The Closure of Patent Foramen Ovale in Preventing Subsequent Neurological Events: A Bayesian Network Meta-Analysis to Identify the Best Device

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Keywords

Cryptogenic · Patent foramen ovale · Ischemic stroke or cerebrovascular accident · Transient ischemic attack · Paradoxical embolism

Abstract

Background: Randomized-controlled trials (RCTs) reported a finding on the safety and efficacy of percutaneous patent foramen ovale (PFO) closure to prevent stroke recurrence. It showed that the Amplatzer (AMP) device appears to be superior to medical therapy (MT) in preventing strokes and episodes of atrial fibrillation (AF), than other devices. We performed a network meta-analysis (NMA) to evaluate the closure of PFO in preventing subsequent neurological events while investigating the results obtained by specific devices. **Methods:** We searched 3 databases (MEDLINE, EMBASE, CENTRAL/CCTR) and identified 6 RCTs until March 2019. We performed an NMA and used pooled ORs. Analyses were done in NetMetaXL1.6-WinBUGS1.4. **Results:** Six RCTs with 3,560 patients (mean age 45.2–46.2 years) were included in the present NMA. Depending on the device, 4 groups of pa-

tients were compared with MT: 1,889 patients undergoing PFO closure were significantly less likely to experience a stroke than 1,671 patients treated with MT (ORs 0.41; 95% Cr.I. 0.27–0.60 with fixed-effects model and ORs 0.22; 95% Cr.I. 0.05–0.70 with random-effects model). The patients with AMP showed a similar risk than those treated with Halex/Cardioform (HLX/CF) or with a group of 11 multiple devices. This suggests the equality between the 2 most currently used devices. When assessing TIA and, for the safety analysis, major bleeding, both models confirm no significant difference between any devices and MT. PFO closure increased the risk of new-onset AF: MT induces AF significantly less than all the devices. In favor of the AMP, there is a reduced number of cases of AF versus MT; however, no device superiority has been established in comparing HLX/CF and other devices in a random effect model. **Conclusions:** Our NMA provides evidence in favor of PFO closure with all the devices currently in use. We can conclude that these devices are better than MT, but not that 1 device is better than the rest in reducing stroke recurrences and AF episodes in the follow-up.

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Introduction

The etiopathogenetic role of patent foramen ovale (PFO) in ischemic stroke and the value of its closure in the prevention of a new event are among the most debated topics of the last decade.

The high prevalence in the general population (about 25% of people are carriers) classifies PFO as an undefined cerebral stroke risk factor. The prevalence of PFO, almost double in younger patients with cryptogenic stroke, was long ago thought of a causal role [1, 2].

Until 2013, the results of the randomized-controlled trials (RCTs) comparing percutaneous PFO closure and medical therapy (MT) have changed the course of events in a negative sense [3–5], thereby generating skepticism around the significance of the presence of PFO in patients with cryptogenic stroke.

Now the landscape has evolved and since 2017 we have witnessed a sea of changes with the publication of long-term follow-up data from RESPECT trial [6] and the results of trials CLOSE, REDUCE and DEFENSE-PFO [7–9].

Throughout 2018 there was a second tidal wave of publications and >30 meta-analyses, of which some network meta-analyses (NMA), but with a frequentist approach [10], demonstrating that PFO closure in patients with cryptogenic stroke aged <60 years (upper age limit adopted in all RCTs) is an option “strongly” recommended by the scientific community.

In the 6 published RCTs, 11 different devices were used; 1 abandoned the market.

Many observations and studies have also stated that the effectiveness of PFO closure depends on the type of device used and that the Amplatzer (AMP) device appear to be better than others in preventing strokes and episodes of atrial fibrillation (AF) [11–14]. In the past, a NMA has been performed [15], demonstrating the superiority of a market-leading PFO occluder, but with “low quality evidence” [16].

We performed an NMA to compare the effectiveness of percutaneous PFO closure with MT among patients with cryptogenic stroke and to investigate device-specific differences and results, to allow a unified and consistent comparison between groups of different devices, while respecting randomization.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols Statement [17] (online suppl. Fig. S1; for all online suppl. material, see www.karger.com/doi/10.1159/000507317).

No patients were involved in this meta-analysis.

Strategy and Selection Criteria

We systematically searched MEDLINE (accessed through PUBMED database), EMBASE and Cochrane Central Register using the following keywords: “Cryptogenic”, “PFO or patent foramen ovale”, “Ischemic Stroke or cerebrovascular accident”, “Transient Ischemic Attack or TIA”, “paradoxical embolism”. The extraction of data was performed independently by 2 authors (L.V. and C.B.), and any discrepancies were resolved by a third author (M.P.). All selected papers required to be RCTs comparing experimental and different approved transcatheter PFO closure devices with MT. After examining 497 studies, we identified 6 RCTs through a literature search from 2012 until March 31, 2019, that assessed the efficacy of transcatheter PFO closure for secondary prevention of cryptogenic strokes or TIA, compared to MT. The 4 groups of devices investigated in randomized trials were AMP PFO Occluder (Abbott, Chicago, IL, USA), STARFlex Septal Occluder (STF, NMT Medical, Boston, MA, USA), Gore Helex Septal Occluder/Gore Cardioform Septal Occluder (HLX/CF, W.L. Gore and Associates, Flagstaff, AZ, USA) and a group in which a variety of 11 devices were used during the CLOSE trial [7] (including 238 patients allocated to PFO closure – mixed devices [MIX] – of whom 138 were with AMP).

Data Collection

We extracted information on study design, outcomes, characteristics of patients, length of follow-up, and components of methodological quality, including concealment of allocation, independent event adjudication, and analysis according to the intention-to-treat principle [18–20]. If multiple reports were available for one trial, we used information of all reports for data extraction, but extracted outcome data only once, based on the intention-to-treat principle and the longest follow-up available. The primary outcome measures of this analysis were recurrences of ischemic stroke. Secondary endpoints included TIA, serious adverse events (major bleeding, death) and new-onset AF. With the exception of the STF device that had a significantly lower procedural success rate, we evaluated the remaining devices similarly, in relation to demonstration of a high and comparable frequency of success.

Data were extracted in duplicate (L.V. and C.B.) and consensus reached in case of disagreement.

For a correct comparison of the data, we reported all AFs and not only those defined as “serious,” published in RESPECT. The data used for AMP derive from the new IFU relating to the January 2018 device, updated by St. Jude Medical in order to collect the extended follow-up of the RESPECT study (data equal to those used to obtain the 2016 FDA approval).

Risk of Bias

We assessed risk of bias in duplicate using a modified Cochrane Collaboration tool [21]. In particular, we assessed for the following characteristics: random sequence generation (randomization); concealment of treatment allocation (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessors (detection bias); incomplete outcome data addressed (attrition bias); selective outcome reporting (reporting bias); and other minor bias (e.g., source of funding). We assigned a low, a moderate, or a high risk of bias to the studies. Reviewers resolved conflicts through discussion.

Statistical Analysis

To compare effects of alternative PFO closure with devices versus medical therapies, for ischemic stroke (primary outcome), recurrent TIA, death, major bleeding and AF (secondary outcomes), we conducted a NMA of RCTs within a Bayesian hierarchical fixed and random effect framework with non-informative priors [22]. We performed an analysis of the Bayesian network using the Markov Chain Monte Carlo simulation without previous information distributions to derive the posterior distribution. We evaluated convergence using the Brooks-Gelman-Rubin method and reported the data as ORs and Bayesian 95% Cr.I.s as statistical indicator, presenting them from both the fixed and random-effects model.

We assessed inconsistency by comparing deviation residues and statistics of deviance information criteria. Analyses were done in NetMetaXL 1.6 [23] and WinBUGS 1.4.3. This program generates the summary tables, the network diagram, the forest plot, the league table, the ranking list (with surface under the cumulative classification curve indicator) and heterogeneity. Information about the effects was converted into a probability that 1 treatment is the best, the second best, and so on, or the ranking of each treatment. A single measurement called surface under the cumulative classification curve was generated, which is expressed as a percentage: it would be 100% when a treatment is certainly the best and 0% when a treatment is definitely the worst.

Numbers-needed-to-treat (NNT) and number-needed-to-harm (NNH) were derived by applying the cumulative incidence of events.

Results

Four hundred and ninety-seven records were found by searching databases and trial registers until end March 2019. Eight randomized, multicenter, controlled open-label trials (with blinded adjudication of outcome events) were identified. Two of them were excluded from qualitative and quantitative syntheses: “*Effect of Device Closure of PFO in Elderly Patients with Cryptogenic Stroke/TCP*” (CryptoCard study – Hansen CS, et al., Hillerød Hospital, Denmark, NCT01018355), because it was prematurely terminated due to the dissatisfactory enrollment rate with no publication provided, and “*Long-term results of a randomized trial comparing 3 different devices of percutaneous closure of a PFO*” [14], because it has different indications of patient enrollment for percutaneous PFO closure (not only ischemic recurrent events but also decompression sickness and migraine).

Accordingly, a total of 6 trials [3–9] and 3,560 patients (mean age 45.4–46.2 years) with cryptogenic stroke and PFO were included in the review and NMA, with 4 treatment groups with devices versus MT, to study the efficacy of PFO closure for secondary prevention. The mean follow-up period of all 6 RCTs was 2–5.9 years. Events

and patient characteristics of the included RCTs are reported in Table 1.

Neither the heterogeneity index nor the qualitative/visual analysis of the funnel plot produced in the exploratory phase or much less the analysis of inconsistency has raised the suspicion that the trials cannot be compared and analyzed jointly in order to produce a synthesis result.

The overall internal validity was considered a whole at “low risk of bias” (Table 2), except for one bias domain. In fact, the attrition bias was considered high in 2 RCTs: PC Trial [4] reported high withdrawal rates for both PFO closure and MT arms (15.2 and 20%, respectively), while RESPECT had a dropout rate of 20.8% in the PFO closure group and 33.3% in the MT group, too high and different between the 2 arms.

Three trials compared PFO closure with AMP vs. MT (group AMP), one PFO closure with STF vs. MT (group STF), and one PFO closure with HLX/CF vs. MT (group HLX/CF). The CLOSE Trial used 11 devices and 238 patients were assigned to the PFO closure versus the antiplatelet-only therapy. We have created a subgroup by extrapolating 138 patients treated with 3 types of AMP (Septal Occluder, Cribiform and Atrial Septal Device) during stroke analysis and moved them to the AMP group, which concerns a total of 901 patients included in 4 trials. The other 100 patients for CLOSE trial remained in a group with 8 different devices (group MIX devices) and were compared with MT. Figure 1 shows the network of evidence.

Patients allocated to PFO closure were significantly less likely to experience a stroke compared with patients allocated to MT. From NMA, the ORs for any device versus MT were 0.41 (95% Cr.I. 0.27–0.60) with fixed-effects model and 0.22 (95% Cr.I. 0.05–0.70) with random-effects model (online suppl. Fig. S2).

The patients allocated to AMP group had similar risk as patients with the HLX/CF group or with group of 8 MIX. The probability to be best in preventing strokes was 91.6% for MIX, 74.7% for HLX/CF, 57.0% for AMP, 15.3% for STF, 11.5% for MT with fixed-effects model and 76.4% for MIX, 72.4% for AMP, 59.0% for HLX/CF, 24.4% for STF and 17.8% for MT with random-effects model (Fig. 2).

When assessing TIA, both models confirm the indifference between any devices and MT (OR 0.75 fixed-effects, 95% Cr.I. 0.50–1.12; OR 0.74 random-effects, 95% Cr.I. 0.38–1.31; online suppl. Fig. S3).

Safety analysis found that the overall risks for major bleeding were similar in both PFO closure and MT: OR

Table 1. Events and patients characteristics in the RCTs*

Study	Defense-PFO ²⁰¹⁸ AMP vs. MT		Close ²⁰¹⁷ MIX vs. MT		Reduce ²⁰¹⁷ HLX/CF vs. MT		Respect ²⁰¹⁷ AMP vs. MT		PC trial ²⁰¹³ AMP vs. MT		Closure I ²⁰¹² STF vs. MT	
	PFO closure	MT	PFO closure	antiplatelet therapy only	PFO closure	MT	PFO closure	MT	PFO closure	MT	PFO closure	MT
Drugs used during therapy	A + C (6 mm)	A or A + C or A + Cz or W	A + C (3 mm), then A or C or (A + D)	A or C or A + D	A + C (3 dd), then same as MT	A or C or A + D	A + C (1 mm), then A (5 mm)	A or W or C or (A + D)	A (5–6 mm) + T or C (1–6 mm)	Antiplatelet or W	A (2 yy) + C (6 mm)	A or W or both
Number of patients	60	60	238	235	441	223	499	481	204	210 [#]	447	462
% data in NMA (weight)	3.3		13.3		18.7		27.5		11.6		25.5	
<i>Patients characteristics</i>												
Age in years, mean (SD)	49 (15)	54 (12)	42.9 (10.1)	43.8 (10.5)	45.4 (9.3)	44.8 (9.6)	45.7 (9.7)	46.2 (10.0)	44.3 (10.2)	44.6 (10.1)	46.3 (9.6)	45.7 (9.1)
Range, years	18–66		16–60		18–59		18–60		<60		18–60	
Males, %	55.0	56.7	57.6	60.4	59.2	61.9	53.7	55.7	45.1	54.3	52.1	51.5
Smoking, %	16.7	26.7	28.6	29.4	14.3	11.2	41.9	41.1	25.5	22.4	21.5	22.6
Coronary artery disease, %	NA	NA	NA	NA	NA	NA	3.8	1.9	2.0	1.9	2.9	2
Diabetes, %	10.0	13.3	1.3	3.8	4.1	4.5	6.6	8.5	2.5	2.9	NA	NA
Dyslipidemia, %	30.0	41.7	12.6	15.3	NA	NA	39.3	40.5	24.5	29.5	47.4	40.9
Hypertension, %	20.0	28.3	11.3	10.2	25.4	26.0	32.1	31.8	24.0	27.6	33.8	28.4
Previous stroke, %	NA	NA	4.2	3.0	9.5	5.8	10.6	10.6	37.3	37.6	72.6	71.4
Atrial septal aneurysm, %	8.3	13.3	24.8	26.4	20.4	NA	36.1	35.3	23.0	24.3	37.6	35.7
Moderate or large shunt, %	51.7	56.7	75.2	73.6	81.9	80.1	49.5	48.0	70.2	60.9	55.9	50.0
Follow-up time, years, mean	2.8		5.3		3.2		5.9		4.1		2	
<i>Events</i>												
Stroke	0	5	0	14	6	12	18	28	1	5	12	13
Stroke Relevance, %	0.00	8.33	0.00	5.96	1.36	5.38	3.61	5.82	0.49	2.38	2.68	2.81
TIA	0	1	8	8	1	1	17	23	5	7	13	17
TIA Relevance, %	0.00	1.67	3.36	3.40	0.23	0.45	3.41	4.78	2.45	3.33	2.91	3.68
AF (any events)	2	0	11 [§]	2	29	1	24	9	6	2	23	3
AF Relevance, %	3.33	0.00	4.62	0.85	6.58	0.45	4.81	1.87	2.94	0.95	5.15	0.65
Major bleeding	0	2	2	5	8	6	3	1	1	3	10	4
Major bleeding Relevance, %	0.00	3.33	0.84	2.13	1.81	2.69	0.60	0.21	0.49	1.43	2.24	0.87

Table 1 (continued)

Study	Defense-PFO ²⁰¹⁸ AMP vs. MT		Close ²⁰¹⁷ MIX vs. MT		Reduce ²⁰¹⁷ HLX/CF vs. MT		Respect ²⁰¹⁷ AMP vs. MT		PC trial ²⁰¹³ AMP vs. MT		Closure I ²⁰¹² STF vs. MT	
	PFO closure	MT	PFO closure	antiplatelet therapy only	PFO closure	MT	PFO closure	MT	PFO closure	MT	PFO closure	MT
Death (any causes)	0	0	0	0	2 ^A	0	7	11	2 ^B	0	2	4
Relevance, %	0.00	0.00	0.00	0.00	0.45	0.00	1.40	2.29	0.98	0.00	0.45	0.87

* No significant difference between arms reported in each study.
Eleven patients with peripheral embolism as index event.
§ AMP = 4 events/138 patients (2.90%); other device = 7 events/100 patients (7.00%).
^A One death is a suicide.
^B One death is not a cardiovascular event.
A, aspirin; C, clopidogrel; Cz, cilostazol; D, dipyridamol; T, ticlopidine; W, warfarin; dd, days; mm, months; yy, years; RCTs, randomized clinical trials; AMP, amplatzer occluder device; HLX/CF, helex/cardioform device; STF, starflex device; MIX, mixed devices; MT, medical therapy; NA, not available; AF, atrial fibrillation; PFO, patent foramen ovale.

0.94 with fixed-effects (95% Cr.I. 0.51–1.71); OR 0.81 with random-effects (95% Cr.I. 0.22–2.32; online suppl. Fig. S4).

Death from any cause was observed in 28 patients: 9 patients were allocated to AMP (0.1%), 2 patients were allocated to STF (0.5%), 2 patients were allocated to HLX/CF (0.45%) and 15 patients were allocated to MT (0.9%); no deaths were reported in the MIX devices group. OR of all-cause mortality in patients randomized to PFO closure versus MT was: OR 1.22 with fixed-effects (95% Cr.I. 0.59–2.55) and OR 0.95 with random-effects (95% Cr.I. 0.17–3.04). It is not possible to make a statistical comparison between devices with the Bayesian method, given the low number of recorded events.

However, in our NMA, PFO closure increased the risk of new-onset AF. The NMA demonstrated that MT induces a number of AF episodes significantly lesser than all the devices (OR 0.20 fixed-effects, 95% Cr.I. 0.11–0.32; OR 0.17 random-effects, 95% Cr.I. 0.05–0.39). In favor of the AMP there would be a greater containment of cases of AF vs. MT, compared to HLX/CF, but not proving the superiority of this device compared to another device when we use the random effect model (Fig. 3; online suppl. Fig. S5).

We have performed a statistical comparison between the 2 most used devices through a bidimensional analysis (Fig. 4).

In order to visualize the performances of the 2 main devices in use relating to the 2 significant events (stroke and AF), a 2-dimensional graph has been built, which highlights once again that (1) both devices are not substantially different from each other (they remain very closed to each other in the fourth quadrant); (2) that AMP has better joint median performances (considering both aspect of AF and of stroke), but not for this statistically different with respect to HLX/CF; (3) the better performance of AMP is mainly linked to the greater containment of AF events and the result is amplified when the method of analysis adopted is that of random effects.

The estimated NNT to prevent one stroke compared with MT was 37 (95% Cr.I. NNT 30 to 57) for PFO closure versus MT; the NNH to cause one case of new-onset AF was 25 (95% Cr.I. NNH 14 to 49) for PFO closure versus MT (Table 3).

Inconsistency plots assessing network inconsistencies between direct and indirect estimates showed a low possibility that the inconsistencies may significantly affect the NMA results (online suppl. Fig. S6, 7).

Table 2. Analysis of risk of bias: internal judgments of the authors for each study examined

Study	Risk of bias						
	random sequence generation	allocation concealment	performance bias	blinding of outcome assessor	incomplete outcome data	selective reporting	other bias
Defense-PFO ²⁰¹⁸	+	?	?	+	+	+	?
Close ²⁰¹⁷	+	+	?	+	+	+	+
Reduce ²⁰¹⁷	+	+	?	+	+	+	?
Respect ²⁰¹⁷	+	+	+	+	–	+	?
PC trial ²⁰¹³	+	+	+	+	–	+	?
Closure I ²⁰¹²	+	+	+	+	+	+	?

+ Low risk.
 ? Unclear risk.
 – High risk.
 PFO, patent foramen ovale.

Fig. 1. Network of comparisons included into the analyses. The size of every yellow circle is proportional to the number of randomized patients in the different trials. The width of the blue line corresponds to the number of trials and it indicates a direct com-

parison. The dashed red lines indicate the comparison relations indirect through the NMA. MT, medical therapy; HLX/CF, Helex/Cardioform; MIX, mixed devices; AMP, Amplatzer; STF, Starflex.

Discussion

This NMA involves 6 RCTs and a total of 3,560 patients. When PFO closure with devices was compared to MT, it demonstrated a statistically significant reduction (58%) in the relative risk of stroke recurrence (2.6% absolute risk reduction).

The findings clearly demonstrate that PFO closure prevents cardioembolic cerebrovascular events in young patients with cryptogenic stroke and PFO. These outcomes have been hypothesized to be linked with the choice of the device; however, such a relationship has never been fully analyzed.

Fig. 2. Bayesian comparison between treatments: stroke's events. League Table (ranking of treatments). In each cell, the OR is reported with its credible 95% interval, for fixed and random models. In relation to green cells, the treatment in the column is significantly better than the other in the line. The Sutra index denotes

the probability to be the best treatment. AMP and HLX/CF change the position in the ranking when we use a fixed or a random model. MT, medical therapy; HLX/CF, Helex/Cardioform; MIX, mixed devices; AMP, Amplatzer; STF, Starflex; SUCRA, surface under the cumulative classification curve.

In the CLOSURE I study, when PFO closure was compared between STF and MT, no significant differences were noted concerning the risk factor for stroke. This finding was further confirmed in our League Table analysis (an alternative numerical method to the Forest Plot method for displaying analysis results). When we omitted the device (withdrawn from use) well known for its thrombogenicity and elevated incidence of AF, we obtained significantly different results. A fixed model approach allowed us to demonstrate that the remaining devices utilized produced statistically significant results in reducing the recurrence of strokes when compared to the MT approach. A variable model effect allowed us to further identify AMP as the single device that, when compared to MT, was able to markedly reduce the risk of a stroke. The success of the AMP device is due to the large number of patients treated with this device, which compresses the Cr.I. In the fixed-effects model, stroke prevention post-PFO closure was the best with the HLX/CF approach (74.7%) with AMP running second (57%). A random approach appeared to reverse these findings, thus suggesting an almost equal efficacy between the 2 devices.

Additionally, it has been demonstrated that when employed, the MIX group (i.e., the group without the AMP device) yields results superior to those of the other devices and to the MT approach. This reinforces the hypothesis that any device on the market is better than MT in reducing the recurrence rate of a stroke. Conclusive statistical results are however not possible due to the limited number of MIX cases, but a basic trend may be hypothesized. Despite the good correlation between CLOSE trial outcomes, one must keep in mind that any reported variations may be due to testing protocol differences among the various centers.

A few observations and related discussions.

Previous NMA and operator observations have rated the various devices assigning levels of efficacy, which have not been however validated by any statistical analysis [16]. Our data confirms the literature findings in this regard and as well as demonstrates that currently, any commercially available device is a valid element in preventing the recurrence of a stroke. These findings are in accordance with a recent European position paper [24]. This allows the operator a relative freedom of choice in select-

Fig. 3. Bayesian comparison between treatments: AF (all events). League Table (ranking of treatments). In each cell, the OR is reported with its credible 95% interval, for fixed and random models. In relation to green cells, the treatment in the column is significantly better than the other in the line. The Sucra index denotes

the probability to be the best treatment. MT, medical therapy; HLX/CF, Helex/Cardioform; MIX, mixed devices; AMP, Amplatzer; STF, Starflex; SUCRA, surface under the cumulative classification curve; AF, atrial fibrillation.

ing the device most suited from a patient's anatomical point of view, without exposure to criticism regarding the efficacy of one device compared to another.

Similarly, the choice of a device may be tailored to the operator's experience as it related to the ease of use and personal outcomes. Factors such as the presence of supra-ventricular extrasystoles, septum hypermobility and thickness, aortic rim length, nickel allergy and other factors will allow the cardiologist to choose from a larger array of devices without penalizing the outcome.

It is noteworthy that, unlike stroke group comparison, our NMA study did not furnish a difference in the risk of a recurrent TIA based on the choice of the device. The difficulty in establishing such a correlation may be due to the non-specific nature of the associated symptoms of a TIA, to its lack of neuroimaging validation [25] and to a short lasting post-TIA antiplatelet therapy.

Hemorrhage and death have always been risks associated with any percutaneous procedure particularly when the patient is on antiaggregant or anticoagulant therapy [26]. Our study demonstrated that transcatheter PFO clo-

sure is a safe approach devoid of significantly increased risks (hemorrhage and/or death) when compared to MT for each RCT.

We further conclude that in our NMA analysis, MT has shown to produce a significant decreased incidence of AF compared to PFO closure (relative risk ratio 400%; absolute risk ratio 4%; NNH 25; 95% Cr.I. 20–35). These data are in agreement with a recent meta-analysis that demonstrated a fourfold increased risk of new onset AF in the PFO closure arm [27]. In the literature, the incidence of these events was lowest with the AMP device [24]. The higher rate of AF in the PFO group may be attributable to several sources such as device triggered arrhythmia and inflammatory mechanisms [28–30]. By evaluating all the AF events in the RESPECT trial, to include not only those defined as serious, we concluded that the AMP group produced fewer AF events; this difference was not however statistically significant when compared to the HLX/CF group. We hope that future clinical studies comparing the effectiveness of analyzed implants versus MT will continue to be aimed at reducing the uncer-

Fig. 4. Two-dimensional analysis of comparisons between treatments: AF and Stroke. The graph (a 2-dimensional forest plot) shows the estimated OR with the Bayesian method and the 95% credibility interval for the AMP and HLX/CF devices in comparison with MT. The more the device has a position oriented toward the lower left corner, the more it is effective in containing stroke and AF events compared to MT. The 45° lines indicate how this result is obtained from the 2 devices. As we can see, at the current state of knowledge, the best performances are attributed to the AMP device by virtue of its greater containment of AF events. The gap between the 2 devices increases when analyzing the results of the random effects model. The credibility intervals of the estimates, however, cannot confirm that this difference in performance is statistically significant. The credibility intervals, indeed, overlap. NMA, network meta-analysis; MT, medical therapy; PFO, patent foramen ovale; AMP, Amplatzer; HLX/CF, Helex/Cardioform; AF, atrial fibrillation.

Table 3. Measures of effectiveness and undesirability

Treatment/device		NNT – stroke median value and 95% Cr.I.	NHH – all events AF median value and 95% Cr.I.
Fixed effects approach	AMP	35 (28–61)	49 (21–156)
	STF	411 (38–∞)	13 (3–49)
	HLX/CF	29 (24–59)	6 (1–35)
	MIX	22 (22–42)	15 (5–69)
	TOT	37 (30–57)	25 (14–49)
Random effects approach	AMP	26 (22–67)	42 (9–463)
	STF	489 (23–∞)	13 (2–575)
	HLX/CF	29 (22–∞)	5 (1–97)
	MIX	22 (22–∞)	13 (2–258)
	TOT	28 (23–75)	22 (7–66)

In the table are shown the median value of NNT and NHH for fixed and random approach, as measures of clinical outcomes in the PFO closure versus medical therapy.

$NNT = (1 - [PEER * (1 - OR)]) / ([1 - PEER] * [PEER] * [1 - OR])$.

$NNH = ([PEER * (OR - 1)] + 1) / ([PEER * (OR - 1)] * [1 - PEER])$.

PEER, patient expected event rate; HLX/CF, Helex/Cardioform; MIX, mixed devices; AMP, Amplatzer; STF, Starflex; AF, atrial fibrillation; NHH, number needed to harm; NNT, number needed to treat; PFO, patent foramen ovale; TOT, total value from the combined devices.

tainty margins associated with the effectiveness of percutaneous PFO closure and the performance of the various individual devices. The research protocols should be strictly standardized as to allow for a valid comparison of the outcomes reported.

Our statistical analysis has demonstrated that the results obtained demonstrate a homogeneous correlation, which allows for the data to be compared. Furthermore, the RCT analyzed are comparable in terms of the applied therapies and the results obtained are consistent.

This does not exclude the possibility that there are hidden protocol differences that are responsible for divergent results. Nonetheless, these differences in the experimental protocol are within the Cr.I.. For this reason, even in the absence of significant heterogeneity, we opted to show the outcomes in terms of a random effect.

Finally, we should point out that there are limitations to this meta-analysis. Unfortunately, RCTs are limited (6). Some devices have been studied only in an RCT, whereas studies that use multiple devices simultaneously

are even less. For these reasons, we preferred (a) to offer the results of both fixed and random effects models; (b) to use a non-informative a priori distribution.

MT was not standardized in all RCTs, which was then responsible for heterogeneity of the results. For this reason, in the CLOSE trial, we only selected patients assigned to the antiplatelet group.

Recent meta-analysis has shown that PFO closure is more efficacious than antithrombotic therapy in preventing stroke recurrence following a cryptogenic stroke [11, 31, 32] but may be associated with a greater risk of bleeding in young patients over a 5-year period.

All RCTs were affected by a slow enrollment process, by varying and changing levels of operator experience, improvement in MT, and by the development of newer devices.

Summary/Conclusions

Our NMA provides evidence supporting PFO closure in young patients with a cryptogenic stroke, with all of the devices currently in use. Our findings support the conclusion that all of the devices analyzed are more efficacious than MT, but no single device predominates (AMP is equal to HLX/CF) in reducing the recurrence of a stroke or AF in the follow-up evaluations. Since the difference

was not statistically significant, HLX/CF and AMP devices can be considered equally effective.

The results on TIA and patient demise are inconclusive.

The increased AF risk suggests the necessity of monitoring cardiac rhythm and monitoring for the treated patients. Long-term follow-up is particularly important, given the enhanced clinical benefits of PFO closure found in the long-term follow-up in recent RCT [33].

Disclosure Statement

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Author Contribution

L.V. and G.B.: conceived, designed, and performed the analysis. C.B., A.D.B., and M.P. verified the analytical methods. L.V. and G.B.: wrote the paper and revised the manuscript for important intellectual content. F.P. revised the manuscript for important intellectual content. All authors discussed the results and contributed to the final manuscript.

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