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THE CLINICAL VALUE OF POST-PCI FRACTIONAL FLOW RESERVE AND POST-PCI QUANTITATIVE FLOW RATIO MEASUREMENTS

PhD thesis

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List of Abbreviations

ACS:	acute coronary syndrome
AUC:	area under the curve
BMS:	bare metal stent
CABG:	coronary artery bypass grafting
CAD:	coronary artery disease
CCS:	chronic coronary syndrome
CD:	cardiac death
CI:	confidence interval
DES:	drug-eluting stent
ESC:	European Society of Cardiology
EGFR:	estimated glomerular filtration rate
FAME:	Fractional Flow Reserve versus Angiography for Multivessel Evaluation
FFR:	Fractional Flow Reserve
HR:	hazard ratio
IQR:	interquartile range
ISR:	in-stent restenosis
IVUS:	intravascular ultrasound
LAD:	left anterior descending artery
LCx:	left circumflex artery
LM:	left main coronary artery
LVEF:	left ventricular ejection fraction
MACE:	major adverse cardiac event
MI:	myocardial infarction
OCT:	optical coherence tomography
OMT:	optimal medical therapy
OR:	odds ratio
PCI:	percutaneous coronary intervention
QFR:	Quantitative Flow Ratio
RCA:	right coronary artery
ROC:	receiver-operating characteristic
SD:	standard deviation

TVF: target vessel failure

TVR: target vessel revascularization

1. Introduction

1.1. The Discovery of Angiography

Angiography is a medical imaging technique that allows visualization of blood vessels, revolutionizing diagnostics and treatment. It originated in the 1920s when Portuguese surgeon and Nobel laureate Egas Moniz developed the first cerebral angiography in 1927 (1). This milestone laid the ground for future advancements. In 1958, Dr. Mason Sones accidentally injected contrast dye into a coronary artery, leading to the first coronary angiogram - a major breakthrough that enabled detailed imaging of coronary arteries (2, 3). Since then, coronary angiography has become essential in diagnosing and managing coronary artery disease, guiding interventions, and evaluating percutaneous coronary intervention (PCI) results.

1.2. Limitations of Coronary Angiography

Although advancements in medical technology and pharmacology have significantly improved the prognosis of coronary artery disease (CAD), it remains one of the leading causes of death in the developed world, including Hungary (4-7). Studies have proven that primary coronary intervention for ST-elevation myocardial infarction significantly reduces mortality (8-10). However, diagnosing stable CAD is more challenging, as the relationship between the "gold standard" coronary angiography and clinical outcomes is tenuous.

Understanding the limitations of coronary angiography is crucial in the management of CAD and essential for improving patient prognosis.

a. Challenges in Anatomical and Technical Assessment

One of the main limitations arises from coronary anatomy. A fundamental requirement for obtaining a clear lumenogram is the complete filling of the vessel with contrast agent. This is particularly challenging around the aortocoronary ostia. The left main coronary

artery (LM) poses a particular challenge for angiographic assessment too due to its short length and overlap with other structures which hampers the identification of a normal reference segment. Additionally, the small diameter of coronary arteries, typically around 3 mm, their tortuosity, and their synchronous movement with the cardiac cycle, combined with the limited resolution of contemporary imaging technology, further complicate the accurate assessment of the vasculature. These factors make it particularly difficult to evaluate bifurcation lesions or sequential stenoses within the same artery.

b. Limited Assessment of Plaque Structure and Composition

Coronary angiography provides only a two-dimensional view of the coronary arteries' inner lumen which might be misleading due to the three-dimensional nature of coronary atherosclerosis, as shown in Figure 1. (11). The evaluation of luminal narrowing in coronary angiography depends on comparisons to surrounding segments, often without solid evidence that these reference areas are unaffected and normal. This approach frequently leads to underestimating the severity of diffuse vascular disease. This limitation can obscure the true complexity of the arterial plaque and its associated risks, as the method does not account for plaque composition or factors like stability, vulnerability, and inflammation - crucial for assessing acute coronary event risks.

To address these shortcomings, advanced imaging technologies such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) offer detailed three-dimensional visualization of the epicardial arteries. While these technologies do not directly visualize inflammation, they provide a comprehensive view of coronary artery disease that surpasses traditional anatomical assessments. They allow clinicians to evaluate detailed structural characteristics of plaques, including calcification and lipid content, enhancing the assessment of associated risks (12). The use of IVUS or OCT is particularly recommended for guiding PCI on complex anatomical lesions like the left main stem, bifurcations, and long lesions (13-15).

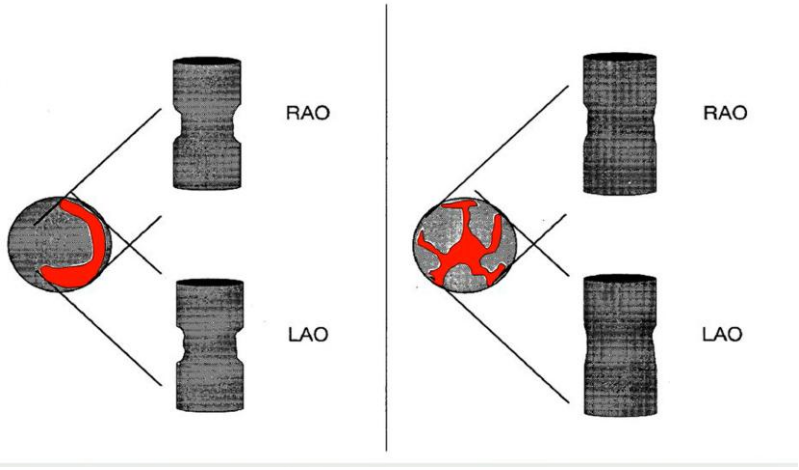


Figure 1. Limitation of projection imaging. The left panel shows a semicircular lumen where both angiographic views underestimate the severity of the luminal obstruction. The right panel illustrates a complex and irregular lumen where no radiographic projection accurately captures the severity of the stenosis. 'RAO' stands for right anterior oblique, and 'LAO' represents left anterior oblique. (11)

c. Limited Evaluation of Ischemia

A third significant limitation of coronary angiography is its inability to directly evaluate myocardial ischemia. Tonino et al. demonstrated that among lesions with an angiographic diameter stenosis of 50% to 70%, 65% were functionally non-significant, while only 35% were functionally significant based on fractional flow reserve (FFR) measurements. Furthermore, even in the case of more severe angiographic diameter stenoses ranging from 71% to 90%, 20% of lesions did not result in reversible myocardial ischemia, as evidenced by FFR values above the ischemic threshold. This highlights that in patients with multivessel CAD, relying solely on angiography to identify ischemia-producing lesions is insufficient for stenoses between 50% and 90%. However, in stenoses with angiographic severity ≥90%, visual assessment aligns well with functional significance, as 96% of such lesions are confirmed as ischemia-producing by FFR. Another critical finding of the study is that FFR assessment of functionally significant coronary lesions often reduces the number of ‘diseased vessels’ compared to angiographic evaluation. For example, in patients with angiographic three-vessel disease, 86% were found to have only two or fewer functionally significantly diseased vessels when assessed using FFR (16).

Over the years substantial evidence has shown that the extent of inducible ischemia significantly determines the prognosis in CAD (17-20). Research by Hachamovitch et al. demonstrated that revascularization offered an increasing survival benefit over medical therapy with increasing extent of inducible ischemia, as identified by myocardial perfusion stress tests in patients without prior myocardial infarction (MI) or revascularization. This benefit appeared to almost neutralize the prognostic impact of ischemia. Particularly in patients with more than 10% ischemic myocardium, revascularization was associated with a 50% risk-adjusted reduction in cardiac death. These findings were consistent when considering all-cause mortality as the endpoint (21).

It is also important to emphasize that the outcome is determined not only by the extent of ischemia but also by its severity. While the presence of non-ischemia-causing (functionally non-significant) stenoses or plaques slightly worsens prognosis with annual mortality and the likelihood of MI remaining below 1% (22), ischemia-causing (functionally significant) narrowings can cause symptoms such as angina pectoris and have a negative impact on prognosis, significantly elevating the risk of death and myocardial infarction, depending on the extent of ischemic myocardium.

The latest 2024 European Society of Cardiology (ESC) guidelines for chronic coronary syndrome (CCS) recommend invasive coronary angiography in cases of very high clinical likelihood of coronary artery disease (>85%), suspected high-risk coronary obstruction, severe myocardial ischemia detected through non-invasive testing, or suspected angina/ischemia with non-obstructive CAD (23). However, determining coronary lesions suitable for revascularization based solely on coronary angiography remains suboptimal (24-27), and non-invasive ischemia testing has limited accuracy in identifying these lesions, especially in the setting of multivessel CAD (28). In Hungary, the availability of advanced non-invasive imaging modalities such as magnetic resonance imaging (MRI), or positron emission tomography (PET-CT) is restricted, making coronary angiography a more feasible and accessible option for clinical decision-making (29).

1.3. Fractional Flow Reserve

1.3.1. Basics of Fractional Flow Reserve

Myocardial ischemia is fundamentally a flow-related pathology caused by impaired blood delivery to the myocardium. While direct measurements of intracoronary flow would provide valuable insights, technical challenges limit their use primarily to research settings. As a result, intracoronary pressure measurements which are simpler to perform, have become a clinically viable surrogate for flow assessment.

Fractional Flow Reserve, introduced by Pijls et al. in 1993, is based on two key principles: first, that maximum achievable flow - not resting flow - determines a patient's functional capacity and exercise tolerance; and second, that during maximal hyperemia (a state of minimal microvascular resistance) or exercise, myocardial blood flow is proportional to myocardial perfusion pressure (30).

$$\Delta P = Q \cdot R$$

This relationship is analogous to Ohm's law (**V = IR)**, where the pressure difference (ΔP) corresponds to voltage (V), blood flow (Q) to current (I), and vascular resistance (R) to electrical resistance (R) in the equation. By inducing maximal vasodilation, the coronary circulation’s autoregulatory mechanisms are overridden, and blood flow becomes solely dependent on perfusion pressure.

FFR is defined as the ratio of mean distal coronary pressure (Pd) measured by the pressure wire to mean aortic pressure (Pa) measured by the guiding catheter simultaneously during maximal hyperemia, shown in Figure 2. This index is independent of variations in systemic blood pressure and heart rate and remains unaffected by conditions that elevate baseline myocardial flow. Furthermore, FFR takes into account the contribution of the collateral blood supply to maximal myocardial perfusion.

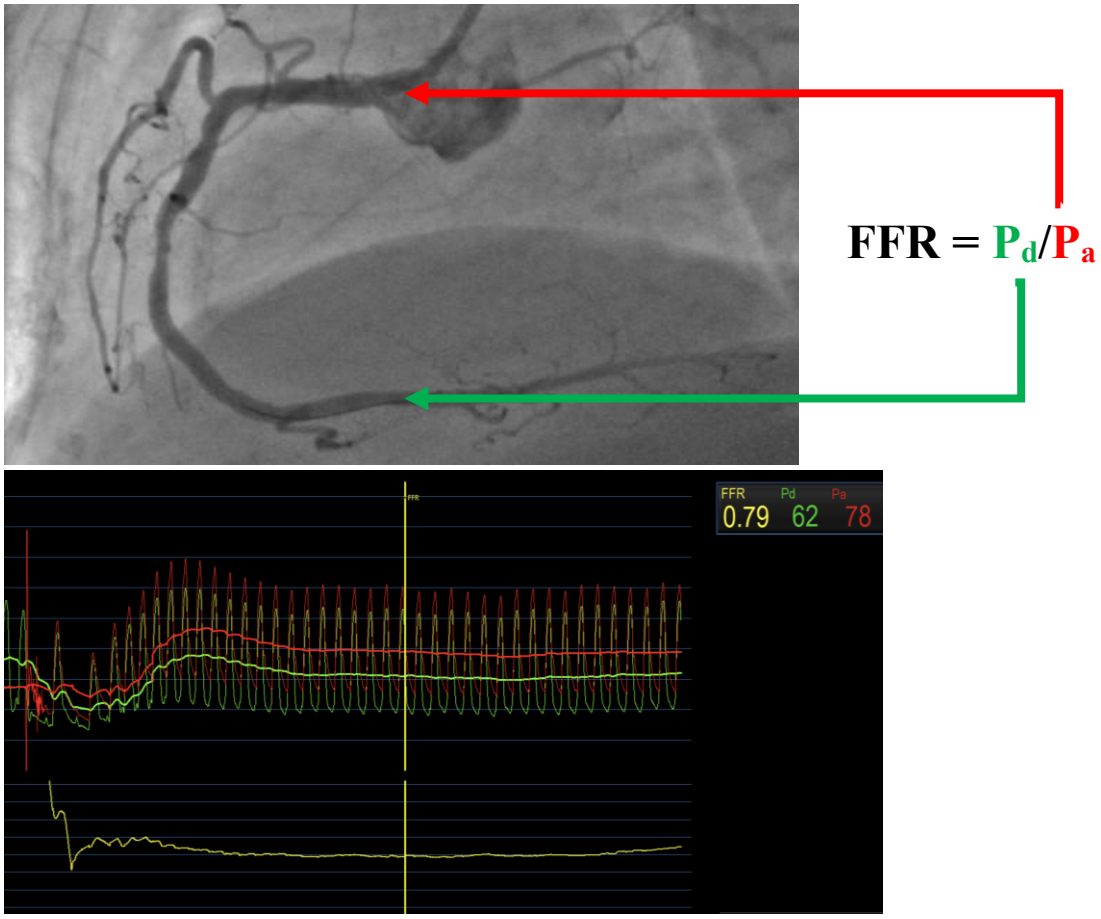


Figure 2. FFR measurement. The coronary angiogram (top) shows an angiographically borderline right coronary artery (RCA) stenosis. The lower panel displays the pressure recordings, where the aortic pressure (Pa) is marked in red and the distal coronary pressure (Pd) in green. In this case, an FFR of 0.79 suggests functionally significant coronary artery disease.

The normal value of the index is 1.0, regardless of the patient or the specific vessel studied. For instance, an FFR value of 0.70 indicates a 30% pressure drop across the stenosis during maximal hyperemia. This approach assumes that venous pressure (Pv) is negligible compared to arterial pressure, making arterial pressure measurements sufficient to determine flow dynamics. To achieve maximal hyperemia, a hyperemic agent is administered intravenously or intracoronarily through the guide catheter (31). The most commonly used agent worldwide is adenosine. Regadenoson and papaverine are also effective in achieving hyperemia. However, regadenoson is currently not available for this purpose in Hungary, primarily due to its high cost. In contrast, the use of papaverine

is limited by concerns regarding its rare but potentially serious side effect of causing torsades de pointes ventricular tachycardia.

1.3.2. Cornerstone Trials in FFR-Guided Coronary Revascularization

FFR received a Class IA recommendation in the 2010 ESC guidelines and has become the gold standard for revascularization decisions, supported by extensive validation through randomized clinical trials and registries (22, 23, 25-27, 30, 32-38).

The **DEFER** trial (1997–1998) showed that deferring PCI in angiographically significant but functionally non-significant lesions (FFR ≥ 0.75) to optimal medical therapy (OMT) is safe. 325 patients were randomized to two groups: the 'Defer group', where PCI was withheld if FFR was ≥ 0.75, and the 'Perform group', where PCI was performed immediately. After 15 years, all-cause mortality was similar across groups (Defer: 33.0%, Perform: 31.1%), but MI was lower in the 'Defer group' compared to 'Perform group' (2.2% vs. 10.0% respectively), despite slightly higher revascularization rates (42.9% vs. 34.4% respectively) (22, 39, 40).

The **FAME** (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial compared FFR-guided PCI to angiography-guided PCI in patients with multivessel disease. FFR guidance reduced stent use by 37%, yet led to fewer major adverse cardiovascular events (MACE 13.2% vs. 18.3%) and lower MI rates after one year, without increasing symptoms or medication use. These benefits persisted at 5 years without adverse effects from deferring FFR-negative lesions (25-27).

The **FAME 2** compared FFR-guided PCI with second-generation drug-eluting stents (DES) plus OMT to OMT alone in 888 patients with FFR-positive lesions (≤0.80). The trial was stopped early due to clear benefit: the primary endpoint occurred in 8.1% of PCI patients vs. 19.5% with OMT alone ($p < 0.001$) at 2 years, driven by a significant reduction in urgent revascularizations (35, 36).

The **FAME 3** compared FFR-guided PCI to CABG in patients with three-vessel disease not involving the left main. While PCI was associated with quicker recovery and lower initial costs, it failed to demonstrate non-inferiority, as it resulted in higher rates of the

primary composite endpoint (death, MI, stroke, or repeat revascularization) at one year. However, there was no significant difference between the two groups in terms of the five-year incidence of death, MI, or stroke (41-46).

1.4. FFR Measured Immediately After PCI

FFR measures the relative resistance to blood flow in the epicardial coronary arteries and can be utilized both before and after PCI. As mentioned above, FFR is widely recognized as a critical tool for identifying functionally significant stenoses prior to PCI, guiding decisions regarding the need for revascularization. However, its utility extends beyond this pre-procedural application. FFR can also be measured immediately after PCI to evaluate the effectiveness of the intervention in restoring coronary flow and to assess residual ischemia.

Studies and analyses have demonstrated the prognostic value of post-PCI FFR measurements (47-50). Lower post-PCI FFR values have been strongly associated with worse clinical outcomes. The first major dataset on post-PCI FFR comes from the Post-Stent Registry in 2002 (51).

1.4.1. FFR Post-Stent Registry

The FFR Post-Stent Registry is a landmark multicenter study conducted during the bare-metal stent (BMS) era, enrolling 750 patients across 15 hospitals in 8 countries. The study aimed to investigate the correlation between FFR measured immediately after angiographically successful stent implantation and the occurrence of MACE within six months. The primary composite endpoint included all-cause mortality, MI, and repeat target vessel revascularization (TVR). The procedure was considered angiographically successful if the residual diameter stenosis was 10% or less. Complete follow-up data were obtained for 744 patients, representing 99.2% of the cohort. During follow-up, 5 deaths (0.7%), 19 MI (2.6%), 12 CABG surgeries (1.6%) and 54 repeat PCI (7.3%) occurred (51).

The results demonstrated a strong inverse correlation between post-PCI FFR values and MACE rates, as shown in Figure 3., primarily driven by TVR:

- FFR ≤ 0.80: Observed in 6%, with an event rate of 29.5%.

- FFR 0.81-0.85: Achieved in 8% of patients, with an event rate of 22.2%.

- FFR 0.86-0.90: Observed in 18%, with an event rate of 16.2%.

- FFR 0.91-0.95: Achieved in 32% of patients, with an event rate of 6.2%.

- FFR ≥ 0.95: Achieved in 36% of patients, with an event rate of 4.9%.

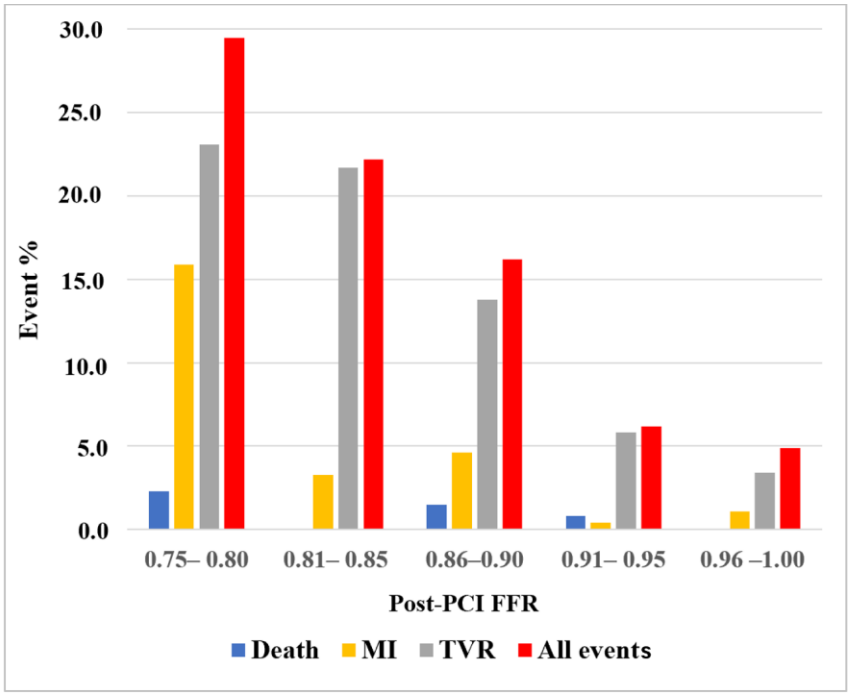


Figure 3. Event rates across post-PCI FFR categories in FFR Post-Stent Registry. Modified from (51). Death: all-cause death (blue); MI: target vessel myocardial infarction (yellow); TVR: target vessel revascularization (gray); All events: composite of death, MI, and TVR.

Univariate analysis identified post-PCI FFR ($p < 0.001$), stent diameter ($p = 0.023$), and stent length ($p = 0.032$) as significant predictors of the primary endpoint. However, angiographic parameters such as residual stenosis percentage and minimal luminal

diameter did not correlate with outcomes, and showed no significant differences across the FFR categories, except for patients with an FFR ≤ 0.80. These patients exhibited slightly worse final angiographic results, including higher residual stenosis and smaller minimal luminal diameter, compared to the other four groups ($p < 0.01$) (51).

Multivariate analysis confirmed that only post-PCI FFR ($p < 0.001$) and stent length ($p < 0.01$) were independent predictors of adverse events. Patients with FFR values < 0.95 had an odds ratio (OR) of 2.3 for adverse events compared to those with FFR ≥ 0.95, even after adjusting for stent length (adjusted OR = 2.78). Importantly, stent length did not act as a confounding factor, as the crude and adjusted OR varied by less than 2% (51).

1.4.2. Prognostic Value of Post-PCI FFR: Insights from a 2014 Meta-Analysis

In 2014, Johnson et al. conducted a study- and patient-level meta-analysis to investigate the prognostic value of FFR. The study hypothesized that lower FFR values were associated with higher clinical risk, leading to greater absolute benefits of revascularization and they found that MACE increased as FFR values decreased. It is essential to point out that the study included data from patients treated with both DES and BMS (49).

Importantly, a subset analysis focused on 966 patients and 970 lesions where FFR was measured immediately after PCI. The lesions were divided into tertiles based on post-PCI FFR values, shown in Figure 4. (A), with the lowest tertile (311 lesions) having a mean post-PCI FFR of 0.83 (interquartile range (IQR): 0.79 - 0.86), the middle tertile (309 lesions) with a mean post-PCI FFR of 0.92 (IQR: 0.90 - 0.93), and the highest tertile (350 lesions) with a mean post-PCI FFR of 0.98 (IQR: 0.96 - 1.00). Kaplan-Meier survival curves revealed that patients with higher post-PCI FFR tertiles experienced fewer adverse events compared to those with lower tertiles, illustrated in Figure 4. (B). The adjusted hazard ratio for clinical events per 0.05 increment in post-PCI FFR was 0.86 (95% CI: 0.80 - 0.93, $p < 0.001$), highlighting the independent prognostic importance of post-PCI FFR. While pre-PCI FFR provided valuable insights into baseline ischemic burden, the study emphasized that post-PCI FFR more accurately reflected the success of revascularization and the presence of residual diffuse disease. When adjusting for both

pre- and post-PCI FFR, the final post-PCI FFR value retained significant prognostic value (adjusted Cox hazard ratio (HR): 0.90, 95% CI: 0.82 - 0.99, p = 0.032). In contrast, pre-PCI FFR lost its prognostic relevance after adjusting for post-PCI measurements (adjusted Cox HR: 0.97, 95% CI: 0.92 - 1.02, p = 0.28) (49).

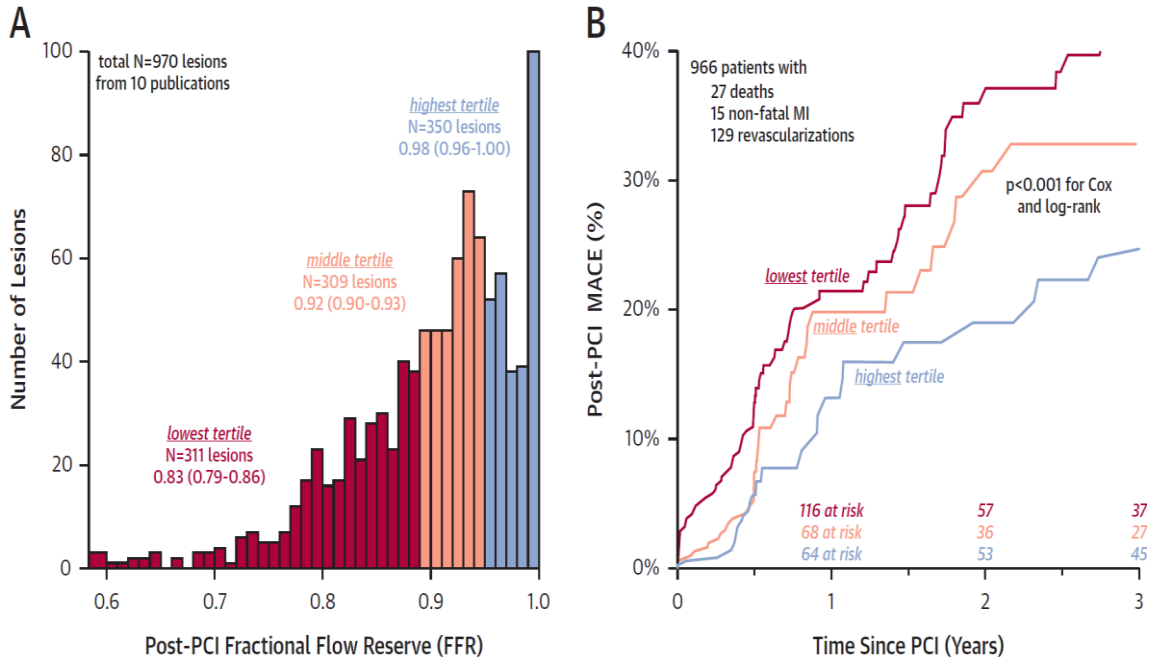


Figure 4. (A) Lesion-level histogram of post–PCI FFR values from the patient-level analysis colored by tertiles (red, peach, blue). **(B)** Survival curves. Kaplan-Meier event curves for tertiles of post-PCI FFR values (colors match those of the histogram) (49).

1.4.3. Why Is FFR after PCI not Always 1.0?

Following PCI with an angiographically satisfactory result, it is expected that resistance to flow is resolved and symptoms subside. However, studies have shown that in a considerable number of cases, residual pressure gradients persist despite satisfactory angiographic result, leading to suboptimal post-PCI FFR (50-59). This raises the question of why FFR does not always return to its normal value of 1.0 after PCI? Several factors contribute to this discrepancy, highlighting the complexity of coronary physiology and the limitations of visual assessment alone.

- **Localized – unnoticed or neglected - stenosis in the index vessel**

It is possible that a focal, overlooked stenosis in the index vessel may be missed during the intervention but can be detected by post-PCI FFR assessment. If an ischemic FFR value is obtained, and revascularization is performed, FFR should be remeasured thereafter, because fixing one lesion may unmask the physiological significance of another (60). Figure 5. illustrates a case of our center where a significant stenosis in the diagonal branch was treated by PCI. However, the post-PCI FFR pullback recording revealed a previously unnoticed and significant (FFR 0.72) LM ostial stenosis (61).

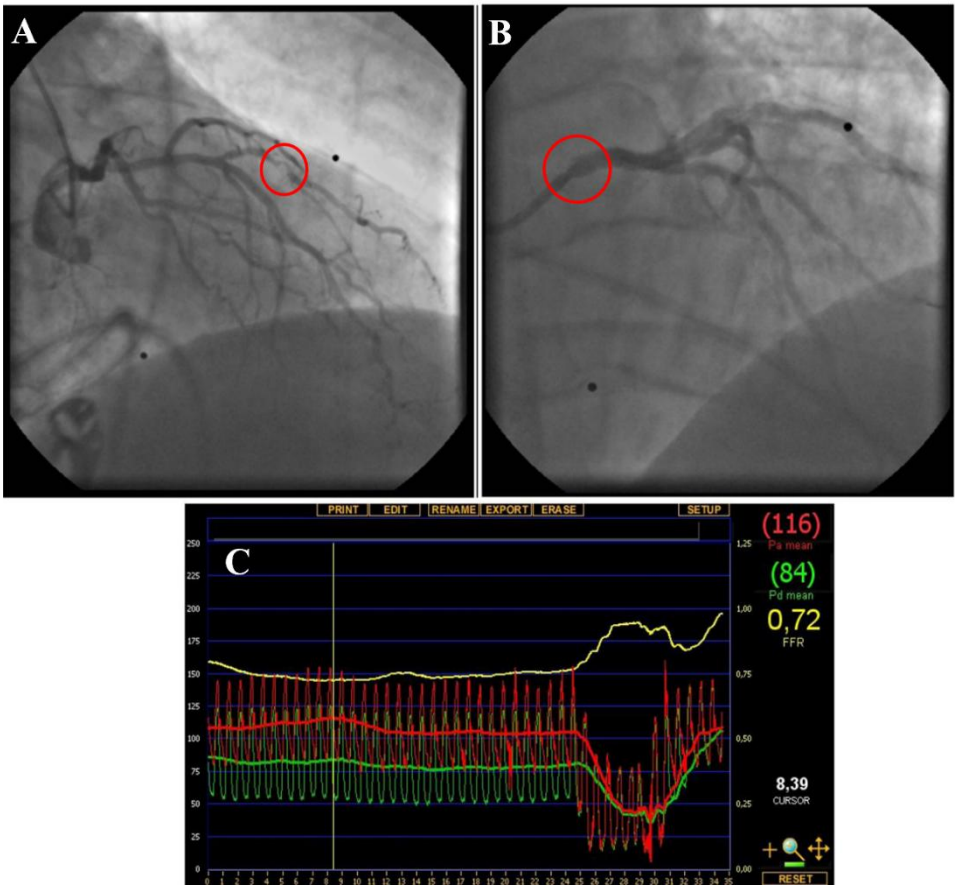


Figure 5. (A) Coronary angiography image showing a significant stenosis of the diagonal branch, circled in red. **(B)** Highly focal LM ostial lesion, circled in red. **(C)** FFR pullback recording demonstrating a significant pressure drop at the LM ostium, resulting in an FFR of 0.72, while wedging the guiding catheter in the LM results in a falsely small pressure gradient (right side of the curve) (61).

- **Diffuse coronary disease**

Residual diffuse disease is identified as the primary factor contributing to lower post-PCI FFR values and higher rates of adverse events, even following optimal stent implantation (49, 62). Using prolonged hyperemia, pullback recording with a pressure wire enables the assessment of how different vessel segments contribute to resistance to flow, providing a lesion-specific index of ischemia. A distal post-PCI FFR without any focal pressure jumps during the pullback indicates the presence of diffuse disease, allowing for a quick and precise evaluation of its severity.

Diffuse disease often coexists with focal stenoses and frequently remains untreated after PCI. Importantly, while stenting may restore hyperemic flow in the treated segment, it can simultaneously amplify the pressure gradient caused by untreated diffuse disease. Notably, severe diffuse disease may respond more effectively to bypass surgery (63), highlighting the importance of tailored revascularization strategies for these complex cases.

- **Suboptimal stent implantation**

Studies using FFR, OCT, and IVUS have demonstrated that relying solely on angiography often results in suboptimal PCI results. Specifically, many patients experience issues such as inadequate stent expansion, malapposition, or edge dissection, which are not always evident on angiography. Research indicates that 15% to 20% of patients with angiographically successful PCI exhibit significant stent underexpansion or other complications on IVUS or OCT which may contribute to unfavorable clinical outcomes (64-66).

- **Drift**

Pressure drift can lead to inaccurate FFR measurements that do not accurately reflect true physiological conditions. The CONTRAST (Can cONTrast Injection Better Approximate FFR compAred to Pure reSTing Physiology?) study highlighted that while drift is small

(≤0.03) in most cases, in approximately 9% of cases, the FFR value appeared inappropriately low after PCI (67).

Several procedural and device-related factors can contribute to this error, including improper aortic pressure transducer height, incorrect wire calibration, failure to remove the needle introducer, the presence of contrast medium in the catheter, or excessive intubation of the guide catheter into the coronary ostium. These factors collectively highlight the importance of careful procedural techniques and equipment handling to ensure accurate pre- and post-PCI FFR measurements.

- **Retrograde filling of the contralateral coronary artery**

Retrograde filling of the contralateral coronary artery by the index vessel can artificially lower the post-PCI FFR value. This occurs because the retrograde flow creates a "steal phenomenon," diverting blood away from the index vessel's territory. As a result, the FFR measurement may underestimate the true functional improvement achieved by the PCI.

- **Hydrostatic pressure and anatomical differences between left anterior descending artery (LAD) and non-LAD vessels**

Several studies have reported significantly lower post-PCI FFR values in the LAD compared to non-LAD vessels (48, 56, 59, 68-70), although a smaller study involving 66 patients did not observe this difference (71). One potential explanation for this phenomenon is the influence of hydrostatic pressure differences. The latter is related to the fact that in a supine patient, the middle and distal segments of the LAD run higher than the aortic root, where the catheter measures the aortic pressure. As a result, the pressure recorded by the sensor of the PressureWire is lower, leading to an underestimation of post-PCI FFR values. This effect is further compounded by the fact that the LAD supplies a larger myocardial territory, resulting in higher flow demand. These factors can contribute to a greater translesional pressure drop, even in the presence of similar angiographic stenosis severity. Additionally, differences in diffuse atherosclerotic disease burden between the LAD and non-LAD vessels may also play a role (72).

1.5. Quantitative Flow Ratio

1.5.1. Basics of Quantitative Flow Ratio

Post-PCI physiological assessment with FFR remains uncommon in clinical practice. This underutilization may stem from the procedural focus on anatomical rather than functional evaluation, the absence of a universally accepted post-PCI FFR cut-off value, requirement of pressure wire insertion and pharmacologically induced hyperemia. In response to these challenges, non-invasive, angiography-based physiological assessment tools have emerged - most notably, the Quantitative Flow Ratio (QFR), which has become one of the most widely studied alternatives (73-76).

QFR estimates the pressure gradient across a narrowed segment of a coronary artery by combining standard angiographic imaging with computational fluid dynamics (CFD). It does not require the use of a pressure wire, nor the administration of hyperemic agents, but there is a need for good quality angiographic images, appropriate contrast filling, and minimal vessel overlap. The QFR calculation process consists of three main steps. Initially, two angiographic projections - taken from angles at least 25 degrees apart - are used to reconstruct a three-dimensional model of the coronary artery. Following this, the software automatically identifies and analyzes the lesion, determining key parameters such as minimal luminal diameter, reference vessel size, and lesion severity. In the final step, CFD algorithms simulate blood flow and estimate the pressure drop along the vessel, enabling the calculation of the QFR value, which ranges from 0 to 1.0. A QFR value of ≤0.80 is typically considered indicative of a hemodynamically significant stenosis, paralleling the threshold used for FFR (77). A QFR measurement is shown in Figure 6.

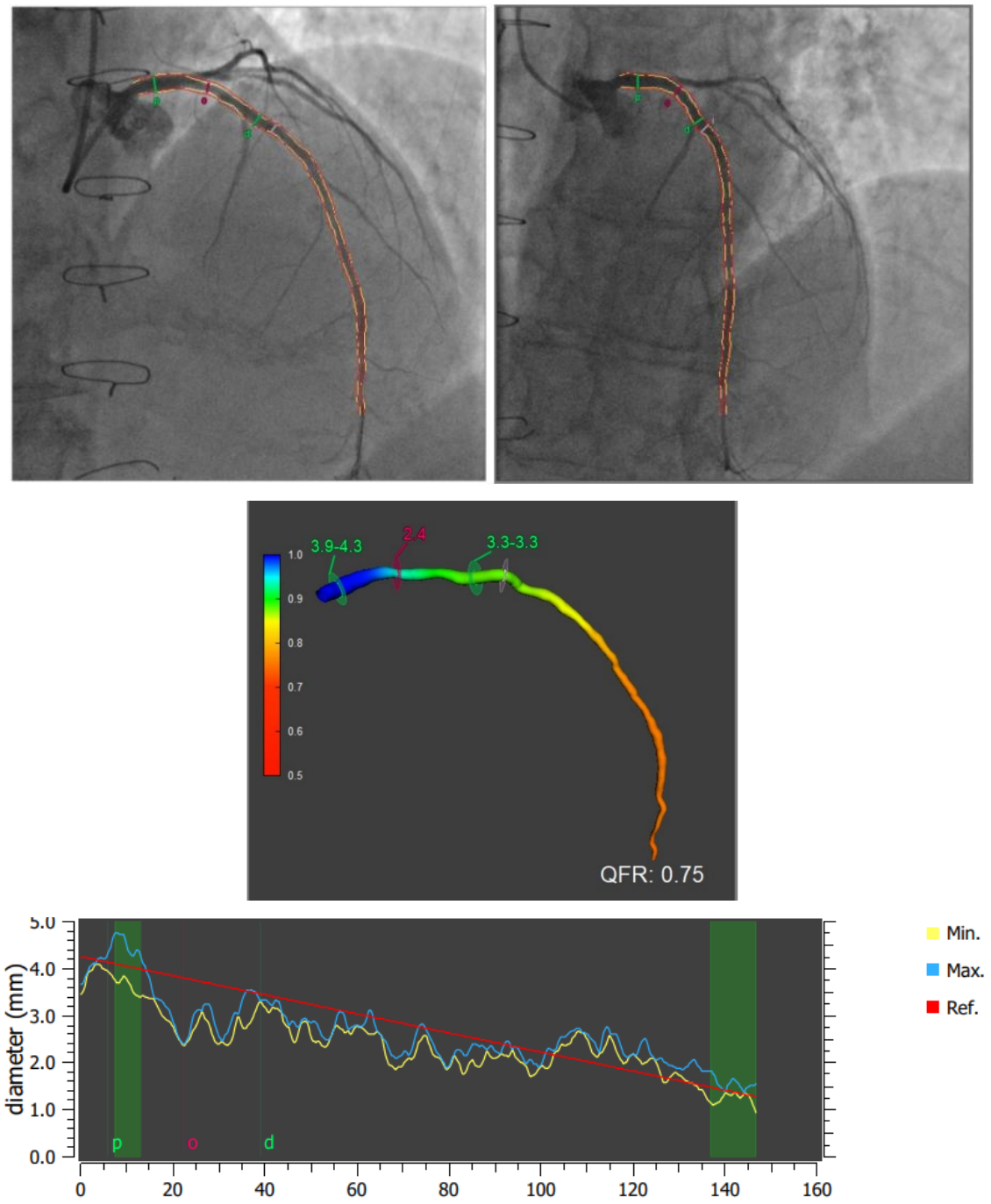


Figure 6. QFR assessment of a coronary stenosis. The top images show two angiographic projections with vessel contouring and reconstruction, which are used for QFR calculation. The middle image presents the three-dimensional reconstructed LAD artery with a color-coded QFR map, where red indicates significant QFR values. The bottom graph displays the vessel diameter profile, highlighting the minimum (yellow), maximum (blue), and reference (red) diameters, providing additional anatomical insight into the severity of the lesion. (Source: Own study)

1.5.2. Evidences behind Quantitative Flow Ratio

A series of prospective studies and randomized trials have demonstrated the diagnostic accuracy, clinical utility of QFR, and its impact on patient outcomes.

The **FAVOR Pilot study** was the first to assess contrast QFR's feasibility, demonstrating a good correlation with invasive FFR ($r = 0.77$, $p < 0.001$), with a diagnostic accuracy of 86%, sensitivity of 74%, and specificity of 91% using a QFR cut-off of 0.80 (77).

This was followed by larger trials such as **FAVOR II Europe-Japan**, which confirmed QFR's diagnostic power in diverse populations. The study included 329 patients and found a per-vessel diagnostic accuracy of 86.8%, with an area under the curve (AUC) of 0.92 (95% CI: 0.89–0.96), sensitivity of 86.5%, and specificity of 86.9% compared to FFR, and demonstrated significantly higher diagnostic accuracy compared to conventional two-dimensional coronary angiography, which showed a sensitivity of only 44.2% and specificity of 76.5% in the same study (75).

The **FAVOR III China trial** marked a turning point by evaluating the clinical outcomes of QFR-guided PCI in a randomized setting. In 3,825 patients, QFR-guided PCI resulted in a significantly lower rate of MACE at 2 years compared to angiography-guided PCI (8.5% vs. 12.5%; HR 0.58; 95% CI: 0.44 - 0.71; $p = 0.0002$) (74).

Based on the evidence of these studies, QFR received a Class I, Level B recommendation in the 2024 ESC guidelines for CCS as a tool for functional assessment of epicardial stenosis during invasive angiography to guide revascularization (23). Although just a few weeks later, at the TCT 2024 Congress, the results of the **FAVOR III Europe study** were presented - the first large randomized trial comparing QFR-guided PCI to FFR-guided PCI - in which QFR failed to demonstrate non-inferiority to FFR (78). Based on these findings, QFR may not be considered a suitable alternative to FFR when FFR is available.

Moreover, limited data are available on the correlation between post-PCI FFR and post-PCI QFR, and even fewer studies have directly compared their predictive value for target vessel failure (TVF).

2. Objectives

2.1. Objectives of the First Study - The POST-PCI FFR STUDY (72)

Residual pressure gradients after PCI, even in cases with an angiographically satisfactory result, have been associated with worse clinical outcomes. Given the uncertainty surrounding the optimal post-PCI FFR threshold and the factors influencing its values, our first study aimed to identify key clinical and procedural determinants and assess their prognostic significance, with a particular focus on vessel-specific cut-off values.

Therefore, our objectives were:

- To investigate the clinical and procedural parameters that influence post-PCI FFR.
- To establish the prognostic value of post-PCI FFR measured immediately after DES implantation. Our primary endpoint was TVF, defined as a composite of cardiac death (CD), nonfatal target vessel-related MI, and target vessel revascularization (TVR).
- To examine the relationship between post-PCI FFR and a composite of CD and MI.
- To determine the optimal post-PCI FFR cut-off value for predicting TVF, with a strong emphasis on assessing whether a vessel-specific cut-off improves its predictive accuracy and enables a more tailored risk assessment.

2.2. Objectives of the Second Study - The POST-PCI QFR STUDY (79)

Data show that FFR after PCI is rarely utilized, yet the high, 19-50% readmission rate after successful PCI within one year due to chest pain highlights the need for more effective methods to assess procedural success beyond angiography alone (80). QFR could serve as a potential alternative; however, limited data exist on the prognostic value of post-PCI QFR.

Therefore, the aims of our second study were:

- To evaluate the correlation between post-PCI FFR and QFR.
- To identify clinical and angiographic factors influencing both.
- To compare their prognostic value following an angiographically successful PCI in a real-world setting. The primary and secondary endpoints in this study were identical to those defined in our first study (72).

3. Methods

3.1. Patients and Procedures

3.1.1. Patients and Procedures: POST-PCI FFR STUDY (72)

Our study included patients with single-vessel or multivessel coronary artery disease who underwent FFR-guided DES implantation and had post-PCI FFR measurements performed in at least one treated vessel at our tertiary care center, with a minimum follow-up period of one year.

Due to the differing in-stent restenosis rates between bare-metal stents and DES (81-83), patients who received a BMS in addition to a DES during the index intervention were excluded from our study. Furthermore, patients with a history of heart transplantation were also excluded. This decision was based on the distinct etiology and pathophysiology of cardiac allograft vasculopathy which differs significantly from atherosclerotic coronary artery disease and remains a major cause of late allograft dysfunction (84, 85). Lastly, we excluded patients in whom post-PCI FFR measurements were performed in vein grafts, as these present unique characteristics distinct from native coronary arteries (86, 87).

Patients included in the study could present with a variety of clinical conditions that justified the need for coronary angiography. Acute coronary syndrome (ACS) was not considered an exclusion criterion. Of note, in cases of ACS, measurements were conducted in the non-culprit vessels. Additionally, patients with heart failure, in whom coronary artery disease was suspected as a contributing factor to impaired cardiac function, were included. Those with arrhythmias, such as atrial fibrillation or ventricular tachycardia who required coronary evaluation to exclude ischemic triggers, were also included in the study.

The approach to performing PCI was left entirely to the clinical judgment and preference of the treating physician, allowing for individualized techniques based on patient-specific factors and anatomical considerations. FFR measurements were obtained using commercially available pressure wires, manufactured by St. Jude Medical (St. Paul, Minnesota), and now Abbott. Hyperemia was primarily induced by the administration of

intracoronary adenosine boluses in 426 patients (98 %), with a standard dosage of 200 μg delivered to the left coronary artery and 100 μg to the RCA or was achieved via intravenous infusion of adenosine at a standardized rate of 140 μg/kg/min in 8 patients (2 %).

All patients were prescribed guideline-directed medical therapy following PCI. It is important to note that all analyzed post-PCI FFR measurements represented the final values recorded at the conclusion of the procedure. No additional interventions or adjustments were made after these FFR values were obtained, ensuring that the data accurately reflected the definitive physiological result of the PCI.

3.1.2. Additional Aspects in the POST-PCI QFR STUDY (79)

As described in Section 1.5.1, QFR is derived from conventional angiography using 3-dimensional reconstruction and computational flow modeling. In our second study (POST-PCI QFR), retrospective, off-line QFR analysis was performed using standard institutional angiograms, without specific acquisition protocols tailored for QFR computation. The analysis was conducted blinded to both invasive FFR results and clinical outcomes. For the purpose of QFR computation, angiographic images acquired both prior to PCI and at the end of the procedure (final post-PCI angiograms) were utilized.

End-diastolic frames at least 25° apart were selected, with careful attention to minimizing foreshortening and overlap. Vessel edge detection was performed automatically by the software, with manual correction applied when necessary. The QFR measurement point was aligned with the location of the pressure wire sensor. Reference diameters were determined based on angiographically healthy vessel segments. Flow velocity was estimated via contrast frame counting; when this was not feasible (n=67), a standard hyperemic velocity was applied. All QFR computations were carried out using Medis Suite 4.0.62.4.

3.2. Ethical Approval (72, 79)

The research permit was issued by the Institutional Committee of Gottsegen National Cardiovascular Center and the Regional Committee of Science and Research Ethics of Semmelweis University, certificate number: 83/2021. All participants provided written informed consent, and the study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

3.3. Endpoints

3.3.1. Endpoints of the Two Studies (72, 79)

The primary endpoint of both studies was TVF, defined as a composite of CD, nonfatal target vessel-related MI, and TVR. All deaths were attributed to a cardiac cause unless there was clear evidence of a definitive non-cardiac etiology. Periprocedural MIs were excluded from the analysis. Both urgent and elective TVRs were included as endpoints in the study. In case of multiple events in a patient, only the first event was counted for analysis. No routine follow-up coronary angiography was performed as part of the study protocol. In cases where a patient had multiple vessels treated, any CD was attributed to all of the involved vessels. Similarly, in instances where a non-fatal MI could not be definitively attributed to a single culprit artery, all vessels in the patient's registry were considered as related to the MI.

We analyzed a range of clinical and procedural parameters to determine their influence on post-PCI FFR values, TVF, and the secondary endpoint which was the composite of CD/MI. The parameters included:

- age
- diabetes mellitus
- estimated glomerular filtration rate (eGFR)
- female vs. male gender
- hyperlipidemia
- hypertension

- indication category (acute vs. chronic coronary syndrome)
- LAD vs. non-LAD location
- lesion location (proximal vs. distal segment)
- lesion type (de novo lesion vs. in-stent restenosis)
- pre-PCI FFR value
- stent diameter
- stent length.

Follow-up information was obtained through a combination of sources, including remote visits, the institutional database, direct telephone contact with patients or their relatives, and the databases of other healthcare centers involved in the patient's care. If no follow-up information could be acquired from these sources, the patient's unique insurance number was cross-referenced with national death records to determine their survival status.

Endpoints were evaluated at both the vessel level and the patient level in the POST-PCI FFR STUDY. For patient-level analysis, the lowest post-PCI FFR value among all vessels with post-PCI FFR measurements was used for each patient.

3.3.2. Differences between the POST-PCI FFR and QFR STUDIES (79)

In the POST-PCI QFR STUDY, one key difference from the POST-PCI FFR STUDY was the inclusion of two additional parameters in the multivariable regression analysis to assess their impact on post-PCI FFR, post-PCI QFR, and clinical outcomes: atrial fibrillation during the procedure and prior MI in the supply area. The rationale behind this inclusion is that QFR measurement relies on a steady-state flow condition which may be compromised in the presence of atrial fibrillation due to beat-to-beat variations in coronary blood flow and pressure gradients. These fluctuations may affect the accuracy and reproducibility of QFR values. Similarly, prior MI in the supply area may alter the physiological significance of QFR measurements, as infarcted myocardial tissue exhibits impaired microvascular function. This could lead to discrepancies between QFR and FFR values and potentially impact their prognostic value in assessing vessel disease severity and predicting adverse cardiovascular events.

Another distinctive feature of the POST-PCI QFR STUDY is that these analyses were conducted exclusively at the vessel level. We also performed sensitivity analyses, specifically by excluding patients with in-stent restenosis, those with a history of MI in the same vascular region, and cases where ACS was the reason for coronary angiography.

Additionally, we assessed the extent of new information provided by post-PCI FFR and post-PCI QFR measurements in comparison to a baseline model. This baseline model incorporated clinical and demographic factors, including age, eGFR, lesion location (LAD vs. non-LAD), gender, indication category (acute vs. chronic coronary syndrome), lesion location (proximal vs. non-proximal), and previous MI in the affected territory.

3.4. Statistical Analysis

3.4.1. Statistical Analysis of the POST-PCI FFR STUDY (72)

Categorical variables are displayed as count (%), while continuous variables are displayed as mean +/- SD or median +/- interquartile range (IQR). Linear regression is used to multivariably model post-PCI FFR. Non-linearity is initially verified using spline expansion; however, all explanatory variables are entered without variable selection (88). Since no substantial nonlinearity was detected, linear models were subsequently employed. Missing data were addressed through multiple imputation using predictive mean matching (89).

Robust covariance matrix estimation was performed using the Hubert-White method for all regression analyses. In vessel-level analyses, clustering was applied at the patient level to account for the correlation of measurements derived from the same individual. The final models include beta coefficients for linear regression and hazard ratios as exponentiated coefficients for Cox regression. Time-dependent receiver-operating characteristic (ROC) curves for the 5-year time point were used to compute survival cut-off values.

Results are presented with 95% CI, and variables were deemed significant if $p \leq 0.05$. All analyses were performed using R statistical software (version 4.2.2).

3.4.2. Additional Statistical Analysis in the POST-PCI QFR STUDY (79)

Equivariant Passing-Bablok regression and Bland-Altman graphs were used to compare the post-PCI FFR and post-PCI QFR approaches. Linear regression was also used to multivariably model post-PCI QFR.

A baseline model with clinical and demographic covariates was fitted first, and either FFR or QFR was then added to the model in order to calculate the added predictive value of both variables. The adequacy index and fraction of new information were used to quantify the increased predictive value, while the likelihood ratio χ^2 was used to measure goodness-of-fit. The R statistical software package, version 4.4.0, was used to do statistical computations.

4. Results

4.1. Result of the POST-PCI FFR STUDY

4.1.1. POST-PCI FFR STUDY: Patients and Vessels (72)

Between March 17, 2009, and January 19, 2021, a total of 1024 patients underwent FFR-guided PCI with DES implantation at Gottsegen National Cardiovascular Center. Of these, 534 patients did not have post-PCI FFR measurements performed in all treated vessels and were therefore excluded. Additionally, 38 patients received a BMS alongside a DES during the index intervention, 6 patients had a history of heart transplantation, and in 12 patients, post-PCI FFR measurements were conducted in a vein graft. These cases were also excluded from the analysis, as they met the three exclusion criteria we had established. The flowchart of patients is shown in Figure 7.

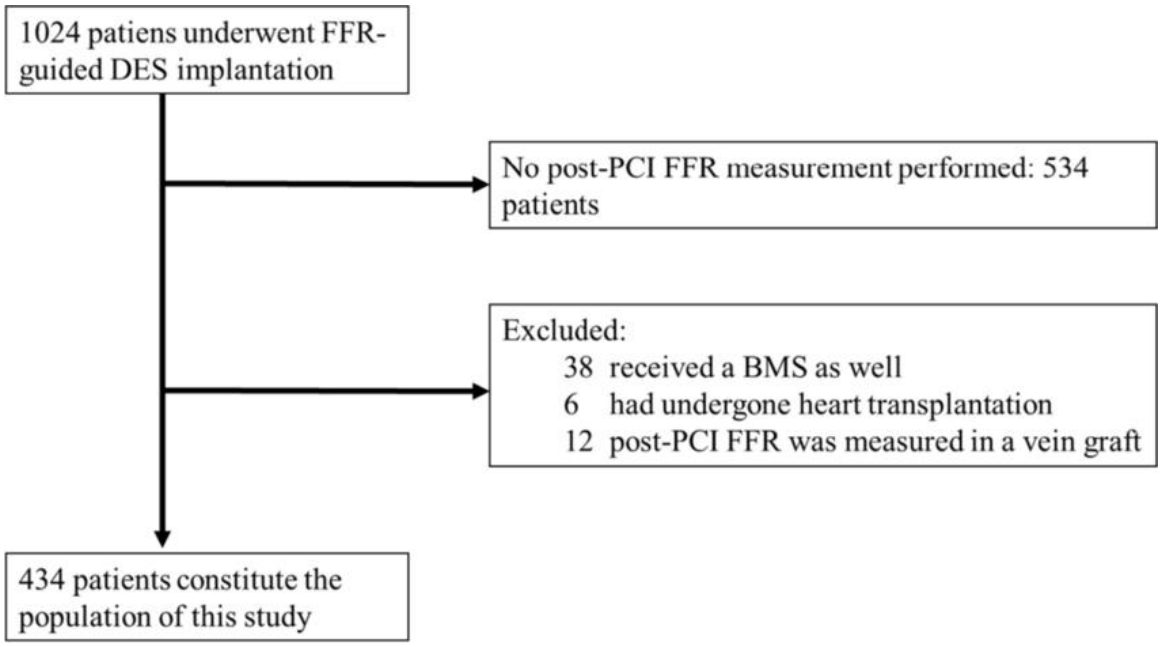


Figure 7. Flowchart of patients

The median age of the study population was 65 years (IQR: 57–71), with 69% of the patients being male. Hypertension was prevalent in 85% of the cohort, and 74% had dyslipidemia. Diabetes mellitus was reported in 49% of the patients, and among these,

27% required insulin therapy. Mean left ventricular ejection fraction (LVEF) was 55% with 27% of patients having an LVEF of less than 50%. Additionally, 44% of the patients had a history of previous PCI, while 2% had undergone CABG surgery. The clinical characteristics of the patient population are detailed in Table 1. Among the 434 patients, 46 had two vessels included in the analysis, and 10 had three vessels analyzed, resulting in a total of 500 vessels.

Table 1. Characteristics of the patients in the POST-PCI FFR STUDY

Total no. of patients	**434**
Age – yr (IQR)	65 (57-71)
Male sex - no. (%)	300 (69%)
Hypertension - no. (%)	369 (85%)
Hypercholesterolemia - no. (%)	321 (74%)
Diabetes mellitus - any - no. (%)	211 (49%)
- treated with insulin - no. (%)	56 (27%)
Smoking - no. (%)	252 (58%)
St/p/PCI - no. (%)	192 (44%)
St/p/CABG - no. (%)	9 (2%)
eGFR – ml/min/1.73m^2 (± SD)	69 (± 18)
LVEF – % (± SD)	55 (± 14)
LVEF <50% - no. (%)	117 (27%)
2 vessels included/patient - no. of patients (%)	46 (11%)
3 vessels included/patient - no. of patients (%)	10 (2%)

Of the 500 vessels, the majority were LAD (333 vessels, 67%), followed by the RCA (100 vessels, 20%) and the left circumflex artery (LCx, 67 vessels, 13%). ACS was the indication for PCI in 77 vessels (15%), while in-stent restenosis was observed in 62 vessels (12%). Nearly half of the lesions (225 vessels, 45%) were located in proximal segments.

Table 2. Procedural characteristics of study vessels in the POST-PCI FFR STUDY

Total no. of vessels	**500**
LAD - no. (%)	333 (67%)
LCx - no. (%)	67 (13%)
RCA - no. (%)	100 (20%)
Acute coronary syndrome indication - no. (%)	77 (15%)
In-stent restenosis - no. (%)	62 (12%)
Proximal lesion - no. (%)	225 (45%)
Stent diameter - mm (± SD)	2.97 (± 0.37)
Total stent length - mm (± SD)	32.3 (± 16.7)
Pre-PCI FFR - (IQR)	0.72 (0.65-0.77)
Post-PCI FFR – (IQR)	0.87 (0.84-0.91)

The overall median pre-PCI FFR was 0.72 (IQR: 0.65-0.77), with comparable values observed in LAD and non-LAD vessels - 0.72 (IQR: 0.66-0.76) and 0.72 (IQR: 0.63-0.77), respectively (p = 0.3011). The distribution of pre-PCI FFR values is illustrated in Figure 8. 3 vessels were treated despite having pre-PCI FFR values greater than 0.80 (shown in red) due to vessel dissection.

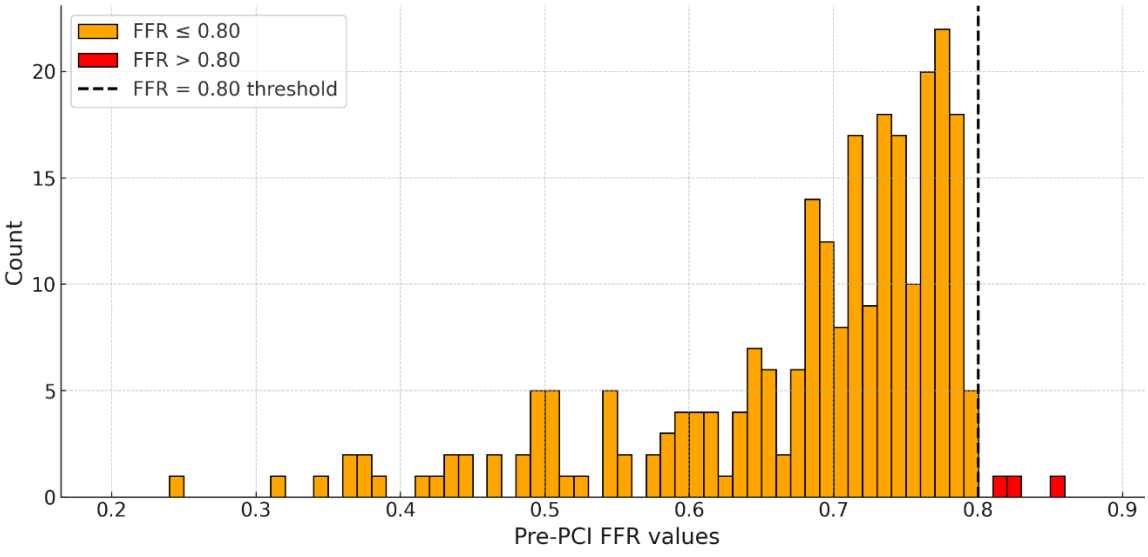


Figure 8. Distribution of the 500 pre-PCI FFR values obtained in 434 patients in the POST-PCI FFR STUDY. Values ≤0.80 are displayed in orange, representing functionally significant lesions. Only three values exceeded the 0.80 threshold (shown in red). The x-axis shows the pre-PCI FFR values, while the y-axis indicates the number of vessels corresponding to each pre-PCI FFR value.

The average number of stents implanted per vessel was 1.40. Specifically, 326 (65.2% of the vessels) had one stent implanted, 147 (29.4%) had two stents, and 44 (5.4%) received three stents.

Figure 9. illustrates the post-PCI FFR values across the study population. The median post-PCI FFR recorded was 0.87 (IQR: 0.84-0.91). Notably, a small proportion of arteries - 21 (4%) in total - had a post-PCI FFR ≤ 0.80 (highlighted in red), which was attributed to diffuse residual disease without a treatable focal lesion, as determined by pullback recordings. Conversely, post-PCI FFR values greater than 0.95 were observed in 44 arteries (9%) (shown in blue). When dissecting the data by vessel type, LAD showed lower post-PCI FFR values with a median of 0.85 (IQR: 0.83-0.89) compared to non-LAD vessels which had a median of value of 0.92 (IQR: 0.88-0.94), the difference being highly statistically significant ($p < 0.001$).

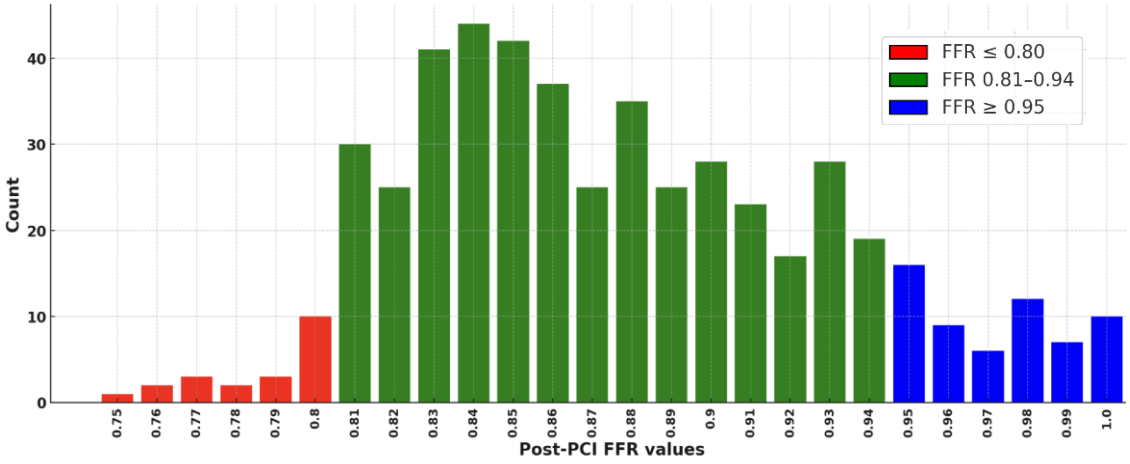


Figure 9. Distribution of the 500 post-PCI FFR values obtained in 434 patients in the POST-PCI FFR STUDY. Post-PCI FFR values ≤ 0.80 are shown in red, values between 0.81 and 0.94 in green, and values ≥ 0.95 in blue. The x-axis shows the post-PCI FFR values, while the y-axis indicates the number of vessels corresponding to post-PCI FFR each value.

Additionally, we analyzed the changes in FFR values from before to after the PCI procedure, referred to as ΔFFR which are shown in Figure 10. This analysis revealed that LAD vessels typically experienced smaller improvements in FFR post-PCI, with a median ΔFFR of 0.14 (IQR: 0.10-0.21), in contrast to non-LAD vessels which showed more substantial improvements with a median ΔFFR of 0.19 (IQR: 0.15-0.29). This difference was statistically significant ($p < 0.001$).

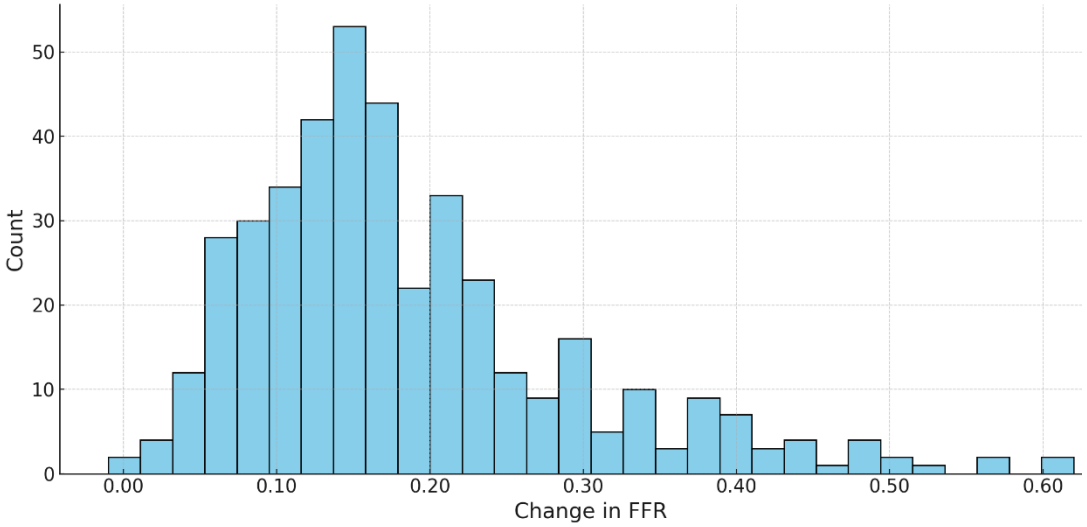


Figure 10. Distribution of ΔFFR values in the POST-PCI FFR STUDY. ΔFFR represents the change in FFR (post-PCI minus pre-PCI). Higher ΔFFR values correspond to greater functional improvement, which potentially translates into better symptomatic outcomes following PCI.

4.1.2. POST-PCI FFR STUDY: Predictors of Post-PCI FFR (72)

Multivariable regression analysis identified significant predictors of lower post-PCI FFR, including LAD location ($p < 0.001$), male gender ($p < 0.001$), smaller stent diameter ($p = 0.006$), and lower pre-PCI FFR ($p = 0.003$). Notably, there were no significant differences in post-PCI FFR between non-culprit vessels in ACS and CCS, nor did in-stent restenosis versus de novo lesions or the presence of diabetes mellitus significantly influence post-PCI FFR values. These findings are illustrated in Figure 11.

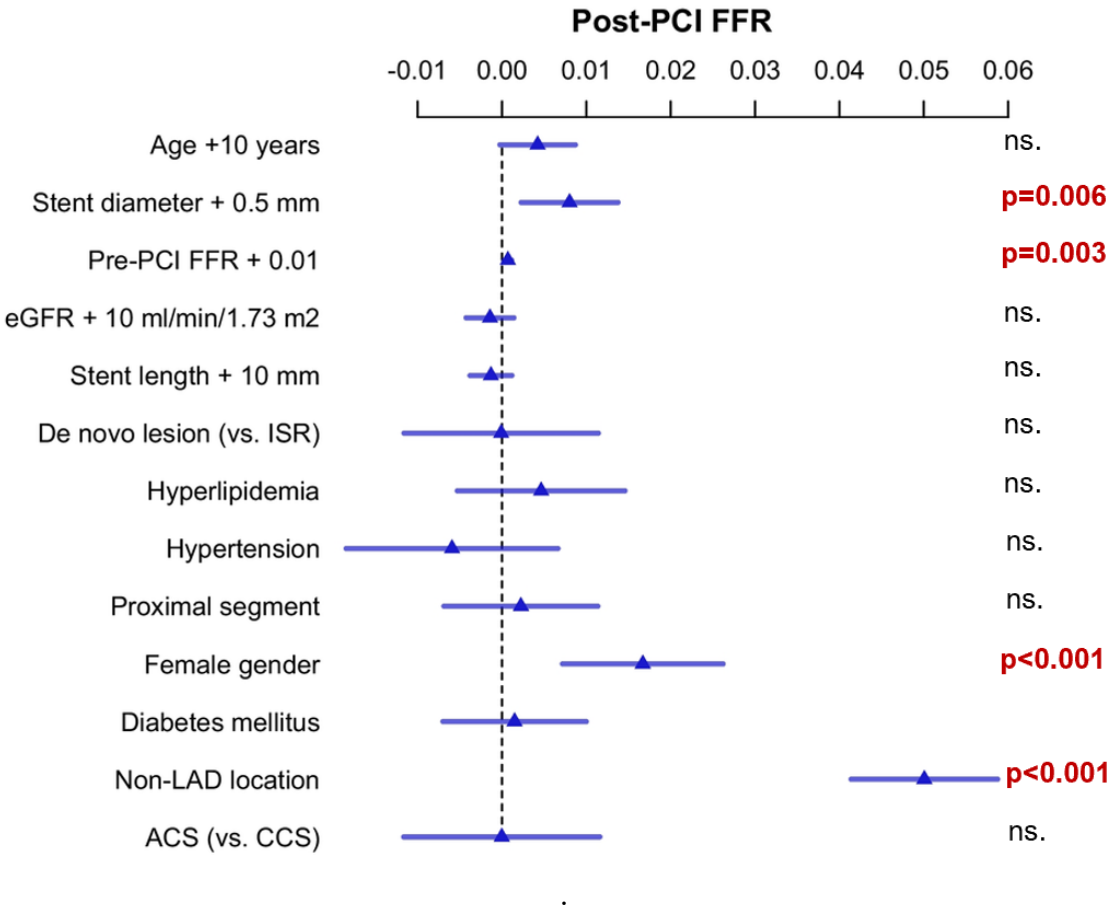


Figure 11. Analysis of the predictors of post-PCI FFR in the POST-PCI FFR STUDY (Small triangles correspond to the beta coefficients, lines indicate 95% confidence intervals)

4.1.3. POST-PCI FFR STUDY: Follow-up (72)

Survival data were available for 433 out of 434 patients (99.8%), and complete follow-up regarding MI and TVR was achieved in 423 patients (97.5%).

During the median follow-up of 37 months (IQR: 20–61),

- 27 patients experienced CD
- 20 patients suffered a nonfatal MI
- 52 TVR were performed.

Among the 52 TVR cases, 10 were performed in the setting of acute MI, while 13 were preceded by a documented FFR ≤ 0.80, guiding the revascularization. In 4 cases, the lesions were considered functionally significant by the operator due to subtotal occlusion, despite the absence of FFR confirmation. The remaining 25 revascularizations were performed based solely on angiographic appearance. In these cases, FFR assessment might have led to the decision to defer intervention. Overall, 73 patients (17%) experienced TVF, while 39 patients (9%) suffered either MI or CD during follow-up.

4.1.4. POST-PCI FFR STUDY: Vessel-level Analysis (72)

At the vessel level, significant predictors of TVF were post-PCI FFR ($p < 0.001$), stent length ($p < 0.001$), and the presence of diabetes mellitus ($p = 0.026$), as shown in Figure 12.

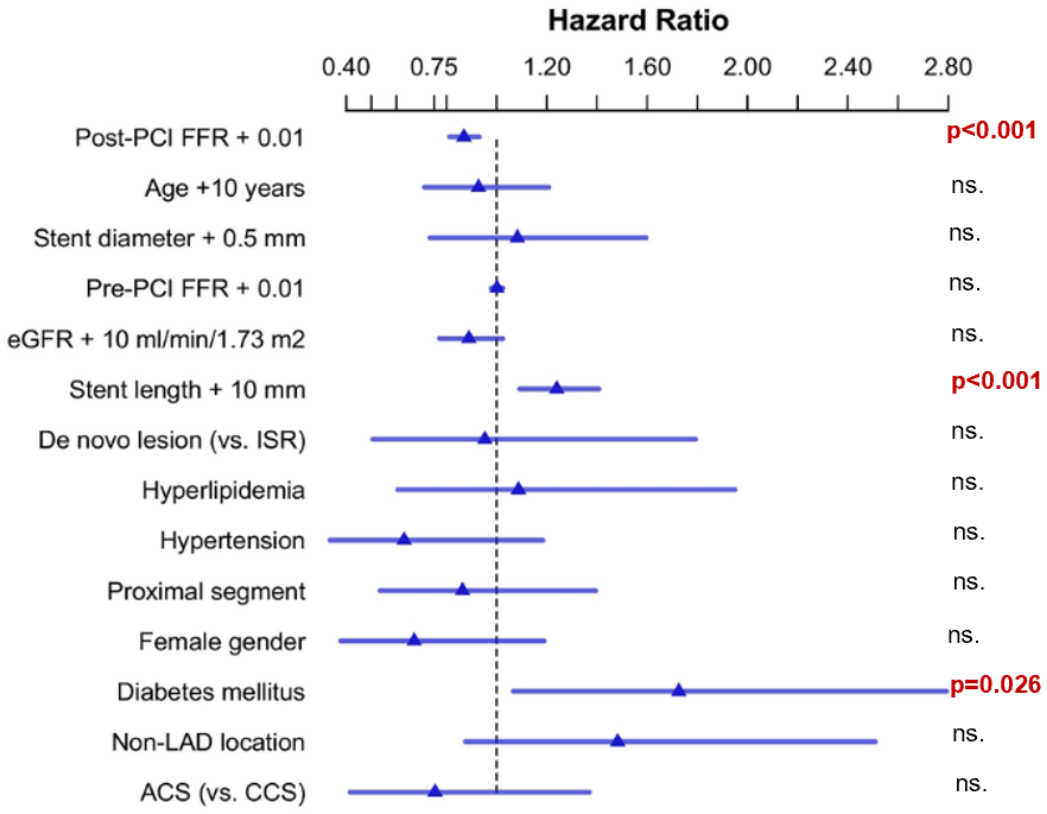


Figure 12. Predictors of TVF in the POST-PCI FFR STUDY. (Small triangles are point estimates of hazard ratios, lines indicate 95% confidence intervals)

The data show that the lower the post-PCI FFR, the higher the frequency of TVF. Specifically, vessels with a post-PCI FFR of ≤ 0.80 experienced the highest frequency of TVF at 47.6%, while those with a post-PCI FFR greater than 0.95 had a notably lower frequency at only 2.3%. Intermediate FFR ranges exhibited a graded reduction in TVF frequency: 21.4% for FFR between 0.81 - 0.85, 13.3% for 0.86 - 0.90, and 12.6% for 0.91- 0.95. The relationship between TVF and post-PCI FFR as a continuous variable is shown in Figure 13.

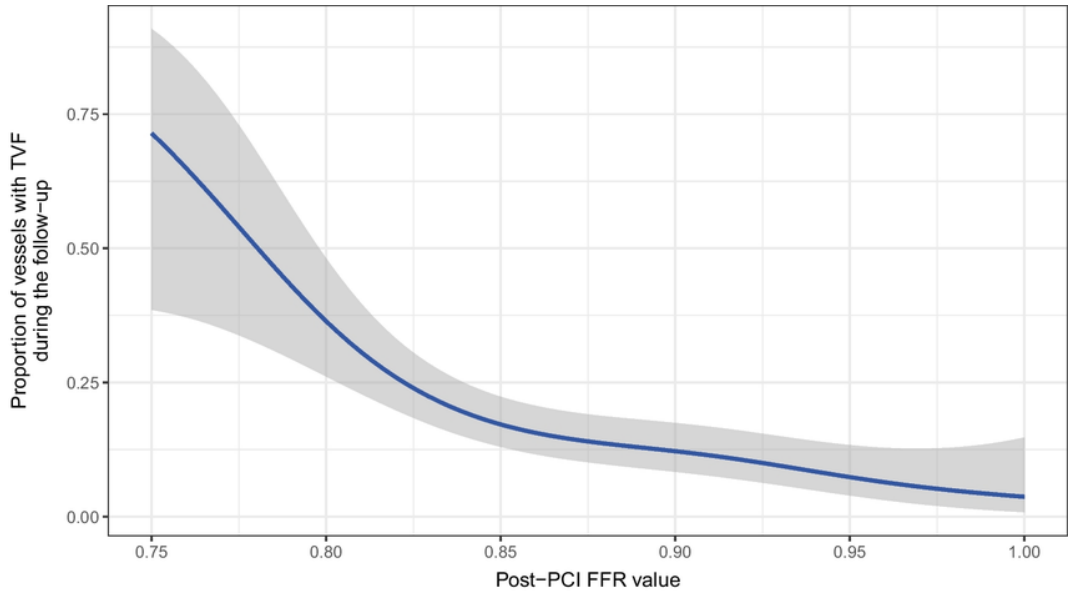


Figure 13. Relationship between post-PCI FFR and TVF in the POST- PCI FFR STUDY.

A post-PCI FFR of 0.83 was identified through univariate ROC analysis as the best cut-off for predicting TVF, with a sensitivity of 45%, specificity of 86%, and an AUC of 0.70. Considering the lower median post-PCI FFR in LAD arteries (two-thirds of vessels) by 0.07 units compared to non-LAD arteries (one-third of vessels), a separate analysis was conducted for these two groups. The optimal post-PCI FFR for predicting TVF was determined to be 0.83 in the LAD territory by univariate ROC analysis, with a sensitivity of 60%, specificity of 82%, and an AUC of 0.75. In contrast, for non-LAD vessels, the best predictive post-PCI FFR value was higher, 0.91, showing a sensitivity of 65%, specificity of 61%, and an AUC of 0.59. The determination of the optimal post-PCI FFR cut-off value for predicting TVF is illustrated in Figure 14.

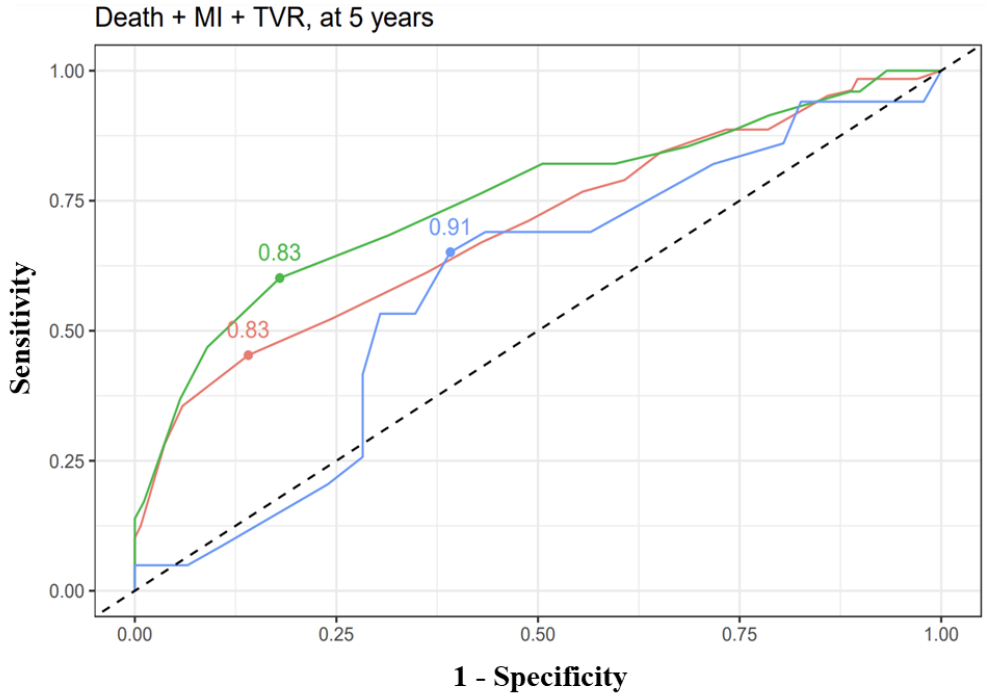


Figure 14. ROC curves for determining the optimal post-PCI FFR cut-off value to predict TVF in the POST-PCI FFR STUDY. The overall patient population is represented by the red curve, LAD vessels by the green curve, and non-LAD vessels by the blue curve.

This study also explored the secondary endpoint, a composite of CD and MI, with post-PCI FFR ($p < 0.001$), stent length ($p < 0.001$), non-LAD location ($p = 0.0026$), and diabetes mellitus ($p = 0.015$) emerging as independent predictors, as demonstrated in Figure 15.

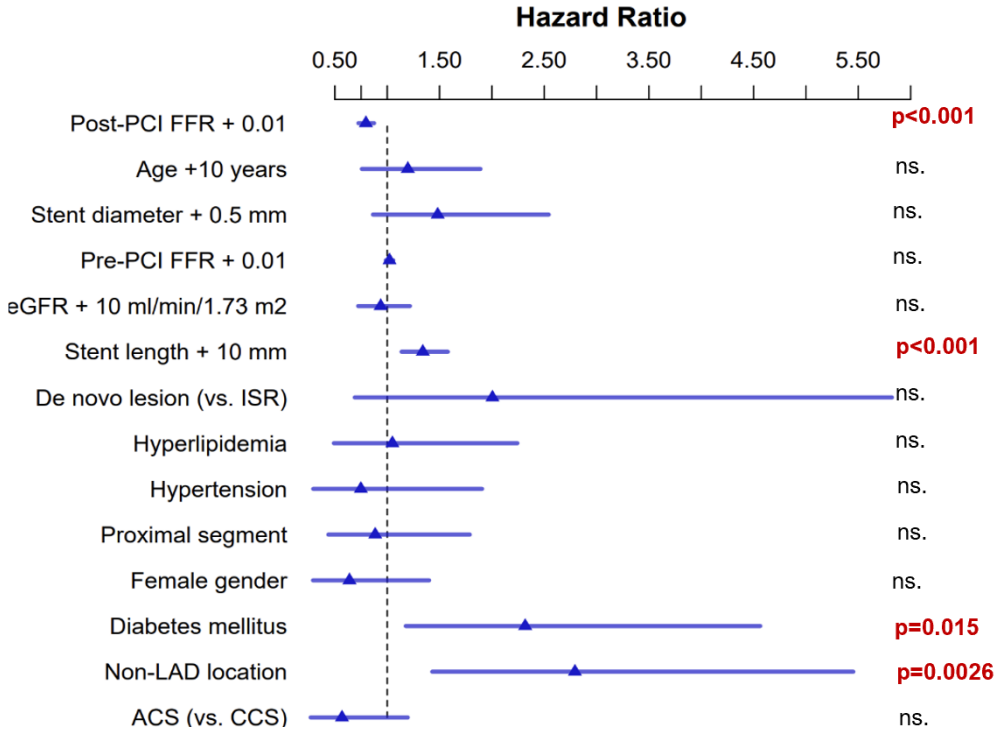


Figure 15. Predictors of the secondary endpoint (CD/MI) in the POST-PCI FFR STUDY (Small triangles are point estimates of hazard ratios, lines indicate 95% confidence intervals)

The relationship between post-PCI FFR and the occurrence of CD/MI (secondary endpoint) is inverse and statistically significant as well, see Figure 16.

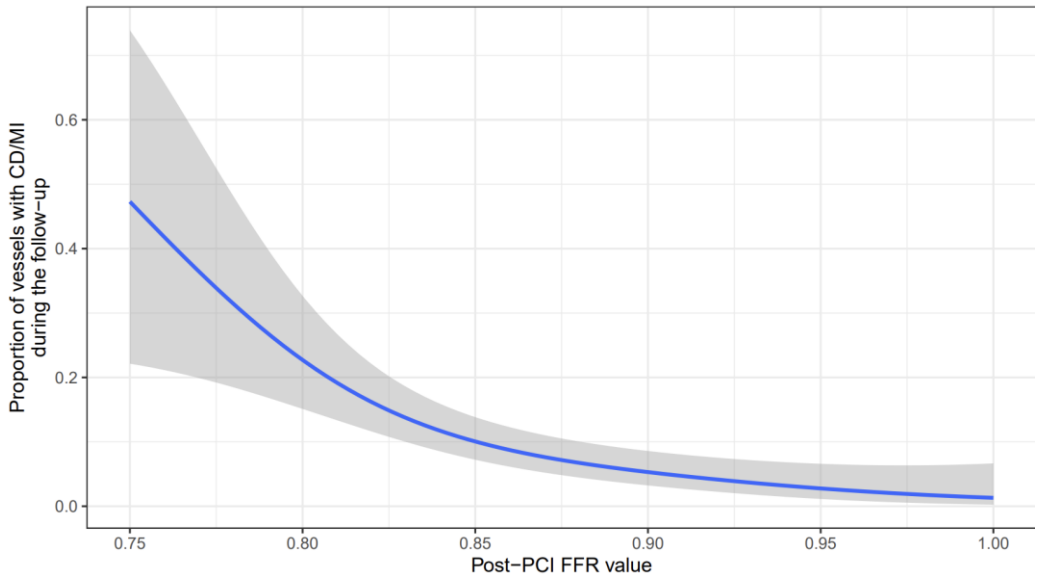


Figure 16. Correlation between post-PCI FFR and CD/MI in the POST-PCI FFR STUDY.

Univariate ROC analysis confirmed that the optimal post-PCI FFR thresholds for CD/MI were identical to those previously identified for TVF. For the overall population, a cut-off of 0.83 yielded a sensitivity of 54%, specificity of 86%, and an AUC of 0.75. In LAD vessels, the same threshold (0.83) resulted in improved performance, with a sensitivity of 72% and specificity of 82% (AUC 0.84). In contrast, in non-LAD vessels, the optimal value remained 0.91, with a sensitivity of 70%, specificity of 61%, and an AUC of 0.60 (see Figure 17.).

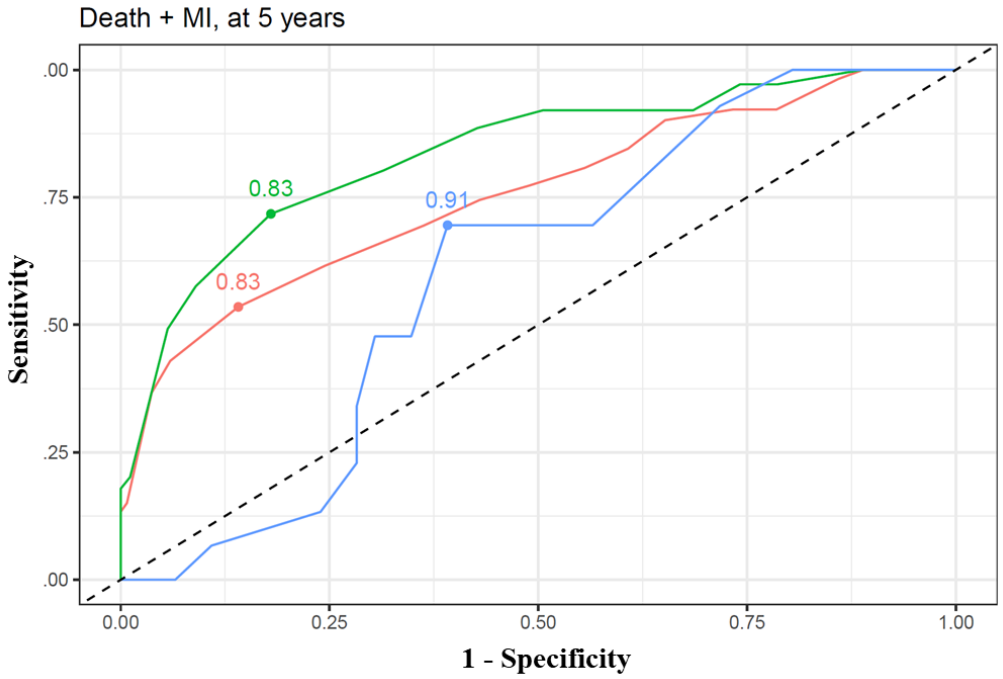


Figure 17. ROC curves for determining the optimal post-PCI FFR cut-off value to predict "hard endpoints" (CD/MI) in the POST-PCI FFR STUDY. The overall patient population is represented by the red curve, LAD vessels by the green curve, and non-LAD vessels by the blue curve.

4.1.5. POST-PCI FFR STUDY: Patient-level Analysis (72)

On a patient level, post-PCI FFR ($p < 0.001$) and stent length ($p = 0.00384$) emerged as independent predictors of TVF. The incidence of TVF varied across the range of post-PCI FFR values, with the highest frequency, 47.6%, observed in patients with the lowest FFR stratum (≤ 0.80). This was followed by 22.2% in the 0.81–0.85 stratum, 11.7% in the

0.86–0.90 stratum, 12.5% in the 0.91–0.95 stratum, and only 2.9% in patients with an FFR > 0.95. The relationship between TVF and the single lowest post-PCI FFR is depicted in Figure 18. which considers the entire follow-up duration for each patient, ignoring variations in follow-up times among individuals.

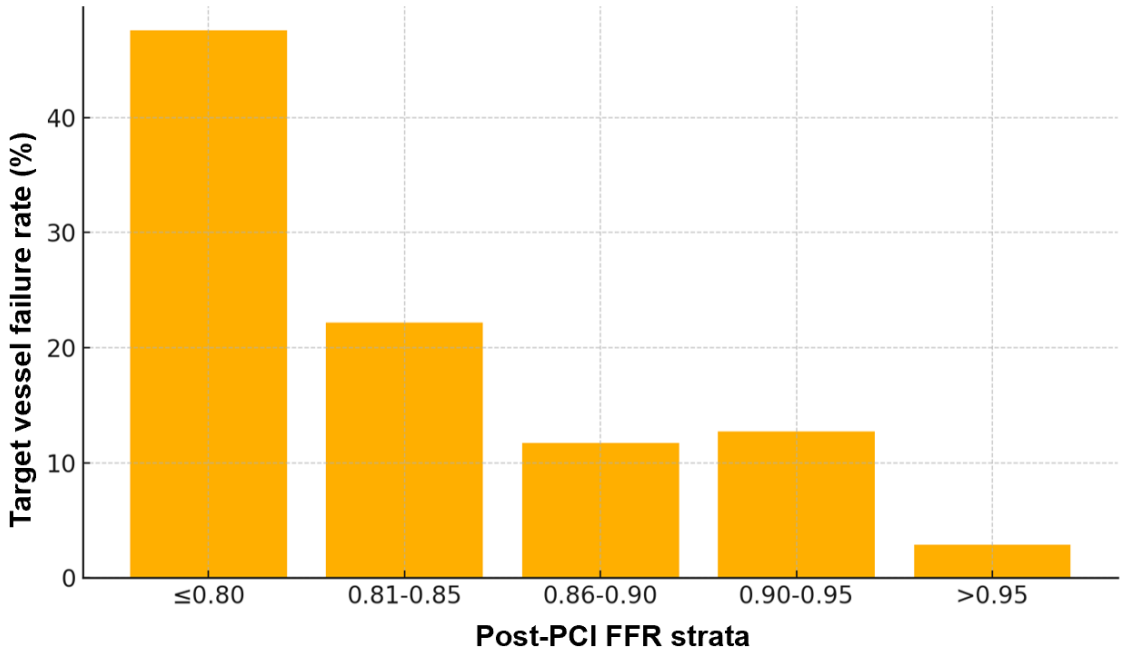


Figure 18. Frequency of TVF in relation to the single lowest post-PCI FFR in the patients of the POST-PCI FFR STUDY stratified in five categories.

Univariate ROC analysis determined that the optimal cut-off of single lowest post-PCI FFR measured in a patient to predict TVF was 0.83, based on the Youden-index, with a sensitivity of 51%, specificity of 85%, and an AUC of 0.73.

Moreover, on a patient level, the key predictors for the composite endpoint of CD/MI included lowest measured post-PCI FFR ($p < 0.001$), stent length ($p < 0.001$), and diabetes mellitus ($p = 0.0337$). Similarly, a post-PCI FFR of 0.83 was identified as the best threshold to anticipate CD/MI, achieving a sensitivity of 62%, specificity of 85%, and an AUC of 0.81.

4.2. Results of the POST-PCI QFR STUDY

4.2.1. POST-PCI QFR STUDY: Patients and Vessels (79)

Off-line QFR measurements were attempted in 500 coronary arteries of 434 patients enrolled in the POST-PCI FFR STUDY. However, QFR analysis could not be completed in 78 vessels (15.6%), shown in Figure 19 due to various limitations, including significant vessel overlap (5%), insufficient angulation difference (less than 25°) between angiograms (4.8%), inadequate contrast filling (3.4%), and suboptimal image quality (2.4%). It is important to note that all angiographic images were acquired at a frame rate of 15 frames per second, and no ostial stenosis was included.

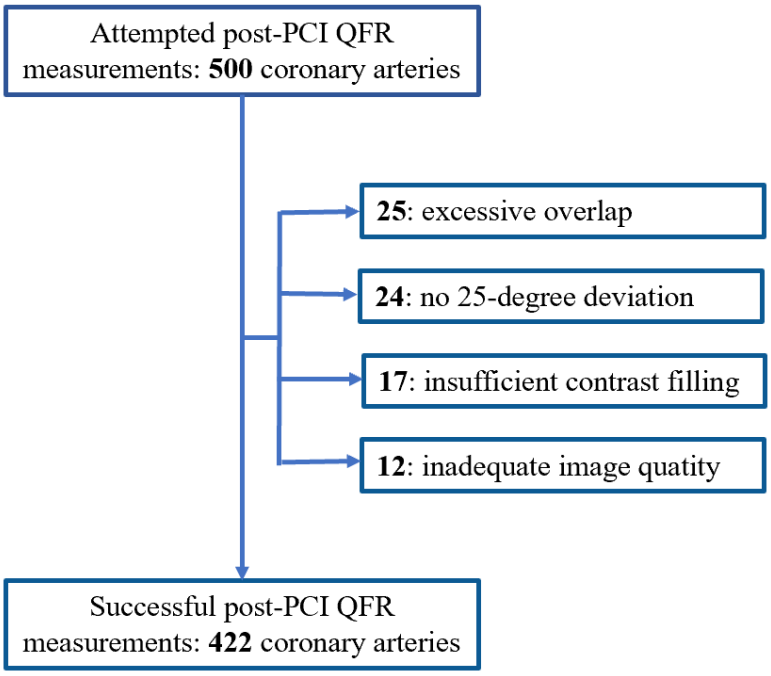


Figure 19. Flowchart of the POST-PCI QFR STUDY

As a result, a total of 422 vessels of 365 patients underwent both post-PCI FFR and post-PCI QFR measurements during the study period. Although the study population was more restricted compared to the POST-PCI FFR study, baseline characteristics were similar in the two study groups. The baseline characteristics of the patients of the POST-PCI QFR STUDY are summarized in Table 3.

Table 3. Baseline characteristics of patients in the POST-PCI QFR STUDY

Total no. of patients	**365**
Age – yr (± SD)	63 (± 10)
Male sex - no. (%)	257 (70%)
Hypertension - no. (%)	311 (85%)
Hypercholesterolemia - no. (%)	274 (75%)
Diabetes mellitus - any - no. (%)	177 (48%)
- treated with insulin - no. (%)	48 (27%)
Smoking - no. (%)	212 (58%)
St/p/PCI - no. (%)	150 (41%)
St/p/CABG - no. (%)	8 (2%)
eGFR – ml/min/1.73m^2 (± SD)	69 (± 18)
LVEF – % (± SD)	55 (± 13)
LVEF <50% - no. (%)	99 (27%)
2 vessels included/patient - no. of patients (%)	39 (11%)
3 vessels included/patient - no. of patients (%)	7 (2%)

In both studies, approximately two-thirds of the analyzed vessels were LAD, and there was no significant difference in the frequency of ACS as the indication for the procedure. The most notable difference between the two studies was the proportion of proximal lesions, which accounted for 60% in the current study compared to 45% in the POST-PCI FFR STUDY. Atrial fibrillation occurred during the procedure in 10% of cases, and a prior myocardial infarction in the corresponding vascular territory was also documented in 10% of the vessels. Procedural characteristics are detailed in Table 4.

Table 4. Procedural characteristics of the POST-PCI QFR STUDY

Total no. of vessels	**422**
LAD - no. (%)	288 (68%)
LCx - no. (%)	55 (13%)
RCA - no. (%)	79 (19%)
Acute coronary syndrome indication - no. (%)	61 (14%)
In-stent restenosis - no. (%)	49 (11%)
Proximal lesion - no. (%)	255 (60%)
Stent diameter - mm (± SD)	2.98 (± 0.37)
Total stent length - mm (± SD)	32.6 (± 16.7)
Prior myocardial infarction in the territory - no. (%)	41 (10%)
Atrial fibrillation during the procedure - no. (%)	42 (10%)
Pre-PCI FFR - (± SD)	0.69 (± 0.10)
Pre-PCI QFR - (± SD)	0.73 (± 0.09)
Post-PCI FFR - (± SD)	0.88 (± 0.05)
Post-PCI QFR - (± SD)	0.93 (± 0.07)

The mean FFR and QFR values measured before PCI in the POST-PCI QFR study were 0.69 and 0.73, respectively. As shown in Figure 20, the pre-PCI distribution curves of FFR and QFR were similar, with the QFR curve shifting slightly to the right. No significant differences were observed between LAD and non-LAD vessels in either pre-PCI FFR or QFR values.

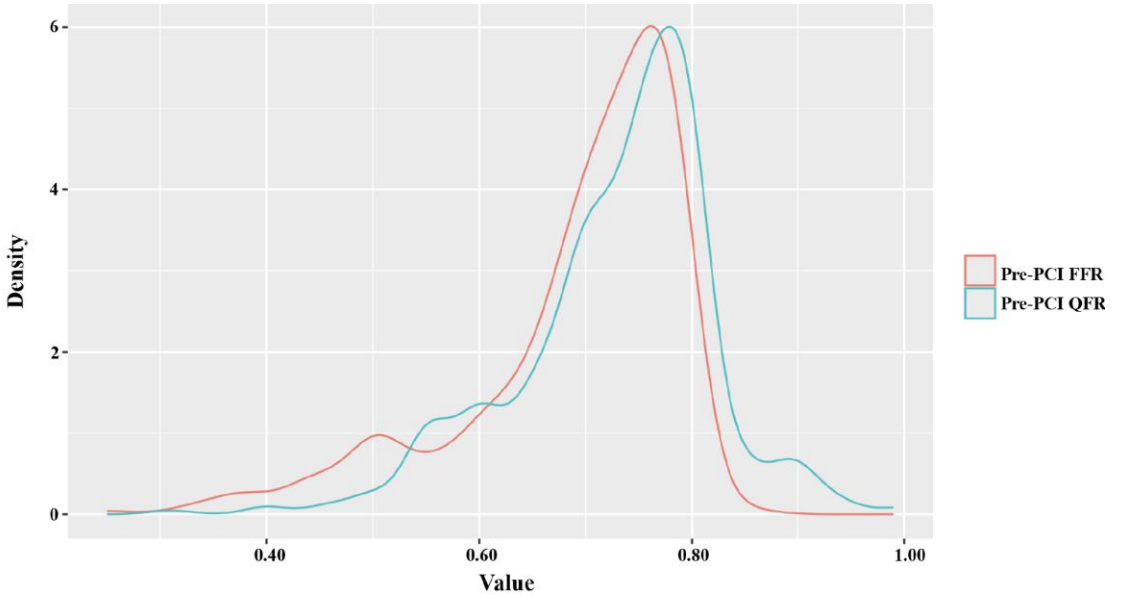


Figure 20. Distribution curves of pre-PCI FFR and QFR values in the POST-PCI QFR STUDY

The mean post-PCI FFR was 0.88 and the mean post-PCI QFR was 0.93. A statistically significant difference was found between LAD and non-LAD vessels, in terms of post-PCI FFR values of 0.86 vs. 0.91 ($p<0.001$) and post-PCI QFR values of 0.89 vs. 0.92 ($p<0.001$), respectively. The distribution curves of post-PCI FFR and QFR differed accordingly, as illustrated in Figure 21.

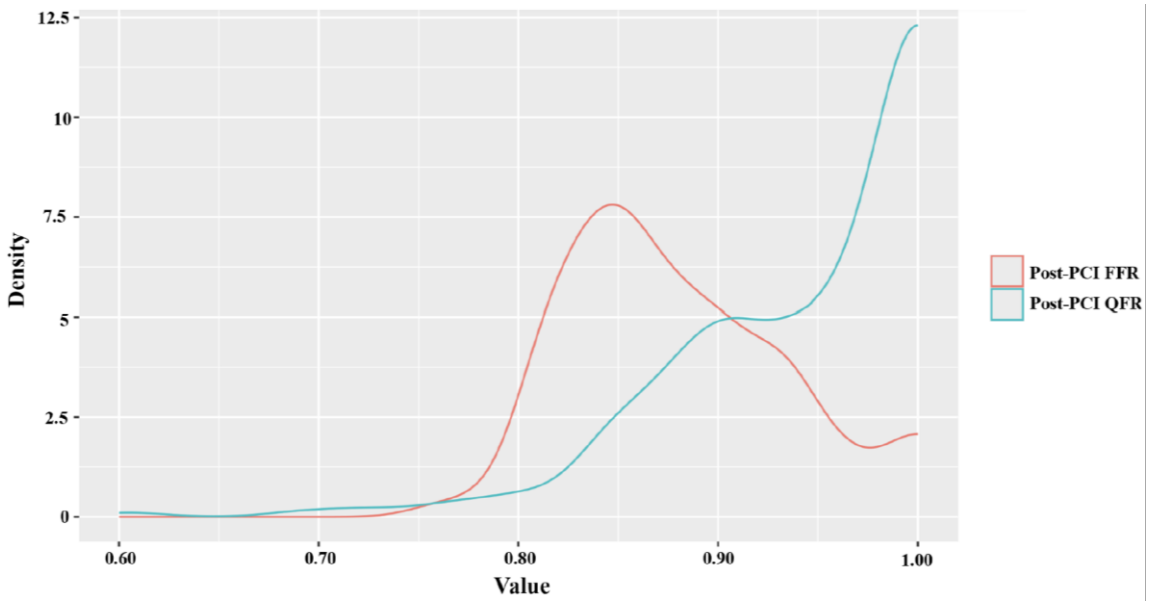


Figure 21. Distribution curves of post-PCI FFR and QFR values in the POST-PCI QFR STUDY

4.2.2. POST-PCI QFR STUDY: Predictors of Post-PCI FFR and Post-PCI QFR (79)

In this study, as in the POST-PCI FFR STUDY, LAD location (compared to non-LAD, p<0.001), male sex (p=0.005), and smaller stent diameter (p=0.007) were identified as significant predictors of lower post-PCI FFR. Additionally, reduced eGFR was associated with lower post-PCI FFR, although this relationship was only marginally significant (p=0.044). Predictors of post-PCI FFR are shown in Figure 22.

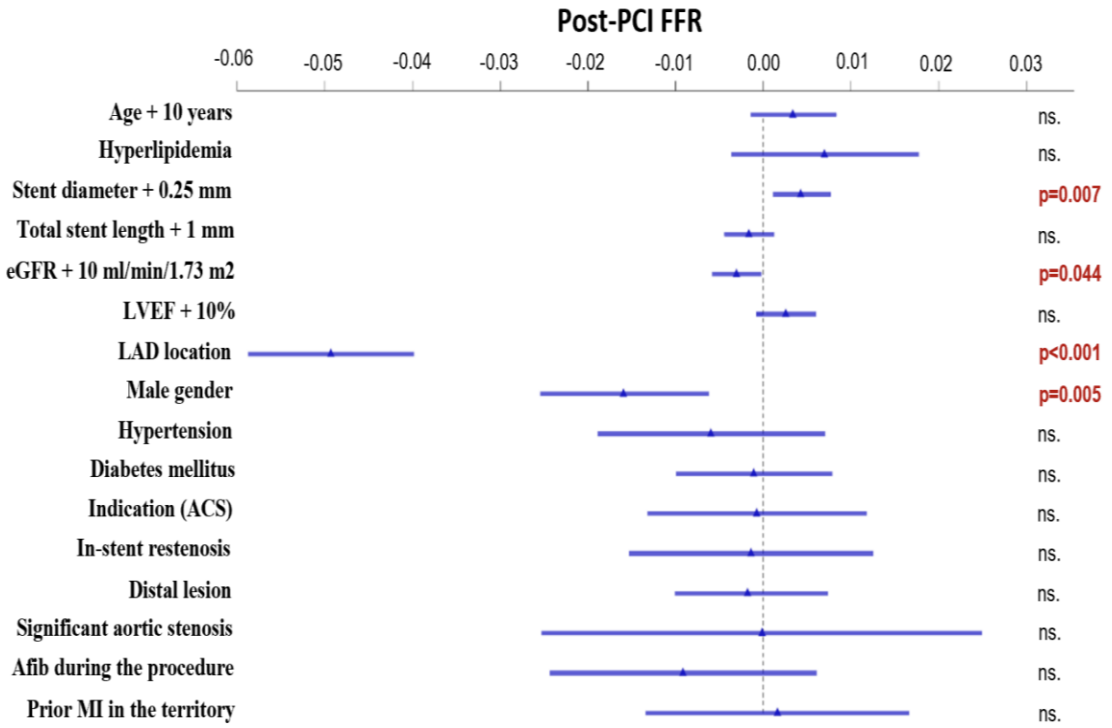


Figure 22. Predictors of post-PCI FFR in the POST-PCI QFR STUDY (Small triangles correspond to the beta coefficients, lines indicate 95% confidence intervals)

Multivariate regression analysis revealed that several factors were independently associated with lower post-PCI QFR values as well, including LAD location (p<0.001), male sex (p=0.045), hypertension (p=0.045), shorter stent length (p<0.001), occurrence of atrial fibrillation during the procedure (p=0.0033), in-stent restenosis (p=0.013), and distal (as opposed to proximal) lesion location (p=0.0049). Importantly, post-PCI FFR values in non-culprit vessels of patients presenting with ACS did not significantly differ

from those presenting with CCS. Similarly, no significant difference was observed in post-PCI QFR values between these two clinical settings.

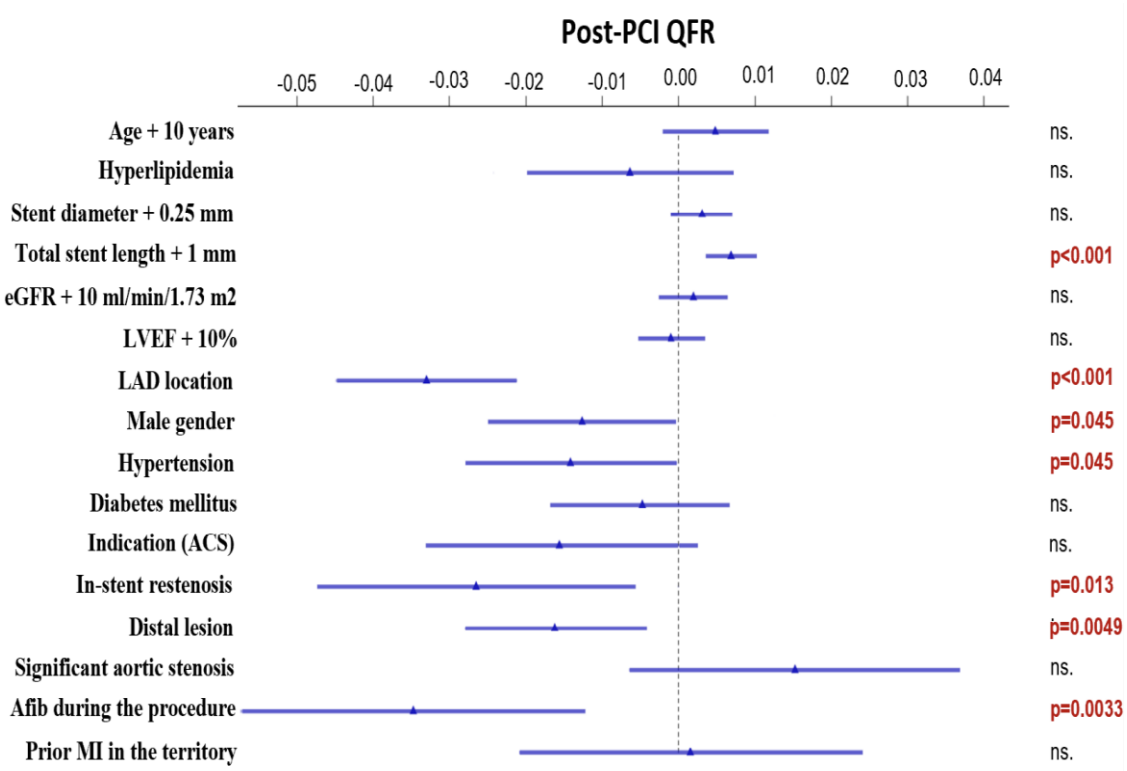


Figure 23. Predictors of post-PCI QFR in the POST-PCI QFR STUDY (Small triangles correspond to beta coefficients, lines indicate 95% confidence intervals)

4.2.3. POST-PCI QFR STUDY: Methods Comparison (79)

Our analysis revealed a consistent discrepancy between post-PCI QFR and post-PCI FFR, with QFR systematically overestimating the invasively measured FFR. The average difference between the two modalities was +0.052 ($p < 0.001$), as illustrated in the Bland-Altman plot (Figure 24.). This overestimation was more pronounced in LAD vessels, where the mean bias reached 0.058 ($p < 0.001$), compared to 0.038 ($p < 0.001$) in non-LAD arteries.

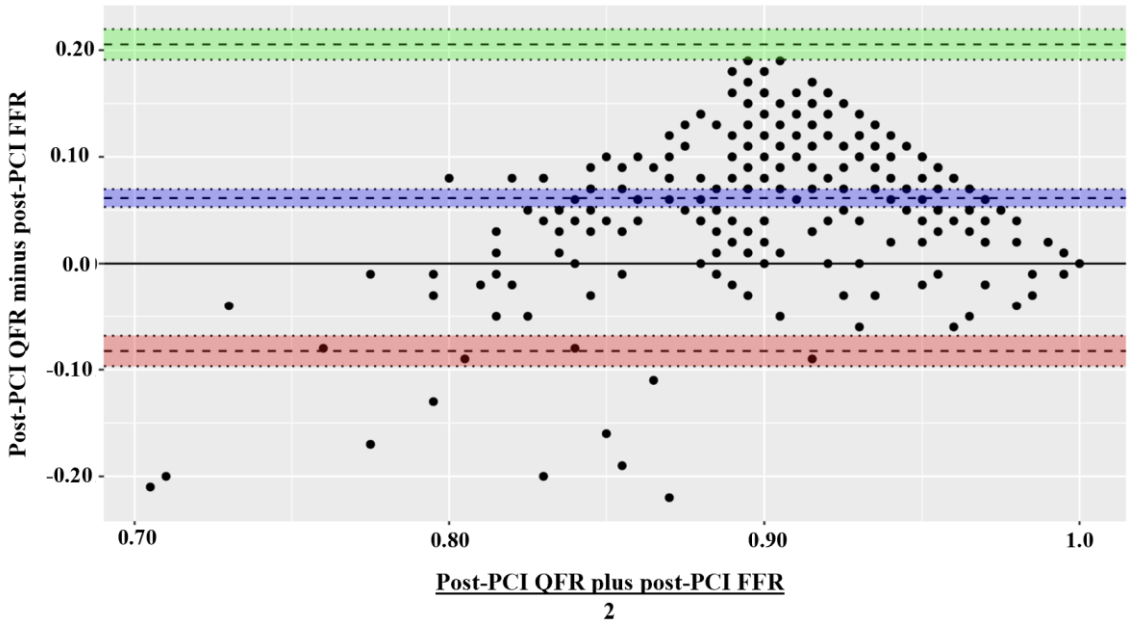


Figure 24. Bland–Altman plot illustrating the agreement between post-PCI FFR and post-PCI QFR values. The x-axis shows the average of the two measurements, while the y-axis represents their difference (post-PCI QFR minus post-PCI FFR). The purple line marks the mean difference between the methods. The green and salmon dashed lines indicate the upper and lower limits of agreement, respectively, with the shaded regions representing their 95% confidence intervals.

A comparable pattern was seen in the pre-PCI measurements, although the degree of discrepancy was smaller. Pre-PCI QFR consistently overestimated the corresponding FFR values, with an average difference of 0.037 ($p < 0.001$). This overestimation was uniform across vessel types, with a mean difference of 0.038 in LAD arteries ($p < 0.001$) and 0.036 in non-LAD vessels ($p < 0.001$), as illustrated in Figure 25.

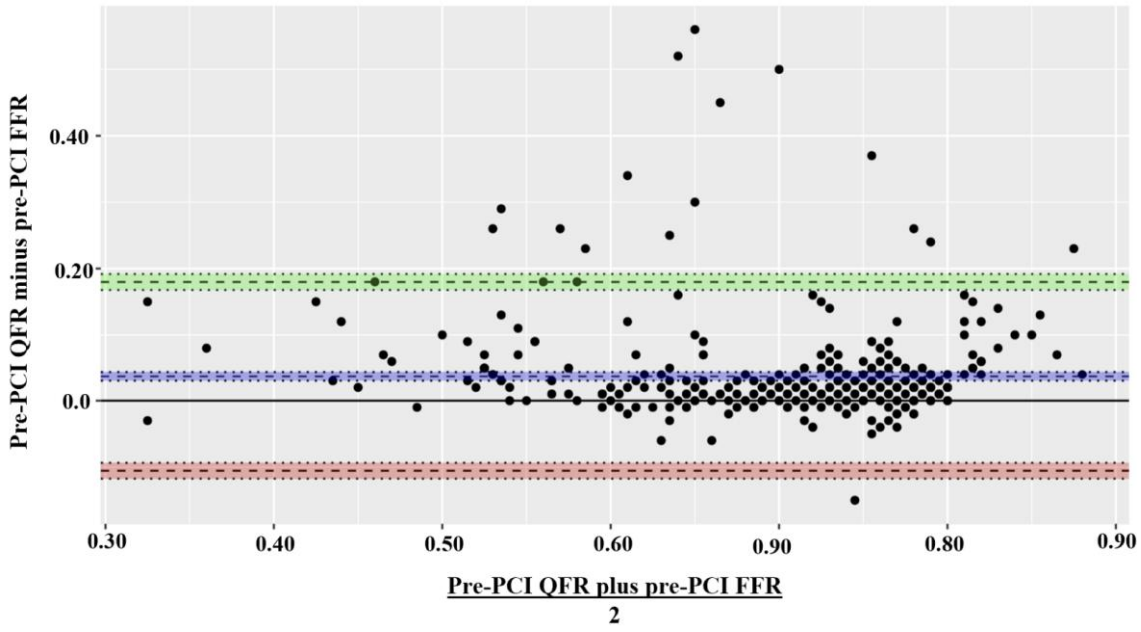
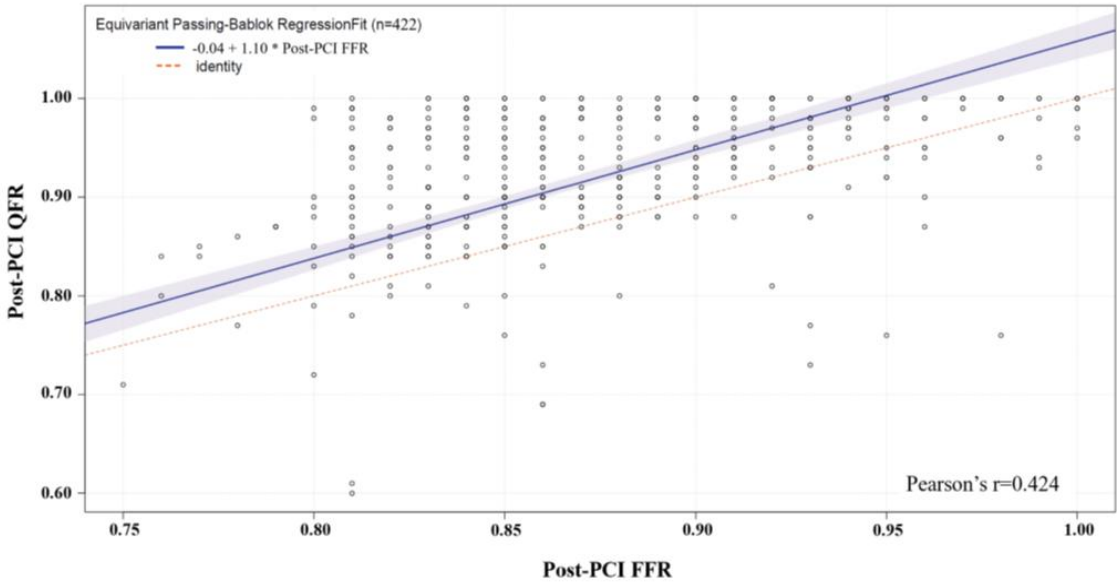


Figure 25. Bland–Altman plot illustrating the agreement between pre-PCI FFR and pre-PCI QFR values. The x-axis shows the average of the two measurements, while the y-axis represents their difference (pre-PCI QFR minus pre-PCI FFR). The purple line marks the mean difference between the methods. The green and salmon dashed lines indicate the upper and lower limits of agreement, respectively, with the shaded regions representing their 95% confidence intervals.

The correlation between post-PCI FFR and QFR was weak, with a Pearson's r of 0.42 overall - further reduced to 0.33 in LAD vessels and slightly better at 0.47 in non-LAD arteries. Similarly, Passing-Bablok regression analysis demonstrated poor agreement, as neither the intercept nor the slope aligned well, suggesting limited calibration between the two modalities. These findings are presented in Figure 26. (A) which displays the results across all vessels. In contrast, the correlation between pre-PCI FFR and QFR was notably stronger, with an overall Pearson's r of 0.73 (0.68 in LAD and 0.82 in non-LAD vessels). The Passing-Bablok regression analysis for pre-PCI values, shown in Figure 26. (B), revealed a much better calibration - highlighted by a slope close to 1 - although the intercept still showed a degree of bias.

A. Post-PCI



B. Pre-PCI

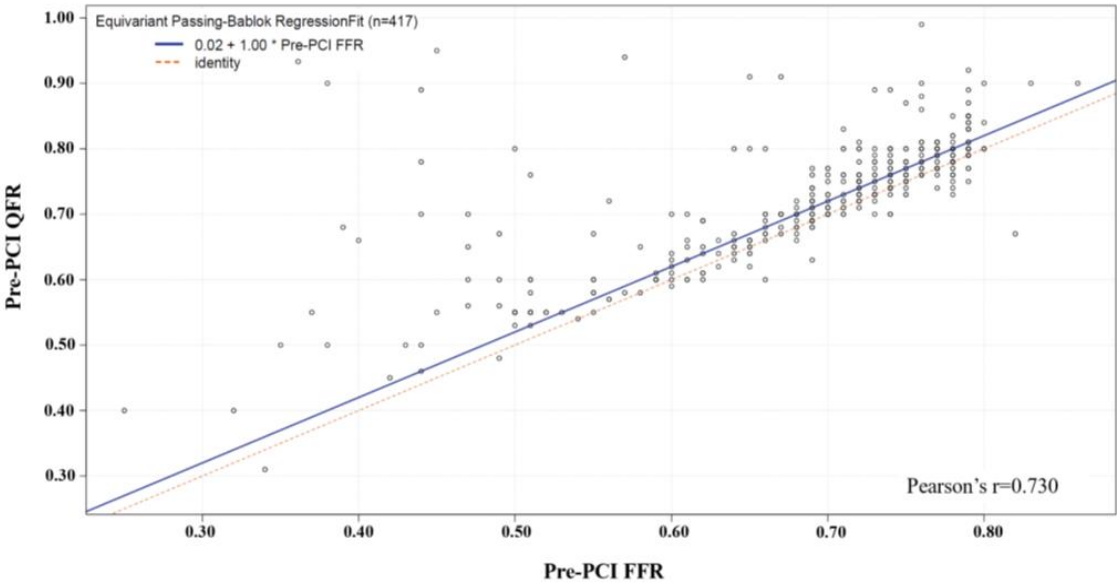


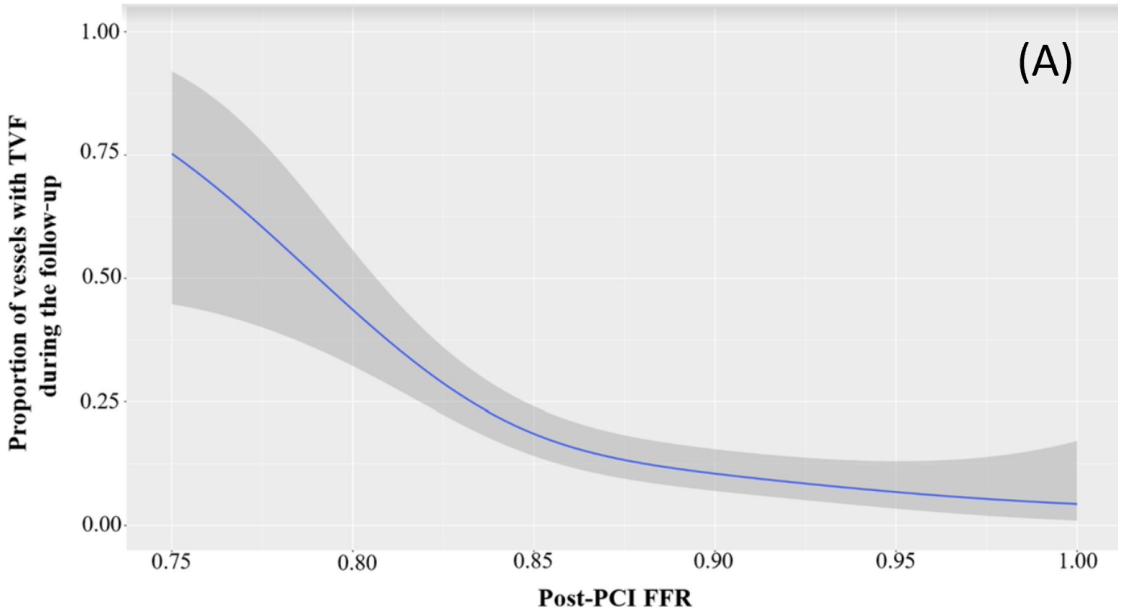
Figure 26. (A) Passing-Bablok Regression Fit shows the correlation between FFR and QFR after PCI, while **(B)** illustrates the correlation between the two measurements before PCI.

4.2.4. POST-PCI QFR STUDY: Follow-up (79)

During a median follow-up of 50 months (IQR: 30–68 months), there were 23 CDs, 14 MIs, and 39 TVRs. Of these 39 TVRs, twenty were guided by physiological assessment with an FFR of ≤0.80 recorded prior to revascularization. In four additional cases, lesions were subtotally occlusive and considered hemodynamically significant by the interventional cardiologist. The remaining 15 revascularizations were based purely on angiographic findings; in these cases, FFR measurement might have resulted in the decision to defer the procedure.

Survival time was calculated from the date of the PCI procedure. Among the 365 patients enrolled, two underwent treatment of more than one vessel at separate time points and were thus included more than once; all other patients had either a single vessel treated or underwent multivessel PCI during the same procedural setting. Complete follow-up was available for all participants (100% follow-up rate).

Univariate analysis identified post-PCI FFR as a strong and statistically significant predictor of TVF ($p < 0.001$), as illustrated in Figure 27. (A). Post-PCI QFR was likewise significantly associated with the primary endpoint of the study - TVF- with a p value of 0.013, as shown in Figure 27. (B).



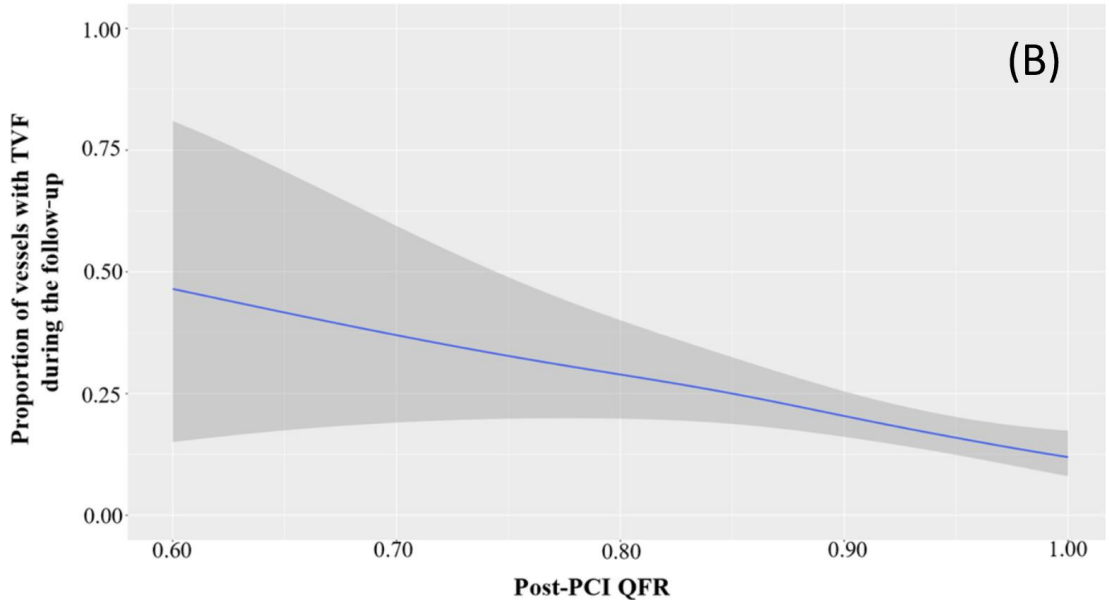


Figure 27. (A) shows the spline-smoothed relationship between post-PCI FFR and the incidence of TVF. **(B)** illustrates the spline-smoothed relationship between post-PCI QFR and the incidence of TVF during the follow-up period. The shaded region represents the 95% CI around the estimated trend.

In the multivariate analysis, post-PCI FFR ($p < 0.001$), LAD location ($p = 0.0379$) and male sex ($p = 0.0333$) emerged as significant predictors of TVF, whereas for the composite endpoint of CD/MI, only post-PCI FFR ($p < 0.001$) and diabetes mellitus ($p = 0.0434$). was identified as a significant predictor.

To test the robustness of our findings, we conducted a sensitivity analysis, excluding individuals with in-stent restenosis, prior MI in the same vessel territory, or ACS as the indication for coronary angiography. The results in this refined cohort closely mirrored those of the overall population, demonstrating consistent correlations between QFR and FFR both before and after PCI. Moreover, the predictive ability of post-PCI FFR and QFR for TVF, CD, and nonfatal target vessel-related MI remained unchanged.

Table 5. summarizes the incremental prognostic value of post-PCI FFR and QFR for TVF and the composite of CD and MI compared to a base model which included age, eGFR, LAD (vs. non-LAD) location, gender, indication category (acute vs. chronic coronary syndrome), proximal (vs. non-proximal) lesion, prior MI in the supply area. The addition of post-PCI QFR provided only limited incremental information. Models incorporating

post-PCI QFR performed similarly to the base model, and the differences in predictive accuracy were not statistically significant for either endpoint. In contrast, post-PCI FFR contributed substantially more prognostic information. Models excluding post-PCI FFR were notably less robust, with statistically significant reductions in predictive performance observed for both endpoints.

Table 5. Fraction of new information provided by post-PCI FFR and QFR for both end points in the POST-PCI QFR STUDY

TVF			
	Likelihood ratio χ^2	**Fraction of new information**	**p**
Base model	21.43		
+ Post-PCI FFR	48.10	55%	< 0.001
+ Post-PCI QFR	22.72	6%	0.255
CD/MI			
	Likelihood ratio χ^2	**Fraction of new information**	**p**
Base model	19.27		
+ Post-PCI FFR	51.70	63%	< 0.001
+ Post-PCI QFR	19.50	1%	0.632

Using univariate ROC analysis in this POST-PCI QFR STUDY, the optimal threshold for post-PCI FFR to predict TVF - identical to that found in the POST-PCI FFR STUDY - was 0.83 (sensitivity: 53%, specificity: 79%, AUC: 0.683). In the LAD group, which comprised approximately two-thirds of all assessed vessels, the optimal threshold remained 0.83, with improved sensitivity and specificity (67% and 71%, respectively) and an AUC of 0.696, indicating better predictive performance in this subset. In contrast, among non-LAD vessels, the best cut-off value was higher, 0.89 (sensitivity: 59%, specificity: 72%, AUC: 0.621). These results are illustrated in Figure 28. (A). On the other hand, no reliable cutoff value could be determined for post-PCI QFR. Across all vessels and subgroups, post-PCI QFR consistently showed poor discriminatory power, with AUC

values near or below 0.55 - indicating minimal predictive utility. These findings are depicted in Figure 28. (B).

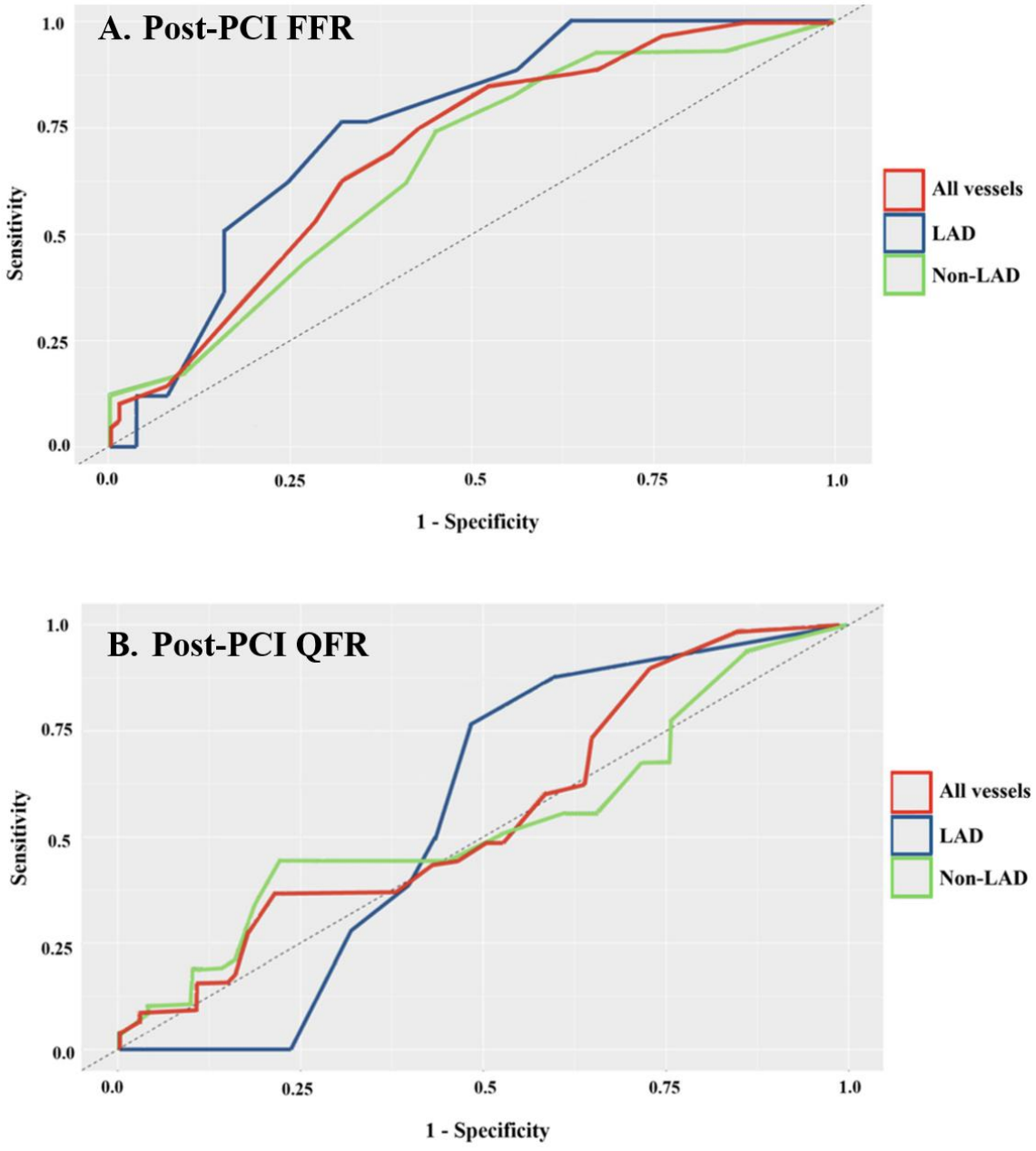


Figure 28. (A) ROC analysis of post-PCI FFR for predicting TVF, stratified by vessel type. **(B)** ROC analysis of post-PCI QFR for predicting TVF, stratified by vessel type.

5. Discussion

5.1. Interpretation of the POST-PCI FFR STUDY Results (72)

In our first analysis (POST-PCI FFR STUDY), we summarized the long-term data regarding post-PCI FFR measurements of our center. The main observations were the following: post-procedural FFR values were significantly influenced by the anatomical location of the lesion (LAD vs. non-LAD), patient sex, stent diameter, and - though to a lesser extent - pre-PCI FFR. On a vessel level, predictors of TVF included post-PCI FFR, stent length, and the presence of diabetes mellitus. We also found that the optimal post-PCI FFR threshold to predict TVF was different in LAD and non-LAD arteries. Most importantly, post-PCI FFR remained an independent predictor of serious adverse outcomes - CD and MI - alongside diabetes and total stent length.

FFR has become a widely accepted tool for guiding PCI, and it is commonly assumed that PCI effectively eliminates epicardial resistance to flow, as well as myocardial ischemia, and anginal symptoms. However, accumulating evidence suggests that this assumption does not hold true in a significant proportion of cases. Many patients continue to experience symptoms and require repeat coronary angiography despite technically successful PCI (80, 90). The persistence of symptoms may be attributed to residual epicardial resistance that was not fully relieved during the initial intervention, microvascular dysfunction or extracardiac causes (23, 91). Furthermore, while FFR-guided revascularization has significantly reduced the need for stent implantation and associated clinical events compared to the angiography-based approach, the occurrence of adverse clinical outcomes in the FAME (28% at 5 years) (26) and FAME 2 (13.9% at 5 years) (92) trials suggests that FFR-based decision-making, followed by angiography-based stent placement, does not always result in a functionally optimized PCI.

Multiple studies have examined the prognostic significance of post-PCI FFR in predicting vessel-related MACE, spanning from the BMS (51) to the DES era (48, 68, 93). However, findings on its predictive value have been inconsistent across studies (54, 55, 71, 94, 95). The variability in these results is likely multifactorial, potentially influenced by differences in follow-up duration, patient populations, and statistical power. A meta-regression analysis at the study level conducted by Rimac et al. (50) identified an inverse

relationship between post-PCI FFR and MACE, and a large patient-level meta-analysis by Johnson et al. (49) also demonstrated an inverse association between post-PCI FFR and adverse event rates. It is important to note that both analyses included patients with BMS and DES, with BMS being associated with a higher incidence of TVR. Consequently, the conclusions drawn from these studies may have limited relevance to current clinical practice, where DES implantation is the standard of care. A cohort study from the International Post-PCI FFR Registry, published in 2024, reinforced both the aforementioned findings and our own results, demonstrating that post-PCI FFR, unlike angiographic parameters, was directly associated with clinical outcomes and inversely related to the occurrence of adverse events (96).

Prior to our study, few publications explored the specific prognostic value of post-PCI FFR for predicting “hard endpoints” (CD/MI). The majority of earlier studies concentrated on composite outcomes such as TVF or MACE, both of which included TVR - a component that tends to occur considerably more often than CD or MI. Some studies identified an association between low post-PCI FFR and an increased incidence of CD and MI (47, 54). In contrast, findings from the DK CRUSH-VII Registry Study indicated a statistically significant difference in mortality between patients with a post-PCI FFR greater than 0.88 and those with lower values, based on 2 versus 6 events, respectively. However, in the same study, the difference in MI incidence was not statistically significant (0 vs. 2 events) (59). On the other hand, in the randomized controlled FAME and FAME 2 trials, post-PCI FFR was not found to be associated with either CD or MI; its predictive value was limited to TVR alone (68).

Non-hyperemic pressure ratios, such as iFR or resting Pd/Pa, have the advantage of not requiring pharmacologically induced hyperemia, making them more convenient and potentially time-efficient than FFR. However, their application immediately after PCI is questionable. Balloon inflation and stent deployment during PCI inevitably induce a certain degree of procedural hyperemia, the extent of which is unpredictable and difficult to measure. As a result, post-PCI non-hyperemic pressure ratio values may be unreliable, potentially overestimating residual epicardial disease.

Post-PCI FFR measurement provides insight into the residual epicardial limitations of maximum achievable blood flow following revascularization. These limitations may be

attributed to diffuse coronary artery disease, angiographically subtle focal lesions in untreated segments, or stent-related issues such as inadequate expansion, malapposition, geographical miss, edge dissections, or tissue protrusion. Additionally, technical factors, such as sensor drift, can affect FFR readings, while the presence of a contralateral chronic total occlusion with retrograde filling from the treated vessel may also variably influence post-PCI FFR values (97). Despite these complexities, hyperemic pullback recordings - which could clarify the underlying mechanisms - are not systemically performed at the conclusion of a procedure. Similarly, pre-PCI FFR is typically considered a single-point measurement that reflects total epicardial resistance proximal to the sensor, without distinguishing the contributions of individual segments. This lack of segmental analysis may impact procedural decision-making. The concept of two-dimensional FFR has been introduced to address this limitation, as hyperemic pullback recordings provide insights into both the severity and spatial distribution of plaques (98).

The distinction between diffuse and focal disease is clinically relevant. Emerging data suggest that greater pressure drops across focal plaques may contribute to plaque instability and subsequent ischemic events (99). However, such detailed assessments are seldom performed which may contribute to discrepancies in reported post-PCI FFR cut-off values for predicting TVF. Collet et al. have further demonstrated that angiography alone is insufficient for accurately characterizing the physiological nature of coronary artery disease, particularly in differentiating between focal and diffuse pathology. By applying the Pullback Pressure Gradient (PPG) index, they reclassified 36% of cases based on physiological rather than angiographic assessment (100).

Hwang et al. (70) proposed that distinct cut-off values may be necessary for LAD and non-LAD vessels when assessing the risk of TVF. However, due to the limited number of CD and MI cases in their study, they were unable to establish precise thresholds for predicting "hard" endpoints. Additionally, unlike our cohort, their results indicated that pre-PCI FFR values were lower in LAD arteries compared to non-LAD arteries. Our analysis further underscores the significance of vessel type in PCI outcomes. We found that while pre-PCI FFR values did not differ between LAD and non-LAD vessels, post-PCI FFR was significantly lower in the LAD. Moreover, post-PCI FFR cut-off values predicting TVF and the composite of CD and MI varied between LAD and non-LAD vessels. Furthermore, the FFR gain (ΔFFR – the difference between post- and pre-PCI

FFR) was lower in LAD compared to non-LAD vessels. This discrepancy may be attributed to several factors, as discussed in Section 1.4.3. One potential explanation is that the LAD supplies a larger myocardial mass, making any residual disease functionally more relevant. Additionally, emerging evidence suggests that hydrostatic pressure differences also contribute to these findings (101). Hydrostatic pressure differences refer to the pressure variations within the coronary arteries that arise due to gravitational forces, depending on the vertical position of the vessel segments. Before PCI, the primary driver of the hyperemic gradient is the stenosis itself, minimizing the effect of hydrostatic pressure. However, after successful PCI, with the removal of the stenotic gradient, the hydrostatic pressure difference becomes more pronounced, influencing post-PCI FFR measurements. In another analysis, Collet et al. (102) performed an individual patient-level meta-analysis, further emphasizing the importance of interpreting post-PCI FFR on a vessel-specific basis. They demonstrated that the LAD was associated with lower post-PCI FFR than non-LAD arteries, reinforcing the need for different cut-off values between vessel types. Their findings also suggested that a 0.10-unit drop in FFR was associated with a 52% higher risk of TVF, largely driven by TVR. However, in contrast to our study, their results indicated that post-PCI FFR had limited predictive power for TVF in LAD arteries and only moderate predictive accuracy for non-LAD arteries.

Investigating the underlying causes of a "suboptimal" functional result through hyperemic pullback recording (54) or intravascular imaging (103) could provide opportunities to optimize post-procedural physiology and potentially enhance clinical outcomes.

5.2. Discussion of the POST-PCI QFR STUDY (79)

Our second investigation (POST-PCI QFR STUDY) explores the prognostic utility of post-PCI FFR and QFR in routine clinical practice. The key observations can be summarized as follows. First, post-PCI QFR assessment was not feasible in 15.6% of coronary vessels. Second, both post-PCI FFR and QFR were influenced by clinical and anatomical characteristics; notably, LAD lesions were associated with lower values of both indices, whereas, importantly, ACS (evaluated in non-culprit vessels) had no

measurable effect. Third, although post-PCI QFR showed a moderate correlation with FFR, it consistently overestimated its values, with a mean bias of +0.05. Fourth, in line with prior evidence and our earlier study, post-PCI FFR demonstrated strong predictive capacity for TVF and the composite of CD and target-vessel-related MI (42, 49, 50, 68, 72, 102, 104). In contrast, while post-PCI QFR exhibited association with TVF, after adjustment for confounding factors, it was not found to be an independent predictor of clinical events. Lastly, post-PCI FFR yielded moderate discriminative performance with AUC values ranging between 0.6 and 0.7, depending on the vessel type, whereas QFR showed limited prognostic accuracy, with AUCs approximating or falling below 0.55.

Angiography has shown inferior performance compared to FFR in guiding multivessel PCI (25), while numerous studies have demonstrated the advantage of intravascular imaging for optimizing complex PCI procedures (13, 105).

In our studies, post-PCI FFR not only predicted TVF but also proved to be a robust independent predictor of hard endpoints. These findings emphasize the clinical value of routine FFR measurement even after angiographically successful PCI. Nevertheless, the adoption of post-PCI FFR assessment remains limited in routine practice.

In an effort to overcome these limitations, advanced three-dimensional reconstruction techniques have been introduced. A notable technique is QFR, a novel method that rapidly estimates FFR based on coronary angiographic images. QFR offers advantages over conventional physiological assessments by eliminating the need for pressure wires or hyperemia, enabling real-time evaluation during angiography. However, its accuracy depends on image quality and proper vessel reconstruction, limiting reliability in cases of poor visualization, vessel tortuosity, or diffuse disease. Manual adjustment of vessel contour detection is often required, and dynamic flow variations may affect results.

QFR has demonstrated a strong correlation with FFR prior to PCI and possesses clinical value in guiding PCI decisions (73-76). However, in the FAVOR III Europe Trial, QFR failed to demonstrate non-inferiority to FFR (78). Clinically, it can be positioned between angiography and FFR as a decision-making tool and serves as a viable alternative when FFR is unavailable (106). However, uncertainty remained as to whether QFR could reliably assess PCI success.

Although post-PCI QFR provides a less invasive alternative to FFR, our results reveal limitations to its predictive accuracy. Unlike post-PCI FFR, it was not an independent predictor of TVF or hard clinical endpoints. Notably, while pre-PCI QFR correlated well with FFR, post-PCI QFR showed poor agreement. This discrepancy may reflect that post-PCI QFR primarily assesses residual native disease, whereas FFR captures both residual disease and trans-stent gradients. As hyperemic pullback and QCA were not performed, this hypothesis could not be fully evaluated.

Our results contrast with those reported in the HAWKEYE trial (Angio-Based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation), where post-PCI QFR served as an independent predictor of adverse clinical outcomes (107). In HAWKEYE, specific imaging protocols were implemented at the end of angiographically successful PCI to optimize QFR assessment, including the acquisition of two angiographic projections separated by at least 25 degrees, with particular attention to minimizing vessel foreshortening and overlap. Despite these optimized conditions, QFR calculation failed in approximately 15% of cases. Moreover, while the HAWKEYE trial followed patients for only 1 year, our study included a substantially longer median follow-up of 50 months. Importantly, the median post-PCI QFR value was higher in HAWKEYE (0.97) compared to our cohort (0.93), and approximately one-third of patients in HAWKEYE exhibited residual diffuse disease, suggesting a more selected population compared to the all-comer design applied in our study. Furthermore, differences in vessel territory may partly explain the variability in QFR performance. We observed greater bias in LAD vessels compared to non-LAD, and LAD lesions accounted for over two-thirds of our cohort, versus 48% in the HAWKEYE trial.

The learning curve associated with QFR measurement is also noteworthy. In our experience, procedural efficiency improved significantly after approximately 300 cases, with both reduced measurement time and improved accuracy, as reflected by a decreased bias relative to FFR (108). QFR analysis still requires operator intervention, including manual adjustments to vessel contour detection. This limitation is expected to diminish over time with the implementation of newer software versions featuring more advanced automation and enhanced user guidance.

A post hoc analysis of the SYNTAX II (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial found post-PCI QFR to be an independent predictor of the 2-year vessel-oriented composite endpoint, including vessel-related CD, MI, and TVR. This study involved patients with de novo three-vessel disease, nearly 80% IVUS guidance, and core lab QFR analysis by certified Medis software users. Notably, both their study and ours consistently showed that higher post-PCI QFR values were associated with better outcomes. Differences in findings may reflect the above-mentioned factors, variations in primary endpoints, and follow-up duration.

The significance of follow-up duration is highlighted by the study of Chen et al. (109), where the prognostic value of low post-PCI 3-vessel QFR shifted over time. At 1 year, neither diabetes status nor 3-vessel QFR predicted clinical outcomes. However, between years 1 and 2, 3-vessel QFR became the strongest predictor of major adverse cardiac events, while after 2 years, diabetes status emerged as the primary determinant.

Conversely, You et al. reported that in patients treated with rotational atherectomy for heavily calcified lesions, post-procedural QFR assessed offline was not associated with target-lesion failure (110). Whether periprocedural microvascular injury influences post-PCI FFR and QFR differently remains unclear. In our study, as microvascular functional indices were not assessed, we were unable to quantify PCI-induced microvascular alterations. Similarly, in another study, QFR measured after successful chronic total occlusion PCI failed to predict 2-year TVF (111).

Our findings regarding optimal post-PCI FFR cutoffs provide practical clinical thresholds to support decision-making, particularly highlighting lower post-PCI FFR values in LAD compared to non-LAD vessels, which may help refine patient management strategies. While previous studies identified post-PCI QFR thresholds ranging from 0.89 to 0.94 (112), no specific cutoff value predictive of TVF could be established in our analysis.

5.3. Limitations of the Two Studies (72, 79)

Each analysis has several limitations that should be acknowledged. First, both are based on a single-center cohort with a limited number of patients. While restricting the

population to patients treated with DES improved cohort homogeneity, it also reduced the overall sample size. The cohorts included a mix of first-, second-, and third-generation DES, with most cases involving second- and third-generation stents; however, the potential impact of stent type was not assessed. Moreover, a notable portion of vessels (15.6%) had to be excluded from the POST-PCI QFR analysis due to suboptimal angiographic projections or inadequate image quality. This limitation is partly attributable to the fact that QFR analysis was performed retrospectively using standard institutional angiograms which were not acquired with the specific aim of QFR computation. Nevertheless, this reflects a real-world scenario, where angiograms are not routinely acquired with the explicit aim of QFR analysis. It also remains unclear how the operator's experience and learning curve may influence the reliability of QFR measurements.

The cause of death could not be definitively identified in all cases and was therefore classified as cardiac death by default. TVR was occasionally performed based solely on angiographic findings without confirmatory FFR measurements. We were also unable to evaluate the anginal status of our patients, preventing any assessment of the relationship between post-PCI FFR or QFR and symptom burden or quality of life. Additionally, PPG was not assessed, intravascular imaging was not routinely used, and pullback recordings were not systemically performed - making it impossible to clearly differentiate between diffuse and focal residual disease, even though diffuse disease is known to impair the prognostic accuracy of post-PCI QFR (113). However, in all cases, pressure drift in FFR was carefully checked, and if a drift of more than 0.03 units was observed, the measurement was either corrected or repeated after re-equalization. While both patients and their treating physicians were informed of the post-PCI FFR results, all procedures were considered angiographically successful, and only a small proportion of vessels showed a post-PCI FFR of ≤ 0.80.

6. Conclusions (72, 79)

This dissertation explored the prognostic value and clinical utility of post-PCI physiological assessments, with a particular focus on FFR and QFR in an unselected, real-world patient population undergoing DES implantation. Our findings underscore the importance of post-PCI functional evaluation in identifying residual ischemia, predicting long-term outcomes, and guiding post-procedural management.

In our first investigation (POST-PCI FFR STUDY), we demonstrated that post-PCI FFR is a strong independent predictor of TVF, as well as hard clinical endpoints such as the composite of CD and MI. We also found that lesion location significantly influenced physiological outcomes: LAD lesions were associated with lower post-PCI FFR values, and this vessel-specific difference affected prognostic interpretation. These findings suggest that a single uniform FFR cut-off may not be appropriate across all coronary territories, and that vessel-specific thresholds may improve the clinical utility of post-PCI FFR. Our results align with recent registry data and meta-analyses, reinforcing the role of FFR as a meaningful physiological endpoint following angiographically successful PCI.

In our second study (POST-PCI QFR Study), we assessed QFR as a less invasive, wire-free alternative to FFR. While QFR has shown good correlation with FFR prior to PCI and offers practical advantages - including the avoidance of hyperemia and wire manipulation - our data reveal significant limitations in the post-PCI setting. We observed that QFR calculation was not feasible in 15.6% of cases, largely due to suboptimal image quality or anatomical complexity. Post-PCI QFR demonstrated modest correlation with and tended to overestimate FFR. Most importantly, QFR failed to independently predict TVF or hard endpoints after adjustment to clinical and procedural variables. Further evidence is needed to establish the utility of post-PCI QFR, and ongoing trials such as the Multivessel TALENT study (NCT04390672) are expected to contribute valuable insights.

7. Summary (72, 79)

The assessment of coronary physiology following PCI plays a pivotal role in understanding residual disease burden and optimizing long-term outcomes. This dissertation examined the utility of two physiological indices – FFR and QFR - when applied after PCI in a real-world setting. While pre-PCI applications of both indices are well-established, their post-procedural prognostic relevance and the optimal threshold values for predicting TVF - particularly when stratified by vessel territory - remain an area of active investigation.

Through two analyses, we evaluated the predictive performance, feasibility, and practical limitations of post-PCI FFR and QFR in an unselected patient population undergoing DES implantation. Our work aimed to go beyond binary angiographic success by introducing functional criteria to identify cases at increased risk of adverse events despite technically successful interventions.

The findings confirmed the prognostic value of post-PCI FFR in detecting suboptimal outcomes, including both soft and hard endpoints. The results also highlighted the influence of anatomical factors - particularly lesion location - on physiological metrics and their interpretation. In contrast, although QFR presents an attractive, non-invasive alternative, its accuracy and reliability in the post-PCI setting were found to be limited, especially in the absence of image optimization and in cases involving complex anatomy.

This research contributes to a growing body of evidence advocating for individualized, physiology-based evaluation after PCI. It also raises important questions about the current readiness of QFR for routine post-PCI use. As the field evolves, future studies with longer follow-up, standardized imaging protocols, and broader patient representation will be crucial to define the role of QFR in post-interventional care. Ultimately, the integration of physiology-guided assessment into daily clinical practice may lead to more refined and patient-specific treatment strategies.

8. References

1. Artico M, Spoletini M, Fumagalli L, Biagioni F, Ryskalin L, Fornai F, et al. Egas Moniz: 90 Years (1927-2017) from Cerebral Angiography. Front Neuroanat. 2017;11:81.

2. Sones FM, Jr. Cine-coronary arteriography. Ohio State Med J. 1962;58:1018-9.

3. Proudfit WL, Shirey EK, Sones FM, Jr. Selective cine coronary arteriography. Correlation with clinical findings in 1,000 patients. Circulation. 1966;33(6):901-10.

4. National center for health statistics. Multiple cause of death 2018–2022 on CDC WONDER Database. Accessed January 3, 2025.

5. Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. Circulation. 2024;149(8):e347-e913.

6. Nemeth N, Endrei D, Elmer D, Csakvari T, Horvath L, Kajos LF, et al. [Epidemiological disease burden and annual health insurance treatment cost of acute myocardial infarction in Hungary]. Orv Hetil. 2021;162(162 Suppl 1):6-13.

7. Janosi A, Pach FP, Erdos G, Toth K, Hari P, Ofner P, et al. [Management of patients treated for myocardial infarction in different regions of Hungary and patient survival for 10 years]. Orv Hetil. 2021;162(36):1438-50.

8. Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. Eur Heart J. 2018;39(13):1065-74.

9. Thrane PG, Olesen KKW, Thim T, Gyldenkerne C, Mortensen MB, Kristensen SD, et al. Mortality Trends After Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol. 2023;82(10):999-1010.

10. Yan F, Zhang Y, Pan Y, Li S, Yang M, Wang Y, et al. Prevalence and associated factors of mortality after percutaneous coronary intervention for adult patients with ST-elevation myocardial infarction: A systematic review and meta-analysis. J Res Med Sci. 2023;28:17.

11. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation. 1995;92(8):2333-42.

12. Noguchi M, Gkargkoulas F, Matsumura M, Kotinkaduwa LN, Hu X, Usui E, et al. Impact of Nonobstructive Left Main Coronary Artery Atherosclerosis on Long-Term Mortality. JACC Cardiovasc Interv. 2022;15(21):2206-17.

13. Holm NR, Andreasen LN, Neghabat O, Laanmets P, Kumsars I, Bennett J, et al. OCT or Angiography Guidance for PCI in Complex Bifurcation Lesions. N Engl J Med. 2023;389(16):1477-87.

14. Lee JM, Choi KH, Song YB, Lee JY, Lee SJ, Lee SY, et al. Intravascular Imaging-Guided or Angiography-Guided Complex PCI. N Engl J Med. 2023;388(18):1668-79.

15. Ali ZA, Landmesser U, Maehara A, Matsumura M, Shlofmitz RA, Guagliumi G, et al. Optical Coherence Tomography-Guided versus Angiography-Guided PCI. N Engl J Med. 2023;389(16):1466-76.

16. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol. 2010;55(25):2816-21.

17. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation. 1997;95(8):2037-43.

18. Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. Circulation. 2000;101(12):1465-78.

19. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol. 2004;11(2):171-85.

20. Erne P, Schoenenberger AW, Burckhardt D, Zuber M, Kiowski W, Buser PT, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. JAMA. 2007;297(18):1985-91.

21. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation. 2003;107(23):2900-7.

22. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007;49(21):2105-11.

23. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-537.

24. Toth G, Hamilos M, Pyxaras S, Mangiacapra F, Nelis O, De Vroey F, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. Eur Heart J. 2014;35(40):2831-8.

25. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.

26. van Nunen LX, Zimmermann FM, Tonino PA, Barbato E, Baumbach A, Engstrom T, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet. 2015;386(10006):1853-60.

27. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol. 2010;56(3):177-84.

28. Lima RS, Watson DD, Goode AR, Siadaty MS, Ragosta M, Beller GA, et al. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of severe three-vessel coronary artery disease. J Am Coll Cardiol. 2003;42(1):64-70.

29. Piróth Z FG, Fülöp G, Szőnyi T, Szőke S, Szabó Gy, Németh J, Ferenci T, Andréka P. Non-invazív kivizsgálás, illetve FFR mérés elektív PCI előtt. Cardiologia Hungarica. 2016;46: F15.

30. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation. 1993;87(4):1354-67.

31. Abo-Aly M, Lolay G, Adams C, Ahmed AE, Abdel-Latif A, Ziada KM. Comparison of intracoronary versus intravenous adenosine-induced maximal hyperemia for fractional flow reserve measurement: A systematic review and meta-analysis. Catheter Cardiovasc Interv. 2019;94(5):714-21.

32. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med. 1996;334(26):1703-8.

33. Pijls NH, De Bruyne B, Bech GJ, Liistro F, Heyndrickx GR, Bonnier HJ, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. Circulation. 2000;102(19):2371-7.

34. De Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. Circulation. 1994;89(3):1013-22.

35. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367(11):991-1001.

36. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014;371(13):1208-17.

37. Muller O, Mangiacapra F, Ntalianis A, Verhamme KM, Trana C, Hamilos M, et al. Long-term follow-up after fractional flow reserve-guided treatment strategy in patients

with an isolated proximal left anterior descending coronary artery stenosis. JACC Cardiovasc Interv. 2011;4(11):1175-82.

38. Puymirat E, Peace A, Mangiacapra F, Conte M, Ntarladimas Y, Bartunek J, et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary revascularization in patients with small-vessel disease. Circ Cardiovasc Interv. 2012;5(1):62-8.

39. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J. 2015;36(45):3182-8.

40. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation. 2001;103(24):2928-34.

41. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360(10):961-72.

42. Piroth Z, Otsuki H, Zimmermann FM, Ferenci T, Keulards DCJ, Yeung AC, et al. Prognostic Value of Measuring Fractional Flow Reserve After Percutaneous Coronary Intervention in Patients With Complex Coronary Artery Disease: Insights From the FAME 3 Trial. Circ Cardiovasc Interv. 2022;15(11):884-91.

43. Piroth Z, Fülöp G, Csanádi B, Fontos G, Andréka P, Nyolczas N, et al. A háromér-betegség kezelése a FAME-3 vizsgálat eredményeinek tükrében. Orvosi hetilap. 2022;163:1032-6.

44. Zimmermann FM, Ding VY, Pijls NHJ, Piroth Z, van Straten AHM, Szekely L, et al. Fractional Flow Reserve-Guided PCI or Coronary Bypass Surgery for 3-Vessel Coronary Artery Disease: 3-Year Follow-Up of the FAME 3 Trial. Circulation. 2023;148(12):950-8.

45. Fearon WF, Zimmermann FM, De Bruyne B, Piroth Z, van Straten AHM, Szekely L, et al. Fractional Flow Reserve-Guided PCI as Compared with Coronary Bypass Surgery. N Engl J Med. 2022;386(2):128-37.

46. Fearon WF, Zimmermann FM, Ding VY, Takahashi K, Piroth Z, van Straten AHM, et al. Outcomes after fractional flow reserve-guided percutaneous coronary intervention versus coronary artery bypass grafting (FAME 3): 5-year follow-up of a multicentre, open-label, randomised trial. Lancet. 2025;405(10488):1481-90.

47. Hakeem A, Uretsky BF. Role of Postintervention Fractional Flow Reserve to Improve Procedural and Clinical Outcomes. Circulation. 2019;139(5):694-706.

48. Nam CW, Hur SH, Cho YK, Park HS, Yoon HJ, Kim H, et al. Relation of fractional flow reserve after drug-eluting stent implantation to one-year outcomes. Am J Cardiol. 2011;107(12):1763-7.

49. Johnson NP, Toth GG, Lai D, Zhu H, Acar G, Agostoni P, et al. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. J Am Coll Cardiol. 2014;64(16):1641-54.

50. Rimac G, Fearon WF, De Bruyne B, Ikeno F, Matsuo H, Piroth Z, et al. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis. Am Heart J. 2017;183:1-9.

51. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation. 2002;105(25):2950-4.

52. Bech GJ, Pijls NH, De Bruyne B, Peels KH, Michels HR, Bonnier HJ, et al. Usefulness of fractional flow reserve to predict clinical outcome after balloon angioplasty. Circulation. 1999;99(7):883-8.

53. Jeremias A, Davies JE, Maehara A, Matsumura M, Schneider J, Tang K, et al. Blinded Physiological Assessment of Residual Ischemia After Successful Angiographic Percutaneous Coronary Intervention: The DEFINE PCI Study. JACC Cardiovasc Interv. 2019;12(20):1991-2001.

54. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv. 2016;9(10):1022-31.

55. van Bommel RJ, Masdjedi K, Diletti R, Lemmert ME, van Zandvoort L, Wilschut J, et al. Routine Fractional Flow Reserve Measurement After Percutaneous Coronary Intervention. Circ Cardiovasc Interv. 2019;12(5):e007428.

56. Uretsky BF, Agarwal SK, Vallurupalli S, Al-Hawwas M, Hasan R, Miller K, et al. Prospective Evaluation of the Strategy of Functionally Optimized Coronary Intervention. J Am Heart Assoc. 2020;9(3):e015073.

57. Dupouy P, Gilard M, Morelle JF, Furber A, Aptecar E, Cazaux P, et al. Usefulness and clinical impact of a fractional flow reserve and angiographic targeted strategy for coronary artery stenting: FROST III, a multicenter prospective registry. EuroIntervention. 2005;1(1):85-92.

58. Jensen LO, Thayssen P, Thuesen L, Hansen HS, Lassen JF, Kelbaek H, et al. Influence of a pressure gradient distal to implanted bare-metal stent on in-stent restenosis after percutaneous coronary intervention. Circulation. 2007;116(24):2802-8.

59. Li SJ, Ge Z, Kan J, Zhang JJ, Ye F, Kwan TW, et al. Cutoff Value and Long-Term Prediction of Clinical Events by FFR Measured Immediately After Implantation of a Drug-Eluting Stent in Patients With Coronary Artery Disease: 1- to 3-Year Results From the DKCRUSH VII Registry Study. JACC Cardiovasc Interv. 2017;10(10):986-95.

60. Kim HL, Koo BK, Nam CW, Doh JH, Kim JH, Yang HM, et al. Clinical and physiological outcomes of fractional flow reserve-guided percutaneous coronary intervention in patients with serial stenoses within one coronary artery. JACC Cardiovasc Interv. 2012;5(10):1013-8.

61. Piroth Z. FFR in Everyday Use: The Case of Ventricular Dysfunction. J Cardiac Disord Therapy 2018;1: 102.

62. Gould KL, Johnson NP. Physiologic severity of diffuse coronary artery disease: hidden high risk. Circulation. 2015;131(1):4-6.

63. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. Circulation. 2015;131(1):19-27.

64. Bertrand OF, De Larochelliere R, Joyal M, Bonan R, Mongrain R, Tardif JC. Incidence of stent under-deployment as a cause of in-stent restenosis in long stents. Int J Cardiovasc Imaging. 2004;20(4):279-84.

65. Im E, Kim BK, Ko YG, Shin DH, Kim JS, Choi D, et al. Incidences, predictors, and clinical outcomes of acute and late stent malapposition detected by optical coherence tomography after drug-eluting stent implantation. Circ Cardiovasc Interv. 2014;7(1):88-96.

66. Raber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. EuroIntervention. 2018;14(6):656-77.

67. Matsumura M, Johnson NP, Fearon WF, Mintz GS, Stone GW, Oldroyd KG, et al. Accuracy of Fractional Flow Reserve Measurements in Clinical Practice: Observations From a Core Laboratory Analysis. JACC Cardiovasc Interv. 2017;10(14):1392-401.

68. Piroth Z, Toth GG, Tonino PAL, Barbato E, Aghlmandi S, Curzen N, et al. Prognostic Value of Fractional Flow Reserve Measured Immediately After Drug-Eluting Stent Implantation. Circ Cardiovasc Interv. 2017;10(8).

69. Collison D, Didagelos M, Aetesam-Ur-Rahman M, Copt S, McDade R, McCartney P, et al. Post-stenting fractional flow reserve vs coronary angiography for optimization of percutaneous coronary intervention (TARGET-FFR). Eur Heart J. 2021;42(45):4656-68.

70. Hwang D, Lee JM, Lee HJ, Kim SH, Nam CW, Hahn JY, et al. Influence of target vessel on prognostic relevance of fractional flow reserve after coronary stenting. EuroIntervention. 2019;15(5):457-64.

71. Leesar MA, Satran A, Yalamanchili V, Helmy T, Abdul-Waheed M, Wongpraparut N. The impact of fractional flow reserve measurement on clinical outcomes after transradial coronary stenting. EuroIntervention. 2011;7(8):917-23.

72. Csanadi B, Ferenci T, Fulop G, Piroth Z. Clinical Implications of Fractional Flow Reserve Measured Immediately After Percutaneous Coronary Intervention. Cardiovasc Drugs Ther. 2024;38(5):917-25.

73. Xu B, Tu S, Song L, Jin Z, Yu B, Fu G, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. Lancet. 2021;398(10317):2149-59.

74. Song L, Xu B, Tu S, Guan C, Jin Z, Yu B, et al. 2-Year Outcomes of Angiographic Quantitative Flow Ratio-Guided Coronary Interventions. J Am Coll Cardiol. 2022;80(22):2089-101.

75. Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, et al. Diagnostic Performance of In-Procedure Angiography-Derived Quantitative Flow Reserve Compared to Pressure-Derived Fractional Flow Reserve: The FAVOR II Europe-Japan Study. J Am Heart Assoc. 2018;7(14).

76. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, et al. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. J Am Coll Cardiol. 2017;70(25):3077-87.

77. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, et al. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. JACC Cardiovasc Interv. 2016;9(19):2024-35.

78. Andersen BK, Sejr-Hansen M, Maillard L, Campo G, Ramunddal T, Stahli BE, et al. Quantitative flow ratio versus fractional flow reserve for coronary revascularisation guidance (FAVOR III Europe): a multicentre, randomised, non-inferiority trial. Lancet. 2024;404(10465):1835-46.

79. Csanadi B, Ferenci T, Gal R, Bora N, Piroth Z. Correlation and Relative Prognostic Power of Post-Percutaneous Coronary Intervention Fractional Flow Reserve and Quantitative Flow Ratio. J Am Heart Assoc. 2025;14(8):e040969.

80. Kwok CS, Narain A, Pacha HM, Lo TS, Holroyd EW, Alraies MC, et al. Readmissions to Hospital After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis of Factors Associated with Readmissions. Cardiovasc Revasc Med. 2020;21(3):375-91.

81. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002;346(23):1773-80.

82. Mohan S, Dhall A. A comparative study of restenosis rates in bare metal and drug-eluting stents. Int J Angiol. 2010;19(2):e66-72.

83. Jensen LO, Christiansen EH. Are drug-eluting stents safer than bare-metal stents? Lancet. 2019;393(10190):2472-4.

84. Rahmani M, Cruz RP, Granville DJ, McManus BM. Allograft vasculopathy versus atherosclerosis. Circ Res. 2006;99(8):801-15.

85. Angelini A, Castellani C, Fedrigo M, de Boer OJ, Meijer-Jorna LB, Li X, et al. Coronary cardiac allograft vasculopathy versus native atherosclerosis: difficulties in classification. Virchows Arch. 2014;464(6):627-35.

86. Avital S, Wacksman R, Rozenman Y, Mosseri M, Lotan C, Hasin Y, et al. [Angioplasty for vein grafts and native coronary arteries after previous coronary artery bypass grafting]. Harefuah. 1995;129(3-4):96-9, 159.

87. Eid-Lidt G, Gaspar J, Adames AE, Damas de Los Santos F, Valdez RI, Ramirez-Gutierrez AE, et al. Long-term outcomes of saphenous vein graft stenting compared with native coronary artery stenting in patients with previous coronary artery bypass graft surgery. Arch Cardiol Mex. 2010;80(1):3-9.

88. Harrell FE, SpringerLink. Regression Modeling Strategies : With Applications to Linear Models, Logistic Regression, and Survival Analysis. 1st 2001. ed: Springer New York : Imprint: Springer; 2001.

89. Buuren Sv, ProQuest. Flexible imputation of missing data. Boca Raton, FL: CRC Press; 2012.

90. Kwok CS, Shah B, Al-Suwaidi J, Fischman DL, Holmvang L, Alraies C, et al. Timing and Causes of Unplanned Readmissions After Percutaneous Coronary Intervention: Insights From the Nationwide Readmission Database. JACC Cardiovasc Interv. 2019;12(8):734-48.

91. Piróth Z, Csanádi B, Bora N, Németh O, Gál R. Microvascularis coronariabetegség, vasospasticus angina. Orvosi Hetilap. 2024;165(41):1613-20.

92. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. N Engl J Med. 2018;379(3):250-9.

93. Doh JH, Nam CW, Koo BK, Lee SY, Choi H, Namgung J, et al. Clinical Relevance of Poststent Fractional Flow Reserve After Drug-Eluting Stent Implantation. J Invasive Cardiol. 2015;27(8):346-51.

94. Matsuo A, Fujita H, Tanigaki T, Shimonaga T, Ueoka A, Tsubakimoto Y, et al. Clinical implications of coronary pressure measurement after stent implantation. Cardiovasc Interv Ther. 2013;28(2):170-7.

95. Ishii H, Kataoka T, Kobayashi Y, Tsumori T, Takeshita H, Matsumoto R, et al. Utility of myocardial fractional flow reserve for prediction of restenosis following sirolimus-eluting stent implantation. Heart Vessels. 2011;26(6):572-81.

96. Zhang J, Hwang D, Yang S, Hu X, Lee JM, Nam CW, et al. Angiographic Findings and Post-Percutaneous Coronary Intervention Fractional Flow Reserve. JAMA Netw Open. 2024;7(6):e2418072.

97. Ladwiniec A, Cunnington MS, Rossington J, Mather AN, Alahmar A, Oliver RM, et al. Collateral donor artery physiology and the influence of a chronic total occlusion on fractional flow reserve. Circ Cardiovasc Interv. 2015;8(4).

98. Johnson NP, Piroth Z. 2-Dimensional Fractional Flow Reserve: Depth and Distribution. JACC Cardiovasc Interv. 2020;13(14):1651-4.

99. Lee JM, Choi G, Koo BK, Hwang D, Park J, Zhang J, et al. Identification of High-Risk Plaques Destined to Cause Acute Coronary Syndrome Using Coronary Computed Tomographic Angiography and Computational Fluid Dynamics. JACC Cardiovasc Imaging. 2019;12(6):1032-43.

100. Collet C, Sonck J, Vandeloo B, Mizukami T, Roosens B, Lochy S, et al. Measurement of Hyperemic Pullback Pressure Gradients to Characterize Patterns of Coronary Atherosclerosis. J Am Coll Cardiol. 2019;74(14):1772-84.

101. Kawaguchi Y, Ito K, Kin H, Shirai Y, Okazaki A, Miyajima K, et al. Impact of Hydrostatic Pressure Variations Caused by Height Differences in Supine and Prone Positions on Fractional Flow Reserve Values in the Coronary Circulation. J Interv Cardiol. 2019;2019:4532862.

102. Collet C, Johnson NP, Mizukami T, Fearon WF, Berry C, Sonck J, et al. Impact of Post-PCI FFR Stratified by Coronary Artery. JACC Cardiovasc Interv. 2023;16(19):2396-408.

103. Wolfrum M, De Maria GL, Benenati S, Langrish J, Lucking AJ, Channon KM, et al. What are the causes of a suboptimal FFR after coronary stent deployment? Insights from a consecutive series using OCT imaging. EuroIntervention. 2018;14(12):e1324-e31.

104. Hwang D, Koo BK, Zhang J, Park J, Yang S, Kim M, et al. Prognostic Implications of Fractional Flow Reserve After Coronary Stenting: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(9):e2232842.

105. Tebaldi M, Biscaglia S, Fineschi M, Musumeci G, Marchese A, Leone AM, et al. Evolving Routine Standards in Invasive Hemodynamic Assessment of Coronary Stenosis: The Nationwide Italian SICI-GISE Cross-Sectional ERIS Study. JACC Cardiovasc Interv. 2018;11(15):1482-91.

106. Fearon WF, Biscaglia S. Guideline recommendations for QFR should be revisited: pros and cons. EuroIntervention. 2025;21(12):e652-e4.

107. Biscaglia S, Tebaldi M, Brugaletta S, Cerrato E, Erriquez A, Passarini G, et al. Prognostic Value of QFR Measured Immediately After Successful Stent Implantation: The International Multicenter Prospective HAWKEYE Study. JACC Cardiovasc Interv. 2019;12(20):2079-88.

108. Gál R, Csanádi B, Ferenci T, Bora N, Piróth Z. Real-World Comparison of FFR and QFR: New Perspectives on the Functional Assessment of Coronary Stenoses. Journal of Clinical Medicine. 2025;14(17):5946.

109. Chen Y, Zhong J, Chen L, Hong R, Yan Y, Chen L, et al. Effects of percutaneous coronary intervention and diabetes mellitus on short- and long-term prognosis assessed by the three-vessel quantitative flow ratio. Diabetes Res Clin Pract. 2023;206:111013.

110. You W, Zhou Y, Wu Z, Meng P, Pan D, Yin D, et al. Post-PCI quantitative flow ratio predicts 3-year outcome after rotational atherectomy in patients with heavily calcified lesions. Clin Cardiol. 2022;45(5):558-66.

111. Elbasha K, Alotaibi S, Heyer H, Mankerious N, Toelg R, Geist V, et al. Predictors of long-term adverse outcomes after successful chronic total occlusion intervention: physiology or morphology? Clin Res Cardiol. 2024;113(7):977-86.

112. Chen H, Hong L, Xi G, Wang H, Hu J, Liu Q, et al. Prognostic value of quantitative flow ratio in patients with coronary heart disease after percutaneous coronary intervention therapy: a meta-analysis. Front Cardiovasc Med. 2023;10:1164290.

113. Dai N, Yuan S, Dou K, Zhang R, Hu N, He J, et al. Prognostic Implications of Prestent Pullback Pressure Gradient and Poststent Quantitative Flow Ratio in Patients Undergoing Percutaneous Coronary Intervention. J Am Heart Assoc. 2022;11(11):e024903.

9. Bibliography of the Candidate's Publications

Original papers, which form the basis of my dissertation:

Csanadi B, Ferenci T, Fulop G, Piroth Z. Clinical Implications of Fractional Flow Reserve Measured Immediately After Percutaneous Coronary Intervention. Cardiovasc Drugs Ther. 2024;38(5):917-25. [IF 3.1]

Csanadi B, Ferenci T, Gal R, Bora N, Piroth Z. Correlation and Relative Prognostic Power of Post-Percutaneous Coronary Intervention Fractional Flow Reserve and Quantitative Flow Ratio. J Am Heart Assoc. 2025;14(8):e040969. [IF 5.3]

Other – Original papers and citable abstracts not utilized in my dissertation or not related to its subject matter:

Piroth Z, Fülöp G, **Csanádi B**, Fontos G, Andréka P, Nyolczas N, et al. A háromér-betegség kezelése a FAME-3 vizsgálat eredményeinek tükrében. Orvosi hetilap. 2022;163:1032-6. [IF 0.6]

Csanadi B, Fulop G, Szoke S, Szonyi T, Dekany G, Pinter T, et al. Correlation of FFR measured after DES implantation with clinical parameters and long-term clinical outcome. European Heart Journal. 2022;43(Supplement_2).

Fülöp G, **Csanádi B**, Fülöp D, Piróth Z. Többszörös coronarialaesiók és diffúz coronariabetegség funkcionális értékelése. Orvosi Hetilap. 2022;163(48):1902-8. [IF 0.6]

Piróth Z, **Csanádi B**, Bora N, Németh O, Gál R. Microvascularis coronariabetegség, vasospasticus angina. Orvosi Hetilap. 2024;165(41):1613-20. [IF 0.9]

Csanadi B, Ferenci T, Gal R, Bora N, Piroth Z. Comparative analysis of post-PCI fractional flow reserve and quantitative flow ratio in predicting long-term Target Vessel Failure and hard endpoints. European Heart Journal. 2024;45(Supplement_1).

Csanádi B, Ferenci T, Gál R, Piroth Z. TCT-219 Comparative Analysis of Post-PCI Fractional Flow Reserve and Quantitative Flow Ratio in Predicting Long-term Target Vessel Failure and Hard Endpoints. JACC. 2024;84(18_Supplement):B24-B5.

Gál R, **Csanádi B**, Ferenci T, Bora N, Piróth Z. Real-World Comparison of FFR and QFR: New Perspectives on the Functional Assessment of Coronary Stenoses. Journal of Clinical Medicine. 2025; 14(17):5946. [IF 2.9]

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