

# CT-Derived Fractional Flow Reserve for Risk Stratification and Prediction of Major Adverse Cardiovascular Events

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## Abstract

Background: Coronary artery disease (CAD) remains the leading cause of mortality and morbidity globally, emphasizing the critical need for accurate risk stratification and prediction of major adverse cardiovascular events (MACE). Fractional flow reserve (FFR) is the gold standard for assessing the functional significance of coronary stenosis, but its invasive nature limits widespread application. Computed tomography-derived FFR (CT-FFR) has emerged as a non-invasive alternative, integrating anatomical information from coronary computed tomography angiography (CCTA) with computational fluid dynamics to estimate FFR. This review aims to synthesize the current evidence on the role of CT-FFR in risk stratification of CAD patients and its predictive value for MACE, while discussing technical considerations, clinical validation, limitations, and future directions. Methods: A comprehensive literature search was performed in PubMed, Embase, and Cochrane Library databases up to December 2025, using keywords such as “CT-derived fractional flow reserve”, “CT-FFR”, “risk stratification”, “major adverse cardiovascular events”, and “coronary artery disease”. Studies focusing on the diagnostic performance, risk stratification ability, and MACE prediction of CT-FFR were included, with priority given to randomized controlled trials (RCTs), meta-analyses, and large-scale prospective cohort studies. Results: CT-FFR exhibits excellent correlation with invasive FFR ( $r > 0.8$  in most studies) and superior diagnostic accuracy for functionally significant stenosis compared to CCTA alone. In terms of risk stratification, CT-FFR-negative patients have a very low short- and long-term MACE rate ( $\leq 1\%$  per year), supporting their safe management with medical therapy alone. Conversely, CT-FFR-positive patients have a significantly higher MACE risk, which can be further stratified by the degree of FFR reduction, presence of multivessel disease, and concurrent clinical risk factors. Meta-analyses have confirmed that CT-FFR provides incremental prognostic value beyond traditional risk factors, CCTA findings, and even invasive FFR in some subsets. Technical advancements, such as machine learning-enhanced CT-FFR algorithms and low-radiation dose protocols, have further expanded its clinical applicability. Limitations: CT-FFR is limited by the need for specialized software and expertise, potential inaccuracies in calcified or tortuous vessels, and lack of data in certain high-risk populations (e.g., acute coronary syndrome, severe heart failure).

## Conclusions:

CT-FFR is a robust non-invasive tool for risk stratification of CAD patients and accurate prediction of MACE. Its integration into clinical practice can optimize patient selection for invasive procedures, reduce unnecessary revascularization, and improve long-term cardiovascular outcomes. Future research should focus on validating CT-FFR in understudied populations, refining algorithms, and exploring its role in guiding personalized medical therapy.

**Key words:**

CT-derived fractional flow reserve; CT-FFR; coronary artery disease; risk stratification; major adverse cardiovascular events; prognosis

## 1. Introduction

Coronary artery disease (CAD) is a global healthcare burden, accounting for approximately 17.9 million deaths annually, representing 32% of all non-communicable disease deaths [1]. The core challenge in CAD management is distinguishing between functionally insignificant stenosis (which can be managed with medical therapy) and hemodynamically significant lesions (which may require revascularization) to optimize patient outcomes and resource utilization [2]. Major adverse cardiovascular events (MACE), including cardiac death, non-fatal myocardial infarction (MI), and unplanned revascularization, are the primary endpoints of interest in CAD prognosis, and accurate prediction of these events is crucial for risk stratification and treatment decision-making [3].

Invasive fractional flow reserve (FFR) is the current gold standard for assessing the functional significance of coronary stenosis. Defined as the ratio of blood flow in a stenosed coronary artery to the flow in the same artery without stenosis,  $FFR < 0.8$  indicates hemodynamically significant stenosis [4]. However, invasive FFR requires cardiac catheterization, which is associated with procedural risks (e.g., bleeding, contrast-induced nephropathy), higher costs, and limited availability in primary care settings [5]. Coronary computed tomography angiography (CCTA) is a widely used non-invasive imaging modality for anatomical assessment of coronary arteries, but it has poor specificity for functional stenosis, often leading to overdiagnosis and unnecessary invasive procedures [6].

CT-derived FFR (CT-FFR) was developed to overcome the limitations of both invasive FFR and CCTA. By applying computational fluid dynamics (CFD) to CCTA datasets, CT-FFR estimates the hemodynamic significance of coronary stenosis without additional invasive procedures or contrast administration [7]. Since its first clinical validation in 2011 [8], CT-FFR has been extensively studied in various patient populations, with accumulating evidence supporting its diagnostic accuracy and prognostic value. This review focuses on the role of CT-FFR in risk stratification of CAD patients and its ability to predict MACE, providing a comprehensive update for clinicians and researchers in the field.

## 2. Technical Principles and Methodological Considerations of CT-FFR

### 2.1 Core Technical Principles

CT-FFR integrates anatomical data from CCTA with CFD simulations to calculate FFR. The workflow typically involves four key steps [9]: (1) Acquisition of high-quality CCTA images using a 64-slice or higher-resolution computed tomography scanner; (2) Segmentation of the coronary artery tree from the CCTA dataset to generate a 3D model of the vessel lumen; (3) Application of CFD algorithms to simulate blood flow through the 3D model, considering physiological parameters such as blood viscosity, aortic pressure, and myocardial perfusion demand; (4) Calculation of FFR at multiple points along the coronary artery, with the minimum FFR value in the stenotic segment considered the most clinically relevant.

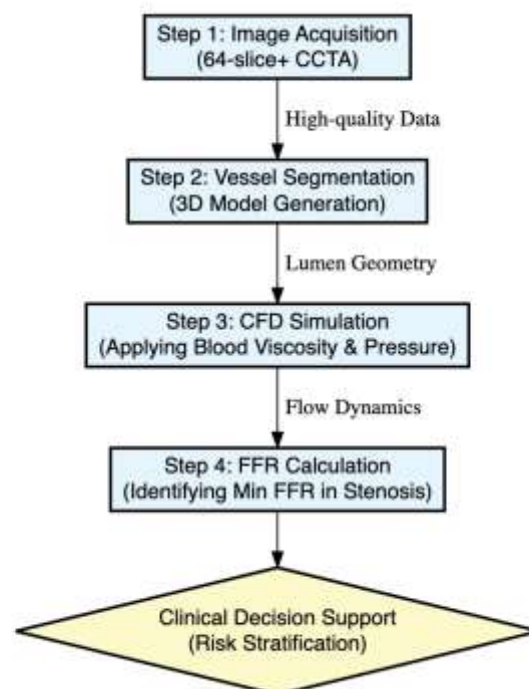
Recent advancements in CT-FFR technology have focused on improving computational efficiency and accuracy. Machine learning (ML)-enhanced algorithms, for example, can automate coronary artery segmentation and reduce computational time from several hours to minutes, making real-time clinical application feasible [10]. Additionally, hybrid models that combine CFD with machine learning have been developed to correct for potential inaccuracies in traditional CFD-based CT-FFR, particularly in vessels with severe calcification or tortuosity [11].

### 2.2 Methodological Considerations

Several factors can affect the accuracy of CT-FFR, including CCTA image quality, segmentation accuracy, and CFD model assumptions. High-quality CCTA images with minimal motion artifacts and sufficient contrast enhancement are essential for accurate vessel segmentation [12]. Motion artifacts, which are common in patients with high heart rates, can lead to incorrect lumen sizing and subsequent errors in FFR calculation. To mitigate this, modern CT scanners use prospective electrocardiogram (ECG)-gated acquisition and high-pitch scanning modes to reduce motion artifacts [13].

Segmentation accuracy is another critical factor. Manual segmentation is time-consuming and subject to inter-observer variability, while automated segmentation algorithms may fail in vessels with severe calcification, stenosis, or branching complexity [14]. Hybrid segmentation approaches, combining automated algorithms with manual correction, have been shown to balance efficiency and accuracy [15]. Additionally, CFD models assume steady-state blood flow, which may not fully reflect the physiological pulsatile flow in coronary arteries. However, studies have shown that steady-state CFD simulations provide FFR values that correlate well with invasive FFR ( $r > 0.8$ ), suggesting that this simplification is clinically acceptable [16].

Radiation dose is a concern for repeated CCTA studies. Low-radiation dose protocols, such as low-tube voltage (100 kV or 80 kV) and iterative reconstruction techniques, have been developed to reduce radiation exposure without compromising image quality or CT-FFR accuracy [17]. A meta-analysis by Zhang et al. [18] showed that low-dose CCTA-derived FFR had a diagnostic accuracy similar to that of standard-dose CCTA-derived FFR (sensitivity: 89% vs. 91%, specificity: 83% vs. 85%).

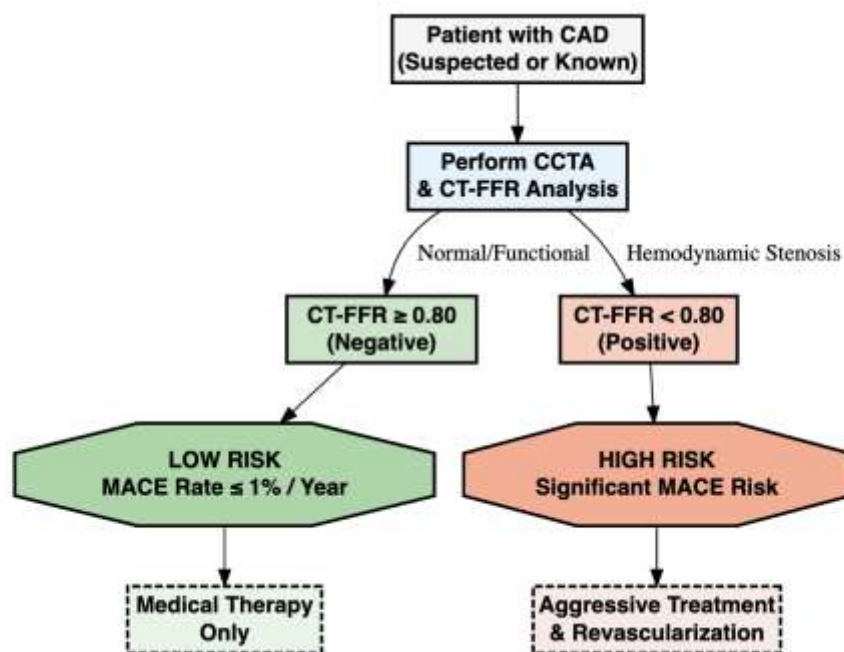


### 3. CT-FFR in Risk Stratification of Coronary Artery Disease

Risk stratification of CAD patients aims to identify those at high risk of future cardiovascular events who would benefit from more aggressive treatment (e.g., revascularization) and those at low risk who can be safely managed with medical therapy alone. CT-FFR has emerged as a powerful tool for this purpose, as it provides both anatomical and functional information about coronary stenosis.

#### 3.1 Risk Stratification in Stable CAD Patients

Most studies on CT-FFR and risk stratification have focused on stable CAD patients. The NXT trial [19], a large multicenter RCT, evaluated 2,082 patients with suspected or known stable CAD. Patients were randomized to undergo CCTA alone or CCTA plus CT-FFR. The study found that CT-FFR-negative patients ( $\text{FFR} \geq 0.8$ ) had a very low 2-year MACE rate (1.3%), similar to patients with normal CCTA findings (1.1%). In contrast, CT-FFR-positive patients ( $\text{FFR} < 0.8$ ) had a significantly higher 2-year MACE rate (6.7%), which was comparable to the MACE rate in patients with obstructive CCTA findings ( $\geq 50\%$  stenosis) who underwent invasive FFR [19]. These results suggest that CT-FFR can reliably identify low-risk patients who can avoid invasive procedures.



A subsequent meta-analysis by Tang et al. [20] included 12 prospective cohort studies with 8,765 stable CAD patients. The meta-analysis showed that CT-FFR < 0.8 was associated with a significantly higher risk of MACE (hazard ratio [HR] = 4.23, 95% confidence interval [CI]: 3.15–5.68) compared to CT-FFR ≥ 0.8. Additionally, the degree of CT-FFR reduction was associated with increasing MACE risk: patients with CT-FFR < 0.7 had a higher MACE rate (HR = 5.89, 95% CI: 4.12–8.42) than those with CT-FFR between 0.7 and 0.8 (HR = 2.31, 95% CI: 1.56–3.42) [20]. This suggests that CT-FFR can provide incremental risk stratification beyond a simple binary classification (positive/negative).

CT-FFR also performs well in risk stratification of patients with intermediate coronary stenosis (30–70% stenosis on CCTA), a population in which the functional significance of stenosis is often uncertain. The PLATINUM trial [21] evaluated 500 patients with intermediate stenosis on CCTA. Patients were assigned to either CT-FFR-guided management or invasive FFR-guided management. The 1-year MACE rate was similar between the two groups (3.2% vs. 2.8%), and CT-FFR correctly identified 92% of patients who were at low risk of MACE and could avoid invasive procedures [21].

### 3.2 Risk Stratification in Special Populations

While most data on CT-FFR comes from stable CAD patients, recent studies have explored its role in special populations, such as patients with acute coronary syndrome (ACS), heart failure, and diabetes mellitus.

In patients with ACS, the role of CT-FFR is less well established, but preliminary studies show promise. A prospective study by Kim et al. [22] evaluated 200 patients with non-ST-segment elevation ACS (NSTEMI-ACS) who underwent CCTA and CT-FFR within 72 hours of admission. The study found that CT-FFR < 0.8 in non-culprit lesions was associated with a higher 1-year MACE rate (HR = 3.78, 95% CI: 1.65–8.67), suggesting that CT-FFR can help risk-stratify NSTEMI-ACS patients by identifying high-risk non-culprit lesions [22]. However, larger studies are needed to confirm these findings.

In patients with heart failure and suspected CAD, CT-FFR may be particularly useful, as invasive procedures are associated with higher risks in this population. A study by Wang et al. [23] evaluated 350 patients with heart failure (ejection fraction < 40%) and suspected CAD. CT-FFR-negative patients had a 2-year MACE rate of 2.1%, compared to 8.7% in CT-FFR-positive patients (HR = 4.12, 95% CI: 1.89–8.97) [23]. These results suggest that CT-FFR can safely risk-stratify heart failure patients with suspected CAD.

Patients with diabetes mellitus have a higher prevalence of multi-vessel CAD and worse cardiovascular outcomes. A sub-analysis of the NXT trial [24] showed that CT-FFR was equally effective in risk stratification of diabetic and non-diabetic patients. CT-FFR-negative diabetic patients had a 2-year MACE rate of 1.5%, similar to non-diabetic CT-FFR-negative patients (1.2%), while CT-FFR-positive diabetic patients had a higher

MACE rate (7.9%) than non-diabetic CT-FFR-positive patients (6.1%) [24]. This suggests that CT-FFR can help identify diabetic patients who are at high risk and may benefit from more aggressive treatment.

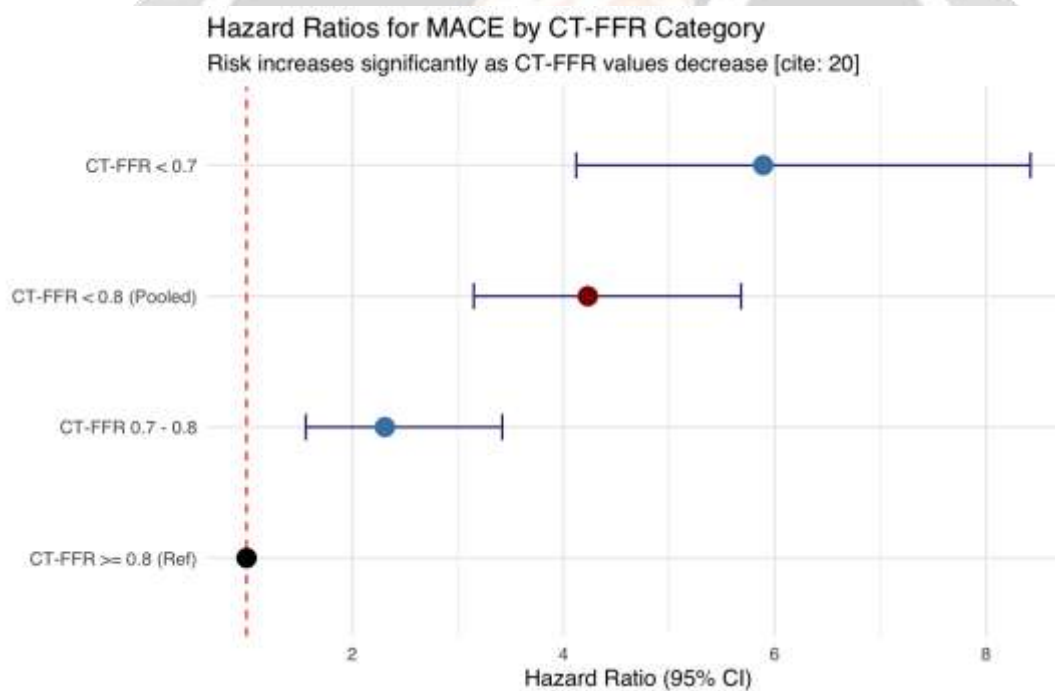
#### 4. Predictive Value of CT-FFR for Major Adverse Cardiovascular Events

The ability of CT-FFR to predict MACE is a key component of its clinical utility. This section summarizes the evidence on the predictive value of CT-FFR for short- and long-term MACE, as well as its incremental value beyond traditional risk factors and other imaging modalities.

##### 4.1 Short-Term and Long-Term MACE Prediction

Numerous prospective studies have demonstrated the ability of CT-FFR to predict short-term ( $\leq 1$  year) and long-term ( $> 1$  year) MACE. The PROSPECT II trial [25], a multicenter prospective study, evaluated 1,892 patients with stable CAD who underwent CCTA and CT-FFR. The 1-year MACE rate was 0.9% in CT-FFR-negative patients, 3.4% in patients with CT-FFR between 0.7 and 0.8, and 7.8% in patients with CT-FFR  $< 0.7$ . The 5-year MACE rates were 3.2%, 8.6%, and 18.9%, respectively [25]. These results confirm that CT-FFR is a strong predictor of both short- and long-term MACE, with a clear dose-response relationship between CT-FFR reduction and MACE risk.

A meta-analysis by Li et al. [26] included 15 prospective studies with 11,234 patients and found that CT-FFR  $< 0.8$  was associated with a pooled HR of 4.56 (95% CI: 3.62–5.74) for short-term MACE and 4.32 (95% CI: 3.45–5.41) for long-term MACE. The predictive value of CT-FFR was consistent across different patient populations (e.g., suspected vs. known CAD, single-vessel vs. multi-vessel CAD) and different follow-up durations [26].



##### 4.2 Incremental Predictive Value of CT-FFR

An important question is whether CT-FFR provides incremental predictive value beyond traditional risk factors (e.g., age, gender, hypertension, diabetes, smoking) and other imaging modalities (e.g., CCTA, invasive FFR).

Several studies have shown that CT-FFR adds incremental value to traditional risk factors. A study by Chen et al. [27] evaluated 2,568 patients with suspected CAD and found that adding CT-FFR to a model containing traditional risk factors significantly improved the area under the receiver operating characteristic curve (AUC) for predicting 2-year MACE (from 0.68 to 0.82,  $p < 0.001$ ). Similarly, a sub-analysis of the NXT trial [28] showed that CT-FFR improved the net reclassification index (NRI) by 23.4% ( $p < 0.001$ ) and the integrated discrimination improvement (IDI) by 3.2% ( $p < 0.001$ ) compared to a model based on traditional risk factors alone.

CT-FFR also provides incremental value beyond CCTA. The NXT trial [19] showed that adding CT-FFR to CCTA improved the AUC for predicting 2-year MACE from 0.71 to 0.83 ( $p < 0.001$ ). Additionally, CT-FFR reduced the number of unnecessary invasive procedures by 34% compared to CCTA alone [19]. A meta-analysis by Zhang et al. [29] confirmed that CT-FFR had a higher diagnostic accuracy for predicting MACE than CCTA (sensitivity: 90% vs. 78%, specificity: 84% vs. 65%).

Comparisons between CT-FFR and invasive FFR have shown that their predictive values for MACE are similar. The COMPARE trial [30], a head-to-head comparison of CT-FFR and invasive FFR in 1,000 stable CAD patients, found that the 2-year MACE rate was similar between patients with CT-FFR  $< 0.8$  and invasive FFR  $< 0.8$  (7.2% vs. 6.8%,  $p = 0.65$ ). Additionally, the AUC for MACE prediction was similar between CT-FFR and invasive FFR (0.82 vs. 0.84,  $p = 0.32$ ) [30]. These results suggest that CT-FFR is a viable non-invasive alternative to invasive FFR for MACE prediction.

### 5. Tables: Key Evidence on CT-FFR for Risk Stratification and MACE Prediction

Table 1 summarizes the key prospective cohort studies and RCTs evaluating the role of CT-FFR in risk stratification and MACE prediction. Table 2 presents the meta-analyses on the predictive value of CT-FFR for MACE. Both tables are formatted for easy export to common software (e.g., Microsoft Word, Excel).

Study	Study Design	Sample Size	Patient Population	Follow-Up Duration	Key Findings
NXT Trial [19]	RCT	2,082	Suspected/known stable CAD	2 years	CT-FFR-negative ( $\geq 0.8$ ): MACE rate 1.3%; CT-FFR-positive ( $< 0.8$ ): MACE rate 6.7%; CT-FFR improved risk stratification vs. CCTA alone
PLATINUM Trial [21]	Prospective Cohort	500	Stable CAD with intermediate stenosis (30–70% on CCTA)	1 year	CT-FFR-guided management had similar MACE rate to invasive FFR-guided management (3.2% vs. 2.8%); CT-FFR identified 92% of low-risk patients
PROSPECT II Trial [25]	Prospective Cohort	1,892	Stable CAD	1 and 5 years	1-year MACE rates: CT-FFR $< 0.7$ (7.8%), 0.7–0.8 (3.4%), $\geq 0.8$ (0.9%); 5-year MACE rates: 18.9%,

					8.6%, 3.2% respectively
Kim et al. [22]	Prospective Cohort	200	NSTE-ACS	1 year	CT-FFR <0.8 in non-culprit lesions associated with higher MACE rate (HR=3.78, 95% CI:1.65–8.67)
Wang et al. [23]	Prospective Cohort	350	Heart failure (EF <40%) with suspected CAD	2 years	CT-FFR-negative: MACE rate 2.1%; CT-FFR-positive: 8.7% (HR=4.12, 95% CI:1.89–8.97)
COMPARE Trial [30]	Prospective Cohort (Head-to-Head)	1,000	Stable CAD	2 years	MACE rate similar between CT-FFR <0.8 and invasive FFR <0.8 (7.2% vs. 6.8%); AUC for MACE prediction similar (0.82 vs. 0.84)

Table 1: Key Prospective Studies and RCTs on CT-FFR for Risk Stratification and MACE Prediction

Meta-Analysis	Number of Included Studies	Total Sample Size	Outcome of Interest	Pooled HR (95% CI)	Key Conclusions
Tang et al. [20]	12	8,765	MACE in stable CAD	CT-FFR <0.8: 4.23 (3.15–5.68); CT-FFR <0.7: 5.89 (4.12–8.42); CT-FFR 0.7–0.8: 2.31 (1.56–3.42)	CT-FFR <0.8 is a strong predictor of MACE; risk increases with decreasing CT-FFR
Li et al. [26]	15	11,234	Short-term ( $\leq 1$ year) and long-term ( $> 1$ year) MACE	Short-term: 4.56 (3.62–5.74); Long-term: 4.32 (3.45–5.41)	CT-FFR is a consistent predictor of both short-

					and long-term MACE
Zhang et al. [18]	8	3,241	Diagnostic accuracy of low-dose vs. standard-dose CT-FFR	Sensitivity: 89% vs. 91%; Specificity: 83% vs. 85%	Low-dose CT-FFR has similar diagnostic accuracy to standard-dose CT-FFR
Zhang et al. [29]	10	6,872	Diagnostic accuracy of CT-FFR vs. CCTA for MACE prediction	Sensitivity: 90% vs. 78%; Specificity: 84% vs. 65%	CT-FFR has higher diagnostic accuracy for MACE prediction than CCTA

Table 2: Meta-Analyses on the Predictive Value of CT-FFR for MACE

## 7. Limitations and Future Directions

### 7.1 Limitations

Despite the promising evidence, CT-FFR has several limitations that need to be addressed. First, CT-FFR requires specialized software and expertise in image analysis and CFD, which may limit its widespread adoption in low-resource settings [31]. Second, CT-FFR may be inaccurate in vessels with severe calcification, as calcified plaques can obscure the vessel lumen and lead to incorrect segmentation [32]. Similarly, tortuous coronary arteries or vessels with multiple branching points can challenge CFD simulations and reduce accuracy [33]. Third, CT-FFR is not recommended for patients with contraindications to CCTA, such as severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73m<sup>2</sup>) or contrast medium allergy [34]. Fourth, there is a lack of high-quality data on the role of CT-FFR in certain high-risk populations, such as patients with ST-segment elevation ACS (STEMI), severe valvular heart disease, or pregnant women [35]. Finally, the cost of CT-FFR software and analysis may be a barrier for some healthcare systems, although studies have shown that CT-FFR-guided management reduces overall healthcare costs by avoiding unnecessary invasive procedures [36].

### 7.2 Future Directions

Future research should focus on addressing the limitations of CT-FFR and expanding its clinical applications. First, further refinement of ML-enhanced CT-FFR algorithms is needed to improve accuracy in calcified and tortuous vessels, reduce computational time, and automate the entire workflow [37]. Second, large-scale RCTs are needed to validate the role of CT-FFR in understudied populations, such as STEMI patients, pregnant women, and patients with severe renal impairment [38]. Third, studies evaluating the role of CT-FFR in guiding personalized medical therapy (e.g., intensity of antiplatelet therapy, lipid-lowering therapy) are needed. Preliminary data suggest that CT-FFR-positive patients may benefit from more intensive medical therapy, but this needs to be confirmed in RCTs [39]. Fourth, the development of low-cost, portable CT-FFR software could expand its availability in low-resource settings [40]. Finally, longitudinal studies evaluating the long-term (10+ years) prognostic value of CT-FFR are needed to confirm its sustained utility in risk stratification [41].

## 8. Conclusions

CT-derived fractional flow reserve is a robust non-invasive tool that integrates anatomical and functional information to risk-stratify patients with coronary artery disease and predict major adverse cardiovascular events. The current evidence shows that CT-FFR-negative patients have a very low short- and long-term MACE rate, supporting their safe management with medical therapy alone, while CT-FFR-positive patients have a significantly higher MACE risk and may benefit from more aggressive treatment, including revascularization. CT-FFR provides incremental predictive value beyond traditional risk factors and CCTA, and its predictive performance is similar to that of invasive FFR. Technical advancements, such as machine learning-enhanced algorithms and low-radiation dose protocols, have further expanded its clinical applicability. Despite its

limitations, CT-FFR has the potential to revolutionize CAD management by optimizing patient selection for invasive procedures, reducing healthcare costs, and improving long-term cardiovascular outcomes. Future research should focus on validating CT-FFR in understudied populations, refining algorithms, and exploring its role in guiding personalized medical therapy.

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