



# Verification of Coronary Computed Tomography-Derived Fractional Flow Reserve Measurement Site for Detection of Significant Coronary Artery Disease

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**Background:** The optimal site for measuring computed tomography (CT)-derived fractional flow reserve (FFR<sub>CT</sub>) to detect significant coronary artery disease (CAD) remains unknown. We investigated how diagnostic performance changes with FFR<sub>CT</sub> measurement site.

**Methods and Results:** The diagnostic performance of FFR<sub>CT</sub>, measured 1–2 cm distal to the stenosis vs. a far-distal site, in detecting significant CAD with invasive fractional flow reserve  $\leq 0.8$  was evaluated in 254 diseased vessels from 146 patients with stable or suspected CAD diagnosed by coronary CT angiography. Receiver operating characteristic curve analysis revealed a significantly larger area under the curve for FFR<sub>CT</sub> measured 1–2 cm distal to the stenosis than at a far-distal site (0.829 vs. 0.791, respectively;  $P=0.0305$ ). The rate of reclassification of positive FFR<sub>CT</sub> was 19% for measurements made 1–2 cm distal to the stenosis, and diagnostic accuracy for FFR<sub>CT</sub> 0.71–0.80 improved from 36% to 58% ( $P=0.0052$ ). Vessel-based diagnostic accuracy of FFR<sub>CT</sub> 1–2 cm distal to the stenosis and at a far-distal site was 75% and 65%, respectively ( $P<0.0001$ ), with corresponding sensitivity of 87% and 94% ( $P=0.0039$ ), specificity of 60% and 29% ( $P<0.0001$ ), a positive predictive value of 73% and 62% ( $P=0.028$ ), and a negative predictive value of 78% and 79% ( $P=0.958$ ).

**Conclusions:** Our data suggest measuring FFR<sub>CT</sub> 1–2 cm distal to the stenosis has better diagnostic performance for detecting physiologically significant CAD.

**Key Words:** Coronary artery disease; Coronary computed tomography angiography (CCTA); Fractional flow reserve (FFR); FFR derived from CCTA (FFR<sub>CT</sub>)

Coronary computed tomography angiography (CCTA) has become widely used in clinical settings. Its diagnostic performance has improved considerably, making it possible to non-invasively evaluate coronary artery lesions. In this context, improvements in computational fluid dynamics technology have allowed for the assessment of coronary ischemia using CCTA data.

Fractional flow reserve (FFR) derived from CCTA (FFR<sub>CT</sub><sup>®</sup>; HeartFlow, Redwood City, CA, USA) is a computed CCTA-derived FFR that has been used in various clinical fields.<sup>1–8</sup> FFR<sub>CT</sub> has enabled both morphological and functional evaluation using one modality, showing higher specificity than conventional CCTA.<sup>1,2,5</sup> FFR<sub>CT</sub> values are generally obtained from far-distal sites of the diseased vessel, but it is known that overestimation of functional ischemia is possible.<sup>9–11</sup> Recently, an expert panel

recommended that FFR<sub>CT</sub> values measured 1–2 cm distal to the stenosis be used to assess the hemodynamic significance of lesions,<sup>11</sup> resulting in potentially improved diagnostic accuracy.<sup>9,12</sup> The aim of the present study was to investigate how diagnostic performance for detecting functional ischemia changes according to the measurement site of FFR<sub>CT</sub>.

## Methods

### Study Design and Population

This was a single-center retrospective analysis conducted in the Shin-Koga Hospital. Data were collected for 437 patients with a stable or suspected coronary artery disease (CAD) diagnosed by CCTA who were enrolled in the Assessing Diagnostic Value of Noninvasive FFR<sub>CT</sub> in

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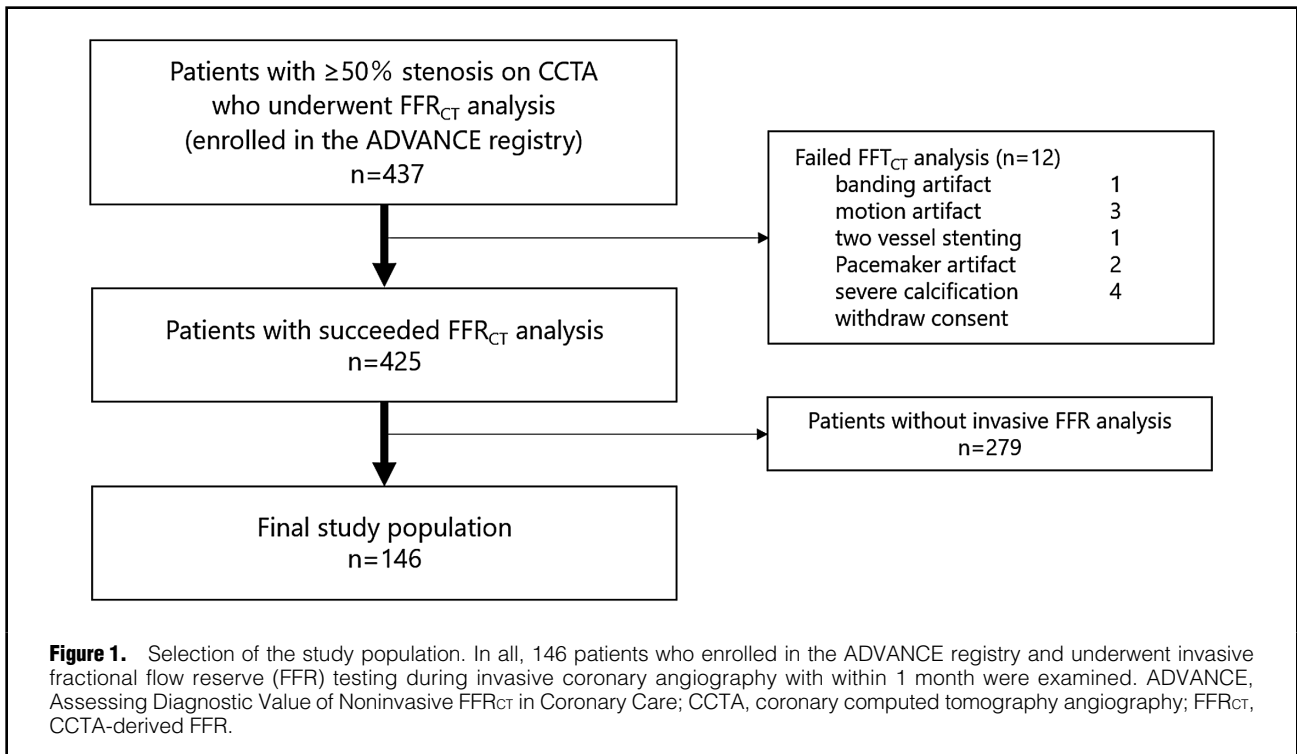
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Coronary Care (ADVANCE) Registry<sup>13</sup> from July 2015 to October 2018. Of these 437 patients, 146 who underwent invasive FFR testing during invasive coronary angiography (ICA) within 1 month of registry enrollment were included in the present study (Figure 1). Physicians in charge of the invasive FFR testing were blinded to the results of FFR<sub>CT</sub>.

This study was approved by the Institutional Review Board of Shin-Koga Hospital, and written informed consent was obtained from all participants.

### CCTA

CCTA was performed using a 320-detector row computed tomography (CT) scanner (Aquilion ONE ViSION; Canon Medical Systems, Tochigi, Japan). All patients received sublingual nitroglycerin and, if necessary, oral metoprolol 20 mg and/or intravenous landiolol 0.125 mg/kg to achieve a target heart rate of  $\leq 60$  beats/min. CT images were acquired at tube voltages of 100, 120, and 135 kV, following the standard protocol. The coronary artery calcium score was calculated using a non-enhanced scan protocol with the following parameters: 120 kV, 150 mA, and thickness 3 mm. The location of the lesions was determined using a 17-segment model by a CT radiologist. Significant stenosis was defined as coronary stenosis  $\geq 50\%$  of a major epicardial artery with a diameter  $\geq 2.0$  mm on CCTA, with the severity of the stenosis defined as moderate (stenosis 50–69%) or severe (stenosis 70–99%).<sup>14</sup>

### Measurement and Analysis of FFR<sub>CT</sub>

CCTA raw data were transferred to core laboratory (HeartFlow) for analysis. The scientific rationale underpinning the computation of FFR<sub>CT</sub> has been described in detail elsewhere.<sup>4</sup> The FFR<sub>CT</sub> indicates the approximate FFR value for each point on major coronary arteries

$>2$  mm in diameter, including the side branches. In the present study, an independent physician blinded to the invasive FFR results performed FFR<sub>CT</sub> measurements on an interactive website. FFR<sub>CT</sub> values were obtained both 1–2 cm distal to the lower border of the stenosis, as per the recommendations of the expert panel,<sup>11</sup> and at a far-distal site corresponding to the site where the invasive FFR was measured for each diseased vessel. To determine the point 1–2 cm distal to the lesion, a point 1–2 cm distal to the lesion was first identified on the workstation during CCTA analysis. Based on this information, a point 1–2 cm distal to the lesion was identified on the 3D analysis preview image of the FFR<sub>CT</sub> on the dedicated website, and the FFR<sub>CT</sub> was measured at this point. In the case of diffuse lesions and multiple lesions, the FFR<sub>CT</sub> was measured 1–2 cm distal to the most severe site and the most proximal lesion, respectively.

### ICA and Invasive FFR

ICA was performed by a physician using a standard technique. Invasive FFR was measured using a pressure wire (Pressure Wire™; Abbott Vascular, Santa Clara, CA, USA). Maximal hyperemia was induced by intravenous adenosine infusion (150–180  $\mu$ g/kg/min) via the forearm or by intracoronary injection of papaverine (8–12 mg) or nicorandil (2 mg). FFR was measured at the far-distal site for all vessels with significant stenosis on CCTA, with values  $\leq 0.80$  representing physiologically significant CAD.

### Statistical Analysis

The diagnostic performance of FFR<sub>CT</sub> measured 1–2 cm distal to the stenosis and at the far-distal site was compared using the area under the curve (AUC) from receiver operating characteristic (ROC) curve analysis; Comparisons of AUCs were made using the DeLong method. The McNemar

<b>Table 1. Baseline Characteristics</b>	
<b>Patient characteristics (n=146)</b>	
Age (years)	70±10
Male sex	98 (67)
Body mass index (kg/m <sup>2</sup> )	24±3
Hypertension	107 (73)
Hyperlipidemia	93 (64)
Diabetes	63 (43)
Smoker	89 (61)
Creatinine (mg/dL)	0.96±0.88
HbA1c (%)	6.4±0.9
LDL-C (mg/dL)	122±30
HDL-C (mg/dL)	51±14
Triglyceride (mg/dL)	164±123
<b>Symptoms</b>	
Typical angina	57 (39)
Atypical angina	52 (36)
No symptom	37 (25)
<b>Patient-based CCTA findings (n=146)</b>	
<b>Vessel severity</b>	
SVD	53 (36)
MVD including LMTD	93 (64)
<b>CAD-RADS</b>	
3	84 (57)
4A	46 (32)
4B	16 (11)
Agatston score (Hounsfield units)	353 [143–846]
Interval between CCTA and ICA (days)	21 [18–24]
<b>Vessel-based CCTA findings (n=254)</b>	
<b>Distribution of diseased vessels</b>	
LAD	134 (53)
LCx	61 (24)
RCA	59 (23)
<b>Lesion severity</b>	
Intermediate stenosis (50–69%)	130 (51)
Severe stenosis (70–99%)	124 (49)
<b>Invasive FFR findings (n=254)</b>	
Invasive FFR	0.79 [0.70–0.87]
Positive FFR (≤0.8)	141 (56)

Values are expressed as n (%) or the mean±SD or median [interquartile range]. CAD-RADS, Coronary Artery Disease – Reporting and Data System; CCTA, coronary computed tomography angiography; FFR, fractional flow reserve; HDL-C, high-density lipoprotein cholesterol; ICA, invasive coronary angiography; LAD, left ascending artery; LCx, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; LMTD, left main trunk disease; MVD, multivessel disease; RCA, right coronary artery; SVD, single-vessel disease.

test was used to compare the reclassification rates of FFR<sub>CT</sub> positivity based on FFR<sub>CT</sub> values measured 1–2 cm distal to the stenosis and at the far-distal site. In addition, the McNemar test was used to compare the sensitivity, specificity, and accuracy of FFR<sub>CT</sub> measured 1–2 cm distal to the stenosis and at the far-distal site. Fisher's exact test and Chi-squared tests were used to compare the positive predictive value (PPV), negative predictive value (NPV), and other optimal proportions. Continuous data are expressed as the mean±SD or as the median with interquartile range (IQR). Categorical data are expressed as

frequencies (%).

All analyses were performed using SPSS version 24.0 for Windows (SPSS Inc., Chicago, IL, USA) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Australia). Statistical significance was set at 2-tailed  $P < 0.05$ .

## Results

The characteristics of the 146 patients examined in this study are presented in **Table 1**. Approximately 98 (67%) patients were male, with a mean age of 70±10 years. According to the CCTA findings, 53 (36%) patients were diagnosed with single-vessel disease, whereas 93 (64%) patients were found to have multivessel disease (MVD), including left main trunk disease (LMTD). In addition, the CAD – Reporting and Data System (RADS) classification system was used: 84 (57%) patients were diagnosed as CAD-RADS 3, 46 (32%) were diagnosed as CAD-RADS 4A, and 16 (11%) were diagnosed as CAD-RADS 4B. The median Agatston score was 353 Hounsfield units (IQR 143–846 Hounsfield units).

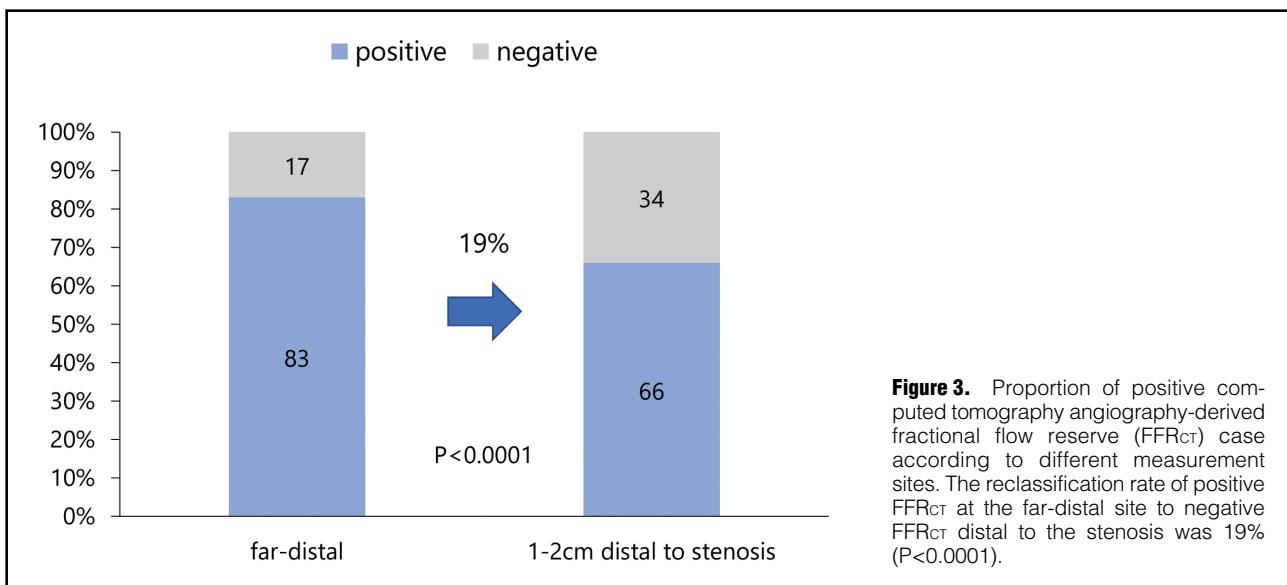
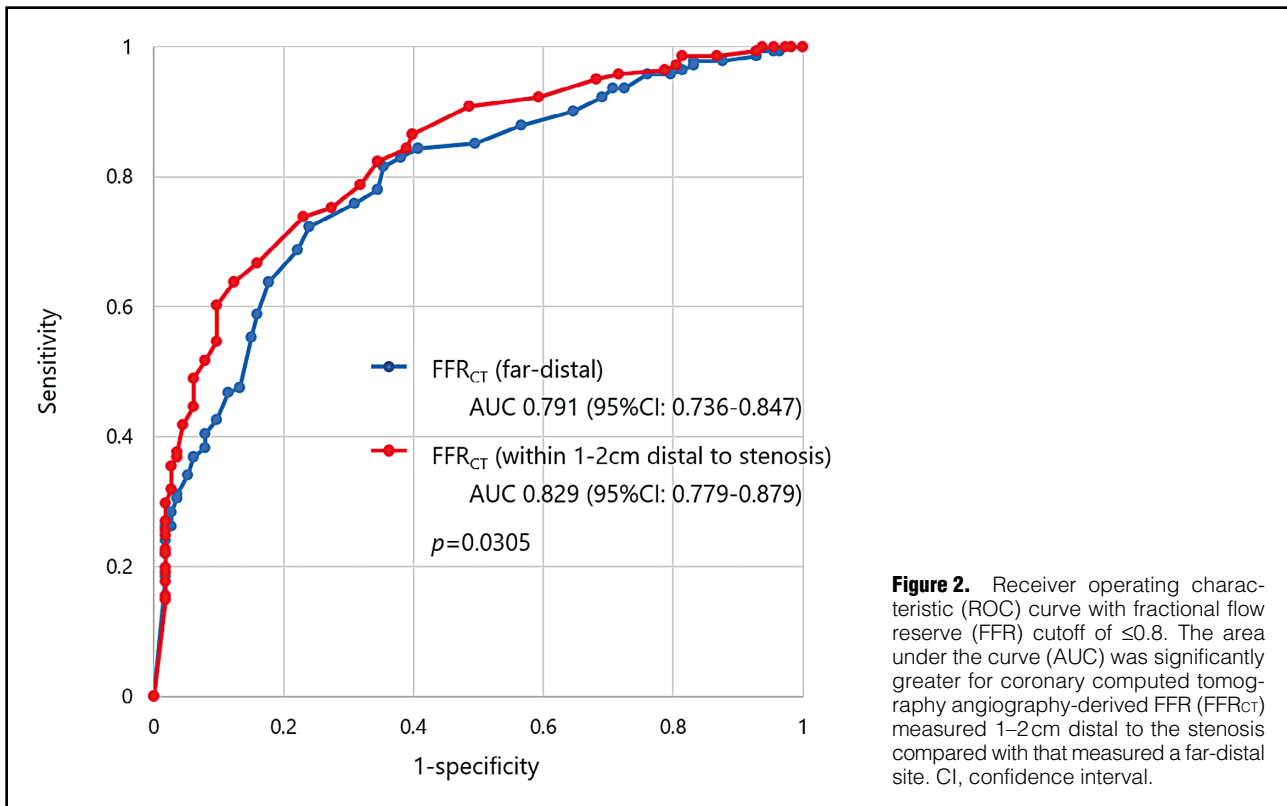
Among the entire population, 254 vessels were confirmed as having significant stenosis. Of these, 134 (53%) involved the left anterior descending artery, 61 (24%) involved the left circumflex artery, and 59 (23%) involved the right coronary artery. Regarding lesion severity, 130 (51%) and 124 (49%) vessels were considered to have intermediate and severe stenosis, respectively. The median interval from CCTA to ICA was 21 days (IQR 18–24 days), and the median invasive FFR value was 0.79 (IQR 0.70–0.87). The distribution of invasive FFR values in the examined diseased vessels is shown in the **Supplementary Figure**. In all, 56% of examined vessels had physiologically significant CAD with an FFR ≤0.8, indicating that many patients with relatively severe stenosis were included in the present study.

### Diagnostic Performance of FFR<sub>CT</sub> Measured 1–2 cm Distal to the Stenosis in Detecting Physiologically Significant CAD

FFR<sub>CT</sub> measurements 1–2 cm distal to the stenosis and at the far-distal site were obtained for a total of 246 diseased vessels. Based on ROC analysis, the AUC of the FFR<sub>CT</sub> values was significantly greater for measurements made 1–2 cm distal to the stenosis than at the far-distal site (0.829 [95% CI 0.779–0.879] vs. 0.791 [95% CI 0.736–0.847], respectively;  $P = 0.0305$ ; **Figure 2**).

The FFR<sub>CT</sub> was positive in 83% and 66% of vessels for measurements taken at the far-distal site and 1–2 cm distal to the stenosis, respectively ( $P < 0.0001$ ). The reclassification rate of positive FFR<sub>CT</sub> was 19% for measurements made 1–2 cm distal to the stenosis (**Figure 3**); therefore, particularly in the FFR<sub>CT</sub> range 0.71–0.80, which was considered a gray zone, diagnostic accuracy improved from 36% to 58% ( $P = 0.0052$ ; improvement rate 61%; **Figure 4**).

In vessel-based diagnostic performance for detecting physiologically significant CAD, FFR<sub>CT</sub> measured 1–2 cm distal to the stenosis compared with FFR<sub>CT</sub> measured at the far-distal site had a sensitivity of 87% vs. 94% ( $P = 0.0039$ ), a specificity of 60% vs. 29% ( $P < 0.0001$ ), a PPV of 73% vs. 62% ( $P = 0.028$ ), a NPV of 78% vs. 79% ( $P = 0.958$ ), and an accuracy of 75% vs. 65% ( $P < 0.0001$ ), respectively; the false-negative rates for FFR<sub>CT</sub> measured 1–2 cm distal to the stenosis and at the far-distal site were 13% and 7% ( $P < 0.0001$ ), respectively, with corresponding

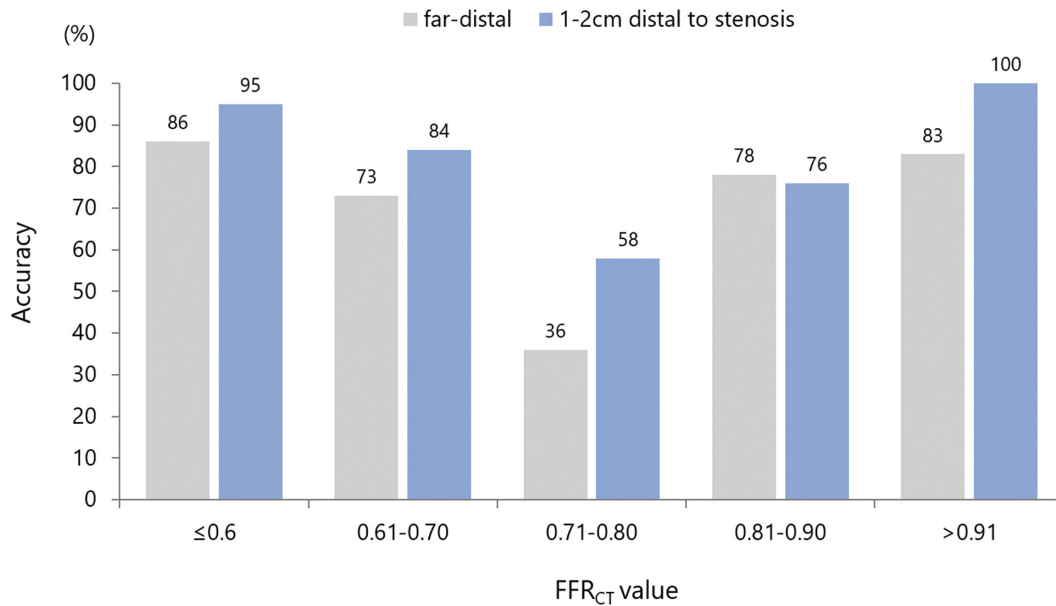


false-positive rates of 40% and 71% ( $P=0.004$ ), respectively (Table 2; Figure 5). Two representative cases are shown in Figure 6.

### Discussion

In the present study we investigated the optimal measurement site of FFR<sub>CT</sub> in the evaluation of physiologically significant CAD with an FFR  $\leq 0.8$ . Using FFR<sub>CT</sub> values

measured 1–2 cm distal to the stenosis, the FFR<sub>CT</sub> positivity rate was reduced from 83% to 66% (reclassification rate 19%) compared with FFR<sub>CT</sub> measured at the conventional distal site, and, in particular, the diagnostic accuracy in the FFR<sub>CT</sub> range 0.71–0.80 was improved by 61%. In addition, the overall diagnostic performance of FFR<sub>CT</sub> for detecting physiologically significant CAD was significantly improved.



**Figure 4.** Diagnostic accuracy of computed tomography angiography-derived fractional flow reserve (FFR<sub>CT</sub>) across FFR<sub>CT</sub> ranges. In the FFR<sub>CT</sub> range 0.71–0.80, diagnostic accuracy improved from 36% to 58% by using values measured 1–2 cm distal to the stenosis (P=0.0052).

Overall (n=146)	Measurement point		P value
	Far-distal	1–2 cm distal to stenosis	
Sensitivity (%)	94 (90–96)	87 (82–91)	0.004
Specificity (%)	29 (24–33)	60 (54–65)	<0.0001
PPV (%)	62 (60–64)	73 (69–76)	0.028
NPV (%)	79 (65–88)	78 (70–85)	0.958
Accuracy (%)	65 (61–68)	75 (69–79)	<0.0001
False-positive rate (%)	71	40	<0.0001
False-negative rate (%)	7	13	0.004

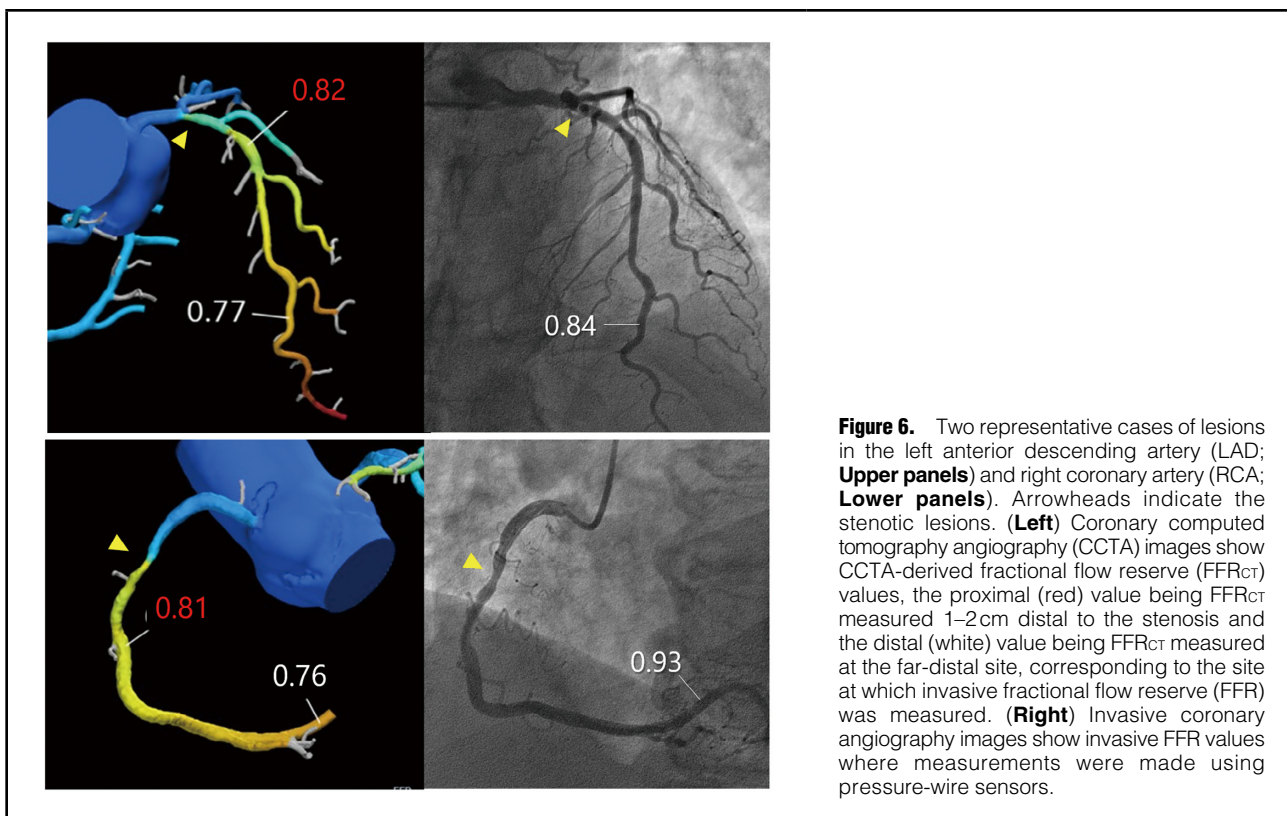
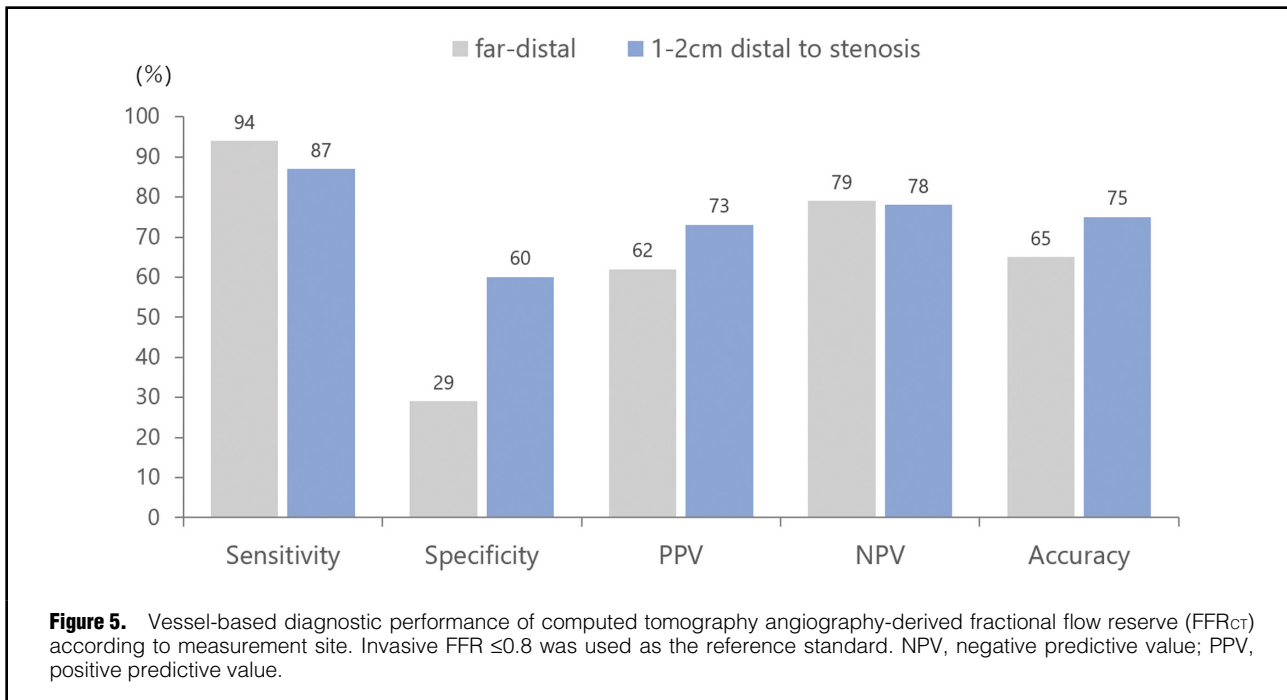
Unless indicated otherwise, data are given as the median (interquartile range). NPV, negative predictive value; PPV, positive predictive value.

#### Adequacy of FFR<sub>CT</sub> Measured 1–2 cm Distal to the Stenosis

In the present study, we used FFR<sub>CT</sub> values measured 1–2 cm distal to the anatomical stenosis rather than using the lowest FFR value measured at the far-distal site, the currently accepted site for evaluating diseased vessels. FFR<sub>CT</sub> values (usually the lowest FFR value measured at the far-distal site of the diseased vessel) have been shown to be reliably correlated with invasive FFR values.<sup>1,5</sup> However, it has been reported that, in addition to assessing decreases in FFR along the length of coronary arteries with diffuse atherosclerosis, FFR<sub>CT</sub> assesses the decrease in FFR along the length of the vessels even in the absence of focal stenoses.<sup>15</sup> Therefore, the lowest FFR<sub>CT</sub> values measured at a far-distal site may sometimes lead to false-positive results, and therefore may not be relevant for clinical decisions regarding ICA.

With regard to the measurement site of FFR<sub>CT</sub>, Cami et

al reported that FFR<sub>CT</sub> values measured 10.5 cm distal to the lesion were most indicative of the extent of ischemia in the lesion,<sup>10</sup> with an expert panel subsequently recommending that FFR<sub>CT</sub> measurements 1–2 cm distal to the stenosis are more appropriate than measurements at conventional distal sites.<sup>11</sup> Kueh et al reported that by using FFR<sub>CT</sub> values measured 1–2 cm distal to the stenoses, 44% of patients positive for the lowest FFR<sub>CT</sub> value were reclassified as negative.<sup>9</sup> Moreover, in patients who underwent ICA, revascularization efficiency was better in those with a positive FFR<sub>CT</sub> measured 1–2 cm distal to the stenosis than in those considered positive based on the lowest FFR<sub>CT</sub> value.<sup>9</sup> Omori et al have also demonstrated better diagnostic performance of FFR<sub>CT</sub> values measured 1–2 cm distal to the stenosis than those measured in a distant segment, with a significant benefit particularly in the diagnosis of LAD lesions.<sup>12</sup> Thus, it seems that using



FFR<sub>CT</sub> values measured 1–2 cm distal to the stenoses may be more practical than relying on the lowest FFR<sub>CT</sub> values in FFR<sub>CT</sub> analysis. For this reason, FFR<sub>CT</sub> values measured 1–2 cm distal to an anatomical stenoses were used in the present study instead of those measured at far-distal sites.

**Impact of Diagnostic Performance Using FFR<sub>CT</sub> Measured 1–2 cm Distal to the Anatomical Stenosis for Detecting Physiologically Significant CAD**

In a meta-analysis of FFR<sub>CT</sub>, the overall diagnostic accuracy of FFR<sub>CT</sub> was 82%, and this threshold was met when

FFR<sub>CT</sub> values were below 0.63 or above 0.83. However, for FFR<sub>CT</sub> values between 0.64 and 0.82, the diagnostic accuracy is low, especially in the FFR<sub>CT</sub> range 0.70–0.80, where diagnostic accuracy drops to approximately 46%; this is a known problem of FFR<sub>CT</sub> analysis. Thus, diagnoses based on FFR<sub>CT</sub> measured conventionally at far-distal sites are overestimated, and decisions based on FFR<sub>CT</sub> alone may lead to overtreatment. In fact, in clinical practice, it is felt that a relatively large number of patients cannot be revascularized on the basis of decisions based on FFR<sub>CT</sub> alone. A remedy for this problem, as described by the expert panel,<sup>11</sup> is to change the point at which FFR<sub>CT</sub> is measured to 1–2 cm distal to the anatomical stenosis. This approach has been shown to improve overestimation, leading to improved diagnostic accuracy and more efficient revascularisation.<sup>9,12</sup> In the present study, using FFR<sub>CT</sub> values measured 1–2 cm distal to the stenosis reduced the FFR<sub>CT</sub> positivity rate from 83% to 66% (reclassification rate 19%) compared with the use of values measured at distal sites. This benefit was particularly marked in the FFR<sub>CT</sub> range 0.7–0.8, which is considered a grey zone in FFR<sub>CT</sub> assessment, with a 61% increase in accuracy in this zone. As a result, there were significant increases in specificity and the PPV, resulting in an improvement in overall diagnostic accuracy. Although the diagnostic sensitivity was slightly reduced for FFR<sub>CT</sub> measured 1–2 cm distal to the stenosis, this was considered acceptable compared with that reported in previous studies. Thus, we believe that measuring FFR<sub>CT</sub> 1–2 cm distal to the stenosis will become a valid solution to improve the diagnostic accuracy of FFR<sub>CT</sub> analysis.

### Usefulness of FFR<sub>CT</sub> as a Screening Method for Significant CAD in Clinical Settings

Stress myocardial perfusion imaging (MPI) has traditionally been used as a first-line non-invasive functional assessment in patients with suspected CAD, and the clinical prognosis in patients with normal findings is good, with few adverse cardiovascular events.<sup>16,17</sup> However, in patients with MVD or LMTD, which may induce “balanced ischemia”, the diagnostic performance of stress MPI is reduced, and consequently patients with severe CAD may be overlooked. In addition, recent reports have suggested that stress MPI using invasive FFR as a reference standard has low diagnostic sensitivity,<sup>18</sup> and there is a risk of overlooking severe disease while screening in clinical settings.

In contrast, FFR<sub>CT</sub> has a high diagnostic sensitivity based on invasive FFR and has a high NPV,<sup>18</sup> making it a useful screening method for patients with CAD, including patients with severe CAD. The previously published PLATFORM study showed that FFR<sub>CT</sub> analysis prior to ICA can reduce unnecessary catheterization without compromising the diagnosis of patients with significant stenosis, resulting in a reduction in healthcare costs.<sup>7</sup> However, the specificity and PPV of FFR<sub>CT</sub> analysis are low, and many false-positives are recorded. Therefore, reconsideration of the measurement site for FFR<sub>CT</sub> in the present study may lead to improved diagnostic accuracy of FFR<sub>CT</sub> analysis, especially specificity and PPV. It has also been reported that reconsideration of the cut-off value of FFR<sub>CT</sub> may improve diagnostic accuracy,<sup>19</sup> and future large-scale studies that consider reconsideration of the measurement site or cut-off value are desirable.

### Study Limitations

The present study has several limitations. First, this study

was a retrospective single-center study with a relatively small number of patients. Second, the present study is a subanalysis of the ADVANCE Registry, which included patients who underwent invasive CAG based on the results of FFR<sub>CT</sub>; therefore, a large number of patients with significant stenosis were enrolled in the registry, whereas patients with non-significant stenosis were excluded, leading to a significant bias in terms of patient selection. In fact, in previous similar reports, only 20–30% of enrolled patients had severe stenosis >70%, with most remaining patients having intermediate stenosis. However, in the present study, approximately half the patients had severe stenosis, and this proportion is thought to be considerably higher than in previous reports. Basically, intermediate stenosis, for which ischemia is difficult to determine, is considered the indication for FFR<sub>CT</sub> analysis, it may be necessary to investigate more patients with intermediate stenoses in future studies.

Third, coronary artery calcification is an important factor related to the overestimation of CAD in CCTA. The patients enrolled in this study had higher Agatston scores than those reported previously, and we may have included more patients with severe coronary calcification unsuitable for FFR<sub>CT</sub> analysis in the present study. Finally, although this study examined the diagnostic accuracy of FFR<sub>CT</sub> values measured 1–2 cm distal to the anatomical stenosis, there are few reports on similar examinations. Therefore, the generalization of our findings to clinical practice should be made with caution.

Because of these limitations, further large-scale studies with a large number of patients are needed to confirm our results.

### Conclusions

The use of FFR<sub>CT</sub> values measured 1–2 cm distal to the anatomical stenosis allowed for a significant reclassification of patients with positive FFR<sub>CT</sub> measured at far-distal sites and significantly increased accuracy in the “gray zone” of FFR<sub>CT</sub> (0.71–0.80), resulting in a significant improvement in the diagnostic performance of FFR<sub>CT</sub>.

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### Disclosures

All authors have no conflicts of interest to disclose.

### IRB Information

This study was approved by the Institutional Review Board of Shin-Koga Hospital (Approval no. 2018-05-14).

### Data Availability

The deidentified participant data will not be shared.

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### Supplementary Files

Please find supplementary file(s);  
<http://dx.doi.org/10.1253/circrep.CR-21-0093>