Catheterization and Cardiovascular Interventions 63:44–51 (2004)

Balloon Angioplasty Plus Cilostazol Administration Versus Primary Stenting of Small Coronary Artery Disease: Final Results of COMPASS

Etsuo Tsuchikane,[1]* MD, Yoshihiro Takeda,[2] MD, Kenya Nasu,[2] MD, Nobuhisa Awata,[2] MD, and Tohru Kobayashi,[2] MD

Efficacy of primary stenting in small coronary artery disease is still controversial. Cilostazol has been reported to control restenosis after balloon angioplasty (BA). The aim was to compare primary stenting with BA plus cilostazol administration in small coronary artery disease. Of 106 lesions located in small coronary artery (reference < 3.0 mm), 50 lesions were randomly assigned to the stenting and 56 lesions to the BA-cilostazol group. Multilink stent was implanted in the stenting group. In the BA-cilostazol group, cilostazol (200 mg/day) without aspirin was administered for 6 months after BA. Ticlopidine was given for 1 month when bailout stent was implanted. Serial quantitative angiography was performed at the procedure and 6 months. The primary endpoint was 6-month angiographic restenosis. Clinical event rates at 1 year were also assessed. Baseline characteristics were similar. All procedures were successful. Bailout stenting was performed in three lesions in the BA-cilostazol group. No side effects of cilostazol were observed. Postprocedural lumen diameter was significantly larger (2.69 vs. 2.03 mm; $P < 0.0001$) in the stenting group. However, the follow-up lumen diameter was not different (1.76 vs. 1.85 mm, stenting vs. BA-cilostazol). Although the difference was not statistically significant, restenosis rate was lower in the BA-cilostazol group (13.2% vs. 24.5%; $P = 0.11$). Subacute thrombosis occurred in one patient and target revascularization rate was higher in the stenting group (22.0% vs. 10.7%; $P = 0.10$). BA plus cilostazol administration seems to be a favorable strategy for small coronary artery disease. *Catheter Cardiovasc Interv 2004;63:44–51.*

Key words: stent; small vessel; restenosis

INTRODUCTION

Percutaneous coronary intervention (PCI) with coronary stents is an established treatment for patients with coronary artery disease. Stents are now used in the majority of PCI cases in many laboratories; however, more than 30% of patients undergoing PCI have small coronary artery disease [1–4]. The efficacy of stenting compared to balloon angioplasty (BA) alone in PCI of small coronary artery disease is still controversial [2,3,5–10]. Cilostazol (Otsuka Pharmaceutical, Tokyo, Japan), an antiplatelet medication developed in Japan, has been reported to control restenosis after PCI, both without stenting [11–13] and with stenting [14–16]. Particularly, the magnitude of reduction in restenosis by cilostazol is significant in PCI using BA alone [12,17]. The present study was designed to compare the efficacy of primary stenting with BA plus the administration of cilostazol for the treatment of small coronary artery disease.

MATERIALS AND METHODS

Study Design

Cilostazol or Multilink for Percutaneous Coronary Angioplasty of Small Vessel Study (COMPASS) was a randomized clinical trial comparing primary stenting with conventional BA strategy with administration of cilostazol for PCI of small coronary artery disease. Suit-

[1]Department of Cardiology, Toyohashi Heart Center, Toyohashi, Aichi, Japan
[2]Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

*Correspondence to: Dr. Etsuo Tsuchikane, Department of Cardiology, Toyohashi Heart Center, 21-1, Gobudori, Oyama, Toyohashi, Aichi, 441-8530, Japan. E-mail: dokincha@aioros.ocn.ne.jp

Received 14 August 2003; Revision accepted 28 February 2004

DOI 10.1002/ccd.20107
Published online in Wiley InterScience (www.interscience.wiley.com).

able lesions for inclusion were selected by angiographical reference vessel diameter (< 3.0 mm by visual estimate) and clinical criteria. Exclusion criteria included lesions located in a vessel of 3.0 mm or larger, or smaller than 2.0 mm as assessed by visual estimate; refractory restenotic lesion after BA (> 2 times); restenotic lesions after stenting or atherectomy; left main trunk lesions; aorto-ostial lesions; bypass graft lesions; thrombotic lesions; acute myocardial infarction within the previous 1 month; stroke within the previous 3 months; severe left ventricular dysfunction; and chronic renal failure.

Eligible patients were asked to participate in this trial. Informed consent was obtained under a protocol approved by our institutional review board. Randomization was performed before the procedure with equal probability of diabetes mellitus, and patients were assigned to the stenting or BA-cilostazol group. The primary endpoint of this study was the 6-month angiographic restenosis rate defined as percent diameter stenosis > 50% estimated by quantitative coronary angiography.

Procedure and Medication

BA was performed using a conventional balloon (balloon:artery ratio of 1.0–1.2) in the both arm groups. The stenting group had one or two Multilink stents (Guidant Vascular Intervention, Temecula, CA) implanted to cover the lesion fully with high pressure. No other type of stent was used. In the BA-cilostazol group, bailout Multilink stents was used if overt or threatened abrupt closure was observed after BA. Abrupt closure was defined as reduced coronary flow (Thrombolysis in Myocardial Infarction flow grade 0 or 1) due to mechanical complications. Threatened abrupt closure was diagnosed by the presence of a National Heart, Lung, and Blood Institute grade B dissection and > 50% diameter stenosis, or a dissection of grade C or worse.

All enrolled patients were given aspirin for at least 1 week prior to the procedure. Patients assigned to the stenting group received ticlopidine (200 mg daily) for 1 month to prevent subacute thrombosis. In the BA-cilostazol group, administration of cilostazol was commenced immediately after the procedure and the use of aspirin was discontinued. The daily dosage of cilostazol was 200 mg, given as 100 mg b.i.d. If no adverse side effects were observed, cilostazol was continued for the full 6 months until follow-up angiography. Patients undergoing bailout stenting in the BA-cilostazol group received additional administration of ticlopidine (200 mg daily) for 1 month. Glycoprotein IIb/IIIa antagonists or clopidogrel were not used in either group since those drugs were not available in Japan.

Quantitative Coronary Angiography

All pre- and postprocedure and follow-up angiography was conducted immediately after the administration of 200 μg of intracoronary nitroglycerin. Angiography was performed so that each lesion was viewed from at least two angles. Offline quantitative coronary angiography was conducted utilizing the view revealing the highest degree of stenosis. Calculations were made using the Cardiovascular Measurement System (CMS-MEDIS Medical Imaging Systems, Leiden, The Netherlands) by an isolated operator who was blinded to the patient's group assignment. The lesion length, reference diameter, minimal lumen diameter (MLD), and diameter stenosis were calculated. Acute gain was defined as the difference between pre- and postprocedural MLD, and late loss was defined as the difference between postprocedural and follow-up MLD. The loss index was calculated as late loss divided by acute gain.

Patient Follow-Up

In-hospital assessment was performed for all clinical outcomes, including hemorrhagic and vascular complications, and routine ascertainment of creatine kinase and creatine kinase-MB before treatment and 4–6 and 24 hr after the procedure. After discharge, clinical follow-up examinations were conducted on an outpatient basis at least once a month. A clinical follow-up examination was performed at 3 months, 6 months, and 1 year to assess the occurrence of an adverse cardiac event (death, myocardial infarction, or any repeat revascularization procedure).

Angiographic follow-up examination was performed routinely at 3 and 6 months. If target lesion revascularization was performed at 3 months due to restenosis, then the preprocedural angiography taken at 3 months were used for the follow-up quantitative coronary angiography analysis of the patient.

Endpoints

The prespecified primary angiographic endpoint was the 6-month angiographic restenosis rate, defined as > 50% diameter stenosis. Other angiographic assessments included initial procedural success (defined as < 50% residual diameter stenosis in the absence of severe dissections or flow limitation) and reference diameter, MLD, and diameter stenosis at baseline, postprocedure, and at follow-up.

Clinical endpoints included short-term procedural safety, clinical restenosis surrogates, and clinical status at 1 year. All deaths were considered cardiac-related unless clearly attributable to a noncardiac cause. Documentation of new pathological Q-waves in two or more contiguous leads in an electrocardiogram associated with any eleva-

TABLE I. Baseline Patient Characteristics*

	Stenting (n = 50)	BA-cilostazol (n = 56)	*P*
Male	39 (78%)	44 (79%)	0.94
Age (years)	64 ± 8	66 ± 7	0.17
Prior myocardial infarction	25 (50%)	26 (46%)	0.71
Prior coronary artery bypass surgery	2 (4%)	4 (7%)	0.48
Multivessel disease	16 (32%)	22 (39%)	0.43
Hypertension	25 (50%)	30 (54%)	0.71
Diabetes mellitus	21 (42%)	23 (41%)	0.92
Hyperlipidemia	25 (50%)	34 (61%)	0.27
History of smoking	31 (62%)	34 (61%)	0.89
Left ventricular ejection fraction (%)	60 ± 12	61 ± 11	0.64

*Data presented are numbers of patients with percent in parentheses or mean value ± SD.

tion of creatine kinase-MB was required for a diagnosis of Q-wave myocardial infarction. Non-Q-wave myocardial infarction was defined as the elevation of creatine kinase to more than twice the upper limit associated with any elevation of creatine kinase-MB without the appearance of Q-waves.

Statistical Analysis

On the basis of results in previous reports [6,7,12], we expected that the angiographic restenosis rate would be 35% in the stenting and 15% in the BA-cilostazol groups. To achieve statistical significance, 40 patients needed to be randomized to each group; hence, the planned sample size was 100 patients. All analyses were done on an intent-to-treat basis. Continuous variables were expressed as mean ± standard deviation. Categorical data were expressed as frequencies of occurrence. The Student's *t*-test or nonparametric analysis by the Mann-Whitney U-test was used for numerical comparisons between groups. Repeated measure analysis of variance was used to compare the paired continuous variables between groups. The chi-square test or the Fisher exact test was used for comparing frequencies of occurrence. Comparison of event-free survival rate was conducted by Kaplan-Meier methods with log-rank test. Statview J-version 5.0 (Abacus Concepts, Berkeley, CA) was used for data analysis. Statistical significance was established at the $P < 0.05$ level.

RESULTS

Patient Characteristics

Patients were enrolled from January 2000 through March 2002. A total of 768 patients were screened, resulting in the enrollment of 106 patients. Fifty patients were assigned to the stenting group and 56 patients assigned to the BA-cilostazol group.

Baseline demographic and clinical data are shown in Table I. No significant differences between the two groups with regard to patient characteristics were observed. The baseline lesion characteristics including preprocedural quantitative coronary angiography data also did not differ between the two groups, as shown in Table II.

Procedure Performance

There were no significant differences between the two groups regarding BA procedure results: balloon size used (2.92 ± 0.33 vs. 2.90 ± 0.32 mm, stenting vs. BA-cilostazol), balloon/artery ratio (1.15 ± 0.13 vs. 1.12 ± 0.13), and the maximum balloon pressure (9.6 ± 2.6 vs. 9.5 ± 3.1 atm). In the stenting group, two stents were implanted in five lesions (10%). Mean stent size was 3.04 ± 0.30 mm and maximum implantation pressure was 12.9 ± 3.0 atm. In the BA-cilostazol group, bailout stent implantation was performed in three lesions (5%) with a 2.83 ± 0.29 mm stent and a pressure of 11.3 ± 3.1 atm. No significant differences between the two groups were observed with regard to fluoroscopy time (17.1 ± 9.6 vs. 15.2 ± 8.9 min) and amount of contrast medium (188 ± 70 vs. 161 ± 68 ml).

Acute Results

The initial procedure was successful in all patients. During hospitalization, no patients developed any major complications (death, Q-wave myocardial infarction, emergent coronary artery bypass surgery); however, subacute stent thrombosis was observed in one patient in the stenting group 13 days after the procedure. This patient was admitted again to undergo target lesion revascularization with another stent implantation, but she developed Q-wave myocardial infarction. Hemorrhagic vascular complications that did not require surgical repair were observed in one patient in the stenting group. Non-Q-wave myocardial infarction occurred in none of the both arm groups.

Quantitative coronary angiography analysis showed that postprocedural MLD was significantly larger

TABLE II. Baseline Lesion Characteristics*

	Stenting (n = 50)	BA-cilostazol (n = 56)	*P*
Vessel treated			
Right coronary artery	15 (30%)	22 (39%)	0.60
Left anterior descending coronary artery	16 (32%)	16 (29%)	
Left circumflex coronary artery	19 (38%)	18 (32%)	
American Heart Association/American College of Cardiology type			
A/B1	31 (62%)	35 (62%)	0.96
B2/C	19 (38%)	21 (38%)	
Calcified	15 (30%)	14 (25%)	0.42
Restenotic	4 (8%)	4 (7%)	0.87
Lesion length (mm)	12.8 ± 4.9	13.6 ± 5.4	0.41
Reference diameter (mm)	2.61 ± 0.34	2.56 ± 0.40	0.44
MLD (mm)	0.99 ± 0.27	0.93 ± 0.28	0.27
Diameter stenosis (%)	62.1 ± 8.3	63.5 ± 8.8	0.40

*Data presented are numbers of patients with percent in parentheses or mean value ±SD.

TABLE III. Analysis of Angiographic Lumen Dynamics

	Stenting (n = 49)	BA-cilostazol (n = 56)	*P*
Prereference diameter (mm)	2.62 ± 0.34	2.56 ± 0.40	0.42
Pre-MLD (mm)	0.99 ± 0.27	0.93 ± 0.28	0.30
Prediameter stenosis (%)	62.3 ± 8.3	63.5 ± 8.8	0.46
Postreference diameter (mm)	2.95 ± 0.33	2.69 ± 0.44	< 0.001
Post-MLD (mm)	2.69 ± 0.38	2.03 ± 0.39	< 0.0001
Acute gain (mm)	1.70 ± 0.37	1.10 ± 0.40	< 0.0001
Postdiameter stenosis (%)	8.4 ± 8.1	24.2 ± 8.6	< 0.0001
Follow-up reference diameter (mm)	2.67 ± 0.40	2.73 ± 0.46	0.50
Follow-up MLD (mm)	1.76 ± 0.62	1.85 ± 0.53	0.42
Late loss (mm)	0.94 ± 0.57	0.18 ± 0.52	< 0.0001
Net gain (mm)	0.77 ± 0.61	0.92 ± 0.50	0.17
Loss index	0.56 ± 0.34	0.12 ± 0.45	< 0.0001
Follow-up diameter stenosis (%)	34.3 ± 20.1	31.9 ± 16.9	0.50
Restenosis rate (%)	24.5 (12/49)	13.2 (7/56)	0.11

(2.69 ± 0.38 vs. 2.03 ± 0.39 mm; $P < 0.0001$) and postprocedural diameter stenosis was significantly smaller (8.3% ± 8.1% vs. 24.2% ± 8.6%; $P < 0.0001$) in the stenting group. Consequently, acute gain was significantly larger in the stenting group (1.70 ± 0.37 vs. 1.10 ± 0.40 mm; $P < 0.0001$).

Angiographic Follow-Up

Follow-up angiography could not be performed in one patients of the stenting group due to withdrawal of the patients' consent. This patient neither had recurrent angina nor showed ST depression on stress electrocardiography, so he declined to participate with further angiography. In patients with 3-month follow-up angiography, 13 patients (9 in the stenting and 4 in the BA-cilostazol group) underwent PCI for target lesion revascularization due to restenosis.

No patients discontinued cilostazol due to side effects during 6-month follow-up in the BA-cilostazol group. Therefore, 6-month follow-up angiography was performed in 49 eligible patients in the stenting and in 56 eligible patients in the BA-cilostazol group 190 ± 56 days after the procedure. The angiographic follow-up rate was 99.1% (105/106).

The analysis of lumen dynamics is shown in Table III, and the change in MLD is shown in Figure 1 for the both arm groups. Follow-up MLD (1.76 vs. 1.85 mm, stenting vs. BA-cilostazol) and diameter stenosis (34.3% vs. 31.9%) were not significantly different between the two groups. Late loss (0.94 vs. 0.18 mm; $P < 0.0001$) and loss index (0.55 vs. 0.12; $P < 0.0001$) were significantly larger for the stenting group. Angiographic restenosis, the primary endpoint, was lower (24.5% vs. 13.2%; $P = 0.11$) in the BA-cilostazol group; however, the difference did not reach statistical significance.

To examine the effect of cilostazol as a vasodilator, change in reference diameter from the time of the procedure until follow-up was analyzed (Fig. 2). The

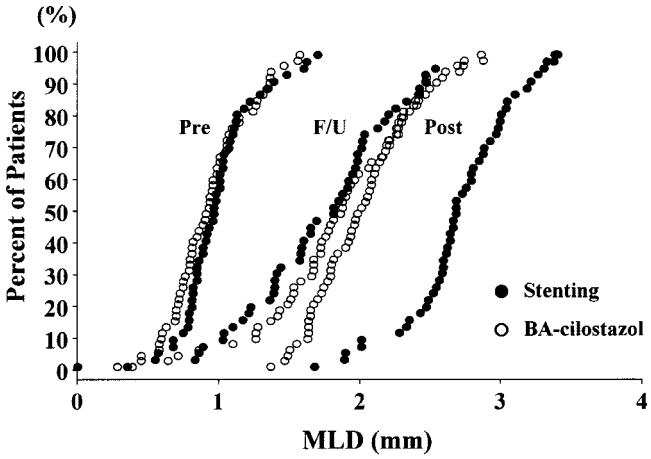

Fig. 1. Cumulative distribution of MLD at preprocedure (Pre), immediately after the procedure (Post), and at the 6-month angiographic follow-up (F/U). Post-MLD was significantly larger (2.69 vs. 2.03 mm; $P < 0.0001$) for the stenting group compared with the BA-cilostzol group. However, MLD at follow-up did not significantly differ between the two groups (1.76 vs. 1.85 mm; $P = 0.42$).

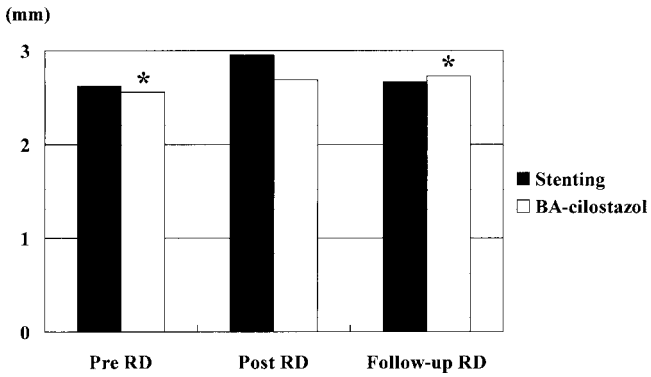

Fig. 2. Change in reference diameter from the time of the procedure until follow-up. The reference diameter significantly enlarged after the procedure compared to preprocedure in both groups. In the stenting group, follow-up reference diameter was not different compared to preprocedure values (from 2.62 to 2.67 mm). However, in the BA-cilostazol group, follow-up reference diameter was significantly larger than preprocedure values (from 2.56 to 2.73 mm; asterisk, $P < 0.0001$). This change in reference diameter was significantly different between the two groups assessed by repeated measure analysis of variance ($P < 0.05$).

reference diameter measured by quantitative coronary angiography significantly enlarged after the procedure compared to preprocedure in both groups due to the PCI procedure, particularly in the stenting group. In the stenting group, follow-up reference diameter was not different compared to preprocedure values (from 2.62 ± 0.34 to 2.67 ± 0.40 mm). However, in the BA-cilostazol group, follow-up reference diameter was significantly larger than preprocedure values

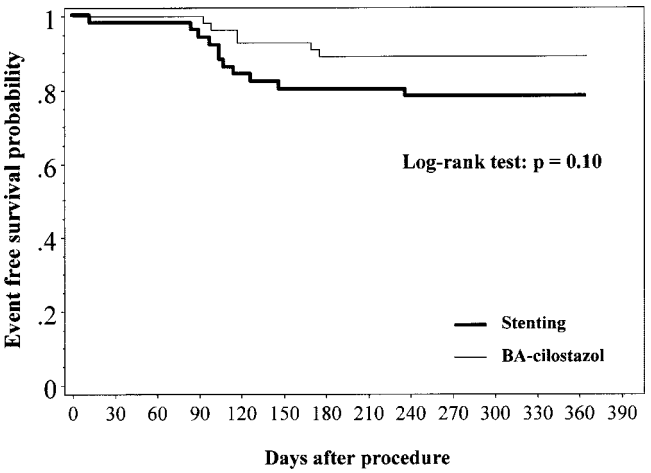

Fig. 3. Kaplan-Meier survival curves free of target lesion revascularization.

(from 2.56 ± 0.40 to 2.73 ± 0.46 mm; $P < 0.0001$). This change in reference diameter significantly differed between the two groups assessed by repeated measure analysis of variance ($P < 0.05$).

Clinical Follow-Up

All patients were followed up for 1 year. By 1-year follow-up, no death or coronary artery bypass surgery was observed. However, Q-wave MI occurred in one patient of the stenting group due to subacute stent thrombosis as previously described. Target lesion revascularization by 1 year was required in 11 patients (22.0%) of the stenting and 6 patients (10.7%) of the BA-cilostazol group. Of those, eight patients (16.0%) of the stenting group and four patients (7.1%) of the BA-cilostazol group demonstrated positive stress electrocardiography. Event-free survival curve from target lesion revascularization was shown in Figure 3. Although there was no statistically significant difference between the two groups, the incidence level was lower in the BA-cilostazol group ($P = 0.10$ by log-rank test).

DISCUSSION

In the present study, although the difference did not reach statistically significance, BA plus cilostazol administration for PCI of small coronary artery disease was associated with a 46% risk reduction of restenosis at 6 months and a 51% risk reduction of target lesion revascularization at 1 year compared with primary stenting. These results may have an important impact, considering the increasing use of stenting as a primary strategy in small coronary artery disease.

Stenting in Small Coronary Artery Disease

Small vessel size is predictive of restenosis after PCI [1–3]. Several retrospective studies in small coronary artery disease have suggested better clinical results and lower restenosis rates with stenting than with BA [2–4]. However, restenosis rate of the stenting group exceeded 30% in those studies. Recent randomized trials also documented safety and early efficacy of stenting in small coronary artery disease; however, the long-term outcome, including the antirestenotic potential, remains still controversial [5–10]. Numerous differences in lesion selection, stenting technique, and the stent design used may explain the divergent results in those trials. In two trials showing positive data [5,9], the majority of lesions were not complex and newly designed stents were implanted with nonaggressive strategy. Two other trials [6,7] including more unfavorable lesions and using Multilink stent showed a higher restenosis rate (35.7% and 35.7%). Since Multilink stent had been reported to be associated with the most favorable outcome in a randomized clinical trial comparing five stent designs [18], we chose the same stent in the present study, which showed a lower restenosis rate (24.5%). Our stenting procedure was similar to these two trials; balloon/artery ratio was 1.12 (vs. 1.13 [6] and 1.10 [7]), maximum stenting pressure was 12.9 atm (vs. 13.5 and 13.3 atm). However, in our study, preprocedural reference diameter (2.61 mm) was a little bit larger and diameter stenosis (62.1%) was smaller, and the majority of lesions were not complex compared with these two trials. These differences in baseline lesion characteristics might influence a lower restenosis rate. Overall, the long-term outcome after stenting in small coronary artery disease is considered to be mainly affected by other lesion characteristics. Therefore, considering the risk of subacute thrombosis (one patient in our study), there are some limitations to choose stenting as a primary strategy for the treatment of small coronary artery disease.

Impact of Cilostazol

Cilostazol, a phosphodiesterase inhibitor, is a potent antiplatelet medication with vasodilatory effects [19]. This agent is approved by the Food and Drug Administration for the treatment of intermittent claudication. Many randomized studies have demonstrated that cilostazol controls restenosis after PCI [11–17]. As previously described [20], cilostazol has several favorable properties in reducing restenosis. Besides the vasodilatory effect, cilostazol directly inhibits smooth muscle cells proliferation [21–23] and enhances reendothelialization after PCI [24,25]. Consequently, the magnitude of the reduction in restenosis is thought to depend on the PCI device used and its interaction with these effects of cilostazol. Since stent induces more aggressive smooth muscle proliferation and decelerates reendothelialization [26,27], cilostazol may be more effective to control restenosis after PCI without stenting. This speculation is supported by a recent clinical report [17].

In the present study, the BA-cilostazol group showed a remarkably low restenosis rate (13.2%) and loss index (0.12). Furthermore, reference diameter of the BA-cilostazol group significantly enlarged until 6-month angiographic follow-up (from 2.56 to 2.73 mm; $P < 0.0001$) because of vasodilatory effect of cilostazol. These results were consistent with a previous randomized trial [12] and confirmed the efficacy of cilostazol on angiographic outcomes after BA. Since the restenosis rate of the stenting group (24.5%) was better than we expected, there was no statistically significant difference ($P = 0.11$). However, it is suggested that BA plus cilostazol administration provides favorable angiographic outcomes in small coronary artery disease.

Clinical Implications

In small coronary artery disease, although primary stenting guarantees acute angiographic result and in-hospital outcome, long-term outcome may depend on several factors as previously described. American College of Cardiology consensus does not recommend stent implantation in small vessels to improve long-term outcomes [28]. This demerit will be overcome by using a drug-eluting stent [29]. However, this special stent is considered to be difficult to use for all patients with small coronary artery disease in the real PCI world because of its higher cost and uncertain very long term outcome. Considering that small coronary artery disease represents a fair amount of the day-to-day angioplasty practice [1–3], BA with provisional stenting plus cilostazol administration also seems to be a reasonable and practical strategy for the treatment of this lesion subset. Cilostazol rarely shows adverse side effects, as shown in the present study and previous reports [12–16,20]. It is important to note that, to enhance the efficacy of the agent, cilostazol should be administered without aspirin. The effect of cilostazol is potentiated by endothelium-derived prostacyclin [30], a compound that is known to possess antithrombotic activity, inhibit platelet aggregation, and relax vascular smooth muscle, and aspirin inhibits prostacyclin synthesis. However, the addition of ticlopidine is mandatory to prevent subacute thrombosis for at least 2 weeks to 1 month when bailout stenting is performed [20].

Study Limitations

This was a small randomized monocentric study (106 patients). A newly designed stent may provide superior outcomes compared with the stenting group in our study

[5,8–10]. Direct stenting instead of primary stenting in the present study may have some advantages [31]. Furthermore, pretreatment of ticlopidine may provide superior outcomes in the stenting group [32]. Although many reports showed the efficacy of cilostazol after PCI [11–17], it has not yet been demonstrated in a placebo-controlled multicenter randomized trial. This confirmation is mandatory.

This study suggested that BA plus cilostazol administration is a favorable strategy for the treatment of small coronary artery disease.

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