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Percutaneous coronary intervention in side branch coronary arteries: Insights from the Japanese nationwide registry

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ABSTRACT

Background: Performance of percutaneous coronary intervention (PCI) in side-branch vessels (SB-PCI) has not been fully investigated despite the technical advancement of PCI.
Methods: We investigated 257,492 patients registered in the Japanese nationwide PCI registry from January to December 2018; 199,767 (78%) underwent PCI for major vessel PCI (MV-PCI), 21,555 (8.4%) underwent SB-PCI, and 24,862 (9.6%) underwent PCI for both vessels (SB + MV-PCI). The frequencies of primary composite adverse events, defined as in-hospital mortality and procedural complications (i.e., *peri*-procedural myocardial infarction, tamponade, new-onset cardiogenic shock, stent thrombosis, emergent surgery, and bleeding), and PCI for restenotic lesions were investigated. Their association with institutional frequency of each PCI was also investigated.
Results: Fewer drug-eluting stents (66% vs. 86%) and more drug-coated balloons (23% vs. 9%) were used in SB-PCI than in MV-PCI ($p < 0.001$). Pre-procedure non-invasive testing was similarly performed in SB-PCI and MV-PCI (57% vs. 61%). The composite endpoint was observed in 0.7%, 1.9%, and 2.2% of the SB-PCI, SB + MV-PCI, and MV-PCI groups, respectively ($p < 0.001$). Institutional frequency of SB-PCI was inversely associated with the composite-endpoint risk for all PCI procedures (odds ratio 1.37, 95% confidence interval 1.04–1.81 in the lowest tertile, with reference to the middle tertile, $p = 0.02$). Frequency of PCI for restenotic lesions was also inversely associated with the institutional frequency of MV-PCI ($p < 0.001$).
Conclusion: SB-PCI was performed safely with a low frequency of acute complications, and higher SB-PCI frequency presented a lower risk of in-hospital adverse events, albeit with a cost of an increase in PCI for restenotic lesions.

1. Introduction

Although the clinical benefit of percutaneous coronary intervention (PCI) has been established in major coronary vessels (MV-PCI) [1], performance of PCI in side-branch vessels (SB-PCI; originating from the adjacent major vessels) has not been studied widely. SB-PCI has historically been considered as clinically insignificant or inappropriate, partially due to the smaller perfusion territory and more frequent restenosis [2,3]. However, with the technical advancement of PCI, including the introduction of the drug-coated balloon and small (2.0–2.25 mm) new-generation drug-eluting stent (DES), SB-PCI is increasingly being performed for symptom relief, as well as for staged procedures in patients with multivessel disease. Indeed, SB-PCI cases are known to account for 18–20% of PCIs in the United States and Japan [4]. Despite the high number of SB-PCIs performed, the present status

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of SB-PCI has not been elucidated. Most of the previous large-scale studies have focused on coronary vessel size (e.g., vessel size ≤ 2.5–3.0 mm or device size ≤ 2.5 mm defined as 'small' vessels) [5–9], and their anatomical relationship with the coronary artery was not taken into account. In this study, we investigated and compared both the current situation and the in-hospital adverse events of SB-PCI, MV-PCI, and the concomitant treatment of both side-branch and adjacent major vessels (SB + MV-PCI), using data from the contemporary Japanese PCI Registry. In addition, the relationships between the institutional frequency of SB-PCI and the frequencies of adverse events and PCI for restenotic lesions were investigated.

2. Methods

The Japanese PCI Registry is a prospective, Japanese, nationwide multicenter registry, designed to survey the clinical data of patients undergoing PCI [10–12]. The registry has been operated by the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) since 2007 [10–12]. Registration in the Japanese PCI database is mandatory for the application and renewal of board certification of the CVIT. The relevant committee and the Board of Directors of the CVIT approved the registry protocol for the collection of variables concerning each patient's background, clinical presentation, angiographic and procedural information, and in-hospital outcomes. The CVIT also holds an annual meeting of data managers, and visits 20 randomly chosen participating institutions annually, to monitor the quality of submitted data. The protocol of the Japanese PCI Registry was approved by the Institutional Review Board Committee at the Network for Promotion of Clinical Studies in a specified non-profit organization affiliated with the Osaka University Graduate School of Medicine (CRPNJSOP-4–5). According to the annual reports of the Japanese Registry of All Cardiac and Vascular Disease, 278,285 PCIs were performed in 2018 (http://www.j-circ.or.jp/jittai_chosa/jittai_chosa2017web.pdf). As 257,492 PCIs were included in the Japanese PCI Registry in 2018, the registry is estimated to account for 93% of all PCI procedures in Japan. The CVIT drafted a research proposal using the Japanese PCI Registry in August 2019, and our proposal was adopted in December. This study was supported by the CVIT and was conducted in accordance with our research proposal. The requirement for obtaining written informed consent from the patients was waived, given the retrospective study design.

We extracted patient-level data for 257,492 cases registered in the Japanese PCI from January 2018 through December 2018. We excluded PCI cases involving SB-PCI and non-adjacent MV-PCI during the same session (n = 9846), and those involving bypass grafts (n = 1462).

Patients were divided into the following groups: those who underwent SB-PCI alone (SB-PCI group), those who underwent PCI for both side-branch and adjacent major vessels (SB + MV-PCI group), and those who underwent MV-PCI alone (MV-PCI group) (Fig. 1A). Side branches were defined as branches originating from the adjacent major vessels, according to the American College of Cardiology/American Heart Association lesion classification, which were as follows: segments #9–10, high lateral branch; and #12, #14, and #4, posterior descending/atrioventricular branches. Distal segments of the left anterior descending artery (#8) and left circumflex artery (#15) were excluded due to their variations in development. The remaining segments were considered major vessels (#1–3, #5–7, #11, and #13). For the SB + MV-PCI group, the following segments were considered as adjacent: #3–4 posterior descending, #3–4 atrioventricular, #6–high lateral, #6–9, #7–9, #7–10, #11–high lateral, #11–12, #13–12, and #13–14 (Fig. 1B).

In the Japanese PCI Registry, ST-elevation myocardial infarction was defined as acute myocardial infarction with electrocardiographic findings of either ST-elevation or new-onset, complete left bundle branch block, or as pure posterior myocardial infarction. Non– ST-elevation myocardial infarction was defined as acute myocardial infarction without ST-elevation. Unstable angina was defined as acute coronary syndrome, without troponin elevation, including new-onset or increased-severity angina within one-month, resting angina, and post-infarction angina. Emergent/urgent PCI was defined as any PCI procedure not planned >1 day in advance. Cardiogenic shock was defined as a sustained episode of systolic blood pressure <80 mmHg, cardiac index <1.8 L/min·m^2 determined to be secondary to cardiac dysfunction, and/or the requirement for a parenteral inotropic or vasopressor agent or mechanical support, including an intra-aortic balloon pump, to maintain blood pressure and cardiac index above the specified levels within 24 h before PCI. Acute heart failure was defined as symptoms of heart failure within 24 h before PCI, including dyspnea on mild activity, orthopnea, body fluid retention, moist rales, neck vein distention, and pulmonary edema, which were equivalent to "Congestive Heart Failure" in the New York Heart Association's functional classification class IV. Chronic kidney disease was defined as the presence of proteinuria, serum creatinine level of ≥1.3 mg/dL, or estimated glomerular filtration rate of ≤60 mL/min·1.73 m^2, according to the guidelines of the Japanese Society of Nephrology [11]. Successful PCI was defined as the achievement of Thrombolysis in Myocardial Infarction flow grade III, with residual stenosis of ≤25% in the target lesion.

The primary outcome of the Japanese PCI Registry and the current analysis was the composite endpoint of in-hospital mortality within 30 days after PCI, procedure-related myocardial infarction with >5 times the upper limit of the normal troponin level, cardiac tamponade, cardiogenic shock requiring mechanical and/or inotropic support, stent thrombosis ("definite" based on the definition of the Academic Research Consortium), emergent surgery, and bleeding requiring transfusion, including access- and nonaccess-site bleeding. The full definitions of these Japanese PCI Registry variables are available online (http://www.cvit.jp/registry/jpci_definition.pdf) and in a previous report [12]. The secondary outcome was the proportion of PCI for restenotic lesions in the institution. The institutional frequencies of SB-PCI, SB + MV-PCI, and MV-PCI were calculated as the proportion of each PCI procedure to all PCI cases in the institute.

Categorical variables are presented as numbers and percentages; continuous variables are presented as mean ± standard deviation for normally distributed data, and as median an interquartile range for non-normally distributed data. Continuous variables were compared between groups by the unpaired Student's *t*-test, whereas categorical variables were compared by the chi-square test. Bonferroni adjustment was used for multiple comparisons. Continuous variables were compared among tertile groups by one-way analysis of variance, and the trend was evaluated by the Cochran-Armitage test.

Logistic regression mixed models were constructed to evaluate the association between the institutional frequency of PCI and the rate of the composite endpoint per patient. We also constructed univariable and multivariable logistic regression mixed models with in-hospital outcomes as a response variable. In the multivariable models, adjustment variables were selected on the basis of clinical relevance and included the following: age, sex, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, prior myocardial infarction, emergent/urgent versus elective PCI, lesion location in the left anterior descending artery, fractional flow reserve measurement, radial approach, DES in major vessels, and DES in side branches. Odds ratios (ORs) and 95% confidence inter-

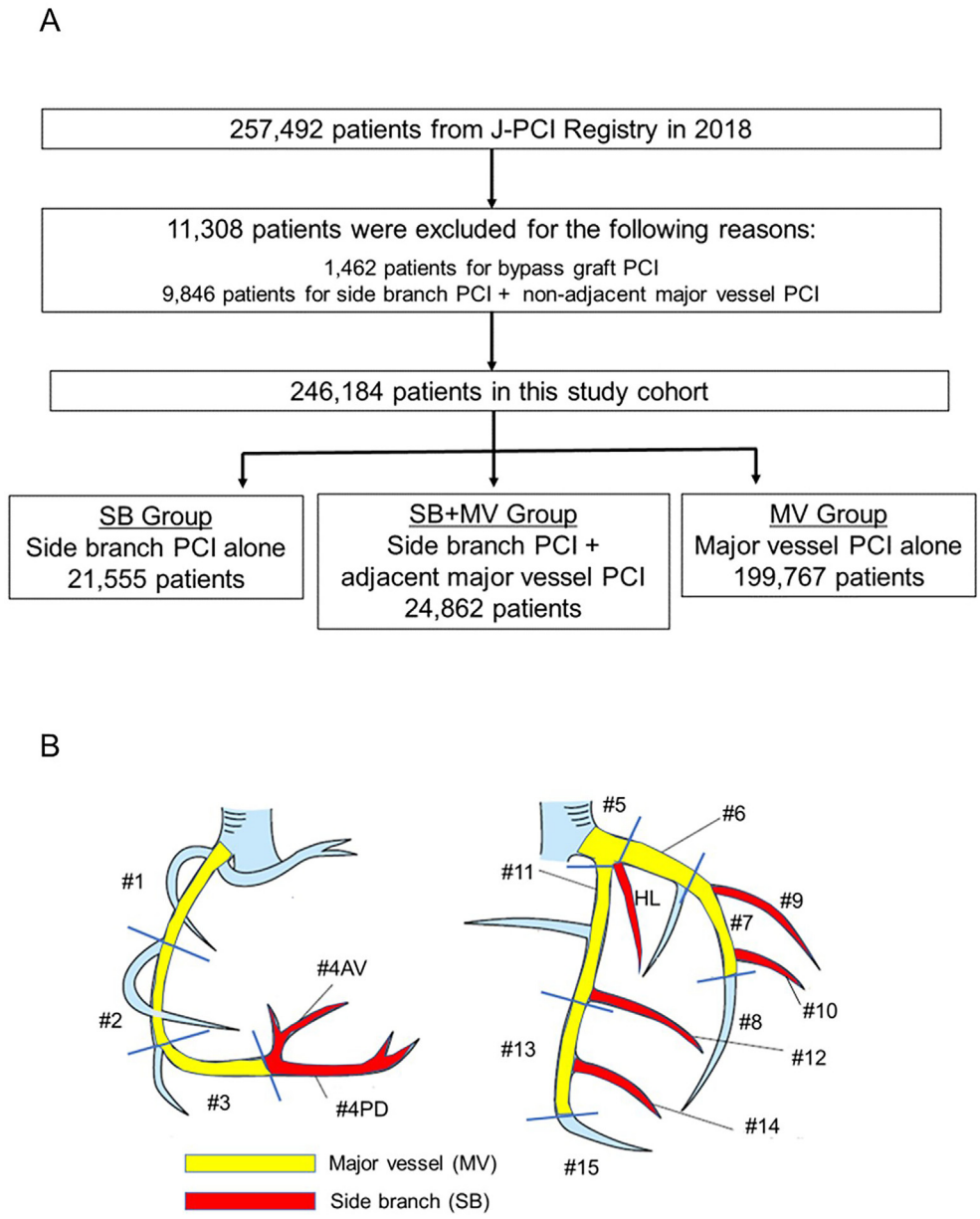


Fig. 1. A: The study flow chart. PCI: percutaneous coronary intervention. B: Scheme of location of major vessel (MV) and side branch (SB) in the coronary artery. The yellow and red labels indicate the MV and SB, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

vals (CIs) were calculated. Institutes were included in the models as random intercepts. We also performed stratified analyses according to the tertiles of the institutional frequency (low-, moderate-, and high-frequency) for each PCI procedure (SB-PCI, SB + MV-PCI, and MV-PCI).

All reported P-values were determined by two-sided analysis, and P-values < 0.05 were considered significant. Analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and Python version 3.7.0 (available at https://www.python.org/).

3. Results

After applying the eligibility criteria, 246,184 patients were included in this study. The distribution of PCI groups is shown in Fig. 1A. The number of patients in the SB-PCI, SB + MV-PCI, and MV-PCI groups was 21,555 (8.4%), 24,862 (9.6%), and 199,767 (78.0%), respectively. The SB-PCI group presented with a higher prevalence of non-ST-elevation myocardial infarction, one-vessel disease, and lesions located in the left circumflex artery. The SB-PCI group also showed a low prevalence of heart failure/cardiogenic shock/cardiac arrest (Table 1). Although myocardial ischemia or coronary stenosis in the SB-PCI group was confirmed by non-invasive testing to a similar extent as that in the MV-PCI group, myocardial scintigram and stress electrocardiogram were performed more often despite the less frequent performance of fractional flow reserve measurement in the SB-PCI group than in the MV-PCI group (Table 2).

DES deployment was less frequently performed in the SB-PCI group than in the MV-PCI group (66% vs. 86%; Table 2). A drug-coated balloon was more frequently used in the SB-PCI group (23% vs. 9.1%). In the SB + MV-PCI group, DES was deployed in the major vessels and side branches in 86% and 42% of patients,

Table 1
Patient and lesion background.

	SB group	SB + MV group	MV group	P-value		
				SB vs. SB + MV	SB vs. MV	SB + MV vs. MV
Patient, n	21,555	24,862	199,767			
Percentage to whole PCI, %	8.4%	9.6%	78.0%			
Age (years)	70 ± 11	70 ± 11	71 ± 11	<0.001	<0.001	<0.001
Male sex	16913(78%)	19487(78%)	151637(76%)	0.84	<0.001	<0.001
History						
Hypertension	16593(80%)	18523(77%)	148208(77%)	<0.001	<0.001	0.36
Dyslipidemia	14230(69%)	16746(70%)	129950(68%)	0.02	0.01	<0.001
Diabetes mellitus	9309(45%)	11535(48%)	87866(46%)	<0.001	0.01	<0.001
Smoker	6291(30%)	7554(31%)	60469(32%)	0.02	<0.001	0.71
Chronic kidney disease	3656(18%)	4799(20%)	40112(21%)	<0.001	<0.001	<0.001
Hemodialysis	1194(5.8%)	1539(6.4%)	14293(7.5%)	0.005	<0.001	<0.001
Prior MI	4747(23%)	5874(24%)	43090(22%)	<0.001	0.007	<0.001
Prior heart failure	2671(13%)	4088(17%)	28458(15%)	<0.001	<0.001	<0.001
Prior PCI	11309(54%)	11737(48%)	86987(44%)	<0.001	<0.001	<0.001
Prior CABG	688(3.3%)	776(3.2%)	6034(3.1%)	0.51	0.07	0.34
Cath lab presentation						
Emergency/urgent procedure	5607(26%)	5472(22%)	58468(29%)	<0.001	<0.001	<0.001
CAD presentation				<0.001	<0.001	<0.001
STEMI	2772(13%)	3208(13%)	36799(18%)			
Non-STEMI	1582(7.3%)	1223(4.9%)	10489(5.3%)			
AMI, unknown type	149(0.69%)	190(0.76%)	1756(0.88%)			
Unstable angina	3185(15%)	3972(16%)	29725(15%)			
Stable angina	8161(38%)	9070(36%)	68635(34%)			
OMI	834(3.9%)	1271(5.1%)	8740(4.4%)			
Silent myocardial ischemia	3129(15%)	3453(14%)	28919(14%)			
Staged PCI	1512(7.0%)	2191(8.8%)	12693(6.4%)			
Other	231(1.0%)	284(1.1%)	2011(1.0%)			
Number of diseased vessels						
One	20950(97%)	21105(85%)	178621(89%)	<0.001	<0.001	<0.001
Two	600(2.8%)	2358(9.5%)	8286(4.1%)			
Three	5(0.023%)	76(0.31%)	184(0.092%)			
Not described	0(0%)	1324(5.3%)	12676(6.3%)			
Target lesion				<0.001	<0.001	0.001
De novo lesion	19936(92.5%)	22210(90.1%)	178567(89.4%)			
Including restenotic lesion	1619(7.5%)	2472(9.9%)	21200(10.6%%)			
Lesion location						
RCA	6610(31%)	6166(25%)	66672(33%)	<0.001	<0.001	<0.001
LAD	5524(26%)	13861(56%)	104672(52%)	<0.001	<0.001	<0.001
LCX	10031(47%)	8122(33%)	37300(19%)	<0.001	<0.001	<0.001
Left main	0(0%)	1323(5.3%)	12676(6.3%)	<0.001	<0.001	<0.001
Heart failure within 24hr	417(2.0%)	941(3.9%)	9133(4.6%)	<0.001	<0.001	<0.001
Cardiogenic shock within 24hr	251(1.2%)	634(2.6%)	7375(3.7%)	<0.001	<0.001	<0.001
Cardiac arrest within 24hr	177(0.85%)	353(1.4%)	4215(2.1%)	<0.001	<0.001	<0.001

Values are mean ± SD or n (%). Duplicated cases were included in lesion location. AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LAD, left anterior descending artery; LCX, left circumflex artery; MI, myocardial infarction; MV, major vessel; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SB, side branch; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

respectively. The fluoroscopy time was the longest in the SB + MV-PCI group and the shortest in the SB-PCI group.

The rates of in-hospital mortality and composite endpoint were the lowest in the SB-PCI group (mortality: SB-PCI, 0.28%; SB + MV-PCI, 0.63%; MV-PCI, 0.96%, $p < 0.001$; composite endpoint: SB-PCI, 0.74%; SB + MV-PCI, 1.9%; MV-PCI, 2.2%, $p < 0.001$).

On multivariable analysis (Fig. 2), the risk factors of the composite endpoint in the whole cohort were age (OR 1.03, 95% CI 1.02–1.04), male sex (OR 0.63, 95% CI 0.52–0.76), chronic kidney disease (OR 1.32, 95% CI 1.08–1.62), prior myocardial infarction (OR 1.24, 95% CI 1.02–1.52), emergent PCI (OR 3.36, 95% CI 2.20–5.15), fractional flow reserve measurement (OR 0.66, 95% CI 0.51–0.85), and transradial approach (OR 0.30, 95% CI 0.25–0.37). The same variables were found to be risk factors in the MV-PCI group. In contrast, emergent PCI (OR 6.38, 95% CI 1.03–39.62), transradial approach (OR 0.28, 95% CI 0.10–0.83), and hypertension (OR 0.28, 95% CI 0.10–0.80) were risk factors of the composite endpoint in the SB-PCI group, and age (OR 1.03, 95% CI 1.00–1.06) and transradial approach (OR 0.26, 95% CI 0.16–0.54) were risk factors of the composite endpoint in the SB + MV-PCI group (Fig. 2).

Fig. 3 indicates the stratification according to the tertiles of the institutional frequencies of each PCI procedure. The numbers of SB-PCI and SB + MV-PCI procedures were greater in proportion to their higher institutional frequencies. Contrarily, the number of MV-PCI procedures was greater in the moderate-frequency tertile of each PCI procedure, than in the low-frequency or high-frequency tertiles.

Fig. 4 shows the adjusted ORs of the tertiles of the institutional frequency of each PCI procedure for whole PCI in the multivariable analysis adjusted for clinical variables. The low-frequency tertile of SB-PCI presented a higher adjusted OR with reference to its moderate-frequency tertile (1.37, 95% CI 1.04–1.81 p = 0.02). Fig. 5 shows the adjusted ORs of the tertiles of the institutional frequency of each PCI procedure for SB-PCI (A), SB + MV PCI (B), and MV-PCI groups (C). A lower adjusted OR of the high-frequency tertile of SB-PCI in the SB-PCI group (0.12, 95% CI 0.02–0.93 p = 0.04) (Fig. 5A) and a higher adjusted OR of the low-frequency tertile of SB-PCI in the MV-PCI group (1.41, 95% CI 1.05–1.89 p = 0.02) (Fig. 5C) were also revealed. A significant association was not found in the stratified analysis for MV-PCI or SB + MV-PCI.

Table 2
Contents of percutaneous coronary intervention (PCI) and clinical outcome.

	SB group	SB + MV group	MV group	P-value		
				SB vs. SB + MV	SB vs. MV	SB + MV vs. MV
Proof of myocardial ischemia or coronary stenosis in non-invasive test	7258(57%)	8869(61%)	64212(58%)	<0.001	0.40	<0.001
Coronary CTA	3559(49%)	4624(52%)	32558(50%)	<0.001	0.01	0.01
Stress ECG	1203(17%)	1361(15%)	9549(15%)	0.03	<0.001	0.25
Myocardial scintigram	1838(25%)	1908(21%)	12968(20%)	<0.001	<0.001	0.004
Stress UCG	48(0.66%)	65(0.73%)	467(0.72%)	0.66	0.59	1.00
FFR measurement	1146(16%)	1513(17%)	12902(20%)	0.04	<0.001	<0.001
Access site						
Transradial	17218(80%)	17653(71%)	140179(70%)	<0.001	<0.001	<0.001
Transfemoral	3219(15%)	5943(24%)	50058(25%)			
Others	1118(5.2%)	1266(5.1%)	9530(4.8%)			
PCI treatment						
Single lesion					<0.001	
DES	14162(66%)	NA	170946(86%)			
DCB	4927(23%)	NA	18157(9.1%)			
POBA	1761(8.2%)	NA	6729(3.4%)			
Others	644(3.0%)	NA	2920(1.5%)			
Multi-lesion, MV + SB						
DES + DES	NA	10336(42%)	NA			
DES + DCB	NA	2989(12%)	NA			
DES + POBA	NA	8006(32%)	NA			
DCB + DES	NA	375(1.5%)	NA			
DCB + DCB	NA	1049(4.2%)	NA			
DCB + POBA	NA	407(1.6%)	NA			
POBA + DES	NA	378(1.5%)	NA			
POBA + DCB	NA	105(0.42%)	NA			
POBA + POBA	NA	457(1.8%)	NA			
Others	NA	760(3.1%)	NA			
Rotablation	201(0.93%)	1013(4.1%)	8768(4.4%)	<0.001	<0.001	0.02
Fluoroscopy time (min)	25 ± 19	39 ± 27	29 ± 24	<0.001	<0.001	<0.001
In-hospital outcome						
Composite endpoint	160(0.74%)	474(1.9%)	4403(2.2%)	<0.001	<0.001	0.003
In-hospital death	60(0.28%)	156(0.63%)	1919(0.96%)	<0.001	<0.001	<0.001
Procedure-related MI	48(0.22%)	249(1.0%)	1039(0.52%)	<0.001	<0.001	<0.001
Cardiac tamponade	31(0.14%)	53(0.21%)	299(0.15%)	0.10	0.91	0.02
Heart failure/cardiogenic shock	52(0.24%)	239(0.96%)	2000(1.0%)	<0.001	<0.001	0.57
Acute or subacute stent thrombosis	7(0.032%)	35(0.14%)	281(0.14%)	<0.001	<0.001	1.00
Emergent surgery	12(0.056%)	15(0.060%)	188(0.094%)	0.99	0.10	0.12
Whole bleeding event	32(0.15%)	89(0.36%)	776(0.39%)	<0.001	<0.001	0.50
Access site	20(0.093%)	57(0.23%)	422(0.21%)	<0.001	<0.001	0.61
Non-access site	12(0.056%)	36(0.14%)	374(0.19%)	0.005	<0.001	0.16

Values are mean ± SD or n (%). CTA, computed tomography angiography; DCB, drug-coated balloon; DES, drug-eluting stent; ECG, electrocardiography; FFR, fractional flow reserve; NA, not available; PCI, percutaneous coronary intervention; MI, myocardial infarction; MV, major vessel; POBA, plain old balloon angioplasty; SB, side branch; SD, standard deviation; UCG, ultrasound cardiography

Fig. 6 shows the distribution of the institutional frequency of PCI for restenotic lesions by the tertiles for each PCI procedure. There were significant differences in restenotic PCI frequency among SB-PCI tertile groups (low-frequency tertile 9.2 ± 4.9%, moderate-frequency tertile 9.9 ± 5.3%, high-frequency tertile 10.4 ± 5.8%, p-value for trend = 0.20), SB + MV-PCI tertile groups (low-frequency tertile 9.0 ± 5.2%, moderate-frequency tertile 10.0 ± 5.3%, high-frequency tertile 10.5 ± 5.4%, p-value for trend = 0.007), and MV-PCI tertile groups (low-frequency tertile 11.0 ± 5.8%, moderate-frequency tertile 9.8 ± 4.8%, high-frequency tertile 8.7 ± 5.2%, p-value for trend = 0.012). For MV-PCI, there were significant differences in restenotic PCI frequency between the moderate-frequency tertile group and the low-frequency (p = 0.01) and high-frequency tertile groups (p = 0.02).

4. Discussion

The present study, involving data from 257,492 cases in the Japanese PCI Registry, demonstrated that SB-PCI alone was performed in 8.4% of the registered cases, and SB + MV-PCI was performed in 9.6%. DES deployment and drug-coated balloon treatment were performed in 66% and 23% of SB-PCI alone cases and in 42% and 17% of SB + MV-PCI cases, respectively. Moreover, the acute complication rate of SB-PCI was lower than that of MV-PCI, and even SB + MV-PCI. Although a higher proportion of institutional frequency of side-branch-related PCI, with less MV-PCI (<75.76%), was associated with frequent performance of PCI for restenotic lesions, a lower proportion of SB-PCI (<6.55%) was associated with more in-hospital adverse events.

Patients in the SB-PCI group presented with lesser lesion complexity (higher prevalence of non-ST-elevation myocardial infarction and one-vessel disease) and lesser comorbidity (e.g., heart failure, cardiogenic shock, and cardiac arrest) than did patients in the MV-PCI group. Notably, the indication for PCI did not seem to differ between SB-PCI and MV-PCI, as the incidence of pre-PCI evaluation, including stress-testing or coronary computed tomography angiography, did not differ between the two groups. The frequency of invasive fractional flow reserve measurement in the SB-PCI group (16%) was higher than that reported in other nationwide registries (4.0% in 2017 for the United States [4], 11.5% in 2014 for South Korea [13], 6.8% in 2014 for Spain [14], and 3.3% in 2010–2013 for Germany [15]). SB-PCI with less frequent use of DES was not associated with an increase in immediate procedure-related complications (Fig. 2B). Notably, while male

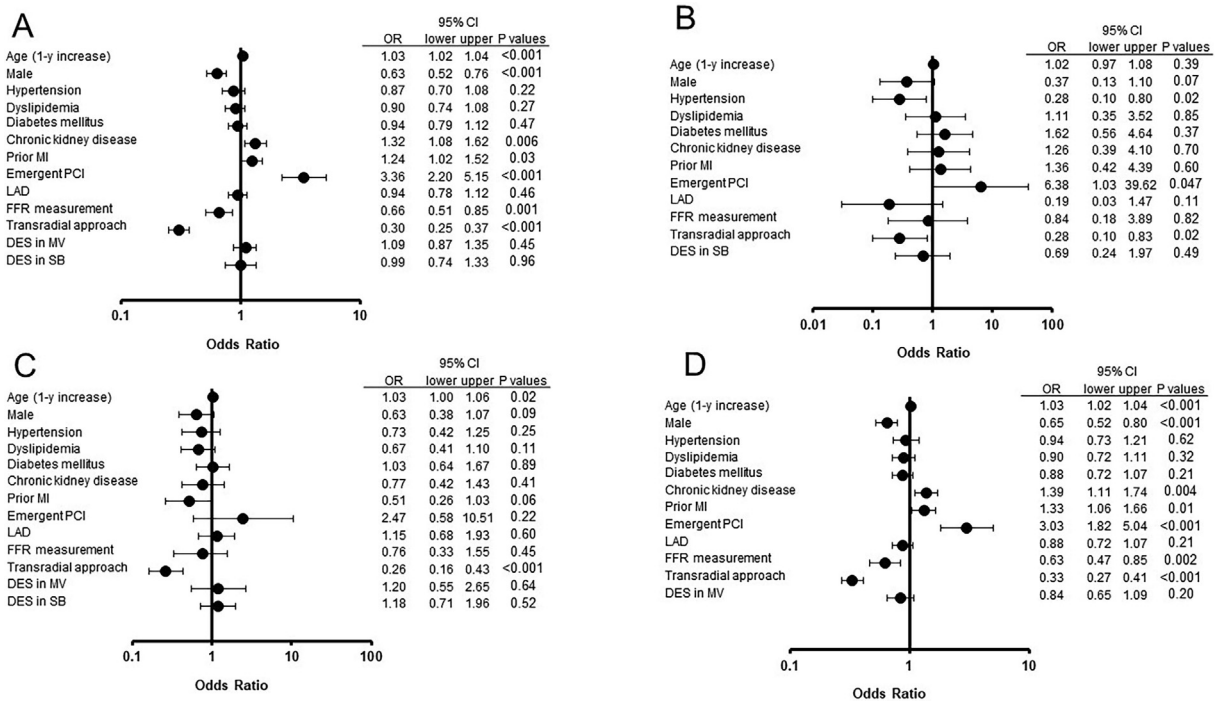


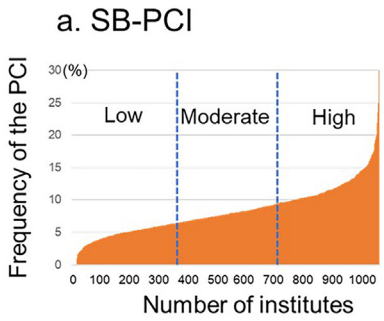
Fig. 2. Adjusted odds ratio (OR) of the composite endpoint of in-hospital adverse events. A. Whole cohort. B. SB-PCI group: side branch PCI alone. C. SB + MV-PCI group: PCI for both side branch and adjacent major vessel. D. MV-PCI group: major vessel PCI alone. MI: myocardial infarction, PCI: percutaneous coronary intervention, LAD: left anterior descending artery, FFR: fractional flow reserve, DES: drug-eluting stent.

sex, chronic kidney disease, prior myocardial infarction, and fractional flow reserve measurement were associated with adverse outcome events in MV-PCI, these factors did not have a significant association with adverse outcomes in SB-PCI.

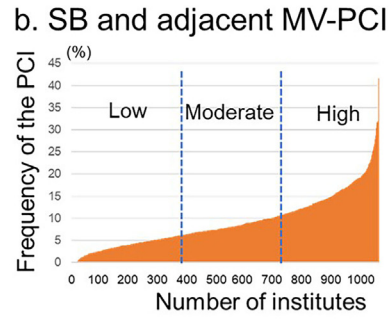
In a previous analysis of coronary computed tomography angiography and fractional flow reserve, the fractional myocardial mass (i.e., the ratio of vessel-specific myocardial mass to the whole myocardium) in the side branch of non-left main bifurcation lesions, was 4–9%, and the proportion of fractional myocardial mass >10% was 21% [2]. In our study, the total frequency of all side-branch-related PCI procedures (SB-PCI and SB + MV-PCI, as well as PCI for a side branch and non-adjacent major vessel) reached 22%. The National Cardiovascular Data Registry CathPCI registry in the United States, which included 550,872 to 637,650 cases from 2013 to 2017, also reported that the frequency of side-branch-related PCI reached 18.2%-19.8% [4]. The high frequency of side-branch-related PCI in our study may reflect cases with progression of myocardial ischemia in the side branch during adjacent MV-PCI in the bifurcation lesion or combined myocardial ischemia in complex cases, due to moderate-to-severe stenosis in multiple side branches in the lateral or inferior area.

Although bifurcation lesions were included in the SB + MV-PCI group, 42% had DES implantation in both the major vessel and side branch, which is lower than that in the SB-PCI group (66%), but higher than that for the two-stent technique in previous coronary bifurcation registries in Japan (13–22%) [16–18]. Since non-bifurcation lesions were included in the SB + MV-PCI group, more frequent side-branch stenting was performed for diffuse or tight stenosis in non-bifurcation lesions. The efficacy of the drug-coated balloon over the new-generation DES is still controversial for such lesions [6,7], albeit our results do suggest the safety of drug-coated balloon use as a secondary treatment in the side branch, despite the possible risks of dissection and acute occlusion. However, lower comorbidity in the SB-PCI group may have attenuated the overall incidence of procedural complications.

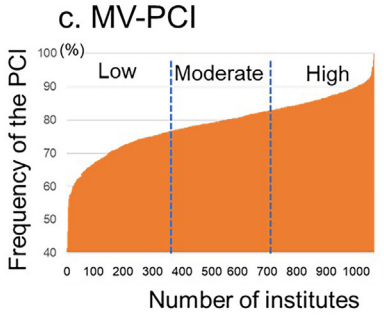
Regarding our analysis on the institutional frequency of SB-PCI, our finding that the institutional frequency of SB-PCI was inversely associated with the adverse event risk in the whole cohort, and in the MV-PCI group, suggests the following: (1) SB-PCI experience may have enhanced the technical skills required for PCI, resulting in a reduction of procedural complications, not only in SB-PCI, but also in MV-PCI; (2) the threshold for performing SB-PCI and MV-PCI might be low in the high-frequency tertile of SB-PCI; (3) the shift towards less frequent SB-PCI may have led to the greater compromise of adjusting a side branch after MV-PCI in the bifurcation lesion; and (4) the shift to MV-PCI may have led to increased lesion severity with a higher risk for acute complication. According to these results, the PCI strategy of eccentric restriction of SB-PCI, with a proportion of <6.55%, might be suboptimal due to the increased risk of acute adverse events. Lastly, the institutional frequency of PCI for restenotic lesions was inversely associated with the frequency of MV-PCI, which indicates that restenotic PCI increased with increased institutional frequency of side-branch-related PCI. The potential causes of this relationship are as follows: (1) the smaller diameter in SB-PCI-targeted arteries could lead to an increase in restenosis; or (2) operators in institutes with high-frequency of SB-PCI may be more likely to treat restenotic lesions. Monitoring MV-PCI, with a proportion of >75.76%, may



	Low	Moderate	High	p-value
Range, %	0-6.54	6.55–9.33	9.34–100	
Median, %	4.83	7.69	11.47	
Institutes, n	364	363	363	
Number of the PCI per institute, median [interquartile range]				
SB PCI	8 [4–15]	16 [10–26]	21 [11–36]	<0.001
SB+MV PCI	11 [5–27]	16 [8–31]	15 [6–32]	0.001
MV PCI	148 [70–244]	172 [101–271]	138 [68–224]	<0.001



	Low	Moderate	High	p-value
Range, %	0–6.53	6.54–11.27	11.28–100	
Median, %	3.68	7.78	14.61	
Institutes, n	364	363	363	
Number of the PCI per institute, median [interquartile range]				
SB PCI	12 [6–21]	16 [9–26]	16 [18–29]	<0.001
SB+MV PCI	5 [2–10]	16 [10–27]	32 [16–51]	<0.001
MV PCI	143 [70–236]	166 [98–262]	148 [80–255]	0.09



	Low	Moderate	High	p-value
Range, %	0–75.76	75.77–82.35	82.36–100	
Median, %	71.25	79.7	86.7	
Institutes, n	364	363	363	
Number of the PCI per institute, median [interquartile range]				
SB PCI	18 [10–33]	16 [9–27]	10 [5–18]	<0.001
SB+MV PCI	28 [13–49]	16 [8–28]	7 [3–13]	<0.001
MV PCI	141 [73–240]	162 [90–256]	148 [76–249]	0.025

Fig. 3. Left panel: Distribution of the frequency of each type of PCI in the institute. (a) SB-PCI alone, (b) SB and adjacent MV-PCI, (c) MV-PCI alone. Right panel: Stratification according to the institutional frequency of each PCI. Low-, moderate-, and high-frequency groups were divided according to the tertiles of the institutional frequency of each PCI. SB: side branch, MV: major vessel.

be helpful to control excessive side-branch-related PCI and reduce restenotic PCI.

This study has some limitations. First, this was a retrospective observational, clinical study, and not a randomized controlled trial. Since a causal relationship between in-hospital adverse events and institutional frequency of SB-PCI was not directly evaluated and the indication of SB-PCI varied among institutes, the results should be cautiously interpreted given the observational nature of the study. Second, the Japanese PCI Registry did not include cases treated with bypass surgery or conservative medical therapy. Comparisons between complex SB + MV-PCI and surgery, or between SB-PCI and medical therapy, could not be performed. Third, data on lesion severity, vessel size, and functional assessment, required for evaluating the appropriateness of the PCI, were lacking. Fourth, cases with dominancy of the side branch over the adjusting major vessel were included (e.g., dominant obtuse marginal branch [#12] over the distal left circumflex artery [#13]). Fifth, the impact of SB-PCI on the clinical outcomes at long-term follow-up and its medical cost were not evaluated. Sixth, an occlusive event in the side branch after stenting in the adjacent major vessel might play a major role, or even a partial role, in the development of worse clinical outcomes after bifurcation stenting. However, the numbers of bifurcation lesions included in the SB + MV-PCI group were uncertain. Seventh, the analysis of restenotic PCI did not directly correspond to the outcome of the present PCI and its institutional frequency was used as a surrogate marker.

In conclusion, in current Japanese clinical practice, SB-PCI is performed after a reasonable pre-PCI assessment, with a low incidence of in-hospital adverse events. A proportional shift to more frequent performance of side-branch-related PCI with less MV-PCI (<75.76% of all PCI cases) presented more risk of frequent restenotic PCI, while an excessive proportional shift to less frequent performance of SB-PCI (<6.55%) presented more risk of in-hospital adverse events.

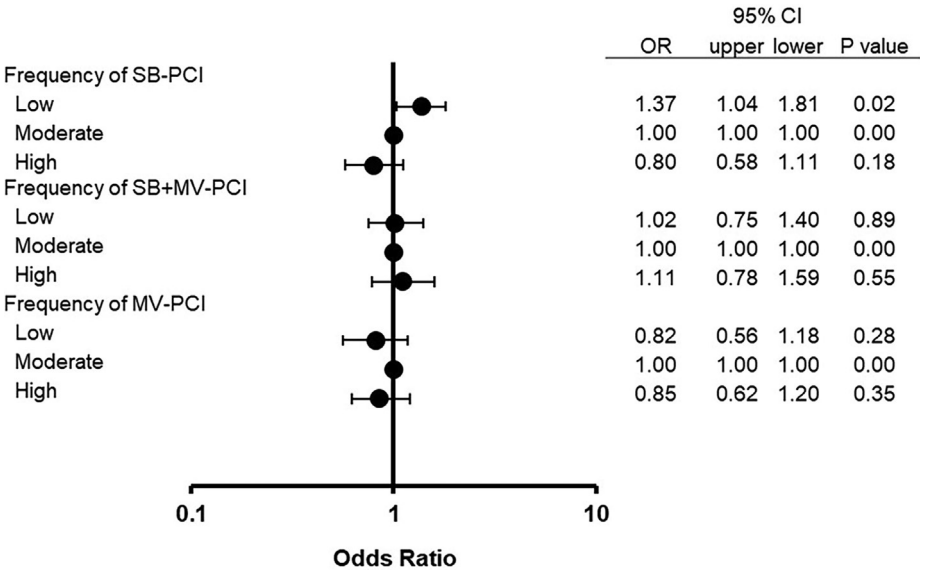


Fig. 4. Adjusted odds ratio (OR) for composite endpoint of in-hospital adverse events according to the tertiles of the institutional frequency of each PCI in the multivariable analysis. Low-, moderate-, and high-frequency groups were divided according to the tertiles of the institutional frequency of each PCI indicated in Fig. 3.

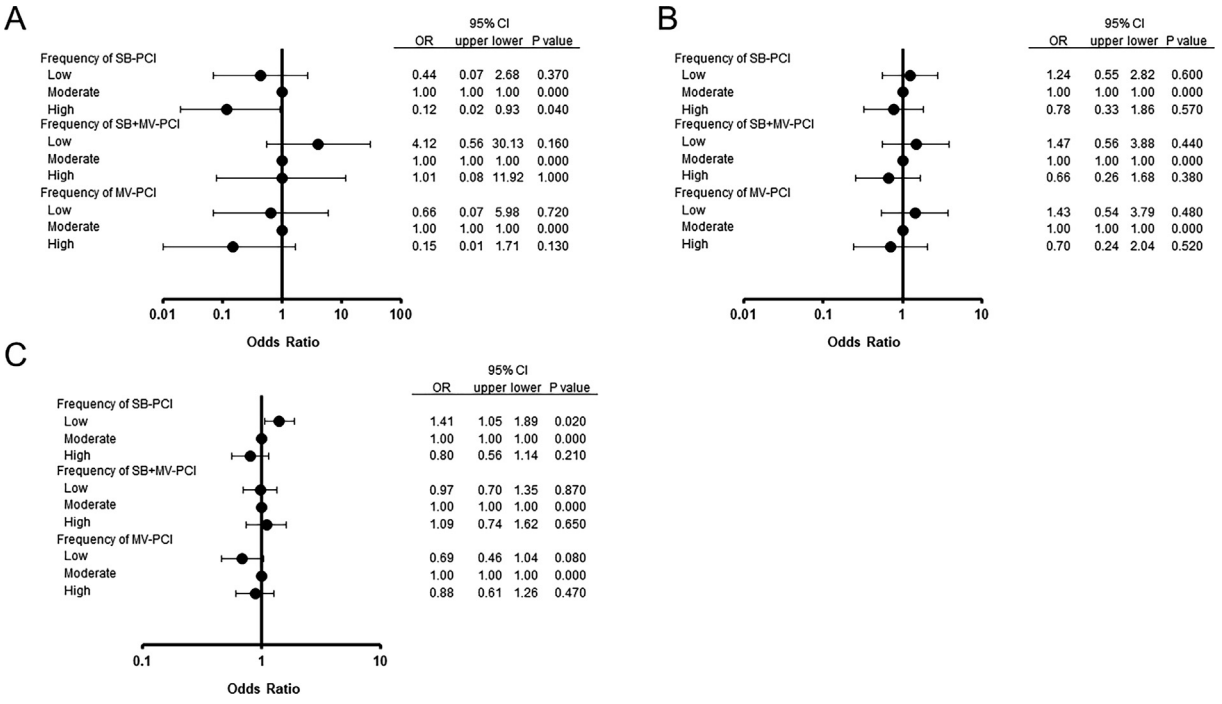


Fig. 5. Adjusted odds ratio (OR) for composite endpoint of in-hospital adverse events according to the tertiles of the institutional frequency of each PCI in the multivariable analysis. A. SB-PCI group: side branch PCI alone. B. SB + MV-PCI group: PCI for both side branch and adjacent major vessel. C. MV-PCI group: major vessel PCI alone.

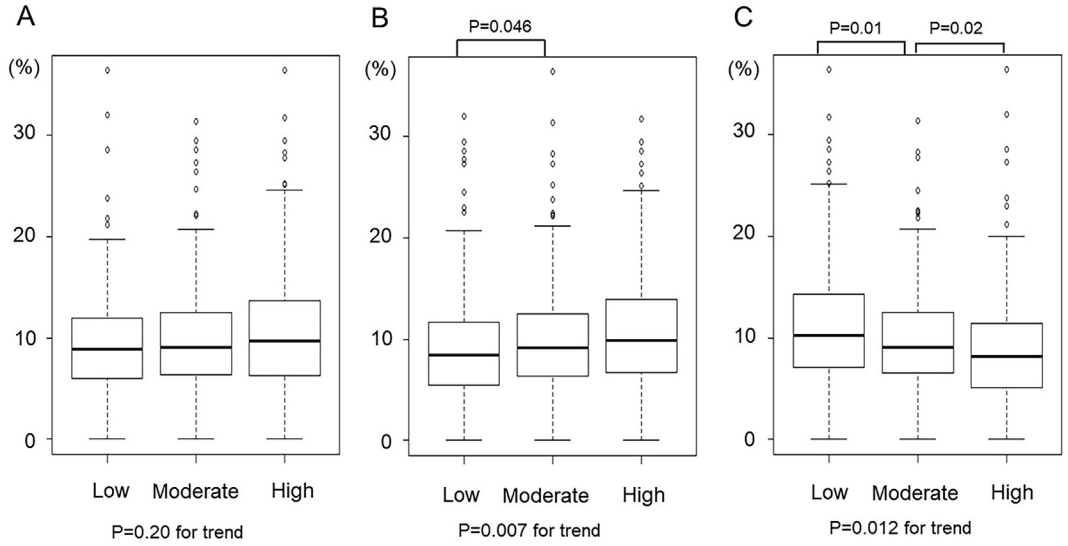


Fig. 6. Distribution of institutional frequency of the PCI for the restenotic lesion according to the tertiles of the institutional frequency of each PCI. Low-, moderate-, and high-frequency groups were divided according to the tertiles of the institutional frequency of each PCI indicated in Fig. 3. A. SB-PCI tertile: side branch PCI alone. B. SB + MV-PCI tertile: PCI for both side branch and adjacent major vessel. C. MV-PCI tertile: major vessel PCI alone.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M.R. Patel, J.H. Calhoon, G.J. Dehmer, J.A. Grantham, T.M. Maddox, D.J. Maron, P.K. Smith, ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/ STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease, J. Am. Coll. Cardiol. 69 (2017) 2212–2241.

[2] H.Y. Kim, J.-H. Doh, H.-S. Lim, C.-W. Nam, E.-S. Shin, B.-K. Koo, J.M. Lee, T.K. Park, J.H. Yang, Y.B. Song, J.-Y. Hahn, S.H. Choi, H.-C. Gwon, S.-H. Lee, S.M. Kim, Y. Choe, J.-H. Choi, Identification of coronary artery side branch supplying myocardial mass that may benefit from revascularization, JACC Cardiovasc. Interv. 10 (6) (2017) 571–581.

[3] B.-K. Koo, H.-J. Kang, T.-J. Youn, I.-H. Chae, D.-J. Choi, H.-S. Kim, D.-W. Sohn, B.-H. Oh, M.-M. Lee, Y.-B. Park, Y.-S. Choi, S.-J. Tahk, Physiologic assessment of jailed side branch lesions using fractional flow reserve, J. Am. Coll. Cardiol. 46 (4) (2005) 633–637.

[4] T. Inohara, S. Kohsaka, J.A. Spertus, F.A. Masoudi, J.S. Rumsfeld, K.F. Kennedy, T. Y. Wang, K. Yamaji, T. Amano, M. Nakamura, Comparative trends in percutaneous coronary intervention in Japan and the United States, 2013 to 2017, J. Am. Coll. Cardiol. 76 (11) (2020) 1328–1340.

[5] S. Rathore, Small coronary vessel angioplasty: outcomes and technical considerations, Vasc. Health Risk Manag. 6 (2010) 915–922.

[6] R.V. Jeger, A. Farah, M.-A. Ohlow, N. Mangner, S. Möbius-Winkler, G. Leibundgut, D. Weilenmann, J. Wöhrle, S. Richter, M. Schreiber, F. Mahfoud, A. Linke, F.-P. Stephan, C. Mueller, P. Rickenbacher, M. Coslovsky, N. Gilgen, S. Osswald, C. Kaiser, B. Scheller, P. Buser, M. Kühne, M. Zellweger, C. Sticherling, B. Wein, R. Twerenbold, G. Fahrni, B. Plicht, B. Struck, I. Önal, B. Cremers, Y. Clever, S. Ewen, S. Schirmer, M. Böhm, A. Wagner, B. Lauer, G. Stachel, R. Höllriegel, E. Winzer, H. Rickli, P. Ammann, P. Haager, L. Trachsel, L. Joerg, D. Nüssli, H. Roelli, M. Maeder, F. Rohner, S. Markovic, R. Paliskyte, D. Buckert, B. Awad, P. Erne, P. Jamshidi, F. Cuculi, I. Kapos, S. Toggweiler, F. Riede, T. Pörner, K. Lenk, M. Noutsias, R. Surber, G. Dannberg, M. Franz, S. Otto, R. Zweiker, E. Nlederl, S. Perl, B. Pieske, A. Schmidt, O. Luha, D. Von Lewinski, F. Krackhardt, B. Kherad, T. Jerichow, C. Butter, M. Neuss, G. Tambor, F. Hölschermann, L. Bruch, S. Winkler, C. Lenz, M. Seidel, B. Keweloh, A. Röttgen, S. Bohl, A. Wolf, A. Hoffmann, Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial, Lancet 392 (10150) (2018) 849–856.

[7] A. Silverio, S. Buccheri, D. Venetsanos, J. Alfredsson, B.o. Lagerqvist, J. Persson, N. Witt, S. James, G. Sarno, Percutaneous treatment and outcomes of small coronary vessels: a SCAAR report, JACC Cardiovasc. Interv. 13 (7) (2020) 793–804.

[8] G.C. Siontis, R. Piccolo, F. Praz, M. Valgimigli, L. Räber, D. Mavridis, P. Jüni, S. Windecker, Percutaneous coronary interventions for the treatment of stenoses in small coronary arteries: a network meta-analysis, JACC Cardiovasc. Interv. 9 (2016) 1324–1334.

[9] H.W. Sim, R. Ananthakrishna, S.P. Chan, A.F. Low, C.H. Lee, M.Y. Chan, E.L. Tay, P.H. Loh, K.H. Chan, H.C. Tan, J.P. Loh, Treatment of very small de novo coronary artery disease with 2.0 mm drug-coated balloons showed 1-year clinical outcome comparable with 2.0 mm drug-eluting stents, J. Invasive Cardiol. 30 (2018) 256–261.

[10] K. Sakakura, T. Inohara, S. Kohsaka, T. Amano, S. Uemura, H. Ishii, K. Kadota, M. Nakamura, H. Funayama, H. Fujita, S.-I. Momomura, Incidence and determinants of complications in rotational atherectomy, Circ. Cardiovasc. Interv. 9 (11) (2016), https://doi.org/10.1161/CIRCINTERVENTIONS.116.004278.

[11] T. Inohara, S. Kohsaka, K. Yamaji, T. Amano, K. Fujii, H. Oda, S. Uemura, K. Kadota, H. Miyata, M. Nakamura, T. Inohara, S. Kohsaka, K. Yamaji, T. Amano, K. Fujii, H. Oda, S. Uemura, K. Kadota, H. Miyata, M. Nakamura, K. Kadota, N. Shiode, N. Tanaka, T. Amano, S. Uemura, T. Akasaka, Y. Morino, K. Fujii, H. Hikichi, T. Amano, K. Fujii, S. Kohsaka, H. Ishii, K. Tanabe, Y. Ozaki, S. Sumitsuji, O. Iida, H. Hara, H. Takashima, S. Shirai, M. Nansato, T. Inohara, Y. Ueda, Y. Numasawa, S. Noma, Impact of institutional and operator volume on short-term outcomes of percutaneous coronary intervention: a report from the Japanese nationwide registry, JACC Cardiovasc. Interv. 10 (9) (2017) 918–927.

[12] M. Sawano, K. Yamaji, S. Kohsaka, T. Inohara, Y. Numasawa, H. Ando, O. Iida, T. Shinke, H. Ishii, T. Amano, Contemporary use and trends in percutaneous coronary intervention in Japan: an outline of the J-PCI registry, Cardiovasc. Interv. Ther. 35 (3) (2020) 218–226.

[13] J.-H. Kim, W. Choi, K.-C. Kim, C.-W. Nam, B.-K. Hong, J.-H. Kim, D.S. Jeon, J.-W. Bae, S.-H. Kim, K.-W. Moon, B.-R. Cho, D.I. Kim, J.-S. Jang, The current status of intervention for intermediate coronary stenosis in the Korean Percutaneous Coronary Intervention (K-PCI) registry, Korean Circ. J. 49 (11) (2019) 1022, https://doi.org/10.4070/kcj.2019.0074.

[14] B. García Del Blanco, F. Hernández Hernández, J.R. Rumoroso Cuevas, Nouche R. Trillo, Spanish Cardiac Catheterization and Coronary Intervention Registry. 24th Official Report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990–2014), Rev. Esp. Cardiol. 68 (2015) 1154–1164.

[15] T. Härle, U. Zeymer, M. Hochadel, R. Zahn, S. Kerber, B. Zrenner, V. Schächinger, B. Lauer, T. Runde, A. Elsässer, Real-world use of fractional flow reserve in Germany: results of the prospective ALKK coronary angiography and PCI registry, Clin. Res. Cardiol. 106 (2) (2017) 140–150.

[16] M. Toyofuku, T. Kimura, T. Morimoto, Y. Hayashi, N. Shiode, T. Okimoto, M. Otsuka, H. Tamekiyo, T. Tamura, K. Kadota, K. Inoue, K. Mitsudo, Comparison of target-lesion revascularisation between left main coronary artery bifurcations and left anterior descending coronary artery bifurcations using the one and two stent approach with sirolimus-eluting stents, EuroIntervention. 7 (7) (2011) 796–804.

[17] K. Kozuma, Y. Ota, Y. Nagai, Y. Katsuta, E. Nozaki, T. Onodera, Y. Ikari, J. Kotani, E. Kyo, H. Yokoi, M. Nakamura, Clinical and angiographic outcomes with sirolimus-eluting stent for coronary bifurcation lesions. The J-PMS study, Circ. J. 75 (2) (2011) 306–314.

[18] M. Ohya, K. Kadota, M. Toyofuku, T. Morimoto, H. Higami, Y. Fuku, K. Yamaji, H. Muranishi, Y. Yamaji, K. Nishida, D. Furukawa, T. Tada, E. Ko, K. Ando, H. Sakamoto, T. Tamura, K. Kawai, T. Kimura, Long-term outcomes after stent implantation for left main coronary artery (from the multicenter assessing optimal percutaneous coronary intervention for left main coronary artery stenting registry), Am. J. Cardiol. 119 (3) (2017) 355–364.