European Heart Journal (2015) **36**, 120–128
doi:10.1093/eurheartj/ehu292

FASTTRACK CLINICAL RESEARCH
Vascular medicine

Percutaneous closure of patent foramen ovale in patients with cryptogenic embolism: a network meta-analysis

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Received 10 August 2013; revised 10 May 2014; accepted 26 June 2014; online publish-ahead-of-print 11 August 2014

See page 80 for the editorial comment on this article (doi:10.1093/eurheartj/ehu343)

Background Up to 40% of ischaemic strokes are cryptogenic. A strong association between cryptogenic stroke and the prevalence of patent foramen ovale (PFO) suggests paradoxical embolism via PFO as a potential cause. Randomized trials failed to demonstrate superiority of PFO closure over medical therapy.

Methods and results Randomized trials comparing percutaneous PFO closure against medical therapy or devices head-to-head published or presented by March 2013 were identified through a systematic search. We performed a network meta-analysis to determine the effectiveness and safety of PFO closure with different devices when compared with medical therapy. We included four randomized trials (2963 patients with 9309 patient-years). Investigated devices were Amplatzer (AMP), STARFlex (STF), and HELEX (HLX). Patients allocated to PFO closure with AMP were less likely to experience a stroke than patients allocated to medical therapy [rate ratio (RR) 0.39; 95% CI: 0.17–0.84]. No significant differences were found for STF (RR 1.01; 95% CI: 0.44–2.41), and HLX (RR, 0.71; 95% CI: 0.17–2.78) when compared with medical therapy. The probability to be best in preventing strokes was 77.1% for AMP, 20.9% for HLX, 1.7% for STF, and 0.4% for medical therapy. No significant differences were found for transient ischaemic attack and death. The risk of new-onset atrial fibrillation was more pronounced for STF (RR 7.67; 95% CI: 3.25–19.63), than AMP (RR 2.14; 95% CI: 1.00–4.62) and HLX (RR 1.33; 95%-CI 0.33–4.50), when compared with medical therapy.

Conclusions The effectiveness of PFO closure depends on the device used. PFO closure with AMP appears superior to medical therapy in preventing strokes in patients with cryptogenic embolism.

Keywords Patent foramen ovale • PFO • Transcatheter closure • Cryptogenic • Stroke • Embolism

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Introduction

Strokes are associated with high rates of morbidity and are the global second leading cause of death.[1] Up to 40% of ischaemic strokes are cryptogenic.[2] A strong association between cryptogenic stroke and the prevalence of patent foramen ovale (PFO) suggests paradoxical embolism via PFO as a potential cause.[3] Even though observational studies indicate a causal relationship between PFO and cryptogenic stroke,[4] recently published randomized trials failed to establish superiority of percutaneous PFO closure over medical therapy in patients with cryptogenic stroke or embolism.[5–7] Possible reasons include unrealistically large treatment effects assumed for sample size considerations and lower event rates than anticipated. In addition, there may be variation in effectiveness and safety between different devices, with potential differences in the effectiveness of the device to close the PFO, the risk of thrombus formation due to

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thrombogenicity of the surface material,[8,9] and the risk of new-onset atrial fibrillation associated with device implantation.[10]

Recently, long-term results of a randomized head-to-head comparison of three frequently used devices became available.[11–13] Network meta-analysis allows a unified,[14,15] coherent analysis of this head-to-head comparison in combination with the currently available randomized trials comparing percutaneous PFO closure against medical therapy, while fully respecting randomization and accounting for potential differences between investigated devices. We performed a network meta-analysis to compare the effectiveness of percutaneous PFO closure with medical therapy among patients with cryptogenic stroke or embolism and to investigate device-specific differences.

Methods

Search strategy and selection criteria

Eligible trials published or presented by March 2013 were identified through a systematic search of MEDLINE, EMBASE, CENTRAL, trial registers, conference proceedings, review and editorial articles and previously published meta-analyses (Supplementary material online). Eligibility of studies was determined in duplicate (S.S. and B.d.C.) and disagreement resolved by consensus. Eligible were randomized trials comparing different devices for percutaneous PFO closure head-to-head or against medical therapy in patients with cryptogenic stroke or embolism. The three devices investigated in randomized trials were Amplatzer PFO Occluder (AMP, St Jude Medical, Plymouth, MN, USA) STARFlex Septal Occluder (STF, NMT Medical, Boston, MA, USA), and HELEX PFO Occluder (HLX, W.L. Gore and Associates, Flagstaff, AZ, USA).

Data collection and quality assessment

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.[16,17] 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 pre-specified primary outcome was stroke. Secondary outcomes were transient ischaemic attack (TIA), all-cause mortality, and atrial fibrillation. Data were extracted in duplicate (S.S. and B.d.C.) and consensus reached in case of disagreement.

Statistical analysis

The network meta-analysis was based on a Bayesian random-effects Poisson regression model, which fully preserves randomized treatment comparisons within trials.[15,18,19] The model uses numbers of patients experiencing an event and accumulated patient-years to estimate rate ratios (RRs). Analyses were performed using Markov–Chain Monte–Carlo methods. The prior distribution for treatment effects was minimally informative: a normal distribution with a mean of 1 and a 95% reference range from 0.01 to 100 on a RR scale. The prior for τ^2 was based on empirical evidence derived from semi-objective outcomes of head-to-head comparisons:[20] a log normal distribution with a geometric mean of τ^2 of 0.04 and a 95% reference range from 0.001 to 1.58. Rate ratios were estimated from the median and corresponding 95% credibility intervals (95% CIs) from 2.5th and 97.5th percentiles of the posterior distribution.

We calculated the probability that each of the compared treatments was the most, second, third, and least effective in terms of preventing stroke by determining the proportion of iterations in which each treatment had the lowest stroke rate, the second lowest, and so on. Numbers-needed-to-treat (NNT) and numbers-needed-to-harm (NNH) were derived by applying the estimated RR to the cumulative incidence of events estimated for 5 years follow-up in patients randomly allocated to medical therapy:[5–7] 5.7% strokes, 5.0% TIAs, 1.6% deaths, and 2.0% new-onset atrial fibrillation.[21] Then, we compared estimated RRs from our network meta-analysis with estimates from Bayesian random-effects meta-analyses of direct randomized comparisons, or from single trials. The goodness-of-fit of the model was assessed using residual deviances,[18] heterogeneity estimated from the median between trial variance τ^2 observed in the posterior distribution, and consistency determined using inconsistency factors,[22] as calculated from the difference in log RRs between direct and indirect comparisons. Analyses were done in Stata 12.1 and WinBUGS 1.4.

Results

We identified 1350 references and found 10 reports on four randomized trials in 2963 patients (Supplementary material online, *Figure S1*). Two trials compared PFO closure with AMP vs. medical therapy,[6,7] one PFO closure with STF vs. medical therapy,[5] and one was a head-to-head comparison of PFO closure with AMP, STF, or HLX.[11,13] *Figure 1* shows the network of evidence. Amplatzer was evaluated in 923 patients with 3300 patient-years of follow-up,[6,7,13] STF in 667 patients with 1978 patient-years,[5,13] HLX in 220 patients with 1084 patient-years,[13] and medical therapy without percutaneous PFO closure in 1153 patients with 2948 patient-years.[5–7]

Methodological characteristics of included trials are summarized in Supplementary material online, *Table S1*. All trials had adequate concealment of allocation and followed the intention-to-treat principle,[5–7,13] independent event adjudication was done in three trials.[5–7] Eligibility criteria are presented in Supplementary material online, *Table S2* and characteristics of included patients in *Table 1*. The mean age ranged from 44.5 to 49.4 years, gender was equally

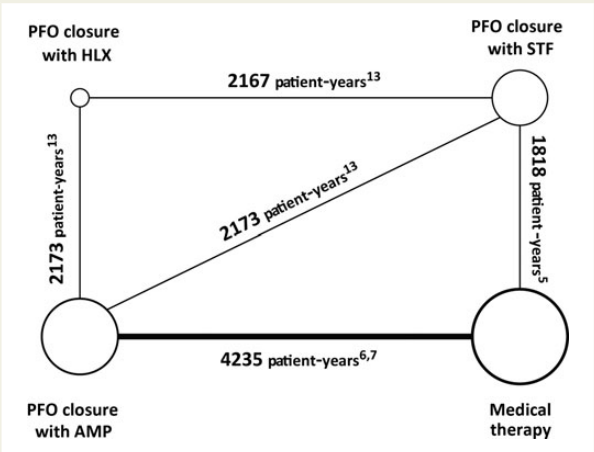

Figure 1 Network of comparisons included into the analyses. The size of every circle is proportional to the number of randomized patients and reflects the sample size, and the width of the lines corresponds to the number of trials. AMP, Amplatzer; STF, STARFlex; HLX, HELEX.

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Table 1 Duration of follow-up and patient characteristics in included trials

Trial	Intervention	Mean Follow-up duration (years)	Patient characteristics							Echocardiographic characteristics		Type of index event		
			Mean age (years)	Gender (% female)	Diabetes (%)	Hypertension (%)	Dyslipidaemia (%)	Migraine (%)	Smoking (%)	Atrial septal aneurysm (%)	Large interatrial shunt (%)	Stroke (%)	TIA (%)	Embolism (%)
Closure I[5]	PFO—closure vs. medical therapy	2.0	46.0	48.2	NR	31.0	44.1	NR	22.1	36.6	20.8	72.0	28.0	—
PC Trial[6]	PFO—closure vs. medical therapy	4.1	44.5	50.2	2.7	25.8	27.1	20.5	23.9	23.7	21.7	79.2	18.1	2.7
Respect[7]	PFO—closure vs. medical therapy	2.6	45.9	45.3	7.4	31.4	39.5	38.8	13.3	35.6	48.8	100.0	—	—
Hornung *et al.*[11–13]	PFO—closure	4.9	49.4	44.9	4.8	34.5	NA	7.6	7.6	36.4	NA	57.7	50.9	4.2

NR, not reported; NA, not available.

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distributed. Echocardiography showed an atrial septal aneurysm in 23.7 to 36.6%, while a large PFO shunt was observed in 20.8–48.8% of patients. The index event that led to enrolment was cryptogenic in all included patients. Two trials required evidence of ischaemia in neuroimaging for acute focal neurological deficits of <24 h duration (Supplementary material online, *Table S2*).[6,7] Patients with cryptogenic stroke were included in 57.7–100%. *Tables 2* presents estimated control group event rates for patients receiving medical therapy. Event rates were similar across all trials and overlapping 95% CIs suggested random variation.

Patients allocated to PFO closure were intended to receive dual antiplatelet therapy for the duration of 5–6 months in three trials,[5,6,13] and dual antiplatelet therapy for 1 month followed by acetylsalicylic acid for 5 months in one trial.[7] Subsequent treatment was left at the discretion of treating physicians in three trials,[6,7,13] whereas acetylsalicylic acid was administered for the duration of 18 months in one trial[5] (Supplementary material online, *Table S2*). Regimens in patients allocated to medical therapy included single or dual antiplatelet therapy or oral anticoagulation at the discretion of the treating physician for the entire duration of follow-up.[5–7] Supplementary material online, *Table S3* presents data on the actual use of antithrombotic treatment up to 12 months. Systematically collected data were available for the PC trial (up to 5 years)[6] and for the trial by Hornung *et al.*[13] (up to 6 months). In the PC trial, use of oral anticoagulation was significantly less common in the closure group at all-time points, including discharge and 6 months, whereas the use of antiplatelets was significantly less frequent in the closure group than in the medical-therapy group from 12 months onwards, up to 5 years.[6] In the trial by Hornung *et al.*,[13] antithrombotic treatment was identical in the three arms at discharge and near identical at 6 months.

Procedural success ranged from 95.9 to 100% for AMP (median 99.1%), 89.4 to 100% for STF (median 94.7%) and was 100% for HLX. Effective PFO closure, defined as no or minimal residual interatrial shunt at 6 months, was found in 93.5–95.9% of patients with AMP (median 95.9%), 86.1–94.5% with STF (median 90.3%), and 85.9% with HLX. An atrial thrombus was observed in 2 out of 923 patients with AMP (0.2%), 15 out of 586 patients with STF (2.6%), and 1 out of 220 patients with HLX (0.5%).

RRs of clinical outcomes of the three devices compared with medical therapy are presented in *Figure 2*. Supplementary material online, *Table S4* presents outcome definitions and Supplementary material online, *Table S5* the numbers of outcome events for all trials. All trials contributed to all analyses: 68 patients had experienced a stroke: 12 out of 923 patients allocated to AMP (1.3%), 18 out of 667 patients allocated to STF (2.7%), 4 out of 220 patients allocated to HLX (1.8%), and 34 out of 1153 patients allocated to medical therapy (2.9%). Patients allocated to AMP were significantly less likely to experience a stroke compared with patients allocated to medical therapy (RR: 0.39; 95% CI: 0.17–0.84). Patients allocated to STF had a similar risk as patients with medical therapy (RR: 1.01; 95% CI: 0.44–2.41), whereas results for HLX were inconclusive due to wide credibility intervals (RR: 0.71; 95% CI: 0.17–2.78).

Sixty-six patients suffered a TIA: 12 patients allocated to AMP (1.3%), 19 patients allocated to STF (2.8%), 4 patients allocated to

Table 2 Control group event rates per 100 patient-years (95% CI)

	Stroke	Transient ischaemic attack	All-cause mortality	Atrial fibrillation
Closure I	1.4 (0.8–2.4)	1.8 (1.1–3.0)	0.4 (0.2–1.2)	0.3 (0.1–1.0)
PC Trial	0.6 (0.3–1.4)	0.8 (0.4–1.8)	0.0 (0.0–0.4)	0.2 (0.1–1.0)
Respect	1.4 (0.8–2.2)	0.6 (0.3–1.2)	0.5 (0.2–1.1)	0.6 (0.3–1.2)
Hornung *et al.*[a]	0.5 (0.2–1.7)	0.5 (0.1–1.8)	0.5 (0.1–2.8)	0.3 (0.1–0.9)

CI, credibility interval
Control group event rates were estimated from observed numbers of events and accumulated follow-up time in patients allocated to medical therapy for Closure I, PC, and Respect trials.
[a]For the trial by Hornung *et al.*, control group event rates were extrapolated from rates in patients allocated to PFO closure with STF and the rate ratios comparing STF with medical therapy estimated from the network meta-analysis. Confidence intervals for event rates of zero were estimated as described by Hanley and Lippman-Hand.[35]

Table 3 Estimated numbers-needed-to treat and numbers-needed-to-harm for primary and secondary outcomes

	PFO closure with AMP vs. medical therapy	PFO closure with STF vs. medical therapy	PFO closure with HLX vs. medical therapy
Stroke	NNT 29 (NNT 21 to NNT 109)	NNH 1518 (NNT 31 to NNH 12)	NNT 60 (NNT 21 to NNH 10)
Transient ischaemic attack	NNT 45 (NNT 25 to NNH 70)	NNH 132 (NNT 39 to NNH 7)	NNH 92 (NNT 26 to NNH 4)
All-cause mortality	NNT 265 (NNT 86 to NNH 44)	NNT 198 (NNT 78 to NNH 41)	NNT 672 (NNT 78 to NNH 18)
Atrial fibrillation	NNH 43 (NNH 14 to NNH ∞)	NNH 7 (NNH 3 to NNH 22)	NNH 150 (NNT 73 to NNH 14)

AMP, Amplatzer; STF, STARFlex; HLX, HELEX.
Presented are data for NNT or NNH (95% credibility interval). NNT, number needed-to-treat-to-avoid one event over 5 years; NNH, number needed-to-harm-to-cause one event over 5 years.

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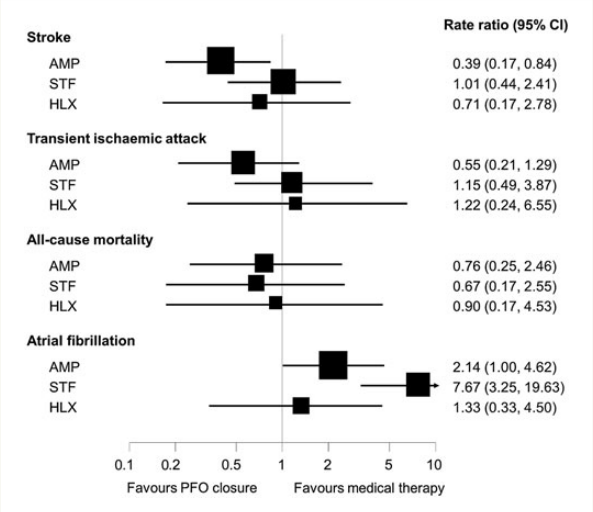

Figure 2 Primary and secondary clinical outcomes with medical therapy as a reference compound. AMP, Amplatzer; STF, STARFlex; HLX, HELEX; CI, credibility interval.

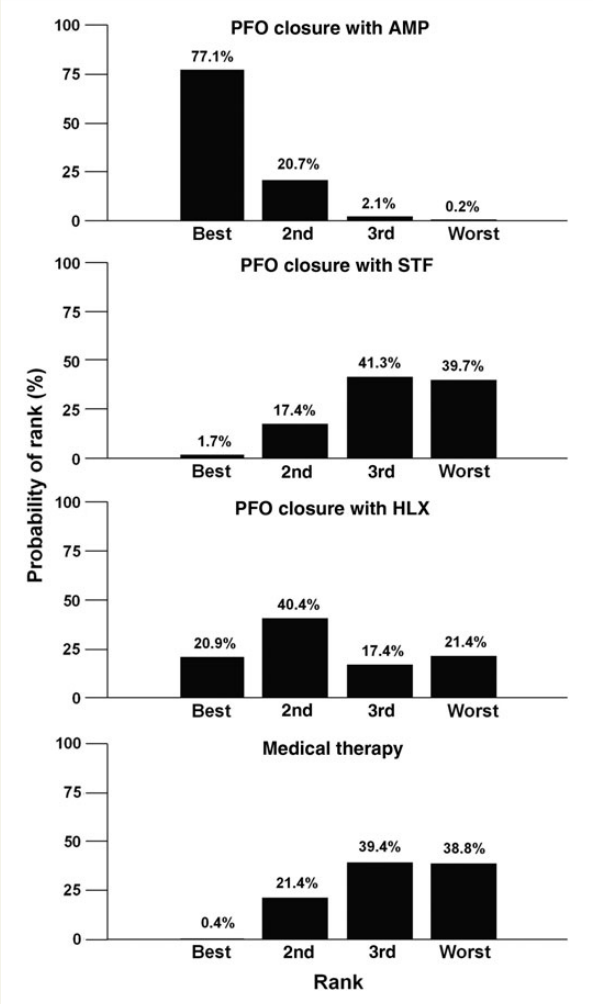

Figure 3 Ranking of the different devices for patent foramen ovale closure and medical therapy according to the primary outcome. The probability of an intervention being best, second, third and worst are given as percentage and displayed in bar graphs. AMP, Amplatzer; STF, STARFlex; HLX, HELEX.

HLX (1.8%), and 31 patients allocated to medical therapy (2.7%). Results were inconclusive for all devices, with RRs of 0.55 for AMP (95% CI: 0.21–1.29), 1.15 for STF (95% CI: 0.49–3.87), and 1.22 for HLX (95% CI: 0.24–6.55) when compared with medical therapy.

Death from any cause was observed in 30 patients: 9 patients allocated to AMP (1.0%), 6 patients allocated to STF (1.0%), 5 patients allocated to HLX (2.3%), and 10 patients allocated to medical therapy (0.9%), with RRs of 0.76 for AMP (95% CI: 0.25–2.46), 0.67 for STF (95% CI: 0.17–2.55), and 0.90 for HLX (95% CI: 0.17–4.53) when compared with medical therapy.

Ninety-six patients had new-onset atrial fibrillation: 29 patients allocated to AMP (3.1%), 50 patients allocated to STF (7.5%), 5 patients allocated to HLX (2.3%), and 12 patients allocated to medical therapy (1.0%). Compared with medical therapy, we found significant differences for PFO closure with STF (RR: 7.67; 95% CI: 3.25–19.63) and AMP (RR: 2.14; 95% CI: 1.00–4.62), while the RR for HLX was near one, albeit with wide credibility intervals (RR: 1.33, 95% CI: 0.33–4.50).

Figure 3 presents the probabilities of each of the four treatments to rank at each of four positions (best to worst) in terms of effectiveness in preventing strokes. The probability to be best was highest for PFO closure with AMP (77.1%) and lowest for medical therapy (0.4%). The cumulative probability to be among the two best treatments was 97.8% for AMP, 61.3% for HLX, 21.8% for medical therapy and 19.1% for STF. The probability to be worst was lowest for AMP (0.2%) and highest for medical therapy (38.8%). The cumulative probability to be among the two worst treatments was 2.3% for PFO closure with AMP, 38.8% for HLX, 78.2% for medical therapy, and 81.0% for PFO closure with STF.

Table 3 presents the estimated NNTs to prevent and NNHs to cause one event over 5 years compared with medical therapy. The NNT to prevent one stroke was 29 for PFO closure with AMP (95% CI NNT 21 to NNT 109). The NNH to cause one case of new-onset atrial fibrillation was 7 for PFO closure with STF (95% CI: NNH 3 to NNH 22) and 43 for PFO closure with AMP (95% CI: NNH 14 to NNH ∞). All other estimates were non-significant and credibility intervals compatible with both, benefit, or harm.

Figure 4 displays the results of network meta-analyses for all possible comparisons alongside results of direct randomized comparisons in standard random-effects meta-analyses or single trials. Rate ratios of stroke were near identical for all comparisons, but 95% CIs of the network meta-analysis were more precise for comparisons that involved AMP. The standard random-effects meta-analysis comparing PFO closure with AMP against medical therapy yielded a RR of 0.41 with a 95% CI from 0.15 to 1.00, while the network meta-analysis showed a RR of 0.39 with a 95% CI from 0.17 to 0.84. Conversely, for comparisons that did not involve AMP, the 95% CIs of the network meta-analysis were wider than the confidence intervals found in analyses of the single trials investigating the other devices.[5] For secondary outcomes, near complete overlap of 95% CIs of estimates

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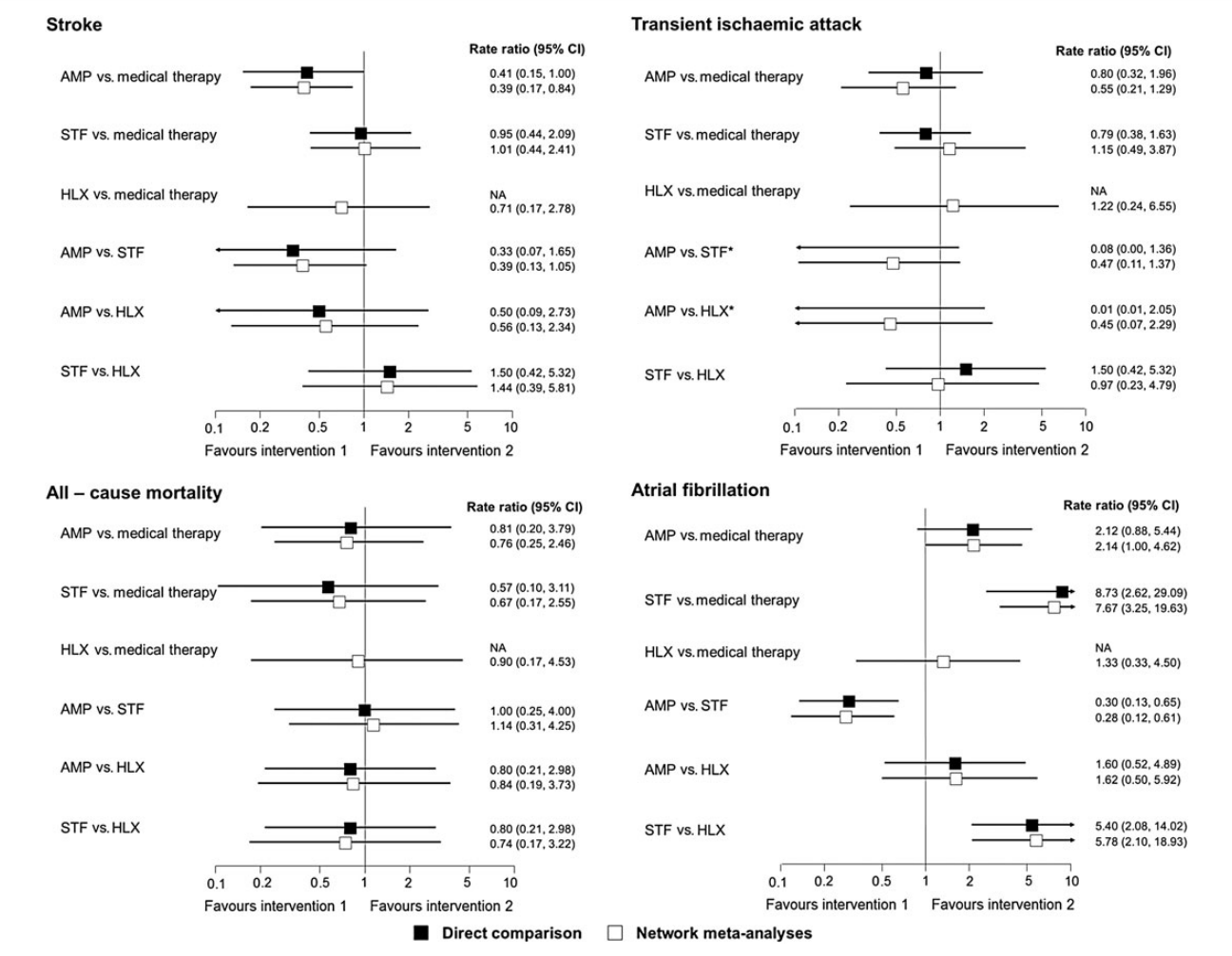

Figure 4 Comparison of results from Bayesian random-effects meta-analyses or single trials (black squares) and network meta-analysis (white squares). *Risk ratios calculated after continuity correction of 0.5 in all cells in case of analyses of single trials with zero events in one trial arm. AMP, Amplatzer; STF, STARFlex; HLX, HELEX; CI, credibility interval.

indicated again full compatibility of network meta-analyses and direct comparisons.

Model fit was adequate (Supplementary material online, *Table S6*) and heterogeneity low for all outcomes (Supplementary material online, *Table S7*). Inconsistency was low for stroke and atrial fibrillation, and low to moderate for TIA and death (Supplementary material online, *Table S8*).

Discussion

In this network meta-analysis of four randomized trials in 2963 patients with 9309 patient-years of follow-up PFO closure with AMP was associated with a 61% relative risk reduction in recurrent stroke when compared with medical therapy, as compatible with results from the recently published RESPECT and PC trials.[6,7] Conversely, closure with STF, compared against medical therapy in the CLOSURE I trial,[5] was not associated with a reduction in stroke risk, neither in our network meta-analysis, nor in CLOSURE I.[5] The network of evidence was consistent and the difference in effectiveness between PFO closure with AMP and STF was reflected in our network meta-analysis and the randomized long-term comparison of the two devices by Hornung *et al.*[13] Accordingly, the probability to be best in preventing strokes was 77.1% for PFO closure with AMP, but only 1.7% for STF. Two mechanisms might explain these findings: First, we found a near eight-fold increase in atrial fibrillation associated with STF when compared with medical therapy, while the estimated risk increase associated with AMP was only two-fold. Second, there is evidence for a higher thrombogenicity of STF than AMP: in their long-term comparison, Hornung *et al.*[13] found no atrial thrombus among 220 patients allocated to PFO closure with AMP, but 11 among 220 patients allocated to STF (risk difference 5.0%, 95% CI: 2.1–7.9%). Differences in the effectiveness of the two devices to close a PFO could additionally explain our results. However, there was no difference between AMP and STF in the head-to-head comparison by Hornung *et al.*,[13] with an effective closure of 95.9% with AMP and 94.5% with STF (risk difference −1.4%, 95% CI: −5.3 to 2.6%). Taken together, these results suggest that the effective PFO closure with STF might have been

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offset by increased risks of stroke through atrial fibrillation and atrial thrombi.

The average event rate of stroke in patients allocated to medical therapy in included trials was only 1.1% per year. However, average event rates in clinical practice might be higher,[23] and the NNT of 29 to prevent one stroke over 5 years through PFO closure with AMP when compared with medical therapy could decrease in clinical routine. The collaborative RoPE study, which aims at developing a risk prediction model for stroke recurrence in patients with cryptogenic embolism, is likely to contribute to our understanding of the clinical and echocardiographic characteristics that are associated with a relevant increase in the risk of stroke and the highest capacity to benefit from PFO closure.[24]

The decision to adopt PFO closure in clinical practice will also depend on financial considerations for reimbursement.[25] The overall costs of one procedure with AMP were reported to range between €6300 and €10 000 in the UK.[26] With an NNT of 29, the costs to prevent one stroke through PFO closure with AMP would therefore range from €182 000 to €290 000, respectively. The occurrence of a stroke is associated with an average loss of 9.2 quality-adjusted life-years in individuals aged 45 years,[27] as was the approximate mean age of patients in included trials (*Table 1*). Under the assumption that 50% of this loss occurs in the investigated population of patients with a history of a cerebrovascular accident, the incremental cost-effectiveness ratio would range between €40 000 and €63 000 per quality-adjusted life-year gained. The cost-effectiveness ratio will be more favourable, if event rates of strokes in clinical routine settings[23] are higher than observed in our network, the loss of quality-adjusted life-years after a second stroke is as pronounced as observed after a first stroke,[27] expenses associated with indefinite antiplatelet or antithrombotic therapy in conservatively treated patients are taken into account, and costs of acute care and rehabilitation after a recurrent stroke are considered. Detailed cost-effectiveness analyses are needed to determine under which conditions cost-effectiveness ratios for PFO closure are below willingness-to-pay thresholds, which range between €26 000 and €52 000 depending on the country.[28]

Results of our network meta-analysis are robust for the primary effectiveness outcome stroke and the safety outcome new-onset atrial fibrillation. Conversely, results were inconclusive for mortality; even though estimated RRs comparing the three devices with medical therapy were below one, credibility intervals were wide because of the low mortality rate: 30 deaths had occurred during 9300 patient-years of follow-up. Given this low event rate, a sample size of ~23 000 patients would be needed to rule out a 30% increase in the relative risk of death associated with PFO closure during 5 years of follow-up.

We are aware of three ongoing trials, which randomize patients to PFO closure or medical therapy. The DEFENSE-PFO trial (NCT01550588) compares PFO closure with AMP against medical therapy in 210 patients during a follow-up of 2 years. This trial has a power of 5% to detect the 61% relative risk reduction in stroke observed in our network meta-analysis for PFO closure with AMP and would need to show a five-fold increase in the risk of stroke for PFO closure with the AMP when compared with medical therapy to render results of our network meta-analysis inconclusive. The Gore REDUCE trial (NCT00738894) compares PFO closure with HLX against medical therapy in 664 patients with an estimated mean follow-up of 6 years. It would have 65% power to detect the 61% relative risk reduction in stroke observed in our network meta-analysis for PFO closure with AMP. This trial is important since it will generate an additional closed loop in the network and could contribute to the confidence in this network meta-analysis, if its results were consistent with remaining trials. Gore REDUCE investigators might, however, consider increasing the sample size to 900 patients to ensure adequate power in detecting the 61% relative risk reduction observed in our analysis after a mean of 6 years follow-up. Finally, the CLOSE trial (NCT00562289) allocates 900 patients either to PFO closure with different devices, antiplatelet, or antithrombotic therapy. The results of our network meta-analysis indicate that the mix of devices will make the interpretation of the results difficult, unless the set-up of the trial allows stratification by type of device.

The limitation of standard meta-analysis is that they are only able to combine data from multiple trials that all compare the same two interventions to derive a single-weighted average. The main assumption of fixed-effect models is that all trials comparing the two interventions estimate the same, common relative treatment effect (such as a RR) and any variation between trials is due to chance alone. The main assumption of random-effects models is that relative treatment effects in different trials do not estimate the same relative treatment effect, but different effects that originate from the same distribution.[29] The smaller the heterogeneity between trials, the more likely relative treatment effects estimate the same effect or originate from the same distribution and the more likely the meta-analysis is valid. If characteristics of patients, co-interventions, or trials act as effect modifiers and influence relative treatment effects, and if these characteristics are unequally distributed across trials, then statistical heterogeneity will be present between trials. The larger the heterogeneity, the less confidence readers should have into standard meta-analysis, irrespective of the model used.[30]

In the case of patients with cryptogenic embolism there are more than two interventions available, but standard meta-analysis does not allow inferences beyond a pairwise comparison of two interventions, neither about the comparative effectiveness of the different interventions [30] nor about the consistency of the different comparisons made in the network of trials.[31] Network meta-analysis has been developed to deal with such situations. It combines experimental evidence from direct randomized comparisons with observational evidence from adjusted indirect comparisons derived from trials, which compare different interventions with a common comparator.[32] It makes similar assumptions to standard meta-analysis, but requires that these assumptions hold over the entire set of trials in the network. The most important assumption is transitivity:[32] there are either no effect modifiers that influence relative treatment effects on a RR scale or the distribution of these effect modifiers is similar in different parts of the network.[32] Three trials [5–7] performed analyses stratified by several patient characteristics, but did not find consistent evidence for the existence of an effect modifier. If there were a currently unknown effect modifier and differences in the presence of this effect modifier had occurred, this should either have introduced statistical heterogeneity between trials, or inconsistency between different parts of the network. Since this was not the case in our analysis, we believe that the assumption of transitivity was

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satisfied. Finally, we found estimated control group event rates for patients receiving medical therapy similar across all trials for all outcomes, which adds to our notion that trials were sufficiently similar to warrant statistical combination in a network meta-analysis.

From a clinical perspective, an informal inspection of results of the three randomized trials comparing PFO closure with AMP or STF against medical therapy suggests that PFO closure with AMP [6,7] is more beneficial in preventing strokes than PFO closure with STF.[5] One of the principal advantages of our analysis is the ability to formally perform an indirect comparison of the two devices using data from the three trials with medical therapy as common comparator [5–7] and to determine whether results from this indirect comparison are consistent with results from the randomised head-to-head comparison of devices by Hornung *et al.*[13] The consistency of direct and indirect comparisons derived from the four different trials in the network, independently performed by four different groups of trialists in different clinical settings, is the most important argument for the validity of our results. However, the role of our results for treatment decisions and future guidelines remains unclear. It will depend on the readers' prior notions about the methodology of network meta-analysis in general and the credibility of our arguments in particular. Reluctance to accept our results may also stem from the fact that none of the three trials comparing PFO closure with medical therapy reached superiority on their primary endpoint. As pointed out by Antman *et al.*[33] in a classic comparison of the results of meta-analyses with expert recommendations in 1992, some experts 'may not appreciate that a small trial whose result is not statistically significant is not necessarily a "negative" trial, suggesting that the treatment does not work. Instead, the RCT may merely lack the power to show a beneficial or detrimental effect'. In any case, a patient should only be considered for PFO closure if he satisfies the selection criteria used in the trials (Supplementary material online, *Table S2*). An extension of the indication for PFO closure should be avoided unless appropriately designed trials support it.

A limitation of our analysis is that systematically collected data on the use of antiplatelets and anticoagulants in experimental and control groups were only available for the PC trial [6] and for the trial by Hornung *et al.*[13] (only including the first 6 months after the intervention) (Supplementary material online, *Table S3*). In the PC trial, the use of oral anticoagulation was significantly less common in the closure group at all-time points, including discharge and 6 months, while the use of antiplatelets was significantly less frequent in the closure group than in the medical-therapy group from 12 months onwards, up to 5 years.[6] Potential performance bias due to differences in antithrombotic co-intervention [16] would therefore have favoured medical treatment and could not explain observed results. In the head-to-head trial by Hornung *et al.*,[13] antithrombotic treatment was identical in the three arms at discharge and near identical at 6 months. The observed advantage of PFO closure with AMP over STF in this trial is therefore unlikely to have occurred due to differences in antithrombotic treatment. For remaining trials, data on medication use during the follow-up were unavailable and we cannot completely rule out that differences in antithrombotic treatment contributed to observed results. However, if differences in antithrombotic treatment had occurred in RESPECT or CLOSURE I,[5,7] and these differences had biased results to a relevant extent, this should either have introduced statistical heterogeneity or inconsistency, with results from either of these trials[5,7] differing systematically from the network of remaining trials.[6,13] This was not the case.

In conclusion, our network meta-analysis provides evidence in favour of percutaneous closure of PFO with one of the examined devices in patients with a history of cryptogenic stroke or embolism and a PFO. The increase in the risk of new-onset atrial fibrillation suggests the necessity of closely monitoring the cardiac rhythm of treated patients, and appropriate management in case of documented atrial fibrillation.[34] The selection of patients for PFO closure should closely reflect eligibility criteria of included trials.[5–7,13] To further improve clinical outcomes after PFO closure, future devices should be designed to minimize thrombogenicity and the risk of atrial fibrillation while ensuring high rates of effective closure.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

P.J. was responsible for conception and design of the study. B.d.C., S.S., S.T., and P.J. performed and interpreted the analysis in collaboration with S.W. and B.M. S.S., B.d.C., and P.J. wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version. S.W. and P.J. gave administrative, technical, and logistical support. S.S. and B.d.C. contributed equally to this manuscript.

Acknowledgements

We thank Stefan C. Bertog for help in accessing data from one of the trials.

Conflict of interest: H.P.M., J.C., S.W., B.M., and P.J. were primary or co-investigators of PC or RESPECT trials comparing Amplatzer PFO Occluder with medical therapy, which were funded by St Jude Medical; M.H. and H.S. were the primary investigators of the head-to-head trial comparing Amplatzer PFO Occluder by St Jude Medical, STARFlex Septal Occluder by NMT Medical and HELEX PFO Occluder by W.L. Gore and Associates without funding by the manufacturers. P.J. is an unpaid steering committee or statistical executive committee member of trials funded by Abbott Vascular, Biosensors, Medtronic and Johnson & Johnson. CTU Bern, which is part of the University of Bern, has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by Abbott Vascular, Ablynx, Amgen, AstraZeneca, Biosensors, Biotronic, Boehrhinger Ingelheim, Eisai, Eli Lilly, Exelixis, Geron, Gilead Sciences, Nestlé, Novartis, Novo Nordisc, Padma, Roche, Schering-Plough, St Jude Medical, and Swiss Cardio Technologies. S.W. has received research contracts to the institution from Abbott, Boston Scientific, Biosensors, Cordis, Edwards Lifesciences, Medtronic and St Jude and speaker honoraria from Abbott, Astra Zeneca, Boston Scientific, Biosensors, Cordis, Edwards Lifesciences, Eli Lilly, Medtronic and St Jude. B.M. has received research grants to the institution from Abbott, Cordis, Medtronic and St Jude and speaker honoraria and consultant fees from St Jude. H.P.M. has received research grants to the

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institution from AstraZeneca, Bayer, Biogen, Boehringer Ingelheim, Bristol-Meyers Squibb, GlaxoSmithKline, March Sharp & Dohme-Chibret, Novartis, Pfizer, Sanofi, Serono, Servier, St Jude, Teva, Swiss Society of Hypertension, Swiss Heart Foudation, Swiss National Science Foundation and consultant fees from Bayer, Biogen, Boehringer Ingelheim, Bristol-Meyers Squibb, Genzyme, Merck Sharp & Dohme-Chibret, Novartis, Sanofi, Serono, Servier, St Jude, Teva. H.S. has received consultant fee/honoraria/speaker's bureau from Abbott, Access Closure, Angiomed, Arstasis, Atritech, Atrium, Avinger, Bard, Boston Scientific, Bridgepoint, Cardiac Dimensions, CardioKinetix, CardioMEMS, Coherex, Contego, CSI, EndoCross, EndoTex, Epitek, Evalve, ev3, FlowCardia, Gore, Guidant, Guided Delivery Systems, Inc., InSeal Medical, Lumen Biomedical, HLT, Kensey Nash, Kyoto Medical, Lifetech, Lutonix, Medinol, Medtronic, NDC, NMT, OAS, Occlutech, Osprey, Ovalis, Pathway, PendraCare, Percardia, pfm Medical, Rox Medic and St Jude Medical. J.C. is a steering committee member of RESPECT and his institution has received research support and consulting fees from St Jude Medical Corp. All other authors have no relationships to disclose.

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