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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2023-074584 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 11-Apr-2023 |
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| Keywords: | Stroke < NEUROLOGY, Pacing & electrophysiology < CARDIOLOGY, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS |
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# Incidence of Atrial Fibrillation in cryptogenic stroke with Patent Foramen Ovale closure: Protocol for the prospective, observational PFO-AF study

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## ABSTRACT

**Introduction**: After closure of patent foramen ovale (PFO) due to stroke risk, atrial fibrillation (AF) occurs in up to one in five patients. However, data are sparse regarding the possible pre-existence of AF in these patients prior to PFO closure, and about recurrence of AF in the long term after the procedure. No prospective study to date has investigated these topics in patients with implanted cardiac monitor (ICM). The PFO-AF study (registered with ClinicalTrials.gov under the number NCT04926142) will investigate the incidence of AF as measured by ICM up to 2 months after percutaneous PFO closure due to stroke. Secondary objectives are to assess incidence and burden of AF in the 2 months prior to, and up to 2 years after PFO closure.

**Methods & Analysis**: Prospective, multicentre, observational study that will include 250 patients with an indication for PFO closure after stroke, as decided by interdisciplinary meetings with cardiologists and neurologists. Patients will undergo implantation of a Reveal Linq ® device (Medtronic). Percutaneous PFO closure will be performed 2 months after device implantation. Follow-up will include consultation, ECG, and reading of ICM data at 2, 12 and 24 months after PFO closure. The primary endpoint is occurrence of AF at 2 months, defined as an episode of AF or atrial tachycardia/flutter lasting at least 30 seconds, and recorded by the ICM, and/or any AF or atrial tachycardia/flutter documented on ECG during the first 2 months of follow-up. PFO-AF is a prospective, observation, multicentre study that will assess incidence and burden of AF at 2 months and 2 years after percutaneous PFO closure in patients with ischemic stroke.

**Ethics & Dissemination:** The study was approved by the Ethics Committee "CPP Sud-Méditerranéen III" on 02 June 2021 and registered with ClinicalTrials.gov (NCT04926142). Findings will be presented in national and international congresses and peer-review journals.

**Strengths & Limitations of the Study**

- We use systematic implantation of cardiac monitoring devices to monitor atrial fibrillation after percutaneous closure of patent foramen ovale in patients with cryptogenic stroke.
- Using implantable cardiac monitoring devices, we can detect the true incidence of atrial fibrillation after closure of patent foramen ovale.
- In previous trials and publications, only symptomatic atrial fibrillation could be detected.
- Implantation of the cardiac monitoring devices makes it possible to distinguish between pre-existing atrial fibrillation, and atrial fibrillation triggered by the procedure.

**Keywords:** patent foramen ovale; atrial fibrillation; biomarkers; implantable cardiac monitor, stroke.

## STUDY RATIONALE

In patients with cryptogenic stroke and patent foramen ovale (PFO), the superiority of percutaneous PFO closure over anti-thrombotic therapy has been clearly demonstrated [5, 10, 13, 14, 20-22]. PFO closure is recommended before the age of 65 years, if it is highly likely that the PFO was the cause of the stroke [11, 18]. Other potential causes of stroke should be ruled out, notably atrial fibrillation (AF). The rate of new onset AF reported in clinical trials after PFO closure ranges from 3 to 7.4% [1, 5, 13, 14, 21], and is significantly higher in patients undergoing PFO closure compared to patients receiving medical therapy alone, with an increase in risk of more than 400% [6, 14, 15, 21]. In these same randomized trials, 72% of new-onset AF after PFO closure resolved spontaneously within 45 days [15]. Screening for AF in these studies was predominantly symptom driven, without systematic use of implantable cardiac monitors (ICM). Therefore, it is likely that actual AF rates are undestimated [4, 19].

When systematic external Holter monitoring or ICM devices are used to monitor AF, incidence rises to more than 20% within the first 28 days after PFO closure [3, 7]. However, there is a paucity of reliable data, obtained by the systematic use of ICM, about the incidence of AF after PFO closure, notably whether the AF existed prior to the procedure, and whether AF recurs in the long term after closure. Such data are essential for decision-making about the treatment of AF, particularly the need for anticoagulant therapy. In the absence of recurrent AF, discontinuation of anticoagulant therapy can be considered, whereas recommendations advise that it must not be discontinued if AF persists in these patients with prior stroke [8].

The objective of the PFO-AF Study ("Incidence of Atrial Fibrillation in cryptogenic stroke with Patent Foramen Ovale closure") is therefore to assess the incidence of AF, using ICM, up to 2 months after percutaneous PFO closure due to ischemic stroke.

Secondary objectives are :

- To evaluate the incidence of AF established based on data collected by ICM in the 2 months prior to, and up to 2 years after percutaneous PFO closure.
- To identify the predictors of AF after PFO closure.
- To evaluate the burden of AF established based on data collected by ICM in the 2 months prior to, and at 2, 12 and 24 months after percutaneous PFO closure.
- To assess the relationship between plasma levels of mid-regional pro atrial natriuretic peptide (MR-proANP) and presence of AF at 2 years after percutaneous PFO closure.
- To describe, for all patients and irrespective of the presence of AF, the rate of recurrence of stroke (ischemic or hemorrhagic), major and minor bleeding, and peripheral emboli up to 2 years after percutaneous PFO closure.

## METHODS & ANALYSIS

### Study design

The PFO-AF Study is a prospective, multicentre, observational cohort study involving 4 university hospitals (Besançon, Lyon, Dijon, Strasbourg) and one non-academic general hospital (Annecy) in France.

### Study population and inclusion/exclusion criteria

The study will include patients have suffered from cryptogenic ischemic stroke and in whom an indication for percutaneous PFO closure has been retained. The detailed inclusion and exclusion criteria are given in Table 1. The indication for PFO closure is consensually determined in interdisciplinary meetings between cardiologists and neurologists, as per current guidelines [18]. The causal role of the PFO in the stroke must be evaluated by a full work-up

including transthoracic (TTE) and trans-esophageal (TEE) echocardiography with bubble study, one (or more) cerebral magnetic resonance imaging (MRI) scans, imaging of the cervical arteries, full biology work-up (notably in search of coagulation disorders), sequential ECG and external Holter ECG examinations. This exhaustive set of examinations is designed to rule out the other major causes of stroke, such as atherosclerosis of the large vessels, arterial dissection, other cardio-embolic causes, AF or lacunar stroke with small vessel disease.

**Primary endpoint *(Table 2)***

The primary endpoint is the occurrence of AF, or atrial tachycardia/flutter during the 2 months following percutaneous PFO closure, and defined as any episode of AF or atrial tachycardia/flutter lasting at least 30 seconds, and recorded on the ICM, and/or any episode of AF or atrial tachycardia/flutter documented by ECG [8].

**Secondary endpoints *(Table 2)***

The second endpoints are:

- Occurrence of AF or atrial tachycardia/flutter during the 2 months prior to, and up to 2 years after percutaneous PFO closure, defined as any episode of AF or atrial tachycardia/flutter lasting at least 30 seconds, and recorded on the ICM, and/or any episode of AF or atrial tachycardia/flutter documented by ECG [8].
- Burden of AF (expressed in days, hours and minutes), as recorded in the ICM, during the 2 months prior to, and up to 2, 12 and 24 months after percutaneous PFO closure.
- Plasma levels of MR-proANP as assayed in peripheral venous blood drawn prior to PFO closure.

- Ischemic or hemorrhagic stroke, peripheral emboli documented on imaging (computed tomography (CT) or MRI), major or minor bleeding according to the ISTH classification.

**Implantable cardiac monitors (ICM)**

The ICM device will be implanted at month (M) 0 (Figure 1). Implantation of ICM devices is done during a consultation or in the outpatient unit of the Cardiology department, under local anesthetic. All ICM devices used in the study will be the same, to minimize detection bias for AF between centres. The device used will be the Reveal Linq® (Medtronic). Device parameters will be standardized, as described in the Supplementary Material. Clinical and biological data as well as the patient's medical history will be recorded on the day of device implantation.

**PFO closure procedure**

Percutaneous PFO closure will be scheduled to take place at M2 (i.e. 2 months after ICM implantation (Figure 1). An ECG and reading of the ICM device will be performed in the 24 hours prior to PFO closure. The PFO closure procedure will be performed by the femoral venous approach under local anesthesia with sedation, or under general anesthesia. Procedures performed under local anesthesia will be guided by TTE or TEE micro-probe. The closure device implanted, and its size, are at the discretion of the operator. Procedural and echocardiographic data will be recorded, namely left ventricular ejection fraction; presence or absence of left ventricular hypertrophy, defined as a maximal septal thickness >15mm in diastole; measure of the left atrium in the parasternal long axis view; measure of the left atrial area in the apical 4 chamber view; measure of left atrial strain. The PFO characteristics, including size, type of shunt, presence of inter-atrial septal aneurysm, and presence of

Eustachian valve, will also be recorded. Unfractionated heparin will be used for periprocedural anticoagulation. Patients will be treated for 3 months after the procedure will dual antiplatelet therapy, followed by single antiplatelet therapy in the absence of any indication for anticoagulant therapy.

## MR-proANP measurement

MR-proANP will be measured in peripheral venous blood drawn within 24 hours before the PFO closure procedure. Tubes will be centrifuged and stored at −20°C for later centralized analysis in the Biochemistry Department of the University Hospital of Besancon. MRproANP will be measured using BRAHMS Kryptor Compact Plus kits (Thermo Fisher Diagnostics SAS, Dardilly, France).

## Follow-up

A clinical consultation with ECG and reading of the ICM device will be performed at 2, 12 and 24 months after percutaneous PFO closure, i.e. at 4, 14 and 26 months after implantation of the ICM (Figure). At each follow-up, the occurrence any intercurrent events or of AF will be noted, and the burden of AF will be calculated. Events will be adjudicated by an independent clinical events committee (GS, MB).

Telecardiology monitoring is recommendation in addition to the 3 follow-up consultations, but is not mandatory.

In cases where AF occurs, the management, particularly the anti-thrombotic therapy, is at the discretion of the treating physician, and should comply with current guidelines. Introduction of curative anticoagulation is recommended [8]. If AF occurs between implantation of the ICM and

the percutaneous PFO closure procedure, the closure procedure must be cancelled, and patient's file must be reviewed again in an interdisciplinary cardiology-neurology meeting. A new decision for PFO closure may be taken, based on the new clinical findings, and in line with current guidelines [8, 9, 18] (Figure). If the AF is considered to be responsible for the stroke, curative anticoagulant therapy should be preferred over PFO closure.

## Data coordination

All data management and analysis will be performed centrally at the Cardiology Department at the coordinating center (University Hospital of Besancon, France), where a dedicated team of data managers will be responsible for data collection and monitoring. Computerized checks will be performed to verify the coherence of the data, and queries will be generated in case of inconsistencies. A formal data monitoring process will be overseen by the Clinical Research Management Department (Délégation à la Recherche Clinique et à l'Innovation) of the coordinating center (University Hospital, Besancon, France), who will be responsible for sending independent monitors to each site regularly to monitor files and check data entry.

## Statistical analysis

Quantitative variables will be expressed as mean ± SD for normally distributed variables, and median (interquartiles) for non-normally distributed variables. Categorical variables will be expressed as number (percentage). Quantitative data will be compared using the Student t test or Mann-Whitney U test, and qualitative variables, using the chi square or Fisher's exact test, as appropriate. Determination of the sample size was based on the width of the 2-sided 95% confidence interval (CI). The inclusion of 250 patients will enable estimation of the incidence of atrial fibrillation within 2 months of the procedure with an accuracy of <6.5% (width of the

2-sided 95% CI of 13% using the Wilson method) even if an incidence of 30% (the most conservative hypothesis) is assumed. Kaplan- Meier curve will be used to depict new onset atrial fibrillation. Risk factors for the primary endpoint will be assessed using a logistic regression model. Univariate analysis (P <0.10) will first be performed to select potential explanatory variables, which will subsequently be tested in a multivariate model (stepwise method with entry and retention significance levels of 0.10 and 0.05, respectively) and presented as adjusted odds ratios (aOR) with 95% CIs. All analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

## Patient and Public Involvement

Patients and the public were not involved in the design of the study. Patients were not invited to assess the burden of the intervention or the time required to participate in the research. All patients are informed, via the information leaflet and informed consent form, that they may be informed of the final results of the study. They may exercise this right by contacting the lead physician in their centre.

## Ethics and dissemination

The study was approved for all sites by the Ethics Committee “Comité de Protection des Personnes (CPP) Sud-Méditerranéen III” on 02/06/2021. The study is registered with ClinicalTrials.gov under the number NCT04926142. The results of the study will be presented at national and international congresses, and submitted for publication in international peer-reviewed journals.

## DISCUSSSION

The incidence of AF occurring after percutaneous PFO closure due to ischemic stroke is likely underestimated in randomized trials and literature data, since only symptomatic AF is detected [5, 12-14, 16, 17, 21]. In patients with systematic investigation of possible AF using Holter ECG monitoring or ICMs, the incidence rises to 20.9% in the 28 days following PFO closure [3, 7]. In this context, reliable data from a population of patients with systematic ICM are needed to show the true incidence of AF post-PFO closure in patients with prior stroke, as well as the rate of recurrence in the long term. The present study is thus designed to answer both these questions, by evaluating the incidence of AF using systematic ICM, in the 2 months following closure of PFO in patients with cryptogenic stroke. We will also investigate AF rates up to 2 years after PFO closure, as well as the burden of AF during this period.

Percutaneous PFO closure is indicated in patients aged 18 to 65 years, following ischemic stroke, when it is highly like that the stroke is attributable to the PFO [14, 18, 21]. The imputability of the stroke to the PFO is confirmed by a full clinical, biological and imaging work-up, to rule out other possible causes, notably AF. Despite this exhaustive panel of examinations to rule out the presence of AF, including ECG, telemonitoring or telemetry during hospitalisation, holter ECG and ICM, at least one in five patients presents AF after PFO closure [7]. The incidence of AF in this context is likely underestimated, since no study to date has included a population of patients with systematic ICM implantation. Indeed, it has been demonstrated that ICM is superior to other methods of AF detection, since many episodes of AF are asymptomatic and therefore, prone to go unnoticed [4, 19]. A prospective study including patients who all receive systematic implantation of an ICM will meet a pressing clinical need to evaluate as accurately as possible the true incidence of AF after PFO closure.

Patients undergoing PFO closure are treated with antiplatelet therapy, but this procedure avoids the need for these patients to be anticoagulated for the long-term, with the risks inherent to such therapy. The occurrence of AF after a PFO closure procedure following stroke, in a patients with a CHA2DS2 VASC score of 2 or more, in principle constitutes an indication for anticoagulation [8, 9]. AF is frequent in this context, but seems to occur predominantly in the weeks immediately following the procedure, with few recurrences in the long-term [1, 6, 7, 14, 21]. Robust data showing the true long-term recurrence rate are necessary to guide therapeutic decision-making, in terms of screening, follow-up and especially anticoagulant therapy. Indeed, there are currently no recommendations for this specific clinical situation.

In our study, implanting the ICM 2 months before the PFO closure procedure should enable us to distinguish between pre-existing AF, and post-procedural AF that is truly triggered by the PFO closure procedure. Based on previous data, the hypothesis of post-procedural AF that resolves spontaneously and with low risk of recurrence, seems the most plausible [1, 6, 7, 14, 21], but remains to be verified. Closure device size ≥25 mm has been shown to be an independent predictor AF occurrence [1, 7]. This finding underlines the arrhythmogenic nature of prosthetic devices inserted into the inter-atrial septum, especially when large. The effect is likely mechanical and should diminish over time. Other independent predictors of AF in this context include age, male sex and diabetes [1, 6, 7, 17], all three also known risk factors for AF [8, 9].

We previously showed that plasma levels of MRproANP prior to ablation of AF independently predictor the recurrence of AF at 1 year after the procedure [2]. The ability of this biomarker to stratify risk of AF occurrence, when assayed prior to PFO closure, will also be assessed in the present study.

Our study has some limitations. Firstly, the results of the study will not enable us to draw definitive conclusions regarding the indication (or absence thereof) for curative anticoagulant therapy in the long-term, in this population of patients with prior stroke and presenting AF after

PFO closure. The aim is to assess the true incidence of AF up to 2 years after the closure procedure, and potentially to stratify the risk by identifying independent predictors of AF occurrence. These data will provide valuable insights to guide therapeutic decision-making during management and follow-up. Only a randomized clinical trial, with a sufficient sample size to evaluate ischemic and haemorrhagic events, and comparing 2 strategies, with long-term follow-up could provide a definitive answer. A second limitation is the anticipated inclusion of 250 patients with 2 years of follow-up. While this sample size is sufficient to evaluate the incidence and recurrence of AF, it will not enable us to evaluate the occurrence of ischemic or haemorrhagic events in patients with AF who may require anticoagulant therapy.

## CONCLUSION

The occurrence of AF after percutaneous PFO closure appears to be quite frequent, but there is a paucity of reliable data or recommendations regarding the true incidence, and the appropriate management. The present PFO-AF study aims to assess the incidence of AF, established objectively using ICMs, in the 2 months following percutaneous PFO closure in patients who have suffered cryptogenic stroke. Patients will followed up to 2 years after the procedure to evaluate the rate of recurrence and persistence of AF in the long-term.

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## Authors' Contributions

Study conception and design: M.Badoz., N.M., R.C.; Investigation: M.Badoz., F.D., G.S., M.Besutti, G.R., P.F., C.G., N.M., R.C.; Data curation: M.Badoz, F.D., G.S., M.Besutti, G.R., P.F., C.G.; Statistical analysis plan: M.Badoz, F.E.; N.M., R.C.; Writing protocol – first draft: M.Badoz, F.E., N.M., R.C.; Final protocol – critical revision & approval: M.Badoz., F.D., G.S., M.Besutti, G.R., P.F., C.G., F.E., N.M., R.C.

## Competing Interests

No author has any competing interests to declare.

## Funding:

The study is partially funded by an unrestricted educational grant from Medtronic SAS, and by the University Hospital of Besancon. The funders have no role in the study design, data collection, or interpretation of the results.

## Figure legend

**Figure 1: Flow chart of the design of the PFO-AF study.**

ICM: implantable cardiac monitor, ECG: electrocardiogram, PFO: patent foramen ovale, AF: atrial fibrillation

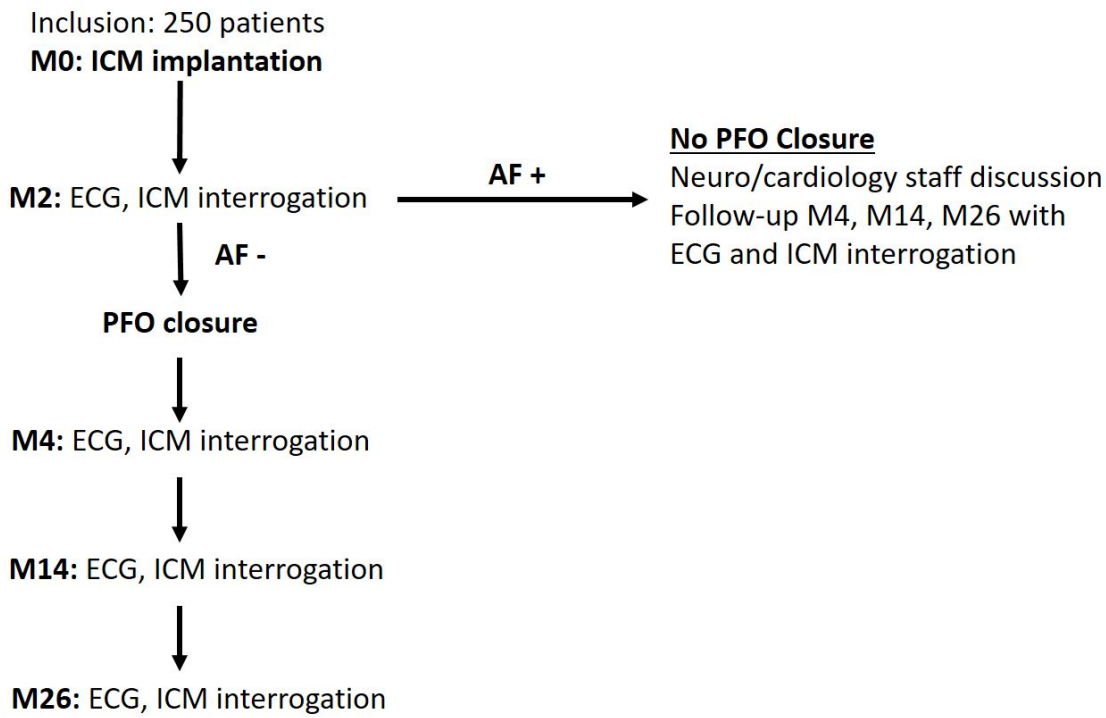
**Table 1. Patient inclusion and exclusion criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Adult patients (aged 18 years or older) | Patients under legal protection of any sort |
| Indication for percutaneous closure of patent foramen ovale due to cryptogenic stroke, validated in an interdisciplinary meeting between cardiologists and neurologists, in compliance with current guidelines. | Patients within the exclusion period of another clinical trial, as noted in the national register of healthcare research volunteers |
| Patients affiliated to a social security system, or beneficiary thereof. | Patients not affiliated to, or beneficiary of any social security system. |
| Written informed consent | |

**Table 2. Primary and Secondary Endpoints of the PFO-AF Study**

| Primary endpoints | Secondary endpoints |
|---|---|
| Any episode of AF or atrial tachycardia/flutter lasting at least 30 seconds, and recorded on the ICM, during the 2 months following percutaneous PFO closure | Any episode of AF or atrial tachycardia/flutter lasting at least 30 seconds, and recorded on the ICM, during the 2 months prior to, and up to 2 years after percutaneous PFO closure |
| **And/or** any episode of AF or atrial tachycardia/flutter documented by ECG during the 2 months following percutaneous PFO closure. | **And/or** any episode of AF or atrial tachycardia/flutter documented by ECG during the 2 months prior to, and up to 2 years after percutaneous PFO closure |
| | Burden of AF (expressed in days, hours and minutes), as recorded in the ICM, during the 2 months prior to, and up to 2, 12 and 24 months after percutaneous PFO closure |
| | Plasma levels of MR-proANP as assayed in peripheral venous blood drawn prior to PFO closure |
| | Ischemic or hemorrhagic stroke, peripheral emboli documented on imaging (computed tomography (CT) or MRI), major or minor bleeding according to the ISTH classification, and up to 2 years after percutaneous PFO closure |

**Figure 1**



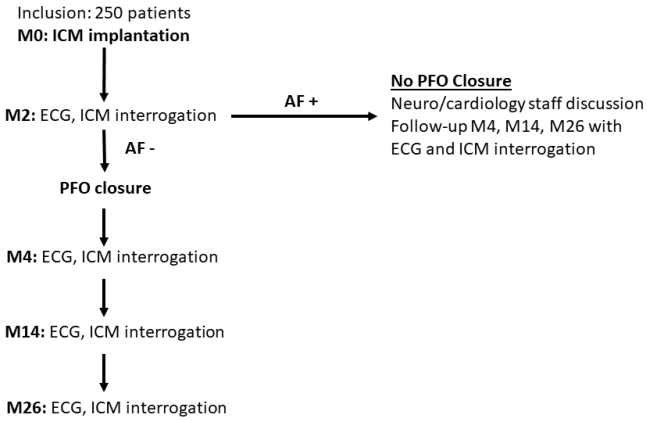



Figure 1

338x190mm (96 x 96 DPI)

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# Incidence of Atrial Fibrillation in cryptogenic stroke with Patent Foramen Ovale closure: Protocol for the prospective, observational PFO-AF study

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2023-074584.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 15-Aug-2023 |
| Complete List of Authors: | Badoz, Marc; Besançon Regional University Hospital Center, Department of Cardiology; Université de Franche-Comté<br>Derimay, François; Hospices Civils de Lyon, Interventional Cardiology<br>Serzian, Guillaume; Besançon Regional University Hospital Center, Department of Cardiology<br>Besutti, Matthieu; Besançon Regional University Hospital Center, Department of Cardiology<br>Rioufol, Gilles; Hospices Civils de Lyon, Interventional Cardiology<br>Frey, Pierre; Centre Hospitalier Annecy Genevois, Department of Cardiology<br>Guenancia, Charles; Centre Hospitalier Universitaire de Dijon<br>Ecarnot, Fiona; Besançon Regional University Hospital Center, Cardiology; Université de Franche-Comté<br>Meneveau, Nicolas; Besançon Regional University Hospital Center, Department of Cardiology; Université de Franche-Comté<br>Chopard, Romain; Besançon Regional University Hospital Center, Department of Cardiology; Université de Franche-Comté |
| Primary Subject Heading: | Cardiovascular medicine |
| Secondary Subject Heading: | Cardiovascular medicine |
| Keywords: | Stroke < NEUROLOGY, Pacing & electrophysiology < CARDIOLOGY, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS |
| | |

# Incidence of Atrial Fibrillation in cryptogenic stroke with Patent Foramen Ovale closure: Protocol for the prospective, observational PFO-AF study

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## ABSTRACT

**Introduction**: After closure of patent foramen ovale (PFO) due to stroke, atrial fibrillation (AF) occurs in up to one in five patients. However, data are sparse regarding the possible pre-existence of AF in these patients prior to PFO closure, and about recurrence of AF in the long term after the procedure. No prospective study to date has investigated these topics in patients with implanted cardiac monitor (ICM). The PFO-AF study (registered with ClinicalTrials.gov under the number NCT04926142) will investigate the incidence of AF occurring within 2 months after percutaneous closure of PFO in patients with prior stroke. AF will identified using systematic ICM. Secondary objectives are to assess incidence and burden of AF in the 2 months prior to, and up to 2 years after PFO closure.

**Methods & Analysis**: Prospective, multicentre, observational study including 250 patients with an indication for PFO closure after stroke, as decided by interdisciplinary meetings with cardiologists and neurologists. Patients will undergo implantation of a Reveal Linq ® device (Medtronic). Percutaneous PFO closure will be performed 2 months after device implantation. Follow-up will include consultation, ECG, and reading of ICM data at 2, 12 and 24 months after PFO closure. The primary endpoint is occurrence of AF at 2 months, defined as an episode of AF or atrial tachycardia/flutter lasting at least 30 seconds, and recorded by the ICM, and/or any AF or atrial tachycardia/flutter documented on ECG during the first 2 months of follow-up.

**Ethics & Dissemination:** The study was approved by the Ethics Committee "CPP Sud-Méditerranéen III" on 02 June 2021 and registered with ClinicalTrials.gov (NCT04926142). Findings will be presented in national and international congresses and peer-review journals.


## Strengths & Limitations of the Study

- PFO-AF is the first prospective, multicentre study to investigate the incidence of AF after PFO closure and using implantable cardiac monitoring devices in all patients
- 2 months of heart rhythm monitoring prior to PFO closure will enable us to detect pre-existing AF
- The planned follow-up period of 2 years will reveal whether AF occurring after PFO closure is transitory or persistent
- The study design and sample size preclude any conclusions regarding the need to initiate therapeutic anticoagulation, in the case of AF occurring post-PFO closure

**Keywords:** patent foramen ovale; atrial fibrillation; biomarkers; implantable cardiac monitor, stroke.

## Introduction

In patients with stroke attributed to patent foramen ovale (PFO), the superiority of percutaneous PFO closure over anti-thrombotic therapy has been clearly demonstrated [1-7]. PFO closure is recommended before the age of 65 years, if it is highly likely that the PFO was the cause of the stroke [8, 9]. Other potential causes of stroke should be ruled out, notably atrial fibrillation (AF). The rate of new onset AF reported in clinical trials after PFO closure ranges from 3 to 7.4% [1, 2, 5, 6, 10], and is significantly higher in patients undergoing PFO closure compared to patients receiving medical therapy alone, with an increase in risk of more than 400% [5, 6, 11-13]. In these same randomized trials, 72% of new-onset AF after PFO closure resolved spontaneously within 45 days [11]. Screening for AF in these studies was predominantly symptom driven, without systematic use of implantable cardiac monitors (ICM). Therefore, it is likely that actual AF rates are underestimated [14, 15].

When systematic external Holter monitoring or ICM devices are used to monitor AF, incidence rises to more than 20% within the first 28 days after PFO closure [16, 17]. However, there is a paucity of reliable data, obtained by the systematic use of ICM, about the incidence of AF after PFO closure, notably whether the AF existed prior to the procedure, and whether AF recurs in the long term after closure. Such data are essential for decision-making about the treatment of AF, particularly the need for anticoagulant therapy. In the absence of recurrent AF, discontinuation of anticoagulant therapy can be considered, whereas recommendations advise that it must not be discontinued if AF persists in these patients with prior stroke [18].

The objective of the PFO-AF Study ("Incidence of Atrial Fibrillation in cryptogenic stroke with Patent Foramen Ovale closure") is therefore to assess the incidence of AF, using ICM, up to 2 months after percutaneous PFO closure due to ischemic stroke.

Secondary objectives are :

- To evaluate the incidence of AF established based on data collected by ICM in the 2 months prior to, and up to 2 years after percutaneous PFO closure.
- To identify the predictors of AF after PFO closure.
- To evaluate the burden of AF established based on data collected by ICM in the 2 months prior to, and at 2, 12 and 24 months after percutaneous PFO closure.
- To assess the relationship between plasma levels of mid-regional pro atrial natriuretic peptide (MR-proANP) and presence of AF at 2 years after percutaneous PFO closure.
- To describe, for all patients and irrespective of the presence of AF, the rate of recurrence of stroke (ischemic or hemorrhagic), major and minor bleeding, and peripheral emboli up to 2 years after percutaneous PFO closure.

## METHODS & ANALYSIS

### Study design

The PFO-AF Study is a prospective, multicentre, observational cohort study involving 4 university hospitals (Besançon, Lyon, Dijon, Strasbourg) and one non-academic general hospital (Annecy) in France.

### Study population and inclusion/exclusion criteria

The study will include patients have suffered from ischemic stroke attributed to PFO and in whom an indication for percutaneous closure has been retained. The detailed inclusion and exclusion criteria are given in Table 1. The indication for PFO closure is consensually determined in interdisciplinary meetings between cardiologists and neurologists, as per current guidelines [9]. The causal role of the PFO in the stroke must be evaluated by a full work-up

including transthoracic (TTE) and trans-esophageal (TEE) echocardiography with bubble study, one (or more) cerebral magnetic resonance imaging (MRI) scans, imaging of the cervical arteries (Doppler ultrasound; magnetic resonance angiography, CT angiography); Doppler ultrasound of the lower limbs (in search of deep vein thrombosis); full biology work-up (notably in search of coagulation disorders (e.g. antithrombin III deficiency, Protein C deficiency, Protein S deficiency, Activated Protein C Resistance, Factor V Leiden mutation, Prothrombin/Factor II 20210GA, anticardiolipin antibodies, lupus anticoagulant, anti-β2-glycoprotein I antibodies), sequential ECG, ECG monitoring during hospitalization in neurology, and external Holter ECG examinations. This exhaustive set of examinations is designed to rule out the other major causes of stroke, such as atherosclerosis of the large vessels, arterial dissection, other cardio-embolic causes, AF or lacunar stroke with small vessel disease.

**Primary endpoint**

The primary and secondary endpoints are detailed in Table 2. The primary endpoint is the occurrence of AF, or atrial tachycardia/flutter during the 2 months following percutaneous PFO closure, and defined as any episode of AF or atrial tachycardia/flutter lasting at least 30 seconds, and recorded on the ICM, and/or any episode of AF or atrial tachycardia/flutter documented by ECG [18].

**Secondary endpoints**

The second endpoints are:

- Occurrence of AF or atrial tachycardia/flutter during the 2 months prior to, and up to 2 years after percutaneous PFO closure, defined as any episode of AF or atrial

tachycardia/flutter lasting at least 30 seconds, and recorded on the ICM, and/or any episode of AF or atrial tachycardia/flutter documented by ECG [18].

- Burden of AF (expressed in days, hours and minutes), as recorded in the ICM, during the 2 months prior to, and up to 2, 12 and 24 months after percutaneous PFO closure.
- Plasma levels of MR-proANP as assayed in peripheral venous blood drawn prior to PFO closure.
- Ischemic or hemorrhagic stroke, peripheral emboli documented on imaging (computed tomography (CT) or MRI), major or minor bleeding according to the ISTH classification.

**Implantable cardiac monitors (ICM)**

The ICM device will be implanted at month (M) 0 (Figure 1), in order to have a two-month "control" period of observation prior to the procedure. Implantation of ICM devices is done during a consultation or in the outpatient unit of the Cardiology department, under local anesthetic. All ICM devices used in the study will be the same, to minimize detection bias for AF between centres. The device used will be the Reveal Linq® (Medtronic). Device parameters will be standardized, as described in the Supplementary Material. Clinical and biological data as well as the patient's medical history will be recorded on the day of device implantation.

**PFO closure procedure**

Percutaneous PFO closure will be scheduled to take place at M2 (i.e. 2 months after ICM implantation (Figure 1), and within 6 months after the qualifying stroke. An ECG and reading of the ICM device will be performed in the 24 hours prior to PFO closure. The PFO closure procedure will be performed by the femoral venous approach under local anesthesia with

sedation, or under general anesthesia. Procedures performed under local anesthesia will be guided by TTE or TEE micro-probe. The closure device implanted, and its size, are at the discretion of the operator. Procedural and echocardiographic data will be recorded, namely left ventricular ejection fraction; presence or absence of left ventricular hypertrophy, defined as a maximal septal thickness >15mm in diastole; measure of the left atrium in the parasternal long axis view; measure of the left atrial area in the apical 4 chamber view; measure of left atrial strain. The PFO characteristics, including size, type of shunt, presence of inter-atrial septal aneurysm, and presence of Eustachian valve, will also be recorded. Unfractionated heparin will be used for periprocedural anticoagulation. Patients will be treated for 3 months after the procedure will dual antiplatelet therapy, followed by single antiplatelet therapy in the absence of any indication for anticoagulant therapy.

**MR-proANP measurement**

MR-proANP will be measured in peripheral venous blood drawn within 24 hours before the PFO closure procedure. Tubes will be centrifuged and stored at −20°C for later centralized analysis in the Biochemistry Department of the University Hospital of Besancon. MRproANP will be measured using BRAHMS Kryptor Compact Plus kits (Thermo Fisher Diagnostics SAS, Dardilly, France).

**Follow-up**

A clinical consultation with ECG and reading of the ICM device will be performed at 2, 12 and 24 months after percutaneous PFO closure, i.e. at 4, 14 and 26 months after implantation of the ICM (Figure). At each follow-up, the occurrence any intercurrent events or of AF will be noted,

and the burden of AF will be calculated. Events will be adjudicated by an independent clinical events committee (GS, MB).

Telecardiology monitoring is recommendation in addition to the 3 follow-up consultations, but is not mandatory.

In cases where AF occurs, the management, particularly the anti-thrombotic therapy, is at the discretion of the treating physician, and should comply with current guidelines. Introduction of curative anticoagulation is recommended [18]. If AF occurs between implantation of the ICM and the percutaneous PFO closure procedure, the closure procedure must be cancelled, and patient's file must be reviewed again in an interdisciplinary cardiology-neurology meeting. A new decision for PFO closure may be taken, based on the new clinical findings, and in line with current guidelines [9, 18, 19] (Figure). If the AF is considered to be responsible for the stroke, therapeutic anticoagulant therapy should be preferred over PFO closure.

## Planned timing

Inclusions began in June 2021, and the last patient was included on 5 July 2023. Follow-up at four months should be completed for all patients (N=250) in November 2024, and final follow-up at 26 months (2 years after PFO closure) by the end of September 2025.

## Data coordination

All data management and analysis will be performed centrally at the Cardiology Department at the coordinating center (University Hospital of Besancon, France), where a dedicated team of data managers will be responsible for data collection and monitoring. Computerized checks will be performed to verify the coherence of the data, and queries will be generated in case of

inconsistencies. A formal data monitoring process will be overseen by the Clinical Research Management Department (Délégation à la Recherche Clinique et à l'Innovation) of the coordinating center (University Hospital, Besancon, France), who will be responsible for sending independent monitors to each site regularly to monitor files and check data entry.

## Statistical analysis

Quantitative variables will be expressed as mean ± SD for normally distributed variables, and median (interquartiles) for non-normally distributed variables. Categorical variables will be expressed as number (percentage). Quantitative data will be compared using the Student t test or Mann-Whitney U test, and qualitative variables, using the chi square or Fisher's exact test, as appropriate. Determination of the sample size was based on the width of the 2-sided 95% confidence interval (CI). The inclusion of 250 patients will enable estimation of the incidence of atrial fibrillation within 2 months of the procedure with an accuracy of <6.5% (width of the 2-sided 95% CI of 13% using the Wilson method) even if an incidence of 30% (the most conservative hypothesis) is assumed. Kaplan- Meier curve will be used to depict new onset atrial fibrillation. Risk factors for the primary endpoint will be assessed using a logistic regression model. Univariate analysis (P <0.10) will first be performed to select potential explanatory variables, which will subsequently be tested in a multivariate model (stepwise method with entry and retention significance levels of 0.10 and 0.05, respectively) and presented as adjusted odds ratios (aOR) with 95% CIs. All analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

## Patient and Public Involvement

Patients and the public were not involved in the design of the study. Patients were not invited to assess the burden of the intervention or the time required to participate in the research. All patients are informed, via the information leaflet and informed consent form, that they may be informed of the final results of the study. They may exercise this right by contacting the lead physician in their centre.

## Ethics and dissemination

The study was approved for all sites by the Ethics Committee "Comité de Protection des Personnes (CPP) Sud-Méditerranéen III" on 02/06/2021. The study is registered with ClinicalTrials.gov under the number NCT04926142. The results of the study will be presented at national and international congresses, and submitted for publication in international peer-reviewed journals.

## DISCUSSSION

The incidence of AF occurring after percutaneous PFO closure due to ischemic stroke is likely underestimated in randomized trials and literature data, since only symptomatic AF is detected [1, 2, 5, 6, 20-22]. In patients with systematic investigation of possible AF using Holter ECG monitoring or ICMs, the incidence rises to 20.9% in the 28 days following PFO closure [16, 17]. In this context, reliable data from a population of patients with systematic ICM are needed to show the true incidence of AF post-PFO closure in patients with prior stroke, as well as the rate of recurrence in the long term. The present study is thus designed to answer both these questions, by evaluating the incidence of AF using systematic ICM, in the 2 months following

closure of PFO owing to stroke. We will also investigate AF rates up to 2 years after PFO closure, as well as the burden of AF during this period.

Percutaneous PFO closure is indicated in patients aged 18 to 65 years, following ischemic stroke, when it is highly like that the stroke is attributable to the PFO [5, 6, 9]. The imputability of the stroke to the PFO is confirmed by a full clinical, biological and imaging work-up, to rule out other possible causes, notably AF. Despite this exhaustive panel of examinations to rule out the presence of AF, including ECG, telemonitoring or telemetry during hospitalisation, Holter ECG and ICM, at least one in five patients presents AF after PFO closure [16]. The incidence of AF in this context is likely underestimated, since no study to date has included a population of patients with systematic ICM implantation. Indeed, it has been demonstrated that ICM is superior to other methods of AF detection, since many episodes of AF are asymptomatic and therefore, prone to go unnoticed [14, 15]. A prospective study including patients who all receive systematic implantation of an ICM will meet a pressing clinical need to evaluate as accurately as possible the true incidence of AF after PFO closure.

Patients undergoing PFO closure are treated with antiplatelet therapy, but this procedure avoids the need for these patients to be anticoagulated for the long-term, with the risks inherent to such therapy. The occurrence of AF after a PFO closure procedure following stroke, in a patients with a CHA2DS2 VASC score of 2 or more, in principle constitutes an indication for anticoagulation [18, 19]. AF is frequent in this context, but seems to occur predominantly in the weeks immediately following the procedure, with few recurrences in the long-term [5, 6, 10, 12, 16]. Robust data showing the true long-term recurrence rate are necessary to guide therapeutic decision-making, in terms of screening, follow-up and especially anticoagulant therapy. Indeed, there are currently no recommendations for this specific clinical situation.

In our study, implanting the ICM 2 months before the PFO closure procedure should enable us to distinguish between pre-existing AF, and post-procedural AF that is truly triggered by the

PFO closure procedure. No study to date has used this type of design to detect potentially pre-existing AF prior to PFO closure. Based on previous data, the hypothesis of post-procedural AF that resolves spontaneously and with low risk of recurrence, seems the most plausible [5, 6, 10, 12, 16], but remains to be verified. Closure device size ≥25 mm has been shown to be an independent predictor AF occurrence [10, 16]. This finding underlines the arrhythmogenic nature of prosthetic devices inserted into the inter-atrial septum, especially when large. The effect is likely mechanical and should diminish over time. Other independent predictors of AF in this context include age, male sex and diabetes [10, 12, 16, 20], all three also known risk factors for AF [18, 19].

We previously showed that plasma levels of MRproANP prior to ablation of AF independently predictor the recurrence of AF at 1 year after the procedure [23]. The ability of this biomarker to stratify risk of AF occurrence, when assayed prior to PFO closure, will also be assessed in the present study.

Our study has some limitations. Firstly, the results of the study will not enable us to draw definitive conclusions regarding the indication (or absence thereof) for therapeutic anticoagulant therapy in the long-term, in this population of patients with prior stroke and presenting AF after PFO closure. The aim is to assess the true incidence of AF up to 2 years after the closure procedure, and potentially to stratify the risk by identifying independent predictors of AF occurrence. These data will provide valuable insights to guide therapeutic decision-making during management and follow-up. Only a randomized clinical trial, with a sufficient sample size to evaluate ischemic and haemorrhagic events, and comparing 2 strategies, with long-term follow-up could provide a definitive answer. A second limitation is the anticipated inclusion of 250 patients with 2 years of follow-up. While this sample size is sufficient to evaluate the incidence and recurrence of AF, it will not enable us to evaluate the

occurrence of ischemic or haemorrhagic events in patients with AF who may require anticoagulant therapy.

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## Authors' Contributions

Study conception and design: M.Badoz., N.M., R.C.; Investigation: M.Badoz., F.D., G.S., M.Besutti, G.R., P.F., C.G., N.M., R.C.; Data curation: M.Badoz, F.D., G.S., M.Besutti, G.R., P.F., C.G.; Statistical analysis plan: M.Badoz, F.E.; N.M., R.C.; Writing protocol – first draft: M.Badoz, F.E., N.M., R.C.; Final protocol – critical revision & approval: M.Badoz., F.D., G.S., M.Besutti, G.R., P.F., C.G., F.E., N.M., R.C.

## Competing Interests

No author has any competing interests to declare.

## Funding:

The study is partially funded by an unrestricted educational grant from Medtronic SAS, and by the University Hospital of Besancon. The funders have no role in the study design, data collection, or interpretation of the results.

## Data Availability Statement:

Not applicable as no datasets have yet been analyzed for this study. Once the study has been completed and the database locked and analysed, all data relevant to the study will be included in future publications and/or uploaded as supplementary information.

## Figure legend

**Figure 1: Flow chart of the design of the PFO-AF study.**

ICM: implantable cardiac monitor, ECG: electrocardiogram, PFO: patent foramen ovale, AF: atrial fibrillation

**Table 1. Patient inclusion and exclusion criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Adult patients (aged 18 years or older) | Patients under legal protection of any sort |
| Indication for percutaneous closure of patent foramen ovale due to stroke, validated in an interdisciplinary meeting between cardiologists and neurologists, in compliance with current guidelines. | Patients within the exclusion period of another clinical trial, as noted in the national register of healthcare research volunteers |
| Patients affiliated to a social security system, or beneficiary thereof. | Patients not affiliated to, or beneficiary of any social security system. |
| Written informed consent | |

**Table 2. Primary and Secondary Endpoints of the PFO-AF Study**

| Primary endpoints | Secondary endpoints |
|---|---|
| Any episode of AF or atrial tachycardia/flutter lasting at least 30 seconds, and recorded on the ICM, during the 2 months following percutaneous PFO closure | Any episode of AF or atrial tachycardia/flutter lasting at least 30 seconds, and recorded on the ICM, during the 2 months prior to, and up to 2 years after percutaneous PFO closure |
| **And/or** any episode of AF or atrial tachycardia/flutter documented by ECG during the 2 months following percutaneous PFO closure. | **And/or** any episode of AF or atrial tachycardia/flutter documented by ECG during the 2 months prior to, and up to 2 years after percutaneous PFO closure |
| | Burden of AF (expressed in days, hours and minutes), as recorded in the ICM, during the 2 months prior to, and up to 2, 12 and 24 months after percutaneous PFO closure |
| | Plasma levels of MR-proANP as assayed in peripheral venous blood drawn prior to PFO closure |
| | Ischemic or hemorrhagic stroke, peripheral emboli documented on imaging (computed tomography (CT) or MRI), major or minor bleeding according to the ISTH classification, and up to 2 years after percutaneous PFO closure |

**Figure 1**

Flowchart of the study design

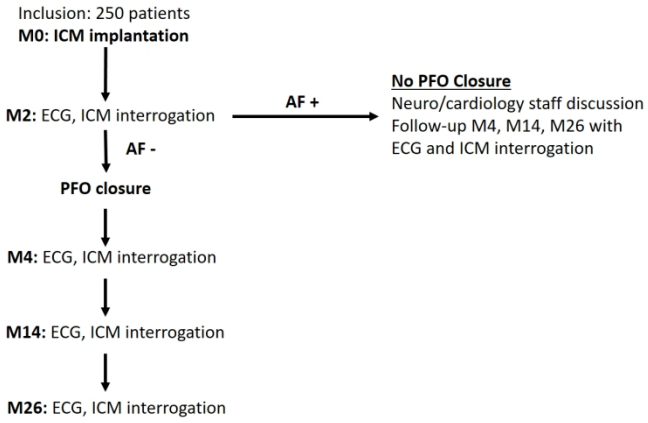


Figure 1

508x285mm (96 x 96 DPI)

# Supplementary material

# Reveal Linq® Medtronic settings

## ***Step 1:***

- Patient and physician details are entered, paying attention to complete all mandatory fields.

## ***Step 2:***

- Cryptogenic stroke is selected as the reason for monitoring.

## ***Step 3 : Settings***

The following settings are entered:

- Symptom => Four 7.5 min Episodes.
- Tachy => Detection: On; Interval: 330ms (182 bpm); duration: 16 beats.
- Brady => Detection: On; Interval: 2000ms (30 bpm); duration: 8 beats.
- Pause => Detection: On; Duration: 4,5 sec.
- AT/AF => AF Only.
    - **For AT/AF:**
        - AT/AT Detection: On
        - Type: AF Only
        - AF Detection: Balanced Sensitivity
        - Ectopy Rejection: Agressive
        - AT/AF Recording Threshold: All Episodes