Preventive health care, 1999 update: 2. Echocardiography for the detection of a cardiac source of embolus in patients with stroke

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Abstract

Objective: To develop guidelines for the use of echocardiography in the investigation of patients with stroke.

Options: (1) Routine transthoracic echocardiography (TTE); (2) routine transesophageal echocardiography (TEE); (3) routine TTE followed by TEE if the TTE findings are noncontributory; (4) selective TTE or TEE in patients with cardiac disease who would not otherwise receive anticoagulant therapy.

Outcomes: This article reviews the available evidence on the yield of TTE and TEE in detecting cardiac sources of cerebral emboli in patients with stroke, the effectiveness of treatment for cardiac sources of emboli and the effectiveness of screening echocardiography for secondary stroke prevention.

Evidence: MEDLINE was searched for relevant articles published from January 1966 to April 1998; also reviewed were additional articles identified from the bibliographies and citations obtained from experts.

Benefits, harms and costs: Echocardiography can detect intracardiac masses (thrombus, vegetation or tumour) in about 4% (with TTE) to 11% (with TEE) of stroke patients. The yield is lower among patients without clinical evidence of cardiac disease by history, physical examination, electrocardiography or chest radiography (less than 2%) than among patients with clinical evidence of cardiac disease (less than 19%). The risks of echocardiography to patients are small. TTE has virtually no risks, and TEE is associated with cardiac, pulmonary and bleeding complications in 0.18%. Patients with an identified intracardiac thrombus are at increased risk for embolic events (absolute risk uncertain, range 0%–38%), and this appears to be reduced with anticoagulant therapy (absolute risk reduction uncertain). Anticoagulant therapy carries a risk of major hemorrhage of 1% to 3% per year. The overall effectiveness of echocardiography in the prevention of recurrent stroke is unknown.

Values: The strength of evidence was evaluated using the methods of the Canadian Task Force on Preventive Health Care.

Recommendations: There is fair evidence to recommend echocardiography in patients with stroke and clinical evidence of cardiac disease by history, physical examination, electrocardiography or chest radiography (grade B recommendation). There is insufficient evidence to recommend for or against TEE in patients with normal results of TTE (grade C recommendation). There is insufficient evidence to recommend for or against routine echocardiography in patients (including young patients) without clinical cardiac disease (grade C recommendation). Routine echocardiography is not recommended for patients with clinical cardiac disease who have independent indications for or contraindications to anticoagulant therapy (grade D recommendation). There is fair evidence to recommend anticoagulant therapy in patients with stroke and intracardiac thrombus (grade B recommendation). There is insufficient

(no) evidence to recommend for or against any specific therapy for patent foramen ovale (grade C recommendation).

Validation: The findings of this analysis were reviewed through an iterative process by the members of the Canadian Task Force on Preventive Health Care.

Sponsors: The Canadian Task Force on Preventive Health Care is funded through a partnership between the Provincial and Territorial Ministries of Health and Health Canada.

Echocardiography uses ultrasonography to provide images of cardiac and great vessel anatomy and blood flow and is commonly used in the investigation of patients with stroke. The purpose of performing echocardiography is to detect cardiac sources of cerebral emboli, thereby allowing the provision of appropriate therapy and preventing recurrent stroke. In this paper we review the available evidence on the yield of echocardiography in patients with stroke, the effectiveness of treatment for cardiac sources of emboli and the effectiveness of screening echocardiography for secondary stroke prevention.

Stroke is the third leading cause of death in Canada. About 200 000 Canadians have experienced stroke, and each year an estimated 50 000 new cases occur in Canadians over 65 years of age.[1] At least 20% of stroke survivors require institutional care, and another 15% require assistance with activities of daily living.[2]

Cardiogenic embolism accounts for 15% to 30% of ischemic strokes.[2,3] Cardioembolic stroke, defined as "the presence of a potential cardioembolic source in the absence of cerebrovascular disease in a patient with nonlacunar stroke,"[3] is a heterogeneous entity, since a variety of cardiac conditions can predispose to cerebral embolism. No "gold standard" exists for the diagnosis, which leads to limitations in accurately determining the frequency and causes of cardioembolic stroke.

Cardiac conditions that are considered potential cardioembolic sources may be classified as major risk, minor risk or uncertain risk (Table 1). Echocardiography is not required for the diagnosis of many of these conditions. For example, atrial fibrillation, recent myocardial infarction and valvular heart disease are often established diagnoses before the cardioembolic event or may be diagnosed by means of other investigative techniques. For other conditions, the results of echocardiography do not lead to a change in management. For example, patients with stroke and atrial fibrillation or mechanical cardiac valves will usually receive anticoagulant therapy regardless of the findings on echocardiography, whereas those with conditions for which there is no proven effective therapy (e.g., atrial septal aneurysm and aortic arch atheromata) will usually be treated with standard antiplatelet therapy.[7]

In contrast, the detection of a previously undiagnosed intracardiac thrombus, vegetation or tumour will often lead to a change in management. Therefore, this guideline article focuses on the use of screening echocardiography for the detection of intracardiac masses. Although the evidence for the risk of recurrent stroke is less definitive, the detection of patent foramen ovale may also result in a change in therapy, and the role of echocardiography in the management of this condition is also reviewed.

Methods

We identified relevant articles by a computerized search of MEDLINE (January 1966 to April 1998) using the MeSH terms "cerebrovascular disorders," "heart diseases," "echocardiography," "thromboembolic disorders," "intracardiac thrombus," "diagnosis," "prevention" and "therapy." A professional librarian assisted with the search. We also performed a manual review of references

Table 1: Potentional cardioembolic sources

Major risk sources	Embolic rate, %	Minor or uncertain risk sources	Embolic rate, %
Atrial fibrillation	1–12/yr[4–6]	Mitral valve prolapse	< 0.02/yr[3,7]
Intracardiac thrombus	0–35[3,8–10]	Mitral annular calcification	?
Atrial myxoma	30–40[11]	Spontaneous echo contrast	?
Mitral stenosis	Normal sinus rhythm: 8–14[12,13] Atrial fibrillation: 31 Prior embolism: 31–65	Left ventricular aneurysm	< 1[3,14]
Mechanical valves (anticoagulated)	Aortic: 1.5/yr[3] Mitral: 3/yr	Atrial septal aneurysm	?
Recent myocardial infarction	1–2/yr[15–17]	Calcific aortic stenosis	?
Infective endocarditis	12–40[18]	Patent foramen ovale	?2/yr[7,19]
Marantic endocarditis	14–90[20]		
Dilated cardiomyopathy	4/yr[3]		
Aortic arch atheromatous plaques	4–16/yr[7,21–23]		

and obtained citations from experts. Studies were included if they were published in manuscript form in peer-reviewed journals. For the evaluation of the yield of echocardiography, studies involving patients referred for echocardiography (rather than consecutive patients with stroke) were excluded from this review because of the potential for selection bias, as were studies that included patients with systemic (peripheral) emboli (references available from the authors on request).

We systematically reviewed the evidence using the method of the Canadian Task Force on Preventive Health Care (formerly the Canadian Task Force on the Periodic Health Examination).[24] The task force, comprising expert clinician/methodologists from a variety of medical specialties, used a standardized evidence-based method for evaluating the effectiveness of this intervention. A manuscript providing critical appraisal of the evidence was prepared by the lead authors. This included identification and critical appraisal of key studies, and ratings of the quality of this evidence using the task force's established methodologic hierarchy (Appendix 1), resulting in a summary of proposed conclusions and recommendations for consideration by the task force. This manuscript was circulated to the task force members in December 1997, and evidence for this topic was presented by the lead author(s) and deliberated on at a meeting in January 1998.

At the meeting the expert panellists addressed critical issues, clarified ambiguous concepts and analysed the synthesis of the evidence. At the end of this process, the specific clinical recommendations proposed by the lead authors were discussed, as were issues related to clarification of the recommendations for clinical application and any gaps in evidence. The results of this process are reflected in the description of the decision criteria presented with the specific recommendations. The final decisions on recommendations were arrived at unanimously by the group and lead authors.

After the meeting, the lead authors revised the manuscript accordingly. After final revision, the manuscript was sent by the task force to 2 experts in the field (identified by task force members at the meeting). Feedback from these experts was incorporated into a subsequent draft of the manuscript, which was then submitted to the *Canadian Medical Association Journal*.

Manoeuvres

Transthoracic echocardiography (TTE) is a noninvasive procedure that poses little or no risk to the patient. The diagnostic accuracy of TTE has been evaluated in patients undergoing cardiac surgery or autopsy (level II evidence). For the detection of left ventricular thrombi, TTE has a sensitivity of 86% to 95% and a specificity of 86% to 95%.[25–27] TTE does not reliably visualize the left atrium or left atrial appendage, and it has a sensitivity of only 39% to 63% for the detection of left atrial thrombi and a sensitivity of less than 50% for the diagnosis of patent foramen ovale.[28–32]

Transesophageal echocardiography (TEE) involves the insertion of an ultrasound transducer into the esophagus. The patient is required to fast for at least 4 hours before the procedure. Sedation may be used. The safety of TEE has been evaluated in a multicentre study of 10 419 attempted examinations.[33] Studies were interrupted in 0.6% of cases because of patient intolerance of the TEE probe and in 0.18% of cases because of reversible pulmonary, cardiac or bleeding complications. One death (0.0098%) occurred, in a patient with malignant esophageal infiltration. The diagnostic accuracy of TEE has been evaluated in patients undergoing surgery or autopsy. For the diagnosis of left ventricular thrombus, TEE has a sensitivity and specificity similar to those of TTE.[34] For the diagnosis of left atrial thrombi, TEE has a sensitivity of 100% and a specificity of 99%.[35] For the diagnosis of patent foramen ovale, contrast TEE (involving intravenous administration of agitated saline or other solutions) has a sensitivity of at least 89% and a specificity of 100%.[32,36]

More than 30 cross-sectional studies (level III evidence) have evaluated the yield of TTE or TEE, or both, in detecting intracardiac masses in patients with stroke. In consecutive patients, the yield of echocardiography for the detection of intracardiac masses ranged from 0% to 21%.[37–55] Pooled data from these studies suggest an overall yield of 4% for TTE and 11% for TEE (Table 2). Patent foramen ovale may be detected by contrast TEE in up to 55% of patients with stroke.[56–58]

In some studies the patients were stratified by the presence or absence of clinically apparent cardiac disease, which is typically defined as the presence of myocardial infarction, angina, arrhythmia, valvular heart disease, congestive heart failure or hypertension by history, physical examination, electrocardiography or chest radiography.[37,40–48,51,52,54] Pooled data from these studies suggest that TTE can detect intracardiac masses in 13% and 0.7% of patients with and without clinical cardiac disease respectively; the corresponding values for TEE are 19% and 1.6% (Table 2). Although the prevalence of intracardiac masses in patients without clinical cardiac disease appears to be very low, it should be

Table 2: Yield of echocardiography in the detection of intracardiac masses in patients with stroke (pooled data)

Manoeuvre	Yield (and range), %		
	Overall	Patients with cardiac disease*	Patients without cardiac disease
Transthoracic echocardiography (TTE)	4 (0–16)	13 (0–40)	0.7 (0–6)
Transesophageal echocardiography (TEE)	11 (0–21)	19 (10–34)	1.6 (0–4)

*Defined as myocardial infarction, angina, arrhythmia, valvular disease, congestive heart failure or hypertension by history, physical examination, electrocardiography or chest radiography.

noted that these estimates are based on a secondary analysis of cross-sectional and case–control studies and may be inaccurate.

Three studies, involving a total of 350 patients, addressed the yield of TEE in detecting intracardiac masses in patients with a negative result of TTE.[45,53,54] Inclusion in these studies was also limited to patients without significant carotid stenosis. The pooled data suggest an incremental yield of 17%, predominantly left atrial thrombi. Of note, in the 2 studies that provided data on the presence or absence of known cardiac disease, the yield of TEE in patients with a negative result of TTE and no clinical cardiac disease was 0%, as compared with 18% among patients with cardiac disease.[45,53]

Some authorities suggest that echocardiography is of greater utility in the investigation of younger patients.[59,60] Several investigators have evaluated the yield of echocardiography in patients under the age of 60 years.[41,42,55,61] Potential cardioembolic sources, particularly patent foramen ovale and mitral valve prolapse, were common in this population (prevalence up to 50%), but intracardiac masses were detected less frequently (0%–11%).

Effectiveness of early detection

Several investigators have assessed the effect of echocardiography on patient management, with inconsistent findings. Two studies (one of TTE only) showed that the results of echocardiography did not alter patient management significantly.[51,62] In one study the authors reported a change in management in 4 (10%) of 39 patients;[63] however, 3 of the 4 had atrial fibrillation and would therefore receive anticoagulant therapy under current standards of care. Two further studies documented a change in management in 5%–10% of patients.[53,64]

A decision analysis of cardiac imaging strategies after stroke showed that echocardiography resulted in improved patient outcomes and that TEE was more cost-effective than TTE.[65] The analysis showed that TEE performed in all patients with stroke cost US$13 000 per quality-adjusted life-year, whereas TEE performed only in patients with cardiac disease cost US$9000 per quality-adjusted life-year.

Effectiveness of treatment

The effectiveness of anticoagulant therapy for intracardiac thrombus has not been properly studied. Observational studies of left ventricular thrombus suggest that the risk of embolization without therapy ranges from 0% to 38% (overall risk 14%).[8,9,66–87] Two small nonblinded randomized trials of warfarin for left ventricular thrombus yielded inconsistent results in the reduction of systemic emboli with anticoagulant therapy, although both documented increased resolution of thrombi.[88,89] Although not specifically designed to address the effectiveness of therapy for intracardiac thrombus, one well-designed randomized trial (level I evidence) of low-dose versus high-dose heparin in patients with myocardial infarction demonstrated a reduction in thrombus formation of 21% and a subsequent absolute reduction in the risk of systemic emboli of 2.8% with high-dose warfarin.[90] Three well-designed randomized trials (level I evidence) of anticoagulant therapy after myocardial infarction did not evaluate thrombus formation but did document an absolute reduction in the risk of stroke of 1.5% to 3.7% with systemic anticoagulant therapy.[15–17]

Many nonrandomized observational studies (level II/III evidence) have suggested a reduction in the risk of systemic emboli with anticoagulant therapy for left ventricular thrombus.[8,9,66–87] A meta-analysis of 7 studies showed the odds of embolization with anticoagulant therapy to be 0.14 (95% confidence interval 0.04–0.52) compared with no anticoagulant therapy.[10] Of note, most of these studies included patients with recent myocardial infarction, and the results may not be generalizable to all patients with intracardiac thrombi. In addition, therapy for left atrial thrombi has not been studied systematically. Anticoagulant therapy carries a risk of major bleeding of about 1% to 3% per year.[4,91,92]

Treatment options for patent foramen ovale include surgical closure, transcatheter closure, systemic anticoagulant therapy (particularly in the setting of deep vein thrombosis and suspected paradoxical embolus) and antiplatelet therapy.[93–95] However, the relative effectiveness of these therapeutic options has not been studied systematically.

Recommendations

Of the Canadian Task Force on Preventive Health Care (Table 3)

- There is fair evidence to recommend echocardiography in patients with stroke and clinical evidence of cardiac disease by history, physical examination, electrocardiography or chest radiography (grade B recommendation). TEE is recommended as the preferred initial screening test, based on sensitivity and cost-effectiveness data. There is insufficient evidence to recommend for or against TEE in patients with normal results of TTE (grade C recommendation).
- There is insufficient evidence to recommend for or against routine echocardiography in patients (including young patients) without clinical cardiac disease (grade C recommendation).
- Routine echocardiography is not recommended for patients with clinical cardiac disease who have independent indications for anticoagulant therapy or contraindications to anticoagulant therapy (grade D recommendation). It should be noted, however, that such patients often have non-stroke-related indications for echocardiography.
- There is fair evidence to recommend anticoagulant therapy in patients with stroke and documented intracardiac thrombus (grade B recommendation). There is insufficient (no) evidence to recommend for or against

any specific therapy for patent foramen ovale (grade C recommendation).

Of other bodies

The American College of Cardiology and the American Heart Association recommend echocardiography in patients with stroke who have clinical evidence of heart disease or who are less than 45 years of age.[59] Routine echocardiography is not recommended in patients over the age of 45 without clinical cardiac disease.

The Cerebral Embolism Task Force recommends "liberal" echocardiography in patients with stroke in whom cerebrovascular mechanisms are deemed unlikely.[3]

The Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks for the Stroke Council of the American Heart Association recommends TTE only in patients with clinical evidence of cardiac disease or young subgroups without major risk factors for primary cerebrovascular disease, and possibly for those in whom no source of transient ischemic attack has been identified after other tests are completed.[96] TEE is not recommended in unselected patients.

Research agenda

- More data are required on the yield of echocardiography in subgroups of patients at low risk.
- The incremental yield of TEE in patients with normal findings on TTE needs further study.

Table 3: Recommendations of the Canadian Task Force on Preventive Health Care — screening and therapy for potential cardioembolic sources in patients with stroke

Manoeuvre	Effectiveness	Level of evidence*	Recommendation*
Echocardiography (TTE or TEE for detection of intracardiac masses)	TTE is safe and has a sensitivity and specificity of 86%–95% for the detection of left ventricular thrombus. Sensitivity for detection of left atrial thrombus is 39%–63%. TEE has a 0.2% risk of adverse effects, and sensitivity of 100% and specificity of 99% for the detection of left atrial thrombi		
Patients with clinical cardiac disease† and no pre-existing indications for anticoagulation	Screening yield is about 13% (TTE) or 19% (TEE). The effect of screening on patient management and outcomes is unknown	Case–control (II-2)[42,51,54] and cross-sectional (III) studies[37,40,41,43–48,52]	Fair evidence to recommend echocardiography for the detection of intracardiac masses in patients with clinical cardiac disease and no pre-existing indications for anticoagulation (grade B).‡ TEE is the preferred initial screening test
Patients with pre-existing indications for anticoagulation or contraindications to anticoagulation§	Screening rarely results in a change in management	Case–control (II-2) and cross-sectional (III) studies[51,62,63]	Fair evidence to recommend against routine echocardiography for patients with pre-existing indications for anticoagulation or contraindications to anticoagulation (grade D)
Patients without clinical cardiac disease	Screening yield is less than 2% in patients aged 45 years or more, and unknown in patients aged less than 45 without clinical cardiac disease	Case–control (II-2) and cross-sectional (III) studies[37,40–48,51,52,54,55,61]	Insufficient evidence to recommend for or against echocardiography in patients without clinical cardiac disease (grade C)
Anticoagulation (warfarin) for intracardiac thrombus to prevent systemic emboli	Anticoagulation for intracardiac thrombus decreases the risk of systemic emboli and stroke, although the magnitude of treatment benefit is unknown. The annual risk of major hemorrhage with systemic anticoagulation is between 1% and 3%	Small flawed randomized controlled trials (II-1),[88,89] case–control studies (II-2) and case series (III).[8,9,66–87] Randomized controlled trials of anticoagulation after myocardial infarction (I)[15–17,90]	Fair evidence to recommend warfarin therapy in patients with stroke and intracardiac thrombus (grade B)
Treatment for patent foramen ovale	Treatment options include surgical closure, transcatheter closure, systemic anticoagulation and antiplatelet therapy	Treatment options have not been systematically evaluated	Insufficient (no) evidence to recommend for or against any specific therapy for patent foramen ovale (grade C)

*See Appendix 1 for definitions of the levels of evidence and grades of recommendations.
†As defined in footnote to Table 2.
‡This recommendation is based on positive test characteristics, prevalence and the availability of effective treatment.
§Such patients may have other indications for echocardiography.

- Further research is needed to determine whether screening echocardiography results in decreased risk of recurrent stroke and improved patient outcomes.
- Further research is required into the optimal management of conditions such as patent foramen ovale and aortic arch atheromata. As this information becomes available, the benefit of screening echocardiography will need to be re-evaluated.

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Appendix 1: Canadian Task Force on Preventive Health Care levels of evidence and grades of recommendations

Levels of evidence

I	Evidence from at least one well-designed randomized controlled trial
II-1	Evidence from well-designed controlled trials without randomization
II-2	Evidence from well-designed cohort or case–control analytic studies, preferably from more than one centre or research group
II-3	Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here
III	Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Grades of recommendations

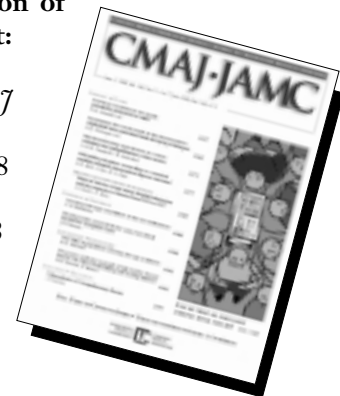|	
A	Good evidence to support the recommendation that the condition or manoeuvre be specifically considered in a periodic health examination (PHE)
B	Fair evidence to support the recommendation that the condition or manoeuvre be specifically considered in a PHE
C	Insufficient evidence regarding inclusion or exclusion of the condition or manoeuvre in a PHE, but recommendations may be made on other grounds
D	Fair evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE
E	Good evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE