EDITORIAL COMMENTARY

# Evidence gaps pertaining to high-risk medications: Commentary on anticoagulation in new-onset postoperative atrial fibrillation

Enoch Akowuah, MD, FRCS (CTh),* Richard Whitlock, MD, PhD, FRCSC†

*From the *James Cook University Hospital, Middlesbrough, United Kingdom, and †McMaster University, Hamilton, Canada.*

Postoperative atrial fibrillation (POAF) is a common problem after cardiac surgery and the incidence is likely to increase as older and sicker patients continue to undergo surgery.[1] The underlying causes are multifactorial and include preexisting atrial myocardial changes; increased noradrenergic tone due to the insult of surgery and perioperative drugs; the systemic inflammatory response resulting from, for example, cardiopulmonary bypass and insults like infection and hypoxia; and surgical incisions in the heart itself during surgery.[2]

Studies have suggested that POAF has a negative impact on short- and long-term clinical outcomes. For example, in 3023 patients randomized to the ARTS trial, of whom 734 (24.3%) developed POAF and 2289 remained in sinus rhythm, patients with POAF after coronary artery bypass grafting were at higher risk of cerebrovascular accident (a cumulative incidence of 6.3% vs 3.7% if no POAF at 10 years follow-up).[3]

Current guideline recommendations from national and international professional societies regarding the use of antithrombotic strategies for POAF after cardiac surgery have a poor evidence base with no high-quality randomized controlled trial data. With some vagueness, the 2016 ESC (European Society of Cardiology) guidelines[4] recommend that long-term anticoagulation should be considered in patients with POAF at risk for stroke, considering individual stroke and bleeding risk (class IIa, level of evidence B). Similar to the ACC/AHA guidelines,[5,6] the ESC guidelines do not provide clear recommendations on the duration and type of oral anticoagulation (OAC) to use in patients who develop POAF.

Despite the uncertainties, current practice in most countries for the management of POAF is guided by data on patients with permanent or persistent atrial fibrillation without data on postoperative cardiac surgery patients specifically—the result of which is that anticoagulation for POAF is common practice in many countries.

A feared adverse effect of anticoagulation is bleeding, the risks of which are well documented. Major bleeding can have a devastating impact on patients, including major morbidity and death. The ACTIVE-Warfarin and RELY trials indicated that risk of death increased 8-fold after an ischemic stroke, but 27-fold after a hemorrhagic stroke, and 5-fold after extracranial bleeding.[7,8] Trials including OASIS 5,[9] HORIZONS-AMI,[10] and ENGAGE-AF[11] demonstrate that reducing major bleeding significantly reduces mortality.

Given this clinical context, the findings of the report by Riad and colleagues[12] are interesting. They obtained data on 768,277 patients undergoing isolated coronary artery bypass graft (CABG) without a history of atrial fibrillation or flutter from July 2011 through December 2016 from The Society of Thoracic Surgeons Adult Cardiac Surgery Database. After exclusions, 38,936 patients, of which 9861 (25%) were discharged on anticoagulation, were included in the analysis. After propensity matching, 19,722 patients remained for adjusted analysis.

The main findings of the paper are that anticoagulation use for POAF is associated with increased mortality and increased readmission for bleeding (with rates of bleeding highest within 30 days of discharge). They found that anticoagulation did not reduce systemic thromboembolic complications after surgery; however, readmission for myocardial infarction was reduced—a finding that is unexplained by the authors. Importantly, there was no interaction between $CHA_2DS_2$-VASc and any of the primary or secondary outcomes, suggesting that the findings in this study are widely applicable to most patients undergoing CABG and suffering POAF.

The study has a number of limitations. The yearly rate of stroke was approximately 4 times lower (1%–2% per year) than would have been predicted by the $CHA_2DS_2$-VASc. It may be that stroke rates in the post-CABG population differ significantly from the population used to validate $CHA_2DS_2$-VASc, or that the use of the Medicare database to assess events resulted in undercapture. There is lack of detail about the impact of different anticoagulation regimes (warfarin vs direct OAC agents), the duration of postoperative anticoagulation therapy

**Address reprint requests and correspondence:** Dr Richard Whitlock, David Braley Research Institute, c/o Hamilton General Hospital, 237 Barton St East, Hamilton, ON L8L 2X2, Canada. E-mail address: richard.whitlock@phri.ca.



https://doi.org/10.1016/j.hroo.2022.07.006

(it would be important if OAC treatment is stopped at 2–6 weeks vs stopped at 2–6 months vs continued in perpetuity), and a lack of information about the burden of POAF in the weeks after surgery. These limitations should be considered when assessing the study's results. Nevertheless, this report highlights the need for well-conducted randomized controlled trial evidence to guide international practice and guidelines. The ongoing Anticoagulation for New-Onset Post-Operative Atrial Fibrillation after CABG (PACeS) Trial (ClinicalTrials.gov Identifier: NCT04045665) is seeking to recruit 3600 patients and will provide robust evidence in this space. The primary objective of this study is to evaluate the effectiveness (prevention of thromboembolic events) and safety (major bleeding) of adding OAC to background antiplatelet therapy in patients who develop new-onset POAF after isolated CABG surgery.

In the interim, this report raises important questions about the current management of POAF after CABG and is a welcome addition to the literature.

**Funding Sources**: None.

**Disclosures**: Dr Whitlock reports grants from Abbott, AtriCure, Boehringer Ingelheim, and BMS Pfizer and consultancy fees from PhaseBio, AtriCure, and Artivion. Dr Akowuah reports no conflicts of interest.

**Authorship**: All authors attest they meet the current ICMJE criteria for authorship.

## References

1. Abdelmoneim SS, Rosenberg E, Meykler M, et al. The incidence and natural progression of new-onset postoperative atrial fibrillation. JACC Clin Electrophysiol 2021;7:1134–1144.
2. Helgadottir S, Sigurdsson MI, Ingvarsdottir IL, Arnar DO, Gudbjartsson T. Atrial fibrillation following cardiac surgery: risk analysis and long-term survival. J Cardiothorac Surg 2012;7:87.
3. Benedetto U, Gaudino MF, Dimagli A, et al. Postoperative atrial fibrillation and long-term risk of stroke after isolated coronary artery bypass graft surgery. Circulation 2020;142:1320–1329.
4. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609–1678.
5. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019; 74:104–132.
6. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021; 143:e72–e227.
7. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774–782.
8. Eikelboom JW, Connolly SJ, Hart RG, et al. Balancing the benefits and risks of 2 doses of dabigatran compared with warfarin in atrial fibrillation. J Am Coll Cardiol 2013;62:900–908.
9. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006; 354:1464–1476.
10. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008; 358:2218–2230.
11. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–2104.
12. Riad FS, Grau-Sepulveda M, Jawitz OK, et al. Anticoagulation in new-onset postoperative atrial fibrillation: an analysis from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Heart Rhythm O2 2022;3:325–332.