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Comparison of Patent Foramen Ovale Closure vs Medical Therapy for the Prevention of Recurrent Cryptogenic Stroke: A Systematic Review

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Abstract

Objectives: **The optimal management approach for patients with cryptogenic stroke and patent foramen ovale (PFO) remains uncertain. Whether medical therapy—using antiplatelet agents or anticoagulants—or transcatheter device closure offers superior protection against stroke recurrence has been a topic of considerable debate. This systematic review aims to assess and compare the effectiveness of these two treatment strategies, incorporating recent studies to provide updated insights on the most effective approach to preventing recurrent cryptogenic stroke.**

Methodology: **We systematically searched PubMed, Scopus, and Ovid database through December 2024. Eligible studies were randomized controlled clinical trials (RCTs) comparing PFO closure versus medical therapy among patients with cryptogenic stroke.**

Results: **This systematic review analyzed 7 RCTs encompassing 4539 patients with a mean age of 43.6 years, 53.38 % of whom were male. Patient characteristics, including comorbidities such as hypertension, hyperlipidemia, and diabetes mellitus, were well-balanced across groups receiving PFO closure or medical therapy. The primary analysis revealed a significant reduction in stroke incidence with PFO closure compared to medical therapy, with no stroke events in the PFO closure groups of the CLOSE and DEFENSE-PFO trials. Similarly, transient ischemic attack (TIA) incidence was consistently lower in PFO closure groups. All-cause mortality was comparable between groups, underscoring the safety profile of PFO closure. However, PFO closure was associated with a higher incidence of atrial fibrillation. Major bleeding risks varied, reflecting the need for tailored risk assessment.**

Conclusion: **PFO closure offers a significant advantage over medical therapy in preventing recurrent cryptogenic stroke and TIA. Nevertheless, the observed increase in atrial fibrillation postclosure highlights the need for additional research to elucidate its long-term implications and to determine whether anticoagulation could benefit specific subsets of patients with PFO and a history of stroke.**

Keywords: Patent foramen ovale, Cryptogenic stroke, Atrial fibrillation, Percutaneous PFO closure, Medical therapy

1. Introduction

Stroke remains one of the leading causes of mortality and disability worldwide, affecting millions of individuals each year. Ischemic stroke, which occurs when blood flow to the brain is obstructed, accounts for the majority of stroke cases. Among these, about 30–40 % are classified as cryptogenic, where no identifiable cause can be determined despite thorough diagnostic evaluation [1,2]. Cryptogenic stroke poses a challenge to both clinicians and researchers, as the inability to pinpoint a clear etiology complicates the development of effective secondary prevention strategies and increases the risk of stroke recurrence [3].

Studies have identified a significantly higher prevalence of patent foramen ovale (PFO)—a congenital defect characterized by failure of complete closure of the atrial septum—in patients with cryptogenic stroke compared to those with strokes

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of known origin [4]. While often asymptomatic, PFO can facilitate paradoxical embolism and is a recognized risk factor for non-lacunar cryptogenic cerebral ischemia, particularly in young adults [5]. This association has led to many ongoing debates regarding the best approach to treating patients with cryptogenic stroke and PFO. Typically, there are two primary approaches to be considered: transcatheter device closure (TDC), often followed by dual antiplatelet therapy such as aspirin and clopidogrel for several months, and antithrombotic drug therapy, which may include either antiplatelet agents or anticoagulants.

While some studies have suggested that PFO closure offers better outcomes than antiplatelet and anticoagulant therapies [6,7], others have revealed no significant difference in outcomes [8]. Furthermore, several studies have reported that while PFO closure reduces the incidence of stroke, it may increase the risk of atrial fibrillation, a known risk factor for embolic events [9,10]. However, findings from recently published randomized controlled trial by Liu et al. (2020) challenge this notion, reporting no significant increase in the occurrence of atrial fibrillation after the procedure [11].

To provide clearer guidance for clinical decision-making and address conflicting data, we conducted this updated systematic review. By incorporating recent studies, we aim to evaluate and compare the efficacy of PFO closure and medical therapy in preventing recurrent strokes in patients with cryptogenic stroke associated with PFO.

Abbreviation List:

AF	Atrial Fibrillation
AC	Anticoagulation
AP	Antiplatelet Therapy
CLOSE	Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence
CLOSURE	Evaluation of the STARFlex Septal Closure System
DAPT	Dual Antiplatelet Therapy
DEFENSE-PFO	Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
INR	International Normalized Ratio
MT	Medical Therapy
PE	Pulmonary Embolism
PFO	Patent Foramen Ovale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
REDUCE	Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke
RESPECT	Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment
ROB	Risk of Bias
TDC	Transcatheter Device Closure
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction

2. Methodology

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines (PRISMA) during the preparation of this systematic review in reporting our methodology and findings.

2.1. Criteria for considering studies for this review

For our systematic review, we established the following inclusion criteria: 1) randomized controlled trials (RCTs) evaluating percutaneous device closure of patent foramen ovale (PFO) as the intervention compared to medical therapy, including antiplatelet and/or anticoagulant treatment. 2) Adult participants (age $\geq$18 years) with a documented history of ischemic neurological events, such as stroke or transient ischemic attack (TIA), and a confirmed PFO diagnosis. 3) Studies reporting outcomes such as all-cause mortality, recurrent ischemic neurological events (stroke and TIA) during the follow-up period, new-onset atrial fibrillation, and major bleeding events. We excluded studies that did not meet these criteria, as well as animal studies, non-English publications, case reports, case series, editorials, reviews, non-randomized study designs, and unpublished studies.

2.2. Search strategy

To identify relevant studies, we performed comprehensive searches across three major medical electronic databases up to December 2024. These databases included PubMed, Scopus, and Ovid. In cases where multiple publications reported data on the same patient population, only the most recent or complete study was included to avoid duplication.

The search strategy employed a combination of targeted keywords and Medical Subject Headings (MeSH) terms tailored to our study objectives. The search terms used were: “Patent Foramen Ovale,” “PFO Closure,” “Percutaneous PFO Closure,” “Percutaneous Closure,” “Medical Therapy,” “Anticoagulant Therapy,” “Antiplatelet Therapy,”

"Cryptogenic Stroke," "Stroke," "Transient Ischemic Attack," and "Recurrent Neurological Events."

2.3. Selection of studies

Two authors (O.H. and S.A.) independently applied the inclusion and exclusion criteria to all records. The screening process occurred in two stages: initially, titles and abstracts of the retrieved studies were assessed for relevance, followed by a full-text review of studies considered potentially eligible. Any discrepancies between the authors were resolved through discussion. Furthermore, the reference lists of relevant publications were manually reviewed to ensure the comprehensive inclusion of all applicable studies, capturing any additional research that may not have been identified through database searches.

2.4. Data extraction

Four authors independently extracted data using an online data extraction form. The data were organized into several key categories: study characteristics, including study design, year of publication, randomization process, types of closure devices used, types of medical therapy in each group, follow-up duration, and primary outcomes; baseline characteristics of the population, which included demographic information and disease history; quality assessment using the Cochrane Risk of Bias (ROB 1) tool; and the number of events for each outcome, such as all-cause mortality, recurrent ischemic neurological events (stroke and TIA), new-onset atrial fibrillation, and major bleeding events.

2.5. Quality assessment of the included studies

Two authors independently assessed the methodological quality of the included RCTs using the Cochrane ROB 1 tool. The assessment focused on seven key domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. For each domain, we rated the risk of bias as high, low, or unclear based on the information provided in the study reports. Any discrepancies in the assessments were resolved through discussion or consultation with a third author.

2.6. Publication bias

Assessment of publication bias was not possible due to the small number of included studies (<10) [12]. This limitation restricted our ability to conduct reliable statistical tests for publication bias, such as funnel plots or Egger's test.

3. Results

3.1. Study selection

A total of 14,384 records were identified through database searching, including 346 from PubMed/Medline, 474 from Ovid, and 559 from Scopus. One additional record was identified through other sources. After removing duplicates, 765 records remained for screening. During the screening process, 755 records were excluded based on title and abstract. The full texts of 10 articles were assessed for eligibility, resulting in the exclusion of 3 articles due to the wrong study design. Finally, 7 studies met the inclusion criteria and were included in the systematic review. The detailed study selection process is illustrated in Fig. 1, the PRISMA flow diagram.

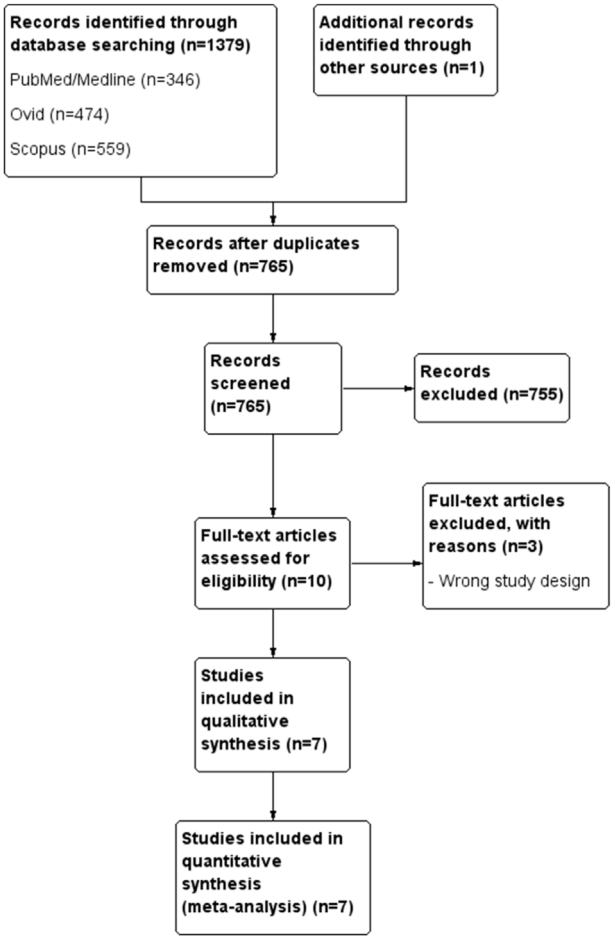

Fig. 1. PRISMA study flow diagram.

3.2. Study characteristics

A total of 7 studies were included in this systematic review. The key characteristics of these studies are summarized in Table 1. These characteristics include enrollment, randomization ratio (PFO closure:MT), intervention details, PFO device type, medical therapy, follow-up years, and primary outcomes.

The analysis included 4539 patients from 7 RCTs, with a mean age of 43.6 years and a male predominance of 53.38 %. Baseline characteristics were well-balanced between the PFO closure and medical therapy groups. Key comorbidities were comparable, including hypertension (24.37 % vs. 25.28 %), hyperlipidemia (27.37 % vs. 29.45 %), diabetes mellitus (4.81 % vs. 6.29 %), smoking (20.87 % vs. 20.96 %), migraine (30.10 % vs. 29.93 %), and previous stroke (45.83 % vs. 46.24 %). Additionally, moderate or higher shunt (66.68 % vs. 62.23 %), atrial septal aneurysm (24.22 % vs. 25.72 %), and DVT/PE (2.60 % vs. 1.84 %) were similarly distributed. Detailed demographics and baseline characteristics are presented in Table 2. Post-procedural anticoagulation was generally initiated immediately after device implantation, but inconsistencies in reporting its timing and discontinuation remain a key limitation.

3.3. Risk of bias in studies

The Cochrane risk of bias tool identified a low-to-moderate risk of bias across the 7 included studies. A summary of the overall risk of bias for each study is presented in Fig. 2.

3.4. Results of individual studies

3.4.1. Stroke

The primary endpoint of stroke incidence demonstrated a significant reduction with PFO closure compared to medical therapy. In the CLOSE and DEFENSE-PFO trials, no stroke events were reported in the PFO closure groups, whereas 17 and 5 strokes occurred in the medical therapy groups, respectively. Similarly, the REDUCE trial showed 6 strokes in the PFO closure group (n = 441) and 12 strokes in the medical therapy group (n = 223). These results highlight the consistent efficacy of PFO closure in minimizing the risk of recurrent stroke.

3.4.2. Transient ischemic attack (TIA)

The incidence of TIA was lower in the PFO closure groups compared to medical therapy across the analyzed trials. In the CLOSE trial, 8 TIAs occurred in the PFO closure group (n = 238) and 13 TIAs in the medical therapy group (n = 422). The RESPECT trial reported 17 TIAs in the PFO closure group (n = 499) compared to 23 TIAs with medical therapy (n = 481). Notably, the DEFENSE-PFO trial recorded no TIA events in the PFO closure group, while 1 TIA in the medical therapy group (n = 60). These findings further support the potential of PFO closure to reduce the risk of cerebrovascular events.

3.4.3. All-cause mortality

All-cause mortality rates were low across all studies, with no significant differences observed between the PFO closure and medical therapy groups. Notably, the CLOSE, DEFENSE-PFO, and Yunbing trials reported no mortality events in either group. In the RESPECT trial, 7 deaths occurred in the PFO closure group (n = 499) compared to 11 deaths in the medical therapy group (n = 481). Similarly, the CLOSURE 1 trial reported 2 deaths the PFO closure group (n = 402) due to cardiac arrest and arrythmia and 4 deaths with medical therapy (n = 458) due to septic shock, suicide, amyotrophic lateral sclerosis, and metastatic cancer. Other reported causes of death across the other included studies were pancreatic cancer, respiratory failure, and myocardial infarction. These findings suggest comparable safety profiles regarding all-cause mortality.

3.4.4. Atrial fibrillation

Across the included trials, atrial fibrillation was most frequently reported within the first 30 days after PFO closure with the incidence of atrial fibrillation was higher in the PFO closure groups compared to medical therapy. In the REDUCE trial, 29 atrial fibrillations occurred in the PFO closure group (n = 441) and 1 atrial fibrillation in the medical therapy group (n = 223), with the majority occurring during this early post-procedure window. Similarly, the CLOSURE 1 trial reported 23 atrial fibrillations in the PFO closure group (n = 402) compared to 3 atrial fibrillations with medical therapy (n = 458). In the CLOSE trial, 11 atrial fibrillations were observed in the PFO closure group (n = 238) and 2 atrial fibrillations in the medical therapy group (n = 422). These findings indicate a higher risk of atrial fibrillation associated with PFO closure immediately after closure, which should be weighed against its benefits in reducing stroke risk. Yet, none of the trials reported subsequent defibrillation procedures in either treatment group.

3.4.5. Major bleeding

The incidence of major bleeding varied across studies, with mixed findings between the PFO

Table 1. Characteristics of included studies.

Study ID	Enrollment	Randomization (PFO closure:MT)	Intervention	PFO device type	Medical therapy	Follow-up, years	Primary outcome
RESPECT [18]	2003−2011; multicenter, randomized	1:1	Amplatzer PFO occluder + aspirin and clopidogrel for 1 month followed by aspirin for at least 5 months	Amplatzer	Aspirin, clopidogrel, warfarin, or aspirin + dipyridamole	5.9	Composite of recurrent non fatal stroke, fatal stroke, or early death
REDUCE [15]	2008−2015; multicenter, randomized	2:1[b]	PFO closure with clopidogrel for 3 days followed by an AP for rest of trial	HELEX or Cardioform	Aspirin (75−325 mg), aspirin + dipyridamole, or clopidogrel	3.2	Clinical stroke and new brain infarction
CLOSE [13]	2008−2014; multicenter, randomized	1:1:1[a]	PFO closure with DAPT for 3 months, then single AP for rest of trial	Multiple (Amplatzer 51.5 %)	AC: vitamin K antagonist (INR 2−3) or DOAC. AP: aspirin or clopidogrel or aspirin + dipyridamole for rest of trial	5.3	Fatal or nonfatal stroke
CLOSURE I [8]	2003−2008; multicenter, randomized	1:1	PFO closure + antiplatelet regimen including clopidogrel for 6 months and aspirin for 2 years	STARFlex	Warfarin, aspirin, or both	2	Composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years.
PC Trial [28]	2000−2009; multicenter, randomized	1:1	Amplatzer PFO occluder + aspirin for at least 5−6 months AND ticlopidine OR clopidogrel or 1−6 months	Amplatzer	Antiplatelet therapy or anticoagulation	4.1	Composite of death, nonfatal stroke, TIA, or peripheral embolism.
DEFENSE-PFO [14]	2011−2017; multicenter, randomized	1:1	Amplatzer PFO occluder + aspirin AND clopidogrel for atleast 6 months	Amplatzer	Single or dual antiplatelet therapy or anticoagulation (warfarin)	2.8	Composite of stroke, vascular death, or TIMI-defined major bleeding.
Liu 2020 [11]	2013−2018; multicenter, randomized	1:1	Implantation of PFO occluders + aspirin for 6 months and clopidogrel for 3 months	Life Tech PFO Occluder	Aspirin as anantiplatelet drug or warfarin as an anticoagulation drug	3.6	Stroke recurrence and TIA

CLOSE: Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; RESPECT: Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; PC Trial: Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; CLOSURE 1: Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale; DEFENSE-PFO, Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale. AC: anticoagulation; AP: antiplatelet; DAPT: dual antiplatelet therapy; INR: international normalized ratio; PFO: patent foramen ovale; TIA: transient ischemic attack; TIMI: thrombolysis in myocardial infarction.

[a] PFO closure:AP alone:AC.

[b] PFO closure:AP.

Table 2. Baseline clinical characteristics in PFO closure versus medical therapy groups.

Study ID	Group	Sample size	Male N (%)	Age (years)	Hypertension	Hyperlipidemia	Diabetes	Smoking	Migraine	Previous stroke	Moderate or higher shunt	Atrial septal aneurysm	DVT/PE
RESPECT [18]	PFO closure	499	268 (53.7)	45.7 ± 9.7	158 (31.7)	194 (38.9)	33 (6.6)	75 (15)	195 (39.1)	53 (10.6)	385 (78)	180 (36.1)	20 (4.0)
	Medical Therapy	481	268 (55.7)	46.2 ± 10.0	150 (31.2)	193 (40.1)	40 (8.3)	55 (11.4)	185 (38.5)	51 (10.6)	352 (72)	169 (35.1)	15 (3.1)
REDUCE [15]	PFO closure	664	261 (59.2)	45.4 ± 9.3	112 (25.4)		18 (4.1)	63 (14.3)		62 (14.1)	348 (81.8)	86 (20.4)	
	Medical Therapy	233	138 (61.9)	44.8 ± 9.6	58 (26.0)		10 (4.5)	25 (11.2)		23 (10.3)	173 (80)		
CLOSE [13]	PFO closure	238	137 (57.6)	42.9 ± 10.1	27 (11.3)	30 (12.6)	3 (1.3)	68 (28.6)	67 (28.2)	10 (4.2)	179 (75.2)		5 (2.1)
	Medical Therapy	422	142 (60.4)	43.8 ± 10.5	24 (10.2)	36 (15.3)	9 (3.8)	69 (29.4)	78 (33.2)	7 (3.0)	173 (73.6)		4 (1.7)
CLOSURE I [8]	PFO closure	447	233 (52.1)	46.3 ± 9.6	151 (33.8)	212 (47.4)		96 (21.5)		324 (72.6)	250 (55.9)	168 (37.6)	0
	Medical Therapy	462	238 (51.5)	45.7 ± 9.1	131 (28.4)	189 (40.9)		104 (22.6)		329 (71.4)	231 (50.0)	165 (35.7)	4 (0.9)
PC Trial [28]	PFO closure	204	92 (45.1)	44.3 ± 10.2	49 (24.0)	50 (24.5)	5 (2.5)	52 (25.5)	47 (23.0)	165 (80.9)	130 (70.2)	47 (23.0)	6 (2.9)
	Medical Therapy	210	114 (54.3)	44.6 ± 10.1	58 (27.6)	62 (29.5)	6 (2.9)	47 (22.4)	38 (18.1)	163 (77.6)	112 (60.9)	51 (24.3)	5 (2.4)
DEFENSE-PFO [14]	PFO closure	60	33 (55.0)	49 ± 15	12 (20.0)	18 (30.0)	6 (10.0)	10 (16.7)		28 (46.7)		5 (8.3)	
	Medical Therapy	60	34 (56.7)	54 ± 12	17 (28.3)	25 (41.7)	8 (13.3)	16 (26.7)		36 (60.0)		8 (13.3)	
Liu 2020 [11]	PFO closure	277	116 (41.9)	30.2 ± 9.7		30 (10.8)	12 (4.33)	68 (24.5)		254 (91.7)	108 (39)	55 (19.9)	4 (1.4)
	Medical Therapy	282	119 (42.2)	31.3 ± 10.1		26 (9.2)	14 (4.96)	65 (23)		256 (90.8)	104 (36.9)	57 (20.2)	3 (1.1)

Data are n, mean ± SD, median (range), or n (%).
PFO, patent foramen ovale, DVT, deep vein thromboembolism, PE, pulmonary embolism.

closure and medical therapy groups. In the CLOSE trial, 2 major bleeding events were reported in the PFO closure group (n = 238) compared to 15 events in the medical therapy group (n = 422). Conversely, the CLOSURE 1 trial reported 10 major bleeding events in the PFO closure group (n = 447) compared to 4 events in the medical therapy group (n = 462). In the REDUCE trial, 8 major bleeding events occurred in the PFO closure group (n = 441) compared to 6 events in the medical therapy group (n = 223). These findings suggest a variable risk of major bleeding, highlighting the need for individualized risk assessment when considering PFO closure.

4. Discussion

This systematic review evaluated the comparative efficacy and safety of patent foramen ovale closure versus medical therapy in preventing recurrent cerebrovascular events. By synthesizing data from seven randomized controlled trials, our findings highlight significant differences between the two approaches in terms of stroke prevention, transient ischemic attack reduction, and associated risks.

Our analysis confirms that PFO closure significantly reduces the incidence of recurrent stroke compared to medical therapy. This finding is consistent with results from pivotal trials such as CLOSE [13] and DEFENSE-PFO [14], which reported no stroke events in the PFO closure groups, contrasting with multiple events in the medical therapy groups. Similarly, the REDUCE trial [15] showed a marked reduction in recurrent stroke rates with closure, corroborated by meta-analyses including those by Spencer et al. [16] and Shah et al. [17]. Interestingly, contrasting evidence from the CLOSURE 1 trial [8] underscores the importance of patient selection, as this study failed to show significant benefits of closure over medical therapy. This divergence may be explained by differences in device technology, procedural expertise, and patient population. The variation highlights the evolving landscape of PFO closure, wherein newer devices and techniques offer enhanced outcomes, as suggested by the long-term analysis in the RESPECT extended follow-up study [18].

The reduction in TIA incidence among PFO closure groups was consistent across trials such as CLOSE [13] and RESPECT [18]. DEFENSE-PFO [14] further supports these findings by reporting a complete absence of TIA events in the closure group. The mechanism likely involves the elimination of paradoxical embolism pathways, as demonstrated in studies investigating microbubble

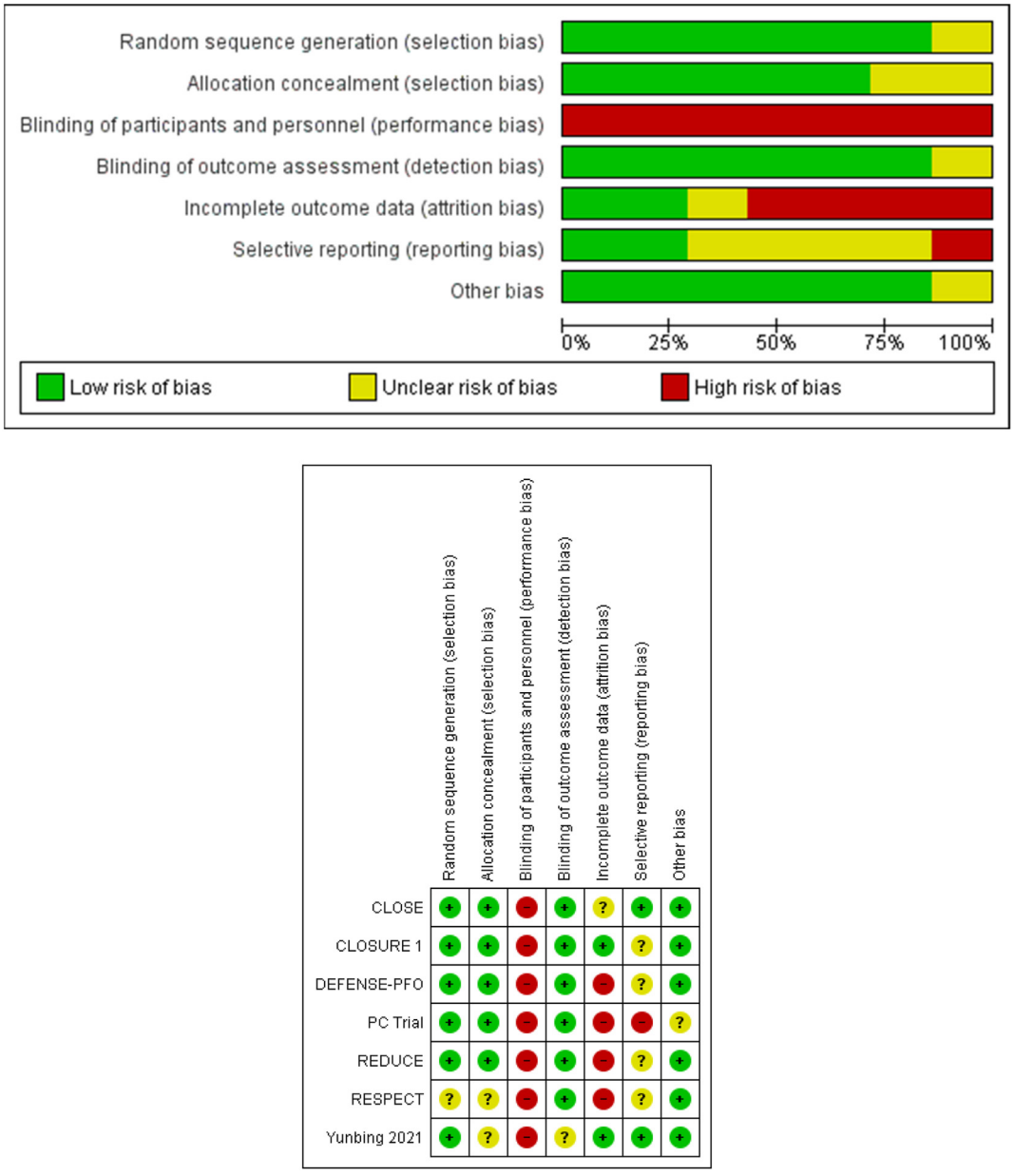

Fig. 2. ROB 1 quality assessment of the included studies.

contrast-enhanced transcranial Doppler outcomes post-closure [19]. Comparative evidence from non-RCT studies, such as the observational analysis by Kitsios et al. [20], reinforces the significant reduction in TIA burden with PFO closure. Moreover, a pooled analysis by Kent et al. [21] has emphasized the importance of device efficacy in preventing TIA, particularly in patients with atrial septal aneurysms.

No significant difference in all-cause mortality was observed between PFO closure and medical therapy, consistent with findings from CLOSE [13], DEFENSE-PFO [14], and REDUCE [15]. However, a meta-analysis by Rengifo-Moreno et al. [22] noted a slight trend favoring medical therapy in older patients, suggesting that the benefits of closure may diminish with age or in patients with complex comorbidities. While mortality outcomes are reassuring regarding the safety of PFO closure, future studies should further investigate potential device-related late complications, as noted by Rigatelli et al. [22].

A notable finding of this review is the increased incidence of atrial fibrillation in the PFO closure groups compared to medical therapy. Trials such as REDUCE [15] and CLOSURE 1 [8] reported significantly higher rates of atrial fibrillation among patients undergoing PFO closure. This adverse event is

likely attributable to procedural factors, including device implantation and mechanical irritation, as noted in previous studies [23]. Our review highlights that new-onset atrial fibrillation after PFO closure typically occurs within the first month. This underscores the need for short-term rhythm monitoring, especially in patients with additional atrial arrhythmia risk factors. Clinicians must weigh the stroke-preventive benefits of PFO closure against this elevated risk, particularly in patients with baseline arrhythmogenic conditions [24].

The risk of major bleeding events varied between the groups, with mixed findings across trials. For instance, the CLOSE trial [13] reported fewer bleeding events in the PFO closure group, whereas the CLOSURE 1 trial [8] showed the opposite trend. These discrepancies may be attributed to differences in study populations, anticoagulation regimens, and definitions of major bleeding. Previous analyses have also noted the importance of individualized anticoagulation strategies tailored to patient-specific risk profiles [25].

The findings of this review provide critical insights for clinicians managing patients with cryptogenic stroke and a PFO. While PFO closure offers substantial benefits in reducing recurrent stroke and TIA, its associated risks, including atrial fibrillation and potential bleeding complications, necessitate a tailored approach. These observations align with recommendations from the American Heart Association/American Stroke Association guidelines [26], which advocate individualized decision-making incorporating patient-specific factors such as shunt size and thrombotic risk profiles. However, it is important to acknowledge that PFO and atrial septal aneurysm were identified as the cardiac source of embolism in only two cases within a large clinical series of 402 consecutive patients with ischemic cardioembolic stroke [27]. This underscores the need for precise risk stratification, as not all PFOs are clinically significant, and indiscriminate closure may not be beneficial for every patient.

4.1. Limitations

While this review provides valuable insights into the comparative outcomes of PFO closure and medical therapy, certain limitations must be acknowledged. The included studies demonstrate significant heterogeneity in patient populations, follow-up durations, and outcome definitions, which may limit the generalizability of findings. A key limitation across the trials was the lack of standardized reporting on anticoagulation timing and duration after PFO closure. This inconsistency hinders direct comparisons and underscores the need for future studies to establish evidence-based post-closure guidelines. Additionally, evidence on long-term durability and device-related complications remains insufficient, leaving critical questions unanswered. Furthermore, the lack of consistent data on cost-effectiveness and patient-reported outcomes represents a notable gap, especially for informing clinical and policy decisions. Future research should prioritize standardized definitions and metrics to reduce heterogeneity and facilitate cross-study comparisons. Long-term follow-up studies are essential for evaluating the durability of closure benefits and the evolution of device-related risks. Comparative studies involving newer closure technologies and advancements in bioresorbable devices could address concerns regarding complications. Lastly, robust analyses of cost-effectiveness and quality-of-life impacts will be instrumental in updating clinical guidelines and improving patient-centered care. Further investigations exploring the role of biomarkers in identifying high-risk PFO-related strokes, the impact of emerging anticoagulation strategies, and the potential for personalized treatment approaches based on genetic predisposition could provide valuable insights into optimizing patient outcomes.

5. Conclusion

This systematic review highlighted a trade-off between treatment strategies for PFO. Patients who underwent PFO closure had a reduced incidence of cryptogenic stroke and TIA but demonstrated a higher rate of AF compared to those treated with medical therapy. These results emphasize the need for a balanced, individualized approach to treatment, taking into account both stroke prevention and the risk of AF. Further research is necessary to investigate the significance of post-closure AF as well as the role of anticoagulation in selected patients with stroke and PFO.

Author contributions

Conception and design of Study: OH, SA. Literature review: OH, SA. Acquisition of data: OH. Analysis and interpretation of data: SA. Research investigation and analysis: OH, SA. Data collection: OH, SA, RY, SK. Drafting of manuscript: OH, SA, RY, SK. Revising and editing the manuscript critically for important intellectual contents: OH, SA, RY, SK. Data preparation and presentation: OH, SA, RY, SK. Research coordination and management: OH, SA. Funding for the research: OH, SA.

Ethical approval

As this systematic review does not involve primary data collection from human participants, ethical approval was not required. The review adheres to the guidelines and principles of evidence synthesis and analysis.

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Conflict of interest

The authors of this study declare no conflict of interest.

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