

Integration of the #Full Physiology Approach in Daily Practice

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William Fulton, MD thesis, University of Glasgow 1963



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.

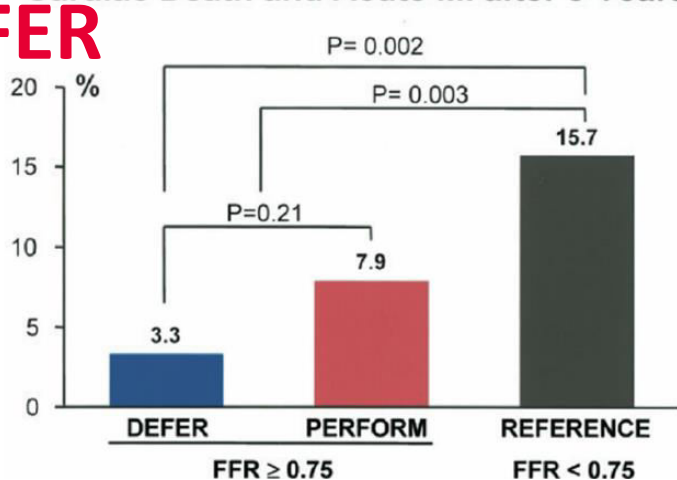
All contents provided by Dr. Leone unless otherwise noted



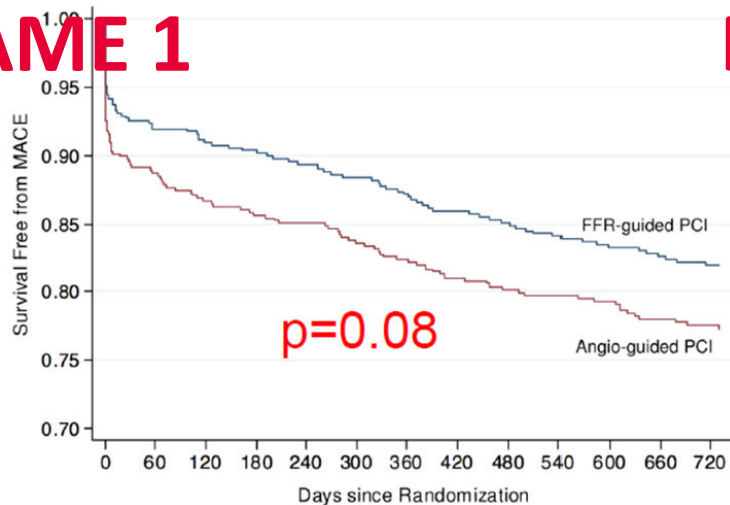
What ICs know about invasive physiology

DEFER

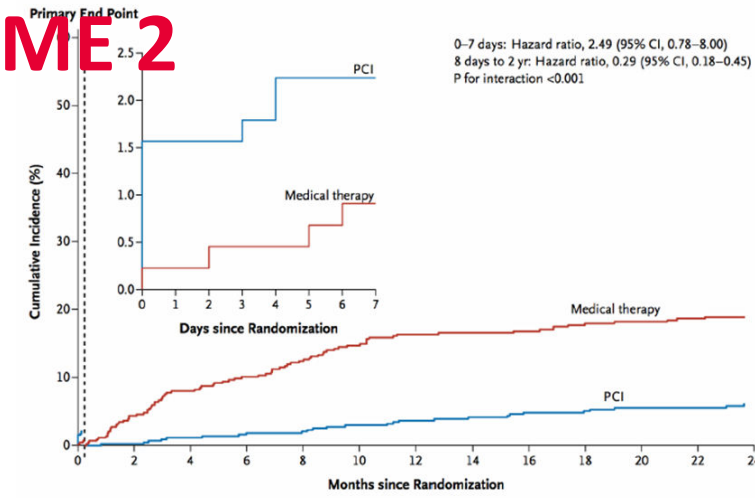
Cardiac Death and Acute MI after 5 Years



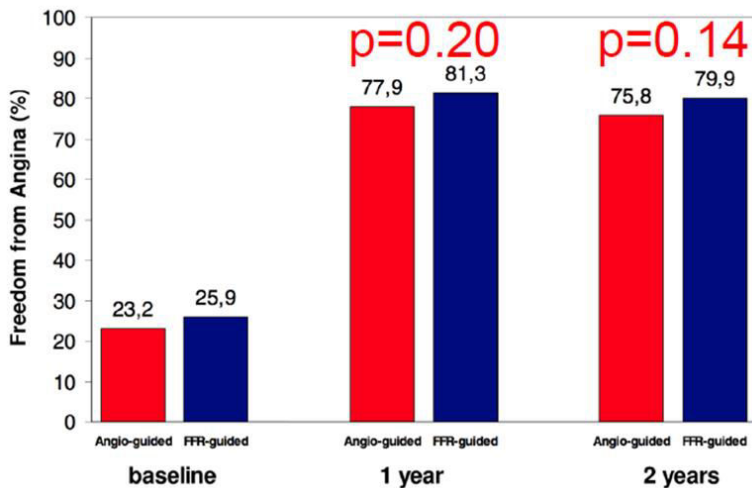
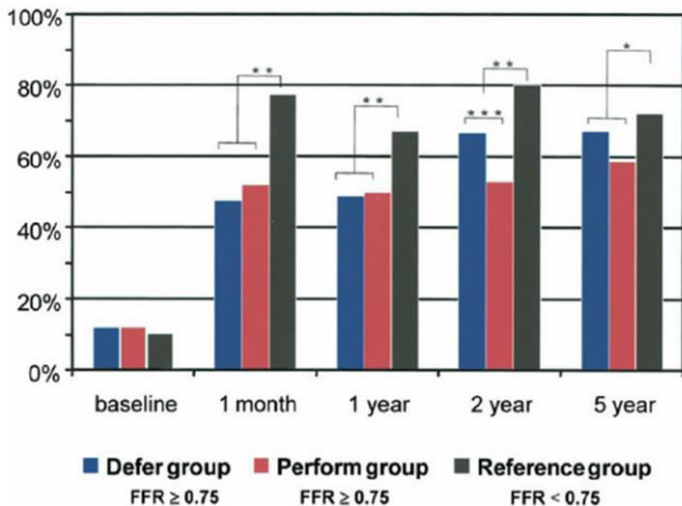
FAME 1



FAME 2



% Patients Free from Chest Pain

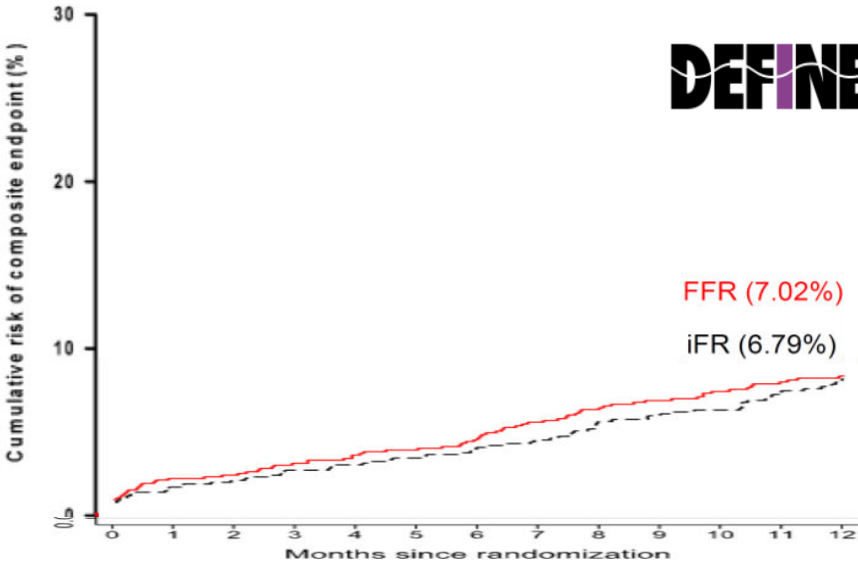


Time Point	No CCS I-II/IV No total	Randomised trial		Randomised trial compared to registry	
		RR (95% CI)	P value	RR (95% CI)	P value
Baseline					
PCI+MT	314/447	1.04 (0.95-1.13)	0.42	1.09 (0.96-1.24)	0.17
MT alone	298/440	1.00 (reference)		1.05 (0.92-1.20)	0.45
Registry	107/166			1.00 (reference)	
30 Days					
PCI+MT	45/441	0.36 (0.26-0.49)	<0.001	0.66 (0.42-1.04)	0.08
MT alone	123/431	1.00 (reference)		1.85 (1.25-2.73)	0.001
Registry	25/162			1.00 (reference)	
6 Months					
PCI+MT	33/440	0.41 (0.28-0.60)	<0.001	0.47 (0.29-0.76)	0.002
MT alone	80/434	1.00 (reference)		1.16 (0.77-1.73)	0.48
Registry	26/163			1.00 (reference)	
12 Months					
PCI+MT	26/437	0.39 (0.25-0.61)	<0.001	0.38 (0.23-0.64)	<0.001
MT alone	65/429	1.00 (reference)		0.96 (0.63-1.47)	0.86
Registry	25/159			1.00 (reference)	
24 Months					
PCI+MT	25/425	0.49 (0.31-0.77)	0.002	0.40 (0.23-0.69)	0.001
MT alone	51/424	1.00 (reference)		0.82 (0.52-1.30)	0.40
Registry	23/157			1.00 (reference)	

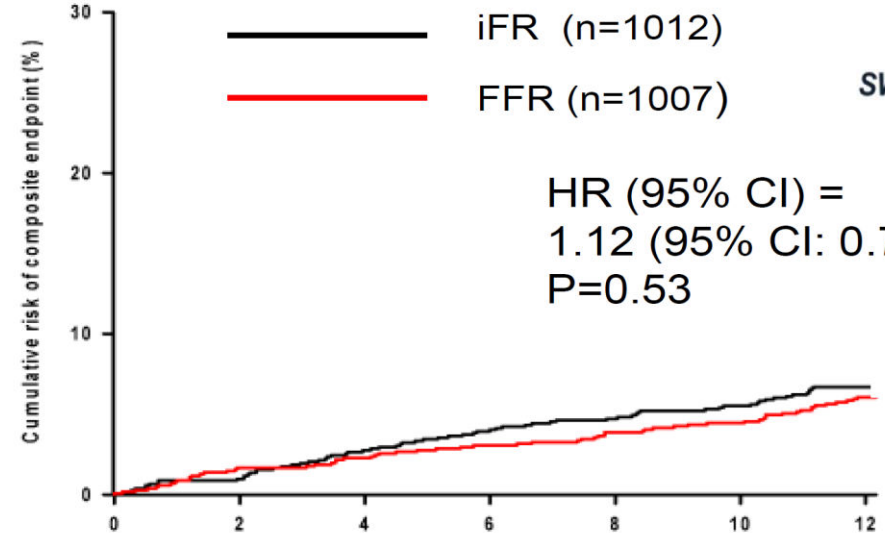


What ICs know about invasive physiology

DEFINE FLAIR



Variable	iFR Group (N=1242)	FFR Group (N=1250)	P Value†
Radial-artery approach — no. of patients (%)	896 (72.1)	888 (71.0)	0.54
Procedure time — min			
Median	40.5	45.0	0.001
Functionally significant lesions — no. (% of total vessels evaluated)‡	451 (28.6)	557 (34.6)	0.004
≥1 Functionally significant lesions present — no. of patients (%)§	426 (34.3)	486 (38.9)	0.02
Mean iFR	0.91±0.09	NA	
Mean FFR	NA	0.83±0.09	
Percent of lesions within the FFR range			
<0.60	NA	1.96	
0.60–0.90	NA	75.08	
>0.90	NA	22.96	
Revascularization performed — no. of patients (%)			
Total	590 (47.5)	667 (53.4)	0.003
CABG	25 (2.0)	42 (3.4)	0.04
PCI	565 (45.5)	625 (50.0)	0.02
Stents placed — no. (% of total stents placed)			
Total	822 (100)	906 (100)	0.86
Drug-eluting stent	811 (98.7)	893 (98.6)	
Bioresorbable vascular scaffold	11 (1.3)	13 (1.4)	
No. of stents placed per patient	0.66±0.92	0.72±0.96	0.09

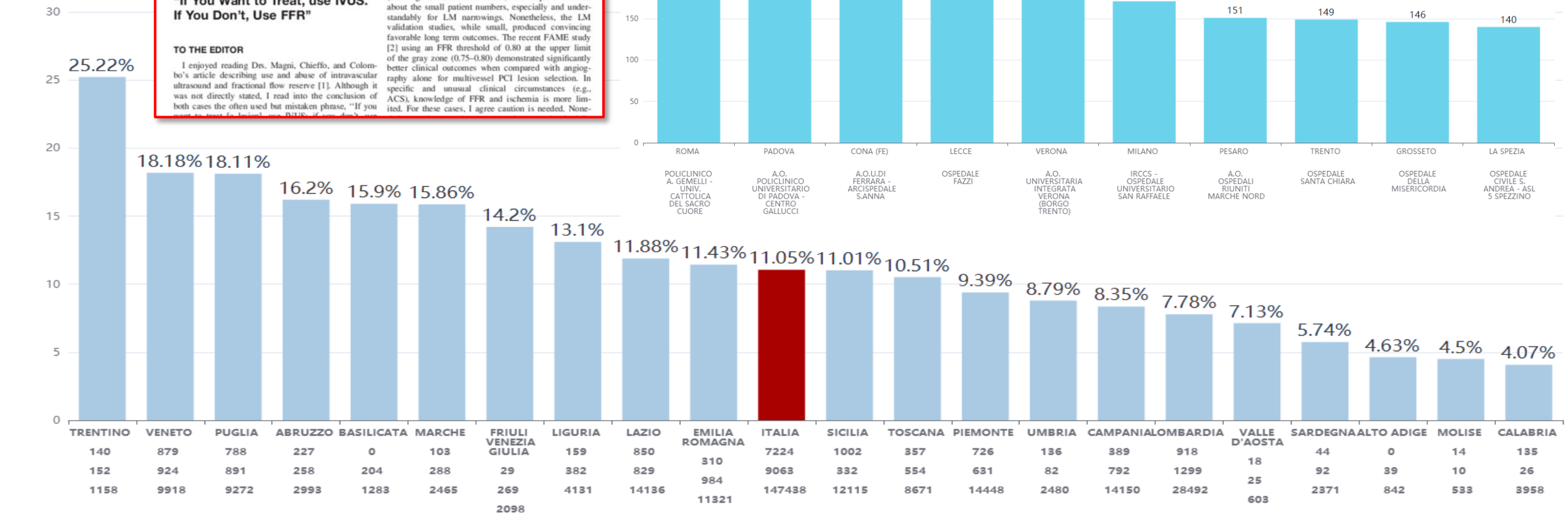


Characteristic	iFR Group (N=1012)	FFR Group (N=1007)	P Value
Procedure time — min†			0.09
Median	50.8	53.1	
Interquartile range	13.8–87.8	18.1–88.1	
Fluoroscopy time — min			0.57
Median	10.5	10.2	
Interquartile range	6.3–16.8	6.5–16.0	
Intravenous adenosine administered — no. of patients (%)	NA	695 (69.0)	
Total no. of lesions evaluated	1568	1436	
No. of lesions evaluated per patient	1.55±0.86	1.43±0.70	0.002
Hemodynamically important lesions — no. (% of total lesions evaluated)‡	457 (29.1)	528 (36.8)	<0.001
No. of hemodynamically important lesions per patient‡	0.45±0.71	0.52±0.68	0.05
Mean iFR	0.91±0.10	NA	
Mean iFR in hemodynamically important lesions‡	0.80±0.13	NA	
Mean FFR	NA	0.82±0.10	
Mean FFR in hemodynamically important lesions‡	NA	0.72±0.08	
Total no. of stents placed	698	787	
No. of stents placed per patient undergoing PCI	1.58±1.08	1.73±1.19	0.05
CABG as primary revascularization procedure — no. of patients (%)	93 (9.2)	113 (11.2)	0.13
Revascularization performed — no. of patients (%)	536 (53.0)	569 (56.5)	0.11



How ICs translate invasive physiology in practice

2021



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

Letter to the Editor

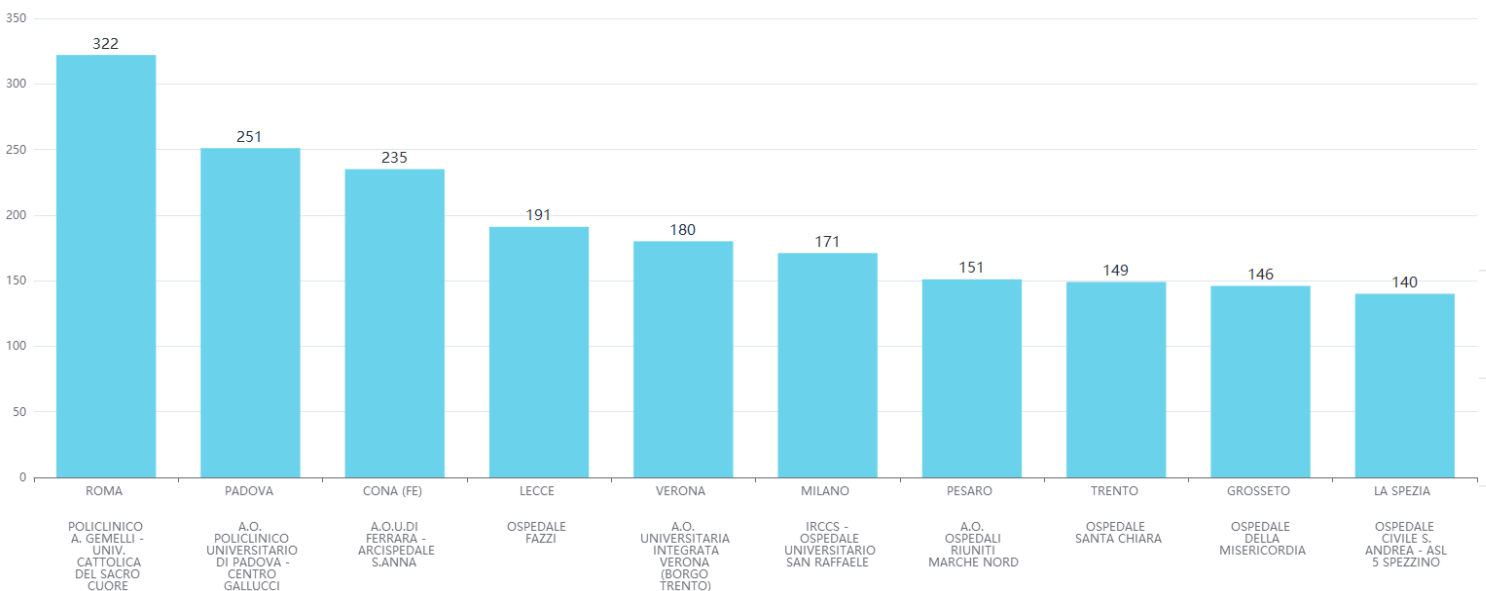
Use and Abuse of IVUS and FFR by Magni V et al. or Why You Shouldn't Believe The Saying, "If You Want to Treat, use IVUS. If You Don't, Use FFR"

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 want to treat, use IVUS; if you don't, use FFR."

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-



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



The #Full Physiology group



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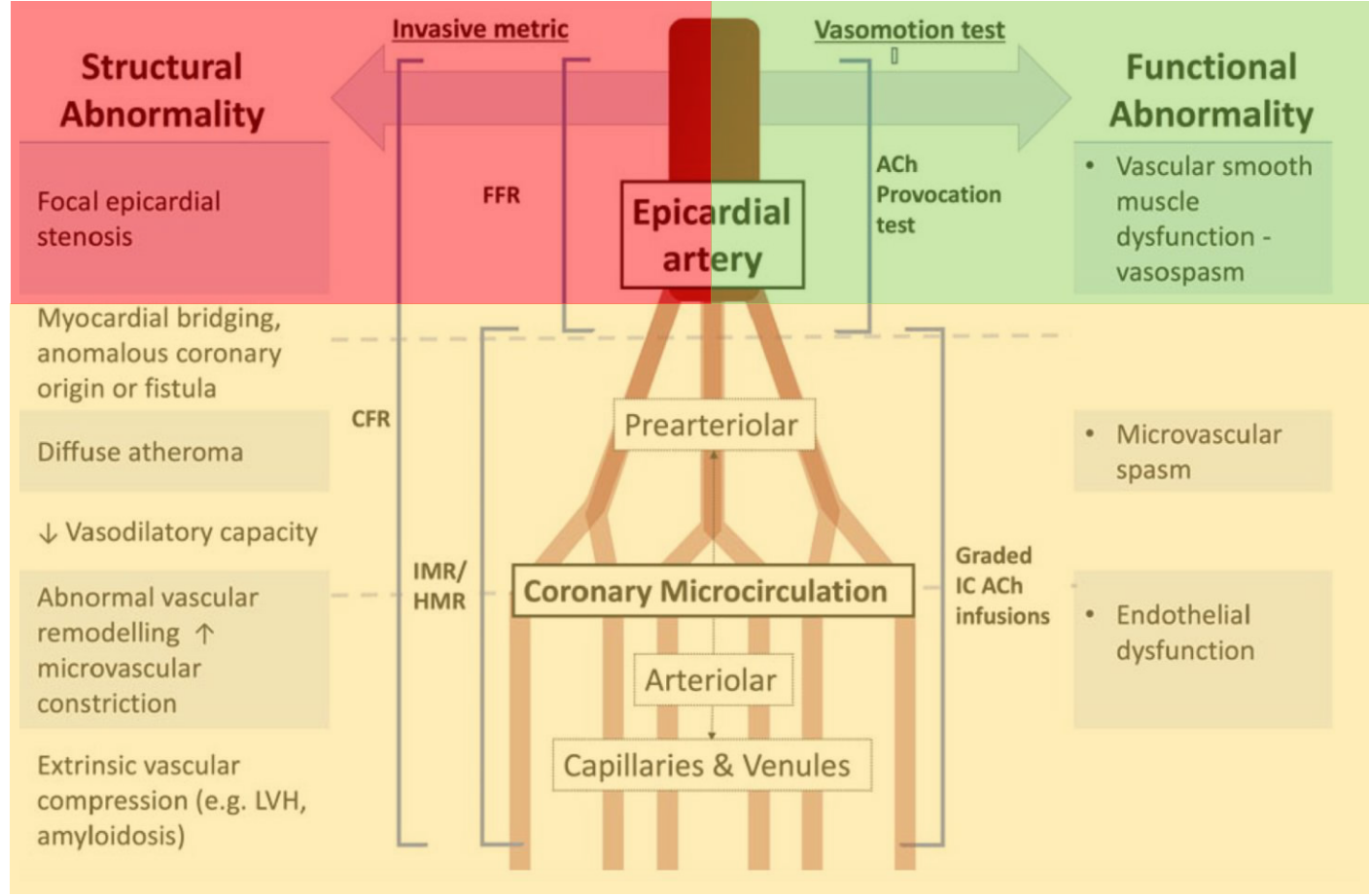
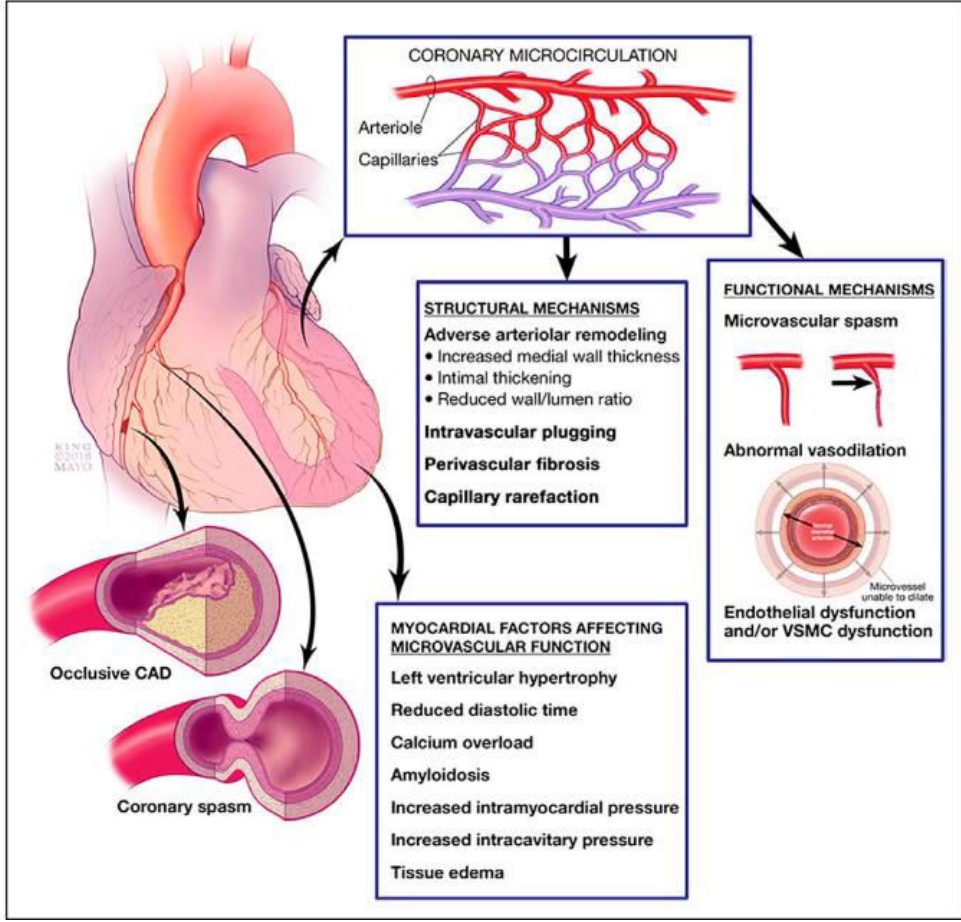
MATTEO TEBALDI
A.O. Ospedali Marche Nord, Pesaro



- No Club / «niche»
- Sharing a common language
- Expressing the full potential of physiology in daily practice (case-based approach)



F. Ph. For Structural and Functional abn.

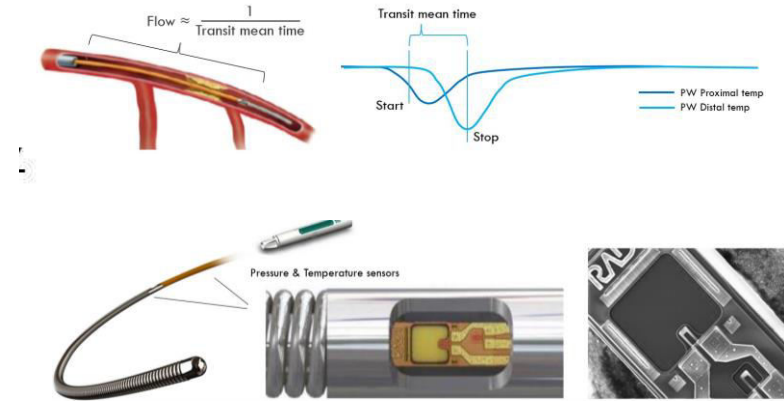
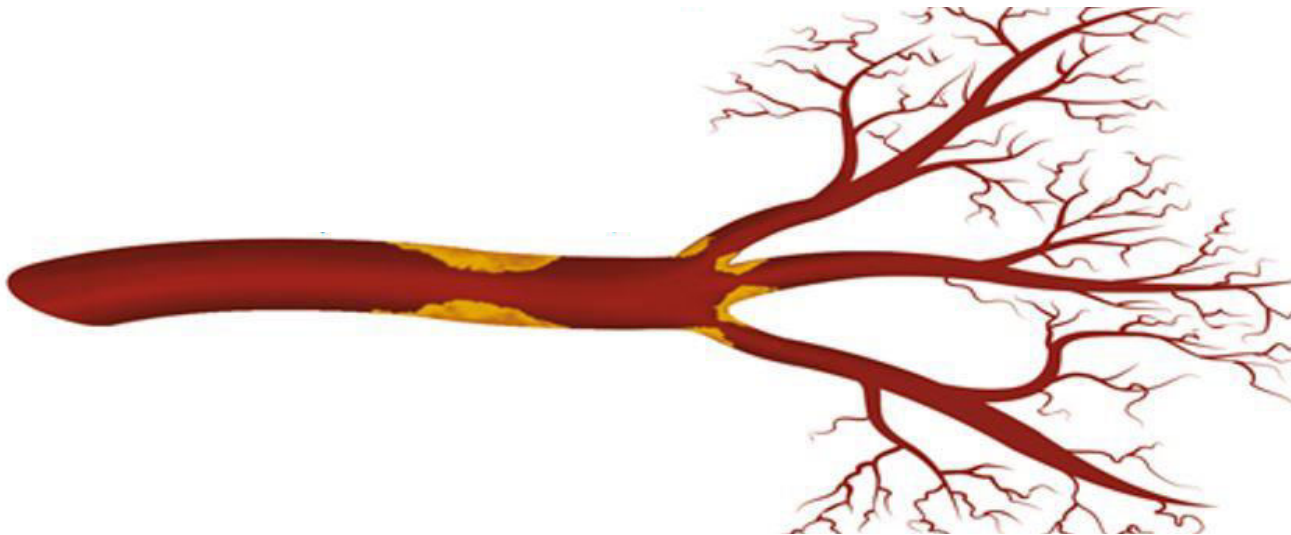


Courtesy from T. Engstroem

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 Ado and Ach protocols

Adenosine 140 mcg/Kg/min

X vials (see below) of Adenosine diluted in 60 ml di NaCl 0.9% and infused in 2'

Weight	Adenosine vials
60 Kg	2.8 vials
70 Kg	3.3 vials
80 Kg	3.7 vials
90 Kg	4.2 vials
100 Kg	4.7 vials

Acetilcholine

- 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)



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 delle disfunzioni vascolari coronariche.

Parere CTS: La CTS esprime parere non favorevole.

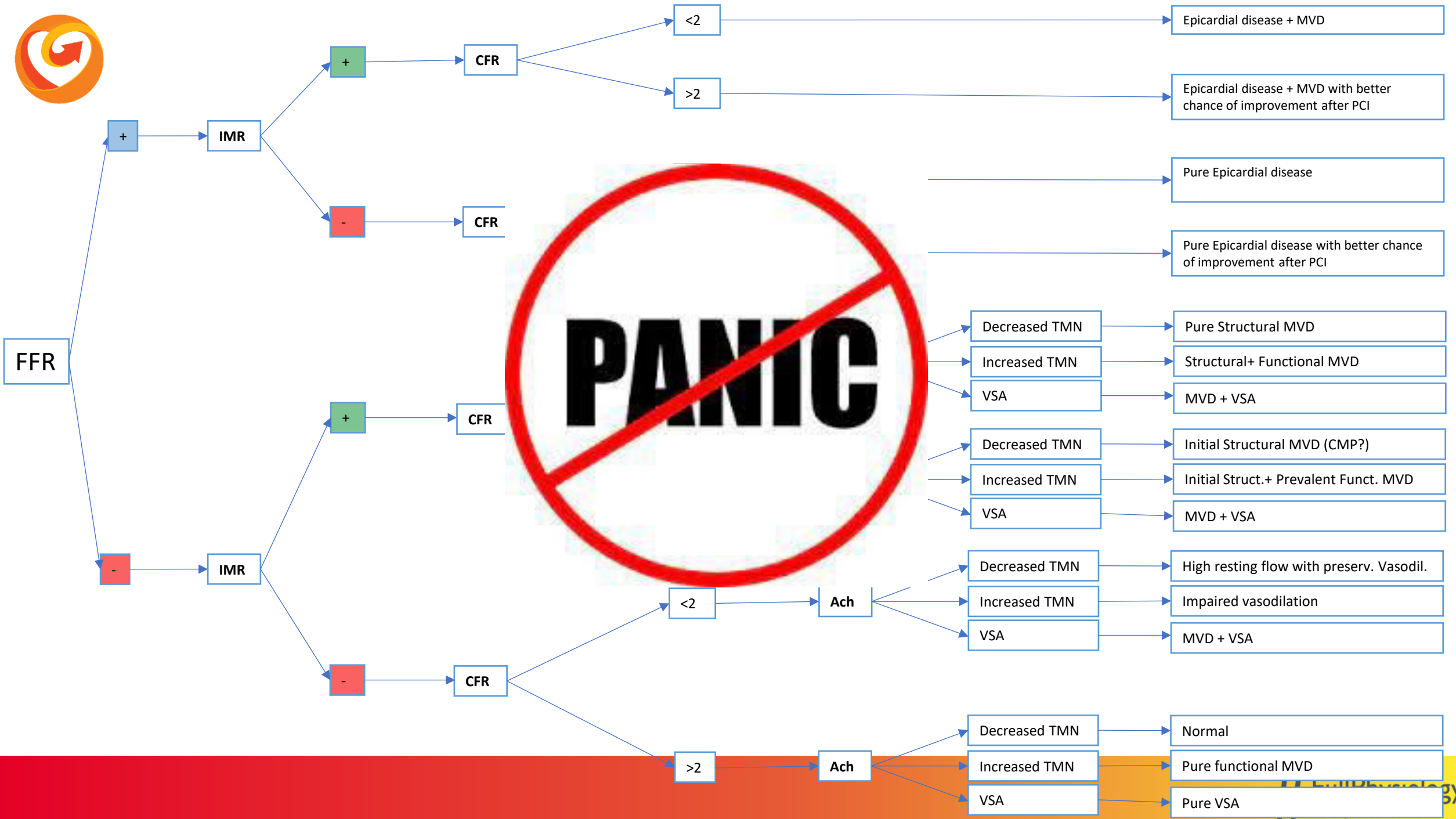
Off label



ESC guidelines for CCS

Recommendations	Class ^a	Level ^b
<u>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.</u> ^{412,413}	IIa	B
<u>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.</u> ^{412,438–440}	IIb	B
<u>Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR.</u> ^{430–432,441}	IIb	B

Recommendations	Class ^a	Level ^b
<u>An ECG is recommended during angina if possible.</u>	I	C
<u>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.</u>	I	C
<u>Ambulatory ST-segment monitoring should be considered to identify ST-segment deviation in the absence of increased heart rate.</u>	IIa	C
<u>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.</u> ^{412,414,438–440}	IIa	B



PANIC



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





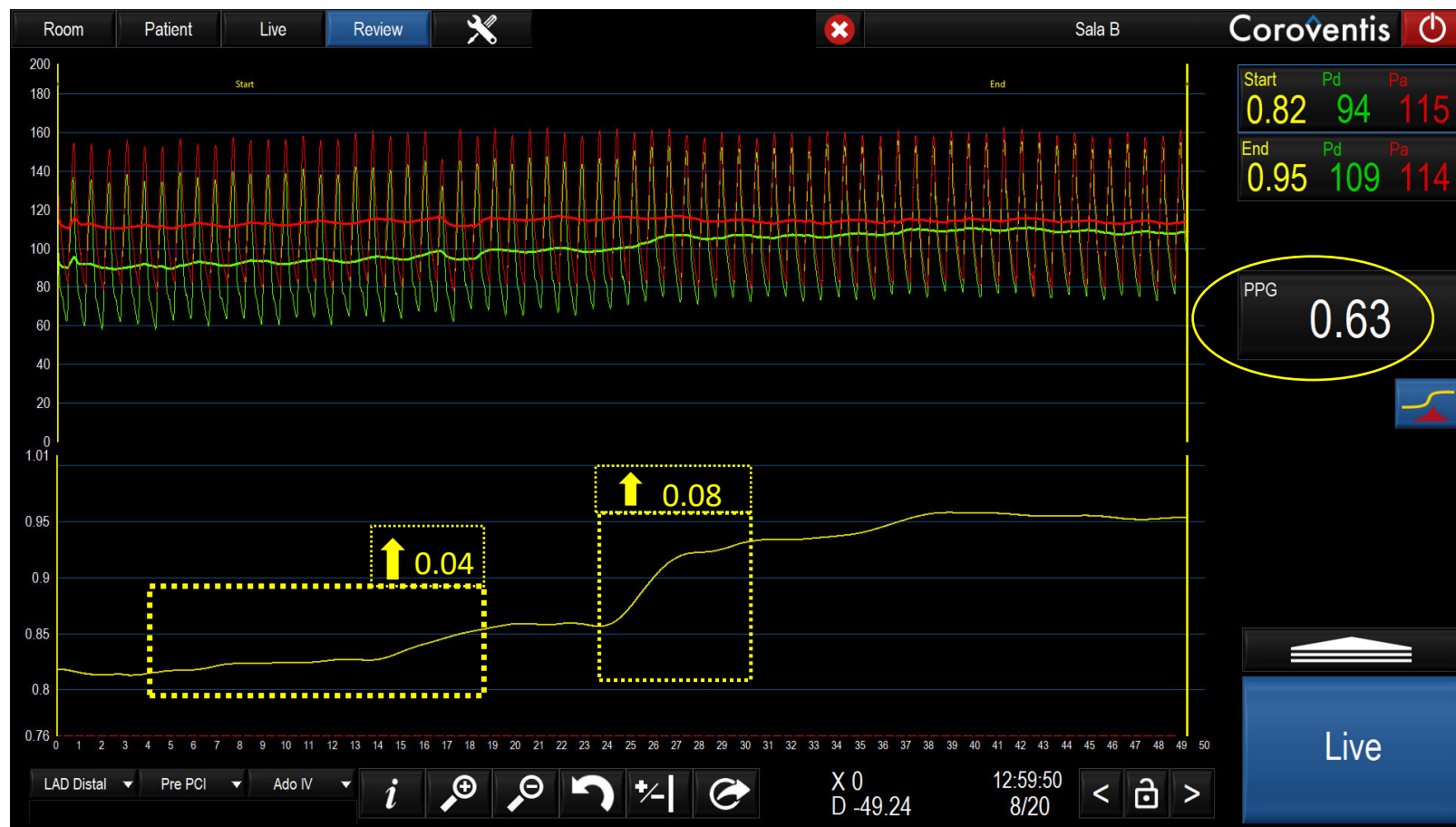
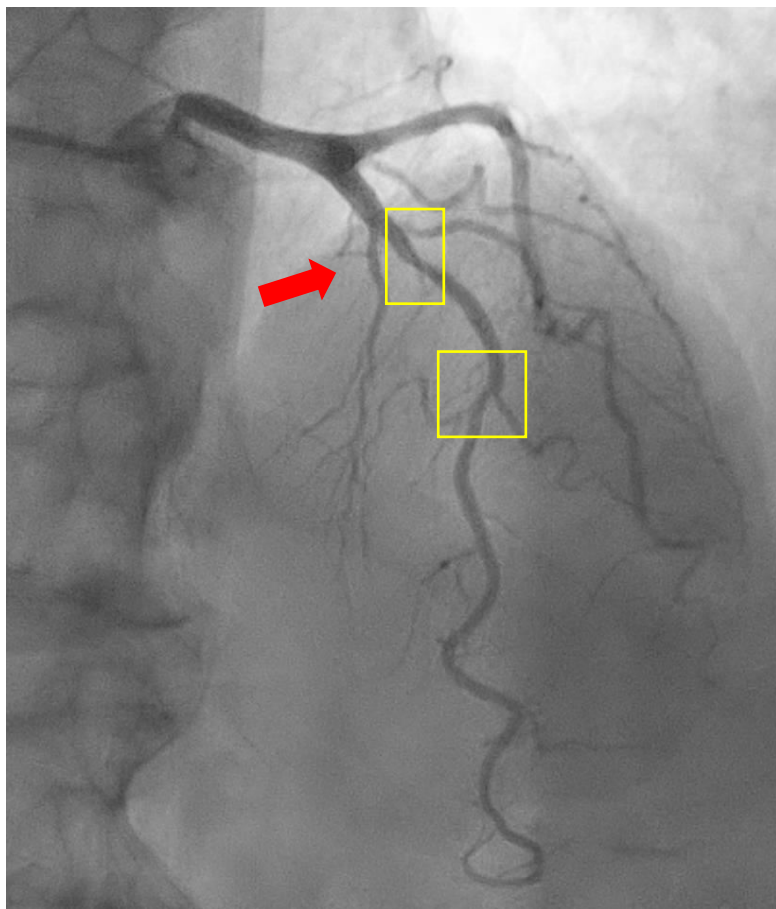
Epicardial disease assessment

The importance of pullback





Clinical case: Epicardial disease assessment



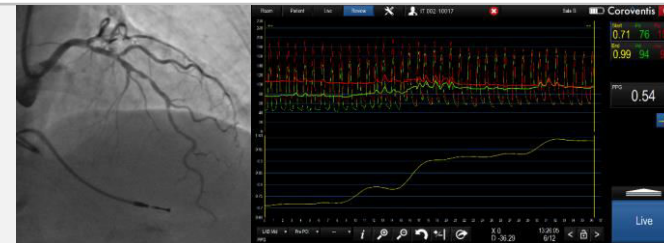


What is #FullPhysiology assessment

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$$*Resistive\ resistance\ ratio = \frac{T_{rm} * P_{dr}}{T_{hm} * P_{dh}}$$



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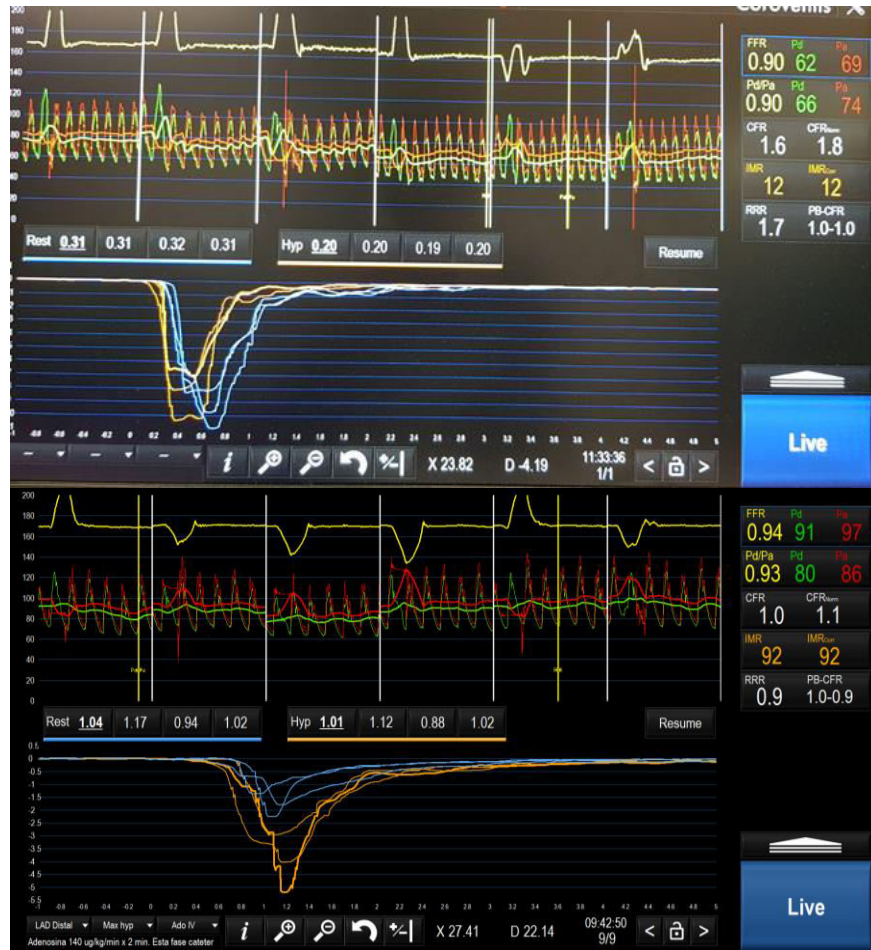
Post PCI Full Physiology assessment if applicable

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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%

CFR > 2
IMR < 25
Normal

CFR < 2
IMR < 25
Impaired Vasodilation

CFR < 2
IMR ≥ 25
Abnormal MV resistance

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

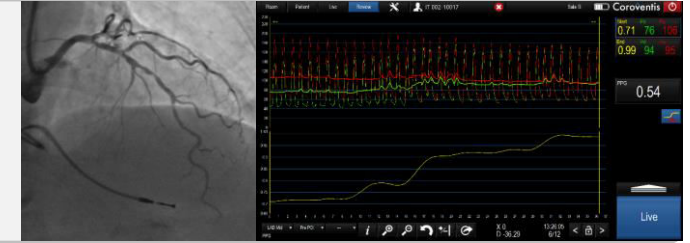


What is #FullPhysiology assessment

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$$*Resistive\ resistance\ ratio = \frac{T_{rm} * P_{dr}}{T_{hm} * P_{dh}}$$



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Vasomotor testing

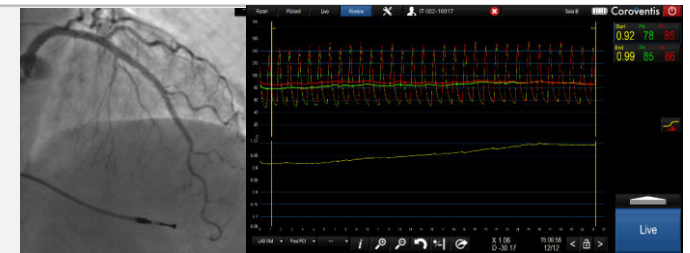
- Ach



4

Post PCI Full Physiology assessment if applicable

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



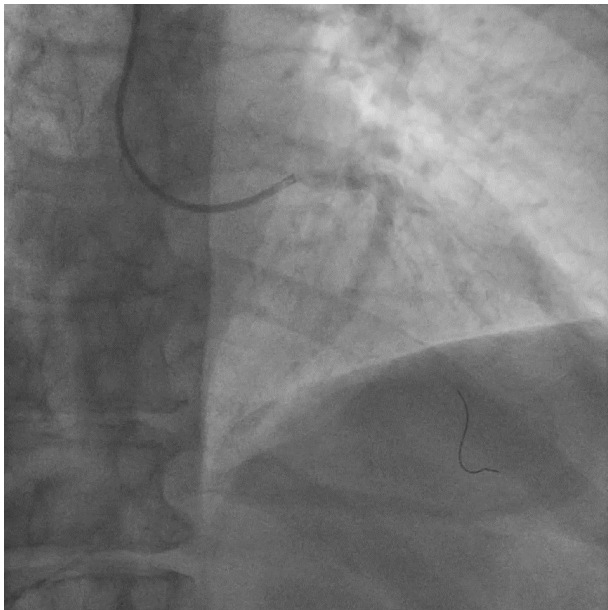
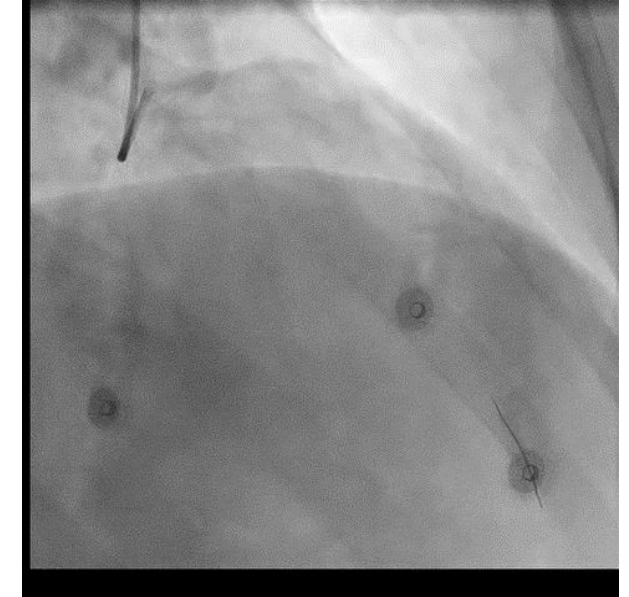


Diagnosis according to COVADIS definitions

Vasospastic angina

J. F. Beltrame et al., Eur Heart J 38, 2565 (2017)

Vasospastic angina	Epicardial spasm	Angina symptoms during ACh bolus (e.g. 100 µg acetylcholine over 20 seconds) AND: <ul style="list-style-type: none"> • ST-segment deviation on ECG • >90% epicardial coronary constriction during ACh reduction[34]
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Coronary Microvascular Dysfunction

P. Ong et al., Int J Cardiol 250, 16 (2018)

Disorder	Symptoms	Clinical measurement
Microvascular angina	Abnormal microvascular resistance	<ul style="list-style-type: none"> • IMR ≥ 25[27] • Hyperaemic microvascular resistance ≥ 2.5 mmHg/cm/s[28]
	Impaired coronary vasorelaxation	<ul style="list-style-type: none"> • CFR by thermodilution < 2.0[25]
Microvascular spasm	Angina symptoms with ACh infusion AND:	<ul style="list-style-type: none"> • ST-segment deviation on ECG • No significant epicardial coronary spasm ($< 90\%$ diameter reduction)



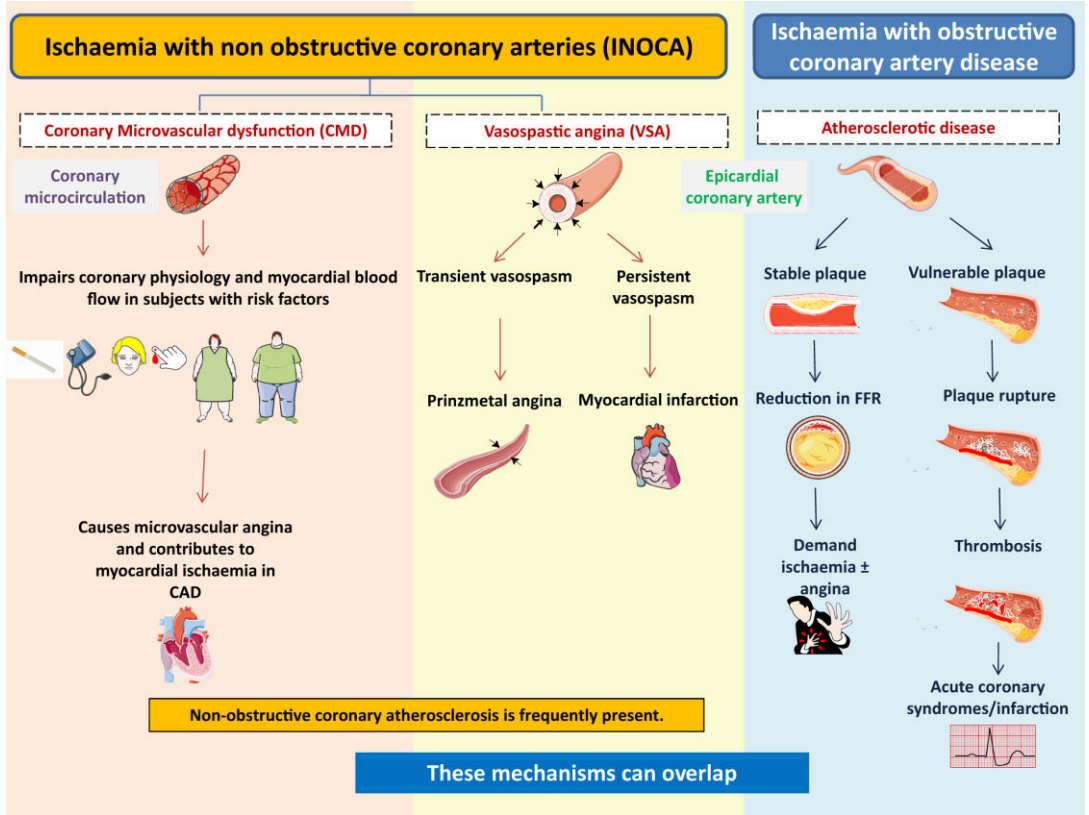
Terminology: A continuum of Angina Endotypes on CCS

- 1 Obstructive Epicardial CAD**
 - NHPR ≤ 0.89 and/or cFFR ≤ 0.83 and/or FFR ≤ 0.80
- 2 Microvascular angina**
 - Structural: IMR >25**
 - Functional*: 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



Kunadian EHJ 2020 (mod)
*+MV spasm: angina + ST changes and no epicardial spasm (+ \uparrow Tmn) by COVADIS definition

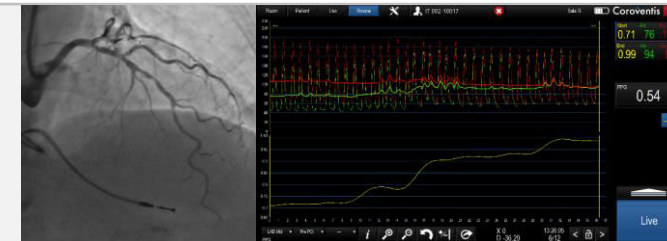


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$$*Resistive\ resistance\ ratio = \frac{T_{rm} * P_{dr}}{T_{hm} * P_{dh}}$$



3

Vasomotor testing

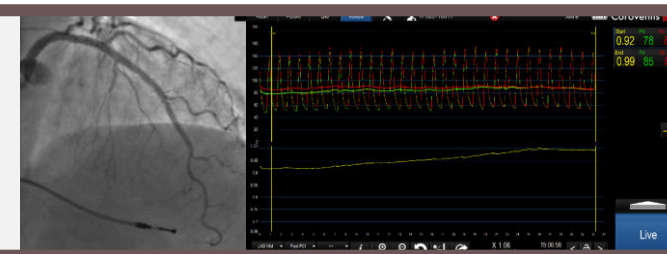
- Ach



4

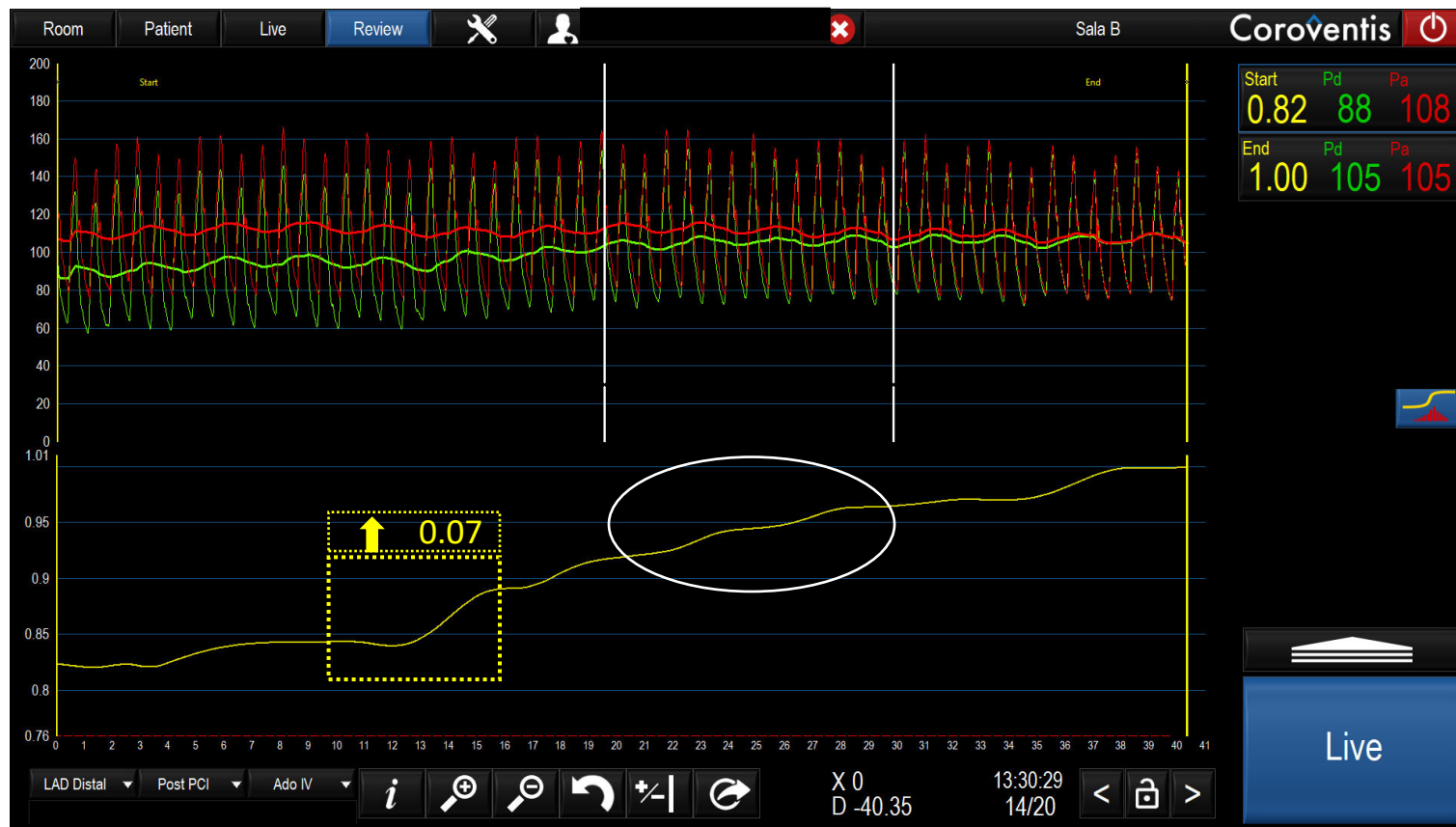
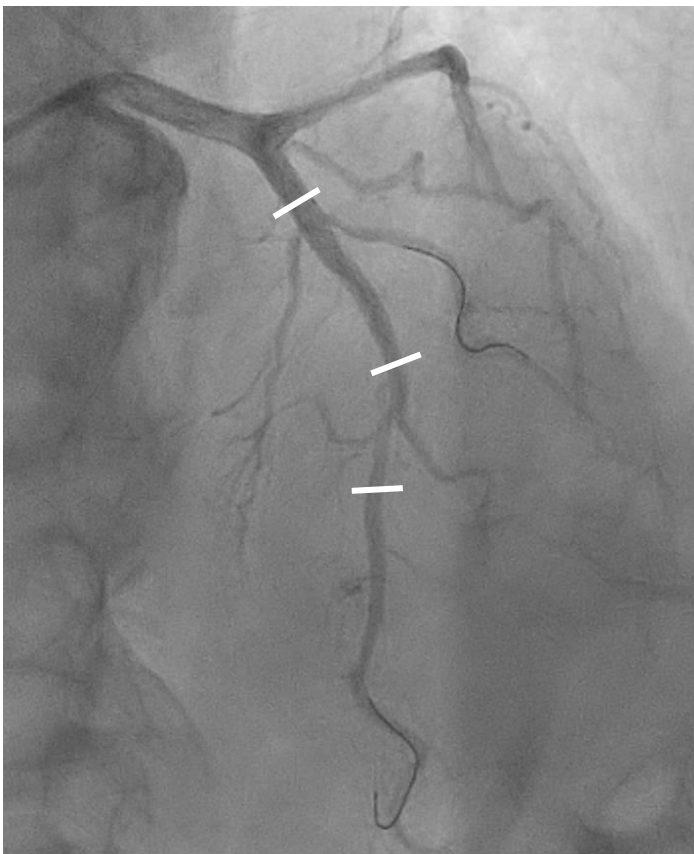
Post PCI Full Physiology assessment if applicable

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





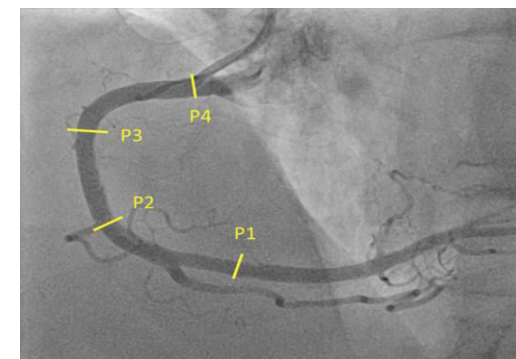
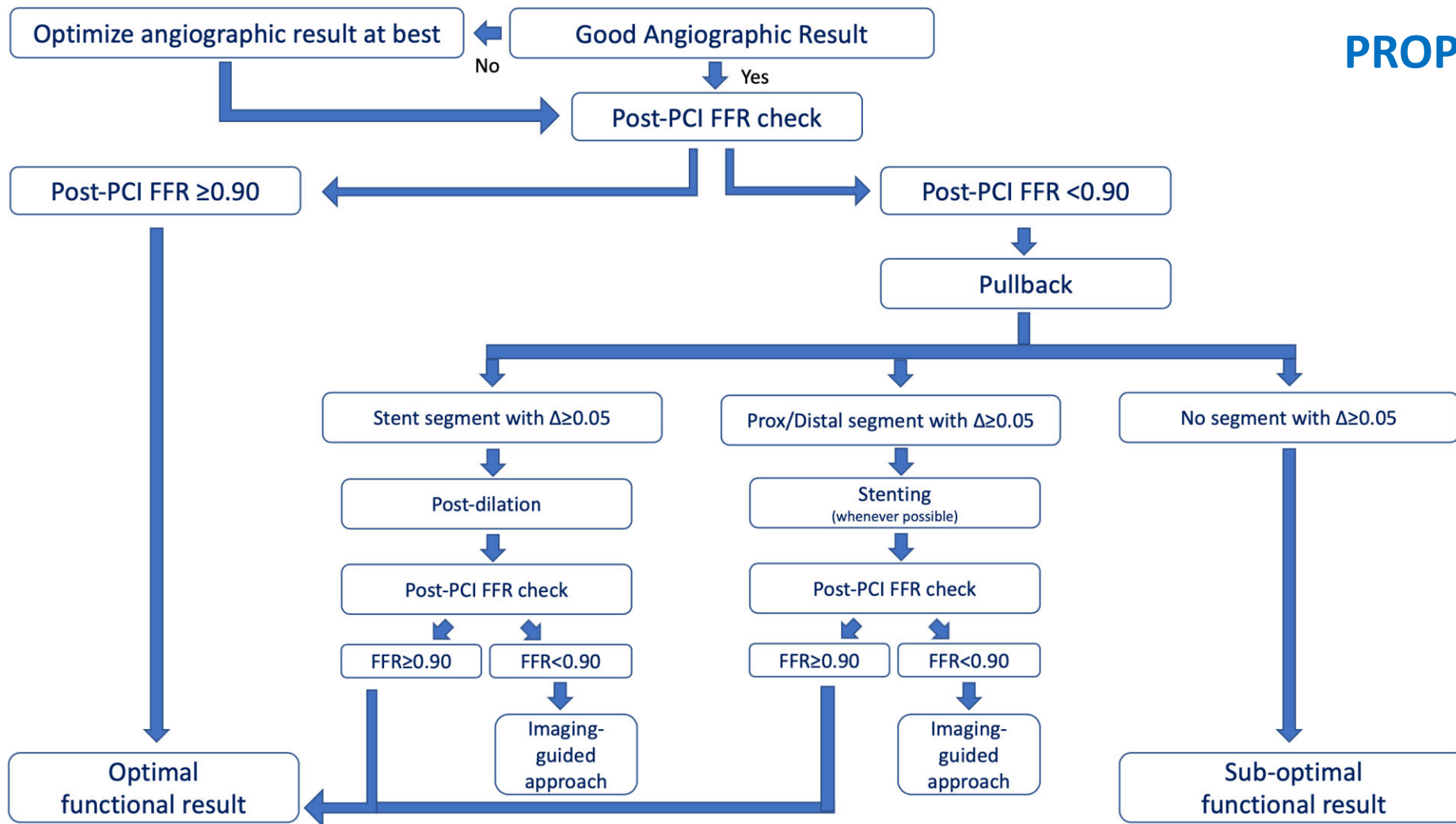
Pullback assessment in hyperemia post PCI





How to manage an unsatisfactory post-PCI FFR

PROPHET-FFR

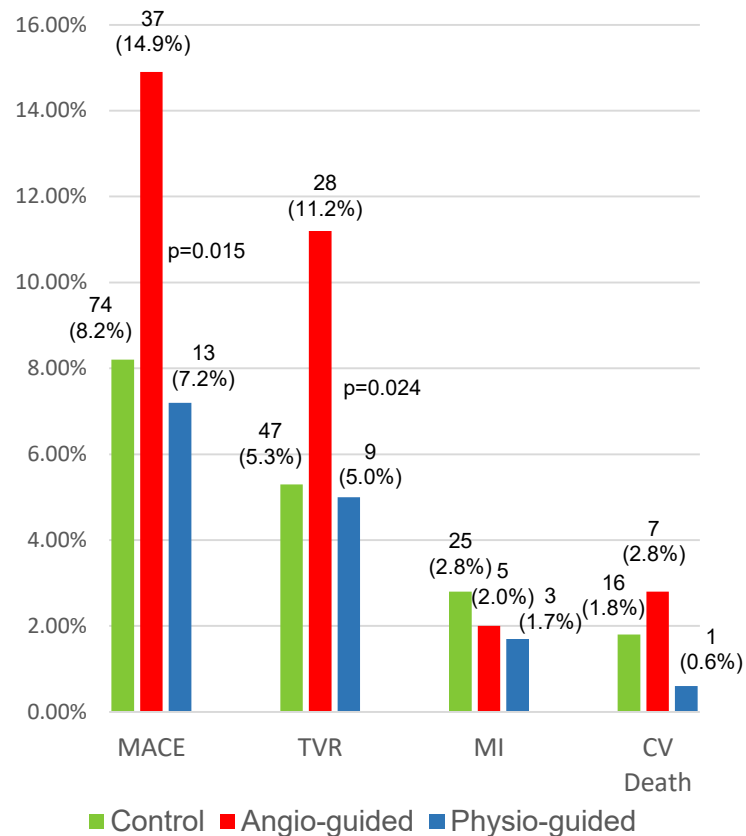


- P1: 20mm distal of stent
- P2: distal stent edge
- P3: proximal stent edge
- P4: ostium (drift)

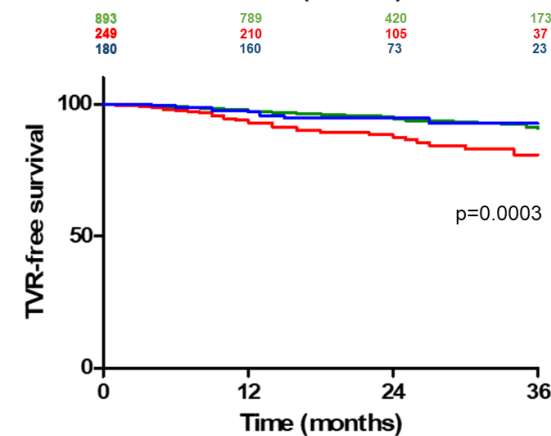
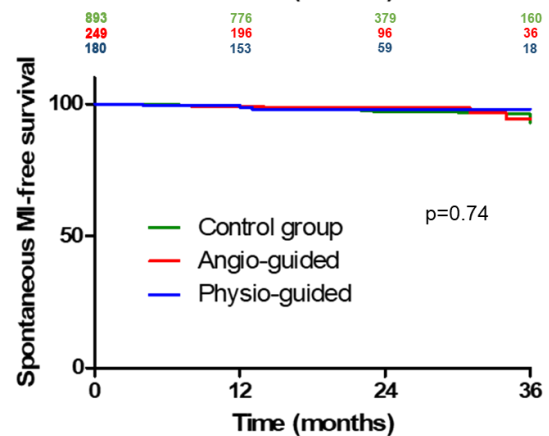
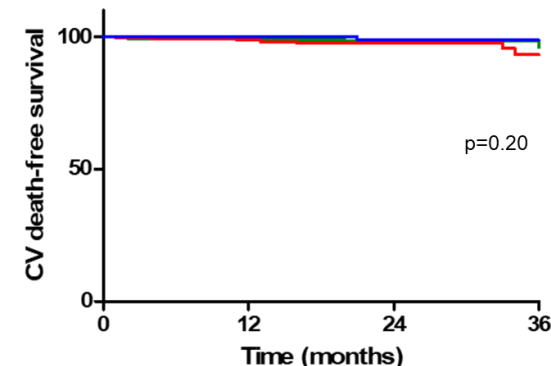
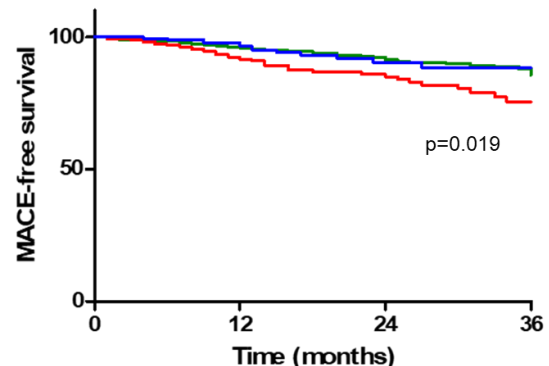


Importance of post PCI physiology

PROPHET-FFR Study



21 months (IQR 14-32)



Leone LBT EuroPCR 2022

Leone Frontiers Cardiovasc Med 2022



My personal «Guidelines»

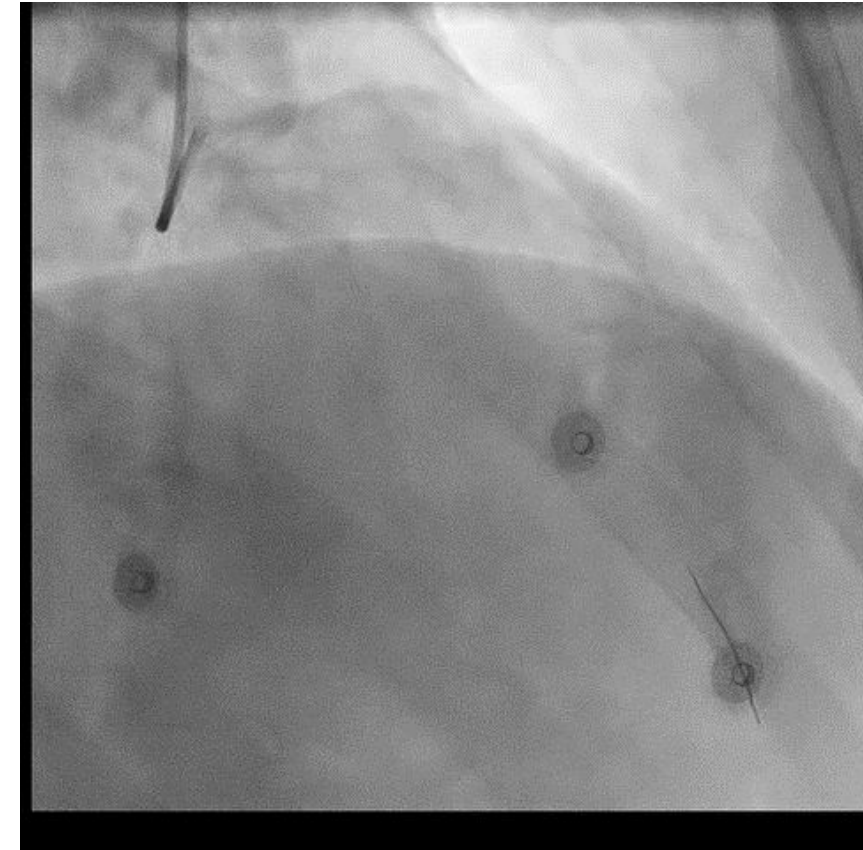
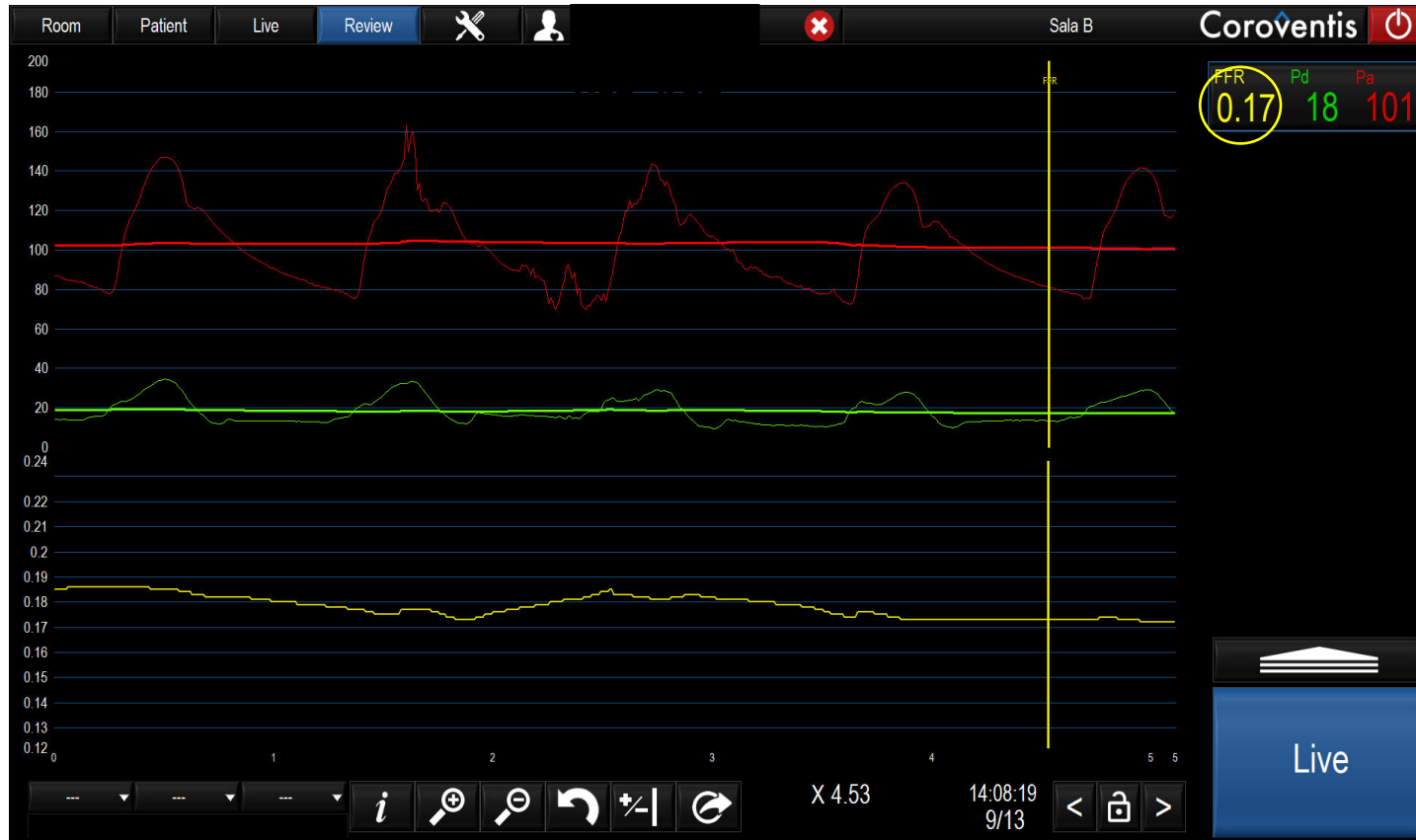
Recommendation	Class	Evidence
Lesion deferral using only a single NHPR	III	C
Assessment of microcirculation (CFR, IMR, RRR etc) and vasoreactivity testing in non-obstructive lesions assessed physiologically (FFR>0.80 a/o NHPR>0.89 a/o cFFR>0.88)	I	A
Vasoreactivity testing using Ach without invasive physiological assessment	III	C
Pullback manoeuvre in physiologically significant lesions (FFR≤0.80 a/o NHPR≤0.89 a/o cFFR≤0.83)	I	A
Pullback Pressure Gradient (PPG) index to quantify disease diffuseness	IIa	A
Physiological re-assessment after PCI in physiologically-indicated lesions treated by PCI	I	A
cFFR/NHPR combined approach before and after PCI in physiologically significant lesions	IIb	C
Physiology-guided PCI with DCB	IIb	B
Physiological assessment with pressure/thermodilution wire during Ach administration	IIb	C



#FullPhysiology 2.0

Invasive Functional demonstration of Epicardial Spasm

- Typical chest pain
- ECG changes: ST segment elevation
- Epicardial spasm (>90%) with distal occlusion of LAD

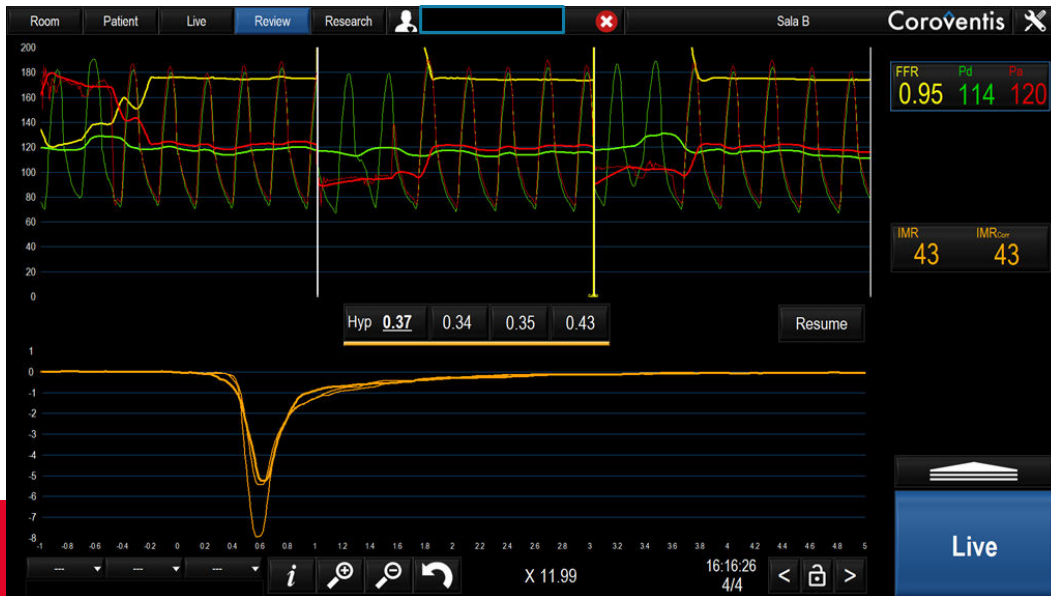
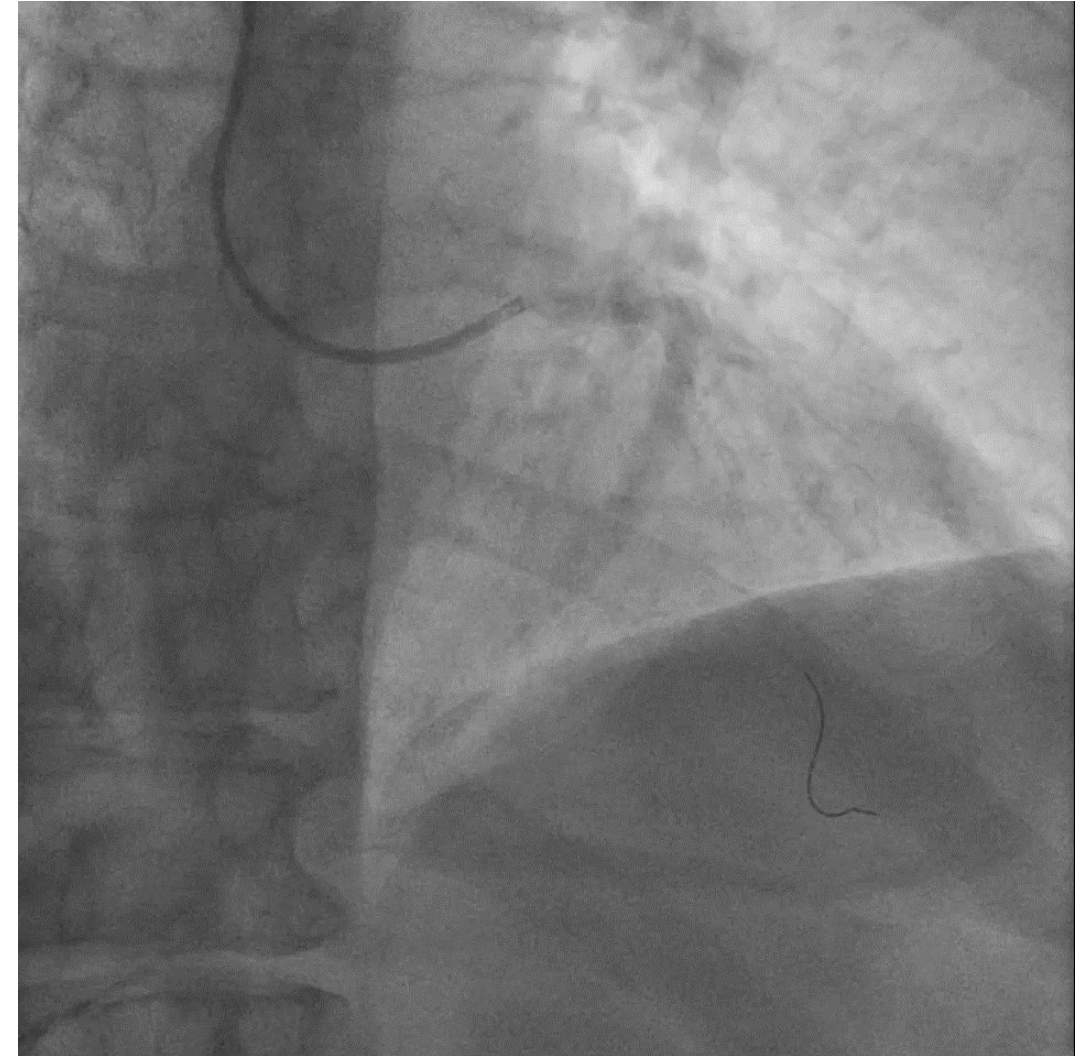
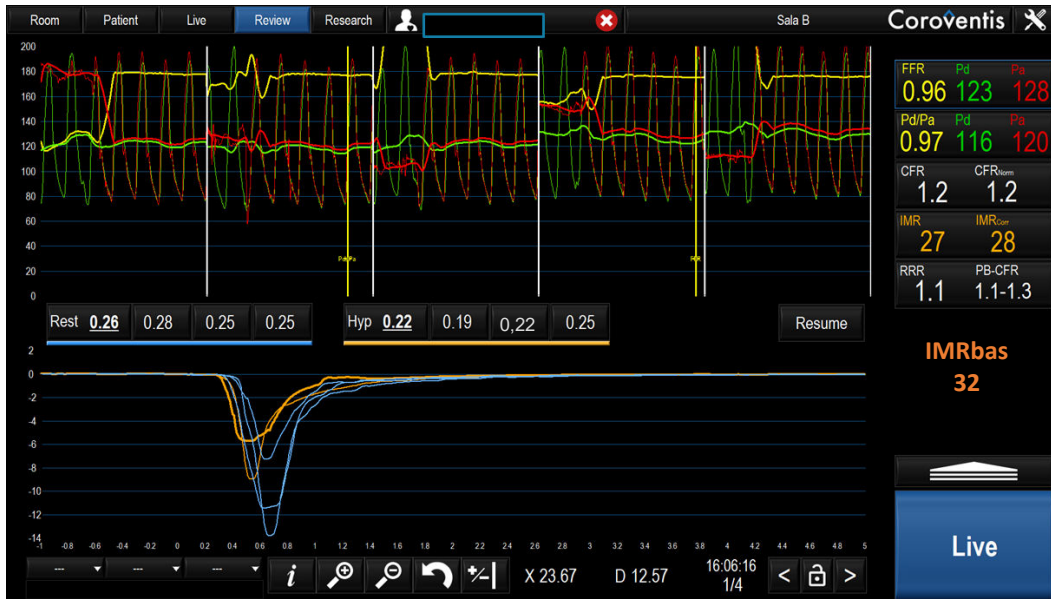




#FullPhysiology 2.0

Invasive Functional demonstration of Microvascular Spasm

- Typical chest pain
- ECG changes
- NO epicardial spasm



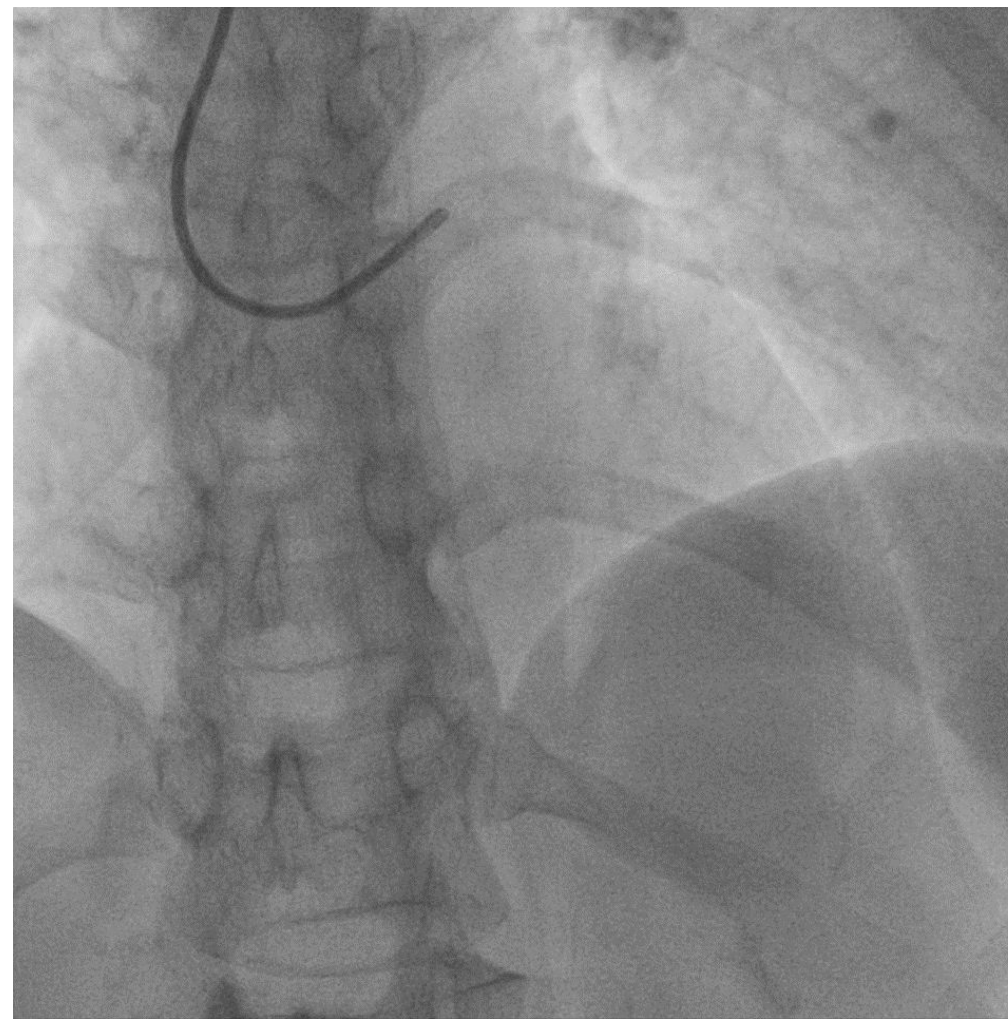
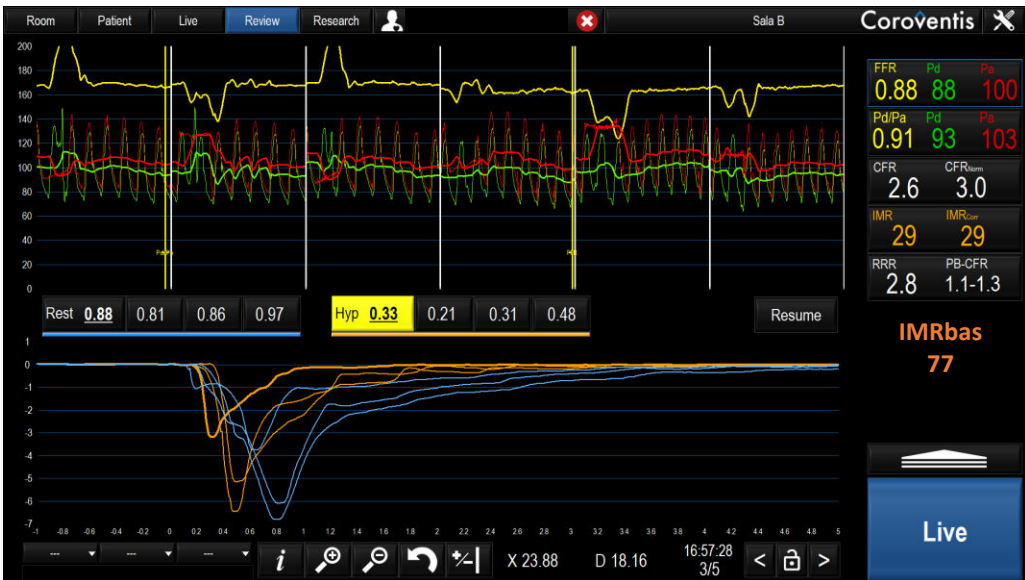
Real Microvascular Spasm



#FullPhysiology 2.0

Invasive Functional demonstration of Microvascular Spasm

- Typical chest pain
- ECG changes
- NO epicardial spasm

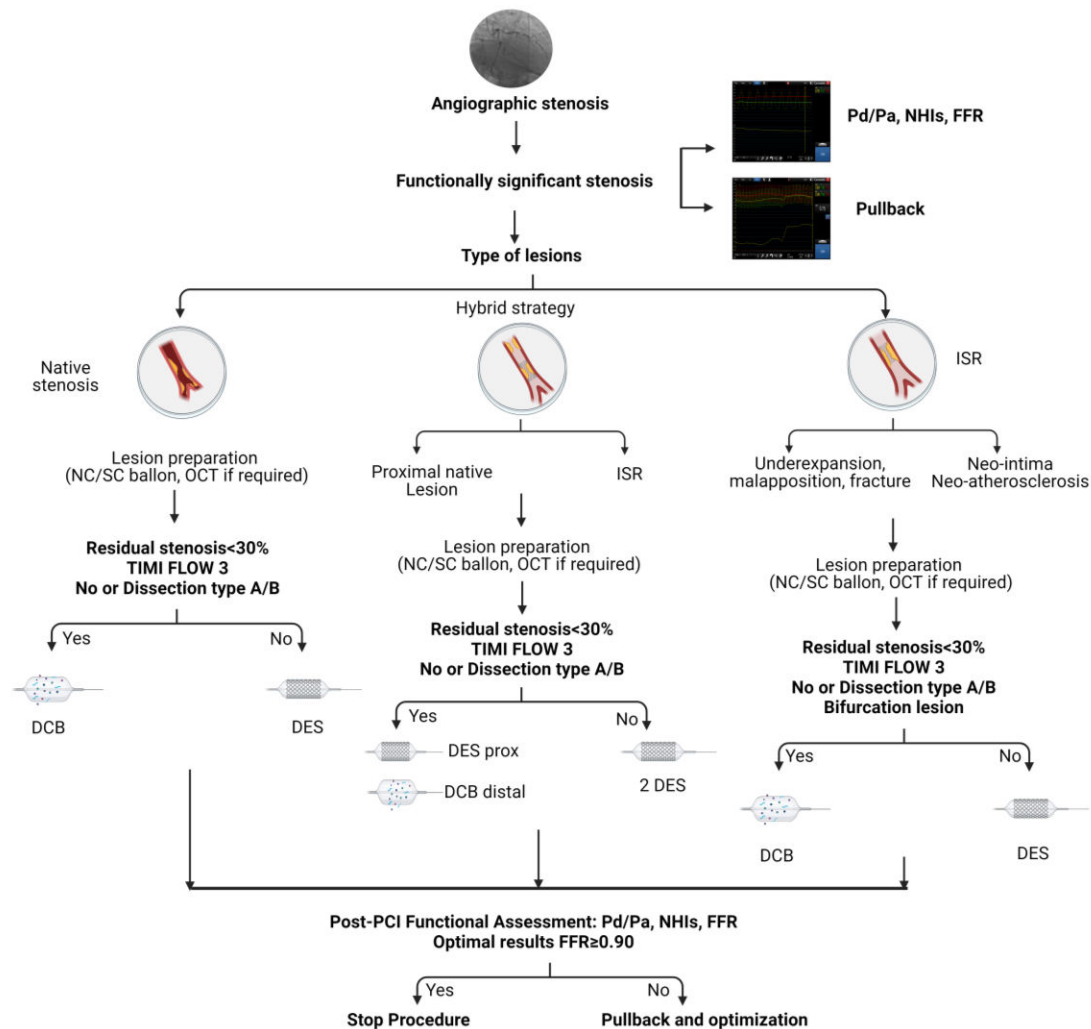


False Microvascular Spasm



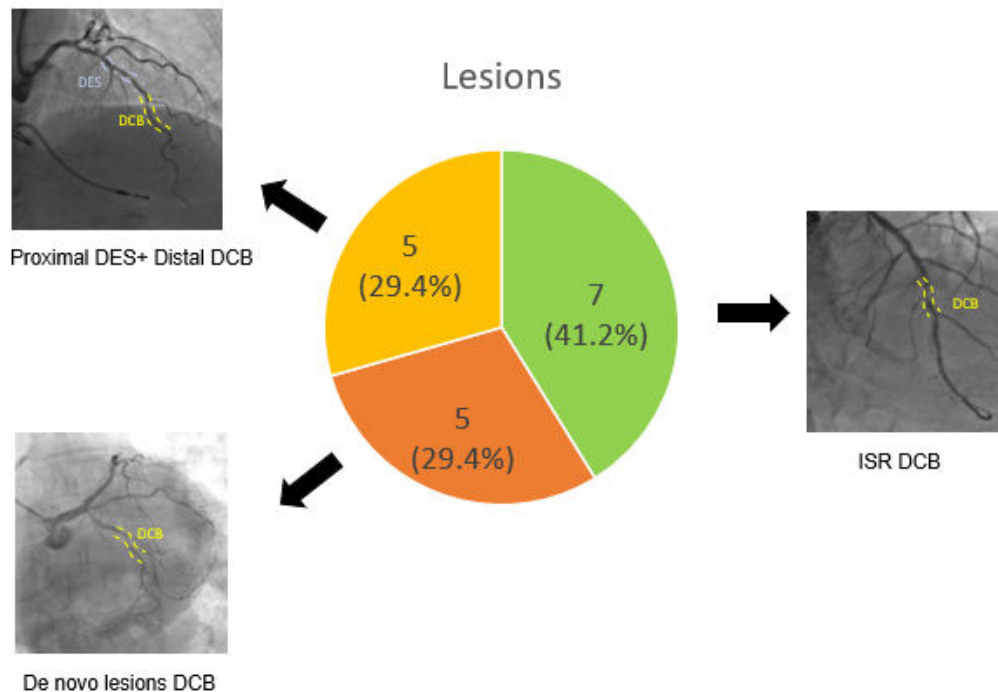
Integration of @Fullphysiology in DCB PCI

Fondazione Policlinico Universitario A. Gemelli IRCCS-Rome (Italy)



- Data collection period: 2018-2022
- Total DCB-PCI (2018-2021): 398.
- Physiology - guided DCB-PCI: 17.

«...utilization of Physiology to optimize an angiographically acceptable DCB-PCI»



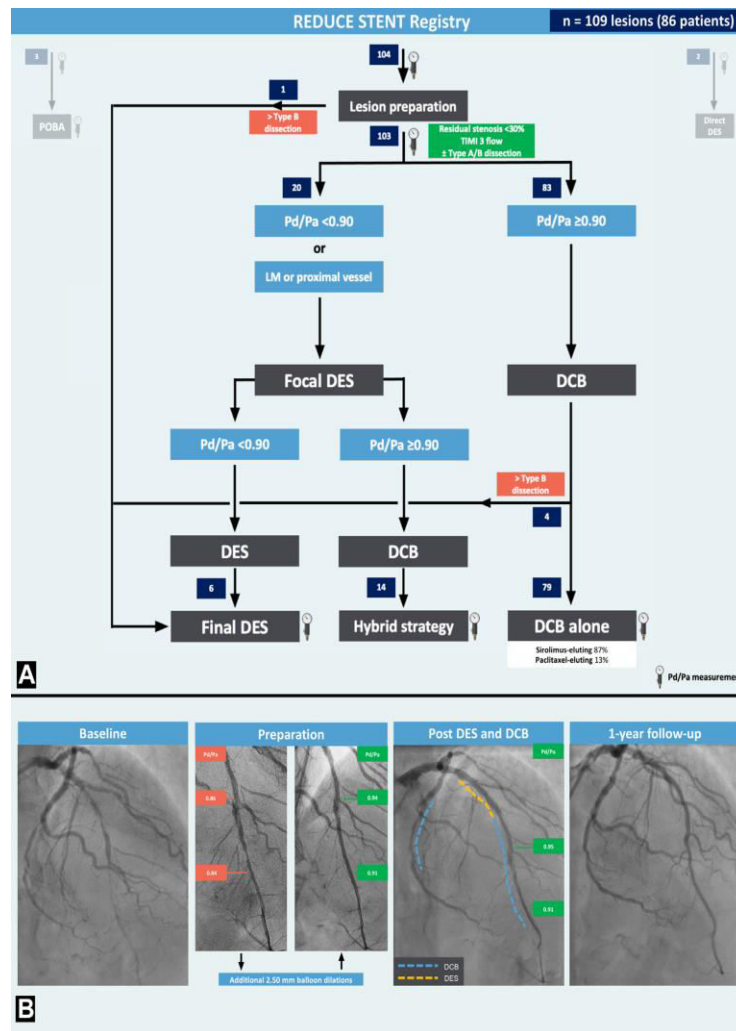


Integration of @Fullphysiology in DCB PCI

Drug-Coated Balloon Angioplasty Guided by Post-Percutaneous Coronary Intervention Pressure Gradient

The REDUCE-STENT Retrospective Registry

«...utilization of the distal coronary-to-aortic pressure ratio (Pd/Pa) post-lesion preparation to safely limit stenting when the result is considered angiographically imperfect...»



TVF

	Definite	Probable
Acute	0	0
Subacute	0	1
Late	1	0
Very late	0	1

Target vessel MI 1(0.01%)

TLF 11 (13.2%)

TVR 8 (8.7%)

Median follow-up 246 days (interquartile range 136-400 days)



Conclusions

1

We have relatively **simple tools** to comprehensively assess coronary circulation in a short time*

2

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

3

INOCA has an important **socio-economic impact** and now can be **treated appropriately** only using an invasive guide using a pressure/thermodilution wire

4

INOCA is a useful model for a variety of clinical settings in which **#FullPhysiology** can make the difference

*Mean procedural time 20 ± 7 minutes from the first NHPR to the end of the test



#Grazie

