International Journal of Stroke
International Journal of Stroke
1–11

Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/17474930241298778
journals.sagepub.com/home/wso
Sage

Stroke recurrence after transcatheter PFO closure in patients with cryptogenic stroke

Bea Goessinger[1], Stefan Greisenegger[2], Stefan Kastl[1], Raphael Rosenhek[1], Wolfgang Serles[2], Christian Hengstenberg[1], Harald Gabriel[1] and Lore Schrutka[1]

Abstract

Background: Patent foramen ovale (PFO) closure is recommended for secondary prevention of cryptogenic stroke. However, data on long-term results are limited. We aimed to evaluate safety and efficacy of transcatheter PFO closure and predict neurologic recurrence.

Methods: Data from patients undergoing PFO closure between 2010 and 2015 were collected to assess the combined endpoint of transient ischemic attack (TIA), stroke, or death from stroke at short- and long-term follow-up.

Results: 330 patients were included, mean age was 49 ($\pm$12) years, and 55.5% were male. Before PFO closure, 86% experienced a stroke and 19% multiple neurological events. Procedure-related complications occurred in 2.4% of patients. Over a median follow-up of 10 years, the combined endpoint occurred in 3.6%, with a recurrence rate of 0.38 per 100 patient-years. Freedom from the combined endpoint at 5 and 10 years was 97.5% and 96.2%, respectively. New-onset atrial fibrillation was detected in 3%. The Risk of Paradoxical Embolism (RoPE) score (adjHR: 0.68; $p = 0.032$), the PFO-Associated Stroke Causal Likelihood (PASCAL) classification system (adjHR: 0.37; $p = 0.042$), and a history of prior neurological events (adjHR: 9.94; $p < 0.001$) were independent predictors of future recurrent neurologic events. Age, sex, and cardiovascular risk factors did not influence outcomes.

Conclusion: In this real-world cohort, transcatheter PFO closure was associated with low long-term recurrence of neurologic events, especially cryptogenic strokes. The RoPE score, the PASCAL score, and history of previous neurological events were predictive of recurrent events. This study supports the safety and efficacy of PFO closure for secondary prevention of cryptogenic strokes, and underscores the importance of patient selection.

Keywords

PFO closure, cryptogenic stroke, outcome, predictors

Received: 19 July 2024; accepted: 14 October 2024

Introduction

The foramen ovale is an interatrial connection that holds physiological significance in fetal blood circulation and typically closes shortly after birth.[1] In about one-third of the population, the opening does not close completely, resulting in a patent foramen ovale (PFO) persisting into adulthood.[2] Usually, the presence of a PFO goes unnoticed. However, patients with cryptogenic strokes have been shown to have a threefold higher prevalence of PFO than the general population, suggesting a causal

[1]Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria
[2]Department of Neurology, Medical University of Vienna, Vienna, Austria

Corresponding author:
Lore Schrutka, Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.
Email: lore.schrutka@meduniwien.ac.at

relationship.[3] The dominant mechanism involves venous thrombi passing through the PFO (right-to-left shunt), resulting in paradoxical emboli.[4] For secondary prevention of PFO-associated strokes, device closure was found to be superior to medical therapy alone.[5–8] Therefore, current guidelines recommend PFO device closure additional to long-term antiplatelet therapy alone in patients with cryptogenic stroke aged 18–65 years.[9,10] However, absolute risks of stroke recurrence remain very low for some patients with medical therapy, and device closure has associated risks and adverse effects.[11] Risk reduction for recurrent stroke with device closure varies across groups classified by their probabilities that the stroke was causally related to the PFO. Application of classification systems has therefore been introduced to guide individualized decision-making.[12–14] Nevertheless, long-term outcome after PFO closure aside from randomized controlled trials (RCTs) has yet only been documented a few times.[15–18] The aim of this study was to assess real-world short- and long-term outcomes and to identify predictors of recurrent neurologic events in patients undergoing transcatheter PFO closure.

Method

Study design

In this retrospective single-center cohort study, we reviewed patient data from all public hospitals in Vienna to obtain short- and long-term outcomes after transcatheter PFO closure. The initial data compilation and recruitment of patients were centered around records from the Cardiology Department at the University Hospital Vienna. This led to the establishment of a clinical registry of patients who had undergone transcatheter PFO closure between 2010 and 2015.

Patient selection

Inclusion criteria for this study mandated that patients underwent successful PFO closure as a secondary prevention to a neurological event, such as transient ischemic attack (TIA), ischemic stroke, or cryptogenic stroke/embolic stroke of undetermined source (ESUS). Exclusion from the study involved all patients with PFO closure for non-neurological reasons (peripheral thromboembolism or decompression sickness), and patients with unsuccessful PFO closure. Patients were referred by neurologists, after other causes of stroke had been fully investigated. Diagnostic tests to determine the causative mechanism of stroke included brain imaging, thrombophilia screening, and Holter monitoring. The presence of a PFO was confirmed by transesophageal echocardiogram (TEE) with bubble test including Valsalva maneuver.

Data sources

After obtaining approval from the local ethics committee (Ethics Committee of the Medical University of Vienna, EK# 1108/2022), a systematic approach was employed for gathering the data. The patient records from the University Hospital Vienna were accessed through the hospital database. In addition, an analysis of data from all hospitals in Vienna was conducted and the Austrian death registry was utilized to identify all patients who had passed away since the procedure. The data collection included a step for anonymization, thereby minimizing the risk of patient data disclosure. Patient consent was not required.

Clinical definitions

Clinical definitions included that a PFO had to be confirmed with a clear sighting of contrast agent in the left atrium using TEE.[19] PFO shunt was classified as large if more than 20 bubbles were visible or if a left-to-right shunt was clearly identifiable without the need for a Valsalva maneuver.[14] Septum abnormalities were reported, and atrial septal aneurysm (ASA) was defined as 10 mm of excursion from midline.[14] A TIA was defined as a short episode of neurological dysfunction without the presence of acute infarction on neurological imaging.[20] Stroke was described as the death of cells of the brain, or retinal cells due to ischemia, as confirmed by neuropathological, neuroimaging, or clinical evidence of permanent damage.[21] Stroke was then subcategorized according to the TOAST classification,[22] and definitions of cryptogenic stroke were adapted to the concept of ESUS.[23]

Procedural description

Transcatheter closure procedures were conducted from 2010 to 2015 with the use of either the 25 mm Amplatzer PFO Occluder (Abbott, Chicago, IL, USA), the 25 mm Gore Helex Occluder (W. L. Gore & Associates, Inc., Newark, DE, USA), the Premere PFO occluder (St Jude Medical), the Solysafe septal occluder (Swissimplant AG, Solothurn, Switzerland), or the Nit-Occlud PFO (PFM medical, Cologne, Germany). All transcatheter occlusions were performed under analgesia with fluoroscopy; TEE was used adjunctively in selected cases. The correct vascular sheath size and its corresponding delivery system were selected based on the specific device used. The septum was crossed with a 5.2-French Multipurpose A (Cordis, Miami Lakes, FL, USA) and a normal J-wire. If the operator failed to cross the PFO, the septum was imaged with angiography in biplane anterior posterior and left anterior oblique projection. The device was inserted again in biplane projections, and transthoracic echocardiogram (TTE) was used to ensure a stable position before releasing the device. Finally, right atrial angiogram was performed after releasing the device to assess for leaks and to ensure a stable position. After device implantation, patients received antithrombotic therapy with Aspirin for six months, with further prescription upon subsequent neurological assessment if deemed necessary.

Outcome measures and follow-up

Using the hospital database, we collected patients' baseline information and data on PFO morphology. We obtained information about the frequency of neurological events leading to the PFO closure and prespecified data about known comorbidities, including hypertension and diabetes to calculate the Risk of Paradoxical Embolism (RoPE) score in all patients.[12] The PFO morphology and absence or presence of ASA were combined with the value of the RoPE score to define probability of PFO-Associated Stroke Causal Likelihood (PASCAL) classification system.[14] After PFO closure the follow-up consisted of a short-term follow-up, with information from the patients' visit at the outpatient clinic 1, 3, and 12 months after the procedure. Long-term follow-up included data from all outpatient clinic visits or hospitalizations and a death registry extract from Statistics Austria up to 10 May 2023.

We collected information on procedure-related adverse events that occurred during the procedure or hospitalization, as well as adverse events reported within follow-up. Also, it was documented which patients received antithrombotic therapy beyond 1 year post-procedure. Through targeted data analysis we searched both for TIA, stroke, or death from stroke as well as the composite outcome of TIA, stroke, and death from stroke. All patients that reached the combined outcome were analyzed by a board-certified neurologist. This involved reviewing the neurological imaging findings and categorizing the events according to the TOAST classification.[22]

Statistical analysis

Characteristics were described with absolute numbers (*n*) and relative frequencies (%), mean and standard deviation (SD) were calculated for metric variables. Comparisons between groups were assessed through chi-square test or Fisher exact test for categorical variables, for continuous variables Student's *t*-test was used. Adverse events and outcomes were disclosed as counts, percentage, and rates per 100 person-years. Event-free periods derived from outcomes were analyzed using the Kaplan–Meier curves. To minimize competing risks in Kaplan–Meier estimation, deaths of other cause were censored at the time of death but recorded and shown in the results.

The study further investigated whether sex, age, known risk factors, or lower RoPE score and PASCAL classification system were associated with a higher risk of recurrent events. To estimate their impact, univariate and multivariate Cox proportional hazards models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI) and *p*-values. Adjustment for age, sex, BMI, hypertension, hyperlipidemia, diabetes, smoking, and a history of more than one neurological event before PFO closure was conducted in the Cox proportional hazards model to address potential confounding effects and evaluate independent influence of variables on hazard rates. Statistical significance was defined by *p*-values below 0.05. For statistical analysis, IBM SPSS Statistics 29 (IBM SPSS, Armonk, NY, USA) and GraphPad Prism version 10.1.1 (GraphPad Software, Boston, MA, USA) were used.

Results

A total of 355 patients underwent percutaneous PFO closure between 2010 and 2015 (Figure 1). Of these, 13 patients were excluded because PFO closure was performed for non-neurological reasons, such as decompression sickness or peripheral arterial embolism. In six patients, a PFO was no longer detectable on TEE, and one attempt to close the PFO was unsuccessful. In addition, five patients had to be excluded due to missing data. After excluding individuals who did not meet the criteria, the study comprised 330 patients who underwent successful transcatheter PFO closure and were included in long-term follow-up.

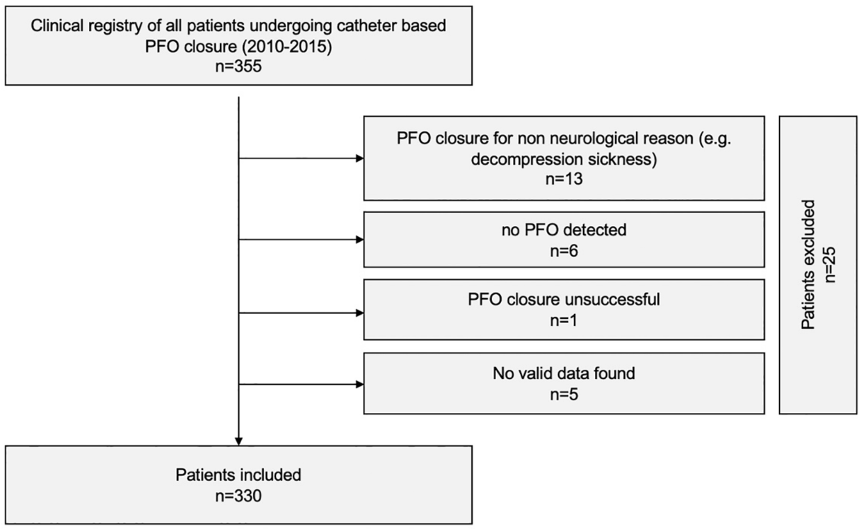
Baseline characteristics

Mean age at the time of PFO closure was 49 years (SD $\pm$ 12), with 72 patients (21.8%) being over the age of 60 years, and 183 (55.5%) being male (Table 1). The index event was a stroke in 283 patients (85.5%), and TIA was the referral diagnosis in 47 patients (14.2%). A total of 63 patients (19.1%) had more than one neurological event prior to device closure. A history of migraine was reported in 40 patients (12.1%). Cardiovascular risk factors, such as arterial hypertension was present in 117 patients (35.5%), hyperlipidemia in 132 patients (40.0%), 20 patients (6.1%) were being treated for diabetes mellitus, and 95 patients (28.8%) were current or former smokers. The mean RoPE score was calculated to be 6.5 ($\pm$1.8), with 171 patients (51.8%) having a RoPE score of 7 or higher. A total of 147 patients (44.5%) presented with large-shunt PFO before closure, and 74 patients (22.4%) with an ASA. According to the PASCAL classification system, 85 patients (25.8%) had a probable, 188 patients (57.0%) a possible, and 57 patients (17.3%) an unlikely PFO-related stroke. Most patients (77.0%) received an Amplatzer PFO Occluder, followed by 13.6% receiving a Gore Helex PFO device.

Adverse events

Adverse events that occurred during the procedure or within the follow-up are summarized in Table 2. Procedure-related

Figure 1. Patient selection. Selection of patients undergoing catheter based PFO closure between 2010 and 2015.



complications occurred in eight patients (2.4%). Of these, four (1.2%) exhibited transient arrhythmias on electrocardiogram (ECG) during device implantation. Two patients (0.6%) revealed a pericardial effusion that did not require treatment, and one patient (0.3%) underwent coronary angiography with stent implantation shortly after device implantation due to ECG abnormalities unrelated to the procedure. One patient (0.3%) presented with a pseudoaneurysm at the puncture site that needed surgical patch repair. After device implantation, 10 patients (3.0%) were found to have new-onset atrial fibrillation (AF) six patients (1.8%) with paroxysmal AF, and four patients (1.2%) presented with permanent AF, of whom two (0.6%) underwent electrical cardioversion. The mean time to new-onset of AF was 0.5 years (IQR 5.8). Numerically, there was a higher prevalence of new-onset AF with the Gore Helex device (6.7%) compared with other devices (Amplatzer 2.0%). Other adverse events reported during the follow-up included 24 patients (7.3%) experiencing palpitations and 18 patients (5.5%) reporting a mild feeling of pressure in the chest region.

Study endpoints

During a median follow-up of 10 years (SD ± 3), 12 patients (3.6%) reached the combined endpoint of TIA, stroke, or death from stroke, with a total of 15 neurological events, corresponding to 0.47 events per 100 person-years (Table 2). Two patients had more than one recurrent event, of those, one patient had two recurrences with one cryptogenic and one cardioembolic event due to AF. The other one had three recurrences with one TIA and two subsequent cryptogenic strokes. After 5 and 10 years the percentage of patients who were free of the composite outcome was 97.5% and 96.2%, respectively. The 1-year follow-up appointment was attended by 308 patients (93.3%); 22 patients (6.6%) were lost to follow-up after 6 months. Figure 2 shows the Kaplan–Meier survival analysis for the occurrence of TIA, stroke, or death from stroke. The total amount of events recorded were identified as a stroke in 12 patients (3.6%), TIA in two patients (0.6%), and one reported death from ischemic stroke (0.3%). Of the strokes, six (1.8%) were identified as cryptogenic. In the remaining patients, another source of embolism was found, such as atherosclerosis of the large arteries ($n=1$), cardioembolic due to AF ($n=1$), and small artery occlusion ($n=4$). Table 3 shows the characteristics of patients with a neurological recurrence compared with patients without a neurological event during follow-up. Patients with a recurrence had a higher proportion of multiple previous events (66.7% vs. 17.3%, $p<0.001$) and a lower mean RoPE score (5.4 vs. 6.6, $p=0.029$). There was no difference between the choice of device or medical therapy. Other neurologic events were experienced by a subgroup of four patients (1.2%) that did not meet the predefined criteria for the primary outcome. In these cases, three patients (0.9%) experienced migraine episodes, while one patient (0.3%) experienced transient unconsciousness. Finally, death from any cause was observed in 24 patients (7.3%) corresponding to 0.76 events per 100 person-years.

Predictors of outcome

Possible predictors of the composite outcome of TIA, stroke, or death from stroke were compared using a Cox proportional hazards model (Table 4). Both the RoPE score (adjHR: 0.68, 95% CI = 0.47–0.97; $p=0.032$) and the

Table 1. Baseline characteristics of registered patients undergoing PFO closure for cryptogenic stroke.

Characteristics	*n* = 330
Age at time of closure, years ± SD	49 ± 12
Male sex, *n* (%)	183 (55.5)
Patients ⩾ 60 years at time of closure, *n* (%)	72 (21.8)
Age of patients ⩾ 60 years, years ± SD	66 ± 6
Body Mass Index, mean kg/m² ± SD	26.5 (4.4)
Neurological event before closure	
TIA, *n* (%)	47 (14.2)
Stroke, *n* (%)	283 (85.8)
Comorbidities and risk factors	
Hypertension, *n* (%)	117 (35.5)
Diabetes, *n* (%)	20 (6.1)
Hyperlipidemia	132 (40.0)
Statin	151 (45.8)
History of > 1 neurological event[a], *n* (%)	63 (19.1)
Smoking, n (%)	95 (28.8)
active smoking at time of closure, *n* (%)	71 (21.5)
former smoking	24 (7.3)
History of migraine, *n* (%)	40 (12.1)
RoPE score, mean ± SD	6.5 ± 1.8
RoPE score ⩾ 7, *n* (%)	171 (51.8)
PFO morphology	
Length, mm ± SD	11 ± 4
Separation, mm ± SD	3 ± 1
Large-shunt PFO, *n* (%)	147 (44.5)
Atrial septal aneurysm, *n* (%)	74 (22.4)
Valvula eustachii, *n* (%)	5 (1.5)
Floating septum, *n* (%)	16 (4.8)
PASCAL classification system	
Probable PFO-related stroke, *n* (%)	85 (25.8)
Possible PFO-related stroke, *n* (%)	188 (57.0)
Unlikely PFO-related stroke, *n* (%)	57 (17.3)
Device	
Amplatzer, *n* (%)	254 (77.0)
Gore, *n* (%)	45 (13.6)
Premere, *n* (%)	26 (7.9)
Nit-Occlud, *n* (%)	3 (0.9)
Solysafe Septal, *n* (%)	2 (0.6)

(Continued)

Table 1. (Continued)

PASCAL: PFO-Associated Stroke Causal Likelihood; RoPE: Risk of paradoxical embolism; SD: standard deviation; TIA: transient ischemic attack.
Values are given as mean ± SD or total number (*n*) and %.
[a]Patients with more than one TIA/stroke before closure.

PASCAL classification system (adjHR 0.37, 95% CI = 0.15–0.96; $p = 0.042$) showed significant influence on the rate of recurrent events. Moreover, history of prior neurologic events revealed to be a strong independent predictor of future recurrent events (adjHR: 9.94, 95% CI = 2.83–34.91; $p < 0.001$). Kaplan–Meier survival analysis stratified by previous number of neurologic events revealed to be statistically significant with $p < 0.001$ (Figure 3). We found no significant effect of age ($p = 0.526$), sex ($p = 0.653$), arterial hypertension ($p = 0.368$), hyperlipidemia ($p = 0.741$), diabetes mellitus ($p = 0.300$), antiplatelet therapy ($p = 0.693$), and new-onset AF ($p = 0.218$) on recurrent neurological events following PFO closure. A stratification of the outcome by type of index event (stroke vs. TIA) showed no statistically significant difference ($p = 0.937$).

Discussion

In this retrospective cohort study involving 330 patients after successful percutaneous PFO closure who were followed for a median of 10 years, we observed a rate of 0.38 recurrent neurologic events per 100 person-years. The predictive ability of the RoPE score and the PASCAL classification system for estimating the risk of neurological recurrence was demonstrated in our study. In addition, the number of previous neurological events had the strongest predictive power for future neurological events. Previous described predictors such as age or comorbidities including diabetes, hyperlipidemia, or hypertension alone had no influence on the recurrence rate.

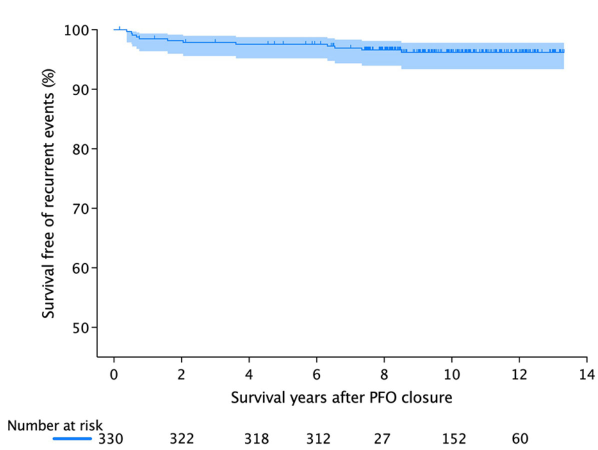
Current guidelines[9,10] are based on the results of published RCTs demonstrating the superiority of PFO closure over medical therapy alone in patients with cryptogenic stroke after a median period of up to 5 years.[5–7,24–26] To our knowledge, there only exist few publications that report

Table 2. Long-term outcome following PFO closure.

Endpoints	PFO-closure ($n = 330$)	Rates per 100 person-years
Neurologic recurrences		
TIA/stroke/death from stroke, *n* (%)	12 (3.6)	0.38
Total number of events (TIA/stroke/death from stroke)	15 (4.5)	0.47
TIA, *n* (%)	2 (0.6)	0.06
Stroke, *n* (%)	12 (3.6)	0.38
Large artery atherosclerosis, *n* (%)	1 (0.3)	0.03
Cardioembolism, *n* (%)	1 (0.3)	0.03
Small artery occlusion, *n* (%)	4 (1.2)	0.13
Stroke of undetermined cause, *n* (%)	6 (1.8)	0.19
Death from ischemic stroke, *n* (%)	1 (0.3)	0.03
Other neurological events	4 (1.2)	0.13
Migraine, *n* (%)	3 (0.9)	0.09
Transient loss of consciousness, *n* (%)	1 (0.3)	0.03
Death any cause[a], *n* (%)	24 (7.3)	0.76
Adverse event		
Procedural event, *n* (%)	8 (2.4)	0.25
Arrhythmia, *n* (%)	4 (1.2)	0.13
NSTEMI needing intervention, *n* (%)	1 (0.3)	0.03
Minor bleeding, *n* (%)	2 (0.6)	0.06
Pseudoaneurysm, *n* (%)	1 (0.3)	0.03
Within follow-up, *n* (%)	61 (18.5)	1.93
New-onset atrial fibrillation, *n* (%)	10 (3.0)	0.32
Electric cardioversion, *n* (%)	2 (0.6)	0.06
Amplatzer, *n* (% of device)[b]	5 (2.0)	0.16
Gore, *n* (% of device)[b]	3 (6.7)	0.09
Premere, *n* (% of device)[b]	2 (7.7)	0.06
Episodes of tachycardia, *n* (%)	9 (2.7)	0.28
Ventricular extrasystoles, *n* (%)	13 (3.9)	0.41
Palpitations, *n* (%)	24 (7.3)	0.76
Thoracic discomfort, *n* (%)	18 (5.5)	0.57

NSTEMI: Non-ST-elevation myocardial infarction; TIA: transient ischemic attack.
Values are given as total number (*n*) and %.
[a]Death by any cause, including stroke.
[b]Values are given as total number (*n*), and in % of the total of patients that received the referred device: Amplatzer $n = 254$, Gore $n = 45$, Premere $n = 26$.

Figure 2. Combined primary outcome of TIA, stroke, or death from stroke. Shown is the Kaplan–Meier curve presenting the years free from recurrent neurological event after transcatheter PFO closure. All patients ($n=330$) are included in the analysis. TIA: transient ischemic attack.



data from observational studies with longer follow-ups.[15–18] In this study, we present comprehensive real-world data, with a median observational time of 10 years, marking one of the longest follow-up periods published. We analyzed a representative patient group with a mean age of 49 years, falling within the range of previous studies.[5–7,15,16] Furthermore, patient baseline characteristics, including sex and comorbidities align with reported rates in other real-world cohorts.[15,16] Our findings are consistent with previous studies and thus demonstrate the safety and efficacy of PFO closure in preventing neurological recurrence. Our study adds a detailed analysis of recurrent neurological outcomes, confirms the predictability of the RoPE score and the PASCAL classification system in assessing the risk of recurrence, and suggests that the number of previous neurological events may play a greater role in patient selection.

Excellent safety of percutaneous PFO closure was demonstrated, with only eight patients (2.4%) experiencing procedure-related complications with no long-term

Table 3. Patient characteristics, stratified by occurrence of the composite outcome of TIA, stroke, and death from stroke.

Characteristics	No recurrent TIA, stroke, or death from stroke ($n=318$)	Recurrent TIA, stroke, or death from stroke ($n=12$)	p
Age at time of closure, years ± SD	49 (12)	54 (11)	0.228
Male sex, *n* (%)	177 (55.7)	6 (50.0)	0.699
Patients ⩾ 60 years at time of closure, *n* (%)	69 (21.7)	3 (25.0)	0.729
Hypertension, *n* (%)	113 (35.5)	4 (33.3)	1.000
Diabetes, *n* (%)	18 (5.7)	2 (16.7)	0.160
Hyperlipidemia	126 (39.6)	6 (50.0)	0.553
History of > 1 neurological event[a], *n* (%)	55 (17.3)	8 (66.7)	< 0.001
Smoking, *n* (%)	91 (28.6)	4 (33.3)	0.749
Active smoking at time of closure, *n* (%)	69 (21.7)	2 (16.7)	1.000
Former smoking	22 (6.9)	2 (16.7)	0.214
History of migraine, *n* (%)	38 (11.9)	2 (16.7)	0.645
RoPE score, mean ± SD	6.6 (1.8)	5.4 (2.1)	0.029
Large-shunt PFO, *n* (%)	144 (45.3)	3 (25.0)	0.238
Atrial septal aneurysm, *n* (%)	71 (22.3)	3 (25.0)	0.735
PASCAL classification system			
Probable PFO-related stroke, *n* (%)	85 (26.7)	0 (0.0)	0.041
Possible PFO-related stroke, *n* (%)	180 (56.6)	8 (66.7)	0.565
Unlikely PFO-related stroke, *n* (%)	53 (16.7)	4 (33.3)	0.239

(Continued)

Table 3. (Continued)

Characteristics	No recurrent TIA, stroke, or death from stroke ($n=318$)	Recurrent TIA, stroke, or death from stroke ($n=12$)	p
Device			
Amplatzer, n (%)	243 (76.4)	11 (91.7)	0.309
Gore, n (%)	45 (14.2)	0 (0)	0.382
Premere, n (%)	25 (7.9)	1 (8.3)	1.000
Nit-Occlud, n (%)	3 (0.9)	0 (0)	1.000
Solysafe Septal, n (%)	2 (0.6)	0 (0)	1.000
Medical therapy[b]			
Antiplatelet, n (%)	110 (34.6)	4 (33.3)	0.928
DOACs, n (%)	2 (0.6)	0 (0)	1.000
Phenprocoumon, n (%)	5 (1.6)	0 (0)	1.000

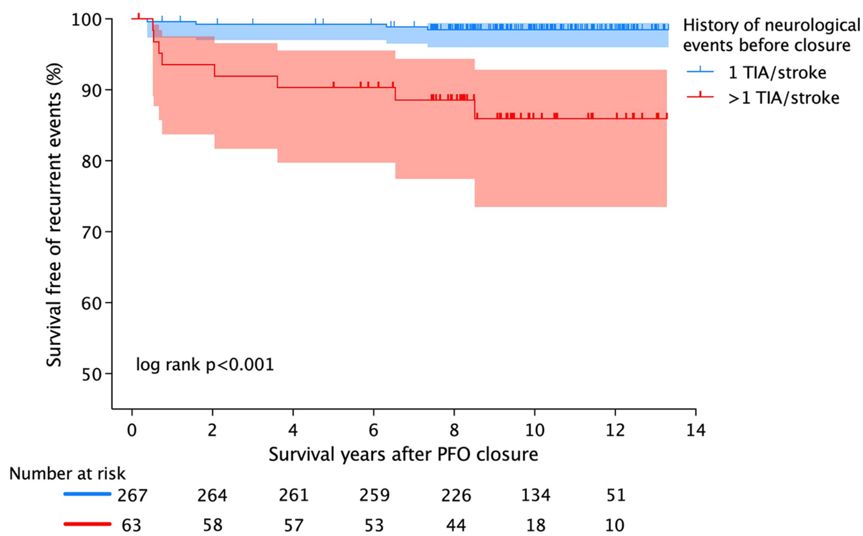
DOAC: direct oral anticoagulants; PASCAL: PFO-Associated Stroke Causal Likelihood; RoPE: Risk of paradoxical embolism; TIA: transient ischemic attack.
Values are given as total number (n) and %.
[a]Patients with more than one TIA/stroke before closure.
[b]Antithrombotic therapy beyond 1 year post-closure.

Table 4. Cox proportional hazard model of predictors for the composite outcome of TIA, stroke, and death from stroke.

Possible risk factors for recurrent events	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
Age at the time of closure	1.03 (0.98–1.08)	0.222	1.02 (0.96–1.08)	0.526
Age $\geqslant$ 60 years[a]	1.21 (0.33–4.47)	0.774	0.70 (0.15–3.21)	0.641
Female sex	1.24 (0.40–3.83)	0.714	1.30 (0.40–4.24)	0.653
Body Mass Index	0.99 (0.87–1.13)	0.926	1.01 (0.87–1.17)	0.869
Hypertension	0.91 (0.28–3.04)	0.885	0.51 (0.12–2.22)	0.368
Hyperlipidemia	1.51 (0.49–4.68)	0.476	1.26 (0.32–4.88)	0.741
Diabetes	3.28 (0.72–14.97)	0.126	2.52 (0.44–14.55)	0.300
History of > 1 neurological event[b]	9.37 (2.82–31.15)	<0.001	9.94 (2.83–34.91)	<0.001
Smoking	1.22 (0.37–4.06)	0.742	1.34 (0.38–4.78)	0.651
RoPE score	0.71 (0.52–0.97)	0.030	0.68 (0.47–0.97)	0.032
Atrial septal aneurysm	1.15 (0.31–4.25)	0.834	1.14 (0.30–4.34)	0.845
Large-shunt PFO	0.41 (0.11–1.51)	0.180	0.42 (0.11–1.58)	0.198
PASCAL classification system	0.36 (0.15–0.89)	0.027	0.37 (0.15–0.96)	0.042
New-onset atrial fibrillation	2.98 (0.39–23.09)	0.296	4.12 (0.43–39.18)	0.218
TIA as index event	1.20 (0.26–5.45)	0.818	1.07 (0.22–5.15)	0.937
Antiplatelet therapy[c]	0.81 (0.22–2.99)	0.750	0.76 (0.19–2.98)	0.693

CI: confidence interval; HR: hazard ratio; PASCAL: PFO-Associated Stroke Causal Likelihood; PFO: Patent foramen ovale; RoPE: risk of paradoxical embolism; TIA: transient ischemic attack.
[a]Age at the time of closure 60 years or older.
[b]Patients with more than one TIA/stroke before closure.
[c]Antiplatelet therapy treatment for longer than 1 year after PFO closure.

Figure 3. Kaplan–Meier curves of the combined primary outcome for TIA, stroke, and death from stroke as a function of the rate of previous neurological events. Shown are the Kaplan–Meier curves of the years free from the primary outcome (TIA, stroke, and death from stroke) stratified by the number of neurologic events before closure. Significantly higher rates of recurrent neurologic events were observed in the group with more than one event prior to closure, log-rank $p < 0{,}001$. TIA: transient ischemic attack.



sequelae. Risk of developing AF after PFO closure is often described and known to increase rapidly within the first months, followed by a slow increase in the further course.[27] We detected new-onset AF in 10 patients (3.0%) within 10 years of follow-up. Previous RCTs report rates over the entire follow-up duration of up to 5 years, leading to elevated figures (5.4% in the REDUCE study,[7] 4.2% in the CLOSE study[5]). Comparable data from real-world cohorts indicated even higher rates of new-onset AF (Kneihsl et al.[16] 5.6%, Oliva et al.[28] 6.3%, and Abrahamyan et al.[15] 7.6%). The heterogeneity in reported rates can be explained by incoherent standards of diagnosis,[29] adding to the current underreporting of asymptomatic patients.[27] Furthermore, data on exact onset and course of AF are limited, demonstrating the need for prospective studies, such as the PFO-AF study,[30] using implanted cardiac monitors to detect new-onset AF following PFO closure in a standardized manner.[30]

The overall rate of the composite endpoint of TIA, stroke, or death from stroke, which was 0.38 per 100 patient-years in our cohort, was in line with the rates observed in RCTs, reporting rates between 0.4 and 0.58.[6,7] Real-world long-term studies report slightly varying but still corresponding rates of 0.34,[18] 0.6,[16] 1.22,[15] and 1.7 events per 100 person-years. [17] In our study a more detailed evaluation of neurological recurrences according to the TOAST classification[22] was possible, which revealed that out of the 12 strokes (3.6%) after PFO closure, only 6 were of cryptogenic origin (1.8%). Given the fact that the mean RoPE score in our cohort was 6.5, the expected rate of recurrent ischemic neurologic events would have been 8% per 2 years with medical therapy alone, as estimated in the corresponding publication by Kent et al.[12] Therefore, emphasizing the efficacy of PFO closure as secondary prevention, especially for cryptogenic strokes.

The RoPE score was specifically developed to estimate the pathologic impact of the PFO on the occurrence of cryptogenic stroke.[12,31,32] Here, we were able to confirm the predictive power of the RoPE score with lower scores having a higher risk of recurrent neurologic events, which may indicate that these patients did not suffer from PFO-associated stroke prior to closure, but had a stroke from another cause. This highlights the importance of careful evaluation of the likelihood of a PFO being causative for stroke and considering all possible criteria, both clinical, as categorized by the RoPE score, and morphological, as categorized by the PASCAL classification system.[13] Moreover, it should also be noted that PFO prevalence may vary in different ethnic or racial groups, which may shift the cut-off point of the RoPE score of 7 for the etiological classification of stroke.[33] It is important to highlight that morphological PFO features, such as the presence of ASA or large-shunt PFO, did not emerge as independent predictors of recurrent events in this cohort. Consequently, the PASCAL classification system serves as an extension of the RoPE score, suggesting that it does not provide additional predictive value beyond what is already captured by the RoPE score. However, we analyzed all factors included in the RoPE score separately and noted that a history of multiple neurological events (>1 TIA or ischemic stroke before

PFO closure) was the strongest predictor of subsequent events in our cohort. A history of neurological events prior to closure accounts for only 10% of the total RoPE score, while age accounts for 50%.[12] Our results suggest that more importance could be attributed to previous neurological events and that, especially in these patients, a more thorough evaluation of the medical history prior to intervention may help to identify other sources of stroke. In addition, these patients may benefit from closer monitoring after PFO closure, potentially including the use of implantable loop recorders, to minimize the risk of recurrent events. Moreover, we found that patients with recurrent events had a lower RoPE score (mean 5.4) and were less likely to be on antiplatelet therapy (25.0%). Therefore, maintenance of antiplatelet therapy in patients with a low RoPE score or multiple events before closure, might be worth considering. With emphasis on careful patient selection, as only those with PFO-associated strokes, as represented in higher RoPE score and higher probability according to the PASCAL classification system, should undergo PFO closure.

Possible predictors for neurological recurrence were investigated. We found that age, sex, and cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, as well as smoking did not appear to have significant predictive power for future neurological events in our cohort. In addition, patients with TIA as an indicative event did not show a higher risk of neurologic recurrences. Although the cohort was similar to other real-world studies, the results differed, showing a significant influence of age,[15,16] hyperlipidemia and smoking,[16] or diabetes.[15] We also performed PFO closure in patients over 60 years of age. This has not been done in RCTs to minimize competing risk factors for neurological events, which are known to increase with age.[5–7,24–26] There are only a few publications investigating PFO closure in older patients, which proved good safety but tended to indicate increased neurologic recurrence rates over the age of 60 years.[15,34] In our cohort, we found no significant age-related differences in neurologic recurrence. We hereby suggest that PFO closure can be safely performed in older patients after careful selection and exclusion of competing risk factors. However, RCTs are still needed to prove this hypothesis.

Limitations

The limitations of this study include the retrospective character which did not allow a detailed examination of the neurological events before PFO closure. Therefore, the majority of patients were diagnosed with stroke and could not be subcategorized according to the TOAST classification.[22] However, this was possible for recurrent events, whereby the effective prevention of cryptogenic strokes could be demonstrated over a long period of time. Next, statistical analysis of subgroups was limited due to the small number of patients ($n = 12$) that reached the primary composite outcome. Hence, hazard ratios are given with relatively large confidence intervals and the assessment of confounding factors, such as long-term medical therapy after PFO closure, was limited. Finally, the follow-up consisted primarily of data accessible from patient records within Vienna, which could have led to a possible underreporting of adverse events and neurological recurrences following PFO closure. In addition, patients aged 60 and older did not undergo extended cardiac monitoring, potentially leading to an underreporting of new-onset AF.

Conclusion

Our experience confirms the safety and efficacy of transcatheter PFO closure for secondary prevention of cryptogenic strokes. The rate of recurrent neurological events was low, especially cryptogenic strokes. Patient selection remains critical, with RoPE score and PASCAL classification system confirming good predictive ability. According to our results, more emphasis should be placed on the number of previous neurological events.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Bea Goessinger https://orcid.org/0009-0009-9891-6466

References

1. Hara H, Virmani R, Ladich E, et al. Patent foramen ovale: current pathology, pathophysiology, and clinical status. *J Am Coll Cardiol* 2005; 46: 1768–1776.
2. Hagen PT, Scholz DG and Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984; 59: 17–20.
3. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988; 318: 1148–1152.
4. Windecker S, Stortecky S and Meier B. Paradoxical embolism. *J Am Coll Cardiol* 2014; 64: 403–415.
5. Mas JL, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017; 377: 1011–1021.
6. Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017; 377: 1022–1032.

7. Søndergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017; 377: 1033–1042.
8. Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol* 2018; 71: 2335–2342.
9. Pristipino C, Sievert H, D'Ascenzo F, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *Eur Heart J* 2018; 40: 3182–3195.
10. Caso V, Turc G, Abdul-Rahim AH, et al. European Stroke Organisation (ESO) Guidelines on the diagnosis and management of patent foramen ovale (PFO) after stroke. *Eur Stroke J*. Epub ahead of print 16 May 2024. DOI: 10.1177/23969873241247978.
11. Ahmad Y, Howard JP, Arnold A, et al. Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials. *Eur Heart J* 2018; 39: 1638–1649.
12. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013; 81: 619–625.
13. Elgendy AY, Saver JL, Amin Z, et al. Proposal for updated nomenclature and classification of potential causative mechanism in patent foramen ovale-associated stroke. *JAMA Neurol* 2020; 77: 878–886.
14. Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke. *JAMA* 2021; 326: 2277–2286.
15. Abrahamyan L, Barker M, Dharma C, et al. Real world long-term outcomes among adults undergoing transcatheter patent foramen closure with amplatzer PFO occluder. *Int J Cardiol* 2023; 371: 109–115.
16. Kneihsl M, Horner S, Hatab I, et al. Long-term risk of recurrent cerebrovascular events after patent foramen ovale closure: results from a real-world stroke cohort. *Eur Stroke J* 2023; 8: 1021–1029.
17. Karagianni A, Mandalenakis Z, Dellborg M, Mirzada N, Johansson MC and Eriksson P. Recurrent cerebrovascular events in patients after percutaneous closure of patent foramen ovale. *J Stroke Cerebrovasc Dis* 2020; 29: 104860.
18. Wintzer-Wehekind J, Alperi A, Houde C, et al. Long-term follow-up after closure of patent foramen ovale in patients with cryptogenic embolism. *J Am Coll Cardiol* 2019; 73: 278–287.
19. Konstantinides S, Kasper W, Geibel A, Hofmann T, Köster W and Just H. Detection of left-to-right shunt in atrial septal defect by negative contrast echocardiography: a comparison of transthoracic and transesophageal approach. *Am Heart J* 1993; 126: 909–917.
20. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 2009; 40: 2276–2293.
21. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44: 2064–2089.
22. Adams HP, Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; 24: 35–41.
23. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014; 13: 429–438.
24. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013; 368: 1092–1100.
25. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012; 366: 991–999.
26. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 2013; 368: 1083–1091.
27. Skibsted CV, Korsholm K, Pedersen L, et al. Long-term risk of atrial fibrillation or flutter after transcatheter patent foramen ovale closure: a nationwide Danish study. *Eur Heart J* 2023; 44: 3469–3477.
28. Oliva L, Huszti E, Hall R, Abrahamyan L and Horlick E. Incidence of new-onset atrial fibrillation after transcatheter patent foramen ovale closure using 15 years of Ontario administrative health data. *Heart Rhythm* 2022; 19: 1414–1420.
29. Oliva L, Huszti E, Barker M, et al. New-onset atrial fibrillation following percutaneous closure of patent foramen ovale: a systematic review and meta-analysis. *J Interv Card Electrophysiol* 2021; 60: 165–174.
30. Badoz M, Derimay F, Serzian G, et al. Incidence of atrial fibrillation in cryptogenic stroke with patent foramen ovale closure: protocol for the prospective, observational PFO-AF study. *BMJ Open* 2023; 13: e074584.
31. Giannandrea D, Padiglioni C, Eusebi P, et al. Clinical RoPE (cRoPE) score predicts patent foramen ovale detection among stroke patients: a multicenter observational study. *Neurol Sci* 2020; 41: 3227–3233.
32. Kent DM, Saver JL, Ruthazer R, et al. Risk of paradoxical embolism (RoPE)-estimated attributable fraction correlates with the benefit of patent foramen ovale closure: an analysis of 3 trials. *Stroke* 2020; 51: 3119–3123.
33. Koutroulou I, Tsivgoulis G, Karacostas D, Ikonomidis I, Grigoriadis N and Karapanayiotides T. Prevalence of patent foramen ovale in the Greek population is high and impacts on the interpretation of the risk of paradoxical embolism (RoPE) score. *Ther Adv Neurol Disord* 2020; 13: 1756286420964673.
34. Alperi A, Guedeney P, Horlick E, et al. Transcatheter closure of patent foramen ovale in older patients with cryptogenic thromboembolic events. *Circ Cardiovasc Interv* 2022; 15: e011652.