Journal of the American Heart Association

EDITORIAL

Real-World Comparison of Ticagrelor and Clopidogrel: Rosetta Stone or Lost in Translation?

Brian A. Bergmark, MD

Patients who experience an acute coronary syndrome (ACS) are at increased risk for additional ischemic events across vascular territories.[1–4] This risk is modifiable, with randomized controlled trials (RCTs) demonstrating the efficacy and safety of several types of interventions in patients with prior myocardial infarction, including antithrombotic agents,[5–8] lipid-lowering therapies,[3,4,9,10] and nonculprit lesion revascularization in the case of hemodynamically stable ST-segment–elevation myocardial infarction.[11]

See Article by Völz et al.

Some of the heightened risk following ACS is attributable to the culprit lesion itself, although many recurrent events are unrelated to the index ACS lesion, vessel, or even vascular bed.[12] This distinction takes on particular salience in the case of patients who undergo percutaneous coronary intervention (PCI) for the index ACS, as these patients remain at risk for nontarget lesion events and are also at risk for stent-related complications, most notably stent thrombosis.

With respect to antiplatelet therapy, PLATO (Study of Platelet Inhibition and Patient Outcomes)[7] and TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction) 38[8] were large RCTs showing greater efficacy of the third-generation $P2Y_{12}$ inhibitors ticagrelor and prasugrel than clopidogrel in patients with ACS treated with aspirin. PLATO enrolled 18 624 patients with ACS who were randomized to ticagrelor, 90 mg twice daily, versus clopidogrel, 75 mg daily, and followed up for 12 months. The rate of major adverse cardiovascular events was 16% lower in patients assigned to ticagrelor, including a lower rate of all-cause mortality. Rates of bleeding were higher with ticagrelor.

Concerning the subset of ACS patients who undergo PCI, the efficacy of ticagrelor in PLATO was consistent in patients with a planned invasive strategy (71% of total population), including a 19% reduction in all-cause mortality and a 36% reduction in definite stent thrombosis.[13] In TRITON-TIMI 38, in which 99% of patients underwent PCI (95% received a stent), definite or probable stent thrombosis was reduced by 52% with prasugrel.[8]

The superior efficacy and acceptable safety profile of ticagrelor and prasugrel have led to major society guidelines favoring these agents over clopidogrel in most patients with ACS, including those treated with PCI.[14–16]

Although large, well-conducted RCTs are the mechanism by which to assess the efficacy and safety of one intervention compared with another, they obviously do not answer every question relevant to the use of these medications in daily practice. Cardiovascular trials typically enroll white men in their 60s from North America and Western Europe, raising legitimate questions about generalizability to more diverse populations and

Key Words: Editorials ■ acute coronary syndrome ■ $P2Y_{12}$ ■ stent thrombosis

Correspondence to: Brian A. Bergmark, MD, TIMI (Thrombolysis in Myocardial Infarction) Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Rd, Ste 7022, Boston, MA 02115. E-mail: bbergmark@bwh.harvard.edu

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

For Disclosures, see page 3.

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

clinical scenarios.[17] Furthermore, societal considerations, such as cost-effectiveness, are simply beyond the scope of a trial designed to understand the efficacy and safety of a drug, device, or therapeutic strategy in a specific patient group or disease state. For these reasons, "real-world" data have the possibility of providing important adjunctive insight into how the internally valid findings of a well-executed trial translate into the external world.

In this spirit, Völz and colleagues have explored, in this issue of the *Journal of the American Heart Association* (*JAHA*), the use of ticagrelor versus clopidogrel in patients with ACS treated with PCI using data from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry).[18] The authors captured information pertaining to all PCIs performed in the setting of ACS at 5 hospitals in a single region of western Sweden over a 10-year period (2005–2015) and compared outcomes in patients treated with ticagrelor with those in patients treated with clopidogrel. The primary end point for this comparison was the composite of all-cause mortality or stent thrombosis at 30 days. The association between antiplatelet therapy and subsequent outcomes was adjusted on the basis of clinical and procedural characteristics using instrumental variable 2-stage least squares regression.

A total of 12 168 patients were treated with clopidogrel during the specified time period, and 2929 were treated with ticagrelor. As would be expected, the proportion of patients treated with ticagrelor increased over time. Patients treated with ticagrelor more frequently had prior myocardial infarction, prior PCI, and prior bypass surgery, whereas patients treated with clopidogrel more commonly presented with non–ST-elevation ACS and cardiogenic shock. Drug-eluting stents, invasive physiologic lesion assessment, and intracoronary imaging were more commonly used in patients treated with ticagrelor, presumably at least in part reflecting secular trends in these procedural characteristics.

There was no difference in the adjusted odds of death or stent thrombosis at 30 days between patients treated with ticagrelor and those treated with clopidogrel. Patients receiving ticagrelor had higher rates of in-hospital bleeding. There continued to be no significant association between initial therapy choice and all-cause mortality at 1 year.

So, what lessons can we draw from these observational comparisons in a setting in which we already have large randomized trial data? Rephrased, in what ways does this analysis help translate the existing efficacy and safety data for ticagrelor into the "real world"?

First, SCAAR is a comprehensive registry and allows for a reasonably complete description of the transition from clopidogrel to ticagrelor in a broad healthcare system. From the first month in which ticagrelor was prescribed, March 2012, it was only 2 months until ticagrelor became the dominant $P2Y_{12}$ inhibitor. This observation highlights the rapid translation of guidelines and health system–level decisions to patient-level care in systems such as Sweden's and therefore speaks to the importance of analyses such as the one by Völz et al.[18]

The rapid transition and relative homogeneity of prescribing patterns also speaks to the fundamental biases present in observational analyses. As the authors note, only 30% of this cohort was treated after ticagrelor became the default $P2Y_{12}$ inhibitor, and of these, only 35% were treated with clopidogrel. Therefore, only about 11% of patients in this analysis received clopidogrel as a real "choice" or "alternative" to ticagrelor. The greater the imbalance between the rates of use of each therapy, the greater concern there is for important unmeasured confounders driving the observed associations.

Second, although this analysis does still rely on a demographic similar to the original PLATO trial, there is an important difference in age. Only ≈15% of patients enrolled in PLATO were at least 75 years of age,[7] whereas nearly 30% of patients in the present analysis were >75 years of age. The median age is about 68 years, which reflects current clinical experience in North America and Europe.[17] As such, there may be important differences in bleeding and ischemic risk in this cohort compared with PLATO. The bleeding rates are difficult to compare given the evaluation of only in-hospital bleeding here, but the absolute rates of all-cause mortality and the composite of death, myocardial infarction, or stroke at 1 year are higher in the SCAAR analysis than in PLATO.

An important limitation is the lack of data on treatment discontinuation. Even in RCTs, there have been appreciable rates of ticagrelor discontinuation,[7,19] and one might conjecture that crossover from ticagrelor to clopidogrel would make these 2 treatment strategies more similar in the "real world" than in the setting of an RCT. This is an important hypothesis raised by this analysis.

It is also relevant to note the low rates of drug-eluting stents, physiologic assessment, intracoronary imaging, and complete revascularization relative to current guidelines and practice, reflecting the overall time period of assessment. Given that these approaches have demonstrated clinical benefit,[11,15,20,21] one might hypothesize that in the modern era there may be less anticipated benefit from potent antiplatelet therapy than has been true historically. This is, of course, speculative, but optimized PCI is evolving rapidly and it is not unreasonable to expect these changes to impact residual risk and, therefore, the absolute marginal benefit of adjunctive medical therapy in the future.

Is there direct clinical application of these findings? As the results presented here are observational, they are vulnerable to important unmeasured confounders. That said, these observations provide an essential

reminder for clinicians that many patients encountered in daily practice do not neatly fit the populations and clinical scenarios investigated in RCTs and careful, patient-centered decision making is required. In particular, the findings here raise valid questions about therapeutic strategy in patients who are older or may be less likely to maintain long-term ticagrelor therapy following PCI for ACS.

In conclusion, Völz and colleagues[18] have examined the use of ticagrelor and clopidogrel in actual clinical practice in Sweden, making important observations about current management of patients with ACS treated with PCI. In so doing, they have raised relevant hypotheses warranting further investigation. Intraprocedural techniques and antithrombotic strategies following ACS and PCI are evolving quickly, with significant promise for impact on long-term clinical outcomes. In the meantime, these 2 trends are playing out in everyday clinical practice: comprehensive data sets, such as SCAAR, provide an invaluable resource as we aim to understand the translation of RCT data into actual patients' lives.

ARTICLE INFORMATION

Affiliations

From the TIMI (Thrombolysis in Myocardial Infarction) Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Disclosures

Dr Bergmark is a member of the TIMI (Thrombolysis in Myocardial Infarction) Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc, BRAHMS, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, and Zora Biosciences. Dr Bergmark has received grant support from AstraZeneca/MedImmune, Abbott Vascular, and Pfizer; and consulting fees from Quark Pharmaceuticals, Abbott Vascular, Philips, Daiichi Sankyo, Servier, and Janssen Pharmaceuticals.

REFERENCES

1. Sabatine MS, De Ferrari GM, Giugliano RP, Huber K, Lewis BS, Ferreira J, Kuder JF, Murphy SA, Wiviott SD, Kurtz CE, et al. Clinical benefit of evolocumab by severity and extent of coronary artery disease: analysis from FOURIER. *Circulation*. 2018;138:756–766.
2. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.
3. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
4. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107.
5. CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;2001:494–502.
6. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9–19.
7. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
8. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F-J, Ardissino D, De Servi S, Murphy SA. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
9. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.
10. Cannon CP, Murphy SA, Braunwald E. Intensive lipid lowering with atorvastatin in coronary disease. *N Engl J Med*. 2005;353:93–96.
11. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks B, Di Pasquale G, Lopez-Sendon J, Faxon DP, et al. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med*. 2019;381:1411–1421.
12. Scirica BM, Bergmark BA, Morrow DA, Antman EM, Bonaca MP, Murphy SA, Sabatine MS, Braunwald E, Wiviott SD. Nonculprit lesion myocardial infarction following percutaneous coronary intervention in patients with acute coronary syndrome. *J Am Coll Cardiol*. 2020;75:1095–1106.
13. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, Husted S, Katus H, Keltai M, Khurmi NS, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet*. 2010;375:283–293.
14. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.
15. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2018;40:87–165.
16. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *J Am Coll Cardiol*. 2016;68:1082.
17. Tahhan AS, Vaduganathan M, Greene SJ, Alrohaibani A, Raad M, Gafeer M, Mehran R, Fonarow GC, Douglas PS, Bhatt D, et al. Enrollment of older patients, women, and racial/ethnic minority groups in contemporary acute coronary syndrome clinical trials: a systematic review. *JAMA Cardiol*. 2020;5:714. [epub ahead of print].
18. Völz S, Petursson P, Odenstedt J, Ioanes D, Haraldsson I, Angerås O, Dworeck C, Hirlekar G, Myredal A, Albertsson P, et al. Ticagrelor is Not Superior to Clopidogrel in Patients With Acute Coronary Syndromes Undergoing PCI: A Report from Swedish Coronary Angiography and Angioplasty Registry. *J Am Heart Assoc*. 2020;9:e015990. DOI: 10.1161/JAHA.119.015990.
19. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, Held C, Andersson M, Himmelmann A, Ridderstrale W, et al. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med*. 2019;381:1309–1320.
20. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Kang WC, Her A-Y, et al. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JAMA*. 2015;314:2155–2163.
21. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van `t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213–224.