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Permalink
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Publication Date
2015-04-24

DOI
10.1007/s10554-015-0666-2

Peer reviewed
Diagnostic performance of Transluminal Attenuation Gradient and Fractional Flow Reserve by coronary computed tomographic angiography (FFR\textsubscript{CT}) compared to invasive FFR: A sub-group analysis from the DISCOVER-FLOW and DeFACTO studies

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Abstract

**Purpose:** Although coronary computed tomographic angiography (CCTA) has been a robust diagnostic tool to identify anatomical significance of coronary artery disease (CAD), the utility of CCTA to assess hemodynamic significance of CAD remains unclear. We investigated the diagnostic performance of transluminal attenuation gradient (TAG) and fractional flow reserve derived from CCTA (FFR$_{CT}$) to predict lesion-specific ischemia by invasive FFR.

**Methods:** We identified 103 patients with suspected or known CAD enrolled from the DISCOVER-FLOW and DeFACTO studies who underwent invasive coronary angiography with FFR and high quality ≥64-slice CCTA. Diagnostic performance for predicting abnormal invasive FFR (≤0.80) was assessed for TAG (≤-1.1 Hounsfield units/mm by the area under the curve [AUC] by receiver-operating characteristic curve analysis [ROC]), FFR$_{CT}$ (≤0.80), and CCTA stenosis (≥50%).

**Results:** On a per-vessel analysis (n=146), 52 vessels (35.6%) had ischemia by invasive FFR. The sensitivity, specificity, positive predictive value and negative predictive value were 53.8%, 45.7%, 35.4%, 64.2% for TAG, 82.7%, 74.5%, 64.2%, 88.6% for FFR$_{CT}$, 84.6%, 39.4%, 43.6%, 82.2% for CCTA stenosis, respectively. The AUC by ROC curve analysis for FFR$_{CT}$ (0.79) demonstrated greater discrimination of hemodynamic ischemia compared to TAG (0.50, p<0.0001 vs. FFR$_{CT}$), CCTA stenosis (0.62, p=0.0004 vs. FFR$_{CT}$) and the combination of the two (0.63, p=0.004 vs. FFR$_{CT}$). These results remained consistent regardless of the number of CTA slices.

**Conclusion:** FFR$_{CT}$ allows identification of lesion-specific ischemia using invasive FFR as a reference standard with greater diagnostic accuracy than TAG, CCTA stenosis, or the combination of the two.

**Keywords:** Coronary computed tomographic angiography, Fractional flow reserve, Transluminal attenuation gradient, Diagnostic accuracy.
Abbreviations

CCTA  Coronary computed tomographic angiography
CAD  Coronary artery disease
FFR  Fractional flow reserve
TAG  Transluminal attenuation gradient
INTRODUCTION

Assessment of the hemodynamic significance of coronary stenosis has become the basis for guiding the management of patients with stable coronary artery disease (CAD). The recent DEFER and FAME trials demonstrated that functional assessment by invasive fractional flow reserve (FFR) was superior to anatomic assessment of coronary stenosis by invasive coronary angiography (ICA) in identifying patients who would benefit from coronary revascularization. Therefore, the AHA/ACC guideline for percutaneous coronary intervention has recommended using FFR for guiding revascularization decisions as class IIa in patients with stable ischemia heart disease. However, invasive assessment by ICA and invasive FFR may incur higher medical costs and expose patients to greater risks when compared to non-invasive assessments.

Coronary computed tomographic angiography (CCTA) has been widely used as a robust non-invasive diagnostic tool to identify anatomic CAD and to correlate highly with stenoses on ICA; however, coronary stenoses observed on CTA has not correlated as highly with noninvasive methods of functional assessment of ischemia or FFR. Recently, techniques for the non-invasive assessment of lesion-specific ischemia by CCTA have been developed. For example, transluminal attenuation gradient (TAG) and FFR derived from CCTA (FFR$^{CT}$) are both methods that require only a single image without any additional image acquisition, contrast, or radiation exposure. However, the comparative utility of TAG and FFR$^{CT}$ for hemodynamic assessment of coronary stenosis has not been well examined. Thus, we investigated the diagnostic performance of TAG and FFR$^{CT}$ to predict lesion-specific ischemia by invasive FFR.

MATERIALS and METHODS

Study population
We studied patients with suspected or known CAD enrolled from the DISCOVER-FLOW and DeFACTO studies, who underwent ICA with FFR and ≥64 slice coronary CCTA. Out of 355 patients from the DISCOVER-FLOW and DeFACTO studies, we reviewed consecutive 199 patients (93 from DISCOVER-FLOW and 106 from DeFACTO) for recalculating $\text{FFR}_\text{CT}$ using the latest-generation of computational fluid dynamic techniques ($\text{FFR}_\text{CT}$ version 1.4; HeartFlow, Inc. Redwood City, California, USA) in order to compare results for the current study, since the original $\text{FFR}_\text{CT}$ measures were performed using the previous versions for DISCOVER-FLOW ($\text{FFR}_\text{CT}$ version 1.1) and DeFACTO ($\text{FFR}_\text{CT}$ version 1.2). Of those, the following patients were sequentially excluded from this study: insufficient image quality and/or no given nitroglycerin before CCTA for the latest software for modeling $\text{FFR}_\text{CT}$ (n=89) and insufficient image quality for the TAG measurements (n=7). One hundred three patients (n=64 from DISCOVER-FLOW and 39 from DeFACTO) were enrolled in the current study. Patients with bypass grafts, stents, and chronic total occlusions were excluded. This study was approved by the Institutional Review Board at each site.

Invasive coronary angiography image acquisition with fractional flow reserve

ICA was performed in accordance with the American College of Cardiology Guidelines for Coronary Angiography, and subsequently, FFR was performed using a pressure-monitoring guidewire (PressureWire Certus, St. Jude Medical Systems, Uppsala, Sweden; ComboWire, Volcano Corporation, San Diego, California) after administration of nitroglycerin in vessels with <99% stenosis as clinically indicated. Hyperemia was induced by administration of intravenous (140 µg/kg/min) or intracoronary (50 µg) adenosine. A threshold of ≤0.80 was considered as an abnormality by FFR. 

CT Image Acquisition Protocol

All patients underwent ≥64-slice CCTA (Lightspeed VCT, GE Healthcare, Milwaukee, WI; Somatom Sensation and Definition CT, Siemens, Forchheim, Germany; Brilliance 256 and 64, Philips, Surrey, United Kingdom; Aquilion One and 64, Toshiba, Otawara, Japan), including 32 patients (31.1%) for 64 slice, 51 patients (49.5%) for 128 slice, 14 patients (13.6%) for 256 slice, and 6 patients (5.8%) for 320 slice. Patients received oral and/or intravenous beta-blockades to achieve the target heart rate, as well as sublingual nitroglycerin for coronary artery dilatation. In accordance with Society of Cardiovascular Computed Tomography guideline 15, scan parameters were obtained as follows: tube voltage 100 or 120 kVp, ≤0.75 mm slice thickness and 512 x 512 matrix size. Helical or axial scan was obtained with prospective or retrospective electrocardiogram triggering.

Out of 103 patients, 52 patients underwent non-contrast CT for coronary artery calcium (CAC) before CCTA scanning. Scan parameters were obtained as follows: prospective electrocardiogram-triggering, 512×512 matrix size, and peak tube voltage of 120 kVp. Acquired images were transferred to a remote Philips workstation for analysis. All coronary calcium score measurements were performed by a CT core laboratory (Harbor UCLA Medical Center) on a Philips workstation (Intelispace Portal 6.0.1, Philips) to quantify coronary artery calcification using the Agatston method 16.

CCTA image analysis for stenosis severity

CCTAs were assessed using an 18-segment American Heart Association coronary tree model in accordance with Society of Cardiovascular Computed Tomography guidelines 15 by CT core laboratories (CVCTA, San Francisco, California, USA, or Harbor UCLA Medical Center, Torrance, California, USA) in a blinded manner. Coronary plaque was identified as any hyper- or hypodense structure distinct from the lumen and >1mm² in size. CAD stenosis severity was visually classified into 0-49%, 50-69%, and ≥70% luminal stenosis groups. Obstructive CCTA
stenosis was defined as ≥50% stenosis.

**CTA image analysis for TAG**

TAG was measured in a blinded fashion by a CT core laboratory at Harbor UCLA Medical Center (Torrance, California, USA). TAG was calculated as the slope of the linear regression on the lumen intensities in the coronary vessel from the ostium to the most distal location with ≥1.5 mm vessel diameter. The lumen intensities were measured at 0.5 mm intervals and defined as the average intensity inside semi-automatically defined lumen boundaries obtained using quantitative CT software (QAngio CT Research Edition 2.0.5, Medis medical imaging systems b.v., the Netherlands).

**CTA image analysis for FFR<sub>CT</sub>**

FFR<sub>CT</sub> was calculated from CCTA data using the latest-generation of computational fluid dynamic techniques (FFR<sub>CT</sub> v1.4) at HeartFlow, Inc. (Redwood City, California, USA), with blinding to the previous FFR<sub>CT</sub> measurements. The anatomy, physiology and fluid dynamics were analyzed for the calculation of FFR<sub>CT</sub>. Anatomic information was derived from CCTA datasets to build 3D models of the epicardial coronary arteries and myocardium. Coronary physiology was calculated with factors including cardiac output, aortic pressure and microcirculatory resistance. These Anatomical and physiological models were used to compute FFR<sub>CT</sub> with computational fluid dynamics.

All analyses of these CT variables incorporating CCTA stenosis severity, TAG and FFR<sub>CT</sub> were performed independently and with blinding to the invasive FFR measurements.

**Statistical analysis**
Continuous variables are expressed as the mean ± SD. Receiver-operating characteristics (ROC) curve analysis was used to assess the diagnostic performance of CTA stenosis, TAG, the combination of the two, FFR\textsubscript{CT}, and the combined FFR\textsubscript{CT} and CTA stenosis in predicting lesion-specific ischemia by invasive FFR (≤0.80). The area under the ROC curves (AUC) was compared between these variables by regression models. From the ROC analysis of our population, -1.1HU/mm was identified as the optimal cutoff for the prediction of abnormal invasive FFR. In addition, two other thresholds of TAG for abnormality (≤-15.1 Hounsfield Units [HU]/10mm or ≤-0.654 HU/mm) from previous studies were used to assess the diagnostic performance. In a sub-analysis, we also examined the ROC curve of the comparative diagnostic performance of vessels scanned by a lower (64 or 128) or higher (256 or 320) slice CT scanner. The agreement between two observers or the comparison between manual and semi-automated techniques in TAG measurements was accessed by an intraclass correlation coefficient. All statistical calculations were performed using SAS (Version 9.3, SAS Inc., Cary, NC) for Windows.

Inter-observer variability and the comparison between semi-automated vs. manual techniques

We randomly selected 20 cases (29 vessels) for inter-observer variability and the comparison between manual and semi-automated assessments. The experienced readers blindly measured TAG using semi-automated quantitative CT software. On per vessel analysis, high correlation was observed between TAG values independently performed by two observers (Correlation coefficient 0.995, 95% CI 0.94-0.99).

For the assessment of TAG using semi-automated measurements vs. manual techniques, we also blindly and manually measured the luminal contrast attenuations across a
coronary vessel ≥1.5 mm from the ostium to a distal point at 2.5 mm intervals using a Philips workstation (Intelispace Portal 6.0.1, Philips). TAG was derived from the linear regression model calculated by these contrast attenuations between different intervals of 2.5 mm, 5mm and 10mm. TAG measured using semi-automated measurements showed high correlation with that measured by manual techniques at 2.5mm (Correlation coefficient 0.960, 95% CI 0.92-0.98), 5.0mm (Correlation coefficient 0.957, 95% CI 0.91-0.98) or 10mm intervals (Correlation coefficient 0.943, 95% CI 0.88-0.97).

RESULTS

Baseline characteristics of this study are listed in Table 1. Among 103 subjects, 68% were men, and the mean age was 62 years. A majority of patients had hypertension (62%) or dyslipidemia (68%) (Table 1). Median and 75th percentile of CAC was 243 Hounsfield Units [HU] and 562 HU among 52 patients who underwent CAC scanning.

One hundred forty six vessels (Left anterior descending artery; n=91, Left circumflex artery; n=26, and right coronary artery; n=29) were evaluated in this current study, and maximal stenosis severities with 0-49%, 50-69% and 70-99% observed on CCTA were 45 (31%), 54 (37%), and 47 vessels (32%), respectively. Among the 146 vessels, overall, 52 vessels (35.6%) met physiological criteria of invasive FFR ≤0.80. Figure 2 shows frequencies of CCTA stenosis<50% or ≥50%, and normal or abnormal TAGs and FFR_{CT} stratified by FFR≤0.8 or FFR>0.8 in the 146 vessels. The frequencies of false negatives in the vessels assessed by TAGs were approximately 3-fold higher compared to those in the vessels assessed by FFR_{CT} or CCTA stenosis. In addition, the incidence of false positives was less frequent in the vessels assessed by FFR_{CT}, compared to those by CCTA stenosis or TAGs (Figure 2).
**Diagnostic accuracy of CCTA stenosis, TAGs and FFR\textsubscript{CT} compared to invasive FFR**

Figure 3a illustrates per-patient diagnostic accuracy by different CCTA variables. The diagnostic accuracy of FFR\textsubscript{CT} (76.7%) demonstrated the highest performance compared to those of CCTA stenosis and TAGs by three thresholds with high specificity (67.9%). On a per-vessel analysis of 146 vessels, similar results were observed. FFR\textsubscript{CT} also demonstrated higher per-vessel diagnostic performance compared to that of CCTA stenosis or TAGs (Figure 3b).

**Receiver-operating characteristic curve analysis in predicting lesion-specific ischemia**

On a per-patient basis, the AUC by ROC curve analysis for FFR\textsubscript{CT} (0.7696) demonstrated greater performance for prediction of hemodynamic ischemia compared to that of obstructive stenosis (0.5532, p<0.0001 vs. FFR\textsubscript{CT}), TAG with ≤-1.1/mm (0.5208, p=0.0001 vs. FFR\textsubscript{CT}), TAG with ≤-0.654/mm (0.5557, p=0.0006 vs. FFR\textsubscript{CT}), TAG with ≤-15.1/10mm (0.5408, p<0.0001 vs. FFR\textsubscript{CT}), and the combinations of each TAG and CCTA stenosis. The diagnostic performance for identifying ischemia did not differ between CCTA stenosis and TAG with ≤-1.1/mm (p=0.59), TAG with ≤-0.654/mm (p=0.96) or TAG with ≤-15.1/10mm (p=0.71). When compared to CCTA stenosis alone (AUC: 0.5532), any TAG values did not add incremental diagnostic yield to CCTA stenosis (AUC: 0.5679 for ≤-1.1/mm, p=0.68; AUC: 0.5879 for ≤-0.654/mm, p=0.62, AUC: 0.5796 for ≤-15.1/10mm, p=0.90). Of note, CCTA stenosis plus FFR\textsubscript{CT} did not demonstrate incremental diagnostic value compared to FFR\textsubscript{CT} alone (0.7762 vs. 0.7696, p=0.66) (Figure 4a).

The AUC by ROC curve analysis in predicting lesion-specific ischemia by per vessel assessment is displayed in Figure 4b. Similarly, the AUC for FFR\textsubscript{CT} demonstrated significantly greater performance compared to that for other CCTA variables including CCTA stenosis, TAGs or these combinations. Compared to CCTA stenosis alone (AUC: 0.6199), the combination of
TAG and CCTA stenosis did not provide a greater diagnostic value (AUC: 0.6281 for ≤-1.1/mm, p=0.76; AUC: 0.6402 for ≤-0.654/mm, p=0.43, AUC: 0.6428 for ≤-15.1/10mm, p=0.36). AUCs were not different between FFR<sub>CT</sub> and the combination of FFR<sub>CT</sub> and CCTA stenosis (0.7858 vs. 0.8117, p=0.09) (Figure 4b).

**Diagnostic accuracy of CCTA stenosis, TAG and FFR<sub>CT</sub> compared to invasive FFR by higher slice (>64 slice) CTs**

Figures 5 show the diagnostic accuracy of CCTA variables on higher slice (>64 slice) CT scanners (n=105 vessels). FFR<sub>CT</sub> had a higher diagnostic accuracy than CCTA stenosis or TAGs regardless. However, excellent sensitivity and negative predictive value for CCTA stenosis was observed in higher slice CT group.

**DISCUSSIONS**

TAG is a novel method developed to assess the hemodynamic significance of CAD, calculated using a linear regression model of luminal contrast attenuations in a coronary vessel obtained by manual or semi-automated techniques. To date, several studies have examined the relation of TAG to invasive FFR, and results have shown a variety in the diagnostic accuracy of TAG in predicting lesion-specific ischemia by invasive FFR<0.80. Yoon et al. investigated the diagnostic accuracy of TAG and FFR<sub>CT</sub> for identifying lesion-specific ischemia among 53 patients who underwent 64 slice CCTA<sup>9</sup>. In a per-vessel analysis, TAG showed a low sensitivity but a high specificity of 38% and 88%, respectively. In addition, the diagnostic performance of TAG was lower but not statistically different from that of CCTA stenosis alone (AUC: 0.63 vs. 0.73, p=0.217)<sup>9</sup>. Choi also demonstrated similar results showing lower diagnostic performance of TAG than that of CCTA stenosis (AUC: 0.696 vs. 0.726) among 63 patients undergoing 64-
slice CCTA. These findings are in line with our results demonstrating only modest diagnostic performance of TAG.

In contrast with these studies, another study of 54 patients undergoing 320 slice CCTA by Wong et al. demonstrated acceptable diagnostic accuracy for the determination of abnormal invasive FFR in addition to CCTA stenosis (AUC: 0.88, p<0.001). The discordance of the study by Wong et al. and the results of our study as well as Yoon and Choi's study may be explained by variations in contrast along vessels using scanners that require sequential heart cycles for image acquisition that do not occur with the 320 slice CT scanner that covers the whole heart within one heartbeat. For solving the issue in assessing TAG by limited CT slices, Stuijfzand et al. prospectively examined the comparative utility of TAG and TAG with corrected coronary opacification (CCO) (TAG-CCO), which potentially corrects the temporal contrast variations in a coronary artery between scans, among 85 patients undergoing 256 slice CCTA. However, the diagnostic performance of TAG-CCO did not differ from that of CCTA stenosis alone (AUC: 0.88 vs. 0.85). Another potential issue may be that an optimal cut-off of TAG has not yet been established and the range of thresholds of TAG to predict lesion-specific ischemia has varied widely, ranging from -0.654 HU/mm (64 slice) to -15.1HU/10mm (320 slice). Although optimal thresholds for TAG were derived from ROC curve analysis among their limited cohort in these previous studies, the cut-off of TAG including various CT slices derived from ROC curve analysis was -1.1HU/mm in our study, which is in line between these ranges. Even when using the two thresholds for abnormality from previous studies, our study demonstrated that the diagnostic performance of TAGs was similarly modest.

With respect to FFRCT, our findings recalculated by the latest-generation are similar to those previously reported in the main DISCOVER-FLOW and DeFACTO studies. The current generation used in the current study allows more time-saving for each case to create 3-D coronary modeling and computed FFRCT while maintaining high diagnostic accuracy for the
The determination of functional significant CAD compared to previous versions, allowing the use of FFR_{CT} to fit into more clinical settings. The diagnostic accuracy of FFR_{CT} was superior to that of TAG or CCTA stenosis, which is concordant with the aforementioned study by Yoon et al. FFR_{CT} is derived from CCTA data at rest using computational fluid dynamic techniques and is not affected by the number of cardiac cycles needed for acquisition. The optimal cut-off value of FFR_{CT} has generally been more consistent and reliable compared to TAG, as it is similar to that of invasive FFR. Since Yoon et al. examined their study among patients undergoing only 64 slices CT, our study is the first study to explore the comparative feasibility and utility of TAG and FFR_{CT} using multi detector CT platforms with broad Z axis coverage among a much larger population. Our current study expanded the patient cohort and the scanner technology with large detector CT scanners to reflect real world use. By our sub-analysis among patients with higher CT slices, the diagnostic performance of FFR_{CT} was always superior to that of TAG. Another potential explanation for the greater diagnostic accuracy of FFR_{CT} compared to that of TAG and the modest diagnostic performance of TAG may be that FFR_{CT} computation considers numerous variables observed on CCTA, estimating coronary blood flow, and pressure at maximum hyperemia. Meanwhile, TAG assesses only a drop in contrast across a stenotic lesion in the coronary vessel in the rest condition and does not take into account the complex array of variables that are used by FFR_{CT} to model flow reserve from the rest CCTA. Therefore, abnormality by TAG is likely to be associated with severe anatomic stenosis as well as limited coronary flow, and TAG may fail to detect stenosis that limits flow as assessed by invasive FFR during pharmacologic stress but does not reduce resting coronary flow. This underlying mechanism may also explain why the combination of TAG and CCTA stenosis did not provide a greater diagnostic performance over CCTA stenosis alone in the current study and the aforementioned study.
Recently, Wong et al. explored that the diagnostic utility of the hybrid assessment by CCTA stenosis ≥50%, TAG, and computed tomography stress myocardial perfusion imaging in identifying lesion-specific ischemia \(^{21}\). This combined assessment by CCTA may have a potential role in more accurately identifying patients who would benefit from ICA and revascularization, while maintaining a higher sensitivity and specificity compared to CCTA stenosis alone. Of importance, our study demonstrated the diagnostic performance of the combined \(\text{FFR}_{\text{CT}}\) and CCTA stenosis ≥50% was similar compared to that of \(\text{FFR}_{\text{CT}}\) alone. This is certainly true because \(\text{FFR}_{\text{CT}}\) is computed from the complex array of numerous CCTA variables including anatomical model or fluid dynamic model and does not require additional CCTA information, resulting \(\text{FFR}_{\text{CT}}\) can be used as a substitute for invasive FFR and that it can be a novel method in guiding patient care.

**Limitation**

There are several limitations in this current study. Given a small sample size including only 6 patients undergoing 320 slice CT; we could not separately analyze the comparative diagnostic accuracy between TAG and \(\text{FFR}_{\text{CT}}\) among this cohort. In addition, since a semi-automated CT software only calculated TAG in coronary arteries and does not provide TAG-CCO for correcting temporal contrast attenuations, we did not assess the diagnostic utility of TAG-CCO among patients with <320 slice CTs. Recent paper has reported quantitative CCTA stenosis improves the identification of functional significant CAD compared to visual CCTA stenosis\(^{25}\). However, we do not have the data regarding quantitative CCTA stenosis in the current study.

**Conclusion**
The innovative technique of FFR$_{CT}$ based on computational fluid dynamics allows for better predictions of lesion-specific ischemia by invasive FFR. In addition, its diagnostic accuracy is greater than TAG, CCTA obstructive stenosis, or these two in combination. The diagnostic performance of TAG is modest and limited in assessing hemodynamic ischemia.

**Acknowledgements**

Dr. Matthew Budoff is a consultant for General Electric. Dr. James K. Min has served on the medical advisory boards of GE Healthcare, Arineta, Astra Zeneca, and Bristol-Myers Squibb; Speakers’ Bureau of GE Healthcare; and received research support from GE Healthcare, Vital Images, and Phillips Healthcare. Dr. Min serves as a consultant to Astra Zeneca and HeartFlow.; the other authors have no conflict of interest. This study is funded in part by HeartFlow Inc. The authors thank Vivek Bhatia, Souma Sengputa, Michael Fahmy, Jeby Abraham, Lucas Cespedes, and Christopher Dailing for contributions to this study.
References


17. Taylor CA, Fonte TA and Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol.* 2013;61:2233-41.


22. Choi JH, Koo BK, Yoon YE, Min JK, Song YB, Hahn JY, Choi SH, Gwon HC and Choe YH. Diagnostic performance of intracoronary gradient-based methods by coronary computed tomography angiography for the evaluation of physiologically significant coronary artery


Figure legends

Figure 1. Study patient with lesion-specific ischemia by invasive FFR.
Invasive FFR demonstrated lesion-specific ischemia with a value of 0.76 in left anterior descending artery (a). FFR\textsubscript{CT} was highly correlated with invasive FFR (FFR\textsubscript{CT} = 0.72) (b). With respect to TAG, a value showed -1.0/mm, indicating no ischemia when using -1.1/mm as a cut-off (c) and CCTA also showed non-obstructive coronary artery disease with <50% stenosis in left anterior descending artery (d).
Abbreviations: FFR- fractional flow reserve, TAG- transluminal attenuation gradient, CCTA- coronary computed tomographic angiography

Figure 2. Frequencies of FFR\textsubscript{CT} ≤ 0.8 or FFR > 0.8, CCTA stenosis < 50% or ≥ 50%, and normal or abnormal TAGs and stratified by FFR ≤ 0.8 or FFR > 0.8 in 146 vessels. False or true negative was defined if the vessel with FFR\textsubscript{CT} > 0.80, CCTA stenosis < 50%, TAG > -1.1/mm, TAG > -0.6254/mm or TAG > -15.1/10mm had evidence of invasive FFR ≤ 0.80 or > 0.8. False or true positive was defined when the vessel with FFR\textsubscript{CT} ≤ 0.80, CCTA stenosis ≥ 50%, TAG ≤ -1.1/mm, TAG ≤ -0.6254/mm or TAG ≤ -15.1/10mm showed invasive FFR > 0.80 or ≤ 0.80.
Abbreviations as Figure 1.

Figure 3a. Per patient analysis for diagnostic accuracy of CCTA stenosis, TAGs using three thresholds, and FFR\textsubscript{CT} in 103 patients

Figure 3b. Per-vessel analysis for diagnostic accuracy of CCTA stenosis, TAG using three thresholds, and FFR\textsubscript{CT} in the 146 vessels
Abbreviations as Figure 1.

Figure 4a. AUCs by receiver-operating characteristic curve analysis to predict lesion-specific ischemia by invasive FFR in 103 patients

Figure 4b. AUCs by receiver-operating characteristic curve analysis to predict lesion-specific ischemia by invasive FFR in the 146 vessels
Abbreviations: AUC- area under the curve, ROC- receiver-operating characteristic curve, FFR- fractional flow reserve, CCTA- coronary computed tomographic angiography, TAG- transluminal attenuation gradient

Figure 5. Diagnostic accuracy of CTA stenosis, TAG using three thresholds, and $\text{FFR}_{CT}$ by >64 slice CT in the 105 vessels

Abbreviations as Figure 1.