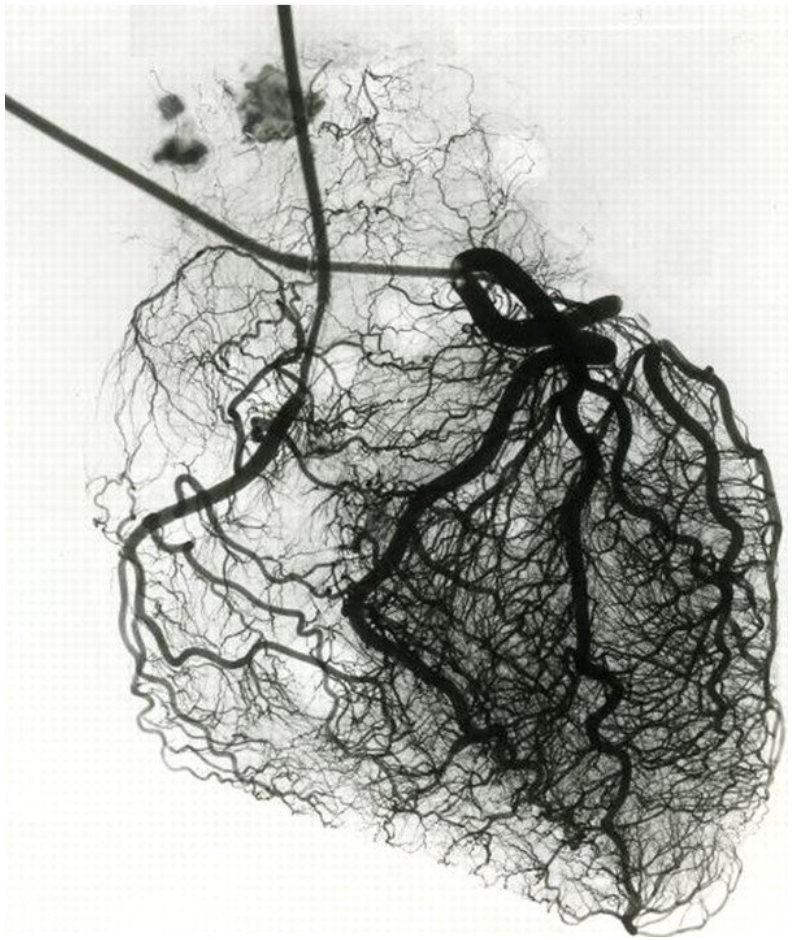
New insights from coronary physiology

From the FFR-based deferral to the #Full Physiology Approach



William Fulton, MD thesis, University of Glasgow 1963

Antonio Maria Leone MD PhD

Director of Chronic Coronary Syndromes Program
Department of Cardiovascular Sciences
Fondazione Policlinico Universitario A. Gemelli IRCCS
Roma

Potential conflicts of interest

Speaker's name: Antonio Maria Leone

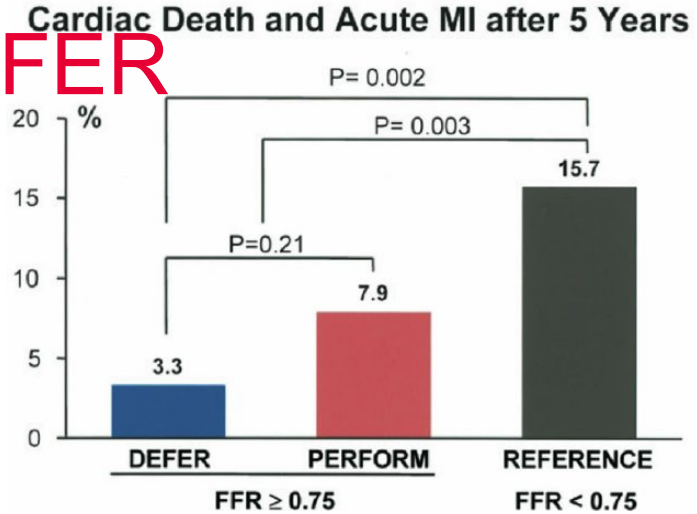
I have the following potential conflicts of interest to report:

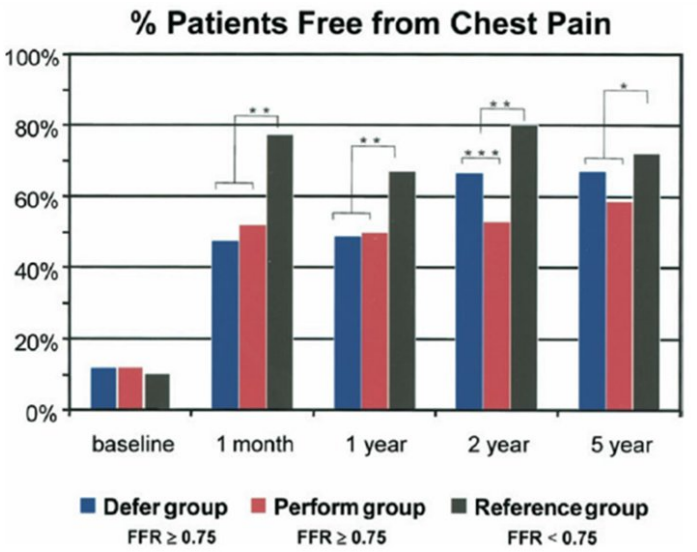
Dr. A.M. Leone is an advisor for Abbott Vascular and Bracco Imaging and received speaking honoraria from Abbott Vascular, Medtronic and Abiomed in the past.

All contents provided by Dr. Leone unless otherwise noted

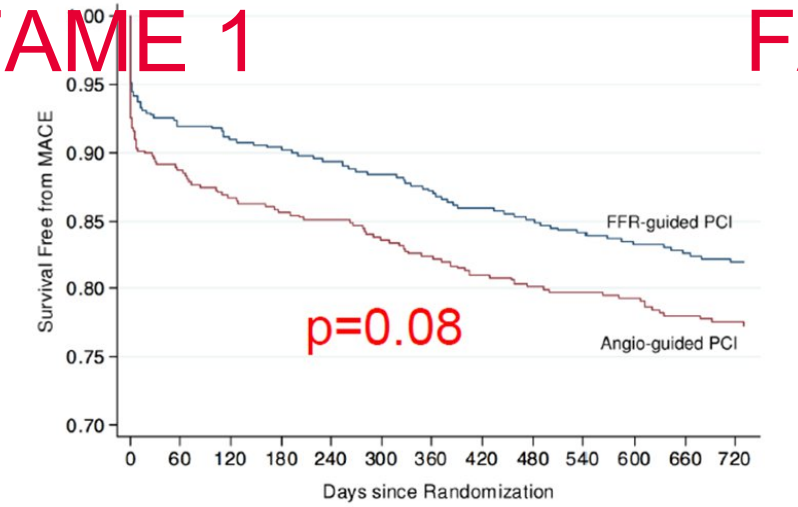
How ICs think about invasive physiology

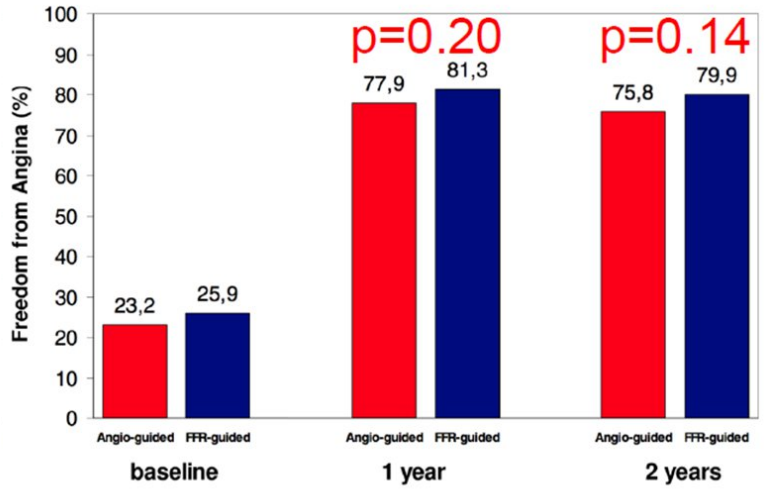
DEFER



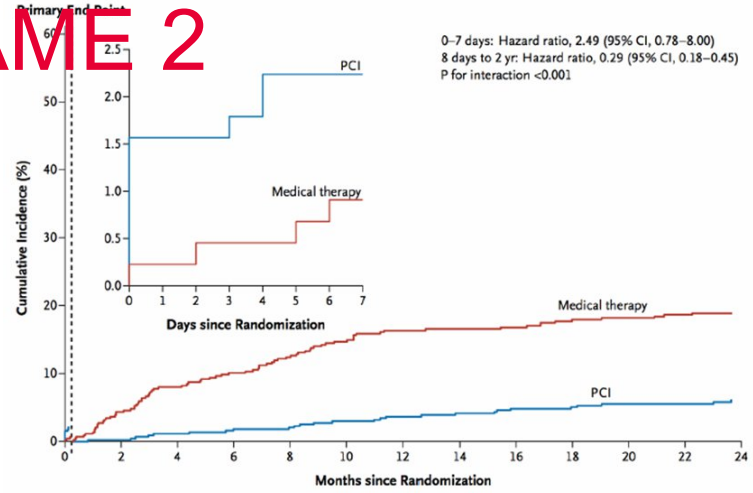


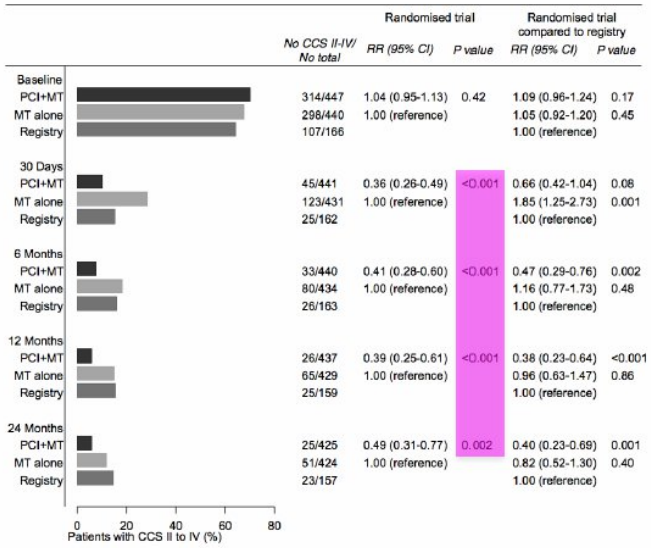
FAME 1





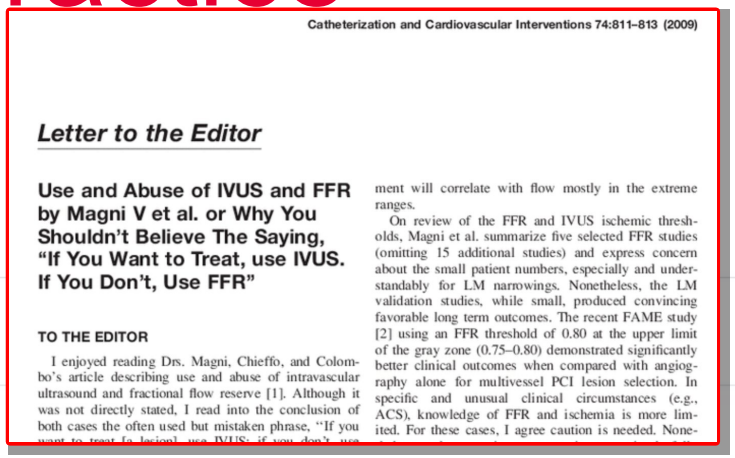
FAME 2





#FullPhysiology InDailyPractice

How ICs translate invasive physiology in practice



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-

$$\frac{\textit{Invasive Assessment}}{\textit{Coronary Angiograms}} = \frac{16.287}{280.604} = 5.8\%$$

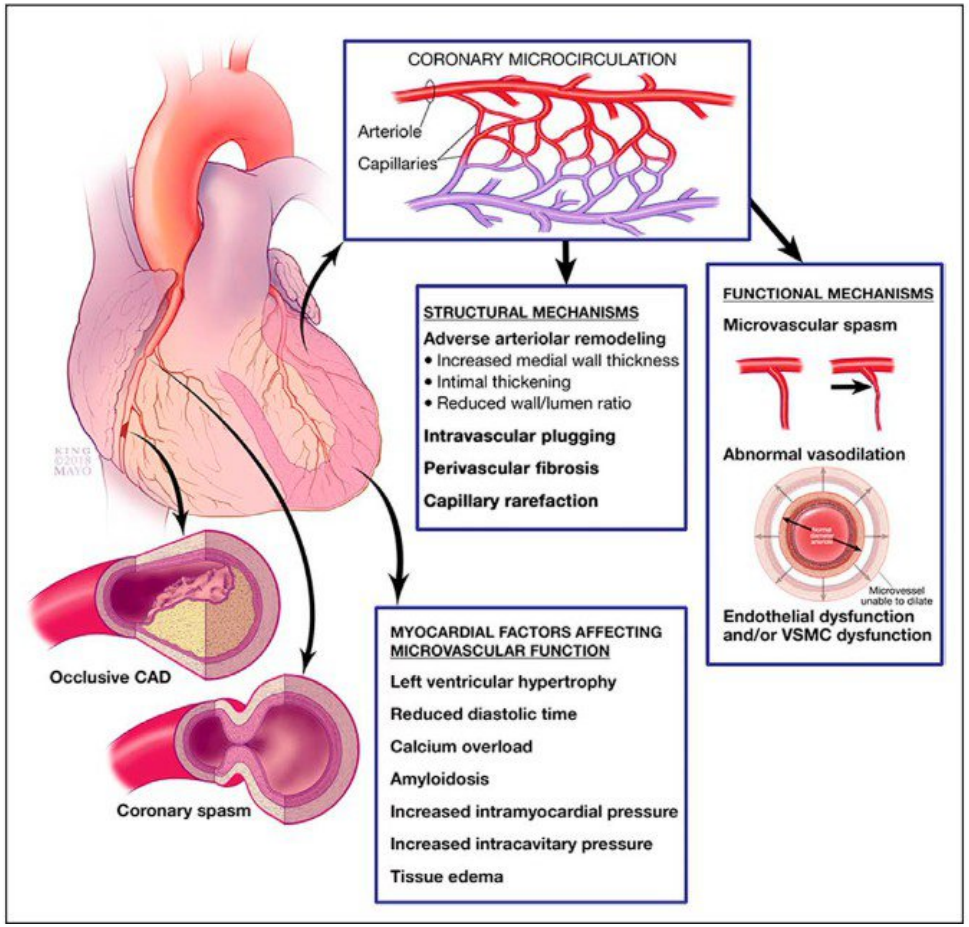
Dati Nazionali GISE 2021

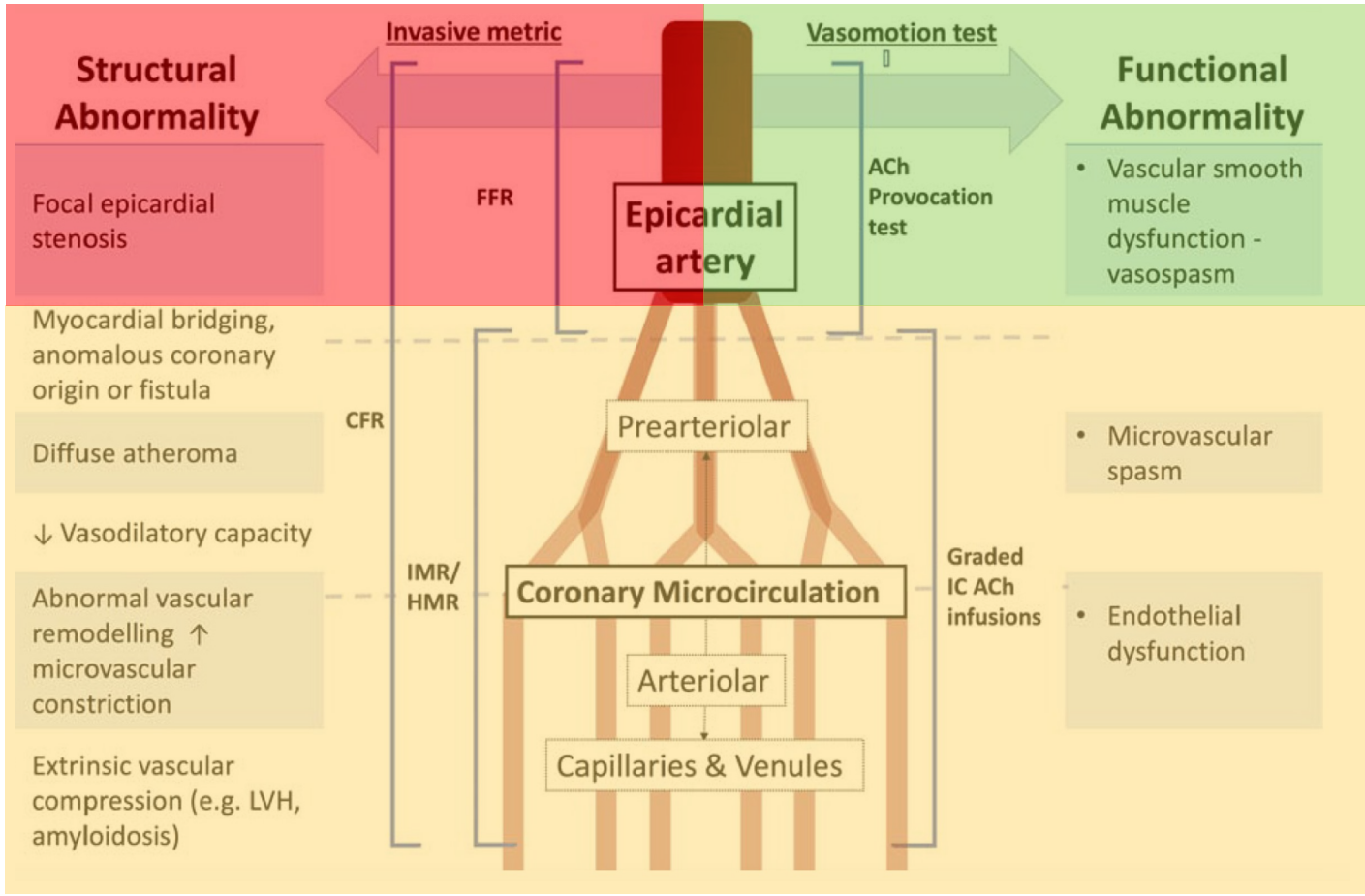
#FullPhysiology InDailyPractice

The #FullPhysiology group

Why Full Physiology?

F. Ph. For Structural and Functional abn.

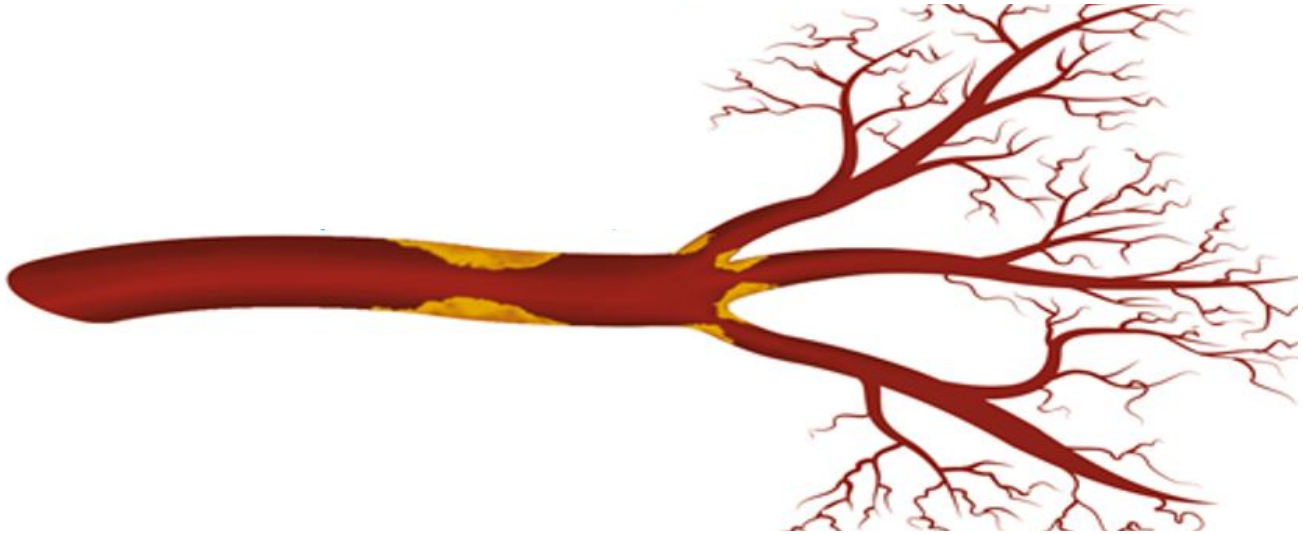


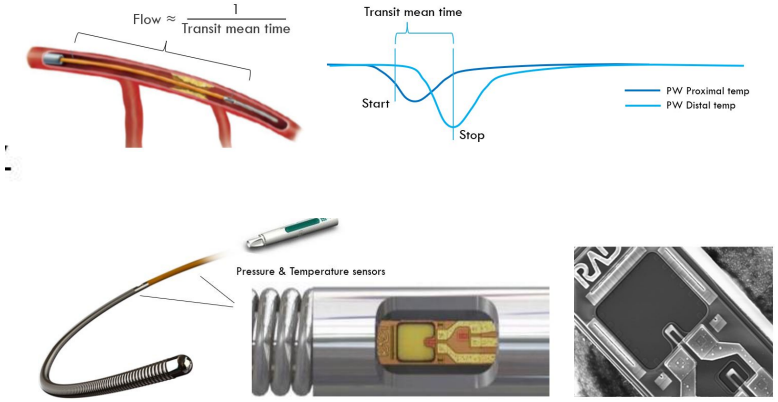


Courtesy from T. Engstroem

Crea F, et al. *Eur Heart J* 2016;37:1514-6

Different indexes for different compartments?





Nico H.J. Pijls, Circulation. 2001;104:2003-2006
Fearon et al. Circulation. 2003;107:3129-3132

Our Ach protocol

- 1 vial of Miovisin 20mg/2ml diluted in 100 ml of NaCl 0.9%

- 1 ml of this solution (200 mcg/ml) diluted with 19 ml of 0.9% NaCl = 20 ml of 10 mcg/ml Ach (Master solution)

- Take from the Master solution:
  2 ml + 18 ml of 0.9% NaCl % (20 mcg)
  5ml + 15 ml of 0.9% NaCl % (50 mcg)
  10 ml + 10 ml of 0.9% NaCl % (100 mcg)
  20 ml (200 mcg)

- infuse manually in the LCA incremental doses oh Ach (20-50-100-200 mg) in 2 minutes
  (rarely we infuse incremental doses of Ach 20-50-80 mg in the RCA)

AIFA
AGENZIA ITALIANA DEL FARMACO

Ufficio Segreteria Organi Collegiali

• Esiti Area PreAutorizzazione CTS 17, 18 e 19 Marzo 2021

Richieste di inserimento nell'elenco istituito ai sensi della Legge n.648/96

6. Inserimento del medicinale Acetilcolina cloruro (Miovisin), per via intracoronarica, nell'elenco istituito ai sensi della Legge n. 648/96 come test farmacologico per la valutazione della funzione vascolare coronarica.
   Parere CTS:La CTS esprme parere non favorevole.

Off label

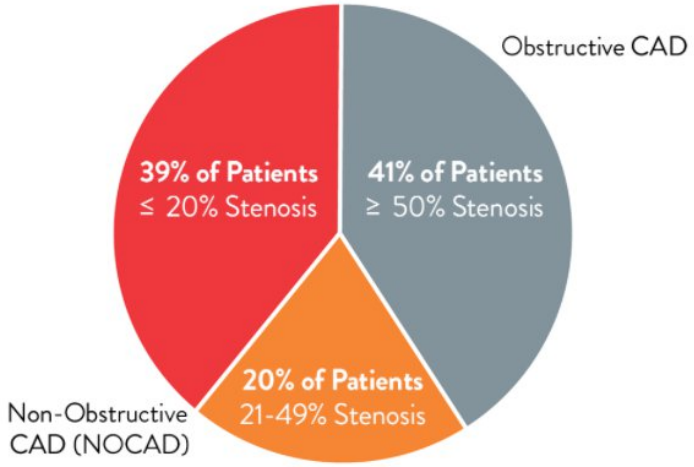
Why perform a comprehensive assessment?

1. To make a correct and complete diagnosis

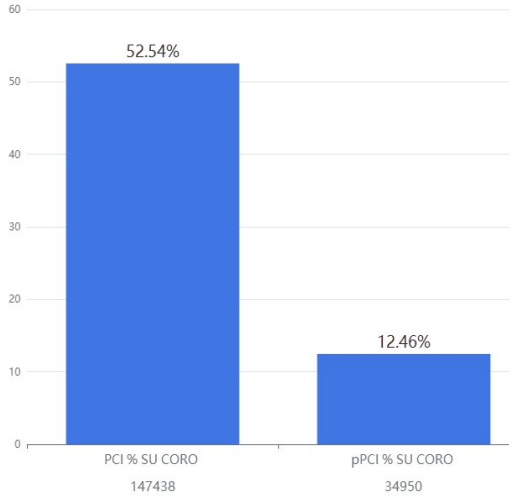
2. To guide a specific treatment

3. To assess prognosis

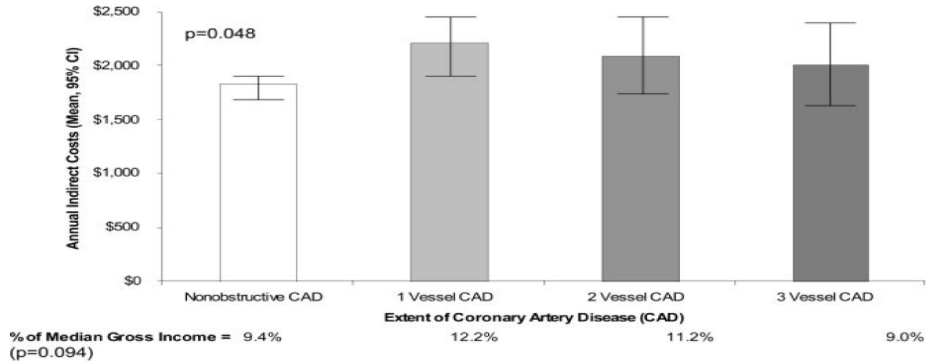
CAD and NOCAD are both clinically relevant



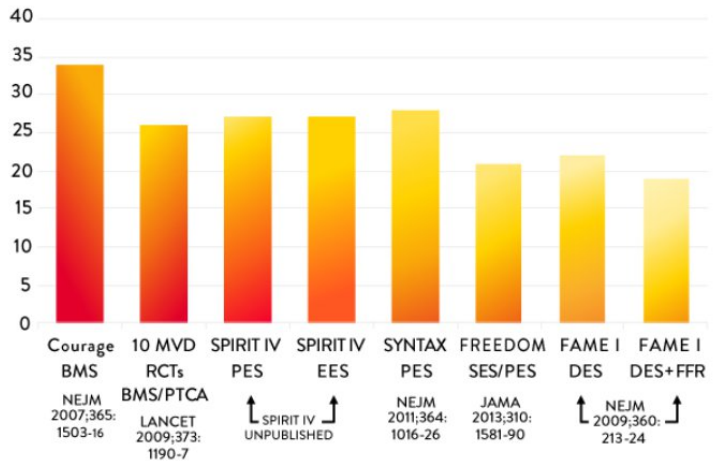
Patel NEJM 2010

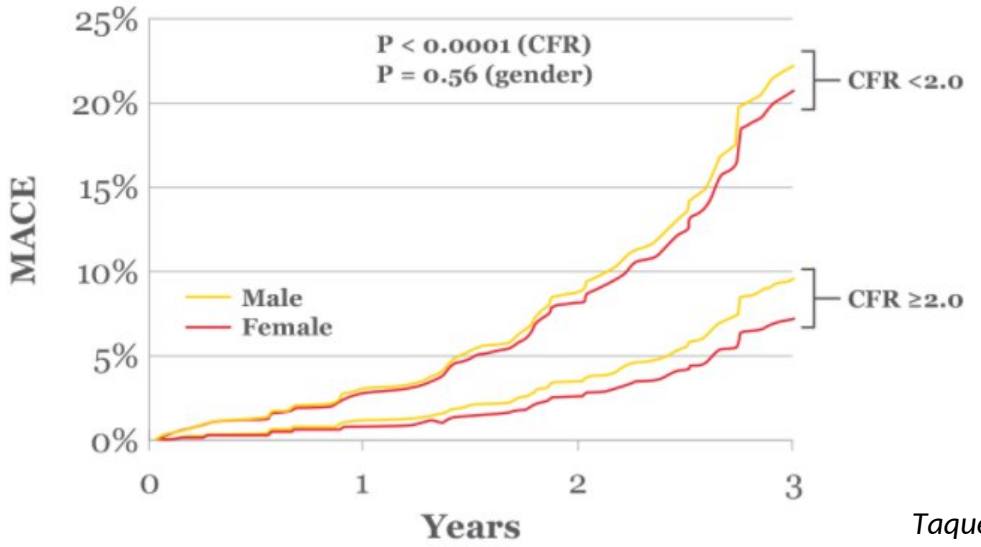


Dati GISE 2021



Shaw Circ 2006



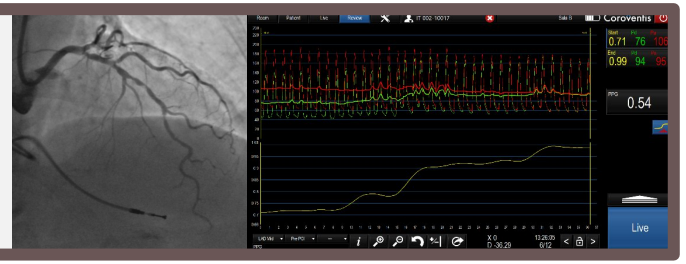


Taqueti JACC 2018

What is #FullPhysiology assessment

1 Epicardial disease assessment

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



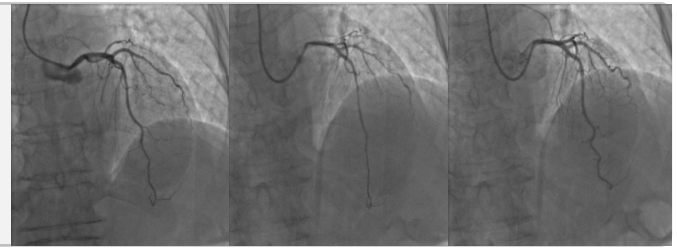
2 Microvascular disease assessment

- 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

Epicardial disease assessment

Pd/Pa

RFR

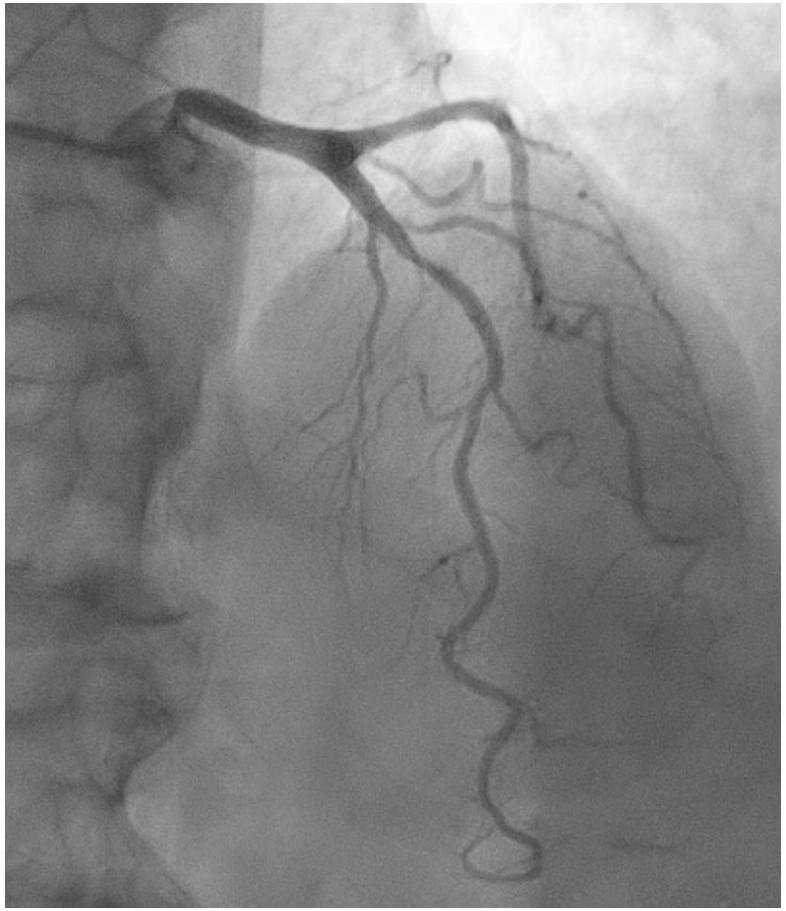
cFFR

FFR

#FullPhysiology
InDailyPractice

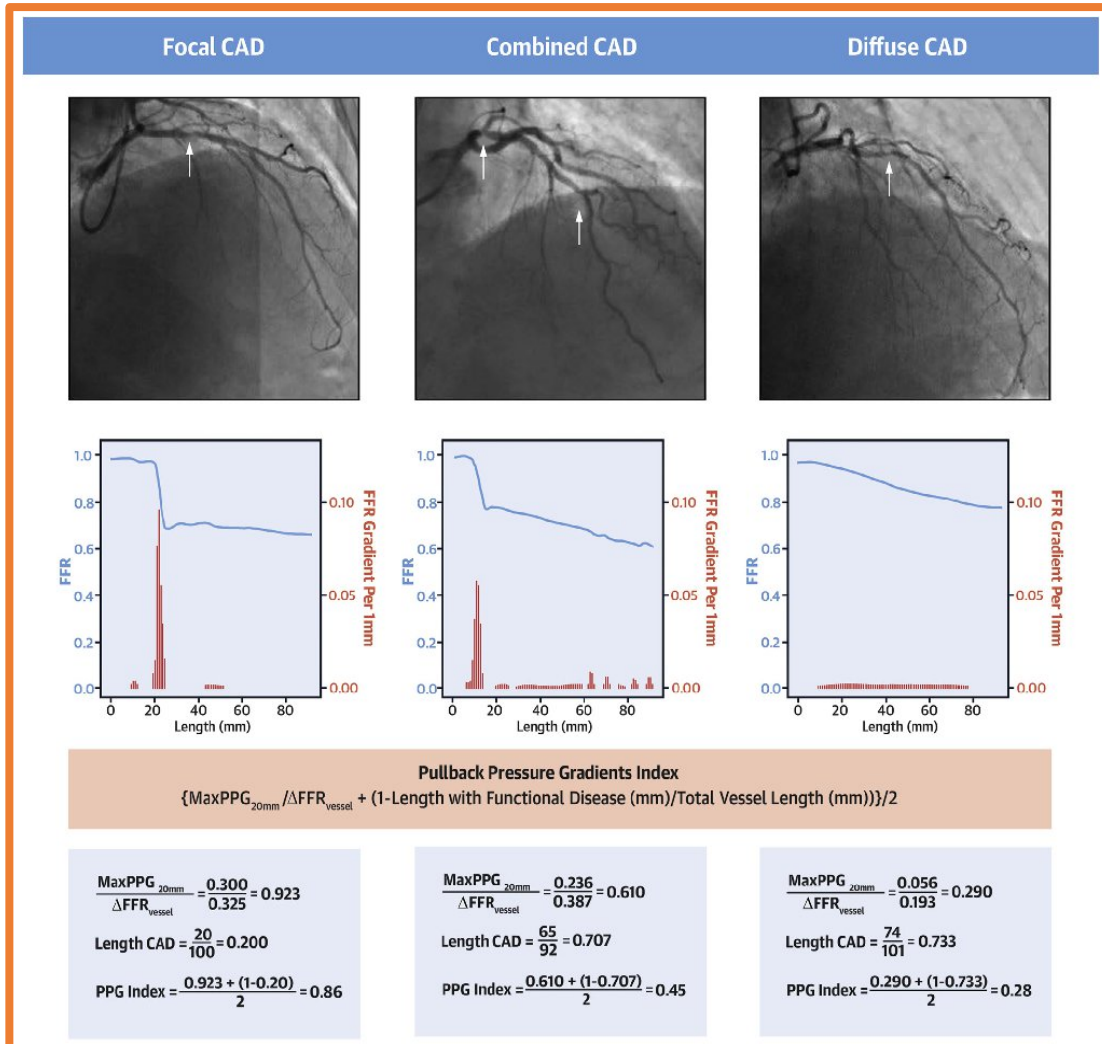
Epicardial disease assessment

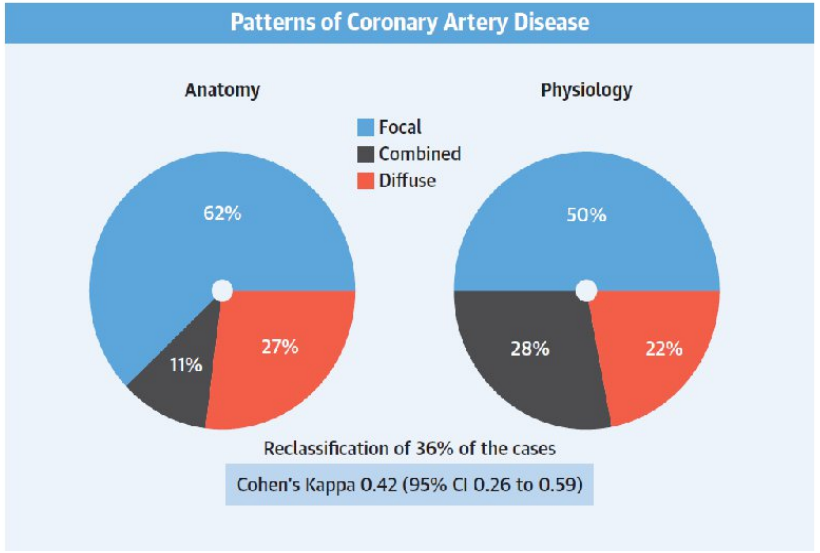
The importance of pullback



Epicardial disease assessment

- Functional mapping can discriminate better mixed patterns
- Diffuse disease is associated with longer stents and myocardial injury
- PPG index is currently tested in a multicenter study





	Low PPG Index Tertile (n = 28)	Intermediate PPG Index Tertile (n = 25)	High PPG Index Tertile (n = 19)	p Value
MACE	7	6	2	0.128*
All-cause death	1	0	0	0.135*
Myocardial infarction	5	5	2	0.276*
Spontaneous MI	0	0	1	0.922*
Peri-procedural MI	5	5	1	0.141*
Target-vessel revascularization	1	1	0	0.250*
Troponin T post-PCI, µg/l	0.14 ± 0.13	0.22 ± 0.24	0.03 ± 0.03	0.196
Creatine kinase post-PCI, U/l	166.1 ± 112.3	156.3 ± 91.5	62.4 ± 23.4	0.033
PCI	13	9	9	0.485*
Number of stents	1.77 ± 0.83	1.5 ± 0.8	1.3 ± 0.5	0.164
Stent length, mm	46.7 ± 21.6	36.1 ± 20.4	31.2 ± 20.5	0.088
Stent diameter, mm	2.9 ± 0.3	3.0 ± 0.2	3.2 ± 0.4	0.025

Collet et al., *JACC* 2019

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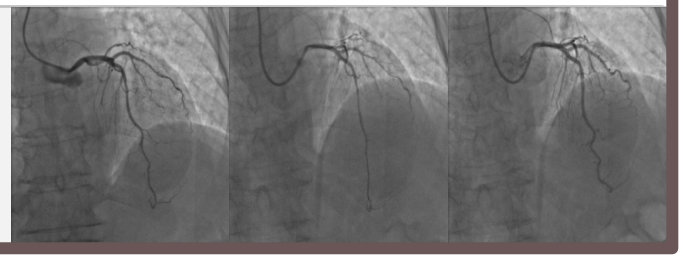

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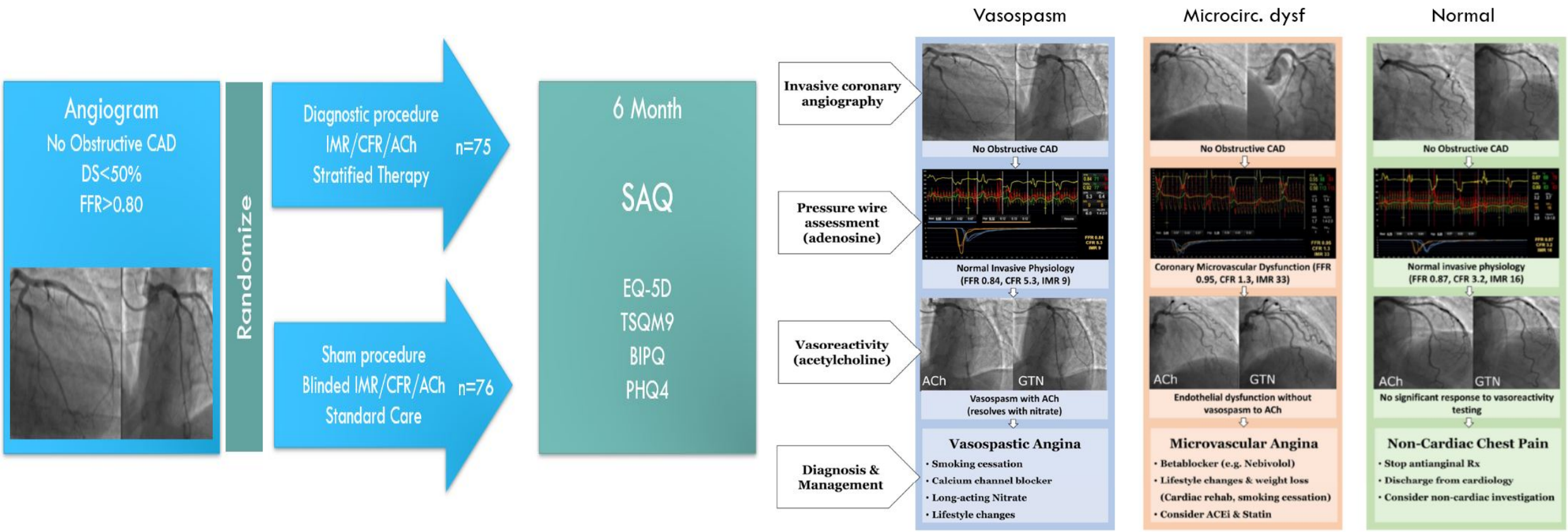
#FullPhysiology InDailyPractice

CORMICA trial: efficacy of a tailored approach

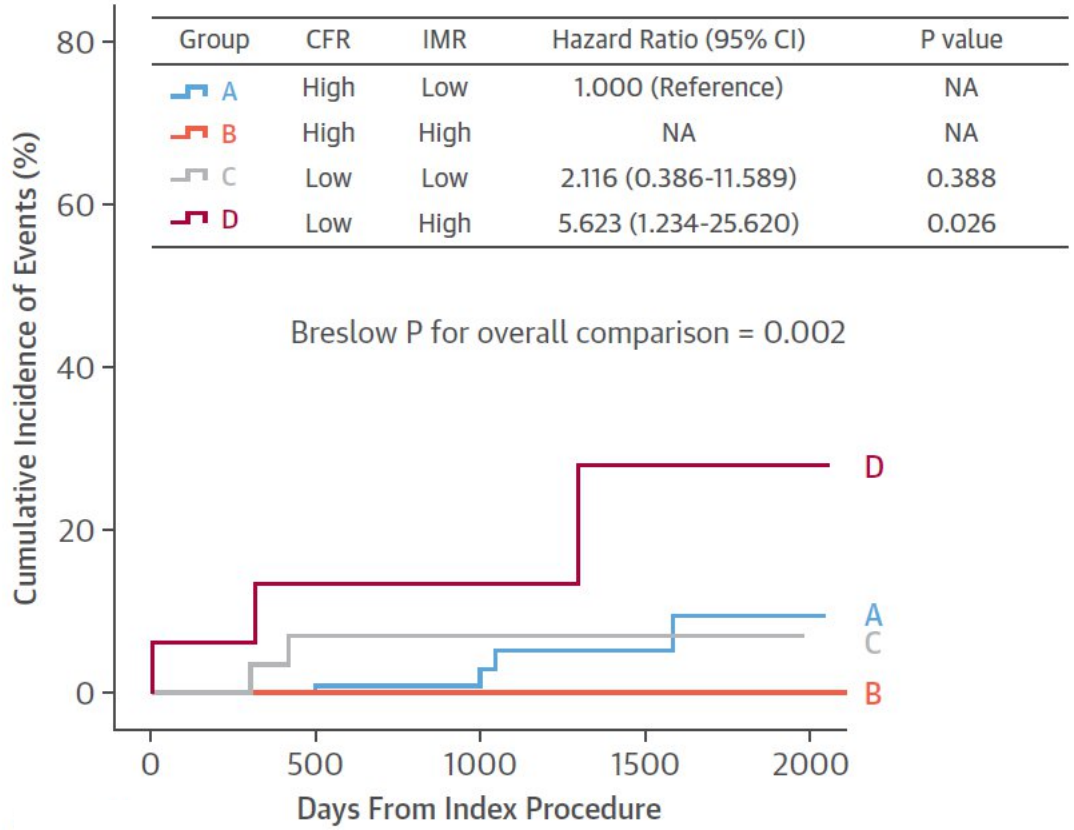


Ford JACC 2018

Importance of microcirculation

In 313 patients with FFR>0.80, those with low CFR and high IMR (microvascular dysfunction) had significantly higher rate of death, MI, or revascularization.

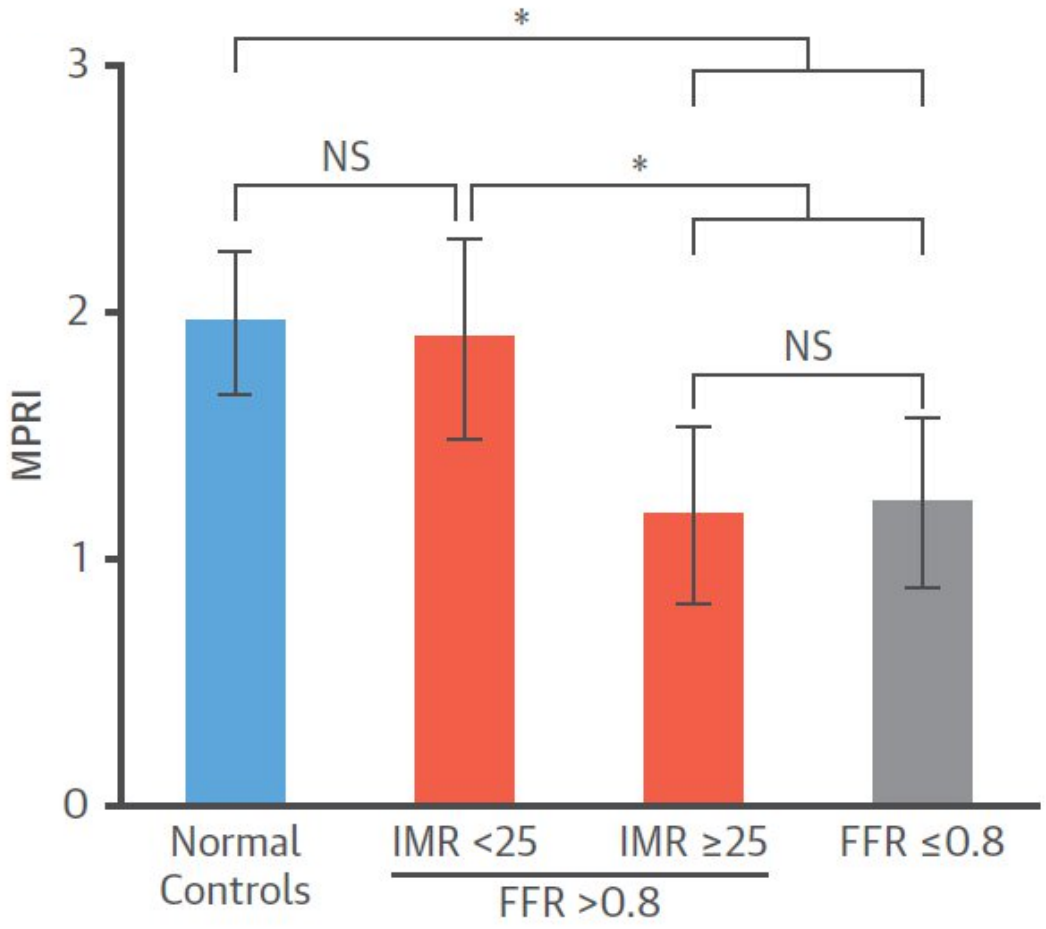
Group	CFR	IMR	Hazard Ratio (95% CI)	P value
A	High	Low	1.000 (Reference)	NA
B	High	High	NA	NA
C	Low	Low	2.116 (0.386-11.589)	0.388
D	Low	High	5.623 (1.234-25.620)	0.026

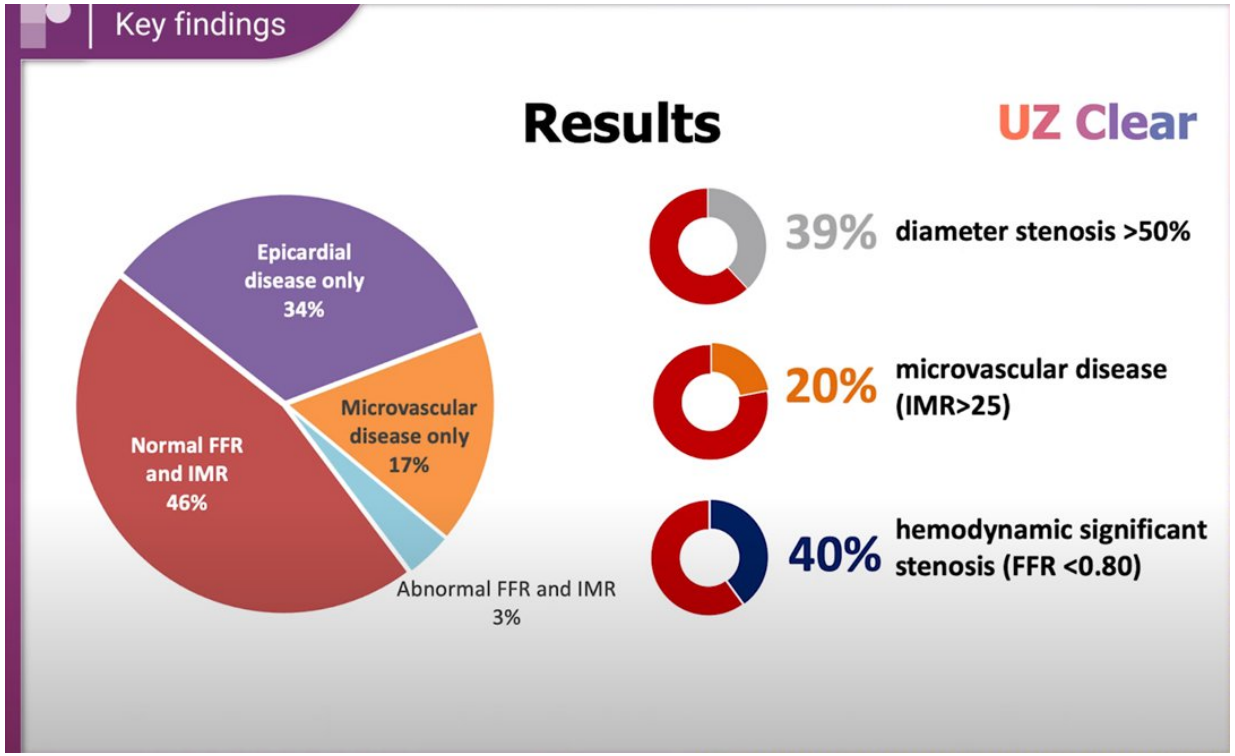


Lee JM, *et al.* Journal of the American College of Cardiology 2016.

Index of microcirculatory resistance

IMR in Comparison with Cardiac MR





Collet CRT 2022
Vandeloo Eurointervention 2022

Liu, et al. Journal of American College of Cardiology 2018

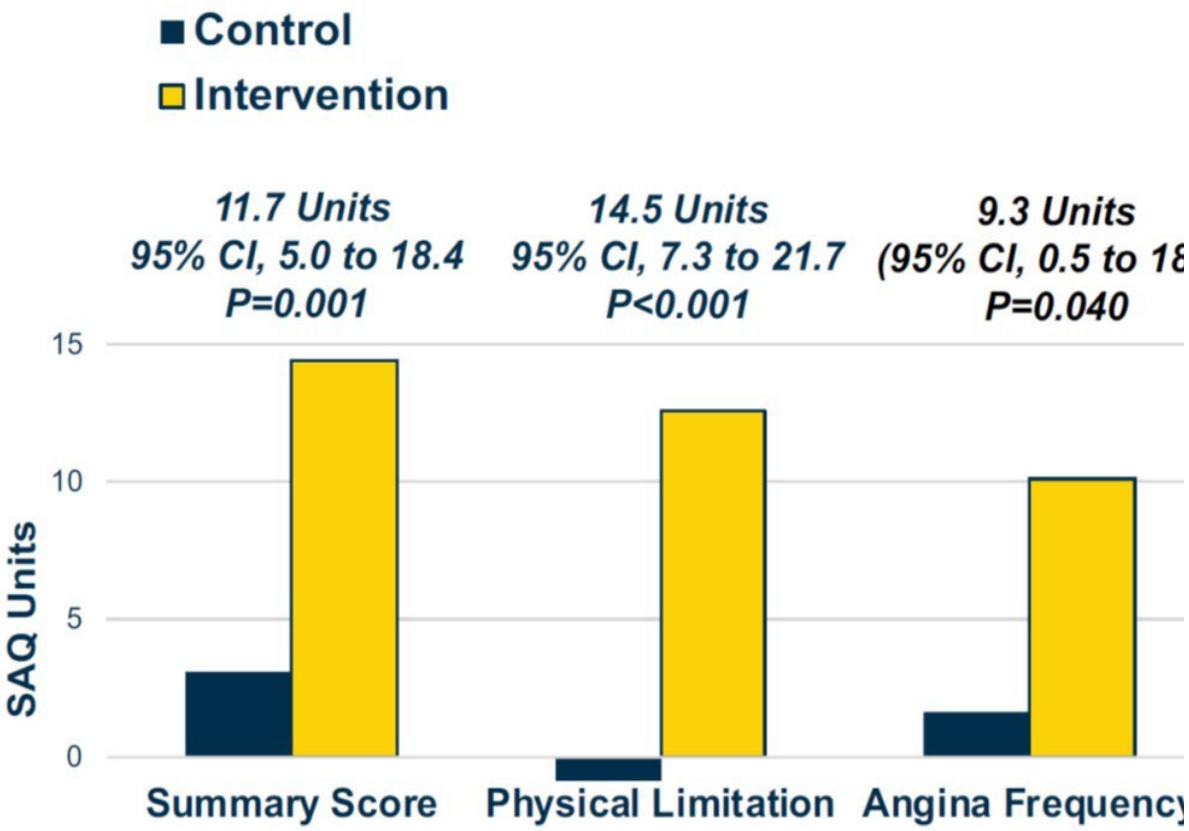
#FullPhysiology InDailyPractice

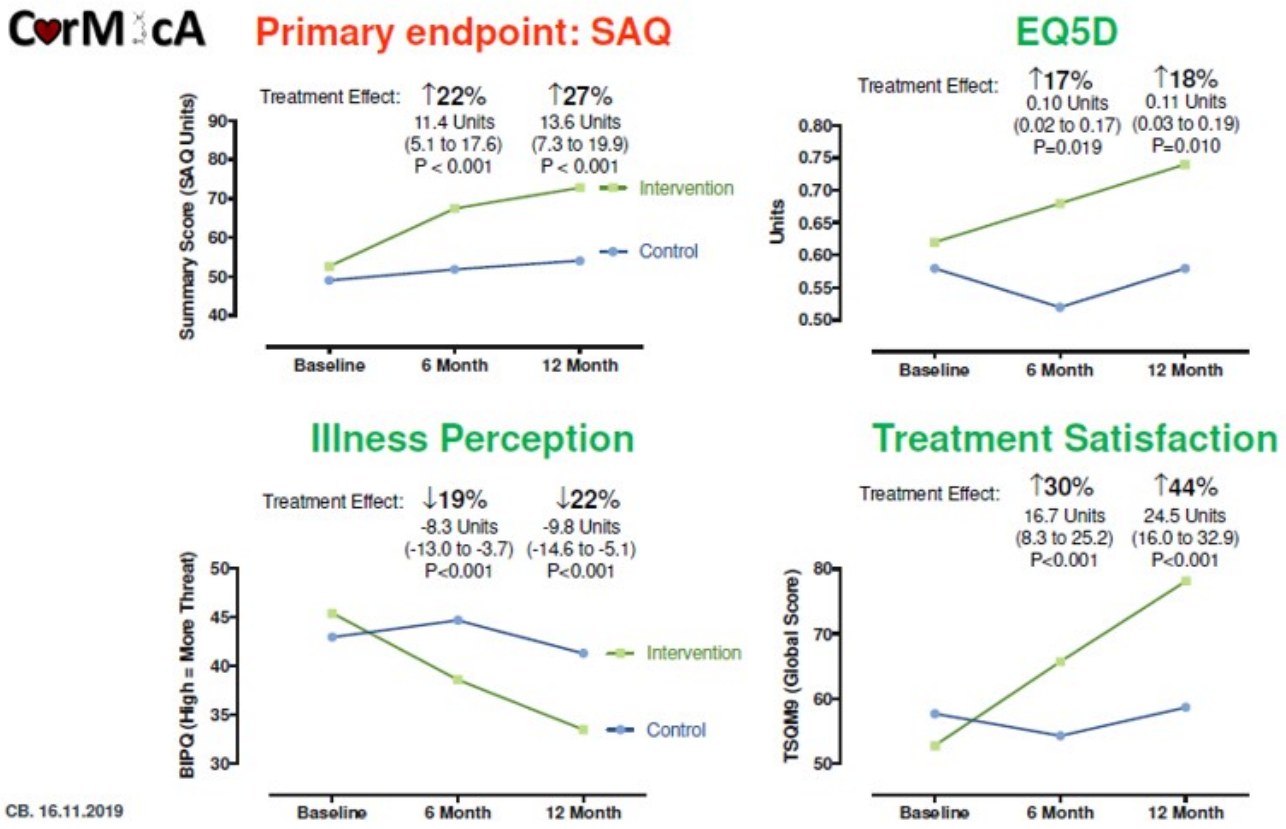
Two types of CMD. Both are bad

	Mechanism	Systemic Vasculature			Myocardium		
		Nitric Oxide Synthase Activity	Acetylcholine Dilatation	Exercise Blood Pressure	NT-proBNP	Exercise Coronary Perfusion Efficiency	Inducible Ischemia
Reference Group (n = 40)	High vascular tone at rest → Low vascular tone at stress	Normal	Normal	Normal	34 pgml^{-1}	65%	22%
Functional CMD (n = 28)	Low vascular tone at rest → Low vascular tone at stress	Increased ↑↑	Normal	Normal	69 pgml^{-1}	46%	77%
Structural CMD (n = 18)	High vascular tone at rest → High vascular tone at stress	Increased ↑	Reduced ↓	High	132 pgml^{-1}	41%	88%

Rahman H et al. JACC 2020;75:2538–2549.

CORMICA trial: efficacy of a tailored approach





CB. 16.11.2019

Ford JACC 2018

ESC guidelines for CCS

Recommendations	Class[a]	Level[b]
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.[412,413]	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.[412,438–440]	IIb	B
Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR.[430–432,441]	IIb	B

Recommendations	Class[a]	Level[b]
An ECG is recommended during angina if possible.	I	C
Invasive angiography or coronary CTA is recommended in patients with characteristic episodic resting angina and ST-segment changes, which resolve with nitrates and/or calcium antagonists, to determine the extent of underlying coronary disease.	I	C
Ambulatory ST-segment monitoring should be considered to identify ST-segment deviation in the absence of increased heart rate.	IIa	C
An intracoronary provocation test should be considered to identify coronary spasm in patients with normal findings or non-obstructive lesions on coronary arteriography and a clinical picture of coronary spasm, to diagnose the site and mode of spasm.[412,414,438–440]	IIa	B

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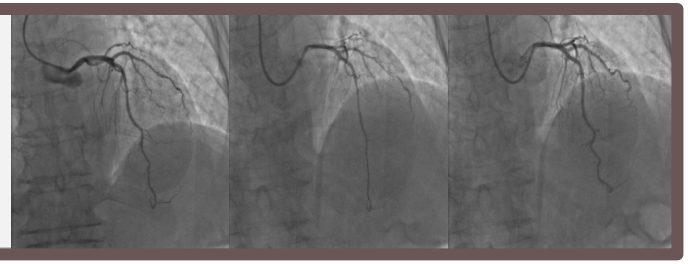
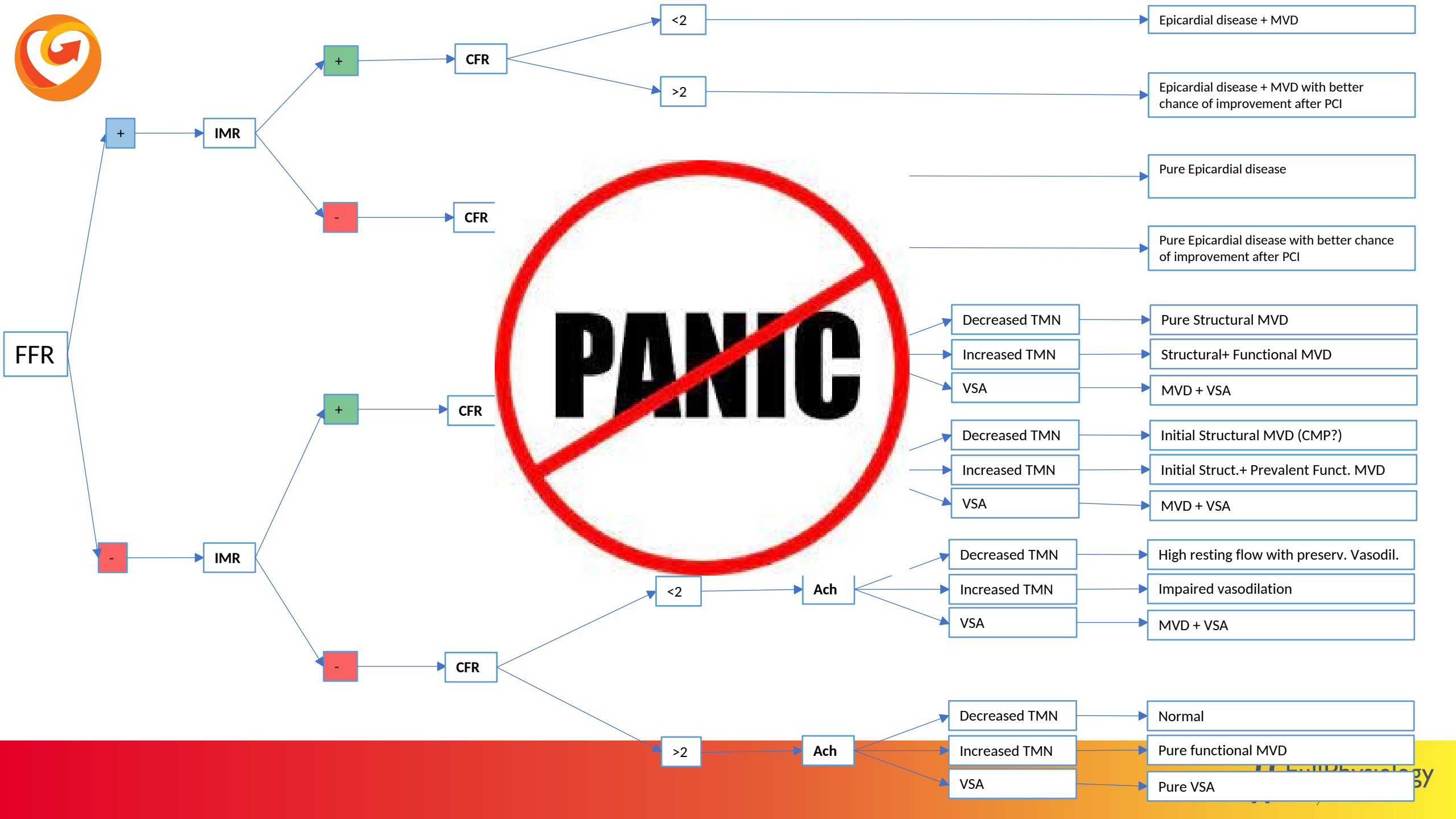
3 Vasomotor testing

- Ach



4 Post PCI Full Physiology assessment if applicable

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


FFR
+
IMR
+
CFR
<2
Epicardial disease + MVD
>2
Epicardial disease + MVD with better chance of improvement after PCI
-
CFR
Pure Epicardial disease
Pure Epicardial disease with better chance of improvement after PCI
PANIC
-
IMR
+
CFR
Decreased TMN
Pure Structural MVD
Increased TMN
Structural+ Functional MVD
VSA
MVD + VSA
-
CFR
<2
Ach
Decreased TMN
Initial Structural MVD (CMP?)
Increased TMN
Initial Struct.+ Prevalent Funct. MVD
VSA
MVD + VSA
Decreased TMN
High resting flow with preserv. Vasodil.
Increased TMN
Impaired vasodilation
VSA
MVD + VSA
>2
Ach
Decreased TMN
Normal
Increased TMN
Pure functional MVD
VSA
Pure VSA

CCS: a continuum of Angina Endotypes

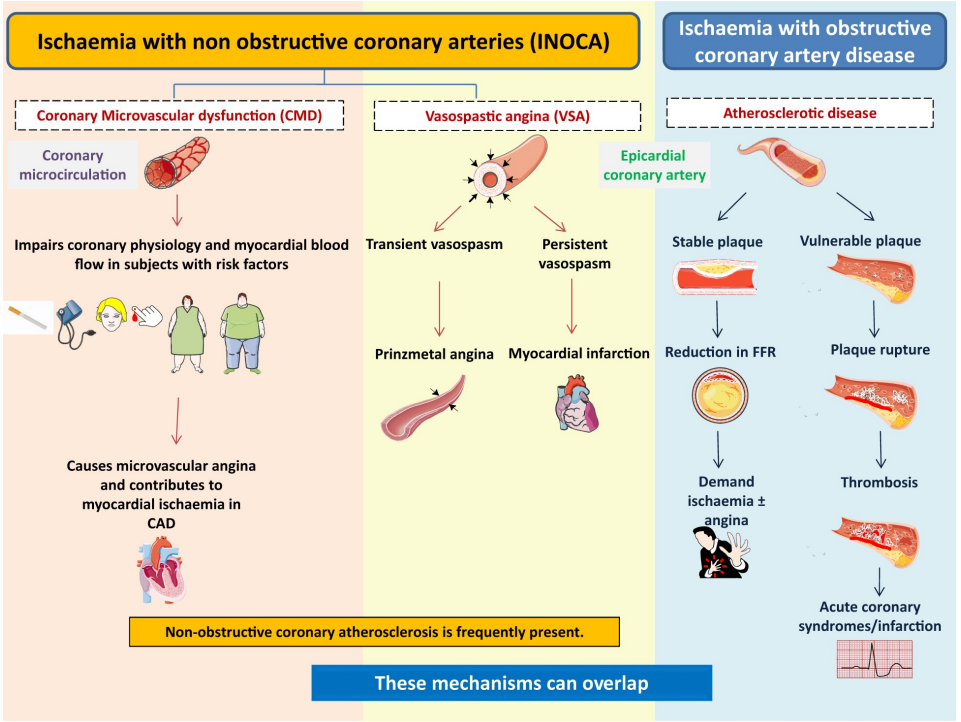
1. **Obstructive Epicardial CAD**
   NHPR ≤0.89 and/or cFFR ≤0.83 and/or FFR ≤0.80

2. **Microvascular angina**
   Structural: IMR >25
   Functional*: MV spasm: angina + ST changes and no epicardial spasm (+ ↑Tmn)
   CFR < 2.0 (+ FFR>0.80 and IMR ≤25)

3. **Vasospastic angina**
   angina + ST changes and >90% epicardial spasm

4. **Mixed Angina**
   combination of 1, 2 and 3

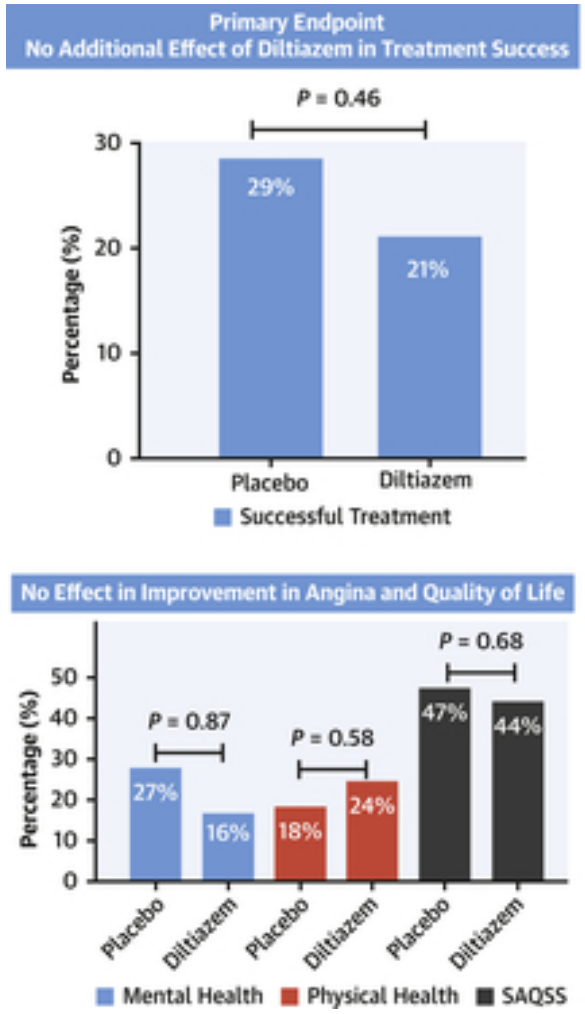
5. **Non cardiac pain**
   exclusion of 1-2-3

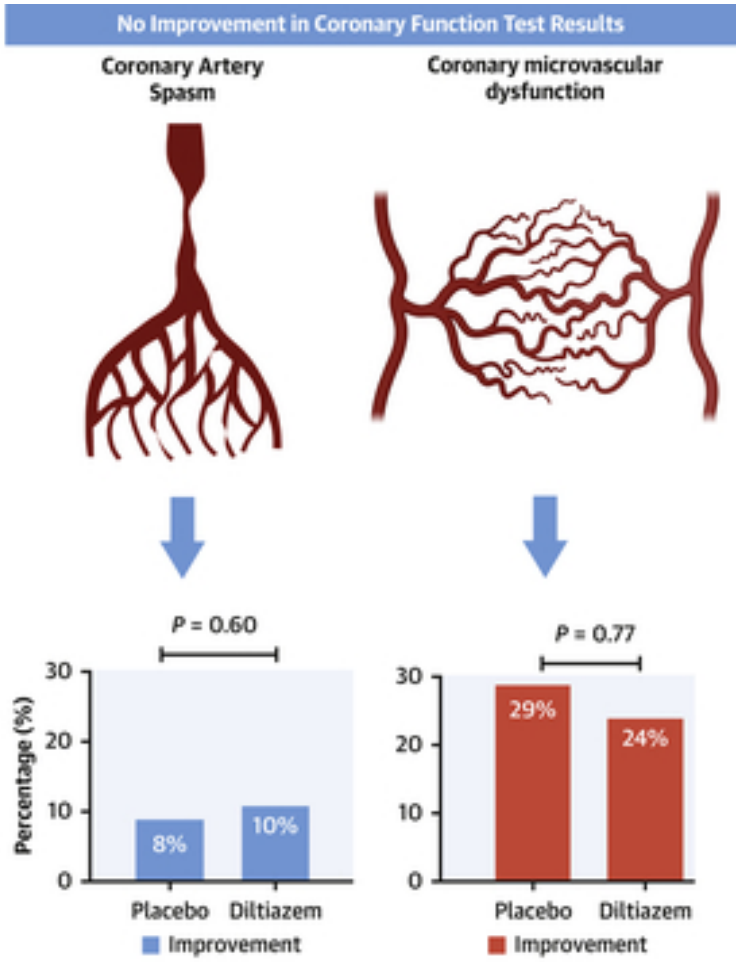


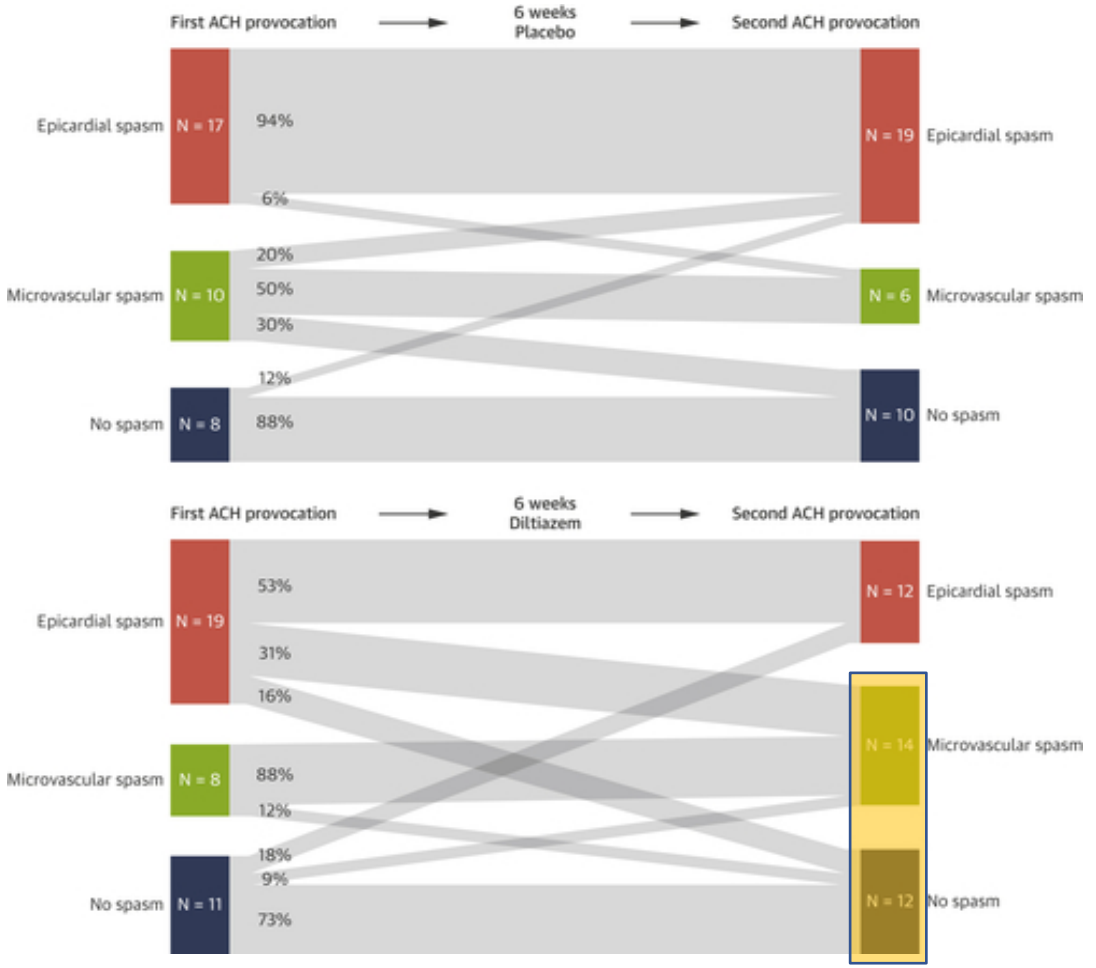
*Selective MV dysfunction: RRR <2.0 (+ IMR ≤25)

Kunadian EHJ 2020 (mod)

Empiric use of CCB: the EDIT-CMD trial







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

#FullPhysiology InDailyPractice

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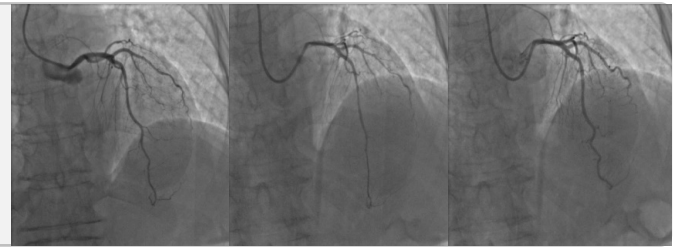
Resistive resistance ratio $= \frac{Trm * Pdr}{Thm * Pdh}$

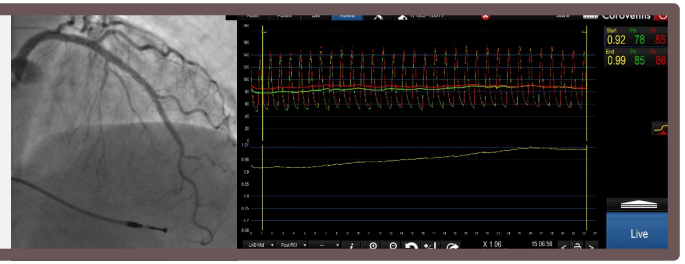
3 Vasomotor testing

- Ach



4 Post PCI Full Physiology assessment if applicable

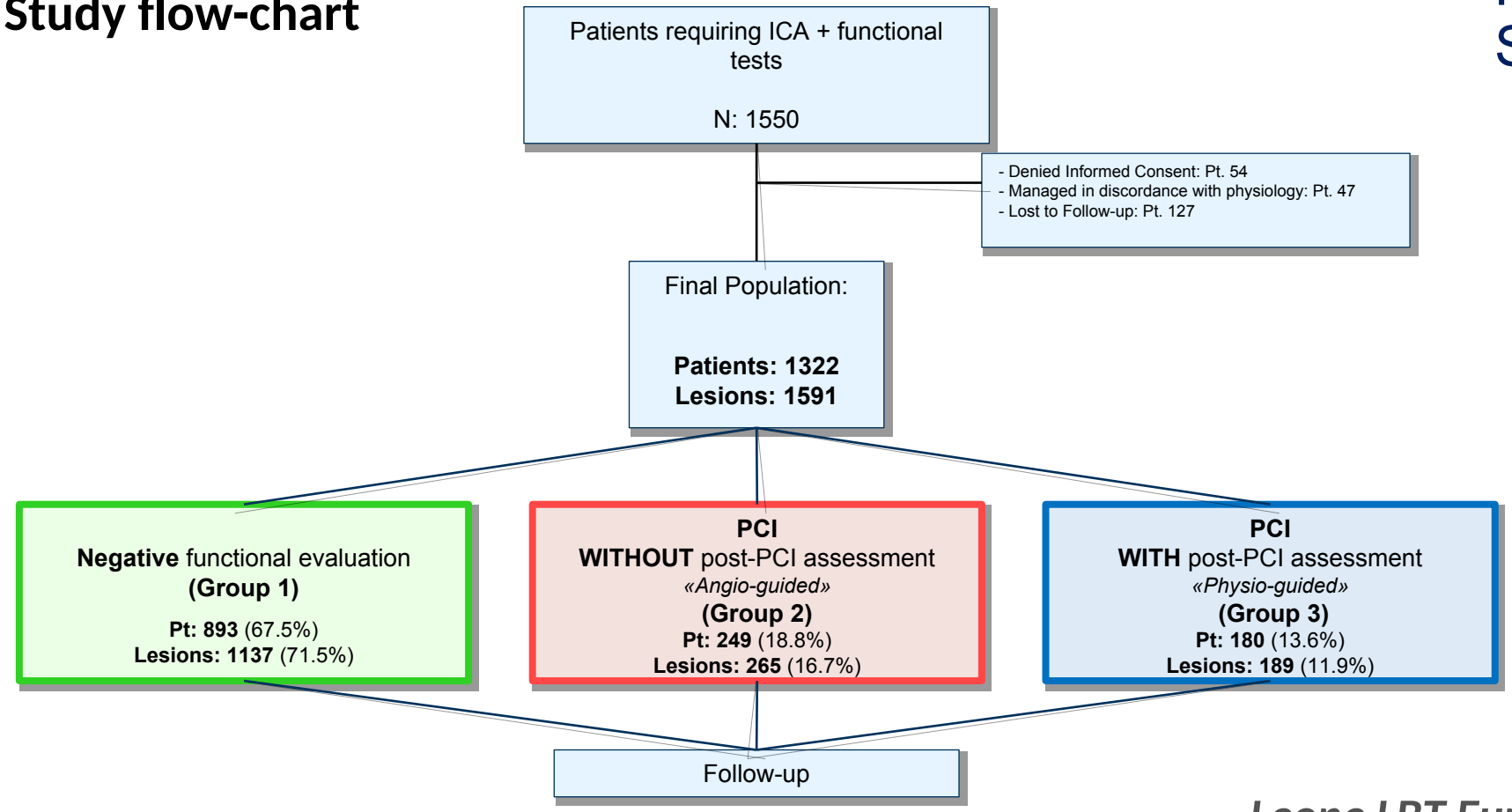
- NHPR/cFFR/IMR/CFR/FFR -> perform pullback



Importance of post PCI physiology

Study flow-chart

PROPHET-FFR Study



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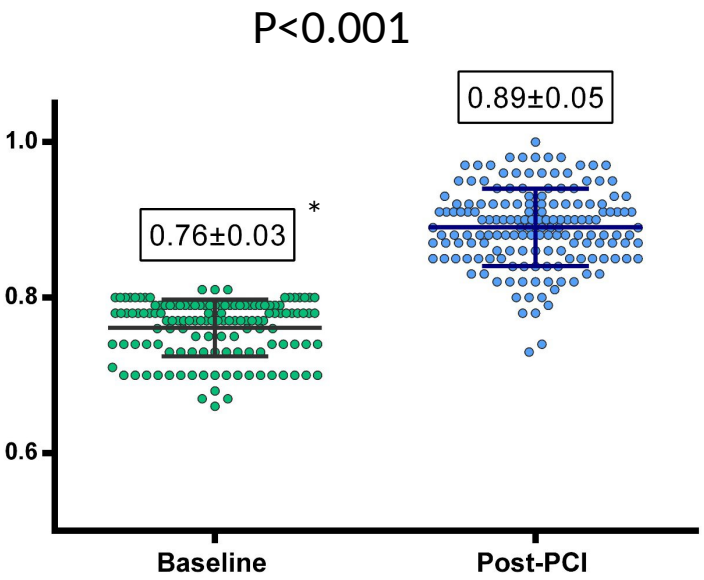
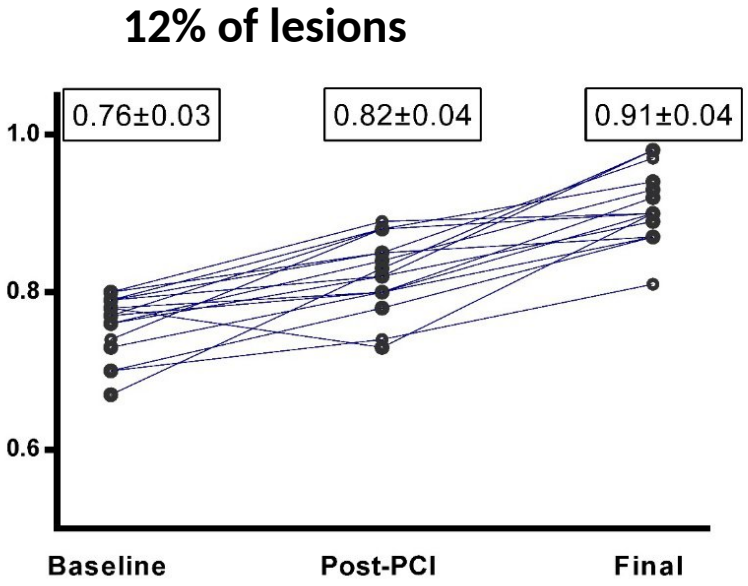
Importance of post PCI physiology

Post – PCI Physiological results (**Group 3**)

PROPHET-FFR Study





*

vs 0.76±0.03 in group 2 (p NS)

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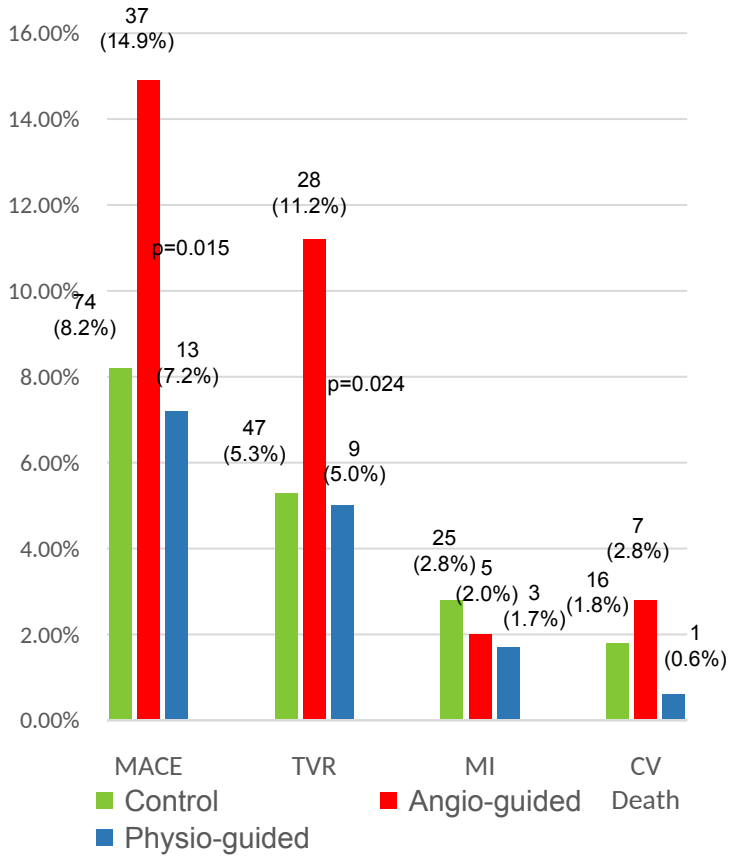
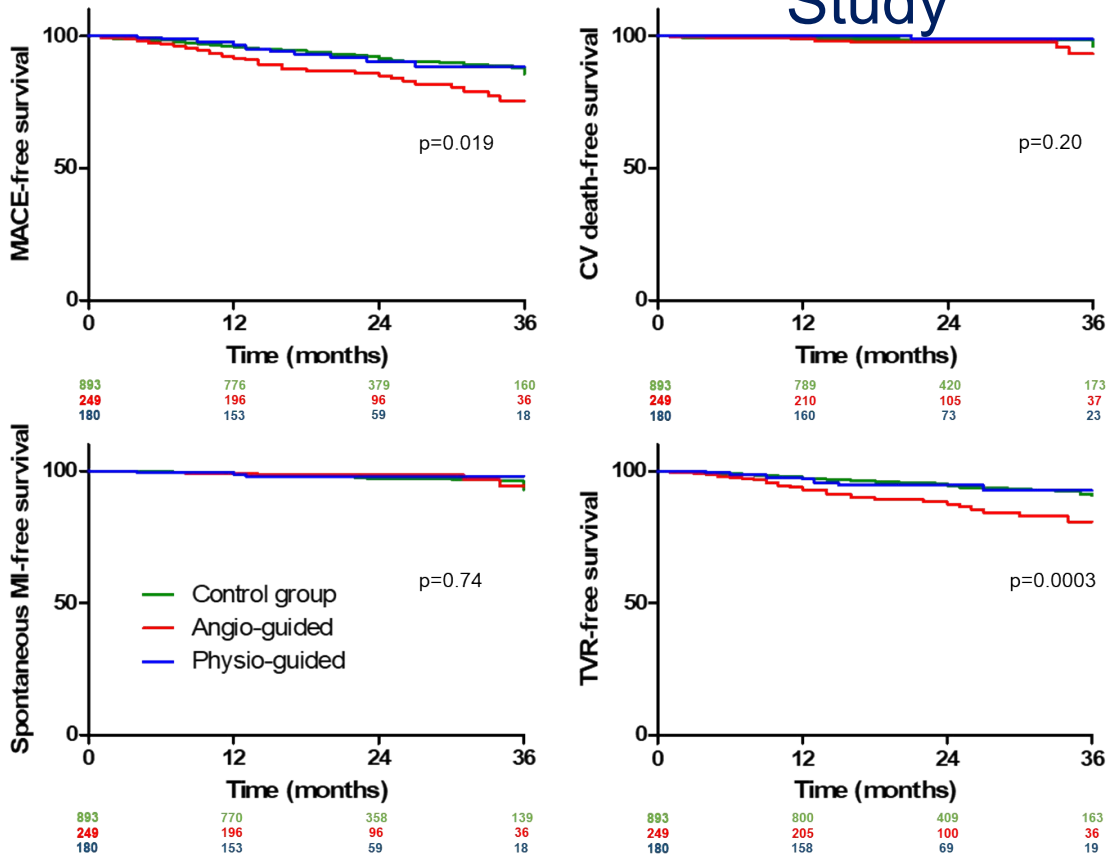
Importance of post PCI physiology

PROPHET-FFR Study



21 months (IQR 14-32)



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Conclusions

- We have relatively simple tools to comprehensively assess coronary circulation
- A correct diagnosis can have important therapeutic and prognostic implications
- INOCA has an important socio-economic impact and now can be treated appropriately only using an invasive guide using a pressure/thermodilution wire
- Comprenhensive functional assessment for INOCA can represent a useful approach also for a variety of other clinical settings

#Grazie