JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 6, NO. 2, 2013

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2012.12.001

EDITORIAL COMMENT

Switching From Prasugrel to Clopidogrel

Navigating in Unknown Waters*

Dominick J. Angiolillo, MD, PhD, Fabiana Rollini, MD

Jacksonville, Florida

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor antagonist is the cornerstone of treatment to prevent recurrent atherothrombotic events in patients with acute coronary syndrome (ACS) and undergoing percutaneous coronary interventions (PCI) (1). Clopidogrel is the most widely used platelet $P2Y_{12}$ receptor inhibitor. Despite the clinical efficacy of clopidogrel, numerous studies have shown a broad inter-individual variability in the response to this antiplatelet agent (2). Importantly, patients with high

See page 158

(HPR) and low (LPR) platelet reactivity while receiving clopidogrel therapy have an increased risk of recurrent ischemic events, including stent thrombosis and bleeding complications, respectively (3,4). These findings have set the basis for investigations aimed to define a "therapeutic window" of platelet reactivity that defines a range of $P2Y_{12}$ receptor-mediated antiplatelet effects associated with a reduced risk of ischemic and bleeding complications (Fig. 1) (5). The broadening of the armamentarium of $P2Y_{12}$ receptor inhibitors currently available for clinical use, including prasugrel and ticagrelor, have indeed represented an important step forward toward reaching such therapeutic goals (6). These novel generation $P2Y_{12}$ receptor inhibitors are characterized by potent antiplatelet effects and a greater reduction in atherothrombotic recurrences compared with clopidogrel in ACS patients (6). However, despite these benefits, numerous reasons account for the need or desire to switch a patient from a more potent $P2Y_{12}$ receptor inhibitor to clopidogrel. These include the higher risk of bleeding, development of side effects, and increased costs of these new agents compared with generic clopidogrel. However, to date studies have mostly focused on the effects of switching from clopidogrel to a novel generation $P2Y_{12}$ receptor inhibitor, and despite being broadly performed in clinical practice, there is a paucity of information on switching from one of the novel generation $P2Y_{12}$ receptor inhibitors to clopidogrel (7).

In this issue of *JACC: Cardiovascular Interventions*, Kerneis et al. (8) describe the results of an observational study evaluating the pharmacodynamic (PD) effects of switching from prasugrel to clopidogrel. In this study, a total of 300 high-risk ACS patients treated with prasugrel (10 mg/day) were studied. Platelet reactivity was assessed with multiple PD assays after 15 days of treatment. The VerifyNow $P2Y_{12}$ assay (Accumetrics, San Diego, California) was used to define the optimal therapeutic window of platelet reactivity, defined as 30 to 208 $P2Y_{12}$ reaction units (PRU). Patients below and above these thresholds were identified as having LPR and HPR, respectively. The primary objective of the study was the variation in LPR and HPR rates before and after the switch. Patients with LPR or those deemed to be at high risk of bleeding were considered for a switch to clopidogrel (75 mg/day) therapy, at the discretion of the treating physician. Platelet reactivity was evaluated again 15 days after switching from prasugrel to clopidogrel. A total of 31 (10.3%) prasugrel-treated patients, mostly (93.5%) pre-

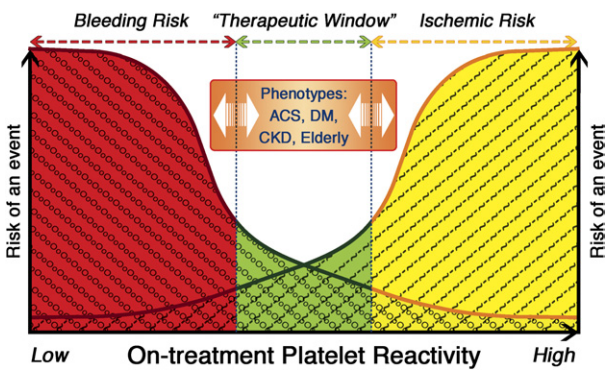

Figure 1. Impact of Platelet Reactivity on the Balance Between Safety and Efficacy

A "therapeutic window" of on-treatment platelet reactivity might delineate the risk for ischemic and bleeding complications. This can potentially vary according to the patient phenotype, such as clinical presentation (acute coronary syndrome [ACS] vs. stable patient), glucose control (diabetes mellitus [DM] vs. non-DM patient), renal function (chronic kidney disease [CKD] vs. normal renal function), and age (elderly vs. non-elderly). Adapted, with permission, from Angiolillo and Ferreiro (5).

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the University of Florida, College of Medicine-Jacksonville, Jacksonville, Florida. Dr. Angiolillo reports receiving honoraria for lectures from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly Company, Daiichi Sankyo, Inc., and AstraZeneca; consulting fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly Co., Daiichi Sankyo, Inc., The Medicines Company, Portola, Novartis, Medicure, Accumetrics, Arena Pharmaceuticals, AstraZeneca, Merck, Evolva, and Abbott Vascular; and research grants from Bristol Myers Squibb, Sanofi-Aventis, GlaxoSmithKline, Otsuka, Eli Lilly Co., Daiichi Sankyo, Inc., The Medicines Company, Portola, Accumetrics, AstraZeneca, and Eisai. Dr. Rollini has reported that she has no relationships relevant to the contents of this paper to disclose.

senting with LPR, were switched to clopidogrel. Switch from prasugrel to clopidogrel was associated with a significant 10-fold increase in platelet reactivity and a marked reduction (<10%) in LPR rates. However, this was associated with an increase in HPR from null while receiving prasugrel to 29% after switching to clopidogrel. Overall, this led to a greater percentage of patients within the optimal therapeutic window following the switch according to VerifyNow PRU thresholds. The exploratory clinical observations showed that minor bleeding decreased after switch from 32.2% to 9.7%; there were no major bleeding events or ischemic recurrences in this study population.

The major strength of this investigation by Kerneis et al. is that it is the first study in a clinical setting to assess the PD effects of switching from prasugrel to clopidogrel. Although the study was not designed to assess the clinical impact of this antiplatelet switching approach, the authors provide PD data that in larger investigations have shown to be surrogates of worse outcomes (3,4). Therefore, although no ascertainments on the safety and efficacy can be made, the data reported can provide some guidance on what to expect from a PD standpoint when switching from prasugrel to clopidogrel in a population with characteristics similar to that studied in the present investigation (mostly represented by patients with LPR while receiving prasugrel). There are, however, some considerations that need to be made that highlight the largely unknown impact of switching from prasugrel to clopidogrel in clinical practice.

First, the study reports the results of an observational registry in which the decision to switch from prasugrel to clopidogrel was at the discretion of the physician who was aware of the PD results. Therefore, this analysis suffers from significant study entry bias. This is further reinforced because most patients (93.5%) being switched had LPR, but not all patients with LPR were switched.

Second, the observation that after switching to clopdigrel more patients were within the therapeutic window with the VerifyNow $P2Y_{12}$ assay needs to be interpreted with caution. In fact, as mentioned in the preceding text, most patients being switched in this study had LPR while receiving prasugrel, and thus these findings might be a reflection that these patients metabolize thienopyridines more efficiently, increasing their likelihood of also being good responders to clopidogrel. Whether this can be attributed to any specific clinical characteristic or genetic make-up of these patients cannot be extrapolated from this study. Of note, although the switching strategy allowed a higher percentage of patients to be within the therapeutic window with the VerifyNow assay, these percentages were actually worse with the other PD assays used in this investigation.

Third, the study does not provide insights on how switching from prasugrel to clopidogrel affects platelet reactivity in patients within the optimal therapeutic window of platelet reactivity while taking prasugrel. This is indeed of crucial importance, because these comprised most of the patients in this study. Prasugrel has been shown to have a more favorable metabolism than clopidogrel, which translates into more consistent PD effects (6). Therefore, this might raise suspicion that switching patients to clopidogrel when they are within the optimal therapeutic window while taking prasugrel might account for an increase in platelet reactivity and thus potentially expose them to a higher risk of atherothrombotic events.

Fourth, the therapeutic window defining optimal levels of platelet reactivity was somewhat arbitrary. In fact, although the threshold of HPR seems to have been validated in several studies, there remains large uncertainty on the best threshold of LPR. In fact not all studies have been successful in identifying a threshold of platelet reactivity associated with increased bleeding and it has also varied in those who have (3). Differences in bleeding definitions, clinical setting, and patient population among other factors can contribute to these findings (Fig. 1) (5). It might also be argued that the therapeutic window might also vary over time in ACS patients, as indirectly reflected by the increase in bleeding complications and reduction in ischemic benefit over time with prasugrel (9). Thus, a switch only after 15 days of prasugrel treatment in LPR patients might be premature, because the highest risk period for ischemic recurrences—including stent thrombosis—is during the first months after an acute event, and thus lower levels of platelet reactivity might be desirable during this time frame.

Ultimately, no conclusions with regard to safety and efficacy should be made on the basis of the clinical findings from this study, which was limited to only 15 days of observation in a highly selected population. Of note, most studies to date have failed to demonstrate that modification of $P2Y_{12}$ receptor inhibiting antiplatelet treatment regimen on the basis of the results of platelet function testing can impact safety and efficacy, underscoring that routine testing is still not ready for prime-time (5).

Defining how and when to optimally switch antiplatelet therapy remains an unmet clinical need. Further studies are required to better define PD profiles of switching strategies of patients with more wide-ranging levels of platelet reactivity while receiving a given $P2Y_{12}$ receptor inhibitor. Most importantly, an improved understanding of how switching from newer-generation $P2Y_{12}$ receptor inhibitors, which provide more effective anti-ischemic protection but increased bleeding potential compared with clopidogrel, impacts patient outcomes. Only larger-scale registry and randomized clinical trial data will better delineate the safety and efficacy of such switching antiplatelet strategy and thus guide clinicians navigating in these unknown waters.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 6, NO. 2, 2013
FEBRUARY 2013:166–8

Reprint requests and correspondence: Dr. Dominick J. Angiolillo, University of Florida College of Medicine-Jacksonville, 655 West 8th Street, Jacksonville, Florida 32209. E-mail: dominick.angiolillo@jax.ufl.edu.

REFERENCES

1. Angiolillo DJ. The evolution of antiplatelet therapy in the treatment of acute coronary syndromes: from aspirin to the present day. Drugs 2012;72:2087–116.
2. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49:1505–16.
3. Bonello L, Tantry US, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010;56:919–33.
4. Rollini F, Tello-Montoliu A, Angiolillo DJ. Advances in platelet function testing assessing bleeding complications in patients with coronary artery disease. Platelets 2012;23:537–51.
5. Angiolillo DJ, Ferreiro JL. Platelet and genetic testing for clopidogrel hyporesponsiveness perspective: use as a research tool. J Am Coll Cardiol 2013. In press.
6. Ferreiro JL, Angiolillo DJ. New directions in antiplatelet therapy. Circ Cardiovasc Interv 2012;5:433–45.
7. Azmoon S, Angiolillo DJ. Switching antiplatelet regimens: alternatives to clopidogrel in patients with acute coronary syndrome undergoing PCI: a review of the literature and practical considerations for the interventional cardiologist. Catheter Cardiovasc Interv 2012 May 14. [Epub ahead of print], doi: 10.1002/ccd.24480.
8. Kerneis M, Silvain J, Abtan J, et al. Switching acute coronary syndrome patients from prasugrel to clopidogrel. J Am Coll Cardiol Intv 2013;6:158–65.
9. Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. J Am Coll Cardiol 2008;51:2028–33.

Key Words: $P2Y_{12}$ receptor antagonist ■ platelet reactivity ■ switch.