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ORIGINAL ARTICLE
Imaging

Effect of Coronary Computed Tomography Angiography-Derived Fractional Flow Reserve on Physicians' Clinical Behavior

— Differences Between Sites With and Without Appropriate Use Criteria as Designated by the Japanese Reimbursement System —

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Background: Coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFR_{CT}) is an established tool for identifying lesion-specific ischemia that is now approved for use by the Japanese insurance system. However, current clinical reimbursement is strictly limited to institutions with designated appropriate use criteria (AUC). This study assessed differences in physicians' behavior (e.g., use and interpretation of FFR_{CT}, final management) according to Japanese AUC and non-AUC site designation.

Methods and Results: Of 5,083 patients in the ADVANCE Registry, 1,829 from Japan were enrolled in this study. Physicians' behavior after interrogating CCTA and FFR_{CT} was analyzed separately according to AUC and non-AUC site designation. Compared with AUC sites, patients referred for FFR_{CT} from non-AUC sites had a higher rate of negative FFR_{CT}, less severe anatomic stenosis, and a slightly lower rate of management plan reclassification (51.2% vs. 61.3%), with near-identical utility in both groups. Actual care corresponded equally well to post-FFR_{CT} plans in both groups. The likelihood of revascularization for positive or negative FFR_{CT} was similar between the 2 groups. Importantly, AUC and non-AUC sites were equally unlikely to revascularize patients with negative FFR_{CT} and stenosis >50% or patients with positive FFR_{CT} and stenosis <50%.

Conclusions: Compared with AUC sites, non-AUC sites had lower disease burden and reclassification of management plans, but nearly identical clinical integration. Actual care corresponded equally well to post-FFR_{CT} recommendations at both sites.

Key Words: Appropriate use criteria (AUC); Coronary artery disease; Coronary computed tomography angiography; FFR_{CT}

Coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFR_{CT}) has been shown to be an accurate and clinically useful tool for the non-invasive assessment of the physiological significance of coronary artery disease (CAD).[1,2] CCTA with FFR_{CT} has been shown to alter downstream clinical management decision making, to spare a considerable number of patients from unnecessary invasive coronary angiography (ICA), and to help identify subjects for percutaneous coronary intervention (PCI) more effectively than computed tomography angiography (CTA) alone.[3,4] These clinical advantages have been recently corroborated in real-world settings by a large international multicenter prospective study, the Assessing Diagnostic Value of

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Non-invasive FFRCT in Coronary Care (ADVANCE) Registry.[5]

In accordance with previous experience, subanalysis of the Japanese population in the global international FFRCT ADVANCE Registry showed that FFRCT considerably modified treatment strategy. For example, a positive FFRCT result was associated with higher rates of ICA showing obstructive CAD and subsequent coronary revascularization, whereas patients with a negative FFRCT result were managed with medical therapy and deferral of ICA, with demonstrable favorable short-term clinical outcomes.[6] FFRCT has recently received funding and support from the Ministry of Health, Labour and Welfare (MHLW) in Japan, but only at approved sites that have satisfied the hospital conditions required by appropriate use criteria (AUC) defined by the MHLW. AUC sites are defined by the MHLW as training facilities of the Japanese Circulation Society (JCS), Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT), and Japan Radiological Society (JRS).[7] Against this background, the present study investigated whether there were differences regarding the clinical integration of FFRCT between AUC and non-AUC sites within the ADVANCE Registry.

Methods

The ADVANCE Registry is an international multicenter prospective registry including 5,083 patients from 38 sites, of whom 1,758 (35%) were enrolled from 13 Japanese institutions (10 AUC sites, 3 non-AUC sites) and were analyzed in the present subanalysis (**Figure 1**). The details of the study protocol and methods have been published previously.[8] Briefly, stable patients who had undergone CCTA and FFRCT were prospectively enrolled in the Registry. Inclusion criteria were age >18 years, the ability to provide informed consent, and CAD. Exclusion criteria were poor-quality CCTA, life expectancy <1 year, and an inability to comply with follow-up requirements.

All patients provided written informed consent. The study protocol was approved by the ethics committees of each participating site, and this study has been registered with ClinicalTrials.gov (ID NCT02499679) and UMIN Clinical Trials Registry (ID UMIN000032186).

Management Strategies

After the acquisition and interpretation of CCTA as part of routine clinical practice, the site investigators reported their initial management plans based on CCTA alone for each patient, and then submitted the computed tomography (CT) data for FFRCT analysis (HeartFlow, Redwood City, CA, USA). Within 48 h after data submission, the site investigators received the FFRCT results and reported their management strategy after taking into account the FFRCT results. FFRCT values ≤0.80 was considered physiologically significant, but decisions whether to medically treat or revascularize patients were made at the discretion of individual physicians. Site management strategies were categorized into the following 4 options: (1) optimal medical therapy; (2) PCI; (3) coronary artery bypass grafting (CABG); or (4) additional diagnostic testing required (e.g., exercise treadmill test or myocardial perfusion scintigraphy, stress echocardiography or ICA). Final actual treatment was stratified into the following groups: (1) medical therapy without ICA; (2) medical therapy with ICA; (3) PCI; and (4) CABG. Actual treatment was stratified into the following 4 categories: (1) medical therapy without ICA; (2) ICA without revascularization followed by medical therapy; (3) PCI; and (4) CABG.

Study Endpoints

We sought to evaluate potential differences in the clinical integration of FFRCT across Japanese hospitals stratified according to AUC status. To that end we evaluated: (1) the referral pattern for CCTA; (2) reclassification rates with FFRCT; (3) downstream clinical management plans stratified according to the severity of stenosis and FFRCT; and (4) predictors of revascularization.

Statistical Analysis

Continuous data are presented as the mean±SD and categorical data are presented as frequency and percentage. Demographic characteristics between AUC and non-AUC sites were compared using a 2-sample t-test for continuous data and a Chi-squared test for categorical data. The significance of differences between anatomic severity and rates of positive FFRCT was assessed by Chi-squared tests for equal proportions. Univariable and multivariable logistic regression models using step-wise selection were used to estimate the odds of revascularization for age >65 years, female sex, the presence of hypertension, the presence of diabetes, hyperlipidemia requiring treatment, current smoker status, typical angina, CT ≥70% stenosis, and

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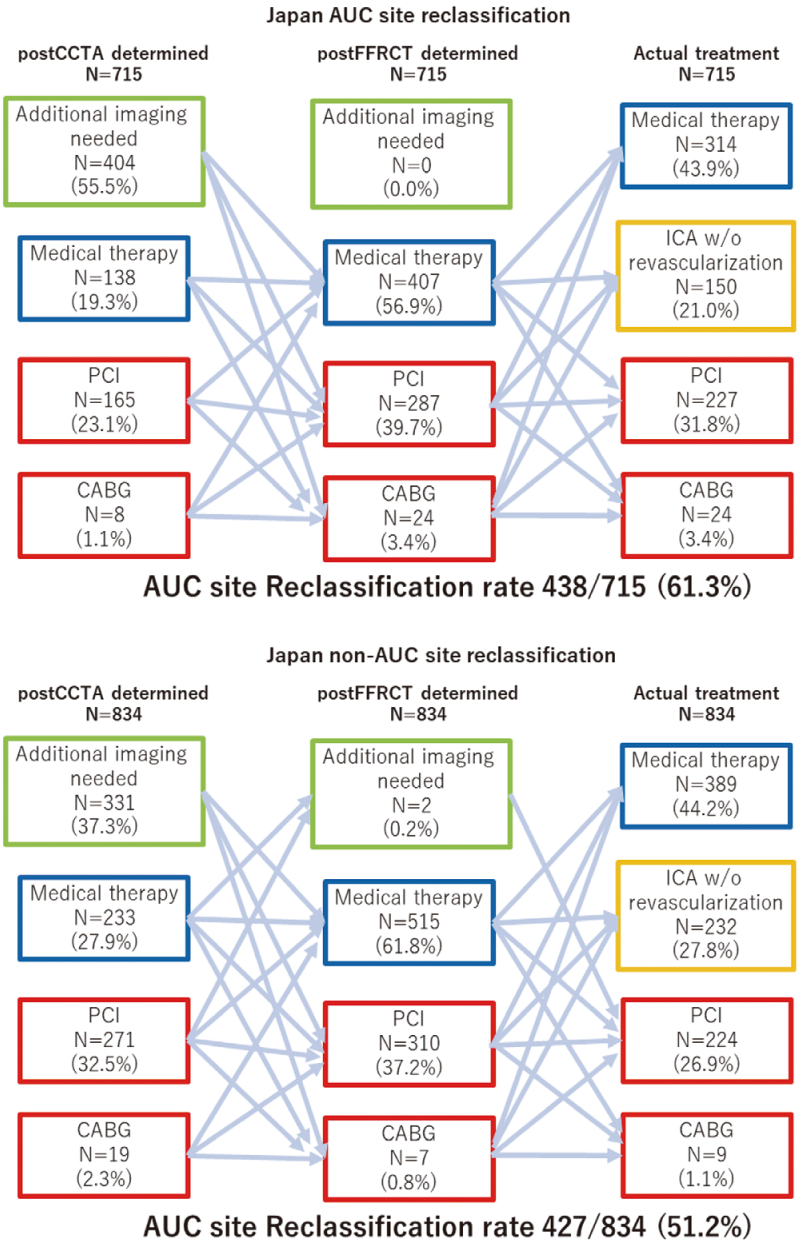

Figure 1. Reclassification of management strategies on site, before and after coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFR_{CT}), and actual management at 90 days at appropriate use criteria (AUC) and non-AUC sites. There was a trend for more frequent reclassification after FFR_{CT} at AUC than non-AUC sites. CABG, coronary artery bypass grafting; ICA, invasive coronary angiography; PCI, percutaneous coronary intervention.

Table 1. Japanese AUC and Non-AUC Sites Participating in the ADVANCE Registry

AUC sites (n=815 patients enrolled at 10 hospitals)	Non-AUC site (n=943 patients enrolled at 3 hospitals)
Kurashiki Central Hospital	Toyohashi Heart Center
Saiseikai Kumamoto Hospital	Shin-Koga Hospital
Saiseikai Nakatsu Hospital	Gifu Heart Center
Okayama University Hospital	
Iwate Medical University Hospital	
Wakayama Medical University	
Kobe University Hospital	
Tokyo Medical University	
Aichi Medical University	
Nihon University Hospital	

AUC, appropriate use criteria.

Table 2. Patient Demographics for AUC and Non-AUC Sites

	AUC site	Non-AUC site	Total	P-value
No. patients	815	943	1,785	
Age (years)	69.3±10.1	69.3±9.9	63.9±10.0	0.9
Sex (no. males/females)	552/263	598/345	1,149/608	0.056
Angina status				
Typical	198 (24.3)	275 (29.2)	473 (26.9)	<0.001
Atypical	256 (31.4)	372 (39.4)	628 (35.7)	
Dyspnea	32 (3.9)	18 (1.9)	50 (2.8)	
Non cardiac pain	5 (0.6)	43 (4.6)	48 (2.7)	
Asymptomatic	316 (38.8)	232 (24.6)	547 (31.1)	
Unknown	8 (1.0)	3 (0.6)	11 (0.6)	
Diamond–Forrester risk score	54.3±20.3	55.6±20.5	55.0±20.4	0.1739
Risk factor				
Diabetes	275 (33.7)	284 (30.1)	559 (33.1)	0.1416
Hypertension	579 (71.0)	610 (64.7)	1,189 (67.7)	0.0053
Hyperlipidemia	492 (60.4)	574 (60.9)	1,065 (60.6)	0.7563
Smoking status				
Current smoker	158 (19.4)	154 (16.3)	312 (17.8)	0.1289
Former smoker	265 (32.4)	320 (33.9)	584 (33.2)	
Never smoker	319 (39.1)	408 (43.3)	727 (41.4)	
Unknown	73 (9.0)	61 (6.5)	134 (7.6)	

Unless indicated otherwise, data are given as the mean±SD or as n (%). Although the proportion of patients with typical angina and atypical chest pain was greater for non-AUC sites and more patients with no symptoms were enrolled at AUC sites, no significant difference in the Diamond–Forrester risk score was observed between the 2 sites. AUC, appropriate use criteria.

Table 3. Rate of Positive CTA Findings and Positive FFRCT Values for Patients From AUC and Non-AUC Sites

	CTA		FFRCT	
	Stenosis ≥50%	Stenosis <50%	FFRCT >0.80	FFRCT ≤0.80
AUC site	708 (82.5)	150 (17.5)	206 (25.3)	609 (74.7)
Non-AUC site	727 (75.0)	242 (25.0)	303 (32.1)	640 (67.9)
P-value	<0.0001			<0.0001

Unless indicated otherwise, data are given as n (%). More patients with negative CTA findings were enrolled at non-AUC than AUC sites. More patients with negative FFRCT findings were enrolled at non-AUC than AUC sites. AUC, appropriate use criteria; CTA, computed tomography angiography; FFRCT, coronary computed tomography angiography-derived fractional flow reserve.

FFRCT <0.80 for the AUC and non-AUC site groups. Odds ratios (ORs) and associated 95% confidence intervals were calculated, along with the P-value testing that the slope of the factor was zero. The fit of the final model was assessed using the log likelihood test and Akaike information criterion. Two-sided P<0.05 was considered significant.

Results

Baseline Patient Characteristics

In all, 1,829 patients from Japan were enrolled in the ADVANCE Registry, of whom 1,758 (815 patients at AUC sites, 943 patients at non-AUC sites) had FFRCT results (**Table 1**). Of the 71 patients who only had CCTA results available, 4 had not been subjected to FFRCT analysis: 2 had been sent directly for ICA based on lesion severity on CCTA, 1 had multiple coronary stents, and 1 did not undergo FFRCT analysis for an unknown reason. In the remaining 67 patients (3.7%), FFRCT results were not available for analysis because of inadequate image quality (e.g., field of view too wide, incomplete myocardial coverage, slice thickness >1.0 mm, motion artifacts). The rejection rate because of inadequate FFRCT image quality did not different between the AUC and non-AUC sites.

Baseline patient demographics are summarized in **Table 2**. Patients from AUC sites were more likely to be hypertensive and asymptomatic than those from non-AUC sites, although there was no significant difference in the Diamond–Forrester classification between the 2 groups. Patient characteristics were otherwise similar between the 2 groups.

Differences in the Extent and Severity of CAD by CCTA and FFRCT Between AUC and Non-AUC Sites

CCTA revealed that the diameter of the stenosis (DS) was ≥50% in 82.5% of subjects from AUC sites and 75% of subjects from non-AUC sites, with 23.2% and18.7% of patients from AUC and non-AUC sites, respectively, having 2-vessel anatomical disease. Similarly, 16.0% and 10.3% of subjects from AUC and non-AUC sites, respectively, had 3-vessel disease. With regard to FFRCT, the rate of lesion-specific FFRCT ≤0.80 was higher in the AUC cohort (74.7% vs. 67.9%; **Table 3**). Therefore, patients referred for FFRCT

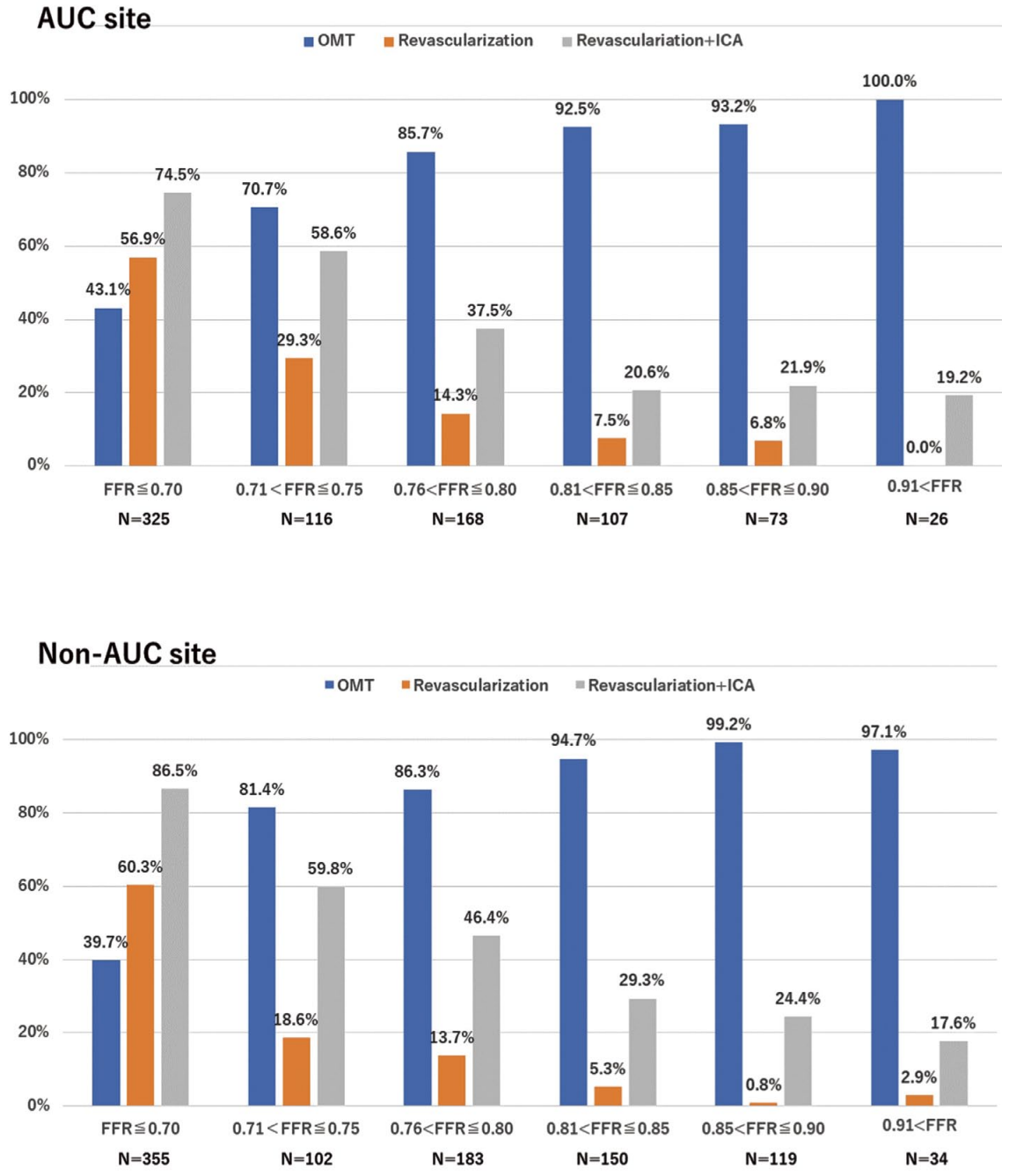

Figure 2. Actual treatment at 90 days stratified by coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFR_{CT}) values at appropriate use criteria (AUC) and non-AUC sites. ICA, invasive coronary angiography; OMT, optimal medical therapy.

by non-AUC sites had less severe anatomical and physiological stenosis than those referred by AUC sites. These differences were statistically significant (**Table 3**).

Reclassification of Treatment Recommendations Following FFR_{CT} and Relationship Between Post-FFR_{CT} Recommendations and Downstream Clinical Management

Changes in clinical management strategies before and after FFR_{CT} were analyzed in 715 patients from AUC sites and 834 patients from non-AUC sites; 100 patients from AUC sites and 107 patients from non-AUC sites were removed from this analysis because of a lack of complete data regarding treatment decisions. The results are summarized in **Figure 1**. Overall, treatment recommendations were modified after FFR_{CT} for 61.3% of patients from AUC sites and 51.2% of patients from non-AUC sites.

At the AUC sites, of the 138 (19.3%) patients who were assigned to medical therapy based on the initial CCTA,

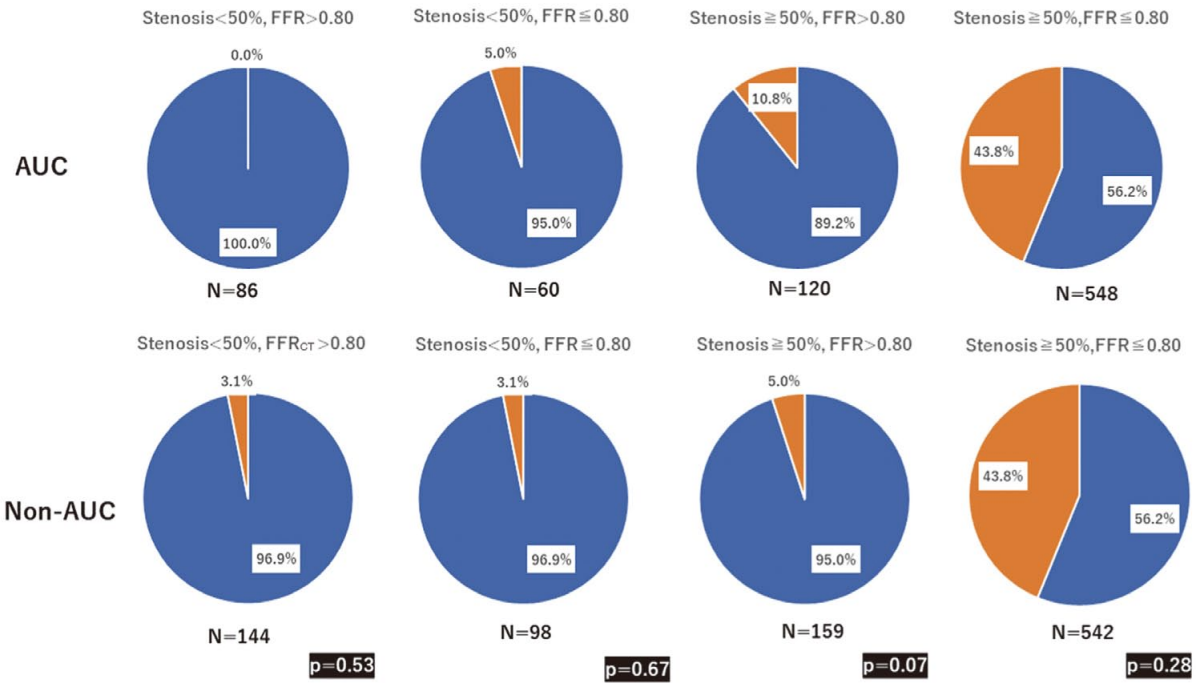

Figure 3. Actual revascularization practice stratified by maximum stenosis severity and minimum coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFRCT) values at appropriate use criteria (AUC) and non-AUC sites. Non-AUC sites less frequently revascularized lesions that were anatomically significant but physiologically insignificant.

132 patients (16.4%) received MT, whereas 5 (0.6%) were reclassified to PCI and 1 (0.1%) was reclassified to CABG. Of the 173 patients for whom revascularization (PCI: n=165; CABG: n=8) was indicated by the initial CCTA, 25 (14.2%) were reclassified to medical therapy (23 [13.1%]) from the PCI group; 2 [1.1%] from the CABG group).

At the AUC sites, 91.5% (379/414) of patients for whom medical therapy was recommended following FFRCT received this strategy, whereas 70.4% (219/311) of those for whom revascularization was recommended underwent the procedure after FFRCT.

Similarly, in the group of patients from non-AUC sites, 97% (500/515) of those for whom medical therapy was recommended following FFRCT received this treatment, and 78.5% (249/317) for whom revascularization was recommended underwent the procedure after FFRCT.

Downstream Clinical Treatment Stratified by FFRCT

Actual treatment according to FFRCT values for patients from AUC and non-AUC sites is shown in **Figure 2**. When stratified by 0.05 categorical FFRCT increments, as FFRCT values decreased, more patients received ICA and underwent revascularization at both AUC and non-AUC sites. **Figure 3** shows physicians' practice according to DS and FFRCT. There were similar rates of revascularization between AUC and non-AUC sites when stratified by DS. The rate of revascularization if the stenosis was <50% was 2.1% at both AUC and non-AUC sites (P=0.99), whereas the rate of revascularization if the stenosis was ≥50% was 37.9% and 37.5% at AUC and non-AUC sites, respectively (P=0.89).

When stratified by FFRCT, similar rates of revascularization were seen between AUC and non-AUC sites. In the setting of FFRCT >0.80, revascularization was performed in 6.3% and 3.3% of patients from AUC and non-AUC sites, respectively (P=0.11), whereas in the case of FFRCT ≤0.80 revascularization was performed in 39.9% and 40.3% of patients from AUC and non-AUC sites, respectively (P=0.90).

When stratified by stenosis and FFRCT, the rates of revascularization were similar between AUC and non-AUC sites, with a trend towards a higher rate of revascularization in the setting of >50% and FFRCT >0.80 at AUC compared with non-AUC sites (10.8% vs. 5.0%, respectively; P=0.07). Conversely, the rate of revascularization with FFRCT ≤0.80 and stenosis >50% did not differ between AUC and non-AUC sites (43.8% vs. 47.0%, respectively; P=0.28), as shown in **Figure 3**.

Predictors of Revascularization

Table 4 summarizes the results of univariate and multivariate analyses of various clinical and CT findings for predicting revascularization. Univariate analysis demonstrated that male sex, the presence of diabetes, dyslipidemia, typical angina, maximum stenosis severity >70%, and FFRCT <0.80 were significantly associated with high revascularization at AUC sites, whereas the presence of hypertension, diabetes, typical angina, maximum stenosis severity >70%, and FFRCT <0.80 were associated with high revascularization at non-AUC sites. Multivariate analysis demonstrated that typical angina, maximum stenosis severity >70%, and a minimum FFRCT value <0.80 were significant independent predictors of revascularization at both AUC and non-AUC sites. Of note, the OR for FFRCT at non-AUC

Table 4. Univariate and Multivariate Analysis of Various Clinical and CT Findings for Predicting Revascularization at AUC and Non-AUC Sites

	Univariate				Multivariate			
	AUC site	P-value	Non-AUC site	P-value	AUC site	P-value	Non-AUC site	P-value
Age >65 years	0.62 (0.46, 0.85)	0.003	0.76 (0.56, 1.03)	0.074	NA		0.68 (0.46, 1.00)	0.049
Female sex	0.57 (0.41, 0.80)	<0.001	0.78 (0.58, 1.05)	0.098	0.55 (0.39, 0.84)	0.023	NA	
Hypertension	1.22 (0.88, 1.70)	0.236	1.45 (1.07, 1.97)	0.017	NA		NA	
Diabetes	1.47 (1.08, 2.00)	0.014	1.61 (1.19, 2.17)	0.002	NA		NA	
Hyperlipidemia	1.86 (1.36, 2.55)	<0.001	1.80 (1.33, 2.44)	<0.001	1.78 (1.19, 2.64)	0.005	1.78 (1.21, 2.62)	0.003
Current smoker	1.36 (0.94, 1.96)	0.101	1.43 (0.99, 2.06)	0.058	NA		NA	
Typical angina	4.74 (3.37, 6.66)	<0.001	4.23 (3.11, 5.73)	<0.001	3.55 (2.33, 5.40)	<0.001	2.53 (1.74, 3.69)	<0.001
CT >70% stenosis	11.67 (7.65, 17.80)	<0.001	10.11 (7.27, 14.11)	<0.001	8.02 (5.04, 12.75)	<0.001	5.82 (4.01, 8.45)	<0.001
FFR_{CT} ≤0.80	9.86 (5.49, 17.68)	<0.001	19.79 (10.33, 37.90)	<0.001	4.13 (2.19, 7.77)	<0.001	12.11 (5.79, 24.59)	<0.001

Unless indicated otherwise, data show odds ratios with 95% confidence intervals in parentheses. CT, computed tomography; NA, not applicable. Other abbreviations as in Table 3.

sites was much stronger than at AUC sites (12.11 vs. 4.13, respectively) suggesting non-AUC sites followed more vigorously with FFR_{CT} value.

Discussion

There is growing evidence of the clinical utility of FFR_{CT} in various healthcare systems across North America, Europe and Japan. Questions remain regarding the comparative clinical integration and utility of FFR_{CT} across centers, with particular interest as to whether there are differences in clinical integration between AUC and non-AUC sites in Japan. The present analysis suggests that although the disease burden according to CCTA and the reclassification rate at non-AUC sites was lower, patient management after FFR_{CT} recommendations was similar between non-AUC and AUC sites: 97% of subjects for whom medical therapy was recommended following FFR_{CT} at non-AUC sites remained on medical therapy. Importantly, the rate of revascularization in the setting of a stenosis but negative FFR_{CT} was numerically lower at non-AUC than AUC sites (5% vs. 10.8%). In addition, although an abnormal FFR_{CT} strongly predicted revascularization at both non-AUC and AUC sites, the relationship was stronger at non-AUC sites. Our data strongly support the notion that FFR_{CT} provides similar clinical utility and has similar effects on clinical decision making at non-AUC and AUC sites in Japan.

Reclassification of and Actual Treatment After FFR_{CT} in AUC and Non-AUC Sites

In the large, international, multicenter population in the ADVANCE Registry, the primary endpoint of reclassification between core laboratory CCTA alone and CCTA plus FFR_{CT}-based management plans occurred in 66.9% of patients.[9] The findings for the Japanese subpopulation enrolled in the ADVANCE Registry revealed the same tendency as global data, with 55.8% reclassification of site-determined treatment plans and 56.9% reclassification of core laboratory-determined treatment plans.[6] The reclassification rate was lower in the present study for non-AUC sites, likely reflecting the lower anatomical coronary disease burden identified on CCTA, with lower rates of anatomical stenosis at non-AUC sites. These findings are in agreement with the growing clinical evidence regarding the use of CCTA in clinical practice, where CCTA has been shown to be a powerful tool for the detection or exclusion of anatomical coronary disease but unable to adjudicate the physiological significance of CAD. Given that the burden of anatomical disease was higher at AUC sites, it is not surprising that the rate of reclassification was higher at these sites.[6]

Safety of Deferral of ICA and Revascularization

There is growing evidence of the safety of deferring invasive angiography and revascularization in the setting of a negative FFR_{CT}.[5] Norgaard et al documented similar downstream clinical outcomes out to 3 years between patients with an anatomical stenosis and negative FFR_{CT} and those patients with more modest coronary stenosis and a positive FFR_{CT}.[4] Importantly, revascularization showed no benefit in the setting of a negative FFR_{CT}. In a recent 5-year outcome analysis of the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps), in which the interventionalists were blinded to CCTA and FFR_{CT} results, no subjects with a negative FFR_{CT} experienced myocardial infarction or died. The present analysis highlights that, regardless of AUC status, clinical sites in Japan are confident in deferring invasive angiography following a negative FFR_{CT} even in the presence of an anatomical stenosis and despite the fact that we are reporting on the early experiences with FFR_{CT} for these sites.

Study Limitations

This study has several limitations. First, the ADVANCE Registry is a prospective registry, and considered reflective of a real-world situation, but inherent biases that affect all registries cannot be excluded, particularly around patient

selection. ADVANCE Registry can enroll patients with <50% stenosis, whereas patients reimbursed for FFRCT in Japan have to have CT stenosis ≥50%. This difference in patient selection criteria for current practice in Japan may have contributed to different behavior with regard to FFRCT at the AUC and non-AUC sites. Second, the non-AUC sites were selected centers, and the practice of these centers may not be the same as average non-AUC sites across Japan.

Conclusions

The present subanalysis of the Japanese population of the ADVANCE Registry suggests that although the disease burden by CCTA and the reclassification rate at non-AUC sites was lower, the utility of FFRCT was identical between AUC and non-AUC sites, with similar revascularization rates in the setting of positive FFRCT and deferral of ICA in the setting of negative FFRCT.

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IRB Information

The ADVANCE Registry was approved by the ethics committees of Wakayama Medical University (No. 1636) and Gifu Heart Center (No. 2015012).

Data Availability

Deidentified participant data will not be shared.

References

1. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms: Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol* 2011; **58:** 1989–1997.
2. Norgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: The NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol* 2014; **63:** 1145–1155.
3. Douglas PS, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA, et al. 1-Year outcomes of FFRCT-guided care in patients with suspected coronary disease: The PLATFORM study. *J Am Coll Cardiol* 2016; **68:** 435–445.
4. Norgaard BL, Terkelsen CJ, Mathiassen ON, Grove EL, Botker HE, Parner E, et al. Coronary CT angiographic and flow reserve-guided management of patients with stable ischemic heart disease. *J Am Coll Cardiol* 2018; **72:** 2123–2134.
5. Patel MR, Norgaard BL, Fairbairn TA, Nieman K, Akasaka T, Berman DS, et al. 1-Year impact on medical practice and clinical outcomes of FFRCT: The ADVANCE Registry. *JACC Cardiovasc Imaging* 2020; **13:** 97–105.
6. Shiono Y, Matsuo H, Kawasaki T, Amano T, Kitabata H, Kubo T, et al. Clinical impact of coronary computed tomography angiography-derived fractional flow reserve on Japanese population in the ADVANCE Registry. *Circ J* 2019; **83:** 1293–1301.
7. Ministry of Health, Labour and Welfare. Implementation notes for partial revision of method of calculating medical fees. Health Insurance Bureau, Medical Economic Director and Dental Medical Administrator Notification. 2018: 1130–1133.
8. Chinnaiyan KM, Akasaka T, Amano T, Bax JJ, Blanke P, De Bruyne B, et al. Rationale, design and goals of the HeartFlow assessing diagnostic value of non-invasive FFRCT in Coronary Care (ADVANCE) Registry. *J Cardiovasc Comput Tomogr* 2017; **11:** 62–67.
9. Fairbairn TA, Nieman K, Akasaka T, Norgaard BL, Berman DS, Raff G, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: Lessons from the ADVANCE Registry. *Eur Heart J* 2018; **39:** 3701–3711.