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ORIGINAL ARTICLE

Selection of patients for percutaneous closure in nonlacunar cryptogenic stroke associated with patent foramen ovale. Data from the NORDICTUS cooperative registry

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KEYWORDS
Stroke;
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Abstract
Introduction: There is an extending use of percutaneous closure of patent foramen ovale (PFO) as therapy for PFO-associated cryptogenic strokes. The aim of our study was to investigate the clinical practice of percutaneous closure of PFO and to analyse the variables for decision-making on the selection of patients for this procedure.

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Method: A prospective observational multicentric survey was conducted using all the cases of cryptogenic stroke/transient ischaemic attack associated with PFO recorded in the NORDICTUS hospital registry during the period 2018-2021. Clinical data, radiological patterns, echocardiogram data and factors related to PFO-associated stroke (thromboembolic disease and paradoxical embolism criteria) were recorded. The indication for closure was analysed according to age (≤/> 60 years) and the characteristics of the PFO.
Results: In the group ≤ 60 years (n = 488), 143 patients (29.3%) underwent PFO closure. The most influential variables for this therapy were detection of a high-risk PFO (OR 4.11; IC 2.6-6.5, *P* < .001), criteria for paradoxical embolism (OR 2.61; IC 1.28—5.28; *P* = .008) and previous use of antithrombotics (OR 2.67; IC 1.38—5.18; *P* = .009). In the > 60 years group (n = 124), 24 patients had PFO closure (19%). The variables related to this option were history of pulmonary thromboembolism, predisposition to thromboembolic disease, paradoxical embolism criteria, and high-risk PFO.
Conclusions: The detection of a high-risk PFO (large shunt, shunt with associated aneurysm) is the main criterion for a percutaneous closure-based therapy. Other conditions to consider in the eligibility of patients are the history of thromboembolic disease, paradoxical embolism criteria or the previous use of antithrombotics.

PALABRAS CLAVE
Ictus;
Foramen oval permeable;
Cierre percutáneo

Selección de pacientes para cierre percutáneo en el ictus isquémico no lacunar criptogénico asociado a foramen oval permeable. Datos del registro cooperativo NORDICTUS

Resumen
Introducción: El tratamiento mediante cierre percutáneo está extendiendo su uso en el Ictus asociado a Foramen Oval Permeable (FOP). El objetivo del estudio es analizar la práctica clínica del cierre percutáneo de FOP y conocer las variables que determinan esta indicación.
Método: Registro observacional prospectivo de casos de ictus isquémico/ataque isquémico transitorio criptogénico asociado a FOP diagnosticados en la red de hospitales NORDICTUS en el periodo 2018—2021. Se registraron datos clínicos, patrón radiológico, datos de ecocardiograma y factores vinculados al ictus asociado a FOP (enfermedad tromboembólica y criterios de embolia paradójica) Se analizó la indicación de cierre según edad (≤/> 60 años) y de las características del FOP.
Resultados: En el grupo ≤60 años (n = 488) se indicó cierre en 143 pacientes (29,3%). Las variables predictoras de esta indicación fueron: detección de un FOP de alto riesgo (OR 4,11; IC 2,6-6,5, p < 0,001), criterio de embolismo paradójico (OR 2,61; IC 1,28-5,28; p = 0,008) y el uso previo de antitrombóticos (OR 2,67; IC 1,38-5,18; p = 0,009). En el grupo de > 60 años (n = 124), el cierre se indicó en 24 casos (19%). Las variables relacionadas con esta opción fueron: antecedente de tromboembolismo pulmonar, predisposición a enfermedad tromboembólica, criterios de embolismo paradójico y FOP de alto riesgo
Conclusiones: En la indicación de cierre percutáneo, el factor principal es la detección de un FOP de alto riesgo (cortocircuito masivo, cortocircuito con aneurisma asociado). Otros factores de interés en la selección de pacientes son: antecedentes de enfermedad tromboembólica, criterios de embolismo paradójico o el uso previo de antitrombóticos.

Introduction

The incidence of stroke in Spain ranges from 150 to 200 cases per 100 000 population, while the age-adjusted prevalence is 7.6%.[1,2] Between 20% and 40% of all ischaemic strokes are classified as cryptogenic after complete evaluation. The aetiological study may detect patent foramen ovale (PFO) in up to 40% of patients with cryptogenic stroke. In clinical practice, this translates into a large number of strokes associated with PFO, which underscores the need to issue treatment recommendations based on solid evidence.[3]

Patients with stroke and PFO constitute a heterogeneous group, presenting considerable differences in the role PFO plays in the development of the cerebrovascular event. This has led to controversy about various questions, ranging from pathogenesis (paradoxical embolism and other mechanisms) to secondary prevention (percutaneous closure and medical treatment).[4—8] Studies

aiming to determine the optimal assessment strategy for these patients present methodological issues linked to multiple hard-to-control variables involved in the relationship between stroke and PFO. In clinical practice, this has led to uncertainty with regard to how best to manage PFO in patients with cryptogenic stroke.[4]

Randomised clinical trials[9—12] published between 2017 and 2018 and subsequent meta-analyses confirmed the superiority of percutaneous closure over antiplatelet therapy.[13—17] Based on these results, scientific societies have issued guidelines and position statements recommending that patient selection and thorough assessment be performed by multidisciplinary teams.[18—20] The most recent guidelines establish a strength of recommendation 2a for indicating percutaneous closure of high-risk PFO (large shunt size or atrial septal aneurysm) in patients aged 18-60 years, especially if they do not present a low Risk of Paradoxical Embolism (RoPE) scale score or do not need anticoagulant therapy.[18] The creation of multidisciplinary teams including cardiologists and neurologists to evaluate the therapeutic options available and to inform patients about the risks and benefits of each treatment helps to make better decisions.[18,19] This may be particularly useful in cases where the published evidence has little clinical applicability. In the light of the above, researchers should seek to analyse groups previously excluded from clinical trials (patients older than 60 years, patients with transient ischaemic attack [TIA] and no lesions on imaging)[9—11] or groups potentially benefiting from PFO closure (patients aged 61-69 years, patients with low-risk PFO).[4,21]

Data from cooperative registries may be useful to evaluate the care provided to these patients in real practice and to address questions that clinical trials have been unable to answer. Therefore, scientific societies recommend using prospective registries to gather data on the practical management of these patients in our hospitals, with a view to evaluating several variables associated with patient management, treatment interventions, and efficacy and safety outcomes.[19,20]

In the light of the above, and with a view to expanding our knowledge of the treatment of stroke associated with PFO, we designed a cooperative registry with the following aims:

1 To evaluate eligibility criteria for percutaneous closure of PFO according to current recommendations.
2 To analyse the indications for patients aged over 60 years and other patient groups (TIA, ages 61-69, low-risk PFO).
3 To determine the safety and efficacy of the procedures.

Material and methods

Protocol approval and informed consent

The study was conducted at 14 centres participating in NORDICTUS, a cerebrovascular disease research network involving a series of hospitals in northern Spain (Aragon, Navarre, the Basque Country, Cantabria, Asturias, Galicia, and Castile-Leon). The study was approved by each centre's research ethics committee. Informed consent was obtained from all participants or their legal representatives. The study was promoted by the Spanish Society of Neurology's Stroke Study Group in the context of its Project Stroke.

Study design and patient selection

We conducted a prospective, observational study of cases of nonlacunar cryptogenic ischaemic stroke associated with PFO diagnosed at any hospital in the NORDICTUS network between 2018 and 2021.

Researchers recruited patients with ischaemic stroke or TIA in whom the aetiological study had failed to identify a specific cause for the cerebrovascular event but had detected PFO (according to the classification of the Spanish Society of Neurology[22]).

The aetiological study included common laboratory tests (complete blood count, biochemical profile, lipid profile), thrombophilia testing, determination of toxic substances (if indicated), venous ultrasound (if indicated), cardiology study (electrocardiography, telemetry at the stroke unit or 24-h Holter monitor, echocardiography), and neurovascular study (transcranial and supra-aortic trunk Doppler ultrasound study, MRI angiography or CT angiography).

The system used a digital data collection platform that is periodically reviewed to ensure the veracity of the data.

Clinical variables, neuroimaging findings, and diagnosis of patent foramen ovale

Clinical variables

From each patient we recorded the following data:

1) Demographic data (age and sex), vascular risk factors (arterial hypertension, diabetes mellitus, dyslipidaemia, ischaemic heart disease, peripheral vascular disease, smoking, alcohol abuse, previous stroke/TIA, migraine), antithrombotic therapy (antiplatelets/anticoagulants), use of drugs or toxic substances (urine toxicology tests).
2) Factors linked to stroke associated with PFO: history of deep vein thrombosis, pulmonary thromboembolism, predisposition to thromboembolic disease (history of deep vein thrombosis/pulmonary thromboembolism, varices, immobility, prothrombotic state), physiological stressors during the stroke (Valsalva manoeuvres, exercising, lifting heavy weights, coughing, yawning, defecating, sexual activity), and criteria of paradoxical embolism (cerebral embolism/deep vein thrombosis or pulmonary thromboembolism/right-to-left shunt).[23,24]
3) Clinical data about stroke: time of onset, severity (National Institutes of Health Stroke Scale score[25]), type (Oxfordshire Community Stroke Project classification[26]), thrombophilia testing results, risk of paradoxical embolism (RoPE scale[27]), and preventive medical treatment.
4) Radiological characteristics of the cerebrovascular event: topography (anterior and/or posterior circulation, no lesion) and neuroimaging lesion pattern (territorial, scattered, involving the territory of the cerebral perforating arteries).

The stroke pattern was considered embolic when it was scattered (multiple lesions in one or several vascular territories) or territorial (corticosubcortical or cortical lesion in one vascular territory).[28]

Diagnosis of patent foramen ovale

Transcranial Doppler ultrasound

The transtemporal window was used to monitor the middle cerebral artery with a 2.5 MHz probe. A syringe was used to inject 1 mL air and 9 mL sterile isotonic saline solution. The study was performed a minimum of 2 times at rest and 2 times after a Valsalva manoeuvre. PFO was classified as small (1-10 microbubbles), medium (> 10 microbubbles with no shower/curtain pattern), or large (shower/curtain pattern).[29]

Cardiac ultrasound

The cardiology study included transthoracic and/or transoesophageal echocardiography studies. For diagnosis of PFO, we injected agitated saline at rest and during Valsalva manoeuvres.

Shunt severity was classified as mild (< 10 microbubbles), moderate (10-30 microbubbles), or severe (> 30 microbubbles).

The study evaluated the presence of other anatomical alterations, such as atrial septal aneurysm (defined as an aneurysm presenting > 10 mm excursion from the atrial septal plane and >

15 mm base diameter) and embryonic remnants (Chiari network, Eustachian valve).[30,31]

PFO was considered to be high-risk when it presented severe shunt or was associated with an atrial septal aneurysm.[18–20]

Patient follow-up and response variables

Patients were recruited between 1 February 2018 and 31 December 2021. All participants underwent periodic follow-up examinations throughout the study period. We recorded the number of days between stroke occurrence and the end of the study. In the group of patients with an indication of PFO closure, the following response variables were analysed: complications during device implantation, late-onset complications (> 7 days after the procedure), and stroke recurrence.

Statistical analysis

Statistical analysis was conducted using SPSS version 15.0 for Windows. Qualitative variables are expressed as number of cases and percentage, and quantitative variables as mean and standard deviation (SD) and median and quartiles 1 and 3 (Q_1-Q_3).

The univariate analysis was performed with the chi-square test or the Fisher exact test for categorical variables. We compared normally distributed quantitative variables with the *t*-test and non–normally distributed quantitative variables with the non-parametric Mann-Whitney *U* test.

The multivariate analysis included those variables presenting *P*-values < .1; through stepwise logistic regression, we determined the factors potentially predicting indication of PFO closure. Values of $P \leq .05$ were considered statistically significant.

Results

Patient characteristics

The registry included a total of 612 patients; 488 were ≤ 60 years old and 124 were > 60 years old (Table 1). As would be expected, all risk factors (except smoking) were more prevalent among patients in the older age group. The cardiology study for detection of PFO included both transthoracic and transoesophageal echocardiography studies in 315 patients (51.4%) and transthoracic echocardiography only in the remaining 297. No significant differences were observed in the presence of anatomical alterations on ultrasound (severe shunt, atrial septal aneurysm, embryonic remnants). However, high-risk PFO (severe shunt or shunt associated with aneurysm) was more frequent in the older group (65.3% vs 54.1%; *P* = .037).

Regarding the variables more closely linked to the pathophysiological mechanism of paradoxical embolism, history of pulmonary thromboembolism (7.3% vs 0.8%; *P* < .001) and predisposition to thromboembolic disease (14.5% vs 6.6%; *P* = .004) were more frequently observed in patients > 60 years of age. Likewise, patients in the older group more frequently met criteria for paradoxical embolism (18.5% vs 9.6%; *P* = .005).

A total of 392 patients (64%) underwent thrombophilia testing, with alterations being detected in 17% of them. These alterations were lupus anticoagulant (20 patients), hyperhomocysteinaemia (13), heterozygous factor V Leiden mutation (11), heterozygous prothrombin gene mutation (11), anticardiolipin antibodies (6), protein S deficiency (3), homozygous factor V Leiden mutation (1), and protein C deficiency (1).

Exploratory analysis of data on the indication of PFO closure by age group

In the ≤ 60 years group, PFO closure was indicated in 143 patients (29.3%). According to the univariate analysis, the variables associated with indication of PFO closure were no history of diabetes, history of stroke/TIA, use of antithrombotics, no history of drug abuse, an embolic stroke pattern on radiological images, predisposition to thromboembolic events, and ultrasound evidence of high-risk PFO (Table 2). In the logistic regression analysis, the variables predicting indication of PFO closure were ultrasound evidence of high-risk PFO (OR = 4.11; 95% CI, 2.6-5; *P* < .001), meeting diagnostic criteria for paradoxical embolism (OR = 2.61; 95% CI, 1.28-5.28; *P* = .008), and prior use of antithrombotics (OR = 2.67; 95% CI, 1.38-5.18; *P* = .009) (Table 3).

In the group of patients aged > 60 years, PFO closure was indicated for 24 patients (19%). The variables associated with indication of PFO closure were history of pulmonary thromboembolism, predisposition to thromboembolic disease, meeting diagnostic criteria for paradoxical embolism, and high-risk PFO (Table 4).

Exploratory analysis of other patient groups: TIA with no lesion on neuroimaging, PFO without anatomical evidence of high risk, and patients aged 61-69 years

This analysis included 76 patients with TIA, 19 of whom (25%) received indication of percutaneous closure (Table 5). A comparative analysis revealed that most patients with an indication for percutaneous closure presented high-risk PFO (78.9%, vs 45.6% of patients without this indication; *P* = .012). No differences were observed in the other factors analysed.

In the group of patients aged ≤ 60 years, 224 patients showed no signs of high-risk PFO (moderate- or low-severity shunt/absence of aneurysm). Thirty-four patients (15.1%) underwent percutaneous closure. A comparative analysis of the study variables found no statistically significant association with this treatment option.

In the group of patients aged 61 to 69 years (n = 69), 45 cases of high-risk PFO were detected (65.2%). Percutaneous closure of PFO was indicated in 15 cases (21.7%). The factors associated with venous thromboembolism (40% vs 0%; *P* < .001) and presence of high-risk PFO (100% vs 55.6%; *P* = .001) were significantly associated with indication of percutaneous closure.

Patient follow-up and response variables

The median follow-up time was 16 months (Q_1-Q_3: 8-24). All patients were followed up throughout the whole study period. In patients undergoing percutaneous closure, the median time from stroke to the intervention was 133 days (Q_1-Q_3: 34-261.5). The following periprocedural complications were reported (Table 6): cardiac perforation (1 case), pulmonary thromboembolism (1), transient atrial fibrillation (2), and puncture-site haematoma without clinical repercussion (8). Among late complications of the procedure, one patient presented chronic atrial fibrillation.

A total of 14 patients presented recurrent stroke: 2 in the group undergoing percutaneous closure (1.2%) and 12 in the group receiving preventive treatment (2.7%; *P* = .207). Recurrence was more frequent in older individuals (6 cases [4.8%] vs 8 [1.6%]; *P* = .033).

Discussion

Based on current knowledge, treatment indications for patients with cryptogenic stroke associated with PFO are based on reasonable, convincing evidence. Epidemiological studies, clinical trials, and recently published treatment guidelines provide reliable evidence supporting percutaneous closure in selected cases. However,

Table 1 Baseline characteristics by age group.

	≤ 60 years (*n* = 488)	> 60 years (*n* = 124)	*P*
Age, mean (SD)	47.25 (8.42)	69.86 (6.36)	
Clinical data			
Women	186 (38.1)	62 (50)	.016
Hypertension	74 (15.2)	57 (46.0)	< .001
Diabetes	22 (4.5)	16 (12.9)	.001
Dyslipidaemia	120 (24.5)	55 (44.4)	< .001
Ischaemic heart disease	11 (2.3)	13 (10.5)	< .001
Active smoking	148 (30.3)	12 (9.7)	< .001
Migraine	65 (13.3)	9 (7.3)	.064
Obesity	71 (14.5)	28 (22.6)	.030
Peripheral vascular disease	5 (1)	4 (3.2)	.169
Alcohol consumption	39 (8)	7 (5.6)	.59
Use of toxic substances	23 (4.7)	0 (0)	.036
Stroke	44 (9)	23 (18.5)	.002
TIA	18 (3.7)	18 (14.5)	< .001
History of stroke/TIA	55 (11.3)	33 (26.6)	< .001
Prior use of antithrombotics	51 (10.5)	35 (28.2)	< .001
Thromboembolic disease			
DVT	19 (3.9)	9 (7.3)	.105
PTE	4 (0.8)	9 (7.3)	< .001
Predisposition to TED	32 (6.6)	18 (14.5)	.004
Physiological stressors	51 (10.5)	10 (8.1)	.428
Thrombophilia/thrombophilia tests	64 (13.1)/328	11 (8.9)/64	.005
Type of event			.595
TIA	101 (20.7)	23 (18.5)	
Stroke	387 (79.3)	101 (81.5)	
NIHSS at admission, mean (SD) and median (Q_1-Q_3)	3.25 (4.95) 2 (0-4)	5.11 (6.25)2 (1-7.5)	< .001
Embolic pattern	290 (59.4)	76 (61.3)	.811
RoPE score, mean (SD)	6.2 (1.74)	3.9 (1.26)	< .001
Median (Q_1-Q_3)	6 (5-7)	4 (3-5)	< .001
Paradoxical embolism	47 (9.6)	23 (18.5)	.005
Echocardiography			
Transthoracic	225 (46.1)	72 (58.1)	
Transthoracic and transoesophageal	263 (53.8)	52 (41.9)	
Echocardiography findings			
High-risk PFO	264 (54.1)	81 (65.3)	.037
Large shunt	236 (48.4)	63 (50.8)	.627
Atrial septal aneurysm	127 (26)	45 (36.3)	.06
Embryonic remnants	26 (5.3)	7 (5.6)	.88
Contrast-enhanced transcranial Doppler ultrasound			
Not performed	48 (9.8)	43 (34.7)	
No shunt	12 (2.5)	3 (2.4)	
< 10	72 (15.3)	8 (6.5)	
10-25	99 (20.2)	18 (14.5)	
Shower/curtain pattern	257 (52.6)	52 (29.5)	
PFO closure	143 (29.3)	24 (19.4)	.026

DVT: deep vein thrombosis; NIHSS: National Institutes of Health Stroke Scale; PFO: patent foramen ovale; PTE: pulmonary thromboembolism; Q_1-Q_3: quartiles 1 and 3; RoPE: Risk of Paradoxical Embolism scale; SD: standard deviation; TED: thromboembolic disease; TIA: transient ischaemic attack.

Data are presented as number and percentage unless otherwise indicated. We did not perform a comparative analysis with examinations for PFO (cardiac ultrasound and transcranial Doppler ultrasound).

Table 2 Variables associated with indication of percutaneous closure in patients ≤ 60 years. Univariate analysis.

N = 488	No PFO closure (*n* = 345)	PFO closure (*n* = 143)	*P*
Age, mean (SD)	47.57 (8.22)	46.47 (8.87)	.187
Clinical data			
Women	139 (40.3)	47 (32.9)	.124
Hypertension	55 (15.9)	19 (13.3)	.457
Diabetes mellitus	20 (5.8)	2 (1.4)	.022
Dyslipidaemia	86 (24.9)	34 (23.8)	.778
Tobacco use	112 (32.5)	36 (25.2)	.257
Obesity	56 (16.2)	15 (10.5)	.132
History of stroke/TIA	33 (9.6)	22 (15.4)	.064
Thrombophilia	43 (12.5)	21 (14.7)	.642
Migraine	41 (11.9)	24 (16.8)	.147
Alcohol consumption	31 (9)	8 (5.6)	.28
Use of toxic substances	21 (6.1)	2 (1.4)	.026
Physiological stressors	31 (9)	20 (14)	.1
Prior use of antithrombotics	29 (8.4)	22 (15.4)	.022
Thromboembolic disease			
DVT	10 (2.9)	9 (6.3)	.078
PTE	2 (0.6)	2 (1.4)	.336
Predisposition to TED	19 (5.5)	13 (9.1)	.224
NIHSS score, mean (SD)	2.94 (4.75)	3.74 (5.33)	.89
Median (Q_1-Q_3)	1 (0-3)	2 (0-5)	
Echocardiography findings			
High-risk PFO	155 (44.9)	109 (76.2)	<.001
Atrial septal aneurysm	73 (21.2)	54 (37.8)	<.001
Embryonic remnants	13 (3.8)	13 (9.1)	.017
Embolic pattern	194 (56.2)	96 (67.1)	.067
Paradoxical embolism	24 (7)	23 (16.1)	.002
RoPE score > 7	157 (45.5)	73 (51)	.264

Data are presented as number and percentage unless otherwise indicated.
DVT: deep vein thrombosis; NIHSS: National Institute of Health stroke scale; Q_1-Q_3: quartiles 1 and 3; PFO: patent foramen ovale; PTE: pulmonary thromboembolism; RoPE: Risk of Paradoxical Embolism scale; SD: standard deviation; TED: thromboembolic disease; TIA: transient ischaemic attack.

Table 3 Multivariate analysis for establishing predictors of indication of percutaneous closure in patients ≤ 60 years of age.

	OR	95% CI	*P*
Diabetes mellitus	0.23	0.05-1.06	.061
Prior use of antithrombotics	2.67	1.38-5.18	.004
History of deep vein thrombosis	1.06	0.35-3.23	.914
High-risk PFO	4.11	2.60-6.5	< .001
Paradoxical embolism	2.61	1.28-5.28	.008

95% CI: 95% confidence interval; OR: odds ratio; PFO: patent foramen ovale.

Table 4 Variables associated with indication of percutaneous closure in patients > 60 years of age.

N = 124	No PFO closure (*n* = 100)	PFO closure (*n* = 24)	*P*
Age in years, mean (SD)	70.07 (6.63)	69 (5.14)	.462
Clinical data			
Female sex	51 (51)	11 (45.8)	.649
Hypertension	42 (42)	15 (62.5)	.070
Diabetes mellitus	13 (13)	3 (12.5)	.948
Hyperlipidaemia	44 (44)	11 (45.8)	.535
Tobacco use	10 (10)	2 (8.3)	.660
Obesity	25 (25)	3 (11.5)	.148
Stroke	23 (23)	10 (41.7)	.063
Ischaemic heart disease	11 (11)	1 (4.2)	.131
Thrombophilia	8 (8)/49	3 (12.5)/15	.464
Migraine	6 (6)	3 (12.5)	.240
Physiological stressors	8 (8)	2 (8.3)	.614
Prior use of antithrombotics	27 (27)	8 (33.3)	.536
Thromboembolic disease			
DVT	8 (8)	1 (4.2)	.449
PTE	4 (4)	5 (20.8)	.013
Predisposition to TED	11 (11)	8 (33.3)	.006
NIHSS score, mean (SD)	4.76 (6.08)	6.58 (6.87)	.20
Median (Q_1-Q_3)	2 (1-6.5)	4 (2-10)	.111
Echocardiography findings			
High-risk PFO	57 (57)	24 (100)	.000
Atrial septal aneurysm	30 (30)	15 (62.5)	.012
Embryonic remnants	4 (4)	3 (12.5)	.131
Embolic pattern	59 (59)	17 (70.8)	.490
Paradoxical embolism	15 (15)	8 (33.3)	.038

Data are presented as number and percentage unless otherwise indicated.
Multivariate analysis was not performed in the group of patients aged > 60 years as stepwise regression halts due to the magnitude of the effect of the variable high-risk PFO.
DVT: deep vein thrombosis; NIHSS: National Institutes of Health Stroke Scale; PFO: patent foramen ovale; PTE: pulmonary thromboembolism; Q_1-Q_3: quartiles 1 and 3; SD: standard deviation; TED: thromboembolic disease.

in view of the distinct characteristics of stroke associated with PFO (prevalence, heterogeneity, level of evidence for indicating percutaneous closure), treatment guidelines and position statements promote the development of prospective registries aimed at understanding real clinical practice.

The main findings of our cooperative registry are as follows:

1) The most relevant factor for indicating percutaneous closure is ultrasound evidence of high-risk PFO.
2) In patients aged $\leq$ 60 years, percutaneous closure may be indicated in the event of paradoxical embolism or history of antithrombotic therapy.
3) In patients older than 60 years, history of thromboembolic disease constitutes an important factor in deciding whether to indicate percutaneous closure.
4) Patients with TIA and no lesions on neuroimaging may benefit from percutaneous closure if they present high-risk PFO.
5) Percutaneous closure was also indicated to some patients with low-risk PFO, although we were unable to identify variables clearly associated with that decision.
6) The rate of stroke recurrence was low, with a slightly higher rate among older individuals.

Presence of atrial septal aneurysm, embryonic remnants (Chiari network, Eustachian valve), or severe shunt has been associated with PFO as the causal agent of cryptogenic stroke.[31–35] Numerous studies support this association.[32–36] Two clinical trials reporting positive results only included patients with severe shunt or aneurysm; therefore, the benefit of percutaneous closure as compared to medical treatment was greater in these patients.[11,12] Furthermore, the notion that PFO with mild or moderate shunts may also be associated with increased risk of recurrence has been confirmed in cooperative observational studies.[37,38]

Treatment guidelines and reports from medical societies have underscored the potential benefit of PFO closure in patients with large shunts, indicating that the procedure is less beneficial in patients with small shunts.[18,19]

Our registry confirms that high-risk PFO is the main indication for percutaneous closure. We analysed the indication of percutaneous closure in patients older than 60 years. Recent studies have found age to be a decisive factor in the risk of stroke recurrence in patients with cryptogenic stroke associated with PFO, and that this increased risk cannot be attributed exclusively to the greater burden of cerebrovascular risk factors associated with ageing.[39,40] This points to the need for clinical trials including patients from these age groups. According to our results, patients aged > 60 years not only presented more risk factors but also showed greater prevalence of predisposition to thromboembolic disease, diagnostic criteria for paradoxical embolism, and high-risk PFO. This represents a challenge for patient selection, but at the same time makes percutaneous closure a reasonable, justified option for stroke prevention. This age group also presents a higher rate of recurrence and is more likely to develop adverse events, which are nonetheless acceptable for this indication.

Other groups of clinical interest, such as patients with TIA or those aged 61-69 years, were also analysed. Patients with TIA and no

Table 5 Variables associated with indication of percutaneous closure in patients with transient ischaemic attack.

N = 76	No PFO closure (*n* = 57)	PFO closure (*n* = 19)	*P*
Age, mean (SD)	48.60 (10.72)	50.89 (7.25)	.38
Clinical data			
Female sex	30 (52.6)	9 (47.4)	.69
Hypertension	15 (26.3)	2 (10.5)	.131
Diabetes mellitus	2 (3.5)	0 (0)	.560
Dyslipidaemia	16 (28)	5 (26.3)	.327
History of stroke/TIA	5 (8.8)	3 (15.8)	.317
Active smoking	13 (22.8)	6 (31.6)	.478
Use of toxic substances	1 (1.8)	1 (5.3)	.151
Migraine	8 (14)	0 (0)	.08
Obesity	9 (15.8)	2 (10.5)	.444
Prior use of antithrombotics	6 (10.5)	4 (21.1)	.211
Physiological stressors	4 (7)	1 (5.3)	.633
Thrombophilia/thrombophilia testing	5 (8.8)/25	3 (15.8)/14	.561
RoPE score > 7	20 (35.1)	3 (15.8)	.094
TED			
DVT	0 (0)	1 (5.3)	.15
PTE	1 (5.3)	0 (0)	.750
Predisposition to TED	6 (10.5)	2 (10.5)	.683
Paradoxical embolism	3 (5.3)	3 (15.8)	.161
Echocardiography findings			
High-risk PFO	26 (45.6)	15 (78.9)	.012
Large shunt	24 (42.1)	13 (68.4)	.047
Atrial septal aneurysm	13 (22.8)	11 (57.9)	.013

Data are presented as number and percentage unless otherwise indicated.
DVT: deep vein thrombosis; PFO: patent foramen ovale; PTE: pulmonary thromboembolism; RoPE: Risk of Paradoxical Embolism scale; SD: standard deviation; TED: thromboembolic disease; TIA: transient ischaemic attack.

Table 6 Patient follow-up, recurrence of cerebrovascular events, and complications, by treatment and age.

	PFO closure	No PFO closure	*P*	≤ 60 years	> 60 years	*P*
Recurrence, n (%)	2 (1.2)	12 (2.7)	NS	6 (1.6)	8 (4.8)	.033
Major periprocedural complications	PTE (1)			PTE (1)	Cardiac perforation (1)	
Minor periprocedural complications				Transient AF (2) Puncture-site haematoma without clinical repercussion (8)		
Late complications					AF (1)	

AF: atrial fibrillation; NS: not significant; PFO: patent foramen ovale; PTE: pulmonary thromboembolism.

neuroimaging lesions were excluded from clinical trials; therefore, treatment recommendations are based on data from these studies and excluding stroke mimics. The interest of studying patients aged 61-69 years lies in the fact that this group shows a lower prevalence of atherothrombotic or cardioembolic disease. In these 2 groups, the main factor for indicating percutaneous closure was detection of high-risk PFO. Among patients aged 61-69 years, history of or predisposition to venous thromboembolism was also associated with indication of percutaneous closure.

Follow-up data support the efficacy and safety of the technique in our centres. Rates of stroke recurrence are low, with similar frequencies to those reported in observational studies and clinical trials.[3]

Time from stroke to percutaneous closure is a variable of practical interest. The median time of 133 days reflects the current management of these patients: complete aetiological study, presentation of results to cardiology-neurology committees, and waiting time until the procedure.

This study presents the limitations inherent to observational multicentre registries. Firstly, data collection is complex in clinical practice, and may cause variability in the interpretation of some studies (anatomical data from a cardiac ultrasound, neuroimaging patterns of brain lesions, etc), which may introduce bias in patient classification. Other limitations include the small size of the sample and the short follow-up period. A larger sample size may have achieved greater validity for specific groups (>60 years, TIA, and low-risk PFO). Furthermore, the follow-up period should have been longer due to the low rate of recurrence of stroke associated with PFO. However, considering that stroke associated with PFO is a major health problem requiring appropriate secondary prevention, our registry provides useful information about the applicability of current recommendations and the use of percutaneous closure in our centres, which may be of interest for the purpose of com-

parison with other centres, as well as for resource planning and management.

Conclusions

In clinical practice, the main factor for indicating percutaneous closure in patients with cryptogenic stroke associated with PFO is the detection of high-risk PFO (large shunt or interatrial septal aneurysm). Other important factors include history of thromboembolic disease, meeting criteria for paradoxical embolism, and prior use of antithrombotics.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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