe (≥70%) Stenosis	36%	38%
Time from QE to Randomization (days)	23 (8,54)	13 (6,44)

* The echocardiogram group indicates whether or not an echocardiogram was done at baseline. The numbers in the table are either mean (standard deviation) or the percent of each echocardiogram group having the characteristic indicated; however, for time from qualifying event to randomization the medians (interquartile ranges) are given.

Abbreviations: Hx=history, QE=qualifying event

Table 2

Outcomes of patient groups with and without echocardiography

Outcome	Echocardiogram Not Done (n = 305)	Echocardiogram Done (n = 264)	Unadjusted p value*	Adjusted p value**
Ischemic stroke	51 (17%)	55 (21%)	0.15	0.44
In territory of stenotic artery	37 (12%)	40 (15%)	0.23	0.47
Not in territory of stenotic artery	14 (5%)	15 (6%)	0.43	0.75
Myocardial infarction (MI)	11 (4%)	8 (3%)	0.91	0.61
Vascular death	14 (5%)	12 (5%)	0.85	0.88
Ischemic stroke, MI, and/or vascular death	68 (22%)	69 (26%)	0.18	0.55

* p-value for the log-rank test comparing echocardiogram done vs not done.

** p-value from a Cox proportional hazards regression model comparing echocardiogram done vs not done adjusted for type of qualifying event, antithrombotic therapy at time of qualifying event, and time to enrollment from qualifying event.

Note that the sum of the individual events is greater than the combined outcome because some patients had more than one outcome.

Table 3

Outcomes associated with prevalent echocardiographic abnormalities

Echocardiographic Abnormality	Prevalence	Risk of IS, MI, VD with echo abnormality	Risk of IS, MI, VD without echo abnormality	p value*
left atrial size>5cm	7%	35%	26%	0.20
patent foramen ovale	7%	19%	28%	0.63
mitral annular calcification	13%	24%	27%	0.65
calcific aortic valve	12%	29%	26%	0.97
left ventricular hypertrophy	42%	27%	25%	0.70
global hypokinesis	6%	27%	26%	0.86
aortic arch atherosclerosis	11%	37%	25%	0.27

* p-value for the log-rank test

Abbreviations: IS=ischemic stroke, MI=myocardial infarction, VD=other vascular death