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CT-FFR to Guide Coronary Angiography and Intervention

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INTRODUCTION

More than a decade ago, the Fractional Flow Reserve versus Angiography for Guiding Percutaneous Intervention (FAME) trial led to a paradigm shift toward using the functional significance of a coronary lesion, as assessed by fractional flow reserve (FFR), rather than the anatomic severity of a coronary stenosis, to drive decision making regarding coronary revascularization. This multicenter trial, which randomized 1005 patients to angiographically guided percutaneous intervention (PCI) versus FFR-guided PCI (threshold FFR <0.8), demonstrated a 72% relative risk reduction of the composite endpoint of death, myocardial infarction, and repeat vascularization at 1 year of followup.¹ In FAME, only 35% of stenosis in the 50% to 70% range were functionally significant by FFR, demonstrating the discordance between hemodynamic significance and visual assessment of lesion severity.² The results after 2 and 5 years of follow-up confirmed long-term efficacy of an FFR-guided strategy.^{3,4} The FAME 2 trial, which sought to assess the efficacy of medical therapy and stenting FFR-positive lesions versus opposed to medical therapy alone, was stopped prematurely because of a significant difference (4.3% in PCI group vs 12.2% in medical-therapy group, $P<.001$) in the primary endpoints between the 2 groups.⁵ FFR currently has a class I recommendation in the 2014 Stable Ischemic Heart Disease guidelines and a score of “appropriate” in the 2017 appropriate use criteria for either PCI or coronary artery bypass grafting in patients with symptomatic physiologically significant stenosis (FFR <0.80).^{6,7}

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The necessity of improved methods for noninvasive evaluation of coronary artery disease (CAD) was highlighted in a retrospective study of the National Cardiovascular Data Registry, which demonstrated that only 37.6% of the 398,987 patients without known CAD who underwent coronary angiography had obstructive CAD, and having a positive noninvasive test only increased the rate of obstructive disease from 35% to 41%.⁸ Over the past 2 decades, coronary computed tomography angiography (CTA) has emerged as a noninvasive methodology for evaluating the coronary arteries with a very high negative predictive value (NPV), and a moderate positive predictive value (PPV) as compared with invasive coronary angiography (ICA) and FFR.^{9,10} Furthermore, CTA provides vessel-specific anatomic information, as opposed to other noninvasive modalities used to detect obstructive CAD.¹¹ Despite the strengths of CTA, the degree of stenosis identified using this modality does not necessarily correlate with the functional significance of the lesion as defined by invasive FFR. In some studies, lesions that were considered severe on CTA have been found to be hemodynamically significant in less than 50% of cases.⁹ The moderate PPV for CTA has remained a challenge and had led to multiple efforts to augment the anatomic information provided by CTA. Although computed tomography perfusion imaging has shown the potential to improve the PPV, this approach significantly complicates image acquisition and lengthens the time a patient would need to be on the CT scanner, while increasing contrast dose and radiation exposure for the patient. Coronary computed tomography fractional flow reserve (CT-FFR) has emerged as a disruptive technology that offers insight into the hemodynamic consequence of a specific anatomic coronary lesion. The CT-FFR technique uses the CTA images and computational fluid dynamic (CFD) techniques to estimate virtual FFR values throughout the coronary tree (Fig. 1).¹² Several multicenter trials have demonstrated that CT-FFR has a significantly higher predictive value for functionally obstructive lesions as defined by invasive FFR, and the technique is poised to become a potential gate-keeper to the catheterization laboratory. This article reviews the hemodynamic concepts and methodology for performing FFR and CT-FFR and reviews the diagnostic and prognostic information from CT-FFR that can be used to guide coronary interventions.

INVASIVE ASSESSMENT OF FRACTIONAL FLOW RESERVE

In 1974, Gould and colleagues¹³ performed a landmark canine study using Technetium-99, a gamma camera, and sodium diatrizoate as a hyperemic agent, demonstrating that although resting perfusion was normal in the setting of a left circumflex (LCX) coronary artery occlusion, perfusion in the LCX territory in the presence of maximal hyperemia was significantly reduced.¹⁴ Therefore, vasodilator stress testing led to the subsequent proliferation of myocardial perfusion imaging to noninvasively assess for obstructive CAD. In 1984, White and colleagues¹⁵ used an intracoronary Doppler flow wire to invasively measure coronary flow reserve (CFR) to determine the functional severity of lesions within a given coronary artery; the investigators demonstrated that visual assessment resulted in the significant overestimation of lesion severity. In the early 1990s, studies^{16–18} revealed that relative CFR, which has become known as FFR, correlated with significant epicardial stenosis and was less impacted by other physiologic factors, such as heart rate and blood pressure, compared with CFR.

FFR is defined as the ratio of the flow through a coronary stenosis (Q_s) to the flow in the coronary artery in the absence of a coronary stenosis (Q_n). By applying Poiseuille's law, the fluid dynamic equivalent of Ohm's law, the laminar blood flow within a vessel (Q) can be equated to the driving pressure (DP) divided by the resistance (R). Under the assumption of minimal contribution of collateral flow, and assuming that in the setting of maximal hyperemia the venous pressure (P_v) is much lower than the pressure distal to the stenosis (P_d) and the arterial pressure (P_a) upstream of the stenosis, the expression for FFR is equivalent to the ratio of P_d to P_a , or:

$$FFR = \frac{Q_s}{Q_n} = \frac{P_d}{P_a} \quad (1)$$

The development of catheters with highly accurate pressure transducers has made it possible to simultaneously measure P_a and P_d in a state of hyperemia with a high degree of fidelity (Fig. 2). This approach of using the ratio of P_d to P_a in a state of hyperemia to calculate FFR was initially validated in a cohort of 45 consecutive patients with moderate coronary stenosis and chest pain who underwent concomitant stress testing.¹⁹ Reversible myocardial ischemia, as defined by the combination of noninvasive stress tests, was identified in all 21 patients with an FFR less than 0.75, resulting in a sensitivity of 88%, a specificity of 100%, and an accuracy of 93% for FFR.¹⁹ Furthermore, a meta-analysis correlating invasive FFR to noninvasive imaging showed a sensitivity and specificity of 76%.²⁰ Reproducibility of invasive FFR is also excellent with standard deviation of 0.018 and coefficient of variation of 2.5%.²¹ FFR is a viable measure of significant epicardial stenosis and a possible application in certain clinical settings.^{22,23}

COMPUTED TOMOGRAPHY FRACTIONAL FLOW RESERVE

In the setting of stable ischemic heart disease, guidelines recommend the use of noninvasive functional imaging before ICA or invasive assessment of FFR to determine the functional significance of a coronary stenosis. Although coronary CTA provides an excellent visual assessment of a stenotic lesion by its anatomic nature, it has limited specificity for predicting the hemodynamic significance of coronary stenosis as defined by invasive FFR.

To overcome this limitation, CT-FFR was developed by Taylor and colleagues¹² using the conceptual framework of FFR and advanced computational modeling. This technique enables an approximation of FFR from standard coronary CTA images without additional imaging or medications. CTA FFR requires the creation of an anatomic model of the coronary vasculature, a mathematical model of coronary physiology, and a computational model of the fluid dynamics (Fig. 3). A patient-specific anatomic model of the aortic root and epicardial coronary arteries is generated from the CTA data using semiautomatic coronary segmentation algorithms. As resting coronary blood flow is proportional to the left ventricular mass downstream of the vessel of interest, resting coronary blood flow can be estimated using allometric scaling laws and an assessment of myocardial mass derived from coronary CTA data. Cardiac output is similarly computed using allometric scaling laws and a patient's mean aortic pressure, which is estimated from a patient's measured mean brachial

pressure. The Navier-Stokes equations, which describe the flow of viscous fluids, are solved numerically using CFD techniques that use anatomic data and boundary conditions, representing cardiac output, aortic pressure, and microcirculatory resistance. Maximal hyperemia is simulated by reducing the peripheral resistance by a factor of 0.24, approximating the effect of 140 mg/kg/min of adenosine typically used for pharmacologic stress testing. From this simulation of blood flow under hyperemic conditions, FFR can be determined by solving for the velocity and pressure distribution within the coronary vessel and proximal aorta. The ratio of computed pressure distal to the lesion of interest in the specific coronary vessel and pressure in the aorta under hyperemic conditions is then used as a surrogate of the invasively derived FFR.¹² Currently, HeartFlow (Redwood City, CA, USA) has the only US Food and Drug Administration approved process for the clinical determination of CT-FFR. The process involves uploading the CTA data to HeartFlow's servers, where the segmentation is performed and CFD are computed; then the coronary tree showing the distribution of CT-FFR throughout the tree is sent back to the provider. Currently, the turnaround time is less than 14 hours in most cases, and the company is aiming for a 1-hour turnaround time in the future.

Because of the high computational demand of CFD, machine-learning approaches are being developed as an alternative approach with the potential for "on-site" rapid evaluation of CT-FFR. In developing this neural-network model, blood flow computations derived from CFDs are simulated in 12,000 unique, realistic, synthetically generated coronary anatomies.²⁴ These data are then used to train a deep learning framework that calculates machine learning based coronary fractional flow reserve (cFFR_{ML}). Once the model is trained, cFFR_{ML} can be determined at each segment of the coronary anatomy. Furthermore, this can be accomplished in seconds instead of hours because it only involves applying the machine learning network to the data, rather than complex, time-consuming computations.²⁴

To validate the machine-learning approach, trained models were compared with CFD in a study of 87 patients, 125 lesions in total.²⁴ The correlation between these 2 approaches was 0.9994 ($P<.001$).²⁴ In this same study, the machine-learning approach was compared with invasive FFR, and a total of 38 of the 125 lesions were found to have a hemodynamically significant lesion using the invasive method, defined as an FFR ≤ 0.80 . With this as the gold standard, machine-learning-based FFR had a sensitivity of 81%, a specificity of 84%, and an accuracy of 83%. The correlation was relatively strong as well, at 0.729 ($P<.001$).²⁴

DIAGNOSTIC PERFORMANCE OF COMPUTED TOMOGRAPHY-FRACTIONAL FLOW RESERVE

As described above, there are 2 primary approaches to CT-FFR that have been evaluated clinically. The commercial product developed by HeartFlow has been used in most clinical validation studies, with a smaller number of studies using cFFR_{ML}, which is currently used in research and not clinically available.

The DISCOVER-FLOW trial was a prospective multicenter study of 103 patients with suspected or known CAD undergoing CTA, ICA, and invasive FFR.²⁵ Per imaged vessel, the accuracy, sensitivity, and specificity were 58.5%, 91.4%, and 39.6%, respectively, for CTA

versus 84.3%, 87.9%, and 82.2%, respectively, for CT-FFR.²⁵ There was a significant improvement in specificity and accuracy with the use of CT-FFR over CTA alone (Fig. 4). The DeFACTO trial was a prospective multicenter study of 252 stable patients with known or suspected CAD. Patients underwent CTA, CT-FFR, ICA, and invasive FFR.²⁶ On a per patient basis, the sensitivity, specificity, and accuracy were 84%, 42%, and 64%, respectively, for coronary CTA and were 90%, 54%, and 73%, respectively, for CT-FFR.²⁶ In this study, roughly 11% of cases had insufficient image quality for assessment of CT-FFR.²⁷ Like DISCOVERFLOW, DeFACTO showed an improvement in specificity of CT-FFR compared with CTA alone; in addition, it also showed evidence of improved discriminatory power with an area under the curve (AUC) of 0.81 for CT-FFR compared with 0.61 for CTA alone ($P < .001$).²⁶ However, this study did not meet its primary endpoint of improved accuracy compared with coronary CTA. The NXT trial was a prospective multicenter study of 254 patients scheduled to undergo coronary angiography.¹¹ NXT used an improved CT-FFR algorithm and had more stringent CTA imaging protocols. On a per-patient basis, the sensitivity, specificity, and accuracy of CTA was 94%, 34%, and 53%, respectively, and was 88%, 79%, and 81%, respectively, for CT-FFR.¹¹

Several meta-analyses of the performance of CT-FFR have been performed. Gonzalez and colleagues¹⁰ pooled data from 18 studies that compared either CTA or CT-FFR to invasive FFR. Although the pooled sensitivities of CT-FFR and CTA were comparable, CT-FFR had a higher per-patient specificity of 77% as compared with that of CT, which had a specificity of only 43% (Fig. 5). A recent meta-analysis by Cook and colleagues²⁸ pooled data from 5 studies that compared CT-FFR to invasive FFR (cutoff 0.8) and found an overall accuracy of CT-FFR of 82% at a CT-FFR cutoff of 0.8. For lesions with a CT-FFR greater than 0.9, there was a 97.8% chance that the invasive FFR was greater than 0.8, indicating the absence of ischemia, whereas for lesions with a CT-FFR less than 0.6, there was 87.5% certainty that the invasive FFR was less than 0.8, indicating ischemia. However, in the CT-FFR range of 0.6 to 0.9, near the critical invasive FFR cut point of 0.8, the agreement was significantly poorer.

Several studies have assessed the diagnostic accuracy of “on-site” CT-FFR_{ML}. Yang and colleagues²⁹ analyzed 72 patients with invasive FFR from a prospective stress CT myocardial perfusion registry. CT-FFR values were determined from the rest phase of the CT perfusion studies and demonstrated sensitivities and specificities of 87% and 77% for CT-FFR_{ML}, respectively, as compared with 94% and 66% for CTA alone.²⁹ There was also a significantly higher AUC (0.913 for CT-FFR vs 0.856 for CTA, $P = 0.004$).²⁹ In a separate study comparing “onsite” evaluation of CT-FFR_{ML} and CT perfusion on 74 patients, there was a significant improvement in specificity and accuracy of 60% versus 49% and 70% versus 63%, respectively, when comparing CT-FFR versus CTA alone.³⁰ A recently published meta-analysis pooled data from 8 total studies, including the “on-site” studies previously discussed, showed a pooled sensitivity and specificity of 93% and 82%, respectively.²⁷ Diagnostic accuracy was near 90% if the CT-FFR range was restricted to less than 0.74 because it has been shown that intermediate stenosis and calcifications can limit diagnostic accuracy.²⁷

USING COMPUTED TOMOGRAPHY FRACTIONAL FLOW RESERVE TO GUIDE CLINICAL MANAGEMENT

Several recent studies have looked at whether the addition of CT-FFR to traditional risk stratification pathways impacts clinical management. In 2015, the PLATFORM trial was the first to study clinical outcomes with the use of CT-FFR compared with “usual care.”³¹ The study enrolled 584 symptomatic patients without known CAD with a planned noninvasive evaluation or planned ICA. In the planned noninvasive test group, patients were randomized to their standard noninvasive test versus CTA with CT-FFR. In the planned invasive group, patients were randomized to ICA versus CTA with CT-FFR.³¹ In patients referred for noninvasive testing, there was no difference between “usual care” and CT-FFR-guided therapy in clinical events at 3 months. However, for patients initially referred for ICA, there were significantly lower rates of nonobstructive CAD in the CT-FFR group.³¹ Cost analysis data from PLATFORM showed a 32% reduction in mean costs in the FFR-CT group compared with the “usual care” group for the planned invasive patients.³² Costs were not different between CT-FFR and “usual care” in the noninvasive group; however, a clear benefit in quality-of-life scores was seen in this group.³²

The PROMISE trial was an observational cohort study of stable chest pain patients randomized to an anatomic (CTA) versus functional analysis that demonstrated similar outcomes for either evaluation strategy. In a post hoc analysis, CT-FFR was performed in patients in the CTA arm who underwent ICA within 90 days.³³ As the CT-FFR was performed after the completion of the trial, the impact on coronary evaluation and treatment could not be directly assessed. Interestingly, a CT-FFR of less than 0.81 was a better predictor of revascularization and major adverse cardiac events (MACE) compared with severe CTA stenosis (hazard ratio of 4.3 vs 2.9; $P = 0.033$).³³ The investigators concluded that the use of CT-FFR and an FFR less than 0.81 could decrease the need for ICA by 44%.³³ The CT-FFR RIPCORD Study asked the question, “Does routine availability of CT-derived FFR influence management of the patient with stable chest pain compared with CTA alone?”³⁴ The study enrolled 200 stable chest pain patients who underwent CTA and CT-FFR. Clinical management was made by consensus from 3 experienced interventional cardiologists based on CTA results alone. Then, CT-FFR results were revealed, and another plan was determined by the same interventional cardiologists. A change in clinical management occurred in 72 cases or 36%.³⁴ The main factor driving the change in management was a CT-FFR calculated as greater than 0.8 in 13 of 44 vessels (29.5%) that were graded as greater than 90% by CTA alone.³⁴ In Denmark, a real world evaluation of CT-FFR was performed at Aarhus University. The investigators reviewed the complete diagnostic workup of 1248 nonemergent patients referred for coronary CTA.³⁵ CT-FFR was performed on 189 patients, and 31% were found to have a CT-FFR of ≤ 0.80 .³⁵ Of those patients, 29% were referred for ICA, and invasive FFR was measured in 19% with another 1% having instantaneous free wave ratio (iFR) performed.³⁵ CT-FFR of ≤ 0.80 correctly identified 73% of patient with an invasive FFR ≤ 0.8 or iFR ≤ 0.9 .³⁵ The accuracy of detecting an abnormal invasive FFR was only 50% for CT-FFR in the range of 0.76 to 0.8, whereas it was 75% in the range of 0.71 to 0.75, and 100% for CT-FFR less than 0.7. Therefore, a lower cutoff for CT-FFR such as less than 0.75 may have greater accuracy with

respect to invasive FFR. Of note, there were no adverse cardiac events seen in patients who had a calculated CT-FFR greater than 0.80.³⁵

In summary, several studies now suggest that CT-FFR could lead to the reduction of unnecessary ICA in patients who are likely to have nonobstructive CAD.^{31,32,34} Despite ICA having a low risk of major adverse events, the risks of bleeding, contrast, radiation, and major vascular injury do exist, and it would be best to prevent unneeded ICA if possible. Per the PLATFORM study, there may also be a cost savings to a CT-FFR strategy, particularly in patients with stable chest pain referred for an invasive strategy, along with improvement in the patient's perception of chest pain in the noninvasive strategy arm.³²

LIMITATIONS OF COMPUTED TOMOGRAPHY-FRACTIONAL FLOW RESERVE

Based on current studies, CT-FFR has primarily been validated against FFR in relatively low-risk patients. Thus, the understanding of the performance of CT-FFR in intermediate-risk patients remains limited.²⁸ In addition, there are some limitations to the technology itself. First, it is based on a proprietary algorithm, and access to the technology is currently limited. However, adoption of payment for CT-FFR by payers will likely broaden the clinical availability of CT-FFR. In addition, image quality is of particular importance.²⁶ In trials including DISCOVERFLOW, NXT, and DeFACTO, CTA data required an independent review from HeartFlow to determine suitability of CT-FFR analysis. In these studies, the number of rejected datasets ranged from 11% to 13%.^{11,25,27} In the PROMISE analysis, 33% of studies sent to the core laboratory were rejected as inadequate for CT-FFR analysis. This population only included patients that underwent ICA in the PROMISE trial, and thus, the cases referred to ICA may have had poorer CTA quality. In a single-center review in a highly experienced center, 10% to 15% of cases that were referred for CT-FFR were rejected because of inadequate image quality.³⁵ Because the boundary conditions for the CFD are derived from the coronary anatomy from CTA, issues such as significant coronary calcifications could limit the quality of the anatomic models.³⁶ One study, however, has demonstrated similar performance of CT-FFR in the presence or absence of coronary calcifications.³⁷ Currently, CT-FFR cannot assess lesions with myocardial stents or bypass grafts.

FUTURE APPLICATIONS AND POTENTIAL FOR COMPUTED TOMOGRAPHY FRACTIONAL FLOW RESERVE

Although CT-FFR is becoming a mature technology, it remains an active area of technical and clinical research. There is significant interest in using machine-learning techniques to improve analysis times, which could broaden the clinical applicability, particularly in the setting of acute chest pain.^{38,39} Several studies are looking at the role of CT-FFR in evaluation of acute chest pain in the emergency room, where CTA has been shown to reduce evaluation time and unnecessary hospitalizations.⁴⁰

CT-FFR may also be useful for planning of complex interventions where “virtual stenting” can be used to predict the hemodynamic effect of coronary stenting.⁴¹ A study of 44 prospectively enrolled patients showed that the diagnostic accuracy of CT-FFR measurement after virtual stenting as compared with invasive FFR following actual stenting was 96%.⁴² There could also be a benefit in the assessment of serial stenosis, which can be a challenge with invasive FFR.⁴³ The clinical impact of virtual stenting has yet to be evaluated. Currently, CT-FFR cannot be performed in coronary artery vein grafts. Further studies are needed to assess the impact of collateralization on noninvasively measured CT-FFR, in addition to assess whether CT-FFR can play a role in vein grafts.

The combination of CT-FFR and CT perfusion has shown promise for further improving the accuracy of CTA in the evaluation of stable chest pain.³⁰ Several ongoing clinical trials, such as [NCT02208388](#), are actively enrolling patients to assess whether the combination of CT perfusion and CT-FFR will be useful to guide therapy. Currently, the clinical impact of the combination of CT perfusion and CT-FFR is unknown.

SUMMARY

Although CTA has high sensitivity and NPV for excluding functionally significant CAD as defined by invasive FFR, its moderate specificity and PPV have remained a significant limitation. CT-FFR can significantly improve the specificity and PPV of CTA, potentially broadening the clinical utility of a coronary CTA evaluation strategy. There is growing evidence demonstrating improvement in important outcomes, such as reducing the need for invasive procedures, improving quality of life, and reducing health care costs. The application of deep learning to CT-FFR analysis has the potential to reduce computational times leading to broader applicability of CT-FFR. CT-FFR has demonstrated significant promise as a noninvasive technique to evaluate the functional severity of coronary stenosis, which has the potential for significant cost savings by serving as a gate-keeper for ICA.

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Keypoints:

- Computed tomography (CT) fractional flow reserve (CT-FFR) uses coronary computed tomography angiography (CTA) images and computational fluid dynamics (CFD) to noninvasively simulate invasive FFR assessment.
- CT-FFR has higher specificity and positive predictive value as compared with visual analysis of coronary CTA stenosis using invasive FFR as the gold standard.
- In patients with a planned invasive coronary angiography, a strategy using CT-FFR as a gatekeeper to angiography is associated with a cost savings.
- In patients with a planned noninvasive assessment, CT-FFR is cost neutral and is associated with improvement in angina scores.
- Because of the high computational demand of CFD, machine-learning approaches are being developed as an alternative approach with the potential rapid evaluation of CT-FFR.

Synopsis:

Computed tomography angiography (CTA) has played a significant role in evaluation of coronary artery disease in the last decade and has demonstrated high sensitivity and negative predictive values. However the positive predictive value as compared to invasive fractional flow reserve (FFR) is limited. CT-FFR has emerged as a disruptive non-invasive technology with higher specificity and diagnostic accuracy for detection of hemodynamically significant coronary lesions as compared to invasive FFR then conventional coronary CTA. CT-FFR has been shown to be cost effective as a gate-keeper to invasive coronary angiography and has the potential to limit unnecessary invasive angiography studies.

Figure 1. (Left) FFR-CT performed using HeartFlow shows hemodynamically significant lesions in the identified arteries. (Right) CT images show greater than 70% lesions (arrow) in both left anterior descending (LAD) and LCx arteries.

Figure 2.

An example of invasive FFR with use of adenosine in a patient with angiographically intermediate lesion but hemodynamically significant by fractional flow reserve.

Figure 3.

(A) Coronary computed tomography angiography data are used to generate a (B) 3-dimensional (3D) anatomic model. (C) Patient-specific physiologic model of microcirculation is created. (D) CFD is used to compute coronary blood flow. (E) CT-FFR is calculated at each location in the coronary tree. (Adapted from Nørgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial. *J Am Coll Cardiol* 2014;63(12):1148; with permission.)

Figure 4.

(A) Correlation between CT-FFR and FFR from DISCOVER-FLOW Trial, $r=0.72$. (B) Bland-Altman Plot showing slight underestimation of CT-FFR and observed FFR. (From Koo BK, Erglis A, Doh Jh, et al. Diagnosis of Ischemia-Causing Coronary Stenoses by Noninvasive Fractional Flow Reserve Computed From Coronary Computed Tomographic Angiograms. *J Am Coll Cardiol* 2011; 58: 1989–97; Figure 4 and Figure 5; with permission)

Figure 5.

Meta-analysis showing significant improvement in specificity with per patient CT-FFR. CI, confidence interval; df, degrees of freedom. (Adapted from Gonzalez JA, Lipinski MJ, Flors L, et al. Meta-analysis of diagnostic performance of coronary computed tomography angiography, computed tomography perfusion, and computed tomography-fractional flow reserve in functional myocardial ischemia assessment versus invasive fractional flow reserve. *Am J Cardiol* 2015;116(9):1472; with permission.)