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 —

Hitoshi Matsuo, MD, PhD; Tomohiro Kawasaki, MD, PhD; Tetsuya Amano, MD, PhD; Yoshiaki Kawase, MD; Yoshihiro Sobue, MD, PhD; Takeshi Kondo, MD, PhD; Yoshihiro Morino, MD, PhD; Shunichi Yoda, MD, PhD; Tomohiro Sakamoto, MD, PhD; Hiroshi Ito, MD, PhD; Junya Shite, MD, PhD; Hiromasa Otake, MD, PhD; Nobuhiro Tanaka, MD, PhD; Mitsuyasu Terashima, MD, PhD; Kazushige Kadota, MD, PhD; Manesh R. Patel, MD, PhD; Koen Nieman, MD, PhD; Campbell Rogers, MD; Bjarne L. Norgaard, MD, PhD; Jeroen J. Bax, MD, PhD; Kavitha M. Chinnaiyan, MD, PhD; Daniel S. Berman, MD, PhD; Timothy A. Fairbairn, MD, PhD; Lynne M. Hurwitz Koweek, MD; Jonathon Leipsic, MD, PhD; Takashi Akasaka, MD, PhD

Background: Coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFRCT) 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 FFRCT, 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 FFRCT was analyzed separately according to AUC and non-AUC site designation. Compared with AUC sites, patients referred for FFRCT from non-AUC sites had a higher rate of negative FFRCT, 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-FFRCT plans in both groups. The likelihood of revascularization for positive or negative FFRCT was similar between the 2 groups. Importantly, AUC and non-AUC sites were equally unlikely to revascularize patients with negative FFRCT and stenosis >50% or patients with positive FFRCT 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-FFRCT recommendations at both sites.

Key Words: Appropriate use criteria (AUC); Coronary artery disease; Coronary computed tomography angiography; FFRCT
Non-invasive FFR_{CT} in Coronary Care (ADVANCE) Registry.\textsuperscript{5} In accordance with previous experience, subanalysis of the Japanese population in the global international FFR_{CT} ADVANCE Registry showed that FFR_{CT} considerably modified treatment strategy. For example, a positive FFR_{CT} result was associated with higher rates of ICA showing obstructive CAD and subsequent coronary revascularization, whereas patients with a negative FFR_{CT} result were managed with medical therapy and deferral of ICA, with demonstrable favorable short-term clinical outcomes.\textsuperscript{6} FFR_{CT} 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).\textsuperscript{7} Against this background, the present study investigated whether there were differences regarding the clinical integration of FFR_{CT} 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.\textsuperscript{8} Briefly, stable patients who had undergone CCTA and FFR_{CT} 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 FFR_{CT} analysis (HeartFlow, Redwood City, CA, USA). Within 48h after data submission, the site investigators received the FFR_{CT} results and reported their management strategy after taking into account the FFR_{CT} results. FFR_{CT} 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 FFR_{CT} across Japanese hospitals stratified according to AUC status. To that end we evaluated: (1) the referral pattern for CCTA; (2) reclassification rates with FFR_{CT}; (3) downstream clinical management plans stratified according to the severity of stenosis and FFR_{CT}; 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 FFR_{CT} 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...
Figure 1. Reclassification of management strategies on site, before and after coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFRCT), and actual management at 90 days at appropriate use criteria (AUC) and non-AUC sites. There was a trend for more frequent reclassification after FFRCT at AUC than non-AUC sites. CABG, coronary artery bypass grafting; 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.
Clinical Impact of FFR<sub>CT</sub> in AUC and Non-AUC Sites

**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 FFR<sub>CT</sub> results (Table 1). Of the 71 patients who only had CCTA results available, 4 had not been subjected to FFR<sub>CT</sub> analysis; 2 had been sent directly for ICA based on lesion severity on CCTA, 1 had multiple coronary stents, and 1 did not undergo FFR<sub>CT</sub> analysis for an unknown reason. In the remaining 67 patients (3.7%), FFR<sub>CT</sub> results were not available for analysis because of inadequate image quality (e.g., field of view too wide, incomplete myocardial coverage, slice thickness >1.0mm, motion artifacts). The rejection rate because of inadequate FFR<sub>CT</sub> image quality did not differ 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 FFR<sub>CT</sub> 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% and 18.7% 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 FFR<sub>CT</sub>, the rate of lesion-specific FFR<sub>CT</sub> ≤0.80 was higher in the AUC cohort (74.7% vs. 67.9%; Table 3). Therefore, patients referred for FFR<sub>CT</sub> <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.

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 2. Patient Demographics for AUC and Non-AUC Sites

|                | AUC site | Non-AUC site | Total   | P-value |
|----------------|----------|--------------|---------|---------|
| No. patients   | 815      | 943          | 1,758   |         |
| 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 FFR<sub>CT</sub> Values for Patients From AUC and Non-AUC Sites

| CTA FFR<sub>CT</sub> | AUC site | Non-AUC site | P-value |
|-----------------------|----------|--------------|---------|
| Stenosis ≥50%         | 708 (82.5) | 150 (17.5) | <0.0001 |
| Stenosis <50%         | 150 (17.5) | 727 (75.0) | 0.001 |
| FFR<sub>CT</sub> >0.80 | 206 (25.3) | 303 (32.1) | 0.001 |
| FFR<sub>CT</sub> ≤0.80 | 609 (74.7) | 640 (67.9) |         |

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 FFR<sub>CT</sub> findings were enrolled at non-AUC than AUC sites. AUC, appropriate use criteria; CTA, computed tomography angiography; FFR<sub>CT</sub>, coronary computed tomography angiography-derived fractional flow reserve.

---
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 UUID 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, 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 UUID and Relationship Between Post-FFR UUID Recommendations and Downstream Clinical Management
Changes in clinical management strategies before and after FFR UUID were analyzed in 715 patients from AUC sites and 305 patients from non-AUC sites. ICA, invasive coronary angiography; OMT, optimal medical therapy.

Figure 2. Actual treatment at 90 days stratified by coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFR UUID) values at appropriate use criteria (AUC) and non-AUC sites. ICA, invasive coronary angiography; OMT, optimal medical therapy.
Clinical Impact of FFR<sub>CT</sub> in AUC and Non-AUC Sites

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 FFR<sub>CT</sub> received this strategy, whereas 70.4% (219/311) of those for whom revascularization was recommended underwent the procedure after FFR<sub>CT</sub>.

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

**Downstream Clinical Treatment Stratified by FFR<sub>CT</sub>**

Actual treatment according to FFR<sub>CT</sub> values for patients from AUC and non-AUC sites is shown in Figure 2. When stratified by 0.05 categorical FFR<sub>CT</sub> increments, as FFR<sub>CT</sub> 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 FFR<sub>CT</sub>. 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 FFR<sub>CT</sub>, similar rates of revascularization were seen between AUC and non-AUC sites. In the setting of FFR<sub>CT</sub> >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 FFR<sub>CT</sub> ≤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 FFR<sub>CT</sub>, 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 FFR<sub>CT</sub> >0.80 at AUC compared with non-AUC sites (10.8% vs. 5.0%, respectively; P=0.07). Conversely, the rate of revascularization with FFR<sub>CT</sub> ≤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 FFR<sub>CT</sub> <0.80 were significantly associated with high revascularization at AUC sites, whereas the presence of hypertension, diabetes, typical angina, maximum stenosis severity >70%, and FFR<sub>CT</sub> <0.80 were associated with high revascularization at non-AUC sites. Multivariate analysis demonstrated that typical angina, maximum stenosis severity >70%, and a minimum FFR<sub>CT</sub> value <0.80 were significant independent predictors of revascularization at both AUC and non-AUC sites. Of note, the OR for FFR<sub>CT</sub> at non-AUC
sites was much stronger than at AUC sites (12.11 vs. 4.13, respectively) suggesting non-AUC sites followed more vigorously with FFR<sub>CT</sub> value.

**Discussion**

There is growing evidence of the clinical utility of FFR<sub>CT</sub> in various healthcare systems across North America, Europe and Japan. Questions remain regarding the comparative clinical integration and utility of FFR<sub>CT</sub> 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<sub>CT</sub> recommendations was similar between non-AUC and AUC sites: 97% of subjects for whom medical therapy was recommended following FFR<sub>CT</sub> at non-AUC sites remained on medical therapy. Importantly, the rate of revascularization in the setting of a negative FFR<sub>CT</sub> was numerically lower at non-AUC sites. Although an abnormal FFR<sub>CT</sub> 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<sub>CT</sub> 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<sub>CT</sub> 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<sub>CT</sub>-based management plans occurred in 66.9% of patients. The findings for the Japanese subpopulation enrolled in the ADVANCE Registry revealed the same trend as global data, with 55.8% reclassification of site-determined treatment plans and 56.9% reclassification of core laboratory-determined treatment plans. 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.

**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<sub>CT</sub>. Norgaard et al documented similar downstream clinical outcomes out to 3 years between patients with an anatomical stenosis and negative FFR<sub>CT</sub> and those patients with more modest coronary stenosis and a positive FFR<sub>CT</sub>. Importantly, revascularization showed no benefit in the setting of a negative FFR<sub>CT</sub>. 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<sub>CT</sub> results, no subjects with a negative FFR<sub>CT</sub> 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<sub>CT</sub> even in the presence of an anatomical stenosis and despite the fact that we are reporting on the early experiences with FFR<sub>CT</sub> 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...
Clinical Impact of FFR<sub>CT</sub> in AUC and Non-AUC Sites

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 tomographic 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 FFR<sub>CT</sub>-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 FFR<sub>CT</sub>: The ADVANCE Registry. *JACC Cardiovasc Imaging* 2020; 13: 97–105.
6. Shiono Y, Matsu 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 of Health Insurance Bureau, Medical Economic Director and Dental Medical Administrator Notification. 2018: 1130–1133.
8. Chimniyan 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 FFR<sub>CT</sub> 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.

Acknowledgments
We sincerely appreciate to Ms. Naoko Sato for her secretarial assistance.

Sources of Funding
This study was supported by HeartFlow (Redwood City, CA, USA), via individual clinical study agreements with each enrolling institution and with the Duke Clinical Research Institute (DCRI) for core laboratory activities and clinical event committee adjudication of adverse events.

Disclosures
H.M. declares speaker fees from Abbott Vascular Japan, Phillips, Zeon Medical, Boston Scientific Japan. H.O. declares payments for lectures, including service on speakers bureaus, from HeartFlow Inc. N.T. declares consulting fees from Abbott Vascular Japan, Boston Scientific Japan and KANEKA Medix Co. C.R. is an employee of and has equity in HeartFlow. G.R. has received an institutional research grant from HeartFlow. L.M.H.K. has received departmental grant funding from Siemens Healthineers, HeartFlow, Verily, and Mallinckrodt. B.L.N. has received institutional unrestricted grants from Siemens and HeartFlow. J.L. declares consultant and stock options with CIRCLE CVI and HeartFlow, and research support from GE Healthcare. H.I. is a member of the Editorial Board of *Circulation Reports*. Y.M. is an Associate Editor of *Circulation Reports*. The remaining authors declare no conflicts of interest.

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

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 FFR<sub>CT</sub> was identical between AUC and non-AUC sites, with similar revascularization rates in the setting of positive FFR<sub>CT</sub> and deferral of ICA in the setting of negative FFR<sub>CT</sub>.

Selection. ADVANCE Registry can enroll patients with <50% stenosis, whereas patients reimbursed for FFR<sub>CT</sub> 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 FFR<sub>CT</sub> 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.