Endotypes are clinically useful and should be determined

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MMM, Madrid, November 29th, 2023

Disclosure Statement of Financial Interest

Receipt of grants / research support:

Abbott, ACIST Medical Systems, Boston Scientific, Medtronic, MicroPort, Pie Medical Imaging, ReCor Medical

Receipt of honoraria or consultation fees:

Abbott, Abiomed, ACIST Medical Systems, Boston Scientific, CardiacBooster, Kaminari BV, Medtronic, Pie Medical Imaging, PulseCath, ReCor Medical, Sanofi, Siemens Healthineers

INOCA
Ischaemia with non-obstructive coronary arteries

- Up to 70% of patients undergoing CAG do not have obstructive CAD
- INOCA in up to 39%
  - Higher frequency in women (50-70%)

Camici et al. New Engl J Med 2007, Pepine et al. J Am Coll Cardiol 2010 and Kunadian V. et al. EuroIntervention 2021

Ischaemia with non obstructive coronary arteries (INOCA)

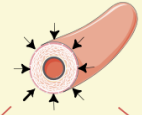
Coronary Microvascular dysfunction (CMD)

Coronary microcirculation

Impairs coronary physiology and myocardial blood flow in subjects with risk factors

Causes microvascular angina and contributes to myocardial ischaemia in CAD

Vasospastic angina (VSA)



Transient vasospasm

Persistent vasospasm

Prinzmetal angina

Myocardial infarction

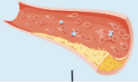
Ischaemia with obstructive coronary artery disease

Atherosclerotic disease

Epicardial coronary artery

Stable plaque

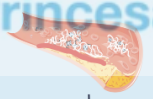
Vulnerable plaque



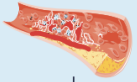
Reduction in FFR

Demand ischaemia ± angina

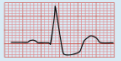
Plaque rupture



Thrombosis



Acute coronary syndromes/infarction



Non-obstructive coronary atherosclerosis is frequently present.

These mechanisms can overlap

Relevance of establishing a diagnosis

- **INOCA rarely correctly diagnosed -> no tailored therapy prescribed**
- **Compared to asymptomatic individuals, INOCA is associated with increased incidence of cardiovascular events, repeated hospital admissions, as well as impaired quality of life and associated increased health care costs**

Kunadian R. et al. EuroIntervention 2021

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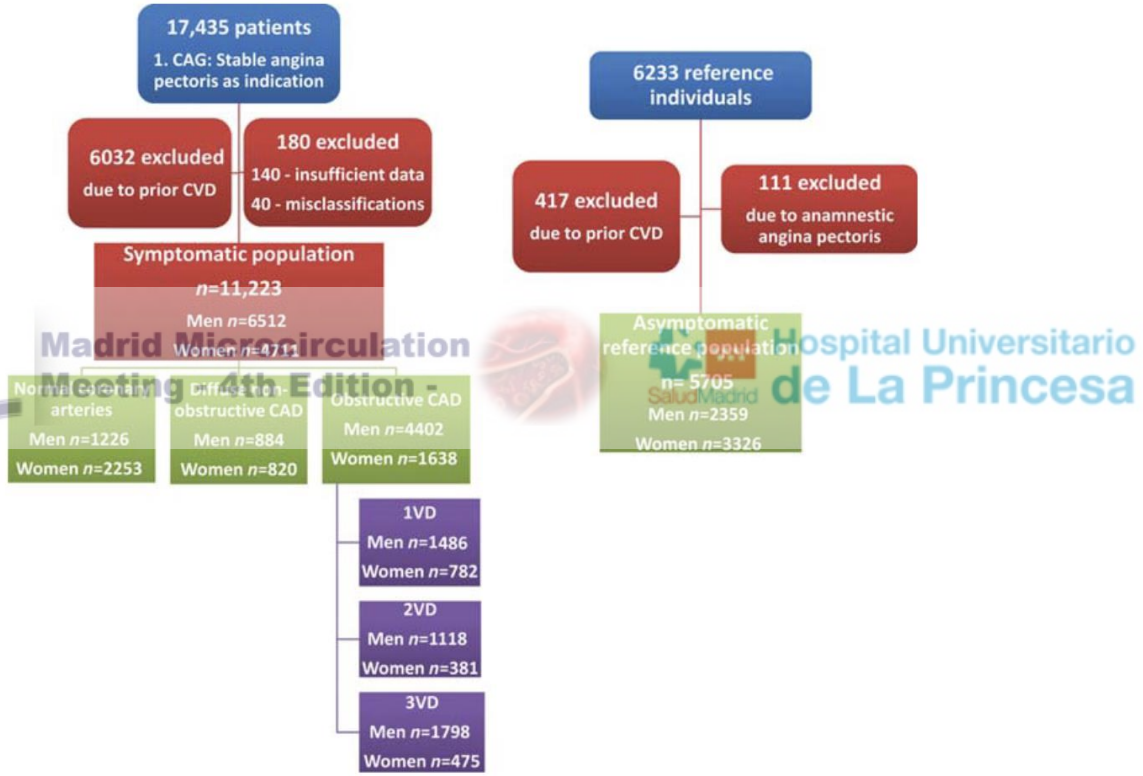
Prognosis of CCS patients with normal epicardial coronaries



Jespersen L. et al. Eur Heart J 2012

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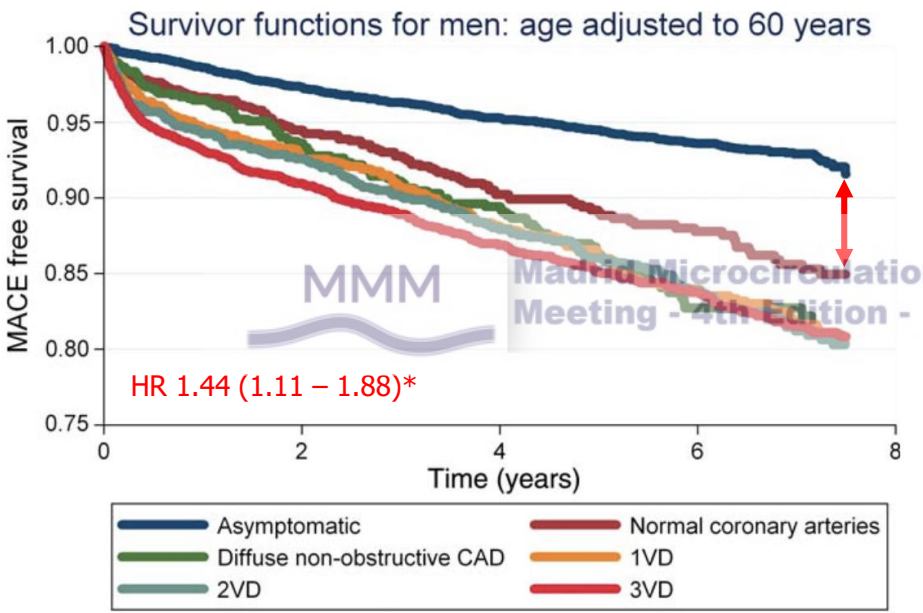
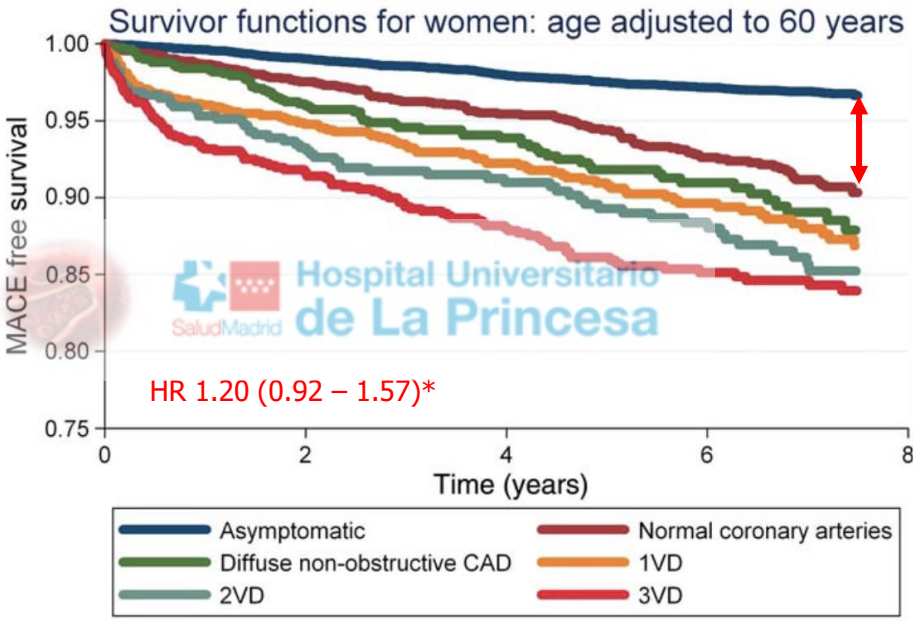
Prognosis of CCS patients with normal epicardial coronaries





* Adjusted for age, BMI, diabetes, smoking status, and use of lipid-lowering and antihypertensive medication

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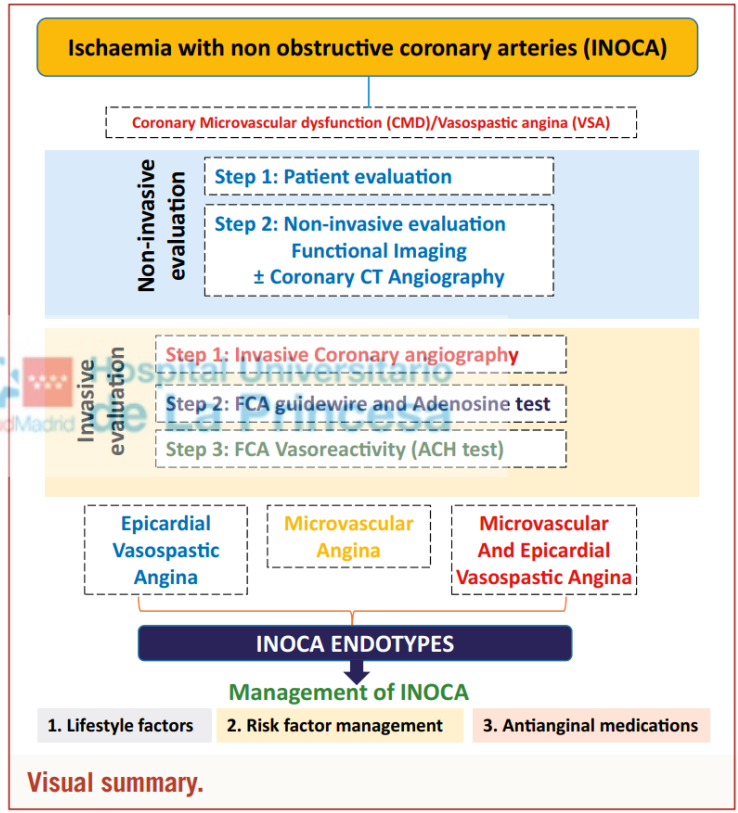
Jespersen L. et al. Eur Heart J 2012

Diagnosis

- Diagnostic guidewire and Adenosine test
  - Fractional Flow Reserve (FFR)
  - Coronary Flow Rate (CFR)
  - Index Microvascular resistance (IMR)
  - Hyperaemic myocardial velocity resistance (HMR)
- Vasoreactivity (acetylcholine test)



Kunadian V. et al. EuroIntervention 2021

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Vasospastic angina

Myron Prinzmetal 1908 - 1987

- Clinical manifestation of myocardial ischaemia caused by dynamic epicardial coronary obstruction caused by a vasomotor disorder
- More prevalent in Asian vs. Western populations (±20 vs 10%)
- Hyperreactive epicardial coronary segment
  - Maximal contraction when exposed to vasoconstrictor stimulus
  - Smoking, drugs, cold, stress, etc.
- Normal CFR (≥ 2,0)
- ACh testing

Prinzmetal Am J Med 1959 and Kunadian V. et al. EuroIntervention 2021

Microvascular dysfunction / angina

- **Microvascular angina (MVA) is the clinical manifestation of ischaemia caused by CMD**
- **Incidence 26 – 39% among patients with AP and normal epicardial coronaries**
- **CFR reduced (<2,0)**
- **Increased IMR (≥25) & HMR (≥1,9)**
- **Subtypes**
  - **Structural microcirculatory remodeling (CMP)**
  - Reduced vasodilatory range, limiting blood and oxygen supply
  - **Functional arteriolar dysregulation**
  - Dysregulation of the upstream vasodilatory cascade in medium to larger arterioles

Kunadian V. et al. EuroIntervention 2021

How to diagnose?

Currently, no technique allows a direct anatomical visualization of the coronary microcirculation in vivo in humans. Therefore, its assessment relies on the measurement of parameters which reflect its functional status, such as myocardial blood flow and CFR

Investigations in patients with suspected coronary microvascular angina

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

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Recommendations for investigations in patients with suspected vasospastic angina

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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Knuuti J. et al. Eur Heart J 2019

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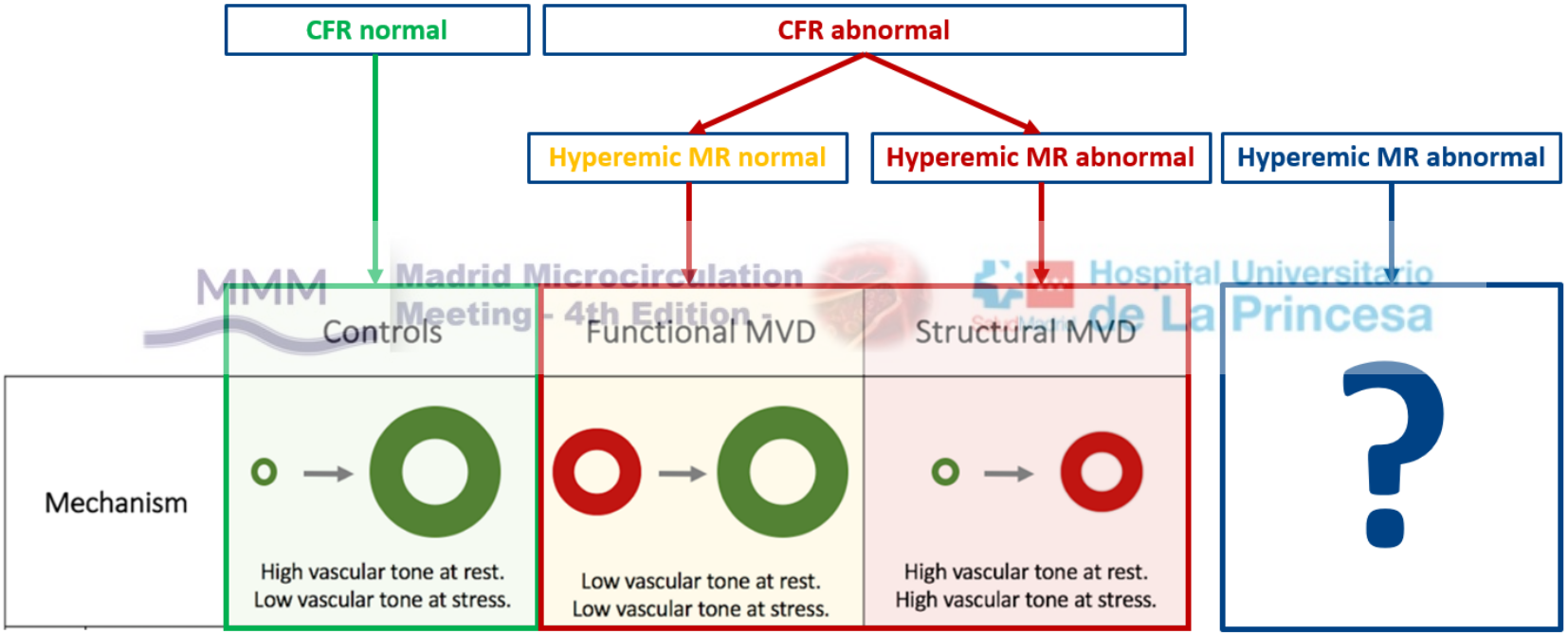
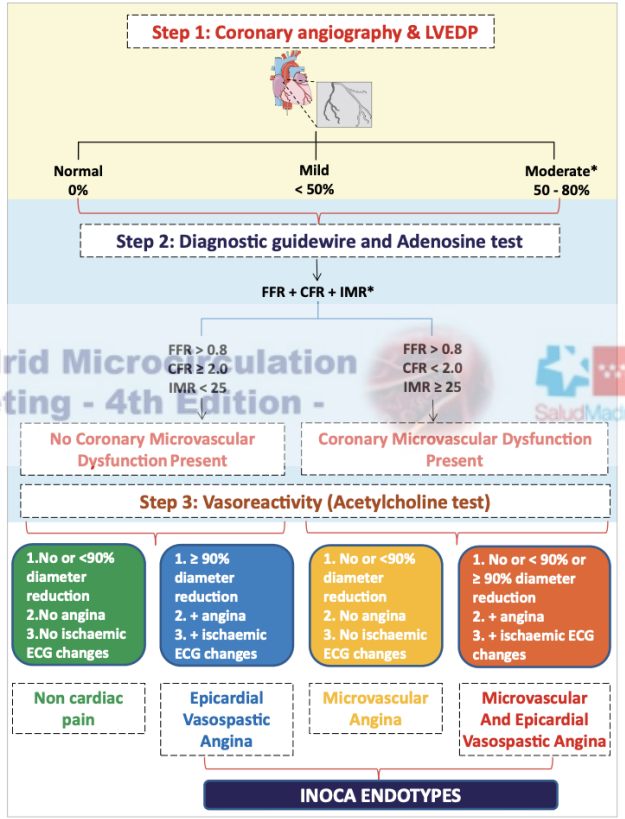
Microvascular dysfunction



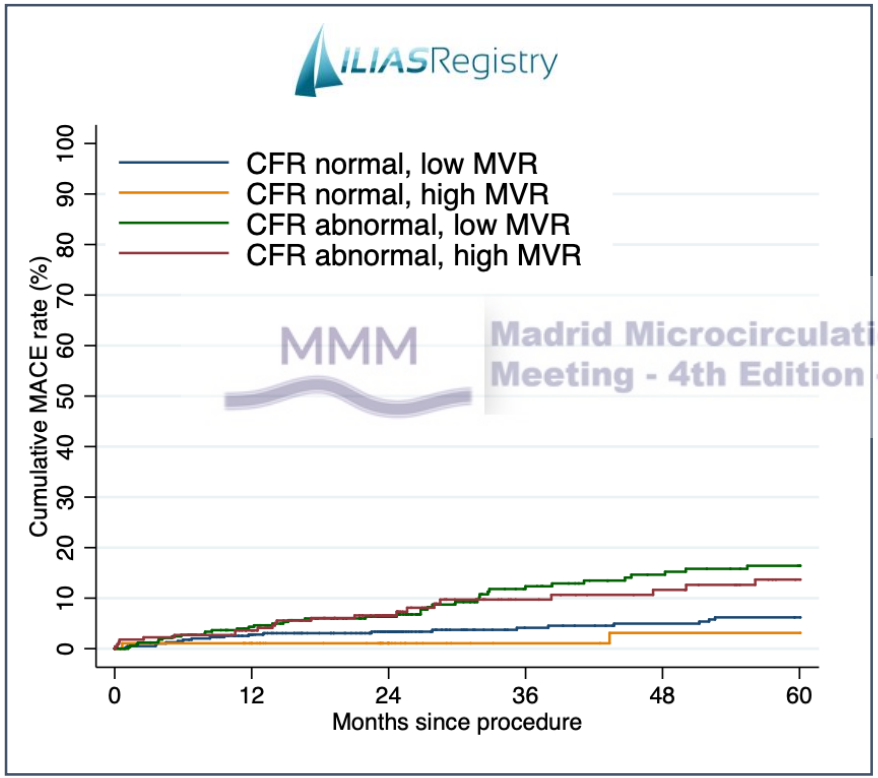
Rahman et al., Circulation 2019

Work-up

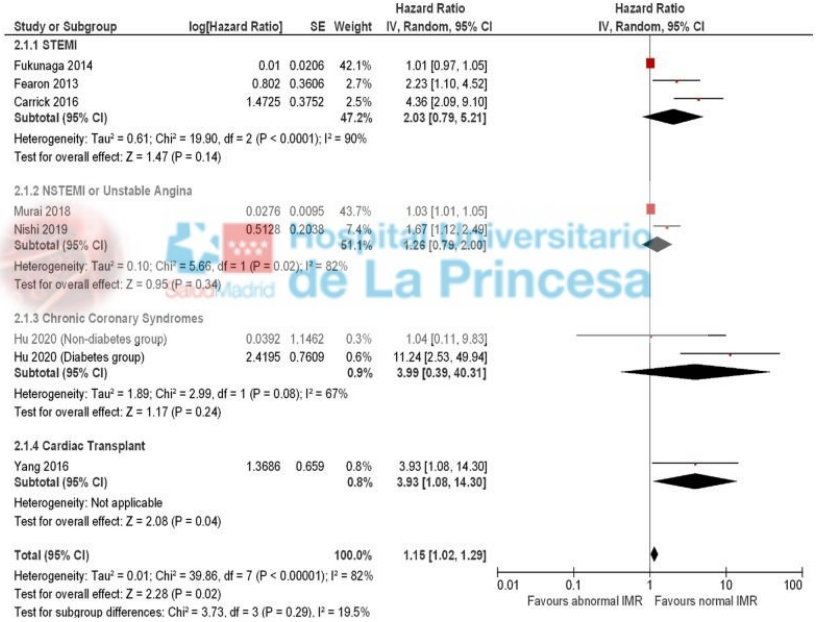


Kunadian V. Euro Intervention 2019

CFR / IMR and outcome



Meta-analysis: 79studies (59 740 subjects)



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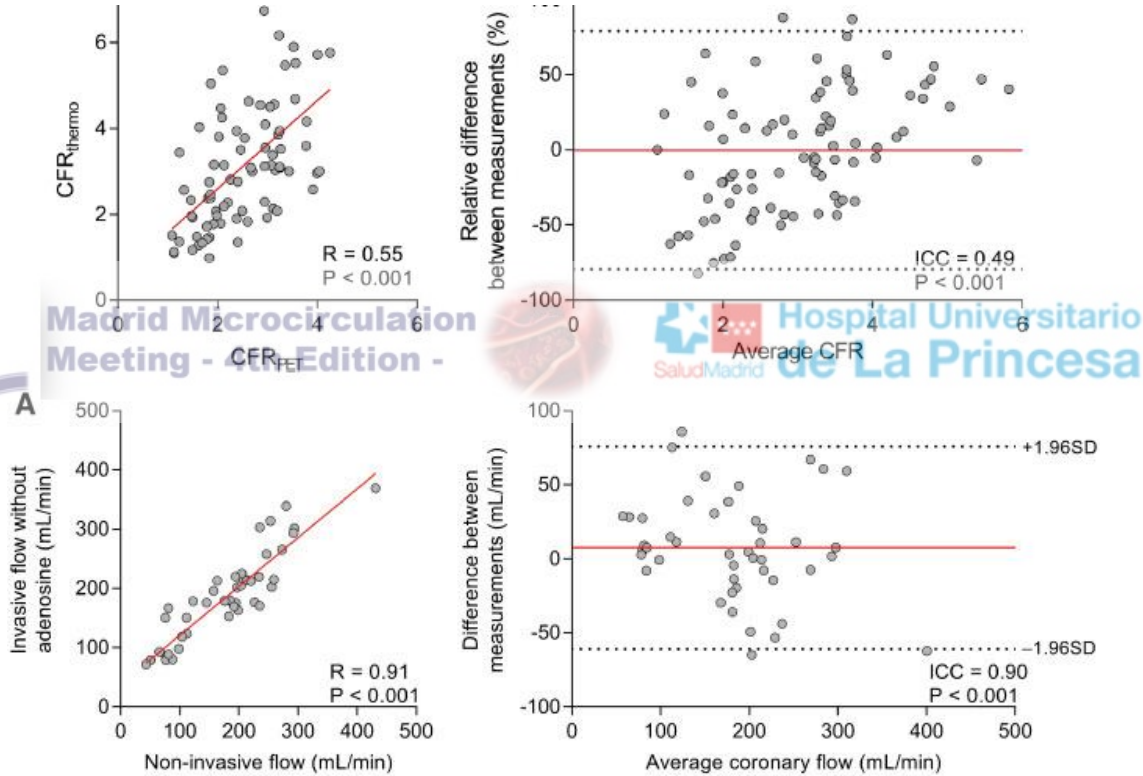
Rahman et al., Circulation 2019, Boerhout et al., EuroIntervention 2022, Kelshiker et al. Eur Heart J 2022

Coronary thermodilution versus PET

Bolus

Continuous



Everaars, et al., JACC interventions 2018, Everaars, et al. Eur Heart J. 2019;40;2350–2359

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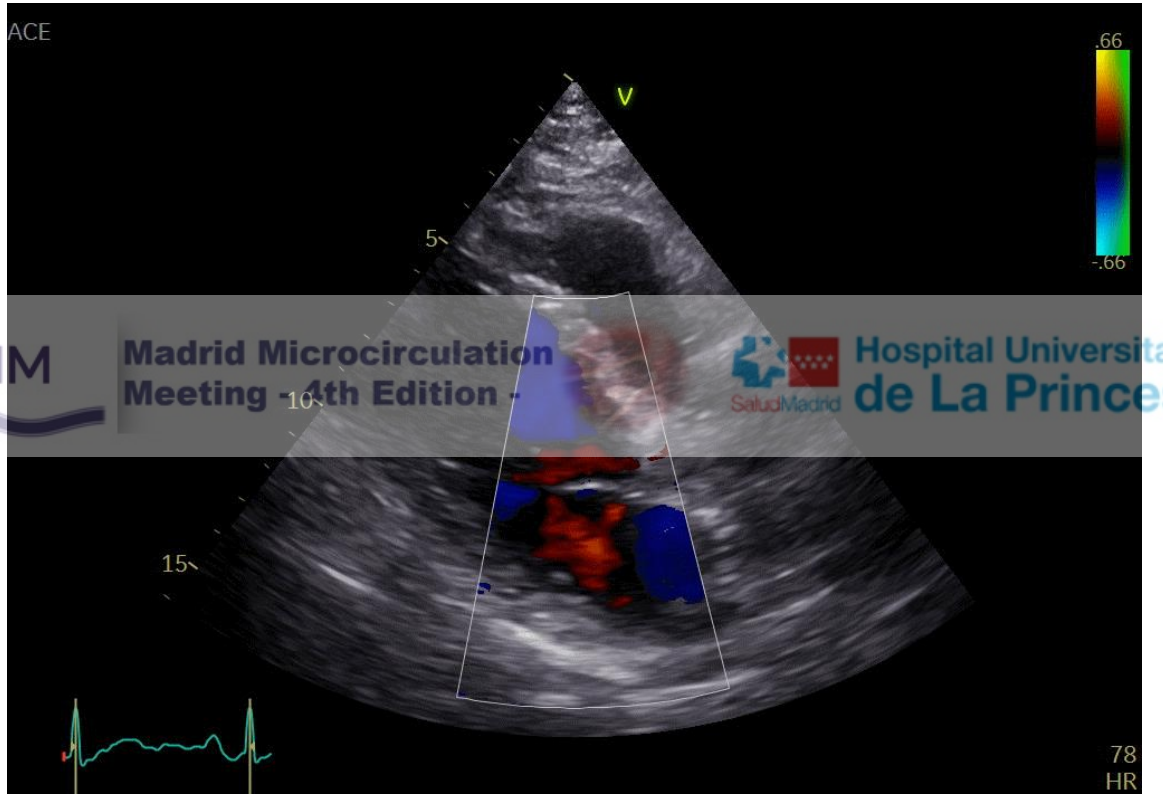
Case example

- 55y/old male
  - 2nd opinion refractory angina
  - Hypertension, hypercholesterolemy
  - TTE & SPECT 2021 normal
  - 2021 CAG referring site, intermediaite lesion mid LAD, FFR negative

Case example



Case example

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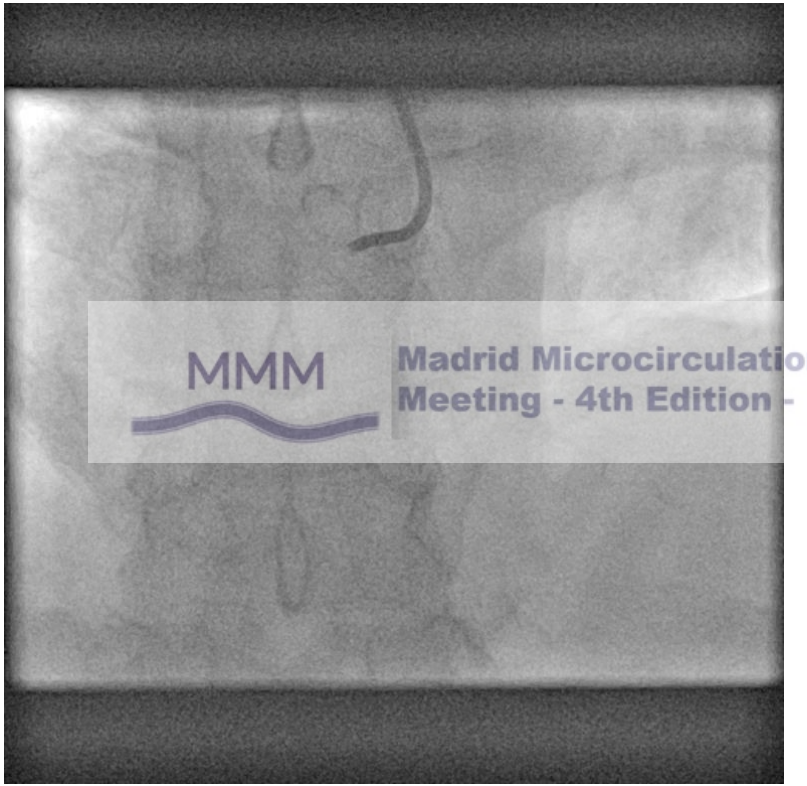
Angio 2022



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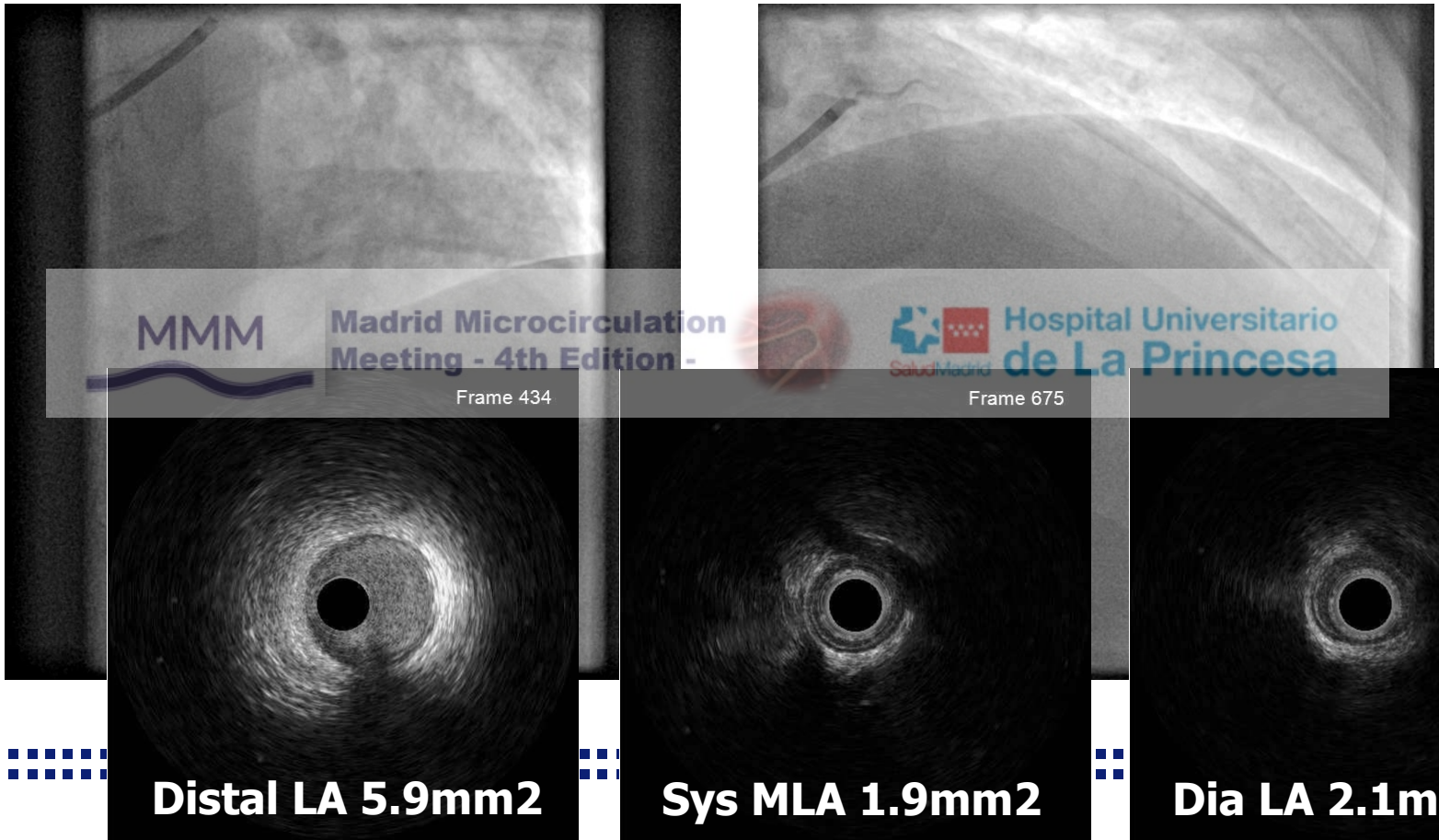
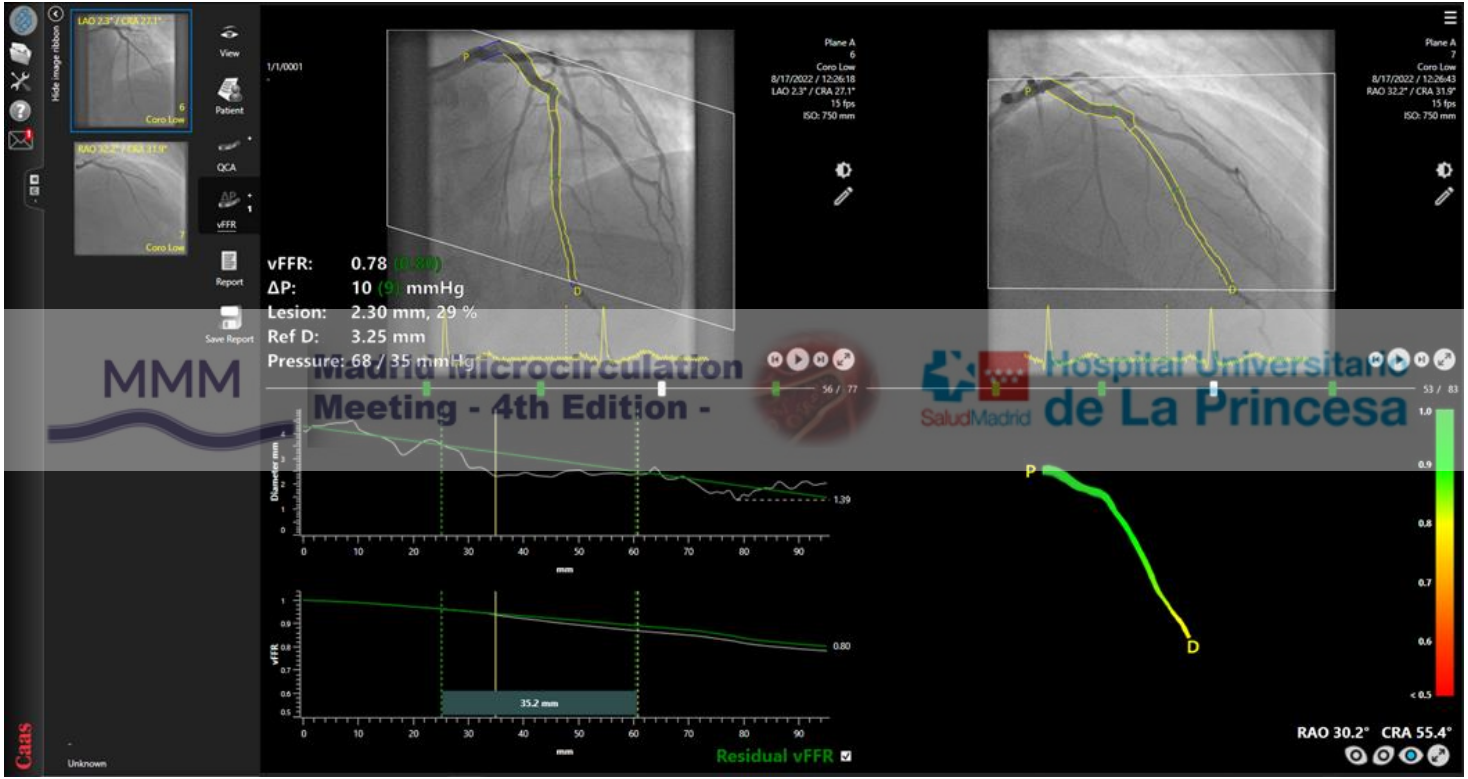
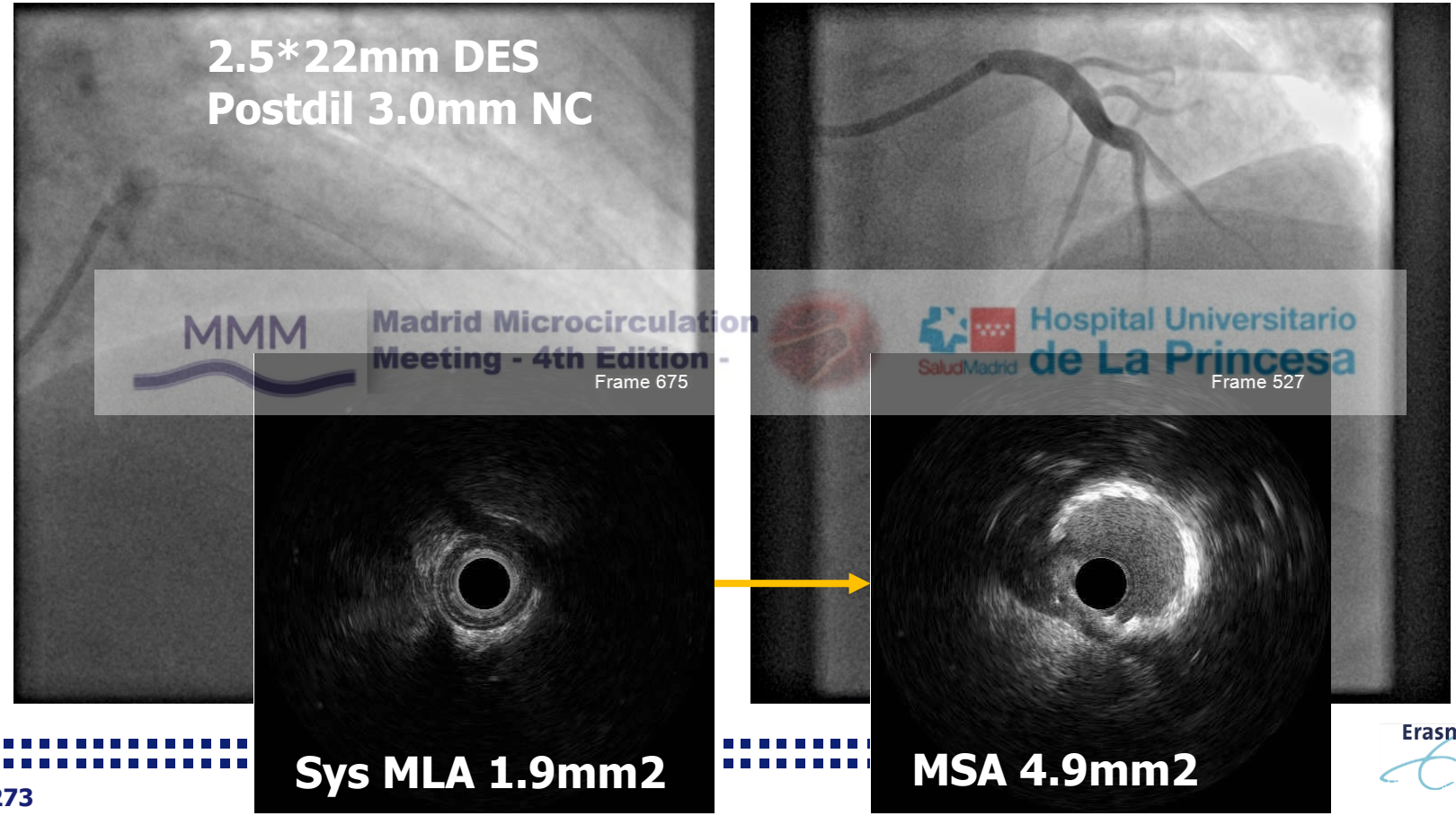
Angio and IVUS 2022



vFFR LAD


vFFR: 0.78
ΔP: 10 mmHg
Lesion: 2.30 mm, 29 %
Ref D: 3.25 mm
Pressure: 68 / 35 mmHg
Residual vFFR
RAO 30.2° CRA 55.4°
Madrid Microcirculation Meeting - 4th Edition -
Hospital Universitario de La Princesa

Angio and IVUS 2022



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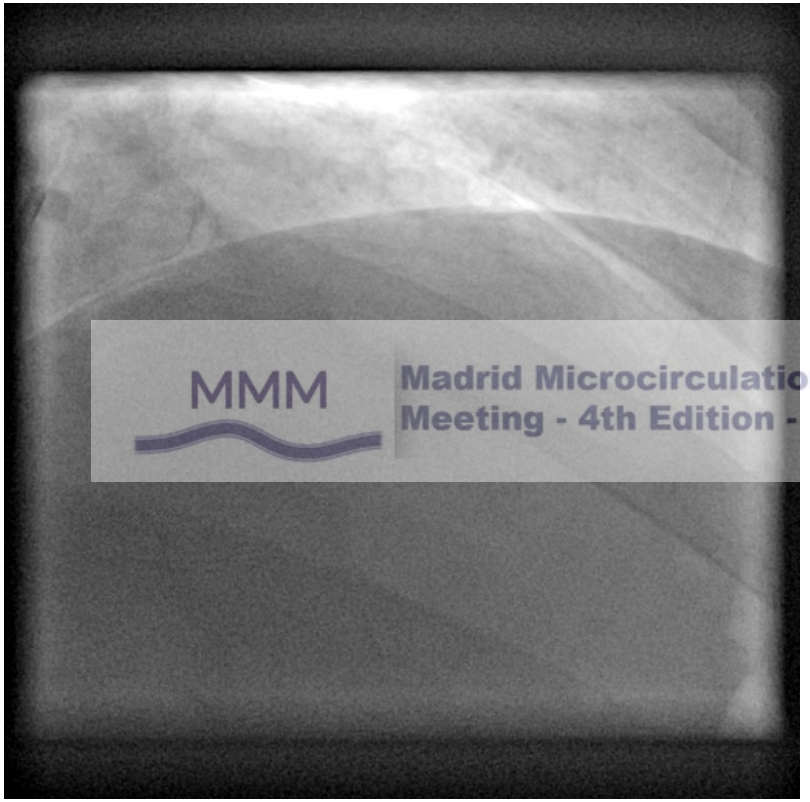
August 2023, again referred

- Slight improvement after cardiac rehabilitation program
- BP 117/74mmHg
- ECG: SR 55bpm, normal repolarization and conduction times
- Persistent limiting angina
  - ASA 80mg
  - Atorvastatin 40mg
  - Diltiazem 200mg
  - Transdermal NTG 10mg/24h

Angio with extensive physiology



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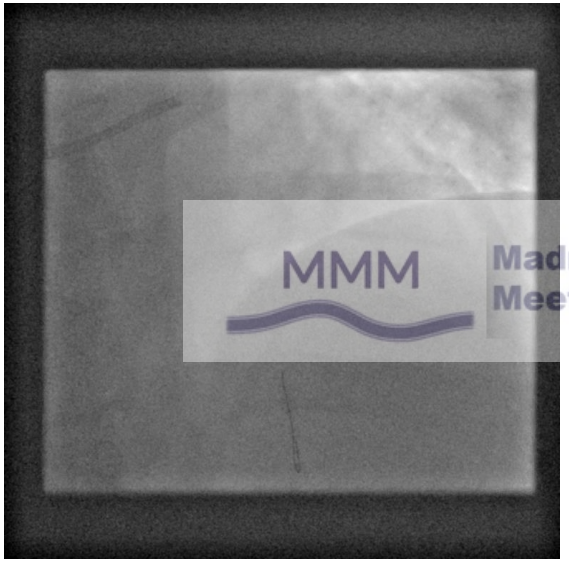
Angio with extensive physiology



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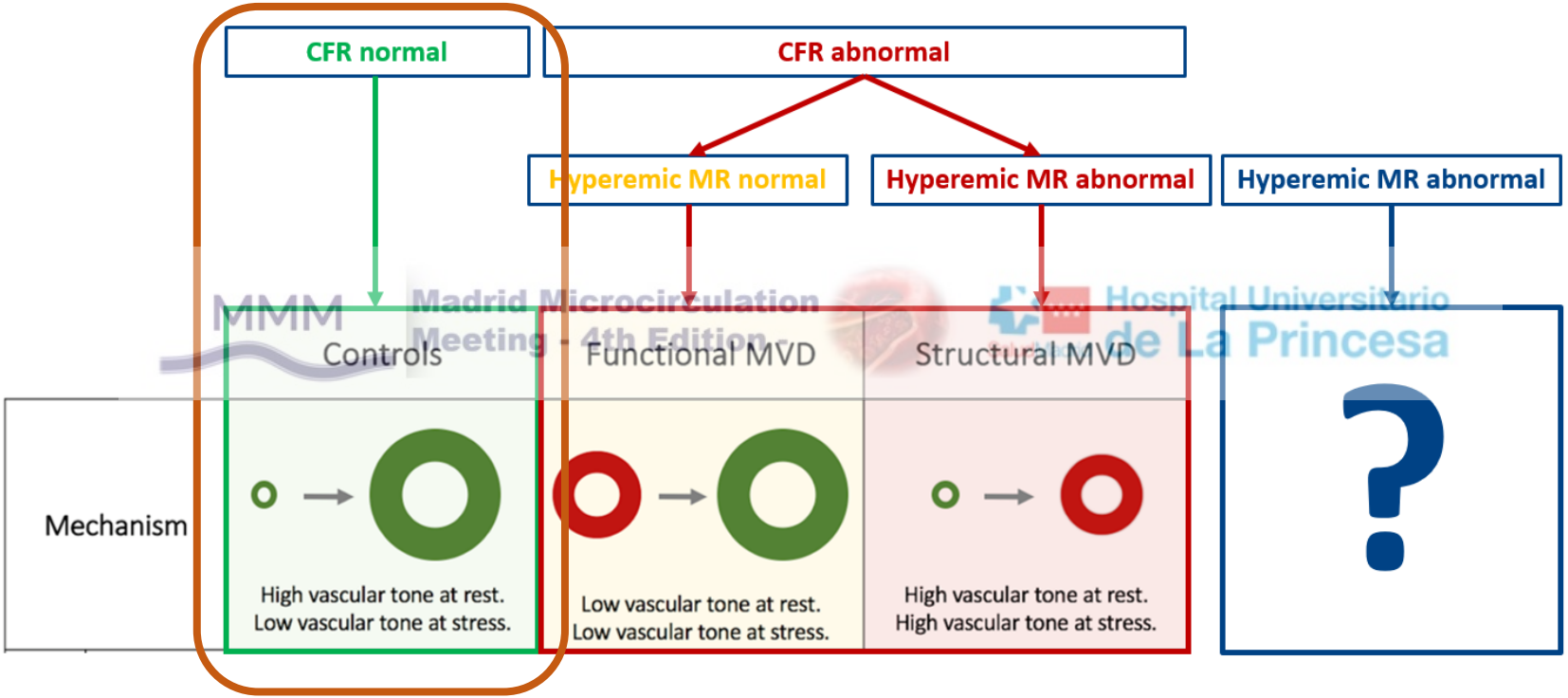
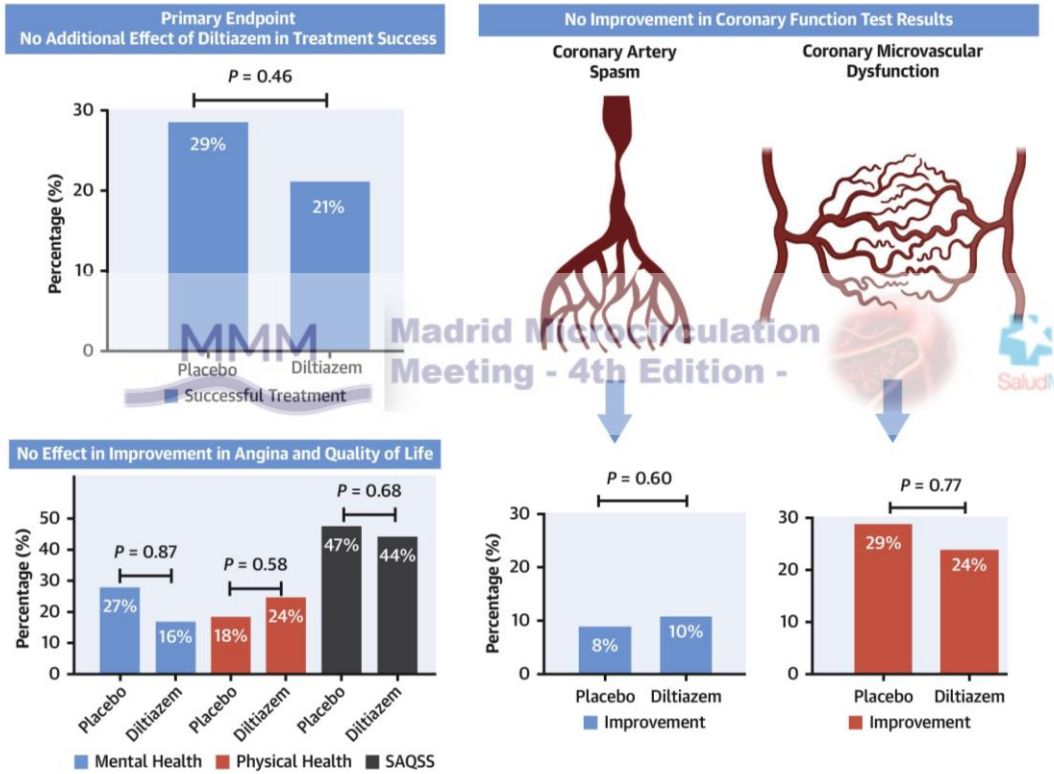
Result?



Efficacy of 6w of Diltiazem to improve vasomotor dysfunction, symptoms and QoL (n=85)



PEP=normalization of 1 abnormal parameter of CVD and no normal parameter becoming abnormal

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More patients on diltiazem treatment progressed from epicardial spasm to microvascular or no spasm (47% vs 6%; P = 0.006)

Jansen T, et al. , JACC Cardiovasc Imaging, 2022

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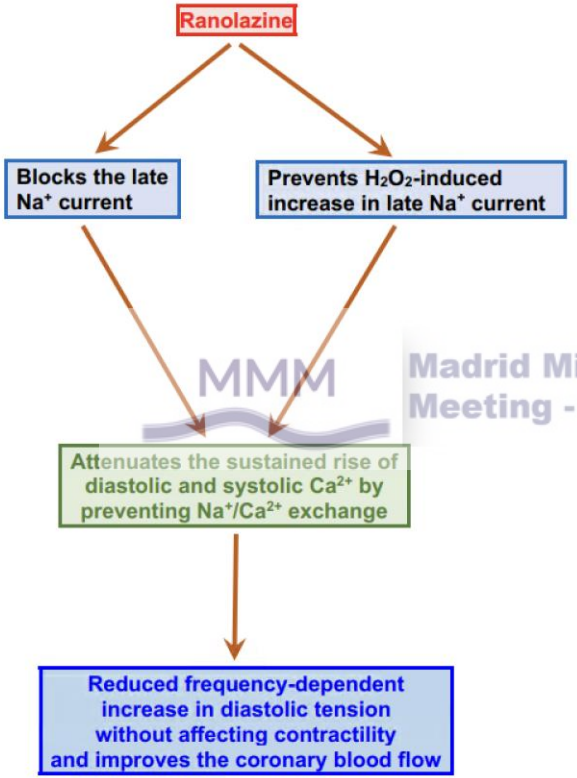
Efficacy of Ranolazine (meta-analysis)



- When added to existing anti-anginal agents, ranolazine may improved QoL.
- Patients with low CFR had signifcant improvement in CFR and suggesting that those with more severe CMD respond more favorably to ranolazine.
- Exercise duration and time to myocardial ischemia were signifcantly increased after treatment with ranolazine.

Sharp et al. AM J Cardiovasc Drugs 2021

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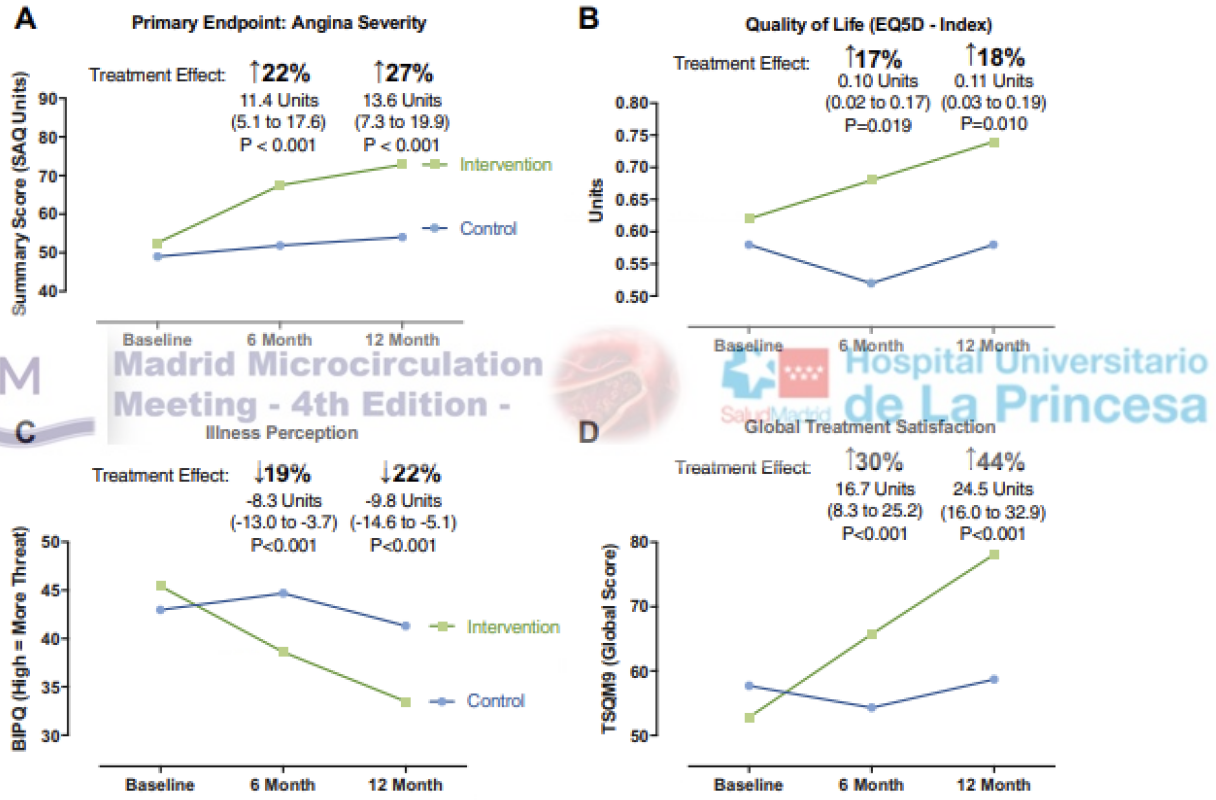
CorMiCa (Coronary Microvascular Angina)



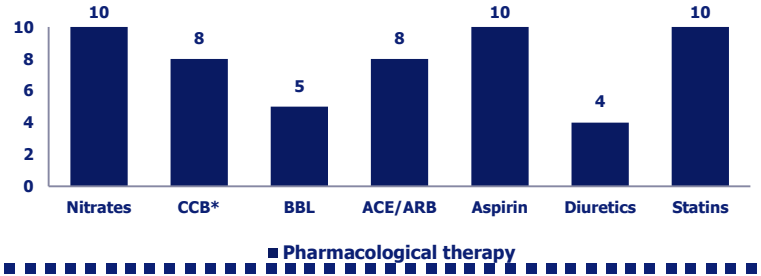
Ford, TJ, et al., JACC Cardiovasc Interv. 2020.

A role for renal denervation?

BACKGROUND: Sympathetic hyperactivity has been linked to vasospastic angina (VSA), although the exact pathophysiology of the disease is poorly understood.

METHODS

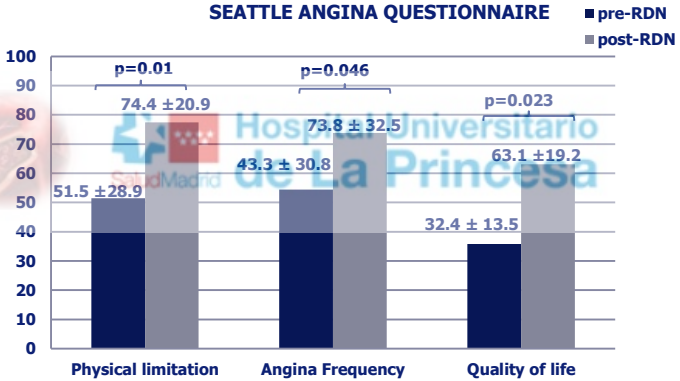
- Ten patients with refractory VSA underwent RDN using a dedicated circumferential ultrasound balloon catheter (Paradise™, ReCor Medical, Palo Alto, CA).
- Cardiac sympathetic nerve activity was assessed pre-procedure and at 6 months post-procedure, using iodine-123-metaiodobenzylguanidine (MIBG) imaging heart to mediastinum (HMR) and washout rates (WR).
- The Seattle Angina questionnaire (SAQ) was used to assess the effect on quality of life.



CARDIAC SYMPATHETIC ACTIVITY USING 123I-MIBG

	pre-RDN	post-RDN	p
Early HMR	2.68 ± 0.71	2.60 ± 0.60	0.43
Late HMR	2.58 ± 0.75	2.46 ± 0.77	0.23
WR	12.1 ± 7.68	16.8 ± 10.2	0.15

SEATTLE ANGINA QUESTIONNAIRE



RDN resulted in significant improvements in quality of life at 6 months follow-up in patients with refractory VSA.
However, RDN did not result in significant changes in cardiac sympathetic activity.

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Feyz L et al. J Nuclear Cardiology 2018

Conclusions

- **INOCA is not a rare phenomon**
- **Causes of INOCA are multifactorial**
- **Difficult to diagnose**
- **Likely even more difficult to treat**

- **Dedicated research focussed on both diagnosis and treatment of coronary microcirculation is eagerly warranted**

Thank You

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