In addition to aspirin, clopidogrel was the most commonly prescribed P2Y12-ADP receptor to prevent recurrent ischemic events in patients suffering acute coronary syndromes (ACS) or undergoing percutaneous coronary intervention (PCI) until the first observations of interindividual variability in the biological response to clopidogrel prompted a large number of studies that confirmed that clopidogrel induced a highly variable level of platelet reactivity (PR) inhibition in patients undergoing PCI. Subsequently, this interindividual variability was shown to be responsible for a significant proportion of ischemic recurrence, including cardiovascular death and early stent thrombosis. In fact, based on studies enrolling more than 10,000 patients and using various platelet assay, a strong correlation between the level of PR inhibition obtained following clopidogrel loading dose (LD) and clinical outcome was demonstrated. On the other hand, evidence is emerging to support a link between excessive PR inhibition and bleeding events. Accordingly, in recent years investigators have underlined the fact that in patients treated with PCI, high levels of PR inhibition translate into increased bleeding rates. Thus, the concept of a therapeutic window of PR inhibition with P2Y12-ADP receptor antagonists to prevent ischemic events without increasing bleeding was hypothesized by Gurbel et al (Figure). Following these observations, investigators have postulated that individualized antiplatelet therapy in order to optimize the level of PR inhibition could carry the promise of an improved clinical outcome in patients undergoing PCI. Consistently, the more potent P2Y12-ADP receptor antagonists, ticagrelor and prasugrel, were associated in randomized trials with less ischemic events but at the cost of higher bleeding rates related to their higher biological efficacy compared with clopidogrel. Thus, the armamentarium at our disposal has significantly improved and now includes 3 P2Y12-ADP receptor antagonists with specific risk/benefit ratios.
Prasugrel is a third-generation thienopyridine that generates similar active metabolites to clopidogrel, but has a more efficacious metabolism that is responsible for the higher potency. In particular, prasugrel is not affected by CYP polymorphism or the other usual factors associated with HTPR in clopidogrel-treated patients. On the other hand, Asian patients have been shown to have a higher exposure to prasugrel active metabolites than Caucasians, which could be related to several factors including genetic polymorphisms and lower average body mass index. It suggests that while clopidogrel and prasugrel are mainly tested in Caucasians, the dosing of these drugs may not be optimal in the Asian population, which is particularly relevant because in the TRITON TIMI 38 trial, bleeding was already significantly increased with prasugrel compared with clopidogrel.

In this issue of the Journal, Kim et al investigate the biological efficacy of a half-dose of prasugrel compared with a 600-mg LD of clopidogrel in healthy Korean volunteers using 3 platelet assays in a well-designed study. Although reduced, compared with the dose recommended according to the TRITON TIMI 38 trial and the ESC guidelines, the 30 mg LD of prasugrel induced a faster, more uniform and pronounced PR inhibition than clopidogrel. In addition, the LD of prasugrel was associated with a significantly lower rate of HTPR compared with 600 mg of clopidogrel. The results are of great interest. In fact, it strongly suggests that optimal dosing of drugs may need to be evaluated in all ethnicities to prevent under- or overdosing because of variations in body weight, body mass index, and genetic polymorphisms that could affect the drug’s efficacy. In the specific case of prasugrel, it may be the first step toward individualized antiplatelet therapy using the new P2Y12-ADP antagonists, which could help reduce bleeding events.

There are, however, some limitations to the study. It was performed in healthy volunteers and not coronary artery disease patients. It is well known that the latter have heightened platelet aggregability and that the metabolism of antiplatelet agents is affected by disease activity. Therefore, the results may not be transposable to real-world ACS patients. In addition, the clinical effect of such intervention is unknown. Finally, although the therapeutic window concept of PR inhibition to optimize antiplatelet therapy relies on a large body of evidence, trials aiming to confirm the ability of individualized therapy to improve clinical outcome have produced controversial results.

It remains to be investigated whether personalized antiplatelet therapy according to PR monitoring can reduce ischemic and bleeding events in high-risk patients undergoing PCI.

References