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ORIGINAL PAPER

Interventional closure vs. medical therapy of patent foramen ovale for secondary prevention of stroke: updated meta-analysis

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Abstract

Background We aimed to explore whether interventional closure of patent foramen ovale (PFO) results in reduction of composite outcome [stroke/transitory ischemic attack (TIA), death, and thrombolysis in myocardial infarction—TIMI bleeding], stroke and stroke/TIA compared to medical treatment in patients with cryptogenic stroke.

Methods and results Searching the PUBMED and Cochrane library database, we performed meta-analysis from all randomized controlled studies that compared effects of interventional PFO closure with medical treatment on stroke prevention. 3560 patients from six randomized trials were included. Interventional PFO closure reduced composite outcome (RR of 0.47, 0.26–0.85, $p=0.01$), stroke (RR of 0.38, 0.18–0.82, $p=0.01$) and stroke/TIA (RR of 0.56, 0.43–0.74, $p<0.0001$). Analysis had 70.5% power to detect observed reduction of RR for the primary outcome, 70.6% for stroke and 98.7% for stroke/TIA. Bleeding rates were comparable (RR of 0.91, 0.60–1.38, $p=0.66$), while there was higher burden of new AF (RR of 5.54, 3–10.2, $p<0.0001$) after interventional closure. Subgroup analysis revealed that patients with large shunts had substantial less recurrent strokes over patients with small shunts (p for interaction = 0.02). Use of Amplatzer PFO device was associated with substantial less AF (RR of 2.36, $p=0.06$) compared with other devices (RR of 8.93, $p<0.0001$) (p for interaction = 0.04), with comparable benefit for stroke prevention (p for interaction = 0.73).

Conclusions Interventional closure of PFO resulted in significant reduction of stroke and stroke/TIA compared with antiplatelets/anticoagulants with comparable bleeding rates between the groups, whereas AF occurred more frequently in the intervention group. Patients with large shunts had more benefit from interventional closure.

Keywords Patent foramen ovale · Interventional PFO closure · Cryptogenic stroke · Meta-analysis

Introduction

Cryptogenic stroke (CS) accounts for a 20–30% of all ischemic strokes. The majority of them are believed to be of thromboembolic origin [1]. The prevalence of a patent foramen ovale (PFO) in patients with CS (37% [2] − 43.9% [3]) compared to those with ischemic stroke (14.3% [3] − 15.9% [2]) of known other causes suggest PFO being causal in paradoxical embolism [2, 3]. It has been hypothesized that PFO closure in patients with CS and PFO should result in significant prevention of strokes. Data from randomized trials are controversial, showing no significant results in the studies published earlier [4–6] and positive results from those published recently [7–10]. To overcome limited power of the single trials and to estimate overall efficacy of transcatheter closure of PFO, we explored whether and to what extent interventional closure of PFO is associated with better outcomes in patients with CS compared to antiplatelet/anticoagulant therapy only. We performed a meta-analysis by pooling the data from all published randomized-controlled trials.

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Methods

Reporting and conducting of this meta-analysis is in accordance with the PRISMA guidelines for meta-analysis [11] and in accordance with the scientific statement from the American Heart Association [12].

Study protocol

All randomized controlled trials that compared effects on recurrent stroke and/or TIA between percutaneous, transcatheter device closure of PFO vs. antiplatelets/anticoagulants (further medical group) in adult patients (> 16 years) with PFO confirmed with transesophageal echocardiography and history of CS were included. Eligible trials need to have a minimum of 100 individuals and duration of follow-up longer than 12 months. We excluded reviews, observational studies, registries and case presentations evaluating effects of transcatheter device closure of PFO on recurrent stroke. Randomized trials evaluating effects on outcomes other than defined in our inclusion criteria (e.g., effects on migraines) were also not considered. In the case of studies reporting follow-up data of the same population, the most comprehensive or latest publications were included.

Data sources and search strategy

We searched PUBMED and Cochrane library database for eligible articles published until March 15 2018, using the key terms patent foramen ovale or PFO, cryptogenic stroke and percutaneous closure in combination, with additionally activated filter "clinical trial" in PUBMED and "trials" using search limits in Cochrane library database.

Selection of studies and data abstraction

Two investigators (D.V., S.H.S.) independently screened the search results for relevance accordingly to their titles and abstracts and reviewed the full-text articles considered for study inclusion. The same investigators extracted the following items from each included articles: type of study design, intervention, study population, follow-up (average follow-up, follow-up as patient-years when reported), dropouts (withdrawal, lost to follow-up, exclusion), rate of successful implantation and effective closure, events of interest (primary outcome for each study, ischemic stroke, ischemic stroke/ TIA, atrial fibrillation/flutter and bleeding), the presence or absence of atrial septal aneurysm (ASA) and moderate to large shunt, rates of stroke or primary outcome in patients under and over 45 years of age. Any disagreements regarding eligibility for inclusion or results of abstracted data were solved out by consensus or after consultation with a third investigator (M.B.).

Assessment of study quality

Quality of each included study was assessed independently by investigators (D.V., S.H.S.) using Jadad score [13], which is proved to be reliable [14]. A score more than ≥ 3 is considered as high range of quality score and ≤ 2 as low range of quality score. Furthermore, we assessed if all trial outcomes were reported based on intention-to-treat analysis and whether some trial have been stopped earlier for benefit.

Statistical analysis

The primary endpoints, for which we pooled data from each trial, were primary outcome (specifically defined in each study), ischemic stroke and ischemic stroke/TIA. Secondary endpoints included rate of bleeding and rate of new atrial fibrillation/flutter. Assessment of primary and secondary endpoints was based on intention-to-treat analysis. Differences in events rates for the primary and secondary endpoints among groups were determined and presented using Forest plot as risk ratios (RR) with the corresponding 95% confidence intervals (CI) for each trial. We used RR as a measure of the relative risk. The data from each trial were pooled using fixed (Mantel–Haenszel, Rothman–Boice)- or random-effects (DerSimonian-Laird) model, as appropriate. Statistical heterogeneity between the trials was assessed using Cochran's Q test and I^2 statistic. Relevant statistical heterogeneity was considered as Cochran's Q test $p < 0.05$ and $I^2 > 50\%$. In this case, we used random-effects model. To standardize different time of follow-up (between the trials and within each trial), we calculated incidence rate ratio (IRR) for endpoints we found appropriate using patient-years instead number of patients on intention-to-treat analysis (initially allocated to one treatment arm). Patient-years represent the sum of years of follow-up from each individual. When these data were not reported we determined this item by multiplying the number of patients from per protocol analysis with average follow-ups in years. The impact of specific anatomical characteristics (the presence of ASA or large shunt), different age (< 45 and > 45 years) on stroke/primary outcome was evaluated using subgroup analysis by determining the p for interaction between subgroups [15]. Additionally, we compared the effects of implanted Amplatzer PFO Occluder vs. other devices in respect to rate of recurrent stroke and AF.

We calculate the power of our meta-analysis for observed relative risk reduction (RRR) for each primary endpoint [16].

A potential presence of publication bias was assessed visually with Funnel plot and formally using the Egger's regression asymmetry test. We used Fisher's exact test analysis to determine whether there was a difference in the rate of event of interest between the interventional closure and the medical therapy arm in each study. All statistical analyses were conducted using StatsDirect version 3.0.150, RevMan 5.3 and R version 3.4.0. All p values were two-sided, with $p < 0.05$ considered as significant.

Results

Initially, our search identified 42 trials in PUBMED and 58 trials in Cochrane library database. After reviewing the titles and abstracts manually, 90 articles were excluded. From ten further full-texts reviewed articles, three did not meet the predefined inclusion criteria. Seven trials met the inclusion criteria but there were two trials reporting the data from same population with a different duration of follow-up (RESPECT trial). In this case, we included the last one published with updated data so that six trials [4, 5, 7–10] entered the final analysis. Study selection process is shown with flow diagram (Supplementary Figure 1). The final analysis comprised 3560 patients. 1889 patients were randomized to interventional transcatheter PFO closure compared to 1671 patients that received antiplatelet/anticoagulant therapy only. Baseline characteristics of the included studies are depicted in Table 1.

Primary endpoints

Primary outcome consisting of stroke/TIA and death [4, 5, 7], stroke alone [8, 9] and stroke/vascular death/thrombolysis in myocardial infarction (TIMI)-major bleeding [10] occurred in 54/1889 (2.8%) patients in interventional group compared to 100/1671 (5.9%) patients in conservative group ($p = 0.01$) (Fig. 1). RR for primary outcome in interventional group was 0.47 (95% CI 0.26–0.85, $p = 0.01$) vs. medical therapy (Fig. 1). The meta-analysis had a power of 70.5% to detect a 53% reduction of primary outcome. Estimated IRR by pooling the patient-years of follow-up (Suppl. Table 1) was 0.58 (95% CI 0.41–0.82, $p = 0.001$).

There was not a significant interaction between treatment (PFO closure compared to controls) effect size regarding primary outcome in patients with ASA (RR of 0.41, 0.13–1.72, $p = 0.14$) compared to those without ASA (RR of 0.7, 0.46–1.1, $p = 0.22$), with p for interaction = 0.39 (Suppl. Figure 3).

Ischemic stroke was reported in 37/1889 (1.9%) patients in the interventional group compared with 77/1671 (4.6%) patients in the medical group ($p = 0.01$) (Fig. 1). The RR for ischemic stroke in interventional group was 0.38 (95% CI 0.18–0.82, $p = 0.01$) vs. medical group (Fig. 1). The meta-analysis had a power of 70.6% to detect 62% RRR in ischemic stroke. Estimated IRR by pooling the patient-years of follow-up (Suppl. Table 1) was 0.52 (95% CI 0.34–0.79, $p = 0.002$). The RR for stroke was 0.27 (95% CI 0.11–0.67, $p = 0.005$) in interventional group vs. conservative group, when excluding the data from CLOSURE I [5] study.

There was a significant interaction between treatment (PFO closure compared to controls) effect size regarding stroke and/or stroke/TIA in patients with large/moderate shunts (RR of 0.39, 0.23–0.65, $p = 0.0004$) compared to those without large/moderate shunt (RR of 0.98, 0.56–1.71, $p = 0.93$), with p for interaction = 0.02 (Suppl. Figure 4).

There was no significant interaction in treatment effect size regarding stroke and/or primary outcome (PC Trial) between patients < 45 years of age (RR of 0.32, 0.16–0.64, $p = 0.001$) and those > 45 years of age (RR of 0.51, 0.31–0.85, $p = 0.01$), with p for interaction = 0.28 (Suppl. Figure 5).

Ischemic stroke/TIA was reported in 79/1889 (4.1%) patients in interventional group compared to 132/1671 (7.8%) patients in medical group ($p < 0.001$) (Fig. 1). The RR for ischemic stroke/TIA in interventional group was 0.56 (95% CI 0.43–0.74, $p < 0.001$) vs. medical group (Fig. 1). The meta-analysis had a power of 98.7% to detect a 54% RRR in ischemic stroke/TIA. Estimated IRR by pooling the patient-years of follow-up (Suppl. Table 1) was 0.55 (95% CI 0.41–0.73, $p < 0.0001$) in interventional vs. medical group.

Secondary endpoints

Newly diagnosed atrial fibrillation/flutter (AF) as adverse event was reported in 78/1844 (4.2%) patients in interventional group and in 12/1667 (0.7%) patients in control group based on intention-to-treat analysis, except in CLOSURE I, where the data for these adverse events were reported from safety analysis. The RR for this secondary endpoint in interventional group was 5.54 (95% CI 3–10.2, $p < 0.0001$) vs. medical group (Fig. 2). Estimated IRR for atrial fibrillation/flutter was 4.18 (95% CI 2.2–7.9, $p < 0.0001$) for patients in interventional vs. medical group.

Bleeding as adverse event was reported in 43/1820 (2.3%) patients in interventional group and in 42/1583 (2.6%) patients in medical group based on intention-to-treat analysis, except in CLOSURE I [5] where the data from safety analyses were used. The RR for this secondary endpoint in interventional group was 0.91 (95% CI 0.6–1.3, $p = 0.66$) vs. medical group (Fig. 2). RR was estimated using random-effects model without the presence of statistical heterogeneity ($p = 0.24$ and $I^2 = 25.2\%$), but there was a slight difference in definition of this reported adverse event among trials (Fig. 2), thus we found random effects more appropriate.

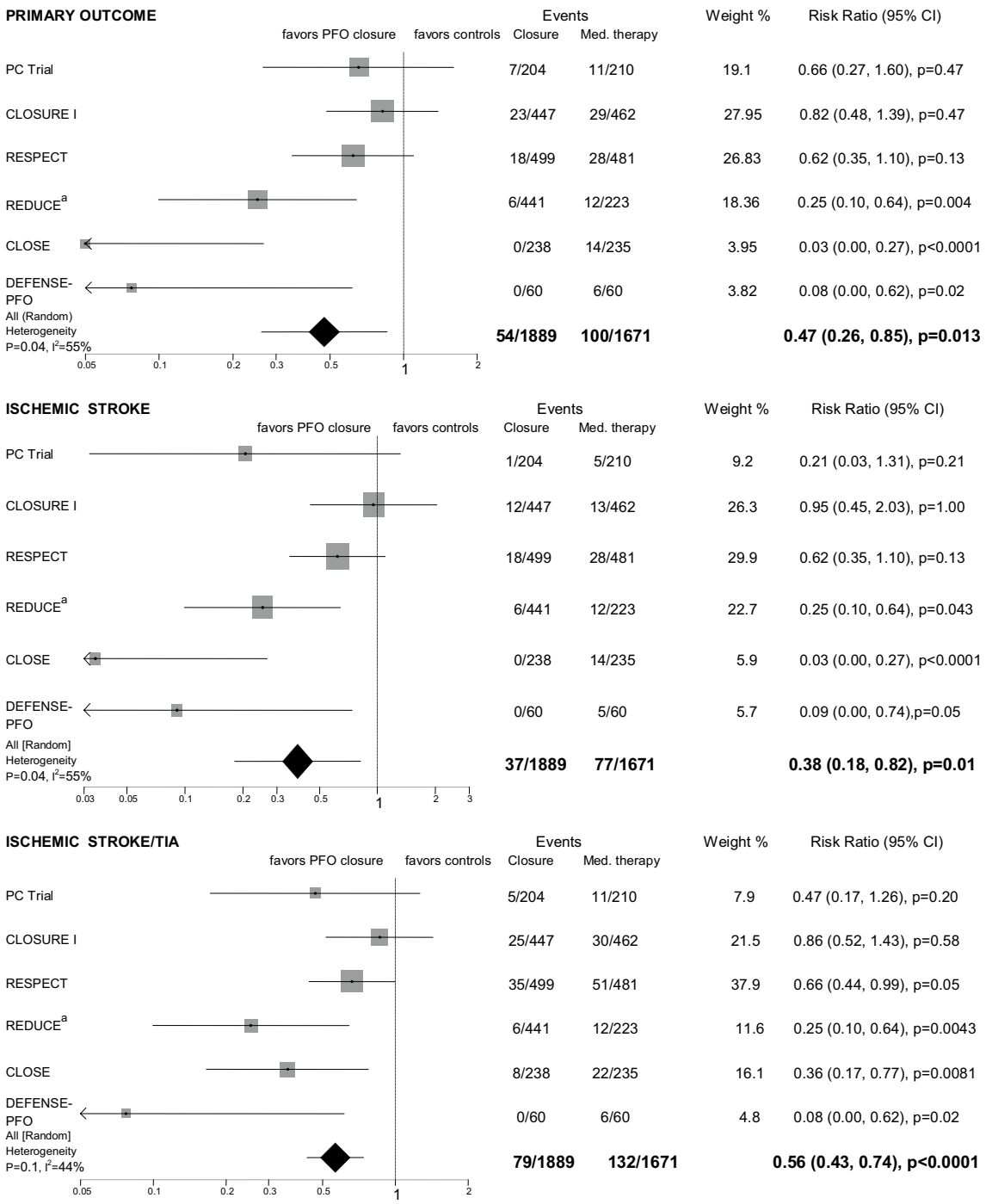

Fig. 1 Forest plot showing summary results for primary endpoints; **a** analyzed data for endpoint clinical ischemic stroke

Amplatzer PFO occluder vs. other devices regarding rate of stroke and AF

There was not a significant interaction between treatment effect size regarding prevention of stroke in trials where Amplatzer PFO Occluder was used (RR 0.43, 0.16–1.11, $p = 0.08$) compared with other devices (RR of 0.31, 0.07–1.38, $p = 0.12$) (p for interaction = 0.73, Suppl. Figure 6).

There was a significant interaction between treatment effect size regarding newly occurred AF between Amplatzer PFO Occluder (RR of 2.36, 0.95–5.86, $p = 0.06$) and other devices (RR of 8.93, 3.78–21.11, $p < 0.0001$) (p for interaction = 0.04, Suppl. Figure 7).

Table 1 Baseline characteristics of included trials

Study acronym	Comparator	Device/medical therapy (*n*)	Baseline characteristics	Primary outcome	Average follow-up (year)	Dropout device/medical therapy (%)	Drugs device/medical therapy
PC trial[4]	PFO closure vs. medical therapy	204/210 414	< 60 y, history of CS or peripheral embolism or TIA, Amplatzer Occluder, randomisation 1:1	Composite of death, nonfatal stroke, TIA or peripheral embolism	4.1 device/4 medical group	15/20	6 months aspirin or clopidogrel or ticlodipin/ at discretion of treating physician (aspirin in 70%)
CLOSURE I[5]	PFO closure vs. medical therapy	447/462 909	18–60 y, CS or TIA, STARFlex, randomisation 1:1	Composite of stroke or TIA within 2y and death	2	15/19	6 months aspirin + clopidogrel, then aspirin/aspirin or warfarin or both
RESPECT[7]	PFO closure vs. medical therapy	499/481 980	18–60 y, CS, Amplatzer Occluder, randomisation 1:1	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke or early death	5.9	21/33	Aspirin + clopidogrel for 1 month, aspirin until 6 months/aspirin, clopidogrel, warfarin, dipyridamole
REDUCE[9]	PFO closure + antiplatelets vs. medical therapy	441/223 664	18–59 y, CS or TIA, HELEX and GSO Occluder, randomisation 2:1	Co-primary endpoints of clinical ischemic stroke and new brain infarction	3.2	13/20	Clopidogrel 300 mg initially + 75 mg for 3 days + medical therapy/aspirin alone or aspirin + clopidogrel or aspirin + dipyridamole
CLOSE[8]	PFO closure + antiplatelets vs. medical therapy	238/235[a] 473	16–60 y, CS with ASA or large interatrial shunt, 11 different devices, randomisation 1:1:1	Fatal or nonfatal stroke	5.4 device/5.2 medical group	9/5	Aspirin + clopidogrel for 3 months + single antiplatelet therapy/ aspirin or clopidogrel or aspirin + clopidogrel or dipyridamole
DEFENSE-PFO[10]	PFO closure vs. medical therapy	60/60 120	Mean age 51.8 y, history of CS with high-risk PFO (ASA, septum hypermobility or large PFO), Amplatzer Occluder, randomisation 1:1	Composite of stroke, vascular death or TIMI major bleeding	2.8	11/6	Aspirin + clopidogrel for 6 months/antiplatelet (aspirin, clopidogrel or cilostazol) or warfarin therapy

CS cryptogenic stroke; *y* year; *ASA* atrial septum aneurysm

[a]Only cohort with antiplatelet therapy

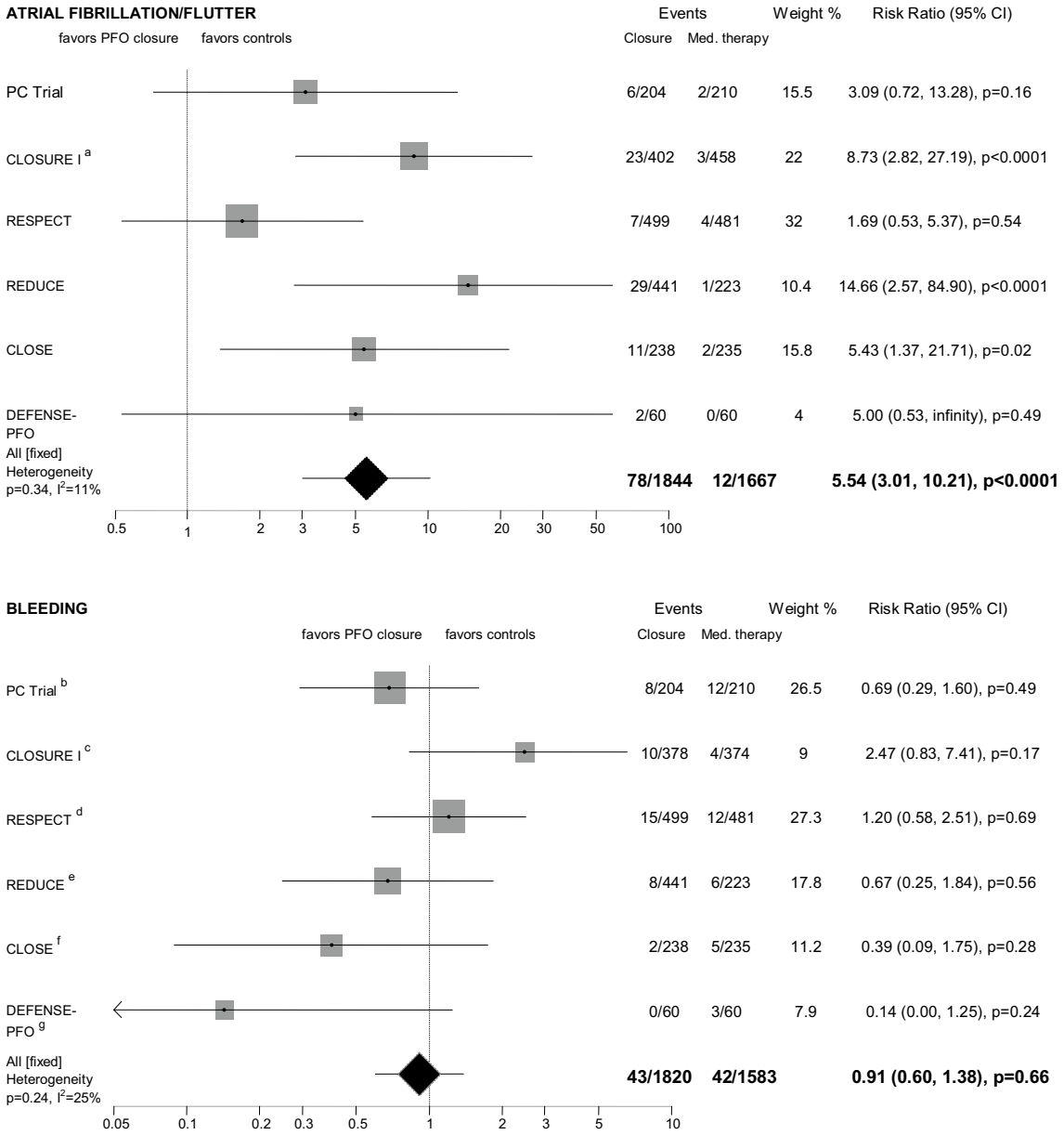

Fig. 2 Forest plot showing summary results for bleeding; **a** data from safety analysis; **b** defined as bleeding; **c** data from safety analysis, major bleeding; **d** bleeding and gastrointestinal bleeding; **e** serious bleeding; **f** major or fatal bleeding; **g** two TIMI-defined major bleeding, one hemorrhagic stroke

Study quality and publication bias

All studies were assessed as high quality trials (with 3 points on Jadad score) from both investigators despite the fact that all trials were open-label trials. One trial was terminated early for benefit [10] (Suppl. Table 4).

There were indications for publication bias from the data which reported about primary outcome and stroke/TIA by according to the funnel plots (Suppl. Figure 2) and accomplished by Egger test.

Number needed to treat/harm analysis

The number needed to treat (NNT) with PFO closure was 32 to prevent one primary outcome compared with medical therapy over a weighted mean follow-up of 3.8 years. Of note, NNT to prevent one primary outcome in patients with ASA was 21 and in those without ASA 61 over 4 years.

The NNT to prevent one stroke and stroke/TIA was 37 and 27 over 3.8 years, respectively. In patients with moderate/large shunts, the NNT for stroke was 24 compared to 221

in patients without moderate/large shunts over a 4.1 years. In patients < 45 years of age, the NNT for stroke was 29, while in those > 45 years was 31, over 4.6 years. The NNT to prevent on stroke using Amplatzer PFO occluder only was 39 over 4.2 years in comparison to 38 over 3.5 years using other devices.

The number needed to harm (NNH) for AF was 29 over 3.8 years for total population. NNH for AF in trials which used only Amplatzer PFO occluder was 86 over 4.2 years in comparison with other devices where NNH was 20 over 3.5 years.

Discussion

The most important finding of this meta-analysis is that interventional transcatheter closure of PFO results in significant reduction of recurrent ischemic stroke and recurrent ischemic stroke/TIA compared with medical therapy alone in patients younger than 60 years of age with previous CS or TIA and confirmed PFO. Our results are in accordance with findings from previous analyses [17, 18].

Single interventional trials evaluating the effects of PFO closure on outcomes have been impeded by the small number of events and subsequently limited power. The results of this meta-analysis suggest that more than 50% of recurrent ischemic strokes and about 40% of ischemic stroke/TIA can be prevented by closing of PFO when compared with medical treatment only. These data indirectly confirm that a PFO is a relevant source of paradoxical embolism as closing results in stroke prevention. Nevertheless, 1.9% (37/1889) of patients in the interventional closure group experienced recurrent ischemic stroke. In six patients, this was related to device implantation procedure (Suppl. Table 1). Of note, PFO closure was not performed in all of the patients initially planned and not all patients with implanted occluders had a successful closure, as indicated by follow-up echocardiography (Suppl. Table 2). This might at least in part explain the reported recurrent strokes in this group of patients.

Hence, despite strict inclusion criteria in analyzed trials, there still could be cases where PFO is an incidental finding and not necessary guilty for stroke. The absence of conventional cardiovascular risk factors (arterial hypertension, diabetes mellitus, smoker), younger age and cortical location of CS are items included in RoPE-Score, whose higher values are associated with higher likelihood that PFO is being the causal rather than incidental in recurrent CS [19]. The score is easy to obtain in clinical settings, which could be the initial step in defining a role of present PFO in etiology of CS. Of note, interventional PFO closure was not more beneficial regarding stroke in patients with higher vs. lower RoPE score (CLOSE), thus negating the prognostic role of this score in predicting which patients would have more benefit from closure. Furthermore, a long-term ECG monitoring could detect the latent AF, whose occurrence is most often asymptomatic and which could in some patients represent an underlying mechanism of CS [20, 21], even in the presence of concomitant PFO.

The combination of PFO and ASA has been associated with substantial higher rates of recurrent stroke in patients no older than 55 years of age [22, 23] after CS, than in those with PFO but without ASA, indicating ASA as a risk factor for recurrent stroke in this population. Data from CLOSE [8] and DEFENSE-PFO [10] study showed convincing results in favor of the interventional closure group vs. medical group, resulting in no patient suffered recurrent ischemic stroke. Interestingly, all patients included in these trials had large shunts and/or the presence of ASA or septum hypermobility. This highlights the fact that with careful selection of patients with high-risk PFO, as defined in DEFENSE-PFO, for a stroke due to paradoxical embolism, a considerable benefit can be achieved.

According to our results, there was no significant interaction in treatment effect for primary outcome in patients with ASA (RR = 0.41, $p = 0.13$) in comparison with those without ASA (RR = 0.7, $p = 0.10$) (p for interaction = 0.39). Results for primary outcome regarding the presence or absence of ASA could be extrapolated for the endpoint ischemic stroke/TIA as the number of deaths ($n = 2$, interventional group CLOSURE I trial) and TIMI major bleeding ($n = 1$, medical therapy group DEFENSE-PFO) accounted for primary outcome was small and where none of these two deaths was associated with intervention [5].

Patients with moderate/large shunts demonstrated clear benefit from interventional PFO closure in prevention of recurrent stroke (RR 0.39, $p = 0.0004$) in variance to those with small shunts (RR 0.98, $p = 0.93$), with significant heterogeneity in treatment effect size between these two groups (p for interaction = 0.02). This indicates that PFO with moderate/large shunt might represent more appropriate target for interventional closure. However, these results are based on the data from three trials and should be therefore interpreted with caution.

Younger subgroup of patients (< 45 years) showed no substantial benefit regarding stroke prevention of interventional PFO closure compared with the older one (> 45 years), as p for interaction was 0.28. This is in accordance with earlier observations that PFO is associated with stroke in both younger (< 55 years) and older (> 55 years) patients [3].

Atrial fibrillation/flutter was more often detected in interventional closure group compared with medical group, while rates of bleeding were comparable in both groups. In the CLOSE [8] study, all 11 patients with AF in the interventional group had paroxysmal AF, without recurrence of AF that was detected in almost all patients (10/11) within the first month after implantation. All patients were

anticoagulated, but half of them < 6 months. Early onset of single episode of AF and no sign of recurrence during follow-up may suggest that AF in these patients is most likely driven by inflammation due to implantation and endothelialization of the occluder device, indicating perhaps a short-term course without high burden for these patients. When adjusting for different duration of follow-up, burden of new AF in patients across interventional closure vs. medical group appears to be smaller but still relevant (IRR of 4.1, $p < 0.0001$ vs. RR of 5.5, $p < 0.0001$).

In patients where Amplatzer PFO occluder was used for implantation, risk of new AF was higher compared to controls showing trend toward to statistical significance (RR 2.36, $p = 0.06$), but substantial lower when compared with other devices (RR 8.93, $p < 0.000001$) (p for interaction = 0.04) (Suppl. Figure 7). The NNH for AF with Amplatzer was four times higher compared to other devices, reflecting once more substantial risk reduction of new AF using this device. There was no difference regarding prevention of stroke between trials with Amplatzer vs. other devices (p for interaction = 0.73). These data suggest that Amplatzer PFO Occluder might possess the optimal benefit/risk ratio for interventional PFO closure compared to other devices currently in the market. Nevertheless, these results should be interpreted with caution, due to very small number of analyzed reported events. Further, this needs to be proved in a direct comparison of two devices in a randomized, double-blind trial.

The majority of patients in the medical group received antiplatelet therapy, mostly aspirin followed by clopidogrel, and minority of patients received anticoagulation with vitamin K antagonist. Assignment of these drugs to the patients was neither standardized across the trials nor within the trials. This was left at discretion of the investigators and event rates across different therapy regimens were not captured. Therefore, it was impossible to estimate whether there was a relevant difference in events of interest across different medical therapy regimens compared to interventional closure group. It has been shown that in patients with cryptogenic stroke and PFO, use of warfarin was not associated with significant prevention of recurrent strokes compared to use of aspirin [24]. The phase III of randomized NAVIGATE ESUS [25] trial, where rivaroxaban was compared vs. aspirin for secondary stroke prevention in patients with an embolic stroke of undetermined source (ESUS), was stopped early, due more bleeding events on rivaroxaban according to results from interim analysis.

Current guidelines of European Society of Cardiology (ESC) from 2010 recommend that PFO closure should be considered in case of systemic embolism probably caused by paradoxical embolism (Class IIa, Level of Evidence C) [26]. American Heart Association/ American Stroke Association (AHA/ASA) guidelines from 2014 are even more restrictive, suggesting that in patients with cryptogenic stroke PFO closure might be considered only in setting of concomitant presence of deep vein thrombosis (DVT) and PFO (Class IIb, Level C), but not in those without DVT (Class III, Level C) [27]. Similar restrictive approach was stated in the guidelines of American Academy of Neurology, who recommended against routine use of interventional PFO closure outside research settings [28]. In clinical settings, Amplatzer PFO Occluder may be considered only in case of recurrent strokes despite adequate medical therapy and no other identified mechanism [28].

Current available level of evidence from randomized trials and summary results presented in this analysis provide a sufficient level of new evidence which support an update of both ESC and AHA/ASA guidelines in favor of interventional PFO closure in patients with CS as definition of a cryptogenic stroke/ESUS. However, this applies only for patients without known other causes such as large vessel disease, and atrial fibrillation. High RoPE score, no detection of AF after long-term monitoring and the presence of high-risk anatomical features of PFO (ASA and large shunt) are items who could be helpful in further evaluation which patient would indeed achieve benefit of PFO closure. Furthermore, one could raise a question whether PFO in patients after ischemic stroke should be also treated (closed) in the presence of concomitant known risk factors, such as large vessel disease. Answer to this question warrants a new trial under these settings.

Limitations and strengths

Inclusion and exclusion criteria were comparable among the trials. Nevertheless, CLOSE and DEFENSE-PFO trials included only patients with either large shunt or ASA, while CLOSURE I trial included also patients with lacunar strokes, which was in variance with other trials. Further, relative high rates of dropouts in some trials (PC Trial, CLOSURE I, RESPECT) and the presence of crossover in others (REDUCE, RESPECT) might affect the final results. As for all studies with invasive treatment, blinding could represent a huge and in some occasions almost impossible challenge. The presence of performance bias cannot be excluded. Still, in all trials there was a clinical event adjudication committee, whose members were unaware of assigned intervention, thereby minimizing detection bias. One trial was stopped early for benefit which could hypothetically overestimate treatment benefit. There were no signs of publication bias for all primary and secondary endpoints, analyzed in our study, but this should be taken with caution due a relative small number of analyzed trials. Due to the lack of individual patient-level data, some subgroup analysis could not be performed, such as impact of different medical therapies

(antiplatelet and anticoagulant), impact of the presence of ASA or moderate/large shunt from all patients on each event of interest among investigated groups. In our analysis, the included trials differed in their length of follow-up. Longer follow-up could result in higher event rates among groups revealing so real effect of some intervention in comparison with the other on outcome of interest. We take this in consideration by determining IRR that normalizes the rates of events of interest for person-year. This additional analysis showed similar results as the primary analysis did; for our all primary endpoints, suggesting that different durations of follow-up had no major impacts on primary endpoints in these trials.

Conclusions

Interventional transcatheter closure of PFO results in significant reduction of recurrent ischemic stroke and ischemic stroke/TIA compared to antiplatelets/anticoagulants in patients < 60 years, while bleeding rates were comparable and AF occurred more frequently in the intervention group. Patients with large shunts had more benefit from interventional closure. Use of Amplatzer PFO occluder had the best risk/benefit ratio in respect to stroke prevention and risk of new AF.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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