International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

INPLASY202670116

doi: 10.37766/inplasy2026.7.0116

Received: 29 July 2026

Published: 29 July 2026

Patent Foramen Ovale Closure for Migraine: A Systematic Review and Meta-Analysis of Efficacy and Safety

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ADMINISTRATIVE INFORMATION

Support - None declared.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202670116

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 July 2026 and was last updated on 29 July 2026.

INTRODUCTION

Review question / Objective To systematically evaluate the efficacy and safety of transcatheter PFO closure compared with medical therapy or sham procedure in patients with migraine and PFO. The primary efficacy outcome is complete migraine cessation (responder rate). Secondary outcomes include changes from baseline in monthly migraine attack frequency, monthly migraine days, Headache Impact Test-6 (HIT-6) score, and Visual Analogue Scale (VAS) score; safety outcomes are also assessed. Subgroup and sensitivity analyses are performed to explore sources of heterogeneity.

Rationale The association between patent foramen ovale (PFO) and migraine, particularly migraine with aura, has been well established. However, the efficacy of transcatheter PFO closure for migraine treatment remains highly controversial. The 2024 European Society of Cardiology/ European Stroke Organisation (ESC/ESO) guidelines and the 2025 American Heart Association/American Stroke Association (AHA/ ASA) scientific statement explicitly do not recommend PFO closure for routine migraine treatment (Class III recommendation). Early sham-controlled RCTs (MIST, PRIMA, PREMIUM) failed to meet their primary efficacy endpoints, while subsequent cohort studies have reported positive results, creating a persistent evidence-practice tension. This updated systematic review and meta-analysis aims to comprehensively evaluate all available evidence from RCTs and observational studies, assess the efficacy and safety of PFO closure for migraine, dissect the sources of heterogeneity, and provide a reference for future research and clinical decision-making.

Condition being studied Migraine (with or without aura) in patients with patent foramen ovale (PFO).

METHODS

Search strategy We systematically searched PubMed, Embase, and the Cochrane Central

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Register of Controlled Trials (CENTRAL) from inception to May 2025. The search strategy combined terms for "patent foramen ovale" or "PFO", "migraine", and "closure" or "occluder" using both MeSH terms and free text. Detailed search strategies are available in the online supplement.

Participant or population Adult patients (≥18 years) with a definite diagnosis of migraine (with or without aura) according to the International Classification of Headache Disorders (ICHD-2 or ICHD-3), and confirmed PFO by transthoracic/transoesophageal echocardiography (TTE/TEE) or transcranial Doppler (TCD.

Intervention Transcatheter PFO closure.

Comparator Medical therapy (e.g., antiplatelet agents, standard migraine prophylactics) or sham procedure.

Study designs to be included Randomised controlled trials (RCTs), non-randomised controlled trials, and prospective or retrospective cohort studies with a control group.

Eligibility criteria Studies reporting at least one of the following outcomes: (i) primary outcome — complete migraine cessation at end of follow-up (responder rate); (ii) secondary outcomes — changes from baseline in monthly migraine attack frequency, monthly migraine days, HIT-6 score, VAS score, and procedure-related adverse events. We excluded case reports, uncontrolled case series, reviews, editorials, animal studies, and studies with insufficient data for extraction.

Information sources PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL).

Main outcome(s) Primary outcome: complete migraine cessation (responder rate) at the end of follow-up.

Additional outcome(s) Secondary outcomes: changes from baseline in monthly migraine attack frequency; changes from baseline in monthly migraine days; changes from baseline in Headache Impact Test-6 (HIT-6) score; changes from baseline in Visual Analogue Scale (VAS) score for pain severity; procedure-related adverse events (including atrial fibrillation, pericardial effusion, access-site haematoma, and device-related thrombosis).

Data management Two reviewers independently screened titles, abstracts, and full texts. Disagreements were resolved by discussion or by consulting a third reviewer. Using standardised forms, we extracted study characteristics (first author, year, country, design), patient demographics (sample size, age, sex, migraine subtype), PFO diagnostic methods and shunt grade, intervention and control details, follow-up duration, and all reported outcomes. For continuous variables, we preferred mean changes from baseline with standard deviations (SD); if not reported directly, we imputed them from baseline and follow-up values according to the Cochrane Handbook methodology. Two reviewers independently extracted data and cross-checked for accuracy.

Quality assessment / Risk of bias analysis Risk of bias was assessed using the Cochrane RoB 2.0 tool for RCTs and the Newcastle-Ottawa Scale (NOS) for observational cohort studies. NOS scores of 0-3, 4-6, and 7-9 denote low, moderate, and high quality, respectively.

Strategy of data synthesis All analyses were performed using Review Manager 5.4 (Cochrane Collaboration). For dichotomous outcomes (migraine cessation), pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated; for continuous outcomes, mean differences (MD) with 95% CI were derived. We applied the DerSimonian-Laird random-effects model for all pooled analyses to account for anticipated between-study heterogeneity. Statistical heterogeneity was assessed using the Cochrane Q test and the I^2 statistic, with I^2 >50% considered substantial. Pre-specified subgroup analyses were performed according to study design (RCT vs. cohort) and control type (sham vs. medical therapy). Sensitivity analyses were conducted by excluding one study at a time to evaluate the influence of individual studies on the pooled estimates. For outcomes with ≥10 included studies, publication bias was assessed by visual inspection of funnel plots. A two-sided P <0.05 was considered statistically significant.

Subgroup analysis Subgroup analyses will be performed according to study design (RCT vs. cohort study) and comparator type (sham procedure vs. medical therapy) to explore potential sources of heterogeneity.

Sensitivity analysis Subgroup analyses will be performed according to study design (RCT vs. cohort study) and comparator type (sham procedure vs. medical therapy) to explore potential sources of heterogeneity.

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Language restriction No language restrictions.

Country(ies) involved China.

Other relevant information None.

Keywords Migraine; Patent Foramen Ovale; PFO; Closure; Meta-Analysis; Systematic Review; Guideline Recommendations.

Dissemination plans The results of this systematic review and meta-analysis will be disseminated through publication in a peer-reviewed academic journal and presentation at relevant national or international conferences. This review does not require ethical approval because all data used have already been published and will be analyzed anonymously during the review process.

Contributions of each author

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