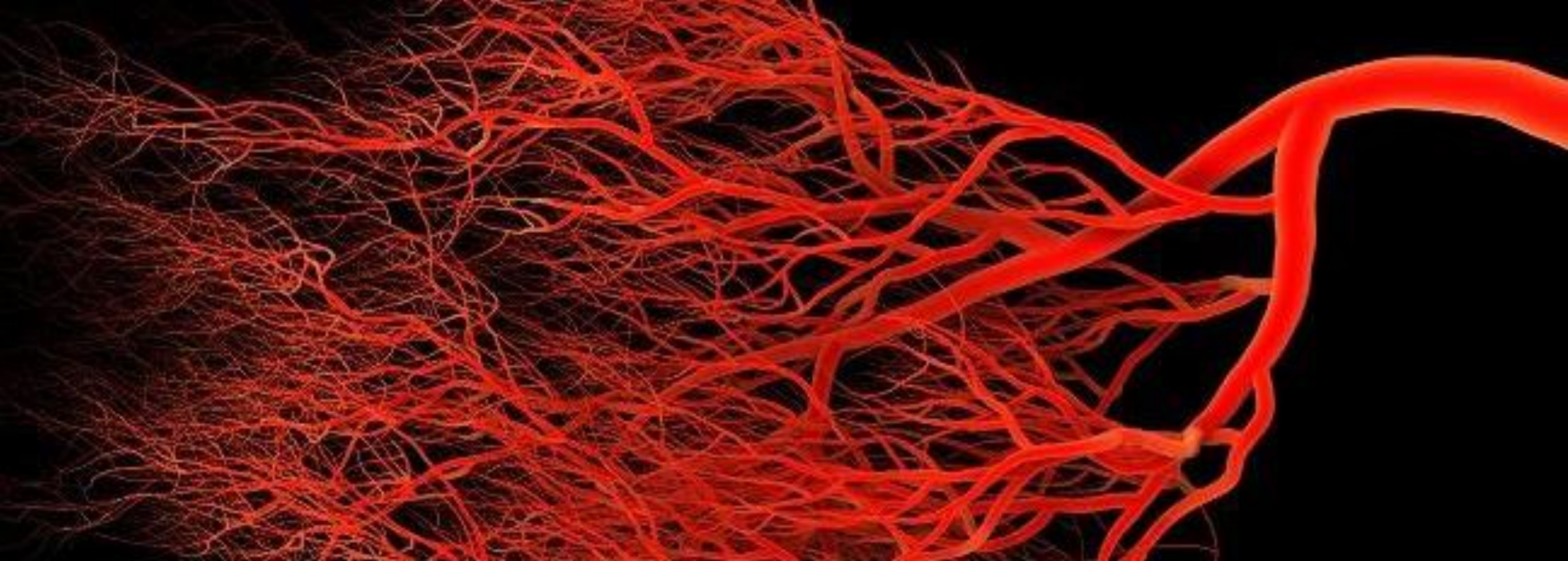




CORONARY MICROVASCULAR DISEASE

Assessment of microvascular fx and angina



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G.J. Vlachojannis MD PhD

Department of Cardiology
University of Athens

High prevalence of Unobstructed Coronary Arteries in symptomatic patients undergoing invasive Coronary Angiography

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.

ACC National Cardiovascular Data Registry

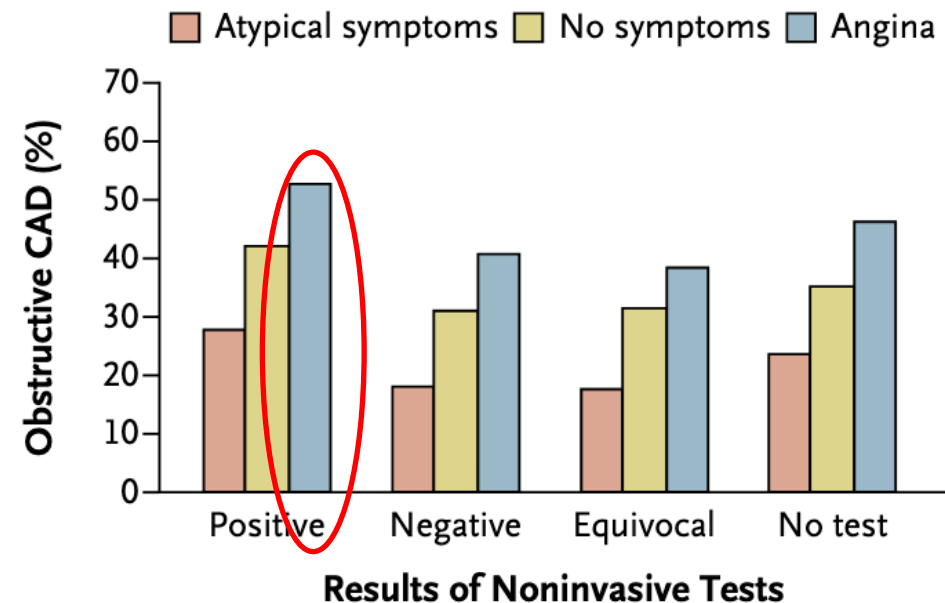
398,978 patients

Patel et al., N Engl J Med 2010;362:886-95



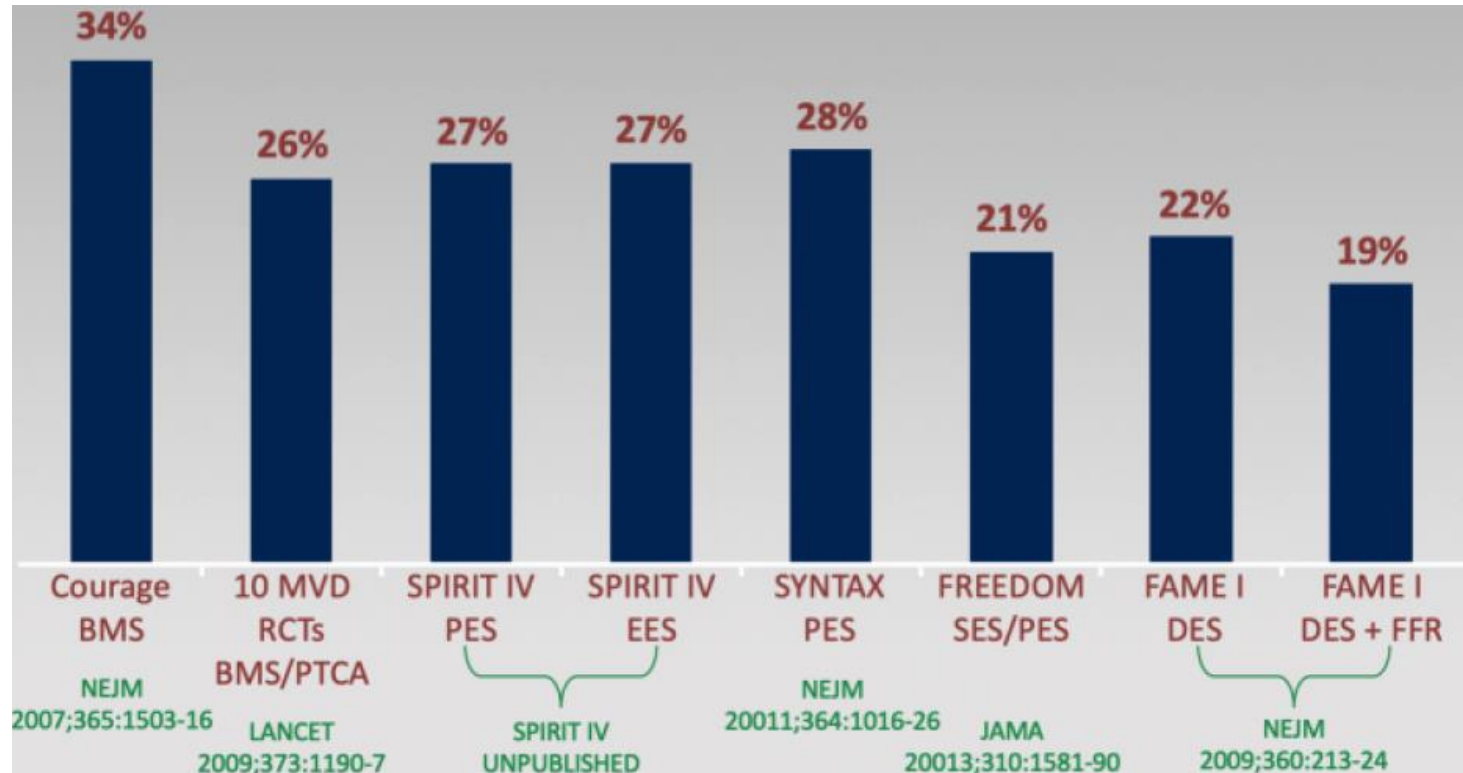
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Patients with Obstructive CAD, according to **Non-invasive Test** Result and **Symptoms**



Recurrence/Persistence of Angina post PCI

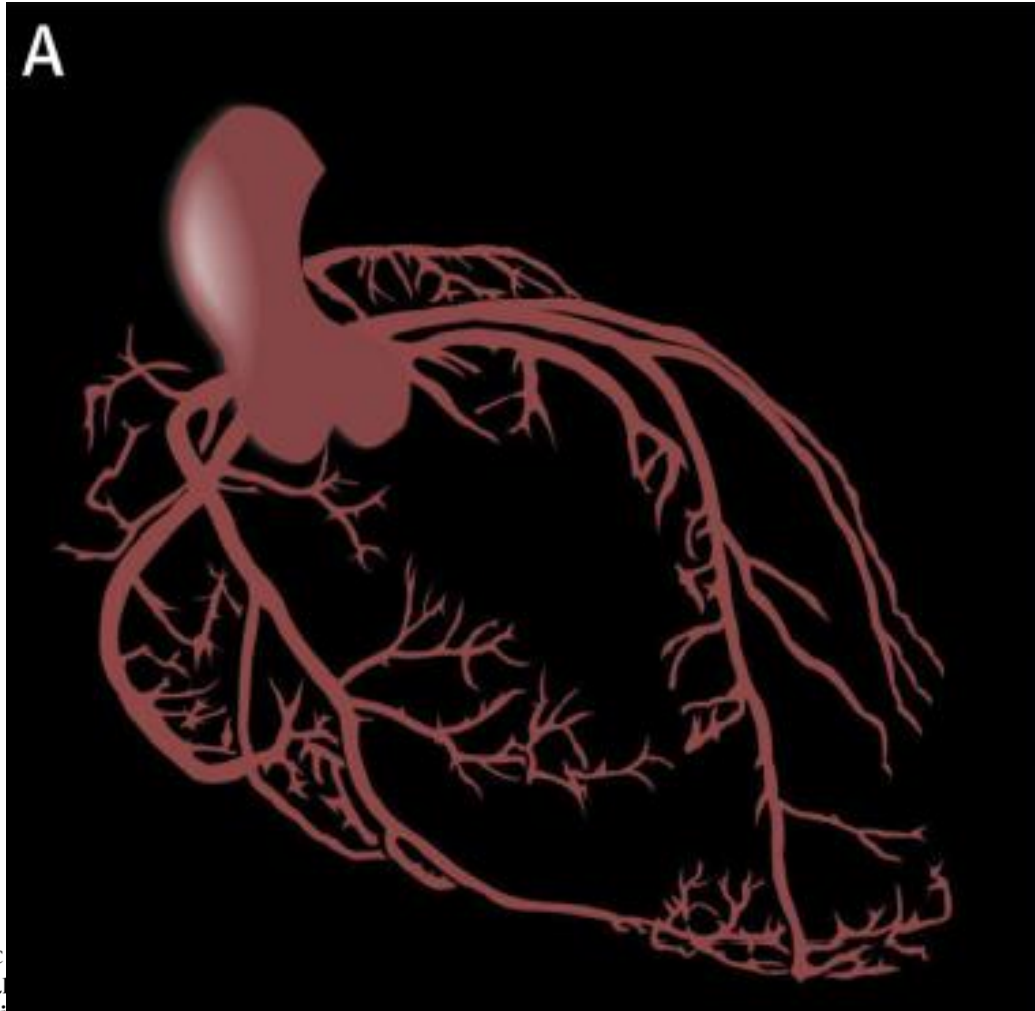
Recurrent angina at 1 year after PCI is present in 20-30% of patients



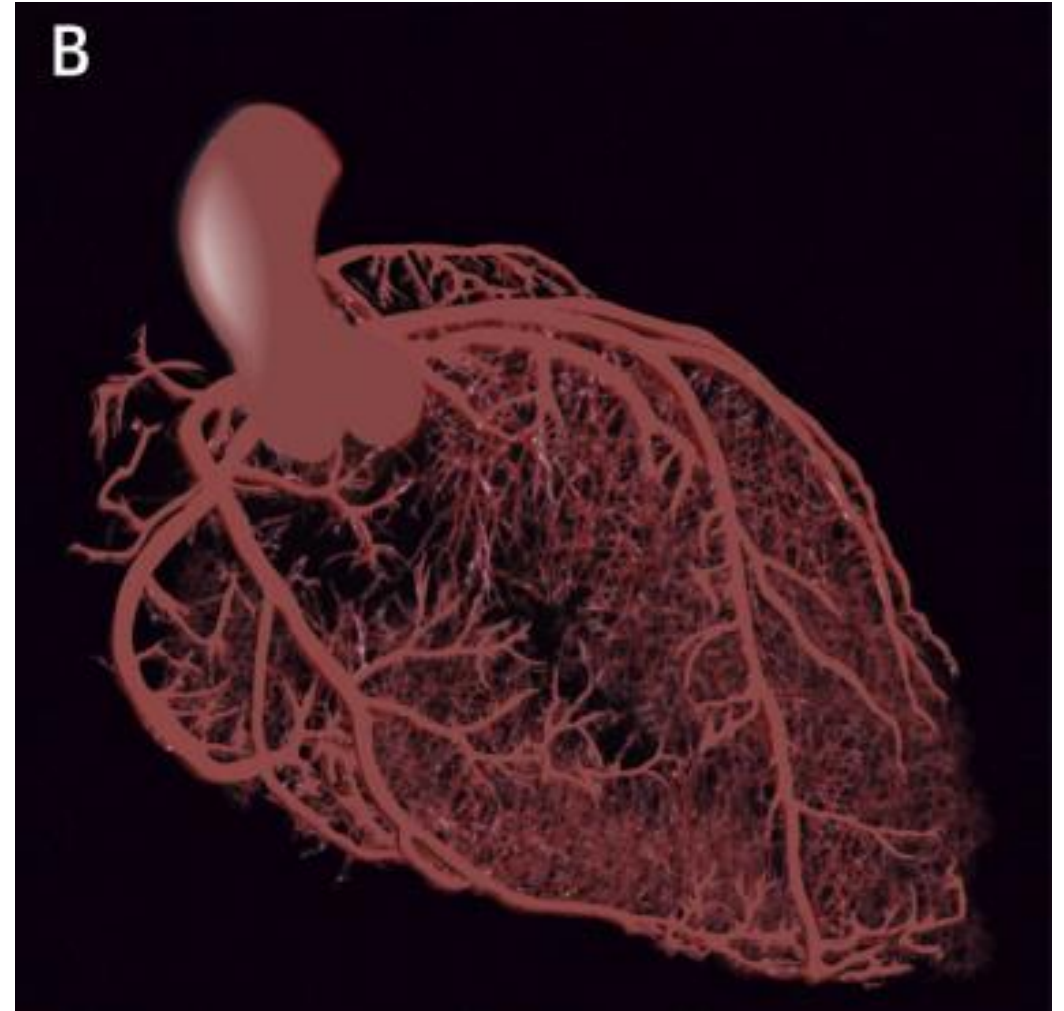
Patel et al. TCT Connect 2020

Schematic of the Epicardial Coronary Arteries and the Full Coronary Circulation

Macrocirculation



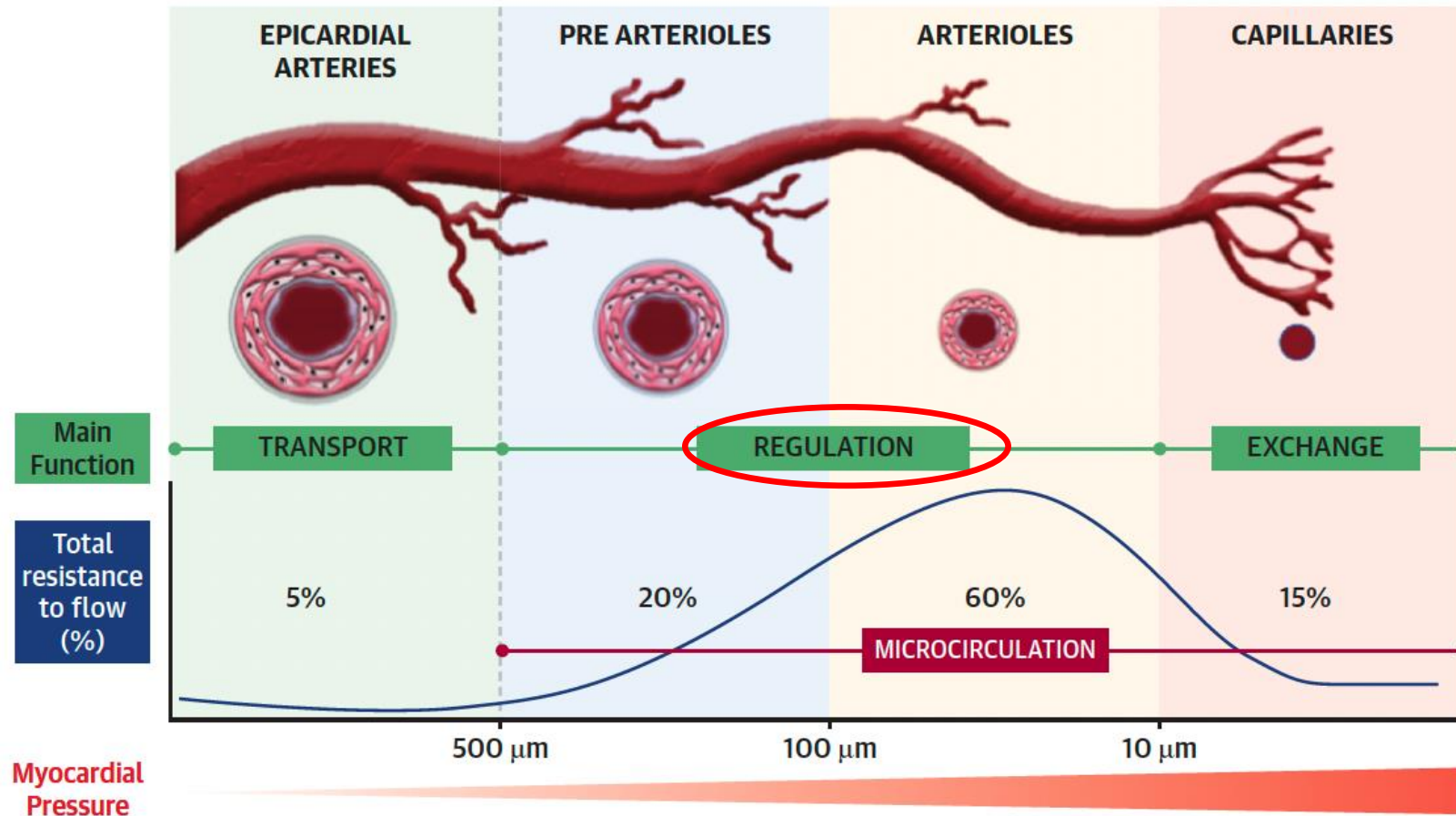
Macro- & Microcirculation



Coronary angiogram detects only 5% of the total coronary tree



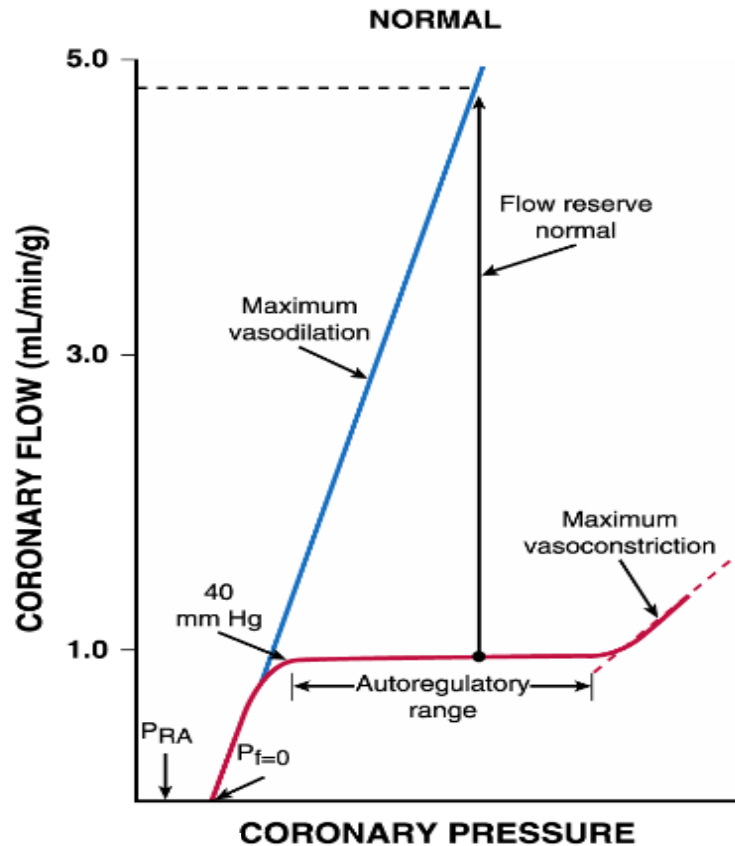
Coronary Circulation – two compartment model



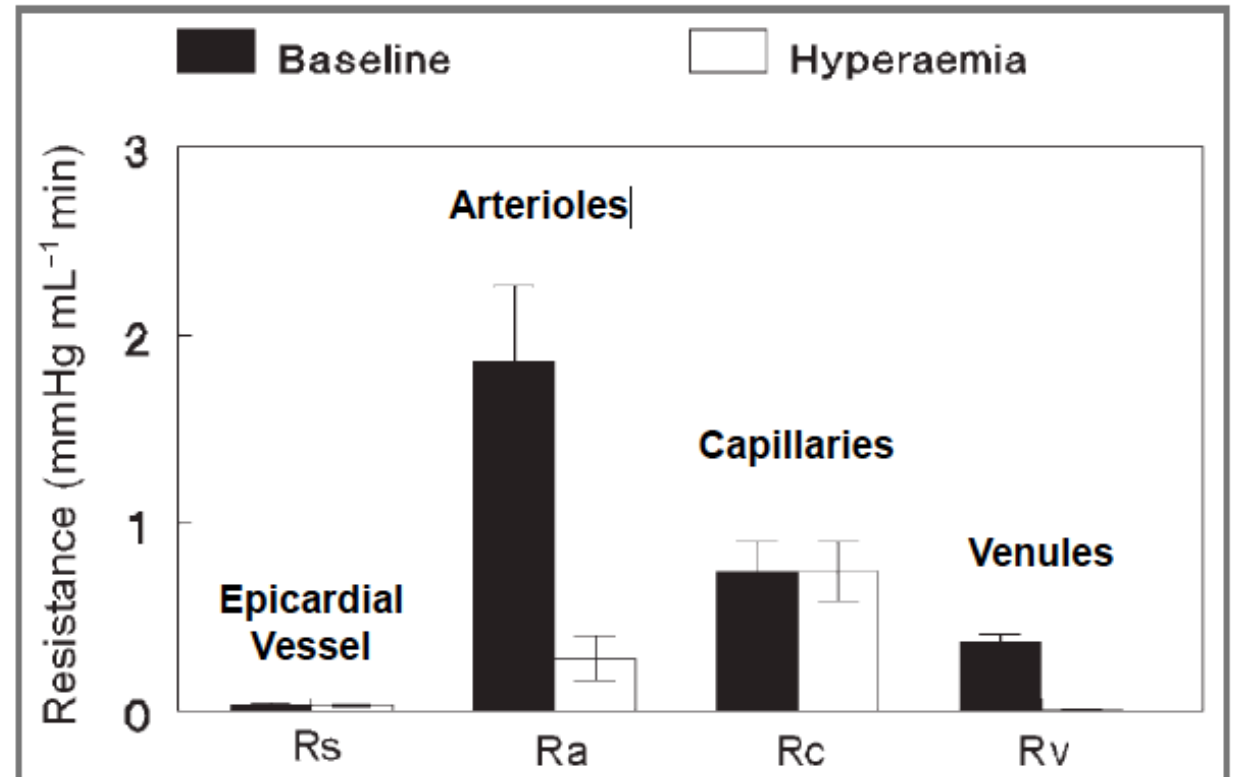
Del Buono et al JACC 2021,78: 1352-71

Value/Role of Microcirculation

Pressure-Flow Relationship: Coronary Autoregulation



Coronary Resistance *Resistance in a Normal Coronary Vessel*



Myocardial ischemia

Causes

Obstructive atherosclerotic epicardial coronary artery disease

Other reasons

- LV hypertrophy / aortic valve stenosis / hypertension
- Coronary spasm (vasospastic angina - variant angina)
- Microvascular dysfunction (microvascular angina - syndrome X)
- Obstructive coronary anomalies
- ...



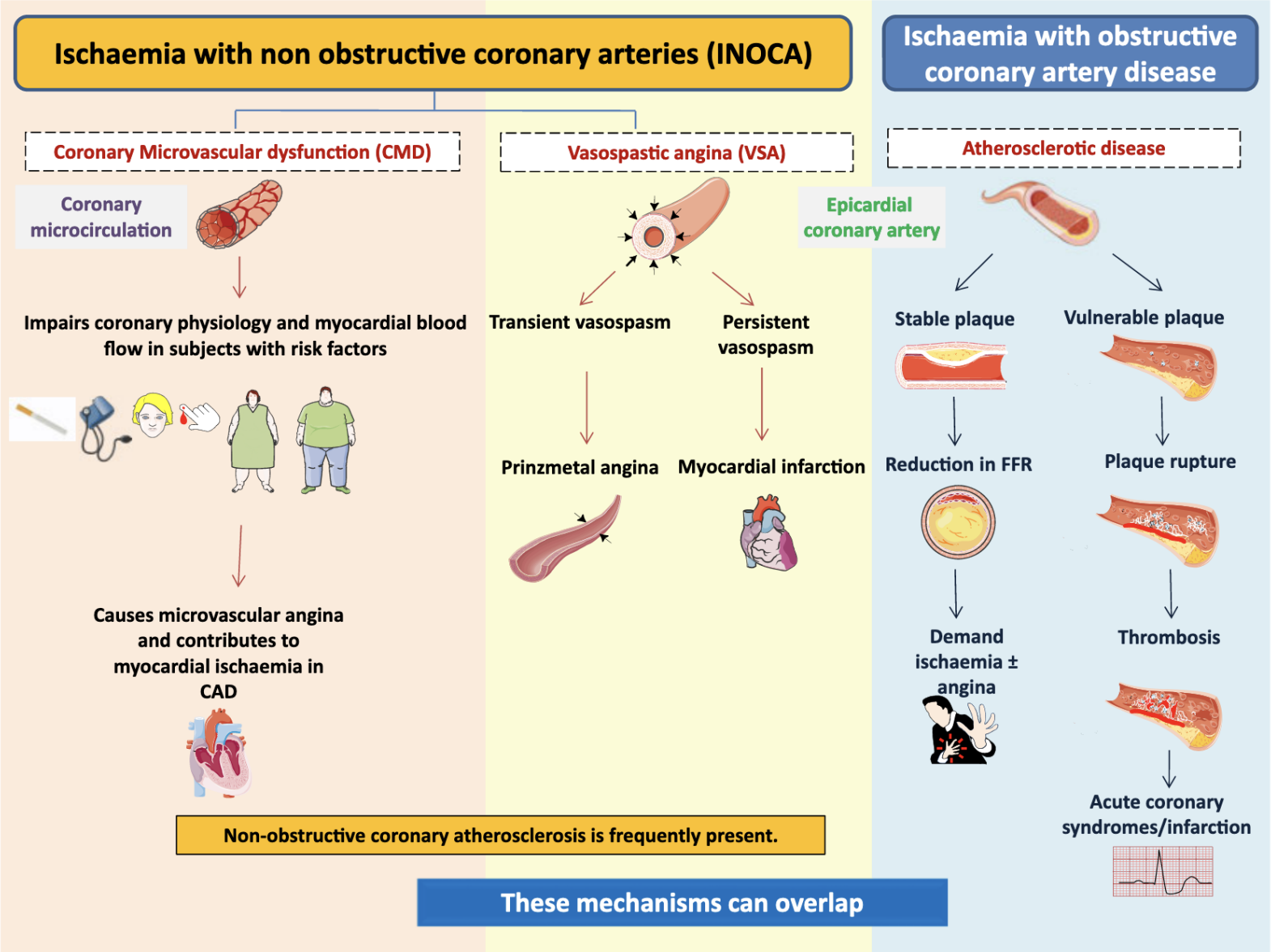
INOCA

Ischemia with no obstructive coronary artery disease

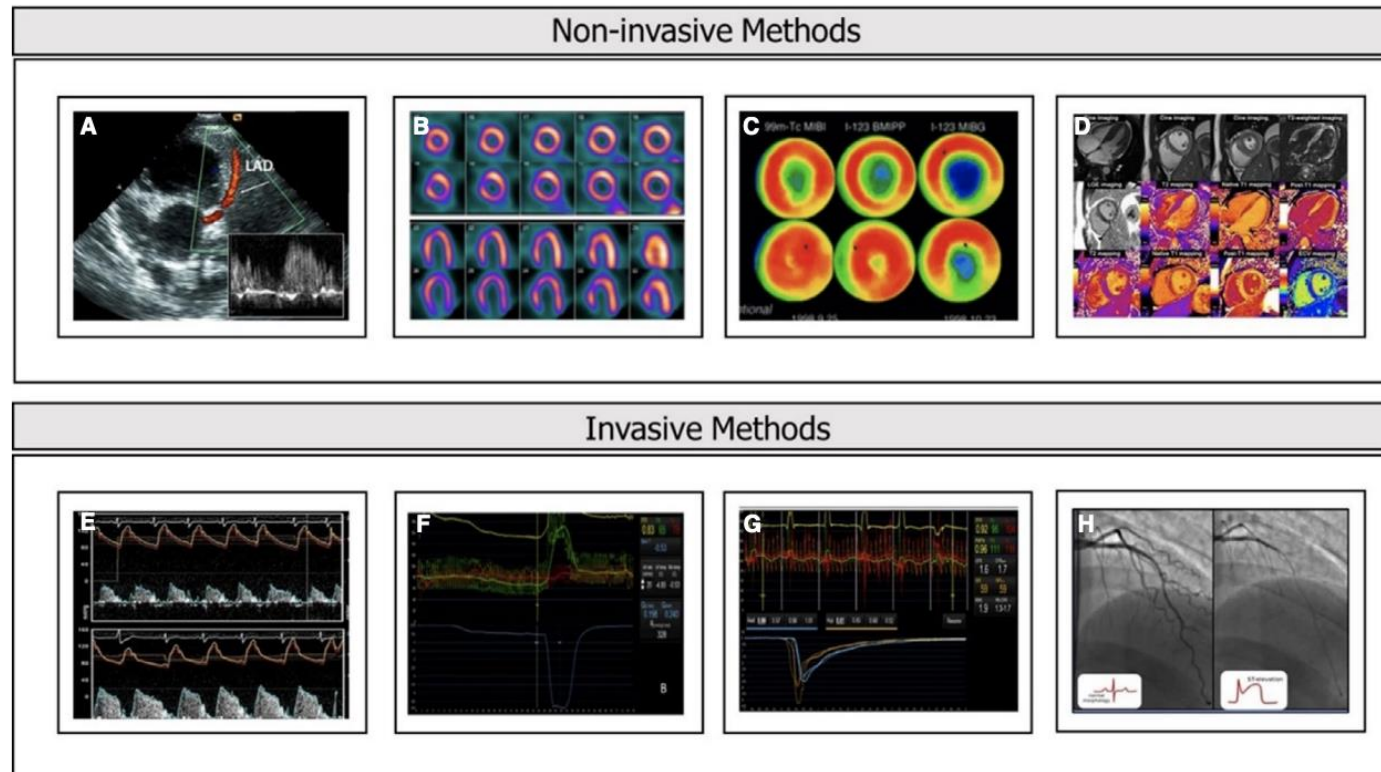
Mechanisms Of Myocardial Ischaemia

EAPCI Expert Consensus Document

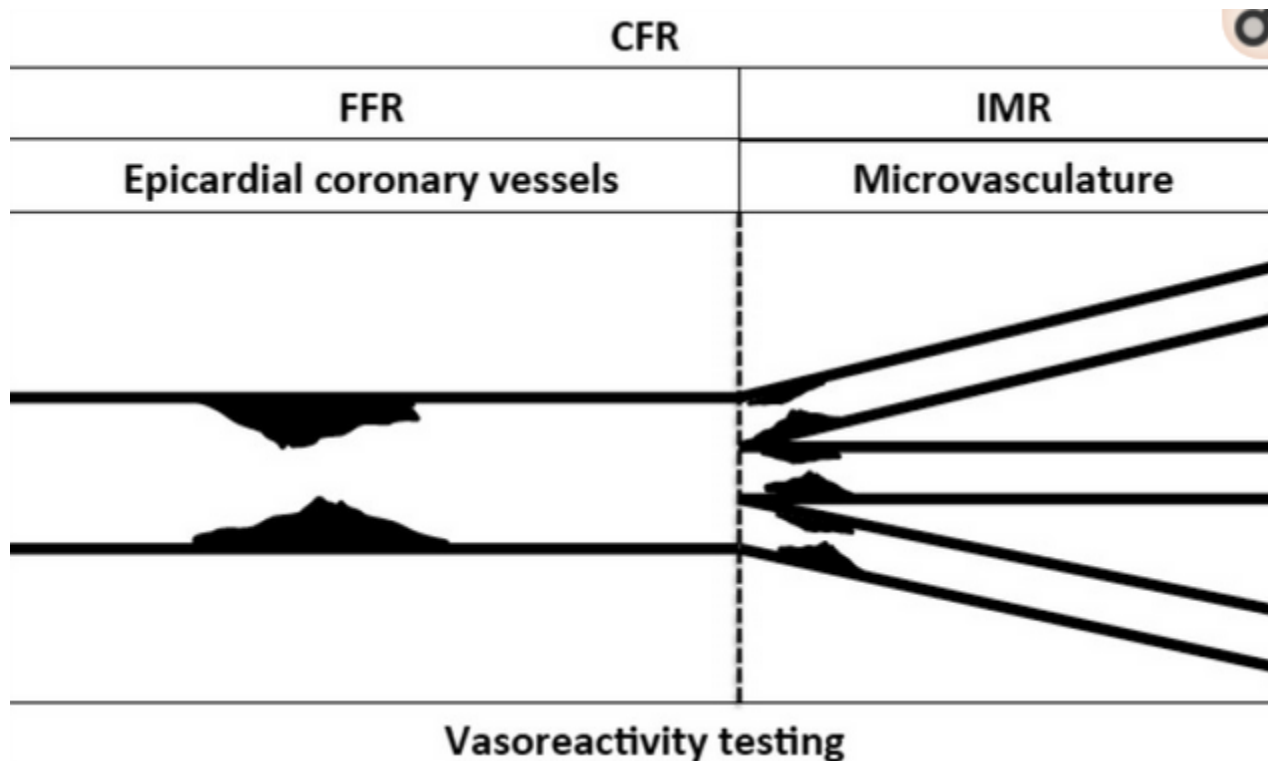
Kunadian et al. Eur Heart J. 2020;41(37):3504-3520



Methods used for evaluation of microvascular disease



Comprehensive assessment of the structural and functional components of the epicardial and microvascular compartments of the coronary tree.



FFR fractional flow reserve – obstructive epicardial disease (≤ 0.80)

IMR index of microcirculatory resistance – microvascular dysfunction ($IMR \geq 25$)

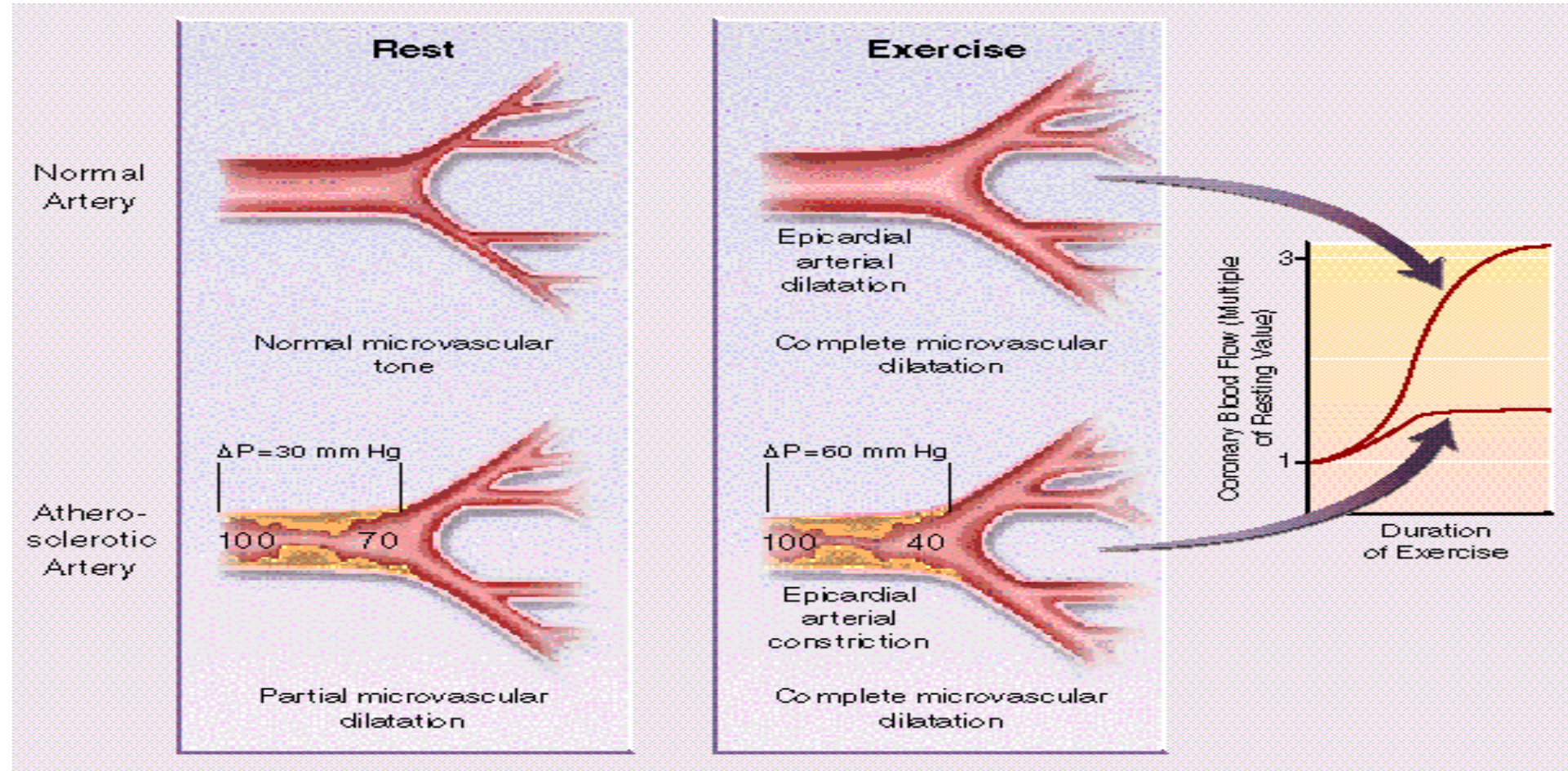
CFR coronary flow reserve – vasodilatory capacity ($CFR < 2.0$)

Coronary flow

Pathophysiology – coronary flow reserve

Normal:
CFR >3-5

Pathological:
CFR <2.0

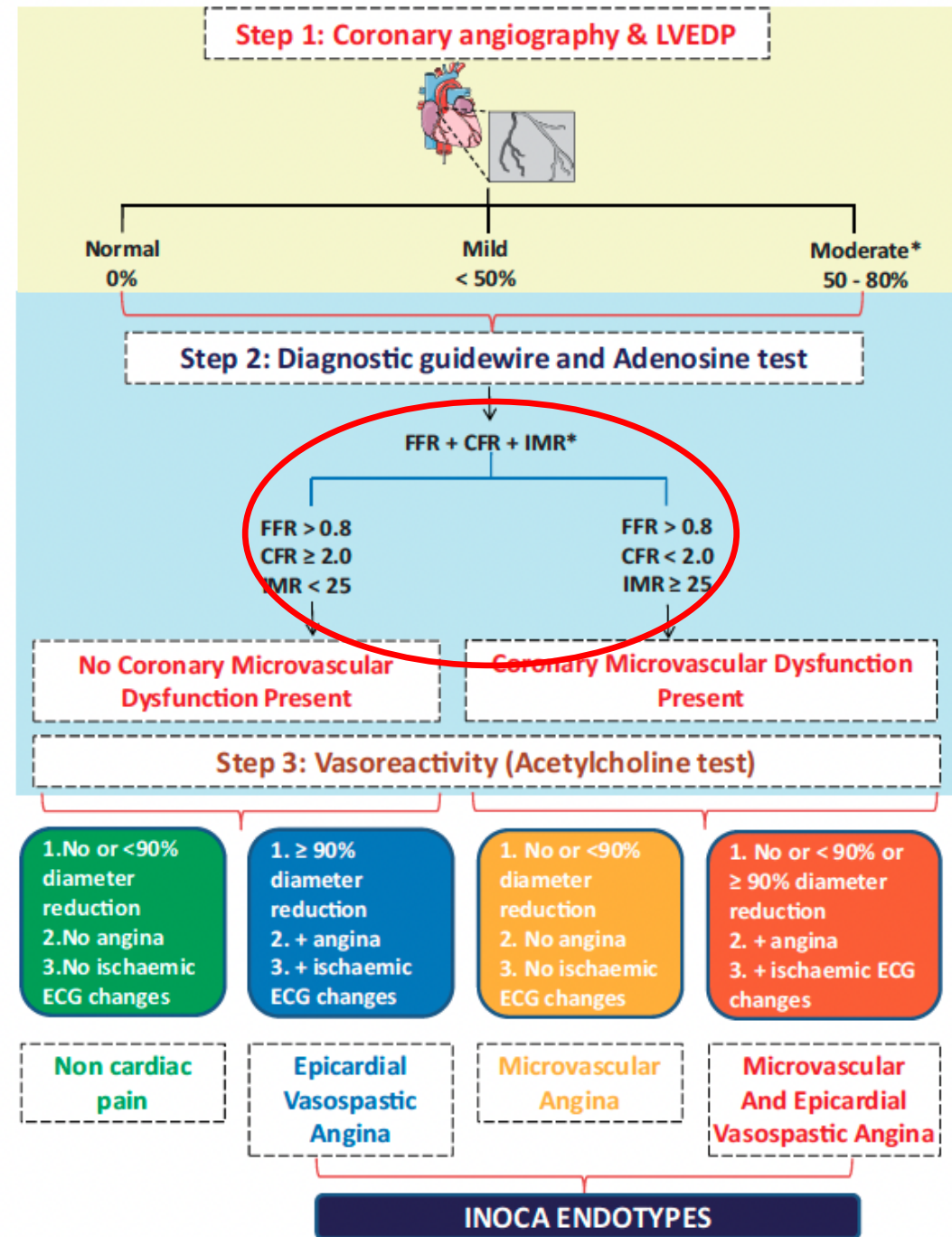


Diagnostic Criteria for Ischemia, or Angina with Non-Obstructive Coronary Arteries

--> INOCA / ANOCA

Criteria	Evidence	Diagnostic parameters
1	Symptoms of myocardial ischaemia ^a	Effort or rest angina Exertional dyspnoea
2	Absence of obstructive CAD (<50% diameter reduction or FFR >0.80)	Coronary CTA Invasive coronary angiography
3	Objective evidence of myocardial ischaemia ^b	Presence of reversible defect, abnormality or flow reserve on a functional imaging test
4	Evidence of impaired coronary microvascular function	Impaired coronary flow reserve (cut-off <2.0), invasive or noninvasively determined Coronary microvascular spasm, defined as reproduction of symptoms, ischaemic ECG shifts but no epicardial spasm during acetylcholine testing Abnormal coronary microvascular resistance indices (e.g. IMR $\geq$ 25)

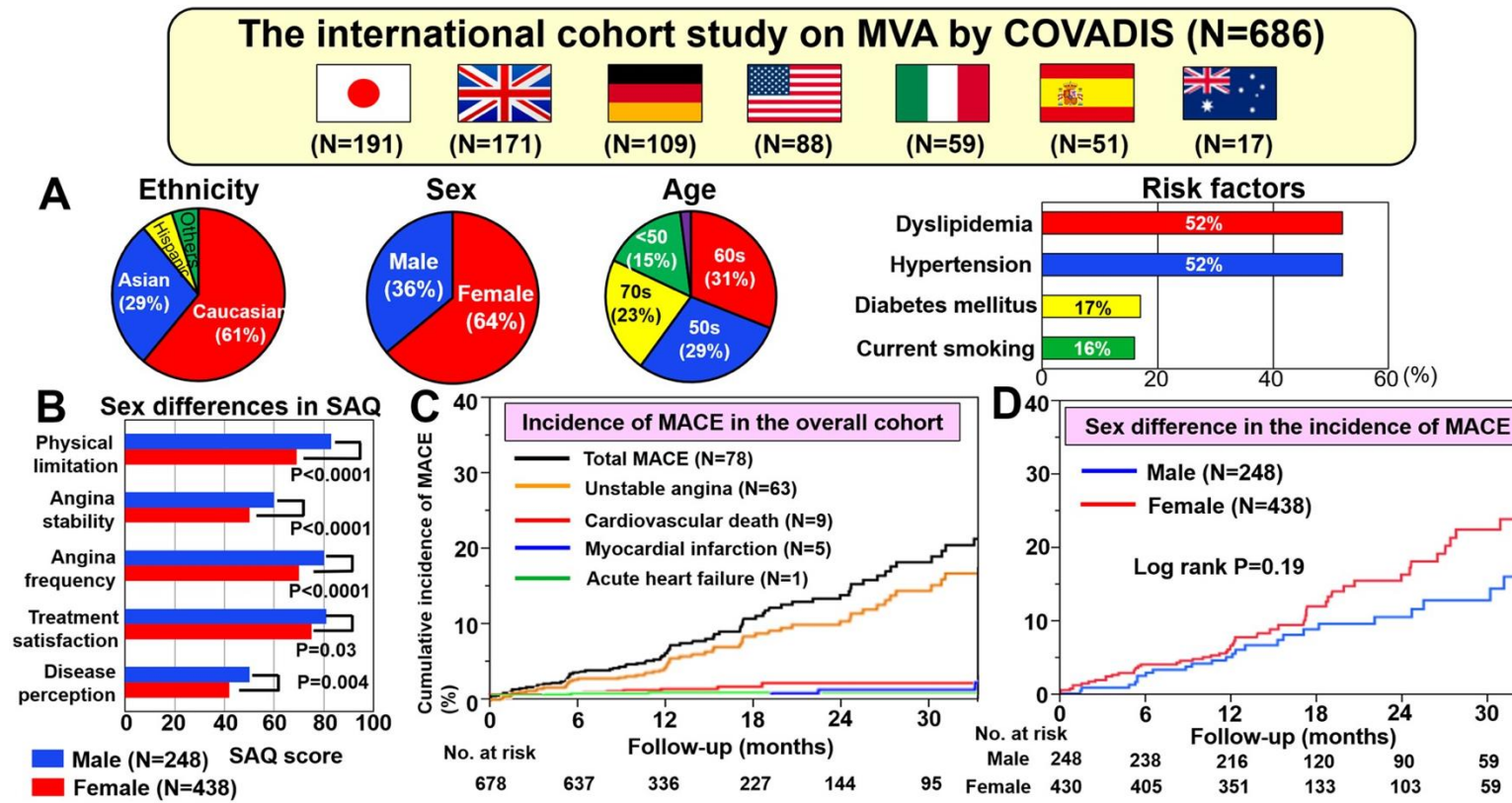
Invasive Evaluation of INOCA/ ANOCA



Kunadian et al. Eur Heart J. 2020;41(37):3504-3520

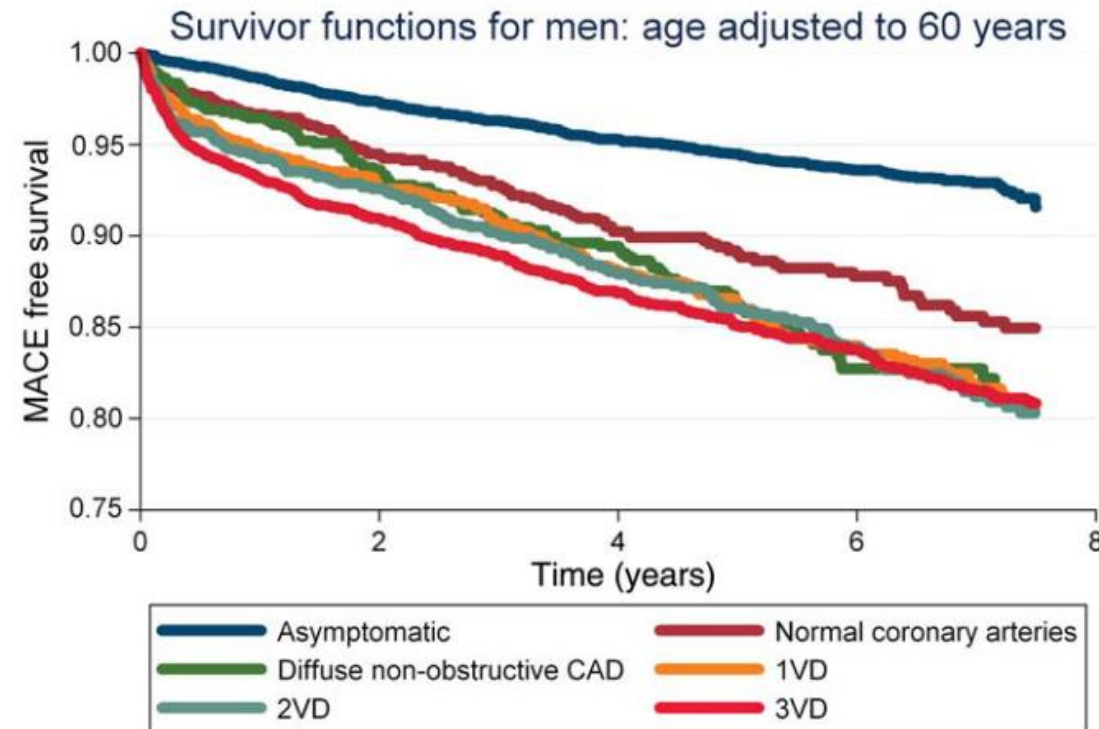
Microvascular angina in the COVADIS registry

Epidemiology



Prognosis of Angina with no obstructive CAD

- N = 5,705 - Asymptomatic Reference
- N=11,223 - Symptomatic No CAD, CAD
- Danish National Patient Registry
- MACE: All-cause & CV death, readmission for MI, HF, or stroke



- Normal = smooth, 0%
- Diffuse No CAD = 1-49%
- 1-3VD = CAD $\geq$ 50%



ESC

European Society
of Cardiology

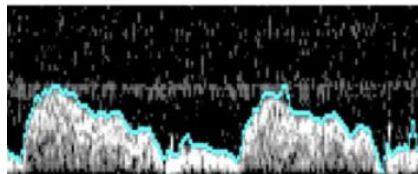
European Heart Journal (2022) 43, 1582–1593
<https://doi.org/10.1093/eurheartj/ehab775>

META-ANALYSIS

Ischaemic heart disease

Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis

Normal coronary flow reserve (CFR) is strongly associated with a reduced risk of death and major cardiovascular events (MACE)

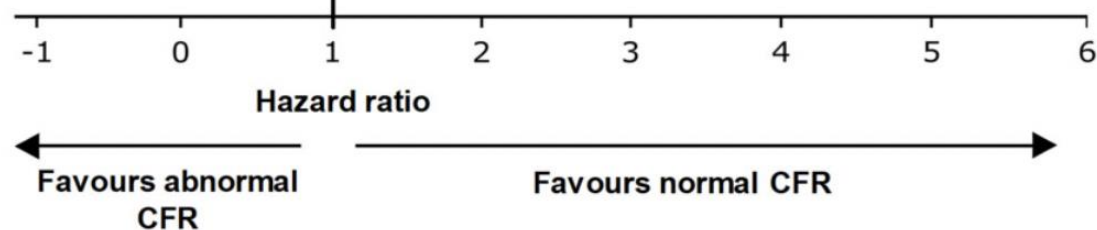


Mortality (16 studies,
8446 subjects)

HR 3.78

MACE (60 studies,
35498 subjects)

HR 3.45



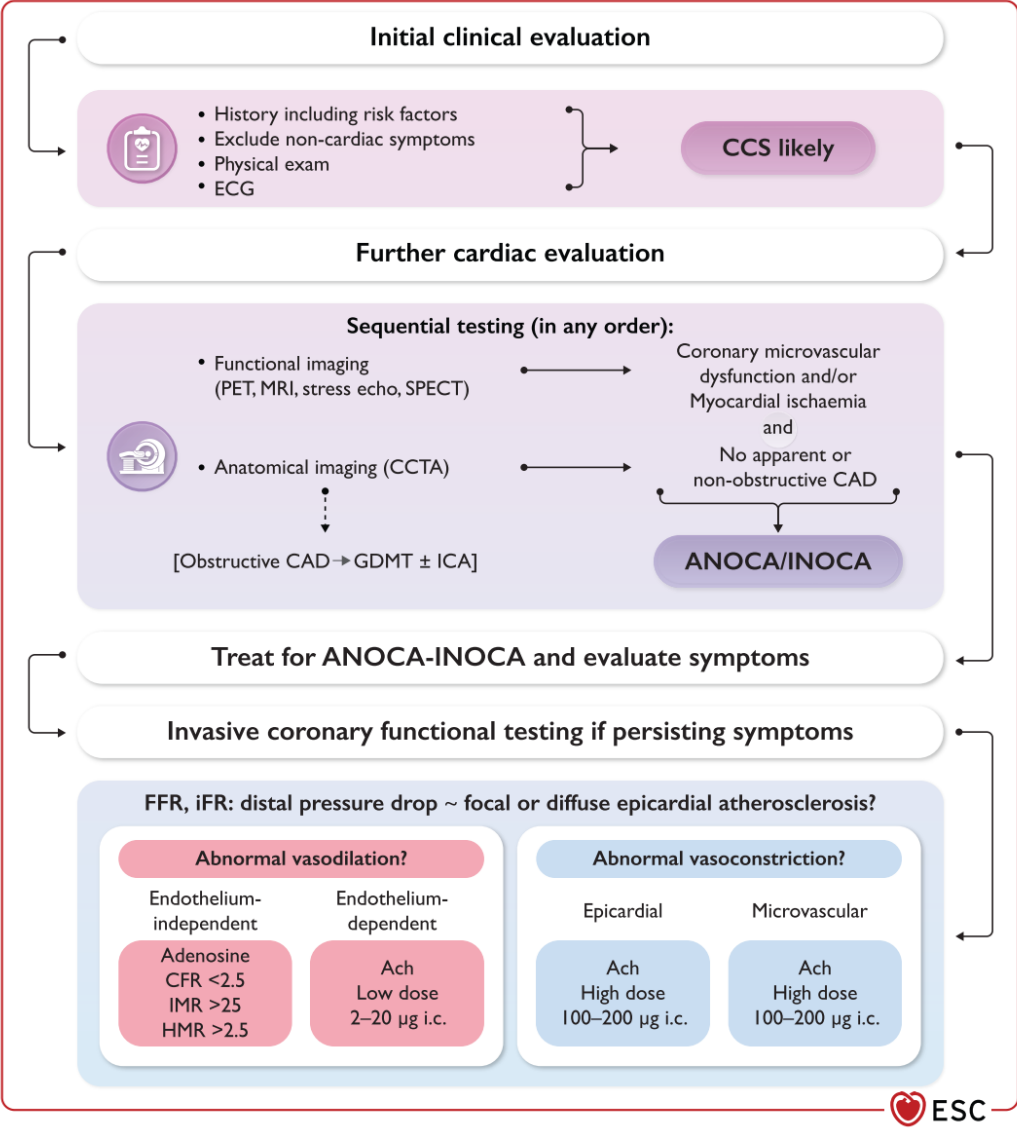
A systematic review and meta-analysis of 79 studies and 59740 individuals across multiple modalities of CFR measurement.



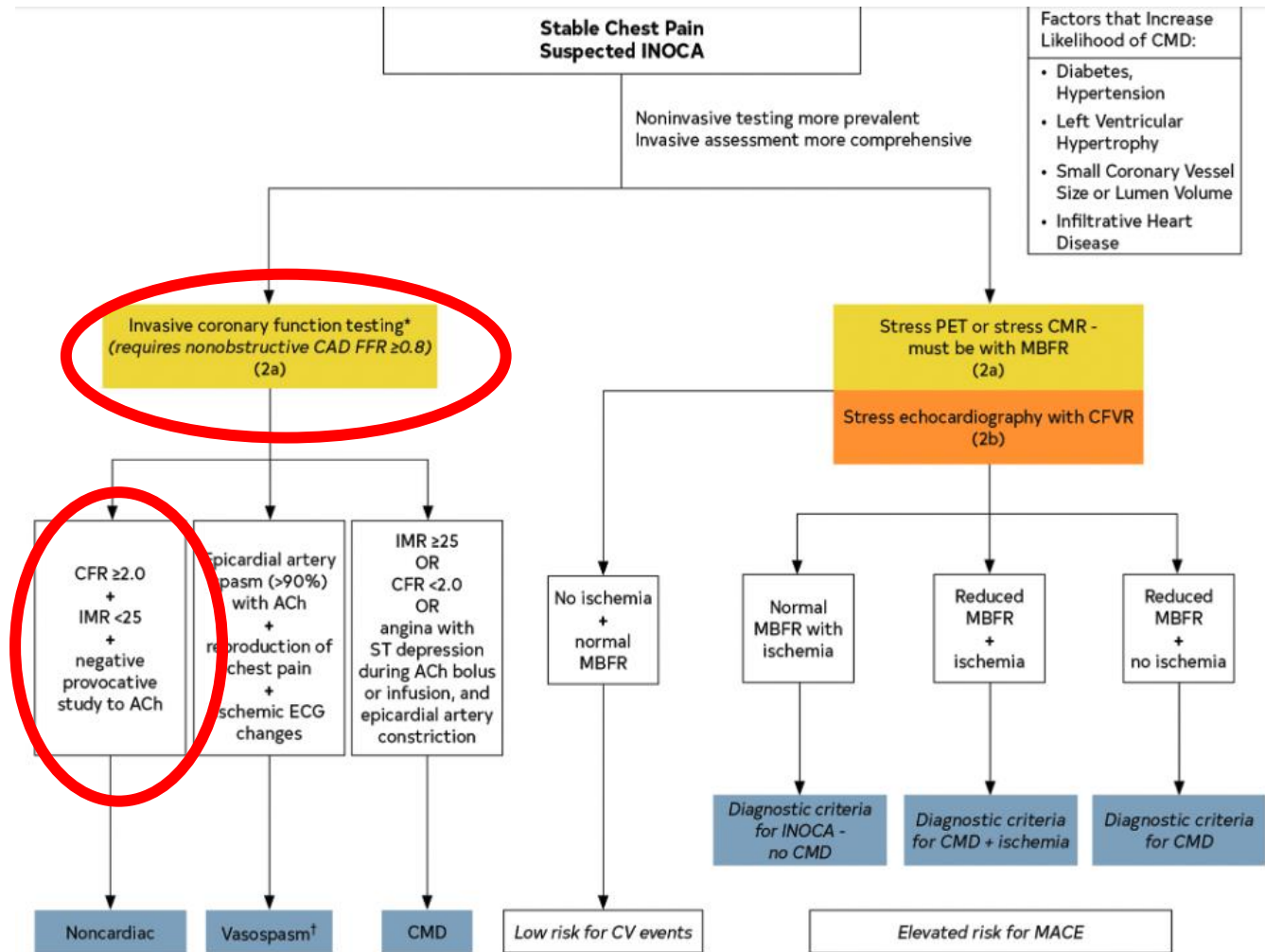
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ESC Guidelines CCS 2024

Recommendations	Class ^a	Level ^b
Diagnosis of ANOCA/INOCA endotypes		
In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e. anginal symptoms with normal coronary arteries or non-obstructive lesions at non-invasive imaging, or intermediate stenoses with normal FFR/iFR at coronary arteriography) and poor quality of life, invasive coronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences. ^{36,37,298,930,939,985}	I	B
In persistently symptomatic patients with documented or suspected ANOCA/INOCA, transthoracic Doppler of the LAD, stress echocardiography, CMR, and PET may be considered for the non-invasive assessment of coronary/myocardial flow reserve. ^{44,231,233–235,300,986,987}	IIb	B



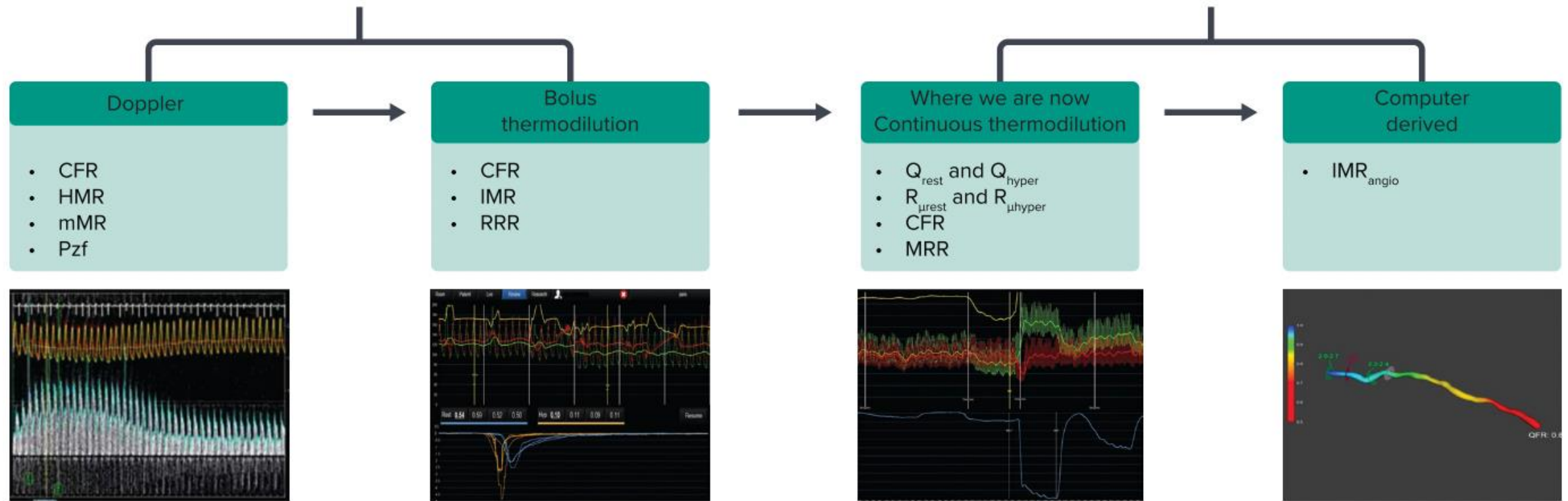
ACC/AHA Clinical Decision Pathway for INOCA



Gulati et al. Circulation. 2021;144:e368–e454



Methods of Quantifying Coronary Microvascular Function in the Cath Lab



Fawaz, Karamasis, Keeble et al. Interv Cardiol. 2023;18:e07

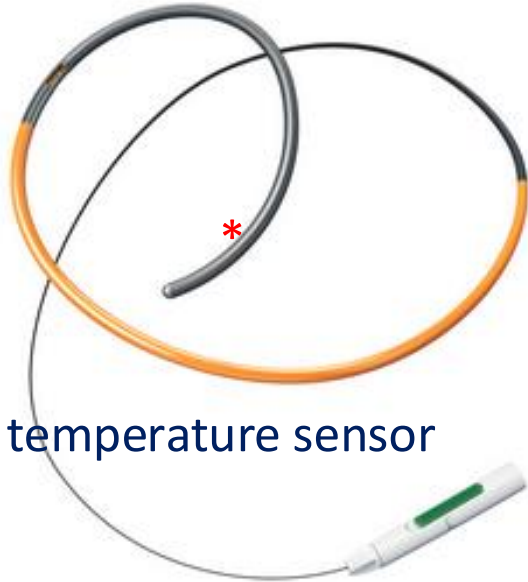
Cath Lab Indices of Microcirculatory Function

Index	Method(s)	Pros	Cons	Abnormal cut-off point
CFR	Doppler Bolus thermodilution Continuous thermodilution	Derived from multiple methods Predicts adverse outcomes Strong evidence base No hyperaemic agent required when using continuous thermodilution	Influenced by fluctuations in resting haemodynamics Influenced by epicardial stenoses; not microcirculation specific	<2.0 <2.5 ⁺
CFR_{pb}	Pressure	Pressure-derived CFR	Inadequate diagnostic accuracy Indeterminate in many cases	<2.0
Pzf	Doppler and pressure	Strong predictor of infarct size, salvage index, LVEF	Post hoc analysis required	≥42 mmHg
HMR	Doppler	Predicts adverse outcomes Can be calculated simultaneously with CFR	Requires adequate Doppler signals Influenced by epicardial stenoses; not microcirculation specific	>3.0
mMR	Doppler	Can be calculated simultaneously with CFR	Requires adequate Doppler signals May be independent of epicardial stenosis Minimal evidence base Lack of outcome data	Not established
IMR	Bolus thermodilution	Predicts adverse outcomes Strong evidence base Microcirculation specific Easy to measure	Inter- and intraobserver variability Requires correction for epicardial stenoses Does not interrogate the resting microcirculation	≥25 (≥40 severe)
RRR	Bolus thermodilution	Specific to the microcirculation	Influenced by fluctuations in resting haemodynamics Requires correction for epicardial stenoses	<3.5
R_μ	Continuous thermodilution	Easy, reproducible, operator independent No hyperaemic agent required	Dependent on myocardial mass subtended Interpatient and intervessel variability Lack of well-established cut-off points Still novel, no outcome studies	No formal cut-off points established >500 WU [±]
MRR	Continuous thermodilution Bolus thermodilution Doppler	Easy, reproducible, operator independent when measured by continuous thermodilution Corrects for epicardial disease measuring true resting resistance No hyperaemic agent required when using continuous thermodilution	No cut-off points due to novelty No outcome studies	No formal cut-off points established
IMR_{angio}	Angiography derived	Pressure-wire-free tool Accessible to the non-interventional CCL	Requires further study May be influenced by inter- and intraobserver variability	≥25 (≥40 severe)

Fawaz, Karamasis, Keeble et al. Interv Cardiol. 2023;18:e07

Coronary Flow Reserve (CFR) & Index Microcirculatory Resistance (IMR)

Hard/Software for Bolus Thermodilution Measurements



* Pressure & temperature sensor

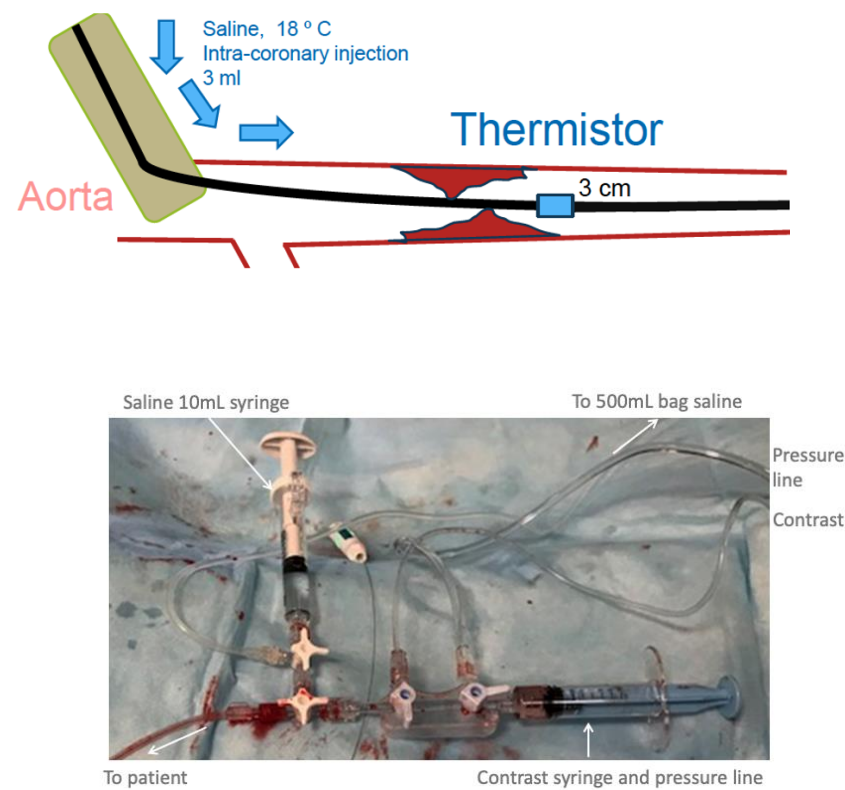


CoroHub Receiver



Coroventis CoroFlow™
Workstation

Coronary Bolus Thermodilution Method



IMR and CFR measurements

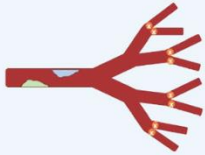


Normal CFR > 2.5

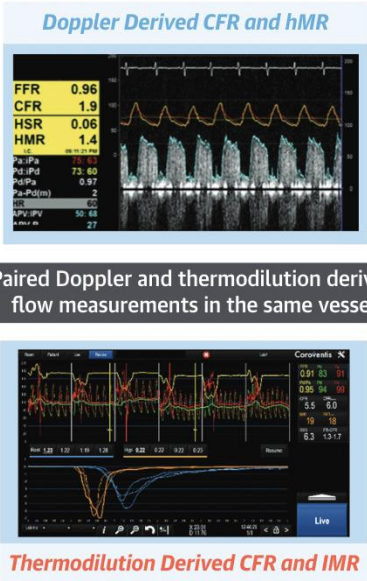
Normal IMR < 25

Moderate/poor agreement between different methods

Evaluation of Epicardial and/or Microvascular CAD

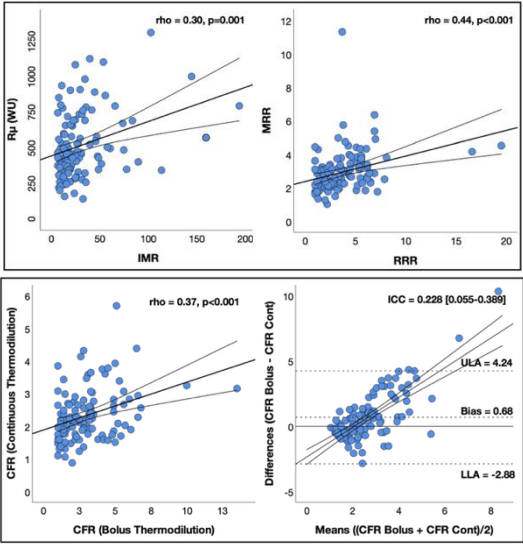
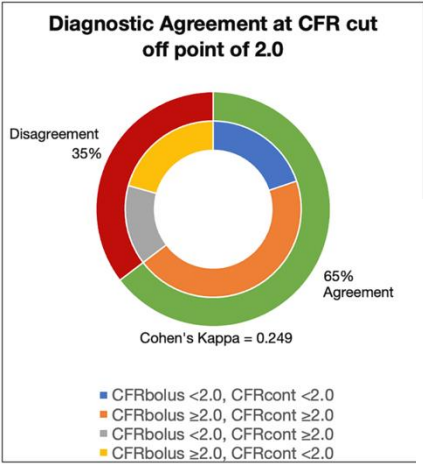


Number of vessels = 250

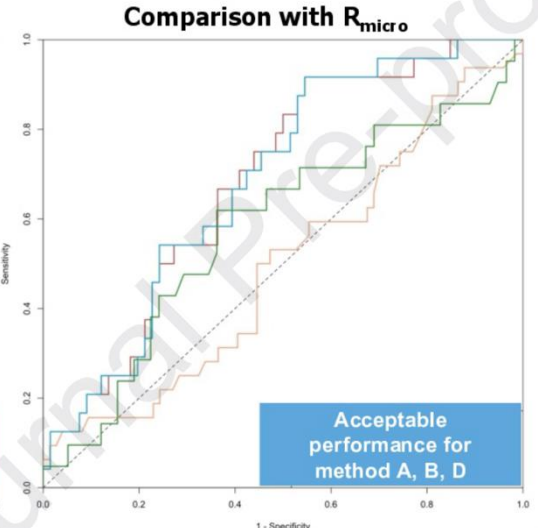
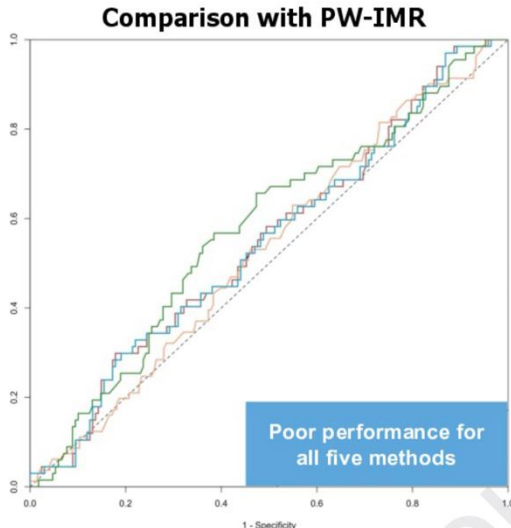


Main Findings

- r^2 There is a modest correlation between CFR_{thermo} and $CFR_{Doppler}$
-  **Thermodilution overestimates CFR**
Optimal CFR_{thermo} threshold is <2.5
- $\neq$ **IMR does not correlate with hMR**
(as transit time $\neq$ flow)



Five Angio-IMR calculated from three software platforms
All Analysts were blinded to the results of the pressure-wire assessment and other Angio-IMR

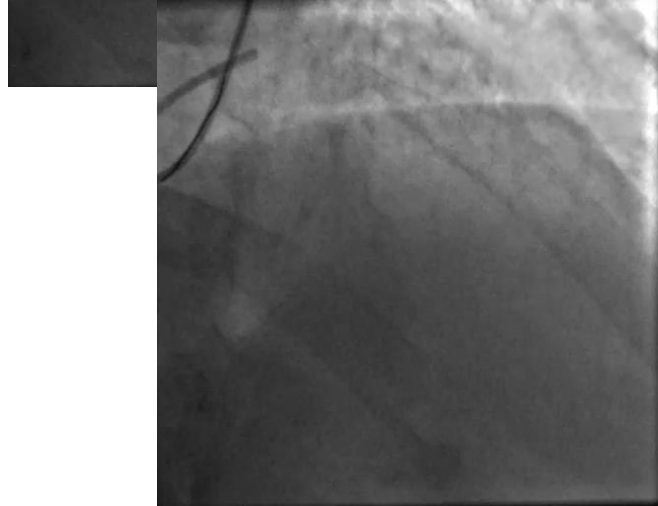
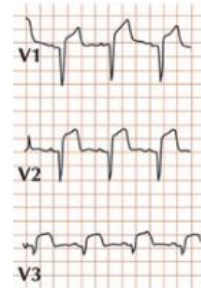


Demir OM, et al. J Am Coll Cardiol Interv. 2022;15(10):1060-1070.

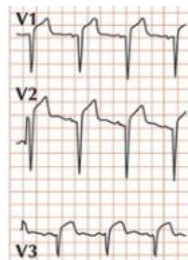
Microvascular Obstruction/Injury in STEMI



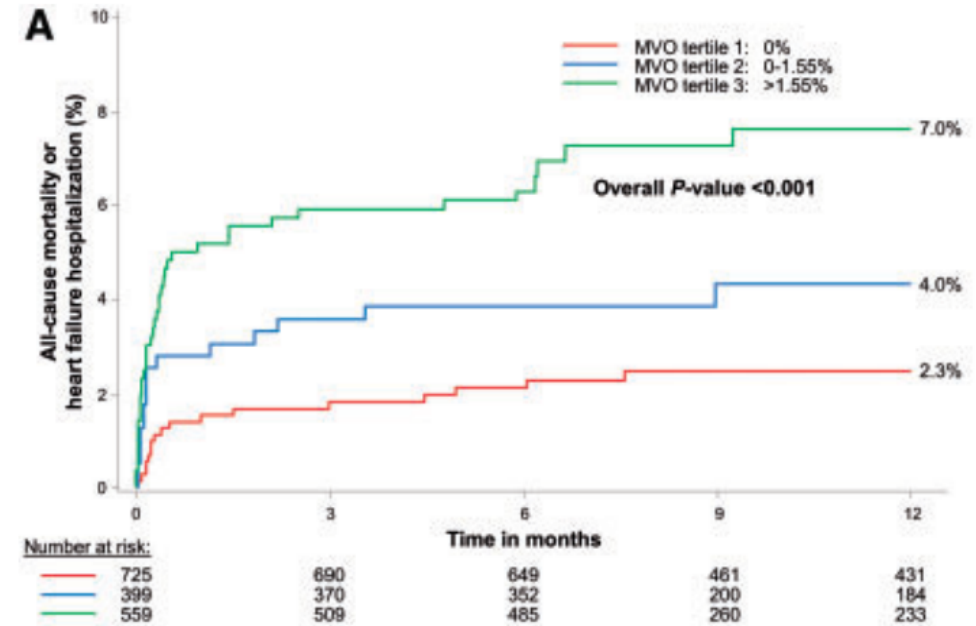
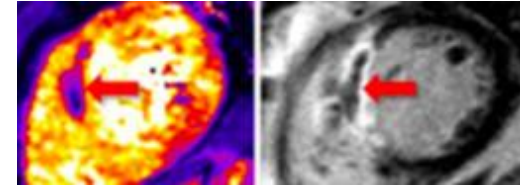
Pre PPCI



Post PPCI



MVO on CMR



Prognostic Value of IMR in STEMI



Bolus
thermolysis
in the culprit
artery to
calculate IMR



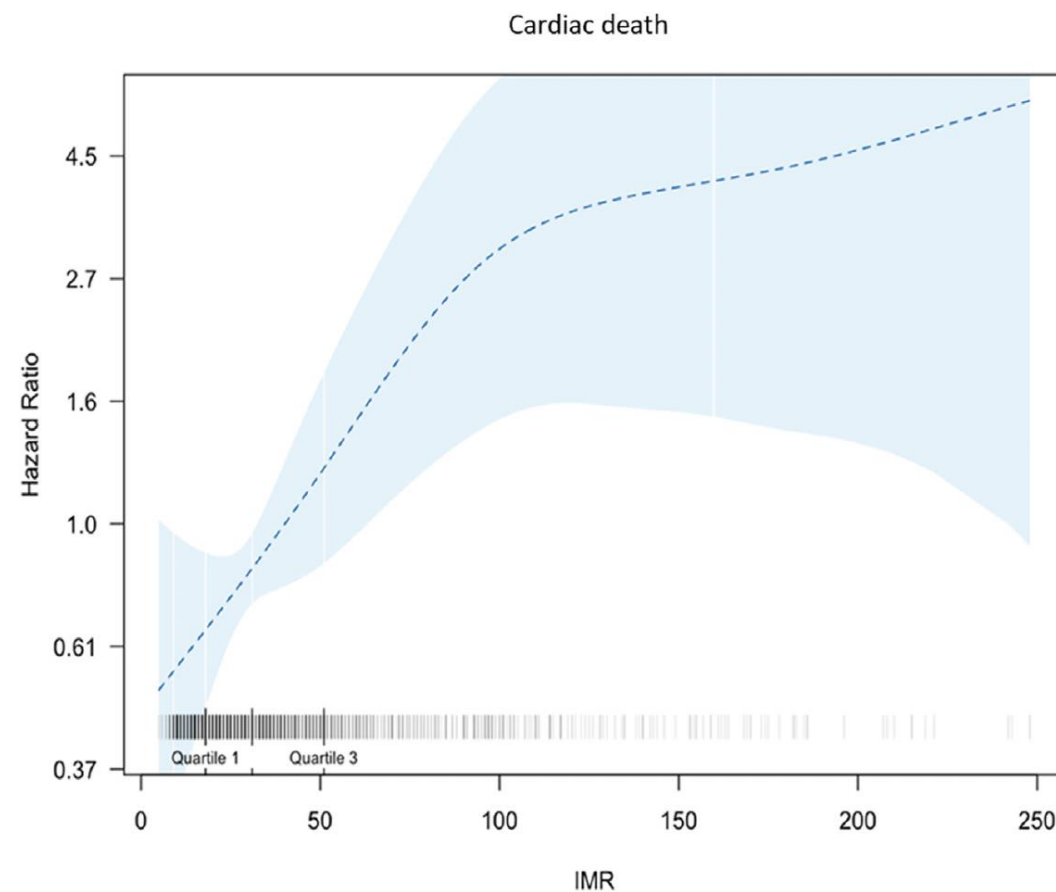
IMR as an independent
predictor of cardiac death:

HR: 1.13 (per 10 increase);
 $P = 0.012$

Optimal cut-off
value for IMR for
prediction of
cardiac death
in this cohort:
70

Higher IMR is associated with:

- Larger infarct size
- Microvascular obstruction
- Intramyocardial hemorrhage



Management of INOCA / ANOCA

Lifestyle factors



Healthy
Nutrition



Physical
Exercise



Weight
management



Smoking
cessation



Coping
with stress

Risk factors management



Hypertension



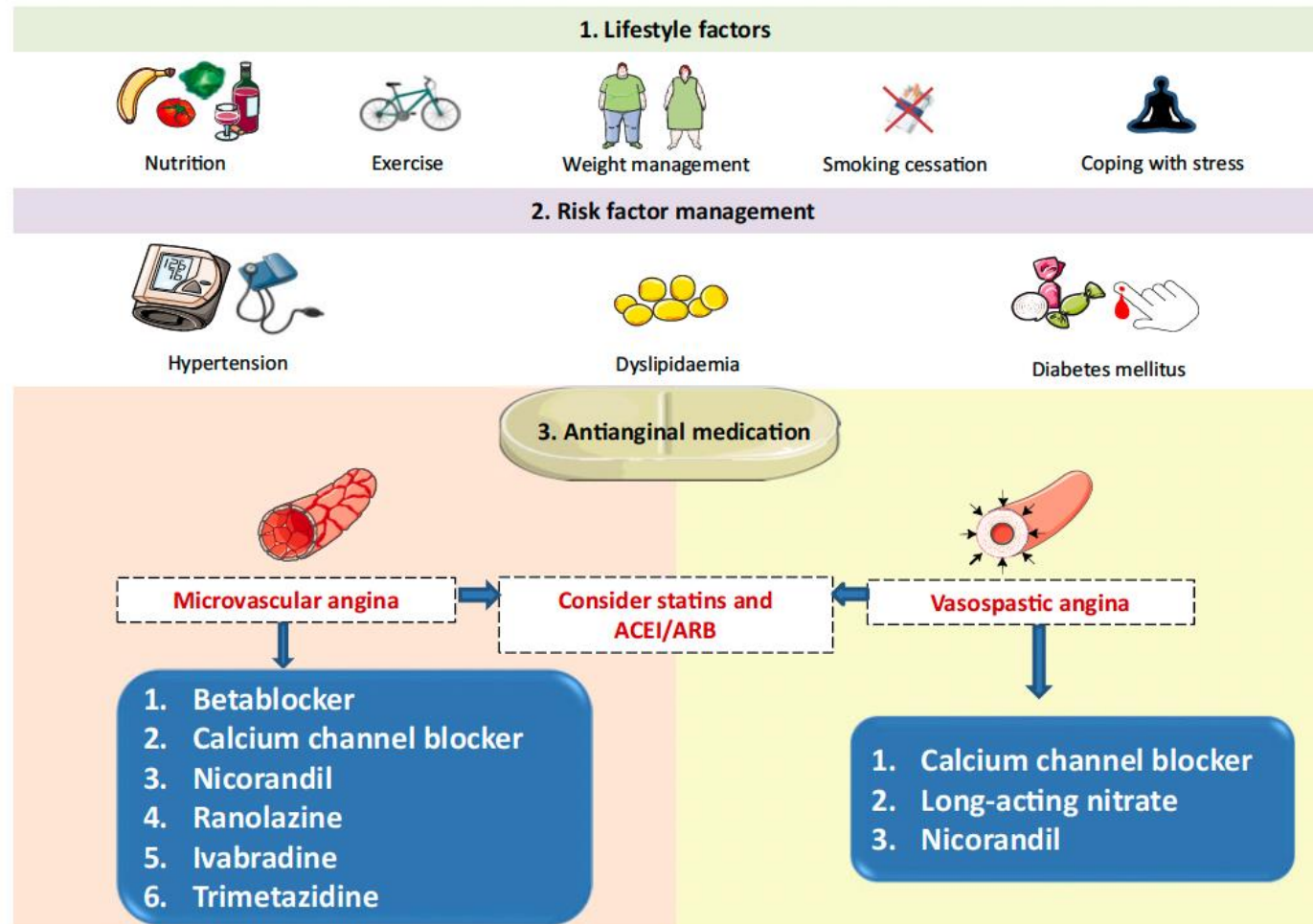
Dyslipidemia



Diabetes mellitus

Management of INOCA / ANOCA

Management of INOCA



Currently Available Medical Treatment Options for INOCA

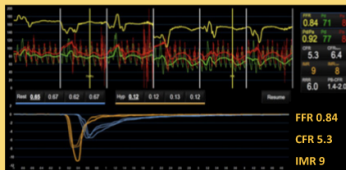
Treatment Agents	Clinical Effects	Applicable Endotypes of INOCA		
		Coronary Microvascular Disease	Epicardial Vasospastic Angina	Microvascular Vasospastic Angina
ACE inhibitor/ARB	• Improve endothelial function • Improve small vessel remodeling • Regress periarteriolar fibrosis	+	—	—
Beta-blocker	• Reduce myocardial oxygen demand and increase diastolic perfusion time by reducing heart rate and contractility • Increase the threshold of ischemic symptom • Improve endothelial function	+	—	—
Nitrates	• Dilate vascular smooth muscle • Reduce preload via systemic vasodilation	—	+	±
CCB	• Dilate vascular smooth muscle • Increase the threshold of ischemic symptom • Reduce myocardial oxygen demand • Improve symptom and exercise tolerance	±	+	+
Statin	• Anti-inflammatory and antioxidant properties • Improve coronary endothelial function	+	—	—
Nicorandil	• Coronary microvascular dilatory effect • Balanced vasodilator in veins and arteries	±	+	+
Ranolazine	• Reduce myocardial oxygen demand and improve microvascular perfusion via improvement of ventricular relaxation	+	—	—
Trimetazidine	• Increase cell tolerance to ischemia via cellular homeostasis	+	-	-

Functional assessment in INOCA

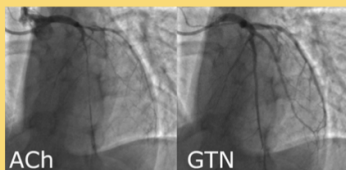
Vasospastic Angina



No Obstructive CAD



Normal adenosine physiology
(FFR 0.84, CFR 5.3, IMR 9)



Occlusive vasospasm with ACh
(resolves with nitrate)

Vasospastic Angina

- 1 - Calcium channel blocker
- 2 - Long-acting Nitrate
- Avoid beta-blockers
- Event prevention: ACEi, Statin
- Lifestyle and cardiac rehabilitation

Invasive Coronary Assessment in INOCA

1 Coronary Angiography

- Consider:
 - Obstructive CAD
 - Myocardial bridging
 - 'Flush' ostial branch occlusion

2 Guidewire (adenosine)



Coronary flow reserve - abnormal CFR ≤ 2.0
Microvascular resistance - IMR ≥ 25 or HMR > 2.4

3 Vasoreactivity (acetylcholine)

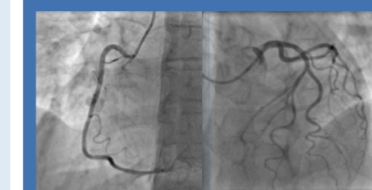


Epicardial vasospasm
Microvascular vasospasm

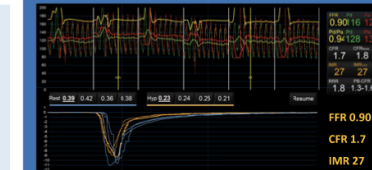
4 Diagnosis & Management

1. Microvascular angina
2. Vasospastic angina
3. Mixed angina
4. Non-Cardiac (normal IDP)

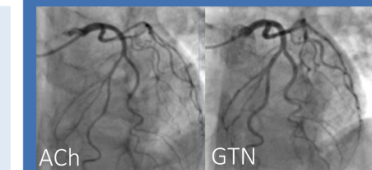
Microvascular Angina



No Obstructive CAD



Microvascular Dysfunction
(FFR 0.90, CFR 1.7, IMR 27)



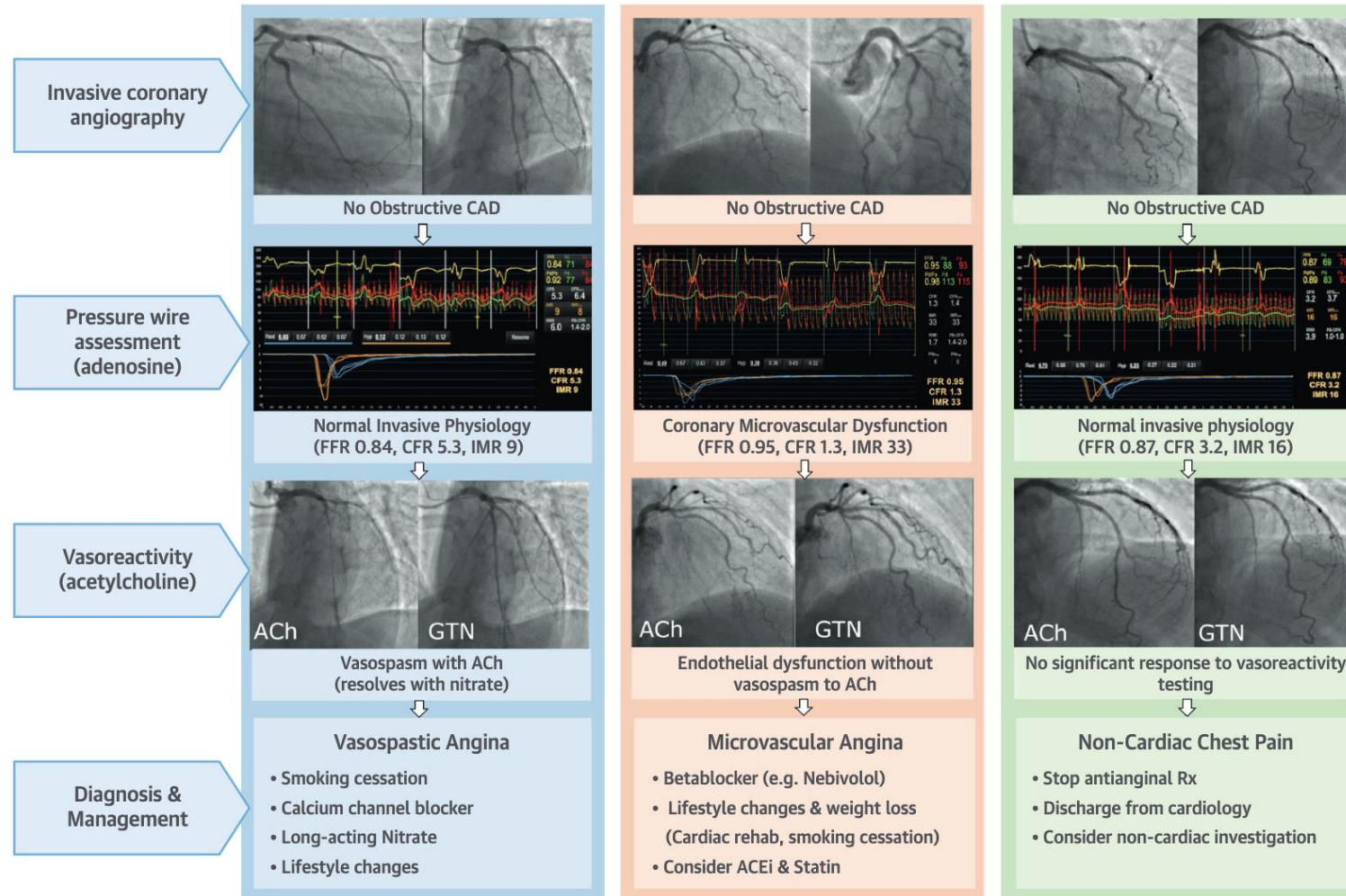
Endothelial dysfunction but no
gross vasospasm to ACh

Microvascular Angina

- 1 - Beta-blocker
- 2 - Calcium channel blocker
- Avoid long acting nitrates
- Event prevention: ACEi, Statin
- Weight loss and cardiac rehabilitation

Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina

The CorMicA Trial



Invasive Coronary Function Testing in Angina

CorMicA RCT

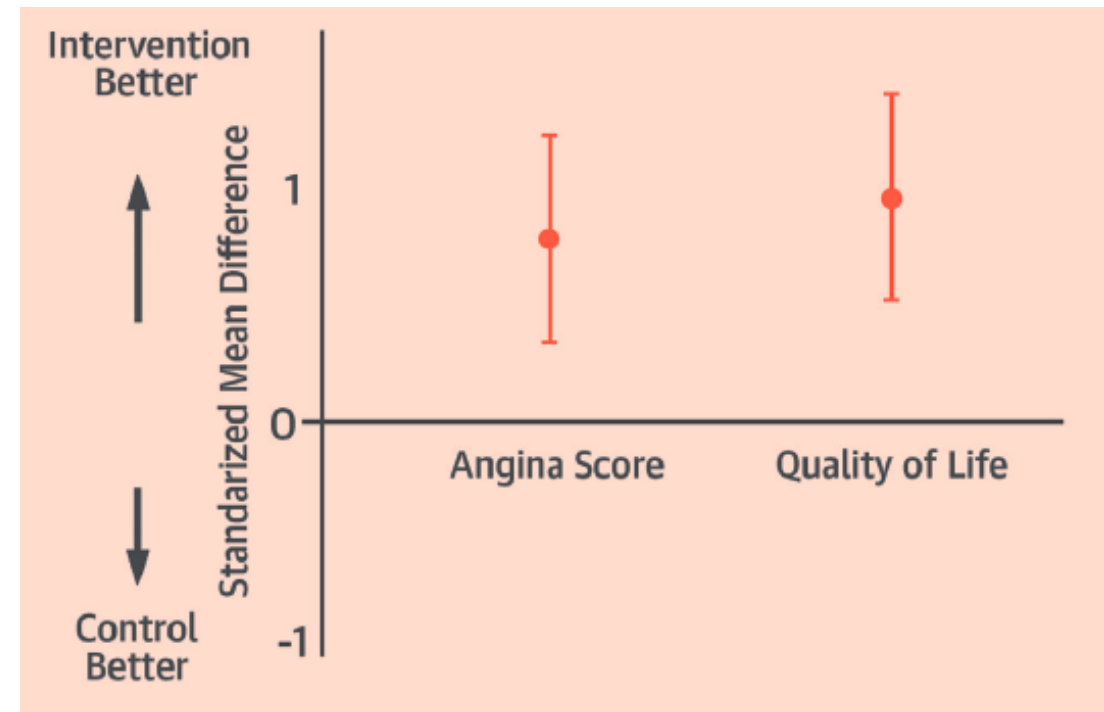
Endotypes

MVA	35 (46.1)	43 (57.3)
VSA	13 (17.1)	12 (16.0)
Mixed MVA/VSA	17 (22.4)	14 (18.7)
Normal coronary artery function	11 (14.5)	6 (8.0)

Stratified Medical Therapy

	Intervention	Control	P-value
CCB	38 (51%)	16 (21%)	<0.001
ISMN	29 (39%)	18 (24%)	0.054
Nicorandil	11 (15%)	6 (8%)	0.209
ACE/ARB	44 (59%)	28 (37%)	0.009
Statin	66 (88%)	41 (54%)	0.001

Improvement on Health Status



1-Year Outcomes of Invasive Coronary Function Testing in Angina

CorMicA 1-Year

Main Results:



**Sustained Benefits:
Improved Angina and
Quality of Life**

Ongoing Studies for Evaluating the Prevalence, Prognosis, and Management of INOCA

INOCAIT (NCT05164640)	Prospective registry	Prevalence, proportion of endotypes, and prognosis of INOCA
DISCOVER INOCA (NCT05288361)	Prospective registry	Prevalence, proportion of endotypes, and prognosis of INOCA
CorCTCA (NCT03477890)	Randomized controlled trial	Impact of invasive diagnostic tests for INOCA in classifying and managing INOCA patients
iCorMicA (NCT04674449)	Randomized controlled trial	Benefit of stratified management of INOCA based on invasive tests
WARRIOR (NCT03417388)	Randomized controlled trial	Prognostic impact of intensive statin/ACE inhibitor/ARB treatment in INOCA patients
PRIZE (NCT04097314)	Randomized controlled trial	Antianginal effect of zibotentan in patients with coronary slow flow phenomenon

Conclusions

- A significant number of symptomatic patients does not have obstructive CAD
- MVD carries a strong prognosis predictive value
- Microvascular function can be assessed in the cath lab
- Invasive assessment of microcirculatory function is supported by International guidelines
- Bolus thermodilution is a simple method to quantify MVD in the cath lab
- More research is needed regarding prognosis and most importantly therapeutic options

Thank you for your attention

