

# Outcome of patients with cryptogenic stroke and patent foramen ovale

K Nedeltchev, M Arnold, A Wahl, M Sturzenegger, E E Vella, S Windecker, B Meier, H P Mattle

*J Neurol Neurosurg Psychiatry* 2002;**72**:347–350

See end of article for authors' affiliations

Correspondence to: Dr H P Mattle, Department of Neurology, University of Bern, Inselspital, CH-3010 Bern, Switzerland; heinrich.mattle@insel.ch

Received 16 June 2001  
In revised form  
12 October 2001  
Accepted  
2 November 2001

The cause of ischaemic stroke in young patients is often not found despite systematic investigations. Such strokes are classified as cryptogenic. In patients with cryptogenic strokes patent foramen ovale (PFO) can be detected in more than 50%, whereas its prevalence in the general population is at least 25%.<sup>1–3</sup> Therefore, PFO is likely associated with cryptogenic stroke. The presumed mechanism is paradoxical embolism of venous thrombotic material across the atrial right to left shunt. A thrombus crossing the PFO and subsequently embolizing to the brain has been rarely detected.<sup>4,5</sup> However, because direct evidence for paradoxical embolisation is rare in the individual clinical situation the potential role of the PFO in stroke is still a matter of debate. Earlier studies have suggested that a patent foramen ovale is an incidental finding in patients with cryptogenic strokes and does not represent a risk factor for cerebral ischaemia.<sup>6,7</sup> On the other hand, later studies and a meta-analysis support PFO as a risk factor for stroke, and more recent investigations also found a strong association between the morphological characteristics of the PFO and the risk of embolic cerebrovascular events.<sup>8–10</sup> The coincidence of an atrial septal aneurysm (ASA) seems to increase the risk of brain infarcts further.<sup>11–13</sup>

Which patient with PFO is at risk of cerebral embolism, the recurrence rates after initial infarction, and the optimal prophylactic strategy have been the objectives of several studies. Controlled trials on therapy and secondary prevention in patients with PFO and cryptogenic stroke have not been performed yet. Well conducted observational studies on large series could therefore provide valuable information on the natural history of PFO and stroke, elucidate the relevance of the risk factors for stroke recurrence, and allow a better estimate of the risks associated with specific medical, endovascular, and surgical preventive measures.<sup>14</sup>

**Objectives.** The aim was to estimate the recurrence rate and to define subgroups at increased risk for recurrent cerebral ischaemia in patients with patent foramen ovale (PFO) and so called cryptogenic stroke due to paradoxical embolism.

**Methods.** Patent foramen ovale was diagnosed in 318 patients with otherwise unexplained ischaemic stroke or transient ischaemic attack (TIA). One hundred and fifty nine were treated medically (oral anti-coagulation 79, platelet inhibitors 80) and represent the study population. The remaining 159 patients underwent endovascular or surgical closure of the PFO and are not part of this study.

**Results.** Mean age was 50.7 (SD 13.5) years. The event leading to the diagnosis of PFO was a TIA in 38 patients (23.9%), an ischaemic stroke in 119 (74.8%), and an amaurosis fugax in two patients (1.3%). Forty four patients (27.7%) had experienced multiple cerebrovascular ischaemic events before the diagnosis of the PFO. During mean follow up of 29 (SD 23) months 21 patients (13.4%) had a recurrent cerebrovascular event (seven strokes and 14 TIAs). The average annual rate of recurrent strokes was 1.8% and that of recurrent strokes or TIAs was 5.5%. When patients with PFO with multiple cerebrovascular events before the diagnosis of the PFO were analyzed separately, the average annual rates of recurrent cerebral ischaemia were 3.6% for recurrent strokes and 9.9% for recurrent strokes or TIAs. These rates were significantly higher than in patients with first ever stroke or TIA ( $p=0.02$ ).

**Conclusions.** The study confirms a risk of stroke recurrence that is similar to the rates of previously published series of patients with PFO and cryptogenic strokes. Patients with more than one previous event were at increased risk of recurrent cerebral ischaemia.

For these reasons we analyzed the recurrence rate in patients with PFO and cryptogenic stroke. Using survival analyses, we aimed to define subgroups at increased risk for recurrent cerebral embolisation and to estimate the effect of oral anticoagulant drugs, platelet inhibitors, or no antithrombotic treatment on stroke recurrence.

## PATIENTS AND METHODS

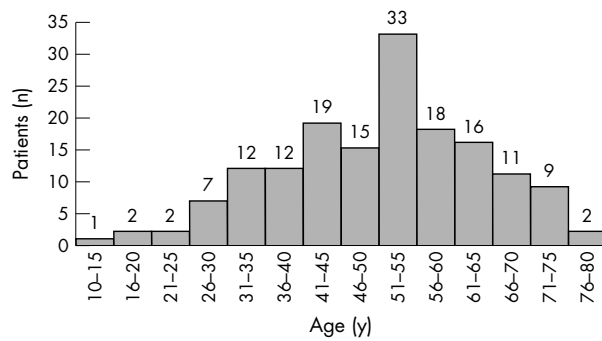
### Patients

We identified all patients with ischaemic stroke, transient ischaemic attacks (TIAs), or amaurosis fugax, who were admitted to our university based stroke centre between January 1994 and July 2000.

The diagnosis of stroke was based on a focal neurological deficit and the corresponding findings on CT or MRI.<sup>15</sup> A TIA was defined as a focal neurological deficit resolving completely within 24 hours.<sup>16</sup> Transoesophageal echocardiography (TEE) had been performed in all patients suspected of paradoxical embolism via right to left shunt. After excluding those with a concurrent aetiology for the cerebrovascular event we identified 318 patients who had a PFO and otherwise unexplained ischaemic stroke or TIA.

The patients were offered several treatment options to prevent a recurrent stroke: endovascular or surgical closure of the patent foramen ovale, or long term antithrombotic treatment.

**Abbreviations:** PFO, patent foramen ovale; TIA, transient ischaemic attack; ASA, atrial septal aneurysm; TEE, transoesophageal echocardiography; BMI, body mass index; INR, international normalised ratio; PICSS, PFO in cryptogenic stroke study; WARSS, warfarin/aspirin recurrent stroke study



**Figure 1** Distribution of patients by age.

One hundred and fifty nine decided to have endovascular or surgical closure of their PFO and 159 patients chose medical treatment (vitamin K antagonists: n=79, platelet inhibitors: n=80). The patients with medical treatment represent the population of our study. Patients after endovascular closure have been published in part previously.<sup>17</sup>

### Transoesophageal echocardiographic criteria for PFO and ASA

The diagnosis of PFO and ASA was based on contrast transoesophageal echocardiography. The right to left shunt was judged to be minimal if there were less than five bubbles, moderate if there were six to 20 bubbles, and severe if there were more than 20 bubbles detected in the left atrium.<sup>18</sup> Atrial septum aneurysm was diagnosed when the interatrial septum was abnormally redundant with an excursion of more than 10 mm into the right or left atrium.<sup>19</sup>

### Vascular risk factors

The following factors considered to increase the risk for stroke or TIA were assessed: hypertension, defined as systolic blood pressure greater than 160 mm Hg, diastolic blood pressure greater than 95 mm Hg, or both; diabetes mellitus defined as symptoms of diabetes plus random blood glucose concentration greater than 11 mmol/l, or fasting blood glucose greater than 7 mmol/l; cigarette smoking; hypercholesterolaemia defined as a total venous plasma cholesterol concentration greater than 5 mmol/l; obesity defined as a body mass index (BMI) greater than 25 kg/m<sup>2</sup>; coronary artery disease, and positive personal and familial history for cerebrovascular events.

### Follow up

Follow up data were obtained retrospectively by reviewing the medical records of all patients and the relevant information concerning recurrent events and treatments. Thereafter, the family physicians of all patients and afterwards the patients themselves were contacted. In order not to miss any recurrent event a standardised telephone questionnaire was used. Follow up data could not be obtained from two patients

because of address changes. Transient ischaemic attacks (confirmed by a neurologist), systemic embolism, ischaemic stroke (confirmed by CT), and death were considered retrospectively as end points of follow up. Twenty patients, who had been on antithrombotic treatment for a prolonged period and then decided for some reason to have endovascular or surgical closure of the PFO, were included in the analysis for the time they had been treated medically.

### Statistics

Continuous variables are expressed as mean (SD). Nominal variables were compared by  $\chi^2$  test for contingency tables. Statistical significance was assumed at a value of  $p < 0.05$ . Actuarial analysis of freedom from recurrent cerebral ischaemic events was calculated according to the Kaplan-Meier method. Average annual event rates were calculated according to the formula  $1 - (1 - P)^{1/n}$ , where P equals the cumulative event rate at n years of follow up.<sup>20</sup> The log rank test was used for univariate analysis of independent variables (age, sex, obesity, coexistence of an ASA, size of the right to left shunt, positive personal history for cerebrovascular ischaemic events, and type of medical treatment) on the rate of recurrence. All analyses were performed with SPSS 10 for MacIntosh statistical software, copyright © 2001, SPSS Inc.

### RESULTS

The study population consisted of 93 men and 66 women. Their mean age was 50.7 (13.5) years (range 15 to 77 years). One hundred and twenty one patients (76.1%) were 60 years old or younger at the time when they experienced the ischaemic event that led to the diagnosis of a PFO (fig 1).

This event was a transient ischaemic attack in 38 patients (23.9%), an ischaemic stroke in 119 (74.8%), and an amaurosis fugax in two patients (1.3%). In 90 patients (56.6%) it occurred in the carotid territory and in 69 patients (43.4%) in the vertebrobasilar territory. Forty four patients (27.7%) had experienced more than one cerebrovascular ischaemic event before the diagnosis of the patent foramen ovale.

The vascular risk factors that were considered to increase the risk for stroke or TIA are summarised in table 1. Hypertension, diabetes mellitus, cigarette smoking, hypercholesterolaemia, and familial history for stroke occurred with similar frequencies in patients with one and in those with multiple previous cerebrovascular events. Obesity was more frequent in the group with more than one prior event ( $p = 0.02$ ). There were five patients with coronary artery disease in the group with one cerebral ischaemic event before diagnosis of the PFO. Fifty of the 159 patients (31.4%) did not show any vascular risk factors.

The right to left shunt was minimal in 19 patients (11.9%), moderate in 44 (27.7%), and severe in 96 (60.4%) patients. Thirty three patients (20.7%) had an ASA in addition to the PFO.

Antithrombotic treatment such as anticoagulation, aspirin, or clopidogrel was given according to the judgement of the attending physician after the event leading to the diagnosis of

**Table 1** Vascular risk factors in patients with one and in patients with multiple ischaemic events before diagnosis of PFO

Risk factor	All patients (n=159)	Patients with one ischaemic event (n=115)	Patients with multiple ischaemic events (n=44)	p Value
Hypertension	52 (32.7)	37 (32.2)	15 (34.1)	0.79
Diabetes mellitus	15 (9.4)	10 (8.7)	5 (11.4)	0.55
Smoking	52 (32.7)	36 (31.3)	16 (36.4)	0.59
Hypercholesterolaemia	48 (30.2)	33 (28.7)	15 (34.1)	0.49
Positive familial history	42 (26.4)	30 (26.1)	12 (27.3)	0.84
Obesity	82 (51.6)	52 (45.2)	30 (68.2)	0.02

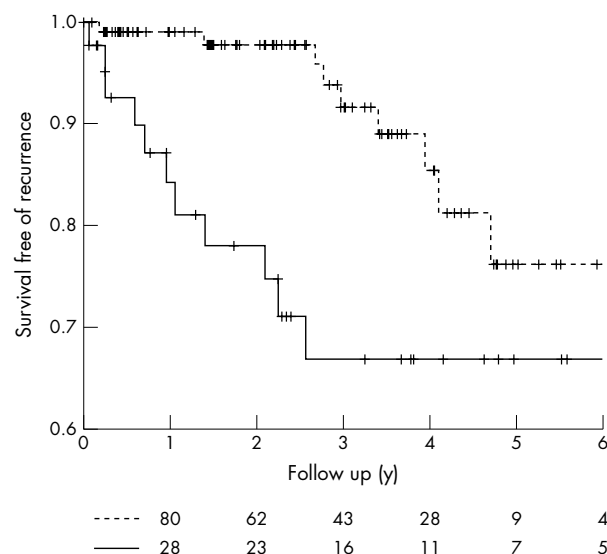
Values are n (%).

**Table 2** Average annual recurrent cerebral ischaemias in patients with one and in patients with multiple ischaemic events before diagnosis of PFO

Patients	Number of recurrent events	Average annual recurrent events	
		Strokes	Strokes and/or TIAs
All (n=157):			
Strokes	7		
TIAs	14	1.8%	5.5%
With one ischaemic event (n=113):			
Strokes	3		
TIAs	7	1.1%	3.7%
With multiple ischaemic events (n=44):			
Strokes	4	3.6%	
TIAs	7		9.9%

PFO. Seventy nine patients received oral anticoagulant drugs. The target international normalised ratio (INR) was 2.0–3.0. In 26 of them the oral anticoagulation was replaced by antiplatelet drugs after 12 (SD 11) months. Platelet inhibitors were given to 80 patients (77 patients were treated with aspirin at a mean dosage of 233 (SD 83) mg/day, three patients received clopidogrel at a dosage of 75 mg/day). Nine patients were non-compliant and discontinued antithrombotic therapy. No bleeding complications were seen either in patients treated with oral anticoagulants or in those with platelet inhibitors.

Mean follow up was 29 (23) months. During this period 21 patients (13.4%) had a recurrent cerebrovascular event, seven strokes and 14 TIAs. Six strokes occurred in patients who were taking aspirin and one stroke in a patient with anticoagulant drugs. Five TIAs occurred in the aspirin group, six in the oral anticoagulant group, and three in patients who had discontinued the antithrombotic therapy.  $\chi^2$  Tests did not show an association between the treatment regimen and the risk for recurrence ( $p=0.99$ ). However, six of the seven strokes occurred in patients, who were treated with aspirin. Despite the absence of clear statistical evidence, there was a trend indicating an increased risk for stroke recurrence in this group ( $p=0.053$ , two tailed Fisher's exact test).



**Figure 2** Kaplan-Meier curve of survival free of recurrence. The x axis indicates the time since the ischaemic event leading to the diagnosis of the PFO. The y axis indicates the proportion of patients surviving free of recurrence. The dotted line represents the patients with one ischaemic event and the continuous line shows the patients with multiple ischaemic events before diagnosis of PFO.

Neither the severity of the right to left shunt, nor the coexistence of an ASA in addition to the PFO were associated with an increased risk for stroke recurrence.

The overall cumulative estimate of risk of stroke or TIA recurrence, at 2 years of follow up, in the whole cohort of patients with PFO was 9.2% (95% CI 6.5% to 11.9%). When only strokes were considered, the cumulative risk of recurrence was 4.5% (95% CI 2.5% to 6.5%), at 2 years of follow up.

The average annual rate of stroke recurrence was 1.8% and that of both recurrent strokes or TIAs was 5.5% (table 2). When patients with multiple ischaemic events before diagnosis of PFO were analyzed separately, the average annual rate of recurrent strokes was 3.6% and the rate of recurrent strokes or TIAs was 9.9%. The log rank test for survival data showed a significantly higher risk for recurrent events in this group than in patients without ischaemic events before the qualifying event ( $p=0.02$ ). However, obesity was more common in the group with multiple ischaemic events.

When patients without obesity were analyzed separately, the risk for recurrent events in the subgroup with multiple ischaemic events before diagnosis of PFO was still significantly higher than in the subgroup with first ever stroke or TIA ( $p=0.02$ ).

Figure 2 shows the Kaplan-Meier survival curves of patients with one event and those with multiple cerebral ischaemic events before diagnosis of PFO.

## DISCUSSION

Previous studies have shown an association between PFO and cryptogenic stroke. However, optimal secondary stroke prevention for such patients is not known because randomised trials have not been performed to date.

There are three major studies that assessed the rate of recurrent cerebrovascular events during 2 to 3 years of antithrombotic treatment (table 3). Bogousslavsky *et al* reported 3.8% of recurrent, non-fatal cerebral ischaemias (stroke and/or TIA)/year during 3 years of prospective follow up in 140 patients.<sup>21</sup> Mas *et al* detected 3.4% annual recurrent events (strokes and/or TIAs) during 2 years of retrospective follow up in 132 patients. A subgroup of 38 patients with an ASA in addition to the PFO showed an increased rate of 9.0% strokes and 22% of TIAs and/or strokes after 2 years.<sup>13</sup> De Castro *et al* reported 7.2% strokes or TIAs at 3 years of prospective follow up in 74 patients.<sup>10</sup> Our 157 symptomatic patients with PFO presented 9.2% recurrent strokes or TIAs and 4.5% strokes at 2 years of retrospective follow up. The average annual rate was 5.5% for strokes and TIAs and 1.8% for strokes only. The rates we found tended to be slightly higher than in the other studies. One reason might be the age of the patients, which exerts an independent effect on the relation between interatrial septal abnormalities and strokes.<sup>8</sup> Bogousslavsky *et al* and Mas *et al* excluded patients older than 60 years whereas

**Table 3** Average annual recurrent cerebral ischemias in patients with PFO. A comparison with other studies

Source (1st author)	Number of patients	Stroke	Stroke and/or TIA
Mas <sup>12</sup>	132	1.2%	3.4%
Bogousslavsky <sup>20</sup>	140	2.4%	3.8%
De Castro <sup>9</sup>	74		2.4%*
Present study	157	1.8%	5.5%

\*In the original article the overall cumulative estimate of risk of cerebrovascular event recurrence is given. We derived the average annual event rate from the overall cumulative estimate of risk of stroke or TIA recurrence, at 3 years of follow up, according to the formula  $1-(1-P)^{1/n}$ , where P equals the cumulative event rate at n years of follow up.

24% of our patients were older than that. However, there was no association between age and stroke recurrence in our series.

A relevant finding of the present study is that patients with a positive personal history of stroke or TIA before the event leading to the detection of the PFO had a higher rate of recurrent cerebral ischaemia (table 2 and fig 2). Obesity was more frequent in the group with multiple ischaemic events before diagnosis of PFO. However, the higher recurrence rate was unlikely to be associated with body weight. When patients with BMI less than 25 kg/m<sup>2</sup> were analyzed separately, the risk of recurrence remained significantly higher in patients with multiple ischaemic events than in those with one stroke or TIA before diagnosis of PFO. Mas *et al* and De Castro *et al* excluded patients with multiple ischaemic events from their studies and Bogousslavsky *et al* tended to treat such patients surgically.

Several authors have found that atrial septal hypermobility and ASA combined with PFO and also the size of the PFO are independent risk factors for stroke.<sup>9, 22, 23</sup> Our data do not support this finding. Neither the coexistence of ASA nor the size of the right to left shunt was associated with an increased recurrence rate in our series. A possible explanation of this disagreement could be the relatively small number of only 33 patients with ASA (21%) in our series. Methodological factors might also play a major part in the proper assessment of the size of a right to left atrial shunt, with difficulties comparing the data of different studies. Grading is usually performed during provocative manoeuvres (Valsalva's manoeuvre or cough) and therefore may depend on the strain exerted by the examined patient, the delay after the beginning of contrast injection, etc. Attempts to standardise the provocative manoeuvres have been shown to improve the sensitivity of the methods used for identification of the PFO.<sup>24</sup> In addition, microbubbles are counted from a single two dimensional imaging plane that does not necessarily reflect the exact amount of all the microbubbles shunted into the left atrium. Therefore, results from grading of the right to left shunts should be interpreted with caution.

Our results do not favour any medical treatment regimen. Six strokes occurred in patients with aspirin and one in a patient with anticoagulation; however, this difference was not significant. The PFO In cryptogenic stroke study (PICSS), an ongoing substudy of the warfarin/aspirin recurrent stroke study (WARSS), is about to address this question. It compares aspirin and anticoagulation in patients with PFO and cryptogenic strokes.<sup>25</sup>

To summarise, our study confirms a risk of recurrent strokes and TIAs that is similar to the rates of previously published series of patients with PFO and cryptogenic strokes. Patients who had experienced multiple cerebrovascular events before diagnosis of PFO were at increased risk of recurrent cerebral ischaemia.

#### Authors' affiliations

**K Nedeltchev, M Arnold, M Sturzenegger, E E Vella, H P Mattle,** Department of Neurology, Inselspital, University of Bern, 3010 Bern, Switzerland

**A Wahl, S Windecker, B Meier,** Department of Cardiology

#### REFERENCES

- 1 **Lechat P, Mas JL, Lascault G, et al.** Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988;**318**:1148–52.
- 2 **Job FP, Ringelstein EB, Grafen Y, et al.** Comparison of transcranial contrast Doppler sonography and transesophageal contrast echocardiography for the detection of patent foramen ovale in young stroke patients. *Am J Cardiol* 1994;**74**:381–4.
- 3 **Hagen PT, Scholz DG, Edwards WD.** Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984;**59**:17–20.
- 4 **Falk V, Walther T, Krankenberg H, et al.** Trapped thrombus in a patent foramen ovale. *Thorac Cardiovasc Surg* 1997;**45**:90–2.
- 5 **Marazano M, Roudaut R, Cohen A, et al.** Atrial septal aneurysm. Morphological characteristics in a large population: pathological associations. A French multicenter study on 259 patients investigated by transesophageal echocardiography. *Int J Cardiol* 1995;**52**:59–65.
- 6 **Ranoux D, Cohen A, Cabanes L, et al.** Patent foramen ovale: is stroke due to paradoxical embolism? *Stroke* 1993;**24**:31–4.
- 7 **Fisher DC, Fisher EA, Budd JH, et al.** The incidence of patent foramen ovale in 1000 consecutive patients. A contrast transesophageal echocardiography study. *Chest* 1995;**107**:1504–9.
- 8 **Overall JR, Bone I, Lees KR.** Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;**55**:1172–9.
- 9 **Schuchlenz HW, Weihs W, Horner S, et al.** The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. *Am J Med* 2000;**109**:456–62.
- 10 **De Castro S, Cartoni D, Fiorelli M, et al.** Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* 2000;**31**:2407–13.
- 11 **Pearson AC, Nagelhout D, Castello R, et al.** Atrial septal aneurysm and stroke: a transesophageal echocardiographic study. *J Am Coll Cardiol* 1991;**18**:1223–9.
- 12 **Hanna JP, Sun JP, Furlan AJ, et al.** Patent foramen ovale and brain infarct. Echocardiographic predictors, recurrence, and prevention. *Stroke* 1994;**25**:782–6.
- 13 **Mas JL, Zuber M.** Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. *Am Heart J* 1995;**130**:1083–8.
- 14 **Kasner SE, Chiu D, Grotta J.** Stroke and PFO: a role for surgery? *Neurology Network Commentary* 1997;**1**:127–31.
- 15 **Aho K, Harmsen P, Hatano S, et al.** Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ* 1980;**58**:113–30.
- 16 **Dyken ML, Conneally M, Haerer AF, et al.** Cooperative study of hospital frequency and character of transient ischemic attacks. I: background, organization and clinical survey. *JAMA* 1977;**237**:882–6.
- 17 **Windecker S, Wahl A, Chatterjee T, et al.** Percutaneous closure of patent foramen ovale in patients with paradoxical embolism. Long-term risk of recurrent thromboembolic events. *Circulation* 2000;**101**:893–8.
- 18 **Webster MW, Chancellor AM, Smith HJ, et al.** Patent foramen ovale in young stroke patients. *Lancet* 1988;ii:11–12.
- 19 **Pearson AC, Nagelhout D, Castello R, et al.** Atrial septal aneurysm and stroke: a transesophageal echocardiographic study. *J Am Coll Cardiol* 1991;**18**:1223–9.
- 20 **Burn J, Dennis M, Bamford J, et al.** Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. *Stroke* 1994;**25**:333–7.
- 21 **Bogousslavsky J, Garazi S, Jeanrenaud X, et al.** Stroke recurrence in patients with patent foramen ovale: the Lausanne study. Lausanne Stroke with Paradoxical Embolism Study Group. *Neurology* 1996;**46**:1301–5.
- 22 **Comess KA, DeRook FA, Beach KW, et al.** Transesophageal echocardiography and carotid ultrasound in patients with cerebral ischemia: prevalence of findings and recurrent stroke risk. *J Am Coll Cardiol* 1994;**23**:1598–603.
- 23 **Cabanes L, Mas JL, Cohen A, et al.** Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. *Stroke* 1993;**24**:1865–73.
- 24 **Droste DW, Silling K, Stypmann J, et al.** Contrast transcranial doppler ultrasound in the detection of right-to-left shunts: time window and threshold in microbubble numbers. *Stroke* 2000;**31**:1640–5.
- 25 **PFO in Cryptogenic Stroke Study.** PICSS. <http://cpmcnet.columbia.edu/dept/cardiology/echo/picss.html>