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Letter to the Editor

An Updated Meta-Analysis Comparing Percutaneous Device Closure with Medical Therapy Alone for Patent Foramen Ovale in Patients with Cryptogenic Stroke

To the Editor

Stroke is a leading cause of mortality and disability worldwide. It is estimated that about 1 of 3 ischemic strokes are cryptogenic. Several observational studies have shown that patent foramen ovale (PFO) is associated with cryptogenic stroke. Although early randomized controlled trials (RCTs) failed individually to prove the superiority of PFO closure over medical therapy alone (MTA), a result of poor patient and device selection [1,2], new trials and meta-analyses in the last year proved device closure was superior [3,4]. However, in recent months, a new positive RCT (DEFENCE-PFO) has been reported, making previous meta-analyses arguably out of date [5].

This meta-analysis was performed according to the PRISMA guidelines. Scientific databases were searched for relevant RCTs. Trials were included if they enrolled cryptogenic stroke patients with PFO and randomly assigned them to either device closure or MTA. Pooled risk ratios were calculated using a random-effects model. In the CLOSURE-I trial, the STARFlex device was used, but it is no longer commercially available because of its low procedural success rate [1]. Therefore, the CLOSURE I trial was excluded from our additional sensitivity analysis to improve the generalizability of our findings. Publication bias was not assessed because the number of included trials was inadequate (<10) to properly assess a funnel plot or to use more advanced regression-based assessments [6].

Data from 6 RCTs enrolling 3747 patients were included. Compared to MTA, PFO closure decreased recurrent stroke risk by 59% (RR, 0.41; 95% CI, 0.20–0.82; $P = 0.012$; Fig. 1A). Statistically significant heterogeneity between trials was not found. The benefits of PFO closure over MTA became even more robust after excluding the CLOSURE I trial (RR, 0.30; 95% CI, 0.13–0.67; $P = 0.003$). Device closure was also associated with a nearly four-fold greater risk of new-onset atrial fibrillation (AF) compared to MTA (RR, 3.94; 95% CI, 2.07–7.49; $P < 0.001$; Fig. 1B). Significant heterogeneity between trials was not found for AF risk ($I^2 = 18.2\%$). Device closure did not decrease risk of transient ischemic attack **TIA** (RR, 0.78; 95% CI, 0.53–1.14; $P = 0.211$) or all-cause mortality (RR, 0.74; 95% CI, 0.35–1.57; $P = 0.445$). In addition, risk of major bleeding was similar between the two therapies (RR, 0.63; 95% CI, 0.23–1.66; $P = 0.353$; Fig. 1C). However, moderate heterogeneity ($I^2 = 48.3\%$) was found for risk of major bleeding. Sensitivity analysis suggests this heterogeneity was derived from the CLOSURE I trial; once it was removed, heterogeneity resolved ($I^2 = 0\%$), and device therapy was associated with a statistically significant decrease in risk of major bleeding (RR, 0.43; 95% CI, 0.20–0.93; $P = 0.032$; Fig. 1D). This heterogeneity is derived from use of an old generation device (the STARFlex, associated with higher complication rates, including bleeding rate) in the CLOSURE I trial.

Several studies have shown strong associations between PFO and cryptogenic stroke, particularly among those aged <60 years. However, the first three RCTs (CLOSURE I, PC, and RESPECT) individually failed to show differences between treatment with a transcatheter device and MTA [1,2]. The 3 more recent trials (CLOSE, REDUCE, and DEFENCE-PFO) and long-term follow-up of RESPECT participants showed the PFO device was superior to MTA [3–5]. It has been suggested that these recent positive results stem from better patient selection using thorough evaluations to identify true cryptogenic stroke [5]. This highlights the importance of a thorough evaluation to identify true cryptogenic stroke before PFO closure with a device.

Previous RCTs as well as this meta-analysis show that device closure is associated with increased risk of new-onset AF. However, absolute risk seems low. At times, AF was transient, occurring only during the procedure. In addition, it seems AF risk is lower when the FDA-approved Amplatzer PFO occluder is used. Nevertheless, it is a critical safety issue, and patients must be informed about this potential risk during shared decision-making.

In conclusion, in this updated meta-analysis of six RCTs involving the largest sample size to date, we found that in patients with cryptogenic stroke, device closure for PFO, compared to MTA, decreases recurrent risk of stroke and increases the incidence of AF. In addition, with the large sample size, we were able to show that the use of new-generation devices is associated with lower risk of major bleeding compared to MTA; this potential benefit of device closure has not yet been reportedly found using meta-analysis (likely because of a type II error).

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Declaration of Competing Interest

None.

Rahman Shah*
Amanda D. Currie
Sajjad Khan
Farhan Ashraf
Department of Medicine, University of Tennessee, Memphis, TN, USA
*Corresponding author at: University of Tennessee, School of Medicine, Division of Cardiovascular Medicine, 1030 Jefferson Avenue, Memphis, TN 38104, USA
E-mail address: Shahcardiology@yahoo.com

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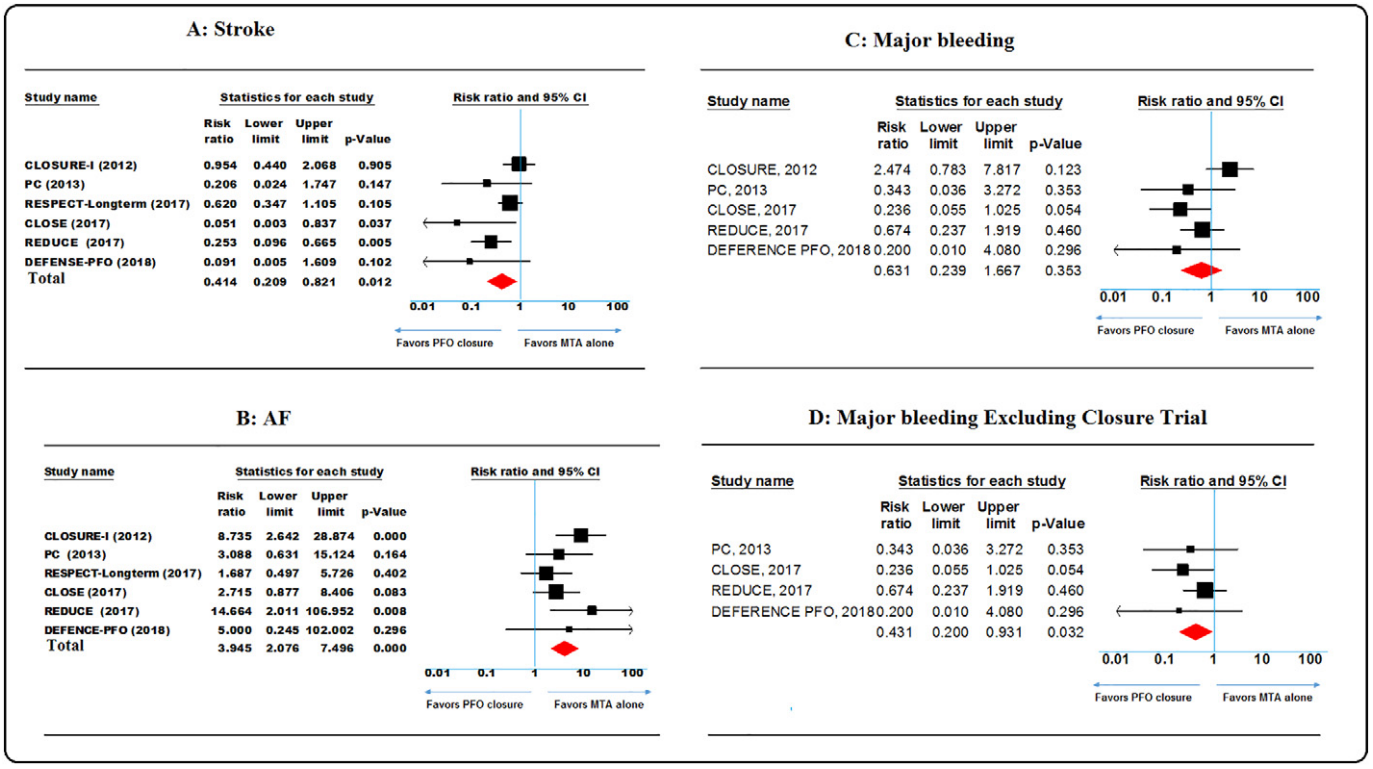

Fig. 1. Individual and pooled risk ratios for (A) recurrent stroke, (B) atrial fibrillation (AF), (C) major bleeding and (D) major bleeding excluding Closure trial.

References

[1] Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. NEJM 2012;366(11):991–9.

[2] Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. NEJM 2013;368(12):1083–91.

[3] Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. NEJM 2017;377(11):1011–21.

[4] Sondergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. NEJM 2017;377(11):1033–42.

[5] Lee PH, Song JK, Kim JS, Heo R, Lee S, Kim DH, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. J Am Coll Cardiol 2018;71:2335–42.

[6] Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.