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Original Article

Amplatzer occluder versus CardioSEAL/STARFlex occluder: a meta-analysis of the efficacy and safety of transcatheter occlusion for patent foramen ovale and atrial septal defect

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Abstract *Objective:* Percutaneous transcatheter occlusion has benefited thousands of patients suffering from patent foramen ovale and atrial septal defect. However, no general agreement has been reached on the superiority among occluders. Thus, a meta-analysis between the two most commonly adopted types of occluders was conducted. *Methods:* The literature review has identified relevant studies up to May, 2011 in the databases of PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and World Health Organization clinical trials registry centre. Meta-analysis was performed in a fixed/random effects model using Revman 5.1.1. Information on complications and outcomes was extracted. *Results:* Analysis from included studies reports an outcome in favour of the Amplatzer. The Amplatzer has proven its superiority in efficacy with a significantly lower risk of early (95% confidence interval = 0.09–0.34) and long-term (95% confidence interval = 0.14–0.97) residual shunt rate for atrial septal defect occlusion, although no significant difference in performance has been reported for patent foramen ovale. In addition, the Amplatzer has also remarkably reduced the risk of embolisation by the device (95% confidence interval = 0.07–0.45) for atrial septal defect and new-set atrial fibrillation (95% confidence interval = 0.18–0.48) for patent foramen ovale. On evaluation of recurrent thrombotic events, it was found that the Amplatzer greatly lowered the rate of thrombus formation on the device (95% confidence interval = 0.02–0.21) for patent foramen ovale; however, no statistical difference was found on atrial septal defect evaluation. However, the result indicated no statistically significant difference between the two kinds of occluders in stroke and transient ischaemic attack of patent foramen ovale. *Conclusion:* The meta-analysis has proven the Amplatzer to be the superior occluder, serving better prognosis with more fluent procedure and less complications.

Keywords: Patent foramen ovale; atrial septal defect; transcatheter intervention; occluder; meta-analysis

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Patent foramen ovale and atrial septal defect are forms of congenital cardiac malformation providing abnormal pathways for harmful haemodynamics between two atria. Atrial septal defect is one of the most common types of congenital heart disease,[1] and patent foramen ovale can be identified in up to 40% of the population by echocardiography. Some of them survive all their life without any treatment. However, some has experienced times of strokes or transient ischaemic attacks that are related to damaged heart atrial function.[2–4] Therefore, occlusion may not be necessary for all patients with patent foramen ovale or atrial septal defect, as some may suffer from its complications, including peripheral embolism,

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thrombosis, and arterial hypertension.[5,6] Moreover, if the patients are troubled with coronary artery disease, arrhythmia, or diabetes, the patent foramen ovale or atrial septal defect may lead to a higher incidence of major cardiovascular complications. Patients are only considered to receive an intervention in cases of cryptogenic stroke or thrombotic attacks. For patients who need interventions, percutaneous closure is an alternative to traditional surgical approach. A meta-analysis made by Tang et al[7] indicated that patients who received transcatheter occlusion for atrial septal defect had comparably better outcomes. Thus, the benefits of percutaneous closure for congenital heart disease have been recognised, and doctors have started to make efforts to provide a better prognosis for such children.

Amplatzer (AGA Medical, Golden Valley, Minnesota, United States of America), CardioSEAL/STARFlex (NMT Medical, Boston, Massachusetts, United States of America), Bio-star (NMT Medical), Helex (Gore and Associates, Flagstaff, Arizona, United States of America), Premere (St. Jude Medical, St Paul, Minnesota, United States of America), and some others have all been used in percutaneous closure in the past several years.[8–14] Among them, the Amplatzer and CardioSEAL/STARFlex have similar indications for patent foramen ovale or atrial septal defect treatment separately. However, no general agreement has been reached with regard to the superiority among the two types of occluders. Thus, on the basis of meta-analysis, a performance test was conducted between the two most commonly adopted types of occluders.

Therefore, the objective of this meta-analysis is to compare the safety, efficacy, and incidence of recurrent thrombotic events between patients with patent foramen ovale or atrial septal defect receiving transcatheter occlusion using the Amplatzer device and the CardioSEAL/STARFlex device.

Methods

Search strategy

We searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and World Health Organization clinical trials registry centre using a highly sensitive and highly specific search strategy. The search keywords included "patent foramen ovale", "persistent foramen ovale", "PFO", "atrial septal defect", "ASD", "amplatzer", "CardioSEAL", and "STARFlex". The search was updated in May, 2011. The language restriction was used only for English published papers.

Study selection

Citations initially selected by systematic search were first retrieved as title and/or abstract and preliminarily screened. Potentially relevant reports were then retrieved as complete manuscripts and assessed for compliance with inclusion and exclusion criteria.

The inclusion criteria were as follows: patients identified as having atrial septal defect or patent foramen ovale by transthoracic echocardiography or transesophageal echocardiography or angiography; a controlled study; the comparison study contained the Amplatzer group and the STARFlex group, or the Amplatzer group and the CardioSEAL group, or both, and the study might have had other device groups, but these group data would not be included into this meta-analysis; contained at least one of the outcomes of recurrent thrombotic events, as well as efficacy and safety evaluation; the patient population enrolled suffered at least one cryptogenic stroke or a thrombotic event.

The exclusion criteria were as follows: total sample size smaller than 15; comparison not focused on recurrent thrombotic events, as well as on the efficacy and safety of the devices; the same cohort being studied in other study; the use of non-standard types of devices; studies with a mix of patent foramen ovale and atrial septal defect cases.

Data collection and quality assessment

The eligibility of the reports at the title and/or at the abstract level was independently assessed by two investigators (Yifei Li, Chuan Wang), with a third reviewer (Kaiyu Zhou) determining the divergences together; studies that met the inclusion criteria were selected for further analysis. The quality assessment was completed by the two investigators independently according to the quality assessment guidelines of non-randomised controlled interventions study by Deeks et al.[15] The main contents were as follows: method of group assignment – assignment made by the doctors carrying out the studies with the patients' consent, combining the two methods; each group was balanced at baseline according to the design of the studies – subgroups had been made by age, weight, types of atrial septal defects, and the diameter of the patent foramen ovale and atrial septal defect; description of the factors that could influence the prognosis – information of the patient, including the gender, age, weight, patent foramen ovale and atrial septal defect, as well as the indications for transcatheter treatment; reducing the bias of studies, including stratified sampling and subgroup analysis.

Evaluation indicators for efficacy, safety, and recurrent thrombotic event

The efficacy was measured by the residual shunt rate of patent foramen ovale and atrial septal defect at early term (observational time after intervention <1 month), middle term (observational time after intervention <6 months and >1 month), and long term (observational time after intervention >6 months). The safety was measured by the indicators for device embolisation and new-set atrial fibrillation. What was most important in evaluating for patent foramen ovale and atrial septal defect treatment was the rate of recurrent thrombotic events, including the rate of the thrombus formation on the device, the recurrent rate of stroke, and the recurrent rate of transient ischaemic attacks. We used these indicators to evaluate the two kinds of devices, and provided creditable evidence for choice.

Statistical analysis

The results of the selected studies were analysed using the statistical free software Revman 5.1.1 published by the Cochrane library. The Q test was conducted on the research effect size to evaluate heterogeneity. If the research effect size was not heterogeneous ($I^2 < 50\%$), count data were analysed using a fixed effects model (Peto's method). If the research effect size was heterogeneous ($I^2 \geq 50\%$), the random effect model was used. A p-value < 0.05 indicated a statistically significant difference. Combined odds ratio and 95% confidence interval were recorded. Measurement data were analysed using the weighted mean difference and 95% confidence interval. The funnel plot was used to evaluate the publication bias. When the figure was symmetric, the data were no bias of publication. However if the figure was asymmetric, the bias of publication existed. The sensitivity analysis was made by larger sample size studies' subgroup analysis – studies with both device groups' sample size >15.

Results

Study evaluation

A total of 164 citations were retrieved by the aforementioned method. After reading the titles and abstracts, 133 citations were excluded according to the selection criteria, and only 31 studies were identified initially.[16–46] Among them, 11 studies were excluded after reading the entire articles,[20,23,25–28,30,32,35,38,44] including three articles with both patent foramen ovale and atrial septal defect cases.[20,35,38] Finally, 20 controlled studies for patent foramen ovale and atrial septal defect were enrolled into the meta-analysis

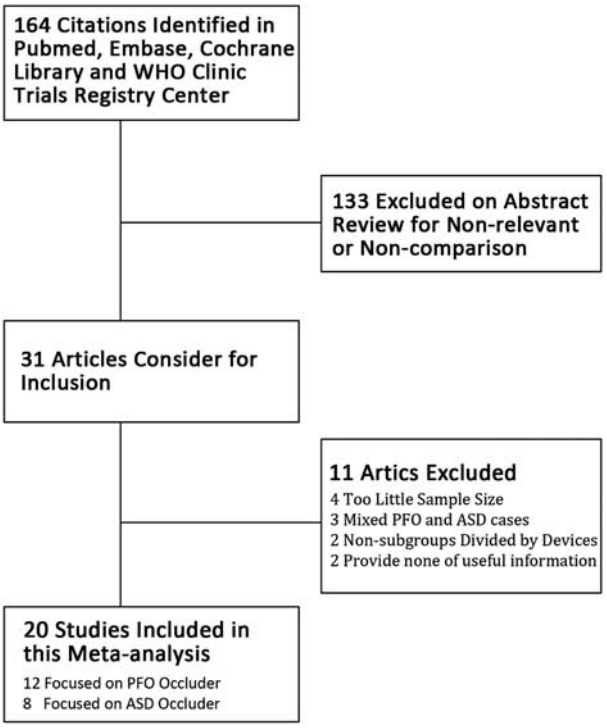

Figure 1.
Flow diagram of study selection process. ASD = atrial septal defect; PFO = patent foramen ovale; WHO = World Health Organization.

(Fig 1).[16–19,21,22,24,29,31,33,34,36,37,39–43,45,46] Among these 20 articles, 12 studies were focused on patent foramen ovale[16,18,19,21,22,24,31,33,34,37,43,45] and eight on atrial septal defect.[17,29,36,39–42,46] A total of 3462 atrial septal defect patients were included, consisting of 2152 patients in the Amplatzer group – 1474 with patent foramen ovale and 678 with atrial septal defect – and 1310 patients in the CardioSEAL/STARFlex group – 810 with patent foramen ovale and 500 with atrial septal defect. There was only one randomised controlled study. The quality of all the articles was acceptable, with the factors that might influence the prognosis and the method of allocation described in detail. Table 1 shows the basic characteristics of the included studies and Table 2 shows the quality evaluation of these studies; all the studies met the inclusion criteria.

Publication bias

Funnel plots were used to evaluate the publication bias of the included studies. Each dot represents a study, and the distance between each dot and the vertical line suggests the bias in each study. The absence of any asymmetric distribution suggested no publication bias. However, asymmetric distribution existed, which indicated that publication bias

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Table 1. Main characteristics of the included studies.

Author	Year	Type of study	Regions of patients	No. of patients*	Study cohort	Version of CardioSEAL/ STARFlex device	Device sizes (mm) (Median (range))	Safety measurements	Recurrent thrombotic event measurements
Hammerstingl et al**,[16]	2011	PCS	Germany	85 (Amplatzer, n = 52 versus CS/SF, n = 33)	PFO	CardioSEAL	Amplatzer (22–35); CS/SF (17–33)	DE new-set AF	None
Luermans et al[17]	2010	RS	The Netherlands	133 (Amplatzer, n = 104 versus CS/SF, n = 29)	sASD	CardioSEAL/ STARFlex	Amplatzer 24 (12–38); CS/SF 33 (20–43)	DE new-set AF	TF stroke TIA
von Bardeleben et al*,**,[18]	2009	PCS	Germany	247 (Amplatzer, n = 199 versus CS/SF, n = 48)	PFO	CardioSEAL/ STARFlex	Amplatzer (25–35); CS/SF (23–33)	New-set AF	TF stroke TIA
Staubach et al***,[19]	2009	RS	Germany	821 (Amplatzer, n = 544 versus CS/SF, n = 227)	PFO	CardioSEAL/ STARFlex	Amplatzer 25 (18–35); CS/SF 23 (23–33)	New-set AF	Stroke
Taaffe et al[21]	2008	RT	Germany	440 (Amplatzer, n = 220 versus CS/SF, n = 220)	PFO	CardioSEAL/ STARFlex	Amplatzer 25 (16–29); CS/SF 23 (23–33)	New-set AF	TF
Luermans et al[22]	2008	RS	The Netherlands	83 (Amplatzer, n = 19 versus CS/SF, n = 64)	PFO	CardioSEAL/ STARFlex	Amplatzer 25 (9–35); CS/SF 28 (23–33)	New-set AF	Stroke TIA
Slavin et al[24]	2007	RS	The United States	131 (Amplatzer, n = 101 versus CS/SF, n = 30)	PFO	CardioSEAL	Amplatzer 25 (18–35); CS/SF 28 (23–40)	None	TF
Post et al[29]	2006	RS	The Netherlands	65 (Amplatzer, n = 39 versus CS/SF, n = 26)	sASD	CardioSEAL/ STARFlex	Amplatzer 24 (12–34); CS/SF 33 (20–43)	DE new-set AF	None
Post et al****,[31]	2005	RS	Belgium	47 (Amplatzer, n = 35 versus CS/SF, n = 12)	PFO	CardioSEAL/ STARFlex	Amplatzer 27.2±5.1; CS/SF 28.4±4.0	DE new-set AF	Stroke
Azarbal et al[33]	2005	RS	The United States	102 (Amplatzer n = 72 versus CS/SF n = 30)	PFO	CardioSEAL/ STARFlex	Not available	None	TF
Varma et al*****,[34]	2004	RS	Canada	92 (Amplatzer, n = 14 versus CS/SF, n = 78)	PFO	CardioSEAL	Amplatzer 25; CS/SF 28	None	TF TIA
Butera et al**,[36]	2004	RS	Italy	274 (Amplatzer, n = 153 versus CS/SF, n = 121)	sASD	CardioSEAL/ STARFlex	Amplatzer (4–38); CS/SF (17–40)	DE new-set AF	None
Braun et al[37]	2004	PCS	Germany	130 (Amplatzer, n = 69 versus CS/SF, n = 61)	PFO	CardioSEAL/ STARFlex	Not available	None	TF TIA
Butera et al******,**,[39]	2003	PCS	Italy	48 (Amplatzer, n = 38 versus CS/SF, n = 10)	sASD	CardioSEAL/ STARFlex	Amplatzer (5–26); CS/SF (17–33)	DE	None

Table 1. *Continued*

Author	Year	Type of study	Regions of patients	No. of patients*	Study cohort	Version of CardioSEAL/ STARFlex device	Device sizes (mm) (Median (range))	Safety measurements	Recurrent thrombotic event measurements
Bialkowski et al**,[40]	2003	PCS	Spain and Poland	181 (Amplatzer, n = 172 versus CS/SF, n = 9)	sASD	CardioSEAL/ STARFlex	Amplatzer (24–34); CS/SF (20–40)	New-set AF	TF
Chessa et al[41]	2002	RS	Italy	417 (Amplatzer, n = 258 versus CS/SF, n = 159)	sASD	CardioSEAL/ STARFlex	Amplatzer 24 (13–34); CS/SF 33 (17–40)	DE new-set AF	TF
Veldtman et al[42]	2001	PCS	Canada	40 (Amplatzer, n = 8 versus CS/SF, n = 32)	sASD	CardioSEAL	Amplatzer 23 (12–36); CS/SF 40 (33–40)	None	None
Sievert et al[43]	2001	RS	Germany	105 (Amplatzer, n = 68 versus CS/SF, n = 37)	PFO	CardioSEAL/ STARFlex	Not available	None	TF
Butera et al[45]	2001	PCS	Italy	27 (Amplatzer, n = 3 versus CS/SF, n = 24)	PFO	CardioSEAL/ STARFlex	Amplatzer 19 (9–25); CS/SF 23 (17–33)	None	None
Acar et al**,[46]	2001	PCS	France	20 (Amplatzer, n = 10 versus CS/SF, n = 10)	sASD	CardioSEAL	Amplatzer (12–26); CS/SF (23–40)	None	None

AF = atrial fibrillation; ASD = atrial septal defect; CS/SF = CardioSEAL/STARFlex; DE = device embolisation; PCS = prospective cohort study; PFO = patent foramen ovale; RS = retrospective study; RT = randomised trial; sASD = secundum atrial septal defect; TF = thrombus formation on the device; TIA = transient ischaemic attacks

*Focused on the influences of atrial septum aneurysm

**The median data of device size were not available

***Only comparison of new-set AF between devices had been made

****Only the form of data as mean ± standard deviation for the used devices were provided

*****Only 25 millimetre Amplatzer devices and 28 millimetre CardioSEAL/STARFlex devices were used for occlusion

******The article only included young children <5 years

Table 2. Main quality evaluation of the included studies.

Studies	How the allocation occurred	Any attempt to balance groups by design	Identification of the prognosis factors	Case-mixed adjustment
Hammerstingl et al[16]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, weight, gender, indications, medications, etc.	None
Luermans et al[17]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, weight, gender, indications, risk factors, defect characteristics, etc.	None
von Bardeleben et al[18]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, weight, gender, indications, risk factors, etc.	None
Staubach et al[19]	By doctors	All the included cases are from the same strategy	Reported the age, weight, indications, defect characteristics, etc.	None
Taaffe et al[21]	Random	All the included cases are from the same research centre, with good homogeneity	Reported the age, weight, gender, indications, risk factors, etc.	Yes
Luermans et al[22]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, weight, gender, indications, defect characteristics, etc.	None
Slavin et al[24]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, weight, gender, indications, risk factors, etc.	None
Post et al[29]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, gender, indications, defect characteristics, etc.	None
Post et al[31]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, gender, indications, defect characteristics, etc.	None
Azarbal et al[33]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, gender, indications, defect characteristics, etc.	None
Varma et al[34]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, gender, indications, defect characteristics, etc.	None
Butera et al[36]	By doctors and patients	All the included cases are from the same research centre, with good homogeneity	Reported the age, weight, gender, indications, risk factors, etc.	Yes
Braun et al[37]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, gender, indications, defect characteristics, etc.	Yes
Butera et al[39]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, weight, gender, indications, risk factors, etc.	Yes
Bialkowski et al[40]	By doctors	All the included cases are from the same strategy	Reported the age, weight, indications, defect characteristics, etc.	None
Chessa et al[41]	By doctors	All the included cases are from the same strategy	Reported the age, weight, indications, etc.	None
Veldtman et al[42]	By doctors	All the included cases are from the same strategy	Reported the age, gender, defect characteristics, etc.	None
Sievert et al[43]	By doctors and patients	All the included cases are from the same research centre, with good homogeneity	Reported the age, weight, gender, indications, risk factors, etc.	Yes
Butera et al[45]	By doctors	All the included cases are from the same strategy	Reported the age, weight, indications, defect characteristics, etc.	None
Acar et al[46]	By doctors	All the included cases are from the same research centre, with good homogeneity	Reported the age, defect characteristics, etc.	Yes

The quality of all the articles were passable

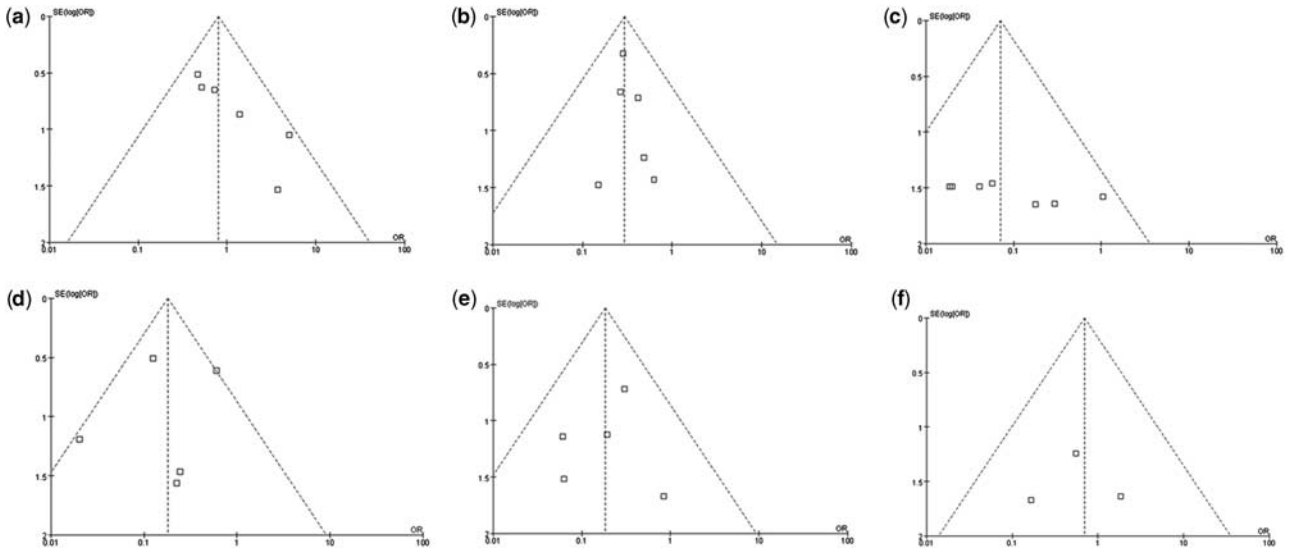

Figure 2.
*Funnel plot of the included trials: (**a**) for residual shunt evaluation of patent foramen ovale, (**b**) for safety evaluation of patent foramen ovale, (**c**) for recurrent thrombotic event evaluation of patent foramen ovale, (**d**) for residual shunt evaluation of atrial septal defect, (**e**) for safety evaluation of the atrial septal defect, and (**f**) for recurrent thrombotic event evaluation of the atrial septal defect. X-axis represents the effect estimate for each study under the outcome. Y-axis represents standard error (log (effect estimate)). Each dot represents a study, and the distance between each dot and the vertical line suggests bias in each study. The absence of any asymmetric distribution suggested no publication bias. SE = standard error; OR = odds ratio.*

existed. Funnel plots were used to identify the efficacy, safety, and recurrent thrombotic events in patients with patent foramen ovale and atrial septal defect separately. The results showed that there was no publication bias in these evaluated studies, with a symmetric triangle figure (Fig 2a–c for patent foramen ovale and d–f for atrial septal defect).

Efficacy evaluation

Early-term residual shunt rate. Early-term residual shunt rate was calculated within a month after the intervention procedure, and the ones with a moderate to large residual shunt need an extra treatment or observation. For patent foramen ovale occluder evaluation, among the 1011 patients in six studies, 127 (12.56%) had residual shunts, consisting of 79 in the Amplatzer group (12.95%) and 48 in the CardioSEAL/STARFlex group (11.97%). There was no significant difference in the early-term residual shunt rate between the Amplatzer group and the CardioSEAL/STARFlex group for patent foramen ovale (odds ratio = 1.09, 95% confidence interval = 0.72–1.63, p = 0.69). There was no heterogeneity across studies ($I^2 = 26\%$), which was analysed by the fixed effects model. For atrial septal defect occluder evaluation, among the 457 patients in five studies, 79 (17.28%) had residual shunts, consisting of 14 in the Amplatzer group (5.65%) and 65 in the CardioSEAL/STARFlex group (31.10%). The early-term residual shunt rate was significantly lower in the Amplatzer group than the CardioSEAL/STARFlex group for atrial septal defect (odds ratio = 0.18, 95% confidence interval = 0.09–0.34, $p < 0.00001$). There was no heterogeneity across studies ($I^2 = 48\%$), which was analysed by the fixed effects model (Table 3).

Middle-term residual shunt rate. Middle-term residual shunt rate was calculated between 1 and 6 months after the intervention procedure, and referred to a moderate to large residual shunt requiring extra treatment or observation. For patent foramen ovale occluder evaluation, among the 673 patients in six studies, 58 (8.62%) had residual shunts, consisting of 33 in the Amplatzer group (7.71%) and 25 in the CardioSEAL/STARFlex group (10.20%). There was no significant difference in the middle-term residual shunt rate between the Amplatzer group and the CardioSEAL/STARFlex group for patent foramen ovale (odds ratio = 0.79, 95% confidence interval = 0.45–1.40, p = 0.42). There was no heterogeneity across studies ($I^2 = 18\%$), which was analysed by the fixed effects model. For atrial septal defect occluder evaluation, among the 320 patients in two studies, 22 (6.88%) had residual shunts, consisting of five in the Amplatzer group (2.79%) and 17 in the CardioSEAL/STARFlex group (12.06%). There was no significant difference in the middle-term residual shunt rate between the

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Table 3. Summary of meta-analysis data of residual shunt evaluation for patent foramen ovale and atrial septal defect.

Variables	Summarised odds ratio	Test for overall effect		Test for heterogeneity		
		Z	p	χ^2	p	I^2 (%)
Patent foramen ovale						
Early-term residual shunt rate	1.09 [0.72–1.63]	0.41	0.69	6.74	0.24	26
Middle-term residual shunt rate	0.79 [0.54–1.40]	0.80	0.42	6.10	0.30	0
Long-term residual shunt rate	0.54 [0.21–1.41]	1.25	0.21	0.66	0.88	18
Atrial septal defect						
Early-term residual shunt rate	0.18 [0.09–0.34]	5.24	<0.00001*	7.77	0.10	48
Middle-term residual shunt rate	0.17 [0.01–5.81]	0.98	0.33	4.99	0.03	80**
Long-term residual shunt rate	0.37 [0.14–0.97]	2.03	0.04*	0.94	0.33	0

*Suggested significant difference between Amplatzer and CardioSEAL/STARFlex evaluation
**Suggested significant heterogeneity among the enrolled studies, using the random effects model for meta-analysis

Amplatzer group and the CardioSEAL/STARFlex group for atrial septal defect (odds ratio = 0.17, 95% confidence interval = 0.01–5.81, p = 0.33). There was heterogeneity across studies (I^2 = 80%), which was analysed by the random effects model (Table 3).

Long-term residual shunt rate. Long-term residual shunt rate was calculated between 6 and 24 months after the intervention procedure, and referred to a moderate to large residual shunt requiring extra treatment or observation. For patent foramen ovale occluder evaluation, among the 544 patients in four studies, 19 (3.49%) had residual shunts, consisting of nine in the Amplatzer group (2.74%) and 10 in the CardioSEAL/STARFlex group (4.63%). There was no significant difference in the long-term residual shunt rate between the Amplatzer group and the CardioSEAL/STARFlex group (odds ratio = 0.54, 95% confidence interval = 0.21–1.41, p = 0.21). There was no heterogeneity across studies (I^2 = 0%), which was analysed by the fixed effects model. For atrial septal defect occluder evaluation, among the 308 patients in two studies, 22 (7.14%) had residual shunts, consisting of 12 in the Amplatzer group (6.35%) and 10 in the CardioSEAL/STARFlex group (8.40%). The long-term residual shunt rate was significantly lower in the Amplatzer group than the CardioSEAL/STARFlex group (odds ratio = 0.37, 95% confidence interval = 0.14–0.97, p = 0.04). There was no heterogeneity across studies (I^2 = 0%), which was analysed by the fixed effects model (Table 3).

Safety evaluation

Embolisation of the device. Because of pressure difference between left and right atria and the special structure of atrial septal and the unstable structure of foramen ovale, the device might migrate to distal vessels. For patent foramen ovale occluder evaluation, among the 187 patients in two studies, embolisation of the device occurred in two (1.07%) patients, both in the Amplatzer group (1.61%) and none in the CardioSEAL/STARFlex group. There was no significant difference in the rate of device embolisation between the Amplatzer group and the CardioSEAL/STARFlex group for patent foramen ovale (odds ratio = 1.59, 95% confidence interval = 0.16–15.59, p = 0.69; Fig 3). There was no heterogeneity across studies (I^2 = 0%), which was analysed by the fixed effects model. For atrial septal defect occluder evaluation, among the 937 patients in five studies, embolisation of the device occurred in 24 (2.56%) patients, consisting of six in the Amplatzer group (1.01%) and 18 in the CardioSEAL/STARFlex group (5.21%). The rate of device embolisation was significantly lower in the Amplatzer group than the CardioSEAL/STARFlex group for atrial septal defect (odds ratio = 0.18, 95% confidence interval = 0.07–0.45, p = 0.0002; Fig 4). There was no heterogeneity across studies (I^2 = 0%), which was analysed by the fixed effects model.

New-set atrial fibrillation. Atrial fibrillation is the most common type of arrhythmia related to device implantation, and is a subsequent risk for neurologic events. For patent foramen ovale occluder evaluation, among the 1723 patients in six studies, new-set atrial fibrillation occurred in 84 (4.88%) patients, consisting of 30 in the Amplatzer group (2.81%) and 54 in the CardioSEAL/STARFlex group (8.26%). The rate of new-set atrial fibrillation was significantly lower in the Amplatzer group than the CardioSEAL/STARFlex group for patent foramen ovale (odds ratio = 0.29, 95% confidence interval = 0.18–0.48, p < 0.00001; Fig 5). There was no heterogeneity across studies (I^2 = 0%), which was analysed by the fixed effects model. For atrial septal defect occluder evaluation, among the 1070 patients in five studies, new-set atrial fibrillation occurred in 33 (3.84%) patients, consisting of 22 in the Amplatzer group (3.03%)

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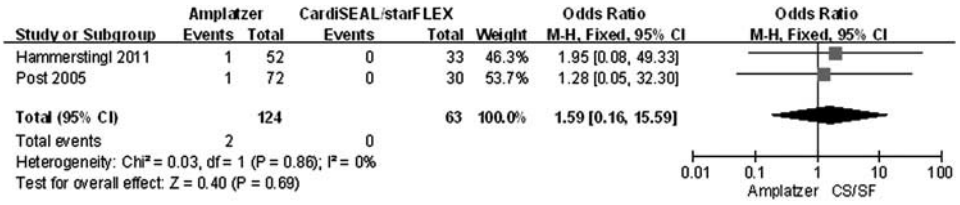

Figure 3.
Forest plot for the embolisation of the device for patent foramen ovale. Overall, no significant difference was found for embolisation of the device with the Amplatzer compared with the CardioSEAL/STARFlex, with a summarised odds ratio of 1.59 (95% CI = 0.16–15.59, p = 0.69). No heterogeneity was detected (p = 0.86, I^2 = 0%). CI = confidence interval; CS/SF = CardioSEAL/STARFlex; df = degrees of freedom.

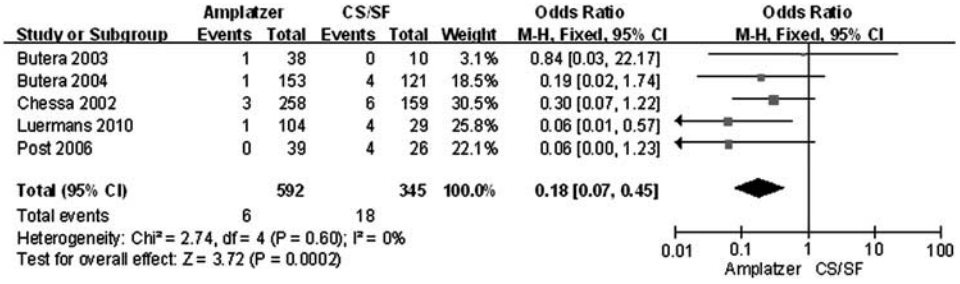

Figure 4.
Forest plot for the embolisation of the device for atrial septal defect. Overall, a significantly lower risk of embolisation of the device with the Amplatzer compared with CardioSEAL/STARFlex was found, with a summarised odds ratio of 0.18 (95% CI = 0.07–0.45, p = 0.69). No heterogeneity was detected (p = 0. 60, I^2 = 0%). CI = confidence interval; CS/SF= CardioSEAL/STARFlex; df = degrees of freedom.

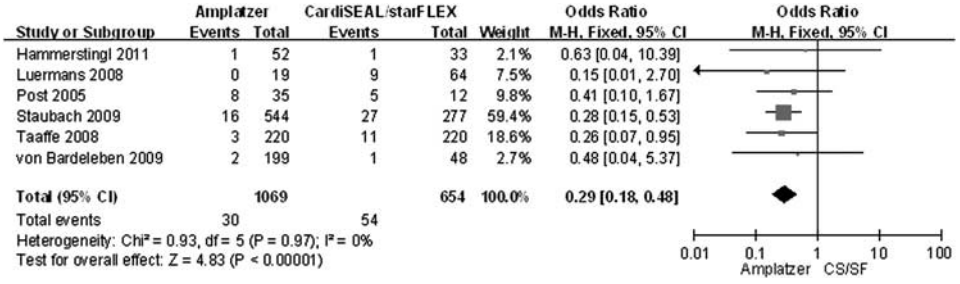

Figure 5.
Forest plot for new-set atrial fibrillation of patent foramen ovale. Overall, a significantly lower risk of new-set atrial fibrillation with the Amplatzer compared with CardioSEAL/STARFlex was found, with a summarised odds ratio of 0.29 (95% CI = 0.18–0.48, p < 0.00001). No heterogeneity was detected (p = 0.97, I^2 = 0%). CI = confidence interval; CS/SF = CardioSEAL/STARFlex; df = degrees of freedom.

and 11 in the CardioSEAL/STARFlex group (3.20%). There was no significant difference in the rate of new-set atrial fibrillation between the Amplatzer group and the CardioSEAL/STARFlex group for atrial septal defect (odds ratio = 0.82, 95% confidence interval = 0.39–1.69, p = 0.58; Fig 6). There was no heterogeneity across studies (I^2 = 38%), which was analysed by the fixed effects model.

Recurrent thrombotic event evaluation

Thrombus formation on the device. Thrombus formation on the device might damage the device and surgical removal of the thrombus would result in injury to the patients. Moreover the thrombus on device was a risk for thrombus embolisation of distal vessels especially for the neural system. For patent foramen ovale occluder evaluation, among the 1221 patients in seven studies, thrombus formation on the device occurred in 29 (2.29%) patients, consisting of none in the Amplatzer group and 29 in the CardioSEAL/STARFlex group (5.75%). The rate of thrombus formation on the device was significantly lower in the Amplatzer group than the CardioSEAL/STARFlex group (odds ratio = 0.07, 95% confidence interval = 0.02–0.21,

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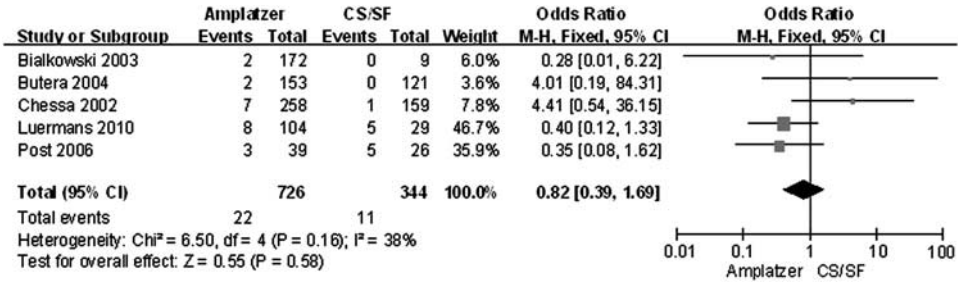

Figure 6.
Forest plot for new-set atrial fibrillation of atrial septal defect. Overall, no significant difference of new-set atrial fibrillation with the Amplatzer compared with CardioSEAL/STARFlex was found, with a summarised odds ratio of 0.82 (95% CI = 0.39–1.69, p = 0.58). No heterogeneity was detected (p = 0.16, I^2 = 38%). CI = confidence interval; CS/SF = CardioSEAL/STARFlex; df = degrees of freedom.

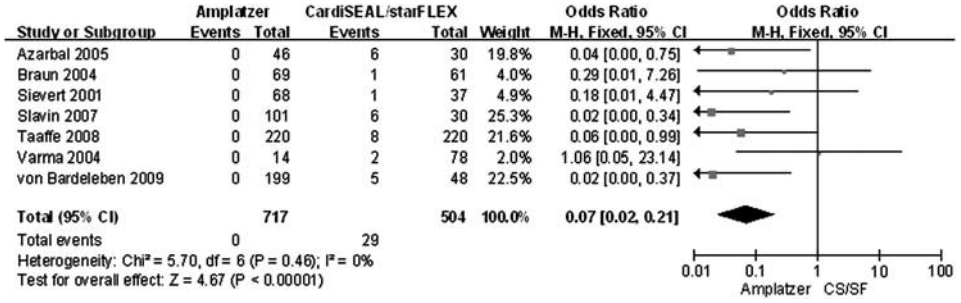

Figure 7.
Forest plot for thrombus formation on the device for patent foramen ovale. Overall, a significantly lower risk of thrombus formation on the device with the Amplatzer compared with CardioSEAL/STARFlex was found, with a summarised odds ratio of 0.07 (95% CI = 0.02–0.21, p < 0.00001). No heterogeneity was detected (p = 0.46, I^2 = 0%). CI = confidence interval; CS/SF = CardioSEAL/STARFlex; df = degrees of freedom.

p < 0.00001; Fig 7). There was no heterogeneity across studies (I^2 = 0%), which was analysed by the fixed effects model. For atrial septal defect occluder evaluation, among the 731 patients in three studies, thrombus formation on the device occurred in five (0.68%) patients, consisting of four in the Amplatzer group (0.75%) and one in the CardioSEAL/STARFlex group (0.51%). There was no significant difference in the rate of thrombus formation on the device between the Amplatzer group and the CardioSEAL/STARFlex group (odds ratio = 0.69, 95% confidence interval = 0.13–3.66, p = 0.67; Fig 8). There was no heterogeneity across studies (I^2 = 0%), which was analysed by the fixed effects model.

Stroke. Stroke was an indicator for treatment of patent foramen ovale, and the purpose of intervention was to prevent its recurrence. Owing to the possibility of recurrence, it is important that this measure be evaluated. All the included studies focused on patent foramen ovale, and thus this remained an important problem affecting the prognosis of such patients. Among the 1193 patients in four studies, nine (1.13%) had a recurrent stroke after treatment, consisting of six in the Amplatzer group (0.75%) and three in the CardioSEAL/STARFlex group (0.74%). There was no significant difference in recurrent stoke rate between the Amplatzer group and the CardioSEAL/STARFlex group (odds ratio = 0.84, 95% confidence interval = 0.25–2.78, p = 0.77; Fig 9). Thus, there was no statistical difference in recurrent stroke after treatment between the Amplatzer group and the CardioSEAL/STARFlex group. There was no heterogeneity across studies (I^2 = 40%), which was analysed by the fixed effects model.

Transient ischaemic attacks. Transient ischaemic attacks are also an indicator for treatment of patent foramen ovale, and the purpose of intervention is to prevent its recurrence. It had more possibilities to re-attack patients and it was considered as a measurement for device evaluation, as it could predict a worse thrombus event. It has been measured only in the patent foramen ovale patient population; however, it may not be an important indication or index for atrial septal defect treatment

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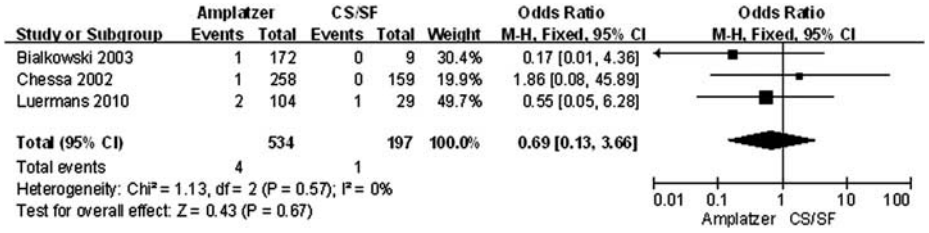

Figure 8.
Forest plot for thrombus formation on the device for atrial septal defect. Overall, no significant difference was found for thrombus formation on the device with the Amplatzer compared with the CardioSEAL/STARFlex, with a summarised odds ratio of 0.69 (95% CI = 0.13–3.66, p = 0.67). No heterogeneity was detected (p = 0.57, I^2 = 0%). CI = confidence interval; CS/SF = CardioSEAL/STARFlex; df = degrees of freedom.

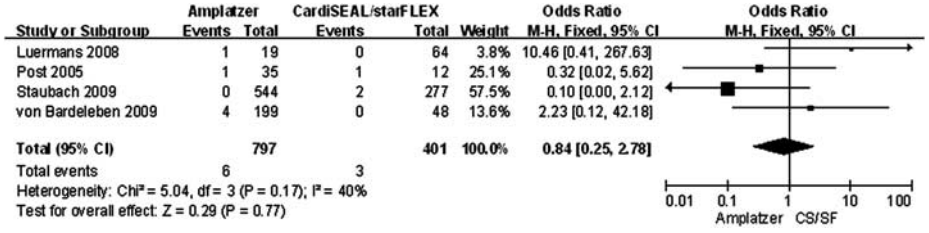

Figure 9.
Forest plot for stroke of patent foramen ovale. Overall, no significant difference of stroke was found for the Amplatzer compared with CardioSEAL/STARFlex, with a summarised odds ratio of 0.84 (95% CI = 0.25–2.78, p = 0.77). No heterogeneity was detected (p = 0.17, I^2 = 40%). CI = confidence interval; CS/SF = CardioSEAL/STARFlex; df = degrees of freedom.

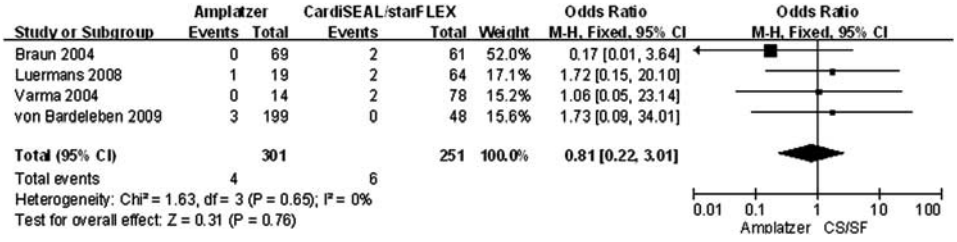

Figure 10.
Forest plot for transient ischaemic attacks of patent foramen ovale. Overall, no significant difference of transient ischaemic attacks was found for the Amplatzer compared with CardioSEAL/STARFlex, with a summarised odds ratio of 0.81 (95% CI = 0.22–3.01, p = 0.76). No heterogeneity was detected (p = 0.65, I^2 = 0%). CI = confidence interval; CS/SF = CardioSEAL/STARFlex; df = degrees of freedom.

and evaluating prognosis. Among the 552 patients in four studies, 10 (1.81%) had transient ischaemic attacks after treatment, consisting of four in the Amplatzer group (1.33%) and six in the CardioSEAL/STARFlex group (2.39%). The recurrent transient ischaemic attack rate suggested no significant difference between the Amplatzer group and the CardioSEAL/STARFlex group (odds ratio = 0.81, 95% confidence interval = 0.22–3.01, p = 0.76; Fig 10). There was no heterogeneity across studies (I^2 = 0%), which was analysed by the fixed effects model.

Finally, sensitivity analysis had been done by a larger sample size subgroup analysis, and every analysis confirmed in both direction and magnitude of statistical significance the findings of the overall analysis.

Discussion

Whether patent foramen ovale is a kind of congenital heart disease remains a debate, although atrial septal defect is one of the most common types of congenital heart disease. Patent foramen ovale usually closes automatically over the years. However, even automatic close haven't been done, both of them just remain a little change of haemodynamics interatrials, providing little damage in their young

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period. However, with age, they may result in severe thrombotic events, including migraine, stroke, transient ischaemic attacks, and paradoxical thrombus embolisation.[47–49] Percutaneous occlusion has been proved to be effective in preventing thrombotic events and is better than surgical repair.[50]

The first percutaneous transcatheter closure of patent ductus arteriosus was performed by Porstmann in 1968.[51] Since then, much work has been done to improve the percutaneous transcatheter technique. Since the early 1990s, nearly 10 types of devices have been developed for patent foramen ovale and atrial septal defect closure.[52–55] Studies on the efficacy and safety of each type therefore began. Results of those studies showed that under certain indications each type of device provided good prognosis and caused few complications.[56–58] Recently, some researchers focused on the comparison between different types of devices to determine which type can provide the best outcome for patent foramen ovale and atrial septal defect. However, still no consensus has been made. The fact that Amplatzer and CardioSEAL/STARFlex are the most frequently used devices worldwide necessitates assessment of their performances. Furthermore, as new materials and devices are driving interventional technique forward, the occluders now possess growing importance in transcatheter treatment for congenital heart disease. Thus, all problems concerning the occluders should be treated seriously.

To the best of our knowledge, this is the first meta-analysis comparing the efficacy and safety of the Amplatzer and CardioSEAL/STARFlex for patent foramen ovale and atrial septal defect, under a situation that lacks randomised controlled trials and a large sample size cohort study. Therefore, the level of the evidence of this comparison between the Amplatzer and CardioSEAL/STARFlex is elevated, and thus leads to some evidence-based medicine progress in this field.

The persistence of left-to-right shunting was associated with factors related to the type of occluder used and the morphology of the septum. Complete closure depends on the growth of the endothelium to cover the device and the septum, known as endothelialisation.[59] Although little is known with regard to what influences the endothelialisation process, flattening of the device and stabilisation of the interatrial septum promote such process. Therefore, different occluders have been developed and modified in order to facilitate patent foramen ovale and atrial septal defect closure.

The Amplatzer showed lower residual shunt than CardioSEAL/STARFlex for atrial septal defect occlusion in this meta-analysis, but there was no statistical difference between the two types of occluders for patent foramen ovale occlusion. Early residual shunt rate in the Amplatzer group (12.95%) and the CardioSEAL/STARFlex group (11.97%) for patent foramen ovale occlusion both exceeded 10%, which may be associated with incomplete endothelialisation. However, early residual shunt rates have been calculated in the Amplatzer group (5.65%) and the CardioSEAL/STARFlex group (31.10%) for atrial septal defect occlusion. Therefore, the Amplatzer occluder could complete its endothelialisation process more quickly with a more regular defect edge of the atrial septal defect, and showed a perfect complete closure rate of about 5%. Although the Amplatzer occluder might encounter difficulties to integrate the patent foramen ovale edge completely leaving a higher residual shunt rate at early period. The middle-term residual shunt rates of the two groups were both lower than that of the early results, which can be explained by the ongoing process of endothelialisation, and fixed occluder position during the contraction and dilation of the heart. However, the comparison in patent foramen ovale and atrial septal defect evaluation provided no significant difference. In the long term, the residual shunt rate decreased further. A significant difference was found only in atrial septal defect occlusion, meaning that the Amplatzer performed better for atrial septal defect occlusion. However, in the early and long-term results for atrial septal defect occlusion the Amplatzer occluder has its advantages for complete occlusion with its special structure and perfect endothelialisation. Both types of occluders are suitable for percutaneous closure of patent foramen ovale and atrial septal defect with acceptable residual shunt rate, yet the Amplatzer occluder can benefit the patients more with its higher complete closure rate for atrial septal defect occlusion.

Embolisation is the most common complication that may be related to the size of the device used and usually occurs in the main pulmonary artery.[60] Once the device embolised, two different options are available: (1) retrieve the device by a gooseneck snare or a basket catheter,[61] (2) refer the patient to the surgeon.[62] Arrhythmia is another common complication, especially the new-set atrial fibrillation represents a higher incidence among all types of arrhythmia, which is reported to be associated with age and the design of the occluder.[63] The average incidence is about 0.7–19%, without a relative fixed incidence.[64] It is also a risk factor for thrombus formation and a second treatment of medication or surgery.[65]

The Amplatzer showed significantly lower incidence of embolisation than CardioSEAL/STARFlex for atrial septal defect occlusion. In the evaluation of patent foramen ovale occlusion, the Amplatzer and

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CardioSEAL/STARFlex reported almost the same incidence for device embolisation, and the incidence rates are lower than that of atrial septal defect occlusion. The diameter of the atrial septal defect is usually larger than that of patent foramen ovale, which leads to a more unstable attachment for atrial septal defect occluder. Moreover, atrial septal defect results in faster residual shunt, which may increase the risk of occluder migration. Therefore, in atrial septal defect occlusion, the Amplatzer occluder shows its advantages on attachment to atrial septal by its double-disk structure. Patent foramen ovale's smaller diameter improves the stability of the CardioSEAL/STARFlex occluder, resulting in almost the same incidence of device embolisation compared with the Amplatzer occluder. The rate of new-set atrial fibrillation in the Amplatzer group (2.81%) was significantly lower than the CardioSEAL/STARFlex group (8.26%) for patent foramen ovale occlusion. However, for atrial septal defect occlusion, no such significant difference has been found. It should be noted that the incidence of new-set atrial fibrillation was at a low level around 5%, and thus all of them were acceptable in clinical practice. Although both types are safe for percutaneous closure by the previous individual studies, according to this meta-analysis the Amplatzer occluder, which has a lower incidence of device embolisation for atrial septal defect and new-set atrial fibrillation for patent foramen ovale, showed its advantages for guaranteeing the patients' safety for both patent foramen ovale and atrial septal defect occlusion.

Thrombotic events pose a great threat to patients with patent foramen ovale and atrial septal defect, which can be effectively prevented by percutaneous closure, as reported in many previous studies.[66] Percutaneous closure can also improve the symptoms of migraine. Many factors are associated with the recurrence of thrombotic events, such as anticoagulation therapy, age, weight, and gender. The thrombus formation on the device calls for more efficient anticoagulation therapy or surgical removal; otherwise, it can compromise the prognosis, or even cause lethal stroke or transient ischaemic attacks in old patients.[67–69] According to this meta-analysis, the rate of thrombus formation of the Amplatzer was significantly lower than that of the CardioSEAL/STARFlex for patent foramen ovale occlusion, which was not found for atrial septal defect occlusion; moreover, the whole incidence was lower for atrial septal defect occlusion than patent foramen ovale. It is suggested that patent foramen ovale's higher thrombus formation rate was due to its higher residual shunt rate and slower blood flow interatrial. The same reason goes for why the Amplatzer performed better in patent foramen ovale occlusion than the CardioSEAL/STARFlex. However, re-attack events such as stroke and transient ischaemic attacks showed no significant difference (0.75% versus 0.74% and 1.33% versus 2.39%, $p > 0.05$). All the included studies for stroke and transient ischaemic attacks concentrated on patent foramen ovale, and this indicated that stroke and transient ischaemic attacks are not serious indications for atrial septal defect treatment or an important index for evaluating the prognosis of atrial septal defect. It is also suggested that the Amplatzer occluder is safer for preventing thrombus formation and recurrent thrombotic events for patent foramen ovale occlusion.

In this study, the Amplatzer occluder had better outcomes than the CardioSEAL/STARFlex, with higher efficacy and safety, and lower incidence of recurrent thrombotic events both in patent foramen ovale and atrial septal defect. Therefore, it is strongly suggested that doctors should pay more attention to the Amplatzer device in practice, given its better outcomes. However, it should also be noted that the type of device is only one factor of multiple factors affecting the prognosis. Therefore, the best clinical decision should be made on behalf of individual situation.

The limitations of this meta-analysis are only English publications were included; and no randomised controlled trial comparing the Amplatzer device and the CardioSEAL/STARFlex device was included. Further design of randomised controlled trials on comparison of different devices for transcatheter occlusion for patent foramen ovale and atrial septal defect on efficacy, safety and recurrent thrombus event is needed. More studies on evaluating the early-term efficacy of percutaneous closure of patent foramen ovale and atrial septal defect are still necessary.

Conclusion

The Amplatzer device and the CardioSEAL/STARFlex device are the most frequently used devices for the closure of patent foramen ovale and atrial septal defect in the world. Although many studies compared the two devices on the efficacy and safety for patent foramen ovale and atrial septal defect, no consensus has been reached. This meta-analysis, for the first time, demonstrated the efficacy, safety, and incidence of recurrent thrombotic events in transcatheter occlusion for patent foramen ovale and atrial septal defect separately using the Amplatzer device and the CardioSEAL/STARFlex device. It suggests that the Amplatzer device is better than the CardioSEAL/STARFlex device for both patent foramen ovale and atrial septal defect patients in terms of the efficacy,

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safety, and lower incidence of recurrent thrombotic events. It is recommended that the Amplatzer device be considered more in practice for such patients in definite indication. This analysis should be considered as a line of evidence, and be incorporated with the specific situation of the patient to make the most appropriate decision for the individual.

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