Journal of the American Heart Association

EDITORIAL

Long-Term Ticagrelor in Stable Patients With Prior Myocardial Infarction: Bleeding Avoidance First and Foremost

Davide Cao, MD; George Dangas, MD, PhD; Roxana Mehran, MD

Over 100 000 patients with different manifestations of cardiovascular disease have been studied in large-scale clinical trials evaluating the safety and efficacy of ticagrelor alone or in combination with aspirin. As a result of these studies, the Food and Drug Administration granted indication to ticagrelor for the secondary prevention of patients presenting with acute coronary syndrome,[1] prior myocardial infarction (MI),[2] and acute noncardioembolic ischemic stroke,[3] as well as for the primary prevention of high-risk patients with stable coronary artery disease.[4] However, given that any advantage in ischemic event prevention may be counterbalanced by an increase in bleeding harm, identifying those patients in whom the ischemia-bleeding trade-off of an intensified antithrombotic regimen provides a net clinical benefit remains a major challenge. International guidelines and academic collaborations have repeatedly emphasized the negative prognostic role of bleeding. Risk prediction models and expert consensus documents have been proposed to untangle the complex interplay between ischemic and bleeding risk and guide clinical decisions.[5–7] Nonetheless, several questions remain to be answered. Although no one would argue on the detrimental consequences of bleeding, the correct characterization of various types of hemorrhagic events and their causative role with respect to subsequent mortality are still a matter of debate. Bleeding in itself can be heterogeneous in cause and magnitude, and can thus impact differently on patient prognosis. A specific bleeding site can be more associated with one antithrombotic agent compared with another (eg, gastrointestinal adverse effects of aspirin). Furthermore, the clinical relevance of bleeding may also depend on the patient comorbid conditions and functional status.

See Article by Magnani et al.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Magnani at al[8] have focused on these subjects by highlighting the results of a post hoc analysis of the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) Trial.[2] Of the 21 000 patients with a prior MI who were enrolled and randomized to ticagrelor, 60 mg, ticagrelor, 90 mg, or placebo on top of aspirin, 432 experienced a TIMI minor or major bleeding event over a median follow-up of 33 months. Presence of anemia at baseline and prior hospitalization for spontaneous bleeding were identified as independent predictors of bleeding but not ischemia and, therefore, were used to stratify the study population into patients with high (4054; 19.4%) and low bleeding risk (16 888; 80.6%). Compared with aspirin

Key Words: Editorials ■ aspirin ■ bleeding ■ coronary artery disease ■ myocardial infarction ■ thrombosis ■ ticagrelor

Correspondence to: Roxana Mehran, MD, Center for Interventional Cardiovascular Research and Clinical Trials, The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, NY 10029-6574. E-mail: roxana.mehran@mountsinai.org

For Disclosures, see page 3.

JAHA is available at: www.ahajournals.org/journal/jaha

alone, ticagrelor, 60 mg, plus aspirin was associated with a similar increase in the risk of bleeding complications in both groups, but the absolute risk difference was nearly tripled in those at high bleeding risk (4.4% versus 1.5%). On the other hand, the composite of cardiovascular death, MI, or stroke was significantly in favor of patients treated with ticagrelor, 60 mg, compared with placebo, with a treatment effect that appeared more pronounced among patients with low bleeding risk (7.1% versus 8.7%; hazard ratio [HR], 0.80; 95% CI, 0.70–0.92) compared with patients with high bleeding risk (10.4% versus 10.4%; HR, 0.98; 95% CI, 0.77–1.26; *P* interaction=0.154). Consistent results were observed for the net benefit end point that also included intracranial and fatal bleeding. Hence, the authors concluded that absence of 2 simple bleeding risk parameters, such as a history of spontaneous bleeding and anemia, may be sufficient for identifying stable patients after MI who derive greater benefit from prolonged dual antiplatelet therapy with ticagrelor, 60 mg. Some limitations to this study, however, deserve to be mentioned. Anemia is a well-known predictor of bleeding but also a widely prevalent condition.[6,9,10] Although lower levels of hemoglobin have been shown to correlate with a stepwise increase in bleeding risk, Magnani et al applied a dichotomous and relatively sensitive cutoff (≤12.0 g/dL for women and ≤13.5 g/dL for men). Anemia was present in 18.8% of the study population, a prevalence considerably larger than that of bleeders (2.1%), which on the whole suggests an only modest discrimination ability. Furthermore, the PEGASUS-TIMI 54 Trial excluded patients with bleeding disorder, history of recent bleeding, or intracranial bleeding at any time, in addition to prior stroke or need for oral anticoagulant therapy. Patients enrolled in the PEGASUS-TIMI 54 Trial were also at high risk of ischemic events (eg, diabetes mellitus, renal disease, multivessel disease, and recurrent MI). Therefore, the net benefit of prolonged ticagrelor therapy may be particularly enhanced in this population and less generalizable to other patient subsets.

The study by Magnani et al[8] is of great value in that it provides important insights on the causes of bleeding and its association with mortality. Nearly half (46%) of patients with a TIMI major or minor bleed were treated conservatively (without transfusion or intervention to reverse bleeding), and 9.7% died within a few days of causes directly related to bleeding. Interestingly, among patients who survived the bleeding event, another 9.7% died after a median time of 207.5 days, a rate of mortality that far exceeds the one observed in the overall PEGASUS-TIMI 54 Trial population. By looking at the causes of late death in bleeding survivors, about half were cardiovascular, to which bleeding may contribute by prompting therapy discontinuation, hemodynamic compromise, and inflammatory reactions.[11] Nonetheless, another 37% were adjudicated as related to malignancy. Notably, the excess in noncardiovascular death associated with prolonged dual antiplatelet therapy was attributed to cancer in both the DAPT (Dual Antiplatelet Therapy) and PEGASUS-TIMI 54 Trials,[2,12] thereby challenging the role of bleeding as a mere disease manifestation or an actual trigger of the downstream fatal outcome.

TIMI major or minor bleeds were increased with the adjunctive use of ticagrelor, regardless of the baseline bleeding risk status. Most bleeds were spontaneous (71%), and similar in location and cause between treatment arms. Of every 4 bleeding events, 3 arose from the gastrointestinal tract, and ticagrelor plus aspirin was associated with a 3-fold increase in their occurrence compared with aspirin alone. Yet, only 26% of patients were treated with proton pump inhibitors, despite their established indication for gastrointestinal prophylaxis among those with cardiovascular disease on antiplatelet therapy.[13] Furthermore, there were no between-group differences in intracranial and fatal bleeding. All these findings should be interpreted in the context of prior studies using different referent treatment arms. No difference in bleeding risk was observed among patients randomized to monotherapy with ticagrelor or aspirin after a cerebrovascular accident.[3] Bleeding risk was also similar between ticagrelor and clopidogrel monotherapy in patients with symptomatic peripheral artery disease.[14] A paradoxically greater proportion of gastrointestinal bleeds was found in patients with an acute coronary syndrome treated with dual antiplatelet therapy with clopidogrel compared with ticagrelor, despite a higher absolute risk with the latter.[15] Taken together, these data suggest that ticagrelor alone does not portend an excess in major bleeding complications if compared with other antiplatelet monotherapies. Nonetheless, when used in combination with aspirin, ticagrelor exerts a significant additive prohemorrhagic effect, especially on the gastrointestinal tract. The hypothesis that an aspirin-free strategy with ticagrelor, or $P2Y_{12}$ inhibitors in general, would guarantee adequate ischemic protection and improved safety has been originally tested among high bleeding risk subgroups (such as those with atrial fibrillation requiring dual antiplatelet therapy) and subsequently extended to broader patient populations undergoing percutaneous coronary intervention.[16,17] Whether this treatment strategy is safe and effective also for the long-term secondary prevention of stable patients with established cardiovascular disease is yet to be proved, although signals of such benefit have already been shown.[18] Finally, findings by Magnani et al are consonant with prior analyses supporting the preeminent role of bleeding risk assessment in guiding intensified or prolonged antithrombotic regimens.[19]

Ongoing studies will help refine the available tools that can inform clinicians of the balance between bleeding and ischemic risk of various treatment combinations relatively to the individual patient profile.

ARTICLE INFORMATION

Affiliations

From the The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY.

Disclosures

Dr Mehran reports grants from Abbott Laboratories, AstraZeneca, Bayer, Beth Israel Deaconess, Bristol Myers Squibb, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, and OrbusNeich; personal fees from Abbott Laboratories, Boston Scientific, Medscape/WebMD, Siemens Medical Solutions, PLx Opco Inc/dba PLx Pharma Inc, Roivant Sciences, Sanofi, Medtelligence (Janssen Scientific Affairs), and Janssen Scientific Affairs; other from Abbott Laboratories, Abiomed, Bristol Myers Squibb, Claret Medical, Elixir Medical, The Medicines Company, Spectranetics/Philips/Volcano Corp, and Watermark Research Partners; and nonfinancial support and other from Regeneron Pharmaceuticals and Idorsia Pharmaceuticals Ltd. Dr Dangas reports consulting fees or honoraria from AstraZeneca, Biosensors, Boston Scientific, and Medtronic; reports research grants to the institution from Biotronik and Abbott Laboratories; and has equity (entirely divested) with Medtronic. Dr Cao has no disclosures to report.

REFERENCES

1. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057. DOI: 10.1056/NEJMoa0904327.
2. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800. DOI: 10.1056/NEJMoa1500857.
3. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med*. 2020;383:207–217. DOI: 10.1056/NEJMoa1916870.
4. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, Held C, Andersson M, Himmelmann A, Ridderstråle W, et al. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med*. 2019;381:1309–1320. DOI: 10.1056/NEJMoa1908077.
5. Yeh RW, Secemsky EA, Kereiakes DJ, Normand S-L, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749. DOI: 10.1001/jama.2016.3775.
6. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong M-K, Kim H-S, Colombo A, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389:1025–1034. DOI: 10.1016/S0140-6736(17)30397-5.
7. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Circulation*. 2019;140:240–261. DOI: 10.1161/CIRCULATIONAHA.119.040167.
8. Magnani G, Ardissino D, Im K, Budaj A, Storey RF, Steg PG, Bhatt DL, Cohen M, Oude Ophius T, Goudev A, et al. Predictors, type and impact of bleeding on the net clinical benefit of long-term ticagrelor in stable patients with prior myocardial infarction. *J Am Heart Assoc*. 2020;9:e017008. DOI: 10.1161/JAHA.120.017008.
9. Kwok CS, Tiong D, Pradhan A, Andreou AY, Nolan J, Bertrand OF, Curzen N, Urban P, Myint PK, Zaman AG, et al. Meta-analysis of the prognostic impact of anemia in patients undergoing percutaneous coronary intervention. *Am J Cardiol*. 2016;118:610–620. DOI: 10.1016/j.amjcard.2016.05.059.
10. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. *J Am Coll Cardiol*. 2016;67:2224–2234. DOI: 10.1016/j.jacc.2016.02.064.
11. Doyle BJ, Rihal CS, Gastineau DA, Holmes DR Jr. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. *J Am Coll Cardiol*. 2009;53:2019–2027. DOI: 10.1016/j.jacc.2008.12.073.
12. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand S-L, Braunwald E, Wiviott SD, Cohen DJ, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155–2166. DOI: 10.1056/NEJMoa1409312.
13. Agewall S, Cattaneo M, Collet JP, Andreotti F, Lip G, Verheugt F, Huber K, Grove EL, Morais J, Husted S, et al. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. *Eur Heart J*. 2013;34:1708–1713, 1713a–1713b. DOI: 10.1093/eurheartj/eht042.
14. Hiatt WR, Fowkes FGR, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017;376:32–40. DOI: 10.1056/NEJMoa1611688.
15. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, French J, Held C, Horrow J, Husted S, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the platelet inhibition and patient outcomes (PLATO) trial. *Eur Heart J*. 2011;32:2933–2944. DOI: 10.1093/eurheartj/ehr422.
16. Capodanno D, Mehran R, Valgimigli M, Baber U, Windecker S, Vranckx P, Dangas G, Rollini F, Kimura T, Collet JP, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol*. 2018;15:480–496.
17. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381:2032–2042. DOI: 10.1056/NEJMoa1908419.
18. Chiarito M, Sanz-Sánchez J, Cannata F, Cao D, Sturla M, Panico C, Godino C, Regazzoli D, Reimers B, De Caterina R, et al. Monotherapy with a P2Y(12) inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet*. 2020;395:1487–1495. DOI: 10.1016/S0140-6736(20)30315-9.
19. Costa F, Van Klaveren D, Feres F, James S, Raber L, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol*. 2019;73:741–754.