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# PHYSIOLOGY TO GUIDE PCI: WHAT AQVA TRIALS TAUGHT US

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# ABSTRACT

## Background

Angiographically successful PCIs are often physiologically suboptimal1,2. Achieving an optimal post–percutaneous coronary intervention (PCI) fractional flow reserve (FFR) should be pursued, as it is associated with a lower incidence of adverse cardiovascular events4,5. Nevertheless, whether coronary physiology–guided PCI is superior to conventional angiography in consistently attaining optimal post-PCI FFR values remains a matter of debate.

## Objectives

To assess whether physiology-based PCI—using angiography-derived quantitative flow ratio (QFR) or fractional flow reserve (FFR), including microcatheter-derived FFR—is superior to conventional angiography-guided PCI in achieving optimal post-PCI physiological outcomes.

## Methods

The AQVA and AQVA-II randomized controlled trials compared physiology-guided strategies to standard angiography-based PCI. In the AQVA trial, 300 patients (356 study vessels) were randomized to QFR-based virtual PCI or angiography-guided PCI, with the primary endpoint being the rate of suboptimal post-PCI QFR (<0.90). In the AQVA-II study, 305 patients (331 vessels) undergoing complex high-risk indicated procedures (CHIPs) were randomized 2:1 to physiology- or angiography-guided PCI; the primary endpoint was post-PCI FFR (>0.86 considered optimal).

## Results

Both studies demonstrated significant improvements in post-PCI physiological results with physiology-guided strategies. In AQVA, suboptimal post-PCI QFR occurred less frequently in the QFR-based PCI group (6.6%) than in the angiography-based group (15.1%; P = 0.009). In AQVA-II, optimal post-PCI FFR was achieved more often with physiology-guided PCI than with angiography alone (77% vs 54%; P < 0.0001). No significant differences were observed between angiography- and microcatheter-derived

FFR guidance, confirming noninferiority. Across both studies, physiology-based approaches tended to optimize stent selection while minimizing unnecessary implantation.

## Conclusions

The AQVA and AQVA-II trials consistently demonstrated the superiority of physiology-based PCI—whether through QFR or FFR guidance—over angiography-guided PCI in achieving optimal post-PCI physiological outcomes. These findings support the integration of physiology-derived indices into routine PCI planning to improve procedural precision and potentially long-term outcomes, warranting confirmation in larger outcome-driven studies

# INTRODUCTION

Coronary artery disease (CAD) remains one of the leading global causes of morbidity and mortality, and percutaneous coronary intervention (PCI) has emerged as a cornerstone of myocardial revascularization strategies. Historically, PCI has relied predominantly on coronary angiography, a luminographic, two-dimensional representation of the vessel lumen. While angiography provides unmatched spatial resolution and continues to be indispensable for anatomical assessment, it is increasingly recognized as an inadequate surrogate for the functional relevance of coronary stenoses. Over the past decades, numerous clinical studies have demonstrated that angiographic severity correlates poorly with the hemodynamic significance of coronary lesions, thereby underscoring the need for adjunctive tools capable of quantifying physiological impairment.

**Evolution of Coronary Physiology in Interventional Cardiology**

The development and application of coronary physiological assessment have transformed the field of interventional cardiology. The introduction of fractional flow reserve (FFR) by Pijls, De Bruyne, and colleagues in the early 1990s enabled a quantitative, reproducible assessment of lesion-specific ischemia using hyperemia-normalized trans-stenotic pressure gradients[1-3]. Early landmark randomized trials, such as DEFER, FAME, and FAME 2, consistently demonstrated that FFR-guided PCI reduces major adverse cardiac events (MACE), prevents unnecessary stent implantation, and optimizes clinical outcomes[4-6].These data firmly established FFR as the gold standard for functional lesion evaluation.

The subsequent development of resting indices, including the instantaneous wave-free ratio (iFR) and resting full-cycle ratio (RFR), facilitated physiological assessment without the need for pharmacologic hyperemia. These modalities broadened the clinical utility of physiology, reduced procedural discomfort and time, and promoted widespread adoption[7-9]. In parallel, advances in computational fluid dynamics enabled the emergence of angiography-derived physiological indices, such as the quantitative flow ratio (QFR), vessel FFR (vFFR), and artificial intelligence–enhanced models, that can estimate pressure-flow relationships noninvasively, wire-free, and within seconds[10-12].

## Beyond Diagnostic Assessment: The Rise of Physiology-Guided PCI Optimization

While the role of physiology as a gatekeeper for PCI is now well established, an equally important evolution pertains to the use of physiology for procedural optimization. An extensive body of evidence has confirmed that post-PCI physiological indices have substantial prognostic value. Suboptimal post-PCI FFR or QFR, typically defined as <0.90 for QFR and <0.86 for invasive FFR, has been strongly associated with higher risks of target vessel failure, restenosis, recurrent ischemia, myocardial infarction, and cardiovascular mortality[13-17].

Studies such as DEFINE-PCI and TARGET-FFR brought renewed attention to the concept of functional optimization, demonstrating that approximately one-third of patients exhibit residual ischemia despite angiographically successful PCI[18,19]. These physiological impairments most frequently reflect residual diffuse disease, untreated segments, stent underexpansion, or geographic mismatch, limitations that angiography alone cannot fully capture. Consequently, contemporary interventional practice increasingly embraces the principle that PCI should aim not only to achieve optimal angiographic results, but also to ensure optimized physiology.

The importance of these concepts has been reinforced by the 2023 consensus statement of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), which emphasizes the role of pre-PCI physiological mapping, virtual PCI simulation, and systematic post-PCI physiological verification[20]. This paradigm shift positions physiology not merely as a diagnostic adjunct, but as a central component of procedural planning, execution, and evaluation[21,22].

## Remaining Knowledge Gaps

It is now well established that achieving an optimal post-PCI physiological result is closely associated with improved long-term prognosis. This evidence naturally raises a fundamental question: how can we systematically enhance the final physiological outcomes of PCI? In particular, can the structured use of coronary physiology during the planning, execution, and optimization phases of the procedure meaningfully contribute to achieving better results?

This issue is accompanied by several related uncertainties. One relates to whether pre-PCI physiological mapping influences procedural decision-making, specifically, whether it leads to more appropriate stent length selection, more precise identification of landing zones, or tangible modifications in overall PCI strategy. Another important issue concerns the accuracy and reproducibility of angiography-derived physiological indices, and whether these tools can reliably guide procedural planning in place of invasive measurements. Further questions relate to the role of microcatheter-derived FFR and whether it can function as a practical alternative to pressure-wire FFR, particularly in the context of complex coronary lesions. Finally, the feasibility and effectiveness of physiology-guided PCI in complex, high-risk indicated procedures (CHIPs) remain areas of active investigation.

These questions remain particularly relevant in contemporary practice, where nearly half of PCI procedures worldwide are still performed without any physiological assessment. Furthermore, complex coronary anatomies, such as bifurcations, diffuse disease, severe calcification, and long lesions, pose distinct challenges for both angiographic and physiological evaluation.

**Rationale for the AQVA and AQVA-II Trials**

The AQVA and AQVA-II randomized controlled trials were specifically designed to address these critical gaps in knowledge.

The AQVA Trial evaluated whether a virtual PCI planning using QFR could reduce the incidence of suboptimal post-PCI physiology compared with conventional angiography-guided PCI.

The AQVA-II Trial extended the investigation to complex, high-risk indicated procedures, comparing angiography-guided PCI to physiology-guided PCI using either wire-based or microcatheter-derived invasive FFR.

Collectively, these two trials represent one of the most comprehensive and methodologically robust efforts to date to evaluate the role of pre- and post-PCI physiology across the full spectrum of lesion complexity. By integrating advances in computational

physiology, invasive assessment, and procedural optimization, AQVA and AQVA-II offer critical insights into the future of precision-guided coronary intervention.

# METHODS

## Overview of Study Designs

This manuscript integrates the methodologies of two complementary investigator-initiated randomized controlled trials, AQVA and AQVA-II, each addressing a different aspect of physiology-guided percutaneous coronary intervention (PCI). Both studies were conducted at high-volume European catheterization laboratories with extensive expertise in coronary physiology. Each trial conformed to the ethical standards of the Declaration of Helsinki and Good Clinical Practice (GCP), and all participants provided written informed consent prior to enrollment.

The AQVA Trial primarily investigated whether preprocedural virtual PCI planning using the quantitative flow ratio (QFR) could improve post-PCI physiological outcomes compared with conventional angiography-guided PCI. The AQVA-II Trial, by contrast, evaluated whether systematic physiology-guided PCI—using either wire-based invasive fractional flow reserve (FFR) or microcatheter-derived FFR—was superior to angiography guidance in achieving optimal post-PCI physiology in complex, high-risk indicated procedures (CHIPs).

### *General PCI Protocol*

Both studies follow the same PCI protocol. All procedures were performed by experienced interventional cardiologists in accordance with contemporary guideline-directed PCI practice. The following elements were standardized:

- Use of sirolimus-eluting ultra-thin drug-eluting stents (Supraflex Cruz, Sahajanand Medical Technologies Ltd., India) for all target-lesion stenting.
- Post-dilation with non-compliant balloons strongly recommended in all lesions.
- Liberal, but not mandated, use of intravascular imaging (IVUS/OCT) at operator discretion.
- Optional use of invasive pressure-wire–based physiology only for lesion selection, not for pullback or PCI guidance/optimization.

**AQVA Trial**

The AQVA (Angio-based Quantitative Flow Ratio Virtual PCI versus Conventional Angio-guided PCI in the Achievement of an Optimal Post-PCI QFR) trial was a multicenter, investigator-driven, randomized, controlled, parallel-group clinical trial. The overarching objective was to determine whether a QFR-based virtual PCI strategy was superior to conventional angiography-guided PCI in achieving an optimal post-PCI physiological result, defined as a post-PCI QFR value ≥0.90.

The study was conducted at two high-volume PCI centers in Italy (Ferrara and Reggio Emilia), both with established expertise in invasive physiology and QFR analysis.

**Patient Population**

*Inclusion Criteria*

- Age ≥18 years.
- Indication for PCI in the context of either acute coronary syndrome (ACS) or chronic coronary syndrome (CCS).
- Presence of at least one coronary vessel with an angiographically severe lesion suitable for PCI.

An angiographically severe lesion was defined as a visually estimated diameter stenosis (DS) ≥70% in the target vessel. Inclusion of lesions with length <20 mm was discouraged but not formally prohibited.

*Exclusion Criteria*

- Culprit lesions of ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI).
- Clinical or angiographic conditions precluding reliable QFR computation, including:
  - Left main coronary artery as target vessel.
  - Ostial right coronary artery lesions.

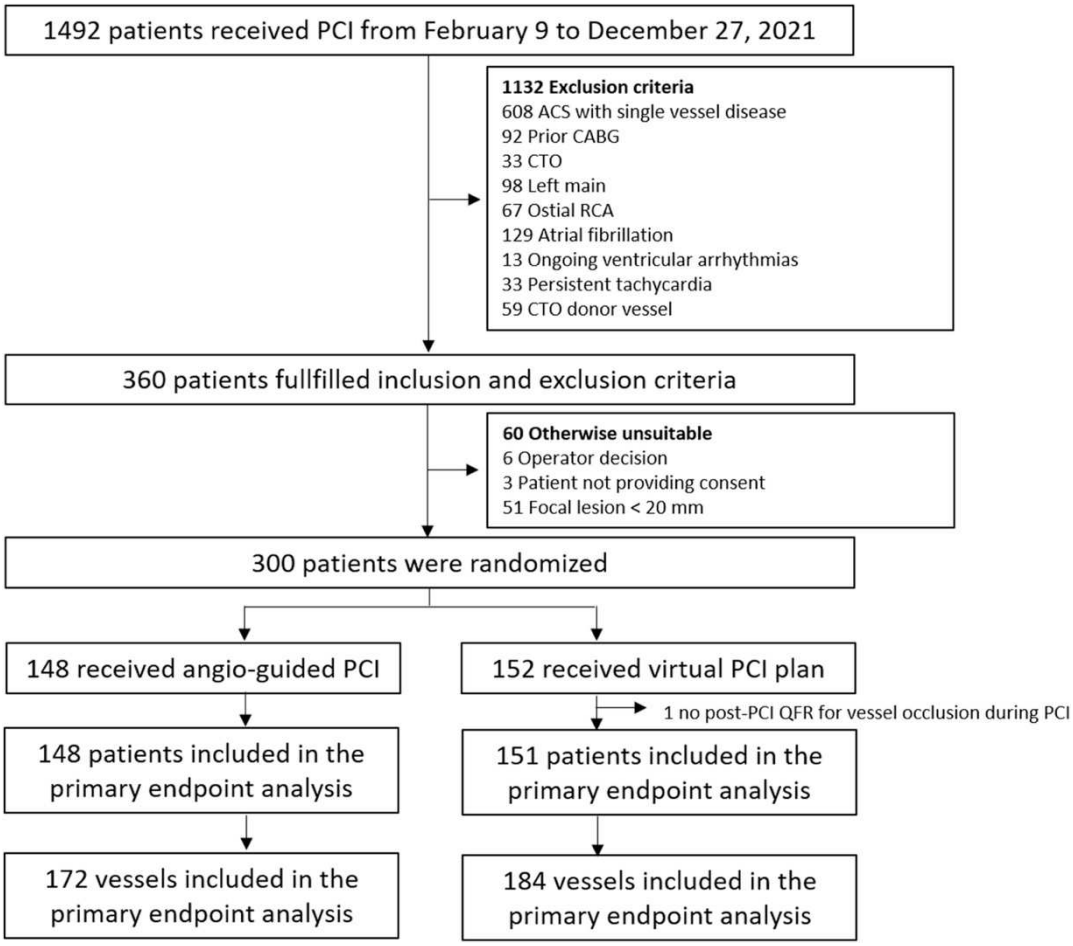
    - Previous coronary artery bypass graft (CABG) surgery involving the target vessel.
    - Atrial fibrillation or significant and persistent ventricular arrhythmias.
    - Significant and persistent tachycardia.
- Planned surgical myocardial revascularization.
- Any prior CABG surgery.
- PCI on a chronic total occlusion (CTO).
- PCI in a target artery providing Rentrop grade 2 or 3 collateral circulation to another vessel.
- Non-cardiovascular comorbidities reducing life expectancy to <1 year.
- Inability to provide informed consent.

Only patients fulfilling all inclusion criteria and none of the exclusion criteria were randomized.

**Randomization and Treatment Allocation**

Randomization was performed at the patient level in the cardiac catheterization laboratory once diagnostic coronary angiography had confirmed the presence of at least one eligible target vessel. Patients were randomized 1:1 to QFR-based virtual PCI group or Conventional angiography-guided PCI group. Randomization utilized a web-based platform was stratified by participating center (Ferrara vs Reggio Emilia), clinical presentation (ACS vs CCS), study vessel (left anterior descending [LAD] vs non-LAD). In patients with more than one target vessel, all eligible vessels were treated according to the strategy assigned to that patient.

**Figure 1 – Study flow chart.**




*ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CTO = chronic total occlusion; PCI = percutaneous coronary intervention; QFR = quantitative flow ratio; RCA = right coronary artery.*

## Study Procedures

### *Angiographic Acquisition for QCA and QFR*

Before randomization and PCI, angiographic projections suitable for both quantitative coronary angiography (QCA) and QFR computation were acquired in both groups. The acquisition protocol included:

* Intracoronary nitroglycerin 100–200 μg immediately prior to imaging.

* Frame rate of 15 frames per second.

* Single contrast injection of 6 mL at 4 mL/s and 300 psi via a power injector, when available.

* Use of pre-specified recommended projection angles to minimize foreshortening and vessel overlap.

*Angiography-Guided PCI Group*

In the angiography-based PCI arm, all PCI procedures were undertaken according to the operator's judgment. The operator was free to plan the procedure in all its steps (including predilation, stenting technique, number of stents, stent diameter and length, post-dilation, use of intravascular imaging), based solely on angiographic and clinical information.

No QFR-based planning or pullback was used for procedural guidance in this arm. Operators were allowed to use invasive physiology (e.g., FFR/iFR) only for lesion selection, and pullback maneuvers were not permitted.

*QFR-Based Virtual PCI Group*

In the QFR-based virtual PCI arm, a structured physiology-guided planning workflow was implemented.

1. Pre-PCI QFR Computation

After randomization, angiographic projections were transferred to the QAngio XA 3D software (Medis Medical Imaging Systems, Leiden, The Netherlands). All operators had received formal training and certification for QFR analysis.

2. Initial Angiographic PCI Plan

Before QFR analysis, the first operator formulated and recorded a preliminary PCI strategy based on angiography alone, including intended stent length and diameter, planned landing zone, number of stents and any special techniques. 3. QFR Computation and Virtual PCI planning

A second operator performed the QFR analysis, generating a full-vessel pullback curve and quantifying the contribution of each coronary segment and lesion to the overall physiological impairment. Then, the first and second operators jointly reviewed the QFR pullback trace and used the residual QFR tool to simulate alternative PCI strategies (**Figure 2**). Specifically, they:

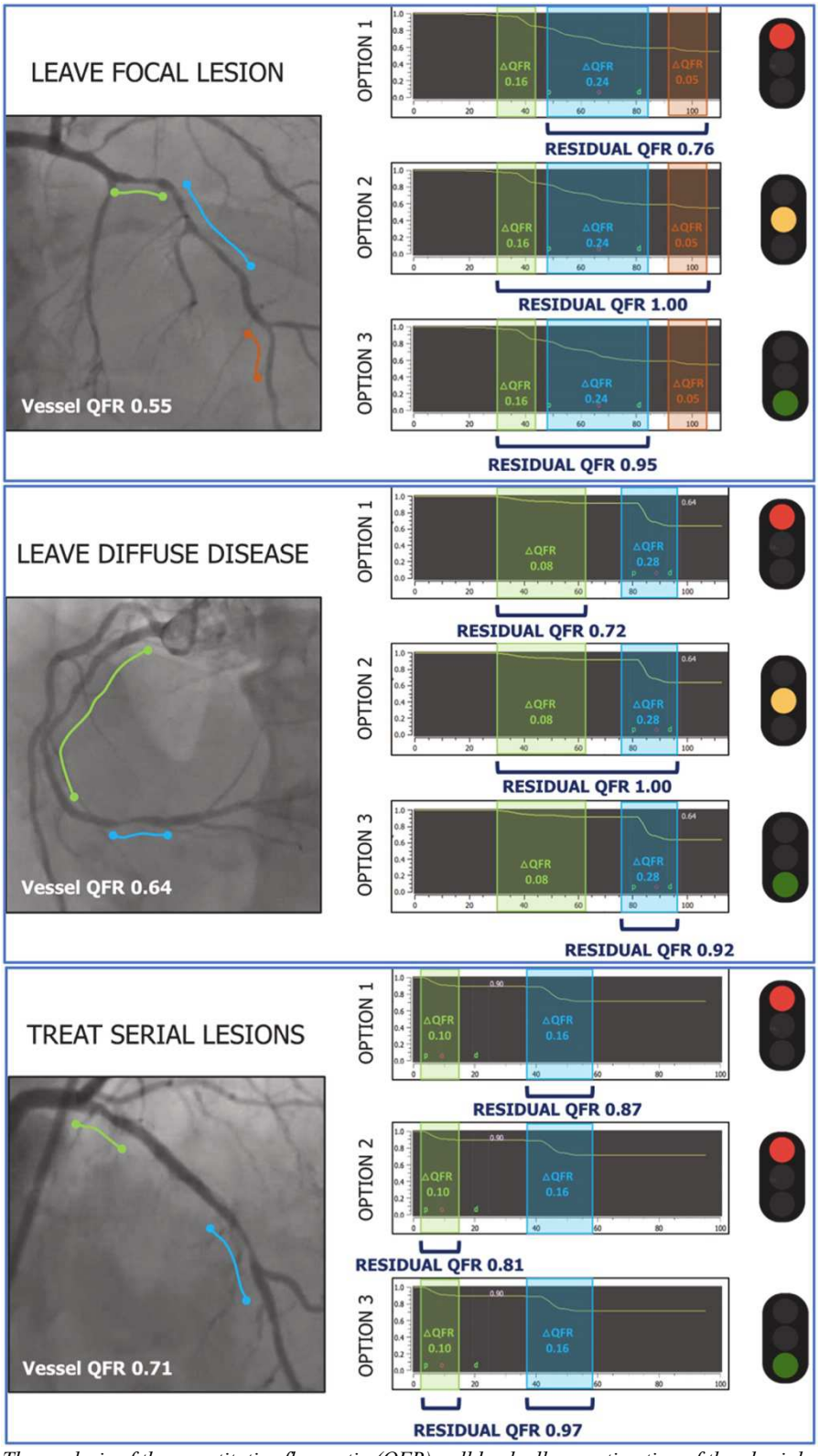
- Moved the proximal (p) and distal (d) markers along the QFR pullback curve to test different stent lengths and landing zones;
- Calculated the predicted post-PCI QFR for each virtual strategy;
- Aimed to identify the shortest stent strategy capable of achieving a predicted residual QFR ≥0.90.

4. Execution of the Virtual PCI Plan

Once the optimal virtual plan was defined, the first operator proceeded to perform PCI strictly according to this plan. Deviations were allowed only in the event of unforeseen technical or anatomical constraints (e.g., stent delivery failure).

Post-dilation, intravascular imaging, and other adjunctive techniques were encouraged but left to operator discretion, provided the core elements of the virtual plan were maintained.

**Figure 2 - Examples of QFR-Based Virtual PCI Plans**




*The analysis of the quantitative flow ratio (QFR) pull back allows estimation of the physiological impact of single segments (ΔQFR). The residual QFR tool allows estimation of the post–percutaneous coronary intervention (PCI) value after the treatment of 1 or more segments. The aim of the QFR-based virtual PCI is to treat the segments, allowing a post-PCI QFR value >0.90 (green light) and avoiding both undertreatment (red light) and overtreatment (yellow light) of coronary lesions/segments. (Top) The analysis suggests leaving a distal focal lesion (residual QFR = 0.95). (Middle) The plan suggests leaving diffuse proximal disease (residual QFR = 0.92). (Bottom) The preprocedural planning suggests treating both serial lesions (residual QFR = 0.97) because the treatment of just 1 lesion was not enough to achieve the optimal post-PCI goal.*

*Post-PCI Angiographic Acquisition*

At the end of the procedure, in both groups, two angiographic projections per study vessel were acquired following the same acquisition protocol used pre-PCI. These images were used by the core laboratory to compute post-PCI QFR, perform QCA and assess the pattern of residual disease.

*Core-Lab Analysis*

All angiographic data were anonymized and analyzed at the core laboratory of the University Hospital of Ferrara by experienced analysts blinded to treatment allocation and procedural details.

Using validated software (CAAS II, Pie Medical Systems, Maastricht, The Netherlands), the following QCA parameters were measured pre-PCI: Reference vessel diameter (RVD), Minimal lumen diameter (MLD), Percentage diameter stenosis (%DS); Lesion length; Percentage area stenosis (%AS).

QFR computation followed a standardized, previously validated workflow[23-25]. Pre- and post-PCI QFR were computed for all study vessels. In addition, for all the cases before PCI and for those with residual vessel QFR <0.90, the physiologic pattern of coronary artery disease was classified as:

- Focal: single QFR drop ≥0.05 within a 10-mm segment;
- Serial lesions: ≥2 focal QFR drops, separated by at least 3×RVD;
- Diffuse disease: gradual QFR decline without distinct focal drops;
- Combination pattern: coexistence of any of the above.

*Data Collection and Follow-Up*

Clinical, procedural, and angiographic data were collected prospectively and entered into a dedicated electronic case report form (eCRF). Collected variables included demographics data, cardiovascular risk factors, clinical presentation and procedural details.

**Study Endpoints**

The primary endpoint of the AQVA trial was the proportion of vessels with a final post-PCI QFR <0.90. This threshold was selected based on prior studies demonstrating that post-PCI QFR values ≥0.90 are associated with lower rates of adverse cardiovascular events.

Key secondary endpoints included: Post-PCI QFR as a continuous variable; ΔQFR (change from pre- to post-PCI); Total stent length per lesion and per patient; Number of stents per patient; Procedure duration (minutes); Contrast volume (mL); Radiation dose expressed as dose–area product (DAP); Distribution and pattern of residual disease in vessels with suboptimal post-PCI QFR.

**Statistical Analysis**

In the HAWKEYE study cohort[17], approximately 16% of vessels treated with angiography-guided PCI had post-PCI QFR <0.90. It was hypothesized that in roughly one-third of these, low post-PCI QFR was driven predominantly by diffuse disease and therefore might not be corrected by stenting. On the basis of this and assuming that a QFR-based virtual PCI would reduce the rate of QFR <0.90 by approximately 60% compared with angiography-guided PCI (β error = 80%, α error = 5%), a minimum of 300 vessels was required. To accommodate clustering of multiple vessels within patients and potential exclusions, 300 patients (356 vessels) were ultimately enrolled.

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), according to distribution. Normality was assessed using the Kolmogorov–Smirnov test. Categorical variables were reported as counts and percentages. Comparisons between groups were performed using Student's t-test or Mann–Whitney U test for continuous variables, Chi-square test or Fisher's exact test for categorical variables, as appropriate. All tests were two-sided unless otherwise specified, and a p-value <0.05 was considered statistically significant.

Because some patients contributed more than one study vessel, a hierarchical (multilevel) modeling approach was used to account for within-patient correlation when estimating treatment effects on the primary endpoint. Treatment group was included as a fixed effect; Patient-specific random effects were used to model intra-patient clustering.

No additional covariates were introduced into the primary model because no significant baseline imbalances were observed between groups.

All statistical analyses were performed by an independent statistician using STATA version 16.0 (StataCorp, College Station, TX, USA).

## AQVA-II Trial

The Angio- or Microcatheter-Quantified FFR Virtual PCI versus Angio-Guided PCI in the Achievement of an Optimal Post-PCI FFR (AQVA-II) trial was a prospective, multicenter, open-label, investigator-initiated, randomized controlled trial designed to evaluate whether a structured, physiology-based approach to planning, guiding, and optimizing percutaneous coronary intervention (PCI) yields superior post-procedural physiological results compared with standard angiography-guided PCI. The trial specifically enrolled patients undergoing complex and high-risk indicated procedures (CHIP), a population in which physiology-based guidance is hypothesized to be particularly impactful.

The study was conducted at two high-volume PCI centers in Italy (Ferrara and Latina), each with extensive experience in coronary physiology.

## Patient Population

*Inclusion Criteria*

- Age ≥18 years.
- Indication for PCI in the context of either acute coronary syndrome (ACS) or chronic coronary syndrome (CCS).
- Presence of at least one coronary vessel with an angiographically severe lesion suitable for PCI.
- Presence of ≥1 CHIP feature, including:
    - Long coronary lesions (>28 mm).
    - Tandem or sequential lesions.
    - Severe calcification.
    - Severe vessel tortuosity.
    - True bifurcation lesions (Medina 1,1,1 or 1,0,1 or 0,1,1).
    - In-stent restenosis (ISR).
    - Left main (LM) stem disease.

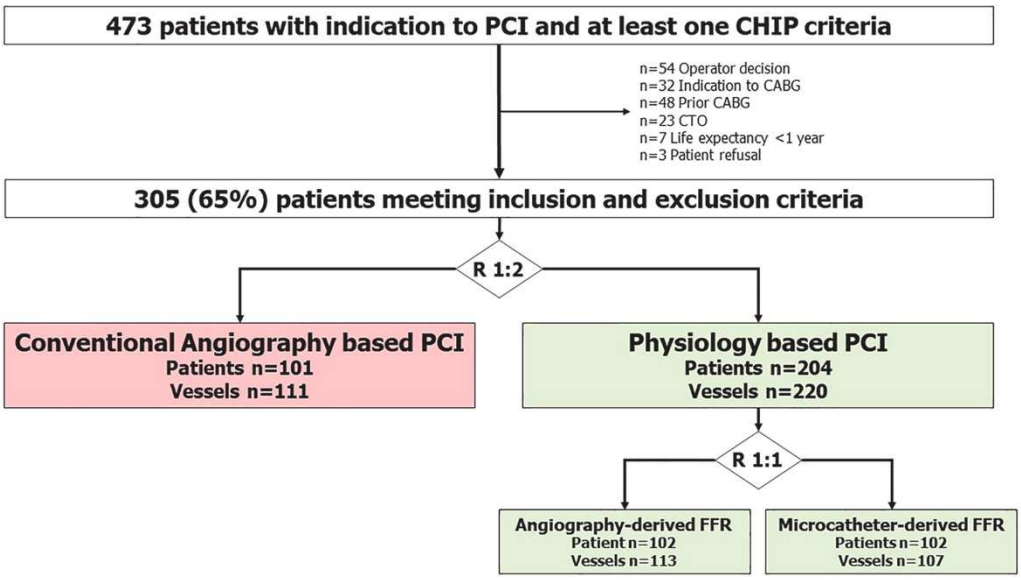
*Exclusion Criteria*

- Planned surgical revascularization.
- Prior CABG surgery.
- Culprit lesion of an ACS.
- Chronic total occlusion (CTO).
- Anticipated life expectancy <1 year due to non-cardiac comorbidities.

**Randomization and Treatment Allocation**

Eligible patients were randomized 2:1 to physiology-guided PCI or conventional angiography-guided PCI. Patients assigned to the physiology-guided group underwent a secondary 1:1 randomization to determine the physiological modality used during PCI: Angiography-derived FFR (QFR), or Microcatheter-derived FFR. Randomization was carried out directly in the catheterization laboratory, stratified by study center (Ferrara vs. Latina) clinical syndrome (ACS vs. CCS) and target vessel (LM/LAD vs. non-LM/LAD). For patients with ≥1 study vessel, all vessels were treated according to the assigned strategy.

**Figure 3 – Study Flowchart.**




*CABG = coronary artery bypass graft; CHIP = complex high-risk indicated procedure; CTO = chronic total occlusion; FFR = fractional flow reserve; PCI = percutaneous coronary intervention; R = randomization.*

**Study Procedures**

*Angiography-Guided PCI Group*

In the angiography-based PCI arm, all PCI procedures were undertaken according to the operator's judgment. The operator was free to plan the procedure in all its steps (including predilation, stenting technique, number of stents, stent diameter and length, post-dilation, use of intravascular imaging), based solely on angiographic and clinical information.

Physiology was not permitted for PCI guidance in this arm. Operators were allowed to use invasive physiology (e.g., FFR/iFR) only for lesion selection.

All patients underwent a blinded post-PCI FFR pullback using IV adenosine.

*Physiology-Guided PCI Group*

Patients randomized to physiology-guided PCI underwent pre-PCI physiological assessment according to their secondary randomization.

In the angiography-derived FFR arm, the Murray law–based quantitative flow ratio (QFR) using the AngioPlus system (Pulse Medical Technology) was computed[11]. All operators involved in the study were trained and certified. The system enables FFR estimation on the basis of 1 or 2 projections. The use of single-projection analysis was suggested. After the analysis, the operator reviewed the pull back trace and simulated a PCI procedural plan by using the residual vessel QFR tool. The goal was to treat only the segment(s) needed to achieve a post-PCI QFR value of ≥0.90. In particular, the operator could decide whether to use 1 or 2 stents, using the dedicated tool, and move the proximal (p) and distal (d) markers of both stents along the QFR pull back to obtain a residual QFR value of ≥0.90 while minimizing stent length[17]. Once the optimal procedural plan, which also took into account lesion length, was identified, the operator was required to adhere to it. The decision to repeat the QFR assessment during the procedure was at the operator's discretion.

In the microcatheter-derived FFR arm, the TruePhysio microcatheter was used in conjunction with the Vivo Cardio cardiovascular pressure measurement system (Insight Lifetech). The microcatheter was advanced over a traditional workhorse coronary

guidewire to position it distally to the target lesion. After the induction of hyperemia, FFR measurement and pull back were performed. Pull back was performed manually by steadily retrieving the microcatheter through the coronary guidewire in 20 to 40 seconds[26]. For both pre- and peri-PCI assessment, operators had the option to use either intravenous adenosine (140 µg/kg/min) or papaverine (15 mg for the left coronary artery, 10 mg for the right coronary artery)[27]. Pull backs were critically reviewed by the operators, and consistent decisions were made accordingly. Operators had the freedom to repeat FFR and pull back assessment during the procedure.

*Core-Lab Analysis*

All angiographic data were anonymized and analyzed at the core laboratory of the University Hospital of Ferrara by reviewers blinded to randomization.

QCA was performed using validated software (CAAS II, Pie Medical Systems, Maastricht, The Netherlands) and included vessel diameter (RVD), minimal lumen diameter (MLD), percentage diameter stenosis (%DS), lesion length and percentage area stenosis (%AS).

Regarding post-PCI FFR, the core lab evaluated the quality of the pull back, validated all FFR values and assessed the presence of drift.

*Data Collection and Follow-Up*

Clinical, procedural, and angiographic data were collected prospectively and entered into a dedicated electronic case report form (eCRF). Collected variables included demographics data, cardiovascular risk factors, clinical presentation and procedural details.

**Study Endpoints**

The primary endpoint of the AQVA II trial was the invasive post-PCI FFR value. The rate of post-PCI FFR >0.86 was the primary endpoint in the comparison between physiology-guided vs. angiography-guided PCI. In case of a patient with ≥2 study vessels, the primary

endpoint was considered met if both study vessels had invasive post-PCI FFR values >0.86.

In the comparison between angiography-derived and microcatheter-derived FFR guidance for PCI, the continuous value post-PCI FFR represented the primary outcome. In case of a patient with ≥2 study vessels, the lowest post-PCI FFR value was considered.

The main secondary endpoints included the ratio of distal pressure to aortic pressure, the rate of lesions with ischemic post-PCI FFR (≤0.80), and the rate of lesions with post-PCI distal pressure/aortic pressure ratio <0.96.16 Procedural aspects such as duration, x-ray time, and contrast medium were also evaluated. All endpoints were assessed at the patient level.

**Statistical Analysis**

For the comparison between physiology-based PCI and conventional angiography-guided PCI, prior evidence suggested that approximately 70% of patients would achieve an invasive post-PCI FFR >0.86[19, 28-31]. Based on these data[19, 28-31], physiology-based PCI was expected to yield at least a 50% relative increase in the occurrence of the primary endpoint. Assuming a 2:1 randomization ratio, a total sample size of 270 patients, 180 assigned to physiology-based PCI and 90 to conventional angiography-guided PCI, was calculated to provide 80% power, with a one-sided significance level of 2.5%, to detect an increase in the proportion of patients achieving an FFR >0.86.

For the comparison between angiography-derived and microcatheter-derived FFR guidance, the sample size estimation was informed by the post-PCI FFR standard deviation reported in the TARGET-FFR trial (SD = 0.08)[19]. A noninferiority margin of -0.032 was therefore selected. Under these assumptions, 198 patients (99 per group) were required to ensure 80% power to demonstrate that the lower bound of the one-sided 97.5% confidence interval would remain above the noninferiority threshold.

In summary, the study required the enrollment of at least 300 participants in total, with 200 allocated to the physiology-based PCI arm and 100 to the conventional angiography-guided PCI arm.

Continuous variables were expressed as mean ± SD or as median (Q1–Q3), according to their distribution. Normality was assessed using the Kolmogorov–Smirnov test. Comparisons between continuous variables were performed using Student's t-test or the Mann–Whitney test, as appropriate. Categorical variables were presented as counts and percentages, and comparisons were carried out using the Pearson chi-square test or Fisher's exact test, as appropriate. All analyses were conducted according to the intention-to-treat principle and at the patient level. One- or two-tailed tests were applied as required, and statistical significance was set at $P < 0.05$. Analyses were performed by an independent statistician (M.M.) using Stata version 16.0 (StataCorp). No missing data were present.

# RESULTS

## Results of AQVA Trial

The study flow is summarized in **Figure 1**. Between February and December 2021, a total of 300 patients met all eligibility criteria, were randomized, and constituted the study population, accounting for 356 study vessels. Baseline clinical, vessel, and procedural characteristics were well balanced across the two groups (**Tables 1** and **2**). Approximately half of the population presented with acute coronary syndrome. In the angiography-guided PCI group (148 patients, 172 vessels), no major procedural complications occurred; invasive physiology was used in 36 procedures (24%) and intracoronary imaging in 33 (22%). In the virtual PCI group (152 patients, 184 vessels), one procedure was complicated by abrupt vessel closure. Use of invasive physiology (35 cases, 23%) and intracoronary imaging (31 cases, 20%) did not differ significantly versus the angiography-guided PCI arm.

**Table 1. Baseline patient characteristics**

| | **Total** **N=300** | **Angio-based** **N=148** | **Virtual PCI** **N=152** | **p-value** |
|---|---|---|---|---|
| Age, years | 70 (62-77) | 71 (63-78) | 69 (62-76) | 0.43 |
| Sex | 83 (27.7%) | 40 (27.0%) | 43 (28.3%) | 0.81 |
| BMI, kg/m$^2$ | 27.5 (24.5-30.1) | 27.6 (24.8-30.1) | 27.4 (24.4-29.7) | 0.75 |
| Hypertension | 250 (83.3%) | 125 (84.5%) | 125 (82.2%) | 0.61 |
| Dyslipidemia | 191 (63.7%) | 95 (64.2%) | 96 (63.2%) | 0.85 |
| Diabetes | 87 (29.0%) | 46 (31.1%) | 41 (27.0%) | 0.43 |
| Current smoker | 73 (24.3%) | 39 (26.4%) | 34 (22.4%) | |
| Prior MI | 80 (26.7%) | 42 (28.4%) | 38 (25.0%) | 0.51 |
| Prior PCI | 80 (26.7%) | 41 (27.7%) | 39 (25.7%) | 0.69 |
| Heart Failure | 38 (12.7%) | 19 (12.8%) | 19 (12.5%) | 0.93 |
| COPD | 29 (9.7%) | 15 (10.1%) | 14 (9.2%) | 0.79 |
| CKD | 52 (17.3%) | 27 (18.2%) | 25 (16.4%) | 0.68 |
| PAD | 67 (22.3%) | 35 (23.6%) | 32 (21.1%) | 0.59 |
| CVA | 16 (5.4%) | 8 (5.5%) | 8 (5.3%) | 0.93 |
| LVEF, % | 53 (47-60) | 55 (48-60) | 52 (45-60) | 0.27 |

| | | | | |
|---|---|---|---|---|
| Clinical presentation | | | | |
| STEMI | 52 (17.3%) | 24 (16.2%) | 28 (18.4%) | 0.61 |
| NSTEMI | 104 (34.7%) | 51 (34.5%) | 53 (34.9%) | 0.94 |
| CCS | 143 (47.7%) | 72 (48.6%) | 71 (46.7%) | 0.74 |
| SBP, mmHg | 134 (121-151) | 137 (122-150) | 132 (120-145) | 0.35 |
| HR, bpm | 72 (65-80) | 73 (65-80) | 72 (62-80) | 0.40 |
| Killip class | | | | 0.024 |
| 1 | 240 (80.5%) | 110 (75.3%) | 130 (85.5%) | |
| 2 | 46 (15.4%) | 31 (21.2%) | 15 (9.9%) | |
| 3 | 12 (4.0%) | 5 (3.4%) | 7 (4.6%) | |
| Creatinine pre-PCI, mg/dl | 1.04 (0.88-1.30) | 1.05 (0.88-1.30) | 1.04 (0.88-1.25) | 0.18 |
| eGFR, mL/min/1.73 m2 | 87 (64-100) | 84 (61-102) | 89 (69-98) | 0.41 |
| Troponin peak pre-PCI, ng/l | 7399.0 (21489.9) | 6599.8 (19553.5) | 8177.2 (23259.6) | 0.53 |
| CK-MB peak pre PCI, ng/ml | 34.46 (72.54) | 29.52 (70.83) | 39.24 (74.07) | 0.25 |
| IVUS utilization | 64 (21) | 33 (22.2%) | 31 (20.3%) | 0.71 |

*Values are median (IQR) or n (%). BMI = body mass index; CCS = chronic coronary syndrome; CKD = chronic kidney diseae; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; HR = heart rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non–ST-segment elevated myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; STEMI = ST-segment elevated myocardial infarction.*

**Table 2. Vessel level characteristics**

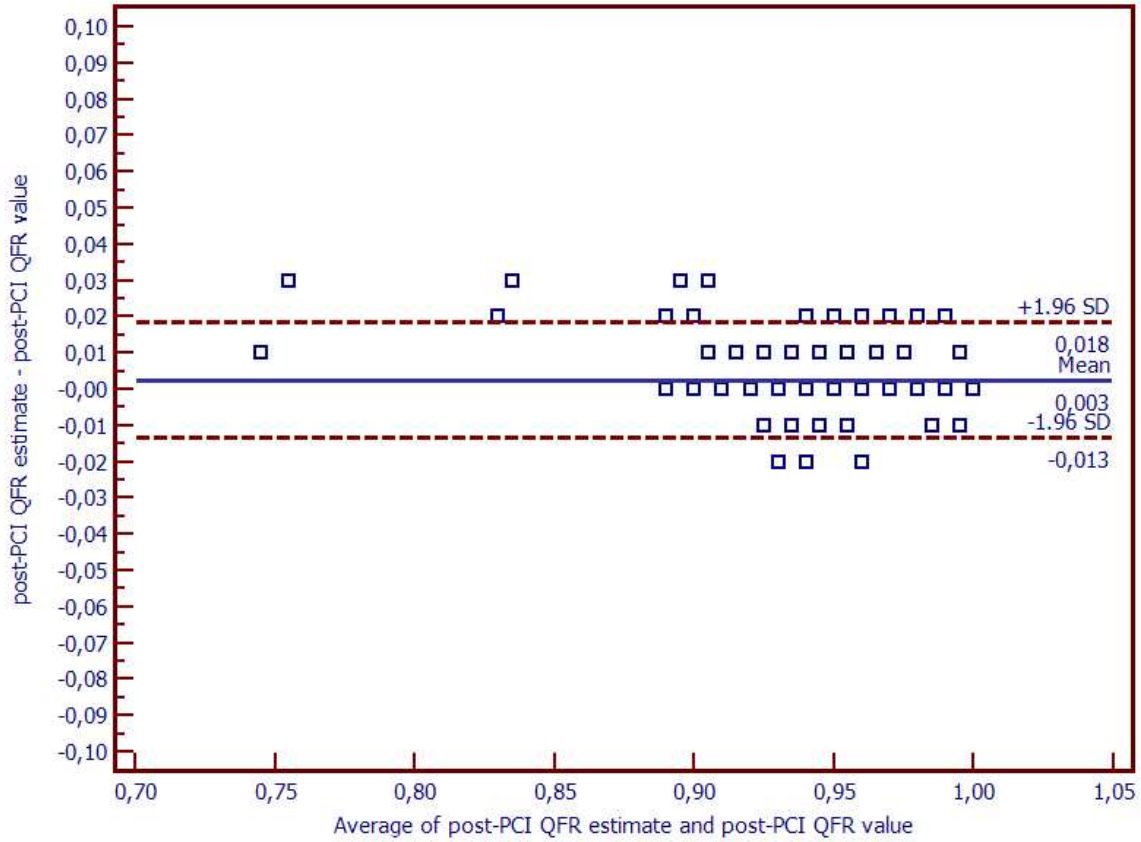
| | Total N=356 | Angio-based N=172 | Virtual PCI N=184 | p-value |
|---|---|---|---|---|
| Coronary vessel | | | | 0.13 |
| RCA | 98 (27.5%) | 40 (23.3%) | 58 (31.5%) | |
| LAD | 202 (56.7%) | 100 (58.1%) | 102 (55.4%) | |
| LCx | 56 (15.7%) | 32 (18.6%) | 24 (13.0%) | |
| Percentage stenosis | 80 (80-90) | 80 (80-90) | 80 (77.5-90) | 0.43 |
| Lesion length, mm | 25 (16-38) | 28 (16-40) | 25 (18-38) | 0.48 |
| RVD, mm | 3 (3-3.5) | 3 (3-3.5) | 3 (3-3.5) | 0.71 |
| Ostial | 34 (9.6%) | 17 (9.9%) | 17 (9.2%) | 0.84 |
| Bifurcation | 134 (37.6%) | 60 (34.9%) | 74 (40.2%) | 0.30 |
| Severe calcification | 94 (26.4%) | 48 (27.9%) | 46 (25.0%) | 0.53 |
| Severe tortuosity | 25 (7.0%) | 10 (5.8%) | 15 (8.2%) | 0.39 |
| Pre-dilation | 326 (91.6%) | 160 (93.0%) | 166 (90.2%) | 0.34 |
| *QCA analysis* | | | | |
| Diameter stenosis | 50 (41-59) | 51 (40-61) | 48.5 (42-58) | 0.42 |
| Area stenosis | 75 (65-83) | 75 (64-85) | 72 (65-82) | 0.40 |
| Lesion length, mm | 21.4 (19-16) | 21.4 (18.7-26.2) | 21.6 (19-25.8) | 0.99 |
| RVD, mm | 2.6 (2.2-2.9) | 2.5 (2.2-2.8) | 2.6 (2.2-3) | 0.21 |
| *QFR pre-PCI* | | | | |
| Value | 0.69 (0.59-0.74) | 0.69 (0.59-0.77) | 0.69 (0.59-0.74) | 0.10 |
| Pattern | | | | 0.07 |
| Focal | 138 (39.0%) | 78 (45.9%) | 60 (32.6%) | |
| Serial | 160 (45.2%) | 70 (41.2%) | 90 (48.9%) | |
| Diffuse | 12 (3.4%) | 4 (2.4%) | 8 (4.3%) | |
| Combined* | 44 (12.4%) | 18 (10.6%) | 26 (14.1%) | |

*Values are median (IQR) or n (%). *Combination of focal or serial and diffuse patterns. LAD = left anterior descending; LCx = left circumflex; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; QFR = quantitative flow ratio; RCA = right coronary artery; RVD = reference vessel diameter.*

In the virtual PCI arm, operators were able to follow the QFR-based treatment plan in 180 cases (97.8%). The virtual strategy modified the prespecified plan in 48 cases (26%; 95% CI: 20%–33%), suggesting deferral of a lesion deemed angiographically significant in two-thirds of cases (32, 67%) and recommending treatment of a lesion considered non-

significant in one-third (16, 33%). Agreement between estimated and measured post-PCI QFR in this arm is depicted in **Figure 4**.

**Figure 4: Bland and Altman plot between estimated post-PCI QFR and measured post-PCI QFR in the virtual PCI arm**



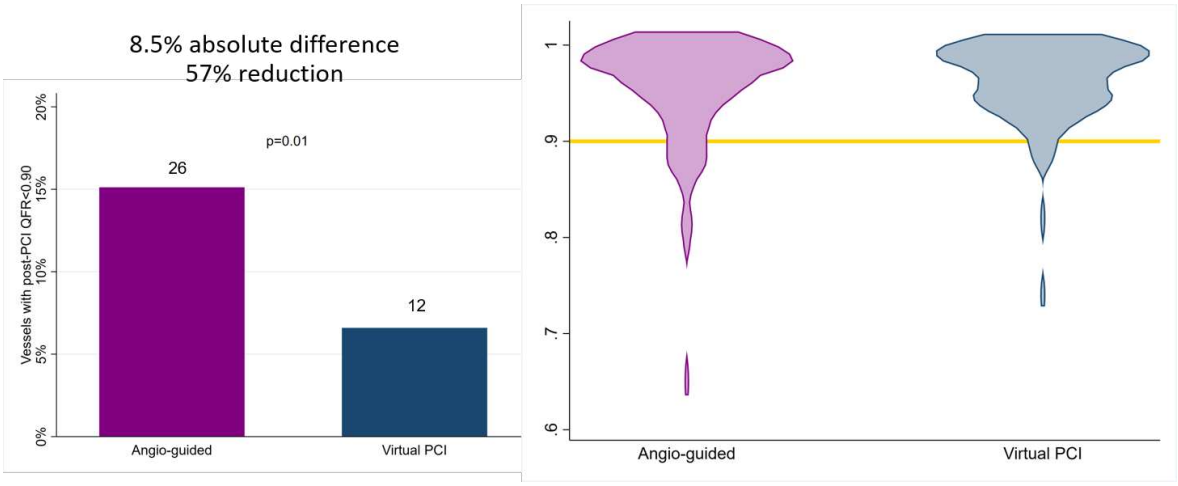

*PCI: percutaneous coronary intervention. QFR: quantitative flow ratio. SD: standard deviation.*

## Primary Endpoint

Across the entire cohort, 38 vessels (10.7%) failed to achieve the prespecified post-PCI QFR ≥0.90. The primary endpoint occurred significantly more often in the angiography-guided PCI group (26 vessels, 15.1%) compared with the virtual PCI group (12 vessels, 6.6%), corresponding to an absolute difference of 8.5% and a relative reduction of 57% (95% CI: 2.2%–15.0%; P = 0.009; (**Figures 5**). In the hierarchical model, treatment group remained independently associated with the primary endpoint (OR: 0.396; 95% CI: 0.192–0.817; P = 0.012).

The mean and distribution of post-PCI QFR values are reported in **Table 3** and **Figure 5**, respectively. The ΔQFR between pre- and post-PCI was higher in the virtual PCI group, reaching borderline statistical significance (median 0.29 [IQR 0.23–0.37] vs 0.27 [0.20–0.36]; P = 0.05).

**Figure 5. Primary endpoint**



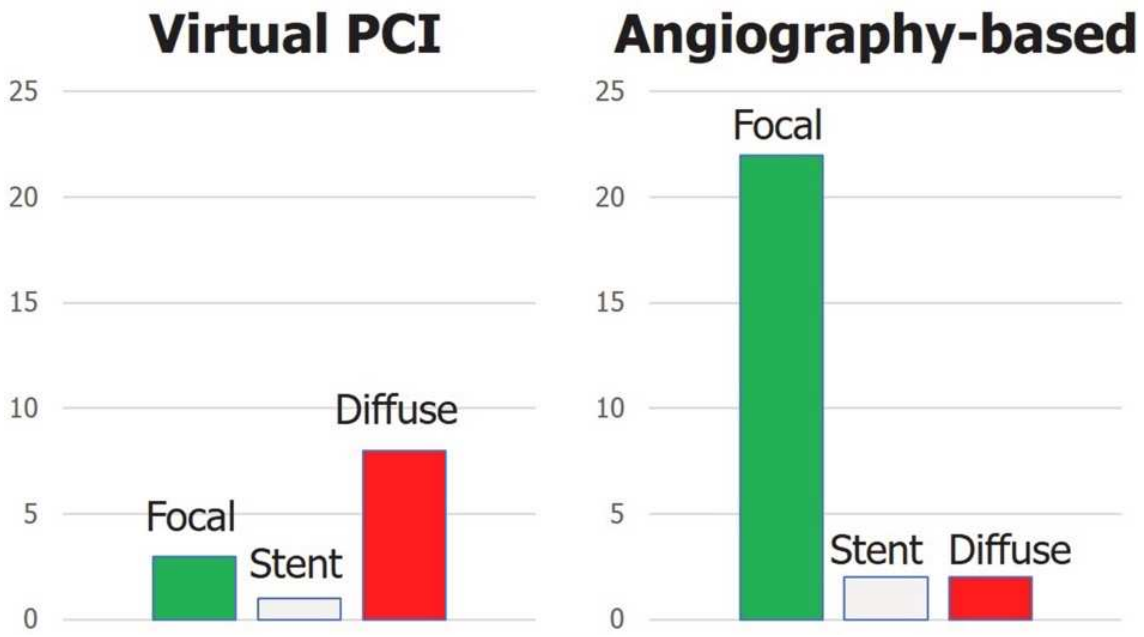

*Left panel: rate and percentage of primary endpoint occurrence between the two groups. Right panel: violin plot showing the distribution of post-PCI values among the two groups. The gold line represents a post-PCI QFR value of 0.90 (threshold).*

## Localization of QFR Drop in Vessels with Suboptimal Physiology

Among the 26 vessels with suboptimal post-PCI QFR in the angiography-based PCI group, the physiological impairment was in-stent in 2 cases (7.5%), focal outside the stent in 22 (85%), and diffuse in 2 (7.5%) (**Figure 6**).

Conversely, in the virtual PCI group, suboptimal results were predominantly driven by diffuse disease (6 vessels, 50%), whereas focal mechanisms, either in-stent (2 vessels, 17%) or outside the stent (4 vessels, 33%), were less frequent (P = 0.004).

**Figure 6. Number of vessels with suboptimal post-pci physiology result stratified according to the different pattern of suboptimal results between the 2 study groups.**




*In the angiography-guided group, the main mechanism underlying a suboptimal result is represented by focal disease outside the stented segment. In the virtual percutaneous coronary intervention (PCI) group, the main mechanism was represented by residual diffuse disease not amenable to improvement with further PCI.*

**Secondary Endpoints**

There were no significant between-group differences in procedural duration, contrast volume, or radiation exposure (Table 3). Stent number per patient and stent length per lesion were numerically lower in the virtual PCI arm (median 1 [IQR 1–2]; 1.4 ± 0.6 vs median 1 [1–2]; 1.6 ± 0.7; P = 0.06; and 40 mm [25–55], 42.7 ± 20.1 vs 44 mm [28–60], 46.1 ± 23.1; P = 0.08, respectively). Conversely, total procedure duration was numerically longer in the virtual PCI group (median 66 min [IQR 51–82]; 69 ± 23.1 vs 67 min [57–88]; 73.9 ± 23.9; P = 0.06).

## Table 3. Secondary endpoints.

| | Total | Angio-based | Virtual PCI | p-value |
|---|---|---|---|---|
| QFR post-PCI value | 0.97 [0.94- 1] | 0.97 [0.94-1] | 0.97 [0.94-0.99] | 0.23 |
| Δ QFR | 0.28 [0.22- 0.37] | 0.27 [0.20-0.36] | 0.29 [0.23-0.37] | 0.053 |
| Stent mm/lesion | 40 [28-58] | 44 [28-60] | 40 [25-55] | 0.08 |
| Number of stent/patient * | 1 [1-2] | 1 [1-2] | 1 [1-2] | 0.06 |
| Procedure length, min* | 67 [54-86] | 66 [51-82] | 67 [57-88] | 0.06 |
| Contrast media, ml* | 177 [137- 222] | 180 [144-217] | 170 [135-239] | 0.59 |
| DAP, cGy/cm2* | 5576 [3276- 6789] | 5450 [3487-6501] | 5612 [3577-6702] | 0.79 |
| Creatinine peak post-PCI, mg/dl* | 1.05 [0.90- 1.31] | 1.05 [0.90-1.39] | 1.05 [0.90-1.3] | 0.74 |
| Hospitalization length, days* | 4 [3-6] | 4[3-6] | 4 [3-6] | 0.86 |

*PCI: percutaneous coronary intervention. QFR: quantitative flow ratio. DAP: dose area product. *data presented at the patient level*

**Results of AQVA II Trial**

The study flow is shown in **Figure 3**. From December 1, 2022, to June 20, 2023, a total of 305 patients met all eligibility criteria and were randomized, with 101 assigned to the conventional angiography-guided PCI group and 204 to the physiology-guided PCI group, accounting for 331 study vessels (111 and 220 vessels, respectively). Baseline clinical, vessel, and procedural characteristics were well balanced between groups (**Tables 4** and **5**), and CHIP criteria were comparable (**Figure 7**). Nearly all lesions were postdilated (323 cases, 98%), and no major intraprocedural complications occurred in either group.

Within the physiology-guided arm, no significant differences were observed between the angiography-derived and microcatheter-derived FFR subgroups (**Tables 4** and **5**), although operators performed multiple physiological measurements more frequently in the microcatheter subgroup (29% vs 5%; $P < 0.01$).

## Table 4. Patient characteristics

| | Angiography-based (n=101) | Physiology-based (n=204) | p-value | Angiography-derived FFR (n=102) | Microcatheter-derived FFR (n=102) | p-value |
|---|---|---|---|---|---|---|
| Age, years | 70 [61-78] | 70 [62-76] | 0.60 | 69 [62-74] | 71 [63-78] | 0.47 |
| Male sex, no. (%) | 82 (81) | 152 (75) | 0.25 | 70 (69) | 82 (80) | 0.09 |
| **Medical History, no. (%)** | | | | | | |
| Hypertension | 80 (79) | 152 (75) | 0.40 | 77 (75) | 75 (73) | 0.87 |
| Dyslipidemia | 80 (79) | 148 (73) | 0.26 | 79 (77) | 69 (67) | 0.16 |
| Diabetes | 27 (27) | 58 (28) | 0.79 | 26 (25) | 32 (31) | 0.44 |
| Current smoker | 29 (29) | 42 (21) | 0.12 | 25 (24) | 17 (17) | 0.22 |
| Prior MI | 14 (14) | 34 (17) | 0.62 | 14 (14) | 20 (20) | 0.35 |
| Prior PCI | 25 (25) | 47 (23) | 0.78 | 24 (24) | 23 (23) | 0.79 |
| COPD | 9 (9) | 12 (6) | 0.34 | 7 (7) | 7 (7) | 0.77 |
| CKD* | 34 (34) | 58 (28) | 0.36 | 29 (28) | 29 (28) | 0.87 |
| PAD | 17 (17) | 42 (21) | 0.54 | 16 (16) | 26 (25) | 0.12 |
| CVA | 4 (4) | 9 (4) | 0.99 | 3 (3) | 6 (6) | 0.49 |
| **Clinical presentation, no. (%)** | | | | | | |
| STEMI | 25 (24) | 58 (28) | | 30 (29) | 28 (27) | |
| NSTEMI | 22 (22) | 34 (17) | 0.21 | 19 (19) | 15 (15) | 0.39 |
| CCS | 55 (54) | 113 (55) | | 53 (52) | 60 (58) | |

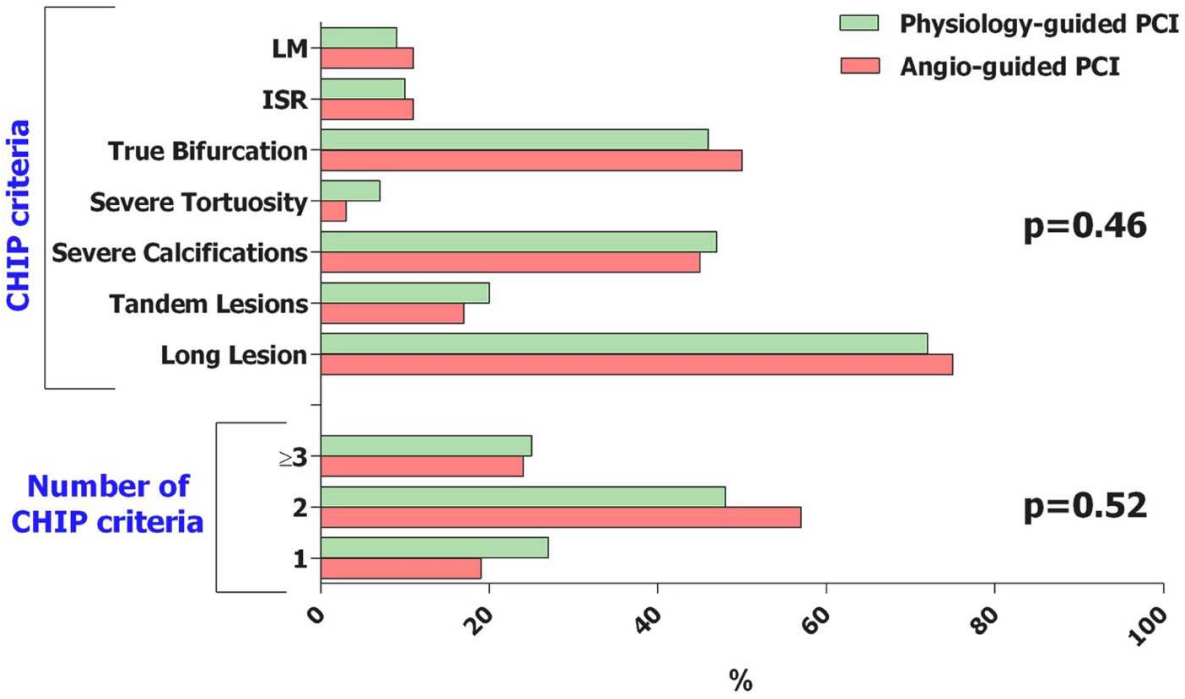
*FFR: fractional flow reserve. MI: myocardial infarction. PCI: percutaneous coronary intervention. COPD: chronic obstructive pulmonary disease. CKD: chronic kidney disease. PAD: peripheral artery disease. CVA: cerebrovascular accident. STEMI: ST-segment elevated myocardial infarction. NSTEMI: non-ST-segment elevation myocardial infarction. CCS: chronic coronary syndrome. *: as defined as estimated glomerular filtration rate <60 ml/min*

## Table 5. Vessel characteristics

| | Angiography-based (n=111) | Physiology-based (n=220) | p-value | Angiography-derived FFR (n=113) | Microcatheter-derived FFR (n=107) | p-value |
|---|---|---|---|---|---|---|
| **Target vessel, no. (%)** | | | | | | |
| LM | 8 (7) | 13 (6) | 0.90 | 6 (5) | 7 (6) | 0.98 |
| LAD | 70 (63) | 139 (63) | | 69 (61) | 70 (65) | |
| LCx | 14 (13) | 32 (15) | | 17 (15) | 15 (14) | |
| RCA | 19 (17) | 36 (16) | | 21 (18) | 15 (14) | |
| **Quantitative coronary analysis** | | | | | | |
| RVD, mm | 3.25±0.37 | 3.22±0.42 | 0.57 | 3.20±0.45 | 3.25±0.40 | 0.48 |
| %DS | 80 [70-90] | 82 [74-90] | 0.11 | 82 [75-89] | 82 [74-90] | 0.61 |
| Lesion length, mm | 30 [20-40] | 31 [22-40] | 0.13 | 32 [21-41] | 31 [20-42] | 0.54 |
| **Procedural details** | | | | | | |
| Predilation, no. (%) | 101 (100) | 204 (100) | 0.97 | 113 (100) | 107 (100) | 0.99 |
| Number of stents | 1 [1-2] | 1 [1-2] | 0.46 | 1 [1-2] | 1 [1-2] | 0.23 |
| 1 | 61 (55) | 137 (62) | 0.17 | 72 (63) | 65 (61) | 0.72 |
| 2 | 39 (35) | 54 (26) | | 28 (25) | 26 (24) | |
| 3+ | 11 (10) | 23 (11) | | 13 (12) | 10 (10) | |
| Total stent length, mm | 40 [28-56] | 36 [24-56] | 0.32 | 38 [24-54] | 36 [25-56] | 0.47 |
| Maximum stent diameter, mm | 3.5 [3-3.5] | 3.5 [3-3.5] | 0.28 | 3.5 [3-3.5] | 3 [3-3.5] | 0.87 |
| Postdilation, no. (%) | 110 (99) | 213 (97) | 0.27 | 107 (95) | 104 (98) | 0.53 |
| Intracoronary imaging, no. (%) | 44 (40) | 89 (40) | 0.89 | 46 (41) | 43 (40) | 0.94 |
| Multiple physiology measurements | - | 37 (17) | - | 6 (5) | 31 (29) | <0.01 |

*FFR: fractional flow reserve. LM: left main. LAD: left anterior descending. LCx: left circumflex. RCA: right coronary artery. RVD: reference vessel diameter. %DS: percentage diameter stenosis.*

**Figure 7. CHIP Criteria in the Enrolled Population Stratified by Group**

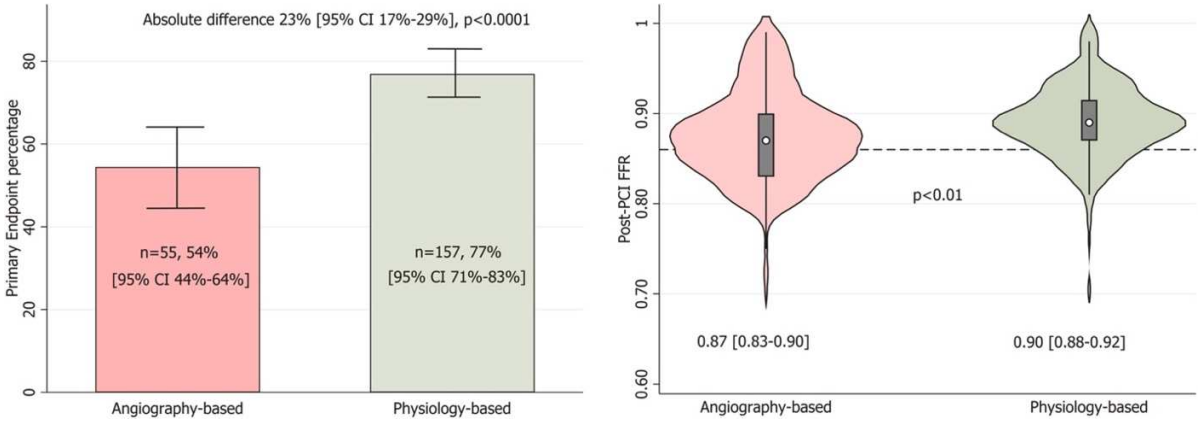



*Rate of single inclusion criteria according to group randomization and number of CHIP criteria per patient. No differences were present for both between the 2 groups.*

## Coprimary endpoint: Physiology-guided vs angiography-guided PCI

Overall, 212 patients (70%) achieved the prespecified invasive post-PCI FFR >0.86. The primary endpoint was reached significantly more often in the physiology-guided group (157 patients, 77%) than in the angiography-guided group (55 patients, 54%), corresponding to an absolute difference of 23% and a relative increase of 30% (95% CI, 17%–29%; P < 0.0001) (**Figure 8**). The values and distribution of post-PCI FFR measurements are reported in **Table 6** and **Figure 8**.

## Figure 8. Coprimary Endpoint: Physiology vs Angiography




*(Left) Rate and percentage of primary endpoint occurrence between the 2 groups. (Right) Violin plot showing the distribution of post-PCI FFR values between the 2 groups. The dotted line represents a post-PCI FFR value of 0.86 (threshold). Circles represent median post-PCI FFR values, boxplots represent 25th and 75th percentiles, and spikes represent upper and lower adjacent values.*

## Table 6. Secondary endpoints at the patient- and vessel-level.

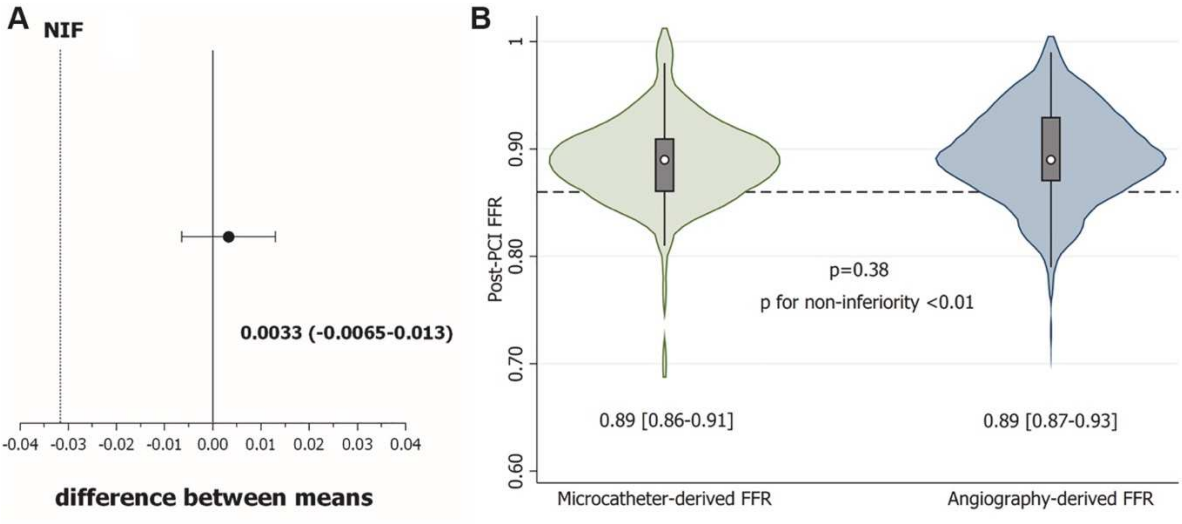
| Patient | Angiography-derived FFR (n=101) | Physiology-based (n=204) | p-value | Angiography-derived FFR (n=102) | Microcatheter-derived FFR (n=102) | p-value |
|---|---|---|---|---|---|---|
| Pd/Pa | 0.935 [0.91-0.96] | 0.95 [0.93-0.97] | 0.0004 | 0.95 [0.94-0.97] | 0.94 [0.93-0.96] | 0.19 |
| Resting index | 0.92 [0.89-0.94] | 0.93 [0.92-0.96] | <0.01 | 0.93 [0.900.96] | 0.93 [0.91-0.94] | 0.65 |
| FFR | 0.87 [0.83-0.90] | 0.90 [0.88-0.92] | <0.01 | 0.89 [0.87-0.93] | 0.89 [0.86-0.91] | 0.38 |
| FFR≤0.80 | 5 (5) | 6 (3) | 0.26 | 2 (2) | 4 (4) | 0.41 |
| Resting index≤0.89 | 30 (30) | 15 (7) | <0.01 | 15 (15) | 10 10) | 0.29 |
| Pd/Pa<0.96 | 83 (82) | 162 (78) | 0.34 | 86 (84) | 76 (75) | 0.11 |
| Procedure length, min | 71 [58-91] | 71 [55-95] | 0.99 | 65 [48-80] | 79 [63-106] | <0.01 |
| X-ray time, min | 15.5 [10-21] | 15 [10-21] | 0.66 | 16 [10-21] | 15 [10-20] | 0.79 |
| Contrast media, ml | 170 [120-212] | 140 [111-180] | <0.01 | 130 [100-160] | 156 [120-198] | <0.01 |

*PCI: percutaneous coronary intervention. QFR: quantitative flow ratio. DAP: dose area product.*

## Coprimary endpoint: Angiography-derived vs microcatheter-derived FFR guidance

The estimated difference in mean post-PCI FFR between the angiography-derived and microcatheter-derived subgroups was +0.0033 (95% CI, −0.0065 to +0.013), with the lower confidence bound above the predefined noninferiority margin (−0.032; P < 0.01), thereby demonstrating noninferiority (**Figure 9**). Consistent with this finding, achievement of post-PCI FFR >0.86 was similar between the microcatheter-derived and angiography-derived subgroups (76 vs 81 cases; absolute difference 4.9%; 95% CI, 1.6%–11%; P = 0.41).

**Figure 9. CHIP Criteria in the Enrolled Population Stratified by Group**




(Left) *Difference between means with 95% CI for post-PCI FFR in the microcatheter- and angiography-derived FFR groups. The dotted line represents the noninferiority (NIF) margin (0.032). (Right) Violin plot showing the distribution of post-PCI FFR values between the microcatheter- and angiography-derived FFR groups. The dotted line represents a post-PCI FFR value of 0.86 (threshold). Circles represent median post-PCI FFR values, boxplots represent 25th and 75th percentiles, and spikes represent upper and lower adjacent values.*

## Secondary endpoints

No significant differences were observed in procedural duration or radiation exposure between the main groups (**Table 6**). However, contrast volume was significantly higher in the angiography-guided group compared with the physiology-guided group (median 170 mL [120–212 mL] vs 140 mL [111–180 mL]; P < 0.0001). This difference was primarily driven by the angiography-derived FFR subgroup (median 130 mL [100–160 mL]; P <

0.001 vs angiography-guided PCI), whereas contrast use in the microcatheter-derived FFR subgroup was comparable to that in the angiography-guided group (median 156 mL [120–198 mL]; P = 0.16).

Within the physiology-guided arm, procedure duration was significantly longer in the microcatheter-derived subgroup than in the angiography-derived subgroup (median 79 minutes [63–106 minutes] vs 65 minutes [48–80 minutes]; P < 0.01). A similar pattern was observed for contrast volume (median 156 mL [120–198 mL] vs 130 mL [100–160 mL]; P < 0.01).

All additional post-PCI physiological metrics were consistent with the primary endpoint, showing significantly greater improvement in the physiology-guided group compared with the angiography-guided group (**Table 6**).

# DISCUSSION

Over the past two decades, the understanding and clinical application of coronary physiology have undergone a profound transformation. Initially reserved for determining the hemodynamic significance of intermediate lesions, physiological assessment has expanded into a comprehensive framework for procedural planning, intraprocedural decision-making, and post-PCI optimization. Seminal studies[4-6] established fractional flow reserve (FFR) as the gold standard for guiding revascularization, demonstrating significant improvements in patient outcomes compared with angiography alone. These foundational trials highlighted a central principle: coronary angiography alone is insufficient to identify ischemia-producing lesions and is an unreliable surrogate for functional disease severity.

Building on this evidence, further investigations explored the utility of physiological indices beyond pre-PCI decision-making, demonstrating that even angiographically successful procedures frequently leave behind physiologically significant residual disease[17-19]. These findings raised critical questions about the role of physiology not only in determining whether to treat but also in informing how to treat and when a PCI result can be considered optimal. The recognition that suboptimal post-PCI physiology correlates with future adverse events, including target vessel failure, myocardial infarction, and restenosis, has repositioned coronary physiology as an essential tool for comprehensive PCI optimization.

Within this context, the AQVA and AQVA-II trials represent landmark contributions. Conducted sequentially and with complementary methodological designs, these trials provide some of the strongest prospective randomized evidence supporting a physiology-driven approach across a spectrum of anatomical complexities.

Both trials independently demonstrated that physiology-based procedural planning is superior to conventional angiography-guided PCI in achieving optimal post-PCI physiological results.

In AQVA trial, QFR-based virtual PCI allowed operators to simulate different stent strategies using angiographic projections, thereby identifying the functionally optimal procedural plan before wire crossing or stent delivery. This approach significantly reduced the incidence of suboptimal post-PCI QFR results and influenced procedural planning in over one-quarter of patients. Notably, this benefit was achieved without increasing

procedural duration, contrast volume, or radiation exposure, an important finding that supports the potential for widespread adoption of angiography-derived physiological guidance.

AQVA II trial extended these principles into a more challenging population undergoing complex high-risk indicated procedures (CHIP). In this setting, a physiology-planned, physiology-guided, and physiology-optimized strategy was not only feasible but also superior to angiography-guided PCI in achieving optimal post-PCI FFR. Importantly, this result was consistent whether physiology was measured using angiography-derived FFR or microcatheter-derived FFR, demonstrating the flexibility and robustness of physiology-based approaches in severe and complex disease.

The value of physiological pullback, whether QFR-derived, wire-based, or microcatheter-based, emerges as a central theme across both trials. Prior evidence has demonstrated that longitudinal physiological mapping allows precise identification of focal versus diffuse disease, geographic mismatch, serial lesions, and residual disease burden[18,19,32]. AQVA trial used these principles by incorporating QFR-based pullback and virtual PCI simulation, enabling computational prediction of the expected functional gain from candidate stent strategies. This approach not only identified optimal landing zones but also prevented both overtreatment and undertreatment.

In AQVA trial, a QFR-derived plan frequently advised against treating lesions deemed significant by angiography, thereby avoiding unnecessary stent placement. Conversely, it often identified physiologically significant stenoses overlooked angiographically, addressing a common mechanism of residual ischemia. These insights highlight a major limitation of angiography: its inability to reliably characterize the functional relevance of disease, particularly in the presence of diffuse atherosclerosis where percent diameter stenosis is an inadequate descriptor of hemodynamic impact.

The AQVA-II trial addressed a key gap in evidence by evaluating physiology-based PCI in CHIP lesions, a setting where anatomical complexity, lesion tortuosity, heavy calcification, bifurcations, long lesions, and hemodynamic instability have historically discouraged the use of pressure-wire based physiology. AQVA-II trial demonstrated conclusively that integrating physiology from the outset of procedural planning increases procedural efficiency, reduces unnecessary steps, and improves final FFR without prolonging the procedure.

Importantly, AQVA-II trial overcame limitations observed in previous trials such as TARGET-FFR[19], where a substantial proportion of physiologically suboptimal cases did not undergo optimization due to operator reluctance or workflow constraints. By contrast, AQVA-II trial included physiology into the planning stage, ensuring that optimization was systematic, anticipated, and feasible, thus avoiding the “post-hoc” approach that had limited the effectiveness of physiology-guided optimization in prior studies.

A major strength of AQVA-II is the direct comparison between angiography-derived FFR (QFR) and microcatheter-derived FFR. Both modalities proved equally effective in guiding PCI and in achieving optimal post-PCI FFR values, although each presents distinct advantages and limitations.

Angiography-derived FFR (QFR) is a wire-free, adenosine-free, and minimally invasive technique that enables rapid computation, full-vessel physiological pullback, and virtual PCI simulation. Its principal limitations relate to its strong dependence on angiographic image quality and on operator expertise, which can influence the accuracy of both the reconstruction and the simulated procedural plan. Furthermore, QFR tends to produce higher post-PCI physiological values compared with invasive FFR. The mechanisms underlying this discrepancy remain incompletely understood, but likely include flow-related factors, limitations in angiography-based reconstruction of long diffuse disease and higher flow rates across stented segments. Despite these differences, the clinical utility of QFR for planning and procedural guidance remains strong, as demonstrated by the improved physiological outcomes and reduced suboptimal physiology observed in AQVA trial.

Microcatheter-derived FFR, on the other hand, is highly reliable even in complex anatomies, facilitates repeated pullbacks, and overcomes several drawbacks associated with pressure-wire handling. However, it shares the inherent disadvantages of invasive physiology, including the requirement for hyperemia and the procedural burden associated with intracoronary instrumentation.

The demonstration of non-inferiority between these tools provides meaningful flexibility to catheterization laboratories, enabling the choice of modality tailored to local expertise, workflow, and patient characteristics.

Together, AQVA and AQVA-II reinforce the limitations of angiography as a standalone tool for PCI guidance. Across simple and complex anatomy, physiology-guided PCI consistently achieves superior functional outcomes. These findings are concordant with the 2023 EAPCI consensus[20], which advocates the integration of pre-PCI physiological assessment, pullback-derived disease pattern recognition, virtual PCI simulation, and systematic post-PCI verification as essential components of modern PCI practice.

These concepts represent a major step toward precision PCI and may ultimately influence long-term clinical outcomes, pending confirmation from ongoing randomized trials.

**Limitations and Future Directions**

Both trials were conducted in high-volume centers with established physiology expertise and dedicated workflows, which may limit generalizability. The selected tools (especially microcatheter-derived FFR and QFR) require proficiency and standardized processes that may not be uniformly available. Additionally, as physiological assessment cannot evaluate stent expansion or apposition, intravascular imaging remains an indispensable complementary tool.

Future research should investigate the clinical outcome benefits of physiology-guided PCI through adequately powered, prospective randomized trials. Additional areas of investigation include the development of integrated procedural planning strategies that combine coronary physiology with intravascular imaging, as well as the use of artificial intelligence–based platforms capable of simulating PCI to support real-time decision-making and optimization.

# CONCLUSIONS

The AQVA and AQVA-II trials collectively represent a pivotal advancement in the field of coronary physiology–guided percutaneous coronary intervention.

Across both trials, physiology-guided PCI, using either angiography-derived quantitative flow ratio (QFR), pressure wire–based FFR, or microcatheter-derived FFR, resulted in substantially higher rates of optimal post-PCI physiological outcomes. The magnitude and consistency of benefit across different modalities and anatomical complexities strongly challenge the continued reliance on angiography alone as the primary determinant of PCI strategy.

AQVA demonstrated that even in non-complex lesions, angiography is insufficient to guide precise stent placement and predict post-procedural physiology. AQVA-II extended these findings to complex high-risk indicated procedures (CHIPs), proving that physiology-guided PCI is feasible, safe, and superior even in the most challenging anatomies.

The AQVA trial demonstrates that physiology-guided planning does not increase procedural time or contrast burden, thereby confirming the scalability of virtual PCI approaches in contemporary practice.

Both AQVA and AQVA-II reinforce the prognostic importance of achieving optimal post-PCI physiology. Suboptimal post-PCI indices reflect residual focal disease, diffuse atherosclerosis, stent underexpansion, or untreated segments, all of which are associated with higher risks of future adverse events. The trials highlight that angiographic success does not equate to physiological success, emphasizing the need for objective, quantifiable functional confirmation.

A major contribution of AQVA-II is the demonstration of noninferiority of microcatheter-derived FFR compared with conventional pressure-wire measurements. Microcatheters offer several practical and procedural advantages in complex anatomical settings, including improved trackability and reduced risk of wire bias during pullback.

The integration of AQVA and AQVA-II findings supports a broader redefinition of PCI quality standards. A physiology-centered workflow should include:

1. Pre-PCI physiological mapping (QFR, FFR, or microcatheter-derived pullback).

2. Functionally informed stent strategy based on pullback analysis or virtual PCI.

3. Post-PCI physiological confirmation to ensure functional completeness and detect residual disease.

4. Targeted optimization when post-procedural indices are suboptimal.

This structured physiology-guided strategy moves PCI toward a more precise, patient-specific, and outcome-driven intervention.

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