Circulation Reports
Circ Rep 2020; 2: 744–752
doi:10.1253/circrep.CR-20-0110

ORIGINAL ARTICLE
Ischemic Heart Disease

Two-Year Outcomes of Asymptomatic vs. Symptomatic Patients After Deferral of Revascularization Based on Fractional Flow Reserve

— Insights From the J-CONFIRM Registry —

Kazunori Horie, MD; Shoichi Kuramitsu, MD, PhD; Hitoshi Matsuo, MD, PhD; Tomohiro Shinozaki, PhD; Hiroaki Takashima, MD, PhD; Yasutsugu Shiono, MD, PhD; Hidenobu Terai, MD; Yuetsu Kikuta, MD; Takayuki Ishihara, MD; Tatsuya Saigusa, MD; Tomohiro Sakamoto, MD, PhD; Taku Asano, MD, PhD; Kenichi Tsujita, MD, PhD; Katsuhiko Masamura, MD, PhD; Tatsuki Doijiri, MD; Manabu Ogita, MD, PhD; Tairo Kurita, MD, PhD; Akiko Matsuo, MD; Shinjo Sonoda, MD, PhD; Hiroyoshi Yokoi, MD; Nobuhiro Tanaka, MD, PhD on behalf of the J-CONFIRM Investigators

Background: The effect of symptoms on clinical outcomes after deferral of revascularization based on fractional flow reserve (FFR) remains poorly understood.

Methods and Results: From the J-CONFIRM (Long-Term Outcomes of Japanese Patients With Deferral of Coronary Intervention Based on Fractional Flow Reserve in Multicenter) Registry, this study evaluated 1,215 patients with stable coronary artery disease, including symptomatic and asymptomatic patients (n=571 and 644, respectively). The primary endpoint was the cumulative 2-year incidence of target vessel failure (TVF), including cardiac death, target vessel-related myocardial infarction (TVMI), and clinically driven target vessel revascularization (CDTVR). An inverse probability weighted analysis was performed to adjust for the differences in baseline clinical characteristics between the 2 groups. At 2 years, the TVF rate did not differ significantly between symptomatic and asymptomatic patients (6.5% vs. 4.9%, respectively; P=0.15) or between symptomatic and asymptomatic patients with lesions with an FFR ≤0.80 (8.0% vs. 12.3%, respectively; P=0.20). Conversely, symptomatic patients showed significantly higher rates of TVF (6.2% vs. 3.3%; P=0.01) and CDTVR (6.2% vs. 3.1%; P=0.009) than asymptomatic patients, regardless of negative FFR values (>0.80).

Conclusions: Despite negative FFR values, symptomatic patients were at higher risk of TVF than asymptomatic patients, driven primarily by a higher rate of CDTVR. Conversely, those with a positive FFR were likely to develop TVF regardless of their symptoms.

Key Words: Angina; Coronary artery disease; Fractional flow reserve; Revascularization

Fractional flow reserve (FFR) is the standard invasive method used to evaluate the functional significance of epicardial coronary artery stenosis.[1] The principle of FFR-guided revascularization is to identify lesions in which revascularization can be safely deferred, resulting in a reduction in unnecessary revascularization and myocardial infarction (MI) compared with angiography-guided revascularization.[2–5] Recently, the J-CONFIRM (Long-Term Outcomes of Japanese Patients With Deferral of Coronary Intervention Based on Fractional Flow Reserve in Multicenter) Registry demonstrated that the 2-year target vessel failure (TVF) rate was 5.5% in deferred lesions, highlighting the safety of FFR-based deferral of revascularization in daily practice.[6]

Received October 18, 2020; accepted October 19, 2020; J-STAGE Advance Publication released online November 18, 2020 Time for primary review: 1 day

Department of Cardiovascular Medicine, Sendai Kousei Hospital, Sendai (K.H.); Department of Cardiology, Kokura Memorial Hospital, Kitakyushu (S.K.); Department of Cardiovascular Medicine, Gifu Heart Center, Gifu (H.M.); Department of Information and Computer Technology, Faculty of Engineering, Tokyo University of Science, Tokyo (T. Shinozaki); Department of Cardiology, Aichi Medical University, Nagakute (H. Takashima); Department of Cardiovascular Medicine, Wakayama Medical University, Wakayama (Y.S.); Department of Cardiology, Kanazawa Cardiovascular Hospital, Kanazawa (H. Terai); Department of Cardiology, Fukuyama Cardiovascular Hospital, Fukuyama (Y.K.); Kansai Rosai Hospital Cardiovascular Center, Amagasaki (T.I.); Department of Cardiovascular Medicine, Shinshu University School of Medicine, Matsumoto (T. Saigusa); Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center, Kumamoto (T. Sakamoto); Department of Cardiology, St Luke's International Hospital, Tokyo (T.A.); Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto (K.T.); Department of Cardiology, Nakamura Hospital, Echizen (K.M.); Department of Cardiology, Yamato Seiwa Hospital, Yamato (T.D.); Department of Cardiology, Juntendo University Shizuoka Hospital,
(Footnote continued the next page.)

Table 1. Patient Characteristics at Baseline

	Symptomatic (n=571)	Asymptomatic (n=644)	P value
Age[A] (years)	70.3±9.1	70.1±10.1	0.65
Male sex[A]	410 (71.8)	496 (77.0)	0.04
Hypertension[A]	442 (77.4)	487 (75.6)	0.50
Diabetes[A]	236 (41.3)	231 (35.9)	0.052
Dyslipidemia[A]	379 (66.4)	399 (62.0)	0.12
Current smoker[A]	186 (32.6)	199 (30.9)	0.54
Hemodialysis[A]	28 (4.9)	35 (5.4)	0.70
Prior MI[A]	130 (22.8)	225 (34.9)	<0.001
Prior PCI[A]	295 (51.7)	432 (67.1)	<0.001
Prior CABG[A]	18 (3.2)	14 (2.2)	0.37
Prior stroke[A]	49 (8.6)	69 (10.7)	0.24
Multivessel disease[A]	63 (11.0)	73 (11.3)	0.93
Medication at discharge			
Antiplatelet therapy	474 (83.0)	541 (84.0)	0.64
Aspirin	444 (77.8)	490 (76.1)	0.50
Thienopyridine	286 (50.1)	337 (52.3)	0.46
Anti-angina drugs	430 (75.3)	470 (73.0)	0.36
β-blocker	169 (29.6)	235 (36.5)	0.01
CCB	307 (53.8)	323 (50.2)	0.23
Nitrate	123 (21.5)	56 (8.7)	<0.001
Statin	349 (61.1)	437 (67.9)	0.02
Oral hypoglycemic agent	154 (27.0)	168 (26.1)	0.75
Insulin	33 (5.8)	23 (3.6)	0.08

Categorical variables are given as n (%), continuous variables are given as the mean±SD. [A]Variables used for multivariable and inverse provability weighted Cox models comparing hazard ratios of asymptomatic and symptomatic patients for the study endpoints (**Table 3** and **Table 4**). CABG, coronary artery bypass grafting; CCB, calcium channel blocker; MI, myocardial infarction; PCI, percutaneous coronary intervention.

An improvement in symptoms and quality of life (QoL) is the main goal for symptomatic patients with stable coronary artery disease (SCAD).[7,8] However, some SCAD patients present without any symptoms. Previous studies reported that silent ischemia was associated with worse clinical outcomes, especially after MI.[9] However, it remains poorly understood whether symptoms affect clinical outcomes in SCAD patients after deferral of revascularization based on the FFR. Thus, the aim of the present study was to compare the clinical outcomes of symptomatic and asymptomatic SCAD patients after FFR-based deferral of revascularization by analyzing the J-CONFIRM Registry.

Methods

Study Population

This study is a post hoc analysis of the J-CONFIRM Registry, a prospective multicenter registry across 28 Japanese centers (**Supplementary Appendix**) designed to investigate the clinical outcomes of Japanese patients with an angiographically intermediate coronary artery lesion in whom revascularization was deferred based on FFR measurement between September 2013 and June 2015. The design and main results of J-CONFIRM have been reported elsewhere,[3] and it has been registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000014473).

Briefly, the J-CONFIRM Registry includes 1,263 patients with 1,447 angiographically intermediate coronary artery lesions in whom revascularization was deferred based on FFR measurement (**Supplementary Appendix**). Patients with acute MI, cardiogenic shock, a chronic total occlusion lesion, a graft lesion, decompensated heart failure, or severe comorbidities (e.g., severe aortic stenosis, respiratory

Shizuoka (M.O.); Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Tsu (T.K.); Department of Cardiology, Japanese Red Cross Kyoto Daini Hospital, Kyoto (A.M.); Second Department of Internal Medicine, University of Occupational and Environmental Health Japan School of Medicine, Kitakyushu (S.S.); Department of Cardiology, Fukuoka Sanno Hospital, Fukuoka (H.Y.); and Department of Cardiology, Tokyo Medical University Hachioji Medical Center, Tokyo (N.T.), Japan

K.T. is a member of *Circulation Reports*' Editorial Team.

The first two authors are equal 1st authors (K.H., S.K.).

The last two authors contributed equally to this work (H.Y., N.T.).

Mailing address: Shoichi Kuramitsu, MD, PhD, Department of Cardiology, Kokura Memorial Hospital, 3-2-1 Asano, Kokurakita-ku, Kitakyushu 802-8555, Japan. E-mail: kuramitsu@circulation.jp

ISSN-2434-0790

Table 2. Lesion Characteristics and Fractional Flow Reserve Measurement

	Symptomatic (n=652)	Asymptomatic (n=743)	P value
Target vessel[A]			0.08
Left main trunk	22 (3.0)	14 (2.2)	
Left anterior descending	336 (51.5)	341 (45.9)	
Left circumflex	129 (19.8)	182 (24.5)	
Right coronary artery	173 (26.5)	198 (26.7)	
ACC/AHA lesion type			0.52
A	66 (10.1)	90 (12.2)	
B1	194 (29.8)	205 (27.7)	
B2	263 (40.4)	310 (41.8)	
C	128 (19.7)	136 (18.4)	
In-stent restenosis lesion[A]	41 (6.3)	62 (8.4)	0.14
Mean FFR[A]	0.86±0.06	0.86±0.07	0.51
FFR categories			0.31
≤0.75	25 (3.8)	45 (6.1)	
0.76–0.80	73 (11.2)	81 (10.9)	
0.81–0.90	397 (60.9)	442 (59.5)	
0.91–1.00	157 (24.1)	175 (23.6)	
Angiographic findings[B]			
Bifurcation lesion[A]	187 (32.2)	212 (30.7)	0.59
Tortuous lesion[A]	106 (18.2)	131 (19.0)	0.77
Moderately to severely calcified lesion[A]	91 (15.7)	89 (12.9)	0.17
Quantitative coronary analysis results[C]			
Reference vessel diameter (mm)	2.80±0.66	2.83±0.64	0.52
Minimum lumen diameter (mm)	1.59±0.42	1.60±0.48	0.68
Diameter stenosis (%)	42.9±11.1	43.2±11.6	0.68
Diameter stenosis >50%	143 (25.0)	181 (26.6)	0.52
Lesion length (mm)	12.7±5.6	13.4±6.5	0.06
Lesion length >20 mm	44 (7.6)	70 (10.2)	0.11

Categorical variables are given as n (%), continuous variables are given as the mean±SD. [A]Variables used for multivariable and inverse provability weighted Cox models comparing hazard ratios of asymptomatic and symptomatic patients for the study endpoints (**Table 3** and **Table 4**). [B]Data available for 581 and 690 lesions in symptomatic and asymptomatic groups, respectively. [C]Data available for 542 and 680 lesions in symptomatic and asymptomatic groups, respectively. ACC, American College of Cardiology; AHA, American Heart Association; FFR, fractional flow reserve.

diseases, and cancer) were excluded from the J-CONFIRM registry.

For the present study, we classified patients into asymptomatic and symptomatic groups according to clinical symptoms at the time of the index procedure. The severity of angina was assessed in each institution using the Canadian Cardiovascular Society angina classes.[10,11] Patients with unstable angina were excluded from the present study. The study protocol was approved by the local ethics committee at all participating centers and the study was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent to be included in the Registry.

Study Endpoints and Definition

The primary study endpoint was the cumulative incidence of TVF, including cardiac death, target vessel-related MI (TVMI), and clinically driven target vessel revascularization (CDTVR) during the 2-year follow-up. Clinically driven target lesion revascularization (TLR) was also assessed. Death was regarded as cardiac death unless other non-cardiac causes could be identified. MI was defined according to the Academic Research Consortium definition.[12] TLR was defined as a repeat revascularization inside or within 5-mm proximal or distal to the target lesion. Target vessel revascularization (TVR) was defined as a repeated percutaneous coronary intervention (PCI) or repeated coronary artery bypass graft on the target vessel. A TLR or TVR was considered clinically indicated if: (1) the angiographic percentage diameter stenosis of the target lesion was ≥50% by qualitative coronary angiographic assessment, in the presence of ischemic signs or symptoms; or (2) the diameter stenosis was ≥70% by qualitative coronary angiographic assessment, regardless of ischemic signs or symptoms.[12]

Statistical Analysis

Categorical variables are presented as numbers with percentages and were compared using Chi-squared or Fisher's exact tests. Continuous variables are expressed as the mean±SD and were compared using Student's t-test or the Mann-Whitney U-test depending on data distribution. The cumulative incidence of study endpoints was estimated by the Kaplan-Meier method. Hazard ratios (HRs) of asymptomatic vs. symptomatic groups for the study endpoints were estimated through a multivariable Cox model and an inverse probability weighted (IPW) Cox

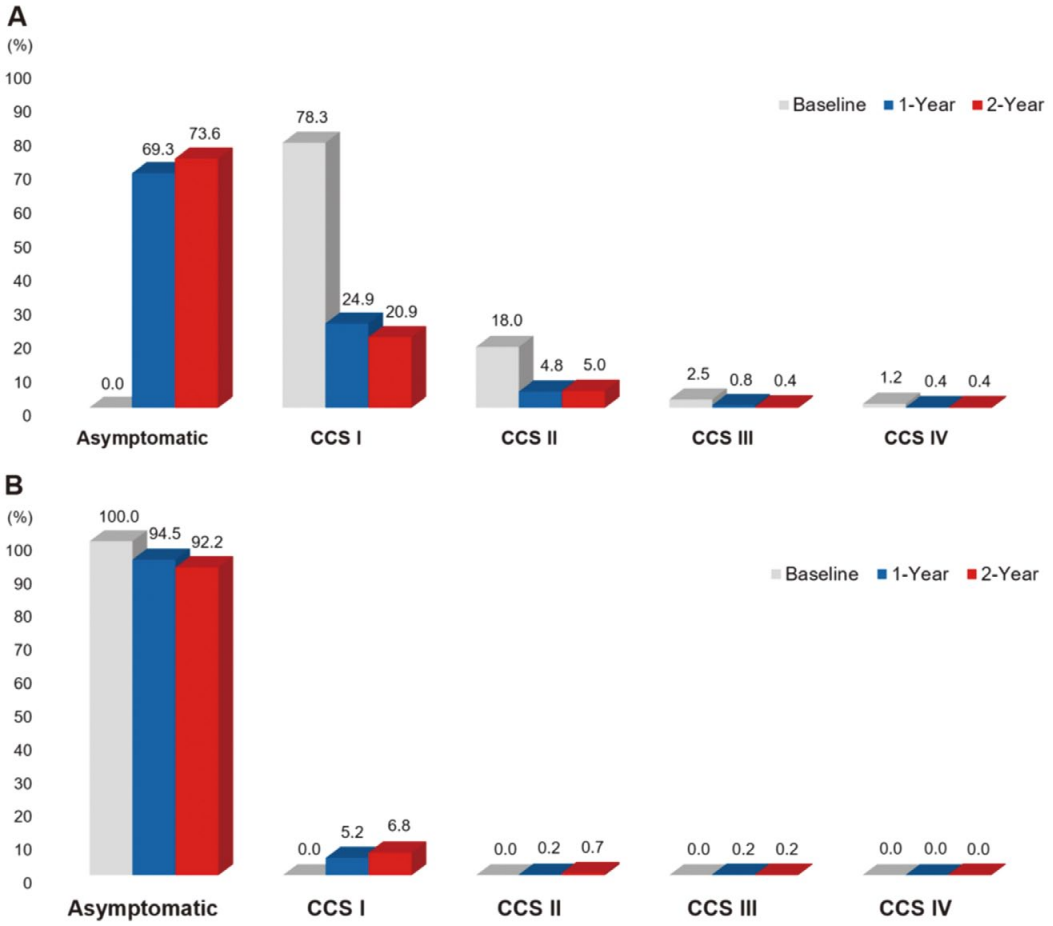


Figure 1. Clinical symptoms during the follow-up period in the (**A**) symptomatic and (**B**) asymptomatic groups. The severity of angina was graded using the Canadian Cardiovascular Society (CCS) system.

model with clinically relevant variables listed in **Table 1** and **Table 2** as covariates. Weights for the IPW methods were estimated through a logistic model for probabilities of symptomatic group conditional on covariates. The IPW maximum partial likelihood estimates were accompanied by sandwich variance estimates to obtain 95% confidence intervals (CI) and P values.

All statistical analyses were performed by 2 physicians (K.H. and S.K.) using JMP version 14 (SAS Institute, Cary, NC, USA) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided $P<0.05$ was considered significant.

Results

Study Population

Of the 1,263 patients in the J-CONFIRM Registry, 48 were excluded due to unstable angina. Thus, 1,215 patients (symptomatic, n=571; asymptomatic, n=644) were enrolled in the present study. A 2-year clinical follow-up was completed for 96.3% and 96.7% of patients in the symptomatic and asymptomatic groups, respectively.

Baseline Clinical Characteristics

Table 1 and **Table 2** show baseline patient and lesion characteristics in the symptomatic and asymptomatic groups. No significant differences in baseline patient characteristics were observed between the 2 groups except for male sex, prior MI, prior PCI, and medication at discharge (β-blocker, nitrate, and statin use). Lesion characteristics did not differ significantly between the 2 groups.

FFR Measurement

Mean FFR was comparable between the symptomatic and asymptomatic groups (0.86±0.06 vs. 0.86±0.07, P=0.51; **Table 2**). Most lesions had an FFR >0.80, although 15.0% and 17.0% of lesions in the symptomatic and asymptomatic groups, respectively, had an FFR ≤0.80 (**Table 2**; **Supplementary Figure 1**).

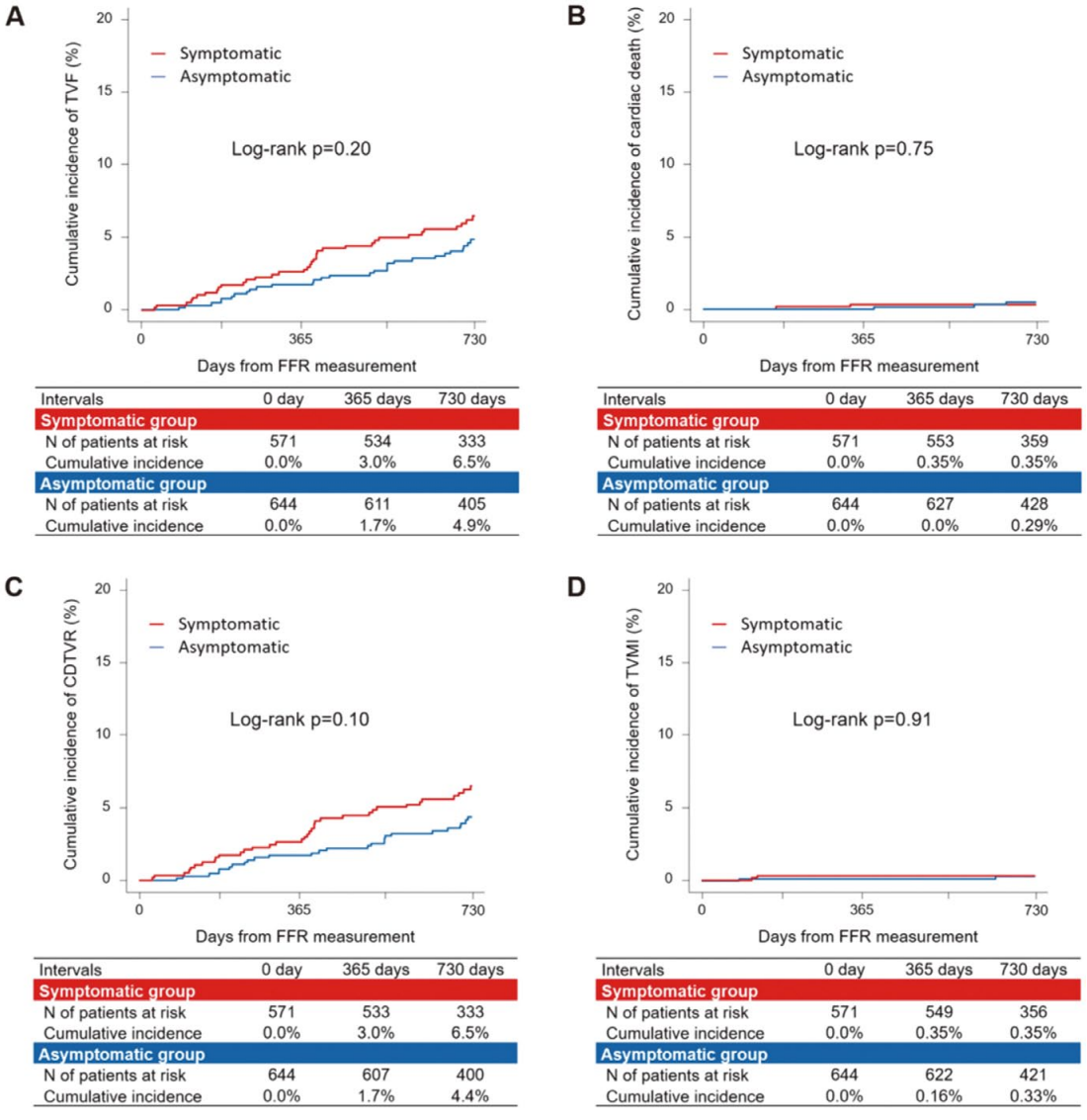
Clinical Symptoms and Medication During Follow-up

Clinical symptoms at the 1- and 2-year follow-up had improved in 72.6% and 77.5% of symptomatic patients, respectively. Conversely, 4.8% and 7.6% of asymptomatic patients experienced angina at the 1- and 2-year follow-up, respectively, although most had mild symptoms (**Figure 1**; **Supplementary Figure 2**). The use of anti-angina drugs did

Table 3. Clinical Events Over the 2-Year Follow-up

Outcome	Rate of events over 2 years (%)		Crude HR		Multivariable aHR[A] (95% CI)		IPW HR[B] (95% CI)	
	Symptomatic patients	Asymptomatic patients	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
TVF	6.5	4.9	1.38 (0.84–2.26)	0.20	1.61 (0.90–2.86)	0.11	1.50 (0.86–2.62)	0.15
Cardiac death	0.35	0.29	0.75 (0.13–4.48)	0.75	1.47 (0.15–14.3)	0.74	0.91 (0.15–5.61)	0.92
CDTVR	6.5	4.4	1.53 (0.92–2.55)	0.10	1.79 (0.99–3.25)	0.06	1.68 (0.95–2.99)	0.08
TVMI	0.35	0.33	1.13 (0.16–7.99)	0.91	1.91 (0.27–13.7)	0.62	1.22 (0.16–9.12)	0.84

[A]Multivariable Cox models adjusting for variables indicated in **Table 1** and **Table 2** as covariates. [B]Univariable propensity score-based inverse probability weighted (IPW) Cox models. aHR, adjusted hazard ratio; CDTVR, clinically driven target vessel revascularization; CI, confidence interval; HR, hazard ratio; TVF, target vessel failure.



Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	571	534	333
Cumulative incidence	0.0%	3.0%	6.5%
Asymptomatic group			
N of patients at risk	644	611	405
Cumulative incidence	0.0%	1.7%	4.9%

Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	571	553	359
Cumulative incidence	0.0%	0.35%	0.35%
Asymptomatic group			
N of patients at risk	644	627	428
Cumulative incidence	0.0%	0.0%	0.29%

Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	571	533	333
Cumulative incidence	0.0%	3.0%	6.5%
Asymptomatic group			
N of patients at risk	644	607	400
Cumulative incidence	0.0%	1.7%	4.4%

Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	571	549	356
Cumulative incidence	0.0%	0.35%	0.35%
Asymptomatic group			
N of patients at risk	644	622	421
Cumulative incidence	0.0%	0.16%	0.33%

Figure 2. Clinical events in symptomatic and asymptomatic patients: (**A**) target vessel failure (TVF), (**B**) cardiac death, (**C**) clinically driven target vessels revascularization (CDTVR), and (**D**) target vessel related myocardial infarction (TVMI). FFR, fractional flow reserve.

Table 4. Clinical Outcomes of Symptomatic and Asymptomatic Patients According to FFR

Outcome	Rate of events over 2 years (%)		Crude HR (95% CI)	P value	aHR (95% CI)			
	Symptomatic patients	Asymptomatic patients			Multivariable aHR[A] (95% CI)	P value	IPW HR[B] (95% CI)	P value
FFR <0.80 (n=201)								
TVF	8.0	12.3	0.68 (0.27–1.70)	0.41	0.37 (0.10–1.30)	0.12	0.52 (0.19–1.42)	0.20
Cardiac death	0.0	1.9	NA		NA		NA	
CDTVR	8.0	10.4	0.89 (0.40–2.01)	0.78	0.57 (0.19–1.71)	0.31	0.60 (0.21–1.69)	0.33
TVMI	1.1	0.0	NA		NA		NA	
FFR >0.80 (n=1,014)								
TVF	6.2	3.3	1.98 (1.07–3.65)	0.03	2.80 (1.31–6.03)	0.008	2.54 (1.22–5.27)	0.01
Cardiac death	0.42	0.20	2.20 (0.20–24.2)	0.52	NA		2.53 (0.23–28.1)	0.45
CDTVR	6.3	3.1	2.09 (1.12–3.92)	0.02	2.98 (1.35–6.54)	0.007	2.73 (1.29–5.81)	0.009
TVMI	0.21	0.40	0.55 (0.05–6.08)	0.63	NA		0.66 (0.06–7.47)	0.74

[A]Multivariable Cox models adjusting for variables indicated in **Table 1** and **Table 2** as covariates. [B]Univariable propensity score-based inverse probability weighted (IPW) Cox models. aHR, adjusted hazard ratio; CDTVR, clinically driven target vessel revascularization; CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio; NA, not applicable; TVF, target vessel failure.

not differ significantly between the 2 groups. However, symptomatic patients took nitrate more frequently than asymptomatic patients (**Table 1**; **Supplementary Figure 3**).

Clinical Outcomes

At 2 years, the TVF rate did not differ significantly between the symptomatic and asymptomatic groups (6.5% vs. 4.9%, respectively; adjusted HR [aHR] 1.50, 95% CI 0.86–2.62; P=0.15). The cumulative incidence of CDTVR tended to be higher in the symptomatic than asymptomatic group (6.5% vs. 4.4%; aHR 1.68, 95% CI 0.95–2.99; P=0.08). CDTVR occurred in 38 and 27 symptomatic and asymptomatic patients, respectively, due to at least 1 of the following reasons: worsening angina (n=26 and 17, respectively), positive non-invasive test (n=10 and 4, respectively), positive FFR measurement (n=14 and 12, respectively), or ischemic changes on an electrocardiogram (n=3 and 4, respectively). Cardiac death and TVMI rarely occurred in either the symptomatic or asymptomatic group (cardiac death, 0.35% vs. 0.29%, respectively [aHR 0.92, 95% CI 0.15–5.61; P=0.92]; TVMI, 0.35% vs. 0.33%, respectively [aHR 1.22, 95% CI 0.16–9.12; P=0.84]; **Table 3**; **Figure 2**).

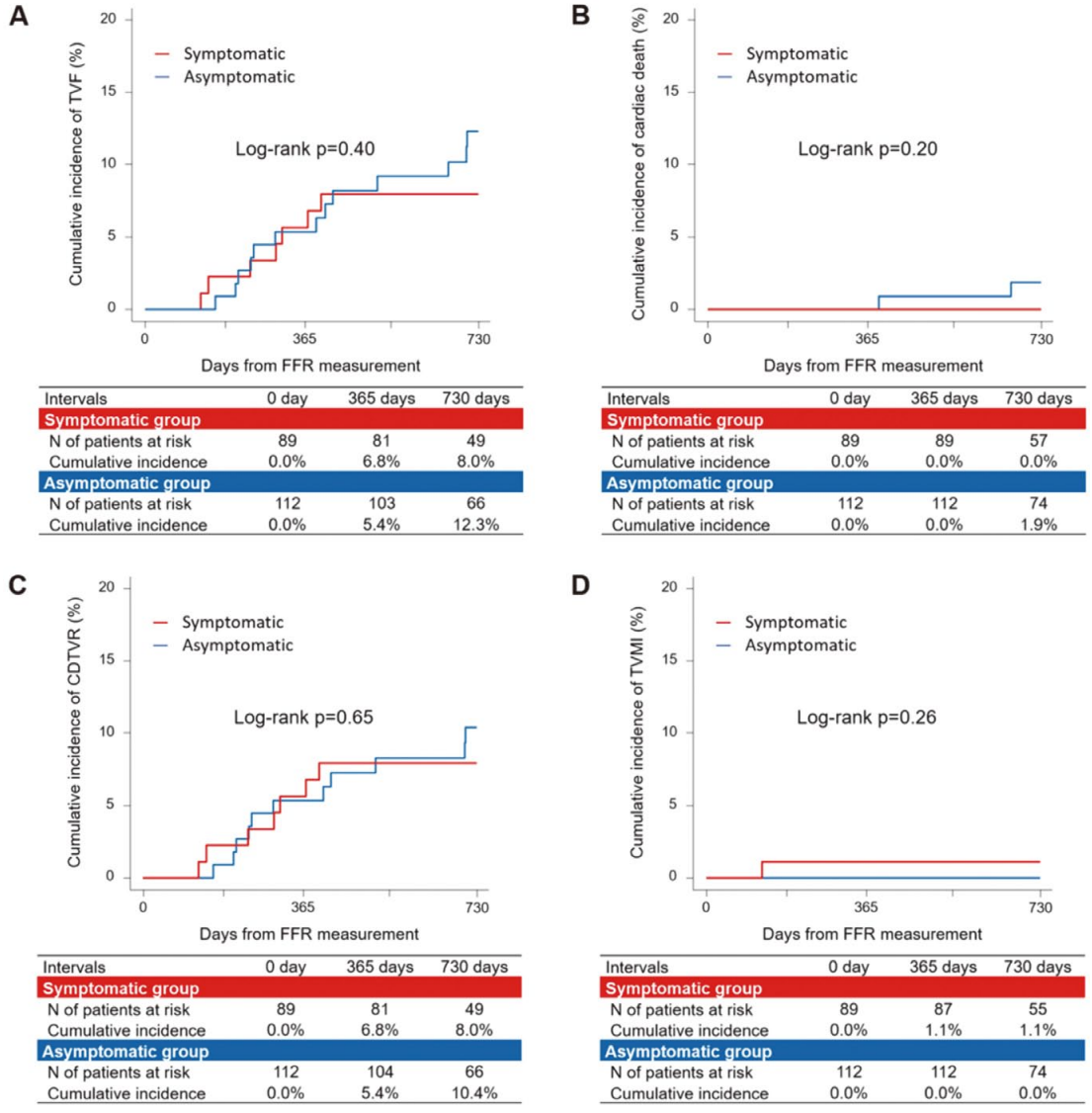
In all, 89 and 112 symptomatic and asymptomatic patients, respectively, had lesions with an FFR ≤0.80. Among these patients, there were no significant difference in the cumulative rates of clinical events between the 2 groups (**Table 4**; **Figure 3**). Conversely, in the case of lesions with an FFR >0.80, TVF (6.2% vs. 3.3%; aHR 2.54, 95% CI 1.22–5.27; P=0.01) and CDTVR (6.2% vs. 3.1%; aHR 2.73, 95% CI 1.29–5.81; P=0.009) occurred more frequently in the symptomatic than asymptomatic group (**Table 4**; **Figure 4**). There was a significant interaction between FFR values (≤0.80 and >0.80) and clinical events (TVF and CDTVR) in both groups (P=0.026 and 0.039, respectively).

Discussion

The main findings of the present study are that: (1) the 2-year TVF rate in deferred lesions did not differ significantly between symptomatic and asymptomatic patients; (2) patients with an FFR ≤0.80 were likely to develop TVF regardless of their symptoms; and (3) among patients with lesions with an FFR >0.80, the rate of TVF was significantly higher for symptomatic than asymptomatic patients.

Deferral of revascularization contributes largely to the benefit of FFR-guided revascularization because of the reduction in unnecessary revascularization and MI compared with angiography-guided revascularization. In clinical practice, some patients with SCAD showed a discordance between clinical symptoms and FFR results. Indeed, the ORBITA (Objective Randomized Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) trial demonstrated that 25.3% of symptomatic patients had a lesion with an FFR >0.80.[10] To date, however, it remains unclear whether baseline clinical symptoms affect clinical outcomes after the deferral of revascularization based on FFR. The present study demonstrated that the 2-year TVF rate did not differ significantly between symptomatic and asymptomatic patients, although the CDTVR rate tended to be higher in symptomatic than asymptomatic patients. Furthermore, cardiac death and MI rarely occurred in either group during the 2-year follow-up. These findings support that FFR-based deferral of revascularization is acceptable in daily practice, regardless of symptoms.

Asymptomatic ischemia is associated with worse outcomes, especially after MI.[9] Recently, a subanalysis of the FAME 2 (Fractional Flow Reserve Guided Fractional Percutaneous Coronary Intervention Plus Optimal Medical Treatment [OMT] Versus OMT) trial demonstrated that the rate of death and MI at 5 years was significantly higher in asymptomatic than symptomatic patients treated with medication alone; PCI led to better outcomes in asymptomatic patients as compared with OMT.[13] In the present study, the 2-year TVF rate was numerically higher in asymptomatic than symptomatic patients with lesions with



Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	89	81	49
Cumulative incidence	0.0%	6.8%	8.0%
Asymptomatic group			
N of patients at risk	112	103	66
Cumulative incidence	0.0%	5.4%	12.3%

Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	89	89	57
Cumulative incidence	0.0%	0.0%	0.0%
Asymptomatic group			
N of patients at risk	112	112	74
Cumulative incidence	0.0%	0.0%	1.9%

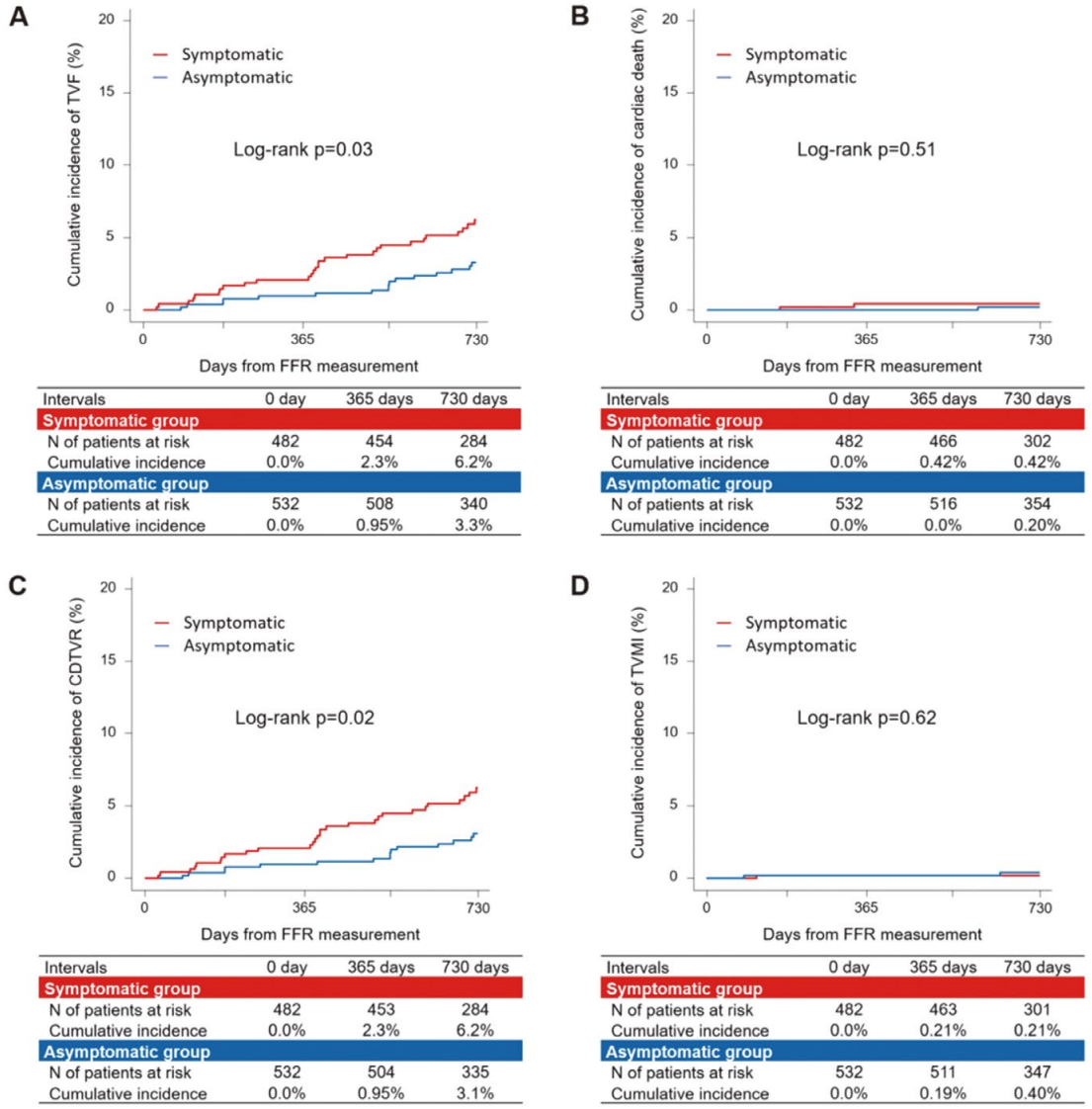
Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	89	81	49
Cumulative incidence	0.0%	6.8%	8.0%
Asymptomatic group			
N of patients at risk	112	104	66
Cumulative incidence	0.0%	5.4%	10.4%

Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	89	87	55
Cumulative incidence	0.0%	1.1%	1.1%
Asymptomatic group			
N of patients at risk	112	112	74
Cumulative incidence	0.0%	0.0%	0.0%

Figure 3. Clinical outcomes of symptomatic and asymptomatic patients with lesions with a fractional flow reserve (FFR) ≤0.80: (**A**) target vessel failure (TVF), (**B**) cardiac death, (**C**) clinically driven target vessels revascularization (CDTVR), and (**D**) target vessel related myocardial infarction (TVMI).

an FFR ≤0.80, although the difference was not statistically significant. These findings may help explain why the absence of symptoms contributes to less revascularization of functionally significant lesions, resulting in an increased risk of future cardiac events. As such, we might have to consider revascularization of lesions with FFR ≤0.80 even in the absence of symptoms. More importantly, careful follow-up is mandatory in those patients in whom revascularization is deferred.

Coronary revascularization can be safely deferred when the FFR is >0.80.[2–6] However, the relationship between baseline symptoms and clinical outcomes after FFR-based deferral of revascularization remains unclear. The present study showed that symptomatic patients had a significantly higher rate of TVF, driven primarily by CDTVR, than asymptomatic patients. In symptomatic patients with non-significant coronary artery stenosis by FFR, microvascular angina should be considered as the underlying mechanism of angina symptoms.[14] Microcirculatory dysfunction leads to the development of epicardial coronary artery stenosis, leading to worse prognosis.[15] Therefore, symptomatic patients with FFR >0.80 require careful follow-up and intensive medical treatment. Conversely, it is intriguing that clinical symptoms improved in 77.5% of symptomatic patients at the 2-year follow-up. Recently, the ORBITA trial demonstrated that PCI did not improve symptoms more than placebo even in patients with ischemic symptoms, and 29.2% of patients with placebo did not feel any angina during the follow-up period.[10,11] Furthermore, the DEFER and FAME 2 trials reported that symptoms were markedly improved by simply telling a patient that the FFR was >0.80.[16] These results suggest the presence of



Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	482	454	284
Cumulative incidence	0.0%	2.3%	6.2%
Asymptomatic group			
N of patients at risk	532	508	340
Cumulative incidence	0.0%	0.95%	3.3%

Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	482	466	302
Cumulative incidence	0.0%	0.42%	0.42%
Asymptomatic group			
N of patients at risk	532	516	354
Cumulative incidence	0.0%	0.0%	0.20%

Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	482	453	284
Cumulative incidence	0.0%	2.3%	6.2%
Asymptomatic group			
N of patients at risk	532	504	335
Cumulative incidence	0.0%	0.95%	3.1%

Intervals	0 day	365 days	730 days
Symptomatic group			
N of patients at risk	482	463	301
Cumulative incidence	0.0%	0.21%	0.21%
Asymptomatic group			
N of patients at risk	532	511	347
Cumulative incidence	0.0%	0.19%	0.40%

Figure 4. Clinical outcomes of symptomatic and asymptomatic patients with lesions with a fractional flow reserve (FFR) >0.80: (**A**) target vessel failure (TVF), (**B**) cardiac death, (**C**) clinically driven target vessels revascularization (CDTVR), and (**D**) target vessel related myocardial infarction (TVMI).

"faith healing" in SCAD patients. Although medical treatment, such as lifestyle modification and OMT, is the first choice for patients with negative FFR results, we should be familiar with the comprehensive management of SCAD harnessing the power of "faith healing".

Study Limitations

The present study has several limitations. First, this study was a post hoc analysis of the J-CONFIRM Registry and therefore the sample size could not be calculated. Although propensity score analysis and multivariable Cox model were used to adjust for differences in baseline clinical characteristics between the 2 groups, we could not adjust for all the confounders due to the observational design of the study. These findings may bias the conclusions in the present study. Second, symptomatic responses to the treatment are subjective and include not only a true therapeutic effect, but also a placebo effect.[17] In the present study, neither physicians nor patients were blinded to the FFR results, which may have affected their decision-making process, especially when the FFR was ≤0.80. Third, the current study population predominately had mild symptoms. Therefore, the results may not be applicable to patients with moderate to severe symptoms. Fourth, we did not use a disease-specific QoL assessment, such as Seattle Angina Questionnaire, in the present study.[18] Finally, lifestyle modification and the control of risk factors play crucial roles in the management of SCAD, but we could not determine whether they were optimally achieved during the follow-up period.

Conclusions

Despite negative FFR values, symptomatic patients were at higher risk of TVF than asymptomatic patients, driven primarily by a higher rate of CDTVR. Conversely, those with a positive FFR were likely to develop TVF regardless of their symptoms.

Acknowledgment

The authors appreciate the efforts of the investigator at the 28 participating centers and Kaori Shimogama for assistance with this work. A list of participating centers and investigators is provided in the **Supplementary Appendix**.

Sources of Funding

This work was supported by Abbott Vascular Japan, Phillips Japan, and Boston Scientific Japan.

Disclosures

S.K. has received lecture fees from Boston Scientific Japan. H.M. has served as an advisory board member for Zeon Medical and has received lecture fees from Abbott Vascular Japan, Phillips Japan, and Boston Scientific Japan. Y.K. has received lecture fees from Abbott Vascular Japan and Phillips Japan. Y.S. has received lecture fees from Abbott Vascular Japan and Phillips Japan. T.A. has received lecture fees from Boston Scientific Japan and Phillips Japan. K.T. is an Associate Editor for *Circulation Reports*. H.Y. has received lecture fees from Boston Scientific Japan. N.T. has served as an advisory board member for Abbott Vascular Japan and Boston Scientific Japan. The other authors have no conflicts of interest to report.

IRB Information

This study was approved by the Institutional Review Board of Kokura Memorial Hospital (Reference no. 18041151).

Data Availability

The deidentified participant data will not be shared.

References

1. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JJ, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996; **334:** 1703–1708.
2. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *Am J Coll Cardiol* 2010; **56:** 177–184.
3. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J* 2015; **36:** 3182–3188.
4. Ahn JM, Park DW, Shin ES, Koo BK, Nam CW, Doh JH, et al. Fractional flow reserve and cardiac events in coronary artery disease: Data from a prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation* 2017; **135:** 2241–2251.
5. Kawase Y, Matsuo H, Akasaka T, Shiono Y, Tanaka N, Amano T, et al. Clinical use of physiological lesion assessment using pressure guidewires: An expert consensus document of the Japanese Association of Cardiovascular Intervention and Therapeutics. *Cardiovasc Interv Ther* 2019; **34:** 85–96.
6. Kuramitsu S, Matsuo H, Shinozaki T, Horie K, Takashima H, Terai H, et al. Two-year outcomes after deferral of revascularization based on fractional flow reserve: The J-CONFIRM Registry. *Circ Cardiovasc Interv* 2020; **13:** e008355.
7. Spertus JA, Maron DJ, Cohen DJ, Kolm P, Hartigan P, Weintraub WS, et al. Frequency, predictors, and consequences of crossing over to revascularization within 12 months of randomization to optimal medical therapy in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. *Circ Cardiovasc Qual Outcomes* 2013; **6:** 409–418.
8. Spertus JA, Jones PG, Maron DJ, O'Brien SM, Reynolds HR, Rosenberg Y, et al. Health-status outcomes with invasive or conservative care in coronary disease. *N Engl J Med* 2020; **382:** 1408–1419.
9. Erne P, Schoenenberger AW, Burckhardt D, Zuber M, Kiowski W, Buser PT, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: The SWISS II randomized controlled trial. *JAMA* 2007; **297:** 1985–1991.
10. Al-Lamee R, Thompson D, Dehbi HK, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): A double-blind, randomised controlled trial. *Lancet* 2018; **391:** 31–40.
11. Al-Lamee R, Howard JP, Shun-Shin MJ, Thompson D, Dehbi HM, Sen S, et al. Fractional flow reserve and instantaneous wave-free ratio as predictors of the placebo-controlled response to percutaneous coronary intervention in stable single-vessel coronary artery disease. *Circulation* 2018; **138:** 1780–1792.
12. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* 2007; **115:** 2344–2351.
13. Fournier S, Kobayashi Y, Fearon WF, Collet C, da Costa BR, Rioufol G, et al. Asymptomatic patients with abnormal fractional flow reserve treated with medication alone or with PCI. *Am J Coll Cardiol* 2019; **74:** 1642–1644.
14. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, et al. International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 2018; **250:** 16–20.
15. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. *Am J Coll Cardiol* 2010; **55:** 2825–2832.
16. Rajkumar CA, Nijjer SS, Cole GD, Al-Lamee R, Francis DP. "Faith healing" and "subtraction anxiety" in unblinded trials of procedures: Lessons from DEFER and FAME-2 for end points in the ISCHEMIA trial. *Circ Cardiovasc Qual Outcomes* 2018; **11:** e004665.
17. Ernst E, Resch KL. Concept of true and perceived placebo effects. *BMJ* 1995; **311:** 551–553.
18. Mark DB. Assessing quality-of-life outcomes in cardiovascular clinical research. *Nat Rev Cardiol* 2016; **13:** 286–308.

Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-20-0110