Mobilization of Progenitor Cells and Vessel Healing After Implantation of Synergytm in Acute Coronary Syndrome

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Abstract

This study was aimed to compare the vascular healing process of a SYNERGY™ stent with that of a PROMUS PREMIER™ stent in patients with acute coronary syndrome (ACS). In 71 patients with ACS, undergoing coronary stent implantation using the SYNERGY™ stent (n=52) or PROMUS PREMIER™ stent (n=19), we measured circulating CD34+/CD133+/CD45^{null} cells and CD34+/KDR+ cells and observed vascular healing at the stented sites using optical coherence tomography (OCT) and coronary angioscopy. On the day 7, circulating CD34+/CD133+/CD45^{null} cells increased in SYNERGY group (P<0.0001), while it did not change in PROMUS group. The CD34+/KDR+ cells also increased in SYNERGY group (P<0.0001) but less significantly in the PROMUS group (P<0.05). The OCT-based neointimal thickness (P<0.0005) and neointimal coverage rate (P<0.05) at 12 months were greater in SYNERGY group, compared with PROMUS group. The coronary angioscopy-based neointimal coverage grade at 12 months was also greater in SYNERGY group (P<0.001). In overall patients, the change in CD34+/KDR+ cells on the day 7 correlated with the OCT-based neointimal thickness at 12 months (R=0.288, P<0.05). SYNERGY™ stent seems to have potential advantages over PROMUS PREMIER™ stent for ACS patients in terms of vascular healing process at the stented sites.

Introduction

Advances in drug-eluting stent (DES) technology have resulted in reduced target lesion revascularization across broad patient and lesion subsets. However, concerns over incomplete stent healing even with second generation DES persist.[1] Re-endothelialization and neointimal coverage over the stent struts are essential for vascular healing after stent deployment. In the process of vascular healing, endothelial (EPCs) as well as smooth muscle (SMPCs) progenitor cells are mobilized from bone marrow and other tissues into injured-vessel sites, possibly triggered by inflammatory response, and serve as a source of both smooth muscle cell and endothelial cell precursors in the healing response.[2–4]

A new generation DES stent, SYNERGY™ (Boston Scientific), consists of a thin strut (74 μm), balloon-expandable platinum-chromium stent platform delivering everolimus from an ultrathin (4 μm) bioabsorbable poly(D,L-lactide-co-glycolic acid) (PLGA) polymer applied to the abluminal surface, has been developed to target optimal vascular healing via its biological and pharmacological characteristics. In the present study, we observed mobilized progenitor cells and assessed the association between their kinetics and vascular healing at the stent-injured vessel sites in patients with acute coronary syndrome (ACS) who underwent implantation of the SYNERGY™ stent, compared with the second generation durable polymer (polyvinylidene difluoride: PVDF) everolimus-eluting stent, PROMUS PREMIER™ (Boston Scientific).

Methods

Study design

We included a total of 71 subjects, being 52 consecutive patients (SYNERGY group; 49 men and 3 women, aged 64 ± 10 year) with ACS between the periods of February 2016, when the SYNERGY™ stent became available in our hospital, to the end of 2017, who underwent emergent stent implantation using the SYNERGY™ stent for an ACS-related lesion. The 19 consecutive ACS patients, who underwent implantation of PROMUS PREMIER™ stent (PROMUS group; 16 men and 3 women, aged 66 ± 9 year) from April 2015 to January 2016 as a historical control. The ACS was defined as follows: presence of chest discomfort or ischemic symptoms lasting ≥ 10 min, ST-segment deviation ≥ 1 mm, or T-wave inversion ≥ 3 mm, or elevated levels of biomarkers for myocardial necrosis, including ST-elevation myocardial infarction, non ST-elevation myocardial infarction and unstable angina. Patients with complications of culprit lesion of left main trunk, acute heart failure of Killip III or IV, serious arrhythmia, and/or systemic complications including infectious diseases, chronic kidney disease over stage III and diabetes mellitus requiring insulin injection, were excluded.

The follow-up coronary angiography was performed for all patients at 3 months and 12 months after stent implantation. All of the patients received dual anti-platelet therapy with 81 mg of aspirin and 75 mg clopidogrel until the follow-up coronary angiography at 12 months. In all patients, peripheral blood sample was collected at baseline before stent implantation, on the day 7 post-implantation, and at the time of 3 and 12 months follow-up coronary angiography. The blood samples were immediately collected into tubes containing ethylene diaminetetraacetate (EDTA). We serially measured the number of circulating progenitor cells using the EDTA blood. At 3 and 12 months follow-up coronary angiography, we assessed re-endothelialization and neointima formation at the site of stent placement using two imaging modalities such as optical coherence tomography (OCT) and coronary angioscopy.

The local institutional review board in Dokkyo Medical University (Mibu, Tochigi, Japan) approved the study protocol, and written informed consent was obtained from each patient.

Measurement of progenitor cells

We measured circulating CD34+/CD133+/$CD45^{null}$ and CD34+/kinase insert domain receptor (KDR) + progenitor cells as EPC linage, using flow cytometry based on a previously described method [5, 6] with minor modifications. In brief, EDTA-treated peripheral blood (3 ml) was incubated with test reagent or control reagent. The reagent mixture consisted of a nucleic acid dye (SY-III-8; Molecular Probe), a peridinine chlorophil protein (PerCP)-conjugated anti-CD45 (Becton Dickinson), a fluorescein isothiocyanate (FITC)-conjugated anti-CD34 (Becton Dickinson), a phycoerythrin (PE)-conjugated anti-CD133 (Miltennyi Biotec) and PE-conjugated anti-KDR (Becton Dickinson). Isotype controls were used as negative controls based on the species and immunoglobulin (Ig) G control antibodies (IgG1 isotype control; Becton Dickinson). The samples were incubated for 20 min at room temperature and after incubation diluted with FACS-lysing solution (Becton Dickinson) for hemolysis. Flow cytometric analysis was then performed using the FACS Calibur laser flow cytometer (Becton Dickinson) according to the manufacturer's instructions. Measurement for CD34+/CD133+/$CD45^{null}$ and CD34+/KDR + cells consisted of 1·106 events of all white blood cells (WBCs) and $2{\cdot}10^5$ events of mononuclear cells (MNCs),

respectively, which exceeded a threshold set on SY-III-8 fluorescence (nucleated cells). The absolute cell number was calculated for both CD34+/CD133+/CD45^{null} cells and CD34+/KDR + cells (Fig. 1). To minimize any methodological variations, each sample was analyzed with two independent experiments, and the mean value was calculated.

Optical coherence tomography imaging and analysis

At the time of follow-up coronary angiography, OCT examination was performed using a frequency-domain system (C7-XR FD-OCT Intravascular Imaging System; St Jude Medical). Cross-sectional OCT images were analyzed at 0.6 mm intervals. In every cross-sectional image, neointimal coverage was assessed for all of the struts, including uncovered struts and malapposed struts. Malapposed struts were defined by the distance between the endoluminal surface of the neointima and the strut ≤ 0μm. The percentage of uncovered struts to total struts in all OCT cross-sections was then calculated. The cross-sections with major side branches (diameter ≥ 2 mm) were excluded from analysis.[7] Strut-level quantitative analysis was performed using all analyzable frames (0.6-mm intervals) along the stented segment. Strut-level intimal thickness was determined based on automated measurements performed from the center of the luminal surface of each strut blooming and its distance to the lumen contour.[8] Struts covered by tissue had positive intimal thickness values, whereas uncovered or malapposed struts had negative intimal thickness values. Mean neointimal thickness was calculated as an average of the intima thickness for all measured struts. The OCT analysis was performed by an independent investigator blinded to the study protocol (Cardiovascular Imaging Core Laboratory, Harrington Heart & Vascular Institute, University Hospitals, Cleveland Medical Center, OH, USA).

Coronary angioscopy and semi-quantitative analysis

Coronary angioscopy was performed using a non-occlusive angioscope system (Visible; Intertec Medicals). The optical fiber was placed at the distal segment of the coronary artery and then carefully pulled back from the distal edge of the stent to the proximal edge. Branch vessels and luminal shapes were utilized as landmarks in order to ensure the same location corresponding with OCT images. The angioscopic images were obtained under an injection of low molecular weight dextran for cleaning red blood cells from imaging site. We assessed grade of neointimal coverage over the stent struts, color of the in-stent segment assessed as the yellow grade, and mural thrombi. Neointimal coverage was classified into 4 grades as previously described: grade 0, stent struts exposed; grade 1, struts bulging into the lumen although covered; grade 2, struts embedded but seen translucently; and grade 3, struts fully embedded and invisible on angioscopy. The yellow color grade was also classified into 4 grades visibly based on the surface color as previously reported: grade 0, white; grade 1, light yellow; grade 2, medium yellow; and grade 3, dark yellow.[9, 10] The exact position of the angioscopic catheter at the stent site was recorded by an angiogram. All angioscopic images were analyzed by observers who were blinded to the study design.

Statistical analyses

Normality of the distribution of variables was assessed using Kolmogorov-Smirnov test with Lilliefors' correlation. Values were presented as the means ± standard deviation for parametric data, and median values and interquartile ranges for non-parametric data. Intergroup comparisons were performed using unpaired t tests for parametric data and Mann Whitney's U tests for non-parametric data. Intragroup comparisons were assessed using paired t tests for parametric data and Wilcoxon Rank Sum tests for non-parametric data. Serial changes in parameters were analyzed using repeated measures analysis of variance. Spearman correlation analyses were used to assess the relationship between 2 parameters. Categorical variables were compared using chi-square tests. $P < 0.05$ was considered to be significant.

Results

Baseline characteristics

Baseline characteristics were compared between two groups of SYNERGY and PROMUS (Table 1). Peak creatine kinase and triglyceride levels were higher in the SYNERGY group than in the PROMUS group. The other parameters were comparable between two groups. The stent implantation procedures were comparable between the two groups, except for the number of stent, which was more in the SYNERGY group than in the PROMUS group (Table 2).

Table 1
Baseline characteristics (full analyses set)

SYNERGY group (n = 52)	PROMUS group (n = 19)	p value
Age, yr	64 ± 10	66 ± 9	0.343
Male gender, n (%)	49 (94)	16 (84)	0.386
Body mass index, kg/m^2	25 ± 3	24 ± 3	0.169
Basal disease, n (%)			
STEMI/ NSTEMI/ Unstable AP	33 (63) / 14 (27) / 5 (10)	8 (42) / 9 (47) / 28 (11)	0.241
Target vessel, n (%)			
LAD/ LCX/ RCA	33 (63) / 6 (12) / 13 (25)	8 (42) / 2 (11) / 9 (47)	0.208
Affected vessel, n (%)			0.792
Single vessel disease	38 (73)	13 (68)	
Multi-vessel disease	14 (27)	6 (32)	
Peak CK-MB, U/L	225 ± 244	113 ± 190	0.049
BNP, pg/mL	53 ± 60	93 ± 93	0.093
Ejection fraction, %	57 ± 6	60 ± 7	0.075
Coronary risk factor			
Hypertension, n (%)	33 (62)	16 (84)	0.052
Diabetes mellitus, n (%)	22 (42)	10 (53)	0.410
Dyslipidemia, n (%)	28 (54)	14 (74)	0.112
Current smoking, n (%)	26 (50)	11 (58)	0.514
LDL-cholesterol, mg/dL	125 ± 35	124 ± 37	0.853
HDL-cholesterol, mg/dL	46 ± 12	51 ± 10	0.085
Triglyceride, mg/dL	157 ± 94	98 ± 60	0.003
Hemoglobin A1c, %	6.2 ± 1.0	6.4 ± 1.1	0.604
eGFR, mL/min/1.73m^2	78.4 ± 21.4	96.8 ± 43.3	0.094
hsCRP, mg/dL	0.16 ± 0.17	0.25 ± 0.38	0.311
Medication, n (%)			

SYNERGY group PROMUS group (n = 52) (n = 19) p value			
Statins	52 (100)	19 (100)	1.000
ACE inhibitors/ARB	51 (98)	17 (89)	0.037
Anti-diabetic agents	19 (37)	7 (37)	0.740

Table 2
Procedural characteristics

	SYNERGY group (n = 52)	PROMUS group (n = 19)	p value
Number of stent, n	1.12 ± 0.33	1.00 ± 0.00	0.013
Total stent length, mm	26.7 ± 11	21.9 ± 8.2	0.054
Stent diameter, mm	3.46 ± 0.45	43.34 ± 0.47	0.360
Pre-dilatation, n (%)	27 (52)	7 (37)	0.295
Post-dilatation, n (%)	19 (37)	6 (32)	0.740
Maximum inflation pressure, atm	14 ± 3.8	14 ± 3.1	0.580
Pre-procedural TIMI flow, n (%)			0.834
Grade 0	29 (56)	9 (47)	
Grade 1	1 (2)	0 (0)	
Grade 2	7 (13)	4 (21)	
Grade 3	15 (29)	6 (32)	
Post-procedural TIMI flow, n (%)			0.773
Grade 0	0 (0)	0 (0)	
Grade 1	0 (0)	0 (0)	
Grade 2	2 (4)	0 (0)	
Grade 3	50 (96)	19 (100)	

Circulating progenitor cells

Serial changes in circulating CD34+/CD133+/$CD45^{null}$ cells and CD34+/KDR + cells are shown in Fig. 2. Baseline levels of CD34+/CD133+/$CD45^{null}$ cells and CD34+/KDR + cells were comparable between both groups of SYNERGY and PROMUS [CD34+/CD133+/$CD45^{null}$ cells: 52 (35–91) and 51 (33–106) cell/$1{\cdot}10^6$ WBCs, respectively; CD34+/KDR + cells: 3 (2–4) and 3 (2–5) cell/$2{\cdot}10^5$ MNCs, respectively].

The CD34+/CD133+/CD45^{null} cells significantly increased on the day 7 in the SYNERGY group [to 84 (52–117) cell/1·10^6 WBCs, P < 0.0001], while it did not change in the PROMUS group [to 67 (43–114) cell/1·10^6 WBCs]. The CD34+/KDR + cells also significantly increased on the day 7 in the SYNERGY group [to 10 (5–16) cell/2·10^5 MNCs, P < 0.0001], while it increased less significantly [to 8 (4–13) cell/2·10^5 MNCs, P < 0.05] in the PROMUS group.

Optical coherence tomographic and coronary angioscopic findings

In the OCT findings, percentage of uncovered struts to total struts and mean neointimal thickness were comparable between the two groups at 3 months follow-up coronary angiography. At 12 months follow-up, however, the percentage of uncovered struts was less (P < 0.05) and the mean neointimal thickness was greater (P < 0.001) in the SYNERGY group, compared with the PROMUS group (Table 3).

Table 3
Quantitative coronary angiographic findings

	SYNERGY group (n = 52)	PROMUS group (n = 19)	p value
3 months follow-up			
Covered struts, %	82.8 ± 12.3	85.9 ± 12.3	0.350
Uncovered struts, %	17.2 ± 12.3	14.1 ± 12.3	0.351
Malaposed Struts, %	0.65 ± 1.13	0.33 ± 0.68	0.147
Mean neointimal thickness, mm	0.07 ± 0.03	0.07 ± 0.02	0.521
12 months follow-up			
Covered struts, %	98.0 ± 3.8	92.5 ± 9.8	0.027
Uncovered struts, %	1.97 ± 3.75	7.50 ± 9.80	0.027
Malaposed Struts, %	0.73 ± 1.84	0.44 ± 0.73	0.337
Mean neointimal thickness, mm	0.16 ± 0.06	0.11 ± 0.04	0.0001

In the coronary angioscopic findings, neointimal coverage grade was higher (P < 0.05) and thrombus was less present (P < 0.05) in the SYNERGY group than in the PROMUS group at the 3 months follow-up. At the 12 months follow-up, neointimal coverage grade was still higher in the SYNERGY group than in the PROMUS group, although presence of thrombus was comparable between the two groups. Yellow color grade was comparable between the two groups at both 3 months and 12 months (Fig. 3).

Representative OCT and coronary angioscopic findings are shown in Fig. 4. In a case of the SYNERGY group (Case 1), although uncovered or malapposed struts were observed at 3 months follow-up, the struts were completely covered by white neointima (neointimal coverage grade 3) at 12 months follow-up. On the other hand, in a case of the PROMUS group (Case 2), mural thrombus in addition to the uncovered stent struts were observed at 3 months follow-up, and neointimal coverage grade was still 0–1 at 12 months follow-up. In another case of the PROMUS group (Case 3), mural thrombus, uncovered struts (neointimal coverage grade 1) and yellow neointima (yellow grade 2) was observed even at 12 months follow-up.

Association between mobilization of progenitor cells and neointima formation

In all 72 patients combined in the SYNERGY and PROMUS groups, there was no relationship between percent change in circulating CD34+/CD133+/$CD45^{null}$ cells on the day 7 from the baseline values and OCT-based mean neointimal thickness at 12 months follow-up coronary angiography (R = 0.136). However, the mean neointimal thickness at 12 months was correlated with percent change in CD34+/KDR + cells on the day 7 (R = 0.288, P < 0.05) (Fig. 5).

Discussion

In the present study, we demonstrated in patients with ACS that circulating CD34+/CD133+/$CD45^{null}$ cells and CD34+/KDR + cells increased significantly on the day 7 after implantation of SYNERGY™ stent, while the CD34+/CD133+/$CD45^{null}$ cells did not change and the CD34+/KDR + cells increased less significantly after implantation of PROMUS PREMIER™ stent. In addition, our OCT findings showed significantly less percentage of uncovered struts and significantly greater mean neointimal thickness at 12 months after SYNERGY™ stent implantation, compared with PROMUS PREMIER™ stent implantation. The coronary angioscopy findings showed that neointimal coverage grade was higher and thrombus was less present in the SYNERGY™ stent than in the PROMUS PREMIER™ stent at the 3 months follow-up. At 12 months follow-up, neointimal coverage grade was still higher in the SYNERGY™ stent than in the PROMUS PREMIER™ stent. Interestingly, the mean neointimal thickness at 12 months was correlated with percent change in CD34+/KDR + cells on the day 7, in combined patients of both SYNERGY and PROMUS PREMIER groups. These results suggest that the SYNERGY™ stent might have some advantage over the PROMUS PREMIER™ stent, in terms of stent-induced mobilization of progenitor cells and subsequent healing of stent-injured vessel sites, in patients with ACS.

Novel concept stent, SYNERGY™

Future DES technology requires a novel concept, optimizing vascular healing.[11] In the process of vascular healing at stent-injured vessel sites, re-endothelialization and subsequent neointima formation are essential.[12] The neointimal stent coverage and maturation of endothelial cells depend on metal alloy,

stent strut thickness, polymer composition, and polymer bioresorption.[13] In this regard, the SYNERGY™ stent was designed to promote and to enhance stent healing. Several clinical trials demonstrated the safety and efficacy of SYNERGY™ stent in a broad range of patients undergoing percutaneous coronary intervention.[14–16] On the other hand, more favorable vascular healing of SYNERGY™ stent has been directly observed by advanced imaging modalities such as OCT [17, 18] or coronary angioscopy,[19] compared with the second generation DESs. In the present study, vascular healing measured by neointima formation, stent coverage and anti-thrombogenicity was compared between the newer generation DES, SYNERGY™ stent and the second generation DES, PROMUS PREMIER™ stent, uniquely using both imaging modalities of OCT and coronary angioscopy at 3 and 12 months. The results of both the OCT and coronary angioscopy findings might indicate potential vascular healing advantages of the SYNERGY™ stent over the second generation DES stents, supporting previous data. In particular, a noteworthy finding is the coronary angioscopy result that demonstrates better vascular healing was evident in the SYNERGY™ stent even at the 3 months follow-up.

Vascular injury and endothelial progenitor cells

The biological response to stent-induced vascular injury is characterized by a cascade of cellular events, including endothelial denudation, platelet deposition, leukocyte recruitment and accumulation, smooth muscle cell proliferation and migration, and the deposition of extracellular matrix proteins.[2] After coronary stent implantation, EPCs mobilize from bone marrow and other tissues, possibly triggered by inflammatory response, migrate to sites of stent-induced vascular injury and differentiate into endothelial cells, contributing in part to re-endothelialization and ultimately stent strut coverage, i.e., vascular healing.[2–4] Previously, we observed that bone marrow-derived progenitor cells including EPCs were mobilized maximally on the day 7 after stent implantation, leading to vascular healing in patients with stable coronary artery disease (CAD) undergoing implantation of bare metal stents. In our observation, however, DESs suppressed mobilization of the progenitor cells and -limus analogues, such as everolimus as well as sirolimus, suppressed differentiation of EPCs into vascular endothelial cells.[20, 21]

In the present study, we used flow cytometric marker CD34+/KDR + cells, in addition to CD34+/CD133+/$CD45^{null}$ cells, both of which abundantly include EPC lineage.[5, 6] As a result, SNYERGY™ stent induced stronger mobilization of both CD34+/CD133+/$CD45^{null}$ cells and CD34+/KDR + cells at early stage, compared with PROMUS PREMIER™ stent, possibly associated with more favorable vessel healing at late stage after the SNYERGY™ stent implantation. The result of correlation between percent change in CD34+/KDR + cells at early stage and OCT-based neointimal thickness at late stage indicates that CD34+/KDR + cells might predict wound healing response at the stent-injured vessel sites. We believe that our findings of progenitor cell kinetics strongly support advantages of SYNERGY™ stent for vascular healing.

Stent healing in acute coronary syndrome

The biological response to stent-induced vascular injury and subsequent healing mechanism in patients with ACS may be different from those in stable CAD patients. Therefore, use of DES stents for ACS should be discussed, separately from that for stable CAD. Because of concerns around inadequate vascular healing, initially the use of DES had not been recommended in the context of ACS, which possesses higher risk of stent thrombosis than stable CAD, in the first generation DES era.[22, 23] However, such a risk has been reduced in the second generation DESs.[24] In regard to the new generation SYNERGY™ stent versus second generation DESs, there are no event-driven clinical trials, but the OCT findings demonstrated more favorable vascular healing after SYNERGY™ stent implantation, compared with the second generation DES also in patients with ACS.[18]

In our previous observations for mobilization of progenitor cells in the vascular healing process after stent implantation, subjects were stable CAD patients.[20, 21] In the present study, we selected ACS patients for the subjects to assess kinetics of progenitor cells after coronary stent implantation for unstable or ruptured plaques, in which local inflammatory reaction is accelerated even at baseline before the procedures. Consequently the CD34+/CD133+/$CD45^{null}$ cells significantly increased on the day 7 even for the second generation PROMUS PREMIER™ stent, which we selected as a control, while did not change in our previous results for the second generation DES in stable CAD patients.[21] The difference in kinetics of these cells between ACS and stable CAD might be based on the difference in baseline local inflammatory status at the stented sites, because mobilization of the progenitor cells might be triggered by inflammatory reaction. From our results we can envision that a new generation SYNERGY™ stent may produce advantageous vascular healing over the second generation DES also in patients with ACS.

Study limitation

The major limitation of our study is the study design. Although we compared mobilization of progenitor cells and subsequent vascular healing at stented sites between SYNERGY™ stent and PROMUS PREMIER™ stent, the comparison was not performed with the randomized design. We designed this study in the beginning of 2015, when we were using the PROMUS PREMIER™ stent for ACS patients and knew the SYNERGY™ stent would become available since in February 2016. Therefore, the subject recruitment was performed from April 2015 to January 2016 for the PROMUS arm as a historical control, and thereafter started at February 2016 for the SYNERGY arm. Therefore, we advanced this study as a comparative study with the historical control. Although an interventional study with a randomized fashion would be more desirable, we believe our data would have value in terms of representing real-world clinical practice.

Clinical Implication/Conclusion

Impaired vascular healing at stented sites is associated with a risk of stent thrombosis, especially in DESs implantation. Despite generational advances in DES technology altering the healing responses, the controversy around dual anti-platelet therapy (DAPT) duration after implantation of DES remains in patients with ACS as well as stable CAD. Even for ACS patients, attempts for shorter DAPT duration is

being explored in the new generation DES era, but such data are insufficient.[24, 25] From our data, we can envision that shorter duration DAPT would be promising with the usage of SYNERGY™ stent.

We observed in this study that mobilization of progenitor cells was more remarkable and subsequent neointima formation and stent coverage were better in the SYNERGY™ stent than in the PROMUS PREMIER™ stent. The results suggest that the SYNERGY™ stent seems to have potential advantages over the PROMUS PREMIER™ stent for ACS patients in terms of vascular healing process at the stented sites.

Declarations

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Conflict of interest

none declared

Human subjects/informed concent statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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Figures

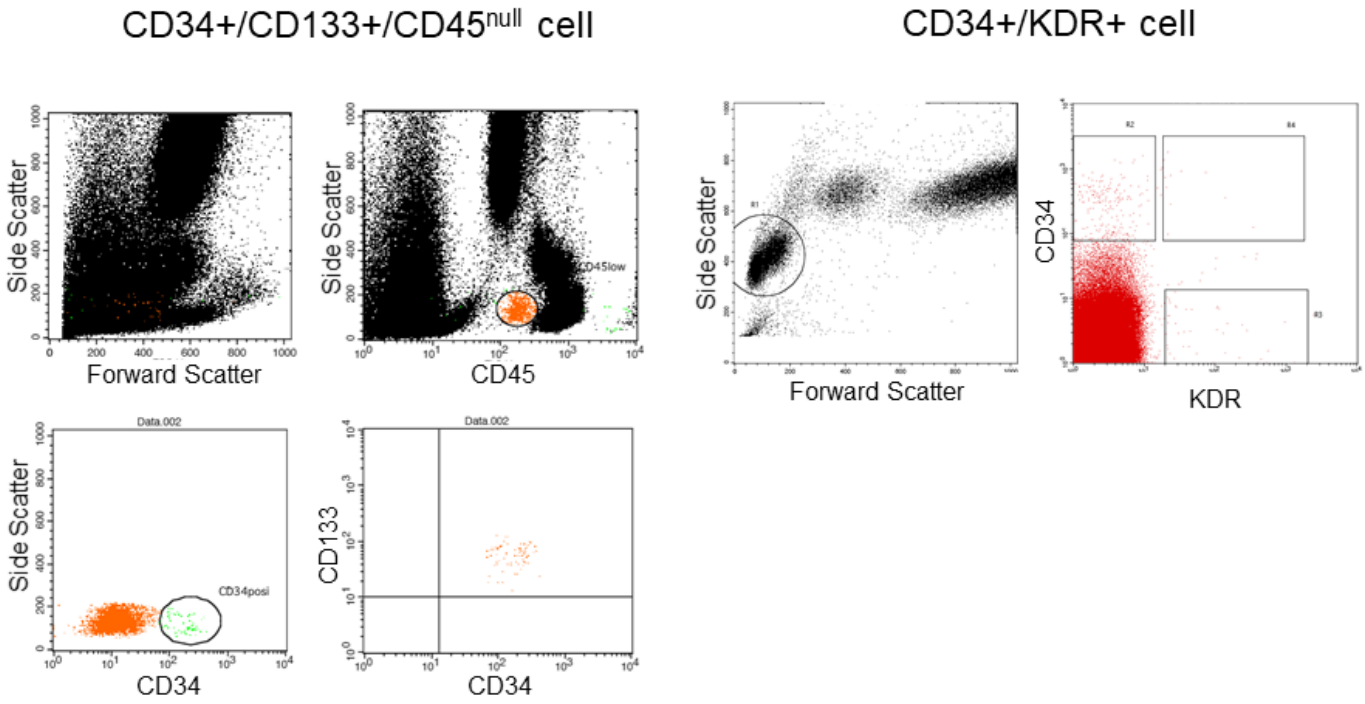

Figure 1

Detection of circulating CD34+/CD133+/CD45null cells and CD34+/KDR+ cells by flow cytomeric analysis. To detect the CD34+CD133+CD45null cells, the mononuclear cell fraction was gated and analyzed for the expression of CD34 and CD45 cells. Only the CD34+/CD45null cells were finally investigated for the count of CD133+ cells. For detection of CD34+/KDR+ cells, the CD34 and KDR double-positive fraction was detected after the gating of mononuclear cells.

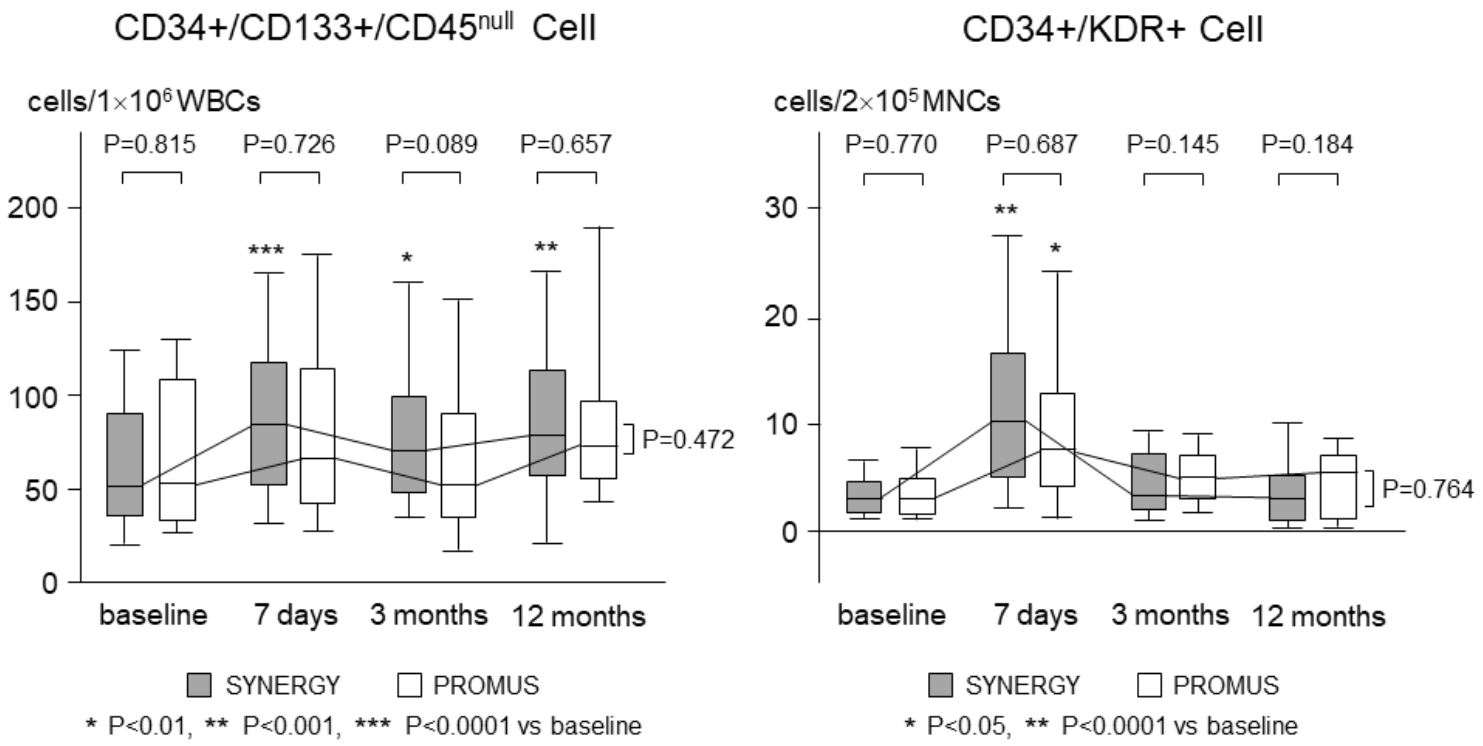

Figure 2

Serial changes in circulating CD34+/CD133+/CD45null cells and CD34+/KDR+ cells after stent implantation.

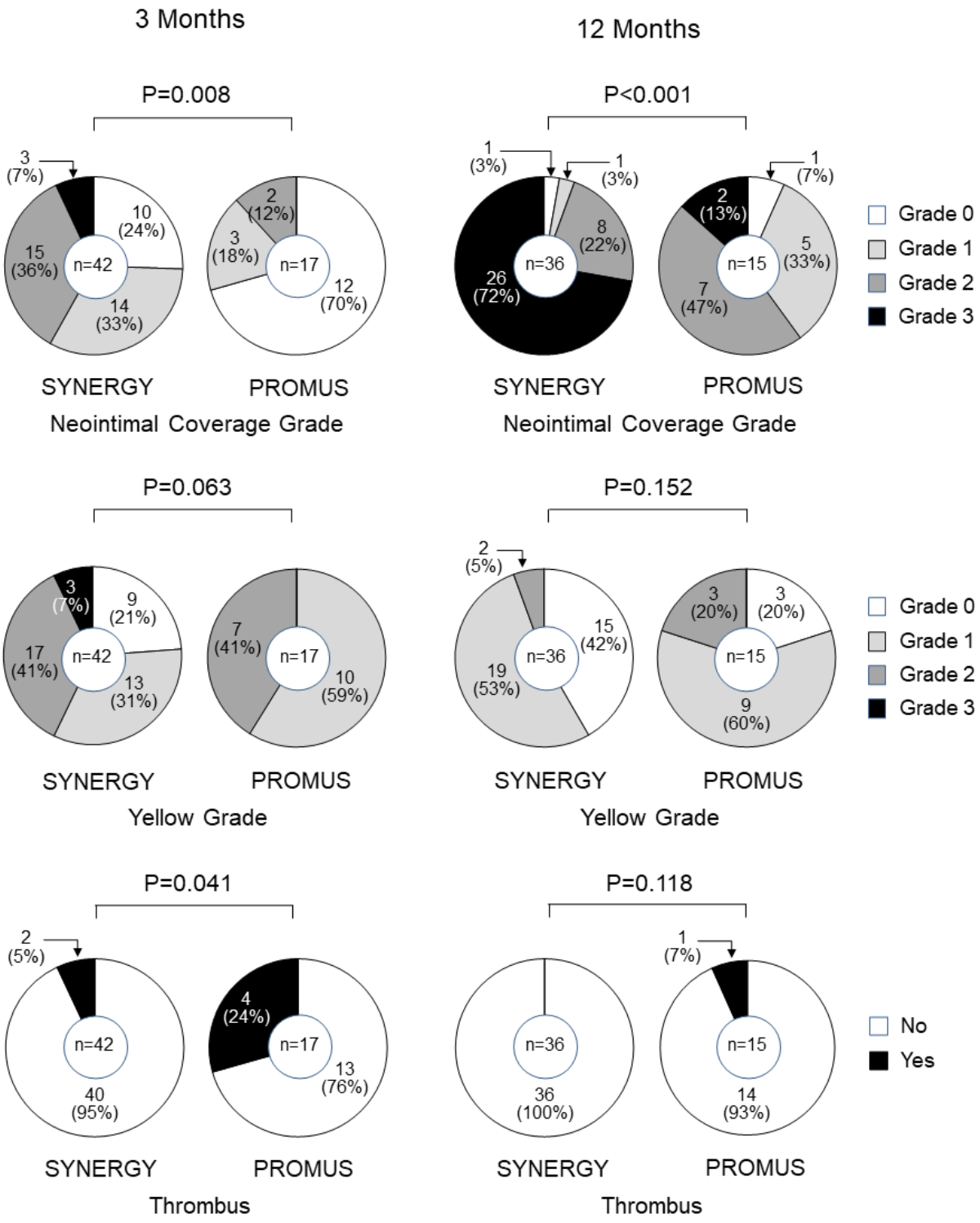

Figure 3

Neointimal coverage grade, yellow color grade and thrombus formation at 3 and 12 months by coronary angioscopy.

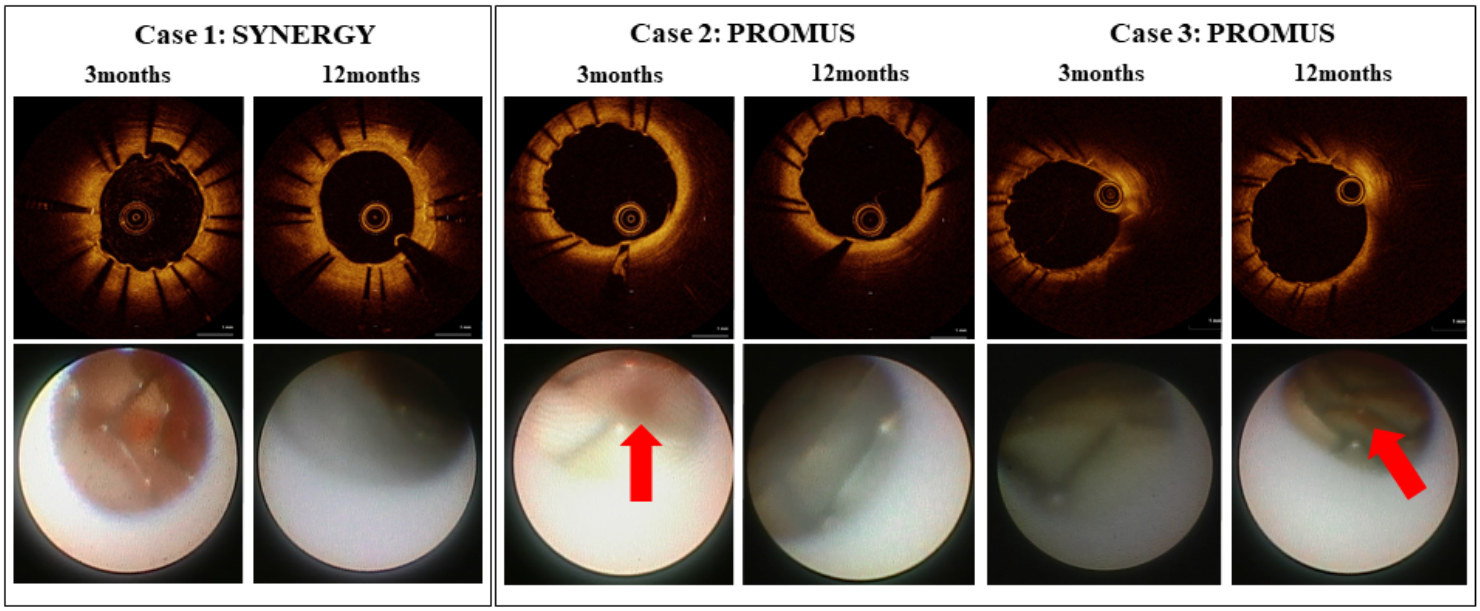

Figure 4

Representative OCT and coronary angioscopic findings. Red arrows, thrombus

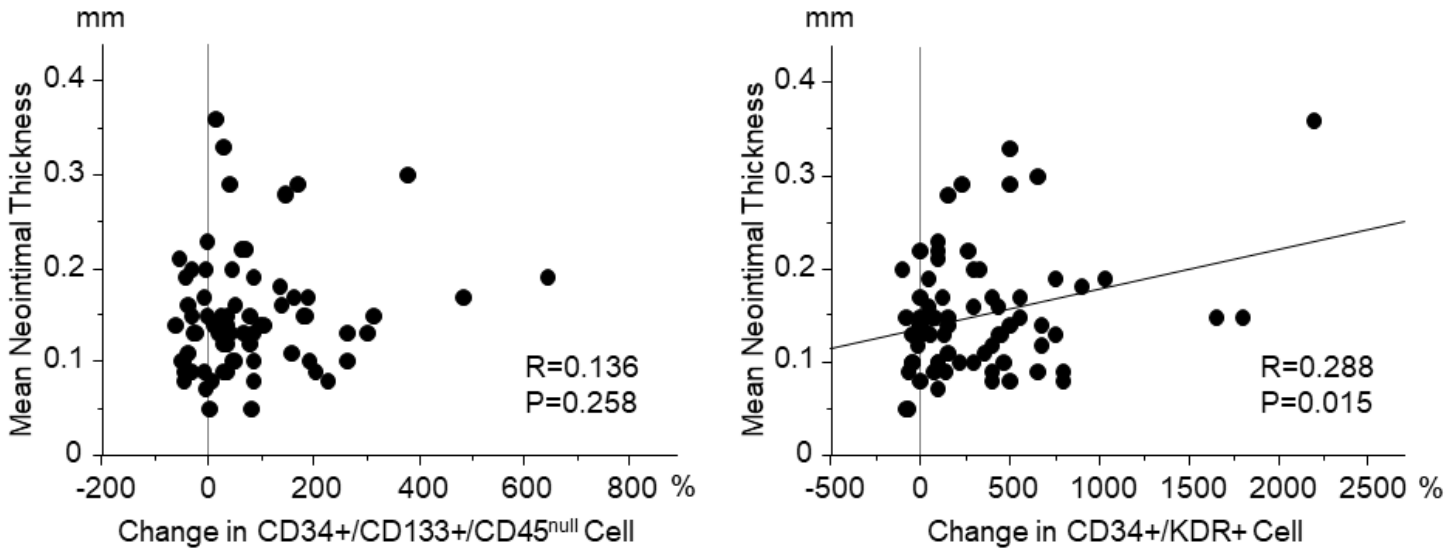

Figure 5

Correlation between kinetics of progenitor cells and OCT-based stent healing in all of 72 patients combined SYNERGY and PREMIER groups.