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Secondary Stroke Prevention in Patients with Patent Foramen Ovale: To Anticoagulate or Not? Fragility Index Meta-analysis of Published Randomized Controlled Studies

Patent Foramen Ovale Hastalarında İnme Tekrarının Önlenmesi: Antikoagülan mı, Değil mi? Yayınlanmış Randomize Kontrollü Çalışmaların Frajilite İndeks Meta-analizi

Mehmet Akif Topçuoğlu, Ethem Murat Arsava
Hacettepe University Faculty of Medicine, Department of Neurology, Ankara, Türkiye

Abstract

Objective: The choice between the use of antiplatelet (APT) treatment and oral anticoagulant (OAC) treatment for the prevention of ischemic stroke recurrence in patients with patent foramen ovale (PFO) requires clarification.

Materials and Methods: A total of 5 randomized controlled trials comparing the preventive effect of APT and OAC therapies, including the use of non-vitamin-K OACs (NOACs), on stroke recurrence in patients with PFO were extracted from a systematic literature search. A standard meta-analysis and determination of fragility indexes were conducted.

Results: The meta-analysis showed that the effectiveness of secondary stroke prophylaxis was higher, albeit remained insignificant, in patients treated with OAC (n = 828) than in patients treated with APT (n = 889; relative risk ratio: 0.76, 95% confidence interval: 0.49–1.19); the difference was not statistically significant, and the publication bias level was acceptable. However, the fragility index of all studies (all negative when assessed individually) was determined as zero. The fragility of the performed meta-analysis was 6 (18.2%), which was 4.6x above the observed value (3.98%) for stroke prevention.

Conclusion: Research data on the use of warfarin or NOAC versus aspirin in secondary stroke prophylaxis in patients with PFO is weak and fragile. A randomized controlled trial could solve this issue.

Keywords: Cryptogenic, idiopathic, stroke, prevention, right-to-left shunt, patent foramen ovale closure

Öz

Amaç: Patent foramen ovale (PFO) saptanan iskemik inmeli olgularda inme tekrarını önlemek için kullanılacak antiplatelet (APT) veya oral antikoagülan (OAC) ajanlar arasındaki tercih netlik kazanmamıştır.

Gereçler ve yöntem: K vitamini antagonisti olmayan OAC (NOAC) dahil olmak üzere OAC tedavilerinin PFO'lu hastalarda inme nüksünü önleyici etkisini APT ile karşılaştıran beş randomize kontrollü çalışma sistematik literatür taramasından elde edilmiştir. Bu çalışmaların frajilite indeksleri hesaplanmış ve ilave olarak standart bir meta-analiz [APT vs. (N)OAC] gerçekleştirilmiştir.

Bulgular: Meta-analiz, OAC ile sekonder inme profilaksisinin etkinliğinin istatistiksel anlamlılık seviyesine varamamakla birlikte APT'ye göre daha iyi olduğunu [sırasıyla; hasta sayıları 828 ve 889; bağıl risk oranı: 0,76 (%95 güven aralığı; 0,49–1,19)] ve sadece kabul edilebilir seviyede bir yayın yanlılığı bulunduğunu göstermiştir. Ancak, tek tek değerlendirildiğinde tamamı negatif sonuç vermiş olan bu beş çalışmanın kırılganlık indeksleri sıfır olarak hesaplanmıştır. Yapılan meta-analizin kırılganlık indeksi ise 6 (%18,2) olup inmeyi önlemek açısından gözlenen değerin (3,98%) 4,6 kat üzerindedir.

Sonuç: PFO'lu inme hastalarında sekonder profilaksi için APT'ye karşı varfarin veya (N)OAC tercihine ilişkin kanıt düzeyi oldukça zayıf ve kırılgandır. Bu bir sorundur ve çözümü ancak yeni ve iyi planlanmış bir randomize kontrollü çalışma olabilir.

Anahtar Kelimeler: Kriptojenik, idiyopatik, inme, önlemek, sağdan sola şant, PFO kapatılması

Address for Correspondence/Yazışma Adresi: Prof. Mehmet Akif Topçuoğlu MD, Hacettepe University Faculty of Medicine, Department of Neurology, Ankara, Türkiye
Phone: +90 312 305 35 35 E-mail: matopcuoglu@yahoo.com ORCID: orcid.org/0000-0002-7267-1431
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Introduction

Medical therapy remains a dependable alternative to percutaneous patent foramen ovale (PFO) closure (PPFOC) in secondary prophylaxis of cryptogenic stroke attributed to PFO (1,2). However, it has not yet been clarified whether the use of aspirin, warfarin, or non-vitamin-K oral anticoagulants (NOACs) is the superior or preferrable choice of medical treatment (3). The present study was conducted with the idea that it would be enlightening to evaluate the direction and robustness of randomized data on the comparative effectiveness of antiplatelet (APT) and OAC agents in the secondary prevention of ischemic stroke in patients with PFO, considering recent additions to the germane literature.

Materials and Methods

The method used in this study was compliant with the PRISMA rules (4). The PubMed database was scanned using the following key words: "patent foramen ovale" or "right-to-left shunt" or "paradoxical" AND "stroke" or "transient ischemic attack" or "cerebrovascular" AND "treatment" or "antiplatelet" or "aspirin" or "anticoagulant" or "anticoagulation" or "warfarin" or "NOAC" or "dabigatran" or "apixaban" or "rivaroxaban" or "edoxaban" in "abstract" or "title". Articles published from the database inception to January 30, 2021, were selected. Additional searches were performed by two authors on Google Scholar [key words: "patent foramen ovale", "Stroke", "antiplatelet", "Anticoagulant", "anticoagulation" (separated with commas), with the first 500 titles reviewed when sorted by relevance] and clinicaltrials.gov [key words: "patent foramen ovale" (limited to the completed trials)]. A total of 958 articles were identified. After duplications were removed, the titles and abstracts were evaluated (in the stated order). Subsequently, 37 articles that were considered relevant to the present study were evaluated based on their full texts. Their references were also assessed for cross-referencing. A total of 5 randomized controlled studies comparing APT and oral OAC treatments (5,6,7,8,9) were found (Figure 1, PRISMA diagram). In addition, this comparison was addressed in 3 meta-analyses (2 new analyses and 1 conducted earlier) (10,11,12), and another study compared APT treatment choices (13).

The efficacy of medication in the APT group and OAC group compared in these 5 studies to assess stroke recurrence and bleeding complications were evaluated; furthermore, the fragility indexes of the individual studies were calculated. The fragility index of a randomized study is a relatively new statistical dimension reflecting the minimum number of participants or sequences being transferred from the active group to another making significant results insignificant with Fisher's exact test (14); the higher the fragility index, the more robust the study is. It is important to note that the fragility index does not have a universal threshold value.

Statistical Analysis

Subsequently, a standard study-level efficacy meta-analysis in the form of a forest plot display was performed using these 5 statistically non-significant studies. The inter-study heterogeneity was assessed using the Q test and I^2 statistics. Given the low heterogeneity, the Mantel–Haenszel method with a fixed effect model was used. The study authors produced a summary of the relative risk ratios and their 95% confidence intervals (CIs) for stroke recurrence and major hemorrhagic complications, including systemic ones. The publication bias was visually examined using the funnel plot method; the web-based system created by Beheshti et al. (15,16) was also used for this purpose (https://meta-mar.shinyapps.io/meta-analysis-calculator/). The fragility index was then calculated for this meta-analysis (17). The method described by Atal et al. (17) was used to calculate the meta-analysis fragility index. In the present study, the descriptive values were calculated using the Tukey hinges method, resulting in a 50% rate (25%–75%). For the statistical calculations, we used IBM SPSS v.23.0 (Armonk, NY, USA) (18) and Meta-Mark v.3.5.1 (15,16) software as well as two web-calculators (14,17). Web-based calculators [https://clincalc.com/Stats/FragilityIndex.aspx#AcceptableFragilityIndex (14) and https://clinicalepidemio.fr/fragility_ma/ (17)] were also used for fragility analyses.

Results

A total of 4 of the 5 randomized controlled studies included in our analysis were multicenter studies (5,6,7,8); 3 included patients with "cryptogenic stroke" (6,8,9), and the other 2 included patients with "Embolic stroke from undetermined source: ESUS" (5,7). A total of 1,717 patients with a median age of 59.5 (51–63) were included in the entire analysis, with 828 and 889 patients in the OAC group and APT group, respectively. The OAC agents used were dabigatran in RESPECT ESUS (5), rivaroxaban in NAVIGATE ESUS (7), and warfarin with different intensities in 3 other included studies (6,8,9). In the CLOSE study (8), 7% of patients were also treated with NOAC. The APT agents used were mostly aspirin with different doses (Table 1). The median number of patients enrolled in the studies was 187 (106–223) in the APT group and 174 (99–225) in the OAC group. The patients were followed up for a median of 1.6 (1.05–3.65) years.

The fragility index values of all the studies were 0 (Table 2). At the end of the study's individualized follow-up period, stroke recurrence with OAC was 3.98% and the significant bleeding rate was 2.7%. Although the efficacy was worse with APT use (recurrence rate: 5.51%) compared with OAC treatment, the bleeding rate was better (1.56%), as expected. In the meta-analysis of all these negative studies, the relative risk ratios for OAC usage were determined as 0.76 [(95% CI: 0.49–1.19)]; Q = 5.607, P = 0.230; I^2 = 29% (95% CI: 0%–74%)] for recurrence (Figure 2A) and 1.66 [(95% CI: 0.83–3.31); Q = 2.03, P = 0.567; I^2 = 0% (95% CI, 0%–81%)] for bleeding (Figure 3A). The funnel plot representation showed slight asymmetry; however, the degree of publication bias was still at an acceptable level (Figure 4A, B).

The fragility index calculation was performed in the reverse direction for this meta-analysis. The study authors searched for the minimum number of cases in the OAC group that would indicate statistical significance if the patients did not develop stroke recurrence. In the case of 6 specific event-status modifications, all patients receiving dabigatran (NOACs) and not experiencing any recurrent event would have indicated statistical significance in the meta-analysis. Thus, the fragility index for recurrence was 6 (Figure 2B). Considering that the observed event number was 33 (Table 2, recurrence section), the fragility corresponded with 18.2% of events, which was considerably higher (4.6x) than the

actual rate of 3.98%. The fragility index for significant bleeding was 3 (Figure 3B). As the number of observed events was 21 (Table 2, bleeding section), the fragility index corresponded with 14.3% of the events, which was considerably higher (5.3x) than the actual rate of 2.67%.

Discussion

The medical secondary prophylaxis options available for treating patients with cryptogenic stroke and PFO are anti-platelets, warfarin, and NOACs. These are used alone or in combination with PPFOC operation. Notably, PPFOC indications are an issue on which no consensus has yet been reached. Furthermore, choosing among these medication options is a matter of significant debate. In cases with stroke demonstrated to be caused by paradoxical embolism in conjunction with PFO, OAC drugs are generally recommended. In cases where venous thrombosis has been documented, it is common practice to perform PPFOC and anticoagulation in line with the basic principles of venous thrombosis prophylaxis. We herein evaluated the scientific data underlying these recommendations by conducting a systematic review and a meta-analysis of the relevant literature, which for the first time included a fragility analysis. In brief, according to our analysis, the available data are rather weak and fragile. Furthermore, not a single study had a positive fragility index and many suggestions were based on expert opinion rather than robust data. As such, a large, preferably non-industry sponsored, randomized, multicenter, double-blind controlled study in this area appears essential.

Selection of medical prevention in PFO has never been made a direct focus of any large, randomized trial. The studies analyzed herein are subgroups of randomized studies, and a subgroup analysis of ESUS studies completed in recent years is far from advancing the subject. NAVIGATE ESUS was unable to measure the effect during the sufficient follow-up period, as the study was terminated quite early on. In addition, only 19% of patients underwent transesophageal echocardiography; hence, the diagnosis of PFO was not established with methods of an appropriate sensitivity (7). Demographic data, even age, were not extractable for the PFO subgroup in the RESPECT-ESUS study because only the main results were published (5). Perhaps most importantly, the number of patients in the PFO subgroup lost to follow-up was not stated in any of the studies.

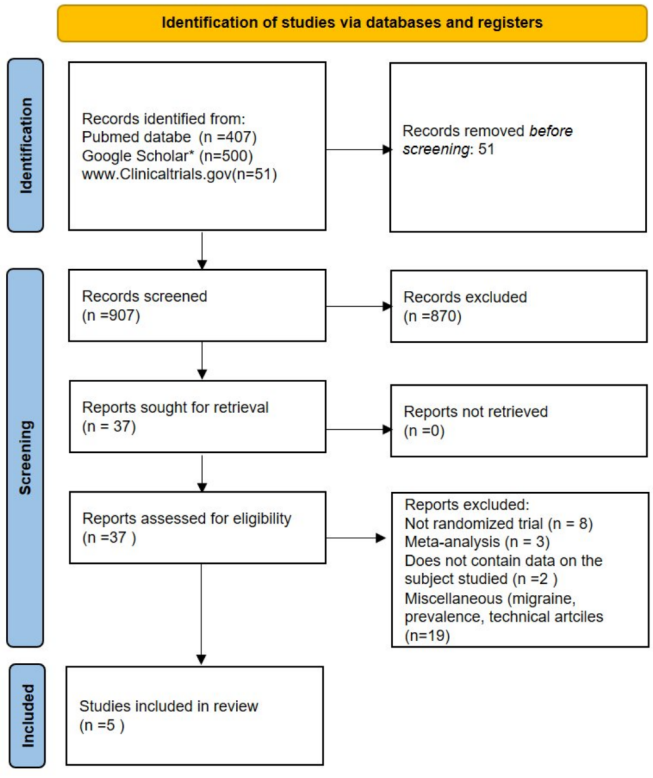

Figure 1. PRISMA diagram

A total of 3 meta-analyses have been conducted on this subject, none of which have produced a positive result and all of which have noted the requirement for a randomized controlled study (10,11,12). Kent et al. (10) evaluated 12 observational studies, involving a total of 804 patients administered with OAC and 1,581 patients administered with APT. The combined risk of stroke, transient ischemic attack recurrence, and death was determined as 0.75 (95% CI: 0.44–1.27) with the use of OAC. This was 25% less than with APT; however, the difference was not statistically significant (10). Romoli et al. (11) evaluated 5 randomized trials (n = 1.565) in their successful meta-analysis and reported that the recurrence of stroke decreased but did not reach statistical significance in 753 OAC users [odds ratio (OR): 0.66; 95% CI: 0.41–1.07] (11). The use of OAC resulted in a relatively high bleeding rate when compared with the platelet treatment; however, the difference was not statistically significant (OR: 1.64, 95% CI: 0.79–3.43). In the present analysis, OAC use was found to be significantly more effective than platelet use in reducing stroke recurrence in patients with a high RoPE score (19) (OR: 0.22, 95% CI: 0.06–0.80). This point requires further detailed study in the future. Finally, 1,720 patients in the same 5 studies (mean follow-up time of 2.3 years) were analyzed in the meta-analysis by Sagris et al. (12). There was no significant difference in annual stroke recurrence rate between OAC and APT users (1.71% in the OAC group vs. 2.39% in the Aspirin group; OR: 0.68, 95% CI: 0.32–1.48). The bleeding complication rate was 1.16% per year in the OAC treatment and 0.68% in the ASA treatment; the difference was not statistically significant (OR: 1.61, 95% CI: 0.65–1.70) (12).

Conclusion

In conclusion, it is noteworthy that although secondary protection with OAC might seem more effective compared with platelet use, some of its benefits are neutralized by the increase in bleeding rate. In our opinion, it is difficult to make an efficient conclusion from the data available in the germane literature. The difficulty of interpretating these results is due to a wide variety of reasons, starting with the high incidence of both diseases, which always challenges the causal relationship, and extending to the absence of a randomized study with a fragility index >0, which was reported herein. Our observation states that there is a serious uncertainty regarding the transfer of available information into the clinical field. The only way to remedy this is a multicenter and preferably multinational randomized controlled trial.

Table 1. Main features of randomized trials of medical therapy for secondary stroke prevention in patent foramen ovale

	RESPECT ESUS*	NAVIGATE ESUS*	CLOSE	Shariat et al. (9)	PICSS
Publication year	2019	2018	2017	2013	2002
n (%)**	680 (12.6%)	534 (7.4%)	361	44	98 (48%)
Mean age (years)	-	65	44	61	58
Duration (years)	1.6	0.9	5.3	1.2	2
Anti-platelet	Aspirin 100 mg	Aspirin 100 mg	Aspirin (87%) Clopidogrel, aspirin-dipyridamole	Aspirin 240 mg	Aspirin 325 mg
Anticoagulant	Dabigatran 2 x 150 mg	Rivaroxaban 15 mg	Warfarin (93%) NOAC (7%)	Warfarin (INR, 2-3)	Warfarin (INR, 1.4-2.8)

*PFO subgroup analysis, **Percent of patients with PFO in whole study population. PFO: Patent foramen ovale, NOAC: Non-vitamin-K oral anticoagulants, INR: International normalised ratio

Table 2. Treatment effect and fragility

	Anti-platelet			Anticoagulant			Fragility	P	
Recurrence	**Event**	**Total**	**%**	**Event**	**Total**	**%**		**Original**	**Fragile**
PICSS, 2002	8	56	14.3	2	42	4.8	0	0.280	0.181
Shariat et al. (9) 2013	2	23	8.7	5	21	23.8	0	0.255	0.245
CLOSE, 2017	7	174	4.0	3	187	1.6	0	ns*	0.206
NAVIGATE-ESUS, 2018	13	275	4.7	7	259	2.7	0	0.258	0.258
RESPECT-ESUS, 2019	19	361	5.3	16	319	5.0	0	ns*	1
Hemorrhage	**Event**	**Total**	**%**	**Event**	**Total**	**%**		**Original**	**Fragile**
Shariat et al. (9) 2013	1	23	4.3	2	21	9.5	0	0.501	0.609
CLOSE, 2017	4	174	2.3	10	187	5.3	0	0.180	0.625
NAVIGATE-ESUS, 2018	3	275	1.1	6	259	2.3	0	0.327	0.327
RESPECT-ESUS, 2019	5	361	1.4	3	319	0.3	0	0.729	0.729

*Non-significant or only OR/HR reported

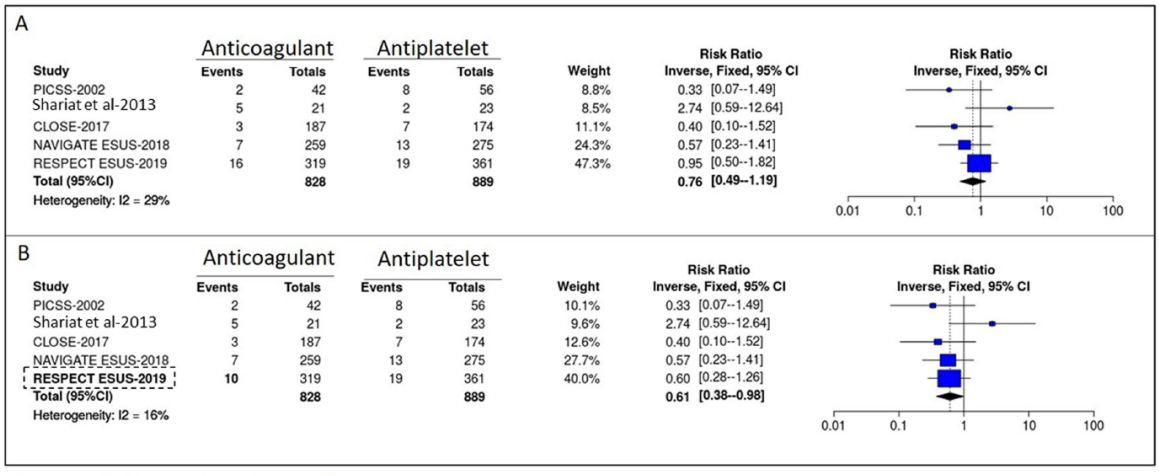

Figure 2. Meta analysis and fragility index meta-analysis for recurrence
Forest plot of a statistically non-significant meta-analysis of 5 trials: a standard meta-analysis is summarized in the upper bank (A). The bottom row summarizes the fragility study of this meta-analysis (B). This figure shows the minimum number of patients without the primary outcome of the meta-analysis becoming "positive." In brief, if 6 patients of RESPECT-ESUS (in dashed-line boxes) did not experience any event, the result would be positive. Please return to the text for details and reference #15

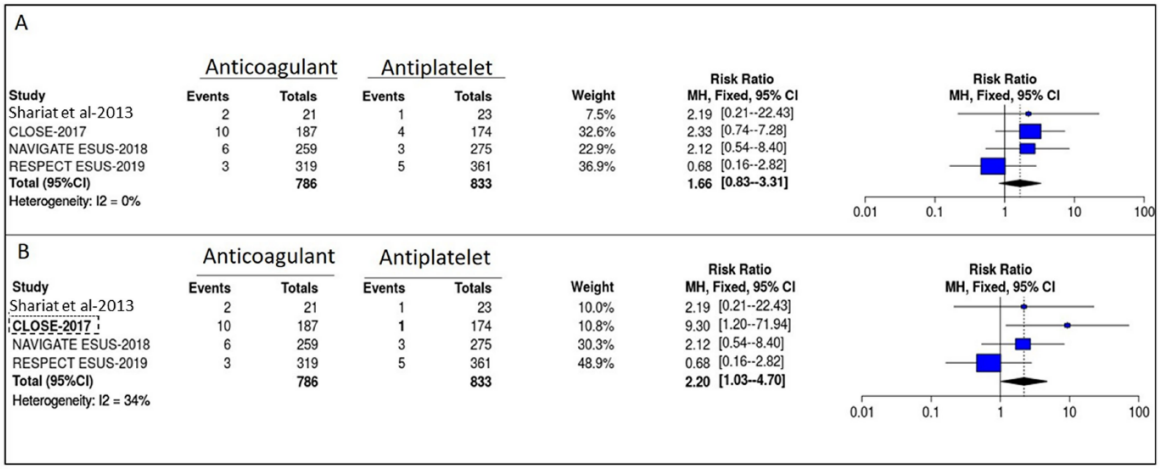

Figure 3. Meta-analysis and fragility index meta-analysis for significant bleeding
Forest plot of a statistically non-significant meta-analysis of 4 trials (since the PICCS study did not provide data in this regard, it was not included in the analysis): a standard meta-analysis is summarized in the upper bank (A). The bottom row summarizes the fragility study of this meta-analysis (B). This figure shows the minimum number of patients without the primary outcome of the meta-analysis becoming "positive." In brief, if 3 patients of the CLOSE study (in dashed-line boxes) did not experience any event, the result would be positive. Please return to the text for details and reference #15

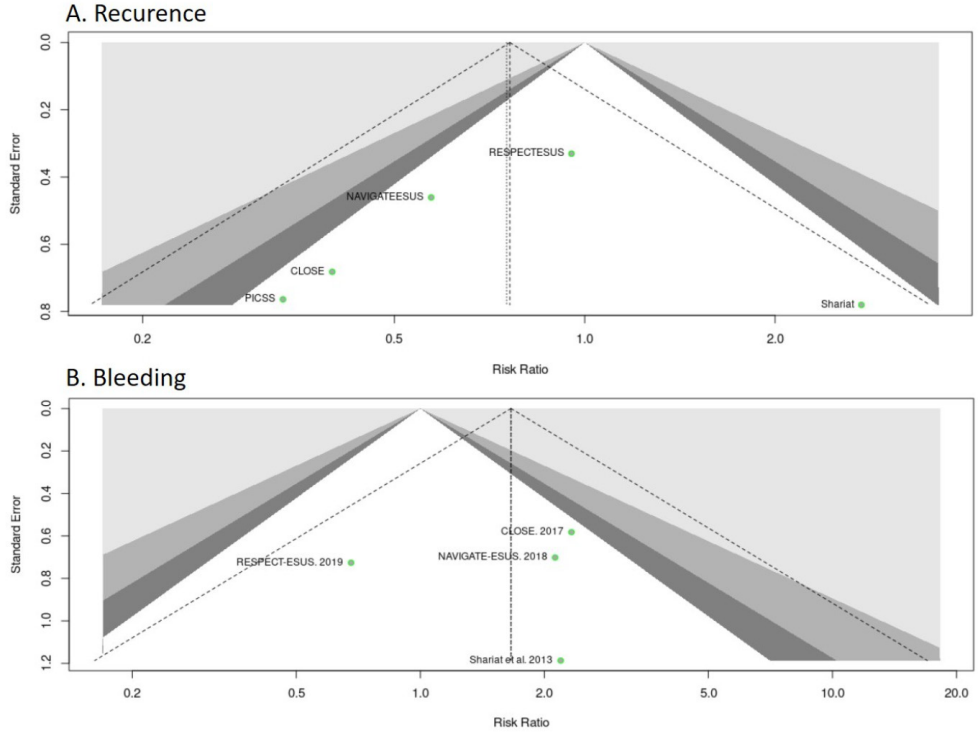

Figure 4. Funnel plot for bias. A contour-enhanced funnel plot for the meta-analyses on recurrence (A, upper) and bleeding (B, lower) is presented. The dashed lines represent the fixed-effect estimate and the 95% confidence interval. The dotted vertical line is the random effect estimate. The *P* values are $0.1 > P > 0.05$ for the dark gray zone; $0.05 > P > 0.01$ for the light gray zone; $P < 0.01$ for the very light gray zone; and $P > 0.1$ for the white zone. Peripheral and asymmetrical distribution in the funnel plot diagram and all studies staying in the white zone can be considered as a publication bias. However, the number of studies with relatively valid results is >9 due to the use of Egger's Regression test performed for publication bias for both analyses. It does not seem possible to reach this number (up to 2x) in the foreseeable future due to the randomized nature of the studies and the lack of an active (ongoing or planned) process. Furthermore, in the fail-safe N calculation using the Rosenthal approach, the *P* values were $P = 0.0854$ and $P = 0.0850$ for bleeding. These all suggest that the publication bias was not statistically significant

Ethics

Ethics Committee Approval: Ethics committee approval is not required.

Informed Consent: Not required.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.M.A., M.A.T., Design: E.M.A., M.A.T., Data Collection or Processing: E.M.A., M.A.T., Analysis or Interpretation: E.M.A., M.A.T., Literature Search: E.M.A., M.A.T., Writing: M.A.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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