# Meta-Analysis of Direct and Indirect Comparison of Ticagrelor and Prasugrel Effects on Platelet Reactivity

Thibault Lhermusier, MD, PhD[a], Michael J. Lipinski, MD, PhD[a], Udaya S. Tantry, PhD[b], Ricardo O. Escarcega, MD[a], Nevin Baker, MD[a], Kevin P. Bliden, MBA[b], Marco A. Magalhaes, MD[a], Hideaki Ota, MD[a], Wenjie Tian, MD[a], Lakshmana Pendyala, MD[a], Saar Minha, MD[a], Fang Chen, PhD[a], Rebecca Torguson, MPH[a], Paul A. Gurbel, MD[b], and Ron Waksman, MD[a,*]

**Studies have linked on-treatment platelet reactivity (PR) to adverse clinical outcomes. Because new $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) have been predominantly tested against clopidogrel, data on pharmacodynamic comparisons between these 2 drugs are scarce. We compared ticagrelor with prasugrel in a network meta-analysis. PubMed, Cochrane, and EMBASE were searched for studies assessing PR in patients with coronary artery disease treated with ticagrelor or prasugrel. All studies using prasugrel and/or ticagrelor providing platelet function measurement data using VerifyNow P2Y12 reaction units (PRUs), platelet reactivity index (PRI) vasodilator-stimulated phosphoprotein phosphorylation, or maximal platelet aggregation (MPA) by light transmission aggregometry were considered eligible. Mixed treatment comparison models directly compared ticagrelor and prasugrel and indirectly compared them using clopidogrel as a comparator with data presented as mean difference (95% confidence interval). Data were extracted from 29 studies, including 5,395 patients. Compared with clopidogrel 75 mg, both prasugrel 10 mg and ticagrelor 90 mg twice daily were associated with lower PRU (mean difference −117 [−134.1, −100.5] and −159.7 [−182.6, −136.6], respectively), a lower PRI (−24.2 [−28.2, −20.3] and −33.6 [−39.9, −27.6], respectively), and lower MPA (−11.8 [−17, −6.3] and −20.7 [−28.5, −12.8], respectively). Similar results were obtained with clopidogrel 150 mg. Ticagrelor 90 mg twice daily was associated with lower PRU (−42.5 [−62.9, −21.9]), lower PRI (−9.3 [−15.6, −3.5]), and lower MPA (−8.9 [−16.4, −1.2]) compared with prasugrel 10 mg. In conclusion, our meta-analysis suggests that ticagrelor achieved significantly lower on-treatment PR compared with prasugrel, with both being superior to clopidogrel standard or high dose.**  **(Am J Cardiol 2015;115:716−723)**

Landmark clinical trials and subsequent supportive data have established clopidogrel in combination with aspirin as the cornerstone of antithrombotic therapy after acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI).[1,2]The $P2Y_{12}$ receptor has, thus, become an established target in the setting of atherothrombosis and PCI. Because of the pharmacodynamic limitations that were associated with adverse clinical events, efforts were focused to develop novel $P2Y_{12}$ inhibitors with improved pharmacodynamic/pharmacokinetic properties. After promising phase II results, prasugrel and ticagrelor have clearly demonstrated in their respective phase III studies, "Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel−Thrombolysis in Myocardial Infarction" (TRITON-TIMI 38)[3] and the "Platelet Inhibition and Patient Outcomes" (PLATO),[4] their superiority over clopidogrel to prevent long-term ischemic end point recurrence after ACS. Thus, they are recommended as first-line agents in the treatment of patients with ACS by the European guidelines.[5] However, it is noteworthy that these 2 trials had different results. In PLATO, ticagrelor decreased cardiovascular mortality and did not increase the rate of overall major bleeding according to the study criteria, whereas in TRITON-TIMI 38, prasugrel did not significantly improve overall mortality and was associated with an increase in TIMI major bleeding and fatal bleeding. These differences in efficacy and safety outcomes were mainly attributed to discrepancies in study design, populations, and end point definitions. A relation between platelet reactivity (PR) and ischemic or bleeding events has been established.[6−9] Prasugrel and ticagrelor demonstrated greater platelet inhibition than clopidogrel, but data regarding head-to-head pharmacodynamic comparison between them are available in studies with a limited number of patients.[10−16] In the following network meta-analysis, we aimed to directly and indirectly compare pharmacodynamic effects of prasugrel with ticagrelor.

## Methods

The primary objective of this meta-analysis was to compare the pharmacodynamic effect of ticagrelor and

[a]Department of Interventional Cardiology, MedStar Washington Hospital Center, Washington, District of Columbia and [b]Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, Baltimore, Maryland. Manuscript received September 25, 2014; revised manuscript received and accepted December 23, 2014.

See page 722 for disclosure information.

*Corresponding author: Tel: (202) 877-8575; fax: (202) 877-3339.
*E-mail address:* ron.waksman@medstar.net (R. Waksman).

0002-9149/15/$ - see front matter 
http://dx.doi.org/10.1016/j.amjcard.2014.12.029

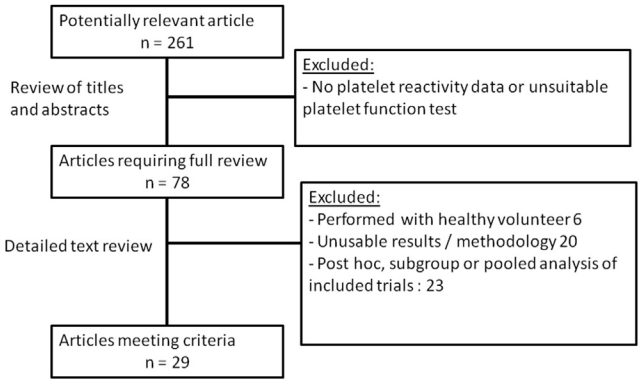


Figure 1. Flow diagram of the study. Twenty-seven publications with 4,689 patients were included in the network meta-analysis.

prasugrel. We included all studies providing PR data assessed in patients on prasugrel or ticagrelor maintenance dose. We selected studies including patients with coronary artery disease with or without PCI and excluded the ones performed in healthy volunteers. We limited our analysis to publications providing PR data according to the 3 most widely used platelet function tests: the VerifyNow P2Y12 assay (VN-P2Y12; Accumetrics Corporation, San Diego, California), the vasodilator-stimulated phosphoprotein phosphorylation (VASP; Biocytex, Marseille, France), and light transmission aggregometry (LTA). We included original publications or abstracts published with adequate data providing results expressed as mean platelet reactivity unit (PRU), mean platelet reactivity index (PRI), or mean maximal platelet aggregation (MPA) obtained with adenosine diphosphate (ADP) 20 μM with corresponding SD or SE for the respective tests.

Relevant publications to include in this meta-analysis were searched through MEDLINE/Pubmed, the Cochrane Collaboration database, and EMBASE with the following key words: "platelet reactivity" and ("prasugrel" or "ticagrelor"). Two physicians independently reviewed the titles, abstracts, and studies to determine whether they met inclusion criteria. No language, publications date, or publication status restrictions were imposed. In the case of duplication of data, the most inclusive data were chosen. Inclusion criteria were controlled comparison of clopidogrel, prasugrel, or ticagrelor in patients with coronary artery disease treated for at least 6 days to determine maintenance PR. The primary efficacy end point was PR expressed appropriately according to 1 of 3 platelet function as previously mentioned.

Continuous variables are presented as mean ± SD, and categorical variables are presented as percentages. Mixed treatment comparison model generation was performed to directly and indirectly compare maintenance therapy platelet function expressed as PRU, VASP, and MPA for different doses of clopidogrel, prasugrel, and ticagrelor using GeMTC 0.14.3 software (GeMTC; *http://drugis.org/mtc*). Bayesian hierarchical random-effects model with directed acyclic graph model for general-purpose Markov chain Monte Carlo analysis was performed with 50,000 tuning iterations and 100,000 simulation iterations for PRU and PRI and 200,000 simulation iterations for MPA. Data are presented as mean difference (95% confidence intervals). Statistical significance was defined as a p value $<0.05$.

## Results

From a total of 268 initial hits, 7 publications (Supplementary Data A) for direct comparison and 22 for indirect comparison (Supplementary Data B; 18 studies for clopidogrel-prasugrel comparison and 3 studies for clopidogrel-ticagrelor comparison) were found. The flow diagram of the study analysis and the design of the included studies are shown in Figure 1 and listed in Table 1, respectively. The clinical characteristics of patients enrolled in the studies included in the meta-analysis are reported in Table 2. The PR results of each study are presented in Table 3.

Nineteen studies provided PRU data. Combined results are illustrated in Figure 2. Lower PRU values were associated with prasugrel 10 mg daily and ticagrelor 90 mg twice daily compared with clopidogrel 75 mg (mean difference −117 [−134.1, −100.5] and −159.7 [−182.6, −136.6], respectively). Prasugrel 10 mg daily and ticagrelor 90 mg twice daily also had lower PRU values compared with a maintenance dose of clopidogrel 150 mg daily (−83 [−105.8, −60.5] and −125.5 [−154.9, −96.4], respectively). Head-to-head comparison of prasugrel 10 mg daily versus ticagrelor 90 mg twice daily showed that ticagrelor is associated with a lower PRU values (−42.5 [−62.9, −21.9]).

PRI results were presented in 12 studies and are summarized in Figure 3. Comparable findings were obtained with VASP to test PR as those obtained with VerifyNow. Both prasugrel 10 mg daily and ticagrelor 90 mg twice daily doses were associated with lower PRI values compared with clopidogrel 75 mg (−24.2 [−28.2, −20.3] and −33.6 [−39.9, −27.6], respectively) and with clopidogrel 150 mg (−15.8 [−21.2, −10.1] and −25.1 [−33.1, −12.7], respectively). Furthermore, ticagrelor 90 mg twice daily was associated with lower PRI values compared with prasugrel 10 mg daily (−9.3 [−15.6, −3.5]).

Ten studies using LTA were included (Figure 4). Both prasugrel 10 mg daily and ticagrelor 90 mg twice daily were associated with lower MPA compared with clopidogrel 75 mg (−11.7 [−16, −7] and −19.9 [−25.2, −14.4], respectively) and clopidogrel 150 mg daily (−12.9 [−17.1, −8.1] and −21.2 [−28, −13.6], respectively). Furthermore, ticagrelor 90 mg twice daily was associated with lower MPA compared with prasugrel 10 mg daily (−8.2 [−14.1, −2.3]).

## Discussion

Our network meta-analysis providing indirect and direct comparison of pharmacodynamic effects of prasugrel, ticagrelor, and clopidogrel in patients with coronary artery disease leads to the following findings: (a) both prasugrel 10 mg daily and ticagrelor 90 mg twice daily had significantly lower on-treatment platelet function values during maintenance therapy compared with clopidogrel 75 mg daily according to VerifyNow P2Y12 assay, VASP assay, and LTA; (b) both prasugrel 10 mg daily and ticagrelor 90 mg twice daily were associated with lower platelet function values during maintenance therapy compared with clopidogrel 150 mg according to all 3 platelet function tests; and (c) ticagrelor 90 mg twice daily appears to have significantly lower platelet function values compared with prasugrel 10 mg daily.