**Final Draft**

of the original manuscript:

DOI: 10.1016/j.ahj.2018.03.025
Revival of Transcatheter PFO Closure: A meta-analysis of randomized controlled trials –Impact of Shunt Size and Age

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Short title:
Meta-analysis transcatheter PFO closure

Key words:
PFO closure, meta-analysis, persistent foramen ovale, cryptogenic stroke

Abstract:
Background: Transcatheter foramen ovale closure (TPC) has emerged as a potential treatment option for patients with cryptogenic strokes and persistent foramen ovale (PFO). However, previous randomized controlled trials could hardly demonstrate any benefit compared to medical treatment (Med-Tx). Recently new data have become available which may change current practice of transcatheter PFO closure.

Methods: A systematic review and meta-analysis comparing TPC and Med-Tx based on all available multicentric randomized controlled trials was performed. The primary outcome of interest was the recurrence of stroke in both groups.
**Results:** Five studies met the inclusion criteria with 1829 patients in the TPC and 1622 in the Med-Tx group. The median follow-up was 4 years. In the intention-to-treat analysis we found a statistically significant relative risk reduction in recurrence of strokes in the TPC group compared to the Med-Tx group (pooled hazard ratio (HR): 0.32; 95% CI: 0.13 - 0.8; p=0.018). Excluding one study due to publication bias resulted in a pooled HR of 0.48 (95% CI: 0.25 - 0.91, p=0.024). Patients younger than 45 years of age (pooled HR: 0.35; 95% CI: 0.16 - 0.75; p=0.007) and those with moderate to severe shunt (pooled HR: 0.28; 95% CI: 0.14 - 0.55; p<0.001) were more likely to benefit from closure.

**Conclusion:** According to our meta-analysis TPC plus antiplatelets was superior in terms of stroke prevention when compared to Med-Tx. Furthermore, patients with moderate to severe shunts and those younger than 45 years of age were found to benefit most from TPC.

**Introduction:**
The presence of persistent foramen ovale (PFO) has been associated with an increased incidence of cryptogenic strokes in several studies [1-4]. Given the high prevalence, and both the individual and societal impact of stroke, especially when occurring in the young, PFOs have received significant attention. Indeed, transcatheter PFO closure (TPC) has emerged as a potential low-risk treatment option beside antithrombotic therapies. Numerous retrospective trials and randomized control trials have addressed the topic [5-10].

Clinical practice guidelines are mainly based on the data of the PC, CLOSURE I and the RESPECT trial, which failed to demonstrate superiority of TPC over medical treatment (Med-Tx) [5-7]. However, due to the low number of events and therefore the potential lack of power of the mentioned studies, these results are still under debate. Recently published long-term data of the RESPECT trial and two other recent randomized studies (CLOSE, GORE-REDUCE) comparing Med-Tx and TPC have now demonstrated recurrent stroke rates in favor of TPC [8-10].

In order to balance these conflicting results and therefore to evaluate possible benefits of TPC in patients with cryptogenic strokes we performed a meta-analysis taking into account all up to date available RCTs.

**Methods**

**Search strategy and selection criteria**
A literature research was performed in PubMed, Medline, Embase and Cochrane using the terms “patent foramen ovale”, “PFO”, “stroke”, “percutaneous closure” and “transcatheter closure” from their inception to October 2017 with no language restrictions. Only multicenter, randomized, controlled trials comparing TPC and Med-Tx in patients with cryptogenic stroke or transient ischemic attack (TIA) and a coincidental finding of a PFO were included in the analysis. Furthermore, eligibility was met when death, TIA and stroke were reported. Characteristics of the included studies are given in Table 1.
### Table 1:
Study characteristics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Randomization</th>
<th>Groups</th>
<th>Device</th>
<th>Med. Therapy</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPECT</td>
<td>1:1</td>
<td>Closure vs. Med-Tx</td>
<td>Amplatzer</td>
<td>Discretion of physician</td>
<td>Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke or early death after randomisation</td>
<td>Complete closure after 6 months, absence of recurrent symptomatic, nonfatal ischemic stroke or cardiovascular death and absence of TIA</td>
</tr>
<tr>
<td>PC</td>
<td>1:1</td>
<td>Closure vs. Med-Tx</td>
<td>Amplatzer</td>
<td>Discretion of physician</td>
<td>Composite of death, nonfatal stroke, TIA or peripheral embolism</td>
<td>Individual endpoints of primary outcome, cardiovascular death, new arrhythmias, hospitalizations due to PFO</td>
</tr>
<tr>
<td>CLOSURE I</td>
<td>1:1</td>
<td>Closure vs. Med-Tx</td>
<td>Starflex</td>
<td>Discretion of physician</td>
<td>Composite of stroke, TIA, death any cause, death from neurologic event between 31 days and 2 years after the procedure</td>
<td>Major bleeding, death from any cause, stroke, TIA, transient neurologic events of unknown cause</td>
</tr>
<tr>
<td>CLOSE</td>
<td>1:1:1</td>
<td>Closure vs. Antiplatelet vs. Anticoagulation</td>
<td>Discretion of physician</td>
<td>Accord. to randomization</td>
<td>Fatal or nonfatal stroke</td>
<td>Composite of ischemic stroke, TIA, systemic embolism, all-cause mortality, device success</td>
</tr>
<tr>
<td>GORE REDUCE</td>
<td>2:1</td>
<td>Closure vs. Antiplatelet</td>
<td>Gore Helex or GSO</td>
<td>ASS, Clopidogrel, Dipyridamole</td>
<td>Recurrence of stroke or deficit with associated Defect on MRI/CT or Incidence of new brain infarction on MRI 24 months after inclusion</td>
<td>Adverse-events, success of closure</td>
</tr>
</tbody>
</table>

Two investigators independently assessed the studies for eligibility and their agreement was tested. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Data on age, sex, cardiovascular risk factors, use of antiplatelet or anticoagulation therapy, shunt magnitude, presence of interatrial aneurysm, success rate for TPC and adverse events, whenever reported in the studies were extracted and reported on standardized data collection sheets.

For each of the included studies, a Jaded score was independently calculated by two investigators for quality assessment (MR, DS). The results were then tested for agreement. In case of disagreement between the two investigators, a meeting including a third investigator was arranged to discuss the different results and to reach agreement.
In general, trials with a score of ≥ 3 are deemed to be of good quality [11-13]. The endpoint of interest in our study was the recurrence of stroke in patients undergoing TPC and Med-Tx versus Med-Tx alone.

**Statistical analyses**

Cohen’s kappa was used to test the agreement between the investigators for inclusion of the studies and quality assessment. Risk estimates (relative risks, odds ratios, and hazard ratios with corresponding 95% confidence intervals) and numbers of adverse events comparing TPC and Med-Tx, were extracted from all publications. Subgroup analyses were defined in advance to assess features that have been suggested as “high-risk PFO” on the development of vascular outcomes [14 – 16]. The following parameters were investigated as “high risk features”: age (<45 vs. ≥45 years), presence or absence of atrial septal aneurysm (ASA), and presence or absence of moderate to severe shunt. A subgroup analysis for a therapy with anticoagulation or antiplatelet was also provided.

Meta-analyses for a comparison of TPC and Med-Tx for the outcome stroke, stroke/TIA, the composite outcome, the defined subgroups, and atrial fibrillation were performed. Pooled risk estimators with 95% confidence intervals (CI) were obtained for the intention-to-treat (ITT) populations of the individual studies. As no complete information on the individual per-protocol sets were provided in the studies, a pooled per-protocol meta-analysis was not possible. We did not adjust for covariates, e.g. devices, because this would result in an unstable model due to the low number of studies included within the meta-analysis. For all time-to-event outcomes of interest pooled hazard ratios (HR) are reported. Depending on the result of the \( \chi^2 \) test for heterogeneity we chose fixed effect models in case of sufficient homogeneity of the treatment effect across studies (\( p \)-value > 0.05) and random effect models in case of heterogeneity (\( p \)-value < 0.05). The parameter \( I^2 \) is provided to quantify the heterogeneity, which is interpreted as the percentage of variability due to heterogeneity between studies rather than sampling error [17].

For the fixed effects models the generic inverse variance weighting method (logarithm of the risk estimate and its standard error) is used. The random effects models are used with a restricted maximum likelihood estimator (REML) with logit transformation. Funnel plots and Egger’s regression were used to check for publication bias. Studies with a potential publication bias were excluded from the meta-analysis. The trim and fill method could not be used because of the low number of studies. The global level of significance was set to 0.05.

All analyses were performed with R, version 3.3.3 (packages “metafor”) R Foundation for Statistical Computing, Vienna, Austria [18-19].

**Results:**

Of the 468 articles initially identified, six studies finally met the inclusion criteria [5-10]. Thereby, the RESPECT trial was first published in 2013 [5] and with an extended follow-up also published in 2017 [8]. For our analysis, only data of the extended trial were used. The agreement for inclusion of the selected studies was excellent (\( \kappa = 1.0 \)).

The five studies included, collected data between 2000 and 2017 in populations from North America, Canada, Europe, Brazil, and Australia. A total of 3630 patients were randomized to TPC or Med-Tx. The remaining numbers of patients for our analysis are 1829 for those that underwent the TPC and 1622 for those that underwent the Med-Tx.

Baseline characteristics, such as age, sex, and cardiovascular risk factors, were similar between treatment groups in all the studies (Table 2). Relevant study characteristics are presented in Table 1.
Table 2: Baseline characteristics of the included studies.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Age (years) means ± SD</th>
<th>Men (%)</th>
<th>Type and Duration of Med - Tx</th>
<th>ASA (%)</th>
<th>Hypertension (%)</th>
<th>Hyperlipidaemia (%)</th>
<th>Smoking (%)</th>
<th>Diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPECT</td>
<td>Device group</td>
<td>499 45.7 ± 9.7</td>
<td>268 (53.7)</td>
<td>DAPT for 1 months followed by aspirin for 5 months.</td>
<td>180 (36.1)</td>
<td>158 (31.3)</td>
<td>194 (38.9)</td>
<td>75 (15.0)</td>
<td>33 (6.6)</td>
</tr>
<tr>
<td></td>
<td>Medical therapy</td>
<td>481 46.2 ± 10.0</td>
<td>268 (55.7)</td>
<td>Warfarin, aspirin, clopidogrel or DAPT</td>
<td>169 (35.1)</td>
<td>150 (31.2)</td>
<td>19 (40.1)</td>
<td>55 (11.4)</td>
<td>40 (8.3)</td>
</tr>
<tr>
<td>PC, n = 414</td>
<td>Device group</td>
<td>204 44.3 ± 10.2</td>
<td>92 (45.1)</td>
<td>Left to discretion to the treating physicians (antiplatelets or anticoagulation)</td>
<td>47 (23.0)</td>
<td>49 (24.0)</td>
<td>50 (24.5)</td>
<td>52 (25.5)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Medical therapy</td>
<td>210 44.6 ± 10.1</td>
<td>114 (54.3)</td>
<td>Left to discretion to the treating physicians (antiplatelets or anticoagulation)</td>
<td>51 (24.3)</td>
<td>58 (27.6)</td>
<td>62 (29.5)</td>
<td>47 (22.4)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>CLOSURE I,</td>
<td>Device group</td>
<td>447 46.3 ± 9.6</td>
<td>233 (52.1)</td>
<td>DAPT for six months, ASS for 2 years</td>
<td>168 (37.6)</td>
<td>151 (33.8)</td>
<td>212 (47.4)</td>
<td>96 (21.5)</td>
<td>NR</td>
</tr>
<tr>
<td>n = 909</td>
<td>Medical therapy</td>
<td>462 45.7 ± 9.1</td>
<td>238 (51.5)</td>
<td>Left to discretion to the treating physicians (warfarin, aspirin or both)</td>
<td>165 (35.7)</td>
<td>131 (28.4)</td>
<td>189 (40.9)</td>
<td>104 (22.6)</td>
<td>NR</td>
</tr>
<tr>
<td>CLOSE, n = 663</td>
<td>Device group</td>
<td>238 42.9 ± 10.1</td>
<td>137 (57.6)</td>
<td>DAPT for 3 months followed by single APT for the rest of study duration</td>
<td>53 (30.6)</td>
<td>27 (11.3)</td>
<td>30 (12.6)</td>
<td>68 (28.6)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Medical therapy</td>
<td>235 43.8 ± 10.5</td>
<td>142 (60.4)</td>
<td>Anticoagulation group: vitamin K antagonists or direct oral anticoagulants. Antiplatelet group: DAPT or single APL.</td>
<td>49 (28.7)</td>
<td>24 (10.2)</td>
<td>36 (15.3)</td>
<td>69 (29.4)</td>
<td>9 (3.8)</td>
</tr>
<tr>
<td>GORE REDUCE</td>
<td>Device group</td>
<td>441 45.4 ± 9.3</td>
<td>261 (59.2)</td>
<td>Antiplatelets (aspirin or DAPT). Anticoagulation not permitted</td>
<td>86/422 (20.4)</td>
<td>112 (25.4)</td>
<td>NR</td>
<td>63 (14.3)</td>
<td>18 (4.1)</td>
</tr>
<tr>
<td>n = 664</td>
<td>Medical therapy</td>
<td>223 44.8 ± 9.6</td>
<td>138 (61.9)</td>
<td>Antiplatelets (aspirin or DAPT). Anticoagulation not permitted</td>
<td>NR</td>
<td>58 (26.0)</td>
<td>NR</td>
<td>25 (11.2)</td>
<td>10 (4.5)</td>
</tr>
</tbody>
</table>

SD: standard deviation, ASA: atrial septal aneurysm, DAPT: dual antiplatelet therapy, APL: single antiplatelet therapy, NR: not reported
The median follow-up time was 4 years with great variation between the studies (5.9 years in the RESPECT trial, 2 years in the CLOSURE I trial). The average lost to follow-up was 17%. There was excellent agreement (κ=1.0) that all studies were of very good quality (≥3 on the Jadad score).

For the primary outcome of our study—stroke recurrence—there was a significant benefit of TPC compared to Med-Tx alone, HR=0.32 (95% CI (0.12, 0.82), p-value=0.018) (Figure 1A). To account for a potential publication bias the analysis was also performed without the CLOSE study as this study showed the most extreme results. The result persisted after exclusion of the CLOSE trial, HR=0.52 (95% CI (0.34, 0.79), p-value=0.002) (Figure 1B). Note that without the CLOSE trial a fixed effects model was used. Overall, there were 109 stroke recurrences in the five studies combined, 37 in the TPC group (1.72 %), and 72 in the Med-Tx group (4.48 %). The combined incidence of strokes and TIAs were not reported in the CLOSURE I trial. In the remaining four studies the relative risk for experiencing TIAs or strokes (both events combined) were significantly reduced in the TPC group compared to the Med-Tx group, HR=0.30 (95% CI (0.13, 0.69), p-value=0.005) (Figure 2A). With exclusion of the CLOSE trial statistical significance was still shown, HR=0.44 (95% CI (0.28, 0.70), p-value<0.001) (Figure 2B). Note that without the CLOSE trial a fixed effects model was used.

(A)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPC</td>
<td>0.20 [0.02, 1.72]</td>
</tr>
<tr>
<td>CLOSURE I</td>
<td>0.90 [0.41, 1.98]</td>
</tr>
<tr>
<td>RESPECT</td>
<td>0.55 [0.31, 0.99]</td>
</tr>
<tr>
<td>CLOSE</td>
<td>0.03 [0.00, 0.26]</td>
</tr>
<tr>
<td>GORE REDUCE</td>
<td>0.23 [0.09, 0.62]</td>
</tr>
<tr>
<td>RE Total</td>
<td>0.32 [0.13, 0.82]</td>
</tr>
</tbody>
</table>

(B)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPC</td>
<td>0.20 [0.02, 1.72]</td>
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<tr>
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<td>0.90 [0.41, 1.98]</td>
</tr>
<tr>
<td>RESPECT</td>
<td>0.55 [0.31, 0.99]</td>
</tr>
<tr>
<td>GORE REDUCE</td>
<td>0.23 [0.09, 0.62]</td>
</tr>
<tr>
<td>RE Total</td>
<td>0.52 [0.34, 0.79]</td>
</tr>
</tbody>
</table>

Figure 1: Forest plot of included RCTs comparing stroke recurrence between TPC (Closure) and Med-Tx. (A) Random effects model including all five studies in ITT analysis with a corresponding p-value of 0.018. Test for heterogeneity: F=73.54%, p-value=0.012. (B) Fixed effects model excluding the CLOSE trial in ITT analysis with a corresponding p-value=0.002. Test for heterogeneity: F=42.88%, p-value=0.154.
The five studies presented a differing primary composite outcome (Table 1). In our pooled analysis a statistical significant benefit of TPC compared to Med-Tx in the intention-to-treat analysis was observed regarding these primary outcome parameters, HR=0.42 (95% CI (0.21, 0.83), p-value=0.012) (Figure 3A). To account for a potential publication bias the analysis was also performed without the CLOSE trial. However, statistical significance could still be shown, HR=0.58 (95% CI (0.41, 0.82), p-value=0.002) (Figure 3B). Note that without the CLOSE trial a fixed effects model was used.

(A)

![Figure 2](image1)

**Figure 2**: Forest plot of included RCTs comparing stroke recurrence or TIA between TPC (Closure) and Med-Tx. (A) Random effects model in ITT analysis with a corresponding p-value of 0.005. Test for heterogeneity: $I^2=61.21\%$, $p$-value=0.048. (B) Fixed effects model excluding the CLOSE trial in ITT analysis with a corresponding p-value<0.001. Test for heterogeneity: $I^2=9.06\%$, p-value=0.333.

A subgroup analyses to assess “high-risk PFO” characteristics regarding the reoccurrence of vascular events, namely the presence of an atrial septal aneurysm (ASA), shunt magnitude at baseline, and age was performed (Figures 4-6). Thereby, only data of three trials each were available. A significant benefit of TPC compared to Med-Tx was found in patients younger than 45 years of age, HR=0.35 (95% CI (0.16, 0.75), p-value=0.007) (Figure 4A) and patients with moderate to severe shunt, HR=0.28 (95% CI (0.14, 0.55), p-value<0.001) (Figure 5A). Figure 4B and 5B show the non-significant results of the subgroups age≥45 and shunt smaller than moderate.
Figure 3: Forest plot of the included RCTs comparing the primary composite endpoint in the studies between TPC (Closure) and Med-Tx (ITT). (A) Random effects model including all five studies in ITT analysis with a corresponding p-value of 0.012. Test for heterogeneity: $I^2=67.66\%$, p-value=0.021. (B) Fixed effects model excluding the CLOSE trial in ITT analysis with a corresponding p-value of 0.002. Test for heterogeneity: $I^2=33.68\%$, p-value=0.21.
Figure 4: Forest plot of included RCTs comparing TPC (Closure) and Med-Tx in patients <45 (A) and ≥ 45 years (B) regarding the composite endpoint. (A) Fixed effects model for subgroup age <45 with a corresponding p-value of 0.007. Test for heterogeneity: $I^2 = 0\%$, p-value=0.58. (B) Fixed effects model for subgroup ≥ 45 with a corresponding p-value of 0.066. Test for heterogeneity: $I^2 = 44.08\%$, p-value=0.167.

The subgroup analysis of no ASA and ASA showed no statistical significance (Figure 6). A significant benefit of TPC over Med-Tx was only evident when medical treatment comprised antiplatelets, HR=0.44 (95% CI (0.23, 0.85), p-value=0.014) (Figure 7A). There was no difference between the groups when patients in the Med-Tx group received anticoagulants (Figure 7B). For both of these analysis only data from two trials were available.

(A)

(B)
Effective closure rates were indicated between 70% in the CLOSURE I trial (starflex) and 99% in the CLOSE trial (device according to choice of physician). Pooled analyzes showed severe adverse events (SAEs) in 24.2% in the closure and 23.8% in the medical therapy group. No fatal events related to TPC were reported in the selected trials. New-onset atrial fibrillation (AF) was not significantly more frequent in the TPC group when compared with medical therapy, respectively, pooled HR 1.73, 95% CI (0.83–3.61), p-value=0.146. (Figure 8).

The funnel plots to check for publication bias are shown in Figure 9.

**Figure 5:** Forest plot of included RCTs comparing TPC (Closure) and Med-Tx in patients with moderate to severe shunt (A) and with shunt smaller than moderate (B) regarding the composite endpoint. (A) Fixed effects model for subgroup moderate to severe shunt with a corresponding p-value=0.001. Test for heterogeneity: $I^2=0\%$, p-value=0.386. (B) Fixed effects model for subgroup $<$ moderate shunt with a corresponding p-value of 0.73. Test for heterogeneity: $I^2=0\%$, p-value=0.601.

**Figure 6:** Forest plot of included RCTs comparing TPC (Closure) and Med-Tx in patients with (A) and without (B) atrial septal aneurysm (ASA) regarding the composite endpoint. (A) Fixed effects model for subgroup ASA with a corresponding p-value of 0.157. Test for heterogeneity: $I^2=62.23\%$, p-value=0.07. (B) Fixed effects model for subgroup No ASA with a corresponding p-value of 0.199. Test for heterogeneity: $I^2=0\%$, p-value=0.402.

**Discussion:**

To the best of our knowledge, this is the first meta-analysis of RCTs demonstrating an obvious benefit of TPC and antiplatelet medication over Med-Tx alone in patients with cryptogenic stroke and PFO. In the pooled analysis, TPC resulted in a significant reduction of neurologic event recurrence when compared to Med-Tx alone with a
pooled hazard ratio of 0.32 (of 0.52 in a reduced analysis). This significance is in contrast to a previous meta-analysis [20].

Figure 7: Forest plot of included RCTs comparing TPC (Closure) and Med-Tx in patients with oral anticoagulation (A) or antiplatelet agents (B) regarding the composite endpoint. (A) Fixed effects model for subgroup anticoagulation with a corresponding p-value of 0.893. Test for heterogeneity: $I^2=0\%$, p-value=0.437. (B) Fixed effects model for subgroup antiplatelet with a corresponding p-value of 0.014. Test for heterogeneity: $I^2=0\%$, p-value=0.385.

Figure 8: Forest plot of included RCTs comparing atrial fibrillation between TPC (Closure) and Med-Tx. Fixed effects model for atrial fibrillation with a corresponding p-value of 0.146. Test for heterogeneity: $I^2=68.7\%$, p-value=0.407.
Since the results of the first RCTs have been published, TPC has only been considered in a minority of patients, as these studies failed to demonstrate a significant benefit over Med-Tx. Based on these trials Med-Tx is as effective as the interventional approach [5-7]. Furthermore, the incidence of new AF in the device group was significantly increased [20].

However, analyses based on the as-treated populations, follow-up studies and meta-analyses have suggested that there may be a possible benefit from the procedure in lowering the risk of stroke recurrence [5-8, 20]. Unlike the PC, the CLOSURE I and the first published RESPECT trial, the two latest studies (CLOSE, GORE REDUCE), which were designed to determine the efficacy and safety of PFO closure followed by antiplatelet therapy, as compared with antiplatelet therapy alone, showed a significant reduction of events in the closure group [9, 10]. Similarly, the recently published extended data of the RESPECT trial also showed a significant benefit of TPC when compared to Med-Tx [8]. These results suggest that previous RCTs have been underpowered [21].

We also explored “high-risk PFO” features in patients with cryptogenic stroke, such as young age, presence of atrial septal aneurysm, and shunt magnitude [14-16].

This analysis showed that patients younger than 45 years of age and those with severe shunt were more likely to benefit from closure than from Med-Tx. There was no difference regarding both treatment modalities in patients older than 45 years of age and patients with mild shunt. Furthermore, ASA was not identified as a risk factor of recurrent vascular events.

It is also important to note that a pooled analysis of the available data showed worse results in patients receiving antiplatelets only, whereas the results after TPC and anticoagulation were comparable. The availability of these data in only two studies need to be noted as a major limitation. Furthermore, a sub-analysis of the CLOSE trial comparing antiplatelet therapy against anticoagulation was underpowered. However, there was a trend of improved outcome with comparable rates of major bleedings in patients assigned to oral anticoagulation [9].

In conclusion, whereas TPC plus antiplatelets seems to be clearly superior to antiplatelet therapy alone, there is currently no general answer to the question whether anticoagulation or transcatheter closure should be the preferred treatment. Considering the bleeding risk of anticoagulation during a long-term treatment, transcatheter closure may also be favored, especially in cohorts with an increased risk of bleeding. In this context it is on the other hand important to mention that TPC was associated with an increased incidence of AF in several studies, which itself is associated with an increased risk of embolic strokes and may require anticoagulation [7, 10]. Although in the present analysis we only found a non-significant trend of increased AF rates following closure and although AF has been reported as a primarily temporary problem in these patients, individualized decision making, weighting the risk of bleeding against the risk of TPC is still necessary. The incidence of AF after TPC may also show a relation to certain device features and should therefore be considered in future device technologies.

The major limitation of our study is that we lacked individual-level data for analyses. The primary endpoint definitions as well as the methodologies used in the different trials showed some diversity. In this context different in- and exclusion criteria, the choice of medical therapy, the 2:1 randomization in the GORE REDUCE study and the design of the CLOSE study need to be mentioned. However, the study populations and the reported secondary endpoints of the studies were similar and we therefore believe our results are robust.

The role of anticoagulation in the setting of PFO and cryptogenic strokes still needs to be elucidated, as the typical patient cohort is young and long-term application of these medications may result in an increased risk of fatal bleeding events. Furthermore, individual data are needed, as they may help to clarify the impact of device-related
new-onset atrial fibrillation and incomplete PFO closure on future neurological events and potential treatment options.

Figure 9: Funnel plots and p-value gained by Egger’s regression to check for publication bias (all studies with available data included).
Figure 9 continued

Figure 9: Funnel plots and p-value gained by Egger's regression to check for publication bias (all studies with available data included).

In conclusion, TPC combined with antiplatelet treatment was associated with a relative risk reduction to suffer from stroke recurrence in patients with cryptogenic stroke and PFO when compared to Med-Tx only with a hazard ratio of 0.32 (of 0.52 in a reduced analysis). Especially patients with large shunts and those who are younger than 45 years of age are likely to benefit from closure. We strongly believe that these data will change current guideline practice in favor of TPC.
Sources of funding / Acknowledgements:
This work was supported by the Helmholtz-Association through program-oriented funding. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the paper and its final contents.

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