- syndromes undergoing coronary artery bypass surgery: the ACUTY (Acute Catheterization and Urgent Intervention Triage strategY) trial. *J Am Coll Cardiol*. 2009;53:1965-72.
3. Berger JS, Frye CB, Harshaw Q, Edwards FH, Steinhilb SR, Becker RC. Impact of clopidogrel in patients with acute coronary syndromes requiring coronary artery bypass surgery: a multicenter analysis. *J Am Coll Cardiol*. 2008;52:1693-701.

4. Qu J, Zhang D, Zhang H, Rao C, Chen S, Zhao Y, et al. Preoperative clopidogrel and outcomes in patients with acute coronary syndrome undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2022;163:1044-52.e15.
5. Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. *Med Care*. 2007;45:S103-7.

See Article page 1044.

Commentary: Rushing to revascularize may be risky, but one size does not fit all

Malak Elbatarny, MD,^a Amr Alsalakawy, MBChB,^b and Stephen E. Fremes, MD, MSc, FRCSC, FACP, FACC^c

Optimal timing of coronary artery bypass grafting (CABG) in the context of acute coronary syndrome (ACS) and dual antiplatelet therapy remains controversial and practice patterns vary. Despite consensus among guidelines that minimum 5-day preoperative clopidogrel cessation is ideal,^{1,2} risk of adverse events during the washout period is dependent on coronary anatomy. Further, baseline bleeding risk varies among patients and the evidence for optimal timing of CABG is mixed.³⁻⁵ Clopidogrel cessation decreases the risk for bleeding and resultant secondary complications, but comes at the cost of a potentially increased risk of recurrent myocardial infarction (MI) or other thrombotic events. We congratulate Qu and colleagues⁶ for addressing this controversy.

Their study is a single-center retrospective observational analysis of 5543 patients undergoing post-ACS CABG.

CENTRAL MESSAGE

Proceeding with CABG before clopidogrel washout is associated with adverse perioperative outcomes. Is this the place for patient-tailored decision making?

Using institutional registry data, the authors compared those receiving clopidogrel within 5 days of CABG ($n = 820$; 15%) versus those for whom clopidogrel was stopped >5 days in advance ($n = 4723$; 85%). The primary outcome, a composite of stroke, all-cause mortality, and MI at 30 days, was worse, not better, in the late cessation group (odds ratio, 1.63; 95% confidence interval, 1.16-2.29; $P = .005$). The same pattern was seen in all secondary 30-day outcomes in descending order of effect size, including stroke, transfusion, major bleeding events (defined by validated CABG-specific bleeding criteria⁷), and re-exploration for bleeding. In other words, early cessation of clopidogrel was associated with both a reduction in bleeding and a reduction in thrombotic events. The authors implemented inverse probability treatment weighting to account for baseline differences and sensitivity analysis with propensity score matching reinforce the robustness of the findings. The small number of patients who did not undergo CABG due to cardiovascular events during the preoperative waiting period were also included in the analysis (0.2% had clopidogrel continued within

From the ^aDivision of Cardiac Surgery, Department of Surgery, University of Toronto, Toronto, Ontario, Canada; ^bDivision of Cardiac Surgery, Magdi Yacoub Foundation, Aswan Heart Centre, Aswan, Egypt; and ^cSchulich Heart Centre, Division of Cardiac Surgery, Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada.

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Address for reprints: Stephen E. Fremes, MD, MSc, FRCSC, FACP, FACC, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Room H4 05, Toronto, Ontario M4N 3M5, Canada (E-mail: stephen.fremes@sunnybrook.ca).

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5 days and 0.06% had clopidogrel stopped). A graded response was observed when comparing <3 day to a 3- to 5-day washout period, as well as an additional 2-fold increased risk of MI.

Bleeding assessment tools based on clinical history represent convenient and effective screening methods to identify at-risk populations⁸ and some have been validated in cardiac surgery.^{9,10} The Papworth score has been correlated with major bleeding post-CABG,⁹ whereas an abbreviated amalgamation of the Transfusion Risk and Clinical Knowledge (TRACK) and Transfusion Risk Understanding Scoring Tool (TRUST) predicts transfusion risk in cardiac surgery with or without cardiopulmonary bypass.¹⁰ Qu and colleagues⁶ found transfusion requirements and major bleeding remained higher with clopidogrel continuation in women, despite a lower incidence of the primary outcome. Older age of presentation, higher degree of anatomical complexity, and smaller vessel size¹¹ possibly render women more susceptible to thrombotic complications. Small body size and anemia on presentation, which are consistent factors in validated risk scores,^{9,10,12,13} may be associated with a greater transfusion risk. Additionally, female sex, older age, type and urgency of surgery, and renal failure seem to increase risk for bleeding.^{9,10} Qu and colleagues⁶ found elderly patients to have greater transfusion requirements with short drug washout, reflecting more liberal transfusion thresholds¹⁴; however, they also had more major bleeding, possibly reflecting increased comorbidities or postoperative anticoagulation for atrial fibrillation.

This study emphasizes the challenges of balancing variable risk profiles for surgical bleeding and thromboembolic complications for individual patients. Although platelet function tests exist with proposed clinical algorithms for lab-target-based transfusion and antiplatelet washout, use in precardiac surgery screening is not routine, and no definitive guidelines exist.^{15,16} By comparison, the study by Qu and colleagues⁶ had very low platelet transfusion rates, although thresholds were not specified. Encouragingly, platelet aggregability-guided, expedited CABG has been found noninferior to standard 5-day washout period with regard to chest tube drainage, and minimum hemoglobin.¹⁷ It also significantly shortened time to CABG by 24 hours.¹⁷ Antiplatelet resistance affects 5% to 30% of patients, has variable effect based on age and gender, and has greater incidence in patients with ACS.¹⁸ An alarming 3-fold risk of perioperative stroke observed in the study population with incomplete clopidogrel washout raises several questions for further study: proportion of hemorrhagic versus ischemic etiology, timing of stroke in-hospital versus postdischarge, and relation to postoperative atrial fibrillation or history of cerebrovascular disease.

Caution must be exercised when interpreting the data in this study and some limitations need to be highlighted. It is important to note that patients with longer drug washout duration are

additionally subject to the confounding effects of delayed revascularization. The use of validated bleeding criteria is commendable; however, in practice, factors such as transfusion and re-exploration for bleeding practices are highly subjective and strongly influenced by known history of clopidogrel administration. As some authors discuss, aspirin is known to augment the effect of clopidogrel.¹⁹ Unlike most Western centers wherein guidelines specify continuation,^{2,20} preoperative aspirin was routinely discontinued. As such, the study in effect compared clopidogrel monotherapy to control, rather than dual antiplatelet therapy to aspirin monotherapy. Clopidogrel pharmacokinetics and baseline bleeding risk are also highly patient-specific, which renders a fixed washout period of limited utility for all-comers.²¹ Preoperative quantitative or qualitative platelet function testing or baseline bleeding risk assessment were outside the scope of the study. Additionally, postdischarge anticoagulation, which was not described in the study, may have influenced the 30-day outcome. Despite rigorous statistical methods, there remains unavoidable bias and unmeasurable confounders related to the observational study design. In practice, many clinical and logistical factors influence the decision to move ahead quickly with surgery or wait for drug washout. This study focused on clopidogrel—ticagrelor or prasugrel are used commonly in Western centers. Finally, generalizability of study findings is limited by the center's extremely large volume and discontinuation of aspirin.

The present study provides important contemporary evidence confirming current guidelines that early surgery without clopidogrel washout after recent ACS should be treated with caution. This is particularly the case among elderly patients and men. There is certainly a need for blinded, randomized controlled trial data to provide strong causal evidence regarding optimal timing of drug washout. Additionally, there may be a role for greater use of preoperative clinical and biochemical assessment tools to facilitate patient-tailored decision making, although validation studies are required.

References

1. Fitchett D, Eikelboom J, Fremes S, Mazer D, Singh S, Bittira B, et al. Dual antiplatelet therapy in patients requiring urgent coronary artery bypass grafting surgery: a position statement of the Canadian Cardiovascular Society. *Can J Cardiol*. 2009;25:683-9.
2. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. *J Am Coll Cardiol*. 2011;58:e123-210.
3. Yerokun BA, Williams JB, Gaca J, Smith PK, Roe MT. Indications, algorithms, and outcomes for coronary artery bypass surgery in patients with acute coronary syndromes. *Coron Artery Dis*. 2016;27:319-26.
4. Nichols EL, McCullough JN, Ross CS, Kramer RS, Westbrook BM, Klemperer JD, et al. Optimal timing from myocardial infarction to coronary artery bypass grafting on hospital mortality. *Ann Thorac Surg*. 2017;103:162-71.
5. Davierwala PM, Verevkin A, Leontyev S, Misfeld M, Borger MA, Mohr FW. Does timing of coronary artery bypass surgery affect early and long-term outcomes in patients with non-ST-segment-elevation myocardial infarction? *Circulation*. 2015;132:731-40.

6. Qu J, Zhang D, Zhang H, Rao C, Chen S, Zhao Y, et al. Preoperative clopidogrel and outcomes in patients with acute coronary syndrome undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg.* 2022;163:1044-52.e15.
7. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. *Circulation.* 2011;123:2736-47.
8. Rydz N, James PD. The evolution and value of bleeding assessment tools. *J Thromb Haemost.* 2012;23:2223-9.
9. Vuylsteke A, Pagel C, Gerrard C, Reddy B, Nashef S, Aldam P, et al. The Papworth bleeding risk score: a stratification scheme for identifying cardiac surgery patients at risk of excessive early postoperative bleeding. *Eur J Cardio-thoracic Surg.* 2011;39:924-30.
10. Krishna NM, Nagaraja P, Singh NG, Nanjappa SN, Kumar KN, Prabhakar V, et al. Evaluation of risk scores in predicting perioperative blood transfusions in adult cardiac surgery. *Ann Card Anaesth.* 2019;22:73-8.
11. Hiteshi AK, Li D, Gao Y, Chen A, Flores F, Mao SS, et al. Gender differences in coronary artery diameter are not related to body habitus or left ventricular mass. *Clin Cardiol.* 2014;37:605-9.
12. Alghamdi AA, Davis A, Brister S, Corey P, Logan A. Development and validation of transfusion risk understanding scoring tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs. *Transfusion.* 2006;46:1120-9.
13. Vanneman MW, Dalia AA. TRACKing down perioperative transfusion in cardiac surgery. *J Cardiothorac Vasc Anesth.* 2019;33:2676-8.
14. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med.* 2017;377:2133-44.
15. Gillissen A, van den Akker T, Caram-Deelder C, Henriquez DDCA, Nij Bijvank SWA, Bloemenkamp KWM, et al. Predictive value of a bleeding score for postpartum hemorrhage. *Res Pract Thromb Haemost.* 2019;3:277-84.
16. Mahla E, Tantry US, Prüller F, Gurbel PA. Is there a role for preoperative platelet function testing in patients undergoing cardiac surgery during antiplatelet therapy? *Circulation.* 2018;138:2145-59.
17. Nakashima CAK, Dallan LAO, Lisboa LAF, Hajjar LA, Soeip AM, Silva BA, et al. Platelet aggregability evaluation in patients with acute coronary syndromes scheduled for coronary artery bypass graft. The PLAT-CABG study. *Eur Heart J.* 2019;40(Suppl 1).
18. Saraf S, Bensalha I, Gorog DA. Antiplatelet resistance—does it exist and how to measure it? *Clin Med Cardiol.* 2009;2009:77-91.
19. Payne DA, Hayes PD, Jones CI, Belham P, Naylor AR, Goodall AH. Combined therapy with clopidogrel and aspirin significantly increases the bleeding time through a synergistic antiplatelet action. *J Vasc Surg.* 2002;35:1204-9.
20. Mehta SR, Bainey KR, Cantor WJ, Lordkipanidzé M, Marquis-Gravel G, Robinson SD, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. *Can J Cardiol.* 2018;34:214-33.
21. Jiang X-L, Samant S, Lesko LJ, Schmidt S. Clinical Pharmacokinetics and Pharmacodynamics of Clopidogrel. *Clin Pharmacokinet.* 2015;54:147-66.

See Article page 1044.

Commentary: Shall we wait for two days more? Can we take this risk?

Stefano D'Alessandro, MD, FECS,^a
 Fabio Guarracino, MD,^b
 Francesco Nicolini, MD, PhD,^c and
 Francesco Formica, MD^c

Dual antiplatelet therapy (DAPT) with P2Y₁₂-receptor inhibitors and aspirin is a well-recognized treatment aiming

Francesco Formica, MD (FF), Stefano D'Alessandro, MD, FECS (SDA), Francesco Nicolini, MD, PhD (FN), and Fabio Guarracino, MD (FG)

CENTRAL MESSAGE

In patients with acute coronary syndrome, mainly in subjects younger than 65 years, waiting for 2 more days before stopping DAPT might be reasonable to reduce the risk of major bleeding complications.

to reduce the incidence and recurrence of ischemic and thrombotic complications in coronary patients suffering from acute myocardial infarction and in patients who

From ^aCardiac Surgery Unit, Cardiac-Thoracic-Vascular Department, San Gerardo Hospital, Monza; ^bDepartment of Anaesthesia and Critical Care Medicine, Cardio-thoracic and Vascular Anaesthesia and Intensive Care, University Hospital, Pisa; and ^cCardiac Surgery Unit, Department of Medicine and Surgery, Parma General Hospital, University of Parma, Parma, Italy.

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Address for reprints: Francesco Formica, MD, UOC Cardiochirurgia, Azienda Ospedaliera Universitaria di Parma, Via A. Gramsci, 14, 43126 Parma, Italy (E-mail: francesco_formica@fastwebnet.it or francesco.formica@unipr.it).

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