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CORRESPONDENCE

Research Correspondence

Platelet Aggregation and Its Association With Stent Thrombosis and Bleeding in Clopidogrel-Treated Patients

Initial Evidence of a Therapeutic Window

To the Editor: Platelet response to clopidogrel is characterized by large interindividual response variability (1). Numerous studies have linked low responsiveness to clopidogrel with the occurrence of thrombotic events, and more recently, data have emerged linking an enhanced response to clopidogrel with a higher risk for bleeding (2). Both associations have important implications for patient outcomes, as both thrombotic and bleeding events significantly affect mortality (3). With the advent of more potent $P2Y_{12}$ receptor inhibitors such as prasugrel and ticagrelor, an important question to be addressed is whether the association of ischemic events with the level of $P2Y_{12}$ receptor inhibition is a linear and thereby continuous association (the more inhibition, the lower the risk for ischemic events) or whether it is characterized by a certain threshold effect. The latter would mean that below a certain threshold value of adenosine diphosphate-induced platelet aggregation, ischemic events could not be further reduced, but in contrast, bleeding events may substantially increase. The existence of efficacy and safety thresholds for patients treated with long-term antithrombotic therapy has been well established with coumarin derivatives (4).

Because we have previously been able to establish cutoff values of adenosine diphosphate-induced platelet aggregation using the Multiplate analyzer (Dynabyte Informationssysteme GmbH, Munich, Germany) for the occurrence of both stent thrombosis (ST) (5) and major bleeding events (2), we sought to analyze the incidence of bleeding and ST comparatively across different levels of $P2Y_{12}$ receptor inhibition to explore threshold effects and a potential therapeutic window for clopidogrel treatment.

Patients (n = 2,533) included in this study underwent coronary stenting after pre-treatment with clopidogrel 600 mg. Adenosine diphosphate-induced platelet aggregation was assessed using a Multiplate analyzer on blood samples obtained directly before percutaneous coronary intervention. Aggregation values are quantified in aggregation units (AU) times minutes (= area under the aggregation curve). For the present analysis, the primary efficacy end point was the 30-day incidence of definite or probable ST, and the primary safety end point was the incidence of in-hospital Thrombolysis In Myocardial Infarction major bleeding. As previously reported, different levels of $P2Y_{12}$ receptor inhibition were defined by cutoff values derived from receiver-operating characteristic curve analyses with a cutoff value of 468 AU × min to define clopidogrel low responders (5) and a cutoff value of 188 AU × min to define enhanced responders (2).

Details of the study population have been reported previously (2). A median platelet aggregation value of 225 AU × min (interquartile range 142 to 374 AU × min) was observed. Using the cutoff values of 188 and 468 AU × min, patients were allocated to 3 different groups: 975 patients (38%) were classified as enhanced responders (≤188 AU × min), 428 patients (17%) as low responders (≥468 AU × min), and 1,130 patients (45%) as normal responders (189 to 467 AU × min). The primary efficacy end point was observed in 22 patients (0.9%; 16 definite ST and 6 probable ST), and the primary safety end point (major bleeding) was observed in 34 patients (1.3%). The incidence of ST was highest (2.8%) in low responders, and the incidence of bleeding was highest in enhanced responders (2.2%) (Fig. 1A). For ST, no significant differences were observed between normal and enhanced responders ($p = 0.38$). Similarly, no significant differences were observed for the incidence of major bleeding between normal and low responders ($p = 0.72$). The overall incidence of adverse events (combined ST and major bleeding) across the 3 groups of patients is shown in Figure 1B. The risk of adverse events was significantly lower in normal responders compared with the remaining patients (n = 1,403; odds ratio: 0.40; 95% confidence interval: 0.22 to 0.75; $p = 0.003$).

To the best of our knowledge, this is the first comparative analysis of the risk for bleeding and ST across different levels of $P2Y_{12}$ receptor inhibition. Our findings support the notion that the association of $P2Y_{12}$ receptor inhibition and ST is characterized by a certain threshold effect, as the incidence of ST does not continuously decrease across increasing levels of $P2Y_{12}$ receptor inhibition. A similar relationship seems to be valid for bleeding events as well, as no significant differences were observed for bleeding risk when comparing normal and low responders. The present analysis provides support for the existence of a "sweet spot" of $P2Y_{12}$ receptor inhibition, or a so-called therapeutic window, as patients with aggregation values in the range of 189 to 467 AU × min showed remarkably low risk for the occurrence of both bleeding and ST.

The proportion of the population classified as being enhanced responders here was nearly 40%. Considering the recognized variability in the metabolism and active metabolite generation of clopidogrel, this is a relatively high percent of patients to be achieving what appears to be greater than necessary levels of $P2Y_{12}$ inhibition. In contrast, <20% of patients were unable to achieve adequate levels of platelet inhibition. With a much greater proportion of patients achieving too high rather than too low levels of platelet inhibition, these results, if confirmed, will have important implications for the application of treatment strategies designed to increase levels of $P2Y_{12}$ inhibition in large, unselected populations. Whether these findings are translatable to nonthienopyridine

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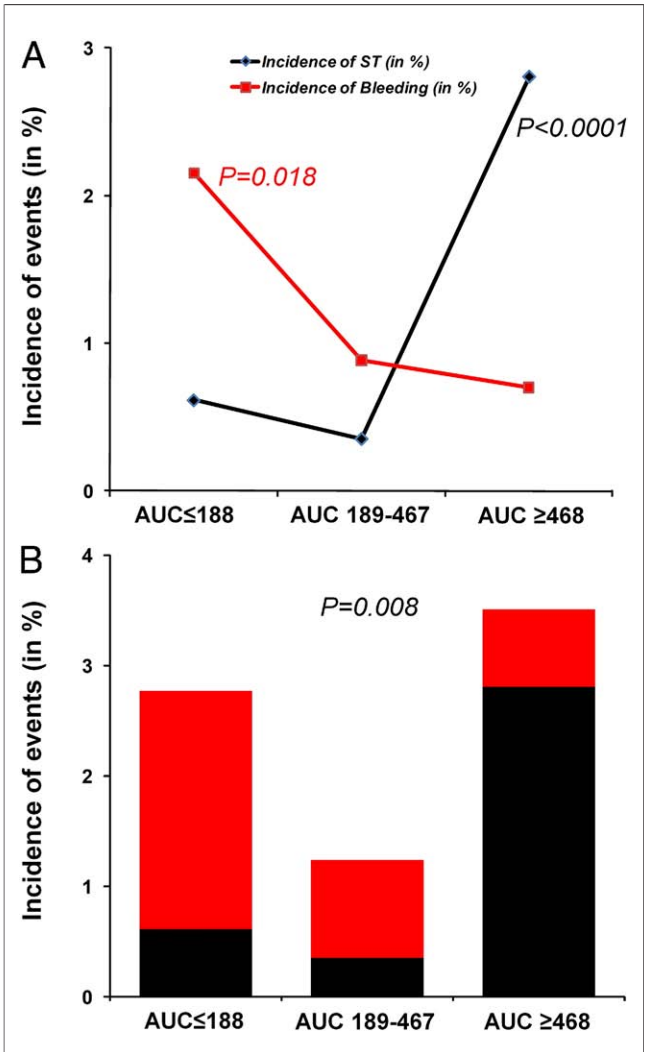

Figure 1 Adverse Events and Levels of $P2Y_{12}$ Receptor Inhibition

(A) Thirty-day incidence of definite or probable stent thrombosis (ST) **(black line)** and incidence of in-hospital major bleeding events **(red line)**. Patients are stratified into groups of enhanced responders (area under the aggregation curve [AUC] ≤188), normal responders (AUC 189 to 467), and low responders (AUC ≥468). **(B)** Incidence of adverse events (combined for ST and major bleeding) across responder groups. p values reported were calculated across all 3 groups using chi-square tests.

$P2Y_{12}$ inhibitors or to the setting of long-term therapy is unclear and requires further study.

Although limitations of this analysis, including a single-time point assessment of platelet function, the lack of a uniformly accepted bleeding definition, and its observational design, need to be recognized, we do think that the present analysis supports the hypothesis that the association of $P2Y_{12}$ receptor inhibition and ischemic events is characterized by a threshold phenomenon and that a therapeutic window of $P2Y_{12}$ receptor inhibition does exist, with patients within this range exhibiting low risk for both bleeding and ST.

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Letters to the Editor

The Coronary Collier

Galiwango et al. (1) recently provided a beautiful coronary computed tomographic angiographic illustration of a rare anomaly, which they termed "the coronary collier." Although this single coronary artery variant (arising from the right coronary cusp and coursing the entire atrioventricular groove before terminating in the anterior interventricular sulcus) is certainly uncommon, it is not "new" to the literature. This coronary artery anomaly was previously identified on the post-mortem examination of the late basketball star Pete Maravich (2). Histology revealed patchy