PFO-Mediated Stroke: Exposing the Misnomer of "Cryptogenic" Stroke

To the Editor,

We read with interest the recent article by Wintzer-Wehekind et al.[1] In an observational study of 453 consecutive patients who underwent patent foramen ovale (PFO) closure due to an ischemic event of no other apparent cause, the authors evaluated the safety of discontinuing antithrombotic therapy following PFO closure. At a median follow-up of 8 years, antithrombotic therapy was associated with a 6% incidence of bleeding, and the subset of patients who discontinued their blood thinners did not have more recurrent ischemic events on long-term follow-up. The authors should be commended for their work, which expands on their earlier report[2] to support the intuitive conclusion that following PFO closure, discontinuing antithrombotic therapy is safe and does not increase risk of recurrent ischemic events, for patients without other co-morbidities. In this letter, we provide additional insight on the misnomer of "cryptogenic" stroke when associated with PFO[3–5]; we describe how an outdated misclassification of stroke from the early 1990s has continued to result in ignoring of a quick, effective, and life-saving percutaneous treatment in the face of a glaring stroke culprit.

There has been limited progress in developing new therapeutic techniques to decrease the incidence of recurrent cryptogenic stroke. A major barrier is that the diagnostic evaluation of "cryptogenic stroke" has yet to be updated to identify occult stroke culprits that were left out of the traditional TOAST (Trial of Org 10172 in Acute Stroke Treatment) or ASCOD (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: dissection) classifications.[6,7] Although atrial fibrillation or flutter (AF) mediated stroke was also included under the heading of "cryptogenic stroke", this was later rectified and AF is now recognized as a common stroke etiology, even when it is detected after the index hospitalization. Unfortunately, the updated term embolic stroke of undetermined source continues to neglect PFO-mediated stroke (i.e., ischemic stroke in the presence of PFO with no other apparent cause) as a separate stroke entity.[8]

Four recent randomized trials and their meta-analyses have unequivocally established the superiority of percutaneous PFO closure over standard of care medical therapy for secondary prevention of PFO-mediated stroke.[9–14] These studies confirmed that there is a causal relationship between PFO and the so called "cryptogenic stroke." Thus, categorizing PFO-mediated stroke as an "unknown etiology" has always been counterintuitive and has now become illogical, ignoring the diagnostic and management strategies proposed by updated international guidelines and the United States Food and Drug Administration. PFO-mediated stroke should be recognized as a unique and distinct ischemic stroke entity when no other etiologies can be identified. This change would be consistent with other well-recognized stroke causes, henceforth promoting an etiology-guided management approach and aiding subsequent research to establish appropriate therapies for stroke with and without PFO. Guidelines from the respective neurologic and cardiovascular national societies must be updated to focus on management strategies of patients with PFO-mediated stroke.

Some may argue that the PFO was an "innocent bystander" or that PFO-mediated stroke is only "presumed" to be from paradoxical embolism. However, this argument should no longer be acceptable; nearly all stroke causes are "presumed" to be from a detected etiology, whether that cause is uncontrolled hypertension or embolism because of AF or a carotid plaque.

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1. Wintzer-Wehekind J, Alperi A, Houde C, Côté JM, Guimaraes LFC, Côté M, Rodés-Cabau J. Impact of discontinuation of antithrombotic therapy following closure of patent foramen ovale in patients with cryptogenic embolism. *Am J Cardiol* 2019. https://doi.org/10.1016/j.amjcard.2019.01.043. Epub ahead of print.
2. Wintzer-Wehekind J, Alperi A, Houde C, Côté JM, Asmarats L, Côté M, Rodés-Cabau J. Long-term follow-up after closure of patent foramen ovale in patients with cryptogenic embolism. *J Am Coll Cardiol* 2019;73:278–287.
3. Mattle HP, Saver JL. Patent foramen ovale increases stroke risk in older people. *Nat Rev Neurol* 2018;14:573–574.
4. Meier B. Optimal stroke prevention in patients with patent foramen ovale. *Lancet Neurol* 2018;17:1027–1028.
5. Meier B, Nietlisbach F. Device closure of the patent foramen, the longer you look, the more you like it. *J Am Coll Cardiol* 2009;73:288–290.
6. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment.. *Stroke* 1993;24:35–41.
7. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (Updated ASCO Phenotyping). *Cerebrovasc Dis* 2013;36:1–5.
8. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnel MJ, Sacco RL, Connolly SJ. Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol.* 2014;13:429–438.
9. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonal LA, Marks DS, Tirschwell DL; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;377:1022−1032.
10. Søndergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjöstrand C, Roine RO, Hildick-Smith D, Spence JD, Thomassen L; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017;377:1033−1042.
11. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, Arquizan C, Béjot Y, Vuillier F, Detante O, Guidoux C, Canaple S, Vaduva C, Dequatre-Ponchelle N, Sibon I, Garnier P, Ferrier A, Timsit S, Robinet-Borgomano E, Sablot D, Lacour JC, Zuber M, Favrole P, Pinel JF, Apoil M, Reiner P, Lefebvre C, Guérin P, Piot C, Rossi R, Dubois-Randé JL, Eicher JC, Meneveau N, Lusson JR, Bertrand B, Schleich JM, Godart F, Thambo JB, Leborgne L, Michel P, Pierard L, Turc G, Barthelet M, Charles-Nelson A, Weimar C,

Moulin T, Juliard JM, Chatellier G; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med.* 2017;377:1011–1021.
12. Lee PH, Song JK, Kim JS, Heo R, Lee S, Kim DH, Song JM, Kang DH, Kwon SU, Kang DW, Lee D, Kwon HS, Yun SC, Sun BJ, Park JH, Lee JH, Jeong HS, Song HJ, Kim J, Park SJ. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol* 2018;71:2335–2342.
13. Mojadidi MK, Zaman MO, Elgendy IY, Mahmoud AN, Patel NK, Agarwal N, Tobis JM, Meier B. Cryptogenic stroke and patent foramen ovale. *J Am Coll Cardiol* 2018;71:1035–1043.
14. Mojadidi MK, Elgendy AY, Elgendy IY, Mahmoud AN, Elbadawi A, Eshtehardi P, Patel NK, Wayangankar S, Tobis JM, Meier B. Transcatheter patent foramen ovale closure after cryptogenic stroke: an updated meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2017;10:2228–2230.

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Meta-analysis of Percutaneous Coronary Intervention Versus Medical Therapy in the Treatment of Coronary Chronic Total Occlusion

Coronary chronic total occlusion (CTO) is a common finding during coronary angiography and is associated with increased morbidity and mortality.[1] Historically, treating a CTO with percutaneous coronary intervention (PCI) was technically difficult with a low success rate and a high rate of complications.[1,2] Technical and operator skill advancements have led to an increased frequency and procedural success rate of contemporary CTO-PCI.[3] Nevertheless, the benefit of this treatment remains controversial. Therefore, we conducted this meta-analysis to evaluate the efficacy and safety of PCI in CTO.

A search through Pubmed, MEDLINE, and Cochrane Library from inception up to September 2018 was performed by 2 independent reviewers and any discrepancy was resolved by a third reviewer. We included only randomized controlled trials (RCTs) that compared CTO-PCI with medical therapy (MT). Two independent reviewers screened and extracted the data using a predefined table. The primary end point was major adverse cardiac and cerebrovascular events (MACCE). Secondary end points included all-cause mortality, cardiac death, spontaneous myocardial infarction (MI), repeat revascularization, target vessel revascularization (TVR), stent thrombosis, and left ventricle ejection fraction (LVEF) change. We calculated the risk ratios (RRs) and 95% confidence intervals (CIs) using a random-effects model with the aid of RevMan v5.3 and CMA v3 software in an intention-to-treat analysis. The meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42019121399).

From a total of 528 screened studies, 5 randomized controlled trials were included, [1,2,4,5,6] with a total of 1,792 patients (mean age 62.7 ± 9.7, 84% male, follow up range 4 to 60 months). The procedural success rate was ~86% (as-treated). The right coronary artery was the most commonly involved artery in the included trials (~54%).

There was no significant difference between CTO-PCI or MT with regard to MACCE (RR 0.83; 95% CI 0.50 to 1.36; $p = 0.45$; $I^2 = 47\%$). In a trial sequential analysis (TSA software)[7] to establish whether the current sample size and events were adequately powered to draw conclusive results (using a 17.8% incidence of MACCE in the MT group, 25% relative risk reduction in the PCI group, 5% type-α error, and 80% power), we found that the optimal information (sample) size was not achieved with the current meta-analysis (1,792 vs 11,895 patients) and the cumulative Z-curve did not cross any trial sequential boundaries, indicating a lack of evidence. A subgroup analysis based on the initial cardiac event (acute coronary syndrome vs stable) showed no evidence of interaction (p for interaction >0.1). Meta-regression analyses based on study-level covariates (SYNTAX score, J-CTO score, LVEF, and left anterior descending [LAD] artery percentages) did not suggest any statistically significant modifier effect. CTO-PCI significantly reduced TVR compared with MT (RR 0.34; 95% CI 0.16 to 0.72; $p < 0.01$; $I^2 = 10\%$). There were no significant differences between both groups with regard to all-cause mortality, cardiac mortality, spontaneous MI, stent thrombosis, repeat revascularization, or LVEF change (Figure 1). Sensitivity analysis by including only the published trials did not change any of the end points results.

A subgroup analysis of the EXPLORE trial showed a better outcome when the target vessel was the LAD.[2] Similarly, a meta-analysis published by Ma et al suggested better outcomes when PCI was done on a CTO involving the left coronary artery or its branches.[3] However, we were not able to demonstrate any effect of LAD CTO-PCI on MACCE.

The complexity of coronary artery disease in the treatment of CTO should always be considered. In the REVASC trial, patients with less complex disease (SYNTAX score ≤13), mainly derived by the CTO lesion itself, had better segmental wall thickening improvement with CTO-PCI.[4] In our meta-regression, there was a nonsignificant trend toward increased MACCE with higher SYNTAX score. Further adequately powered trials are needed to examine the clinical outcomes of CTO-PCI in those with CTO driven ischemia.

In conclusion, in patients with CTO, PCI was not associated with significant reductions in MACCE, all-cause mortality, MI, stent thrombosis, or repeat revascularization, though there was a significantly lower incidence of TVR compared with MT. However, further adequately powered and long-term trials are required to identify the best treatment strategy of CTOs.

Disclosures

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