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# BMJ Open 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 be 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 and 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 s, 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 and dissemination** The study was approved by the Ethics Committee 'Comité de Protection des Personnes (CPP) Sud-Méditerranéen III' on 2 June 2021 and registered with ClinicalTrials.gov (NCT04926142). Findings will be presented in national and international congresses and peer-reviewed journals.

**Trial registration number** NCT04926142.

## INTRODUCTION

In patients with stroke attributed to patent foramen ovale (PFO), the superiority of

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Patent foramen ovale-atrial fibrillation (PFO-AF) is the first prospective, multicentre study to investigate the incidence of AF after PFO closure using implantable cardiac monitoring devices in all patients.
- ⇒ About 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.

percutaneous PFO closure over antithrombotic therapy has been clearly demonstrated.<sup>1-7</sup> PFO closure is recommended before the age of 65 years, if it is highly likely that the PFO was the cause of the stroke.<sup>8,9</sup> 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%,<sup>1 2 5 6 10</sup> and is significantly higher in patients undergoing PFO closure compared with patients receiving medical therapy alone, with an increase in risk of more than 400%.<sup>5 6 11-13</sup> In these same randomised trials, 72% of new-onset AF after PFO closure resolved spontaneously within 45 days.<sup>11</sup> 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.<sup>14 15</sup>

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.<sup>16 17</sup> 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.<sup>18</sup>

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 ischaemic 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 midregional proatrial 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 (ischaemic or haemorrhagic), major and minor bleeding and peripheral emboli up to 2 years after percutaneous PFO closure.

## METHODS AND ANALYSIS

### Study design

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

### Study population and inclusion/exclusion criteria

The study will include patients who have suffered from ischaemic 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.<sup>9</sup> The causal role of the PFO in the stroke must be evaluated by a full work-up including transthoracic (TTE) and transoesophageal (TEE) echocardiography with bubble study, one (or more) cerebral 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 (eg, antithrombin III

**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	

deficiency, Protein C deficiency, Protein S deficiency, Activated Protein C Resistance, Factor V Leiden mutation, Prothrombin/Factor II 20210GA, anticardiolipin antibodies, lupus anticoagulant and anti- $\beta$ 2-glycoprotein I antibodies), sequential ECG, ECG monitoring during hospitalisation 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 cardioembolic 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 30s, and recorded on the ICM and/or any episode of AF or atrial tachycardia/flutter documented by ECG.<sup>18</sup>

### Secondary endpoints

The second endpoints are s follows:

- ▶ 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 30s, and recorded on the ICM and/or any episode of AF or atrial tachycardia/flutter documented by ECG.<sup>18</sup>
- ▶ Burden of AF (expressed in days, hours and min), 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.
- ▶ Ischaemic or haemorrhagic stroke, peripheral emboli documented on imaging (CT or MRI), major or minor bleeding according to the International Society on Thrombosis and Haemostasis (ISTH classification).

**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 30s, and recorded on the ICM, during the 2 months following percutaneous PFO closure	Any episode of AF or atrial tachycardia/flutter lasting at least 30s, 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 min), 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
	Ischaemic or haemorrhagic stroke, peripheral emboli documented on imaging (CT or MRI), major or minor bleeding according to the ISTH classification, and up to 2 years after percutaneous PFO closure

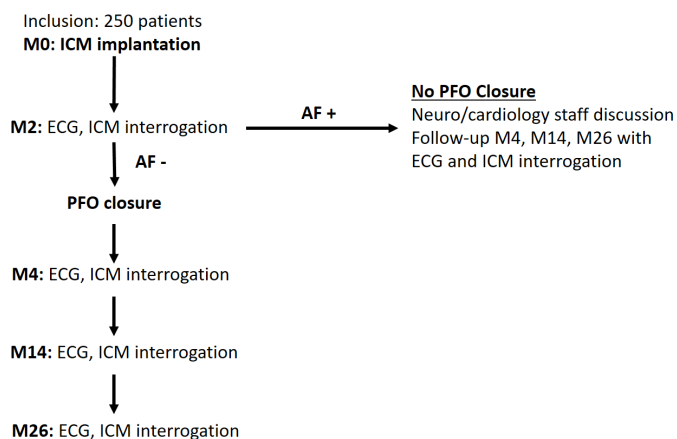
AF, atrial fibrillation; ICM, implanted cardiac monitor; ISTH, International Society on Thrombosis and Haemostasis; MR-proANP, midregional proatrial natriuretic peptide; PFO, patent foramen ovale.

### Implantable cardiac monitors (ICM)

The ICM device will be implanted at month (M) 0 (figure 1), in order to have a 2 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 anaesthetic. All ICM devices used in the study will be the same, to minimise detection bias for AF between centres. The device used will be the Reveal Linq (Medtronic). Device parameters will be standardised, as described in the online supplemental 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 (ie, 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



**Figure 1** Flow chart of the design of the PFO-AF study. AF, atrial fibrillation; ICM, implantable cardiac monitor; PFO, patent foramen ovale.

24 hours prior to PFO closure. The PFO closure procedure will be performed by the femoral venous approach under local anaesthesia with sedation, or under general anaesthesia. Procedures performed under local anaesthesia will be guided by TTE or TEE microprobe. 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 >15 mm in diastole; measure of the left atrium in the parasternal long axis view; measure of the left atrial area in the apical four chamber view; measure of left atrial strain. The PFO characteristics, including size, type of shunt, presence of interatrial 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 with 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  $-20^{\circ}\text{C}$  for later centralised 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, that is, at 4, 14 and 26 months after implantation of the ICM (figure 1). At each follow-up, the occurrence of 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 and MBa).

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

In cases where AF occurs, the management, particularly the antithrombotic therapy, is at the discretion of the treating physician, and should comply with current guidelines. Introduction of curative anticoagulation is recommended.<sup>18</sup> 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<sup>9 18 19</sup> (figure 1). 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 4 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 centrally performed at the Cardiology Department at the coordinating centre (University Hospital of Besançon, France), where a dedicated team of data managers will be responsible for data collection and monitoring. Computerised 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 centre (University Hospital, Besançon, 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  $\chi^2$  or Fisher's exact test, as appropriate. Determination of the sample size was based on the width of the two-sided 95% CI. The inclusion of 250 patients will enable estimation of the incidence of AF within 2 months of the procedure with an accuracy of <6.5% (width of the two-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 AF. 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 ORs with 95% CIs. All analyses will be performed using SAS V.9.4 (SAS Institute, 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 2 June 2021. The results of the study will be presented at national and international congresses, and submitted for publication in international peer-reviewed journals.

## DISCUSSION

The incidence of AF occurring after percutaneous PFO closure due to ischaemic stroke is likely underestimated in randomised trials and literature data, since only symptomatic AF is detected.<sup>1 2 5 6 20–22</sup> 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.<sup>16 17</sup> 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 18–65 years, following ischaemic stroke, when it is very likely that the stroke is attributable to the PFO.<sup>5 6 9</sup> 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.<sup>16</sup> 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.<sup>14 15</sup> 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.<sup>18 19</sup> 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.<sup>5 6 10 12 16</sup> 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 postprocedural 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 postprocedural AF that spontaneously resolves and with low risk of recurrence, seems the most plausible,<sup>5 6 10 12 16</sup> but remains to be verified. Closure device size  $\geq 25$  mm has been shown to be an independent predictor AF occurrence.<sup>10 16</sup> This finding underlines the arrhythmogenic nature of prosthetic devices inserted into the interatrial 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,<sup>10 12 16 20</sup> all three also known risk factors for AF.<sup>18 19</sup>

We previously showed that plasma levels of MRproANP prior to ablation of AF independently predict the recurrence of AF at 1 year after the procedure.<sup>23</sup> 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. First, 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 randomised clinical trial, with a sufficient sample size to evaluate ischaemic and haemorrhagic events, and comparing two 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 ischaemic or haemorrhagic events in patients with AF who may require anticoagulant therapy.

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**Contributors** Study conception and design: MBa, NM and RC; investigation: MBa, FD, GS, MBe, GR, PF, CG, NM and RC; data curation: MBa, FD, GS, MBe, GR, PF and CG; statistical analysis plan: MBa, FE, NM and RC; writing protocol—first draft: MBa, FE, NM and RC; final protocol—critical revision and approval: MBa, FD, GS, MBe, GR, PF, CG, FE, NM and RC.

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#### REFERENCES

- Carroll JD, Saver JL, Thaler DE, *et al.* Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013;368:1092–100.
- Lee PH, Song J-K, Kim JS, *et al.* Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol* 2018;71:2335–42.
- Kasner SE, Rhodes JF, Andersen G, *et al.* Five-year outcomes of PFO closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2021;384:970–1.
- Saver JL, Carroll JD, Thaler DE, *et al.* Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;377:1022–32.
- Mas J-L, Derumeaux G, Guillon B, *et al.* Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017;377:1011–21.



- 6 Søndergaard L, Kasner SE, Rhodes JF, *et al*. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017;377:1033–42.
- 7 Turc G, Calvet D, Guérin P, *et al*. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. *JAHA* 2018;7.
- 8 Kleindorfer DO, Towfighi A, Chaturvedi S, *et al*. Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2021;52:e364–467.
- 9 Pristipino C, Sievert H, D'Ascenzo F, *et al*. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *EuroIntervention* 2019;14:1389–402.
- 10 Andersen A, Matzen KL, Andersen G, *et al*. Atrial fibrillation after closure of patent foramen ovale in the REDUCE clinical study. *Catheter Cardiovasc Interv* 2022;99:1551–7.
- 11 Ntaios G, Papavasileiou V, Sagris D, *et al*. Closure of patent foramen ovale versus medical therapy in patients with cryptogenic stroke or transient ischemic attack: updated systematic review and meta-analysis. *Stroke* 2018;49:412–8.
- 12 Chen JZ-J, Thijs VN. Atrial fibrillation following patent Foramen Ovale closure: systematic review and meta-analysis of observational studies and clinical trials. *Stroke* 2021;52:1653–61.
- 13 Skibsted CV, Korsholm K, Pedersen L, *et al*. Long-term risk of atrial fibrillation or flutter after transcatheter patent foramen ovale closure: a nationwide Danish study. *Eur Heart J* 2023;ehad305.
- 14 Sanna T, Diener H-C, Passman RS, *et al*. Cryptogenic stroke and atrial fibrillation. *N Engl J Med* 2014;371:1261.
- 15 Bernstein RA, Kamel H, Granger CB, *et al*. Effect of long-term continuous cardiac monitoring vs usual care on detection of atrial fibrillation in patients with stroke attributed to large- or small-vessel disease: the STROKE-AF randomized clinical trial. *JAMA* 2021;325:2169–77.
- 16 Guedeney P, Laredo M, Zeitouni M, *et al*. Supraventricular arrhythmia following patent foramen ovale percutaneous closure. *Eur Heart J* 2022;43.
- 17 Baron SJ. Atrial fibrillation after percutaneous PFO closure: not so rare after all. *JACC Cardiovasc Interv* 2022;15:2323–5.
- 18 Hindricks G, Potpara T, Dagres N, *et al*. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC), developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42:373–498.
- 19 January CT, Wann LS, Calkins H, *et al*. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of cardiology/American Heart Association task force on clinical practice guidelines and the heart rhythm society. *J Am Coll Cardiol* 2019;74:104–32.
- 20 Oliva L, Huszti E, Hall R, *et al*. Incidence of new-onset atrial fibrillation after transcatheter patent foramen ovale closure using 15 years of Ontario administrative health data. *Heart Rhythm* 2022;19:1414–20.
- 21 Oliva L, Huszti E, Barker M, *et al*. New-onset atrial fibrillation following percutaneous closure of patent foramen ovale: a systematic review and meta-analysis. *J Interv Card Electrophysiol* 2021;60:165–74.
- 22 Leclercq F, Odorico X, Marin G, *et al*. Atrial fibrillation screening on systematic ambulatory electrocardiogram monitoring after percutaneous patent foramen ovale closure: a prospective study. *Int J Cardiol Heart Vasc* 2021;37:100919.
- 23 Badoz M, Serzian G, Favoulet B, *et al*. Impact of midregional N-terminal pro-atrial natriuretic peptide and soluble suppression of tumorigenicity 2 levels on heart rhythm in patients treated with catheter ablation for atrial fibrillation: the Biorhythm study. *J Am Heart Assoc* 2021;10:e020917.