EDITORIAL

Ticagrelor — Is There Need for a New Player in the Antiplatelet-Therapy Field?

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The thienopyridine clopidogrel, which irreversibly blocks the adenosine diphosphate (ADP) receptor P2Y12 on platelets, has become an essential component of therapy in patients with acute coronary syndromes, because it significantly improves the outcomes.[1] However, clopidogrel has at least three drawbacks: delayed onset of action, large interindividual variability in platelet response, and irreversibility of its inhibitory effect on platelets (Fig. 1). The two-step activation process, involving a series of cytochrome P-450 (CYP) isoenzymes, is susceptible to the interference of genetic polymorphisms[2] and drug–drug interactions.[3] Patients with a poor response to clopidogrel have an increased risk of coronary thrombosis.[4] The increased risk of bleeding due to prolonged persistence of the clopidogrel effect is of concern when patients need nondeferrable surgery such as urgent coronary-artery bypass grafting (CABG).

Prasugrel is a newer thienopyridine that also irreversibly binds to P2Y12. It has a more rapid onset of action and a stronger inhibitory effect than clopidogrel.[5] As compared with clopidogrel, prasugrel shows lower variability in platelet response[6] and no measurable vulnerability to genetic variation in CYP isoenzymes (Fig. 1).[7] However, the limitation of the irreversibility of the thienopyridine effect is even more evident with prasugrel than with clopidogrel. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38, there was a significant increase in the risk of CABG-related bleeding with prasugrel.[8]

Ticagrelor is an orally active drug that binds reversibly to P2Y12 (Fig. 1), with a stronger and more rapid antiplatelet effect than clopidogrel. In this issue of the *Journal*, Wallentin et al. report on the results of the Study of Platelet Inhibition and Patient Outcomes (PLATO), comparing ticagrelor with clopidogrel.[9] As compared with clopidogrel, ticagrelor was associated with a 16% relative risk reduction with regard to the primary end point — a composite of death from cardiovascular causes, myocardial infarction, and stroke — but no significant increase in the overall risk of major bleeding.

PLATO is the third randomized trial evaluating novel antagonists of platelet ADP receptors in patients with acute coronary syndromes, following the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial and TRITON–TIMI 38 (Table 1).[1,8] Two striking differences among the outcomes of these three trials deserve special consideration (Table 1). First, in both the CURE trial and TRITON–TIMI 38, stronger platelet inhibition was associated with an increased risk of bleeding, whereas in PLATO, the risk of major bleeding was not increased with ticagrelor. As compared with clopidogrel, ticagrelor was associated with more frequent non–CABG-related bleeding, but it was safer than clopidogrel in patients undergoing CABG. This result highlights the important advantage of reversibility in the mechanism of action of ticagrelor.

Second, neither the CURE study nor TRITON–TIMI 38 showed a significant reduction in the mortality rate in association with stronger platelet inhibition. In PLATO, the rates of death from any cause were 4.5% with ticagrelor and 5.9% with clopidogrel, with a significant relative risk reduction (22%). This finding may simply reflect

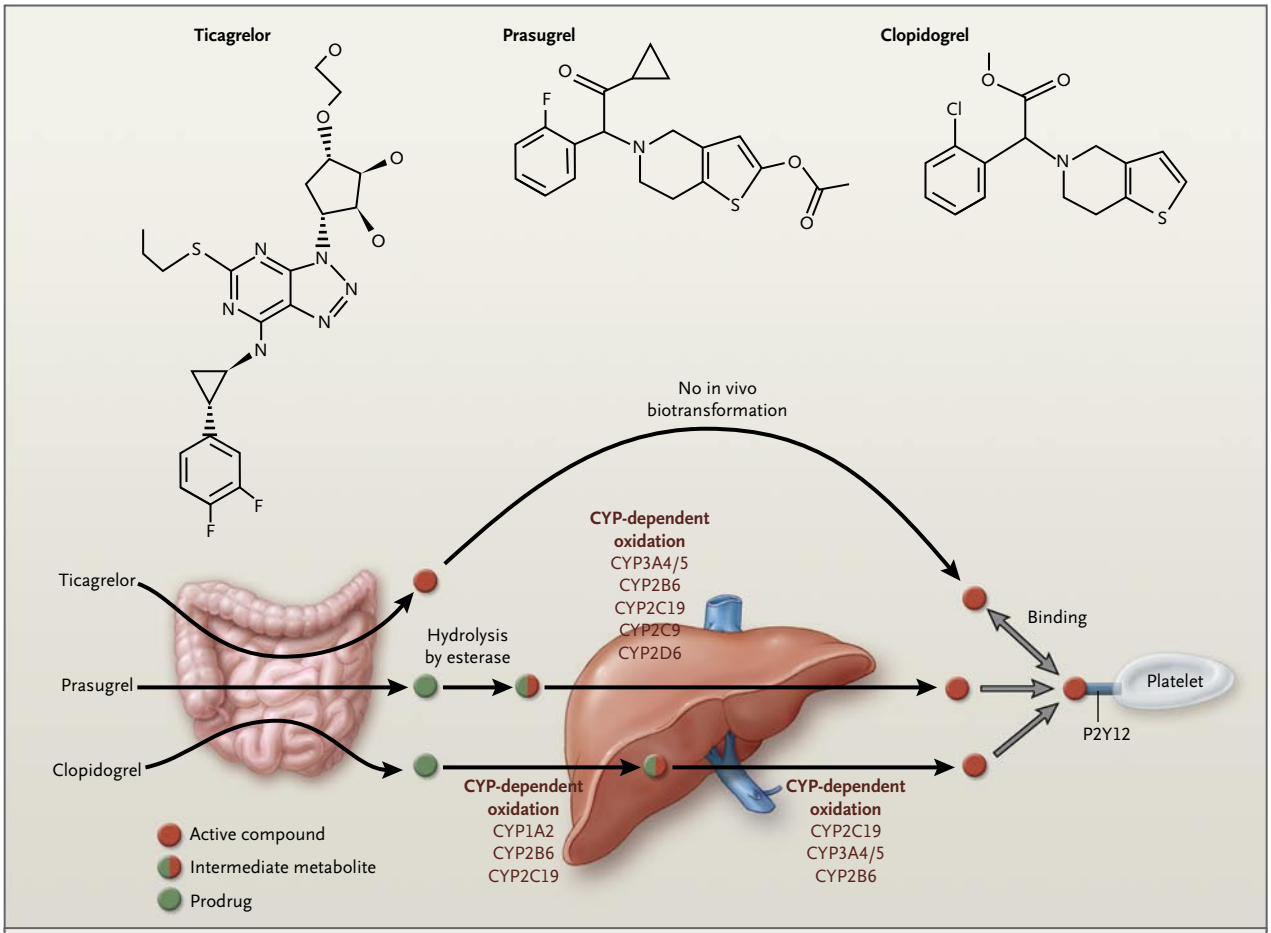

Figure 1. Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor.

Ticagrelor, a cyclopentyl triazolopyrimidine, is rapidly absorbed in the intestine. The absorbed drug does not require further biotransformation for activation. It directly and reversibly binds to the platelet adenosine diphosphate (ADP) receptor P2Y12. The half-life of ticagrelor is 7 to 8 hours. The thienopyridines prasugrel and clopidogrel are prodrugs. Their active metabolites irreversibly bind to P2Y12 for the platelet's life span. After intestinal absorption of clopidogrel, it requires two cytochrome P-450 (CYP)–dependent oxidation steps to generate its active compound. After intestinal absorption of prasugrel, it is rapidly hydrolyzed, by means of esterases, to an intermediate metabolite and requires one further CYP-dependent oxidation step to generate its active compound. Most of the CYP-dependent activation occurs in the liver. Relevant CYP isoenzymes involved in the activation of both clopidogrel and prasugrel are also shown. Their activity may be affected by genetic polymorphisms.

the play of chance, because the trial was not powered to detect differences in the mortality rate. However, since the mortality rate in patients treated with antiplatelet drugs is determined by the risks of both ischemia and bleeding, ticagrelor may reduce the mortality rate by reducing the risk of death from ischemia without increasing the risk of death from bleeding. This hypothesis needs to be addressed in future investigations.

Third, new side effects, not seen with clopidogrel or prasugrel, were seen with the use of ticagrelor. These include dyspnea, bradyarrhythmia, and increased serum levels of uric acid and creatinine. Although they do not seem to have put patients at higher risk for death, these side effects may certainly have a negative effect on the quality of life. There was also a trend toward a higher risk of hemorrhagic stroke with ticagrelor than with clopidogrel, which becomes significant if cases of stroke classified as being of unknown origin are also counted as hemorrhagic strokes.

Although PLATO was thoughtfully designed and conducted, it did have some limitations. In my opinion, the trial would have been stronger if the study drug had been administered for at least 1 year, if clopidogrel loading (preferably in a 600-mg dose) had been used for all patients in

the clopidogrel group irrespective of whether they had been treated previously with clopidogrel, and if proton-pump inhibitors had been used less frequently after randomization (to reduce any potentially negative interference with clopidogrel efficacy).

The availability of three agents for antagonizing platelet ADP receptors may make it possible to individualize antiplatelet therapy. In particular, ticagrelor therapy may be preferred in patients whose coronary anatomy is unknown and for whom a CABG procedure is deemed probable. If patients who are receiving clopidogrel or prasugrel need elective surgery, it is reasonable to switch them to ticagrelor 5 to 7 days before surgery. Avoidance of the use of prasugrel in patients with a history of stroke or transient ischemic attacks has been advised.[10] It seems prudent to apply the same advice to ticagrelor. The use of prasugrel has been discouraged in patients with an excessively high risk of bleeding.[10] It might also be prudent to avoid the use of ticagrelor in patients with a high bleeding risk (presumably those with multiple risk factors). Ticagrelor therapy should be discouraged in patients who have chronic obstructive pulmonary disease, hyperuricemia, moderate or severe renal failure, bradyarrhythmias unprotected by pacemakers, a history of syncope, or a need for treatment with an ADP-receptor antagonist for more than 1 year. We should further recognize that the rapidly reversible effect of ticagrelor makes careful surveillance of patients' compliance with the drug mandatory. For all remaining patients with acute coronary syndromes, either ticagrelor or prasugrel may be preferred, at least until data from studies specifically comparing these two agents become available.

The whole story concerning the adverse effects of ticagrelor may require evaluation in a much larger number of patients, something that may be beyond the capacity of a randomized trial. We should carefully monitor patients receiving this drug to establish the overall impact of its side effects. Finally, efforts to develop new effective and safe antithrombotic drug regimens should not be discouraged by the perception that an increase in antithrombotic efficacy is necessarily associated with a higher risk of bleeding.

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Table 1. Risks Associated with Platelet Adenosine Diphosphate–Receptor Antagonists in Patients with Acute Coronary Syndromes, According to Trial.*

Event	CURE Trial (N = 12,562)			TRITON–TIMI 38 (N = 13,608)			PLATO (N = 18,624)		
	Clopidogrel Group	Placebo Group	Relative Risk with Clopidogrel (95% CI)	Prasugrel Group	Clopidogrel Group	Relative Risk with Prasugrel (95% CI)	Ticagrelor Group	Clopidogrel Group	Relative Risk with Ticagrelor (95% CI)
Death from any cause	5.7	6.2	0.93 (0.81—1.07)	3.0	3.2	0.95 (0.78–1.16)	4.5	5.9	0.78 (0.69–0.89)
Death from cardiovascular causes	5.1	5.5	0.93 (0.79–1.08)	2.1	2.4	0.89 (0.70–1.12)	4.0	5.1	0.79 (0.69–0.91)
Myocardial infarction†	5.2	6.7	0.77 (0.67–0.89)	7.3	9.5	0.76 (0.67–0.85)	5.8	6.9	0.84 (0.75–0.95)
Stroke†	1.2	1.4	0.86 (0.63–1.18)	1.0	1.0	1.02 (0.71–1.45)	1.5	1.3	1.17 (0.91–1.52)
Death from cardiovascular causes, myocardial infarction, or stroke†‡	9.3	11.4	0.80 (0.72–0.90)	9.9	12.1	0.81 (0.73–0.90)	9.8	11.7	0.84 (0.77–0.92)
Major bleeding	3.7	2.7	1.38 (1.13–1.67)	2.5	1.7	1.45 (1.15–1.83)	11.6	11.2	1.04 (0.95–1.13)

* The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial[1] included patients who had acute coronary syndromes without ST-segment elevation; both PLATO (Study of Platelet Inhibition and Patient Outcomes)[9] and TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38)[8] included patients who had acute coronary syndromes with or without ST-segment elevation.
† TRITON–TIMI 38 counted only nonfatal myocardial infarction and nonfatal stroke.
‡ Death from cardiovascular causes, myocardial infarction, or stroke was the primary end point in all three studies.

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