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Meta-Analysis of Transcatheter Closure Versus Medical Therapy for Patent Foramen Ovale in Prevention of Recurrent Neurological Events After Presumed Paradoxical Embolism

Shikhar Agarwal, MD, MPH, CPH,* Navkaranbir Singh Bajaj, MD,†
Dharam J. Kumbhani, MD, SM,‡ E. Murat Tuzcu, MD,* Samir R. Kapadia, MD*

Cleveland, Ohio; and Boston, Massachusetts

Objectives In this study, a meta-analysis of observational studies was performed to compare the rate of recurrent neurological events (RNE) between transcatheter closure and medical management of patients with cryptogenic stroke/transient ischemic attack (TIA) and concomitant patent foramen ovale (PFO).

Background A significant controversy surrounds the optimal strategy for treatment of cryptogenic stroke/TIA and coexistent PFO.

Methods We conducted a MEDLINE search with standard search terms to determine eligible studies.

Results Adjusted incidence rates of RNE were 0.8 (95% confidence interval [CI]: 0.5 to 1.1) events and 5.0 (95% CI: 3.6 to 6.9) events/100 person-years (PY) in the transcatheter closure and medical management arms, respectively. Meta-analysis of the limited number of comparative studies and meta-regression analysis suggested that the transcatheter closure might be superior to the medical therapy in prevention of RNE after cryptogenic stroke. Comparison of the anticoagulation and antiplatelet therapy subgroups of the medical arm yielded a significantly lower risk of RNE within patients treated with anticoagulants. Device-related complications were encountered at the rate of 4.1 (95% CI: 3.2 to 5.0) events/100 PY, with atrial arrhythmias being the most frequent complication. After transcatheter closure, RNE did not seem to be related to the pre-treatment shunt size or the presence of residual shunting in the follow-up period. Significant benefit of transcatheter PFO closure was apparent in elderly patients, patients with concomitant atrial septal aneurysm, and patients with thrombophilia.

Conclusions Rates of RNE with transcatheter closure and medical therapy in patients presenting with cryptogenic stroke or TIA were estimated at 0.8 and 5.0 events/100 PY. Further randomized controlled trials are needed to conclusively compare these 2 management strategies. (J Am Coll Cardiol Intv 2012;5:777–89) © 2012 by the American College of Cardiology Foundation

From the *Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio; †Internal Medicine, Cleveland Clinic, Cleveland, Ohio; and ‡Cardiovascular Medicine, Brigham & Women's Hospital, Boston, Massachusetts. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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funnel plot method as well as Egger regression asymmetry testing (3). In case of significant publication bias, we adjusted the pooled effect estimate with the Duval and Tweedie nonparametric "trim and fill" method of incorporating the estimates theoretically from the missing studies (4).

Due to a relatively small number of RNE in each study, the data were assumed to follow a Poisson distribution. For each study, a 95% confidence interval (CI) estimate for RNE was computed with Poisson tables. Pooled incidence rates for the transcatheter closure arm or the medical therapy arm were calculated with the respective single-arm studies and by splitting the 2 arms of the comparative studies and including them in the respective groups. The pooled incidence rates for the RNE and composite complication rates were expressed as events/100 person-years (PY), whereas individual complication rates were more appropriately expressed as event/100 patients followed. The comparative estimates were derived only from the studies, which reported direct comparison of the transcatheter closure and medical therapy. Odds ratios, relative risk (RR), and/or risk differences (RD) were used to report pooled estimates for various comparisons. Meta-regression analysis was conducted to determine the difference in RNE rates between the 2 strategies after adjusting for age, sex, and presence of ASA. The meta-analysis has been reported in accordance with the Metaanalysis of Observational Studies in Epidemiology guidelines (5).

Results

Study population. The search strategy retrieved 1,056 title abstracts for review. Of these 1,056 title abstracts, 257 full-text articles were retrieved and reviewed in detail (Fig. 1).

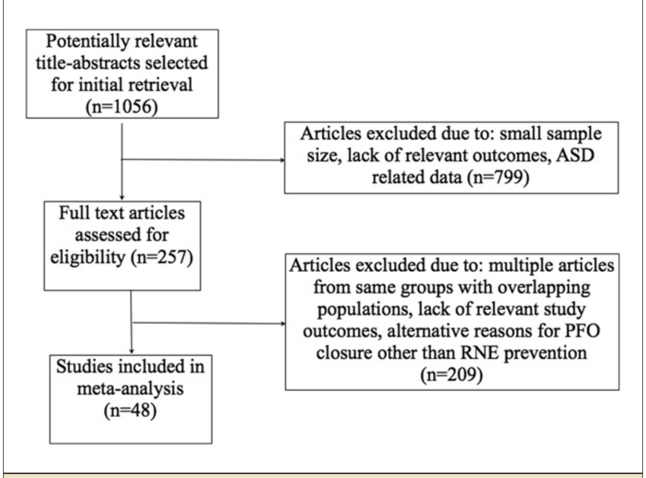

Figure 1. Flow Diagram Demonstrating Selection of Studies for Meta-Analysis

ASD = atrial septal defect; PFO = patent foramen ovale; RNE = recurrent neurological event.

Data for RNE after transcatheter closure and medical therapy were derived from 39 studies with 8,185 patients and 19 studies with 2,142 patients, respectively (6–53). Of these, 10 studies with 1,886 patients reported comparison of the 2 treatment modalities and were included for pooled comparative analysis (10,14,18,20,22,23,31,37,41,42). The distribution of patients in different study groups, along with their baseline characteristics, is demonstrated in Table 1. Because there are no validated scales for assessment of quality of prospective case series, we assessed the quality on the basis of selection characteristics, ascertainment of outcome, and loss to follow-up. For comparative studies, comparability of cohorts was assessed on the basis of differences in baseline characteristics. Due to the inherent differences in the selection as well as baseline characteristics of these cohorts, we refrained from making firm conclusions on the basis of the pooled estimates derived from these comparative studies. The individual components of each of these quality parameters are demonstrated in Online Table 1. Although administration of antiplatelet and/or anticoagulant therapy was observed to be a common practice after device closure, the regimen and the dosage varied considerably across the studies (Online Table 2). Low-dose aspirin with or without clopidogrel was the most common regimen used for thromboprophylaxis in the immediate post-closure period.

RNE. Figure 2 demonstrates the pooled incidence of RNE among the transcatheter PFO closure and the medical therapy arms. The pooled incidence of RNE/100 PY among the transcatheter closure was estimated as 0.76 (95% CI: 0.48 to 1.05) events as compared with 4.39 (95% CI: 3.20 to 5.59) events in the medical therapy arm. With comparative studies, we calculated that there was a significantly reduced number of RNE among patients undergoing transcatheter closure as compared with those managed medically (RR: 0.25 [95% CI: 0.11 to 0.58]) (Fig. 2B).

Figure 3 demonstrates the comparison of RNE among the patients managed medically with anticoagulants versus antiplatelet medications. The incidence of RNE/100 PY in the antiplatelet arm was estimated as 4.2 (95% CI: 2.9 to 5.4) events as compared with 2.2 (95% CI: 1.1 to 3.4) events observed among patients receiving anticoagulation. Pooled analysis of the comparative studies yielded significantly lower risk of RNE among patients receiving anticoagulation as compared with those receiving antiplatelet medications (RR: 0.58 [95% CI: 0.41 to 0.82]).

Device-related complications. Table 2 demonstrates the complications encountered in the post-procedural and follow-up period in the 2 study arms. The composite complication rate/100 PY in the transcatheter closure and the medical management arm was estimated as 4.1 (95% CI: 3.2 to 5.0) events and 0.4 (95% CI: 0 to 0.9) events, respectively. Transcatheter closures have been associated with a high rate of procedural success (failure rate: 0.01%). The reintervention rate in the follow-up period was esti-

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Table 1. Baseline Characteristics

Author/Year (Ref. #)	n	Mean Follow-Up (Yrs)	Devices Used	Age (yrs) (mean ± SD)	Men	ASA	Hypertension	Hyperlipidemia	Smoking	Diabetes
Transcatheter closure										
Sievert/2001 (6)	281	1.0	1, 3, 4, 7, 8, 9, 10, 11	46.8 ± 13.2	—	23%	—	—	—	—
Braun/2002 (7)	276	1.3	10	45.3 ± 13.7)	53%	22%	18%	—	—	3%
Martín/2002 (8)	110	2.3	1, 8	47 ± 14.0	53%	15%	16%	26%	20%	—
Onorato/2003 (9)	256	1.6	1, 4, 10	48 ± 15.0	41%	41%	—	—	—	—
Windecker/2004 (10)	150	2.3	1, 2, 8, 10, 11	50 ± 12	53%	25%	28%	—	33%	4%
Braun/2004 (11)	130	1.8*	1, 3	45.5 ± 14.8	58%	25%	20%	9.2%	31%	6.1%
Knebel/2004 (12)	113	1.4	1, 2, 7	46.8 ± 11.0	—	31%	—	—	—	—
Alameddine/2004 (13)	272	0.1	2, 3	51 ± 14.2	47%	33%	—	—	—	—
Schuchlenz/2005 (14)	167	2.8	1, 2, 3, 7	44 ± 11.0	53%	25%	17%	12.6%	5.4%	6.6%
Post/2005 (15)	112	1.9*	1, 3, 4, 10	52.1 ± 12.5	56.3%	18.8%	—	—	—	—
Tande/2005 (16)	120	1.1	1, 2, 6	NR	42.5%	34.2%	40%	53.3%	34.2%	14.2%
Billinger/2006 (17)	128	1.8	4	50 ± –	51.6%	29.7%		—		
Harrer/2006 (18)	34	2.1	1, 2, 7, 8, 9, 10	49.5 ± 14.5	44.1%	32.4%	17.6%	8.8%	29.4%	2.9%
Giardini/2006 (19)	131	1.9	1, 2, 4	45 ± 13.0	51.9%	51.1%	—	—	—	—
Thanopoulos/2006 (20)	48	2.0	1	43 ± 11.0	56.3%	27.1%	12.5%	25%	12.5%	4.2%
Kiblawi/2006 (21)	456	1.5	2	51.1 ± 15.5	—	—	—	—	—	—
Cerrato/2006 (22)	21	2.6	NR	45 ± 13.5	—	33.3%	—	—	—	—
Casaubon/2007 (23)	47	2.7	1, 2	43 ± –	53.2%	29.8%	6.4%	17%	29.8%	4.3%
Slavin/2007 (24)	131	2.5	1, 2	52.4 ± 13.1	50.4%	11.5%	29.8%	34.4%	15.3%	10.7%
Harms/2007 (25)	237	1.6	1, 2	53 ± 15	48.1%	32.1%	43.0%	37.1%	—	—
Egred/2007 (26)	109	1.4	1, 3	45.3 ± 10	64.2%	—	—	—	—	—
Dubiel/2008 (27)	125	3.3	1, 2, 3, 5, 10	48.3 ± 13.4	59.2%	50.4%	—	—	—	—
Luermans/2008 (28)	430	0.8*	12	50.7 ± 13	53.7%	44.9%	—	—	—	—
Spies/2008 (29)	1,055	1.5*	1–9, 11–14	50.4 ± –	51.4%	40.5%	20.9%	20.9%	11.1%	7.2%
Taffe/2008 (30)	660	0.1	1, 3, 4	49.3 ± 12.9	55.2%	36.4%	34.5%	—	—	4.8%
van de Wyngaert/2008 (31)	66	3.7	1, 3, 4, 10	41.5 ± –	53%	51.5%	6%	16.7%	—	—
Balbi/2008 (32)	128	2.7	1, 4, 6	—	49.2%	22.7%	19.5%	25.8%	18%	7.8%
Kutty/2008 (33)	216	2.1	2	50 ± –	49.5%	—	30.1%	—	22.2%	—
Fischer/2008 (34)	154	2.2	3	43.9 ± 12.5	61%	37%	24.7%	26%	26%	0.6%
Wahl/2009 (35)	620	3.0	1	51 ± 12	60.8%	33.4%	31.9%	—	30.3%	4.2%
Sievert/2009 (36)	144	0.5	15	46 ± 11	54.9%	18.1%	—	—	—	—
Weimar/2009 (37)	117	2.4	NR	46 ± –	62.4%	29.1%	34.2%	—	—	7.7%
von Bardeleben/2009 (38)	357	3.8	1, 3, 4	51 ± 14	59.1%	28.6%	41.5%	45.9%	34.7%	6.7%
Greutmann/2009 (39)	135	0.5	1	51 ± 12	57.8%	60.7%	27.4%	39.3%	22.2%	2.2%
Presbitero/2009 (40)	216	1.6	1, 4, 5, 6	52.5 ± 13.5	54.6%	12%	—	—	—	—
Lee/2010 (41)	22	2.9	1, 2	41 ± 12	68.2%	4.5%	9%	27.2%	36.4%	0
Paciaroni/2011 (42)	121	2.0	1, 3, 10, 15	43.4 ± 9.5	48.8%	62%	19.8%	19%	27.3%	4.1%
Thaman/2011 (43)	166	1.4	1, 4, 5	47 ± 12	48.2%	27.1%	22.9%	19.9%	24.7%	22.9%
Hammerstingl/2011 (44)	124	6.7	1, 2, 4, 5	49.2 ± 13.3	46.8%	54.8%	40.3%	21.8%	50%	4.8%

Continued on next page

mated as 0.9% (95% CI: 0.2 to 1.6). The most frequent complication after transcatheter closure was reported to be atrial arrhythmias (incidence: 3.9% [95% CI: 2.7 to 6.1]). The incidence of device-related thrombosis was estimated as 0.6% (95% CI: 0.3 to 0.9). The proportion of patients with complications requiring surgical intervention was estimated as 0.3% (95% CI: 0.1 to 0.5). The rate of bleeding complications in the transcatheter closure arm was estimated as 1.7% (95% CI: 1.1 to 2.4). In comparison, the rate of bleeding complications in the medical therapy arm was estimated as 1.1% (95% CI: 0 to 2.5).

To determine the impact of improvement of procedural technique and device design, we analyzed the complication rate in the early period (2001 to 2005) and the late period (2006 to 2011) separately. Although there was a trend toward a reduction in the complication rate from the early period to the late period in both study groups, this difference was not statistically significant ($p > 0.05$ for both compar-

Table 1. Continued

Author/Year (Ref. #)	n	Mean Follow-Up (Yrs)	Devices Used	Age (yrs) (mean ± SD)	Men	ASA	Hypertension	Hyperlipidemia	Smoking	Diabetes
Medical therapy										
Hanna/1994 (45)	16	2.3	—	43*	69%	38%	—	—	—	—
Mas/1995 (46)	107	1.9	—	39.4 ± 10.5	50%	35.5%	7%	21%	48%	3%
Hausmann/1995 (47)	51	4.9	—	46.1 ± 13.7	61%	7.8%	—	—	—	—
Bougousslavsky/1996 (48)	140	3.0	—	44 ± 14	60%	25%	14%	14%	31%	4%
Cujec/1999 (49)	52	3.6	—	38 ± 11.0	60%	23%	—	—	—	—
De Castro/2000 (50)	74	2.6*	—	53 ± 14.0	—	36%	—	—	—	—
Mas/2001 (51)	277	3.2	—	40.3 ± −	53%	22%	9%	12%	44%	3%
Anzola/2003 (52)	59	5.1	—	45.3 ± 13	39%	12%	31%	12%	25%	—
Windecker/2004 (10)	158	2.4	—	50.7 ± 13.5	58.9%	20.8%	32.9%	30.4%	32.9%	9.5%
Schuchlenz/2005 (14)	113	2.6	—	47.7 ± 12.7	54.9%	23.9%	21.2%	23.9%	19.5%	7.9%
Harrer/2006 (18)	83	4.6	—	52.5 ± 15.4	63.9%	22.9%	27.7%	6%	18.1%	4.8%
Thanopoulos/2006 (20)	44	2.0	—	40 ± 12	47.8%	22.7%	27.0%	29.5%	25%	8.3%
Cerrato/2006 (22)	59	4.7	—	45 ± 13.5	—	23.7%	—	—	—	—
Casaubon/2007 (23)	61	2.7	—	50.3 ± −	54.1%	16.4%	24.6%	29.5%	41%	6.6%
van de Wyngaert/2008 (31)	66	2.7	—	41.5 ± −	53%	51.5%	6%	16.7%	—	—
Serena/2008 (53)	297	1.9	—	53.2 ± 14.8	62%	38.4%	27.6%	—	33%	6.4%
Weimar/2009 (37)	234	2.4	—	57 ± −	65.8%	20.1%	48.3%	14.1%	—	—
Lee/2010 (41)	159	3.5*	—	53 ± 13	73.6%	11.3%	51.6%	24.5%	36.5%	17%
Paciaroni/2011 (42)	117	2.0	—	40.9 ± 10.3	50.4%	41%	17.1%	19.7%	32.5%	0

Device key: 1: Amplatzer; 2: CardioSEAL; 3: Starflex; 4: Helex; 5: Premere; 6: Cardia; 7: Rashkind; 8: Sideris; 9: ASDOS; 10: PFOstar; 11: Angelwings; 12 Intrasept; 13: Atriasept; 14: Occlutech; 15: Radiofrequency.
*Median reported.
ASA = atrial septal aneurysm; NR = not reported.

isons). In the transcatheter closure arm, there was a small nonsignificant reduction in the incidence of perforation, device-related thrombosis, air embolism, bleeding complications, mortality, and residual shunting in the late period compared with the early period. In the medical therapy arm, there was a trend toward reduction in bleeding complications as well as mortality in the late period compared with the early period.

Table 3 demonstrates the rates of RNE and major complications across the most common devices used in the included studies. Amplatzer (AGA Medical Corporation, Golden Valley, Minnesota) was the most common device used (38.5%), followed by the CardioSEAL (NMT Medical, Boston, Massachusetts) device (18.6%). The rates of RNE ranged from 0.1 to 1.7 events/100 PY across the various device types. Atrial arrhythmias were most frequently encountered with CardioSEAL (10.2/100 PY) and Starflex (NMT Medical) devices (9.0/100 PY) and least commonly with Amplatzer and Helex (Gore Medical, Flagstaff, Arizona) devices. Among all the devices used, device-related thrombosis was most commonly encountered with the Starflex (3.3/100 PY) and the PFO Star device (2.8/100 PY). Helex devices seemed to have the highest rates of medium- to long-term (14.8%) residual shunting and a slightly higher risk of device embolization or malposition (1.4/100 PY) as compared with other device types.

PFO morphology. In the transcatheter closure arm, the incidence of RNE/100 PY among patients with PFO alone versus those with PFO and ASA was estimated as 0.3 (95% CI: 0.1 to 0.6) events and 0.4 (95% CI: 0.1 to 1.0) events, respectively. In the medical management arm, the respective incidence of RNE/100 PY among patients with PFO alone and PFO and ASA was estimated as 2.4 (95% CI: 0.9 to 4.0) events and 6.2 (95% CI: 2.8 to 9.6) events. In the transcatheter closure arm, there was no significant difference observed in RNE between the 2 morphological groups (RD: 0 [95% CI: −0.01 to 0.01]). However, in the medical management arm, there was significantly increased RNE observed in patients with PFO and ASA as compared with patients with PFO alone (RD: 0.03 [95% CI: 0.01 to 0.05]) (Fig. 4).

Figure 5 demonstrates the effect of increasing proportion of a large pre-treatment shunt upon incidence of RNE in both study arms. With an increasing proportion of patients with large shunts, a significant increase was lacking in the rate of RNE after transcatheter PFO closure. Although there was no apparent trend toward increasing RNE with increasing proportion of patients with large shunts in the medical arm, the rate of RNE in the medical arm was significantly higher than the transcatheter arm in corresponding shunt categories.

Effect of age. Across the published data, studies used different cutoffs for defining "old" versus "young" popula-

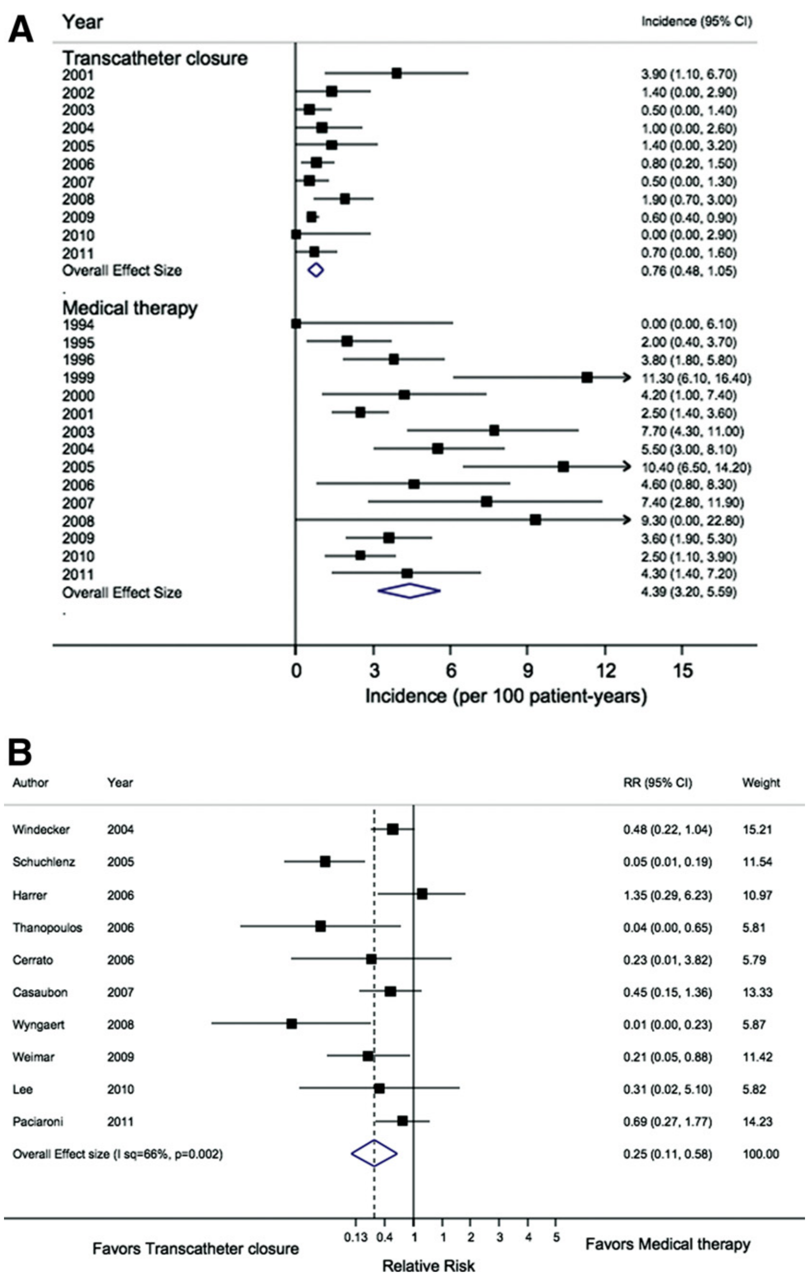

Figure 2. Incidence of Recurrent Neurological Events in the 2 Study Groups

(A) Incidence (per 100 patient-years) of recurrent neurological events in the medical management arm and transcatheter closure arm stratified by year of publication. **(B)** Forest plot comparing the risk of recurrent neurological events between the transcatheter closure and medical management arm in comparative studies. CI = confidence interval; RR = relative risk.

tions. For this subgroup analysis, we used a maximum age of 60 years to define the "young" subgroup. The data for this subgroup analysis was derived from 6 studies with transcatheter closure (8,21,29,32,37,38) and 2 studies with medical management (37,53). There was no significant difference in the risk of RNE between the old and the young subgroups in the transcatheter closure arm (RR: 1.28 [95% CI: 0.77 to 2.14]). However, in the medically managed arm, there was a significantly higher risk of RNE in the older subgroup as compared with the younger subgroup (RR: 3.27 [95% CI: 1.48 to 7.22]).

Effect of thrombophilia. Due to significant paucity of articles studying the effect of thrombophilia on the optimal management strategy for stroke prevention due to PTE

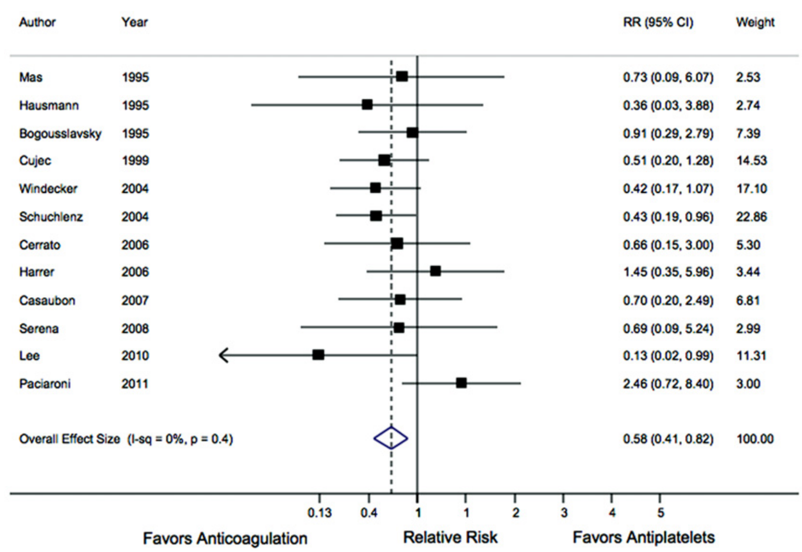

Figure 3. Incidence of Recurrent Neurological Events in the Anticoagulation and Antiplatelet Arms

Forest plot comparing the risk of recurrent neurological events between the anticoagulation subgroup and antiplatelet subgroup of the medical management arm. CI = confidence interval; RR = relative risk.

from PFO, we included all studies, regardless of the sample size for this particular subgroup analysis. Comparison of outcomes after transcatheter closure of PFO among patients with or without hypercoagulable thrombophilia was performed with 9 observational studies (16,19,24,54–59). The incidence of RNE/100 PY among the patients with thrombophilia undergoing transcatheter PFO closure was estimated as 0.3 (95% CI: 0 to 3.2) events as compared with 1.3 (95% CI: 0 to 2.9) events in patients without thrombophilia. Pooled analysis of comparative estimates failed to reveal any significant difference in RNE between the 2 subgroups (RD: 0 [95% CI: −0.04 to 0.03]).

Residual shunting after transcatheter closure. Among the patients undergoing transcatheter PFO closure, the incidence of residual shunt in the immediate post-procedure period was estimated as 25.4% (95% CI: 17.4 to 33.5) (Table 2). This reduced to an estimated rate of 12.5% (95% CI: 9.6 to 15.5) in the first year of follow-up. On long-term follow-up beyond 1 year, this rate further dropped down to 6.3% (95% CI: 0.1 to 18.2) (Table 2].

Figure 6 demonstrates the relationship between RNE and residual shunting reported in the respective studies. There was no particular trend noted in the incidence of RNE with increasing residual shunting reported during the follow-up period across the analyzed studies. In addition, we observed that the presence of residual shunting did not predispose individuals to increased risk of RNE in the follow-up period. Among the patients with RNE, the odds of having a residual shunt were significantly lower as compared with the odds of not having a residual shunt. This implies that the cause of RNE in the follow-up period in most individuals might be actually unrelated to the PFO and its closure.

Meta-regression analysis. Due to significant differences in the baseline characteristics of the included studies, a significant limitation exists in terms of interpretation of pooled effect estimates derived from these studies. Meta-regression analysis was performed to ascertain empirical differences in RNE rates between the 2 groups, after adjustment for mean age, proportion of men in the study, and the proportion of patients with ASA. Interaction of the choice of strategy with each of these variables was tested individually and collectively, and was not statistically significant. After adjustment of these variables, there was a significant reduction of RNE in patients undergoing transcatheter closure by 3.5 (95% CI: 2.1 to 5.0) events/100 PY, in comparison with those managed medically ($p < 0.001$).

Publication bias. The effects of publication bias on the meta-analysis of RNE in the 2 study arms are demonstrated in Online Figures 1 and 2. We observed that there was no significant publication bias in the meta-analysis of RNE after transcatheter closure ($p = 0.8$). However, the meta-analysis of RNE after medical therapy has significant publication bias ($p = 0.015$), which persisted even after restricting the studies to include only those with $n > 100$. With the “fill and trim” method, the corrected effect estimate for RNE after medical therapy was estimated as 5.0 (95% CI: 3.6 to 6.9) events/100 PY (4).

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Table 2. Device-Related Complications Stratified by Treatment Arm

Complication	n	Complication Rate	95% CI
Transcatheter closure			
Procedural failures	6,288	0.01%	0–0.2
Effusion or tamponade	3,123	0.3%	0–0.6
Pericardial effusion	3,123	0.1%	0–0.2
Tamponade	3,123	0.2%	0–0.5
Perforation	1792	0.1%	0–0.3
Embolization/malposition	4,724	0.4%	0.2–0.7
Embolization	4,724	0.1%	0–0.3
Malposition	4,724	0.2%	0–0.5
Infection	537	0.1%	0–0.8
Thrombus	7,065	0.6%	0.3–0.9
Atrial arrhythmia	3,496	3.9%	2.7–6.1
Atrial fibrillation	2,635	1.2%	0.7–1.7
Atrial flutter	2,635	0.1%	0–0.2
Air embolism	2,819	0.6%	0.2–1.0
Any bleeding complication	4,546	1.7%	1.1–2.4
Minor hematoma	548	0.8%	0.3–1.3
Major hematoma	548	0.1%	0–0.2
AV fistula	1882	0.2%	0–0.5
Pseudoaneurysm	1,093	0.6%	0.1–1.2
Reintervention	3,017	0.9%	0.2–1.6
Surgical intervention	4,700	0.3%	0.1–0.5
Total death	3,445	0.4%	0.1–0.8
Related death	3,445	0.1%	0–0.3
Unrelated death	3,445	0.3%	0–0.6
Any above complication excluding unrelated death	7,414	4.1/100 PY	3.2–5.0/100 PY
Residual shunt			
Post-procedure	3,440	25.4%	17.4–33.5
12 months or less	4,513	12.5%	9.6–15.5
More than 12 months	406	6.3%	0.1–18.2
Medical therapy			
Any bleeding complication	707	1.1%	0–2.5
Minor	707	0.2%	0–0.9
Major	707	0.4%	0–1.4
Total death	929	1.1%	0.1–2.0
Related death	929	0.2%	0–0.7
Unrelated death	929	0.6%	0–1.4
Any above complication excluding unrelated death	1,234	0.4/100 PY	0–0.9/100 PY

CI = confidence interval; PY = person-years.

Discussion

Our meta-analysis seeks to understand the available evidence for transcatheter closure in prevention of recurrent PTE in patients with cryptogenic stroke or TIA, compared with medical management. The incidence of RNE/100 PY was estimated at 0.8 and 5.0 events in the transcatheter closure arm and medical therapy arm, respectively. Meta-analysis of the small number of comparative studies and the meta-regression analysis indicated that there might be a significant benefit in reduction of RNE with transcatheter closure in comparison with the medical therapy alone. Moreover, in the medical management arm, the risk of RNE was significantly lower with anticoagulation therapy compared with antiplatelet therapy.

The device-related complication rate was estimated as 4.1 complications/100 PY in the closure arm. The most common complication after transcatheter closure was development of atrial arrhythmias. The incidence of residual shunt was 12.5% in the first year of follow-up, which reduced to 6.3% on long-term follow-up beyond 1 year. We did not observe an increase in the risk of RNE during the follow-up period among individuals with persistent residual shunt in the post-procedure period, as compared with those without residual shunt. Moreover, among individuals with RNE, the odds of lacking a residual shunt were significantly higher than having one. This might suggest that a non-PFO-related cause is often responsible for recurrent thromboembolic events in individuals who have undergone a transcatheter PFO closure in the past. In patients with small residual shunts noted on medium-term follow-up after closure, a trend toward complete elimination of the shunt has been observed, justifying a conservative attitude in management of residual shunt, although there are reports of using a second device for management of moderate to large residual shunts (60).

Age and transcatheter closure. A strong association has been demonstrated between cryptogenic stroke and PFO in patients <55 years of age (61). Due to the greater number of stroke causes in older patients, the relationship between cryptogenic stroke and PFO is harder to establish in these patients (62). We observed a significantly higher rate of RNE in the older age group managed medically as compared with the younger age group. However, the rate of RNE was similar between the older and younger age groups undergoing transcatheter closure. This implies that older individuals with cryptogenic stroke/TIA might derive a benefit of lower rate of RNE by undergoing transcatheter PFO closure.

Morphology and transcatheter closure. There have been several morphological attributes of PFO—such as tunnel length, size, presence or absence of multiple fenestrations, relative thickness of the septal components, ASA, and septal hypermobility—that have influenced the choice of devices across the published data. The prevalence of ASA in the general population has been estimated to range between 1% in autopsy studies to 2.2% in the echocardiography-based studies (63). The presence of PFO with ASA has been shown to increase the risk of RNE (51). Our meta-analysis demonstrated an increased rate of RNE among individuals with PFO and ASA undergoing medical management in comparison with patients with PFO alone. However, in the transcatheter arm, there was no significant difference in the rate of RNE between the 2 subgroups, indicating a beneficial effect of transcatheter closure in preventing recurrent thromboembolic events in

Table 3. Recurrent Neurological Events and Major Complications Stratified by Device Type

	Amplatzer	CardioSEAL	PFOStar	Starflex	Helex
Proportion of total procedure	38.5%	18.6%	11.0%	9.3%	8.9%
Stroke or TIA	0.6 (0.3–0.8)	1.7 (0.1–3.2)	1.6 (0–3.3)	0.9 (0–2.0)	0.1 (0–0.5)
Effusion or tamponade	0.2 (0–0.8)	0.1 (0–2.8)	0.1 (0–1.1)	0.1 (0–0.8)	0.5 (0–1.7)
Embolization/malposition	0.1 (0–0.5)	0.3 (0–0.9)	0.7 (0–1.7)	0.6 (0–2.0)	1.4 (0–3.0)
Thrombus	0.1 (0–0.5)	0.6 (0–1.5)	2.8 (1.0–4.7)	3.3 (1.5–5.1)	0 (0–0.7)
Atrial arrhythmia	1.8 (0.8–2.7)	9.0 (0.2–17.9)	6.9 (0–18.7)	10.2 (4.9–15.4)	0.1 (0–8.0)
Bleeding complications	1.6 (0.1–3.1)	2.6 (0.6–3.4)	4.7 (1.0–13.7)	0.2 (0–1.0)	2.0 (0–6.1)
Reintervention	0.8 (0–1.8)	0 (0–3.2)	0 (0–2.9)	1.8 (0–7.2)	2.1 (0–4.6)
Surgical intervention	0.2 (0–0.8)	0.4 (0–1.0)	0.8 (0–2.0)	2.2 (0–4.5)	0 (0–1.7)
Related death	0 (0–0.3)	0 (0–0.4)	0 (0–1.0)	0 (0–1.1)	0 (0–1.4)
Residual shunt					
Post-procedure	17.3 (8.4–26.3)	13.6 (5.4–21.8)	46.9 (36.5–57.3)	33.6 (19.1–48.1)	46.1 (23.7–68.5)
12 months or less	6.3 (2.5–10.2)	6.2 (0–12.4)	11.8 (2.4–21.2)	8.8 (4.8–12.9)	21.3 (1.0–51.7)
More than 12 months	1.8 (0–5.2)	1.5 (0–4.9)	—	1.8 (0–3.6)	14.8 (0–48.5)

Values are incidence (95% confidence interval)/100 person years. All major device types have been represented in this table.
TIA = transient ischemic attack.

patients with PFO and ASA. In addition, we observed that the rate of RNE was similar, regardless of pre-treatment shunt size among patients undergoing transcatheter closure. These data might serve to demonstrate the efficacy of transcatheter closure independent of the pre-closure PFO morphology and/or functionality.

Thrombophilia and transcatheter closure. It has been suggested that presence of thrombophilia in the presence of

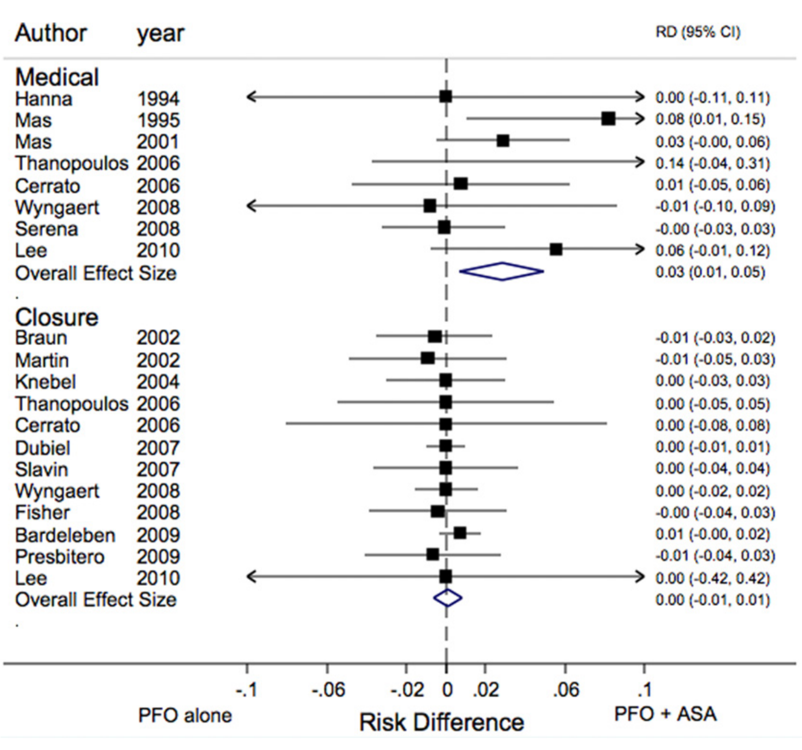

Figure 4. Comparison of Recurrent Neurological Events Between PFO and PFO With ASA Groups

Forest plot comparing the risk of recurrent neurological events between the patients with patent foramen ovale only versus patients with patent foramen ovale and atrial septal aneurysm, stratified by the treatment arm. RD = risk difference; other abbreviations as in Figures 1 and 2.

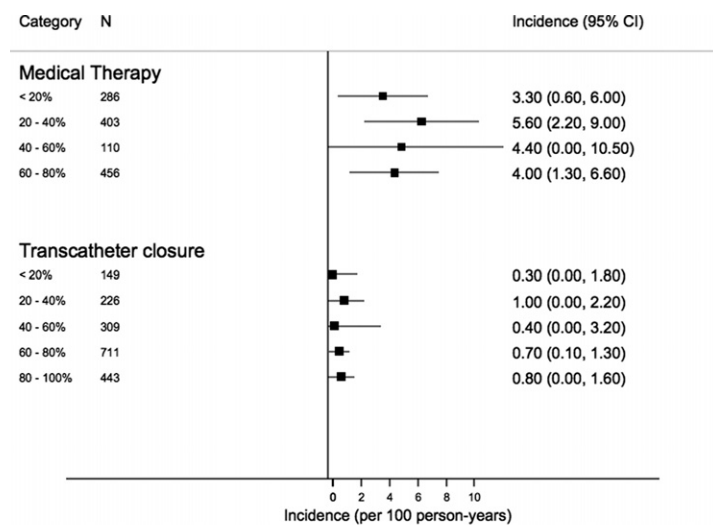

Figure 5. Impact of Pre-Treatment Shunt Size Upon Recurrent Neurological Events

Incidence (per 100 person-years) categorized by the proportion of patients with pre-treatment large shunts in the 2 treatment arms. CI = confidence interval.

PFO significantly increases the risk of recurrent thromboembolic episodes (19,64). Our meta-analysis demonstrated that there was no significant difference in the rate of RNE between patients with or without thrombophilia undergoing transcatheter closure. This might imply that the transcatheter PFO closure helps alleviate the risk of RNE among patients with thrombophilia to the levels encountered by those without any hypercoagulable state.

Clinical perspective. Despite over 15,000 closure procedures reported in the published data, controversy still persists with regard to indication for transcatheter PFO closure over medical therapy. There are several ongoing randomized trials comparing the efficacy of transcatheter PFO closure with medical therapy in prevention of recurrent thromboembolic events; the CLOSURE 1 trial is the only completed trial (2). Why do we find suggestion of benefit with observational studies but were not able to prove that in the CLOSURE 1 trial? There are several interesting points about the trial that are worth considering. One, the trial included patients with stroke and TIA. Two, many recurrent strokes reported in the trial were device-related. Three, the cause of recurrent stroke was not PTE in most patients. The trial suggested that all patients with neurological symptoms and concomitant PFO should not undergo transcatheter PFO closure. However, our meta-analysis suggests that real-world selection of high-risk patients where PFO was more likely to be the cause of the stroke is likely to be a more beneficial strategy in successful prevention of RNE after transcatheter closure. How would we accomplish this? Meticulous attention to patient selection with detailed history and work-up to eliminate other etiologies of stroke and maximizing the likelihood of PTE as an etiology for stroke by detailed evaluation of PFO morphology and thrombophilia can help identify patients at risk of RNE secondary to PTE through a PFO. Furthermore, our meta-analysis clearly suggests that, among patients destined to medical management, use of anticoagulant therapy is far superior to antiplatelet therapy alone for prevention of RNE. Barring definite contraindication to warfarin use, anticoagulant therapy should be strongly preferred for stroke prevention in medically managed patients who present with PTE.

Study limitations. The choice of medical therapy versus transcatheter closure is usually dependent on the preference of the patient for a particular therapy, allowing a self-selection bias. Systematic pooling of different observational studies with different baseline characteristics might induce some imprecision in the results due to heterogeneity. Several studies included in the meta-analysis have small numbers or have short follow-up periods. Due to relative rarity of RNE after transcatheter closure, recurrent events are more likely to be observed in larger study samples with a longer follow-up period.

The present meta-analysis is limited by the possibility of a strong selection bias, which forms at least 1 rationale for conducting the study. Several studies might report erroneous estimates due to inclusion of patients who have “undiagnosed yet unrelated” source of thromboembolism rather than PTE secondary to PFO (Fig. 7). There exists a chance that the results might be fundamentally skewed in a nonrandom fashion when comparing one population (transcatheter) to another (medical therapy). Despite these limitations, our meta-analysis seeks to clarify an extensive and confusing published data by systematic organization and aggregation of available information.

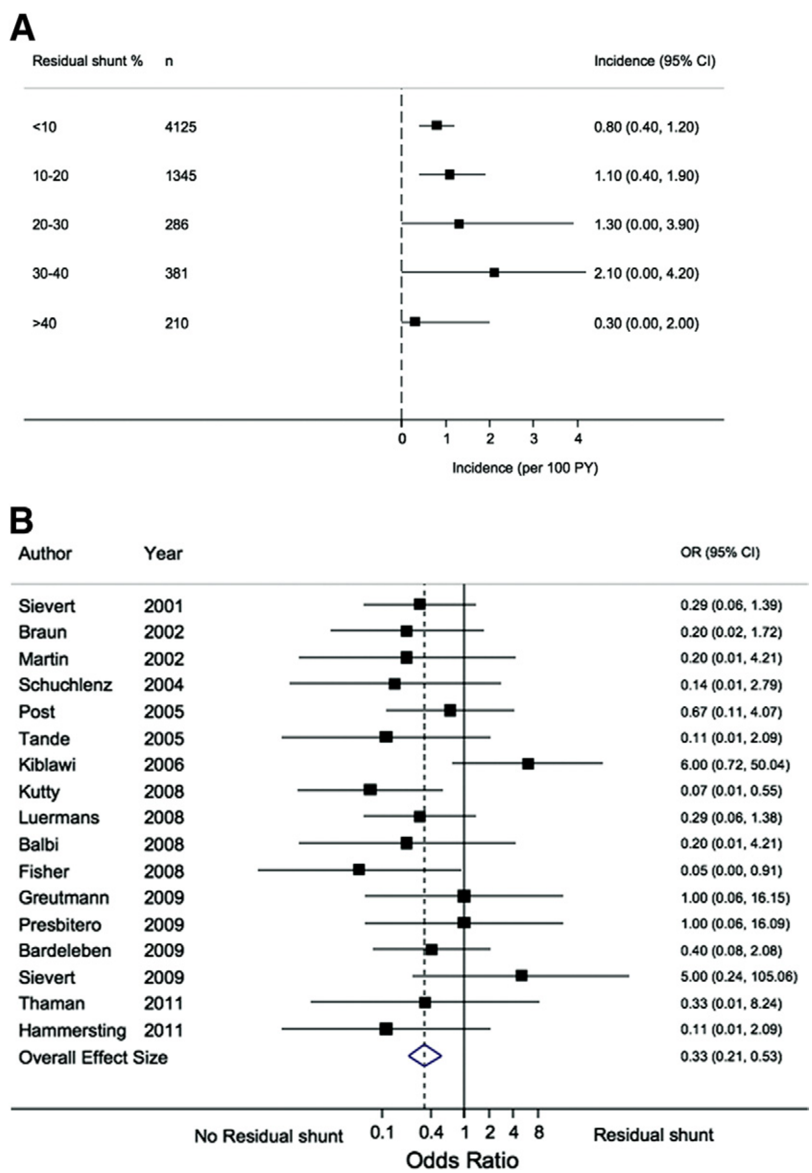

Figure 6. Effect of Post-Procedure Residual Shunt on Recurrent Neurological Events

(A) Incidence of recurrent events stratified by percent residual shunt reported. **(B)** Odds of presence versus absence of residual shunt in patients with a recurrent thromboembolic event. CI = confidence interval; OR = odds ratio; PY = person-years.

Conclusive data from the ongoing randomized control trials would help clarify this question in a more definitive manner.

Conclusions

Accepting the limitations of this comparative meta-analysis of observational studies, we observed that transcatheter PFO closure was associated with an 84% reduction in the rate of RNE compared with medical management (0.8 events/100 PY compared with 5.0 events/100 PY). Comparison of the anticoagulation and antiplatelet therapy subgroups of the medical arm yielded a significantly lower risk of RNE in patients treated with anticoagulants. Device-related complications were encountered at the rate of 4.1 events/100 PY, with atrial arrhythmias being the most frequent complication. The risk of recurrent thromboembolism did not seem to be related to presence of residual shunting in the follow-up period. Significant benefit of transcatheter PFO closure was apparent in elderly patients, patients with concomitant ASA, and patients with thrombophilia.

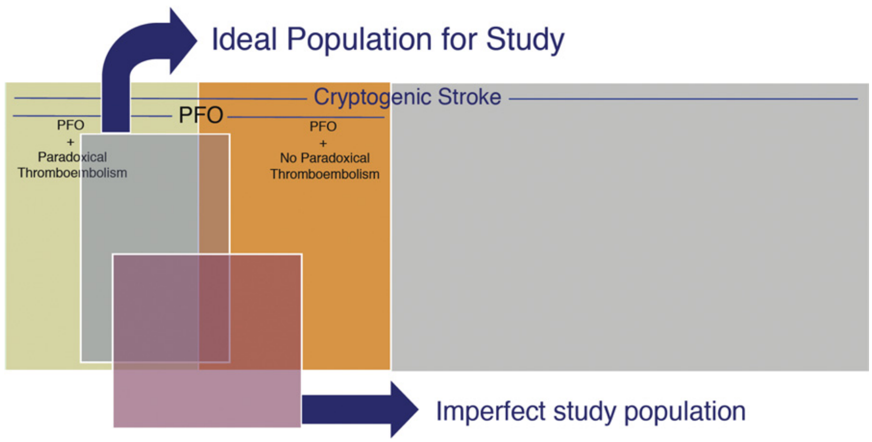

Figure 7. Choice of Patient Population for Transcatheter Closure of PFO

Schematic diagram depicting an ideal population for transcatheter closure of patent foramen ovale (PFO) that would likely benefit from this treatment. On the contrary, the "imperfect population" where PFO is not the cause of thromboembolism is unlikely to derive any benefit from transcatheter PFO closure.

Reprint requests and correspondence: Dr. Samir R. Kapadia, Sones Cardiac Catheterization Laboratories, Department of Cardiovascular Medicine, J2–3, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: kapadis@ccf.org.

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