Proximal optimisation technique versus final kissing balloon inflation in coronary bifurcation lesions: the randomised, multicentre PROPOT trial

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KEYWORDS

- bifurcation
- drug-eluting stent
- optical coherence tomography

Abstract

Background: Clinical implications of the proximal optimisation technique (POT) for bifurcation lesions have not been investigated in a randomised controlled trial.

Aims: This study aimed to investigate whether POT is superior in terms of stent apposition compared with the conventional kissing balloon technique (KBT) in real-life bifurcation lesions using optical coherence tomography (OCT).

Methods: A total of 120 patients from 15 centres were randomised into two groups - POT followed by side branch dilation or KBT. Finally, 57 and 58 patients in the POT and KBT groups, respectively, were analysed. OCT was performed at baseline, immediately after wire recrossing to the side branch, and at the final procedure.

Results: The primary endpoint was the rate of malapposed struts assessed by the final OCT. The rate of malapposed struts did not differ between the POT and KBT groups (in-stent proximal site: 10.4% vs 7.7%, p=0.33; bifurcation core: 1.4% vs 1.1%, p=0.67; core's distal edge: 6.2% vs 5.3%, p=0.59). More additional treatments were required among the POT group (40.4% vs 6.9%, p<0.01). At one-year follow-up, only one patient in each group underwent target lesion revascularisation (2.0% vs 1.9%).

Conclusions: POT followed by side branch dilation did not show any advantages over conventional KBT in terms of stent apposition; however, excellent midterm clinical outcomes were observed in both strategies.

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Abbreviations

KBT	kissing balloon technique
MV	main vessel
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
POT	proximal optimisation technique
QCA	quantitative coronary angiography
SB	side branch
SBD	side branch dilation
TIMI	Thrombolysis In Myocardial Infarction
TLR	target lesion revascularisation

Introduction

Coronary bifurcation lesions are involved in 15-20% of percutaneous coronary interventions (PCI) and represent a highly challenging lesion subset in interventional cardiology[1]. Provisional stenting is generally accepted as the first-line treatment for coronary bifurcation lesions. The kissing balloon technique (KBT) after crossover main vessel (MV) stenting is considered effective in securing side branch (SB) patency and removing jailed struts. Nonetheless, KBT efficacy has recently been questioned. KBT may lead to asymmetric proximal MV stent deformation or overexpansion, resulting in dissection due to inflation of two aligned balloons[2-4].

The European Bifurcation Club recommends MV stenting with the proximal optimisation technique (POT) and provisional SB stenting as the primary approach for coronary bifurcation lesions[1]. POT involves balloon dilation at the proximal stent segment for apposition to the vessel wall before exchanging the SB wire. This enables easier SB wire access and reduces stent strut distortion and malapposition[5,6]. POT has been confirmed in bench testing; however, clinical evidence is still lacking[7,8]. Hence, this prospective open-label randomised study aimed to investigate whether POT is superior in stent apposition compared with conventional KBT in real-life bifurcation lesions by strut-level analyses with optical coherence tomography (OCT).

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Methods

STUDY POPULATION AND DESIGN

This was a prospective, open-label, randomised study designed to compare POT with KBT after zotarolimus-eluting stent implantation (either Resolute Integrity® or Resolute Onyx™; Medtronic Vascular, Santa Rosa, CA, USA). Patients who underwent bifurcation PCI eligible for a provisional SB stenting strategy using a zotarolimus-eluting stent were enrolled, randomised into groups (POT followed by SB dilation [SBD] or KBT) using a web-based allocation system, and followed up for one year.

Inclusion criteria were: (1) SB bifurcation lesions ≥2.0 mm in diameter; (2) main branch stenosis within 5 mm from the SB ostium; (3) lesions treatable by a provisional SB stenting strategy in accordance with the European Bifurcation Club consensus; (4) lesion length ≤38 mm without other stenosis in the same vessel; (5) reference vessel diameter ≥2.5 mm; and (6) proximal bifurcation lesions among multiple bifurcations. Exclusion criteria are shown in the study protocol **(Supplementary Appendix 1)**.

A total of 120 patients from 15 centres were enrolled and randomised between April 2016 and July 2018. Three patients withdrew consent, one patient had anaphylaxis, and one patient was excluded because of unsuccessful PCI due to wire perforation before stent implantation. Finally, 115 patients were analysed (POT group: 57 patients; KBT group: 58 patients).

All patients provided written informed consent. The study protocol was developed in accordance with the Declaration of Helsinki. This trial was registered in the University Hospital Medical Information Network (UMIN-ID: UMIN000019105) prior to enrolment initiation.

ENDPOINTS

The primary endpoint was the rate of malapposed struts in each subsegment, assessed by final OCT **(Figure 1)**. Secondary endpoints were stent and lumen area, stent eccentricity index, malapposition area/distance, proximal edge dissection assessed by final OCT, total procedural time, fluoroscopic time, amount of contrast, SB wire crossing time after MV stenting, death/cardiac death, myocardial infarction, stent thrombosis, clinically driven target lesion revascularisation (TLR), and target vessel revascularisation up to one year. Definite stent thrombosis was defined according to the Academic Research Consortium classification[9]. TLR was defined as repeat PCI revascularisation or target lesion surgery.

PCI PROTOCOL

All patients were treated with aspirin, clopidogrel, prasugrel, and periprocedural heparin in accordance with institutional policies.

POT GROUP

Crossover stenting was performed from the proximal to distal bifurcated MV in the lesion. Stent size was decided based on the distal MV reference diameter under visual or quantitative coronary angiography (QCA) guidance. Immediately after stent implantation, POT dilation was performed before SB wiring. POT balloon size was selected based on the proximal MV reference diameter. Locating the POT balloon distal marker at the carina was encouraged. The jailed wire technique for the SB was mandatory until guidewire recrossing, aimed at a distal cell of the jailed struts. SBD was performed using a short non-compliant balloon (length: 4-8 mm).

KBT GROUP

Crossover stenting was performed as in the POT group. The conventional KBT, in which MV and SB balloons were aligned at the proximal stent edge, was employed after changing the MV and SB wires[10]. KBT balloon size was selected by matching the MV and SB balloons to the distal MV and SB reference diameters, respectively.

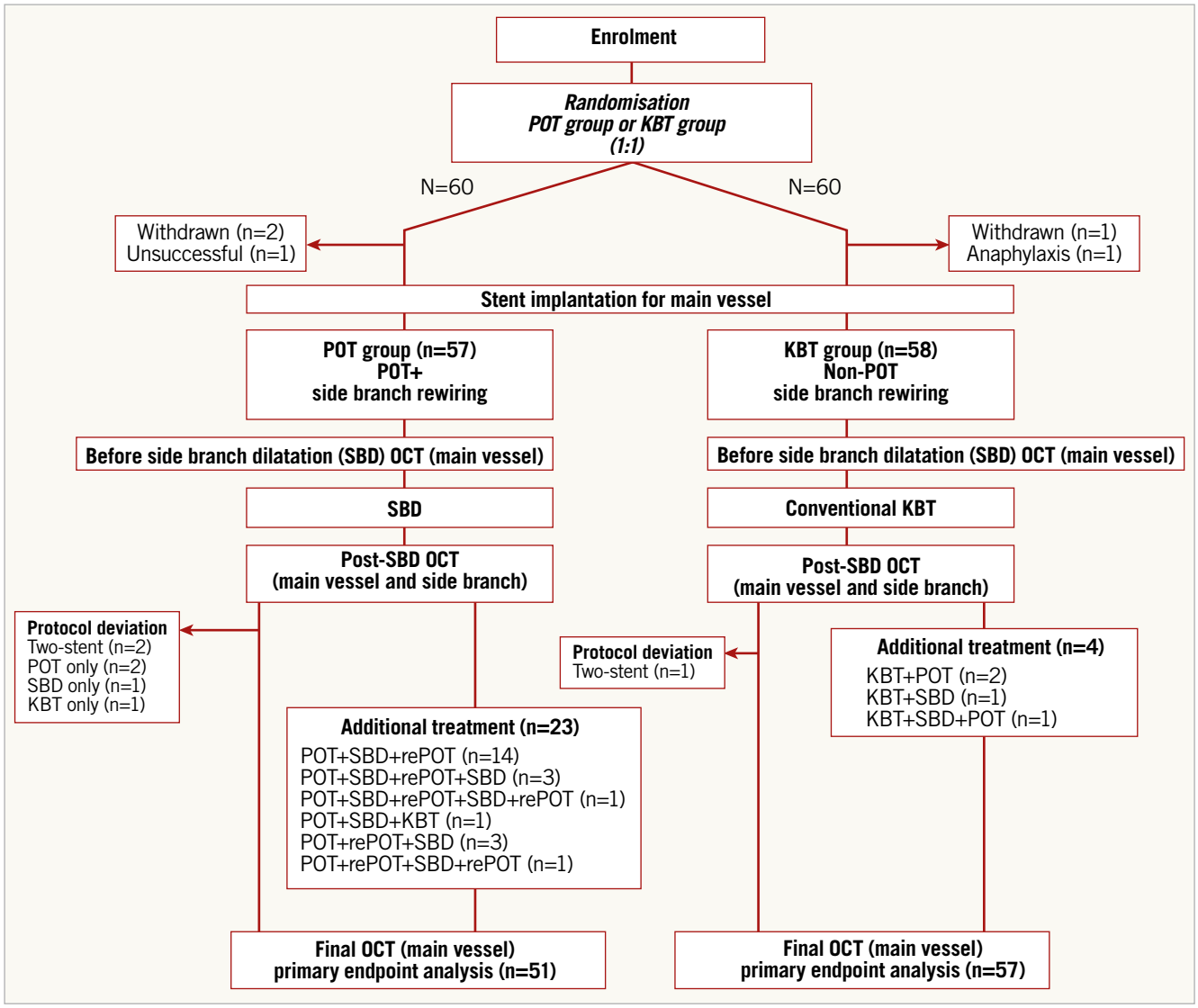


Figure 1. *Trial profile. KBT: kissing balloon technique; OCT: optical coherence tomography; POT: proximal optimisation technique; SBD: side branch dilation*

OCT IMAGING

OCT imaging was performed with either the protocol-recommended frequency-domain OCT (ILUMIEN™ OCT imaging system; Abbott Vascular, Westford, MA, USA) or optical frequency-domain imaging (Lunawave®; Terumo Corp., Tokyo, Japan). Nitroglycerine or other vasodilators were used prior to OCT image acquisition. A high-resolution pullback mode with 100% contrast for blood clearance was recommended; low-molecular-weight dextran-L or lactated Ringer's solution was allowed for renal failure patients. OCT images were obtained after z-offset calibration to include at least 5 mm distal and proximal edges of the target lesion. OCT image acquisition was performed before SBD, at the end of the procedure.

OTHER TECHNICAL CONSIDERATIONS

All procedures were performed under angiographic guidance. OCT results were not used for stent sizing. A provisional stenting strategy was mandatory. The SB stenting criterion was Thrombolysis In Myocardial Infarction (TIMI) 0 or TIMI 1 SB flow after treatment, as previously reported[7]. To avoid fatal adverse events, additional treatment including re-POT or additional KBT was allowed after procedure completion for cases with stent malapposition >400 µm from the vessel wall in any part of the stent. The choice of additional treatment, re-POT or additional KBT, was at the operators' discretion. Protocol deviation was defined as procedures in which the protocol was not completed, including the need for two stents, performing only POT, or only KBT or SBD without POT.

QCA ANALYSIS

QCA was performed in an independent core laboratory (Cardiocore Japan, Tokyo, Japan) using a semi-automated bifurcation analysis software. QAngio® XA (Medis Medical Imaging Systems, Leiden, the Netherlands) was used[11]. For each subsegment, minimal lumen

diameter, reference vessel diameter, percent diameter stenosis, and lesion length were measured before and at the end of the procedure, as previously reported[11]. Preprocedural analysis included five subsegments: MV, proximal MV, distal MV, bifurcation core, and SB **(Figure 2)**.

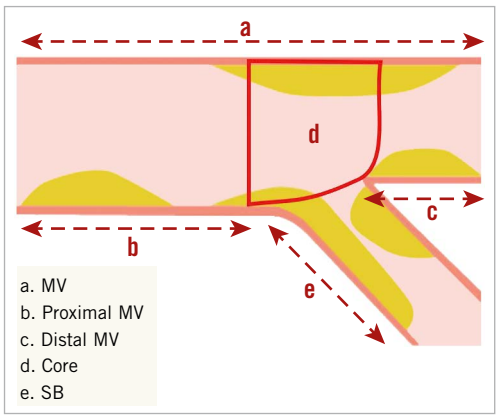


Figure 2. *Subsegment analysis by quantitative coronary angiography. MV: main vessel; SB: side branch*

OCT IMAGE ANALYSIS

OCT image analysis was conducted using QIvus (Medis Medical Imaging Systems) in an independent core laboratory (Cardiocore Japan, Tokyo, Japan). Five subsegments were defined: proximal edge, in-stent proximal site, core's proximal edge, bifurcation core, and core's distal edge **(Figure 3)**. Excluding the bifurcation core, subsegment lengths were 5 mm from the border, which was the end of the stent or bifurcation core. Quantitative analysis was performed for all frames except for measurements regarding the stent at the proximal edge. To compare subtle differences, quantitative analysis was conducted for every frame, especially at the bifurcation core subsegment. Otherwise, all quantitative analyses were performed at every 1 mm interval along the entire target segment. For quantitative strut-level analysis, malapposed strut rate and maximum malapposition distance were estimated for all subsegments except for the proximal edge, and the jailed strut rate only at the bifurcation core was determined. A jailed strut was defined as a strut floating at the SB orifice. Malapposition was adjudicated when the distance between the lumen and stent contour was greater than the strut thickness (Resolute Integrity: 91 µm; Resolute Onyx: 81 µm). Qualitative assessment for evaluation of edge dissection, including all visible ones irrespective of range or depth, was performed for all frames at the proximal edge.

STATISTICAL ANALYSIS

Sample size calculation was based on the assumption that the incidence of the primary endpoint would be 10.0% in the POT group and 35% in the KBT group[7]. Therefore, we estimated that 51 patients in each group would allow the trial to have 80% power with a two-sided alpha level of 0.05 (according to the chi-square test) to detect a significant difference in the primary endpoint. Compensation for 20% suboptimal imaging required enrolment

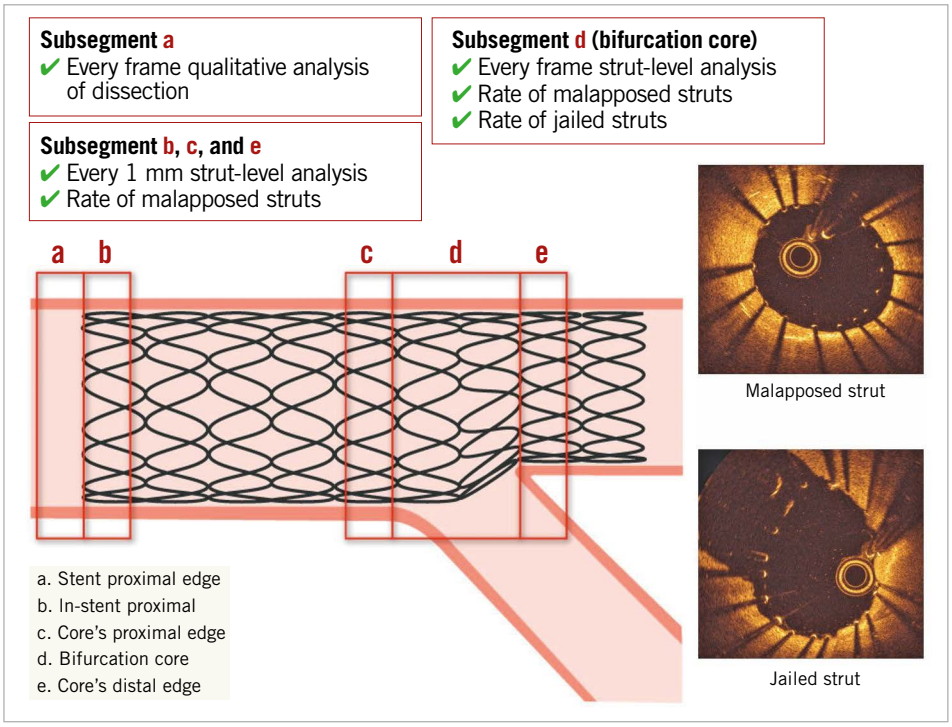


Figure 3. *Subsegment analysis by optical coherence tomography. Except for the bifurcation core (segment d), subsegment length was 5 mm from the border. The border denotes the end of the stent and bifurcation core. Strut-level analysis was performed for every frame, and the rate of jailed struts at the bifurcation core was estimated. Dissection at the proximal edge (subsegment a) and distal edge was adjudicated.*

of 60 patients per group. Analyses were performed on an intention-to-treat basis. Continuous variables were assessed for normal distribution using the Shapiro-Wilk test and are expressed as mean±standard deviation or as median (interquartile range). Categorical variables were compared using the chi-square test or Fisher's exact test and are presented as numerical values and percentages. Depending on the distribution of variables, continuous variables were compared using an unpaired Student's t-test or the Wilcoxon rank-sum test. All p-values were two-sided; p<0.05 was considered statistically significant. Data were analysed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

PATIENT CHARACTERISTICS

Baseline patient characteristics, lesion characteristics, Medina classification, and true bifurcation rate were similar between the groups **(Table 1)**.

PROCEDURAL CHARACTERISTICS AND OUTCOMES

Procedural characteristics are presented in **Figure 1**. Procedural outcomes are summarised in **Table 2**. Stent diameter and length were not significantly different between the groups. In the POT group, the POT and SB balloon sizes were 3.4±0.5 mm and 2.4±0.4 mm, respectively. Furthermore, the POT and SB balloon/artery ratios, calculated using the reference diameter from the QCA analysis, were 1.05±0.13 and 0.73±0.12, respectively. In the KBT group, the MV and SB balloon sizes were 2.9±0.4 mm and 2.3±0.3 mm, respectively. Moreover, the MV and SB balloon/artery ratios were 1.20±0.20 and 0.72±0.11, respectively. Additional treatment was performed for 40.4% and 6.9% of patients in the POT and KBT groups, respectively (p<0.01). The POT+SBD+re-POT sequence most frequently required additional treatment in the POT group (24.6%). Protocol deviation was observed in 6 patients in the POT group and 1 in the KBT group. In the POT group, protocol

Table 1. Study population.

		POT (n=57)	KBT (n=58)	*p*-value
Age, years		67.9±10.6	69.5±9.5	0.39
Male		46 (80.7%)	46 (79.3%)	0.85
Diabetes mellitus		19 (33.3%)	23 (39.7%)	0.48
Dyslipidaemia		48 (84.2%)	38 (65.5%)	0.02
Hypertension		39 (68.4%)	46 (79.3%)	0.18
ACS		10 (17.5%)	9 (15.5%)	0.77
Prior MI		6 (10.5%)	9 (15.5%)	0.43
Target lesion	LMCA	2 (3.5%)	1 (1.7%)	0.14
	LAD	42 (73.7%)	41 (70.7%)	
	LCX	13 (22.8%)	11 (19.0%)	
	RCA	0 (0.0%)	5 (8.6%)	
ACC/AHA type	B2/C	55 (96.5%)	54 (93.1%)	0.68
Lesion length	discrete	9 (15.8%)	9 (15.5%)	0.74
	tubular	33 (57.9%)	30 (51.7%)	
	diffuse	15 (26.3%)	19 (32.8%)	
Severe/moderate calcification		11 (19.3%)	12 (20.7%)	0.85
Medina classification	1,1,1	11 (19.3%)	11 (19.0%)	0.89
	1,1,0	20 (35.1%)	15 (25.9%)	
	1,0,0	10 (17.5%)	11 (19.0%)	
	1,0,1	1 (1.8%)	1 (1.7%)	
	0,1,1	4 (7.0%)	4 (6.9%)	
	0,1,0	11 (19.3%)	16 (27.6%)	
	0,0,1	0 (0.0%)	0 (0.0%)	
True bifurcation		16 (28.1%)	16 (27.6%)	0.95

Values are expressed as n (%) or mean±SD. ACS: acute coronary syndrome; LAD: left anterior descending artery; LCX: left circumflex artery; LMCA: left main coronary artery; MI: myocardial infarction; RCA: right coronary artery

Table 2. Procedural outcomes.

	POT (n=57)	KBT (n=58)	*p*-value
Stent diameter, mm	2.9±0.4	2.9±0.3	0.63
Stent length, mm	24.7±6.7	25.2±6.7	0.68
Pressure, atm	11.1±4.3	11.6±2.8	0.46
POT balloon size, mm	3.4±0.5		
Pressure, atm	14.9±4.0		
B/A ratio	1.05±0.13		
SB balloon size, mm	2.4±0.4		
Pressure, atm	10.2±4.8		
B/A ratio	0.73±0.12		
MV balloon size, mm		2.9±0.4	
Pressure during KBT, atm		12.1±4.8	
B/A ratio		1.20±0.20	
SB balloon size, mm		2.3±0.3	
Pressure during KBT, atm		10.3±3.5	
B/A ratio		0.72±0.11	
Additional treatment	23 (40.4%)	4 (6.9%)	<0.01
POT+SBD+rePOT	14 (24.6%)		
POT+SBD+rePOT+SBD	3 (5.3%)		
POT+SBD+rePOT +SBD+rePOT	1 (1.8%)		
POT+SBD+KBT	1 (1.8%)		
POT+rePOT+SBD	3 (5.3%)		
POT+rePOT+SBD+rePOT	1 (1.8%)		
KBT+POT		2 (3.5%)	
KBT+SBD		1 (1.8%)	
KBT+SBD+POT		1 (1.8%)	
Procedural time, min	70.0 (55.0-85.0)	67.5 (55.0-85.0)	0.34
Fluoroscopic time, min	28.5 (20-40)	28.0 (19.0-38.8)	0.26
Wire recrossing time for side branch, sec	50 (35-152)	60 (30-114)	0.20
Amount of contrast, ml	201±80.2	174±76.4	0.07

Values are expressed as n (%), mean±standard deviation or median (interquartile range). KBT: kissing balloon technique; MV: main vessel; POT: proximal optimisation technique; SB: side branch; SBD: side branch dilation

deviations included the need for a second stent (n=2), POT only (n=2), SBD without POT (n=1), and KBT without POT (n=1). In the KBT group, protocol deviation included the need for a second stent (n=1). SB stenting was applied in 3.5% and 1.7% of patients in the POT and KBT groups, respectively (p=0.62). No significant differences in procedural time, fluoroscopic time, wire crossing time for the SB, and amount of contrast were noted between the groups.

QCA RESULTS

Results of preprocedural and post-procedural QCA measurements are presented in **Table 3**. No significant difference in preprocedural QCA measurements was observed between the groups. However, regarding post-procedural QCA measurements, in-stent percent diameter stenosis was higher in the POT group (18.5±8.2 vs 15.3±6.3, p=0.02).

OCT RESULTS

The malapposed strut rate as assessed by final OCT, the primary endpoint, was 10.4% and 7.7% at the in-stent proximal site (**Figure 3C**, p=0.33), 1.4% and 1.1% at the bifurcation core (**Central illustration**, **Figure 3D**, p=0.67), and 6.2% and 5.3% at the core's distal edge (**Figure 3E**, p=0.59) in the POT and KBT groups, respectively **(Figure 4)**. The malapposed strut rate as assessed by pre-SBD OCT was 14.5% and 17.0% at the in-stent proximal site (**Figure 3B**, p=0.58) in the POT and KBT groups, respectively **(Figure 4)**. The jailed strut rate at the bifurcation core, the secondary endpoint, was 16.1% and 14.7% (p=0.44) by pre-SBD OCT and 9.9% and 7.6% (p=0.16) by final OCT in the POT and KBT groups, respectively **(Central illustration, Figure 5)**. Lumen area, stent area, and stent eccentricity index in the final OCT were not significantly different between the POT and KBT groups **(Table 4)**. The maximum malapposition distance of the core's distal edge **(Figure 3E)** as assessed by final OCT was greater in the POT group (0.34±0.18 vs 0.22±0.15, p<0.01). The dissection rates at the proximal **(Figure 3A)** and distal edges **(Table 4)** were not significantly different between the groups.

PROCEDURAL OUTCOMES

One-year clinical outcomes are summarised in **Table 5**. No death or cardiac death was observed in either group. One patient (1.9%) in the KBT group had a myocardial infarction. Clinically driven TLR was performed for one patient in each group (2.0% vs 1.9%). The TLR site was located in the MV in both groups. Target vessel

Table 3. QCA results.

Pre procedure		POT (n=57)	KBT (n=58)	*p*-value
MV	MLD	1.0±0.4	0.9±0.3	0.42
	RD	2.7±0.6	2.6±0.4	0.48
	%Diameter stenosis	63.1±10.0	63.9±9.5	0.65
	Lesion length	16.3±7.0	17.3±8.4	0.48
Proximal MV	MLD	2.0±0.9	1.9±1.0	0.66
	RD	3.1±0.6	2.9±0.6	0.12
	%Diameter stenosis	35.2±26.5	35.8±25.3	0.90
	Segment length	10.7±6.9	11.9±7.0	0.38
Distal MV	MLD	1.2±0.5	1.2±0.5	0.64
	RD	2.5±0.5	2.5±0.5	0.92
	%Diameter stenosis	53.2±15.1	50.0±20.8	0.35
	Segment length	18.7±7.8	19.8±9.3	0.52
SB	MLD	1.6±0.6	1.6±0.4	0.96
	RD	2.3±0.5	2.3±0.5	0.66
	%Diameter stenosis	30.8±21.0	28.1±18.2	0.46
	Segment length	2.3±0.9	2.2±0.9	0.74
Core	MLD	2.0±0.8	2.0±1.0	0.79
	RD	2.9±0.5	2.8±0.6	0.33
	%Diameter stenosis	31.2±25.8	29.7±26.5	0.77
	Length	3.1±1.5	2.5±1.6	0.07
	Segment length	3.8±0.7	3.7±0.7	0.52
Post procedure				
In-stent	MLD	2.5±0.4	2.6±0.4	0.18
	Acute gain	1.5±0.5	1.7±0.3	0.07
	RD	3.1±0.4	3.1±0.4	0.88
	%Diameter stenosis	18.5±8.2	15.3±6.3	0.02
	Segment length	23.9±7.0	25.2±7.3	0.37

Post procedure (cont'd)		POT (n=57)	KBT (n=58)	*p*-value
In-segment	MLD	2.3±0.5	2.3±0.4	0.88
	RD	3.0±0.5	2.9±0.5	0.34
	%Diameter stenosis	22.4±9.4	20.0±6.5	0.10
	Length	4.9±2.0	4.4±2.2	0.19
	Segment length	33.4±6.7	34.2±7.5	0.53
Proximal edge	MLD	2.8±0.5	2.8±0.5	0.87
	RD	3.2±0.4	3.2±0.5	0.72
	%Diameter stenosis	12.7±9.3	12.2±9.1	0.80
	Segment length	4.9±0.3	4.9±0.5	0.63
Distal edge	MLD	2.2±0.5	2.1±0.4	0.66
	RD	2.5±0.4	2.5±0.4	0.73
	%Diameter stenosis	13.0±9.7	13.2±7.1	0.90
	Segment length	5.0±0.0	5.0±0.0	0.32
Side branch	MLD	1.6±0.5	1.6±0.4	0.87
	RD	2.2±0.7	2.2±0.5	0.72
	%Diameter stenosis	26.2±19.8	24.2±17.4	0.58
	Length	2.2±0.9	2.2±1.0	0.92
	Segment length	3.0±0.0	3.0±0.0	N/A
Core	MLD	3.1±0.5	3.2±0.6	0.37
	RD	3.2±0.4	3.3±0.6	0.55
	%Diameter stenosis	3.8±10.1	2.7±8.1	0.54
	Length	2.3±1.9	2.4±2.0	0.74
	Segment length	4.0±0.8	4.1±0.7	0.77

Values are expressed as n (%) or mean±SD. MLD: minimum lumen diameter; MV: main vessel; RD: reference diameter; SB: side branch

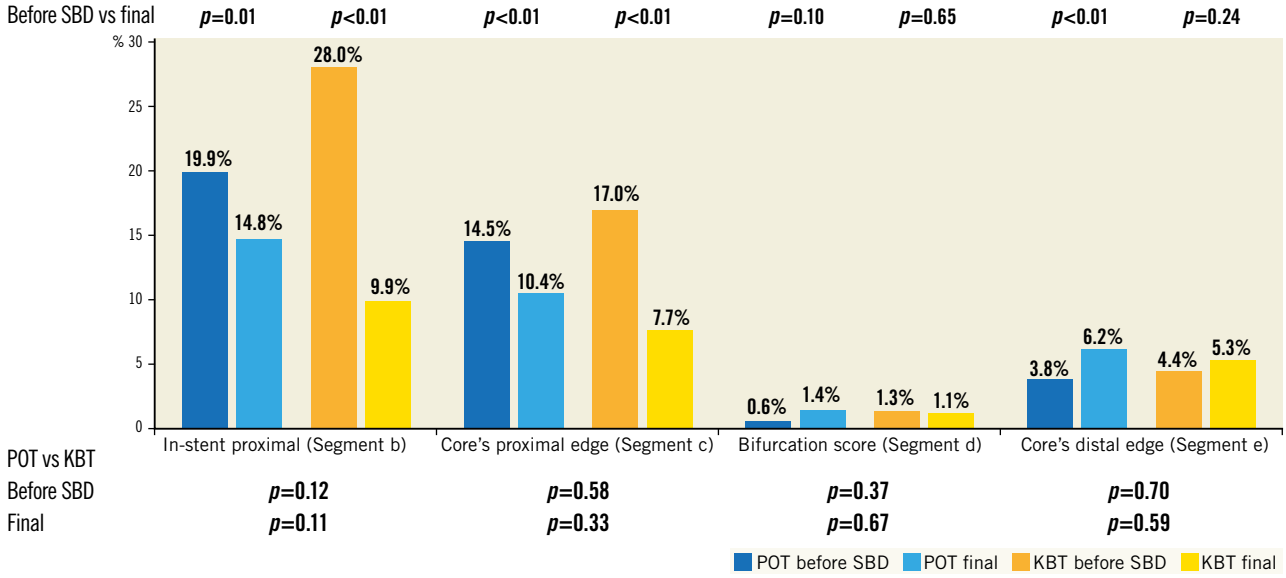


Figure 4. *Rate of malapposed struts at each segment before side branch dilation and at the end of the procedure. KBT: kissing balloon technique; POT: proximal optimisation technique; SBD: side branch dilation*

Table 4. OCT results (final).

			POT (n=51)	KBT (n=56)	*p*-value
Lumen area, mm^2	Core's proximal	Minimum	6.7±1.8	7.1±2.3	0.37
		Mean	7.6±2.0	7.9±3.2	0.50
	Bifurcation core	Minimum	5.6±1.7	5.7±1.7	0.70
		Mean	6.6±1.9	6.8±1.8	0.48
	Core's distal	Minimum	5.4±1.8	5.6±1.6	0.60
		Mean	6.1±1.8	6.2±1.7	0.59
Stent area, mm^2	Core's proximal	Minimum	6.6±1.8	7.0±2.2	0.27
		Mean	7.4±1.9	7.7±2.5	0.46
	Bifurcation core	Minimum	5.5±1.6	5.7±1.6	0.41
		Mean	6.5±1.9	6.9±1.8	0.26
	Core's distal	Minimum	5.3±1.8	5.6±1.6	0.42
		Mean	6.0±1.8	6.2±1.6	0.61
Stent eccentricity index	In-stent proximal		0.93±0.04	0.91±0.05	0.09
	Core's proximal		0.90±0.07	0.92±0.04	0.07
	Bifurcation core		0.87±0.07	0.85±0.08	0.14
	Core's distal		0.91±0.06	0.92±0.06	0.41
Maximum malapposed distance, mm	Core's proximal		0.27±0.21	0.26±0.37	0.87
	Bifurcation core		0.35±0.18	0.30±0.12	0.65
	Core's distal		0.34±0.18	0.22±0.15	<0.01
Malapposed area, mm^2	Core's proximal		0.35±0.43	0.44±1.27	0.62
	Bifurcation core		0.27±0.35	0.18±0.15	0.09
	Core's distal		0.25±0.21	0.23±0.26	0.67
Dissection	Stent proximal edge		7 (13.2%)	6 (11.1%)	0.74
	Stent distal edge		5 (9.4%)	5 (9.3%)	0.98

Values are expressed as n (%) or mean±SD.

Table 5. One-year clinical outcomes.

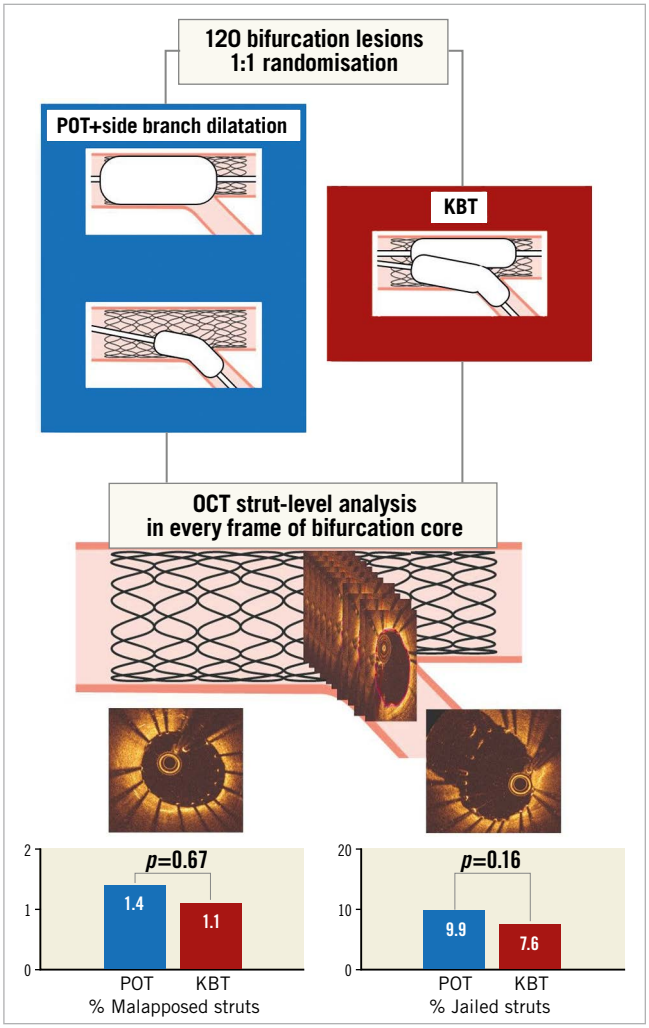
	POT (n=51)	KBT (n=52)
Death/cardiac death	0 (0.0%)	0 (0.0%)
Myocardial infarction	0 (0.0%)	1 (1.9%)
Clinically driven TLR	1 (2.0%)	1 (1.9%)
In-stent restenosis (MV)	1 (2.0%)	
Proximal edge restenosis (MV)		1 (1.9%)
TVR	1 (2.0%)	2 (3.8%)
Stent thrombosis	0 (0.0%)	0 (0.0%)

Values are expressed as n (%). MV: main vessel; TLR: target lesion revascularisation; TVR: target vessel revascularisation

revascularisation was performed for one patient (2.0%) in the POT group and two (3.8%) in the KBT group. No patient had stent thrombosis in either group.

Discussion

This is the first prospective, open-label, randomised study to investigate whether POT is superior in terms of stent apposition compared with the conventional KBT in real-life bifurcation lesions using OCT. The main findings were the following. (1) Malapposed strut rates around the bifurcation were not significantly different between the POT and KBT groups. (2) Jailed strut rates at the SB ostium before SB treatment or at final OCT did not differ between the groups. (3) No significant differences in stent area, stent eccentricity index, dissection rate, procedural time, fluoroscopic time, SB wire crossing time, and amount of contrast were observed between the groups. (4) One-year clinical outcomes were excellent in both groups.



Central illustration. *An overview of the PROPOT trial. Malapposed strut rate assessed by final OCT, the primary endpoint of this study, was 1.4% and 1.1% at the bifurcation core (p=0.67). Jailed strut rate at the bifurcation core was 9.9% and 7.6% (p=0.16) by final OCT in the POT and KBT groups, respectively. KBT: kissing balloon technique; OCT: optical coherence tomography; POT: proximal optimisation technique*

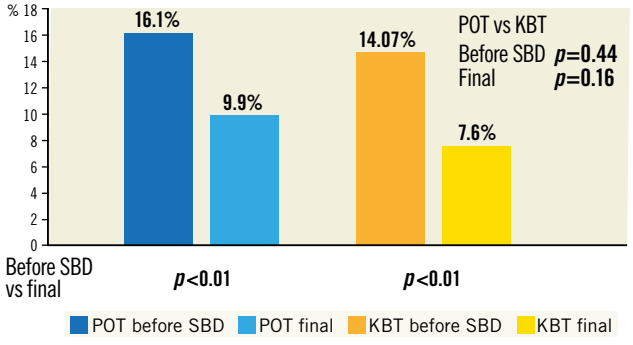


Figure 5. *Rate of jailed struts at the bifurcation core before side branch dilation and at the end of the procedure. KBT: kissing balloon technique; POT: proximal optimisation technique; SBD: side branch dilation*

Provisional stenting followed by KBT as bifurcation lesion treatment is widely used in clinical practice. Although a limited advantage regarding SB restenosis reduction has been reported[4], randomised controlled trials comparing one-stent strategies with or without KBT showed no advantage[12] or an adverse effect[13] on clinical outcomes. Hence, KBT efficacy remains controversial. In bench testing, KBT has a potential risk of ellipsoid stent deformation and MV overexpansion, leading to coronary dissection of the proximal part of the stent[3]. In previous studies, elliptical MV overexpansion resulted in more frequent MV reintervention[2,14].

POT involves dilation of a short balloon at the proximal segment of the stent for apposition to the MV before SB wiring. This enables easier wire access to the SB and reduces distortion and stent strut malapposition[5,6]. Although this technique's efficacy has been confirmed in bench testing, clinical evidence is limited[7,8]. In this study, POT and SBD did not show any advantage over conventional KBT regarding stent apposition and procedural convenience. The malapposition rate for each OCT timing, either after wire recrossing or after SB treatment, did not significantly differ between groups. Furthermore, the final stent area was similar in both groups, and no clinical benefits were gained in procedural time, SB wire crossing time, or amount of contrast.

Possible reasons for the non-superiority of POT followed by SBD over conventional KBT include the following. (1) The POT balloon might not have been correctly placed; the distal marker and balloon shoulder were not placed just at the carina. (2) Visualisation of the actual part of the carina by angiography was not correct. (3) KBT balloon size was large enough to effectively reduce malapposition at the proximal MV and bifurcation core. A previous study using bench testing suggested that appropriate POT balloon positioning is essential to avoid a carina shift[15]. Inappropriate distal location of the POT balloon risks distal MV overstretch and carina shift to the SB, while inappropriate proximal location may lead to stent malapposition and underexpansion around the carina[16] **(Figure 6)**. Nonetheless, in daily clinical practice, visualisation of the actual part of the carina by angiography is difficult due to foreshortening or vessel overlap. For suitable POT performance, intracoronary imaging is useful for accurate carina identification; however, the identification of the actual part of the carina is still a challenging issue given the anatomical complexity that cannot be fully captured even with the use of a single intracoronary imaging modality[17]. Regarding carina shift prevention, KBT is more reliable than POT followed by SBD[15]. Using adequately sized KBT balloons could also reduce malapposition at the proximal MV and bifurcation core at a level similar to that after POT. In this study, operators were likely to select a larger balloon for the MV in the KBT group because the MV balloon/artery ratio was significantly greater than the POT balloon/artery ratio (1.20±0.20 vs 1.05±0.13, p<0.01). However, they selected a relatively smaller balloon with a similar balloon/artery ratio for the SB in both groups (0.73±0.12 vs 0.72±0.11, p=0.41) **(Table 2)**. Consequently, favourable outcomes regarding rates of malapposed struts and jailed struts were observed in the KBT group.

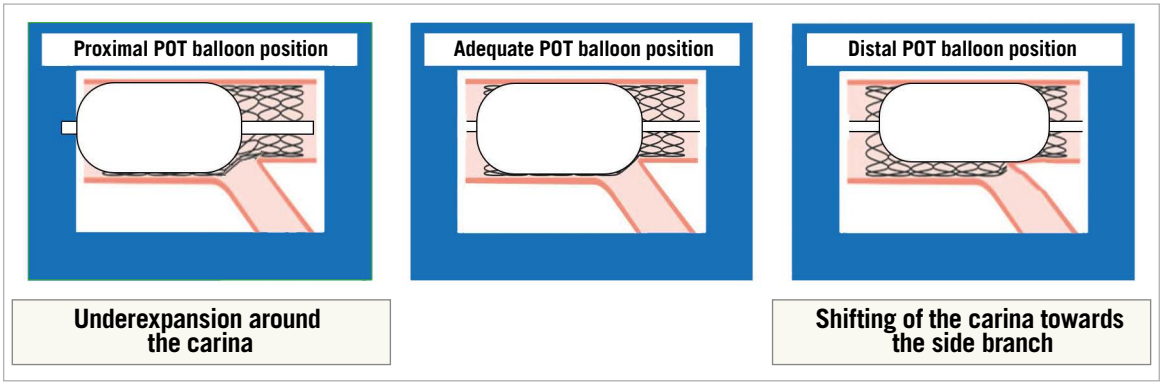


Figure 6. *Importance of POT balloon position. POT: proximal optimisation technique*

In our study, additional treatment was performed for 40.4% of the POT group, 24.6% of which underwent re-POT. The POT+SBD+re-POT sequence is generally recommended for correcting carina deviation or stent deformation induced by SBD[18]. However, it risks jailed strut re-protrusion or SB ostial area narrowing after re-POT across the SB ostium[19,20]. While POT followed by SBD seems to be a simple strategy, additional treatment is more frequently required and intravascular imaging is necessary for optimal POT balloon size selection and its positioning, and correction of SBD-induced stent deformation.

The guidewire recrossing point into the stent-jailed SB would also have affected both POT and KBT results in this study. Previous studies showed that selecting the distal recrossing point under 3D-OCT guidance was effective in achieving a better SB opening and stent apposition for link-free stent types[21,22]. Although this study did not include a protocol for the illustration of the wire recrossing point, it was adjusted under 3D-OCT guidance in several participating institutes, which might have contributed to the excellent clinical outcomes in both groups.

One-year outcomes in this study were excellent, and major adverse clinical events were observed in only 3% of patients across both groups. TLR performance had an acceptably low incidence and was limited to the MV despite routine SB treatment. Treatment of coronary bifurcation lesions using an adequately sized balloon and optimisation under OCT guidance might result in good clinical outcomes for both POT and KBT.

Limitations

This randomised study had an open-label design and included a small number of patients. Furthermore, operators and patients were aware of the technique used, potentially introducing bias and/or affecting procedural results. Clinical implications of OCT-guided surrogate imaging endpoints are unknown and limited; nonetheless, previous studies showed that stent malapposition was associated with stent failure and thrombosis[23,24]. Target lesions were mainly located in the left anterior descending artery; left main lesions accounted for only 1.7-3.5%, which may not reflect a certain benefit derived from POT in bifurcations with large vessel tapering. Although regulated in the protocol, several device-related variables (e.g., balloon size, length, pressure, and non-compliant-type), as well as procedural variables (e.g., the position of the POT and KBT balloons, and the sequence of balloon inflation for KBT) might have influenced the results. Additionally, higher protocol deviation rates in the POT group (10.4% vs 1.7% in the KBT group) might have affected results. The degree of operator skill was inherent and could have led to technical bias or affected procedural decisions. Post-PCI OCT data were obtained after the final procedure, which did not completely reflect conditions immediately after POT or KBT. The protocol recommended angio-guided device selection; however, performing OCT in every phase would affect device selection and procedural decisions, irrespective of whether additional treatment was performed or not. Additional treatment was carried out only in case of stent malapposition >400 μm from the vessel wall in any part of the stent to avoid future adverse events; however, it might significantly affect the results, and might not allow generalisability to a non-OCT-guided PCI.

Conclusions

In this randomised study, regarding treatment following crossover stenting in coronary bifurcation lesions, POT followed by SBD did not show any advantages over conventional KBT in terms of stent apposition or procedural convenience; however, excellent midterm clinical outcomes were observed in both strategies. Further trials are required to confirm the long-term clinical benefit of POT for bifurcation lesions.

Impact on daily practice

This is the first randomised study to investigate whether POT is superior in terms of stent apposition compared with the conventional KBT in bifurcation lesions using OCT. Malapposed strut and jailed strut rates around the bifurcation were not significantly different between the POT and KBT groups. One-year clinical outcomes were excellent in both strategies. Further trials are required to confirm the long-term clinical benefit of POT for bifurcation lesions.

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Conflict of interest statement

N. Suzuki has received speaker fees from Abbott Vascular, Actelion Pharmaceuticals, Astellas, Astellas-Amgen, Bayer Healthcare Pharmaceuticals, Boston Scientific, Bristol Myers Squibb, Daiichi Sankyo, Nipro, Otsuka, Sanofi and Toa Eiyo. Y. Numasawa reports personal fees and lecture fees from Abbott and Terumo, and being a consultant for Nipro. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Study protocol.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-01386

Supplementary data

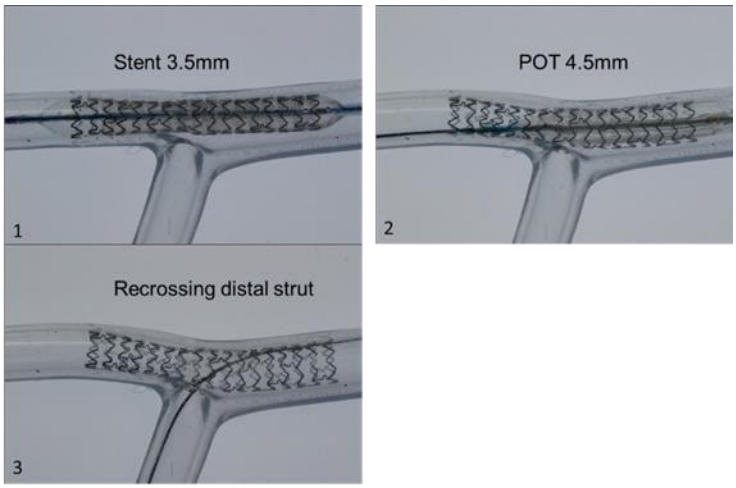
Supplementary Appendix 1. Study protocol.

Study overview.

Study Title	**PRO**spective randomized study to evaluate **P**roximal **O**ptimization **T**echnique in coronary bifurcation lesions (**PROPOT**)
Study Overview	The present study will evaluates the efficacy of the proximal optimization technique (POT) in coronary bifurcation lesions
Study Design	Multi-center, prospective, randomized, open-label, comparative study
Study Phase	Phase Ⅳ
Investigational Device	Zotarolimus-eluting stent（ZES）: Resolute integrity™ （Zotarolimus-eluting stent : Medtronic）
Inclusion Criteria	Patients who meet all of the following criteria. ①Bifurcation lesions with a collateral of ≧2.0 mm that can be identified by CAG ②Lesions with ≧75% stenosis in main vessel that is side branch within about 5mm ③Bifurcation lesions that can be treated by provisional side branch stenting ④Lesion length ≦ 38mm and it is target lesions that doesn't have remote lesions in the same vessel. ⑤Lesions in which stenting is feasible ⑥The visually estimated reference diameter of the main vessel is≧2.5 mm ⑦If two or more bifurcation lesions are found in the reference lesion, the proximal lesion will be studied.
Exclusion criteria	Patients who meet either of the following criteria should NOT be enrolled into the study. ①Contraindications to antiplatelet drugs/anticoagulant drugs ②Significant allergic reactions for contrast agents ③EF<30% ④Graft lesions ⑤In-stent restenotic lesions ⑥Chronic total occlusion ⑦Lesion length ≧38mm ⑧Lesions of high-lime that impossible to extend completely Based on the Provisional stenting, the following cases should be exclusion and considered to be used "Planned 2-stent" ⑨Side brunch ≧5mm than ostium and ≦TIMI Ⅱ or whole lesion 99%

	stenosis ⑩ Expect to fail that serious hemodynamics cause by SB occlusion ⑪ Expect the high risk to be side brunch occlusion by the operator
Endpoints	Primary Endpoint The primary endpoint is the rate of malapposed stent struts after procedure OCT.(efficacy primary endpoints) Analysis object are the ITT that are patients has been attempted stent placement with the index procedure. Secondary Endpoint 1)Finding from OCT · Stent Area (mm^2), Lumen Area (mm^2) · Stent Eccentricity Index (SEI) = Minimum Stent Diameter / Maximum Stent Diameter · Degree of malapposition (highest distance between strut and wall) · Malaposition area（mm^2） · Frequency of Jailed Strut at Bifurcation Segment · Dissect or not dissect Stent proximal edge · Treat or not treat additional treatment after Final OCT in this protocol. · Procedure time · Fluoroscopy time · Amount of contrast media · The time to exchange side branch wire Definition: In the case of using new GW for recross, the transit time is through between the point of GC edge and SB distal. If reuse the GW for the main vessel, the time starts at the starting point of pull back. If a crusade is used, the time is designated GC edge as one's starting point. 2) Clinical follow-up · Death / MI at 1 year · Death at 30 days, 1 year · Cardiac death at 30 days, 1 year · MI at 30 days, 1 year · ST at 30 days, 1 year (ARC definition) · Stroke at 30 days, 1 year · Clinically-driven TLR at 30 days and 1year · CABG at 1 year · TVR at 1 year

	・Revascularization at 1 year 3) Angiography Assessment Core Lab examine QCA for the stent struts that are placed by index procedure before operation, after operation and 9month later. ・MLD, RVD and %DS before operation, after operation and 9month later. ・Analyze QCA/OCT for all patients before and after index procedure
Study Method	1)Study type and design This is a multi-center, prospective, randomized, open-label, comparative study to investigate the efficacy of the POT technique with the DES, ZES (Resolute Integrity™). Patients with bifurcation lesions who are eligible for DES treatment will be enrolled in the study. 2) Outline Patients with bifurcation lesions who are scheduled to undergo PCI with DES will randomly be assigned to the POT technique group and the non-POT technique group at 1:1 ratio on the Web database before PCI. They will undergo PCI by the assigned technique. At the point of Informed Consent and intended to treat using stent (implanted the stent) recognized patient enrolled into the study. Method of randomization: After obtaining the informed consent from the patient who is satisfied the registration conditions, enter the following data into Web database. 1. Sex (male or female), 2. Age. Then displayed POT or Non-POT, and perform procedure according to the allocation. Due to unavoidable circumstances, it was not able to perform with the indicated allocation, record to the eCRF ①Method of POT Group ・Perform the treatment based on angiography guide. ・Place the stent in the main vessel with the reference diameter (QCA or visual) of distal.（Figure 1） ・Perform the POT. Extent and crimp the stent with the balloon of the reference diameter of proximal (balloon artery ratio 1.0). POT needs to reach the balloon distal marker to the carina and crimp proximal of the stent. The wire for the side branch must be remained in jail.（Figure 2） ・POT balloon will be used Non-compliant balloon. The level of extended pressure will be decided by the operator. ・Exchange the wire of the bifurcation. Preferably aim the strut of distal. To

	use a crusade or new wire will be decided by the operator.（Figure 3） ・Perform the side branch treatment. Use preferably short size Non-compliant balloon (6mm – 8mm) or the glider balloon (4mm) with reference diameter of the side branch. ・The size of balloon for the Side branch treatment will be balloon artery ratio 0.8-1.0 but the operator can decided. The level of extended pressure will be decided by the operator.  ②Method of non-POT Group ・Perform the treatment based on angiography guide. ・Place the stent in the main vessel with the reference diameter (QCA or visual) of distal Not operate the same procedures as POT pulling the balloon to proximal and crimp after the stenting ・Exchange the wire of the bifurcation. Preferably aim the strut of distal. To use a crusade or new wire will be decided by the operator. ・Perform the KBD. On the size of KBD balloon, the balloon for the main vessel must be matched the reference diameter of bifurcation distal. The balloon for the side branch must be matched the reference diameter of side branch. ・The size of balloon for the KBD will be balloon artery ratio 0.8-1.0 but the operator can decided. The level of extended pressure and size will be decided by the operator. ・KBD must be aligned and not protruded along with the proximal edge. ③Method of OCT Observation For both group, observe and compere the stent implanted by the optical coherence tomography（OCT）. The timing of the OCT, 2 times at the baseline for main vessel and side branch, for the main vessel 1 time after

	the exchange the wire, and after the operation, 2 times for the main vessel and side branch. It hopefully observes 5 times in total but assuming difficult to take the baseline OCT depending on the lesions and procedure. In this case, for both group, the timing of the OTC may 3 times in total, at the exchange the wire for the main vessel, and 2 times after the operation for the main vessel and side branch. If possible follow up OCT after 9 months.(Main or side branch)
Sample size	Sample size: 120 subjects (POT group 60 subjects, Non POT group 60 subjects)
Study Period	Study period: After Ethics committee approval ~ 1year from Last patient in Subjects enrollment period: After Ethics committee approval ~ 1year
Ethics	The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH.
Ethics Committee	Prior to the implementation of the study, the ethical committee reviews the ethical, scientific and medical validity of the study. The study is carried out after obtaining the approval of the ethics committee. If the ethics committee of deliberation result is "to approve on the modification", protocol, case report form and informed consent form are modified based on the deliberation results, and after the modifications were made carry out the study. Actual date of start, study status (number of cases), ethical considerations, occurrence of disadvantages, adverse events, research results and the interim report will be reported once a year, also at the end of the study, the final report is submitted to the committee.

LIST OF ABBREVIATIONS (GENERAL EXAMPLE)

Abbreviation	Explanation
%DS	Percent Diameter Stenosis
ACC	American College of Cardiology
AHA	American Heart Association
CABG	Coronary Artery Bypass Graft
CEC	Clinical Event Committee
CFR	Coronary Flow Reserve
ECG	Electrocardiogram
FFR	Fractional Flow Reserve
GPSP	Good Post-marketing Study Practice
KBD	Kissing balloon dilatation
MLD	Minimum Luminal Diameter
OCT	Optical coherence tomography
PCI	Percutaneous Coronary Intervention
POT	Proximal optimization technique
QCA	Quantitative Coronary Angiography
RVD	Reference Vessel Diameter
TLR	Ischemia-driven Target Lesion Revascularization
TVF	Ischemia-driven Target Vessel Failure
TVR	Ischemia-driven Target Vessel Revascularization

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1 INTRODUCTION

1.1 Background and Rationale

Percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) is established as revascularization technique for patients with coronary artery disease.

However, treating bifurcation lesions, which account for 15% to 20% of coronary artery lesions, is not simple and needs to be planned carefully both in a technical manner and as a therapeutic strategy, because they may require retreatment or may cause thrombosis. Historically, the 2-stent strategy involving two stents of which one is placed in the side branch of the bifurcation lesion showed no additional efficacy compared to the 1-stent strategy in which a stent is only placed in the main vessel (1-6).

Technically, the efficacy of kissing balloon dilatation (KBD), in which the main vessel and side branch of the bifurcation lesion are eventually dilated simultaneously after stenting as a therapeutic strategy for bifurcation lesions, has widely been demonstrated in daily clinical practice. The efficacy and safety of the 1-stent strategy with DES + KBD was shown in the Japanese Singlekiss trial (7). However, no particular difference was observed between the results of the 1-stent strategy with KBD and without KBD in the recently published NORDIC-III trial, and the efficacy of KBD itself remains controversial (8,9).

Proximal optimization technique (POT) is one of the therapeutic strategy that has been suggested in recent years for bifurcation lesions and is a technique involving dilation of a balloon at the proximal stent for apposition to the vessel before exchanging the side branch wire and performing KBD after stenting in the main vessel over the bifurcation.

This enables easier access of the wire to the side branch and decreases distortion and malapposition of the stent struts. (10,11). This technique efficacy is confirmed with bench test but clinical evidence is poor.

A Zotarolimus-eluting stent (ZES) Resolute Integrity^{TM}, a second-generation DES that is generally used worldwide, has a 2-link structure, is good at accessing the bifurcation, and shows efficacy and safety in bifurcation lesions. Under these circumstances, we planned a multi-center, prospective, randomized, open-label, comparative study with ZES, a DES that is now widely used worldwide, to investigate the efficacy of the POT technique.

2 OBJECTIVE AND ENDPOINT

This is a multi-center, prospective, randomized, open-label, comparative study to

investigate the efficacy of the POT technique with the DES, ZES (Resolute IntegrityTM).

2.1 Endpoints

2.1.1 Primary Endpoint

The primary endpoint is the rate of malapposed stent struts after procedure OCT.
(efficacy primary endpoints)

Analysis object are the ITT that are patients has been attempted stent placement with the index procedure.

2.1.2 Secondary Endpoint

2.1.2.1 Clinical Assessments

1)Finding from OCT

・Stent Area (mm^2), Lumen Area (mm^2)

・Stent Eccentricity Index (SEI) = Minimum Stent Diameter / Maximum Stent Diameter

・Degree of malapposition (highest distance between strut and wall)

・Malaposition area（mm^2）

・Frequency of Jailed Strut at Bifurcation Segment

・Dissect or not dissect Stent proximal edge

・Treat or not treat additional treatment after Final OCT in this protocol

・Procedure time

・Fluoroscopy time

・Amount of contrast media

・The time to exchange side branch wire

Definition: In the case of using new GW for recross, the transit time is through between the point of GC edge and SB distal. If reuse the GW for the main vessel, the time starts at the starting point of pull back. If a crusade is used, the time is designated GC edge as one's starting point.2) Clinical follow-up

・Death / MI at 1 year

・Death at 30 days, 1 year

・Cardiac death at 30 days, 1 year

・MI at 30 days, 1 year

・ST at 30 days, 1 year (ARC definition)

・Stroke at 30 days, 1 year

・Clinically-driven TLR at 30 days and 1year

・CABG at 1 year

・TVR at 1 year

・Revascularization at 1 year

2.1.2.2 Angiography Assessment

Core Lab examine QCA for the stent struts that are placed by index procedure before operation, after operation and 9month later.

・MLD, RVD and %DS before operation, after operation and 9month later.

・Analyze QCA/OCT for all patients before and after index procedure

3 STUDY DESIGN

Multi-center, prospective, randomized, open-label, comparative study

3.1 Study type and design

This is a multi-center, prospective, randomized, open-label, comparative study to investigate the efficacy of the POT technique with the DES, ZES (Resolute Integrity^{TM}).

Patients with bifurcation lesions who are eligible for DES treatment will be enrolled in the study.

3.2 Outline

Patients with bifurcation lesions who are scheduled to undergo PCI with DES will randomly be assigned to the POT technique group and the non-POT technique group at a 1:1 ratio on the Web database before PCI. They will undergo PCI by the assigned technique.

3.2.1 Method of POT Group

・Perform the treatment based on angiography guide

・Place the stent in the main vessel with the reference diameter (QCA or visual) of distal

（Figure 1）

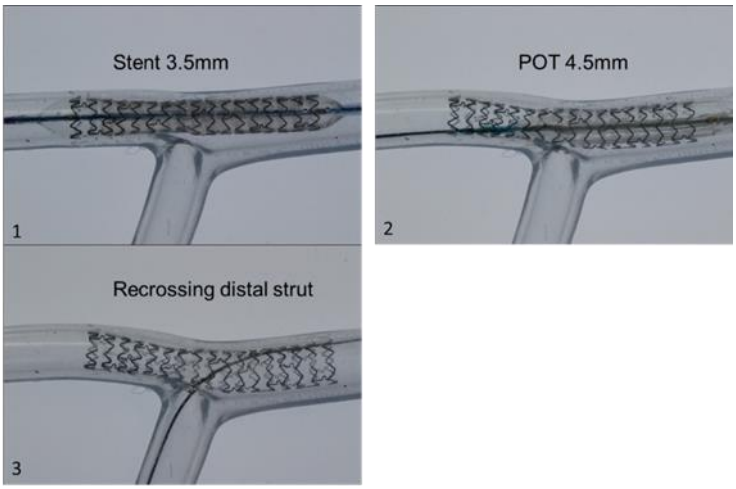
・Perform the POT. Extent and crimp the stent with the balloon of the reference diameter of proximal (balloon artery ratio 1.0). POT needs to reach the balloon distal marker to the carina and crimp proximal of the stent. The wire for the side branch must be remained in jail.（Figure 2）

・POT balloon will be used Non-compliant balloon. The level of extended pressure will be decided by the operator.

・Exchange the wire of the bifurcation. Preferably aim the strut of distal. To use a crusade or new wire will be decided by the operator.（Figure 3）

・Perform the side branch treatment. Use preferably short size Non-compliant balloon (6mm – 8mm) or the glider balloon (4mm) with reference diameter of the side branch.

・The size of balloon for the Side branch treatment will be balloon artery ratio 0.8-1.0 but the operator can decided. The level of extended pressure will be decided by the operator.



3.2.2 Method of non POT Group

・Perform the treatment based on angiography guide.

・Place the stent in the main vessel with the reference diameter (QCA or visual) of distal Not operate the same procedures as POT pulling the balloon to proximal and crimp after the stenting.

・Exchange the wire of the bifurcation. Preferably aim the strut of distal. To use a crusade or new wire will be decided by the operator.

・Perform the KBD. On the size of KBD balloon, the balloon for the main vessel must be matched the reference diameter of bifurcation distal. The balloon for the side branch must be matched the reference diameter of side branch. The size of balloon for the KBD will be balloon artery ratio 0.8-1.0 but the operator can decided. The level of extended pressure and size will be decided by the operator.

・KBD must be aligned and not protruded along with the proximal edge.

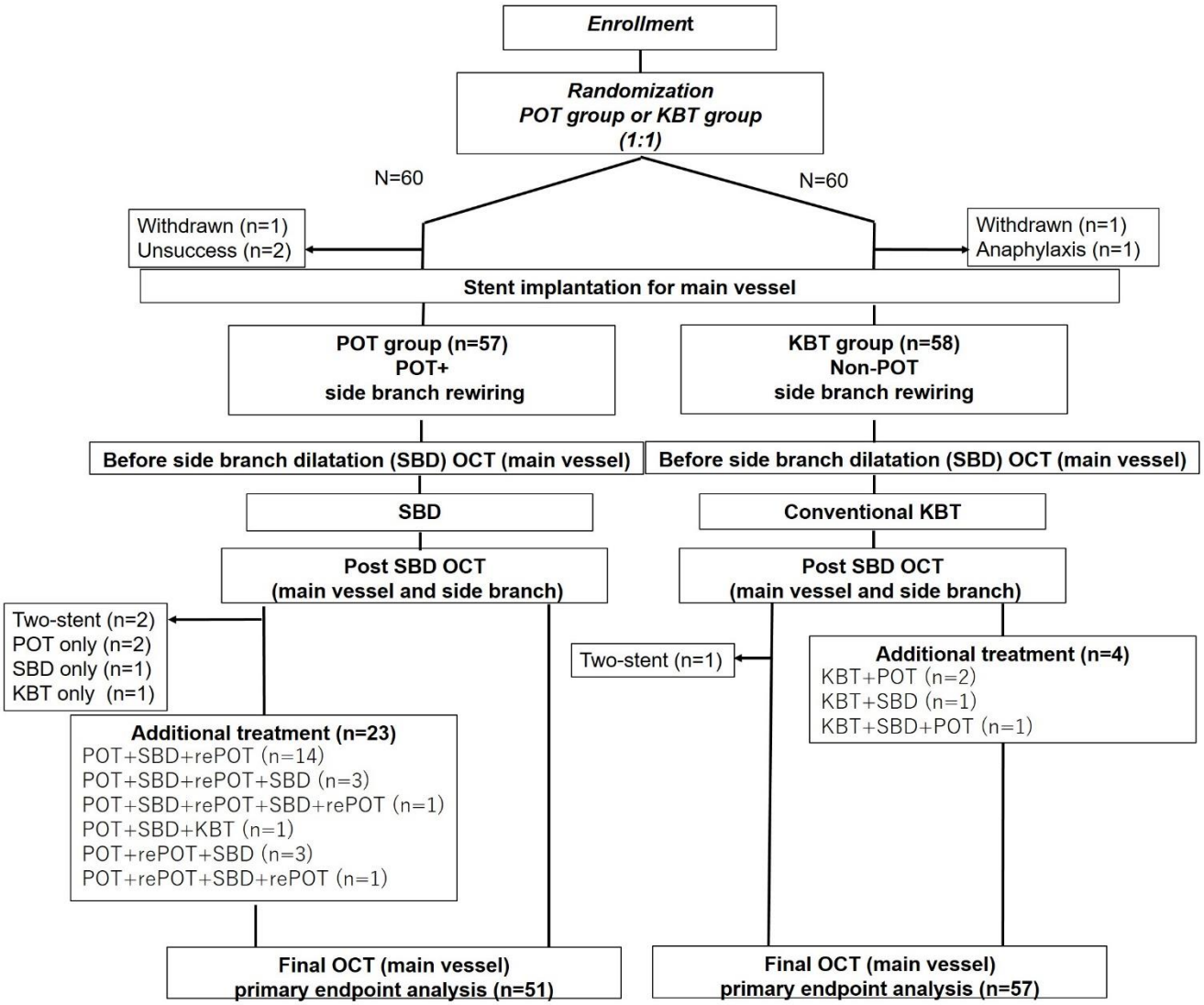
3.2.3 Method of OCT Observation

For both group, observe and compere the stent implanted by the optical coherence

tomography（OCT）. The timing of the OCT, 2 times at the baseline for main vessel and side branch, for the main vessel 1 time after the exchange the wire, and after the operation, 2 times for the main vessel and side branch. It hopefully observes 5 times in total but assuming difficult to take the baseline OCT depending on the lesions and procedure. In this case, for both group, the timing of the OTC may 3 times in total, at the exchange the wire for the main vessel, and 2 times after the operation for the main vessel and side branch.

If possible follow up OCT after 9 months.(Main or side branch）

3.3 Study Method



4 ANALYSIS

4.1 Angiographic Analysis

4.1.1 Overview

1. The 9-month (Day 241-365) follow-up angiography is mandatory.
2. Primary endpoint
   ・In-segment late loss
3. Secondary endpoints

・In-stent late loss
・%DS
・Binary restenosis (In-stent, In-segment, Peri-stent) and restenosis site/pattern
・MLD
・Angiographic stent fracture (according to Popma classification)

4.1.2 QCA Analysis

1. On the day of the procedure and at 9 months post-procedure, QCA analysis will be performed in all subjects at the independent core laboratory (Cardiocore Japan).
2. If coronary angiography is performed before 9 months post-procedure due to recurrent ischemia, etc., it will be considered as the follow-up angiography.
   Necessary information for analysis (catheter size and target lesion) should be entered in the technician worksheet. It is especially important to specify the size of the catheter used for angiography during the procedure and at 9 months post-procedure.

4.1.2.1 Caution for Coronary Angiography

When coronary angiography is performed at each medical institution, attention should be paid to the following points, and the necessary information should be entered in the appropriate sections of the technician worksheet.

・Angiograms should be taken in two directions from which, at least, the lesion is clearly visible and not shortened. These two directions should be at least 30° apart from each other.
・Angiograms during the procedure and at 9 months post-procedure should be taken in the same directions. Therefore we record an angle, SID, scan stand high projection at preoperative scan and set it in the same condition. Nitrates should be administered before angiography.
・The size of the catheter used, treated lesion, and the number of stents implanted should be recorded. (The size of the catheter to be used for the follow-up angiography should be 5Fr or more to ensure precision of the analysis.)
・Perioperative stenting and balloon dilation should be all recorded as cine images.
・Postoperative angiography should be performed after removing the guidewire.
・Angiograms should be taken at a rate of 15 frames/second or more.
・During imaging, the catheter tip should be placed inside the frame.
・The DICOM format is used to record angiography.
・It is preferable to record angiography with DICOM files only, without using viewer software, if a setting of not burning the viewer software together is possible.

4.1.2.2 About QCA

A computer-automated contour detection system CAAS II (Pie Medical Ver. 5) will be used for QCA. The catheter tip will be used for calibration. The minimum lumen diameter (MLD), reference diameter, %DS, and lesion length will be determined. The acute gain can be obtained by comparing preoperative and postoperative MLDs. The late loss can be obtained by comparing postoperative and follow-up MLDs. The use of the DES program will enable evaluations of the stent alone (in-stent), only 5 mm from stent edges (Proximal edge & Distal edge), and their combination (in-lesion).

Restenosis at the follow-up QCA is defined as %DS >50%; %DS >70% should be included in clinically driven TLR even without symptoms or ischemic findings on ECG, etc.

4.1.2.3 Qualitative Evaluation

The following qualitative evaluation will be performed on preoperative lesion morphology:

- Lesion length: discrete, tubular, diffuse
- Thrombus: No, Yes
- Haziness: No, Yes
- Concentricity: Concentric, Eccentric
- Regularity: Smooth, irregular
- Bend: <45°, 45° to <90°, ≧90°
- Calcification: None/Mild, Moderate, Severe
- Ulceration: No, Yes
- Tortuosity; None, Moderate, Severe
- Ostial: No, Yes
- Bifurcation: No, double GW, unprotected
- Total Occlusion: No, Yes (<3 months, ≧3 months)
- Aneurysm: No, Yes
- Degenerative SVG: No, Yes
- American College of Cardiology (ACC)/AHA Classification: A, B1, B2, C
- TIMI flow grade: 0, 1, 2, 3

The following qualitative evaluation will be performed on postoperative lesion morphology:

- TIMI flow grade: 0, 1, 2, 3
- Thrombus: No, Yes
- Aneurysm: No, Yes
- Distal embolization: No, Yes

The following qualitative evaluation will be performed on lesion morphology during the follow-up angiography:

- TIMI flow grade: 0, 1, 2, 3
- Thrombus: No, Yes
- Aneurysm: No, Yes
- Restenosis pattern: focal, diffuse, proliferative, occlusion
- Stent fracture: No, Yes
- Peri-stent staining: No, Yes

4.2 OCT

4.2.1 Overview

OCT will be performed five times in total; preoperative twice of truncus and the collateral, once of truncus both POT enforcement group and non-enforcement group after wire recross, twice of truncus and the collateral at the procedure end. It is advisable to analyze it for five times, but when it is difficult for the symptoms of the lesion, it is not essential. OCT will be performed for nine months after post-procedure if possible.

- Primary endpoint
  Percentage of stent strut coverage (%)
- Secondary endpoints
  - Stent Area(mm^2)　Lumen Area(mm^2)
  - Stent Eccentricity Index(SEI)=Minimum Stent Diameter/Maximum Stent Diameter
  - Degree of malapposition (highest distance between strut and wall)
  - Malapposition area(mm^2)
  - Frequency of Jailed Strut at Bifurcation Segment

4.2.2　OCT Analysis

- On the day of the procedure (9 months past procedure), OCT analysis will be performed at the independent core laboratory.
- OCT analysis will be performed before the procedure (before stenting; as far as possible. truncus or the collateral), during the procedure (both POT enforcement group and non-enforcement group after exchanging a wire, truncus)), after the procedure (final imaging after stenting truncus or the collateral), and at 9 months post-procedure, when possible. If an event such as recurrent ischemia occurs and PCI is considered necessary within 9 months post-procedure, OCT should be performed before and after treatment as far as possible. However, OCT may be skipped depending on the subject’s condition.

・Necessary information for analysis, especially the size and length of the stent used, should be entered in the technician worksheet.

4.2.3 Caution for OCT

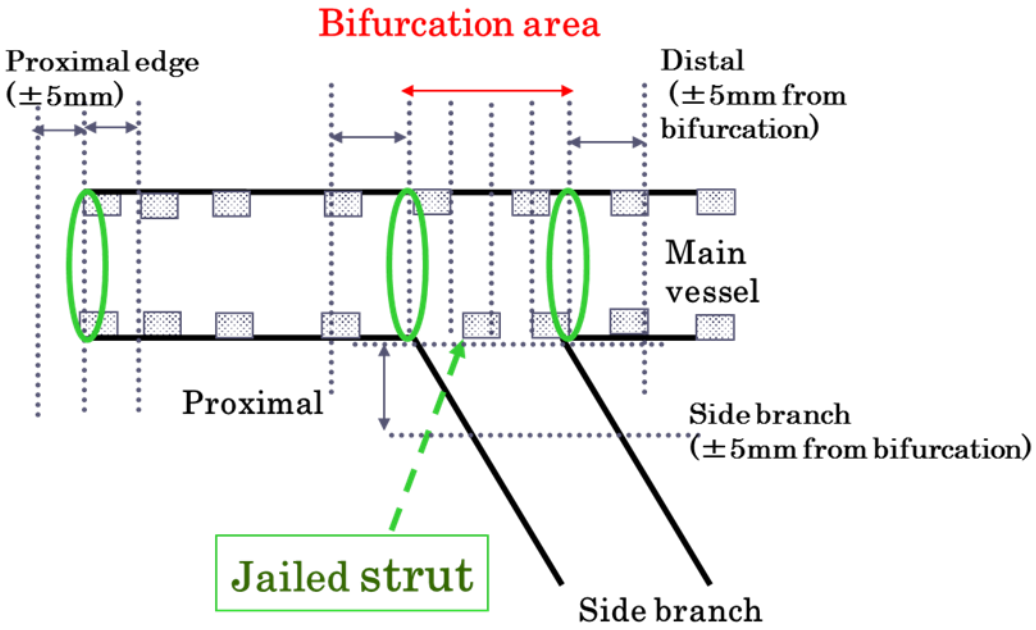
When OCT is performed at each medical institution, attention should be paid to the following points, and the necessary information should be entered in the appropriate sections of the technician worksheet.

- It is desirable to use OTC of SJM but It is assumed that it is possible in OFDI
- OCT imaging should be performed before and after the stenting procedure and at 9 months post-procedure using the same devices and the same imaging conditions. For imaging data, raw data should be recorded on CD-R.
- Treated lesions should be recorded at a rate of 0.5 mm/sec with an automated pull-back device. File names should be created to save the imaging data. File names should be created for each lesion, and an OCT Data Form should be prepared in a manner that the recording times and sites of lesions (Seg#) are clarified.
- OCT should be performed at the final stage after all procedures involved in PCI have been completed. If ballooning and stenting are performed during the follow-up at 9 months post-procedure, OCT should be performed before these procedures.
- OCT should be performed after sufficient vasodilation with vasodilators such as nitrates.
- Truncus pull-back from at least 5 mm distal to 5 mm proximal to the edge should be recorded.
- Collateral pull-back from at least 5 mm distal to 5 mm proximal to the edge target lesion should be recorded.
- Flash method of the contrast media is desirable for red blood cell removal method from a target lesion. If you are concerned about renal impairment from the contrast media which passes to several times, we can use lactated Ringer's solution or low molecular weight dextran (mixture of Ringer’s lactate and Dextran 40)
- Cine images should be taken before the start of each OCT session in a manner that the pull-back starting position is clarified.

4.2.4 About OCT Analysis (Cf. figure)

- OCT analysis will be performed with reference to the stent length provided in the technician worksheet.
- Proximal conducts qualitative fixed-quantity analysis to 5 mm in cross section every 15 frames from bifurcation of the truncus

・ We conduct 1 mm of cross section analysis in around 5 mm, the section of 10 mm in total from Proximal edge



4.2.5 Qualitative Evaluation

The following qualitative evaluation will be performed:

1. Dissection (proximal edge)
2. Incomplete stent apposition
3. Tissue protrusion

4.2.6 Quantitative Evaluation

The following quantitative evaluation will be performed:

From bifurcation of the truncus the proximal part in cross section every 15 frames

- The stent maximal inside diameter, the smallest inside diameter, asymmtrucal index
- The number of the depicted struts
- Well apposition, icomeplete apposition number
- Malapposition area(mm2)

  cross section in all bifurcation area
- The number of the depicted struts, jailed strut number, non-jailed(wall)strut number
- Well apposition, incomplete apposition number (only wall)
- Malapposition area(mm2) (only wall)

5 DEFINITIONS OF ENDPOINTS

5.1 Death

The definition of death is based on classification by the Academic Research Consortium (ARC).

- **Cardiac death**

  All Death due to cardiac cause (e.g., myocardial infarction, low-output cardiac failure, fatal arrhythmia), unwitnessed death, death of unknown cause, and all procedure-related deaths (including those related to concomitant treatment) .will be classified as cardiac death. All deaths are considered cardiac unless an unequivocal noncardiac cause can be established; specifically, any unexpected death, even in patients with coexisting potentially fatal noncardiac disease (e.g., cancer), should be classified as cardiac.

- **Vascular death**

  Death caused by non-coronary vascular causes, such as cerebrovascular disorder, pulmonary embolism, aortic aneurysm rupture, dissecting aneurysm, or other vascular diseases.

- **Non-cardiovascular death**

  Death not covered by the above definitions, such as death caused by infection, malignant tumor, sepsis, lung disease, accident, suicide, or trauma.

5.2 Myocardial Infarction (MI)

The definition of MI is based on ARC classification. Periprocedural MI will be evaluated with CKMB because the evaluation with troponin is too sensitive.

- **Assessment of preprocedural MI**

  ST elevation, new pathologic Q waves, MI-specific clinical symptoms, troponin or CK-MB above the reference value by ECG

- **Periprocedural MI**

  - Any of the following within 48 hours after PCI procedure:
    - CK-MB **≥3 times the reference value** (A pre-procedure cardiac enzyme level equal to or above the reference value is not considered a new MI but baseline MI.)
    - Abnormal ECG (new Q wave, left bundle branch block)
    - Troponin or CK-MB **≥5 times the reference value** within 72 hours of the CABG procedure, along with any of the following (A pre-procedure cardiac

enzyme level equal to or above the reference value is not considered a new MI but baseline MI.):

- ・Abnormal ECG (new Q wave, left bundle branch block)
- ・Self-coronary artery or new coronary vessel occlusion of graft
- ・Decrease viable myocardium by diagnostic imaging

・**Spontaneous MI**

・Any of the following after 48 hours of the PCI procedure or 72 hours of the CABG procedure is assessed as MI. The definition of periprocedural MI is applied to MI caused by revascularization procedures such as TLR and TVR:

- ・Abnormal ECG (new Q wave, left bundle branch block)
- ・Troponin or CK-MB **≥ the reference value** (A pre-procedure cardiac enzyme level equal to or above the reference value is not considered a new MI but baseline MI.):

・**Sudden death**

・For death before biomarkers are obtained or before they are expected to be increased, assessment of MI is based on the following:

- ・Clinical symptoms suggestive of ischemia and any of the following:
  - ・New ST elevation or left bundle branch block
  - ・Documented thrombus by angiography or autopsy

・**Reinfarction**

・After the occurrence of myocardial infarction, stable or decreasing values on two samples and ≥20% increase at 3 to 6 hours after the second sample:

- ・If an increase in biomarkers or the peak is not reached, data are insufficient to diagnose recurrent MI.

・**Assessment on ECG**

- ・**Q wave MI (QMI)**
  - ・Pathological Q waves in at least two contiguous leads, with or without increases in cardiac biomarkers
- ・**Non-Q wave MI (NQMI)**
  - ・Any MI other than Q-wave MI

・**Assessment based on the ST segment**

- ・**ST elevation myocardial infarction (STEMI)**
  - ・New or apparently new ST elevation at the J point in at least two contiguous leads. The cutoff points are ≥0.2mV for leads V1, V2 and V3 and ≥0.1mV for the others.
- ・**Non-ST elevation myocardial infarction (NSTEMI)**

  Any other MI than STEMI

5.3 Revascularization

Classification:

·Target lesion revascularization (TLR)

PCI for the target lesion (including the segment 5 mm proximal and distal to the stent) or CABG for restenosis or other complication of the target lesion

·Target vessel revascularization (TVR)

Revascularlization for the target vessel by PCI or CABG. TVR include TLR.

·Target vessel revascularization-remote (TVR-Remote)

Revascularlization for the non-target lesion in the target vessel

·Non-target vessel revascularization (Non-TVR)

Revascularlization for the non-target vessel

·Non-target lesion revascularization (Non-TLR)

Revascularlization for the non-target lesion

Non-TLR = TVR-Remote + Non-TVR

Clinically indicated revascularization:

·Revascularization procedure is considered clinically indicated if one of the following occurs. The presence/absence of a clinical indication is assessed by the person in charge of the procedure before revascularization.

- ·Recurrence of angina pectoris that presumably related to the target vessel
- ·The ischemia that presumably related to the target vessel when while resting or the exercise test.
- ·Functional ischemia by the invasive clinical examination (e.g., Doppler flow velocity reserve [FVR], fractional flow reserve [FFR])
- ·≥70% stenosis of the diameter, even in the absence of the above-mentioned ischemic signs or symptoms (TLR and TVR are assessed based on quantitative analysis at the angiographic core laboratory.)

5.4 Stent Thrombosis

Based on the ARC definition, stent thrombosis is classified into definite, probable and possible thrombosis according to its “probability”. It’s also classified into acute, subacute, late and very late thrombosis according to the time when it developed.

·Definite stent thrombosis

- ·Finding stent thrombosis by Angiographic:

・Finding thrombosis from the segment that was stented(including the segment 5 mm proximal and distal to the stent) by angiographic and finding any of the following criteria within 48-hours.
  ・Acute ischemia when while rest
  ・New ECG changes that is assessed acute ischemia
  ・Typical increase and decrease in cardiac enzyme levels (Refer to the definition of spontaneous MI.)
  ・Non-occlusive thrombus
・Intracoronary thrombus is defined as a non-calcified filling defect (spheric, ovoid, or irregular) or lucency surrounded by contrast agent (on three sides or within stenosis of a coronary artery) seen in multiple projections, or persistence of contrast material within the lumen, or visible embolization.
  ・Occlusive thrombus
  ・TIMI 0 or TIMI 1 in the stent or proximal to the stent up to the closest proximal side branch or main branch
・Finding recent thrombosis by Pathological confirmation:
  ・Finding recent thrombus by autopsy or thrombectomy

・**Probable stent thrombosis**
  ・Any of the following after stenting:
    ・Unexplained death within 30 days after stenting
    ・Myocardial infarction that around stent segment doesn't have the evidence from angiographic or other responsible lesions in spite of days after the procedure.

・**Possible stent thrombosis**
  ・Unexplained death more than 30 days after stenting
    ・When clinical finding is not considered, it's not stent thrombosis even if the obstruction is assessed. (Silent occlusion).
    ・Intracoronary thrombus

・**Acute stent thrombosis**

0 to 24 hours after the procedure (Time 0 is defined as the time point immediately after the guide catheter has been removed.)

・**Subacute stent thrombosis**

24 hours to 30 days after the procedure

・**Late stent thrombosis***

31 days to 1 year after the procedure

・**Very Late Stent Thrombosis***

After 1 year

* Not only primary stent thrombosis but also include secondary stent thrombosis that cause by the revascularization of around stent segment.

5.5 Definition of Other Endpoints

- **Procedural success**
  - When the stenting for main vessel succeed, indicated the TIMI3 Flow and the Remaining degree of stenosis <30% by visual examination.
  - Indicated the TIMI3 Flow and nothing the ischemia that cause by the stricture
  - When need to bailout that it is not recognized the procedural success.
  - When need to add stent(s) for proximal in the main vessel cause by the dissociation and so on, it's not success.

5.6 Stroke or Cerebrovascular Accident

Neurologic disorder that develops rapidly, persists for at least 24 hours, and is caused by the disruption of cerebrovascular blood flow by hemorrhage or ischemia

Those in which symptoms disappear within 24 hours are transient brain disorder and do not correspond to stroke or cerebrovascular accident.

5.7 Classification of Angina Pectoris

- **Braunwald Classification of Unstable Angina**
  - **Class I:** New onset severe or accelerated angina. Patients with new onset (<2 months in duration) exertional angina pectoris that is severe or frequent (>3 episodes/day) or patients with chronic stable angina who develop accelerated angina (i.e., angina that is more frequent, more severe, longer in duration, or precipitated by less exertion than previous) but who have not experienced pain at rest during the preceding 2 months.
  - **Class II:** Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.
  - **Class III:** Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

- **Canadian Cardiovascular Society (CCS)**
  - **Class I:** Ordinary physical activities, such as walking and climbing stairs, do not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
  - **Class II:** Slight limitation of ordinary activities. Pain is induced with walking or climbing stairs rapidly, walking uphill, or walking or climbing stairs after meals, in the cold, under windy conditions, under emotional stress, or during few hours after awakening. Angina occurs

with walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and under normal conditions.

・**Class III:** Marked limitation of ordinary physical activities. Angina occurs with walking one or two blocks on the level or climbing one flight of stairs at a normal pace.

・**Class IV:** Inability to perform any physical activities without discomfort. Angina symptoms may be present while resting.

6 SAMPLE SIZE AND STUDY PERIOD

Sample size: 120 subjects (POT group 60 subjects, Non POT group 60 subjects)

【Rationale for values】

Primary endpoint is the malapposition percentage of stent struts.

According to the report by Foin N et. al., the malapposition percentage of stent struts after KBD was 35%. The malapposition percentage of stent struts that after KBD and additional dilation was 10%.

It's not exist that is similar to this study. So calculated like below, according to the report by Foin N et. Al.

Malapposition in POT group: 10%

Malapposition in Non POT group: 35%

Alpha= 0.05, Beta= 0.8

51 patients per group with 20% of suboptimal imaging

Each group 60 subjects. Total 120 subjects.

Study period: After Ethics committee approval ~ 1year from Last patient in

Subjects enrollment period: After Ethics committee approval ~ 1year

Study will end when target number of subjects were achieved.

7 INCLUSION CRITERIA AND ENROLLMENT

Patients that fulfills the following inclusion criteria and not applicable with the following exclusion criteria are eligible.

7.1 Inclusion Criteria

1) Bifurcation lesions with a collateral of ≧2.0 mm that can be identified by CAG
2) Lesions with ≧75% stenosis in main vessel that is side branch within about 5mm
3) Bifurcation lesions that can be treated by provisional side branch stenting
4) Lesion length ≦38mm and it is target lesions that doesn't have remote lesions in the same vessel.

5) Lesions in which stenting is feasible; the visually estimated reference diameter of the main vessel is ≧2.5 mm; if two or more bifurcation lesions are found in the reference lesion, the proximal lesion will be studied.

7.2 Exclusion Criteria

1) Contraindications to antiplatelet drugs/anticoagulant drugs
2) Significant allergic reactions for contrast agents
3) EF <30%
4) Graft lesions
5) In-stent restenotic lesions
6) Chronic total occlusion
7) Lesion length ≧38mm
8) Lesions of high-lime that impossible to extend completely
9) Provisional stenting is principle, so in the following case is exclusion and consider to use "planned 2-stent"
   ① Side brunch ≧5mm than ostium and ≦TIMI Ⅱ or whole lesion 99% stenosis
   ② Expect to fail that serious hemodynamics cause by SB occlusion
   ③ Expect the high risk to be side brunch occlusion by the operator

7.3 Other Considerations

・Patients should be enrolled and assigned by the time to stent. It prefer to assign before PCI angiography and after the confirmation that can stent.
・First patient in and data that include PCI form will be entered by clinical investigator, the person who entry the data in catheter laboratory or CRC.
・This study is an open-label comparative study, but assigning procedures will be blinded the core laboratory evaluations, the event fix by the clinical event evaluation committee and data analysis.

In the procedure, it prefer to use ZES when need to stent for the side branch cause by the dissection of the side branch.
・The criteria to use the side branch stenting are when stent main vessel and side brunch flow is TIMI0 or TIMI1 after the treatment as with the criteria of Nordic bifurcation study1, expect occlusion cause by dissection flap or continue ischemia cause by side brunch stenosis. The operator chose the stent technique for side brunch. But it will exclusion when stent for side brunch.
・Observe for all patients angiography analysis and OCT analysis before and after the procedure.
・Prefer to observe for main vessel and side brunch by OCT before stent, but it need not to observe when it's difficult cause by myocardial ischemia or stenosis.
・Basically, PCI by the Angio guide.

・IVUS is unavailable because the result may be bias.
・When treat the additional treatments after Final OCT on this study protocol, it should submit the OCT data before and after the additional treatment.
・Prefer to use OCT that is made in St.Jude Medical.
・When need to add the stent for proximal stent cause by the dissection, it will be exclusion. However, it will report as AE when the dissection cause by POT or KBD.
・In case of Final OCT, it can treat additional treatment when the lesion is about 5mm from the bifurcation and fulfill the following criteria.

1. When distal MV ostium in bifurcated site will be distal area>30% and MSA<2.5mm^2
2. Malapposition>400 ㎛

When treat the additional treatments, it will count as “additional treatment” and it will be secondary endpoint. When treat the additional treatment, it will be exclusion from follow-up analysis. The additional treatments prefer to treat each group method like POT group add POT, Non-POT add KBD. When treat the additional treatment to improve the apposition of proximal, it will not be event.
・Staged PCI that has already been planned will not be considered a follow-up event (revascularization). Events associated with staged PCI, such as myocardial infarction, will not be handled as follow-up events.
・Protocol F/U CAG should be performed after at least 240 days post-procedure, unless clinically indicated.
・When coronary angiography is scheduled, the presence/absence of recurrent angina symptoms and the results of ischemia evaluation will be clearly described in the medical record before the angiography.
・To appropriately assess Target Lesion Revascularization (TLR) and Target Vessel Revascularization (TVR), qualitative and quantitative analyses of the cine frames at stenting and TLR in patients who have undergone TVR will be performed at the angiographic core laboratory.
・When angiography is performed, it will be assessed whether the angiography is clinically indicated.

・Ischemic symptoms and test findings suggestive of ischemia
・The presence/absence of recurrent angina symptoms and the results of ischemia evaluation at the time of TLR should be clearly described in the medical chart.
・To appropriately assess TVR-Remote, cine frames of it and those of the procedure should be sent to the core laboratory for patients who have undergone TVR.

・Regarding the antiplatelet therapy protocol, such as type, dosage, and duration of treatment of aspirin and thienopyridine, the institutional policy should be followed.

8 ETHICAL CONSIDERATIONS/INFORMED CONSENT

8.1 Protection of Patients' Human Rights

Compliance with the Declaration of Helsinki

The investigator will conduct the present study in compliance with the latest revision of the Declaration of Helsinki or the Ethical Guidelines for Clinical Studies(April 1, 2015 enforcement), whichever maximizes patient protection.

8.2 Informed Consent

(1) The responsibility investigator or the Allotment investigator explain it for patients using an explanation document enough to decide to participate with this study and get to an agreement by the free will from participate as a document.

(2) When the responsibility investigator or the allotment investigator obtain the document of consent, they should confirm that patients (or legal representative) consent after having understood enough. The responsibility investigator or the allotment investigator write down explanation day and do signature sealing or celebrity the consent form. Patients (or legal representative) consent after having understood enough and do signature sealing or celebrity the consent form. The responsibility investigator or the allotment investigator issue copy of the consent form that they signed and keep the consent form original at the medical institution concerned.

(3) When there is a matter affecting decision making of the participation in this study continuation, the responsibility investigator or the allotment investigator revise an explanation document, explain it using an explanation document for patients (or legal representative), obtain to an consent by the free will from participate about the continuation of the trial participation as a document. The responsibility investigator or the allotment investigator.

(4) When patients (or legal representative) offer the withdrawal of the consent of the trial participation, the responsibility investigator or the allotment investigator describes it in a clinical record. When making is possible, the responsibility investigator or the allotment investigator make "a consent withdrawal book". Patients (or legal representative) write down the day of consent withdrawal book and do signature sealing or celebrity the consent form. The participation in this study continuation, the responsibility investigator issue copy of the consent withdrawal book that they signed and keep the consent form original at the medical institution concerned.

9 TESTING AND ASSIGNMENT

After the responsibility investigator or the allotment investigator obtain consent from

patients(or legal representative) as a document, they should conduct a screening test before study start.

10 REGISTRATION AND ASSIGNMENT

The principal investigator or the responsible investigator conduct case registration that are sexuality and age in web database after obtaining consent from patients (or legal representative) who meet a registration condition. With case registration, the assignment method with the substitution block procedure should be performed After Assignment, the procedure which are displayed with POT group and non-POT group in web database should be performed. as required, items and the screen in which assignment group was described are printed and kept. If the principle investigator or the responsible investigator were not able to perform a procedure according to assignment, they should write down that. The registration system of this study is made by Hassai K.K. After start up the study, it is administered by INCREASE Co.,Ltd. Access privileges to the registration system of each institution are issued by the study secretariat and administered. Access privileges to the principal investigator or the responsible investigator are set a limit for the assignment practice of the own institution and reading of the assignment information. the principal investigator or the responsible investigator can not read assignment information of other institutions.

11 INVESTIGATIONAL DEVICE

Refer the latest package insert about investigational device's details and handling.
The investigational device that using this study is below.

Common name	Coronary stent
Brand name	Resolute Integrity SV
Production	Medtronic, Inc.
Approval number	22400BZX00176000
Shape/Structure	The balloon was mounted, and it's built by Parylene C, BioLinx, the stent that made of cobalt alloy was coated by Zotarolimus and the delivery system that rapid exchange type.
Conservation condition	Room temperature
Purpose of use/Effect	To treat for the symptomatic patient with ischemic heart disease that control vascular diameter is within 2.5mm to 4.2mm and having new

	coronary lesion (lesion length≦35mm)
Contraindication/ Prohibition	Prohibition re-sterilization or reuse. Don't use when Expiration date is over. Don't use for the following patients and lesions. 1. The patients have allergy to Zotarolimus or some drugs like that. 2. The patients have allergy to BioLinx,Parylene C or that unit compositions. 3. The patients have the tortuous blood vessel around the obstruction or proximal lesion. 4. The patients have unstable angina before procedure and it seems dangerous to stent. 5. The patients that finding serious thrombosis around lesion by coronary arteriography. 6. The patients have blood circulation disorder in distal part from lesion. 7. The patients can't use antiplatelet therapy and anticoagulant therapy those are recommended. 8. The patients are pregnant or potentially pregnant. 9. The patients that the stent over AC bypass anastomotic region.
Malfunction	Using this device, it will may happen the following malfunction. ・Explosion and tear of balloon ・Transformation, movement, crush and tear of stent ・Stent misplacement ・Difficult to delivery stent ・Tear and injury of catheter ・Withdrawal and difficult to insert catheter ・Stent dropout ・Poor in stent expansion ・Malapposition for vessel wall ・Poor in balloon expansion/shrinkage ・Unexpected shrinkage of balloon
AE	There are AE that related to percutaneous coronary diagnosis (Angiography, IVUS, etc.) and the treatment using this device. These are included the following SE. ・Death

	·Myocardial infarction ·Acute or pressure coronary occlusion ·Coronary occlusion, puncture, explosion or dissection ·Explosion of native blood vessel or bypass graft ·Cardiac tamponade ·Restenosis of stent blood vessel. ·Pain, hematoma and bleeding of catheterization site. ·Unstable angina ·Arrhythmia (Include ventricular fibrillation) ·Allergy (contrast media, antiplatelet therapy, stent materials or drugs and polymer coating) ·Stenting for outside of the lesion ·Embolism (air, tissue, device or thrombus) ·Hypotension/Hypertension ·Infection or fever ·Complications of puncture ·Ooronary vasospasm ·Aneurysms, pseudoaneurysm or AVF ·Thrombosis (acute, subacute, late onset or super late onset) ·Emergency surgery (peripheral vessel or coronary artery bypass grafting) ·Stroke/Transient ischemic attack ·Shock/Pulmonary oedema ·Peripheral ischemia/Peripheral neuropathy ·Myocardial ischemia ·Bradycardia/Palpitations ·Cerebrovascular disorder ·Endocarditis ·Sepsis ·Renal failure ·Pain/Tenderness/Chest pain ·Bleeding or Hemorrhagic complications (include when it need the transfusion) ·Cardiac rupture ·Heart failure ·Interstitial pneumonia

AE about Zotarolimus	When inject Zotarolimus to vein for human, there are the following side effects (single dose MAX 900μga and 14days repeated doses MAX 800μgb) There are potential AE when placement this device, but Zotarolimus that coating this device effects are unknown for whole body. ・Anemia ・Hematuria ・Reaction of application site ・Infection ・Diarrhea ・Pain (Abdomen, Joint) ・Dry skin ・Rash ・Headache

12 TEST, OBSERVATION, EVALUATION, METHOD AND TIME TO IMPLEMENT

12.1 Schedule and Procedure

Schedule of observation, test and evaluation is below.

Principal investigator or sub-investigator perform observation, test and etc according to the schedule.

Test list / Time to implement		Hospitalization/ Before procedure	While procedure	After procedure /Before Discharge	9 months Re-cystography	1year later	Event occurrence
Basic information		○					
Blood test	Bio-chemistry	○		○	○		○
ECG		○		○	○		○
PCI information		○	○		○		○
CAG information					○		○
QCA analysis			○	○	○		○
OCT analysis			○		△		△
Event			○	○	○	○	○

On this study, the time to implement the test is below.

1) Hospitalization/Before procedure

2) While procedure
3) After procedure/Before Discharge
4) Re-cystography 9 months later after procedure
5) 1year later follow-up after procedure（In principle hospital visiting but possible telephone）
6) Event occurrence

No allowance of follow-up, but perform follow-up about every 1month after 9months. This study collects the information of before procedure, while procedure, after procedure/before discharge, 9month later after 9months and 1year later after procedure, and enter it to eCRF.

The clinical evaluation is evaluated by principal investigator or sub-investigator. And same investigator evaluation same patient.

This study data that patient's blood test, biochemistry, ECG, information, medical records, CAG and OCT archive according to SOP.

12.2 Necessary Tests

The following tests are mandatory. Regarding other tests, the institutional standards should be followed.

1) Before the procedure:

・Cardiac enzymes
  ・Troponin I or troponin T, CK-MB, and CK will be measured because the ARC definition is used for the assessment of myocardial infarction in this study.
・Echocardiography
  ・12-lead resting ECG

2) After the procedure to before discharge:

・Cardiac enzymes
  ・Troponin I or troponin T, CK-MB, and CK will be measured because the ARC definition is used for the assessment of myocardial infarction in the present study. They will be measured in the morning of the day following PCI or at the time of discharge, whichever comes earlier.
  ・If acute myocardial infarction is suspected, cardiac enzyme levels may be continuously measured; regarding the method of measurement, the institutional standards should be followed.
・Echocardiography
  ・12-lead resting ECG (in the morning of the day following PCI or at the time of discharge, whichever comes earlier)

3) At the time of revascularization:

・Whether revascularization is “clinically indicated” according to the ARC definition will be assessed in the present study. Therefore, it is recommended to perform the following tests before or during angiography to evaluate the presence/absence of ischemia:

・12-lead resting ECG

・When resting ECG is negative, the following tests should also be performed:

・Stress test (either exercise or medication)

・Functional ischemia test such as Fractional Flow Reserve (FFR)

・The cine frames will be sent to the core laboratory according to the designated method because the angiograms of the patients who have undergone TVR are analyzed at the core laboratory.

12.3 Observation Items

Regarding observation items, various tests, interview, angiography, etc. will be performed before the procedure and during follow-up. The results will all be entered in the corresponding sections of the eCRF.

12.3.1 Observation Items before the Procedure

1. Enrollment information
2. Institution name, enrollment date, patient enrollment number, patient’s initials, name of the physician in charge
3. Basic information
4. Age, sex, height, body weight, hospitalization date, blood pressure on admission, pulse rate on admission
5. Whole log
6. The number of the lesion that have bifurcation lesion during entry period
7. Diagnostic name of myocardial infarction or angina pectoris (Choose from the following.)
8. ST-elevation acute MI, non-ST-elevation acute MI, stable angina, unstable angina, silent myocardial ischemia, old myocardial ischemia, coronary artery stenosis
9. Cardiac medical history

10. History of PCI, history of coronary artery bypass graft (CABG), past history of myocardial infarction, past history of cardiac failure, past history of stroke, past history of atrial fibrillation, past history of COPD
11. Complications
12. Presence/absence of the complication of cardiac failure at the present hospitalization, presence/absence of cardiac failure (present or past), presence/absence of carotid stenosis, presence/absence of dialysis
13. Risk factors
14. Presence/absence of hypertension, presence/absence of dyslipidemia, presence/absence of smoking, presence/absence of diabetes mellitus, presence/absence of a family history of coronary artery disease
15. Findings of coronary angiography
16. Number of affected branches, presence/absence of a treated lesion in the unprotected left main vessel, presence/absence of a treated lesion of chronic total occlusion, presence/absence of a treated lesion responsible for ST-elevation acute myocardial infarction, presence/absence of a treated bifurcation lesion, presence/absence of two or more treated branches, presence/absence of three or more treated branches, left ventricular ejection fraction, method of measurement of left ventricular ejection fraction, presence/absence of mitral insufficiency, method of evaluation of mitral insufficiency
17. Pre-procedure cardiac enzyme levels
    CK, CK-MB, troponin T or troponin I
18. Before procedure ECG

Note: Definition of observation items

1. Diabetes mellitus
   Patients with a blood glucose level of 200 mg/dL or more at 2 hours after glucose load by the glucose tolerance test, a casual blood glucose level of 200 mg/dL or more, or a fasting blood glucose level of 126 mg/dL or more.
   Patients are considered to have diabetes mellitus if they have already been diagnosed clinically as diabetes mellitus although the above tests have not been performed.
2. Dyslipidemia
   Patients with a total cholesterol level of 240 mg/dL or more, an HDL cholesterol

level of less than 40 mg/dL, or statin use.

3. Evaluation of renal function

   The e-GFR calculation formula for Japanese proposed by the Japanese Society of Nephrology will be used.

   $eGFR = 194 \times Cr^{-1.094} \times Age^{-0.287}$ ($\times$ 0.739 for females)

   End-stage renal failure: e-GFR <30 mL/min/1.73 mm^2

   Chronic kidney disease: e-GFR <60 mL/min/1.73 mm^2

4. Other items

   Other items will be assessed based on the clinical diagnosis provided in the medical record.

12.3.2 Observation Items at the Time of the Procedure

1. Enrollment information
2. Date of PCI
3. Patient information
4. Puncture site, start time of guide catheter insertion, time of guide catheter removal, contrast medium dose, time of fluoroscopy, presence/absence of clinical success of the present PCI, time to recross the wire
5. Lesion information (to be recorded depending on the number of lesions)
6. Segment, classification, and nature of the lesion(s)
7. Procedure data
8. Presence /absence of stenting; (regarding the following, stents implanted in the side branch and unsuccessfully implanted stents are included) stent diameter, stent length, success of implantation, dilation pressure, implantation site, presence/absence of device success in the present lesion, presence/absence of OCT, presence/absence of success of the PCI procedure in the present lesion, type and diameter of the post-dilation balloon, post-dilation pressure, site of lesion in the side branch, type of bifurcation lesion, treatment method for bifurcation lesion, pre-PCI lesion length, vessel diameter, percent diameter stenosis (%DS) and TIMI flow in the main branch, post-PCI vessel diameter, %DS and TIMI flow in the main branch, pre-PCI lesion length, vessel diameter, %DS and TIMI flow in the side branch, type of side branch treatment, balloon size when perform KBD and pressure, balloon size when perform only side branch dilatation and pressure

9. QCA analysis
10. Quantitative analysis by QCA using the angiograms before and after the index procedure will be performed in all subjects in principle (see the section on QCA analysis for the method and items).
11. OCT analysis
12. Quantitative analysis by OCT using the angiograms before and after the index procedure will be performed in all subjects in principle (see the section on OCT analysis for the method and items).

12.3.3 Observation Items after the Procedure to before Discharge

1. Enrollment information
2. Discharge date
3. Thienopyridines
4. Presence/absence of use during hospitalization, drug name, start time of use
5. Aspirin
6. Presence/absence of use during hospitalization, start time of use
7. Post-procedure test values for myocardial infarction
8. Test date, CK, CK-MB, troponin T or troponin I
9. Postoperative ECG
10. Test date
11. Staged PCI after discharge
12. Presence/absence of planned staged PCI, planned time, target branch
13. Events by the time of discharge
14. Observation item information will be recorded

12.3.4 1-Year Follow-up

The following information will be recorded at the follow-up at 1 year post-procedure:

1. Death
   Method of investigation of vital status, date of final confirmation of vital status, presence/absence of death, date and time of death, classification of cause of death, cause of death
2. Other events than death
   Method of investigation of other events than death, date of final confirmation of

other events than death, presence/absence of other events than death

3. Myocardial infarction
   Presence/absence of myocardial infarction, date of onset, ST-elevation myocardial infarction, Q-wave myocardial infarction, relationship with stent thrombosis, ARC classification, presence/absence of evaluation of the maximum cardiac enzyme value, date of cardiac enzyme testing, CK, CK-MB, troponin T, troponin I, presence/absence of fatality
4. ACS
   Presence/absence of emergency hospitalization due to ACS, date of onset, ACS classification, relationship with stent thrombosis, presence/absence of fatality
5. Definite stent thrombosis according to the ARC definition
   Presence/absence of stent thrombosis, date of onset, situation at onset, presence/absence of evaluation of the maximum cardiac enzyme value, test date, CK, CK-MB, troponin T, troponin I, presence/absence of Interim TVR attempt, relationship with the surgical procedure, presence/absence of hemorrhagic complications before onset of stent thrombosis, antiplatelet therapy at onset of stent thrombosis (aspirin and thienopyridines), presence/absence of fatality
6. Probable stent thrombosis according to the ARC definition
   Presence/absence of stent thrombosis, date of onset, classification (unexplained death within 30 days/myocardial infarction in the target vascular area)
7. Possible stent thrombosis according to the ARC definition
   Presence/absence of stent thrombosis, date of onset
8. Stroke
   Presence/absence of stroke, date of onset, stroke classification, presence/absence of fatality
9. Coronary artery bypass graft (CABG)
   Presence/absence of CABG, date of CABG
10. Other revascularization than TLR
    Presence/absence of other revascularization than TLR, date of other revascularization than TLR, method of revascularization, presence/absence of other TVR than TLR and clinically indicated revascularization
11. Planned staged PCI
    Presence/absence of planned staged PCI, date of planned stage PCI, timing of planned staged PCI
12. TLR

Presence/absence of TLR, date of TLR, method of revascularization, presence/absence of clinically indicated revascularization

13. TLR information by lesion (to be recorded for each lesion)
    Presence/absence of TLR, date of TLR, method of revascularization, PCI device, presence/absence of clinically indicated revascularization, presence/absence of follow-up angiography, date of follow-up angiography, reason for follow-up angiography, evaluation method of follow-up angiography, presence/absence of restenosis in the main branch, presence/absence of reocclusion in the main branch, presence/absence of restenosis in the side branch, presence/absence of reocclusion in the side branch

12.3.5 270-Day Follow-up

QCA analyses will be performed by the core laboratory in all subjects in principle at the 9-month follow-up. If each medical institutions can, perform OCT analysis.

1. Enrollment information
   Presence/absence of implementation of angiography, date of angiography
2. 270-day lesion evaluation
   American Heart Association (AHA) classification number of the lesion, reference vessel diameter, lesion length, percent in-stent diameter stenosis, percent in-segment diameter stenosis, presence/absence of a bifurcation lesion, AHA classification number of the side branch lesion, reference vessel diameter of the side branch, lesion length of the side branch, percent in-stent diameter stenosis of the side branch, percent in-segment diameter stenosis of the side branch

12.3.6 Completion/Premature Termination of the Study

When the present study is completed or prematurely terminated, the date of final contact with the subject, presence/absence of study completion in the subject, and reason for premature termination will be recorded in the corresponding sections of the eCRF. If the subject is prematurely withdrawn from the study, the reason for premature withdrawal will also be recorded.

12.4 Discontinuation Criteria

Principal investigator or sub-investigator discontinue this study when fulfill the following criteria.

1) When patients decline the entry this study or retraction the informed consent.

2) When patients not fulfill the inclusion criteria after the entry.
3) When patients not good continue this study because the disease get worse.
4) When patients hard to continue this study because the complication get worse.
5) When patients hard to continue this study because of AE
6) When turn out the pregnancy.
7) When this study is discontinued.

The investigators decide to discontinue this study because of the other reason.

12.5 Combined Drug

Investigate the time to start administration and presence/absence of administration of Thienopyridines and Aspirin. When administer the other combined drug, enter to eCRF

12.6 Safety Item

12.6.1 Definition of Adverse Events

"Adverse Event" is the disease that is not good for patient after informed consent or the disease that is not intended or that sign (include abnormality laboratory values). The causal relationship does not matter in this study.

12.6.2 Serious Adverse Events

Serious adverse event is the adverse event that fulfill the following case.

1) Death
2) life-threatening
3) Disability
4) Lead to disability
5) Hospitalization (initial or prolonged)
6) Serious Adverse Events according to the above 1) to 5)
7) Congenital Anomaly/Birth Defect

12.6.3 Non-Serious Adverse Events

"Non-Serious Adverse Events" is AE that without AE was determined to "Serious" The decision perform by principal investigator or sub-investigator

12.6.4 Recovery of AE and The Causal Relationship with This Study

"The loss of the adverse event" is the state that nothing AE or recover to the state before the administration. In AE, the causal relationship with this study is judged from patient's overall status, complications, combined medicine/combination therapy

and relationship of the time.

13 SUPPORT AND REPORT

13.1 Correspondence at Adverse Event Occurrence

The responsibility investigator or the allotment investigator should immediately provide the appropriate treatment the time they recognize it as adverse event Occurrence. That should be written down to a medical record without disagreement.

13.2 Correspondence at Serious Adverse Event Occurrence

1) The responsibility investigator or the allotment investigator should provide the appropriate treatment and try for the investigation of the cause regardless of an association of this study the time they recognize it as serious adverse event occurrence.
2) The responsibility investigator of each institutes should immediately report the adverse event information concerned in head physician of the own institution, medical safe committee of the own institution and the study secretariat. The report assumes it the first report which is given the information as far as it is possible by the urgent report, adverse event report in e-mail, phone, FAX either .and the second report which is written all predetermined matters in a detailed report, an adverse event report and they should report in e-mail, phone, FAX either. The responsibility investigator or the allotment investigator report about the lethal adverse event after having grasped that within 72 hours. The second report should be reported within 15 days.
3) The study secretariat and the responsibility investigator report the information concerned as soon as possible to responsibility physician of the study entry institutions except adverse event occurrence institutions. Depending on emergency, the telephone communication is possible, but performs the written communication which is e-mail, FAX mail, delivery by hand either later. The responsibility physician of each institution report that to head physician of the own institution. Coordinate investigator judges the emergency of report contents, importance, degree of the influence. As required they should take measures such as the urgent communication of the well-known matter to stop and participation institutions of the registration.

14 STATISTICAL CONSIDERTIONS

14.1 Analysis

When a case having difficulty in handling occurs, it is decided the handling in case study Committee.

14.1.1 Full Analysis Set

The FAS is the group which excluded the following from a registered case.

1) The case of the medical equipment GCP unobservance
2) The case that patients do not procedure by PRO
3) The case that does not meet registration criteria
4) The case that effective evaluation data after the procedure are not obtained

14.1.2 Per Protocol Set

It assumes a study enforcement plan observance case.

14.1.3 Per safe Analysis Set

The case that patients do procedure by the protocol

14.2 Statistical Analysis

Primary endpoint and secondary endpoints are conducted the statistical analysis between both groups. In addition, the level of significance when the scholar of statistics examine it is assumed to be 5% of both sides and the trust coefficient of the confidence interval is assumed to be 95%. The scholar of statistics set it of the statistical analysis plan to make before data fixation particularly about the statistical analysis item and the method.

15 REPORT OF THE OBSERVANCE AND THE DEVIATION (FOR THE ENFORCEMENT PLAN)

1) The principal investigator or the responsible investigator should not do the deviation and the revision from a study enforcement plan without permission of hospital head physician of the own institution based on the examination.
2) The principal investigator or the responsible investigator can do the deviation and the revision from a study enforcement plan without Prior agreement with the study representative and Prior approval of the Ethical Review Board because of evading the urgent risk of subjects. On this occasion, the principal investigator or the responsible investigator submit the document about the deviation and the revision from a study enforcement plan and revision of the enforcement plan to

a study representative and Ethical Review Board if necessary. Therefore they obtain approval of the coordinate investigator and the ethical Review Board, hospital head physician of the own institution.

3) The principal investigator or the responsible investigator should record a deviation matter with the reason when there is deviation. The responsibility investigator should report to head physician of the own institution about that. When they report that, the document should be the predetermined style that was determined with the own institution. The responsibility investigator should store these copying.

16 REVISION PROTOCOL, CASE REPORT FORM OR STATICAL PLAN

16.1 Revision Protocol and Case Report Form

When it revises a study enforcement plan and a case report, it is carried out by the following procedures.

1) The principal investigator provides the study enforcement plan revision plan and the case report revision plan, the latest study drug summary book, other necessary documents, information to the responsibility investigator.
2) The principal investigator examine the documents and information of the study enforcement plan and revision plan enough which are given by the responsible investigator and provide time necessary to discuss it to the responsible investigator.
3) After having discussed it with the principal investigator and the principal investigator submit the study enforcement plan, revision edition and the Case Report Form (EDC). The principle investigator should obtain approval of the Ethical Review Board via head physician of the own institution.
4) The responsibility investigator can revise the Instructions of head physician of the own institution based on the opinion of the Ethical Review Board. In the case of EDF, it is similar.

17 DISCONTINUATION AND COMPLETION OF THE STUDY

17.1 Discontinuation of the Study

1) If the following matters, the principal investigator considers discontinuation of the study.

· When the critical information were obtained on quality, safety and efficacy of the product.

· When it is determined to be difficult to subject recruitment and achieve number of cases

as scheduled.

· When the objectives of the study have been achieved prior to the planned number of cases or period（by the results of the intermediate statistics etc.）

2) By the safety evaluation committee, there is indication of change in the implementation plan, etc., when it is determined that it is difficult to accept this.
3) By the safety evaluation committee, if there is a recommendation or instruction of the termination, terminate the study.
4) The principal investigator considers above matters and continuation of the study.
5) When the decision were made to terminate or interruption of the study, immediately reported in writing along with the reason to the site.
6) In the process of the study, if there were reasons for termination of the study, the principal investigator consults the study caretaker on this matter and promptly report the termination of the study and reasons in writing to the Ethics Committee of each site.

17.2 Completion of the Study

In principle the study must be continued until the scheduled all subjects are registered and completed the evaluation of all cases. When there were serious adverse events associated with the study, the independent safety assessment committee discuss the continuation of the study.

At the time of registration has been completed of all cases, the Principal investigator reports the completion of the case registration for the study. And the principal investigator of each site stop the patient registration. At the time of the follow up for all cases were confirmed the principal investigator reports the completion of the case follow-up to the principal investigator of each site. The principal investigator of each site, submit a final report to the head of institutions.

At the end of the study at each site, the principal investigator submits promptly the end of the study report to the head of institutions.

18 CASE REPORT FORM

18.1 Collect the Data

The principal investigator or sub-investigator enter the case report form using the software that supported by the Ethical Guidelines for Clinical Studies.

The principal investigator or sub-investigator perform change, revision or postscript of

the case report form on the software, and report as the electronic intelligence.

18.2 Definition of The Data is entered directly and "Original Data"

In this study, the following documents are "original data".

1) The patient's agreement and the reports that are the provision of information for patients.
2) The record that entering CRF based on Medical examination record, Nurse's record, Laboratory study data, Image examination film and etc. And the data in electronic chart are also "original data".
3) The records of using this device
4) The records are the document related this study

In the data that entered to CRF, the following list is "original data" with entering to CRF. However, the medical examination record is "original data" when it is entered to the medical examination record.

1) Purpose of combined medicine/combination therapy
2) AE grade, outcome (include the result of follow-up examination), severity, judgement of the causal relationship with this study and the rationale of the judgement.
3) The reason why patients discontinue the study.
4) Comments from the principal investigator or responsible investigator.

19 SAVE SOURCE DOCUMENTS AND OTHER RECORDS

19.1 Save Records at Study Institution

The documents and records need to save those are related with this study should save 3 years from the study discontinuation or the end of study at the study institution.

20 SOURSE DATA VERIFICATION

Head of institution and the principal investigator assure to access to the records (original data and etc.) by the CRO that is consigned by the principal investigator when perform the monitoring, audit and investigation from the safety assessment committee. The CRO confirm that to perform appropriately this study and to make sure of the data reliability.

21 QUALITY CONTROL AND QUALITY ASSURANCE

21.1 Quality Control

The monitor performs monitoring, and confirm that this study observes in protocol and GCP at study institution. And perform direct access the original data that is related with this study and confirm the entering of CRF or the other records are accurate.

21.2 Quality Assurance

To assurance that this study of perform and data entry, the records and the reports observe appropriately protocol, the auditor independent from the sector that related with this study include the monitoring sector perform the audit and confirm to perform appropriately the quality control at study institution and the other institution that is related with this study.

22 ETHICAL CONSIDERATION

The persons who are involved must follow ”WMA Declaration of Helsinki”（2013, 64th WMA revision） and ”the Ethical Guidelines for Clinical Studies”, (2014 MEXT・MHLW Notification No.3)

22.1 Protection of Personal Information

The persons who are involved must make serious effort that to protect patient’s information. The handling method of this study data is the linkable anonymizing that based on”the Ethical Guidelines for Clinical Studies” definition: 2 (23)

Each patient’s information that is name, medical record number and etc are added Subject Identification Code. And it will be blinded by when it is added the case number from datacenter. When the data is published outside of the institution, it will be changed to the form that is not guessed the information that is name and etc. On this occasion,”Anonymous number comparison chart” is saved strictly in each study institution, it will only use when inquire the study data.（Linkable Anonymizing）

22.2 Informed Consent

Principal investigator makes informed consent form about Multi-center, prospective, randomized, open-label, comparative study. And that informed consent form must be recognized from ethics committee before this study start.

Principal investigator/sub-investigator should explain this study using informed consent form before the patient enter this study. And then, get the recognition by document that decide depends on own’s free will about entry this study from

themselves.

When get the recognition by document, Principal investigator/sub-investigator who explained about this study and the patients enter the date, sign the name and put one's seal on the letter of consent after the patients understand about the contents of informed consent form.

Principal investigator/sub-investigator deliver the copy that is the letter of consent that signed the name and put one's seal, and informed consent form. And the original letter of consent saves in own institution with informed consent form.

When the informed consent form has the serious revision, principal investigator/sub-investigator explain for the patients using the informed consent form that was revised again. And then, get the recognition by document that decide depends on own's free will about continue this study from themselves.

When the patients who entered this study offer withdrawal of recognition, Principal investigator/sub-investigator enter the date of withdrawal and the data of availability until then for the questionnaire. When use the withdrawing consent form, confirm same contents. And principal investigator/sub-investigator and patients sign and seal it, and then deliver the copy for patients, and save the withdrawing consent form.

22.3 The contact address and method when Question, Withdraw informed consent and etc.

Yusuke Watanabe, M.D., Teikyo University Hospital
2-11-1 Kaga,Itabashi-ku,Tokyo 162-0845,Japan
TEL：03－3964－1211（Ext. 30415）

【If the informed consent of patients is NOT obtained】

Not registered in this study.

【If the study required to perform Monitoring/Audit】

As the premise for the patient's secret is preserved, monitor, auditor and ethics committee outlook the sample and the information related with patients

23 HOSPITAL ETHICS COMMITTEE

Prior to the implementation of the study, the ethical committee reviews the ethical, scientific and medical validity of the study. The study is carried out after obtaining the approval of the ethics committee. If the ethics committee of deliberation result is "to approve on the modification", protocol, case report form and informed consent form are modified based on the deliberation results, and after the modifications were made carry out the study. Actual date of start, study status (number of cases), ethical considerations,

occurrence of disadvantages, adverse events, research results and the interim report will be reported once a year, also at the end of the study, the final report is submitted to the committee.

When serious adverse event has occurred, report in accordance with the "standard operating procedures related to the serious adverse events report in clinical studies."

24 PRIVACY CONSIDERATION

Medical records, test data, and records of informed consent by subjects will be retained at the applicable medical institution. The case report forms and equivalent documents will be retained at the Data Center, The Department of Medicine (Cardiology), Teikyo University School of Medicine. These records must be maintained to be searched as needed.

All parties involved in the present study must in principle make every effort to protect patients' personal information because they have a duty to keep the records confidential as data handlers. If personal information of patients is used outside the institution, patients' names must be changed to initials at the applicable institution to prevent identification by anybody except the responsible person at the applicable institution. Thus, the names of study subjects will not be disclosed by the participating institution to the central office/data center. In addition, patient medical chart numbers at each institution, which are also used as patient identification numbers, will not be disclosed to the central office/data center because the patient identification numbers entered on the Web are automatically encrypted.

Encrypted patient identification numbers and patient initials will be used for identification of enrolled patients and inquiries to each institution. Regarding the use of patient initials in the present study as the minimum identification information, the risk of leakage of personal information only based on patient initials is considered extremely low. If patient initials are not used, it will not be possible to identify patients because patient identification completely depends on the personal information management structure of the institution, and the conduct of the study itself will probably be impossible.

25 HANDRING OF SERIOUS ADVERSE EVENTS

If a serious adverse event occurs in a subject in the present study, the procedures for reporting and handling of such events defined at each study site will be followed.

If an adverse event occurs due to the conduct of the present study and causes health

injury of the subject, the investigator or the physician in charge will immediately provide appropriate medical treatment and take other optimal measures. Although medical expenses will be covered by health insurance, compensation for loss of earnings and medical benefits, etc. will not be made.

26 COMPENSATION FOR HEALTH INJURY

Medical expenses for health injury in the present study will be covered by health insurance and will not be compensated. Compensation for health injury associated with the study will only be paid in case of legal liability for negligence. Handling of health injury caused by the medical practice itself, not associated with the study, will be up to each institution. The study office will not buy liability insurance because the risk of health injury from which legal liability for negligence arises in association with the present clinical study is expected to be extremely low.

27 PAYMENT FOR MEDICAL EXPENSES

All tests and treatments related to the present study are basically within the range of daily clinical practice. Thus, the medical expenses for patients participating in the study will be covered by health insurance in principle. However, part of the blood test (troponin T, troponin I, CK-MB) and imaging (OCT only for examination) not reimbursed by health insurance will be covered by study expenses.

28 ENROLLMENT OF STUDY PLAN AND PUBLICATION OF STUDY RESULT

This study was registered into the University hospital Medical Information Network (UMIN), and it will also be registered into the National Institutes of Health (NIH) after the protocol is approved. It is possible to browse the data of study plan and study method. Contents are the primary endpoint and secondary endpoints will be post to the English magazine. In spite of the study was performed correctly the result also publishes as the treatise when it is not intended. The treatise primacy/the corresponding author is the principal investigator, the author is principal investigator. The exploratory endpoints of the analysis contents post for English magazine.

29 REVERSION OF INTELLECTUAL PROPERTY RIGHTS

There is no possibility to obtain patent right by this study.

30 PROTECTION OF PERSONAL INFORMATION

1) The parties involved in this study, comply with laws and regulations. When the principal investigator and the responsible investigator submit the patient registration forms and the case report forms, they newly provides cord of subject in order to make the connection can be anonymous. Outsider from the institutions, information that can identify the subject (name, address, phone number, etc.) will not be described. Data center issue query on a specific subject using the case number to the institutions. When the investigators will publish the information obtained in the study, they must be performed by fully considered so that the subject cannot be identified.
2) On the imaging file, it is assumed to make the consolidated possible anonymous at each site in principle, if anonymous at each site is difficult, make anonymous in the data center.

31 STUDY ORGANIZATION

31.1 Principal Investigator

Ken Kozuma, M.D, Teikyo University Hospital

31.2 Lead Investigator

Yusuke Watanabe, M.D., Teikyo University Hospital

31.3 Steering Committee

Yoshinobu Murasato, M.D., National Hospital Organization Kyushu Medical Center
Toshiro Shinke, M.D., Kobe University Hospital
Yoshihisa Kinoshita, M.D., Toyohashi Heart Center
Masahiro Yamawaki, M.D., Saiseikai Yokohamashi Tobu Hospital
Jiro Aoki,M.D,Mitsui Memorial Hospital
Gaku Nakazawa,M.D, Tokai University Hospital
Kazuhiko Yuzumoto,M.D,Yokohama Rosai Hospital
Yoshihiro Takeda,M.D,Rinku General Medical Center
Tatsuya Ito,M.D,Nagoya Heart Center
Munenori Okubo,M.D,Gifu Heart Center

Institut Cardiovasculaire Paris Sud Bernard Chevalier

31.4 Study Office

INCREASE Co.,Ltd.
Forecast Ichigaya Bldg.4F,3-29,Ichigaya Honmura-cho,Shinjuku-ku,Tokyo 162-0845,Japan
TEL：03-5227-3690　　FAX：03-5227-3691

31.5 Random Program

Hachisai Co., Ltd.
3-9-2,Sakashita,Itabashi-ku,Tokyo 174-0043,Japan
TEL： 03-6314-7200

31.6 Data Center

INCREASE Co.,Ltd.
Forecast Ichigaya Bldg.4F,3-29,Ichigaya Honmura-cho,Shinjuku-ku,Tokyo 162-0845,Japan
TEL：03-5227-3690　　FAX：03-5227-3691

31.7 Statistical Analysis Officer

INCREASE Co.,Ltd.　Dpt,Clinical Statistics

31.8 Angiography/OCT Core Laboratory

Kick core lab division Cardiocore Japan
202 Fujiwa city corpo Itabashi, Itabashi-ku, Tokyo 173-0004
Tel&FAX: 03-3579-3151

31.9 Data Safety Monitoring Board (DSMB)

Yasuyuki Maruyama, M.D., Iwatsuki-minami hospital

31.10 Clinical Events Committee

Takaki Ishiki，M.D.，Ageo Central General Hospital

31.11 Participating Institution

The candidate medical institutions:
Japan

Teikyo University Hospital
National Hospital Organization Kyushu Medical Center
Kobe University Hospital
Toyohashi Heart Center
Saiseikai Yokohamashi Tobu Hospital
Mitsui Memorial Hospital
Tokai University Hospital
Yokohama Rosai Hospital
Rinku General Medical Center
Nagoya Heart Center
Gifu Heart Center

France
Institut Cardiovasculaire Paris Sud

31.12 Monitoring

The monitoring will be performed by kitasato Academic Research Organization (ARO).

The target institutions (2 study institutions) are selected considering the evaluation of investigator and experience of study institution/investigator. Timing of implementation, is during the study or complete the study.

In this study, the monitoring is scheduled to be on-site monitoring. The clinical research associate has a right to conduct monitoring at appropriate sites timely. When the clinical research associate conducts monitoring, he or she submits the monitoring report to the principal investigator each time.

The documents related the monitoring should be archived by the research office of the study.

Monitoring Agency
kitasato Academic Research Organization (ARO)
Annex Bldg.5F,5-9-1,Shirogane,Minato-ku,Tokyo 108-8642,Japan
TEL:03-5791-6404 FAX:03-3444-5850

31.13 Audit

Audit of this study will be conducted by the Audit division of Increase Co., Ltd. The principal investigator confirms that the auditor has qualified as audit personnel and

assigned as auditor of the study.
Objected sites will be selected 3 sites includes Teikyo University by reference to the evaluation of the principal investigator and the clinical research associate.
In the audit, informed consents, Ethics Committee documents, contracts and medical records will be investigated the storage situation with the contents of the documents. The auditor reports audit results to the principal investigator and audit sites. At the audit, if the critical findings were observed, the site representative creates the answer confirming the contents of the indication and submit the report as a basic rule.
Documents relating to the audit should be archived by the research office of the study.

Audit：INCREASE Co.,Ltd. Audit Sector
Forecast Ichigaya Bldg.4F,3-29,Ichigaya Honmura-cho,Shinjuku-ku,Tokyo 162-0845,Japan

In the Increase Co., Ltd., Clinical Development Division and Audit Division are independent each other, and the Audit Division reports directory to the President of Increase Co., Ltd. Therefore, the "audit of independence" is considered to be collateral.

In the Increase Co., Ltd., a clinical development department and the audit department is an independent department, further audit department is present as an independent department of the representative director under the direct control. Therefore, "audit of independence" is considered to be collateral.

31.14 The Date of Custody and Discard after Study

Documents related to this study will be anonymous. The principal investigator / the responsible investigator newly provides cord of subject in order to make the connection can be anonymous and using the anonymity of the data Outsider from the institutions, information that can identify the subject (name, address, phone number, etc.) will not be described. At that time, a consolidated table of the personal information "anonymous number sheet" is strictly managed within each site, only be used the data when query is issued (Consolidated possible anonymous).

For storage location and storage method of the documents, in the like contract documents with other sites, Teikyo University is in charged, on the other documents, stored by Increase Co., Ltd. in charge of the research secretariat of the study. Also, Documents relating to the image analysis (Angio, OCT image) are stored by the K.K. kick which is an angiography OCT core laboratory for the study. In addition, supervision

of outsourcing is carried out by the Department of Cardiology Yusuke Watanabe Teikyo University. Storage method is compliant with the "standard operating procedures related to record retention in clinical research", is saved for 10 years and then discarded.

31.15 Study Sponsor

Medtronic Japan Co., Ltd

This study is an investigator-initiated clinical study, and the sponsor will not be involved in the conduct, data collection, event finalization, or statistical analysis of the study.

31.16 Data Ownership and Publication

The study office has the ownership and publication rights of the study data and results, but the method and timing of publication will be discussed by the lead investigator and the study office. For presentations at academic conferences and paper submissions, the study office should submit a copy of the publication or presentation to the study sponsor and obtain approval at least 30 days before the publication/presentation. The study sponsor has the non-exclusive rights to use all information or data obtained from the study.

31.17 Study Funds and Conflicts of Interests

We confirm that no “possible conflicts of interests” that may affect the study results and their interpretation exist in the planning, implementation, or reporting of the study, and that the conduct of the study will not compromise the rights/interests of patients.

32 REFERENCES

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