Intracoronary Physiology and Imaging

Amir Lotfi, M.D. FRCPC FSCAI
Chief, Division Cardiovascular Medicine
Professor of Medicine
UMass Chan School of Medicine-Baystate
May 16, 2026

Conflict of Interest

- Microvascular advisory board – Phillips

Objectives

- Explained the physiological principles of underlying invasive and noninvasive coronary measurement
- Interpret the randomized evidence of physiology-guided PCI and distinguish settings where FFR/IFR strongly used to perform settings where routine or universal use is not supported
- Compare OCT and IVUS for lesion assessment
- Apply a mechanism-based approach to MINOC/INCOA

Why this matters

Angiography shows anatomy. Physiology and imaging explain mechanism.

Angiography

The silhouette: stenosis, vessel course, TIMI flow, collaterals

→

Mechanism

Ischemia? plaque rupture? erosion? calcium? underexpansion? spasm? microvascular disease?

→

Actionable decision

Defer, optimize, modify calcium, treat spasm, intensify prevention, or stent safely

Clinical frame: Treat the mechanism — not just the angiographic appearance.

Bridge slide for intracoronary physiology + imaging

Case 1: 56-Year-Old Woman with Inferior Ischemia

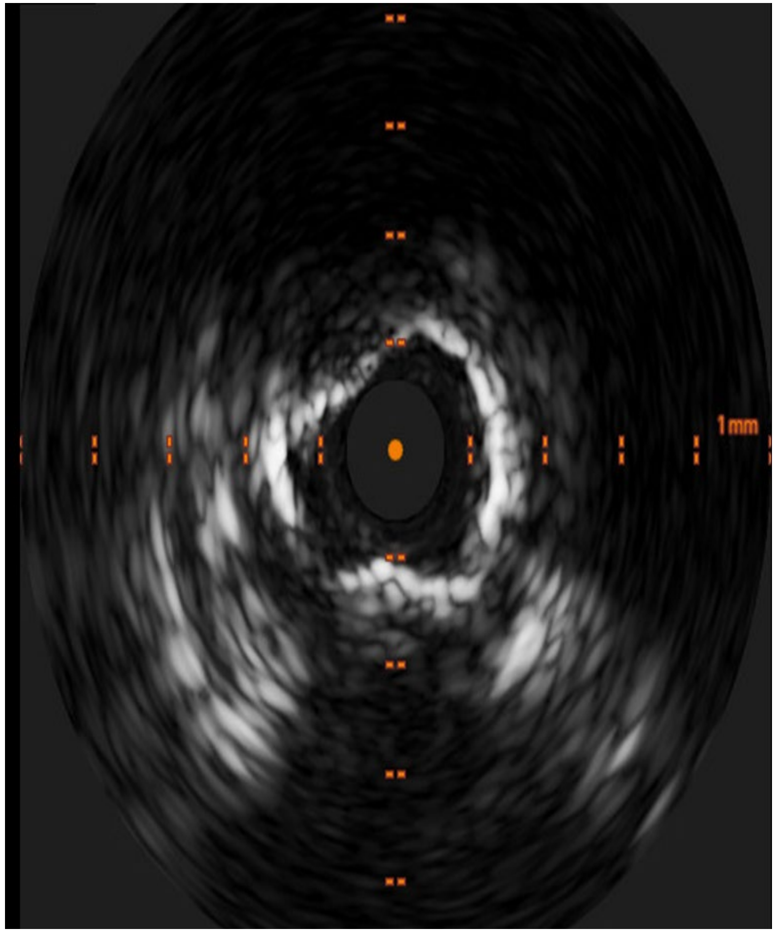
- 56-year-old woman with past medical history of
- diabetes mellitus,
- hypertension,
- dyslipidemia,
- class II obesity,
- coronary artery disease status post LAD stenting December 14, 2018
- who had an episode of shortness of breath and chest heaviness and subsequently had a stress test which demonstrated inferior ischemia

Case 1: RCA Angiogram

Case 1: iFR Assessment — RCA

Case 1: FFR Measurement — RCA

Case 1: Pre-PCI IVUS — RCA



Pre-PCI IVUS of the proximal RCA demonstrates a large-caliber vessel with eccentric, heterogeneous atherosclerotic plaque burden. The lumen is preserved in this frame, without clear evidence of severe circumferential calcification or major acoustic shadowing.

Case 1: Post-PCI RCA Angiogram

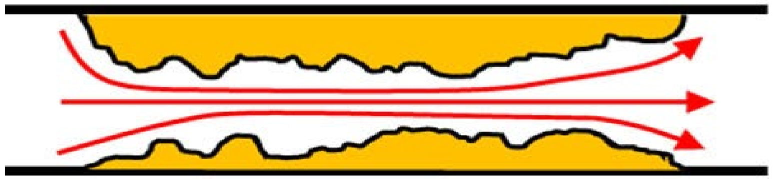
Case 1: Post-PCI FFR — Confirm Physiological Success

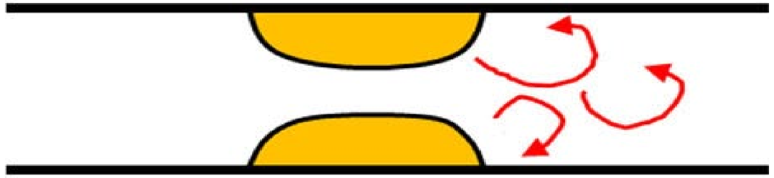
FFR/iFR Discordance: Pressure Wire Pullback

$$\Delta P = f.Q + s.Q^2$$

f. = friction coefficient

s. = separation coefficient



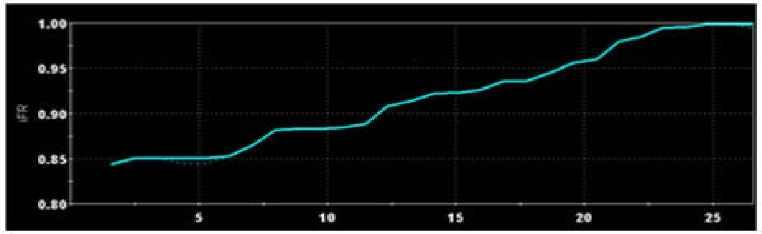


Moderate Gradient at Rest

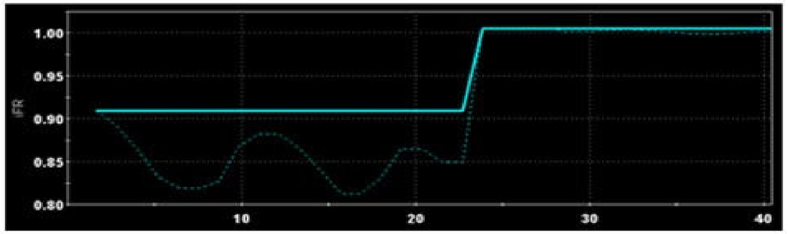
Mild Increase at Hyperemia

Small Gradient at Rest

Large Increase at Hyperemia



FFR 0.82 iFR 0.85



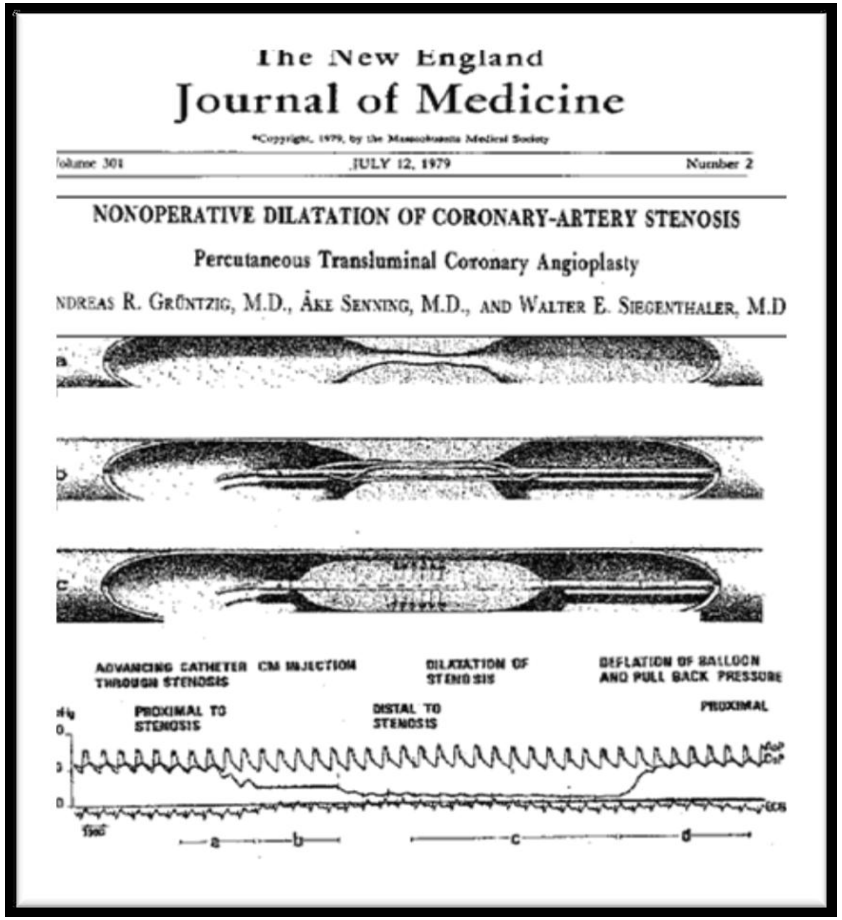
FFR 0.79 iFR 0.91

FFR-/iFR+ in Diffuse disease

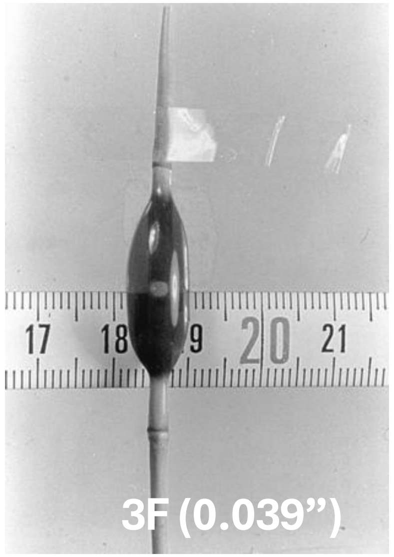
FFR+/iFR- in Focal disease

Takayuki Warisawa. Circulation: Cardiovascular Interventions. Physiological Pattern of Disease Assessed by Pressure-Wire Pullback Has an Influence on Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance, Volume: 12, Issue: 5, DOI: (10.1161/CIRCINTERVENTIONS.118.007494)

Coronary Hemodynamics: The Gruentzig Legacy


The New England
Journal of Medicine
*Copyright, 1979, by the Massachusetts Medical Society
Volume 301 JULY 12, 1979 Number 2

NONOPERATIVE DILATATION OF CORONARY-ARTERY STENOSIS
Percutaneous Transluminal Coronary Angioplasty
ANDREAS R. GRÜNTZIG, M.D., ÅKE SENNING, M.D., AND WALTER E. SIEGENTHALER, M.D.

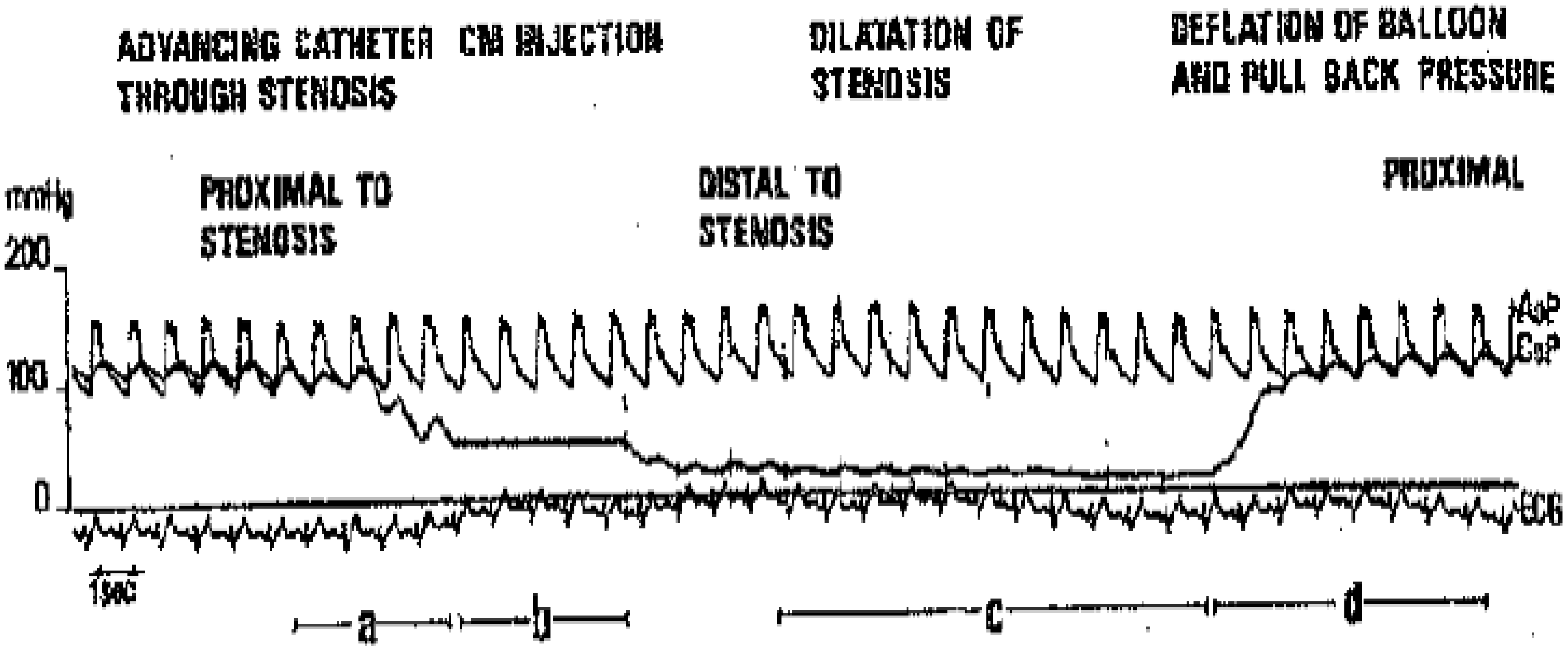


First Measurement of trans-coronary pressure gradient

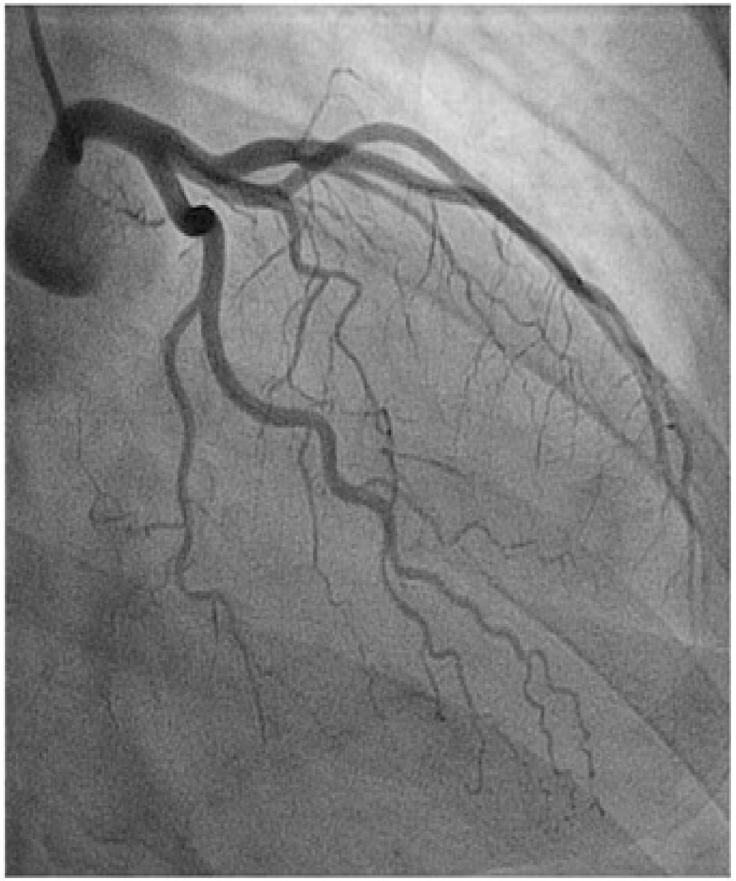
Andreas Gruentzig first reported that a pressure gradient ≤15 mm Hg after percutaneous coronary angioplasty is associated with a lower risk of restenosis

Circulation, 73 (1986), pp. 1223–1230

Trans Coronary Pressure Gradient



Epicardial Coronary Artery and Microcirculation

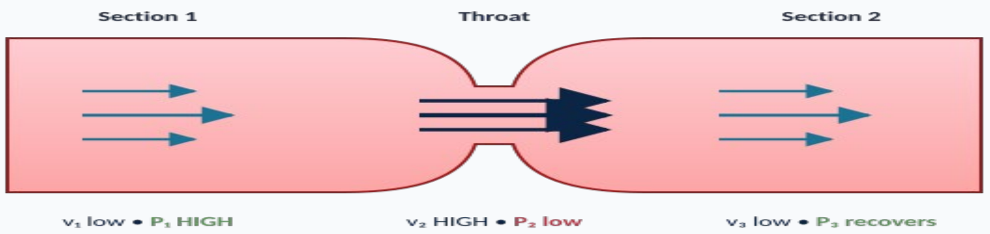


Fluid Dynamics of Coronary Physiology

Four physical principles that underpin pressure-flow relationships in the coronary circulation

1 Bernoulli's Principle

Conservation of energy: as velocity rises, pressure falls

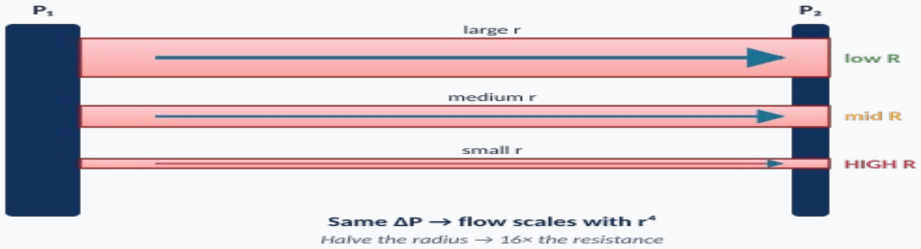


$P + \frac{1}{2}\rho v^2 = \text{constant} \quad \rightarrow \quad \Delta P \approx 4 \cdot v^2$ (modified clinical form)

Basis for echo-Doppler valve gradients and intracoronary pressure drops

2 Resistance

Ohm's law analog for hemodynamics

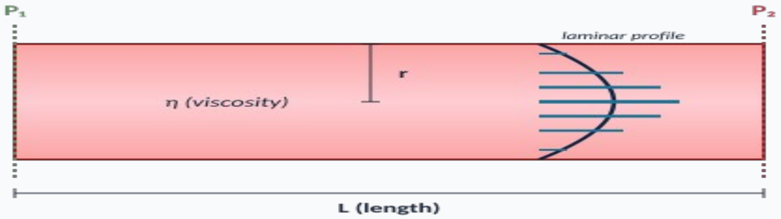


$R = \Delta P / Q \qquad SVR = (MAP - CVP) / CO \times 80$

Quantifies microvascular tone — basis of IMR and CFR

3 Poiseuille's Law

Laminar flow through a rigid cylindrical tube

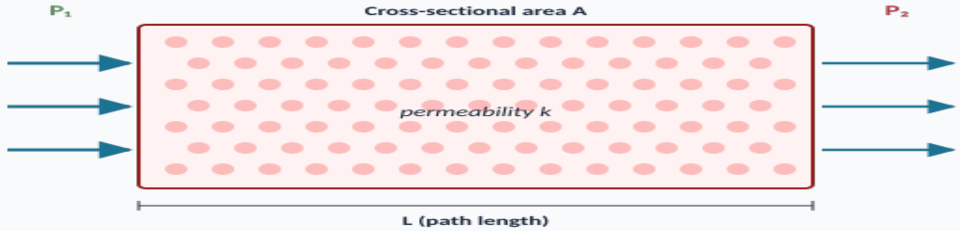


$Q = (\pi \cdot \Delta P \cdot r^4) / (8 \cdot \eta \cdot L) \qquad R = 8\eta L / \pi r^4$

Why a small luminal narrowing causes a disproportionate fall in flow

4 Darcy's Law

Flow through a porous medium — capillary perfusion



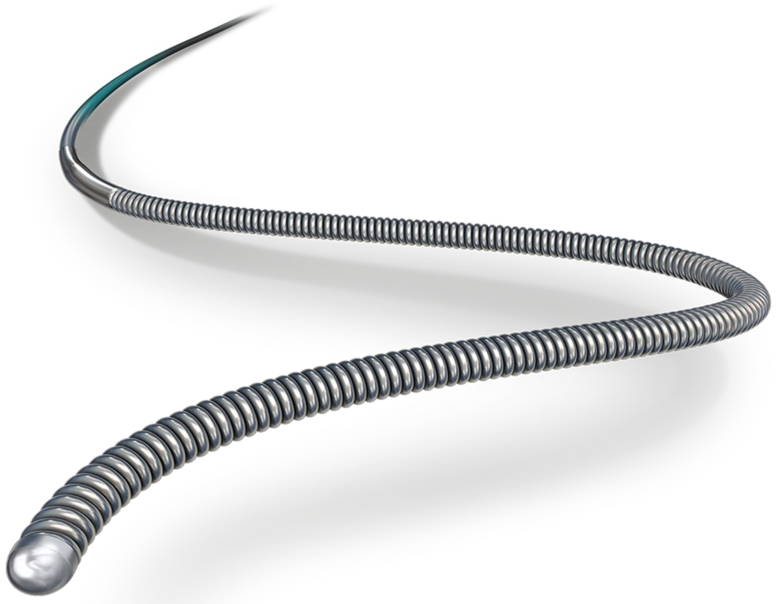
$Q = (k \cdot A \cdot \Delta P) / (\mu \cdot L) \quad \rightarrow \quad Q \propto \Delta P / R$

Framework for tissue perfusion and myocardial blood-flow models

CLINICAL SYNTHESIS: *FFR Bernoulli (pressure drop across a stenosis) and Poiseuille (r^4 dependence); IMR isolates resistance; perfusion imaging probes Darcy-type flow.*

The 0.014" Pressure Sensor Guidewire

$$FFR = \frac{\text{Maximum flow in presence of stenosis}}{\text{Normal maximum flow}} = \frac{Q^S_{max}}{Q^N_{max}} = \frac{(Pd-Pv)/R}{(Pa-Pv)/R}$$



0.014 inch (0.3556 mm) sensor tipped guidewire

FFR Validation — Pijls et al. NEJM 1996

Overall results for FFRmyo	Percentage
Sensitivity	88 %
Specificity	100 %
Pos. Pred. Value	100 %
Neg. Pred. Value	88 %
Accuracy	93 %

All pts with FFR below 0.75 (21 pts) had inducible ischemia whereas in the majority, 87.5 % (21/24 pts) of patients with FFR higher than 0.75 ischemia could not be induced.

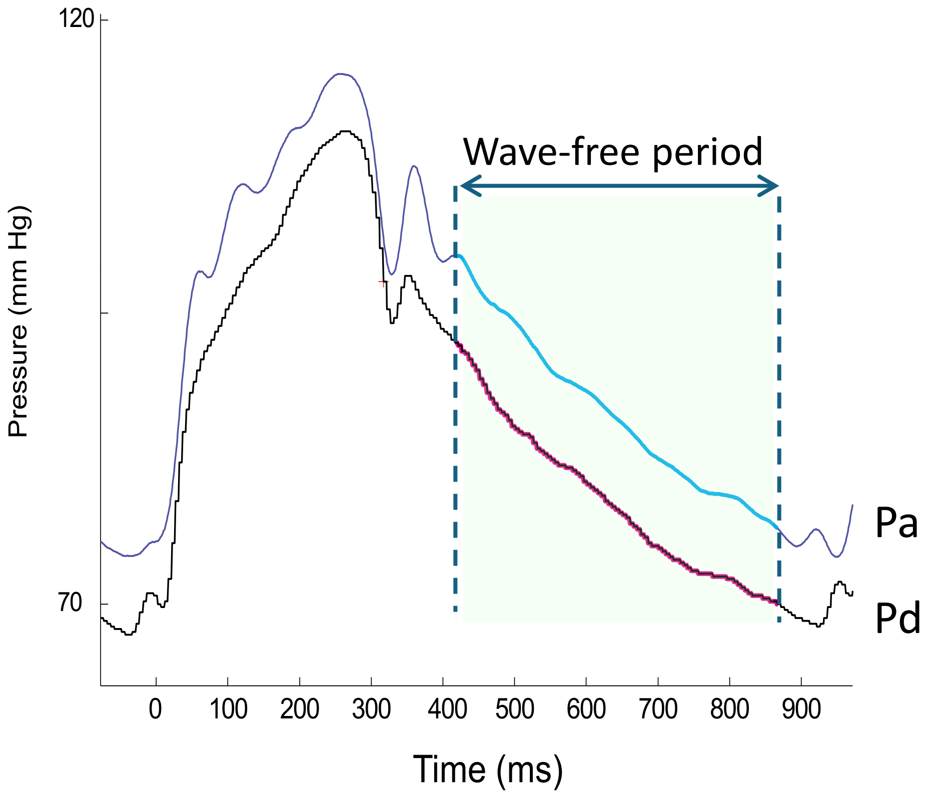
Pijls et al. NEJM 1996;334

Instantaneous Wave-Free Ratio (iFR)

iFR = instantaneous wave-free ratio

Definition:

Instantaneous pressure gradient, across a stenosis during the wave-free period, when resistance is constant and minimised in the cardiac cycle



EVIDENCE SYNTHESIS • 2007 – 2022

FFR and iFR randomized evidence

A critical appraisal of DEFER, FAME, FAME 2, DEFINE-FLAIR, iFR-SWEDEHEART, FLOWER-MI, RIPCORD 2, FUTURE, FAME 3, and FLAVOUR

DEFER 2007	**FAME** 2009	**FAME 2** 2012	**DEFINE-FLAIR** 2017
iFR-SWEDEHEART 2017	**FLOWER-MI** 2021	**FAME 3** 2022	**FLAVOUR** 2022

■ supportive ■ equivalence ■ neutral / negative

Synthesizing data from ~14,000 randomized patients across 10 RCTs

Limitations of Routine Physiology Guidance — A Structured Appraisal

Eight domains where the FFR / iFR evidence does not support universal application

Domain	Limitation	Trial Evidence	Effect Size / Magnitude
1. No benefit from routine systematic FFR	Wiring every epicardial vessel does not improve hard outcomes over angiography alone	RIPCORD 2 (n = 1,100) FUTURE (n = 927; stopped early)	**RIPCORD 2: 8.7% vs 9.5% (P = 0.64). FUTURE: trend toward harm with FFR**
2. No benefit in STEMI multivessel revasc.	FFR-guided complete revascularization did not outperform angiography in post-STEMI patients	FLOWER-MI (n = 1,170) STEMI + multivessel disease	**Death / MI / urgent revasc HR 1.32 (0.78–2.23) P = 0.31**
3. Did not match CABG in 3-vessel CAD	FFR-guided PCI failed non-inferiority vs surgery in three-vessel disease	FAME 3 (n = 1,500) 48 centers, 1-yr follow-up	**10.6% FFR-PCI vs 6.9% CABG HR 1.50 (1.10–2.20) CABG favored**
4. Early periprocedural harm with PCI	Even in FFR-positive stable lesions, the first week after PCI carries a sharp excess hazard	FAME 2 (n = 888) landmark 0–7 d vs 8 d–2 yr	**0–7 d: HR 9.01 (1.13–72.0) for death / MI in PCI arm P-interaction = 0.002**
5. Benefits driven by revasc., not mortality	The dominant signal across positive trials is fewer repeat procedures — not fewer deaths	FAME (1-yr): MACE driven by revasc. FAME 2 (5-yr): urgent revasc, not death/MI	**Mortality reductions absent or inconsistent across the physiology trial portfolio**
6. Hemodynamic confounders degrade accuracy	Microvascular disease, LV hypertrophy, prior MI, and aortic stenosis distort pressure-derived indices	Mechanistic / physiologic literature; reflected in trial exclusion criteria	**Inadequate hyperemia and wire drift produce false negatives & positives**
7. FFR vs iFR — no clinical winner	Two large RCTs show iFR and FFR are clinically equivalent; choice is operator / system, not evidence	DEFINE-FLAIR (n = 2,492) iFR-SWEDEHEART (n = 2,037)	**DEFINE-FLAIR: HR 0.95 (0.68–1.33). SWEDEHEART: HR 1.12 (0.79–1.58)**
8. Procedural burden & equipment cost	Adds pressure wire, adenosine (for FFR), time, and per-case cost without consistent hard-event payoff	All trials — extra wire, time, adenosine vasodilation (iFR removes adenosine only)	**Cost per case and lab throughput must be weighed against marginal benefit**

BOTTOM LINE: *Physiology guides lesion selection well in stable disease — but routine, systematic, or universal use is not evidence-based across every PCI scenario.*

The Physiology Evidence Splits Three Ways

Supportive trials, equivalence trials, and neutral / negative trials — by clinical setting

SUPPORTIVE

DEFER

2007 • n = 325

Intermediate stenoses, FFR ≥0.75

5-yr cardiac death / MI

Defer 3.3% vs Reference 15.7% (P = 0.003)

FAME

2009 • n = 1,005

Multivessel CAD; FFR-guided vs angio

1-yr MACE

13.2% FFR vs 18.3% Angio (P = 0.02)

FAME 2

2012 • n = 888

Stable CAD with FFR ≤0.80; PCI+MT vs MT

Death / MI / urgent revasc

Significantly lower with PCI (driven by urgent revasc)

EQUIVALENCE

DEFINE-FLAIR

2017 • n = 2,492

iFR vs FFR-guided revascularization

1-yr MACE (non-inferiority)

HR 0.95 (0.68–1.33) P = 0.78

iFR-SWEDEHEART

2017 • n = 2,037

Stable angina / ACS; iFR vs FFR

1-yr MACE (non-inferiority)

HR 1.12 (0.79–1.58) P = 0.007 for NI

FLAVOUR

2022 • n = 1,682

Intermediate stenoses; FFR vs IVUS

24-mo death / MI / revasc

8.1% FFR vs 8.5% IVUS (P = 0.01 for NI)

NEUTRAL / NEGATIVE

FLOWER-MI

2021 • n = 1,170

STEMI + multivessel disease

Death / MI / urgent revasc

HR 1.32 (0.78–2.23) P = 0.31 — no superiority

RIPCORD 2

2022 • n = 1,100

Stable angina / NSTEMI; systematic FFR

Composite hierarchical

8.7% Angio vs 9.5% +FFR P = 0.64 — no benefit

FAME 3

2022 • n = 1,500

Three-vessel CAD; FFR-PCI vs CABG

1-yr death / MI / stroke / revasc

10.6% vs 6.9% — HR 1.50 Non-inferiority NOT met

Physiology works best for stable-disease lesion selection. Outside that niche, the evidence base softens or disappears.

From Universal Tool to Targeted Decision Aid

Reframing the role of FFR and iFR in 2026

CHALLENGED: Routine physiology in every PCI

1. **Systematic FFR in every epicardial vessel**

   RIPCORD 2 and FUTURE show no benefit; FUTURE stopped early

2. **FFR-guided complete revasc. in STEMI**

   FLOWER-MI shows angiography is at least as good

3. **FFR-PCI as a CABG substitute in 3VD**

   FAME 3 failed non-inferiority — CABG remains preferred

4. **Mortality-reduction expectations**

   Benefits in positive trials are driven by revascularization, not death

SUPPORTED: Physiology as a targeted decision aid

1. **Deferring PCI in functionally non-significant lesions**

   DEFER: 5-yr cardiac death/MI 3.3% with deferral — safe

2. **Lesion selection in stable multivessel CAD**

   FAME / FAME 2: fewer events when FFR drives the decision

3. **Intermediate stenoses: FFR matches IVUS**

   FLAVOUR: FFR non-inferior, with ~20% fewer PCIs performed

4. **iFR substitutes for FFR when adenosine is undesirable**

   DEFINE-FLAIR + iFR-SWEDEHEART: clinically equivalent

SYNTHESIS: Physiology earned its place by identifying which stable lesions to **leave alone** — not by becoming a universal mandate. Best used as a **targeted decision aid**, *chosen by clinical context, not by reflex.*

CIRCULATION · 2026 · ORIGINAL RESEARCH

Determining the Physiological Threshold for Angina

ORBITA-FIRE: A Double-Blind, Randomized, Placebo-Controlled Study

Ahmed-Jushuf F, Foley MJ, Chotai S, Rajkumar CA, et al.
for the ORBITA-FIRE Investigators

National Heart and Lung Institute, Imperial College London

Circulation. 2026;153:00–00 · DOI: 10.1161/CIRCULATIONAHA.125.078738

The clinical problem

In stable coronary artery disease, the principal goal of percutaneous coronary intervention (PCI) is symptom relief.

Current guidelines give a Class I (Level A) recommendation for ischemia-guided PCI using fixed physiological thresholds:

FFR	RFR
≤ 0.80	≤ 0.89
hyperemic threshold	*non-hyperemic threshold*

Fractional flow reserve (FFR) and resting full-cycle ratio (RFR)

The disconnect

These thresholds were validated to detect flow-limiting stenoses — **not to predict symptom relief.**

59%

of patients remained symptomatic after PCI in ORBITA-2 despite normalized post-PCI physiology

⅓

of patients in ISCHEMIA were asymptomatic despite moderate-to-severe ischemia

STUDY DESIGN

A placebo-controlled mechanistic study

Multicenter (6 UK sites) | Double-blind | Randomized | Placebo-controlled

65
patients enrolled
Sept 2022 – Mar 2025

1-vessel
severe CAD
with confirmed ischemia

12 wk
follow-up
with daily ORBITA app symptom logging

KEY INNOVATION

After successful PCI, an in-stent balloon was incrementally inflated to titrate Pd/Pa until angina occurred — at rest, low-, and high-intensity supine bicycle exercise.

Each angina threshold was validated against a placebo (deflated) balloon inflation in randomized, blinded fashion.

A 3-step protocol, at 3 workloads

1 Find the threshold

Incremental balloon inflation lowers Pd/Pa by ~0.02 every 5–10 sec until angina onset. Threshold Pd/Pa recorded.

2 Verify with placebo

Two paired inflations in randomized order: one real (at threshold Pd/Pa), one placebo (deflated). Both patient and assessor blinded.

3 Measure physiology

At threshold Pd/Pa: record RFRangina (non-hyperemic), then adenosine-induced FFRangina.

Repeated in randomized order across 3 cardiac workloads

REST

no exercise · mean HR 67 bpm

LOW INTENSITY

50 W supine cycling · mean HR 90 bpm

HIGH INTENSITY

peak target HR · mean HR 108 bpm

A symptomatic, medically treated cohort

63.9

± 8.7 yrs

Mean age

74%

Male

91%

CCS class II–III angina

69%

Hypertension

23%

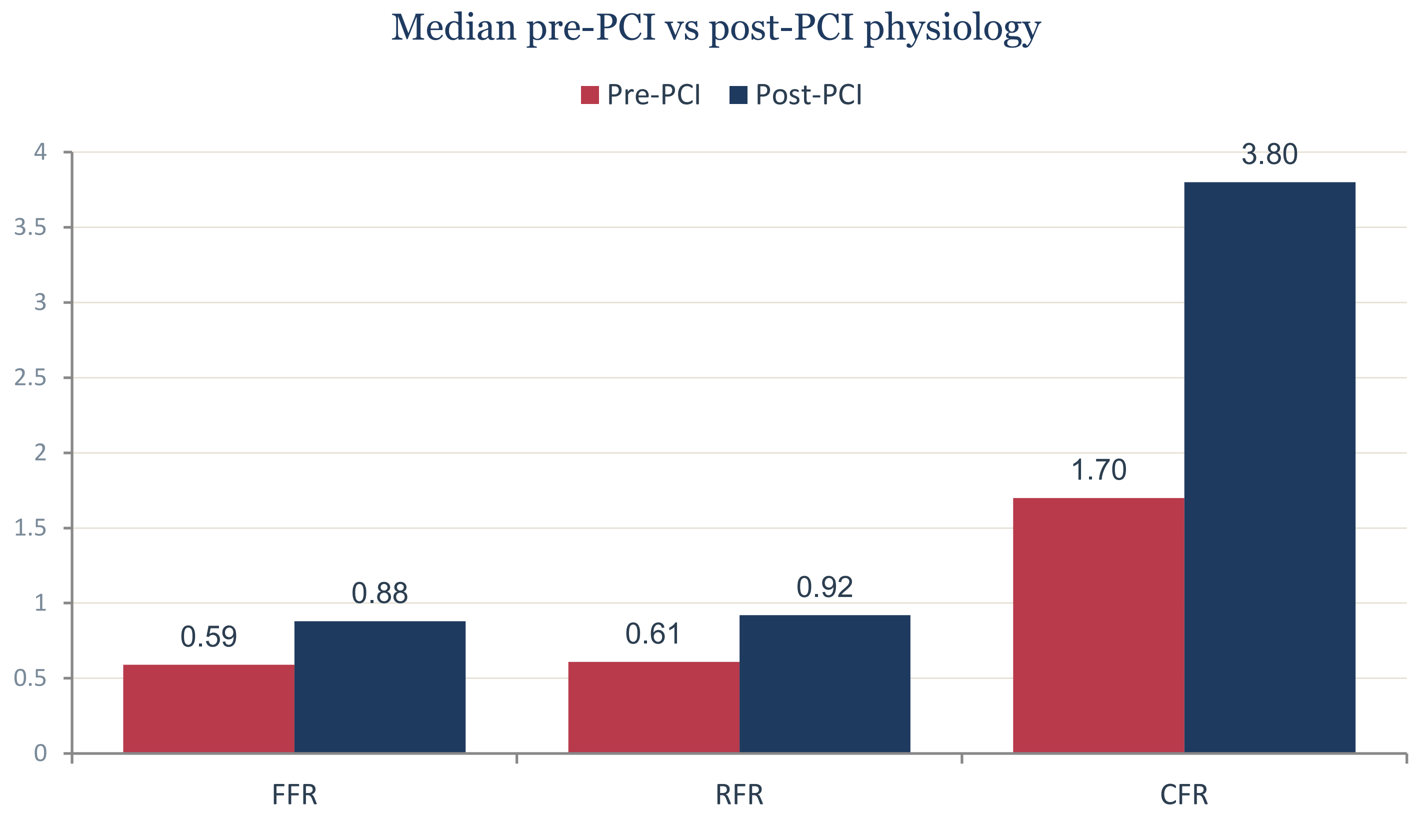
Diabetes

85%

On ≥1 antianginal drug

Median angina duration before enrollment: 36 weeks (IQR 26–53). 78.5% had Rose angina. Target vessel: LAD 72%, RCA 19%, other 9%.

Physiology was fully normalized after PCI



Successful PCI

100%

imaging-guided stent optimization

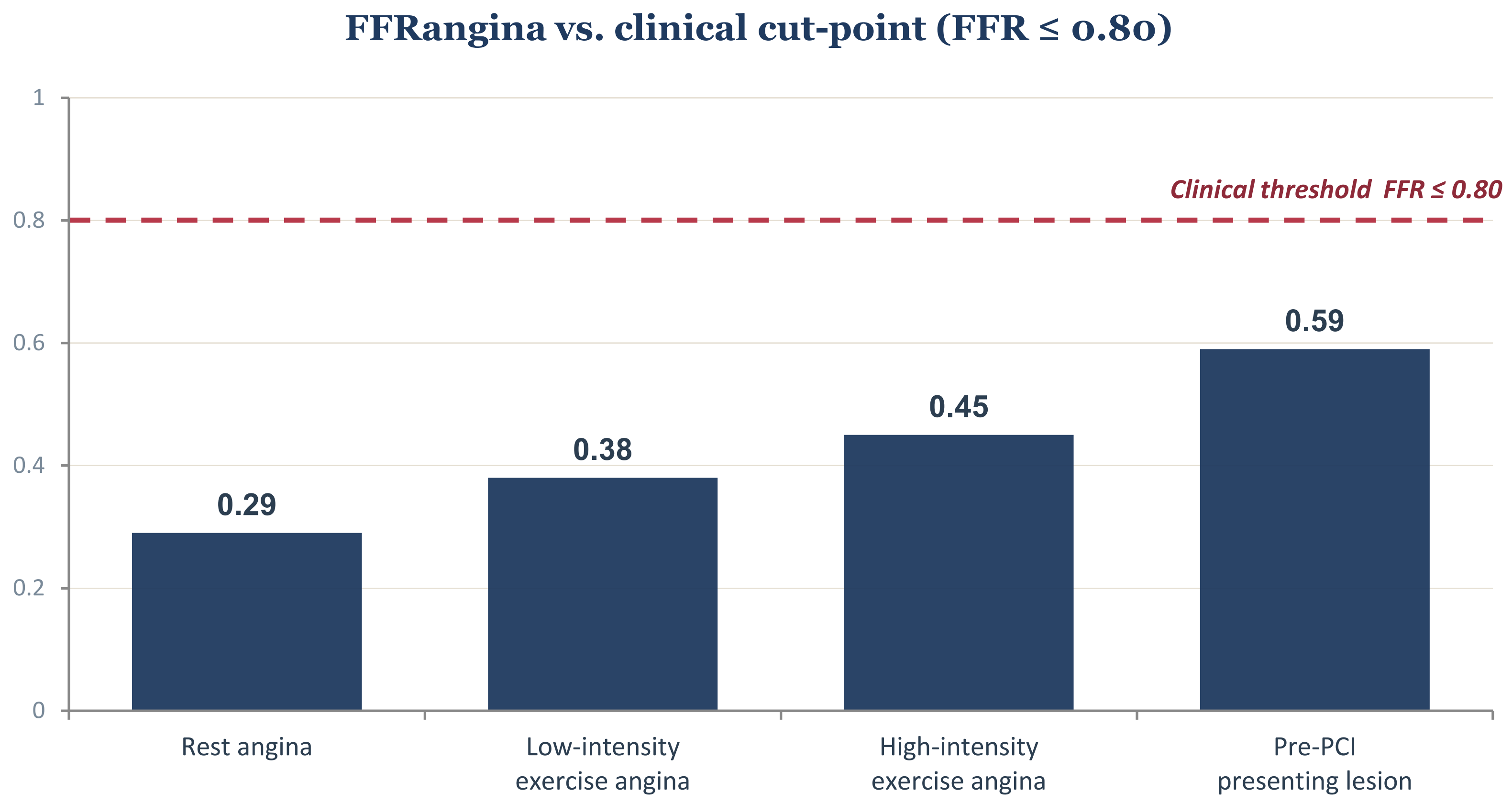
0

serious adverse events, dissections, stent thromboses or periprocedural MI

Index of microvascular resistance also fell (29 → 20)

CFR = coronary flow reserve. Values are medians.

FFRangina was far below the clinical threshold



All thresholds

# P < 0.001

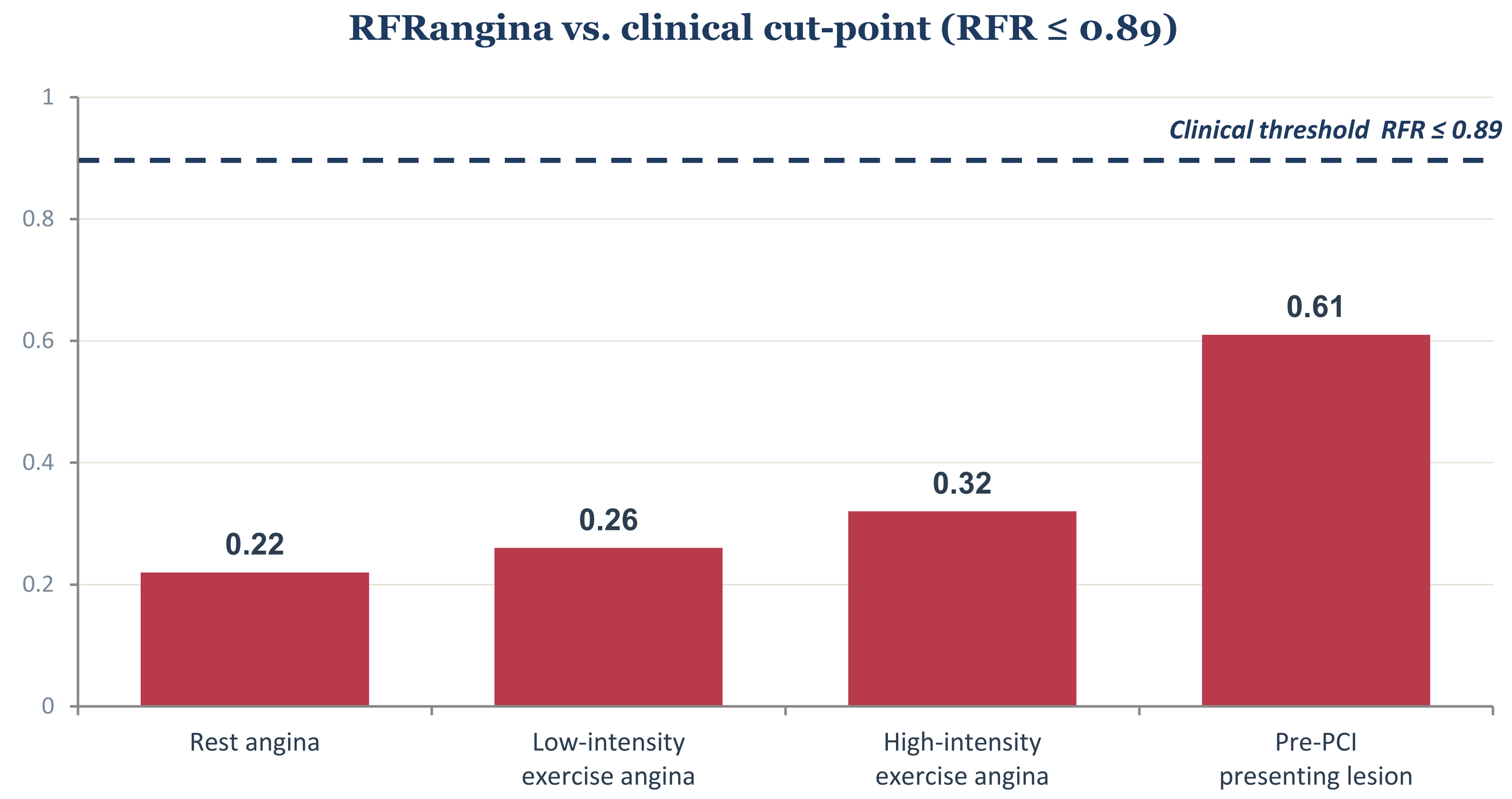
vs. FFR ≤ 0.80

FFRangina rose progressively with workload (P < 0.001 between every pair).

Symptom onset is workload-dependent — a single fixed cut-point cannot capture it.

Values are cohort medians; n = 65 (rest, high) and n = 61 (low-intensity).

RFRangina: same pattern, well below 0.89



Highest threshold

0.32

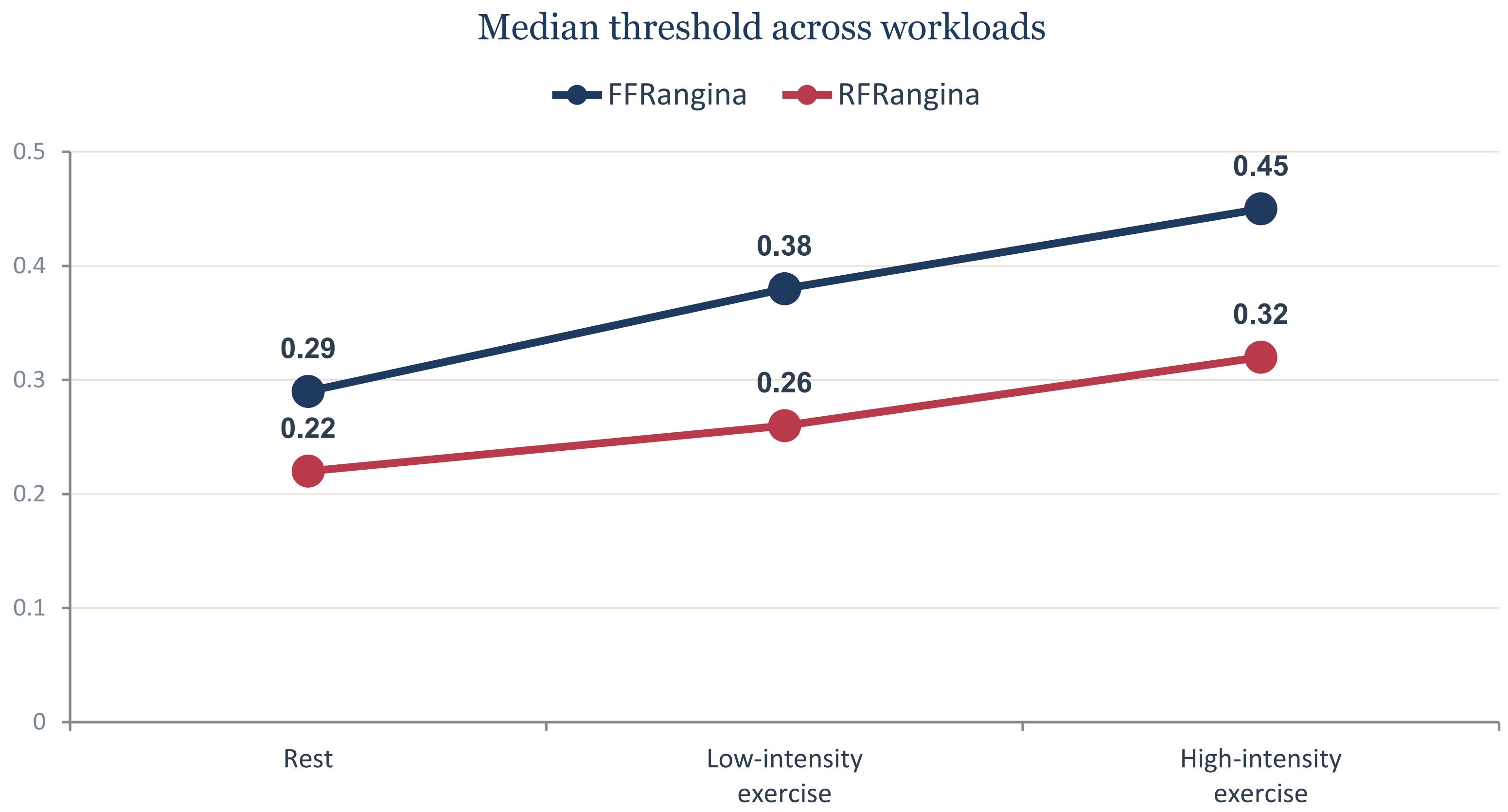
median RFRangina at peak exercise — still well below 0.89

Rest → low: P = 0.007
Low → high: P = 0.007
Rest → high: P < 0.001

Patients develop angina at lesion severities most cardiologists would not intervene on.

Values are cohort medians. Within-patient comparisons by Friedman test.

Higher workload, higher threshold



Cardiac workload achieved

	HR	Lac	RPP
Rest	67	1.1	9 094
Low	90	3.0	13 429
High	108	4.3	17 128

HR = supine peak heart rate (bpm). Lac = lactate (mmol/L). RPP = rate-pressure product.

RPP and HR rose significantly across every pair-wise comparison (P < 0.001).

Angina thresholds were highly reproducible

Rest	Low-intensity exercise	High-intensity exercise
76.9%	**80.3%**	**80.0%**
50 / 65	*49 / 61*	*52 / 65*

KEY FINDING

Lower FFRangina and RFRangina thresholds were consistently associated with greater symptom reproducibility ($P \leq 0.015$ across all workloads) — patients with the strictest physiological threshold for angina had the most reliably reproducible symptoms.

Lower thresholds = greater PCI benefit

During high-intensity exercise, patients with the lowest FFRangina and RFRangina experienced the largest reduction in daily angina episodes after PCI.

Lower quartile vs upper quartile

Bayesian ordinal regression of daily angina counts, follow-up conditioned on baseline; lower physiological thresholds → fewer post-PCI angina episodes.

In contrast, at rest the benefit was attenuated — both quartile groups improved similarly.

FFRangina

OR 0.49

95% CrI 0.33 – 0.66 · Pinteraction > 0.999

Lower odds of higher angina-frequency category per unit decrease in FFRangina.

RFRangina

OR 0.37

95% CrI 0.18 – 0.55 · Pinteraction > 0.999

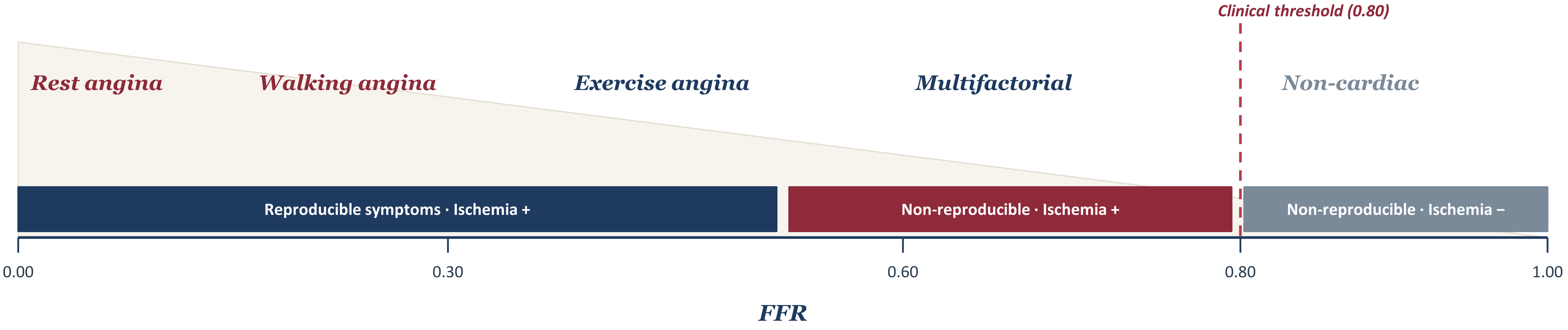
Same direction — lower RFRangina, greater symptom relief with PCI.

High-intensity exercise quartile comparison. CrI = credible interval. CCS class, Rose, Seattle Angina Questionnaire, and Pain Sensitivity Questionnaire did not correlate with thresholds.

One FFR, many patients — a continuum, not a cliff

Two patients with identical FFR can have very different angina profiles.

A sedentary patient may only develop reproducible angina at very low FFR values. An active patient may become symptomatic earlier, at higher FFR values — yet both are mapped to the same dichotomous clinical threshold of 0.80.



The FFR threshold for angina is unique to each patient and their daily activity level.

CLINICAL IMPLICATIONS

What this means at the bedside

01 Cut-points are population averages

FFR ≤ 0.80 and RFR ≤ 0.89 reliably detect flow limitation but do not identify the patient-specific threshold for angina.

02 Workload context matters

The same lesion can be symptomatic or silent depending on daily activity. Static catheter-lab physiology cannot fully predict exertional symptoms.

03 Symptom-linked physiology selects responders

Lower FFRangina and RFRangina identify patients whose angina is tightly coupled to epicardial disease — the ones most likely to gain from PCI.

04 Higher thresholds → look beyond the epicardium

Patients with less reproducible angina at higher thresholds may have microvascular dysfunction, vasospasm, or altered pain processing.

LIMITATIONS

What the study cannot conclude

Small, selected cohort

65 patients with single-vessel CAD and objective ischemia, fit enough to exercise.

Mostly LAD lesions (72%)

Limited insight into vessel-specific differences in angina threshold.

Post-PCI provocation model

Performed after PCI for safety; microvascular integrity may have been altered.

Balloon-simulated stenosis

May not reproduce the flow dynamics or plaque biology of native lesions.

Supine bicycle exercise only

Real-world upright exertion involves additional emotional and neurohormonal factors.

Unblinded follow-up

PCI was required by design; symptom response captured without sham comparator.

Angiography-derived FFR: AngioFFR / QFR / vFFR

Mechanism of action: convert routine angiography into a lesion-specific pressure-drop map — no pressure wire, no adenosine.

Mechanism: anatomy + flow assumptions → virtual FFR

1 Acquire
≥2 projections with minimal overlap / foreshortening; good contrast opacification.

2 Reconstruct
3D QCA centerline, lumen contours, reference diameter and lesion length.

3 Model flow
Contrast frame count / TIMI-flow, CFD or simplified pressure-loss equations estimate hyperemic flow.

4 Output
Virtual pressure pullback: segmental FFR / QFR / vFFR. Treat physiology, not percent stenosis.

Clinical threshold: **≤0.80 abnormal** • best used as a physiology-first layer during diagnostic angiography

Outcome evidence: angiography-based physiology now has randomized outcomes data

ALL-RISE / FFRangio N=1,930; intermediate lesions; FFRangio vs wire-based physiology

6.9%	FFRangio primary endpoint	**7.1%**	wire-based primary endpoint	**Noninferior**

FAST III / vFFR N=2,211; 37 European sites; vFFR-guided vs FFR-guided revascularization

7.5%	vFFR primary endpoint	**7.5%**	FFR primary endpoint	**Noninferior**

Expert cath-lab interpretation: The technology does not "see ischemia"; it computes pressure loss from lumen geometry plus modeled flow. It can normalize physiology use, shorten wire/adenosine workflows, and provide pullback-style planning. Interpret cautiously with poor angiographic quality, ostial/overlapped segments, severe tortuosity, serial/diffuse disease, microvascular disturbance, or prior complex PCI.

Sources: Fearon WF et al. NEJM 2026; Daemen J et al. NEJM 2026; QFR/angiography-derived FFR reviews. Numbers shown are 1-year Kaplan–Meier or trial estimates from the abstracts.

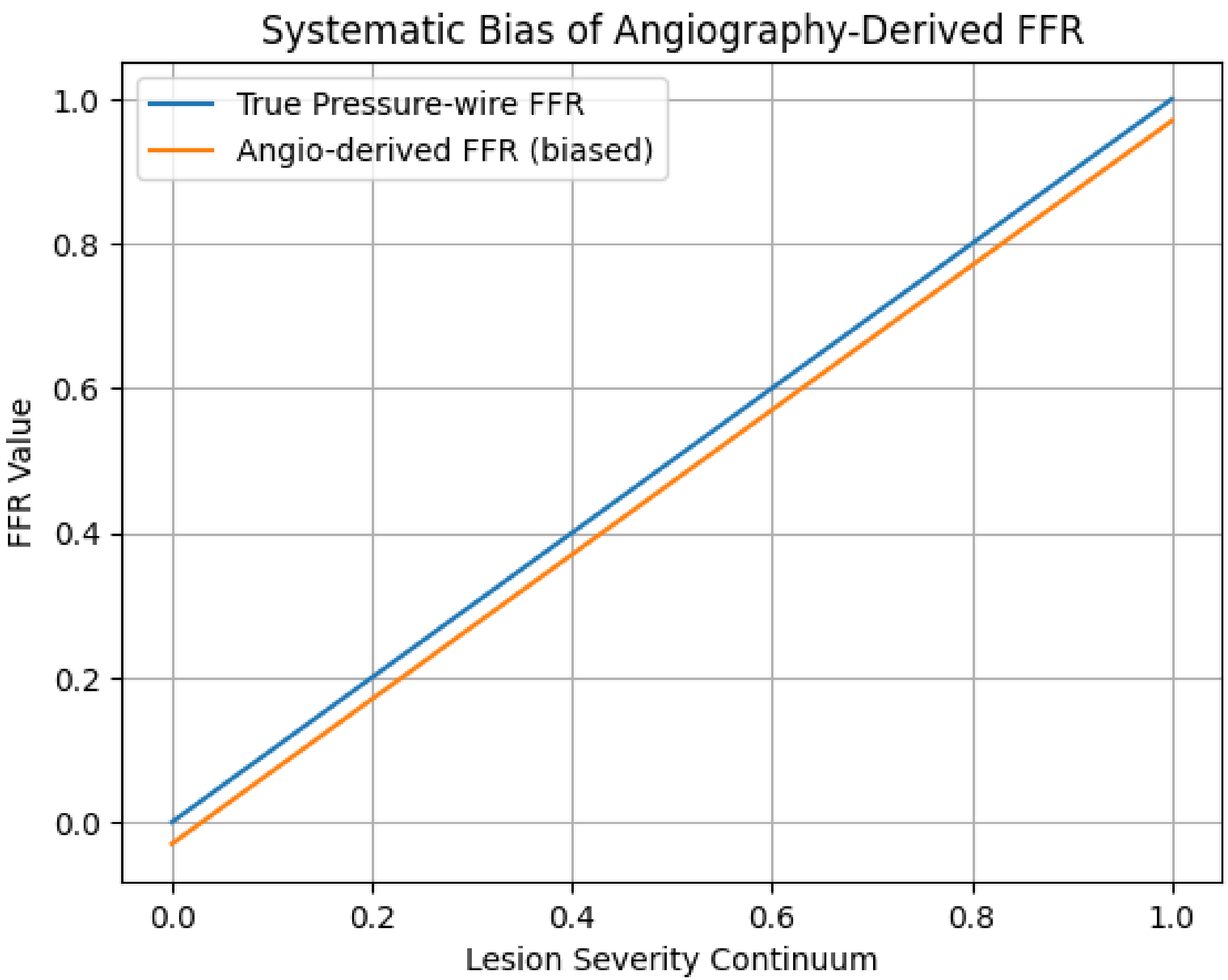
Key Quantitative Findings-Angiography-Derived FFR

Parameter	Pressure-wire FFR	Angio FFR (Estimate)
Mean FFR	0.84	0.80–0.81
Bias	Reference	~ -0.03 lower
PCI Rate	35–46%	44–55%
Relative Increase	—	~20–25%

Systematic underestimation leads to overcalling lesion severity and increased PCI without outcome benefit.

Johnson, N.P. Fractional flow reserve estimated from the invasive angiogram: limitations and next steps. *Nat Rev Cardiol* (2026).

Mechanism of Bias



A consistent downward shift (~0.03) makes lesions appear more severe, pushing borderline lesions below treatment thresholds.

Clinical & Trial-Level Implications

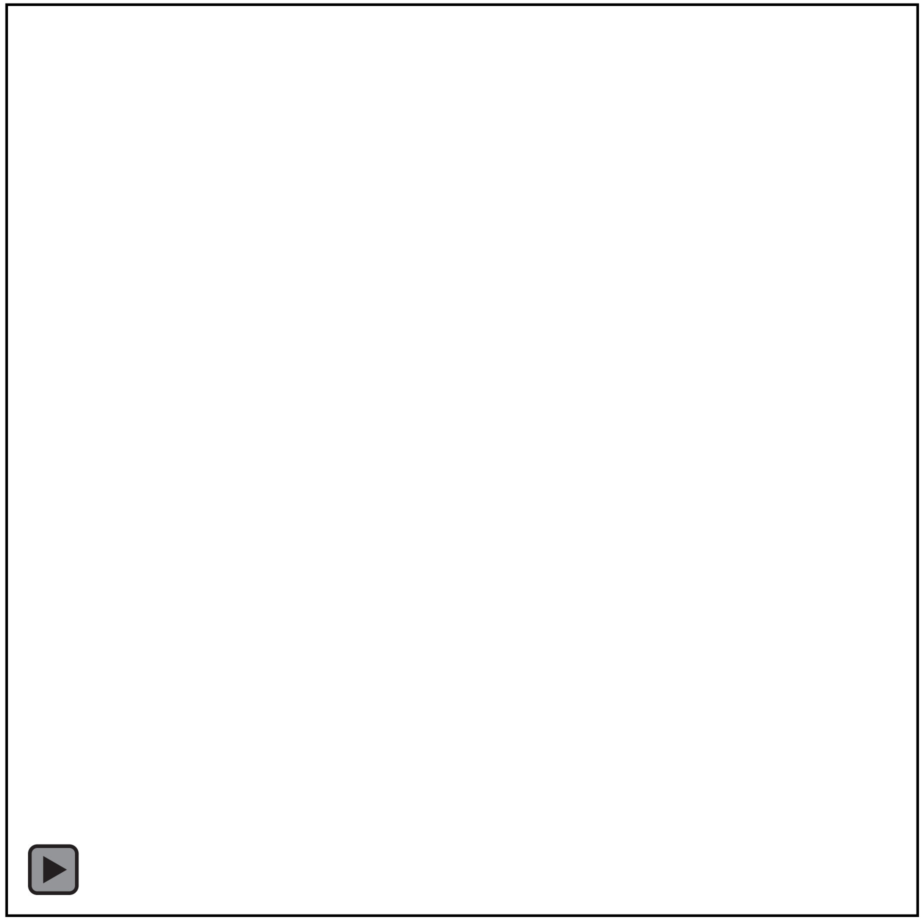
- Why this matters clinically
  - Overestimation of disease severity → unnecessary PCI
  - No improvement in outcomes despite higher intervention rates
  - Trials enrolled low-risk populations (mean FFR ~0.84)
  - Design limitations bias results toward non-inferiority
  - Priority should be better patient selection and upstream testing

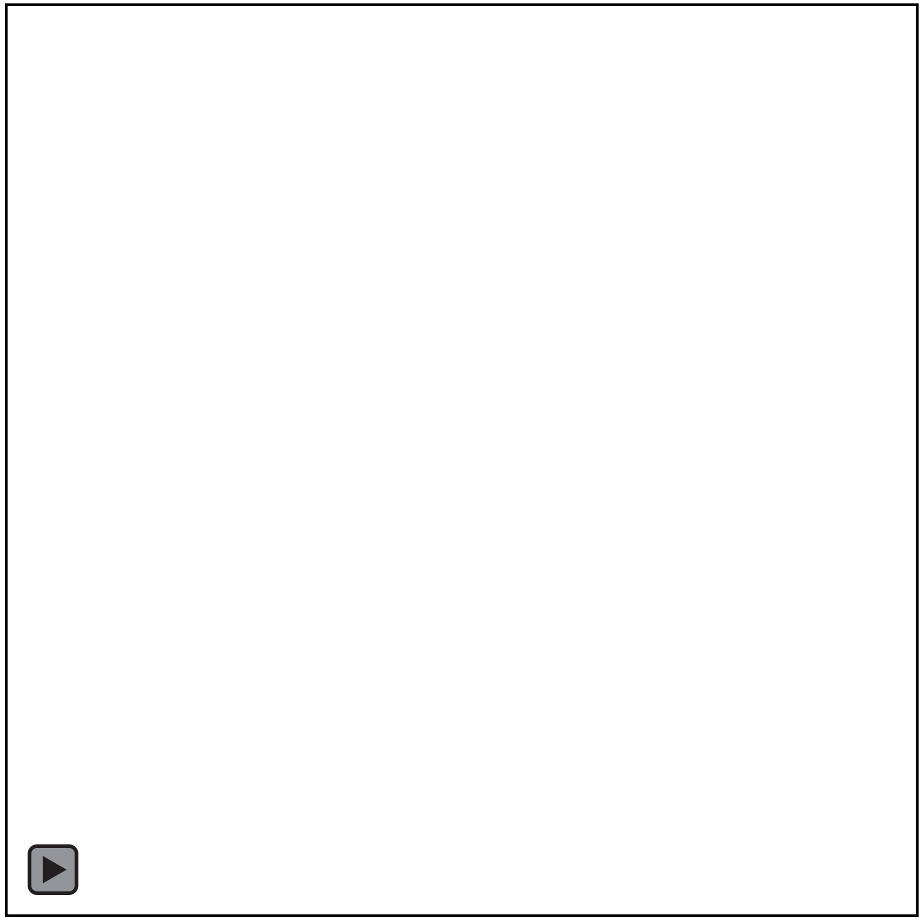
Johnson, N.P. Fractional flow reserve estimated from the invasive angiogram: limitations and next steps. *Nat Rev Cardiol* (2026).

Case 2: 36-Year-Old Male with Inferior Injury Pattern

- 36-year-old man with past medical history of nephrolithiasis and gallstone pancreatitis who presented to outside with chest discomfort intermittently for 1 or 2 weeks
- Echocardiogram which demonstrated ejection fraction of 50 to 55% with apical anterior and mid anterior apical lateral and mid anterolateral segments were hypokinetic. His troponin T at Baystate on April 29 1232 ng/L his alkaline phosphatase appeared to be elevated IgA was 466 mg/dL with tissue transglutaminase IgA of less than 2.
- Cardiac catheterization on April 2025 demonstrated normal coronary arteries of note the left radial was used at that time his LVEDP was 8 mmHg.
- Day of presentation at rest he developed sudden chest discomfort nausea vomiting diaphoresis and presented to the emergency department 1 hour after his symptoms he had inferior lateral ST elevations and it was decided to emergently to bring him to the cardiac Cath Lab.

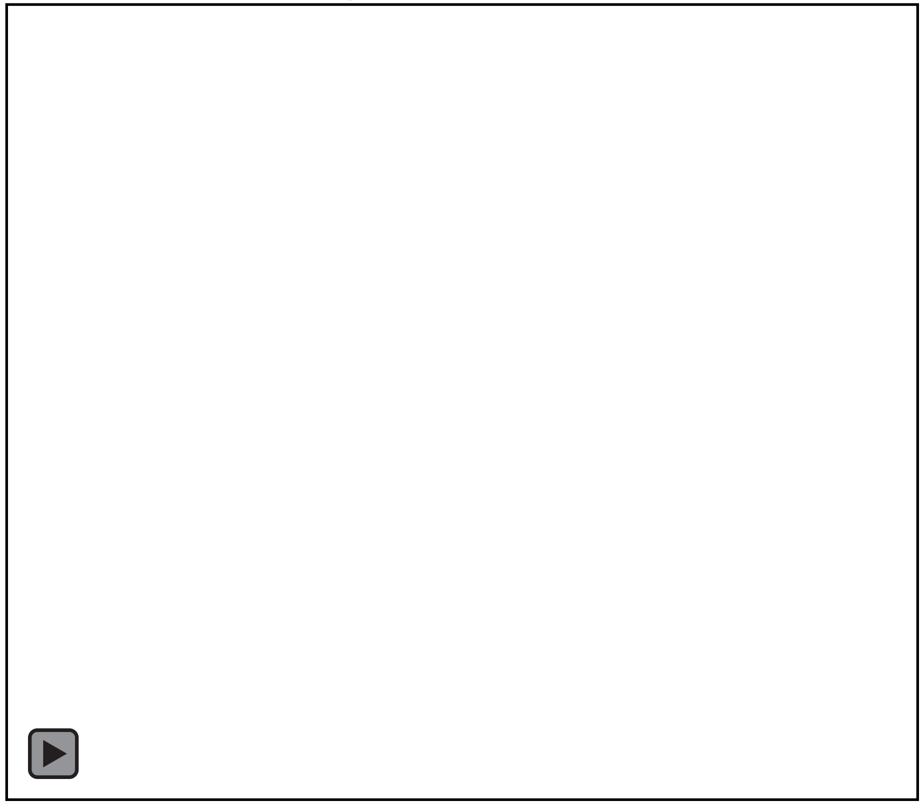
April Angiogram



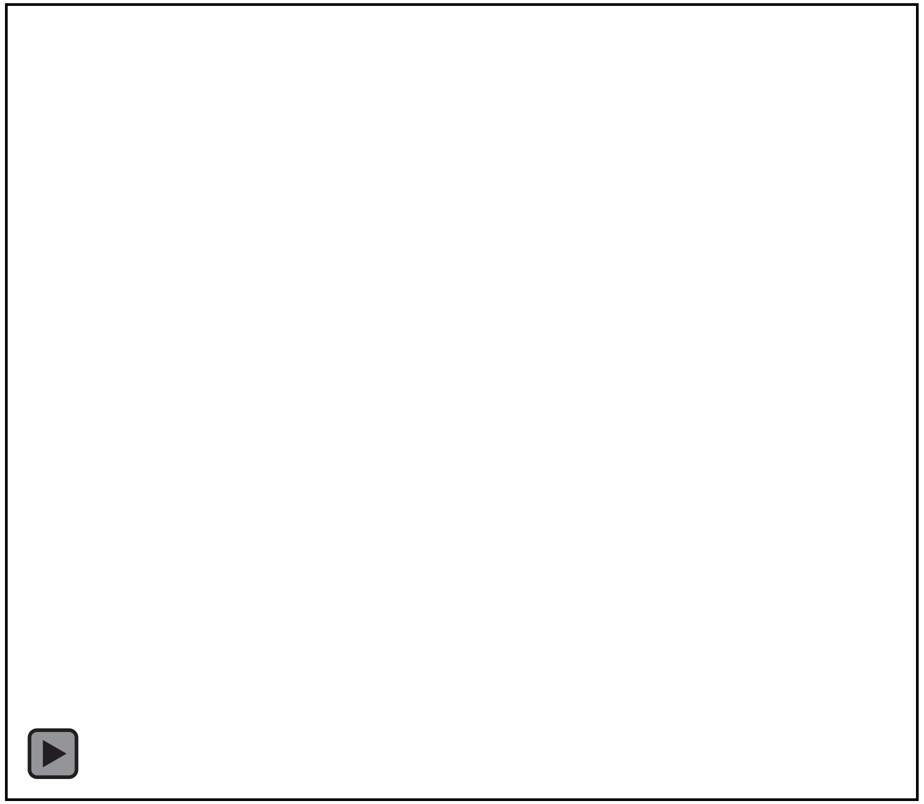


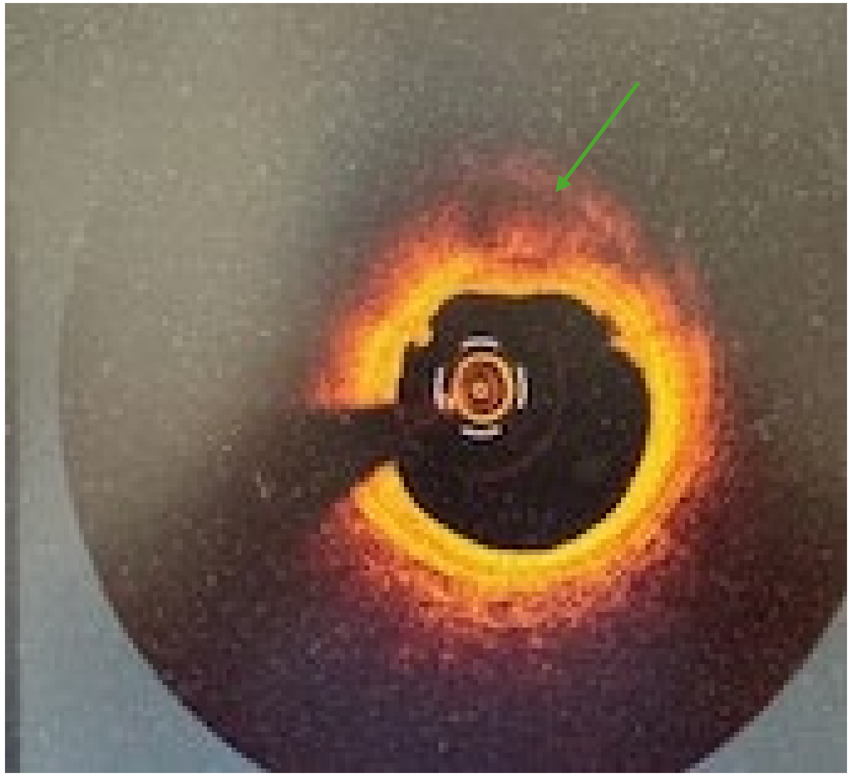
Angiogram

RCA April



RCA November

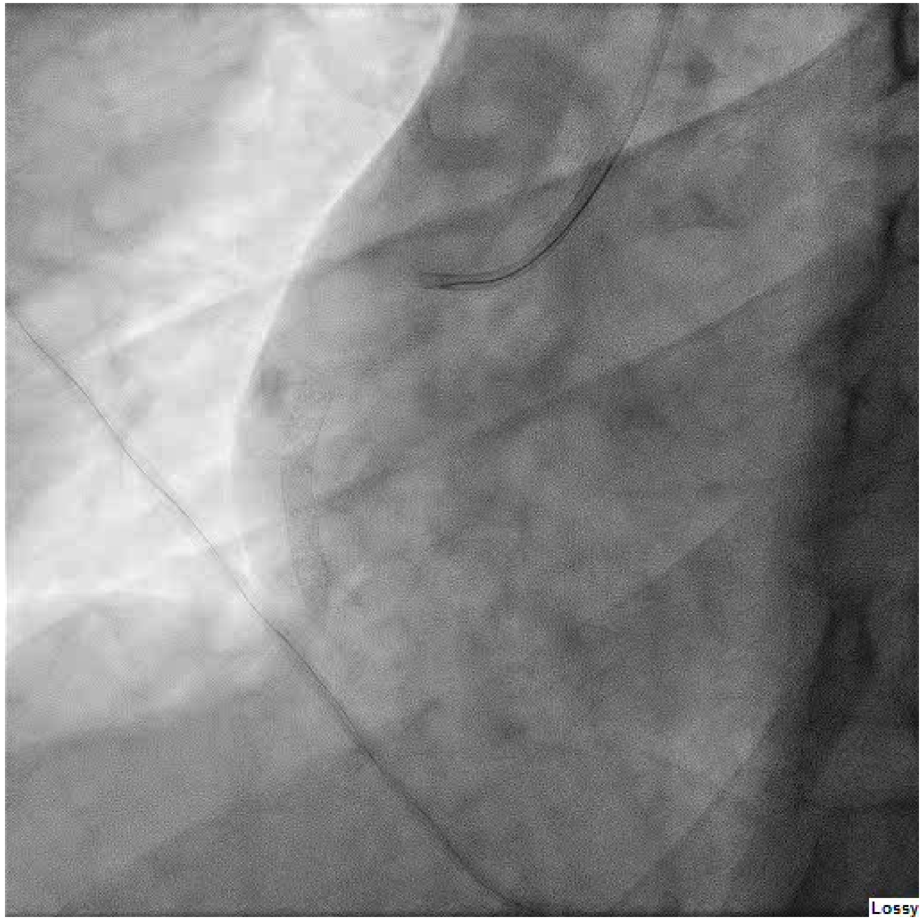


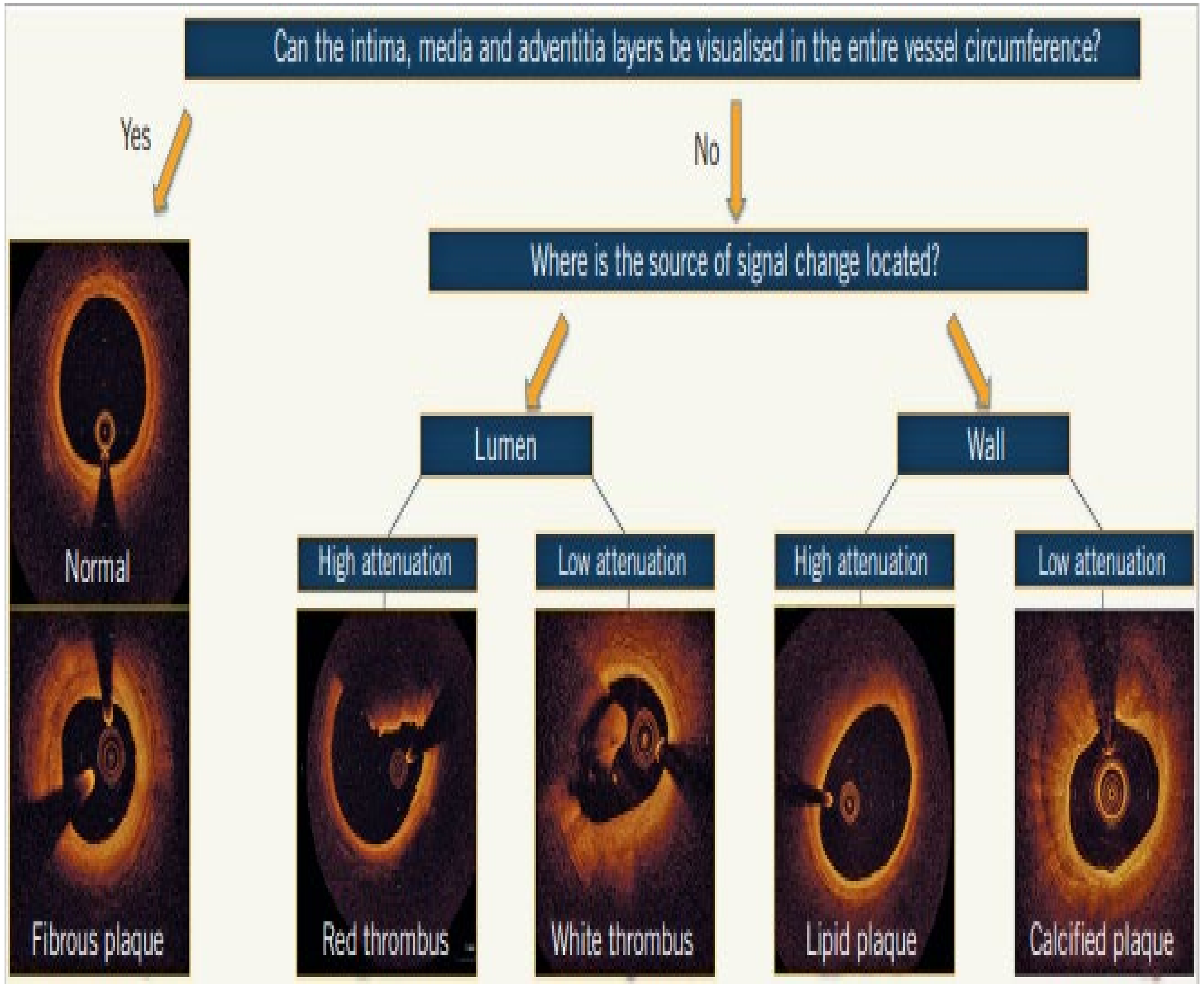


- The OCT frame demonstrates a thrombotic mid-RCA culprit lesion with signal attenuation consistent with lipid-rich plaque (green arrow)and overlying thrombus. Findings are suspicious for plaque erosion remains

- OCT of the mid RCA demonstrates a large-caliber vessel with a thrombotic culprit lesion and associated signal attenuation consistent with lipid-rich plaque and overlying thrombus. No severe calcific arc is evident in the displayed frames. Findings are suspicious plaque erosion.

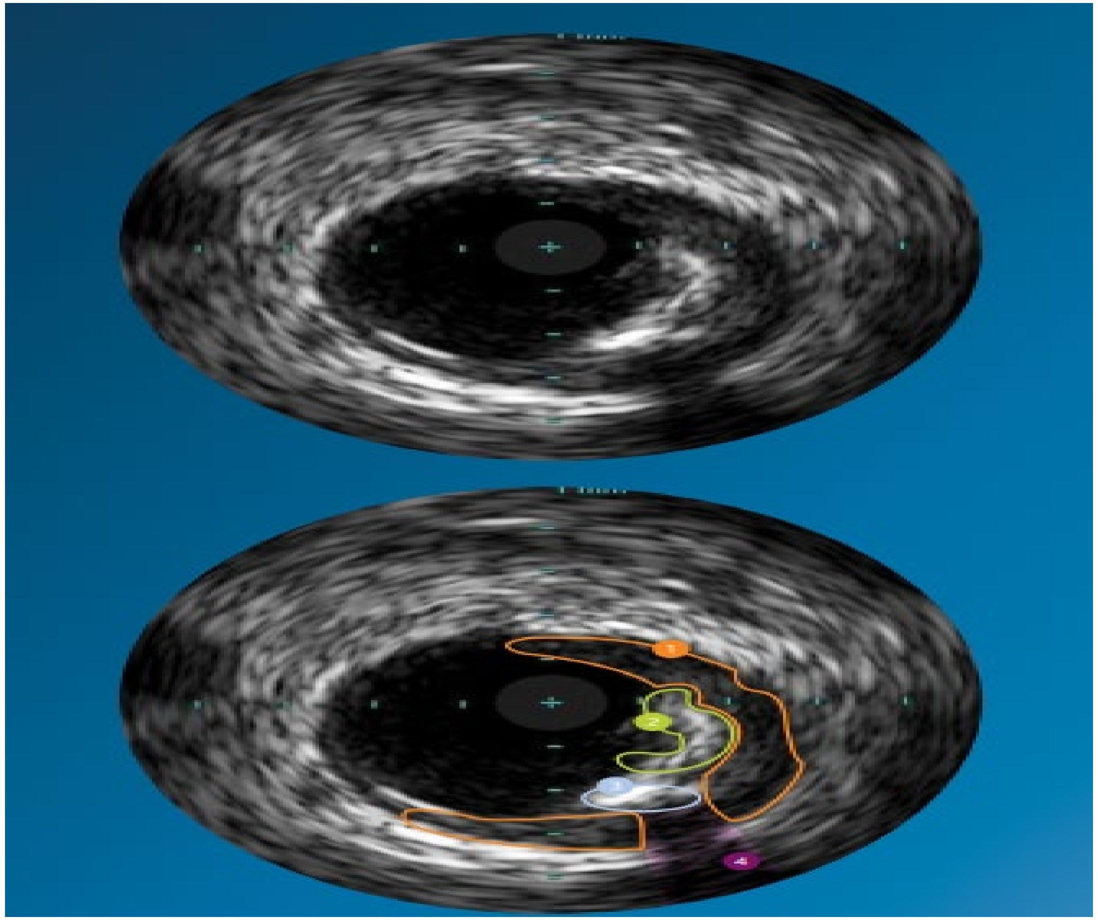
4.0 x 28 mm Stent





- The tri-laminar appearance of the normal vessel or fibrous plaque represents light scattering reflecting from the layers of the vessel without light attenuation.
- Hence, when the intima, media, and adventitia can be visualised for the entire vessel circumference, the cross-section represents either a normal segment or fibrous plaque; the latter of these can be differentiated by eccentric intimal thickening.
- The morphological characteristics of different plaque constituents exhibit different light attenuating properties.
- High attenuation occurs when there is complete absorbance of the near-infrared light, and low attenuation when the light is refracted, yet continues to allow visualisation of vessel characteristics towards the adventitia.
- When the source of the attenuation is in the lumen, high attenuation represents red thrombus and low attenuation represents white thrombus.
- When the source of the attenuation is in the vessel wall, high attenuation represents lipidic plaque, and low attenuation represents calcification

doi/10.4244/EIJ-D-21-00089



- Eccentric plaques are distributed non-circumferentially in the vessel; this makes the assessment of disease by angiography especially prone to underestimation or overestimation depending on the angle of view.
- Orange- echolucent plaque
- Green – echogenic plaque
- Drop out- calcium with acoustic shadowing

EVIDENCE SYNTHESIS • 2021 – 2026

Routine IVUS Guidance

in Complex and Left Main Percutaneous Coronary Intervention

critical appraisal of OPTIMAL, IVUS-CHIP, RENOVATE-COMPLEX-PCI, and ULTIMATE

2026

2026

2023

2021

Synthesizing data from 5,913 randomized patients across 4 RCTs

Limitations of Routine IVUS Guidance — A Structured Appraisal

Eight domains where the evidence does not support universal application

Domain	Limitation	Trial Evidence	Effect Size / Magnitude
1. No benefit in left main PCI	Routine IVUS did not reduce stroke / MI / revascularization / death vs. angiography	OPTIMAL (2026) n = 806, median 2.9 yr	**33.7% vs 30.9% HR 1.11 (P = 0.40)**
2. No benefit in complex high-risk PCI	Routine IVUS did not reduce target-vessel failure in Western complex PCI	IVUS-CHIP (2026) n = 2,020, median 19 mo	**13.9% vs 11.1% HR 1.25 (P = 0.08)**
3. Stent-optimization criteria often unmet	Even with imaging, only ~half of lesions meet pre-specified optimization thresholds	IVUS-CHIP: 48% of lesions RENOVATE: 56% IVUS / 66% OCT	**Plaque burden at stent edges is the main barrier**
4. Substantial procedural burden	Adds operative time, contrast load, catheter cost without clear ischemic-event payoff	IVUS-CHIP: +22.6 min OPTIMAL: +24.7 min	**~30–40% longer procedures plus added device cost**
5. Generalizability of positive trials	The strongest evidence is geographically narrow; Western RCTs do not replicate the benefit	RENOVATE: South Korea only (60% from 1 center); ULTIMATE: China	**Pattern: positive in Asia, neutral in Europe / US**
6. Competing & equivalent strategies	Physiology- and angiography-derived strategies match IVUS in head-to-head RCTs	FLAVOUR: FFR non-inferior GUIDE-DES: QCA non-inferior	**Imaging is not the only route to optimization**
7. Diminishing returns in expert centers	In high-volume centers where IVUS shaped routine practice, the marginal benefit collapses	OPTIMAL operators used IVUS in 50–100% of routine LM PCI	**Angio-guided algorithms already encode IVUS learnings**
8. Unexplained safety signal	Higher stroke incidence in the IVUS arm of OPTIMAL — likely chance, but unexplained	OPTIMAL: 3.0% vs 1.0% HR 3.11 (1.00–9.65)	**Hypothesis-generating; not mechanistically linked**

BOTTOM LINE: *IVUS is a valuable selective adjunct — not a universal requirement — for complex or left main PCI.*

The Evidence is Geographically and Temporally Split

Positive Asian trials (2021–2023) vs. neutral Western trials (2026)

POSITIVE TRIALS • Asia

ULTIMATE
n = 1,448

2021 • China • 8 centers

All-comers DES implantation

Primary endpoint:

3-yr target-vessel failure

HR **0.60** (0.42–0.87) **P = 0.01**

RENOVATE
n = 1,639

2023 • South Korea • 20 sites

Complex coronary lesions (60% from 1 center)

Primary endpoint:

Target-vessel failure

HR **0.64** (0.45–0.89) **P = 0.008**

NEUTRAL TRIALS • Europe

IVUS-CHIP
n = 2,020

2026 • Europe • 37 centers

Complex high-risk PCI (real-world)

Primary endpoint:

Target-vessel failure

HR **1.25** (0.97–1.60) **P = 0.08**

OPTIMAL
n = 806

2026 • Italy, Spain, UK • 28 centers

Unprotected left main coronary disease

Primary endpoint:

Patient-oriented composite

HR **1.11** (0.87–1.42) **P = 0.40**

The two large 2026 Western RCTs (n = 2,826) failed to confirm the benefit shown in earlier Asian trials.

From Routine Use to Selective Adjunct

Reframing the role of intravascular ultrasonography in 2026

CHALLENGED: Routine IVUS for every complex / LM case

1. **No mortality, MI, or revascularization benefit**

   in two large 2026 Western RCTs (OPTIMAL, IVUS-CHIP)

2. **~25 minutes added per procedure**

   with extra catheter cost and contrast load

3. **Stent optimization criteria met in only ~50%**

   of lesions even when imaging is performed

4. **Class IA guideline status may be too strong**

   given the absence of confirmatory Western data

SUPPORTED: IVUS as a selective adjunct

1. **Lesion characterization & vessel sizing**

   calcium, ambiguous lesions, ostial measurements

2. **Diagnostic uncertainty after angiography**

   luminal haze, suspected dissection, edge problems

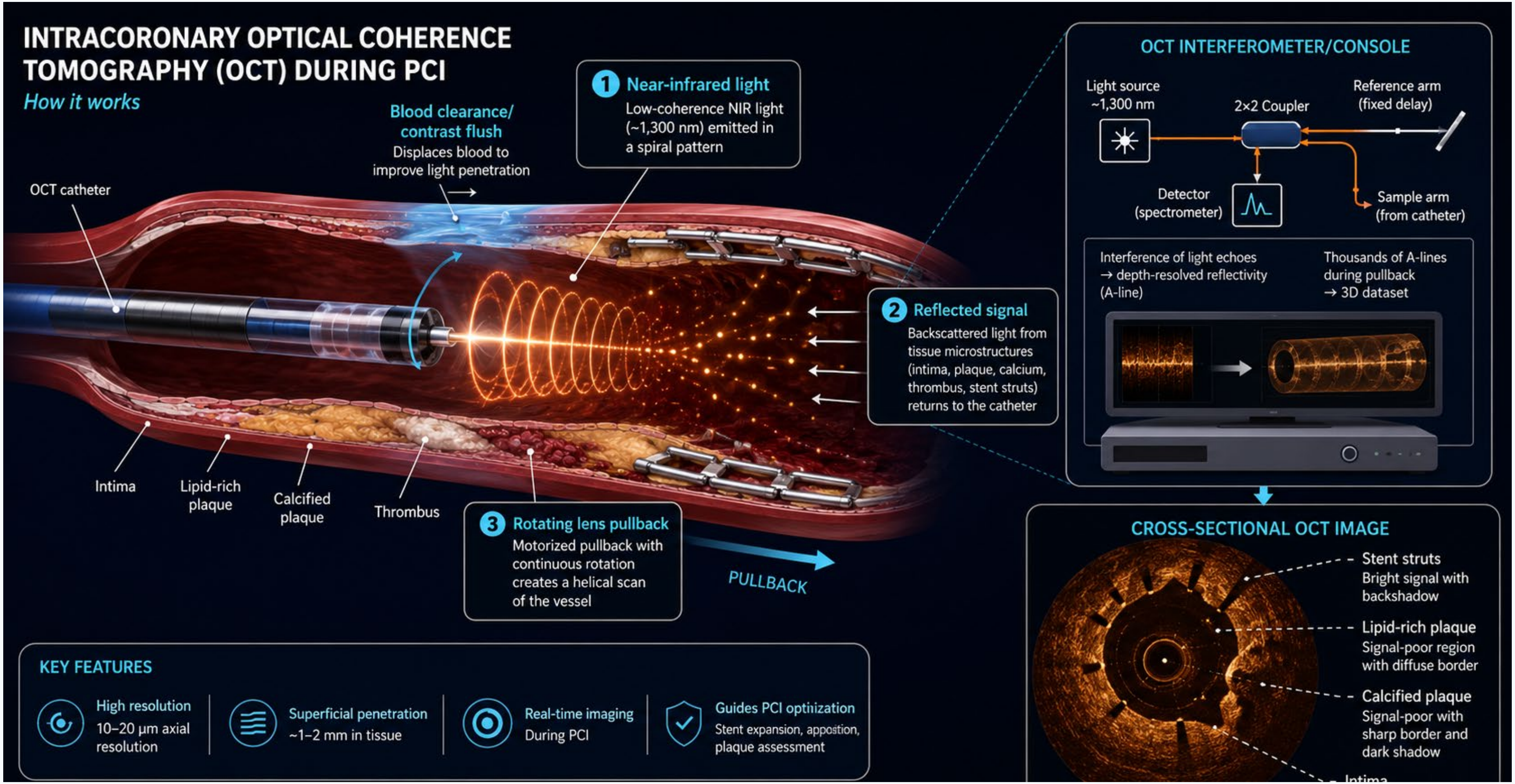
3. **Targeted stent optimization**

   lower stent thrombosis signal across both 2026 trials

4. **Operator/center development**

   expertise built via IVUS now informs angio practice

SYNTHESIS: The pending IMPROVE trial will provide a broader Western test. Until then, the evidence supports IVUS as an **important selective adjunct** *rather than a routine requirement in every complex or left main case.*



How OCT works: near-infrared light, blood clearance, rotating pullback, interferometric depth reconstruction

Source: Almajid et al. EuroIntervention 2024.

Contemporary randomized evidence: what OCT has proven

Mechanistic gains are consistent; clinical benefit depends on lesion complexity and baseline event risk.

Trial	Design / population	Comparator	Primary result	Expert interpretation
ILUMIEN IV	2,487 pts; diabetes or complex lesions; 80 sites	OCT vs angiography	MSA larger with OCT: 5.72 vs 5.36 mm^2; TVF 7.4% vs 8.2% at 2 yr; stent thrombosis 0.5% vs 1.4%	Improves stent dimensions and safety signals; clinical endpoint neutral in broad high-risk population
OCTOBER	1,201 pts; complex bifurcation lesions	OCT vs angiography	MACE 10.1% vs 14.1% at median 2 yr; HR 0.70	Strongest OCT clinical-outcome signal; highly relevant for complex bifurcation PCI
OCTIVUS	2,008 pts; broad PCI population in pragmatic trial	OCT vs IVUS	TVF 2.5% vs 3.1% at 1 yr; noninferior; CIN 1.4% vs 1.5%; major procedural complications 2.2% vs 3.7%	OCT and IVUS are both safe/effective when used with protocolized optimization

Sources: OCTOBER NEJM 2023; ILUMIEN IV NEJM 2023; OCTIVUS Circulation 2023.

OCT vs IVUS: modality selection should be lesion-specific

The best imaging tool is the one that answers the decision question safely.

Clinical / lesion setting	OCT strength	IVUS strength	Practical choice
ACS / ambiguous culprit	Thrombus, rupture, TCFA, erosion, plaque morphology	Deep plaque burden / vessel size	OCT favored when blood clearance and stability allow
Renal insufficiency	Requires contrast flush	No blood clearance contrast requirement	IVUS favored in severe CKD
Ostial left main	Limited by ostial clearance and catheter position	Excellent EEL/vessel assessment	IVUS favored
Mid–distal left main / bifurcation	High-resolution struts, rewiring cell, SB ostium	Vessel sizing and deep assessment	Both; OCT excellent for stent geometry
Calcified lesion	Calcium arc/thickness/length; fracture detection	Deep vessel sizing	OCT favored for calcium modification decisions
ISR / stent failure	Neoatherosclerosis, malapposition, thrombus, strut coverage	Underexpansion and vessel dimensions	Often complementary; OCT often clearer for mechanism

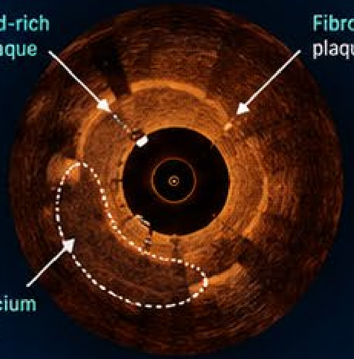
Source: Almajid et al. EuroIntervention 2024.

OCT-GUIDED PCI WORKFLOW

OPTIMIZE LESION ASSESSMENT. TAILOR THERAPY. CONFIRM RESULTS.

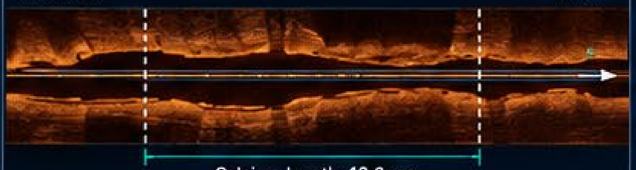
1 PRE-PCI OCT
DEFINE LESION MORPHOLOGY AND CALCIUM

CROSS-SECTION



CALCIUM ASSESSMENT
- Arc: 210°
- Thickness: 0.85 mm
- Length: 12.6 mm

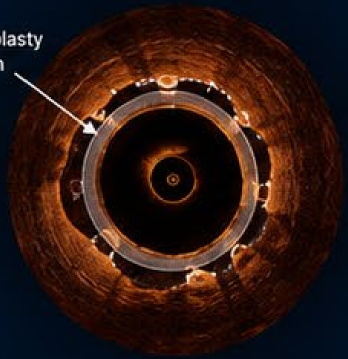
LONGITUDINAL (PULLBACK)



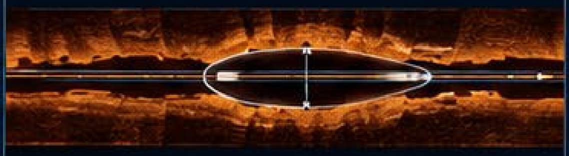
KEY FINDINGS
- Mixed plaque with lipid pool
- Calcium arc, thickness, and length defined
- Reference lumen and EEL dimensions measured
- Lesion length and disease distribution assessed

2 LESION PREPARATION
MODIFY PLAQUE AND FACILITATE STENT DELIVERY

CROSS-SECTION



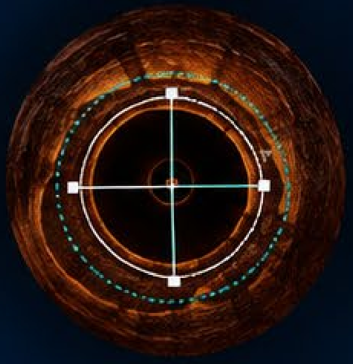
LONGITUDINAL (PULLBACK)



KEY OBJECTIVES
- Modify calcified plaque
- Improve lesion compliance
- Optimize lumen gain
- Prepare for stent delivery

3 STENT SIZING
SIZE TO REFERENCE LUMEN AND EEL

CROSS-SECTION



MEASUREMENTS

Reference EEL
5.10 x 4.40 mm
(Avg. 4.75 mm)

Reference Lumen
3.60 x 2.90 mm
(Avg. 3.25 mm)

STENT SELECTION

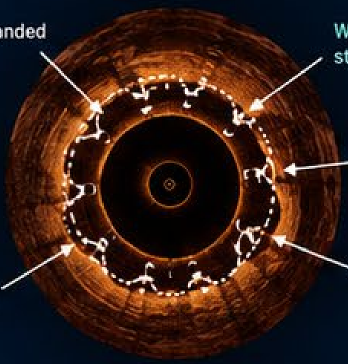
Diameter: 4.0 mm
Length: 20 mm

LONGITUDINAL (PULLBACK)

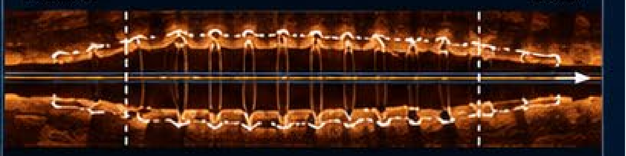
KEY CONSIDERATIONS
- Use EEL for sizing in disease
- Use lumen for functional assessment
- Select stent diameter and length
- Plan landing zones

4 POST-PCI OCT
CONFIRM OPTIMAL RESULT AND IDENTIFY RESIDUAL ISSUES

CROSS-SECTION



LONGITUDINAL (PULLBACK)



POST-PCI CHECKLIST
- ✔ Stent expansion
- ✔ Stent apposition
- ✔ Edge dissection
- ✔ Tissue prolapse
- ✔ Thrombus
- ✔ Residual disease

OCT GUIDES EVERY DECISION | **MEASURE ACCURATELY** | **OPTIMIZE OUTCOMES**

Source: Almajid et al. EuroIntervention 2024.

Take-home messages

Use OCT to make better procedural decisions—not simply to obtain prettier pictures.

- OCT provides high-resolution, light-based intravascular imaging that improves plaque, calcium, thrombus, and stent assessment.
- The highest-yield use is a protocol: pre-PCI diagnosis → lesion preparation → sizing/landing zones → post-PCI audit.
- RCT evidence supports improved procedural mechanics; OCTOBER shows clinical benefit in complex bifurcation PCI.
- OCT and IVUS are complementary. IVUS remains preferred for ostial left main and severe renal dysfunction.

expert framing: OCT is a decision tool

Key references

1. Holm NR et al. OCT or Angiography Guidance for PCI in Complex Bifurcation Lesions. NEJM 2023.

2. Ali ZA et al. OCT-Guided versus Angiography-Guided PCI. NEJM 2023.

3. Kang D-Y et al. OCT-Guided or IVUS-Guided PCI: OCTIVUS. Circulation 2023.

4. Almajid F et al. Optical coherence tomography to guide PCI. EuroIntervention 2024.

Suggested use: place a practical OCT checklist at the console and review images with the team before and after stenting.

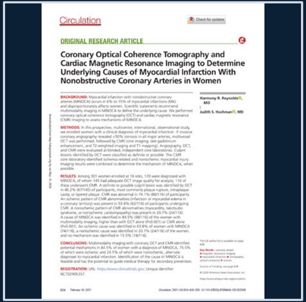
Sources: OCTOBER NEJM 2023; ILUMIEN IV NEJM 2023; OCTIVUS Circulation 2023; Almajid et al. EuroIntervention 2024.

NONOBSTRUCTIVE CORONARY SYNDROMES

From “normal angiogram” to mechanism-guided care

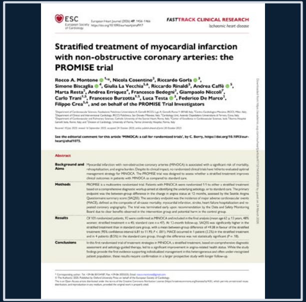
Five-article expert review • 3 slides per article • Healthcare audience

Storyline: diagnose the mechanism → stage the risk → match therapy to biology


Circulation

ORIGINAL RESEARCH ARTICLE

Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of Myocardial Infarction With Nonobstructive Coronary Arteries in Women


ESC

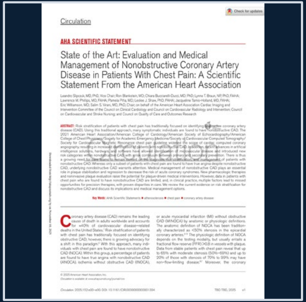
FASTTRACK CLINICAL RESEARCH

Stratified treatment of myocardial infarction with non-obstructive coronary arteries: the PROMISE trial


ESC

CLINICAL RESEARCH

Endotypes of angina with non-obstructive coronary arteries: a prospective multicentre study


Circulation

AHA SCIENTIFIC STATEMENT

State of the Art: Evaluation and Management of Nonobstructive Coronary Artery Disease in Patients With Chest Pain: A Scientific Statement From the American Heart Association


ARTICLE IN PRESS

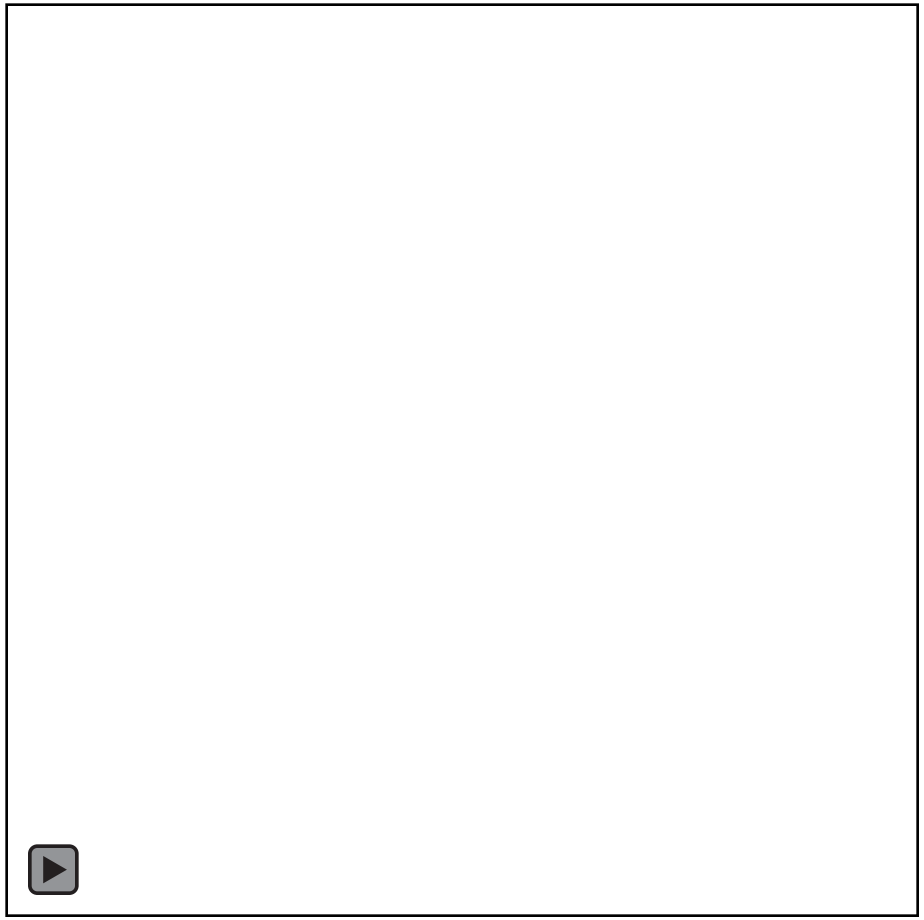
Cardiovascular Revascularization Medicine

Indications, contraindications, and usefulness of acetylcholine testing?

Prepared for clinical, imaging, cath lab, nursing, and operational stakeholders

Case 3: 36-Year-Old Female with chest pain

- 36-year-old woman with past medical history of congenital pulmonary stenosis (postnatal diagnosis) Balloon valvulotomy was performed at 4 months old
- Surgical valvotomy was performed at 6 months old in 1990, Pulmonary valve replacement using a 25-mm Mitroflow bioprosthetic valve was performed on January 20, 2010
- A reoperative sternotomy was performed. A 25-mm mitral flow valve September 9, 2025
- Left heart catheterization demonstrated an LV pressure of 90/-/12mmHg. There was no gradient from LV to Asc Ao (90/57/72 mmHg) or across the aortic arch (90/51/71mmHg).
- Balloon dilation and fracture of the prosthetic valve was performed with a 24mm balloon after which a 23mm SAPIEN S3 balloon expandable valve was then implanted inside the surgical prosthetic valve. 9. Post TPVR, the RV systolic pressure decreased to 28mmHg (AO 106mmHg) with only 6mmHg gradient (expected) to the MPA (22/11/16 mmHg). The RVEDp decreased to 9 mmHg. There was no residual pulmonary regurgitation. 5.)
- Cardiac catheterization was performed on September 17, 2025 angiography of the left coronary system showed no occlusion, narrowing, or dissection of the left main, LAD, Cx or distal branches. Angiography of the right coronary artery showed a right dominant system with RCA giving rise to PDA. No occlusion, narrowing, stenosis or dissection of the RCA, PDA, or branch coronary arteries. Ascending aorta. Injection into aorta shows non-dilated aortic root, unobstructed aortic arch. Normal coronary origins. Patent RCA and LCA with smooth distal flow. 2-3, right dominant system. Normal coronaries.
- Continue chest pain referred for coronary functional testing. Her symptoms started after September 8 for sharp squeezing discomfort in the chest extending to the jaw okay the left hand there is no exacerbating or mitigating factors he lasts a few minutes and at times he can last the entire day intermittently.




Run:24
Coronary Tools
Date:2/27/2026
Time: 8:33 AM
Procedure: Cath, Diagnostic Cardiac Cath , Miscellaneous, Moderate Sedation, PCI
SMUDA, SARAH
ID 0487708
DOB 07-Aug-1989
System
Help
Select Coronary Tools on the touch screen module for additional functionality.
RAO 10°
CRAN 38°

Epicardial and microvascular evalution

RFR

CFR/IMR

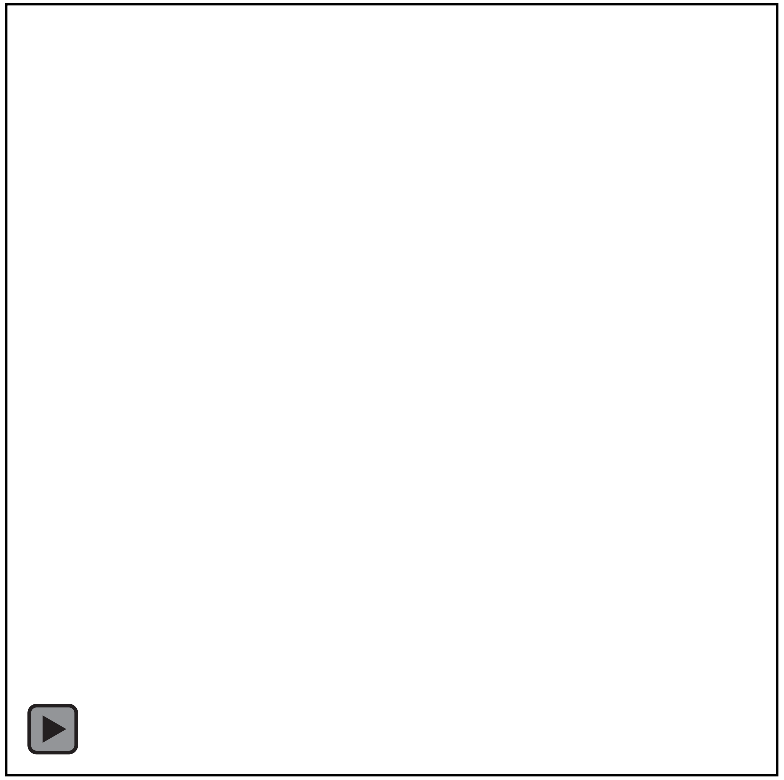
Vasospasm testing

Baseline

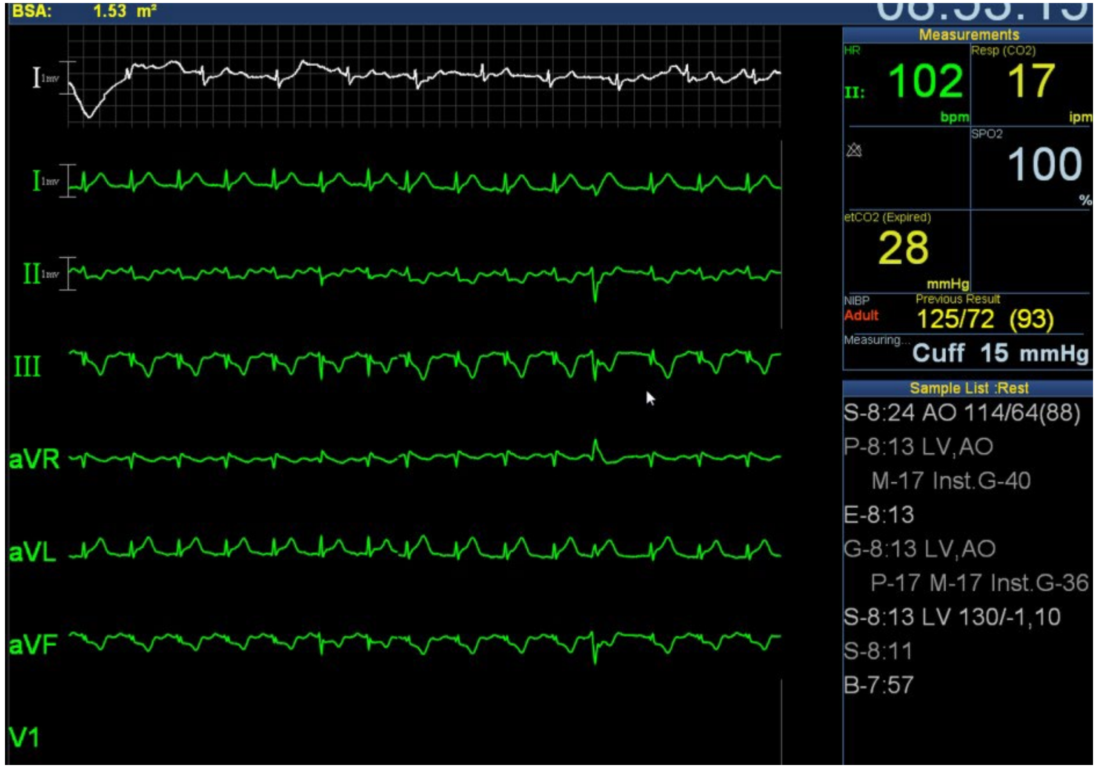
2 mcg/ml Ach

Vasospasm testing 2

20 mcg/ml Ach

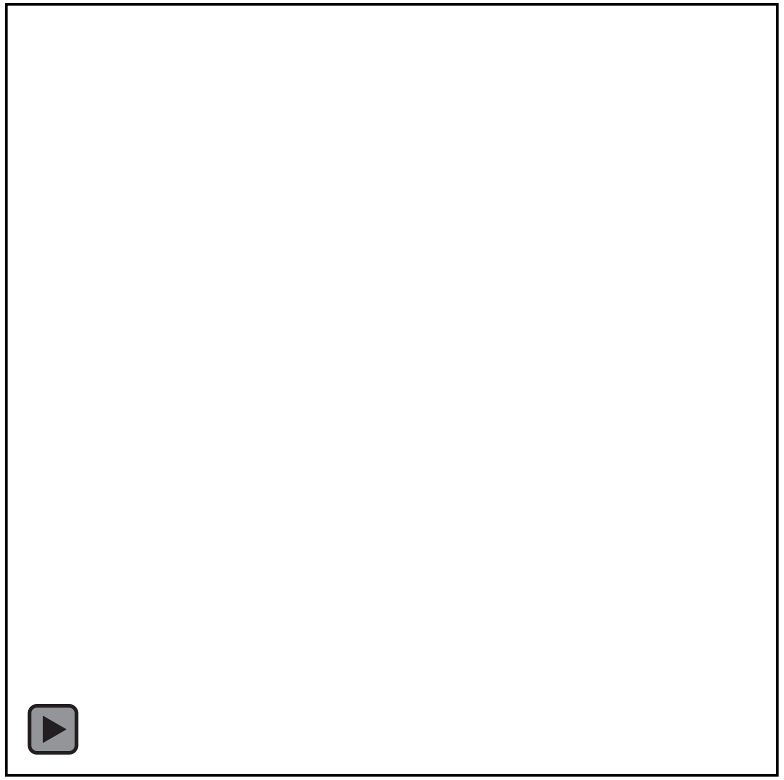


ECG

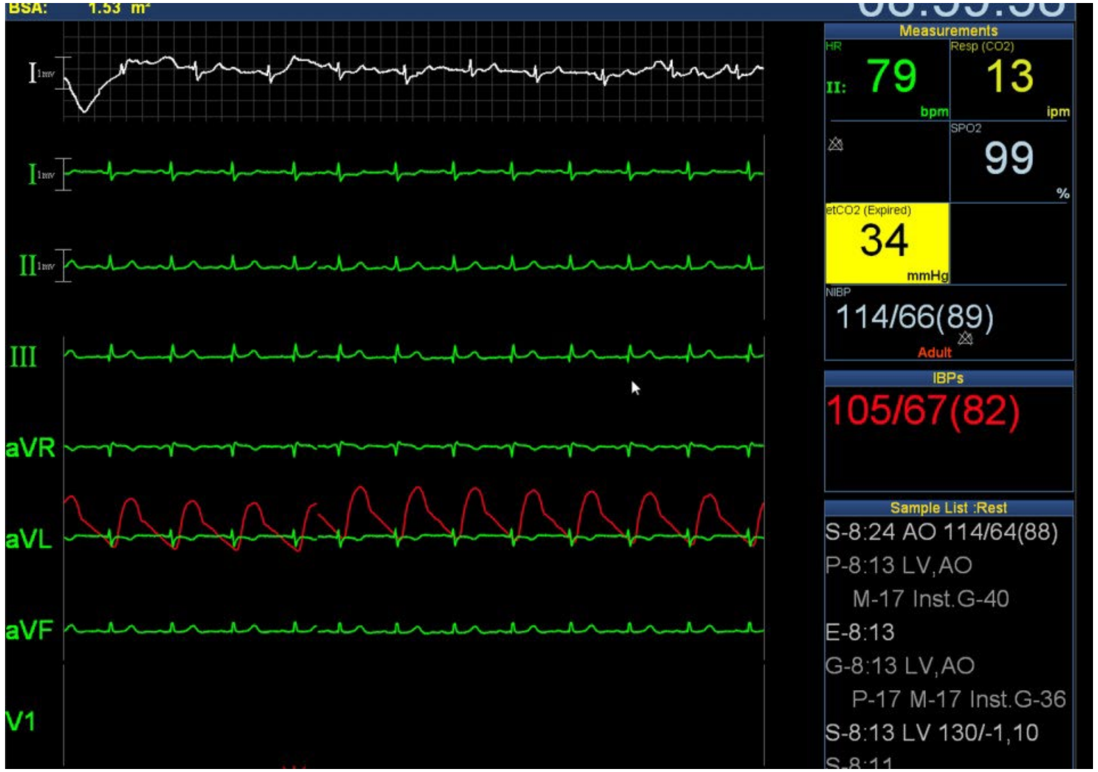


Vasospasm testing 3

IC nitro



Post nitro ECG



MINOCA in women: OCT + CMR reveals the diagnosis

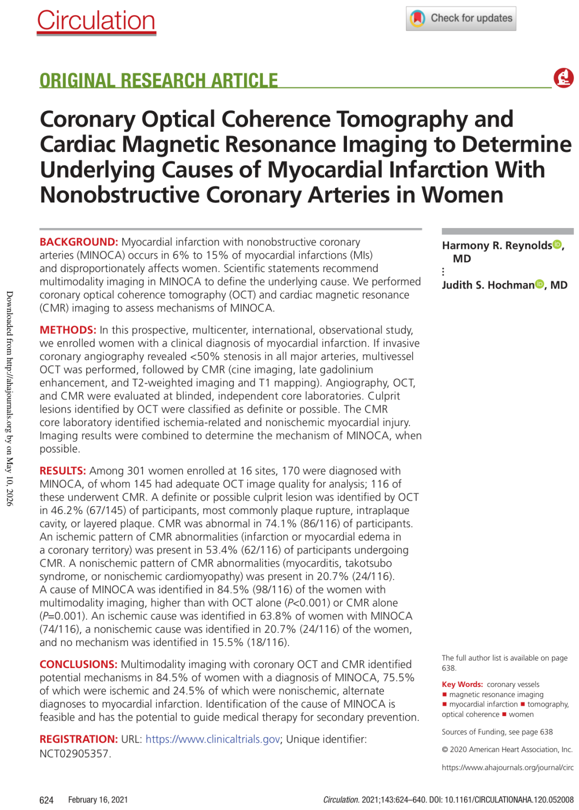
Clinical problem

- MINOCA accounts for a meaningful minority of MI and disproportionately affects women.
- Angiography alone misses plaque disruption, infarction pattern, myocarditis, and takotsubo mimics.
- The study tested a diagnostic sequence: multivessel OCT during angiography, then early CMR.

1 Angiography → **2 OCT** → **3 CMR**

1. **Angiography** — <50% stenosis in all major epicardial vessels
2. **OCT** — 3-vessel goal; plaque rupture/erosion/layered plaque/SCAD
3. **CMR** — LGE + edema mapping to identify ischemic vs nonischemic injury

Presenter framing: MINOCA is not a final diagnosis — it is a working diagnosis that demands mechanism clarification.


Circulation

Check for updates

ORIGINAL RESEARCH ARTICLE

Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of Myocardial Infarction With Nonobstructive Coronary Arteries in Women

Harmony R. Reynolds, MD
⋮
Judith S. Hochman, MD

BACKGROUND: Myocardial infarction with nonobstructive coronary arteries (MINOCA) occurs in 6% to 15% of myocardial infarctions (MIs) and disproportionately affects women. Scientific statements recommend multimodality imaging in MINOCA to define the underlying cause. We performed coronary optical coherence tomography (OCT) and cardiac magnetic resonance (CMR) imaging to assess mechanisms of MINOCA.

METHODS: In this prospective, multicenter, international, observational study, we enrolled women with a clinical diagnosis of myocardial infarction. If invasive coronary angiography revealed <50% stenosis in all major arteries, multivessel OCT was performed, followed by CMR (cine imaging, late gadolinium enhancement, and T2-weighted imaging and T1 mapping). Angiography, OCT, and CMR were evaluated at blinded, independent core laboratories. Culprit lesions identified by OCT were classified as definite or possible. The CMR core laboratory identified ischemia-related and nonischemic myocardial injury. Imaging results were combined to determine the mechanism of MINOCA, when possible.

RESULTS: Among 301 women enrolled at 16 sites, 170 were diagnosed with MINOCA, of whom 145 had adequate OCT image quality for analysis; 116 of these underwent CMR. A definite or possible culprit lesion was identified by OCT in 46.2% (67/145) of participants, most commonly plaque rupture, intraplaque cavity, or layered plaque. CMR was abnormal in 74.1% (86/116) of participants. An ischemic pattern of CMR abnormalities (infarction or myocardial edema in a coronary territory) was present in 53.4% (62/116) of participants undergoing CMR. A nonischemic pattern of CMR abnormalities (myocarditis, takotsubo syndrome, or nonischemic cardiomyopathy) was present in 20.7% (24/116). A cause of MINOCA was identified in 84.5% (98/116) of the women with multimodality imaging, higher than with OCT alone ($P<0.001$) or CMR alone ($P=0.001$). An ischemic cause was identified in 63.8% of women with MINOCA (74/116), a nonischemic cause was identified in 20.7% (24/116) of the women, and no mechanism was identified in 15.5% (18/116).

CONCLUSIONS: Multimodality imaging with coronary OCT and CMR identified potential mechanisms in 84.5% of women with a diagnosis of MINOCA, 75.5% of which were ischemic and 24.5% of which were nonischemic, alternate diagnoses to myocardial infarction. Identification of the cause of MINOCA is feasible and has the potential to guide medical therapy for secondary prevention.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02905357.

The full author list is available on page 638.

Key Words: coronary vessels ■ magnetic resonance imaging ■ myocardial infarction ■ tomography, optical coherence ■ women

Sources of Funding, see page 638

https://www.ahajournals.org/journal/circ

624 February 16, 2021 *Circulation.* 2021;143:624–640. DOI: 10.1161/CIRCULATIONAHA.120.052008

Key result: multimodality imaging finds a mechanism in ~85%

145

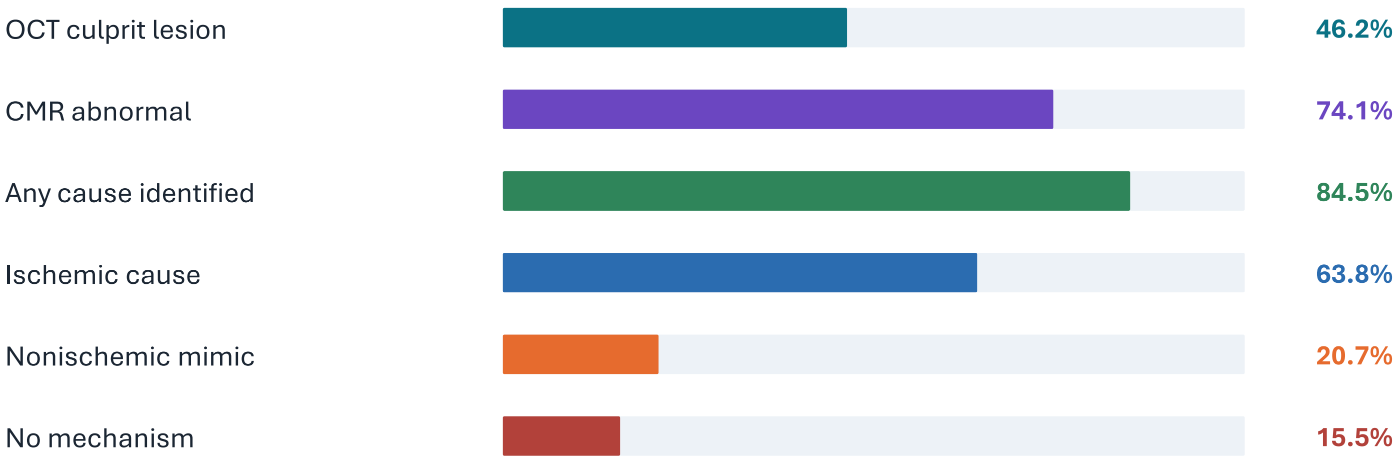
women with adequate OCT imaging

116

also underwent interpretable CMR

84.5%

mechanism identified with OCT + CMR



Reynolds et al — Imaging for Mechanisms of MINOCA

ORIGINAL RESEARCH ARTICLE

Figure 6. Representative cases of plaque disruption causing MINOCA.
Top, Representative case of plaque rupture with red thrombus in a wraparound LAD coronary artery with associated apical inferior wall infarction. A 44-year-old woman with no coronary artery disease risk factors who presented with chest pain persisting after transfusion in the context of heavy menstrual bleeding, hemoglobin 7 mg/dL. Peak troponin I was 3.25 ng/mL. **A,** Angiography of the LAD coronary artery demonstrated a lucency in the proximal LAD with <50% angiographic stenosis. Note that the LAD terminates well past the apex at the inferior wall of the left ventricle. **B,** OCT image showed a protruding mass with irregular surface indicating mural red thrombus (→). Proximally, there is a low intensity region (*** in B1**) with clear demarcation indicating cavity in the lipidic plaque. Adjacent thin cap fibroatheroma was observed (▷). **C** and **D,** CMR late gadolinium enhanced images, short (**C**) and long axis (**D**). There is a small, transmural infarction in the mid-to-apical inferior wall, corresponding with the terminus of the LAD. **Bottom**, Representative case of layered plaque in LAD coronary artery with associated anterior wall infarction. A 41-year-old woman with hypertension and history of cerebral sinus venous thrombosis who presented with 4.5 hours of midsternal chest pain at rest. The presenting ECG showed equivocal ST elevation in the anterior precordial leads, and cardiac troponin I was 5.1 ng/mL. She was taken urgently for cardiac catheterization showing mild-moderate LAD stenosis after intracoronary nitroglycerin; no intervention was performed. Four days later, because of nonsustained ventricular tachycardia, the patient was referred for repeat coronary angiography (**E**), showing 20% to 30% LAD stenosis. **F1** through **F3,** OCT images corresponding with proximal mild stenosis showed a layered plaque (white triangles) underlying lipidic plaque (*); images are arranged from distal to proximal, **left to right**. **G** through **M,** The myocardial extent of infarction (**H, I, L,** and **M**) was matched by regional wall motion abnormality and evidence of edema on the postcontrast cine SSFP (T2/T1-weighted) imaging (**G, J,** and **K**). CMR indicates cardiac magnetic resonance; LAD, left anterior descending; MINOCA, myocardial infarction with nonobstructive coronary arteries (<50% stenosis in all major epicardial vessels); OCT, optical coherence tomography; and SSFP, steady-state free precession.

636 February 16, 2021 *Circulation.* 2021;143:624–640. DOI: 10.1161/CIRCULATIONAHA.120.052008

The image evidence matters

Subtle plaque disruption can exist despite <50% stenosis and may correspond to infarction on CMR.

Clinical interpretation: change the question after the angiogram

What I would teach

- Do not tell patients “your coronaries are normal” when the clinical event is MI.
- Order early CMR when feasible to separate MI from myocarditis/takotsubo/nonischemic cardiomyopathy.
- Consider intracoronary imaging when plaque disruption would alter antithrombotic and lipid strategy.

Limits that should temper overreach

- Women only; no conclusion about sex differences.
- Small sample; not powered for outcomes or therapy effect.
- No provocative spasm testing; vasomotor causes likely underestimated.

Bottom line

MINOCA should launch a diagnostic algorithm, not end the workup.

Practical workflow

A — CMR first

Fastest way to adjudicate myocardium

B — OCT/IVUS

When plaque disruption or SCAD is plausible

C — Vasomotor

ACh testing if spasm remains suspected

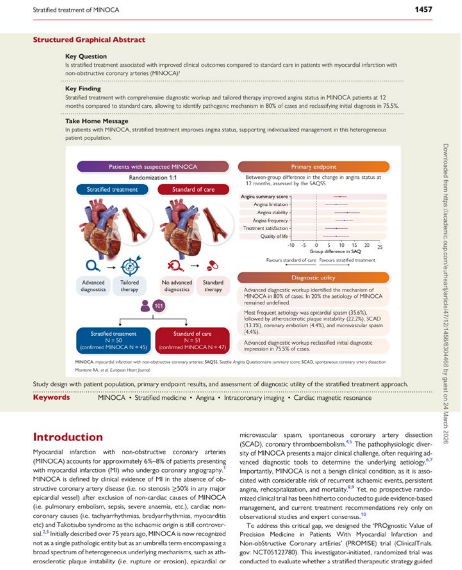
D — Therapy

Mechanism-specific prevention

PROMISE: the first randomized test of stratified MINOCA care

Trial design

- Multicenter, prospective, open-label RCT in suspected MINOCA.
- 101 randomized; 92 confirmed MINOCA analyzed: stratified treatment n=45, standard care n=47.
- Primary endpoint: change in Seattle Angina Questionnaire summary score at 12 months.


Stratified treatment of MINOCA 1457

Structured Graphical Abstract

Key Question
Is stratified treatment associated with improved clinical outcomes compared to standard care in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA)?

Key Finding
Stratified treatment with comprehensive diagnostic workup and tailored therapy improved angina status in MINOCA patients at 12 months compared to standard care, allowing to identify pathogenic mechanism in 80% of cases and reclassifying initial diagnosis in 75.5%.

Take Home Message
In patients with MINOCA, stratified treatment improves angina status, supporting individualized management in this heterogeneous patient population.

Study design with patient population, primary endpoint results, and assessment of diagnostic utility of the stratified treatment approach.

Keywords MINOCA • Stratified medicine • Angina • Intracoronary imaging • Cardiac magnetic resonance

Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA) accounts for approximately 6%–8% of patients presenting with myocardial infarction (MI) who undergo coronary angiography.[1] MINOCA is defined by clinical evidence of MI in the absence of obstructive coronary artery disease (i.e. no stenosis ≥50% in any major epicardial vessel) after exclusion of non-cardiac causes of MINOCA (i.e. pulmonary embolism, sepsis, severe anaemia, etc.), cardiac non-coronary causes (i.e. tachyarrhythmias, bradyarrhythmias, myocarditis etc) and Takotsubo syndrome as the ischaemic origin is still controversial.[2,3] Initially described over 75 years ago, MINOCA is now recognized not as a single pathologic entity but as an umbrella term encompassing a broad spectrum of heterogeneous underlying mechanisms, such as atherosclerotic plaque instability (i.e. rupture or erosion), epicardial or microvascular spasm, spontaneous coronary artery dissection (SCAD), coronary thromboembolism.[4,5] The pathophysiologic diversity of MINOCA presents a major clinical challenge, often requiring advanced diagnostic tools to determine the underlying aetiology.[6,7] Importantly, MINOCA is not a benign clinical condition, as it is associated with considerable risk of recurrent ischaemic events, persistent angina, rehospitalization, and mortality.[8,9] Yet, no prospective randomized clinical trial has been hitherto conducted to guide evidence-based management, and current treatment recommendations rely only on observational studies and expert consensus.[10]

To address this critical gap, we designed the 'PROgnostic Value of Precision Medicine in Patients With Myocardial Infarction and Non-obStructive Coronary artEries' (PROMISE) trial (ClinicalTrials.gov: NCT05122780). This investigator-initiated, randomized trial was conducted to evaluate whether a stratified therapeutic strategy guided

Intervention logic

1 Advanced diagnostics
CMR + intracoronary imaging + coronary functional assessment when indicated

2 Etiology assigned
Spasm, plaque instability, SCAD, embolism, microvascular spasm, undefined

3 Tailored therapy
Treatment chosen to match the mechanism rather than the label

The trial was stopped early by the DSMB because of clear benefit in the intervention group and potential harm in control.

PROMISE results: better angina health status, high reclassification

+9.38

SAQ summary score treatment effect at 12 months

80%

mechanism identified in stratified arm

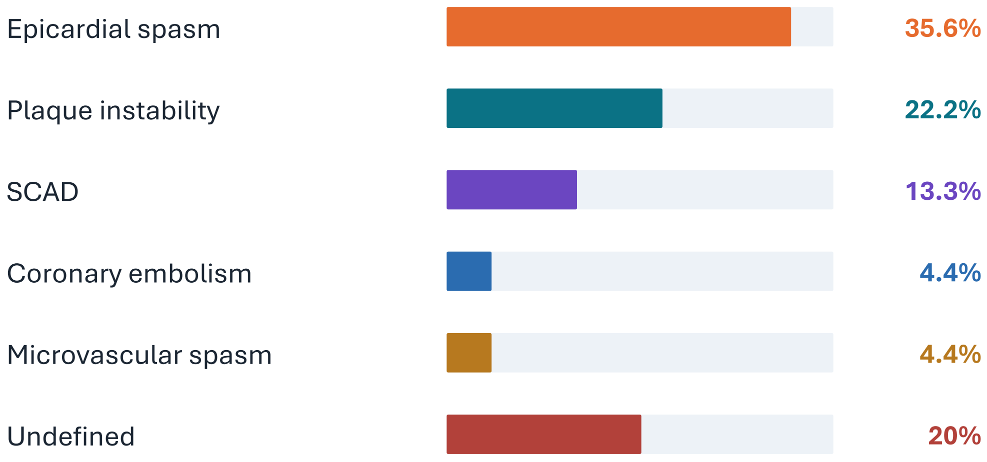
75.5%

initial diagnosis reclassified

2.2 vs 8.5%

MACE %, stratified vs standard; not statistically significant

Mean between-group differences in SAQ domains



Etiology in the stratified-treatment group

How to use PROMISE: compelling, but implementation-sensitive

Why this changes the conversation

- First randomized evidence that “diagnose-then-treat” improves MINOCA angina outcomes.
- Epicardial spasm was common, reinforcing the need for vasomotor assessment.
- Reclassification in three quarters shows how unreliable clinical impression can be.

What it does not prove

- Not powered for mortality, recurrent MI, HF hospitalization, or stroke.
- Small, open-label, tertiary Italian centers — generalizability is the key question.
- PCI in selected cases should not be read as routine PCI for MINOCA.

Operational translation

Build a MINOCA pathway: CMR access + intracoronary imaging + CFT/ACh capability + medication algorithms.

Measure success by symptom burden, repeat ED visits, testing duplication, and therapy alignment — not only MACE.

Start with high-yield patients: recurrent angina, troponin-positive events, suspected spasm, or unexplained MINOCA after CMR.

ANOCA endotypes: beyond one-size-fits-all microvascular angina

1001

patients with suspected ANOCA

9

centres across Europe and North America

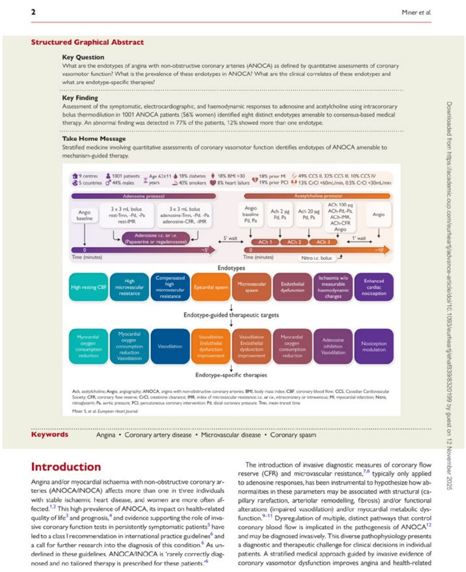
56%

women; mean age 62 years

Study design in one sentence

- Consecutive patients with angina/equivalent symptoms, no severe stenosis, FFR >0.80.
- Bolus thermodilution measured CFR and IMR at rest, after adenosine, and after acetylcholine.
- Symptoms and ECG ischemia were integrated with hemodynamics to classify endotypes.

Core idea: symptoms + ECG + physiology are more informative than angiography alone.


2 Miner *et al.*

Structured Graphical Abstract

Key Question
What are the endotypes of angina with non-obstructive coronary arteries (ANOCA) as defined by quantitative assessments of coronary vasomotor function? What is the prevalence of these endotypes in ANOCA? What are the clinical correlates of these endotypes and what are endotype-specific therapies?

Key Finding
Assessment of the symptomatic, electrocardiographic, and haemodynamic responses to adenosine and acetylcholine using intracoronary bolus thermodilution in 1001 ANOCA patients (56% women) identified eight distinct endotypes amenable to consensus-based medical therapy. An abnormal finding was detected in 77% of the patients, 12% showed more than one endotype.

Take Home Message
Stratified medicine involving quantitative assessments of coronary vasomotor function identifies endotypes of ANOCA amenable to mechanism-guided therapy.

Ach, acetylcholine; Angio, angiography; ANOCA, angina with non-obstructive coronary arteries; BMI, body mass index; CBF, coronary blood flow; CCS, Canadian Cardiovascular Society; CFR, coronary flow reserve; CrCl, creatinine clearance; IMR, index of microvascular resistance; i.c. or i.v., intracoronary or intravenous; MI, myocardial infarction; Nitro, nitroglycerin; Pa, aortic pressure; PCI, percutaneous coronary intervention; Pd, distal coronary pressure; Tmn, mean transit time

Miner S, *et al.* *European Heart Journal.*

Keywords Angina • Coronary artery disease • Microvascular disease • Coronary spasm

Introduction

Angina and/or myocardial ischaemia with non-obstructive coronary arteries (ANOCA/INOCA) affects more than one in three individuals with stable ischaemic heart disease, and women are more often affected.[1,2] This high prevalence of ANOCA, its impact on health-related quality of life[3] and prognosis,[4] and evidence supporting the role of invasive coronary function tests in persistently symptomatic patients[5] have led to a class I recommendation in international practice guidelines[6] and a call for further research into the diagnosis of this condition.[6] As underlined in these guidelines, ANOCA/INOCA is 'rarely correctly diagnosed and no tailored therapy is prescribed for these patients.'[6]

The introduction of invasive diagnostic measures of coronary flow reserve (CFR) and microvascular resistance,[7,8] typically only applied to adenosine responses, has been instrumental to hypothesize how abnormalities in these parameters may be associated with structural (capillary rarefaction, arteriolar remodelling, fibrosis) and/or functional alterations (impaired vasodilation) and/or myocardial metabolic dysfunction.[9–11] Dysregulation of multiple, distinct pathways that control coronary blood flow is implicated in the pathogenesis of ANOCA[12] and may be diagnosed invasively. This diverse pathophysiology presents a diagnostic and therapeutic challenge for clinical decisions in individual patients. A stratified medical approach guided by invasive evidence of coronary vasomotor dysfunction improves angina and health-related

Eight endotypes were identified; abnormal physiology was common

77%

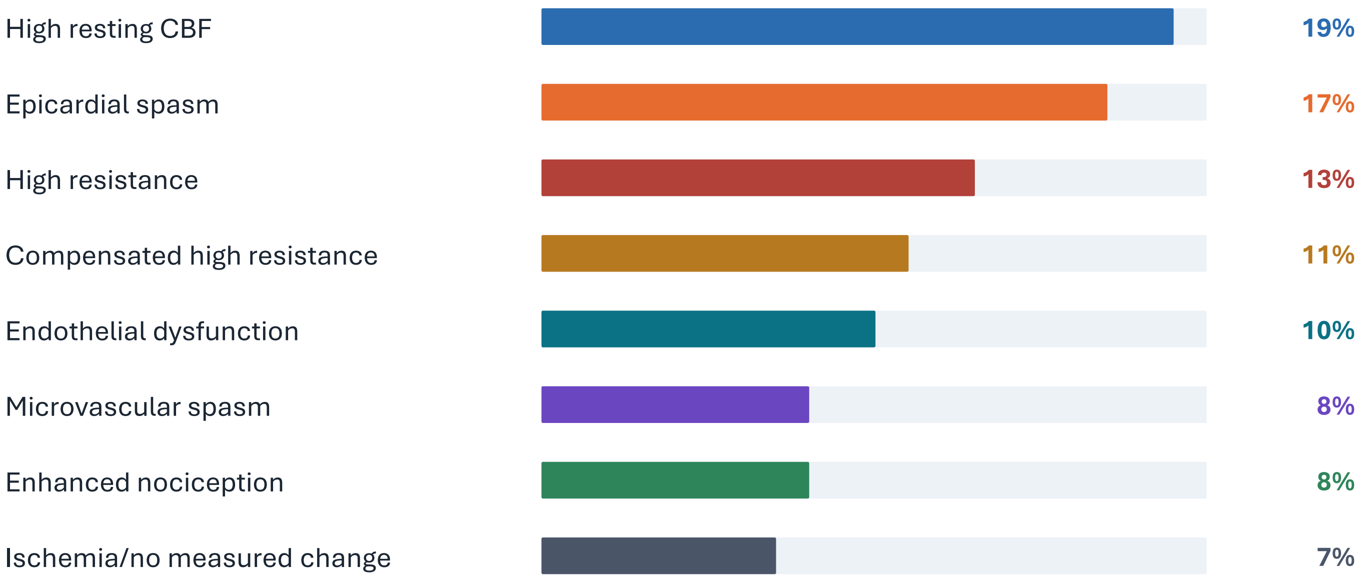
had an abnormal finding

12%

had more than one endotype

23%

had normal responses



Prevalence of distinct endotypes

Two pathways to the phenotype

Adenosine: endothelial-independent vasodilator reserve and microvascular resistance

Acetylcholine: endothelial-dependent vasomotion, spasm, and pain–ischemia mismatch

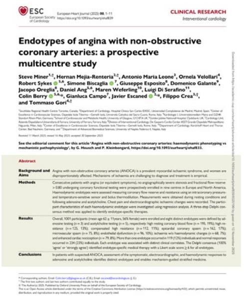
Delphi consensus linked each endotype to targeted medical therapy

Source: Miner et al. EHJ 2025. CBF=coronary blood flow; CFR=coronary flow reserve; IMR=index of microvascular resistance.

Clinical use: endotype determines treatment target

Phenotyping converts “reassurance” into a treatment plan

High resting CBF	→	Reduce myocardial O_2 demand / consider adenosine pathway physiology
High resistance / compensated high resistance	→	Vasodilation + demand reduction
Epicardial or microvascular spasm	→	Vasodilator strategy; CCBs ± nitrates/nicorandil where appropriate
Endothelial dysfunction	→	Endothelial risk-factor optimization; lipid/BP/lifestyle focus
Enhanced cardiac nociception	→	Pain modulation, rehab, noncardiac overlap assessment


ESC European Society of Cardiology
European Heart Journal (2025) 00, 1–11
https://doi.org/10.1093/eurheartj/ehaf839
CLINICAL RESEARCH
Interventional cardiology

Endotypes of angina with non-obstructive coronary arteries: a prospective multicentre study

Steve Miner[1,†], Hernan Mejia-Renteria[2,†], Antonio Maria Leone[3], Ornela Velollari[4], Robert Sykes[5,6], Simone Biscaglia[7], Giuseppe Esposito[8], Domenico Galante[9], Jacopo Oreglia[8], Daniel Ang[5,6], Maren Weferling[10], Luigi Di Serafino[11], Colin Berry[5,6,*], Gianluca Campo[7], Javier Escaned[2,*], Filippo Crea[3,†], and Tommaso Gori[4,†]

See the editorial comment for this article 'Angina with non-obstructive coronary arteries: haemodynamic phenotyping vs mechanistic pathophysiology', by G. Heusch and P. Kleinbongard, https://doi.org/10.1093/eurheartj/ehaf833.

Abstract

Expert caveat

The taxonomy is persuasive, but not yet definitive outcomes evidence. Use it to structure care, not to overclaim prognosis.

AHA statement: nonobstructive CAD is a risk spectrum

The paradigm shift

- Traditional chest-pain workflows focused on obstructive stenosis; CCTA now uncovers large numbers with NOCA.
- Nonobstructive plaque can still drive ACS risk, especially when plaque burden and high-risk features are present.
- Management should align with individualized risk, not a binary primary vs secondary prevention label.

50%

symptomatic CCTA patients may have NOCA

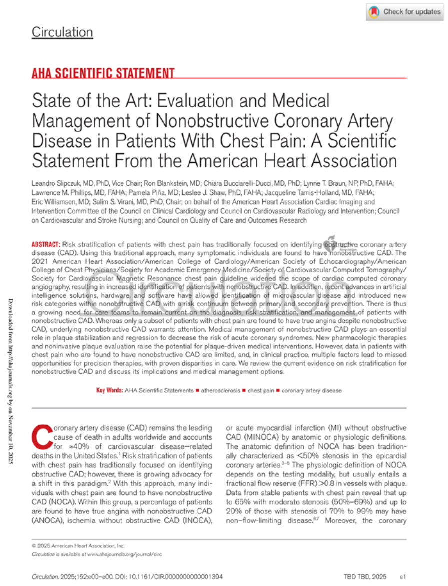
57.1%

AI-QCT changed diagnosis or management

30–50%

CMD may be present without obstructive CAD

Healthcare message: “nonobstructive” should not mean “no disease.”



Circulation

AHA SCIENTIFIC STATEMENT

State of the Art: Evaluation and Medical Management of Nonobstructive Coronary Artery Disease in Patients With Chest Pain: A Scientific Statement From the American Heart Association

Leandro Slipczuk, MD, PhD, Vice Chair; Ron Blankstein, MD; Chiara Bucciarelli-Ducci, MD, PhD; Lynne T. Braun, NP, PhD, FAHA; Lawrence M. Phillips, MD, FAHA; Pamela Piña, MD; Leslee J. Shaw, PhD, FAHA; Jacqueline Tamis-Holland, MD, FAHA; Eric Williamson, MD; Salim S. Virani, MD, PhD, Chair; on behalf of the American Heart Association Cardiac Imaging and Intervention Committee of the Council on Clinical Cardiology and Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research

ABSTRACT: Risk stratification of patients with chest pain has traditionally focused on identifying obstructive coronary artery disease (CAD). Using this traditional approach, many symptomatic individuals are found to have nonobstructive CAD. The 2021 American Heart Association/American College of Cardiology/American Society of Echocardiography/American College of Chest Physicians/Society for Academic Emergency Medicine/Society of Cardiovascular Computed Tomography/Society for Cardiovascular Magnetic Resonance chest pain guideline widened the scope of cardiac computed coronary angiography, resulting in increased identification of patients with nonobstructive CAD. In addition, recent advances in artificial intelligence solutions, hardware, and software have allowed identification of microvascular disease and introduced new risk categories within nonobstructive CAD with a risk continuum between primary and secondary prevention. There is thus a growing need for care teams to remain current on the diagnosis, risk stratification, and management of patients with nonobstructive CAD. Whereas only a subset of patients with chest pain are found to have true angina despite nonobstructive CAD, underlying nonobstructive CAD warrants attention. Medical management of nonobstructive CAD plays an essential role in plaque stabilization and regression to decrease the risk of acute coronary syndromes. New pharmacologic therapies and noninvasive plaque evaluation raise the potential for plaque-driven medical interventions. However, data in patients with chest pain who are found to have nonobstructive CAD are limited, and, in clinical practice, multiple factors lead to missed opportunities for precision therapies, with proven disparities in care. We review the current evidence on risk stratification for nonobstructive CAD and discuss its implications and medical management options.

Key Words: AHA Scientific Statements ■ atherosclerosis ■ chest pain ■ coronary artery disease

Coronary artery disease (CAD) remains the leading cause of death in adults worldwide and accounts for ≈40% of cardiovascular disease–related deaths in the United States.[1] Risk stratification of patients with chest pain has traditionally focused on identifying obstructive CAD; however, there is growing advocacy for a shift in this paradigm.[2] With this approach, many individuals with chest pain are found to have nonobstructive CAD (NOCA). Within this group, a percentage of patients are found to have true angina with nonobstructive CAD (ANOCA), ischemia without obstructive CAD (INOCA), or acute myocardial infarction (MI) without obstructive CAD (MINOCA) by anatomic or physiologic definitions. The anatomic definition of NOCA has been traditionally characterized as <50% stenosis in the epicardial coronary arteries.[3–5] The physiologic definition of NOCA depends on the testing modality, but usually entails a fractional flow reserve (FFR) >0.8 in vessels with plaque. Data from stable patients with chest pain reveal that up to 65% with moderate stenosis (50%–69%) and up to 20% of those with stenosis of 70% to 99% may have non–flow-limiting disease.[6,7] Moreover, the coronary

Circulation is available at www.ahajournals.org/journal/circ

Circulation. 2025;152:e00–e00. DOI: 10.1161/CIR.0000000000001394 TBD TBD, 2025 e1

The proposed staging framework ties plaque burden to treatment intensity

NOCA stages

Stage	Criteria	Management
Stage 0	**CAC 0 / no plaque**	Lifestyle; statin only for selected high-risk features
Stage 1	**CAC 1–99 or mild CCTA plaque**	LDL-C goal <100 mg/dL; risk-factor optimization
Stage 2	**CAC 100–299 or intermediate CCTA burden**	LDL-C goal <70 mg/dL; consider aspirin
Stage 3	**CAC ≥300 or high CCTA burden/high-risk modifiers**	LDL-C goal <55 mg/dL; aspirin; consider additional therapy in extreme risk

Increasing plaque burden / risk → increasing prevention intensity

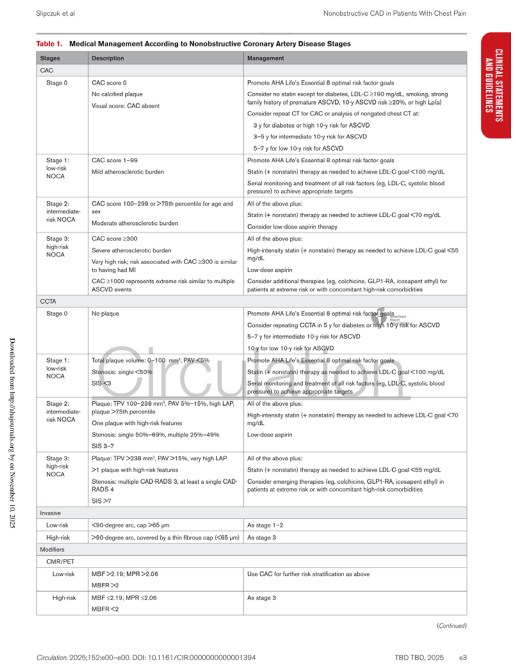


Table 1. Medical Management According to Nonobstructive Coronary Artery Disease Stages

Stages	Description	Management
CAC		
Stage 0	CAC score 0 No calcified plaque Visual score: CAC absent	Promote AHA Life's Essential 8 optimal risk factor goals Consider no statin except for diabetes, LDL-C ≥190 mg/dL, smoking, strong family history of premature ASCVD, 10-y ASCVD risk ≥20%, or high Lp(a) Consider repeat CT for CAC or analysis of nongated chest CT at: 3 y for diabetes or high 10-y risk for ASCVD 3–5 y for intermediate 10-y risk for ASCVD 5–7 y for low 10-y risk for ASCVD
Stage 1: low-risk NOCA	CAC score 1–99 Mild atherosclerotic burden	Promote AHA Life's Essential 8 optimal risk factor goals Statin (+ nonstatin) therapy as needed to achieve LDL-C goal <100 mg/dL Serial monitoring and treatment of all risk factors (eg, LDL-C, systolic blood pressure) to achieve appropriate targets
Stage 2: intermediate-risk NOCA	CAC score 100–299 or >75th percentile for age and sex Moderate atherosclerotic burden	All of the above plus: Statin (+ nonstatin) therapy as needed to achieve LDL-C goal <70 mg/dL Consider low-dose aspirin therapy
Stage 3: high-risk NOCA	CAC score ≥300 Severe atherosclerotic burden Very high risk; risk associated with CAC ≥300 is similar to having had MI CAC ≥1000 represents extreme risk similar to multiple ASCVD events	All of the above plus: High-intensity statin (+ nonstatin) therapy as needed to achieve LDL-C goal <55 mg/dL Low-dose aspirin Consider additional therapies (eg, colchicine, GLP1-RA, icosapent ethyl) for patients at extreme risk or with concomitant high-risk comorbidities
CCTA		
Stage 0	No plaque	Promote AHA Life's Essential 8 optimal risk factor goals Consider repeating CCTA in 5 y for diabetes or high 10-y risk for ASCVD 5–7 y for intermediate 10-y risk for ASCVD 10 y for low 10-y risk for ASCVD
Stage 1: low-risk NOCA	Total plaque volume: 0–100 mm³, PAV <5% Stenosis: single <50% SIS <3	Promote AHA Life's Essential 8 optimal risk factor goals Statin (+ nonstatin) therapy as needed to achieve LDL-C goal <100 mg/dL Serial monitoring and treatment of all risk factors (eg, LDL-C, systolic blood pressure) to achieve appropriate targets
Stage 2: intermediate-risk NOCA	Plaque: TPV 100–238 mm³, PAV 5%–15%, high LAP, plaque >75th percentile One plaque with high-risk features Stenosis: single 50%–69%, multiple 25%–49% SIS 3–7	All of the above plus: High-intensity statin (+ nonstatin) therapy as needed to achieve LDL-C goal <70 mg/dL Low-dose aspirin
Stage 3: high-risk NOCA	Plaque: TPV >238 mm³, PAV >15%, very high LAP >1 plaque with high-risk features Stenosis: multiple CAD-RADS 3, at least a single CAD-RADS 4 SIS >7	All of the above plus: Statin (+ nonstatin) therapy as needed to achieve LDL-C goal <55 mg/dL Consider emerging therapies (eg, colchicine, GLP1-RA, icosapent ethyl) in patients at extreme risk or with concomitant high-risk comorbidities
Invasive		
Low-risk	<90-degree arc, cap >65 µm	As stage 1–2
High-risk	>90-degree arc, covered by a thin fibrous cap (<65 µm)	As stage 3
Modifiers		
CMR/PET		
Low-risk	MBF >2.19; MPR >2.06 MBFR >2	Use CAC for further risk stratification as above
High-risk	MBF ≤2.19; MPR ≤2.06 MBFR <2	As stage 3

(*Continued*)

Implications for a health system: find, stage, treat, track

What to operationalize

1 Report plaque burden

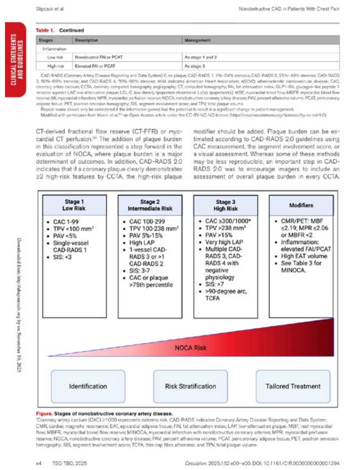
CCTA reports should capture plaque extent, high-risk features, CAD-RADS, and CAC where available.

2 Assign stage

Translate anatomy and physiologic modifiers into a treatment-intensity tier.

3 Close the loop

Ensure lipid targets, aspirin decisions, BP/diabetes/weight therapy, and follow-up are documented.



CT-derived fractional flow reserve (CT-FFR) or myocardial CT perfusion.[30] The addition of plaque burden in this classification represented a step forward in the evaluation of NOCA, where plaque burden is a major determinant of outcomes. In addition, CAD-RADS 2.0 indicates that if a coronary plaque clearly demonstrates ≥2 high-risk features by CCTA, the high-risk plaque modifier should be added. Plaque burden can be estimated according to CAD-RADS 2.0 guidelines using CAC measurement, the segment involvement score, or a visual assessment. Whereas some of these methods may be less reproducible, an important step in CAD-RADS 2.0 was to encourage imagers to include an assessment of overall plaque burden in every CCTA.

Figure. Stages of nonobstructive coronary artery disease.

*Coronary artery calcium (CAC) ≥1000 represents extreme risk. CAD-RADS indicates Coronary Artery Disease Reporting and Data System; CMR, cardiac magnetic resonance; EAT, epicardial adipose tissue; FAI, fat attenuation index; LAP, low-attenuation plaque; MBF, rest myocardial flow; MBFR, myocardial blood flow reserve; MINOCA, myocardial infarction with nonobstructive coronary arteries; MPR, myocardial perfusion reserve; NOCA, nonobstructive coronary artery disease; PAV, percent atheroma volume; PCAT, pericoronary adipose tissue; PET, positron emission tomography; SIS, segment involvement score; TCFA, thin-cap fibro atheroma; and TPV, total plaque volume.

e4 TBD TBD, 2025 *Circulation.* 2025;152:e00–e00. DOI: 10.1161/CIR.0000000000001394

Expert critique

- Conceptually strong: aligns prevention with risk burden rather than stenosis alone.
- Evidence gap: many therapy recommendations extrapolate from obstructive CAD, CAC cohorts, diabetes/HF trials, or secondary-prevention populations.
- Equity issue: CCTA/AI/plaque quantification can widen disparities if access and reporting standards vary.

Acetylcholine testing: the endothelium as a diagnostic target

Why ACh matters

- Gold-standard provocation test for endothelial-dependent dysfunction, epicardial spasm, and microvascular spasm.
- Normal endothelium: nitric-oxide mediated vasodilation. Diseased endothelium: paradoxical vasoconstriction.
- Complements adenosine-based testing, which assesses endothelial-independent vasodilator reserve and resistance.

Endotypes it helps unmask

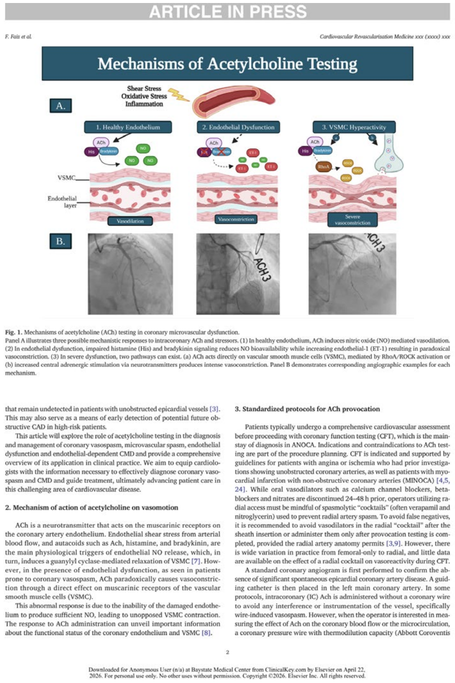
Epicardial spasm

Microvascular spasm

Endothelial dysfunction

Enhanced nociception

Pain–ischemia dissociation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F. Faiz et al. — Cardiovascular Revascularization Medicine xxx (xxxx) xxx

Fig. 1. Mechanisms of acetylcholine (ACh) testing in coronary microvascular dysfunction.
Panel A illustrates three possible mechanistic responses to intracoronary ACh and stressors. (1) In healthy endothelium, ACh induces nitric oxide (NO) mediated vasodilation. (2) In endothelial dysfunction, impaired histamine (His) and bradykinin signaling reduces NO bioavailability while increasing endothelial-1 (ET-1) resulting in paradoxical vasoconstriction. (3) In severe dysfunction, two pathways can exist. (a) ACh acts directly on vascular smooth muscle cells (VSMC), mediated by RhoA/ROCK activation or (b) increased central adrenergic stimulation via neurotransmitters produces intense vasoconstriction. Panel B demonstrates corresponding angiographic examples for each mechanism.

that remain undetected in patients with unobstructed epicardial vessels [3]. This may also serve as a means of early detection of potential future obstructive CAD in high-risk patients.

This article will explore the role of acetylcholine testing in the diagnosis and management of coronary vasospasm, microvascular spasm, endothelial dysfunction and endothelial-dependent CMD and provide a comprehensive overview of its application in clinical practice. We aim to equip cardiologists with the information necessary to effectively diagnose coronary vasospasm and CMD and guide treatment, ultimately advancing patient care in this challenging area of cardiovascular disease.

2. Mechanism of action of acetylcholine on vasomotion

ACh is a neurotransmitter that acts on the muscarinic receptors on the coronary artery endothelium. Endothelial shear stress from arterial blood flow, and autacoids such as Ach, histamine, and bradykinin, are the main physiological triggers of endothelial NO release, which, in turn, induces a guanylyl cyclase-mediated relaxation of VSMC [7]. However, in the presence of endothelial dysfunction, as seen in patients prone to coronary vasospasm, ACh paradoxically causes vasoconstriction through a direct effect on muscarinic receptors of the vascular smooth muscle cells (VSMC).

This abnormal response is due to the inability of the damaged endothelium to produce sufficient NO, leading to unopposed VSMC contraction. The response to ACh administration can unveil important information about the functional status of the coronary endothelium and VSMC [8].

3. Standardized protocols for ACh provocation

Patients typically undergo a comprehensive cardiovascular assessment before proceeding with coronary function testing (CFT), which is the mainstay of diagnosis in ANOCA. Indications and contraindications to ACh testing are part of the procedure planning. CFT is indicated and supported by guidelines for patients with angina or ischemia who had prior investigations showing unobstructed coronary arteries, as well as patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) [4,5,24]. While oral vasodilators such as calcium channel blockers, beta-blockers and nitrates are discontinued 24–48 h prior, operators utilizing radial access must be mindful of spasmolytic "cocktails" (often verapamil and nitroglycerin) used to prevent radial artery spasm. To avoid false negatives, it is recommended to avoid vasodilators in the radial "cocktail" after the sheath insertion or administer them only after provocation testing is completed, provided the radial artery anatomy permits [3,9]. However, there is wide variation in practice from femoral-only to radial, and little data are available on the effect of a radial cocktail on vasoreactivity during CFT.

A standard coronary angiogram is first performed to confirm the absence of significant spontaneous epicardial coronary artery disease. A guiding catheter is then placed in the left main coronary artery. In some protocols, intracoronary (IC) Ach is administered without a coronary wire to avoid any interference or instrumentation of the vessel, specifically wire-induced vasospasm. However, when the operator is interested in measuring the effect of Ach on the coronary blood flow or the microcirculation, a coronary pressure wire with thermodilution capacity (Abbott Coroventis

2

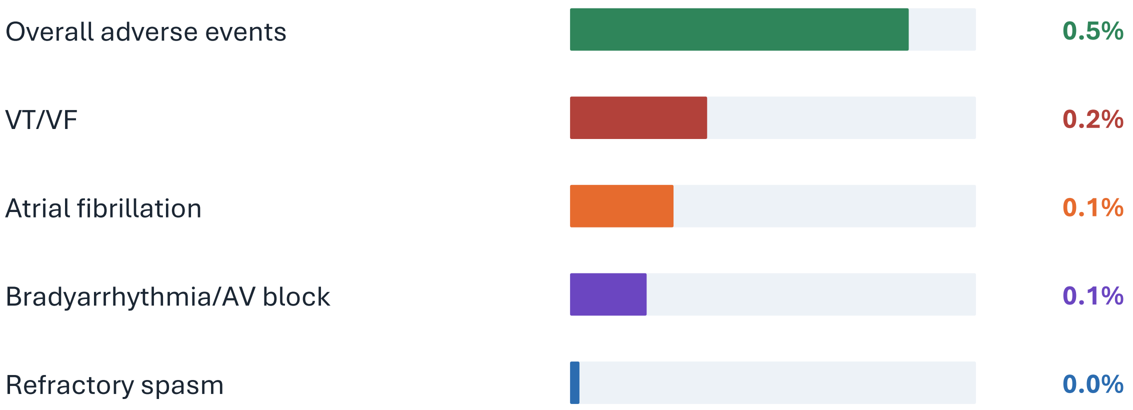
Safety profile: low major complication rates when protocolized

0.50%
overall adverse events

0.20%
VT/VF

0.15%
atrial fibrillation

0%
death reported in summarized table



Do not test casually

- Avoid severe LV dysfunction (LVEF <30%) and severe aortic stenosis.
- Avoid recent MI with clear obstructive culprit disease; consider in MINOCA after plaque rupture/thrombosis ruled out.
- Avoid high-grade AV block/sick sinus; use caution in severe asthma/COPD, uncontrolled hypertension, pregnancy, or allergy.

Testing should be performed in a controlled cath-lab environment with immediate rescue vasodilators and rhythm support available.

Source: Faiz et al. CRM 2026. Safety table and contraindication summary.

Implementation playbook: how to make ACh testing clinically useful

Before the case

- Confirm indication: persistent ANOCA/INOCA symptoms or MINOCA with suspected spasm.
- Hold oral vasodilators 24–48 hours when clinically safe.
- Avoid radial vasodilator “cocktail” before provocation when feasible.

During the case

- Use standardized stepwise dosing and continuous ECG/hemodynamic monitoring.
- Record symptoms, ischemic ECG changes, angiographic constriction, Pd/Pa, CFR and IMR when wire-based testing is used.
- Terminate and reverse promptly with intracoronary nitroglycerin or other vasodilator if needed.

After the case

- Deliver a written endotype diagnosis, not a descriptive cath report only.
- Start endotype-specific therapy before discharge or clinic follow-up.
- Track angina burden, ED visits, medication tolerance, and repeat testing.

1 Indication

2 Protocol

3 Diagnosis

4 Therapy

Bottom line: ACh testing is most valuable when the lab report directly changes the prescription and follow-up plan.

Backup

A randomized, double-blind, placebo-controlled mechanistic study

THE COUNTERINTUITIVE FINDING

Sublingual NTG

decreased resting absolute coronary flow by **− 13.3%**

— directly challenging the simple teaching that NTG relieves angina by increasing total coronary blood flow at rest.

n = 40 patients • Sublingual NTG 800 µg vs placebo • Continuous LAD thermodilution

Study Design

Invasive mechanistic physiology with direct volumetric flow measurement

POPULATION

n = 40

patients referred for invasive coronary angiography for suspected angina or CAD

RANDOMIZATION

20 vs 20

double-blind allocation: sublingual NTG or matched placebo

INTERVENTION

800 µg

sublingual nitroglycerin vs matched sublingual placebo

MEASUREMENT

Thermodilution

continuous intracoronary thermodilution in the LAD — direct volumetric flow (ml/min)

TIMING

0, 5, 10 min

measurements at baseline and 5 / 10 min post-intervention; LVEDP at protocol end

PRIMARY OUTCOME

Δ flow @ 10 min

change in absolute resting coronary blood flow at 10 minutes after intervention

WHY IT MATTERS: *Continuous thermodilution yields direct ml/min flow — avoiding the velocity-only ambiguity of Doppler when the epicardial vessel changes diameter.*

Key Results

Eight hemodynamic and coronary physiology parameters at 10 minutes after sublingual NTG

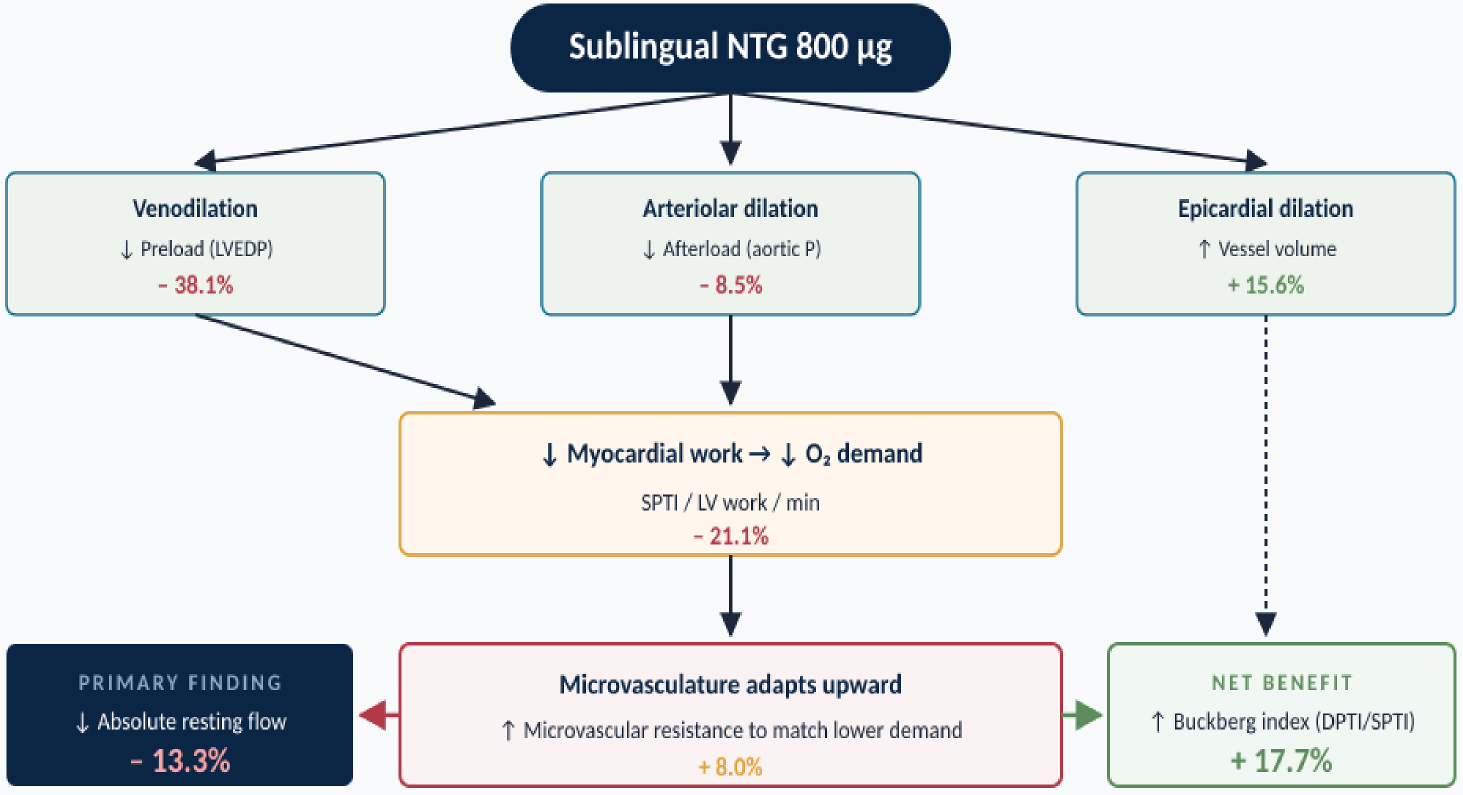
Parameter	Direction	% Change	Interpretation
LVEDP / preload	▼	– 38.1%	*Venodilation reduces LV filling pressure*
Aortic pressure / afterload	▼	– 8.5%	*Reduced systemic afterload from arteriolar vasodilation*
Distal coronary pressure	▼	– 7.4%	*Lower driving pressure tracks the systemic effect*
Myocardial work	▼	– 21.1%	*Direct demand reduction — principal antianginal mechanism*
Vessel volume (epicardial)	▲	+ 15.6%	*Confirms the epicardial vasodilatory effect of nitrate*
Microvascular resistance	▲	+ 8.0%	*Adaptive upregulation matching the lower metabolic demand*
Absolute resting coronary flow	▼	– 13.3%	*PRIMARY FINDING — challenges the 'flow goes up' teaching*
Buckberg index (DPTI / SPTI)	▲	+ 17.7%	*Improved myocardial O_2 supply : demand balance*

PATTERN: *Every load and work index falls; epicardial volume rises; microvascular tone adjusts upward; absolute flow falls — yet supply–demand balance improves.*

Physiologic Mechanism — and the Buckberg Index

How a fall in absolute flow can coexist with an improvement in supply–demand balance

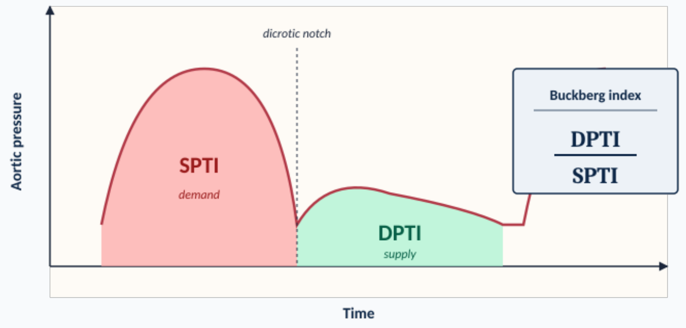
Mechanism Cascade



Net result: improved oxygen supply–demand balance, not increased absolute flow

Buckberg Index

Myocardial O_2 supply ÷ demand from the aortic waveform



SPTI = demand

Area under aortic curve from systole onset to the dicrotic notch

DPTI = supply

Area during diastole — when subendocardial perfusion happens

↑ Buckberg = better balance

After NTG: +17.7% — supply gains relative to demand

THE TEACHING POINT: *Nitrates relieve angina by reducing demand and improving the supply–demand ratio — not by simply raising absolute resting coronary flow.*

Limitations and Clinical Takeaway

A high-quality mechanistic study with important scope boundaries

STRENGTHS

1. **Randomized, double-blind, placebo-controlled**
   Highest mechanistic-evidence design class
2. **Direct volumetric flow measurement**
   Continuous intracoronary thermodilution; avoids Doppler-velocity ambiguity when vessel size changes
3. **Clean physiologic protocol**
   Vasoactive medications carefully withheld before and during the study
4. **Multi-parameter integration**
   Hemodynamics + coronary pressure + flow + microvascular resistance + work, all in the same protocol
5. **Clinically relevant dose**
   Standard 800 µg sublingual nitroglycerin

LIMITATIONS

1. **Resting-only protocol**
   Does not address exercise, pharmacologic hyperemia, or active angina
2. **Small sample (n = 40)**
   Mechanistic-scale; limits subgroups and generalizability
3. **Selected population**
   Severe stenosis, HF, valve disease, prior CABG, arrhythmia excluded
4. **Mostly mild–moderate disease**
   Don't extrapolate to critical stenoses, ACS, or collateral-dependent territories
5. **LAD-only measurement**
   RCA, LCx and regional flow redistribution not assessed

CLINICAL TEACHING WORDING

"Sublingual NTG relieves angina largely by reducing preload, afterload, wall stress, and myocardial O_2 demand. Although it dilates epicardial coronary arteries, resting absolute coronary flow may decrease because metabolic demand falls and the microcirculation adapts accordingly."

NEXT STEP: *A parallel study during exercise or pharmacologic hyperemia — especially in physiologically significant epicardial disease or established microvascular dysfunction.*