The Fragility Index in Randomized Controlled Trials for Patent Foramen Ovale Closure in Cryptogenic Stroke

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Background and Purpose: The routine use of percutaneous transcatheter patent foramen ovale closure (PPFOC) to prevent recurrent stroke in patients with cryptogenic stroke is still a matter of debate after completion major randomized controlled trials (RCTs). *Methods*: The fragility index of RCTs evaluating effect of PPFOC against medial therapy alone in stroke prevention was calculated to assess the robustness of statistically significant findings. *Results*: Literature search with PubMed identifies 6 RCTs on PPFOC. Median number of patients who underwent PPFOC and medical treatment were 340 and 229, respectively. Median number of the patients lost to follow-up was 20 in PPFOC and 18 in medical group. Fragility index was 0 for 4 studies. Median fragility index was also 0 for both "stroke" (interquartile range: 0-5.3) and "combined stroke and TIA" (interquartile range: 0-2) endpoints. In all studies except CLOSE, fragility index was smaller than or equal to the number of the subjects lost to follow-up. *Conclusions*: Recent positive results of PFO closure studies should be interpreted cautiously because of their fragile characteristics. Routine PFO closure should be reserved for prevention of recurrence when suspicion for paradoxical embolism is high. Detailed individualized decision-making is crucial before ordering PPFOC for stroke prevention in patients with cryptogenic embolism.

Key Words: Stroke—ESUS—idiopathic—paradoxical embolism—PFO—closure device

Introduction

Four randomized controlled trails, published within the last 1 year, have demonstrated the effectiveness of percutaneous transcatheter patent foramen ovale closure (PPFOC) in secondary stroke prevention in patients with cryptogenic stroke.[1-6] Now, medical communities are evaluating the transmission of these apparently positive results into the clinical routine.[7] Not only the latest, partially revised American Heart Association ischemic stroke management guideline,[8] but also many meta-analyses, reviews, and opinion or argumentation articles indicate absence of wide consensus among experts.[7,9-24] In addition, some experts are, indeed, quite skeptical against PPFOC in this indication. Many reasons can be quoted for this skepticism. One reason, perhaps the most important, is probably nonconvincing robustness of the results and nonclarification of some study characteristics. We herein reported that structural analysis of these results may provide additional view in this respects.

Methods

Literature search with PubMed identifies 6 multicenter RCT on PPFOC. The fragility index of these 6 studies was calculated with using their intention-to-treat population. The fragility index is a number indicating how many patients would be required to transform a RCT from being statistically significant to nonsignificant.[25] It is the minimum number of converted events, resulting in increase of P value above .05 with Fisher's exact test. A higher fragility index indicates an increase of robustness of the study.[26] Descriptive values were given as median and interquartile range (IQR). SPSS version 22 was used for descriptive statistics.

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Results

General characteristics of the 6 RCTs analyzed are summarized in Table 1. Median number of centers participated in these studies is 49 (IQR: 23-74). A median of 340 (IQR: 168-460) patients were scheduled to PPFOC, while 229 (IQR: 173-467) served as controls. Success of device implantation procedure was very high (99.3%, IQR: 94.3-99.7%). Follow-up duration ranged from 2 to 5.9 years with median of 3.65 years. The number of patients lost to follow-up was not different between PPFOC (20, IQR: 0-55) and control (18, IQR: 2-72) arms (P = .818).

The results of fragility analyses are summarized in Table 2. When primary endpoint was chosen as "stroke," fragility index was 0 in 4 out of 6 studies. The median fragility index was 0 (IQR: 0-5.3) in these studies with a mean of 1.8. For the primary endpoint of combined transient ischemic attack and stroke, fragility index could be calculated for 5 studies. It was 0 for 3 studies, with median of 0 (IQR: 0-2.5), and mean of .8.

Discussion

RCTs and their meta-analyses indicate less recurrence of stroke with PPFOC compared with medical therapy alone. Relative risk reduction with PPFOC varies from 38% to 50.5%, but the upper limit of 95% confidence interval is as high up as .91 indicating marginality of the significance of the results in these meta-analyses.[9,13,14,16,22] Accordingly, the number needed to treat for reducing recurrent stroke for 1 patient with PFO closure is not small, albeit still in an acceptable range, varying from 38 to 43.[7,12,15,23,24] Several post hoc analyses indicate that benefit from device closure was better in, if not confined to, some subgroups of PFO such as large shunting ones.[11,13] These meta-analyses also documented that PPFOC is not devoid of adverse effects. Devices were unanimously connected to increased risk of new-onset atrial fibrillation[9,11,13,22,23] albeit transient in the most, risk of pulmonary embolism[9] and device-related complications.[9,16,22] After a very brief summary of all these critical features of PPFOC studies, we herein discuss their data solidity in the light of our analyses.

We report the fragility indexes of RCTs testing PFO closure in stroke prevention. It is clear that in these studies, positive results were achieved despite a small number of primary outcomes. Moreover, rate of disabling stroke is too infrequent to perform any statistical analyses. Accordingly, their fragility indexes are very small. The index is 0 in two thirds of the studies. Albeit there is no specific threshold for lower limit of the fragility index to categorize a study as "fragile" or "robust," zero fragility index emphasizes a total lack of robustness of trial data. A meta-analysis performed by Walsh et al on 399 RCTs from 5 high-impact journals documented that median fragility index was 8 (0-109).[27] Based on this data, we can say that fragility index of PFO studies are below the average

Table 1. *Study characteristics*

	Year	Centers		PPFOC			Control		Follow-up
		N	Countries	n	Lost-to follow-up(n)	Success of device implantation (%)	n	Lost to follow-up (n)	(in years)
CLOSURE-1[11]	2012	87	US, Canada	447	8	89.4	462	3	2
PC TRIAL[3]	2013	29	Europe, Canada, Brazil, Australia	204	31	95.9	210	42	4.1
RESPECT[4]	2017	69	US, Canada	499	104	99.1	481	160	5.9
CLOSE*[2]	2017	34	France, Germany	238	0	99.6	235	2	5.3
Gore REDUCE[5]	2017	63	Canada, Denmark, Finland, Norway, Sweden, UK, US	441	39	98.8	223	33	3.2
DEFENSE-PFO[6]	2018	2	South Korea	60	0	100	60	0	2.8

Abbreviations: PPFOC, percutaneous trans-catheter PFO closure; UK, United Kingdom; US, United States.
*Control group did not include patients randomized to anticoagulation.

Table 2. *Fragility analysis*

	PPFOC			Control			Fragility	*P*		
STROKE	n	N	%	N	N	%		Original study	Exact test	Fragile study
CLOSURE11	12	447	2.7	13	462	2.8	0	.79	1.00	1.00
PC TRIAL3	1	204	.5	5	210	2.4	0	.14	.216	.216
RESPECT4	18	499	3.6	28	481	5.8	0	.046	.13	.13
CLOSE2	0	238	.0	14	235	6.0	6	<.001	<.001	.071
Gore REDUCE5	6	441	1.4	12	223	5.4	5	.002	.004	.071
DEFENSE-PFO6	0	60	.0	5	60	8.3	0	.023	.057	.057
STROKE + TIA										
CLOSURE11	23	447	5,1	29	462	6.3	0	.37	.479	.479
PC TRIAL3	5	204	2.5	11	210	5.2	0	.14	.202	.202
RESPECT4	35	499	7.0	51	481	10.6	0	.055	.055	.055
CLOSE2	8	238	3.4	21	235	8.9	3	.01	.013	.069
Gore REDUCE*,5	-	441	-	-	223	-	-	-	-	-
DEFENSE-PFO6	0	60	.0	6	60	10.0	1	.027	.027	.114

*TIA not reported in REDUCE.

of usual RCTs, and therefore might not be robust enough for implementation to clinical routine. But this statement may not be completely true, because direct comparison of fragility indexes of different categorical studies is not recommended.[25,28] Another way to determine the value of the fragility index is to compare it with the number of subjects who are lost to follow-up. As a general rule of thumb, if the number of patients lost to follow-up is greater than the fragility index, the study should be considered less robust.[25] All of the PFO studies except CLOSE[2] are fragile when this criterion is applied. For comparison, Walsh's meta-analysis indicated that the fragility Index was less than the number of patients lost to follow-up in 53% of trials.[27]

The fragility index is a newly defined statistical marker. Like *P* values, the fragility index is not an absolute measure of the effect. Furthermore, it may not be appropriate to use the fragility index as a strict measure of the strength of the effect. And also, its dependence on sample size is a limiting characteristic. Another limitation is the lack of time phenomena encompassed. Moreover, it is in conflict with the well-established principle of randomized controlled trials, where working with the minimal number of subjects is suggested to prove efficacy due to the economics.[28] Similarly, trial sequential analysis, in which crossing of the cumulative z-score's line and monitoring boundaries indicates true positivity which is the superiority of PPFOC over medical management herein, provides firm evidence earlier than reaching the required information size.[24] Despite all of these, fragility index is still valuable in showing the direction and stability of study results, and this direction can be kept in our minds during clinical decision-making processes.

Some of the features of accumulated knowledge in the PFO literature such as low rate of effectiveness in stroke prevention, lack of reported efficacy in disabling stroke prevention, absence of comparison with anticoagulants and unknown long-term consequence of reported side effects prevent acceptance of PPFOC as a routine in the stroke prevention. We add unfavorable fragility index of the PPFOC studies to available quandaries in the clinical decision-making processes. Unless new studies with robust data become available, PPFOC for stroke prevention will continue to be a topic of debate in patients who cannot meet paradoxical cerebral embolism criteria.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.02.029.

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