Comparison of Outcomes of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting Among Patients With Three-Vessel Coronary Artery Disease in the New-Generation Drug-Eluting Stents Era (From CREDO-Kyoto PCI/CABG Registry Cohort-3)

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There is a scarcity of data comparing long-term clinical outcomes between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in patients with three-vessel coronary artery disease (3VD) in the new-generation drug-eluting stents era. CREDO-Kyoto PCI/CABG registry Cohort-3 enrolled 14927 consecutive patients who had undergone first coronary revascularization with PCI or isolated CABG between

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January 2011 and December 2013. We identified 2525 patients with 3VD (PCI: n = 1747 [69%], and CABG: n = 778 [31%]). The primary outcome measure was all-cause death. Median follow-up duration was 5.7 (interquartile range: 4.4 to 6.6) years. The cumulative 5-year incidence of all-cause death was significantly higher in the PCI group than in the CABG group (19.8% vs 13.2%, log-rank p = 0.001). After adjusting confounders, the excess risk of PCI relative to CABG for all-cause death remained significant (HR, 1.45; 95% CI, 1.14 to 1.86; p = 0.003), which was mainly driven by the excess risk for non-cardiovascular death (HR, 1.88; 95% CI, 1.30 to 2.79; p = 0.001), while there was no excess risk for cardiovascular death between PCI and CABG (HR, 1.19; 95% CI, 0.87 to 1.64; p = 0.29). There was significant excess risk of PCI relative to CABG for myocardial infarction (HR, 1.77; 95% CI, 1.19 to 2.69; p = 0.006), whereas there was no excess risk of PCI relative to CABG for stroke (HR, 1.24; 95% CI, 0.83 to 1.88; p = 0.30). In conclusion, in the present study population reflecting real-world clinical practice in Japan, PCI compared with CABG was associated with significantly higher risk for all-cause death, while there was no excess risk for cardiovascular death between PCI and CABG. **(Am J Cardiol 2021;145:25−36)**

A pooled analysis from 11 randomized controlled trials comparing percutaneous coronary intervention (PCI) with stents and coronary artery bypass grafting (CABG) in patients with multivessel coronary artery disease has demonstrated the higher mortality risk with PCI than with CABG, especially in those with diabetes or higher coronary anatomic complexity.[1] Accordingly, current practice guidelines for the treatment of three-vessel coronary artery disease (3VD) recommend PCI as a good alternative to CABG only in non-diabetic patients with low coronary anatomic complexity, and CABG remains the standard of care for patients with 3VD.[2-4] However, the available data comparing long-term clinical outcomes between PCI using new-generation drug-eluting stents (DES) and CABG in patients with MVD, particularly 3VD, are still insufficient to adequately guide the clinical practice. Therefore, we evaluated long-term clinical outcomes after PCI versus CABG among patients with 3VD in the new-generation DES era using a large Japanese observational database of patients who underwent first coronary revascularization.

Methods

The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG registry Cohort-3 is a physician-initiated, non-company-sponsored, multicenter registry enrolling consecutive patients who underwent first coronary revascularization with PCI or isolated CABG without combined noncoronary surgery among 22 Japanese centers between January 2011 and December 2013 (Supplementary Appendix). Both PCI and CABG were available in 16 centers, while there was no cardiovascular surgery division and only PCI was available in 6 centers. The relevant ethics committees in all the participating centers approved the study protocol. Because of the retrospective enrollment, written informed consents from the patients were waived; however, we excluded those patients who refused participation in the study when contacted for follow-up. This strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor and Welfare.

A total of 14927 patients who had undergone first coronary revascularization with PCI or isolated CABG (PCI: N=13307, and CABG: n = 1620) were enrolled in the CREDO-Kyoto PCI/CABG registry Cohort-3 (Supplementary Figure 1). In consistent with the report from the CREDO-Kyoto PCI/CABG registry Cohort-2,[5] we further excluded those patients with refusal for study participation (n = 60), acute myocardial infarction (n = 5510), left main disease (n = 855), and 1 or 2-vessel disease (n = 5977), and identified 2525 patients with 3VD for the comparison of long-term clinical outcomes between PCI and CABG (Figure 1).

The primary outcome measure of this study was all-cause death. The secondary outcome measures included cardiovascular death, cardiac death, sudden cardiac death, non-cardiovascular death, non-cardiac death, myocardial infarction, definite stent thrombosis or symptomatic graft occlusion, stroke, hospitalization for heart failure, major bleeding, target-vessel revascularization (TVR), any coronary revascularization, and a composite of all-cause death, myocardial infarction, or stroke.

Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Cardiovascular death included cardiac death and other vascular death related to stroke, renal disease, and vascular disease. Death of unknown cause and any death during the index hospitalization for coronary revascularization were regarded as cardiac death. Sudden cardiac death was defined as unexplained death in previously stable patients. Definitions of baseline characteristics and other outcome measures are described in Supplementary Methods. Duration of dual antiplatelet therapy (DAPT) was left to the discretion of each attending physician. Persistent discontinuation of DAPT was defined as withdrawal of either thienopyridines or aspirin for at least 2 months.

Clinical, angiographic, and procedural data were collected from hospital charts or hospital databases according to the pre-specified definitions by the experienced clinical research coordinators from an independent clinical research organization (Research Institute for Production Development, Kyoto, Japan) (Supplementary Appendix). Follow-up data were collected from the hospital charts and/or obtained by contacting with patients, their relatives, or referring physicians between January 2018 and December 2019.

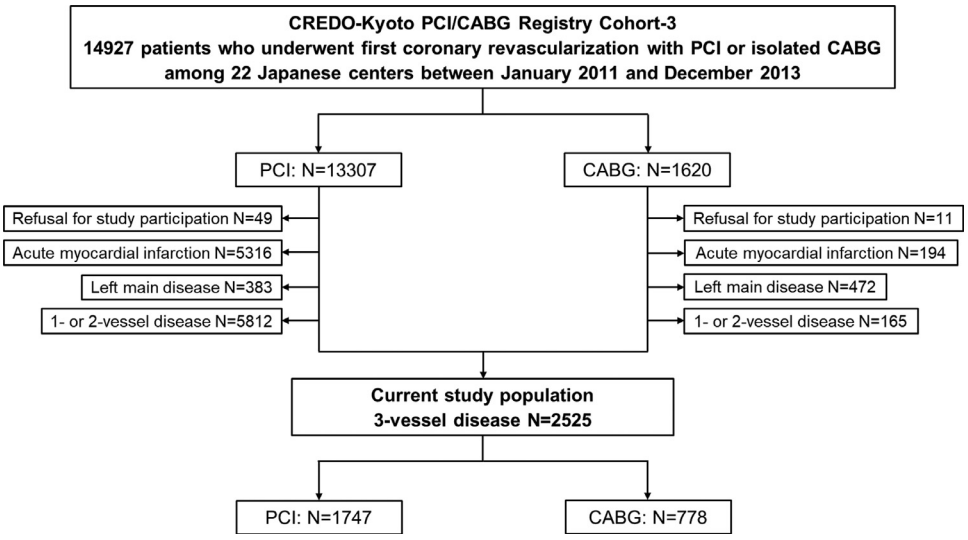


Figure 1. Study flow chart. CREDO-Kyoto PCI/CABG Registry Cohort-3=Coronary Revascularization Demonstrating Outcome Study in Kyoto PCI/CABG Registry Cohort-3; CABG=coronary artery bypass grafting; PCI=percutaneous coronary intervention.

Follow-up was regarded as completed, if follow-up data beyond July 1, 2017 were obtained. The clinical event committee adjudicated those events such as death, myocardial infarction, stent thrombosis, stroke, and major bleeding (Supplementary Appendix). Coronary anatomic complexity was evaluated according to the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score, which was calculated by the experienced cardiologists (Supplementary Appendix).

Categorical variables were presented as number and percentage, and compared with the chi-square test. Continuous variables were expressed as mean ± standard deviation or median (interquartile range). Continuous variables were compared with the Student's *t* test or Wilcoxon rank sum test based on their distributions. Cumulative incidence of the outcome measures was estimated by the Kaplan-Meier method, and the differences were assessed with the log-rank test. We also performed 30-day landmark analyses to estimate the cumulative incidence of myocardial infarction, stroke, and major bleeding within or beyond 30 days after the index coronary revascularization procedure. The cumulative incidence of a given event beyond 30 days was estimated by the Kaplan-Meier method among patients who were free from the event at 30 days. The effects of PCI relative to CABG for the outcome measures were expressed as hazard ratios (HRs) and their 95% confidence intervals (CIs). The HRs were estimated by the Cox proportional hazard models adjusting the 27 clinically relevant factors listed in Table 1. Continuous variables were dichotomized by clinically meaningful reference values to make proportional hazard assumptions robust and to be consistent with our previous reports.[6,7] Proportional hazard assumptions for the primary variable (PCI vs CABG) and the risk-adjusting variables were assessed on the plots of log (time) versus log (-log [survival]) stratified by the variable. The assumptions were verified to be acceptable for all the variables. To avoid overfitting, we constructed the parsimonious models with the 8 risk-adjusting variables including advanced age (≥75 years), men, diabetes, heart failure, prior myocardial infarction, prior stroke, end-stage renal disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2 or hemodialysis), and severe frailty for sudden cardiac death and hemorrhagic stroke due to limited number of patients with event. In the subgroup analyses, all-cause death and cardiovascular death were compared between PCI and CABG stratified by age, gender, diabetes, heart failure, end-stage renal disease, target of proximal left anterior descending coronary artery (LAD), and the SYNTAX score. We also conducted the propensity score matching analysis as a sensitivity analysis (Supplementary Methods). Status of DAPT was evaluated throughout the follow-up period, and the cumulative incidence of persistent discontinuation of DAPT in the PCI group was estimated by the Kaplan-Meier method. Statistical analyses were performed with JMP 14.0 software (SAS Institute Inc., Cary, North California). All statistical analyses were 2 tailed, and p values of <0.05 were considered statistically significant.

Results

The current study population consisted of 1747 patients (69%) who underwent PCI, and 778 patients (31%) who underwent CABG (Figure 1). Among 2248 patients who were enrolled from those centers with both PCI and CABG facilities, there were 1470 (65%) patients treated with PCI, and 778 (35%) treated with CABG.

Patients in the PCI group was significantly older and more often had severe frailty and malignancy, but not active malignancy, than those in the CABG group, whereas patients in the CABG group had higher prevalence of men, eGFR <30 mL/min/1.73m^2 without hemodialysis, and chronic obstructive pulmonary disease than those in the PCI group (Table 1). Regarding the angiographic and procedural characteristics, the CABG group had greater number of target lesions or anastomoses and higher coronary anatomic complexity as indicated by the greater SYNTAX

Table 1
Baseline characteristics and management during the index hospitalization

	PCI (N=1747)		CABG (N=778)		P value
(A) Clinical characteristics					
Age (years)	70.5±10.6		68.6±9.6		<0.001
Age ≥75 years*	669	(38.3%)	232	(29.8%)	<0.001
Men*	1278	(73.2%)	602	(77.4%)	0.02
Body mass index (kg/m^2)	23.9±3.7		23.8±3.5		0.35
Body mass index <25.0 kg/m^2*	1148	(65.7%)	519	(66.7%)	0.63
Unstable angina	42	(2.4%)	13	(1.7%)	0.23
Hypertension*	1529	(87.5%)	667	(85.7%)	0.22
Diabetes mellitus*	888	(50.8%)	424	(54.5%)	0.09
on insulin therapy	251	(14.4%)	169	(21.7%)	<0.001
Current smoking*	377	(21.6%)	142	(18.3%)	0.054
Heart failure*	410	(23.5%)	203	(26.1%)	0.16
LVEF	58.4±13.7		58.1±14.5		0.59
LVEF ≤40 %	173	(11.3%)	102	(13.8%)	0.10
Mitral regurgitation grade ≥3/4	116	(7.5%)	53	(7.1%)	0.72
Prior myocardial infarction*	396	(22.7%)	203	(26.1%)	0.06
Prior stroke (symptomatic)*	302	(17.3%)	136	(17.5%)	0.91
Peripheral vascular disease*	239	(13.7%)	110	(14.1%)	0.76
eGFR <30 mL/min/1.73m^2 or hemodialysis	220	(12.6%)	116	(14.9%)	0.12
eGFR <30 mL/min/1.73m^2 without hemodialysis*	84	(4.8%)	53	(6.8%)	0.04
Hemodialysis*	136	(7.8%)	63	(8.1%)	0.79
Atrial fibrillation*	153	(8.8%)	57	(7.3%)	0.22
Anemia (Hemoglobin <11.0 g/dL)*	304	(17.4%)	146	(18.8%)	0.41
Thrombocytopenia (Platelet <100 × 10^9 /L)*	31	(1.8%)	17	(2.2%)	0.49
Chronic obstructive pulmonary disease*	69	(4.0%)	46	(5.9%)	0.03
Liver cirrhosis*	55	(3.2%)	20	(2.6%)	0.42
Malignancy	234	(13.4%)	80	(10.3%)	0.03
Active malignancy*	44	(2.5%)	19	(2.4%)	0.90
Severe frailty*	73	(4.2%)	15	(1.9%)	0.003
(B) Procedural characteristics					
Number of target lesions or anastomoses	2.1±1.0		3.5±0.9		<0.001
Target of proximal LAD*	1166	(66.7%)	731	(94.0%)	<0.001
Target of chronic total occlusion*	383	(21.9%)	380	(48.8%)	<0.001
Emergency procedure	78	(4.5%)	19	(2.4%)	0.01
SYNTAX score	23 (17-29)		29 (23.5-34.5)		<0.001
Low <23	849	(49.1%)	135	(21.3%)	<0.001
Intermediate 23-32	643	(37.2%)	288	(45.5%)	
High ≥33	239	(13.8%)	210	(33.2%)	
Total number of stents	2 (2-4)				
Total stent length (mm)	56 (30-88)				
Stent use	1698	(97.2%)			
DES use	1596	(91.4%)			
New-generation DES use	1567	(89.7%)			
Everolimus-eluting stent (XIENCE^{TM})	946	(54.2%)			
Everolimus-eluting stent (PROMUS^{TM})	418	(23.9%)			
Biolimus-eluting stent (NOBORI^{TM})	468	(26.8%)			
Zotarolimus-eluting stent (RESOLUTE^{TM})	127	(7.3%)			
Zotarolimus-eluting stent (ENDEAVOR^{TM})	23	(1.3%)			
IVUS or OCT use	1423	(81.5%)			
IVUS use	1416	(81.1%)			
OCT use	50	(2.9%)			
Staged PCI	704	(40.3%)			
Internal thoracic artery graft use			760	(97.7%)	
Off pump surgery			472	(60.7%)	
(C) Baseline medications					
Antiplatelet therapy					
Thienopyridines	1736	(99.4%)	166	(21.3%)	<0.001
Ticlopidine	52	(3.0%)	13	(1.7%)	
Clopidogrel	1681	(96.2%)	153	(19.7%)	
Unknown	3	(0.2%)	0	(0.0%)	
Aspirin	1736	(99.4%)	766	(98.5%)	0.03
Cilostazol	64	(3.7%)	24	(3.1%)	0.46

(*continued*)

Table 1 (*Continued*)

	PCI (N=1747)		CABG (N=778)		P value
Other medications					
Statins*	1286	(73.6%)	506	(65.0%)	<0.001
High-intensity statins	31	(1.8%)	5	(0.6%)	0.02
Beta-blockers*	657	(37.6%)	435	(55.9%)	<0.001
ACE-I/ARB*	1107	(63.4%)	233	(30.0%)	<0.001
Nitrates	464	(26.6%)	94	(12.1%)	<0.001
Calcium channel blockers*	895	(51.2%)	294	(37.8%)	<0.001
Nicorandil	330	(18.9%)	285	(36.6%)	<0.001
Oral anticoagulants*	165	(9.4%)	413	(53.1%)	<0.001
Warfarin	141	(8.1%)	407	(52.3%)	<0.001
DOAC	24	(1.4%)	6	(0.8%)	0.18
Proton pump inhibitors or histamine type-2 receptor blockers*	1265	(72.4%)	719	(92.4%)	<0.001
Proton pump inhibitors	1086	(62.2%)	658	(84.6%)	<0.001
Histamine type-2 receptor blockers	192	(11.0%)	62	(8.0%)	0.02

Values were missing for LVEF in 255 patients, for mitral regurgitation in 235 patients, and for SYNTAX score in 161 patients.

* Risk-adjusting variables selected for the Cox proportional hazard models.

ACE-I=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; CABG=coronary artery bypass grafting; DES=drug-eluting stents; DOAC=direct oral anticoagulants; eGFR=estimated glomerular filtration rate; IVUS=intravascular ultrasound; LAD=left anterior descending coronary artery; LVEF=left ventricular ejection fraction; OCT=optical coherence tomography; PCI=percutaneous coronary intervention; SYNTAX=SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.

score than the PCI group. In the PCI group, DES and new-generation DES were used in 91.4% and 89.7% of patients, respectively, and intracoronary imaging devices were used during the PCI procedure in 81.5% of patients. In the CABG group, at least 1 internal thoracic artery graft was used in 97.7% of patients, and off-pump surgery was performed in 60.7% of patients (Table 1). In terms of baseline medications, thienopyridines were prescribed in 166 (21.3%) of patients in the CABG group, but were discontinued before the index procedure in 102 (13.1%) of patients. Oral anticoagulants were more often prescribed in the CABG group than in the PCI group, partly because newly diagnosed atrial fibrillation occurred after the index procedure in 161 (20.7%) of patients in the CABG group.

Median follow-up duration was 5.7 (interquartile range: 4.4 to 6.6) years, and complete 1-, 3-, and 5-year clinical follow-up data were obtained in 96.6%, 94.0%, and 83.2% of patients, respectively. Complete 1- and 3-year follow-up rates were lower in the CABG group than in the PCI group (94.1% vs 97.7%, and 91.8% vs 95.0%, respectively), although complete 5-year follow-up rate was similar between the 2 groups (82.3% in the CABG group vs 83.7% in the PCI group).

The cumulative 5-year incidence of all-cause death was significantly higher in the PCI group than in the CABG group (19.8% versus 13.2%, log-rank p = 0.001). However, the cumulative 5-year incidence of cardiovascular death was not significantly different between the 2 groups (10.2% in the PCI group vs 9.2% in the CABG group, log-rank p = 0.60), while the cumulative 5-year incidence of non-cardiovascular death was significantly higher in the PCI group than in the CABG group (10.7% vs 4.4%, log-rank p <0.001) (Figure 2). After adjusting confounders, the excess risk of PCI relative to CABG for all-cause death remained significant (HR, 1.45; 95% CI, 1.14-1.86; p = 0.003). However, the excess mortality risk of PCI relative to CABG was mainly driven by the excess risk for non-cardiovascular death (HR, 1.88; 95% CI, 1.30 to 2.79; p = 0.001). The excess risk of PCI relative to CABG for cardiovascular death was not significant (HR, 1.19; 95% CI, 0.87 to 1.64; p = 0.29) (Table 2). The proportion of non-cardiovascular death among the causes of death was numerically higher in the PCI group than in the CABG group (50.4% vs 35.8%). Dominant causes of cardiovascular death were sudden cardiac death, heart failure, and death of unknown cause, but not myocardial infarction (Supplementary Table 1).

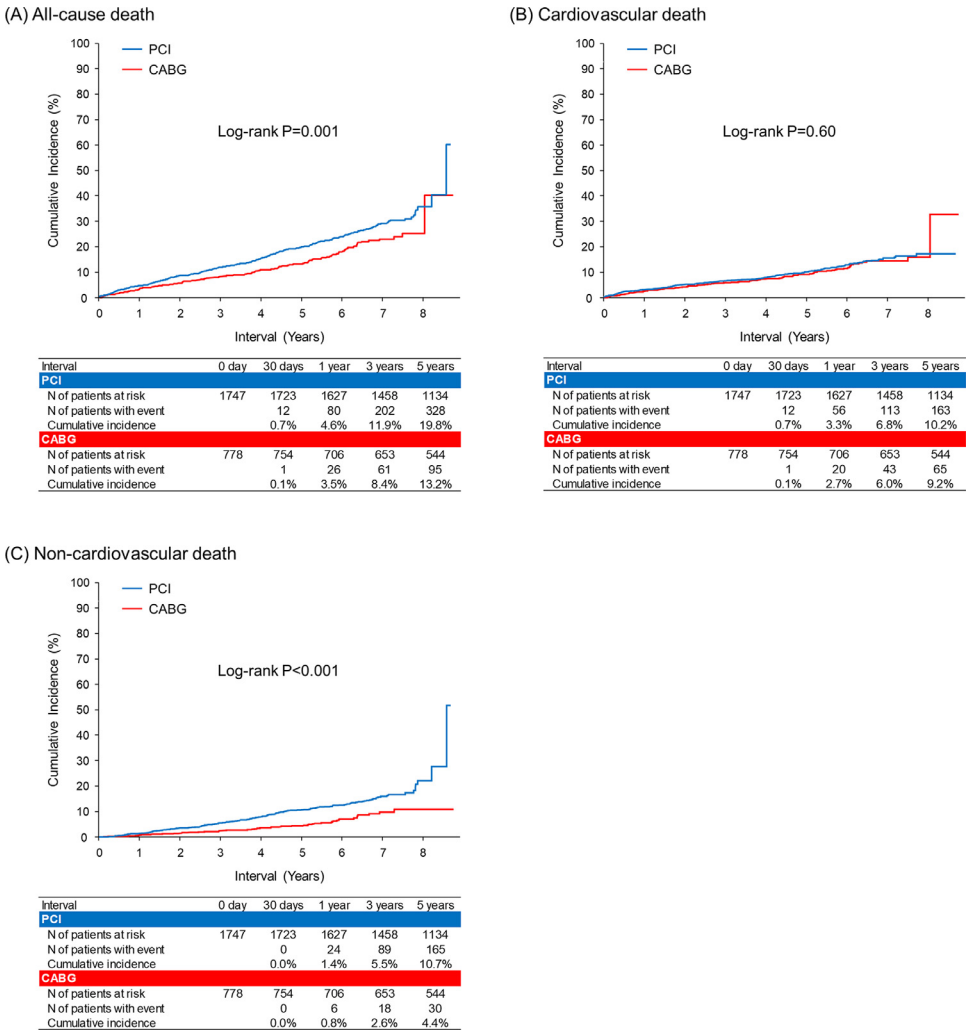
The cumulative 5-year incidence of and the adjusted risks for myocardial infarction, TVR, any coronary revascularization, and a composite of death, myocardial infarction, or stroke were significantly higher in the PCI group than in the CABG group (Figure 3 and Table 2). The cumulative 5-year incidence of definite stent thrombosis or symptomatic graft occlusion was very low in both groups. The cumulative 5-year incidence of and the adjusted risk for major bleeding were significantly lower in the PCI group than in the CABG group. The results of the 30-day landmark analyses are shown in Supplementary Tables 2, 3, and 4. The cumulative 1-, 3-, and 5-year incidence of persistent discontinuation of DAPT in the PCI group was 22.1%, 55.3%, and 69.2%, respectively (Supplementary Figure 2).

In the subgroup analyses, there was no significant interaction between the subgroup factors and the effects of PCI relative to CABG for all-cause death and for cardiovascular death (Table 3).

After propensity score matching, baseline characteristics of the PCI and CABG groups were much more comparable than those in the entire study population (Supplementary Table 5). Results from the propensity score matching analyses were consistent with those results derived from the Cox proportional hazard models in the entire cohort (Supplementary Table 6).

Discussion

The main findings of this study comparing PCI with CABG in patients with 3VD in the new-generation DES era



Interval	0 day	30 days	1 year	3 years	5 years
PCI					
N of patients at risk	1747	1723	1627	1458	1134
N of patients with event		12	80	202	328
Cumulative incidence		0.7%	4.6%	11.9%	19.8%
CABG					
N of patients at risk	778	754	706	653	544
N of patients with event		1	26	61	95
Cumulative incidence		0.1%	3.5%	8.4%	13.2%

Interval	0 day	30 days	1 year	3 years	5 years
PCI					
N of patients at risk	1747	1723	1627	1458	1134
N of patients with event		12	56	113	163
Cumulative incidence		0.7%	3.3%	6.8%	10.2%
CABG					
N of patients at risk	778	754	706	653	544
N of patients with event		1	20	43	65
Cumulative incidence		0.1%	2.7%	6.0%	9.2%

Interval	0 day	30 days	1 year	3 years	5 years
PCI					
N of patients at risk	1747	1723	1627	1458	1134
N of patients with event		0	24	89	165
Cumulative incidence		0.0%	1.4%	5.5%	10.7%
CABG					
N of patients at risk	778	754	706	653	544
N of patients with event		0	6	18	30
Cumulative incidence		0.0%	0.8%	2.6%	4.4%

Figure 2. Kaplan-Meier event curves for all-cause death, cardiovascular death, and non-cardiovascular death
(A) all-cause death, (B) cardiovascular death, and (C) non-cardiovascular death. CABG=coronary artery bypass grafting; PCI=percutaneous coronary intervention.

were as follows; (1) In the present study population reflecting real-world clinical practice in Japan between 2011 and 2013, PCI was the preferred modality of coronary revascularization used in almost two-thirds of patients with 3VD; (2) PCI compared with CABG was associated with significantly higher risk for all-cause death, which was mainly driven by the excess risk for non-cardiovascular death; (3) The excess risk of PCI relative to CABG for cardiovascular death was not significant; (4) PCI as compared with CABG was associated with significantly higher risks for myocardial infarction and any coronary revascularization.

Before introduction of new-generation DES, in the two randomized controlled trials, PCI using first-generation DES was associated with higher 5- to 10-year mortality rate as compared with CABG among patients with MVD.[8–11] However, the use of new-generation DES led to better outcomes after PCI by reducing the risks for stent thrombosis and target-lesion revascularization compared with the use of first-generation DES.[12–14] Moreover, changes in PCI strategies and improved medical therapy might have influenced the clinical outcomes after PCI relative to CABG in patients with MVD.[15–18] In the new-generation DES era, the survival benefit of CABG over PCI has not yet been demonstrated. In a small randomized controlled trial, BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease), PCI using everolimus-eluting stents (EES) was associated with higher rate of a composite of death, myocardial infarction, or TVR than CABG, but with similar 5-year mortality rate in patients with MVD.[19] However, this trial was not statistically powered for patient end points. A large observational registry in New York showed similar mortality risk through 4 years between PCI with EES and CABG in patients with MVD, although PCI was associated with higher risks for myocardial infarction and repeat revascularization.[20] However, the PCI group in the New York registry included only 8.6% of patients with 3VD and proximal LAD lesion.

In the present study, PCI was associated with higher mortality risk than CABG. However, the higher mortality risk of PCI relative to CABG was mainly driven by the

Table 2
Clinical outcomes

Endpoints	PCI (N=1747)		CABG (N=778)		Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
	N of patients with event (Cumulative 5-year incidence)							
All-cause death	423	(19.8%)	137	(13.2%)	1.38 (1.14-1.68)	0.001	1.45 (1.14-1.86)	0.003
Cardiovascular death	210	(10.2%)	88	(9.2%)	1.07 (0.84-1.38)	0.60	1.19 (0.87-1.64)	0.29
Cardiac death	165	(8.2%)	63	(7.3%)	1.17 (0.88-1.58)	0.28	1.24 (0.87-1.80)	0.25
Sudden cardiac death	38	(2.0%)	18	(2.2%)	0.94 (0.54-1.68)	0.82	0.99 (0.57-1.78)	0.96
Non-cardiovascular death	213	(10.7%)	49	(4.4%)	1.94 (1.44-2.68)	<0.001	1.88 (1.30-2.79)	0.001
Non-cardiac death	258	(12.7%)	74	(6.5%)	1.56 (1.21-2.03)	<0.001	1.63 (1.19-2.27)	0.003
Myocardial infarction								
ARC definition	185	(10.2%)	48	(6.4%)	1.73 (1.27-2.40)	<0.001	1.77 (1.19-2.69)	0.006
ARTS definition	135	(7.3%)	25	(3.4%)	2.43 (1.62-3.81)	<0.001	2.24 (1.34-3.86)	0.003
Definite stent thrombosis or symptomatic graft occlusion	11	(0.7%)	9	(1.4%)	0.54 (0.22-1.35)	0.17	NA	NA
Stroke	138	(7.5%)	55	(6.0%)	1.14 (0.84-1.57)	0.42	1.24 (0.83-1.88)	0.30
Ischemic stroke	112	(5.8%)	43	(4.6%)	1.18 (0.84-1.69)	0.35	1.25 (0.80-2.00)	0.33
Hemorrhagic stroke	34	(2.1%)	13	(1.4%)	1.18 (0.64-2.32)	0.60	1.22 (0.65-2.41)	0.55
Major stroke	101	(5.5%)	39	(4.6%)	1.17 (0.82-1.72)	0.40	1.46 (0.91-2.38)	0.12
Hospitalization for heart failure	207	(11.2%)	89	(10.8%)	1.02 (0.80-1.31)	0.88	0.99 (0.72-1.38)	0.97
Major bleeding								
BARC type 3, 4, or 5	334	(19.6%)	300	(37.4%)	0.42 (0.36-0.49)	<0.001	0.40 (0.32-0.49)	<0.001
BARC type 5	16	(0.9%)	6	(0.7%)	1.20 (0.50-3.36)	0.70	NA	NA
GUSTO moderate or severe	278	(16.3%)	486	(61.9%)	0.18 (0.16-0.21)	<0.001	0.18 (0.15-0.22)	<0.001
GUSTO severe	138	(8.2%)	80	(10.1%)	0.74 (0.56-0.98)	0.03	0.74 (0.52-1.06)	0.10
Target-vessel revascularization	446	(25.9%)	92	(11.6%)	2.32 (1.86-2.92)	<0.001	2.94 (2.22-3.94)	<0.001
Ischemia-driven target-vessel revascularization	217	(11.9%)	54	(6.6%)	1.85 (1.38-2.52)	<0.001	1.78 (1.24-2.61)	0.002
Any coronary revascularization	657	(38.1%)	104	(13.0%)	3.26 (2.66-4.03)	<0.001	3.52 (2.73-4.58)	<0.001
Ischemia-driven any coronary revascularization	340	(18.8%)	59	(7.0%)	2.76 (2.11-3.67)	<0.001	2.22 (1.60-3.12)	<0.001
A composite of death, myocardial infarction, or stroke*	619	(30.7%)	207	(22.0%)	1.37 (1.17-1.60)	<0.001	1.39 (1.14-1.70)	0.002

Number of patients with event was counted until the end of follow-up. Cumulative 5-year incidence was estimated by the Kaplan-Meier method. HRs with 95% CIs of the PCI group relative to the CABG group for the outcome measures were estimated throughout the entire follow-up period by the Cox proportional hazard models.

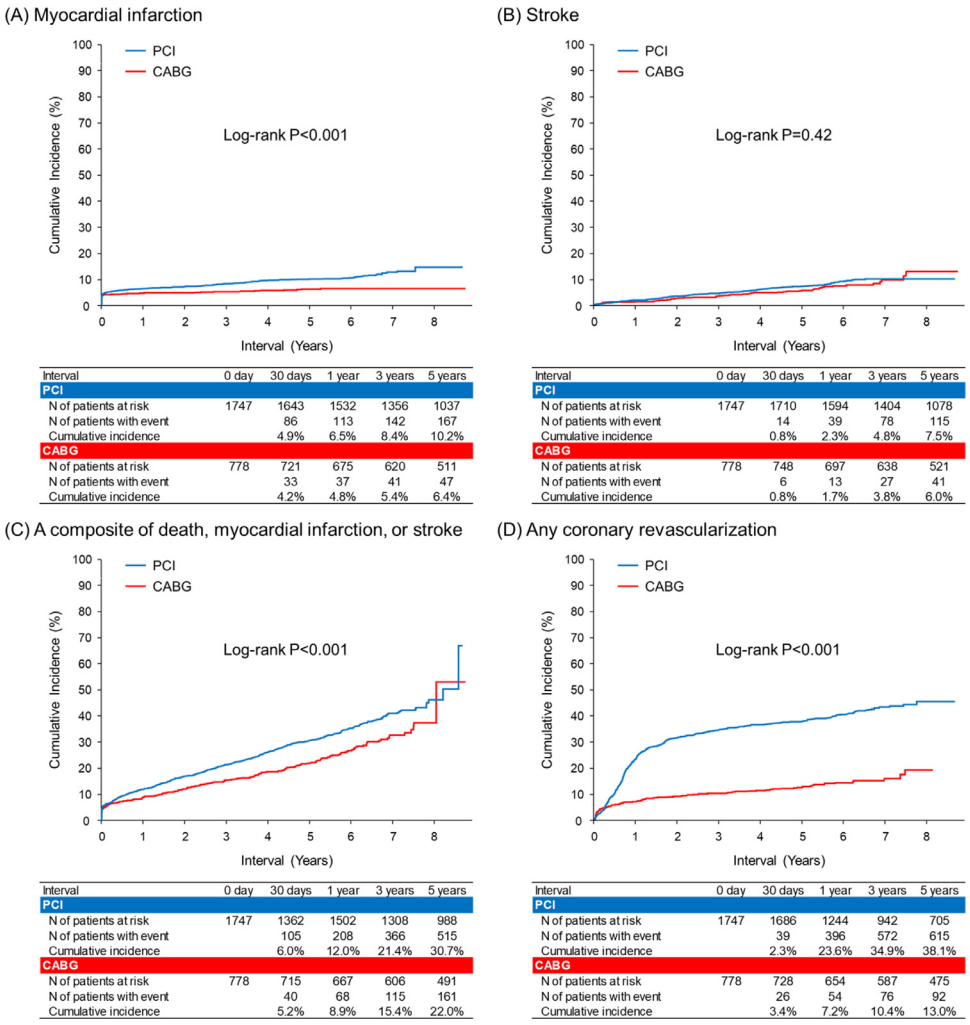
* Myocardial infarction as a component of the composite outcome measure was adjudicated according to the ARC definition.

ARC=Academic Research Consortium; ARTS=Arterial Revascularization Therapy Study; BARC=Bleeding Academic Research Consortium; CABG=-coronary artery bypass grafting; CI=confidence interval; eGFR=estimated glomerular filtration rate; GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HR=hazard ratio; NA=not assessed; PCI=percutaneous coronary intervention.

excess risk for non-cardiovascular death. The practice pattern in patients with 3VD in Japan has been markedly different from those outside Japan.[5,20,21] In this study, it was noteworthy that almost two-thirds of patients with 3VD were treated with PCI rather than CABG, and the prevalence of diabetes was not different between the 2 groups. CABG might have been performed only in selected patients with low risk for surgery. One might argue that it might be inappropriate to compare these 2 substantially different subsets of patients with 3VD. Nevertheless, it is important to note that there was no significant excess risk for cardiovascular death among patients with 3VD treated with PCI as compared with those treated with CABG. Therefore, the present study findings might suggest that the Japanese clinical practice with dominant use of PCI in patients with 3VD was not reckless, although it has not yet been established as the guideline-directed treatment strategy.

Consistent with the previous studies,[5,8,10,20] the advantage of CABG over PCI was clearly demonstrated in terms of the risks for myocardial infarction and repeat coronary revascularization in this study, which was not translated into the excess risk of PCI relative to CABG for cardiovascular mortality. Previous studies have demonstrated that CABG as compared with PCI was associated with markedly higher rates of major periprocedural adverse events such as stroke, major arrhythmia, major bleeding requiring transfusion, infection, renal failure, etc.[22,23] Therefore, we should make shared decision making with patients, providing unbiased information on the risk-benefit balance between PCI and CABG. In the current aging societies, appropriate patient selection for either PCI or CABG should be performed with careful consideration of all factors including age, co-morbidities, coronary anatomic complexity, and patients' preference. Moreover, optimal medical therapy alone without invasive coronary revascularization might also be a viable treatment option for some patients with stable 3VD.[24]

CABG as compared with PCI is an established mature treatment in patients with severe coronary artery disease, however, PCI still has the potential to fill this gap. Physiology-guided PCI using fractional flow reserve (FFR) was associated with lower rate of a composite of all-cause death,



Interval	0 day	30 days	1 year	3 years	5 years
PCI					
N of patients at risk	1747	1643	1532	1356	1037
N of patients with event		86	113	142	167
Cumulative incidence		4.9%	6.5%	8.4%	10.2%
CABG					
N of patients at risk	778	721	675	620	511
N of patients with event		33	37	41	47
Cumulative incidence		4.2%	4.8%	5.4%	6.4%

Interval	0 day	30 days	1 year	3 years	5 years
PCI					
N of patients at risk	1747	1710	1594	1404	1078
N of patients with event		14	39	78	115
Cumulative incidence		0.8%	2.3%	4.8%	7.5%
CABG					
N of patients at risk	778	748	697	638	521
N of patients with event		6	13	27	41
Cumulative incidence		0.8%	1.7%	3.8%	6.0%

Interval	0 day	30 days	1 year	3 years	5 years
PCI					
N of patients at risk	1747	1362	1502	1308	988
N of patients with event		105	208	366	515
Cumulative incidence		6.0%	12.0%	21.4%	30.7%
CABG					
N of patients at risk	778	715	667	606	491
N of patients with event		40	68	115	161
Cumulative incidence		5.2%	8.9%	15.4%	22.0%

Interval	0 day	30 days	1 year	3 years	5 years
PCI					
N of patients at risk	1747	1686	1244	942	705
N of patients with event		39	396	572	615
Cumulative incidence		2.3%	23.6%	34.9%	38.1%
CABG					
N of patients at risk	778	728	654	587	475
N of patients with event		26	54	76	92
Cumulative incidence		3.4%	7.2%	10.4%	13.0%

Figure 3. Kaplan-Meier event curves for the other outcome measures
(A) Myocardial infarction, (B) stroke, (C) a composite of death, myocardial infarction, or stroke, and (D) any coronary revascularization. Myocardial infarction was adjudicated according to the Academic Research Consortium (ARC) definition. CABG=coronary artery bypass grafting; PCI=percutaneous coronary intervention.

myocardial infarction, or repeat revascularization than angiography-guided PCI in patients with MVD.[15] Complete revascularization was reported to be associated with similar mortality risk between PCI and CABG in a patient-level pooled analysis of patients with left main disease or MVD.[25] The SYNTAX II PCI strategy encouraged appropriate patient selection by a heart team with use of SYNTAX II score considering both coronary anatomic complexity and patients' clinical backgrounds, use of new-generation DES, intravascular ultrasound-guided procedures, complete revascularization of physiologically significant stenoses, contemporary chronic total occlusion revascularization techniques, and use of guideline-directed medical therapy.[16] The 2-year rate of major adverse cardiac and cerebrovascular events in the SYNTAX-II PCI was lower than that in the historical SYNTAX-I PCI, and similar to that in the historical SYNTAX-I CABG among patients with 3VD.[17]

Optimal medical therapy is also important to improve outcomes of PCI. In the present study, duration of DAPT after PCI was longer than the current standard, and the risk for major bleeding beyond 30 days after procedure was significantly higher in the PCI group than in the CABG group. There has been accumulating evidence confirming the substantial impact of major bleeding on mortality,[26,27] and reduction of major bleeding was confirmed with very-short DAPT after PCI.[28,29] Also, the high-intensity statin therapy is an established secondary preventive measure in reducing cardiovascular events,[18] although the prevalence of high-intensity statin therapy was extremely low in the present study.

This study has several limitations. First and most importantly, the observational study design precluded any definitive conclusions regarding the superiority of either PCI or CABG due to serious selection bias and residual confounders. In an attempt to overcome the issues related to selection bias, we evaluated severe frailty defined as documentation of the inability to perform usual activities of daily living in the hospital charts. However, we could not deny ascertainment bias for severe frailty, because the prevalence of severe frailty in the present study was apparently lower than those reported in previous studies.[30] Furthermore, we

Table 3
Subgroup analyses for all-cause death and cardiovascular death

	PCI (N=1747)		CABG (N=778)		Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value	P value for interaction
	N of patients with event/N of patients at risk (Cumulative 5-year incidence)								
(A) All-cause death									
Age									
≥75 years	233/669	(29.7%)	61/232	(23.0%)	1.34 (1.02-1.79)	0.04	1.46 (1.02-2.12)	0.04	0.96
<75 years	190/1078	(13.8%)	76/546	(9.1%)	1.25 (0.96-1.63)	0.11	1.44 (1.04-2.02)	0.03	
Sex									
Men	315/1278	(19.8%)	112/602	(14.2%)	1.33 (1.08-1.66)	0.01	1.37 (1.05-1.81)	0.02	0.26
Women	108/469	(19.9%)	25/176	(9.8%)	1.65 (1.09-2.61)	0.02	1.95 (1.11-3.54)	0.02	
Diabetes mellitus									
Yes	238/888	(21.7%)	77/424	(14.2%)	1.47 (1.14-1.92)	0.003	1.52 (1.09-2.12)	0.01	0.64
No	185/859	(17.9%)	60/354	(12.1%)	1.28 (0.97-1.73)	0.09	1.39 (0.97-2.02)	0.08	
Heart failure									
Yes	162/410	(36.3%)	55/203	(21.9%)	1.60 (1.18-2.19)	0.003	1.71 (1.17-2.51)	0.006	0.40
No	261/1337	(15.0%)	82/575	(10.2%)	1.35 (1.06-1.74)	0.02	1.23 (0.89-1.71)	0.21	
eGFR <30 mL/min/1.73m^2 or hemodialysis									
Yes	112/220	(47.0%)	41/116	(29.0%)	1.64 (1.16-2.37)	0.007	1.50 (0.96-2.38)	0.08	0.80
No	311/1527	(16.0%)	96/662	(10.5%)	1.38 (1.11-1.75)	0.005	1.48 (1.11-2.01)	0.009	
Target of proximal LAD*									
Yes	278/1166	(19.4%)	129/731	(13.2%)	1.34 (1.09-1.66)	0.006	1.31 (1.01-1.71)	0.04	0.19
No	145/581	(20.6%)	8/47	(13.6%)	1.55 (0.81-3.45)	0.23	2.45 (1.13-6.10)	0.04	
SYNTAX score									
Low <23	189/849	(17.4%)	29/135	(16.6%)	1.03 (0.71-1.55)	0.88	1.54 (0.90-2.72)	0.13	0.63
Intermediate 23-32	158/643	(21.6%)	49/288	(12.2%)	1.48 (1.08-2.06)	0.02	1.57 (1.07-2.36)	0.02	
High ≥33	73/239	(24.3%)	39/210	(15.2%)	1.62 (1.10-2.41)	0.02	1.67 (1.01-2.79)	0.047	
(B) Cardiovascular death									
Age									
≥75 years	124/669	(16.7%)	38/232	(16.9%)	1.15 (0.81-1.67)	0.45	1.21 (0.84-1.77)	0.31	0.32
<75 years	86/1078	(6.4%)	50/546	(6.0%)	0.86 (0.61-1.23)	0.40	0.99 (0.70-1.42)	0.97	
Sex									
Men	152/1278	(9.9%)	70/602	(9.9%)	1.03 (0.78-1.37)	0.84	1.05 (0.79-1.40)	0.75	0.66
Women	58/469	(11.1%)	18/176	(6.9%)	1.23 (0.74-2.14)	0.45	1.40 (0.81-2.51)	0.24	
Diabetes mellitus									
Yes	125/888	(11.8%)	51/424	(9.8%)	1.18 (0.86-1.65)	0.32	1.21 (0.87-1.70)	0.26	0.41
No	85/859	(8.7%)	37/354	(8.6%)	0.95 (0.65-1.42)	0.80	0.92 (0.63-1.39)	0.69	
Heart failure									
Yes	99/410	(23.7%)	38/203	(15.4%)	1.41 (0.98-2.07)	0.07	1.31 (0.90-1.94)	0.17	0.16
No	111/1337	(6.4%)	50/575	(7.1%)	0.95 (0.68-1.33)	0.76	0.94 (0.67-1.33)	0.71	
eGFR <30 mL/min/1.73m^2 or hemodialysis									
Yes	78/220	(34.4%)	31/116	(23.4%)	1.51 (1.00-2.32)	0.048	1.35 (0.89-2.10)	0.17	0.19
No	132/1527	(6.9%)	57/662	(6.8%)	1.00 (0.73-1.37)	0.98	0.96 (0.70-1.32)	0.78	
Target of proximal LAD*									
Yes	131/1166	(9.7%)	82/731	(9.0%)	1.00 (0.76-1.32)	0.99	1.03 (0.78-1.37)	0.84	0.48
No	79/581	(11.3%)	6/47	(11.6%)	1.13 (0.54-2.90)	0.78	1.36 (0.62-3.59)	0.48	
SYNTAX score									
Low <23	96/849	(8.9%)	19/135	(12.1%)	0.80 (0.50-1.35)	0.38	0.88 (0.55-1.51)	0.63	0.67
Intermediate 23-32	76/643	(11.0%)	29/288	(8.2%)	1.19 (0.79-1.86)	0.42	1.23 (0.80-1.93)	0.36	
High ≥33	37/239	(13.3%)	27/210	(10.7%)	1.19 (0.73-1.97)	0.50	1.20 (0.71-2.04)	0.49	

Number of patients with event was counted until the end of follow-up. Cumulative 5-year incidence was estimated by the Kaplan-Meier method. HRs with 95% CIs of the PCI group relative to the CABG group for all-cause death and cardiovascular death were estimated throughout the entire follow-up period by the Cox proportional hazard models. We used the parsimonious models with the 8 risk-adjusting variables including advanced age (≥75 years), men, diabetes, heart failure, prior myocardial infarction, prior stroke, end-stage renal disease (eGFR <30 mL/min/1.73m^2 or hemodialysis), and severe frailty for cardiovascular death due to the small numbers of patients with event across subgroups. Values were missing for SYNTAX score in 161 patients.

* Proximal LAD was defined as segment #6 or #7 according to the American Heart Association classification.

CABG=coronary artery bypass grafting; CI=confidence interval; eGFR=estimated glomerular filtration rate; HR=hazard ratio; LAD=left anterior descending coronary artery; PCI=percutaneous coronary intervention; SYNTAX=SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.

could not assess other important factors such as moderate frailty and cognitive impairment, which might have a great influence on the choice between PCI and CABG, as well as on clinical outcomes. Second, cardiovascular death is a less robust end point than all-cause death because of the need for its adjudication. Third, the results of the subgroup analyses were inconclusive due to lack of adequate power, and/or imbalance of sample sizes across subgroups. Fourth, the assessment of lesion-specific ischemia by FFR was performed only in a small proportion of patients in the PCI group, that is different from the current clinical practice. In addition, it was unknown whether patients underwent complete or incomplete revascularization. Finally, complete follow-up rate was lower in the CABG group than in the PCI group. Thus, the incidence of adverse events in the CABG group might have been underestimated.

In conclusion, in this observational study that evaluated patients with 3VD in the new-generation DES era, PCI was the preferred modality of first coronary revascularization used in almost two-thirds of patients. PCI compared with CABG was associated with significantly higher risk for all-cause death, which was mainly driven by the excess risk for non-cardiovascular death, while there was no excess risk for cardiovascular death between PCI and CABG.

Author Credit Statement

Yukiko Matsumura-Nakano: Methodology, Formal analysis, Investigation, Data curation, Writing-Original Draft; Hiroki Shiomi: Methodology, Investigation, Data curation, Writing-Review and Editing, Supervision, Project administration; Takeshi Morimoto: Methodology, Formal analysis, Writing-Review and Editing, Supervision; Kyohei Yamaji: Investigation, Resources, Writing-Review and Editing; Natsuhiko Ehara: Investigation, Resources; Hiroki Sakamoto: Investigation, Resources; Yasuaki Takeji: Investigation, Data curation; Yusuke Yoshikawa: Investigation, Data curation; Ko Yamamoto: Investigation, Data curation; Kazuaki Imada: Investigation, Data curation; Takeshi Tada: Investigation, Resources; Ryoji Taniguchi: Investigation, Resources; Ryusuke Nishikawa: Investigation, Resources; Tomohisa Tada: Investigation, Resources; Takashi Uegaito: Investigation, Resources; Tatsuya Ogawa: Investigation, Resources; Miho Yamada: Investigation, Resources; Teruki Takeda: Investigation, Resources; Hiroshi Eizawa: Investigation, Resources; Nobushige Tamura: Investigation, Resources; Keiichi Tambara: Investigation, Resources; Satoru Suwa: Investigation, Resources; Manabu Shirotani: Investigation, Resources; Toshihiro Tamura: Investigation, Resources; Moriaki Inoko: Investigation, Resources; Junichiro Nishizawa: Investigation, Resources; Masahiro Natsuaki: Writing-Review and Editing; Hiroshi Sakai: Investigation, Resources; Takashi Yamamoto: Investigation, Resources; Naoki Kanemitsu: Investigation, Resources; Nobuhisa Ohno: Investigation, Resources; Katsuhisa Ishii: Investigation, Resources; Akira Marui: Investigation, Resources; Hiroshi Tsuneyoshi: Investigation, Resources; Yasuhiko Terai: Investigation, Resources; Shogo Nakayama: Investigation, Resources; Kazuhiro Yamazaki: Investigation, Resources; Mamoru Takahashi: Investigation, Resources; Takashi Tamura: Investigation, Resources; Jiro Esaki: Investigation, Resources; Shinji Miki: Investigation, Resources; Tomoya Onodera: Investigation, Resources; Hiroshi Mabuchi: Investigation, Resources; Yutaka Furukawa: Investigation, Resources; Masaru Tanaka: Investigation, Resources; Tatsuhiko Komiya: Investigation, Resources; Yoshiharu Soga: Investigation, Resources; Michiya Hanyu: Investigation, Resources; Kenji Ando: Investigation, Resources; Kazushige Kadota: Investigation, Resources; Kenji Minatoya: Investigation, Resources; Yoshihisa Nakagawa: Investigation, Resources; Takeshi Kimura: Conceptualization, Methodology, Writing-Review and Editing, Supervision, Project administration, Funding acquisition

Disclosures

Dr. Shiomi reports honoraria from Abbott Vascular, and Boston Scientific. Dr. Morimoto reports honoraria from Bayer and Kowa, and expert witness from Boston Scientific and Sanofi. Dr. Ehara reports honoraria from Abbott Vascular, Bayer, Boston Scientific, Medtronic, and Terumo. Dr. Furukawa reports honoraria from Bayer, Kowa, and Sanofi. Dr. Nakagawa reports research grant from Abbott Vascular and Boston Scientific, and honoraria from Abbott Vascular, Bayer, and Boston Scientific. Dr. Kimura reports honoraria from Abbott Vascular, and honoraria from Astellas, AstraZeneca, Bayer, Boston Scientific, Kowa, and Sanofi. All the other authors have nothing to disclose.

Declaration of Interests

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 study.

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Supplementary materials

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