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# Patent foramen ovale closure in ischemic stroke patients with and without thrombophilia: a systematic review and meta-analyses

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## Abstract

Ischemic stroke patients with thrombophilia and patient foramen ovale (PFO) may have an increased risk of recurrent stroke and transient ischemic attack (TIA), and may benefit from PFO closure. However, screening for thrombophilia is not routinely performed and the impact of thrombophilia on prognosis after PFO closure is uncertain. We aim to compare the risk of recurrent stroke and TIA after PFO closure in patients with thrombophilia versus those without. We performed a systematic review and meta-analyses of the literature, with a comprehensive literature search performed on 12 January 2023. Studies comparing the outcomes of patients with and without thrombophilia after PFO closure were included. The primary outcome evaluated was a recurrence of acute cerebrovascular event (ACE), a composite of recurrent ischemic stroke and recurrent TIA. The secondary outcomes included recurrent ischemic stroke only or TIA only. A total of 8 cohort studies were included, with a total of 3514 patients. There was an increased risk of stroke/TIA in patients with thrombophilia compared to those without thrombophilia after PFO (OR: 1.42, 95% CI: 1.01–1.99, $I^2 = 50\%$). The association between risk of TIA only (OR: 1.36, 95% CI: 0.77–2.41, $I^2 = 0\%$) and stroke only (OR: 1.09, 95% CI: 0.54–2.21, $I^2 = 0\%$) with thrombophilia did not reach statistical significance. There is an increased risk of recurrent cerebral ischemia event in patients with thrombophilia compared to those without thrombophilia after PFO closure. Future large prospective studies are necessary to characterise the risk and benefits of PFO closure, as well as the appropriate medical treatment to reduce the risk of recurrent stroke and TIA in this high-risk population.

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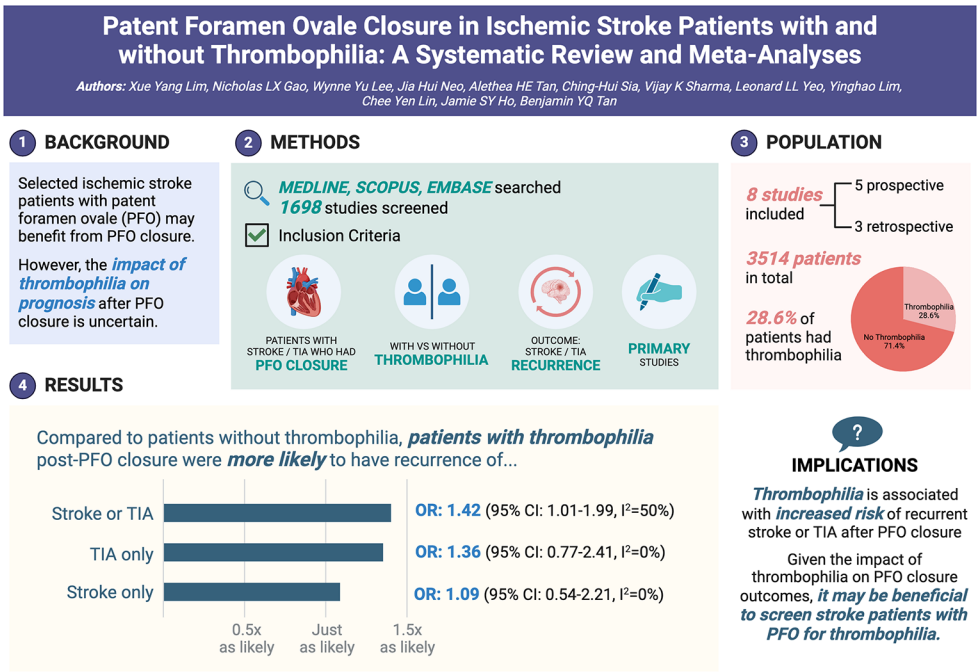
## Graphical Abstract




**Keywords** Patent foramen ovale · Closure · Thrombophilia · Ischemic stroke · Transient ischemic attack · Recurrence

## Introduction

A patent foramen ovale (PFO) is a potential source of cryptogenic stroke, with a 40–50% prevalence of PFO found in patients with cryptogenic stroke [1]. Percutaneous transcatheter closure of PFO has been shown to reduce the rate of recurrent cerebrovascular events and is considered a safe and effective treatment in selected patients with PFO-related stroke. However, careful patient selection for PFO closure is necessary as PFO may be incidental in many cases of stroke, and the procedure itself may be associated with adverse events such as thrombus formation and atrial fibrillation [2].

Thrombophilia is defined as a condition which predisposes to, or tendency to form thrombi, and is associated with both venous and arterial thromboses, and increased risk of acute ischemic strokes. The prevalence of thrombophilia in patients with PFO is around 3–41% [3], although the decision to test for thrombophilia in stroke patients is also clinician-dependent, and the American Heart Association/American Heart Association guidelines do not recommend routine testing [4]. The impact of thrombophilia on the outcomes of PFO closure is also uncertain. Due to the exclusion of patients with thrombophilia from many randomized controlled trials, current European and American guidelines do not make definitive recommendations for the use of PFO closure in patients with PFO-related stroke and thrombophilia [5].

Recently, several observational studies have explored PFO closure in patients with thrombophilia, and it is of clinical importance to understand the risk and benefits of PFO closure in this high-risk population. Therefore, in this systematic review, we aim to compare the risk of recurrence of cerebrovascular events after PFO closure in patients with and without thrombophilia.

## Methods

### Search strategy and inclusion criteria

We performed a literature search in MEDLINE, SCOPUS and EMBASE for papers published from inception to 12 January 2023. The search strategy made use of a combination of relevant keywords and Medical Subject Headings (MeSH) terms, such as “PFO or patent foramen ovale or septal defect” and “thrombophilia or hypercoagulability or coagulopathy”. The reference lists of included papers were hand-searched for relevant papers that were not identified in the database search. Only English language studies were included from the results.

Studies which met the following criteria were included in the systematic review: [1] Population: patients with a history of stroke or transient ischemic attack (TIA) who underwent PFO closure; [2] Intervention: presence of thrombophilia; [3] Comparison: absence of thrombophilia [4], Outcome: recurrent stroke or TIA; [4] Study design: primary study. Studies also needed to include a subgroup analysis for patients with thrombophilia. Conference abstracts, singular case reports and case series with less than 10 cases were excluded.

The title and abstract of each study were independently reviewed by two authors according to the pre-defined inclusion criteria. Potentially relevant studies were then advanced to full text screening for further assessment. The full text of an article was also reviewed when there was uncertainty in the title and abstract screening. Disagreements were resolved through discussion and consensus between the reviewers.

### Data extraction

The extraction of data from each included study was performed independently by two reviewers. Any uncertainty or discrepancies were resolved through discussion and consensus among the reviewers. Data extracted included study characteristics (authors and year), study design, total study population, number of participants with thrombophilia, types of thrombophilia, participant characteristics (mean age, gender, cardiovascular risk factors including diabetes mellitus, hypertension, hyperlipidemia and smoking, and high and low risk anatomical features), mean follow-up duration, and the number of events for each outcome.

### Diagnosis of stroke and TIA

Ischemic stroke is defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction by the American Heart Association/American Stroke Association, while TIAs are brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction [6]. PFO closure was only performed in patients with cryptogenic stroke, according to the TOAST (Trial of Org 10,172 in Acute Stroke Treatment) definition, where no cause of stroke was identified despite extensive investigations, and stroke attributable to paradoxical embolization [7].

### Definition of thrombophilia

Hypercoagulability work-up with functional assays that included homocysteine, proteins C and S, antithrombin III, factor II mutation, factor V Leiden mutation and antiphospholipid antibodies (including lupus anticoagulant, anticardiolipin antibodies) were performed for patients. The presence of a positive test helps to define thrombophilia in these studies.

## Outcomes

The primary outcome of this systematic review was the recurrence of an acute cerebrovascular event (ACE), a composite of recurrent ischemic stroke and recurrent TIA. The secondary outcomes were recurrent ischemic stroke only or TIA only.

### Risk of bias assessment

The quality of the included observational cohort studies was assessed using the Newcastle–Ottawa scale. The assessment criteria include selection, comparability and outcome. In accordance with the Newcastle–Ottawa quality assessment scale, most observational cohort studies were assessed to be of low risk of bias (Table 1).

### Statistical analysis

All analyses were performed with the Review Manager (RevMan) version 5.1 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2011). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each outcome using the Mantel–Haenszel random-effects method. Heterogeneity between trials was assessed by measuring inconsistency using the $I^2$ index, which measures the proportion of the variability in effect estimates that can be attributed to heterogeneity rather than chance. $I^2$ is calculated as follows: $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran heterogeneity statistic and of the degrees of freedom. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Mean follow-up duration was calculated by the follow-up duration reported in the trials.

## Results

### Study selection

A total of 1698 studies were screened for eligibility. Eight studies were included (5 prospective cohort studies and 3 retrospective cohort studies) [8–15], with a total of 3514 patients. Among the 3514 patients who had undergone PFO closure in the 8 studies, 1006 patients (28.6%) had thrombophilia. The follow up duration of the studies ranged from an

**Table 1** Quality assessment of included studies with the newcastle ottawa scale

| Author | Year | Selection (Max ☆☆☆☆) | | | | Comparability (Max ☆☆) | | Outcome (Max ☆☆☆) | | | Total Score (Max 9☆) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Outcomes absent at study start | Study controls for age | Study controls for gender or other factors | Assessment of outcome | Appropriate follow-up time | Adequate follow-up of cohorts | |
| Lusine Abrahamyan | 2023 | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | 9 |
| Ben-Assa et al. | 2021 | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | 9 |
| Deng Wenjun | 2020 | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | 9 |
| Wintzer-Wehekind et al. | 2019 | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | 9 |
| Kefer et al. | 2012 | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | 9 |
| Ford et al. | 2009 | ☆ | ☆ | ☆ | | ☆ | ☆ | ☆ | ☆ | ☆ | 8 |
| Bartz et al. | 2006 | ☆ | ☆ | ☆ | | ☆ | ☆ | ☆ | ☆ | ☆ | 8 |
| Giardini et al. | 2004 | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | 9 |

average of 5.3 months to 12 years. The flow chart detailing the study selection process is shown in Fig. 1.

## Incidence of cerebrovascular events

All 8 studies reported varying incidences of cerebrovascular events among patients who had undergone PFO closure ranging from 1.7 to 9.7% (Table 2). Across the 8 studies, there were a total of 3514 patients who underwent PFO closure. Among these patients, recurrent acute cerebrovascular events were reported in 155 patients, yielding an overall pooled incidence of 4.4%.

## Clinical characteristics of patients

The mean patient age ranges from 29 to 53.4 years across the studies. The distribution of patient genders is fairly even across the studies, with the percentage of female participants ranging from 40.9 to 61%, and male participants from 39 to 59.1%. Common co-morbidities include diabetes mellitus, hypertension, hyperlipidaemia and smoking. Common PFO closure device types include AMPLATZER occluder, CardioSEAL STARFlex device and HELEX PFO occluder. In 4 out of the 8 studies [10, 11, 13, 15], considerations were made regarding the features of PFO shunts before closure, leading to the classification of patients based on high and low-risk anatomical shunt features. The risk factors included shunt size, grade of right to left shunt and presence of high-risk features such as atrial septal aneurysm and intracardiac thrombus. The baseline characteristics of included studies are shown in Table 3.

The common types of thrombophilia recorded across the studies include antiphospholipid syndrome, protein S deficiency, protein C deficiency, factor V Leiden, antithrombin III deficiency, prothrombin gene mutation and hyperhomocysteinemia. The breakdown of positivity for each thrombophilia test is shown in Table 4.

## Patient outcomes

There was an increased risk of an acute cerebrovascular event (stroke/TIA) in patients with thrombophilia compared to those without thrombophilia after PFO closure (OR: 1.42, 95% CI: 1.01–1.99), with moderate study heterogeneity ($I^2 = 50\%$). (Fig. 2)

We evaluated the primary outcome of prospective and retrospective studies separately and we note that the moderate heterogeneity in results could be contributed by the higher heterogeneity when we evaluated retrospective studies alone (Fig. 3). However, the overall association between thrombophilia and recurrent acute cerebrovascular events is still significant. Leave on out sensitivity analysis was also

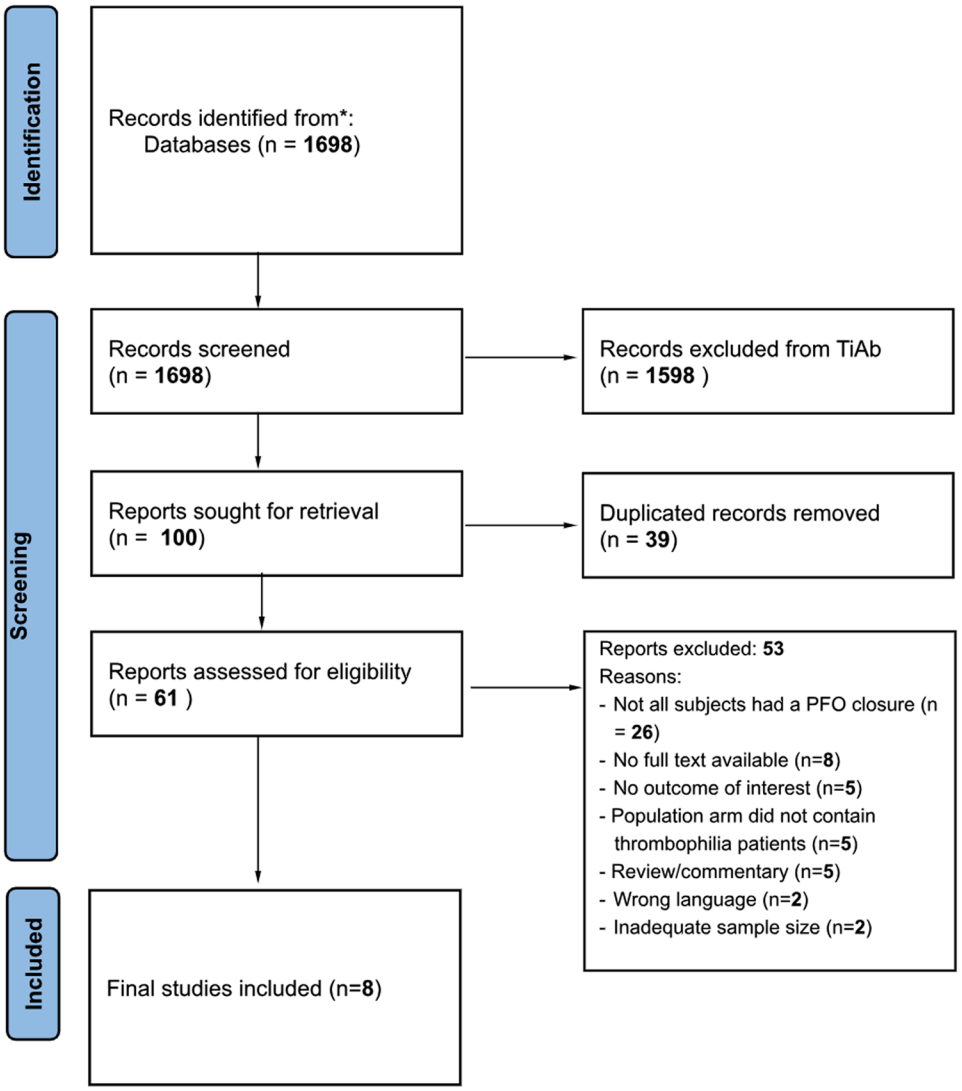



**Fig. 1** PRISMA flow diagram of the study selection process

**Table 2** Incidence of cerebrovascular event in post-PFO patients in included studies

| Study | Total number of patients | Total number of patients with cerebrovascular event | Number of thrombophilia patients with Cerebrovascular event | Number of non-thrombophilia patients with cerebrovascular event |
|---|---|---|---|---|
| Lusine Abrahamyan | 669 | 57 (8.5%) | 16 (9.2%) | 41 (8.3%) |
| Ben-Assa et al., 2021 | 800 | 22 (2.8%) | 8 (1%) | 14 (1.8%) |
| Deng et al., 2020 | 1088 | 42 (3.9%) | 19 (1.7%) | 23 (2.2%) |
| Wintzer-Wehekind et al., 2019 | 201 | 8 (4%) | 3 (1.5%) | 5 (2.5%) |
| Kefer et al., 2012 | 287 | 5 (1.7%) | 1 (0.3%) | 4 (1.4%) |
| Ford et al., 2009 | 352 | 8 (2.3%) | 5 (1.4%) | 3 (0.9%) |
| Bartz et al., 2006 | 45 | 1 (2.2%) | 0 (0%) | 1 (2.2%) |
| Giardini et al., 2004 | 72 | 3 (4.2%) | 1 (1.4%) | 2 (2.8%) |

**Table 3** Baseline characteristics of included studies

| Authors, Year | Study design | n | Thrombophilia (%) | Mean Age ± SD (Median) | Female (%) | CVD Risk Factors | | | High Risk Anatomical Features* | Low Risk Anatomical Features** | Mean Follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Total | Thrombophilia | No Thrombophilia | | | |
| Lusine Abrahamyan, 2023 | Retrospective cohort | 669 | 26.0 | 46.4 +-12.1 | 44.5 | DM – 41 (6.1%)<br>HTN – 181 (27.1%)<br>HLD – 244 (36.5%)<br>Smoking – 226 (33.8%) | DM – 6 (0.9%)<br>HTN – 50 (7.5%)<br>HLD – 71 (10.6%)<br>Smoking – 56 (8.4%) | DM – 35 (5.2%)<br>HTN – 131 (19.6%)<br>HLD – 173 (25.9%)<br>Smoking – 170 (25.4%) | NA | NA | 139.2 |
| Ben-Assa et al., 2021 | Prospective cohort | 800 | 29.9 | 50 ± 14 | 47.8 | DM – 48 (6%)<br>HTN – 245 (30.6%)<br>HLD – 276 (34.5%)<br>Smoking – 75 (9.4%) | DM – 14 (1.75%)<br>HTN – 76 (9.5%)<br>HLD – 91 (11.4%)<br>Smoking – 22 (2.8%) | DM – 34 (4.25%)<br>HTN – 169 (21.1%)<br>HLD – 185 (23.1%)<br>Smoking – 53 (6.6%%) | NA | NA | 41.9 |
| Deng et al., 2020 | Prospective cohort | 1078 | 43.2 | 49.3 ± 13.7 | 45.4 | DM – 65 (6%)<br>HTN – 285 (26.2%)<br>HLD – 317 (29.1%)<br>Smoking – 119 (11%) | NA | NA | 11 (1%) | 7(0.64%) | 44.4 |
| Wintzer-Wehekind et al., 2019 | Prospective cohort | 201 | 8.0 | 47 ± 12 | 50.7 | DM – 9 (4.5%)<br>HTN – 48 (23.9%)<br>HLD – 46 (22.9%)<br>Smoking – 22 (10.9%) | NA | NA | 37 (18.4%) | 74 (36.8%) | 144 (120–204) |
| Kefer et al., 2012 | Prospective cohort | 287 | 10.1 | 43 ± 14 | 61 | DM – 11 (3.8%)<br>HTN – 72 (25%)<br>HLD – 82 (28.6%)<br>Smoking – 84 (29.3%) | NA | NA | NA | NA | 60 (9.6-134.9) |
| Ford et al., 2009 | Retrospective cohort | 352 | 10.0 | 53.4 | 40.9 | DM – 25 (7.1%)<br>HTN – 130 (36.9%)<br>HLD – 146 (41.5%)<br>Smoking – 31 (8.8%) | NA | NA | 41 (11.6%) | 86 (24.4%) | 37 |
| Bartz et al., 2006 | Retrospective cohort | 45 | 15.6 | 29 | 48.9 | HTN – 3 (6.7%)<br>HLD – 2 (4.4%)<br>Smoking – 10 (22.2%) | NA | NA | NA | NA | 63.6 |
| Giardini et al., 2004 | Prospective cohort | 72 | 27.8 | 42 ± 13 | NA | DM – 1 (1.4%)<br>HTN – 11 (15.3%)<br>HLD – 11 (15.3%)<br>Smoking – 19 (26.4%) | DM – 0<br>HTN – 4 (5.6%)<br>HLD – 3 (4.2%)<br>Smoking – 5 (11.1%) | DM – 1 (1.4%)<br>HTN – 7 (9.7%)<br>HLD – 8 (11.1%)<br>Smoking – 14 (15.3%) | 44 (61.1%) | 28 (38.9%) | 238.8 |

*High risk anatomical features: moderate to large shunt size, moderate to severe grade right to left shunt, presence of atrial septal aneurysm, presence of intracardiac thrombus

**Low risk anatomical features: small shunt size, minimal grade right to left shunt

performed, and the result remained statistically significant on the removal of any one study (Supplementary Materials).

The association between the risk of TIA with thrombophilia did not reach statistical significance (OR: 1.36, 95% CI: 0.77–2.41), with no observed heterogeneity ($I^2 = 0\%$) (Fig. 4).

The association between the risk of ischemic stroke with thrombophilia did not reach statistical significance (OR: 1.09, 95% CI: 0.54–2.21), with no observed heterogeneity ($I^2 = 0\%$) (Fig. 5).

## Discussion

This meta-analysis shows that there is an increased risk of recurrent ACE after PFO closure in patients with thrombophilia compared to patients without thrombophilia. The association with individual outcomes of ischemic stroke or TIA did not reach statistical significance, possibly due to the secondary outcomes being underpowered. Therefore, identification of thrombophilia in patients with suspected PFO-related stroke may have prognostic importance.

Patients with thrombophilia may face an increased risk of ischemic stroke in general and also in patients with PFO. In a meta-analysis of 68 studies on 11,916 stroke patients and 96,057 controls, ischemic stroke was significantly more common in patients with factor V Leiden (OR 1.25), prothrombin G20210A mutation (OR 1.48), protein C deficiency (OR 2.13) and protein S deficiency (OR 2.26) [16]. Specifically in patients with PFO, a meta-analysis of 6 studies found that prothrombin G20210A mutation was associated with increased risk of PFO-related stroke compared to controls and those with cryptogenic stroke without PFO, but factor V Leiden did not reach statistical significance. Another meta-analysis of 11 studies showed that inherited or acquired thrombophilia was associated with increased risk of recurrent stroke in patients with cryptogenic stroke and PFO (OR 2.41) [17]. A large observational study of 591 patients with cryptogenic stroke and PFO identified 22.7% with thrombophilia, and they also had increased risk of recurrent stroke or TIA (HR 1.85) [18]. Thrombophilia may lead to ischemic stroke via paradoxical embolism through a PFO, or in-situ development of thrombus at the level of PFO, thus increasing the risk of PFO-related events [19].

For PFO-related stroke, current guidelines recommend that PFO closure may be an effective and safe therapeutic option, in those with no alternative mechanisms of stroke. Data from 4 major trials (RESPECT, CLOSE, DEFENSE-PFO, REDUCE) demonstrated the superiority of PFO closure over medical management alone in preventing cryptogenic stroke recurrence. In an individual patient data-level meta-analysis of 3 RCTs, which included data on 2 devices (STARFlex and Amplatzer PFO Occluder) the outcome of recurrent stroke with PFO closure was significantly reduced (adjusted HR 0.58) (20). Many trials excluded a significant proportion of patients who could have benefited from percutaneous PFO closure due to coexisting potential confounders such as additional thromboembolic risk factors, namely thrombophilia. The paucity of data on the effectiveness of PFO closure in preventing recurrent stroke in patients with thrombophilia are reflected in the lack of recommendations in current guidelines.

Of the included studies in our systematic review, the prevalence of thrombophilia in screened PFO patients was 29.3%, and the overall proportion ranged from 3 to 41% in the literature [17]. A substantial group has an overlap of PFO and thrombophilia, but screening for thrombophilia can be costly and the clinical significance of thrombophilia even in young stroke is uncertain. The AHA/ASA guidelines do not recommend routine screening of thrombophilia in stroke (21), and whether thrombophilia patients with PFO should be treated with anticoagulation or PFO closure, or both remains a knowledge gap. In a previous meta-analysis conducted in 2019, results from 4 studies showed that the risk of recurrent events after PFO closure in thrombophilia patients was not significantly different from those without thrombophilia (OR 2.07, CI 0.95–4.48) [17]. This could be in part due to a lack of statistical power, owing to a moderate sample size. Since then, 3 other studies were published, and we found that our updated meta-analysis confirmed that the risk of ischemic stroke or TIA remain elevated in patients with thrombophilia even after PFO closure (OR 1.42, 95% CI: 1.01–1.99). However, there was moderate study heterogeneity, which may be contributed by the differences in types of thrombophilia, medical treatments provided post-closure and devices used in PFO closure. There were also variations in the duration of follow-up, which ranged from 5.3 months to 12 years. Fewer studies reported TIA and stroke outcomes separately, thus the secondary outcomes may be underpowered, thus further evidence is required. Nevertheless, conducting a randomized trial to assess the impact of PFO closure in patients with cryptogenic stroke and thrombophilia presents practical challenges. Hence, our current meta-analysis provides valuable insights to help address this clinical question and guide therapeutic approaches. Given the impact of thrombophilia on PFO closure outcomes, it may be beneficial to screen stroke patients with PFO for thrombophilia [3].

The increased risk of stroke and TIA in patients with thrombophilia after PFO closure may be due to the persistent increased thrombotic tendencies and in-situ clot formation independently of paradoxical embolism through PFO. Unbalanced thrombin activation in patients with thrombophilia may contribute to the formation and progression of

**Table 4** Types of thrombophilia reported in included studies

| Study | Prevalence of thrombophilia | Protein C deficiency | Protein S deficiency | Antithrombin III deficiency | Prothrombin gene mutation | Factor V Leiden | Antiphospholipid syndrome | Homocysteine | Others | Duration between stroke and thrombophilia screen |
|---|---|---|---|---|---|---|---|---|---|---|
| Lusine Abrahamyan | 174 (26%) | 47 (27.0%) | 66 (38.0%) | 35 (20.1%) | 21 (12.1%) | 33 (19.0%) | Anticardiolipin – 16 (9.2%)<br>Lupus anticoagulant – 9 (5.2%) | NR | None | NR |
| Ben-Assa et al., 2021 | 239 (29.9%) | 7 (2.9%) | 30 (12.6%) | 17 (7.1%) | 22 (9.2%) | 27 (1.3%) | 82 (34.3%) | 23 (9.6%) | None | NR |
| Deng et al., 2020 | 470 (43.2%) | 30 (6.4%) | 130 (27.7%) | 56 (11.9%) | 28 (6.0%) | 39 (8.3%) | 172 (36.6%) | 81 (17.2%) | None | NR |
| Wintzer-Wehekind et al., 2019 | 16 (14.9%) | 0 (0%) | 0 (0%) | 0 (0%) | 3 (18.8%) | 6 (37.5%) | Anticardiolipin – 4 (25.0%)<br>Lupus anticoagulant – 3 (18.8%)<br>Anti-b2 glycoprotein-I antibodies – 1 (6.3%) | NR | None | NR |
| Kefer et al., 2012 | 29 (17%) | 1 (3.4%) | 6 (20.7%) | NR | 2 (6.9%) | 3 (10.3%) | Anticardiolipin – 1 (3.4%)<br>Antiphospholipid – 1 (3.4%) | 16 (55.2%) | None | NR |
| Ford et al., 2009 | 32 (10.0%) | 13 (40.6%) | 9 (28.1%) | NR | NR | 12 (37.5%) | Anticardiolipin – 9 (28.1%)<br>Lupus anticoagulant – 3 (9.4%) | NR | None | NR |
| Bartz et al., 2006 | 7 (15.6%) | 0 (0%) | 0 (0%) | NR | 4 (57.1%) | 3 (42.9%) | 0 (0%) | 0 (0%) | None | NR |
| Giardini et al., 2004 | 20 (28%) | Tested | Tested | Tested | Tested | Tested | Tested | Tested | Activated protein-C resistance | < 1 week and 2–3 months after |

NR: Not reported

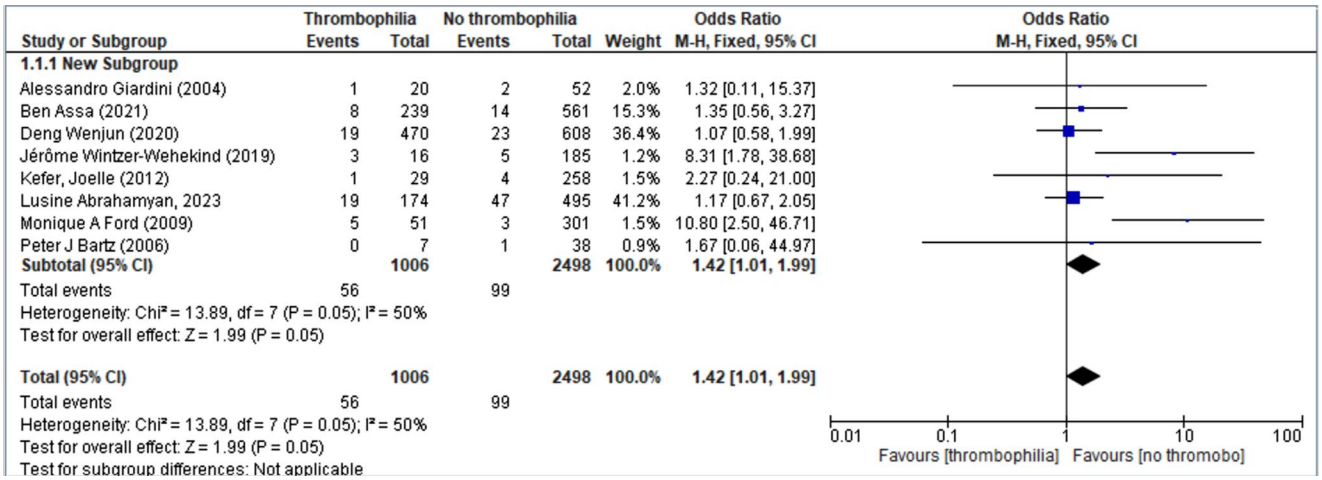



**Fig. 2** Forest plot of the analysis of thrombophilia with ischemic stroke or TIA post-PFO closure

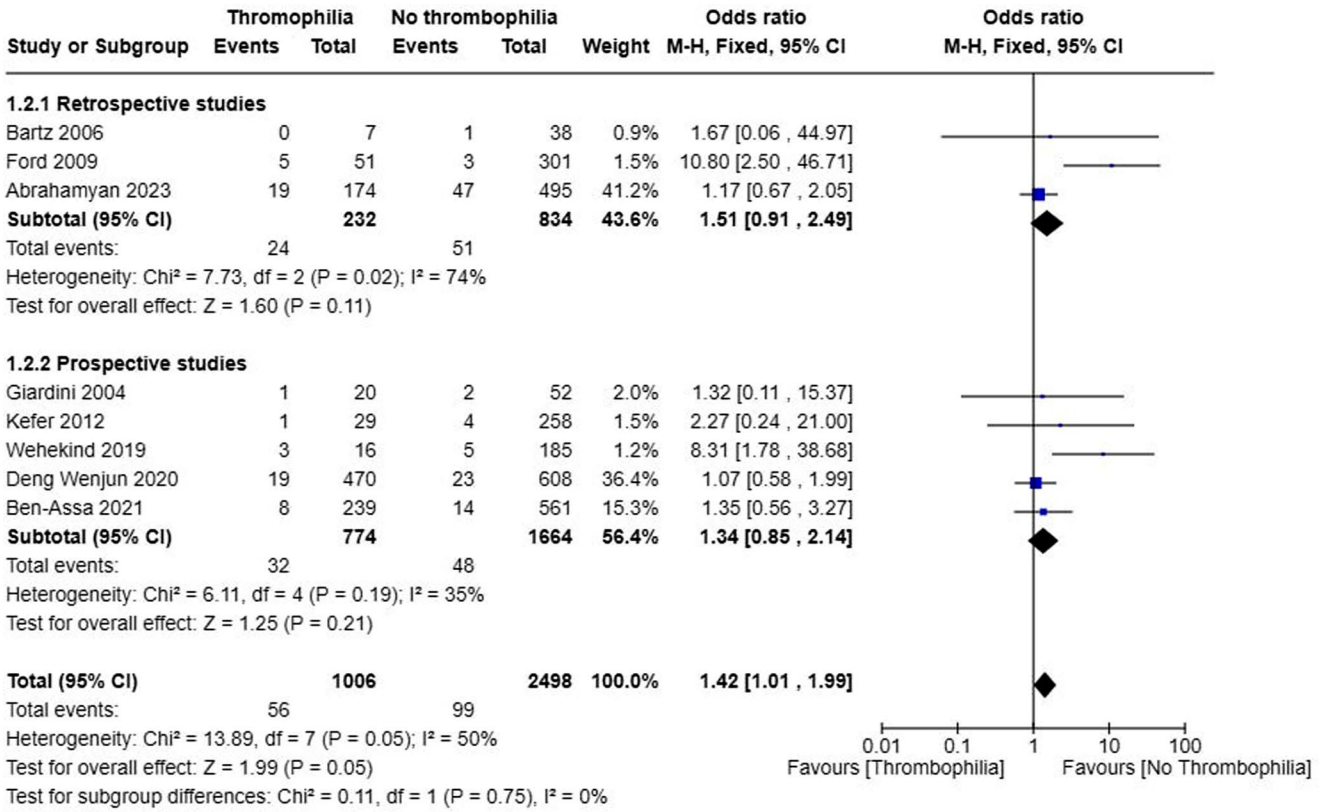



**Fig. 3** Forest plot of retrospective and prospective studies alone

atherosclerotic disease via platelet activation, recruitment of immune cells such as macrophages and endothelial cell dysregulation (22). Procedural complications of PFO closure include thrombus formation, and venous thrombotic events occurred more frequently in device closure than in medical therapy in some studies (23). However, evidence from real-world studies did not find increased adverse events in patients with thrombophilia in the context of PFO closure [8]. Therefore, management of stroke associated with PFO and thrombophilia may require a multi-pronged approach including appropriate medical management, and risk of ischemic stroke or TIA may remain elevated even after PFO closure compared to those without thrombophilia.

The benefit of PFO closure is dependent on the likelihood of the PFO being pathological and contributory to the cause of stroke, and PFO closure appears to be beneficial in those with thrombophilia. Compared to medically managed patients with thrombophilia and PFO, those with PFO

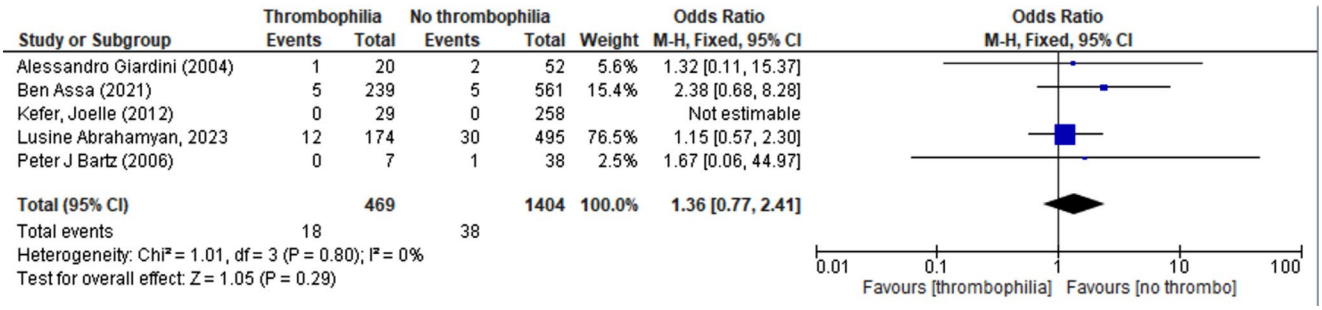



**Fig. 4** Forest plot of the analysis of thrombophilia with TIA only post-PFO closure

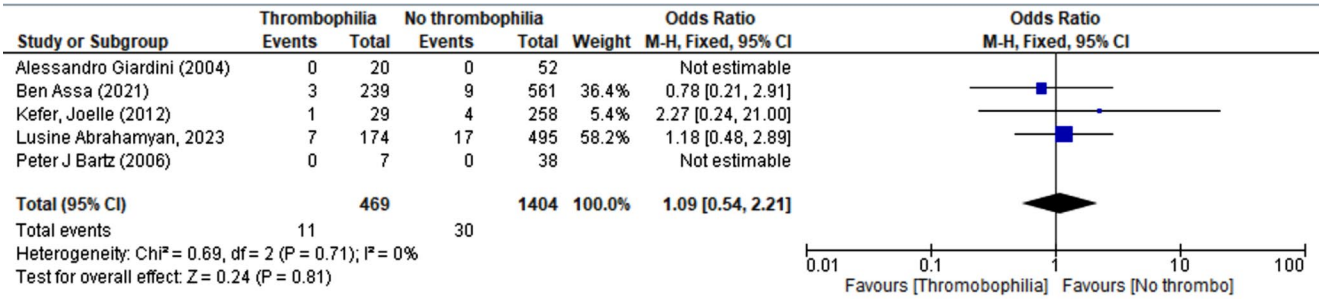



**Fig. 5** Forest plot of the analysis of thrombophilia with ischemic stroke only post-PFO closure

closure seemed to have lower risk of recurrent stroke and TIA in large prospective and retrospective studies. Recent results from Liu et al. (2020) on 591 patients with cryptogenic stroke and PFO and 53 months of follow up found a 1.85-times increase in risk of recurrent stroke or TIA in those with thrombophilia, but the risk was reduced by 75% in the PFO closure group compared to medical therapy alone [18]. The RoPE score has helped clinicians identify patients with cryptogenic stroke and PFO who might have PFO-associated stroke (24). However, risk stratification tools such as RoPE were not adopted in the studies on patient with thrombophilia, and need to be validated in this high-risk subgroup. Thus, there is a need for further research to identify studies that has incorporated PFO closure in the management of thrombophilia patients and review the long-term outcomes of this group of patients.

The optimal pharmacotherapy after PFO closure in patients with thrombophilia is uncertain, and practice differed widely among the included studies. For example, Abrahamyan et al. prescribed dual antiplatelet therapy only in 61% of patients with thrombophilia, anticoagulation only in 6.3% and a combination of both in 20.8% [8]. Ben-Assa et al. and Deng et al. opted for warfarin for 3 months then aspirin lifelong for patients with one episode of thrombotic event, while warfarin lifelong for patients with more than one episode [9, 10]. Other studies such as Kefer et al. only prescribed aspirin for 6 months post-procedure [12], while Giardani et al. and Ford et al. instead used warfarin for 6 months post-procedure in patients with thrombophilia [13, 15]. This variation in practice is also reflected in the lack of clinical guidelines on this issue and the significant divergence in opinions of 51 cardiologists, internal medicine physicians and neurologists surveyed in a recent study (25). Research on the comparison of anticoagulation and antiplatelet therapy post-PFO closure in patients with thrombophilia is necessary to reduce the risk of recurrent stroke and TIA in this high-risk population.

## Limitations

The main limitation in this meta-analysis is the heterogeneity in the methods and study population among the studies, including differences in the selection criteria, types of thrombophilia, length of follow-up and specific anticoagulation or antiplatelet regimen in the medical treatment groups. There is also a lack of randomized controlled trials and results were reliant on cohort studies susceptible to confounding factors, and causality cannot be inferred. In addition, the diagnostic approach of cryptogenic stroke was prespecified for each study but not uniform across trials. In the study by Deng et al. and Ben-Assa et al., selection of patients for PFO closure involved multidisciplinary discussion among specialists in neurology, cardiology, hematology, and vascular medicine, while this decision was made by neurologists in the studies by Wintzer-Wehekind et al. and Kefer et al. instead. Thrombophilia work-up was also prespecified for each study but not uniform across trials, as well as the post-PFO closure medical management may

differ, due to the lack of consensus on the optimal regimen for thrombophilia and PFO. Moreover, different devices for PFO closure were used in the trials. However, the overall heterogeneity was moderate, and thus the impact of these factors on the risk of events post-PFO closure may be small.

Although the overall effect of thrombophilia in patients with PFO closure on the risk of cerebrovascular events recurrence is evident by the present meta- analysis, an individual patient data pooled analysis of all studies of PFO closure would provide further insight into the role of other factors that may contribute to outcomes after closure. These factors include the size of PFO shunt before closure, the age of the patient, the use of antithrombotic treatments before or after PFO closure, and other patient or PFO parameters. Thrombophilia screen performed during the acute phase of the stroke may also be inaccurate, and acquired causes were often excluded. Due to the lack of study data, we were unable to perform subgroup analysis and meta-regressions to identify factors that may influence the prognosis after PFO-closure. The impact of screening for thrombophilia and performance of PFO closure in these patients require further validation in prospective randomized trials.

## Conclusion

In conclusion, this meta-analysis shows that there is an increased risk of recurrent cerebral ischemia event in patients with thrombophilia compared to those without thrombophilia after PFO closure. Given the impact of thrombophilia on PFO closure outcomes, it may be beneficial to screen stroke patients with PFO for thrombophilia. Future large prospective studies are necessary to characterise the risk and benefits of PFO closure, as well as the appropriate medical treatment to reduce the risk of recurrent stroke and TIA in this high-risk population.

### Abbreviations

| | |
|---|---|
| CVD Risk Factors | Cardiovascular Disease Risk Factors |
| PFO | Patent Foramen Ovale |
| Total ACE | Total Acute Cerebrovascular Events |
| TIA | Transient Ischaemic Attack |
| DM | Diabetes Mellitus |
| HTN | Hypertension |
| HLD | Hyperlipidaemia |
| Smoking | Current smokers only |
| NA | Not Applicable/ Available |

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## Declarations

**Competing interests** There were no competing conflicts of interests of review authors present.

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