Journal of the Society for Cardiovascular Angiography & Interventions 3 (2024) 101304

JSCAI

The official journal of the Society for Cardiovascular Angiography & Interventions

Comprehensive Review

Noninvasive Coronary Physiological Assessment Derived From Computed Tomography

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ABSTRACT

Identifying functional significance using physiological indexes is a standard approach in decision-making for treatment strategies in patients with coronary artery disease. Recently, coronary computed tomography angiography-based physiological assessments, such as computed tomography perfusion and fractional flow reserve derived from coronary computed tomography angiography (FFR-CT), have emerged. These methods have provided incremental diagnostic values for ischemia-causing lesions over anatomical stenosis defined solely by coronary computed tomography angiography. Clinical data have demonstrated their prognostic value in the prediction of adverse cardiovascular events. Several randomized controlled studies have shown that clinical use of FFR-CT can reduce unnecessary invasive procedures compared to usual care. Recent studies have also expanded the role of FFR-CT in defining target lesions for revascularization by acquiring noninvasive lesion-specific hemodynamic indexes like ΔFFR-CT. This review encompasses the current evidence of the diagnostic and prognostic performance of computed tomography-based physiological assessment in defining ischemia-causing lesions and adverse cardiac events, its clinical impact on treatment decision-making, and implications for revascularization.

Introduction

The physiological indexes, such as fractional flow reserve (FFR) or nonhyperemic pressure ratio, are currently used to determine the functional significance of coronary lesions and guide treatment decision-making in the catheterization laboratory.[1,2] Meanwhile, coronary computed tomography angiography (CCTA) has emerged as a primary noninvasive modality with its high-negative predictive value (NPV) for the presence of anatomical stenosis.[3] With technological advancement, noninvasive physiological assessments have currently become feasible using CCTA. It has expanded the scope of physiological assessment, enabling physicians to define myocardial ischemia, stratify risk for clinical outcomes, and select target lesions for revascularization before referring patients to the catheterization laboratory.[4] Therefore, understanding the clinical and prognostic implications of CCTA-based physiological assessment and its application in clinical practice is crucial for the improved management of patients with coronary artery disease (CAD). In this review, we aimed to explore the clinical implications of noninvasive physiological assessments on CCTA in identifying functional significance and predicting clinical outcomes and its impact on treatment decision-making and percutaneous coronary intervention (PCI) strategy from an interventionist's perspective (Central Illustration).

Physiological assessment of CAD

Role of coronary physiology in the catheterization laboratory

In patients with stable CAD, the presence of myocardial ischemia, which is an impaired coronary blood flow relative to myocardial oxygen demand, serves as a significant prognostic determinant and a surrogate of benefits from revascularization.[5,6] Anatomical stenosis measurement on invasive coronary angiography (ICA) is the gold standard method for evaluating the severity of CAD, with >70% stenosis indicating a reduction in hyperemic flow.[7] However, the limitations of angiographic luminal narrowing to detect ischemia-causing lesions have also been well-acknowledged, as mismatches between anatomical and physiological severities occur in approximately 30%-40% of cases.[8] In the catheterization laboratory, the functional significance of coronary

Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CTP, computed tomography perfusion; FFR, fractional flow reserve; FFR-CT, fractional flow reserve derived from coronary computed tomography angiography; ICA, invasive coronary angiography; MACE, major adverse cardiac events; MBF, myocardial blood flow; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Keywords: coronary computed tomography angiography; coronary physiology; fractional flow reserve; myocardial ischemia; myocardial perfusion.

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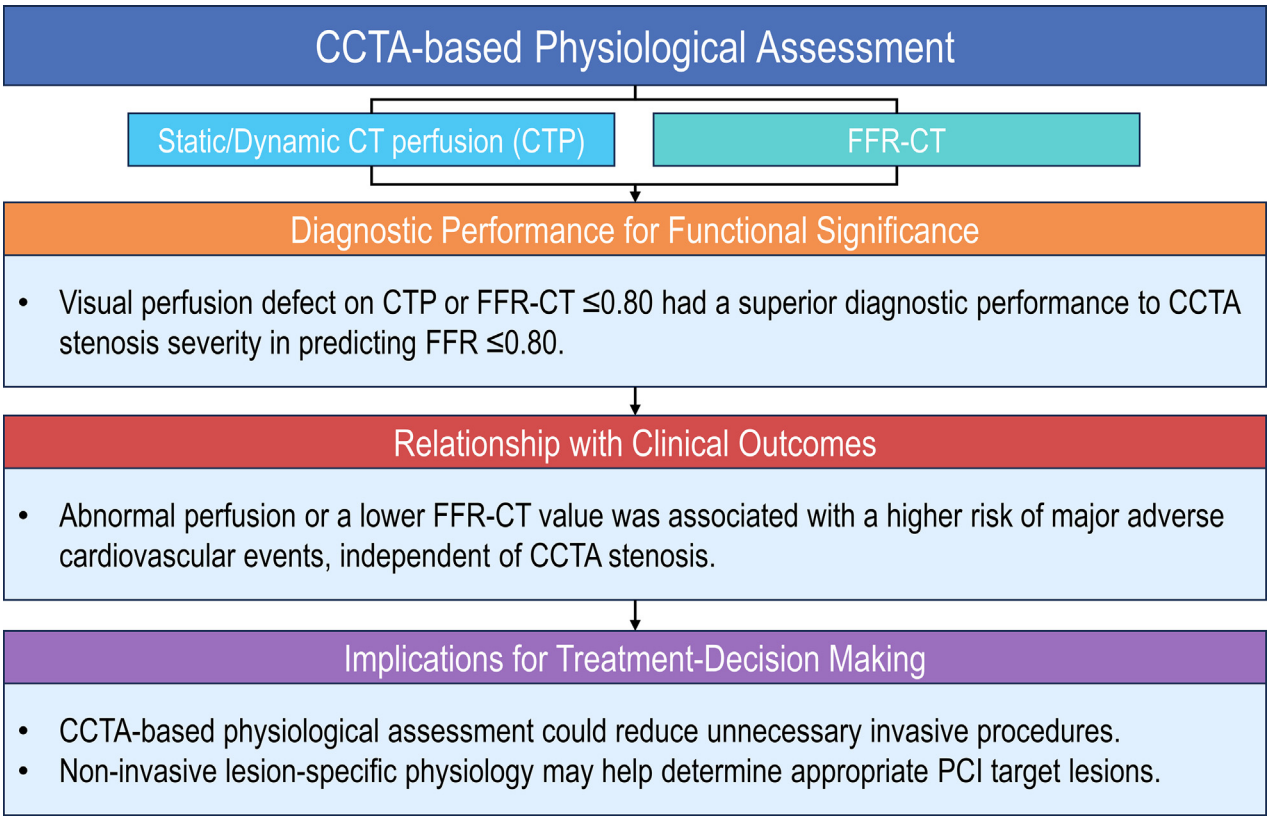
https://doi.org/10.1016/j.jscai.2024.101304
Received 4 December 2023; Received in revised form 8 January 2024; Accepted 10 January 2024
Available online 26 March 2024



Central Illustration.
Clinical implications of coronary computed tomography angiography (CCTA)-based physiological assessment. CCTA-based physiological assessments, including computed tomography perfusion (CTP) and fractional flow reserve derived from coronary computed tomography angiography (FFR-CT), offer enhanced predictive values for functional significance than CCTA alone. They hold independent prognostic values for predicting clinical outcomes and can contribute to reducing unnecessary invasive procedures. Noninvasive lesion-specific physiology such as ΔFFR-CT, may further assist in identifying lesions that may benefit from PCI. FFR, fractional flow reserve; PCI, percutaneous coronary intervention.

stenosis can be evaluated using FFR, the ratio of the poststenotic coronary pressure to the aortic pressure during maximal hyperemia.[9] In the assessment of intermediate coronary stenosis, ICA complemented by FFR is currently recommended for physiological assessment.[10,11] Multiple studies have shown that lesions with an FFR >0.80 can be safely deferred, whereas revascularization on top of medical therapy for those with FFR ≤0.80 is associated with a lower risk of adverse clinical events compared with medical treatment alone.[12,13] Nonhyperemic pressure ratio measured during a certain period of cardiac cycles without hyperemic agents can also be used for physiological assessment.[14] Despite substantial evidence and recommendations for pressure wire-based physiological assessments, their use remains low, reported at <20% in patients with intermediate stenosis, and highly variable depending on the sites and countries.[15] This is attributed to concerns about the additional use of pressure wire, cost, time, and labor required to measure physiological indexes.

CT-based noninvasive physiological assessment

CCTA is one of the first-line modalities for evaluating the anatomical severity of coronary stenosis in whole coronary trees.[3] Its high specificity for obstructive lesions has led the current guidelines to recommend CCTA as the primary test in patients with a relatively low likelihood of obstructive CAD.[10,11] Beyond its ability to exclude significant coronary stenosis, the advent of CT-derived noninvasive physiological assessments has enhanced the diagnostic capacity of CCTA to identify ischemic-causing lesions. Computed tomography perfusion (CTP) and FFR derived from coronary computed tomography angiography (FFR-CT) have been validated and offer additional diagnostic value in detecting myocardial ischemia over CCTA alone.[16] CTP can be used to determine perfusion defects similar to single photon emission computed tomography (SPECT) or positron emission tomography. Two distinct methodologies are employed in myocardial CTP imaging. Static CTP captures a single image of the heart at peak contrast enhancement, and dynamic CTP involves a sequence of CT images to track contrast agent movement through the myocardium.[17-19] FFR-CT is calculated using several techniques that stimulate invasive FFR.[20-28] Although CT-based physiological assessment has prognostic value for clinical outcomes in patients with relatively low-risk populations,[29] several data have shown its effectiveness in risk stratification across various severity of CAD, including multivessel disease.[30-32] According to the current standard CCTA reporting criteria, CAD-RADS 2.0, CTP, or FFR-CT are recommended equally for indicating the presence of myocardial ischemia, especially in those with moderate-to-severe anatomical stenosis.[16] The National Institute for Health and Care Excellence (NICE) guidelines suggest using FFR-CT for evaluating lesion-specific physiology in patients with CAD.[33,34] Similarly, the 2021 AHA/ACC chest pain guideline recommends CCTA or FFR-CT for identifying vessel-specific ischemia as class 2A in intermediate-risk patients with 40% to 90% stenosis in proximal or middle segments.[35]

Diagnostic performance of CTP and FFR-CT in predicting low FFR

Static and dynamic CTP and functional significance

The diagnostic performance of CTP and FFR-CT in prediction of FFR ≤0.80, a standard physiological indication for revascularization,

Table 1. Prospective studies comparing diagnostic performance of CTP and FFR-CT with CCTA-defined stenosis in prediction of FFR ≤0.80.

Reference, year	Study population	Modalities	Predictors	Sensitivity	Specificity	PPV	NPV	Accuracy
Ko et al,[36] 2012	Symptomatic patients with CAD referred for ICA (40 patients/118 vessels)	Static CTP	CCTA stenosis ≥50%	0.95	0.78	0.68	0.97	0.83
			CCTA stenosis ≥50% + visual perfusion defect	0.87	0.95	0.89	0.94	0.92
Bettencourt et al,[37] 2013	Symptomatic patients with CAD and intermediate/high pretest probability (101 patients/303 vessels)	Static CTP	CCTA stenosis ≥50%	0.95	0.67	0.48	0.97	0.74
			CCTA stenosis ≥50% + visual perfusion defect	0.71	0.90	0.68	0.91	0.85
Pontone et al,[38] 2018	Symptomatic patients with CAD and referred for ICA (88 patients/106 vessels)	Static CTP	CCTA stenosis ≥50%	0.99	0.75	0.61	0.99	0.82
			CCTA stenosis ≥50% + visual perfusion defect	0.92	0.92	0.82	0.97	0.92
Greif et al,[39] 2013	Patients with typical or atypical chest pain (65 patients/195 vessels)	Dynamic CTP	CCTA stenosis ≥50%	0.98	0.54	0.37	0.99	0.63
			MBF <75 mL/100 mL/min	0.95	0.74	0.49	0.98	0.78
Li et al,[40] 2019	Patients with suspected or known CAD referred for ICA (86 patients/157 vessels)	Dynamic CTP	CCTA stenosis ≥71.2%	0.81	0.63	0.67	0.79	0.72
			MBF ≤99 mL/100 mL/min	0.96	0.93	0.92	0.96	0.94
Pontone et al,[41] 2019	Symptomatic patients referred for ICA (85 patients/255 vessels)	Dynamic CTP and FFR-CT	CCTA stenosis >50%	0.83	0.66	0.54	0.89	0.71
			CCTA stenosis >50% + visual perfusion defect	0.73	0.86	0.72	0.87	0.82
			CCTA stenosis >50% + FFR-CT <0.80	0.86	0.75	0.60	0.93	0.78
Li et al,[42] 2021	Symptomatic patients with intermediate/high pretest probability (62 patients/95 vessels)	Dynamic CTP	CCTA stenosis >62.5%	0.88	0.55	0.69	0.80	0.73
			Visual perfusion defect	0.63	0.98	0.97	0.69	0.79
			MBF <89.5 mL/100 mL/min	0.84	0.98	0.98	0.84	0.91
Nous et al,[43] 2022	Symptomatic patients with suspected stable CAD and referred for ICA (114 patients/289 vessels)	Dynamic CTP	CCTA stenosis >50.0%	0.96	0.72	0.54	0.98	0.78
			CCTA stenosis >50.0% + CT-MPI	0.84	0.89	0.73	0.94	0.88
Koo et al. (2011)[44]	Stable patients with suspected or known CAD (103 patients/159 vessels)	FFR-CT	CCTA stenosis >50.0%	0.91	0.40	0.47	0.89	0.59
			FFR-CT ≤0.80	0.88	0.82	0.74	0.92	0.84
Min et al,[45] 2012	Stable patients with suspected or known CAD (252 patients/407 vessels)	FFR-CT	CCTA stenosis >50.0%	0.84	0.42	0.61	0.72	0.64
			FFR-CT ≤0.80	0.90	0.54	0.67	0.84	0.73
Nørgaard et al,[46] 2014	Patients with suspected CAD clinically indicated ICA (251 patients/484 vessels)	FFR-CT	CCTA stenosis >50.0%	0.83	0.60	0.33	0.92	0.65
			FFR-CT ≤0.80	0.84	0.86	0.61	0.95	0.86

CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CTP, computed tomography perfusion; FFR, fractional flow reserve; FFR-CT, fractional flow reserve derived from coronary computed tomography angiography; ICA, invasive coronary angiography; MBF, myocardial blood flow; NPV, negative predictive value; PPV, positive predictive value.

is compared with CCTA-defined stenosis in Table 1.[36-46] In the study by Ko et al,[36] the addition of visually assessed perfusion defect using static CTP increased the positive predictive value (PPV) for FFR ≤0.80 from 0.68 to 0.89, while maintaining NPV from 0.97 to 0.94. Similar results were reported in subsequent studies.[37,38] Since static CTP might not always capture myocardial images at the optimal timing of peak enhancement, it could potentially lead to an underestimation of perfusion defects. Dynamic CTP addresses this limitation by tracing multiple phases of contrast enhancement over time, providing a time-resolved assessment of myocardial blood flow (MBF).[19] This approach allows for the quantification of MBF and volume. In the study by Li et al,[42] impaired CT-derived MBF exhibited the highest PPV and diagnostic accuracy for FFR ≤0.80, followed by visual analysis of perfusion defects and CCTA-derived stenosis. Further studies have shown that CT-derived MBF can detect functionally significant lesions with better diagnostic performance than CCTA alone.[39-41,43,47] When its diagnostic ability for invasive FFR was compared with other noninvasive modalities, the negative likelihood ratios of CTP were comparable with those of stress imaging by magnetic resonance imaging or positron emission tomography and superior to SPECT in a pooled meta-analysis.[48] The use of advanced CT scanners and dual-source CT technology is expected to reduce radiation doses and beam-hardening artifacts in dynamic CTP.[49] These advancements could render the combined use of CTP and CCTA a viable option for simultaneous noninvasive anatomical and physiological assessment.[50]

Current status of FFR-CT

The DISCOVER-FLOW study was the first-in-human study, prospectively demonstrating the diagnostic accuracy of FFR-CT compared with invasive FFR. In 103 stable patients with CAD enrolled in 4 centers across 3 countries, FFR-CT was shown to be superior to CCTA-derived stenosis in identifying lesions with FFR ≤0.80 (area under the curve [AUC] 0.90 vs 0.75), increasing PPV from 0.47 to 0.74.[44] This finding was further reinforced by subsequent prospective studies, such as DeFACTO and NXT trials (Table 1). A subanalysis of the PACIFIC trial also demonstrated that the diagnostic accuracy of FFR-CT was superior to that of CCTA or SPECT.[51]

Following the clinical application of the FFR-CT prototype, various types of CT-derived FFR have been developed. These use modified CFD and machine learning analyses provided by different manufacturers, including uFFR-CT (United Imaging Healthcare),[22] DEEPVESSEL-FFR (Keya Medical),[23] cFFR (Siemens AG Healthcare),[24] FFR-CT from 1-D CFD (Toshiba Medical Systems Corp),[25] FFR-CT from IntelliSpace Portal Version (Philips Healthcare),[26] or FFR-CT from HeartMedi (AI Medic),[27,28] among others. The burgeoning variety of FFR-CT technology has expanded its application in clinical practice.

Several studies have directly compared the diagnostic performance of FFR-CT with that of CTP in assessing functional significance. Although both FFR-CT and CTP significantly enhance the diagnostic yield of CCTA, their diagnostic accuracies were found to be comparable (FFR-CT vs CT-MPI, AUC 0.78 vs 0.78).[52] This finding was also observed in other populations (CCTA + FFR-CT vs CCTA + CTP, AUC 0.93 vs 0.92, $P = .13$).[53] Interestingly, the diagnostic accuracy was significantly improved when FFR-CT or CTP was added to each combination (CCTA + FFR-CT + CTP vs CCTA + FFR-CT, AUC 0.92 vs 0.88, $P = .03$; CTA + FFR-CT + CTP vs CCTA + CTP, AUC 0.92 vs 0.88, $P = .02$).[41] This suggests the potential incremental value of an integrative assessment of CCTA, FFR-CT, and CTP, as seen in the complementary prognostic value among invasive pressure and flow indexes in predicting clinical outcomes.[54,55]

Table 2. Natural history of coronary atherosclerosis assessed by FFR and FFR-CT.

FFR				FFR-CT			
Reference, year	Clinical outcomes	Follow-up duration	Results	Reference, year	Clinical outcomes	Follow-up duration	Results
Xaplanteris et al,[13] 2018 (FAME II trial)	Composite of death from any cause, MI, or urgent revascularization	60.5 mo (59.8-61.7)	FFR >0.80: 15.7% FFR ≤0.80: 27.0%	Nørgaard et al,[60] 2018	Composite of all-cause death, MI, hospitalization for unstable angina, and unplanned revascularization	24 mo (8-41)	FFR-CT >0.80: 3.9% FFR-CT ≤0.80: 9.4%
Barbato et al,[59] 2016	Composite of cardiovascular death, target vessel MI, and ischemic-driven TVR	23 ± 2 mo	HR, 0.87; 95% CI, 0.83-0.91 per FFR 0.05 increase	Yang et al,[61] 2023	Composite of cardiovascular death, target vessel MI, and clinically driven TVR	10.1 y (9.3-10.2)	HR 0.75 (0.61 – 0.92) per FFR-CT 0.05 increase

FFR, fractional flow reserve; FFR-CT, fractional flow reserve derived from coronary computed tomography angiography; HR, hazard ratio; MI, myocardial infarction; TVR, target vessel revascularization.

Prognostic value of CT-based noninvasive physiological assessment

Association of CT-based functional significance with clinical outcomes

The established diagnostic value of CT-based physiological assessment for detecting low FFR raises the question of whether they also provide additional and independent prognostic information, aiding in more effective treatment decision-making. Nakamura et al[56] reported that abnormal perfusion identified by dynamic CTP was associated with a higher risk of major adverse cardiac events (MACE) independent of CCTA stenosis (hazard ratio [HR], 5.4; 95% CI, 1.7-16.7) and demonstrated incremental prognostic value over CCTA. In the 5-year follow-up of the NXT trial, the risk of MACE was higher in patients with FFR-CT ≤0.80 than those with FFR-CT >0.80 (HR, 5.5; 95% CI, 1.6-19), and the predictability for MACE was superior to that of CCTA stenosis (AUC 0.71 vs 0.52; P <.001).[57] In the ADVANCE registry, which prospectively enrolled 5083 patients from 38 international sites, 1-year follow-up data indicated a trend toward a higher rate of all-cause death or myocardial infarction (MI) in patients with FFR-CT ≤0.80 than with FFR-CT >0.80 (1.2% vs 0.6%, P =.06).[58] This association became significant in the recently reported 3-year follow-up data of 900 patients from 3 Danish sites. A meta-analysis further supports the prognostic value of FFR-CT.[29] Nørgaard et al[29] conducted a systematic meta-analysis involving 5460 patients with available prespecified 1-year hard outcomes. The risk of all-cause death or MI was significantly higher in 3334 patients with FFR-CT ≤0.80 than in 2126 patients with FFR-CT >0.80 (1.4% vs 0.6%; relative risk [RR], 2.31; 95% CI, 1.29-4.13). Additionally, FFR-CT showed a risk continuum for death or MI (RR, 1.67; 95% CI, 1.47-1.87, per 0.10 FFR-CT decrease).

Natural history of coronary atherosclerosis according to FFR-CT strata

In light of the current evidence for the association of FFR-CT with clinical outcomes, it is important to comprehend the natural history of coronary atherosclerosis based on FFR-CT in patients who have deferred revascularization. This understanding is key to determining the efficacy of FFR-CT-based treatment decision-making. Clinical outcomes in patients with deferral of PCI are presented in Table 2[13,59-61] according to binary and continuous FFR and FFR-CT. In the 5-year follow-up of the FAME II study, the composite of death, MI, or urgent revascularization was 15.7% and 27.0% in medically treated patients with FFR >0.80 and FFR ≤0.80, respectively.[13] Similarly, Nørgaard et al[60] investigated the clinical outcomes relative to FFR-CT and treatment types in a real-world registry of stable patients with CAD undergoing CCTA and FFR-CT analysis. They found that the composite rate of death, MI, or urgent revascularization over a median follow-up duration of 24 months was 9.4% in medically treated patients with an FFR-CT ≤0.80, compared with 3.9% in those with an FFR-CT >0.80.[60] The relationship of continuous FFR-CT with outcomes in deferred vessels was also found to be similar to that of FFR. Barbato et al[59] prospectively tracked outcomes of medically treated patients across a whole range of FFR, finding that an increase in 0.05 of FFR was associated with 13% risk reduction for MACE (HR, 0.87; 95% CI, 0.83-0.91). In deferred vessels following FFR-CT measurement from the DISCOVER-FLOW study, a similar risk continuum was observed for the composite of cardiovascular death, target vessel MI, and target vessel revascularization (HR, 0.75; 95% CI, 0.61-0.92, per FFR-CT 0.05 increase).[61] Although more data are required for the direct comparison, the current evidence suggests that the prognostic implications of FFR-CT might be similar to those of FFR, justifying the decision to perform or defer PCI based on low FFR-CT.

Utilizing FFR-CT in clinical settings: Outside and inside the catheterization laboratory

Clinical impact of FFR-CT on downstream testing

Prior studies have evaluated the clinical efficacy of FFR-CT, adding to standard care in the management of patients with CAD. In the PLATFORM study, patients with new-onset stable chest pain were randomly assigned either to usual testing or to CCTA with FFR-CT. The CCTA with FFR-CT group showed a significantly lower rate of ICA with negative findings compared to the usual testing group (73.3% vs 12.4%; P <.001), and there were no significant differences in the rates of death, MI, and unplanned revascularization at 1 year between the 2 groups.[62] In the ADVANCE registry, the addition of FFR-CT to CCTA led to a reclassification of clinical management strategies in about two-thirds of cases and was significantly associated with fewer negative ICA.[63] Another observational study directly compared the efficacy of FFR-CT with myocardial perfusion imaging, showing that FFR-CT usage reduced downstream ICA utilization (absolute risk difference: –4.2%; 95% CI, –6.9 to –1.6) and was associated with a lower rate of no obstructive lesions on ICA (absolute difference: –12.8%; 95% CI, –22.2 to –3.4) and a higher rate of coronary revascularization (absolute difference: 14.1%; 95% CI, 3.3-4.9).[64] In the FORECAST trial, 1400 patients with stable chest pain were randomized to either standard care or CCTA with selective FFR-CT. Although the primary end points, total cardiac costs, and clinical outcomes were not different between the 2 groups, the CCTA with selective FFR-CT group showed a lower rate of ICA (19% vs 25%, P =.01). These findings support the beneficial impact of FFR-CT on treatment decision-making before ICA. The recently published PRECISE trial further highlighted the impact of FFR-CT on clinical practice. A total of 2103 patients with stable symptoms of CAD across 65 international sites were randomized to either a precision

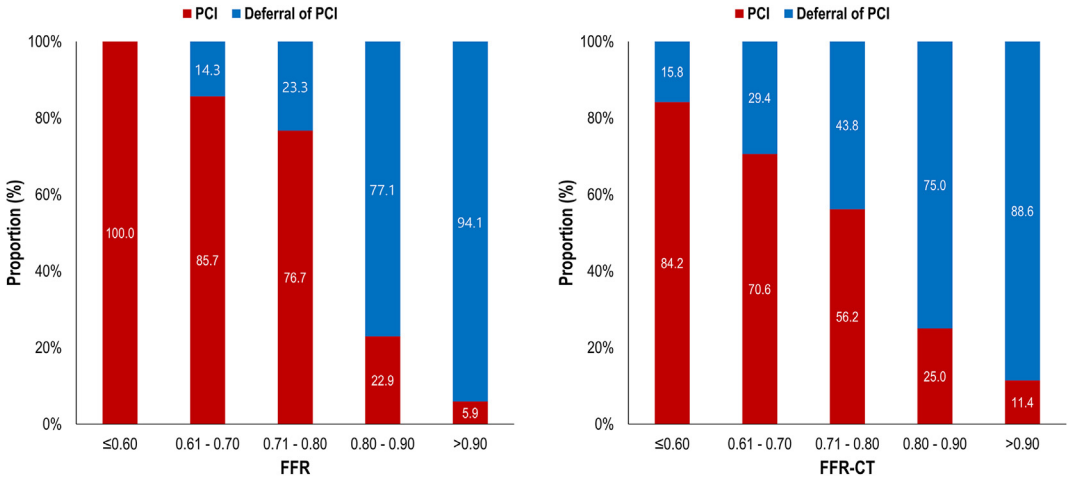


Figure 1.
Revascularization rate according to fractional flow reserve (FFR) and fractional flow reserve derived from coronary computed tomography angiography (FFR-CT). In the DISCOVER-FLOW, the first-in-human study where the diagnostic accuracy of FFR-CT was demonstrated, the actual revascularization rate after FFR and FFR-CT measurement is presented. PCI, percutaneous coronary intervention.

strategy group or a usual testing group. In the precision strategy group, CCTA with selective FFR-CT was performed except for those with minimal risk scores, whereas site-selected stress testing or catheterization was conducted in the usual testing group. During the median 11.8 months of follow-up, the precision strategy group showed significantly lower rates of catheterization with no obstructive lesions (2.6% vs 10.2%; HR, 0.24; 95% CI, 0.16-0.36), whereas the rates of death or MI were similar between the 2 groups.[65] Consequently, current evidence indicates that FFR-CT can reduce unnecessary downstream ICA without increasing adverse clinical events or total cost. This benefit may be attributed to the advantages of coronary physiology-based approaches. Figure 1 illustrates similar PCI trends according to FFR and FFR-CT values in the DISCOVER-FLOW study. Given that a significantly lower rate of PCI was observed in the FFR-guided treatment than the intravascular ultrasound-guided treatment (44.4% vs 65.3%) with similar clinical outcomes in the FLAVOUR trial,[66] similar characteristics of FFR-CT can be expected. Thus, the accumulating evidence supports the use of FFR-CT to avoid unnecessary invasive procedures during CAD management.

Lesion-specific hemodynamic assessment in the selection of target lesion for PCI

Although FFR or FFR-CT are per-vessel indexes that provide information on the functional significance of a target vessel, PCI is a lesion-specific treatment, and selecting the appropriate target lesion is crucial in the catheterization laboratory.[67,68] The beneficial effect of PCI is associated not only with the presence of functional significance but also with physiological focal disease and/or a higher local physiological severity.[69-72] Sakai et al[73] reported that the prevalence of optical coherence tomography-derived lipid-rich plaque or thin-cap fibroatheroma was significantly higher in physiological focal disease, whereas calcifications were more predominant in physiological diffuse disease.

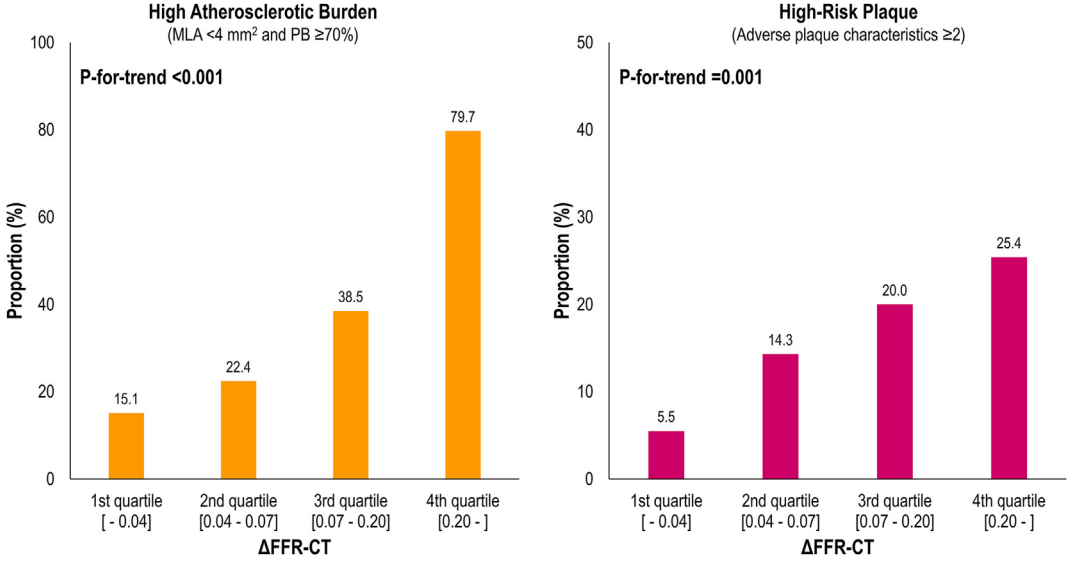


Figure 2.
Association of ΔFFR-CT with plaque quantity and quality. In the lesion-level analysis of the DISCOVER-FLOW study, the prevalence of high-atherosclerotic burden (ie, the presence of both MLA <4 mm^2 and PB ≥70%) and high-risk plaque (ie, the number of adverse plaque characteristics [low-attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign] ≥2) according to the quartile of ΔFFR-CT is shown. FFR-CT, fractional flow reserve derived from coronary computed tomography angiography; MLA, minimum lumen area; PB, plaque burden.

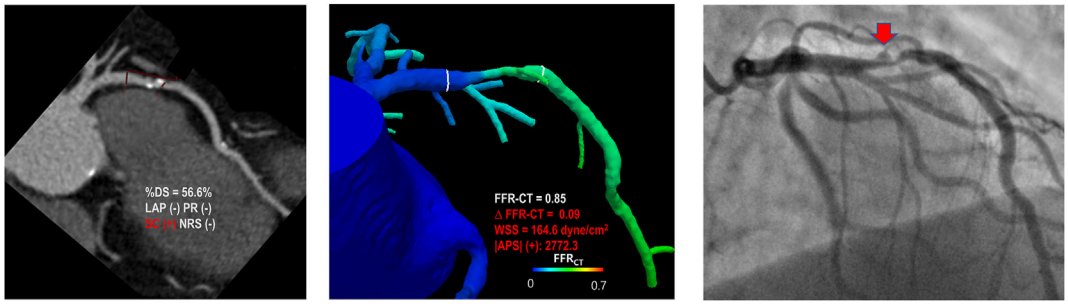


Figure 3.
Representative case. At the time of index coronary computed tomography angiography (CCTA), the lesion in left anterior descending coronary artery showed intermediate stenosis with spotty calcification (left panel) and adverse hemodynamic characteristics (mid panel). The patient had acute myocardial infarction 655 days after CCTA, and the angiogram revealed the progression of the lesion with rupture. APS, axial plaque stress; DS, diameter stenosis; FFR-CT, fractional flow reserve derived from coronary computed tomography angiography; LAP, low-attenuation plaque; MI, myocardial infarction; NRS, napkin-ring sign; PR, positive remodeling; SC, spotty calcification; WSS, wall shear stress.

Furthermore, Sato et al[74] recently showed that the benefit of revascularization might be present in lesions with both FFR-CT ≤0.80 and high-risk plaque, whereas it may be diminished in lesions with FFR-CT ≤0.80 without high-risk plaque. This finding aligns with the post hoc analysis of the FAME II study, which indicated that MI events were predicted by high wall shear stress in medically treated patients with low FFR,[75] suggesting that identifying lesion-specific plaque and hemodynamic characteristics is important for optimizing post-PCI outcomes, even in vessels with low FFR. From this perspective, one of the strengths of FFR-CT analysis is its ability to derive FFR-CT at any point on the target vessel, enabling physicians to obtain lesion-specific physiological information for each lesion prior to the procedure.[76,77] Among various local hemodynamic indexes, ΔFFR-CT, defined as the difference in FFR-CT across the lesions, is a simplified index that can be used as an indicator of local hemodynamic environment, representative of shear stress or pressure gradient acting on the plaque.[78] It also correlates with the presence of high disease burden and adverse plaque characteristics, generally regarded as a marker of plaque vulnerability (Figure 2). The prognostic value of ΔFFR-CT has been described in functionally significant vessels. In the post hoc analysis of the EMERALD study comparing plaque and hemodynamic characteristics between culprit and nonculprit lesions in patients with acute coronary syndrome (ACS), high ΔFFR-CT was associated with a higher risk of ACS culprit lesions among those with FFR-CT ≤0.80.[78] A representative case illustrating the prognostic value of ΔFFR-CT in predicting ACS is presented in Figure 3. In a lesion-level outcome analysis of the DISCOVER-FLOW study, ΔFFR-CT showed a risk continuum for 10-year target lesion failure, independent of lesion stenosis and adverse plaque characteristics.[61] In a post hoc analysis of the ADVANCE registry, Takagi et al[79] reported that ΔFFR-CT was an indicator of early revascularization and suggested that ΔFFR-CT >0.13 was related to an increase in revascularization to ICA ratio in patients with obstructive lesion and FFR-CT ≤0.80. Therefore, acquiring noninvasive local hemodynamics such as ΔFFR-CT could provide additional lesion-specific prognostic information beyond functional significance and may help in defining appropriate PCI target lesions before ICA.

Limitations and future perspectives in CT-based physiological assessment

Although CCTA and CT-based physiological assessment have widely been adopted with their advancement in enhanced resolution, improved diagnostic accuracy, and reduction in radiation dose, it is important to recognize their inherent limitations. The image quality of CCTA is limited when evaluating heavily calcified lesions or in-stent segments due to blooming artifacts. Additionally, despite its excellent NPV, the PPV of CCTA is relatively low, which may lead to unnecessary referral for excessive downstream testing.[80,81] It is also crucial to note that not all patients are suitable for CT-based physiological assessment. For instance, the rejection rate of FFR-CT analysis was 2.9% in the ADVANCE registry and as high as 33% in the PROMISE trial.[82] Section thickness and heart rate have been identified as predictors of unsuccessful FFR-CT analysis.[83] Moreover, CTP is not recommended for patients with severe obesity and those who have implantable cardioverter-defibrillator and pacemaker leads due to the potential for unreliable results.[19] The requirement for additional adenosine and contrast injections is a limitation of CTP that hinders its integration into routine clinical practice. The additional time needed for CT-based physiological assessment, as compared with CCTA alone, could delay clinical decision-making, which may be unsuitable in urgent clinical settings. Thus, understanding and appropriately using these technologies in consideration of both their strengths and limitations, is vital in daily practice.

Upcoming studies will further provide insights into the efficacy of CT-based physiological assessment. The DYNAMITE trial (NCT04709900) aims to assess 3-year MACE following CAD management using CCTA combined with dynamic CTP or FFR-CT vs standard care. The ACCURATE II trial (NCT05824520) will compare 1-year MACE in patients with FFR-CT ≤0.80, treated with either optimal medical therapy alone or combined with PCI. Additionally, the P4 study (NCT05253677) will evaluate the noninferiority of CT-based PCI against IVUS-based PCI in patients with myocardial ischemia, in terms of 1-year MACE. These studies are expected to provide clinical evidence on the effectiveness of CCTA and CT-based physiological assessment in guiding treatment decisions for patients with CAD.

Conclusion

Noninvasive physiological assessment using CCTA has enhanced the diagnostic performance of CCTA in predicting functional significance. By offering additional prognostic value over CCTA, it has been demonstrated to reduce unnecessary invasive procedures. Moreover, noninvasive lesion-specific hemodynamic assessments could further assist in identifying target lesions that may benefit from revascularization in the catheterization laboratory. Therefore, understanding and appropriate use of CT-based physiological indexes will aid in selecting treatment strategies and optimizing the management of patients with CAD.

Declaration of competing interest

Bon-Kwon Koo received an institutional research grant from Abbott Vascular, Philips Volcano, Boston Scientific, and HeartFlow. Seokhun Yang reported no financial interests.

Funding sources

This work was not supported by funding agencies in the public, commercial, or not-for-profit sectors.

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