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Physiological Phenotyping of Intermediate Coronary Lesions with RFR Pullback and Hydrostatic Pressure Correction Results From the READY Registry

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	Objectives The READY registry assessed how invasive coronary physiology, including distal resting full-cycle ratio (RFR), the pullback-derived local RFR drop (ΔRFR) and hydrostatic pressure correction, modifies the angiographic classification of intermediate lesions. Methods In this prospective multicenter registry, 144 intermediate lesions in 114 patients were assessed and classified as non-significant, focal, diffuse or mixed using distal RFR, ΔRFR and fractional flow reserve (FFR). Mixed disease was further characterized by a novel RFR-based pullback pressure gradient index (RFR-PPGi). Pressure-predicted microvascular resistance reserve (MRRp) was assessed as a marker of microvascular function. Physiological measurements were additionally evaluated after hydrostatic pressure correction. Results Visual angiographic assessment classified lesions as focal (47.9%), diffuse (24.3%), non-significant (16.7%), and mixed (11.1%). Integrated pressure-wire assessment changed the phenotype of 65.3% of lesions compared with angiography. Hydrostatic pressure correction reclassified a further 25.0% of lesions, predominantly in the left anterior descending artery (LAD) (36.2% vs 4.0% in other vessels; p<0.001). Microvascular dysfunction (MRRp <2.50) was identified in 47.8% of evaluable lesions. Conclusions Angiographic assessment frequently differs from the physiological pattern of disease. Integrating distal RFR, ΔRFR and hydrostatic correction substantially modifies lesion phenotyping and identifies focal, diffuse, and mixed patterns not reliably characterized by angiography alone. These findings support an integrated physiological approach to coronary lesion characterization.
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Physiological Phenotyping of Intermediate Coronary Lesions with RFR Pullback and Hydrostatic Pressure Correction: Results From the READY Registry

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Abstract

Background: Angiographic assessment of intermediate coronary lesions provides limited information on their functional significance and disease pattern. Integrated pressure-wire assessment may allow more precise characterization of focal, diffuse, and mixed coronary disease.

Objectives: The READY registry assessed how invasive coronary physiology, including distal resting full-cycle ratio (RFR), the pullback-derived local RFR drop (ΔRFR) and hydrostatic pressure correction, modifies the angiographic classification of intermediate lesions.

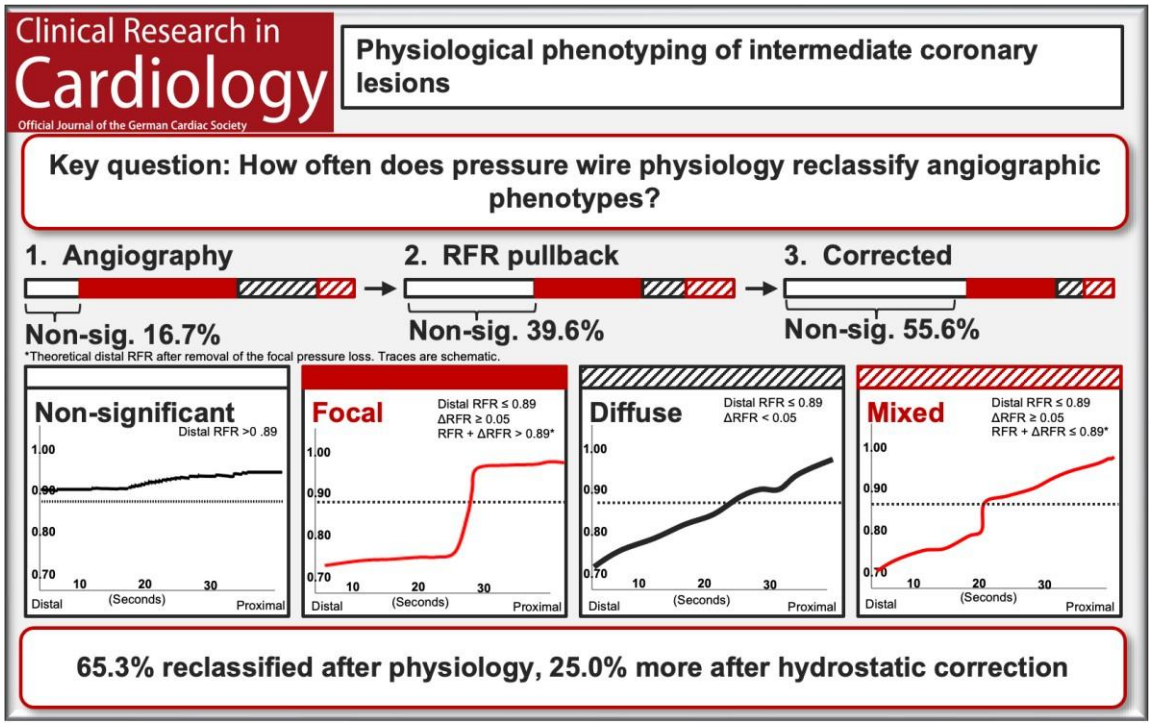
Methods: In this prospective multicenter registry, 144 intermediate lesions in 114 patients were assessed and classified as non-significant, focal, diffuse or mixed using distal RFR, ΔRFR and fractional flow reserve (FFR). Mixed disease was further characterized by a novel RFR-based pullback pressure gradient index (RFR-PPGi). Pressure-predicted microvascular resistance reserve (MRRp) was assessed as a marker of microvascular function. Physiological measurements were additionally evaluated after hydrostatic pressure correction.

Results: Visual angiographic assessment classified lesions as focal (47.9%), diffuse (24.3%), non-significant (16.7%), and mixed (11.1%). Integrated pressure-wire assessment changed the phenotype of 65.3% of lesions compared with angiography. Hydrostatic pressure correction reclassified a further 25.0% of lesions, predominantly in the left anterior descending artery (LAD) (36.2% vs 4.0% in other vessels; p<0.001). Microvascular dysfunction (MRRp <2.50) was identified in 47.8% of evaluable lesions.

Conclusions: Angiographic assessment frequently differs from the physiological pattern of disease. Integrating distal RFR, ΔRFR and hydrostatic correction substantially modifies lesion phenotyping and identifies focal, diffuse, and mixed patterns not reliably characterized by angiography alone. These findings support an integrated physiological approach to coronary lesion characterization.

Trial registration: ClinicalTrials.gov NCT04857762, registered 23 April 2021

Graphic Abstract



Keywords: coronary physiology, resting full-cycle ratio (RFR), fractional flow reserve (FFR), microvascular resistance reserve (MRR), hydrostatic pressure correction, lesion phenotyping

Abbreviations

- ΔRFR: Maximum pullback-derived RFR drop within a predefined 25-mm segment
- AUC: Area under the curve
- CABG: Coronary artery bypass grafting
- CCS: Chronic coronary syndrome
- CFR: Coronary flow reserve
- CFRpb: Pressure-bounded coronary flow reserve
- CT-FFR: Coronary computed tomography angiography-derived fractional flow reserve
- FFR: Fractional flow reserve
- iFR: Instantaneous wave-free ratio
- IQR: Interquartile range
- LAD: Left anterior descending artery
- LCx: Left circumflex artery
- MACE: Major adverse cardiovascular events
- MRR: Microvascular resistance reserve
- MRRp: Pressure-predicted microvascular resistance reserve
- MRRpb: Pressure-bounded microvascular resistance reserve
- OMT: Optimal medical therapy
- Pa: Aortic pressure
- PCI: Percutaneous coronary intervention
- Pd: Distal coronary pressure
- PPG: Pullback pressure gradient
- PPGi: Pullback pressure gradient index
- QCA: Quantitative coronary angiography
- RCA: Right coronary artery
- RFR: Resting full-cycle ratio
- RFR-PPGi: RFR-based pullback pressure gradient index
- ROC: Receiver operating characteristic
- SD: Standard deviation

1 Introduction

1.1 From anatomical stenosis to physiological lesion phenotyping

Coronary angiography provides detailed anatomical visualization of the coronary tree; however, the clinical significance of an intermediate stenosis resides in its functional capacity to limit coronary flow and induce ischemia. It is well established that the anatomical and physiological severity of coronary lesions correlate poorly, frequently leading to diagnostic ambiguity in clinical practice [1–3].

Fractional flow reserve (FFR), defined as the ratio of distal coronary pressure (Pd) to aortic pressure (Pa) during maximal hyperemia, has been established as a reference standard for invasive assessment of lesion-specific coronary physiology. An FFR ≤0.80 is widely used to define hemodynamically significant epicardial coronary disease and to guide revascularization decisions [4, 5]. Resting pressure indices, including instantaneous wave-free ratio (iFR) and the resting full-cycle ratio (RFR), subsequently provided hyperemia-free alternatives for physiological lesion assessment [6, 7].

Relying solely on single distal pressure values provides a binary assessment of ischemia but fails to characterize spatial disease distribution. Noninvasive longitudinal pressure mapping by coronary computed tomography angiography-derived fractional flow reserve (CT-FFR) suggested that local pressure changes along epicardial vessels may be as prognostically significant as the distal pressure value itself [8]. Invasive pressure-wire studies have similarly demonstrated that accurate differentiation between focal and diffuse coronary disease requires combining distal pressure measurements with continuous pullback data [9–11].

The pullback pressure gradient (PPG) index was developed to quantify the relative contribution of focal and diffuse pressure loss along the coronary vessel, with values approaching 1 indicating predominantly focal disease and lower values indicating a more diffuse pattern [10–17].

1.2 Study objectives

The READY registry was designed to prospectively compare angiographic assessment with invasive physiological characterization of intermediate coronary lesions [18]. We sought to determine the extent to which integration of distal RFR and pullback-derived ΔRFR (the maximum RFR drop within a predefined 25-mm segment) modifies the classification of coronary disease into non-significant, focal, diffuse, and mixed phenotypes.

Furthermore, we sought to explore the prognostic value of local pressure loss (ΔRFR) in FFR-negative lesions, hypothesizing that steep focal pressure drops might identify vulnerable physiology. Finally, we investigated the effect of individualized hydrostatic pressure correction on physiological measurements and lesion classification.

Secondary objectives included 1-year major adverse cardiovascular events (MACE), defined as a composite of all-cause mortality, myocardial infarction, and target-vessel repeat revascularization, and characterization of microvascular function using pressure-derived indices.

2 Methods

2.1 Study design and patient population

The "Anatomical Assessment vs. Pullback **RE**sting full-cycle r**A**tio (RFR) Measurement for Evaluation of Focal and **D**iffuse Coronar**Y** Disease" (READY) registry was an investigator-initiated, prospective, multicenter, observational study (ClinicalTrials.gov identifier: NCT04857762) [18]. Patients undergoing clinically indicated invasive physiological assessment of an intermediate coronary stenosis (40%–90% diameter stenosis by visual estimation) in a major epicardial coronary artery were eligible for inclusion. The study protocol was approved by the Hungarian National Institute of Pharmacy and Nutrition (OGYÉI/9093-8/2021).

2.2 Inclusion criteria

All patients provided written informed consent for registration and analysis of their clinical and physiological data. Patients with chronic coronary syndrome (CCS), a clinical indication for intracoronary physiological assessment, and an intermediate stenosis in a major epicardial coronary artery were eligible. Pressure quality criteria included absence of catheter damping, signal artifact and stable resting and hyperemic pressure recordings. Only traces with pressure drift of <2 mmHg after pullback of the sensor to the guide catheter tip were included in the analysis.

2.3 Exclusion criteria

In accordance with the prespecified study protocol, exclusion criteria were acute coronary syndrome, left main coronary artery disease, contraindication to adenosine administration, previous coronary artery bypass grafting (CABG) involving the investigated vessel, severe renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 m^2), and a life expectancy <12 months because of severe noncardiac comorbidities.

2.4 Angiographic assessment and invasive physiological measurements

Coronary angiography was performed according to standard clinical practice. Before physiological assessment, the operator visually estimated the percentage diameter stenosis of the target lesion and categorized the angiographic disease pattern as non-significant, focal, diffuse or mixed.

Angiographic findings were additionally entered into the modified SYNTAX framework using the dedicated online CORONART platform (https://coronart.hu), which incorporates myocardial territory assignment using a polar map.

The protocol of the intracoronary measurements and a representative pullback recording (Online Resource 1, Fig. S1) are detailed in Online Resource 1.

Fig. 1 shows the study flowchart of the READY registry.

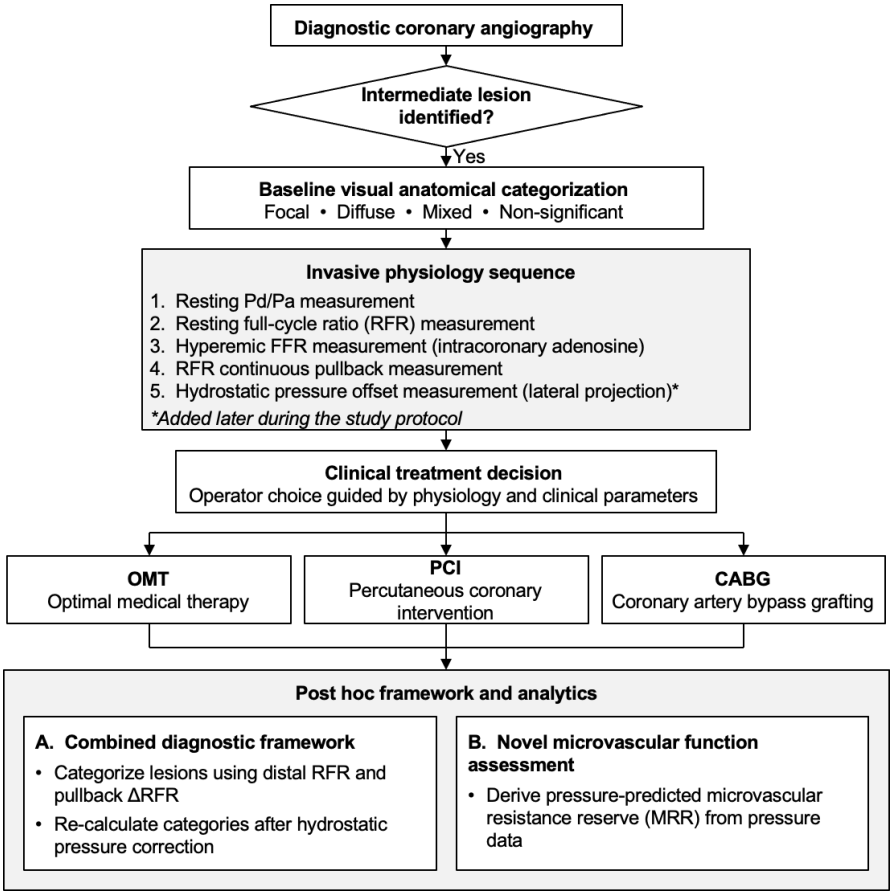


Fig. 1 READY registry procedural sequence and analytical framework. Study flowchart showing the procedural sequence, initial treatment decision-making and post hoc analytical framework, from baseline visual anatomical categorization to

comprehensive invasive physiological assessment incorporating resting, hyperemic and continuous pullback indices with hydrostatic pressure offset measurement. CABG, coronary artery bypass grafting; FFR, fractional flow reserve; MRR, microvascular resistance reserve; OMT, optimal medical therapy; Pa, aortic pressure; PCI, percutaneous coronary intervention; Pd, distal coronary pressure; RFR, resting full-cycle ratio; ΔRFR, pullback-derived RFR drop

2.5 Hydrostatic pressure correction

The hydrostatic pressure correction was performed by determining the vertical height difference between the coronary artery ostium (level of the guiding catheter tip, Pa measurement) and the pressure sensor position (Pd measurement). The vertical height difference in centimeters was measured directly from the lateral angiographic projection, providing an individualized correction factor for each vessel and sensor position. A vertical height difference of 1 cm was considered to correspond to a correction of 0.77 mmHg in the distal pressure [19].

2.6 Physiological lesion phenotyping

Lesion phenotype was determined using distal RFR and pullback-derived ΔRFR. FFR was measured in all lesions but was not used as the primary parameter for spatial lesion classification because conventional FFR provides a distal, binary assessment of physiological significance without defining the longitudinal distribution of pressure loss.

Lesions were categorized into four physiological phenotypes:

Non-significant: distal RFR >0.89.

Diffuse: distal RFR ≤0.89 and maximum ΔRFR <0.05 over the predefined 25-mm lesion segment.

Focal: distal RFR ≤0.89 and ΔRFR ≥0.05, with a theoretical distal RFR >0.89 after removal of the pressure loss represented by ΔRFR. This phenotype was considered consistent with predominantly focal epicardial disease amenable to percutaneous coronary intervention (PCI).

Mixed: distal RFR ≤0.89 and ΔRFR ≥0.05, but the theoretical distal RFR remained ≤0.89 after removal of the pressure loss represented by ΔRFR, indicating coexisting focal and diffuse physiological disease.

2.7 RFR-based pullback pressure gradient index (RFR-PPGi)

In the mixed phenotype, to further characterize the relative contribution of focal and diffuse physiological disease, we developed the RFR-based pullback pressure gradient index (RFR-PPGi). The RFR-PPGi quantifies the proportion of the total vessel pressure loss attributable to the most pronounced local pressure gradient within a predefined 25-mm segment.

The RFR-PPGi was calculated as:

$$\text{RFR} - \text{PPGi} = \frac{\Delta\text{RFR}}{1 - \text{distal RFR}}$$

where ΔRFR represents the maximum RFR pressure drop within the predefined 25-mm segment and (1 − distal RFR) represents the total resting pressure loss across the interrogated coronary vessel. An RFR-PPGi cutoff of 0.50 was used to distinguish predominantly focal from predominantly diffuse physiological disease. An RFR-PPGi ≥0.50 indicates that more than one-half of the total vessel pressure loss is attributable to the most pronounced 25-mm segment, whereas an RFR-PPGi ≤0.50 indicates a predominantly diffuse distribution of pressure loss. *Thus, targeting this predominant focal gradient with*

PCI is hypothesized to achieve significant functional improvement with comfortable stent length, but according to our definition of the conceptual RFR, the resulting poststent RFR will still below the 0,89 cutoff. A lower initial distal RFR, in adjunction with the RFR-PPGi, will determine the magnitude of the difference of distal RFR and the cut off value.

On the other hand, in a predominantly diffuse disease profile, stenting will likely result in less improvement of the distal RFR, therefore, a higher magnitude of the difference between distal RFR and the cut off. The clinical improvement may also not be substantial.

Fig. 2 illustrates the integrated physiological classification algorithm used in the READY registry.

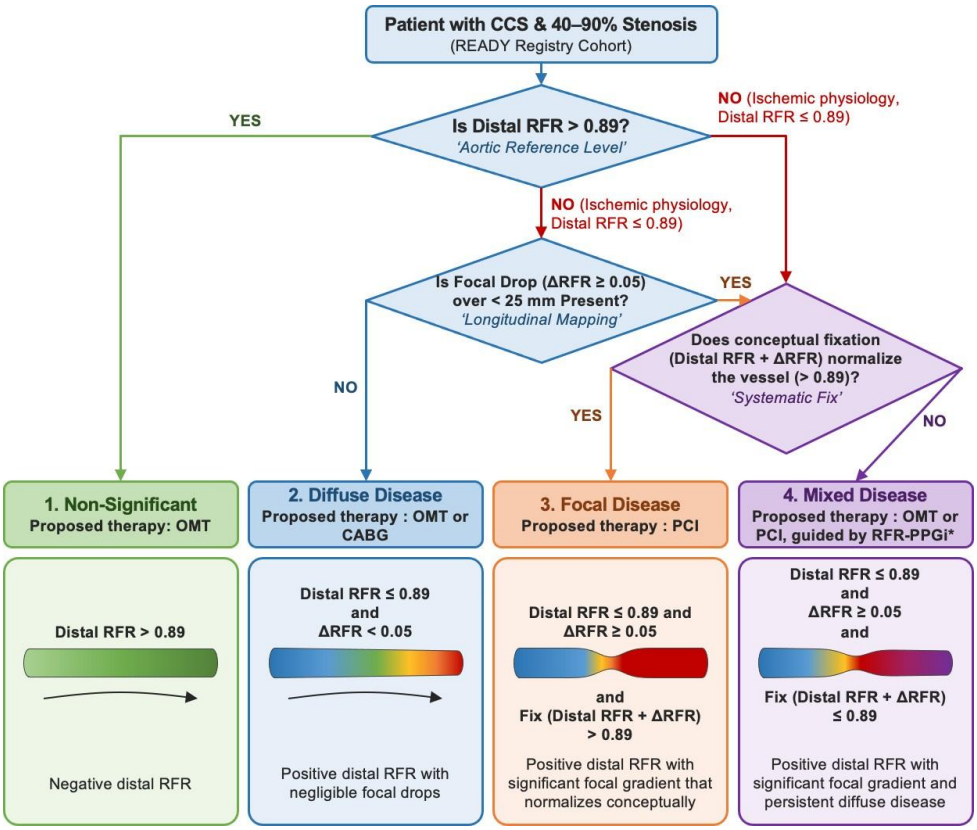


Fig. 2 Combined physiological classification algorithm of coronary lesions. Distal RFR and pullback-derived local ΔRFR are used to classify intermediate stenoses into four hemodynamic phenotypes (non-significant, diffuse, focal and mixed), with the proposed management for each phenotype; in mixed disease, the RFR-based pullback pressure gradient index (RFR-PPGi) guides the decision. CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; RFR, resting full-cycle ratio; RFR-PPGi, RFR-based pullback pressure gradient index

2.8 Microvascular function analysis

Microvascular function was assessed using intracoronary pressure-derived indices according to our previously published methodology [20, 21].

2.8.1 Pressure-bounded coronary flow reserve (CFRpb) and microvascular resistance reserve (MRRpb)

Coronary flow reserve (CFR) is an established index of the vasodilatory capacity of the coronary circulation. In the absence of obstructive epicardial coronary disease, a CFR <2 is generally considered to be indicative of impaired coronary microvascular function. Zimmermann et al. introduced the concept of pressure-bounded CFR (CFRpb), which allows estimation of CFR from intracoronary pressure measurements without direct flow measurement [22].

To further characterize microvascular function, microvascular resistance reserve (MRR) was estimated from the pressure-bounded CFR measurements. We focused on the maximal pressure-bounded MRR (MRRpbmax), consistent with the parameter used in our previous study to develop a model predicting Doppler-derived MRR from pressure measurements, the pressure-predicted MRR (MRRp) [21]; the calculations are given in Online Resource 1. For the present analysis, MRRp values outside the prespecified physiologically plausible range of 1.0 to 8.0 were excluded as outliers likely due to measurement artifacts. Microvascular dysfunction was defined as MRRp <2.50, adopting the prespecified cutoff used in the recent prognostic evaluation by Nishi et al. [23].

2.9 Statistical analysis

Statistical analyses were performed using MedCalc Statistical Software, version 14.8.1 (MedCalc Software, Ostend, Belgium). Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), and categorical variables as counts and percentages. Categorical differences, including physiological phenotypes, reclassification rates, and coronary territory proportions (left anterior descending artery [LAD], left circumflex artery [LCx] and right coronary artery [RCA]), were assessed using the Pearson chi-square or Fisher exact test.

Microvascular dysfunction (MRRp <2.50) prevalence was assessed via the Fisher exact test. MRRp values were compared between RFR/FFR concordance groups using Welch's t-test. Associations between the RFR–FFR difference and MRRp were evaluated by Spearman rank correlation and, additionally, by Pearson correlation, and diagnostic performance by receiver operating characteristic (ROC) curve analysis using the Youden index.

RFR (≤0.89) and FFR (≤0.80) concordance/discordance, changes after hydrostatic pressure correction, and reclassification differences between LAD and non-LAD vessels were analyzed using contingency tables and paired categorical-data analyses.

Event-free survival in patients with and without significant focal disease (ΔRFR ≥0.05 over 25 mm) and 12-month MACE rates in prespecified discordant subgroups were compared.

All statistical tests were 2-sided; $p<0.05$ was considered statistically significant.

3 Results

The study population comprised 114 patients from 3 participating centers, with 144 coronary lesions evaluated. Baseline patient characteristics and laboratory findings at the index evaluation are presented in Online Resource 1 (Table S1).

3.1 Visual angiographic assessment

On initial visual angiographic assessment, lesions were classified as focal in 47.9% (69/144), diffuse in 24.3% (35/144), non-significant in 16.7% (24/144), and mixed in 11.1% (16/144). Based on the initial angiographic assessment, the intended management strategy was PCI in 55.6% of lesions (80/144), OMT in 42.4% (61/144), and CABG in 2.1% (3/144). CABG

was recommended in cases of multivessel disease.

The mean visually estimated diameter stenosis across all evaluated lesions was 53.5 ± 8.4%.

3.2 Physiological assessment

At rest, mean Pd/Pa was 0.91 ± 0.06, distal RFR was 0.86 ± 0.09, and ΔRFR was 0.07 ± 0.07. During hyperemia, mean FFR was 0.81 ± 0.09.

Using the conventional threshold of distal RFR ≤0.89, 87 lesions (60.4%) were classified as physiologically significant. Applying combined physiological criteria incorporating distal RFR and pullback-derived ΔRFR yielded the following physiological phenotypes: non-significant in 57 lesions (39.6%), focal in 47 (32.6%), mixed in 21 (14.6%), and diffuse in 19 (13.2%). The proportion of lesions classified as non-significant increased from 16.7% by visual assessment to 39.6% after physiological phenotyping.

3.3 Impact of hydrostatic correction on lesion characterization

Mean vertical distance between the aortic pressure reference level and the distal pressure sensor was −5.08 ± 1.21 cm for LAD lesions, 2.81 ± 0.95 cm for LCx lesions, and 1.48 ± 1.70 cm for RCA lesions. After hydrostatic pressure correction, based on a pressure difference of 0.77 mmHg per centimeter of vertical separation, mean FFR increased to 0.83 ± 0.09 and mean RFR to 0.88 ± 0.09. Hydrostatic correction significantly changed both RFR and FFR measurements ($p<0.001$ for both) and changed FFR classification according to the threshold of ≤0.80 in 13.9% of lesions and distal RFR classification according to the threshold of ≤0.89 in 19.4%. When the combined physiological phenotype was considered according to distal RFR and pullback-derived ΔRFR, hydrostatic correction resulted in reclassification of 36 of 144 lesions (25.0%) compared with the uncorrected physiological assessment.

3.4 Reclassification of lesion phenotypes across diagnostic modalities

Fig. 3 illustrates changes in lesion classification between visual angiographic assessment and physiological phenotyping, as well as changes following hydrostatic pressure correction.

There was substantial discordance between angiographic classification and combined physiological phenotyping. Visual assessment classified 24 lesions as non-significant, 69 as focal, 35 as diffuse, and 16 as mixed, whereas combined physiological assessment classified 57 as non-significant, 47 as focal, 19 as diffuse, and 21 as mixed. Overall, the physiological phenotype differed from the initial visual classification in 94 of 144 lesions (65.3%). Reclassification was most frequent among lesions initially classified as diffuse by visual assessment, of which 80% were assigned to a different physiological phenotype. Among lesions classified visually as focal, 30 were classified as physiologically non-significant; corresponding numbers were 11 among visually diffuse lesions and 4 among visually mixed lesions.

The proportion of non-significant lesions increased progressively across the assessment modalities, from 16.7% by visual assessment to 39.6% after uncorrected physiological assessment and 55.6% after hydrostatic pressure correction. Conversely, the proportion of focal lesions decreased from 47.9% to 32.6% and subsequently to 27.1%. The proportion of diffuse lesions decreased from 24.3% by visual assessment to 13.2% with uncorrected physiology and 8.3% after hydrostatic correction. The mixed phenotype increased from 11.1% by visual assessment to 14.6% with uncorrected physiology and subsequently decreased to 9.0% after hydrostatic correction. The impact of hydrostatic correction differed according to coronary territory.

Reclassification occurred in 36.2% of LAD lesions compared with 4.0% of non-LAD lesions (p<0.001).

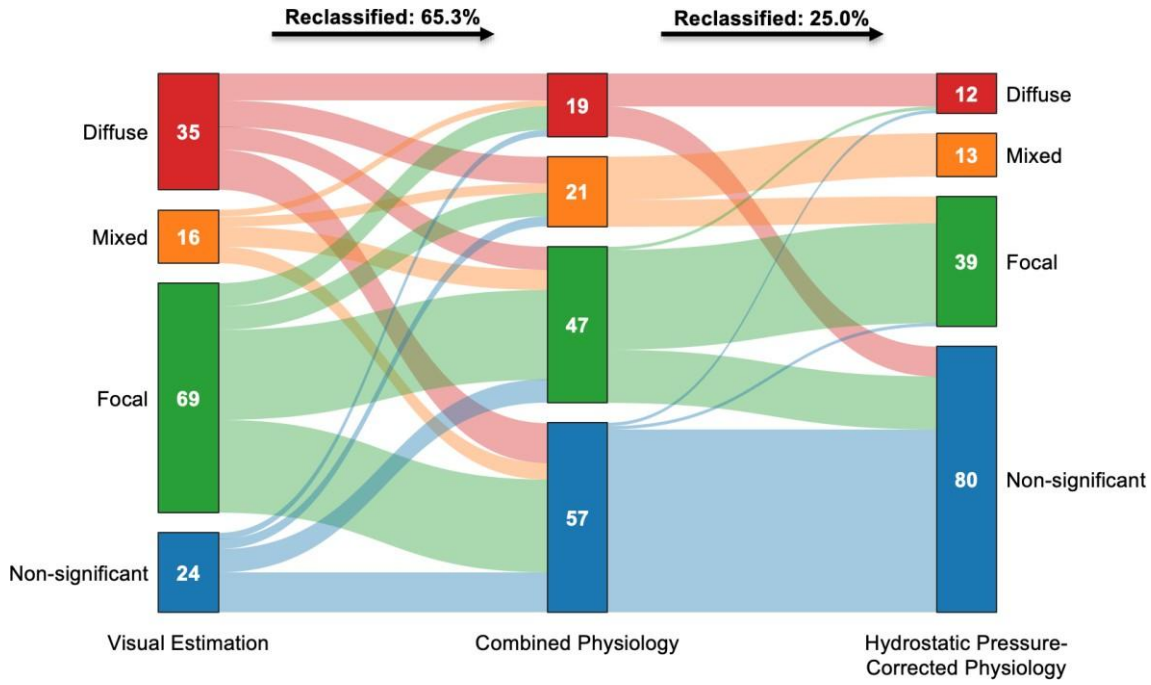


Fig. 3 Stepwise reclassification of coronary lesion phenotypes. Sankey diagram showing proportional shifts in lesion categorization (non-significant, focal, mixed, diffuse) across three sequential steps: visual estimation, uncorrected combined physiology (distal RFR and pullback-derived ΔRFR) and hydrostatic pressure-corrected physiology. Numbers indicate the lesions in each category (n=144). Combined physiological assessment reclassified 65.3% of lesions relative to visual estimation, and hydrostatic pressure correction reclassified a further 25.0%. RFR, resting full-cycle ratio

3.5 RFR versus FFR concordance

Concordance between corrected distal FFR and corrected distal RFR was observed in 103 of 144 lesions (71.5%), whereas 41 lesions (28.5%) demonstrated discordant results. Among discordant lesions, the predominant pattern was positive RFR (≤0.89) despite negative FFR (>0.80), observed in 35 of 41 discordant lesions.

3.6 Microvascular function and its relation to RFR/FFR concordance

To further characterize the hemodynamic profile of the study population, microvascular function was assessed using the pressure-predicted MRR (MRRp). After exclusion of predefined outliers, MRRp measurements were available for 136 lesions. The mean MRRp was 2.70 ± 0.84. Using the prespecified threshold of MRRp <2.50, microvascular dysfunction was identified in 65 of 136 lesions (47.8%).

Mean MRRp was numerically lower in women than in men (2.20 ± 3.60 vs 2.77 ± 2.74; p=0.372). Mean FFR was numerically higher in women (0.82 ± 0.07 vs 0.80 ± 0.10; p=0.157). Distal RFR and ΔRFR were similar between women and men. Lesion-level physiological parameters according to sex are presented in Online Resource 1 (Table S2).

3.6.1 MRRp according to RFR/FFR concordance

MRRp values differed across RFR/FFR concordance patterns (Fig. 4).

The highest mean MRRp was observed in the FFR-positive/RFR-negative discordant group (2.99 ± 0.67), whereas the lowest mean MRRp was observed in the FFR-negative/RFR-positive discordant group (2.28 ± 0.78).

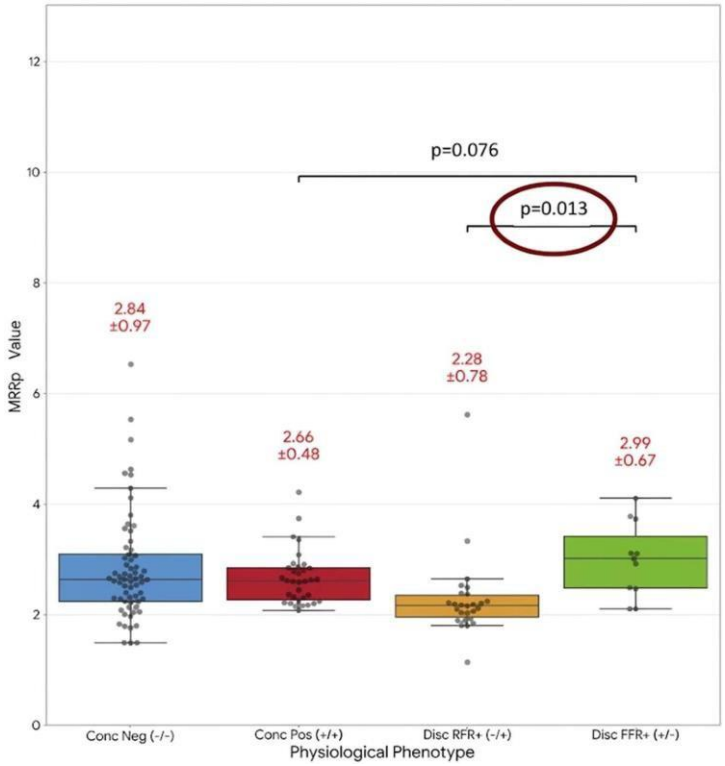


Fig. 4 Pressure-predicted microvascular resistance reserve (MRRp) according to RFR/FFR concordance. Box plots with individual lesion values; numbers above the boxes indicate mean ± SD. Signs in parentheses indicate FFR/RFR status (positive: FFR ≤0.80 and RFR ≤0.89, respectively). Discordant FFR-positive/RFR-negative lesions (isolated hyperemic ischemia) had the highest MRRp and discordant FFR-negative/RFR-positive lesions (isolated resting ischemia) the lowest; the difference between the two discordant groups was statistically significant (p=0.013, Welch's t-test), whereas the difference between the FFR-positive/RFR-negative and the concordant positive group was not (p=0.076). Conc, concordant; Disc, discordant; FFR, fractional flow reserve; Neg, negative; Pos, positive; RFR, resting full-cycle ratio

Welch's t-test showed that MRRp was significantly higher in the FFR-positive/RFR-negative group than in the FFR-negative/RFR-positive group (p=0.013). MRRp was also numerically higher in the FFR-positive/RFR-negative group than in the concordant-positive group, although this difference did not reach statistical significance (p=0.076).

3.6.2 Relationship between the RFR–FFR difference and MRRp

The mean difference between distal RFR and FFR was 0.055 ± 0.070. The RFR–FFR difference showed a positive association with MRRp (Spearman ρ=0.32; p=0.0002); Pearson correlation analysis yielded a correlation coefficient of r=0.26 (p=0.002).

ROC analysis was performed to assess the ability of the absolute RFR–FFR difference to identify preserved microvascular function, defined as MRRp ≥2.50. The area under the curve (AUC) was 0.673. An absolute RFR–FFR difference threshold of 0.02 yielded a sensitivity of 88.4% and a specificity of 40.0% for identifying preserved microvascular function (Online Resource 1, Fig. S2).

3.7 Follow-up outcomes

At 12 months, all-cause death had occurred in 4.4% of patients (5/114), myocardial infarction in 2.6% (3/114), and target-vessel PCI in 4.2% of lesions (6/144). Among lesions with negative FFR and positive ΔRFR, 12-month clinical event rates were low, with no statistically significant difference compared with the remaining study population. Clinical outcomes in this subgroup were also similar before and after application of hydrostatic pressure correction.

4 Discussion

4.1 Angiographic versus physiological assessment

Angiographic assessment remains the initial framework for evaluating coronary stenosis severity, although anatomical stenosis and physiological significance are imperfectly related. Early experimental work by Gould et al. established the concept that approximately 50% diameter reduction may represent a threshold for impaired hyperemic coronary flow [24]. Subsequent clinical studies demonstrated substantial discordance between angiographic severity and physiological significance, particularly among intermediate lesions [1, 25–27]. In the FAME study, for example, only approximately one-third of visually estimated 50%–70% stenoses were associated with an FFR ≤0.80 [1]. Quantitative coronary angiography (QCA) does not overcome this limitation, as anatomical measures remain an imperfect surrogate for lesion-specific physiology [25]. The introduction of resting physiological indices, including iFR and RFR, has provided additional approaches for lesion assessment without pharmacological hyperemia, with clinical outcome data supporting the use of resting pressure indices in appropriate patient populations, as shown in the DEFINE-FLAIR and iFR-SWEDEHEART trials [6, 28–30].

In the DEFINE REAL study, systematic physiological assessment in patients with multivessel coronary disease resulted in substantial reclassification of lesion significance (up to 67%) [31]. In our present study, integrated assessment incorporating distal RFR and pullback-derived ΔRFR changed the assigned physiological phenotype in 65.3% of intermediate lesions compared with visual angiographic assessment.

4.2 Phenotyping coronary lesions by focality versus diffuseness using RFR

Pressure-wire pullback provides a longitudinal assessment of pressure loss distribution along the coronary artery. The previously described pullback pressure gradient index (PPGi) transforms the spatial distribution of hyperemic pressure loss into a continuous metric from 0 to 1, with higher values indicating focal disease and lower values reflecting a diffuse pattern. Higher PPGi values are associated with greater post-PCI FFR improvement and favorable symptomatic responses, whereas lower values characterize diffuse disease where focal stenting is less likely to normalize vessel physiology [11–17]. Nevertheless, management strategies for intermediate PPGi values (the ‘gray zone’, typically 0.40–0.62) remain incompletely defined. Although PPGi was derived from hyperemic FFR, recent data suggest that resting PPG provides a reasonable approximation of hyperemic pressure-gradient distribution [32]. However, conventional PPGi summarizes relative pressure loss distribution without directly defining the precise location, physiological length, or magnitude of individual pressure gradients [33].

In the READY registry, we integrated distal RFR with pullback-derived ΔRFR to provide an adenosine-free framework for longitudinal physiological phenotyping. In line with the study design, a focal pressure drop was defined as ΔRFR ≥0.05 within

a 25-mm segment [18]. This corresponds to a pressure-gradient density of approximately 0.002 RFR units/mm, consistent with the gradient criterion used for iFR pullback in the DEFINE PCI study [9].

For mixed disease, we further explored an RFR-based PPGi (RFR-PPGi), calculated as the maximum ΔRFR within a predefined 25-mm segment divided by the total resting pressure loss across the interrogated vessel. Thus, the index estimates the proportion of total resting pressure loss attributable to the most pronounced local pressure gradient within the predefined segment. An RFR-PPGi of 0.50 indicates that approximately one-half of the total resting pressure loss is concentrated within that segment. In the present study, an RFR-PPGi threshold of 0.50 was used to distinguish predominantly focal from predominantly diffuse physiological disease. This threshold may be regarded as a physiological phenotyping criterion. Whether RFR-PPGi can prospectively identify patients who derive greater benefit from focal PCI, versus alternative management strategies, requires dedicated outcome-based validation.

Fig. 5 is a good example to show the increase in delta RFR in the stented section (only about 25mm) but the overall post-stent RFR still remains significant. For focal pressure drops, the conceptual post stent RFR can be normalized, however, for a mixed disease, the post stent distal RFR will theoretically remain below 0.89 even though an improvement may be possible due to the normalization of the focal pressure drop component in the vessel. Calculating the RFR-PPGi value can be a good guide in evaluating focal or diffuse disease.

$$\text{RFR-PPGi} = \frac{\Delta\text{RFR}}{1 - \text{distal RFR}} =$$

$$= \frac{0.07}{1 - 0.80} = 0.35$$

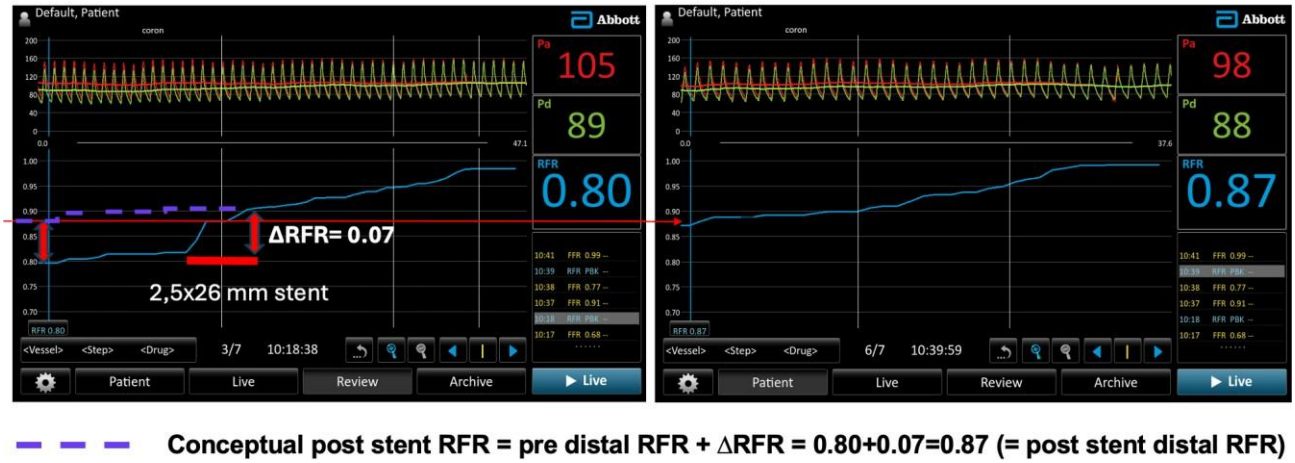


Fig. 5. Pressure traces displaying predominantly diffuse disease according to the PPGi in the mixed phenotype in the pre-stent and post-stent period. In the pre-stent (left) image, the purple dashed lines and the red arrows help visualize the ΔRFR of 0.07, indicating a focal pressure drop. Over this segment a 2,5 x 26mm stent was placed. The post stent image (right) shows a corresponding improvement in the distal RFR by 0.07 to a final value of 0.87. Predictably, this value remains ≤0.89 corresponding to the calculated PPGi value of 0.35. PCI; percutaneous coronary intervention, RFR; resting full-cycle ratio, RFR-PPGi; RFR pullback pressure gradient index, ΔRFR; change in RFR across the focal segment.

An important potential advantage of resting pullback is the absence of pharmacologically induced hyperemia and the resulting simplification of longitudinal physiological assessment. Furthermore, because resting volumetric flow practically does not change after stenting, serial disease and interactions between stenoses may have less influence on the prediction of post-intervention physiology than with hyperemic pullback [7, 32, 33].

4.3 Hydrostatic pressure error: a potentially relevant source of systematic bias

Our findings indicate that hydrostatic pressure differences between the coronary ostium and distal sensor materially influence physiological lesion classification. Across 144 lesions, hydrostatic correction resulted in reclassification in 25.0% of cases, with a substantially greater effect in the LAD than in non-LAD vessels (36.2% vs 4.0%). This territory-specific effect reflects differences in the distal sensor's vertical position relative to the reference pressure level. Importantly, correction altered both FFR- and RFR-based classification, particularly in the LAD. Therefore, hydrostatic pressure differences should be considered when interpreting distal measurements, particularly near established physiological thresholds, although the consequences of routine correction and its impact on clinical outcomes require prospective evaluation.

4.4 Microvascular function: prevalence and phenotypic association

In our cohort, pressure-derived assessment identified impaired microvascular function (MRRp <2.50) in 47.8% of evaluable lesions, emphasizing that physiological abnormalities in intermediate lesions are not confined to the epicardial circulation. MRRp also differed across RFR/FFR discordance patterns, with the highest mean MRRp in the FFR-positive/RFR-negative phenotype and the lowest in the FFR-negative/RFR-positive phenotype.

Our findings support an integrated approach to coronary physiology extending beyond a binary determination of epicardial ischemia. A standard pressure-wire platform can provide distal resting and hyperemic physiology, longitudinal pressure loss, and pressure-derived microvascular function within a single invasive assessment. Whether this integrated characterization improves clinical decision-making or patient outcomes requires prospective validation.

5 Limitations

Several limitations should be acknowledged.

First, the moderate sample size (114 patients, 144 lesions) limited statistical power. For clinical outcomes in the FFR-negative/ΔRFR-positive subgroup, the sample size did not reach the number required by the power calculation of the study design [18].

Second, pressure-derived MRRp relies on a previously validated model [21] and remains sensitive to pressure measurement errors and hydrostatic correction. Eight cases (5.6%) were excluded due to nonphysiological or non-interpretable MRRp values. Six yielded negative values, likely reflecting combined pressure drift and hydrostatic correction uncertainty where corrected distal pressure exceeded baseline aortic pressure. Conversely, two cases demonstrated MRRp values >8.0, potentially reflecting an unusually large hyperemic response or an obvious error in the exact determination of the resting pressure gradient.

Third, the RFR-PPGi threshold of 0.50 represents a novel, physiologically derived criterion for distinguishing predominantly

focal from diffuse pressure loss in mixed lesions. Although conceptually based on the proportion of total vessel pressure loss attributable to the most pronounced 25-mm segment, it was not prospectively validated against an independent cohort or clinical outcomes. Accordingly, this threshold should be regarded as hypothesis-generating rather than a validated treatment threshold.

Fourth, because the study was observational, the integrated physiological classification was not prospectively used to assign treatment. Therefore, observed changes in lesion phenotype cannot be interpreted as evidence that this physiology-guided framework improves clinical outcomes. Treatment decisions remained at the treating physicians' discretion, incorporating the overall clinical and anatomical context.

Finally, follow-up was limited to 12 months. Moreover, the study did not reach the prespecified sample size of 425, further limiting statistical power for clinical outcome analyses [18]. Consequently, the absence of statistically significant differences in MACE should not be interpreted as evidence of equivalence or the absence of clinically meaningful differences between physiological phenotypes.

6 Clinical implications and future directions

The READY registry provides an integrated approach to coronary physiological phenotyping that extends beyond conventional single-point pressure measurement.

The combination of distal RFR and pullback-derived ΔRFR provides a longitudinal physiological assessment that can distinguish non-significant, focal, mixed, and diffuse patterns of disease. The RFR-PPGi further quantifies the relative contribution of the most pronounced local pressure gradient to total vessel pressure loss. Whether these physiological phenotypes can improve selection among PCI, CABG, and medical therapy remains to be determined in prospective studies and should not be inferred from the present observational data.

Hydrostatic pressure differences physically influence intracoronary physiological measurements and should be considered when interpreting pressure-derived indices, particularly in LAD lesions, in which the sensor–ostium height difference may be substantial. Incorporating hydrostatic correction into analysis systems, either by post-processing of the distal pressure or by simultaneously setting the level of the aortic pressure transducer to the position of the intracoronary pressure sensor, may facilitate more precise application.

Pressure-wire assessment may provide complementary information regarding the coronary microcirculation in addition to epicardial physiology. The observed prevalence of impaired MRRp and the association between MRRp and RFR–FFR discordance suggest that combined resting and hyperemic pressure measurements may capture distinct components of coronary pathophysiology.

Large-scale studies to determine whether ΔRFR-based physiological phenotypes are associated with subsequent clinical outcomes are warranted. Validation of the RFR-PPGi and its 0.50 threshold is required, including assessment of its reproducibility and its relationship to post-PCI physiological improvement and patient-centered outcomes.

7 Conclusions

In patients undergoing evaluation of intermediate coronary lesions, comprehensive invasive physiological assessment

substantially changed lesion phenotyping compared with angiographic assessment alone. Hydrostatic pressure correction further influenced physiological classification, particularly in the LAD. Pressure-derived microvascular assessment identified impaired microvascular function in a substantial proportion of evaluable lesions. These findings support an integrated pressure-wire approach incorporating resting and hyperemic measurements, longitudinal pressure gradients, and appropriate hydrostatic correction to provide comprehensive information on epicardial and microvascular coronary physiology. Prospective studies are required to determine whether this approach improves revascularization decision-making and clinical outcomes.

Statements and Declarations

Artificial Intelligence was used to improve stylistic choices and improve coherence.

Funding

Premier G Med Cardio Ltd supported the study financially.

Competing interests

The authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval

This study was performed in line with the principles of the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the Hungarian National Institute of Pharmacy and Nutrition (OGYÉI/9093-8/2021), and the study was registered on ClinicalTrials.gov (NCT04857762). The study was conducted in accordance with applicable local legislation and institutional requirements.

Consent to participate

All participants provided written informed consent for participation and for the collection and analysis of their clinical and physiological data.

Consent to publish

Not applicable. The manuscript contains no information or images that could identify individual participants.

Data availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

ÁA: Formal analysis, Writing – original draft, Data curation, Writing – review & editing, Visualization, Validation, Investigation. ÁP: Writing – original draft, Formal analysis, Visualization, Software, Methodology. JA: Data curation,

Writing – original draft. ÁÜ: Writing – original draft, Validation, Data curation. BAP: Project administration, Writing – original draft. Formal analysis, Visualization, Data curation. BT: Supervision, Writing – review & editing. ZT: Supervision, Writing – review & editing. MK: Writing – original draft, Conceptualization, Supervision. GTS: Supervision, Writing – original draft. GTS: Writing – review & editing, Supervision. TS: Writing – review & editing, Supervision. JB: Writing – review & editing, Supervision. DC: Writing – review & editing, Supervision. CAD: Writing – review & editing, Supervision. ZR: Writing – review & editing, Supervision. ZK: Conceptualization, Investigation, Writing – review & editing, Formal analysis, Validation, Writing – original draft, Methodology, Project administration, Supervision, Data curation.

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Figure 1

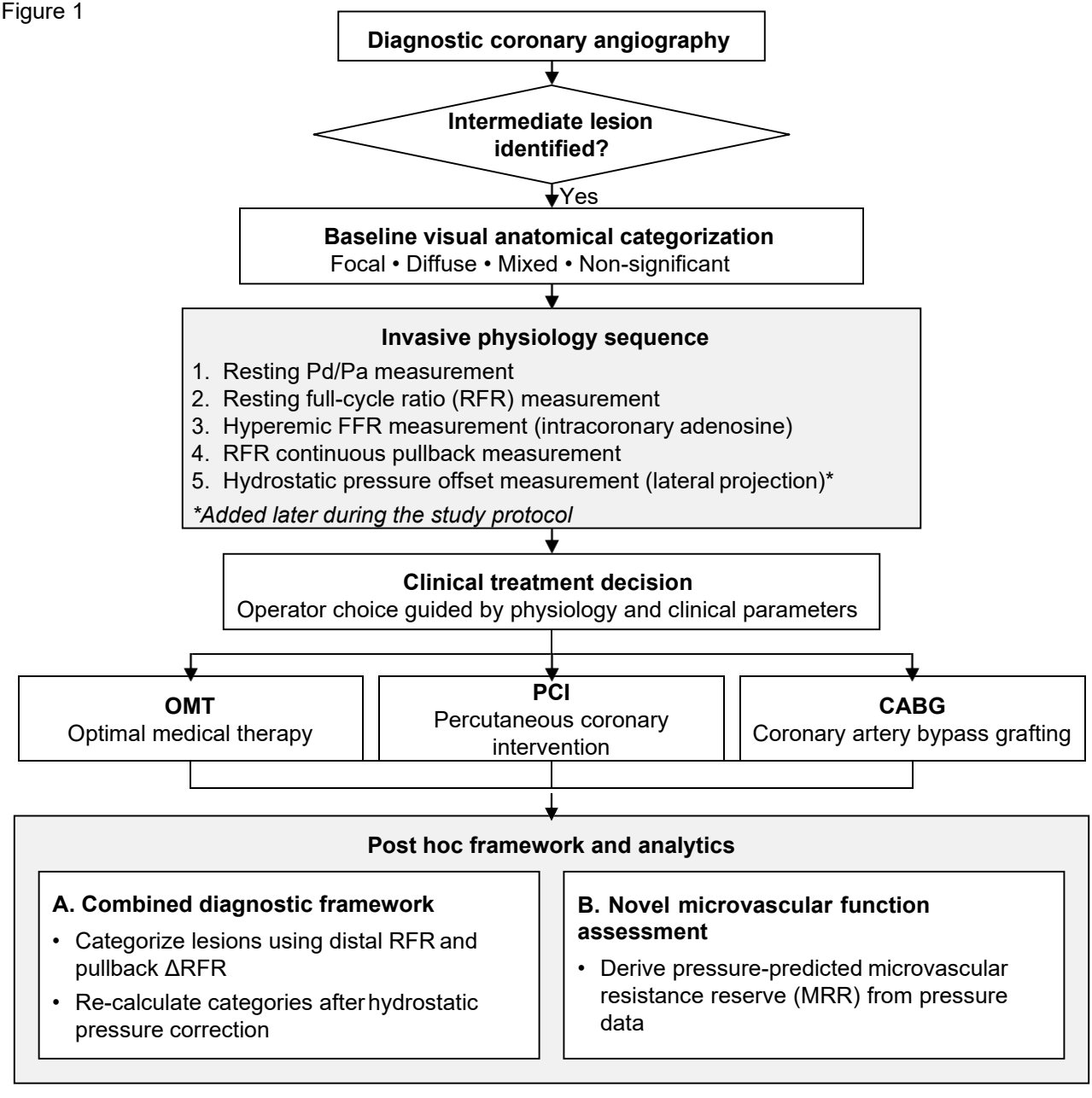

Diagnostic coronary angiography
Intermediate lesion identified?
Yes
Baseline visual anatomical categorization
Focal • Diffuse • Mixed • Non-significant
Invasive physiology sequence
1. Resting Pd/Pa measurement
2. Resting full-cycle ratio (RFR) measurement
3. Hyperemic FFR measurement (intracoronary adenosine)
4. RFR continuous pullback measurement
5. Hydrostatic pressure offset measurement (lateral projection)*
*Added later during the study protocol
Clinical treatment decision
Operator choice guided by physiology and clinical parameters
OMT
Optimal medical therapy
PCI
Percutaneous coronary intervention
CABG
Coronary artery bypass grafting
Post hoc framework and analytics
A. Combined diagnostic framework
• Categorize lesions using distal RFR and pullback ΔRFR
• Re-calculate categories after hydrostatic pressure correction
B. Novel microvascular function assessment
• Derive pressure-predicted microvascular resistance reserve (MRR) from pressure data

Figure 2

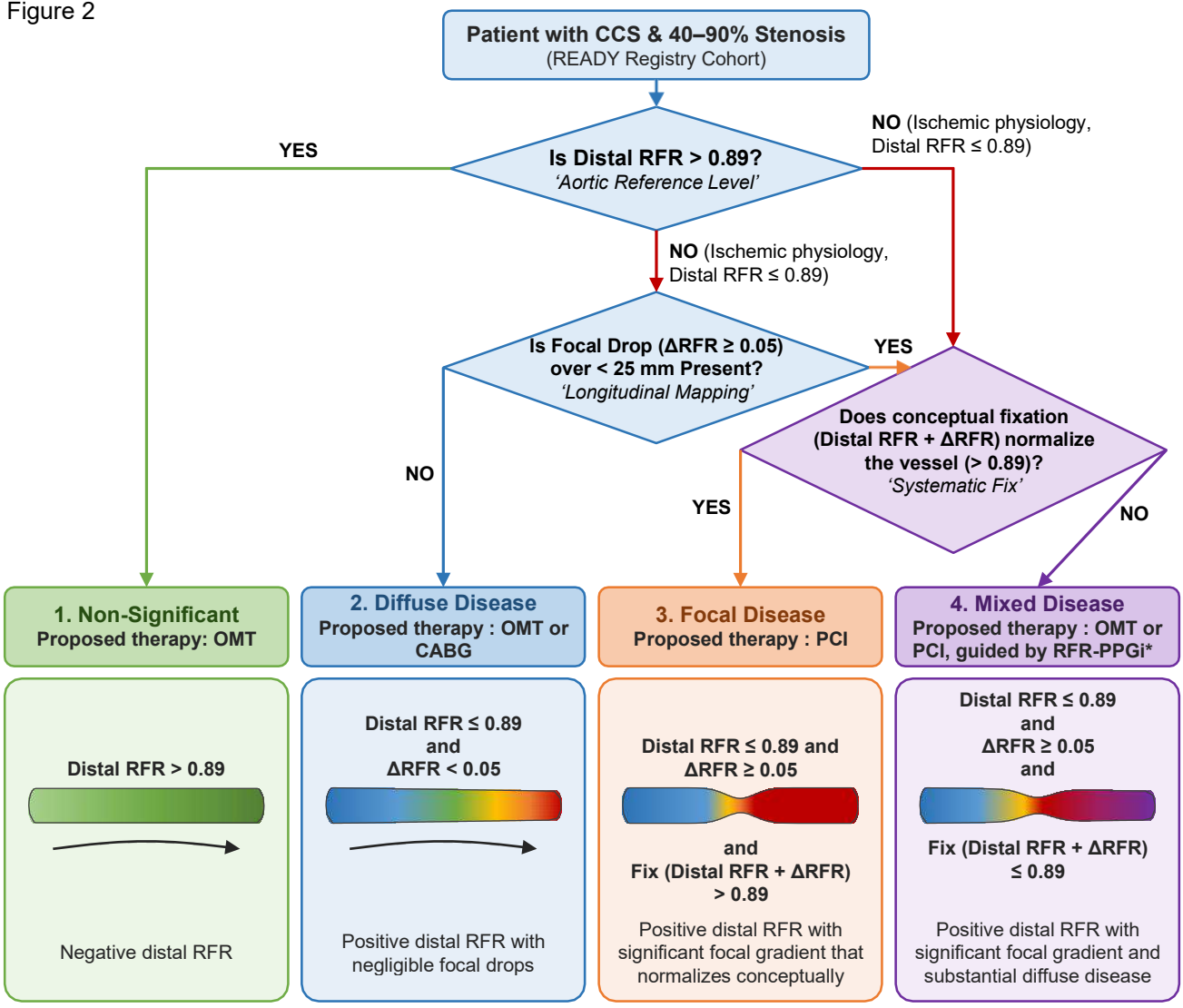

Patient with CCS & 40–90% Stenosis
(READY Registry Cohort)
Is Distal RFR > 0.89?
'Aortic Reference Level'
YES
NO (Ischemic physiology, Distal RFR ≤ 0.89)
NO (Ischemic physiology, Distal RFR ≤ 0.89)
Is Focal Drop (ΔRFR ≥ 0.05) over < 25 mm Present?
'Longitudinal Mapping'
YES
NO
Does conceptual fixation (Distal RFR + ΔRFR) normalize the vessel (> 0.89)?
'Systematic Fix'
YES
NO
1. Non-Significant
Proposed therapy: OMT
2. Diffuse Disease
Proposed therapy : OMT or CABG
3. Focal Disease
Proposed therapy : PCI
4. Mixed Disease
Proposed therapy : OMT or PCI, guided by RFR-PPGi*
Distal RFR > 0.89
Negative distal RFR
Distal RFR ≤ 0.89 and ΔRFR < 0.05
Positive distal RFR with negligible focal drops
Distal RFR ≤ 0.89 and ΔRFR ≥ 0.05
and
Fix (Distal RFR + ΔRFR) > 0.89
Positive distal RFR with significant focal gradient that normalizes conceptually
Distal RFR ≤ 0.89 and ΔRFR ≥ 0.05 and
Fix (Distal RFR + ΔRFR) ≤ 0.89
Positive distal RFR with significant focal gradient and substantial diffuse disease

Figure 3

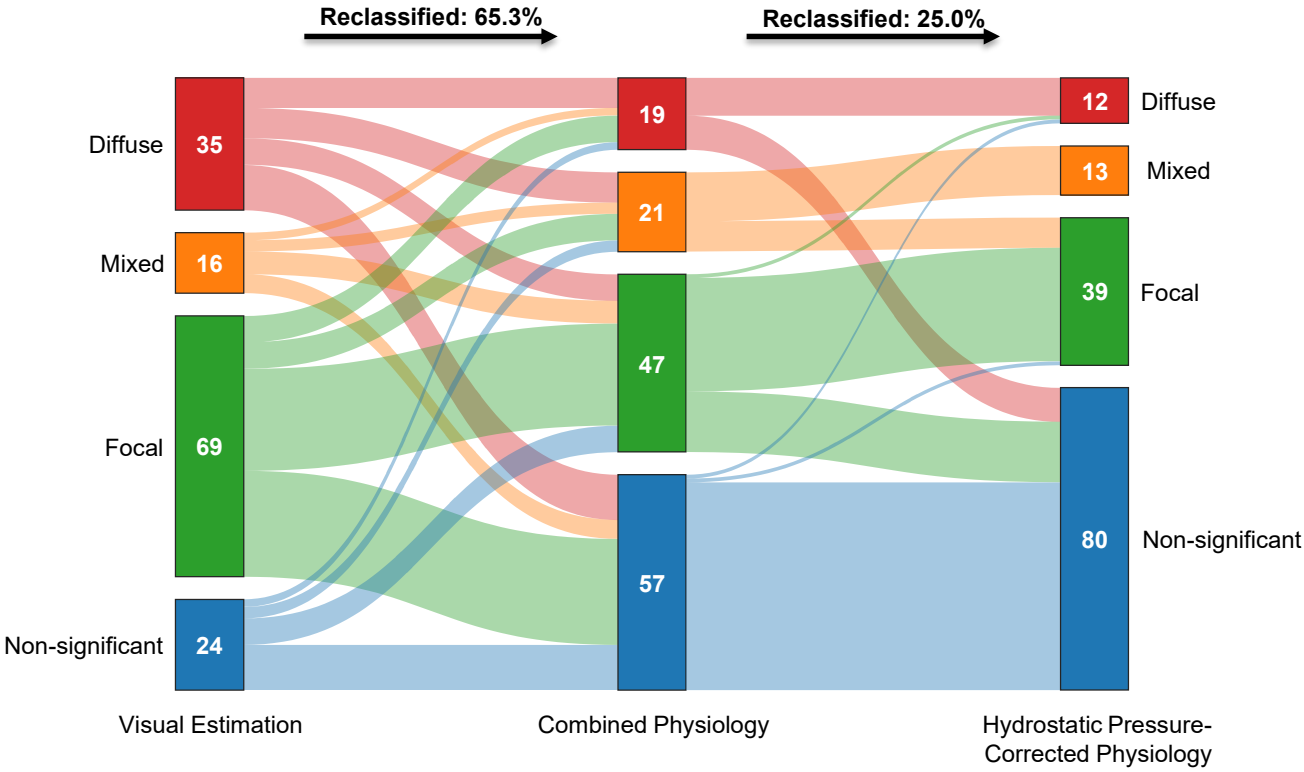
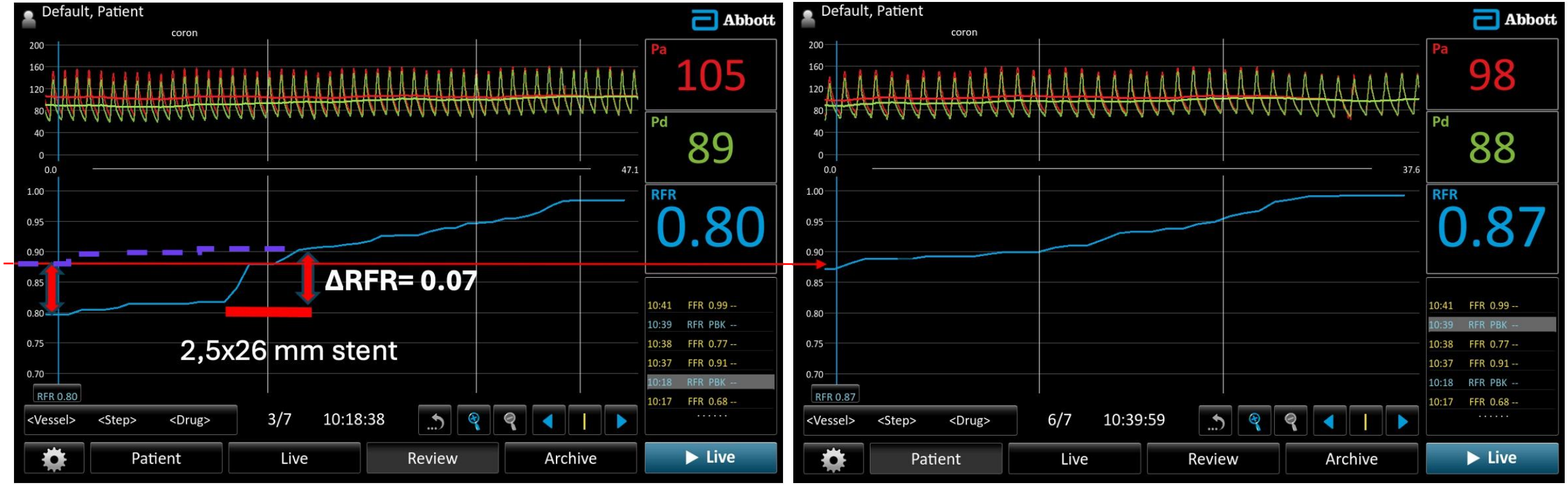

Reclassified: 65.3%
Reclassified: 25.0%
Diffuse
Mixed
Focal
Non-significant
35
16
69
24
19
21
47
57
12
13
39
80
Diffuse
Mixed
Focal
Non-significant
Visual Estimation
Combined Physiology
Hydrostatic Pressure-Corrected Physiology

Figure 5

$$\text{RFR–PPGi} = \frac{\Delta\text{RFR}}{1 - \text{distal RFR}} =$$

$$= \frac{0.07}{1 - 0.80} = 0.35$$



Conceptual post stent RFR = pre distal RFR + ΔRFR = 0.80+0.07=0.87 (= post stent distal RFR)



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Supplementary Material

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Graphical Abstract

