TALLER DE FISIOLOGÍA CORONARIA

Hernán Mejía Rentería, MD, PhD, FESC

Cardiología Intervencionista
Hospital Clínico San Carlos, Madrid

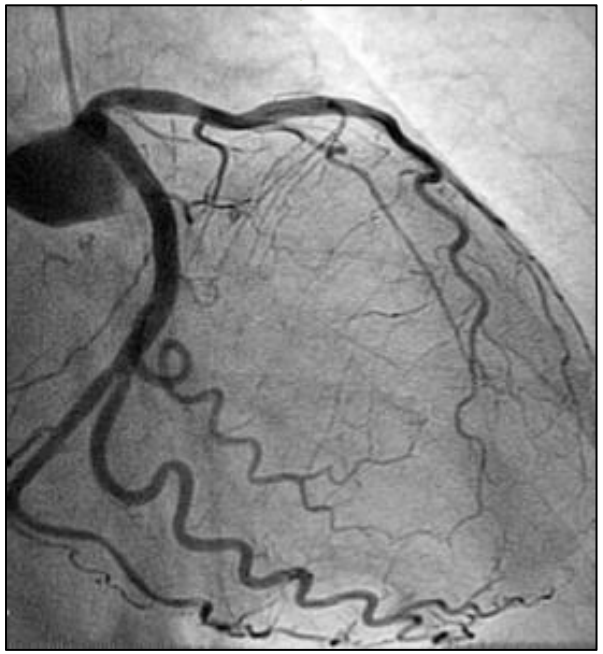
Contenido

1. Relevancia clínica de la microcirculación coronaria
2. Recomendaciones de las guías de práctica clínica
3. Métodos para la evaluación funcional coronaria
4. Evaluación funcional coronaria, paso a paso
5. Hands-on con modelo de agua

Densidad vascular coronaria

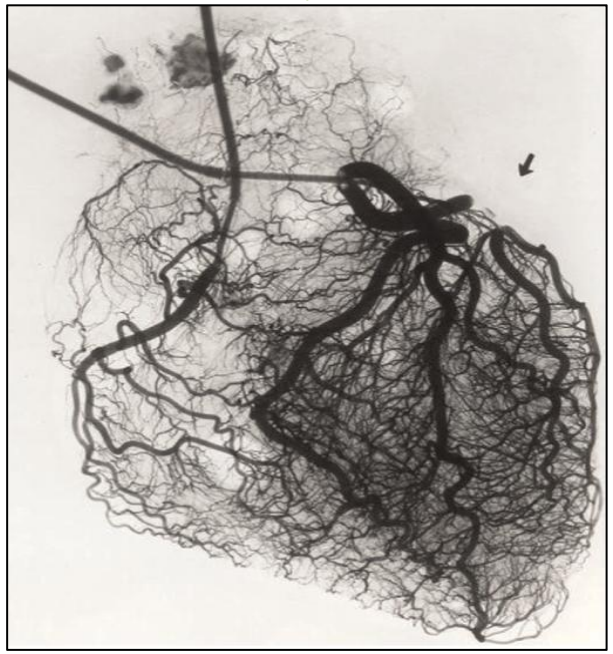
Circulación coronaria

Arterias epicárdicas



Vasos de conductancia

Microcirculación coronaria



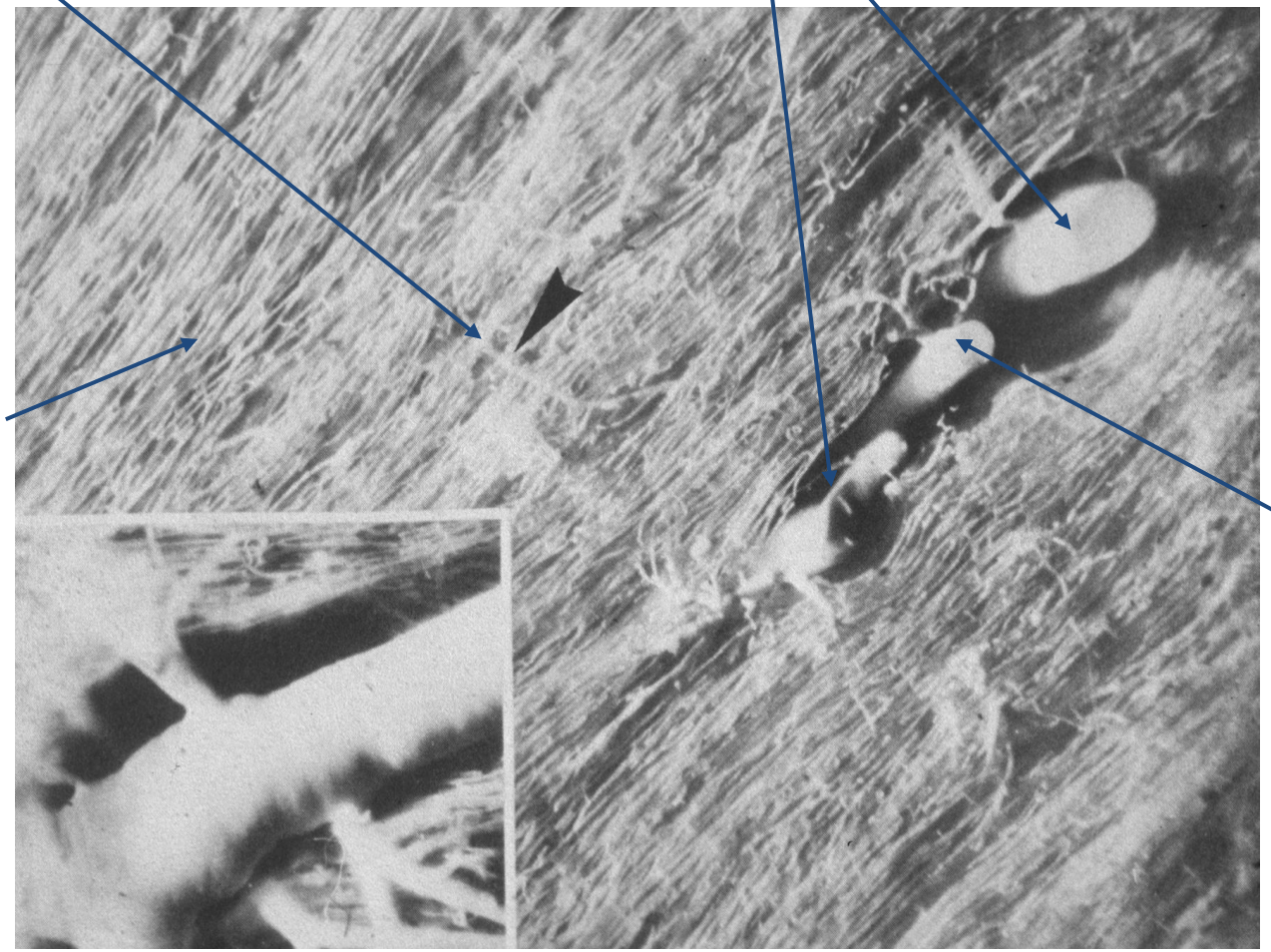
Vasos de resistencia

Componentes de la Microcirculación coronaria

Arteriola terminal
(Control metabólico)

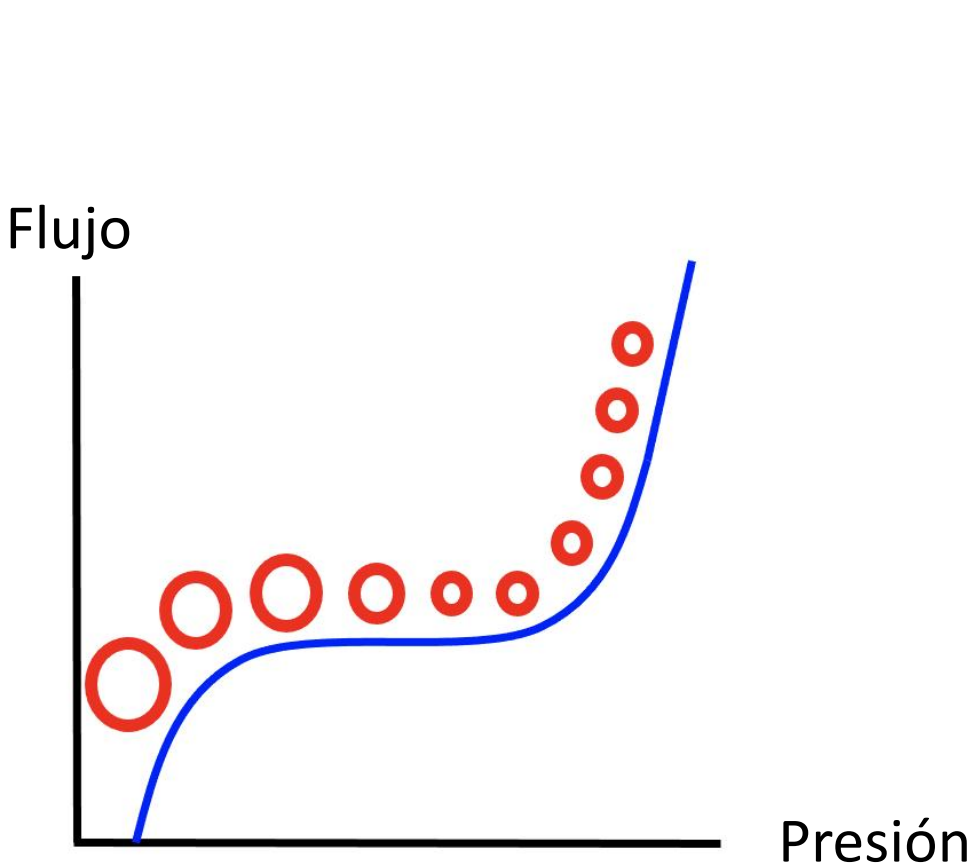
Vénulas *(sensibles a compresión)*

Capilares
(sensibles a compresion)



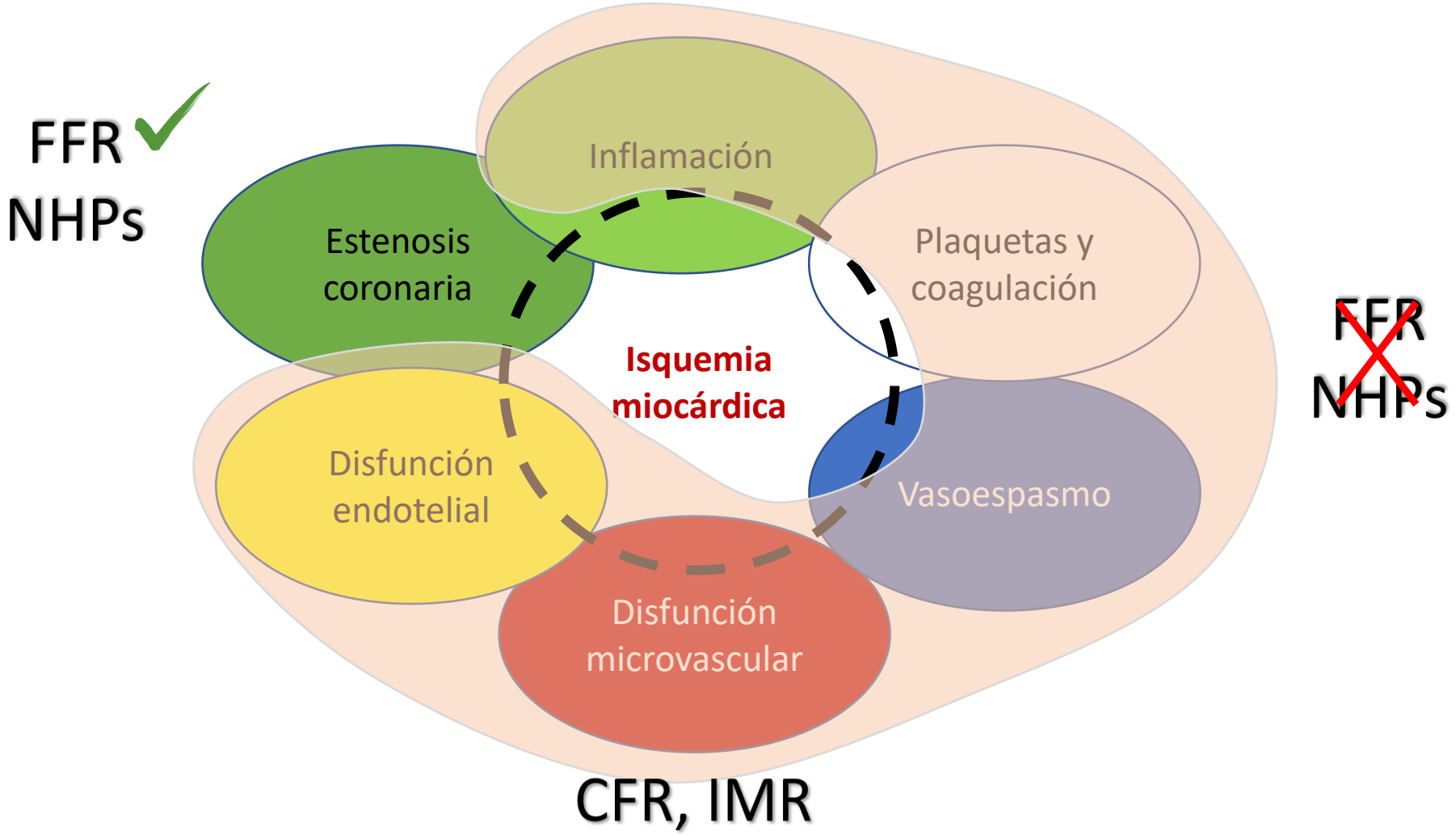
Arteriola 50 µm
(estímulos miogénicos)

Autorregulación coronaria



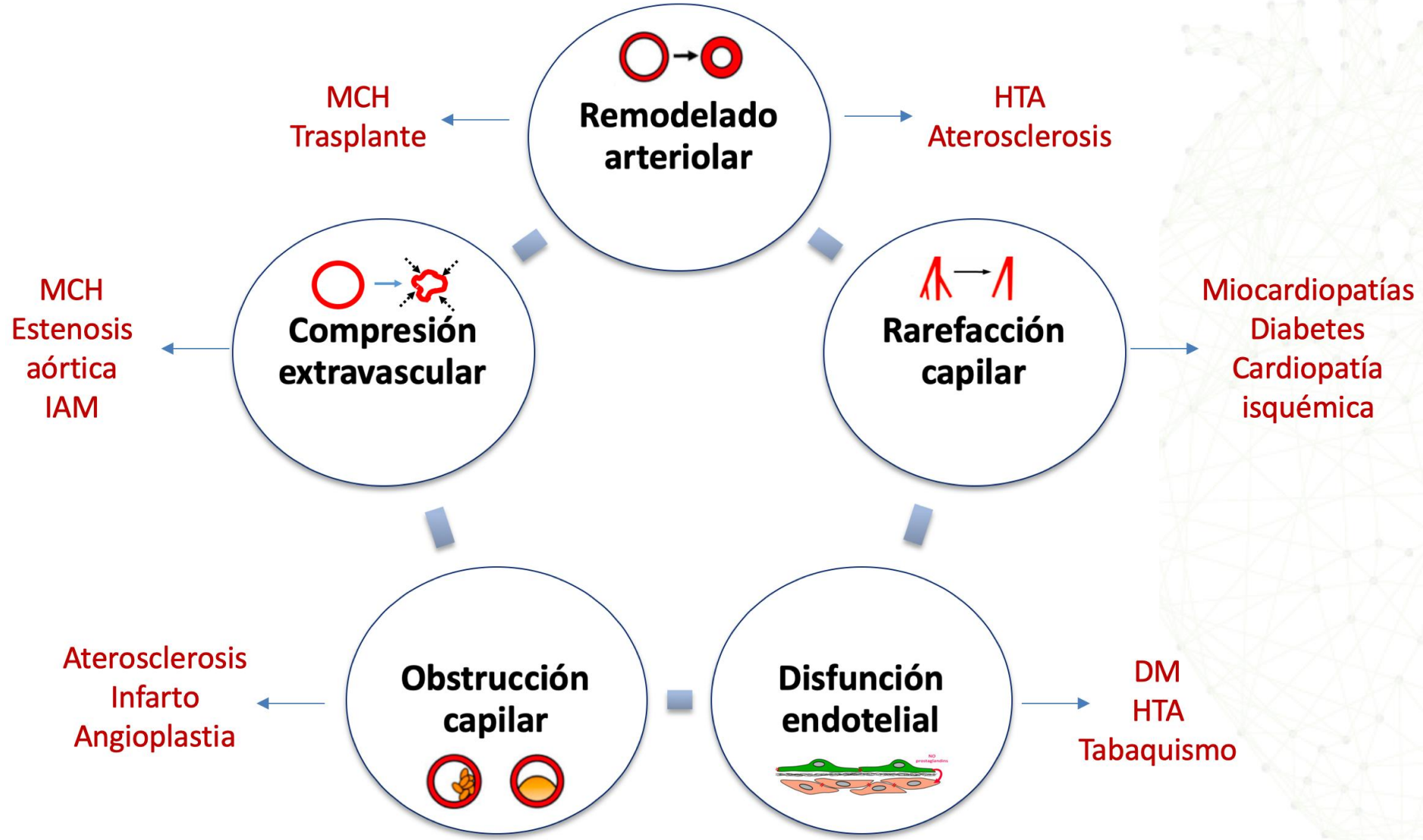
Situación de reposo

Mecanismos de isquemia miocárdica



Marzilli et al. J Am Coll Cardiol 2012;60:951–6

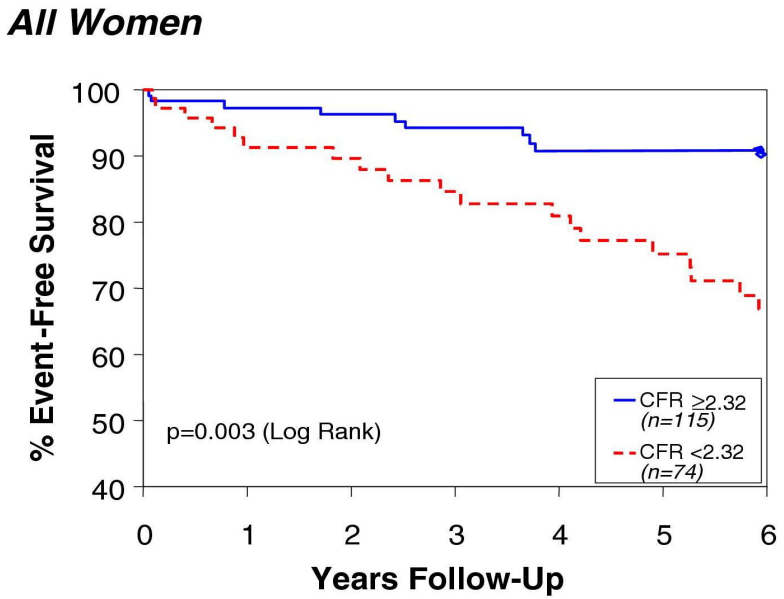
Mecanismos de disfunción microvascular coronaria

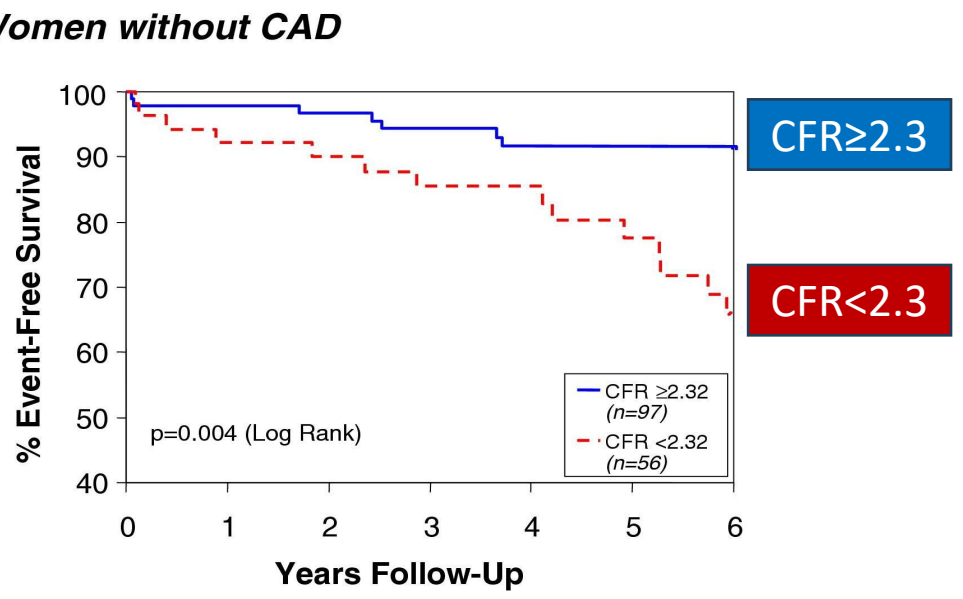


Mejia-Renteria et al. Int J Cardiovasc Imaging. 2017 Jul;33(7):1041-1059.

Impacto clínico de la disfunción microvascular coronaria

En mujeres sin enfermedad coronaria aterosclerótica





CFR≥2.3

CFR<2.3

MACE:
Muerte cardíaca
IAM
Ictus o
Ingreso por ICC

Valor de corte CFR: <2.3

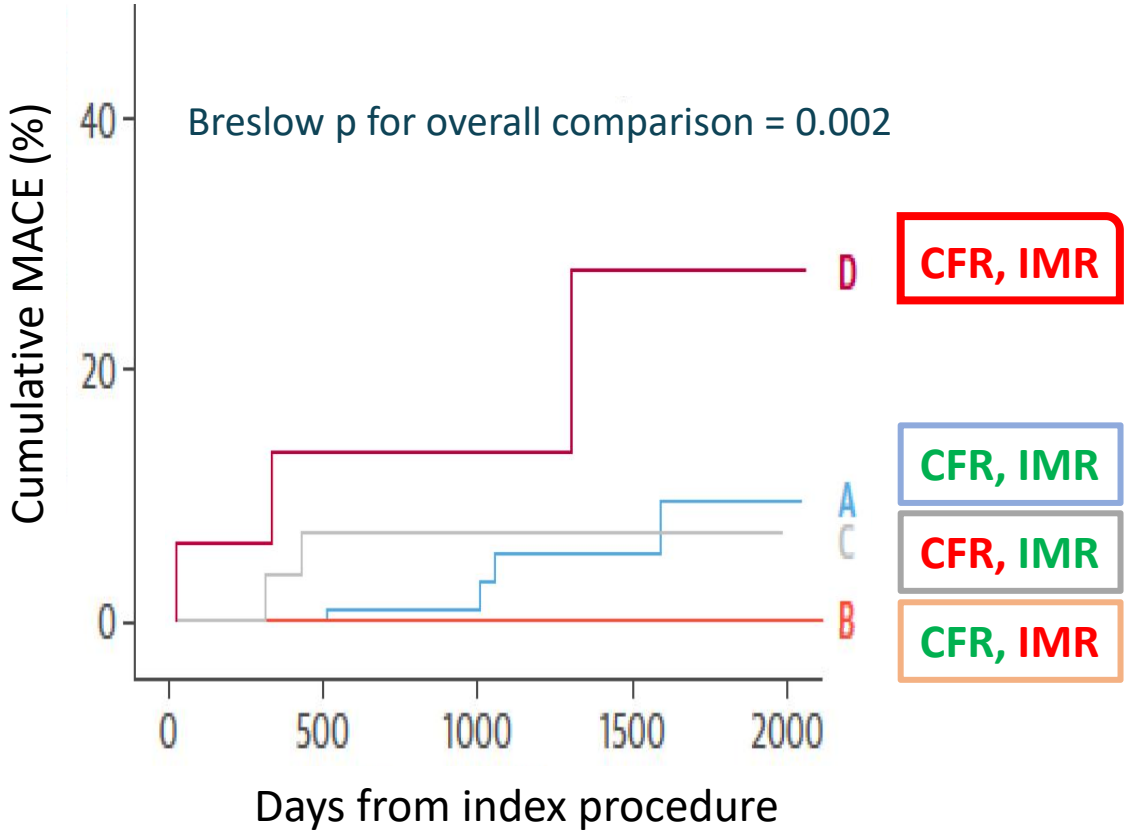
Asociación significativa entre la reserva coronaria y el pronóstico cardiovascular en mujeres con clínica de cardiopatía isquémica sin enfermedad coronaria.

Pepine et al. J Am Coll Cardiol 2010;55:2825–32

Impacto clínico de la disfunción microvascular coronaria

En pacientes con estenosis coronarias estables

313 pacientes (663 vasos) con **FFR > 0.80**



CFR, IMR

CFR, IMR

CFR, IMR

CFR, IMR

Verde: valores normales

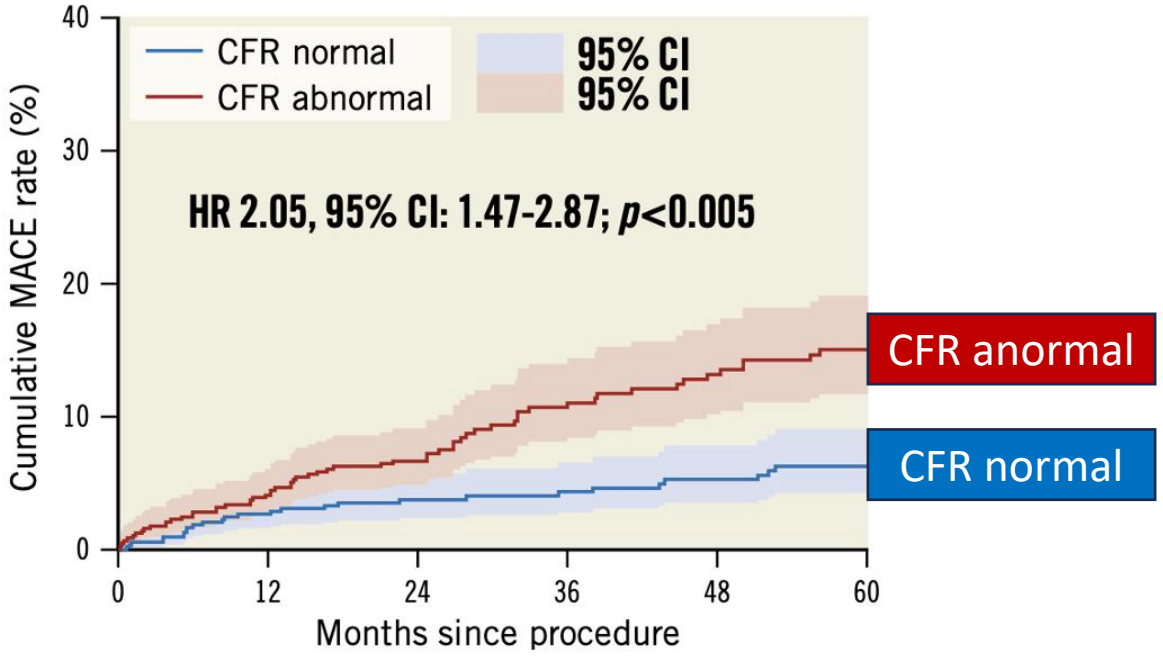
Rojo: valores anormales

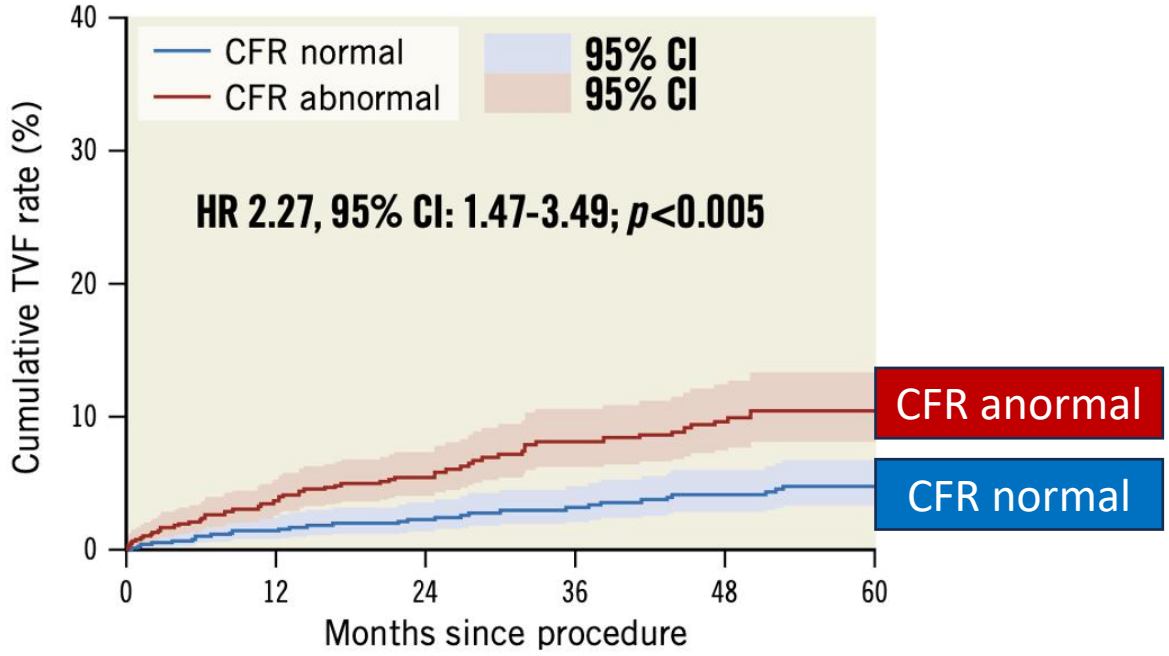
Lee et al. J Am Coll Cardiol. 2016 Mar 15;67(10):1158-69

Impacto clínico de la disfunción microvascular coronaria

En pacientes con estenosis coronarias estables

1102 pacientes sin enf coronaria obstructiva (FFR > 0.80)
5 años de seguimiento

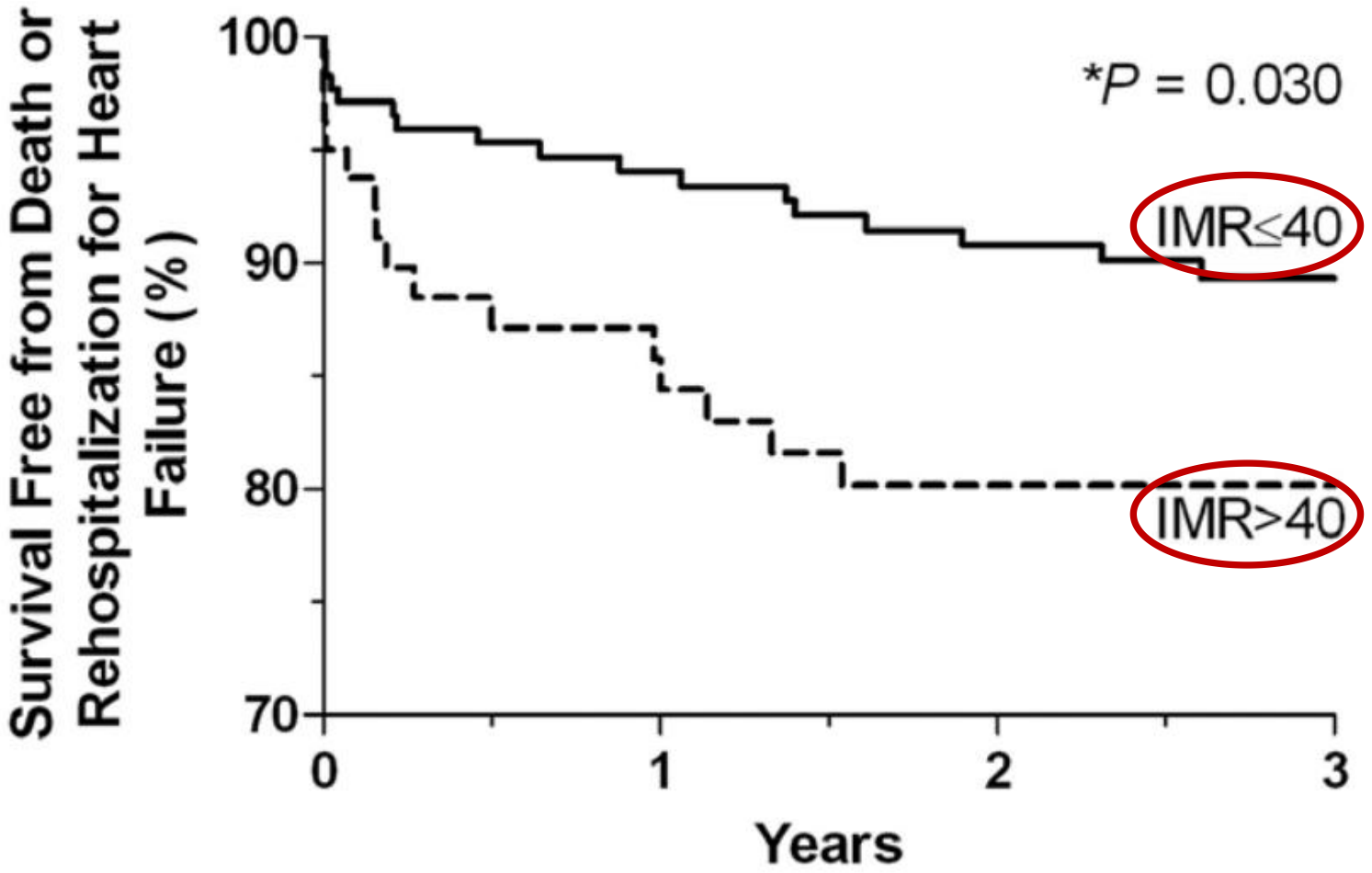




Coen K.M. Boerhout et al. EuroIntervention. 2022 Oct 21;18(9):719-728

Impacto clínico de la disfunción microvascular coronaria

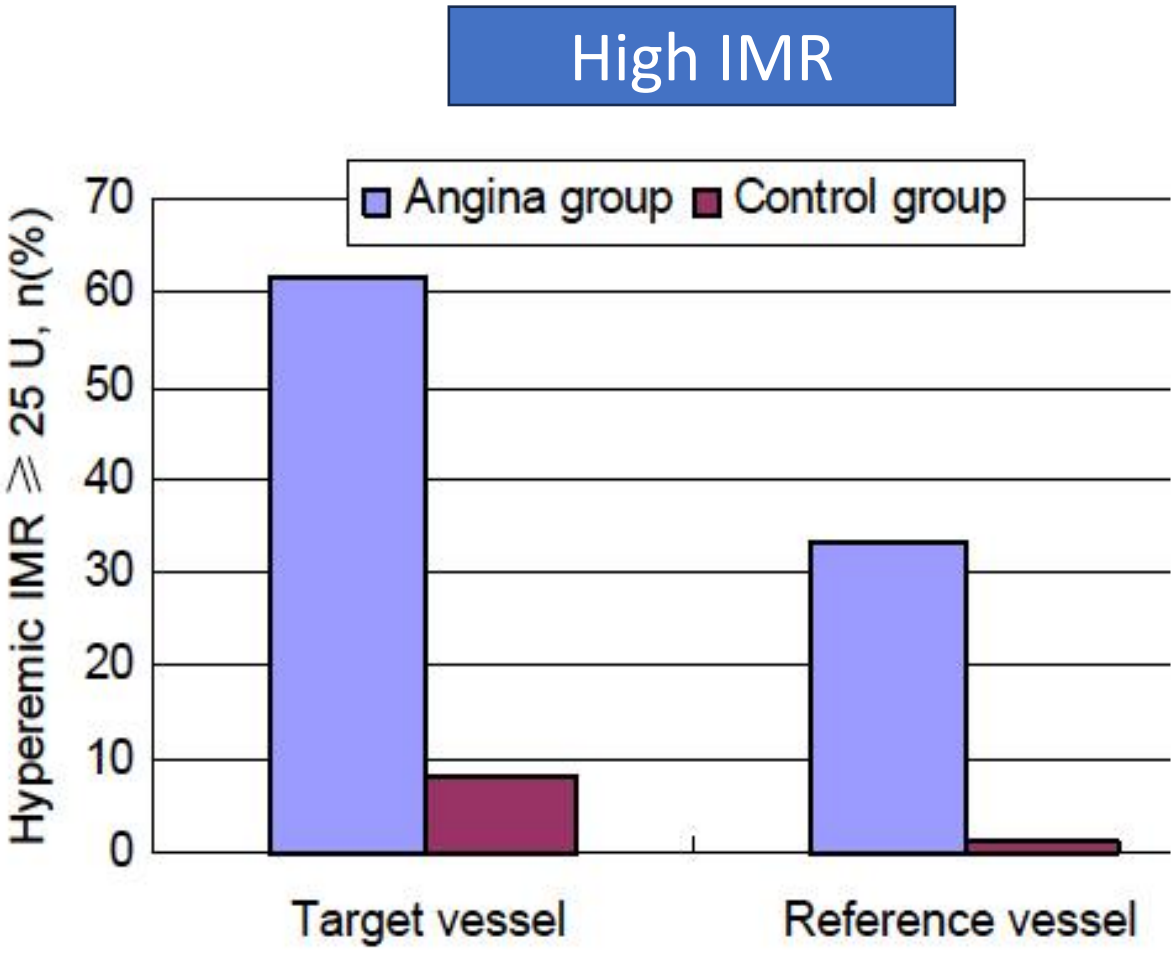
En pacientes con IAMCEST

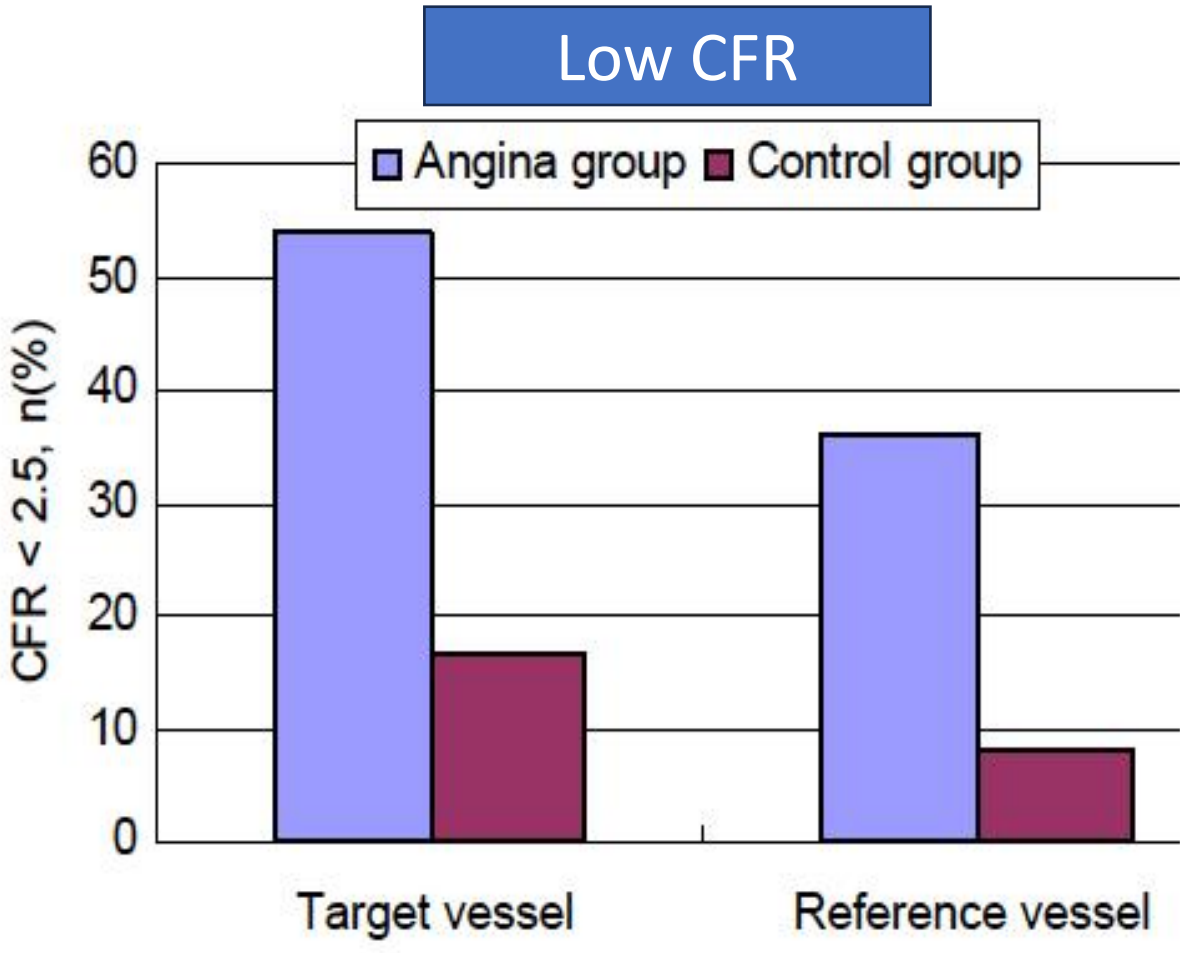


Fearon et al. Circulation. 2013 Jun 18;127(24):2436-41

Impacto clínico de la disfunción microvascular coronaria

En pacientes con angina post-ICP



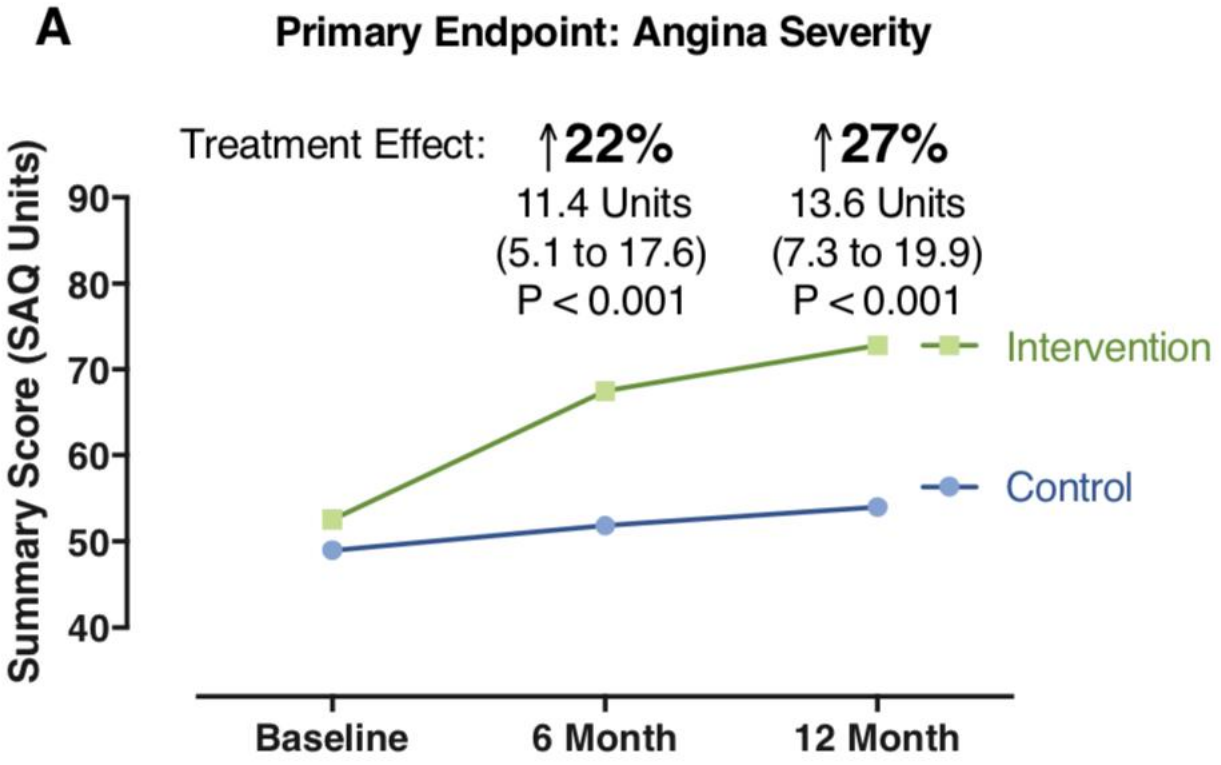


Li et al. Canadian Journal of Cardiology 31 (2015) 989e997

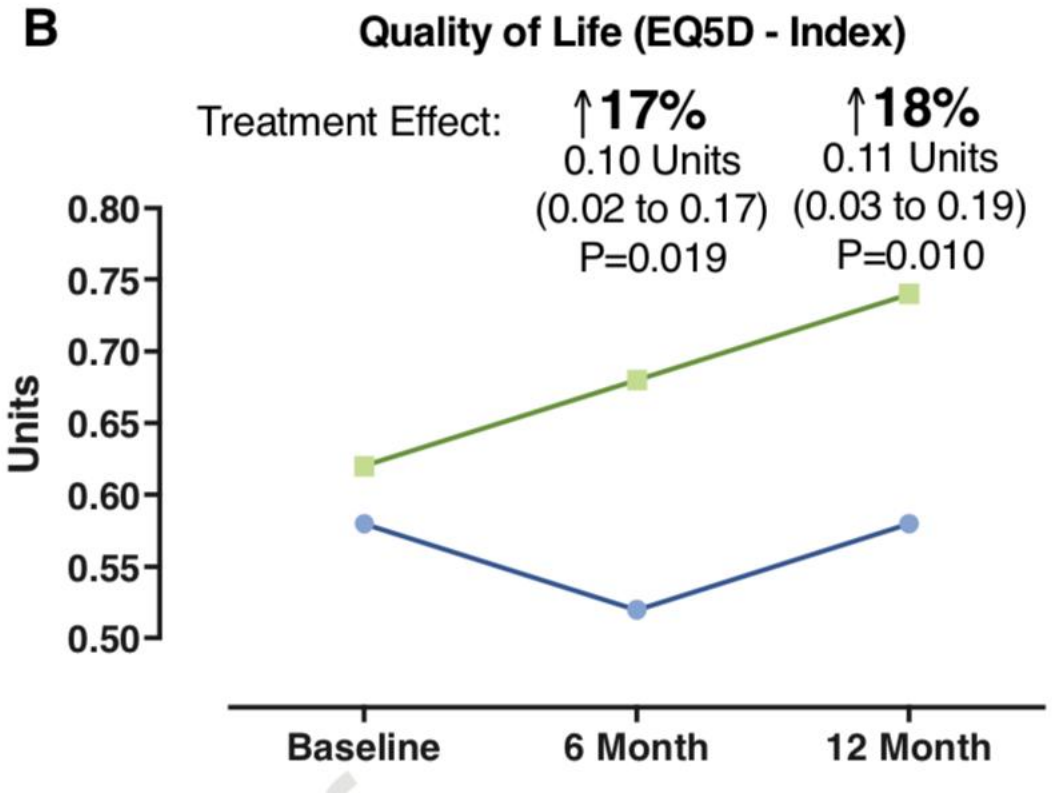
Impacto clínico de la disfunción microvascular coronaria

En la calidad de vida

Angina



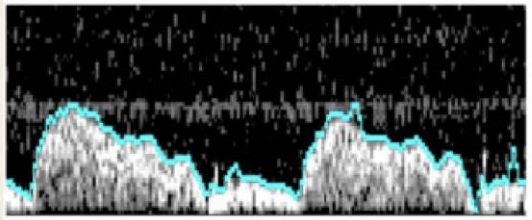
Calidad de vida

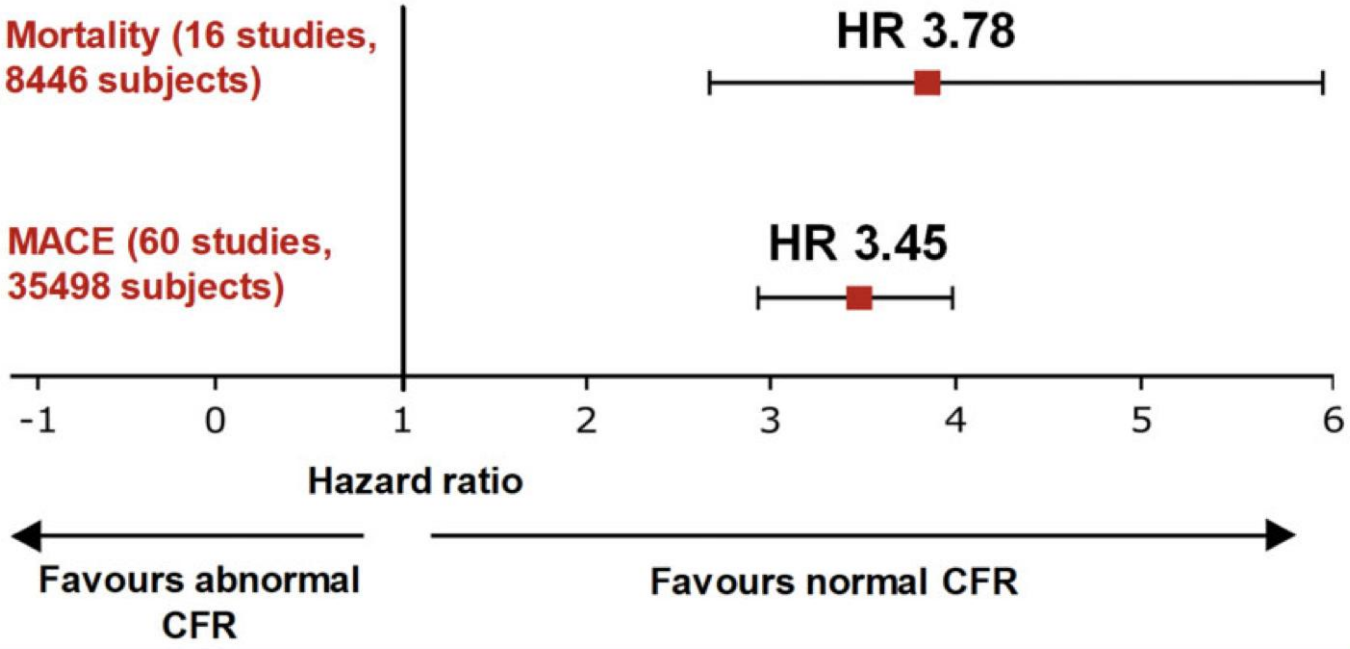


Ford TJ et al. JACC Cardiovasc Interv. 2019 Nov 8. pii: S1936-8798(19)32366-

Impacto clínico de la disfunción microvascular coronaria

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

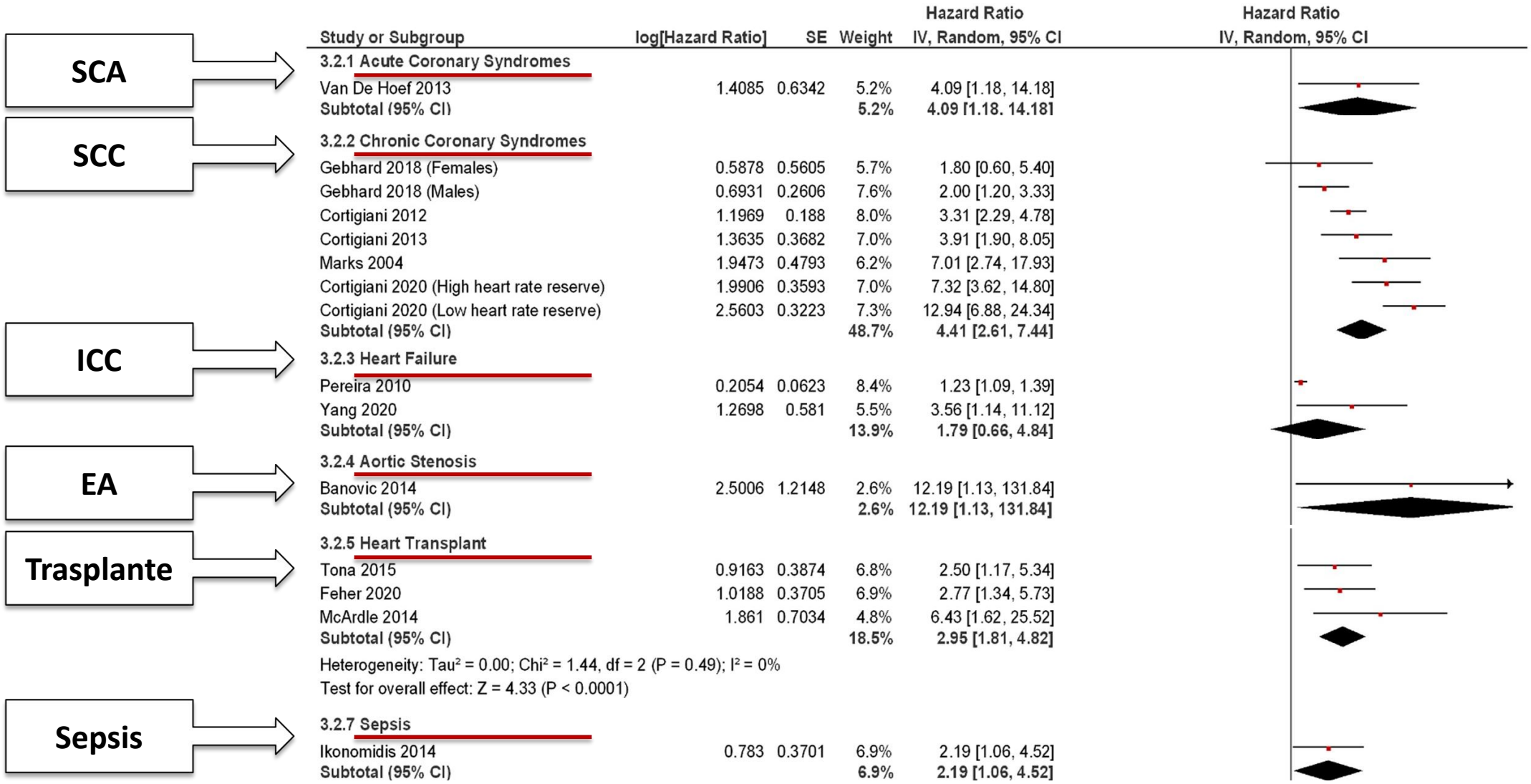




A systematic review and meta-analysis of 79 studies and 59740 individuals across multiple modalities of CFR measurement.

Kelshiker and Petraco, et al. Eur Heart J. 2022 Apr 19;43(16):1582-1593.

Impacto clínico de la disfunción microvascular coronaria



Kelshiker and Petraco, et al. Eur Heart J. 2022 Apr 19;43(16):1582-1593.

Main mechanisms of myocardial ischaemia in chronic coronary syndromes

ESC

Epicardial

FFR / NHP

Structural

Atherosclerosis (focal or diffuse)

Stabilized intramural haematoma

Myocardial bridge

Coronary aneurysm

Acetilcolina

Functional

Epicardial vasospasm

Endothelial dysfunction and/or VSMC hyperreactivity

Autonomic dysregulation

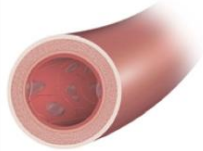
Microvascular

Adenosina

Structural

- Inward arteriolar remodelling
- Capillary rarefaction
- Intravascular plugging
- Perivascular fibrosis or infiltration
- Extramural compression (myocardial hypertrophy, increased LVEDP)

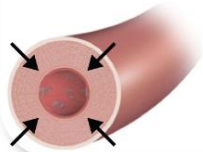
Functional



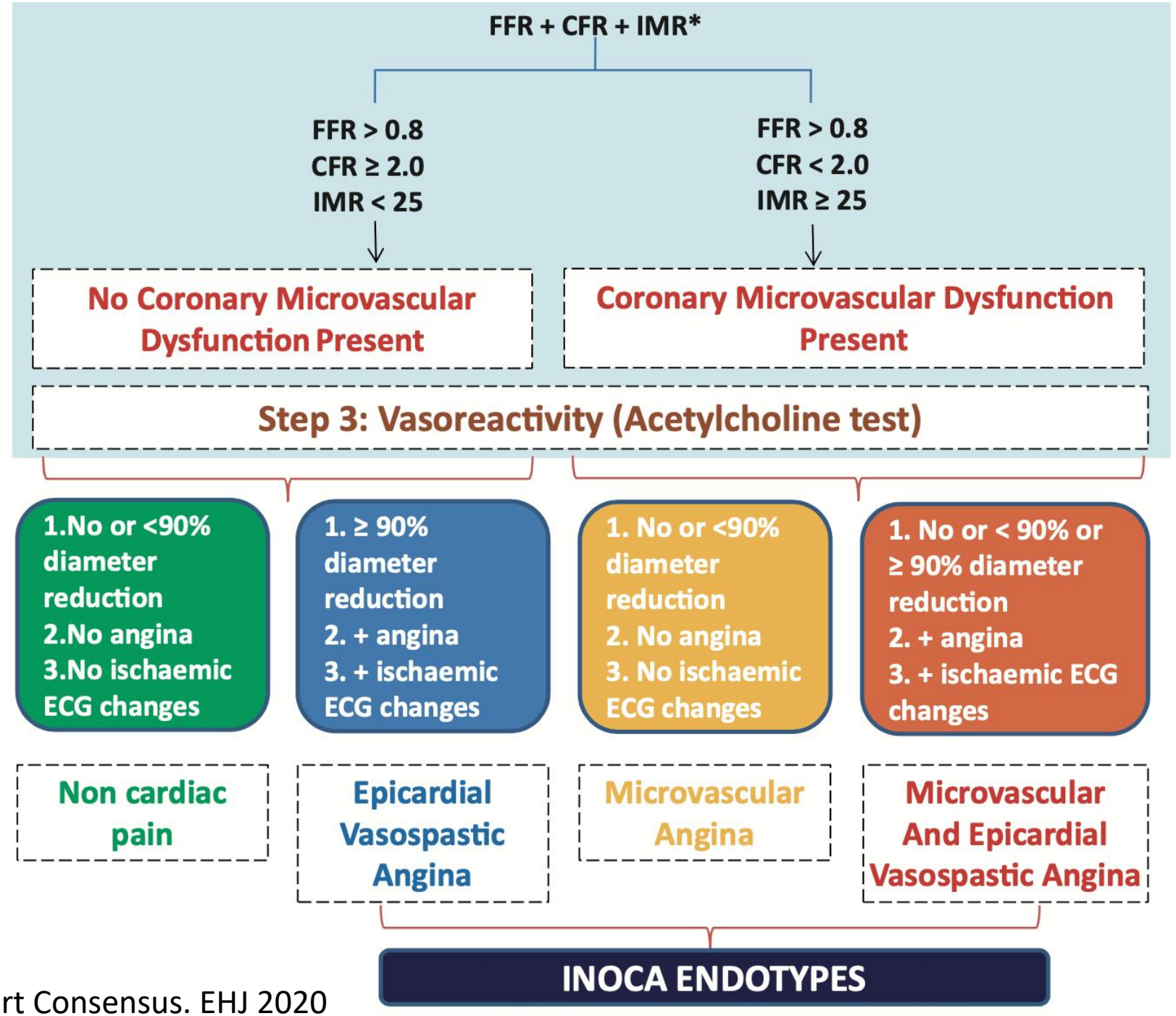
Impaired vasodilation

Endothelial dysfunction and/or VSMC hyperreactivity

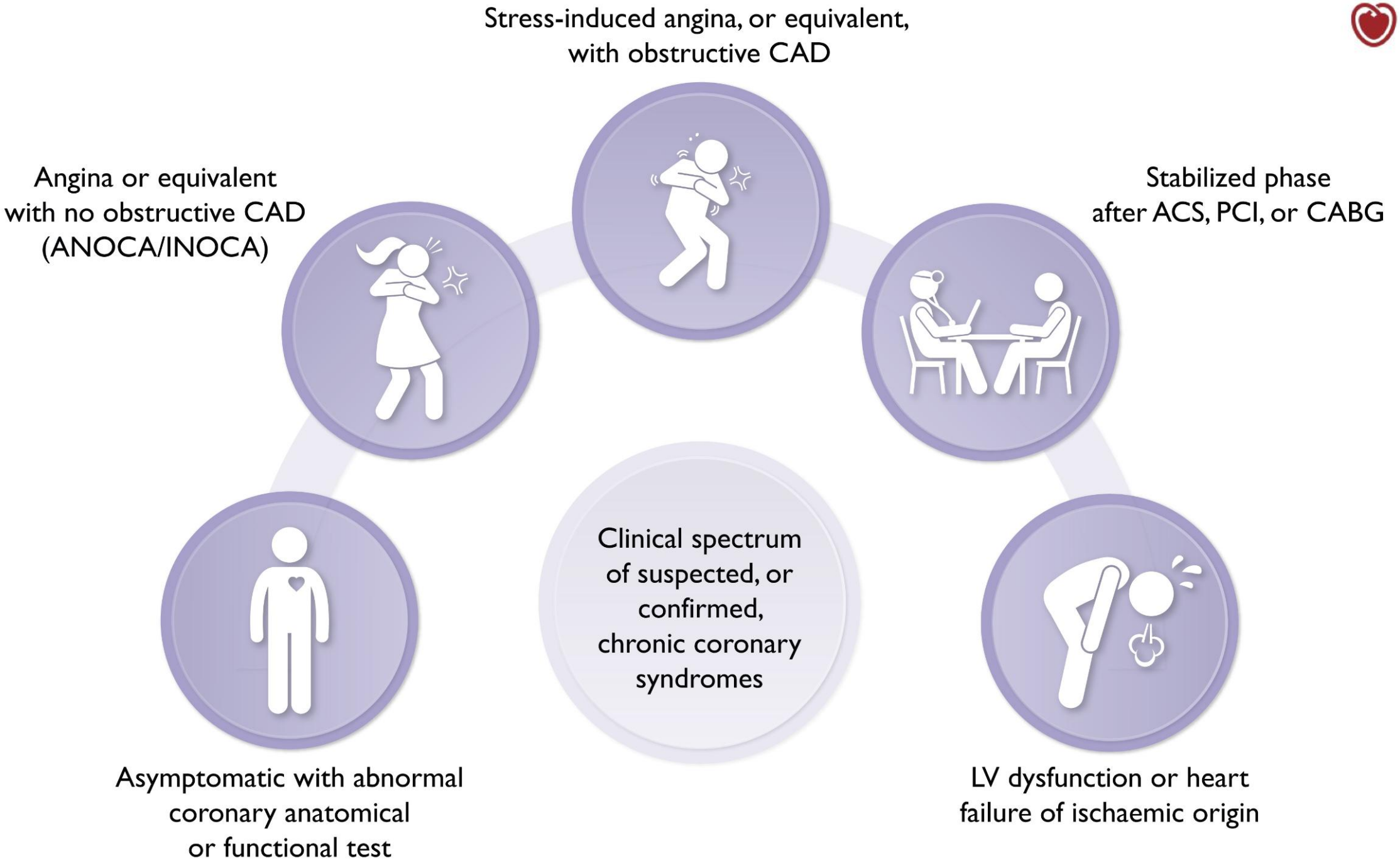
Autonomic dysregulation



Increased vasoconstriction



Kunadian. EAPCI Expert Consensus. EHJ 2020


Stress-induced angina, or equivalent, with obstructive CAD
Angina or equivalent with no obstructive CAD (ANOCA/INOCA)
Stabilized phase after ACS, PCI, or CABG
Clinical spectrum of suspected, or confirmed, chronic coronary syndromes
Asymptomatic with abnormal coronary anatomical or functional test
LV dysfunction or heart failure of ischaemic origin

Management of INOCA

1. Lifestyle factors

Nutrition

Exercise

Weight management

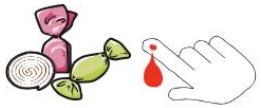
Smoking cessation

Coping with stress

2. Risk factor management

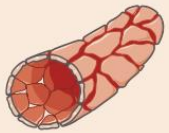
Hypertension

Dyslipidaemia



Diabetes mellitus

3. Antianginal medication



Microvascular angina

Consider statins and ACEI/ARB

Vasospastic angina

1. Betablocker
2. Calcium channel blocker
3. Nicorandil
4. Ranolazine
5. Ivabradine
6. Trimetazidine

1. Calcium channel blocker
2. Long-acting nitrate
3. Nicorandil

Kunadian. EAPCI Expert Consensus. EHJ 2020

New recommendations

Recommendations	Class	Level
Functional assessment of epicardial artery stenosis severity during invasive coronary angiography		
During ICA, selective assessment of functional severity of intermediate diameter stenoses is recommended to guide the decision to revascularize, using the following techniques:		
• FFR/iFR (significant ≤0.8 or ≤0.89, respectively);	I	A
• QFR (significant ≤0.8).	I	B
In addition:		
• CFR/HSR/CFC should be considered as a complementary investigation;	IIa	B
• resting invasive measurement of Pd/Pa, dPR, RFR, or angiography-derived vessel FFR may be considered as alternative parameters.	IIb	C
Systematic and routine wire-based coronary pressure assessment of all coronary vessels is not recommended.	III	A

New recommendations

Recommendations	Class	Level
Selection of individual diagnostic tests in individuals with suspected chronic coronary syndrome		
To rule out obstructive CAD in individuals with low or moderate (>5%–50%) pre-test likelihood, CCTA is recommended as the preferred diagnostic modality.	I	B
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD if functional imaging for myocardial ischaemia is not diagnostic.	I	B
Invasive coronary angiography with the availability of invasive functional assessment is recommended to confirm or exclude the diagnosis of obstructive CAD or ANOCA/INOCA in individuals with an uncertain diagnosis on non-invasive testing.	I	B
In patients with a known intermediate coronary artery stenosis in a proximal or mid coronary segment on CCTA, CT-based FFR may be considered.	IIb	B

New recommendations

Recommendations	Class	Level
Recurrent or refractory angina/ischaemia		
In patients with refractory angina leading to poor quality of life and with documented or suspected ANOCA/INOCA, invasive coronary functional testing is recommended to define ANOCA/INOCA endotypes and appropriate treatment, considering patient choices and preferences.	I	B

Revised recommendations

2019 Guidelines	Class	Level	2024 Guidelines	Class	Level
Diagnosis and management of patients with angina/ischaemia with non-obstructive coronary arteries					
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.	IIa	B	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.	I	B

2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Revised recommendations

2019 Guidelines	Class	Level	2024 Guidelines	Class	Level
Diagnosis and management of patients with ANOCA/INOCA cont.					
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.	IIb	B	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 iFR/FFR at coronary arteriography) and poor quality of life, intracoronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences.	I	B

2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

New recommendations

Recommendations	Class	Level
Diagnosis and management of patients with angina/ischaemia with non-obstructive coronary arteries		
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.	IIa	A
For the management of endothelial dysfunction, ACE-I should be considered for symptom control.	IIa	B
For the management of microvascular angina associated with reduced coronary/myocardial blood flow reserve, beta-blockers should be considered for symptom control.	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;	I	A
• nitrates should be considered to prevent recurrent episodes.	IIa	B
In patients with evidence of overlapping endotypes, combination therapy with nitrates, calcium channel blockers, and other vasodilators may be considered.	IIb	B

2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

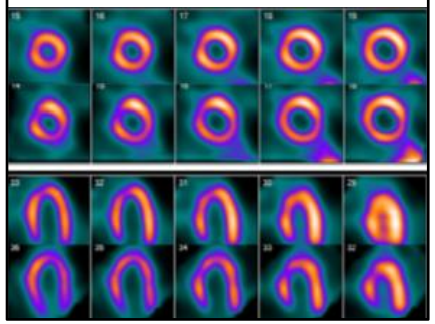
Métodos de fisiología coronaria

Técnicas
Índices
Fármacos

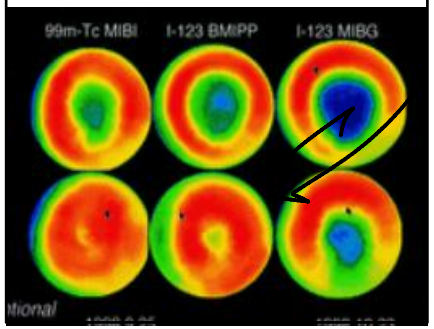
Técnicas

Métodos no invasivos

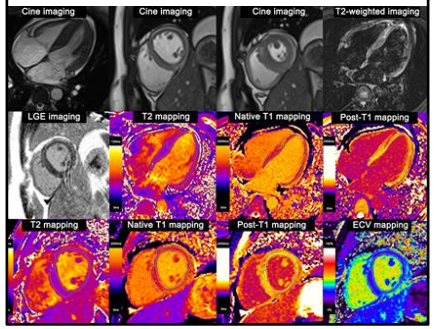
Scintigraphy



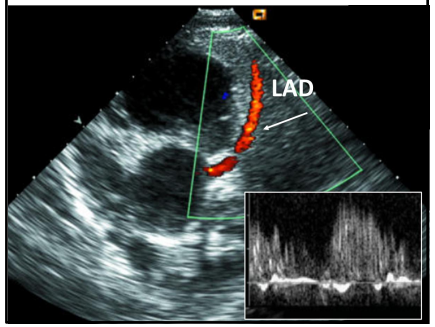
PET



RMC

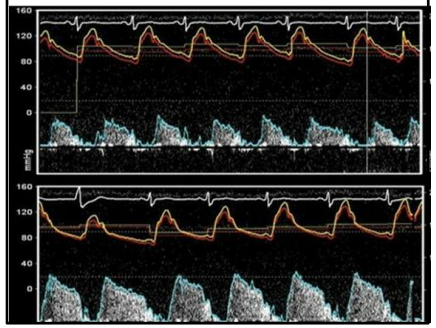


Doppler

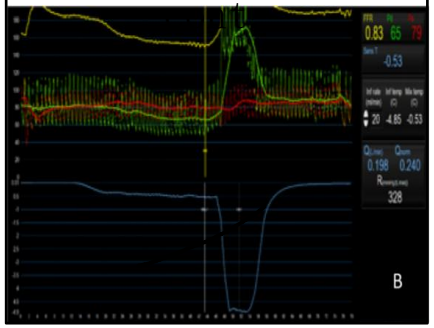


Métodos invasivos

Doppler

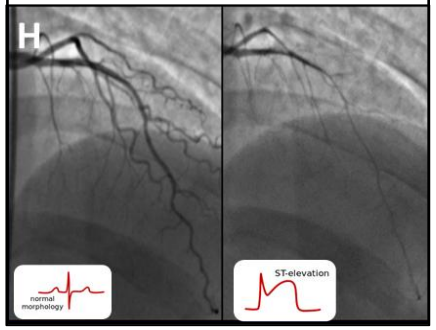


Termodilución

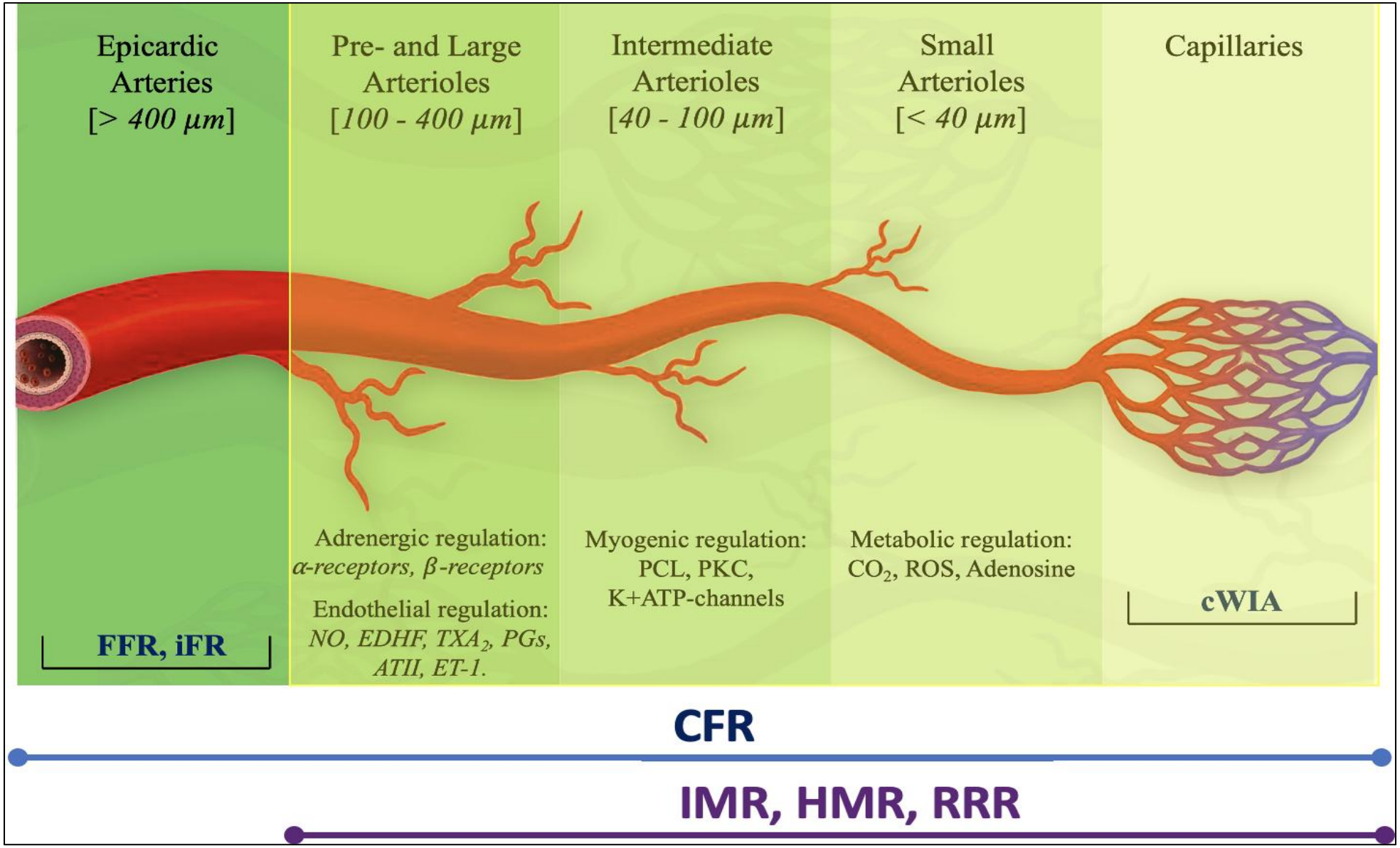


Termodilución bolos

Acetilcolina

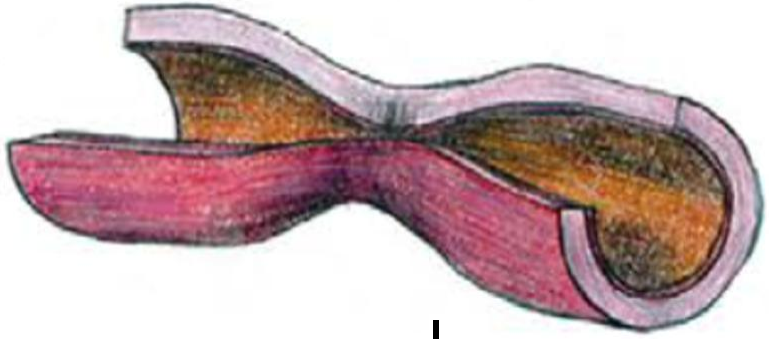


Índices


Epicardic Arteries [> 400 μm]
Pre- and Large Arterioles [100 - 400 μm]
Intermediate Arterioles [40 - 100 μm]
Small Arterioles [< 40 μm]
Capillaries
Adrenergic regulation: α-receptors, β-receptors
Endothelial regulation: NO, EDHF, TXA2, PGs, ATII, ET-1.
Myogenic regulation: PCL, PKC, K+ATP-channels
Metabolic regulation: CO2, ROS, Adenosine
FFR, iFR
cWIA
CFR
IMR, HMR, RRR

Dos fármacos

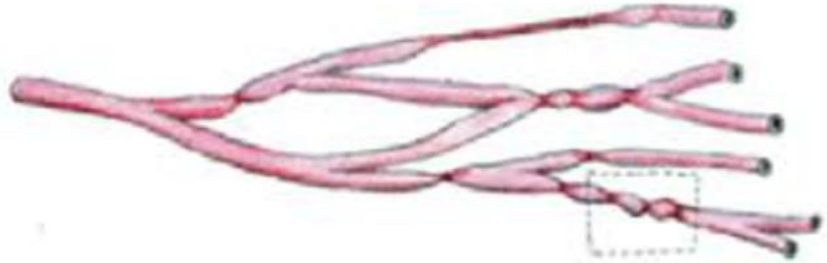
Vasoespasmo coronario



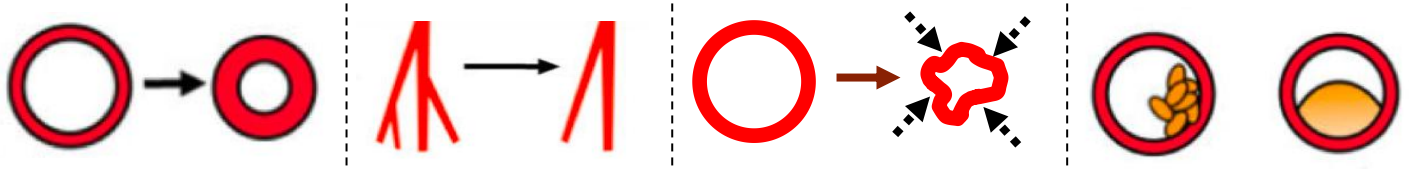
- Epicardial vasospasm
- Microcirculatory vasospasm

Acetilcolina

Disfunción coronaria microvascular



- Remodelling
- Rarefaction
- Compression
- Plugging



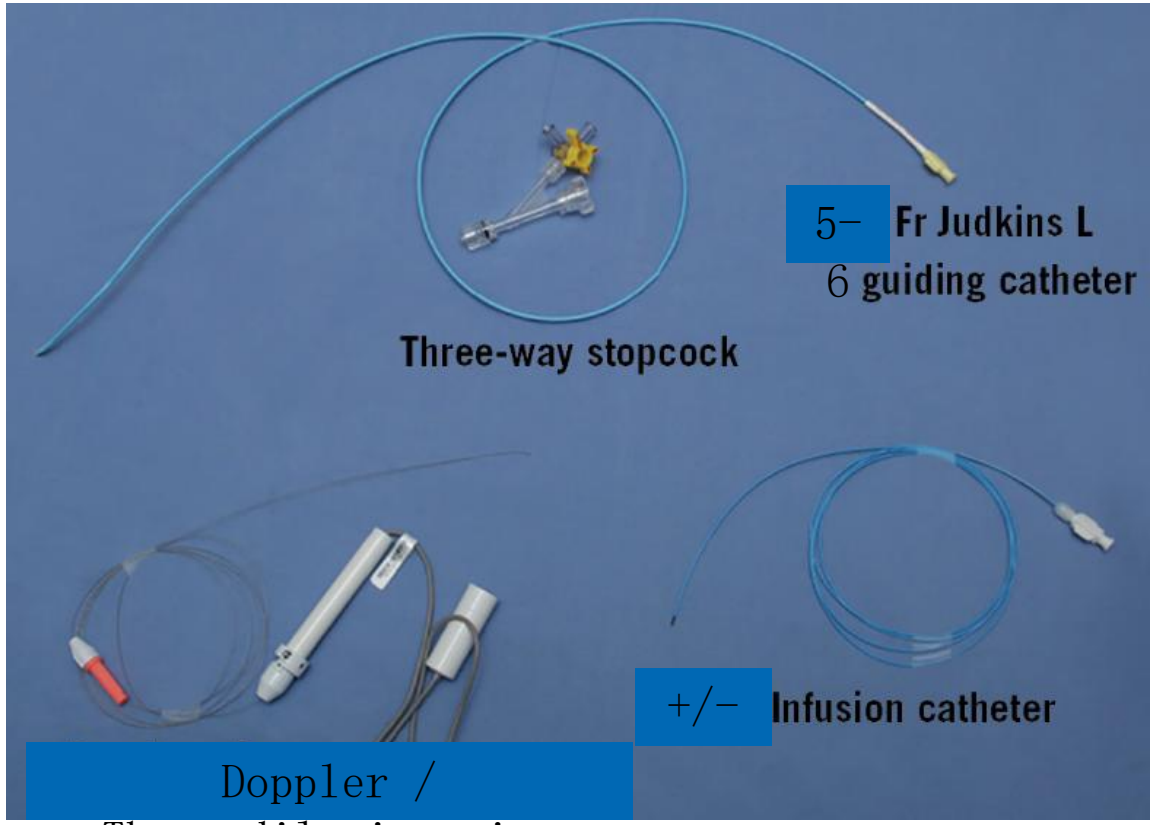
Adenosina

Invasive functional coronary angiography

Set-up

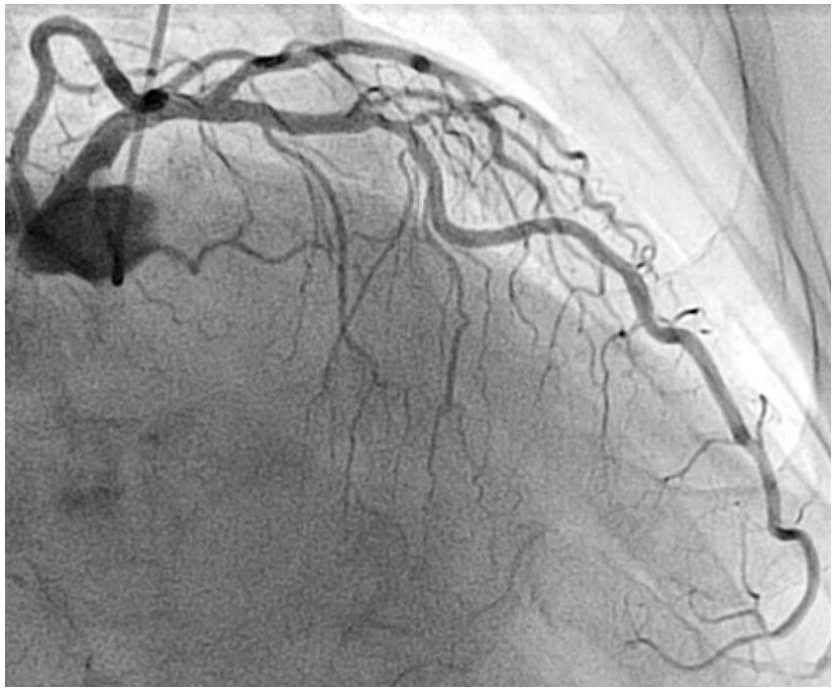
- Preparation of the patient:
  - Avoid caffeine and nicotine for ⩾24 hours.
  - Withdraw of vasodilators (CCB, nitrates) ⩾18 hours before the procedure.

- LAD (pre-specified target vessel).
  - RCA or LCx, if indicated by regional abnormalities in non-



Set-up

- Projection showing long axis of target vessel
- Full heparinization (50 – 70 U/kg, ACT>250 s).

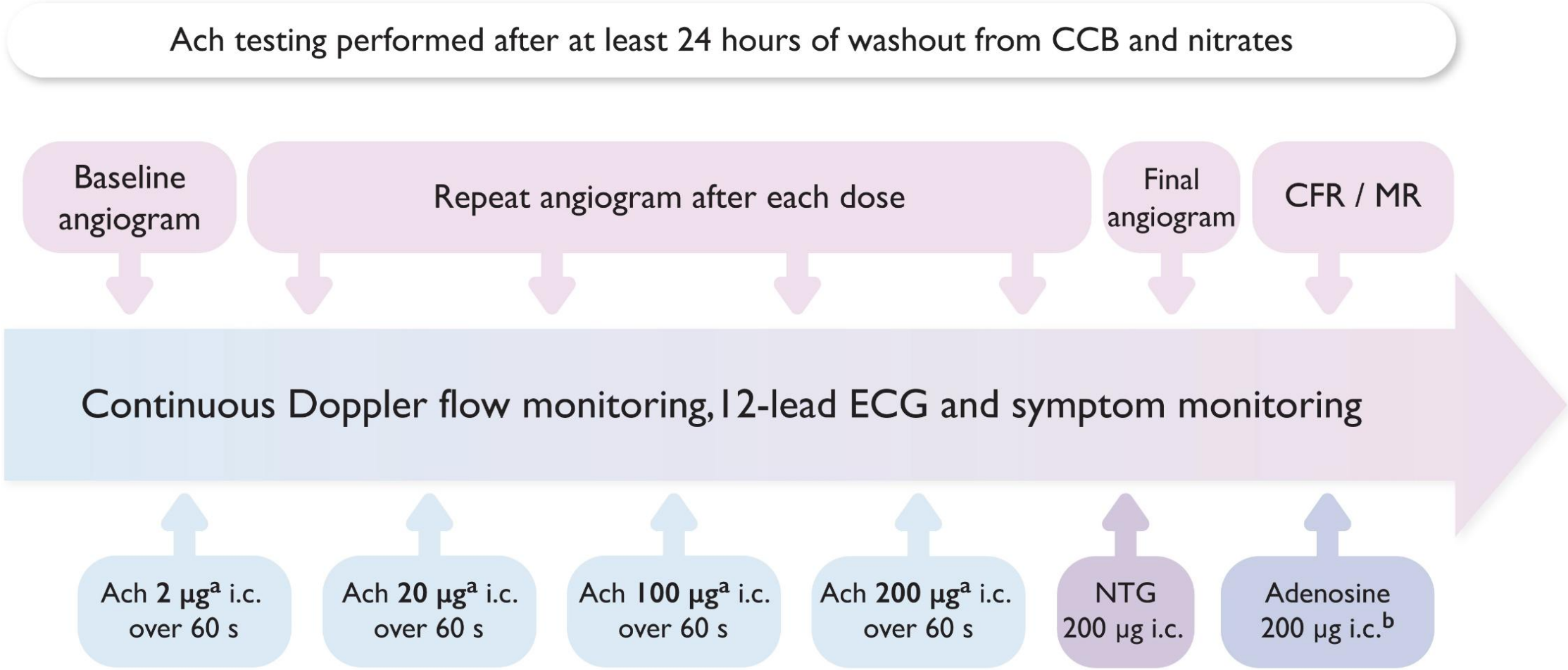


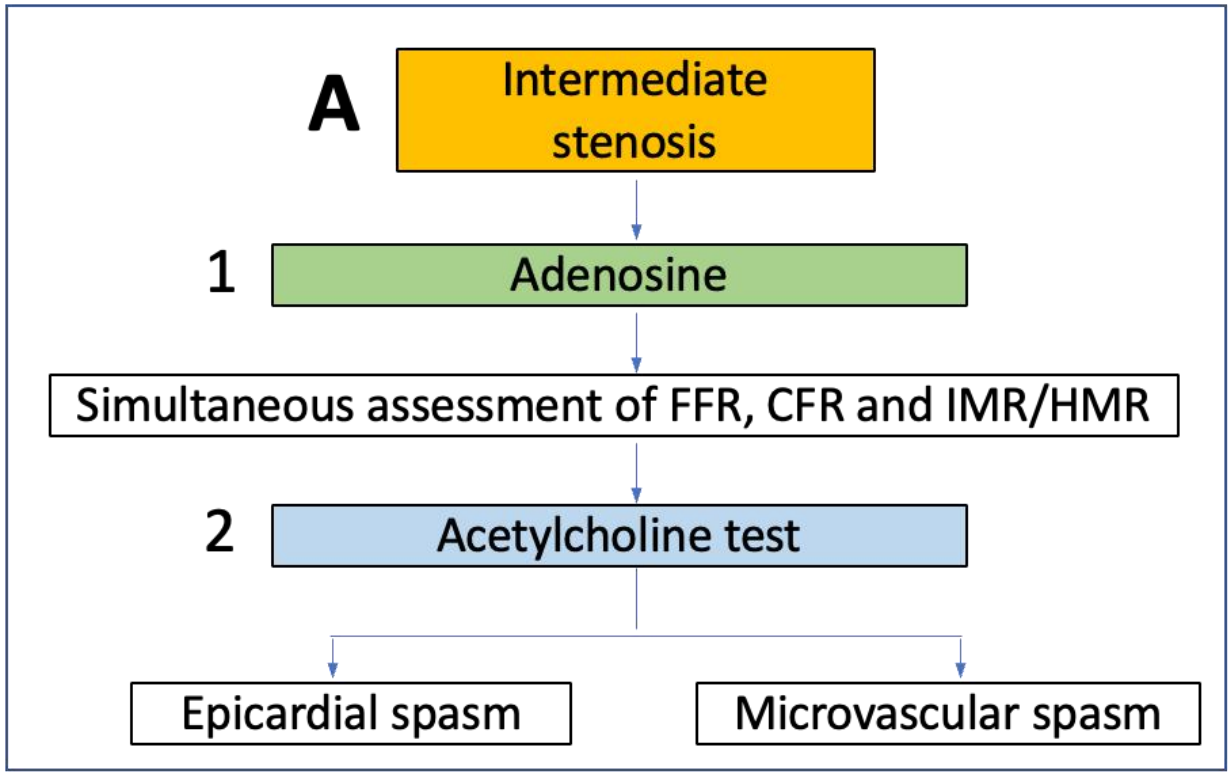
Contraindications to adenosine:
Asthma
2nd or 3rd grade atrioventricular block without pacemaker
History of a non-ablated accessory pathway

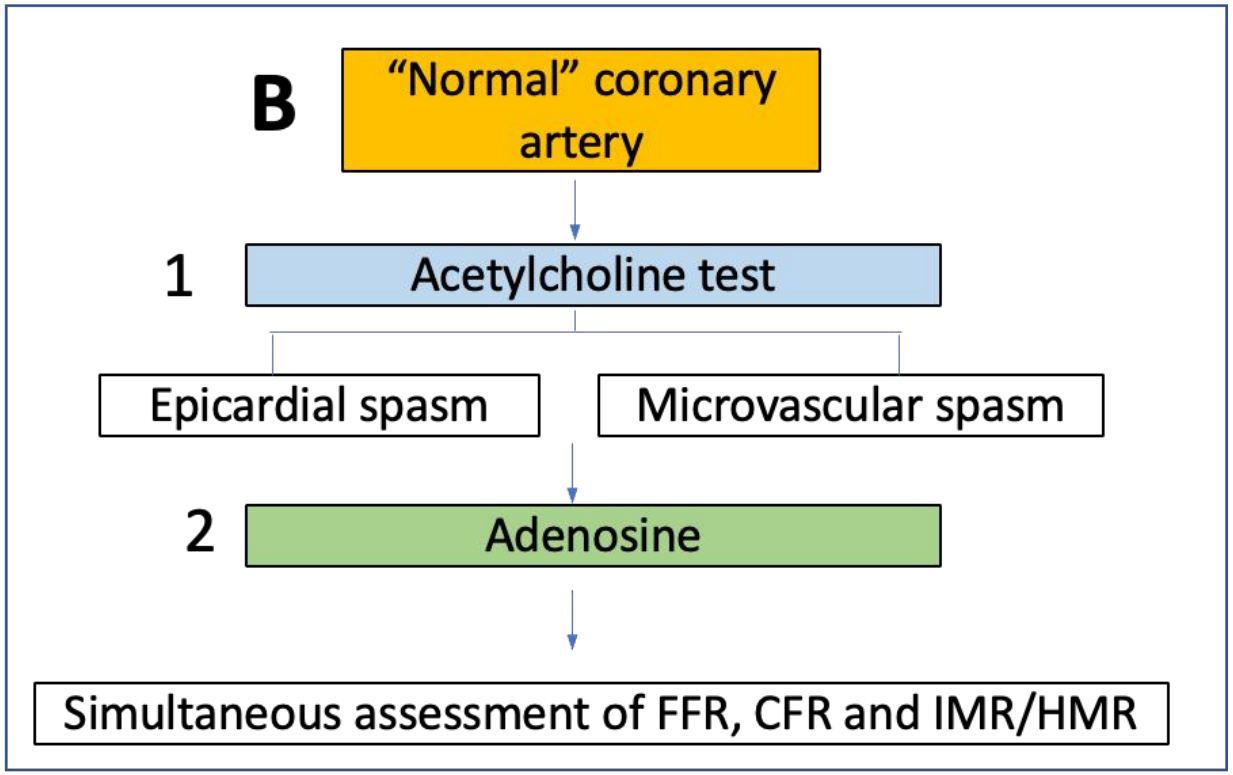
Contraindications to acetylcholine:
Asthma
2nd or 3rd grade atrioventricular block without pacemaker
Paroxysmal atrial fibrillation

How to proceed

Ach- and adenosine-based vasoreactivity protocol







- Nitroglycerine half-life: 2 min → only 3% at 10 min.

Grupo	Método de infusión	Dosis utilizadas	Tiempo de administración por dosis	Comentarios
Grupo de Harvard[30]	Infusión por microcatéter y bomba de infusión	4 diluciones de 10^{-7}, 10^{-6}, 10^{-5} y 10^{-4} por litro (infusión a 0,8 ml/min) en la CI	2 minutos	– Ideado para valorar la función endotelial – Se estima una concentración final de 10^{-9}, 10^{-8}, 10^{-7} y 10^{-6} (equivalente a una dosis total selectiva en una arteria de 0,03, 0,3, 3 y 30 µg) – Se realiza en la CI
Clínica Mayo[32]	Infusión por microcatéter y bomba de infusión	3 diluciones de 10^{-6}, 10^{-5} y 10^{-4} por litro (infusión a 1 ml/min) seguidas de un bolo de 100 µg (por el mismo microcatéter)	3 minutos (el bolo final durante 20-30 segundos)	– Protocolo mixto para valorar la función endotelial (equivalente a 0,5, 5 y 50 µg selectivo por arteria) y el vasoespasmo con bolo de 100 µg – Incluye una valoración funcional de la microcirculación con guía Doppler durante la infusión de acetilcolina – Se realiza en la CI
Grupo de Korea[33]	Infusión manual por catéter guía	3 dosis de 20, 50 y 100 µg en la CI	1 minuto	– Se realiza en la CI
Japanese Circulation Society[10]	Infusión manual por catéter guía	3 dosis de 20, 50 y 100 µg en la CI Si no hay vasoespasmo se recomiendan 2 dosis de 20 y 50 µg en la CD	20 segundos	– Provocación de vasoespasmo en la CI y la CD – Se recomienda la implantación de un electrocatéter para su realización
Grupo de Standford[19]	Infusión manual por catéter guía	4 dosis de 20, 50, 100 y 200 µg en la CI	1 minuto	– Se realiza en la CI
Grupo de Stuttgard[34]	Infusión manual por catéter guía	4 dosis de 2, 20, 100 y 200 µg en la CI En ausencia de vasoespasmo en la CI se recomienda una dosis de 80 µg en la CD	20 segundos	– Estudia la CI y la CD
Estudio CorMicA y grupo COVADIS[6,29]	Infusión mixta con bomba y manual	3 dosis crecientes de 0,18, 1,82 y 18,2 µg/ml infundidas por bomba en el catéter guía Finaliza con un bolo manual de 100 µg (50 µg en la CD)	2 minutos para cada dosis y 20 segundos para el bolo final	– Se realiza en la CI tras el estudio de la microcirculación con adenosina mediante guía de presión – Valora la función endotelial y la provocación de vasoespasmo en el mismo procedimiento
Protocolo de la ACI-SEC (presente documento)	Infusión manual por catéter guía	3 dosis de 2, 20 y 100 µg en la CI En caso de sospecha de vasoespasmo de CD se empieza la prueba en esta arteria con dosis de 2, 20 y 50 µg	20 segundos	– Si se quiere valorar la función endotelial las dosis deben administrarse más lentamente, durante 2-3 minutos – Se realiza en la CI

- Way of administration
- Number of doses
- Whole amount of Ach
- Infusion duration

Assessment of endothelium-dependent function

Acetylcholine test

- Preparation of acetylcholine:
  - Drug unstability → preparation just before the procedure (valid for consecutive studies).

1 mL (10 mg) in 500 mL of saline → 20 µg/mL

20 mg

2 mL
10 mg/mL

- Coronaria izquierda:
1. **ACH IC 2mcg**. Coger 1cc, diluir hasta 10cc (2mcg/ml). Desechar 9cc, y volver a diluir hasta 10cc = (**2mcg/10ml**)
2. **ACH IC 20mcg**. Coger 1cc (20mcg) y diluir hasta 10cc SSF= (**20mcg/10ml**)
3. **ACH IC 100mcg**. Coger 5cc (100mcg) y diluir hasta 10cc SSF= (**100mcg/10ml**)
4. **ACH IC 200mcg**.Coger 10cc (200mcg) = (**200mcg/10ml**)

- Coronaria derecha:
1. **ACH IC 2mcg**. Coger 1cc, diluir hasta 10cc (2mcg/ml). Desechar 9cc, y volver a diluir hasta 10cc = (**2mcg/10ml**)
2. **ACH IC 20mcg**. Coger 1cc (20mcg) y diluir hasta 10cc SSF= (**20mcg/10ml**)
3. **ACH IC 80mcg**. Coger 4cc (80mcg) y diluir hasta 10cc SSF= (**80mcg/10ml**)

Spasm provocation

- Increasing doses of Ach:
  - Left coronary artery: 2 → 20 → 100 µg (→ 200 µg).
  - Right coronary artery: 2 → 20 → 50 µg (→ 80 µg).

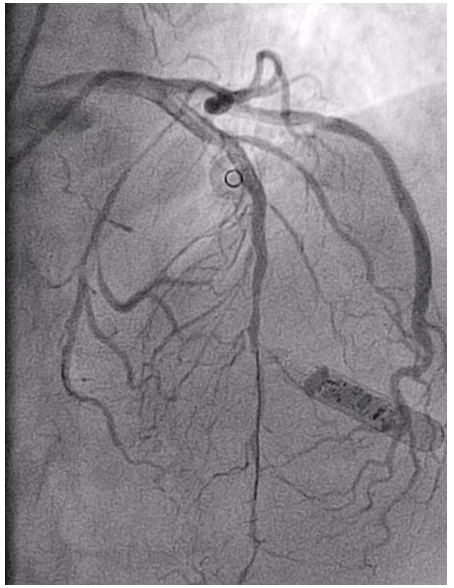
- Administration as a bolus (20-30 s) + slow flush with saline.
  - 2 min between doses.

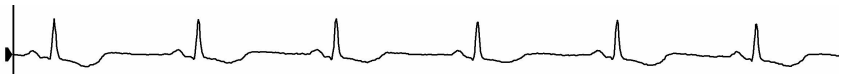
- Symptoms (reproduction).
- ECG ischaemic abnormalities.
- Epicardial spasm.

Epicardial vs microvascular spasm

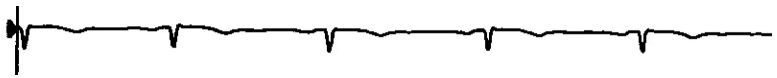
- Nitroglycerine (200-300 µg).

Epicardial spasm
Symptoms
ECG ischaemic abnormalities
Reduction in coronary diameter >90% from baseline





Microvascular spasm
Symptoms
ECG ischaemic abnormalities
No epicardial spasm (<90% reduction in coronary artery diameter)



Ong P, Int J Cardiol. 2018

Assessment of endothelium-independent function

- Use of a dedicated guidewire

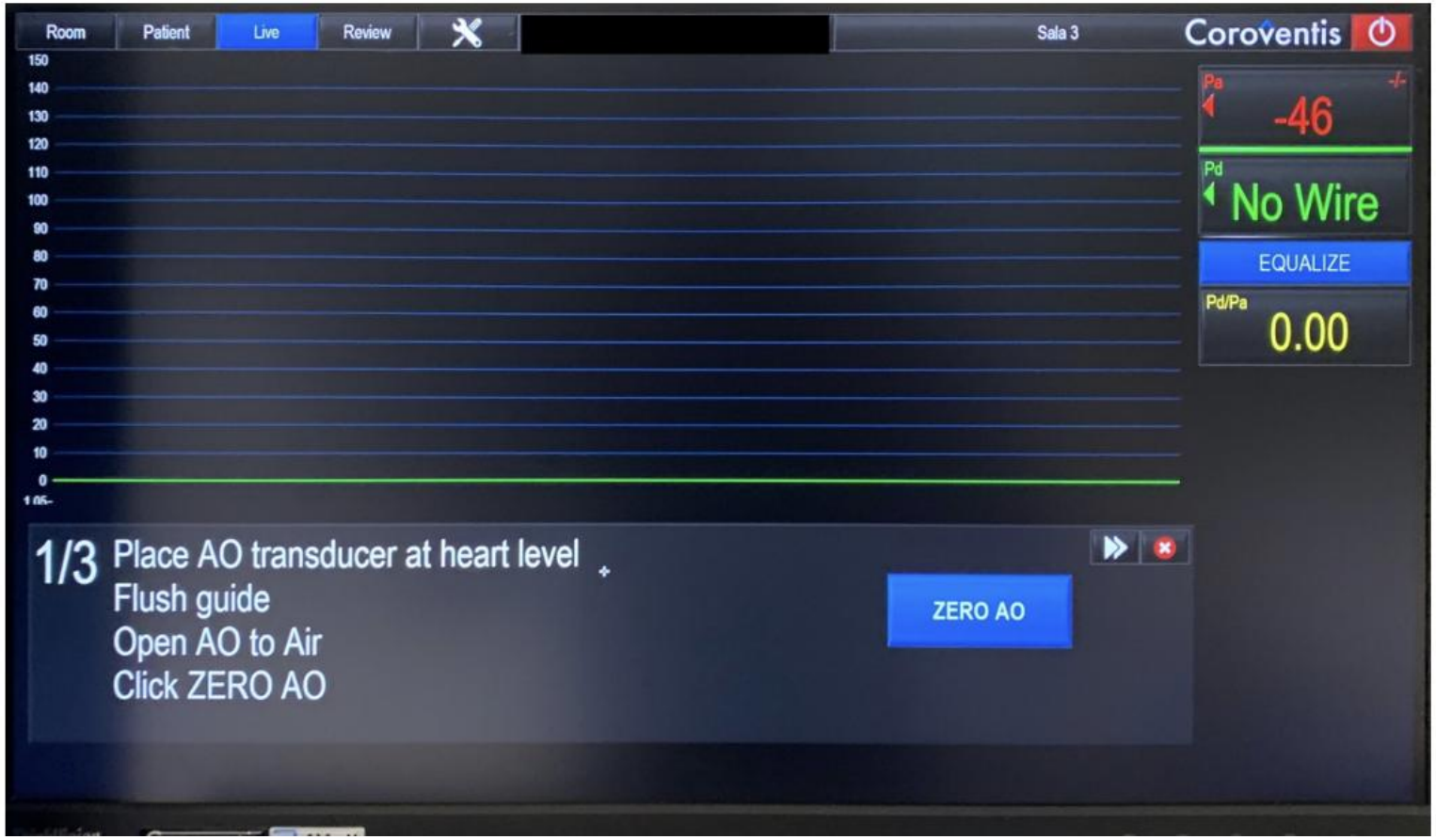
Thermodilution

PressureWire X (Abbott)

Doppler

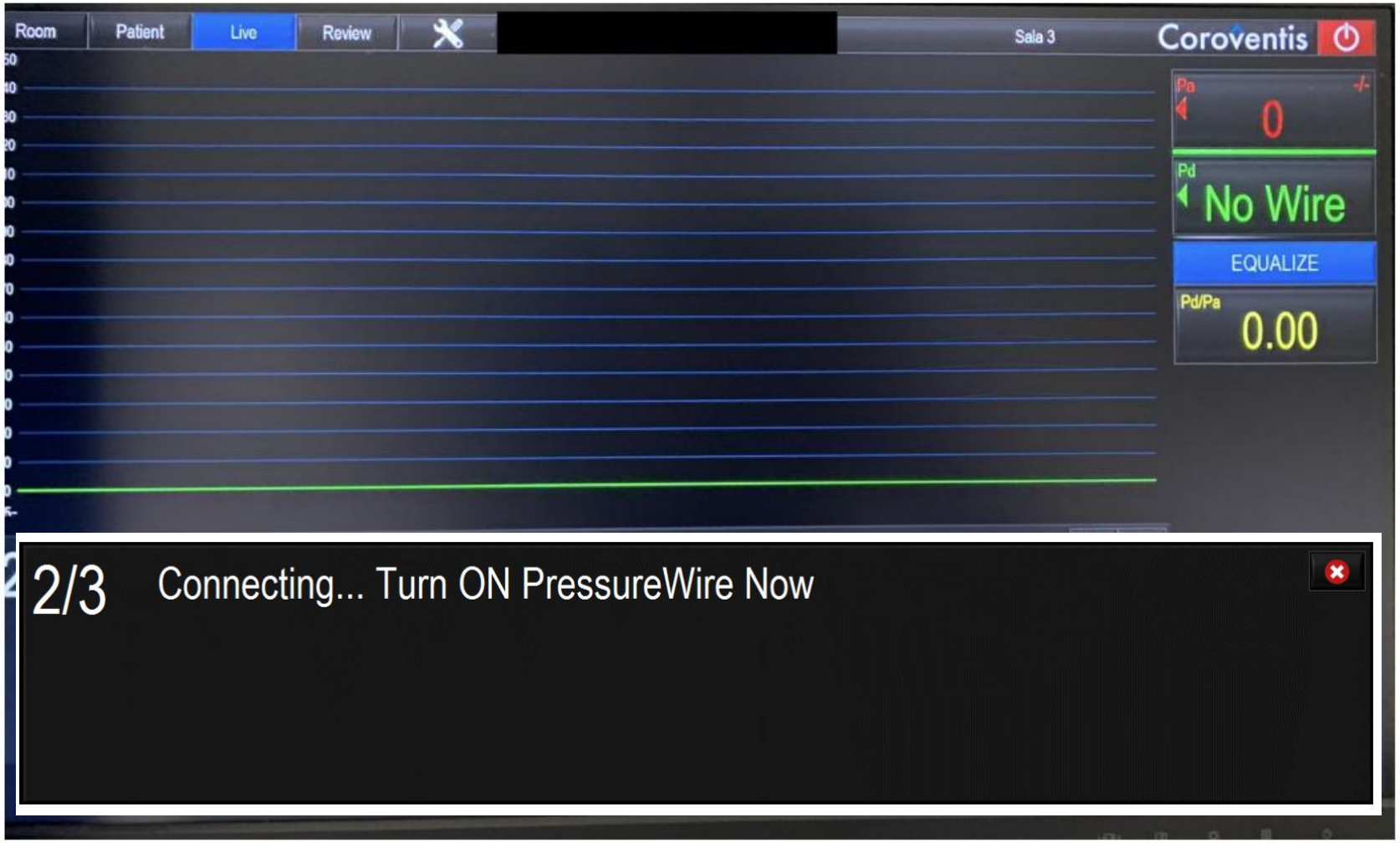
ComboWire XT *Flowire*

PressureWire X & Coroventis management



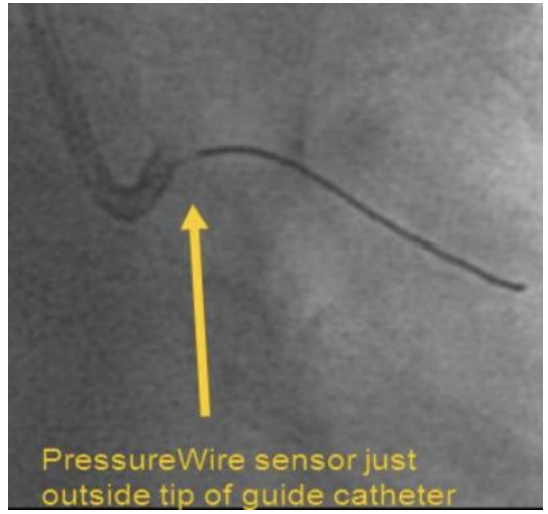
- Flush the guide catheter
- Zero in aortic pressure

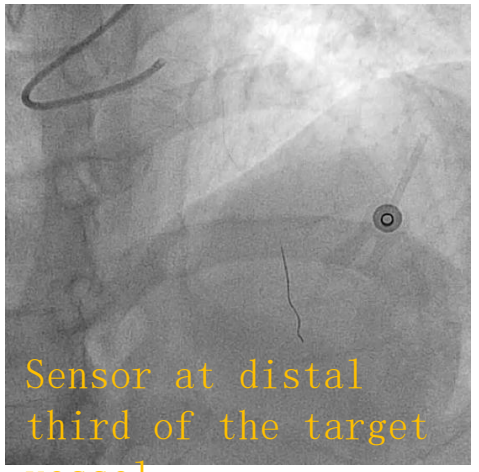
PressureWire X & Coroventis management



- Flush PressureWire X
- Do not turn it on YET


Room
Patient
Live
Review
Sala 3
Coroventis
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Pa
98/46
68
Pd
108/54
78
EQUALIZE
Pd/Pa
0.00
3/3 Advance PressureWire to catheter opening
Click EQUALIZE
EQUALIZE


PressureWire sensor just
outside tip of guide catheter



- Flush guide catheter
- Select measure

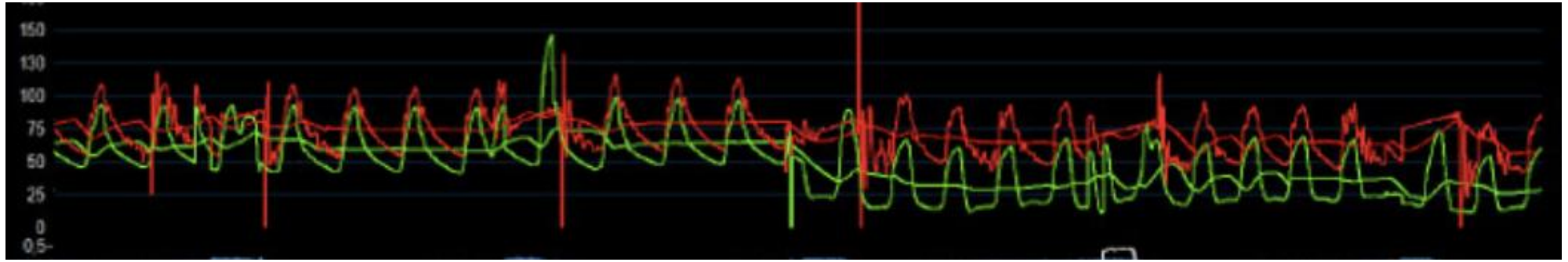
- 3 intracoronary injections of saline (3-4 ml) at room temperature.

→ Resting mean transient time

- Ensure correct catheter canulation
- Most frequent alarms
- Discordant values

- Steady-state hiperemia: intravenous adenosine (140 μg/kg/min).

- Alternative: bolus of adenosine (200 μg for LCA, 100 μg for RCA).



Assess hemodynamic markers of coronary hiperemia:

1) "Ventricularization" of the distal pressure waveform.
2) Disappearance of distal dicrotic pressure notch.
3) Separation of mean aortic and distal pressures

- Wait until stable hyperemia is achieved.
- Then, click in "Induce Hyperemia & Press here"

- At steady-state hyperemia: 3 new injections.

→ Hyperemic mean transient time