ORIGINAL ARTICLE

Recurrent cerebrovascular events in patients with a history of cryptogenic stroke or transient ischemic attack and patent foramen ovale in a long-term follow-up

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KEY WORDS

cryptogenic stroke, patent foramen ovale, patent foramen ovale closure, transient ischemic attack

ABSTRACT

INTRODUCTION Cryptogenic stroke may be associated with a patent foramen ovale (PFO). Both cardiovascular risk factors and transcatheter closure of PFO may have an impact on the risk of recurrent cerebrovascular events.

OBJECTIVES The aim of the study was to assess the occurrence and risk factors of recurrent cerebrovascular events (rCVE) in patients with a history of cryptogenic stroke or transient ischemic attack (TIA) and PFO.

PATIENTS AND METHODS Overall, 392 patients (median [interquartile range, IQR] age 39.5 [30–49] years, 64.3% women, 35.7% men) with a history of cryptogenic stroke/TIA and confirmed PFO underwent a long-term follow-up with a median (IQR) of 51.5 (35–65) months. The primary end point was defined as rCVE including stroke and TIA.

RESULTS During the follow-up, 17 patients with a history of cryptogenic stroke/TIA and confirmed PFO (4.3%, 11 women, 6 men) developed rCVE. In a multivariable analysis, the Risk of Paradoxical Embolism (RoPE) score was associated with a lower risk of rCVE (odds ratio [OR], 0.61 per 1 point; 95% CI, 0.45–0.84; $P = 0.002$). The transcatheter closure of PFO did not have a significant impact on rCVE in the study population ($P = 0.19$).

CONCLUSIONS The occurrence of rCVE in the patients with cryptogenic stroke/TIA and PFO reached 4.3% regardless of a high percentage of patients who underwent the PFO closure. RoPE score was associated with a lower risk of rCVE in the study population.

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INTRODUCTION Stroke is one of the most common causes of death and the main cause of persistent and acquired disability in adults worldwide.[1] It is estimated that approximately 70% to 80% of all diagnosed strokes are ischemic.[2]

In 25% of patients with an acute ischemic stroke the causality cannot be determined and the stroke is classified as one of undetermined etiology or cryptogenic. The patients who have had a cryptogenic stroke are less likely to have classic risk factors of cardiovascular events (eg, hypertension, hyperlipidemia, diabetes, and smoking).[3] These patients are more likely to have a patent foramen ovale (PFO) than the patients with a stroke of an unknown etiology.[4]

PFO is present in about 20% of the general population and can serve as a passage for paradoxical embolism, allowing venous thrombi to enter the arterial circulation, avoiding filtration by the lungs, and causing ischemic stroke. Other mechanisms that can lead to PFO-associated stroke include intracardiac thrombus that can be formed in the tunnel of the PFO or on the atrial septal aneurysm surface.[5] Randomized controlled trials did not definitively establish that

WHAT'S NEW?

In our study, we present our 10-year experience in diagnosing the patent foramen ovale (PFO) that allows us to summarize the risk factors of recurrent cerebrovascular events (rCVE) in patients with confirmed PFO and cryptogenic stroke or transient ischemic attack. Our follow-up duration was one of the longest in comparison with other PFO closure randomized trials. In our study, the rCVE occurred regardless of a high percentage of patients who underwent PFO closure. Our analysis showed that the Risk of Paradoxical Embolism score was associated with a lower risk of rCVE in the study population.

closing the PFO reduces the risk of subsequent stroke. CLOSURE I study[6] and PC trial[7] did not prove the superiority of the PFO closure over a pharmacological therapy. However, more recent randomized trials have demonstrated that PFO closure is superior to a pharmacological therapy in the prevention of stroke.[8,9]

Of note, PFO is associated not only with paradoxical embolism but also with other neurological conditions. Observational studies have indicated the association between PFO and migraine headaches. PFO is present in 40% to 60% of patients with migraine with aura, as compared with 20% to 30% of the general population. It is suspected that migraine, especially with aura, may be triggered by hypoxemia or vasoactive factors (eg, serotonin), which are generally metabolized in the pulmonary circulation.[10]

The indications for PFO diagnosis are not well established and slightly differ between cardiological and neurological recommendations.[11,12]

The aim of the study was to analyze the occurrence and risk factors of recurrent cerebrovascular event (rCVE) in patients with PFO and a history of a cryptogenic stroke or transient ischemic attack (TIA) in a long-term follow-up.

PATIENTS AND METHODS

Patients Overall, 392 patients with a history of cryptogenic stroke / TIA and confirmed PFO were included in a long-term follow-up. The patients with a known cause of cerebrovascular ischemic event were excluded from the analysis. The exclusion criteria comprised: a) the presence of structures or vegetation in the heart cavities (thrombus in the left ventricle, myxoma, atrial septal defect or ventricular septal defect), b) the presence of atherosclerotic plaques in the intracranial arteries, aortic arch, and ascending aorta, c) congestive heart failure, d) other congenital heart defects, e) atrial fibrillation (AF), and f) life expectancy of less than 2 years.

The patients were referred to cardiological diagnostics by neurologists from outpatient clinics and hospital departments. All consecutively diagnosed patients who met the inclusion criteria were enrolled in the study. All patients were diagnosed according to the same protocol.

At baseline, 290 patients (74%); (64.5% women, 35.5% men) underwent a transcatheter PFO closure. The criteria for the transcatheter PFO closure included: a) the history of a cryptogenic stroke / TIA, b) age below 65 years, c) presence of right-to-left shunt trough PFO in contrast transesophageal echocardiography (TEE), d) exclusion of other known causes of the cerebrovascular episodes, e) patient's informed consent. The decision to qualify a patient for PFO closure was made individually for each patient by the Heart Team.

For each patient the Risk of Paradoxical Embolism (RoPE) score[13] was evaluated retrospectively.

Tests and data analysis The following factors were assessed: age, sex, previous neurological events (stroke / TIA), and migraine. The analysis included the presence of arterial hypertension, diabetes mellitus, smoking, hyperlipidemia, and the use of hormonal contraception in women. Ischemic stroke / TIA was diagnosed in relevant neurology departments according to the European Stroke Organization guidelines.[14] Arterial hypertension, hyperlipidemia, and diabetes were diagnosed according to the current European Society of Cardiology guidelines.[15-17] AF was verified based on the case history data (ie, 12-lead electrocardiogram [ECG], Holter monitoring).

For all patients included in the study, we collected data on their demographics, medical history, biochemical tests with the assessment of cardiovascular risk factors, 12-lead ECG, transthoracic echocardiography (TTE), and TEE.

Patent foramen ovale confirmation PFO was diagnosed using contrast TEE. The interatrial septum was analyzed in the following views: mid-esophageal 4-chamber, mid-esophageal short axis, and bicaval. PFO with transient right-to-left leak was confirmed using an intravenous contrast (0.9% saline mixed with 1 ml of air) and Valsalva maneuver. The results were rated on a scale of 0 to 3, where 0 meant no bubbles moving through the interatrial septum into the left atrium, and 3 meant a large cloud of bubbles crossing into the left atrium. The same TEE methodology was used for all the patients. TEE was performed by the same physician over the study.

Patent foramen ovale closure The PFO closure was conducted by a single operator. The procedure was performed via the femoral vein, using local anesthesia and short 6F sheath. At least 5000 IU of heparin were administrated via the sheath. The occluder was implanted across the septum, guided with fluoroscopy and TEE. Cardia Intrasept (Cardia, Eagan, Minnesota, United States) and Occlutech Figula (Occlutech, Jena, Germany) devices were implanted. The patients were routinely hospitalized for 3 to 4 days. No PFO closure–related complications were observed.

After the closure, the patients were treated with dual antiplatelet therapy (aspirin and clopidogrel) for 6 months, followed by aspirin in monotherapy for the rest of the study. The patients did not receive oral anticoagulation during the study.

TABLE 1 Demographic and clinical characteristics of patients with and without recurrent cerebrovascular events

Variable	Non-rCVE group (n = 375)	rCVE group (n = 17)	*P* value
Age, y	39 (30–49)	49 (42–52)	0.03
Female sex	241 (64.3)	11 (64.7)	0.97
History of stroke	165 (44.0)	8 (47.1)	0.80
History of TIA	200 (53.3)	9 (52.9)	0.96
Migraine	193 (51.5)	6 (35.3)	0.19
PFO closure	275 (73.3)	15 (88.2)	0.17
HA	117 (31.2)	9 (52.9)	0.06
Hyperlipidemia	115 (30.7)	9 (52.9)	0.05
DM	5 (1.3)	1 (5.9)	0.14
Smoking	89 (23.8)	7 (41.2)	0.10
Syncope	73 (19.5)	2 (11.8)	0.43
Hormonal contraception	59 (15.7)	1 (5.9)	0.27
RoPE score, points	7 (6–8)	5 (5–7)	0.004

Data are presented as median (interquartile range) or number (percentage) of patients.

Abbreviations: DM, diabetes mellitus; HA, arterial hypertension; PFO, patent foramen ovale; rCVE, recurrent cerebrovascular events; RoPE, Risk of Paradoxical Embolism scale; TIA, transient ischemic attack

TABLE 2 Factors that contributed to cerebrovascular events recurrence

Variable	Univariable analysis		
	OR	95% CI	*P* value
Age (per 1 year)	1.04	1.00–1.09	0.04
History of stroke	3.22	0.86–12.06	0.08
History of TIA	0.96	0.46–2.00	0.91
Migraine	0.51	0.19–1.42	0.20
Migraine with visual aura	0.76	0.26–2.20	0.61
Migraine without visual aura	0.32	0.04–2.42	0.27
Syncope	0.55	0.12–2.47	0.44
RoPE score (per 1 pt)	0.61	0.45–0.84	0.002
HA	2.48	0.93–6.60	0.07
Hyperlipidemia	2.54	0.96–6.76	0.06
DM	4.63	0.51–41.93	0.17
Smoking	2.24	0.83–6.06	0.11
PFO closure	2.72	0.61–12.14	0.19

Abbreviations: see TABLE 1

The participants who were not referred for PFO closure received single antiplatelet therapy with 150 mg of aspirin daily.

Follow-up The patients with a history of a cryptogenic stroke / TIA and confirmed PFO (n = 392) were observed during a long-term follow-up with a median (interquartile range [IQR]) of 51.5 (35–65) months. The primary end point was defined as rCVE including stroke or TIA.

Statistical analysis Statistical analysis was performed using IBM SPSS Statistics 25 (IBM, New York, New York, United States) software. The normally distributed quantitative variables are presented as a mean value (SD). The non-normally distributed quantitative variables are presented as median IQR. The qualitative parameters are expressed as a number and percentage. The type of distribution was verified using the Shapiro–Wilk test. In the event of normally-distributed variables, the *t* test for unpaired samples was used. The Mann–Whitney test was used in the case of non-normally distributed parameters. All variables were included in the univariable analysis as potential predictors of rCVE. Subsequently, all the variables with *P* below 0.1 were included in the stepwise logistic regression analysis. The association between the RoPE score and rCVE was established using the receiver operating characteristic curve (ROC) analysis. The cut-off value for ROC was estimated using Youden J index with further calculation of the associated criterion, along with the corresponding sensitivity and specificity. A *P* value lower than 0.05 was regarded significant.

Ethics The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board or Ethics Committee (KNW/0022/KB/146/16) of the Medical University of Silesia, Katowice, Poland. Informed consent was obtained from all participants of the study.

RESULTS

Follow-up: recurrent cerebrovascular events in patients with cryptogenic stroke/transient ischemic attack and confirmed patent foramen ovale

Overall, 392 patients with a history of cryptogenic stroke / TIA and confirmed PFO were included in the long-term follow-up. At baseline in this population 290 patients (74%); (64.5% women, 35.5% men) underwent transcatheter PFO closure. For each patient the RoPE score was evaluated retrospectively.

Among the 392 patients with a history of cryptogenic stroke / TIA and confirmed PFO during the follow-up, 17 patients (4.3%) (11 women, 6 men) developed rCVE. The rCVE subgroup did not differ in terms of traditional cardiovascular risk factors (arterial hypertension: 52.9% vs 31.2%; *P* = 0.06; diabetes: 5.9% vs 1.3%; *P* = 0.14; hyperlipidemia: 52.9% vs 30.7%; *P* = 0.05; smoking: 41.2% vs 23.8%; *P* = 0.10), as compared with the rest of the study population. The prevalence of PFO closure was similar in both groups (88.2% vs 73.3%; *P* = 0.17) (TABLE 1).

In univariable analysis, the only factor that influenced the risk of rCVE was age (per 1 year; OR, 1.04; 95% CI, 1.0–1.1; *P* = 0.045). Other factors were statistically insignificant: hypertension (OR, 2.5, 95% CI, 0.93–6.6; *P* = 0.07), hyperlipidemia (OR, 2.54; 95% CI, 0.96–6.76; *P* = 0.06). In multivariable analysis, the RoPE score was associated with a lower risk of rCVE (OR, 0.61 per 1 point; 95% CI, 0.45–0.84; *P* = 0.002). The transcatheter closure of PFO did not have an impact on the incidence of rCVE (OR, 2.72; 95% CI, 0.61–12.14; *P* = 0.19) (TABLE 2).

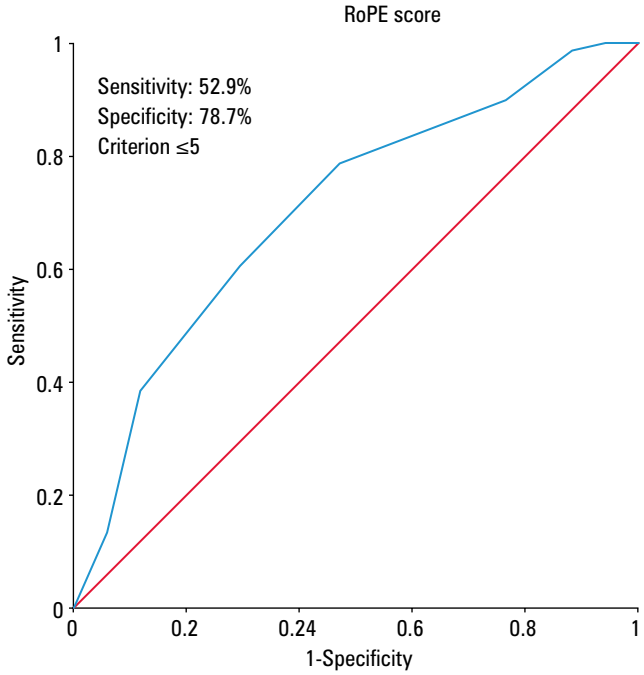

FIGURE 1 Receiver operating characteristic curve analysis of the Risk of Paradoxical Embolism scale score in the prediction of recurrent cardiovascular events

ROC analysis showed that a higher RoPE score (per 1 point) predicted a lower risk of rCVE in the study population with sensitivity of 52.9% and specificity 78.7% for the threshold equal to or below 5 points (FIGURE 1).

DISCUSSION A cryptogenic ischemic stroke is diagnosed by excluding alternative etiologies, including small-vessel disease, arrhythmias, aortic arch atheroma, intracranial stenosis, or thrombophilia. The association between PFO and the cerebrovascular event must be carefully considered, because cryptogenic strokes in patients with PFO may also be due to PFO-unrelated mechanisms.[18]

Experts in the European position paper[11] on the management of patients with PFO recommend careful selection of patients for percutaneous closure of PFO in the case of cryptogenic ischemic stroke, TIA, or another systemic thromboembolism. Other possible causes of ischemic events must be excluded in the first place. Similar guidelines were given in the practice advisory update summary[12] of the American Academy of Neurology.

In this study, we present the results of our unique 10-year experience in diagnosing the risk factors for rCVE in patients with confirmed PFO and cryptogenic stroke / TIA.

During the long-term observation, 4.3% of the patients with cryptogenic stroke / TIA and confirmed PFO developed rCVE, regardless of a high percentage of patients who underwent PFO closure. The follow-up duration was one of the longest as compared with other randomized trials on the PFO closure.[22-25]

In the univariable analysis, older age and lower RoPE score were the risk factors of rCVE. Arterial hypertension and hyperlipidemia tended to be more prevalent in the patients with rCVE. A relatively small number of patients with rCVE was probably the reason why the statistical significance was not achieved. There are many well-established risk factors of ischemic stroke, such as age, arterial hypertension, hyperlipidemia, diabetes mellitus, smoking, and AF.[19] The patients with diagnosed AF were excluded from the current study. However, both hyperlipidemia and arterial hypertension are risk factors for atrial arrhythmias. Recent studies showed that clinically silent AF is probably the cause of substantial portion of cryptogenic ischemic strokes.[20] Prolonged ECG-monitoring (at least 28 days) should be recorded in selected patients considered for PFO closure after an ischemic event according to the contemporary neurologic recommendation.[12]

The first studies failed to prove superiority of PFO closure over a pharmacological therapy alone to prevent rCVE in the patients with cryptogenic stroke / TIA and PFO. Similar results were obtained in the CLOSURE I[6] and PC[7] trials. There were several factors that might have contributed to such results. First, one should consider the above-mentioned propensity for higher prevalence of hyperlipidemia and hypertension in the group with rCVE. Second, the first patients were recruited for PFO closure in 2010 and since then the RoPE score has been invented, and several recommendations for AF detection after ischemic stroke have appeared.[21]

However, more recent studies have proved that PFO closure reduces rCVE, both stroke and TIA, as compared with the pharmalogical therapy. In the CLOSE trial,[22] the PFO closure was associated with approximately 60% reduction of rCVE (OR, 0.38; 95% CI, 0.17–0.85), with 8/238 rCVE in the treatment group vs 12/235 in the control. Gore REDUCE study[23] proved a slightly lower but still significant reduction of rCVE in the PFO closure group (OR, 0.56; 95% CI, 0.31–1.00) with 22/441 vs 20/223 events in the closure and control group, respectively.[23] Similar results were demonstrated in the RESPECT study[24] (OR, 0.62; 95% CI, 0.35–1.11), with 18/499 events in the study group and 28/481 in the control.

In recent trials, the PFO closure was associated with a significant reduction in the risk of stroke. The beneficial effect of PFO closure was shown especially in the patients with PFO and substantial interatrial shunt. It was also proved that the reduction of the stroke risk was greater in the patients with a PFO-associated atrial septal aneurysm. Age did not influence the benefit of the PFO closure.[25]

We retrospectively stratified patients by means of the RoPE score, which was designed to identify the stroke-related PFO. In the multivariable logistic regression analysis, the RoPE score was linked to a lower risk of rCVE. The more points the patient received, the more likely the stroke was related to PFO. The median RoPE score in the patients with no rCVE in the current study was 7 points, which meant a 72% chance

that thromboembolism was due to PFO, as compared with only 34% chance in the rCVE group (RoPE score of 5). This finding also supports the hypothesis that classical risk factors for cardiovascular events, independently of the presence of PFO, were responsible for neurological incidence, even in the relatively young group of patients. The risk of recurrence of PFO-related thromboembolic events is generally lower in comparison with those caused by more common risk factors.[26]

Clinical grading scores may be useful for stratification of patient risk and estimation of prognosis. In our analysis, the RoPE score (per 1 point) was linked to a lower risk of rCVE in the study population with sensitivity of 52.9% and specificity of 78.7% for a threshold equal to or below 5 points. Another clinically tested scale was the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) score.[27] The authors of this study showed an association between the ASTRAL score and a 3-month functional outcome in patients with cryptogenic stroke. Higher ASTRAL score was related with unfavorable outcome at 3 months. ASTRAL score of 31 was associated with 50% likelihood of a poor outcome (with sensitivity of 52.2% and specificity of 95.6%).[28]

A decision on PFO closure still remains challenging. The etiology of cryptogenic stroke is heterogeneous, hence it is imperative that patients are considered for PFO closure with due caution following meticulous clinical assessment.

Limitations This was a single-center, nonrandomized study. The indication for PFO closure might be subject to changes within upcoming years. Nevertheless, the present results are compelling as they reflect present characteristics, long-term prognosis, and a real-life approach to patients with cryptogenic stroke / TIA and PFO.

Patients with AF were excluded from the study. We are aware that over the long-term follow-up some patients might have developed silent arrhythmia and our monitoring methods have limitations. AF was verified based on the case history data, ECG, and Holter monitoring.

We did not observe any clinically important periprocedural complications after PFO closure but data on postdischarge period are limited.

Our patients received a standard antiplatelet therapy. However, due to the retrospective nature of the analysis, it was not possible to precisely assess all data on the pharmacological treatment.

Regardless of the indications for PFO closure, not all patients consented to the procedure. The study analyzed the occurrence of rCVE with regards to PFO closure. We finally established that the rCVE rate was low and the transcatheter closure of PFO did not affect rCVE occurrence.

Conclusions In the long-term follow-up, the occurrence of rCVE in the patients with cryptogenic stroke / TIA and confirmed PFO reached 4.3%, regardless of a high percentage of patients who underwent PFO closure. The RoPE score was associated with a lower risk of rCVE in the study population.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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