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ORIGINAL ARTICLE

Impact of antiplatelet therapy on tissue prolapse at super acute phase after stenting: serial OCT study in acute coronary syndrome patients

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Abstract

Although drug-eluting stents have improved clinical outcomes, percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) remains a challenging procedure in terms of thrombus management. A new-generation P2Y12 receptor inhibitor, prasugrel, provides more rapid and potent antiplatelet action compared with clopidogrel. Prasugrel achieved significant reduction of ischemic events compared with clopidogrel in ACS. The aim of this optical coherence tomography (OCT) study was to evaluate temporal changes in tissue prolapse after stenting under different antiplatelet regimens (aspirin plus prasugrel or clopidogrel) in ACS patients. A total of 119 ACS patients were randomized to either prasugrel or clopidogrel at the time of PCI. OCT analysis was available in 119 patients at baseline (just after stenting), 77 patients at 2 weeks, and 62 patients at 4 months after stenting. Cross-sectional analysis for every 1 mm was performed at in-stent and adjacent reference segment. Tissue prolapse area was calculated by lumen area minus stent area within the stented segment. Baseline patient and procedural characteristics were not different between the prasugrel and clopidogrel groups. Tissue prolapse area was significantly lower in the prasugrel compared with the clopidogrel group after stenting (0.24 ± 0.23 vs. 0.36 ± 0.23 mm^2, $p = 0.003$) and at 2 weeks (0.11 ± 0.13 vs. 0.19 ± 0.16 mm^2, $p = 0.005$). However, there was no significant difference at 4 months. In conclusion, our study suggests prasugrel was effective in reducing tissue prolapse in the super acute phase in ACS patients compared with clopidogrel. However, the effect of tissue prolapse reduction was not different up to 4 months follow-up.

Keywords Acute coronary syndrome · Optical coherence tomography · Prasugrel · Tissue prolapse

Introduction

Antiplatelet therapy is an important treatment to prevent ischemic complications in patients undergoing percutaneous coronary intervention (PCI). PCI patients are usually prescribed dual antiplatelet therapy with aspirin and a thienopyridine, such as clopidogrel, which is widely used to prevent thrombotic events [1, 2]. However, clopidogrel has some limitations, such as interpatient variability and delayed onset of action, which might cause ischemic events including early stent thrombosis, a critical issue in the treatment of acute coronary syndrome (ACS) [3]. Therefore, ACS mainly associated with thrombus is still a challenging population in terms of thrombus management and PCI.

A new-generation P2Y12 receptor inhibitor, prasugrel, provides more rapid and potent antiplatelet action compared with clopidogrel. A previous study showed significant reduction of clinical ischemic events with prasugrel compared with clopidogrel in ACS patients [2]; however, the effects of different antiplatelet therapies on in-stent tissue prolapse following stent implantation in ACS have not yet been investigated using intracoronary imaging.

Optical coherence tomography (OCT) is a high-resolution intracoronary modality which can display lipid, calcium and fibrous tissue with clear reproducibility compared with

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intravascular ultrasound (IVUS) [4, 5]. In addition, due to ten times greater resolution than IVUS, OCT can detect small amounts of malapposition, tissue prolapse, stent strut coverage or fibrous cap thickness. Thus, the aim of this OCT study was to evaluate the temporal change of tissue prolapse under different antiplatelet regimens (aspirin plus either prasugrel or clopidogrel) in ACS patients.

Methods

Study design and study population

This study was a single-center, prospective, randomized study. From March 2015 to July 2017, we screened consecutive ST-elevation acute myocardial infarction (STEMI) or non-ST elevation myocardial infarction (non-STEMI) patients. Patients were randomly assigned to either the prasugrel or clopidogrel group in a 1:1 manner. The loading dose of prasugrel (20 mg) or clopidogrel (300 mg) was administered before PCI. All patients underwent OCT examination after stenting, at 2 weeks, and at 4 months.

Exclusion criteria were as follows: (1) PCI without OCT guidance; (2) PCI without stent; (3) culprit lesion with in-stent restenosis/occlusion or graft occlusion; and (4) cardiogenic shock or post resuscitation.

STEMI was defined as continuous chest pain lasting > 30 min, arrival at the hospital within 12 h from the onset of chest pain, ST-segment elevation > 0.1 mV in two contiguous leads, or new left bundle-branch block on the 12-lead electrocardiogram (ECG) and elevated cardiac markers (creatine kinase-MB or troponin I). Non-STEMI was defined as ischemic symptoms with elevated cardiac markers in the absence of ST-elevation on ECG. The primary end point of this study was tissue prolapse area after stenting between the prasugrel and clopidogrel groups.

This study protocol was approved by the Ethics Committee of Aichi Medical University and all patients provided written informed consent to participate in this study.

Antiplatelet agents

According to the regimen of dual antiplatelet therapy recommended by the Japanese Association of Cardiovascular Intervention and Therapeutics, a loading dose of 200 mg aspirin was administered to all patients prior to emergency cardiac catheterization [6]. After diagnostic cardiac catheterization, patients received the loading dose of either prasugrel (20 mg) or clopidogrel (300 mg). The maintenance dose of prasugrel (3.75 mg/day, adjusted for Japanese population) or clopidogrel (75 mg/day) was administered once daily, along with a maintenance dose of aspirin (100 mg/day) [2].

PCI procedure

PCI was performed utilizing standard methods with OCT guidance. 6 Fr or 7 French guide catheters were used through the radial or femoral artery approach. During the PCI procedure, patients received 8000 IU of intravenous heparin at first, and 1000 IU per hour thereafter. Selection of the balloon and stent sizes were based on the OCT image. Either Xience™ everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA) or Synergy™ everolimus-eluting stent (Boston Scientific, Natick, MA, USA) was used in this study. In addition to selection of stent type and size, use of an aspiration device, pre-dilatation, post-dilatation, intra-aortic balloon pump or temporary pacing was left to operator discretion. After the PCI procedure, patients received continuous intravenous infusion of heparin, which was aimed to achieve an activated clotting time of 250–300 s for several days.

Acquisition and analysis of OCT images

OCT images were acquired with the frequency-domain OCT catheter (Dragonfly JP or Dragonfly OPTIS; St. Jude Medical, St. Paul, MN, USA) using a motorized pullback system. The OCT catheter was advanced over a 0.014-inch guide wire to the distal end of the target lesion. Automated OCT pullback with a speed of 18–36 mm/s was performed with continuous injection of contrast medium from the guide catheter [7].

Off-line OCT analysis was performed using dedicated software (LightLab Imaging Inc., Westford, MA, USA). All OCT images were analyzed by an experienced investigator who was blinded to the clinical information, angiographic findings, and PCI characteristics.

OCT cross-sectional images were evaluated every 1 mm for the entire stented segment and adjacent reference segments (Fig. 1). Reference lumen areas within 5 mm of the proximal and distal edges and minimal stent area were measured. Stent expansion was defined as minimum stent area divided by nominal stent area × 100. Tissue prolapse, defined as an intraluminal tissue extrusion through the stent struts including thrombus, protrusion and/or neointima, was calculated by stent area minus lumen area for every 1 mm within the stented segment. Volume data were calculated as the summation of area for measurement cross section. Average area was defined as volume data divided by the number of measurement cross sections. As qualitative analysis, type of tissue prolapse was evaluated. Tissue prolapse (protrusion) was divided into three categories: smooth protrusion, disrupted fibrous tissue protrusion, and irregular

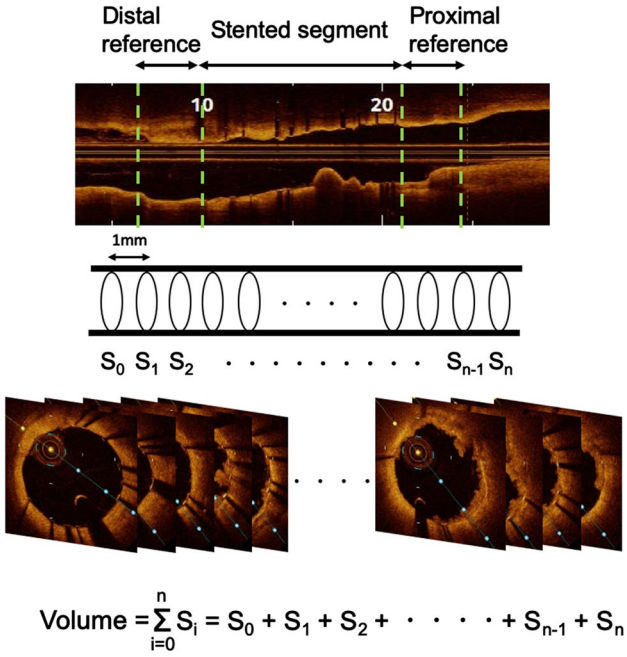

Fig. 1 OCT analysis. OCT images were evaluated at every 1 mm for in-stent and 5 mm adjacent reference segment. Tissue prolapse was obtained by stent area minus lumen area. Volume data were calculated as the summation of area. Average area was calculated as volume data divided by number of measurement cross section. *OCT* optical coherence tomography

protrusion. Smooth protrusion was defined as the bowing of plaque into the lumen between stent struts, without intimal disruption, appearing as a smooth semicircular arc connecting adjacent struts, and likely representing compression of soft plaque by the stent. Disrupted fibrous tissue protrusion was defined as disruption of underlying fibrous tissue protruding in between stent struts into the lumen. Irregular protrusion was defined as protrusion of material with an irregular surface into the lumen between stent struts [8].

Statistical analysis

Statistical analysis was performed using SPSS 25.0 statistical software (SPSS Inc., Chicago, IL, USA). Continuous values are reported as mean ± standard deviation. Statistical significance of comparisons between continuous variables was determined using the Student's *t* test for normally distributed variables and the Mann–Whitney *U* test for nonparametric variables. Categorical values are presented by patient number (%) and are analyzed using Chi-squared test. A p value < 0.05 was considered to indicate statistical significance.

Results

Study flow

A total of 242 consecutive ACS patients were identified from March 2015 to July 2017. Out of 242 patients, 119 patients were available for OCT-guided PCI and were enrolled in this study. Patients were randomly assigned to two groups: prasugrel ($n=61$) or clopidogrel ($n=58$) (Fig. 2). After excluding patients with poor OCT image quality, early discharge, death, and refusing cardiac catheterization at 2 weeks, OCT analysis at 2 weeks was available for 40 patients in the prasugrel and 37 patients in the clopidogrel group. Serial (after stenting, 2 weeks, and 4 months) OCT analysis was available for 33 patients in the prasugrel group and 29 patients in the clopidogrel group.

Patients and lesion characteristics

The baseline patient characteristics are summarized in Table 1. There were no significant differences between the prasugrel and clopidogrel groups in terms of age, sex, coronary risk factors, and medications. β-Blocker use was relatively higher in the prasugrel group compared with the clopidogrel group (90.9% vs. 72.4%, $p=0.057$), and diabetics tended to be lower in the prasugrel group. Lesion and procedural characteristics, including stent selection and post dilatation strategy, are shown in Table 2. There were no significant differences between the 2 groups except for initial TIMI flow grade.

OCT analysis

The duration between administration of thienopyridines and OCT image acquisition after stenting was 56.3 ± 26.8 min for the prasugrel group and 54.2 ± 14.3 min for the clopidogrel group ($p=0.734$).

Lumen area at both proximal and distal reference and stent area were not different between the 2 groups after stenting (Table 3). Figure 3 shows that the average and maximum tissue prolapse areas and tissue prolapse volume after stenting were significantly lower in the prasugrel group compared with the clopidogrel group (0.24 ± 0.23 vs. 0.36 ± 0.23 mm^2, $p=0.003$, 1.21 ± 0.67 vs. 1.57 ± 0.75 mm^2, $p=0.038$, 4.57 ± 4.30 vs. 6.36 ± 4.07 mm^3, $p=0.032$, respectively). At 2 weeks, average tissue prolapse area and tissue prolapse volume were significantly lower in the prasugrel group compared with the clopidogrel group (0.11 ± 0.13 vs. 0.19 ± 0.16 mm^2, $p=0.005$, 2.24 ± 2.43 vs. 3.12 ± 2.45 mm^3, $p=0.035$, respectively). Consequently, delta average tissue prolapse area and tissue prolapse volume area were not different

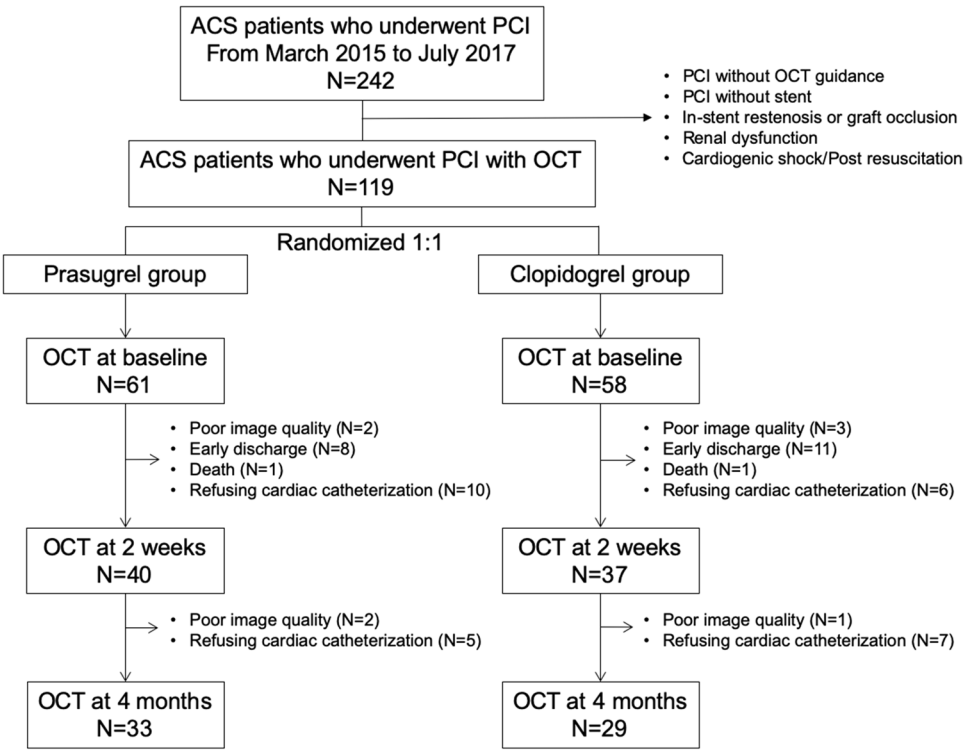

Fig. 2 Study flow. Among 242 consecutive ACS patients who underwent PCI, 119 patients with OCT-guided PCI were randomly assigned to 1 of 2 groups: prasugrel group ($n=61$) or clopidogrel group ($n=58$). After excluding patients with poor OCT image quality, early discharge, death, and refusal of cardiac catheterization at 2 weeks, OCT analysis at 2 weeks was available for 77 patients (prasugrel:40; clopidogrel:37). Complete serial (after stenting, 2 weeks, and 4 months) OCT analysis was available for 33 patients in the prasugrel group and 29 patients in the clopidogrel group. *ACS* acute coronary syndrome, *OCT* optical coherence tomography, *PCI* percutaneous coronary intervention

Table 1 Patient characteristics

	Prasugrel ($n=33$)	Clopidogrel ($n=29$)	p value
Age, years	65.5 ± 12.8	61.0 ± 12.9	0.170
Male, *n* (%)	26 (78.8%)	22 (75.9%)	0.783
BMI (kg/m^2)	25.0 ± 4.0	25.6 ± 4.1	0.280
Diagnosis			0.163
STEMI, *n* (%)	30 (90.9%)	21 (72.4%)	
NSTEMI, *n* (%)	1 (3.0%)	3 (10.3%)	
UAP, *n* (%)	2 (6.1%)	5 (17.2%)	
Coronary risk factors			
Hypertension, *n* (%)	16 (48.5%)	15 (51.7%)	0.799
Dyslipidemia, *n* (%)	13 (39.4%)	12 (41.4%)	0.874
Diabetes mellitus, *n* (%)	3 (9.1%)	8 (27.6%)	0.057
Current smoker, *n* (%)	19 (57.6%)	22 (75.9%)	0.129
Family history, *n* (%)	8 (24.2%)	5 (17.2%)	0.499
Hemodialysis, *n* (%)	0 (0%)	0 (0%)	1.000
Medications at 2 weeks			
Aspirin, *n* (%)	33 (100.0%)	29 (100.0%)	1.000
Warfarin, *n* (%)	2 (6.1%)	0 (0%)	0.178
DOAC, *n* (%)	0 (0%)	0 (0%)	1.000
Statin, *n* (%)	33 (100.0%)	29 (100.0%)	1.000
EPA, *n* (%)	1 (3.0%)	4 (100.0%)	0.120
ACEI, *n* (%)	25 (75.8%)	18 (62.1%)	0.243
ARB, *n* (%)	4 (12.1%)	7 (24.1%)	0.217
β-blocker, *n* (%)	30 (90.9%)	21 (72.4%)	0.057
Ca-blocker, *n* (%)	3 (9.1%)	3 (10.3%)	0.868

Values are given as *n* (%) or mean ± standard deviations

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *BMI* body mass index, *DOAC* direct oral anticoagulant, *EPA* eicosapentaenoic acid, *STEMI* ST-elevation myocardial infarction

Table 2 Procedural characteristics

	Prasugrel ($n=33$)	Clopidogrel ($n=29$)	p value
Target lesion			0.449
LAD, *n* (%)	20 (60.6%)	13 (44.8%)	
LCX, *n* (%)	2 (6.1%)	3 (10.4%)	
RCA, *n* (%)	11 (33.3%)	13 (44.8%)	
Initial TIMI flow grade, *n* (%)			0.011
0 or 1	27 (81.8%)	15 (51.7%)	
2	6 (18.2%)	14 (48.3%)	
3	0 (0%)	0 (0%)	
Final TIMI flow grade, *n* (%)			0.479
0 or 1	0 (0%)	0 (0%)	
2	1 (3.0%)	2 (6.9%)	
3	32 (97.0%)	27 (93.1%)	
Stent type			0.464
Xience, *n* (%)	19 (57.6%)	14 (48.3%)	
Synergy, *n* (%)	14 (42.4%)	15 (51.7%)	
Stent diameter (mm)	3.1 ± 0.4	3.2 ± 0.5	0.490
Stent length (mm)	20.5 ± 6.6	17.8 ± 5.2	0.107
Aspiration device, *n* (%)	29 (87.9%)	22 (75.9%)	0.217
IABP usage, *n* (%)	7 (21.2%)	4 (13.8%)	0.445
Pre dilatation, *n* (%)	25 (75.8%)	19 (65.5%)	0.357
Post dilatation			
Frequency, *n* (%)	33 (100.0%)	27 (93.1%)	0.125
Maximum inflation pressure (atm)	12.5 ± 2.4	12.8 ± 2.4	0.610
Total inflation times (s)	24.7 ± 6.4	25.6 ± 6.4	0.606
Balloon diameter (mm)	3.3 ± 0.5	3.4 ± 0.5	0.522
Balloon length (mm)	18.1 ± 8.1	16.2 ± 5.5	0.312

Values are given as *n* (%) or mean ± standard deviations

IABP intra-aortic balloon pump, *LAD* left anterior descending coronary artery, *LCX* left circumflex coronary artery, *RCA* right coronary artery, *TIMI* thrombolysis in myocardial infarction

Table 3 Quantitative and qualitative OCT analysis after stenting

	Prasugrel ($n=33$)	Clopidogrel ($n=29$)	p value
Lumen area at distal reference (mm^2)	6.83 ± 2.49	6.98 ± 2.53	0.800
Lumen area at proximal reference (mm^2)	7.82 ± 3.10	8.22 ± 2.63	0.320
Minimum stent area (mm^2)	5.99 ± 1.97	6.16 ± 2.04	0.735
Average stent area (mm^2)	7.21 ± 2.29	7.32 ± 2.16	0.846
Stent expansion (%)	82.7 ± 7.4	81.1 ± 8.0	0.397
Stent volume (mm^3)	148.73 ± 66.56	130.46 ± 56.60	0.355
Type of tissue prolapse, *n* (%)			
Smooth protrusion	33 (100%)	29 (100%)	1.000
Disrupted fibrous tissue protrusion	29 (87.9%)	26 (90.0%)	0.574
Irregular protrusion	32 (97.0%)	26 (90.0%)	0.259
Thrombus	29 (87.9%)	27 (93.1%)	0.400

Values are given as *n* (%) or mean ± standard deviations

OCT optical coherence tomography

between the two groups (Fig. 4). At 4 months, the amount of tissue prolapse was not statistically different between the two groups. Change of tissue prolapse amount between the two groups was not different from 2 weeks to 4 months, and from after stenting to 4 months. No statistically significant differences were observed between Xience and Synergy stents in

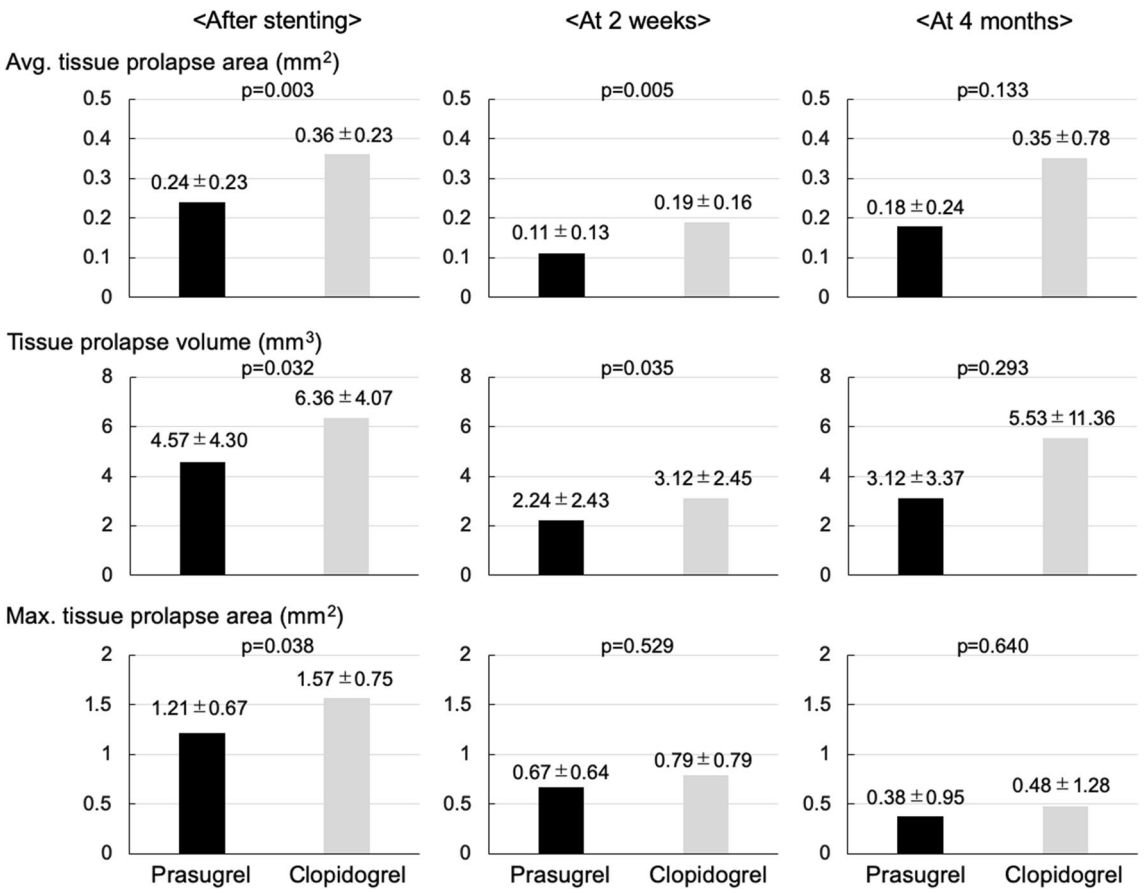

Fig. 3 OCT cross-sectional analysis after stenting, at 2 weeks, and at 4 months. Average and maximum tissue prolapse areas and tissue prolapse volume after stenting were significantly lower in the prasugrel group compared with the clopidogrel group. At 2 weeks, average tissue prolapse area and tissue prolapse volume were significantly lower in the prasugrel group compared with the clopidogrel group. At 4 months, the amount of tissue prolapse was not statistically different between the two groups. *OCT* optical coherence tomography

both treatment groups (Supplemental Table 1). Additional detailed analysis of strut-level analysis showed that the percentage of covered struts was significantly lower in the prasugrel group compared with the clopidogrel group after stenting. However, no differences were observed between the two groups at 2 weeks (Table 4).

Lesions with irregular protrusion after stenting were observed in 32 cases for prasugrel and 26 cases for clopidogrel ($p = 0.259$) and the amount of tissue prolapse was lower or tended to be lower in the prasugrel compared with clopidogrel (Table 3 and Supplemental Table 2). Representative cases are shown in Fig. 5.

Discussion

The main findings of this study are as follows: (1) amount of tissue prolapse after stenting was lower in the prasugrel group compared with the clopidogrel group; (2) amount of tissue prolapse at 4 months was not different between the two groups; and (3) change of tissue prolapse amount between the two groups was not observed in any follow-up periods.

Effect of prasugrel in acute phase

Although DES have reduced clinical events, such as target lesion revascularization, after stenting, patient with ACS still represent a challenging population in terms of thrombus management [9]. Therefore, platelet inhibitor action would be an important adjunct to reduce adverse events after PCI for ACS patients. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, antiplatelet therapy with prasugrel demonstrated fewer ischemic stent thrombosis events than clopidogrel [10]. The PRASFIT ACS study also showed lower incidence of ischemic events in the prasugrel compared with clopidogrel group in Japanese ACS population. In these trials, differences of event rates

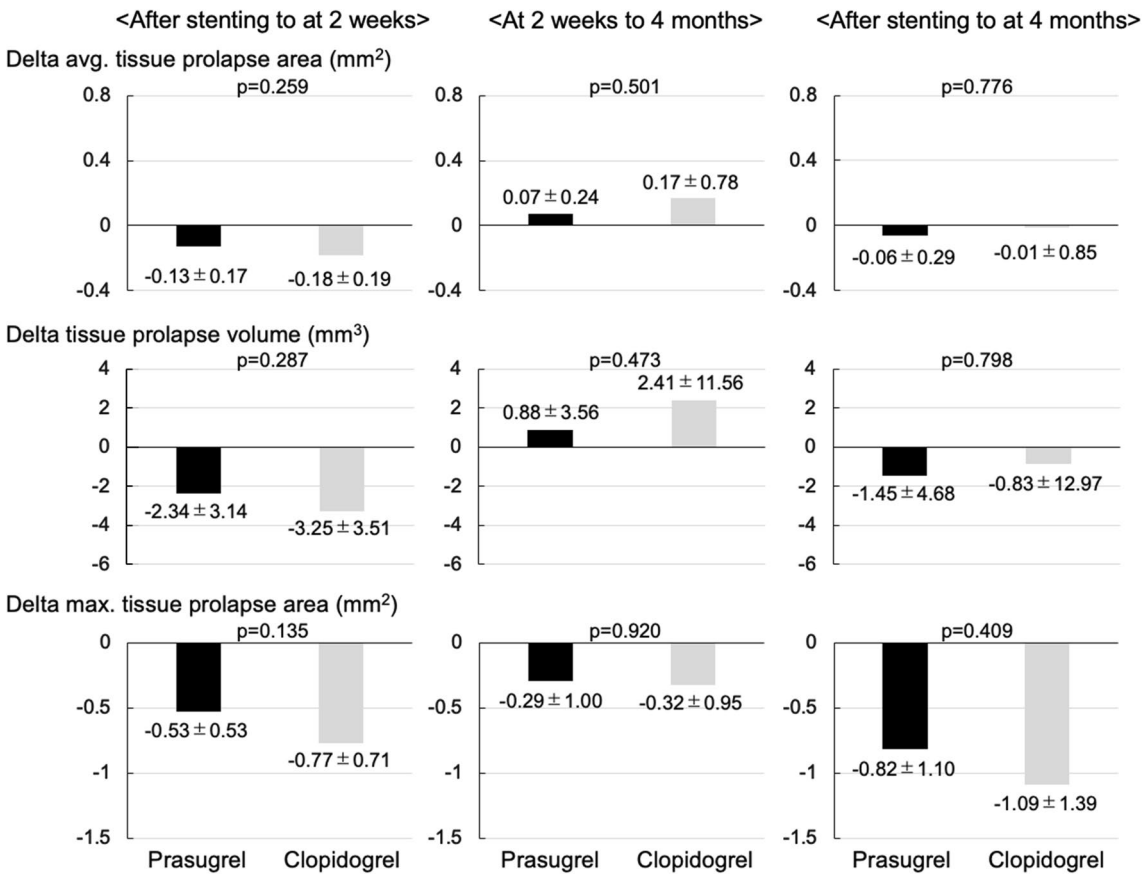

Fig. 4 OCT cross-sectional analysis of tissue prolapse change. Change of tissue prolapse amount between the two groups was not observed from after stenting to 2 weeks, 2 weeks to 4 months, and after stenting to 4 months. *OCT* optical coherence tomography

Table 4 OCT analysis: strut- and cross-sectional level analysis

	After stenting			At 2 weeks			At 4 months		
	Prasugrel	Clopidogrel	*p* value	Prasugrel	Clopidogrel	*p* value	Prasugrel	Clopidogrel	*p* value
Struts level analysis									
No. of struts	6412	5045		5632	4723		5700	4344	
Covered struts, *n* (%)	1234 (19.2)	1286 (25.5)	< 0.001	1759 (31.2)	1507 (31.9)	0.461	3961 (69.5)	2547 (58.6)	< 0.001
Uncovered struts, *n* (%)	5178 (80.8)	3759 (74.5)		3873 (68.8)	3216 (68.1)		1739 (30.5)	1797 (41.4)	
Malapposed struts, *n* (%)	749 (11.7)	406 (8.0)	< 0.001	369 (6.6)	243 (5.1)	0.002	135 (2.4)	163 (3.8)	< 0.001
Cross-section level analysis									
Malapposed struts in each cross section	1.0 ± 0.8	0.9 ± 0.8	0.365	0.6 ± 0.6	0.5 ± 0.6	0.836	0.2 ± 0.2	0.3 ± 0.4	0.107

Values are given as *n* (%) or mean ± standard deviations

OCT optical coherence tomography

were observed from early phase after stenting, mainly due to non-fatal MI/periprocedural MI.

Although it is controversial whether tissue prolapse is associated with clinical events such as early stent thrombosis, recent studies demonstrated that tissue prolapse was an independent predictor of composite of acute and subacute stent thrombosis [11, 12].

The present OCT study revealed that in-stent tissue prolapse after stenting was significantly lower in patients treated with prasugrel compared with clopidogrel. Therefore, our

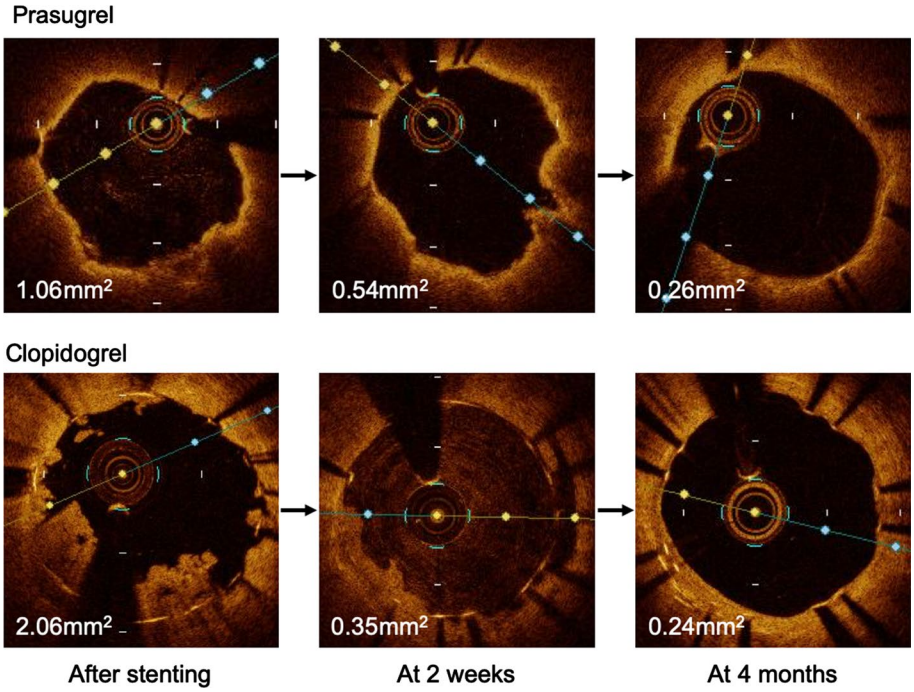

Fig. 5 Representative cases. Representative OCT images after stenting, at 2 weeks and at 4 months are shown. These cross-sectional images were corresponding site of stetted segment after stent, at 2 weeks and at 4 months. Upper panels showed temporal change for patient treated with prasugrel, and lower panels for patients treated with clopidogrel

study might explain the mechanism of reduction in onset of early stent thrombosis and non-fatal MI, which was observed in the TRITON-TIMI 38 and PRASFIT ACS studies.

Pharmacokinetics of prasugrel

Differences in the amount of tissue prolapse were observed in the super acute phase in this study. One of the possible mechanisms to explain these differences would be different metabolic processes to active metabolites, although both prasugrel and clopidogrel are thienopyridine prodrugs. Prasugrel is rapidly hydrolyzed by intestinal carboxyesterase to intermediate metabolites, most of which are then further metabolized in the small intestine and liver by cytochrome P450 (CYP) into an active metabolite. On the other hand, clopidogrel does not metabolize during absorption from the intestine and transforms into the active compound for the first time by two-step CYP-dependent procedures [13]. Therefore, the plasma concentration of the active metabolite of prasugrel increased more rapidly compared with clopidogrel, and reached a maximum level at 30 min after administration in prasugrel and 1 h in clopidogrel [14]. Thus, production of active metabolite is fast and the effect is quickly expressed [15].

In this study, patients received prasugrel or clopidogrel after diagnostic cardiac catheterization (and not in the ER), since a consistent protocol for thienopyridines administration regardless of ACS type is needed. Although the duration between drug administration and OCT study after stenting was relatively short (approximately 60 min), both prasugrel and clopidogrel had theoretically reached their maximum plasma concentration levels by that time. Due to the rapid metabolic process of prasugrel, prasugrel might be effective in the super acute phase, resulting in that amount of tissue prolapse, including thrombus, was lower in the prasugrel group compared with the clopidogrel group. Furthermore, crushed prasugrel leads to faster drug absorption, and, consequently, more prompt and potent antiplatelet effects compared with whole tablet ingestion [16]. If patients received crushed prasugrel in this study, the effect of prasugrel to reduce the amount of tissue prolapse would be apparent. Since prasugrel is a more effective inhibitor of platelet aggregation than clopidogrel, administration of prasugrel would be reasonable for ACS patients whose lesions usually consist of much thrombus.

CYP2C19 genotype variations and clinical outcomes

Cytochrome P4502C19 (CYP2C19) is one of the key factors to metabolize from prodrug to active metabolites for both thienopyridine agents. CYP2C19 genotype variations are recognized and classified into three types based on genotype: extensive metabolizer, intermediate metabolizer and poor metabolizer. Of note, the Japanese population is frequently seen as poor metabolizers.

Active metabolites of clopidogrel are produced after two steps of CYP2C19 metabolism, whereas prasugrel is metabolized by intestinal carboxyesterase and one step of CYP2C19. Therefore, clopidogrel is more affected by the CYP2C19 genotype than prasugrel. Previous reports

revealed relationships of CYP2C19 genotype variations and antiplatelet reactivity being observed with clopidogrel, but not much in prasugrel [17, 18]. Another report demonstrated the impact of CYP2C19 genotype variations on clinical events. As such, prasugrel would be effective to suppress platelet aggregation, regardless of CYP2C19 genotype. This is another hypothesis in the reduction in the amount of tissue prolapse by prasugrel in this study. Since the target population in this study was ACS patients, suggesting patients with much thrombus, antiplatelet therapy would be more important compared with stable angina pectoris. As mentioned previously, the Japanese population showed a relatively higher incidence of being a non-responder (poor metabolizer) to metabolize thienopyridine agents. Therefore, prasugrel would be especially useful for the Japanese ACS population to manage tissue prolapse (thrombus) in the acute phase.

Other factors affecting tissue prolapse

This study investigated the effects of different antiplatelet agents on tissue prolapse. The amount of tissue prolapse might also be affected by underlying plaque morphologies in the target lesion and/or type of stents implanted there. Our preliminary analysis regarding plaque morphology before stenting showed plaque rupture was observed in 21 lesions (10 lesions for prasugrel and 11 for clopidogrel). The incidence of plaque rupture was not different between the prasugrel and clopidogrel groups among lesions with available OCT image before stenting. The effect of plaque morphology on tissue prolapse was minimum between the two treatment groups (prasugrel: 0.20 ± 0.13 and clopidogrel: $0.38 \pm 0.33 mm^2$, $p = 0.111$). However, since cases of lesions without plaque rupture were limited, we could not assess tissue prolapse between lesions with and without plaque rupture with appropriate statistical methods.

Previous studies reported that larger tissue prolapse might be related to larger plaque burden, which suggests that STEMI patients have larger tissue prolapse after stenting [19–21]. STEMI ratio was relatively higher in the prasugrel group compared with the clopidogrel group in the present study. Nevertheless, the present study demonstrated that the amount of tissue prolapse after stenting was lower in the prasugrel group than in the clopidogrel group, perhaps caused by an early effect of prasugrel.

In addition, PCI procedural characteristics such as implanted stent type and post-dilatation strategy might affect tissue prolapse. Our study showed no statistically significant differences between the prasugrel and clopidogrel groups. In terms of stent type selection, Supplemental Table 2 revealed that the amount of tissue prolapse (average area and volume) was not significantly different between Xience and Synergy in either treatment group. Differences in tissue prolapse between the prasugrel and clopidogrel groups were not observed in either stent type due to insufficient statistical power.

Protrusion type would also be affected by tissue prolapse. In this study, the incidence of each protrusion type was not different between the prasugrel and clopidogrel groups. Irregular protrusion was observed in the majority of cases (prasugrel: 97.0% and clopidogrel: 90%) after stenting and the amount of tissue prolapse was lower or tended to be lower in the prasugrel group compared with the clopidogrel group. A previous paper showed irregular protrusion was one of the predictors for 1-year clinical outcome [8]. Although our study could not evaluate long-term clinical outcomes due to small sample size, we confirmed that a similar amount of tissue prolapse/neointimal proliferation was observed at 4 months.

Study limitations

There were several limitations in this study. First, the study population was relatively small, with a single-center study and therefore may have risk of selection bias. Second, assessments of platelet aggregation, including P2Y12 reaction unit (PRU) and CYP2C19 genotype, were not evaluated. Third, assessment of plaque morphology before stent implantation was limited due to the ACS population. Therefore, the relationship between plaque morphology and amount of tissue prolapse could not be evaluated with appropriate statistical methods due to small sample size. Fourth, the amount of thrombus before PCI and/or residual thrombus after thrombus aspiration were not assessed in this study. Therefore, any relationship between amount of thrombus before PCI and tissue prolapse after stenting could not be evaluated. Finally, as we discussed, there were several factors affecting tissue prolapse formation. Multivariate analysis would be needed to detect which factors were most affected tissue prolapse formation. However, since our study was relatively of small sample size for multivariate analysis, it would be difficult to clarify clinical significance.

Conclusion

OCT examination demonstrated that prasugrel was effective to reduce tissue prolapse in the super acute phase in Japanese ACS patients compared with clopidogrel. However, the effect was minimized in the chronic phase. Further large-scale studies with long-term follow-up would be needed to confirm the clinical benefits seen in our study.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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