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## EDITORIALS



## P2Y<sub>12</sub> Inhibition in Patients with NSTEMI — Can Later Be Better?

John F. Keane, Jr., M.D.

Acute coronary syndrome is an umbrella term that is used to describe the abrupt reduction of blood flow to myocardial tissue, typically associated with the rupture of a coronary atherosclerotic plaque. Rupture exposes the blood to plaque contents, resulting in the deposition and activation of platelets and the formation of thrombi. Complete thrombotic occlusion produces ST-segment elevation myocardial infarction, whereas incomplete impairment of coronary blood flow results in unstable angina or, when biomarkers for myocardial injury are present, non-ST-segment elevation myocardial infarction (NSTEMI). Because the rupture of a plaque incites platelet activation and thrombosis, treatments for unstable angina and NSTEMI have focused on inhibiting platelet function and the coagulation cascade. In patients at high risk for future events (i.e., reinfarction or recurrent ischemia), an early invasive strategy of cardiac catheterization and revascularization is recommended, and in most of these patients intracoronary stents are implanted to treat the plaque rupture. Since stents can produce further plaque trauma, platelet-dependent thrombosis, and embolization into the coronary microcirculation, it is best practice to treat patients with agents that inhibit platelet activation to prevent recurrent ischemia after percutaneous coronary intervention (PCI). As a consequence, current guidelines recommend dual antiplatelet therapy with aspirin plus another agent in patients with NSTEMI who are undergoing PCI.<sup>1,2</sup>

Among the agents available to complement aspirin are three approved inhibitors of the platelet P2Y<sub>12</sub> receptor — clopidogrel, prasugrel, and ticagrelor — that are known to reduce ischemic events in patients with NSTEMI who are

undergoing PCI.<sup>3-5</sup> Despite this proven efficacy, our knowledge about the administration of dual antiplatelet therapy remains incomplete. For example, the timing for starting P2Y<sub>12</sub> inhibition is not clear. In one pivotal trial, patients were treated for several days to weeks before revascularization,<sup>6</sup> whereas other trials involved treatment around the time of cardiac catheterization.<sup>4,5</sup> Guidelines recommend that clopidogrel be administered soon after hospital admission,<sup>1,2</sup> but this recommendation has, to my knowledge, never been tested directly in a randomized trial. The trial data for the second-generation agents, prasugrel and ticagrelor, are more limited than are those for clopidogrel and have not specifically tested this question.

Montalescot and colleagues<sup>7</sup> offer new insight into the timing of prasugrel administration in patients with NSTEMI who are scheduled to undergo catheterization. In their study, now reported in the *Journal*, they randomly assigned 4033 patients to receive prasugrel as pretreatment (2 to 48 hours before cardiac catheterization) or to receive prasugrel after catheterization if PCI was planned. They found that pretreatment with prasugrel clearly provided better inhibition of platelet function at the time of catheterization. However, the pretreatment strategy as compared with the late-administration strategy had no significant effect on the rate of major ischemic events over the course of the 30-day study period. In fact, the trial was terminated because prasugrel pretreatment produced harm, with more bleeding events that were categorized as major or life-threatening.

The findings of Montalescot and coworkers highlight the difference between first-generation

and second-generation P2Y<sub>12</sub> inhibitors. Clopidogrel produces irreversibly, but sometimes incomplete, P2Y<sub>12</sub> inhibition through conversion of the drug to an active metabolite. Clopidogrel is typically administered well before PCI, since this strategy appears to ensure adequate platelet inhibition at the time of PCI and is the most effective strategy for reducing ischemic events.<sup>8</sup> Prasugrel, although also a prodrug, undergoes more efficient metabolism, producing faster and more complete platelet inhibition,<sup>9</sup> thus obviating the need for pretreatment. In the study by Montalescot et al., pretreatment with prasugrel afforded maximal platelet inhibition at the time of vascular access, which explains why excess procedure-related bleeding was observed. Overall, these results indicate that patients with NSTEMI who are selected for an early invasive strategy will be best served by administration of prasugrel only after angiographic definition of their coronary anatomy. It remains to be seen whether a similar strategy could be applied to ticagrelor, the other high-potency P2Y<sub>12</sub> antagonist currently available.

The work by Montalescot and colleagues may streamline the care of patients with NSTEMI in the hospital. Up to 16% of patients with NSTEMI ultimately undergo coronary-artery bypass grafting (CABG).<sup>3</sup> Because current guidelines recommend P2Y<sub>12</sub> inhibition soon after hospital admission, many patients with NSTEMI who need CABG will have received P2Y<sub>12</sub> antagonists before the catheterization. Administration of P2Y<sub>12</sub> inhibitors within 5 days before CABG has been linked to excess bleeding<sup>3</sup> and prolonged hospitalization,<sup>10</sup> prompting recommendations that CABG be delayed until 5 to 7 days after discontinuation of P2Y<sub>12</sub> antagonists.<sup>1,2</sup> As a consequence, early P2Y<sub>12</sub>-inhibition therapy is an important cause of delay in performing CABG, adding inefficiency and cost to the care of patients with NSTEMI. However, the work of Montalescot and coworkers indicates that one can safely pursue a more parsimonious approach of reserving prasugrel administration until after angiography. With this strategy, P2Y<sub>12</sub> treatment can be limited to patients who will be undergoing PCI, and patients with NSTEMI who require

CABG will be able to avoid unnecessary delays. Further studies will be needed to determine whether newer agents, administered only after angiography, can improve the efficiency of caring for patients with NSTEMI.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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