Short-Term Safety and Mid-Term Efficacy of Prasugrel Versus Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention

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Abstract

[Objective] Although several clinical trials demonstrated improved mid- and long-term safety and efficacy of prasugrel compared with clopidogrel after percutaneous coronary intervention (PCI), there are few data regarding short-term safety. [Methods] In this study, we retrospectively analyzed short-term (72 hours) PCI-related bleeding complications and mid-term (12 months) efficacy in 250 consecutive coronary artery disease patients who underwent PCI and received aspirin plus prasugrel (prasugrel group; 67.7±10.0 years, 200 males). [Patients] The comparison group consisted of 250 age- and gender-matched patients who received aspirin plus clopidogrel (clopidogrel group: 67.2±11.2 years, 199 males). [Results] The incidence of a composite of PCI-related bleeding complications in the acute phase post-PCI was significantly higher in the prasugrel group than the clopidogrel group (22.4% vs 13.2%, P=0.007), although the incidence of non-PCI-related bleeding complications during 12 months was comparable between the two groups. The cumulative incidence of major cardiovascular events (MACE) was comparable between 2 groups of prasugrel and clopidogrel (log-rank test; P=0.561). Multivariate logistic regression analysis in the 250 prasugrel-treated patients showed that acute coronary syndrome tended to be associated with a lower incidence of PCI-related bleeding complications (P=0.061). Prasugrel and clopidogrel may have similar efficacy to prevent cardiovascular events as the post-PCI antiplatelet regimen; however, prasugrel should be used cautiously because of PCI-related bleeding complications.

Key words: prasugrel, clopidogrel, dual-antiplatelet therapy, percutaneous coronary intervention, bleeding complication

Introduction

Generational advances in percutaneous coronary intervention (PCI) have greatly contributed to reducing acute phase mortality in patients with ST-elevation myocardial infarction as well as relieving symptoms in those with angina pectoris. Thus, PCI has become an established treatment strategy for coronary artery disease. After coronary stent implantation, dual antiplatelet therapy (a thienopyridine antiplatelet agent plus aspirin) is critically important for the prevention of stent thrombosis, and this therapy is currently recommended for 6 to 12 months after implantation of a drug-eluting stent (DES) (1, 2). Clopidogrel, a thienopyridine antiplatelet agent and P2Y12 receptor antagonist, has long been used in the dual antiplatelet regimen based on its established safety and efficacy (3). However, clinical events, including myocardial infarction and coronary stent thrombosis, are still observed after PCI in patients treated with clopidogrel. One of the reasons is that the pharmacologic response to clopidogrel is affected by CYP2C19 gene polymorphisms such that inhibition of platelet aggregation is decreased in poor metabolizers (4).

Like clopidogrel, prasugrel is also a prodrug that requires conversion to an active metabolite before binding to the platelet P2Y12 receptor to confer antiplatelet activity (5). This new-generation thienopyridine inhibits adenosine diphosphate-induced platelet aggregation more rapidly, more consistently and to a greater extent than standard or higher doses of clopidogrel (6-8). In addition, prasugrel showed a trend toward fewer ischemic events than clopidogrel, and it had an acceptable safety profile in patients

undergoing PCI as well as those with acute coronary syndrome in global as well as Japanese clinical trials (9-11). Since prasugrel is less affected by CYP2C19 gene polymorphisms than clopidogrel, this property may account for the advantageous effects of prasugrel over clopidogrel (11).

Although previous clinical trials on the safety and efficacy of prasugrel assessed mid-term (6-15 months) outcomes, there are few data regarding short-term safety. Since prasugrel exhibits a stronger inhibitory effect on platelet aggregation than clopidogrel early after administration (11), prasugrel might cause more bleeding complications than clopidogrel in the acute phase post-PCI. In this study, we retrospectively analyzed bleeding complications including PCI-related bleeding as well as mid-term (12 months) efficacy in patients with coronary artery disease who underwent PCI. We compared two dual antiplatelet regimens that are used in routine clinical practice: aspirin plus prasugrel versus aspirin plus clopidogrel.

Materials and Methods

Study design

This study was a single-center, observational, retrospective, age/gender-matched cohort study. We recruited 250 consecutive patients with coronary artery disease including both chronic coronary artery disease and acute coronary syndrome who underwent PCI and received aspirin plus prasugrel after PCI between October 2015 and

July 2016 (prasugrel group; 67.7±10.0 years, 200 males). The comparison group consisted of age- and gender-matched coronary artery disease patients (n=250) who underwent PCI and received aspirin plus clopidogrel after PCI between October 2014 and September 2015 (clopidogrel group; 67.2±11.2 years, 199 males). For emergent PCI cases, the loading dose of prasugrel (20 mg) or clopidogrel (300 mg) was administered within 1 hour of the patient leaving the cardiac catheterization laboratory. The maintenance dose of prasugrel (3.75 mg) or clopidogrel (75 mg) was administered once daily, starting on the next day after PCI. For elective PCI cases, the maintenance doses of both drugs were started at least 96 hours before PCI without a loading dose. Aspirin 100 mg per day was concomitantly administered during the treatment period. Dual antiplatelet therapy with aspirin plus thienopyridines was continued in principle at least until at the time of follow-up coronary angiography, i.e, during 6 months for balloon angioplasty alone or bare metal stent implantation, or during 12 months for DES implantation, or until the major bleeding complications (defined as below) developed.

We collected data on PCI-related bleeding complications in the acute phase after PCI within 72 hours and outcome data, such as non-PCI-related bleeding events, ischemic events or death, during 12 months after PCI. Patients were excluded if they met any of the following criteria: hemodynamic instability that required circulatory assist with intra-aortic balloon pumping or percutaneous cardiopulmonary support; hemodialysis or hemofiltration; the use of antiplatelet drugs other than thienopyridines and aspirin; the continuous administration of oral acidic non-steroidal anti-inflammatory drugs during the 12-month observation period; and the lack of follow-up data at 12

months after PCI.

In all patients, PCI was performed via a standard radial or femoral approach. Intravenous heparin 100 IU/kg was administered prior to the procedure. The choice of DES, bare-metal stent or balloon angioplasty alone was left to the discretion of the operator. Following the procedures, we used a compression device for hemostatic treatment of the radial access sites or a closure device for treatment of the femoral access sites. When hemostatic treatment failed based on the routine protocol for each device, additional hemostatic treatment was performed using manual compression, based on the discretion of the physician.

We retrospectively collected clinical and laboratory data on these 500 patients. The data were obtained from medical charts of hospital days, discharge letters, cardiac catheterization reports at PCI and laboratory data, and were confirmed via a clinic medical examination. We collected information on the safety as well as efficacy endpoints.

Endpoints

The safety endpoints included PCI-related bleeding events during the acute phase after PCI. First, we calculated the reduction of blood hemoglobin from baseline before PCI to the morning after PCI. Next, we assessed the incidence of the following events: hemoglobin reduction ≥3.0 g/dl, hematoma formation at the puncture sites, additional hemostatic treatment, blood transfusion, and a composite of these 4 events. The incidence of non-PCI-related bleeding events was evaluated up to 12 months after PCI.

These events were based upon the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria and included the following: 1) major bleeding defined as intracranial or clinically significant bleeding with a decrease in hemoglobin of ≥5 g/dl, 2) minor bleeding defined as clinically significant bleeding with a decrease in hemoglobin of 3–5 g/dl, and 3) clinically relevant minimal bleeding with a decrease in hemoglobin of <3 g/dl. We evaluated bleeding from critical sites (e.g., retroperitoneal, intra-pericardial, intra-vitreous/retinal, intra-spinal and intra-articular hemorrhage), gastrointestinal bleeding accompanied by decreased hemoglobin, gross hematuria not attributed to external factors, epistaxis requiring otolaryngology, gingival bleeding requiring dental treatment and bleeding requiring discontinuation of the study drug at the investigator's discretion.

The efficacy endpoints included the cumulative incidence of the following events during 12 months after PCI: all-cause death; major cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction and non-fatal ischemic stroke; MACE plus coronary revascularization; and heart failure requiring hospitalization.

Statistical analysis

Values are expressed as the mean ± standard deviation for continuous variables and the number (percent) of patients for categorical variables. For intergroup comparisons of baseline characteristics and the incidence of events for safety endpoints, we used the unpaired t-test for continuous variables and the chi-square test for

categorical variables. The cumulative incidence of events for the efficacy endpoints was assessed by the Kaplan-Meier method, and the groups were compared by the log-rank test. To determine if DES usage affected the efficacy of prasugrel relative to clopidogrel, a Cox proportional hazards regression analysis was performed, and the results were expressed as hazard ratios with 95% confidence intervals. Logistic regression analysis was performed to assess the factors associated with PCI-related bleeding in the prasugrel group. First, we performed univariate analysis using several factors that might affect bleeding risk, and then we performed multivariate analysis using those factors that showed $P<0.3$ in the univariate analyses. These results were expressed as the odds ratios with 95% confidence intervals. All values of $P<0.05$ were considered significant.

Results

Baseline characteristics

The baseline characteristics of the prasugrel and clopidogrel groups are shown in Table 1. Although there were no differences in most of the clinical, angiographic and procedural characteristics between the two groups, the prevalence of dyslipidemia tended to be higher (70.8% vs 63.6%, P=0.086) and syntax score was significantly higher (14.0±9.3 vs 12.1±8.0, P=0.013) in the prasugrel group than the clopidogrel group. Furthermore, DES usage was significantly higher in the prasugrel group than the clopidogrel group (79.6% vs 51.2%, P<0.0001).

Study endpoints in the prasugrel and clopidogrel groups

Regarding PCI-related bleeding complications as safety endpoints in the acute phase, the reduction of blood hemoglobin level, incidence of hemoglobin reduction ≥3.0 g/dl, incidence of puncture site hematoma formation and incidence of blood transfusion were comparable between the two groups. However, the incidence of additional hemostatic treatment (11.6% vs 6.0%, P=0.027) and the composite of PCI-related bleeding complications (22.4% vs 13.2%, P=0.007) were significantly higher in the prasugrel group than the clopidogrel group. The non-PCI-related bleeding complications during 12 months after PCI were comparable between the two groups (Table 2).

Regarding the efficacy endpoints, all-cause death was seen in 3 patients (1.2%) in the prasugrel group, whereas there were no deaths in the clopidogrel group (P=0.082). The cause of death in 3 prasugrel group patients was ventricular fibrillation in one and pneumonia in the remaining 2 patients. The incidence of MACE was similar between the two groups of prasugrel and clopidogrel. However, the incidence of MACE plus coronary revascularization was significantly lower in the prasugrel group compared with the clopidogrel group (4.0% vs 10.4%, P=0.018). The incidence of heart failure requiring hospitalization was comparable between the two groups. Kaplan-Meier survival analysis demonstrated that the cumulative incidence of MACE was similar between the two groups (log-rank test; P=0.561) (Fig. 1). However, the cumulative incidence of MACE plus coronary revascularization was significantly lower in the prasugrel group than the clopidogrel group (log-rank test; P=0.046) (Fig. 2-A). Since

the rate of DES usage was significantly higher in the prasugrel group than the clopidogrel group, this confounding factor might have affected the incidence of MACE plus coronary revascularization. Thus, we performed the Kaplan-Meier survival analysis to compare the cumulative incidence of MACE plus coronary revascularization among the following 4 subgroups: patients in the prasugrel group with DES usage (prasugrel/DES subgroup), those in the prasugrel group without DES usage (prasugrel/no DES subgroup), those in the clopidogrel group with DES usage (clopidogrel/DES subgroup), and those in the prasugrel group without DES usage (clopidogrel/no DES subgroup). Although there were no significant differences among the 4 subgroups, the incidence of MACE plus coronary revascularization appeared to be lower in patients with than without DES implantation. In the patients with DES implantation, the incidence of MACE plus coronary revascularization appeared to be similar between the prasugrel and clopidogrel subgroups; however, in the patients without DES implantation, the incidence appeared to be lower in the prasugrel subgroup than the clopidogrel subgroup (Fig. 2-B). Next, we performed Cox proportional hazards regression analysis to compare prasugrel and clopidogrel in prespecified subgroups that were based on DES usage. This analysis showed there was no significant interaction between the subgroup factor (DES usage) and the efficacy endpoint (MACE plus coronary revascularization; Fig. 3).

Analysis of bleeding risk in the prasugrel group

We performed logistic regression analyses to assess PCI-related bleeding risk in

the 250 patients in the prasugrel group. For this analysis, the dependent variable was a composite of PCI-related bleeding complications that included hemoglobin reduction ≥3.0 g/dl, puncture site hematoma formation, additional hemostatic treatment, and the need for blood transfusion. The independent variables included factors possibly related to bleeding risk: age, gender, low body weight (<50 kg), hypertension, acute coronary syndrome, estimated glomerular filtration rate (eGFR), DES usage and oral anticoagulant usage. Univariate analysis showed that acute coronary syndrome tended to be associated with a lower incidence of PCI-related bleeding complications (P=0.071). In multivariate analysis that included only independent variables that showed P<0.3 in univariate analysis (age, eGFR, anticoagulant usage and acute coronary syndrome), acute coronary syndrome tended to be independently associated with a lower incidence of PCI-related bleeding complications (P=0.061) (Table 3).

Discussion

In the present study, we compared the safety of prasugrel and clopidogrel based on a retrospective analysis of bleeding complications. The major finding of the present study was that the incidence of additional hemostatic treatment at the puncture site and the composite of PCI-related bleeding complications during the acute phase after PCI were higher in patients treated with prasugrel than in those treated with clopidogrel.

Clopidogrel is converted by the cytochrome P450 (CYP) enzyme system to an

active antiplatelet metabolite that binds to the P2Y12 receptor. Since the transformation of clopidogrel into an active compound greatly depends on the CYP enzymes, the CYP2C19 loss-of-function alleles affect the responsiveness of platelets to clopidogrel (12, 13). Like clopidogrel, prasugrel is also an inactive prodrug that requires metabolic processing *in vivo* to generate an active antiplatelet metabolite that binds to the P2Y12 receptor. However, the enzymatic generation of the active metabolite of prasugrel depends less on the CYP enzyme system compared with clopidogrel, so that prasugrel is less influenced by CYP2C19 gene polymorphisms. Thus, the more rapid onset, higher potency and lower inter-individual variability of the antiplatelet effects of prasugrel compared with clopidogrel *in vivo* are due to the more efficient pharmacokinetics of prasugrel (12, 14). These pharmacokinetic characteristics of prasugrel offer an advantage over clopidogrel for the prevention of thrombotic events, although the use of prasugel may lead to a higher bleeding risk during the acute phase after PCI. A global clinical trial, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38 study), showed that there was a lower incidence of ischemic cardiovascular events but a higher incidence of bleeding events with prasugrel than clopidogrel in patients with acute coronary syndrome (9). In contrast, a Japanese trial, Prasugrel Compared with Clopidogrel for Japanese Patients with Acute Coronary Syndrome Undergoing PCI (PRASFIT-ACS) demonstrated that the incidence of bleeding complications was comparable between prasugrel and clopidogrel in acute coronary syndrome patients, whereas the incidence of ischemic events was lower with

prasugrel (10). The Prasugrel for Japanese Patients with Coronary Artery Diseases Undergoing Elective PCI (PRASFIT-Elective) study also showed that prasugrel reduced ischemic events compared with clopidogrel, but bleeding complications were similar in chronic coronary artery disease patients undergoing elective PCI (11). The discrepancy in the incidence of bleeding events between the TRITON-TIMI 38 trial and the PRASFIT trial might be due to the difference in the dose of prasugrel (loading dose/maintenance dose: 60/10 mg in the TRITON-TIMI 38 trial and 20/3.75 mg in the PRASFIT trial). Both of these trials mainly focused on mid-term (6-15 months) bleeding events, but not on those during the acute phase after PCI. In a post-hoc analyses of the PRASFIT-ACS study, Nishikawa et al. (15) assessed platelet reactivity defined as the P2Y12 reaction unit (PRU) (VerifyNow® P2Y12 assay) or the vasodilator-stimulated phosphoprotein phosphorylation reactivity index (VASP-PRI). Their results showed that both PRU and VASP-PRI during the acute phase after PCI (5-12 hours) and during steady-state conditions (4 weeks) were not associated with either the acute (day 0 to 3) or chronic (day 4 to 12 months) risk of bleeding. In the present study, in which the dose of prasugrel was equivalent to that used in the PRASFIT trial, non-PCI-related mid-term (up to 12 months) bleeding complications, based on the TIMI bleeding criteria, were comparable in the prasugrel and clopidogrel groups, and this was similar to the results of the PRASFIT trial. However, PCI-related bleeding complications during the acute phase after PCI were more frequent in the prasugrel group than the clopidogrel group. This result might be caused by the stronger antiplatelet action of prasugrel over clopidogrel, and conflicts with the previous report

of Nishikawa et al (15).

In the present study, we also compared the efficacy of prasugrel and clopidogrel on the incidence of ischemic events using Kaplan-Meyer survival analysis. Contrary to the results of several previously reported prospective randomized studies (9-11), our retrospective analysis found that the cumulative incidence of MACE was similar between two groups of prasugrel and clopidogrel. However, the cumulative incidence of MACE plus coronary revascularization was lower in the prasugrel group compared with the clopidogrel group. Although age- and gender-matched patient selection was performed for both groups, the severity of coronary artery disease as demonstrated by the syntax score was higher in the prasugrel group compared with the clopidogrel group, possibly leading to a significantly higher rate of DES usage in the prasugrel group. Considering such background might have affected the result, we performed Kaplan-Meier survival analysis to compare among 4 subgroups (prasugrel/DES, prasugrel/no DES, clopidogrel/DES and clopidogrel/no DES). As a result, the incidence of MACE plus coronary revascularization tended to be lower in the prasugrel/no DES group than in the clopidogrel/no DES group, suggesting some advantage of prasugrel over clopidogrel in cases of PCI without DES implantation. In addition, we performed Cox proportional hazards regression analysis using prespecified subgroups that were based on DES usage. This analysis showed that there were no significant interactions between the subgroup factor (DES usage) and the efficacy endpoint (MACE plus revascularization). Thus, the lower incidence of MACE plus coronary revascularization in the prasugrel group appears to be independent of DES

usage. Since very long-term safety and efficacy of the current DES may be affected by impaired wound healing at the stent site (16-18), PCI without DES implantation should be reevaluated. We believe our results may have some value for the selection of the post-PCI antiplatelet regimen in the future. Nevertheless, we cannot conclude an advantage of prasugrel over clopidogrel in terms of its efficacy, since MACE alone was similar between both groups of prasugrel and clopidogrel.

Finally, we evaluated the factors associated with PCI-related bleeding complications in the prasugrel group. Contrary to our expectation, univariate and multivariate logistic regression analyses indicated that acute coronary syndrome tended to be independently associated with a lower incidence of PCI-related bleeding complications. This result might be due to a difference in the timing of prasugrel administration between patients with acute coronary syndrome and those with chronic coronary artery disease. A maintenance dose of prasugrel was started at least 96 hours before elective PCI in chronic coronary artery disease patients, so that blood concentrations of the drug were sufficient to inhibit platelet function immediately after PCI. In contrast, in acute coronary syndrome patients, prasugrel loading was not started until after the patients had left the cardiac catheterization laboratory, so that an effective blood concentration was not achieved immediately after PCI. Thus, a delayed effect of prasugrel in the acute coronary syndrome patients might have reduced PCI-related bleeding complications. Furthermore, other established risk factors for bleeding complications in patients on antiplatelet drugs, such as older age, hypertension, renal dysfunction and low body weight (19, 20), were not associated with PCI-related

bleeding complications.

In the present study, we focused on PCI-related bleeding complications during the acute phase after PCI in patients treated with either prasugrel or clopidogrel. These complications may not be directly life threatening and may not be associated with long-term prognosis, but they can impair quality of life and increase anxiety in both patients and physicians; thus, these complications should be also avoided as much as possible. Our study suggests that prasugrel has an advantage over clopidogrel in terms of its efficacy when it is used as the post-PCI antiplatelet regimen, and this confirms the results of previous reports. However, prasugrel should be used cautiously because of an increased risk of short-term PCI-related bleeding complications.

Limitations

This study has several potential limitations. It was a single-center, retrospective, observational study in a small number of patients. It might be also a limitation of the retrospective, observational study that the choice of PCI strategy, such as DES usage, was left to the discretion of the operator. Moreover, the observation periods (based on the date of PCI) were different between the prasugrel and clopidogrel groups, so that severity of coronary artery disease was higher; possibly thus, the usage of DES was higher in the prasugrel group than the clopidogrel group. Although we adjusted our analyses to account for the difference in DES usage, other confounding factors might have affected the results. Actually, patients with diabetes, acute coronary syndrome, multi-vessel disease, and syntax score were higher in prasugrel group. Although they

were not significantly different in each factor, patients' accumulation of these might need to be considered as complicated. Therefore, a specified method such as propensity score matching analysis would be needed. In the present study, however, the sample size may be too small for the stringent propensity score matching. In the patients selected for this study, dual anti-platelet therapy was continued in principle at least until at the time of follow-up coronary angiography or until major bleeding complications developed. However, we did not include in the analyses the detailed data for continuation of anti-platelet agents. Thus, precise re-analyses including such data would be needed. In the present study, sample size determination was not performed; thus, a relatively small number of events might also contribute to the lack of significant differences between the two groups. The PCI-related bleeding complications that we selected as safety endpoints included a reduction of blood hemoglobin level, the incidence of hemoglobin reduction ≥3.0 g/dl, the incidence of hematoma formation at the puncture sites, the incidence of additional hemostatic treatment and the incidence of blood transfusion. However, the diagnosis of hematoma and the execution of additional hemostatic treatment were based on each physician's discretion; thus, the incidence of these complications was considerably biased. We should explore more adequate methods to evaluate the PCI-related bleeding complications. We did not assess CYP2C19 gene polymorphisms, which could affect the pharmacokinetics of clopidogrel and the magnitude of the differences between the prasugrel and clopidogrel groups. In addition to these limitations, there are some other potential weaknesses in the present study. Nevertheless, we believe the results of the present study have some value as a real-world clinical

practice data.

Conclusions

Although prasugrel and clopidogrel may have similar efficacy to prevent cardiovascular events as the post-PCI antiplatelet regimen, prasugrel should be used cautiously in this setting because of short-term PCI-related bleeding complications.

Disclosure

Conflict of interest: There are no conflicts of interest to declare.

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Figure legends

Figure 1 Comparison of the cumulative incidence of major cardiovascular events (MACE) between the prasugrel and clopidogrel groups by Kaplan-Meier survival analysis. The incidence was similar between the two groups of prasugrel and clopidogrel.

Figure 2 **(A)** Comparison of the cumulative incidence of MACE plus coronary revascularization between the prasugrel and clopidogrel groups by Kaplan-Meier survival analysis. The incidence was significantly lower in the prasugrel group than the clopidogrel group. **(B)** Comparison of the cumulative incidence of MACE plus coronary revascularization among the following 4 subgroups: prasugrel/DES, prasugrel/no DES, clopidogrel/DES, and clopidogrel/no DES. Although there were no significant differences among the 4 subgroups, the incidence appeared to be lower in patients with than without DES usage. In the patients with DES implantation, the incidence of MACE plus coronary revascularization was similar between the prasugrel and clopidogrel subgroups; however, in the patients without DES implantation, the incidence appeared to be lower in the prasugrel subgroup than the clopidogrel subgroup.

MACE, major adverse cardiovascular events; DES, drug-eluting stent; PCI, percutaneous coronary intervention.

Figure 3 Cox proportional hazards regression analysis to compare the efficacy of prasugrel and clopidogrel in prespecified subgroups that were based on DES usage. There was no significant interaction between the subgroup factor (DES usage) and the efficacy endpoint (MACE plus coronary revascularization).