Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 15, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.11.032

Pharmacodynamic Evaluation of Switching From Ticagrelor to Prasugrel in Patients With Stable Coronary Artery Disease

Results of the SWAP-2 Study (Switching Anti Platelet-2)

Dominick J. Angiolillo, MD, PhD,* Nicholas Curzen, BM (Hons), PhD,† Paul Gurbel, MD,‡ Paul Vaitkus, MD,§ Fred Lipkin, PharmD,§ Wei Li, PhD,§ Joseph A. Jakubowski, PhD,‖ Marjorie Zettler, PhD, MPH,‖ Mark B. Effron, MD,‖ Dietmar Trenk, PhD¶

Jacksonville, Florida; Southampton, United Kingdom; Baltimore, Maryland; Parsippany, New Jersey; Indianapolis, Indiana; and Bad Krozingen, Germany

Objectives The goal of this study was to evaluate the pharmacodynamic effects of switching patients from ticagrelor to prasugrel.

Background Clinicians may need to switch between more potent $P2Y_{12}$ inhibitors because of adverse effects or switch to the use of a once-daily dosing regimen due to compliance issues.

Methods After a 3- to 5-day run-in phase with a ticagrelor 180-mg loading dose (LD) followed by a ticagrelor 90-mg twice-daily maintenance dose (MD), aspirin-treated patients (N = 110) with stable coronary artery disease were randomized to continue ticagrelor or switch to prasugrel 10-mg once-daily MD, with or without a 60-mg LD. Pharmacodynamic assessments were defined according to $P2Y_{12}$ reaction unit (PRU) ($P2Y_{12}$ assay) and platelet reactivity index (vasodilator-stimulated phosphoprotein phosphorylation assay) at baseline (before and after the run-in phase) and 2, 4, 24, and 48 h and 7 days after randomization.

Results Platelet reactivity was significantly greater at 24 and 48 h after switching to prasugrel versus continued therapy with ticagrelor, although to a lesser extent in those receiving an LD. Mean PRU remained significantly higher in the combined prasugrel groups versus the ticagrelor group (least-squares mean difference: 46 [95% confidence interval 25 to 67]) and did not meet the primary noninferiority endpoint (upper limit of the confidence interval ≤45), although PRU in the prasugrel cohort was lower at 7 days than at 24 or 48 h. Accordingly, rates of high on-treatment platelet reactivity were higher at 24 and 48 h in both prasugrel groups. At 7 days, there was no difference in high on-treatment platelet reactivity rate between the combined prasugrel and ticagrelor groups.

Conclusions Compared with continued ticagrelor therapy, switching from ticagrelor to prasugrel therapy was associated with an increase in platelet reactivity that was partially mitigated by the administration of an LD. (J Am Coll Cardiol 2014;63:1500–9) © 2014 by the American College of Cardiology Foundation

The addition of clopidogrel to aspirin therapy reduces ischemic events in patients with acute coronary syndrome (ACS) (1–3). However, clopidogrel is characterized by variability in platelet inhibitory response, which is associated with adverse clinical outcomes (4–7). More potent platelet $P2Y_{12}$ receptor inhibitors have been developed that are associated with improved clinical efficacy compared with clopidogrel (8). In particular, the TRITON–TIMI 38 (Trial

From the *Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida; †Southampton University Hospital, Southampton, United Kingdom; ‡Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, Baltimore, Maryland; §Medical Affairs, Daiichi Sankyo, Inc., Parsippany, New Jersey; ‖Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana; and the ¶Department of Clinical Pharmacology, Clinic for Cardiology and Angiology II, Universitäts-Herzzentrum Freiburg-Bad Krozingen, Bad Krozingen, Germany. This study was sponsored by Daiichi Sankyo, Inc., and Eli Lilly and Company. Dr. Angiolillo received payment as an individual for the following: consulting fee or honorarium from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Daiichi Sankyo, Inc., The Medicines Company, AstraZeneca, Merck, Evolva, Abbott Vascular, and PLx Pharma; participation in review activities from Johnson & Johnson, St. Jude Medical, and Sunovion; institutional payments for grants from Bristol-Myers Squibb, Sanofi-Aventis, GlaxoSmithKline, Otsuka, Eli Lilly, Daiichi Sankyo, Inc., The Medicines Company, AstraZeneca, Evolva, and Gilead; and grants from the James and Esther King Biomedical Research Program. Dr. Curzen received unrestricted research grants from Haemonetics, St. Jude Medical, and Medtronic; and speaker fees/consultancy from Haemonetics, St. Jude Medical, Medtronic, Boston Scientific, Daichii Sankyo, Inc., and Abbott Vascular. Dr. Gurbel has served as a consultant for Daiichi Sankyo, Inc., Lilly, Pozen, Bayer, AstraZeneca, Accumetrics, Merck, Medtronic, CSL, and Haemonetics; received grants from the National Institutes of Health, Daiichi Sankyo, Inc., Lilly, Pozen, CSL, AstraZeneca, Haemoscope Corporation,

to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial (9) and the PLATO (Platelet Inhibition and Patient Outcomes) trial (10) of prasugrel and ticagrelor, respectively, have shown them to be superior to clopidogrel in reducing thrombotic events. On the basis of these results, prasugrel was approved to reduce the rate of thrombotic cardiovascular events in patients with ACS who are to be managed with percutaneous coronary intervention (PCI), and ticagrelor was approved for the prevention of atherothrombotic events in all patients with ACS (1–3). Prasugrel is a prodrug with an active metabolite that binds irreversibly to the $P2Y_{12}$ receptor and is dosed once daily (QD) (11), whereas ticagrelor binds reversibly to the $P2Y_{12}$ receptor and has a twice-daily (BID) dosing regimen (12).

In certain clinical situations, switching from ticagrelor to prasugrel therapy may be considered; for example, in patients experiencing dyspnea or because QD administration might improve compliance. However, the pharmacodynamic effects of switching from ticagrelor to prasugrel are unknown. It has been reported that ticagrelor binds to a site on the $P2Y_{12}$ receptor distinct from the adenosine diphosphate–binding site. However, it is unknown whether ticagrelor, or its active metabolite (AR C124910XX), interferes with the binding of the prasugrel-active metabolite to $P2Y_{12}$, which has a short half-life in plasma (approximately 7 h) (11), leading to a pharmacodynamic interaction induced by competition for the binding site.

The objective of the present study was to compare the pharmacodynamic effects of switching from ticagrelor to prasugrel therapy in patients with stable coronary artery disease (CAD).

Methods

Study design. SWAP-2 (Switching Anti Platelet–2) was a Phase IV, randomized, multicenter, open-label (blinded pharmacodynamic results), 3-arm, parallel-design study (Fig. 1). The study consisted of a run-in phase in which all patients received a ticagrelor 180-mg loading dose (LD) and then a ticagrelor 90-mg BID maintenance dose (MD) for 3 to 5 days. After the 3- to 5-day ticagrelor run-in phase, patients were randomized (1:1:1) to receive 1 of the following 3 regimens: 1) prasugrel 60-mg LD followed by prasugrel 10-mg QD MD; 2) prasugrel 10-mg QD MD; or 3) continuation on ticagrelor 90-mg BID MD for 7 days.

All subjects provided written informed consent before participation in the study. The SWAP-2 study was conducted in compliance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation consolidated guidelines. It was approved by the institutional review board of each study site (Online Appendix).

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
ANCOVA = analysis of covariance
BID = twice daily
BMI = body mass index
CAD = coronary artery disease
CI = confidence interval
HPR = high on-treatment platelet reactivity
LD = loading dose
LS = least-squares
MD = maintenance dose
PCI = percutaneous coronary intervention
PRI = platelet reactivity index
PRU = $P2Y_{12}$ reaction unit
QD = once daily

Patients. Patients aged 18 to 75 years and weighing ≥60 kg with stable CAD and on low-dose aspirin therapy (75- to 150-mg daily) for ≥7 days before screening were eligible for enrollment. Stable CAD was defined as any of the following: 1) history of a positive result on stress testing; 2) previous coronary revascularization; 3) angiographic demonstration of CAD (≥1 lesion with ≥50% stenosis); 4) presence of at least moderate plaque according to computed tomography angiography; or 5) electron beam computed tomography coronary artery calcification score ≥100 Agatston units. Female subjects of childbearing potential were required to practice at least 1 form of birth control (excluding partner's use of condoms or partner's vasectomy). Subjects were excluded if they had a defined recommendation for $P2Y_{12}$ receptor antagonist therapy such as being within 12 months of an ACS diagnosis or PCI (1–3). Prohibited medications included antiplatelet agents other than aspirin, warfarin, nonsteroidal anti-inflammatory drugs, or cyclooxygenase-2 inhibitors (exceeding 3 doses per week), strong inhibitors/inducers of cytochrome P450 3A4, and higher doses of simvastatin or lovastatin (>40 mg/day). Full inclusion and exclusion criteria are included in the Online Appendix.

Assessment of platelet function. Blood samples were collected for platelet function testing at 7 time points: before the ticagrelor LD (pre–run-in baseline), immediately before the first dose of randomized drug (pre-randomization baseline), and at 2, 4, 24, and 48 h and 7 days after the first dose of randomized treatment (Fig. 1). Samples were processed within 1 h by operators who were blinded to treatment. The VerifyNow P2Y12 assay (Accumetrics, Inc., San Diego, California), reported as P2Y12 reaction units (PRU), and the vasodilator-stimulated phosphoprotein phosphorylation assay (Biocytex, Inc., Marseille, France), expressed as

Harvard Clinical Research Institute, and Duke Clinical Research Institute; received payment for lectures, including service on speakers' bureaus, from AstraZeneca, Lilly, Daiichi Sankyo, Inc., and Merck; received payment for development of educational presentations from Merck, the Discovery Channel, and Pri-Med; holds stock or stock options in Merck, Medtronic, and Pfizer; and holds patents in the area of personalized antiplatelet therapy and interventional cardiology. Dr. Vaitkus was an employee of Daiichi Sankyo, Inc., during the design and initiation of the study. Drs. Lipkin and Li are employees of Daiichi Sankyo, Inc. Drs. Jakubowski and Effron are employees and shareholders of Eli Lilly and Company. Dr. Zettler is an employee of Eli Lilly and Company. Dr. Trenk received payment as an individual for consulting fees or honorarium from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Inc., Eli Lilly and Company, and Merck; participation in review activities from Otsuka; and received institutional payments for grants from Eli Lilly. Dr. Vaitkus is currently affiliated with Bay Pines VA Healthcare System, Bay Pines, Florida.

Manuscript received October 28, 2013; revised manuscript received November 15, 2013, accepted November 26, 2013.