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Review Article

CT derived fractional flow reserve: Part 2 – Critical appraisal of the literature

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ABSTRACT

The integration of computed tomography-derived fractional flow reserve (CT-FFR), utilizing computational fluid dynamics and artificial intelligence (AI) in routine coronary computed tomographic angiography (CCTA), presents a promising approach to enhance evaluations of functional lesion severity. Extensive evidence underscores the diagnostic accuracy, prognostic significance, and clinical relevance of CT-FFR, prompting recent clinical guidelines to recommend its combined use with CCTA for selected individuals with with intermediate stenosis on CCTA and stable or acute chest pain. This manuscript critically examines the existing clinical evidence, evaluates the diagnostic performance, and outlines future perspectives for integrating noninvasive assessments of coronary anatomy and physiology. Furthermore, it serves as a practical guide for medical imaging

Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT-FFR, computed tomography-derived fractional flow reserve; CFD, Computational Fluid Dynamics; ICA, Invasive coronary angiography; MACE, major adverse cardiovascular outcomes; MI, Myocardial infarction; AI, Artificial Intelligence.

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professionals by addressing common pitfalls and challenges associated with CT-FFR while proposing potential solutions to facilitate its successful implementation in clinical practice.

1. Introduction

Coronary computed tomography (CCTA) is a well-established non-invasive test for the evaluation of patients with suspected coronary artery disease (CAD). The strength of CCTA lies in its high negative predictive value and ability to identify prognostically important coronary atherosclerosis.[1] Historically, CCTA has been criticized for having modest specificity for identifying functionally significant CAD.

Physiological or functional assessment of CAD using invasive fractional flow reserve has been demonstrated in randomized trials and real-world registries to facilitate revascularization decision-making and improve clinical outcomes.[2–5] In recent years, it has become feasible to complement the anatomical assessment of lesion severity provided by CCTA with an estimate of invasive fractional flow reserve (CT-FFR) that is derived using computational fluid dynamics and aided by artificial intelligence (AI) from routine CCTA images. There is a reasonably sized body of evidence that has demonstrated the diagnostic accuracy, prognostic value, and clinical utility of CT-FFR, with recent clinical guidelines integrating its use to complement CCTA evaluation of patients with stable or acute chest pain.

This paper offers a review of the clinical evidence, critical appraisal, and future perspective of a test that offers the ability to combine non-invasive assessment of coronary anatomy and physiology. Furthermore, our review aims to provide a practical guide to imagers describing common pitfalls and challenges of CT-FFR and presents possible solutions.

2. Diagnostic performance

The most used U. S. Food and Drug Administration-cleared solution, FFR_{CT} (HeartFlow Inc, Redwood City, USA), derives CT-FFR values based on computational fluid dynamics (CFD) principles that mathematically model coronary flow, pressure, and resistance utilizing off-site, cloud-based supercomputers. Several clinical trials have demonstrated high diagnostic accuracy of CT-FFR to identify flow-limiting lesions (FFR $\leq$0.8) as compared to the invasive reference standard of FFR.[6–8] In the NXT (Analysis of Coronary Blood Flow Using Coronary CT Angiography: NeXT sTeps) study,[8] compared to invasive FFR, the area under the receiver-operating characteristics curve (AUC) for CT-FFR was 0.90 (95 % confidence interval [CI]: 0.87 to 0.94) versus 0.81 (95 % CI: 0.76 to 0.87) for CCTA ($p = 0.0008$). The main advantage of CT-FFR over CCTA was its significantly higher per-patient and per-vessel specificity (79 % vs 34 % and 86 % vs 60 %) with comparable sensitivity. CT-FFR correctly reclassified 68 % of patients with CCTA false positives to true negatives.

The diagnostic performance of CT-FFR was compared against SPECT and positron emission tomography (PET) in the PACIFIC-1 (Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography With Invasive Coronary Angiography) sub-study.[9] The per-vessel and per-patient diagnostic performance of CT-FFR (AUC 0.94 and 0.92) compared to the reference standard of invasive FFR was superior to CCTA (0.83 and 0.81; $p < 0.01$ for both) and SPECT (0.70 and 0.75; $p < 0.01$ for both). CT-FFR also outperformed PET on a per-vessel basis (AUC 0.87; $p < 0.01$), although it was comparable on a per-patient analysis (AUC 0.91; $p = 0.56$).

It is important to mention some of the limitations of these studies. In the PACIFIC-1 trial, a noteworthy aspect was the exclusion of 25 % of CT-FFR studies, a practice that bears implications for bias in favor of CT-FFR. In the PACIFIC-1 intention-to-diagnose (considering missing values positive) analysis, the performance of CT-FFR was reduced to an AUC of 0.79. The basis for exclusion primarily revolved around the criteria of suboptimal image quality, raising concerns about the comparability of the included studies and their representativeness of real-world clinical scenarios.

The NXT study also exhibits certain limitations, primarily stemming from the high proportion of patients (68 %) with normal FFR values, and it was notable that the CT-FFR performance was lower at lower FFR values. It is crucial to recognize that the demonstrated accuracy in cases of normal FFR may not be readily extrapolated to the broader clinical population with abnormal values. Furthermore, in this study, the exclusion of patients characterized by elevated BMI and known CAD has the potential to exert influence on the anticipated clinical performance within specific patient subgroups.

Several on-site CT-FFR algorithms exist, which can be derived at point of care using a standard desktop computer.[10–15] This has the potential advantage of avoiding costs and issues associated with remote data-transfer and analysis. These techniques have not yet been cleared for clinical use in the United States or Europe. These methods utilize more simplified fluid dynamic simulations and, in some cases, apply artificial intelligence to provide CT-FFR values. They have demonstrated good diagnostic performance compared with invasive reference standards.[16] Although most on-site techniques have reduced analysis times compared with off-site CT-FFR, a significant limitation is that the luminal segmentation of the coronary arteries required for CT-FFR analysis requires significant human input, thereby limiting translation into clinical practice.[12] Artificial intelligence techniques have shown promise in automating both segmentation and analysis time; however, require further validation in real-world settings.[17]

3. Prognostic value

The prognostic value of CT-FFR has been evaluated in a number of large-scale multicenter observational studies and post-hoc retrospective registries with follow-up to 5 years.

In the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) CT-FFR sub-study,[18] CT-FFR of $\leq$0.80 was a significantly better predictor for revascularization or major adverse cardiovascular outcomes (MACE) than severe stenosis on CCTA (HR: 4.3 [95 % confidence interval [CI]: 2.4 to 8.9] vs. 2.9 [95 % CI: 1.8 to 5.1]; $p = 0.033$).

Results of the ADVANCE (Assessing Diagnostic Value of noninvasive CT-FFR in Coronary Care) study, a real-world international registry of 5083 patients with suspected CAD and >30 % stenosis on CCTA,[19] demonstrated an increased risk of incident cardiovascular death or MI at one-year in patients that have reduced CT-FFR $\leq$0.80 as compared with patients with CT-FFR values > 0.80, with HR: 4.22 (95 % confidence interval [CI]: 1.3–13), $p = 0.01$. While the ADVANCE registry successfully enrolled a diverse cohort of real-world patients, it is important to acknowledge its inherent limitations as a registry study. Referral bias, reflective of local practices, may have influenced the patient population. Additionally, the study did not attempt to precisely co-localize the specific coronary segment with stenosis to a corresponding CT-FFR value, potentially leading to the grouping of discordant vessels in the patient-level analysis.

Further reinforcing the long-term prognostic utility of CT-FFR, the 3-year follow-up of the ADVANCE-DK registry demonstrated that an abnormal CT-FFR ($\leq$0.80) was associated with a significantly increased risk of all-cause death and spontaneous myocardial infarction (MI) compared to patients with a normal CT-FFR. Notably, this association persisted even in patients with high coronary artery calcium (CAC) scores ($\geq$400), highlighting the robustness of CT-FFR in risk stratification across a broad range of CAD severity.[20]

A recent meta-analysis on long-term outcomes[21] in a population of patients of 5689 from five observational studies and registries with follow-up ranging from 1 to 5 years demonstrated that a CT-FFR value of ≤0.80 identified an increased risk of MI, unplanned coronary revascularization and major adverse cardiac events (HR 2.31; 95 % CI: 1.29 to 4.13). Importantly, a risk-continuum was observed with each 0.10-unit reduction in CT-FFR values associated with greater risk of MACE (RR 1.67; 95 % CI 1.47 to 1.87; $p < 0.001$). This highlights that CT-FFR, similar to invasive FFR,[22] should not be interpreted in a binary dichotomous manner but rather as a continuous variable, with lower values associated with a greater risk of adverse outcomes.

It is important to recognize that although the studies mentioned above provide valuable and favorable results of the prognostic value of CT-FFR, they are results from mostly retrospective registries and post hoc analyses.

4. Clinical utility

Evidence from contemporary trials on the clinical utility of CT-FFR has established its use in multi-society guidelines as a safe and feasible, non–invasive alternative to functional assessment of coronary artery stenosis for the management of patients with CAD. Most recently, in the 2021 American College of Cardiology (ACC) and American Heart Association (AHA) Guidelines for the Evaluation and Diagnosis of Chest Pain, use of CT-FFR was given a Class 2a recommendation for further evaluation of lesions with 40–90 % stenosis on CCTA, in patients presenting with acute or stable chest pain 23. These recommendations align with those from the National Institute for Health and Care Excellence (NICE) in the United Kingdom in 2017, for noninvasive assessment of functional significance of coronary artery stenosis by CT-FFR.[24]

Clinical data support the utility of CT-FFR in impacting clinical workflow with an CT-FFR-guided diagnostic strategy associated with less downstream testing, fewer inappropriate referrals for invasive angiography, and better identification of patients who may require revascularization.[25]

Recent trials, including ISCHEMIA,[26] FAME-3,[27] and FUTURE,[28] have provided nuanced insights into the utility of fractional flow reserve (FFR) in contemporary clinical practice. ISCHEMIA showed no reduction in major adverse cardiovascular events (MACE) with an invasive strategy, though symptomatic relief was noted in certain patients. However, it is important to note that invasive FFR was used in only ~20 % of patients in the ISCHEMIA trial, limiting its direct applicability to FFR-guided decision-making. FAME-3 demonstrated that FFR-guided PCI was not non-inferior to CABG in multivessel CAD, while FUTURE was terminated early without showing superiority of an FFR-based approach over angiography. Despite these findings, FFR remains an essential tool in risk stratification across the CAD spectrum and, particularly in the setting of multivessel disease, helps identify ischemia-producing lesions that may benefit from revascularization for symptomatic relief.

Despite some negative trial results, invasive FFR is broadly accepted as superior to visual stenosis assessment on invasive coronary angiography and is supported by clinical guidelines. The 2021 ACC/AHA/SCAI Revascularization Guidelines designate FFR as a Class 1 recommendation for guiding revascularization in patients with chronic coronary syndromes, especially for angiographically intermediate stenoses where the functional significance is uncertain29. Non-invasive FFRCT further refines pre-test risk assessment, guiding decisions on invasive testing, while invasive FFR confirms lesion-specific ischemia, optimizes PCI versus CABG selection, and prevents unnecessary revascularization. Additionally, FFRCT assesses both focal and diffuse disease burden, supporting a more tailored management approach that aligns with contemporary best practices.

Several mostly observational studies have shown the application of CT-FFR in mainstream clinical practice. PLATFORM (Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts) and RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain) have demonstrated that functional assessment of coronary stenosis can effectively triage patients for ICA and enrich the therapeutic yield of referral to catheterization lab.[25,30]

In a posthoc analysis of the observational cohort study in the PROMISE trial that included patients with stable chest pain who were referred to ICA within 90 days after CCTA, an CT-FFR of ≤0.80 was a superior predictor of revascularization or major adverse cardiac events than severe stenosis on CCTA (HR: 4.3 [95 % confidence interval [CI]: 2.4 to 8.9] vs. 2.9 [95 % CI: 1.8 to 5.1]; $p = 0.033$). In addition, they observed that the addition of CT-FFR improved the efficiency of ICA referral by increasing the proportion of ICA, leading to revascularization by 24 %, compared to CCTA alone strategy.[31] The ADVANCE registry showed that the addition of CT-FFR influenced clinical management, such as the need for further downstream testing and revascularization.[32] CT-FFR-based management was associated with less negative invasive coronary angiography (ICA), predicted revascularization in patients undergoing ICA with CT-FFR ≤0.80 (72.3 %) and identified patients at low risk of major adverse cardiac events within 90 days [No death/myocardial infarction (MI) in CT-FFR >0.80 vs 19 (0.6 %) events in CT-FFR ≤0.80 (HR 14.68, CI 0.88–246, $P = 0.039$)].[19]

Most recently, the PRECISE Trial was a pragmatic RCT ($n = 2103$) that investigated a diagnostic strategy's clinical efficiency and outcomes for stable chest pain ('Precision Pathway'), mirroring the recently published ACC/AHA guidelines. The investigators utilized a risk score to defer testing in minimal-risk patients with CCTA with selected CT-FFR (30–90 % stenosis) in remaining patients and compared this to a group undergoing usual testing. The ' Precision Pathway' - improved diagnostic accuracy, reduced unnecessary testing with a significant reduction in unnecessary ICA and was 75 % more likely to identify the appropriate patient for revascularization. At one year follow-up, the Precision Pathway centered around CCTA + CT-FFR as a gatekeeper in the evaluation of stable chest pain, significantly reduced the composite primary endpoint of all-cause death, nonfatal MI, or catheterization without obstructive disease relative to traditional testing ($p < 0.001$).[33] Table 1 (advantages and disadvantages of CT FFR) summarizes some of the advantages of using CT FFR described above and the limitations of CT-FFR further explained below.

5. Limitations and optimizing CT-FFR results

The accuracy of FFR simulation on CCTA is based on the ability to derive an accurate patient-specific anatomical coronary model. Therefore, image quality plays a crucial role in the feasibility and performance of CT-FFR techniques. Like any technology, CT-FFR requires best

Table 1
Advantages and disadvantages of CT FFR. Summary of the advantages and disadvantages of using CT FFR.

Advantages	Disadvantages
• Allows anatomical and functional evaluation in a single test	• Not useful for distal lesions (best for proximal to mid vessels)
• No need for additional testing for patients	• Not useful for vessels with stents
• No need for additional medications	• Less reliable with extensive calcifications
• No need for additional contrast	• Highly dependent on image quality
• No need for additional radiation	• Additional cost and reimbursement can be challenging
• Assessment of lesion specific ischemia	• Offsite analysis challenges usage in urgent settings
• May prevent unnecessary invasive coronary angiograms	
• Determine physiological pattern of disease and focal pressure gradients	
• Using virtual stenting tools can guide revascularization strategies.	

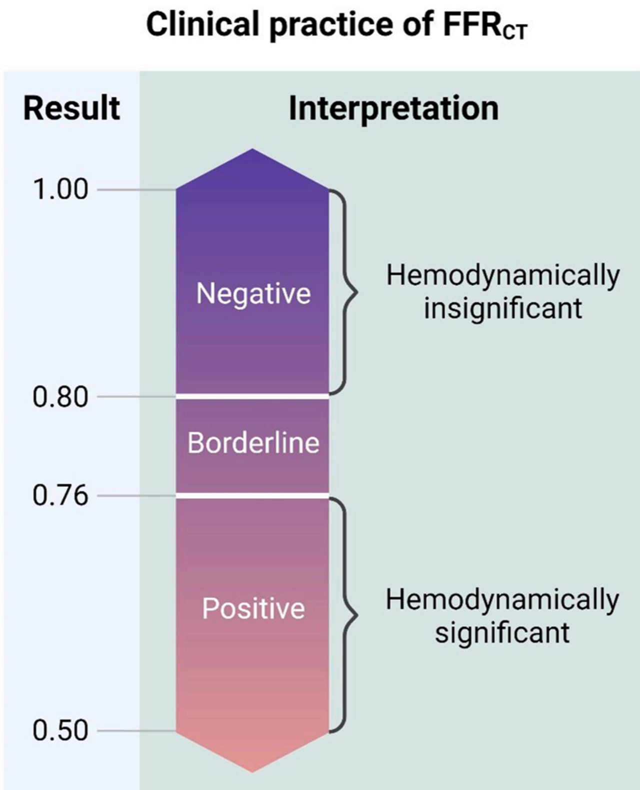

Fig. 1. illustrates a guide in interpreting CT-FFR values. The diagram delineates key thresholds providing a visual aid for imagers in deciphering the functional significance of coronary lesions during CCTA analysis.

practices to achieve optimal performance. Therefore, it is vital to follow SCCT guideline-based recommendations to optimize image quality and reduce artifacts.[34] Patient preparation with administration of oral short-acting beta blockers (± additional IV if needed) helps reduce motion artifacts secondary to cardiac motion. Coaching the patient on breath holding prior to scan acquisition can minimize respiratory motion artifacts. Sublingual nitroglycerin administration for coronary vasodilation is essential to facilitate optimal visualization and a more accurate coronary anatomical model central to the derivation of CT-FFR.

Coronary calcification remains a formidable Achilles heel for CCTA, with blooming artifacts impacting coronary luminal evaluation and, therefore, the accuracy of coronary geometry needed for CT-FFR simulation. Early data from the NXT study[8] suggested that the diagnostic performance of CT-FFR was maintained with the increasing burden of calcification and remained superior to CCTA alone. Subsequent real-world registries highlighted that in the presence of significant calcification with an Agstaton score >400, the agreement of CT-FFR with invasive FFR was reduced, although it remained superior to CCTA([35],[36]).

CT-FFR has also not been validated in patients with coronary stents, bypass grafts, and following acute coronary syndrome. A previous study in patients following ST-elevation myocardial infarction demonstrated that the diagnostic performance of CT-FFR in this setting was modest and weakly correlated with invasive FFR[37]

6. Interpretation of CT-FFR

The interpretation of CT-FFR involves a careful analysis of both anatomical and physiological data obtained from CCTA. After processing, three-dimensional model is provided with allows the assessment of CT-FFR across the whole coronary tree for vessels >1.8 mm in diameter.

To assess the lesion-specific ischemia, CT-FFR should be measured 1–2 cm distal to the stenosis, in alignment with clinical utility studies, expert consensus recommendations (CAD-RADS 2.0), and large-scale trials (ADVANCE(32), PRECISE,[38] Denmark Real-World Registry.[39] This differs from early diagnostic validation studies, where measurement location was aligned with invasive FFR wire positioning to match anatomical reference points.

A study comparing the accuracy of lesion-specific CT-FFR (measured 2 cm distal to the stenosis) versus distal-vessel CT-FFR in predicting the need for revascularization demonstrated that 44 % of positive distal CT-FFR values were reclassified as negative when assessed lesion-specifically, avoiding overestimation of ischemia due to distal tapering vessel artifacts.[40,41] Additionally, the revascularization rate when referred for an invasive coronary angiogram after a positive CT-FFR was

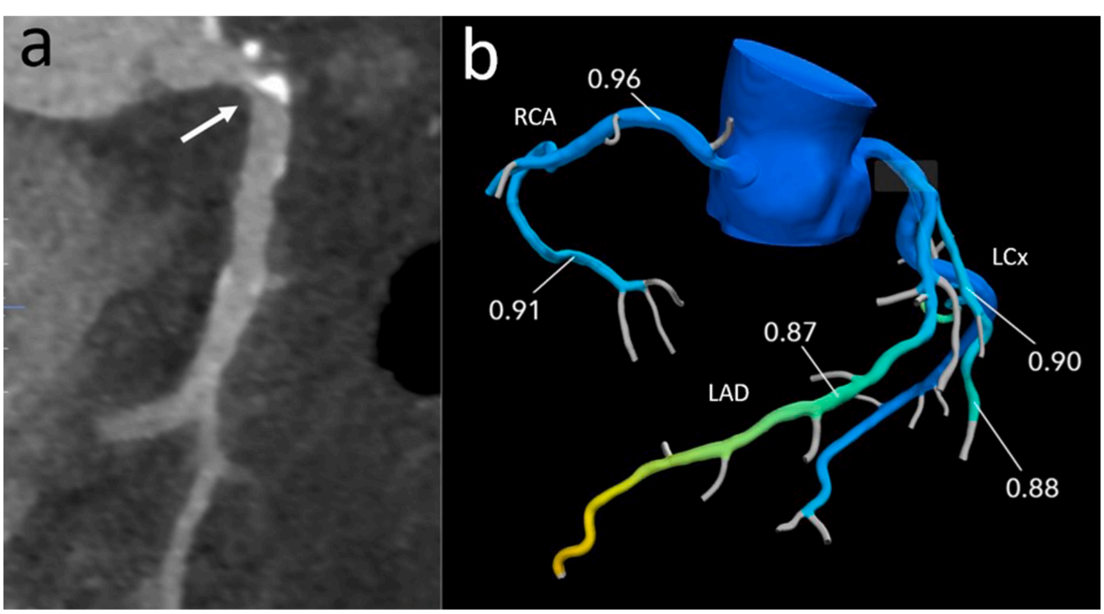

Fig. 2. Case of a 71 year old female with exertional chest pain. a. Coronary CTA: eccentric partially calcified plaque in the right coronary artery causing moderate stenosis. b. Fractional flow reserve CT shows that the RCA stenosis is hemodynamically insignificant with a CT FFR value of 0.96 distal to the lesion. Final score CAD-RADS 3/P2/I-.

higher in the cohort with lesion-specific CT-FFR than at the distal end of the vessel. Fig. 1 delineates how to interpret CT-FFR values obtained after completing the analysis. If the lesion-specific CT-FFR value (measured 1–2 cm distal to the stenosis) is > 0.80, the lesion is considered non-significant and unlikely to benefit from revascularization. Conversely, a lesion-specific FFRCT value ≤ 0.75 is predictive of hemodynamic significance, warranting further clinical evaluation, as demonstrated with the example case in Fig. 2, if the CT-FFR value distal to the stenosis in question is lesser than or equal to 0.75, the lesion is categorized as positive by CT-FFR or hemodynamically significant. Demonstrated with the example case in Fig. 3, In the intermediate range (0.76–0.80), additional clinical factors—symptom burden, high-risk plaque features, and pressure gradients—should be considered to guide decision-making. The pattern of pressure loss across a lesion (ΔCT-FFR) can further improve discrimination, especially in borderline cases. Taken together, lesion-specific FFRCT measurement aligns with current evidence-based best practices, providing a more accurate assessment for clinical decision-making compared to relying solely on distal vessel values.

The pressure gradient across coronary stenosis, also known as ΔCT-FFR provides additional functional insight beyond binary CT-FFR thresholds, particularly for intermediate lesions (CT-FFR 0.71–0.80) where ischemia assessment is less definitive. ΔCT-FFR has been demonstrated as a clinically relevant marker for distinguishing focal from diffuse coronary disease and guiding revascularization versus medical therapy.[40] Additionally, landmark studies such as EMERALD I [42] and EMERALD II [43] have highlighted ΔCT-FFR as a predictor of future myocardial infarction in patients with non-obstructive CAD. To ensure consistent and reproducible ΔCT-FFR assessment, a standardized approach should be followed. First, the extent of the stenosis is visually evaluated using a three-dimensional (3D) FFRCT model. Proximal and distal measurement points are identified in regions immediately

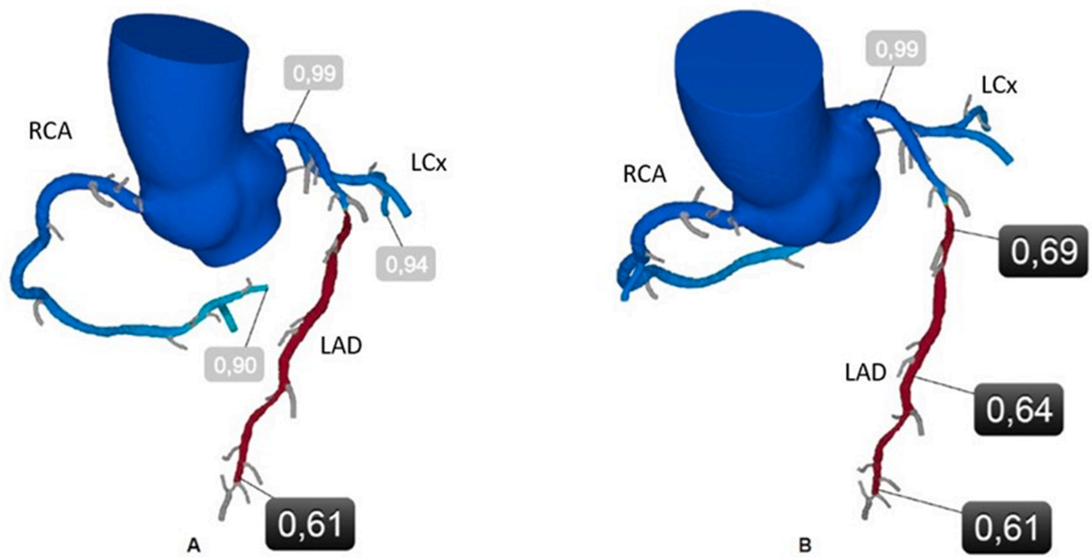

Fig. 3. Case of a 56 year old male with typical angina. Coronary CTA (not shown) showed a severe stenosis in the proximal and mid portions of the left anterior descending artery (LAD). Fractional flow reserve CT shows that this was a hemodynamically significant stenosis with a drop in CT-FFR to 0.69 just after the lesion.

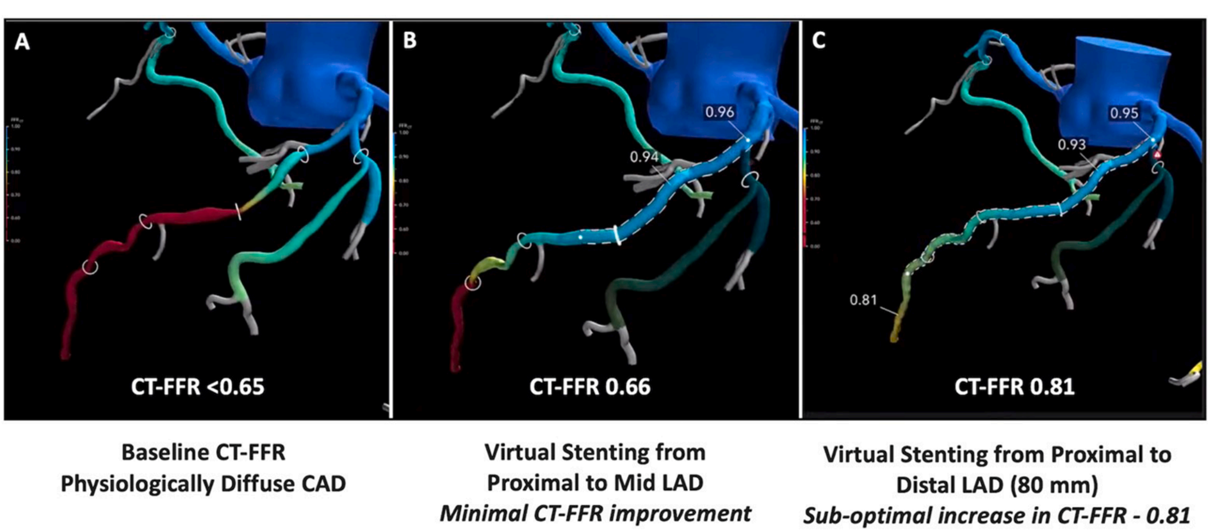

Fig. 4. This is a case example highlighting the value of phenotyping the physiological pattern of coronary artery disease using CT-FFR and the utility CT-FFR virtual stenting planner. 67 year old male with exertional angina. A) Baseline CT-FFR model demonstrates highly positive CT-FFR <0.65 with diffuse physiological disease along the course of the LAD. B) Virtual stenting from the proximal to mid-LAD results in a minimal improvement to CT-FFR C) Despite extensive virtual stenting of 80 mm from the proximal to distal LAD, the maximal improvement in CT-FFR was only 0.81, which represents a sub-optimal-result-.

adjacent to the stenosis that appear free of luminal narrowing, with the proximal reference point positioned 1–2 cm before the stenosis and the distal reference point positioned 1–2 cm beyond the stenosis. The ΔCT-FFR value is then calculated as the difference between these two CT-FFR measurements. This methodology aligns with CAD-RADS 2.0,[44] which recommends considering invasive angiography for individuals with significant ΔCT-FFR (≥0.12), particularly those with symptoms or lesions in high-risk locations. The inclusion of ΔCT-FFR in clinical decision-making provides a more refined assessment of lesion severity and ischemic burden, improving patient selection for invasive angiography and optimizing revascularization strategies. Fig. 5 illustrates this standardized approach to ΔCT-FFR measurement, highlighting its role in lesion evaluation and ischemia assessment in contemporary clinical practice.

7. Sex-differences in CT-FFR

Significant differences exist between men and women in terms of cardiac and coronary anatomy. Even after adjusting for various factors such as age, body mass index, body surface area, and left ventricular mass, women typically have smaller epicardial coronary arteries compared to men. This size disparity poses challenges for accurately assessing distal coronary arteries through CCTA. However, CT-FFR presents an opportunity to enhance the differentiation between

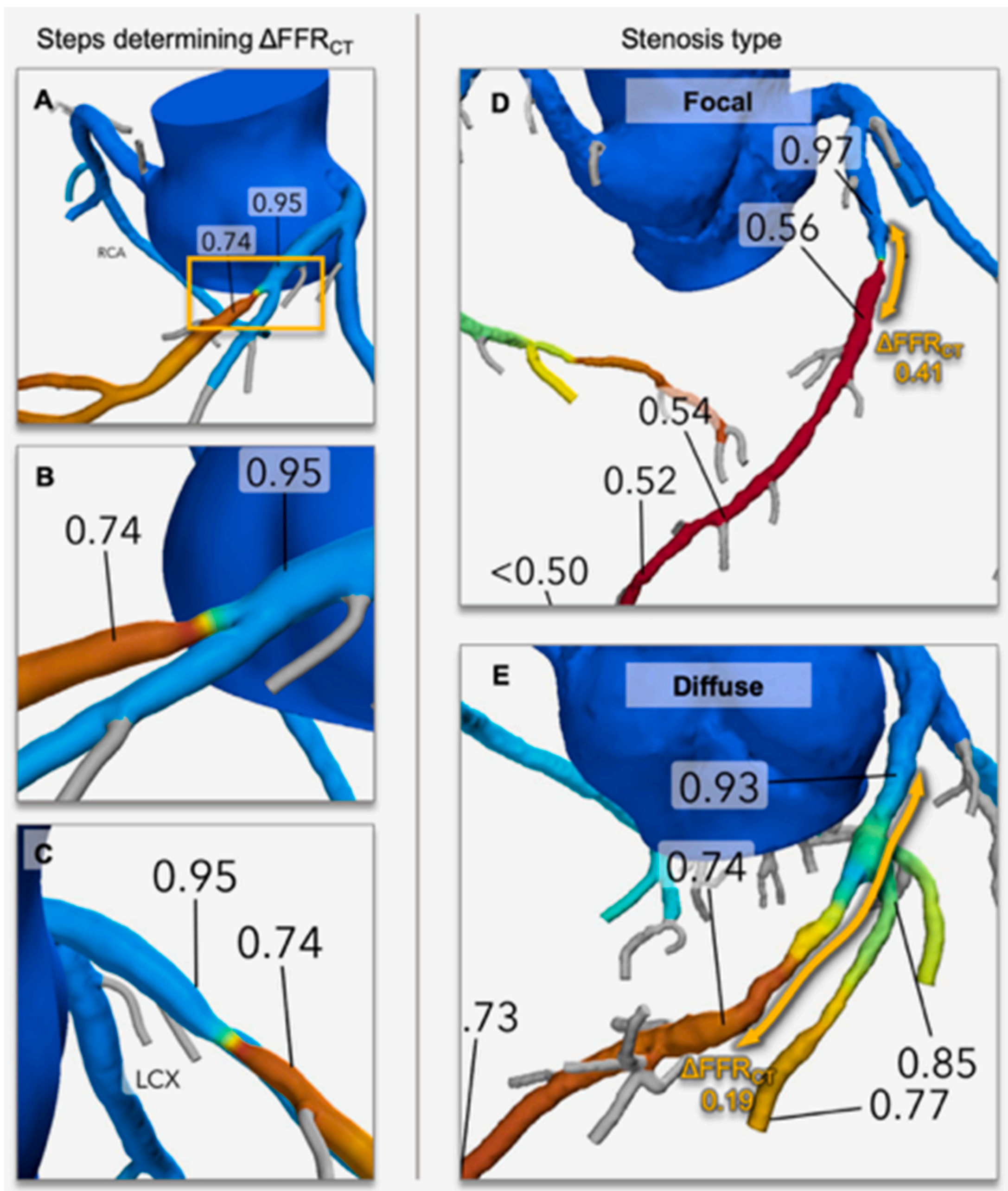

Fig. 5. Methodology for Determining ΔFFRCT and Stenosis Type: A Guide to Functional Lesion Assessment. This diagram illustrates the standardized approach for determining ΔFFRCT and categorizing stenosis type based on coronary CT-FFR analysis. The process involves visually assessing stenosis extent using a 3D FFRCT model, identifying proximal and distal reference points at regions free of luminal narrowing, and calculating ΔFFRCT as the difference in FFRCT values between these two points. The stenosis type is further classified as focal or diffuse based on lesion length, aiding in clinical decision-making for revascularization. Adapted from Takagi et al., ADVANCE Registry, J Cardiovasc Comput Tomogr. 2022 (https://doi.org/10.1016/j.jcct.2021.08.003).

ischemia and other noninvasive tests. Studies have shown that CT-FFR demonstrates comparable diagnostic accuracy and discriminatory power for detecting ischemia in both sexes (AUC: 0.93 vs. 0.90, P = 0.43).[45] CT-FFR has been shown to reduce the incidence of non-obstructive CAD at invasive coronary angiogram[46] and increases the ability of CCTA to identify revascularization[47] with no sex-differences. To explore the potential benefits, particularly for women who historically undergo revascularization less frequently, a post hoc analysis of the ADVANCE registry was conducted. This analysis revealed that women consistently exhibited fewer instances of obstructive CAD on CCTA, higher CT-FFR values, and a reduced likelihood of a positive CT-FFR $\leq$0.80 for the same degree of stenosis ($p < 0.0001$). Despite similar referral rates to ICA following a positive CT-FFR, women experienced higher rates of nonobstructive CAD and lower rates of revascularization unless the CT-FFR was $\leq$0.75, where revascularization rates aligned.[48] A positive CT-FFR resulted in an equal referral to ICA but more non-obstructive CAD and less revascularization in women unless the CT-FFR was $\leq$0.75 where revascularization rates were similar. The integration of anatomical and functional data from CCTA and CT-FFR appears to offer a more uniform approach to patient management, irrespective of sex. This study also sheds light on how CT-FFR can enhance our understanding of physiological changes and the intricate relationship between coronary anatomy and flow. Additionally, the investigation explored the potential utility of the coronary vessel volume (V), myocardial mass (M), and the V/M ratio as indicators of microvascular disease, which has been found to be more prevalent and prognostically significant in women. Previous CT-FFR studies have shown a lower V/M ratio in those with microvascular disease, suggesting that this could be an alternative measurement for coronary microvascular dysfunction (CMD)[49]; this is potentially more relevant in women as several studies have shown that women have greater prevalence of CMD compared to men and higher prognostic significance in women.[50]

8. Beyond computational fluid dynamics - alternative methods for deriving CT-FFR

Given the significant computational requirements and assumptions used to derive CT-FFR using computational fluid dynamics, there has been some investigation into alternate methods that derive FFR utilizing machine learning. Utilizing 12,000 synthetic coronary geometries of varying vessel sizes, branching patterns, and stenoses, a machine learning CT-FFR algorithm was developed. It demonstrated high and comparable performance to a CFD-based CT-FFR approach.[51] Analysis time was impressive at 2 s. However, an important caveat is that accurate coronary lumen segmentation remains essential in deriving machine learning CT-FFR. In this study, coronary segmentation required manual human input of approximately 30–60 min per case, limiting its broader application in clinical practice.

In light of the growing recognition of the interplay between plaque morphology and coronary physiology, a recent advancement in machine learning has led to the development of a novel CT-FFR technique. This approach utilizes coronary geometry, plaque volume, and characteristics within the vessel wall to derive FFR values. Notably, this technique incorporates a plaque analysis method that has been histologically validated (vascuCAP®, Elucid Bioimaging, Inc., Boston, MA). Early feasibility studies have shown promising results, with the technique demonstrating high diagnostic accuracy when compared to invasive FFRThe results demonstrated this plaque-based CT-FFR technique outperformed traditional CCTA, exhibiting an area under the receiver operating characteristic curve, sensitivity, and specificity of 0.94, 0.90, and 0.81, respectively, compared to 0.71, 0.71, and 0.50 for CCTA alone.[52]

Several other techniques utilize AI to predict the presence of ischemia as defined by a positive FFR. A recently developed AI- algorithm, AI-QCT$_{\text{ISCHEMIA}}$ (Cleerly Inc, New York, USA), utilizes coronary atherosclerosis and vascular characteristics to determine the likelihood of coronary ischemia. The AI-enabled tool provides a binary indication of ischemia, categorizing it as either unlikely or likely present based on a threshold equivalent to invasive fractional flow reserve (FFR) measures of >0.80 vs. $\leq$0.80, respectively, with its diagnostic performance recently evaluated in a post-hoc analysis of the PACIFIC-1 and CREDENCE trial,[53] where it outperformed SPECT and CT-FFR in the intention-to-diagnose analysis. The AUCs were 0.85 (95 % CI: 0.79–0.91) for AI-QCT$_{\text{ISCHEMIA}}$, 0.78 (95 % CI: 0.72–0.84; P = 0.037) for CT-FFR, 0.89 (95 % CI: 0.84–0.93; P = 0.262) for PET, and 0.72 (95 % CI: 0.67–0.78; $P < 0.001$) for SPECT. Furthermore, multiple studies have recently shown the prognostic value of AI-QCT$_{\text{ISCHEMIA}}$.[54] An additional plaque-based machine learning (ML) technique was trained using data from the prospective NXT trial to develop an ML score that predicts ischemia as defined by an FFR$\leq$0.80. The ML algorithm was then validated using data from the PACIFIC-1 study and demonstrated that for the prediction of FFR-defined ischemia, the ML score showed an area under the receiver-operating characteristic curve of 0.92, which was significantly higher than that of visual stenosis grade (0.84; $P < 0.001$) and equivalent with that of CT-FFR (0.89, P = 0.26).

These novel algorithms show important promise in predicting hemodynamically significant CAD with at least similar accuracy as CT-FFR, without the need for complex CFDs. It is well recognized that the utility of FFR goes beyond an isolated number or a binary ('positive/negative') result. Rather, FFR represents a risk continuum and the pattern of pressure loss across a vessel or stenosis, which can be readily obtained from commercially available CT-FFR models. This data provides essential information on the disease pattern and more appropriately influences decision-making on downstream testing and referral for revascularization. Future studies will have to demonstrate the clinical utility of these promising novel ML/AI algorithms on a continuous basis as is currently clinical practice for CT-FFR. Table 3 provides a comparison of available FFRCT solutions, summarizing their modeling methodologies, validation studies, advantages, limitations, and clinical adoption to enhance understanding of their respective roles in clinical decision-making.

9. Emerging directions

Utilization of CCTA with CT-FFR has the potential to enhance decision-making by combining both anatomic and physiology data. The SYNTAX (Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) III Revolution trial demonstrated that in patients with complex multi-vessel CAD, clinical decision-making guided by CCTA + CT-FFR was highly concordant with treatment guided by ICA (concordant decision 93 %, Cohen's kappa 0.82).[55]

There is increasing emphasis in the literature that the physiological pattern of disease identifies patients who will potentially benefit from PCI. Patients with a high *trans*-lesional gradient typically represent focal lesions in which PCI is associated with a significant increase in the post-PCI FFR and a greater freedom from angina.[56] Conversely, in patients with diffuse functional disease where *trans*-lesional gradients are less pronounced, there is often limited improvement in the FFR following PCI, which translates into poorer outcomes and less symptom improvement.[56] The 3D CT-FFR model allows clinicians to determine a virtual 'CT-FFR pullback' across the entire coronary tree, providing a noninvasive appreciation on the physiological pattern of disease. The CT-FFR technology has also evolved to allow clinicians to perform 'virtual stenting' and thereby accurately predict the improvement in FFR after PCI in both diffuse and focal lesions, including patients with high calcium burden.[57,58] This tool, known as the 'CT-FFR planner,' allows clinicians to determine pre-procedural revascularization strategies and identify a sub-group of patients with physiologically significant CAD where PCI may provide limited benefit (Fig. 4). The clinical impact of the PCI planner is currently being investigated in a randomized control trial investigating outcomes of CT-guided PCI with PCI planning

Table 2
Ongoing studies in CT-FFR. Exploring emerging directions in noninvasive coronary artery assessment.

Name of Trial	Goal/Objective	Summary	Location	Completion date	Link
The MATCH investigation: CT myocardial perfusion and CT-FFR vs PET MPI	To compare results from a computed tomography (CT) myocardial perfusion imaging (CT-MPI) scan and CT-fractional flow reserve (FFR) with the actual standard clinical care represented by a PET myocardial perfusion imaging (PET-MPI) study.	The overall goal of this project is to compare the absolute quantification of myocardial perfusion done by using CT myocardial perfusion imaging (CT-MPI) and the coronary flow measured by using CT fractional flow reserve analysis (CT-FFR) to the gold standard represented by PET myocardial perfusion imaging (PET-MPI).	USA	2023-09-30	https://clinicaltrials.gov/study/NCT04316676
DEFINing the PrEvalence and characteristics of coronary Artery disease among patients with TYPE 2 myocardial infarction using CT-FFR (DEFINE TYPE2MI)	To Assess the prevalence of obstructive CAD in type II MI patients	The primary objectives of this study include: 1. Determine the prevalence of coronary artery disease among patients with type 2 myocardial infarction 2. Determine the prevalence of hemodynamically significant stenosis among patients with type 2 myocardial infarction The investigators hypothesize that patients with type 2 myocardial infarction will have a high burden of coronary artery plaque and a high prevalence of obstructive coronary artery disease with hemodynamic significance.	USA	Recently completed	https://clinicaltrials.gov/study/NCT04864119
Evaluation of diagnostic Accuracy, safety, and cost-effectiveness of the noninvasive cardiolens[1] FFR-CT pro method to measure the fractional flow reserve in diagnostics of chronic coronary syndromes versus the standard diagnostic modalities.	A multicentre post-marketing trial of a class 2a Medical device, cardiolens FFR-CT pro - software for noninvasive determination of haemodynamic parameters in coronary Arteries.	Patients with medical history for ischaemic heart disease will take part in noninvasive determination of haemodynamic parameters in coronary arteries with cardiolens FFR-CT pro technology.	Poland	Recently completed	https://clinicaltrials.gov/study/NCT04777513
CMR versus CT in coronary Artery disease (CONCORD)	CONCORD is a prospective observational study evaluating the diagnostic accuracy of cardiovascular magnetic resonance (CMR) and computed tomography with fractional flow reserve (CT-FFR) in patients with suspected coronary artery disease, using invasive fractional flow reserve (FFR) as the reference standard.	The purpose of this prospective observational study is to evaluate the diagnostic performance of all three modalities (CT-FFR and qualitative and quantitative CMR perfusion imaging), involving 300 patients with suspected coronary artery disease referred for invasive coronary angiography. A subset of 167 subjects will undergo an additional accelerated CMR scan for comparison. Invasively measured fractional flow reserve (FFR) will serve as the reference standard.	UK	2025-06-05	https://clinicaltrials.gov/study/NCT04761991
Risk evaluation by COronary CTA and Artificial intelliGence based fuNctIonal analyZing tEchniques - I (RECOGNIZE-I)	The purpose of the study is to establish a coronary artery disease risk stratification system by coronary CTA and anatomic, functional and radiomic analysis, assisted by artificial intelligence.	This study is a multicenter, retrospective imaging study. The study intends to retrospectively enroll patients with acute myocardial infarction who had received coronary CTA in a certain time-window before this event. All coronary CTA will be analyzed by anatomic, functional and radiomic analysis, assisted by artificial intelligence. The purpose of this study is to establish a coronary artery disease risk stratification system by coronary CTA.	China	2025-12-31	https://clinicaltrials.gov/study/NCT05884008
Complete functional Assessment of intermediate coronary Artery stenosis before and After transcatheter aortic valve implantation (TAVI) in patients with severe symptomatic aortic valve stenosis (CHOICE-FR)	The purpose of the current study is to assess complete coronary physiology (FFR, RFR, CFR, IMR, and CT-FFR) in TAVI candidates with intermediate coronary artery stenosis before and 6 months after TAVI. This aims to determine how TAVI affects coronary blood flow and coronary microcirculatory function after longer-term follow-up, and how these effects influence FFR and RFR values. In addition, it is aimed to correlate invasive functional testing (FFR and RFR) with noninvasive CT-FFR before and 6 months after TAVI.	Prospective, single center, open-label study to 1. Compare coronary flow reserve (CFR), index of microvascular resistance (IMR), fractional flow reserve (FFR) and resting full cycle ratio (RFR) values before TAVI and 6 months after TAVI 2. Correlate testing of microcirculatory function (IMR) with measurements of functional testing (FFR and RFR) before and six months after TAVI 3. Correlate functional testing (FFR and RFR) with computed tomography (CT) derived fractional flow reserve (CT-FFR) before and six months after TAVI.	Germany	2024-06-30	https://clinicaltrials.gov/study/NCT05133843
CT-FFR for coronary in-stent stenosis based on ISR-Net[2] Algorithm	Assessing the flow of coronary in-stent stenosis using ISR-Net algorithm and comparing CT-FFR value with invasive FFR.	To predict the sensitivity, specificity and accuracy of CT-FFR in the functional sense of in stent lesions based on ISR-Net algorithm.	China	June 1, 2024	https://classic.clinicaltrials.gov/ct2/show/NCT05131191

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Table 2 (*continued*)

Name of Trial	Goal/Objective	Summary	Location	Completion date	Link
Role of on-site CT-derived FFR in the management of suspect CAD (TARGET trial)	Studying the impact of on-site CT-derived FFR on managing patients with stable chest pain.	The primary aim of this registry is to evaluate whether the availability of CTA/CT-FFR procedure could effectively optimize the flow of clinical practice of stable chest pain versus conventional clinical pathway in decision making, avoid the overuse of invasive procedure, finally improve clinical prognosis and reduce total medical expenditure.	China	Recently completed	https://clinicaltrials.gov/study/NCT03901326
Clinical outcomes of CT-FFR versus QFR-guided strategy for decision making (CONFIDENT trial)	Comparing CT-FFR guided group with QFR guided group in a multicenter, prospective, randomized controlled trial.	This study is a multicenter, prospective, blinded (blinding of clinical evaluators), randomized controlled, event-driven non-inferiority clinical trial. Eligible subjects who meet the inclusion criteria will be registered in the central randomization system and randomized in a 1:1 ratio to either the experimental group (CT-FFR guided group) or the control group (QFR guided group).	China	May 2028	https://clinicaltrials.gov/study/NCT05857904
Assessing diagnostic value of noninvasive FFR-CT: In coronary care in the emergency department (ADVANCE-ED)	Prospective multicenter study to assess the impact of CT-FFR on patient management and treatment costs; compared to CCTA alone.	To assess reclassification rate and cost between the coronary management plan based on the review of the CCTA alone compared to the coronary management plan based on the review of the CCTA and the FFR-CT analysis.	USA	Recently completed	https://clinicaltrials.gov/study/NCT05325112
CABG based on CT-FFR versus conventional coronary Angiography (CABG-COREA trial)	Randomized comparison of coronary artery bypass grafting based on CT-derived FFR versus angiography.	The aims of study are (1) to compare early and 1-year graft patency rates in patients who underwent coronary artery bypass grafting (CABG) based on conventional coronary angiography (CAG) versus cardiac computed tomography (CT)-derived fractional flow reserve (FFR), and (2) to demonstrate difference in clinical outcomes between the 2 groups.	South Korea	2024-10-01	https://clinicaltrials.gov/study/NCT06028165
Follow-up with CT-FFR in CHD patients After DCB[3]	Using AI-based CT-FFR to analyze coronary artery lesions in patients after DCB treatment.	A self-developed CT-FFR based on artificial intelligence is used to analyze coronary artery lesions in patients after DCB, and to compare the guiding value of CT-FFR and simple CCTA in ICA and revascularization, to provide an ideal noninvasive imaging follow-up tool for elderly patients after DCB.	China	2024-06-30	https://clinicaltrials.gov/study/NCT04664439
Dynamic CT perfusion for functional Assessment of coronary Artery disease	Assessment of cardiac biomarkers including FFR and myocardial perfusion from a single dynamic imaging sequence.	The objective of this multicenter study is to evaluate the diagnostic accuracy of dynamic cardiac CT perfusion (CTP) imaging for noninvasive functional assessment of coronary artery disease (CAD). The proposed CTP technique allows concomitant assessment of two imaging-derived cardiac biomarkers including fractional flow reserve (FFR) and myocardial perfusion from a single dynamic imaging sequence, which facilities simultaneous evaluation of the hemodynamics in epicardial coronary arteries and coronary microcirculation in patients with CAD. The CTP results will be compared with invasive coronary angiography/FFR assessment and noninvasive cardiac magnetic resonance imaging (CMR)/radionuclide perfusion assessment.	Canada	2024–03	https://clinicaltrials.gov/study/NCT04712513
Diagnostic performance of fractional flow reserve derived from coronary CT Angiography (ACCURATE-CT)	Determining the diagnostic performance of CT-FFR from CCTA compared to CCTA alone.	This is a blind evaluation, self-control, multicenter clinical trial designed to determine the diagnostic performance of CT-FFR from coronary computed tomographic angiography (CCTA), as compared to CCTA alone, for noninvasive diagnosis of the presence of a hemodynamically significant coronary stenosis, using invasive fractional flow reserve (FFR) as the reference standard.	China	Recently completed	https://clinicaltrials.gov/study/NCT04426396

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Table 2 (*continued*)

Name of Trial	Goal/Objective	Summary	Location	Completion date	Link
Clinical evaluation of magnetic resonance imaging in coronary heart disease 3 (CE-MARC 3)	Evaluate pragmatic ESC-based testing vs NICE-first anatomical strategy.	Large UK RCT (n = 4000) comparing ESC guideline-driven functional/anatomic testing to NICE-mandated CTCA-first strategy in stable chest pain; primary endpoint includes cardiovascular death, MI, or normal angiography	UK	Ongoing (expected April 2027)	https://doi.org/10.1186/ISRCTN88179970

Table 3
Comparison of FFRCT Solutions. Table 3 provides a structured comparison of commercially available and emerging FFRCT solutions, distinguishing between computational fluid dynamics (CFD)-based models, hybrid CFD-AI models, and machine learning (ML)-driven approaches. The table includes key diagnostic and prognostic validation studies, clinical applicability, and limitations of each method. Traditional CFD-based models (e.g., HeartFlow, Siemens) require hemodynamic modeling for flow simulations, while AI-driven solutions (e.g., DeepVessel, Elucid, Cleerly) use data-driven algorithms to predict ischemia and assess plaque characteristics.

Technique	Modelling Method	Diagnostic Studies	Clinical Utility Studies	Advantages/Disadvantages	Validation Status
HeartFlow FFR_{CT}	Computational Fluid Dynamics (CFD)	DISCOVER-FLOW, DeFACTO, NXT, PACIFIC-1	PLATFORM, ADVANCE, PRECISE	+ Most validated, widely adopted + High diagnostic accuracy - Requires high-quality CTA images - Off-site cloud processing required	FDA-approved, widely used in clinical practice
Siemens CT-FFR	CFD-based with AI enhancements	MACHINE registry, Siemens internal validation	Ongoing clinical studies	+ Rapid CT-FFR processing + Point of care technique - Less validation compared to HeartFlow -Still requires manual, time-consuming luminal segmentation	Not yet FDA approved, available in select regions
Canon CT-FFR	Reduced-order CFD Model	Small-scale validation studies	Ongoing research	+ Point of care technique - Requires multiple CTCA phases - Higher radiation exposure	Needs larger scale validation
Elucid	AI-driven plaque assessment	Small-scale studies, internal validation	Ongoing studies	+ Incorporates plaque characteristics for potentially improved risk stratification + Potentially lower computational cost - Less clinical validation	Emerging technology, pending large-scale validation
Keya Medical DeepVessel CT-FFR	AI-based model	ADAPT	TARGET	+ Uses AI for automated segmentation + Faster than CFD models - Limited independent validation	FDA approved, used in clinical practice
Cleerly AI-QCT	AI-based plaque modeling for ischemia prediction	PACIFIC-1, CREDENCE	Initial clinical utility studies	+Automated AI segmentation -Binary ischemia assessment - No real-world validation	FDA-approved, undergoing further validation

compared with PCI guided by intravascular ultrasound (IVUS) (NCT05253677).

The application of computational fluid dynamics to derive CT-FFR also permits the derivation of wall shear stress (WSS). The WSS represents the force of blood flow exerted on the arterial wall. The WSS plays an important role in plaque progression and plaque rupture. There is increasing evidence that the substrate for lesions leading to myocardial infarction includes a combination of the plaque composition (*i.e high risk features)* in addition to haemodynamic environment (ie *wall shear stress)*. The EMERALD study (Exploring the Mechanism of Plaque Rupture in Acute Coronary Syndrome Using Coronary CT Angiography and Computational Fluid Dynamic) demonstrated that investigated the utility of both CCTA and CFD assessment in the identification of high-risk plaque in patients with acute coronary syndromes (ACS). In seventy-two patients with documented ACS, the integration of noninvasive hemodynamic assessments improved the identification of high-risk plaques for future cardiac events.[42] Given the low positive predictive value of high-risk plaque on CCTA(50), the integration of CT-derived hemodynamic parameters such as CT-FFR and WSS has the potential to refine personalized cardiovascular risk assessment. Table 2 presents an overview of ongoing studies in the field of CT-FFR, highlighting emerging directions in noninvasive coronary artery assessment.

10. Conclusion

In conclusion, integrating CT-FFR with computational fluid dynamics and artificial intelligence into routine CCTA holds significant promise for enhancing the assessment of anatomical lesion severity.

Furthermore, ongoing research into alternative methods for deriving CT-FFR, such as machine learning algorithms ($AI\text{-}QCT_{ISCHEMIA}$), and emerging directions in utilizing CT-FFR to predict the response to percutaneous coronary intervention and assess hemodynamic parameters like wall shear stress offer exciting opportunities to refine personalized cardiovascular risk assessment and optimize patient management strategies.

Overall, the integration of CT-FFR into clinical practice represents a significant advancement in noninvasive coronary artery disease assessment, offering a comprehensive approach that combines anatomical and physiological data to improve diagnostic accuracy, prognostic value, and patient outcomes. Continued research and innovation in this field hold the potential further to enhance our understanding and management of coronary artery disease.

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