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Full Length Article

No association between on-treatment platelet reactivity and bleeding events following percutaneous coronary intervention and antiplatelet therapy: A post hoc analysis☆

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ABSTRACT

Introduction: Few studies have examined the relationship between the pharmacodynamics of antiplatelet drugs and the risk of clinically significant bleeding following percutaneous coronary intervention (PCI) for treating acute coronary syndrome (ACS). We examined the associations between the pharmacodynamics of prasugrel and clopidogrel and the incidence of bleeding events in the acute and chronic phases after PCI.

Materials and methods: We performed a post hoc analysis of the PRASFIT-ACS (PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI) study of patients in whom platelet reactivity was determined as $P2Y_{12}$ reaction units (PRU; VerifyNow® $P2Y_{12}$ assay) or vasodilator-stimulated phosphoprotein-phosphorylation reactivity index (VASP-PRI). Japanese patients were randomized to prasugrel (loading/maintenance dose: 20/3.75 mg) or clopidogrel (300/75 mg), both in combination with aspirin, for 24–48 weeks. The bleeding outcome was a composite of major, minor, and clinically relevant bleeding.

Results: Overall, 66/685 (9.6%) and 65/678 (9.6%) of prasugrel- and clopidogrel-treated patients, respectively, experienced major, minor, or clinically relevant bleeding. PRU and VASP-PRI at 5–12 h or in steady state conditions (at 4 weeks) were not associated with the risk of bleeding in the acute (to day 3) or chronic (from day 4 to 14 days after treatment discontinuation) phases of treatment, respectively. Less than 9% of patients with low on-treatment platelet reactivity (defined as PRU < 85 or VASP-PRI < 16) experienced bleeding events.

Conclusion: No direct association of the pharmacodynamics of prasugrel and clopidogrel with the risk of bleeding was observed in this cohort of Japanese ACS patients following PCI.

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; CABG, coronary artery bypass graft; HR, hazard ratio; LD, loading dose; MACE, major adverse cardiovascular events; MD, maintenance dose; PCI, percutaneous coronary intervention; PRASFIT-ACS, PRASugrel compared with clopidogrel For Japanese patIenTs with Acute Coronary Syndrome undergoing PCI; PRI, phosphorylation reactivity index; PRU, $P2Y_{12}$ reaction unit; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38; VASP, vasodilator-stimulated phosphoprotein.

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1. Introduction

Patients undergoing elective or emergent percutaneous coronary intervention (PCI) are routinely prescribed antiplatelet drugs, including aspirin and thienopyridines (e.g., prasugrel and clopidogrel), to reduce the risk of stent thrombosis and major adverse cardiovascular events (MACE).

Although clopidogrel is one of the most widely used drugs in this setting, TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) [1] showed that prasugrel was associated with a lower incidence of ischemic events, but a higher incidence of bleeding events than clopidogrel. Similar efficacy results were obtained in the Japanese PRASFIT-ACS (PRASugrel compared with clopidogrel For Japanese patIenTs with Acute Coronary Syndrome [ACS] undergoing PCI) study [2]. In that study, the hazard ratio (HR) for the incidence of MACE in the prasugrel group relative to the clopidogrel group over 24 weeks of treatment was 0.77 (95% confidence interval [CI] 0.56–1.07), corresponding to a risk reduction of 23%.

In TRITON-TIMI 38 [1], prasugrel (loading dose [LD]: 60 mg; maintenance dose [MD]: 10 mg) was associated with a higher incidence of non-coronary artery bypass graft (CABG)-related TIMI major or minor bleeding events than clopidogrel (HR 1.31, 95% CI 1.11–1.56), However, in PRASFIT-ACS, the incidence of major or minor bleeding events was 5.7% (39/685) in the prasugrel group (LD: 20 mg; MD: 3.75 mg) and 4.3% (29/678) in the clopidogrel group (HR 1.30, 95% CI 0.81–2.11), and the incidences of non-CABG-related major, minor, or clinically relevant bleeding were similar in both groups (HR 0.98, 95% CI 0.70–1.38).

The results of the TRITON-TIMI 38 and PRASFIT-ACS studies, as well as other clinical trials and clinical experience, are indicative of a therapeutic window for antiplatelet drugs, in which the prescribed drug must achieve sufficient platelet inhibition to prevent MACE, but avoid excessive platelet inhibition that might increase the risk of bleeding events.

In clinical practice, the risk of thrombotic events is increased in patients with high on-treatment platelet reactivity, indicative of a low response to antiplatelet drugs [3–6], but the risk of bleeding is increased in patients with low on-treatment platelet reactivity, indicative of a high response to antiplatelet drugs [6–8]. To date, however, few studies have examined the relationship between the pharmacodynamics of antiplatelet drugs and the risk of clinically significant bleeding following PCI to treat ACS.

Retrospective analyses of the results of the PRASFIT-ACS study showed that the incidence of thrombotic events was increased in patients with a $P2Y_{12}$ reaction unit (PRU) of ≥262 at 5–12 h after PCI [9], representing one end of the therapeutic window. To optimize prasugrel therapy, clinicians should also be aware of the other end of the therapeutic window so that increasing the risk of bleeding can be avoided.

Therefore, the aim of the present analyses was to elucidate the relationship between platelet reactivity (i.e., PRU) and bleeding events in the PRASFIT-ACS study to determine the optimal therapeutic window for dual antiplatelet therapy in Japanese ACS patients undergoing PCI.

We first examined the relationship between platelet reactivity at 5–12 h after starting treatment (i.e., acute phase of treatment) and bleeding events occurring from Day 4 onwards. We then examined whether the extent of platelet inhibition at steady state levels (4–5 days) is associated with bleeding events occurring from Week 4 onwards in the chronic phase of treatment.

2. Materials and methods

The design of the PRASFIT-ACS study is described in more detail in our prior report [2] and the patients included in the present analyses are the same as those included in an earlier post hoc analysis [9]. The trial was registered with Japan Pharmaceutical Information Center (identifier: JapicCTI-101339).

The PRASFIT-ACS study enrolled Japanese ACS patients aged ≥20 years who were scheduled for coronary artery stenting if they had symptoms lasting ≥10 min within 72 h before randomization, ST-segment deviation ≥1 mm or T-wave inversion ≥3 mm, or elevated cardiac biomarkers associated with necrosis.

Eligible patients were randomized in a 1:1 ratio to receive either prasugrel (LD: 20 mg; MD: 3.75 mg) or clopidogrel (LD: 300 mg; MD: 75 mg). The LD was administered before PCI or up to 1 h after leaving the cardiac catheter laboratory in urgent cases. The MD was administered once daily after breakfast. All patients received aspirin (81–330 mg for the first dose and 81–100 mg thereafter). Treatments were continued for 24–48 weeks depending on the stent type and recommended duration of thienopyridine administration stated in the package inserts for the stents. This duration of dual antiplatelet therapy was necessary because bare metal stents were used to treat ACS in many patients.

The primary efficacy outcome was the incidence of MACE, which was defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke. Safety outcomes included non-

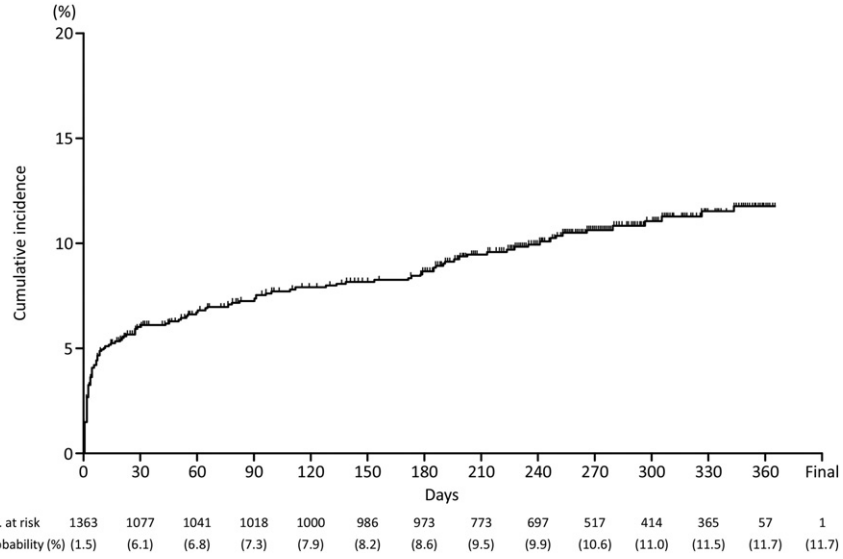

Fig. 1. Kaplan–Meier plot of the cumulative incidence of bleeding events (major bleeding, minor bleeding, and clinically relevant bleeding combined) in all patients throughout the study period (from the start of study drug administration to 14 days after the completion of treatment or discontinuation). Vertical lines indicate censored events.