Circulation Reports
Circ Rep 2024; 6: 313–321
doi:10.1253/circrep.CR-24-0069

ORIGINAL ARTICLE
Ischemic Heart Disease

Impact of Antiplatelet Therapy on 5-Year Outcomes After Fractional Flow Reserve-Guided Deferral of Revascularization in Nonsignificant Obstructive Coronary Artery Disease

Tairo Kurita, MD, PhD; Shoichi Kuramitsu, MD, PhD; Masanobu Ishii, MD, PhD; Akihiro Takasaki, MD; Takenori Domei, MD; Hitoshi Matsuo, MD, PhD; Kazunori Horie, MD; Hirohiko Ando, MD, PhD; Hidenobu Terai, MD; Yuetsu Kikuta, MD; Takayuki Ishihara, MD; Tatsuya Saigusa, MD; Tomohiro Sakamoto, MD, PhD; Nobuhiro Suematsu, MD, PhD; Yasutsugu Shiono, MD, PhD; Taku Asano, MD, PhD; Kenichi Tsujita, MD, PhD; Katsuhiko Masamura, MD, PhD; Tatsuki Doijiri, MD; Fumitoshi Toyota, MD; Manabu Ogita, MD, PhD; Jun Shiraishi, MD, PhD; Ken Harada, MD, PhD; Hiroyuki Isogai, MD, PhD; Reo Anai, MD; Shinjo Sonoda, MD, PhD; Hiroyoshi Yokoi, MD; Nobuhiro Tanaka, MD, PhD; Kaoru Dohi, MD, PhD; on behalf of the J-CONFIRM Investigators

Background: Because the clinical benefit of antiplatelet therapy (APT) for patients with nonsignificant coronary artery disease (CAD) remains poorly understood, we evaluated it in patients after fractional flow reserve (FFR)-guided deferral of revascularization.

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), we investigated 265 patients with deferred lesions who did not require APT for secondary prevention of cardiovascular disease. A 2-year landmark analysis assessed the relationship between APT at 2 years and 5-year major cardiac adverse events (MACE: composite of all-cause death, target vessel-related myocardial infarction, clinically driven target vessel revascularization). Of the 265 patients, 163 (61.5%) received APT. The 5-year MACE did not significantly differ between the APT and non-APT groups after adjustment for baseline clinical characteristics (9.2% vs. 6.9%, inverse probability weighted hazard ratio, 1.40 [95% confidence interval, 0.53–3.69]; P=0.49). There was a marginal interaction between the effect of APT on MACE and FFR values (< or ≥0.84) (P for interaction=0.066).

Conclusions: The 5-year outcomes after FFR-guided deferral of revascularization did not significantly differ between the APT and non-APT groups, suggesting that APT might not be a critical requirement for nonsignificant obstructive CAD patients not requiring APT for secondary prevention of cardiovascular disease.

Key Words: Antiplatelet therapy; Coronary artery disease; Fractional flow reserve

Fractional flow reserve (FFR) is an invasively measured physiological index of the functional significance of epicardial coronary artery stenosis.[1] However, measuring FFR avoids unnecessary revascularization for intermediate coronary artery stenosis without proven myocardial ischemia, saving medical resources and costs, together with improved clinical outcomes.[2,3] Recently, the J-CONFIRM Registry (Long-Term Outcomes of Japanese Patients with Deferral of Coronary Intervention Based on Fractional Flow Reserve in Multicenter Registry) reported that 5-year target vessel failure (TVF) was 11.6% in deferred lesions, mainly clinically driven target vessel

Received June 25, 2024; accepted June 25, 2024; J-STAGE Advance Publication released online July 20, 2024 Time for primary review: 1 day

Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Mie (T.K., A.T., K.D.); Department of Cardiovascular Medicine, Sapporo Cardiovascular Clinic, Sapporo Heart Center, Sapporo (S.K.); Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto (M.I., K.T.); Department of Cardiology, Kokura Memorial Hospital, Fukuoka (T. Domei); Department of Cardiovascular Medicine, Gifu Heart Center, Gifu (H.M.); Department of Cardiovascular Medicine, Sendai Kousei Hospital, Sendai (K.H.); Department of Cardiology, Aichi Medical University, Aichi (H.A.); Department of Cardiology, Kanazawa Cardiovascular Hospital, Ishikawa (H.T.); Department of Cardiology, Fukuyama Cardiovascular Hospital, Hiroshima (Y.K.); Kansai Rosai Hospital Cardiovascular Center, Hyogo (T.I.); Department of Cardiovascular Medicine, Shinshu University School of Medicine, Nagano (T. Saigusa); Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center, Kumamoto (T. Sakamoto); Department of Cardiology, Saiseikai Fukuoka General Hospital, Fukuoka (N.S.); Department of Cardiovascular Medicine, Wakayama Medical University, Wakayama (Y.S.);
(Footnote continued the next page.)

revascularization (CDTVR); cardiac death and target vessel-related myocardial infarction (TVMI) rarely occurred during the follow-up.[4] These findings highlight the feasibility and long-term safety of FFR-guided deferral of revascularization in patients with chronic coronary syndrome (CCS).

The pharmacological management of CCS patients plays a crucial role in reducing angina symptoms and preventing future cardiovascular events. Current guidelines recommend antiplatelet therapy (APT), β-blocker, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, and statins for event prevention in CCS patients, especially those at high risk of cardiovascular events.[2,5] Among these recommended drugs, APT is the cornerstone of secondary prevention for patients with a prior myocardial infarction (MI) and revascularization.[2,5,6] However, whether APT has clinical benefit for CCS patients after FFR-guided deferral of revascularization remains poorly understood, so in this regard, we sought to assess the impact of APT on long-term outcomes in CCS patients after deferring revascularization based on FFR by analyzing patients from the J-CONFIRM registry.

Methods

Study Design and Study Population

This study was a post hoc analysis of the J-CONFIRM registry, a prospective multicenter observational study investigating the clinical outcomes of patients who deferred revascularization based on FFR measurements at 28 Japanese hospitals (**Supplementary Appendix**) between September 2013 and June 2015, as previously described.[4,7] In brief, the J-CONFIRM registry prospectively enrolled 1,263 patients with 1,447 angiographically intermediate coronary artery stenoses and deferral of revascularization based on FFR measurement after excluding patients with AMI, cardiogenic shock, chronic total occlusion lesion, graft lesion, or limited life expectancy due to comorbidity. For the present study, a 2-year landmark analysis was conducted to investigate the impact of APT (aspirin and/or P2Y12 inhibitors) on the 5-year outcomes after FFR-guided deferral of revascularization. The exposure period for the implementation adherence measurement was set to 2 years because we sought to confirm reliable continuing APT,[8] which was defined as the continuation of APT during the 2-year follow-up and confirmed at discharge and the 1- and 2-year follow-up by each site investigator. The selection of APT was left to the discretion of the attending physician at each institution. Patients with (1) FFR <0.80, (2) major adverse cardiac events (MACE) within the 2-year follow-up, (3) APT requirement for secondary prevention (i.e., prior history of MI, revascularization, peripheral artery disease, and cerebrovascular disease); (4) who used anticoagulants at the 2-year follow-up, and (5) with unstable angina at the index FFR measurement were excluded from the present analysis.

This study protocol was approved by the local ethics committee at all participating centers and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for participation in this registry. The research was funded by an unrestricted grant from Abbott Vascular Japan, Phillips Japan, and Boston Scientific Japan, none of which had oversight or input into data gathering, data interpretation, or the preparation of this manuscript. This study was registered with http://www.umin.ac.jp, unique identifier UMIN000014473. The data, analytic methods, and study materials will not be made available to other researchers for the purposes of reproducing the results or replicating the procedure.

Data Collection and Follow-up

All baseline and clinical follow-up data were prospectively collected from the medical records or by telephone contact with the patients, relatives, referring physicians at discharge and the 1-, 2-, 3-, 4-, and 5-year follow-ups by each site investigator. All clinical events were judged by an independent clinical events committee.

Study Endpoints and Definitions

The primary endpoint was MACE at 5 years. MACE was defined as a composite of all-cause death, TVMI, and CDTVR during the follow-up period that began from the date of 2-year follow-up to the date of the first event or until 5-year follow-up. Cardiac death and TVF (cardiac death, TVMI, and CDTVR) were also assessed. Death was regarded as cardiac unless other noncardiac causes could be identified. MI was defined according to the Academic Research Consortium definition.[9] TVR was defined as repeated percutaneous coronary intervention or repeated coronary artery bypass graft on the target vessel. 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, irrespective of ischemic signs or symptoms.[9]

Department of Cardiology, St. Luke's International Hospital, Tokyo (T.A.); Department of Cardiology, Nakamura Hospital, Fukui (K.M.); Department of Cardiology, Yamato Seiwa Hospital, Kanagawa (T. Doijiri); Department of Cardiology, Chidoribashi Hospital, Fukuoka (F.T.); Department of Cardiology, Juntendo University Shizuoka Hospital, Shizuoka (M.O.); Department of Cardiology, Japanese Red Cross Kyoto Daini Hospital, Kyoto (J.S.); Department of Cardiology, Chubu Rosai Hospital, Nagoya (K.H.); Department of Cardiology, Juntendo University Urayasu Hospital, Chiba (H.I.); The Second Department of Internal Medicine, University of Occupational and Environmental Health Japan School of Medicine, Kitakyushu (R.A.); Department of Cardiovascular Medicine, Saga University, Saga (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

The first two authors contributed equally to this work (T.K., S.K.).

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

CLINICAL TRIAL REGISTRATION: URL: https://www.umin.ac.jp, unique identifier: UMIN000014473.

Mailing address: Shoichi Kuramitsu, MD, PhD, Department of Cardiovascular Medicine, Sapporo Cardiovascular Clinic, Sapporo Heart Center, North 49, East 16, 8-1, Higashi-ku, Sapporo, Hokkaido 007-0849, Japan. email: kuramitsu@heart-kizuna.com

ISSN-2434-0790

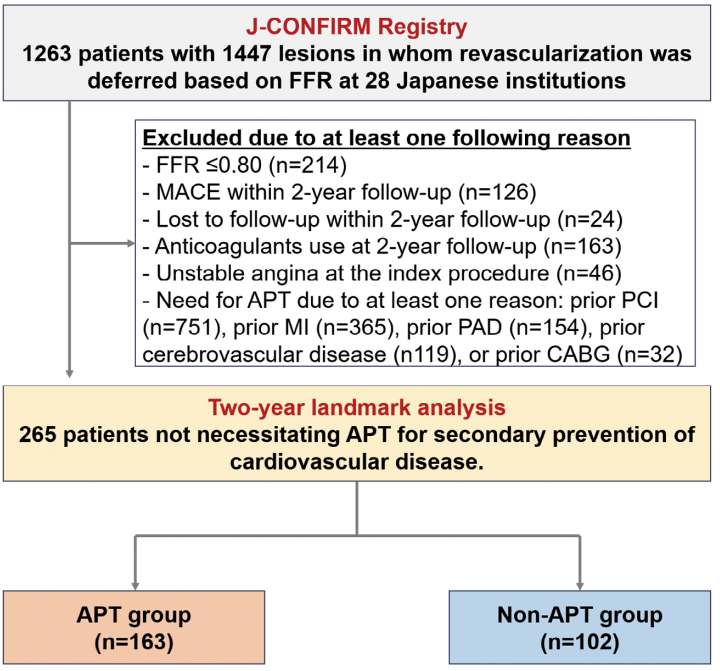

Figure 1. Study flowchart. APT, antiplatelet therapy; CABG, coronary artery bypass graft; FFR, fractional flow reserve; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

Statistical Analysis

Data are expressed as the median and interquartile range for continuous variables, and number (percentage) for categorical variables. Group comparisons were performed using the Mann-Whitney U test for continuous variables, the Chi-squared test or Fisher's exact test for categorical variables, and the log-rank test for Kaplan-Meier curves, as appropriate. Logistic regression analysis was performed to investigate the clinical characteristics of patients who took APT at the 2-year follow-up. Because there are no reports regarding factors associated with those patients, variables that might be clinically relevant to APT was used in the multivariable logistic analysis. Event rates (per 100 person-years) and the 95% confidence intervals (CIs) for both the APT and non-APT groups were calculated for quintiles of FFR values and presented as a plot with a natural cubic spline. The landmark analysis comparing APT treatments (dual or single) during the follow-up period between 2 and 5 years was conducted after deferral of revascularization among patients who were event-free at 2 years. Hazard ratios (HRs) with 95% CIs of the APT group relative to the non-APT group for the outcome measures were estimated during the follow-up period between 2 and 5 years by an inverse probability of treatment weighted Cox model and a multivariable Cox model, with mixed effects account for institutional variety.[10] The HRs were adjusted for covariates such as age, sex, the lowest value of FFR, left main coronary artery lesion, diabetes mellitus, dyslipidemia, prior heart failure, multivessel disease, CREDO-Kyoto thrombotic risk, statin use, and nitrate use.[11] The predicted probability of receiving APT was calculated by fitting a logistic regression model, using all clinically relevant variables as mentioned above and was used as weights for the inverse probability of treatment weighted model. To confirm the robustness of the results, propensity score matching analysis was performed as the sensitivity analysis for the same outcomes. One patient on APT was matched to 1 patient not treated with APT using nearest-neighbor matching within a caliper width of 0.1 SD without replacement. Additionally, subgroup analysis stratified by FFR value (FFR < or ≥0.84) was performed to estimate the interaction between the effect of APT or other optimal medical therapy (OMT) agents on MACE and FFR values. A two-sided P value <0.05 indicated statistical significance. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA), and R software Version 4.3.1. (http://www.r-project.org).

Results

Study Population and Baseline Clinical Characteristics

Of the initial 1,263 patients, 265 were enrolled in the present analysis (**Figure 1**) and their baseline clinical characteristics are summarized in **Table 1**. No differences were observed between the APT and non-APT groups except for the prevalence of dyslipidemia and statin use. The CREDO-Kyoto thrombotic risk did not differ between groups (P=0.55) and the median lowest FFR value was comparable between them (0.86 [0.83, 0.90] vs. 0.86 [0.84, 0.90], P=0.81). A similar trend was observed among the dual-APT, single-APT, and non-APT groups (**Supplementary Table 1**).

Factors Associated With APT

Dyslipidemia (odds ratio [OR], 3.48 [95% CI, 1.95–6.19]; P<0.001), symptomatic patients (OR, 2.18 [95% CI, 1.21–3.92]; P=0.009) and lesion length ≥20 mm (OR, 3.06 [95% CI, 1.01–9.23]; P=0.048) were associated with the patients receiving APT at the 2-year follow-up (**Table 2**).

Clinical Outcomes

The 5-year clinical follow-up after FFR measurement

Table 1. Baseline Clinical Characteristics

	Overall (n=265)	APT (n=163)	Non-APT (n=102)	P value
Age, years	71 (65, 77)	71 (65, 78)	71 (64, 76)	0.70
Male sex	169 (64%)	107 (66%)	62 (61%)	0.43
Body mass index, kg/m^2	23.7 (21.9, 25.9)	23.6 (21.7, 26.8)	23.8 (22.0, 25.1)	0.66
Current smoking	78 (29%)	47 (29%)	31 (30%)	0.78
Hypertension	177 (67%)	111 (68%)	66 (65%)	0.59
Diabetes mellitus	89 (34%)	58 (36%)	31 (30%)	0.42
Dyslipidemia	157 (59%)	114 (70%)	43 (42%)	<0.001
Prior heart failure	12 (4.5%)	6 (3.7%)	6 (5.9%)	0.55
LVEF, %	66 (61, 70)	66 (62, 70)	66 (60, 72)	0.71
≤40%	7 (3.0%)	3 (2.0%)	4 (4.4%)	0.43
CCS functional class				0.15
Asymptomatic	101 (38%)	54 (33%)	47 (46%)	
Class I	130 (49%)	89 (55%)	41 (40%)	
Class II	27 (10%)	15 (9.2%)	12 (12%)	
Class III	4 (1.5%)	3 (1.8%)	1 (1.0%)	
Class IV	3 (1.1%)	2 (1.2%)	1 (1.0%)	
Target lesion				
LMCA	5 (1.9%)	4 (2.5%)	1 (1.0%)	0.65
LAD	160 (60%)	93 (57%)	67 (66%)	0.20
LCX	57 (22%)	37 (23%)	20 (20%)	0.65
RCA	66 (25%)	46 (28%)	20 (20%)	0.14
No. of target vessels				0.49
1	246 (93%)	150 (92%)	96 (94%)	
2	16 (6.0%)	10 (6.1%)	6 (5.9%)	
3	3 (1.1%)	3 (1.8%)	0 (0.0%)	
Multivessel disease	19 (7.2%)	13 (8.0%)	6 (5.9%)	0.63
Proximal location	232 (88.5%)	143 (88.8%)	89 (88.1%)	0.85
Bifurcation lesion	73 (29%)	41 (27%)	32 (33%)	0.32
Calcified lesion	27 (10.2%)	18 (11.8%)	9 (9.3%)	0.68
Diameter stenosis, %	45 (38, 53)	46 (38, 52)	44 (38, 53)	0.95
≥50%	83 (34%)	49 (33%)	34 (36%)	0.68
Lesion length, mm	12.8 (9.5, 16.2)	12.9 (9.6, 16.6)	12.3 (9.4, 15.7)	0.43
≥20	22 (8.8%)	17 (11.2%)	5 (5.2%)	0.11
CREDO-Kyoto thrombotic risk				0.55
High	11 (4.2%)	5 (3.1%)	6 (5.9%)	
Intermediate	54 (20%)	33 (20%)	21 (21%)	
Low	200 (76%)	125 (77%)	75 (74%)	
Lowest FFR value	0.86 (0.83, 0.90)	0.86 (0.83, 0.90)	0.86 (0.84, 0.90)	0.81
Medication at 2 years				
Aspirin	145 (55%)	145 (89%)	0 (0%)	<0.001
P2Y12 inhibitor	75 (28%)	75 (46%)	0 (0%)	<0.001
Dual antiplatelet therapy	57 (22%)	57 (35%)	0 (0%)	<0.001
ACEI/ARB	120 (45%)	78 (48%)	42 (41%)	0.31
β-blocker	49 (19%)	30 (18%)	19 (19%)	1.00
Calcium-channel blocker	135 (51%)	56 (55%)	79 (49%)	0.32
Statin	151 (57%)	110 (68%)	41 (40%)	<0.001
Nitrate	54 (20%)	38 (23%)	16 (16%)	0.16

Categorical variables are expressed as number and percentage. Continuous variables are indicated as median (interquartile range). ACEI, angiotensin-converting enzyme inhibitor; APT, antiplatelet therapy; ARB, angiotensin II receptor blocker; CCS, Canadian Cardiovascular Society; FFR, fractional flow reserve; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; LCX, left circumflex coronary artery; LVEF, left ventricular ejection fraction; RCA, right coronary artery.

Table 2. Logistic Regression Analyses for Associated Factors of APT

	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Age ≥75 years	1.00	0.98–1.03	0.75	1.02	0.99–1.05	0.15
Male	1.23	0.74–2.06	0.42	1.18	0.66–2.12	0.58
Current smoking	0.93	0.54–1.59	0.79			
Hypertension	1.16	0.69–1.96	0.57			
Dyslipidemia	3.19	1.91–5.35	<0.001	3.48	1.95–6.19	<0.001
Diabetes mellitus	1.27	0.75–2.15	0.38	1.01	0.55–1.85	0.97
Hemodialysis	0.72	0.23–2.20	0.56			
LVEF ≤40%	0.45	0.10–2.05	0.30			
Symptomatic (vs. asymptomatic)	1.73	1.04–2.87	0.035	2.18	1.21–3.92	0.009
LMCA	2.54	0.28–23.1	0.41			
Multivessel disease	1.39	0.51–3.77	0.52	1.16	0.38–3.56	0.79
Proximal location	1.07	0.49–2.33	0.86	1.24	0.51–2.99	0.64
Bifurcation lesion	0.75	0.43–1.31	0.31			
Calcified lesion	1.31	0.57–3.06	0.53			
Diameter stenosis ≥50%	0.89	0.52–1.53	0.67	0.86	0.48–1.55	0.61
Lesion length ≥20 mm	2.32	0.83–6.50	0.11	3.06	1.01–9.23	0.048
FFR ≤0.85	0.96	0.58–1.58	0.87	0.78	0.44–1.37	0.39

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

Table 3. Clinical Events From 2 to 5 Years

	All (n=265)	APT (n=163)	Non-APT (n=102)	P value
MACE	22 (8.3%)	15 (9.2%)	7 (6.9%)	0.65
TVF	11 (4.2%)	7 (4.3%)	4 (3.9%)	1.00
All-cause death	12 (4.5%)	8 (4.9%)	4 (3.9%)	1.00
Cardiac death	1 (0.4%)	0 (0%)	1 (0.9%)	0.39
Noncardiac death	11 (4.2%)	8 (4.9%)	3 (2.9%)	0.54
CDTVR	11 (4.2%)	7 (4.3%)	4 (3.9%)	1.00
TVMI	2 (0.8%)	0 (0%)	2 (2.0%)	0.15

Categorical variables are expressed as number and percentage. APT, antiplatelet therapy; CDTVR, clinical driven target vessel revascularization; MACE, major adverse cardiac event; TVF, target vessel failure; TVMI, target vessel myocardial infarction.

was completed in 94.0% of patients. The 5-year MACE and TVF rates did not differ between the APT and non-APT groups (9.2% vs. 6.9%, P=0.65; 4.3% vs. 3.9%, P=1.00, respectively) (**Table 3**, **Figure 2A**). After adjustment for baseline clinical characteristics, no significant differences in the 5-year MACE and TVF rates were observed between groups (inverse probability weighted HR, 1.40 [95% CI, 0.53–3.69]; P=0.49 and inverse probability weighted HR, 0.85 [95% CI, 0.23–3.06]; P=0.80, respectively) (**Table 4**). Other outcomes (i.e., all-cause death, cardiac death, CDTVR, and TVMI) did not differ between groups (**Tables 3**,**4**). The all-cause deaths were: renal failure (n=3), malignancy (n=2), acute MI (n=1), cerebral hemorrhage (n=1), pneumonia (n=1), sepsis (n=1), and others (n=3). Among these causes, acute MI and cerebral hemorrhage occurred in 1 case each in the non-APT and APT groups. A similar trend was observed among the dual-APT, single-APT, and non-APT groups (**Supplementary Table 2**). Although patients with %DS ≥50 had a higher TVF rate than those with %DS <50, there was no involvement of APT in this respect (**Supplementary Table 3**).

Sensitivity Analysis

After propensity score matching, the study population consisted of 81 matched patients in each group. The baseline characteristics of this matched population are summarized in the **Supplementary Table 4**. The 5-year MACE rate was higher in the APT group than in the non-APT group, although it did not reach statistical significance (11.4% vs. 7.7%, P=0.43, **Figure 2B**). These results of the sensitivity analysis were mostly consistent with the primary study results (**Table 4**).

Impact of APT on MACE According to FFR Values

Figure 3 shows the relationship between the MACE rate and APT according to FFR values. The 5-year MACE rate was lower in the APT group than in the non-APT group in patients with lesions of FFR <0.84 (17.4% vs. 7.7%, P=0.23), and this relationship was inversely observed in those with FFR ≥0.84 (10.1% vs. 4.0%, P=0.12). This subgroup analysis observed a potential interaction between

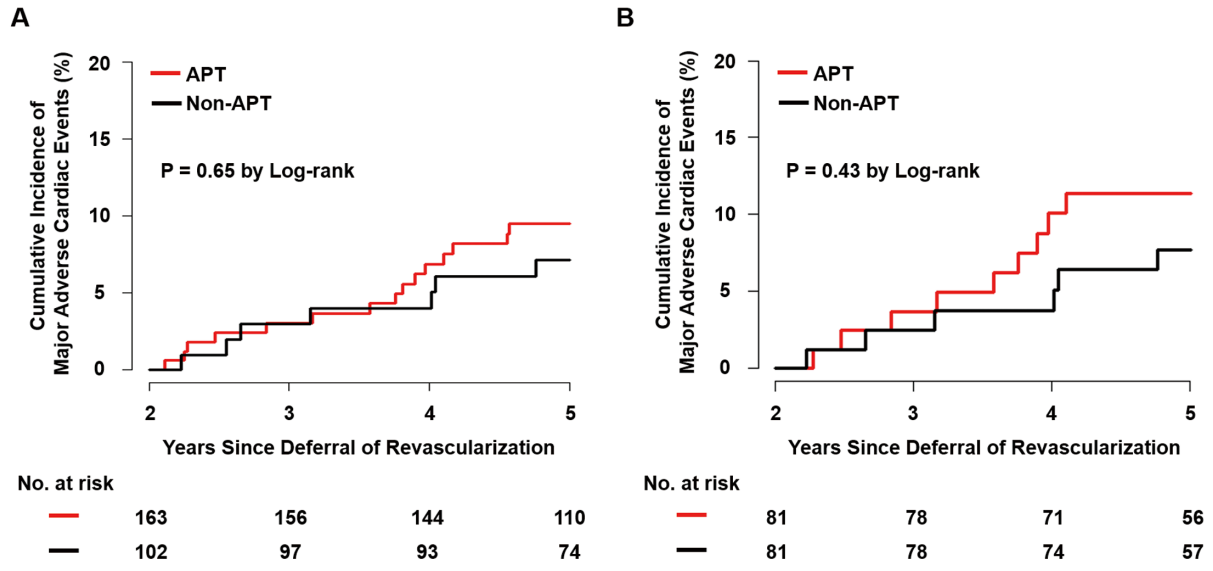

Figure 2. Cumulative incidence of major adverse cardiac events from 2 to 5 years. (**A**) Crude cohort and (**B**) propensity score matched cohort. APT, antiplatelet therapy.

Table 4. Adjusted Risk of Outcomes According to APT

	MACE			TVF			All-cause death		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Univariable analysis									
Antiplatelet therapy	1.22	0.47, 3.13	0.69	1.04	0.27, 3.92	0.96	1.14	0.32, 3.96	0.84
Inverse probability weighted*									
Antiplatelet therapy	1.40	0.53, 3.69	0.49	0.85	0.23, 3.06	0.80	2.03	0.59, 6.93	0.26
Multivariable analysis*									
Antiplatelet therapy	1.12	0.40, 3.19	0.82	0.31	0.06, 1.73	0.18	1.57	0.35, 7.11	0.56
Propensity score matching*									
Antiplatelet therapy	1.51	0.54, 4.25	0.43	1.02	0.25, 4.07	0.98	1.69	0.40, 7.09	0.47

*Adjusted for covariates such as age, sex, lowest fractional flow reserve value, left main coronary artery lesion, diabetes mellitus, dyslipidemia, prior heart failure, multivessel disease, CREDO-Kyoto thrombotic risk, statin use, and nitrates use. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 3.

the effect of APT on MACE and FFR values (< or ≥0.84) (P for interaction=0.066), suggesting clinical relevance (**Figure 4**, **Supplementary Figure**). There was no significant interaction between the effect of other OMT agents on MACE and FFR values (**Supplementary Figure**). The baseline clinical characteristics and clinical outcomes of patients with lesions of FFR <0.84 and ≥0.84 were summarized (**Supplementary Tables 5**,**6**). There was no significant difference between groups except for dyslipidemia and target lesion location (**Supplementary Table 5**). In lesions with FFR <0.84, the cumulative incidence of CDTVR was higher in the non-APT group than in the APT group (13.3% vs. 2.9%, P=0.10), but the APT group showed a higher rate of CDTVR than the non-APT group for patients with FFR ≥0.84 (4.5% vs. 1.4%, P=0.24) (**Supplementary Table 6**). The interaction between the effect of APT on MACE and FFR values did not differ after adjustment for baseline differences between groups (P for interaction=0.066).

Discussion

The main findings of the present study can be summarized as follows. (1) The cumulative 5-year incidence of MACE and TVF did not differ between the APT and non-APT groups. (2) Dyslipidemia, symptomatic patients, and lesion length ≥20 mm were associated with patients receiving APT at the 2-year follow-up. (3) A clinically relevant interaction may exist between the effect of APT on MACE and FFR values in deferred lesions.

FFR measurement can avoid unnecessary revascularization for intermediate coronary artery stenosis, significantly reducing APT- and stent-related clinical events (i.e., bleeding, target lesion revascularization, and stent thrombosis).[1–5] Although the safety of FFR-guided deferral of revascularization has been well established in previous studies, clinical events continue to occur in deferred lesions with an annual incidence of 2–3%.[3,4,7] Thus, OMT plays a crucial role in minimizing the risk of future cardiovascular events

after deferring revascularization based on the FFR value. OMT is a goal-targeted intensification of pharmacologic treatment in combination with lifestyle modification for symptom relief and event prevention.[2,5] However, given that the efficacy of OMT has been mainly proven in patients with obstructive CAD, it remains poorly understood whether to extend OMT to patients with nonsignificant obstructive CAD (e.g., coronary stenosis >50% with FFR >0.80).[5]

Recently, a substudy of the J-CONFIRM registry reported that optimal guideline-directed medical therapy (GDMT), defined as combining 4 types of medications (APT, statin, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, and β-blocker), was associated with a lower risk of 5-year MACE in CCS patients after FFR-guided deferral of revascularization, indicating the importance of OMT on the long-term prognosis in patients with nonsignificant coronary artery lesions.[8] Intriguingly, among the individual medications comprising OMT, β-blockers and statins exhibited favorable outcomes after deferring revascularization based on FFR results, but APT did not.[8] Furthermore, Shiono et al. reported that APT was associated with a higher risk of 5-year TVF and MACE in patients with deferred lesions.[12] Given these findings, APT could be dispensed with for patients with nonsignificant CAD as prevention of future cardiovascular events. However, those substudies of the J-CONFIRM registry included patients with significant CAD (i.e., lesions with FFR <0.80) and a prior history of cardiovascular disease, including MI, revascularization, peripheral artery disease, and cerebrovascular disease. Therefore, as mentioned in the current guideline,[5] the prognostic implication of administering APT for patients with nonsignificant CAD remains poorly understood. To fill the gap between clinical practice and current guidelines, the present study focused on patients with nonsignificant CAD (i.e., lesions with FFR ≥0.80) who do not require APT for secondary prevention of cardiovascular disease. In the present study, the cumulative 5-year incidence of MACE and TVF did not differ between the APT and non-APT groups, and similar results were obtained after adjustment for baseline clinical characteristics. Although these results warrant cautious interpretation due to the retrospective study design with a relatively small population, they suggest that APT might not be imperative for patients with nonsignificant CAD who do not require secondary prevention of cardiovascular disease.

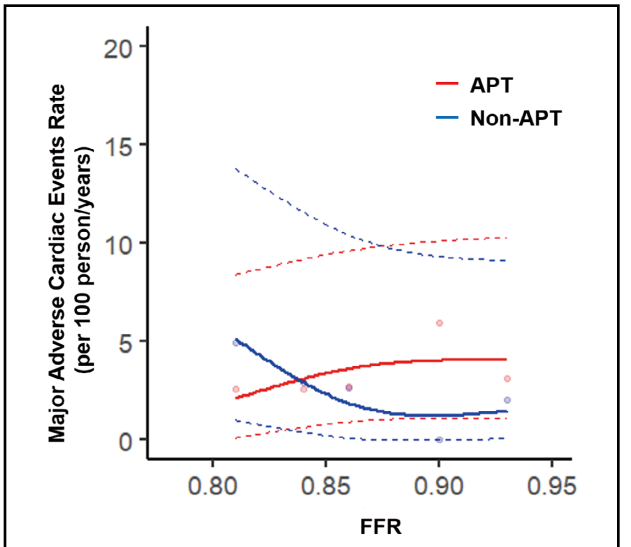

Figure 3. Rate of major cardiac adverse events (MACE) according to fractional flow reserve (FFR) in the APT and non-APT groups. The intersection of the lines is located around an FFR value of 0.838. APT, antiplatelet therapy.

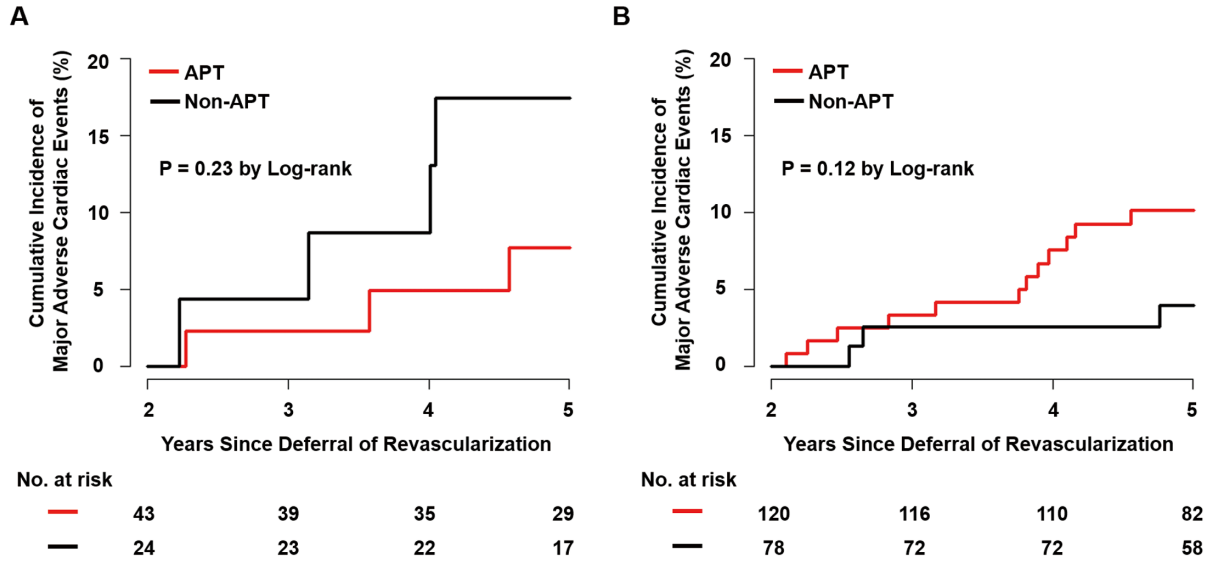

Figure 4. Cumulative incidence of major adverse cardiac events from 2 to 5 years according to fractional flow reserve: (**A**) <0.84 and (**B**) ≥0.84. APT, antiplatelet therapy.

The guidelines aim to assist physicians in prescribing evidence-based therapy to improve patients' symptoms and outcomes, but some gaps between guideline recommendations and clinical practice exist for several reasons.[13] Recently, Ishii et al. revealed that optimal GDMT was achieved only in 12.5% of patients at 2 years following FFR-guided deferral of revascularization; significant factors associated with achieving optimal GDMT included dyslipidemia, prior MI, prior percutaneous coronary intervention (PCI), left ventricular dysfunction, and left main coronary artery disease.[8] Current guidelines do not address the necessity for APT in patients with nonsignificant CAD, thus leaving the decision at the discretion of the physician. The present study results demonstrated that dyslipidemia, symptomatic patients, and lesion length ≥20 mm were significant predictors of patients requiring APT at 2-year follow-up, of which dyslipidemia was in line with the results of the previous study.[8] Regarding other factors, diffuse CAD is characterized by diffuse coronary atherosclerosis, which contributes to poor prognosis and persistent angina after PCI compared with focal CAD.[14] Furthermore, a previous study reported that symptomatic patients showed a higher incidence of TVF in deferred lesions with FFR >0.80 than asymptomatic patients.[15] Although the present study could not specify the exact reasons for prescribing antiplatelet drugs, APT might be best chosen for patients with these factors because they are high-risk indicators for future cardiovascular events in nonsignificant CAD patients without secondary prevention indications of APT.

FFR represents a continuum risk in coronary stenosis, where a lower FFR value is associated with a higher incidence of cardiac events; lesions with lower FFR values receive more significant benefit from revascularization.[16] A substudy of the J-CONFIRM registry showed that the benefits of optimal GDMT following deferring revascularization based on FFR appeared smaller as the FFR value decreased.[8] However, because APT was not associated with favorable outcomes among the individual medications of OMT in this study, the clinical implication of APT remains inconclusive. In the current study, the 5-year MACE rate was comparable between the APT and non-APT groups, suggesting that APT may not be essential for all patients with nonsignificant CAD. On the other hand, we found potential interactions between the effect of APT on MACE and FFR values in deferred lesions. These findings indicate that APT may reduce the risk of MACE when FFR <0.84. The 5-year follow-up data of the J-CONFIRM registry demonstrated that lesions with FFR 0.81–0.85 exhibited a similar incidence of TVF as those with FFR 0.75–0.80 but higher than those with FFR 0.86–1.00.[4] Those findings suggest that an FFR of 0.84 or 0.85 could be a potential threshold for the clinical benefit of APT in patients with nonsignificant CAD. However, due to the retrospective nature of this study, our results should be considered hypothesis-generating. Further studies are warranted to investigate the relationship between FFR values and the impact of APT on clinical outcomes in patients who have revascularization deferred based on their FFR values.

Study Limitations

First, this was a post hoc analysis of the J-CONFIRM registry; therefore, the decision to administer APT was left to the physician's discretion. Although we performed multivariable and inverse probability weighted Cox methods to adjust for differences in the baseline clinical characteristics of the 2 groups, unmeasured confounding factors might have biased the results. Second, APT plays a crucial role in reducing thrombotic events among patients with CAD, but is associated with increased bleeding risk.[2,5] Although we could not obtain information on bleeding events, acute MI and cerebral hemorrhage accounted for the primary cause of death in 1 case each in the non-APT and APT groups. Because our findings might indicate the risk and benefit of APT in patients with nonsignificant CAD, further studies are required to address them soon. Third, the clinical impact of APT type (i.e., aspirin and P2Y12 inhibitor) could not be investigated due to the relatively small study population. Fourth, in the stratified analysis of FFR values, spline curves and Cox regression model suggested an effect modification of APT on the incidence of MACE. However, due to the limited sample size, it is necessary to confirm the threshold FFR values in further studies with larger sample sizes. Finally, extrapolating our results outside Japan requires caution because the study population consisted solely of Japanese patients.

Conclusions

The 5-year outcomes after FFR-guided deferral of revascularization did not significantly differ between the APT and non-APT groups. Although that implies APT might not be a critical requirement for all patients with nonsignificant obstructive CAD, prospective large-scale studies are warranted to further evaluate the prognostic implications of APT in such patients.

Acknowledgment

We appreciate the efforts of the investigators in the 28 participating centers.

Funding Sources

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

Disclosure

S.K. receives lecture fees from Abbott Vascular Japan and Boston Scientific Japan; H.M. receives lecture fees from Abbott Vascular Japan, Boston Scientific Japan, and Phillips Japan; Y.K. receives lecture fees from Abbott Vascular Japan and Phillips Japan; Y.S. receives lecture fees from Abbott Vascular Japan and Phillips Japan; T.A. receives lecture fees from Abbott Vascular Japan and Phillips Japan; K.T. is a member of *Circulation Journal*'s and *Circulation Reports*' Editorial Team; N.T. receives lecture fees from Abbott Vascular Japan and Boston Scientific Japan; H.Y. receives lecture fees from Boston Scientific Japan. The other authors report no conflicts.

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 J, 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. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and

management of chronic coronary syndromes. *Eur Heart J* 2020; **41:** 407–477.
3. Kawase Y, Matsuo H, Kuramitsu S, Shiono Y, Akasaka T, Tanaka N, et al. Clinical use of physiological lesion assessment using pressure guidewires: An expert consensus document of the Japanese Association of Cardiovascular Intervention and Therapeutics – Update 2022. *Cardiovasc Interv Ther* 2022; **37:** 425–439.
4. Kuramitsu S, Matsuo H, Shinozaki T, Horie K, Takashima H, Terai H, et al. Five-year outcomes after fractional flow reserve-based deferral of revascularization in chronic coronary syndrome: Final results from the J-CONFIRM Registry. *Circ Cardiovasc Interv* 2022; **15:** e011387.
5. Nakano S, Kohsaka S, Chikamori T, Fukushima K, Kobayashi Y, Kozuma K, et al. JCS 2022 Guideline focused update on diagnosis and treatment in patients with stable coronary artery disease. *Circ J* 2022; **86:** 882–915.
6. Kawashima H, Serruys PW, Ono M, Hara H, O'Leary N, Mack MJ, et al. Impact of optimal medical therapy on 10-year mortality after coronary revascularization. *J Am Coll Cardiol* 2021; **78:** 27–38.
7. 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.
8. Ishii M, Kuramitsu S, Yamanaga K, Matsuo H, Horie K, Takashima H, et al. Association of guideline-directed medical therapy adherence with outcomes after fractional flow reserve-based deferral of revascularization. *Eur Heart J Cardiovasc Pharmacother* 2022; **8:** 600–608.
9. 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.
10. Austin PC. A Tutorial on multilevel survival analysis: Methods, models and applications. *Int Stat Rev* 2017; **85:** 185–203.
11. Capodanno D, Mehran R, Valgimigli M, Baber U, Windecker S, Vranckx P, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018; **15:** 480–496.
12. Shiono Y, Kuramitsu S, Matsuo H, Horie K, Takashima H, Terai H, et al. Thrombotic risk and cardiovascular events in patients with revascularization deferral after fractional flow reserve assessment. *JACC Cardiovasc Interv* 2022; **15:** 427–439.
13. Hoorn CJGM, Crijns HJGM, Dierick-van Daele ATM, Dekker LRC. Review on factors influencing physician guideline adherence in cardiology. *Cardiol Rev* 2019; **27:** 80–86.
14. Crea F, Bairey Merz CN, Beltrame JF, Berry C, Camici PG, Kaski JC, et al. Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization. *Eur Heart J* 2019; **40:** 2455–2462.
15. Horie K, Kuramitsu S, Matsuo H, Shinozaki T, Takashima H, Shiono Y, et al. Two-year outcomes of asymptomatic vs. symptomatic patients after deferral of revascularization based on fractional flow reserve: Insights from the J-CONFIRM registry. *Circ Rep* 2020; **2:** 744–752.
16. 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.

Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1253/circrep.CR-24-0069