Prognosis and clinical outcomes in stroke patients with transcatheter closure of an atrial shunt

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2022

Cover illustration: Blommande hjärta, By IssaJosephine Art, Isabell Leoson

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ISBN 978-91-8009-598-3 (PRINT)
ISBN 978-91-8009-599-0 (PDF)
http://hdl.handle.net/2077/70231

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Printed by Stema Specialtryck AB, Borås, Sweden 2022

« ἕν οἶδα ὅτι οὐδὲν οἶδα » Σωκράτης

” The one thing I know is that I know nothing” Socrates

To my father

ABSTRACT

Background: The percutaneous transcatheter closure of a patent foramen ovale (PFO) after a cryptogenic cerebrovascular event (CVE) has been performed for more than two decades. In contrast with previous randomized studies, recent randomized studies support the closure of the PFO after a cryptogenic CVE in preference to medical treatment alone. Although the absolute number of recurrent CVEs is low after closure of a PFO, they can still occur, and the reason remains unknown.

Methods: Papers I and II are single-center studies using the medical records of patients who, after a cryptogenic CVE, underwent transcatheter closure of a PFO at the Center for Adults with Congenital Heart Disease at Sahlgrenska University Hospital in Gothenburg, Sweden. In Paper I, patients who received a biodegradable device, BioSTAR, were compared with patients who received another widely used device. In Paper II, all the patients who underwent PFO closure because of a CVE were included and followed up with a telephone interview. Patients with a recurrent CVE were identified and matched with patients who did not have a recurrent CVE, as a comparison group. The patients in the matched groups were also invited for a clinic visit. In Papers III and IV, the Swedish National Patient Register, the Cause of Death Register and the Swedish Prescribed Drug Register were used. Patients with an ischemic CVE and a diagnosis of atrial shunt were identified and categorized into patients who received the intervention treatment of closure of the atrial shunt and patients who received medical treatment alone. From the Total Population Register, we identified matched controls without a diagnosis of ischemic CVE or atrial shunt. In Paper IV, we used the same groups of patients and controls but restricted to age 60 years and above. In Paper III and IV, the patients in the two treatment groups were matched using propensity score matching. The cumulative incidence of recurrent stroke and the hazard ratios among the groups were calculated with Cox regression analyses.

Results: Although the BioSTAR device was feasible and appropriate for small shunts, the risk of a recurrent CVE was twice as high in patients who received the BioSTAR device compared to patients with other devices. This was confirmed in Paper II, where the main reason for a recurrent CVE was residual shunting and having a BioSTAR device at a mean follow-up of 8.4±2 years. Moreover, through the national registries we found that although the absolute risk of recurrent stroke after transcatheter closure of an atrial shunt is low, it is 10 times as high compared to controls. Patients aged 60 years or older can undergo transcatheter closure of an atrial shunt because of an ischemic CVE after thorough assessment and they develop less vascular disease (Paper IV).

Conclusion: The risk of recurrent stroke after transcatheter closure of an atrial shunt because of a cryptogenic CVE remains, and it depends mostly on the device used and the residual shunting rather than the selection of the patients who undergo closure of the atrial shunt. However, the selection of the patients who undergo intervention is crucial, and further investigations need to exclude occult atrial fibrillation, especially in older patients.

Keywords: Atrial shunt, patent foramen ovale, cryptogenic stroke, transcatheter intervention, cerebrovascular event, residual shunting

ISBN 978-91-8009-598-3 (PRINT) http://hdl.handle.net/2077/70231
ISBN 978-91-8009-599-0 (PDF)

LIST OF PAPERS

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

I Alexia Karagianni, Putte Abrahamsson, Eva Furenäs, Peter Eriksson & Mikael Dellborg. Closure of persistent foramen ovale with the BioSTAR biodegradable PFO closure device: Feasibility and long-term outcome
Scandinavian Cardiovascular Journal, 2011; 45:267-272

II Alexia Karagianni, Zacharias Mandalenakis, Mikael Dellborg, Naqibullah Mirzada, Magnus Carl Johansson and Peter Eriksson. Recurrent cerebrovascular events in patients after percutaneous closure of patent foramen ovale
Journal of Stroke and Cerebrovascular Diseases. Vol. 29, No.8 (August), 2020: 104860

III Alexia Karagianni, Zacharias Mandalenakis, Savvas Papadopoulos, Mikael Dellborg, Peter Eriksson. Percutaneous atrial shunt closure and the risk of recurrent ischemic stroke: a register-based, nationwide cohort study
Submitted

IV Alexia Karagianni, Zacharias Mandalenakis, Savvas Papadopoulos, Mikael Dellborg, Peter Eriksson. Long-term outcome after closure of an atrial shunt in patients aged 60 years or older with ischemic stroke: A nationwide, registry-based, case-control study
Manuscript

SAMMANFATTNING PÅ SVENSKA

Bakgrund
Kateterburen slutning av öppetstående (patent) foramen ovale (PFO) efter en kryptogen cerebrovaskulär händelse (stroke eller TIA) utan påvisbar orsak, (kryptogen CVE) är idag standardbehandling efter de stora randomiserade studier som publicerades under 2017 och som samtliga visade bättre effekt av katerburen slutning jämfört med läkemedelsbehandling. Trots att antalet nya stroke minskar efter stängning av PFO förekommer det att patienten får en ny stroke. Orsaken till nya stroke, trots att PFO slutits, är oklar.

Syfte
Att undersöka långsiktiga vinster och risker efter kateterburen slutning av PFO hos patienter med kryptogen CVE.

Metod
Delarbetar I och II är singel- centerstudier. Patientens journal genomgicks och i delarbete I studerades patienter, vilka genomgått PFO-slutning med biologisk nedbrytningsbar device, BioSTAR, och resultaten jämfördes med patienter som fick annan, sedan tidigare välbeprövad device. I delarbete II, studerades alla patienter som genomgått kateterburen stängning av PFO vid ACHD centrum på Östra sjukhuset sedan åtgärden introducerades 1997. Patienterna följdes upp i första hand med telefonintervju. Patienter som drabbats av ny stroke (recidiverande ischemisk CVE) identifierades och matchades med patienter (1:2) från samma population som inte drabbats av recidiv. Patienter och kontroller följdes upp i andra hand kliniskt med kontrastekokardiografi med syfte att hitta orsaker till recidivet. I delarbete III och IV, samlades data från det Svenska Nationella Patientregistret, dödsorsaksregistret och läkemedelsregistret. Identifierade patienter med förmaksseptumdefekt som först drabbats av ischemisk CVE fick sedan diagnosen PFO/förmaksseptumdefekt. Patienter som genomgick kateterburen slutning av PFO jämfördes efter matchning med patienter som bara fick medicinsk behandling samt även kontroller, friska från ischemisk stroke och PFO/förmaksseptumdefekt. I delarbete III inkluderas alla patienter med ischemisk CVE och diagnos förmaksseptumdefekt, medan i delarbete IV bara de som var över 60 år gamla. Patienter och kontroller följdes upp till 20 år.

Resultat
Patienter slutna med BioSTAR device hade dubbelt så stor andel recidiv av CVE jämfört med patienter slutna med andra device. Detta bekräftades i delarbete II som visade att huvudorsakerna till recidiv av CVE hos patienter som behandlades med kateterburen slutning av PFO efter kryptogen CVE under långtidsuppföljning, över åtta år i genmomsnitt, var restshunt respektive implantation av BioSTAR device. Dessutom kunde vi i delarbete III och IV visa att patienter som genomgick stängning av PFO/förmaksseptumdefekt, på grund av ischemisk CVE, hade samma risk för recidivstroke som medicinskt behandlade patienter och högre risk för återkommande stroke än kontroller. I delarbete IV utvecklade patienter som genomgått kateterburen slutning av sitt PFO i mindre utsträckning vaskulär sjukdom under uppföljning.

Slutsats
Trots låg risk för utveckling av recidiv stroke efter kateterburen slutning av PFO kvarstår risken. Restshunt och typ av använd device verkar spela stor roll för risken för recidivstroke hos dessa patienter. Rätt urval av patienter som genomgår PFO-slutning är viktig för att utesluta framför allt tyst förmaksflimmer, särskilt hos äldre patienter som förefaller drabbas mindre vaskulär sjukdom jämfört med medicinskt behandlade patienter.

ΠΕΡΙΛΗΨΗ ΔΙΔΑΚΤΟΡΙΚΗΣ ΔΙΑΤΡΙΒΗΣ

Το ανοιχτό ωοειδές τρήμα είναι μια επικοινωνία μεταξύ των κόλπων της καρδιάς. Έχει βρεθεί ότι μπορεί να προκαλέσει κρυπτογενή εγκεφαλικά. Πρόσφατες διεθνείς μελέτες έδειξαν ξεκάθαρα ότι η σύγκλειση του ανοιχτού τρήματος σε ασθενείς με κρυπτογενή εγκεφαλικά προστατεύει από το επόμενο εγκεφαλικό σε μεγάλο ποσοστό.

Η παρούσα διδακτορική διατριβή αναφέρεται στην ανάλυση και προσπάθεια ανεύρεσης των αιτιών της υποτροπής ισχαιμικού εγκεφαλικού επεισοδίου σε ασθενείς που είχαν κάνει διαδερμική επέμβαση ανοιχτού ωοειδούς τρήματος λόγω προηγούμενου κρυπτογενή εγκεφαλικού.

Περιλαμβάνονται συνολικά τέσσερις μελέτες, δυο μελέτες που αφορούν ένα από τα μεγαλύτερα κέντρα για γενετικές παθήσεις της καρδιάς στην Σουηδία και οι άλλες δυο είναι εθνικές μελέτες και αφορούν όλους τους ασθενείς της Σουηδίας από το 1997 μέχρι το 2017 που έκαναν την επέμβαση της διαδερμικής σύγκλεισης του ανοιχτού ωοειδούς τρήματος λόγω ισχαιμικού εγκεφαλικού επεισοδίου.

Τα αποτελέσματα των μελετών συγκλίνουν στο ότι οι κύριες αιτίες του επόμενου εγκεφαλικού, παρόλη την επέμβαση της σύγκλεισης είναι, είτε ο τύπος της ομπρελίτσας που χρησιμοποιείται για την σύγκλειση, είτε η μη αποτελεσματική σύγκλειση που μπορεί να οδηγήσει σε επανάληψη ενός εγκεφαλικού επεισοδίου.

Επίσης, από τα αποτελέσματα των μελετών που συμπεριλαμβάνονται στην παρούσα διδακτορική διατριβή παρατηρούμε ότι η θεραπεία της σύγκλεισης του ανοιχτού ωοειδούς τρήματος δεν είναι πανάκεια καθώς αυτοί οι ασθενείς βρίσκονται σε περίπου δεκαπλάσιο κίνδυνο για επόμενο εγκεφαλικό επεισόδιο σε σχέση με ανθρώπους χωρίς διάγνωση προηγούμενου εγκεφαλικού ή ανοιχτού ωοειδούς τρήματος.

Τέλος, με βάση την τελευταία μελέτη της διδακτορικής διατριβής θεωρούμε ότι οι ασθενείς άνω των 60 χρονών μπορούν να κάνουν την επέμβαση μετά από εκτενή έλεγχο που θα έχει αποκλείσει άλλες αιτίες εγκεφαλικού και ότι αυτοί οι ασθενείς έχουν μικρότερη πιθανότητα να εκδηλώσουν καρδιαγγειακά νοσήματα σε σχέση με αντίστοιχους που υπέστησαν εγκεφαλικό αλλά δεν έκαναν την επέμβαση.

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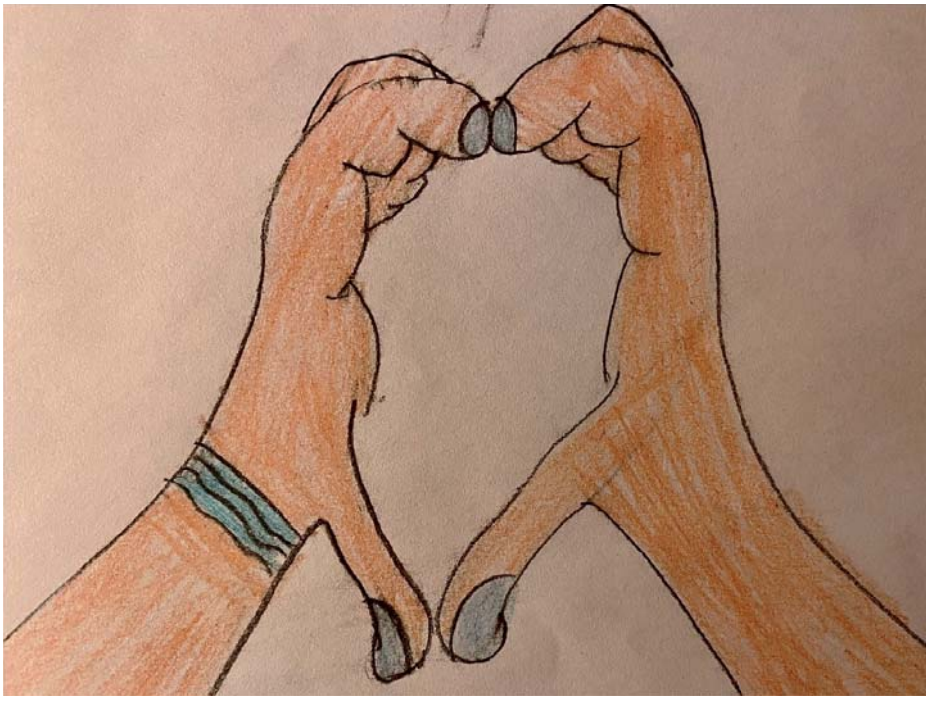
ABBREVIATIONS

ACHD	adults with congenital heart disease
ASA	atrial septal aneurysm
ASD	atrial septal defect
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CVE	cerebrovascular event
ECG	electrocardiogram
ESUS	embolic stroke of uncertain source
GSO	GORE® CARDIOFORM Septal Occluder
ICD	International Statistical Classification of Diseases and Related Health Problems
MRI	magnetic resonance imaging
NPR	National Patient Register
OR	odds ratio
PASCAL	PFO-Associated Stroke Causal Likelihood
PFO	patent foramen ovale
RoPE	Risk of Paradoxical Embolism
SPDR	Swedish Prescribed Drug Register
TCD	transcranial doppler
TIA	transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography

PREFACE

It is always challenging to study a subject that has been controversial for many years. Fortunately, the science of medicine gives a lot of opportunities to take on this challenge. As a clinician, I strongly believe that in medicine there are only a few situations that are crystal clear and few therapies that are a panacea. The remaining alternatives need to be investigated.

This thesis investigates the medium and long-term outcomes of transcatheter closure of an atrial shunt in patients after a cryptogenic cerebrovascular event (CVE) caused by the atrial shunt.



BACKGROUND

Atrial shunt

Anatomical features

The atrial shunt is defined as a deficiency in the septum separating the two atrial chambers leading to interatrial communication [1]. The focus of this thesis is on the small defects of the secundum atrial septum (ASD) without significant hemodynamic effect, and on the patent foramen ovale (PFO) (Figure 1). An ASD of the secundum type is defined as a direct communication between the atrial cavities because of holes

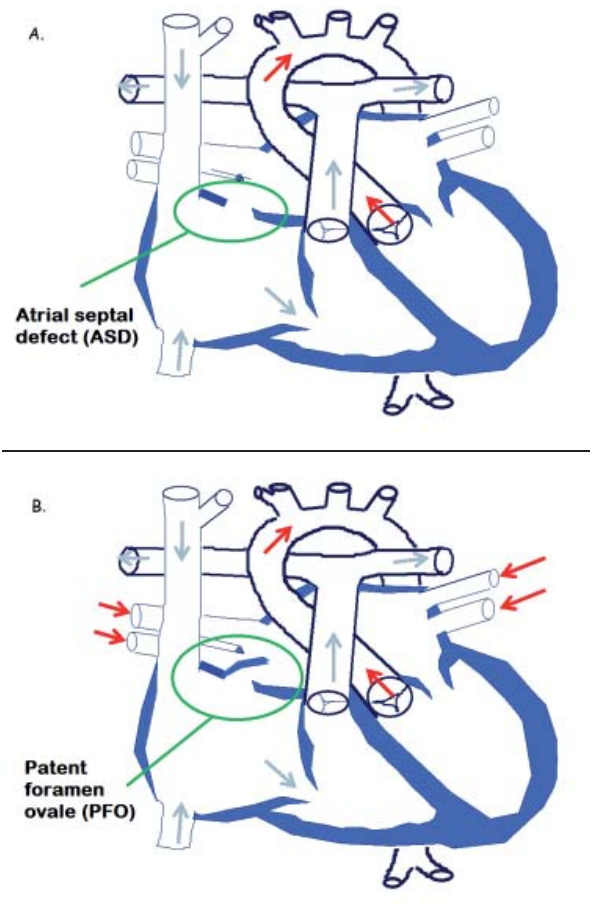


Figure 1. Atrial septal defects studied in this thesis. A. Atrial septal defect (ASD): Demonstration of ASD defect of the secundum type, defined as a direct communication between the atrial cavities because of holes in the septum primum. B. Patent foramen ovale (PFO): Demonstration of incomplete closure of the central foramen ovale by the septum primum after birth. red arrow: The flow of the oxygenated blood in the heart after birth. grey arrow: The flow of the unoxygenated blood in the heart after birth.
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in the septum primum, causing shunting of the blood both from the right to left atrium and from the left to right atrium [1]. During fetal life, there is a flap valve between the septum primum and the septum secundum that allows the communication for fetal blood flow through the opening known as the foramen ovale. This opening closes after birth when the flap valve or the floor of the foramen ovale is pushed against a muscular rim, due to higher pressure in the left atrium [1] (Figure 2). In some cases, the flap valve remains open, and we have a patent foramen ovale, PFO. The PFO can persist into adulthood and is a common finding, with a prevalence of 25%–30% in the general population, with higher prevalence during the first three decades of life (34.3%), declining to 25.4% during the following five decades [2]. The PFO may be a tunnel-like passageway, with a diameter of around 1–10 mm. The length of the PFO tunnel varies depending on the overlap between the rim and the flap valve [2, 3].

There are two types of anatomical PFO. The one is *valve-competent PFO*, where the valve overlaps the muscular rim without any gaps, not allowing blood flow in rest. The other type is called *valve-incompetent PFO* due to inadequate overlap between the rim and the valve. This can be caused by a defect in the rim or inadequate valve tissue, and in some instances it may be similar to a small ASD [1]. The shunting of the blood in PFO occurs from the right to left atrium but if there is an inadequate overlap, shunting can occur in both directions, depending on pressure conditions. The PFO can coexist with an atrial septal aneurysm (ASA) and/or prominent eustachian valve. The ASA is a deformity of the atrial septum consisting of superfluous and mobile tissue in the fossa ovalis, causing bulging of the septum primum into the right atrium of at least 10 mm beyond baseline [4-7]. The prevalence of ASA in adults is around 2% to 3% and may coexist with a PFO or an ASD [8, 9]. The prominent Eustachian valve is an embryological remnant of the inferior vena cava which helps divert oxygenated blood from the vena cava inferior towards the PFO to the left atrium, avoiding the pulmonary circulation [10]. This remnant usually regresses after birth, but in some cases it remains and coexists with a PFO [11].

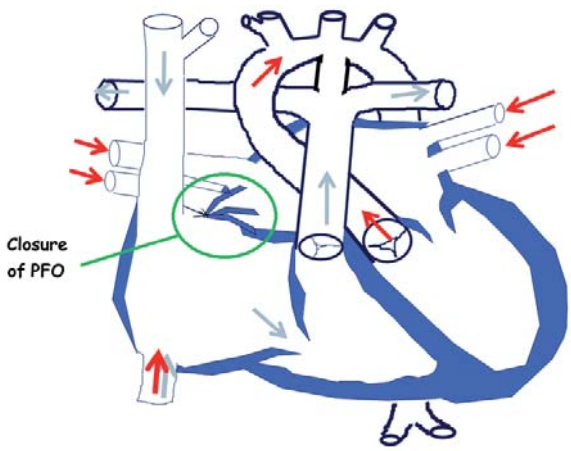

Figure 2. Closure of PFO after birth in a normal heart. red arrow: The flow of the oxygenated blood in the heart after birth. grey arrow: The flow of the unoxygenated blood in the heart after birth.
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Physiological features

An ASD can enable more bi-directional shunting, which may result in increased volume and enlargement of the right heart and pulmonary hypertension, heart failure, arrhythmias, and cyanotic disease [12]. However, a PFO has no hemodynamic effects, but under several conditions it can provide paradoxical embolism due to venous clots, which may be transported through the PFO to the systemic circulation instead of to the lungs, causing an ischemic CVE, such as cryptogenic ischemic stroke or transient ischemic attack (TIA) (Figure 3).

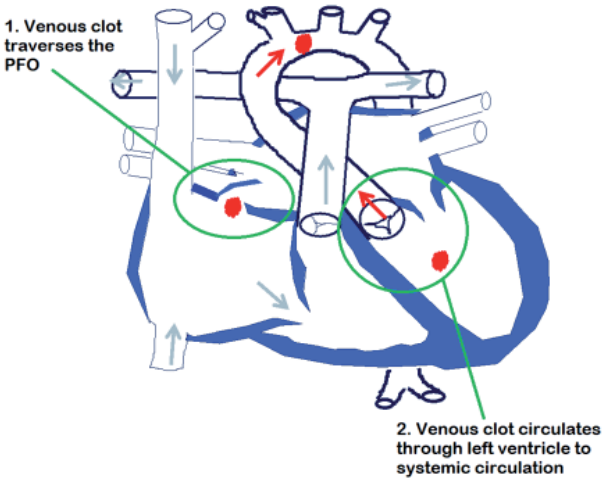

Figure 3. The possible mechanism of a cryptogenic stroke because of a PFO. red arrow: The flow of the oxygenated blood in the heart after birth. grey arrow: The flow of the unoxygenated blood in the heart after birth. •: The venous clot which traverses from the right atrium through the PFO to the left atrium and left ventricle and through the aorta to the cerebral arteries, causing a cryptogenic stroke.
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Although an ASD is usually diagnosed because of its hemodynamic effects, a small ASD without hemodynamic effects can present with a similar clinical manifestation to a PFO. Thus, a small ASD can cause a cryptogenic CVE by paradoxical embolism of a venous clot in the systematic circulation, a mechanism similar to a PFO-caused cryptogenic CVE [13]. Clinicians may occasionally find it difficult to distinguish between a PFO and a small ASD.

PFO has been correlated with several conditions beside cryptogenic CVE:

- *Arterial deoxygenation syndromes [14*]

a) Platypnea-orthodeoxia syndrome: This is a clinical situation that causes dyspnea when adopting an upright position, due to desaturation. It is relieved by lying in a supine position. The presence of a PFO plays a significant pathogenetic role when a functional component causes rheological deformity of the atrial septum [15]. Such functional components are pericardial effusion or constrictive pericarditis, emphy-

sema in the lungs, pneumonectomy, arteriovenous malformation, amiodarone toxicity in the lungs, cirrhosis of the liver or ileus, aortic aneurysm, and aortic elongation [16]. According to current guidelines, PFO closure could be appropriate in many of these cases [14].

b) Obstructive sleep apnea: The presence of a PFO is associated with an increased number of apneas and more severe oxygen desaturation [17-19]. However, because of conflicting results of studies on the effect of PFO closure on obstructive sleep apnea, the current guidelines do not recommend the transcatheter closure of a PFO in these patients [14, 20, 21].

c) Chronic obstructive pulmonary disease (COPD): Although studies have shown that the shunt through a PFO increases in patients with severe COPD, this does not influence exercise performance [22]. Therefore, the clinical role of a PFO on severe COPD is still debated and closure is not recommended [14].

- *Migraine with aura*

The association between migraine and PFO is supported by observational studies, although migraine can also be incidental. Factors that increase the pathogenic role of a PFO in migraine are the presence of an aura or a previous stroke [14]. Three randomized studies and three meta-analyses failed to demonstrate any statistically significant effect of PFO closure in patients with migraine [23-28]. In the current guidelines, PFO closure is recommended only in clinical trials or for compassionate use in migraine with aura [14].

- *Decompression sickness*

Decompression sickness occurs because of gas emboli in vessels and tissues when a person moves quickly from a higher pressure area to a lower pressure area. The presence of a PFO has been associated with decompression sickness, and PFO screening is recommended in such cases. Secondary prevention by PFO closure may be considered if lifestyle, behavioral, and technical changes (such as reducing smoking and alcohol consumption, avoiding riskier dives, ensuring adequate hydration pre and post dive, and breathing high concentrations of oxygen before the ascent) are not sufficient, but primary prevention is not recommended [14]. Interestingly, residual shunting after PFO closure in divers has been reported to correlate with recurrent decompression sickness [29].

Cerebrovascular event

A CVE is a clinical syndrome caused by disruption of the blood supply to the brain. It is characterized by disturbance of focal or global cerebral functions. By definition, a stroke lasts for more than 24 hours, while a TIA refers to a similar presentation that resolves within 24 hours [30].

An ischemic stroke represents 87% and hemorrhagic stroke 13% of stroke cases in adults [31]. Hemorrhagic stroke is further subdivided into intracerebral hemorrhage and subarachnoid hemorrhage and is associated with severe morbidity and high mor-

tality [32]. As the World Stroke Organization Fact Sheet 2019 highlights, more than 13 million strokes occur annually [33]. Stroke remains the second-leading cause of death (11.6% [10.8–21.2] of total deaths) and the third-leading cause of death in combination with a disability (5.7% [5.1–6.2]) [34].

According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, five subtypes of ischemic stroke are identified: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology [35] (Figure 4) .

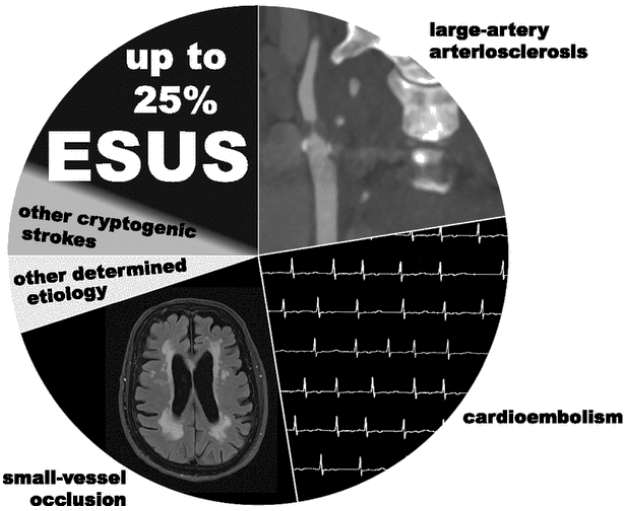

Figure 4. Causes of an ischemic stroke. ESUS: Embolic stroke of uncertain source. Other cryptogenic strokes: Stroke cases with more than one cause of stroke and/or incomplete evaluation. Reproduced with permission from Drugs 78, 823–831 (2018). https://doi.org/10.1007/s40265-018-0912-8

1) *Stroke caused by large-artery atherosclerosis:* This is defined as ischemic stroke in the vascular distribution of a major intracranial or extracranial artery with >50% stenosis or occlusion on angiographic imaging. It involves the cerebral cortical areas or brainstem, or cerebellar dysfunction, and the lesions are larger than 1.5 cm in diameter. Diagnostic tests should exclude cardioembolic stroke [36].

2) Cardioembolic stroke: This is a stroke that is caused by an embolus that presumably arose in the heart. Clinical and brain imaging findings are similar to those for stroke caused by large-artery atherosclerosis. However, if brain imaging indicates that more than one territory is involved, the clinical diagnosis of cardioembolic stroke is supported. Cardioembolic strokes can be caused mainly by atrial fibrillation, while other conditions such as recent myocardial infarction, mechanical prosthetic valve, dilated myocardiopathy, and mitral valve stenosis can be also related [37].

3) Small-vessel occlusion and lacunar syndrome: This includes strokes in patients with normal computed tomography or magnetic resonance imaging (MRI) or subcor-

tical stroke measuring <1.5 cm in diameter on imaging. It accounts for approximately 25% of ischemic strokes and is often associated with arterial hypertension, diabetes, and dyslipidemia [38].

4) Stroke of other determined etiology: This type of ischemic stroke represents around 3% of all ischemic strokes and includes rare causes of stroke, such as nonatherosclerotic vasculopathies, hypercoagulable states, and hematologic disorders [35].

5) Stroke of undetermined cause: Cryptogenic stroke, or stroke of undetermined cause, is defined in three circumstances: 1) the diagnostic assessment is incomplete, 2) no cause is found despite extensive assessment, or, most commonly, 3) a cause cannot be established because more than one plausible explanation exists [35]. A reassessment of cryptogenic stroke has become feasible over recent years due to improvements in imaging techniques and understanding of stroke patients. It is estimated that cryptogenic ischemic stroke accounts for about 25% of all ischemic CVEs [39].

Embolic stroke of uncertain source (ESUS) is a new term used for a subset of patients with cryptogenic stroke who had embolic strokes and sufficient diagnostic assessment to exclude major-risk cardioembolic sources, occlusive atherosclerosis, and lacunar stroke [39, 40]. The association between the presence of a PFO and a cryptogenic stroke has been well established.

Risk factors for ischemic CVE

Ageing: The prevalence of stroke increases with age (6% prevalence at ages 60–79 years and 12% at 80 years and older); thus, ageing is a significant risk factor for stroke [31, 41, 42]. Nonetheless, it is noteworthy that there is globally an increasing incidence of strokes at a younger age. In the US, the incidence of stroke in adults aged 20–44 years has increased from 17 per 100,000 adults in 1993 to 28 per 100,000 in 2015 [43].

Prior ischemic stroke or TIA: The incidence of recurrent stroke or TIA in patients with a prior CVE has reduced during the last five decades. The annual event rates for recurrent stroke have declined by on average 0.996% per decade, probably because of improved secondary prevention [44]. However, prior stroke or TIA has been reported as a strong independent risk factor for mortality and stroke or systemic embolism [45].

Lifestyle: Important risk factors associated with cerebrovascular disease are smoking, which doubles the risk of stroke [46], obesity, and physical inactivity. In population studies, obesity increases the risk of ischemic stroke by 50% to 100% compared to normal-weight individuals [36, 47-49]. Physical inactivity is associated with other health conditions, such as obesity, high blood pressure, high cholesterol, and diabetes, which all raise the risk of stroke. Furthermore, physical inactivity has been correlated with acute, subacute, and chronic phases of stroke [50, 51].

Cardiovascular comorbidities: As numerous studies have shown, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, and heart failure are risk factors that are associated with the occurrence of ischemic stroke [52-58].

Atrial fibrillation: This is the major cause of cardioembolic stroke. An ischemic CVE caused by atrial fibrillation is often clinically identified as a stroke or TIA and the occult atrial fibrillation is subsequently diagnosed. Treatment with oral anticoagulants is indicated to minimize the risk of a recurrent CVE, considering that these patients have a higher risk of recurrent CVEs than the general population [59, 60]. In the past decade, the detection of atrial fibrillation after an ischemic CVE has been improved, and heart rhythm monitoring for occult atrial fibrillation is usually recommended.

Presence of an atrial shunt: PFO has been identified as an etiology for cryptogenic stroke. The most likely mechanism of a PFO-caused stroke is that the PFO can serve as a conduit for paradoxical embolization by maintaining the communication between the right-sided and left-sided circulation [61]. Thus, venous clots can move from the right-side circulation through the PFO to the systemic circulation, bypassing the pulmonary circulation and causing an ischemic stroke. Another assumption is that a primary thrombus formation within a high-risk PFO canal, as well as arrythmias related to a PFO can cause an ischemic CVE [62]. Finally, paradoxical embolism can be caused by a concomitant hypercoagulable state that predisposes to thrombus formation or venous clotting [62-66].

Before the widespread clinical use of echocardiography during the 1980s, it was difficult to establish an association between PFO and stroke. This association has become evident with the use of contrast echocardiography, especially for otherwise healthy young patients with cryptogenic stroke, as observational studies published in the late 1980s have shown [67-69]. There is an established correlation between a PFO and a cryptogenic stroke occurring during the Valsalva maneuver. The following factors have also been correlated with a cryptogenic stroke caused by a PFO: large septal excursion distance, concomitant atrial septal aneurysm, and large right-to-left shunt [70]. Of note, the relationship between ASD and stroke is less well studied because it is usually diagnosed and treated earlier (before a cryptogenic CVE occurs) to avoid clinical manifestations [62].

- *Imaging for a diagnosis of PFO:* Screening for a PFO is currently indicated only in patients who have experienced an ischemic CVE of undetermined cause [71].The gold standard method for detecting a PFO and observing its anatomical characteristics is contrast transesophageal echocardiography (TEE) [72] (Figure 5 A). Gelofusine or agitated saline is injected just before the release of the Valsalva maneuver and if at least three bubbles are observed in the left atrium within three cardiac cycles, a PFO is diagnosed [6]. An alternative screening test for a PFO is contrast transthoracic echocardiography (TTE) (Figure 5 B); it has lower sensitivity than contrast TEE but extremely high specificity [73, 74], and it is less time-consuming and more accessible than contrast TEE. Last, contrast transcranial doppler (TCD) (Figure 5 C) is a noninvasive diagnostic method and can be used for the diagnosis of a PFO with excellent accuracy. Nevertheless, it cannot provide the precise anatomy of the PFO and cannot exclude the presence of arteriovenous fistulas which may explain the presence of bubbles [75].

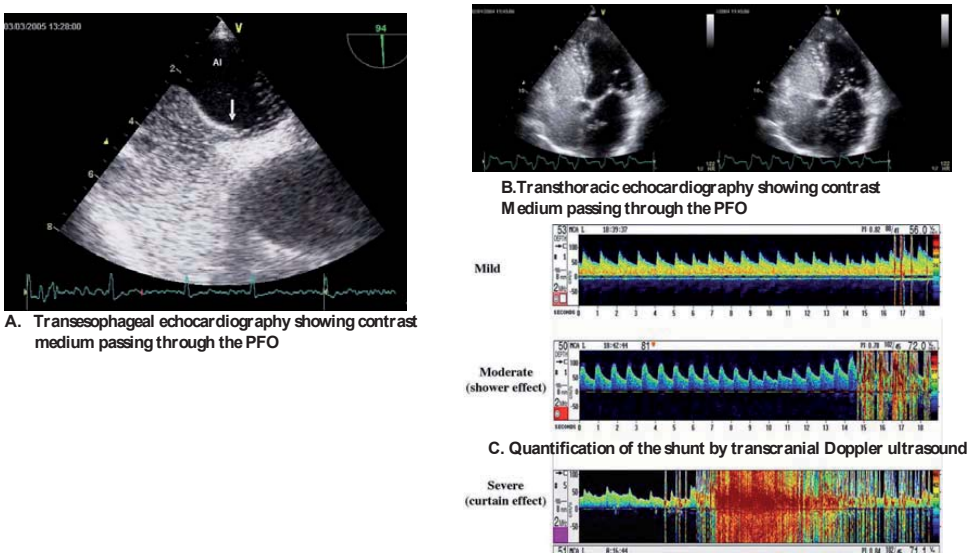

Figure 5. Imaging of a patent foramen ovale (PFO). A. Contrast transesophageal echocardiography (TEE); B. Contrast transthoracic echocardiography (TTE); C. Contrast transcranial Doppler ultrasound (TCD). Reproduced with permission from Revista Espanola de Cardiologia Vol 64, Num 2, pages 133–139, February 2011.

- *RoPE score and age:* An index has been developed to distinguish stroke-related PFO from incidental PFO in cryptogenic stroke [76]. The RoPE (Risk of Paradoxical Embolism) score will identify patients with cryptogenic stroke and a PFO where there is a high likelihood that their stroke occurred because of the PFO, that is, if no vascular risk factors are present (diabetes, hypertension, smoking, recurrent stroke or TIA, or older age) and if there is a verified cortical infarction on imaging. A high RoPE score (≥7) implies that the patient most likely has a pathogenic PFO, while a low score indicates that the finding of a PFO is possibly incidental [77, 78] (Table 1 and Figure 6).

A high RoPE score is mainly associated with younger patients, considering that patients up to 29 years old automatically score 5 points in comparison to the oldest patients scoring 0 points. This is because atherosclerotic disease develops with age and because age itself is a risk factor for stroke. Thus, a PFO is often incidental in older patients [31, 42]. Furthermore, PFO prevalence is lower in older patients [2].

However, factors that trigger paradoxical embolism, such as hypercoagulability and venous thrombosis, increase with age [79]. In a series of patients aged over 60 years with an ischemic CVE, Mazzucco et al. showed that the prevalence of PFO is significantly higher in patients with cryptogenic stroke than in patients with stroke of known cause [80].

Table 1. Calculator for the Risk of Paradoxical Embolism (RoPE) score

RoPE SCORE CALCULATOR	
Patient Characteristic	Points
No history of hypertension	+1
No history of diabetes	+1
No history of stroke or TIA	+1
Non-smoker	+1
Cortical infarct on imaging	+1
Age	
18–29	+5
30–39	+4
40–49	+3
50–59	+2
60–69	+1
≥ 70	0

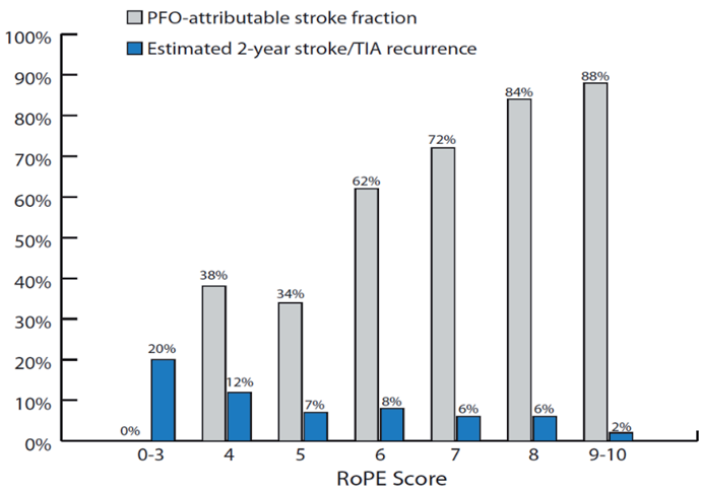

Figure 6. Risk of Paradoxical Embolism (RoPE) score interpretation. A higher RoPE score indicates a higher likelihood that stroke or transient ischemic attack (TIA) was related to a patent foramen ovale (PFO) and a low likelihood of recurrence. A lower RoPE score indicates a higher likelihood that stroke or TIA was caused by factors unrelated to PFO and higher likelihood of recurrence. Reproduced with permission from Cardiac Interventions Today MAY/JUNE 2017 VOL. 11, NO.

The PFO-Associated Stroke Causal Likelihood (PASCAL) classification algorithm combines the RoPE score with PFO characteristics, including 1) a straddling thrombus through a PFO, 2) a large shunt size, and 3) co-existence of ASA [81]. In the PASCAL algorithm, the likelihood of a PFO-associated stroke is classified as definite, highly probable, probable, possible, or unlikely [81].

Treatment of a cryptogenic CVE associated with a PFO

The therapeutic strategies for secondary prevention of a recurrent cryptogenic CVE associated with a PFO are oral anticoagulation or antiplatelet medication, or transcatheter PFO closure using a septal occlude device.

Percutaneous transcatheter closure of a PFO has been shown to be a safe and feasible procedure associated with a small periprocedural risk [82-85]. However, three randomized studies published between 2012 to 2013 failed to show superiority of transcatheter PFO closure compared to medical treatment [86-88]. The main limitation of these studies was that many of the patients, especially in the medically treated arm, were lost to follow-up [89].

In contrast, three subsequent randomized studies published during 2017, with better design, using better devices and with stricter inclusion criteria compared to the previous ones, as well as extended follow-up of prior randomized studies, indicated greater benefit from PFO closure than from medical treatment in patients with a cryptogenic CVE and a PFO [90-94]. These studies and their meta-analyses suggest a significant reduction of recurrent CVEs after transcatheter PFO closure compared to medical treatment [95-97].

Current guidelines recommend transcatheter PFO closure in preference to medical therapy alone in eligible patients to avoid a recurrent stroke [71]. They also highlight that high-risk PFO features, such as the presence of ASA, prominent Eustachian valve, or large right-to-left shunt, strengthens the indication for transcatheter closure of the PFO as secondary prevention after stroke caused by a PFO [36, 98].

In the process of selecting patients for transcatheter PFO closure, it is strongly recommended that a multidisciplinary team evaluation is conducted, including a neurologist to confirm that the cryptogenic stroke is of an embolic source, as well as a general cardiologist and an interventional cardiologist. Patients eligible for transcatheter closure of a PFO for secondary prevention of stroke are defined as younger patients who have experienced a stroke where no other cause than PFO can be determined. The eligible age is defined as up to 60 years old according to American guidelines and up to 65 years old in the European guidelines [36, 71]). The number needed to treat with PFO closure to prevent one stroke is calculated to be 37 [95% confidence interval (CI): 26–68], and 21 in patients with high-risk PFO features (95% CI: 16–61) [71].

The heterogeneity of the treatment effects of PFO closure on stroke recurrence in patients in different PASCAL subgroups is outlined in a recently published meta-analysis of the six randomized studies. When patients treated with PFO closure were compared to those treated with medical therapy alone, the hazard ratios of recurrent stroke were 1.14 (95% CI 0.53–2.46), 0.38 (95% CI 0.22–0.65), and 0.10 (95% CI 0.03–0.35) respectively, for PFO classified as an unlikely, possible, or probable cause of the stroke according to the PASCAL classification [99].

The benefit of PFO closure in elderly patients remains unclear, as small retrospective studies do not provide definitive answers because of the limited number of enrollees aged over 60 years old and the short-term follow-up [100, 101].

Patients with a cryptogenic CVE and thrombophilia were not included in the randomized trials and they were generally excluded for PFO closure in the past, given that they need lifelong anticoagulation therapy, regardless of the presence of a PFO. However, a recently published study highlights the need for PFO closure even in these patients [102].

In patients for whom transcatheter PFO closure after a stroke caused by a PFO is not feasible, oral anticoagulation is recommended in preference to antiplatelet therapy [103].

However, oral anticoagulation treatment has been associated with more bleeding events compared to transcatheter PFO closure [104].

Transcatheter closure of a PFO

The procedure of PFO closure

Transcatheter closure of a PFO is a procedure requiring expertise and responsiveness beyond the formal protocols of the different intervention centers around the world.

In a recently published review, PFO closure is described as an intervention performed in a catheter laboratory with fluoroscopic guidance and physiological monitoring. Either TEE or intracardiac echocardiography are used during the procedure. Therefore, to facilitate the TEE, general anesthesia is recommended [105]. Anticoagulation with unfractionated heparin is administered to maintain clotting time at >250 sec. After cannulation of the femoral vein, a stiff wire is advanced through the defect and is placed in the left upper pulmonary vein.

The size and anatomy of the defect can be detected through compliant balloons with marked graduations. After careful balloon sizing, the appropriate device for delivery into the left atrium is selected [105]. The discs are deployed, first the left atrial disc, followed by the right disc. Before the device release, it is recommended that a thorough control of the device positioning with fluoroscopy and echocardiography (Figure 7) is performed. Color Doppler is used to check whether there is any residual shunting directly after the device deployment [106].

Devices used for PFO closure

The selection of the device is mainly in accordance with the preference of the interventionist. In recent decades, several types of devices have been used for transcatheter closure of a PFO. The manufacturer of each device provides recommendations regarding the pre- and post-medication of the patients and the procedure itself.

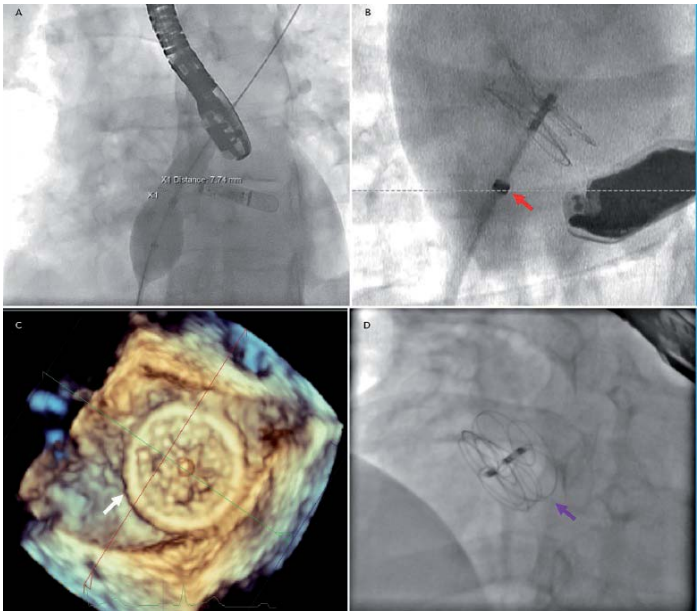

Figure 7. The PFO closure procedure. (A) Wire crossing a PFO into the left upper pulmonary vein. A sizing balloon is deployed and the quantitative angiographic analysis to size the defect is shown. (B) The Gore Cardioform septal occluder has been deployed through the delivery sheath (red arrow) but has not yet been released. (C) 3D transesophageal echocardiography image of the device (white arrow) viewed from the left atrium. (D) The device is shown in place after release (purple arrow). Reproduced with permission from Interventional Cardiology Review 2019;14(1):34–41.

The devices used mainly in the sub-studies of this thesis are shown in Figures 8 and 9. One of the most common devices is the Amplatzer occluder device, which can be applied in both PFO and ASD closure. The Amplatzer™ PFO Occluder device (AGA Medical, Golden Valley, MN) consists of two discs of woven nitinol wires and a short connecting waist. The right atrial disc is larger than the left [107] (Figure 8 B). However, the risk of developing a low-grade inflammatory response because of the polyester fabric and the nitinol wires has been reported [108], and nickel allergy is a very rare complication that may require explantation of the device [109].

To minimize this risk from the implanted device, the biodegradable closure device BioSTAR® was introduced in 2006. The hypothesis was that a biodegradable device could efficiently close the PFO and then degrade, leaving very little exogenous material in the atrial septum [110]. The BioSTAR® bioabsorbable septal repair implant was made from bioabsorbable fabric, a bioengineered, highly purified, acellular matrix consisting primarily of a layer of intestinal collagen (Organogenesis Inc.; Canton, Mass.) instead of polyester [111, 112] (Figure 9). The application of BioSTAR® was stopped because of reported serious complications following implantation.

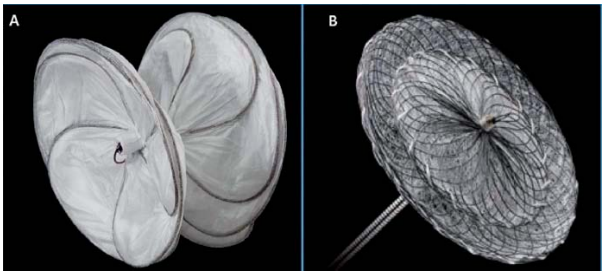

Figure 8. Common devices for PFO closure. (A) The Gore Cardioform septal occluder. (B) The AMPLATZER PFO Occluder. Reproduced with permission from Interventional Cardiology Review 2019;14(1):34.

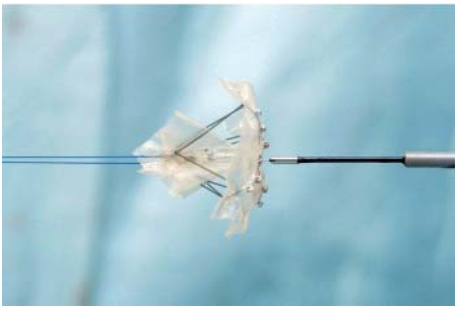

Figure 9. BioSTAR PFO Occluder. Reproduced with permission from JACC: Cardiovascular Interventions, Volume 3, Issue 9, September 2010, pages 968–973.

The GORE® HELEX® Septal Occluder and the next generation GORE® CARDIOFORM Septal Occluder (GSO) have been found to be safe and efficient in observational studies and in a randomized study [113-116]. The HELEX® occluder was associated with residual shunting [117], but this complication was mitigated with the next generation GSO occluder (Figure 8 A).

Selection of the appropriate device during transcatheter closure of a PFO is essential for effective closure of the defect and for avoiding periprocedural complications.

Complications of PFO closure

Intra-operative and in-hospital complications

Air or thrombotic embolization: During the delivery of the device, there is a risk of air or thrombotic embolism that can cause an iatrogenic stroke or TIA. In order to minimize the risk, de-air and flush of the delivery sheath is recommended and anticoagulation with unfractionated heparin administered to maintain clotting time at >250 sec [105].

Malposition of the device and device embolization: A limited number of cases of perforation of the atrium or the aortic root because of malposition of the device have been reported [109, 118]. Device embolization following PFO closure is as low as 0.7% [119].

Device or sheath thrombus: The presence of a thrombus on the device or on the sheath may be observed by the interventionist when using TEE guidance, despite periprocedural anticoagulation [120]. In this case, intensive anticoagulation is recommended and, if possible, interruption of the procedure.

Device erosion and cardiac perforation: This is a very rare but most likely underreported (0.028%) life-threatening complication of PFO closure [106]. Device erosion usually appears shortly after the implantation, but there have been reported cases of late erosions [109].

Pericardial effusion without perforation/erosion: This is an iatrogenic complication that usually does not require any treatment and resolves after some days. In rare situations it may require pericardiocentesis [121].

Arrhythmias: Atrial or ventricular arrhythmias, usually transient, may be detected during or directly after the procedure.

Chest pain: During the procedure, transient ST elevation on electrocardiogram (ECG) followed by chest pain may emerge. This is most often due to air embolism in the right coronary artery. In some cases, chest pain presents shortly after device implantation due to a nickel allergy, which is very rare and further described below.

Hematoma: This may be observed after the cannulation of the femoral vein. It often resolves by itself, but in rare cases a pseudoaneurysm persists, requiring intervention.

Mortality: Death is a very rare complication. The rate of in-hospital death during PFO closure was reported to be up to 0.3% (95% CI, 0.1%–0.6%) [122].

Control TTE prior to discharge is recommended for all patients who undergo transcatheter closure of a PFO, to exclude pericardial effusion and device embolization [105].

Mid-term and long-term complications

a) thrombus formation: The incidence differs among the various types of devices. The incidence was found to be 0.8% for the GORE® HELEX® device and 0% for the Amplatzer device, but the patients were successfully treated with anticoagulation [123]. *b) pericardial effusion:* Dressler's syndrome with pericardial effusion has been reported as a mid-term complication [124]; this is an inflammatory response to the device. *c) device erosion:* This has been reported as a very rare complication, usually requiring explantation of the device [109].

Nickel allergy: Patients with hypersensitivity to nickel, which can be verified by skin tests, may experience chest pain, dyspnea or palpitations after PFO closure [125]. Nickel allergy has been reported after implantation for several of the devices; it is extremely rare and it can present directly after the procedure or some months later [126]. In some cases of nickel allergy, explantation of the device may be required to relieve the symptoms [109].

Endocarditis: Infection of the PFO closure device is extremely rare. Nevertheless, in some case reports, prolonged intravenous antibiotics or surgical extraction of the device was required [127]. Due to lack of data and the low rate of endocarditis, endocarditis prophylaxis for several dental procedures is recommended for the first six months post-procedurally and it can be considered lifelong treatment if the closure of the PFO is not complete [71].

Atrial fibrillation: The incidence of atrial fibrillation after PFO closure is four to five times as high as the incidence in medically treated patients, as meta-analyses of observational studies and clinical trials have recently reported [128, 129]. Atrial fibrillation appears mostly as a mid-term complication after device implantation, most frequently within 45 days post-operatively [128]. It has been reported that post-procedural new-onset atrial fibrillation is transient and resolves after some time. However, in a recent meta-analysis, a higher incidence of atrial fibrillation in the late post-PFO closure period was observed than that seen in population studies [128]. There are some possible mechanisms that may trigger atrial fibrillation after PFO closure, such as the procedure itself irritating the atrium, or the device triggering an inflammatory response or acting as a mechanical barrier to depolarization [130]. The reported incidence of post-procedural atrial fibrillation is higher in studies including older patients [130, 131].

Furthermore, the type of PFO device seems to play a crucial role; for instance, a higher incidence of new-onset atrial fibrillation has been reported with the STARFlex device compared to the Amplatzer PFO Occluder or the HELEX® device [132], and the GSO device also showed a high incidence of new-onset atrial fibrillation in the REDUCE study [90]. In some cases, new-onset atrial fibrillation after PFO closure may become persistent, and medical treatment or ablation can be required to preserve the sinus rhythm. In addition, occult atrial fibrillation not detected before PFO closure, which may have caused the initial cryptogenic cerebrovascular event, can present as new-onset atrial fibrillation after PFO closure of the incidental PFO.

Mid-term and long-term mortality: Death as a mid-term and long-term complication after PFO closure is correlated with other complications, such as late device dislocation and pericardial effusion, and with recurrent CVEs. Late cardiovascular mortality related to PFO closure was not reported in randomized studies or other reports [90-92, 133].

Residual shunting after PFO closure

The Achilles heel of the devices used for PFO closure is the residual shunting after implantation. In an observational prospective study, the incidence was up to 22% during the first month after the device implantation and sank to 9% after 12 months [134].

This successive mitigation can be explained by the continuous endothelialization of the device during the first months after the procedure. However, in the REDUCE randomized study, minor to large residual shunting was reported in up to 25% of the patients [90]. Residual shunting has been associated with the presence of an ASA, a longitudinal fossa ovalis dimension larger than 20.8 mm, and the type of device [117, 135]. The BioSTAR® device has demonstrated a higher incidence of residual shunting compared to other devices [136]. Furthermore, in an extension of an observational study of patients who received the BioSTAR® device, new-onset residual shunting after the 12-month follow-up was reported, justifying the recommendation that these patients should have an extended follow-up [137].

Recurrent CVE after PFO closure

Recurrent CVE is the primary end point of all studies reporting the results of the transcatheter PFO closure. Although randomized studies have shown that the risk of a recurrent CVE is mitigated significantly after PFO closure, this risk still exists and varies among the studies [90-94]. Two of the randomized studies differentiated clinical stroke from new-onset brain lesions on imaging during the follow-up [90, 92]. They reported 0–1.8% clinical strokes and 5.7–8.8% new ischemic lesions on imaging. The reason for the high number of silent brain lesions after transcatheter closure of a PFO is unclear; in the REDUCE study, the suggested definition of a lesion was 3 mm or larger in the beginning of the study on T2-weighted sequence magnetic resonance imaging (MRI). However, this definition was changed over the course of the study, to include higher MRI field strength, multiple acquisition sequences and varying criteria regarding the size of the ischemic lesion depending on its location [90]. On the other hand, in the DEFENCE-PFO study, a similar difference was found but was not further analyzed [92].

There are several potential explanations regarding the cause of a recurrent stroke after PFO closure. The PFO may have been incidental and not the cause of the initial ischemic CVE. Thus, extensive investigation of other causes of stroke, especially the presence of occult atrial fibrillation, are necessary before taking the decision to perform PFO closure. However, the assessment of PFO-caused stroke has improved in recent years with better diagnostic tools. Prolonged ECG monitoring and better imaging of the stroke are tools that improve the selection of patients for PFO closure. The procedure-related new-onset atrial fibrillation following PFO closure can be the cause of a recurrent stroke. Furthermore, comorbidities that were underestimated or not diagnosed after the initial ischemic CVE and are not under adequate treatment may cause a recurrent stroke after PFO closure [138].

In addition, late thrombus formation on the device may cause a recurrent CVE because of emboli. Finally, residual shunting presenting in up to 25% after PFO closure has been suspected as the main cause of recurrent stroke [90, 139].

Post-procedural care after PFO closure

The patient usually remains in the hospital overnight after PFO closure, and an ECG is obtained to detect any atrial arrhythmias or evidence of atrioventricular blocks. As

a routine in some centers, ECG monitoring is conducted for the first 24 hours post-procedurally. A TTE is performed before the patient is discharged from hospital in order to detect any pericardial effusion, malposition of the device, deformation of surrounding structures, or evidence of device erosion [140].

A clinical evaluation, including contrast echocardiography, is recommended six months post-operatively, mainly to detect residual shunting and very rare late erosion of the device or late pericardial effusion [90, 91]. Thereafter, contrast echocardiography is only recommended for follow-up in cases of persistent residual shunting [141].

The choice of the echocardiography method varies among the different centers. Contrast TEE has been reported to be no better at detecting residual shunting compared to the other echocardiographic methods. TEE is an invasive method, whilst contrast TCD is a non-invasive method with high sensitivity for detecting residual shunting. However, contrast TCD cannot identify the positioning of the device, the presence of pericardial effusion, or erosion of the device, which are all diagnoses identified by contrast TTE [73, 75].

The type and duration of antithrombotic treatment after PFO closure remains controversial. Currently, the recommendation is dual antiplatelet therapy for at least one month and up to six months post-operatively, followed by monotherapy for at least two to five years post-operatively [90-92, 94]. The selection of drugs used, as well as the duration of dual antiplatelet therapy, depends on the device manufacturer. For instance, the manufacturer of GSO devices recommends initially dual antiplatelet therapy (aspirin combined with clopidogrel). After one to six months, clopidogrel is discontinued and followed by aspirin monotherapy [90]. Prolonged antithrombotic treatment after PFO closure may be considered, but bleeding events may exceed ischemic events over the long term (more than 10 years) according to one study [133].

Medical therapy for secondary prevention of cryptogenic stroke in patients with a PFO

In patients who are ineligible for PFO closure after a stroke related to their PFO, a prolonged medical therapy is recommended, while balancing the risk of bleeding versus the risk of recurrent stroke because of the remaining PFO [98]. Long-term anticoagulation with vitamin K antagonists is preferred in patients with good compliance and low risk of major bleeding. However, in patients who do not fulfill these criteria, an antiplatelet agent is chosen over anticoagulation [71].

Based on the results of two studies, current guidelines do not recommend direct oral anticoagulant treatment in preference to antiplatelet agents. The NAVIGATE-ESUS trial randomized patients with ESUS, including a subgroup with a PFO, to aspirin or rivaroxaban, and reported no significant differences in recurrent stroke between the treatment arms of the study [142]. Likewise, the RESPECT-ESUS trial did not show any difference on incidence of recurrent stroke between the aspirin-treated arm and the dabigatran-treated arm, in patients with ESUS and a PFO [143]. Major bleeding risk was not significantly different for the groups in the NAVIGATE-ESUS trial, and it was not reported specifically for PFO patients in the RESPECT-ESUS trial [142, 143].

THE RATIONALE FOR THIS THESIS

In late 1996, the interventionists in the Center for Adults with Congenital Heart Disease at Sahlgrenska University Hospital/Östra (the ACHD center) in Gothenburg started performing transcatheter closure of PFOs. From the beginning, the interventionists expressed the need for multidisciplinary consensus to identify patients eligible for PFO closure. In the early years, few interventions were made but the number increased rapidly; by the end of 2000, more than 60 PFO closure interventions were performed yearly. Following the local protocol, the patients were selected through a multidisciplinary conference including a neurologist, cardiologist, and interventionist [144] (see Appendix). After the first three randomized studies of PFO closure gave negative results [86-88], the intervention was limited to compassionate use or as part of a clinical trial. The ACHD center in Gothenburg was one of the centers participating in the REDUCE study [90]. In late 2017, when three randomized studies were published with positive results [90, 91, 94], PFO closure interventions increased, and they followed a more systematic selection of patients according to guidelines published in 2018 [36, 71, 98].

At the time when this thesis work started, there were no guidelines suggesting the superiority of transcatheter closure of a PFO over medical treatment after a cryptogenic stroke. At the same time, a thesis from our department, based on observational studies, did not show superiority of PFO closure over medical treatment. On the other hand, the quality of life of patients who underwent PFO closure was better compared to the medically treated patients [145, 146].

Today, there is a global consensus that PFO closure is superior to medical treatment after cryptogenic stroke in well-selected patients. However, the randomized studies underlying this consensus used selected devices, selected patients, and selected antithrombotic medicines during a follow-up period of up to five years. During this time, thousands of other patients underwent closure of a PFO, using various devices and antithrombotic treatment, without their outcomes being systematically studied. Furthermore, the intervention has now been in use for 25 years, meaning that PFO closure patients are getting older and potentially developing vascular disease and new CVEs. Given that the ACHD center in Gothenburg and the registries of the Swedish National Board of Health and Welfare contain complete data [147, 148], we aimed to shed light on the mid-term and long-term outcomes for patients who underwent PFO closure because of a cryptogenic CVE.

AIM

The overall aim of this thesis was to study the patients who underwent closure of an atrial shunt after a cryptogenic CVE and to investigate the mid-term and long-term outcomes after the intervention. We also aimed to compare these outcomes between different devices, as well as with patients who received medical treatment instead and with the general population.

The specific aims and hypotheses of the Papers included in the thesis were as follows:

Paper I: To study the mid-term outcomes after closure of a PFO with the BioSTAR device in comparison with widely used devices. The hypothesis of the study was that BioSTAR was as feasible and appropriate as the widely used devices at that time.

Paper II: To identify recurrent CVEs in patients who underwent PFO closure and to investigate the cause of the recurrent CVE. The hypothesis of the study was that patients with a recurrent CVE were ineligible for PFO closure or that occult atrial fibrillation was the cause of the recurrent CVE.

Paper III: To compare the incidence of recurrent stroke in patients after closure of an atrial shunt because of a cryptogenic CVE with the incidence among patients receiving medical treatment only, and with the incidence of index stroke in controls without a previous CVE. The hypothesis of the study was that the incidence of recurrent stroke in the atrial shunt closure group was lower compared to the medical treatment group and similar to the controls.

Paper IV: To investigate whether patients over 60 years old with a cryptogenic CVE and an atrial shunt are eligible to undergo closure of the atrial shunt instead of medical treatment and to compare their outcomes with controls without a previous CVE. The hypothesis of the study was that patients over 60 years old are eligible for closure of the atrial shunt after a cryptogenic CVE and experience recurrent stroke at a lower rate than medically treated patients and a similar rate to the controls without a previous CVE.

PATIENTS AND METHODS

Data sources

In Papers I and II, we used the Swedish personal identity number to search the medical records of the patients who underwent PFO closure at the ACHD center. In Papers III and IV, the Swedish registries described below were used.

Swedish National Patient Register (NPR)

The NPR is administrated by the Swedish National Board of Health and Welfare. It was initiated in 1964, and since 1987 it contains complete data for all patients admitted for inpatient care in a Swedish hospital. At this point, it is important to mention that the Swedish health care system is state financed, offering health care to all individuals permanently living in Sweden, at a very low individual cost. Every month, each Swedish hospital reports to the NPR, and this is mandatory. Since 2001, diagnoses of all outpatient visits are also reported to the NPR, including visits to outpatient hospital-based clinics or other specialized outpatient clinics. The diagnoses in the NPR are coded in accordance with the Swedish version of the International Statistical Classification of Diseases and Related Health Problems (ICD) system [148]. The surgical procedures for the cardiovascular system were identified by the NOMESCO classification of surgical procedures, version 1.9, Swedish version 1997 [149].

All individuals permanently living in Sweden, even the ones without Swedish nationality but with permanent residence, have a personal identity number, a system introduced in 1947 which makes it possible to link patients across the different registries. The amount of missing data in the NPR is less than 1% [148]. The registry has been validated, and in general a high validity of the diagnoses has been reported, with a positive predictive value of 85–95% for most diagnoses [148].

Cause of Death Register

The Cause of Death Register is also administrated by the Swedish National Board of Health and Welfare. It was initiated in 1961 and records the primary and the underlying cause of death of an individual permanently living in Sweden, even if the death occurred abroad. It is linked with the NPR.

Swedish Prescribed Drug Register (SPDR)

The SPDR was established in July 2005 and includes data on all prescribed drugs purchased at Swedish pharmacies. The SPDR contains information about the patient's age, sex, and personal identity number, as well as the prescriber's profession and practice. The data collection is administered by the National Corporation of Swedish Pharmacies, a state-owned company, and information from all prescriptions dispensed is transferred monthly to the National Board of Health and Welfare [150]. The SPDR is linked to other health registries, such as NPR, and provides information about the actual use of the drugs purchased.

The procedure of PFO closure at the ACHD center in Gothenburg

PFO closure was performed in a catheterization laboratory, with fluoroscopy and TEE imaging, under general anesthesia. The patients received antibiotics perioperatively and the day after the implant. Intravenous heparin was injected, maintaining clotting time at >250s during the procedure. After cannulation of the femoral vein with a 12-F insertion sheath, a super-stiff guide wire was advanced through the defect and placed in the upper pulmonary vein. The size and anatomy of the PFO were determined by gentle inflation of a compliant-sized balloon (NuMED PTS; NuMed, Hopkinton, NY, USA) until a waist was apparent and the flow stopped. The choice of the device was at the interventionist's discretion, depending on the size and anatomy of the defect.

Devices used at the ACHD center in Gothenburg

Eight different devices were used between 2006 and 2014 (Paper II). The AMPLATZER® PFO Occluder device (AGA Medical Corp, Plymouth, MN, USA) was used mainly in the early decades of the procedure. In cases of a large shunt (≥15 mm), an AMPLATZER Septal Occluder (ASD closure device) or an AMPLATZER Multi-Fenestrated Septal Occluder "Cribriform" (multi-fenestrated ASD closure device) was used. The STARFlex Septal Occlusion System (NMT Medical, Inc., Boston, MA, USA) was used for smaller defects and its newer version, BioSTAR® (NMT Medical, Inc., Boston, MA, USA), which was biodegradable, was used from 2007 to 2008. The Solysafe® Septal Occluder (Swissimplant AG, Solothurn, Switzerland) was another option for small defects. The GORE® HELEX® Septal Occluder (WL Gore and Assoc, Inc, Newark, DE, USA) device was used for some years during the 2010s. Since then, the ACHD center has mainly used the next generation GORE® CARDIOFORM® Septal Occluder.

In Paper I, patients were implanted with the BioSTAR® device (NMT Medical, Inc., Boston, MA, USA), the AMPLATZER® PFO or ASD or Cribriform Occluder device, or the Solysafe® Septal Occluder.

Each manufacturer recommended a different line for antithrombotic medications. For the BioSTAR device, the use of double antithrombotic treatment on discharge was recommended, while those implanted with an Amplatzer occluder were under single antiplatelet therapy on discharge.

The methods used in Papers I–IV of this thesis are summarized in Table 2.

Study populations

Papers I and II

From the data collected at the ACHD center at Sahlgrenska University Hospital/Östra in Gothenburg, medical records were obtained and all patients who underwent closure of a PFO because of a cryptogenic CVE were identified.

Table 2. Overview of the Papers included in this thesis

	Paper I	Paper II	Paper III	Paper IV
Study design	Case-control, cross-sectional, single center study	Case-control, cross-sectional, single center study	Retrospective, register-based cohort study	Retrospective, register-based cohort study
Data sources	Medical records and telephone follow-up	Medical records, telephone follow-up and current clinical data	National Patient Register, Cause of Death Register, Swedish Prescribed Drug Register	National Patient Register, Cause of Death Register, Swedish Prescribed Drug Register
Study population	Patients with PFO closure using the BioSTAR occluder device and patients using other occluder devices	Patients with PFO closure who developed a recurrent CVE and control patients with PFO closure with no recurrent CVE	Patients with transcatheter closure of an atrial shunt after a CVE, patients medically treated after a CVE, and controls from the general population	Older patients (aged 60 years or above) with transcatheter closure of an atrial shunt after a CVE, age-matched patients medically treated after a CVE, and controls from the general population
Number included	59 patients, 30 with BioSTAR and 29 with other devices	282 patients (the initial population), 13 patients with a recurrent CVE and 22 control patients at clinical follow-up	663 patients with closed atrial shunt, 1,671 medically treated patients, and 6,302 controls	112 patients with closed atrial shunt, matched with 112 medically treated patients and 112 controls
Follow-up period	2008–2011	2006–2018	1997–2017	1997–2017
Statistical analyses	Descriptive only	Descriptive, Fisher's exact test, Kaplan–Meier survival analysis	Propensity score matching, Cox regression analysis univariate and multivariate	Mean-difference T-test, propensity score matching, univariate Cox regression analysis
Primary endpoint	Feasibility and efficacy of the BioSTAR device	Recurrent CVE after PFO closure	The incidence of a recurrent CVE	The incidence of a recurrent CVE
Secondary endpoints	Mid-term outcomes after BioSTAR implantation	Investigate the risk factors for a recurrent CVE	The incidence of atrial fibrillation, cardiovascular comorbidities, and major bleeding	The incidence of atrial fibrillation, cardiovascular comorbidities, and major bleeding

In Paper I, all patients from the ACHD center in Gothenburg who received the BioSTAR device, delivered between 2007–2008, were identified. Patients who received another widely used device during the same period were identified and used as a comparison group. BioSTAR carriers and the control patients in the comparison group were contacted by telephone at a mean time of 1.5 years post-operatively and they were asked about their current clinical status. They were also asked whether they experienced any adverse events, including a recurrent CVE, or whether they needed hospitalization any time after PFO closure. The medical records of the patients hospitalized post-operatively were obtained after the patients gave consent.

In Paper II, we identified all the patients who underwent PFO closure because of a cryptogenic CVE between 2006 and 2014 at the ACHD center in Gothenburg. The procedural records were obtained, as well as the six-month follow-up visit and the 12-month follow-up if there was any. All the patients were contacted for a telephone interview. If patients reported that they remained in the hospital after the procedure, their medical records were obtained, with their consent, and patients with a recurrent CVE were identified. These patients were asked to participate in a clinical study to identify the cause of the recurrent event. They were matched for age and sex with two control patients who underwent PFO closure during the same period but did not experience a recurrent CVE. Control patients were also asked to participate in the clinical study. Patients with a recurrent CVE and their controls were called for clinical examination during 2018 in the ACHD center in Gothenburg.

Papers III and IV

The NPR was searched to identify patients who had a diagnosis of an atrial shunt (Q22.1) from January 1996 until December 2016. Of these, we selected patients who had experienced an ischemic CVE before or on the same date as the diagnosis of the atrial shunt. Patients with transcatheter closure of the atrial shunt (using the operation code FFC22, from the Swedish version of the NOMESCO classification of surgical procedures [149]) were identified.

In Paper III, each patient from the intervention group was propensity-score matched with a patient who did not undergo closure of the atrial shunt despite the diagnosis of a prior ischemic CVE. Subsequently, the patients from the intervention group were matched with 9 control individuals of the same age and sex from the Total Population Register who did not have a diagnosis of atrial shunt or ischemic CVE.

In Paper IV, patients aged 60 years or older from the intervention group were matched using propensity score matching with patients in the same age group from the medically treated group. The intervention group patients were also propensity-score matched with controls from the general population in the same age group, sex and with similar cardiovascular comorbidities, but who did not have a diagnosis of atrial shunt or ischemic CVE, from the Total Population Register.

The patients and controls in Papers III and IV were followed up from the time of study inclusion to 31 December 2017 through the NPR, Cause of Death Register, and SPDR.

Methods

Papers I and II

The ACHD center at Sahlgrenska University Hospital SU/Östra is one of seven such centers in Sweden and has a catchment area of 3.5 million inhabitants. The medical records were obtained for the patients who underwent transcatheter closure of a PFO in our institute after a cryptogenic CVE through multidisciplinary conference. The hospital's electronic medical system was searched using the personal identity number of the patients. The diagnosis of cryptogenic CVE was verified by a neurologist through evaluation of the clinical status of the patient, the imaging of the brain, and the clinical history.

In Paper II, the *RoPE score* of all patients who underwent closure of the PFO between 2006 and 2014 at the ACHD center was calculated retrospectively, referring to the time of the diagnosis of the cryptogenic CVE. In order to calculate the RoPE score, we searched the patient's medical records at baseline to identify the comorbidities. The imaging records for the cryptogenic CVE were also obtained, and a consultant radiologist was asked to review the imaging in cases that diagnosis of cortical infarction was not clear.

Echocardiography for diagnosis of PFO and follow-up after PFO closure

The patient's PFO was detected by a contrast TEE and its anatomical features were studied before the intervention. The contrast TEE was performed by an experienced clinical physiologist or cardiologist by injecting gelofusine during the Valsalva maneuver. A PFO was defined as high or low risk depending on the size of the defect and the presence of a prominent Eustachian valve and/or an ASA. A larger PFO and the coexistence of an ASA and/or a prominent Eustachian valve suggested a high-risk PFO [6, 7, 84, 92]. We defined a low-risk morphological defect as a small shunt (3–9 bubbles) or a large shunt (≥10 bubbles) without ASA. The contrast TEE was repeated at six months post-operatively.

In Paper II, we performed contrast TTE to detect the position of the device and the level of residual shunting. It was performed by the authors of Paper II with the help of an experienced nurse. Agitated saline was injected during the release of the Valsalva maneuver. Residual shunting was determined as either mild or large (>10 bubbles) [90].

Follow-up

Data regarding comorbidities, short-term complications up to six months, medications, ECG rhythm, and contrast TEE at six months after the procedure were also obtained through the medical records. If no residual shunting was presented on the six-month follow-up, the patient was discharged from the ACHD center and continued with follow-ups from his or her neurologist or general practitioner. In patients with residual shunting at the six-month follow-up, the contrast TEE was repeated at 12 months.

In Paper I, we investigated the medical records of the BioSTAR carriers between 2007 and 2008. We also obtained medical records for patients who underwent closure of the PFO during the same period, who were ineligible for the BioSTAR device and were implanted with another device. All patients and controls were sent a written invitation to a telephone interview. The observation time of the study was 1.5 years (6–36 months) post-operatively. The protocol of the study is presented in Table 3.

Table 3. Protocol of the study, Paper I

Serial number:
Personal identity number:
Name:

Contrast TEE before the procedure:

- Number of bubbles
  - <3 bubbles ☐
  - 3–10 bubbles ☐
  - >10 bubbles ☐
- Atrial septal aneurysm (ASA) with 10 mm amplitude Yes No
- Electrocardiography (ECG)
  - Sinus rhythm ☐
  - Atrial fibrillation ☐
  - Other rhythm disturbance ☐

Decision of the PFO conference

- Indication
  - At least 2 cryptogenic strokes/TIAs + at least low risk PFO (at least 3 bubbles, no ASA) ☐
  - At least 1cryptogenic stroke/TIA + high risk PFO (at least 3 bubbles + ASA) ☐
  - At least 1 cryptogenic stroke/TIA + at least low-risk PFO + another risk factor (disturbance of the coagulation mechanism). ☐
  - Other indication (describe) ☐

Medical records during PFO closure:

- Age ☐
- Weight ☐
- Height ☐
- TPC ☐
- HB ☐
- Medication during hospitalization
  - Vitamin K antagonist ☐
  - Acetylsalicylic acid ☐
  - Acetylsalicylic acid + clopidogrel ☐
  - Clopidogrel ☐

TEE: transesophageal echocardiography, PFO: patent foramen ovale, TIA: transient ischemic attack, TPC: total platelet count, HB: hemoglobin.

In Paper II, all patients who underwent PFO closure between 2006 and 2014 were contacted and interviewed via telephone by a physician during 2015–2016. The protocol of the interview is summarized in Table 4. Patients who experienced a recurrent CVE were identified and their medical records were obtained. The recurrent CVE was defined as ischemic stroke or TIA by the ICD-10 codes I63, I64, and G45.

Table 4. Protocol for telephone follow-up, Paper II

Patient info:	**Serial number:**
Sex	
Age	
Weight	
Height	
BMI	
Risk factors	Yes No
Smoking	
Ex-smoker	
Heart disease	
Hypertension	
Hyperlipidemia	
Diabetes type 1 or 2	
Atrial fibrillation	
Thromboembolic disease (DVT, PE)	
Physical activity	
Medications	Yes No
Acetylsalicylic acid	
Clopidogrel	
Ticagrelor	
Vitamin K antagonist	
Dipyridamole	
Dabigatran	
Rivaroxaban	
Low molecular heparin	
Admission to hospital after PFO closure	
For recurrent stroke:	
Hospital name + date……	
For recurrent TIA:	
Hospital name + date……	
mRS (modified Rankin Scale)	0 1 2 3 4 5
Interviewer's name and date	

BMI: body mass index, DVT: deep vein thrombosis, PE: pulmonary embolism, TIA: transient ischemic attack, PFO: patent foramen ovale.

The patients with a recurrent CVE and their controls were invited to the ACHD center in Gothenburg for a clinical examination with the help of a nurse from the research team. The examination included clinical status, ECG, contrast TTE with agitated saline, and 48-hour prolonged (Holter) ECG to detect occult atrial fibrillation. The protocol of the clinical study is summarized in Table 5.

Table 5. Protocol for clinical visit, Paper II

Personal identity number:	Serial number:	
Name:		
Address:		
Phone number:		
Weight:		
Height:		
BMI:		
Blood pressure:		
Electrocardiography	Yes	No
• Sinus rhythm		
• Atrial fibrillation		
• Other		
Comorbidity on follow-up	Yes	No
• Hyperlipidemia on treatment		
• Hypertension on treatment		
• Atrial fibrillation		
• Diabetes mellitus		
• Chronic ischemic heart disease		
• Smoking		
• Ex-smoker		
Antithrombotics on follow-up	Yes	No
• Vitamin K antagonist		
• Acetylsalicylic acid		
• Acetylsalicylic acid + clopidogrel		
• Clopidogrel		
• Acetylsalicylic acid + Dipyridamol		
• Dipyridamol		
• Novel anticoagulant		
• Other antithrombotic		
• No antithrombotics		
Long-term complications	Yes	No
• Recurrent stroke/TIA after PFO closure		
• "New onset" atrial fibrillation (AF/SVT)		
• Migraine		
• Other		
Contrast transthoracic echocardiography (cTTE)	Yes	No
• Device dislocation		
• Late pericardial effusion		
• Late erosions		
Residual shunting on follow-up		
If Yes, new onset		
o <3 bubbles		
o 3–10 bubbles		
o >10 bubbles		
Holter electrocardiography 48 hours	Yes	No
• Sinus rhythm		
• Atrial fibrillation		
• Supraventricular tachycardia		
• Ventricular tachycardia		

BMI: body mass index, SVT: Supraventricular tachycardia, TIA: transient ischemic atta
PFO: patent foramen ovale.

Papers III and IV

In Papers III and IV, we used the NPR and the Cause of Death Register to identify patients with a previous CVE and thereafter a diagnosis of atrial shunt, and to identify the ones selected for transcatheter closure of the atrial shunt. We also used the Total Population Register to find matched controls. The SPDR was searched to identify all antiplatelet and anticoagulant agents purchased during the follow-up period. We defined patients with an isolated shunt as those with at least one hospitalization and either outpatient visits or a death certificate with an ICD code diagnosis Q211. Transcatheter closure of the atrial shunt was defined by the operation code FFC22. The diagnoses of ischemic stroke, TIA, atrial fibrillation, hypertension, diabetes mellitus, and cardiovascular disease were defined through the ICD codes summarized in Table 6.

Table 6. ICD diagnostic codes for the outcomes and comorbidities, Papers III and IV

Diagnosis	ICD-8	ICD-9	ICD-10
Ischemic stroke	434	436	I63, I64
Transient ischemic attack	435	435	G45
Atrial fibrillation	427.92	427D	I48
Ischemic heart disease	410,411,412,413,414	410,411,412,413,414	I20,I21,I22,I23,I24,I25
Myocardial infarction	410	410	I21
Heart failure	427.00	428	I50
Diabetes mellitus	250	250	E10,E11, E12,E13,E14
Hypertension	400,401,402,403,404	401,402,403,404,405	I10,I11,I12,I13,I14,I15
Major bleeding			I61, K92.0,K92.1, K92.2

The baseline of the studies was defined as the date of transcatheter closure of the atrial shunt for patients in the intervention group, using the same date for their matched general population controls, and as the date of the atrial shunt diagnosis for the medically treated patients.

We defined recurrent ischemic stroke as an ischemic stroke where the ICD code diagnosis appeared in the registries at least four weeks after the index stroke and atrial shunt diagnosis. To be classified as a new-onset atrial fibrillation, the ICD code diagnosis had to appear at least 48 hours after the intervention.

In Paper III, we split the follow-up time into three periods: The first period, 2001–2005, referred to the time when the intervention treatment first started and there were only small observational studies; the second period, 2006–2011, was when the volume of interventions increased; and the third period, 2012–2017, was when the intervention was part of a clinical trial or carried out for compassionate reasons.

Statistical analyses

For descriptive statistics in Papers I, II, III, and IV, continuous variables are expressed as means with standard deviations or as medians with minimum and maximum values. Categorical variables are expressed as counts and percentages. In Paper II, the p value of the Fisher's exact test was considered significant at $p \leq 0.05$, and the survival analysis is presented as a Kaplan–Meier curve.

In Paper IV, we used the mean difference t-test to assess the difference on age, sex, and comorbidities between the intervention group and the medically treated group.

In Papers III and IV, the propensity score was calculated using logistic regression with 1:1 matching, where each patient from the intervention group is matched with a patient from the medically treated group, within the area of common support (the range in which the propensity scores for the two groups overlap), without replacement, and with a caliper (the maximum permitted difference between matched patients) of 0.2 standard deviations. The propensity score model was adjusted for age, sex, coronary heart disease, heart failure, diabetes, atrial fibrillation, and hypertension. A similar model was used for propensity score matching of patients and controls in Paper IV.

In Papers III and IV, odds ratio (OR) and 95% confidence intervals (CI) were estimated at follow-up. Furthermore, a Cox regression model using univariate analysis, and in Paper III a multivariate analysis, was used to estimate the hazard ratios and 95% CI. The cumulative incidence of recurrent stroke was presented for patients and controls.

Software used

In Papers I and II, all data analyses were performed using SPSS version 20.0 (IBM SPSS, Armonk, NY, USA). In Papers III and IV, data analyses were performed using Stata software (StataCorp, College Station, TX, USA). The statistical analyses of Papers III and IV were performed by a Gothenburg University statistician and by the first author.

Ethical considerations

The Regional Medical Research Ethics Committee of Gothenburg approved all studies. In Papers I and II, a letter was sent to the patients asking them to contact the research team or to inform us if they did not want to participate in the study. In Paper II, an informed written consent was obtained from all participants of the clinical examination. Data were registered according to the Personal Data Act in transition to GDPR.

In Papers III and IV, consent was waived because only anonymized register data was included. All personal identity numbers were removed by the Swedish National Board of Health and Welfare and replaced by a unique code for each individual.

The four studies comply with the Declaration of Helsinki and were approved by the Swedish Ethical Review Authority. (Approval numbers for Papers I–II were: 029-09, T 409-11, T 164-18; approval numbers for Papers III–IV were: 912-16, T 619-18)

RESULTS

Closure of PFO with the BioSTAR biodegradable PFO closure device: Feasibility and long-term outcome (Paper I)

Over the period October 2007 to December 2008, 30 patients had their PFO closed by the BioSTAR device and 29 patients by other widely used devices. All devices were implanted successfully. The mean size of the defect was 6.6 ± 2.1 mm in the BioSTAR group and 11.7 ± 4.6 mm in the comparison group with other devices. The peri-procedural characteristics for the two groups were otherwise similar and are summarized in Table 7.

Table 7. Procedural characteristics and complications, Paper I

Procedural characteristics and complications (<24 h from implant)	BioSTAR Mean ± SD or n (%)	All other devices Mean ± SD or n (%)
Duration of operation (min)	76 ± 21	72 ± 31
Duration of fluoroscopy (min)	13 ± 9	12 ± 7
First postoperative ACT (sec)	294 ± 59	286 ± 53
Atrial arrhythmias	1 (3%)	1 (3%)
Size of defect	6.6 ± 2.1	11.7 ± 4.6

ACT: Activated clotting time

At the six-month contrast TEE, 13% of patients from BioSTAR group had large residual shunting compared to 21% of the patients in the comparison group. Patients with residual shunting underwent a new contrast TEE at 12 months and, at that time, only one patient (3%) from the BioSTAR group and four (14%) from the comparison group had remaining residual shunting. However, patients in the BioSTAR group experienced more adverse events compared to patients in the comparison group, as shown in Table 8. Four patients in the BioSTAR group and two patients in the comparison group experienced a recurrent CVE during follow-up.

Table 8. Events during follow-up, Paper I

Events n (%)	BioSTAR 30	All other devices 29
Short-term follow-up (24 h – 6 m)		
Atrial arrhythmias	4 (13%)	1 (3%)
Stroke/TIA	1 (3%)	0
Epilepsy	0	1 (3%)
Unclear neurologic symptoms	1 (3%)	0
Nosebleeds	1 (3%)	0
Bleeding/hematoma, minor/major	1 (3%)	0
Long-term follow-up (at least 18 m up to 36 m)		
New stroke/TIA	3 (10%)	2 (7%)
Atrial arrhythmias	1 (3%)	2 (7%)
Other heart problems	0	1 (3%)
No new event	26 (87%)	24 (83%)

TIA: Transient ischemic attack

Recurrent CVEs in patients after percutaneous closure of PFO (Paper II)

Between October 2006 and March 2014, 282 patients underwent successful PFO closure at the ACHD center because of a cryptogenic CVE. The median RoPE score for the patients was 7 (range 3–10).

Fourteen patients (5.0%) suffered a recurrent CVE at mean follow-up of 8.4 ± 2 years. The contrast TEE identified residual shunting in 64 patients (24%) six months post PFO closure and in 47 patients (17.3%) at 12 months post PFO closure.

Eight different devices were used during the study period, of which the BioSTAR device had the highest incidence of recurrent CVE (16%). None of BioSTAR carriers who experienced a recurrent CVE had residual shunting or any other major risk factor that could explain the recurrent CVE.

Within six months after PFO closure, 6.4% had a documented episode of transient atrial fibrillation and a further 2.5% developed new-onset atrial fibrillation later than six months post-operatively.

Follow-up clinical examination identified 13 patients with a recurrent CVE after PFO closure (one died before the beginning of the study of non-vascular disease) and 22 control patients without a recurrent CVE. Their clinical features are presented in Table 9. All residual shunts detected previously with contrast TEE were also shown on contrast TTE. Furthermore, seven patients were found on Holter ECG to have paroxysmal atrial fibrillation; in one patient this was not previously detected.

The most common risk factor for a recurrent CVE was large residual shunting, present in 46% of the patients with a recurrent CVE. The risk ratio of recurrent CVEs was three times as high in patients with residual shunting compared to patients without residual shunting (95% CI: 1.4–6.1). When carriers of the BioSTAR device with a recurrent CVE were excluded from analysis, the incidence of residual shunting in the remaining patients with a recurrent CVE increased to 67% (Figure 10).

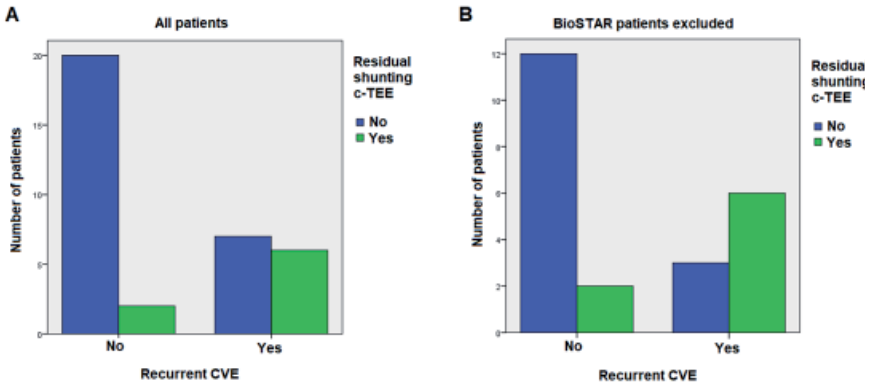

Figure 10. Recurrent cerebrovascular event (CVE) and residual shunting, Paper II. A. All patients. B. BioSTAR patients excluded.

Table 9. Follow-up visit, Paper II

	Patients with recurrent CVE N=13	Patients without recurrent CVE N=22	p-value
Age (mean ± SD)	59 (± 13)	60 (± 11.5)	
BMI (mean ± SD)	27.3± 3.7	26 ± 4	
RoPE score (min, max)	6 (4,10)	6 (4,10)	
Men n (%)	10 (77%)	17 (77%)	
Blood pressure, systolic (mean ± SD)	137± 16.8mmHg	130 ± 15mmHg	
Blood pressure, diastolic (mean ± SD)	80 ±8.5mmHg	78 ± 8.5mmHg	
Diabetes n (%)	1 (7.6%)	3 (14%)	0.59
Hyperlipidemia n (%)	4 (30%)	10 (45%)	0.49
Hypertension n (%)	5 (38.4%)	7 (32%)	0.73
Coronary disease n (%)	1 (7.6%)	0 (0%)	0.04
Smoking n (%)	0 (0%)	0 (0%)	
Previous smoking n (%)	6 (46%)	4 (18%)	0.12
Atrial fibrillation n (%)	3 (23%)	3 (14%)	0.65
Residual shunt on c-TEE (%)	6 (46%)	2 (9%)	0.03*
Medication at rCVE n=14 (note 1)			
Anticoagulant (note 2)	0/14	NA	
Antiplatelets	6/14	NA	
No medication	6/14	NA	
Medication at long-term follow-up n (%):			
Anticoagulant	8/13	3/22	
Antiplatelets	3/13	13/22	
No medication	2/13	6/22	

*significant at $p \leq 0.05$. (note 1)One patient with rCVE died because of respiratory insufficiency two years after the recurrent CVE. (note 2)Two patients were on anticoagulants but not in the therapeutic range at the time of the recurrent CVE. CVE: Cerebrovascular event, rCVE: recurrent cerebrovascular event, c-TEE contrast transesophageal echocardiography, RoPE: Risk of Paradoxical Embolism.

Percutaneous atrial shunt closure and the risk of recurrent ischemic stroke: a register-based, nationwide cohort study (Paper III)

A total of 2,334 patients with an atrial shunt and a prior ischemic CVE were identified in the NPR during the study period. Of these, 1,671 patients were under medical treatment and 663 patients underwent transcatheter closure of the atrial shunt. The 663 patients in the intervention group were matched using propensity scores with 663 patients from the medically treated group. They were also matched with a general population control group of 6,302 individuals without a history of CVE or atrial shunt, selected from the Total Population Register. The average follow-up time was over five years.

The risk of recurrent ischemic stroke was at the same level in the intervention group and the matched medically treated group. However, the risk of recurrent ischemic stroke during the follow-up period was much higher in the intervention group compared to the risk of a first ischemic stroke in the population control group (Figure 11). The hazard ratios of the univariate and multivariate analyses are presented in Paper III. The difference in cumulative incidence of recurrent stroke in the intervention group compared to index stroke of the population control group did not change during different time periods, as shown in Figure 11.

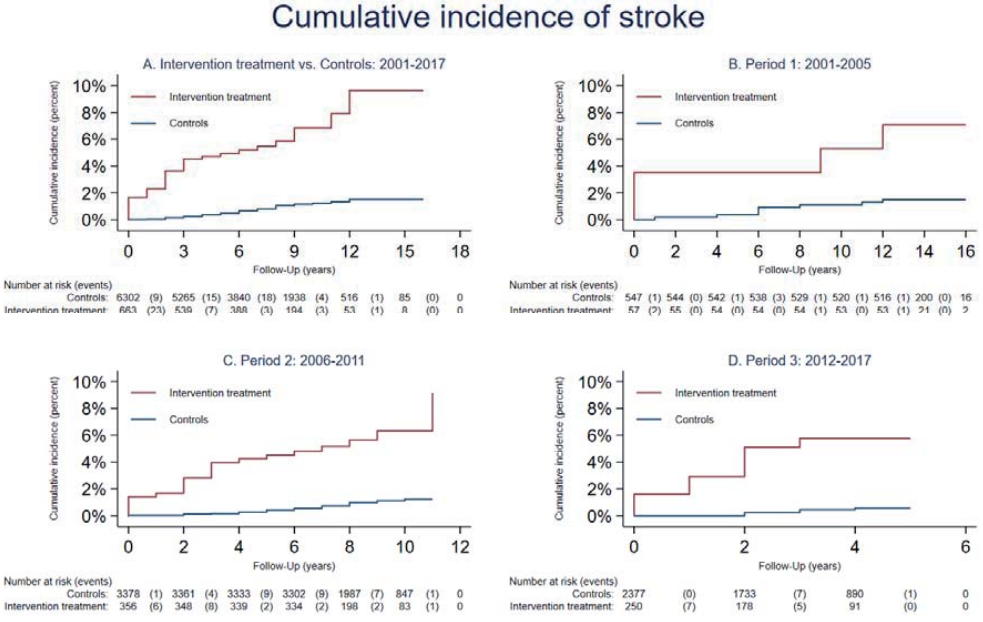

Figure 11. Cumulative incidence of stroke, Paper III. A. Cumulative incidence of stroke on follow-up during the total period (2001–2017). B. Period 1: 2001–2005. C. Period 2: 2006–2011. D. Period 3: 2012–2017.

The incidence of newly diagnosed atrial fibrillation was at the same level in the intervention and medically treated groups, and higher in the intervention group than in the population control group. Major bleeding occurred at a lower level in the intervention group than in the medically treated group. In the intervention group, more patients were on antiplatelet agents compared to the medically treated group. The incidence of comorbidities during the follow-up was similar in the treatment groups. The odds ratios and CIs during the follow-up are presented in Table 2 of Paper III.

Long-term outcome after closure of an atrial shunt in patients aged 60 years or older with ischemic stroke: A nationwide, registry-based, case-control study (Paper IV)

The NPR was searched and 809 patients aged 60 years or older with a diagnosis of atrial shunt and a prior ischemic CVE were identified. Of those, 112 patients underwent closure of the atrial shunt and 697 were given medical treatment only. The 112 patients in the intervention group were matched by propensity score with 112 medically treated patients and with 112 control patients with similar cardiovascular comorbidities but without an ischemic CVE or atrial shunt. Patients and controls included in the study were aged 60–78 years old.

We followed up patients and controls through registries for an average of seven years and identified the incidence of recurrent stroke, atrial fibrillation, comorbidities, and major bleeding (Table 2 of Paper IV).

The incidence of recurrent ischemic stroke was similar in the intervention and medically treated groups and lower in the control group compared to the intervention group (Figure 2, Paper IV). The hazard ratios of recurrent ischemic stroke in the intervention group, the propensity-score-matched medically treated group and the propensity-score-matched control group are shown in Paper IV. More than 20% of patients who experienced recurrent ischemic stroke in both the intervention and the medically treated group died during follow-up.

The rate of atrial fibrillation was similar in the intervention and medically treated groups and lower in the control group compared to the intervention group. Nonetheless, fewer patients in the intervention group developed vascular disease compared to the medically treated group. Moreover, less major bleeding occurred in the intervention group than in the medically treated group (manuscript Paper IV).

Recurrent stroke after closure of an atrial shunt in patients with a prior CVE

The experience of the ACHD center in Gothenburg

Studies have shown that PFO closure in patients with a prior cryptogenic CVE is effective in reducing the risk of a recurrent CVE [90-92, 94]. However, PFO closure does not remove this risk entirely, although the absolute risk is low. The recurrent CVE may be due to inaccurate patient selection for the treatment, the procedure, the device, or incomplete closure following the implantation. In the recent randomized studies, the inclusion criteria were stricter compared to the previous studies [86-88]. However, only patients in the DEFENCE and CLOSE studies underwent Holter ECG to exclude prior occult atrial fibrillation [91, 92].

Because of limited knowledge in this area, and with the advantage of complete follow-up at the ACHD center, we tried to investigate the incidence and the cause of the recurrent CVE in patients after PFO closure in everyday clinical practice. We were aware that during the period of our research, there was no international or national consensus for selecting patients for PFO closure caused by a cryptogenic CVE. Nevertheless, the patients selected for PFO closure at the ACHD center had been thoroughly discussed at a multidisciplinary conference, mitigating the risk of selecting ineligible patients [144].

In order to investigate the selection of patients for PFO closure at the ACHD center, the RoPE score was calculated retrospectively in Paper II. In previous studies, a RoPE score of 7 or above has been established as a cutoff point for a cryptogenic CVE likely caused by a PFO [91, 151]. In our study, the median RoPE score was 7.

The PASCAL score introduced recently has been reported to reflect the heterogeneity of the patients who undergo transcatheter PFO closure after a cryptogenic CVE, as it includes both the RoPE score and the anatomical features of the PFO [99]. However, in our study we did not use the PASCAL score, and as yet, there are no studies that indicate that it improves patient selection for transcatheter closure of a PFO after a cryptogenic CVE compared to the RoPE score alone.

Our investigation showed that, among our patients, the main reason for a recurrent CVE after PFO closure was residual shunting (and, during a specific period, use of the BioSTAR device), rather than patient selection or occult atrial fibrillation.

Nonetheless, in Paper I, the BioSTAR device was shown to be feasible and suitable for small defects (≤8 mm), but the incidence of recurrent CVEs was higher than in the comparison group. This finding was verified in Paper II, where 16% of BioSTAR carriers experienced a recurrent CVE, without any other obvious cause for the ischemic CVE. One previous study has reported re-opening of the PFO and recurrence of the shunting after two years from the implantation of a BioSTAR device [137]. In Paper I, BioSTAR patients did not undergo control echocardiography in the research lab. However, in Paper II, none of the BioSTAR carriers who experienced a recurrent CVE had a residual shunting on contrast TTE in the research lab, meaning that no obvious factor (residual shunting or comorbidities) could explain the high incidence of recurrent CVEs in BioSTAR carriers at the ACHD center. Therefore, BioSTAR carriers may have a higher risk of a recurrent CVE compared to carriers of other devices. A potential explanation for the high incidence of recurrent CVEs in BioSTAR carriers could be that inflammation or thrombogenesis is triggered by remnants of the device. A single-center study showed that although a biodegradable device is theoretically more favorable than a device made of nickel, there could be immunological reactions to the biodegradable parts of the BioSTAR device that may cause severe clinical problems [124].

Moreover, studies have shown that a large PFO is more likely to cause a cryptogenic CVE than a small PFO [90, 92]. However, the BioSTAR device was used only for small defects, and the BioSTAR carriers in Papers I and II may therefore be more likely to have had an incidental PFO rather than a pathogenetic PFO.

In Paper II, contrast TTE was used as the diagnostic tool for residual shunting at late follow-up in connection with a clinical visit. We observed no new residual shunting during the long-term follow-up.

The presence of residual shunting was 17.3% in this study, which is comparable to the results of the REDUCE (24.4%) and CLOSE (11.4%) studies [90, 91]. Multiple fenestrations of the atrial septum and the design of the devices are the main causes of residual shunting after PFO closure. In Paper II, 3.2 patients with residual shunting

per 100 patient-years, compared with 0.8 patients without residual shunting per 100 patient-years, experienced a recurrent CVE. A recently published study by Deng et al. has shown similar results, with increased incidence of recurrent stroke in patients with residual shunting, mainly with a moderate or large shunt, after PFO closure (2.32 per 100 patient-years, compared to 0.75 per 100 patient-years in patients without residual shunting) [139].

Our findings imply that the possible mechanism for a recurrent CVE after PFO closure may be triggered by the same path as the prior cryptogenic CVE. In other words, a venous clot that moves from right to left through the residual shunting may cause the recurrent CVE, or a hypercoagulable state may be propagated by the residual shunting [62]. Furthermore, in our study, patients with residual shunting who experienced a recurrent CVE were either on antiplatelet drugs, inadequate anticoagulant treatment or on no medications. This indicates that more intensive antithrombotic treatment should be initiated in patients with residual shunting after PFO closure. Moreover, cases of large residual shunting can be managed by implanting a second device, according to other studies [152, 153], or by surgical intervention, but our experience of such procedures at the ACHD center is limited.

Multicenter experience through national registries

In Papers III and IV, we investigated the risk of recurrent stroke after closure of an atrial shunt in patients with a prior CVE, comparing them with patients with the same background who received medical treatment instead and separately with general population controls, using national registries.

In Paper III, all patients from 1997 to 2016 with an atrial shunt and a prior CVE were included. The risk of recurrent stroke was similar in the intervention and medical treatment groups and over nine times as high as in the population control group. Based on the results in Paper III but also in Paper IV, a prior ischemic CVE seems to be an independent risk factor for recurrent stroke.

In Paper IV, only patients aged 60 years and above with an atrial shunt and a prior CVE between 1997 and 2016 were included. The risk of recurrent stroke was again similar in the intervention and medical treatment groups. However, the risk of recurrent stroke in the intervention group tended to be higher than in the matched population control group.

In Paper III, the study period was divided into three time spans due to the different criteria for PFO closure during these periods; nonetheless, no difference in the risk of recurrent stroke was found among the three periods. Moreover, the incidence of recurrent stroke was higher in the first year after the intervention.

The comorbidity rates in Paper III were similar in the intervention group, medical treatment group, and control group. In Paper IV, vascular comorbidities occurred at a lower rate in the intervention group compared to the medical treatment group and were comparable to the control group.

Overall, in Papers III and IV, the risk of recurrent stroke in patients with an atrial shunt and a prior CVE was similar, regardless of whether they received closure of the atrial shunt or medical treatment. This finding stands in contrast to what randomized studies and their meta-analyses have shown [90-92, 94, 95, 97]. In Paper III, all patients with an atrial shunt and a prior ischemic CVE were included, without any further selection. The anatomical features of the atrial shunt might be more complicated than in randomized studies where patients were carefully selected. Another explanation could be the inclusion of all ischemic CVEs without selection of cryptogenic ones. Moreover, even small ASDs were included in Paper III, indicating the possibility of co-existence of occult atrial fibrillation.

In Paper IV, we selected patients aged 60 years or older, an age group that has not been studied previously in randomized studies. Studies indicate that the likelihood of a PFO causing a cryptogenic CVE may mitigate with age. However, Mazzucco et al. observed a higher prevalence of right-to-left shunt in patients aged 60 years or older with cryptogenic stroke compared to patients who had a stroke of other causes without a PFO [80].

Comparing Papers III and IV, the relative risk of a recurrent stroke in the intervention group compared to index stroke in matched population controls was higher in Paper III compared to the same risk in Paper IV. It could be that the study reported in Paper IV was underpowered, because of the small number of enrollees. However, some conclusions can be drawn. In particular, it can be presumed that, as patients get older during a follow-up period of up to 20 years, they develop more risk factors for an ischemic stroke of other causes. Studies recommend the intervention in patients up to 60 years old; however, the outcomes for these patients when they become older is not yet well investigated. To date, while the selection of patients for the intervention has been established and guidelines are definitive, little is known about the long-term outcome of this treatment and the duration of antithrombotic treatment.

Furthermore, in Paper IV, patients aged 60 years or older in the intervention group were probably eligible to undergo closure of the atrial shunt, considering their age and the increased risk of stroke from other causes. It can therefore be assumed that these patients were well investigated, and that other causes of stroke were excluded prior to the procedure, which was not the case for the younger patients in Paper III.

In Paper IV, patients aged 60 years or older who underwent closure of the atrial shunt after an ischemic CVE may have had an anatomically simple atrial shunt. Thus, a larger right-to-left shunt with multiple fenestrations and complex anatomy could possibly cause an ischemic CVE earlier in life. It has been stated that, in older patients, a shunt can become larger mostly because the volume of the right atria increases with age. Moreover, a hypercoagulable state in older patients can cause an ischemic CVE through an atrial shunt [79]. Thus, patients with a smaller uncomplicated shunt, with less risk of residual shunting after the intervention procedure, were probably included in the intervention group in Paper IV rather than patients with a more complicated anatomical shunt. In contrast, in Paper III, some patients in the intervention group

probably had a shunt with more complicated anatomical features, making it more difficult to avoid residual shunting, which is a major cause of recurrent CVEs. However, this cannot be proved because residual shunting could not be identified through registries.

New-onset atrial fibrillation after closure of an atrial shunt

The experience of the ACHD center in Gothenburg

Studies have shown a high incidence of mainly transient atrial fibrillation in patients after PFO closure, often occurring during the first months after implantation [128, 129, 154]. At the ACHD center, the rate of new-onset atrial fibrillation was higher during the first six months after the implantation of the device, which is in line with other reports [90, 91]. Of note, only 2.5% of all patients who underwent PFO closure between 2006 and 2014 reported at least one confirmed atrial fibrillation episode at long-term follow-up. Moreover, the rate of persistent atrial fibrillation at long-term follow-up was low. However, it should be borne in mind that prolonged ECG was not included in the routine follow-up after PFO closure and therefore we may have missed cases of transient atrial fibrillation. Previous studies have shown that occult atrial fibrillation can be the cause of 12.4% to 14% of cryptogenic CVEs and that age over 60 years and prior cortical or cerebellar infarction are independent predictors for an ischemic CVE [155, 156].

In Papers I and II, the prevalence of atrial fibrillation after implantation of the BioSTAR device, especially during the first months, was almost twice as high compared to the group implanted with other devices. Notably though, BioSTAR patients with new-onset atrial fibrillation did not experience a recurrent CVE.

Although more cases of new-onset atrial fibrillation were observed in patients with recurrent CVE, the rate was not significantly higher compared to patients without a recurrent CVE in Paper II. Furthermore, Holter ECG during the clinical visit in Paper II did not identify significantly more cases of occult atrial fibrillation.

Overall, our findings imply that the BioSTAR device was responsible for more new-onset atrial fibrillation, and that new-onset atrial fibrillation was not the main reason for recurrent CVEs after PFO closure.

Multicenter experience through national registries

The rate of new-onset atrial fibrillation was high in the intervention group compared to general population controls (Paper III), even in the subgroup of patients aged 60 years or older (Paper IV), which is in line with previous reports regarding intervention [90, 129, 157]. However, this rate was similar in both studies between the intervention group and the medically treated group. In Papers III and IV, even non-hemodynamical ASDs were included, and remodeling of atria may have occurred, especially in the medically treated group. This could explain partially the similar rate of new-onset atrial fibrillation in the two treated groups. Furthermore, occult atrial fibrillation not diagnosed before the intervention treatment could result in new diagnosed atrial fibril-

lation. Though, the last decade the diagnosis of occult atrial fibrillation has nationally improved by the establishment of Holter ECG in all patients with an ischemic CVE without any other obvious reason.

In patients aged 60 years or older (Paper IV), the risk of new-onset atrial fibrillation was almost double in both treated groups compared to the total population study (Paper III). This finding was expected, as the prevalence of atrial fibrillation increases with age [158]. Nonetheless, the relative risk of new-onset atrial fibrillation of the total intervention group versus matched population controls (Paper III) is higher compared to the older subgroup receiving the intervention versus matched controls (Paper IV). This implies that more new-onset atrial fibrillation occurs after implantation in younger patients. A potential explanation could be that younger patients' atria are not remodeled or fibrotic prior to the procedure, whereas older patients may have fibrotic or remodeled atria. Therefore, in younger patients, the implantation of a device may trigger fibrotic mechanisms which can cause an atrial fibrillation, a reaction that may not occur in older patients. This could also explain the finding in our studies that most of the new-onset atrial fibrillation in older patients occurred later on during the follow-up, in contrast to what prior studies have shown [128]. We can conclude that implantation of a device in patients aged 60 years or older does not seem to cause increased new-onset atrial fibrillation as it does in younger patients. The STROKE-STOP study showed that more than 20% of randomly selected adults aged 75 and 76 years developed atrial fibrillation during seven years of follow-up [159]. Therefore, we presume that occult atrial fibrillation rather than new-onset atrial fibrillation caused by the intervention, is probably more prevalent in this older age group.

Vascular disease during follow-up

The development of comorbidities during the follow-up in Paper II did not differ significantly among patients with a recurrent CVE and those without a recurrent CVE. However, it should be noted that the number of patients included in the clinical study of Paper II was low.

The incidence of vascular disease as a post-hoc tertiary endpoint, including hypertension, myocardial infarction, coronary artery disease, heart failure, and cerebrovascular disease (ischemic stroke and cerebral hemorrhage) was lower in the intervention group than the medically treated group during the follow-up in Papers III and IV. This incidence was comparable to the general population. The medically treated group had more comorbidities at baseline in both Papers III and IV, but after propensity-score matching with the intervention group and adjusting for age, sex, and comorbidities, patients in the two groups were similar at baseline. Less intensive medical treatment could be one reason for the observed lower incidence of vascular disease in the intervention group compared to the medically treated group. Still, it can be hypothesized that the intervention prevents the development of vascular disease in some way.

Investigators have tried to map the metabolomic profile of other mediators after PFO closure; they found that homocysteine and cholesterol levels may be affected after PFO closure [65, 66]. These and other mediators are affected after PFO closure and

therefore PFO closure could be related to a lower rate of development of vascular disease compared to medical treatment. However, this assumption is speculative and not yet well studied.

Antithrombotic treatment and major bleeding

The antithrombotic treatment was variable among patients who underwent transcatheter closure of the PFO at the ACHD center. It depended mostly on the manufacturer of the device used for implantation and the decision of the interventionist the first six months post-operatively. Thereafter, the neurologist or general practitioner decided whether and when to discontinue or change the antithrombotic medicines.

Until recently, there was no consensus regarding which antithrombotic medications should be chosen at long-term follow-up after implantation of the device, nor the optimal duration of the medical treatment. Therefore, this was at the discretion of the physician. Following the recent randomized studies, the current guidelines recommend double antiplatelet therapy for the first three to six months and thereafter by single antiplatelet therapy at long-term follow-up for two to five years post-operatively [71].

Among our patients in Paper II, around 70% were under antithrombotic treatment during a mean follow-up period of 8.4 years, with the majority being under single antiplatelet therapy, and no increase in the rate of intracranial bleeding or other major bleeding was reported during the follow-up.

In Papers III and IV, more patients in the intervention group were under antiplatelet therapy compared to the medically treated group during the follow-up. This is in line with previous reports and current guidelines. A lower rate of major bleeding, including gastrointestinal bleeding and cerebral hemorrhage, occurred in the intervention group compared to the medically treated group in both Papers. Our findings imply that major bleeding in the intervention group was avoided by less intensive single antiplatelet therapy compared to more intensive treatment in the medically treated group.

Strengths and limitations

Paper I

The strengths of this study were the complete follow-up of the patients included in the study, as well as the inclusion of a similar number of enrollees in the two device groups during the same period. However, the study was small, non-randomized, and with a limited follow-up period. Moreover, the comparison group included more than one device.

Paper II

This is a well-designed cross-sectional study with complete follow-up. Another strength of the study was the use of RoPE scores to evaluate, if retrospectively, the selection of patients for intervention. Moreover, to validate the follow-up contrast TEE and to identify current complications, we performed a contrast TTE. Lastly, the

patients with a recurrent CVE were matched with a comparison group of patients with similar baseline characteristics but no recurrent CVE, who had their PFO closed in the same period as the patients with a recurrent CVE.

Nevertheless, this was a single-center and non-randomized study with a limited number of patients. Furthermore, the diagnosis of recurrent CVE was driven by clinical manifestation, and therefore several silent CVEs may have missed, as the REDUCE study has shown [90]. Moreover, the selection of antithrombotic drug was at the discretion of individual physicians. Finally, devices no longer used in clinical praxis were included in the study, because there are past recipients of these devices who may be at risk of a recurrent CVE.

Papers III and IV

Both studies are national and multicenter. In Paper III, we included all patients with atrial shunt and a prior CVE over the 20 years that the intervention treatment has been performed nationally. Likewise, in Paper IV, all patients aged 60 years or older with atrial shunt and a prior CVE were included. Moreover, the follow-up time was longer than most of the studies to date. The data included are unique and complete.

However, both Papers III and IV have their limitations. First, they are cohort studies using registries, and there is a risk of misclassification of the diagnosis of both stroke and atrial shunt. Nevertheless, there are studies that have validated the NPR and SPDR, and they have shown high validity of the diagnoses used in these studies and the medicines purchased by the Swedish pharmacies [148, 150]. The SPDR was introduced in 2005, and medications purchased before this time are not included.

Second, we were aware that including TIA patients with an atrial shunt would increase the chance of misclassification. TIA is a subjective diagnosis and has a reported low validity; therefore, we chose not to include it as an endpoint in either of the two studies.

A third limitation is that the diagnosis of a PFO has the same ICD code as an ASD, and we were aware that even ASDs were included in the studies. However, by including only patients with an ischemic CVE prior to the diagnosis of the atrial shunt, patients with large hemodynamical ASDs were most likely excluded. Similarly, there is not a unique ICD code for cryptogenic ischemic stroke, but by including only patients with an atrial shunt diagnosis after an ischemic CVE, we tried to mitigate the inclusion of other causes of ischemic stroke.

An additional limitation in Paper IV is the small number of enrollees. However, patients aged 60 years or older had been excluded from all randomized studies, and this was the first study to focus on this age group to assess long-term outcomes of closure of an atrial shunt.

CONCLUSIONS

PFO closure in patients with a cryptogenic CVE is not a panacea, as the absolute risk of a recurrent CVE, although low, remains after the intervention. This risk is higher than for general population controls without a prior CVE or known PFO, and it seems to be greater in younger patients compared to older patients.

The main cause of a recurrent CVE, at least in our patient groups, is residual shunting rather than incorrect patient selection for intervention, or other factors such as undiagnosed occult atrial fibrillation.

BioSTAR recipients seem to be at greater risk of a recurrent CVE compared to recipients of other devices. This risk is independent of the presence of other risk factors, such as cardiovascular comorbidities, occult atrial fibrillation, or residual shunting.

Patients aged 60 years or older may undergo PFO closure after thorough screening of other potential causes of their ischemic CVE, especially occult atrial fibrillation. Even for this age group, intervention seems to mitigate the development of vascular disease compared to conventional medical treatment.

Atrial fibrillation is more prevalent during the first months after PFO closure for young and middle-aged patients, in line with other studies.

Major bleeding may depend on the intensity of the antithrombotic treatment.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

This thesis has several clinical implications. First, our findings imply that BioSTAR carriers should continue to receive clinical follow-up with contrast TTE, to identify potential new-onset residual shunting or other late complications. Moreover, lifelong antithrombotic treatment in BioSTAR recipients needs to be evaluated.

The selection of patients for PFO closure after a cryptogenic CVE is important, and RoPE and PASCAL scores should be further studied and validated against each other. Considering that residual shunting is a major cause of recurrent stroke, patients with residual shunting after PFO closure may need clinical follow-up with contrast TTE for several years post-operatively, re-evaluation of their antithrombotic treatment, and evaluation of whether implanting a new device could be appropriate. Regarding antithrombotic treatment, Vitamin K antagonists are probably indicated until new studies establish specific recommendations. These patients may need a multidisciplinary assessment by neurologists, cardiologists, vascular specialists, and primary care clinicians to determine the optimal management plan, as Deng et al. have proposed [139]. Future studies should establish which patients with residual shunting are eligible for re-intervention and implantation of a new device.

Furthermore, the findings of this thesis imply that the patients who underwent closure of an atrial shunt after a cryptogenic CVE are not cured. Therefore, the clinical follow-up of those patients should be considered at least for the first year, if not several years, following the intervention. Moreover, the choice of antithrombotic treatment and the optimal duration is still unclear, and this should be further investigated in future studies, to underpin more definitive future guidelines.

Finally, patients aged 60 years or older should be considered eligible for closure of an atrial shunt after an ischemic CVE, if all other causes of stroke are excluded in a thorough screening. Further studies should investigate the low incidence of vascular disease in this age group.

ACKNOWLEDGEMENTS

This is an important chapter of the thesis because it is difficult to express with words your gratefulness to your mentors, colleagues, friends, and family.
I would like to thank the following people:

My main supervisor, *Peter Eriksson*, not only for your support and encouragement to complete this thesis, but because you have been beside me during my whole journey as a clinician and as a PhD student. Thank you, Peter, for all our discussions, for helping me get over my problems in science and my self-doubts, for making me believe in myself, but also for helping me to understand the loss of my father. You are my role model as a doctor and as a human being.

Mikael Dellborg, my co-supervisor, for the constructive criticism of my thesis, for building bridges for me and then destroying them to help me build bridges of my own, as Kazantzakis defined the "perfect teacher". Thank you for all the support in all aspects, not forgetting the practical ones.

Zacharias Mandalenakis, my co-supervisor, for supporting me when I was lost, for encouraging me, for reading the manuscripts critically and trying to improve them, even when you were very busy with all the other projects.

I would not have come this far without the three of you. You are each the perfect mentor for a PhD student, very different but so perfectly combined.

The research coordinators *Helena Dellborg* and *Görel Hultsberg-Olsson* for your dedicated work on Papers I and II. Without your experience the data would not be complete. Thank you for your valuable help and input, and for sharing your experience. Thank you for your support in this research and in everyday life.

The research team, especially *Eva Furenäs*, my co-author on Paper I, for your great input, for sharing your clinical experience, and for your constructive criticism, *Kristofer Skoglund* for our discussions and your tips about how to organize my research time, *Anders Arnefeldt* for your clinical input, and the ACHD center staff for helping me to orient myself in the unit.

Naqibullah Mirzada, my colleague and co-author on Paper II. Thank you for sharing your experience and your data, and for giving me some good advice.

Magnus Carl Johansson, clinical physiologist and co-author on Paper II, for your help in understanding the contrast echocardiography and for sharing your experience in this field.

Nazir Sultani, a colleague who contacted all the patients by telephone during the first part of the Paper II study.

Evangelos Fragkiskos, a friend and a radiologist colleague who helped me understanding the brain imaging. Thank you for taking time to explain the basics of brain imaging to an amateur! Thank you for your support to my family during the time I wrote this thesis.

Ulrica Forslund-Grenheden and *Eva Thydén*, for your excellent administrative help. Thank you for keeping me updated about deadlines, other formalities, and regulations, and for helping me with formatting documents. Your help is more than valuable and your encouragement so precious!

Kaj Stenlöf and *Anna Newmark*, the heads of Carlanderska Medical Clinic, for giving me the time I needed to complete this thesis under difficult circumstances.

Lennart Falk and *Beata Zabecka* for taking care of my patients while I was away and for your patience.

All *the staff* in *Carlanderska Medical Clinic*, for your patience while I was preparing this thesis, for allowing me time to do my research, and for the nice discussions.

Erik Thunström, colleague and current head of the *Sahlgrenska University Hospital/Östra,* Cardiology Clinic, for our discussions regarding research and all your practical help.

Thanks also to all my *colleagues* from the *Sahlgrenska University Hospital/Östra* Cardiology Clinic.

Putte Abrahamsson, my co-author on Paper I and former head of Cardiology Clinic, Sahlgrenska University Hospital/Östra, for his support when I started as a clinician.

The head of department, *Sofia Ekdahl*, and the head of the research unit, *Helen Sjöland*, for all your practical help.

Maria Fedchenko, a colleague, for all your practical tips regarding research, your companionship, and our beautiful discussions.

Georg Lapas and *Kok Wai Giang* for your consultancy in statistics.

Thorarinn Gudnasson, a colleague in Iceland, for the pathway you showed me and the help you gave me to choose to move to Sweden, to become a cardiologist and work with your former colleagues. Thank you Thorarinn for not giving me that recommendation letter I asked you for and instead finding me a position at the SU/Ö cardiology clinic.

My friend *Christina* for being at my side the last 20 years.

All my dear friends, especially *Katerina* for your support and love and *Athina*.

My brother-in-law *Dimitrios* as well as *Georgios* and *Elpida* for our discussions and your support.

My "big Greek family", my sister, *Anna* and her family, my parents in law, my uncles and aunts in Greece, for your support all these years and for encouraging me.

My mother Katerina, for believing in me, for supporting me through all the steps of my life, and for your unconditional love. *My father Yannis*, although he will never read this, I only wish he knew how much of me is the outcome of the way he and my mother raised me, and how much I loved him.

My kids, *Zoi and Yannis*, for the meaning you give to my life. You mean everything to me! Thank you for the love you give me every day and for your support and understanding during these recent months.

And of course, my husband, and statistician for Papers III and IV, *Savvas Papadopoulos*. I am so grateful that I am sharing my life with you, for all your support in this thesis, for making me understand a small part of statistics, for our endless discussions, for your patience, for your love.

The studies in this thesis were supported by grants from the Swedish State under agreement between the Swedish goverment and county councils (Vetenskapsrådet), the ALF agreement and the Swedish Heart-Lung Foundation.

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APPENDIX

PFO Conference basis 2006

Referral date:

Personal number:

Name:

The referring hospital:

The referring doctor:

CVE

Date for actual CVE event:

Clinical status corresponding changes on the brain imaging? Yes No

Previous known CVE Yes No
- TIA
- Ischemic stroke
- Another CVE disease

Indication for PFO investigation
- Stroke/TIA
- Arterial deoxygenation
- Decompression sickness

Another embolic source Yes No
- Atrial fibrillation
- Myocardial infarction <4w
- Carotid Artery Stenosis>50%
- MR/CTangio investigate back circulation

Allergies
- No allergies
- Serious allergies against medicines
- Unknown

Vitamin K antagonist
- Treatment with Warfarin
- Another indication than PFO for Warfarin

Social, language
Need of translator, language?

Patient´s consent:
The patient is informed and interested in PFO-closure and accepts to be included in the Kvalitetsuppfölknings Register of SU/Östra in Gothenburg regarding PFO?

Yes No

Cryptogenic stroke
Does the referring doctor assess that it is a cryptogenic stroke, meaning not a stroke from other causes like large-or small-vessel disease or cardioembolic stroke of Other cause?

Yes No Unsure

Brief summary history of the actual event:

Venous or arterial thrombosis/embolic event:

- Not Known
- Previous thrombosis or embolic event

Is there any coagulation disorder Yes No Unknown

Smoking Yes No

- Active smoking
- Ex-smoker
- Never smoked

Hypertension

- Not known
- Known hypertension, medicines?

Diabetes mellitus

- Not known
- Known diabete
  - Typ I
  - Typ II
  - Complications related

Cardiovascular disease

- Not known
- Known Yes No
  - Chronic ischemic disease
  - Suspected ischemic disease
  - Heart failure
  - Hypercholesterolemia
  - Peripheral vascular disease
  - Kidney failure

Other diseases

- No other diseases
- Other diseases: Yes No
  - Lung disease, under treatment
  - Psychological disease, under treatment
  - Endocrinological disease
  - Hematological disease
  - IBD
  - Lever disease
  - Cancer
  - Rheumatological disease
  - Another disease

Increased bleeding tendency

Not known Known, details

Length:
Weight:
Blood pressure:
Hb: Kreatinin:
Kolesterol:

Medicines:

During the conference:

TEE date:

- Contrast through PFO? Yes No
- Atrial septal aneurysm?
- Aorta plaque?
- Hypertrophy of left ventricle?
- Known Valve disease?

EF

The interventionist:

The neurologist:

The internal medicine doctor:

The cardiologist:

Decision:

- Accepted
- Not accepted
- Incomplete investigation

Date of the decision: