Coronary Microvascular Dysfunction & Vasospasm

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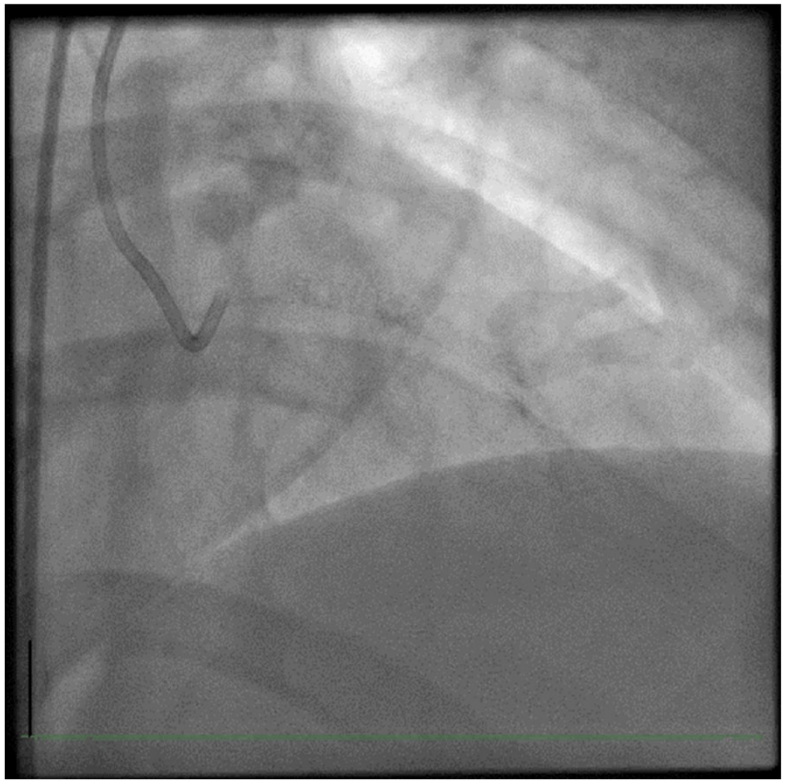
Disclosures
Grant/Research Support: NIH
Consulting/ Advisory or Honoraria: Abbott, Philips, Zoll

Key Topics to Discuss

- Prevalence and pathophysiology of Coronary Microvascular Dysfunction (CMD)
- ANOCA, INOCA, MINOCA
- The diagnosis of CMD and vasospasm in the cath lab
- Why we need to know? The prognosis of CMD
- What can we do? The current treatment options for CMD

Case presentation

58-year-old female with a past medical history significant for poliomyelitis and resultant post-polio syndrome impacting the R lower extremity, GERD, COVID-19 (9/2021), hypertension, dyslipidemia, prediabetes, family history of premature CAD, and CAD s/p anterior STEMI with s/p PCI s/p 2 overlapping DES in ostial to mid LAD; PTCA of the ostial diagonal in 2020, who has recently been evaluated for dyspnea and fatigue. She underwent a stress echo in 2022, notable for ischemia of the apical septum. She presents to the catheterization laboratory to evaluate hemodynamics and coronary anatomy.



Case presentation

Given her abnormal stress test and symptoms and otherwise reassuring angiogram, microvascular testing was pursued. The LVEDP was 20 mm Hg, suggesting optimal treatment for HFpEF may also help.

IMR= 59
CFR= 1.6

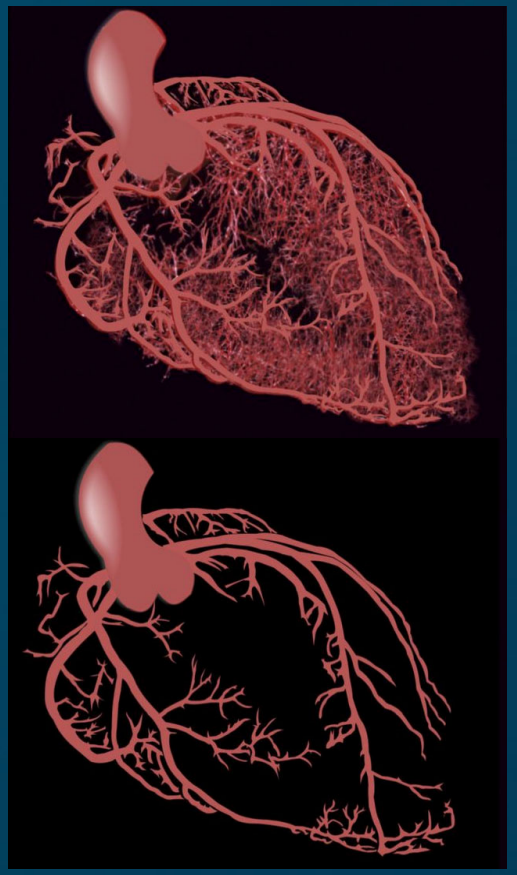
Dx: Microvascular Angina

Already on beta-blocker (Coreg)
Calcium channel blocker added

Why are we doing this?

CMD is common

- In the catheterization lab, out of 397,954 patients, no coronary artery disease was reported in 39.2% of patients.[1]
- Coronary microvascular dysfunction (CMD) in patients with normal or non-obstructive CAD (~30–50%) and is associated with a higher risk of major adverse cardiovascular events (MACE).[2, 3]



1. Patel M. NEJM 2010 ;362:886-95
2. P. Ong et al. International Journal of Cardiology 2018: 250; 16–20
3. Rahman, H., et al., Heart 2019;105:1536-1542
4. Taqueti et al. J Am Coll Cardiol. 2018 November 27; 72(21): 2625–2641

Definitions

INOCA = Ischemia with Non-obstructive Coronary Arteries
ANOCA = Angina with Non-obstructive Coronary Arteries

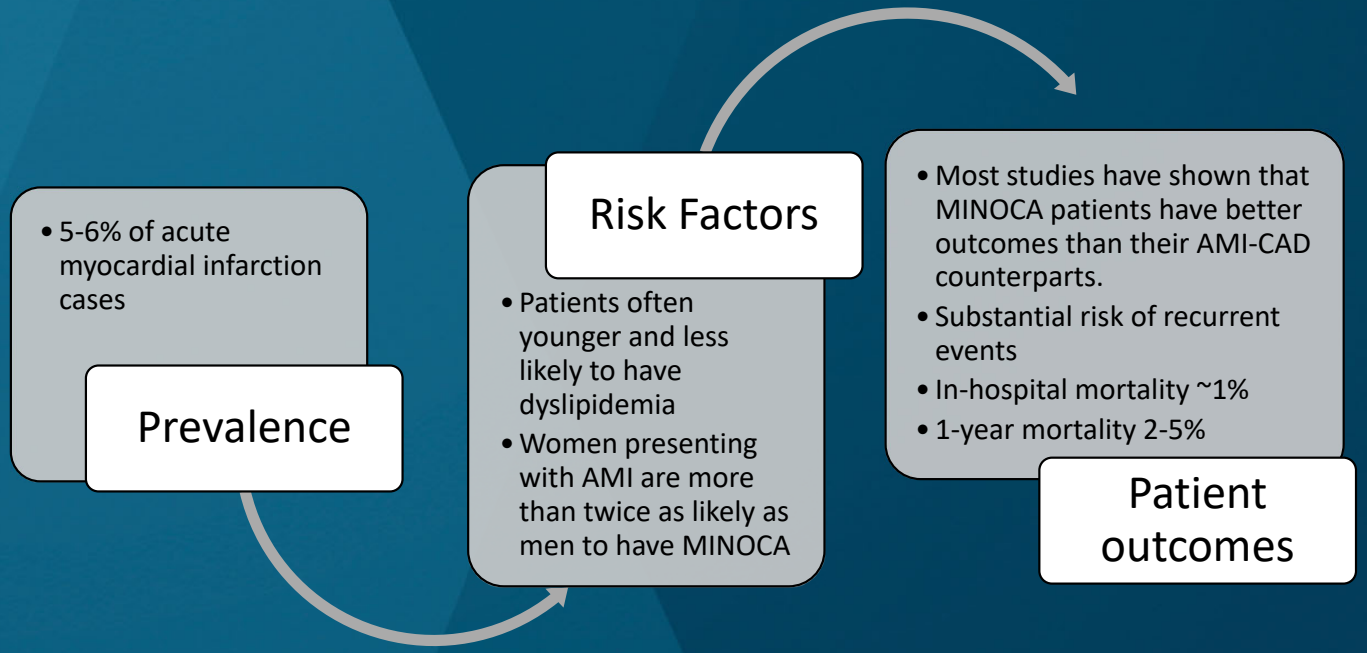
- In INOCA, the mismatch between blood supply and myocardial oxygen demands may be caused by coronary microvascular dysfunction and/or epicardial coronary artery spasm.

Definition

MINOCA = Myocardial infarction with non-obstructive coronary artery disease

1. AMI criteria as defined by the “Fourth Universal Definition of Myocardial Infarction”
2. Non-obstructive coronary arteries, with no lesions ≥50% in a major epicardial vessel
3. No other clinically overt specific cause that can serve an alternative cause for the acute presentation.

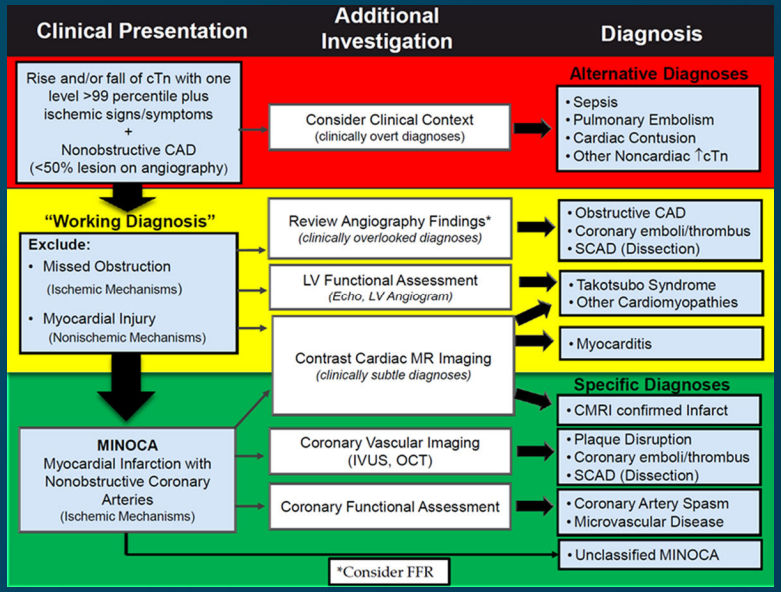
MINOCA: Prevalence, Risk Factors, and Outcomes



Differential Diagnosis for MINOCA

The diagnosis of MINOCA should exclude:

1) Other overt causes for elevated troponin (e.g., pulmonary embolism, sepsis, etc.)
2) Overlooked obstructive coronary disease (e.g., distal stenosis or occluded small branches)
3) Nonischemic causes for myocyte injury (e.g., myocarditis)

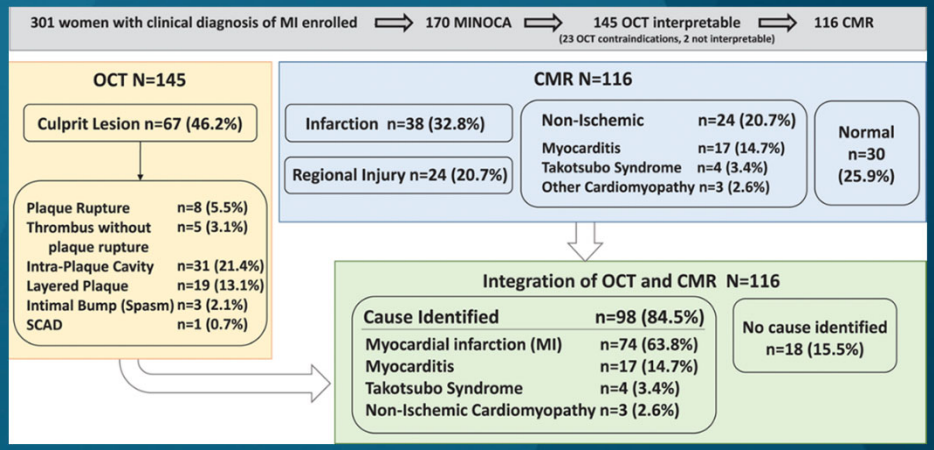


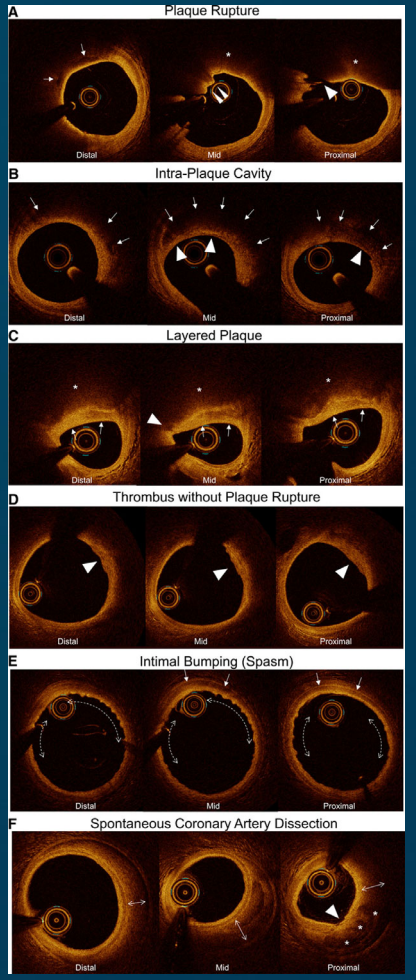
Tamis-Holland J et al. Circulation 2019

Diagnostic options

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

- Prospective, multicenter, international, observational study of women (301) with MINOCA
- If non-obstructive coronary artery disease (< 50% stenoses) on angiography, multivessel OCT and cardiac MRI were performed
- 84.5% of women had an identifiable cause of their MI with this strategy.



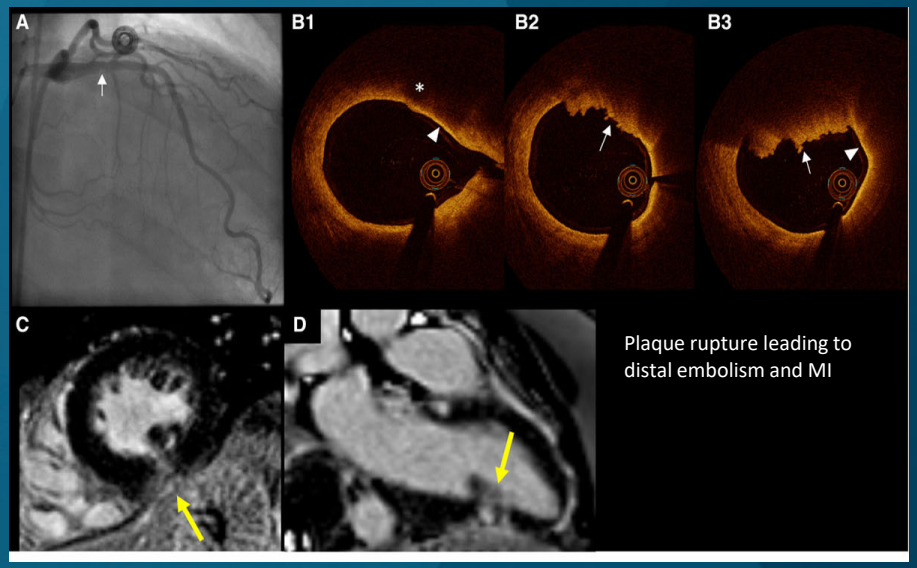


Plaque disruption is common in MINOCA and encompasses plaque rupture, plaque erosion, and calcific nodules. Optical coherence tomography (OCT) or intravascular ultrasound (IVUS) imaging in patients with evidence of nonobstructive CAD by angiogram may be considered.

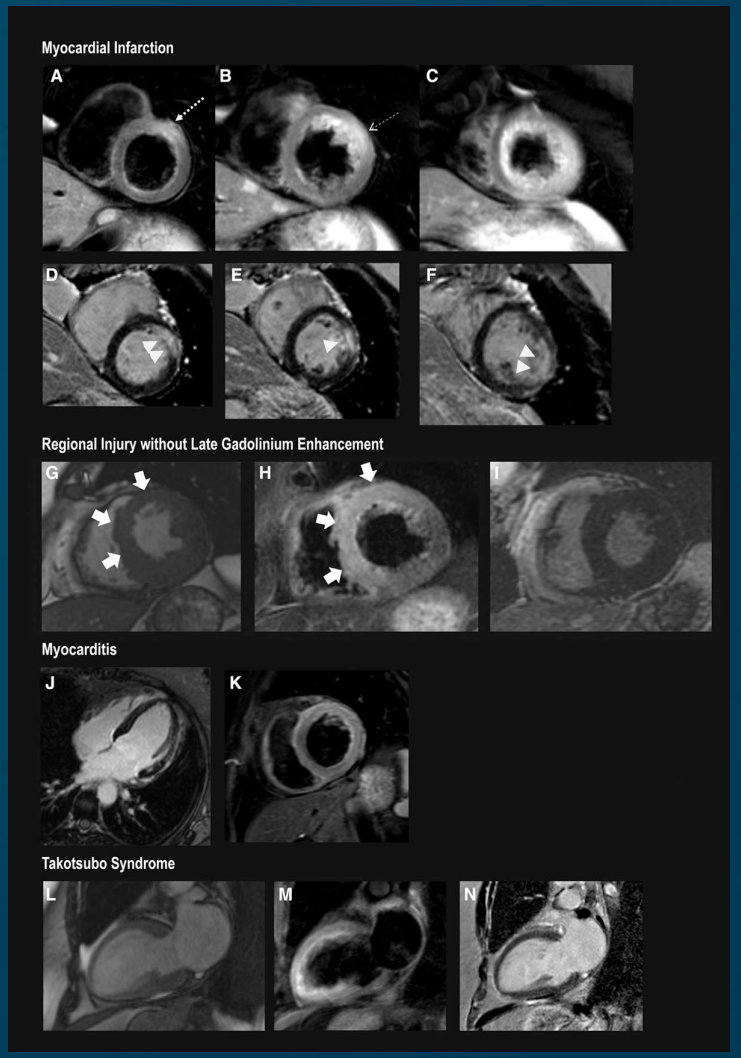
Reynolds H et al. Circulation 2021

Diagnostic options

- Cardiac MRI can reveal evidence of myocardial infarction, myocarditis, Takotsubo Syndrome.
- Coronary thrombosis or embolism can result in MINOCA, either with or without a hypercoagulable state.



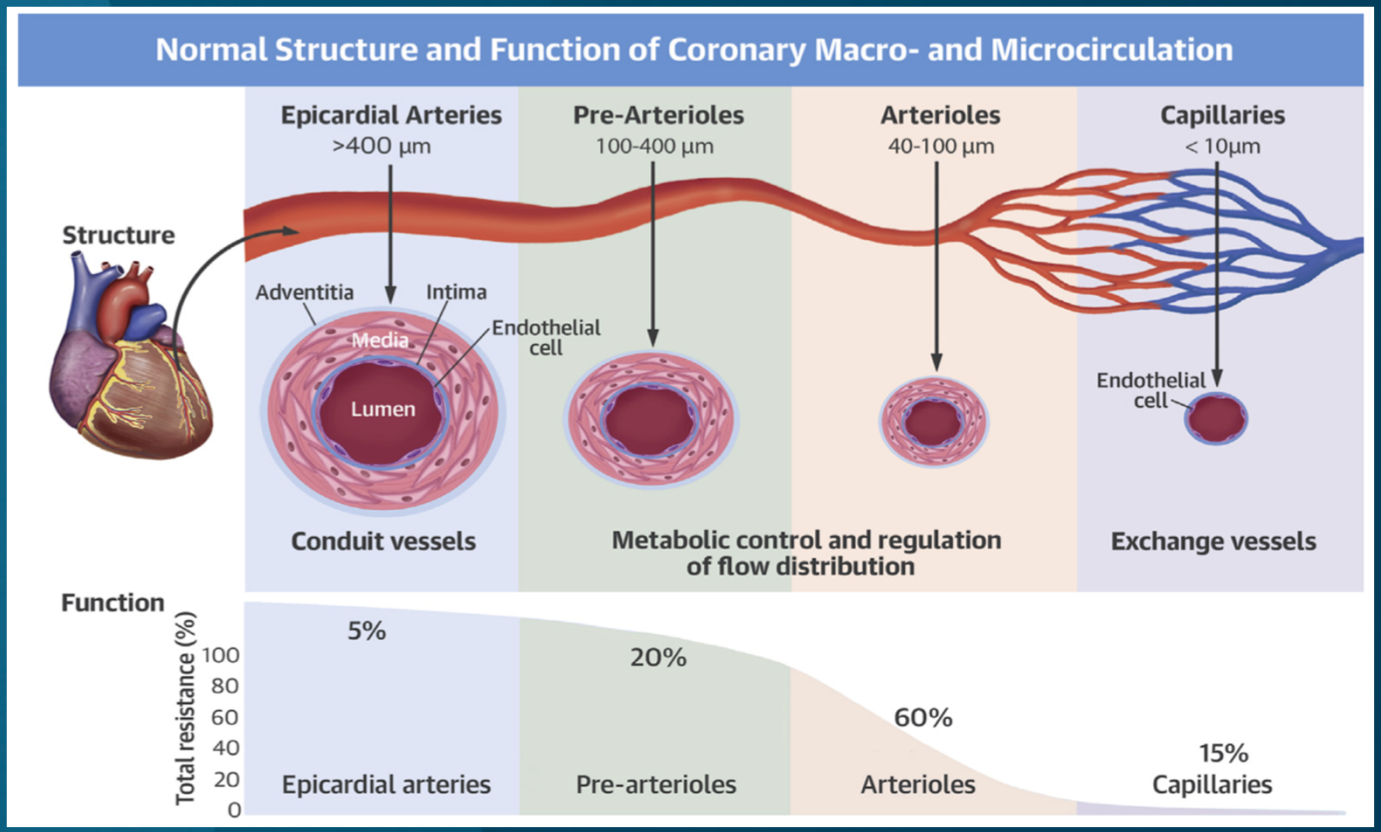
Reynolds H et al. Circulation 2021



Coronary Macro vs. Microcirculation

The **macrocirculation** (epicardial arteries) has a **conductance function** exhibiting minimal resistance to coronary flow.[1,2]

The **microcirculation** is responsible for **regulation and distribution** of blood flow matching the needs of local tissue.[1,2]



Taqueti et al. J Am Coll Cardiol. 2018
Schelbert, H.R. *J. Nucl. Cardiol.* 2010

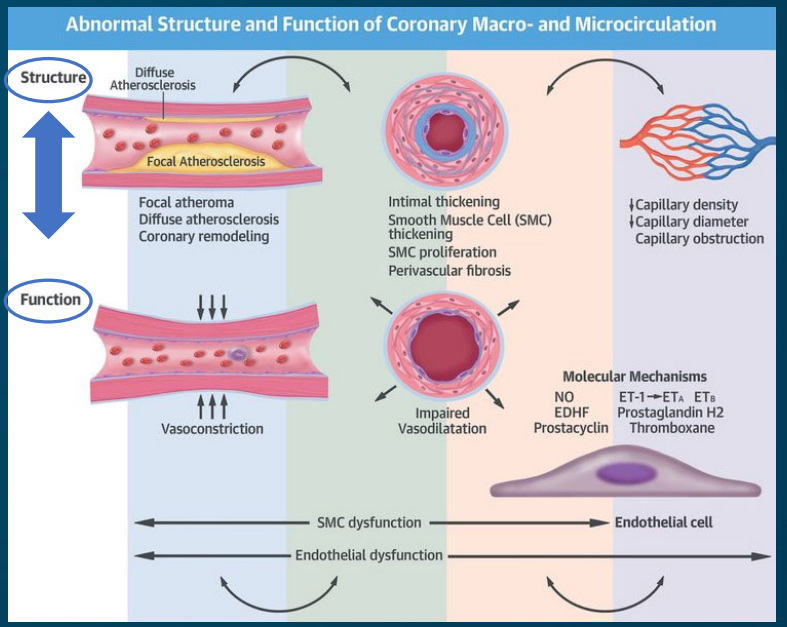
Pathophysiology of coronary microvascular dysfunction

1. ***Structural*** *changes* or microvascular remodeling
2. ***Functional*** *abnormalities*

Both changes have been associated with CMD.[1]

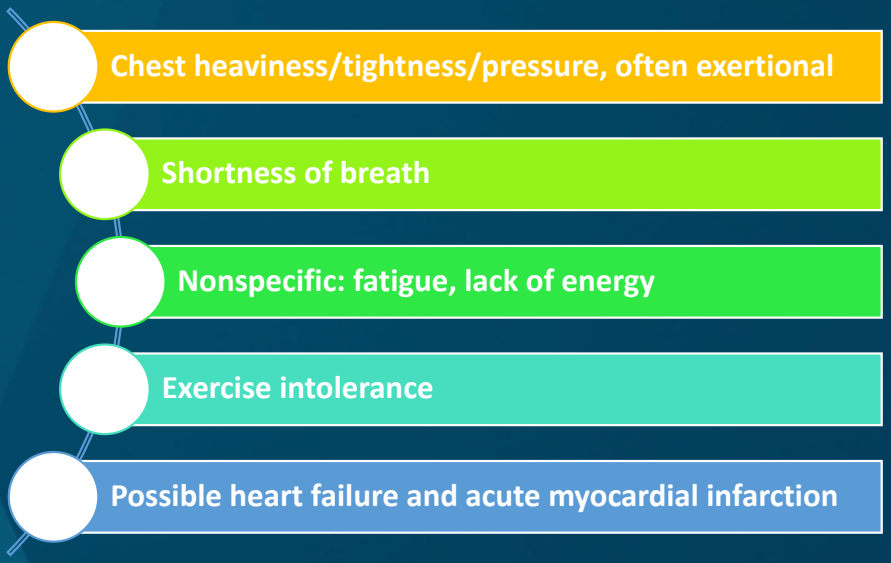
This spectrum of abnormalities does not include atheroma, which occurs in epicardial arteries, but is nonetheless likely magnified by the presence of atherosclerosis, particularly in patients with CVD risk factors.[1]

These changes lead to microvascular obstruction with luminal narrowing of the intramural arterioles and capillaries.[1]



Taqueti et al. J Am Coll Cardiol. 2018

Symptoms of microvascular dysfunction



Definition of Chest Pain

TOP 10 TAKE-HOME MESSAGES FOR THE EVALUATION AND DIAGNOSIS OF CHEST PAIN

1. **Chest Pain Means More Than Pain in the Chest.** Pain, pressure, tightness, or discomfort in the chest, shoulders, arms, neck, back, upper abdomen, or jaw, as well as shortness of breath and fatigue should all be considered anginal equivalents.

Recommendation for Considerations for Older Patients With Chest Pain

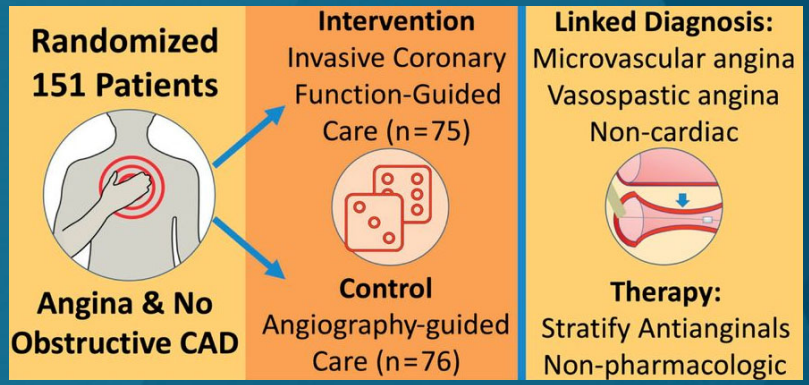
COR	LOE	RECOMMENDATION
1	C-LD	1. In patients with chest pain who are >75 years of age, ACS should be considered when accompanying symptoms such as shortness of breath, syncope, or acute delirium are present, or when an unexplained fall has occurred (1).

Gulati M et al., JACC 2021

CorMicA Trial

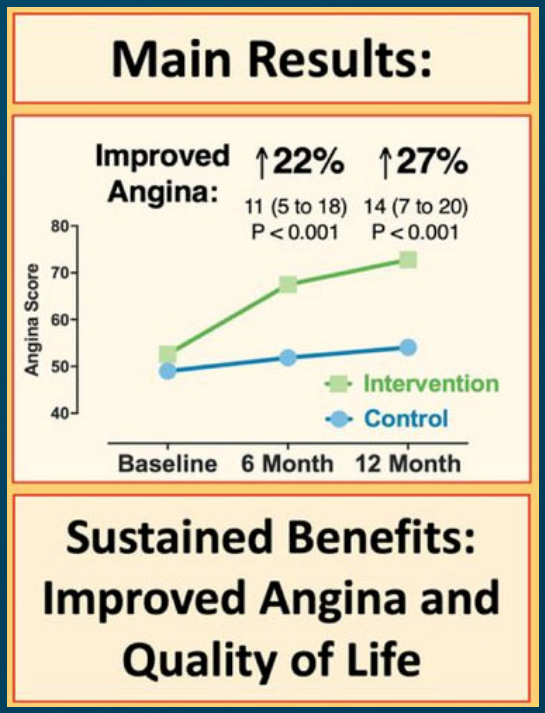
A randomized, controlled, blinded trial of medical therapy versus standard care in INOCA patients

Purpose: Test whether an interventional diagnostic procedure (IDP) linked to stratified medicine improves health status in patients with INOCA



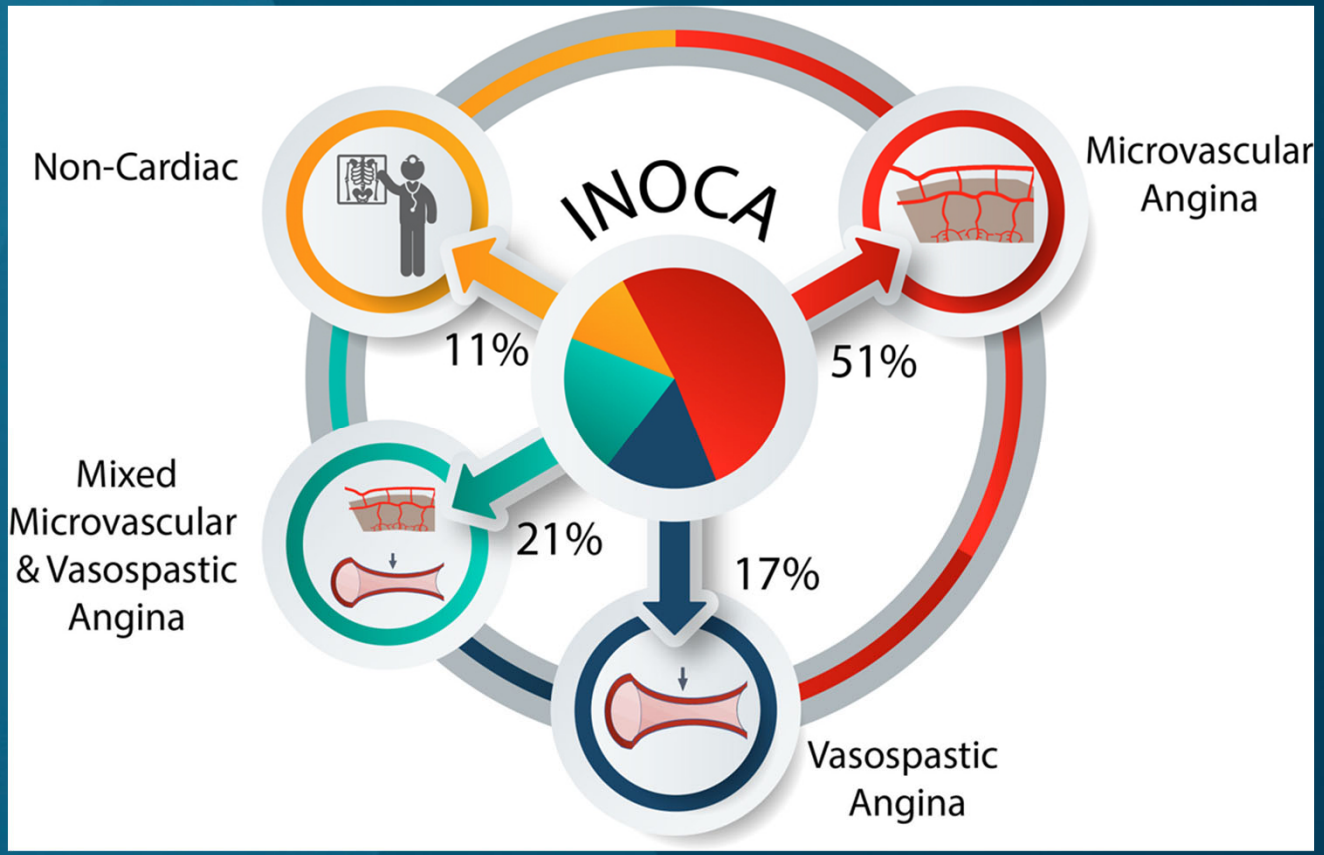
Guidewire-based assessment of coronary flow reserve, index of microcirculatory resistance, fractional flow reserve, followed by vasoreactivity testing with acetylcholine.

Primary endpoint: Mean difference in angina severity at 6 months



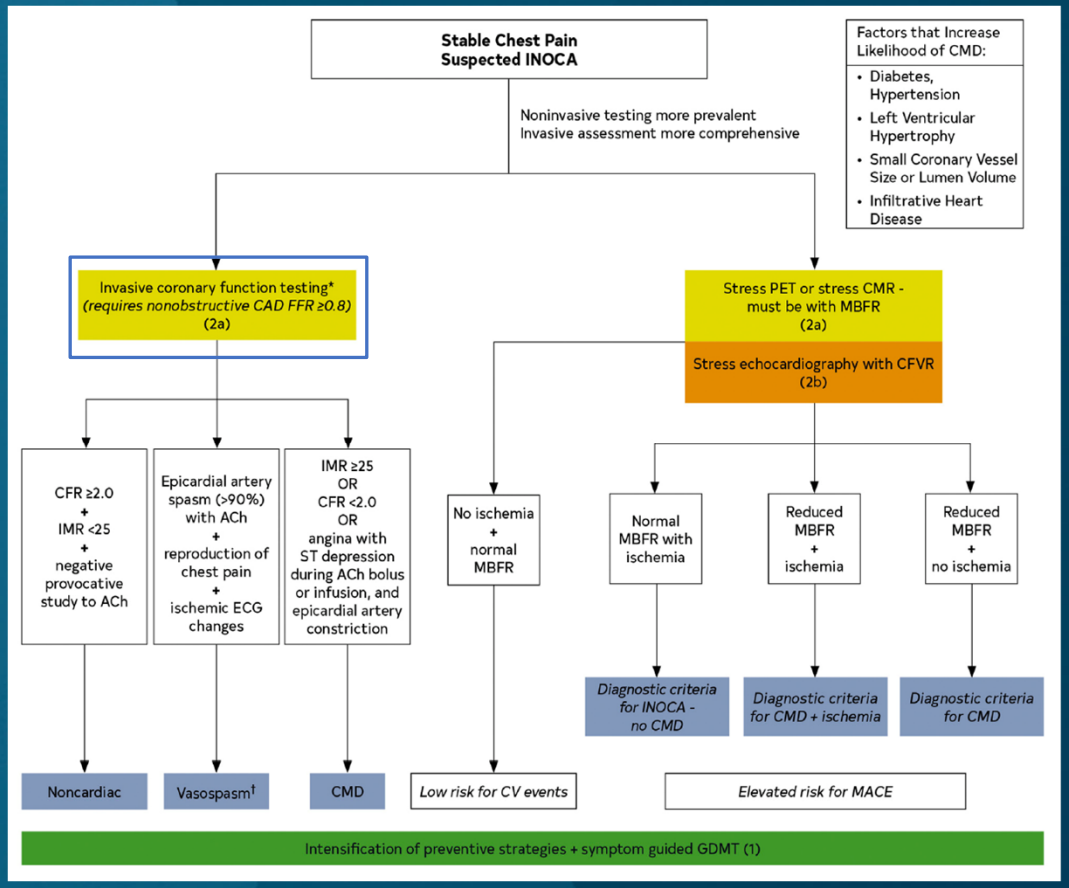
1. Ford et al. J Am Coll Cardiol Intv 2020;13:33-45

High Prevalence of Microvascular Angina



Ford T et al. Circ Interventions 2019

Stable Ischemic Heart Disease: INOCA

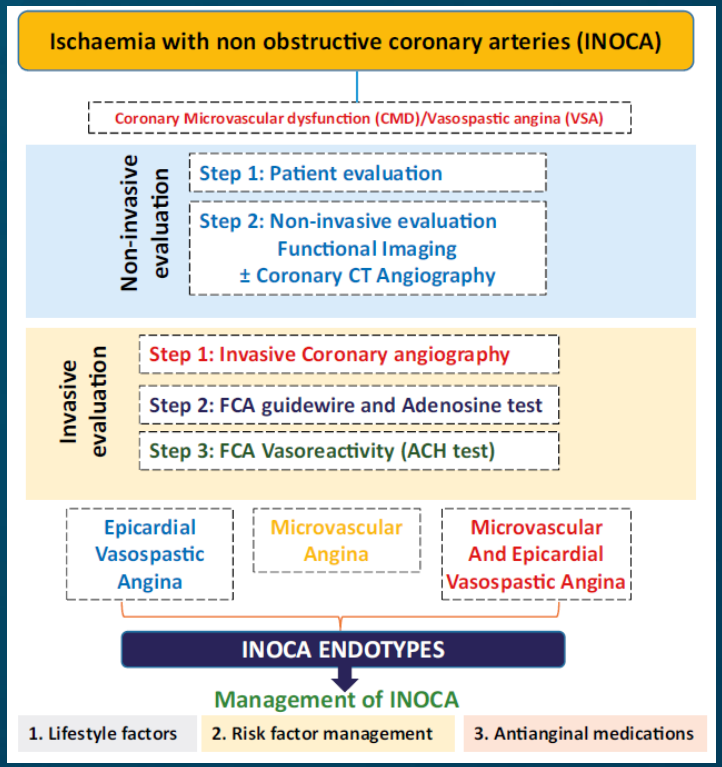


Gulati M et al., JACC 2021

EAPCI Consensus Document 2020[1]

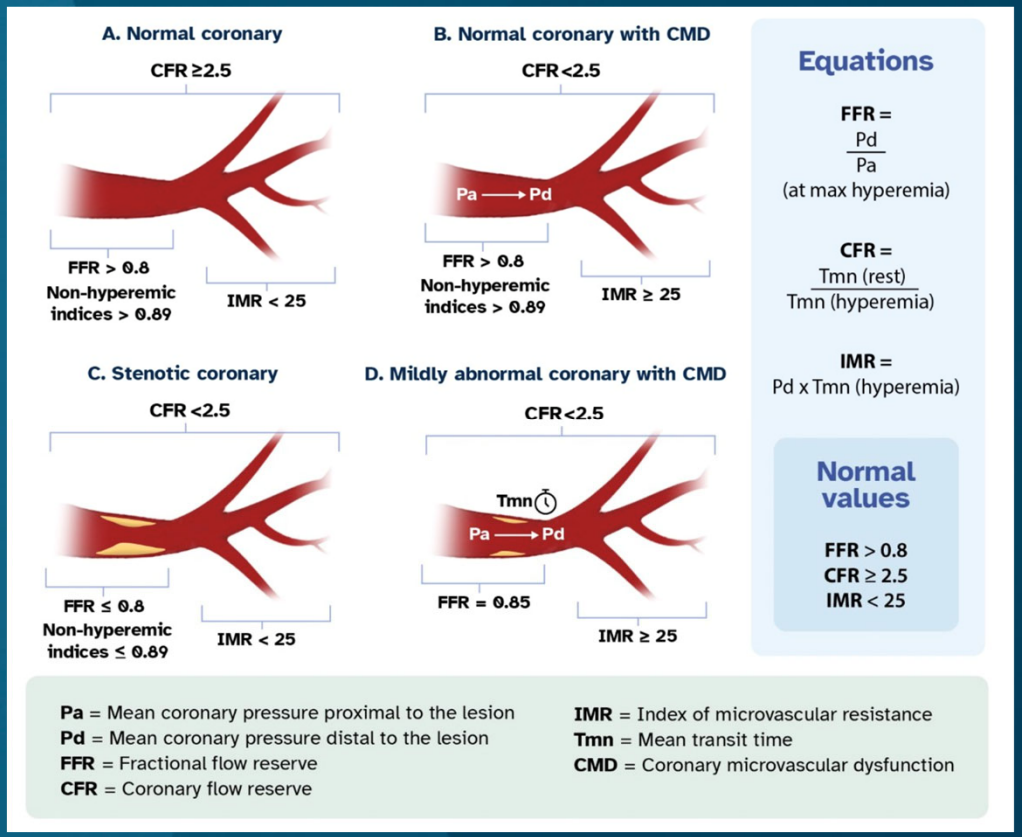
Recommendations

1. INOCA should be recognized as a clinically important entity in daily clinical practice.
2. A systematic approach to diagnose and treat these patients should be implemented by clinicians and interventional cardiologists dealing with these patients.
3. National and international scientific societies, as well as the pharmaceutical and biomedical industries to support future research to address the incomplete understanding of the pathophysiology, the lack of targeted pharmacological treatment, and the evidence-based management of patients with INOCA.
4. Creating awareness of this condition through campaigns and media to ensure timely provision of care to these patients.



1. Kunadian, Vijay; EAPCI Expert Consensus Document *EHJ & Eurointervention* 2020: ehaa503

Physiological Indices Assess Different Parts of the Circulation



Kerkar A et al.,…Sutton NR. Current Treatment Options 2023

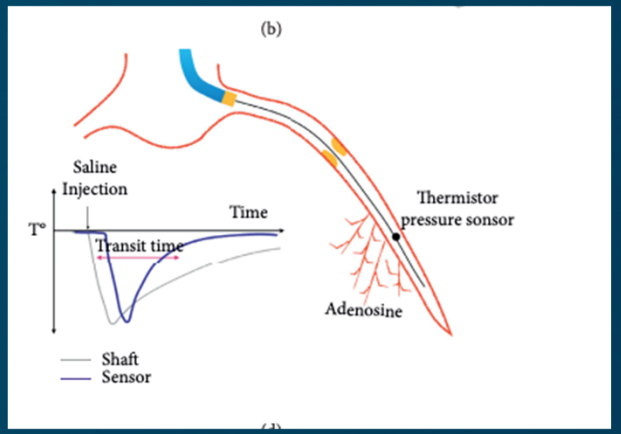
Comparison of CMD Diagnostic Options

	Method	Quantification	Tracer	Spatial resolution	Recording time
Noninvasive	SPECT	None	Radio isotopes	Very low	Long
	PET	Perfusion (mL/min/g) gold standard	Radio isotopes (cyclotron-generated)	Low	Long
	CT	Perfusion (mL/min/g)	Contrast agent	Very high	Low
	MRI	Perfusion (mL/min/g)	Contrast agent	Moderate	Moderate
	Ultrasound	Perfusion (mL/min/g)	Microbubbles	High	Real time
Invasive	Doppler wire	Flow velocity (mm/s)	None	Selective assessment in target vessel territory	
	Thermodilution	Blood flow (mL/min)	Saline (body temperature)		
	CTFC	None	Contrast agent		

Maas et al. EMJ Int Cardiol. 2019;7[Suppl 1]:2-17 (reproduced from Frishman WH. Pharmacology of the nitrates in angina pectoris. Am J Cardiol. 1985;56(17):8I-131)

Microvascular Dysfunction

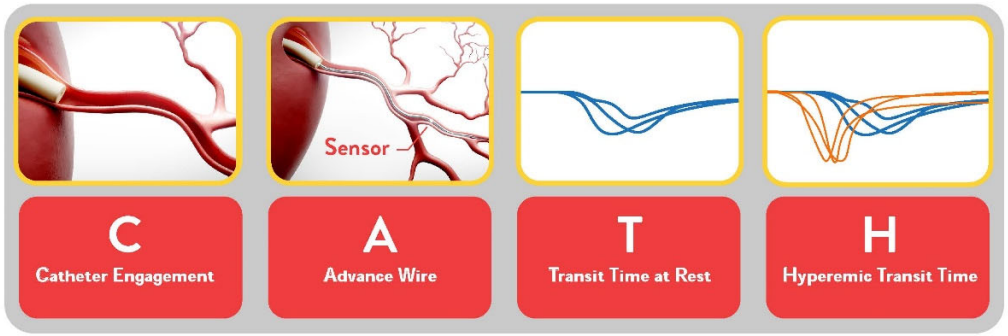
- Coronary microvascular dysfunction may contribute to MINOCA and requires further investigation.
- CFR may be measured invasively (Doppler or Thermodilution) or non-invasively (e.g. by PET)
- Defined as Index of Microvascular Resistance ≥ 25 and Coronary Flow Reserve < 2.5, 2.0-2.4 considered CFR “grey zone”

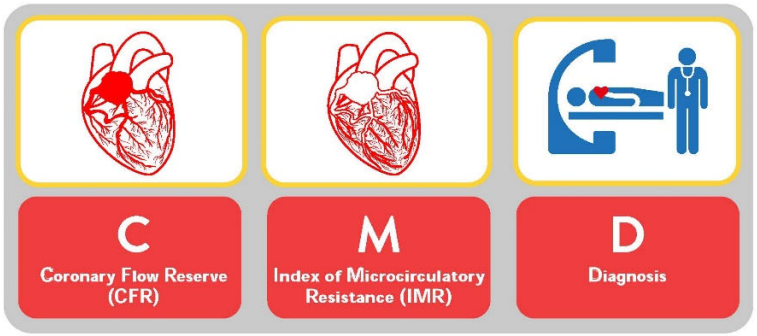


IMR = Index of microvascular resistance

IMR = Mean transit time (Tmn) at hyperemia x distal pressure

CATH CMD





C — Catheter Engagement

- Flush thoroughly[1]
- Coaxial guide engagement[1]
- Ensure no damping[1]

A — Advance Wire

- Interrogate LAD unless there is a specific territory of interest[2]
- Advance wire sensor 2/3 distally in vessel[2]
- Administer GTN/NTG[1]

T — Transit Time at Rest

- Flush/purge pre-Tmn_{rest} to clear any blood and contrast[3]
- Room temperature saline[3]
- Brisk 3 mL x 3 injections[3]
- Address outliers (± 0.15s) before proceeding[3*]

*Repeat measurement of Tmn_{rest}

H — Hyperemic Transit Time

- Induce hyperemia[5]
- Confirm hyperemia[*,6]
- Flush/purge pre-Tmn_{hyp} to clear any blood and contrast[6]
- Room temperature saline[6]
- Brisk 3 mL x 3 injections[6]
- Address outliers (± 0.15s) before proceeding[6**]

*Decrease in pressure, patient symptoms, FFR drop

**Repeat measurement of Tmn_{hyp}

C — Coronary Flow Reserve (CFR)

- CFR <2.5*[1]
- CFR grey zone 2.0-2.4*[7]

*Evolving consensus

M — Index of Microcirculatory Resistance (IMR)

- IMR ≥25[2]
- Use IMRcorr if FFR <0.80[6]

D — Diagnosis

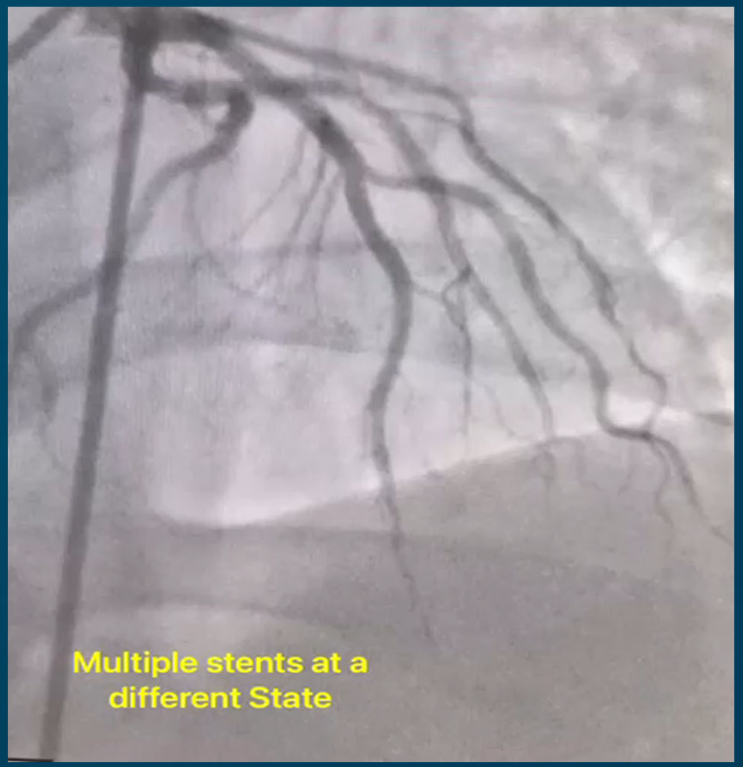
- Diagnosis of CMD based on IMR ≥25 and CFR <2.5*[2,4]
- CFR grey zone 2.0-2.4*[7]
- Refer to guidelines and consensus document[2,3,8-10]

*Evolving consensus

Developed by Abbott Vascular

Case presentation

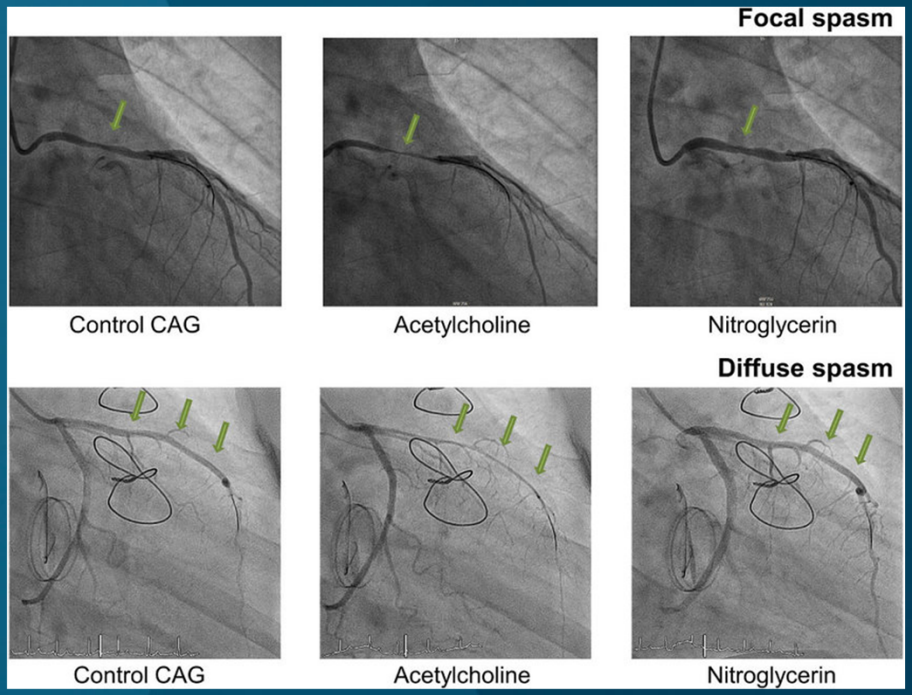
- 47 year-old female with a history of mild depression and anxiety
- Remote prior tobacco use
- 2 normal pregnancies
- Multiple (5+) primary care and cardiology visits for atypical chest pain even after prior PCIs. CP occurs at rest and with exertion, of variable duration, with prior reassuring treadmill stress echo test.
- Currently on an anti-depressant



Video credit: Dr. Hady Lichaa

Coronary Vasospasm

- Coronary vasospasm is another common cause of MINOCA / INOCA / ANOCA, defined as >90% vasoconstriction of an epicardial coronary artery resulting in compromised coronary blood flow.
- The gold standard technique for diagnosing coronary spasm is administration of high-dose intracoronary acetylcholine boluses with the response evaluated by invasive contrast angiography.



Tamis-Holland J et al. Circulation 2019 and
Vlastra et al. Netherlands Heart Journal 2017

How?

PREP

D/C CAFFEINE, LONG-ACTING NITRATES, BETA-BLOCKERS, CALCIUM CHANNEL BLOCKERS (CCB), AND ACE-I/ARBS FOR > 24 HOURS PRIOR TO PROCEDURE

CONSCIOUS SEDATION SHOULD BE LIGHT

THERAPEUTIC ANTICOAGULATION

MONITOR, DEFIBRILLATOR, PERIPHERAL INTRAVENOUS LINES

How?

Vascular access

- Avoid vasodilators (relevant for radial access)
- 6 F preferred
- Generally, operator preference

How?

Choice of Coronary Artery

- LAD only vs. LAD & RCA?

Considerations:

- Time (and timing relative to MVD adenosine testing)
- Arrhythmias
- Suspicion for regional spasm
- Prior extensive stenting
- ?Need for temp transvenous pacemaker

How?

- Graded doses of Ach
  - Starting dose of 20 mcg
  - Higher (spasm dose) of 50 mcg for RCA or 100 mcg for LAD
  - 200 mcg dose if no spasm at lower doses and spasm strongly suspected (LAD only)

Safety

TABLE 1 Major and Minor Complications During Provocative Testing With Intracoronary ACh Administration

First Author	All Major Complications	Death	VT/VF	MI	Shock	All Minor Complications	Transient Hypotension	AF	Bradycardia With Management	PVC	Other
Bill et al[19]	0	0	0	0	0	0.9	–	0.9	–	–	7.6% transient bradycardia
Deyama et al[20]	1.4	0	1.4	0	0	NR	NR	NR	NR	NR	–
Ford et al[21]	0	0	0	0	0	9.3	–	5.9	3.3	–	30.5% transient bradycardia
Konst et al[22]	0	0	0	0	0	0	–	–	–	–	13.1% transient bradycardia
Lee et al[23]	0	0	0	0	0	2.3	–	0.1	2.1	–	26.5% transient bradycardia
Montone et al[24]	0.3	0	1.0	0	0	2.6	0	2.6	–	–	6.1% transient bradycardia
Ong et al [25]	0.1	0	1.0	0	0	0.2	0	0.1	0.1	–	0.6% transient bradycardia
Pargaonkar et al[26]	0	0	0	0	0	1.1	–	1.1	0	–	10.1% transient bradycardia
Probst et al[27]	0	0	0	0	0	3.9	1.1	1.6	–	1.1	12.8% transient bradycardia
Sara et al[28]	0	0	0	0	0	NR	NR	NR	NR	NR	–
Sato et al[29]	1.0	0	1.0	0	0	NR	NR	NR	NR	NR	–
Sueda et al[30]	3.2	0	2.3	0	0.9	24.8	–	24.8	–	–	0.1% cardiac tamponade
Takagi et al[31]	4.9	0	4.9	0	0	0.7	–	–	–	0.7	4.1% transient bradycardia
Tateishi et al[32]	1.7	0	0.9	0.2	0.6	10.2	–	10.2	–	–	0.4% stroke
Tio et al[33]	0.7	0	0	0	0.7	1.3	0	0	1.3	–	2.0% transient bradycardia
Wei et al[34]	0.3	0	0	0.3	0	NR	NR	NR	NR	NR	0.3% air embolism, (coronary dissection[a])

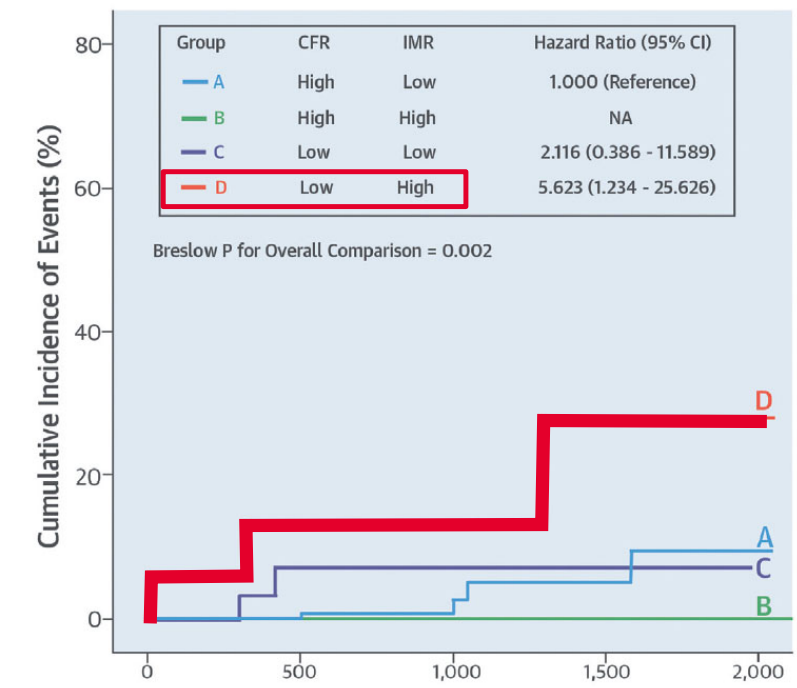
Values are %. [a]Wei et al reported 1 adverse event with non-flow-limiting coronary dissection, which likely resulted from Doppler wire advancement.

ACh = acetylcholine; AF = atrial fibrillation; NR = not reported; PVC = premature ventricular contraction; VF = ventricular fibrillation; MI = myocardial infarction; VT = ventricular tachycardia.

Takahashi et al. JACC 2022

Prognosis

CFR and IMR Can Identify Patients With High Risk of Future Events

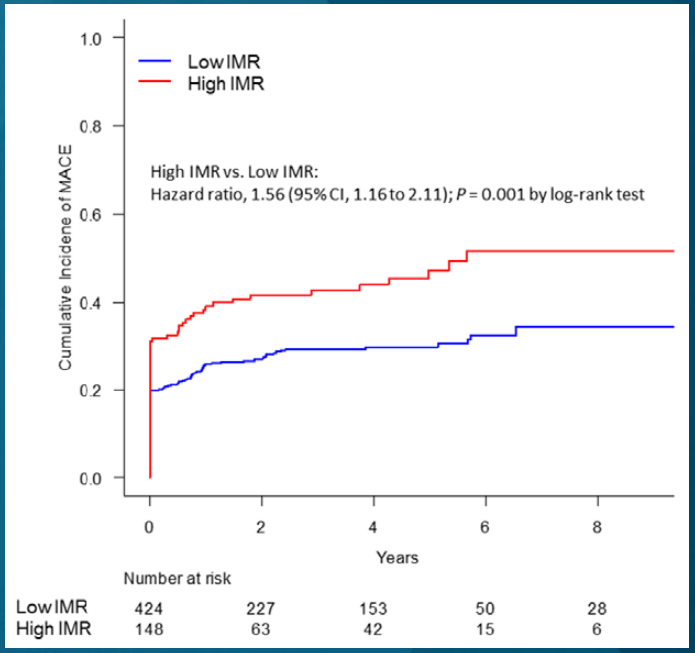


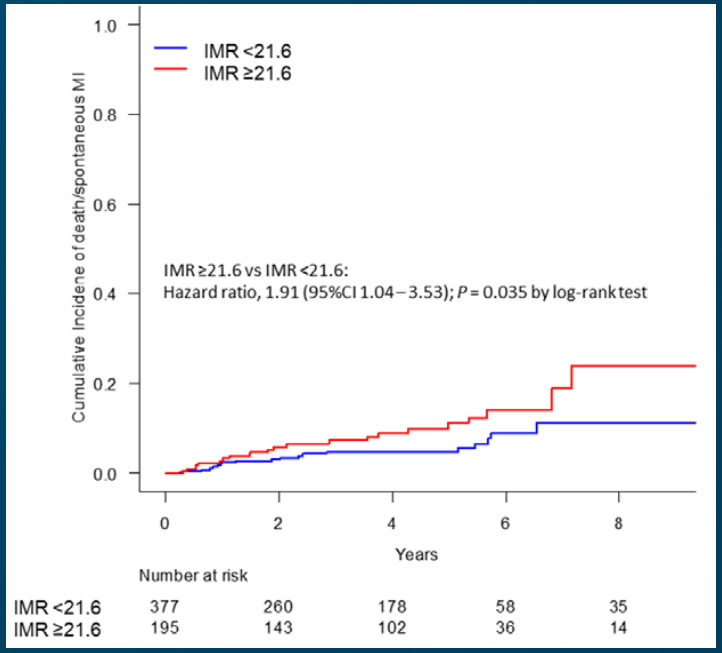
"These results suggest that invasive physiological assessment for microvascular disease with CFR and IMR can be helpful to identify patients at high risk for future cardiovascular events among those with high FFR"

1. Lee JM et al; JACC Interv 2016;67:1158- 1169

Post-PCI IMR Predicts MACE

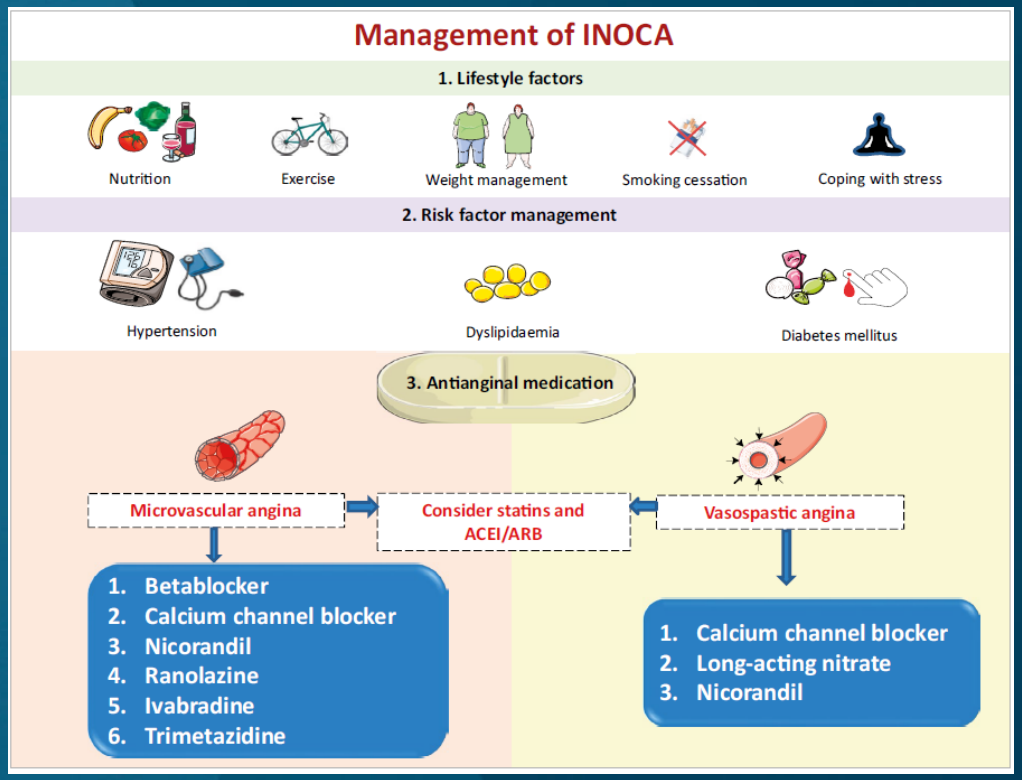
Prognosis in Stable CAD





1. Nishi et al: *Circ Cardiovasc Interv.* 2019;12:e007889

Management of INOCA



1. Kunadian, Vijay; EAPCI Expert Consensus Document *EHJ & Eurointervention* 2020: ehaa503

Case Presentation

- 62 year old female with hyperlipidemia, breast cancer s/p lumpectomy, chemo/radiation, depression, and a family history of premature coronary artery disease.
- Shortness of breath with steep inclines, occasional right sided chest discomfort not related to effort.
- She is a standardized patient and participated in several cardiology scenarios, and she is concerned about her symptoms.

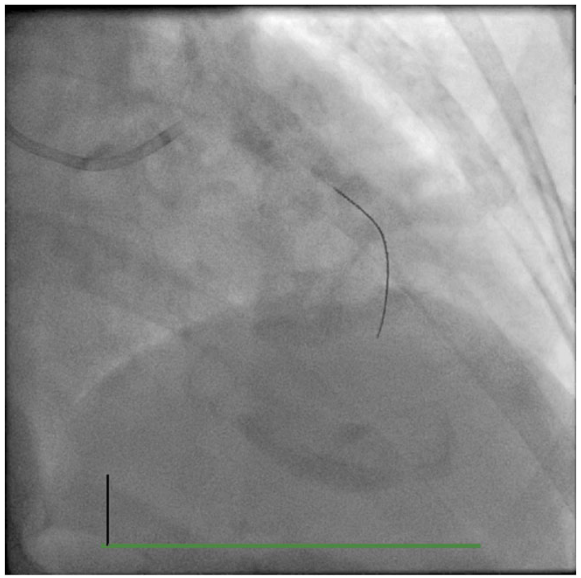
Case Presentation

Exercise stress echo: EF 60%, no significant valve issues, baseline wall motion normal, post-exercise images are technically difficult, reported as distal inferoseptal akinesis, distal inferior hypokinesis, distal lateral hypokinesis, possible distal LAD territory inducible ischemia.

Case Presentation

- Findings discussed with patient in clinic.
- Coronary anatomy evaluation was recommended.
- Coronary CTA and invasive angiography were discussed.
- The option for invasive microvascular testing if coronary angiography was reassuring was discussed as a consideration.
- The patient opted for an invasive coronary angiogram.
- Antianginals were discussed/recommended.

Case Presentation



Case Presentation

Key Takeaways

- Common problem
- User-friendly system
- Results help patients
- Increasing interest from patients and clinicians

Thank you for your attention!

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