Prasugrel is an antiplatelet agent that was developed in Japan and belongs to the thienopyridine class, which includes ticlopidine and clopidogrel. These drugs inhibit platelet aggregation by irreversibly binding to the platelet P2Y12 receptor. Prasugrel was first approved for clinical use in Europe and the USA before Japan based on the results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI 38 study), a global clinical trial. The TRITON-TIMI 38 study was designed to compare the efficacy and safety of prasugrel with that of clopidogrel. In this study, patients with acute coronary syndrome received a 60-mg loading dose and a 10-mg maintenance dose of prasugrel, or a 300-mg loading dose and a 75-mg maintenance dose of clopidogrel. No Japanese patients participated in the study because there was concern that the optimal dose of prasugrel for Japanese patients might be lower than that for non-Japanese patients. Because the TRITON-TIMI 38 was a global clinical trial, it was conducted under a common study protocol in all of the participating countries. Therefore, the same dose of prasugrel would have been provided to Japanese patients as well as the other patients.

Whether medical experts should consider differences between Japanese patients and Caucasian patients when determining an optimal antiplatelet agent dose has been debatable for many years. For ticlopidine, a first-generation thienopyridine antiplatelet agent, a dose lower than half of the common international dose was chosen in Japan (Japan: 200 mg/day, Europe and the USA: 500 mg/day). For clopidogrel, a second-generation thienopyridine antiplatelet agent, the administration dose in Japan was determined to be 75 mg/day, which is identical to that in Europe and the USA. However, a lower dose of clopidogrel (50 mg/day) was also approved for prevention of recurrent cerebral infarction in aged and/or underweight patients. The reason for this is that the potential risk of adverse effects, such as hemorrhage, may be higher in Japanese patients who are, in general, physically smaller than Caucasian patients. Therefore, Japan adjusted the dose based on its own criteria for the use of first- and second-generation thienopyridine antiplatelet agents. For deciding the optimal dose of prasugrel, a third-generation thienopyridine antiplatelet agent, there is difficulty in choosing between the dose used in TRITON-TIMI 38 and the dose calculated based on Japan's criteria. In the TRITON-TIMI 38 study, the rates of myocardial infarction, stroke, and cardiovascular death were lower in the prasugrel group than in the clopidogrel group, whereas the rate of serious hemorrhagic events, including fatal hemorrhage, was higher in the prasugrel group than in the clopidogrel group. In general, the higher the efficacy is of antithrombotic agents, including antiplatelet agents, the more likely it is that hemorrhage occurs. The biggest challenge for physicians is to determine the optimal dose of prasugrel for Japanese patients by minimizing the risk of hemorrhage without compromising the efficacy demonstrated in the TRITON-TIMI 38.

Kimura et al. report the results of a study that aimed to identify the optimal dose of prasugrel for Japanese patients in this issue of the Journal of Atherosclerosis and Thrombosis. Based on their results, the optimal loading and maintenance doses of prasugrel in Japanese patients were determined to be 20 mg and 3.75 mg, respectively. This is as low as approximately one third of the dose that has been approved in Europe and the USA. The PRASFIT-ACS and PRASFIT-Elective studies adopted the above-mentioned doses and showed a favorable outcome. These data were used as bridging data of the TRITON-TIMI 38, which consequently led to approval of prasugrel in Japan.

The finding that one third of the dose of prasug-
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The approved dose in Europe and the USA is three times as high as that in Japan for awareness-raising purposes. If a Japanese patient is treated with prasugrel at an overseas healthcare facility, he or she may be provided the same dose as that for Caucasian patients, which may induce hemorrhagic complications. Conversely, there are no clear dosage rules applicable to cases where a Caucasian patient with Japanese health insurance coverage visits a medical institution in Japan. Healthcare services covered by Japanese health insurance tend to be designed with Japanese patients in mind. When we adopt a Japan-specific dose of a drug, we need to act responsibly as medical experts to address such social problems.

**Fig. 1.** Factors contributing to variability in drug responses
Adapted from Burroughs et al.7).

**References**


**Disclosures**

The author declares that there is no conflicts of interest.
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