Incidence and predictors of lesion-specific ischemia by FFRCT

Learnings from the international ADVANCE registry

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Incidence and Predictors of Lesion-Specific Ischemia by FFR\textsubscript{CT}:
Learnings from the International ADVANCE Registry

**Brief Title:** Incidence and predictors of ischemia by FFR\textsubscript{CT}

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**Background:** To date, the clinical utility of coronary computed tomography angiography (CTA)-derived fractional flow reserve (FFR\textsubscript{CT}) has been limited to trials and single center experiences. We herein report the incidence of abnormal FFR\textsubscript{CT} (≤0.80) and the relationship of lesion-specific ischemia to subject demographics, symptoms, and degree of stenosis in the multicenter, prospective ADVANCE registry.

**Methods:** One thousand patients with suspected angina having documented coronary artery disease on coronary CTA and clinically referred for FFR\textsubscript{CT} were prospectively enrolled in the registry. Patient demographics, symptom status, coronary CTA and FFR\textsubscript{CT} findings were recorded. Univariate and multivariate analyses were performed to investigate the predictors related to abnormal FFR\textsubscript{CT}.

**Results:** FFR\textsubscript{CT} data were analyzed in 952 patients (95.2%). Overall, 51.1% patients had a positive FFR\textsubscript{CT} value (≤0.80). Patients with ≥3 risk factors had a significantly higher rate of abnormal FFR\textsubscript{CT} than those with <3 risk factors (60.2% vs. 43.9%, p=0.0001). On multivariate analysis, baseline diabetes (odds ratio [OR] 1.52, 95% confidence interval [CI] 1.04-2.21, p=0.030) and hypertension (OR 1.56, 95%CI 1.14-2.14, p=0.005) were both predictive of abnormal FFR\textsubscript{CT}. In addition, >70% stenosis was significantly associated with low FFR\textsubscript{CT} (OR 31.16, 95%CI 12.25-79.22, p<0.0001) vs.
<30% stenosis. Notably, stenosis 30-49% vs. <30% had an increased likelihood of ischemia (OR 3.74, 95%CI 1.52-9.17, p<0.0001).

**Conclusions:** In this real-world registry, CT angiographic stenosis severity in addition to baseline cardiovascular risk factors conferred an increased likelihood of an abnormal FFR\textsubscript{CT}. Importantly, however, mild CT angiographic stenoses were noted to have an increased hazard for ischemia and the converse holding true for more severe stenoses as well.

**Key words:** coronary artery disease, FFR\textsubscript{CT}, ischemia

**Clinical Trial Registration**-https://clinicaltrials.gov. Unique Identifier: NCT02499679.
Abbreviations

ADVANCE = Assessing Diagnostic Value of Non-invasive FFR<sub>CT</sub> in Coronary Care

BMI = body mass index

CAD = coronary artery disease

CI = confidence interval

CTA = computed tomography angiography

FFR = fractional flow reserve

FFR<sub>CT</sub> = fractional flow reserve derived by coronary computed tomography angiography

ICA = invasive coronary angiography

LAD = left anterior descending artery

LCX = left circumflex artery

OR = odds ratio

PCI = percutaneous coronary intervention

RCA = right coronary artery

SCCT = Society of Cardiovascular Computed Tomography
Previous randomized studies have shown that stable coronary artery disease (CAD) patients gain a benefit from FFR-guided treatment strategy when compared to angiography-guided treatment strategy.\textsuperscript{1-3} Thus, currently, physiologic assessment by fractional flow reserve (FFR) at the time of invasive coronary angiography (ICA) is considered the gold standard method to identify hemodynamically significant stenosis, inducing ischemia, and justifying revascularization.\textsuperscript{4} Anatomic assessment by coronary computed tomography angiography (CTA) has emerged as a noninvasive method for direct visualization of CAD, demonstrating high diagnostic performance.\textsuperscript{5,6} Coronary lesions with a stenosis severity of $\geq50\%$ on visual coronary CTA are generally considered for referral to ICA.\textsuperscript{7} Coronary CTA, however, may result in both underestimation and overestimation of a lesion’s severity and is often inaccurate in identifying lesions that cause ischemia.\textsuperscript{7,8} Thus, the ideal test for assessing suspected obstructive CAD should yield both anatomic and physiologic information regarding coronary lesions.

Recent technological advances in computational fluid dynamics and individual image-based modeling allow for the noninvasive calculation of FFR (fractional flow reserve derived by coronary computed tomography angiography [FFR$_{\text{CT}}$]) from standard coronary CTA datasets, without the need for additional radiation exposure or
administration of hyperemic agents such as adenosine. Three prospective multicenter trials have demonstrated that FFR\textsubscript{CT} accurately predicts the hemodynamic significance of a coronary stenosis when compared to invasively measured FFR and the availability of FFR\textsubscript{CT} data in addition to coronary CTA provides a markedly improved diagnostic performance in comparison with stenosis assessment according to coronary CTA alone. FFR\textsubscript{CT} has been shown to have strong clinical utility in recent clinical trials (PLATFORM) and multiple single center studies of patients with stable CAD. In fact, deferring ICA in patients with an FFR\textsubscript{CT} value of >0.8 had a favorable short-term prognosis (no cardiac events during a median follow-up period of 12 months). To date, however, the clinical utility of FFR\textsubscript{CT} has been limited to trials and single center experiences.

Hence, we conducted the Assessing Diagnostic Value of Non-invasive FFR\textsubscript{CT} in Coronary Care (ADVANCE) registry to observe the “real-world” utility and impact of FFR\textsubscript{CT} on clinical decision-making, outcomes and resource utilization in a broad variety of healthcare settings, regions and patient subsets.

We herein report the incidence and predictors of lesion-specific ischemia by FFR\textsubscript{CT} from the results of the first 1,000 patients enrolled in the ADVANCE registry.

1. Methods
1.1. Study design and population

The ADVANCE registry is a multicenter, prospective registry that will enroll 5,000 patients with suspected stable symptomatic CAD diagnosed by coronary CTA from 38 sites in Europe, North America and Asia. Patients with prior revascularization were not included in the registry. The rationale, design and goals of this registry have previously been described.\textsuperscript{16} The primary endpoint of the registry is the rate of reclassification between the management plan on the basis of coronary CTA alone versus coronary CTA plus $\text{FFR}_{\text{CT}}$ data. In the present study, we report the results of the first 1,000 patients enrolled from July 14\textsuperscript{th}, 2015 to June 15\textsuperscript{th}, 2016. CTA data sets were submitted for $\text{FFR}_{\text{ct}}$ analysis based on the clinical decision of the interpreting physician but it required confirmation of CAD and a focal >25\% stenosis.

Clinical and demographic information, medical history, and cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, body mass index [BMI] > 30 kg/m$^2$, current smoking, and being male) were prospectively collected.

The study protocol was designed by the steering committee and approved by the institutional review board at each site, and the subjects gave written informed consent prior to participation.

1.2. Image acquisition and analysis for CT
Coronary CTA was performed on 64- or higher detector row scanners at each site. Sublingual nitrates were administered prior to scanning in all patients. If necessary, beta-blockers were orally or intravenously administered targeting a heart rate <60 beats per minute. The protocol for coronary CTA image acquisition was recommended to comply with the Society of Cardiovascular Computed Tomography (SCCT) guideline.17 Assessment of luminal diameter stenosis was performed using an 18-segment coronary model17; the strategy of stenosis quantification was left to the discretion of the local investigator at each site. Vessel segments ≥2mm in diameter were evaluated for luminal narrowing, and the per-vessel maximum stenosis was categorized as 0%, 1% to 29%, 30% to 49%, 50% to 70%, 71% to 90%, or >90%. Non-evaluable (n=8) or occluded (n=15) vessel segments were excluded from analysis.

1.3. $FFR_{CT}$ analysis

Standard coronary CTA datasets were submitted to HeartFlow (Redwood City, CA, USA) for analysis. The $FFR_{CT}$ results were made available to the interpreting physician within 48 h for evaluation and treatment planning of each subject provided that coronary CTA image quality was acceptable for analysis. The scientific basis behind the computation of $FFR_{CT}$ have been described in detail in previous reports.9-12 $FFR_{CT}$ was displayed for each point in the coronary tree. The lowest $FFR_{CT}$ values in the major
epicardial (left main, left anterior descending [LAD], left circumflex [LCX], and right coronary [RCA]) arteries (including side branches) >2 mm in diameter were registered and lesion-specific ischemia was defined as FFR\textsubscript{CT} \leq 0.80.

1.4. Statistical analysis

Data were reported as mean±SD or number (%). Categorical variables were compared using the chi-square test. To identify independent predictors of abnormal FFR\textsubscript{CT} (\leq 0.80), clinical and coronary CTA variables were entered into a multivariate logistic regression model if their univariate p value was <0.1. Results were expressed as odds ratios with 95% confidence intervals. A p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA).

2. Results

2.1. Patient characteristics

Of 1,000 patients, 154 subjects (15.4%) were enrolled from North America, 377 (37.7%) from Europe, and 469 (46.9%) from Japan. Baseline patient characteristics are summarized in Table 1. The mean patient age was 66.1±10.4 years and 65.5% were male. The mean BMI was 25.8±4.3 kg/m\textsuperscript{2}. Hypertension was present in 59.9%,
diabetes in 24.0%, hyperlipidemia in 53.1%, and current smoker in 18.7%. The median heart rate at the time of CTA was 58.1 +/- 7.2 beats per minute. All subjects had CCTA findings of CAD with all but 5.4% having at least a stenosis of 30% in one epicardial coronary territory.

Symptom status and nature is available in Table 1 with the majority having typical (27.7%) and atypical angina (38.2%) with 20.6% being asymptomatic. In patients with typical angina, Canadian Cardiovascular Society grade II angina was most commonly observed.

2.2. FFR\textsubscript{CT}

FFR\textsubscript{CT} results were available in 952 (95.2%) patients. As shown in Table 2, coronary CTA image quality was not acceptable for FFR\textsubscript{CT} analysis in 33 (3.3%) patients, and FFR\textsubscript{CT} was not requested in 15 (1.5%) patients as decision making was made on the basis of CTA.

2.3. Rate of FFR\textsubscript{CT} positivity and relationship to stenosis severity

Overall, 486 (51.1%) of 952 patients had a positive FFR\textsubscript{CT} value (\(\leq 0.80\)). An abnormal FFR\textsubscript{CT} was observed in 44.2% of the LAD lesions, 17.7% of the LCX lesions, and 21.9% of the RCA lesions, respectively.
On a per-vessel level analysis, there was a mismatch between the CT angiographic and FFR\textsubscript{CT} assessments of lesion severity, as shown in Figure 1. Specifically, FFR\textsubscript{CT} was \(\leq 0.80\) in 742 (32.1%) of a total of 2,315 vessels. Out of 1,282 vessels (55.4% of the total vessels analyzed) categorized as having diameter stenosis < 50%, FFR\textsubscript{CT} was \(\leq 0.80\) in 183 (14.3%). On the contrary, FFR\textsubscript{CT} was negative for ischemia (>0.8) in 474 (45.9%) of 1,033 vessels categorized as having coronary CTA stenosis severity \(\geq 50\%\) diameter stenosis. Importantly, of all vessels with a diameter stenosis of 30% to 49%, 20.8% were below the ischemic threshold (FFR\textsubscript{CT} \(\leq 0.80\)) and in the category 71% to 90% stenosis, 28.4% were not hemodynamically significant with an FFR\textsubscript{CT} value over 0.8. Of all vessels having 50% to 70% stenosis, in 382 (58.6%), FFR\textsubscript{CT} was >0.80 and in 270 (41.4%), FFR\textsubscript{CT} was \(\leq 0.80\). Representative cases are displayed in Figure 2 and 3.

2.4. Predictors of abnormal FFR\textsubscript{CT}

The results of univariate analysis for predicting abnormal FFR\textsubscript{CT} are shown in Table 3. On multivariate analysis (Table 4), diabetes (OR: 1.52, 95% CI: 1.04-2.21, \(p=0.030\)) and hypertension (OR: 1.56, 95% CI: 1.14-2.14, \(p=0.005\)) at baseline were the independent predictors of abnormal FFR\textsubscript{CT}. Patients with \(\geq 3\) risk factors had a significantly higher rate of abnormal FFR\textsubscript{CT} than those with <3 risk factors (60.2% vs.}
43.9%, p=0.0001). In addition, >70% stenosis vs. <30% stenosis was significantly associated with abnormal FFR\(_{CT}\) (OR: 31.16, 95%CI: 12.25-79.22, p<0.0001). Of note, stenosis 30-49% vs. <30% was more likely to have ischemia (OR: 3.74, 95%CI: 1.52-9.17, p<0.0001). Furthermore, there was a trend for more abnormal FFR\(_{CT}\) values in LAD lesions (OR: 2.13, 96%CI: 0.74-6.09) in comparison with RCA lesions.

3. Discussion

The present study investigated the incidence and predictors of lesion-specific ischemia by FFR\(_{CT}\) in the ADVANCE registry. The major findings were as follows: Approximately half of stable patients diagnosed with CAD by coronary CTA were positive for ischemia with an FFR\(_{CT}\) value of \(\leq 0.8\). Patients having \(\geq 3\) risk factors were associated with a significantly higher incidence of abnormal FFR\(_{CT}\) than those having fewer than 3 risk factors, with both diabetes and hypertension at baseline being independent predictors of abnormal FFR\(_{CT}\). Interestingly, neither symptom status nor symptom typicality were found to be independent predictors of lesion specific ischemia. Importantly, when analyzed on a per-vessel basis, there was a significant discordance between coronary CTA anatomic stenosis severity and functional stenosis severity assessed by FFR\(_{CT}\).
Coronary CTA has asserted itself as an important noninvasive imaging tool for patients with symptoms and suspected CAD.\textsuperscript{18,19} It is well established that anatomic imaging by coronary CTA or ICA correlates poorly with functional stenosis severity.\textsuperscript{8} Physiologic assessment by FFR\textsubscript{CT} is a new noninvasive diagnostic method to identify the functional significance of a coronary stenosis from standard coronary CTA images, without the need for modification of acquisition protocols, or administration of a vasodilator.\textsuperscript{9} A meta-analysis of 3 FFR\textsubscript{CT} trials demonstrated its superior diagnostic accuracy compared to coronary CTA alone (area under receiver-operating characteristic curve: 0.89 for FFR\textsubscript{CT} versus 0.74 for coronary CTA alone) when using invasive FFR assessment as the reference standard.\textsuperscript{20} In the present study, of all vessels with a stenosis severity of 50\% to 70\%, FFR\textsubscript{CT} indicated 58.6\% to be functionally nonsignificant and 41.4\% to be functionally significant. Even in more severe stenoses between 71\% and 90\% CT angiographic stenosis severity, 28.4\% of all vessels were negative for lesion-specific ischemia as determined by FFR\textsubscript{CT}. Our findings are in line with prior large-scale invasive FFR studies of over 1,300 coronary artery lesions demonstrating that 65\% of all stenoses with 50\%-70\% diameter stenosis and 20\% of all stenoses with 71\%-90\% diameter stenosis were not hemodynamically significant (FFR>0.80).\textsuperscript{21} In contrast, even in vessels with 30\% to 49\% stenosis, traditionally
considered non-causative of ischemia, lesion-specific ischemia (FFR<sub>CT</sub> ≤ 0.80) was more frequently observed than in vessels with <30% stenosis severity (20.8% vs. 8.7%; OR 3.74, 95%CI 1.52-9.17, p<0.0001). Only in the CT angiographic stenosis categories of >90% and <30% did visual lesion assessment by coronary CTA corresponded well with lesion severity by FFR<sub>CT</sub>. These findings are consistent with those seen in previous invasive FFR studies. Thus, the initial results from the real-world international ADVANCE registry confirm that there is a visual-functional mismatch between FFR<sub>CT</sub> and coronary CTA, regarding lesion severity. Consequently, the addition of FFR<sub>CT</sub> to coronary anatomy from the CTA could lead to significant reclassification of vessels thought to be causal of ischemia when compared with CT alone thereby potentially enabling more appropriate decision-making around invasive assessment and revascularization. The recent FFR<sub>CT</sub> RIPCORD study reported that the routine availability of FFR<sub>CT</sub> data disclosed a change in clinical management based on coronary CTA alone in 36% of the patients with stable chest pain.

3.1. Study limitations

Several limitations of this study should be acknowledged. First, good image quality is critical for the reliable calculation of FFR<sub>CT</sub>. Although coronary CTA image acquisition was performed in accordance with SCCT guidelines and uninterpretable
coronary CTA images by site assessment were excluded from enrolling in the registry. 3.3% of patients were judged to have unsuitable coronary CTA images for analysis. This proportion was similar to or lower than that (2%-13%) seen in previous studies.\(^\text{12,13,15}\) However, we cannot comment on how many additional coronary CTA examinations were not submitted out of concerns for image quality. Second, direct comparison of per-vessel \(\text{FFR}_{\text{CT}}\) to invasively measured FFR was not performed. However, it has already been demonstrated that there is a good correlation between \(\text{FFR}_{\text{CT}}\) values and FFR values.\(^\text{10,12,15}\) Third, information regarding other factors including location of stenosis and plaque morphology by coronary CTA,\(^\text{25,26}\) which may be related to lesion-specific ischemia, were not collected. Finally, with the early integration of \(\text{FFR}_{\text{CT}}\), many sites used the nadir \(\text{FFR}_{\text{CT}}\) value per vessel rather than the now more accepted practice of adjudication of lesion-specific ischemia 2 cm distal to a stenosis.\(^\text{27,28}\) Future analyses of the entire ADVANCE registry will enable a deeper understanding of which metric is more appropriate to guide decision-making and yield more prognostic information.

4. Conclusions

In this real-world registry, while CT angiographic stenosis severity conferred an increased likelihood of an abnormal \(\text{FFR}_{\text{CT}}\), the relationship is not consistent enough to
enable clinical decision-making. Mild CT angiographic stenoses can result in ischemia and intermediate to severe stenosis can be non-flow limiting.

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Disclosures/conflict of interest

HK has no disclosures; JL has served as a consultant and holds stock options with HeartFlow; MRP has received grants from HeartFlow, Jansen, Bayer, Astra Zeneca, and NHLBI and served as a consultant for Jansen, Bayer, Astra Zeneca, Genzyme, and Merck; KN has received grants from Siemens, Bayer, GE, and HeartFlow and has personal fees from Siemens; BDB has received grants from Abbott, St Jude Medical, and Medtronic, and other support from St Jude Medical, Boston Scientific, Opsens, Omega Pharma, Siemens, Edwards, GE, Sanofi, HeartFlow, and Bayer; CR receives salary and equity in HeartFlow and is a full-time employee HeartFlow; GP has received grants from GE Healthcare and HeartFlow and personal fees from GE, Bracco, and Medtronic; BLN has received institutional unrestricted research grants from Siemens, Edwards Lifesciences, and HeartFlow; JB has received grants from Boston Scientific,
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References


9. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol.* 2013;61:2233-2241.


**Figure legends**

**Figure 1.**

Title: Distribution of lesion severity of individual coronary vessels according to visual assessment of coronary CTA alone and distribution of FFR\textsubscript{CT} categorized as positive or negative for ischemia according to cutoff value \( \leq 0.80 \) or \( > 0.80 \), respectively

Caption: CTA = computed tomography angiography; FFR\textsubscript{CT} = fractional flow reserve derived by coronary computed tomography angiography.

**Figure 2.**

Title: A representative case with obstructive coronary artery disease on coronary CTA but negative FFR\textsubscript{CT}

Caption: A 61-year-old man with a history of diabetes mellitus presented with atypical chest pain on exertion. Coronary CTA (curved multiplanar reconstructions) showed
75% stenosis (orange arrow) in the proximal LAD and no significant stenosis in the LCX and RCA. However, FFR\textsubscript{CT} value of the LAD system was 0.86, indicating absence of lesion-specific ischemia. FFR\textsubscript{CT} values in the LCX and RCA were 0.97 and 0.96, respectively. Invasive coronary angiography demonstrated 50% stenosis (yellow arrow) in the proximal LAD (C1) and no significant stenosis in the LCX (C1) and RCA (C2). An invasively measured FFR value of the LAD system was 0.91, indicating no ischemia (C1). RCA = right coronary artery; LAD = left anterior descending artery; LCX = left circumflex artery. Other abbreviations as in Figure 1.

**Figure 3.**

Title: A representative case with obstructive coronary artery disease on coronary CTA and positive FFR\textsubscript{CT}

Caption: An 88-year-old man presented with new-onset typical chest pain on exertion. Coronary CTA (curved multiplanar reconstructions) showed 75% stenosis (orange arrow) in the proximal LAD and no significant stenosis in the LCX and RCA. FFR\textsubscript{CT} analysis indicated that the LAD stenosis is ischemia-causing lesion with an FFR\textsubscript{CT} value of 0.61. FFR\textsubscript{CT} values in the LCX and RCA were 0.88 and 0.86, respectively. Invasive coronary angiography demonstrated 75% stenosis (yellow arrow) in the proximal LAD (C1) and no significant stenosis in the LCX (C1) and RCA (C2). Invasive FFR measurement in the LAD system demonstrated a hemodynamically significant stenosis of 0.70. Abbreviations as in Figure 1 and 2.
### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age (years)</td>
<td>66.1±10.4</td>
</tr>
<tr>
<td>Male gender</td>
<td>655 (65.5%)</td>
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<tr>
<td>Height (m)</td>
<td>1.67 ±0.11</td>
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<tr>
<td>Body weight (kg)</td>
<td>72.6±16.6</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>25.8±4.3</td>
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<tr>
<td>Hypertension</td>
<td>599 (59.9%)</td>
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<td>Diabetes mellitus</td>
<td>240 (24.0%)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>531 (53.1%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>187 (18.7%)</td>
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<tr>
<td>Angina status</td>
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<tr>
<td>Typical angina</td>
<td>277 (27.7%)</td>
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<tr>
<td>Atypical angina</td>
<td>382 (38.2%)</td>
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<td>Dyspnea</td>
<td>55 (5.5%)</td>
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<td>64 (6.4%)</td>
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<td>None</td>
<td>206 (20.6%)</td>
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<td>Canadian Cardiovascular Society classification</td>
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<td>Grade I</td>
<td>79 (7.9%)</td>
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<tr>
<td>Grade II</td>
<td>145 (14.5%)</td>
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<tr>
<td>Grade III</td>
<td>37 (3.7%)</td>
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<tr>
<td>Grade IV</td>
<td>8 (0.8%)</td>
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<tr>
<td>Unknown</td>
<td>8 (0.8%)</td>
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**Table 2. Reasons that FFR\textsubscript{CT} analysis was not performed**

<table>
<thead>
<tr>
<th>Reason</th>
<th>n</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>FFR\textsubscript{CT} was not requested because the invasive treatment decision was made due to the stenosis severity</td>
<td>15</td>
<td>1.5%</td>
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<td>Coronary CTA image quality was not acceptable for analysis</td>
<td>33</td>
<td>3.3%</td>
</tr>
<tr>
<td>- Blooming artifacts</td>
<td>8</td>
<td>0.8%</td>
</tr>
<tr>
<td>- Misalignment</td>
<td>3</td>
<td>0.3%</td>
</tr>
<tr>
<td>- Motion</td>
<td>12</td>
<td>1.2%</td>
</tr>
<tr>
<td>- Only systolic imaging and prior PCI</td>
<td>10</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

CTA = computed tomography angiography; FFR\textsubscript{CT} = fractional flow reserve derived by coronary computed tomography angiography; PCI = percutaneous coronary intervention.
Table 3. Univariate regression analysis for predictors of FFR<sub>CT</sub> ≤ 0.8
(per-patient analysis)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.01 - 1.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.74</td>
<td>0.57 - 0.96</td>
<td>0.026</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.00</td>
<td>0.97 - 1.03</td>
<td>0.91</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.01</td>
<td>1.48 - 2.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.93</td>
<td>1.49 - 2.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipideima</td>
<td>1.42</td>
<td>1.10 - 1.82</td>
<td>0.007</td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>Current Smoker vs Never Smoked</td>
<td>1.21</td>
<td>0.85 - 1.71</td>
<td></td>
</tr>
<tr>
<td>Former Smoker vs Never Smoked</td>
<td>1.56</td>
<td>1.17 -2.09</td>
<td></td>
</tr>
<tr>
<td>Angina Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptoms vs Asymptomatic</td>
<td>1.101</td>
<td>1.01 0.81-1.49</td>
<td>p=0.119</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical versus Atypical</td>
<td>3.05</td>
<td>2.20 - 4.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum FFR&lt;sub&gt;CT&lt;/sub&gt; vessel</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAD vs. RCA</td>
<td>2.06</td>
<td>0.79 - 5.37</td>
<td></td>
</tr>
<tr>
<td>LCX vs. RCA</td>
<td>0.73</td>
<td>0.47 - 1.13</td>
<td></td>
</tr>
<tr>
<td>Max coronary CTA stenosis</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30-49% vs. &lt; 30%</td>
<td>1.73</td>
<td>0.95 - 3.14</td>
<td></td>
</tr>
<tr>
<td>&gt; 70% vs. &lt; 30%</td>
<td>14.57</td>
<td>0.22 - 27.28</td>
<td></td>
</tr>
</tbody>
</table>

CTA = coronary computed tomography angiography; CI = confidence interval; FFR<sub>CT</sub> = fractional flow reserve derived by coronary computed tomography angiography; LAD = left anterior descending artery; LCX = left circumflex artery; OR = odds ratio; RCA = right coronary artery.
Table 4. Multivariate regression analysis for predictors of FFR_{CT} ≤ 0.8  
(per-patient analysis)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.52</td>
<td>1.04 - 2.21</td>
<td>0.030</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.56</td>
<td>1.14 - 2.14</td>
<td>0.005</td>
</tr>
<tr>
<td>Minimum FFR_{CT} vessel</td>
<td></td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>LAD vs. RCA</td>
<td>2.13</td>
<td>0.74 - 6.09</td>
<td></td>
</tr>
<tr>
<td>LCX vs. RCA</td>
<td>0.84</td>
<td>0.51 - 1.38</td>
<td></td>
</tr>
<tr>
<td>Max coronary CTA Stenosis</td>
<td></td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>30-49% vs. &lt; 30%</td>
<td>3.74</td>
<td>1.52 - 9.17</td>
<td></td>
</tr>
<tr>
<td>&gt; 70% vs. &lt; 30%</td>
<td>31.16</td>
<td>12.25 - 79.22</td>
<td></td>
</tr>
</tbody>
</table>

CCTA = coronary computed tomography angiography; CI = confidence interval; FFR_{CT} = fractional flow reserve derived by coronary computed tomography angiography; LAD = left anterior descending artery; LCX = left circumflex artery; OR = odds ratio; RCA = right coronary artery.
Figure 1

Coronary CTA stenosis severity (%)

- FFR\textsubscript{CT} ≤ 0.8
- FFR\textsubscript{CT} > 0.8

n = 2,315 vessels

<table>
<thead>
<tr>
<th>Stenosis Severity (%)</th>
<th>Number</th>
<th>FFR\textsubscript{CT} ≤ 0.8</th>
<th>FFR\textsubscript{CT} &gt; 0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-29</td>
<td>630</td>
<td>60 (8.7%)</td>
<td>570 (91.3%)</td>
</tr>
<tr>
<td>30-49</td>
<td>469</td>
<td>123 (20.8%)</td>
<td>346 (79.2%)</td>
</tr>
<tr>
<td>50-70</td>
<td>270</td>
<td>270 (41.4%)</td>
<td>11 (58.6%)</td>
</tr>
<tr>
<td>71-90</td>
<td>219</td>
<td>87 (28.4%)</td>
<td>132 (71.6%)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>70</td>
<td>70 (93.3%)</td>
<td>5 (6.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

Coronary CTA stenosis severity (%)

- 1-29: 630 vessels (91.3%)
- 30-49: 469 vessels (79.2%)
- 50-70: 270 vessels (58.6%)
- 71-90: 219 vessels (28.4%)
- >90: 70 vessels (93.3%)
Figure 2

A: LAD, LCX, RCA

B: RCA FFR<sub>CT</sub>, LCX FFR<sub>CT</sub>, LAD FFR<sub>CT</sub>

C1: LAD FFR 0.91

C2:
Figure 3

A: LAD, LCX, RCA

B: RCA FFR\(_{CT}\) 0.86, LAD FFR\(_{CT}\) 0.86, LCX FFR\(_{CT}\) 0.88

C1: LAD FFR 0.70

C2: