JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 4, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

# Clash of Oral $P2Y_{12}$ Receptor Inhibitors in Acute Coronary Syndromes*

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*"Ωφελέειν ἡ μη βλάπτειν [First do no harm]."*
—Hippocrates, 460 to 370 BC (1)

$P2Y_{12}$ receptors on platelet membrane are key modulators of platelet aggregation and thrombosis in acute coronary syndromes (2). Oral $P2Y_{12}$ receptor inhibitors (clopidogrel, ticagrelor, and prasugrel) combined with aspirin (dual antiplatelet therapy [DAPT]) have revolutionized the antithrombotic management of acute coronary syndromes (3-5). Ticagrelor and prasugrel, the newer members of oral $P2Y_{12}$ receptor inhibitors, have a stronger and more predictable antiplatelet profile than clopidogrel, resulting in reduced thrombotic outcomes in patients with acute coronary events at the expense of increased bleeding risk (4,5). The duration and potency of DAPT have been an ongoing challenge. Potent $P2Y_{12}$ receptor inhibition significantly decreases the thrombotic risk related to a culprit lesion, stenting of that lesion, or remote nonculprit lesions in acute coronary syndromes, especially during the first 3 months post-percutaneous coronary intervention (PCI) (6). Hence, the current practice guidelines on the management of acute coronary events recommend the preferential use of potent DAPT with ticagrelor or prasugrel for 12 months after an acute coronary syndrome treated with PCI (7,8). Depending on the individualized thrombotic and bleeding risk, shorter or longer DAPT can be considered.

Despite our progress in understanding the pharmacodynamics of $P2Y_{12}$ receptor inhibitors in acute coronary syndromes, there are still unanswered questions: Is there any difference between ticagrelor and prasugrel in terms of thrombotic and bleeding outcomes; and is there any net benefit in de-escalating from potent DAPT with ticagrelor or prasugrel to traditional DAPT with clopidogrel in the era of next-generation drug-eluting stents? In real-world experience, ticagrelor or prasugrel is switched back to clopidogrel before or after hospital discharge in 5% to 15% of patients with acute coronary syndrome requiring PCI (2,9). The current guidelines do not provide any clear recommendations on de-escalation of $P2Y_{12}$ inhibitors, leaving clinicians uninformed on how to manage these patients, who are frequently encountered in daily practice.

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In this issue of the *Journal*, Motovska et al. (10) present the 1-year outcomes of patients with acute myocardial infarction treated with primary angioplasty and randomized to prasugrel versus ticagrelor: the PRAGUE-18 (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction) study. This is an open-label, multicenter study conducted in the Czech Republic in 1,230 patients with ST-segment elevation myocardial infarction or high-risk non-ST-segment elevation myocardial infarction, undergoing primary or emergent PCI, respectively. The patients were randomized to ticagrelor (n = 596) or prasugrel (n = 634) for an intended duration of treatment of 12 months. The study had 2 major objectives: 1) to compare the efficacy and safety of ticagrelor versus prasugrel at 12 months post-primary PCI; and 2) to assess the ischemic and bleeding risk of economically motivated, post-discharge de-escalation to clopidogrel. There were no significant differences between ticagrelor and prasugrel in the composite endpoint (5.7% vs. 6.6%; p = 0.503), cardiovascular death (3.0% vs. 3.3%;

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

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2017.12.004

p = 0.769), myocardial infarction (2.5% vs. 3.0%; p = 0.611), stroke (0.7% vs. 1.1%; p = 0.423), all-cause death (4.2% vs. 4.7%; p = 0.654), definite stent thrombosis (1.5% vs. 1.1%; p = 0.535), all bleeding (11.1% vs. 10.9%; p = 0.999), and Thrombolysis In Myocardial Infarction major bleeding (0.7% vs. 0.9%; p = 0.754). Similar ischemic and bleeding outcomes between ticagrelor and prasugrel were also observed in the subgroup analysis. Approximately one-half of the patients switched to clopidogrel at any stage throughout the follow-up. In fact, more than 70% of patients switched to clopidogrel due to economic motivation (i.e., patients were not willing to accept the costs associated with ticagrelor or prasugrel and switched to clopidogrel after obtaining the treating physician's approval). More than 70% of the economically driven switches were done within the first 30 days post-hospital discharge. An economically motivated switch from ticagrelor or prasugrel to clopidogrel was associated with lower ischemic and bleeding risk compared with "no switch," whereas noneconomically driven transition to clopidogrel resulted in a significant increase of the ischemic endpoints. There was no difference in ischemic and bleeding outcomes between patients who switched from ticagrelor to clopidogrel and those who switched from prasugrel to clopidogrel. Notably, patients who de-escalated to clopidogrel due to economic reasons had lower risk compared with those who continued on ticagrelor or prasugrel.

PRAGUE-18 is a purely academic study, free from industry support and associated biases. The study was meticulously executed, achieving excellent follow-up of all patients. It provides original and clinically relevant head-to-head comparison of potent oral $P2Y_{12}$ receptor inhibitors post-primary PCI, as well as real-world data on the efficacy and safety of switching from stronger to traditional DAPT.

The study has several caveats that need to be acknowledged. This is an open-label study with inherent bias. Due to premature termination of enrollment secondary to futility, the study ended underpowered with limited sample size. However, the primary outcomes between treatment groups were consistently similar throughout the enrollment period, suggesting that a sample size increase would likely not make any major difference. The de-escalation strategy was heterogeneous, non-randomized, and biased, as it was primarily driven by patients' cost sharing. The frequency of de-escalation for any reason in the study was much higher than previous, large, and consistent registry data (54% vs. 5% to 15%) (2,9), and this actually represents one of the reasons for the study's reduced power. The discrepancy in de-escalation frequency is likely attributed to the fact that economic reasons for de-escalation are more applicable in the Czech Republic compared with the United States and other European countries, and/or are more applicable recently than the past. Despite these limitations, the current study is hypothesis-generating and deserves our attention.

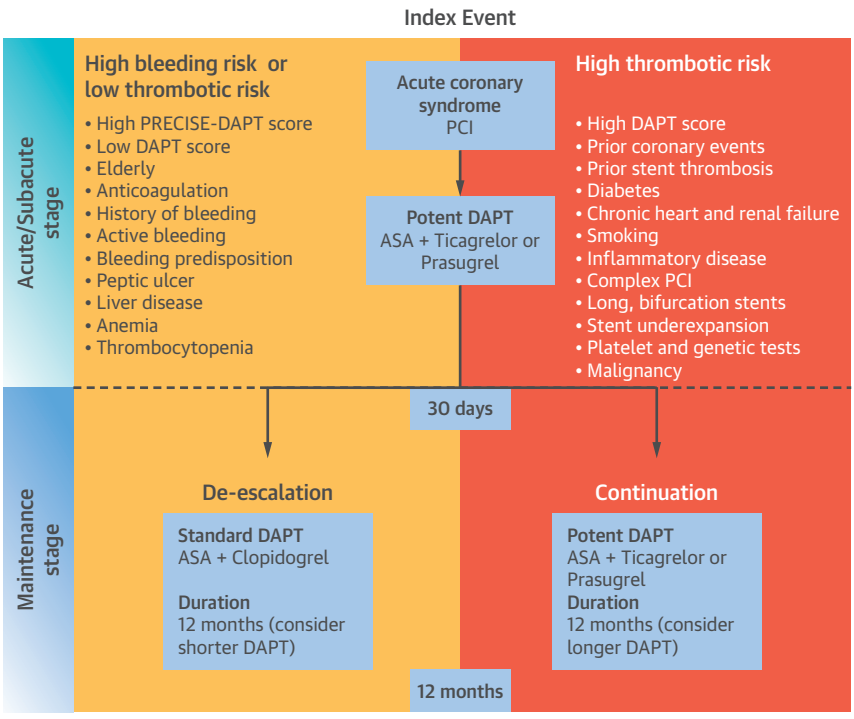
## HEAD-TO-HEAD COMPARISON BETWEEN TICAGRELOR AND PRASUGREL

Even though switching between new oral $P2Y_{12}$ receptor inhibitors is not very common, ranging between 2% to 4% (9,11,12), there are clinical scenarios that require changing from ticagrelor to prasugrel (e.g., in patients with dyspnea or compliance issues, given that ticagrelor is administered twice daily), or from prasugrel to ticagrelor (e.g., in patients with cerebrovascular events). Large-scale clinical studies to guide the transition between new $P2Y_{12}$ inhibitors are limited, and most data are derived from pharmacodynamic studies. The PRAGUE-18 study, even though very underpowered, is the first randomized study that provides head-to-head comparison of ticagrelor versus prasugrel in terms of efficacy and safety in patients with high-risk acute coronary events undergoing primary or emergent PCI. The acute/subacute phase (7 days) and 1-year outcomes did not support the hypothesis that one of the potent $P2Y_{12}$ inhibitors was more effective or safer than the other (10,13). Overall, the PRAGUE-18 study provides important preliminary evidence on the feasibility of switching between potent oral $P2Y_{12}$ receptor inhibitors. A larger, purely academic study comparing the efficacy and safety of ticagrelor versus prasugrel in patients with acute coronary syndromes treated with early invasive strategy is now under way (NCT01944800) (14).

## DE-ESCALATION FROM TICAGRELOR OR PRASUGREL TO CLOPIDOGREL

Switching from potent to standard DAPT is a real-world challenge. Reduced costs associated with a generic formulation of clopidogrel, as well as increased bleeding risk associated with the new potent $P2Y_{12}$ inhibitors—sometimes in the context of concomitant anticoagulation—represent the most important reasons for switching to clopidogrel (6,11). Nonbleeding side effects, such as dyspnea; patient characteristics and social issues; medication adherence; and patient/physician preference are additional reasons for de-escalating to traditional DAPT (6,11). Given the absence of large trials specifically designed

**FIGURE 1 Proposed Clinical Decision Pathways for DAPT Potency and Duration in Acute Coronary Syndromes**




ASA = aspirin; DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy.

to assess the safety and efficacy of de-escalation strategies, we rely on data from pharmacodynamic studies and existing clinical trials and registries. Pharmacodynamic studies showed that de-escalation, especially from ticagrelor to clopidogrel, increases platelet reactivity and theoretically increases the thrombotic propensity at the acute/subacute stage of acute coronary events (11). In line with these pharmacodynamic observations, the SCOPE (Switching from Clopidogrel to New Oral Antiplatelet Agents During Percutaneous Coronary Intervention) registry showed that early de-escalation increased the thrombotic events, without reducing the bleeding outcomes (15). In contrast, TRANSLATE-ACS (Treatment With Adenosine Diphosphate [ADP] Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome), a large, multicenter, longitudinal registry, showed that early switching from ticagrelor or prasugrel to clopidogrel was not associated with increased thrombotic events when compared with continuation on the higher-potency agent in myocardial infarction patients treated with PCI (9). Small-scale and relatively underpowered randomized clinical trials (TOPIC [Timing Of Platelet Inhibition After Acute Coronary Syndrome] [16] and TROPICAL-ACS [Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes] [17]), as well as nonrandomized data from PRAGUE-18, consistently provided evidence that early downgrading from ticagrelor or prasugrel to clopidogrel, with or without platelet function test guidance, is a feasible strategy, leading to reduced bleeding risk without increasing the ischemic risk.

Taken together, these data might challenge the current guidelines, which recommend preferential use of potent versus traditional DAPT for 1 year. Given that the majority of stent thrombosis occurs during the first month, whereas the majority of bleeding events happen after the first month, a strategy of a potent DAPT with ticagrelor or prasugrel during the first 1 to 3 months to reduce the ischemic events succeeded by a less-potent DAPT with clopidogrel thereafter to reduce the bleeding risk appears attractive (**Figure 1**). Tailored assessment of thrombotic/bleeding risk and platelet function and genetic testing have the potential to identify the patients who will benefit from shorter

and less-potent DAPT, as well as those who will benefit from longer and more-potent DAPT (**Figure 1**). Alternative strategies with single antiplatelet therapy with potent $P2Y_{12}$ inhibitors also have the potential to reduce bleeding without jeopardizing ischemic efficacy (18,19).

Preliminary data from existing clinical trials show that DAPT de-escalation in low-thrombotic-risk patients is feasible. Large randomized controlled trials focused on outcomes and cost-effectiveness are needed before a $P2Y_{12}$ de-escalation strategy is widely adopted. Such trials should investigate the role of de-escalation in high- and lower-risk acute coronary syndromes requiring PCI. It might not be straightforward to conduct those trials, given the lack of interest and support from the pharmaceutical industry, but at the end of the day the academic cardiology community has the responsibility to advance science in an unbiased manner and deliver the best and safest patient care, in line with the Hippocratic principle of "primum non nocere [first do no harm]" (1).

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**KEY WORDS** de-escalation, myocardial infarction, outcome, prasugrel, primary percutaneous coronary intervention, ticagrelor