Cardioembolic Stroke

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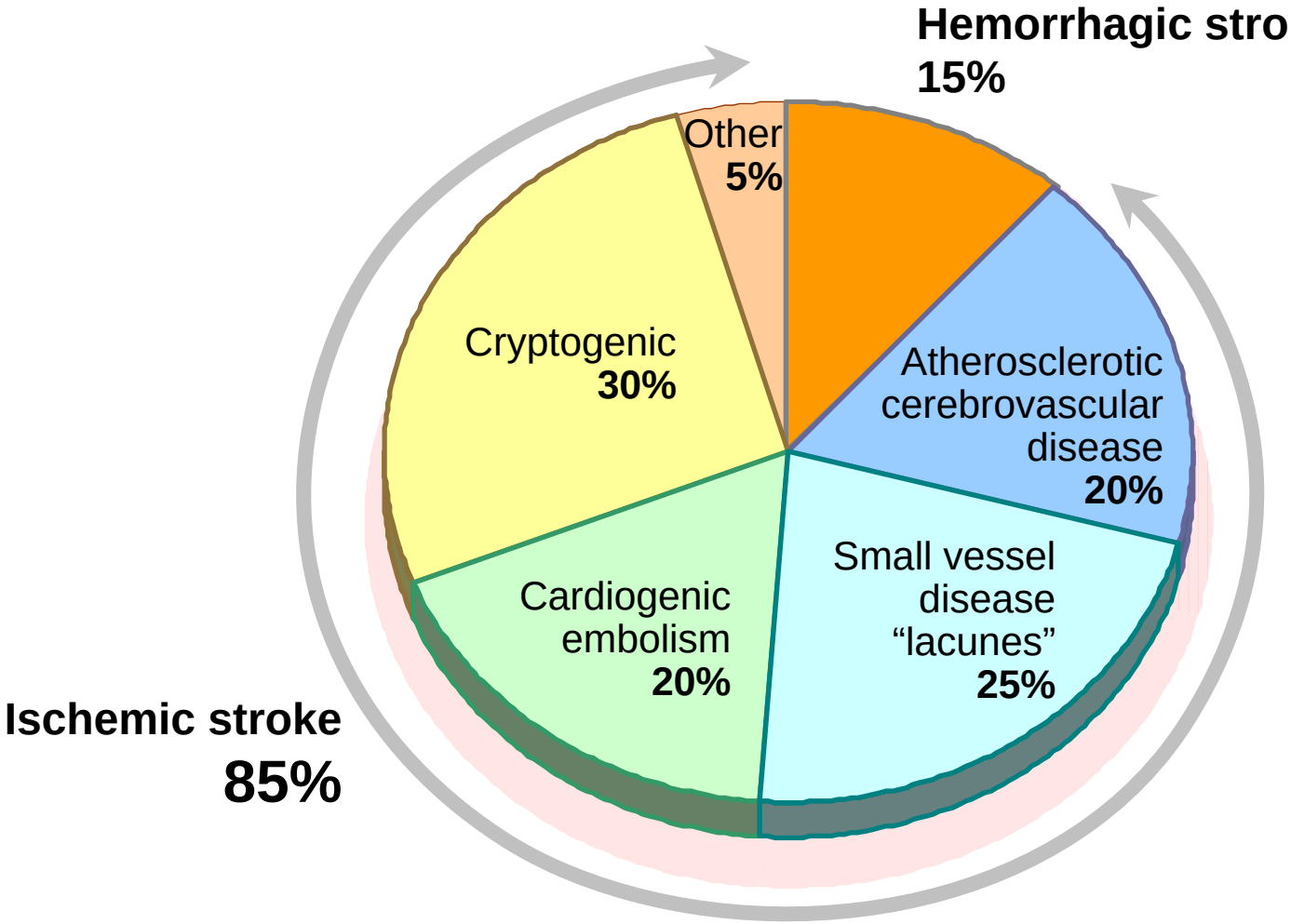
Stroke Subtypes and Incidence



Albers et al. *Chest* 2004; 126 (3 Suppl): 438S–512S.

Ischemic Stroke- Etiologic Subtypes

Table 1 Characteristics of patients included in the four studies included in the meta-analysis

Parameters	OXVASC	OCSP	Erlangen	Rochester
Etiologic subtypes, no. (%)				
Large-artery atherosclerosis	26 (17.2)	78 (13.5)	71 (13.4)	74 (16.3)
Small-vessel stroke	33 (21.9)	119 (20.6)	120 (22.6)	72 (15.9)
Cardioembolic	37 (24.5)	127 (22.0)	143 (26.9)	132 (29.1)
Undetermined	54 (35.8)	220 (38.1)	188 (35.4)	164 (36.1)
Other	1 (0.7)	33 (5.7)	9 (1.7)	12 (2.6)
Total	151	577	531	454

Etiologic subtype	% total patients, n = 1,709
Large-artery atherosclerosis	14.3
Small-vessel stroke	20.1
Cardioembolic	25.7
Undetermined	36.6

NEUROLOGY 2004;62:569–573

TABLE 1. TOAST Classification of Subtypes of Acute Ischemic Stroke

Large-artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Possible or probable depending on results of ancillary studies.

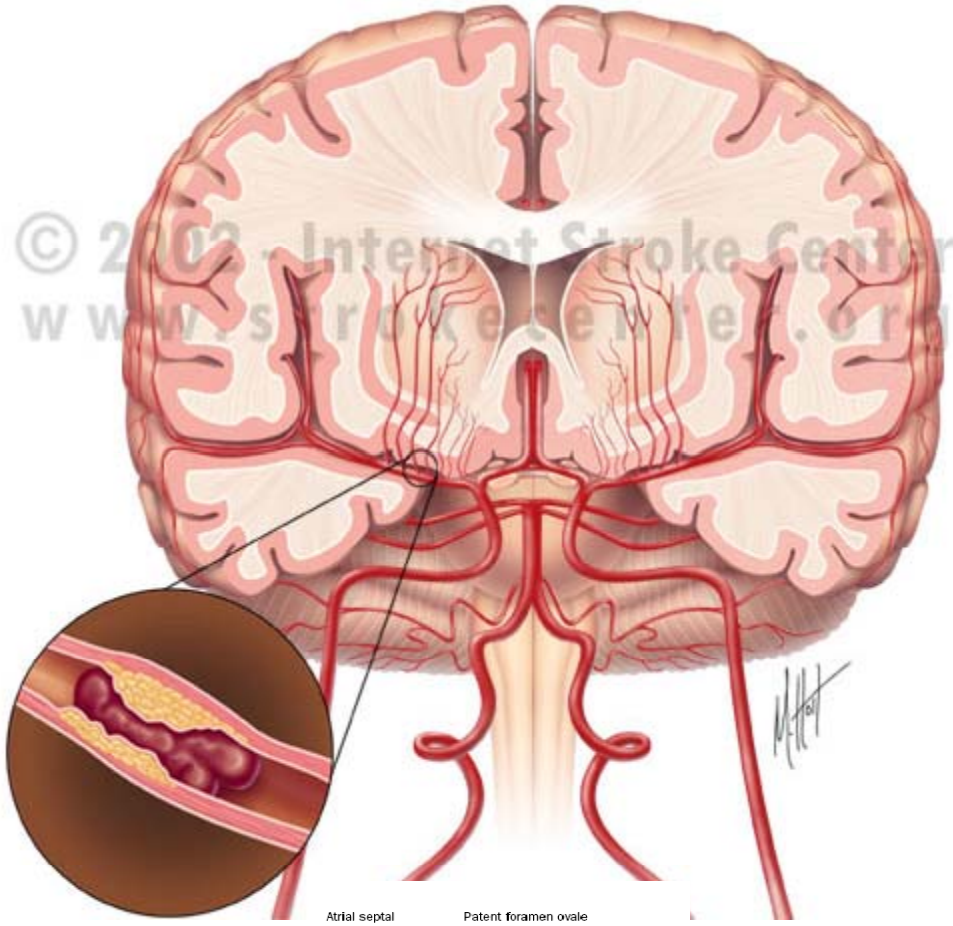
TOAST subtype classification Cardioembolic Strokes

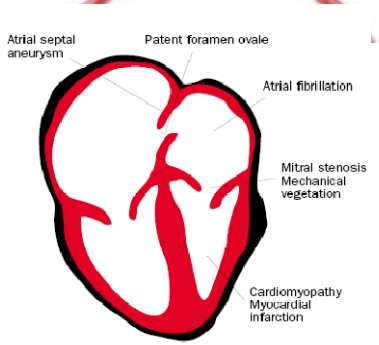
- Cardiac source for embolus
- Infarct > 1.5 cms in size on neuroimaging
- Clinical findings often include cortical features such as aphasia or neglect.
- Imaging studies rule out large vessel disease

Cardioembolic Stroke Diagnosis

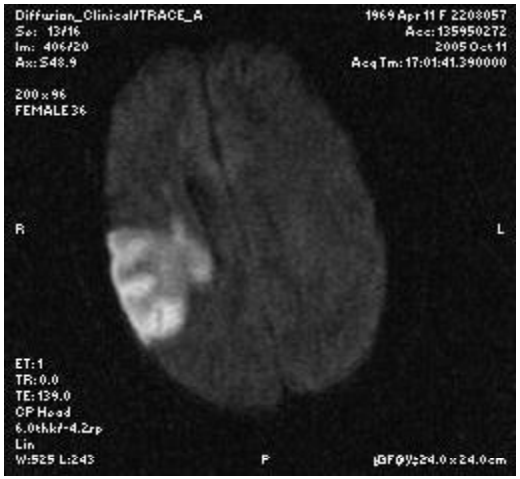
- Large strokes-alteration of consciousness
- Multiple vascular territories involved
- Maximal deficit at onset (?)
- Hemorrhagic transformation more likely

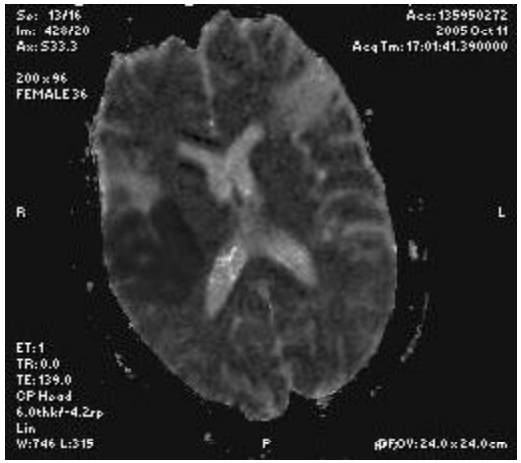
NONE OF THESE ARE VERY SPECIFIC!

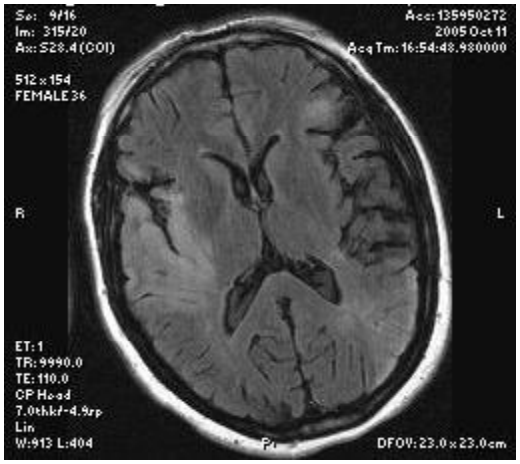


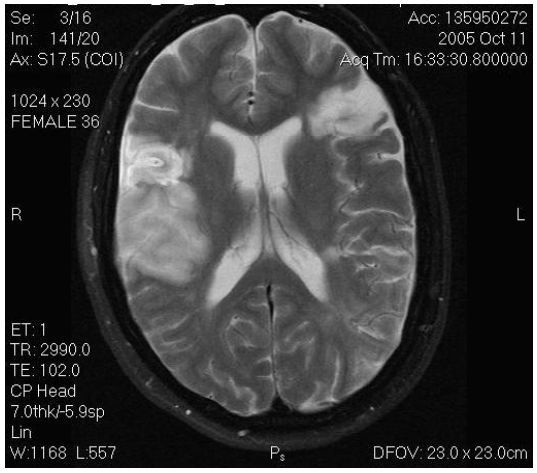


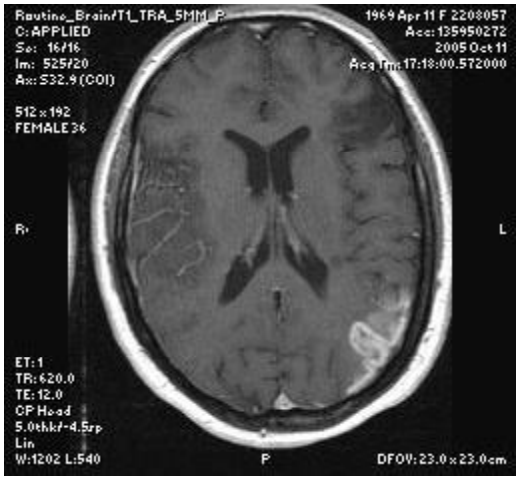
MRI-showing (cardio) embolic strokes











Sources of Cardioembolism

Table 1. Cardioembolic sources and embolic risk

High risk	Low/uncertain risk
Atrial	
Atrial fibrillation	Patent foramen ovale
Sustained atrial flutter	Atrial septal aneurysm
Sick sinus syndrome	Atrial auto-contrast
Left atrial thrombus	
Left atrial appendage thrombus	
Left atrial myxoma	
Valvular	
Mitral stenosis	Mitral annulus calcification
Prosthetic valve	Mitral-valve prolapse
Infective endocarditis	Calcified aortic stenosis
Non-infective endocarditis	Fibroelastoma
	Giant Lambl's excrescences
Ventricular	
Left ventricular thrombus	Akinetic/dyskinetic ventricular wall segment
Left ventricular myxoma	Subaortic hypertrophic cardiomyopathy
Recent anterior myocardial infarct	Congestive heart failure
Dilated cardiomyopathy	

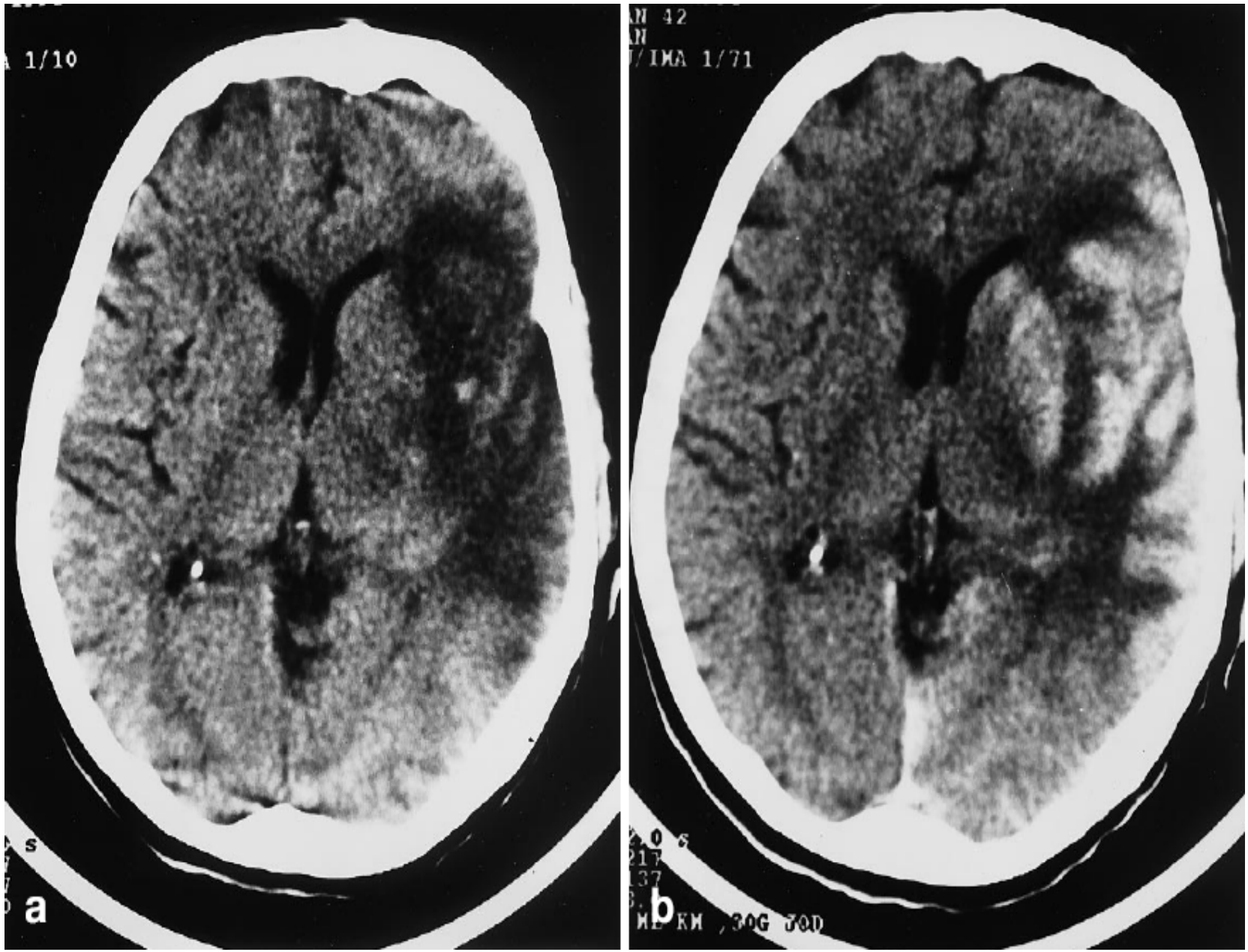
Common Cardioembolic Causes

- AF
- Mitral Regurgitation
- Recent MI (< 6 weeks)
- Prosthetic Heart valve
- Mitral Stenosis
- Paradoxical Embolism

Table 3 Number of lesions identified using TTE and TEE in the 73 patients

Injury	TTE	TEE
Thrombi	2	6
Tumors	1	2
Echocontrast	2	11
Strands	0	6
Aortic plaques	0	10
PFO	0	17
Atrial septal aneurysm	4	9
Dystrophy and calcification	5	9
Total	14	70

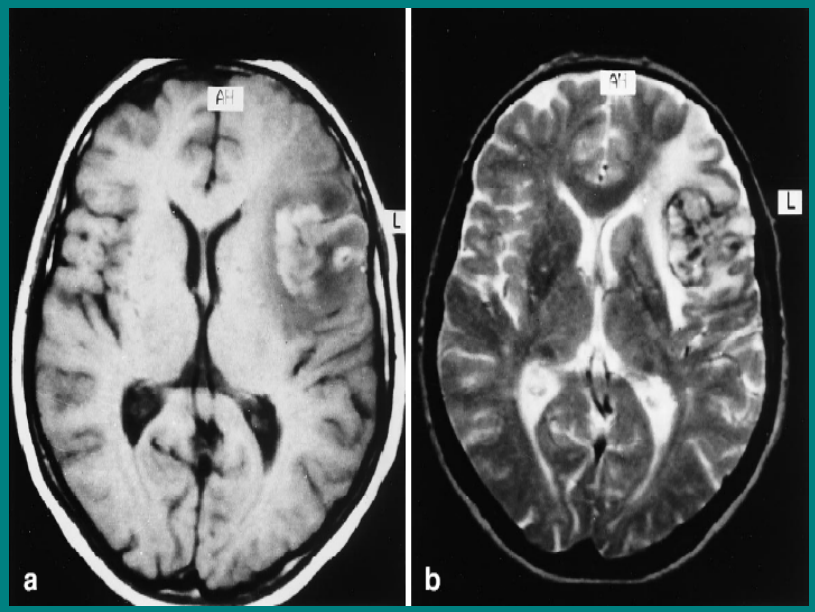
PFO, patency of the foramen ovale; *TTE*, transthoracic echocardiography; *TEE*, transesophageal echocardiography


1/10
a
IMA 1/71
b

Hemorrhagic Transformation

- Is common after cardioembolic stroke
- MRI detects HT more often than CT
- 36% in 48hrs* and 80%** by 2 weeks

*Mayer et al. Neuroradiology 2000
**Molina et al. Stroke 2001



Hemorrhagic Transformation

Associated with

- large infarcts
- NIHSS > 14
- Proximal MCA occlusion
- Delayed recanalization > 6 hrs after stroke onset
- Contrast enhancement, i.e. breakdown of BBB
- The larger the hematoma, more likely is it to cause neurologic worsening.

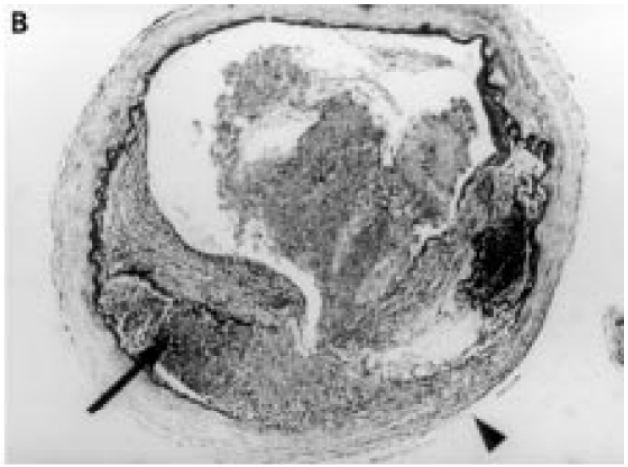
Hemorrhagic Transformation

- Injured vessels allow abnormal permeability
- There has to be recanalization and hence reperfusion
- The breakdown of blood brain barrier allows passage of RBCs
- HT could be petechial or when confluent could be large and cause mass effect

J Neurol Neurosurg Psychiatry 2001;**70**:672–674

Massive haemorrhagic transformation in cardioembolic stroke: the role of arterial wall trauma and dissection

G R de Freitas, A Carruzzo, A Tsiskaridze, J A Lobrinus, J Bogousslavsky

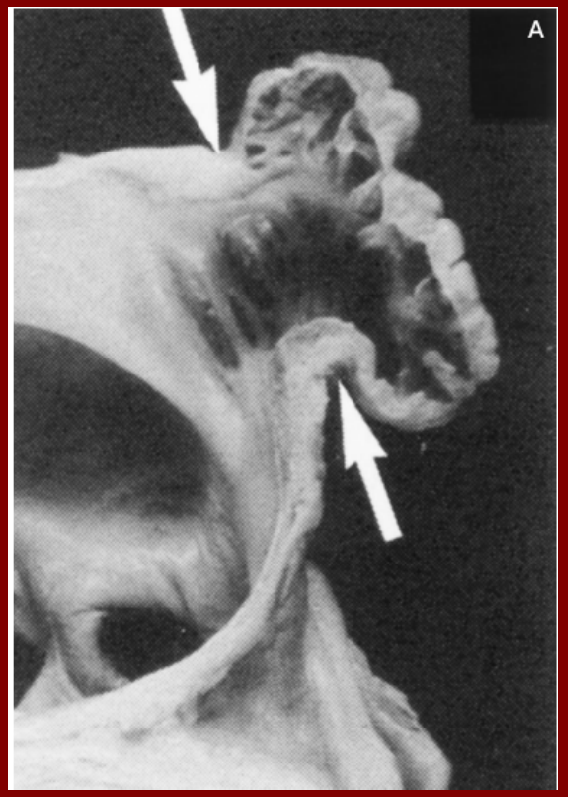


Atrial Fibrillation

- A very common arrhythmia
- Prevalence in the USA is about 2.3 million
- More in the elderly, 3.8% among > 60yrs and 9% among >80 yrs
- Risk of stroke ~6% per year- but variable
- The risk is just as great in intermittent AF, or atrial flutter as it is in permanent AF.
- Rhythm control *does not prevent strokes*

AF and stroke

- Strokes are often large and disabling
- Contractility of LA appendageis reduced in AF- stasis
- TTE may miss these, TEE required , which may reveal clots in 10% asymptomatic and 20-40% after thromboembolism.



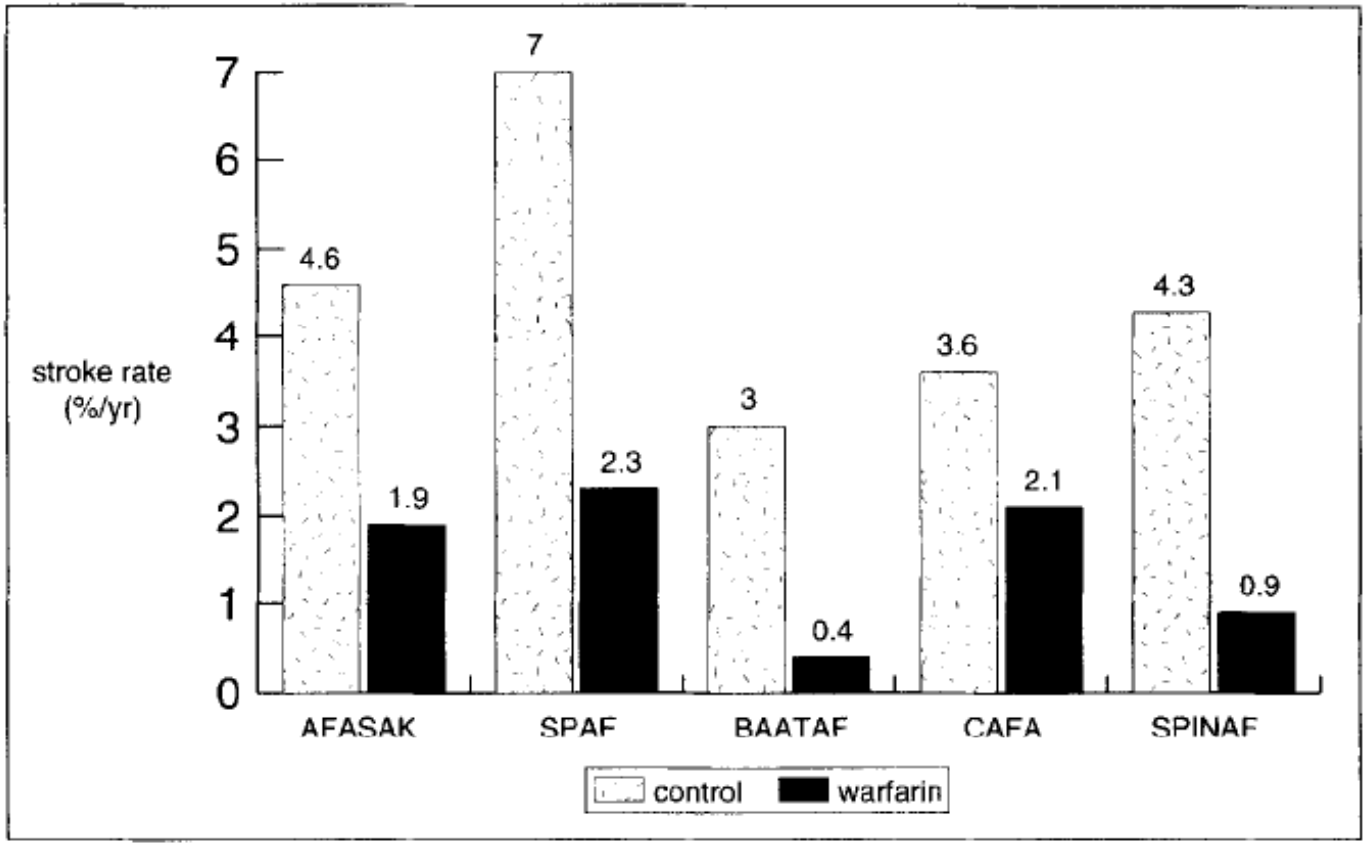


Figure 1. Results of intention to treat analysis in five prospective trials of warfarin for prevention of stroke in nonvalvular atrial fibrillation. AFASAK = Copenhagen AFASAK study,[16] SPAF = Stroke Prevention in Atrial Fibrillation study,[13] BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation,[12] CAFA = Canadian Atrial Fibrillation Anticoagulation trial,[18] SPINAF = Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation.[17]

Brickner E. Am J Med 1996

Primary Stroke Prevention trials

Lessons from the Stroke Prevention in Atrial Fibrillation Trials

Robert G. Hart, MD; Jonathan L. Halperin, MD; Lesly A. Pearce, MS; David C. Anderson, MD; Richard A. Kronmal, PhD; Ruth McBride, Elaine Nasco, BA; David G. Sherman, MD; Robert L. Talbert, PharmD; and John R. Marler, MD, for the Stroke Prevention in Atrial Fibrillation Investigators*

Table 1. The Stroke Prevention in Atrial Fibrillation Clinical Trials*

Trial	Time Interval	Main Findings
SPAF I		
Warfarin vs. placebo	1987–1989	Warfarin substantially reduces stroke
Aspirin vs. placebo	1987–1990	Aspirin reduces stroke
SPAF II		
Warfarin vs. aspirin, age ≤ 75 y	1987–1992	Small absolute reduction in stroke by warfarin over aspirin in unselected patients
Warfarin vs. aspirin, age > 75 y	1989–1992	High rate of intracranial bleeding with warfarin (INR, 2–4.5) in patients >75 years of age offset reduction in ischemic stroke
SPAF III		
Warfarin INR 2–3 vs. aspirin plus low-intensity, fixed-dose warfarin in selected high-risk patients	1993–1995	Warfarin INR 2–3 offers large benefits over aspirin plus low-intensity, fixed-dose warfarin for high-risk patients
Aspirin-treated low-risk cohort	1993–1997	Patients whose stroke risk is low when given aspirin can be identified (validation of the SPAF risk stratification scheme)

Ann Intern Med. 2003;138:831-838.

Table 4. Choosing Antithrombotic Therapies for Patients with Atrial Fibrillation*

Risk Strata	Stroke Rate with Aspirin, %/y	Relative Risk Reduction: Warfarin vs. Aspirin, %†	NNT_B‡	General Recommendation
Previous stroke or transient ischemic attack	10	60	17	Warfarin (INR, 2–3)
Primary prevention				
High risk	>4	55	35	Warfarin (INR, 2–3)
Moderate risk	2–4	45	75	Warfarin or aspirin§
Low risk	<2	35	>200	Aspirin (81–325 mg/d)

*

- High risk
  - Previous stroke or transient ischemic attack
  - Systolic blood pressure > 160 mm Hg
  - Heart failure‡
  - Women > 75 y
- Moderate risk
  - Hypertension
  - No high-risk features
- Low risk
  - No hypertension
  - No high-risk features

CHADS2 Score

- C CHF 1
- H HTN 1
- A Age > 75 1
- D Diabetes 1
- S Stroke or TIA 2

Gage, BF, Waterman, AD, Shannon, W, JAMA 2001; 285:2864.

Annual Stroke Risk

CHADS 2 score	Stroke risk %
0	1.9
1	2.8
2	4
3	5.9
4	8.5
5	12.5
6	18.2

***Gage et al. JAMA* 285 (22): 2864–70 (2001)**

Table 1. Guidelines for Antithrombotic Therapy in Atrial Fibrillation.

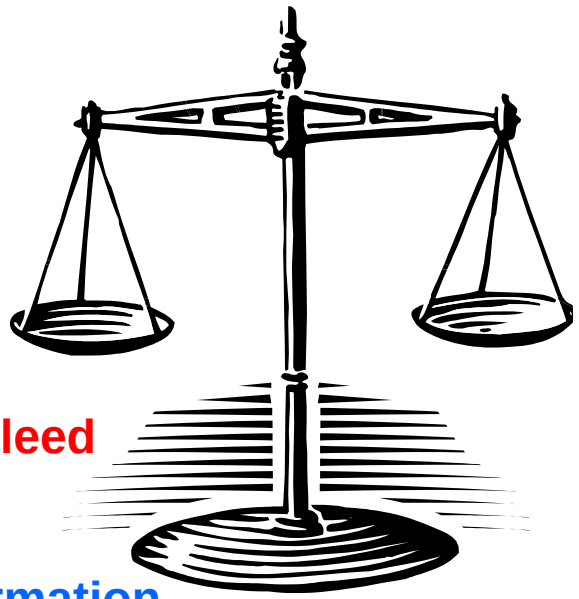
Characteristic	Therapy Recommended by the ACC–AHA and ESC	Differences in ACCP Guidelines
Age		
<60 yr, no heart disease	Aspirin at a dose of 325 mg per day, or no therapy	Aspirin at a dose of 325 mg for patients <65 yr of age with no risk factor†
<60 yr, with heart disease but no risk factors*	Aspirin at a dose of 325 mg per day	No divergence
≥60–75 yr, no risk factors*	Aspirin at a dose of 325 mg per day	Option of aspirin at a dose of 325 mg per day or warfarin (INR, 2.0–3.0) for patients 65–75 yr of age
≥60 yr, with diabetes mellitus or coronary artery disease	Warfarin (INR, 2.0–3.0), aspirin optional in addition (at a dose of 81–162 mg per day)	Option of aspirin at a dose of 325 mg per day or warfarin (INR, 2.0–3.0) for patients with diabetes alone or coronary artery disease alone who are <65 yr of age
>75 yr, especially among women	Warfarin (INR, approximately 2.0; target INR, 1.6–2.5)	Warfarin (INR, 2.0–3.0), but no recommendation for INR value <2.0

*HTN, DM, CAD, CHF, EF < 35%, previous TIA stroke or thromboembolism

NEJM 2004,351:23

Timing of anticoagulation after acute cardioembolic stroke

- There are no ‘good’ data
- The rationale is to achieve a good risk-benefit ratio



Risk of bleed

‘Large’ infarct
Hemorrhagic transformation

Risk of stroke recurrence

Atrial size, mech heart valve
Clots in LAA
Low EF
Prior embolism

Anticoagulation After Cardioembolic Stroke
To Bridge or Not to Bridge?

- Retrospective analysis of cardioembolic strokes at UT Houston
- Grouped into -No treatment, aspirin only, aspirin followed by warfarin, heparin followed by warfarin (heparin bridging), & enoxaparin bridging
- Outcome measures were symptomatic ICH, recurrent stroke, stroke progression, & discharge mRS

Arch Neurol. 2008;65(9):1169-1173

Table 1. Baseline Characteristics

Characteristic	NT (n=8)	ASA (n=88)	HB (n=44)	WAR (n=35)	EB (n=29)	*P* Value
Age, mean±SD, y	73±8	67±15	67±12	67±15	67±14	.70[a]
Female, No. (%)	3 (38)	46 (52)	18 (41)	15 (43)	10 (34)	.70[b]
Baseline NIHSS score, median (range)	13 (3-30)	10 (0-34)	7 (0-32)	8 (0-36)	6 (0-40)	.30[c]
Interval to treatment, median (range), d	NA	1 (1-8)	1 (1-12)	2 (0-15)	2 (1-20)	.11[c]
Cardiac cause, No. (%)						
AF	6 (75)	65 (70)	29 (74)	30 (83)	26 (90)	
VP	1 (12)	2 (2)	6 (15)	1 (3)	1 (3)	
VS	0	13 (14)	3 (8)	2 (6)	1 (3)	
PFO	0	11 (12)	2 (5)	1 (3)	2 (2)	

Arch Neurol. 2008;65(9):1169-1173

Table 2. Adverse Events

Adverse Event	No. (%)					
	NT (n=8)	ASA (n=88)	HB (n=44)	WAR (n=35)	EB (n=29)	Total (N=204)
Recurrent stroke	0	1 (1)	0	1 (3)	0	**2 (1)**
Progressive stroke	0	10 (11)	1 (2)	0	0	**11 (5)**
PH2	0	0	0	0	3 (10)	**3 (1)**
Benign HT	2 (25)	8 (9)	4 (9)	4 (11)	2 (7)	**20 (10)**
Systemic bleeding	0	0	2 (5)	0	0	**2 (1)**

Atrial Fibrillation, Stroke, and Acute Antithrombotic Therapy

Analysis of Randomized Clinical Trials

Robert G. Hart, MD; Santiago Palacio, MD; Lesly A. Pearce, MS

Background—Strokes in patients with atrial fibrillation (AF) are typically larger, are associated with higher early mortality, and occur in older patients versus strokes in patients with sinus rhythm. Until recently, the value of antithrombotic therapies for acute stroke management has been based on empiric evidence.

Summary of Review—We present a critical review of 3 randomized clinical trials testing aspirin, heparin/heparinoid, or both involving 5029 patients with AF and acute stroke. Early recurrent ischemic stroke occurred in about 5% of patients during the 2 to 4 weeks after initial stroke. Data conflict about whether early use of heparin/heparinoid reduced early recurrent ischemic stroke but are consistent regarding its lack of overall benefit on long-term functional outcome. Modest benefits for reduction of early recurrent stroke and functional outcome were associated with aspirin use, based largely on subgroup analysis from a single, large, unblinded trial.

Conclusions—No benefit of heparin has been demonstrated for acute stroke patients with AF; whether selected subgroups would respond differently remains to be proven. Aspirin followed by early initiation of warfarin for long-term secondary prevention is reasonable antithrombotic management. (***Stroke.*** **2002;33:2722-2727.)**

Key Words: aspirin ■ atrial fibrillation ■ heparin ■ stroke ■ thrombolysis

Aortic Arch Atheroma

- Autopsy and TEE evidence of protuding aortic arch atheroma (>4mm) is 3-9 times commoner in stroke pts compared to controls
- Seen in 60% of stroke pts > 60 years of age
- Besides size, ulcerated, mobile, and non-calcified plaques are more likely to cause embolism

Table 3. Incidence of Events According to Plaque Thickness in the Aortic Arch Proximal to the Ostium of the Left Subclavian Artery.

Plaque Thickness (mm)	Recurrent Brain Infarction			Any Vascular Event*		
	Person-Years of Follow-up†	No. of Events	Incidence per 100 Person-Years of Follow-up	Person-Years of Follow-up†	No. of Events	Incidence per 100 Person-Years of Follow-up
<1	359.3	10	2.8	354.0	21	5.9
1–3.9	312.6	11	3.5	308.2	28	9.1
≥4	92.4	11	11.9	88.4	23	26.0

Conclusions. Atherosclerotic plaques ≥4 mm thick in the aortic arch are significant predictors of recurrent brain infarction and other vascular events. (N Engl J Med 1996; 334:1216-21.)

Treatment of Aortic Atheroma

- No RCTs yet
- Antiplatelets with statins recommended
- Anticoagulation for mobile plaques, or recurrence on antiplatelets(?)
- Surgery has been performed –

- ‘ARCH’ trial (RCT) warfarin vs ASA+clopidogrel in stroke with complex atheroma

MVP and Stroke

- MVP is common in the general population
- An autopsy study has shown presence of MVP in 4.5% among large a series of consecutive autopsies (Br Heart J 1978)
- Framingham study-2.4% prevalence (NEJM-1999;341:1-7), much less than the 17% reported by the Framingham study in 1983.(Am Heart J 1983;106;571)
- MVP can cause AF, mitral regurgitation, acute (chordae tendinae rupture) or chronic heart failure.
- Prone to bacterial endocarditis

MVP and Stroke

- The literature reflects an evolution of our understanding of its association with stroke
- NEJM,1980; 302: 139 – Barnett et al. in a case control study reported 40% incidence of MVP among young persons with stroke. (OR 9, $p<0.001$)
- Ricci, S. Neurol Sci. 2003;24:S13-S14 ‘uncomplicated MVP should no longer be considered a cause for brain embolism’

MVP and Stroke

TABLE 2. Incidence of INEs in Residents Olmsted County (Minn) With MVP in Sinus Rhythm at Diagnosis

	Observed Rates in MVP		Comparison With Community INE Rates*	
	5-Year Rate	10-Year Rate	RR (95% CI)	*P*
Life time risk				
Overall	3±0.7	7±1	2.2 (1.5–3.2)	<0.001
<50 y of age	0	0.4±0.4	1.7 (0.4, 9.5)	0.6
≥50 y of age	7±2	16±3	2.3 (1.5, 3.3)	<0.001
No AFib in follow-up	2±1	4±1	1.7 (1.04, 2.6)	0.02
AFib in follow-up	16±5	41±9	5.9 (3.4, 9.5)	<0.001
Thickened leaflets	4±1	7±2	3.5 (2.2, 5.3)	<0.001
Nonthickened leaflets	2±1	6±2	1.1 (0.5, 2.2)	0.7

(*Stroke*. 2003;34:1339-1345.)

MVP and Stroke

- Not as common as previously thought, but still important, newer diagnostic criteria
- Risk of stroke based on community based studies is <1% per year
- Risk is higher in
  - age > 50
  - Development of AF
  - Thickened leaflets
  - Significant MR
  - Cardiac surgery

MVP and Stroke Treatment

- There are no data
- Low risk groups including age<50, no AF, no valve thickening, no MR probably need only observation

Class I

1. **Aspirin therapy (75 to 325 mg per day) is recommended for symptomatic patients with MVP who experience cerebral transient ischemic attacks.** ***(Level of Evidence: C)***

2. **In patients with MVP and atrial fibrillation, warfarin therapy is recommended for patients aged greater than 65 or those with hypertension, MR murmur, or a history of heart failure.** ***(Level of Evidence: C)***
3. **Aspirin therapy (75 to 325 mg per day) is recommended for patients with MVP and atrial fibrillation who are less than 65 years old and have no history of MR, hypertension, or heart failure.** ***(Level of Evidence: C)***
4. **In patients with MVP and a history of stroke, warfarin therapy is recommended for patients with MR, atrial fibrillation, or left atrial thrombus.** ***(Level of Evidence: C)***

Recommendations for Aspirin and Oral Anticoagulants in Mitral Valve Prolapse

Indication	*Class*
1. Aspirin therapy for cerebral transient ischemic attacks.	I
2. Warfarin therapy for patients aged ≥65 years, in atrial fibrillation with hypertension, MR murmur, or history of heart failure.	I
3. Aspirin therapy for patients aged <65 years in atrial fibrillation with no history of MR, hypertension, or heart failure.	I
4. Warfarin therapy for poststroke patients.	I
5. Warfarin therapy for transient ischemic attacks despite aspirin therapy.	IIa
6. Aspirin therapy for poststroke patients with contraindications to anticoagulants.	IIa
7. Aspirin therapy for patients in sinus rhythm with echocardiographic evidence of high-risk MVP.	IIb

ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease - Circulation-1998

PFO and Stroke

Prevalence:

- This is a common finding in the general population: autopsy series report an overall prevalence ranging from 17% to 27% while echocardiographic studies demonstrate a prevalence ranging from 3.2% to 18%.
- An ASA is found in combination with a PFO in up to 70% of cases and its incidence has been estimated to be between 1% and 8% in an unselected population.
- Among patients under 55 years of age, as many as 40% of strokes are found to be cryptogenic, with no identified etiology.

CME

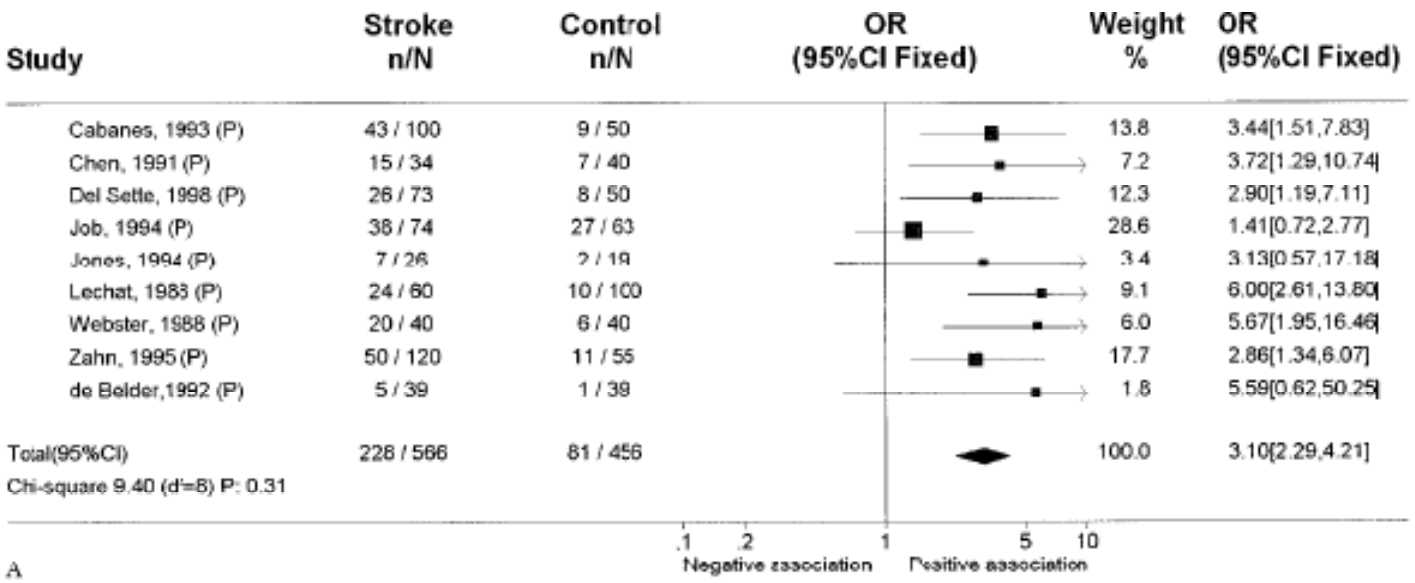
Interatrial septal abnormalities and stroke

A meta-analysis of case-control studies

J.R. Overell, MRCP; I. Bone, FRCP; and K.R. Lees, MD, FRCP

Article abstract—*Objective:* To examine the association between patent foramen ovale (PFO) and atrial septal aneurysm (ASA) and stroke. *Method:* Data from case-control studies that examined the relative frequency of PFO, ASA, or both, in all patients with ischemic stroke, cryptogenic stroke, and known stroke cause as well as control subjects were included. Trials were categorized by age, clinical comparison, and abnormality. Combined OR were calculated using fixed effect (FE) and random effect (RE) methods. *Results:* Comparing patients with ischemic stroke with control subjects using RE, OR for all ages was 1.83 (95% CI, 1.25 to 2.66) for PFO (15 studies), 2.35 (95% CI, 1.46 to 3.77) for ASA (nine studies), and 4.96 (95% CI, 2.37 to 10.39) for PFO plus ASA (four studies). Homogeneous results were found within the group younger than age 55: using FE, OR was 3.10 (95% CI, 2.29 to 4.21) for PFO, 6.14 (95% CI, 2.47 to 15.22) for ASA, and 15.59 (95% CI, 2.83 to 85.87) for PFO plus ASA. For patients older than age 55, using FE, OR was 1.27 (95% CI, 0.80 to 2.01) for PFO, 3.43 (95% CI, 1.89 to 6.22) for ASA, and 5.09 (95% CI, 1.25 to 20.74) for PFO plus ASA. Comparing cryptogenic stroke with known stroke cause, heterogeneous results were derived from total group examination using RE: OR was 3.16 (95% CI, 2.30 to 4.35) for PFO (22 studies), 3.65 (95% CI, 1.34 to 9.97) for ASA (five studies), and 23.26 (95% CI, 5.24 to 103.20) for PFO plus ASA (two studies). In patients younger than age 55, using FE the OR was 6.00 (95% CI, 3.72 to 9.68) for PFO; only one study examined ASA or PFO plus ASA. In patients aged 55 years or older, three studies produced heterogeneous results for PFO: using RE, OR was 2.26 (95% CI, 0.96 to 5.31); no data were available on ASA prevalence. *Conclusions:* PFO and ASA are significantly associated with ischemic stroke in patients younger than 55 years. Further studies are needed to establish whether an association exists between PFO and ischemic stroke in those older than 55.

NEUROLOGY 2000;55:1172–1179



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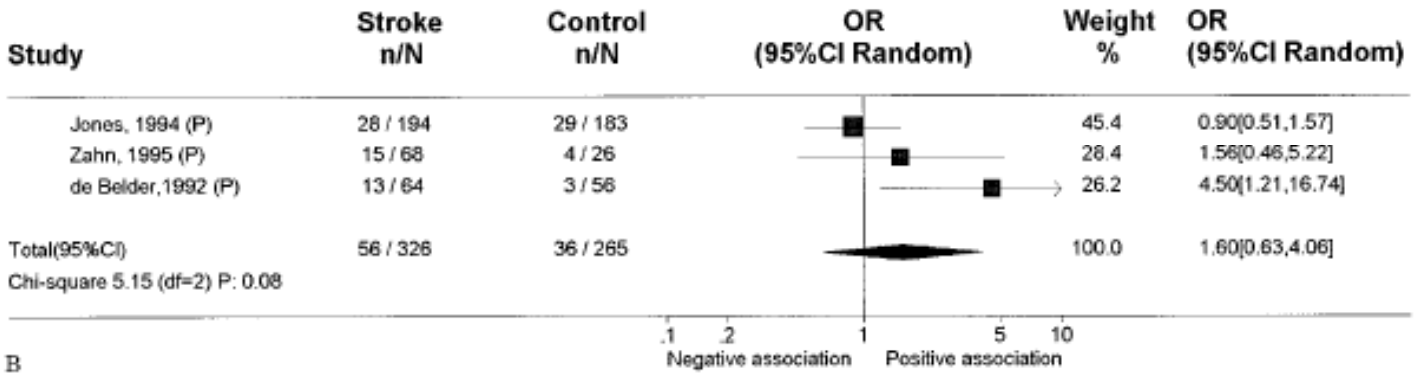
AGE < 55



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AGE > 55

Mechanisms of Stroke

- Paradoxical Embolism
- Associated DVT
- Hypercoagulable states
- AF (?)
- Associated Atrial Septal aneurysm seems to increase risk

RECURRENT CEREBROVASCULAR EVENTS ASSOCIATED WITH PATENT FORAMEN OVALE, ATRIAL SEPTAL ANEURYSM, OR BOTH

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ABSTRACT

Background Patent foramen ovale and atrial septal aneurysm have been identified as potential risk factors for stroke, but information about their effect on the risk of recurrent stroke is limited. We studied the risks of recurrent cerebrovascular events associated with these cardiac abnormalities.

Methods A total of 581 patients (age, 18 to 55 years) who had had an ischemic stroke of unknown origin within the preceding three months were consecutively enrolled at 30 neurology departments. All patients received aspirin (300 mg per day) for secondary prevention.

Results After four years, the risk of recurrent stroke was 2.3 percent (95 percent confidence interval, 0.3 to 4.3 percent) among the patients with patent foramen ovale alone, 15.2 percent (95 percent confidence interval, 1.8 to 28.6 percent) among the patients with both patent foramen ovale and atrial septal aneurysm, and 4.2 percent (95 percent confidence interval, 1.8 to 6.6 percent) among the patients with neither of these cardiac abnormalities. There were no recurrences among the patients with an atrial septal aneurysm alone. The presence of both cardiac abnormalities was a significant predictor of an increased risk of recurrent stroke (hazard ratio for the comparison with the absence of these abnormalities, 4.17; 95 percent confidence interval, 1.47 to 11.84), whereas isolated patent foramen ovale, whether small or large, was not.

Conclusions Patients with both patent foramen ovale and atrial septal aneurysm who have had a stroke constitute a subgroup at substantial risk for recurrent stroke, and preventive strategies other than aspirin should be considered. (N Engl J Med 2001; 345:1740-6.)

ability in the diagnosis of these septal abnormalities was usually not taken into account.

This follow-up study was designed to assess the absolute and relative risks of recurrent cerebrovascular events associated with these septal disorders in young patients with an otherwise unexplained ischemic stroke who were receiving aspirin and to identify subgroups of patients with a high risk of recurrent stroke.

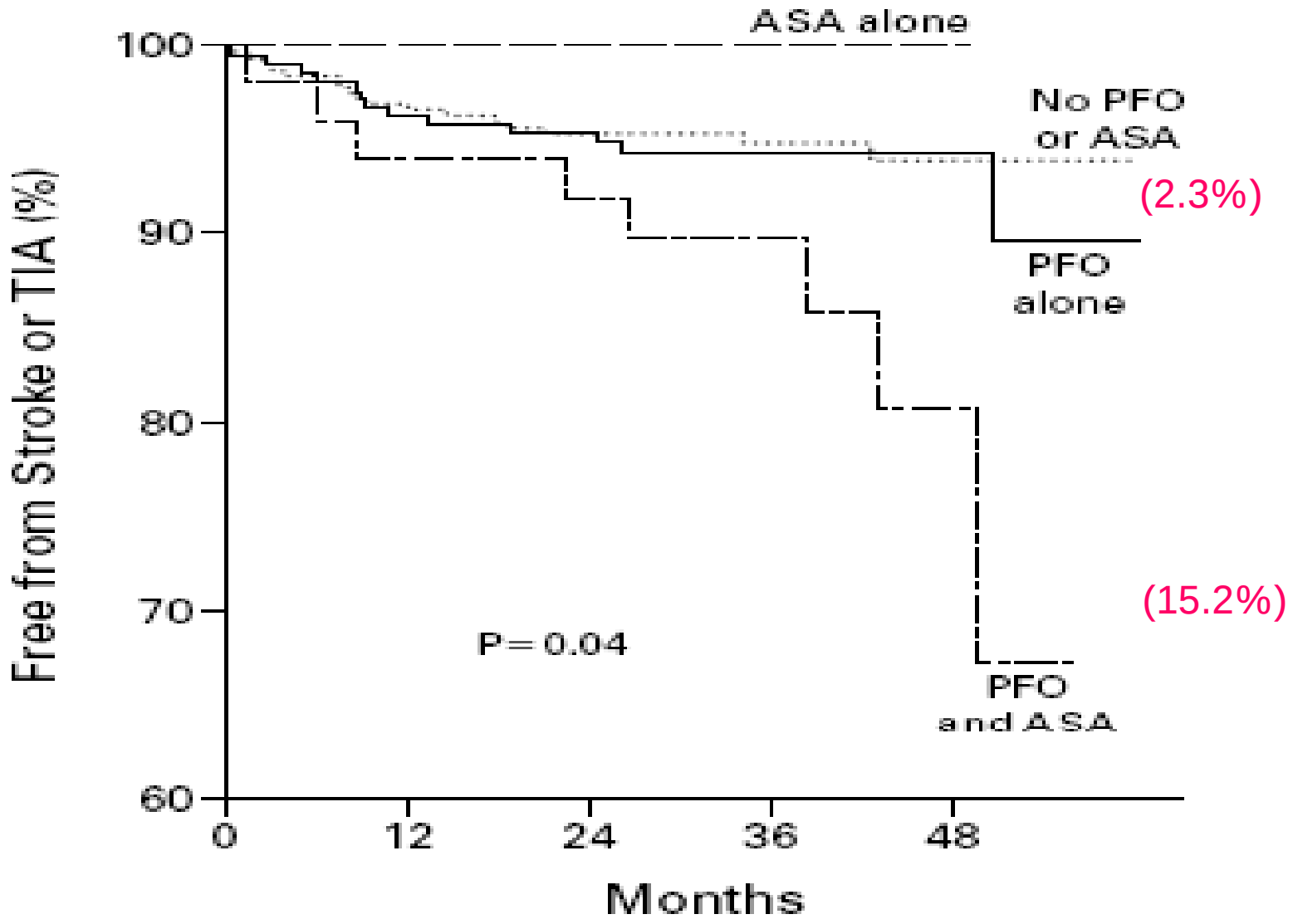
METHODS

Patients were consecutively enrolled at 30 neurology departments in Europe between May 1, 1996, and December 31, 1998, and were followed until December 31, 2000. Eligible patients were 18 to 55 years of age and had had an ischemic stroke (defined as a neurologic deficit that lasted more than 24 hours) within the preceding three months for which no definite cause had been identified after a standardized workup. Patients were excluded if the workup had been incomplete, if there was a contraindication to aspirin therapy, or if certain circumstances made follow-up impractical or compliance with treatment uncertain.

To assess the overall proportion of patients who were included in the study, 18 centers kept a registry of all patients 18 to 55 years of age with a recent (within three months) history of ischemic stroke who were seen during the enrollment period, with the reasons for exclusion from the study. The protocol conformed to the ethical guidelines of our institutions, and all participants gave written informed consent.

Data Collection

Risk factors for stroke, past vascular events, neurologic features, and the severity of stroke[15] were systematically recorded. In addition to cerebral computed tomography (in 535 patients) or magnetic resonance imaging (in 428), all patients had a standardized workup to rule out definite causes of stroke. The workup comprised routine blood tests and a coagulation study (including tests for protein S, protein C, antithrombin III, and antiphospholipid antibodies), 12-lead electrocardiography and echocardiography, and at least one of the following vascular studies (within one month after the onset of stroke): catheter angiography (in 360 patients)



NEJM 2001;345:1740

Practice Parameter: Risk of Recurrent Stroke and Secondary Stroke Prevention in Patients With Interatrial Septal Abnormalities (An Evidence-Based Review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

Neurology 2004

Recommendations

- Among patients with a cryptogenic stroke and atrial septal abnormalities, there is insufficient evidence to determine the superiority of aspirin or warfarin for prevention of recurrent stroke or death (**Level U**), but the risks of minor bleeding are possibly greater with warfarin (**Level C**).
- There is insufficient evidence regarding the effectiveness of either surgical or percutaneous closure of PFO (**Level U).**

My Approach to patient <55 with cryptogenic stroke and PFO

- Carefully evaluate pt for cause of the stroke
- Just because pt has a PFO does not mean it the culprit
- Younger pt, presence of DVT, cough or valsalva manuver , hypercoagulable state
- Discuss the options with the patient and lay out the uncertainties

AMI and stroke

Ischemic

- Embolism from Ventricular mural thrombus
- Low Flow infarcts-hypotension
- Instrumentation of coronary/aorta
- AF and embolism from L atrium

Hemorrhagic

- Use of thrombolytics
- Use of anticoagulants/antithrombotics

AMI and stroke

Rarer causes

GCA affecting coronary and carotids

Infective Endocarditis

Dissection of Aorta

Stroke in patients with heart failure and reduced left ventricular ejection fraction

P.M. Pullicino, MD, PhD; J.L. Halperin, MD; and J.L.P. Thompson, PhD

NEUROLOGY 2000;54:288–294

Table 1 Rates of stroke in heart failure treatment studies

Study	NYHA class (median)	EF (%)	Stroke rate/y (%)	Antithrombotics (%)	Afib (%)
SOLVD[12]	1.7	27	1.3	63	0
SAVE[14]	1	31	1.5	87	10
V-Heft I[37]	2 or 3	30	2.0	37	16
V-Heft II[37]	2 or 3	29	1.9	68	13
PROMISE[38]	3.4	21	3.5	81	NA
Katz et al.[24]	2.5	27	1.7	49	13
Cioffi et al.[39]	2.7	23	2.0	67	16
CONSENSUS[40]	4.0	NA	2.4	26	42

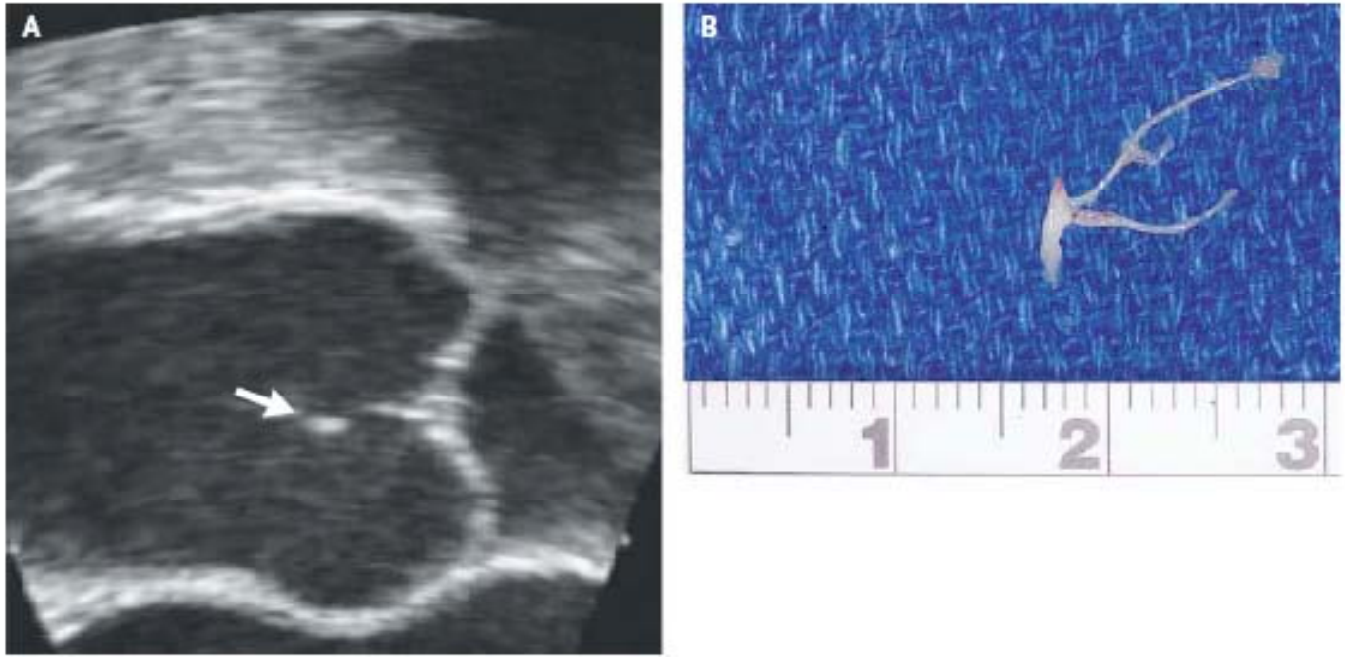
-probably underestimated
-87% pts were on warfarin or asa
-Stroke was not primary outcome event

-Sacco et al. 45% stroke recurrence in 5 years in CHF pts (NOMASS)

Table 3 *Main features of the WARCEF and WATCH studies*

Feature	WATCH	WARCEF
Blinding	Aspirin and clopidogrel blinded; warfarin unblinded	Blinded
Study arms	3 (warfarin, aspirin, clopidogrel)	2 (warfarin, aspirin)
Target INR	2.5–3.0	2.5–3.0
NYHA class for entry	II, III, or IV	I, II, or III
Entry ejection fraction	≤30%	≤30%
Echo entry criteria	LV end diastolic dimension ≥6 cm (men) or ≥5.6 cm (women) and fractional shortening <22%	Wall motion index ≤2
Primary endpoint	Death, stroke, and myocardial infarction	All-cause mortality and stroke
Study duration	5-y with 3-y enrollment	5-y with 3-y enrollment
Sample size	4,500 patients	2,860 patients

Giant Lambl's Excrescences



NEJM 2003-349:25 Images in medicine

PROGNOSIS

TABLE 2. Kaplan-Meier Estimates of Probabilities of Recurrent Stroke After First Ischemic Stroke for Common Ischemic Stroke Subtypes, 1985–1989

Time After First Stroke	Percent With Recurrent Stroke (95% CI) Among Each Ischemic Stroke Subtype			
	Atherosclerosis With Stenosis	Cardioembolic	Lacunar	Ischemic Stroke of Uncertain Cause
7 d	8.5 (2.0–14.9)	2.4 (0.0–5.2)	1.4 (0.0–4.1)	1.9 (0.0–4.1)
30 d	18.5 (9.4–27.5)	5.3 (1.2–9.6)	1.4 (0.0–4.1)	3.3 (0.4–6.2)
90 d	21.4 (11.8–31.0)	8.6 (3.2–14.2)	1.4 (0.0–4.1)	4.8 (1.3–8.2)
6 mo	22.9 (13.0–32.8)	9.9 (4.0–15.8)	5.7 (0.3–11.1)	9.3 (4.4–14.1)
1 y	24.4 (14.3–34.5)	13.7 (6.6–21.0)	7.1 (1.1–13.2)	13.2 (7.5–18.9)
2 y	29.3 (18.4–40.1)	16.8 (8.8–25.1)	11.6 (4.0–19.2)	20.6 (13.6–27.7)
5 y	40.2 (27.9–55.0)	31.7 (18.2–47.3)	24.8 (14.1–39.3)	33.2 (24.2–42.3)

Thirty-day recurrence rates were significantly different among subtypes (log rank, $P<0.0001$) but long-term recurrence rates were not (log rank, $P=0.12$).

Petty et al. Stroke 2000, 31:1062

PROGNOSIS

Stroke **May 2000**

TABLE 4. Kaplan-Meier Estimates of Probabilities of Death After First Ischemic Stroke for Common Ischemic Stroke Subtypes, 1985–1989

	% Dead (95% CI) Among Each Ischemic Stroke Subtype			
Time after First Stroke	Atherosclerosis With Stenosis	Cardioembolic	Lacunar	Ischemic Stroke of Uncertain Cause
7 d	4.1 (0.0–8.5)	15.2 (9.0–21.3)	0.0 (0.0–1.0)	7.3 (3.3–11.3)
30 d	8.1 (1.9–14.3)	30.3 (22.5–38.1)	1.4 (0.0–4.1)	14.0 (8.7–19.3)
90 d	8.1 (1.9–14.3)	37.9 (29.6–46.2)	2.8 (0.0–6.6)	17.7 (11.8–23.5)
6 mo	8.1 (1.9–14.3)	40.9 (32.5–49.3)	2.8 (0.0–6.6)	22.6 (16.2–29.0)
1 y	10.8 (3.7–17.9)	53.0 (44.5–61.5)	6.9 (1.1–12.8)	25.6 (18.9–32.3)
2 y	18.9 (10.0–27.8)	61.4 (53.1–69.7)	12.5 (4.9–20.1)	32.3 (25.2–39.5)
5 y	32.2 (21.1–43.8)	80.4 (73.1–88.1)	35.1 (23.6–47.6)	48.6 (40.5–56.8)

Both 30-day and long-term death rates were significantly different among subtypes (log rank, $P<0.0001$).

Ximelagatran vs Warfarin for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation

A Randomized Trial

SPORTIF Executive Steering Committee for the SPORTIF V Investigators*

Context In patients with nonvalvular atrial fibrillation, warfarin prevents ischemic stroke, but dose adjustment, coagulation monitoring, and bleeding limit its use.

Objective To compare the efficacy of the oral direct thrombin inhibitor ximelaga-

JAMA, February 9, 2005—Vol 293, No. 6 (Reprinted)

-Ximelagatran is a direct thrombin inhibitor
-No need for monitoring (INR)
-Was shown to be as effective as Warfarin in AF stroke prevention

BUT

6% risk of liver failure, hence not FDA approved

What is in the pipeline?

- Rivaroxaban- oral Xa inhibitor compared to warfarin in AF pts (ROCKET-AF)

Thank you for your attention!