Systematic Review and Meta-Analysis

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Long-term efficacy after closure of patent foramen ovale for ischemic neurological events in young adults

A systematic review and meta-analysis

Liang Xu, MD[a], Xuemei Pan, MD[b], Chang Zhou, MD[a,*], Jie Li, MD[a], Fangyuan Wang, MD[a]

Abstract

Background: The efficacy of patent foramen ovale (PFO) closure remains controversial, and it is unclear which patient groups are best benefited. We performed this meta-analysis to clarify the efficacy of PFO closure of younger patients for prevention of recurrent ischemic neurological events.

Methods: We systematically searched for studies of PFO closure for younger patients under the age of 55, and pooled available data on PFO closure of younger vs older patients and on PFO closure of younger patients vs medical therapy. The primary endpoints were the composite outcome of recurrent ischemic neurological events [stroke and/or transient ischemic attack (TIA)]. The secondary endpoints included recurrent stroke, TIA, atrial fibrillation (AF) and bleeding events. We calculated the odds ratios (OR) and 95% confidence interval (CI) using fixed-effect and random-effect models.

Results: Three randomized controlled trials (RCT) and 13 observational studies were eligible. Compared with older patients undergoing PFO closure, younger patients undergoing closure had a lower risk of composite outcome (OR: 0.40, 95% CI: 0.28 to .56; $P < .001$) and AF (OR: 0.25, 95% CI: 0.10–0.61; $P = .003$). Compared with medical therapy, PFO closure of younger patients reduced the risk of composite outcome (OR: 0.50, 95% CI: 0.33–0.75; $P < .001$); there was no statistical difference in total complications of AF and bleeding events (OR: 2.15, 95% CI: 0.15–30.37; $P = .57$). Separate analysis of stroke and TIA showed that PFO closure in younger patients was more effective in preventing stroke (OR: 0.45, 95% CI: 0.28–0.72; $P < .001$) and TIA (OR: 0.35, 95% CI: 0.21–0.58); $P < .001$) compared with older patients. Compared with medical therapy, PFO closure of younger patients reduced the risk of stroke (OR: 0.26, 95% CI: 0.13–0.51; $P < .001$); but there was no difference in the risk of TIA (OR: 1.07, 95% CI: 0.16–7.01; $P = .94$).

Conclusions: Compared with PFO closure of older patients and medical therapy, PFO closure of younger patients can benefit more for the prevention of recurrent ischemic neurological events. Our results indicate that PFO closure is the best treatment strategy for younger patients under the age of 55.

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

Keywords: meta-analysis, patent foramen ovale, secondary prevention, stroke

1. Introduction

The optimal treatment strategy for PFO and abnormal embolism events has not yet been determined. Although long-term follow-up data from RCTs support PFO closure, a meta-analysis of the net benefit of PFO closure shows that patients undergoing PFO closure do not benefit significantly.[1] PFO closure is still the focus of debate. It is unclear which patients benefit more from PFO closure. Several studies have shown that in younger patients without risk factors of cerebrovascular disease, the probability of abnormal embolism caused by PFO is higher.[2–4] Therefore, PFO closure of these patients may get more benefits. In this meta-analysis, we pooled data on PFO closure of younger patients vs older patients and on PFO closure of younger patients vs medical therapy to clarify the efficacy of PFO closure of younger patients for prevention of recurrent ischemic neurological events.

2. Methods

This meta-analysis was performed according to the preferred reporting items for systematic review and meta-analysis

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LX and XP contributed equally to this article as first author.

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[a] Department of Ultrasound, The First College of Clinical Medical Sciences, China Three Gorges University, [b] Department of Ultrasound, The Third People's Hospital of Yichang City, 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).

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(PRISMA) statement.[5] Ethical approval and patient consent were not required, as the data of this study were based on published literature.

2.1. Search strategy

We systematically searched databases of PubMed, Embase, and MEDLINE from inception through July 2019 with no language restriction using the search terms: "patent foramen ovale" OR "PFO" OR "right to left shunt" OR "RLS" AND "closure" AND "stroke" OR "transient ischemic attack" OR "TIA" OR "recurrent cerebral ischemia" OR "recurrent ischemic neurological events". In addition, we searched the references of the retrieved papers, related reviews and meta-analysis to identify potentially eligible studies.

2.2. Study selection and inclusion

The following inclusion criteria were used in this meta-analysis:

Patients with ischemic neurological events (stroke and/or TIA) and PFO;

Young adult age $\leq$55 years;

Follow-up of clinical data $\geq$1 year;

RCTs or observational studies.

The following studies were excluded:

Reviews, case reports, cross-sectional studies, and conference abstracts;

Repeated papers.

2.3. Data extraction and quality assessment

Data extraction was performed independently by 2 researchers (Liang Xu and Xuemei Pan) according to inclusion criteria and exclusion criteria. Any disagreement between the 2 researchers was resolved by discussion or referral to a third researcher. The primary endpoints of this meta-analysis were the composite outcome of recurrent ischemic neurological events (stroke and/or TIA). Secondary endpoints included recurrent stroke, TIA, new-onset AF and bleeding events. The quality of RCT studies was assessed according to Cochrane Handbook,[6] and the quality of observational studies was assessed according to Newcastle-Ottawa Scale.[7] Two researchers independently assessed the quality of the studies and the differences were resolved through negotiation.

2.4. Statistical analysis

All analyses were performed using the Review Manager 5.3 software (The Cochrane Collaboration, Oxford, UK). Long-term follow-up data from each study were used. We calculated the OR and 95% CI for each study and pooled values. In case zero endpoint events occurred in 1 arm of a study, we used a continuity correction of 1/2; In case zero endpoint events occurred in both arms of a study, continuity correction was not used and the corresponding estimates were designated as not estimable.[8] According to heterogeneity detected, we used a fixed-effect model (Mantel-Haenszel method) and a random-effect model (DerSimonian-Laird method) to calculate both the overall estimates and the pooled values of each subgroup.[9] The equivalent Z test was performed for each pooled OR, and P values $<.05$ was considered as statistically significant. Study heterogeneity was assessed with I^2 statistics and chi-squared test.[10] P values $<.10$ or $I^2 > 50\%$ were considered to have significant heterogeneity. We planned pre-specified subgroup analyses based on type of study, age demarcation for younger/older, and duration of follow-up. Sensitivity analysis was used to evaluate the stability of meta-analysis results by taking each study away from the total. Funnel plots were used to test the possibility of publication bias.

3. Results

3.1. Description of included studies

The study selection process was shown in Figure 1. In the initial search, we identified 656 articles. After layer-by-layer selection,16 studies were finally selected for the current meta-analysis, including 3 RCTs and 13 observational studies. In order to evaluate the efficacy of PFO closure of younger patients, we included 12 studies comparing the efficacy of PFO closure of younger patients and older patients,[11–19,24–26] including 2671 younger patients and 1764 older patients. Mean duration of follow-up ranged from 1.5 to 7 years. In addition, in order to further explore the efficacy of PFO closure of younger patients and whether younger patients are the best suitable groups of PFO closure, we also compared the long-term efficacy of PFO closure and medical therapy of younger patients. A total of 7 studies provided data,[20–26] including 3 RCTs and 4 observational studies. Mean duration of follow-up ranged from 2 to 5.9 years. The main descriptions and patient characteristics of the included studies are shown in Table 1. The quality assessment of the included studies is summarized in Table 1 and Table 2.

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

Younger patients undergoing PFO closure had a lower risk of composite outcome of recurrent ischemic neurological events than older patients undergoing PFO closure (incidence 2.2% vs 5.0%; OR: 0.40; 95% CI: 0.28–0.56; $P<.001$) (Fig. 2A); Heterogeneity between studies was not significant ($I^2=37\%$; $P=.10$). Compared with medical therapy, PFO closure of younger patients reduced the risk of composite outcome of recurrent ischemic neurological events (3.3% vs 7.2%; OR: 0.50; 95% CI: 0.33–0.75; $P<.001$) (Figure 2B); Heterogeneity between studies was not significant ($I^2=0\%$; $P=.63$).

3.3. Recurrent stroke

The stroke rates were 1.1% with PFO closure of younger patients vs 2.7% with PFO closure of older patients. PFO closure of younger patients was more effective for prevention of recurrent stroke (OR: 0.45; 95% CI: 0.28–0.72; $P<.001$) (Fig. 3A). In addition, the stroke rates were 1.2% with PFO closure vs 4.7% with medical therapy in younger patients; PFO closure of younger patients was superior to medical therapy (OR: 0.26; 95% CI: 0.13–0.51; $P<.001$) (Fig. 3B).

3.4. Transient ischemic attack

The recurrence rates of TIA in younger patients undergoing PFO closure was lower than that in older patients undergoing PFO closure (1.3% vs 3.3%; OR: 0.35; 95% CI: 0.21–0.58; $P<.001$) (Fig. 4A), but there was no difference in the comparisons of PFO closure of younger patients vs medical therapy (4.587% vs 4.591%; OR: 1.07; 95% CI: 0.16–7.01; $P=.94$) (Fig. 4B).

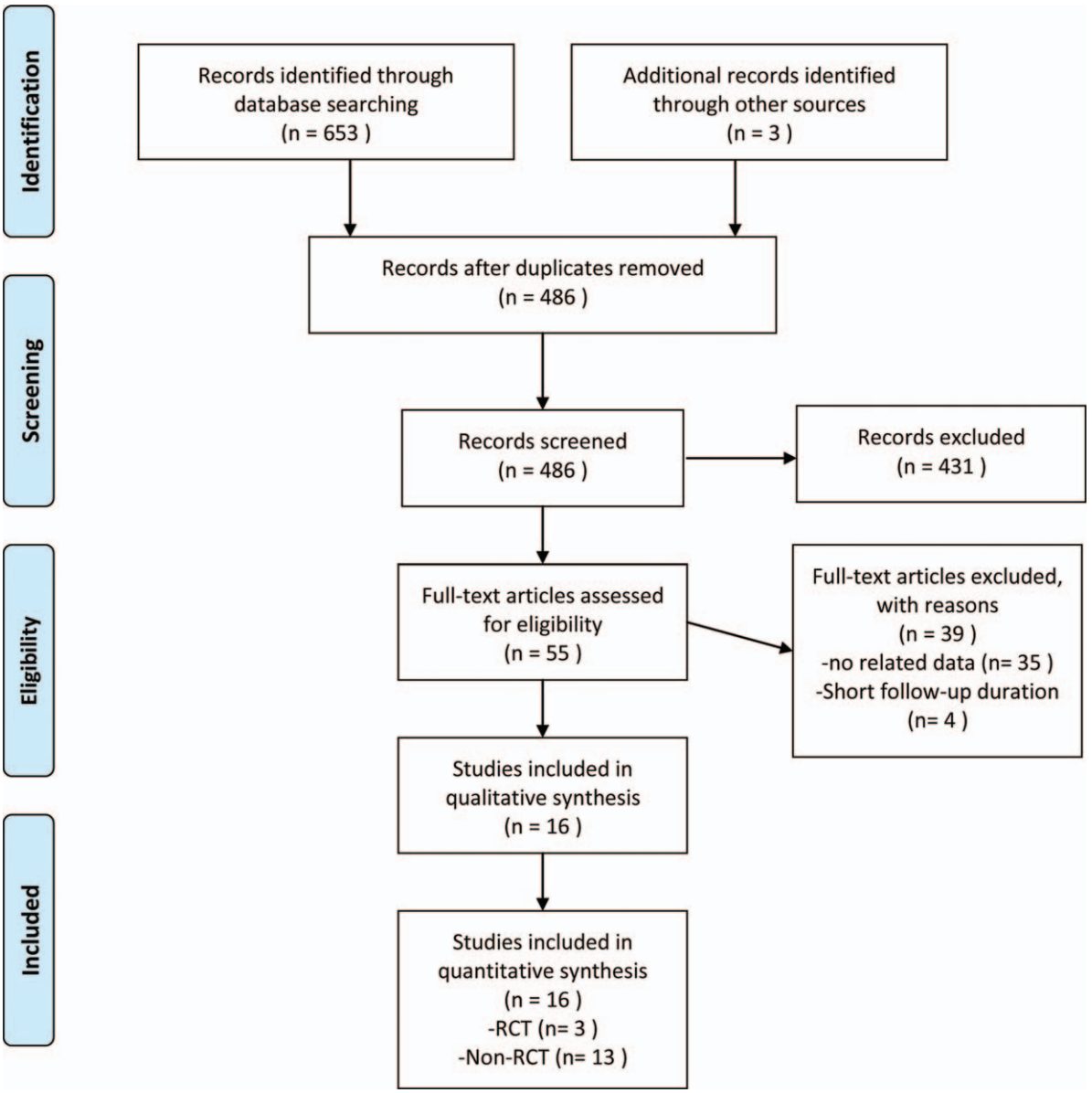

Figure 1. Flow diagram of study selection. RCT=randomized controlled trial, non-RCT=nonrandomized controlled trial.

Table 1

Main descriptions and patient characteristics of the included studies.

Studies	Type of study	Inclusion criteria	Primary end point	Main complications	Definition of younger (years)	Mean follow-Up (years)	NOS score
Homma 1997[11]	Observational	CS	Stroke, TIA	NR	<45	1.6	7
Cifarelli 2010[12]	Observational	IS/TIA	TIA	NR	≤55	3	8
Harms 2007[13]	Observational	IS	TIA	NR	≤55	1.6	6
Scacciatella 2016[14]	Observational	CS/TIA	Stroke, TIA	AF	<55	4.5	8
Spies 2008[15]	Observational	CS/TIA	Stroke, TIA	NR	≤55	1.5	7
Kiblawi 2006[16]	Observational	IS/TIA	Stroke, TIA	AF	≤55	1.5	6
Luermans 2011[17]	Observational	CS	Stroke, TIA	NR	<55	4	7
Mariucci 2017[18]	Observational	CS/TIA	Stroke, TIA	AF	<55	7	8
Dearani 1999[19]	Observational	IS/TIA	TIA	NR	<55	2	7
Danese 2017[20]	Observational	CS	Stroke	AF, Bleeding	≤55	4.3	7
Horner 2013[21]	Observational	CS/TIA	Stroke, TIA	NR	≤55	2	8
Pezzini 2016[22]	Observational	CS	Stroke, TIA	AF, Bleeding	≤45	3	8
Paciaroni 2011[23]	Observational	CS/TIA	Stroke, TIA	NR	≤55	2	8
REDUCE 2017[24]	Randomized	CS	Stroke	NR	≤45	3.2	NA
CLOSE 2017[25]	Randomized	CS	Stroke	AF	≤45	5.3	NA
RESPECT 2017[26]	Randomized	CS	Stroke	NR	≤45	5.9	NA

AF=atrial fibrillation, CS = cryptogenic stroke, IS = ischemic stroke, NA=not available, NOS=Newcastle-Ottawa Scale, NR=not reported, TIA=transient ischemic attack.

Table 2

Risk of bias of included randomized trials.

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
REDUCE 2017	Unclear risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
CLOSE 2017	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk
RESPECT 2017	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk	Low risk

3.5. Atrial fibrillation and bleeding events

The risk of AF in younger patients undergoing PFO closure was lower than that in older patients undergoing PFO closure (1.7% vs 7.3%; OR: 0.25; 95% CI: 0.10–0.61; $P=.003$) (Fig. 5A). There was no significant difference in total complications from AF and bleeding in the comparisons of PFO closure of younger patients vs medical therapy (2.1% vs 0.8%; OR: 2.15; 95% CI: 0.15–30.37; $P=.57$) (Fig. 5B).

3.6. Major subgroup analyses

Several subgroup analyses were planned in advance. Compared with PFO closure of older patients, PFO closure of younger patients reduced the risk of composite outcome in RCT subgroup (OR: 0.68; 95% CI: 0.29–1.57; $P=.37$) and subgroup demarcated by 45 years of age (OR: 0.50; 95% CI: 0.23–1.09; $P=.08$), but did not reach statistical significance. The results of subgroup analysis for composite outcome of recurrent ischemic neurological events were shown in Table 3.

3.7. Sensitivity analyses and publication bias

In sensitivity analysis, excluding the included studies one by one, the overall conclusion remained unchanged. In comparison with PFO closure of older patients, the OR decreased to 0.32 (95% CI: 0.21–0.49) after excluding the study of Spies. In comparison with medical therapy, the OR decreased to 0.40 (95% CI: 0.23–0.68) after excluding the study of Pezzini. Although these 2 studies had a great influence on the total outcomes, it is worth noting that the excluded outcomes were more favorable to the PFO closure group of younger patients. The results of publication bias showed no publication bias in the composite outcome of recurrent ischemic neurological events (Fig. 6).

4. Discussion

In this meta-analysis of the long-term efficacy of PFO closure of younger patients, our results showed that PFO closure of younger patients was more effective for prevention of recurrent ischemic

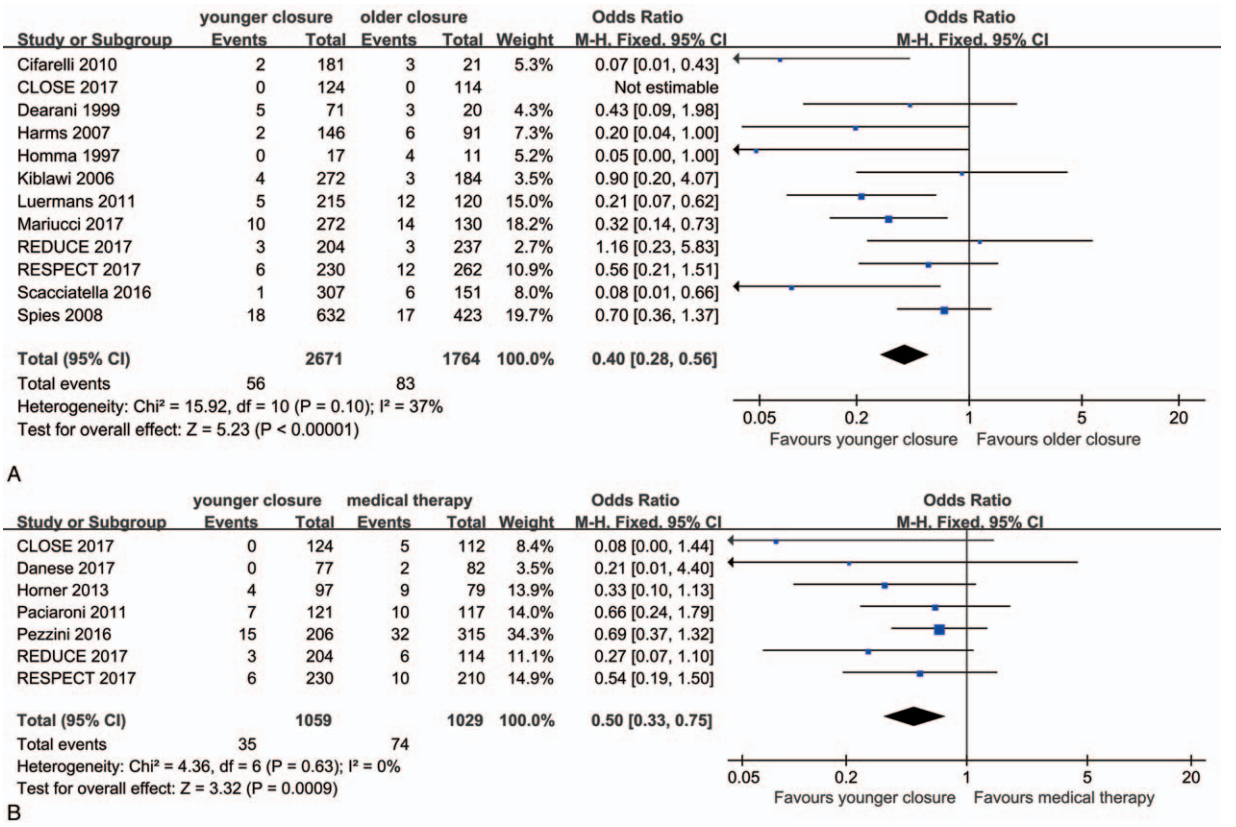

Figure 2. Forest plots comparing the risk of recurrent ischemic neurological events (stroke and/or transient ischemic attack) between younger PFO closure and older PFO closure (A) and between younger PFO closure and medical therapy (B). CI = confidence interval, PFO = patent foramen ovale.

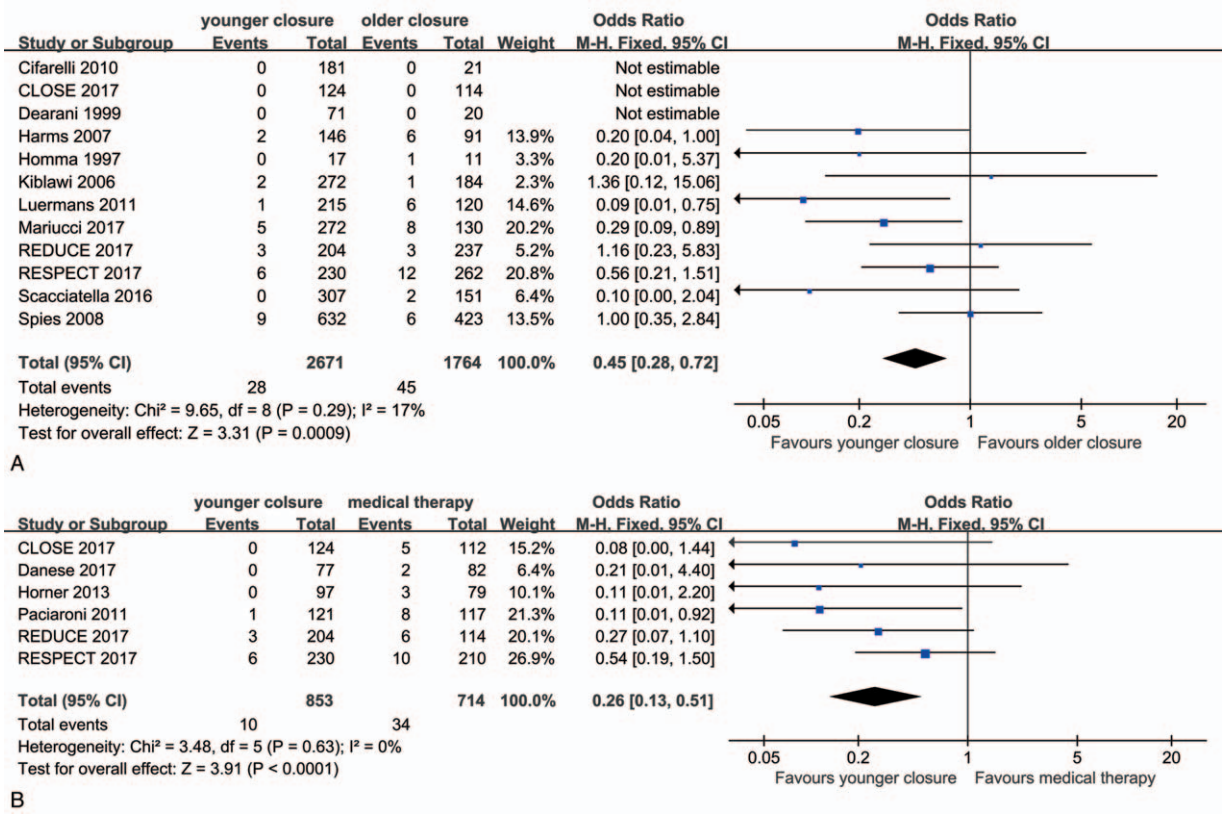

Figure 3. Forest plots comparing the risk of recurrent stroke between younger PFO closure and older PFO closure (A) and between younger PFO closure and medical therapy (B). CI = confidence interval, PFO = patent foramen ovale.

neurological events and had a lower risk of AF than PFO closure of older patients. On the other hand, PFO closure of younger patients also significantly reduced the risk of recurrence ischemic neurological events compared with medical therapy, and there was no statistical difference in total complications from AF and bleeding events. Therefore, PFO closure of younger patients can benefit significantly in comparison with PFO closure of older patients and medical therapy of younger patients.

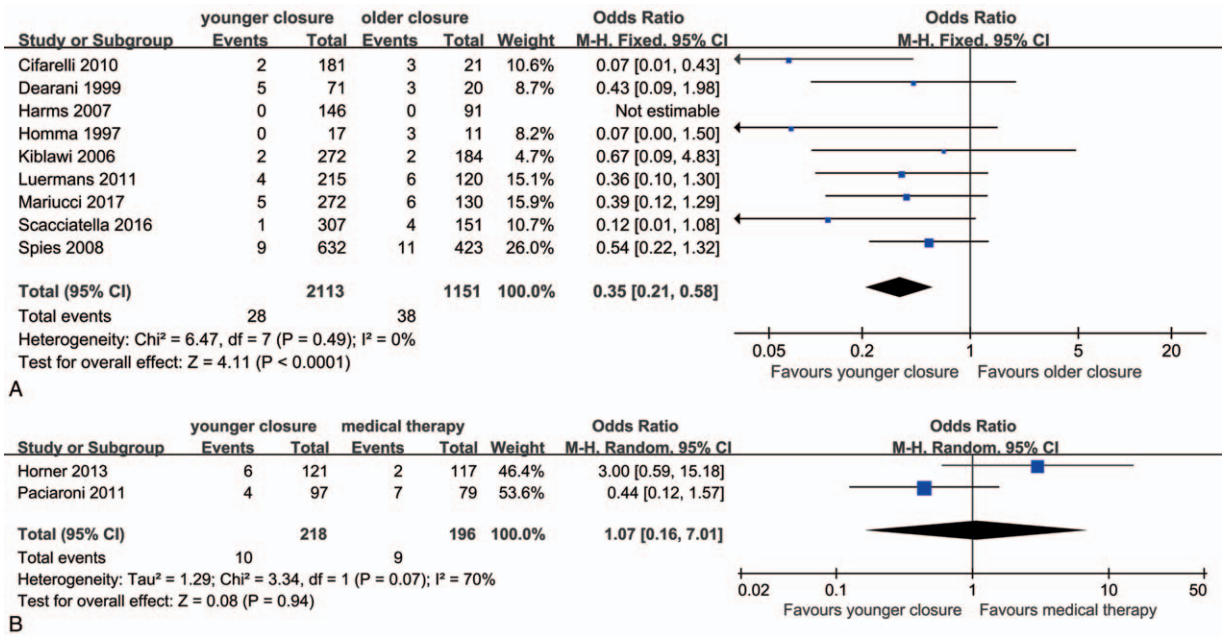

Figure 4. Forest plots comparing the risk of recurrent transient ischemic attack between younger PFO closure and older PFO closure (A) and between younger PFO closure and medical therapy (B). CI = confidence interval, PFO = patent foramen ovale.

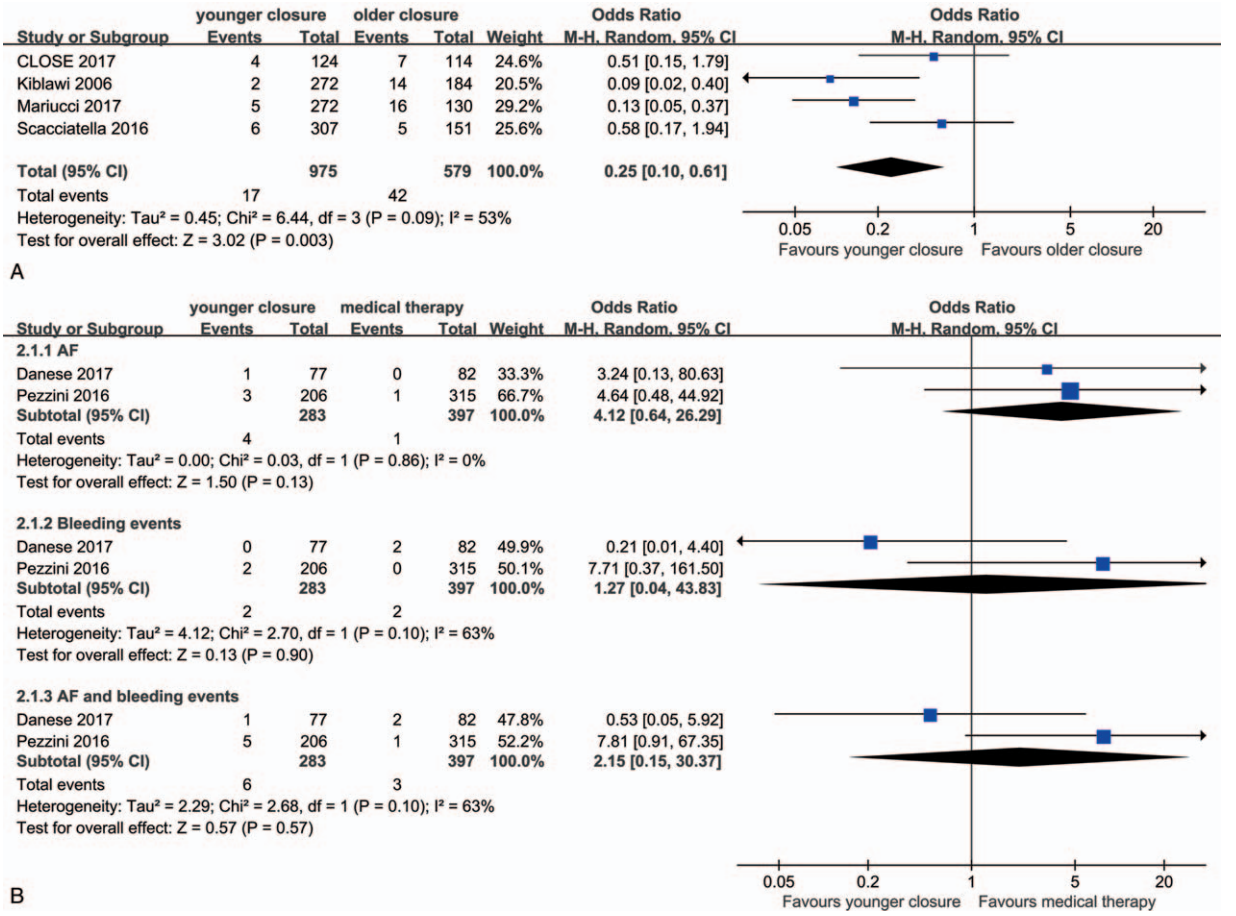

Figure 5. Forest plots comparing the risk of AF between younger PFO closure and older PFO closure (A) and the risk of AF and bleeding events between younger PFO closure and medical therapy (B). AF = atrial fibrillation, CI = confidence interval, PFO = patent foramen ovale.

Table 3

Subgroup analysis for composite outcome of recurrent ischemic neurological events.

	No. of studies	OR (95% CI)	*P* value	I^2 (%)	*P* value of heterogeneity
Younger PFO closure vs older PFO closure	12	0.40 (0.28–0.56)	<.001	37	.10
Type of study					
RCT	3	0.68 (0.29–1.57)	.37	0	.45
Observational study	9	0.35 (0.24–0.51)	<.001	41	.09
Age demarcation for younger/older					
Demarcation by 45 years of age	4	0.50 (0.23–1.09)	.08	41	.18
Demarcation by 55 years of age	8	0.37 (0.25–0.55)	<.001	41	.11
Duration of follow-up					
>3 years	6	0.34 (0.21–0.56)	<.001	30	.22
≤3 years	6	0.46 (0.28–0.75)	.002	48	.09
Younger PFO closure vs medical therapy	7	0.50 (0.33–0.75)	<.001	0	.63
Type of study					
RCT	3	0.34 (0.16–0.73)	.006	0	.40
Observational study	4	0.58 (0.36–0.94)	.03	0	.67
Age demarcation for younger/older					
Demarcation by 45 years of age	4	0.51 (0.31–0.84)	.008	6	.36
Demarcation by 55 years of age	3	0.46 (0.22–0.97)	.04	0	.60
Duration of follow-up					
>3 years	4	0.33 (0.15–0.69)	.003	0	.58
≤3 years	3	0.60 (0.37–0.58)	.04	0	.58

CI = confidence interval, OR = odds ratios, PFO = patent foramen ovale, RCT = randomized controlled trials.

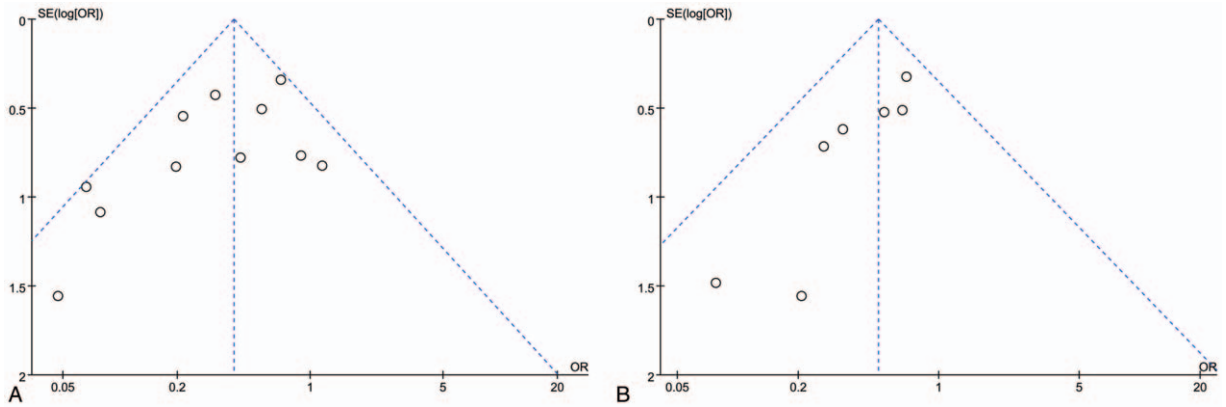

Figure 6. Funnel plots comparing the risk of recurrent ischemic neurological events (stroke and/or transient ischemic attack) between younger PFO closure and older PFO closure (A) and between younger PFO closure and medical therapy (B). PFO = patent foramen ovale.

The optimal strategy for secondary prevention of ischemic neurological events in patients with PFO and cryptogenic stroke remains controversial. So far, several large, multi-center RCT studies have yielded inconsistent results.[24–29] Meta-analysis of these RCTs showed that the recurrence rate of ischemic neurological events after PFO closure was lower than that of medical therapy. However, due to the low recurrence rate of endpoint events and increased risk of AF, the benefit of PFO closure remains uncertain.[30] Pasceri et al performed a meta-analysis of the net benefit of PFO closure, and the results showed that the clinical net benefit of PFO closure was similar to that of medical therapy.[1] To date, the best indications and patient selection for PFO closure have not been well defined in the guidelines.[31]

To the best of our knowledge, this meta-analysis was the first to provide a comprehensive assessment of the efficacy of PFO closure in younger patients (including RCTs and observational studies). In order to clarify that PFO closure may be the best treatment strategy for younger patients, we included a comparison of PFO closure vs medical therapy in younger patients in addition to the comparison of PFO closure between younger patients and older patients. Our results indicated that younger patients with PFO closure benefited from comparison with older patients and with medical therapy, which may be related to the high probability of abnormal embolism in younger patients. In addition, recent meta-analysis of RCT showed that AF was an important factor affecting the efficacy of PFO closure.[32] Of note, we found that ischemic neurological events and AF mainly occurred in older patients, while younger patients had a lower incidence of ischemic neurological events and AF, which had never been classified in previous RCTs and meta-analysis.

In the separate analysis of stroke and TIA, we found that PFO closure of younger patients reduced the risk of recurrent stroke compared with closure therapy of older patients and medical therapy of younger patients; However, there was no significant difference in the risk of TIA compared with medical therapy, which may be a matter of sample size. In addition, different cutoffs were used to define the older and younger in the published studies; The RCT studies and two observational studies defined younger at the maximum age of 45 years, while other observational studies defined younger at the maximum age of 55 years; Our subgroup analysis showed that there was no significant heterogeneity in the different demarcation of age for younger/older and we therefore believe that PFO closure is the best treatment for younger patients under the age of 55. In comparison with PFO closure of older patients, PFO closure of younger patients reduced the risk of recurrent ischemic neurological events in RCT subgroup and subgroup demarcated by 45 years of age, but did not reach statistically significance; Overall, the results of the 2 subgroups were similar, and the main reason may be related to the fact that the RCT studies did not include patients over 60 years of age.

Several meta-analyses based on RCT studies yielded similar results to our study in a subgroup analysis of patients under 45 years of age[30,33]; However, due to the problem of sample size in subgroup studies and the lack of analysis of complications in younger patients, it was not enough to obtain the true efficacy of PFO closure of younger patients. Our meta-analysis not only summarized the RCT studies, but also provided 13 observational studies to enhance the reliability of our results. In addition, only the comparison of PFO closure of younger patients and older patients cannot show that younger patients are the optimal groups for PFO closure; Efficacy of PFO closure and medical therapy in younger patients remains unclear; Therefore, we consider it necessary to add two comparisons together in our meta-analysis.

In published studies on stroke project of young adults, some studies of PFO closure had been extended to younger age groups. In the IPSYS study, patients enrolled in the study ranged from 18 to 45 years of age, and the results showed that the subgroup of patients aged 18 to 36 years benefited significantly from PFO closure.[22] Similarly, a meta-analysis from 3 RCTs showed that PFO closure was significantly superior to medical therapy in subgroups under 45 years old, while there was no significant difference in subgroups over 45 years old.[33] These results suggest that PFO closure may be more effective in younger age groups. However, our meta-analysis pooled data from studies under the age of 55, which allowed our study to incorporate more available data and made the results more reliable. In addition, as far as we know, there was no research report on the PFO closure effect of adolescents aged 16–18 years in the world literature. Whether the benefits of PFO closure increase from the decrease of age remains to be further studied.

Our meta-analysis had several limitations. In the studies we included, there was a lack of age-stratified data on secondary endpoint events in some studies, and we were unable to extract

more data on complications, which may affect the outcomes. In addition, previous studies have shown that AF and bleeding events are the main factors affecting the net benefit of PFO closure, and are also the focus of controversy. Therefore, our study on complications mainly focused on AF and bleeding events, and did not analyze surgical complications, residual shunt, and death from PFO closure. Finally, the limitations of non-randomized studies include selection bias, heterogeneity in the definition of events, and differences in "duration" and "intensity" of event follow-up.

5. Conclusions

In summary, younger patients under the age of 55 with ischemic stroke /TIA benefit significantly from PFO closure. Further studies on device selection and complications are needed in the future.

Author contributions

Conceptualization: Liang Xu, Jie Li.
Data curation: Liang Xu, Xuemei Pan.
Formal analysis: Liang Xu, Xuemei Pan, Chang Zhou.
Funding acquisition: Chang Zhou.
Investigation: Jie Li, Xuemei Pan, Fangyuan Wang.
Methodology: Liang Xu, Xuemei Pan, Chang Zhou.
Software: Jie Li, Fangyuan Wang.
Supervision: Liang Xu, Chang Zhou.
Writing – original draft: Liang Xu, Xuemei Pan.
Writing – review & editing: Chang Zhou, Jie Li.
Chang Zhou orcid: 0000-0003-3899-690X.

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