Protocol

Patent Foramen Ovale Closure Outcomes in Patients of Advanced Age (PFO-COPA): Protocol for a Multicenter Retrospective Cohort Study

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Abstract

Background: Patent foramen ovale (PFO) is a common cardiac abnormality associated with paradoxical embolism and ischemic stroke. Randomized trials have demonstrated the benefit of percutaneous PFO closure in patients aged <60 years with cryptogenic stroke, but nearly all trials have excluded individuals aged ≥60 years, leaving a critical evidence gap in older populations, in whom competing stroke mechanisms are prevalent. There is currently no dedicated, validated framework to guide closure decisions in this age group. Consequently, clinical practice remains highly variable, and closure decisions are made based on extrapolation from younger cohorts rather than robust evidence.

Objective: This study aims to evaluate the effectiveness and safety of PFO closure compared with medical therapy in patients aged ≥60 years with cryptogenic stroke and a confirmed PFO.

Methods: This multicenter international retrospective cohort study will include consecutive patients aged ≥60 years with imaging-confirmed ischemic stroke, a confirmed PFO, and no alternative definite etiology of stroke after standard diagnostic evaluation, who underwent either percutaneous PFO closure or medical therapy between 2015 and 2025. Outcomes will be collected through standardized chart review and entered into a centralized REDCap database. The primary outcome will be the risk of recurrent ischemic stroke. Secondary outcomes will include major bleeding, new-onset atrial fibrillation, device-related complications, and mortality. Time-to-event analyses, Cox regression, and propensity score methods will be used to adjust for confounding.

Results: As of October 2026, 51 centers from 10 countries (Argentina, Brazil, Colombia, Greece, Italy, Japan, Mexico, Portugal, Spain, and the United States) have formally agreed to participate in the study. Each site is currently in the process of securing institutional review board (IRB) approval and executing data use agreements. A standardized variable dictionary has been distributed to all centers to ensure consistency in data collection. As of October 2026, 45 centers have applied for local IRB approval, 5 centers have obtained IRB approval, and 3 centers have begun data entry into REDCap. The projected end date of data collection is June 2027. Participating centers are encouraged to propose independent research questions leveraging the pooled dataset. As of October 2026, 23 project titles have been submitted by investigators. These proposals will be evaluated once sufficient data have been accrued. Preliminary pooled analyses are anticipated for release in July 2027.

Conclusions: The PFO-COPA (Patent Foramen Ovale Closure Outcomes in Patients of Advanced Age) study will generate the most comprehensive real-world evidence to date on PFO closure in adults aged ≥60 years. By evaluating both effectiveness and safety in this understudied age group, the study will fill a major evidence gap and help guide clinical decision-making. Ultimately, these findings may inform future guideline updates and lay the groundwork for prospective multicenter trials focused specifically on older adults.

International Registered Report Identifier (IRRID): PRR1-10.2196/104052

JMIR Res Protoc 2026;15:e104052; doi: 10.2196/104052

Keywords: foramen ovale, patent; ischemic stroke; patent foramen ovale closure; PFO closure; medical therapy; aged

Introduction

Background

Patent foramen ovale (PFO) is a common structural cardiac abnormality, present in about 1 in 4 individuals in the general population, that may contribute to paradoxical embolism and ischemic stroke [1]. Although PFO is benign in most individuals, it can provide a conduit for paradoxical embolism when a transient or sustained right-to-left shunt permits venous thromboemboli to enter the systemic circulation and potentially cause ischemic stroke [1,2].

Management of PFO-associated stroke includes antithrombotic therapy and, in appropriately selected patients, percutaneous PFO closure [3]. Several pivotal randomized clinical trials, including RESPECT, CLOSE, REDUCE, PC, CLOSURE I, and DEFENSE-PFO, have demonstrated that percutaneous PFO closure reduces the risk of recurrent ischemic stroke compared with medical therapy in carefully selected patients aged <60 years with cryptogenic stroke [4-9]. These studies have significantly influenced contemporary guideline recommendations and clinical practice [10]. Current guidelines generally support PFO closure in selected patients aged 18 to 60 years with a PFO-associated ischemic stroke after a thorough evaluation has excluded an alternative stroke mechanism [11]. Antiplatelet therapy remains an important component of secondary prevention; however, whether PFO closure is better than long-term anticoagulation in patients aged ≥60 years remains unknown [12]. The 2024 European Stroke Organisation guidelines similarly recommend closure plus antiplatelet therapy in appropriately selected patients aged 18 to 60 years but conclude that the evidence remains insufficient to establish an evidence-based recommendation for patients aged >60 years [10].

Patient selection for PFO closure requires integration of the clinical stroke phenotype, neuroimaging pattern, exclusion of competing etiologies, and anatomical characteristics of the PFO. High-risk features, particularly a large right-to-left shunt and the presence of an atrial septal aneurysm, increase the likelihood that a PFO is pathogenically relevant and may identify patients deriving greater benefit from closure [13]. The Risk of Paradoxical Embolism (RoPE) score was developed to estimate the probability that a PFO discovered in a patient with otherwise cryptogenic stroke is causally related to stroke rather than incidental [14]. The subsequent PFO-Associated Stroke Causal Likelihood (PASCAL) classification integrates RoPE-related clinical characteristics with high-risk PFO anatomy (including shunt size and the presence of an atrial septal aneurysm, as well as evidence of venous thromboembolism) to optimize risk stratification. The PASCAL classification categorizes the probability of stroke attributable to a PFO into 5 categories: definite, probable, highly probable, possible, and unlikely. These categories are intended to refine causal attribution and estimates of expected treatment benefit [15]. However, both approaches are strongly influenced by age, and the populations informing these frameworks predominantly consisted of patients aged <60 years. Therefore, these tools were not specifically derived or validated in patients aged >60 years and may not fully account for age-specific confounding mechanisms [16,17].

This limitation becomes particularly important in patients aged >60 years. Identifying a PFO in an older patient with an embolic-appearing infarct does not necessarily establish causality, even when high-risk PFO features are present. Conversely, attributing such events solely to age-associated vascular risk factors may result in underrecognition of a clinically relevant PFO. The RoPE score compounds this uncertainty because increasing age directly lowers the score, potentially assigning a low PFO-attributable fraction to older patients despite an otherwise strongly embolic phenotype and high-risk PFO anatomy. Although PASCAL improves causal attribution by incorporating anatomical characteristics, it was not specifically derived or validated to guide treatment decisions in patients aged >60 years. This uncertainty largely reflects the evidence base from which current recommendations were derived. All major randomized PFO closure trials, except DEFENSE-PFO, excluded patients aged >60 years [16,17]. Accordingly, adults aged >60 years remain substantially underrepresented in randomized evidence despite representing a large proportion of patients with ischemic stroke.

In summary, as life expectancy increases and the diagnostic evaluation of embolic stroke becomes more comprehensive, clinicians are likely to encounter increasing numbers of older patients with otherwise unexplained embolic-appearing infarcts and a PFO. Yet there is currently no dedicated, validated framework for determining PFO causality or selecting patients for closure specifically among adults aged >60 years. Decisions therefore frequently require extrapolation from younger trial populations and individualized assessment of PFO anatomy, stroke phenotype, vascular risk factors, and competing mechanisms.

The present multicenter study was developed within an established international stroke research network, with initial recruitment involving centers that had participated in the STOP-CAD collaborative studies. STOP-CAD was a large, international, multicenter study designed to evaluate antithrombotic treatment and recurrent ischemic events in patients with cervical artery dissection, enrolling patients across 63 centers in 16 countries [18]. These collaborations provided an established network of stroke centers with experience in standardized multicenter data collection and etiologic evaluation of ischemic stroke. Leveraging this network has enabled the present study to establish the

foundation for a large, multicenter dataset of adults aged >60 years with cryptogenic ischemic stroke and confirmed PFO.

Objectives

We hypothesize that among patients aged >60 years with embolic-appearing ischemic stroke and PFO, those treated with percutaneous PFO closure will have a lower risk of recurrent ischemic stroke than those treated with medical therapy alone, after adjusting for competing stroke etiologies and baseline clinical differences.

The primary objective of this study is to establish a large, multicenter dataset of adults aged >60 years with cryptogenic ischemic stroke and confirmed PFO. Because older patients undergoing PFO closure are uncommon, pooling data across centers is essential to create a sufficiently powered cohort that can support multiple analytic aims. This dataset will enable robust comparisons of the risks of recurrent ischemic stroke between patients treated with percutaneous PFO closure and those managed with medical therapy alone.

Secondary objectives include evaluating differences in key safety outcomes, including major bleeding, new-onset atrial fibrillation, and device-related procedural complications, and identifying clinical, imaging, and anatomical predictors of recurrent ischemic stroke in this older PFO population. The dataset will also facilitate exploratory analyses to compare the performance of existing risk attribution tools, including the RoPE score and PASCAL classification, in patients aged >60 years.

Methods

Study Design

This investigation is a multicenter, international, retrospective cohort study. Participating sites will include comprehensive stroke centers and high-volume referral centers with established capabilities for performing PFO closure and conducting advanced diagnostic evaluations of stroke. This study is retrospective and will involve the collection of deidentified clinical data.

Ethical Considerations

PFO-COPA (Patent Foramen Ovale Closure Outcomes in Patients of Advanced Age) is a retrospective chart review involving deidentified data, and the University of California San Diego's (UCSD) institutional review board (IRB) has reviewed the study and determined that it is exempt from IRB review (IRB number 814336). Therefore, no consent forms, participant information sheets, privacy notices, or invitation letters were required or created, because patients are not contacted or prospectively enrolled in the study. Each participating center will obtain local IRB approval or an exemption, in accordance with institutional, regional, or local requirements. A waiver of informed consent is anticipated due to the retrospective design and minimal risk. The study will adhere to the Declaration of Helsinki. No patient will be exposed to any inconvenience in relation to this study because all data will be obtained retrospectively. Results will be published in a peer-reviewed journal, and the study will be reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist [17].

Recruitment

Centers were recruited using a multimodal outreach strategy. The corresponding author contacted investigators from sites that had previously participated in the STOP-CAD study via email, outlining the study objectives and inviting collaboration. In parallel, study invitations were disseminated through professional social media platforms, including posts on the research team's X account and LinkedIn page, to broaden visibility among stroke and cardiology networks. Interested centers subsequently contacted the study team to obtain further details and initiate participation.

Following the execution of a data use agreement (DUA) and local IRB approval, each site will retrospectively identify consecutive eligible patients over a 10-year inclusion period (January 1, 2015, to January 1, 2025). Data will be abstracted from electronic medical records and institutional databases and then entered into a centralized, secure REDCap system (Vanderbilt University) hosted at the UCSD. All data will be deidentified prior to entry, with each site maintaining a local linkage file for internal auditing in accordance with institutional requirements.

Study Subjects

Inclusion Criteria

The study will be conducted across multiple comprehensive stroke centers. Each center will identify eligible patients using institutional stroke registries, cardiology procedure logs, neurosonology laboratory databases, echocardiography reports, and PFO closure procedure records.

Patients will be included if they meet all of the following criteria:

- Age ≥60 years
- Imaging-confirmed acute ischemic stroke (magnetic resonance imaging [MRI] diffusion-weighted imaging [DWI]–positive or computed tomography [CT]–confirmed infarct), defined as index event
- Undetermined etiology of stroke after standard diagnostic workup (cryptogenic stroke)
- Confirmed PFO based on transesophageal echocardiography or transthoracic echocardiography combined with a transcranial Doppler bubble study
- Treatment strategy following the index stroke consisting of either percutaneous PFO closure or medical therapy alone (antiplatelet therapy and/or anticoagulation)
- A minimum follow-up duration of 12 months after the index stroke, unless follow-up is truncated due to death

Exclusion Criteria

Patients will be excluded if they have any of the following:

- A definite alternative stroke mechanism likely to be causal, including the following:

    - Atrial fibrillation or another major cardioembolic source
    - Large artery atherosclerosis (≥50% stenosis or high-risk plaque)
    - Small vessel disease consistent with a lacunar infarct pattern
    - Other determined etiologies (eg, dissection, vasculitis)
- A mechanical heart valve or significant congenital heart disease (other than an isolated PFO or atrial septal defect)
- Active infective endocarditis
- Inadequate clinical follow-up (<12 months), unless death occurred within the follow-up window

Data Collection

All data will be collected through standardized retrospective chart review and entered into the REDCap database. REDCap is a secure, web-based platform that streamlines data collection by offering an intuitive interface for validated data entry, audit trails to monitor data changes and exports, automated options for exporting datasets to common statistical programs, and tools for importing information from external sources. Each participating center will designate a site principal investigator and at least 1 trained research coordinator responsible for local chart review and REDCap entry. The coordinating center (UCSD) will provide standardized definitions, training documents, and data entry guidance to ensure consistency across sites. If questions arise, the final decision on data entry will rest with the principal investigator of the coordinating center (RBS). Each site will maintain local identifiers for internal verification, if required, but only anonymous study IDs will be uploaded to the central database.

Variables and Definitions

Table 1 presents the baseline characteristics. A REDCap variable dictionary has been provided by the coordinating center to ensure the feasibility of data collection and will be shared with each participating center. Table 2 presents stroke characteristics and PFO diagnostic evaluation. Table 3 presents treatment variables, and Table 4 presents outcome variables. The full variable dictionary is available in Multimedia Appendix 1.

Table 1. Baseline characteristics.

Categories	Variables
Treatment assignment	Patent foramen ovale closure; medical therapy only
Demographics	Age at index ischemic stroke, sex, race, and ethnicity
Anthropometric measures	Height, weight, and BMI
Vascular risk factors	Hypertension, diabetes mellitus, dyslipidemia, smoking status, sleep apnea, continuous positive airway pressure use, chronic kidney disease, coronary artery disease, prior myocardial infarction, heart failure, pulmonary hypertension, and treatment for pulmonary hypertension
Cardiac arrhythmias	History of atrial fibrillation or atrial flutter
Thromboembolic history	Deep venous thrombosis, pulmonary embolism, and cerebral venous sinus thrombosis
Cancer history	Active noncutaneous malignancy and cancer type
Hormonal factors	HRT[a] and HRT type
Hypercoagulable states	History of thrombophilia or hypercoagulability; thrombophilia subtype (antiphospholipid syndrome, protein C deficiency, protein S deficiency, antithrombin deficiency, factor V Leiden, and prothrombin mutation)
Hypercoagulability evaluation	Poststroke thrombophilia testing, positive findings, established diagnosis, and treatment initiation
Risk scores	Risk of Paradoxical Embolism score and PASCAL[b] classification

[a]HRT: hormone replacement therapy.
[b]PASCAL: PFO-Associated Stroke Causal Likelihood.

Table 2. Stroke characteristics and patent foramen ovale (PFO) diagnostic evaluation.

Categories	Variables
Index stroke characteristics	Date of index ischemic stroke and National Institutes of Health Stroke Scale score at presentation
Prestroke antithrombotic therapy	Prior antiplatelet therapy and prior anticoagulation
Neuroimaging findings	Magnetic resonance imaging or computed tomography confirmation of infarction, embolic infarct pattern, infarct location, and number of vascular territories involved
Large artery assessment	Presence of nonstenotic carotid disease, carotid disease characteristics, and carotid web
Intracranial vascular imaging	Presence and location of intracranial occlusion
Cardiac evaluation	Transthoracic echocardiography performed, transesophageal echocardiography performed, and dates of studies
Transcranial doppler evaluation	Transcranial Doppler performed, date of examination, and Spencer grade
Cardiac rhythm monitoring	Rhythm monitoring performed, monitoring duration, and detection of atrial fibrillation or atrial flutter

Categories	Variables
Venous thromboembolism workup	Venous duplex ultrasonography performed, detection of deep vein thrombosis or pulmonary embolism, and timing of diagnosis
Cardiac structure and function	Ejection fraction, left atrial diameter, left atrial volume index, intracardiac thrombus, diastolic dysfunction grade, left ventricular mass index, right atrial size, and right atrial pressure
PFO anatomical characteristics	Shunt size by bubble count, shunt size by tunnel length, spontaneous shunt, Valsalva-induced shunt, presence of an atrial septal aneurysm, tunnel length, presence of a Eustachian valve, and presence of a Chiari network

Table 3. Treatment variables.

Categories	Variables
Patent foramen ovale closure procedure	Date of closure, device type, and procedural success
Procedural safety	Procedural complications and complication type
Postclosure medical therapy	Single antiplatelet therapy, dual antiplatelet therapy, anticoagulation, and no antithrombotic therapy
Specific antithrombotic agents	Antiplatelet agents and anticoagulant agents
Medical therapy cohort	Antithrombotic regimen at discharge (single antiplatelet therapy, dual antiplatelet therapy, anticoagulation, or none)
Specific medical therapy agents	Antiplatelet agents and anticoagulant agents

Table 4. Outcome variables.

Categories	Variables
Follow-up duration	Date of last follow-up and time from index stroke to last follow-up or death
Primary outcome	Recurrent ischemic stroke
Recurrent stroke details	Number of recurrent strokes, date of first recurrence, and imaging confirmation
Posttreatment atrial arrhythmias	New-onset atrial fibrillation or atrial flutter, timing of diagnosis, diagnostic modality, and persistence beyond 6 months
Mortality	All-cause mortality and date of death
Functional outcomes	Modified Rankin Scale score at discharge, at 90 days (±15 days), and at the most recent follow-up
Closure-specific outcomes	Follow-up echocardiography, follow-up transcranial Doppler examination, residual shunt size, and residual shunt Spencer grade

Study Groups

Participants will be categorized into two groups based on their treatment strategy:

1. PFO closure group: patients who underwent percutaneous PFO closure after the index ischemic stroke using a Food and Drug Administration (FDA)–approved closure device. The date of closure and the type of device will be recorded. The postprocedural antithrombotic regimen will also be documented.
2. Medical therapy group: patients managed without percutaneous closure. This group will include patients treated with antiplatelet therapy alone, anticoagulation therapy alone, or a combination of both. The type, dose, and duration of antithrombotic therapy will be recorded.

Outcome Measures

The outcomes to be collected will include recurrent ischemic stroke, major bleeding events, new-onset atrial fibrillation, device-related complications, all-cause mortality, and the modified Rankin Scale (mRS) score at follow-up. For patients in the closure group, the timing of closure relative to the index stroke will be recorded. The date of occurrence for each outcome will also be recorded.

Data Management and Quality Control

All sites will enter deidentified data into the centralized REDCap database based on the instructions in the variable dictionary and definitions manual. Each variable will include structured response options to minimize heterogeneity. Regular data quality audits will be performed, including range checks, evaluations of missing data, and random sampling of records for accuracy verification. Sites will maintain a local reidentification log stored securely at their respective institutions. The coordinating center will not have access to identifiable information. To ensure the feasibility of data entry, a pilot data entry platform will be available to participating centers before formal data entry.

Statistical Analysis Plan

Baseline characteristics will be summarized using descriptive statistics. Continuous variables with a normal distribution will be reported as means and SDs, whereas skewed variables will be presented as medians and IQRs. Categorical variables will be reported as frequencies and percentages. The distribution of variables will be visually assessed using Q-Q plots and box plots and formally evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Variability will also be examined through inspection of box plots. Descriptive statistics will be reported, and group differences will be analyzed using the chi-square test, Fisher exact test, or univariate logistic regression, depending on the nature of the data. Group differences in continuous variables will be assessed using the Student *t* test for normally distributed data and the Mann-Whitney *U* test for skewed data. Variables demonstrating significance in univariate analyses ($P<.20$) will be

considered for inclusion in multivariable regression models to adjust for potential confounders. Given the nonrandomized retrospective design, propensity score methods and inverse probability of treatment weighting (IPTW) will be used to reduce treatment selection bias. Propensity score matching will be performed using nearest-neighbor 1:1 matching with a predefined caliper width of 0.2 SDs of the logit of the propensity score, consistent with established methodological recommendations. Covariate balance between treatment groups will be assessed using standardized mean differences (SMDs), with values <0.1 considered indicative of adequate balance. Both prematching and postmatching SMDs will be reported for all baseline variables. To visually display covariate balance, Love plots will be generated, illustrating the distribution of SMDs across covariates before and after matching. These plots will provide a clear graphical summary of improvements in covariate balance and highlight any residual imbalances requiring further adjustment.

The primary outcome is recurrent ischemic stroke. Time-to-event analysis will be performed using Kaplan-Meier survival curves with log-rank testing to compare the closure and medical therapy groups. Cox proportional hazards regression modeling will be used to estimate hazard ratios (HRs) for recurrent ischemic stroke associated with closure after adjustment for confounders, including age, sex, and vascular risk factors.

Secondary outcomes, including major bleeding, new-onset atrial fibrillation, device-related complications, and mortality, will be compared between groups using time-to-event analyses, where appropriate. For outcomes with competing risk of death, competing risk regression models (Fine-Gray subdistribution hazard models) will be performed.

Multivariable Cox regression modeling will be used to identify independent predictors of recurrent ischemic stroke in the full cohort. Candidate predictors will include PFO anatomical variables, stroke phenotype markers, comorbidity burden, malignancy-related markers, and atrial cardiopathy indicators. All analyses will be conducted using R (version 4.5.2; R Foundation for Statistical Computing). Multimedia Appendix 2 outlines the planned data presentation.

Sample Size

Given the retrospective multicenter design, the study sample size is primarily determined by the number of eligible patients available across participating centers rather than by a prospective power calculation for a single predefined treatment effect. Based on preliminary feasibility assessments across participating sites, we anticipate including approximately 800 patients aged ≥60 years with cryptogenic ischemic stroke and confirmed PFO between January 2015 and January 2025.

For context, prior projections for randomized trials in older patients with cryptogenic stroke and PFO, based on pooled observational and randomized trial data from the RoPE-Ox and SCOPE databases, estimated that 471 and 630 participants with high-risk PFO features would be required to achieve 80% and 90% power, respectively, over 5 years of follow-up [19]. These estimates are provided as contextual benchmarks and will not be used as a formal power calculation for the present study. The anticipated cohort of approximately 800 patients is therefore considered a feasibility-based target sample size intended to provide a large multicenter dataset for estimating and comparing recurrent ischemic stroke and safety outcomes between the PFO closure and medical therapy groups.

Patient and Public Involvement Statement

Because all data will be retrieved from medical records without affecting the patients' future treatment, we did not involve patients or the public in designing this study or writing the protocol.

Results

As of October 2026, 51 centers from 10 countries (Argentina, Brazil, Colombia, Greece, Italy, Japan, Mexico, Portugal, Spain, and the United States) have formally agreed to participate in the study. Each site is in the process of obtaining IRB approval and executing DUAs. A standardized variable dictionary has been distributed (Multimedia Appendix 1), and centers are expected to commence data entry into the REDCap database hosted at UCSD in December 2026. As of October 2026, 45 centers had applied for local IRB approval, 5 had obtained local IRB approval, and 3 had begun entering data into REDCap. The projected end date of data collection is June 2027. A total of 23 research proposals have been submitted by collaborating investigators, which will be reviewed and prioritized once sufficient data have been collected. Preliminary pooled analyses are anticipated for release in July 2027. The study is not funded.

Discussion

Anticipated Findings

The PFO-COPA study is the first large, multicenter retrospective cohort specifically designed to evaluate the outcomes of PFO closure in patients aged ≥60 years with cryptogenic ischemic stroke. By pooling data across collaborating centers, this study directly addresses the evidence gap left by randomized trials that systematically excluded older adults [17,20,21]. This gap is also reflected in contemporary guidelines. The 2024 European Stroke Organisation guideline recommends PFO closure in appropriately selected patients aged 18 to 60 years but concludes that the evidence remains insufficient to formulate an evidence-based recommendation for patients aged >60 years, specifically encouraging their inclusion in randomized trials or prospective registries [10]. The establishment of a centralized dataset will enable robust comparisons of PFO closure and medical therapy, while also supporting secondary analyses of safety outcomes and predictors of stroke recurrence.

Although randomized evidence in older adults remains sparse, recent reviews of observational studies suggest that PFO closure may be feasible and potentially beneficial in carefully selected patients aged ≥60 years. In a systematic review and meta-analysis by Jazayeri et al [17], PFO closure was associated with a lower risk of recurrent stroke than antithrombotic therapy alone (5.48% vs 10.05%; HR 0.56, 95% CI 0.43-0.74), as well as lower all-cause mortality (1.73% vs 7.59%; HR 0.41, 95% CI 0.19-0.90), without a significant difference in new-onset atrial fibrillation (HR 1.13, 95% CI 0.53-2.44). However, patients aged ≥60 years undergoing PFO closure remained at higher risk of recurrent stroke and new-onset atrial fibrillation than younger patients, highlighting the distinct risk profile of this population [17]. Similarly, a recent meta-analysis by de Deus et al [20], including 6,725 patients aged ≥60 years, found that PFO closure was associated with lower risks of recurrent ischemic stroke or transient ischemic attack (risk ratio [RR] 0.49, 95% CI 0.35-0.67) and all-cause mortality (RR 0.39, 95% CI 0.18-0.87) than medical therapy alone, without significant differences in new-onset atrial fibrillation or atrial flutter or major bleeding [20]. Nevertheless, both meta-analyses were predominantly based on observational data, leaving substantial potential for selection bias, residual confounding, and heterogeneity in patient selection. These limitations underscore the need for large, systematically characterized multicenter cohorts such as PFO-COPA to better define outcomes and identify older patients most likely to benefit from closure.

Several methodological strengths enhance the anticipated impact of this work. The multicenter design will ensure diversity in practice patterns and patient populations, thereby improving generalizability. Standardized definitions and a shared variable dictionary (Multimedia Appendix 1) promote consistency across sites, while centralized data entry into REDCap will provide strong quality control [22]. Importantly, the retrospective design will allow rapid accrual of a large sample size (approximately 800 patients), which would be difficult to achieve in a prospective randomized trial involving older patients [19].

Nonetheless, several limitations inherent to the retrospective design must be acknowledged. A key limitation is the uncertainty in attributing ischemic events to PFO in patients aged ≥60 years, among whom competing stroke mechanisms, including occult atrial fibrillation, aortic arch atheroma, and small vessel disease, are increasingly prevalent [23]. Even with strict eligibility criteria and comprehensive diagnostic evaluation, alternative or coexisting stroke mechanisms may remain undetected, resulting in potential misclassification of PFO-associated events. Furthermore, data collection may be incomplete and heterogeneous across centers, with site-level differences in diagnostic intensity, including rhythm monitoring and imaging protocols, as well as the duration and completeness of follow-up. Although standardized data collection and predefined definitions are intended to minimize this variability, they cannot eliminate it entirely. Treatment assignment is nonrandomized, introducing potential selection bias, and although propensity score methods and multivariable adjustment will mitigate measured confounding, residual and unmeasured confounding cannot be excluded. Harmonization of anatomical PFO risk features, such as shunt size and the presence of an atrial septal aneurysm, across centers also poses challenges despite mapping efforts. Accordingly, the planned matching, adjustment, and standardization strategies are intended to mitigate, rather than eliminate, these inherent sources of bias.

Despite these limitations, the PFO-COPA study is expected to provide the largest real-world evaluation of closure outcomes in older adults to date. As of October 2026, 51 centers have agreed to participate, IRB approvals and DUAs are underway, and 23 research proposals have already been submitted by investigators. Data entry began in September 2026, and preliminary pooled analyses are anticipated in July 2027. The resulting dataset will not only inform clinical practice and guideline development but also serve as a foundation for future prospective studies and risk stratification tools tailored to older populations.

Expected Impact

The PFO-COPA study will deliver the most comprehensive real-world evaluation of PFO closure outcomes in patients aged 60 to 80 years, a population systematically excluded from pivotal randomized closure trials. By quantifying both effectiveness and safety outcomes in this understudied age group, the study will address a major clinical evidence gap and guide practice patterns. Furthermore, the dataset will enable the development of an advanced-age risk-selection framework, providing clinicians with a practical tool to improve patient selection, reduce unnecessary closure procedures in patients with incidental PFOs, and identify those most likely to benefit. These findings may support future guideline updates and serve as the foundation for prospective multicenter trials specifically designed for older adults.

Generative AI Use

The authors declare the use of generative AI (GenAI) during manuscript preparation. According to the Generative AI Delegation Taxonomy (2025), the following tasks were delegated to GenAI tools under full human supervision: proofreading and editing, synthesizing text, and reformatting. The GenAI tools used were ChatGPT (GPT-6; OpenAI) and Claude (version 5.5; Anthropic); multiple model versions were used during manuscript preparation. Responsibility for the final manuscript lies entirely with the authors.

Funding

The authors declare that no financial support was received for this work.

Data Availability

Participant-level data are held solely at the University of California San Diego (UCSD), the coordinating center, and will not be transferred to participating sites or third parties, in accordance with the data use agreements and local institutional review board (IRB) approvals governing this study. Data are therefore not publicly available. Aggregate results will be reported in publications. Reasonable requests for additional analyses may be submitted to the corresponding author; approved analyses will be performed by the coordinating center, and only aggregate results will be released. Deidentified participant-level data, the data dictionary, and the analysis code will be made available by the corresponding author upon reasonable request after publication of the primary results. Requests will be reviewed by the PFO-COPA (Patent Foramen Ovale Closure Outcomes in Patients of Advanced Age) steering committee, and access will require a data use agreement with UCSD and approval from the requesting investigator's IRB. Data from sites whose local regulations or data use agreements restrict onward transfer will be excluded or shared only with the permission of the respective site.

Authors' Contributions

SBJ, SY, and RBS contributed to conceptualization; CP and AE contributed to methodology and project administration; and BCM, DMM, SY, and RBS supervised the project. SBJ wrote the original draft, and all authors reviewed and edited the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1

REDCap variables and definitions for the PFO-COPA (Patent Foramen Ovale Closure Outcomes in Patients of Advanced Age) study.
[DOCX File (Microsoft Word File), 27 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Template for presenting baseline characteristics of patients before and after matching.
[DOCX File (Microsoft Word File), 21 KB-Multimedia Appendix 2]

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Abbreviations

CT: computed tomography
DUA: data use agreement
DWI: diffusion-weighted imaging
FDA: Food and Drug Administration
HR: hazard ratio
IPTW: inverse probability of treatment weighting
IRB: institutional review board
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
PASCAL: PFO-Associated Stroke Causal Likelihood
PFO: patent foramen ovale
PFO-COPA: Patent Foramen Ovale Closure Outcomes in Patients of Advanced Age
RoPE: Risk of Paradoxical Embolism
RR: risk ratio
SMD: standardized mean difference
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
UCSD: University of California San Diego

Edited by Amy Schwartz; peer-reviewed by Muhammad Haris; submitted 08.Jun.2026; initial comments to author 17.Sep.2026; final revised version received 27.Sep.2026; accepted 16.Oct.2026; published 20.Nov.2026

Please cite as:
Jazayeri SB, Phan C, Eghbalnejadmofrad A, Meyer BC, Meyer DM, Yaghi S, Bavarsad Shahripour R

Patent Foramen Ovale Closure Outcomes in Patients of Advanced Age (PFO-COPA): Protocol for a Multicenter Retrospective Cohort Study
JMIR Res Protoc 2026;15:e104052
URL: https://www.researchprotocols.org/2026/1/e104052
doi: 10.2196/104052

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