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Practice Guidelines

# Fractional flow reserve in coronary computed tomography angiography: An expert consensus document of the society of cardiovascular computed tomography (SCCT) and the society for cardiovascular angiography and interventions (SCAI). Endorsed by the American college of cardiology (ACC)☆,☆☆

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## Abbreviations

| | |
|---|---|
| ACC | American College of Cardiology |
| ACP | Acute Chest Pain |
| ACR | American College of Radiology |
| ACS | Acute Coronary Syndrome |
| ADVANCE | Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care |
| AHA | American Heart Association |
| ANOCOR | Anomalous Connections of the Coronary Arteries |
| AUC | Area Under the Curve |
| CAD | Coronary Artery Disease |
| CAD-RADS | Coronary Artery Disease Reporting and Data System |
| CABG | Coronary Artery Bypass Grafting |
| CACS | Coronary Artery Calcium Score |
| CCTA | Coronary CT Angiography |
| CE | Conformité Européenne |
| CFD | Computational Fluid Dynamics |
| CI | Confidence Interval |
| CMR | Cardiac Magnetic Resonance |
| CTA | Computed Tomography Angiography |
| CT-FFR | CCTA Derived Fractional Flow Reserve |
| Δ CT-FFR / delta CT-FFR | Change in CT-FFR across a lesion (translesional gradient) |
| DS | Diameter Stenosis |
| ECG | Electrocardiogram |
| EMERALD | Exploring the Mechanism of Plaque Rupture in Acute Coronary Syndrome Using Coronary Computed Tomography Angiography and Computational Fluid Dynamics |
| ESC | European Society of Cardiology |
| FDA | Food and Drug Administration |
| FFR | Fractional Flow Reserve |
| FFRCT / FFRCT | CT-Derived Fractional Flow Reserve (branded/ formal variant, e.g., HeartFlow) |
| FISH&CHIPS | FFR-CT In Stable Heart disease and Coronary Computed Tomography Angiography Help Improve Patient care and Societal costs |
| FORECAST | Fractional Flow Reserve-Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain |
| HR | Hazard Ratio |
| HRP | High-risk plaque |
| ICA | Invasive Coronary Angiography |
| IVUS | Intravascular Ultrasound |
| kVp | Kilovoltage Peak |
| LAD | Left Anterior Descending artery |
| LM | Left Main (Coronary Artery) |
| LOE | Level of Evidence |
| MB | Myocardial Bridging |
| MACE | Major Adverse Cardiovascular Events |
| MI | Myocardial Infarction |
| ML | Machine Learning |
| MRI | Magnetic Resonance Imaging |
| NICE | National Institute for Health and Care Excellence |
| NXT | Analysis of Coronary Blood Flow Using CT Angiography: Next Steps |
| OMT | Optimal Medical Therapy |
| Pa | Aortic Pressure |
| PACIFIC | Prospective Comparison of Cardiac PET/CT, SPECT/ CT Perfusion Imaging and CT Coronary Angiography With Invasive Coronary Angiography |
| PCCT | Photon counting computed tomography |
| PCI | Percutaneous Coronary Intervention |
| Pd | Distal Coronary Pressure |
| PLATFORM | Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impacts |
| PPV | Positive Predictive Value |
| PRECISE | Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization |
| SCCT | Society of Cardiovascular Computed Tomography |
| SPECT | Single-Photon Emission Computed Tomography |
| STEMI | ST-Elevation Myocardial Infarction |
| SYNTAX | Synergy Between PCI With Taxus and Cardiac Surgery (used in scoring system) |
| TARGET | Effect of On-Site CT-Derived Fractional Flow Reserve on the Management of Decision Making for Patients With Stable Chest Pain |
| TAVR | Transcatheter Aortic Valve Replacement |

## 1. Introduction and preamble

Coronary CT Angiography (CCTA) is an established first line test in international chest pain guidelines, with clinical utilization growing rapidly.[1–3] Despite its high accuracy for the detection of atherosclerosis and quantifying anatomical stenosis, there is often a discordance between anatomical severity and physiological flow restriction across a lesion, resulting in lower specificity in detecting flow limiting disease.[4] CCTA derived fractional flow reserve (CT-FFR) estimates the physiological significance of a lesion using the anatomical data from the CCTA study, modelling the expected results obtained using pressure wire measured invasive fractional flow reserve (FFR) performed during invasive coronary angiography (ICA). CT-FFR has been recognized within guidelines as a useful adjunct in patients with intermediate stenosis in order to determine whether there is lesion-specific flow limitation, which is used as a surrogate for downstream myocardial ischemia to help guide patient management.[1,5] This consensus statement seeks to provide an evidence based framework for the: 1) optimal acquisition of CCTA for the use of CT-FFR; 2) appropriate selection of cases for CT-FFR usage; 3) interpretation and 4) reporting of the outputs of CT-FFR. Standardization of the interpretation and reporting of CT-FFR is key to clear and consistent communication across clinical and research teams. This consensus statement builds on, but does not replace, the best practice guidance already in existence for the acquisition of CCTA, and the reporting framework set-out in the Coronary Artery Disease Reporting and Data System (CAD-RADS) 2.0.[6,7]

There are multiple approaches and technologies for the modelling of FFR from CCTA. As these are all derived from the CCTA dataset they share many similar principles. As such, CT-FFR, which is an umbrella term including all these technologies, will be used throughout the manuscript except where there are important distinctions that must be drawn. These include instances such as prospective randomised controlled trials of clinically available tools, where the shorthand will follow that laid out in Table 1.

The development and conduct of this consensus statement have been performed in accordance with the Society of Cardiovascular Computed Tomography (SCCT) scientific document development standards.[8]

**Table 1**
Summary of the current clinical and research CT-FFR tools available.

| Technology | CT-FFR modelling approach | Approvals[a] |
|---|---|---|
| **Clinically available** | | |
| $FFR_{CT}$, Heartflow[41] | 3D CFD model | US, Europe, UK, Japan, Canada, India |
| DEEPVESSEL FFR, Keya Medical Technology Co.[88] | DL based model trained on CCTA and invasive FFR | US, Europe, UK, China, India |
| skCT-FFR, Shukun Technology Inc[89] | ML model trained on reduced order CFD models | China |
| RuiXin-FFR, Raysight Medical[154] | Reduced order CFD model | China |
| AccuFFRct, ArteryFlow Technology[155] | Reduced order CFD model | China |
| uAI-FFRCT, United Imaging Healthcare[156] | Reduced order CFD model | China, India |
| HeartMedi+, AiMedic[157] | Reduced order CFD model | South Korea |
| **Research only tools with diagnostic accuracy data** | | |
| cFFR, Siemens[24] | ML model trained on synthetic CFD models | |
| XFFR, GE[158] | ML model trained on synthetic CFD models | |
| Toshiba CT-FFR, Toshiba[159] | Reduced order CFD model | |
| CT-FFR, Heartcentury co. Ltd[160] | Reduced order CFD model | |
| uCT-FFR, United Medical[156] | Reduced order CFD model | |
| CT-QFR, Pulse Medical[161] | Reduced order CFD model | |
| $FFR_{AI}$, Spimed[162] | DL based model trained on CCTA and invasive FFR | |
| **Research only tools with no diagnostic accuracy data**[a] | | |
| CT-$FFR_B$, National Heart Centre Singapore | Reduced order CFD model | |
| Elucid FFR-CT, Elucid Inc | DL based on post processed CT features | |
| CardioSimFFRct, Shengshi Technology Co. | Reduced order CFD model | |

CFD = Computational Fluid dynamics; DL = Deep learning; ML = Machine Learning.
[a] As of May 2026.

A literature review was performed to inform the writing of the manuscript, with an example of the search terms used for this in the supplemental materials. A Delphi process was used to formulate the wording and strength of the recommendations, with 2 rounds of voting. An 80% concordance was required for a consensus statement to be reached. Where ≥80% of the group agreed that a statement was appropriate, but could not agree on the strength of this, the average score was calculated from the individual responses (whereby 3 = strong; 2 = moderate; 1 = weak; 0 = more evidence required; −1 = recommended not to do).

The SCCT ensures compliance with all existing standards for the declaration of conflict of interest by all authors and reviewers for the purpose of clarity and transparency.[8] SCCT Guidelines Committee documents provide population-based recommendations based on current published data and expert consensus. Experts consider a variety of locations and practice settings, independent of cost or local availability, when making recommendations. Imaging is assumed to be interpreted by an expert imager. Individual patient care decisions should always take into account patient-specific factors, site resources, and local practice guidelines.

## 2. Fractional flow reserve

### 2.1. Overview of fractional flow reserve

Coronary atherosclerosis causes anatomic changes to the vessel wall that may ultimately progress to physiological reduction in flow that, in turn, can cause downstream myocardial hypoperfusion and ischemia. Whilst resting perfusion is often maintained until 80–90% stenosis, hemodynamic pressure loss may occur under hyperemic or physiologic stress at 30% stenosis and above, with increasing frequency of flow limitation with increasing severity.[9–11] However there is a high rate of discordance between the anatomical and functional assessment of a stenosis, with mild anatomical plaques associated with flow limitation, and plaques resulting in >70% diameter stenosis may often be associated with no downstream ischemia.[9,10] These observations relate to a variety of interacting factors such as stenosis severity, length, plaque burden and type, the size of the subtended myocardium, and state of the microvasculature.[12]

Direct invasive measurements using pressure sensor guidewires can determine the hemodynamic significance of a stenosis. One of the most commonly used invasive physiologic standard is FFR, defined as the ratio of maximal hyperemic flow across an epicardial coronary stenosis compared to the maximal hyperemic flow in the same artery without the stenosis. By eliminating autoregulation, hyperemia causes a low and stable microvascular resistance, which allows a ratio of distal coronary pressure to aortic pressure (Pd/Pa) obtained during hyperemia to be a good estimator of the ratio of flow. Although non-hyperemic pressure ratios such as the instantaneous wave-free ratio (iFR) have increasingly been used clinically due to their simplicity and clinical noninferiority compared with FFR, CT-FFR has been validated primarily against FFR.

An FFR of ≤0.75 has the highest correlation to abnormal ischemic testing while an FFR <0.67 has been identified as the point at which

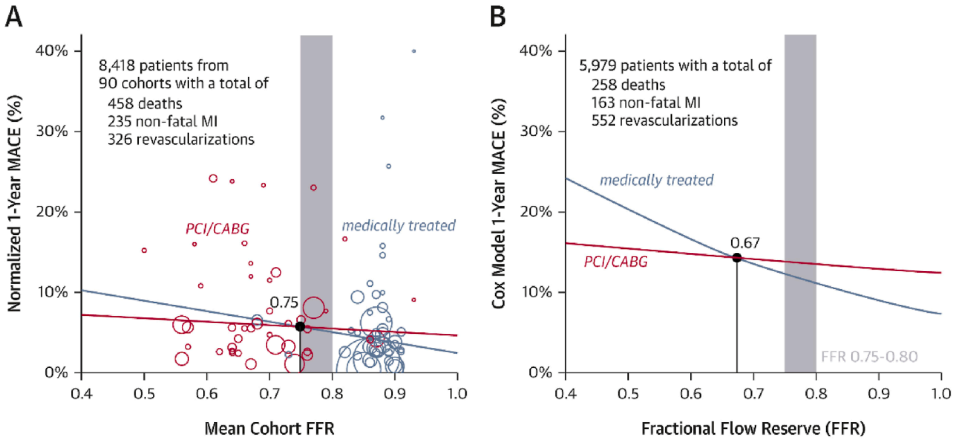



**Fig. 1.** Continuum of risk across FFR values in A) study-level and B) patient-level meta-analyses of outcomes from published studies. From Ref. 153 with permission.

revascularization may start to provide greater benefit than medical therapy for the prevention of cardiovascular events (Fig. 1). In clinical practice an FFR ≤0.80 is used as a threshold to suggest that the patient may benefit from coronary revascularization. While randomised trials that have compared comprehensive invasive pressure wire assessment of all major coronary vessels to angiographic assessment alone in stable chest pain (such as FAME-3, RIPCORD 2, FUTURES) have consistently failed to demonstrate a reduction in hard end-points, this strategy does yield lower rates of downstream tests, and repeat hospital visits.[13–15] The availability of systematic invasive FFR data across all vessels improves and homogenises the decision-making pathway for patients with stable chest pain within the heart team.[16] Despite this, its use in clinical practice remains variable: only 18.5% of intermediate stenoses undergo routine invasive FFR, which increases to 75% among lesions that ultimately proceed to PCI.[17] Even in clinical trials stipulating for comprehensive FFR assessment, only 80% of stenoses can undergo invasive FFR due to technical challenges.[15] The principle of routine comprehensive physiological assessment would inevitably be more easily achieved if this data could be generated non-invasively, and available in advance of any invasive procedures.

## 3. CT-FFR principles

CT-FFR uses the anatomical structures from the CCTA to provide an estimation of the FFR within the coronary vessels. Multiple computational solutions have been developed to estimate the hemodynamic significance of angiographic CAD, of which only a few are currently available for clinical use – Table 1. These are broadly split into computational fluid dynamics (CFD) based techniques, and machine learning (ML) based techniques.

CFD is a branch of fluid mechanics that uses numerical analyses and data structures to analyze and solve problems that involve fluid flows.[18] For the computation of FFR from CCTA, CFD techniques are combined with physiological models to estimate the hemodynamic conditions in the coronary arteries, with the CT-FFR applications developed to date varying in design and complexity (Fig. 2). The quality of CT-FFR models depends on the model design as well as the quality of the CT data, with a critical step being the extraction of an accurate 3D model of the coronary lumen. Typically, color-coded display of the calculated FFR values (as the ratio of the calculated coronary and aortic root pressures) are presented onto a volume-rendered coronary angiogram (Fig. 3).[19]

The complexity of the coronary CFD models can be expanded to achieve closer approximation to true physiology (e.g. individually measured physiological parameters, dynamic vessel models, fluid-structure interactions), or simplified to reduce computation times (e.g. reduced spatial dimensions, generalized boundary conditions).[20,21] Currently $FFR_{CT}$ (Heartflow), which is a full 3D CFD based algorithm, is the only tool with widespread approval for use outside of China. CT-FFR solutions that combine 3D CFD for diseased segments with reduced-order approaches for normal coronary sections are less computationally demanding and can be performed rapidly on regular workstations.[22] Although CT-FFR is derived from an individual patient's coronary anatomy, its computational model relies on physiological parameters drawn from general - or at least broadly representative - population cohorts. While individually measured parameters seem

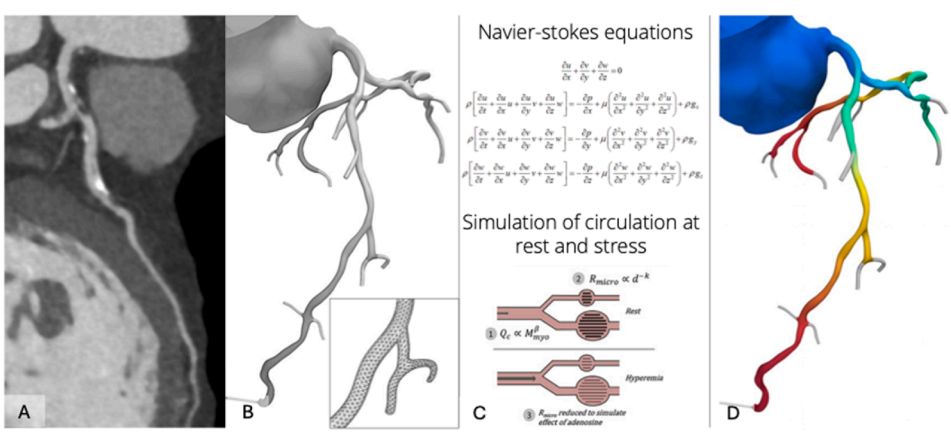



**Fig. 2.** Schematic Presentation of a CFD based CT-FFR analysis pipeline. CCTA data (A) is used to generate a quantitative 3-dimensional anatomic model (B) from which a finite element mesh is generated. A physiological model of the coronary microcirculation is derived with 3 main principles: 1) resting coronary flow proportional to myocardial mass; 2) microvascular resistance inversely proportional to vessel size; and 3) microvascular resistance reduced to simulate maximal hyperemia (C). From this physical laws of fluid dynamics are applied to compute coronary blood flow following which a simulated FFR is calculated for each point in the coronary tree (D).

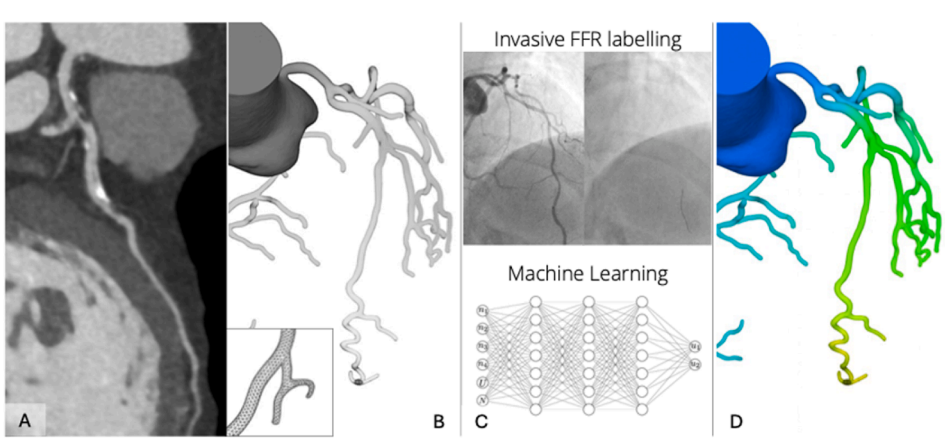



**Fig. 3.** Schematic Presentation of a ML based CT-FFR analysis pipeline. CCTA data (A) is used to generate a quantitative 3-dimensional anatomic model (B) from which a finite element mesh may be generated. Using invasive pressure wire fractional flow reserve (FFR) measurement to label the data, a convolutional neural network is trained using the anatomical data from the CCTA as the input and the invasive FFR as labelling (C). Based on training in a large number of cases a simulated FFR can then be calculated for each point in the coronary tree for any anatomy (D).

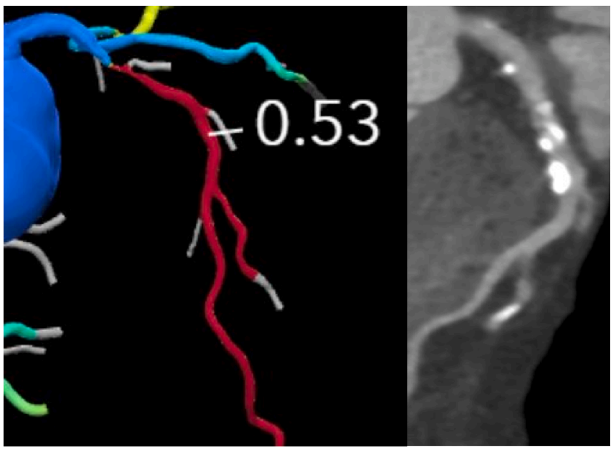



**Fig. 4.** CAD-RADS 4A/P2/I+: A severe (70–90% diameter stenosis) in the proximal LAD artery with a stenosis specific value of 0.53 and high translesional delta CT-FFR (0.40 – from 0.93 pre stenosis). This pattern of focal disease is amenable to percutaneous intervention.
LAD – left anterior descending; LCx – Left circumflex; LM – left main; CTA – computed tomography angiography; I – Ischemia; IV - intravenous; P – Plaque; PDA – posterior descending; RCA – right coronary artery. Displayed analysis performed using $FFR_{CT}$.

preferable, applications that initially included blood pressure measurements and hematocrit samples have since removed these requirements for pragmatic reasons.[23]

As an alternative to individual CFD simulations, accurate prediction of FFR values can be derived using ML algorithms using the anatomical features from CCTA.[24] The approach to how these ML models are trained differ substantially from model to model but ultimately rely on measurements of physiology to inform the ground truth for image labelling and model training. The two most common approaches use either CCTA based CFD models or invasive pressure wire measurements as the ground truth for model training. In the former, CFD-based CT-FFR can be generated in thousands of synthetic coronary models simulating varying anatomy and stenosis severity, before then applying machine learning to these synthetic CFD models to identify morphological features associated with hemodynamic significance.[24] The second approach is to train the model using invasive pressure wire FFR measurements to label the training data (Fig. 4). This latter approach has been used to develop DEEPVESSEL CT-FFR, which is currently the only ML CT-FFR model with approval for clinical use.

ML based techniques have also been used to develop predictive models that provide vessel/patient level probabilities of ischemia using imaging features. These models use a dichotomous cut point for training with vessels labelled as either positive or negative for flow limitation based on invasive FFR, and combine measures of lumen volume, narrowing and atherosclerotic plaque burden from CCTA to predict the presence of physiological flow limitation.[25,26] These show promising diagnostic accuracy and prognostic information in retrospective analysis, with one of these models having been approved for clinical use (Cleerly).[26,27] Currently there is no prospective diagnostic accuracy studies of these technologies. The models provide a probability of flow limitation at a vessel level rather than a CT-FFR, with the output of these tests not directly translatable to CT-FFR. While an $AI\text{-}QCT_{ISCHEMIA}$ of 0.31 shows a high accuracy for the prediction of an invasive FFR value of $\leq$0.80, it remains unclear whether there is a linear, quadratic or other relationship between this and a CT-FFR. It also does not provide continuous and spatially resolved CT-FFR values, meaning that post stenosis CT-FFR or delta CT-FFR cannot be examined. As a result, they are considered beyond the scope of this consensus statement, but can be easily used within the framework of CAD-RADS 2.0 which utilizes an additional classifier to being ischemia positive or negative, with an $AI\text{-}QCT_{ISCHEMIA}$ $\geq$0.31 being considered I+, and <0.31 as I-.[7]

## 4. Acquisition of CCTA for CT-FFR

Image quality is of paramount importance to the robust and reliable extraction of the coronary anatomy to allow for CT-FFR computation. An analysis of over 13,000 CCTA datasets submitted for CT-FFR assessment identified that motion artefacts were the most common reason for a failure to generate CT-FFR (resulting in a 6.7% rejection rate), with this influenced by the heart rate and the temporal resolution of the scanner.[28] These factors also impact the accuracy of CT-FFR which has improved specificity and positive predictive value (PPV) at lower heart rates.[29,30] As a result, adequate heart rate control remains as central to the conductance of CT-FFR as it does CCTA. Administration of nitroglycerin during CCTA acquisition has been shown to result in higher CT-FFR values due to changes in coronary lumen volume, with a consequent improvement in the specificity.[29,31–33] The ability to perform CT-FFR using CCTA data is also improved by higher attenuation in the aorta (and by inference, the coronaries), and spatial resolution, which can be improved by coning in the reconstructed field of view to include just the heart without extraneous capture of the surrounding anatomical structures.[28] High image quality also has beneficial impact in improving the precision of CT-FFR measurement, with reduced interscan variability evident in scans with the highest image quality.[34]

The diagnostic accuracy of CT-FFR has been assessed in relation to patient specific factors impacting CCTA acquisition that may impact change in coronary blood flow, including luminal size, duration of diastolic relaxation, outflow vessels size, and microvascular resistance.[35] Varying reports regarding calculation of CT-FFR along the cardiac cycle have shown stability in some studies,[36,37] as well as small differences in absolute CT-FFR values in systole compared to diastole.[38] These differences increase with increasing severity of flow limitation, with no differences between systolic or diastolic measured CT-FFR when invasive FFR is > 0.80, but with increasing variability between systolic CT-FFR and invasive FFR as pressure loss increases. This resulted in a higher accuracy of diastolic CT-FFR (AUC 0.94) than systolic CT-FFR (AUC 0.77, $p < 0.001$).[38] Thus while CT-FFR can be assessed irrespective of phase, systolic acquisitions with grey zone values must be interpreted with caution.

- ***CT-FFR should be performed only in high image quality CCTA with the use of heart rate control when required; and should be performed in CCTA acquired using nitroglycerin.***

### 4.1. Challenges

CT-FFR depends on precise anatomical luminal definition for accurate physiological modelling. Any inaccuracies in modelling can lead to subsequent errors in the values and interpretation of CT-FFR.[39,40] The presence of extensive calcification and the resulting blooming artefact and beam hardening can hinder the accurate segmentation of coronary luminal boundaries needed for CFD simulations. A sub-analysis of the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps[41]) trial demonstrated that the diagnostic performance of CT-FFR remained high over a wide range of coronary calcification severity.[42] Similarly, ML based CT-FFR showed superior diagnostic performance over CCTA alone in coronaries with extensive calcification, although the performance of CT-FFR diminished as the Agatston-score increased.[43] A contemporary prospective multicentre observational study which enrolled patients with an Agatston-score $\geq$400 examined the utility of CT-FFR in high-risk patients with suspected CAD in the presence of high coronary artery calcium scores (CACS).[44] The per-patient accuracy of CT-FFR was incrementally higher than CCTA in this cohort with a high burden of calcification, but the overall accuracy compared to invasive FFR is lower and with wider limits of agreement than in low calcium cohorts.[44] Despite this, CT-FFR >0.80 in patients with severe calcification is associated with an excellent short to medium term (3 years)

clinical outcome.[44–46] As such, there is no absolute CACS score above which CT-FFR becomes contra-indicated, with the decision as to the appropriateness of the CT-FFR guided by the image quality achieved in those with high calcium burden.

Use of higher kilovoltage peak (kVp ≥120) scanning can reduce blooming artefacts related to high calcium. While this also reduces contrast to noise ratio, its use can still be beneficial in those with high calcium burden if this is known in advance of the contrast enhanced portion of the examination.[47] Higher strength iterative reconstruction techniques have been associated with higher variability in CT-FFR measurements between scans.[34] However further research is required to understand the optimal reconstruction algorithms, with greater understanding of the impact of reconstruction techniques such as high kernel reconstructions, high iteration reconstructions and ML based models on CT-FFR accuracy, particularly in high calcium burden patients.

Several other factors may result in inaccurate luminal segmentation and subsequent modelling error. Low intraluminal contrast opacification, small coronary diameters, misalignment and motion artefacts may cause erroneous CT-FFR values, therefore, it is pivotal to correlate the CT-FFR values with the CCTA images.[39] Notably, total coronary occlusions and vessels with small diameter (usually <1.8 mm) are not modelled, but are commonly referenced with color or graphical symbol.[39,48]

## 5. CT-FFR in stable coronary artery disease

### 5.1. Current usage internationally, and overview of recommendations in current guidelines

The European Society for Cardiology (ESC) 2024 chronic coronary syndrome guidelines and the American Heart Association and American College of Cardiology (AHA/ACC) 2021 chest pain guidelines support the use of CT-FFR in those with intermediate stenosis.[1,5,49] AHA/ACC state that CT-FFR may particularly be beneficial for intermediate stenosis lesions in proximal or mid coronary artery segments (Class 2a recommendation). In the ESC guidelines, CT-FFR has a class 2b recommendation for use in intermediate coronary artery stenosis in the proximal or mid vessel.[5] The UK National Institute for Health and Care Excellence (NICE) in 2017 specifically recommended $FFR_{CT}$ (Heartflow), as an additional test in patients with stable chest pain and intermediate stenosis on CCTA,[50] in contrast to the ACC/AHA/ESC which do not distinguish between CT-FFR models. NICE, ESC and AHA/ACC all conclude that CT-FFR may be useful for diagnosis of vessel-specific ischemia and for guiding decision-making regarding ICA and revascularization.[1,50] The American College of Radiology (ACR) considers the use of CT-FFR as appropriate in the management of low, intermediate and high-risk patients with chronic chest pain in their national guidelines 2018 and 2021.[51,52] CT-FFR has been included in the SCCT guidelines on CCTA, planning revascularization and CAD-RADS 2.0.[7,53,54]

### 5.2. Diagnostic accuracy

CT-FFR has been shown to be accurate in the diagnosis of lesion-specific ischemia. A recent meta-analysis examined 16 studies including 1852 patients covering a wide range of CT-FFR technologies. Using invasive FFR as the reference standard (threshold ≤0.80), there was a pooled sensitivity of 89%, specificity of 71% and area under the receiver-operating characteristic curve (AUC) of 0.90 on a patient level compared with 93% and 32% for CCTA. On a per vessel level, CT-FFR had 85% sensitivity and 82% specificity and an AUC of 0.90, compared with 88% and 46% for CCTA.[55] The improved accuracy for CT-FFR compared with CCTA is maintained when a diameter stenosis of 70% is used for CCTA when the sensitivity and specificity are 70% and 84% respectively (compared with 86% and 79% for CT-FFR).[41] This compares well with perfusion testing, with the PACIFIC study showing greater accuracy of CT-FFR compared with SPECT and PET/CT for the identification of vessel specific ischemia (AUC 0.94, 0.70 and 0.87 respectively).[56] Currently CT-FFR is not approved for use in stented vessels, although preliminary results suggest good accuracy for determining flow limitation associated with in-stent restenosis as well as informing short to medium term prognosis.[57]

A limitation of many diagnostic accuracy studies is that they examine the accuracy of CT-FFR in all vessels irrespective of the degree of stenosis, while most guidelines advocate for its use in those with intermediate stenosis. In two single centre studies focusing on only vessels with intermediate stenosis, the sensitivity was 84–91%, specificity was 55–68%, with an overall accuracy of 70–74%.[58,59] The range of these values reflects the use of lesion specific CT-FFR in one study (where overall accuracy was higher), versus distal vessel CT-FFR values in the other study (see later section for discussion on these). Indeed, in the study examining post-lesional CT-FFR, an additional analysis was performed looking at distal vessel CT-FFR, showing the accuracy of 74% reported in this study fell to 61% if the distal vessel CT-FFR had been used instead of the post lesional CT-FFR. While the overall accuracy is still lower than previous unselected trials, these results were largely comparable to the performance of single-photon emission computed tomography (SPECT) and stress cardiac magnetic resonance (CMR) examined in the same studies. These studies found higher sensitivity in CT-FFR, higher specificity in SPECT and stress CMR, and equivalent overall accuracy (SPECT 68% and CT-FFR 70% in one trial, CMR 74%, CT-FFR 74% in the other).[58,59]

### 5.3. Prognosis

Prospective trials, observational registries and meta-analyses have shown the prognostic value of CT-FFR on clinical outcomes out to 10-years.[45,60–73] In symptomatic patients, a negative CT-FFR result (>0.80) has been consistently associated with a very low risk of myocardial infarction (MI) or cardiovascular death, with a 2.4% 10 year event rate in those with a CT-FFR >0.80.[66] This is consistently seen in CT-FFR studies, even when coronary revascularization is deferred based upon a CT-FFR >0.80.[60,74–76] By contrast, a positive result (≤0.80) predicts a 2-3-fold higher risk of MI, cardiovascular and all cause-death.[65] Furthermore, the total burden of CT-FFR positivity (number of vessels with positive CT-FFR, weighted by severity of flow limitation) correlates with future event rates.[77] This risk-stratification has also been reported in high calcium score cohorts in which CT-FFR remains an independent predictor.[45] A positive CT-FFR result or a failure to achieve complete revascularization of CT-FFR positive disease may also be associated with increased angina recurrence rates and reduced quality of life.[78] CT-FFR must be seen as a continuum rather than an artificial binary cut off value, with increasing severity of flow limitation associated with an increasing risk of ischemia and of adverse outcomes.[65,78,79] Such an approach may further improve prediction of outcome and allow for more patient-tailored and sex-specific strategies. However more data is required, as the majority of the current data on the continuous nature of the risk spectrum is driven by revascularization rather than MI or mortality.

Of the potential measurement locations 1–2 cm distal to the stenosis of interest versus in the distal most point of the vessel (nadir), the CT-FFR at 2 cm distal to the stenosis has been demonstrated to be a strong predictor of major adverse cardiovascular outcomes (Fig. 5). A post stenosis CT-FFR ≤0.80 (often referred to as lesion specific ischemia) is associated with an 6–8 fold greater risk of unplanned revascularization, MI and cardiac death. In comparison, there is no difference in outcomes based on the nadir (lowest distal) CT-FFR.[67] The CT-FFR translesional gradient across an anatomic stenosis has also shown prognostic potential, with high translesional gradients (≥0.06 in one study,[80] and ≥0.10 in another[81]) associated with higher risk of acute coronary syndrome. Nadir CT-FFR values need to be interpreted within the context of anatomic disease along the entire length of the vessel.

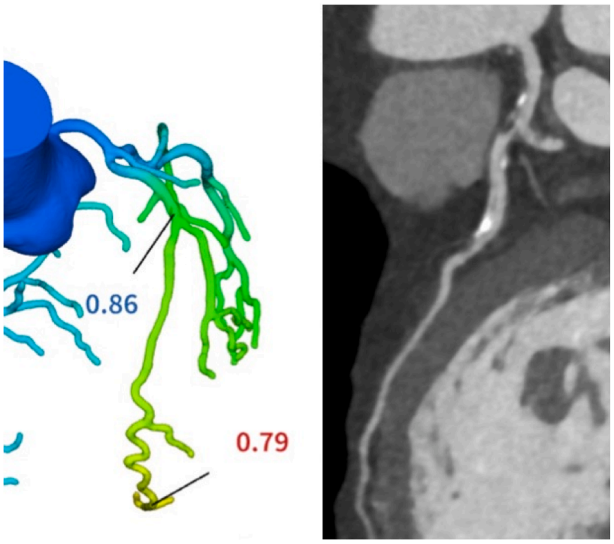



**Fig. 5.** CAD RADS 3/P3/I+: A moderate (50–70% diameter stenosis (DS)) ostial left anterior descending (LAD) stenosis. The post stenosis CT-FFR at 2cm distal to the stenosis is 0.86 in keeping with no lesion specific flow limitation. There is further mild (25–49% DS) mid vessel stenosis. While there is a borderline distal vessel positivity (0.79) there is no acute drop-off in CT-FFR associated with the mid vessel stenosis. This diffuse disease was not considered to derive benefit from percutaneous intervention and was managed with optimal medical therapy.
LAD – left anterior descending; LCx – Left circumflex; LM – left main; CTA – computed tomography angiography; I – Ischemia; IV - intravenous; P – Plaque; PDA – posterior descending; RCA – right coronary artery. Displayed analysis performed using DEEPVESSEL FFR.

### 5.4. Clinical impact

Clinical trials using CT-FFR have generated several consistent findings: 1) a reduced rate of use of invasive coronary angiography; 2) a reduction in the proportion of these invasive coronary angiograms showing no significant coronary disease; 3) a higher conversion rate from ICA to revascularization; 4) no excess in clinical events such as death or MI.[60,74,82–85] The need for additional non-invasive or invasive tests has also been shown to be significantly lower in following implementation of a $FFR_{CT}$ program.[86]

CT-FFR has been demonstrated to change the treatment plan in up to two-thirds of patients as compared to CCTA alone.[82,87] In line with these observations, the PRECISE (Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization) prospective randomized trial showed that CCTA with optional $FFR_{CT}$ (performed in 39% of CCTA) improves clinical efficiency (reduced catheterization without obstructive CAD) with no impact on safety (death, nonfatal MI) after a 1-year follow up period compared with standard of care, predominantly formed of functional imaging.[75] The TARGET (Effect of On-Site CT-Derived Fractional Flow Reserve on the Management of Decision Making for Patients With Stable Chest Pain) trial compared DEEPVESSEL FFR with functional testing in those with intermediate stenosis on CCTA. This study reported lower use of ICA and higher rates of revascularization in the arm guided by DEEPVESSEL FFR.[88] Similar findings have also been observed for skCT-FFR in the China CT-FFR study 3.[89] These trial results have been replicated in the real world in the FISH&CHIPS study (does FFR-CT In Stable Heart disease and Coronary Computed Tomography Angiography Help Improve Patient care and Societal costs?) which examined >90,000 patients in 27 hospitals before and after $FFR_{CT}$ was made available.[86] It showed that second line stress tests and ICA were reduced when $FFR_{CT}$ was available compared to when only CCTA was available, and of those who did go to ICA, they were more likely to be revascularized. With this increased efficiency of the catheter laboratory has come a higher absolute number of PCI, found in TARGET, PRECISE and FISH and CHIPS in the short term, as well as a trend for higher rates of non-fatal MI.[75,86,88] Longer term follow-up is required to understand whether this is due to a higher rate of unnecessary PCIs, or whether this is a cohort receiving PCI who would have been unnecessarily delayed in receiving treatment had they been assessed with other functional tests. Further research is also required to understand whether the signal for MI reflects periprocedural MI secondary to the higher rates of revascularization, or arising from another source, as well as further understanding of what the implications of these MIs are given that these have not translated to higher short term cardiovascular mortality even in large scale population studies.[86]

### 5.5. Cost effectiveness

Cost effectiveness analysis have been conducted examining the current approved CT-FFR technologies, based on multiple randomised control trials[74,88,90] However it should be recognized that cost-effectiveness, and health economic analysis are heavily dependent on the local system costs. As this is an expert consensus document with an international focus and scope, we steer readers to analysis relevant to their local healthcare system.

- ***It is recommended that CT-FFR be used in stable chest pain***

### 5.6. Use in multivessel disease

The availability of CCTA with CT-FFR may allow for a comprehensive identification of functionally significant coronary obstruction, thereby facilitating bespoke targeting for revascularization.[91] In patients with three-vessel disease and/or left main (LM) CAD, the SYNTAX III REVOLUTION trial demonstrated that clinical decision-making between CABG and PCI using CCTA and $FFR_{CT}$ had a high level of agreement with treatment decisions based on ICA and provide a similar prognostic value at 5-years.[92,93] In the FASTTRACK CABG trial, patients already deemed suitable for CABG were worked up for CABG using only CCTA data and $FFR_{CT}$, with surgical planning feasible in 99% of cases, and 90% graft patency at 30 days.[94] Randomised control trials are now necessary to further evaluate the role of CCTA and CT-FFR in guiding decisions on surgical management in multivessel disease. Such decisions on considering PCI or CABG (or indeed neither) are complex, and wherever possible should be taken in the context of a heart team discussion.

U.S. Food and Drug Administration (FDA) approved and CE (Conformité Européenne)-marked tools are becoming available (such as Planner, HeartFlow), that allows the simulation of stenting diseased segments, modelling the anticipated $FFR_{CT}$ outcome post intervention, thus facilitating the projected ability of stenting to improve blood flow within that vessel.[95] The accuracy of this simulation is favourable in validation studies against invasive physiology and optical coherence tomography.[95] Preliminary studies suggest that this may usefully inform PCI strategy,[96] and potentially help guide therapeutic decisions, with prospective trials currently ongoing to test these hypothesis.

- ***CT-FFR is reasonable in the evaluation of three vessel obstructive coronary artery disease.***

### 5.7. Use in stents, bypass grafts, and chronic total occlusions

CT-FFR has not been validated in stents and bypass grafts, therefore it should not be used in clinical decision making at this time. In those with stents, CT-FFR can be still performed in non-stented coronary arteries. CT-FFR cannot be performed in chronic total occlusive lesions due to a lack of lumen in which to model flow, but can be considered for use for evaluation of other non-occluded vessels if PCI is considered.[39] However caution should be used in the interpretation of CT-FFR in such situations. While CTO has not commonly been an exclusion criterion in diagnostic accuracy trials, dedicated reports of the accuracy of CT-FFR

in patients with a CTO are not available. The accuracy may also be impacted by the CT-FFR model being used. The non occluded vessels in patients with CTO will have increased blood flow across stenosis, meaning there is a greater flow limitation for the same degree of stenosis in the presence of a CTO. In CFD models which use the myocardium to determine the flow within the coronaries (such as $FFR_{CT}$), this increased flow is accounted for in the modelling. Reduced order CFD models will not account for this and may underestimate the degree of flow limitation. It is not possible to comment on the accuracy of ML-based models in CTOs, as it is not clear whether CTOs were present in the training data of any of these models, nor how the class imbalance may have been handled if they were present.

## 6. Acute chest pain

CCTA is recommended in both the European and American Guidelines (Class IIa) for the evaluation of acute chest pain (ACP) patients with normal or intermediate troponin levels with a normal electrocardiogram (ECG).[1,97] The addition of CT-FFR has been proposed as an option to improve specificity and better refine decision-making for these patients. There remains, however, a lack of conclusive data supporting its use in this setting. Factors that have limited its use to date include the strength of conventional treatment pathways reliant on highly sensitive serum biomarkers and ECG changes, greater challenges in acquiring high-quality CCTA studies in this cohort, processing times required for segmentation and computation of CT-FFR, as well as the fundamental pathophysiological differences between acute and chronic coronary syndromes. In those with ST-elevation myocardial infarction (STEMI) the assumption upon which the principle of FFR is based, i.e. a negligible downstream resistance in the microvascular compartment, is violated in the culprit vessel territory, and to some extent unpredictably in bystander territories. This results in poorer agreement with invasive FFR during the acute period.[98,99] Interestingly, CT-FFR values obtained in the acute period better reflect the hemodynamic significance of non-culprit lesions at follow-up than the acute invasive FFR performed during the index event, and may better reflect the true hemodynamic significance outside of the acute event.[100] Further studies are required to determine which better directs the revascularization strategy of non-culprit lesions. The barriers to implementation of CT-FFR in the ACP setting are reducing - in one study the median turnaround time for the cloud based $FFR_{CT}$ declined from 12 hours in 2015 to just over 2 hours in 2018 bringing this within the expected decision making window required for these patients.[101]

The presence of a positive CT-FFR is associated with a 4 fold higher risk of being diagnosed with an acute coronary syndrome.[102] As in stable CAD, there is often a discordance between the anatomical severity of stenosis and its flow limitation in ACP, suggesting the potential use of CT-FFR to reclassify risk in ACP.[101] In line with ACP patients being in a more unstable condition, with more challenging pre-scanning preparation, CT-FFR analysis has been reported to only be possible in 59–68% of the eligible study population.[102,103]

Incorporation of CT-FFR within the clinical workflow of ACP patients can be implemented effectively with no difference in major adverse cardiac events in a cohort study comparing before and after the implementation of $FFR_{CT}$ within their unit, with no difference in costs between those with CCTA without the option of CT-FFR versus CCTA $\pm$ $FFR_{CT}$.[101] In the ACP setting, CT-FFR better predicts the need for revascularization and MACE events than coronary stenosis severity alone.[104]

Overall, the data evaluating the use of CT-FFR in acute chest pain is limited and derived from a few retrospective, small to medium sized studies. To date, these studies have consistently highlighted the need for good image quality for CT-FFR feasibility, which can be challenging in ACP patients.

- ***CT-FFR might be reasonable in the evaluation of acute chest pain***

## 7. CT-FFR in special circumstances

### 7.1. Surgical and procedural work up

Applications of CT-FFR are being assessed in periprocedural workup in non-coronary cardiac surgeries and procedures. Of these, the use of CT-FFR has been best explored in transcatheter aortic valve replacement (TAVR). The safety of nitroglycerin has been demonstrated in severe AS with preserved left ventricular function in two studies now – an essential step for CT-FFR given the impact of nitroglycerin on accuracy.[105,106] A single centre study of 240 patients in Aarhus administered 800 mcg of nitroglycerin in 79% of patients, and 400 mcg in the other 21% without any adverse events.[105] The CAST-FFR study of 42 patients with severe aortic stenosis demonstrated safety of using low dose nitroglycerin in stable severe aortic stenosis patients without left ventricular systolic impairment or significant aortic regurgitation. It also demonstrated a good diagnostic accuracy for $FFR_{CT}$ (AUC of 0.81) against invasive FFR and that this performed significantly better than CCTA alone.[106] A retrospective analysis of 196 patients with CCTA imaging who were referred for transcatheter aortic valve replacement (TAVR) reported that abnormal CT-FFR signaled a 4 fold increase in the risk of nonfatal MI, unstable angina, cardiac death, or heart failure admission, with improved prediction compared with CCTA alone.[107]

- ***CT-FFR might be reasonable in TAVR work up.***

In the assessment of CAD post-heart transplantation, positive CT-FFR with focal stenosis was present in 25% and, even in the absence of focal stenosis, CT-FFR values were abnormal in the distal coronary segments in 74% of the cases.[108] Diffuse CT-FFR pressure loss shows good performance against the gold standard of invasive angiography and intravascular ultrasound, and it is also able to monitor temporal shifts in flow restriction.[109,110] However prospective trials are required.

- ***Further data is required before a recommendation can be made on the use of CT-FFR in the assessment of coronary allograft vasculopathy.***

Another emerging application of CT-FFR is the periprocedural workup of patients undergoing non-cardiac surgery, such as organ transplantation. Organ failure and transplantation is associated with increased cardiovascular risk and non-invasive diagnostic testing alternatives are frequently utilized to supplement preoperative evaluation.[111] High accuracy has been confirmed in transplant cohorts,[112] with a positive CT-FFR associated with a 4 fold increased risk of cardiac death, resuscitated cardiac arrest, non-fatal MI independent of risk factors and transplantation.[113] CT-FFR has also been evaluated in risk assessment prior to vascular surgery. In a prospective analysis of patients scheduled to undergo peripheral vascular surgery for limb-threatening ischemia, a strategy incorporating $FFR_{CT}$ reduced all-cause death (8.1% vs 20.0%; Hazard Ratio (HR) = 0.38; 95%-confidence interval (CI):0.18–0.84; $p = 0.016$) and the composite of major adverse cardiovascular events of cardiovascular death, MI, unplanned coronary revascularization, stroke (10.8% vs 23.3%; HR = 0.44; 95% CI:0.22–0.88; $p = 0.021$) when compared to standard of care.[114] Prospective randomized controlled trials are now required to substantiate the potential impact of this approach.

- ***CT-FFR might be reasonable in the assessment of CAD in non-coronary pre-surgical assessment (in asymptomatic patients when a CCTA has already been performed for CAD assessment).***

### 7.2. Anomalous coronary arteries and myocardial bridges

CCTA has detection rates for myocardial bridging (MB) higher than other modalities when compared with the gold standard of autopsy, and

is far superior to ICA.[115] Although most MB are considered benign, some MB may cause angina and myocardial infarction.[116] While myocardial bridges have not been excluded from any prospective diagnostic accuracy study of CT-FFR, the potential impact of this must not be overlooked, especially if systolic acquisition is being performed given the dynamic interaction between the bridge and luminal diameter. CT-FFR remains appropriate to determine the significance of a stenosis in a patient with coincident myocardial bridging remote to the stenosis of interest. In the assessment as to whether a MB is causative of symptoms, or associated with significant pressure loss, the existing literature is conflicted. In a retrospective multi-center study of 104 patients with left anterior descending (LAD) MB, CT-FFR performed well with a sensitivity, specificity, and accuracy of 96%, 84%, and 89%, respectively, for detection of ischemia associated with MB, as compared with invasive FFR.[117,118] In comparison, in 49 symptomatic patients with myocardial bridges who underwent comprehensive invasive evaluation and CCTA, ML-based CT-FFR values did not correlate with invasively measured dobutamine-stress diastolic FFR, conventional FFR, or with systolic coronary compression on IVUS.[119]

- ***Further data is required before a recommendation can be made on the use of CT-FFR in the assessment of the functional significance of a MB.***

Although CCTA is accurate for evaluation of the presence of anomalous coronary arteries and aneurysms, limited data exists about CT-FFR for the hemodynamic evaluation of these abnormalities. Current registry data from the observational multicentric Anomalous Connections of the Coronary Arteries (ANOCOR) registry, which included 62 CCTAs with CT-FFR analysis showed that reduced CT-FFR values are common in this group, particularly in the presence of a slit like orifice and acute angulation – both common findings in intra-mural courses. This cohort revealed that CT-FFR values were lower in those with an inter-arterial course and that the threshold for identification of intramural path was a CT-FFR $\leq$0.83, which is higher than the value validated for coronary stenosis assessment in stable CAD.[120]

- ***Further data is required before a recommendation can be made on the use of CT-FFR in the assessment of the functional significance of anomalous coronary arteries.***

## 8. Clinical use criteria

The use of CT-FFR in dependent on clinical and CCTA findings. CT-FFR is appropriate in patients with 50–90% stenosis in vessels other than the LM. It should be performed when the information it provides would change the investigation or management of patients, over the CCTA information alone.

Variations by gender and age in CT-FFR interpretation should be taken into account as these differences may affect therapeutic decision making and clinical outcomes.[79,121] CT-FFR differs between the sexes, as women have a higher CT-FFR for the same degree of stenosis. In CT-FFR-positive CAD, women have less obstructive CAD at ICA and less revascularization.[79] However, when a more stringent cut-point for CT-FFR is used, with a CT-FFR <0.75 considered positive, the prevalence of obstructive disease on ICA and rates of revascularization do not differ by sex.[79] With regard to age, some studies indicate a low risk of MACE events or need for revascularization in those aged $\geq$65 years, or <65 with a CT-FFR >0.80, despite the higher incidence of anatomic obstructive CAD in those $\geq$65 years, showing the clinical utility of CT-FFR is largely constant regardless of age.[121] A negative CT-FFR has consistently been associated with a low event rate and favors conservative management, with CT-FFR improving the net reclassification of CAD by 68% and decreasing non-obstructive disease in ICA by 44%.[1,64,76,84,93,122,123]

CT-FFR is not appropriate in coronary CTA with <30% stenosis, who are managed with optimal medical therapy (OMT).[39] CT-FFR has a low incidence of flow limitation in the 30–49% stenosis range (6–21% for a positive post stenosis CT-FFR).[61,82,124–126] Despite this, a positive CT-FFR in non-obstructive disease is associated with a higher rate of adverse events compared with non-obstructive disease without any flow limitation, and a negative CT-FFR may be reassuring for those with 30–49% stenosis and chest pain.[127] LAD stenosis are associated with a two-fold increased risk of positive CT-FFR, with typical angina, stenosis in the proximal segment of a vessel, long segment stenosis, and high risk plaque also associated with an increased likelihood of a positive CT-FFR value.[124,126] As a result, location and extent of stenosis may be considered in deciding on whether or not to perform CT-FFR in stenosis of 30–49%, although at present the evidence is insufficient to warrant more concrete recommendations. Further evidence is needed to understand the clinical outcomes and management strategies in those with stenosis of 30–49% and positive CT-FFR to better inform decisions in this group.

CT-FFR may be useful in severe (70–90%) stenosis given the data that ICA may be safely deferred if CT-FFR is negative.[64,76] Traditionally, CT-FFR has not been regarded as appropriate in patients with high-risk anatomy, i.e $\geq$ 50% LM stenosis where the evidence for both FFR and CT-FFR is limited, or three-vessel severe stenosis, since these patients typically require ICA.[1,64,84,93,122,123] However, growing evidence suggests CT-FFR may still be appropriate for revascularization planning, selection of target vessel and appropriate classification of physiologically flow limiting disease in those with multivessel disease.[29,82,83,91,93,128,129] Total (all 3 major epicardial) vessel CT-FFR analysis allows comprehensive pre-invasive angiography flow assessment that can lead to improved revascularization planning. It may result in downgrading of CABG cases to 1 or 2 vessel PCI cases and improve the overall catheterization lab efficiency and revascularization ratio.[82,129]

CT-FFR cannot be performed in occlusive lesions due to a lack of lumen in which to model flow, but can be used for evaluation of other non-occluded vessels if PCI is considered.[39] CT-FFR is not appropriate in small vessels (<1.8 mm), or distal vessels, where the imaging resolution of CT becomes less reliable, in addition to which these are typically not good targets for revascularization and hence managed medically.[48] In serial stenosis, CT-FFR provides geometric information and modeling of hemodynamic interplay for each lesion, which simulate post-revascularization pressure loss.[96,130] As explored in more detail in an earlier section, the additive benefit of CT-FFR above CCTA remains even in those with a high CACS. Hence in the presence of high image quality, heavily calcified plaques should not exclude CT-FFR, however the results must be interpreted within the limitations of a reduced specificity in this cohort.[42–44,102] In those with stents, CT-FFR can be still performed in non-stented coronary arteries.

CT-FFR might be reasonable in ACP with intermediate to low probability of acute coronary syndrome (ACS).[101,102] CT-FFR has poor accuracy in the evaluation of ischemia of nonculprit lesions in STEMI and is currently not appropriate (see Acute chest pain section).[98,131] As covered in the prior section, CT-FFR is not validated in the evaluation of coronary artery bypass grafts. CT-FFR has shown potential in the evaluation of patients with coronary stents, especially with in-stent restenosis <50%, but it is currently only appropriate only for evaluation of other vessels without stents.[57] Recent studies have shown moderate progressive reduction of CT-FFR in coronary artery anomalies; however, no significant differences were observed to enable risk-stratification and there is insufficient evidence for utility of CT-FFR in this setting.[132,133] Similarly, CT-FFR should be used with caution in the presence of MB where the phase of acquisition can significantly impact CT-FFR values.[118] A full summary of the recommendations can be found in Table 2.

- **CT-FFR is recommended for the assessment of coronary artery diameter stenosis of 50–90%.**
- **CT-FFR should be performed when the information it provides could change downstream investigation or management over the CCTA information alone.**

**Table 2**
Consensus statements and level of associated evidence (LOE) for these.

| Consensus statements[a] | LOE |
|---|---|
| CT-FFR should be performed only in high image quality CCTA with the use of heart rate control where required; and should be performed in CCTA acquired using nitroglycerin. (2.9) | B |
| CT-FFR is recommended for the assessment of coronary artery diameter stenosis of 50–90%. (2.6) | B |
| CT-FFR should be performed when the information it provides could change downstream investigation or management over the CCTA information alone. (2.4) | C |
| Post lesional CT-FFR (measured 2 cm distal to stenosis) should be included in all reports where CT-FFR has been performed. (2.8) | B |
| Delta CT-FFR can be considered for inclusion in reports. (1.4) | C |
| **Use of CT-FFR in specific clinical scenarios**[b] | |
| CT-FFR is recommended in stable chest pain. (2.9) | A |
| CT-FFR might be reasonable in acute chest pain. (1.5) | B |
| CT-FFR is reasonable in the evaluation of three vessel obstructive coronary artery disease. (1.95) | B |
| CT-FFR might be reasonable in TAVI work up. (1.3) | C |
| CT-FFR might be reasonable in the assessment of CAD in non-coronary pre-surgical assessment (in asymptomatic patients when a CCTA has already been performed for CAD assessment). (1.25) | C |

LOE: A = Multiple randomised control trials or meta-analysis of RCTs; B = 1 RCT, Large sized prospective non randomised study, or meta-analysis of medium quality RCTs; C = Retrospective studies, registry data or meta-analysis of non randomised studies; D = Expert consensus, or case series.

[a] Formal level of recommendation has not been provided as this is an expert consensus document. Rather than a dedicated LoR, the numbers in brackets (.) represent the average score from the writing group as to the strength of the recommendation (where 0 = insufficient evidence, 1 = weak, 2 = moderate and 3 = strong recommendation) with the wording reflective of the strength of recommendation from should be performed/is recommended (strong), might be reasonable (moderate) and can be considered (weak).

[b] The use in these specific scenarios is predicated upon these satisfying the prior broader criteria of degree of stenosis, and likelihood of affecting management.

## 9. Recommendation for reporting

The reporting of CT-FFR should be seen not as an isolated result but be interpreted and integrated into the CCTA report in accordance with existing Guidelines (CAD-RADS 2.0).[7] The precise structure in which this will occur will vary from site to site, with some incorporating this in the primary report, others issuing addendums after the CT-FFR becomes available, while others still will have a separate secondary analysis of the CT-FFR. Irrespective of the framework in which the CT-FFR is analysed, the principles of interpreting this within the context of the underlying anatomy, and providing written documentation of this interpretation are essential.

### *9.1. How and where to measure*

CT-FFR provides values along the length of the coronary tree in all epicardial vessels. The location and gradation of CT-FFR value is important:

- Stenosis specific values are measured 2 cm distal to a stenotic plaque
- Delta (Δ) CT-FFR is the difference between the stenosis specific value and the value immediately proximal to the stenosis. This provides a translesional gradient.
- Distal vessel values are reported as the lowest value per vessel in the distal tip

Of these, CT-FFR measured 2cm distal to the most severe stenosis has the most robust evidence base and higher specificity for diagnosis and risk stratification for future events.[67,134] As a result it is recommended that this is included in all reports (Fig. 4). This is in accordance with best practices for invasive FFR, as well as providing stenosis specific information.[135] Readers should be aware of the finding of pressure recovery, whereby maximum pressure loss occurs within the stenosis, but improves post stenosis, with maximum pressure recovery at 0.8–1.7 mm post stenosis.[136,137] These transient pressure drops within a stenosis should not be misinterpreted as a restriction in flow, rather they are an inevitable consequence of the Venturi effect as blood is accelerated through the point of stenosis. It is the pressure in the vessel post pressure recovery that drives distal perfusion, with this being a key reason for measuring the CT-FFR at a point 2 cm distal to the stenosis.

- **Post lesional CT-FFR (measured 2 cm distal to stenosis) should be included in all reports where CT-FFR has been performed.**

Delta CT-FFR has a reported improved specificity for lesion-specific ischemia and may therefore be particularly useful when post stenosis CT-FFR values range from 0.70-0.80.[138,139] A higher agreement for the detection of lesion-specific ischemia has been shown using delta CT-FFR (values ≥ 0.12) compared to lesion-specific CT-FFR (≤0.80) with the lowest diagnostic accuracy compared to invasive FFR reported for the lowest-value CT-FFR obtained from the distal most aspect of the vessel (≤0.80).[138] A stenosis specific value of ≤0.80 combined with higher *trans*-lesional gradients (≥0.12) improves the overall specificity and positive predictive value of the CT-FFR, has a closer correlation with measures of ischemia (invasive FFR) and improved prediction of the benefit from revascularization.[80,139] As a result, it is reasonable that delta-CT-FFR be included in the CCTA report, particularly where there is concern as to whether a low CT-FFR is due to a specific stenosis or the gradual drift of diffuse disease. This may also be of use in serial stenosis, where multifocal stenosis can result in a low CT-FFR value distal to the most distal stenosis. Here, the delta CT-FFR can provide weight to each of the stenosis' contribution to flow limitation, with a low delta CT-FFR in the presence of a 'positive' post stenosis CT-FFR in a distal segment suggesting this is the result of diffuse disease and high plaque burden, with no lesion specific ischemia. However a definitive cut-off for flow limitation has not been prospectively evaluated for delta-CT-FFR, and a lower value (≥0.06 to 0.10) has been associated with higher risk of acute coronary syndromes.[80,81] Where available, the use of virtual stenting to model the effects of relieving each of the stenosis in turn can provide more accurate estimations as to the relative contribution of serial stenosis to flow restriction and to potential treatment impact.[130]

- **Delta CT-FFR can be considered for inclusion in reports.**

The distal vessel CT-FFR may reflect the overall vascular health and plaque burden with positive values frequently observed despite mild coronary stenosis (Fig. 5).[82] In some cases it may help diagnose angina and have prognostic implications, but positive distal values should be interpreted with caution as they may also represent false positive values in small poorly defined distal vessels reducing CT-FFR specificity for flow limitation.[140] It should also be noted that distal CT-FFR represents the FFR at the most distal point of the modelled vessel while 'distal' FFR on invasive pressure wire measurement typically reflects only the proximal aspect of the distal third of the vessel. CT-FFR has only been validated as distal in the vessel as a pressure wire can be placed, thus distal CT-FFR values which occur far past this should not be used for decisions relating to revascularization or percutaneous intervention.[124] As a result there

**Table 3**
Key considerations in the use of CT-FFR and areas for future research in areas not reaching consensus.

| Pearls | Future research |
|---|---|
| Perform CT-FFR in high quality CCTA | Optimal reconstruction techniques for CCTA for use in CT-FFR calculation |
| Consider CT-FFR as a continuous value<br>- The lower the CT-FFR the higher the probability of flow limitation and long-term adverse events<br>- Grey zone values (0.70–0.80) have intermediate probability of flow limitation and adverse events | Determining the CT-FFR values that best identify long term risk, and their utility in guiding management. |
| Consider delta CT-FFR in grey-zone CT-FFR values, and distal positive CT-FFR values, particularly in proximal lesions | Current studies suggest a cut point of 0.12 for determining the functional significance of a focal stenosis, however prospective validation of delta CT-FFR cutpoints is required. |
| Consider CT-FFR in allograft vasculopathy in cases where revascularization is to be considered | Prospective diagnostic accuracy studies are required to determine optimal cut points and outcomes from |
| Be aware of limitations of CT-FFR in chronic total occlusions, and how this varies with specific CT-FFR solutions | Diagnostic accuracy of CT-FFR in CTO cohorts, and how this relates to pre and post CTO procedure coronary flow. |
| Discuss complex cases in coronary artery multidisciplinary teams | Use of virtual stent planning in CT-FFR models, and how these affect both symptomatic improvement as well as prognosis |
| Pitfalls | |
| Don't use CT-FFR for assessment of the significance of left main disease | Cut-points and threshold to use in LM disease - particularly in how to consider the differential flow drop-off in the LAD and LCx - need determined and validated |
| Don't use CT-FFR for assessing the functional significance of myocardial bridges | While CT-FFR can be used in the presence of myocardial bridges, more research is required to determine cut points across bridges, as well as the impact of systolic versus diastolic imaging |
| Don't use CT-FFR for assessing the functional significance of anomalous coronary arteries | While CT-FFR can be used in the presence of anomalous coronary arteries, particularly in the assessment of the non-anomalous vessel, more research is required to determine cut points |
| Don't interpret an isolated positive distal vessel CT-FFR as indicative of the functional significance of a single lesion | Optimal management strategies in lesions without lesion specific flow limitation but positive distal vessel CT-FFR requires further investigation. |

**Table 4**
Exemplar report template (based on the clinical case presented in Fig. 6B).

| |
|---|
| CLINICAL HISTORY |
| Typical angina. Hypertension and hypercholesterolaemia. |
| COMPARISON |
| No prior study available for comparison |
| TECHNIQUE |
| Non-contrast prospective ECG-gated scan of the heart was performed for calcium scoring, followed by a prospective ECG-gated coronary CTA performed post administration of intravenous contrast medium. |
| Good quality images with minor coronary motion artefact. |
| Total DLP = 112 mGycm. |
| No prior test for comparison. |
| MEDICATIONS |
| 800 mcg of sublingual nitroglycerin and 10 mg intravenous metoprolol administered prior to the start of the study. |
| TECHNICAL QUALITY |
| Excellent with no artefacts |
| CORONARY FINDINGS |
| The coronaries arise in normal position. There is right coronary dominance. |
| Coronary artery calcium score = 84. |
| RCA: Non-calcified plaque in the mid RCA causing mild (25–49%) stenosis. Non-calcified plaque in the distal RCA causing mild (25–49%) stenosis. |
| LM: The left main is a medium sized vessel and bifurcates into the LAD and LCx. It demonstrates no evidence of plaque or stenosis. |
| LAD: Calcified plaque in the proximal LAD causing severe stenosis (>70%). This involves the bifurcation extending into the mid LAD and a large first diagonal causing severe stenosis (>70%) in both. Further focus of non-calcified plaque in the mid LAD distal to this causing mild stenosis (25–49%) which has evidence of positive remodelling. In the single diagonal vessel there is a further focus of non-calcified plaque distal to the bifurcation lesion causing mild stenosis (25–49%). |
| LCx: Normal vessel with no evidence of coronary artery disease. Non-calcified plaque in the OM1 causing mild (25–49%) stenosis. |
| CT-FFR: |
| The proximal LAD stenosis demonstrates a high probability of significant flow limitation with a post stenosis (measured at 2cm distal to the stenosis) CT-FFR of 0.58 in both the LAD and D1, and a delta CT-FFR across the stenosis of 0.36. The OM1 stenosis shows a post stenosis CT-FFR of 0.94, while the RCA stenosis shows a post stenosis CT-FFR of 0.93, both in keeping with a low probability of flow limitation. The low CT-FFR in the PDA occurs in a region of minor artefact without evident plaque, and is likely artefactual. |
| NON-CORONARY CARDIAC FINDINGS |
| Cardiac valves: The aortic valve is trileaflet. There is no thickening or calcifications in the aortic or mitral valves. |
| Pericardium: The pericardial contour is preserved with no effusion, thickening or calcifications. |
| EXTRACARDIAC FINDINGS |
| There are no significant extra-cardiac findings in the available limited views of the lungs, mediastinum or upper abdomen. |
| OPINION: |
| Moderate burden of coronary atherosclerotic plaque, for which aggressive risk factor modification and preventative pharmacotherapy should be considered. |
| Calcified plaque of the proximal LAD involving the bifurcation into the mid LAD and a large first diagonal causing severe stenosis of all three. This shows a high probability of flow limitation of both the LAD and diagonal. |
| CAD RADS 4A/P3/HRP/I+. |

Nb. This is an exemplar report, and the precise format will depend on each centres organisation for the reporting of CT-FFR. The reporting of the coronary plaque location, morphology and severity as well as the cardiac and extra-cardiac findings all follow the recommendations in CAD-RADS 2.0.

CAD-RADS - Coronary Artery Disease Reporting and Data System; DLP – Dose length product; LAD – left anterior descending; LCx – Left circumflex; LM – left main; CTA – computed tomography angiography; HRP – high risk plaque; I – Ischemia; P – Plaque; PDA – posterior descending; RCA – right coronary artery.

is currently insufficient evidence to recommend the routine reporting of distal CT-FFR, although it may be useful for understanding the global state of the vessels flow. In vessels with proximal stenosis (supplying a large myocardial territory) without lesion-specific ischemia, but with CT-FFR values ≤ 0.80 in nearby mid-segments, assessment for the extent of upstream disease and myocardium at risk may be useful.[141,142] Positive CT-FFR values in such cases may be clinically relevant requiring invasive assessment, although more research is needed to determine the best management strategy in these cases (see Table 3).

- ***Further data is required before a recommendation can be made on the routine reporting of distal vessel CT-FFR.***

### 9.2. How to integrate the report

Stenosis specific CT-FFR should be reported on a per vessel and per stenosis basis (see Table 4 for an exemplar report integrating CCTA and CT-FFR findings). When there are multiple stenoses in the same vessel these should be reported individually (Figs. 5 and 6).

Post stenotic CT-FFR interpretation:

>0.80 - low probability of flow limitation.

0.70–0.80 - intermediate probability of significant flow limitation.

<0.70 - high probability of significant flow limitation.

Delta CT-FFR can be used to improve the specificity of the assessment of a stenosis. A delta CT-FFR of 0.12 combined with a CT-FFR ≤0.80 should be interpreted as being at high probability of significant lesion specific flow limitation.

Distal vessel CT-FFR >0.80 is in keeping with a low risk of flow limitation, however a CT-FFR ≤0.80 should not be interpreted as indicative of a focal flow limiting lesion. It should instead be interpreted in the context of the post stenotic CT-FFR and disease distribution on the CCTA. A high post stenotic CT-FFR (>0.80) and low distal vessel CT-FFR (nadir) may arise secondary to diffuse CAD (which should be managed by OMT – see next section) or arise secondary to artefact from subtle vessel motion, or small distal vessels. It is also important to consider image quality and the indication for the CT-FFR when the analysis was performed. An incidental 'positive' CT-FFR (either post stenosis or distal vessel) in a vessel where no anatomical stenosis was originally reported requires further inspection of the vessel to determine whether a stenosis was missed on the original report, or whether this is a false positive secondary to an artefact or lack of nitrate administration.

### 9.3. Clinical management recommendations based on CT-FFR

The level of detailed information available from the combination of CCTA and CT-FFR means clinical interpretation is essential for next step patient management. CT-FFR reports (whether generated at the time of CCTA reporting, or remotely) should include guidance on downstream investigation or referral, rather than just reports of numbers (Fig. 7). As such, CT-FFR should be interpreted and reported by those with appropriate expertise, whether this be a cardiologist with an imaging interest, a radiologist with cardiac interest, or interventionist with appropriate dedicated training. Where the CT-FFR report is part of the CCTA report, it should be emphasized that guidance is exactly this. The final treatment decision rests on the holistic discussion between the patient and their

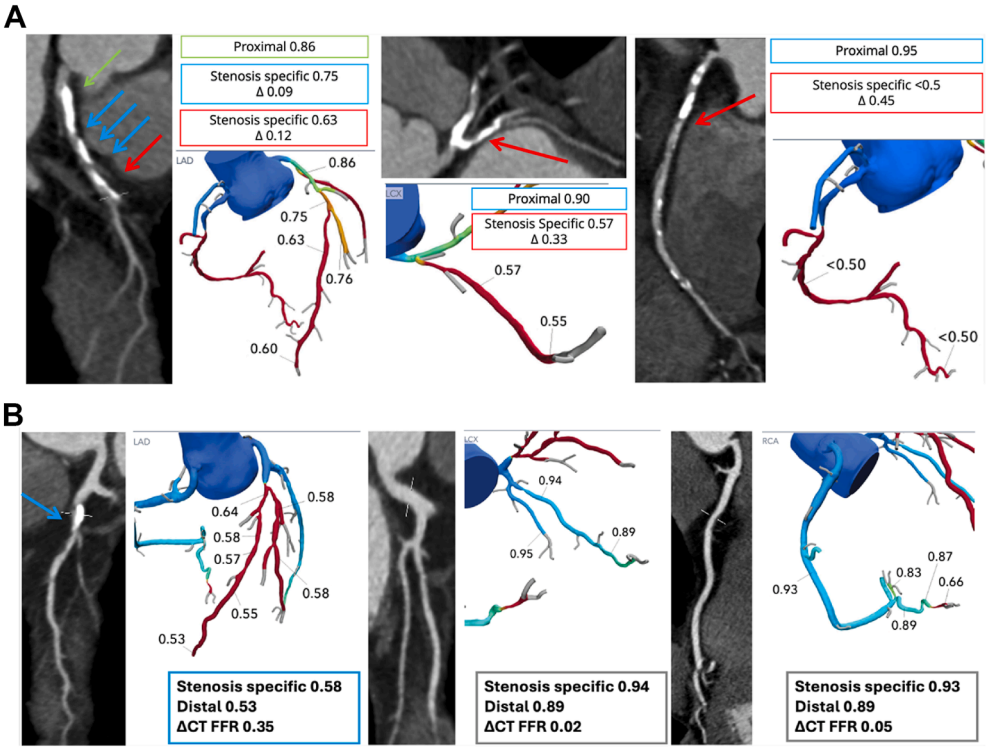
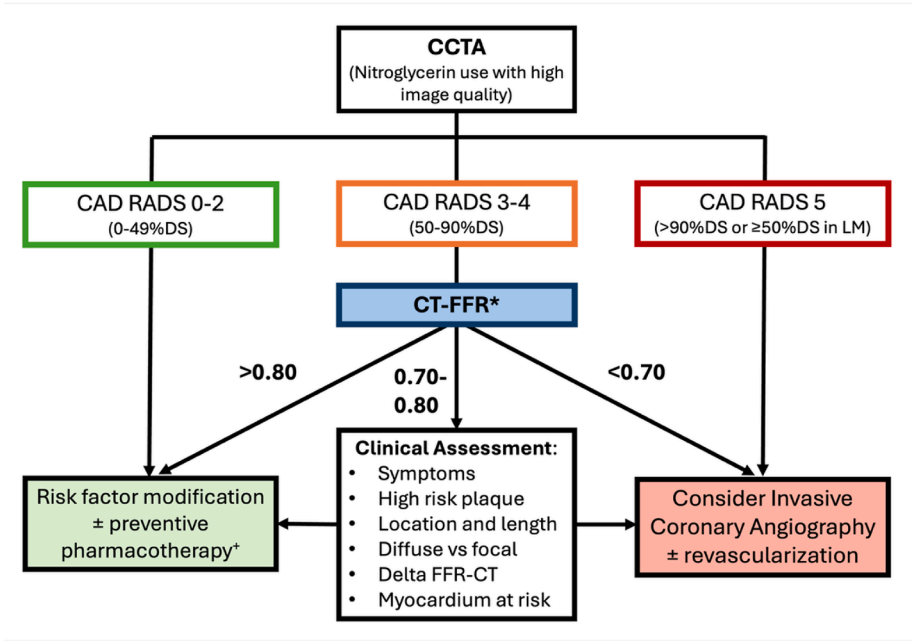



**Fig. 6. A.** CAD RADS 4B/P3/I+. CT FFR shows significant flow limitation in all 3 coronary arteries.
Left anterior descending artery (LAD) distal 0.60, stenosis specific 0.63 and delta 0.12; Left Circumflex (LCx) distal 0.55, stenosis specific 0.57 and delta 0.33. Right coronary artery (RCA) distal <0.50, stenosis specific 0.55 and delta 0.45.
The LAD has a long segment of proximal diffuse disease and the LCx stenosis is focal at the ostium of the vessel. The RCA stenosis is focal. RCA would be amenable to PCI but given the LAD and LCX anatomy and flow limitation, assessment for consideration of CABG in a heart MDT would be a key consideration.
**B.** CAD RADS 4A/P3/HRP/I+: CT FFR shows significant flow limitation in the LAD/diagonal and a focal stenosis in the distal PDA.
LAD distal 0.53, stenosis specific 0.58 and delta 0.36; LCx distal 0.89, stenosis specific 0.94. RCA distal 0.89, stenosis specific 0.93. PDA distal value 0.66, delta 0.21.
The LAD stenosis is focal with moderate calcium and would be amenable to PCI but involves the diagonal bifurcation which will need adequate consideration and planning. The distal PDA is < 2 mm so may not be amenable to PCI.
LAD – left anterior descending; LCx – Left circumflex; LM – left main; CTA – computed tomography angiography; HRP – high risk plaque; I – Ischemia; IV - intravenous; P – Plaque; PCI – percutaneous coronary intervention; PDA – posterior descending; RCA – right coronary artery. Displayed analysis performed using $FFR_{CT}$.




*Where the use of CT-FFR would change downstream management or investigation

+Following CAD-RADS 2 recommendations informed by stenosis and plaque burden

**Fig. 7.** Flow diagram for the use of CT-FFR and clinical management based on this
*Where the use of CT-FFR would change downstream management or investigation
+ Following CAD-RADS 2 recommendations informed by stenosis and plaque burden.

physician based on the scan findings, their symptom burden, their response to medical therapy, and their personal preferences.

Stenosis specific and distal vessel values are known to be influenced by several factors including stenosis location (proximal vs distal, LAD vs non-LAD), coronary volume to myocardial mass ratio (i.e. hypertension, MI or cardiomyopathies), gender, ethnicity and risk factors (diabetes, obesity).[79,143–145] Therefore, clinical management recommendations should take these into account as well as patient symptoms, anatomical risk factors (proximal disease, main vessel, dominance), plaque features and the CT-FFR value. The lower the CT-FFR value, the higher the likelihood of ischemia and future major cardiac events, including death.[45,65] A recommendation of consideration of invasive angiography should include details that will be of use if an invasive procedure should occur including the nature of the pressure drop, and anatomical features such as severity of calcification.[54] Focal stenoses with a large peak pressure drop on invasive FFR are more appropriate to treat with PCI resulting in improved post-PCI FFR and clinical outcomes compared to diffuse disease, where the pressure drop is small and across the length of the vessel (Fig. 6A and B).[146] Ultimately, at the current time the decision making with regard to ICA, and subsequent revascularization will fall to a cardiologist and/or surgeon, who may then bring the case to a heart team discussion as per national guidelines. The use of the comprehensive data available from CT-FFR can enable the heart team discussion to decide on optimal management based upon the non-invasive data.

## 10. Future directions and evidence gaps

### 10.1. Additional CFD parameters

Since CT-FFR is underpinned by CFD, additional hemodynamic parameters beyond pressure gradient can be calculated without additional segmentation or computational cost. The EMERALD and EMERALD II studies demonstrated that the integration of delta $FFR_{CT}$, wall shear stress, and axial plaque stress onto $FFR_{CT}$ alone significantly improved the predictability of future occurrence of acute coronary syndrome.[80,81] Given that these forces interact with the adjacent plaque, with the structural integrity of this dependent on the tissue type, it would follow that risk of ACS would depend not only on the forces within the lumen, but the plaque composition. Indeed, this is what was also observed in EMERALD studies whereby low attenuation plaque further improved the model for predicting future ACS. Prospective work is now required to understand how to integrate plaque, CT-FFR and other CFD parameters together to best guide management.[147]

### 10.2. Stent planning

This combination of focality and hemodynamic significance may aid anatomic selection for revascularization. Preliminary studies suggest that this may be further augmented using simulated stent deployment within the anatomical model underpinning the CFD analysis. The diameter, length and position of the stent can be varied, with the CT-FFR model rerun under these new assumptions of geometry to estimate the functional impact of any percutaneous intervention. Stent simulation $FFR_{CT}$ models have been shown to have better agreement with post-PCI FFR, and to anticipate the post-PCI FFR more accurately than estimation based on pre-PCI FFR pullback, with prospective trials of their clinical impact underway.[95,130] In the future this may add significantly to the ability to make provisional decisions regarding need and suitability for revascularization and even whether it should be by PCI or CABG in an heart team employing just non-invasive data.

### 10.3. Photon counting CT

Currently the single greatest source of error in calculating CT-FFR are inaccuracies in the geometry of the artery secondary to the limited spatial resolution of CCTA. This is constrained by the inherent limitations of scintillator detectors as used in the current generation of energy integrated detectors. Photon counting detectors overcome this technical

limitation, significantly boosting the accuracy of coronary delineation, stenosis assessment and reduction in calcification blooming.[148] Early studies show good agreement between CT-FFR derived from photon counting and energy integrated detectors.[149–151] PCCT also provides the opportunity for spectral imaging, with 70kev virtual monoenergetic reconstructions demonstrating the best agreement with standard CT for the calculation of CT-FFR.[152] Prospective studies against the invasive FFR are awaited to provide further insights on the impact on CT-FFR of standard resolution versus ultrahigh resolution, reconstruction techniques, and spectral imaging.

## 11. Conclusion

In patients undergoing CCTA, CT-FFR expands the traditional assessment from that of anatomy and plaque to one incorporating physiological significance. Its use can reduce the number of invasive coronary angiograms, in a cost-effective/cost-neutral manner. The production of high-quality CCTA is critical to the accuracy of the subsequent CT-FFR models, and continued efforts must be focused on optimizing the patient and the scan parameters to achieve this. Based on the combined CCTA and CT-FFR results, a structured approach to the interpretation and reporting of CT-FFR in the context of patient symptoms and coronary anatomy will maximize the yield of this technology, and improve communication and patient decision making. The expanding ability of CT-FFR to assess anatomy, flow limitation and identify high risk plaque features means that it is likely that the clinical value and range of these technologies will increase in routine practice in the next few years.

## Declaration of competing interest

Jonathan Weir-McCall, Gianluca Pontone, Timothy Fairbairn, and Ed Nicol are Associate Editors at the Journal of Cardiovascular Computed Tomography. These Editors had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor acting on behalf of the Society of Cardiovascular Computed Tomography.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://ars.els-cdn.com/content/image/1-s2.0-S1934592526001012-mmc1.docx.

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