Study Protocol and Statistical Analysis Plan

Title:

Patent foramen ovale–related stroke management and outcome: age-dependent risk prediction and atrial cardiopathy study:

SENIOR: Stroke prevention in the elderly by patent foramen Ovale closuRe vs anticoagulation

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Research Background and Motivation

Current treatment for patent foramen ovale related stroke

Acute ischemic stroke is a leading cause of disability. Even after comprehensive evaluation, one quarter of patients are classified as embolic stroke of undetermined source (ESUS), for which patent foramen ovale (PFO) is a key mechanism [1]. Current international guidelines recommend transcatheter PFO closure for patients <60 years with high-risk PFO, showing superiority over antiplatelet therapy in preventing recurrence [2]. For patients >60 years, however, the optimal strategy remains uncertain. Nevertheless, emerging evidence indicates that the risk profile in older adults is shifting. In particular, studies show that ESUS patients with PFO aged >60 have a 1.64-fold higher risk of recurrent stroke than their younger counterparts [3]. Moreover, with an aging population, over 65% of stroke patients are now older than 60 [4]. There is a substantial cohort that warrants re-evaluation of PFO management strategies. Furthermore, studies focused on elderly PFO related stroke were justified [3].

The comparison between PFO closure vs. antiplatelet vs. anticoagulant

Prior investigations indicate that anticoagulation is associated with a lower risk of recurrent events than antiplatelet therapy in PFO related stroke [5], and pooled analyses suggest effectiveness approaching that of PFO closure [6]. However, the historical evidence base is predominantly warfarin-based and therefore accompanied by higher hemorrhagic risk. Data on direct oral anticoagulants (DOACs) point to a more favorable safety profile [7], but rigorous head-to-head evaluations of PFO closure versus optimized DOAC therapy, particularly in older adults, are absent. Notably, only one randomized controlled trial in patients

younger than 60 years with PFO-related stroke included a very small number of participants treated with a DOAC [5]. Accordingly, the comparative benefits and risks of closure, antiplatelet therapy, and DOACs in patients aged ≥60 years remain insufficiently defined.

The preliminary data from TCVGH

An institutional retrospective cohort from Taichung Veterans General Hospital (2013–2023), published in June 2025, demonstrated that among ESUS patients with PFO, transcatheter closure was associated with an approximately 90% reduction in recurrent stroke compared with antiplatelet therapy, with safety outcomes comparable to those observed in younger populations [8]. These findings suggest that advanced age alone should not be considered a contraindication to closure. However, the analysis did not include patients using DOAC, leaving an important evidence gap. As a real-world study, it also encountered substantial challenges related to treatment selection and baseline imbalance; notably, patients who underwent closure had a higher prevalence of high-risk PFO features. Consequently, the comparison may be more accurately conceptualized as closure in patients with PFO related stroke versus medical therapy in patients with incidental PFO [9]. These limitations underscore the need for a prospective, multicenter investigation with rigorous eligibility criteria, standardized assessments, and prespecified treatment allocation to more definitively establish comparative effectiveness [10].

The cardiac physiology from PFO closure

During transcatheter PFO closure, catheter access to the left atrium permits direct recording of left atrial (LA) pressure waveforms. Prior investigations in PFO cohorts have relied predominantly on noninvasive

speckle-tracking measures, with reports of early, transient decrements in LA strain after closure and device-related alterations in atrial function [11]; however, systematic, serial profiling that integrates invasive hemodynamics with imaging remains limited [12]. The cardiac physiological substudy in our protocol, leveraging catheter-accessed LA pressure waveforms, is pivotal for elucidating post-closure remodeling dynamics and for directly linking mechanistic changes in LA compliance to clinical outcomes.

Motivation

Therapeutic uncertainty persists for patients aged >60 years with ESUS and concomitant PFO due to the paucity of head-to-head data directly comparing transcatheter closure with DOAC therapy, underscoring the need for robust multicenter evidence. The SENIOR registry is a hybrid retrospective and prospective observational cohort designed to evaluate the comparative effectiveness and safety of PFO closure, DOACs, and antiplatelet therapy in real-world practice, incorporating prespecified endpoints, standardized outcome adjudication, and rigorous risk adjustment. A cardiac physiological substudy will longitudinally quantify left atrial compliance and heart rhythm before and after closure. The objective is to generate generalizable, decision-relevant evidence to inform individualized management of older adults with PFO related stroke.

Study Aims

This is a multicenter, observational cohort study that includes both retrospective and prospective enrollment of patients with patent foramen ovale (PFO)–related stroke. The study aims are:

1. To optimize an age-inclusive risk prediction system for the causal attribution of PFO-related stroke across all age.
2. To compare the effectiveness and safety of transcatheter PFO closure versus medical therapy alone (direct oral anticoagulants [DOAC] or antiplatelet agents if protocol-defined DOAC ineligibility) for prevention of recurrent stroke among patients aged ≥60 years with high-risk PFO.
3. To investigate the role of atrial cardiopathy (AC) in PFO-related stroke, and to further analyze changes in cardiac physiological parameters—such as left atrial (LA) compliance and LA strain—before and after PFO closure and medical therapy alone (optional nested substudy).

Literature Review

Based on anatomical and imaging studies, the prevalence of PFO in healthy adults is approximately 25%–30% [13]. Among stroke patients—particularly those diagnosed with embolic stroke of undetermined source (ESUS)—the detection rate of PFO reaches 40% or higher [14]. Using Taichung Veterans General Hospital (TCVGH) as an example, real-world data from Taiwan show that approximately 31% of ESUS patients have concomitant PFO; the positivity rate is 24.0% in patients younger than 60 years, while PFO is identified in 44% of those aged 60 years or older [10], indicating that advanced age is not an exclusion factor for the presence of PFO (Figure 1). Notably, multiple randomized controlled trials evaluating PFO closure for stroke prevention restricted enrollment to patients younger than 60 years, resulting in limited data for older patients and constraining the applicability of current international guidelines in this population [5, 15].

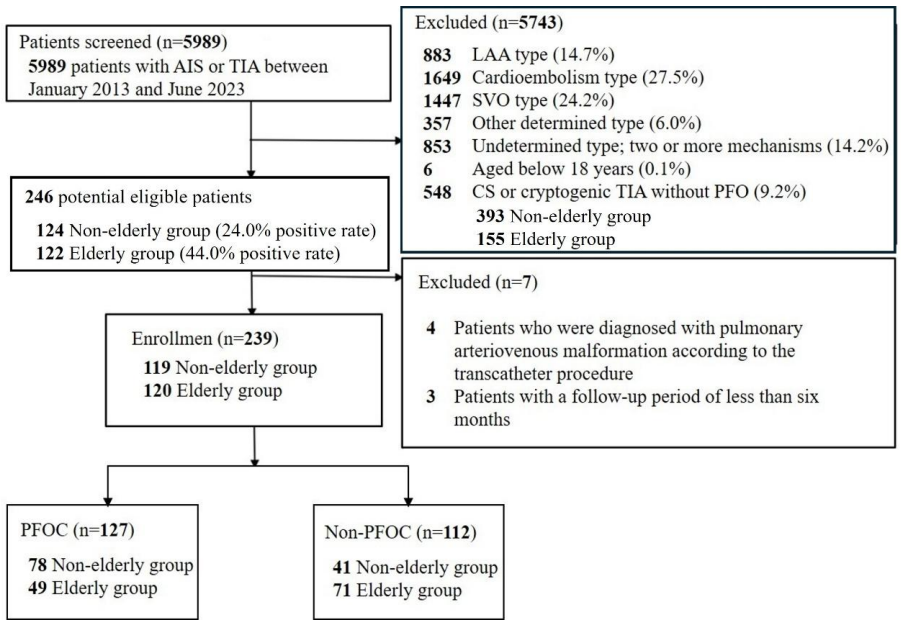


Figure 1 Single center study from TCVGH
AIS: acute ischemic stroke; TIA: transient ischemic attack; LAA: large artery atherosclerosis; SVO: small vessel occlusion; CS: cryptogenic stroke; Elderly: aged ≥60; PFOC: patent foramen ovale closure

The treatment of PFO related stroke

According to the 2021 guidelines from the American Heart Association/American Stroke Association and

the 2024 European Stroke Organisation guidelines [2, 16], in patients aged 18–60 years who have been appropriately evaluated and diagnosed with PFO-related ischemic stroke, transcatheter PFO closure significantly reduces the risk of recurrent stroke compared with antiplatelet therapy alone.

If, after shared decision-making between physicians and patients, medical therapy alone is chosen, evidence regarding drug selection is limited. A meta-analysis published by Turc et al. in 2018 [17], which included six randomized controlled trials, compared three strategies—PFO closure, antiplatelet therapy, and anticoagulation—in terms of stroke recurrence and safety. PFO closure was clearly superior to antiplatelet therapy alone in preventing recurrent stroke (RR 0.36, 95% CI 0.17–0.79), but showed no statistically significant difference when compared with all medical therapies combined, including anticoagulants (RR 0.57, 95% CI 0.28–1.15), suggesting that anticoagulation may be more effective than antiplatelet therapy. However, it should be noted that only one randomized controlled trial included anticoagulant therapy [5], with a limited sample size, and its study design did not directly compare PFO closure with anticoagulation alone. Therefore, it remains unclear whether anticoagulation can be considered a definitive treatment option for PFO-related stroke at this stage.

In addition, the 2018 treatment guideline published in the BMJ [18], which synthesized multiple studies, suggested that anticoagulation may have a comparable effect to PFO closure in reducing recurrent stroke, but with a relatively higher risk of bleeding—particularly in older patients or those with bleeding risk factors—necessitating careful clinical assessment.

Importantly, the number of patients treated with DOACs in these randomized trials was very small (with explicit reporting only in the CLOSE trial, totaling 13 patients [5]), which is insufficient to provide evidence for a DOAC versus PFO closure comparison. Currently, a phase III trial, CLOSE-2 (NCT05387954), is

ongoing to include DOAC ad the medication arm in high-risk PFO patients aged 60–80 years.

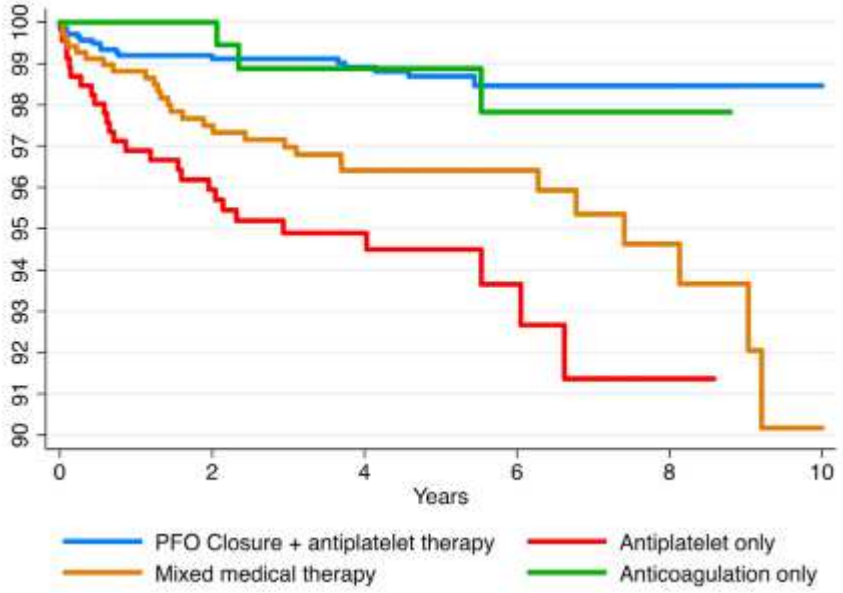


Figure 2 The treatment efficacy between different therapy
(1) Y-axis is truncated from 90% to 100% event-free survival. (2) Mixed medical therapy includes studies where the proportion of antiplatelet agents was 25%. (3) Proportion of patients: patent foramen ovale (PFO) closure+antiplatelettherapy (n=1829; 50%), mixed medical therapy (n=1153; 32%), antiplatelet therapy (n=458; 13%) and anticoagulation (n=210; 6%)
Mir H, et al. BMJ Open 2018 [19]

The justification of research in elderly PFO related stroke

In older patients, although evidence from randomized controlled trials is lacking, an increasing number of retrospective studies suggest that patients aged >60 years may also benefit from PFO closure, highlighting the need for new RCT evidence integrating anatomical risk factors and individualized assessment [20, 21].

In a meta-analysis published in 2020 by Sara Mazzucco et al., among patients with ESUS and concomitant PFO treated with medical therapy alone, those aged ≥60 years had a 1.64-fold higher risk of recurrent stroke than those aged <60 years, supporting the rationale for PFO closure in older patients [3].

Our retrospective study published in the European Stroke Journal in 2025 included 239 patients with ESUS or cryptogenic TIA, of whom 127 underwent PFO closure and 112 did not (Figure 1). The overall mean age

was 57.2 years, and the mean follow-up duration was 3.1 years. The study specifically analyzed 49 patients aged >60 years who underwent PFO closure. The results showed that PFO closure significantly reduced the risk of recurrent ischemic stroke by nearly 90% (adjusted HR 0.10; 95% CI 0.03–0.29; p = 0.001). A significant benefit was also observed in the older subgroup (adjusted HR 0.11; 95% CI 0.03–0.49; p = 0.003), and the effectiveness did not differ significantly between older and younger groups. Regarding safety, the rates of procedural complications (subcutaneous hematoma, pericardial effusion, etc.) were comparable between younger and older patients (5.1% vs. 6.1%, p = 1.000), and there was no significant difference in peri-procedural atrial fibrillation (3.8% vs. 6.1%, p = 0.675) [8]. However, the control group did not control for the use of antiplatelet therapy alone versus anticoagulation, and a prospective multicenter registry study is still needed to confirm effectiveness.

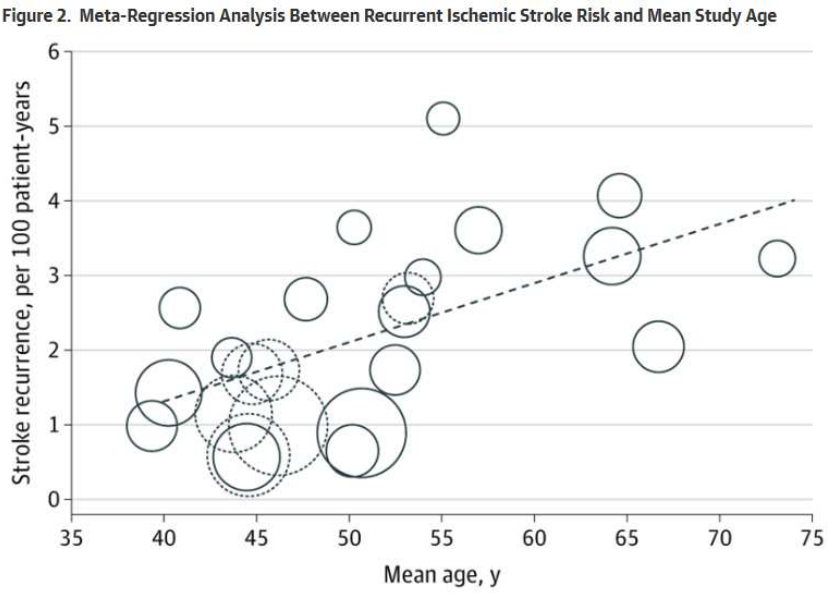


Figure 3
Dotted circles represent the medical arm of patent foramen ovale closure trials.
Mazzucco S, et al. JAMA Neurol. 2020 [3]

Methods

1. Inclusion and exclusion criteria

Prospective registration: as table

Inclusion criteria for prospective registration	
Aged: 18-90 years old	
Patient or his/her legal representative signs a written informed consent	
Participants who have diagnosed as PFO related stroke	
ESUS diagnosed by Neurologist by standard pathway, aged 18-59 years And **PFO diagnosed by TCD-microbubble test, or TEE-microbubble test** And **PASCAL classification possible/probable**	**ESUS diagnosed by Neurologist by standard pathway, aged 60-90 years** And **High risk PFO, diagnosed by TCD-microbubble test (>10 HITS in 30 s), or TEE-microbubble test (>30 bubbles in 3 cardiac cycle)** OR **PFO diagnosed by TCD-microbubble test, or TEE-microbubble test, with RoPE score ≥ 4, with cortical infarct**

Exclusion criteria for prospective registration
Follow-up less than 6 months
Extracardiac right-to-left shunt
Inability to provide informed consent
Known stroke mechanism other than PFO

Retrospective registration:

Inclusion criteria:

(1) Patients with ESUS and concomitant PFO.

(2) Age between 18 and 90 years.

Exclusion criteria:

(1) Incomplete clinical data (missing data).

(2) Human immunodeficiency virus (HIV)–positive patients.

2. Sample size

(1) For the prospective registry, a total of 200 patients aged >60 years and 200 patients aged ≤60 years are planned to be enrolled (total across all participating centers).

(2) For the retrospective registry, a total of 500 patients across all age groups are planned to be enrolled (total across all participating centers).

3.1 PFO related patient enrolled

This multicenter, observational registry combines a retrospective cohort (Jan 1, 2013–Sep 1, 2025) and a prospective cohort (Sep 15, 2025–Dec 31, 2031). Eligible participants are adults (≥18 years) with ESUS and concomitant PFO based on a standardized etiologic work-up (CTA/MRA, ECG, carotid ultrasound and TCD, 24-hour Holter ECG, transthoracic echocardiography [TTE]/ transesophageal echocardiography [TEE], blood test, including hypercoagulable state, autoimmune disease, hereditary diseases, malignancy; and an optional

cardiac MRI), with TOAST classification applied to ischemic stroke and prespecified criteria for TIA (unilateral weakness, lasting for > 10 minutes and diagnosed by Neurologist). Genetic testing data (array/WES/WGS per site) may be incorporated for secondary analyses (optional). While an etiology for the index ischemic event could not be identified, the ESUS was diagnosed. A TCD and/or TEE based microbubble test was performed to ascertain the presence of PFO. Patients with an abnormal microbubble test were assumed to have PFO.

The retrospective arm will enroll patients aged between 18-90 years with ESUS and concomitant PFO. The prospective arm will focus on patients aged ≥60 years with high-risk PFO. Inclusion and exclusion criteria are presented as section 1.

3.2 The diagnosis of high-risk PFO

After ESUS is established, right-to-left shunt testing is performed by TCD and/or TEE based microbubble test. High-risk PFO is defined as: (1) TCD with >10 high-intensity transient signals within 30 seconds, or (2) TEE/TTE with >20 microbubbles entering left-sided chambers within three cardiac cycles, or (3) presence of atrial septal aneurysm. RoPE and PASCAL scales are recorded to estimate PFO-attributable stroke probability. To confirmed the diagnosis, an anatomic PFO is documented by TEE or catheter passage.

3.3Treatment allocation

This is a non-interventional registry; therapy is determined by the treating physician and the local PI through shared decision-making. For patients aged <60 years, management follows international guidelines—transcatheter PFO closure for PFO-related stroke, defined after a standardized etiologic work-up and

adjudicated using the ROPE/PASCAL classification. In the prospective arm, patients aged 60-90 years may receive transcatheter PFO closure, standard-dose DOAC, or antiplatelet therapy when DOAC is contraindicated or intolerance. At each study center, the local PI finalizes treatment selection as part of routine care discussions, typically within 2 months of the index event. All decisions and their clinical rationale are prospectively documented.

3.4 Cardiac physiological analysis

Baseline transthoracic echocardiography will capture core measurements (LVIDs, LVIDd, IVSd, LVPWd, LAD, LA volumes in apical 2- and 4-chamber views, LA strain, and LVEF by modified Simpson's in apical 2- and 4-chamber views) and late contrast enhancement if cardiac MRI was performed. During PFO closure, left-atrial pressure waveforms may be recorded via catheter; when combined with chamber volumes, these data enable LA compliance estimation. Post-closure rhythm surveillance (ECG or 24-hour Holter) is performed within 1 week to detect procedure-related arrhythmias. A 6-month TTE repeats the core measurements to quantify remodeling; additional center-specific measures are permitted (e.g. optional cardiac MRI).

3.5 Follow-up

3.5.1 Retrospective arm

Participants are followed from the index event until the occurrence of the primary outcome, all caused mortality, or the end of the retrospective observation window.

3.5.2 Prospective arm

Follow-up is event-driven with a minimum observation period of 6 months. Participants are assessed at prespecified time points—1 week, 3, 6, and 12 months—via clinic visit or structured telephone contact, with long term interim surveillance (typically 1 year) until an endpoint occurs. At each contact, we systematically ascertain the primary endpoint (date and mechanism of recurrent ischemic stroke/TIA) and all-stroke events. Functional status (mRS) is recorded at 6 months. A TTE is scheduled at 6-12 months to quantify LA structure/strain; centers may optionally arrange cardiac imaging for the cardiac pathophysiological aim. Peri-procedural rhythm surveillance (ECG or 24-hour Holter within1 week after closure) is captured in the safety dataset.

3.6 Data analysis and interpretation.

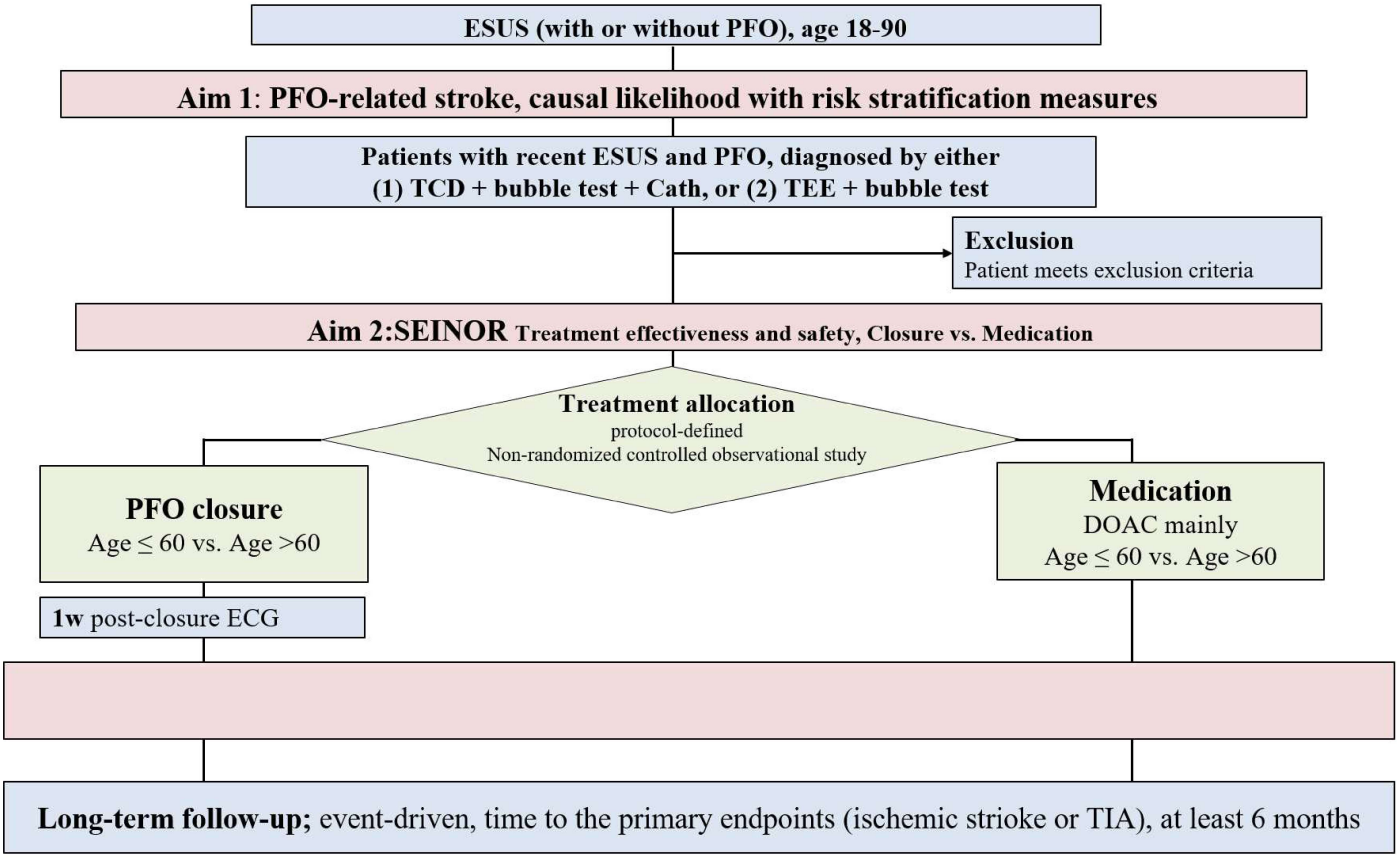
The primary endpoint is recurrent AIS or TIA. Secondary endpoints include all strokes (ischemic, hemorrhagic, and TIA) and 3-month/1-year functional outcomes; safety endpoints include peri-procedural adverse events (including new-onset AF), major bleeding, and all-cause mortality. Clinical, imaging, cardiac, biomarker, and genetic variables will be recorded. For descriptive analyses, continuous variables will be summarized as mean±SD and categorical variables as percentages; between-group comparisons will use Mann–Whitney U tests and χ^2 or Fisher's exact tests. Variables with $p<0.10$ in univariable analyses and prespecified risk factors will enter multivariable logistic regression to assess associations with outcomes; significance is set at $p<0.05$. Retrospective and prospective cohorts will be analyzed separately and in pooled exploratory analyses, with subgroup analyses emphasizing patients ≥60 years with high-risk PFO.

3.7 Sample size calculation

We will use an event-driven design with a two-sided $\alpha=0.05$ and 80% power, analyzed by a log-rank/Cox model (Schoenfeld event-count framework), assuming equal allocation and proportional hazards. The expected annual primary-endpoint rates are 1.4% for the PFO-closure group and 4.38% for medical treatment. The 4.38% control rate is a weighted average prespecified for real-world practice: ~50% treated with DOACs (estimated 2.96%/year in older adults according to Kasner SE, et al. Lancet Neurol. 2018 and Mazzucco S, et al. JAMA Neurol. 2020) and ~50% with antiplatelets (5.8%/year according to Farjat-Pasos JI, et al. J Stroke. 2023).

Under these assumptions, the required information size is 11 primary events, with a minimum follow-up of ≥3 months and ≥30 participants per group to trigger the analysis. Accounting for ~10% overall attrition, the corresponding total sample size is at least 224 (at least 112 per group).

3.8 Study flow diagram



4. Treatment allocation

Treatment allocation

	Age 18-59	Age 60-90
High risk PFO feature Large shunt and/or Atrial septal aneurysm	Suggest PFO closure	PFO closure or anti-coagulant (if tolerable)
RoPE 1. Cortical infarct on image 2. No HTN 3. No DM 4. No prior stroke or TIA 5. No smoking 6. Age	**≥ 7** Suggest PFO closure	**≥ 4, must include cortical infarct** PFO closure or anti-coagulant (if tolerable) Suggest **medication** if 1. CHA2DS2-VASc ≥ 4 2. LA size > 45mm

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