Review

Percutaneous Closure versus Medical Therapy Alone

for Cryptogenic Stroke Patients with a Patent Foramen Ovale: Meta-Analysis of Randomized Controlled Trials

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Of cryptogenic stroke patients younger than 55 years of age, up to 61% have had a patent foramen ovale (PFO). Observational studies have revealed reductions in recurrent neurologic events through PFO closure versus medical therapy, and randomized controlled trials have shown nonsignificant trends toward benefit. We systematically searched for randomized controlled trials of percutaneous PFO closure with medical therapy versus medical therapy alone in patients with cryptogenic stroke and performed a meta-analysis of treatment outcomes. The primary endpoint was combined death, stroke, and transient ischemic attack.

We included 3 trials. Of 2,303 total patients, 1,150 underwent PFO closure and 1,153 received medical therapy (median follow-up period, 2.6 yr). The pooled incidence of the primary endpoint was 1.2 events per 100 patient-years in the closure group (95% confidence interval [CI], 0.2–2.3) and 1.8 in the therapy group (95% CI, 0.7–2.9) (P=0.32); the number needed to treat was 167 (range, 100–500). The corresponding pooled hazard ratio was 0.67 (95% CI, 0.44–1.01; P=0.054) in favor of closure. Closure was associated with an increased risk of atrial fibrillation: relative risk=3.51 (95% CI, 1.44–8.55; P=0.006). When stratified by device, use of the AMPLATZER™ PFO Occluder resulted in significant stroke-prevention benefit over medical therapy alone: hazard ratio=0.44 (95% CI, 0.21–0.95; P=0.037).

When compared with medical therapy alone, PFO closure with medical therapy showed a trend toward a decreased hazard of combined events, although the absolute event reduction was small and the number needed to treat was high. ***(Tex Heart Inst J 2014;41(4):357-67)***

Key words: *Cerebral infarction/etiology; foramen ovale, patent/complications/drug therapy/economics/surgery; ischemic attack, transient/etiology/prevention & control; logistic models; meta-analysis; odds ratio; randomized controlled trials as topic; risk factors; septal occluder device; stroke/drug therapy/etiology/prevention & control*

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Up to 61% of cryptogenic stroke patients younger than 55 years of age have reportedly had a patent foramen ovale (PFO), and evidence from observational studies suggests an association between cryptogenic stroke and PFO.[1-5] Furthermore, the presence of PFO is associated with a 3-fold increased risk of recurrent stroke.[6] Therefore, it has been postulated that PFO closure would result in a decreased risk of recurrent neurologic events (transient ischemic attack [TIA], stroke, or death due to stroke) through the elimination of the conduit for paradoxical embolism. One meta-analysis of observational studies of cryptogenic stroke patients yielded a rate of 0.8 recurrent neurologic events per 100 patient-years after percutaneous PFO closure, versus 5 events among patients on medical therapy.[7] In randomized controlled trials (RCTs) in which percutaneous PFO closure plus medical therapy was compared with medical therapy alone in patients with cryptogenic stroke or TIA, results have shown a nonsignificant trend toward the benefit of PFO closure.[8-10] We undertook a meta-analysis of RCTs to investigate whether percutaneous PFO closure plus medical therapy reduces the risk of stroke, TIA, and death in comparison with medical therapy alone.

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Patients and Methods

We systematically searched PubMed®, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials for RCTs of PFO closure that had been published from January 1996 through 21 September 2013.[11] We used the search terms and corresponding MeSH headings for "patent foramen ovale closure" limited to adult human RCTs from 1996 through 21 September 2013. The full syntax was as follows: ((("foramen ovale, patent"[MeSH terms] OR ("foramen"[All Fields] AND "ovale"[All Fields] AND "patent"[All Fields]) OR "patent foramen ovale"[All Fields] OR ("patent"[All Fields] AND "foramen"[All Fields] AND "ovale"[All Fields])) AND closure[All Fields]) AND Clinical Trial[ptyp].

We did not limit the search by language. In addition, we searched the references of all retrieved articles. We excluded observational studies and studies that had not enrolled cryptogenic stroke or TIA patients.

Two investigators (CAP and TCV) independently abstracted the following data with use of a standardized data-extraction form: characteristics of the study, intervention, and patients; and outcomes, including the composite or combined endpoint (CEP) as defined by the trials, as well as stroke, TIA, death, major vascular sequelae, and atrial fibrillation.

We evaluated the incidence of each clinical outcome per patient-year. Outcomes were organized into 2 × 2 tables and were pooled by means of fixed- and random-effects models for the primary analysis of the incidence of the CEP, stroke, TIA, and death. There was no difference in results between the 2 models. Log relative risks were calculated from events per patient-year reported within each study and were similarly pooled. Log hazard ratios (HRs) were pooled from the HRs and corresponding confidence intervals (CIs) reported in each study. To pool adverse events, we created 2 × 2 tables for reported major bleeding, major vascular sequelae, and atrial fibrillation. The HRs for individual and combined adverse events were pooled in accordance with a random-effects model. The primary outcome of each trial was pooled through an intention-to-treat (ITT) approach. In addition, per-protocol comparison and stratification by closure device were performed.

Heterogeneity was examined visually by using Galbraith plots, and statistically by using Q statistics and I^2. The I^2 statistic provides an estimate of the variance due to heterogeneity rather than chance and is based on the traditional measure of variance, the Cochrane Q statistic.[12] We evaluated small-study effects by using the method of Peters and colleagues.[13]

Two investigators (CAP and TCV) independently evaluated study quality on a 0–8 scale in accordance with the Jadad criteria for RCT reporting.[14] The same investigators also evaluated studies by means of the Cochrane tool for determining the risk of bias in randomized trials.[15] Disagreements were resolved by consensus.

All statistical analyses were performed with use of Stata® v12.1 software (StataCorp LP; College Station, Texas) and the metan commands. All *P* values were 2-sided with an alpha of 0.05.

Results

Figure 1 shows the results of the literature search. Three RCTs were included: the Evaluation of the STARFlex® Septal Closure System in Patients with a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin through a Patent Foramen Ovale (CLOSURE I),[8] the RESPECT PFO Clinical Trial,[9] and the PC Trial: Patent Foramen Ovale and Cryptogenic Embolism.[10] Of the 2,303 patients included, 1,150 underwent PFO closure plus medical therapy, and 1,153 were given medical therapy alone. The CLOSURE I trial involved the use of the STARFlex® Septal Closure System (no longer manufactured); the other 2 trials used the AMPLATZER™ PFO Occluder (AGA Medical, now part of St. Jude Medical, Inc.; St. Paul, Minn).

Table I shows the baseline characteristics of the patients. The mean age of the population was 45.7 ± 9.7 years, and there were 1,213 males (52.7%). The baseline risk factors did not differ significantly between PFO closure and medical therapy alone as reported in the individual trials. In all the studies, the PFO-closure patients tended to have a higher degree of shunting across the PFO; and in the closure group of the CLOSURE I trial, there was a significantly higher prevalence of hyperlipidemia.

The trials had similar eligibility criteria. However, CLOSURE I included patients who had a clinically verified TIA, whereas the PC Trial and the RESPECT Trial required clinical and radiologic verification of the neurologic event (Table II). The PC Trial investigators enrolled a small number of patients who had been referred for PFO closure after peripheral thromboembo-

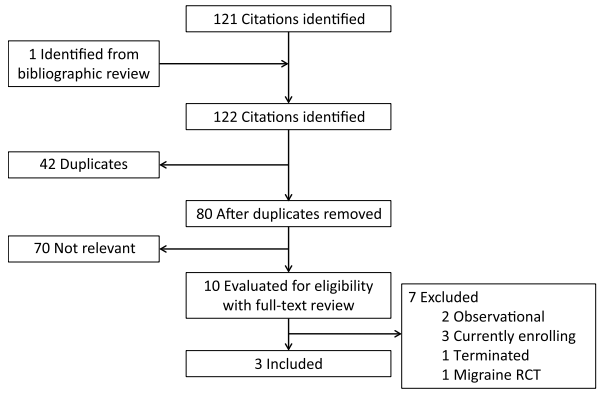

Fig. 1 *Diagram shows the results of the literature search.*

RCT = randomized controlled trial

TABLE I. Characteristics of the Patients in the Meta-Analysis

Variable	CLOSURE I[8]	PC Trial[10]	RESPECT[9]	Pooled
Device	STARFlex® Septal Closure System	AMPLATZER™ PFO Occluder	AMPLATZER™ PFO Occluder	—
Location	United States	Europe, Canada, Australia, and Brazil	United States and Canada	—
Total patients	909	414	980	2,303
PFO closure	447 (49.2)	204 (49.3)	499 (50.9)	1,150 (49.9)
Medical therapy	462 (50.8)	210	481 (49.1)	1,153 (50.1)
Follow-up (yr)	2	4.1	2.6	2.6
Medical therapy for closure patients	Aspirin and clopidogrel	Aspirin and ticlopidine or clopidogrel for 6 mo	Clopidogrel for 1 mo and aspirin for 6 mo	—
Medical therapy for nonclosure patients	PI: aspirin, warfarin, or both	PCM: aspirin or warfarin	PCM: aspirin, warfarin, clopidogrel, aspirin and dipyridamole, or aspirin and clopidogrel	
Closure Patients				
Age (yr)	46.3 ± 9.6	44.3 ± 10.2	45.7 ± 9.7	45.7 ± 9.7
Age range (yr)	18–60	<60	18–60	—
Male	233 (52.1)	92 (45.1)	268 (53.7)	593 (51.6)
Smoker	96 (21.5)	52 (25.5)	75 (15)	223 (19.4)
Hypertension	151 (33.8)	49 (24)	158 (31.7)	358 (31.1)
Hyperlipidemia	212 (47.4)	50 (24.5)	194 (38.9)	456 (39.7)
Diabetes mellitus	NR	5 (2.5)	33 (6.6)	38 (5.4)
Family history of stroke or CAD	247 (55.3)	53 (26)	135 (27.1)	435 (37.8)
Migraine headache	NR	47 (23)	195 (39.1)	242 (34.4)
Congestive heart failure	2 (0.4)	NR	3 (0.6)	5 (0.5)
CAD	6 (1.3)	4 (2)	19 (3.8)	29 (2.5)
Myocardial infarction	7 (1.6)	3 (1.5)	5 (1)	15 (1.3)
Valvular disease	49 (11)	8 (3.9)	NR	57 (8.8)
Arrhythmia	26 (5.8)	NR	NR	26 (5.8)
Cardiac catheterization	23 (5.1)	NR	NR	23 (5.1)
PTCA	6 (1.3)	NR	NR	6 (1.3)
Peripheral vascular disease	5 (1.1)	3 (1.5)	5 (1)	13 (1.1)
Stokes-Adams syndrome	4 (0.9)	NR	NR	4 (0.9)
Pulmonary embolism	0	NR	NR	0
Pericarditis	2 (0.4)	NR	NR	2 (0.4)
Cardiomyopathy	1 (0.2)	NR	NR	1 (0.2)
Index cryptogenic stroke	324 (72.5)	165 (80.9)	53 (10.6)	542 (47.1)
Index TIA	122 (27.3)	33 (16.2)	58 (11.6)	213 (18.5)
Index peripheral embolism	NR	6 (2.9)	20 (4) [DVT]	26 (3.7)
>1 previous TIA or stroke	NR	76 (37.3)	NR	76 (37.3)
TEE with moderate-to-severe shunt	250 (55.9)	130/185* (70.2)	385 (77.2)	765 (67.6)
Atrial septal aneurysm >10 mm	168 (37.6)	47 (23)	180 (36.1)	395 (34.3)

Table 1 continues on next page.

TABLE I continued. Demographic Characteristics of the Patients in the Meta-Analysis

Variable	CLOSURE I[8]	PC Trial[10]	RESPECT[9]	Pooled
Medical Therapy Patients				
Age (yr)	45.7 ± 9.1	44.6 ± 10.1	46.2 ± 10	45.7 ± 9.7
Age range (yr)	18–60	<60	18–60	—
Male	238 (51.5)	114 (54.3)	268 (55.7)	620 (53.8)
Smoker	104 (22.5)	47 (22.4)	55 (11.4)	206 (17.9)
Hypertension	131 (28.4)	58 (27.6)	150 (31.2)	339 (29.4)
Hyperlipidemia	189 (40.9)	62 (29.5)	193 (40.1)	444 (38.5)
Diabetes mellitus	NR	6 (2.9)	40 (8.3)	46 (6.7)
Family history of stroke or CAD	257 (55.6)	40 (19)	108 (22.5)	405 (35.1)
Migraine headache	NR	38 (18.1)	185 (38.5)	223 (32.3)
Congestive heart failure	0	NR	0	0
CAD	4 (0.9)	4 (1.9)	9 (1.9)	17 (1.5)
Myocardial infarction	5 (1.1)	1 (0.5)	2 (0.4)	8 (0.7)
Valvular disease	45 (9.7)	5 (2.4)	NR	50 (7.4)
Arrhythmia	19 (4.1)	NR	NR	19 (4.1)
Cardiac catheterization	17 (3.7)	NR	NR	17 (3.7)
PTCA	2 (0.4)	NR	NR	2 (0.4)
Peripheral vascular disease	7 (1.5)	2 (1)	1 (0.2)	10 (0.9)
Stokes-Adams syndrome	3 (0.6)	NR	NR	3 (0.6)
Pulmonary embolism	4 (0.9)	NR	NR	4 (0.9)
Pericarditis	3 (0.6)	NR	NR	3 (0.6)
Cardiomyopathy	0	NR	NR	0
Index cryptogenic stroke	329 (71.2)	163 (77.6)	51 (10.6)	543 (47.1)
Index TIA	132 (28.6)	42 (20)	61 (12.7)	235 (20.4)
Index peripheral embolism	NR	5 (2.4)	15 (3.1) [DVT]	20 (2.9)
>1 previous TIA or stroke	NR	79 (37.6)	NR	79 (37.6)
TEE with moderate-to-severe shunt	231 (50)	112/184* (60.9)	352 (73.2)	695 (61.7)
Atrial septal aneurysm >10 mm	165 (35.7)	45 (21.4)	169 (35.1)	379 (32.9)

CAD = coronary artery disease; DVT = deep vein thrombosis; NR = not reported; PCM = primary care manager determined the medical therapy; PFO = patent foramen ovale; PI = primary investigator determined the medical therapy; PTCA = percutaneous transluminal coronary angioplasty; TEE = transesophageal echocardiography; TIA = transient ischemic attack

*Only 185 of the closure patients and 184 of the medical therapy patients underwent transesophageal echocardiography in advance.

Data are expressed as mean ± SD or as frequency and percentage.

TABLE II. Inclusion Criteria by Study

CLOSURE I[8]	PC Trial[10]	RESPECT[9]
TIA or stroke within 6 mo	Clinically or image-confirmed stroke, TIA with image-confirmed ischemia, or clinically or image-confirmed extracranial embolic event	Image-confirmed ischemia if <24 hr; clinical ischemia if >24 hr

TIA = transient ischemic attack

lism (2.7%). With minor deviation, the 3 trials also had similar definitions of the CEP (Table III). The RESPECT investigators did not include TIA in the primary endpoint (6 TIAs occurred after PFO closure vs 4 in the medical therapy group), and the PC Trial investigators included peripheral embolism in the CEP (however, no events of that type occurred).

Table IV shows the absolute incidence of clinical outcomes for each study. The pooled estimate of the CEP for PFO closure was 1.2 events per 100 patient-years (95% CI, 0.2–2.3) versus 1.8 for medical thera-

py (95% CI, 0.7–2.9; P=0.32; I^2=0) (Fig. 2A). The number needed to treat (NNT) to prevent one CEP by means of closure was 167 (95% CI, 100–500; P=0.32). In comparing closure with therapy, the HR for the CEP was 0.67 (95% CI, 0.44–1.01, P=0.054; I^2=0) (Fig. 3). Upon analysis of patients who were successfully treated according to protocol assignment (per-protocol analysis), the HR for the CEP in closure versus therapy was 0.64 (95% CI, 0.41–0.98; P=0.04; I^2=0) (Fig. 4).

The pooled estimate of death for PFO closure was 0.2 events per 100 patient-years (95% CI, 0–0.5), versus 0.4 for medical therapy alone (95% CI, 0–0.8; P=0.4; I^2=0) (Fig. 2B). The NNT to reduce one death with closure was 500 (95% CI, 167–**; P=0.4) (** = the upper limit of NNT could not be estimated, because the 95% CI for the pooled absolute risk difference crossed zero). Because of incomplete survival data in the original studies, the HR in support of closure was not calculated.

The pooled estimate of stroke for PFO closure was 0.9 events per 100 patient-years (95% CI, 0.2–1.5) versus 1.0 for medical therapy (95% CI, 0.4–1.5; P=0.44; I^2=0) (Fig. 2C). The NNT to reduce one stroke with closure was 250 (95% CI, 111–**; P=0.44). The HR in support of closure was 0.62 (95% CI, 0.35–1.11) (Fig. 5).

The pooled estimate of TIA for PFO closure was 0.6 events per 100 patient-years (95% CI, 0.1–1.1) versus

TABLE III. Definition of Primary Endpoint by Study

Variable	CLOSURE I[8]	PC Trial[10]	RESPECT[9]
Device	STARFlex Septal Closure System	AMPLATZER PFO Occluder	AMPLATZER PFO Occluder
Definition of primary endpoint	Sum of stroke + TIA + any death <30 d + death from neurologic cause >30 d	Sum of stroke + TIA + any death + peripheral embolism*	Sum of stroke + any death <30 d + stroke death

PFO = patent foramen ovale; TIA = transient ischemic attack

*No peripheral embolization occurred

TABLE IV. Outcomes by Study

Variable	CLOSURE I[8]	PC Trial[10]	RESPECT[9]
Device	STARFlex Septal Closure System	AMPLATZER PFO Occluder	AMPLATZER PFO Occluder
Total patients	909	414	980
Closure	447	204	499
Medical therapy	462	210	481
Follow-up (yr)	2	4.1	2.6
Follow-up SD (yr)	NR	NR	2
Primary endpoint			
Closure patients	23	7	9
Medical therapy patients	29	11	16
Stroke			
Closure patients	12	1	9
Medical therapy patients	13	5	16
Transient ischemic attack			
Closure patients	13	5	6
Medical therapy patients	17	7	4
Death			
Closure patients	2	2	3
Medical therapy patients	4	0	6
Major vascular sequela			
Closure patients	13	0	2
Medical therapy patients	0	0	0
Atrial fibrillation			
Closure patients	23	6	15
Medical therapy patients	3	2	7

NR = not reported; PFO = patent foramen ovale

Absolute incidences are reported, which differ from pooled weighted incidences.

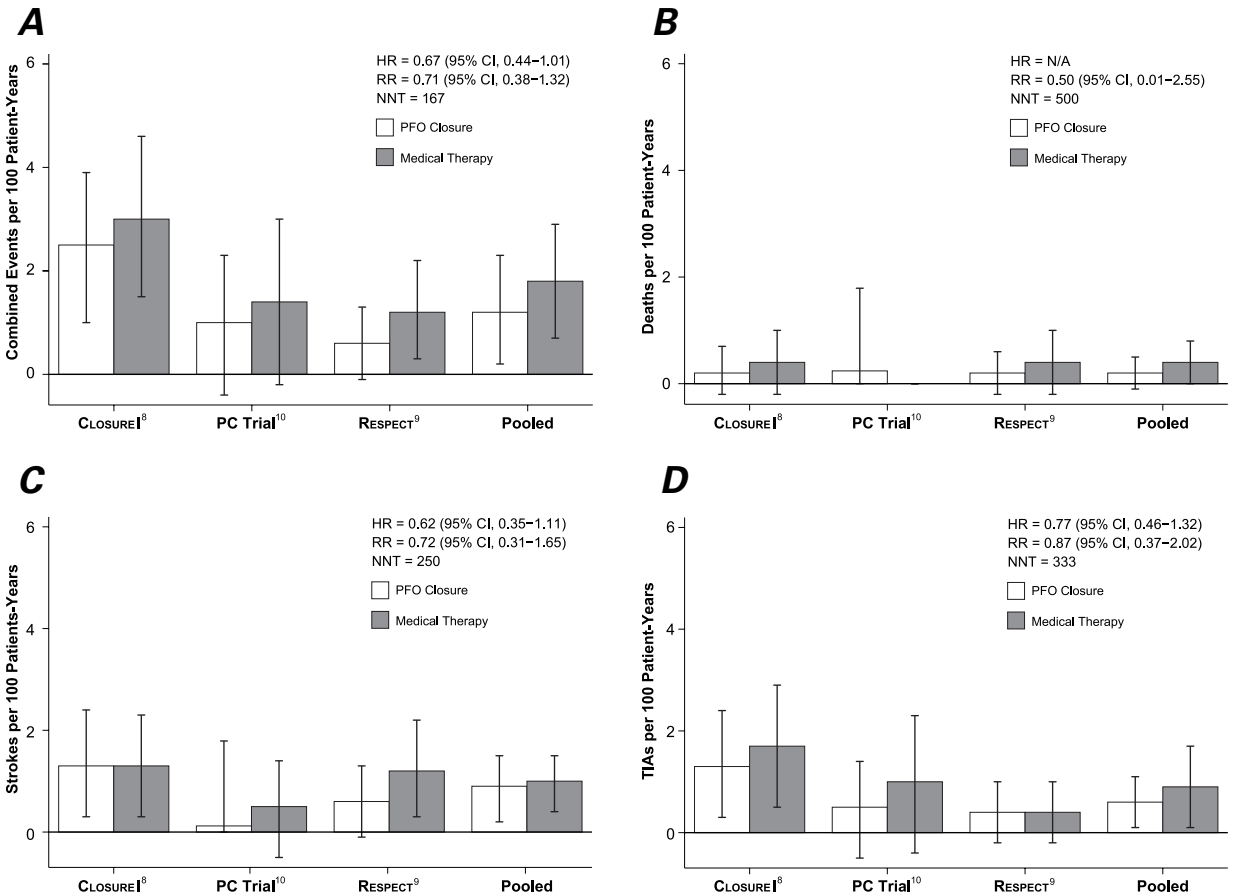

Fig. 2 *Graphs show the pooled rates of **A**) the primary endpoint, **B**) death, **C**) stroke, and **D**) transient ischemic attack, per 100 patient-years. The upper limit of NNT could not be estimated, because the 95% CI for the pooled absolute risk difference crosses zero.*

CI = confidence interval; HR = hazard ratio; NNT = number needed to treat; PFO = patent foramen ovale; RR = relative risk; TIA = transient ischemic attack

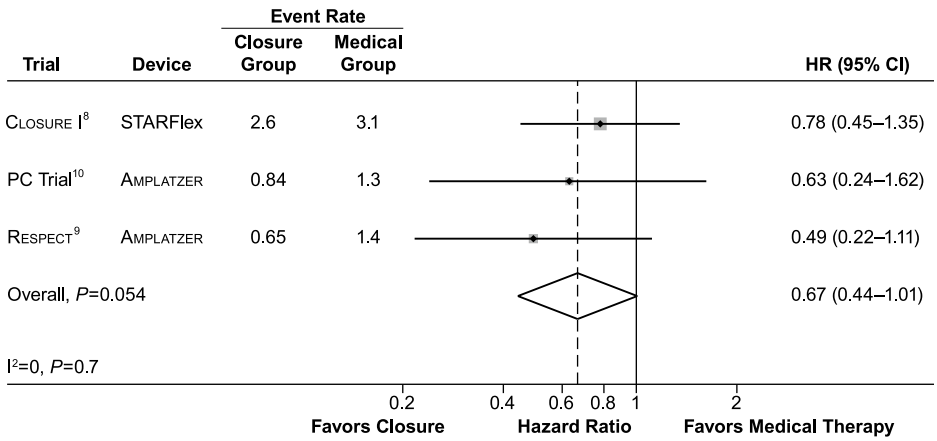

Fig. 3 *Forest plot shows the hazard ratio of the primary endpoint (intention-to-treat analysis). Event rates are per 100 patient-years.*

CI = confidence interval; HR = hazard ratio

P <0.05 was considered statistically significant.

0.9 for medical therapy alone (95% CI, 0.1–1.7; P=0.7; I^2=0) (Fig. 2D). The NNT to reduce one TIA with closure was 333 (95% CI, 167–**; P=0.7). The HR in support of closure was 0.77 (95% CI, 0.46–1.32) (Fig. 6).

Fifteen major vascular sequelae occurred in the closure group (Fig. 7). By design, no procedural sequelae occurred during medical therapy; therefore, no relative risk (RR) could be calculated. The prevalence of atrial fibrillation was also higher in the closure group: RR=3.51 (95% CI, 1.44–8.55; P=0.005; and I^2=99%, P <0.001). The rate of major bleeding episodes was similar: RR=1.3 (95% CI, 0.34–4.98; P=0.7; and I^2=99%, P <0.001). The absolute incidence of adverse events was not high,

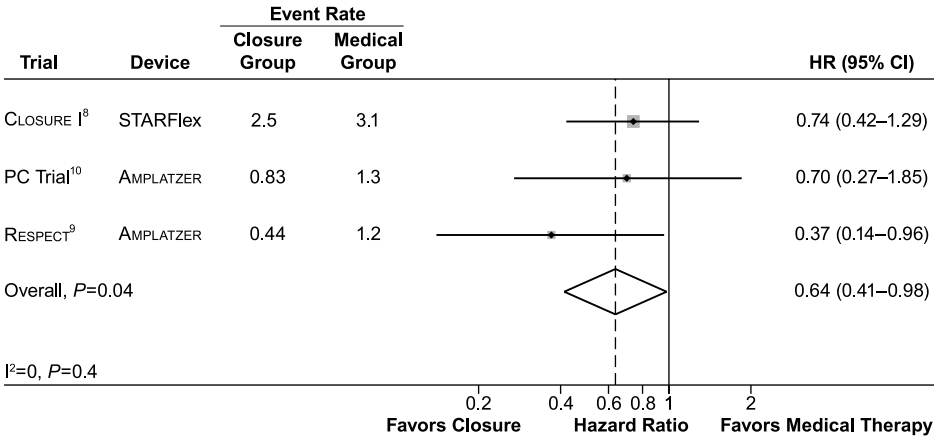

Fig. 4 *Forest plot shows the hazard ratio of the primary endpoint (per-protocol analysis). Event rates are per 100 patient-years.*

CI = confidence interval; HR = hazard ratio

P *<0.05 was considered statistically significant.*

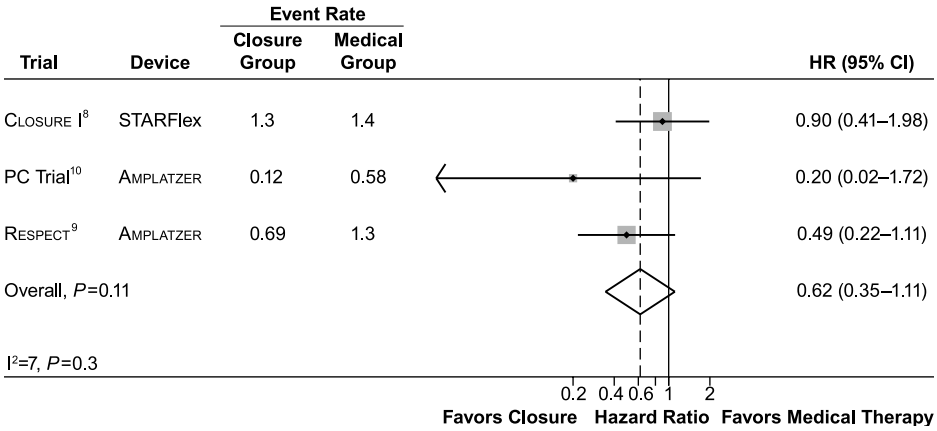

Fig. 5 *Forest plot shows the hazard ratio of stroke. Event rates are per 100 patient-years.*

CI = confidence interval; HR = hazard ratio

P *<0.05 was considered statistically significant.*

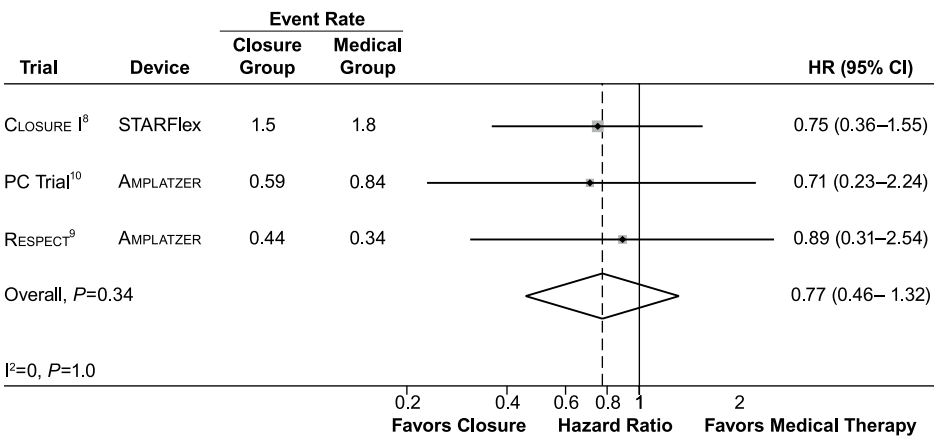

Fig. 6 *Forest plot shows the hazard ratio of transient ischemic attack. Event rates are per 100 patient-years.*

CI = confidence interval; HR = hazard ratio

P *<0.05 was considered statistically significant.*

and the pooled risk estimate should be considered exploratory, because of high heterogeneity (I^2=99%).

The PC Trial and RESPECT investigators reported losses to follow-up that were greater in each trial's medical therapy group (Fig. 8). For closure versus medical therapy, the overall odds ratio (OR) of being lost to follow-up was 0.76 (95% CI, 0.39–1.45; *P*=0.4). The significant heterogeneity in losses to follow-up between studies (I^2=70%; *P*=0.035) was probably due to the small number of included studies.

All 3 studies were considered to be of high quality (median Jadad score, ≥5 of 8). Inter-rater agreement was excellent for data extraction (κ=1), and agreement was good for the Jadad (κ=0.89) and Cochrane (κ=0.57) quality-assessment criteria. All 3 studies were open-label and unmasked. Blinding to study group was performed

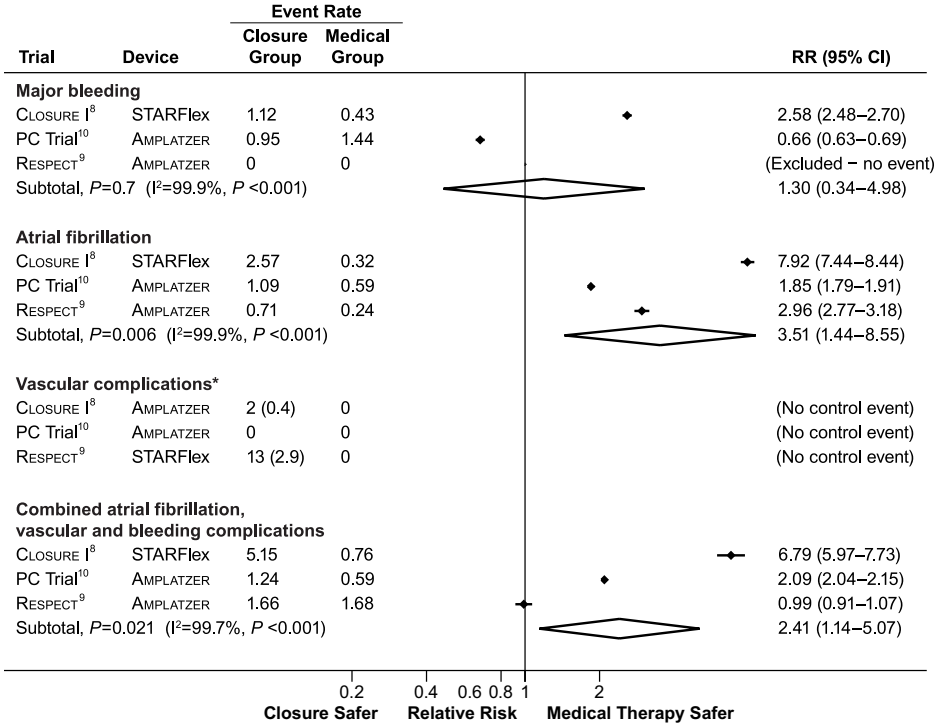

Fig. 7 *Forest plot shows the relative risk of major vascular sequelae.**

CI = confidence interval; RR = relative risk

**Depicted as incidental events; no relative risk is presented, because of no event in the control group for this outcome.*

P <0.05 was considered statistically significant.

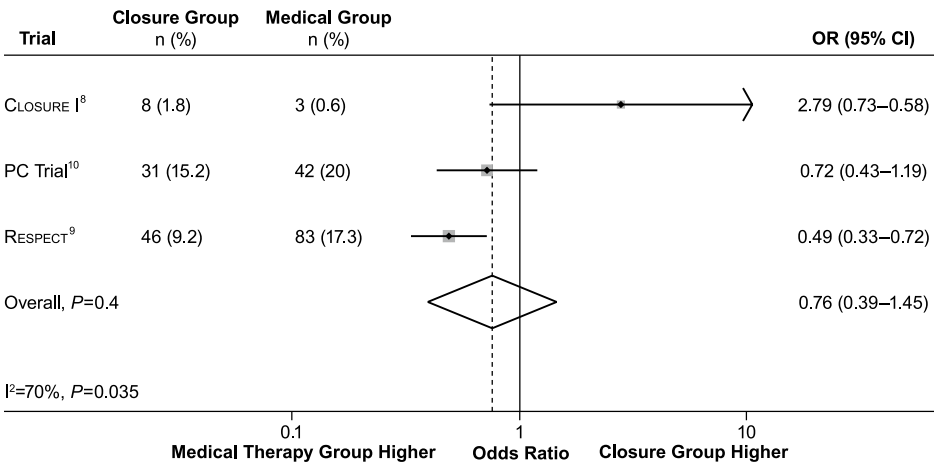

Fig. 8 *Forest plot shows the loss to follow-up in the trials.*

CI = confidence interval; OR = odds ratio

P <0.05 was considered statistically significant.

during event adjudication. There was no evidence of publication bias ($P=0.6$). However, given the small number of studies included in our analysis, the addition of even one trial could easily change our conclusion about the presence or absence of publication bias.

No single study excessively influenced the outcome of the primary analyses. A subgroup analysis of the AMPLATZER device trials (PC Trial and RESPECT) (Fig. 9) shows that the HR for the CEP remained similar: HR=0.55 (95% CI, 0.29–1.02; $P=0.056$; $I^2=0$). However, the HR for stroke became significant: HR=0.44 (95% CI, 0.21–0.95; $P=0.037$; $I^2=0$).

Procedural Costs. Assuming a Medicare reimbursement of $8,703 per PFO closure[16] and an NNT of 167 (95% CI, 100–500), the estimated procedural cost to prevent one combined event would be $1,453,401 (95% CI, $870,300–$4,351,500).

Discussion

In this meta-analysis, we observed that closure was associated with a nonsignificant trend toward reduced combined adverse events in the ITT analysis and a significant reduction of events in the per-protocol analysis.

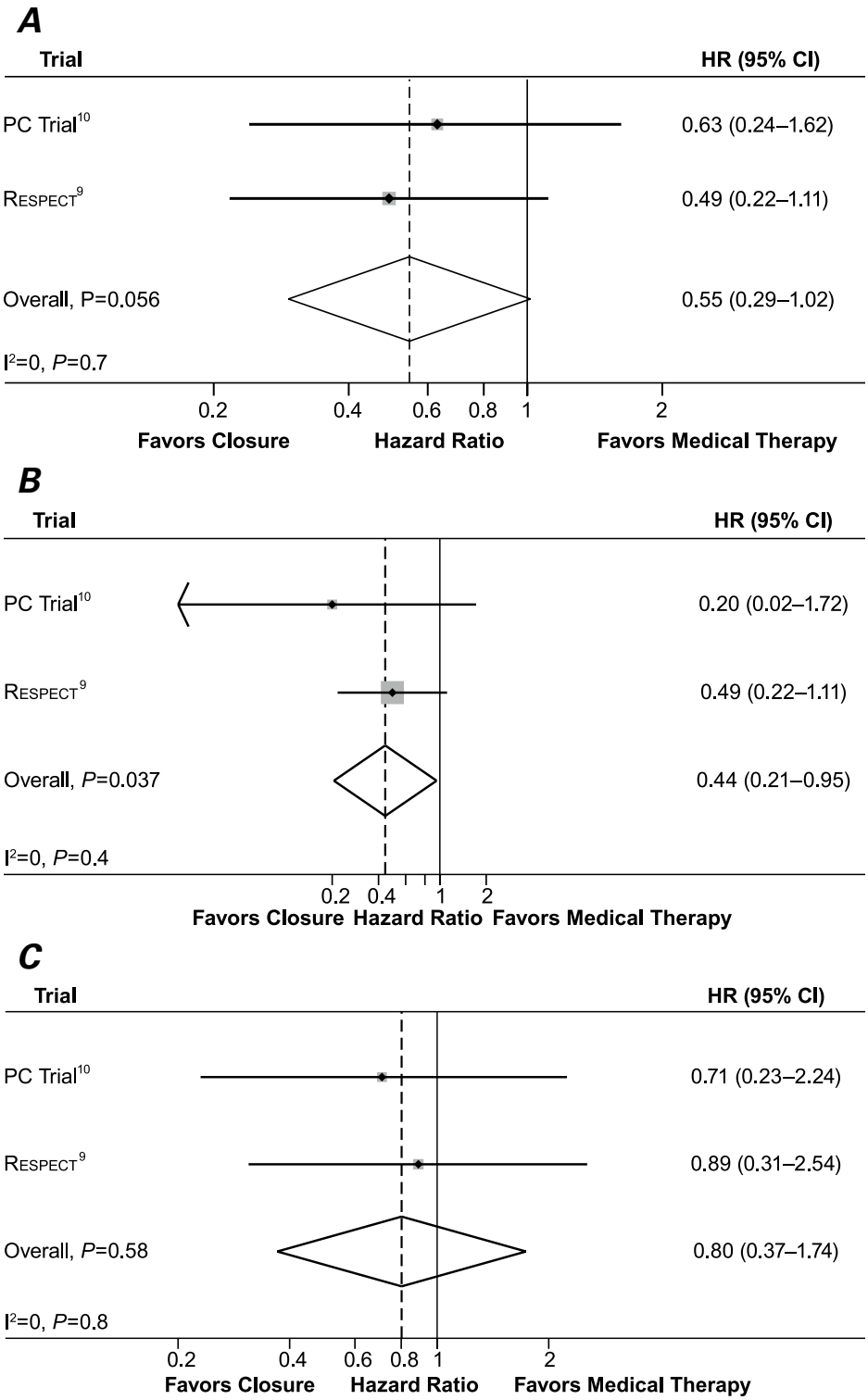

Fig. 9 *Forest plots show* AMPLATZER *subgroup analysis of* ***A****) the primary endpoint,* ***B****) stroke, and* ***C****) transient ischemic attack.*

CI = confidence interval; HR = hazard ratio

P *<0.05 was considered statistically significant.*

In the ITT analysis, stroke reduction was significant when only the AMPLATZER device trials were considered. However, the absolute risk reduction for the total CEP and each subordinate CEP was small when analyzed from the ITT approach.

These data suggest that, in the included trials, the clinical benefit of PFO closure is minimal and unclear in comparison with the relatively heterogeneous medical therapy; this conclusion requires further study. Other investigators[17-21] concurrently conducted similar analyses of RCT studies of PFO closure (although some also pooled their data with those of observational studies) and published their findings during 2013 and 2014. Our meta-analysis independently confirms their

important finding that PFO closure in RCTs has a nonsignificant hazard reduction for stroke. In addition, our analysis reveals the small clinical-event rates, the small absolute risk reduction for PFO closure, and the high NNT, which are important considerations in any preventive intervention. As we and the other investigators noted, PFO closure is associated with higher rates of incident atrial fibrillation, major vascular sequelae, and initial cost. Although we did not choose to pool observational and randomized data, we noted, as did Wolfrum and colleagues,[17] that meta-analysis of RCTs revealed less benefit for PFO closure than did a prior meta-analysis of observational studies.[7] This is most likely due to referral bias and uncontrolled confounding in nonrandomized trials.

Although the small number of RCTs restricted our ability to conduct extensive subgroup analysis, we nevertheless observed important differences between the studies. First, CLOSURE I had the least significant result for PFO closure, but notably used the STARFlex device, which is no longer manufactured. Results of the subgroup analysis of the 2 AMPLATZER trials showed significance for the reduction of recurrent stroke, although the absolute risk reduction was small. In addition, the RESPECT investigators sought to enroll higher-risk patients—excluding TIA as an enrollment criterion—which might have led to a stronger effect size for this trial. In contrast, the PC Trial investigators included a small subgroup of patients who had been referred because of peripheral embolism (2.7%). This was perhaps a lower-risk group than were patients with cryptogenic stroke or TIA, although the overall impact of such a small subgroup might have been negligible.

The comparative safety of the closure devices (STARFlex vs AMPLATZER) should be considered. In CLOSURE I, the rate of atrial fibrillation was higher than in the PC Trial. An increased risk of atrial fibrillation from the STARFlex device had been shown previously, and this occluder was also known for a higher risk of device thrombus.[22] Our pooled analysis showed that the rate of atrial fibrillation for all devices was significantly higher than that for medical therapy alone. Another consideration is the overall low absolute-event rate of recurrent neurologic events. The debilitating public-health and economic consequences of recurrent neurologic events in this relatively young population should be weighed against the estimated $1.5 million cost of the procedures and devices needed to prevent one event. This calculation does not include the higher cost of sequelae in PFO closure, which should be weighed against the cost of medical therapy—typically lifelong antiplatelet or anticoagulation therapy—and its potential sequelae and monitoring costs. To evaluate these important competing issues, a detailed cost-effectiveness analysis is warranted. Finally, the optimal medical therapy for this patient population is undefined.

Limitations of the Meta-Analysis

Although the primary CEP of the 3 trials was similarly defined to include death and recurrent stroke, CLOSURE I and the PC Trial included TIA, whereas RESPECT did not. Accordingly, the results of RESPECT might have lowered the combined-event rate. Because of the relatively high dropout rate in 2 of the trials (particularly within the medical arms), the risk of bias is a concern. There was clinical heterogeneity both in the allocated medical therapy (no standardized definition, and varying usage of anticoagulation and antiplatelet therapy) and in the type of closure device. Additional patient-level data to examine the devices' differences and to better define optimal medical therapy are needed. Finally, this meta-analysis included only 3 studies, so the tests of publication bias are underpowered. However, the likelihood is remote that unpublished trials were excluded, given that device trials of PFO closure would be registered with the U.S. Food and Drug Administration and published on ClinicalTrials.gov.

Conclusion

In our meta-analysis of 3 large RCTs of patients with a PFO and cryptogenic stroke or TIA, we found that percutaneous PFO closure with medical therapy, when compared with medical therapy alone, showed a trend toward reducing the CEP of recurrent stroke, TIA, and death. The absolute event reduction was small, and a high NTT was necessary to prevent one recurrent event, at the expense of major vascular sequelae and atrial fibrillation.

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