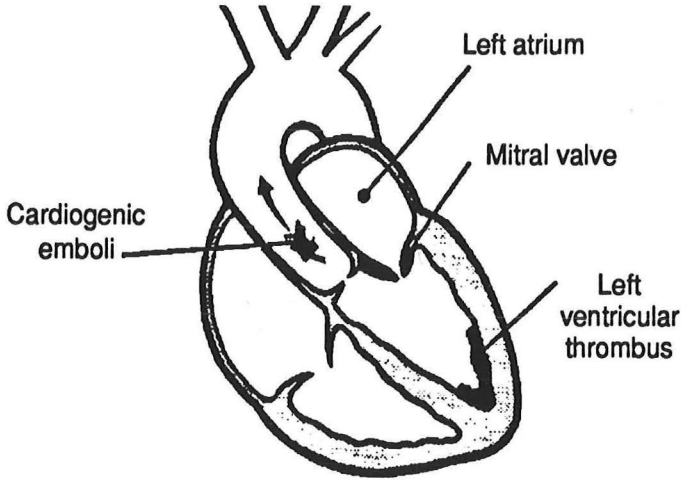
Cardioembolic Stroke



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It is estimated that 500,000 people suffer a new or recurrent stroke each year. According to data from the American Heart Association, stroke killed 144,070 people in 1991, the latest year for which data are available.[1] On average, someone suffers a stroke in the United States every minute and approximately 3,060,000 stroke victims are alive today. Stroke remains the third leading cause of death in the United States and the leading cause of serious disability.

In general, stroke can be divided into either ischemic or hemorrhagic types. Ischemic cerebral infarcts, which account for approximately 80% of all strokes, occur when there is an area of the brain that is deprived of adequate blood supply. Ischemic strokes can be caused by systemic hypoperfusion, in situ thrombosis, or embolism. Embolism can occur from the vascular system (extracranial arteries or the aorta) or from the heart. Hemorrhagic strokes, including subarachnoid and intracerebral bleeds, account for the remaining 20% of strokes.[2]

Embolism from a cardiac source is now recognized to account for a significant percentage of ischemic strokes and, in recent years, an increasing number of cardiac conditions have been identified as potential sources of cardiac embolism. Anticoagulation has been shown to be effective at preventing embolic complications in a number a cardiac conditions and, since a cardiac "substrate" may be clinically apparent before a stroke occurs, a significant number of cardioembolic strokes could potentially be prevented.

It has been estimated that one out of every six ischemic strokes are cardioembolic in origin.[3] Whether or not this estimation is accurate is a matter of some debate. However, if we assume that this 17% figure is accurate, we can calculate that approximately 68,000 strokes per year in the United States are cardioembolic in origin (500,000 strokes per year times 80% ischemic times 1/6 cardioembolic = 68,000 cardioembolic strokes per year). In fact, this number may be substantially higher. Thus, cardioembolic stroke is a significant health problem.

Part of the difficulty in determining the frequency of cardioembolic stroke lies in the fact that there are significant limitations in making the clinical diagnosis of cardioembolic stroke. The Cerebral Embolism Task Force, in their "Review of Cardiogenic Brain Embolism" published in 1986 proposed clinical features which suggested cardioembolic stroke.[3] They described three primary features and five secondary features which favored the diagnosis of cardioembolic stroke (table 1).

Table 1. Clinical Features Suggestive of Cardiogenic Brain Embolism

Primary features

1. Abrupt onset of maximal deficit
2. Presence of a potential embolic source
3. Multiple brain infarcts in multiple vascular territories

Secondary features

4. Hemorrhagic infarct by computed tomography
5. Absence of atherosclerotic vascular disease by angiography
6. Angiographic evidence of vanishing occlusions
7. Evidence of embolism to other organs
8. Demonstration of cardiac thrombi

from reference 3

However, the second report of the Cerebral Embolism Task Force, published in 1989, shed significant doubt on the utility of many of these clinical features.[4]

Classical teaching states that an embolic stroke is characterized by the abrupt onset of a maximal neurologic deficit. This has been reported to occur in anywhere from 25-82% of patients who have potential cardioembolic sources but also occurs in a significant number of patients with other causes for ischemic stroke.[4] Cardiogenic embolic most commonly lodge in the middle cerebral artery or its branches. However, emboli to the vertebrobasilar or anterior cerebral artery can occur. Thus, the location of the infarct, in terms of its vascular territory, is not helpful. Likewise, the size of the stroke is not helpful, since the average size of the embolic fragment varies with the cardioembolic source. Also a "local" artery-to-artery emboli from proximal arterial sources such as the carotid arteries may have a similar presentation to a cardioembolic stroke. Thus, individual neurologic features of stroke are neither sensitive or specific indicators of the mechanism of stroke.[4]

The presence of a potential cardioembolic source in the absence of significant cerebrovascular disease remains the mainstay of clinical diagnosis. However, the presence of a potential cardioembolic source does not, by itself, justify the diagnosis of cardioembolic stroke since atherosclerotic cerebrovascular disease and cardiac disease often coexist.[5-6] The finding of multiple brain infarcts in multiple vascular territories involving the cortex or the cerebellum is felt to be more suggestive of a cardioembolic stroke.

Secondary features include evidence of hemorrhagic transformation and specific angiographic findings. Although large areas of hemorrhagic transformation deep within the infarct are more common with cardiogenic brain embolism, the finding of hemorrhagic transformation by CT scan is not specific for cardioembolic stroke. Angiographic findings that are suggestive of cardioembolic stroke include the absence of atherosclerotic vascular disease and angiographic evidence of "vanishing occlusions." This refers to finding

intraluminal filling defects that disappear on repeated angiography. This finding is felt to be strongly suggestive of embolic fragments. Evidence of embolism to other organs also suggests that a cardioembolic source is likely.[3,4]

Table 2. Features Suggestive of Cardioembolic Stroke

- clinical presentation - abrupt onset - seen in 25-80%
  - location - usually MCA distribution
  - size of infarct - varies
- Evidence of hemorrhagic transformation by CT scan - common, not specific
- Evidence of multiple infarcts in different vascular territories, embolism to other organs
- Angiographic evidence - absence of atherosclerosis
  - evidence of "vanishing occlusions"
- Demonstration of a potential cardioembolic source

adapted from reference 4

In summary, there is no gold standard for making the diagnosis of cardioembolic stroke. Perhaps the best diagnostic test would be early angiography to show embolic arterial occlusion in a patient without atherosclerosis. However, this is seldom practical and it is not clear, with the limited therapeutic options available to date, that this approach is justified.

It is important to emphasize that cardiac disease and cerebrovascular disease often coexist. It is estimated that approximately one-third of patients with a potential cardioembolic source also have concomitant cerebrovascular disease that could account for their stroke.[4] When cardiac disease and cerebrovascular disease coexist in the same patient, determining the etiology of an ischemic stroke may become more difficult.

STROKE REGISTRIES

In the late 1970's and early 1980's several large stroke registries were established.[5-11] For the most part, these registries consisted of patient demographics and features of the patients clinical presentation. Stroke type was determined by the patient's clinical presentation as analyzed by their attending physician. CT scans were available in some but not all patients. In some of these registries, cardioembolism was classified separately from embolic strokes from extracranial cerebrovascular disease where in other registries these two "embolic sources" were not differentiated. Table 3 lists that prevalence of cardioembolic stroke in several of the large stroke data bases. The overall prevalence of cardioembolic stroke, combining all 7 studies, is 15%. The most recent of these stroke data bases was published in 1988 and reported a 19% prevalence of cardioembolic stroke.[11] In this particular study, cerebral infarction was confirmed by CT scan in 97% and cardioembolic stroke was classified separately from other "embolic" strokes.

Thus, the 19% incidence reported in this study is frequently quoted as a more accurate estimation of the frequency of cardioembolic stroke.[4]

Table 3. Frequency of Cardioembolic stroke in national registries

	N =	% Cardioembolic
Harvard Cooperative Registry, 1978	579	19
Framingham Study, 1983	384	23
Michael Reese Stroke Registry, 1983	540	13
Tilburg, The Netherlands, 1982	431	11
Austin Hospital, New Zealand, 1982	700	14
National Survey of Stroke, 1981	1614	6
The Stroke Data Bank, 1988	1805	19

from references 5-11

In all of these studies, the diagnosis of cardiac disease was made largely on the basis of history, physical examination and electrocardiogram. Echocardiography was not routinely used in any of these early stroke data bases. A limited number of cardiac conditions were considered to be potential sources of emboli in these studies. Table 4 demonstrates the frequency of various cardiac sources in the first six studies.[3]

Table 4. Cardiac sources of embolic stroke

Source	Fraction of all embolic strokes (%)
Nonvalvular atrial fibrillation	45
Acute myocardial infarction	15
Chronic LV aneurysm	10
Rheumatic heart disease	10
Prosthetic cardiac valves	10
Miscellaneous	10

from reference 3

Miscellaneous sources (included in some, but not all studies) were: mitral valve prolapse, mitral annular calcification, nonbacterial thrombotic endocarditis, calcific aortic stenosis, cardiac myxoma, paradoxical embolism and congenital heart disease, nonischemic cardiomyopathy, and bacterial endocarditis. In current clinical practice, echocardiography is often included in the evaluation of patients with ischemic stroke and this has led to identification of an increased number of potential cardiac sources of embolism.

POTENTIAL CARDIAC SOURCES OF EMBOLISM:

1. Atrial fibrillation:

Atrial fibrillation is the most common cause of cardioembolic stroke, accounting for nearly half of cases.[3] Chronic atrial fibrillation without rheumatic valvular disease (so-called nonvalvular atrial fibrillation) accounts for approximately 70% of patients with atrial fibrillation (table 5) and is associated with approximately a five-fold increase in risk of stroke (table 6).[12]

Table 5. Diseases associated with atrial fibrillation

- Rheumatic valvular heart disease - 20%
- Nonvalvular heart disease - 70%
- Lone atrial fibrillation - 5-10%

Table 6. Risk of stroke in atrial fibrillation - Framingham data

	stroke rate (% per year)		relative risk
	atrial fib	no atrial fib	
valvular heart disease	4.5	0.26	17.6X
nonvalvular heart disease	4.1	0.74	5.6X

from reference 12

The risk of stroke in atrial fibrillation is clearly linked with age, as the risk of stroke increases with increasing patient age (table 7).[13] The risk of stroke is also felt to be highest during the first year of onset of atrial fibrillation.

Table 7. Relationship of atrial fibrillation to age - Framingham data

age (years)	prevalence of atrial fibrillation	strokes attributable to atrial fibrillation
50-59	0.5%	6.7%
60-69	1.8%	8.1%
70-79	4.8%	21.3%
80-89	8.8%	36.2%

from reference 13

Current data would suggest that paroxysmal atrial fibrillation carries a similar risk of thromboembolism (table 8).

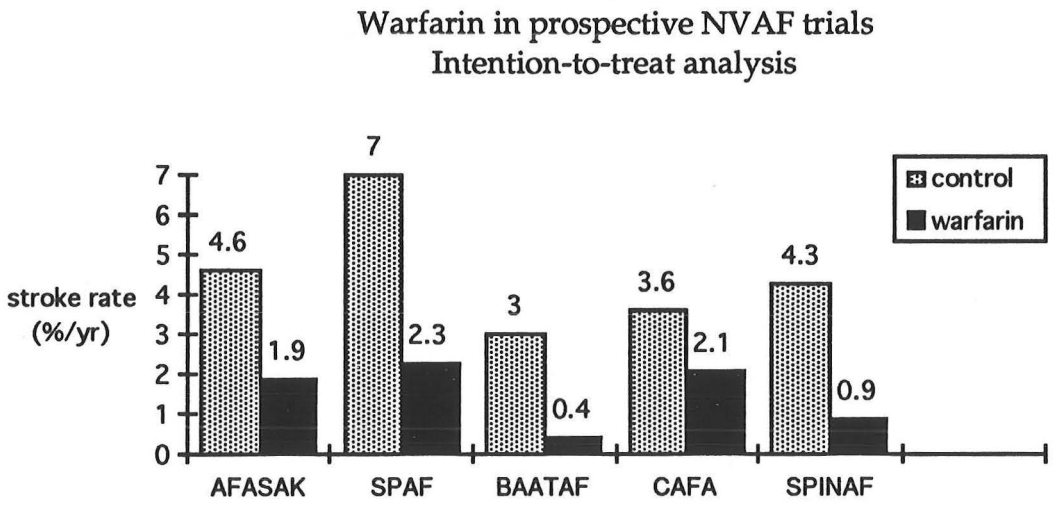
Table 8. Risk of stroke in paroxysmal atrial fibrillation

Study	Stroke rate (%/yr)	
	paroxysmal	chronic
BAATAF	2.5	2.8
SPAF	5.6	5.9
Peterson et al	2.0	5.1
Roy et al	5.3	5.4

from references 14-17

There are now four prospective studies that have demonstrated the efficacy of anticoagulation in the primary prevention of embolic complications (mainly stroke) in patients with atrial fibrillation.[14,15.18,19] The Canadian trial of anticoagulation in atrial fibrillation also demonstrated a trend towards a benefit with warfarin but did not achieve statistical significance as it was terminated early.[20]

Figure 1.



While the studies differ in terms of the type and intensity of anticoagulation, the consensus opinion is that warfarin is effective in decreasing risk of stroke while the role of aspirin remains controversial.

The role of aspirin in primary prevention of embolic complications of atrial fibrillation remains controversial. Low-dose aspirin (75mg/day) was not effective in preventing thromboembolic complications in the AFASAK

study but a higher dose of aspirin (325 mg/day) appeared to have some effect in the SPAF trial.[15,18] However, the original SPAF trial was not designed to compare warfarin and aspirin. The SPAF 2 trial was designed to compare the efficacy of aspirin versus warfarin in the prevention of thromboembolic events and preliminary results have been released.[21] In patients under the age of 60, aspirin appeared to be as effective as warfarin. In older patients, aspirin was less effective than warfarin but there was a significantly higher bleeding rate with patients randomized to warfarin therapy. Further studies are ongoing to further address the role of aspirin and combination therapy with warfarin and aspirin.

Patients who present with a systemic embolic event in the setting of atrial fibrillation are at very high risk for a recurrent systemic embolic event (10-20% incidence per year). Anticoagulation is extremely important in this patient population for secondary prevention of embolic complications.[22]

Patients with lone atrial fibrillation appear to be at lower risk for embolic complications, although this in an area of controversy (table 9). Data from the Mayo Clinic indicated that the risk of embolic events was very low (1.3% incidence at 15 years). However, their criteria for lone atrial fibrillation were very strict and do not apply to the majority of patients with atrial fibrillation.[23] Exclusion criteria included: coronary artery disease, hyperthyroidism, valvular heart disease including mitral valve prolapse, congestive heart failure, cardiomyopathy, obstructive pulmonary disease, cardiomegaly on CXR, hypertension, insulin-dependent diabetes or other potentially life-shortening non-cardiac disease, and atrial fibrillation only during trauma, surgery, or an acute medical illness. Data from the Framingham study, in which lone atrial fibrillation was defined as atrial fibrillation without preexisting coronary artery disease, rheumatic valvular disease, or hypertensive heart disease, demonstrated a risk of stroke four times that of the control population.[24] In general, these patients were significantly older and patients with hypertension were not excluded.

Table 9. Thromboembolic risk of lone atrial fibrillation

Study	Age	Patient-years observation	Thromboembolic events
Framingham	70	327	2.6%/yr
Mayo Clinic	44	1440	0.4%/yr

from references 23,24

In general, most patients with chronic atrial fibrillation should receive life-long anticoagulation with warfarin at a dose to achieve an INR of 2.0-3.0.[25] Patients who are not candidates for warfarin should receive aspirin at a dose of 70-325 mg daily although the efficacy of aspirin has not been clearly

established. In theory, restoration of sinus rhythm (either by chemical or electrical cardioversion) should be effective in decreasing the risk of cardioembolic events. However, this theoretical benefit has never been demonstrated.

2. Rheumatic valvular disease:

The relationship between mitral stenosis and embolic complications has been well described. Systemic embolism has been reported to occur in 9-14% of patients with mitral stenosis and, in fact, a systemic embolic event may be the initial presentation of a patient with mitral stenosis. Unfortunately, the majority of these embolic events (60-75%) are cerebral emboli.[26] In the Framingham study, the risk of stroke for patients with mitral stenosis and atrial fibrillation was seventeen times the risk of stroke in the general population.[12] While systemic embolic events related to mitral stenosis usually occur in patients with atrial fibrillation, up to 20% of embolic events may occur in patients with sinus rhythm.[27]

Anticoagulation is strongly believed to decrease the risk of embolic complications in mitral stenosis, although this has never been proven in a randomized, prospective trial. Definite indications for anticoagulation in patients with mitral stenosis include the presence of atrial fibrillation (chronic or paroxysmal) or a history of a systemic embolic event (regardless of the patient's rhythm). Less well established indications include patient age greater than 40 and a dilated left atrium (greater than 5.5 cm).[28] Recurrent systemic embolic events despite adequate anticoagulation is an indication for mitral valve surgery (commissurotomy versus replacement).

3. Acute myocardial infarction:

Stroke occurs as a complication of acute myocardial infarction in about 2-4% of patients.[29,30] There is some data to suggest that the incidence of embolic stroke is lower in the era of thrombolytic therapy.[31,32] It is commonly believed that embolic stroke is more common in anterior infarcts than with other locations, although this has not been consistently demonstrated.[30,33] Most left ventricular thrombi occur over dyskinetic wall segments and embolization is most common within the first 3-4 months with the highest risk during the first month. The risk for embolization is highest for thrombi which are highly mobile and pedunculated.[34] Anticoagulation has been demonstrated to reduce the risk of thrombus formation and perhaps the risk of embolization. Anticoagulation can be given prophylactically for all large, anterior infarcts or may be given based on echocardiographic findings.[29,35] In general, anticoagulation is given for 3-6 months. It is important to recall that 20-60% of nonfatal acute myocardial infarctions are silent.[36] The patient may not seek medical attention until a complication such as stroke occurs. Thus, it is important to exclude acute myocardial infarction in all patients who present with stroke.

After the initial 3-6 months post-infarction, a left ventricular aneurysm is considered a chronic aneurysm.[37] In contrast to acute myocardial infarction, stroke is an uncommon complication of chronic left ventricular aneurysm. While thrombi are frequently demonstrated in chronic left ventricular apical aneurysms, the risk of embolic complications for chronic LV aneurysm is low.[38] Thus, anticoagulant therapy is not recommended for chronic LV aneurysms.[29]

4. Dilated cardiomyopathy:

Patients with severely depressed LV systolic function and normal coronary arteries (idiopathic cardiomyopathy) have a high incidence of left ventricular thrombus formation and are at increased risk of embolic complications.[39] There is limited data on patients with idiopathic dilated cardiomyopathy demonstrating that anticoagulation is effective in decreasing the risk of embolic complications. In a retrospective review , Fuster and colleagues found evidence of systemic emboli in 18% of patients not on anticoagulant therapy (103 patients) compared to no emboli in patients receiving chronic anticoagulation (n=32).[40] The association of atrial fibrillation with a dilated cardiomyopathy doubles the risk of embolic complications. For this reason, chronic anticoagulation is recommended for all patients with idiopathic dilated cardiomyopathy, especially when combined with atrial fibrillation.

Table 10. Embolic complications in patients with idiopathic dilated cardiomyopathy

	patients with emboli	
	N=	%
anticoagulation		
yes (n=32)	0	0
no (n=103)	19	18
atrial fibrillation		
yes (n=24)	8	33
no (n=80)	11	14

from reference 40

There is less information regarding risk of systemic emboli and the role of anticoagulation in patients with severe left ventricular dysfunction resulting from coronary artery disease (so called "ischemic cardiomyopathy"). While some practitioners use chronic anticoagulation for all patients with severe LV dysfunction, the utility of this approach has not been clearly shown. In ambulatory populations with congestive heart failure where the majority of

patients have ischemic disease, the incidence of stroke appears to be low (1.7 to 1.8 thromboembolic events per 100 patient-years).[41,42]

The presence of a thrombus on echocardiogram does appear to increase the risk of embolism.[43] While as many as 30% of left ventricular thrombi may resolve spontaneously and anticoagulation appears to increase the rate of thrombus resolution, it has not been proven that resolution of a thrombus is associated with a reduction in embolic risk.[44]

There is preliminary data from the PROMISE trial suggesting that anticoagulation may be beneficial in patients with severe LV dysfunction and significant heart failure symptoms. This trial consisted of patients with ejection fractions ≤ 35% and persistent class III of IV congestive heart failure. A retrospective review of the benefits of anticoagulation indicated that in patients with ejection fractions < 20%, warfarin appeared to be beneficial in reducing the prevalence of stroke (table 11).[45]

Table 11. Prevalence of stroke at 6 month median follow-up

	Warfarin	No Warfarin	P value
Ischemic	2/153 (1.3%)	10/433(2.3%)	0.3
Non-ischemic	1/171(0.6%)	9/331(2.7%)	0.1
EF > 20%	2/143(1.4%)	7/403(1.7%)	0.9
EF ≤ 20%	1/181 (0.6%)	12/361(3.3%)	<0.05

from reference 46

5. Prosthetic Valves:

Systemic embolization is a known complication of both bioprosthetic and mechanical valves, occurring in 1-4% per year. The majority (80%) of thromboemboli associated with prosthetic valves involve the cerebral circulation.[46] Grunkemeier and Rahimtoola analyzed a series of studies with bioprosthetic and mechanical valves and demonstrated that the average weighted risk for thromboembolism did not differ between valve types.[47] However, the absolute risk of thromboembolic events was higher for valves in the mitral position (2-3.5% events per year) than in the aortic position (1-2% events per year). For patients with intermittent or chronic atrial fibrillation, the risk of systemic embolization is substantially higher.[48]

The optimal level of anticoagulation for mechanical valves is a target INR of 2.5 to 3.5.[49] Anticoagulation is recommended for bioprosthetic valves under certain circumstances. Bioprostheses implanted in the mitral position should be anticoagulated for 3 months post-operatively. Chronic anticoagulation is recommended for patients in atrial fibrillation, those with a left atrial thrombus demonstrated at the time of surgery, or those with a history of a systemic embolic event. The target INR for bioprosthetic valves is between 2.0 to 3.0. For both mechanical and bioprosthetic valves, higher

intensity anticoagulation does not appear to further decrease the incidence of embolic complications but is associated with a higher incidence of bleeding.[50,51] For those patients who have evidence of embolic complications despite adequate levels of anticoagulation, antiplatelet therapy with aspirin should be added.[52,53]

6. Mitral valve prolapse:

Mitral valve prolapse is a common cardiac condition, estimated to occur in approximately 4% of the general population, affecting more than 12 million Americans.[54] Many reports have suggested an association between mitral valve prolapse and cerebral ischemic events in young adults, with the reported incidence of MVP ranging from 2-30% of young patients with cerebral ischemia.[4] Specific criteria have been published for the echocardiographic diagnosis of mitral valve prolapse and when these criteria are applied, there does appear to be some increased risk of stroke in patients with mitral valve prolapse. In one retrospective review of 456 patients with echocardiographically documented mitral valve prolapse, stroke occurred in 32 patients (7%).[55] However, in another prospective study of 343 patients with echocardiographically documented prolapse, stroke occurred in only 2 patients (0.8%).[56] In both studies, the presence of thickened or redundant leaflets was not predictive of cerebral embolic events. In general, the risk of thromboembolic complications for patients with mitral valve prolapse is felt to be quite low (estimated at 1/6000/year).[4]

Table 12. Incidence of stroke in mitral valve prolapse

	N =	Cerebral embolic event
Marks, et al	456	7%
Nishimura, et al	237	0.8%

from references 56,57

The mechanism of stroke in patients with mitral valve prolapse is not clearly understood. It is postulated that platelet-fibrin thrombi may form on the surface of the redundant leaflet tissue and may embolize.[57] Empiric antiplatelet agents (aspirin) are currently recommended for patients with mitral valve prolapse who have symptomatic cerebral ischemia.[4] There is no published data on the utility of antiplatelet therapy or anticoagulation in patients with mitral valve prolapse and cerebral ischemia.

7. Atherosclerotic debris in the aorta:

The widespread use of transesophageal echocardiography in the evaluation of patients with stroke has led to the description of atherosclerotic "debris" in the thoracic aorta.[58-61] This is a relatively new potential

cardioembolic source of stroke, although by strict criteria it is not really a cardiac source. Obviously, only lesions in the ascending aorta or aortic arch could result in emboli to the cerebral circulation. Several investigators have examined the prevalence of this "debris" in patients with stroke.[59,61] While this may represent a potential source of embolism, there is no data regarding the utility of any treatment intervention for this entity.

8. Atrial septal aneurysm:

Strictly defined, an atrial septal aneurysm is a redundancy of the tissue of the fossa ovalis that is at least 1.5cm in length and demonstrates mobility (maximal excursion between the left and right atria of at least 1.5cm).[62] From autopsy data, atrial septal aneurysms occur in approximately 1% of the population.[63] By standard transthoracic echo, the diagnosis is made infrequently. Because of the superiority of the transesophageal technique for visualizing posterior structures, such as the atrial septum, atrial septal aneurysms have been described much more frequently by TEE.

Atrial septal aneurysms appear to be associated with embolic events although the mechanism by which atrial septal aneurysm may be related to cardioembolic stroke has not been clearly defined.[64-66] While isolated case reports of thrombus in the atrial septal aneurysm have been described,[67] why and how frequently thrombi form within an atrial septal aneurysm is unknown. An interatrial communication (either a patent foramen ovale or an atrial septal defect) is present in nearly all atrial septal aneurysms.[68] Thus, the potential for paradoxic emboli is present. There is no data regarding treatment for patients with stroke who are found to have an atrial septal aneurysm.

9. Patent foramen ovale:

The role of patent foramen ovale in cardioembolic stroke is an area of significant controversy. Persistent patency of the foramen ovale is considered a normal anatomic variant, found in 27-35% of persons by autopsy series.[69,70] While the incidence of a patent foramen ovale declines with advancing age, the size of the defect tends to increase with advancing age. While providing a potential route for paradoxic embolization to the cerebral circulation, this was previously felt to be an uncommon occurrence.

Lechat, et al, first described an association between stroke and patent foramen ovale (table 13).[71] He studied 65 patients with an ischemic stroke who were under the age of 55 and had a normal cardiac examination. A patent foramen ovale was demonstrated by transthoracic contrast echocardiography in 40%. These patients were then further divided into three groups, based on whether or not a definite or possible cause of stroke was present. Among the 26 patients without any identifiable cause, the prevalence of patent foramen ovale was 54%.

Table 13. Prevalence of PFO by transthoracic echocardiography (Lechat, et al)

Group	# of patients	%PFO
Control	100	10
Ischemic stroke	60	40
Group A (cause identified)	19	21
Group B (risk factors present- MVP, OCP, migraines)	15	40
Group C (no cause, no risk factors)	26	54

from reference 71

A similar study by Webster, et al demonstrated a 50% prevalence of a patent foramen ovale detected by transthoracic contrast echocardiography in young patients (age under 40) with unexplained ischemic stroke or transient ischemic attacks compared to a 15% prevalence in control subjects.[72]

In contrast to transthoracic echocardiography, transesophageal echocardiography provides superior visualization of the atrial septum and is the technique of choice for making a diagnosis of patent foramen ovale.[73] A patent foramen ovale can be demonstrated by color flow mapping or by contrast injection. Right to left shunting may be demonstrated at rest or only during maneuvers which transiently reverse the normal interatrial pressure gradient (Valsalva maneuver or cough). It is interesting to note that in transesophageal studies of patients with unexplained stroke, the prevalence of patent foramen ovale is substantially lower than would be expected from the transthoracic studies discussed above (table 14).

Table 14. Prevalence of PFO by TEE in patients with stroke

Study	Indication for TEE	n =	PFO
Khanderia, et al	Suspected embolism	339	27%
Stahl, et al	stroke	69	10%
deCoodt, et al	ischemic stroke	64	27%
Pearson, et al	stroke of uncertain etiology	79	16%
Sadler, et al	ischemic stroke	57	11%
Zahn, et al	cerebral ischemia - stroke or TIA	50	32%
DiTullio, et al	cryptogenic stroke	45	42%
	stroke of known cause	101	7%
Lee, et al	embolic stroke	18	11%
deBelder, et al	embolic stroke, TIA or systemic emboli	104	28%
TOTAL		926	21%

Some TEE studies have supported the PFO hypothesis. In the study by DiTullio, et al,[74] the prevalence of PFO was 42% in patients with cryptogenic stroke, compared to a prevalence of 7% in patients with stroke of known cause. In this study, the association between PFO and stroke was seen in all age groups. De Belder, et al studied 104 patients with a possible embolic event, compared to 94 patients undergoing TEE for another indication (table 15). The prevalence of PFO was 18% in patients with a possible embolic event, compared to 3.2% of controls.[75] In contrast, data from the Mayo Clinic suggests that PFO is not be associated with systemic embolic events (table 16).[76] In 195 patients with no obvious risk factors for systemic embolic events who underwent transesophageal echocardiography, a PFO was found in 42% of patients with systemic embolic events (37/115) and in 38% of patients without systemic emboli (30/80).

Table 15. Prevalence of PFO by transesophageal echocardiography - DeBelder, et al

	n =	prevalence of PFO
possible embolic event	104	18%
TEE for other indication	94	3.2%

from reference 75

Table 16. Prevalence of PFO by transesophageal echocardiography - Mayo Clinic experience

	n =	prevalence of PFO
systemic embolic event	115	42%
TEE for other indication	80	38%

from reference 76

The absolute diagnosis of paradoxical embolism requires that thrombus be demonstrated crossing the interatrial septum (either by echocardiography or autopsy).[77] A presumed diagnosis of paradoxical embolism requires the following: a venous source of embolism, a intracardiac right to left shunt, and an arterial embolism without another cardiac source identified. Transesophageal echocardiography can demonstrate the intracardiac shunt and the absence of another cardiac source. However, the finding of a patent foramen ovale by itself is insufficient evidence to presume a diagnosis of paradoxic embolism. Stollberger, et al have demonstrated that clinically silent deep venous thrombosis may occur in as many as half of patients with suspected paradoxic embolism through a patent foramen ovale.[78] In a study

of 42 patients with a clinically suspected embolic event and a patent foramen ovale demonstrated by transesophageal echocardiography, twenty-four (57%) had evidence of deep venous thrombosis. While this finding is intriguing, evaluation for the presence of deep venous thrombosis is usually not performed as part of the evaluation of a patient with a suspected paradoxical embolism.

The management of a patient with a presumed paradoxic emboli through a patent foramen ovale remains an area of controversy. There is no data regarding the natural history of recurrent emboli in these patients. Likewise, there is no data on treatment options. Many patients are empirically treated with anticoagulation and surgical closure of the opening is occasionally performed.

10. Spontaneous echo contrast:

Spontaneous echo contrast refers to the finding of a swirling, amorphous cloud of echodensity seen within a cardiac chamber or vessel. Although its precise etiology remains somewhat unclear, it is generally believed to be caused by aggregation of red blood cells in the setting of low blood velocity.[79] It has been well described in association with conditions such as atrial fibrillation, mitral stenosis, prosthetic mitral valves, and severe left ventricular dysfunction.[80,81] In small, retrospective studies, the finding of spontaneous echo contrast has been associated with an increased incidence of thromboembolic complications.[80,82-84]

The role of anticoagulation in patients with spontaneous echo contrast is unclear. In in vitro studies, the addition of heparin does not prevent the development of spontaneous echo contrast during stasis of blood.[85] In addition, in clinical studies of transesophageal echocardiography, the status of anticoagulation has been shown to have no correlation with the presence or absence of spontaneous echo contrast within cardiac chambers .[80,82] Thus, while spontaneous echo contrast appears to be a marker for increased thromboembolic risk, there is no evidence to date that anticoagulation can lower that risk.

11. Bacterial endocarditis:

The prevalence of ischemic stroke in patients with infective endocarditis ranges between 15 and 20%, with the majority of strokes occurring at presentation or within 48 hours of diagnosis. The risk of a late stroke in patients with controlled infection is less than 5%.[86] Appropriate treatment for stroke complicating endocarditis involves control of infection. Anticoagulation has no role. Echocardiography can be useful to help confirm the clinical diagnosis of infective endocarditis and to assess valve dysfunction.

12. Nonbacterial thrombotic endocarditis:

Nonbacterial thrombotic endocarditis refers to valvular thrombi (usually <3mm) associated with a pre-thrombotic state which occurs as a complication of malignancy as well as other nonmalignant wasting illnesses, including the acquired immunodeficiency syndrome. This condition is fairly common, present in 0.5-1% of autopsies and is a common cause of ischemic stroke in patients with cancer. Emboli are present in the majority of autopsy cases and clinically-evident emboli are present in nearly 1/3 of patients.[87,88] Treatment of NBTE is directed towards treatment of the underlying condition. There is some evidence that heparin may be effective in preventing thromboembolic complications but warfarin therapy does not appear to be effective.[28]

13. Mitral annular calcification:

Calcification of the mitral annulus refers to a chronic, noninflammatory, degenerative process involving the fibrous support structure of the mitral valve.[89] Data from the Framingham Heart Study demonstrated that the presence of mitral annular calcification was associated with a relative risk of stroke of 2.10.[90] While an association between stroke and mitral annular calcification has been demonstrated, no causal relationship has been established. It is likely that MAC represents a marker for generalized atherosclerosis or other cardiovascular disease.

14. Calcific aortic stenosis:

Embolic complications are uncommon in patients with calcific aortic stenosis. Emboli are usually small, often clinically occult or producing transient monocular blindness. Larger emboli have been associated with cardiac catheterization and percutaneous balloon valvuloplasty.[91,92]

15. Cardiac tumors:

Atrial myxomas are the most common primary cardiac tumor and these tumors frequently embolize and can cause stroke. The prevalence of atrial myxoma in unselected patients presenting with ischemic strokes or transient ischemic attacks is approximately 1 in 750.[4] Other primary and metastatic cardiac tumors can also cause embolic stroke.

16. Intracardiac thrombus:

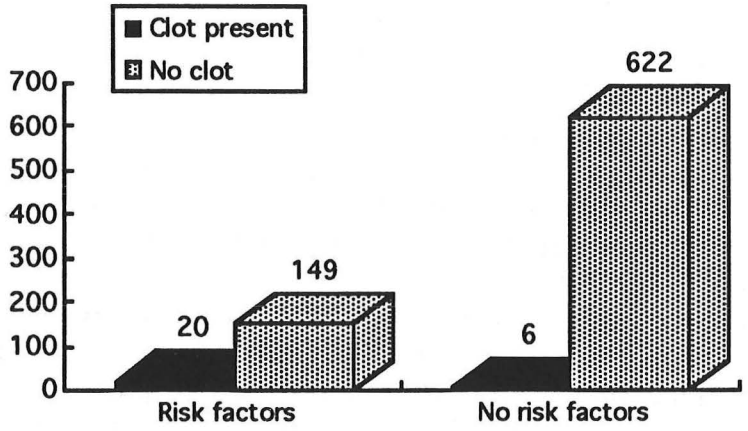
Thrombus within the left ventricle has been well described to occur in the setting of acute myocardial infarction, dilated cardiomyopathy and chronic left ventricular aneurysm, as discussed above. Thrombus in the left ventricle, as well as the underlying condition responsible for its formation, can usually be well demonstrated by transthoracic echocardiography.

The majority of thrombi in the left atrium occur within the left atrial appendage, an area which is not well visualized by transthoracic

echocardiography but can be well visualized by transesophageal echocardiography. For this reason, routine use of transesophageal echocardiography in all patients with ischemic stroke has been advocated by some authors to exclude an atrial appendage thrombus. Data from our institution suggests that left atrial appendage thrombi usually occur in association with one of five clinical conditions: atrial fibrillation, mitral stenosis, prosthetic mitral valves, severe left ventricular dysfunction, or left atrial dilatation.[93] In a series of 1000 consecutive transesophageal echocardiograms, left atrial appendage thrombus was found in 18 patients. Sixteen of the eighteen patients had at least one risk factor for left atrial appendage thrombus formation, although two did not. Thus, atrial appendage thrombi rarely occur in patients without a clinical risk factor for thrombus formation. The presence or absence of these risk factors can be determined by physical examination, ECG, and transthoracic echocardiography.

Figure 2.

Incidence of left atrial appendage thrombus by TEE



from reference 93

ROLE OF ECHOCARDIOGRAPHY

Echocardiography is a powerful tool for evaluation of many of the cardioembolic sources which we have discussed. For this reason, echocardiography is often part of the evaluation of patients with presumed ischemic stroke. However, there have been several studies performed to address the utility of routine transthoracic echocardiography in patients with ischemic stroke. Lovett, et al studied the utility of transthoracic echocardiography in 138 patients with focal cerebral ischemic events (either stroke or transient ischemic attack) who were either suspected of having a cardioembolic source or had no obvious etiology of their ischemic event.[94]

Subjects were divided into 4 groups on the basis of clinical evaluation (table 17). Among 34 patients with no clinical evidence of cardiac disease, transthoracic echo was normal in all but one patient (dilated left atrium). Among 21 patients with hypertension only, transthoracic echo was noncontributory in all but one patient (questionable thrombus seen). The yield of transthoracic echo was substantially higher in those patients with clinical evidence of cardiovascular disease.

Table 17. Yield of transthoracic echocardiography in patients with stroke.

Clinical findings	Transthoracic echo findings
No cardiac disease	1/34 (3%)
Hypertension only	1/21 (5%)
Cardiac disease	24/53 (45%)
Atrial fibrillation	15/30 (30%)

from reference 94

On the basis of this and similar studies, the American Society of Echocardiography and the American Heart Association Committee on the Use of Echocardiography have recommended that transthoracic echocardiography not be used as part of the routine evaluation of patients with ischemic stroke, unless there is clinical evidence of heart disease. For patients under the age of 45, an age group in which atherosclerotic cerebrovascular disease is less prevalent and cardioembolic stroke may be more likely, transthoracic echocardiography may be indicated.[95]

The routine use of transesophageal echocardiography for evaluation of patients with ischemic stroke is even more controversial. There have been a large number of studies comparing the yield of transesophageal compared to transthoracic echocardiography in the evaluation of stroke patients and all of these studies have consistently shown a higher yield of positive echocardiographic findings using the transesophageal technique (table 18).

At first glance, the increased yield of "positive findings" by transesophageal echocardiography is very impressive. However, it is important to consider that some of these "positive findings" were conditions or findings that are not proven cardioembolic sources of stroke. For example, in the study by Pearson, et al, if we exclude atrial septal aneurysm, patent foramen ovale and left atrial spontaneous contrast (all of which are potential but as yet unproven sources of cardioembolic stroke), the yield of transesophageal echo is 16% versus 9% for transthoracic echocardiography.[97]

We performed transthoracic and transesophageal echocardiography in a prospective series of 200 consecutive patients admitted to Parkland with a diagnosis of ischemic stroke (n=162) or transient ischemic attack (n= 38) and divided these patients into three clinical groups on the basis of their history, physical examination and ECG findings (figure 3). As expected, the yield of

Table 18. Trials comparing Transthoracic (TTE) and Transesophageal Echocardiography (TEE)

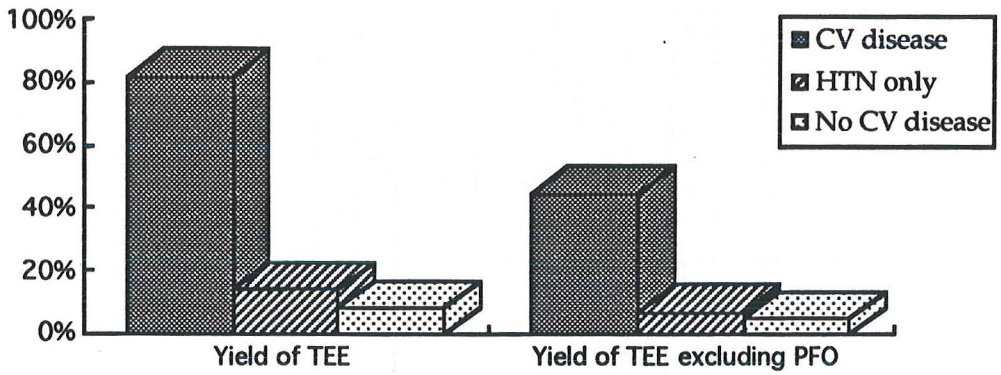
Study	Cujec (96)	Pearson (97)	Lee (98)	Pop (99)	Hoffman (100)	DeRook (101)	Zenker (102)	
n =	63	79	50	72	153	66	40	29
Diagnosis	CVA/TIA	CVA/TIA	CVA/TIA	TIA/minor stroke	embolic events (1/3 non-CNS)	CVA/TIA	CVA/RIND /TIA	Control
Clinical heart disease	38%	52%	58%	26%	30%	70%	?	
Carotid disease excluded	No	?	Yes	Yes	Yes	No	No	
Yield of TTE	14%	15%	0%	8%	40%	23%	50%	10%
Yield of TEE	41%	57%	52%	68%	58%	71%	60%	17%

from reference 103

abnormal findings was higher by transesophageal echocardiography (32% potential source of emboli versus 13% for transthoracic echocardiography). The yield of TEE was highest in those patients with clinical evidence of cardiovascular disease and was substantially lower in those patients without clinical evidence of cardiovascular disease or those patients with hypertension only.[104] While the yield was lower in these patients, it was not zero.

Figure 3.

Yield of TEE in 200 consecutive pts with ischemic stroke/TIA



from reference 104

It is important to recognize that transthoracic and transesophageal echocardiography are complementary procedures (table 19). The transthoracic approach is superior for visualizing the left ventricular apex, left ventricular thrombus, and certain aspects of prosthetic valves. The strengths of transesophageal echocardiography include superior visualization of the left atrium and its appendage (thus better visualization of atrial thrombi), the interatrial septum, valves (important for visualizing small abnormalities), and the ability to visualize the thoracic aorta.

Table 19. Relative strengths of transthoracic and transesophageal echocardiography

Transthoracic echocardiography

- better visualization of LV apex/LV thrombus
- specific diagnostic criteria defined for MVP
- better to visualize some aspects of prosthetic valves
- noninvasive

Transesophageal echocardiography

- better visualization of left atrium and its appendage
- better visualization of interatrial septum
- better visualization of valves
- allows inspection of thoracic aorta
- high quality images in nearly all patients

At this time, no official recommendations have been issued regarding the appropriate use of transesophageal echocardiography in the evaluation of patients with ischemic neurologic events. Routine use of transesophageal echocardiography in all patients presenting with ischemic stroke is a costly proposition and may not be cost effective.

Several algorithms for utilization of echocardiographic imaging in the evaluation of ischemic stroke or transient ischemic attack have been proposed.[104] Figure 4 is an algorithm which we have proposed for use at our institution. In patients who are not considered to be candidates for anticoagulation or surgery, echocardiographic evaluation is probably not warranted since positive findings would not impact the clinical management of the patient. If an indication for anticoagulation already exists (such as atrial fibrillation), echocardiography is not warranted unless needed to clarify the underlying cardiac pathology. For the remaining patients, in my opinion, transthoracic echocardiography should always be performed first since it is non-invasive and may identify an embolic source, especially in patients with clinical evidence of cardiovascular disease. If a clear indication for anticoagulation is identified on the transthoracic study, further evaluation (i.e. transesophageal echocardiography) is not needed. If the transthoracic echocardiogram is negative, transesophageal echocardiography is indicated.

In summary, cardioembolic stroke is an important cause of ischemic neurologic events and a potential cardiac source should be considered in all patients presenting with stroke or transient ischemic attack. While echocardiographic imaging may be warranted, clinical evaluation for evidence of cardiovascular disease should be undertaken first. While secondary prevention of cardioembolic stroke is clearly an important issue, primary prevention of cardioembolic stroke is extremely important. Anticoagulation has a proven role in the prevention of stroke for patients with atrial fibrillation, dilated cardiomyopathy, acute myocardial infarction, mitral stenosis, and mechanical prosthetic valves and should be used appropriately in these patients.

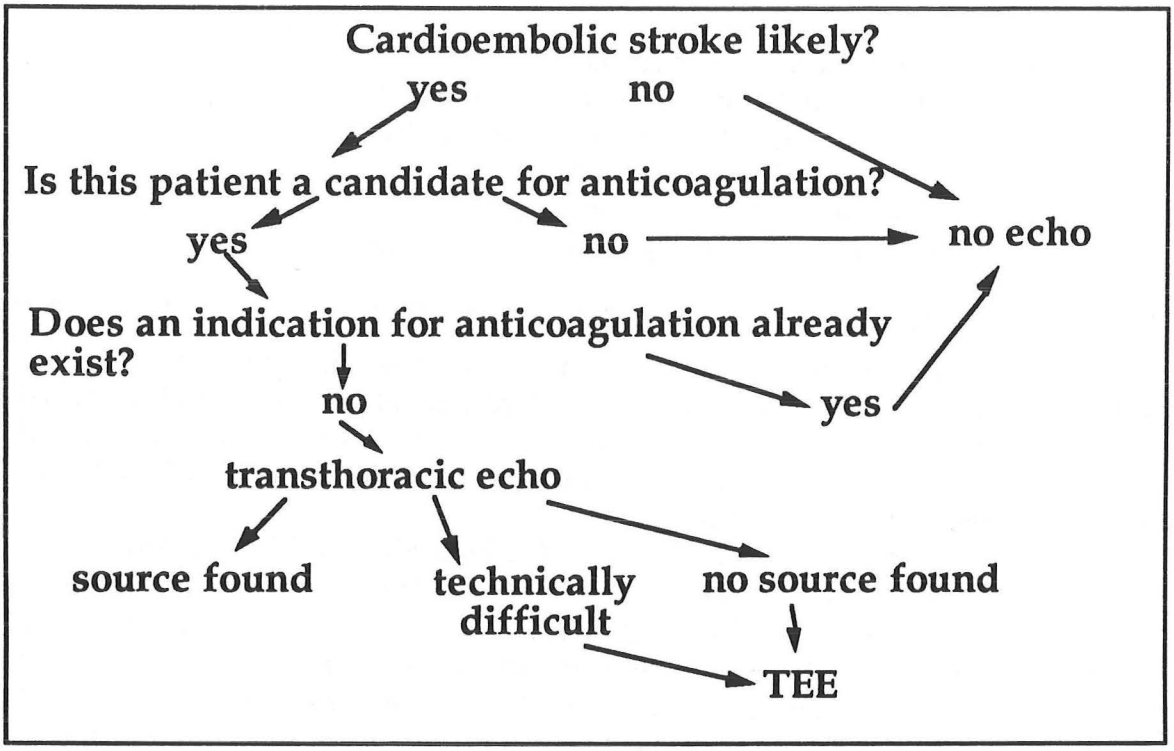


Figure 4. Proposed algorithm for use of echocardiography in patients with stroke.

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