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MINOCA e INOCA: terapia ottimale

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Università del Piemonte Orientale, Novara

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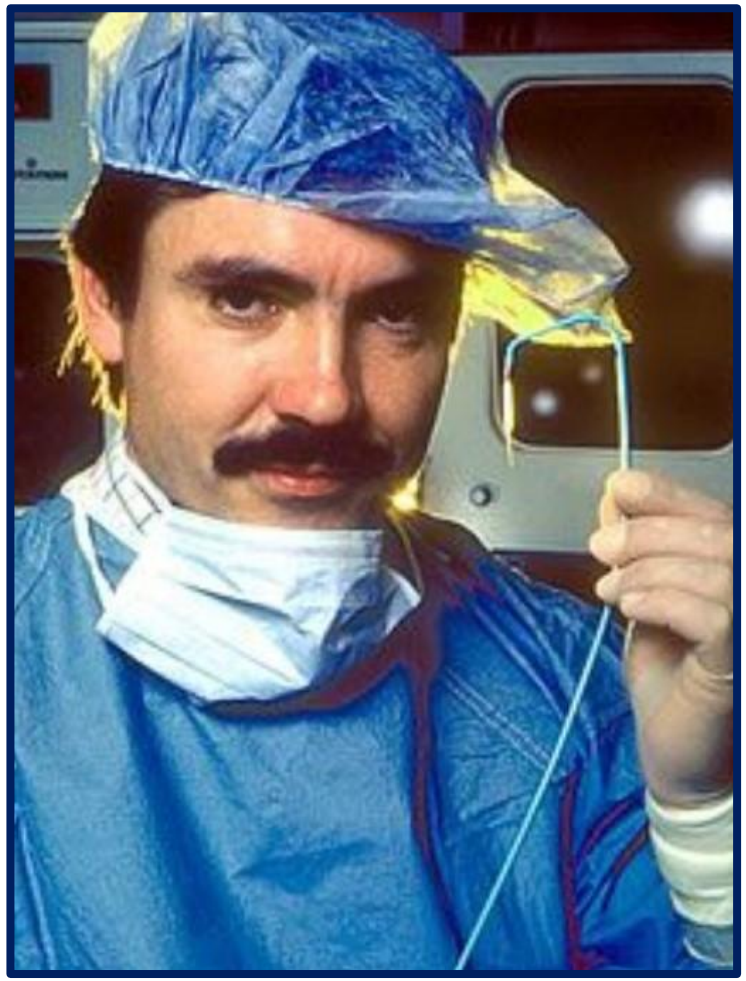
Potential Conflict of Interest



I'm an interventionalist and I love PCI

ESC European Society of Cardiology
European Heart Journal (2025) **00**, 1–3
https://doi.org/10.1093/eurheartj/ehaf692

EDITORIAL
Ischaemic heart disease

Angina with non-obstructive coronary arteries: a success story

Rocco A. Montone[1], Antonio Maria Leone[2,3], and Filippo Crea[2,3,*]

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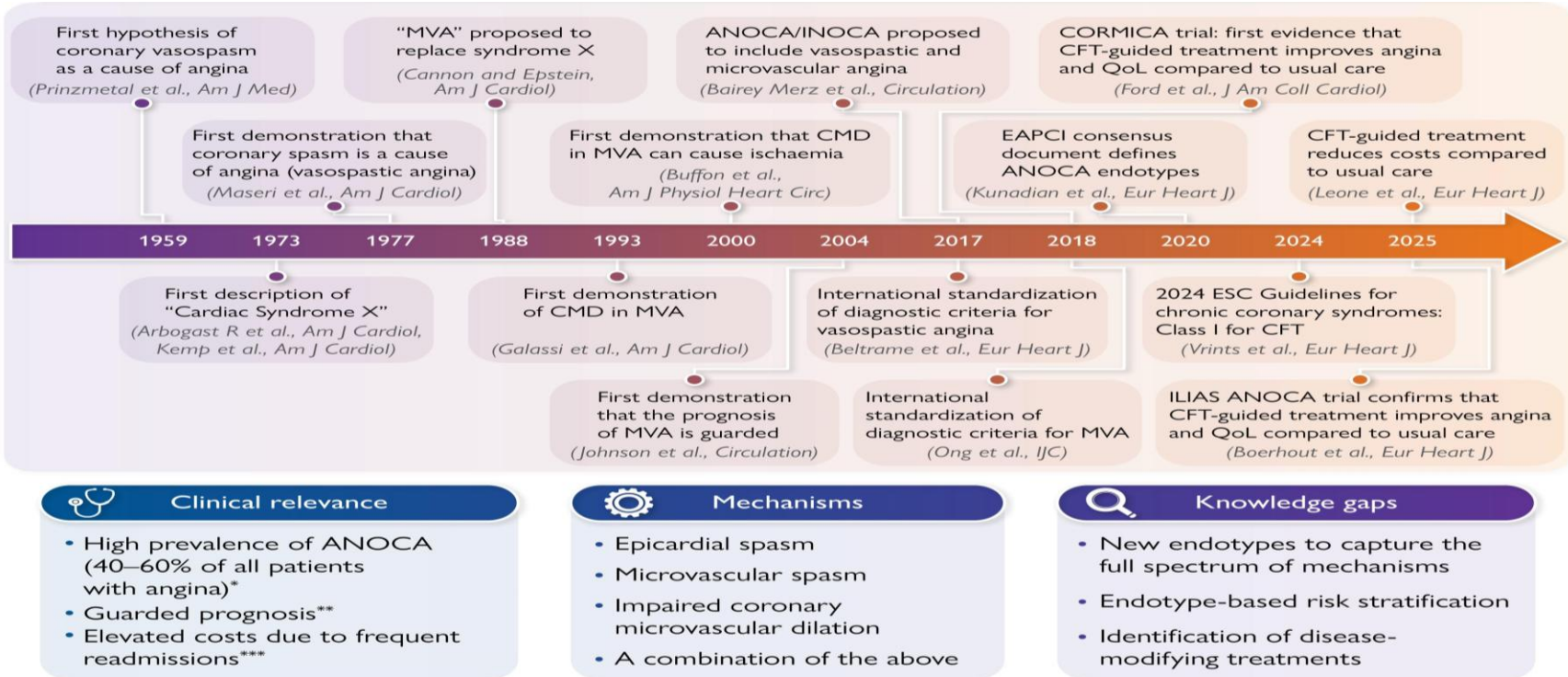
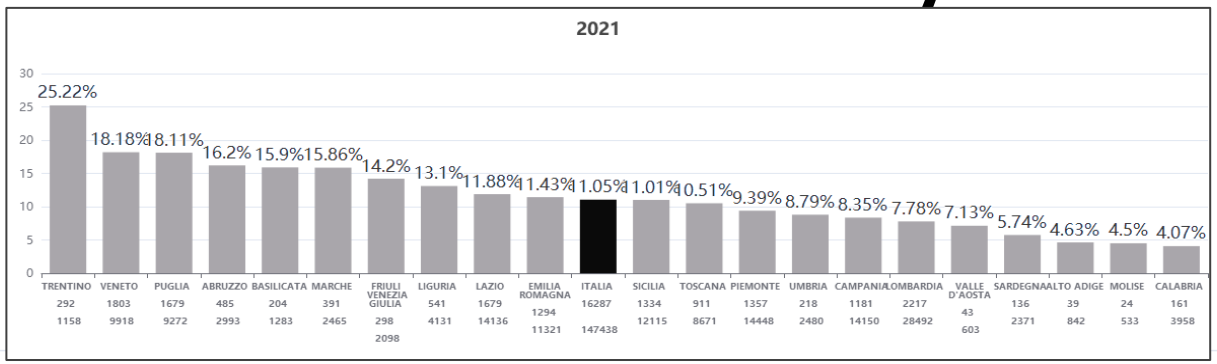


ANOCA, angina with non-obstructive coronary arteries; CFT, coronary functional testing, CMD, coronary microvascular dysfunction; INOCA, ischaemia with non-obstructive coronary arteries, MVA, microvascular angina, QoL, quality of life

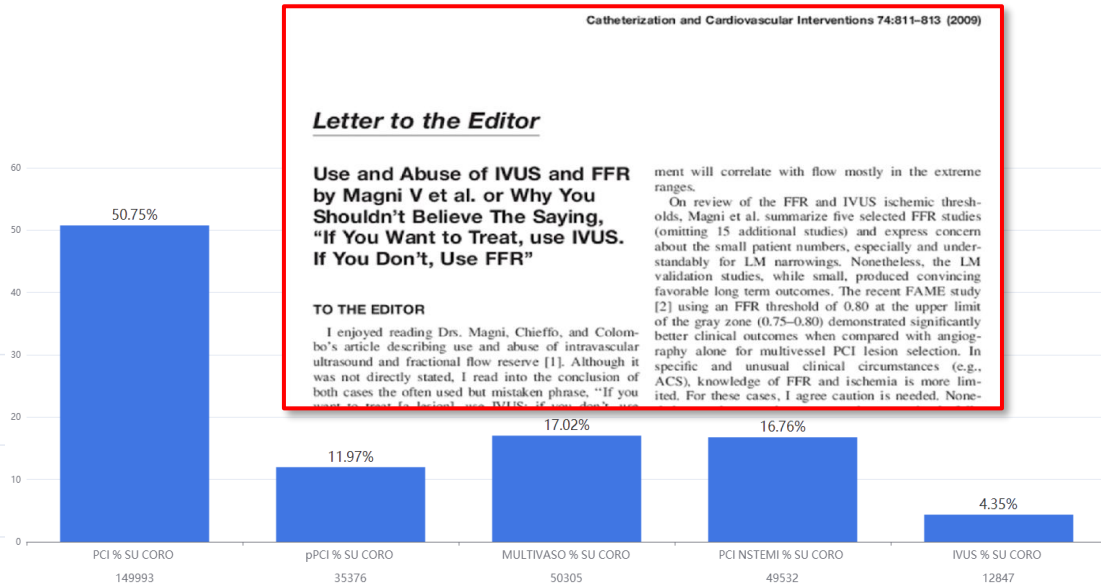
* Patel MR, *et al. N Engl J Med.* 2010;362:886-95. **Kelshiker MA, *et al. European Heart Journal.* 2022;43:1582-1593. Montone RA, *et al. EuroIntervention.* 2022;18:e666-e676. ***Leone AM, *et al. European Heart Journal.* 2025;46:978-980.

Montone RA, *et al. European Heart Journal.*

BUT…… do we really care?????



2022



Catheterization and Cardiovascular Interventions 74:811–813 (2009)

Letter to the Editor

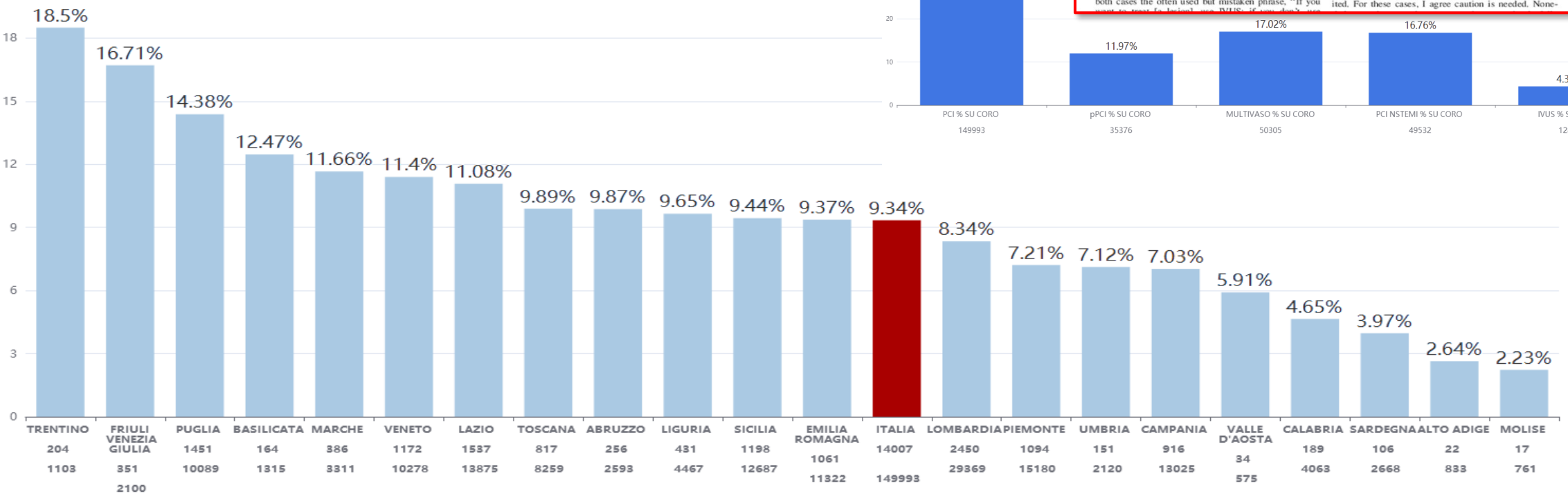
Use and Abuse of IVUS and FFR by Magni V et al. or Why You Shouldn't Believe The Saying, "If You Want to Treat, use IVUS. If You Don't, Use FFR"

TO THE EDITOR

I enjoyed reading Drs. Magni, Chieffo, and Colombo's article describing use and abuse of intravascular ultrasound and fractional flow reserve [1]. Although it was not directly stated, I read into the conclusion of both cases the often used but mistaken phrase, "If you

ment will correlate with flow mostly in the extreme ranges.

On review of the FFR and IVUS ischemic thresholds, Magni et al. summarize five selected FFR studies (omitting 15 additional studies) and express concern about the small patient numbers, especially and understandably for LM narrowings. Nonetheless, the LM validation studies, while small, produced convincing favorable long term outcomes. The recent FAME study [2] using an FFR threshold of 0.80 at the upper limit of the gray zone (0.75–0.80) demonstrated significantly better clinical outcomes when compared with angiography alone for multivessel PCI lesion selection. In specific and unusual clinical circumstances (e.g., ACS), knowledge of FFR and ischemia is more limited. For these cases, I agree caution is needed. None-



$$\frac{Invasive\ Assessment}{Coronary\ angiograms} = \frac{14007}{295576} = 4.7\%$$

Dati Nazionali GISE 2023

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EDITORIAL
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In conclusion, *OCA progressed from the initial skepticism of the scientific community regarding its **existence** to the demonstration of its clinical relevance and the **need for a standardized diagnostic algorithm** (as recommended in the current ESC Guidelines),

which leads **to the identification of successful treatments** for patients who frequently present with invalidating symptoms.

Thus, although unfinished, this is a «success» story.

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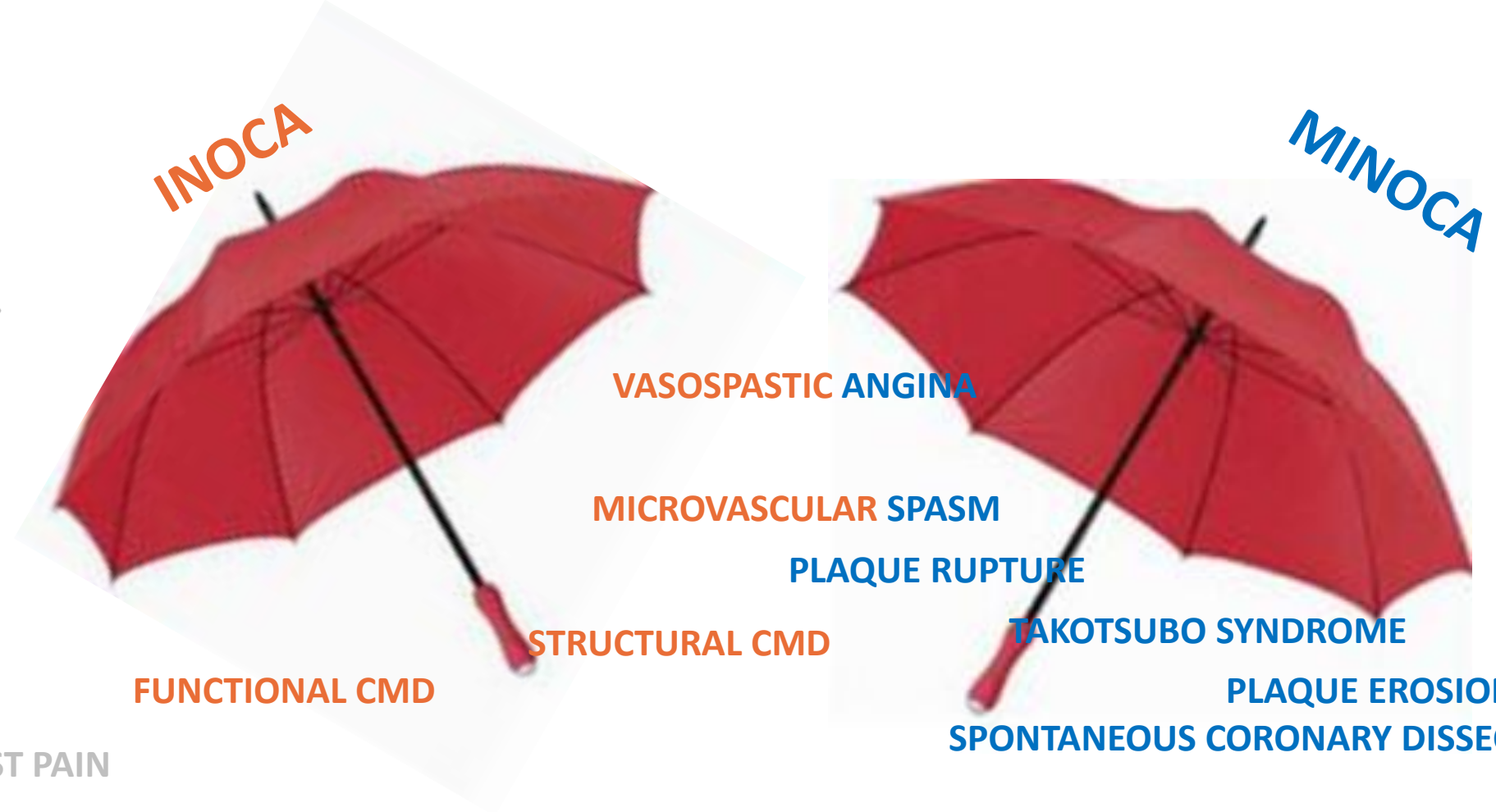
Definition of --NOCA: evidence of ischemia in the abscence of obstructive CAD

CHRONIC CORONARY SYNDROMES

ACUTE CORONARY SYNDROMES



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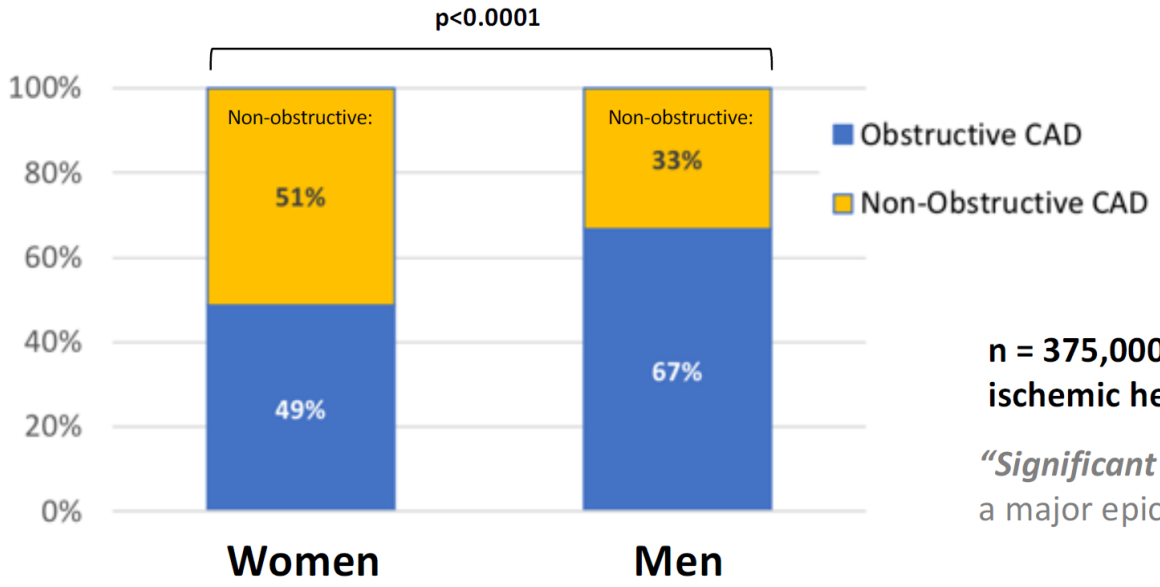
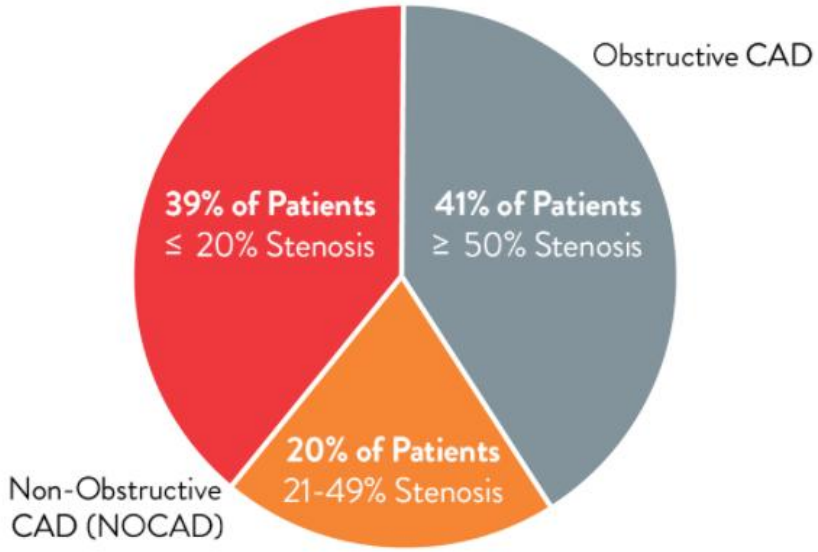
---NOCA: a real phenomenon?

≥40% of patients with **stable chest pain syndromes** have no obstructive CAD at angiography



n = 375,000 patients with stable ischemic heart disease

"Significant CAD": ≥70% stenosis in a major epicardial coronary artery.



Shaw, Circulation. 2008;117:1787–1801

Patel NEJM 2010

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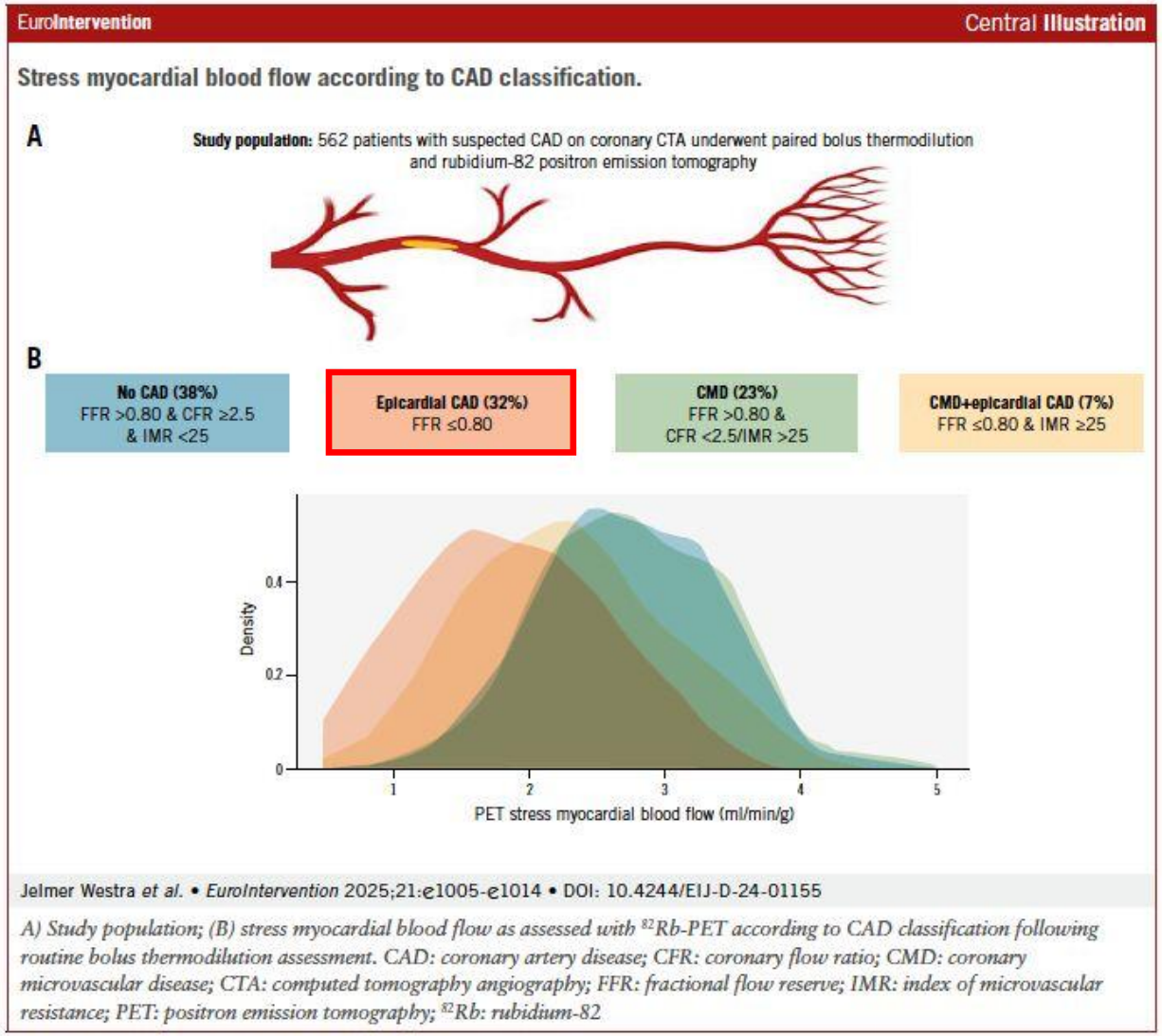
---NOCA: a real phenomenon?



Jelmer Westra *et al.* • *EuroIntervention* 2025;21:e1005-e1014 • DOI: 10.4244/EIJ-D-24-01155

A) Study population; (B) stress myocardial blood flow as assessed with ^{82}Rb-PET according to CAD classification following routine bolus thermodilution assessment. CAD: coronary artery disease; CFR: coronary flow ratio; CMD: coronary microvascular disease; CTA: computed tomography angiography; FFR: fractional flow reserve; IMR: index of microvascular resistance; PET: positron emission tomography; ^{82}Rb: rubidium-82

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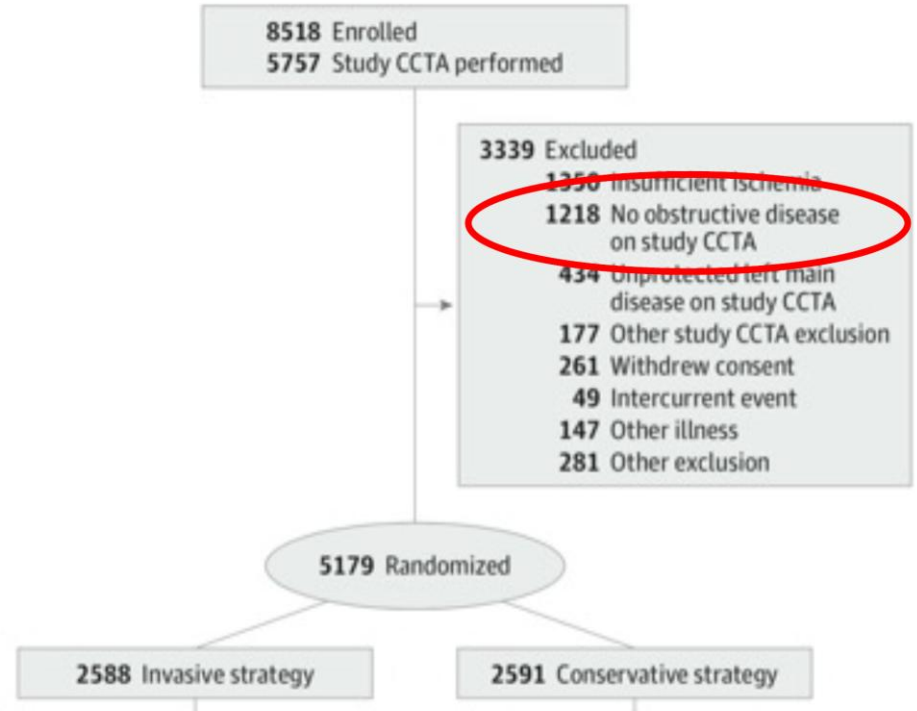
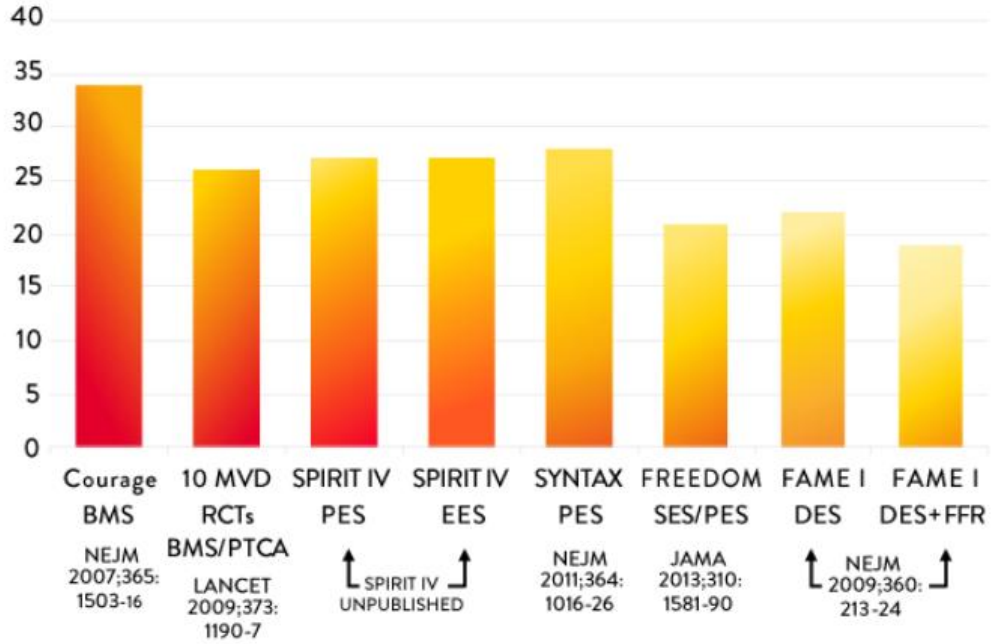
INOCA: a real phenomenon?

Data from the ISCHEMIA trial suggest that **~20% of patients** with moderate to severe ischemia **have non-obstructive CAD.**





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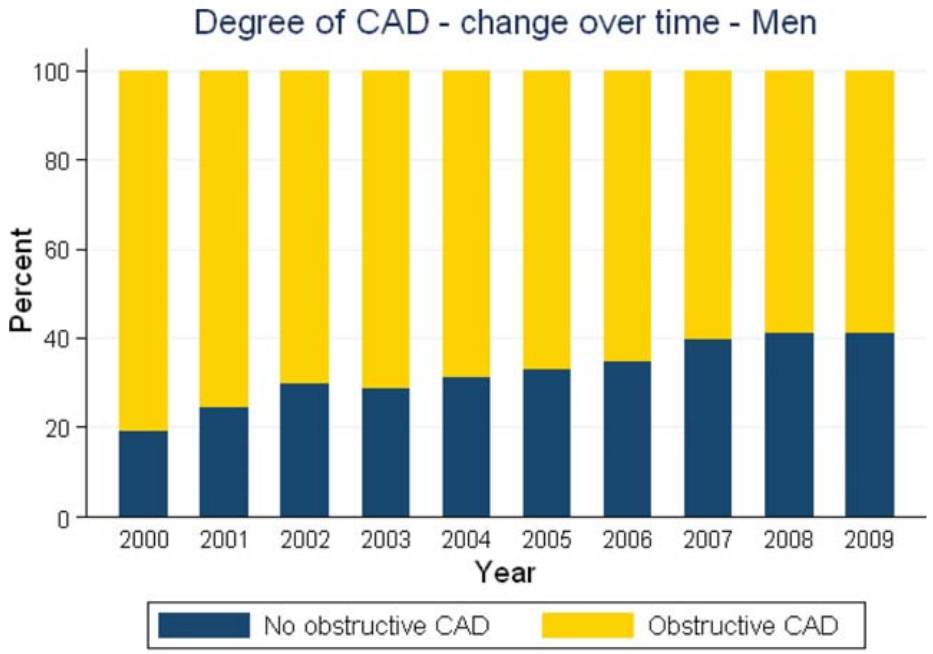
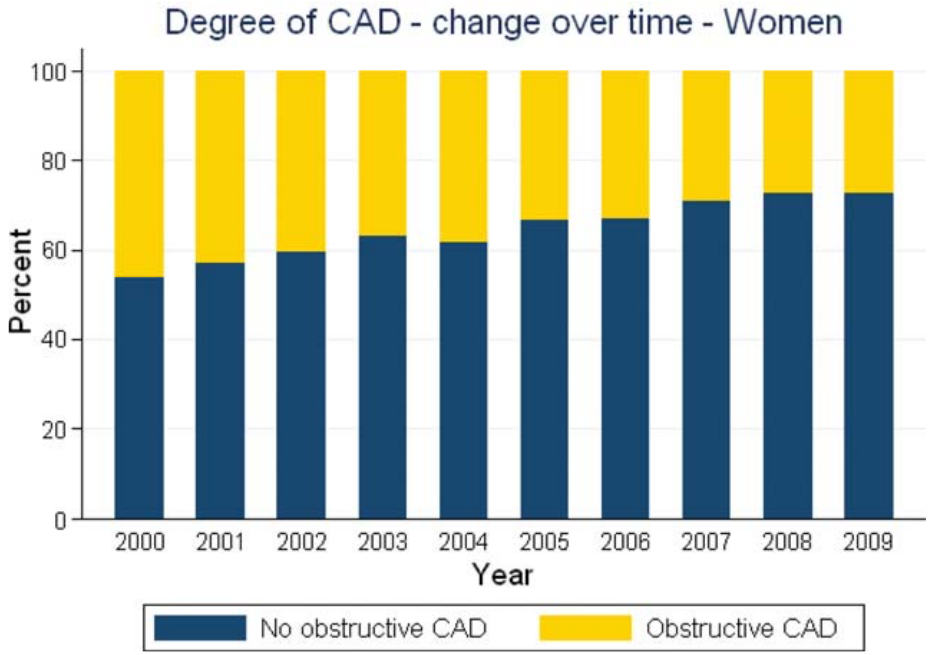
--- NOCA: a real phenomenon?





- Within the symptomatic population of 4711 women and 6512 men,

a larger proportion of women than men had no obstructive CAD (p<0.001).

- Over the study period, the proportion of patients with no obstructive CAD

increased from 54 to 73% in women and from 19 to 41% in men

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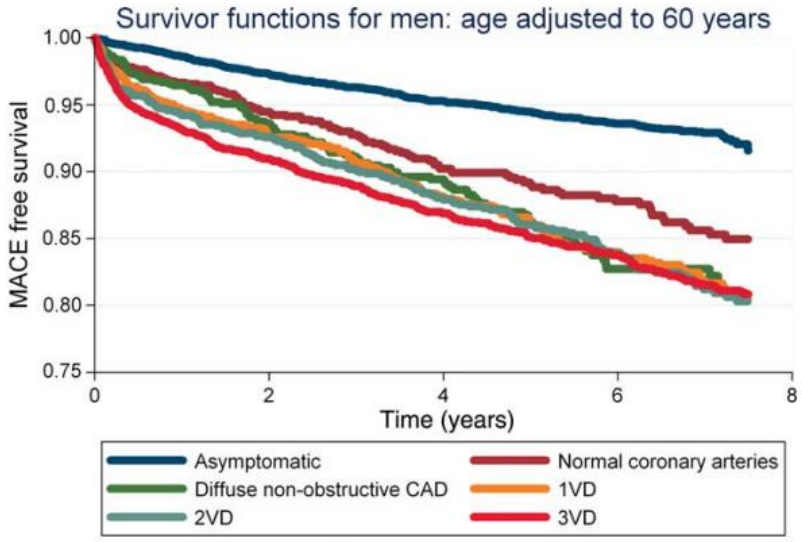
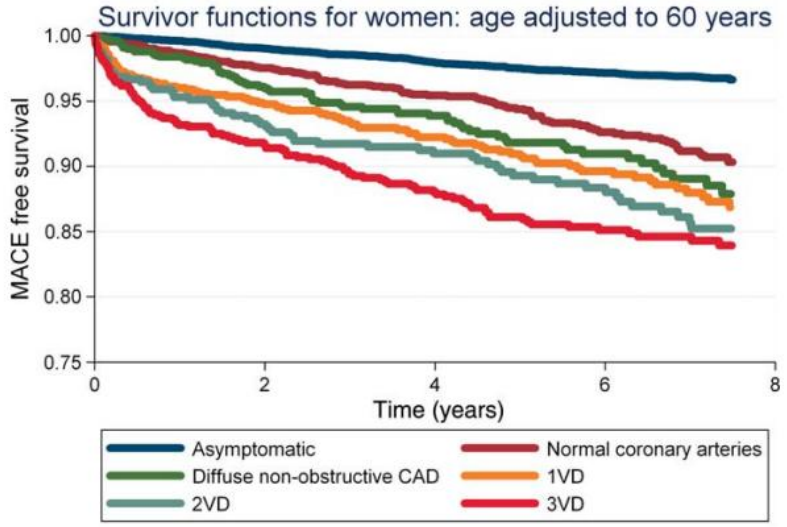
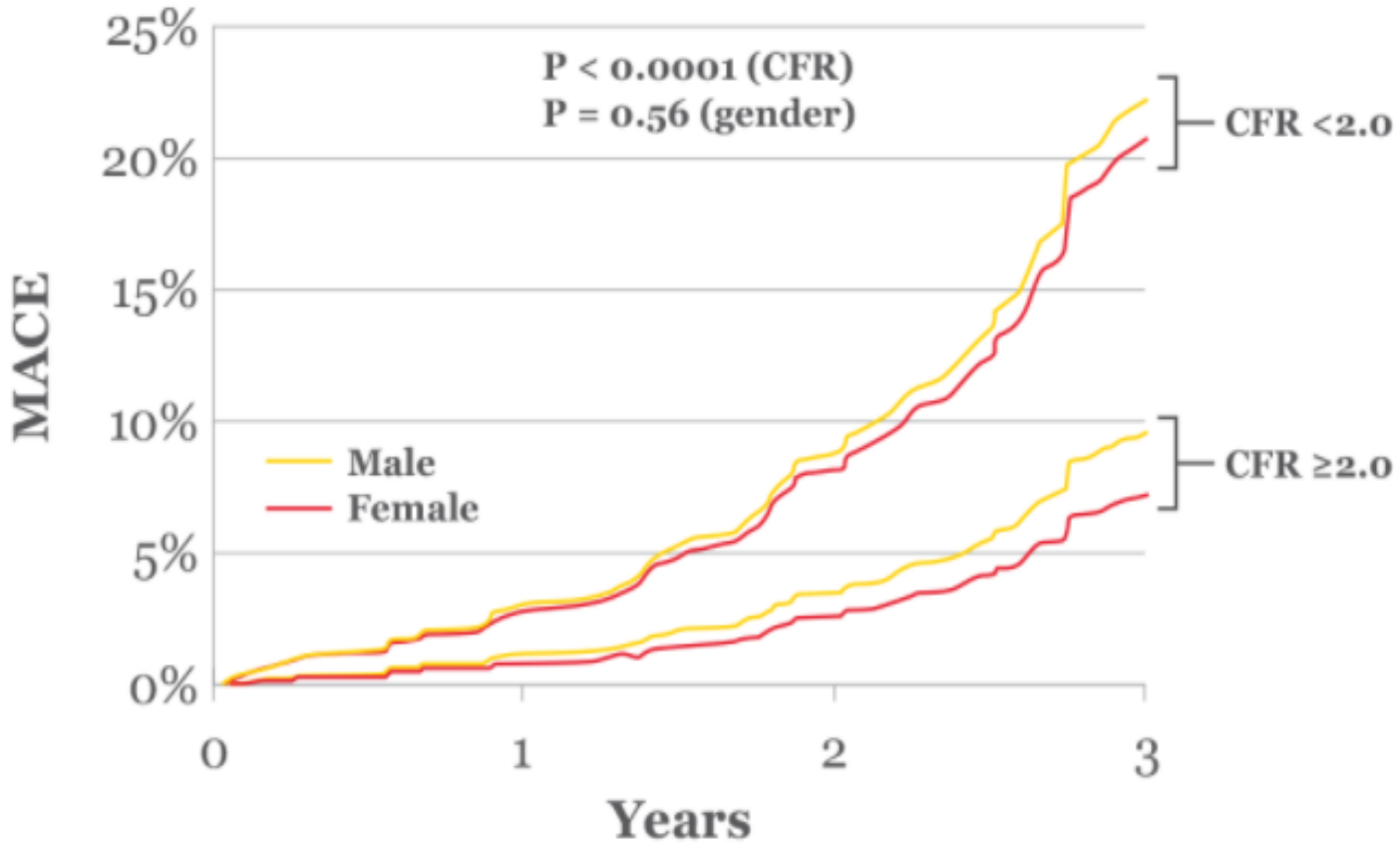
Fake it… until you find it!!

---NOCA: a benign phenomenon?



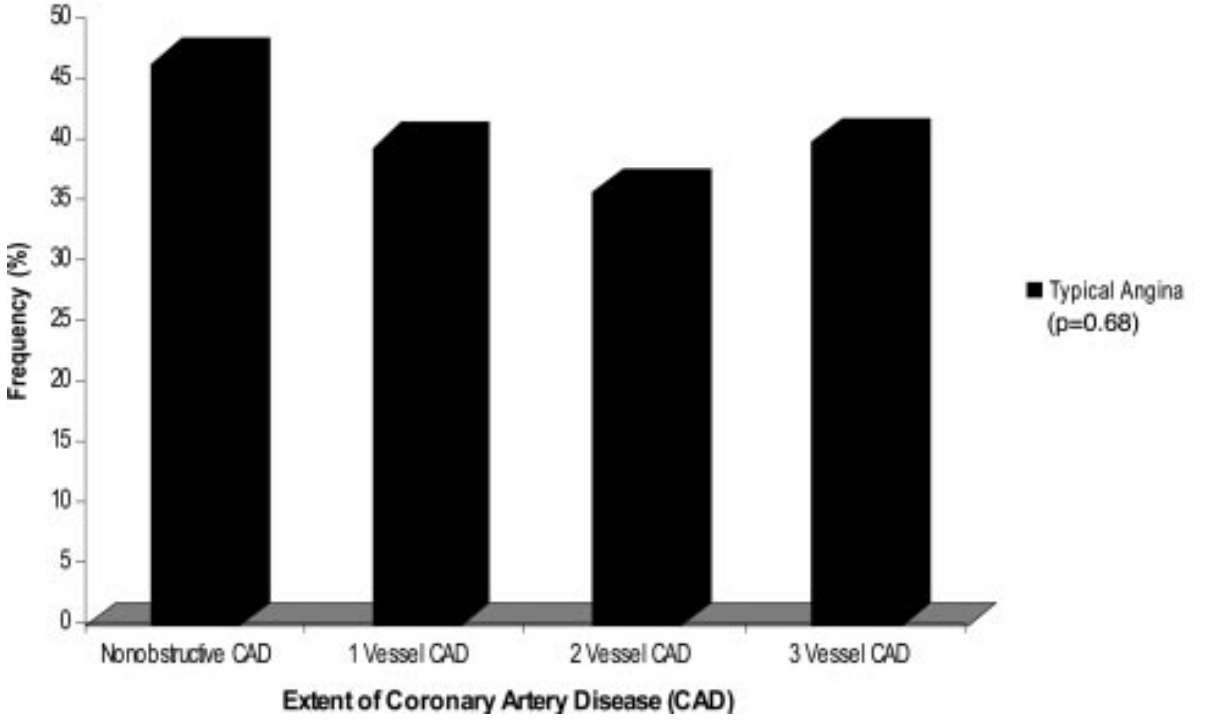


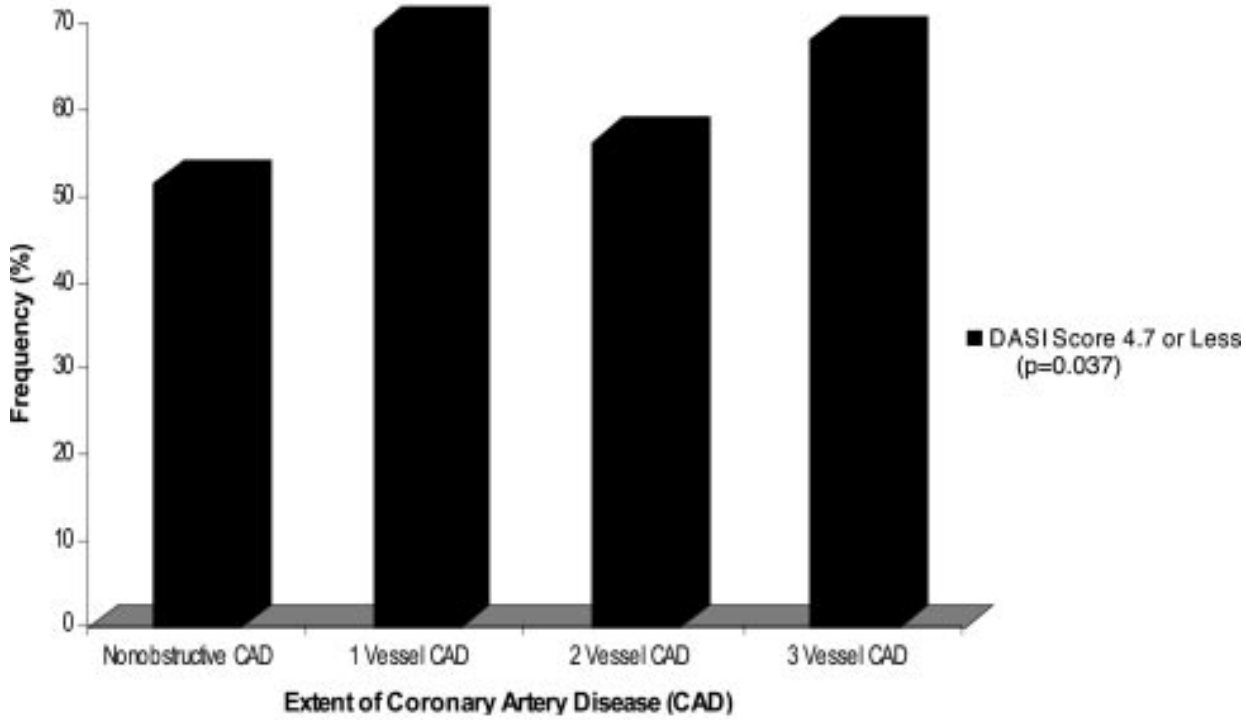


Jespersen et al. EHJ 2012

Taqueti JACC 2018

*NOCA: a benign phenomenon?

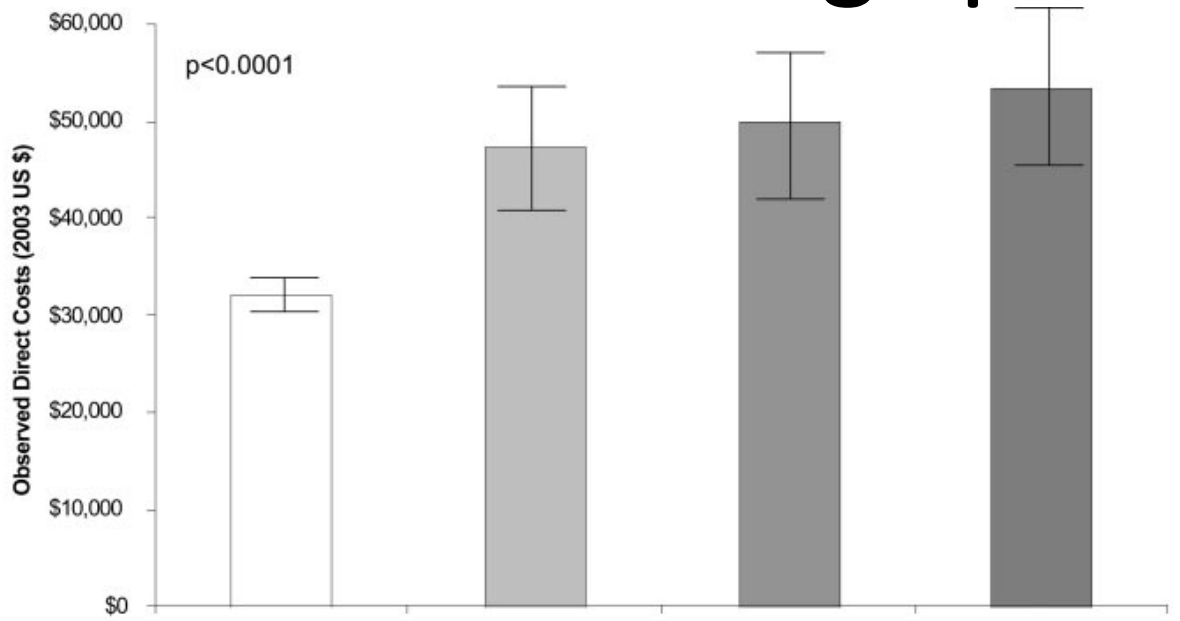




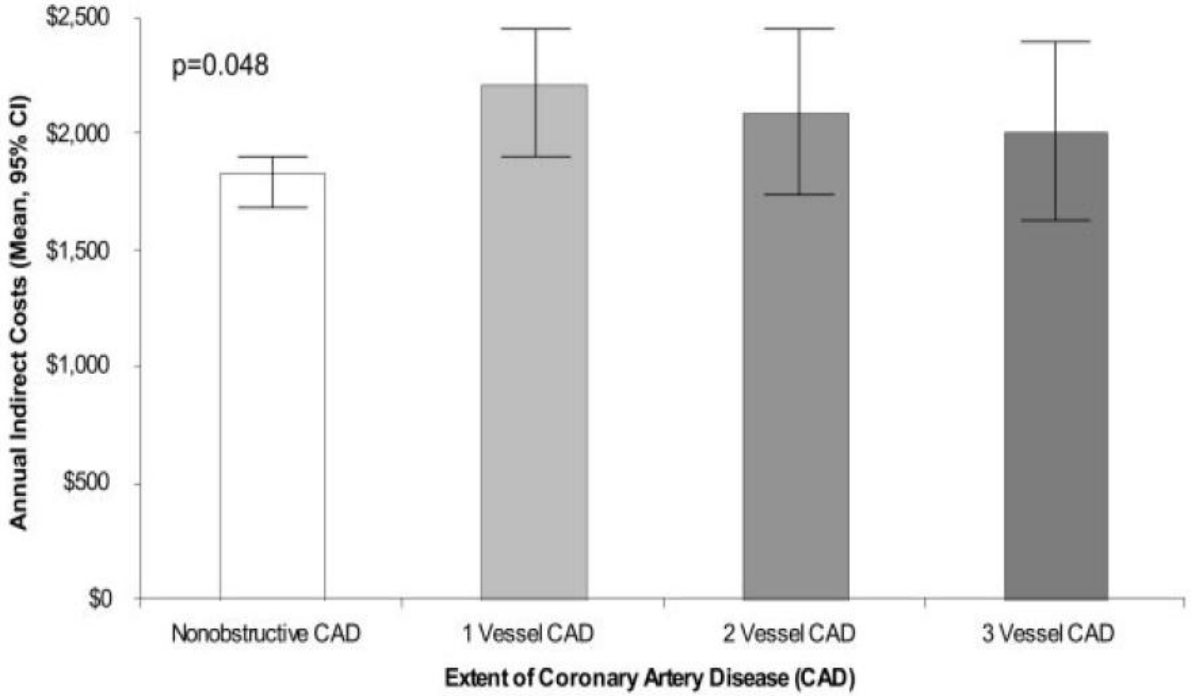
Despite a similar frequency of typical angina at 5 years of follow-up (p=0.68), nearly half of women with nonobstructive CAD reported functional disability compared with 57% to 70% of women with 1-vessel to 3-vessel CAD (p=0.037).

Shaw L.J. et al. Circulation. 2006;114:894-904

*NOCA: a benign phenomenon/costs



Cost Components	Nonobstructive CAD	1 Vessel CAD	2 Vessel CAD	3 Vessel CAD
Outpatient	6.7%	5.8%	14.3%	14.8%
Drug	32.6%	29.5%	27.0%	25.5%
Hospitalization	60.7%	64.7%	58.7%	59.7%



% of Median Gross Income = 9.4% 12.2% 11.2% 9.0%
(p=0.094)

- **Catheterizations or angina hospitalizations were 1.8-fold higher in women with INOCA vs 1V-CAD @ 1y (P < 0.0001).**
  - **Drug treatment was highest for those with nonobstructive or 1-vessel CAD (P < 0.0001).**
- **The proportion of costs for anti-ischemic therapy was higher for women with nonobstructive CAD (P < 0.0001).**

Shaw Circ 2006

The essential is invisible to the eyes!

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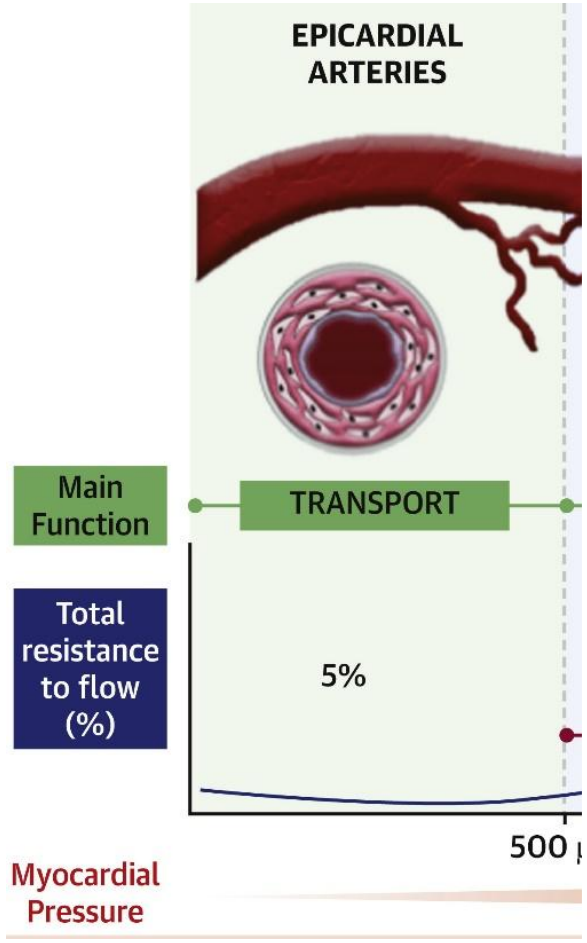
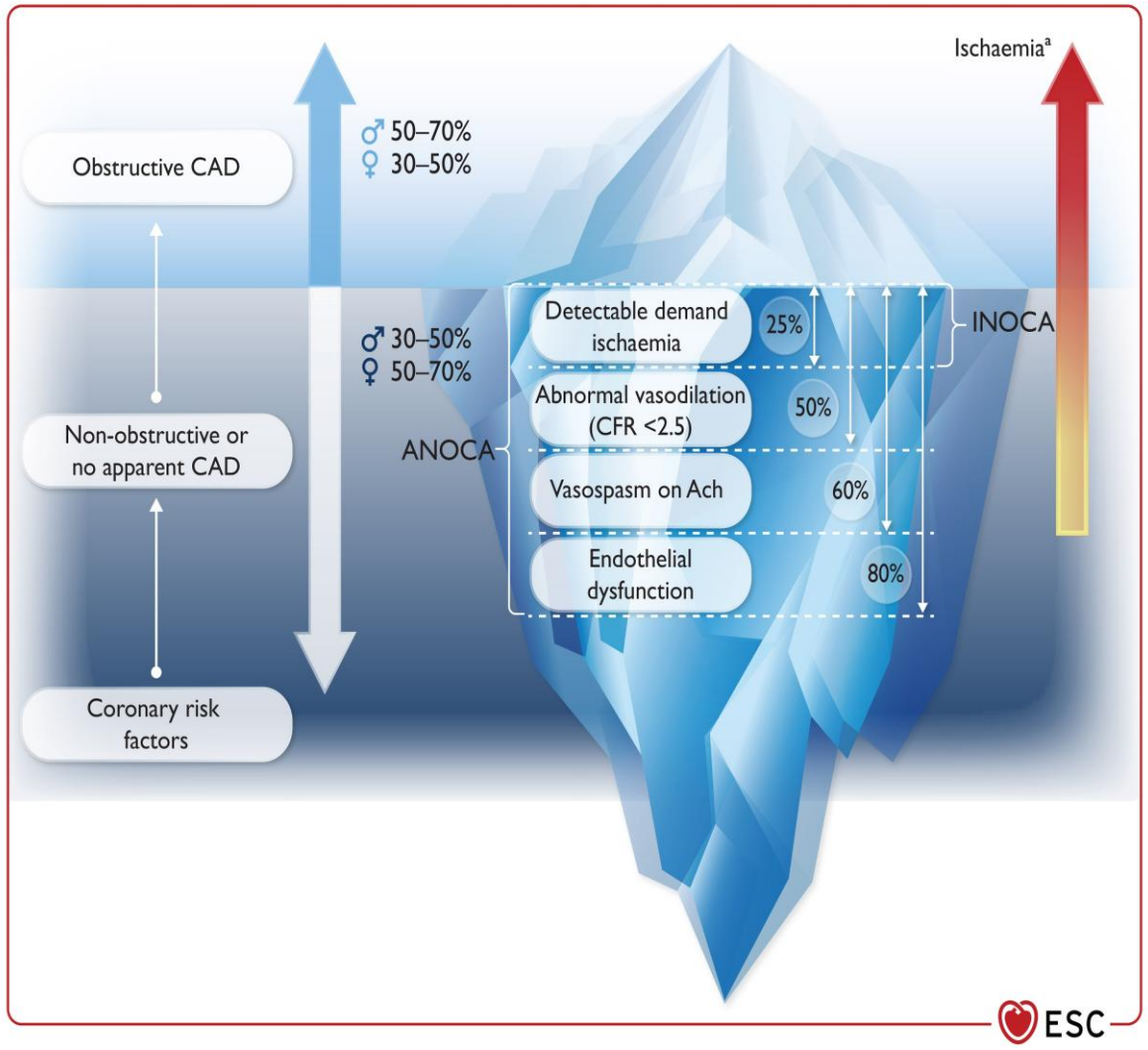
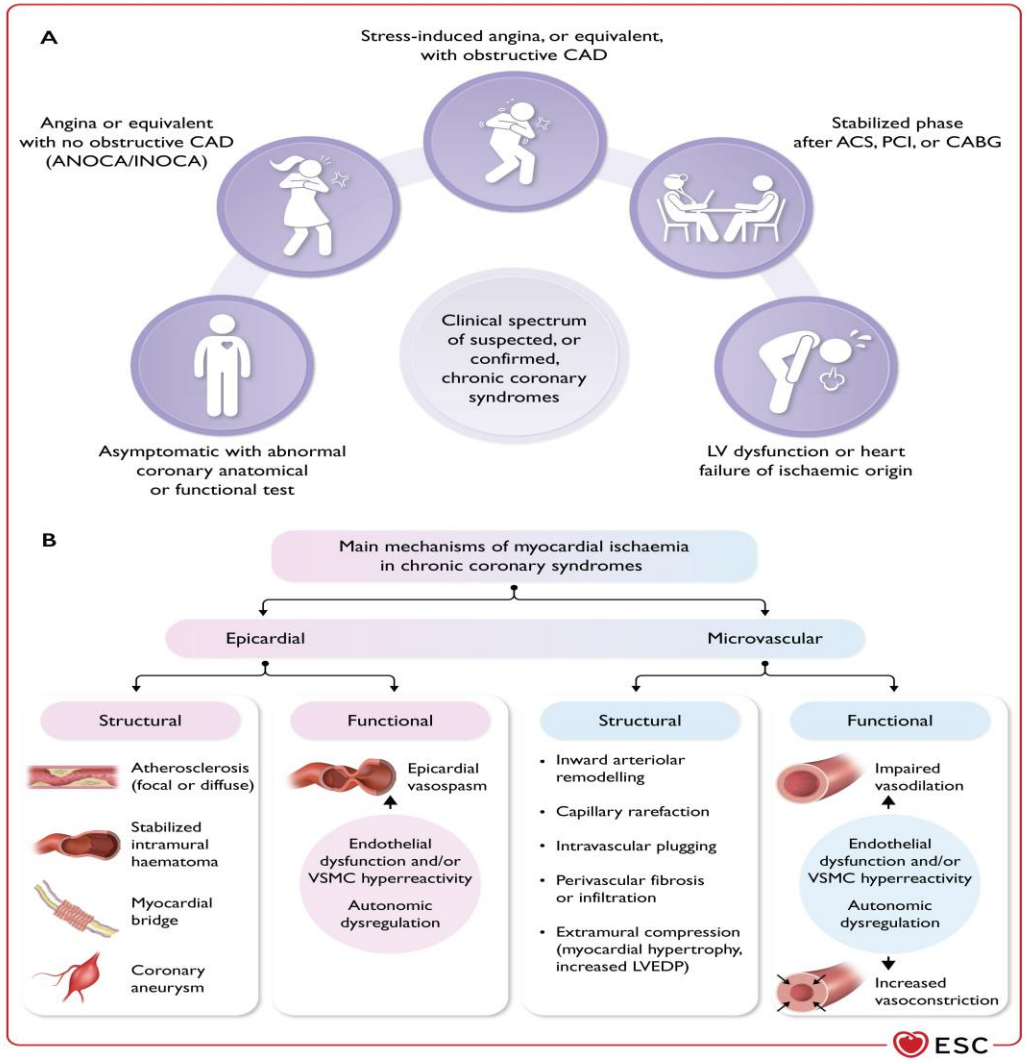
Coronary Blood Flow: Principles



Crea F and D'Amario, EHJ 2016

Are obstructive Epicardial Stenosis overrated?





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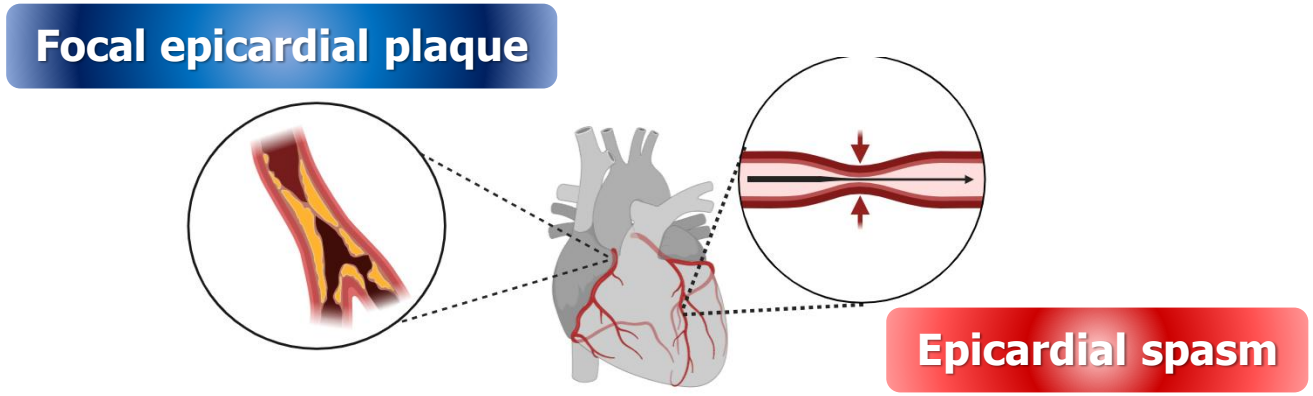
Pathophysiological Mechanisms

Epicardial



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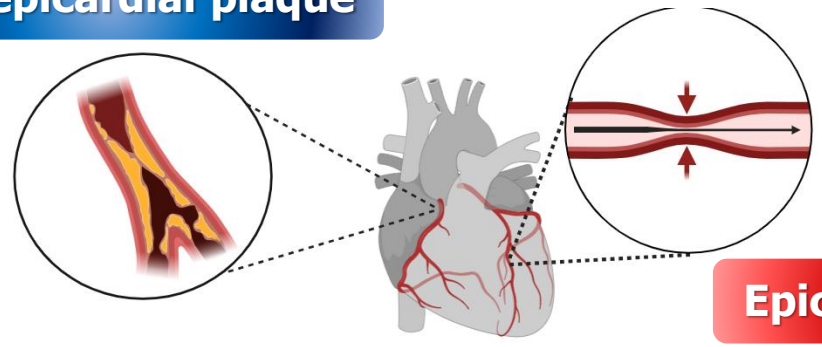
Pathophysiological Mechanisms

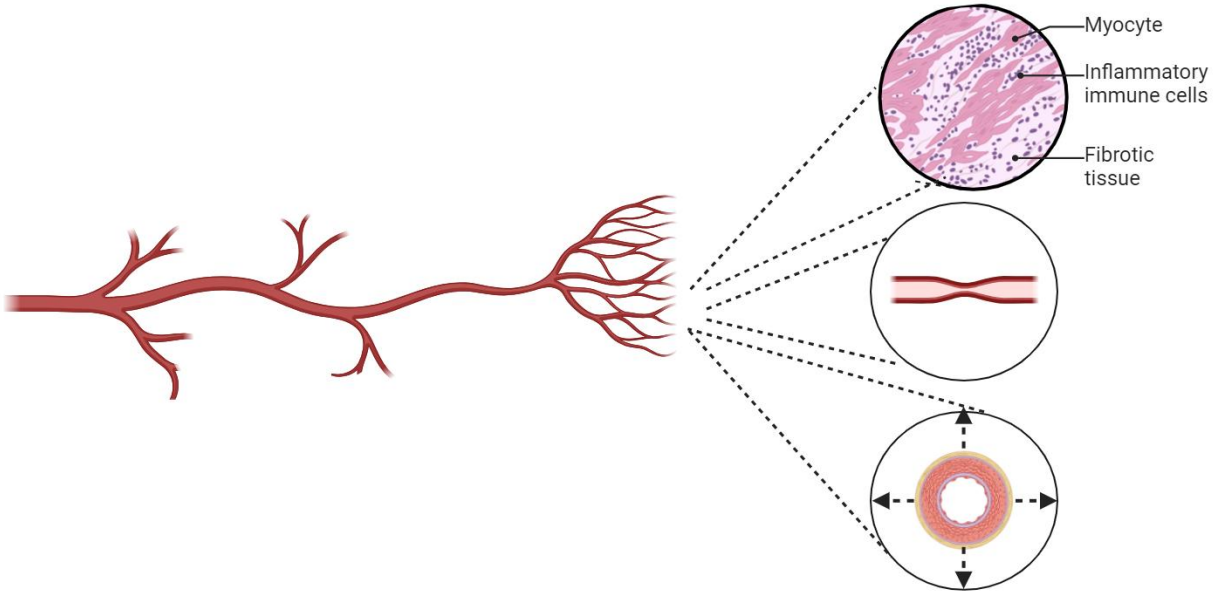
Epicardial

Focal epicardial plaque



Epicardial spasm

Microvascular

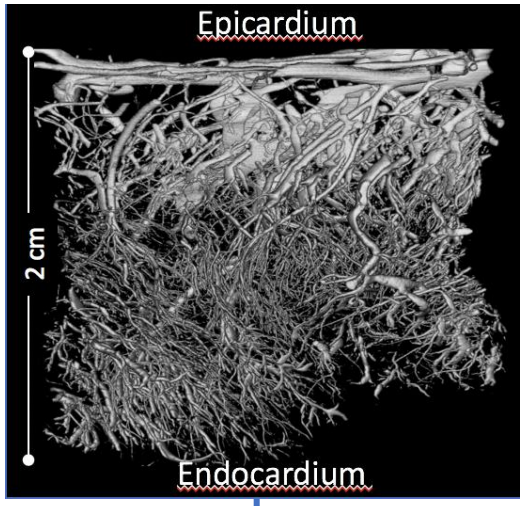


Structural damage

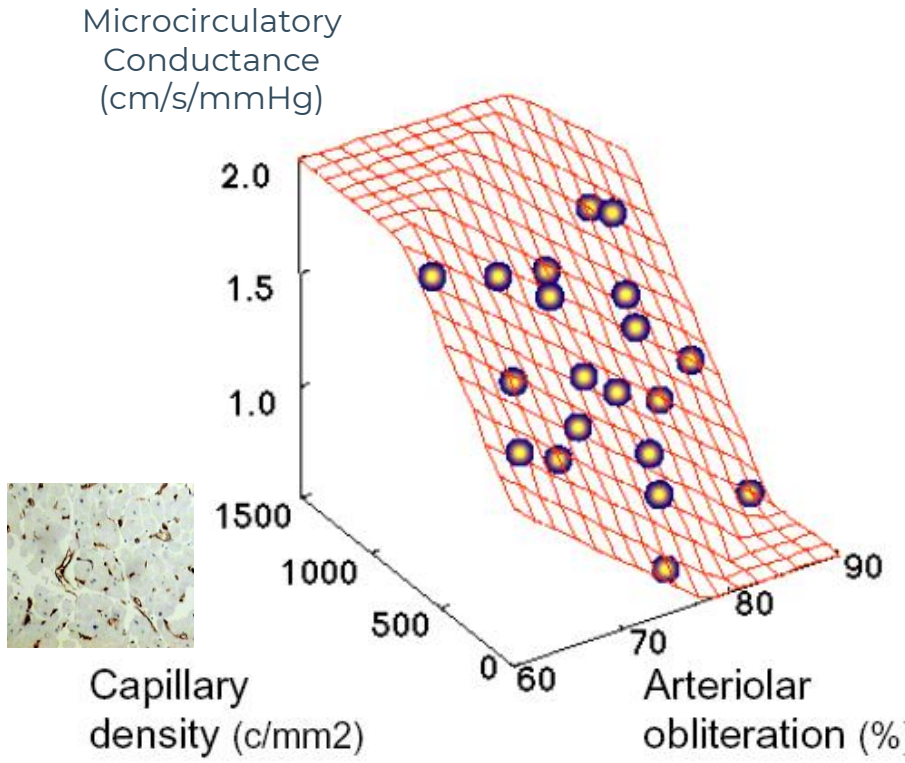
Spasm

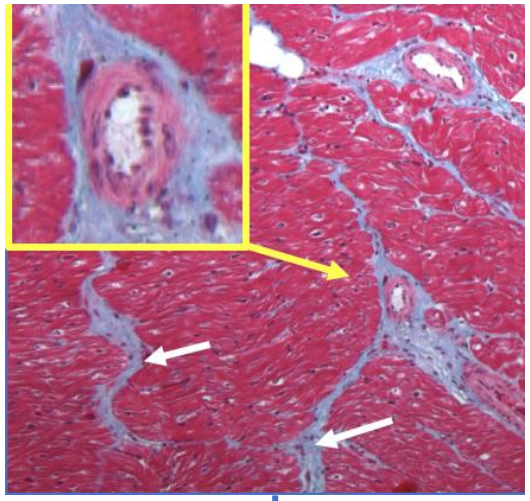
Impaired vasodilation

Pathophysiological Mechanisms of Structural CMD



Microvascular rarefaction

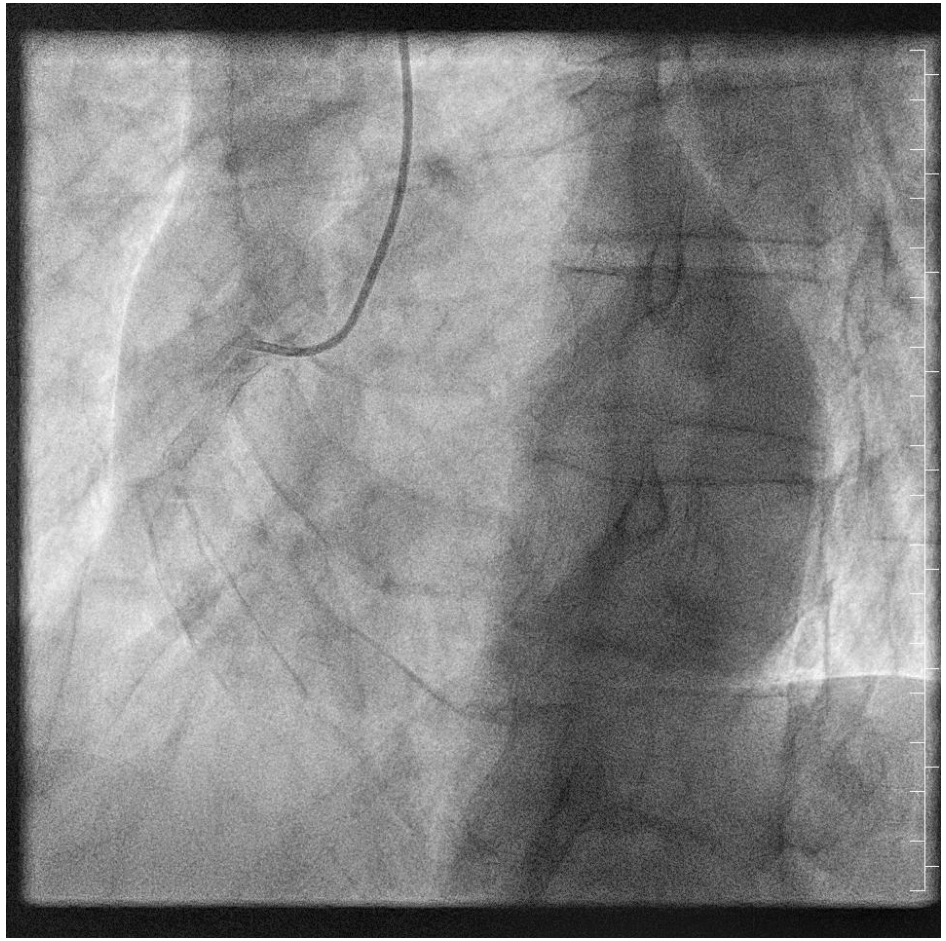


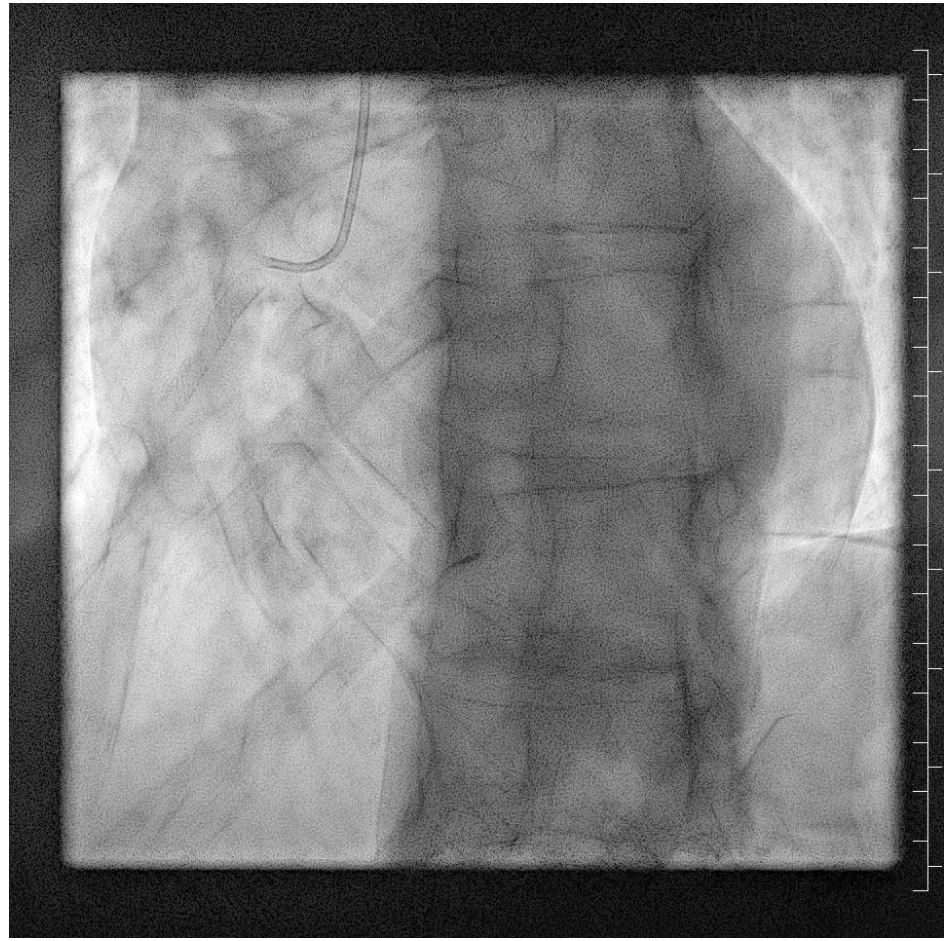


Arteriolar remodelling

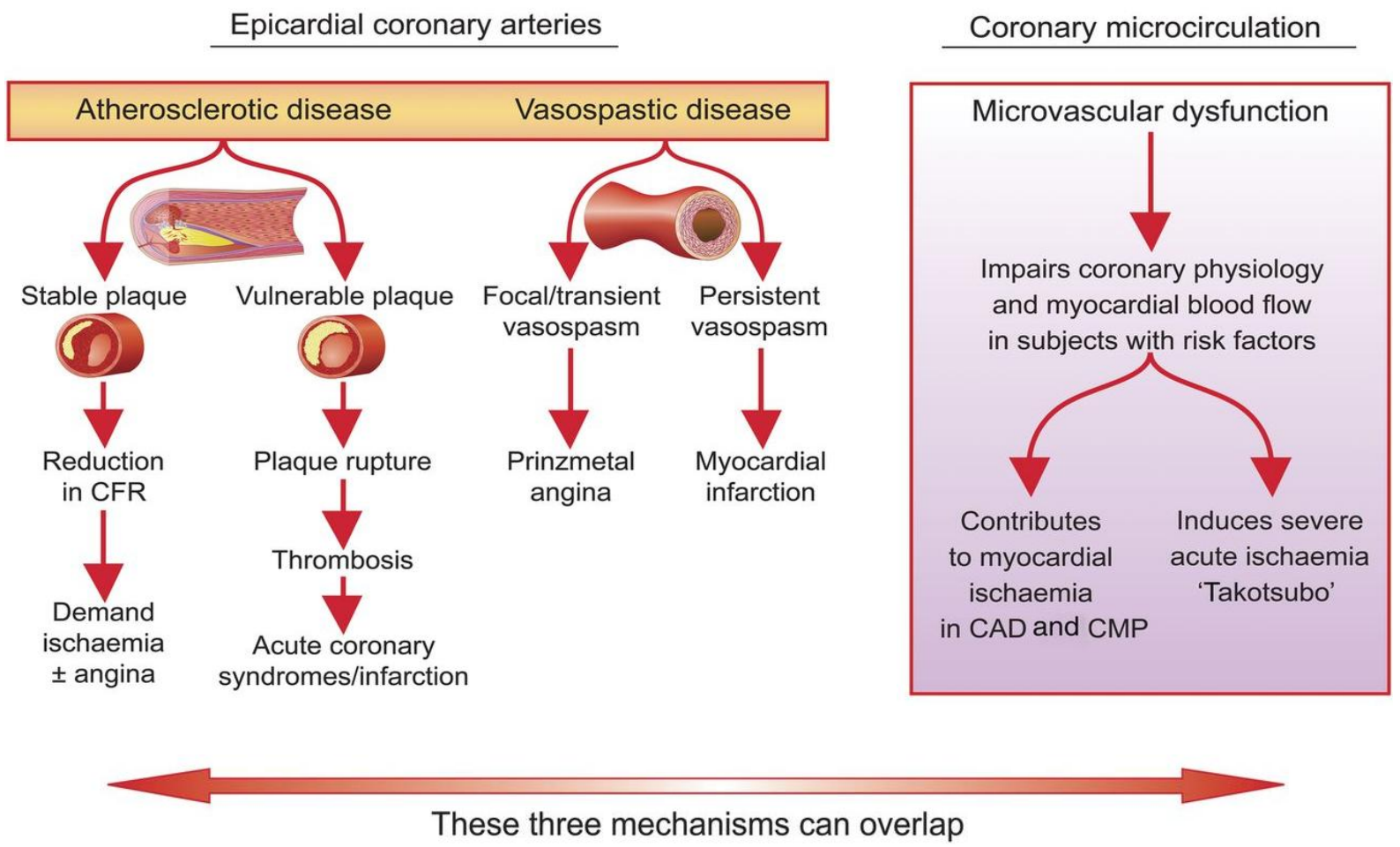
Courtesy from J. Escaned

Escaned J et al. Circulation. 2009; 20;120:1561-8 / Escaned J Lerman LO EHJ 2020 ;41:2376-2378



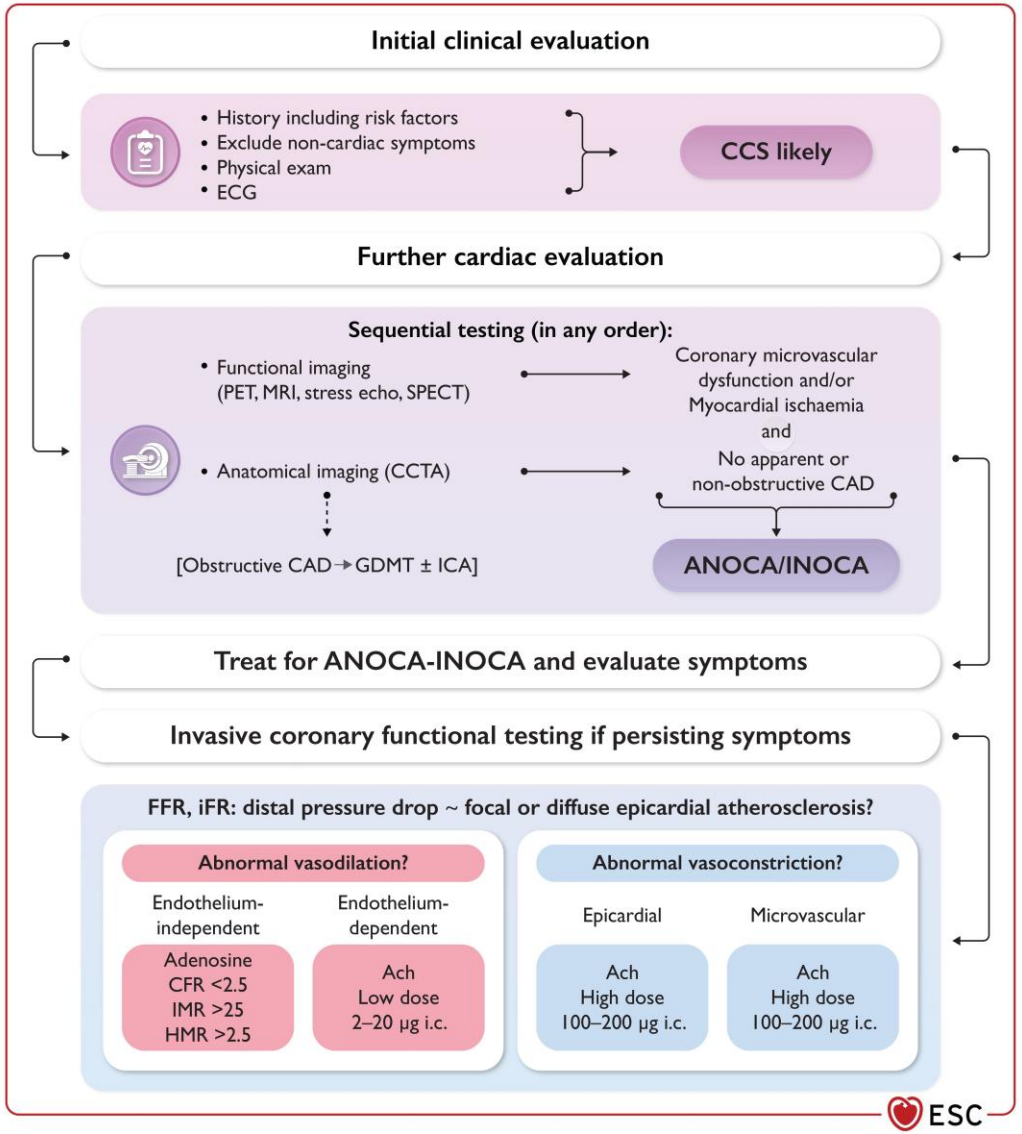


Meccanismi di Ischemia

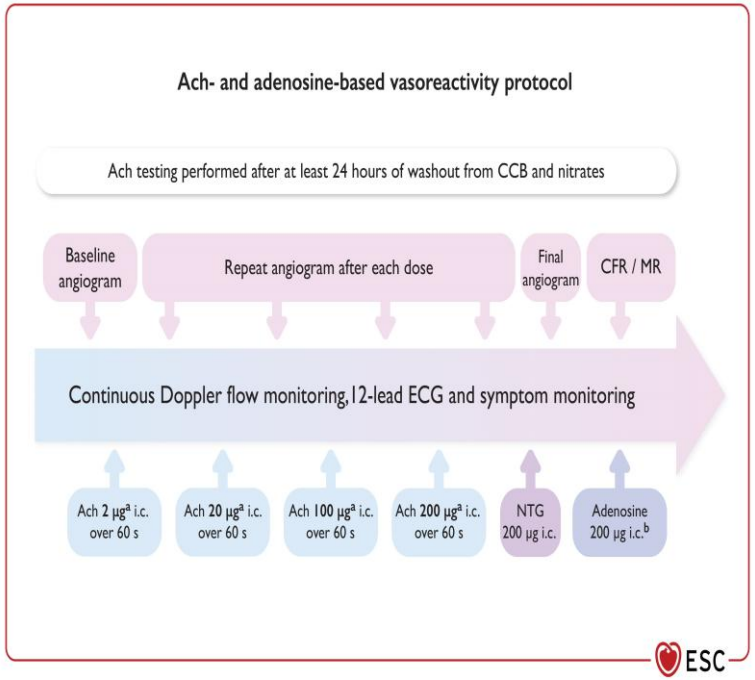


Crea F and D'Amario, EHJ 2016

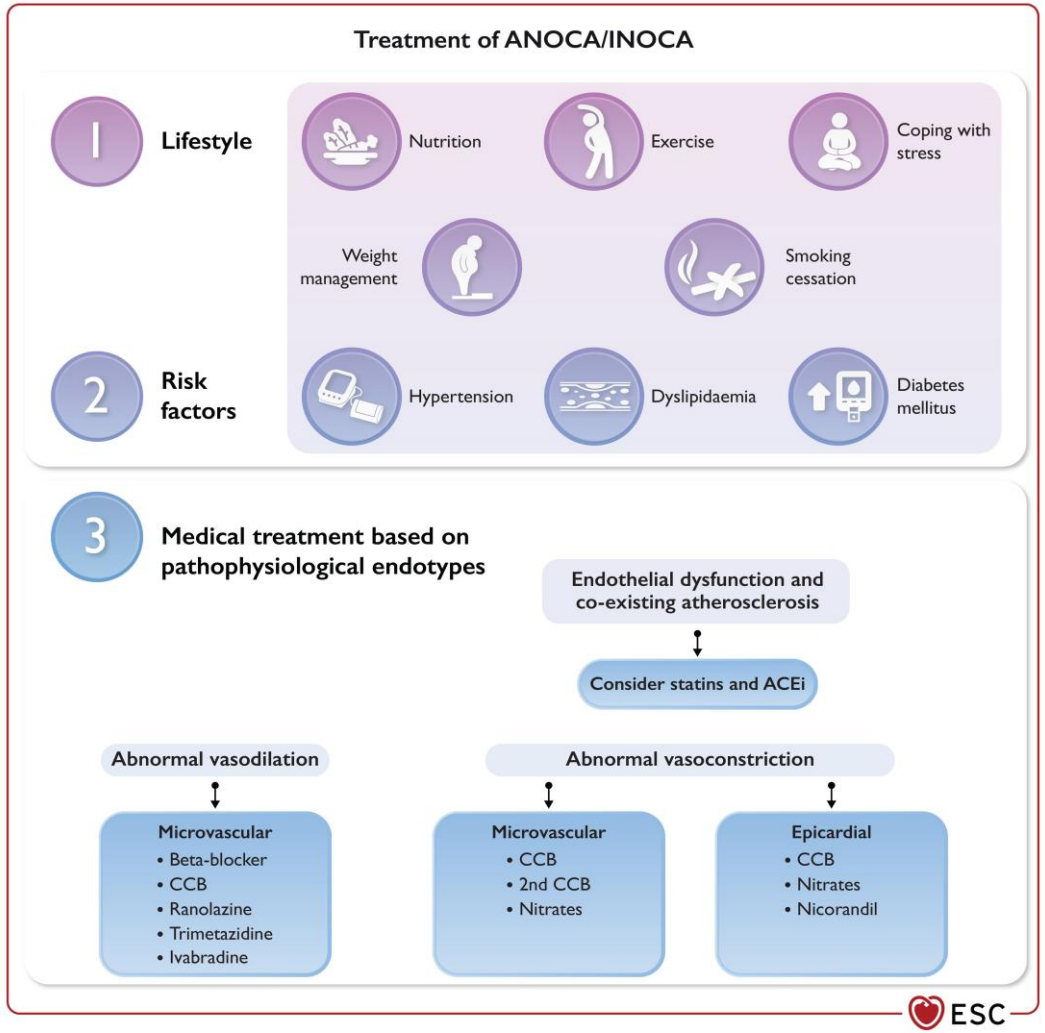
What do the Guidelines say (CCS 2024)? /Diagnosis



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



What do the Guidelines say (CCS 2024)? /Treatment



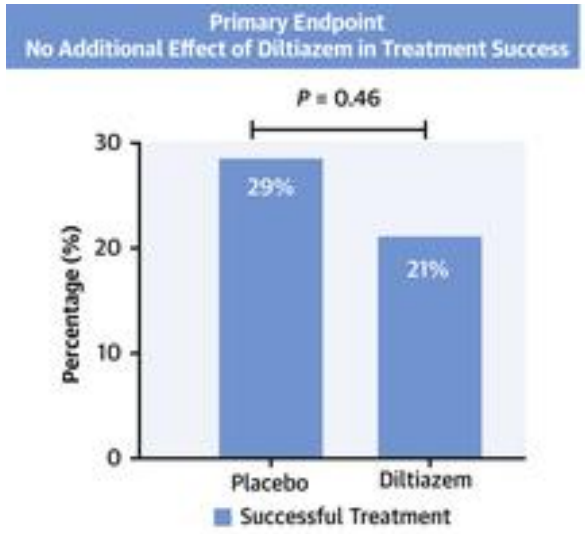
But…not many «greens» (class I)!!

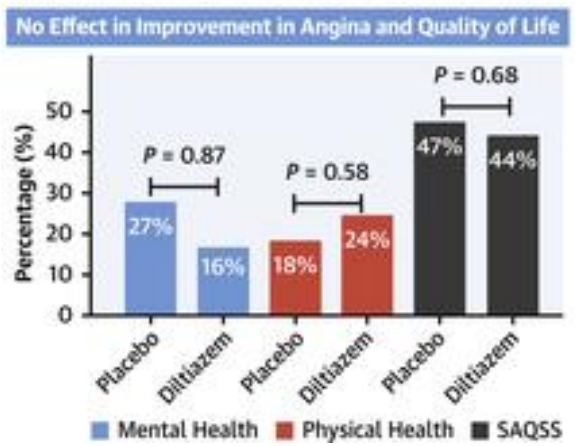
Management of ANOCA/INOCA		
In symptomatic patients with ANOCA/INOCA, medical therapy based on coronary functional test results should be considered to improve symptoms and quality of life.[298,977]	IIa	A
For the management of endothelial dysfunction, ACE-I should be considered for symptom control.[988]	IIa	B
For the management of microvascular angina associated with reduced coronary/myocardial blood flow reserve, antianginal medications aiming at preventing demand myocardial ischaemia should be considered for symptom control.[989,990]	IIa	B
For the treatment of isolated vasospastic angina		
Calcium channel blockers are recommended to control symptoms and to prevent ischaemia and potentially fatal complications.[991–996]	I	A
Nitrates should be considered to prevent recurrent episodes.[993,997,998]	IIa	B
For the treatment of overlapping endotypes		
In patients with evidence of overlapping endotypes, combination therapy with nitrates, calcium channel blockers, and other vasodilators may be considered.[999,1000]	IIb	B

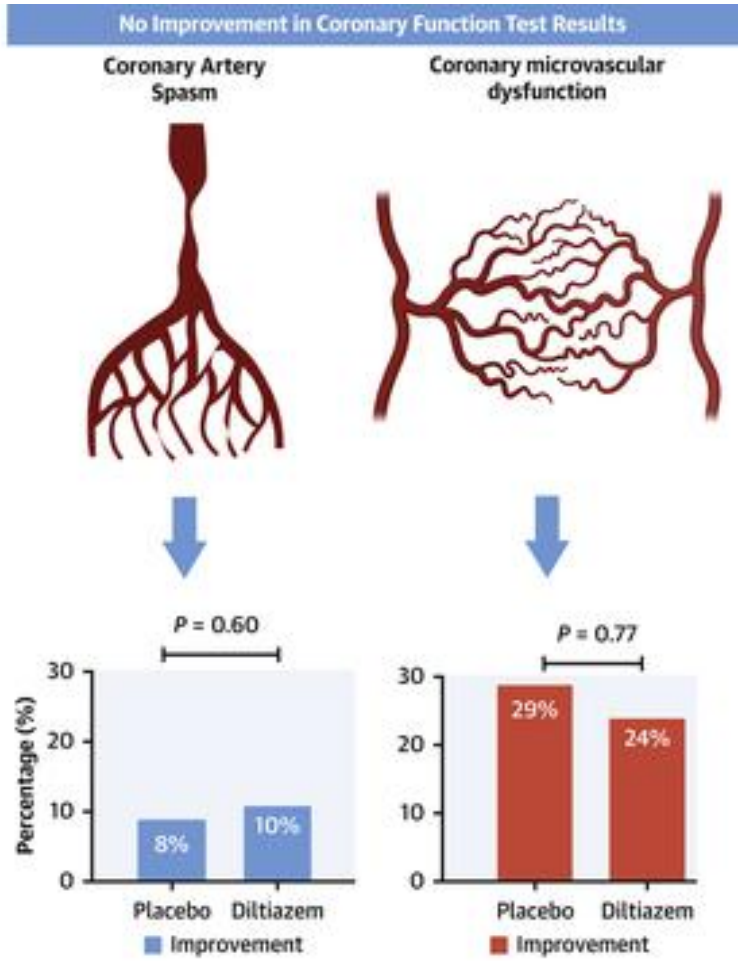
Eur Heart J, ehae177, https://doi.org/10.1093/eurheartj/ehae177

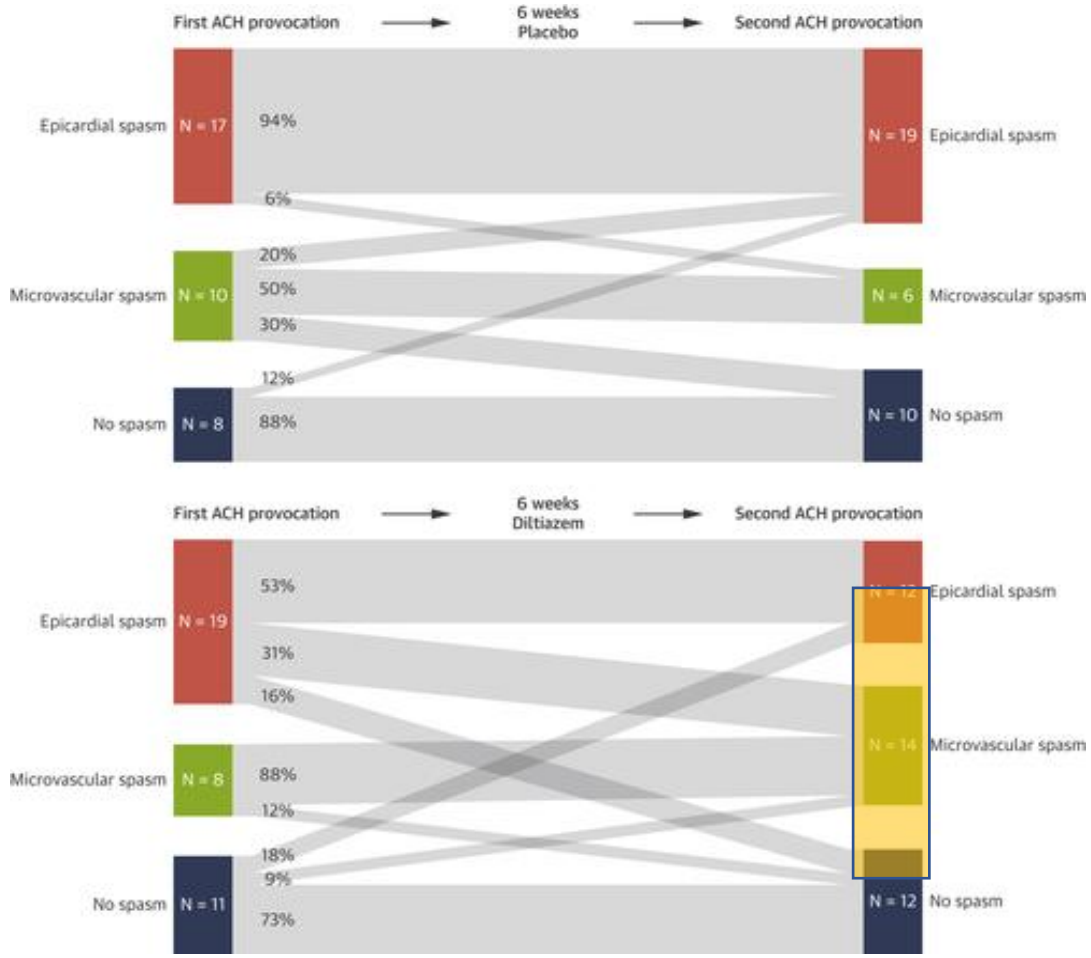
ESC European Society of Cardiology

Empiric use of CCB: the EDIT-CMD trial









Tijn P.J. Jansen et al. *J Am Coll Cardiol Img* 2022;

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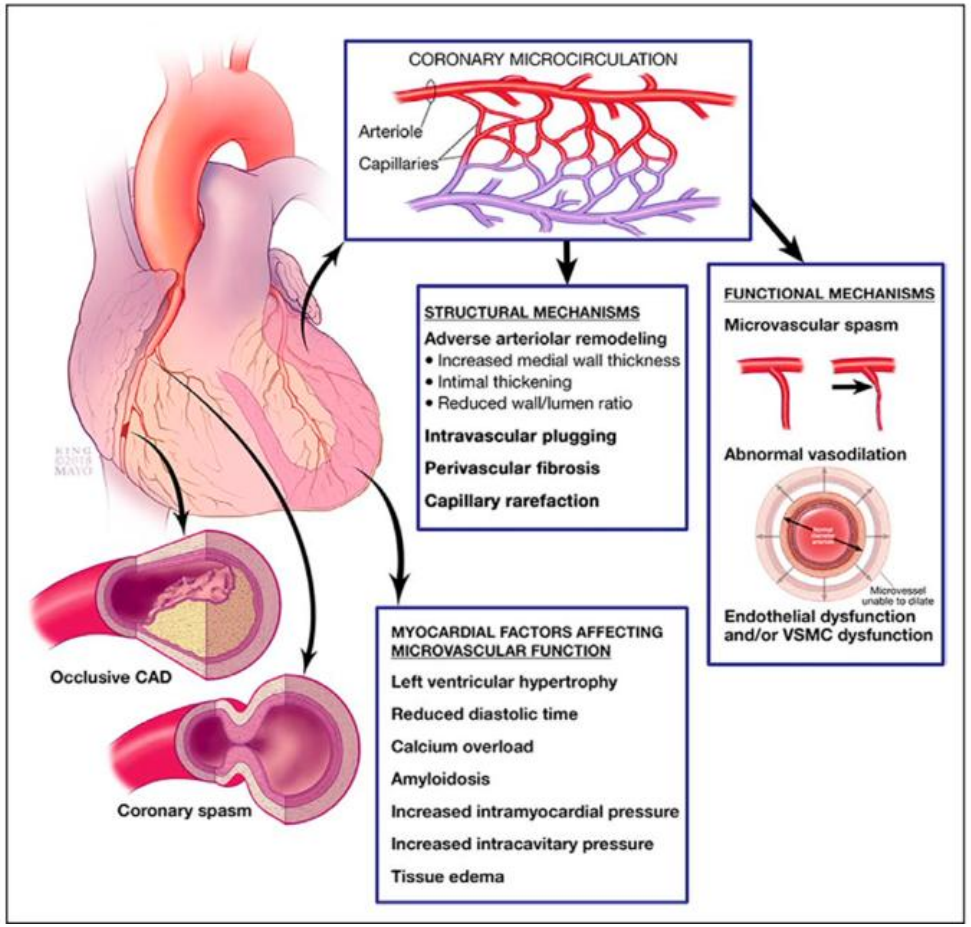
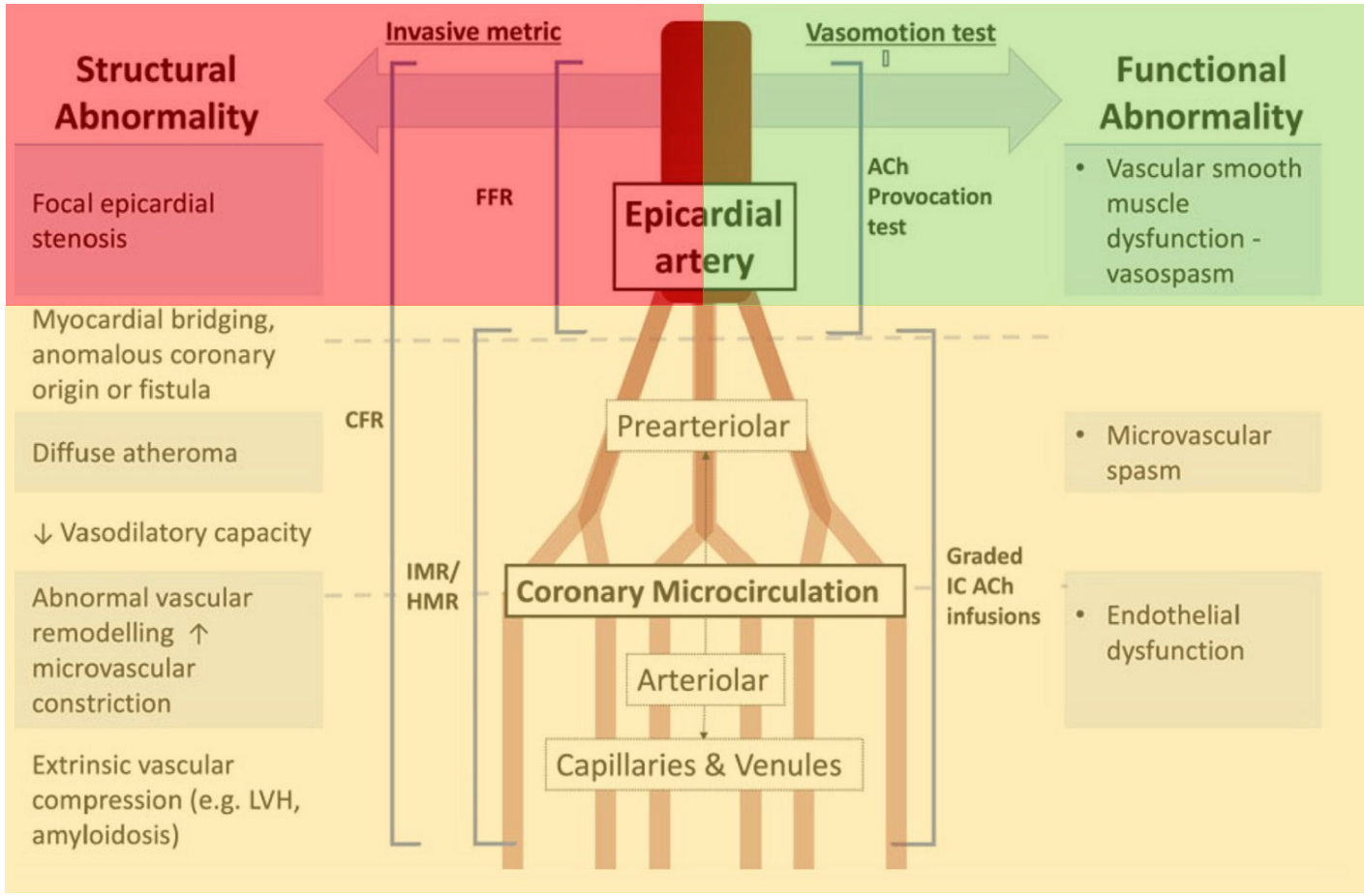
SCUOLA DI MEDICINA

Full Physiology For Structural and Functional abnormalities





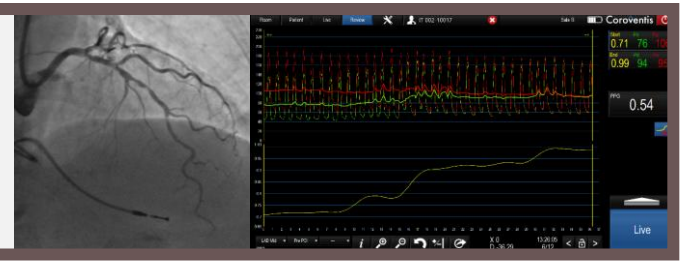
Crea F and D'Amario D, EHJ 2016

What is #FullPhysiology assessment

1

Epicardial disease assessment

- NHPR (≤0.89)
- cFFR (≤0.83)
- FFR (≤0.80) -> perform pullback



2

Microvascular disease assessment

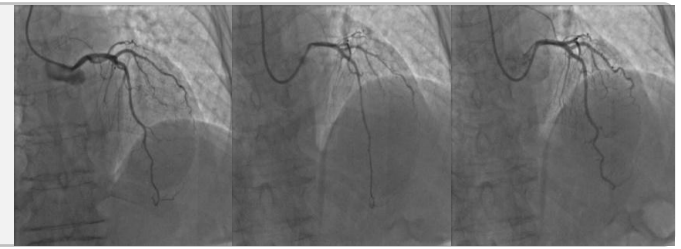
- IMR (>25)
- CFR (< 2.0)
- RRR (<2.0)*

Resistive resistance ratio $= \frac{Trm * Pdr}{Thm * Pdh}$

3

Vasomotor testing

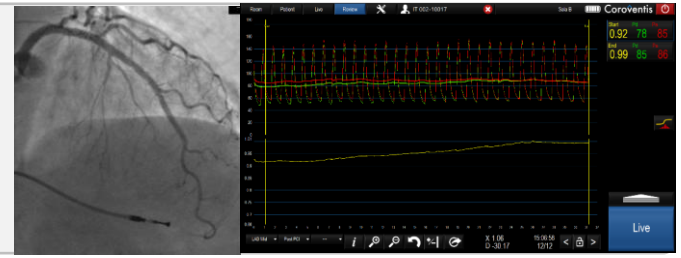
- Ach



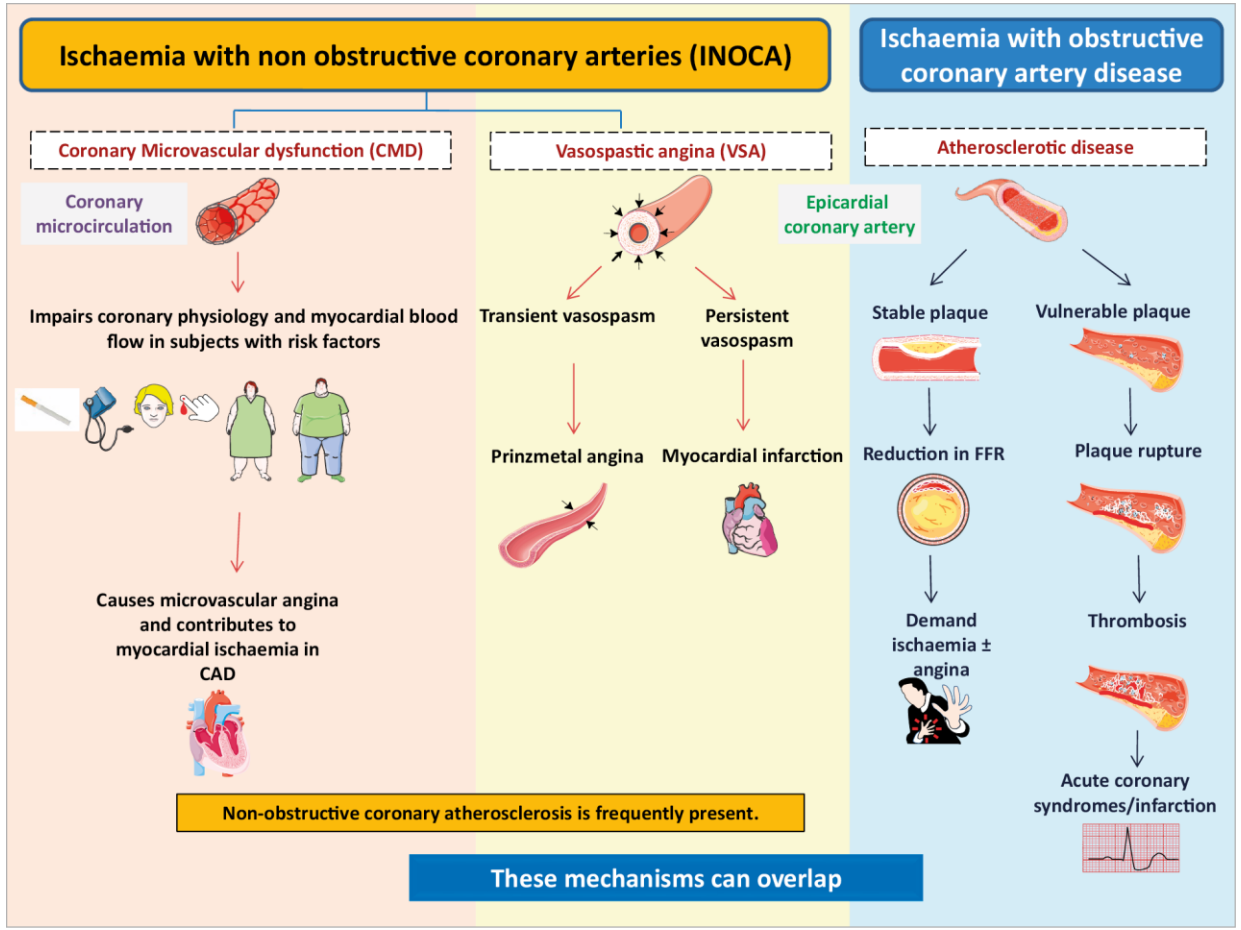
4

Post PCI Full Physiology assessment if applicable

- NHPR/cFFR/IMR/CFR/FFR -> perform pullback



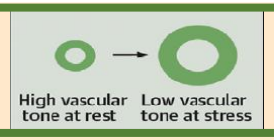
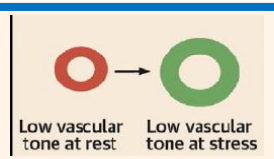
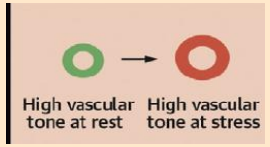
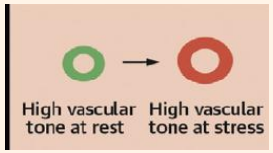
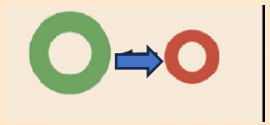
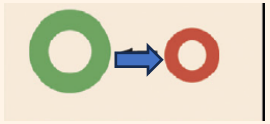
Nobody said it was easy… (Coldplay)



Kunadian V et al, Eurointervention 2024

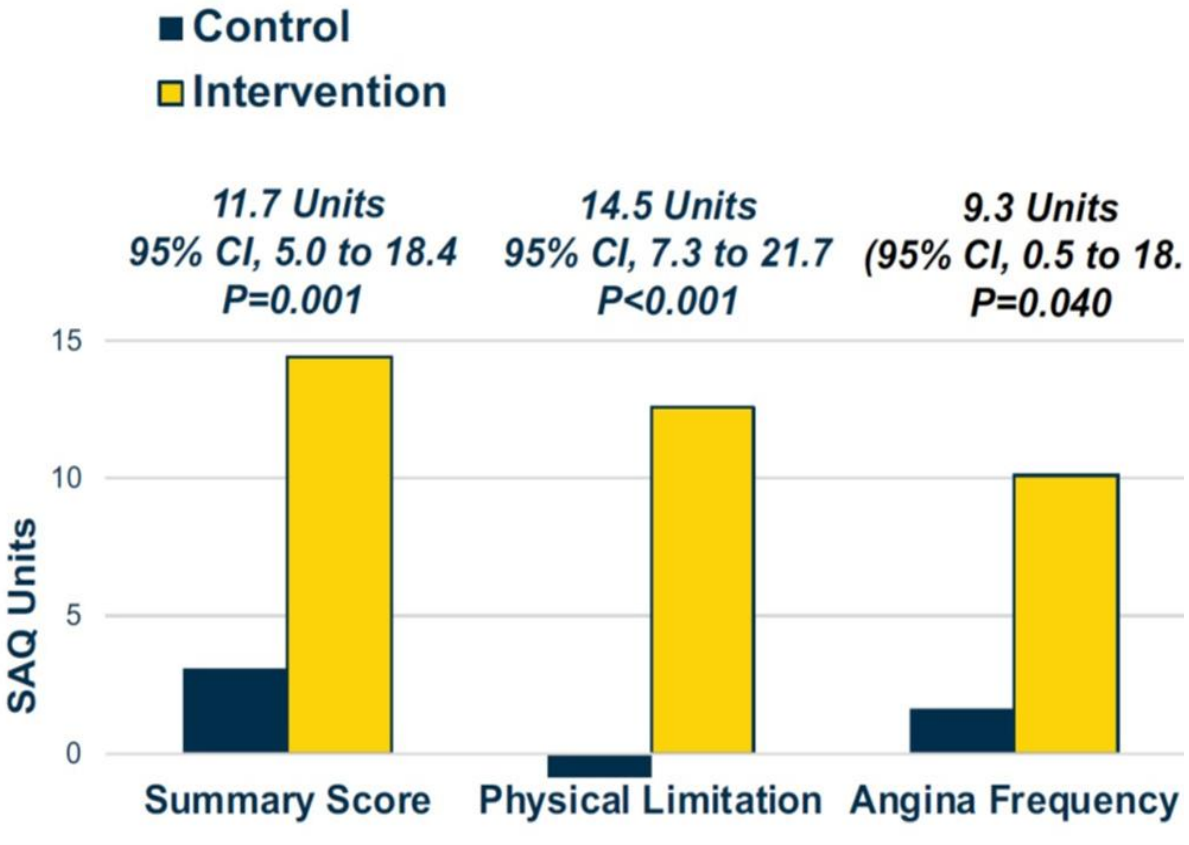
	Pathological mechanisms	Therapy
CV risk factors	Microvascular inflammation and damage	1.Exercise activity, weight reduction 2. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins 3. SGLT-2 for the association with HF
High IMR/HMR, low CFR (high microvascular resistance)	Microvascular remodeling and inability to increase myocardial flow during exercise (fibrosis, capillary rarefaction, vascular remodeling)	1. Beta-blockers (nebivolol, carvedilol) 2. Ranolazine, 2nd generation DHP Ca-antagonists 3. SGLT-2 for the association with HF 4. Coronary sinus reducer
Low CFR, normal IMR/HMR (high flow at rest)	Increased resting flow probably caused by impaired oxygen utilization. Preserved microvascular resistance	1. Beta-blockers, ivabradine 2. Verapamil/diltiazem 3. Ranolazine, SGLT-2 for the association with HF 4. Coronary sinus reducer
Epicardial/microvascular spasm	Endothelial dysfunction and/or hypercontractility of smooth muscle cells	1. Verapamil/diltiazem 2. 2nd generation DHP Ca-antagonists 3. Nicorandil, fasudil
Persistent angina despite of optimal medical therapy	Enhanced nociception	1. Xanthines (theophylline) 2. Tricyclic antidepressants (Imipramine) 3. Non-pharmacological interventions

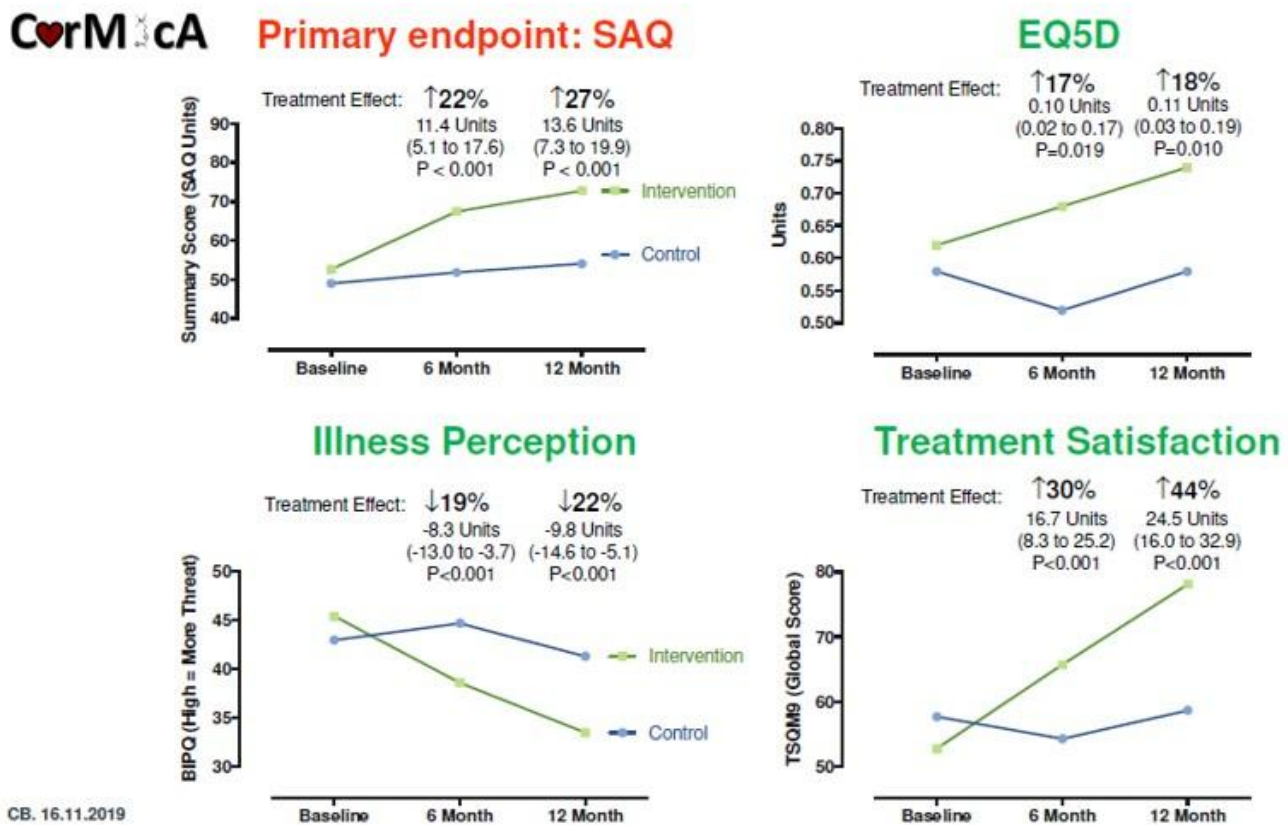
Different endotypes of *NOCA

	Mechanism		Invasive Physiology	Therapy
Normal	Normal		CFR>2 AND IMR<25	Primary prevention
Functional CMD	Impaired Vasodilation		CFR<2 (2.5) AND IMR<25	Treat non cardiac disease ARBs β-Blockers (nebivolol) Ranolazine
Compensated Structural CMD	Early abnormal MV resistance		CFR>2 (2.5) AND IMR≥25	Lifestyle (rehabilitation?) ARBs β-Blockers (nebivolol) Ranolazine
Structural CMD	Abnormal MV resistance		CFR<2 (2.5) AND IMR≥25	Lifestyle (rehabilitation?) ARBs β-Blockers (nebivolol) Ranolazine
Vasospastic Angina	Epicardial spasm		Angina + ST deviation with epicardial spasm	CCB Nitrates
Microvascular Spasm ?	Impaired ED vasodilatation / MV spasm		Angina + ST deviation w/o epicardial spasm	CCB Nitrates ?

Rahman H et al. JACC 2020
COVADIS criteria
Scarsini et al. Minerva Cardiol Angiology 2023

CORMICA trial: efficacy of a tailored approach





CB. 16.11.2019

Ford JACC 2018

1

*NOCA is a real, demanding phenomenon with relevant clinical implications

2

A **correct diagnosis** can have important therapeutic and prognostic implications

3

*NOCA mechanisms should be dissected in order to **treat appropriately** by using an invasive guide a pressure/thermodilution wire

4

*NOCA is a useful model for a variety of clinical settings in which **#FullPhysiology** can make the difference together with the clinical assessment


CHANGE
IN CARDIOLOGY
3.0
TRANCE