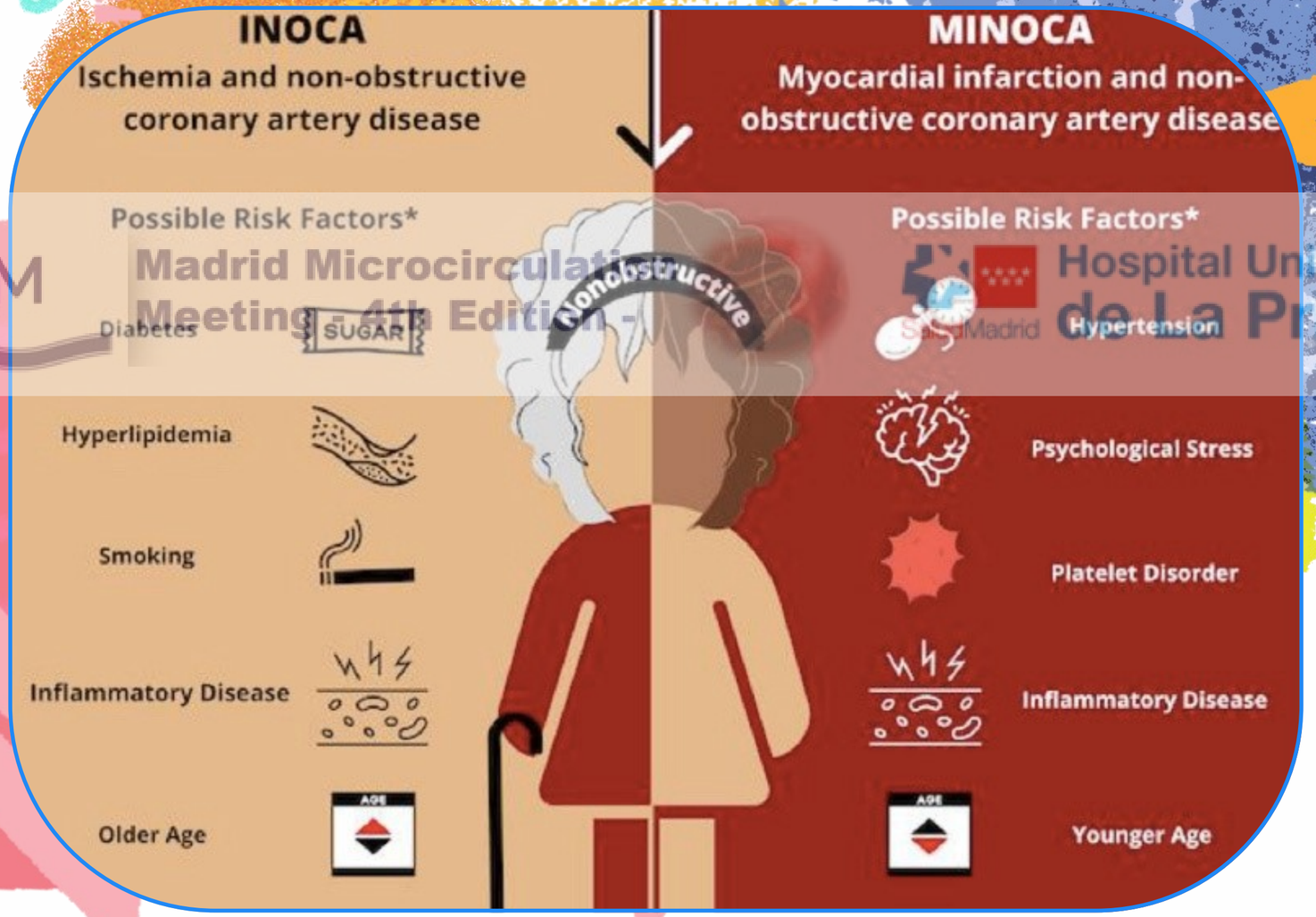
CLINICAL MANAGEMENT OF INOCA patients

Jessica Roa-Garrido

JUAN RAMÓN JIMENEZ HOSPITAL, HUELVA, SPAIN

My patient

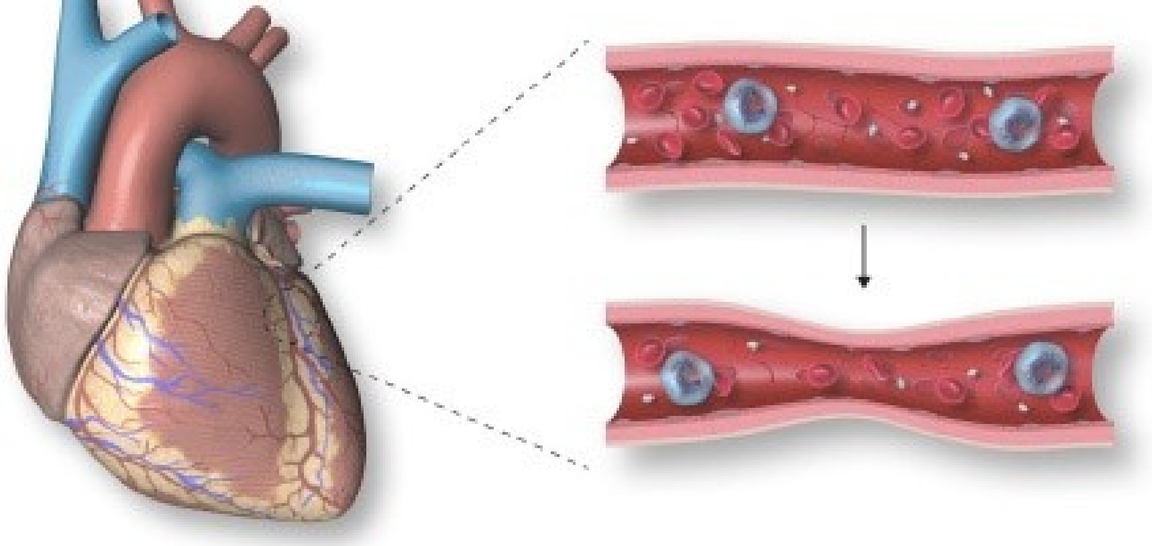


Management of INOCA

Although INOCA is associated with an increased risk of MACE and a decrease in quality of life, prior data demonstrate less than half of patients are appropriately treated with anti-ischemic agents.

Eur Heart J 2012;33(6):734-44.
Curr Probl Cardiol 2023;48:1014-20.

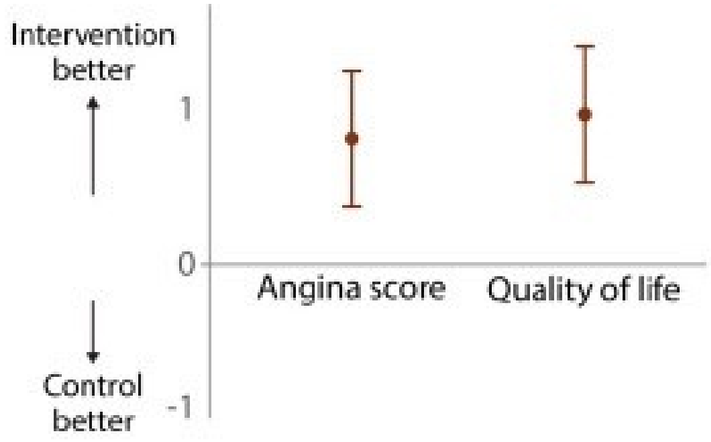
CorMICA trial



Stratified medicine in patients with INOCA

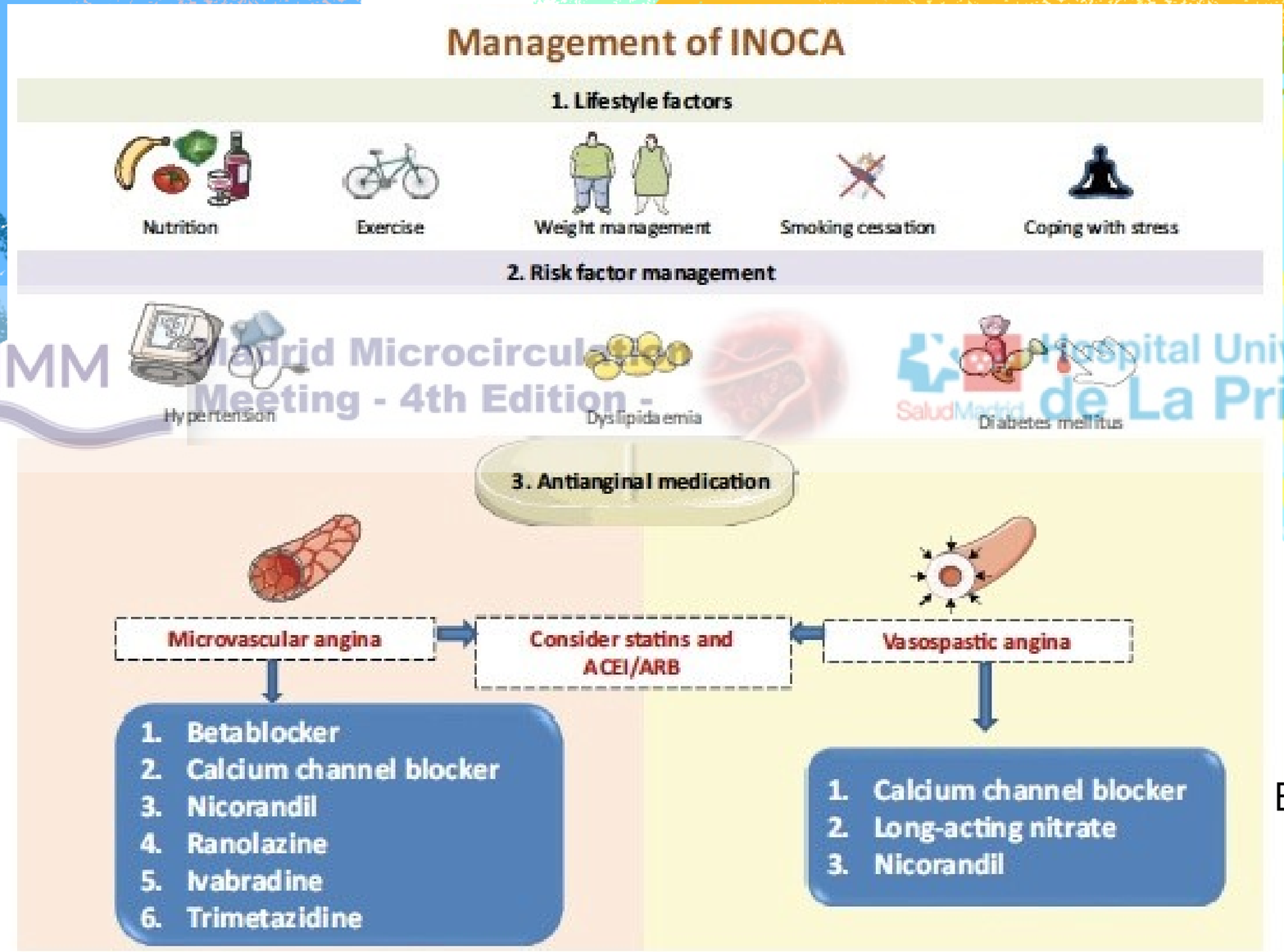
- Microvascular angina
- Vasospastic angina
- Non-cardiac chest pain

Improved angina and quality of life



Cardiovascular Research (2020) 116, 856–870.

Expert consensus document



European Heart Journal (2020) 41, 3504–3520.

Endotypes of INOCA

TABLE 1 Endotypes of INOCA

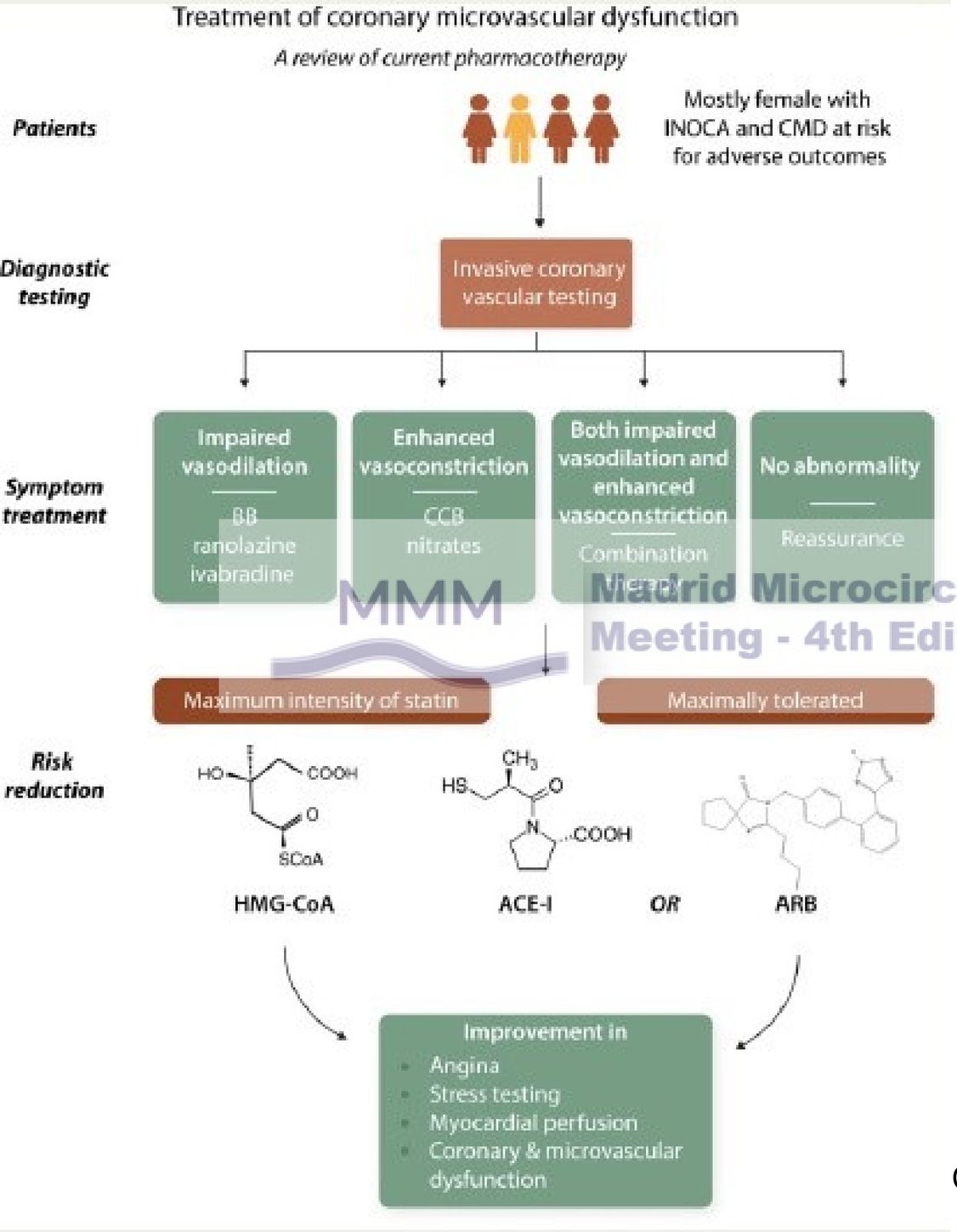
Endotypes	Features	Diagnosis
Coronary microvascular disease	Structural and/or functional abnormalities in the microvascular system A limitation in the vasodilatory ability and absolute conductance ability of the microvascular system Associated with risk factors of cardiovascular disease, ventricular hypertrophy, or cardiomyopathies	Based on invasive physiologic assessment • FFR >0.80 or NHPR >0.89 • CFR <2.0-2.5 • IMR >25 U or HMR >2.5 mm Hg/cm/s
Epicardial vasospastic angina	Hyper-reactive response of the epicardial coronary artery segment to vasoconstrictive stimuli	Based on provocation test using ergonovine or acetylcholine • Ischemic symptom during provocation test • A transient total or subtotal coronary artery occlusion • Ischemic ECG changes (ST-segment depression or elevation ≥0.1 mV) in at least 2 contiguous leads
Microvascular vasospastic angina	Spasm of vascular smooth muscle cells in prearteriolar vessels and arterioles	Based on the provocation test using acetylcholine • Ischemic symptom during provocation test • Without significant epicardial artery constriction during provocation test • Ischemic ECG changes (ST-segment depression or elevation ≥0.1 mV) in at least 2 contiguous leads
Masked diffuse disease	Coronary angiography can underestimate diffuse coronary atherosclerosis. Invasive physiologic assessment and/or intravascular coronary imaging can reveal hidden coronary atherosclerosis.	Based on invasive physiologic assessment • FFR ≤0.80 or NHPR ≤0.89 with gradual step-up during pull back tracing Based on intravascular imaging studies

CFR = coronary flow reserve; ECG = electrocardiogram; FFR = fractional flow reserve; HMR = hyperemic microvascular resistance; IMR = index of microcirculatory resistance; INOCA = ischemia with nonobstructive coronary artery disease; NHPR = nonhyperemic pressure ratio.

JACC Asia 2023 Apr 18;3(2):169-184.

Current therapeutic recomendations

European Heart Journal (2023) 44, 2829–2832



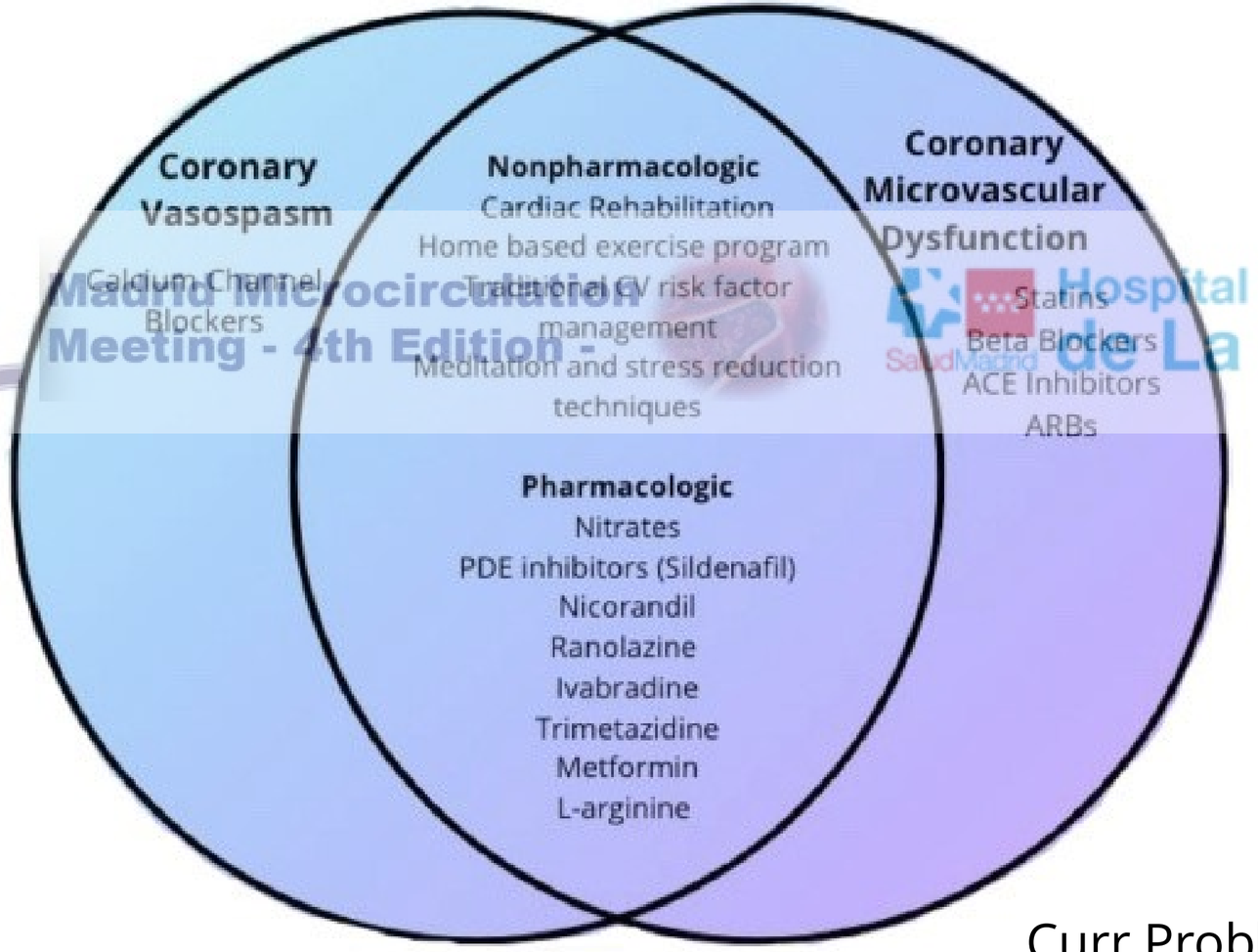
Cardiovascular Research (2020) 116, 856–870.

Currently Available Medical Treatment Options for INOCA

JACC Asia 2023 Apr 18;3(2):169-184.

Treatment Agents	Clinical Effects	Applicable Endotypes of INOCA		
		Coronary Microvascular Disease	Epicardial Vasospastic Angina	Microvascular Vasospastic Angina
ACE inhibitor/ARB	• Improve endothelial function • Improve small vessel remodeling • Regress periarteriolar fibrosis	+	−	−
Beta-blocker	• Reduce myocardial oxygen demand and increase diastolic perfusion time by reducing heart rate and contractility • Increase the threshold of ischemic symptom • Improve endothelial function	+	−	−
Nitrates	• Dilate vascular smooth muscle • Reduce preload via systemic vasodilation	−	+	±
CCB	• Dilate vascular smooth muscle • Increase the threshold of ischemic symptom • Reduce myocardial oxygen demand • Improve symptom and exercise tolerance	±	+	+
Statin	• Anti-inflammatory and antioxidant properties • Improve coronary endothelial function	+	−	−
Nicorandil	• Coronary microvascular dilatory effect • Balanced vasodilator in veins and arteries	±	+	+
Ranolazine	• Reduce myocardial oxygen demand and improve microvascular perfusion via improvement of ventricular relaxation	+	−	−
Trimetazidine	• Increase cell tolerance to ischemia via cellular homeostasis	+	-	-

Therapeutic options for INOCA



Curr Probl Cardiol 2023;48:1014-20.

MMM

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Clinical case

09

74 year-old women

Personall history

Hypertension

Dyslipidemia

Hypothyroidism

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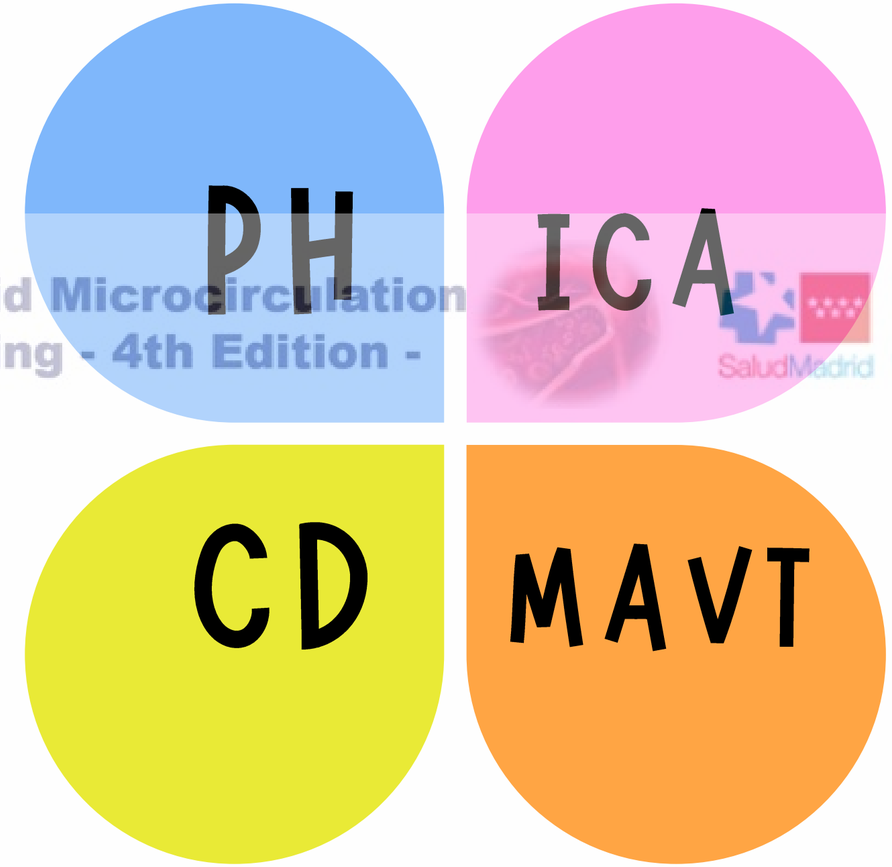
Current desease

Chest pain since 2013

Clinical and electric positive stress test



Invasive Coronary angiography

No stenosis

Microvascular assesment and vasoactivity test


FFR
Pd
Pa
0.94
93
99
Pd/Pa
Pd
Pa
0.94
94
99
CFR
CFRNorm
0.7
0.7
IMR
IMRCorr
106
107
RRR
0.7
Pd/Pa
FFR
Resting 0.78s 0.74 0.73 0.88
Hyperemic 1.13s 1.08 1.15 1.18
Resume
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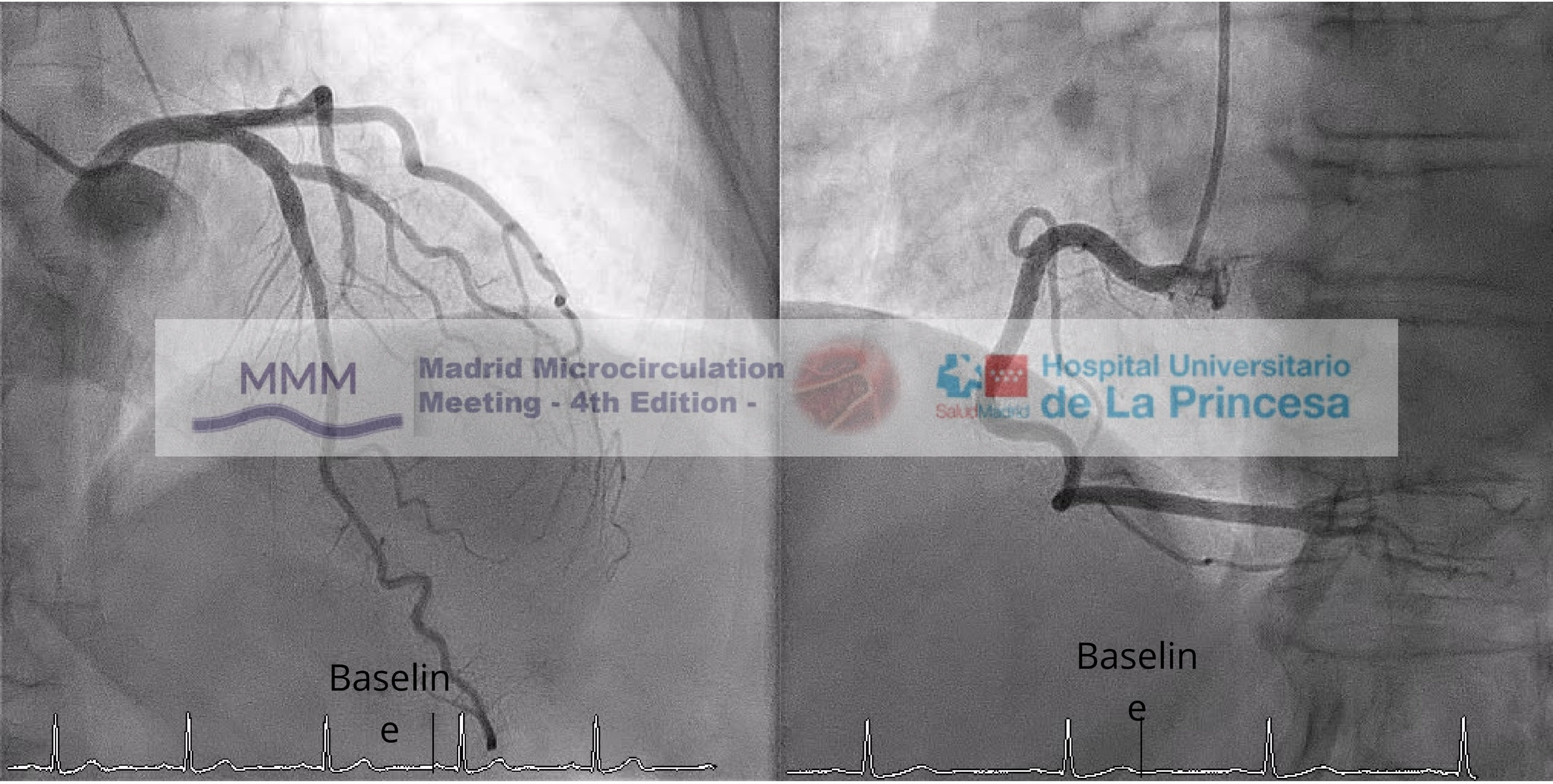
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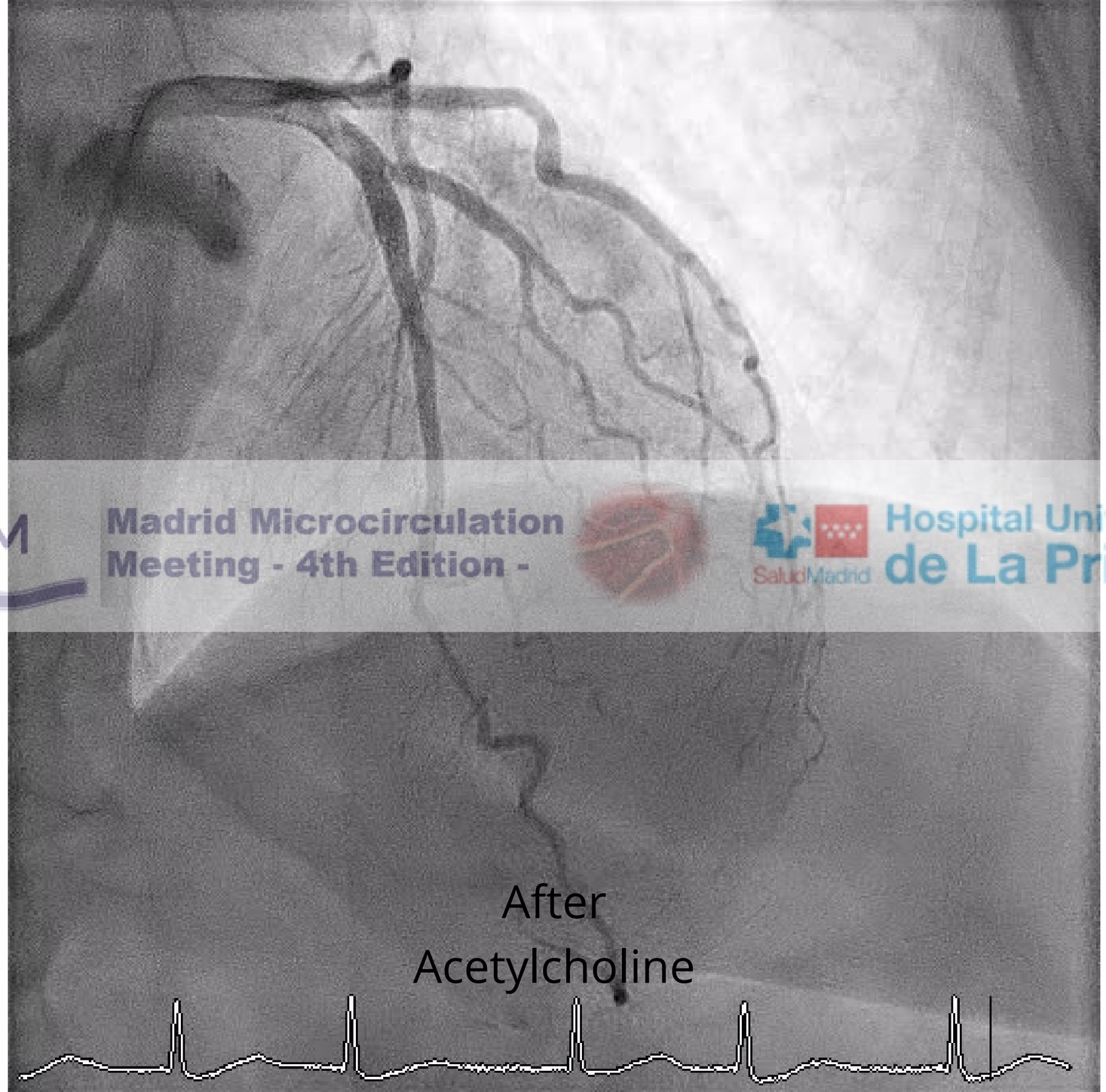
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After
Acetylcholine

09

74 year-old women

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MMM

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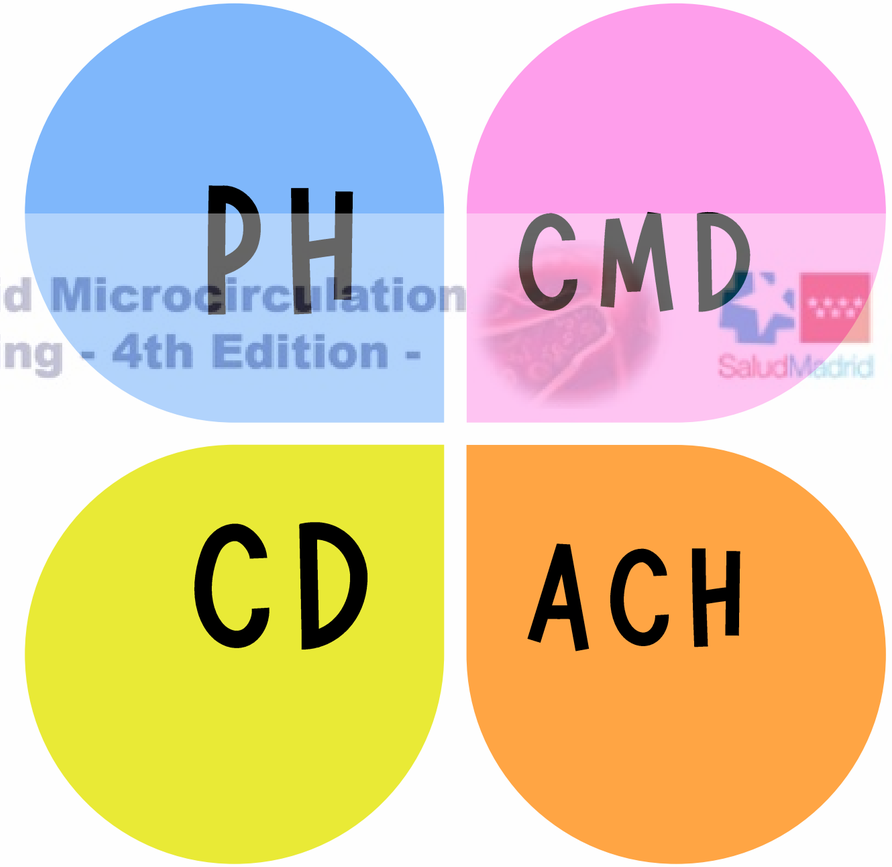


Coronary Microvascular dysfunction

FFR 0.94, RFR 0.92

CFR 0.7

IMR 107

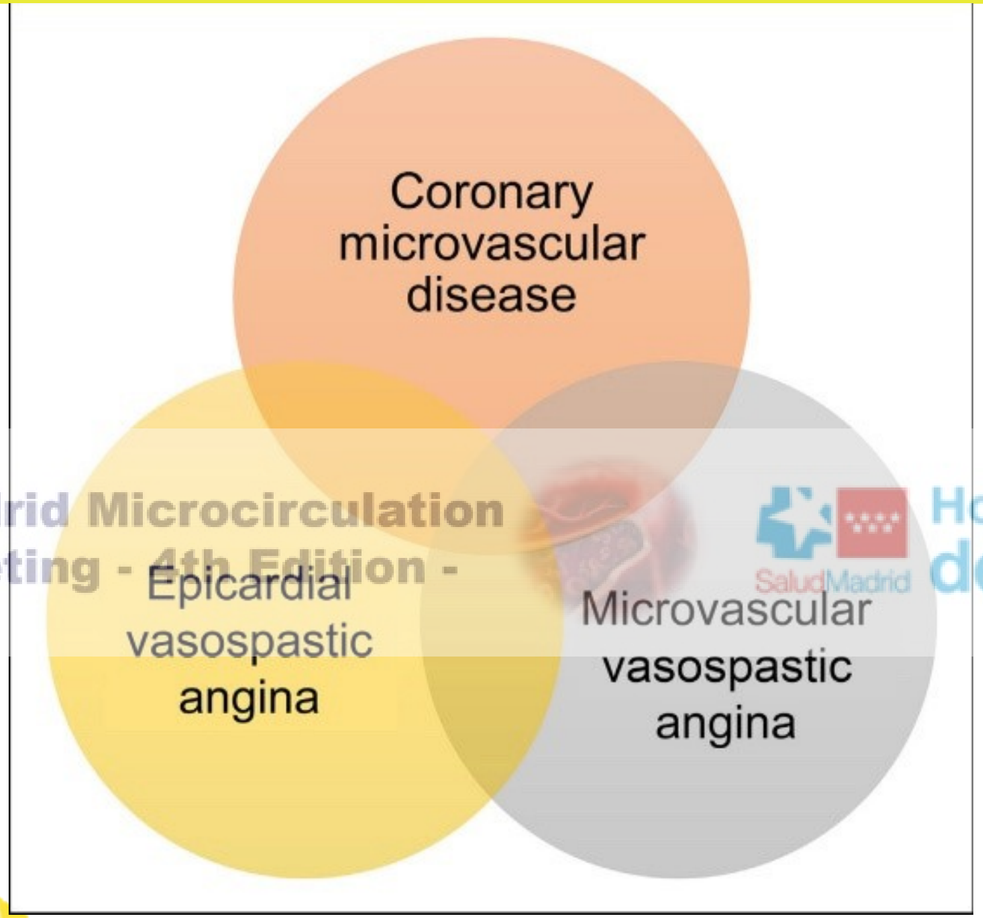
Acetilcholine testing

Chest pain

Electrocardiogram changes

Focal epicardic spasm 40%

Ocurrence and overlap of INOCA Endotypes



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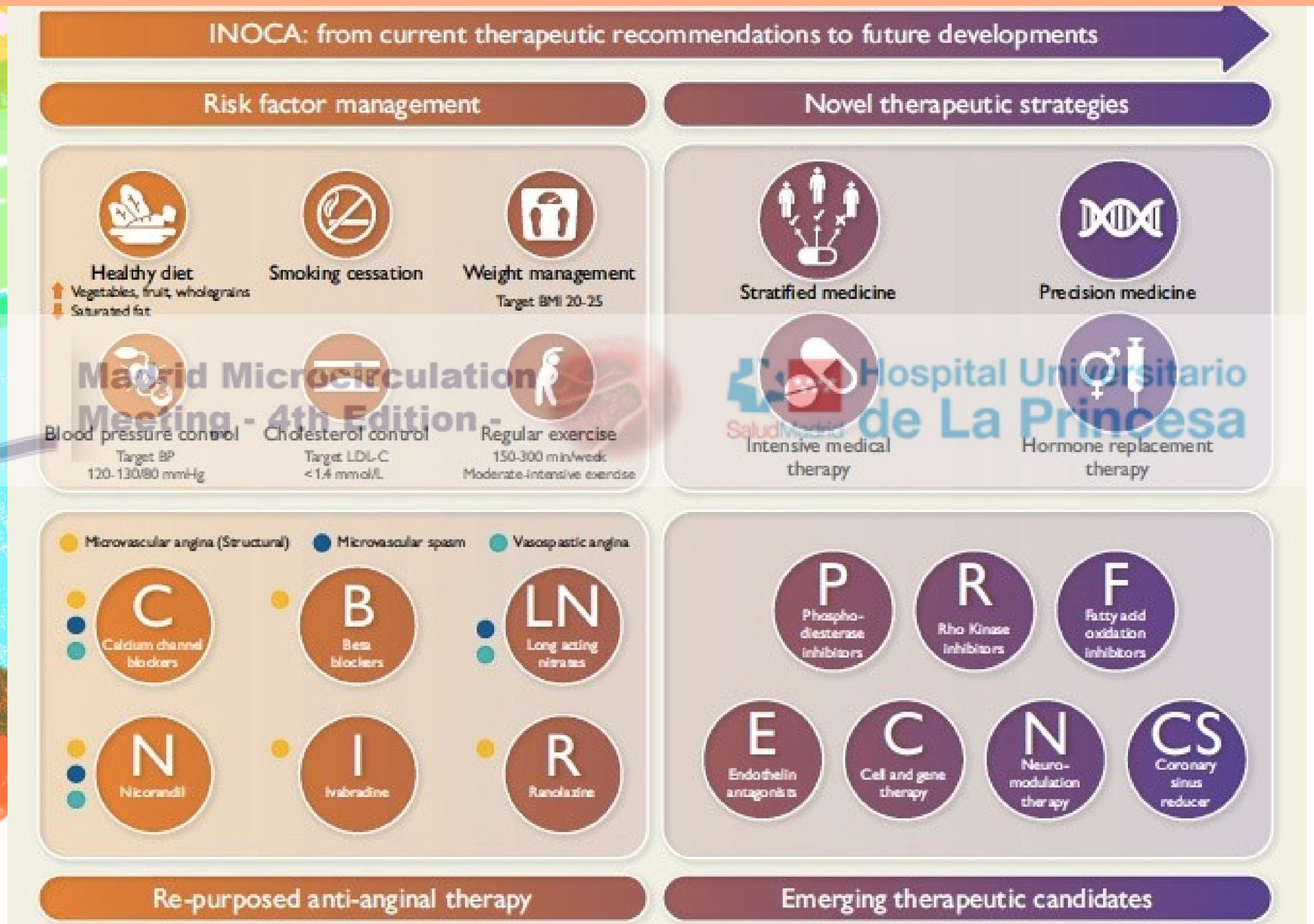
Novel therapy for INOCA



European Heart Journal (2023) 44, 2829–2832

Table 1 Pharmacotherapy of coronary microvascular dysfunction mechanistic trials

Conventional treatments	Intermediate outcome impact
Anti-atherosclerosis treatment	
Statins	+
ACE-I, angiotensin renin blockers	+
Low-dose aspirin	+
Anti-angina treatments	
Calcium antagonists	+
Alpha beta-blockers	+
Beta-blockers	+
Nitrates	+
Ranolazine	+/-
Exercise	+
Enhanced external counter-pulsation	+
Imipramine, amitriptyline, nortriptyline	+
L-arginine	+
Spinal cord stimulation	+
Novel treatments	
RAAS active agents	
ACE-I quinapril	+
Mineralocorticoid inhibition-eplerenone	-
PDE	
PDE type 3 inhibition—cilostazol	+
PDE type 5 inhibition—sildenafil	+
Calcium channel antagonism—benidipine	+
Selective If-channel blockade—ivabradine	+/-
Rho-kinase inhibition—fasudil	+
Endothelin receptor antagonists—darusentan and atrasentan	+
Adenosine active agents—dipyridamole, caffeine, aminophylline, paraxanthine, pentoxifylline, theobromine, and theophylline	+/-
Myocardial metabolic active agents	
Dichloroacetate	-
Carnitine analogues—acetyl-L-carnitine, propionyl-L-carnitine, and L-carnitine	-
Perhexiline	-
Trimetazidine	+
Metformin	+
Amiodarone/dronedarone	+
Anti-inflammation agents	
IL-1b inhibition-canakinumab, rilonacept	-
Methotrexate	-
Hormone therapy	-
IL-1a-anakinra	-
IL-6-Tocilizumab	-
TNF-α inhibitors	+
Glycaemic active agents—SGLT 1 and 2 inhibitors, GLP-1 agonists	-
Androgen analogues—testosterone (T), low-dose T (transdermal patch), and T undecanoate injection	+
Oestrogen analogues—norethindrone/ethinyl oestradiol, CEOs and medroxyprogesterone acetate, and CEO	+/-
Nervous system active agents—neuropeptide Y and selective serotonin reuptake inhibitors (escitalopram)	+/-
Gene and cell-based therapies—autologous CD34 cells	-
Small-molecule targets	-

+, benefit; +/-, no benefit; -, mixed benefit and no benefit. ACE-I, angiotensin-converting enzyme inhibitor; CEO, conjugated equine oestrogen; GLP-1, glucagon-like peptide 1;

Cardiovascular Research (2020) 116, 856–870.

Ongoing studies of INOCA

TABLE 4 Ongoing Studies for Evaluating the Prevalence, Prognosis, and Management of INOCA

Diagnosis	Diagnosis	Diagnosis
INOCAIT (NCT05164640)	Prospective registry	Prevalence, proportion of endotypes, and prognosis of INOCA
DISCOVER INOCA (NCT05288361)	Prospective registry	Prevalence, proportion of endotypes, and prognosis of INOCA
CorCTCA (NCT03477890)	Randomized controlled trial	Impact of invasive diagnostic tests for INOCA in classifying and managing INOCA patients
iCorMicA (NCT04674449)	Randomized controlled trial	Benefit of stratified management of INOCA based on invasive tests
WARRIOR (NCT03417388)	Randomized controlled trial	Prognostic impact of intensive statin/ACE inhibitor/ARB treatment in INOCA patients
PRIZE (NCT04097314)	Randomized controlled trial	Antianginal effect of zibotentan in patients with coronary slow flow phenomenon

CorCTCA = Coronary Microvascular Function and CT Coronary Angiography; DISCOVER INOCA = Determining the Cause of Coronary Vasomotor Disorders in Patients With Ischemia and No Obstructive Coronary Artery Disease; iCorMicA = International Study of Coronary Microvascular Angina; INOCAIT = Ischemia in Patients With Non-obstructive Disease [INOCA] in Italy INOCA IT Multicenter Registry; PRIZE = Precision Medicine With Zibotentan in Microvascular Angina; WARRIOR = Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD; other abbreviations as in Table 3.

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Conclusions

01 Health impact therapy of INOCA: Mejoran calidad de vida y sintomas de angina

02 Clinical guidelines prioritize stratified medicine according to endotypes INOCA (Heterogeneous mechanisms).

03 No standard evidence-based treatment of INOCA

04 Always ... Risk factor control is essential

05 Lack of well-designed clinical trials.

06 Novel studies and therapeutic strategies are on going.

Thank you!

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Jessica Roa
jroa.garrido@gmail.com