Korean Circ J. 2017 Sep;47(5):689-691
https://doi.org/10.4070/kcj.2017.0161
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

Effects of Ticagrelor on Myocardial Infarct Size

Joo-Yong Hahn, MD, PhD

Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

▸ See the article "Comparison of Ticagrelor and Clopidogrel on Myocardial Infarct Size in Patients Undergoing Primary Percutaneous Coronary Intervention" in volume 47 on page 705.

Received: Jul 18, 2017
Accepted: Aug 6, 2017

Correspondence to
Joo-Yong Hahn, MD, PhD
Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Tel: +82-2-3410-6653
Fax: +82-2-3410-3849
E-mail: jyhahn@skku.edu

ORCID iDs
Joo-Yong Hahn
https://orcid.org/0000-0002-4412-377X

Conflict of Interest
The author has no financial conflicts of interest.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

Ticagrelor (Brilinta; AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA) is a direct acting, reversible, oral P2Y12 inhibitor.[1] In the PLATelet inhibition and patient Outcomes (PLATO) study, compared to clopidogrel (Plavix; Bristol-Myers Squibb/Sanofi Pharmaceuticals, Bridgewater, NJ, USA), ticagrelor reduced the rate of death from vascular causes, myocardial infarction (MI), or stroke in patients with acute coronary syndrome.[2] Prevention of MI and stent thrombosis, and thus cardiac death, may result from fast, potent and consistent inhibition of platelets by ticagrelor.[3] However, the mechanism of ticagrelor benefits has not been fully elucidated. Recent animal studies demonstrated that ticagrelor reduces reperfusion injury and limits myocardial infarct size.[4][5] On the contrary, in an electrocardiography substudy of the PLATO trial, ticagrelor did not improve ST-segment resolution in patients with ST-segment elevation.[6] To date, data are limited regarding whether or not ticagrelor reduces myocardial infarct size compared with clopidogrel.

In the current issue of the *Korean Circulation Journal*, Yun et al.[7] reported the results of a single-center, randomized, open-label study that compared the effects of ticagrelor and clopidogrel on myocardial infarct size assessed by technetium-99m tetrofosmin single-photon emission computed tomography (SPECT) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). In the ticagrelor group, patients received a 180-mg loading does followed by a maintenance dose of 90 mg twice daily. In the clopidogrel group, patients received a 600-mg loading does followed by a maintenance dose of 75 mg daily. A total of 194 patients were eligible and 92 patients in the clopidogrel group and 96 patients in the ticagrelor group were finally evaluated with respect to myocardial infarct size. Infarct size was similar (32.8%±29.2% in the ticagrelor group compared to the clopidogrel group 28.1%±34.5%, p=0.170). Although this study was not a large study, sample size was not so small compared with other studies regarding infarct size and it was based on rational assumptions. Baseline characteristics of enrolled patients were representative. Only 6 patients did not undergo SPECT, which minimized selection bias. I would like to commend and congratulate the authors for this study. However, the major limitation of this study was that infarct size was measured by SPECT. Although correlation between infarct size measured using SPECT and cardiac magnetic resonance imaging (CMR) was good as the authors stated in the manuscript, CMR is superior to SPECT for measuring infarct size, especially when an infarct is small or nontransmural. In addition to infarct size, CMR can

assess microvascular obstruction. In the post hoc analysis of the Complete Versus Lesion-Only PRImary PCI Trial-CMR (CvLPRIT-CMR) substudy, ticagrelor was associated with smaller infarct size and lower microvascular obstruction incidence versus clopidogrel in patients with STEMI.[8] The only randomized trial to compare ticagrelor and clopidogrel for infarct size using CMR was performed by our group.[9] A total of 110 patients with STEMI undergoing primary PCI were randomly assigned to the ticagrelor group (180-mg loading does, 90 mg twice daily thereafter) or the clopidogrel group (600-mg loading dose, 75 mg daily thereafter) in a 1:1 ratio. CMR examinations were available in 45 and 50 patients of the ticagrelor group and the clopidogrel group, respectively. Myocardial infarct size was significantly smaller in the ticagrelor group than in the clopidogrel group (21.5%±10.9% vs. 26.5%±11.3%, p=0.030). The extent of microvascular obstruction was also significantly smaller and the myocardial salvage index tended to be greater in the ticagrelor group than in the clopidogrel group (3.9%±4.1% vs. 6.4%±6.3%, p=0.020 and 41.9%±10.8% vs. 38.3%±8.7%, p=0.080, respectively). However, the cardioprotective effect of ticagrelor may be not tremendous because traditional surrogates for myocardial injury such as myocardial blush grade or complete ST-segment resolution were not significantly different between ticagrelor and clopidogrel in the current study as well as ours.

How ticagrelor reduces myocardial infarct size is uncertain. Ticagrelor may facilitate reperfusion more completely or rapidly, and decrease myocardial infarct size compared with clopidogrel. However, the results of our study suggest a platelet-independent cardioprotective effect of ticagrelor because the degree of platelet inhibition was comparable between the ticagrelor and clopidogrel groups at the time of PCI. There was no significant difference in residual platelet reactivity at the time of PCI between ticagrelor and clopidogrel (P2Y12 reaction units by VerifyNow; 216.1±83.6 vs. 231.0±64.0, p=0.340). Ticagrelor achieved faster and greater antiplatelet effects than clopidogrel in several studies, but, in patients with STEMI undergoing primary PCI, both ticagrelor and prasugrel exhibited an initial delay in the onset of their antiplatelet action.[10] In animal studies, ticagrelor and clopidogrel achieved a similar degree of platelet inhibition in spite of a significant difference in myocardial infarct size and ticagrelor reduced reperfusion injury and myocardial infarct size by increasing myocardial adenosine levels and activating adenosine receptors.[4][5]

In summary, a CMR study, but not a SPECT study, demonstrated that ticagrelor had cardioprotective effects with respect to reducing myocardial infarct size and microvascular obstruction in patients with STEMI undergoing primary PCI. Benefits of ticagrelor observed in the PLATO trial may result from reducing myocardial injury as well as prevention of recurrent vascular events.

REFERENCES

1. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J* 2006;27:1038-47.
PUBMED | CROSSREF
2. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
PUBMED | CROSSREF
3. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol* 2007;50:1852-6.
PUBMED | CROSSREF

https://doi.org/10.4070/kcj.2017.0161

4. Nanhwan MK, Ling S, Kodakandla M, Nylander S, Ye Y, Birnbaum Y. Chronic treatment with ticagrelor limits myocardial infarct size: an adenosine and cyclooxygenase-2-dependent effect. *Arterioscler Thromb Vasc Biol* 2014;34:2078-85.
PUBMED | CROSSREF
5. Ye Y, Birnbaum GD, Perez-Polo JR, Nanhwan MK, Nylander S, Birnbaum Y. Ticagrelor protects the heart against reperfusion injury and improves remodeling after myocardial infarction. *Arterioscler Thromb Vasc Biol* 2015;35:1805-14.
PUBMED | CROSSREF
6. Armstrong PW, Siha H, Fu Y, et al. ST-elevation acute coronary syndromes in the Platelet Inhibition and Patient Outcomes (PLATO) trial: insights from the ECG substudy. *Circulation* 2012;125:514-21.
PUBMED | CROSSREF
7. Yun KH, Rhee SJ, Ko JS. Comparison of ticagrelor and clopidogrel on myocardial infarct size in patients undergoing primary percutaneous coronary intervention. Korean Circ J. 2017;47:705-13.
CROSSREF
8. Khan JN, Greenwood JP, Nazir SA, et al. Infarct size following treatment with second- versus third-generation P2Y12 antagonists in patients with multivessel coronary disease at ST-segment elevation myocardial infarction in the CvLPRIT study. *J Am Heart Assoc* 2016;5:e003403.
PUBMED | CROSSREF
9. Kim EK, Park TK, Yang JH, et al. Ticagrelor versus clopidogrel on myocardial infarct size in patients undergoing primary percutaneous coronary intervention. *J Am Coll Cardiol* 2017;69:2098-9.
PUBMED | CROSSREF
10. Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2012;5:797-804.
PUBMED | CROSSREF