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Editorial

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Prasugrel for Secondary Prevention of Thrombotic Stroke

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It is widely accepted that antiplatelet therapy, especially therapy using thienopyridine derivatives, is effective for the secondary prevention of thrombotic stroke[1, 2]. Thienopyridine derivatives have been reported to significantly reduce recurrent ischemic stroke in patients with prior ischemic stroke. However, approximately 10% of patients treated with thienopyridine derivatives had recurrent ischemic stroke for approximately 2 years[2]. Thus, the development of more effective drugs is expected for the secondary prevention of ischemic stroke.

Until now, clopidogrel has been the most commonly used thienopyridine derivative for preventing ischemic stroke, and CYP2C19 genetic polymorphisms may be related to clopidogrel resistance[3]. Because prasugrel, another thienopyridine derivative, requires fewer metabolic steps than clopidogrel and is expected to reduce the influence of CYP2C19 polymorphisms, it may effectively prevent ischemic stroke in more patients. However, prasugrel has not been used due to concerns of hemorrhagic adverse events in patients with prior stroke, as indicated in the TRITON-TIMI38 study[4]. This study used 10-mg prasugrel per day as a maintenance dose; a lower dose has been reported to be preferable for Japanese patients with acute coronary syndrome[5].

In the current issue, Kitazono et al report the results of PRASTRO-III[6]. Previously, PRASTRO-I and II investigated the effect of prasugrel 3.75 mg or 2.5 mg/day on the secondary prevention of noncardioembolic ischemic stroke in Japanese patients[7, 8]. In those studies, more major bleeding events or hemorrhagic strokes were not observed in patients treated with prasugrel than in those treated with clopidogrel. Subanalysis suggested that the effect of prasugrel is comparable to clopidogrel in patients with thrombotic stroke with large-artery atherosclerosis and small vessel occlusion[9]. PRASTRO-III was a study on patients with thrombotic stroke and indicated the efficacy and safety of prasugrel compared with clopidogrel.

According to these results, prasugrel is available for the secondary prevention of thrombotic stroke in Japan. The benefit of prasugrel may be assumed in some cases. First, prasugrel may be preferable for treating recurrent cases that have been treated with clopidogrel as some patients may exhibit resistance to clopidgrel. It has been reported that the risk of thrombotic events is lower in patients treated with prasugrel than in those treated with clopidgrel among the poor metabolizers of CYP2C19 polymorphism[7]. Second, thienopyridine derivative-naïve patients with high recurrent risk of thrombotic stroke may be candidates. The probability of being effective is higher in prasugrel due to the limited influence of CYP2C19 polymorphism.

However, some points need further investigation and discussion. The participants in the PRASTRO studies were enrolled between 7 days and 26 weeks after index stroke. Although the risk of thrombotic stroke recurrence is higher in the acute phase, the effect of prasugrel has not been assessed in that period. Because antiplatelet effects appear more quickly than those with clopidgrel, the effect of prasugrel in preventing acute recurrence is expected to be clarified. Next, the incidence of thrombotic events was different in the patients classified under undetermined etiology in the prasugrel and clopidgrel group. Stroke of undetermined etiology is a diverse category that includes patients with various causes, and prasugrel may be effective in some cases in this category. Identifying a marker to distinguish between suitable and unsuitable candidates for prasugrel may be useful for secondary prevention for the patients in this category. Third, amassing real world data may be necessary to evaluate the hemorrhagic risk of prasugrel in patients with stroke. Although prasugrel can now

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be used for the secondary prevention of thrombotic stroke in Japan, it has not been approved in several other countries. A major problem is the concern of hemorrhagic events[4]. If this concern is reduced with low-dose prasugrel, it may be used more widely. Further investigation can help determine the next steps of antiplatelet therapy for the secondary prevention of stroke.

Conflict of Interest

Yoshiki Yagita reports honoraria from Daiichi Sankyo Co., Ltd.

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