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The effectiveness of patent foramen ovale closure and antiplatelet or anticoagulant therapies for cryptogenic ischemic stroke

Michał Marciniec[1], Anna Szczepańska-Szerej[1], Marcin Kulczyński[1], Sylwia Popek-Marciniec[2], Katarzyna Pasterczyk*, Konrad Rejdak[1]

[1]Chair and Department of Neurology, Medical University of Lublin, Poland

[2]Department of Cancer Genetics with Cytogenetics Laboratory, Medical University of Lublin, Poland

*E-mail address: lekpasterk@gmail.com

ABSTRACT

Patent foramen ovale (PFO) occurs in approximately 50% cryptogenic strokes cases. One of the most clinically important consequences of PFO is paradoxical embolization of venous thrombus resulting in recurrent stroke. The aim of this meta-analysis is to compare the efficacy and safety of PFO closure and antiplatelet or anticoagulant therapy alone (medical therapy, MT) in the secondary stroke prevention. Eligible studies for meta-analysis published from May 2008 to May 2018 were identified through a search of PubMed database and two clinical trial registries websites: ClinicalTrials.gov and EU Clinical Trials Register. A meta-analysis was conducted with the use of Statistica software version 13.1. Three studies comprising 2'307 patients were included. The main outcomes were: recurrent stroke occurrence during follow-up period, the frequency of serious adverse events (SAE) and the mortality rate. Statistical significance was found in the assessment of recurrent stroke occurrence when the comparison referred to PFO closure and antiplatelet therapy (RR 0,30, $p < 0,05$, 95% CI 0,11 – 0,85). There were no significant differences between PFO closure and MT in the frequency of SAE occurrence (RR 1,03, $p = 0,73$) and mortality rates (RR 0,69, $p = 0,39$). Current clinical data indicate that PFO closure devices applied to the carefully selected group of young and middle-aged patients with cryptogenic ischemic stroke may be as or more effective than antiplatelet therapy.

***Keywords*:** Patent Foramen Ovale, Anticoagulation Agents, Antiplatelet Agents, Cerebrovascular Stroke, Cerebral Infarction

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1. INTRODUCTION

The cryptogenic strokes account for about 25-30% of all ischemic strokes cases and approximately half of them are associated with the occurrence of patent foramen ovale (PFO) (Figure 1) [1-3]. The worldwide PFO occurrence is estimated at 25% and therefore it is the most common congenital heart abnormality in adults [4]. One of the clinically important consequences of PFO is paradoxical embolization of venous thrombus resulting in stroke or systemic embolism [5]. PFO closure is a procedure performed in the secondary stroke prevention. For over a decade many clinical studies have been performed to answer the question whether PFO closure reduces the rate of recurrent stroke among patients who have a PFO and have had a cryptogenic ischemic stroke [6]. Treatment options for secondary prevention of recurrent stroke in cryptogenic ischemic stroke patients include antiplatelet or anticoagulant therapy alone and PFO closure followed by antiplatelet treatment [1]. The aim of this meta-analysis is to compare the efficacy and safety of PFO closure and antiplatelet or anticoagulant therapy alone in secondary stroke prevention.

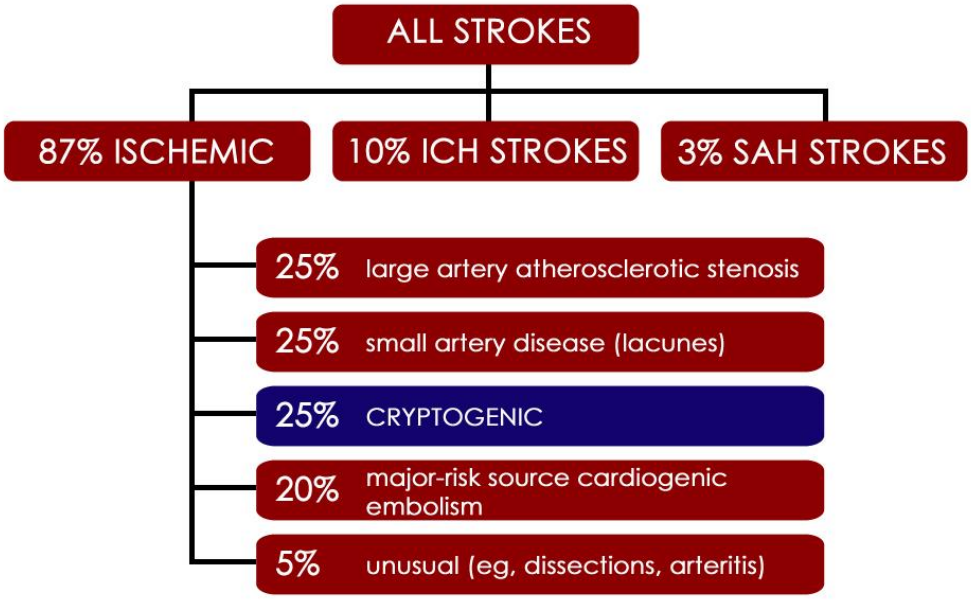

Figure 1. Distribution of stroke subtypes. ICH – intracranial hemorrhage. SAH – subarachnoid hemorrhage [2,3].

2. MATERIALS AND METHODS

2. 1. Search strategy

Systematic literature searches of NCBI/NLM PubMed database published from the last 10 years to 29th May 2018 were performed. The following combinations of search terms were used: "(patent foramen ovale) AND ((anticoagulants) OR (anticoagulation) OR (antiplatelets) OR (antiplatelet therapy) OR (medical therapy)) AND ((stroke) OR (cerebral infarction) OR (brain infarction) OR (brain ischemia))". Two clinical trial registries websites were also analyzed: ClinicalTrials.gov and EU Clinical Trials Register.

2. 2. Inclusion and exclusion criteria

For this review we included only randomized controlled trials comparing PFO closure with medical therapy (anticoagulant or antiplatelet) for ischemic stroke. Participants of the studies were patients who had had a recent stroke attributed to PFO aged 16 to 60 years. The only one included type of ischemic stroke was cryptogenic.

The studies were excluded if the antiplatelet treatment group was not clearly separated from anticoagulant group and if the primary outcome was to assess the effectiveness of medical therapy alone or PFO closure alone without comparison of the results.

2. 3. Search strategy and data extraction

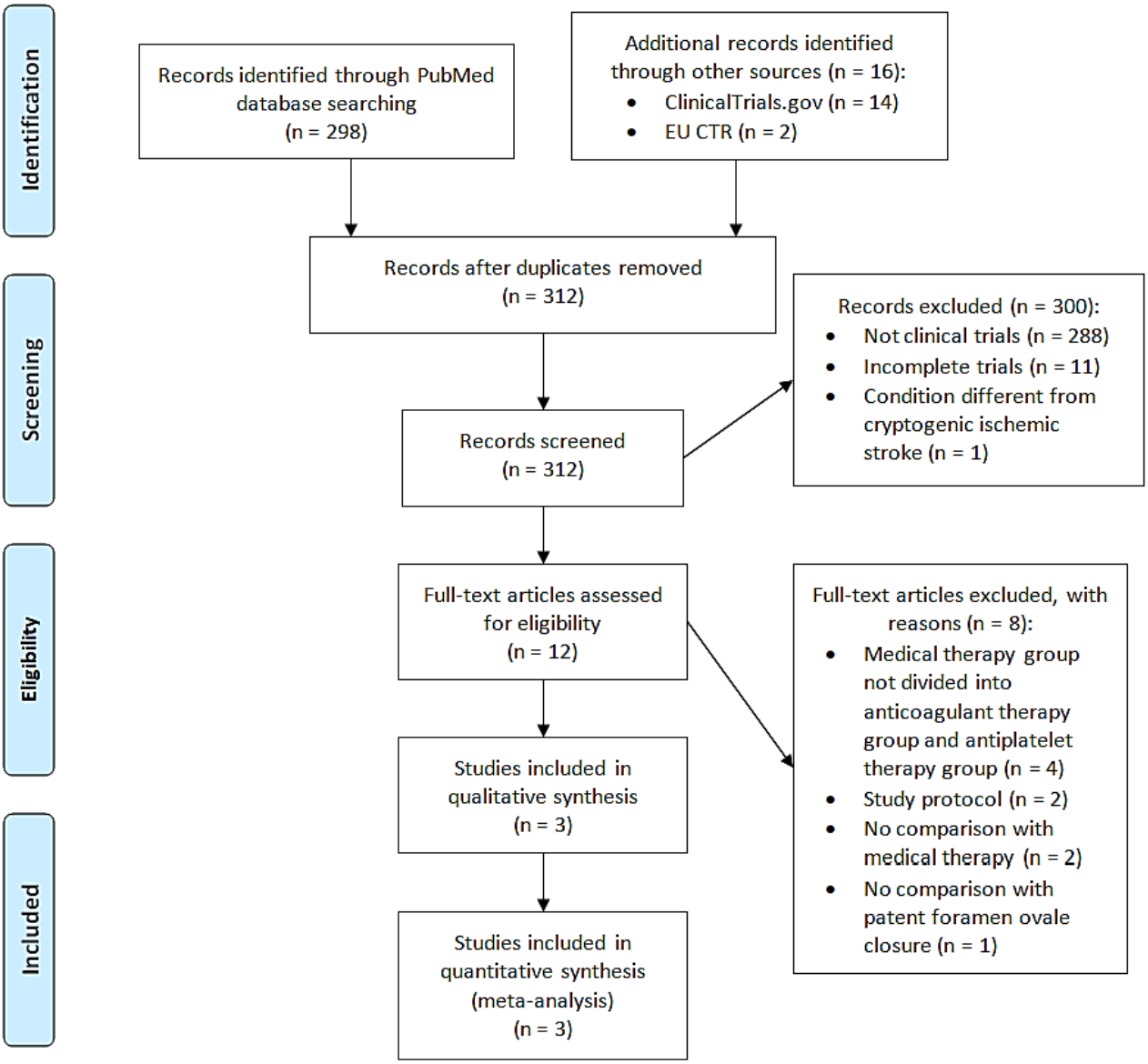

Figure 2. The consecutive phases of a systematic review shown in PRISMA flow diagram [7].

The searching criteria described above resulted in 312 studies extracted. Studies were excluded with following reasons: not clinical trial (288), incomplete trial (11), lack of division of medical therapy group into antiplatelet therapy and anticoagulant therapy (4), no comparison with medical therapy (2) or patent foramen ovale closure (1), study protocol as a type of publication (2), condition different from cryptogenic ischemic stroke (1). After rejection of above findings, three published randomized trials enrolled 2'307 patients were included in this meta-analysis (Figure 2) [7].

Data from the three included studies were extracted using a Microsoft Excel spreadsheet. Details obtained from the articles were: author's name, publication year, number of participants, study design, time of follow-up and outcome measures.

2. 4. Main outcomes

This meta-analysis measured three main outcomes:

1. Recurrent stroke occurrence (number of patients developed any type of stroke during follow-up period).
2. The frequency of serious adverse events (SAE).
3. All-cause mortality.

The main results of the included studies were presented in Table 1 [8-10].

Table 1. Studies on comparison between patent foramen ovale closure and antiplatelet or anticoagulant treatment.

Sample size				Study design	Time of follow-up	RESULTS	Study
All	PFOC	APT	ACG				
663	238	235	187	multicenter, randomized, open-label	5,3 years	Recurrent stroke occurrence: PFOC v. APT – HR 0,03 (p < 0,001) Higher rate of atrial fibrillation in PFOC v. APT group (4.6% vs. 0.9%) No significant difference between the frequency of SAE in treated groups (35,7% PFOC v. 33,2% APT).	CLOSE 2017 [8]
980	499	360	121	multicenter, randomized, open-label	5,9 years	Recurrent stroke occurrence: PFOC v. MT – HR 0,55 (p = 0,046) Recurrent ischemic stroke occurrence: PFOC v. MT – HR 0,38 (p = 0,007)	RECPECT 2017 [9]

						No significant difference between the frequency of SAE in treated groups (40.3% PFOC v. 36.0% MT).	
664	441	223	-	multinational, randomized, open-label	3,2 years	Recurrent stroke occurrence: PFOC v. APT – HR 0,51 (p = 0,04) Recurrent ischemic stroke occurrence: PFOC v. APT – HR 0,23 (p = 0,002) No significant difference between the frequency of SAE in treated groups (23,1% PFOC v. 27,8% APT). PFO closure was associated with higher rates of device complications and atrial fibrillation	REDUCE 2017 [10]

PFOC – patent foramen ovale closure, APT – antiplatelet therapy, ACT – anticoagulant therapy, MT – medical therapy (include antiplatelet and anticoagulant medications administration), HR – hazard ratio, RR – relative risk, CI – confidence interval

2. 5. Statistical analysis

Statistical treatment of results was performed with the use of Statistical software version 13.1. Data from published studies were used to generate risk ratio (RR) with 95% confidence intervals (CIs). A summary RR with 95% CIs was calculated having regard to the weights of included studies. Statistical significance was identified as $p \leq 0.05$. The main outcomes were assessed as the comparisons of PFO closure with anticoagulant therapy and antiplatelet therapy. Due to the inability to obtain separate data on anticoagulant and antiplatelet groups relating to safety outcomes from two studies, these two groups were merged into one group called medical therapy (MT).

3. RESULTS

3. 1. Efficacy outcomes

Among patients who had a PFO and had had an initial cryptogenic ischemic stroke, a lower rate of recurrent stroke was found among patients underwent PFO closure procedure than among those assigned to antiplatelet therapy alone. Statistical significance was found in the assessment of recurrent stroke occurrence when the comparison referred to PFO closure and antiplatelet therapy (RR 0,30, $p < 0,05$, 95% CI 0,11 – 0,85). No significant correlation was found between PFO closure and anticoagulant treatment (RR 0,51, $p = 0,46$, 95% CI 0,09 – 2,98). Above outcomes were presented on Table 2, Figure 3 and Figure 4.

Table 2. Statistical analysis of the efficacy outcomes.

		CLOSE 2017 [8]	RESPECT 2017 [9]	REDUCE 2017 [10]
Sample size		**653**	**980**	**664**
PFOC	Total	238	499	441
	Stroke	0	18	6
	Without stroke	238	481	435
APT	Total	235	360	223
	Stroke	14	23	12
	Without stroke	221	337	211
TOTAL PFOC v. APT		**RR 0,30** ($p < 0,05$) 95% CI 0,11 – 0,85		
ACG	Total	187	121	-
	Stroke	3	5	-
	Without stroke	184	116	-
TOTAL PFOC v. ACT		**RR 0,51** ($p = 0,46$) 95% CI 0,09 – 2,98		

PFOC – patent foramen ovale closure, APT – antiplatelet therapy, ACT – anticoagulant therapy, RR – relative risk, CI – confidence interval

3. 2. Safety outcomes

There was no significant difference in the frequency of SAE occurrence between PFO closure and MT with antiplatelet and anticoagulant treatment (RR 1,03, p = 0,73, 95% CI 0,88 – 1,21). Similarly, no significant difference was found in the mortality rates during follow-up period (RR 0,69, p = 0,39, 95% CI 0,29 – 1,63). Above outcomes were presented on Table 3, Figure 5 and Figure 6.

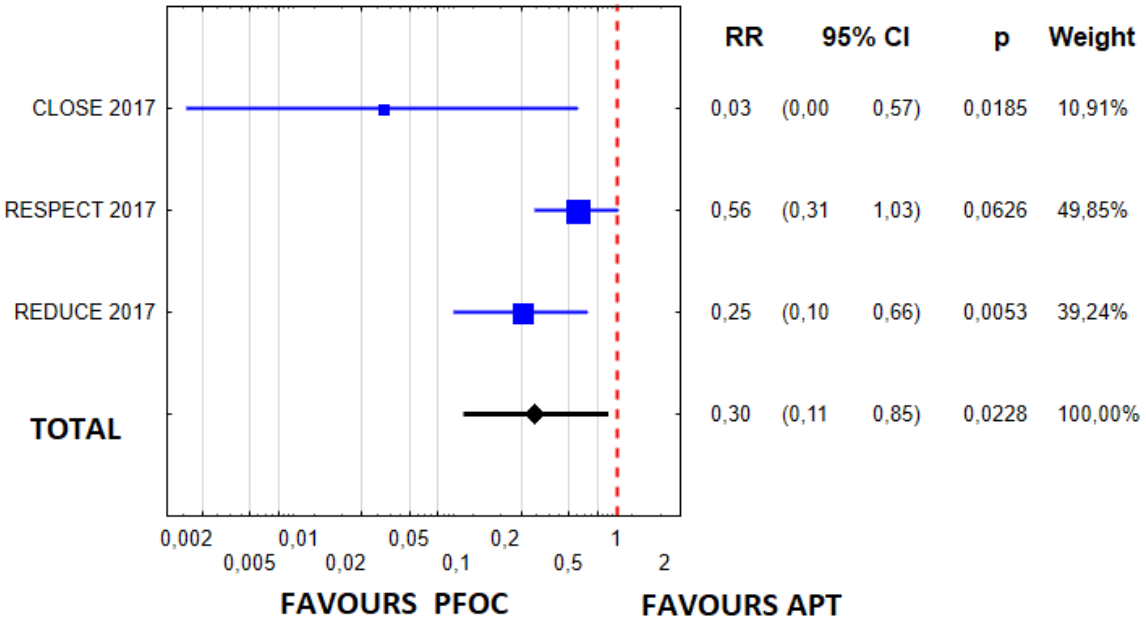

Figure 3. The relative risk of stroke after patent foramen ovale closure (PFOC) and antiplatelet therapy (APT). RR – relative risk, CI – confidence interval.

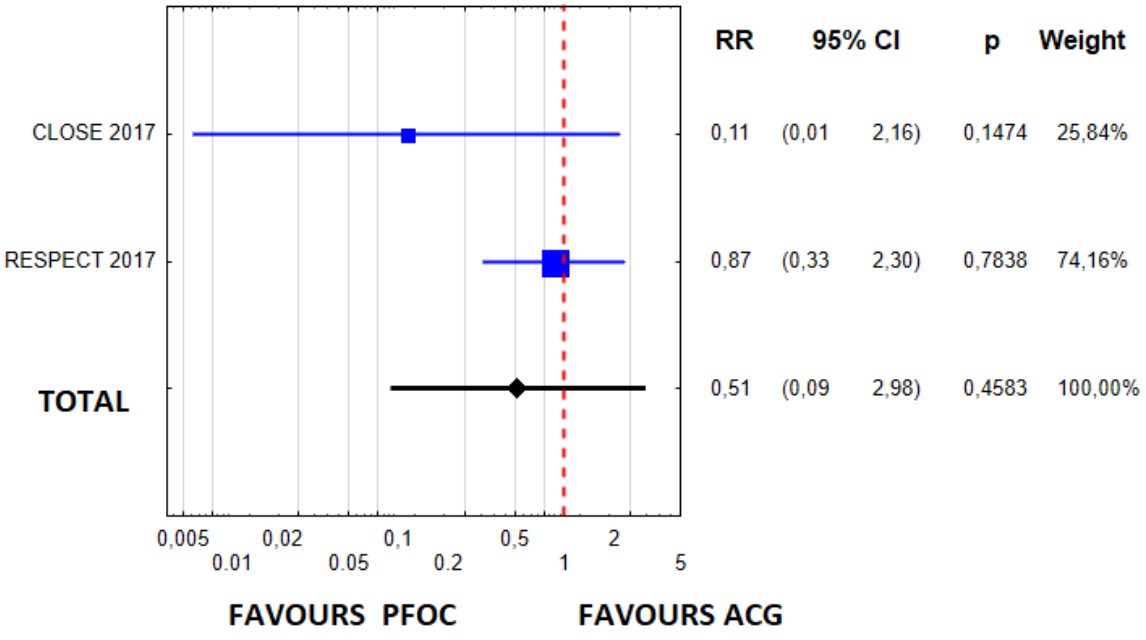

Figure 4. The relative risk of stroke after patent foramen ovale closure (PFOC) and anticoagulation therapy (ACG). RR – relative risk, CI – confidence interval.

Table 3. Statistical analysis of the safety outcomes.

		CLOSE 2017 [8]	RESPECT 2017 [9]	REDUCE 2017 [10]
Serious Adverse Events				
PFOC	Total	238	499	441
	Number of SAE	85	201	102
	Without SAE	153	298	339
MT	Total	422	481	223
	Number of SAE	140	173	62
	Without SAE	282	308	161
PFOC v. MT		**RR 1,03** (p = 0,73) 95% CI 0,88 – 1,21		
Number of deaths				
PFOC	Total	238	499	441
	Number of SAE	0	7	2
	Without SAE	238	492	439
MT	Total	422	481	223
	Number of SAE	1	11	0
	Without SAE	421	470	223
PFOC v. MT		**RR 0,69** (p = 0,39) 95% CI 0,29 – 1,63		

PFOC – patent foramen ovale closure, MT – medical therapy (include antiplatelet and anticoagulant medications administration), SAE – serious adverse events, RR – relative risk, CI – confidence interval

4. DISCUSSION

The lower risk of recurrent stroke referred to PFO closure procedure was the major outcome of this meta-analysis in comparison to antiplatelet therapy. The efficacy of anticoagulant treatment and the safety of comparator groups did not differ significantly. These results comply with the outcomes of 3 recently published clinical trials [8-10], although studies prior to mentioned above did not show the statistically significant superiority of PFO closure over anticoagulant and antiplatelet therapy in the prevention of stroke recurrence [11-13]. However, in one of the above studies, extending of follow-up period supported the significance of results (prolonged follow-up period from 2,6 to 5,9 years resulted in increase of PFO closure HR from 0,49 to 0,55 and changed the statistical significance from p=0,08 to p<0,05) [9,12].

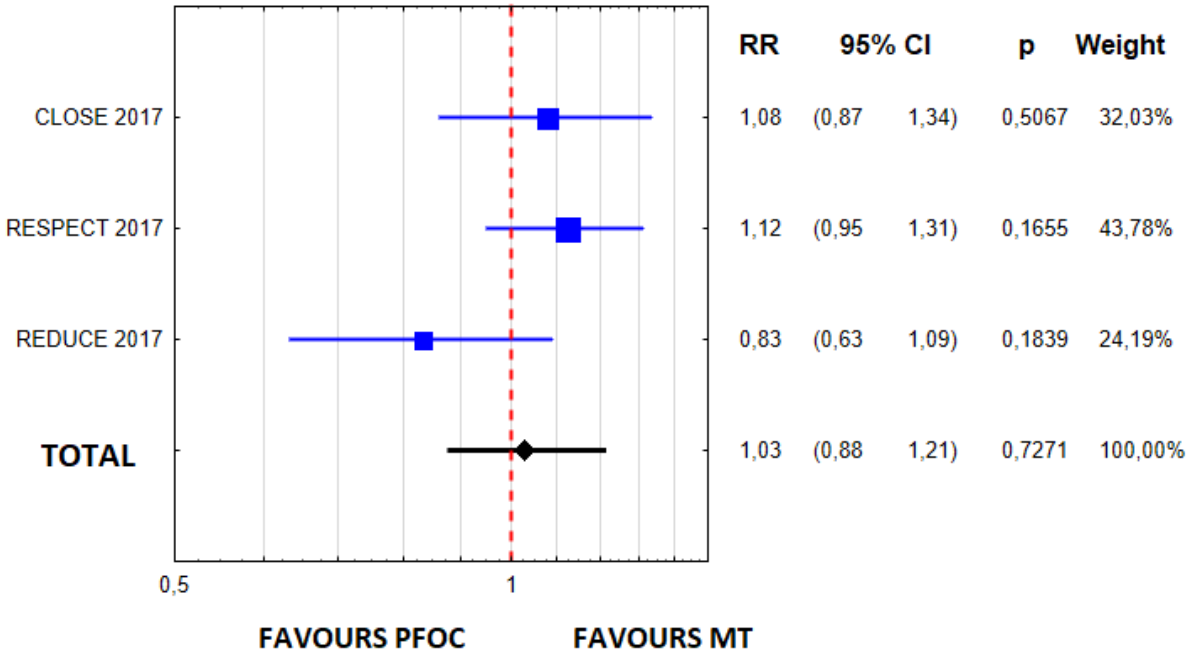

Figure 5. The relative risk of serious adverse events after patent foramen ovale closure (PFOC) and medical therapy (MT) includes antiplatelet and anticoagulant agents. RR – relative risk, CI – confidence interval.

Following the recommendations published by American Heart Association/American Stroke Association, patients with acute ischemic stroke should be treated with antiplatelet agent within 24 to 48 hours after ischemic stroke onset, however urgent anticoagulation is not recommended (no benefit in early recurrent stroke prevention) [14]. Oral anticoagulation therapy for stroke prevention is recommended when the patient is diagnosed with AF and the

total score in CHA_2DS_2-VASc scale (evaluation of stroke risk factors) is higher than 1 (males) or 2 (females) [15].

This meta-analysis have some limitations. Firstly, all included studies recruit patients suffered from only one type of stroke (cryptogenic) [8-10] or concrete conditions (atrial septal aneurysm or large interatrial shunt [8]) which could be identified as potential risk factors for stroke [16]. Secondly, decrease in recurrent stroke occurrence may be related to certain type of stroke, which was not taken into account in this meta-analysis (PFO closure seems to correlate better with recurrent ischemic stroke occurrence than other types of stroke) [9,10]. Thirdly, prolonged electrocardiographic monitoring to detect occult atrial fibrillation (AF) before enrollment was absent in most included studies, however in patients under the age of 60 occult AF is uncommon condition [17]. It is worth reminding that in patients of all ages with cryptogenic stroke, asymptomatic AF detection rate range from 12% to 23% and the first episode of AF may be asymptomatic even up to 80% of cases [3].

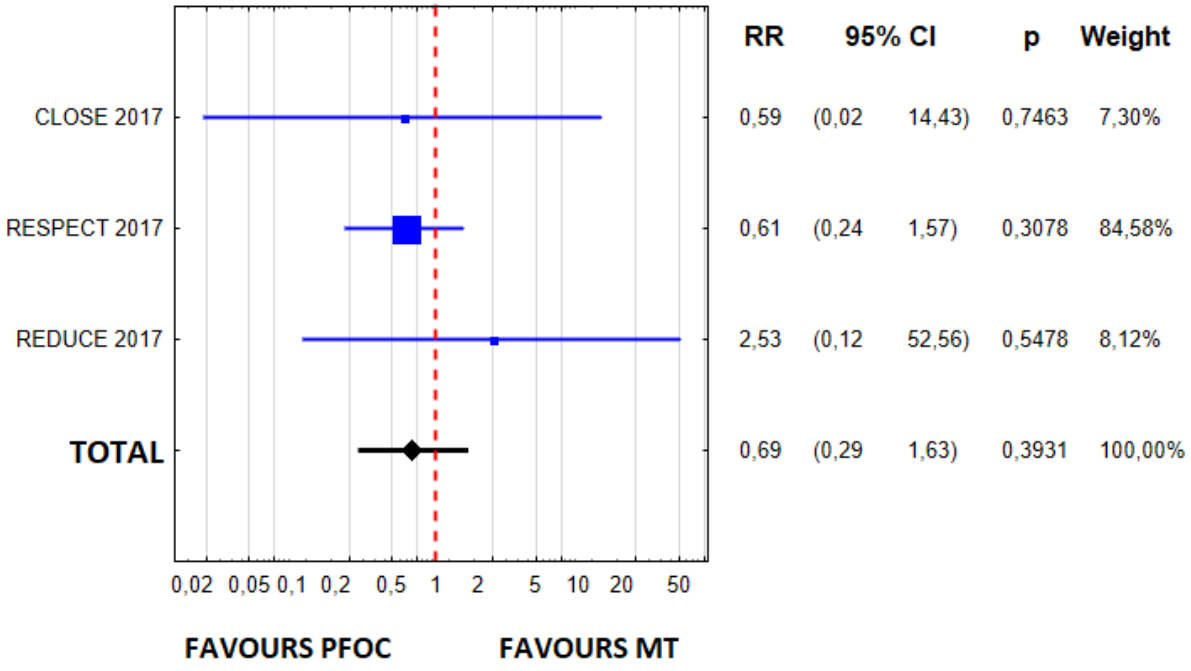

Figure 6. The relative risk of death after patent foramen ovale closure (PFOC) and medical therapy (MT) includes antiplatelet and anticoagulant agents. RR – relative risk, CI – confidence interval.

AF has been also reported as a one of the most frequent SAEs which occurred in patients underwent PFO closure procedure. For instance, in one of the studies the rate of atrial fibrillation was 4.6% in the PFO closure group and only 0.9% in the antiplatelet-only group (p=0,02) [8]. Future studies are needed to evaluate whether these patients require anticoagulant therapy due to the AF occurrence.

5. CONCLUSION

PFO closure followed by antiplatelet therapy is most effective in the secondary stroke prevention than antiplatelet therapy alone. The similar frequency of serious adverse events referred to PFO closure procedure as well as antiplatelet or anticoagulant therapies. Current clinical data indicate that PFO closure devices applied to the carefully selected group of young and middle-aged patients with cryptogenic ischemic stroke may be as or more effective than medical therapy.

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