Clinical Impact of Coronary Computed Tomography Angiography-Derived Fractional Flow Reserve on Japanese Population in the ADVANCE Registry

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Background: Coronary computed tomography angiography (cCTA)-derived fractional flow reserve (FFRCT) is a promising diagnostic method for the evaluation of coronary artery disease (CAD). However, clinical data regarding FFRCT in Japan are scarce, so we assessed the clinical impact of using FFRCT in a Japanese population.

Methods and Results: The ADVANCE registry is an international prospective FFRCT registry of patients suspected of CAD. Of 5,083 patients, 1,829 subjects enrolled from Japan were analyzed. Demographics, symptoms, cCTA, FFRCT, treatment strategy, and 90-day major cardiovascular events (MACE) were assessed. Reclassification of treatment strategy between cCTA alone and cCTA+FFRCT occurred in 55.8% of site investigations and in 56.9% in the core laboratory analysis. Patients with positive FFR (FFRCT ≤0.80) were less likely to have non-obstructive disease on invasive coronary angiography than patients with negative FFR (FFRCT >0.80) (20.5% vs. 46.1%, P=0.0001). After FFRCT, 67.0% of patients with positive results underwent revascularization, whereas 96.1% of patients with negative FFRCT were medically treated. MACE occurred in 5 patients with positive FFRCT, but none occurred in patients with negative FFRCT within 90 days.

Conclusions: In this Japanese population, FFRCT modified the treatment strategy in more than half of the patients. FFRCT showed potential for stratifying patients suspected of CAD properly into invasive or non-invasive management pathways.

Key Words: Coronary artery disease; Coronary CT angiography; FFRCT

P hysiological assessment is paramount in the management of patients with coronary artery disease (CAD). Invasive fractional flow reserve (FFR) has proven to have excellent diagnostic accuracy and to improve the clinical outcome.1-3 As a result, the international guidelines strongly endorse invasive FFR in the management of CAD patients.4 However, the adoption of FFR is limited in the real world and its invasive nature is thought to be a major hindrance to its use.5

Coronary computed tomography angiography (cCTA)-
derived FFR (FFR\textsubscript{CT}) has recently evolved as a novel non-invasive physiological assessment.\textsuperscript{6,8} It has a strong correlation with invasive FFR and high diagnostic accuracy in terms of identifying flow-limiting coronary stenoses. As well as its diagnostic performance, the clinical utility of FFR\textsubscript{CT} has been demonstrated. For instance, FFR\textsubscript{CT} significantly modifies the downstream clinical management actions, spares a considerable number of patients from unnecessary invasive coronary angiography (ICA), and improves outcomes following FFR\textsubscript{CT}-directed management strategies.\textsuperscript{9,11} This clinical utility has been recently corroborated in real-world settings by a large international multicenter prospective study, the Assessing Diagnostic Value of Non-invasive FFR\textsubscript{CT} in Coronary Care (ADVANCE) registry.\textsuperscript{12}

However, FFR\textsubscript{CT} is not yet widely used in clinical settings in Japan because it was not covered by health insurance until December 2018. Thus, because clinical FFR\textsubscript{CT} data in Japan are scarce, it remains unknown whether the clinical utility shown in the international studies will directly apply to the Japanese population. Therefore, we conducted this subanalysis of the ADVANCE registry to assess the clinical impact of FFR\textsubscript{CT} in Japan.

Methods

The ADVANCE registry is an international, multicenter, prospective registry including 5,083 patients from 38 international sites, of whom 1,758 (35\%) enrolled in 13 Japanese institutions were analyzed in this subanalysis. The details of the study protocol and methods have been published previously.\textsuperscript{2,11} In brief, stable patients in whom cCTA was clinically indicated and who demonstrated >30\% diameter stenosis (DS) were prospectively enrolled based on clinical need. Inclusion criteria were age ≥18 years, ability to provide informed consent, and CAD on cCTA. Exclusion criteria were poor quality cCTA images, 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 ethical committees at each participating site and the study was registered with NCT [NCT02499679] and UMIN [UMIN000032186].

CT Interpretation and Management Strategies

After the acquisition of cCTA images, the site investigators interpreted them part of routine clinical practice. They reported their initial management plans for each patient based on cCTA alone, and then submitted the CT data for FFR\textsubscript{CT} analysis (HeartFlow, Redwood City, CA, USA). Vessel segments ≥2 mm in diameter were evaluated for luminal narrowing, and the per-vessel maximum stenosis was categorized as 0\%, 1–29\%, 30–49\%, 50–70\%, 71–90\%, >90\%, or total occlusion. Within 48 h after data submission, the site investigators received the FFR\textsubscript{CT} results and reported their management strategy after taking account of the FFR\textsubscript{CT} results. FFR\textsubscript{CT} value ≤0.80 was considered physiologically significant, but the actual decision as to treating medically or to revascularize was made at the discretion of the referring physicians.

cCTA and FFR\textsubscript{CT} findings were also analyzed in a core laboratory blinded to clinical information, symptom status, and outcomes (Duke Clinical Research Institute (DCRI) [Durham, NC, USA]). The core laboratory reviewed the cCTA findings and defined their independent management plans on the basis of cCTA alone, and then defined a second management plan after the FFR\textsubscript{CT} information was provided. This involved adjudication of vessel- and lesion-specific ischemia, measuring the FFR\textsubscript{CT} 2 cm distal to focal lesions. Both the site and laboratory management strategies were categorized into the following options: (1) optimal medical therapy (MT), (2) percutaneous coronary intervention (PCI), (3) coronary artery bypass grafting (CABG), or (4) additional diagnostic testing required. The additional diagnostic testing was selected when a further non-invasive ischemic test was thought to be required and was assigned in the core-lab in the setting of a 40–90\% stenosis given the need to determine the hemodynamic significance of a lesion to guide ICA, PCI, or CABG referral.

Results

Baseline Patient Characteristics

Baseline patient demographics are summarized in Table 1. In total, 1,829 patients were enrolled into this study, of whom 1,758 had FFR\textsubscript{CT} results available and 71 had cCTA results alone. With regard to the latter, 4 cases were not submitted to FFR\textsubscript{CT} analysis, 2 of those were directly sent to ICA based on the lesion severity on cCTA, 1 had multiple coronary stents, 1 for other reason (marked unknown by the site). The remaining 67 (3.7\%) subjects were rejected owing to a cCTA image quality not being suitable for...
FFR<sub>CT</sub> analysis (e.g., field of view too wide, incomplete myocardial coverage, slice thickness >1.0 mm, or severe motion and/or blooming artifacts). In terms of the symptoms, angina including typical and atypical was most frequently found (62.3%). The mean Diamond-Forrester pretest probability for obstructive coronary disease was 55.0%. There was no significant difference in demographics between those who received cCTA alone vs. cCTA plus FFR<sub>CT</sub>.

**Extent and Severity of CAD by cCTA and FFR<sub>CT</sub>**

cCTA revealed coronary DS ≥50% in 77.9% of subjects (n=1,369) and >70% DS in 46.9% (n=824), and demonstrated 2- or 3-vessel disease (≥50% DS) in 20.8% and 12.9%, respectively. An ischemia-generating lesion defined as FFR<sub>CT</sub> ≤0.80 was present in at least 1 coronary territory in 71.0% (n=1,249) of patients. As shown in Figure 1, LAD had more frequently anatomically severe (>70% DS) coronary disease (33.8%) and physiologically significant (FFR<sub>CT</sub> ≤0.80) lesions (n=1,131, 65.4%) compared with the other 2 coronary arteries: left circumflex (LCX) had 15.6% (>70% DS) and positive FFR<sub>CT</sub> (n=456, 26.4%), (P<0.001), and right coronary artery (RCA) had 18.1% (>70% DS) and positive FFR<sub>CT</sub> (n=422, 24.4%), (P<0.001). Overall, the LAD demonstrated significantly lower median FFR<sub>CT</sub> values (0.77: IQR - 0.68 - 0.84) compared with the LCX (0.88: IQR - 0.81 - 0.93) and RCA (0.87: IQR - 0.80 - 0.91), (P<0.001). In the moderate (30–70%) stenosis, the proportion of physiologically significant stenosis (FFR<sub>CT</sub> ≤0.80) was significantly higher in the LAD (59.0%) compared with LCX (31.8%) and RCA (28.6%), (P<0.001).

**Clinical Management Strategies Following FFR<sub>CT</sub>**

The classification changes in clinical management strategies before and after FFR<sub>CT</sub> are summarized in Figure 2. Overall, treatment recommendations were modified after FFR<sub>CT</sub> in 865 (55.8%) patients according to site-based plan, and in 987 (56.9%) patients according to core laboratory analysis. Interestingly, when a lesion of interest, which was defined as a vessel with the highest degree of %DS on cCTA, was located in LAD, the treatment strategy was more often modified after FFR<sub>CT</sub> than when in non-LAD (LAD, 71.5%; LCX, 65.4%; and RCA, 62.4%; P=0.0272) in the site-based plans.

In the site-based plans, among 797 (45.3%) patients in whom additional testing was thought to be required at the initial evaluation by cCTA alone, FFR<sub>CT</sub> reclassified 466 (58.5%) patients to MT, 229 (28.7%) to PCI, 20 (2.5%) to CABG; 110 subjects did not have any post-FFRCT determination entered by the site. Of 389 (22.1%) patients who were assigned to MT by the initial cCTA, 349 (89.7%) remained as MT, 20 (5.1%) patients were reclassified to PCI, and 1 (0.3%) patient to CABG. Among 467 patients in whom revascularization (PCI: n=440, CABG: n=27) was indicated by the initial cCTA, 107 (22.9%) were reclassified to MT (PCI to MT: n=102, CABG to MT: n=5, 18.5%) Of note, most patients (n=946, 96.1%) in whom MT was indicated after FFR<sub>CT</sub> had MT as their actual treatment, and 444 (67%) patients indicated for revascularization actually underwent revascularization.
less frequent in patients with $\text{FFR}_{\text{CT}} \leq 0.80$ (20.5%) than in those with $\text{FFR}_{\text{CT}} > 0.80$ (46.1%), (OR 3.29, CI 2.19–4.95, $P<0.0001$). Invasive FFR adjudication was performed in 78 of 509 (15.3%) patients with negative FFRCT and 557 of 1,249 (44.6%) with positive FFRCT ($P<0.0001$). More patients underwent revascularization among those who had $\text{FFR}_{\text{CT}} \leq 0.80$ (67%) compared with $\text{FFR}_{\text{CT}} > 0.80$ (3.9%) (Figure 3).

When stratified by 0.05 categorical $\text{FFR}_{\text{CT}}$ increments,

(Figure 3). In addition, the lower the $\text{FFR}_{\text{CT}}$ values, the more patients were revascularized (Figure 4).

**Rate of Invasive Angiography and Revascularization After FFRCT Evaluation**

After $\text{FFR}_{\text{CT}}$, 115 of 509 (22.6%) patients with negative $\text{FFR}_{\text{CT}}$, and 771 of 1,249 (61.7%) with positive $\text{FFR}_{\text{CT}}$ received ICA, and anatomically defined ‘non-obstructive’ disease at ICA (no stenosis $>50\%$ at ICA) was markedly

*Figure 1.* Distribution of positive or negative FFRCT according to the cCTA-derived anatomical degree of coronary artery stenosis in each coronary artery territory. (A) Left anterior descending artery (LAD), (B) left circumflex (LCX), and (C) right coronary artery (RCA). cCTA, coronary computed tomography angiography; FFRCT, cCTA-derived fractional flow reserve.
as the FFR_{CT} values were lower, more patients received ICA and underwent revascularization (Figure 4). Multivariate analysis demonstrated that diabetes, hyperlipidemia, typical angina symptom, stenosis of >70% DS/occluded vessel, and FFR_{CT} ≤ 0.80 were significant predictors of revascularization (Table 2).

**MACE**
No MACE occurred within 90 days in subjects with FFR_{CT} >0.80 (n=509). On the other hand, 5 (0.4%, P=0.15) MACE occurred in subjects with FFR_{CT} ≤ 0.80 in at least 1 coronary artery (n=1,249). The MACE included 2 urgent unplanned hospitalizations for ACS and urgent revascularization, and 3 deaths.

**Discussion**
The main findings of this study are: (1) FFR_{CT} modified the treatment strategy in more than 50% of patients in Japan; (2) actual treatment closely followed FFR_{CT} recommendations with 96.1% in whom MT was recommended receiving MT and 67% in whom revascularization was recommended receiving revascularization within 90 days; (3) patients with positive FFR_{CT} who underwent ICA were unlikely to reveal non-obstructive disease; and (4) positive FFR_{CT} was a strong predictor of subsequent revascularization.

**Impact of FFR_{CT} on Treatment Strategy Modification**
cCTA offers excellent performance for detection of CAD.\textsuperscript{14,15} However, not all anatomic stenoses detected by cCTA are physiologically important or relevant to symptoms or clinical events.\textsuperscript{9,16,17} Discordance between anatomy and physiology is not uncommon and when discordance is present, a physiology-guided approach has been shown to lead to better clinical outcomes than anatomy-guided management.\textsuperscript{2,3,18,19} Given the superiority of a physiology-guided approach, it is not surprising that substantial...
strategy modifications were made based on FFR\textsubscript{CT} analysis and cCTA findings when compared with the management plan based on cCTA alone. Similar strategy modification has been also reported for invasive angiography and FFR.\textsuperscript{20,21} However, it should be noted that not all cases indicated for revascularization either in the core-lab or site investigations underwent revascularization. This means that although FFR\textsubscript{CT} ≤0.80 was considered physiologically significant and as an indication for revascularization, actual treatment decisions were made by referring physicians after taking account of other factors such as lesion locations (proximal or distal), morphologies (focal or diffuse), or vessel sizes etc. as well as FFR\textsubscript{CT}. In fact, only two-thirds of the patients to whom revascularization was recommended after FFR\textsubscript{CT} actually underwent coronary revascularization. The actual treatment decision might have been also affected by symptom status, patient age, and different practice patterns across facilities even in the same country. It should be borne in mind that although FFR\textsubscript{CT} gives valuable information for decision-making of treatment strategy, it is just one piece of clinical information that physicians need to take into consideration.

**FFR\textsubscript{CT} Reduced Additional Testing and Stratified Patients**

Evaluation of chest pain by cCTA has proven to be safe and clinically effective.\textsuperscript{23,24} However, the problem when using cCTA as the first-line assessment is that it may increase invasive cardiac catheterizations and subsequent
coronary revascularizations, many of which may not have clinical benefit if there is no physiological significance. In this context, additional non-invasive functional testing (e.g., nuclear myocardial perfusion imaging) may help select patients for further invasive procedures. However, such functional testing in addition to cCTA can be inaccurate (false negative or false positive), costly, and requires an additional hospital/clinic visit as well as more radiation exposure.\textsuperscript{25-27} FFR\textsubscript{CT} may provide advantages in each of these areas, because of its accuracy\textsuperscript{6-8} and elimination of additional visits and radiation exposure. Our analysis demonstrated that the proportion of patients deemed to require additional testing in Japan, at nearly 45\% following the initial assessment by cCTA, was reduced to nearly zero (0.02\%) after FFR\textsubscript{CT} analysis.

Figure 5. Cumulative events curves within 90 days between patients with positive (≤0.80) and negative (>0.80) FFR\textsubscript{CT}. (A) Major adverse cardiac events (all-cause mortality, myocardial infarction, unplanned hospitalization leading to urgent revascularization), and (B) all-cause mortality and myocardial infarction alone. Abbreviations as in Figure 1.
Downstream Clinical Decision-Making in Japan Following FFR\textsubscript{CT}

In this broad early clinical experience with FFR\textsubscript{CT} in Japan, patients with positive FFR\textsubscript{CT} were much more likely to have obstructive CAD on ICA and to undergo revascularization than patients with a negative FFR\textsubscript{CT} result. These findings were consistent with the broader cohort examined in the ADVANCE registry and highlighted the early clinical adoption of FFR\textsubscript{CT} across sites participating in the registry, including Japan. When FFR\textsubscript{CT} was negative, patients were less likely to have obstructive CAD, and the vast majority was medically treated and had safe outcomes through 90 days. These findings indicated that FFR\textsubscript{CT} can be used to assign invasive procedures to those who truly benefit from them.

MACE After FFR\textsubscript{CT}

In terms of the clinical outcomes, no MACE were reported within 90 days in patients with negative FFR\textsubscript{CT}, whereas MACE did occur in those who had positive FFR\textsubscript{CT}. As the event rate was limited, even in patients with positive FFR\textsubscript{CT}, the difference was not statistically significant in this subanalysis. However, very similar findings were reported with statistical significance in the full cohort of this registry.\textsuperscript{12} These observations indicated that patients with positive FFR\textsubscript{CT} are at higher risk of MACE compared with those with negative FFR\textsubscript{CT}, which is clinically relevant because patients with negative FFR\textsubscript{CT} can be safely deferred from not only revascularization but also invasive catheterization, considering that most of them were medically treated in the end. The ability of FFR\textsubscript{CT} to differentiate patients who require further invasive diagnostic testing and possible intervention from those who do not need them has also been reported in another cohort.\textsuperscript{10}

FFR\textsubscript{CT} as a Continuous Variable

In clinical trials, invasive FFR is usually used in a dichotomous fashion; for example, ≤0.80 is for revascularization and >0.80 is for medical treatment, and it is often the case in clinical settings as well (Figure 5).\textsuperscript{2,3,17} Recently, however, it has been recognized that FFR\textsubscript{CT} is not such a black-and-white index but a continuous variable such that those patients with the lowest values have the worst prognosis and the largest benefit from revascularization.\textsuperscript{26,28} Our data suggested that FFR\textsubscript{CT} is similar, with subjects with lower FFR\textsubscript{CT} values being more likely to undergo revascularization. These findings are clinically important because it might be possible to estimate future events and stratify the patients for risk and referral to invasive angiography according to the degree of reduction in the FFR\textsubscript{CT} value. FFR\textsubscript{CT} has the potential to be used not only for decision-making about invasive procedures but also for optimization of medical treatment.

Discordance Between Anatomy and Function on Coronary CT

For intermediate lesions, FFR\textsubscript{CT} was more likely to be positive in the LAD than in the non-LAD (RCA or LCX) vessels. Moreover, in mild or almost normal-looking vessels (%DS: 0–50%), the proportion of positive FFR\textsubscript{CT} was higher in the LAD than in the non-LAD. On the other hand, in more severe stenoses (%DS >70%) negative FFR\textsubscript{CT} was more frequent in non-LAD compared with the LAD. These discrepancies between anatomy and physiology are well known as a visual-functional mismatch on invasive angiography and FFR.\textsuperscript{26} The findings also demonstrated that such discordance is present for cCTA and FFR\textsubscript{CT} as well, which further confirms the importance of functional assessment in non-invasive testing. If lesions are assessed solely anatomically, they are likely to be underdiagnosed in the LAD and overdiagnosed in the remaining vascular territories from a physiological perspective (Figure 1). It has been reported that age, lesion location, plaque morphology, and vessel size contribute to the mismatch on invasive angiography and FFR.\textsuperscript{29} Further studies are necessary to investigate the factors that are associated with the discordance between cCTA and FFR\textsubscript{CT}.

Potential of FFR\textsubscript{CT} in Japan

This study suggests that FFR\textsubscript{CT} can be used in the same way in Japan as in other Western countries because the patients in this Japanese subanalysis showed almost comparable demographics, pretest probability, and cCTA acceptance rate, and then demonstrated similar clinical outcomes as in the whole cohort.\textsuperscript{14} cCTA is widely available and being used as the first-line non-invasive assessment for many patients across Japan. Therefore, it is presumed that many patients suspected of having CAD are undergoing cCTA, subsequent ICA, and eventually revascularization. Our findings highlighted the potential of FFR\textsubscript{CT} to help facilitate combined anatomical and physiological decision-making to more appropriately guide medical management and ICA referral. The high acceptance rate of cCTA for FFR\textsubscript{CT} analysis in Japan (96.5%) confirms the robustness of FFR\textsubscript{CT} and its clinical feasibility in practice in Japan. Importantly, these decisions are enabled without the need for additional testing or radiation exposure. The combination of these factors suggests that FFR\textsubscript{CT} will facilitate a more physiology-oriented approach in Japan.

Study Limitations

Firstly, because this was a subanalysis with a smaller sample size than the full global study cohort, clinical outcomes between patients with positive and negative FFR\textsubscript{CT} were not statistically significant. However, similar findings reaching statistical significance have been reported in the full cohort.\textsuperscript{12} Also this is only the first 90-day results, and longer-term follow-up at 1 and 3 years is underway. Secondly, this is a prospective registry and considered reflective of a real-world situation, but selection bias cannot be totally excluded. Lastly, because a certain number of patients underwent invasive FFR adjudication, their actual treatment strategies might have been based not only on FFR\textsubscript{CT} but also invasive FFR.

Conclusions

This subanalysis of the Japanese population in the global international FFR\textsubscript{CT} ADVANCE registry showed that FFR\textsubscript{CT} considerably modified treatment strategy and that positive FFR\textsubscript{CT} was associated with higher rates of ICA showing obstructive CAD and subsequent coronary revascularization. Importantly, a negative FFR\textsubscript{CT} result was managed with MT in nearly all subjects and was associated with excellent outcomes through 90 days.

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Any Potential Conflicts of Interest

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