Patent Foramen Ovale (PFO) and Cryptogenic Stroke or Transient Ischemic Attack: a Follow-up Study

Naqibullah Mirzada

UNIVERSITY OF GOTHENBURG

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Patent foramen ovale (PFO) and crptogenic stroke or transient ischemic attack: a follow-up study

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naqibullah.mirzada@vgregion.se
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"Absence of understanding does not warrant absence of existence"

Words of Abu Ali Ibn-Sina Balkhi, known as Avicenna

To my family

ABSTRACT

Aims: The overall aim of this thesis was to study the long-term clinical outcomes in terms of survival, complications, recurrent stroke or transient ischemic attack (TIA), and quality of life in a group of patients with patent foramen ovale (PFO) and cryptogenic stroke. Patients who had undergone PFO closure were compared with patients who had not. The first aim was to provide a long-term clinical follow-up of patients who had undergone PFO closure. The second aim was to study whether a multidisciplinary PFO conference could maintain stringent criteria for PFO closure to identify patients at high risk of paradoxical embolization. The third aim was to compare long-term outcomes of PFO closure versus non-closure in patients who had been carefully selected by a multidisciplinary PFO conference. The fourth aim was to assess health-related quality of life after PFO closure compared to a normal population and compared to patients with a PFO and ischemic stroke who had not undergone PFO closure.

Methods: Paper I was a retrospective long-term follow-up study that included all patients who between 1997 and 2006 underwent PFO closure in the GUCH center in Gothenburg. Paper II is a descriptive study of the PFO conferences and includes all patients with a PFO who were referred to our GUCH center for PFO closure between 2006 and 2009. Paper III is a prospective clinical follow-up study and includes all the patients discussed at PFO conferences in 2006–2009. Paper IV is a prospective study in which quality of life was assessed using the SF-36 Health Survey in all patients included in Paper I and III, compared with an age- and gender-matched reference group from the Swedish SF-36 normative database.

Results: In Paper I, percutaneous PFO closure was successfully performed in 85 of 86 patients. The follow-up rate was 100%. No cardiovascular or cerebrovascular deaths occurred. Two patients (both women) died of lung cancer during follow-up. The mean follow-up time was 7.3 years (5 to 12.4 years). Mean age at PFO closure was 49 years. Two patients suffered from recurrent stroke or TIA, a recurrence rate of 0.3% per year. No long-term device-related complications were observed. In Paper II, 311 patients were evaluated at the PFO conferences. The acceptance rate for closure was similar throughout these years, with an average of 46%. Patients accepted for closure were younger (mean age 50 years vs. 58 years, $p<0.001$). In Paper III, all patients in Paper II were followed up almost five years later. Of 314 patients, 151 (48%) were accepted for closure and 163 (52%) were not accepted. PFO closure did not provide significant benefit compared with the non-closure group for the primary endpoint (a composite of all-cause mortality, stroke and TIA) or for the secondary endpoints (stroke, TIA or all-cause mortality in isolation), either in the intention-to-treat analysis or in the as-treated analysis. Finally, Paper IV demonstrated that device closure of a PFO provides significantly better health-related quality of life at long-term follow-up, in comparison to the non-closure group; closure patients reported similar quality of life compared to an age- and gender-matched normative population ($p<0.05$). The non-closure group showed poorer quality of life compared to both the closure group and to an age- and gender-matched normative population ($p<0.05$).

Conclusions: Percutaneous PFO closure is associated with very low risk of recurrent stroke and is feasible in most patients. No mortality and no long-term device-related complications related to PFO closure were observed. The acceptance rate of less than 50% at the PFO conference underscores the complex relationship between cryptogenic stroke and PFO and the importance of a multidisciplinary approach. PFO closure does not provide any improved clinical outcomes regarding the composite of all-cause mortality, stroke and TIA compared to the non-closure group. Neither could any significant differences be demonstrated regarding recurrent stroke or TIA or regarding all-cause mortality. However, percutaneous PFO closure appears to have a favorable impact on quality of life. Larger prospective observational studies and randomized studies are necessary to assess the real benefit of PFO closure and its influence on quality of life.

Keywords: Patent foramen ovale (PFO), cryptogenic stroke, PFO closure.

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their roman numerals.

I Mirzada N, Ladenvall P, Hansson P-O, Johansson MC, Furenäs E, Eriksson P, Dellborg M. Seven-year follow-up of percutaneous closure of patent foramen ovale.
IJC Heart & Vessels. 2013; 1: 32-6

II Mirzada N, Ladenvall P, Hansson PO, Eriksson P, Dellborg M. Multidisciplinary management of patent foramen ovale (PFO) and cryptogenic stroke/ TIA.
Journal of multidisciplinary healthcare. 2013; 6: 357-63

III Mirzada N, Ladenvall P, Hansson PO, Eriksson P, Dellborg M. Recurrent stroke in patients with patent foramen ovale: An observational prospective study of percutaneous closure of PFO versus non-closure.
Submitted

IV Mirzada N, Ladenvall P, Hansson PO, Eriksson P, Charles Taft, Dellborg M. Quality of life after percutaneous closure of patent foramen ovale in patients after cryptogenic stroke.
Submitted

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CONTENTS

ABREVIATIONS

AF	Atrial fibrillation
ASAn	Atrial septal aneurysm
A-S-C-O	Atherosclerosis - small vessel disease - cardiac source - other cause
CCS	Causative Classification System
CS	Cryptogenic stroke
CT	Computed tomography
DALY	Disability-adjusted life-year
GUCH	Grown-up congenital heart disease
HRQoL	Health-related quality of life
ITT	Intention to treat
MRI	Magnetic resonance imaging
OCSP	Oxford Community Stroke Project
PFO	Patent foramen ovale
RCT	Randomized clinical trial
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment

OVERVIEW OF THE THESIS

This thesis will start with a background about stroke and classification systems for stroke subtypes, including ischemic stroke subtypes. There follows a review of the existing literature on cryptogenic stroke and patent foramen ovale (PFO), and on the association between the two. The methods and results of the papers in this thesis are then discussed, and conclusions are drawn about the long-term clinical outcomes of PFO closure versus non-closure (Figure 1).

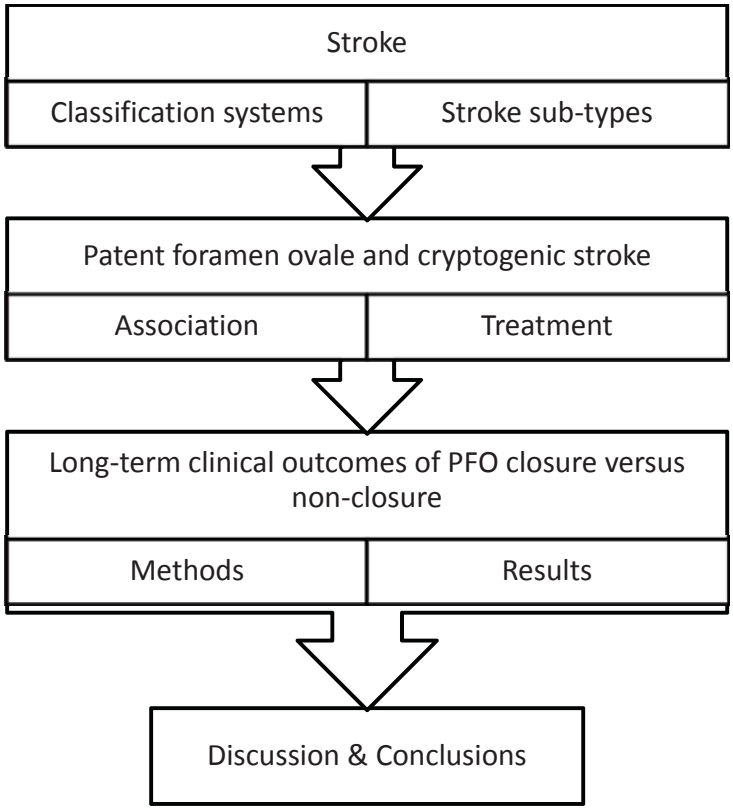

Figure 1. Overview of the thesis

INTRODUCTION

Stroke

Stroke is defined by the World Health Organization (WHO) as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, with symptoms, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin".[1]

A stroke is caused by the interruption of the blood supply to the brain, from either lack of blood flow (ischemia) or leakage of blood (hemorrhage). This disruption to the supply of oxygen and nutrients causes damage to the brain tissue. In a transient ischemic attack (TIA), the interruption of the blood supply to the brain is temporary and, by definition, the symptoms last less than 24 hours. The most common symptom of a stroke or TIA is sudden weakness or numbness to the face, arm or leg, most often on one side of the body.

The effects of a stroke depend on which part of the brain is affected and the severity of the damage. As the management of ischemic stroke is different than for hemorrhagic stroke, the distinction between these subtypes is important for acute management.

Although age-standardized rates of stroke mortality have decreased significantly in both high-income and low- to middle-income countries worldwide in the past two decades, the absolute number of people who have a stroke every year is substantial, and the overall global burden of stroke, in terms of disability-adjusted life-years (DALYs) lost, is increasing. Worldwide in 2010, there were 16.9 million recorded first strokes, 33 million stroke survivors, 5.9 million stroke-related deaths, and 102 million DALYs. The numbers had significantly increased since 1990, with most of the burden in the low-income and middle-income countries. More than 62% of new strokes, 69.8% of stroke prevalence, 45.5% of stroke deaths, and 71.7% of DALYs lost because of stroke were in people younger than 75 years.[2]

Many patients surviving stroke will be dependent on other people's continuous support in everyday life. In Sweden, approximately 30 000 people suffer strokes every year[3] and, for the majority, it is their first-ever stroke.[4]

The number of stroke victims is expected to rise as the percentage of senior citizens in the country increases,[5] and reducing the stroke burden through prevention and care for first and recurrent stroke events is a major task for health care systems. The management of stroke includes primary interventions (before a stroke) and secondary interventions (after a stroke), both in the acute phase and in the long term thereafter.

Major risk factors for stroke

Risk factors for stroke may be divided into *non-modifiable* and *modifiable* factors. *Non-modifiable* risk factors for stroke include age, sex, ethnicity, low birth weight and heredity. Established *modifiable* risk factors for stroke include hypertension, smok-

ing, diabetes, atrial fibrillation, dyslipidemia, unhealthy diet, obesity, and physical inactivity.[6, 7]

The risk factors for stroke are essentially the same for both men and women,[8] even if some risk factors, such as atrial fibrillation (AF), increase the risk of developing stroke proportionally more among women.[9] In both sexes, increasing age is a strong risk factor for both ischemic and hemorrhagic strokes, with half of all strokes occurring in people aged 75 years or older.[10]

Stroke subtypes

The pathological background for stroke may either be ischemic or hemorrhagic disturbances of the cerebral blood circulation. As the management of ischemic and hemorrhagic stroke is different, the distinction between these subtypes is important for acute management. Accurate stroke classification requires integration of multiple aspects of diagnostic stroke evaluation in a standardized manner.

Comparability of subtype assignments is vital to valid communication of research results across the field. Classifying patients according to pathophysiology is the key to understanding stroke. Stroke sub-types are illustrated in Figure 2.

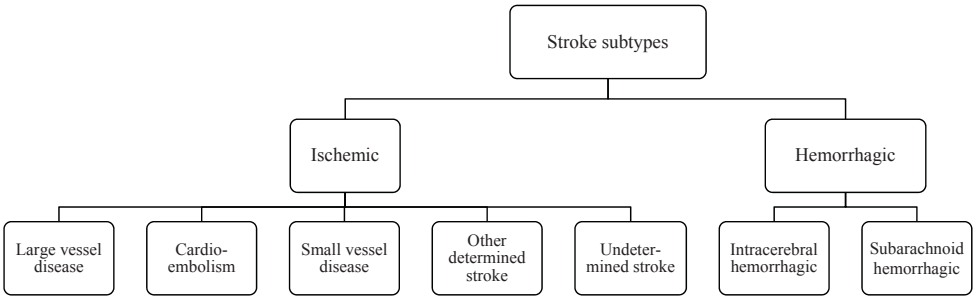

Figure 2. Stroke subtypes. Ischemic subtypes according to Trial of Org 10172 in Acute Stroke Treatment (TOAST).[11]

Hemorrhagic stroke

Hemorrhagic stroke accounts for 22% of all stroke worldwide and 9% of all stroke types in high-income countries.[12] Spontaneous intracerebral hemorrhages (as opposed to traumatic ones) are mainly due to arteriolar hypertensive disease, and more rarely due to coagulation disorders, vascular malformation within the brain, and abuse of alcohol and other drugs. Cortical amyloid angiopathy (a consequence of hypertension) is a cause of cortical hemorrhages especially occurring in older adults and it is becoming increasingly frequent as populations become older.[13]

The WHO definition of hemorrhagic stroke includes subarachnoid hemorrhage[1] whereas other definitions include tumor or trauma-related hemorrhages.[14]

Ischemic stroke

Ischemic strokes constitute approximately 78% of all stroke cases worldwide, and 91% in high-income countries (Figure 3). [12]

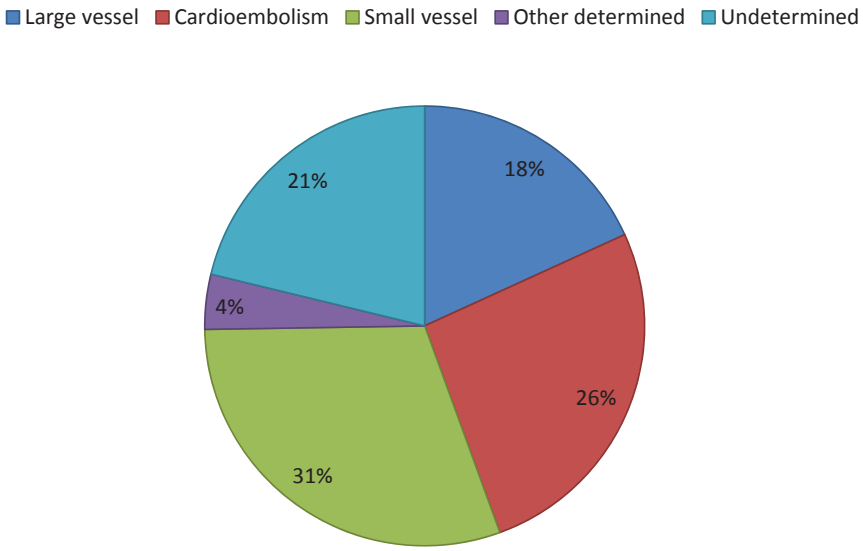

Figure 3. Presumed primary etiology of ischemic stroke in high-income countries. Data taken from the Interstroke study.[12]

Classification systems of ischemic stroke subtypes

Several etiological classification systems have been developed for ischemic stroke. The most modern and commonly applied classification systems are the Trial of Org 10172 in Acute Stroke Treatment (TOAST) system,[11] the Causative Classification System (CCS),[15] the A-S-C-O classification system[16] and the Bamford classification (also called the Oxford Community Stroke Project, OCSP).[17] There is no single widely accepted classification system.

The TOAST classification system

The TOAST system has been a reflection of the way neurologists have thought about recognizing and understanding stroke for almost two decades and is the most widely used type of classification in stroke research. It was originally created in a study of low-molecular-weight heparin in acute ischemic stroke. The original study failed to show a favorable outcome,[18] but the subtyping of stroke etiology was a useful contribution to the scientific community and the classification has since then been widely used in clinical studies of ischemic stroke. Nevertheless, it suffers from only moderate reliability.

The system is based primarily on clinical features but also uses existing diagnostic information from computed tomography (CT), magnetic resonance imaging (MRI), transthoracic echocardiography, extracranial carotid ultrasonography, and, when available, cerebral angiography. The subtypes included in the TOAST classification are *large-vessel disease, small-vessel disease, cardioembolic stroke*, and *other determined* and *undetermined/mixed cause*.

The major weakness of the TOAST classification is the fairly large proportion of patients classified as undetermined or mixed stroke etiology (commonly around 30–40%) even after extensive investigations. Yet another problem, though not specific to the TOAST classification, is the difficulty of detecting "silent atrial fibrillation". This probably leads to underestimation of the prevalence of the cardioembolic stroke subtype.

TOAST-CCS system

The automated TOAST-Causative Classification System (CCS)[15] carries on the TOAST tradition and is designed to overcome the major limitations of the TOAST system.
It is a more complex system, but it provides causative subtype assignments with higher reliability than TOAST[19] and facilitate the classification procedure in large multicenter trials. Agreement between TOAST and CCS ranges from good to excellent.[20] The CCS is available at http://ccs.martinos.org.

The Oxford Community Stroke Project (OCSP) classification system

The OCSP classification system[17] for ischemic stroke (also known as the Bamford or Oxford classification system) relies primarily on the initial stroke symptoms. It focuses on the extent of the patient's symptoms before any of the investigations into etiology have been performed.

According to OCSP, the stroke episode is classified as:

- Total anterior circulation stroke (TAC)
- Partial anterior circulation stroke (PAC)
- Lacunar stroke (LAC)
- Posterior circulation stroke (POC)

The type of stroke is then coded by adding a final letter to the above: I for infarct (e.g. TACI), H for hemorrhage (e.g. TACH), S for syndrome, i.e. intermediate pathogenesis prior to imaging (e.g. TACS). These four entities predict the extent of the stroke, the area of the brain affected, the underlying cause, and the prognosis.

The ASCO Classification of Ischemic Stroke

The A-S-C-O system is the most recent classification of stroke[16] which allows stratification of stroke patients based on their phenotypic characteristics. This classification better takes into consideration the different levels of evidence (grades 1–3, where 1 stands for high evidence level) regarding A=atherosclerosis, S=small vessel disease,

C=cardiac source and O=other causes of ischemic stroke. This system has promising utility in large epidemiological or genetic studies but, due to the large number of possible categories, this system is not suitable for studies with relatively small sample sizes.

Variety between different stroke classification systems makes it difficult to interpret the outcomes of stroke studies. There is a need for an optimal classification system which should provide a common language in the field to ensure unity among physicians and comparability between studies. This system must be simple and logical. Additionally, the system should focus on the pathophysiology, use rules and criteria based on evidence rather than ideas, be flexible enough to accommodate new information as it emerges, and allow categorization of patients into the fewest possible subtypes with discrete phenotypic, therapeutic, and prognostic features. Finally, the optimal system should have proven utility in diverse clinical settings. However, in clinical assessment of a specific stroke patient, it is most important to discriminate between cardioembolic and non-cardioembolic stroke, because efficient treatment with oral anticoagulants is available if an atrial fibrillation is found; if there is no atrial fibrillation, an antiplatelet agent is considered sufficient as secondary prophylaxis.

Large-vessel ischemic stroke

Large-vessel (artery) ischemic stroke accounts for about 18% of all cerebral infarcts in high-income countries[12] and is mainly a result of a stenosis or atherosclerotic plaque in the internal carotid or vertebral arteries as a result of atherosclerosis. A history of intermittent claudication, TIAs in the same vascular territory, a carotid bruit, or diminished pulses help to support the clinical diagnosis. Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on a CT or MRI scan are considered to be of potential large-artery atherosclerotic origin. Supportive evidence by duplex imaging or arteriography of a stenosis greater than 50% of an appropriate intracranial or extracranial artery is needed. Diagnostic studies should exclude potential sources of cardiogenic embolism. The diagnosis of stroke secondary to large artery atherosclerosis cannot be made if duplex or arteriographic studies are normal or show only minimal changes.

Cardioembolic ischemic stroke

Cardioembolic strokes account for about 25% of all cerebral ischemic infarcts[12, 21] and are most commonly due to embolization of a thrombus formed in the atrial appendage of the fibrillating left atrium (atrial fibrillation). Emboli into the cerebral circulation follow the bloodstream and often end up in larger arteries (e.g. arteria media circulation) where they occlude the vessel and generate strokes with more severe neurological deficits and subsequently a worse prognosis.[21] As mentioned above, atrial fibrillation is the most common source of cardiac emboli. Other risk sources of cardioembolism are: recent anterior myocardial infarction, dilated cardiomyopathy, left atrial or ventricle thrombus, prosthetic valves, endocarditis, and left atrial or ventricular myxoma.[22, 23] The role of patent foramen ovale (PFO) and atrial septal aneurysm (ASAn) as medium-risk sources of cardioembolism suggested by TOAST[11] is debatable.[21]

Small-vessel ischemic stroke

Small-vessel disease (lacunar stroke) accounts for 30% of all cerebral infarcts in high-income countries[12] and is currently regarded as a sign of microscopic (lipohyaline) changes of the vessel wall with subsequent occlusion of the nutritional blood flow and a plausible cell death at the end artery area.[24, 25] In late stages of the lacunar disease, a microthrombus is believed to be formed secondary to stagnation of blood flow.[26] According to TOAST, a history of diabetes mellitus or hypertension supports the clinical diagnosis.

Acute stroke of other determined etiology

Acute stroke of other determined etiology represents about 4–5% of all cerebral ischemic infarcts.[12] This category includes patients with rare causes of stroke, such as non-atherosclerotic vasculopathies or vasculitis[27], hypercoagulable states such as antiphospholipid syndrome,[28] hematologic disorders,[29] arterial dissections,[30] and rare monogenic disorders.[31] Patients in this group should have clinical and CT or MRI findings of an acute ischemic stroke, regardless of the size or location. Diagnostic studies such as blood tests or arteriography should reveal one of these unusual causes of stroke. Cardiac sources of embolism and large-artery atherosclerosis should be excluded.

Undetermined ischemic stroke

Undetermined strokes are defined as cerebral ischemia of obscure or unknown origin according to both the TOAST and OCSP classification systems. Undetermined strokes account for 22–40% of all ischemic strokes.[12, 32] The cause of stroke remains undetermined because the event is transitory or reversible, because investigators did not look for all possible causes, because two or more potential causes of stroke were identified, because the evaluation was cursory, or because some causes truly remain unknown (cryptogenic). The term *cryptogenic* derives from the Greek word *kruptos* ("hidden") and refers to diseases of obscure or unknown origin.

It is a challenge to identify an ischemic stroke as undetermined or cryptogenic. Cryptogenic stroke is rather a diagnosis of exclusion and is defined as a stroke which cannot be attributed to any specific cause after an extensive search for the most common causes; these include large-artery atherosclerosis, small-vessel occlusion, stroke of other determined etiology, and cardioembolism.[11] Diagnostic work-up for undetermined or cryptogenic stroke includes transesophageal echocardiography, long-term ECG recordings, CT or MRI angiography of the aorta, transcranial Doppler sonography, imaging for venous thrombosis in the case of paradoxical embolism, and blood chemical investigations and coagulation tests.[33]

As in the TOAST system, the "undetermined" category in the TOAST-CCS[15] is broken into subcategories: unknown, incomplete evaluation, unclassified stroke (more than one etiology), and cryptogenic embolism. The last subgroup, cryptogenic embolism, is a new category aiming to identify patients with angiographic evidence of an abrupt cutoff in an otherwise normal-looking artery or subsequent complete recanalization of

a previously occluded artery. Segregation of such patients into a distinct category may give researchers the opportunity to study new emboli sources in a more refined way. Many studies have suggested an association between PFO and cryptogenic stroke, but before examining this issue further, PFO will be explained below.

Patent foramen ovale (PFO)

Foramen ovale (Latin for 'oval opening') is an essential part of the fetal circulation. The dividing wall between the right and left atria is formed via two embryonic structures, the septum primum and the septum secundum (Figure 4).

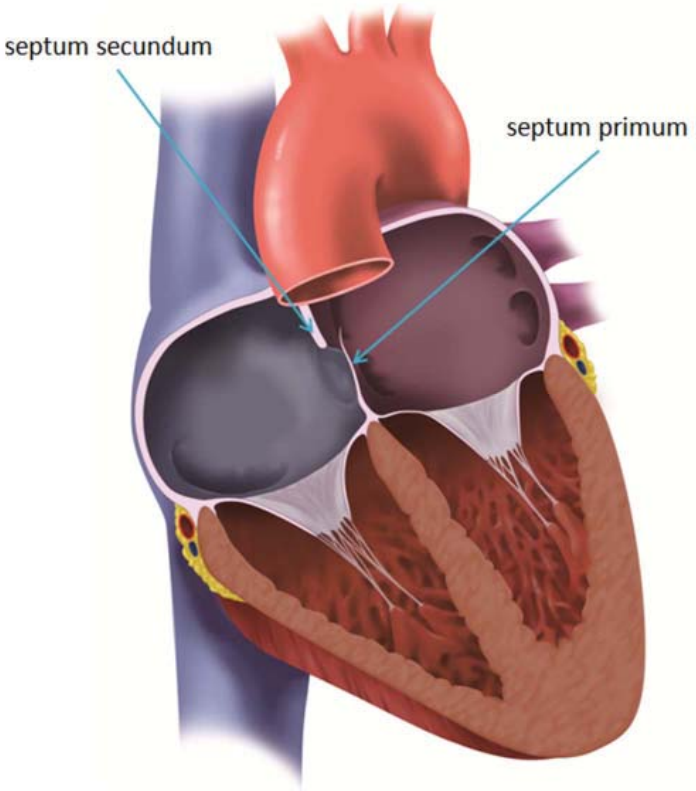

Figure 4. The septum primum and the septum secundum. Illustration is re-published by permission from St. Jude Medical, Inc.

During fetal life, these blades are not fused together; instead, they function as a wedge valve so that the oxygen-rich blood from the placenta is able to flow directly from the inferior vena cava to the left atrium without passing through the lungs.

After birth it will close with a thin flap which will fuse with the rims of the foramen ovale during the first years of life in most people. However, in approximately one in four normal people the foramen ovale can still remain open. This is called a patent foramen ovale (abbreviated to PFO). It has no hemodynamic adverse effects, but a

PFO provides the conditions for paradoxical embolism from upstream veins. In other words, venous clots are able to get out to the systemic circulation instead of to the lungs (Figure 5).

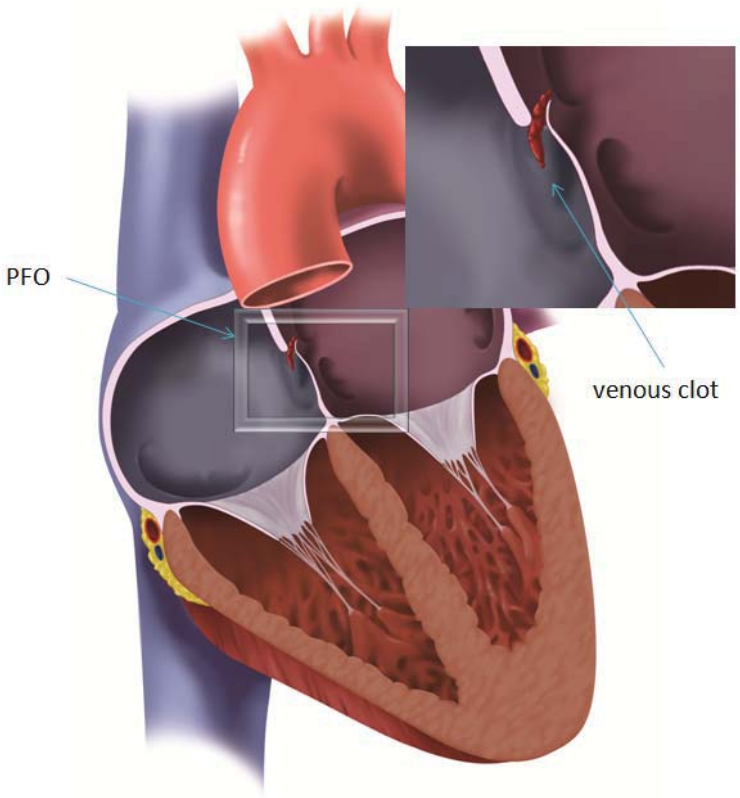

Figure 5. Patent foramen ovale at the atrial septum, showing a venous clot. Illustration is re-published by permission from St. Jude Medical, Inc.

According to the study by Hagen et al.,[34] the overall incidence of PFO was 27.3%, but it progressively declined with increasing age from 34.3% during the first three decades of life to 25.4% during the 4th through 8th decades and to 20.2% during the 9th and 10th decades. Neither incidence nor size of the PFO was significantly different between men and women.

The diagnosis of PFO has increased in the last decade with the increasing use of transesophageal echocardiography. This has made it possible to conduct research which has revealed an association between PFO and a variety of clinical conditions, such as hypoxemia, decompression sickness, migraine with aura, and the most debated issue, which this thesis will discuss: the association between PFO and cryptogenic stroke or TIA.

A variety of hypoxemia conditions are suspected to be due to venous mixture through the PFO,[35] as follows:

a. Chronic obstructive pulmonary disease. The prevalence of PFO in severe chronic obstructive pulmonary disease is high,[36] but this condition is no longer considered to be a clinical indication for PFO closure.

b. Obstructive sleep apnea: Impaired inhalation against a closed airway causes intrathoracic pressure changes affecting the central hemodynamics. In obstructive sleep apnea, hypoxemia occurs shortly after apnea. The degree of hypoxemia correlates strongly with the existence of a PFO.[37] Nonetheless, obstructive sleep apnea does not constitute an indication for PFO closure, except for research purposes.

c. Platypnea-orthodeoxia is a rare condition in which the rheological flows force the venous blood to go through the PFO into the arterial circulation, especially when the body is in an upright position. The condition can cause severe hypoxemia in an apparently normal heart without pulmonary hypertension. Most likely this is an under-diagnosed condition. This condition is often seen in conjunction with right-sided pulmectomy when the heart changes position in the thorax.[38] A few patients undergo PFO closure for this indication each year.

d. *Migraine with aura*
One study found that the prevalence of PFO in patients with migraine with aura is twice as common as in controls.[39] Thus it has been hypothesized that migraine is triggered by micro-embolism, or by vasoactive substances which are not metabolized in the pulmonary endothelium. The preliminary data were so convincing that a randomized study of 150 patients, called MIST, was performed.[40] PFO closure did not show any clear effect on the occurrence of migraine, but there was a slight reduction in migraine severity. The MIST trial has been debated intensively. At present, migraine is not considered to be an indication for PFO closure.

e. *Decompression sickness*
As pressure decreases during ascent from a dive with a gas cylinder, nitrogen can form bubbles, particularly in the venous blood. These bubbles go into the lungs and disappear with exhalation. Thus, a person with a PFO can get paradoxical nitrogen-gas embolism. For divers with a PFO, the risk of severe decompression sickness is five times larger.[41] European diver guidelines do not include PFO screening for divers because the absolute risk of decompression sickness is low and the majority regain neurological function completely after hyperbaric treatment.[42] In divers with a PFO and a history of decompression sickness, the clinical advice is to stop diving. Occasionally, professional divers with a PFO and decompression sickness have to undergo PFO closure.

Association between PFO and ischemic stroke

Cryptogenic ischemic stroke is defined as a stroke which cannot be attributed to any specific cause after an extensive search for the most common causes, such as, large-artery atherosclerosis, small-vessel occlusion, stroke of other determined etiology, and cardioembolism.[11] Cryptogenic stroke is present in about 25% of ischemic stroke patients under 70 years of age.[43] PFO has been implicated as a risk factor for cryptogenic stroke because paradoxical embolism and because several studies have reported

a significantly higher prevalence of PFO in patients with cryptogenic stroke than in healthy controls (44–66% vs. 0–27%).[44-46] A meta-analysis of 23 case-control studies suggested that the odds of the patient having a PFO were 2.9 times higher in patients with cryptogenic stroke as compared with controls (95% CI: 2.1 to 4.0).[47] Patients with cryptogenic stroke or TIA that is presumed to be related to a PFO are at risk for recurrent cerebrovascular events. In comparison with PFO alone, PFO and atrial septal aneurysm (ASAn) have been reported to be associated with an increased risk of recurrent thromboembolic stroke[48, 49] and a large PFO as a predictor for recurrent cerebrovascular ischemic events.[50, 51]

Treatment of patients with a PFO and cryptogenic stroke or TIA

Currently available therapeutic strategies for secondary prevention of paradoxical embolic stroke include long-term oral anticoagulation or antiplatelet medication or percutaneous PFO closure with a catheter-based procedure using a septal occluder device. Surgical closure is associated with a significant morbidity and mixed results regarding stroke prevention, and has been used only rarely in the last 14 years.[52-54] Percutaneous PFO closure has been shown to be safe and feasible.[55-58] Several different devices and different regimens of antiplatelet or anticoagulant therapy are used at present. A recently published non-randomized study showed a 0.4% recurrent stroke rate per year in PFO patients who underwent percutaneous closure and 3.4% per year in PFO patients who received medical treatment.[59] Although device closure of a PFO has been performed increasingly since the early 1990s, it has still not been established with sufficient certainty whether device closure is more efficient than medical treatment.

On the one hand, one systematic review pooled the five largest observational trials that have studied recurrent stroke or TIA after PFO closure, with a total of 1155 patients (516 undergoing PFO closure and 506 given medical therapy). The meta-analysis indicated that the relative risk reduction effect of PFO closure was over 80% (95% CI 41–94%). This systematic review was performed by Sahlgrenska Academy 2010 and is available online (HTA rapport 2010:31)[60], Figure 6.

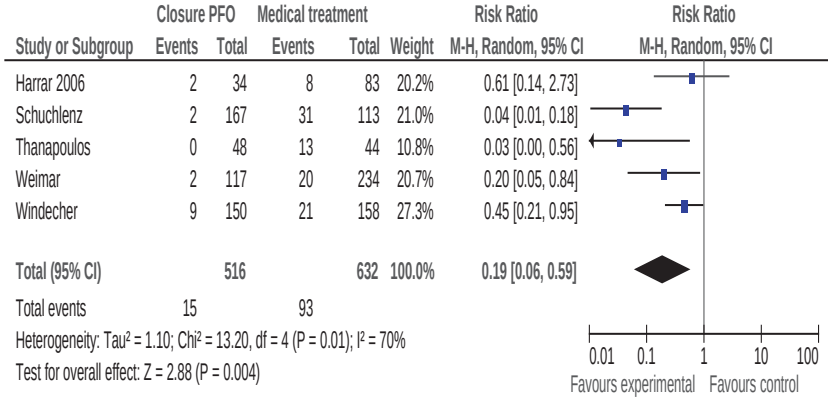

Figure 6. Meta-analysis of the five largest observational studies on PFO closure versus medical treatment. This figure is modified from the Sahlgrenska Academy HTA report 2010:31[60] and the individual studies are referenced in this thesis.[61-65]

On the other hand, three moderately sized randomized trials, shown in Table 1, concluded that percutaneous PFO closure plus medical therapy did not offer any significant benefit over medical therapy alone for the prevention of recurrent stroke or TIA in patients up to 60 years of age presenting with cryptogenic stroke or TIA and a PFO.[66-68]

Table 1. Outcomes in three RCT trials of PFO closure

RCT trial	Mean follow-up (years)	PFO closure group	Medical therapy group	*P*-value
Closure I: (Patients n=909)	*2*	(n=447)	(n=462)	
Composite: death, stroke,TIA, n (%)		23 (5.5)	29 (6.8)	0.37
Stroke, n (%)		12 (2.9)	12 (2.9)	0.79
TIA, n (%)		13 (3.1)	13 (3.1)	0.44
PC Trial: (414)	*4.1*	(n= 204)	(n=210)	
Composite: death, stroke, TIA, n (%)		7 (3.4)	11 (5.2)	0.34
Stroke, n (%)		1 (0.5)	5 (2.4)	0.14
TIA, n (%)		5 (2.5)	7 (3.3)	0.56
RESPECT (980)	*2.6*	(n=499)	(n=481)	
Non-fatal ischemic stroke, n (%)		9/499 (1.8)	16/481(3.3)	0.08
RESPECT, Per-protocol, n (%)		6/471 (1.3)	14/473 (3.0)	0.03
RESPECT, As-treated, n (%)		5/474 (1.1)	16/484 (3.3)	0.007

These RCT trials merit additional comments. First, the CLOSURE I trial showed no significant benefit of device closure over medical therapy during two years of follow-up. The primary outcomes of the most recent trials, RESPECT and the PC Trial, were not significantly affected by which treatment was given. All three trials recruited small numbers of patients over a long period; given that many of these patients were treated at the same institutions on clinical grounds, a significant degree of selective recruiting can be assumed.

All three trials are also subject to relatively large proportions of patients lost to follow-up or patients who withdrew consent, making firm conclusions about the results even more difficult. Also, time to follow-up was modest in all three trials, considering that PFO closure is an irreversible treatment given to comparatively young patients. The true long-term outcomes (i.e. 30–40 years) are not known, since RCT trials with long-term follow-up are lacking. There are few non-randomized studies reporting long-term clinical outcomes of device closure vs. medical therapy. Two studies with long-term follow-up showed a relatively low yearly rate of recurrent stroke (1–2%).[69, 70]

Studies about the impact of PFO closure on quality of life are lacking. It is important to know how patients feel about the fact that they consider themselves to have a hole in the heart. Do they think that closing the hole will give them a second chance to live and therefore feel better about the procedure? These and similar questions need to be answered by measuring quality of life (QoL) in a large number of patients in a long-term follow-up after PFO closure.

The only two studies[71, 72] that have investigated the psychological aspects of PFO closure have been small-scale. In the study by Cohen et al.,[71] 89 of 114 patients who had undergone PFO closure since 1998 because of stroke or TIA were enrolled and followed up in 2007; the dropout rate was 22%. The Hospital Anxiety and Depression Scale (HADS) was used,[73] and quality of life was assessed using the TaaQoL (TNO/AZL adult quality of life) questionnaire.[74] Patients were compared with 60 age-matched controls both pre-closure (1998) and post-closure (2007). The study found that levels of quality of life, depression and anxiety were comparable between PFO closure patients and the control group, but the PFO closure group reported a higher level of optimism.

In the study by Evola et al.,[72] 29 of 34 patients who had undergone PFO closure between 2009 and 2012 because of stroke or TIA answered the SF-36 questionnaire before closure and six months after closure. After PFO closure they showed significantly higher levels of physical and mental health.

Although the number of patients was small in both studies, they point toward a positive effect of PFO closure on quality of life and optimism. It is also known that other cardiac catheterization, such as percutaneous coronary intervention (PCI), has been shown to be associated with improved QoL after ST-elevation myocardial infarction (STEMI), Non-ST elevation myocardial infarction (Non-STEMI) and SIHD (stable ischemic heart disease) in patients without severe comorbidities.[75]

A decision to close or not to close a PFO should preferably involve experts in interventional cardiology as well as neurology, internal medicine, cardiac imaging and cardiology. The lack of widely accepted and undisputed indications has made it difficult to clinically define whether cryptogenic stroke is present or not. For such a critical matter, hospital administrators, financing bodies, and public confidence in the health care system all demand the establishment of clear guidelines as well as a system to promote adherence to such guidelines. A multi-disciplinary approach that involves stakeholders of various backgrounds has the potential to enhance adherence and promote transparency in clinical decision-making. Furthermore it is necessary to study the long-term effects of PFO closure on the heart structure, complications of PFO closure, recurrence of stroke or TIA, and quality of life after PFO closure.

The Gothenburg Center for Grown-Up Congenital Heart Disease (GUCH) has performed percutaneous PFO closure in order to reduce the risk of recurrent stroke in selected patients since 1997. Our center has over ten years of experience, and our large number of patients and extensive data facilitate studies on these patients, expanding current understanding about PFO and cryptogenic stroke.

AIMS

The overall aim of this thesis was to study the long-term clinical outcomes regarding survival, complications, recurrent stroke or TIA and quality of life in patients who have undergone PFO closure versus those who have not.

The specific aims were:

Paper I
To provide a long-term clinical follow-up of patients who have undergone a percutaneous PFO closure after a cryptogenic stroke by looking at survival, complications, recurrent stroke, and other adverse events.

Paper II
To study whether a multidisciplinary approach, involving experts from stroke, echocardiography, intervention cardiology and an expert in thromboembolism, can maintain stringent criteria for PFO closure to avoid inconsistent clinical decision-making between doctors.

Paper III
To compare long-term outcomes of PFO closure versus non-closure in PFO patients who have been carefully selected by a multidisciplinary panel discussion (PFO conference). PFO closure was recommended according to strict criteria intended to identify patients at high risk of paradoxical embolization.

Paper IV
To assess health-related quality of life after PFO closure compared to age-and gender matched reference group from general population and compared to patients with a PFO and a stroke who had not undergone PFO closure.

Ethics
The Regional Medical Research Ethics Committee of Gothenburg approved all studies including in this thesis (DNR=029-09). Informed written consent was obtained from all participants.

PATIENTS AND METHODS

Paper I

This retrospective follow-up study included all eligible patients who underwent PFO closure between 1997 and 2006 in the Gothenburg GUCH center at Sahlgrenska University Hospital/Östra, which serves a population of 1.7 million inhabitants. This is the only GUCH center in the western region of Sweden where this procedure is carried out. Patients were referred from hospitals in the central and western part of Sweden. All these patients were diagnosed with cryptogenic stroke or TIA associated with PFO by neurologists and cardiologists at local hospitals before they were referred to Gothenburg. However, further evaluation of the patient's clinical data and medical records, including transesophageal echocardiography (TEE), CT or MRI brain scan, was made by our interventional cardiologists, who took the final decision about PFO closure after consulting the TEE imaging expert and stroke expert.

The follow-up was conducted in two phases: short-term follow-up at six months and long-term follow-up after almost five years. At six months, a TEE was performed with color Doppler and contrast injections during the Valsalva maneuver in all patients who had undergone PFO closure. The referring physician was responsible for the final decision about whether to continue with acetylic acid or anticoagulants after six months The follow-up was conducted between 2011 and 2012. All surviving patients were invited to clinical follow-up and personal interviews. Patients who agreed to attend follow-up at our center were examined with electrocardiogram (ECG) and transthoracic echocardiography. The patient's neurological status was assessed using the modified Rankin Scale.[76-78] Patients who could not attend our center were followed up with a structured telephone interview.

Information about recurrent stroke or TIA after the PFO closure was obtained from medical records of patients who were admitted to any hospital for a new clinical event of ischemic stroke or TIA. Vital status was ascertained from hospital records, public civil registries and the *Swedish* Cause of *Death Register for more information see website: http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish*

Paper II

Paper II was a descriptive study of the PFO conference and included all patients with a PFO who were referred to our GUCH centre for PFO closure between 2006 and 2009. A neurologist or internal medicine specialist working with stroke medicine made the primary diagnosis of TIA or ischemic stroke before patients were referred to our unit. The referrals had to be accompanied by a completed standardized PFO questionnaire.

PFO Questionnaire

The PFO questionnaire is a standardized protocol addressing patients' risk data and indications for closure; from this we could identify patients who were not suitable for closure. In the questionnaire we received all information about the patient's history,

the investigation process for the diagnosis of cryptogenic stroke e.g. CT or MRI scan of the brain and vertebrae circulation, carotid Doppler, serum lipids, presence or absence of thrombophilia, medical treatment, other concomitant diseases and detailed information about the TEE. See Appendix 1 which is available on website http://www.guch.nu/guch%20hemsida/Gbg/information_lakare/PFO_konferensunderlag.pdf

PFO conference

Specialists in neurology, cardiology, and internal medicine attended the PFO conference. Clinical data from the PFO protocol, medical records, including TEE, CT and MRI brain scans, were discussed at our PFO conference and stroke etiology and morphological risk were re-evaluated for each patient. Decisions were made by consensus (Figure 7).

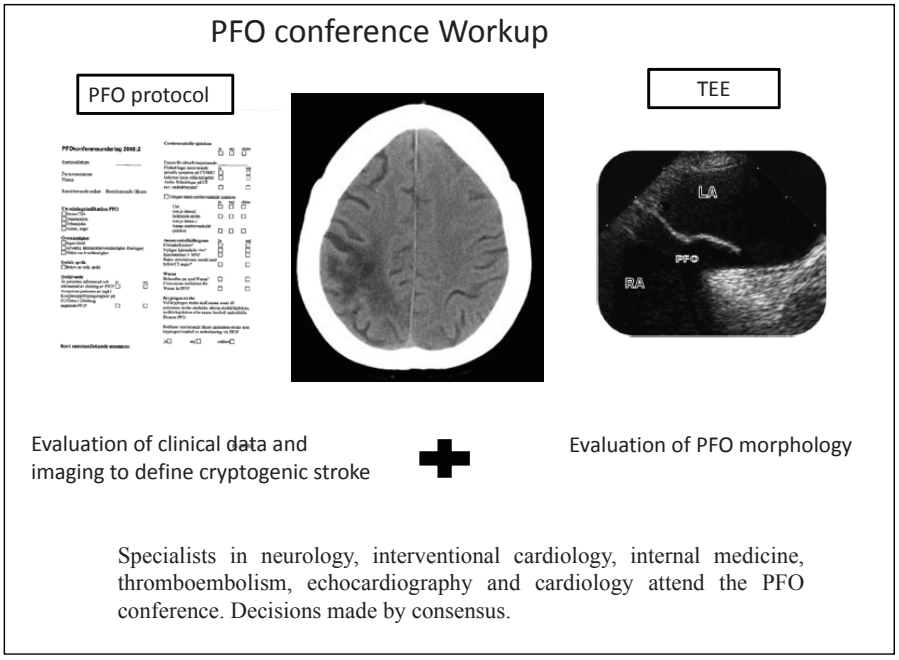

Figure 7. PFO conference work-up.

Paper III

As in Paper II, all patients who had been discussed at PFO conferences between 2006 and 2009 were invited to a clinical follow-up visit, starting 1 December 2012. However, we identified three additional patients not included in Paper II; these cases had been discussed during beginning of 2006 at our PFO conferences and they had all undergone a full investigation. This gave a new total of 314 patients in Paper III. A routine follow-up TEE was performed six months after PFO closure in patients who

underwent the procedure, to determine whether there was complete closure or residual shunting. A total of 314 patients were followed up. A structured medical history, including items on recurrent stroke or TIA, risk factors for stroke, and potential complications to PFO closure treatment, was obtained for all patients. If any suspected cerebrovascular or cardiovascular events were noted, the patient's medical records were retrieved from their hospital for more information. A color Doppler transthoracic echocardiogram was performed on all patients in the closure group at the long-term follow-up visit.

Study endpoints

The primary outcome was defined as a composite of all-cause mortality, stroke and TIA. The secondary outcomes were either recurrent stroke or TIA or all-cause mortality.

Paper IV

Paper IV was a prospective study in which quality of life was assessed in all the patients included in Paper I and III. Patients with cryptogenic stroke or TIA strongly suspected to be related to a PFO underwent PFO closure, whereas those with stroke of known origin or a diagnosis other than stroke or TIA did not. All included patients were invited for a long-term clinical follow-up visit during the period 2012 to 2014.

At the clinical follow-up visit, health-related quality of life (HRQoL) was assessed using the Swedish version of the Medical Outcomes Study Short Form 36 Health Survey (SF-36).[79] The questionnaire was mailed to patients who were unable to attend the clinic. An age- and gender-matched reference sample (n=344) was randomly drawn from the Swedish SF-36 normative database (n=8930).[79]

The SF-36 is a widely used 36-item generic questionnaire that measures HRQoL in eight domains: *physical functioning* (PF), *role limitation – physical* (RP), *bodily pain* (BP), *general health* (GH), *vitality* (VT), *social functioning* (SF), *role limitation – emotional* (RE), and *mental health* (MH). Item ratings are transformed using a standard algorithm such that domain scores range from 0 to 100, where higher scores represent better HRQoL. The Swedish version of the SF-36 has been shown to have good reliability and validity.[80, 81]

Definitions used in Paper I–IV

- A diagnosis of TIA was given by the treating neurologist if acute neurological deficits with a probable vascular (ischemic) cause completely resolved within 24 hours.
- Ischemic stroke was defined as a sudden new focal neurological deficit lasting more than 24 hours.[82]
- Stroke etiology was defined according to the modified TOAST criteria.[11]
- Cryptogenic stroke (CS) was defined as a stroke which cannot be attributed to any specific cause after an extensive search for the most common causes of ischemic

stroke; these include large-vessel disease, small-vessel disease, stroke of other determined etiology, and cardioembolism.

- Intraprocedural catheter-related complications were defined according to Khiary et al.[83]
- Major complications were defined as death, hemorrhage requiring blood transfusion, cardiac tamponade, need for surgical intervention, and massive fatal pulmonary emboli.[83] Any additional adverse events are reported by each study.
- Minor complications were defined as bleeding not requiring transfusion, periprocedural atrial arrhythmias, transient atrioventricular node block, device arm fractures, device embolization with successful catheter retrieval, asymptomatic device thrombosis, need for recatheterization, symptomatic air embolism, transient ST-segment elevation, arteriovenous fistula formation, and femoral hematoma.[83]
- A PFO was defined as the appearance of microbubbles in the left atrium within three heartbeats from when the contrast filled the right atrium in the absence of a tissue defect.[37] It is important to mention that a PFO is functionally closed most of time, due to higher pressure in the left atrium than in the right atrium. A provocation such as the Valsalva maneuver may be used in order to invert the interatrial pressure gradient and thus open the PFO; however, a right-to-left shunting may also occur without the Valsalva maneuver, for example, in large PFOs. Right-to-left shunting at rest or during the Valsalva maneuver was detected in all patients by TEE before the PFO conferences (Figure 8).

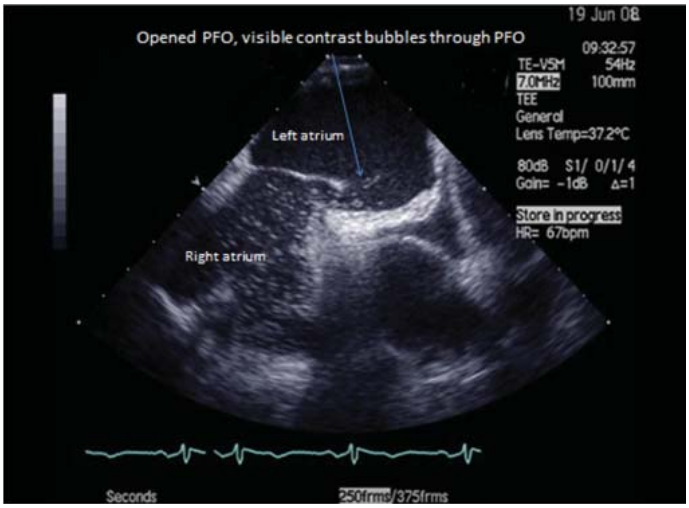

Figure 8. Transesophageal echocardiography picture of right-to-left passage of contrast bubbles through a PFO.

- Residual shunting was defined as minimal when 1–20 microbubbles were seen in the left atrium or when the shunt was seen only with color Doppler despite multiple contrast injections during the Valsalva maneuver. When more than 20 bubbles were seen in the left atrium, the shunt was considered substantial.[84]

- An atrial septal aneurysm (ASAn) was defined as 15 mm phasic excursion of the atrial septum from side to side or into the right or left atrium.[85] An aneurysm is a balloon-like bulge, and in an ASAn the septum primum forms a flap that undulates in the foramen ovale, partially explaining that inter-atrial communication is open. A PFO with or without ASAn will in the majority of cases never give any symptoms or have any clinical significance.

Closure and exclusion criteria for PFO closure used in Paper I–IV

- The main criteria for closure were patients with a first ever cryptogenic stroke with high-risk morphology (a PFO with ASAn), or recurrent cryptogenic stroke and a PFO with or without ASAn (high-risk or low-risk morphology).

- Patients with stroke of known origin, such as cardiac events (atrial fibrillation, acute myocardial infarction within the previous four weeks, or large apical infarction at any time), patients without PFO, and patients with major aortic plaques, as well as patients with decompression sickness or orthodeoxia–platypnea, were excluded from the study.

Implementation of treatment used in Paper I–IV

We clearly recommended one treatment for each patient but the final treatment decision was left to the patient and their referring physician. However, a decision to close by catheter could only be made by the panel and could not be overruled by the preferences of the patient or the referring physician. Furthermore, we invited patients who wanted to have more information about the operation. The time from decision to operation was between three and five months. At operation, measurements of the PFO were performed initially by using fluoroscopy and transesophageal echocardiography. Finally, the appropriate device according to the size of the PFO was implanted in the atrial septum. All patients received intravenous prophylactic antibiotics during the procedure and were loaded with aspirin 320 mg or 300 mg clopidogrel and low molecular weight heparin. The day after the closure, before patients were discharged from hospital a transthoracic echocardiogram was performed to confirm proper positioning of the device (Figure 9).

Transesophageal echocardiography (TEE)

TEE is considered to be the method of choice for PFO detection.[86] All patients were investigated with TEE before they were referred to us. A PFO was diagnosed if contrast bubbles entered the left atrium through the oval structure or if color Doppler detected right-to-left flow between the two septa (Figure 8). Agitated NaCl or polypeptide colloidal solution was used as contrast medium by repeated and forceful injection from one syringe to another through a three way stopcock.

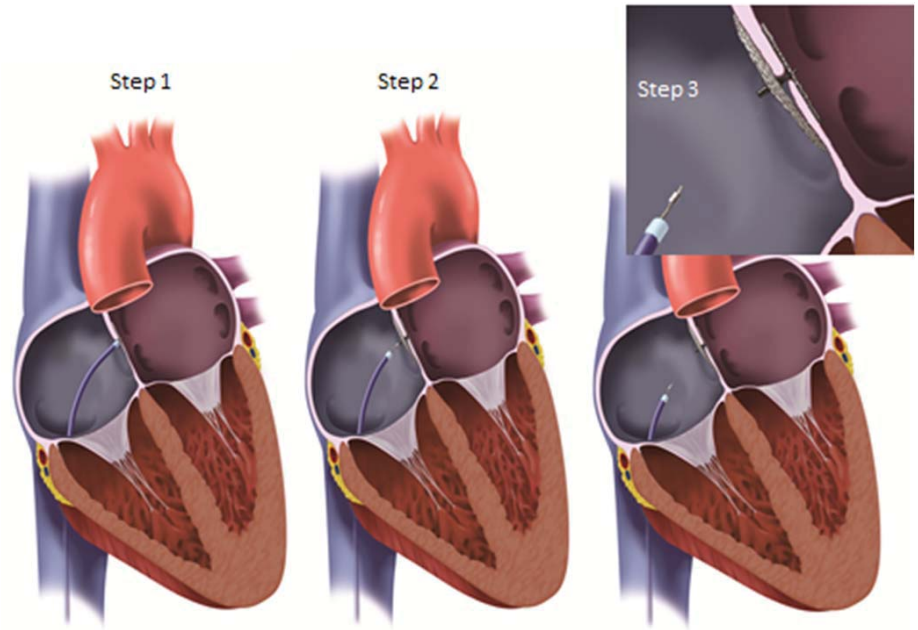

Figure 9. Device transfer via catheter over the atrial septum, where the left disc developed (step 1). Then the catheter backs up into the right atrium where the second disc developed (step 2). The optimal results are assessed by fluoroscopy and echocardiography after the device is released (step 3). These illustrations are re-published by permission from St. Jude Medical, Inc.

Devices used in Paper I–IV

The device was chosen according to the size of the PFO, measured by balloon sizing and morphology visualized by TEE at the time of device closure. The vast majority of closures used an AMPLATZER® PFO Occluder device (AGA Medical Corp, Plymouth, MN, USA). If the PFO size was more than 15 mm, an AMPLATZER Septal Occluder (ASD closure device) or an AMPLATZER Multi-Fenestrated Septal Occluder "Cribriform" (multi-fenestrated ASD closure device) could be used; if the PFO was less than 7 mm, a BioSTAR® (NMT Medical, Inc., Boston, MA, USA), a Solysafe® Septal Occluder (Swissimplant AG, Solothurn, Switzerland), or a GORE® HELEX® Septal Occluder (WL Gore and Assoc, Inc, Newark, DE, USA) device could be considered, at the operator's discretion.

Economic aspects

Health economic studies and analyses are still lacking. The cost of catheter closure of a PFO in the GUCH center in Gothenburg is approximately 110 000 SEK (12 000 EUR) per patient. If further research shows that the procedure reduces the recurrence of stroke or TIA, then the cost of the procedure would be compensated by the reduced need for stroke treatment and hospitalization for recurrent stroke or TIA. It may even contribute to reducing current treatment costs.

Statistics

Paper I–II

Analyses in Paper I and II were performed using PASW Statistics v.18 SPSS software for PC (IBM Corp, Armonk, NY, USA). Variables in Paper II were compared using Pearson's chi-square test, and $p<0.05$ was considered to be a significant difference between groups.

Paper III

The statistical analysis in Paper III was performed using SPSS v.22 (IBM Corp, Armonk, NY, USA). Two sets of analyses were pre-specified: an intention-to-treat (ITT) analysis, which included all patients according to the group to which they were assigned at the PFO conference, and an as-treated analysis, which included patients who actually received the assigned treatment.

The cumulative incidence of study endpoints was studied using the Kaplan–Meier estimate. Overall survival between groups was compared using the log-rank (Mantel–Cox) test and $p<0.05$ was considered to be a significant difference between groups. For multivariate comparisons, we used Cox proportional hazards models to derive hazard ratios, comparing the accepted and not-accepted groups based on the initial decision at the PFO conferences. All variables competed in the model by backward elimination with the Wald statistic and were adjusted for age, sex, and risk factors for stroke (hypertension, diabetes, hyperlipidemia and smoking).

Paper IV

Data were analyzed using SPSS v.22.0 (IBM Corp, Armonk, NY, USA). For the descriptive analysis, means and standard deviations were used. Comparisons between patient groups (closure and non-closure) and reference values were performed using the parametric Paired Sample t-test. Due to differences in age between the closure and non-closure groups, analyses of SF-36 variables were performed using ANOVA with adjustment for age. A p-value below 0.05 was considered to be significant.

RESULTS

Paper I

Percutaneous PFO closure was successfully performed in 85 of 86 patients. The remaining patient had several septal defects and was not suitable for percutaneous closure, remaining instead on lifelong treatment with warfarin. Of the 86 patients, two (2.3%) died of lung cancer at 39 and 60 months after PFO closure. Both of these patients were free from recurrent events before death. No cardiovascular or cerebrovascular deaths occurred. The long-term follow-up was successfully performed in all the 84 live patients within a mean of 7.3 years (minimum 5.0 years – maximum 12.4 years) after the PFO closure (follow-up rate 100%). Follow-up visits were conducted for 64 patients and the remaining 20 patients were followed up by phone. Information about recurrent stroke/TIA was obtained from medical records of patients if they were admitted at any hospital for a new clinical event of ischemic stroke or TIA after PFO closure. See Table 2 for patient characteristics and medication at closure and at follow-up.

Table 2. Patient characteristics and medication at closure and at follow-up

Characteristics	**No. (%) of patients**	
	At baseline (n=86)	**At long-term follow-up (n=84)**
Mean age (range)	49 (± 10.6)	56 (± 10.44)
Hypertension, n (%)	15 (17)	20 (23)
Hyperlipidemia, n (%)	15 (17)	22 (26)
Diabetes mellitus, n (%)	2 (2)	2 (2)
Atrial fibrillation, n (%)	0 (0)	0 (0)
PVD, n (%)	1 (1)	1 (1)
Current smoker, n (%)	11 (13)	9 (11)
CT/MRI-verified infarcts, n (%)	68 (79)	-
PFO + ASAn, n (%)	61 (71)	-
PFO alone, n (%)	25 (29)	-
First-time stroke or TIA, n (%)	48 (56)	-
Recurrent stroke or TIA, n (%)	38 (44)	
Medication:		
Warfarin, n (%)	55 (64)	2 (2)
Aspirin, n (%)	25 (29)	46 (54)
Clopidogrel, n (%)	1 (1)	0 (0)
Assasantin, n (%)	4 (5)	2 (2)
Dipyridamol, n (%)	0 (0)	1 (1)
No medication, n (%)	0 (0)	33 (38)

PFO=patent foramen ovale, PVD=peripheral vascular disease, ASAn=atrial septal aneurysm, TIA=transient ischemic attack, CT=computed tomography scan, MRI=magnetic resonance imaging of the brain.

As shown in Figure 10, the main indications for closure were patients with a first ever cryptogenic stroke with high-risk morphology (a PFO with ASAn), or recurrent cryptogenic stroke and a PFO without ASAn.

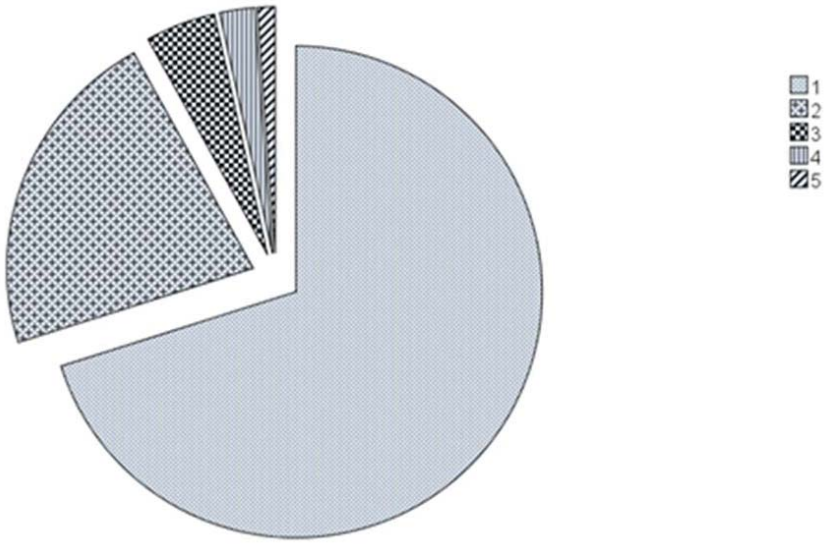

Figure 10. Indications for PFO closure in Paper I (86 patients) (1=at least one previous cryptogenic stroke (CS) or transient ischemic attack (TIA) + atrial septal aneurysm (ASAn); 2=two previous CS or TIA without ASAn; 3=one CS or TIA without ASAn but huge right-to-left passage; 4=only one CS or TIA without ASAn; 5=brain abscess and PFO).

One patient had a minor stroke one month after PFO closure and a TIA two years after PFO closure. One other patient had a TIA six years after closure. Both neurological events occurred in patients who had undergone successful PFO closure and had no evidence of thrombus formation or residual leaking during the follow-up. No long-term device-related complications were observed. After on average 18 months, the TEE showed complete device closure in 93% of patients; six patients (7%) still showed small shunts but none showed substantial shunts.

Complications

There were no procedure-related major complications during the implantation of the closure device. One patient with several septal defects was not suitable for percutaneous closure. Three patients (3.5%) suffered from AF during the first six months after PFO closure and this was converted to sinus rhythm by electrical cardioversion. One of these patients was still in AF at the six-month follow-up, but it was in due course converted and the patient was in sinus rhythm at the long-term follow-up. No further hospitalization was reported and this patient had no recurrent events. No long-term complications related to PFO closure, such as death, device embolization, or chronic AF was found.

Paper II

Between 2006 and 2009 a total of 311 patients were evaluated at the PFO conferences. Using the clinical algorithm shown in Figure 11 to identify high-risk patients, we accepted 144 patients for PFO closure (99 men and 45 women) whereas 167 patients were not recommended for closure (93 men and 74 women).

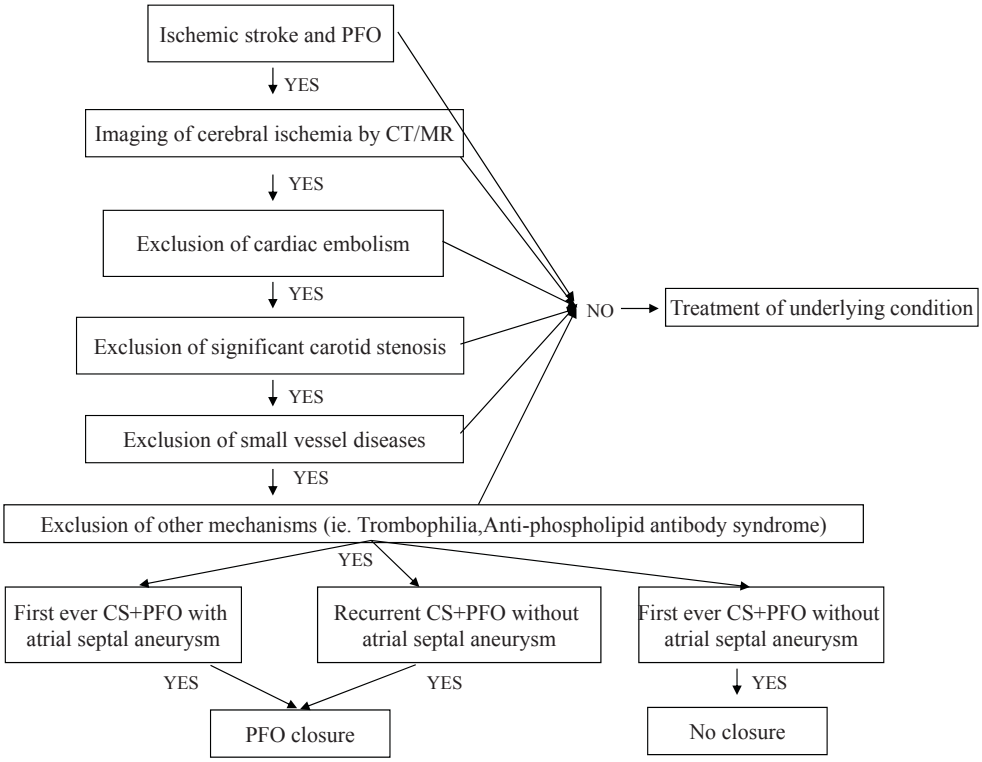

Figure 11. Clinical algorithm for a multi-disciplinary decision on PFO closure in cryptogenic stroke, PFO=patent foramen ovale, CT=computed tomography, MR=magnetic resonance, CS=cryptogenic ischemic stroke.

Our acceptance rate for PFO closure was similar throughout these years, with an average of 45% (43% in 2006, 42% in 2007, 52% in 2008, and 42% in 2009) (Figure 12). Patients accepted for closure were younger than those who were rejected (mean 50 years vs. 58 years, $p<0.001$). The mean age was 51 years for men and 47 years for women in the closure group vs. 57 years for men and 59 years for women in the group that was rejected for closure. Of the patients in the closure group, 84% were under 60 years and 94% were under 65 years.

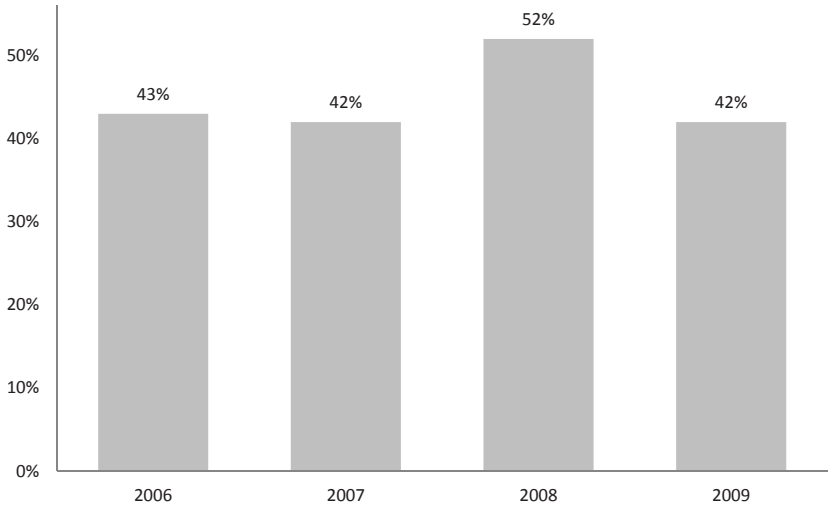

Figure 12. Acceptance rate at PFO conferences 2006–2009.

Paper III

As in Paper II, all patients evaluated for PFO closure at our PFO conference between 2006 and 2009 were followed up almost five years later. Their baseline characteristics are shown in Table 3.

Table 3. Baseline characteristics of 314 patients evaluated at PFO conferences 2006–2009

	All groups	Accepted for closure	Not recommended for closure
Total patients, n	**314**	**151**	**163**
Age in years (±SD)	54 (12)	49.99 (±10.9)	57.95 (±12)
Gender, male, n (%)	195 (62)	105 (69)	90 (56)
Body mass index (±SD)	26 (±3.5)	26.2 (±3.2)	25.59 (±12)
Arterial hypertension, n (%)	90 (29)	29 (19)	61 (38)
Diabetes mellitus, n (%)	19 (6)	3 (2)	16 (10)
Current smoker, n (%)	47 (15)	18 (12)	29 (18)
Ex-smoker >3 months, n (%)	93 (30)	41 (27)	52 (32)
Carotid stenosis >50%	9 (2.8)	0	9 (5.5)
Recent myocardial infarction <4 weeks	1(0.3)	0	1 (0.6)
Hypercholesterolemia, n (%)	69 (22)	25 (16)	44 (27)
Atrial fibrillation, n (%)	16 (5)	1 (0.6)	15 (9)
Cerebrovascular index event, n (%)			
Ischemic stroke, n (%)	213 (68)	118 (78)	95 (59)
TIA, n (%)	87 (28)	34 (22)	53 (33)
Other diagnosis, n (%)	14 (4.5)	0	14 (9)
Previous cerebrovascular events			
Ischemic stroke, n (%)	49 (16)	30 (20)	19 (12)
TIA, n (%)	61 (19)	30 (20)	31 (19)
Unknown, n (%)	25 (8)	7 (5)	18 (11)
Atrial septal anatomy			
PFO only, n (%)	160 (51)	50 (33)	110 (68)
PFO & atrial septal aneurysm, n (%)	154 (49)	102 (67)	52 (32)

Other diagnoses were: non-cerebrovascular event (n=8), peripheral embolism (n=1), neurological symptoms but not verified diagnosis of stroke or TIA (n=5). TIA=transient ischemic attack; PFO=patent foramen ovale.

Of 314 patients, 151 (48%) were accepted for closure and 163 (52%) were not accepted (mean age 50 vs. 58 years). Two patients (1.3%) unwilling to undergo PFO closure crossed over to the non-closure group. Three patients (1.8%) from the non-closure group crossed over to the closure group. Criteria for closure and reasons why closure was not recommended are described in Figures 13 and 14. As mentioned previously, in contrast to Paper II, criteria for closure and non-closure in Paper III were registered after a complete investigation, which led to the identification of three more patients who had undergone PFO closure during the same period 2006–2009. This explains the difference in numbers of patients in Paper II and III.

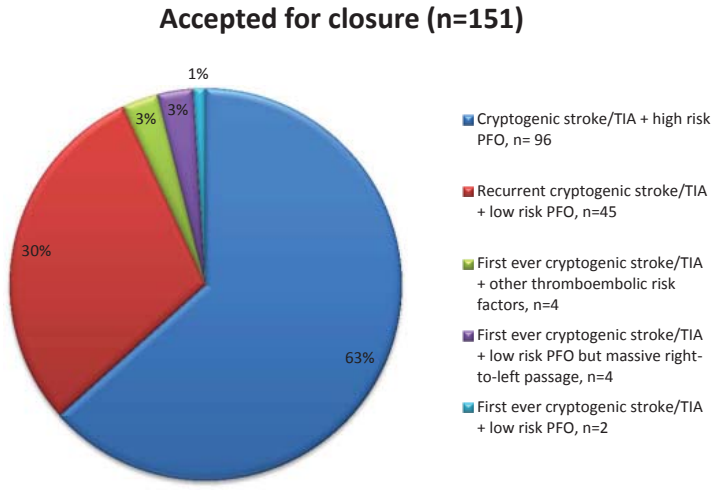

Figure 13. Indications for PFO closure in Paper III (n=151). PFO=patent foramen ovale, high risk PFO=PFO with atrial septal aneurysm, low-risk PFO=PFO without atrial septal aneurysm or other thromboembolic risk factor or patients with APC resistance, TIA=transient ischemic attack.

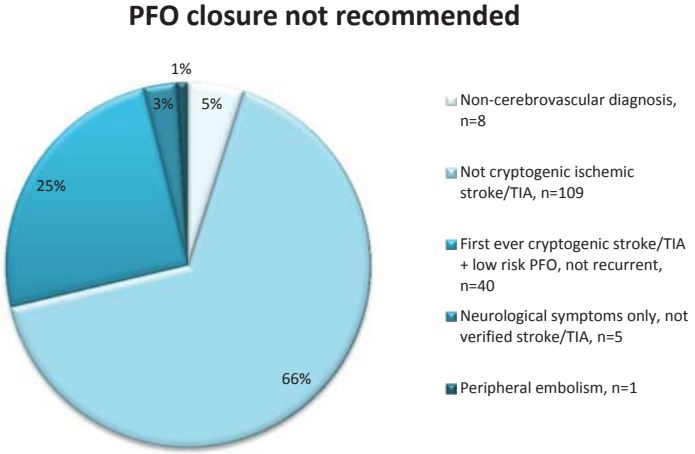

Figure 14. Reasons why PFO closure was not recommended in Paper III (n=163). PFO=patent foramen ovale, low-risk PFO=PFO without atrial septal aneurysm, TIA=transient ischemic attack, non-cerebrovascular diagnosis=incidentally detected PFO in patients with, for example, atrial fibrillation, endocarditis, or vertigo.

Anticoagulation or anti-platelet therapy at baseline and at follow-up is shown in Table 4.

Table 4. Anticoagulation or antiplatelet therapy at baseline and at follow-up

	Baseline (PFO conference) n=314		At follow-up n=300*	
	Closure group	Non-closure group	Closure group	Non-closure group
Patients, n	**151**	**163**	**145**	**155**
Warfarin	104 (69)	47 (29)	14 (9.6)	22 (14)
Aspirin only	33 (22)	49 (30)	62 (43)	61(39)
Clopidogrel only	3 (1.9)	0	6 (4)	8 (5)
Aspirin + clopidogrel	0	0	1 (0.7)	1 (0.6)
Dipyridamol + Aspirin	6 (3.9)	11(6.7)	8 (5.5)	29 (19)
Dipyridamol only	0	0	0	2 (1.3)
LMWH	2 (1.3)	2 (1.2)	0	0
Unknown	3 (1.9)	50 (31)	4 (2.7)	5 (3.2)
No anticoagulation & no anti-platelet therapy	0	4 (2.4)	50 (34)	27 (17.4)
Total n, (%)	151 (100)	163 (100)	145 (100)	155 (100)

PFO = patent foramen ovale; LMWH = low molecular weight heparin. *Information about medications is missing on patients who died (n=12) or declined follow-up (n=1). Missing data (n=1).

In the intention-to-treat analysis, the cumulative incidence of all-cause mortality, stroke or TIA for closure vs. non-closure over a mean follow-up time of five years was 10.6% (16 events) vs. 12.9% (21 events), p=0.53. Six patients (3.9% vs. 3.7%, p=0.87) died in each group, but no deaths were associated with PFO closure, recurrent stroke or TIA. The incidence of recurrent stroke or TIA for closure vs. non-closure was 6.6% (10 events) vs. 9.2% (15 events), p=0.63 (Figure 15). The respective event rates for stroke were 3.9% (six events) vs. 5.5% (nine events), p=0.50 and for TIA, 2.6% (four events) vs. 3.7% (six events), p=0.59.

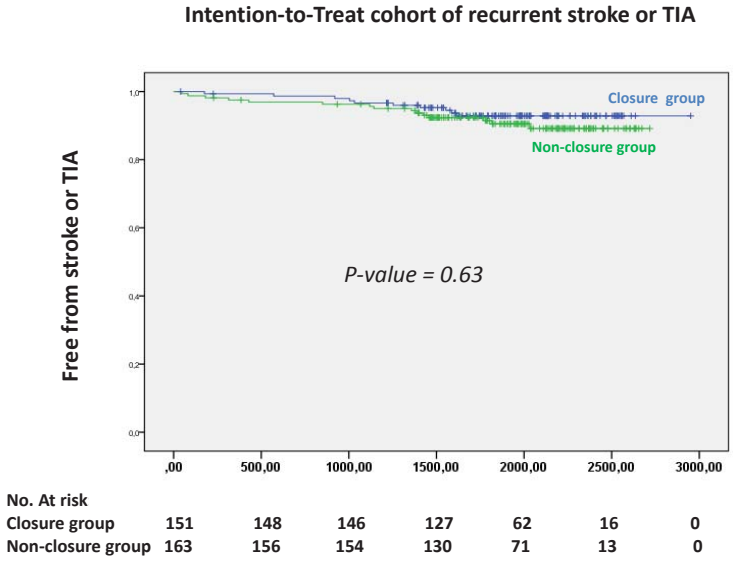

FIgure 15. Intention-to-treat cohort of recurrent neurological events. p=0.63 by log-rank test.

The as-treated analysis included 151 patients (48%) who actually underwent PFO closure and 162 patients (52%) who did not. All-cause mortality did not differ between the closure and non-closure group in the as-treated analysis, 3.3% (five deaths) vs. 3.7% (six deaths), p=0.85). The cumulative incidence (Kaplan–Meier estimate) of the primary endpoint during this mean follow-up time of 5±1 years (range 3–8 years) was 9.3% (14 events) in the closure group, compared with 12.2% (20 events) in the non-closure group, p=0.41.

The incidence of recurrent stroke or TIA for closure vs. non-closure in the as-treated analysis was 5.9% (nine events) vs. 8.6% (14 events), p=0.58 (Figure 16). The respective event rates for stroke were 3.9% (six events) vs. 4.3% (seven events), p=0.98 and for TIA, 1.9% (three events) vs. 4.3% (seven events), p=0.24.

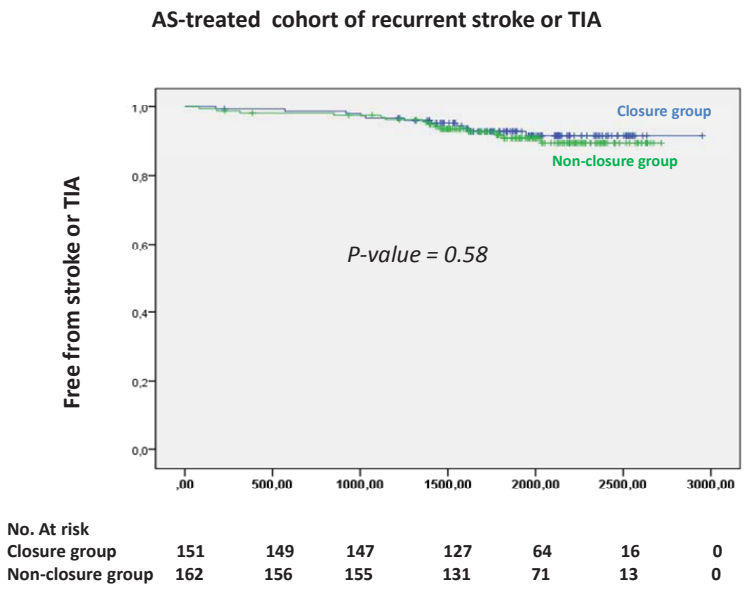

Figure 16. As-treated cohort of recurrent neurological events. p=0.58 by log-rank test.

We used a multivariate Cox proportional-hazards model with PFO closure, age, sex and risk factors for stroke (hypertension, diabetes, hyperlipidemia and smoking). Using this model we found that age had a small but significant effect on the primary composite endpoint: all-cause mortality, stroke or TIA (hazard ratio 1.043; 95% CI 1.013 to 1.074; p=0.005). Current smoking seems to increase the risk of the primary composite endpoint (hazard ratios 2.983; 95% CI 1.498 to 5.942; p=0.002). PFO closure was not associated with increased risk for the primary endpoint. Cox proportional hazards models in the as-treated analysis for the primary endpoint showed similar result as the ITT analysis.

Complications

The total numbers of procedure-related and device-related adverse events are shown in Table 5. There were 12 (8.2%) serious adverse events in this study, of which four events (2.8%) were procedure-related and eight (5.4%) were device-related.

Table 5. The observed adverse events related to the procedure or device among 149 patients who underwent successful percutaneous closure of a PFO

Adverse events	Total events (%)	Procedure-related events within 48 hours (%)	Device-related events within six months (%)	Device-related events within five years (%)
Serious adverse events				
Stroke	1 (0.7)	1 (0.7)	-	-
Sepsis	1 (0.7)	1 (0.7)	-	-
Thrombus on device	1 (0.7)	-	-	1 (0.7)
Atrial fibrillation	8 (5.4)	1 (0.7)	7 (4.7)	-
Atrial flutter	1 (0.7)	1 (0.7)		
Total serious adverse events	12 (8.2)	4 (2.8)	7 (4.7)	1 (0.7)
Minor adverse events				
Temporary ST-segment elevation	2 (1.3)	2 (1.3)	-	-
Hematoma	1 (0.7)	1 (0.7)	-	-
Asymptomatic thrombosis on catheter	3 (2.0)	3 (2.0)	-	-
Palpitations not requiring hospital admission	10 (6.7)	-	10 (7.0)	-
Asymptomatic AV block II, type 1	1 (0.7)	-	1 (0.7)	-
Total minor adverse events	17(11.4)	6 (4.0)	11 (7.0)	

Of 151 patients who were accepted for closure, one underwent surgical closure and in one patient PFO closure could not be performed due to multiple atrial septal defects. All information about procedure or device-related events was obtained from the patients' medical records. Reports of palpitations are based on information reported by patients. (AV=atrioventricular)

Paper IV

A total of 400 patients with cryptogenic stroke or TIA who had been referred to our hospital for PFO closure, between 1997 and 2009, were invited to a long-term clinical follow-up (mean follow-up 5.5 years; range 3–13 years). HRQoL was assessed using the SF-36 Health Survey and data were compared with an age- and gender-matched reference group from the Swedish SF-36 normative database. Fifteen patients had died and 41 did not complete the SF-36 questionnaire. Of 344 patients who completed the SF-36, 208 had undergone PFO closure and were on average eight years younger than the non-closure group (n=136). Baseline characteristics and modified Rankin Scale score at follow-up are described in Table 6.

The closure group showed similar levels of quality of life to the reference group. The non-closure group had significantly lower scores than the closure group, using ANOVA with adjustment for age, in physical functioning (PF), role limitation – physical aspects (RP), vitality (VT), and general health (GH) ($p<0.05$). They also had significantly lower scores than the reference group in RP, VT, GH, and mental health (MH), $p<0.05$. Social functioning (SF) approached significance ($p=0.05$) (Figure 17).

Table 6. Baseline characteristics of 344 PFO patients with ischemic stroke or transient ischemic attack

Total Respondents, n	All groups 344	Closure group 208	Non-closure group 136
Baseline characteristics			
Mean age (±SD)	52 (11.9)	49 (10.7)	57 (11.7)
Gender, female, n (%)	129 (37)	74 (36)	55 (40)
Arterial hypertension, n (%)	82 (24)	34 (16)	48 (35)
Diabetes mellitus, n (%)	16 (5)	5 (2)	11 (8)
Current smoker, n (%)	47 (14)	26 (13)	21 (15)
Ex-smoker >3 months, n (%)	92 (27)	48 (23)	44 (32)
Hypercholesterolemia, n (%)	73 (21)	38 (18)	35 (26)
Cerebrovascular index event n (%)			
Ischemic stroke	173 (65)	98 (47)	75 (55)
Transient ischemic attack	80 (30)	32 (15)	48 (35)
Previous cerebrovascular events n (%)			
Ischemic stroke	49 (14)	35 (17)	14 (10)
Transient ischemic attack	74 (22)	52 (25)	22 (16)
Modified Rankin Scale at follow-up			
No symptoms at all	219 (66)	137 (66)	82 (60)
No significant disability despite symptoms	65 (19)	41 (20)	24 (18)
Slight disability	36 (11)	16 (8)	20 (15)
Moderate disability	7 (2)	5 (2.4)	2 (1.4)
Moderately severe disability	3 (0.9)	0	3 (2.2)
Severe disability	1 (0.3)	0	1 (0.7)

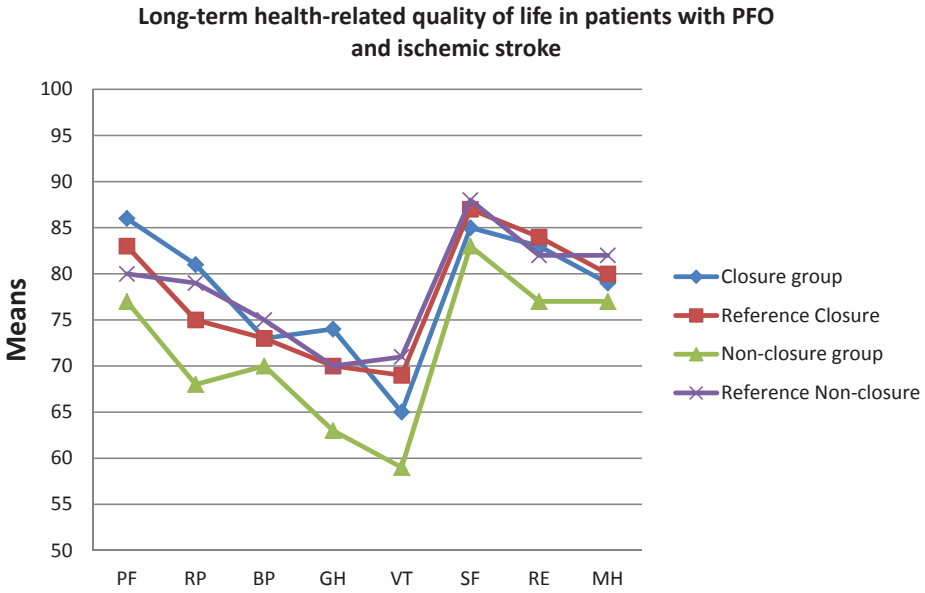

Figure 17. Comparisons of SF-36 subscale scores between PFO patients in each group (closure and non-closure) versus age- and gender-matched reference values. (PF=physical functioning, RP=role limitation – physical aspects, BP=bodily pain, GH=general health, VT=vitality, SF=social functioning, RE=role limitation – emotional aspects, MH=mental health)

DISCUSSION

Complexity of the relationship between PFO and cryptogenic stroke

PFO is common in the general population: one in four healthy people has a PFO without having any hemodynamic adverse effects of it. PFO prevalence declines slightly with age.[34] Screening the general population for the presence of PFO, and monitoring those with a PFO with respect to ischemic stroke is controversial, as the PFO-related risk of stroke is considered very low.[87, 88] Nonetheless, PFO is significantly overrepresented among patients with a first cryptogenic stroke. Several studies have shown an association between PFO and cryptogenic stroke. The prevalence of PFO may be as high as 56% in patients under 55 years of age who have a cryptogenic stroke.[89-91] Even older patients with cryptogenic stroke have a higher prevalence of PFO than controls: 28% compared to 12%.[92] The mechanism by which PFO is associated with cryptogenic stroke is believed to be paradoxical embolism. A thrombus is formed in the peripheral or central venous circulation and is passed to the arterial circulation by accident or by being pushed through the PFO by a Valsalva maneuver.

The causes of cryptogenic stroke are heterogeneous and diagnosing paradoxical embolism precisely is difficult. A combination of PFO and cryptogenic stroke does not necessary indicate paradoxical embolism. In the majority of cases, a cryptogenic stroke is likely to be caused by other mechanisms than paradoxical embolism and an alternative explanation for recurrent stroke or TIA is probably apparent, for example, atrial fibrillation, as found in the CLOSURE I trial.[66] Thus, closure of a PFO may serve as a curative treatment preventing recurrent stroke if (a) the patient really had a cryptogenic stroke i.e. all other causes, including atrial fibrillation, have been excluded, (b) paradoxical embolism was indeed responsible for the arterial embolism, (c) device closure of PFO is performed and the PFO is effectively closed, and (d) device closure per se does not cause any longstanding serious side effects.

There is no widely accepted definition of cryptogenic stroke. This is probably a major source of error or uncertainty when comparing results from different studies.Identifying which patients with PFO and cryptogenic stroke would actually benefit from PFO closure has been a challenging issue not only in observational studies but also in RCT trials.

In an attempt to identify patients more likely to have paradoxical embolism we used a clinical algorithm and a rigorous process with strict criteria for closure, as described in Paper II and III. We included patients with cryptogenic stroke and TIA, as in the CLOSURE I trial[66] and the PC trial.[68] We were careful to exclude patients with stroke of known origin(as in the RESPECT trial).[67]

Despite the difficulties in identifying cryptogenic stroke caused by paradoxical embolism through a PFO, we achieved the following results using our algorithm: all possible identifiable reasons for ischemic stroke were excluded, such that more than 50% of cases referred as suspected cryptogenic stroke had an identifiable cause according to our criteria. The remaining 50% were accepted for PFO closure over four

years and we had a low rate of re-referrals (1.8%). As a result, as described in Paper III, PFO closure appeared to be feasible in most of the patients; with careful patient selection and follow-up, low event rates were attained in both groups. Only one patient (0.8%) experienced a long-term device-related adverse event, namely, a thrombus on the device, which was successfully resolved after one month's treatment with anticoagulants.

As shown in Table 3, page 34 the non-closure patients were eight years older on average and had a higher prevalence of cerebrovascular risk factors such as hypertension, diabetes, hypercholesterolemia, documented atrial fibrillation, and significant carotid stenosis. MRI or CT scans were performed on 306 of the 314 patients (97.5% of the study population, Paper III). Of these, 247 patients (79%) had a CT scan, 149 (45%) had an MRI scan, and 90 (29%) had both MRI and CT scans. TEE was performed in all patients. Of 151 patients accepted for closure, 118 (78%) had ischemic stroke and 34 (22%) had a TIA. Despite high diagnostic accuracy and strict closure criteria, we found no differences in the primary outcome (a composite of all-cause mortality, stroke and TIA) or the secondary outcomes (stroke, TIA or all-cause mortality in isolation) in Paper III, which underscores the difficulties in finding patients whose stroke is caused by paradoxical embolism through their PFO. However, a multidisciplinary PFO conference, as presented in Paper II, may ensure adherence to the clinical treatment algorithm.

In a previous study by Steven et al.[93] with a relatively small numbers of patients (n=95), of whom 46 patients (48%) had cryptogenic stroke and 61% of these had a PFO, MRI venogram (MRV) was used within 72 hours of stroke symptom onset to detect pelvic deep vein thrombosis (pelvic DVT). The results showed that the prevalence of pelvic DVT was significantly higher in cryptogenic stroke patients compared to those with stroke of known origin. Most patients with cryptogenic stroke and pelvic DVT also had a PFO, a combination of results that suggests paradoxical embolism as the stroke mechanism. Further studies in this field would increase our understanding of the relationship between PFO and paradoxical embolism originating from the venous side.

Major strengths of this thesis; the long-term follow-up and the minimal number of cases lost to follow-up.

To understand the long-term consequences of PFO closure in patients with a history of cerebrovascular events associated with PFO, it is very important to maintain a longer follow-up time and to keep the number of cases lost to follow-up to a minimum. In Paper I we provided a mean follow-up time after PFO closure of 7.3 years (Range 5 to 12 years). Paper I was the first long-term clinical follow-up of PFO patients with a follow-up rate of 100%, and with a large proportion of patients given a clinical examination at clinic visits. The time from index event to follow-up ranged from 5 to 19 years with a mean follow-up time of 8.2 years (SD 3.01). Two earlier studies have reported comparable follow-up periods but both had a lower follow-up rate. The mean follow-up in the study by Fischer et al.[69] was 15.4 years but their follow-up rate after PFO closure was only 89%. The mean follow-up after index event in the study by

Wahl et al.[70] was 10 years with a follow-up rate of 98%. When the event rate is low it is of great importance to have a high follow-up rate in order to eliminate the risk of bias. In Paper III we had a very high rate of follow-up over a long period – up to 19 years from index event and 8 years from closure – with only a 0.3% dropout rate and a 100% follow-up rate for mortality. The mean follow-up time for RCT studies, according to a review by Moreno et al.,[94] was 3.5 years. Moreover, RCT studies had difficulties in recruiting patients and a significant number of patients (12%) who either withdrew consent or were lost to follow-up. Furthermore, there were lower-than-expected event rates in these studies, which makes it hard to compare groups. Overall, there were 95 vascular events in these three studies combined: 39 (3.39%) in the closure groups and 56 (4.85%) in the medically treated groups. Thus, the results of Paper III, which was designed as a prospective observational study, may function as complement to RCT trials and contribute to increased understanding of the role of PFO closure in patients with cryptogenic stroke and PFO.

Recurrent neurological events and long-term mortality after PFO closure vs. non-closure

In Paper I, PFO closure appeared to be associated with a very low recurrent event rate of 0.3% per year, which was lower than the 0.8% per year reported in a meta-analysis of 48 observational studies.[95] No long-term complications related to PFO closure, such as death, device embolization, or chronic AF were found. Two patients (2.3%) died of lung cancer. The results of Paper I were promising despite the absence of a multidisciplinary approach to find cryptogenic stroke.

Due to the lack of widely accepted guidelines on the management of PFO and cryptogenic stroke and the increasing number of cases, we started working according to our PFO conference clinical algorithm 2006, as described in Paper II The algorithm enabled us to maintain stringent criteria for PFO closure. As a result we noticed that same proportion of patients (42–52%) was accepted for PFO closure over four years. Five years later, we reported the clinical follow-up of 314 patients discussed at our PFO conferences between 2006 and 2009 (Paper III). Neither the ITT analysis nor the as-treated analysis showed any significant benefits of PFO closure compared with the non-closure group for the primary endpoint or for the secondary endpoints.

The incidence of recurrent stroke or TIA for closure vs. non-closure under a mean follow-up time of 5±1 years (range 3–8 years) was 6.6% (10 events) vs. 9.2% (15 events), p=0.63, giving an annual recurrence rate of stroke or TIA of 1.3% vs 1.8% in respective group.

Our results in contrast to observational studies and systematic reviews of observational studies

A recently published non-randomized study showed 0.4% recurrent stroke rate per year in PFO patients who underwent percutaneous closure and 3.4% per year in PFO patients who received medical treatment.[59] A systematic review by Wohrle et al.[96] compared the results of 12 series (2,016 patients) of PFO closures with eight series (998 patients) of medical therapy. At two years of follow-up, the range of recurrent

stroke was 0–1.6% for PFO closure and 1.8–9.0% for medical therapy. The combined annual incidence of stroke or TIA was 1.3% (95% CI: 1.0–1.8%) following PFO closure, compared with 5.2% (95% CI: 4.4–6.2) for medical therapy. Kitsios et al.[97] published a systematic review of observational studies and the only RCT in 2012. This review included 52 single-arm studies, seven non-randomized comparative studies, and one randomized study (the CLOSURE I trial[66]). The combined incident rate for recurrent stroke was lower for patients treated with PFO (0.36 events per 100 patient-years, 95% CI: 0.24–0.56) compared to patients treated medically (2.53 events per 100 patient-years, 95% CI: 1.91–3.35). The incident rate ratio was 0.19 (95% CI: 0.18–0.98), which indicated an approximately 80% reduction in the rate of strokes for the closure group. This systematic review noted that the incident rate for recurrent strokes in patients treated with closure devices was much lower in the RCT compared to the observational studies, while the incident rate for recurrent stroke in patients treated medically was only slightly lower in the RCT compared to observational studies. This finding raises the possibility that ascertainment bias in the observational studies may have led to a spuriously low rate of recurrent stroke reported for patients treated with PFO closure.

Our results in contrast to RCT trials and meta-analysis of RCT trials

As mentioned in the Introduction, the primary results of the CLOSURE I, RESPECT and PC trials[66-68] were the same: the ITT analysis for the primary endpoint in all three trials failed to demonstrate superiority of device closure over medical therapy. In all three trials, low numbers of outcome events in both groups certainly limited the power to detect differences between groups. The annual risk of stroke was low in all three studies. Per-protocol analyses for stroke were negative in the CLOSURE trial and the PC trial[66, 68] but in the RESPECT trial[67] a device was superior to medical therapy only in the per-protocol analysis. Meta-analyses of these three RCT trials point toward positive effects of PFO closure: Moreno et al.[94] reported a statistically significant risk reduction in stroke and/ or TIA on a pooled hazard ratio of 0.59 (95% CI: 0.36–0.97, p=0.04) and Kitsios et al. reported a trend toward benefit which did not reach statistical significance, with a hazard ratio of 0.55 (95% CI: 0.26–1.18).[98]

A recently published meta-analysis and systematic review of 14 studies[99] (three RCT trials and 11 non-randomized observational studies, with a total of 433 patients) showed that, among the three randomized trials, the weighted incidence of recurrent stroke was 1.7% in the closure group and 2.9% in the best medical therapy group. For the non-randomized trials, the rates were 0.7% and 6.9%, respectively. PFO closure did not show a significant treatment effect for stroke reduction in the randomized trials (RR 0.66, 95% CI 0.37–1.19, p=0.171). However, a reduction in stroke risk could be seen in the non-randomized trials (RR 0.37; 95% CI 0.20–0.67; p< 0.001). In addition, a time-to-event analysis that considered the time to a recurrent stroke, based on the three randomized trials and the two non-randomized studies that performed strict multivariate adjustments, showed a borderline significant risk reduction with PFO closure (hazard ratio 0.58, 95% CI 0.33–0.99, p=0.047). There were no differences between PFO closure and best medical therapy in the risk of TIA, bleeding, or mortality, in the randomized or non-randomized trials. However, the risk of atrial fibrillation was greater after PFO closure.[99] While these results suggest that there might be

a benefit, the evidence is not definitive and the risk–benefit ratio is not well-defined. In line with clinical trials we noticed that, by careful selection of patients and careful follow-up, the event rate tends to be very low in both groups.

Although our study was not randomized, in PFO conference, we did select patients for closure who we considered would benefit from intervention and who would have benefit of a good secondary prophylaxis. It can simply be that we chose the "right" patients for closure and also the right treatment for the rest, because we had a low recurrence rate in both groups. Having low recurrent event rates in both groups can also be seen in the RCT and observational trials that used strict selection criteria for PFO closure, such as the RESPECT trial.[67]

In terms of complications, PFO closure was generally associated with a low rate of adverse events in our studies, which is comparable with the results of observational studies and RCT trials. In Paper I a total of three (3.5%) adverse events occurred, all cases of atrial fibrillation. No long-term closure-related adverse events were observed. The procedure-related serious adverse event rate in Paper III was 8.2% and the minor adverse event rate was 11.4%. See Table 5, page 38 for all types of adverse events. Looking at these adverse events in terms of the complications defined and reported by Khairy et al.[83] (major complications 1.5% and minor complications 7.9%), we had no major complications; however, we did report in Paper III one ischemic stroke, which should be deemed as a major complication. but this was not considered in the Khairy et al. study.[83] The prevalence and types of adverse events vary in RCT studies, and serious adverse events in the PFO closure group were reported to be 4.2% in the RESPECT trial[67] and 21.1% in the PC trial.[68] More systematic reviews of observational studies and RCT trials are warranted to list all the possible adverse events observed in studies, in order to create a common classification system for adverse events or complications.

Quality of life after percutaneous closure of patent foramen ovale in patients experiencing cryptogenic stroke

Though catheter closure of PFO compared to non-closure did not show a clear effect on reducing the risk of recurrent stroke or TIA in Paper III, Paper IV demonstrated that device closure of PFO provided significantly better quality of life at long-term follow-up, in comparison to non-closure group and showed similar HRQoL levels compared to age- and gender-matched normative population. Perceived mental health in the closure group was as positive as that for the general population despite the fact that 10% of patients in the closure group had not recovered completely from their stroke: they had a modified Rankin Scale score of >1, see Table 6, page 39. These findings are analogous with findings from two other stroke studies[100, 101] showing good physical, social, and mental well-being among those who survive several years after a stroke.

In contrast to one study concerning patients after negative health events such as stroke,[102] patients in Paper IV reported as good HRQoL after PFO closure as their counterparts in the general population. This might be explained by the characteris-

tics of patients who were candidates for PFO closure: they were otherwise relatively healthy, without additional uncontrolled diseases, and they had also by this time adapted to the consequences of stroke.

In Paper IV we also found that non-closure patients had lower scores in both physical and mental health in comparison with both the reference data and the closure group, Figure 17, page 39. The prospect of an effective secondary prevention of recurrent ischemic events through a permanent treatment could certainly contribute to improving the quality of life and interpersonal relationships of these subjects. Paper I showed that PFO closure is a low-risk intervention; this may offer a sense of control and strengthen patients' optimistic outlook about their future health, thus enhancing quality of life and psychological well-being. While it is true that our data are post-treatment, they do reflect the long-term outcome regarding quality of life for younger patients with cryptogenic stroke.

Final discussion

Unfortunately, neither published RCT data nor observational studies have given us the final answer as to whether PFO closure prevents recurrent events or not. Unlike other observational studies, we could not show any clear effect of PFO closure compared to the non-closure group; nonetheless, our results, in particular the results from Paper III, are analogous to the main results from the RCT trials and might hopefully function as a complement to the RCT trials. This would thus contribute to increased understanding of the role of PFO closure as an effective treatment in patients with PFO and cryptogenic stroke. However, Paper I–III suggest that PFO closure may be suitable in most patients and Paper IV indicates that it has a favorable impact on quality of life.

As yet, two RCT trials listed on https://clinicaltrials.gov – the Gore REDUCE Clinical Study and the Defense-PFO trial – are actively recruiting patients and merit discussion. The Gore REDUCE Clinical Study is a multicenter study and its aim is to determine whether closing a patient's PFO with the GORE® Septal Occluder in addition to taking medication is more effective at reducing the risk of having another stroke or TIA than taking medications alone without closing the PFO. This study started January 2008 and the primary completion date for recruitment is the first quarter of 2015. The inclusion criteria are age of 18–60 years, PFO with right-to-left shunting at rest or under Valsalva maneuver, cryptogenic ischemic stroke or TIA of presumed embolic infarction verified by a neurologist within 6 months prior to randomization, absence of an identifiable source of thromboembolism in the systemic circulation, and no evidence of a hypercoagulable state. The estimated enrollment is 664 patients.

The strength of the Gore REDUCE study, apart from these meticulous inclusion criteria, is the primary endpoint: blinded assessment of MRI at two years after randomization. The Defense-PFO trial aims to assess whether device closure with the Amplatzer Occluder is superior to medical therapy; it is a single blind study with an estimated enrollment of 210 patients. This study started February 2012 and the estimated completion date is February 2017. Inclusion criteria in this study are radiologically verified cryptogenic stroke within the previous 3 months, diagnosis of an echocardiographi-

cally verified high-risk PFO (PFO size ≥2 mm, or ASAn, or hypermobility by TEE), and absence of other potential causes of stroke. This study includes patients from 18 to 80 years. All patients will be followed up for two years.

The inclusion criteria differ in these ongoing RCT studies: the Gore REDUCE study focuses on younger patients and PFO alone, whereas the Defense-PFO trial focuses on high risk features of PFO and includes patients up to 80 years of age. In the absence of widely accepted inclusion and exclusion criteria for closure it seems that even future studies, including ongoing RCT studies, will likely have the same statistical challenges as experienced by the CLOSURE I, RESPECT and PC trials.[66-68] Some uncertainty may always exist.

Stroke is potentially devastating and serious, especially when younger adults are affected. As with any stroke patient, young patients with cryptogenic stroke are probably highly motivated to do anything that can prevent a recurrent stroke. But they have no obvious risk factor to treat, no lifetime habit to kick, no chronic abuse to drop. Observational studies indicate that closure of a PFO to prevent recurrent cryptogenic stroke is highly effective. However, randomized trials cannot confirm this. We found that the patients most suitable for PFO closure can be selected when the procedure is strictly organized and performed, but this does not seem to lower the risk of recurrent stroke, in line with published RCT trials. Quality of life after stroke was better in patients with cryptogenic stroke who had their PFO closed. This may be a random effect or it may indicate that patients who have had their PFO closed have not actually been cured but interpret the treatment as a cure, which will enhance their quality of life.

The level of rigor applied in studies of medical therapy is another topic that demands focus in future studies. Unfortunately, there have been no RCT trials adequately comparing specific antiplatelet or antithrombotic therapies for this indication. In two of the studies, dose and type of antithrombotic therapy in the medical therapy arm were left to the treating physician's discretion, which may have led to the bias that clinicians encouraged compliance with antithrombotic prophylaxis in medical patients. In the Patent Foramen Ovale in Cryptogenic Stroke Study (sub-study of the randomized Warfarin–Aspirin Recurrent Stroke Study), there were 98 patients with cryptogenic stroke and PFO: 42 were randomized to warfarin and 56 received aspirin. Two-year rates of recurrent stroke were lower in patients receiving warfarin (9.5% vs. 17.9%) but chance may explains this, as the difference was not significant (p=0.28).[103]

Subsequent trials must give this issue careful thought. One option for the medical arm would be careful exploration of individual patient values and preferences. Patients highly averse to bleeding risk and the burdens of anticoagulant therapy could receive only an antiplatelet agent, whereas those less averse to bleeding and therapy burden could receive an anticoagulant. The use of a new oral anticoagulant, non-vitamin-K oral anticoagulants (NOACs) rather than warfarin in those choosing anticoagulation would be a possibility. Such an approach might represent optimal medical care and thus be a more appropriate comparator to PFO closure. Another option would be a three-arm study with closure plus antiplatelet, anti-platelet and anticoagulant arms. Non-inferiority designed studies such as REDUCE may be the most promising study

design because the question in such case would be whether PFO closure and medical therapy combined is as good as medical therapy alone.

In Paper III, 66% of patients in the closure group were still receiving some form of antiplatelet or anticoagulation therapy after 5 years vs. 88% in the non-closure group, which may have led to the low recurrence rate in both groups. See Table 4, page 36, for a complete list of medications.

Although RCT trials do not strongly support PFO closure, they do show a trend towards benefit in as-treated analysis. Certainly there might be a benefit of PFO closure with the Amplatzer device, as suggested by the as-treated analysis in RCT trials; there might also be a benefit in some subgroups, such as patients aged under 50 years with a substantial shunt, no vascular risk factors and a cortical infarct discernible on diffusion-weighted MRI, based on the results of the RESPECT trial. If a stricter definition of cryptogenic ischemic stroke and appropriate study design are applied,[104] the results of the RCT trials might have been different. These hypotheses would have to be tested in larger sample-size randomized studies, either by recruiting more patients or by maintaining a longer follow-up period with few patients lost to follow-up.

LIMITATIONS

There are some limitations that need to be addressed. The patient population in Paper I–IV was a selected group referred to our hospital in a non-randomized and consecutive order; thus there may be selection bias. Paper I was a retrospective study and additionally suffered from not having a control group. HRQoL variables in Paper IV were measured after treatment, whereas assessing HRQoL variables before and after PFO closure with an additional long-term follow-up would have been the ideal study design. In Paper IV there is no information on depression, socioeconomic status, education, or other relevant information which can extensively influence quality of life.

CONCLUSIONS

- Percutaneous PFO closure is associated with a very low risk of recurrent stroke or TIA and is feasible in most patients.
- No mortality and no longstanding device-related complications related to PFO closure were found, indicating that percutaneous PFO closure is a safe treatment option even in the long term.
- A standardized multidisciplinary approach is important for a proper assessment of patients with PFO and cryptogenic stroke.
- In comparison with non-closure, percutaneous PFO closure appears to have a favorable impact on quality of life.
- However, compared with the non-closure group, percutaneous PFO closure does not seem to provide any improved clinical outcomes regarding the composite of all-cause mortality, stroke and TIA. Nor could any significant differences be demonstrated regarding recurrent stroke or TIA or all-cause mortality in isolation between the closure and non-closure groups.
- Larger prospective observational studies and randomized studies are necessary to assess the real benefit of PFO closure and its influence on quality of life.

CLINICAL IMPLICATIONS

While the superiority of percutaneous closure of PFO as an effective treatment option is now in doubt, conducting PFO closure is valuable within research studies. Good secondary prevention treatment in all patients with ischemic stroke, including cryptogenic stroke, should be sought. Due to the complexity of cryptogenic stroke and the difficulties in defining whether a cryptogenic stroke is present or not, it is of great importance that the concerned patients should be discussed by a panel of experts in interventional cardiology, neurology, internal medicine, cardiac imaging, thromboembolism and cardiology. Careful patient selection can avoid under- as well as overtreatment of PFO patients.

After negative results from published RCT trials, we have tightened our criteria for PFO closure at the Gothenburg GUCH center. First, cryptogenic stroke is strictly defined and includes at least 72 hours of verified holter monitoring without evidence of atrial fibrillation, absence of coagulation disorder, absence of risk factors for atherosclerotic disease, and a clearly demonstrated PFO on TEE investigation. Patients aged 18 to 60 years with MRI-confirmed cryptogenic stroke or TIA within the previous six months are invited to participate in the REDUCE study. Patients with objectively proven paradoxical embolization through their PFO are offered closure. As a compassionate exception to the above, a maximum of 15 patients per year with cryptogenic stroke confirmed by individual assessment will be offered closure. This includes patients with low age, a history strongly suggestive of paradoxical embolism, or a morphologically high-risk PFO. We exclude as far as possible other sources of stroke, multiple simultaneous emboli to different vascular beds, or age under 55 with recurrent cryptogenic stroke/TIA despite adequate antiplatelet medication. Several of these factors should be present to motivate compassionate use.

FUTURE PERSPECTIVES

Given the complexity of the relationship between PFO and cryptogenic stroke or TIA, more research is warranted to identify high-risk patients who actually are at risk for paradoxical embolism. The REDUCE study may be pivotal to answering this question if it is performed appropriately. We are therefore trying to recruit patients to the REDUCE study. Studying clinical outcomes in patients who are offered "compassionate closure" in our center may lead us to a better understanding of this issue and increase our chances of identifying patients who are actually at risk of paradoxical embolism. Elmariah et al.[105] showed that an alternative etiology to paradoxical embolism was frequently responsible for recurrent events within the CLOSURE I trial.[66] In a future study we intend to examine recurrent neurologic events by using the RoPE (risk of paradoxical embolism) score[106] to evaluate the relationship of recurrent events to the likelihood that the index event was PFO-related. For these reasons, recurrent events for all patients in Paper I–III will be studied and reevaluated using the RoPE score.

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Med kryptogen stroke eller kryptogen TIA (transitorisk ischemisk attack) menas en ischemisk stroke eller TIA där en definitiv orsak inte kan identifieras trots en utförlig utredning. Kryptogen stroke motsvarar cirka 25% av alla ischemiska stroke dvs stroke som orsakas av bristande blodtillförsel/syrebrist. PFO är en rest av den nyföddes cirkulation som förekommer hos 25% av friska personer, något avtagande med stigande ålder. Flera studier har rapporterat en betydligt högre förekomst av PFO hos patienter med kryptogen stroke än hos friska kontroller (44-66% mot 0–27%). Kryptogen stroke med PFO som potentiell orsak drabbar framförallt yngre personer. Risken för sjuklighet och död är betydande liksom risken för återkommande stroke som i olika studier varierar mellan 1–5% per år. Potentiella nuvarande behandlingsstrategier för att minska risken för återinsjuknande hos patienter med kryptogen stroke och PFO inkluderar långvarig blodförtunnande behandling med antikoagulantia eller trombocythämmande medicinering, eller perkutan PFO-slutning med ett kateterbaserad procedur.

De vetenskapliga beläggen för behandling av patienter med kryptogen stroke och PFO är motsägelsefulla. Å ena sidan finns en metaanalys av de fem kontrollerade studier som rapporterade recidivfrekvens av stroke-TIA indikerar att riskminskningen vid kateterburen slutning av PFO jämfört med medicinsk behandling är över 80% (95% CI 41–94%), men dessa siffror måste tolkas med stor försiktighet eftersom de baseras på studier av delvis låg kvalitet och med begränsad uppföljningstid. Huvudresultatet, den primära utfallshändelsen i de tre randomiserade studierna, visade ingen skillnad mellan kateterburen slutning och medicinsk behandling av PFO. Medianuppföljningstiden för dessa tre randomiserade studier var 3,4 år, vilket får anses vara ganska kort. Långtidsstudier på dessa patientgrupper är av stort värde. Livskvalitet, dvs hur patienterna mår, efter kateterburen slutning av PFO respektive efter medicinsk behandling, har heller inte värdrats i någon större studie eller i studier med längre uppföljningstid.

Syfte

Det övergripande syftet med avhandlingen var att studera de långsiktiga kliniska resultaten avseende överlevnad, komplikationer, återkommande stroke eller TIA och livskvalitet hos patienter som genomgått kateterburen PFO-slutning kontra de som inte har gjort det. De specifika målen med delarbetena var;

Delarbete I
Att göra en långsiktig klinisk uppföljning av patienterna som genomgått en kateterburen PFO-slutning efter en kryptogen stroke avseende överlevnad, komplikationer, återkommande stroke och andra biverkningar.

Delarbete II
Att studera om en tvärvetenskaplig paneldiskussion med experter från stroke, ekokardiografi, interventionskardiologi och experter på tromboembolism kan skapa och

vidmakthålla strikta kriterier för kateterburen PFO-slutning. Detta för att undvika variation i kliniskt beslutsfattande mellan olika läkare och undvika glidning i indikationerna för kateterslutning av PFO.

Delarbete III
Att jämföra långsiktiga resultat av kateterburen PFO-slutning kontra icke slutning på patienter som är noggrant utvalda av en tvärvetenskaplig PFO-konferens. Kateterburen PFO-slutning rekommenderades enligt strikta kriterier syftande till att identifiera högriskpatienter för paradoxal embolisering och därmed återkommande stroke.

Delarbete IV
För att bedöma hälsorelaterad livskvalitet efter kateterburen PFO-slutning jämfört med en normal population och patienter med PFO och en stroke som inte hade genomgått kateterburen PFO-slutning.

Resultat

I delarbete I utfördes kateterburen PFO-slutning framgångsrikt på 85 av 86 patienter och uppföljning gjordes på samtliga. Två patienter dog av lungcancer (uppföljning för dödlighet 100%). Genomsnittlig ålder vid stängning var 49 år och vid uppföljning 56 år. Två patienter (2%) hade en återkommande stroke/TIA under drygt 7 års uppföljning, vilket ger recidivrisk på 0,3% per år. Inga långsiktiga komplikationer av kateterburen PFO-slutning observerades. I delarbete II–III diskuterades 314 patienter för kateterburen PFO-slutning på våra PFO-konferenser mellan 2006 och 2009. Av dessa patienter godkändes 151 (48) för kateterburen PFO-slutning och 163 (52%) godtogs inte (medelålder 50 vs 58 år).

I genomsnitt fem år senare gjordes en klinisk uppföljning av dessa patienter, vilken inte visade någon större skillnad för patienter som genomgått kateterburen PFO-slutning jämfört med den icke slutna gruppen för det primära effektmåttet (en blandning av total mortalitet, stroke och TIA) eller för de sekundära utfallshändelserna (stroke, TIA eller mortalitet av alla orsaker för sig).

Även om kateterburen PFO-slutning jämfört med icke slutning inte visade någon tydlig skillnad på risken för återkommande stroke eller TIA i delarbete III, kan vi visa att kateterslutning av PFO är ett säkert behandlingsalternativ. Patienter som genomgått PFO-slutning har dessutom en signifikant bättre livskvalitet vid långtidsuppföljning, i jämförelse med de patienter vars PFO inte slutits. Den upplevda psykiska hälsan i den kateterslutna gruppen var lika positiv som hos befolkningen i allmänhet, trots att 10% av patienterna i den slutna gruppen inte hade återhämtat sig fullt ut från sin stroke rent funktionsmässigt.

Slutsats

Perkutan PFO-slutning är förenat med mycket låg risk för återkommande stroke eller TIA och är möjlig för de flesta patienter utan tecken till några långtidskomplikationer. Jämfört med den icke slutna gruppen förefaller perkutan PFO-slutning inte minska risken för total mortalitet, stroke eller TIA. I brist på allmänt accepterade indikationer

för hantering av PFO-patienter och i väntan på resultat från pågående randomiserade studier, är det viktig med ett standardiserat tvärvetenskapligt tillvägagångssätt. Noggrant patienturval kan undvika såväl under- som överbehandling av PFO-patienter.

Perkutan PFO-slutning har en positiv inverkan på livskvaliteten och patienter med tidigare kryptogen stroke, vilka fått sitt PFO stängt med kateterteknik, har en livskvalitet som är likvärdig jämfört med köns- och åldersmatchad referensgrupp i normalbefolkningen.

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