

Stronger inhibitory effects of Ticagrelor plus aspirin compared with Clopidogrel plus aspirin on arachidonic acid-induced platelet aggregation in patients with acute coronary syndrome with PCI

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Abstract

Antagonists of the Adenosine Diphosphate (ADP) receptor, P2Y₁₂, may inhibit platelet aggregation as a result of stimulation with arachidonic acid (AA). The potent P2Y₁₂ blocker, Ticagrelor has greater anti-platelet effects than Clopidogrel. We explored the effects of Ticagrelor versus Clopidogrel on mean maximum aggregation ratios (MAR%) in response to AA stimulation in patients receiving aspirin in conventional doses. A total of 613 acute coronary syndrome (ACS) patients were followed from October 2017 to October 2018. At the one- and six-month follow-up visit, mean AA-MAR% was lower in the Ticagrelor group when compared with the Clopidogrel group (28.9% vs 31.7%, 28.4% vs 31.0%, $p < 0.001$ and $p = 0.001$, respectively). BARC1-2 bleeding occurred with greater frequency with Ticagrelor than in patients treated with Clopidogrel (29.3% vs 9.5%, $p < 0.001$; 23.5% vs 9.3%, $p < 0.001$). Excessive platelet inhibition and decreased AA-MAR% were considered the main reasons for the severe subcutaneous/dermal bleeding in Ticagrelor treated patients.

Keywords: Antiplatelet therapy, Platelet function, P2Y₁₂ blocker

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Introduction

Co-administering potent P2Y₁₂ receptor antagonist Ticagrelor with aspirin reduces the rate of death from vascular causes, myocardial infarction, or stroke as compared with Clopidogrel, while it is also associated with increased non-coronary artery bypass grafting (CABG) and non-procedure-related major bleeding after 30 days.¹ To counterbalance the increased bleeding risk related to dual antiplatelet therapy (DAPT), Twilight trial has evaluated aspirin cessation shortly after percutaneous coronary intervention (PCI). Ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than Ticagrelor plus aspirin, with no higher risk of ischaemia.²

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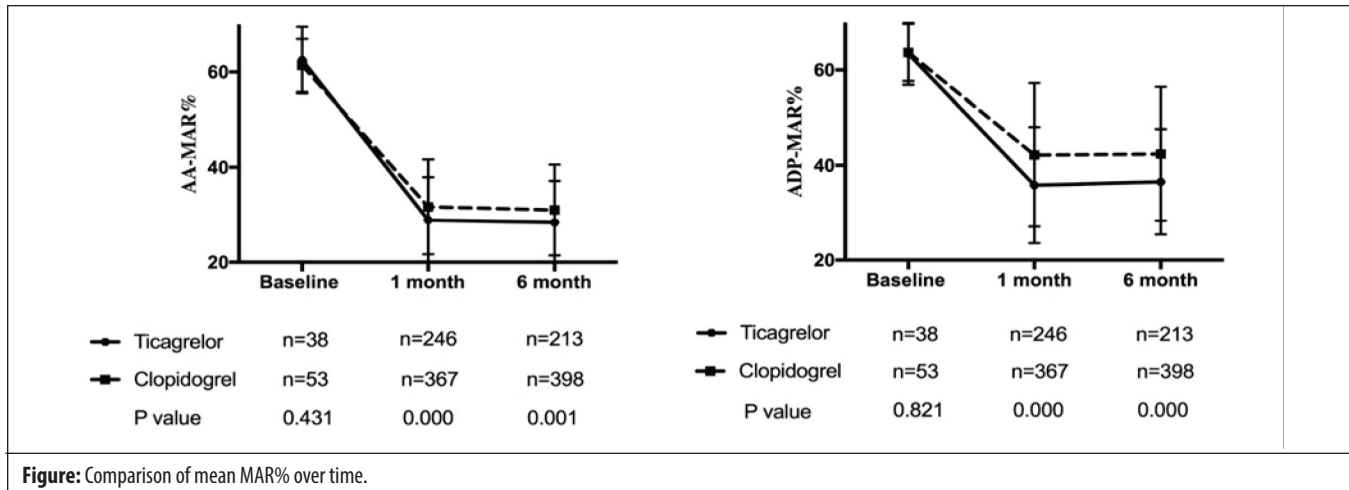
Antagonists of Adenosine Diphosphate (ADP) receptor P2Y₁₂ may block the P2Y₁₂-dependent pathway of platelet aggregation and sufficiently inhibit platelet aggregation resulting from stimulation with arachidonic acid (AA).³⁻⁵ The more potent P2Y₁₂ receptor antagonist Ticagrelor used alone may result in a consistent and full platelet inhibition, and that little further platelet inhibition is achieved by the addition of aspirin as compared with Clopidogrel. The question is: what is the effect of different P2Y₁₂ receptor antagonists on mean maximum aggregation ratios (MAR%) in response to AA in patients receiving conventional dosages of aspirin? To optimise an antiplatelet treatment strategy, it is important to explore the effects of Ticagrelor versus Clopidogrel on AA-MAR% in patients who have undergone percutaneous coronary intervention (PCI) due to acute coronary syndrome (ACS).

Methods and Results

In this single-centre study, the primary aim was to determine the extent of platelet inhibition with mean MAR% at the one- and six-month follow-up visits. The secondary aim was to explore the effects of different antiplatelet agents, especially on BARC1-2 bleeding.⁶ Platelet reactivity was assessed in all patients by a PL-11 analyser (SINNOWA Co., Nanjing, China).⁷ AA (2 mg/ml) and adenosine diphosphate (ADP, 50 μmol/L) were used as agonists.

From October 2017 to October 2018, a total of 613 ACS patients were consecutively included in the study in the Cardiology Department of the First Affiliated Hospital of Dalian Medical University. A total of 246 (40.1%) patients received Ticagrelor, while 367 (59.9%) received Clopidogrel, in the first month after discharge. (Table 1). One month later, there were two deaths, 39 patients were switched from Clopidogrel to Ticagrelor, and seven patients were switched from Clopidogrel to Ticagrelor. In all, 213 (34.9%) patients received Ticagrelor and 398 (65.1%) received Clopidogrel, between one and six months after discharge. (Figure).

At six-month follow-up, cardio-cerebrovascular events in the Clopidogrel group were as follows: one sudden death, two cerebrovascular accidents, one severe gastrointestinal



bleeding, two nonfatal myocardial infarctions, one unplanned revascularisation, and one additional hospitalisation due to heart failure. In the Ticagrelor group, there was one death due to cerebral haemorrhage, one unplanned revascularisation, one stent restenosis, and three readmissions due to heart failure. BARC1-2 bleeding occurred with greater frequency in Ticagrelor than in Clopidogrel treated patients (29.3% vs 9.5%, $p < 0.001$; 23.5% vs 9.3%, $p < 0.001$) at the one- and six-month follow-up post-discharge visit.

For patients who did not receive any antiplatelet therapy on admission, there was no difference in the mean MAR% in response to AA and ADP between the Ticagrelor and Clopidogrel groups (Figure). At the one- and six-month follow-up visits, mean ADP-MAR% was lower in the Ticagrelor as compared with Clopidogrel group (35.8% vs 42.2%, 36.5% vs 42.4%, both $P < 0.001$), and mean AA-MAR% was also lower in the Ticagrelor as compared with Clopidogrel group (28.9% vs 31.7%, 28.4% vs 31.0%, $p < 0.001$ and $p = 0.001$, respectively; (Figure).

MAR% in response to ADP and AA for the transition from Clopidogrel to Ticagrelor declined (44.0% vs 32.4%, 34.3% vs 27.1%, both $p < 0.001$, $n = 7$). MAR% in response to ADP and AA for the transition from Ticagrelor to Clopidogrel was obviously increased (33.1% vs 38.9%, 28.6% vs 30.2%, both $p < 0.001$; $n = 39$).

At the one-month follow-up visit, severe spontaneous subcutaneous/dermal bleeding with extensive ecchymosis was reported in 10 patients in the Ticagrelor group and required medical intervention. The mean AA- and ADP-MAR% were 13.5% and 27.6%, respectively; apparently, excessive platelet inhibition and AA-MAR% was considered the main reason for the severe subcutaneous/dermal bleeding. At the six-month follow-up examination, after aspirin dosage was reduced to 50 mg daily, skin

subcutaneous/dermal bleeding was significantly alleviated and the mean AA-MAR% improved to 26.9%.

Discussion

Aspirin may inhibit the TXA₂-dependent pathway of platelet activation; but, does the new P2Y₁₂ receptor antagonist Ticagrelor display a synergistic effect with the AA associated with aspirin? Earlier studies have shown that Clopidogrel is not only important to platelet TXA₂ production in vitro, but is also central to the process of platelet activation in vivo, leading to the production of TXA₂ under physiological conditions.³ Ticagrelor and Prasugrel can inhibit both the ADP-P2Y₁₂-dependent and the TXA₂-dependent pathways of platelet aggregation, independently of aspirin.⁵ Platelet function testing by the PL-11 analyser in our study showed that Ticagrelor and aspirin had a lower AA-MAR% than Clopidogrel plus aspirin. This further shows that Ticagrelor plus aspirin can result in stronger additive effects of irreversible aggregation through the TXA₂-dependent pathway, compared with Clopidogrel plus aspirin.

There is accumulating evidence that there may be an overlap in effects even though a high level of P2Y₁₂-receptor inhibition can reduce both platelet responses to TXA₂ and platelet production of TXA₂.⁸ That may explain why more BARC1-2 bleeding, especially subcutaneous/dermal bleeding, occurred in patients taking Ticagrelor as compared with Clopidogrel. However, for severe spontaneous subcutaneous/dermal bleeding in patients on Ticagrelor plus aspirin, aspirin dosage reduction is a better choice. Our previous study found that Ticagrelor monotherapy could also reduce the production of TXA₂; a strong P2Y₁₂ receptor will also challenge the current paradigm mandating the universal need for aspirin after PCI.⁹ Our study proposes that the influence of aspirin dosage in the presence of potent P2Y₁₂ antagonist

Ticagrelor requires further investigation, although aspirin still remains the cornerstone of secondary prevention after PCI, with a dose of 75-150 mg daily.

Conclusion

Our initial findings demonstrated that there was a stronger inhibitory effect of Ticagrelor plus aspirin as compared with Clopidogrel plus aspirin on AA induced platelet aggregation in patients with ACS with PCI. This finding will aid in the optimisation of antiplatelet treatment strategies using Ticagrelor in patients with ACS.

Abbreviation

ADP: adenosine diphosphate; AA: arachidonic acid; MAR%: maximum aggregation ratios; ACS: acute coronary syndrome; DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.

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Conflict of interest: None

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