Percutaneous PFO closure for cryptogenic stroke in the setting of a systematic cardiac and neurological screening and a standardised follow-up protocol

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ABSTRACT
Background: There are no uniform workup and follow-up (FU) protocols for patients presenting with cryptogenic embolism (CE) who undergo percutaneous closure of a patent foramen ovale (PFO).
Methods: We prospectively performed a systematic cardiac and neurological FU protocol in all patients who underwent percutaneous PFO closure in order to assess the incidence of subsequent cardiac and neurological adverse events. All patients received dual antiplatelet therapy for 6 months and were systematically included in a 12-month standardised FU protocol including: clinical evaluation—transthoracic and transoesophageal echocardiography, 24-hour Holter monitoring and/or 1-week R-test, and transcranial Doppler. Late FU (>12 months) was performed by reviewing medical records.
Results: Over a 10-year period, 221 consecutive patients underwent PFO closure for CE and 217 of them (98%) completed the 12-month FU. Ischaemic event recurrence at 12-month and late FU (mean time 69±35 months, median time 65 months, Q1:38 months, Q3:98 months) was observed in 6 (2.8%) and 3 patients (1.4%), respectively. The initial diagnosis of CE was reconsidered in 17 cases (7.8%), as the clinical and paraclinical FU exams showed possible alternative aetiologies for the initial event: 13 patients (6.0%) presented at least 1 episode of atrial fibrillation, while in 4 cases (1.8%) a non-ischaemic origin of the initial symptoms was identified.
Conclusions: Alternative diagnoses explaining the initial symptoms are rarely detected with an in-depth screening for alternative diagnoses before PFO closure. Despite extensive screening, atrial fibrillation is the most frequently observed alternative aetiology for cryptogenic stroke.

INTRODUCTION
Cryptogenic embolism, the most frequent presentation being cryptogenic stroke, is diagnosed in the absence of alternative

KEY QUESTIONS
What is already known about this subject?
► There are no uniform workup and follow-up (FU) protocols for patients presenting with cryptogenic embolism (CE) who undergo successful percutaneous closure of a patent foramen ovale (PFO).
What does this study add?
► This study outlines our own centre’s experience in percutaneous PFO closure using a standardised cardiac and neurological assessment programme and strict FU protocol. The aim of this prospective study was to report the incidence of recurrent embolic events in the first 12 months and at late FU and to assess whether at FU alternative causes emerged for the index embolic event. We showed that alternative diagnoses explaining the initial clinical presentation are rarely detected with an in-depth screening before PFO closure, a multidisciplinary consensus for device closure and a meticulous FU programme in the first year after the procedure. However, despite our meticulous arrhythmia screening algorithm, we found a new onset of atrial fibrillation (AF) during FU in ∼3% of the cohort when excluding potential procedure-related AF.

How might this impact on clinical practice?
► In patients without any ischaemic lesions on the initial MRI, an indication for PFO closure should be reserved, and if proposed it should only be considered for selected patients with clinical elements strongly in favour of paradoxical embolisation through the PFO, and following multidisciplinary team discussions in order to keep the rate of alternative diagnosis as low as possible. In addition, extensive screening of alternative diagnoses to CE and multidisciplinary agreement on PFO closure should be embraced in all centres dealing with such patients. Finally, systematic FU should be performed at least during the first year after percutaneous PFO closure.
explanations for the ischaemic event after extensive neurological, vascular, cardiac workup and blood tests for coagulopathy. Among patients with cryptogenic stroke, the prevalence of patent foramen ovale (PFO) or small atrial septal defect (ASD) is higher compared with patients presenting with a stroke of known origin.10 Device closure for ASD is recommended in the European Guidelines (class IIa, C) for patients with a suspected paradoxical embolism after exclusion of other causes.2

With respect to PFO, despite the fact that several anatomical characteristics (eg, large PFO, associated atrial septal aneurysm, important right-to-left shunt at rest) have been associated with a higher stroke recurrence rate,3 until now it remains to be elucidated which patients may benefit most from device closure. Three randomised controlled trials comparing device closure with antithrombotic treatment (with antiplatelet agents or anticoagulants) were not conclusive for the superiority of one strategy over another in terms of reduction of stroke recurrence.4-6 Although more than 20 years have passed since the first percutaneous closure in 1992,9 recommendations regarding optimal workup for patients with cryptogenic embolism as well as follow-up (FU) after percutaneous PFO closure are lacking.7-10

We report the results of a prospective standardised screening and FU programme performed at a single tertiary academic centre in consecutive patients presenting with cryptogenic embolism, in whom the PFO/ small ASD was deemed to be responsible for the embolic event by a multidisciplinary team and successfully closed using a percutaneous approach. The aim of this prospective study was to report the incidence of recurrent embolic events in the first 12 months and at late FU and to assess whether alternative causes for the index embolic events emerged at FU despite extensive initial workup.

MATERIAL AND METHODS

From December 2001 to November 2011, all patients presenting with a suspected cryptogenic embolism (ie, transient ischaemic cerebral attack (TIA), stroke or a peripheral ischaemic event) at our institution underwent extensive neurological, vascular, cardiac by cardiac workup and blood tests for coagulopathy. Patients for whom percutaneous closure was performed, following a paradoxical embolisation through a PFO or a small ASD (considered to be the most likely underlying favouring condition by a multidisciplinary team), were included in the standardised FU protocol. Patients with an indication for ASD closure for haemodynamic reasons were not included.

Investigations to justify PFO closure

In order to establish the diagnosis of cryptogenic stroke, a complete standardised neurological investigation was performed, including a clinical examination, a carotidovertebral duplex ultrasound, transcranial Doppler (TCD) with microbubble injection and a cerebral MRI, as well as extensive screening for infection, inflammatory diseases and coagulation disorders. Finally, a complete cardiac evaluation was performed for all patients, including a protocol to rule out arrhythmia, a transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE). The arrhythmia rule-out protocol included a standard 12-lead ECG at hospital admission, an in-hospital 24-hour 3-lead ECG recording (Holter) (Avia, Del Mar Reynolds Medical Systems) and/or an ambulatory 7-day event-loop-recording (ELR) (R-test evolution, 3rd generation: Novacor Enterprise, Physicor, Geneva, Switzerland) according to previously validated protocols.910 Of note, in patients considered at high risk for atrial fibrillation (AF) (ie, with high blood pressure, atrial dilation, a history of palpitations), we routinely performed two ELR. Finally, all patients were discussed by a multidisciplinary team involving specialists in neurology, cardiology, haemostasis and neuroradiology in order to confirm the absence of any other possible aetiology as the cause of the index ischaemic event.

If the multidisciplinary team confirmed the indication for percutaneous closure and the patient accepted, the PFO/small ASD closure procedure was performed according to standard practice13 and the patients were included in the standardised FU programme.

Study FU protocol

This standardised FU protocol (PFO-HUG (Hôpitaux Universitaires de Genève) study: NCT01149447) was approved by the local ethics committee. The antiplatelet regimen consisted of a loading dose of 200 mg of aspirin (for patients not already treated with aspirin) as well as 300 mg of clopidogrel the day before the procedure, followed by aspirin 100 mg/day and clopidogrel 75 mg/day for 6 months. In patients on oral anticoagulants (at the time of the study exclusively acenocoumarol), the drug was stopped 48 hours prior to the procedure. The FU protocol consisted of a chest X-ray at day 1 postprocedure, 7-day ELR in the days following the procedure, and complete cardiological and neurological clinical evaluation at 6 and 12 months, including TTE, TEE, TCD and a 7-day ELR. The 12-month TEE examination was not routinely performed in all patients, but only if judged necessary on a clinical basis or if indicated following the results of the scheduled 6-month FU examination. A 7-day ELR was performed when there was the slightest suspicion of arrhythmia up to 2005 and routinely postprocedure and during the first 12 months post-PFO closure from 2006 onwards.

After the 12-month FU visit, patients were not routinely followed. In order to establish a long-term FU of patients, the electronic medical database of our tertiary centre, which is the only stroke centre in the region, was retrospectively analysed. All medical records were reviewed for death and any recurrent neurological or cardiovascular events up to December 2012, and all events were included in the study’s database.

Statistical analysis

The data are expressed as means and SD or IQR for continuous variables and as numbers and percentages
for categorical variables. We excluded 4 (1.8%) patients from the analysis who did not complete the prospective FU at 12 months post-PFO closure.

RESULTS
Out of the 221 consecutive patients who were treated by percutaneous PFO or small ASD closure for a cryptogenic event at our institution between December 2001 and November 2011, the final analyses were performed on the 217 patients (98%) who completed the 12-month FU. Table 1 shows the study population characteristics, cardiovascular risk factors, the numbers of stroke or TIA or peripheral embolism and the medical treatment before PFO closure. Table 2 summarises the characteristics of the anatomical right-to-left shunt responsible for the paradoxical embolism. PFO was present in the majority of cases (210, 96.7%), while in the remaining seven cases (3.2%) the ischaemic event was related to a small ASD. During the study period, the mean annual rate of PFO/small ASD closure for cryptogenic embolism at our institution was 22±10. The median time interval between the initial event and the PFO closure was 208 days (IQR 80–208).

Long-term FU information concerning the neurological and cardiological adverse events was available in 213 (98.2%) of the cohort and only 4 (1.8%) patients were lost to FU beyond 1 year.

Residual shunt
Complete PFO closure (ie, no residual shunt) and effective PFO closure (ie, no or mild residual shunt) at 12 months were observed in 152 (70%) and 197 (91%) patients, respectively. None of the 217 followed patients required a second percutaneous or surgical intervention in order to definitively close the PFO.

Recurrent ischaemic events
We recorded a total of nine (4.1%) recurrent ischaemic events at a median time of 580 days (Q1: 170, Q3: 420 days) after PFO closure. All were neurological events and four of them (1.8%) were associated with new ischaemic brain lesions on MRI. In six cases (2.8%), the recurrence occurred in the first year (at 92, 139, 170, 184, 190 and 358 days after PFO closure) and in three cases (1.4%) at late FU (at 420, 800 and 2866 days after PFO closure). Table 3 shows the details of the recurrent events, highlighting the fact that in all these patients but one only a mild residual right-to-left shunt was detected at echocardiography during Valsalva manoeuvre. Indeed, most of these events might not be related to the PFO closure: in two patients older than 65 years (one with a small ASD closure), AF was suspected to be the cause of TIA, in one patient worsening language difficulties were attributed to side effects of anti-epileptic drugs, and one patient had intense headache in the context of lupus disease, but with no new lesions at the MRI, while one patient receiving aspirin and clopidogrel had a haemorrhagic transformation 10 days post-PFO closure and 17 days post the initial stroke.

Other cardiac/neurological entities
During the scheduled FU visits (ie, ≤12 months) and at late FU (ie, >12 months), the initial diagnosis of a cryptogenic ischaemic event was systematically reviewed by the same multidisciplinary team, and in 17 cases (7.8%) alternative potential causes of the initial symptoms were identified.

Of these 17 patients, 13 (6.0%) manifested evidence of episodes of AF, which were detected during the

| Table 1 | Population characteristics, cardiovascular risk factors and medical treatment before PFO closure |
|---------|-------------------------------------------------------------------------------------------------|
| Patients’ characteristics (n=217) | n (%) |
| Age (years) (mean±SD) | 49±12 |
| Male gender | 121 (55.8) |
| Dyslipidaemia | 74 (34.0) |
| Smoking: current or history | 69 (31.8) |
| Arterial hypertension | 46 (21.2) |
| Diabetes mellitus | 8 (3.7) |
| Stroke before PFO closure | 171 (78.8) |
| TIA before PFO closure | 42 (19.4) |
| Peripheral embolism | 4 (1.8) |

| Antithrombotic treatment before PFO closure (n=217) | n (%) |
|-----------------------------------------------------|-------|
| No treatment | 19 (8.8) |
| Aspirin alone | 32 (14.7) |
| Clopidogrel alone | 4 (1.8) |
| Oral anticoagulation | 152 (70.0) |
| Low-molecular-weight heparin | 11 (5.0) |
| Aspirin and clopidogrel | 17 (7.8) |
| Oral anticoagulation+aspirin or clopidogrel | 9 (4.1) |

Data are presented as n (%), unless otherwise indicated. PFO, patent foramen ovale; TIA, transient ischaemic attack.

| Table 2 | Characteristics of shunts, devices and residual shunts after closure |
|---------|-------------------------------------------------------------------|
| Anatomical shunt type (n=217) | n (%) |
| ASD | 7 (3.2) |
| PFO | 210 (96.7) |

| Type of device (n=217) | n (%) |
|------------------------|-------|
| Amplatzer PFO Occluder | 192 (88) |
| Amplatzer Septal Occluder | 6 (2.8) |
| Biostar | 8 (3.7) |
| CardioStar | 15 (6.9) |
| Premere | 2 (0.8) |

| Residual shunt at 1 year* (n=217) | n (%) |
|-------------------------------|-------|
| No residual shunt | 152 (70.1) |
| Mild residual shunt | 45 (20.7) |
| Moderate/important residual shunt | 20 (9.2) |

Data are presented as n (%). ASA, atrial septal aneurysm; ASD, atrial septal defect; PFO, patent foramen ovale.
was challenged and revised because of the diagnosis of cryptogenic stroke (two strokes and two cases (1.8% of the global cohort) in which the initial cardiac symptoms were detected at late FU due to associated three (23.1% of the AF episodes, 1.4% of the global cohort) were detected at 1 year. The remaining potentially in relation to periprocedural atrial irritation, the early postprocedural phase (ie, <48 hours), thus the AF episodes, 2.8% of the global cohort) occurred in late FU (>12 months). Six of the AF episodes (46% of the total number of patients with AF episode after PFO closure n (%) 13 (6.0) Stroke as initial diagnosis in AF at late follow-up 2/3 (66.7) TIA as initial diagnosis in AF at late follow-up 1/3 (33.3) Stroke or TIA recurrence after PFO closure n (%) 9 (4.1) New ischaemic lesion at MRI 4 (1.8) Days between PFO closure and cerebral recurrence (mean±SD) 294±233 Mild residual shunt at Valsalva in patients with recurrence 8 (88.9) Data are presented as n (%), unless otherwise indicated. AF, atrial fibrillation; PFO, patent foramen ovale; TIA, transient ischaemic attack.

Table 3 Characteristics of AF episode and neurological events post-PFO closure

scheduled 7-day ELR (at day 1, and 6–12 months) and at late FU (>12 months). Six of the AF episodes (46% of the AF episodes, 2.8% of the global cohort) occurred in the early postprocedural phase (ie, <48 hours), thus potentially in relation to periprocedural atrial irritation, while four (23.5% of the AF episodes, 1.8% of the global cohort) were detected at 1 year. The remaining three (23.1% of the AF episodes, 1.4% of the global cohort) were detected at late FU due to associated cardiac symptoms.

Furthermore, as shown in table 4, we identified four cases (1.8% of the global cohort) in which the initial diagnosis of cryptogenic stroke (two strokes and two TIA) was challenged and revised because of the presence of other non-ischaemic entities which better explained the patients’ initial symptoms. Indeed, the clinical and paraclinical FU examinations confirmed the presence of two cases of cerebral multiple sclerosis, one case of peripheral lesions of the cochlear-vestibular system and one case of optic neuritis. In all four patients, no clinical or paraclinical signs for these diagnoses were present during the index hospitalisation for the presumed ‘ischaemic’ event, or at the time of the closure procedure.

**DISCUSSION**

Our single centre prospective registry on percutaneous PFO closure using standardised extensive screening and FU protocols as well as multidisciplinary consensus for the percutaneous closure showed that at FU, up to 7.8% of patients may in fact have another underlying aetiology which could be responsible for the initial event. This observation raises several questions: Was the PFO really implicated in the initial ischaemic event? Were these other possible aetiologies pre-existing and simply misdiagnosed? Or were they secondary to the PFO closure procedure or induced by the PFO device itself? Indeed, cerebral or peripheral ischaemic events due to paradoxical embolism are frequently suspected, especially in the absence of other plausible ischaemic aetiologies, although direct visualisation of thrombus migration through the PFO has only been rarely reported.15–17 Before considering an ischaemic stroke as cryptogenic and especially before planning PFO closure, a multidisciplinary team should systematically and conclusively rule out all other possible aetiologies.

Considering that in our series the most frequently observed alternative aetiology for cryptogenic stroke was the presence of paroxysmal AF, the use of currently available new-generation insertable cardiac monitors (ICM) may be an option to increase the detection of silent AF. Indeed, in 2014, the randomised controlled Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL-AF) trial showed the superiority of ICM compared with conventional FU for the detection of AF after cryptogenic stroke.18 The detection rate of AF in the CRYSTAL-AF population with a mean age of 61.6±11.4 years—a cohort older than our series which has a mean age of 49 ±12 years—was 8.9% in the ICM group versus 1.4% in the conventional group at 6 months and 12.4% compared with 2%, respectively at 12 months. Importantly, in the CRYSTAL-AF trial, nearly three quarters of AF episodes were asymptomatic. Nevertheless, implanting an ICM increases the cost and is more invasive (2.5% of retrieval mainly because of infection or pain) than ELR and at the time of our study the ICM devices were bigger than the latest generation used in the CRYSTAL-AF trial. Indeed, the 2016 guidelines from the European Society of Cardiology on AF, for patients with TIA or ischaemic stroke, recommend screening for AF
by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours (class I, level of evidence B) and that long-term non-invasive ECG monitoring or implanted loop recorders should be considered to document silent atrial AF in patients with stroke (class IIa, level of evidence C).19

The presence of AF after percutaneous PFO closure is reported in the majority of PFO closure series.13–20,23 and this arrhythmia may be observed in up to 15% of patients older than 55 years when a 7-day ELR is performed at 3 and 6 months postprocedure.20 Of note, the type of device used may play a role in the risk of postprocedural AF. Indeed, according to the three randomised trials, the use of the Starflex (NMT Medical, USA) device in the Closure trial was associated with a significant increase in postprocedural AF, while in the Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism (PC-trial) and Randomized Evaluation of recurrent Stroke comparing PFO closure to Established Current standard of care Treatment (RESPECT) trials the incidence of postprocedural AF was similar in the medical groups and the device groups which used the Amplatzer PFO Occluder (St Jude Medical, USA).3–8 In our series, 6% of the patients followed presented at least one episode of AF after PFO closure, despite the fact that we used the Amplatzer PFO Occluder in approximately 90% of the procedures.

Slightly less than half of the AF cases were periprocedural AF (ie, <48 h post-PFO closure). The potential causes for these episodes may have been atrial irritation during the closure intervention (ie, catheter manipulation) or the device itself. When we exclude these cases of periprocedural AF, we encountered 1.8% of patients with reported AF episodes occurring up to the 12-month FU, and a further 1.5% reported AF episodes at late FU. The initial diagnosis of ischaemic cryptogenic stroke was finally rejected only in four cases (1.8%), suggesting that our prescreening assessment was useful. Importantly, in these four patients, the suspicion of cryptogenic stroke was based on clinical findings (ie, no specific ischaemic lesions at cerebral MRI) and it was only during FU of these patients that new specific findings (eg, lesions at MRI compatible with multiple sclerosis) were detected.

**Clinical consequences**

Our series suggests that with an in-depth workup and a multidisciplinary indication for PFO closure, the rate of alternative diagnoses is low even with an extensive search (ie, R-test for AF postprocedure). Nevertheless, alternative diagnoses may still be unmasked in the FU post-PFO closure, especially when no specific ischaemic lesions are detected on the initial MRI assessment. Indeed, in 1.8% of our patients, the initial symptoms were not ischaemic, but secondary to other neurological (ie, multiple sclerosis) or peripheral diseases (ie, optic neuritis, inner ear disease). Therefore, these findings encourage the application of the exclusion criteria of the RESPECT trial,7 namely exclusion of patients with only a TIA or with a lacunar stroke probably related to intrinsic cerebral small-vessel disease, in clinical practice.

Furthermore, despite our meticulous arrhythmia screening algorithm including at least one ECG, one 24-hour Holter monitoring and/or one 7-day ELR, we found new onset of AF during FU in ∼3% of the cohort when excluding potential procedure-related AF. This AF incidence is lower or comparable with the majority of reported PFO series,6–9,13–21,23 even when we consider the series with a specific AF screening following PFO closure (7-day ELRs performed at 3 and 6 months postprocedure).20

The fact that only 2/3 of our patients had a complete PFO closure at 12 months was probably due to the high sensitivity of combining TTE and TEE with TCD detecting a single bubble passage through the PFO device, but the effective PFO closure (ie, no or minimal residual shunt) rate was 91%, which is similar to the recently published randomised trial using the Amplatzer device6–7 that was used in 88% (192 patients) of our procedures.

The major strength of the study is that we performed a standardised and meticulous screening before PFO closure, a multidisciplinary consensus with respect to the appropriateness of PFO closure was obtained, and a strict FU examination programme was carried out for all included patients up to 1 year. The major limitation of the present study is that the prospective FU was limited to the first 12 months postprocedure. We may have under-reported long-term events, especially minor events, since the patients were not prospectively followed beyond 1 year. However, our tertiary centre is the reference centre for all the suspected neurological events in the region and longer term FU was retrospectively performed by reviewing all patient records. We may have underdetected paroxysmal AF already present before the PFO closure considering the superiority of ICM compared with conventional FU for the detection of AF after cryptogenic stroke. Finally, we cannot exclude that the postprocedural investigations will provide the same detection rate of events with or without PFO closure in this population. Indeed, PFO closure can only reduce the risk for recurrent strokes caused by paradoxical embolism and as patients age during the FU, we can expect an increase in non-cryptogenic strokes as shown in the extended FU of the RESPECT trial presented at the Transcatheter Cardiovascular Therapeutics (TCT) meeting in 2015.24

In conclusion, our study suggests that alternative diagnoses explaining the initial symptoms are rarely detected with an in-depth screening before PFO closure, a multidisciplinary consensus for device closure, and a meticulous FU programme in the first year after the procedure. In patients without any ischaemic lesions on the initial MRI, an indication for PFO closure should be reserved, and if proposed it should only be considered for selected patients with clinical elements strongly in favour of paradoxical embolisation through the PFO, and
following multidisciplinary team discussions in order to keep the rate of alternative diagnosis as low as possible. Finally, extensive screening of alternative diagnoses to cryptogenic embolism and multidisciplinary agreement on PFO closure should be embraced in all centres dealing with such patients. Furthermore, systematic FU of patients, at least during the first year after percutaneous PFO closure, should be performed to assess the result of PFO closure (ie, residual shunt, thrombus formation on the device, look for rare cases of erosions of adjacent cardiac structures). When there is the slightest suspicion of paroxysmal arrhythmia, ELR should be performed at any time point of FU.

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