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Patent Foramen Ovale Closure Versus Medical Therapy After Cryptogenic Stroke

To the Editor:

We read with great interest the recent updated meta-analysis by Vaduganathan et al evaluating patent foramen ovale closure for prevention of cryptogenic stroke.[1] Although we congratulate and applaud their excellent work, we would like to comment on several important issues in the study.

First, they mistakenly take counting patients as counting events. The results of the outcomes of interest (eg, primary outcome, transient ischemic attack [TIA], stroke) are counts that may occur more than once for an individual participant. In the 5 included randomized controlled trials (RCTs), they all reported counts (numbers or ratios) of patients suffering events, but not the counts of events themselves whereas Vaduganathan et al mistakenly used the numbers of patients as the numbers of events for the primary outcome. Additionally, for outcomes of stroke or TIA, they calculated the events of stroke or TIA incorrectly, combining the numbers of patients undergoing stroke and the numbers of patients suffering TIA. Besides 1 participant being subjected to the same event more than once, the situation that both TIA and stroke may occur in the same individual participant was also involved.

Second, time-to-event data with hazard ratios (HRs) and 95% confidence intervals (CIs), but not incidence rates with risk ratios and 95% CIs, should be used to calculate pooled estimate. In the 5 included RCTs, all reported primary outcomes as time-to-event data with HRs and 95% CIs, indicating the instantaneous risks over the study time period but not the cumulative risks over the entire study (risk ratios). According to the Cochrane handbook for systematic review of intervention,[2] the data forms in which they were originally reported are generally used for count data. Therefore, HR and 95% CIs should be used to calculate the pooled estimates, as shown in the **Figure**.

Third, though TIA is a mini-stroke, we separately pooled estimates for TIA and stroke, as the included RCTs reported. The null association of TIA between patent foramen ovale closure and medical therapy might be attributed to the small sample and potential clinical heterogeneity.

Fourth, subgroup analysis according to gender, medical therapy (anticoagulation, anticoagulation plus antiplatelet, or antiplatelet), and shunt size should be addressed. No beneficial effects of patent foramen ovale closure were observed in patients with small or moderate shunt size or female patients. Additionally, benefit of patent foramen ovale closure for primary outcomes existed only by comparison with antiplatelet therapy, but not anticoagulation or anticoagulation plus antiplatelet therapy. Therefore, further studies are urged to focus on these factors.

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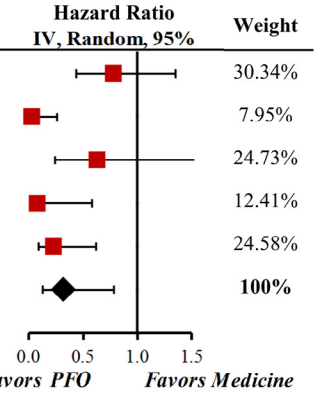
References

1. Vaduganathan M, Qamar A, Gupta A, et al. Patent foramen ovale closure for secondary prevention of cryptogenic stroke: updated meta-analysis of randomized clinical trials. *Am J Med*. 2017; doi:10.1016/j.amjmed.2017.11.027.
2. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. [updated March 2011]. The Cochrane Collaboration, 2011. Available at: http://handbook.cochrane.org. Accessed December 20, 2017.

A) Primary outcome

StudyID	Primary outcome definition	Hazard Ratio IV, Random, 95%	Weight
Furlan 2012	Stroke or TIA, death	0.78 (0.44 to 1.35)	30.34%
Mas 2017	Fatal or nonfatal stroke	0.03 (0.00 to 0.26)	7.95%
Meier 2013	Death, nonfatal stroke, TIA, or peripheral embolism	0.63 (0.24 to 1.62)	24.73%
Saver 2017	Fatal or nonfatal stroke,or early death	0.08 (0.01 to 0.58)	12.41%
Søndergaard 2017	Clinical ischemic stroke	0.23 (0.09 to 0.62)	24.58%
Total (95%CI)	**Primary outcome**	**0.32 (0.13 to 0.78)**	**100%**

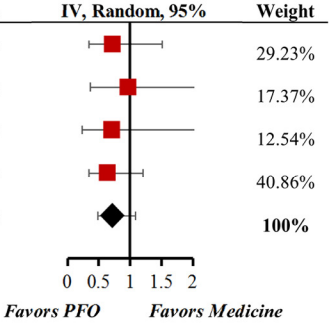
Heterogeneity: I^2=67.2%, P = 0.016
Test for over effect size: Z = 2.51 P = 0.012



B) Transient ischemic attack

StudyID	No. of patients PFO	No. of patients Medicine	Hazard Ratio IV, Random, 95%	Weight
Furlan 2012	447	462	0.72 (0.34 to 1.51)	29.23%
Mas 2017	238	235	0.97 (0.37 to 2.56)	17.37%
Meier 2013	204	210	0.71 (0.23 to 2.24)	12.54%
Saver 2017	449	481	0.64 (0.34 to 1.20)	40.86%
Total (95%CI)	**1338**	**1388**	**0.72 (0.48 to 1.08)**	**100%**

Heterogeneity: I^2 = 0%, P = 0.919
Test for over effect size: Z = 1.59, P = 0.112



C) Stroke

StudyID	No. of patients PFO	No. of patients Medicine	Hazard Ratio IV, Random, 95%	Weight
Furlan 2012	447	462	0.94 (0.43 to 2.07)	29.57%
Mas 2017	238	35	0.03 (0.00 to 0.26)	11.94%
Meier 2013	204	210	0.20 (0.02 to 1.72)	14.94%
Saver 2017	449	481	0.08 (0.01 to 0.58)	16.52%
Søndergaard 2017	441	223	0.23 (0.09 to 0.62)	27.62%
Total (95%CI)	**1779**	**1411**	**0.23 (0.07 to 0.72)**	**100%**

Heterogeneity: I^2 = 66.4%, P = 0.018
Test for over effect size: Z = 2.53, P = 0.011

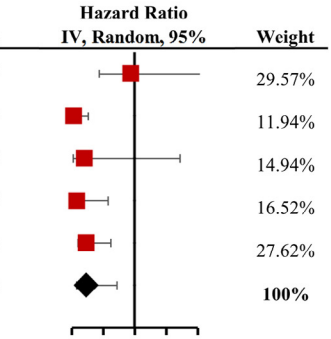


Figure Forest plots for the primary outcome (**A**), transient ischemic attack (**B**), and stroke (**C**). CI = confidence interval; IV = inverse variance; PFO = patent foramen ovale; TIA = transient ischemic attack.