

Physiological Assessment of Non-obstructive Coronary Disease (INOCA)

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Disclosures / Conflicts of interest

Speaker's name: Javier Escaned

I have the following potential conflicts of interest to report in the field of this presentation:

Speaker at educational events and consultancies: Abbott, Philips Healthcare

Background: ischemia and non-obstructive CAD

- 20-30% of patients presenting with chest discomfort characteristic of angina demonstrate no signs of obstructive CAD (NOCAD).
- Frequent clinical scenarios :
 - Angiographically normal coronary arteries
 - Functionally non-obstructive CAD (non-ischaemic iFR/FFR)
 - Persistent post-PCI angina
- Causes severe impairment of quality of life and large healthcare costs.

Diagnostic yield of angiography and non-diagnostic tests

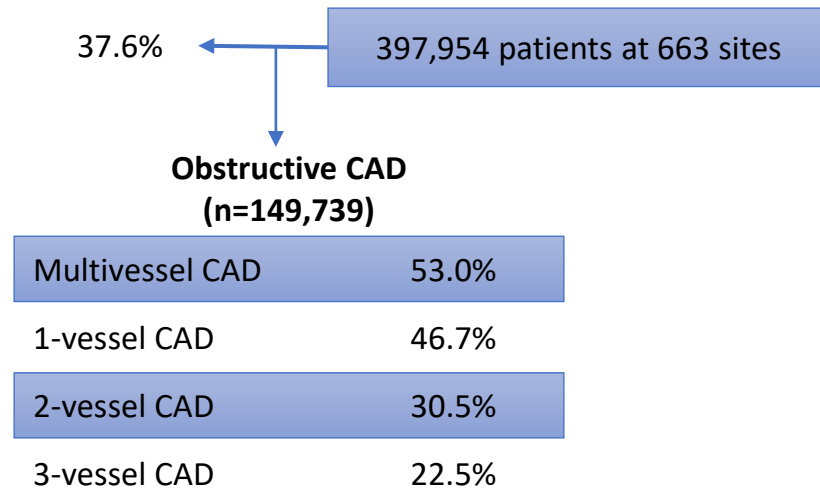
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Low Diagnostic Yield of Elective Coronary Angiography

Manesh R. Patel, M.D., Eric D. Peterson, M.D., M.P.H., David Dai, M.S., J. Matthew Brennan, M.D., Rita F. Redberg, M.D., H. Vernon Anderson, M.D., Ralph G. Brindis, M.D., and Pamela S. Douglas, M.D.

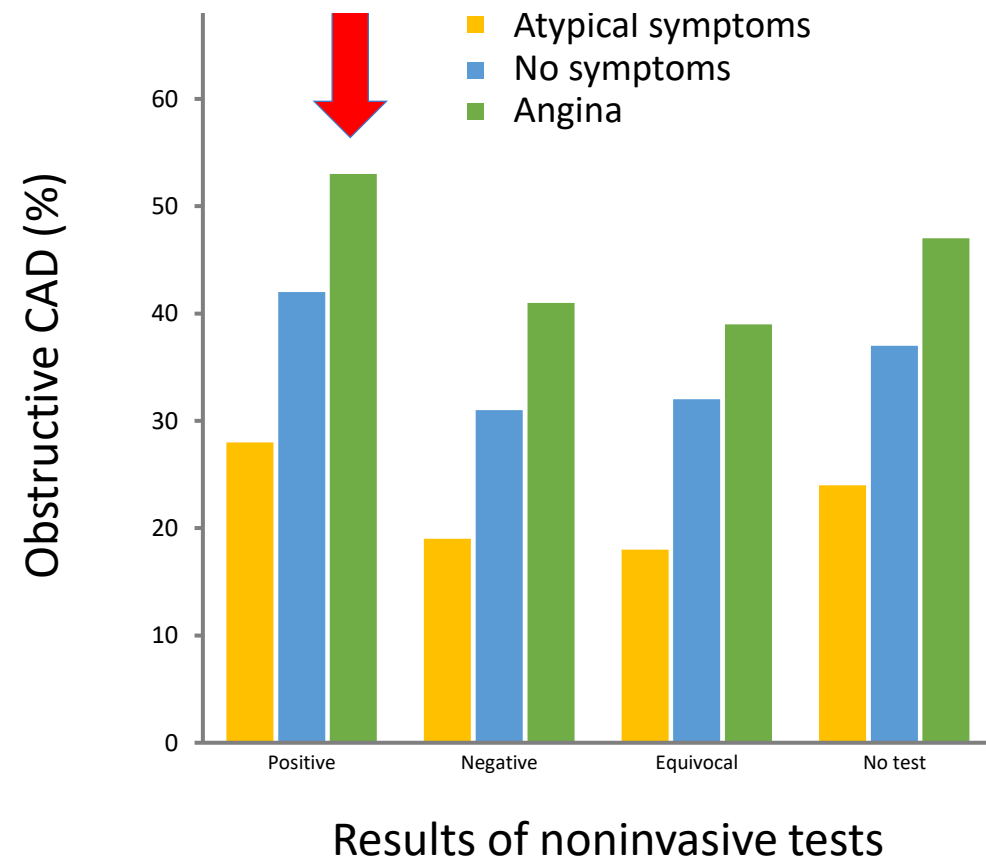
Study Population and Rates of Obstructive Coronary Artery Disease



Best possible scenario:

angina + demonstrated ischaemia:

>45% have no obstructive CAD (ANOCA)



Knowledge shifts in INOCA over last 10 years

- From Syndrome X to NOCAD
- From a single physiological index to combined tests
- From microcirculatory disease to endotypes of vascular dysfunction
- From cardiovascular events to patient symptoms

From Syndrome X to INOCA

1985



The American Journal of Cardiology
Volume 55, Issue 3, 25 January 1985, Pages B50-B60



Chest pain and “normal” coronary arteries—Role of small coronary arteries

Richard O. Cannon III MD ^{1,2}, Martin B. Leon MD, Rita M. Watson MD, Douglas R. Rosing MD, Stephen E. Epstein MD

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[https://doi.org/10.1016/0002-9149\(85\)90613-7](https://doi.org/10.1016/0002-9149(85)90613-7)

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Abstract

To study the mechanism of chest pain in patients with insignificant epicardial coronary artery disease, 50 patients underwent great cardiac vein (GCV) flow, oxygen content and lactate determinations at rest and during pacing, and left ventricular end-diastolic pressure (LVEDP) measurements at rest and after pacing. Twenty-four patients having typical chest discomfort during pacing demonstrated significantly lower increase in flow from baseline ($36 \pm 18\%$ versus $86 \pm 24\%$, $p <$

Syndrome X
Unknown etiology
Diagnosis by exclusión
Considered a benign condition

2019

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VOL. 73, NO. 6, 2019

Impact of Abnormal Coronary Reactivity on Long-Term Clinical Outcomes in Women



Ahmed AlBadri, MD,¹ C. Noel Bailey Merz, MD,² B. Della Johnson, PhD,³ Janet Wei, MD,¹ Puja K. Mohta, MD,² Galen Cook-Wiens, MS,⁴ Steven E. Reis, MD,⁵ Sheryl F. Kelsey, PhD,⁶ Vera Bittner, MD,⁶ George Sopko, MD,⁷ Leslee J. Shaw, PhD,⁴ Carl J. Pepine, MD,⁸ Bina Ahmed, MD¹

ABSTRACT

BACKGROUND Currently as many as one-half of women with suspected myocardial ischemia have no obstructive coronary artery disease (CAD), and abnormal coronary reactivity (CR) is commonly found.

OBJECTIVES The authors prospectively investigated CR and longer-term adverse cardiovascular outcomes in women with and with no obstructive CAD in the National Heart, Lung, and Blood Institute-sponsored WISE (Women's Ischemia Syndrome Evaluation) study.

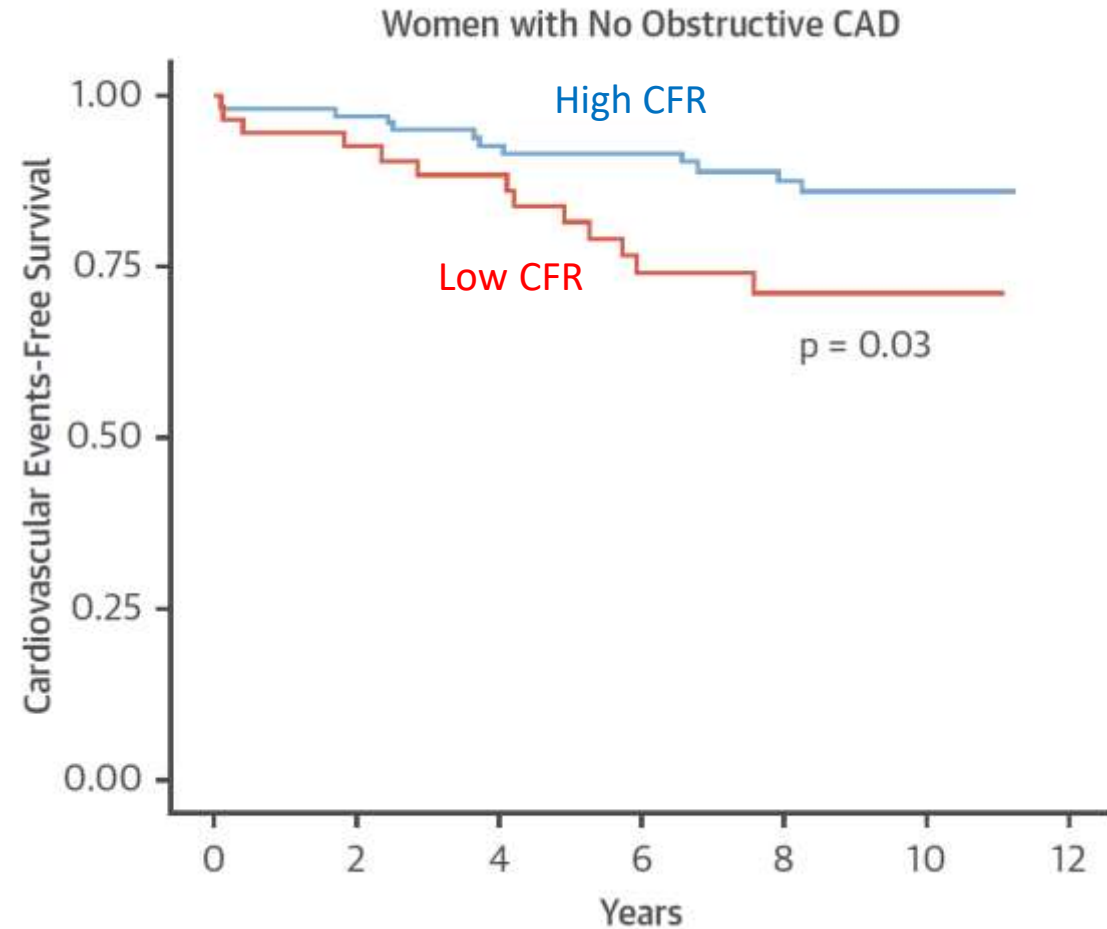
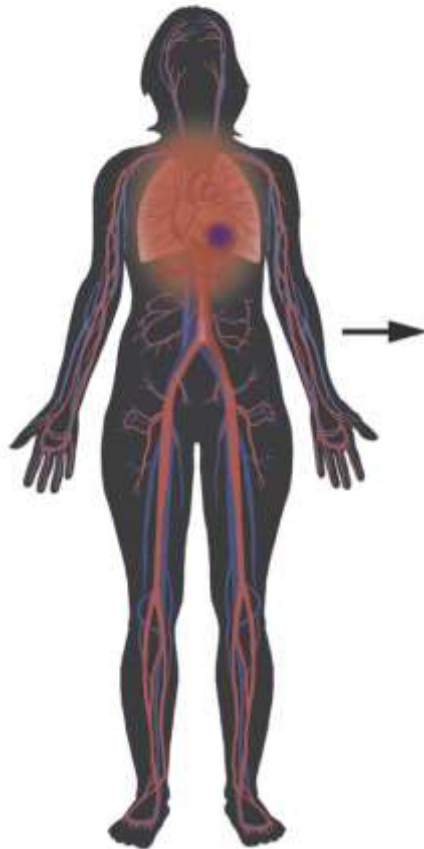
METHODS Women ($n = 224$) with signs and symptoms of ischemia underwent CR testing. Coronary flow reserve and coronary blood flow were obtained to test microvascular function, whereas epicardial CR was tested by coronary dilation response to intracoronary (IC) acetylcholine and IC nitroglycerin. All-cause mortality, major adverse cardiovascular events (MACE) (cardiovascular death, myocardial infarction, stroke, and heart failure), and angina hospitalizations served as clinical outcomes over a median follow-up of 9.7 years.

RESULTS The authors identified 129 events during the follow-up period. Low coronary flow reserve was a predictor of increased MACE rate (hazard ratio [HR]: 1.06; 95% confidence interval [CI]: 1.01 to 1.12; $p = 0.021$), whereas low coronary blood flow was associated with increased risk of mortality (HR: 1.12; 95% CI: 1.01 to 1.24; $p = 0.038$) and MACE (HR: 1.11; 95% CI: 1.03 to 1.20; $p = 0.002$), after adjustment for confounding risk factors. In addition, a decrease in

INOCA
Clear dysfunction pathways
Diagnosis based on objective evidence
Entails a bad prognosis

Abnormal CFR in women with INOCA

Women with Signs and Symptoms of Ischemia



Knowledge shifts in INOCA over last 10 years

- From Syndrome X to NOCAD
- From a single physiological index to combined tests
- From microcirculatory disease to endotypes of vascular dysfunction
- From cardiovascular events to patient symptoms

Interrogating epicardial vessels and the microcirculation



Main function:

Conductance

Tests :

-FFR, iFR

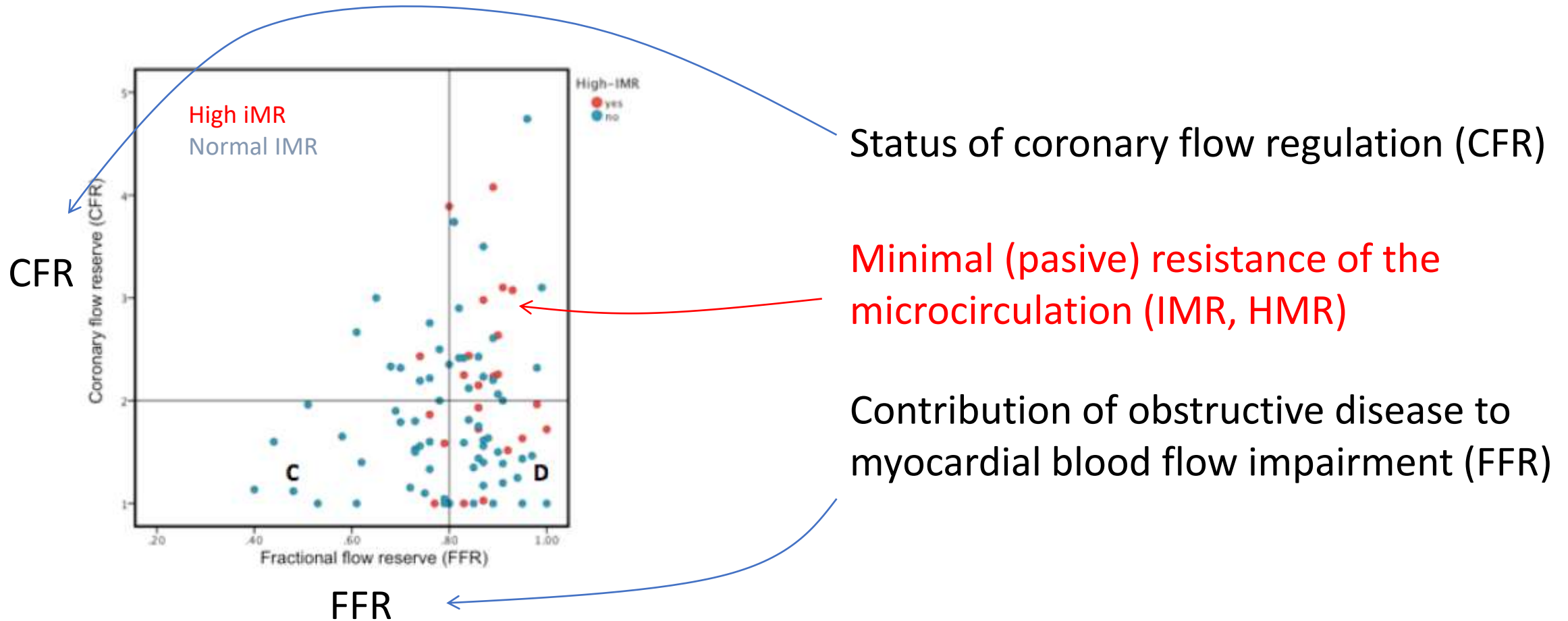
Main function:

Regulation blood supply + conductance

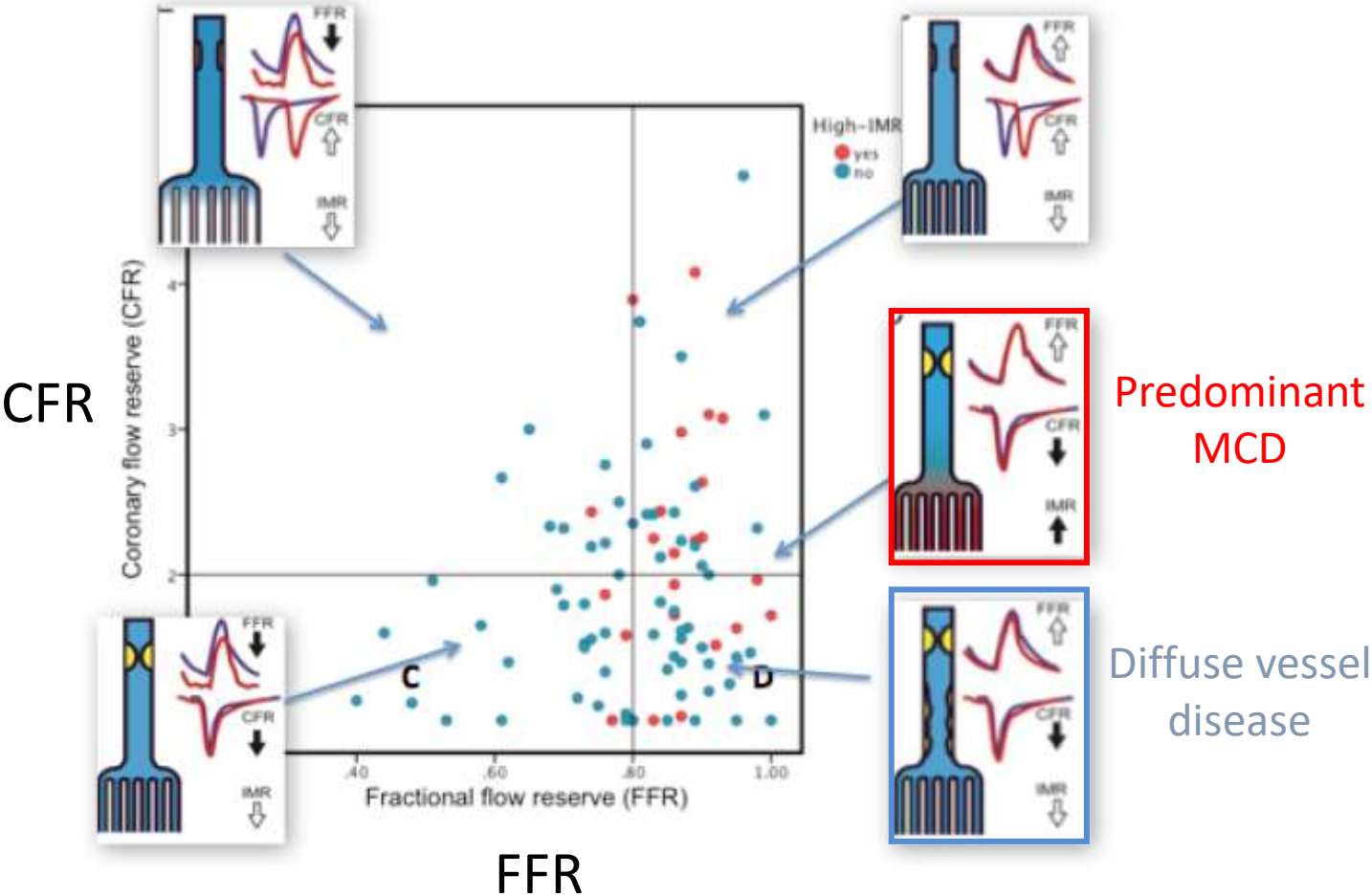
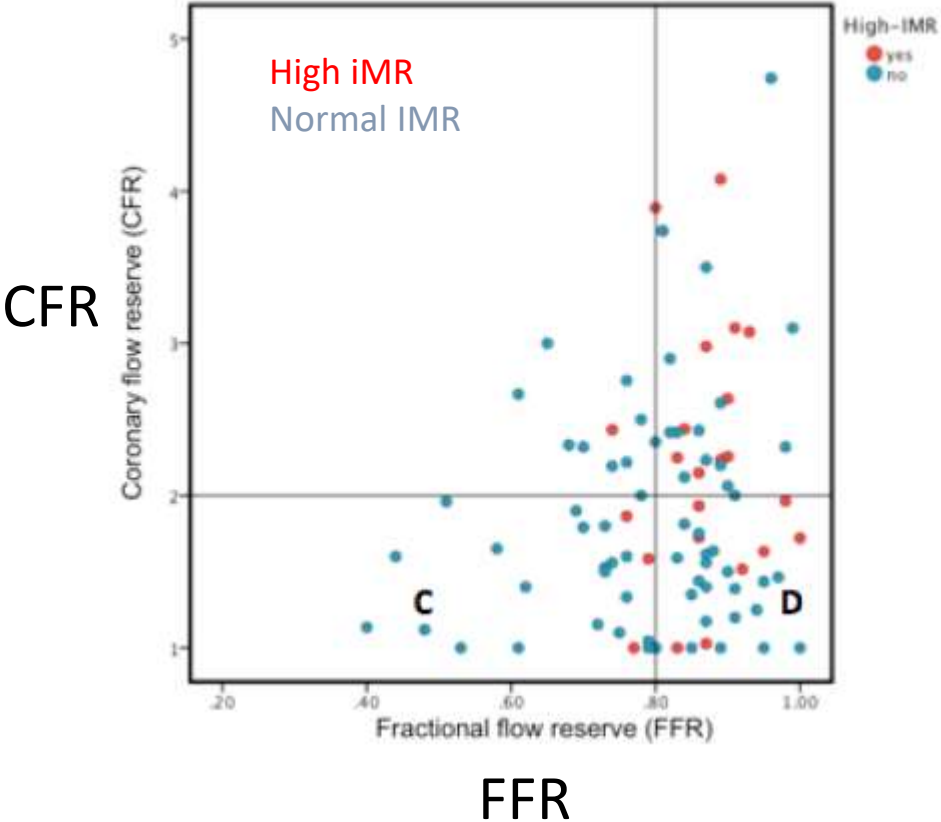
Tests:

-CFR (endothelial- and non-endothelial dependent)
-Minimal resistance (i.e. decreased conductance)

Combining FFR, CFR and microvascular resistance



Combining FFR, CFR and resistance



Knowledge shifts in INOCA over last 10 years

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- From cardiovascular events to patient symptoms

From microcirculatory disease to endotypes of vascular dysfunction

2017

Int J Cardiovasc Imaging
DOI 10.1007/s10554-017-1136-9



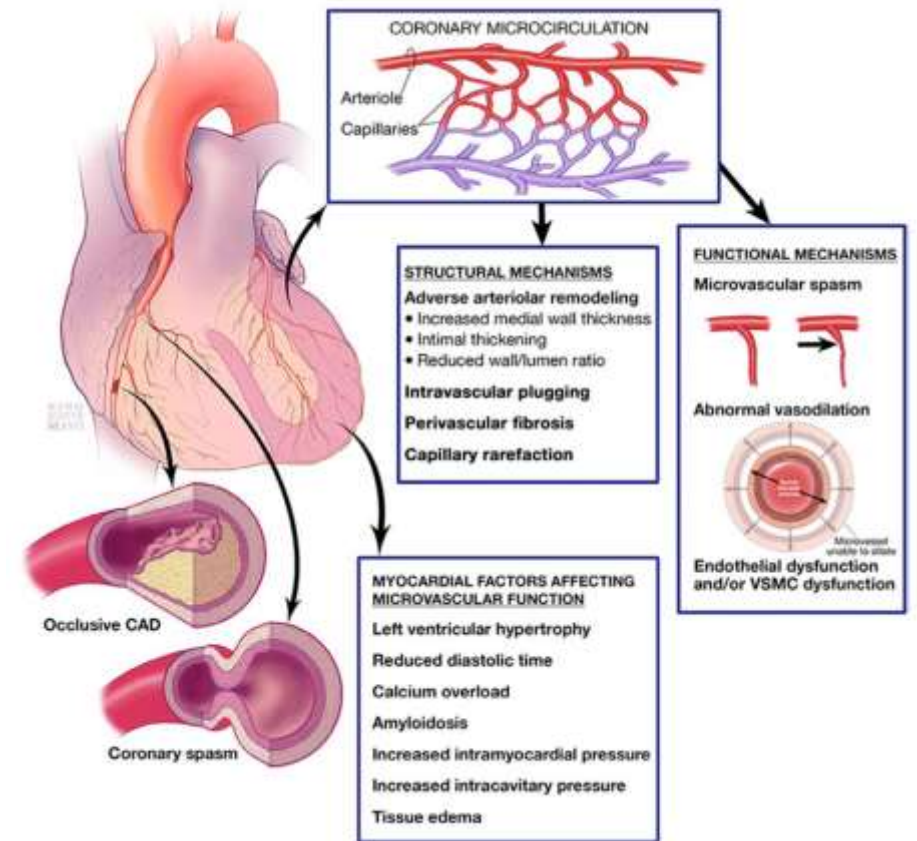
REVIEW PAPER

Targeting the dominant mechanism of coronary microvascular dysfunction with intracoronary physiology tests

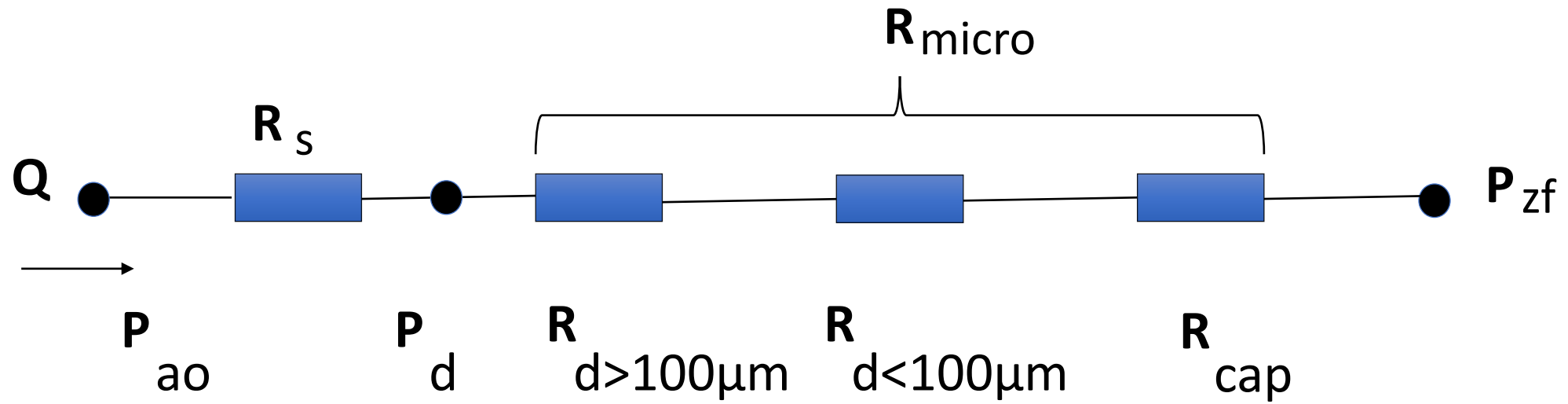
Hernán Mejía-Rentería^{1,3} · Nina van der Hoeven⁴ · Tim P. van de Hoef⁵ · Julius Heemelaar⁴ · Nicola Ryan¹ · Amir Lerman⁶ · Niels van Royen⁴ · Javier Escaned^{1,2,3}

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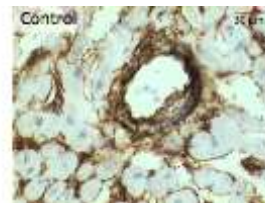
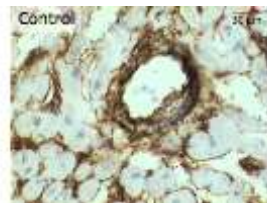
Abstract The coronary microcirculation plays a key role in myocardial perfusion. In this paper we discuss the mechanisms of coronary microvascu-



A resistive map of the coronary circulation



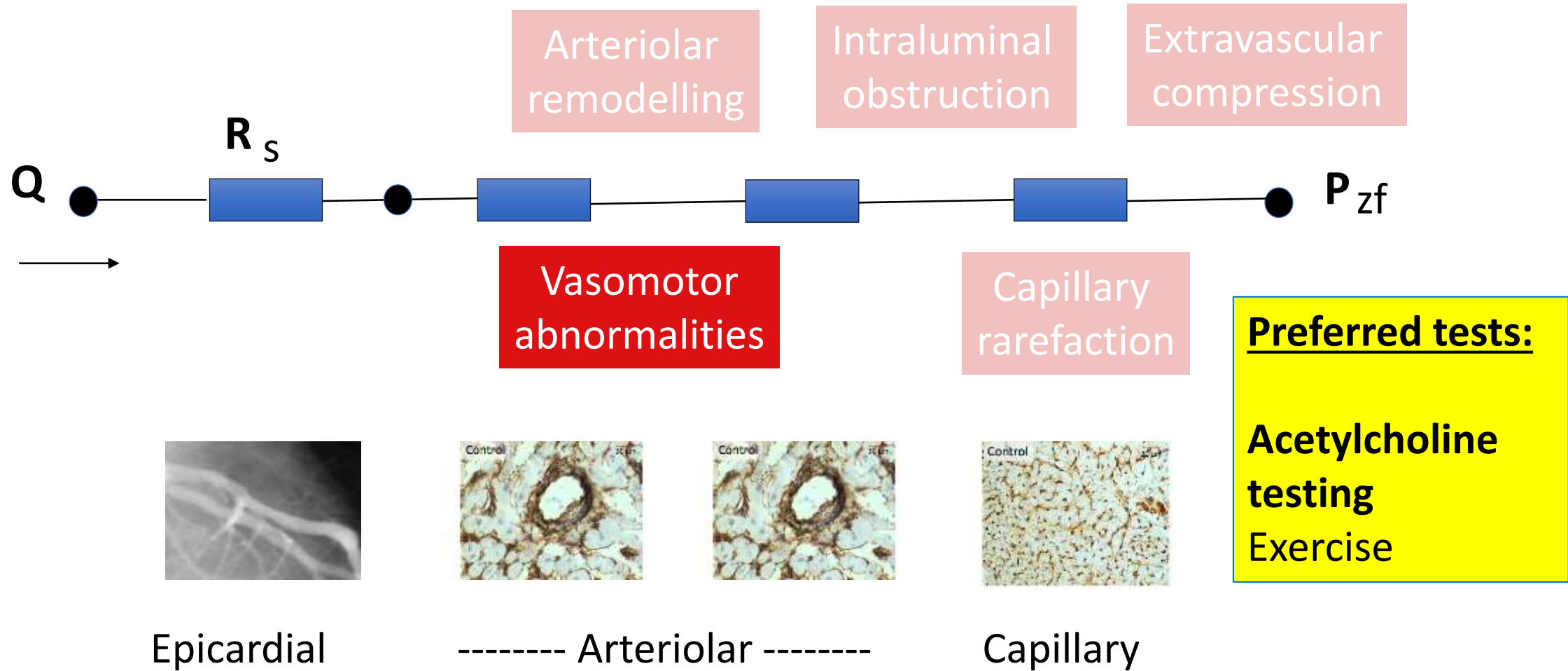
Epicardial



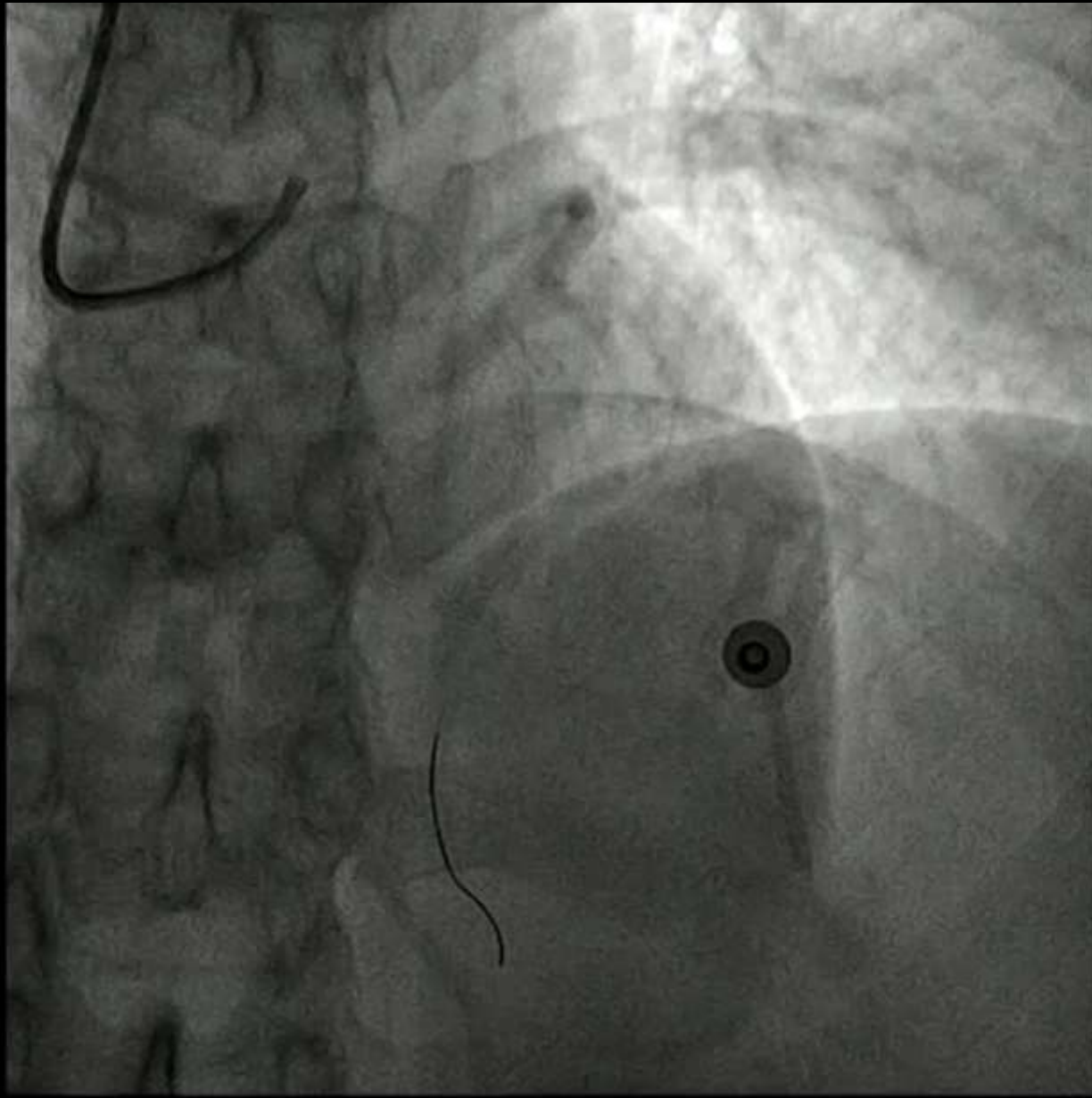
----- Arteriolar -----

Capillary

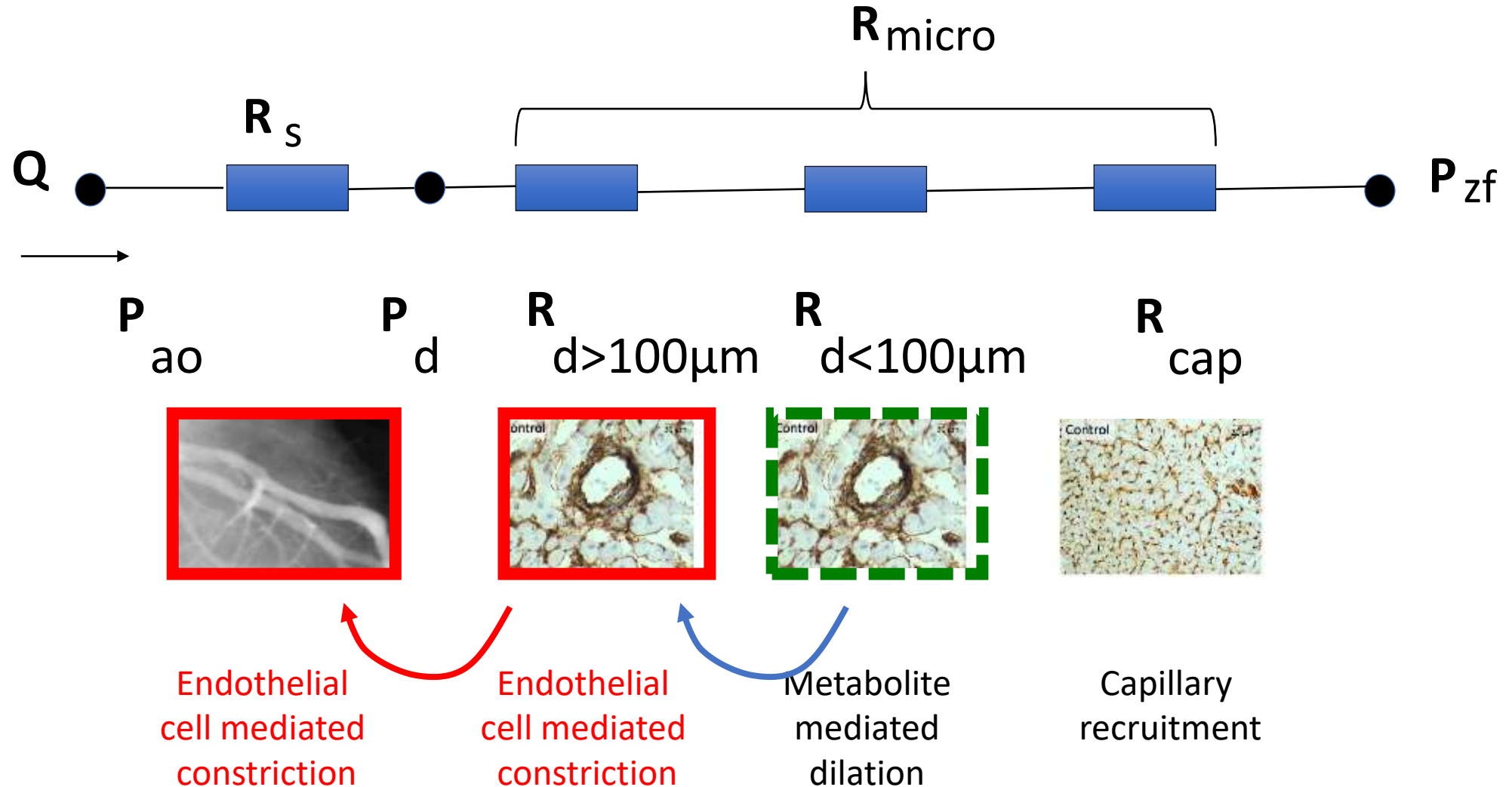
Vasomotor INOCA endotype



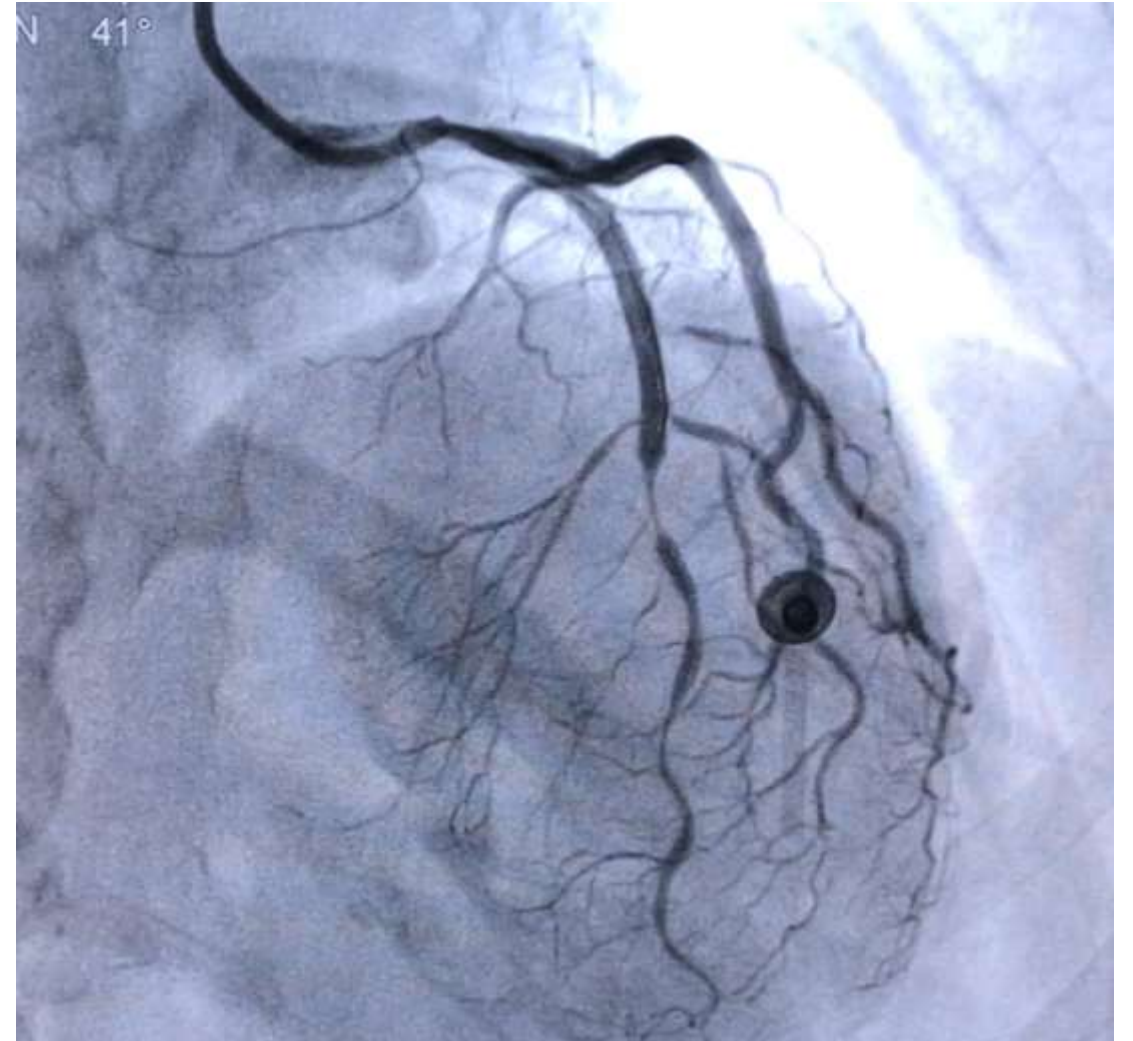
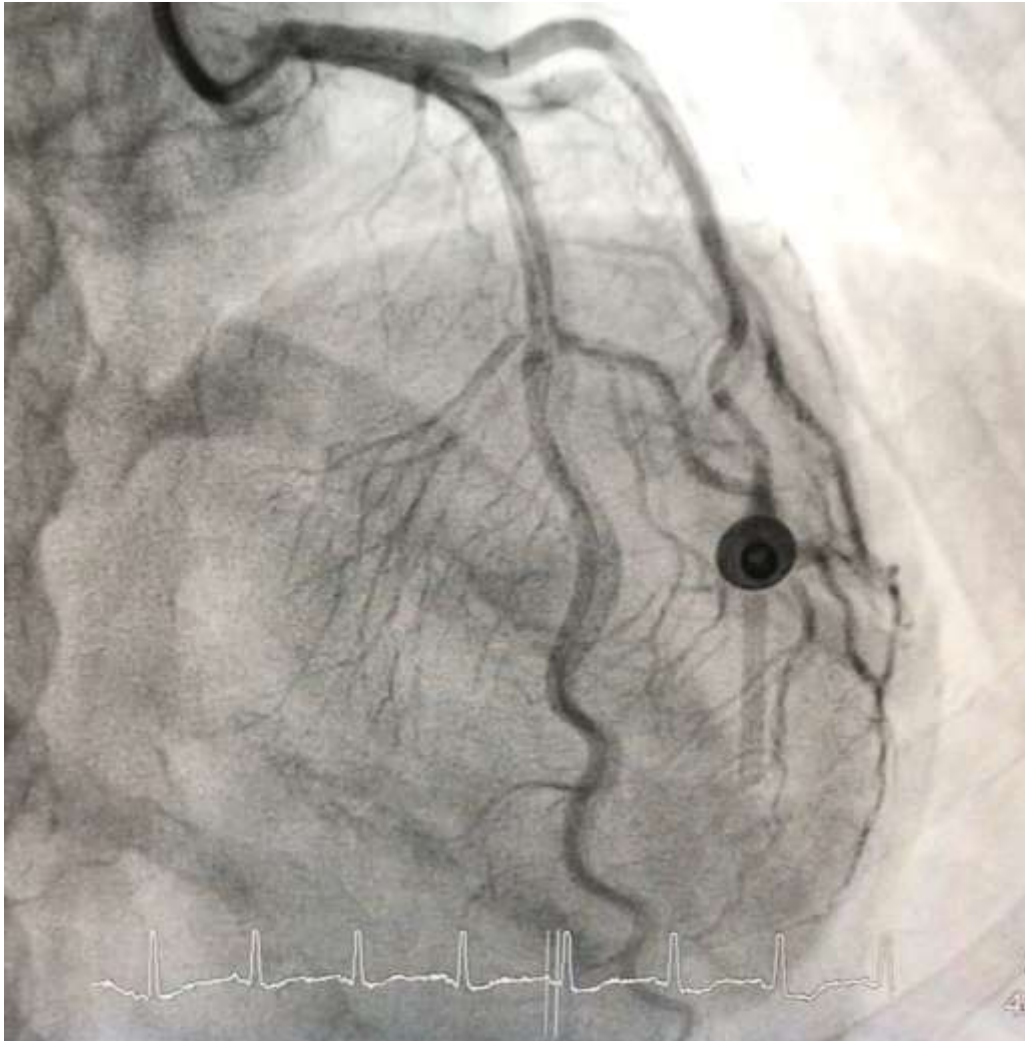
Female patient, prior stenting LAD/DX, persisting angina



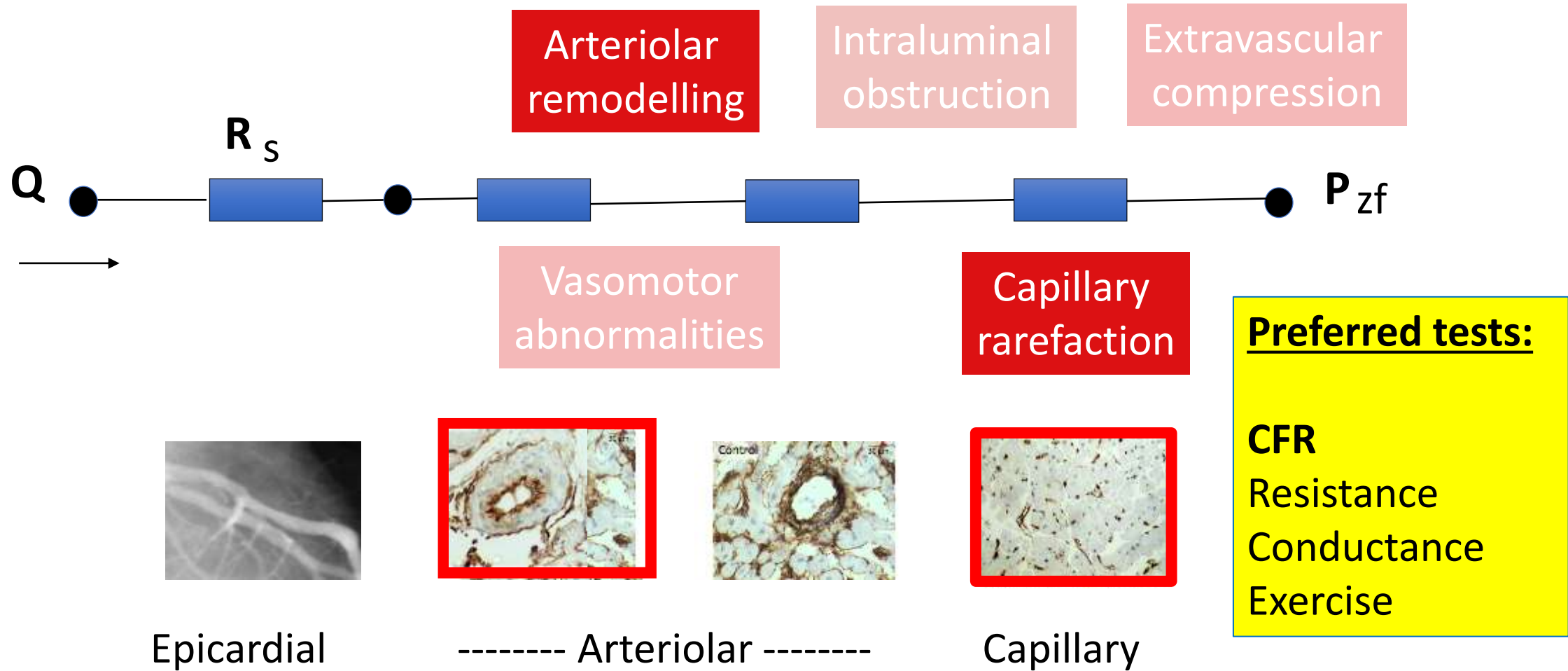
Vasomotor INOCA endotype



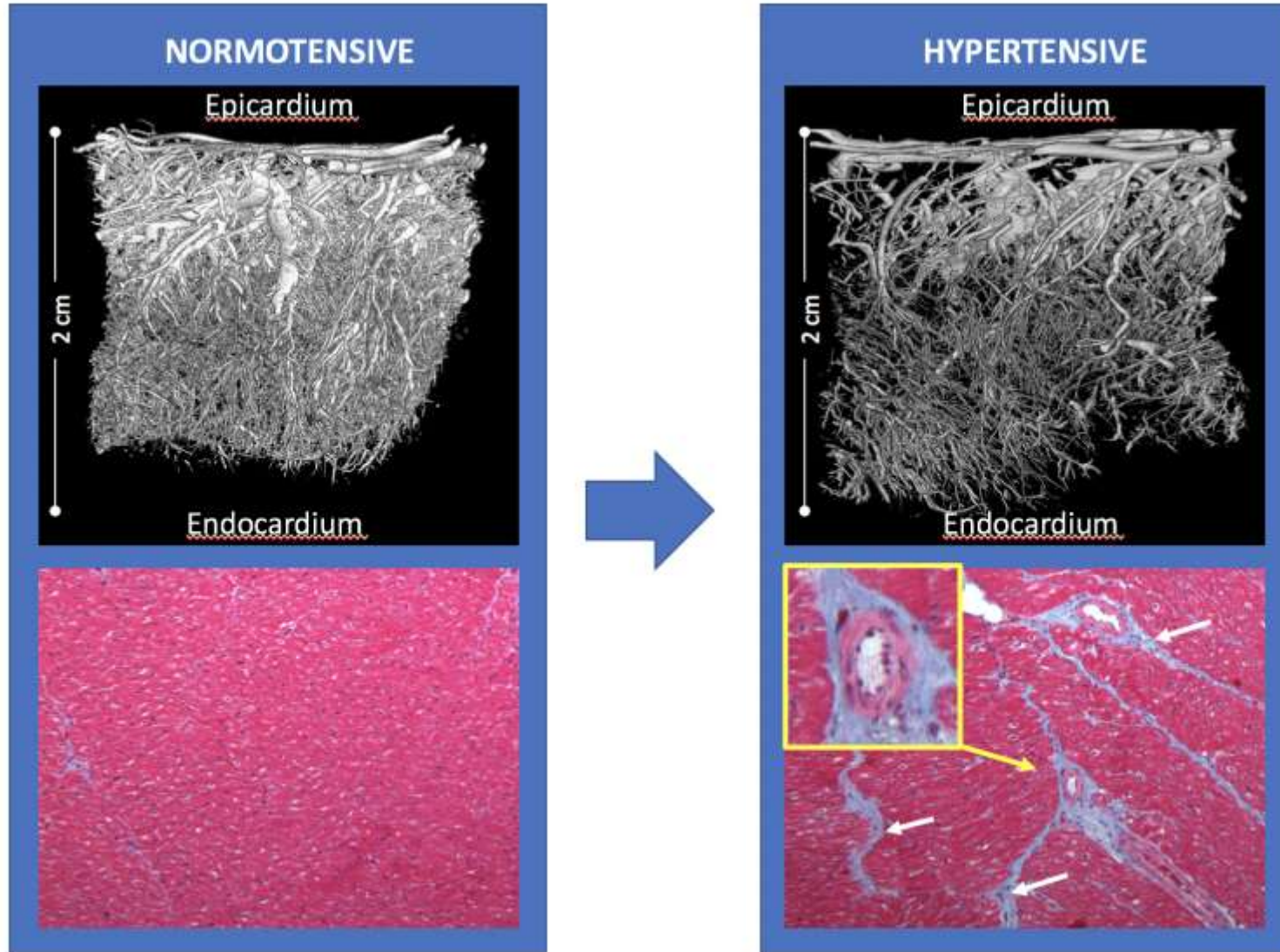
Persistent angina after stent implantation



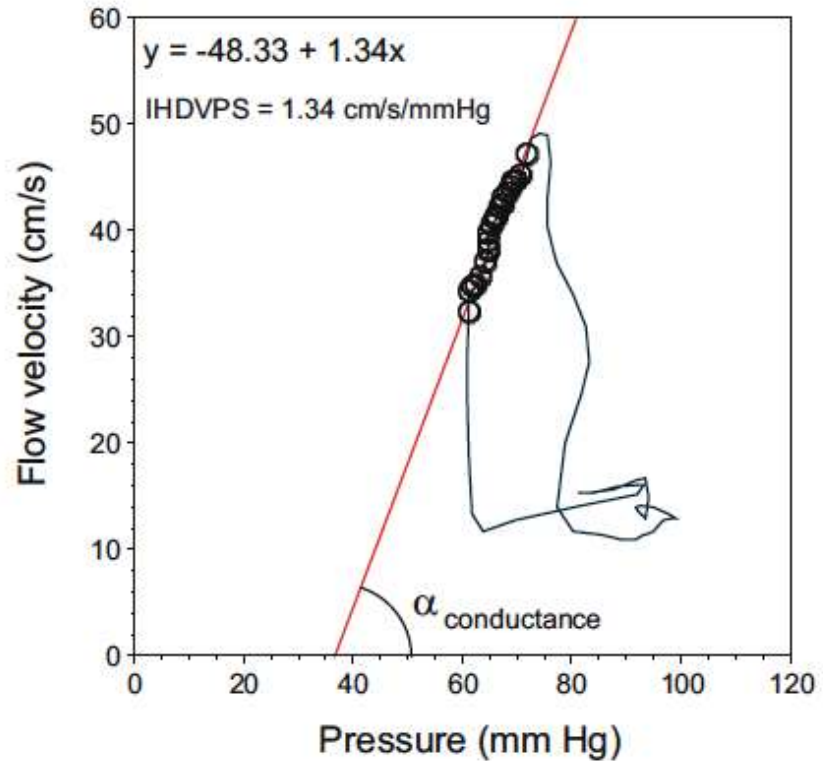
Structural microvascular remodelling INOCA endotype



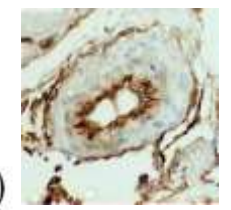
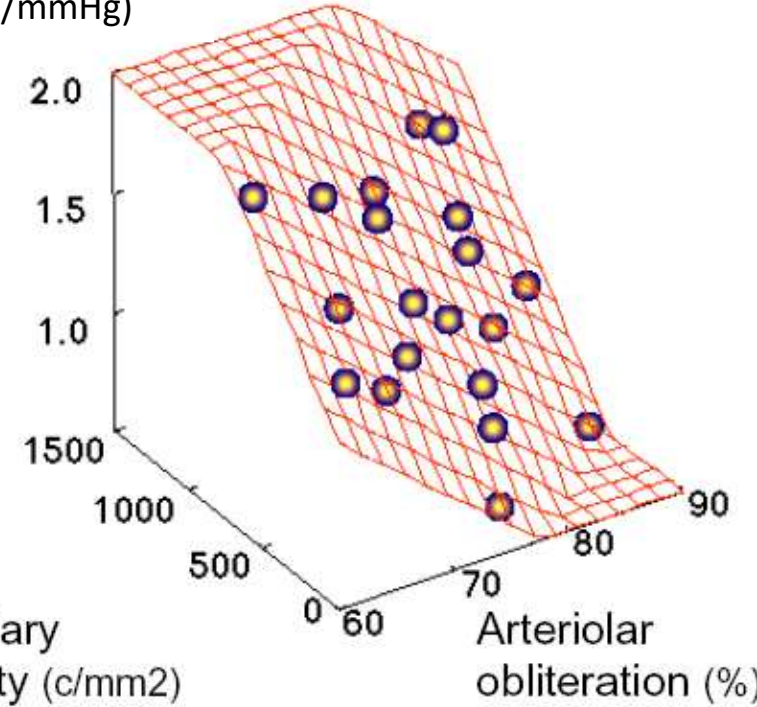
Microvascular remodelling in HTN



Microcirculatory conductance and structural remodelling of arterioles and capillaries

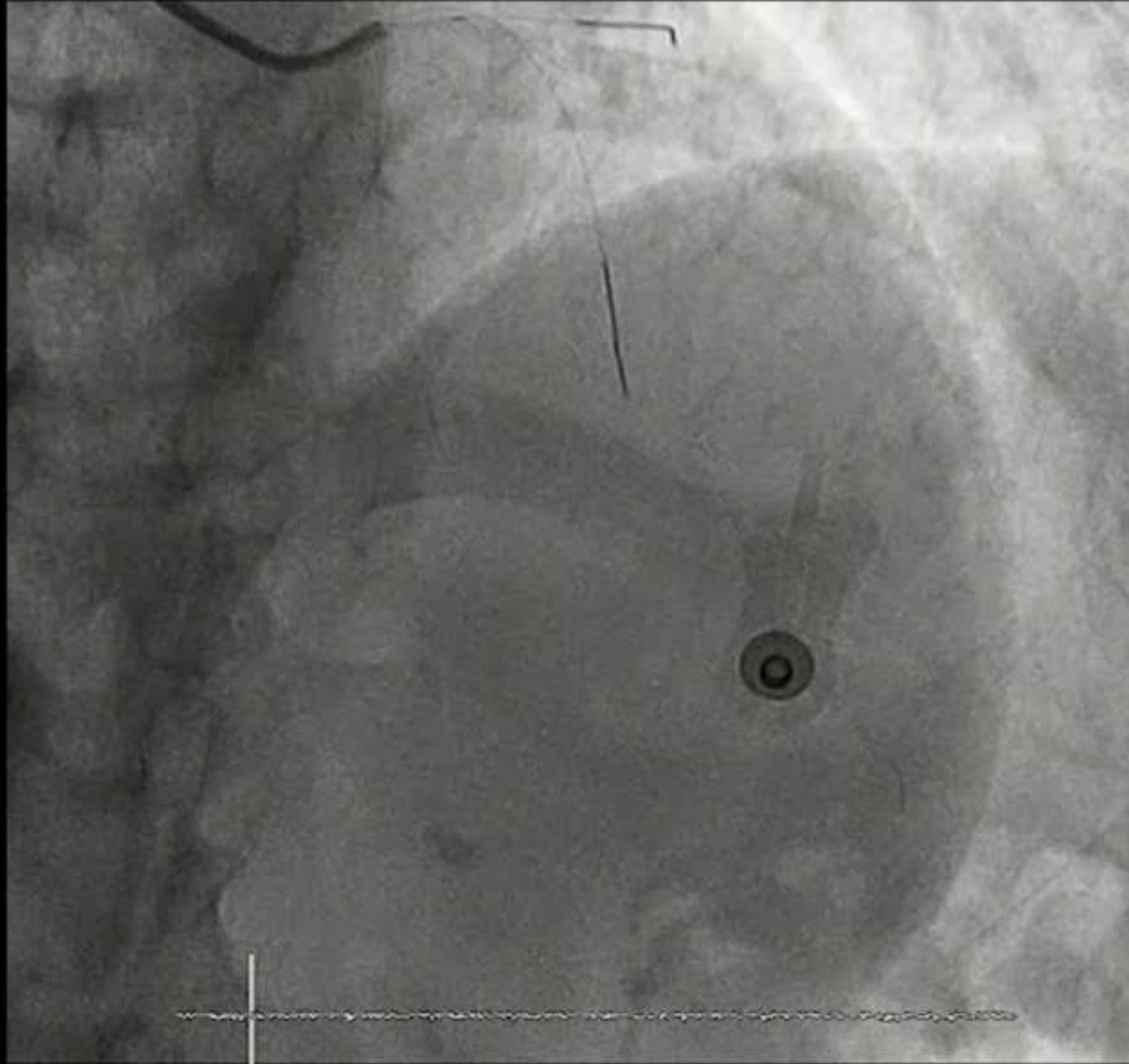


Microcirculatory
Conductance
(cm/s/mmHg)



Validation of physiology measurements against endomyocardial biopsies.
Both arteriolar obliteration and myocardial capillary rarefaction are independent contributors to decreased microvascular conductance.

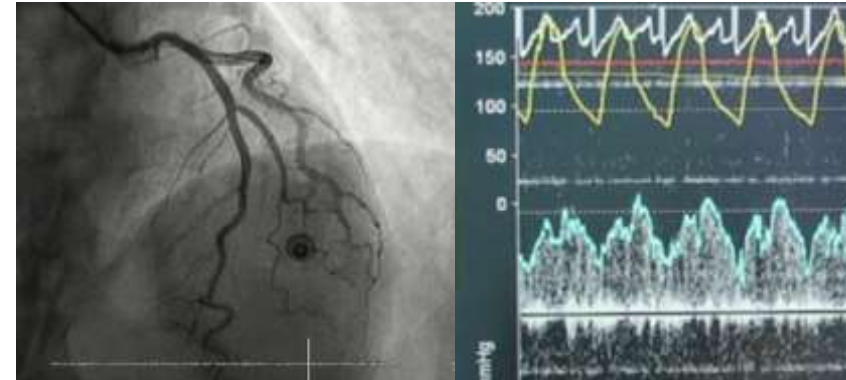
Female patient, hypertension + LVH, positive ET (LBBB)



Case examples of structural microvascular remodelling

Clinical case #1

- Reduced CFR (1.4)
- High resting flow (41 cm/s)
- High microvascular resistance (HMR = 2.6)



Clinical case #2

- Reduced CFR (1.6)
- High microvascular resistance (IMR = 31)



Assessment of pathways of dysfunction in a nutshell

Structural endotype

Endothelium-independent pathways of dysfunction (adenosine)

Thermo + pressure

- $CFR \leq 2.0$
- $IMR > 25$ units

Doppler + pressure

- $CFR \leq 2.5$
- $HMR > 2.5$ mmHg/cm/s

Vasomotor endotype

Endothelium-dependent pathways of dysfunction (Ach)

EKG / Angio

- EKG changes (12 lead)
- Epicardial / arteriolar spasm (\downarrow flow)
- $CFR_{Ach} \leq 1.5$ (Doppler)

Knowledge shifts influencing ESC guideline recommendations

- From Syndrome X to NOCAD
- From a single physiological index to combined tests
- From microcirculatory disease to endotypes of vascular dysfunction
- From cardiovascular events to patient symptoms

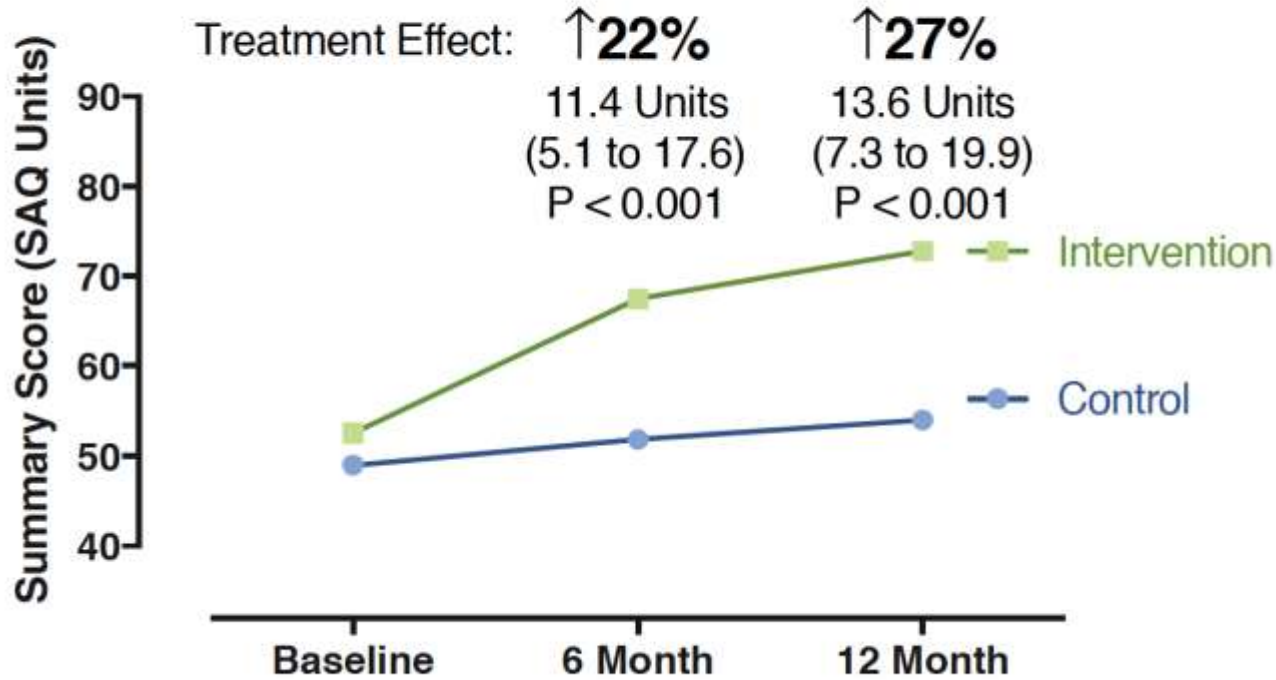
Stratified treatment of INOCA in a nutshell

- **Structural remodeling?** (Low CFR/high IMR) → Reduce VO₂ (BB, CCB) and control triggering factors of MV remodeling (CRF and other), statins.
- **Vasomotor disorders?** (abnormal Ach testing) → Control vascular tone (CCB, nitrates, vasodilators), ACE inhibitors, statins
- **Pain triggered by adenosine or iodinated contrast?** → Consider aminophylline / caffeine, tricyclic antidepressants

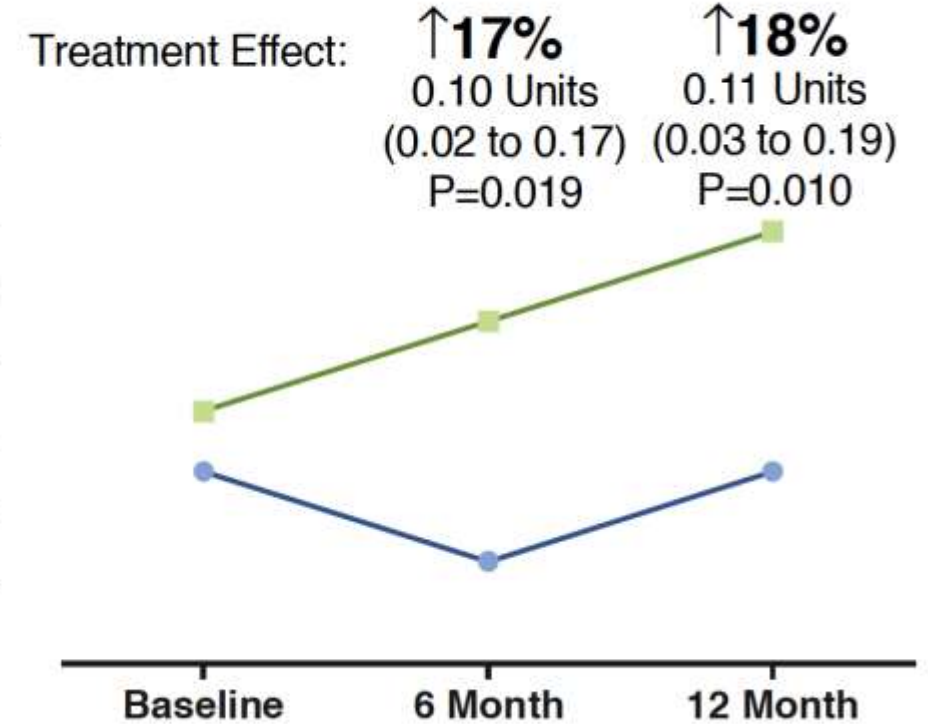
In all cases: lifestyle modification, quantification of therapeutic progress (SAQ)

CORMICA study population / 6 and 12 month FU

Primary Endpoint: Angina Severity

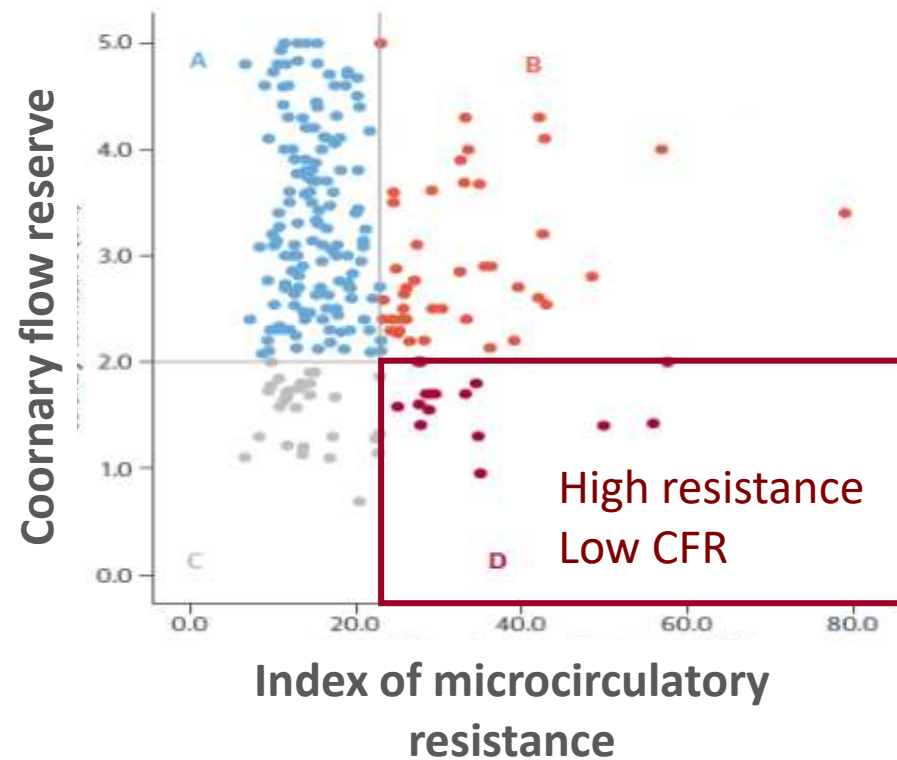


Quality of Life (EQ5D - Index)

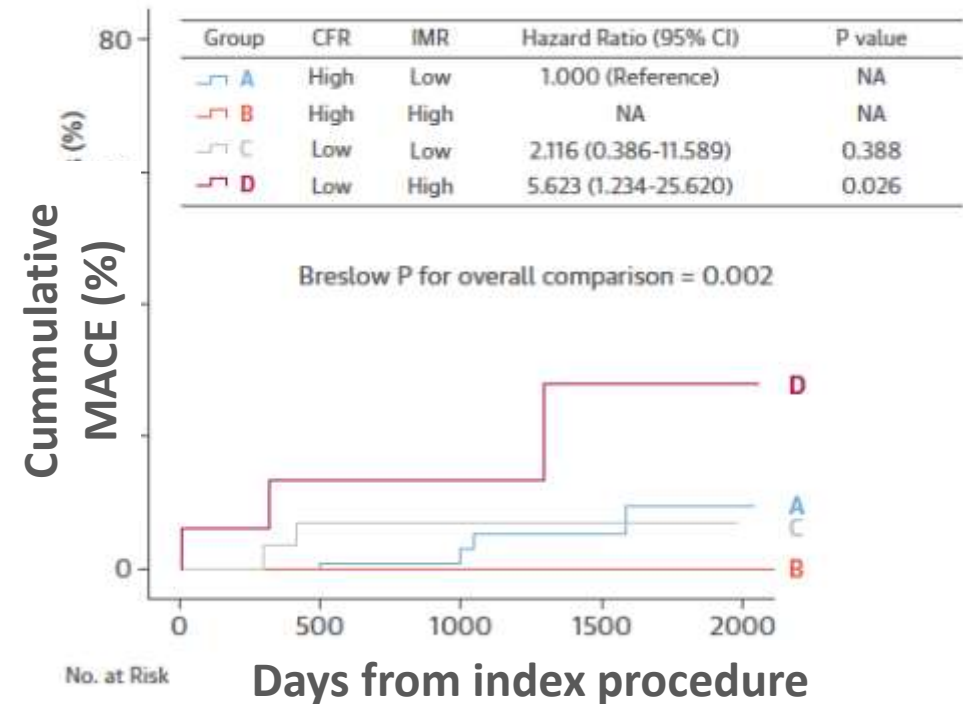


Structural microvascular remodelling and prognosis

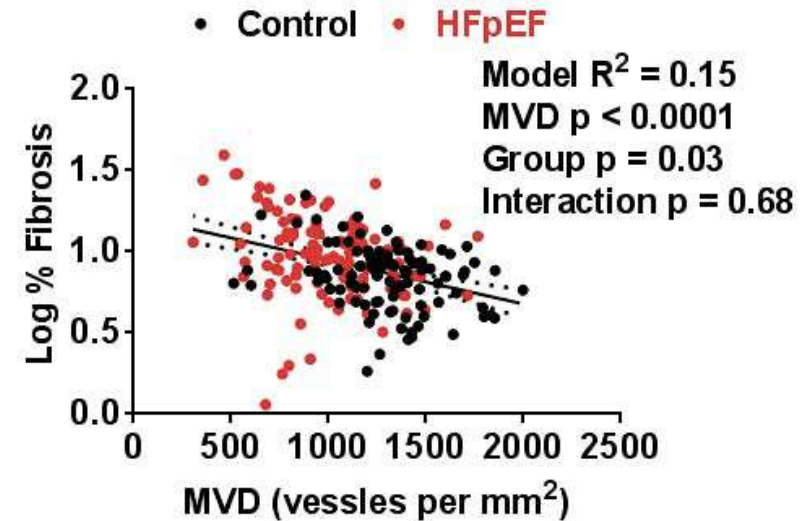
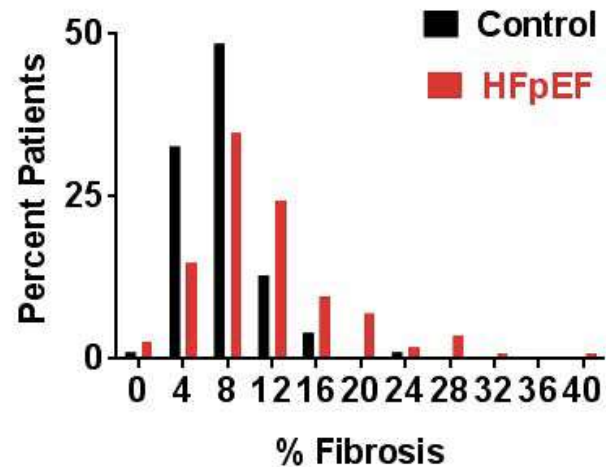
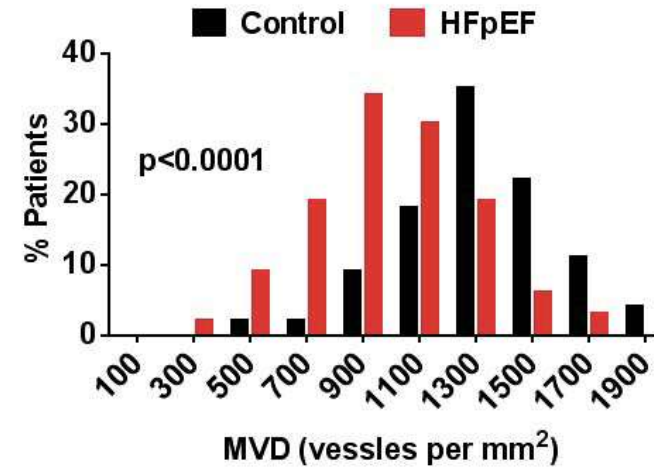
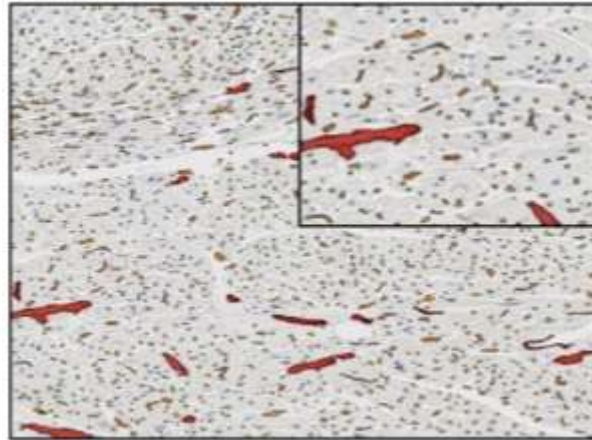
CFR and IMR in stenoses with FFR>0.80



Overall study population
Stratified by CFR and IMR



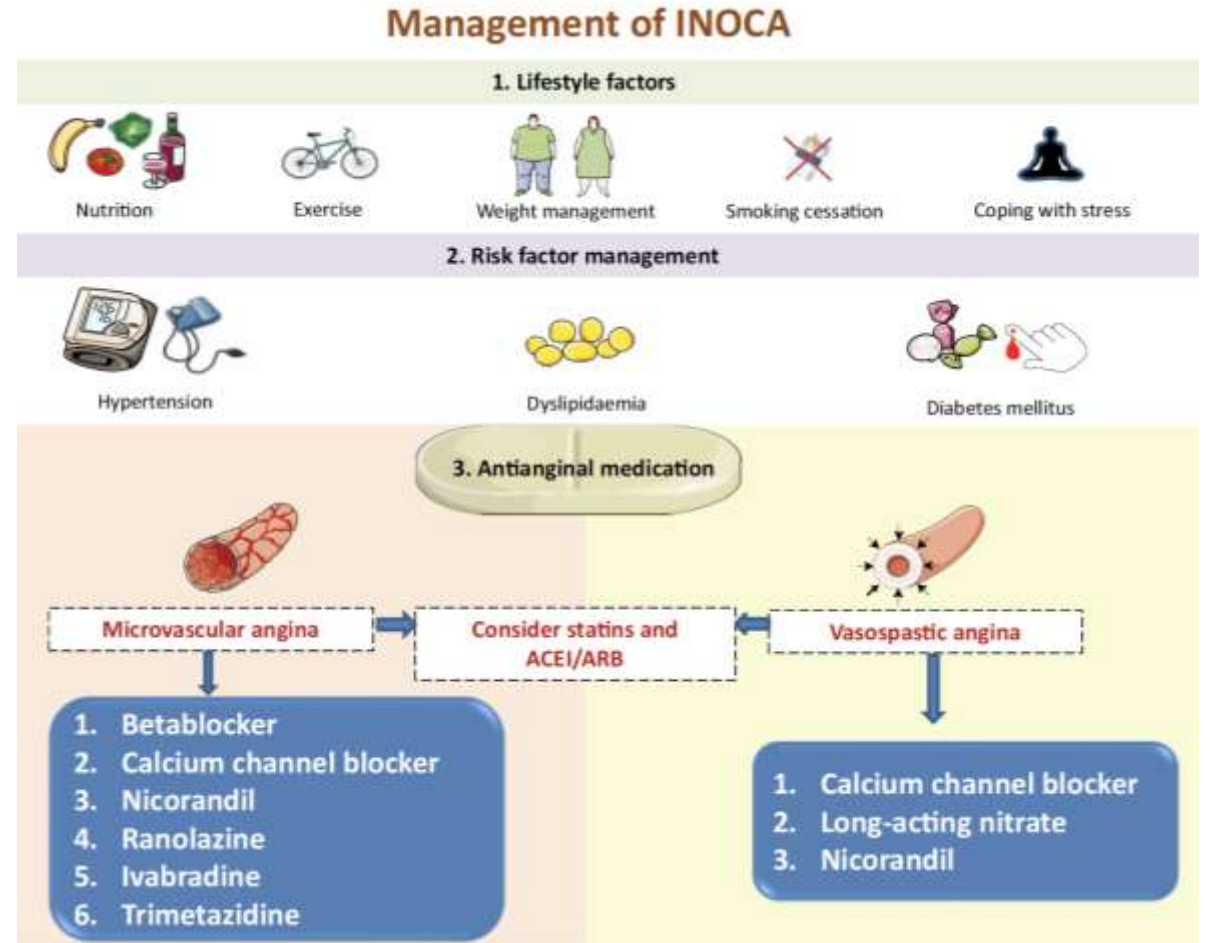
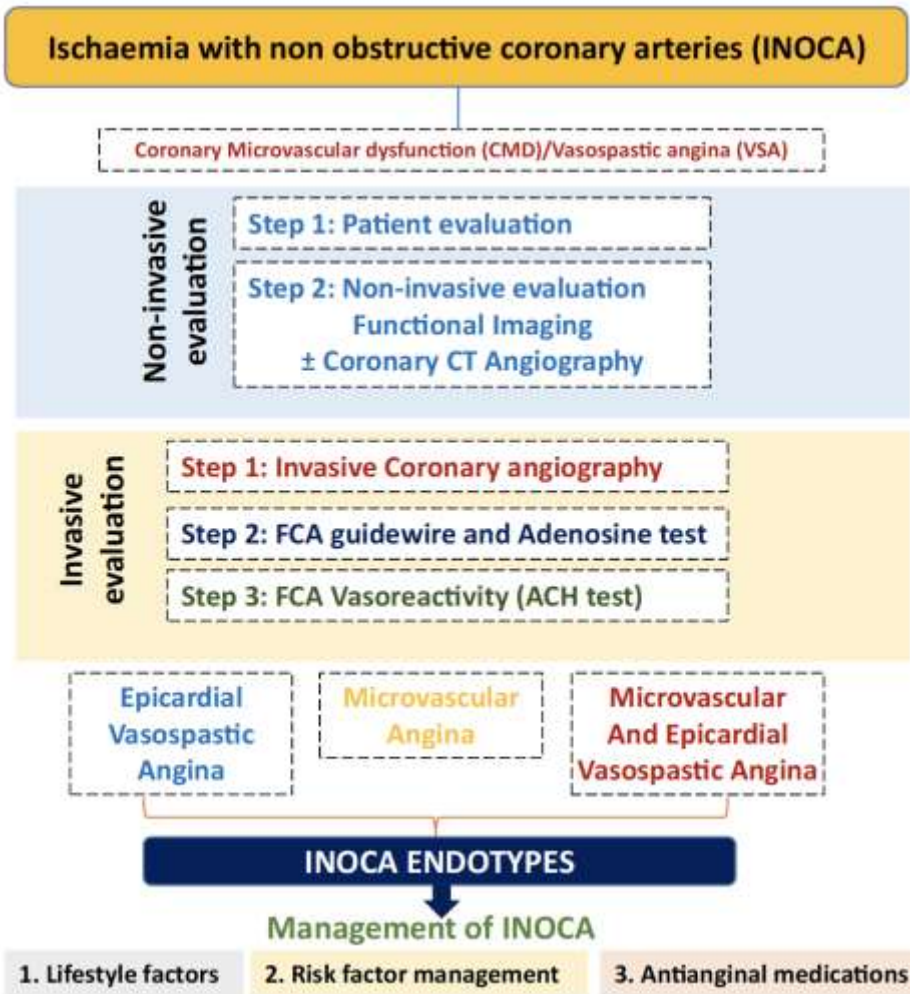
Microcirculatory rarefaction in HFpEF



2019 ESC guidelines recommendations / Microvascular angina

Recommendations	Class	Level
Guidewire-based CFR and/or microcirculatory resistance measurements should be considered in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with preserved iwFR/FFR. Microvascular structural remodelling	IIa	B
Intracoronary acetylcholine with ECG monitoring may be considered during angiography, if coronary arteries are either angiographically normal or have moderate stenoses with preserved iwFR/FFR, to assess microvascular vasospasm. Microvascular vasomotor disorders	IIb	B
Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR.	IIb	B

Additional information: EAPCI consensus document



Thank you for your attention

26th
TCTAP 2021

