

Meta-analysis of patent foramen ovale closure versus medical therapy for prevention of recurrent ischemic neurological events

Impact of medication type

Xuemei Pan, MD^a, Liang Xu, MD^b, Chang Zhou, MD^{b,*} , Zhi Zhang, MD^a, Heng Sun, MD^b

Abstract

Background The optimal treatment strategy for patent foramen ovale (PFO) patients with cryptic stroke remains controversial. We performed this meta-analysis to evaluate the effect of PFO closure versus different types of medical therapy.

Methods We searched PubMed, Embase, and Cochrane databases. The primary efficacy endpoints were the composite outcome of recurrent stroke and/or transient ischemic attack (TIA). Secondary efficacy endpoints included separate stroke and TIA. Safety endpoints included new-onset atrial fibrillation (AF)/atrial flutter and bleeding.

Results Compared with antiplatelet therapy, PFO closure significantly reduced the risk of composite outcome (odds ratio [OR] 0.37, 95% confidence interval [CI] 0.27–0.51), stroke (OR 0.22, 95% CI 0.13–0.36), and TIA (OR 0.57, 95% CI 0.34–0.98); Compared with the mixed medical therapy group (consist of antiplatelet therapy, anticoagulant therapy, or both), PFO closure still showed some benefits, but the effect was not as significant as that of antiplatelet therapy (composite outcome: OR 0.53, 95% CI 0.41–0.69; stroke: OR 0.48, 95% CI 0.34–0.68; TIA: OR 0.69, 95% CI 0.50–0.96); Compared with anticoagulant therapy, PFO closure showed no benefit (composite outcome: OR 0.77, 95% CI 0.46–1.28; stroke: OR 0.59, 95% CI 0.28–1.25; TIA: OR 1.01, 95% CI 0.50–2.04). In terms of safe endpoints, compared with antiplatelet therapy and anticoagulant therapy, PFO closure increased the risk of AF/atrial flutter (OR 9.56, 95% CI 2.85–32.06; OR 18.96, 95% CI 1.11–323.8, respectively) and reduced the risk of bleeding (OR 0.50, 95% CI 0.24–1.05; OR 0.13, 95% CI 0.04–0.46, respectively); compared with mixed medical therapy, PFO closure increased the risk of AF/atrial flutter (OR 4.40, 95% CI 2.24–8.67), but there was no difference in bleeding (OR 0.97, 95% CI 0.56–1.68).

Conclusions With the addition of anticoagulants, the benefit of PFO closure decreased gradually. Patient groups that adopt individualized medical therapy strategies may benefit more.

Abbreviations: AF = atrial fibrillation, CI = confidence interval, OR = odds ratios, PFO = patent foramen ovale, RCT = randomized controlled trials, TIA = transient ischemic attack.

Keywords: medical therapy, patent foramen ovale, secondary prevention, stroke

Editor: Manal fuad Elshamaa.

XP and LX contributed equally to this article.

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

^a Department of Ultrasound, The Third People's Hospital of Yichang City,

^b Department of Ultrasound, The First College of Clinical Medical Sciences, China Three Gorges University, Yichang, Hubei Province, China.

* Correspondence: Chang Zhou, Department of Ultrasound, the First College of Clinical Medical Sciences, China Three Gorges University, Yiling Road 183, Yichang 443000, Hubei Province, China (e-mail: zhouchang1243@163.com).

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Pan X, Xu L, Zhou C, Zhang Z, Sun H. Meta-analysis of patent foramen ovale closure versus medical therapy for prevention of recurrent ischemic neurological events: Impact of medication type. *Medicine* 2021;100:25 (e26473).

Received: 30 January 2021 / Received in final form: 4 June 2021 / Accepted: 8 June 2021

<http://dx.doi.org/10.1097/MD.00000000000026473>

1. Introduction

Ischemic stroke is an important cause of death and disability in adults. About 30%–40% of ischemic strokes cannot be found any cause and are classified as cryptic stroke.^[1] Numerous studies have shown that PFO is associated with cryptic stroke, and abnormal embolism is currently considered as a possible pathogenesis.^[1–4] The treatment strategy for PFO and abnormal embolism events include PFO closure and medical therapy (anticoagulation or /and antiplatelet therapy). However, the effect of PFO closure versus medical therapy on the prevention of secondary stroke has long been controversial.^[5] The current evidence are insufficient to demonstrate the superiority of PFO closure due to the low incidence of end-point events, the occurrence of bleeding and new-atrial fibrillation, and differences in medical type selection between studies.^[6] We pooled available data on comparisons between PFO closure and different types of medical therapy (antiplatelet therapy alone; anticoagulant therapy alone; a mixed medical therapy group consisting of antiplatelet therapy, anticoagulant therapy, or both), and performed a meta-analysis to further evaluate the optimal treatment strategy. In addition, observational studies were included to enhance the reliability of the results.

2. Methods

We performed this meta-analysis according to the preferred reporting items for systematic review and meta-analysis (PRISMA) statement.^[7] As the data in this study were based on published literature, ethical approval and patient consent were not required.

2.1. Search strategy

We systematically searched electronic databases of PubMed, Embase, and the Cochrane Central Register of Controlled Trials with no language restriction from inception to June 2020. The following search terms were used: “patent foramen ovale,” “PFO,” “closure,” “medical therapy,” “anticoagulant therapy,” “antiplatelet therapy,” “stroke,” “transient ischemic attack,” “TIA,” “recurrent neurological events.” The references of the retrieved papers, related reviews and meta-analysis were also reviewed for the purpose of finding potentially eligible studies.

2.2. Study selection and inclusion

The inclusion criteria were: adult patients (age ≥ 18 years) with a history of ischemic neurological events (stroke or transient ischemic attack [TIA]) and PFO; follow-up period ≥ 1 year; and randomized controlled trials (RCTs) or observational studies comparing patent foramen ovale (PFO) closure and medical therapy. Case reports, cross-sectional studies, and conference abstracts were excluded.

2.3. Data extraction and quality assessment

Two researchers (XP and LX) independently screened studies and abstracted the data according to inclusion criteria and exclusion criteria. Any disagreement was resolved by a third researcher (CZ). Outcomes of this meta-analysis were classified as primary efficacy endpoints, secondary efficacy endpoints, and safety endpoints. The primary efficacy endpoints were the composite outcome of recurrent ischemic neurological events (stroke and/or TIA). Secondary efficacy endpoints included separate recurrent stroke and TIA. Safety endpoints included new-onset AF/atrial flutter, and bleeding events. Assessment for quality of studies was independently performed by 2 researchers (XP and LX). Discrepancies were resolved through negotiation. The quality of RCTs and observational studies was assessed according to Cochrane Handbook^[8] and Newcastle- Ottawa Scale,^[9] respectively.

2.4. Statistical analysis

Statistical analysis was performed with the Review Manager 5.3 (The Cochrane Collaboration, 2014, Copenhagen, Denmark). The longest follow-up data from each study were used. We calculated the odds ratio (OR) and their corresponding 95% confidence interval (CI) for each study and pooled values using fixed-effect (Mantel-Haenszel method) or random-effect model (DerSimonian-Laird method) according to heterogeneity detected.^[10] Heterogeneity between studies was assessed with I^2 index and χ^2 test. $I^2 > 50\%$ and P value of the χ^2 test $< .1$ were considered to have significant heterogeneity.^[11] In case zero endpoint events occurred in one of the treatment arms, continuity correction of 1/2 was used.^[12] To explore the possible sources of heterogeneity of the results, several prespecified subgroup analyses were conducted, which included type of study and

duration of follow-up. Sensitivity analysis was tested by taking each study away from the total. Publication bias was assessed using funnel plots. For the effect estimate, P values were 2-tailed, and $< .05$ was considered as statistically significant.

3. Results

3.1. Description of included studies

The flow diagram of study selection was shown in Figure 1. We identified 859 articles through electronic database searching. After layer-by-layer screening, 19 studies met the predetermined inclusion criteria and were used for qualitative and quantitative analysis, including 6 RCTs and 13 observational studies.^[13–31] Mean duration of follow-up ranged from 1.8 to 9 years. One of these RCTs, the RESPECT trial, was reported at different follow-up periods. In our meta-analysis, we used data from extended trials.

In the medical therapy group, 10 studies (4 RCTs,^[13–16] 6 observational studies^[24,26,28–31]) exclusively used antiplatelet therapy and 7 studies (3 RCTs,^[13–15] 4 observational studies^[26,28–30]) exclusively used anticoagulant therapy; In addition to that, in 15 studies (4 RCTs,^[13,15,17,18] 11 observational studies^[19–26,28–30]), patients of medical therapy group received a mixed type (anticoagulant therapy, antiplatelet therapy, or both), and the detailed therapy regimen was determined by the physician. Table 1 shows the main descriptions and patient characteristics of the included studies. The quality evaluation of RCTs is shown in Supplementary Table 1, <http://links.lww.com/MD/G210> and the quality evaluation of observational studies is shown in Supplementary Table 2, <http://links.lww.com/MD/G211>.

3.2. Composite outcome of recurrent ischemic neurological events (stroke and/or TIA)

Compared with antiplatelet therapy, PFO closure had a significant benefit for the prevention of the composite outcome of recurrent ischemic neurological events (odds ratio [OR] 0.37, 95% confidence interval [CI] 0.27–0.51; $P < .00001$) (Fig. 2A); Compared with mixed medical therapy, the benefit of PFO closure was second only to that of antiplatelet therapy and also had statistical difference (OR 0.53, 95% CI 0.41–0.69; $P < .00001$) (Fig. 2B); compared with anticoagulant therapy, PFO closure showed no significant benefit, and there was no statistical difference between the two groups (OR 0.77, 95% CI 0.46–1.28; $P = .31$) (Fig. 2C).

3.3. Recurrent ischemic stroke

Compared with antiplatelet therapy, PFO closure had a significant benefit for the prevention of recurrent ischemic stroke (OR 0.22, 95% CI: 0.13–0.36; $P < .00001$) (Fig. 3A); compared with mixed medical therapy, PFO closure reduced the risk of recurrent ischemic stroke, but the effect was not as significant as that of antiplatelet therapy (OR 0.48, 95% CI 0.34–0.68; $P < .0001$) (Fig. 3B); compared with anticoagulant therapy, PFO closure showed no significant benefit, and there was no statistical difference (OR 0.59, 95% CI: 0.28–1.25; $P = .17$) (Fig. 3C).

3.4. TIA

PFO closure significantly reduced the risk of TIA in comparison with antiplatelet therapy (OR 0.57, 95% CI 0.34–0.98; $P = .04$)

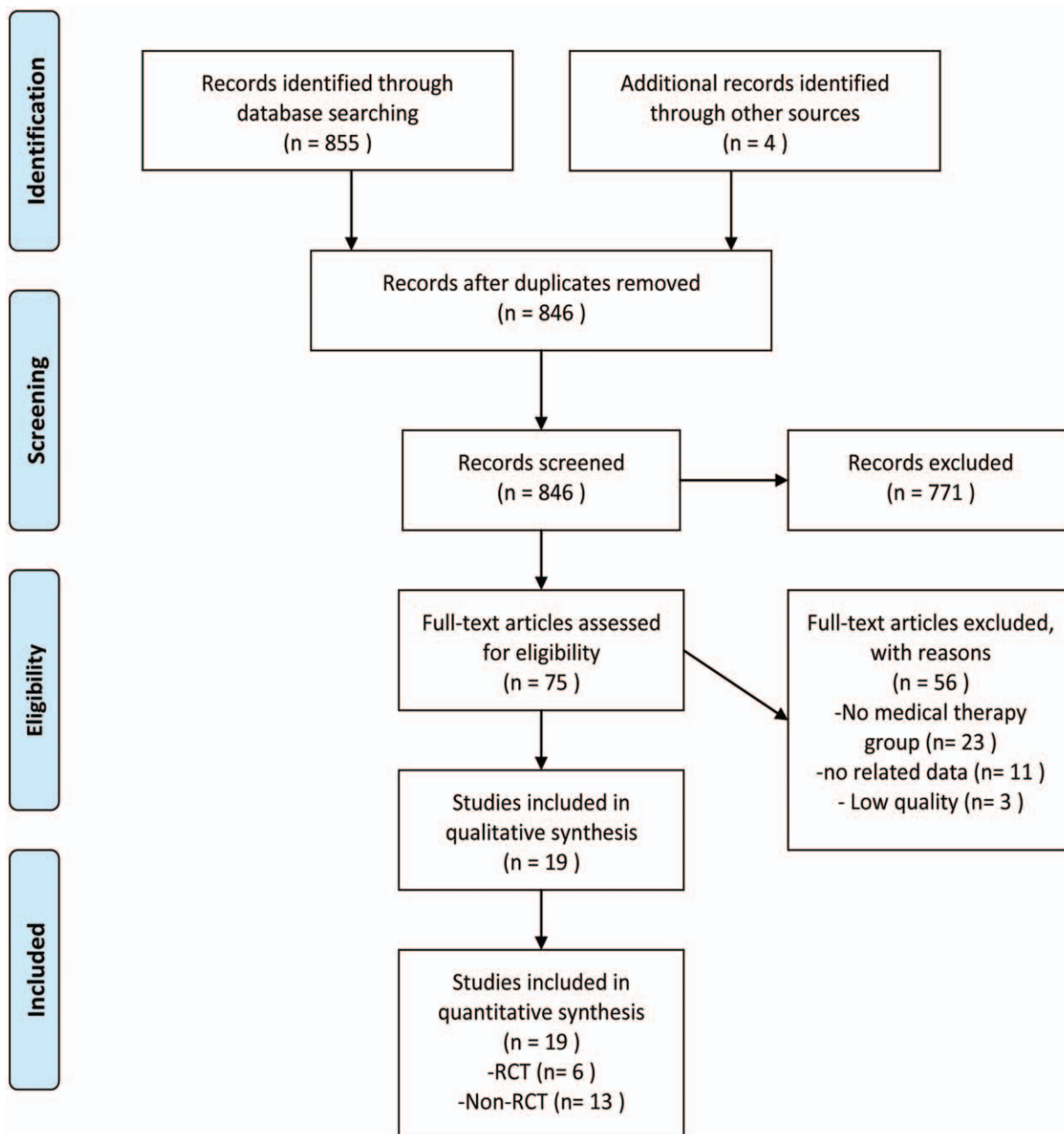


Figure 1. Flow diagram of study selection. RCT = randomized controlled trial.

(Fig. 4A) and mixed medical therapy (OR 0.69, 95% CI 0.50–0.96; $P=.03$) (Fig. 4B); However, PFO closure showed no significant benefit compared with anticoagulant therapy, and there was no statistical difference (OR 1.01, 95% CI 0.50–2.04; $P=.98$) (Fig. 4C).

3.5. Safety endpoints

Compared with various types of medical therapy, PFO closure increased the risk of AF/atrial flutter (PFO closure vs antiplatelet therapy [OR 9.56, 95% CI 2.85–32.06; $P=.0003$] [Fig. 5A]; PFO closure vs mixed medical therapy [OR 4.40, 95% CI: 2.24–8.67; $P<.0001$] [Fig. 5B]; PFO closure vs anticoagulant therapy (OR 18.96, 95% CI 1.11–323.80; $P=.004$) (Fig. 5C)].

In terms of bleeding events, PFO closure reduced the risk of bleeding events compared with antiplatelet therapy alone, but no statistical difference was observed (OR 0.50, 95% CI 0.24–1.05; $P=.07$) (Fig. 6A); compared with mixed medical therapy, PFO closure was similar to mixed medical therapy (OR 0.97, 95% CI 0.56–1.68; $P=.90$) (Fig. 6B); compared with anticoagulant therapy alone, PFO closure reduced the risk of bleeding events (OR 0.13, 95% CI 0.04–0.46; $P=.001$) (Fig. 6C).

3.6. Major subgroup analyses

We performed a subgroup analysis of the main results by study type and duration of follow-up.

Table 1
Baseline characteristics and main descriptions of the included studies.

Studies	Type of study	Inclusion criteria	Main complications	Type of medical therapy	Mean follow-up, y
CLOSURE I, 2012 ^[12]	Randomized	CS, TIA	AF, bleeding	Antiplatelet therapy, anticoagulation or both at the discretion of the principal investigator	2
CLOSE 2017 ^[13]	Randomized	CS	AF or flutter, Bleeding	Antiplatelet therapy only or anticoagulation only	5.3
RESPECT 2017 ^[14]	Randomized	CS	AF or flutter, bleeding	Antiplatelet therapy or anticoagulation	5.9
REDUCE 2017 ^[15]	Randomized	CS	AF or flutter, bleeding	Antiplatelet therapy only	3.2
PC 2013 ^[16]	Randomized	IS, TIA	AF, bleeding	Antiplatelet therapy or anticoagulation at the discretion of physician	4.1
DEFENSE-PFO 2018 ^[17]	Randomized	CS	AF, bleeding	Antiplatelet therapy or anticoagulation at the discretion the local investigator	2.8
Wahl et al, 2012 ^[18]	Observational	IS, TIA	Bleeding	Antiplatelet therapy or anticoagulation	9
Kim et al, 2018 ^[9]	Observational	CS, TIA	Bleeding	Antiplatelet therapy or anticoagulation at the discretion of physician	2.3
Alushi et al, 2014 ^[20]	Observational	CS, TIA	NR	Antiplatelet therapy and/or anticoagulation at the discretion of the attending neurologist.	5.9
Moon et al, 2016 ^[21]	Observational	IS, TIA	AF, bleeding	Antiplatelet therapy or anticoagulation at the discretion of physician	1.8
Harrer et al, 2006 ^[22]	Observational	CS, TIA	NR	Antiplatelet therapy or anticoagulation at the discretion of the presence of deep venous thrombosis	4.5
Mazzucco et al, 2012 ^[23]	Observational	CS	Bleeding	Antiplatelet therapy for most cases, anticoagulation for three cases	2.3
Lee et al, 2010 ^[24]	Observational	CS	NR	Antiplatelet therapy or anticoagulation	3.5
Windecker et al, 2004 ^[25]	Observational	CS	Bleeding	Antiplatelet therapy or anticoagulation at the discretion of the attending neurologist	4
Pezzini et al, 2016 ^[26]	Observational	CS	AF	Antiplatelet therapy or anticoagulation at the discretion of physician	3
Cerrato et al, 2006 ^[27]	Observational	CS, TIA	NR	Antiplatelet therapy or anticoagulation at the discretion of physician	5.3
Casaubon et al, 2007 ^[28]	Observational	CS, TIA	Bleeding	Antiplatelet therapy or anticoagulation	2.7
Paciaroni et al, 2011 ^[29]	Observational	CS, TIA	Bleeding	Antiplatelet therapy or anticoagulation at the discretion of the attending physician	2
Thanopoulos et al, 2006 ^[30]	Observational	CS	Bleeding	Antiplatelet therapy only	2

AF = atrial fibrillation, CS = cryptogenic stroke, IS = ischemic stroke, NR = not reported, TIA = transient ischemic attack.

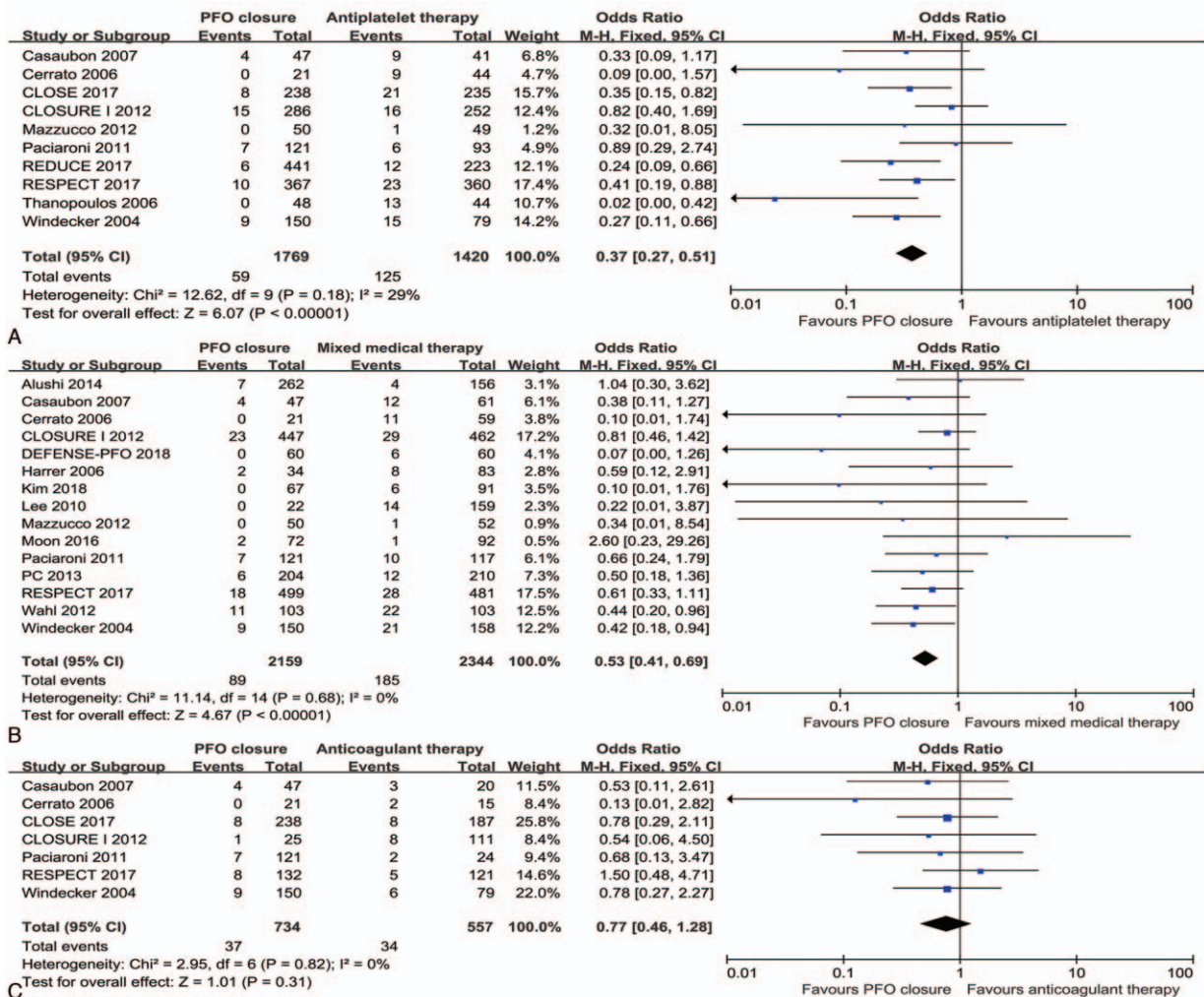


Figure 2. Forest plots comparing the risk of recurrent ischemic neurological events between PFO closure and different types of medical therapy. (A) PFO closure vs antiplatelet therapy. (B) PFO closure vs mixed medical therapy. (C) PFO closure vs anticoagulant therapy. CI = confidence interval, PFO = patent foramen ovale.

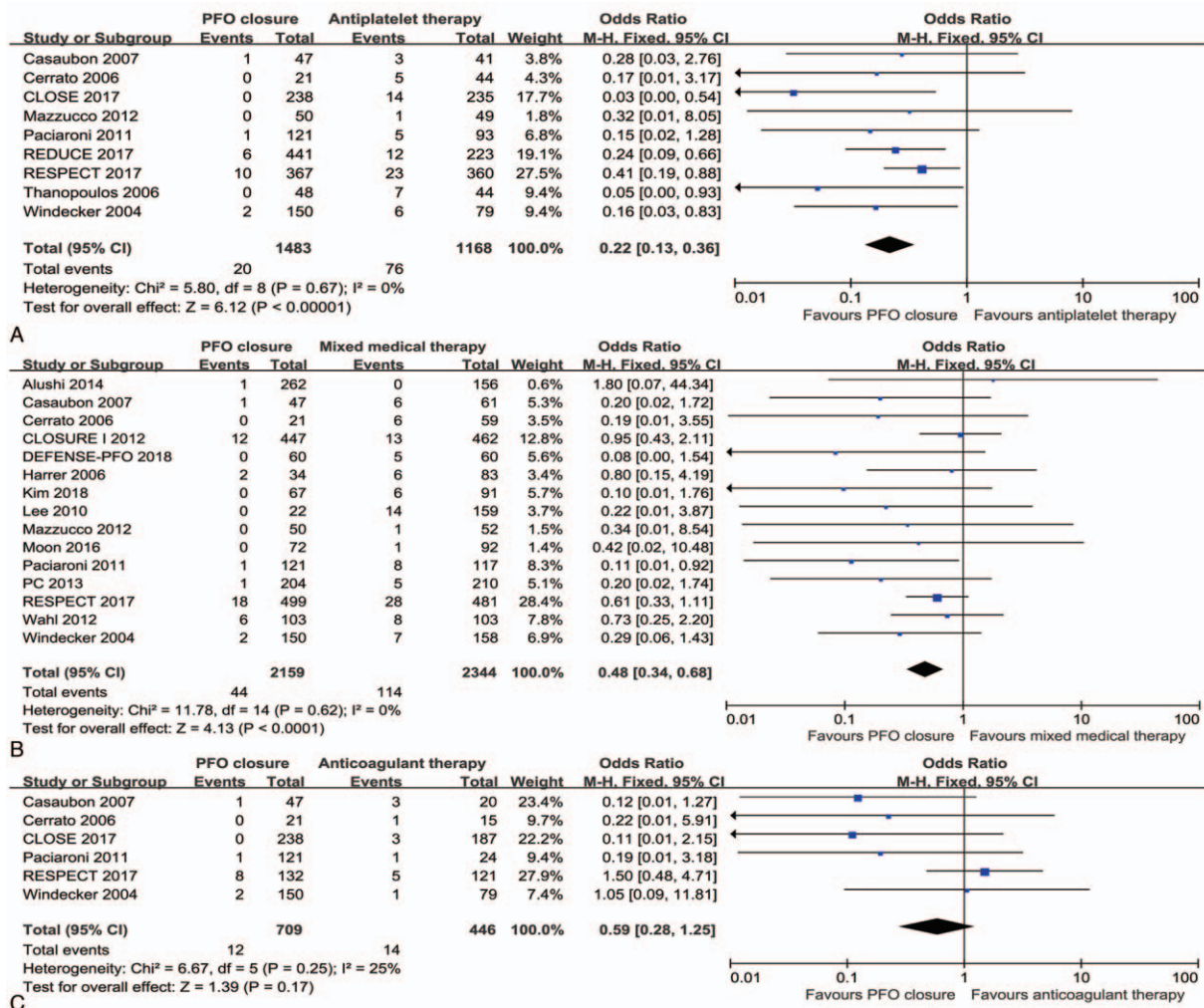


Figure 3. Forest plots comparing the risk of recurrent ischemic stroke between PFO closure and different types of medical therapy. (A) PFO closure vs antiplatelet therapy. (B) PFO closure vs mixed medical therapy. (C) PFO closure vs anticoagulant therapy. CI = confidence interval, PFO = patent foramen ovale.

Our subgroup analysis showed no significant differences between the subgroups. The subgroup analysis results for composite outcome of recurrent ischemic neurological events were shown in Supplementary Figure 1, <http://links.lww.com/MD/G207> and Supplementary Figure 2, <http://links.lww.com/MD/G208>.

3.7. Sensitivity analyses and Publication Bias

In the sensitivity analysis, the overall conclusion remained unchanged when the included studies were excluded one by one. Publication bias results showed no publication bias for composite outcome of recurrent ischemic neurological events (Supplementary Figure 3, <http://links.lww.com/MD/G209>).

4. Discussion

In this meta-analysis of 6 RCTs and 13 observational studies, we found significant differences in the benefits of PFO closure compared with different types of medical therapy for the prevention of recurrent ischemic neurological events. Compared with antiplatelet therapy alone, PFO closure significantly reduced

the risk of recurrent ischemic neurological events; compared with the mixed medical therapy group, PFO closure still showed some benefits for prevention of recurrent ischemic neurological events, but the effect was not as significant as that of antiplatelet therapy; compared with anticoagulant therapy alone, PFO closure showed no benefit. We believe that the reason for this difference may be the proportion of patients who received anticoagulant therapy; with the addition of anticoagulant patients in the medical therapy group, the benefit of PFO closure was reduced. In terms of safe endpoints, in general, PFO closure showed a risk of AF/atrial flutter compared with various types of medical therapy, whereas medical therapy showed a risk of bleeding.

The optimal treatment strategy for PFO patients with cryptic stroke has long been controversial.^[6] Previous studies and meta-analysis have shown that PFO closure can reduce the risk of stroke recurrence compared with medical therapy.^[5] However, considering the risk of AF in PFO closure and the low stroke recurrence rate, it is not clear whether PFO closure is superior to medical therapy. In addition, due to the potential heterogeneity of medical treatment regimens in different studies, there may be differences in comparison with PFO closure. Therefore, in our study, we focused on the analysis of medication types. Of note, in

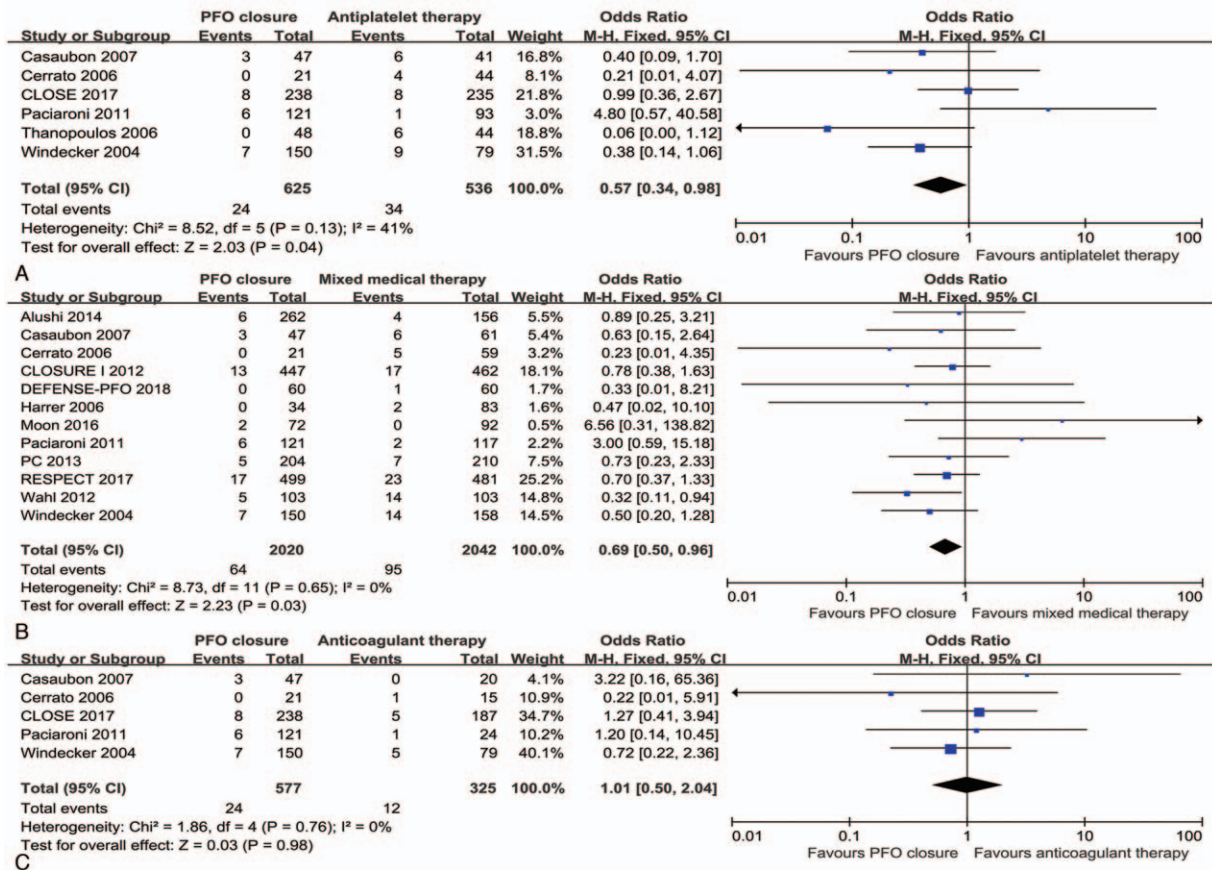


Figure 4. Forest plots comparing the risk of recurrent TIA between PFO closure and different types of medical therapy. (A) PFO closure vs antiplatelet therapy. (B) PFO closure vs mixed medical therapy. (C) PFO closure vs anticoagulant therapy. CI = confidence interval, PFO = patent foramen ovale.

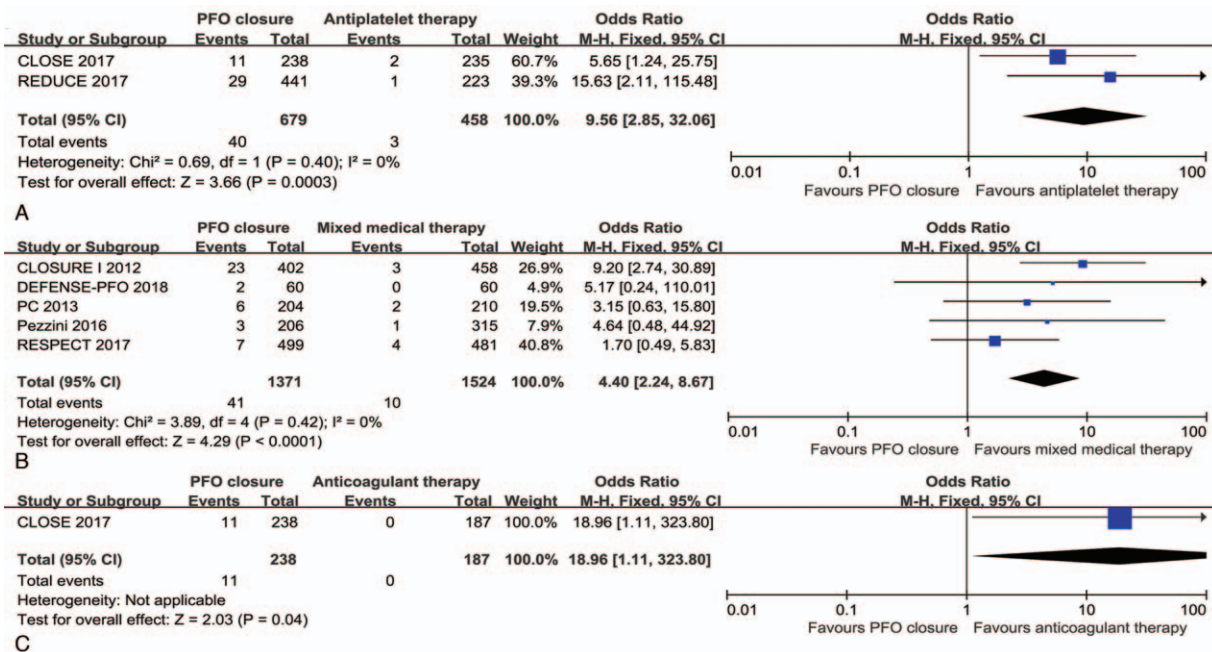


Figure 5. Forest plots comparing the risk of AF/atrial flutter between PFO closure and different types of medical therapy. (A) PFO closure vs antiplatelet therapy. (B) PFO closure vs mixed medical therapy. (C) PFO closure vs anticoagulant therapy. AF = atrial fibrillation; CI = confidence interval, PFO = patent foramen ovale.

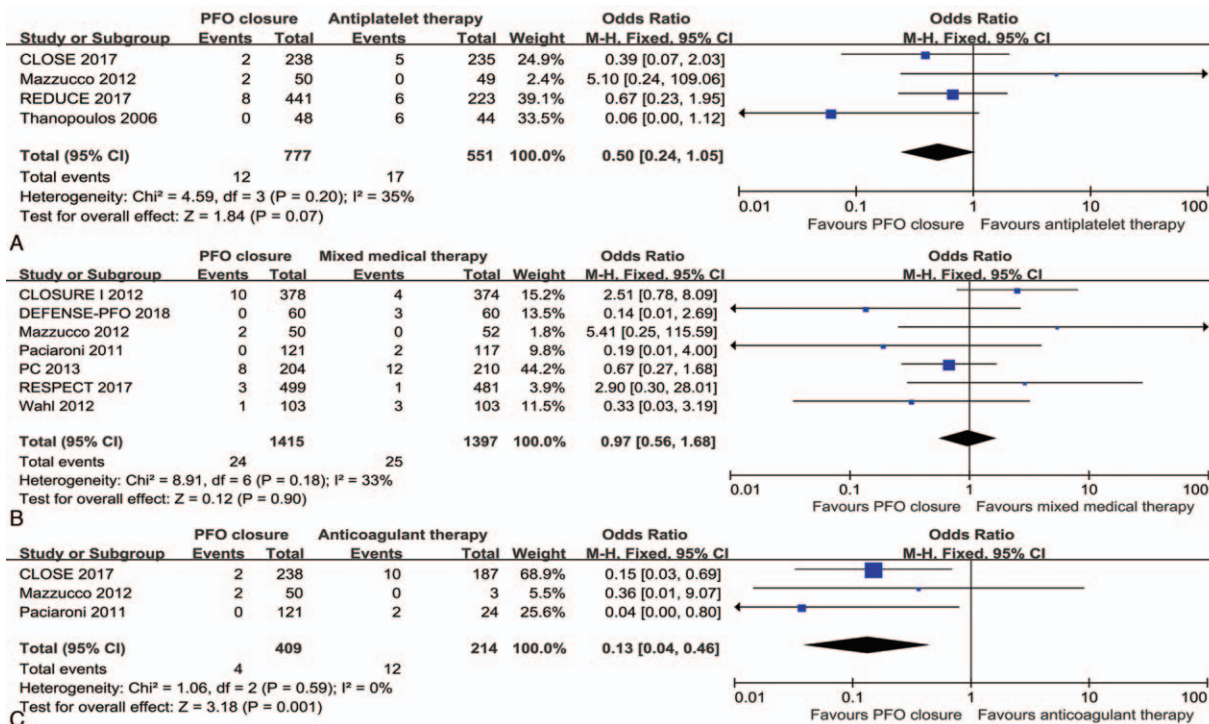


Figure 6. Forest plots comparing the risk of bleeding events between PFO closure and different types of medical therapy. (A) PFO closure vs antiplatelet therapy. (B) PFO closure vs mixed medical therapy. (C) PFO closure vs anticoagulant therapy. PFO = patent foramen ovale.

addition to comparing PFO closure with antiplatelet therapy alone and anticoagulant therapy alone, we also compared for the first time the mixed medical therapy group with two types of antiplatelet therapy and anticoagulation therapy. We believe that the different proportion of patients treated with antiplatelet therapy and anticoagulant therapy may influence the outcome to some extent; In addition, the medical therapy regimen in most studies was determined by physicians independently, and in these studies, physicians may adopt personalized treatment strategies for some patients, which was consistent with our research starting point.

Our study included observational studies in addition to RCT studies in the comparison of PFO closure versus different types of medical therapy to enhance the reliability of our results. Garg et al’s study^[32] compared PFO closure with antiplatelet therapy alone and anticoagulation therapy alone in the subgroup analysis, but the analysis results were questioned due to the inclusion of only RCTs and the low sample size of the subgroup. Patti et al’s study^[33] included observational studies, but only compared PFO closure with antiplatelet and anticoagulant therapy separately. It should be noted that, in most cases, the medication regimen in clinical practice was determined by physicians independently, rather than mechanically using antiplatelet and anticoagulant medications. Therefore, we added a comparison of PFO closure versus mixed medical therapy group in our study. Our results showed that with the addition of anticoagulants, the benefit of PFO closure decreased gradually, and the risk of bleeding could be effectively reduced through the discretion of physicians, which provided guidance and basis for the formulation of medical therapy strategies. In addition, our preset subgroup analysis showed no significant heterogeneity, which indicated that our results had good stability.

The American Academy of Neurology guidelines recommend antiplatelet medications as routine medications for patients with cryptogenic stroke and PFO, rather than anticoagulation.^[32] Patti et al’s meta-analysis shows that all medical therapy had a risk of bleeding, especially anticoagulation^[33]; similar results had been obtained in our study. In the comparison of PFO closure versus mixed medical therapy, the incidence of bleeding events was similar between PFO closure and medical therapy, which indicated that the incidence of bleeding events could be effectively reduced in the medical therapy group through the independent decision of physicians. However, bleeding and atrial fibrillation are unavoidable for PFO closure. Therefore, we believe that medical therapy may be more beneficial than PFO closure when the adverse events are fully evaluated and the optimal medical therapy strategy is formulated.

There are several limitations in our meta-analysis. First, our study on safety endpoints mainly focused on new-onset AF /atrial flutter and bleeding events, and did not analyze surgical complications and death. Second, there was heterogeneity in inclusion criteria across studies. Finally, the limitations of observational studies included selection bias and differences in “duration” and “intensity” of follow-up among the treatment groups.

5. Conclusions

Whether PFO closure is superior to medical therapy for the prevention of recurrent ischemic neurological events may depend on the proportion of anticoagulant therapy in medical-treated patients; antiplatelet therapy or anticoagulation therapy should be personalized based on the risk of patients’ own bleeding. Based on the full assessment of adverse events and the formulation of

the optimal treatment strategy, medical therapy may be more beneficial. It is important to further study the optimal medical therapy strategy.

Author contributions

Conceptualization: Xuemei Pan, Liang Xu.

Data curation: Xuemei Pan, Chang Zhou.

Formal analysis: Xuemei Pan, Liang Xu, Chang Zhou.

Funding acquisition: Chang Zhou.

Investigation: Xuemei Pan, Zhi Zhang, Heng Sun.

Methodology: Liang Xu, Xuemei Pan, Chang Zhou.

Software: Liang Xu, Heng Sun.

Supervision: Xuemei Pan, Chang Zhou.

Writing – original draft: Liang Xu, Xuemei Pan.

Writing – review & editing: Chang Zhou, Zhi Zhang.

References

- [1] Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;55:1172–9.
- [2] Yaghi S, Bernstein RA, Passman R, et al. Cryptogenic stroke: research and practice. *Circ Res* 2017;20:527–40.
- [3] Nayor M, Maron BA. Contemporary Approach to paradoxical embolism. *Circulation* 2014;129:1892–7.
- [4] Ma Y, Li D, Bai F, et al. Patent foramen ovale closure or medical therapy for secondary prevention of cryptogenic stroke: an update meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2018;97:e11965.
- [5] Pasceri V, Pelliccia F, Bressi E, et al. Net clinical benefit of patent foramen ovale closure in patients with cryptogenic stroke: Meta-analysis and meta-regression of randomized trials. *Int J Cardiol* 2018;266:75–80.
- [6] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9.
- [7] Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.
- [8] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Metaanalyses. Ottawa, Ontario, Canada: Ottawa Hospital Research Institute; 2013.
- [9] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trial* 1986;7:177–88.
- [10] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- [11] Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004;23:1351–75.
- [12] Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012;366:991–9.
- [13] Mas JL, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017;377:1011–21.
- [14] Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;377:1022–32.
- [15] Søndergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017;377:1033–42.
- [16] Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 2013;368:1083–91.
- [17] Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: The DEFENSE-PFO trial. *J Am Coll Cardiol* 2018;71:2335–42.
- [18] Wahl A, Jüni P, Mono ML, et al. Long-term propensity score-matched comparison of percutaneous closure of patent foramen ovale with medical treatment after paradoxical embolism. *Circulation* 2012;125:803–12.
- [19] Kim M, Kim S, Moon J, et al. Effect of patent foramen ovale closure for prevention on recurrent stroke or transient ischemic attack in selected patients with cryptogenic stroke. *J Interv Cardiol* 2018;31:368–74.
- [20] Alushi B, Biasco L, Orzan F, et al. Patent foramen ovale treatment strategy: an Italian large prospective study. *J Cardiovasc Med* 2014;15:761–8.
- [21] Moon J, Kang WC, Kim S, et al. Comparison of outcomes after device closure and medication alone in patients with patent foramen Ovale and cryptogenic stroke in Korean population. *Yonsei Med J* 2016;57:621–5.
- [22] Harrer JU, Wessels T, Franke A, et al. Stroke recurrence and its prevention in patients with patent foramen ovale. *Can J Neurol Sci* 2006;33:39–47.
- [23] Mazzucco S, Bovi P, Carletti M, et al. A model of multi-disciplinary approach to the diagnosis and treatment of young patients with cryptogenic stroke and patent foramen ovale. *Cardiol Young* 2012;22:327–34.
- [24] Lee JY, Song JK, Song JM, et al. Association between anatomic features of atrial septal abnormalities obtained by omni-plane transesophageal echocardiography and stroke recurrence in cryptogenic stroke patients with patent foramen ovale. *Am J Cardiol* 2010;106:129–34.
- [25] Windecker S, Wahl A, Nedeltchev K, et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J Am Coll Cardio* 2004;44:750–8.
- [26] Pezzini A, Grassi M, Lodigiani C, et al. Propensity score-based analysis of percutaneous closure versus medical therapy in patients with cryptogenic stroke and patent foramen ovale: the IPSYS registry (Italian project on stroke in young adults). *Circ Cardiovasc Interv* 2016;9:e003470.
- [27] Cerrato P, Priano L, Imperiale D, et al. Recurrent cerebrovascular ischaemic events in patients with interatrial septal abnormalities: a follow-up study. *Neurol Sci* 2006;26:411–8.
- [28] Casaubon L, McLaughlin P, Webb G, et al. Recurrent stroke/TIA in cryptogenic stroke patients with patent foramen ovale. *Can J Neurol Sci* 2007;34:74–80.
- [29] Paciaroni M, Agnelli G, Bertolini A, et al. Risk of recurrent cerebrovascular events in patients with cryptogenic stroke or transient ischemic attack and patent foramen ovale: the FORI (foramen Ovale Registro Italiano) study. *Cerebrovasc Dis* 2011;31:109–16.
- [30] Thanopoulos BV, Dardas PD, Karanasios E, et al. Transcatheter closure versus medical therapy of patent foramen ovale and cryptogenic stroke. *Catheter Cardiovasc Interv* 2006;68:741–6.
- [31] Garg A, Thawabi M, Rout A, et al. Recurrent stroke reduction with patent foramen ovale closure versus medical therapy based on PFO characteristics: a meta-analysis of randomized controlled trials. *Cardiology* 2019;144:40–9.
- [32] Patti G, Pelliccia F, Gaudio C, et al. Meta-analysis of net long-term benefit of different therapeutic strategies in patients with cryptogenic stroke and patent foramen ovale. *Am J Cardiol* 2015;115:837–43.
- [33] Messe SR, Gronseth G, Kent DM, et al. Practice advisory: recurrent stroke with patent foramen ovale (update of practice parameter): report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology* 2016;87:815–21.