Patent Foramen Ovale and Atrial Septal Aneurysm in Young Adults with Ischemic Stroke

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Tiivistelmä – Referat – Abstract

Ischemic stroke in young adults with patent foramen ovale (PFO) and/or atrial septal aneurysm is underinvestigated.

Methods: We investigated 86 such patients (age 16-49 years) with long-term follow-up.

Results: Most patients recovered well, one died and 15 retired prematurely due to the index stroke. Seven patients underwent PFO closure. Few stroke recurrences occurred (4%) either on aspirin or warfarin during the 6.5 years of follow-up.

Conclusions: Our data suggest good outcome, low morbidity, and low recurrence. Finding the best secondary prevention measures requires randomized trials.

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List of Abbreviations:

PFO = patent foramen ovale

ASA = atrial septal aneurysm

CI = cerebral infarction

TTE = transthoracic echocardiography

TEE = transesophageal echocardiography

TCD = transcranial Doppler ultrasound

TOAST = Trial of Org 10172 in Acute Stroke Treatment

HUCH = Helsinki University Central Hospital

CT = computer tomography

MRA = magnetic resonance angiography

MRI = magnetic resonance imaging

mRS = modified Rankin Scale

NIHSS = National Institutes of Health Stroke Scale

GCS = Glasgow Coma Scale

TIA = transient ischemic attack

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1 Introduction

Ischemic stroke is the second leading cause of death and the most important cause for long-term disability in adults worldwide. Approximately 5-10 % appears in young patients, i.e. in those aged below 50 years at stroke onset (1). It is generally recognized that young patients have better chances for surviving a stroke than older individuals. However, stroke at young ages may have devastating and long-lasting socio-economical consequences, because the young have a long expected life span ahead and often under-aged children at their custody. Moreover, many young stroke survivors have impaired quality of life (2-4).

In the elderly, the major causes and risk factors for stroke are atherosclerosis and atrial fibrillation. Among young patients, these are, however, relatively rare findings, and the known causes form a wide spectrum, of which the most common are carotid artery dissection and cardio embolism (4-11). However, in more than one third of the cases the etiology of the stroke still remains unidentified (1,11).

Recent investigations revealed that, particularly in young patients, patent foramen ovale (PFO), with or without atrial septal aneurysm (ASA), constitutes an independent risk factor for stroke (12). PFO is detected twice more often in young patients with a cryptogenic stroke (46%) (13) than in the general population. Estimates of the prevalence of PFO originate from a remote autopsy study of 965 studied cases, in whom PFO appeared in 27.3% (14).

Causes of stroke in young adults are currently underinvestigated, and most of the knowledge to date arises from small series of patients. Only a few large series have been published (4,6-11,15-17). Long-term prognosis and its predictive variables are not well investigated. It is of particular importance to investigate the causes of and risk factors for stroke, as well as to develop models for long-term prognosis and provide these patients with the best possible secondary prevention (18).

In the present study, we review the current literature regarding PFO, ASA, and stroke risk. In addition, we aimed to investigate features of patients with first-ever ischemic stroke with PFO/ASA as their only recognized cause for stroke based on data from a large cohort of consecutive young stroke patients.

2 Review of the literature

2.1 Pathophysiology of PFO

Foramen ovale is a vestige from embryonal age, when it allows the oxygenated blood from placenta to bypass lungs from the right atrium directly to the left atrium and to systemic circulation. Normally, the foramen closes after birth due to the changing pressure circumstances in heart when the baby first starts to breath on her own, and a few weeks later the septum secundum fuses with the septum primum, and a continuous wall is formed. In many cases, however, this fusing fails to happen properly (19). In addition, PFO is relatively commonly associated with other congenital heart defects (20). Based on autopsy series of 965 patients, prevalence of PFO in the general population was estimated to be 27.3% (14). Figure 1 illustrates the structure of PFO (left) and its percutaneous closure technique (circles).

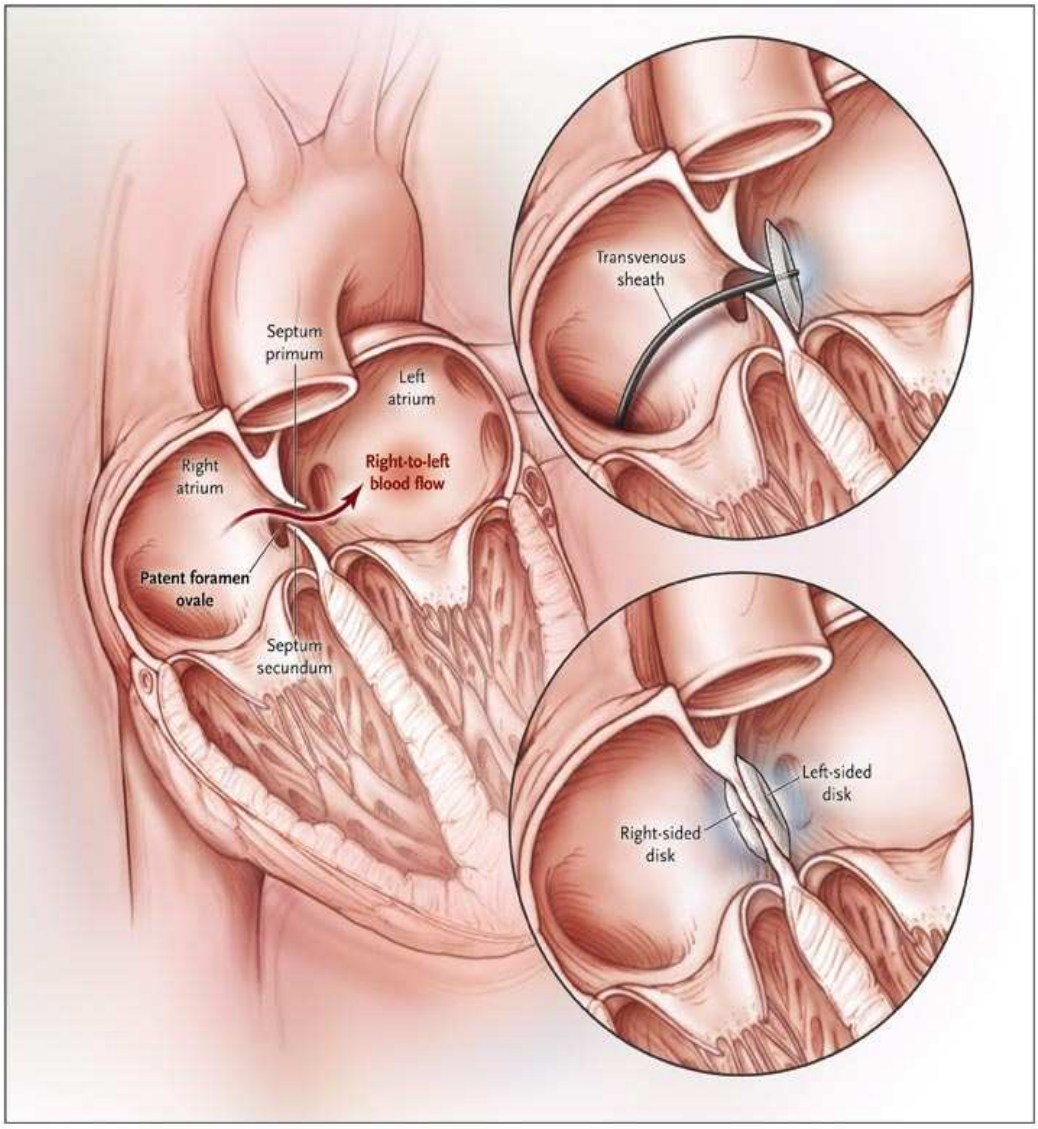

Figure 1. The structure of PFO and its percutaneous transcatheter closure (1)

2.2 Mechanisms contributing to stroke

The classical assumption of how PFO predisposes to stroke is paradoxical embolization. Bypassing the pulmonary circulation, a PFO serves as a route for venous tromboemboli to enter the systemic circulation and lodge to a cerebral artery in most cases. It is thought that in order a paradoxical embolization to occur, both venous embolism and a right-to-left shunt promoting pressure difference are required (19).

Such venous thrombi may form in deep veins spontaneously, following prolonged immobility or minor trauma (21). The shunt in the association of PFO is usually directed from left-to-right atrium due to the physiological pressure differences between the systemic and pulmonary circulation and thus between right and left atrium. The direction shifts to drive blood from right-to-left atrium when intra-thoracic pressure elevates. This could occur e.g. when making a strong physical effort, such as Valsalva maneuver, which means a situation in which the patient's intrathoranic pressure rises due to a physical effort in association with breath holding. Based on clinical experience, such circumstances appear most commonly when lifting a heavy cargo, during physical exercise, coughing, or during sexual intercourse. Pulmonary hypertension, as with massive pulmonary embolism, can also promote right-to-left shunting (1). In many cases PFO appears as a valve like structure, in where valve cusps open to the left atrium, and as such remains closed in the physiological pressure differences, but opens and allows a right-to-left shunt in circumstances in which the right atrial pressure exceeds the left atrial pressure (19).

The theory of paradoxical embolization is still controversial, however. Venous thrombosis and Valsalva-inducing activities are relatively rarely documented in these stroke patients. (22). The Stroke Prevention Assessment of Risk in Community (SPARC) study (23) even suggested that PFO is not an independent risk factor for cerebrovascular events. On the other hand, Kizer et al. (1) remark that a transient reversal of the left-to-right transseptal gradient does occur normally in early systole, and lack of detectable venous thrombosis may reflect challenges in its identification rather than genuine absence. Another suggested mechanism contributing to the elevated risk for cerebrovascular events in individuals with PFO, as well as with ASA, is its association with atrial vulnerability to arrhythmia, including fibrillation (24). Additionally, local thrombus formation within the foramen and/or the atrial septal aneurysm with later embolization is another potential mechanism (25).

2.3 Pathogenesis of ASA

ASA is present when redundant tissue in the fossa ovalis results in excessive septal wall motion during respiration, and it is usually defined as >10 to 15 mm of protuberance (19). The aneurysm may develop in patients with a raised intra-atrial pressure but most seemed associated with normal intra-atrial pressures. A particular morphology of the fossa ovalis region may predispose the septum to aneurysm formation. The prevalence of ASA in the general population is 1% based on an autopsy study and 1.9% by transthoracic echocardiography (TTE) (19,26).

One explanation for the increased risk of stroke in individuals with PFO is the high prevalence (50-90%) of other anatomical abnormalities in heart associated with PFO, such as ASA**,** prominent Eustachian valves, Chiari networks and atrial septal defect (27), which distracting the normal blood flow in the left atrium predispose embolus formation in the atrium per se (25). The risk of stroke in individuals with PFO associated with ASA has been shown to be nearly four times higher than in those without ASA (27).

In association with PFO, ASA may also facilitate the event of paradoxical embolisation by increasing the PFO diameter (28,29), or promoting left-to-right shunting by redirecting blood flow from the inferior vena cava toward the PFO (30), or both (20).

2.4. PFO detection

TEE is regarded as the golden standard in detecting interatrial cardiac abnormalities in adult patients with suspected paradoxical embolism (31), and its advance compared to the other methods is the possibility to directly detect the embolic source localized inside the heart or in the epiaortic vessels (32). Its sensitivity is 89% and specificity 100% in detecting PFO compared with autopsy diagnosis. The echocardiography can also be performed totally noninvasively by transthoracic echocardiography (TTE), but its sensitivity is only 50-60% compared to TEE. (21) Adding a contrast media improves both the sensitivity and specificity of the detection mechanism. A generally used mechanism is to infuse agitated saline to a peripheral vein in order to induce microbubbles that in the presence of PFO

would shunt directly from right to left atrium. The bubbles can be detected either in the left side of heart by TEE (contrast-enhanced TEE, c-TEE) or as microemboli in the middle or posterior cerebral artery in transcranial color Doppler ultrasound (contrast-enhaced TCD, c-TCD) (33) . Compared with TEE, TCD detects approximately 90-110% of PFOs (21,34).

In addition to methods based on ultrasound, interatrial shunt can be detected noninvasively by dye-dilution or ear oximetry methods. In the dye dilution method an intravenous indocyanine green solution (Cardiogreen®) is injected to a peripheral vein and the dilution curves are recorded from the ear by a dichromatic earpiece densitometer. PFO is considered as present if a small deflection from the baseline is seen before the main upstroke part of the dye dilution curve. The shunt gradient can also be objectively assessed at the same time. In the ear oximetry method, arterial oxygen saturation is continuously measured with a small earpiece oxymeter, and PFO is diagnosed when a characteristic transient drop in the oxygen saturation curve is seen during each cardiac cycle or after Valsalva maneuver. The sensitivity of dye dilution is 76% and specificity 100%, in ear oximetry the sensitivity is 85% and specificity 100% (35).

Within all mechanisms described, asking the patient to perform Valsalva maneuver reveales the shunt direction and size, and potential valve-like structure.

2.5 Treatment aspects

Specific treatment recommendations have been made based on patient characteristics (e.g., age, hypercoagulable state, and history of stroke) and morphologic features of the interatrial communication (e.g., size of PFO and associated atrial septal aneurysm). However, a lack of consensus regarding the optimal management strategy remains (31).

Medical prevention of recurrent stroke includes an antiplatelet agent, usually aspirin, clopidogrel, dipyridamole, or anticoagulant treatment with warfarin sodium. Warfarin has been noted superior to antiplatelet agents and comparable to surgical closure (36,37). In

addition, stroke patients with PFO usually receive lipid lowering and antihypertensive medication.

PFO can be closed surgically by thoracotomy, or percutaneously by inserting a special catheter via the femoral vein. Operative treatment can potentially permanently close the interatrial defect, eliminating the need for medical therapy. The major disadvantage of surgical closure is that it requires thoracotomy or cardiopulmonary bypass (21). Percutaneous PFO transcatheter closure (Figure 1) has been suggested to be safe and effective in preventing recurrent strokes. Several studies (31,37-43) have suggested that patients with recurrent paradoxical embolisms have better prognosis if treated with percutaneous PFO closure compared with medical therapy (44). Many studies have also shown an association between degree of shunt or size of PFO and the risk of stroke and stroke recurrence (12,28,45,46), and that is why in larger PFOs the physicians' interest in mechanical closure is higher. However, some studies have shown that the risk for recurrent stroke in patients with PFO vs. those without PFO do not differ, and thus surgical closure should not be recommended before further studies (37).

2.6 Outcome

Data on risk of recurrent stroke in patients with PFO, ASA, or both, are inconsistent. A prospective multicenter European study showed that young PFO patients treated with aspirin have only a modest risk of recurrent stroke in a follow-up period of four years. The average annual rate of subsequent stroke or death in PFO patients compared to non-PFO patients was 1.5% versus 1.8%. The risk of recurrent stroke in patients with PFO alone was 0.6% per year compared to those without PFO 1.1%. However, the patients with both PFO and ASA had a significantly higher risk of recurrent stroke at 4 years (3.8% per year). PFO shunt size was not significantly associated with the risk of recurrent cerebrovascular events (47). A meta-analysis of medically treated stroke patients with PFO also showed a low recurrence rate. The pooled absolute rate of recurrent stroke or TIA was 4.0 events for 100 person years, and for recurrent stroke alone 1.6 events for 100 person years (37). There are insufficient data to accurately estimate the relative risk of recurrent stroke associated with

ASA alone (48). Data on functional outcome in young patients with PFO and/or ASA are scarce.

3 Patients and methods

This study was approved by the relevant authorities and was carried out at the Department of Neurology, Helsinki University Central Hospital (HUCH), and was based on data collected for the Helsinki Young Stroke Registry (11). The registry includes detailed data on all 15 to 49 years-old patients with first-ever brain infarction treated at our hospital between January 1994 and May 2007. In the present study, we included those who had a PFO, ASA, or both, as the only explaining etiologic factor for stroke. Thus, of the 1008 patients, we included 86 patients; 83 (97%) of them had PFO, 17 (20%) had both PFO and ASA and 3 (3%) patients had only ASA. The mean follow-up period was 6.5 ± 3.7 years, range 1.1 - 14.4 years, and it consisted of 498.9 patient years.

Ischemic stroke was defined as a quickly developing neurological defect lasting longer than 24 hours, caused by ischemic lesions in the brain (or lasting lesser than 24 hours with imaging detected ischemic lesions in correspondence with the acute symptoms). According to the TOAST criteria (5) all of our patients were classified in the TOAST 2 subgroup, which includes cerebral infarctions of cardioembolic etiology.

Most of the data were collected from hospital records. The data of three months survival were collected face-to face at outpatient visit, and the long-term survival data were obtained by telephone contact. Those patients we could not reach by phone (8 patients) were sent a letter to, and one of them replied. We found outcome data in hospital records of some of those unreachable patients. The contact information was obtained from HUCH patient files, district registry, or private contact information suppliers.

For further analyses, the patient population was dichotomized by gender and age (15-34 years and 35-49 years). All data were entered into an EXCEL-based database and further analyzed using the SPSS software package (SPSS Inc., Chicago, Ill., USA).

In case of missing data, the patient was not included into the percentage models. In all models the percentage values were calculated from the *possible* index patients e.g. the percentage value of PFO closure was calculated by dividing the number of the patients that received PFO closure by the number of patients that had a PFO and survived the first stroke.

3.1 Patient Characteristics

3.1.1 Stroke Risk Factors

We registered a range of stroke risk factors according to a predefined protocol: use of oral contraceptives, hormone replacement therapy, congestive heart failure, obstructive sleep apnea, hematological disorders, pregnancy or postpartum state, subacute or acute infection, malignancy in an acute state or previous malignancy, and previous cerebrovascular disease.

Hypertension was defined as systolic blood pressure > 140 mmHg or diastolic blood pressure >90 mmHg or patient was already on antihypertensive treatment. Obesity was diagnosed when body mass index was ≥ 30 kg/m² or it was mentioned in hospital records that the patient was heavily obese. Diabetes mellitus was defined according to the World Health Organization criteria (WHO Consultation 1999) whereby diabetes mellitus was considered present if fasting plasma glucose was over 7.0 mmol/l (126 mg/dL, in more than one measurement) or 2-hour plasma glucose was over 11.1 mmol/l (199 mg/dL). Types 1 and 2 diabetes were registered separately. Hypercholesterolemia was diagnosed if the patient was on lipid lowering medication at the time of stroke onset or the fasting total blood cholesterol was ≥ 5.0 mmol/L. Hypertriglyceridemia was considered present if the fasting blood level of triglyceride was ≥ 2.0 mmol/L. A current smoker was considered to be a patient who smokes one or more cigarettes per day or has stopped smoking within a year before cerebral infarction. Alcohol consumption was regarded excessive (i.e. clearly

more than moderate drinking) if the weekly alcohol use was over 200g of pure alcohol, and alcohol use was acute when patient had used alcohol at least 40g within 24 hours stroke onset. Illicit drug use was determined to be a risk factor if the use had been within four weeks prior to stroke onset. Hormone replacement therapy and use of oral contraceptives were defined as risk factors if the patient had frequently used the drug within six months preceding the stroke. Migraine was determined by the criteria of the International Headache Organization (IHO), and it was recorded separately whether the patient suffered from migraine with or without aura. Obstructive sleep apnea was present if it already was diagnosed prior to stroke onset or if apena-hyponea index was 5 or more (49). Cardiovascular disease was recognized according to four symptoms: atrial fibrillation, intermittent claudication, coronary artery disease, or myocardial infarction. Subacute or acute infection was considered to be present if there were signs of a clinical infection at the onset of stroke or the patient had had infection within four weeks before the stroke. Malignancy was defined acute if the diagnosis was made within one year of stroke onset and malignancy was not in remission. Postpartum stage was defined for the 2 months following labour. Positive family history was defined present if a first-degree relative had an ischemic brain infarction under 60 years of age.

A history of transient ischemic attack (TIA) was defined as a momentary cerebral malfunction caused by focal dysfunction of the brain or retinal ischemia that usually lasts less than an hour without any findings in imaging (50). A silent infarction was defined as absolute absence of clinical findings of ischemic stroke in patient's history (33), but detection of one or more chronic infarction(s) in brain imaging.

3.1.2 Risk Factors for Deep Vein Thrombosis and Paradoxical Embolism Promoting Action

The risk factors for deep vein thrombosis were evaluated for the hypercoagulable states and immobilization (recent flight, plaster). A potential Valsalva-inducing activity was also reported, and we included straining activities such as ascending stairs, lifting a baby, standing up from bed, defecation associated with heavy effort, and sexual intercourse. In addition, we registered whether the stroke symptoms had developed during sleep (already

symptomatic when waking) and whether symptoms arose immediately after waking when getting up. If there was no documented characteristics associated with the infarction event in the patient history, we assumed them not be present.

3.2 Examinations and imaging

3.2.1 Laboratory examination

A wide array of diagnostic tests were registered for all patients: cardiac enzymes, chest x-ray, electrolytes, urine analysis, cholesterol levels, triglycerides, blood glucose, international normalized ratio, activated partial thromboplastin time, creatinine, blood cell counts, gamma-glutamyl transferase, creatine kinase, alanine aminotransferase, thyroid stimulating hormone, C-reactive protein, erythrocyte sedimentation rate, and coagulation factors. If any abnormal result was found in the routine tests, more studies were made. Testing of genetic mutations in clotting factor II (prothrombin) and factor V (Leiden) was performed in 64 (74%) and 75 (87%) patients, respectively.

3.2.1 Brain imaging

Brain and carotid artery imaging were performed in all patients. 81 patients (94%) underwent computed tomography (CT) and 72 patients (84%) magnetic resonance imaging (MRI). In addition, magnetic resonance angiography (MRA) was performed in 58 patients (67%), cerebral artery angiography in 58 patients (67%), and carotid artery ultrasound imaging in 44 patients (51%).

3.2.3 Detection and assessment of PFO and ASA

Cardiac examination and potential PFO and ASA detection was performed by ultrasound imaging in all patients that survived the first stroke (number = 85) by transthoracic (TTE) and/or transesophageal echocardiography (TEE). Bubble test with agitated saline was performed during the TEE in 17 patients.

Dye dilution test was performed in 81 patients in order to detect any interatrial shunt. PFO size, multiplicity, and a potential valve-like structure were assessed, when possible. P/S - value at rest was also registered. TCD was performed in two patients.

PFO was considered large if the shunt in dye dilution exceeded 5% or if the greatest diameter of PFO was assumed to be 7 mm or more in TEE or in autopsy. PFO was considered multiple if more than one shunt were seen in TTE, TEE, bubble test, or in autopsy. PFO was considered to have a valve if no shunt was detected in dye dilution and/or the P/S value was 1.0 at rest. ASA was considered present when it was detected in TTE and/or TEE.

3.3 Stroke evaluation, treatment, and secondary prevention

At arrival, all patients were evaluated according to the National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) scales. Seven patients received thrombolysis, the remaining were treated with anticoagulation by heparin or received only aspirin at acute stage.

The duration of in-patient period and possible additional institutional care in a rehabilitation ward, as well as received rehabilitation in neuropsycology, physiotherapy, speech therapy, or occupational therapy were registered. Secondary preventive medication (anticoagulant or antithrombotic treatment) at three months after the index stroke, and at later follow-up was registered. The medication for the major risk factors for ischemic stroke (high cholesterol, elevated blood pressure) was registered at follow-up. Mechanical PFO closure was also registered.

The data of the stroke evaluation, hospital treatment and secondary preventive medication at three months could be evaluated in all patients. We could not reach 8 patients, but we found some of the data of their current secondary prevention medication and in case records.

3.4 Outcome

Data regarding 3-month outcome were evaluated from all survived patients (n = 85), and the respective percentage models were calculated for those 85 patients that survived. **(**The respective percentage models are calculated for 85 patients, and for 46 females and for 57 patients in the age group of 35 to 49 years.) We could not reach 8 patients (9.4 % of the survivors), and the models reflecting the patients' current functional and occupational state were calculated for 77 patients.

Data of 3-month outcome were evaluated from all survived patients (n = 85), and the respective percentage models were calculated for those 85 patients that survived (39 males and 46 females, 28 aged 16-34 and 57 aged 35-49). We could not reach 8 patients (9.4 % of the survivors), and the models reflecting the patients' current functional and occupational state were calculated for 77 patients (34 males and 43 females, 25 aged 16-34 and 52 aged 35-49).

3.4.1 Functional outcome, sick leave, and occupational status

Functional outcome at three months was evaluated using the modified Rankin Scale (mRS). As our patients were young, scores 0-1 in mRS corresponded to favorable outcome (the patient was able to return to work and to normal daily life) and scores 2-6 corresponded to unfavorable outcome. Long term functional outcome was evaluated using the same parameters. We analyzed all the risk factors, stroke mechanisms and PFO features (e.g. PFO size, valve-like structure, multiplicity or association with ASA) as possible predictive variables for favorable/ unfavorable outcome (at three months) using Chi-Square test or Fisher's exact test. We used the same tests to find out whether the stroke mechanisms or PFO features had a connection with stroke severity (NIHSS score) or future ischemic cerebrovascular events (stroke or TIA).

The duration of sick leave and possible retirement due to the index stroke were registered. The duration of sick leave was not always shown in case reports, so we could evaluate it from only 78 patients. The patients' occupational status before the index stroke, at three

months and at later follow-up were registered by dividing them in five categories: 1) working or studying, 2) unemployed or maternity leave/ housewife, 3) sick leave, 4) institutional care, and 5) retirement.

3.4.2 End-points

The end-points used for outcome were stroke and TIA recurrence, myocardial infarction, postinfarct epilepsy, and death. The annual stroke and TIA recurrence rates were calculated by dividing the number of recurrent events by the total amount of patient years.

3.4.3 Quality of life at follow-up

A survey of the quality of life experienced by the patient was performed using the EQ5D (The EuroQol Group, 1990) and Barthel Index (BI). The patients were asked to assess their current heath status at the time of follow up as a whole, thus other ailments could affect the results independent of the post stroke state. The survey encompasses five domains: 1) mobility, 2) self-care, 3) usual activities, 4) pain/discomfort, and 5) anxiety/depression. Each domain was assessed in a three-scale (1, 2, or 3) ranking indicating no problems, some problems, or major problems in the respective domain. The patients were also asked to evaluate their own subjective heath state at the follow-up moment with the aid of a visual analogue scale (thermometer), ranging from 0 to 100 (51).

4 Results

Of our 86 patients, 39 (45.3%) were men and 47 (54.7%) women. Mean age for all patients was 37.6 ± 8.5 years and range 16 - 49 years. A total of 28 patients fell in the age group of 16-34 (32.6%) years and 58 (67.4%) patients fell into the age group of 35-49 years. For patients with PFO and shunt (with or without ASA) the mean age was 37.5±8.6 and range 16 to 49 years. Of these, 55% were women and 45% men. For patients with only ASA (number=3; 2 males, 1 female) the mean age was 41.3 and range 35-46 years.

4.1 Risk Factors and Stroke Mechanism

Documented risk factors are listed in Table 1. Only one patient had diabetes mellitus, and it was type 1. Hypercholesterolemia was detected in 29 patients. None of the patients had cardiovascular disease or congestive heart failure. One patient had an intrauterine device, and no one used hormone replacement therapy (HRT). Usually only one third of migraine patients suffer from migranous aura, in our data however the proportion was 86% (52). None of the included patients had experienced an earlier symptomatic cerebral infarction, but two patients had a history of TIA. None of the patients tested had mutations in prothrombin (factor II) gene or Leiden (factor V) gene.

The characteristics of the index event are listed in Table 2. In our data for Valsalva inducing activity lifting a child from bed, rising the stairs or sexual intercourse were typical findings. In addition, one patient was diagnosed to have acute pulmonary hypertension at the time of stroke due to massive pulmonary embolization. For immobilization a long flight was the most common underlying condition.

RISK FACTOR	All	Males	Females	Age 15-34	Age 35-49
Age (mean ± SD) **Range**	37.6 ±8.5 16-49	39.1 ±8.2 16-49	36.3 ±8.7 18-48	-	-
Gender	86	39 (45)	47 (55)	11/17 (28/36)	28/30 (72/64)
Hypertension	12 (14)	7 (18)	5 (11)	0 (0)	12 (21)
Obesity	7 (8)	2 (5)	5 (11)	0 (0)	7 (12)
Hypertriglyceridemia	7 (9)	5 (14)	2 (4)	1 (4)	6 (11)
Hypercholesterolemia	29 (34)	15 (39)	14 (30)	6 (21)	23 (40)
Current smoking	27 (31)	11 (28)	16 (34)	11 (39)	16 (28)
Heavy drinking	4 (5)	2 (5)	2 (4)	1 (4)	3 (5)
Acute drinking	2 (2)	0 (0)	2 (4)	0 (0)	2 (3)
Oral contraceptive	-	-	14 (34)	8 (47)	6 (20)
Migraine	30 (35)	7 (18)	23 (49)	10 (36)	20 (34)
Migraine with aura	27 (31)	5 (13)	22 (47)	9 (32)	18 (31)
Sleep apnea	4 (5)	3 (8)	1 (2)	0 (0)	4 (7)
History of TIA	2 (2)	1 (3)	1 (2)	0 (0)	2 (3)
Recent infection	10 (12)	6 (15)	4 (9)	4(14)	6 (10)
Family history of stroke	4 (5)	2 (5)	2 (4)	1 (4)	3 (5)
Pregnancy or postpartum period	-	-	4 (9)	3 (18)	1 (3)

Table 1. Major and minor risk factors for cerebrovascular diseases, n(%)

	All	Males	Females	Age 15-34	Age 35-49
Valsalva inducing activity (n=83)	13 (16)	6 (16)	7 (15)	6 (22)	7 (13)
Immobilization (n=85)	5 (6)	3 (8)	2 (4)	1 (4)	4 (7)
CI when sleeping or immediately after wakening (n=84)	28 (33)	11 (29)	17 (37)	6 (22)	22 (39)

Table 2. Identified mechanisms or predisposing factors for deep vein thrombosis and paradoxical embolism, n(%)

4.2 Stroke localization

The localization, multiplicity, and visibility of the index strokes are shown in Table 3. The silent infarctions diagnosed at the time of the index stroke are listed in the same table.

Anterior territory	47 (55)		Hemisphere	75 (87)
			Left	42 (49)
Posterior territory	36 (42)		Right	33 (38)
Both ant & post territories	3 (4)		Cerebellum	21 (24)
			Left	12 (14)
Multiple infarction	17 (20)		Right	9 (10)
No visible actual infarction	3 (3)		Brainstem	5 (6)
			Left	3 (3)
Silent infarction	7 (8)		Right	2 (2)

Table 3. Stroke localization, n(%)

4.3 Detection and features of PFO and ASA

The results of different methods for PFO detection are listed in Table 4, and the features of PFO are listed in Table 5. The percentage value in *PFO detected* is calculated by dividing the detection rate by the number of the index test performed.

Contrast-enhanced transcranial Doppler (TCD) was performed in two patients, and PFO was found in both cases. Interestingly, also contrast-enhanced TEE was performed in those same patients, but no interatrial shunt was detected with c-TEE.

	Done	PFO detected	Existing PFO detected
Echo	85 (99) TTE[1] 79 (92) TEE[2] 55 (64) Both 48 (56)	35 (42)	43% (35/82)
Contrast echo	21 (24)	14 (67)	70% (14/20)
Dye dilution	81 (94)	79 (98)	98.8% (79/80)[3]

Table 4. Cardiac examinations and findings n,(%) unless otherwise mentioned

[1] Transthoranic echocardiography (ultrasound)
[2] Transesophageal echocardiography (ultrasound)
[3] In one patient the PFO was not detected in dye dilution. However PFO was considered existing due to oxygen saturation measurements.

	All	Only PFO	PFO + ASA
PFO size, n (%)			
Small	67 (82)	55 (85)	12 (71)
Large	15 (18)	10 (15)	5 (29)
PFO as a valve, n (%)	35 (43)	27 (42)	8 (47)
Multiple PFO	4 (5)	4 (6)	0 (0)
P/S value (mean ± SD, range)			
All patients with PFO	1.15± 0.2, 1.0-1.9		
Patients with constantly open PFO (n=42)	1.27± 0.19, 1.1-1.9		

Table 5. PFO structure

4.4 Stroke severity

Most of the patients were fully conscious on admission, and only 5 patients were scored below the maximum 15 points on Glasgow Coma Scale (2 patients: 14 points, 2 patients: 11 points, one patient: 6 points) giving a median value of 15 for the whole and subgroups. The distribution of NIH Stroke Scale (NIHSS) –points is shown in Table 6. The duration of hospital stay and the possible discharge to institutional rehabilitation ward are expressed in the same table.

	All	**Males**	**Females**	**Age 15-34**	**Age 35-49**
NIHSS score (median)	2	2	3	2; 3	2
0-6	70 (81)	33 (85)	37 (79)	22 (79)	48 (83)
7-15	13 (15)	5 (13)	8 (17)	6 (21)	7 (12)
>15	3 (3)	1 (3)	2 (4)	0 (0)	3 (5)
GCS score					
(mean ± SD)	14.78±1.142	14.97±0,160	14.62±1.526	14.68±1.056	14.83±1.187
< 15	5 (6)	1 (3)	4 (9)	3 (11)	2 (3)
Thrombolysis	7 (8)	2 (5)	5 (11)	4 (14)	3 (5)
Hospital stay, days					
Mean ±std	17.6 ±28.0	20.0 ±32.7	15.7 ±23.6	11.9 ±11.0	20.3 ±32.9
Range	0-140	2-140	0-120	0-49	2-140
Discharged to rehab ward	12 (14)	7 (18)	5 (11)	2 (7)	10 (17)

Table 6. Stroke severity at admission, n(%)

4.5 Rehabilitation

Rehabilitation in forms of neuropsychology, physiotherapy, logopedics, and occupational therapy was offered to all patients. 39% of the patients received at least one of these therapy modalities. Most of the rehabilitation was given in an outpatient clinic, but 14 % of the patients were discharged to a rehabilitation ward. The distribution of the rehabilitation modalities in each patient group is shown as percentage values in Figure 2. The difference between the two age groups in physiotherapy was statistically significant (p-value = 0.029).

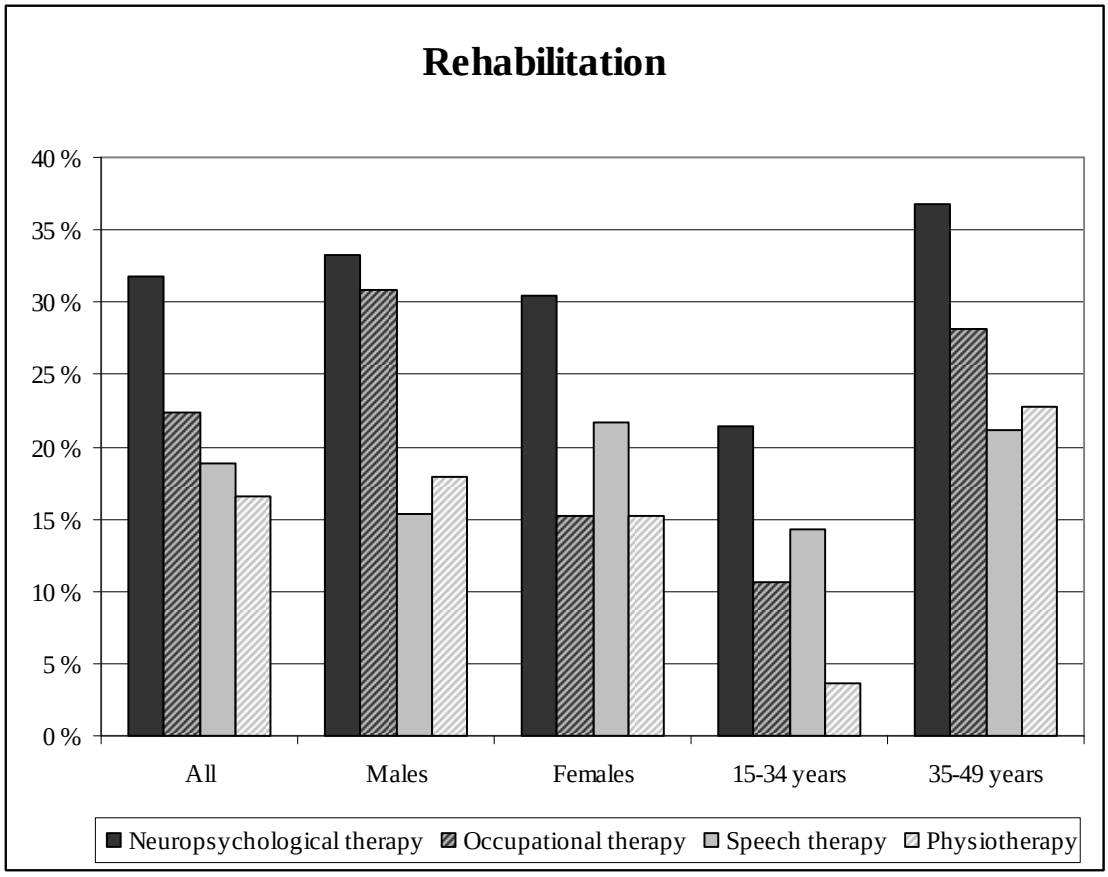

Figure 2. Rehabilitation in each domain (%)

4.6 Secondary Prevention

All patients were prescribed an oral antiplatelet or anticoagulant agent. 26% of the patients receiving aspirin at 3 months and at later follow-up were also prescribed dipyridamol. Only one patient was prescribed dipyridamol alone at later follow-up. About a third of the patients was prescribed a lipid lowering medication (statin) and a fifth of the patients received antihypertensive medication. The distribution of the prescribed medication at 3 months and at follow-up is shown in Table 7. We could receive the current information from 80 (94%) patients.

The distribution of mechanical PFO closure is shown in the same Table 7. The difference in PFO closure was statistically significant between the two age groups (p=0.006). The procedure was done percutaneously or with open thoracotomy.

	All	**Males**	**Females**	**Age 15-34**	**Age 35-49**
Varfarin					
At 3 months	45 (53)	19 (49)	26 (53)	16 (57)	29 (51)
At follow up	24 (30)	11 (31)	13 (30)	4 (16)	20 (37)
Aspirin					
At 3 months	39 (46)	19 (49)	20 (44)	13 (46)	26 (46)
At follow up	46 (58)	20 (57)	26 (59)	15 (60)	31 (57)
Dipyridamol					
At 3 months	10 (12)	5 (13)	5 (11)	2 (7)	8 (14)
At follow up	13 (17)	8 (23)	5 (11)	2 (8)	11 (20)
Clopidrogrel					
At 3 months	2 (2)	1 (3)	1 (2)	0 (0)	2 (4)
At follow up	1 (1)	1 (3)	0 (0)	0 (0)	1 (2)
Statin	27 (35)	13 (37)	14 (33)	6 (24)	21 (40)
β-blocker	5 (6)	4 (11)	1 (2)	0 (0)	5 (9)
ACE-blocker	7 (9)	4 (11)	3 (7)	1 (4)	6 (11)
ATR-antagonist	6 (8)	3 (9)	3 (7)	0(0)	6 (11)
PFO closure	7 (9)	3 (8)	4 (9)	6 (21)	1 (2)

Table 7. Secondary prevention method, n (%)

4.7 Outcome

One patient (female, age 44) died due to the index stroke. No other patients died during the follow-up period. Most of the rest recovered from their stroke symptoms and could return to their previous professional and personal activities.

4.7.1 Functional outcome

The majority of patients recovered excellently. At 3 months 70 % and at later follow-up as much as 78% of the patients reported a favorable outcome (mRS 0-1), and 94% of the patients were independent at follow-up (mRS 0-2). The only statistically significant positive or negative prognosis factor was NIHSS score at hospitalization. A favorable outcome at three months was achieved by 83% (p=0.000) of the patients with NIHSS score 0-6, by 15% (p=0.000) of those with NISHH score 7-14, and in none of the patients with NIHSS score over 15 (p=0.025). At later follow-up a favorable outcome was achieved by 86% (p=0.001) of the patients with NIHSS score 0-6, by 50% (p=0.000 of those with NIHSS score 7-14 and by none of the patients with NIHSS score over 15. Expect the only death, no other patient received less than 3 points in the modified Rankin Scale (mRS). The distribution of mRS scores at 3 months and at follow-up are shown in the Figures 3 and 4.

0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Table 8. Definition of the points in mRS scale

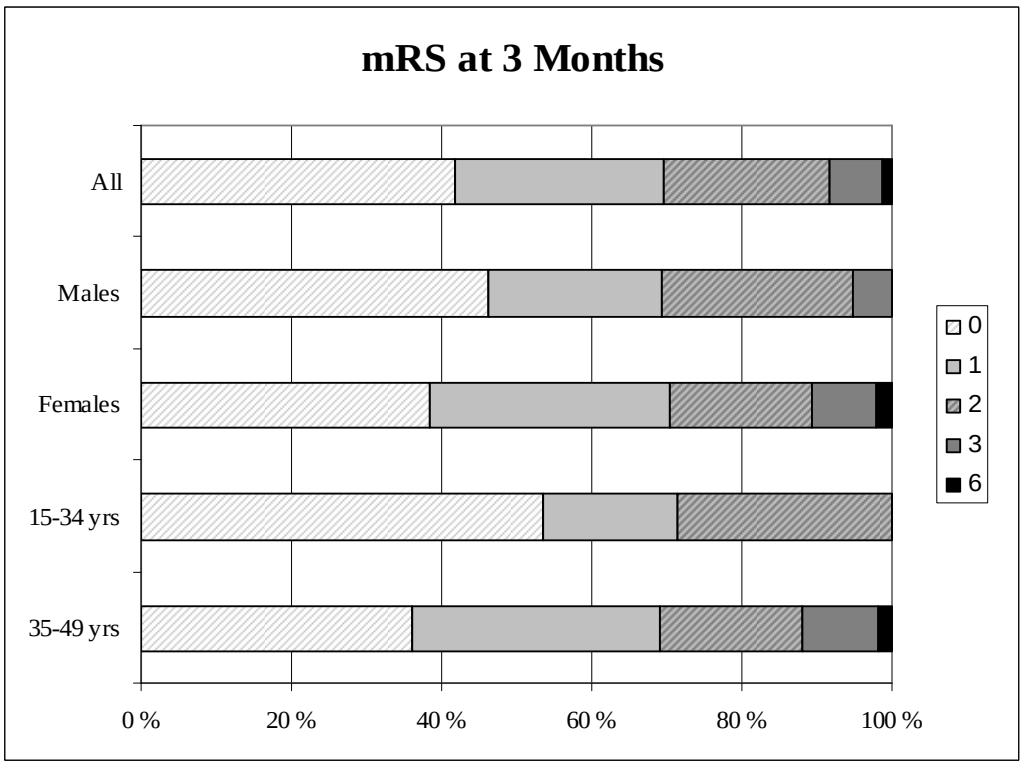

Figure 3. Ratios of mRS scores received at 3 months after the index stroke

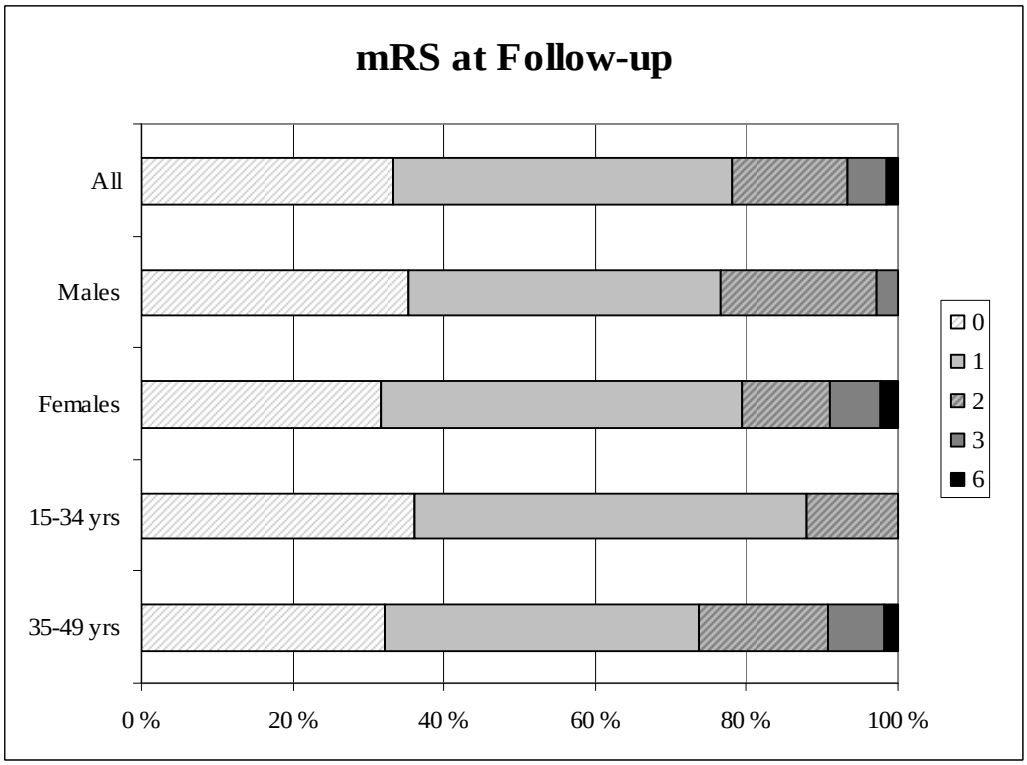

Figure 4. Ratios of mRS scores received at later follow-u

4.7.2 Sick Leave and Occupational Status

The mean duration of sick leave was 120.7 ± 123.6 days (range 0 to 540 days). The distribution of the duration of sick leave is displayed in Figure 5. The exact duration of the sick leave could be evaluated from 79 patients, the rest (n = 6) were already out of the professional life before the index stroke for varying reasons: sick leave, sick benefit, maternity leave, and being a housewife.

The patients' occupational status before the index event, three months later and at the current moment are displayed in Figure 6. For the *Maternity/ Unemployment* column, before the index stroke four patients were on maternity leave, two patients were housewives and one patient was unemployed, at three months and at follow-up all the patients in that column were on maternity leave.

Altogether there were 13 patients (15%) that were active in the professional life before the index stroke, but had to prematurely retire straight after the end of the sick leave or after a short working trial after the index stroke. Six of them were men and seven were women, all fell in the age group of 35-49.

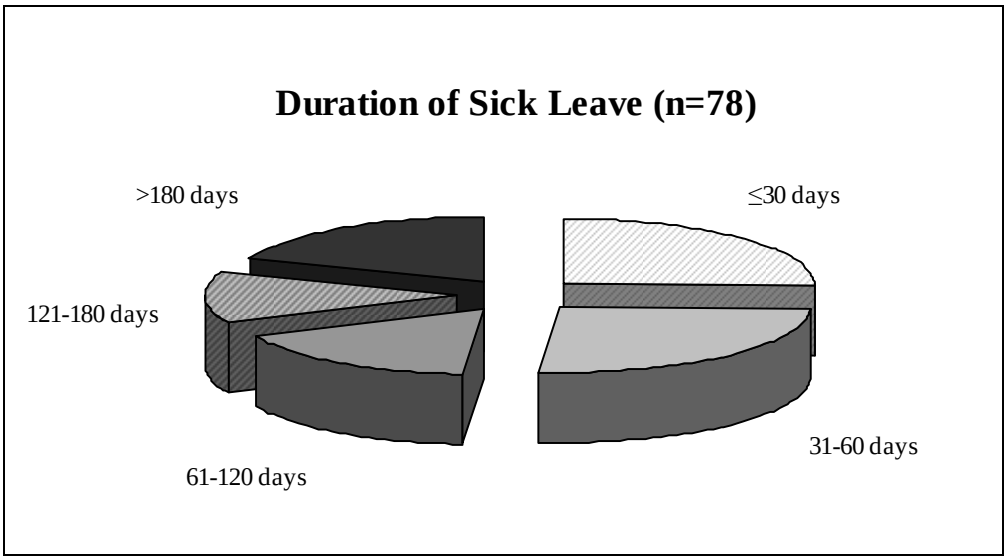

Figure 5. The distribution of the duration of sick leave

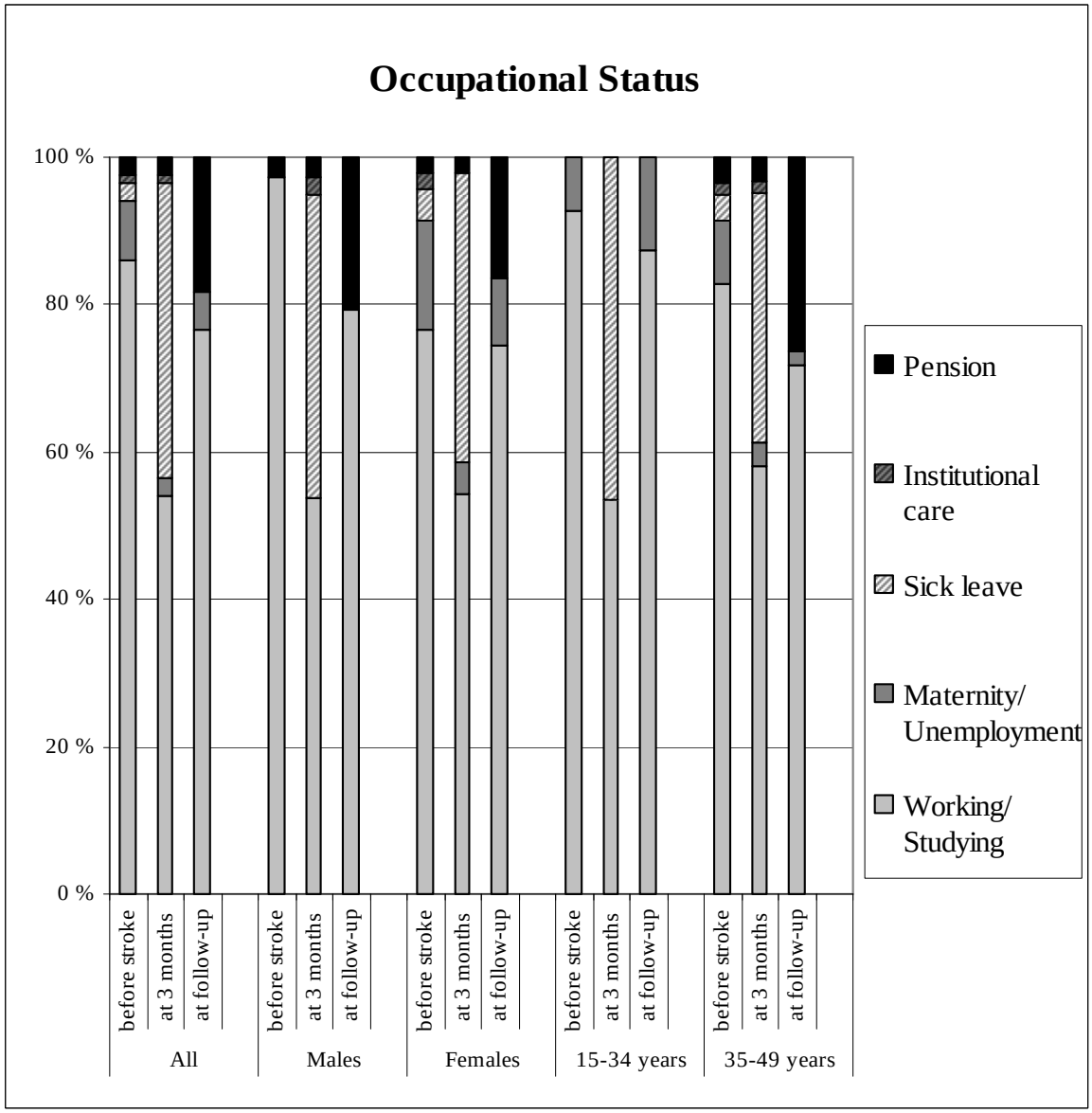

Figure 6. The patients' occupational status before the index stroke, at three months and at later follow-up

4.7.3 Recurrent vascular events and post infarct epilepsy

Recurrent TIAs, strokes, and postinfarct epilepsy are listed in Table 8. None of the recurrent strokes happened during the first year after the index stroke, the mean time to have a recurrent stroke was 4.7 years. The average annual recurrence rate for stroke was 1.8%. Only one patient had had both a recurrent stroke and TIA, but three patients had had

multiple TIAs. The average annual rate for recurrent stroke or TIA was 2.4%. The rate of recurrent stroke or TIA was slightly lower among patients receiving warfarin than aspirin as secondary preventive medication, but the difference was not statistically significant. None of the patients had a myocardial infarction during the follow-up period.

	All	Males	Females	Age 15-34	Age 35-49
Recurrent TIA	9 (12)	4 (11)	5 (12)	2 (8)	7 (13)
Recurrent Stroke	3 (4)	3 (9)	0 (0)	1 (4)	2 (4)
Post infarct epilepsy	4 (5)	2 (6)	2 (5)	1 (4)	3 (6)

Table 9. Recurrent cerebrovascular events and postinfarct epilepsy, n (%)

4.7.4 Quality of Life at Follow-up

Most of the patients reported value 1 (no problems) to all five parameters evaluating the current independency and troubles (EQ-5D scale). There was only one patient reporting to have major problems in any domain. The case was a woman falling in the age group of 35-49 years who had major problems (value 3) in her usual activities. All the other problems reported were of value 2 (some problems). Interestingly, even though most of the patients reported having no depression or anxiety at the time of follow-up, many patients admitted they did suffer from depression and/or anxiety some time after the index stroke. To simplify, in Figure 7 we show the ratios of all values reported to be above one in each domain at the time of follow-up. Younger patients reported significantly lesser problems exept for depression.

5 patients (6%) received less than 100 points on Barthel Index at three months: 4 of them received 95 points and 1 received 90 points. At follow-up, all patients we could reach received 100 points.

The frequency distribution of patients' answers on their own health state evaluation in the visual analogue scale is shown in Figure 8.

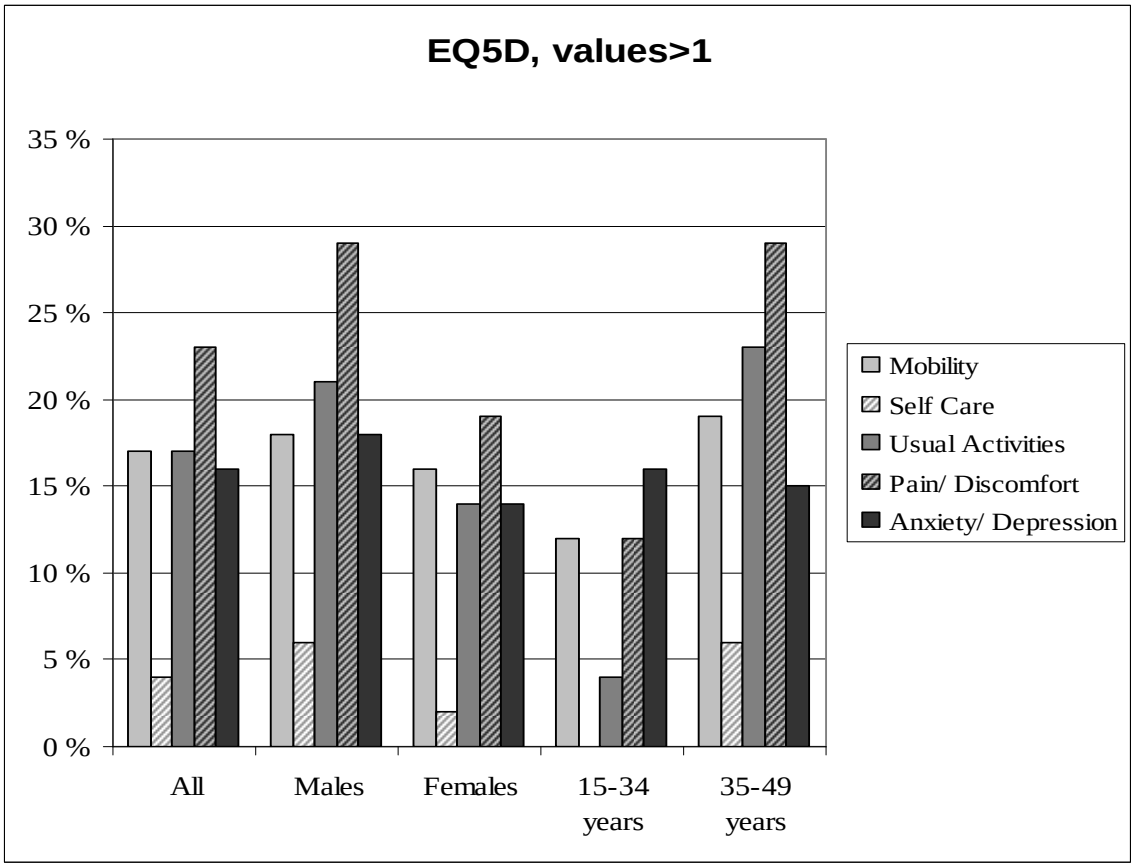

Figure 7. The percentage ratios of some or major problems in each domain

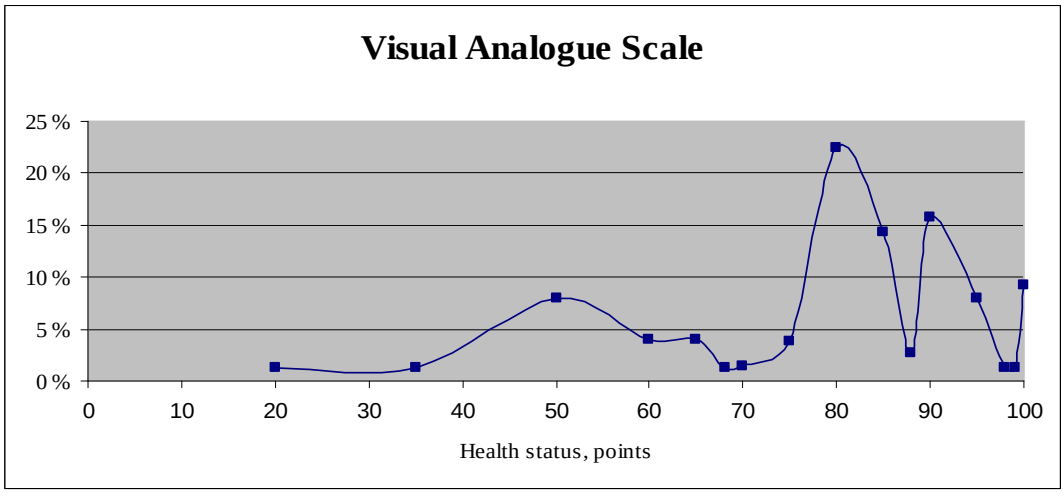

Figure 8. Frequency distribution of patients' answers on their own heath status

5 Discussion

We evaluated the characteristics and followed up 86 young stroke patients with PFO and/or ASA as the only explaining factor for stroke for a mean follow-up period of 6.5 years. The most common stroke risk factors in our patients were hypercholesterolemia, smoking, and oral contraceptives. Migraine, particularly with aura, was clearly more common in our patients than in the general population (18% vs. 13% in men and 49% vs. 33% in women). A Valsalva inducing activity, which is considered to be required in paradoxical embolization, was reported only in 15% of the cases in our data. However as much as in a third of the cases the stroke arose during sleep or immediately after waking.

Most patients (82%) had a small PFO, and a valve-like structure was detected in almost a half (43%) of the patients with PFO. A large PFO was found twice as often if the PFO was in association with ASA. The stroke severity was the only significant prognostic factor for favorable or unfavorable outcome. The mean hospital stay after the index stroke was about two and half weeks, after which 14 % of the patients were discharged to a rehabilitation ward. 39% of the patients needed some rehabilitation, of which the most common form was neuropsycological therapy. The patients in the older age group needed clearly more rehabilitation than those in the younger age group, the distribution between men and women was more even.

The stroke recurrence rate was 4% and the annual recurrence rate 1.8%. 5% of the patients developed postinfarct epilepsy and none of them suffered myocardial infarction during the follow-up period. Most of the patients recovered excellently from their stroke symptoms, and at follow-up as much as 78 % of the patients reported the possible residual symptoms to give them no extra burden in daily life (mRS = 0-1), and as much as 94% could live independently (mRS = 0-3). No correlation was found between stroke/TIA recurrence rate or functional outcome and PFO features. One-third of the patients were on sick leave at three months' follow-up, and one-fifth of the patients had a sick leave longer than six months. 15% of the patients had to retire prematurely because of their index stroke. No

correlation was found between unfavorable outcome or stroke severity and any stroke risk factor, stroke mechanism, or PFO feature.

For secondary prevention medication the patients were prescribed warfarin or aspirin therapy almost evenly for the first three months, at later follow-up 60% of the patients had still aspirin and a third of the patients had warfarin. A quarter of the patients receiving aspirin were also prescribed dipyridamol. In addition, one-third of the patients were prescribed lipid lowering and one-fifth blood pressure lowering medication after the index stroke. The PFO was mechanically closed in 9 % of the patients.

Our results agree with the few previous studies. Our patients had few major risk factors for stroke as previously recognized (1). A paradoxical embolization explaining Valsalva-inducing activity was relatively rarely reported, as indicated in older studies (22). However there were a significant number of cases in which the stroke occurred during sleep or immediately after waking. Stroke recurrence has been found low in most of the other studies as well (37,47). The rate of independency after stroke (94% in our study) was at the same level as what Leys et al. and Nedelchev have found before (4,18). The mechanical closure of PFO was low in our data compared to some other studies (9% vs. 33% at Weimara's), but the distribution of different secondary prevention medication was similar (53). In previous studies warfarin has been noted to be superior to aspirin therapy and comparable with mechanical PFO closure (36,37); in our study there was only a slight nonsignificant difference between these groups.

The main limitation of this study was the nonsystematic examination and reporting of the PFO features. For the stroke mechanism investigation, venous thrombus should also have been systematically studied and reported in every patient in order to make reliable conclusions. In addition, the small number of patients and the small number of recurrent ischemic events substantially hampered firm conclusions on secondary prevention.

6 Conclusions

Our study depicted the characteristics, the course of hospital stay, secondary prevention methods, and outcome of all young stroke patients with PFO and/or ASA as the only explaining factor for stroke treated in our hospital. Our main findings are that most of these patients have a favorable outcome, and that the recurrent stroke rate is relatively low. For future studies cardiac examinations for these patients should be more uniform and systematic to assess the possible association between PFO features and stroke outcome and survival. In order to study the other characteristics of these patients (e.g. best secondary prevention measure) larger patient series are needed.

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