Impact of the Adjusted Dosing Regimen of Prasugrel for Japanese Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Jun Takahashi, MD

In recent years, the incidence of acute coronary syndrome (ACS) has been increasing in Japan, but prognosis has improved dramatically because of progress in treatment, particularly primary percutaneous coronary intervention (PCI).1 The performance rate of primary PCI increased drastically in the 1990s,1 which was the corresponding period when the benefits of the prevention of recurrent ischemia and of stent thrombosis by dual antiplatelet therapy (DAPT) with aspirin and a thienopyridine drug were established. The interaction of adenosine diphosphate (ADP) with purergic P2Y1 and P2Y12 receptors amplifies and sustains platelet aggregates. The active metabolite of the thienopyridine binds irreversibly to the P2Y12 receptors, blocking the binding of ADP and thereby inhibiting platelet activation and aggregation.

Currently, 3 classes of the thienopyridine are available for clinical use: ticlopidine, clopidogrel, and the focus of this article, prasugrel. Of these 3 agents, the benefits of ticlopidine in preventing stent thrombosis after PCI were established first.2 However, the poor tolerability of ticlopidine was soon revealed, with particularly severe side effects including bone marrow disorders, so DAPT with a combination of aspirin and clopidogrel has become mainstream based on better tolerability. Moreover, large clinical trials established the efficacy of the addition of clopidogrel to aspirin throughout the spectrum of ACS, including unstable angina, non-ST-elevation myocardial infarction (MI), and ST-elevation MI.3 Despite its usefulness alone or in combination with aspirin for ACS patients, clopidogrel has 2 major faults. It has a delayed onset of action of its antiplatelet effects and there is substantial variability in response among patients. Nearly one-quarter of patients have diminished response to clopidogrel and a number of studies have indicated that adverse clinical outcomes, particularly coronary ischemia and stent thrombosis, are more frequent in those patients.4 Thus, there is a certain frustration to utilizing more intensive and consistent antiplatelet therapy for patients undergoing stenting, particularly in cases of ACS. Prasugrel, a third-generation thienopyridine, has the ability to inhibit ADP-induced platelet aggregation more rapidly and more consistently than clopidogrel.5 Additionally, prasugrel has minimal interpatient variability in efficacy and appears to be effective in poor responders to clopidogrel.6 The TRITON TIMI-38 study was conducted as a phase 3 trial involving 13,000 patients with ACS undergoing PCI in the USA and Europe.7 Patients were randomly assigned to the prasugrel group (loading dose [LD]/maintenance dose [MD] 60/10 mg) or clopidogrel group (LD/MD 300/75 mg). The results demonstrated that prasugrel significantly reduced the incidence of ischemic events, including stent thrombosis, compared with clopidogrel. However, this beneficial effect was accompanied by an increase in the rate of major bleeding. Consequently, the regimen of prasugrel therapy used in the TRITON TIMI-38 study resulted in making clinicians choose between the efficacy benefits of intensive inhibition of platelet aggregation and the risks of bleeding complications. Additionally, recent studies reported that the potency of prasugrel might be exerted more easily in Asians than in Caucasians.8 Taking these findings together, randomized studies have been expected to confirm the clinical efficacy and safety of prasugrel with appropriate dose adjustment in Asian patients.

In this issue of the Journal, Saito et al report on the efficacy and safety of prasugrel at LD/MD of 20/3.75 mg in Japanese patients with ACS undergoing PCI.9 Their multicenter, double-blind, randomized study demonstrated that prasugrel administered at the adjusted dose was associated with a low incidence of MACE (cardiovascular death, non-fatal MI, and non-fatal ischemic stroke). The incidence of MACE at 24 weeks was 9.4% in the prasugrel group and 11.8% in the clopidogrel group (LD/MD 60/10 mg). The results demonstrated that prasugrel administered at the adjusted dose was associated with a low incidence of MACE (cardiovascular death, non-fatal MI, and non-fatal ischemic stroke). The incidence of MACE at 24 weeks was 9.4% in the prasugrel group and 11.8% in the clopidogrel group (risk reduction 23%, hazard ratio 0.77, 95% confidence interval 0.56–1.07). Although the study excluded patients with previous stroke, the incidence of major bleeding was similar in both groups (1.9% vs. 2.2% at 24 weeks). Furthermore, in the subgroup analysis of patients aged ≥75 years or weighing ≤60 kg, identified as the high risk group for bleeding in TRITON TIMI-38, the frequency of bleeding complications was also comparable between groups.

In the PRASFIT-ACS study,9 it may be said that the adjusted dosing regimen of prasugrel for Japanese patients provided a perfect balance between the benefits of intensive platelet inhibition and possible risks of bleeding complications, and it produced favorable results. Although both the LD and MD of prasugrel administered in the PRASFIT-ACS study were approximately one-third of those in TRITON TIMI-38, the efficacy of prasugrel was maintained in Japanese patients as
successfully as observed in TRITON TIMI-38. As recently demonstrated in the PACIFIC registry, a high proportion of ACS patients undergo PCI with stenting in Japan today.\(^1,0\)

The J-AMI registry also reported that clopidogrel (LD/MD 300/75 mg) with aspirin was the current standard regimen of DAPT in Japan and in-hospital stent thrombosis or bleeding complication occurred in 1.5% and 1.9%, respectively.\(^0\) Furthermore, >60% of in-hospital cases of stent thrombosis occurred within 24 h after PCI and delayed clopidogrel loading was significantly correlated with the incidence of stent thrombosis. These results suggest that the slow onset of action of clopidogrel could be actually harmful in clinical practice of ACS treatment in Japan and several patients complicated by stent thrombosis might be poor metabolizers of CYP2C19 substrates, carrying genetic polymorphisms that are more prevalent in Japanese.\(^1,2\)

As a recent study showed that prasugrel at lower than the recommended dose, as used in the PRASFIT-ACS study (LD/MD 20/3.75 mg), was superior to clopidogrel at the standard regimen (LD/MD 300/75 mg) in terms of antplatelet effects,\(^3\) prasugrel has great potential to decrease in-hospital stent thrombosis. Importantly, the adjusted dosing regimen of prasugrel for Japanese patients also succeeded in minimizing the risk of bleeding compared with that of TRITON TIMI-38 (Figure). Because bleeding is known as an independent predictor of mortality of ACS patients,\(^4\) the reduction of bleeding complications with low-dose prasugrel as observed in the PRASFIT-ACS study would make Japanese interventional cardiologists accept the brand-new drug without hesitation.

In conclusion, the adjusted dosing regimen of prasugrel for Japanese patients (LD/MD 20/3.75 mg) could optimize the balance between the beneficial and adverse effects of antplatelet therapy in Japanese patients with ACS undergoing PCI.

**Disclosures**

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**References**


