



From INROAD to SAMCRO

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Patient with CMD diagnosis

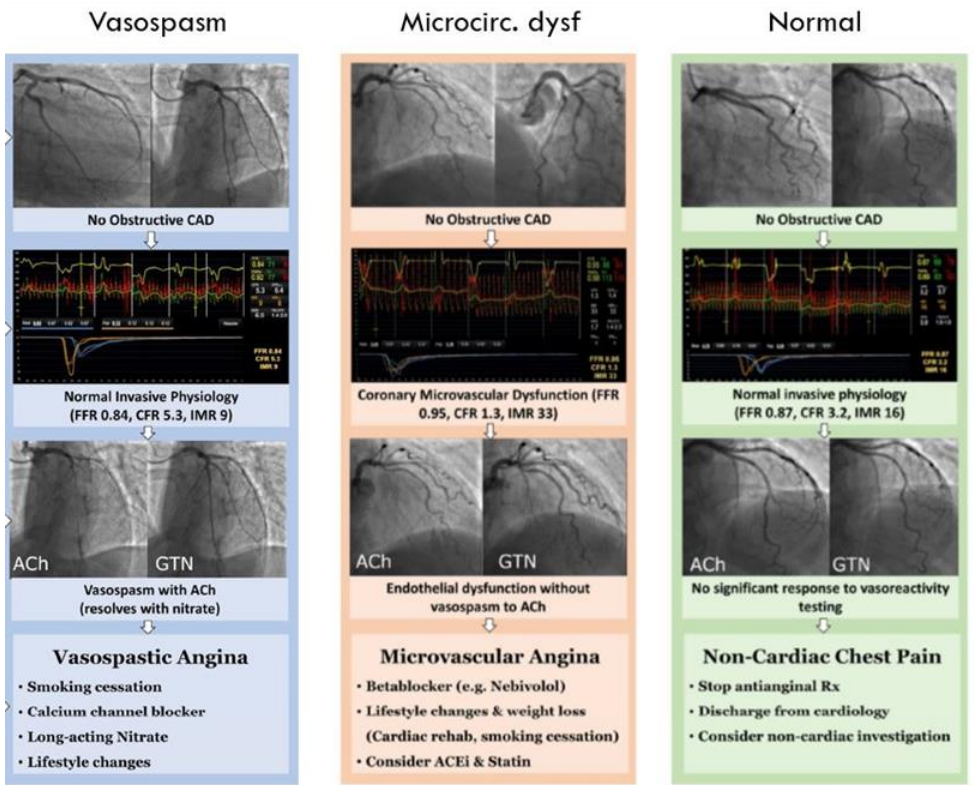
"Who cares? There is nothing to be done!!!"



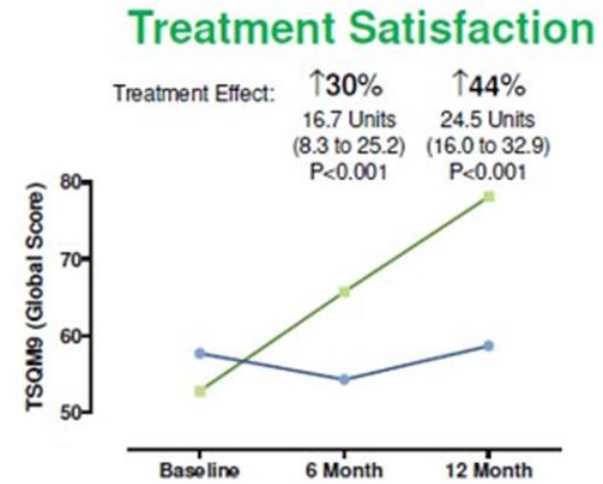
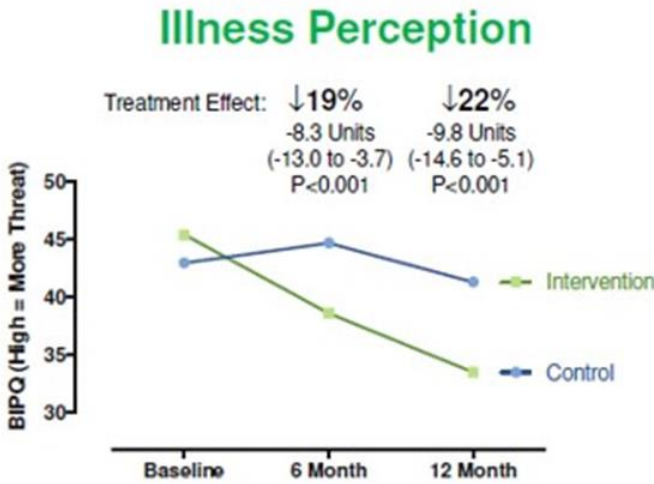
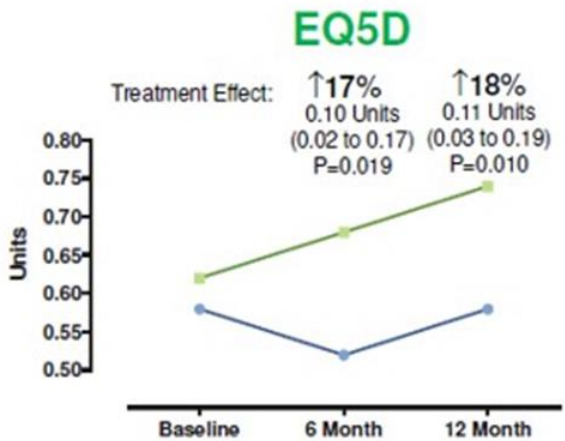
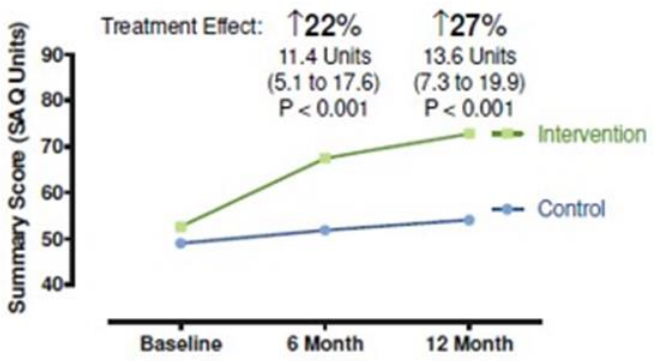


CorMICA trial

CorMICA Primary endpoint: SAQ



CB. 16.11.2019

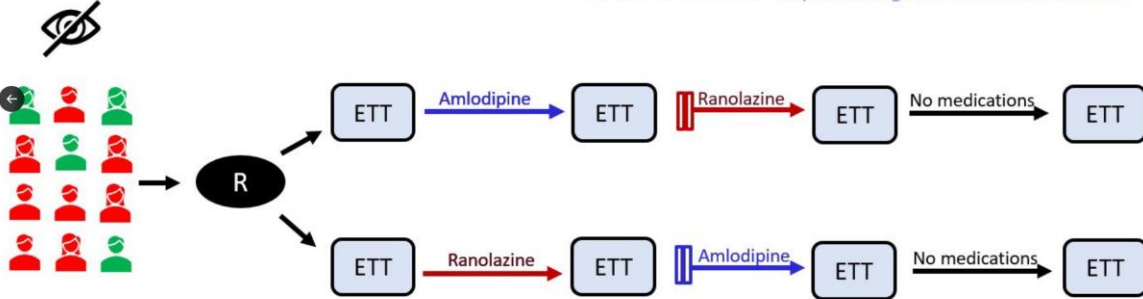




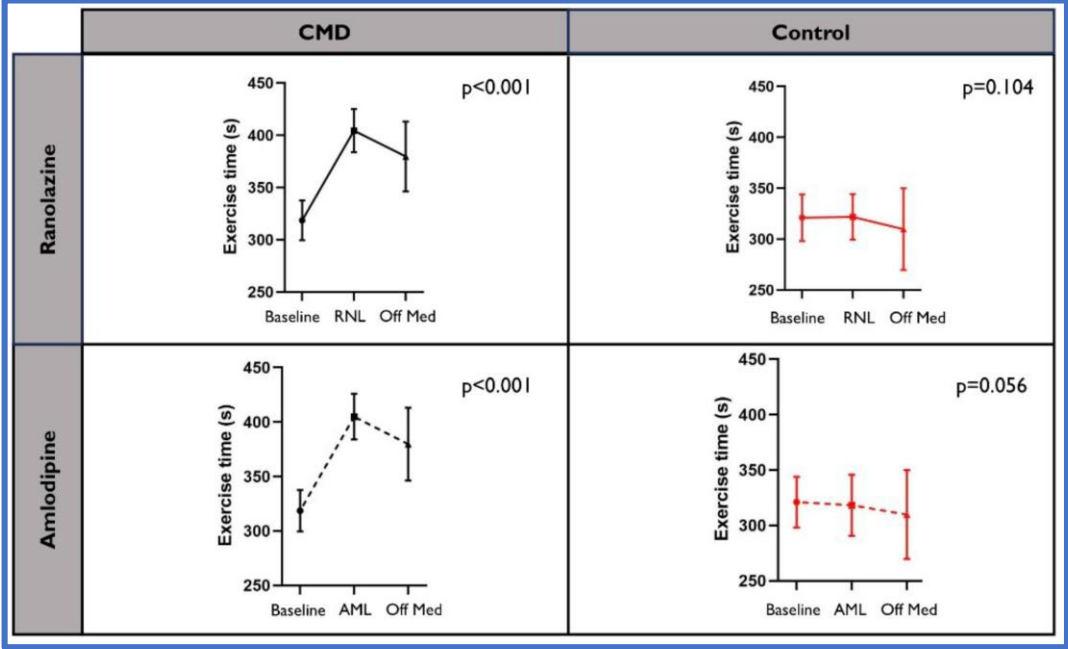
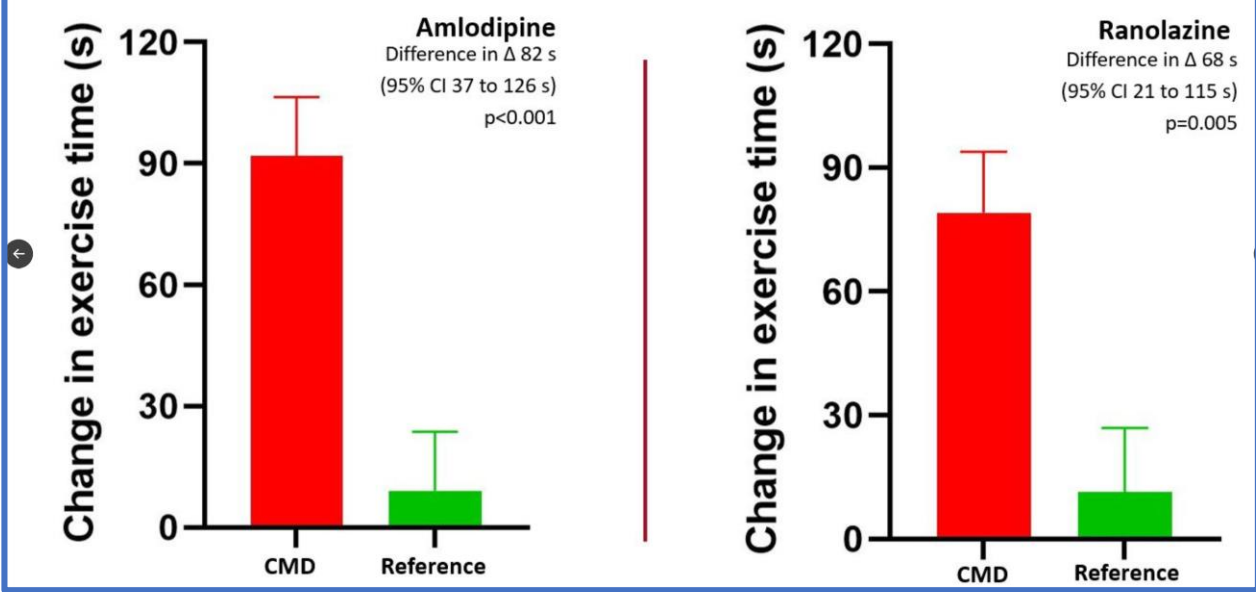
ChaMP-CMD trial

Phenotype-blinded randomised crossover intervention

ISRCTN94728379 <https://doi.org/10.1186/ISRCTN94728379>



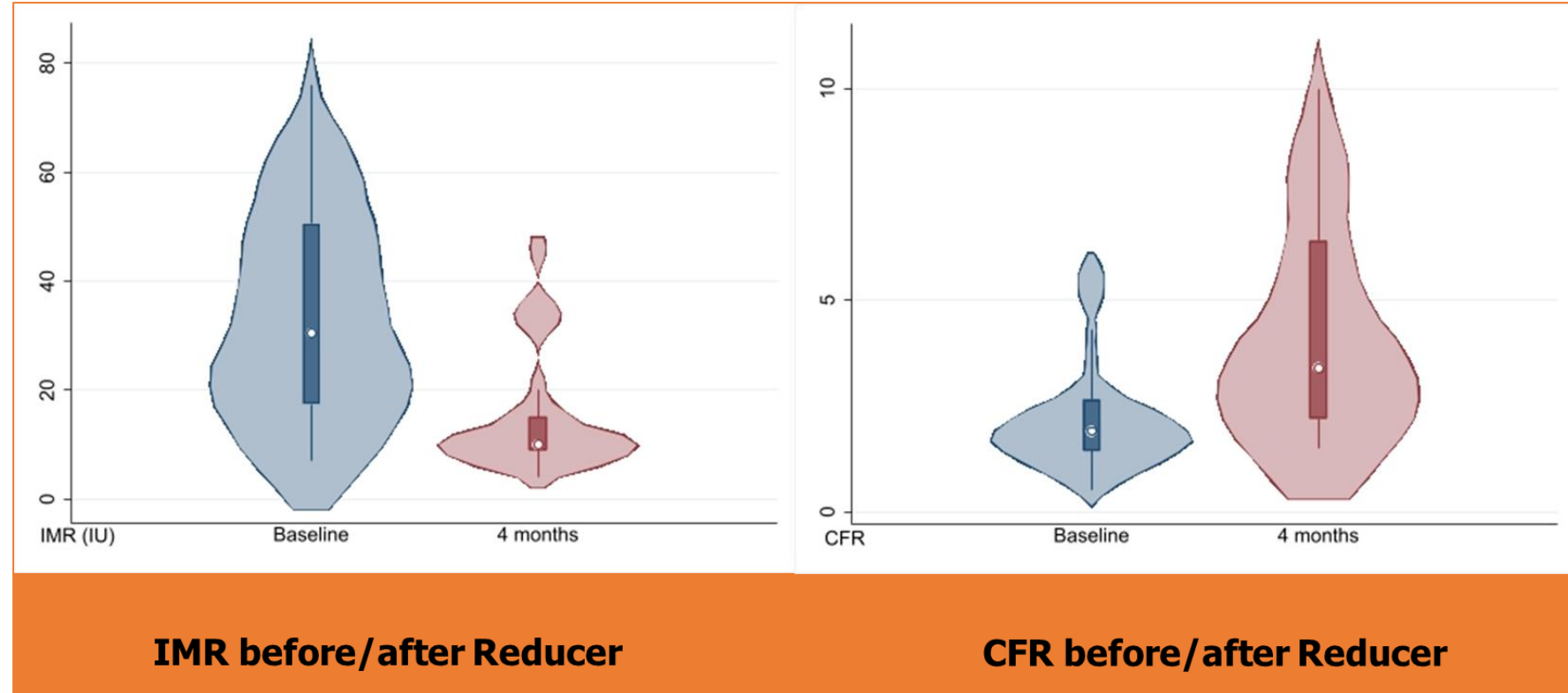
H1: Does CFR predict change in exercise time in response to therapy?





INROAD trial

	Patients (n=24)
Age, years	67.7±8.9
Female sex, no. (%)	4 (16.6)
CV risk factors, no. (%)	
Diabetes	6 (25.0)
Hypertension	21 (87.5)
Hyperlipidemia	18 (75.0)
Current or previous smoker	16 (66.6)
Medical history, no. (%)	
MI	15 (62.5)
PCI	17 (70.8)
CABG	8 (33.3)
CVA	3 (12.5)
PAD	10 (41.6)
Chronic kidney disease *	12 (50.0)
Left ventricle ejection fraction (%)	50.5±10.5
CCS angina class, no. (%)	
I	0 (0)
II	7 (29.2)
III	16 (66.6)
IV	1 (4.2)
Antianginal medication, no. (%)	
Beta-blockers	21 (87.5)
Calcium-channel blocker	16 (66.6)
Nitrates	12 (50.0)
Ranolazine	19 (79.1)
Ivabradine	5 (20.8)
≥3 antianginal medications	17 (70.8)



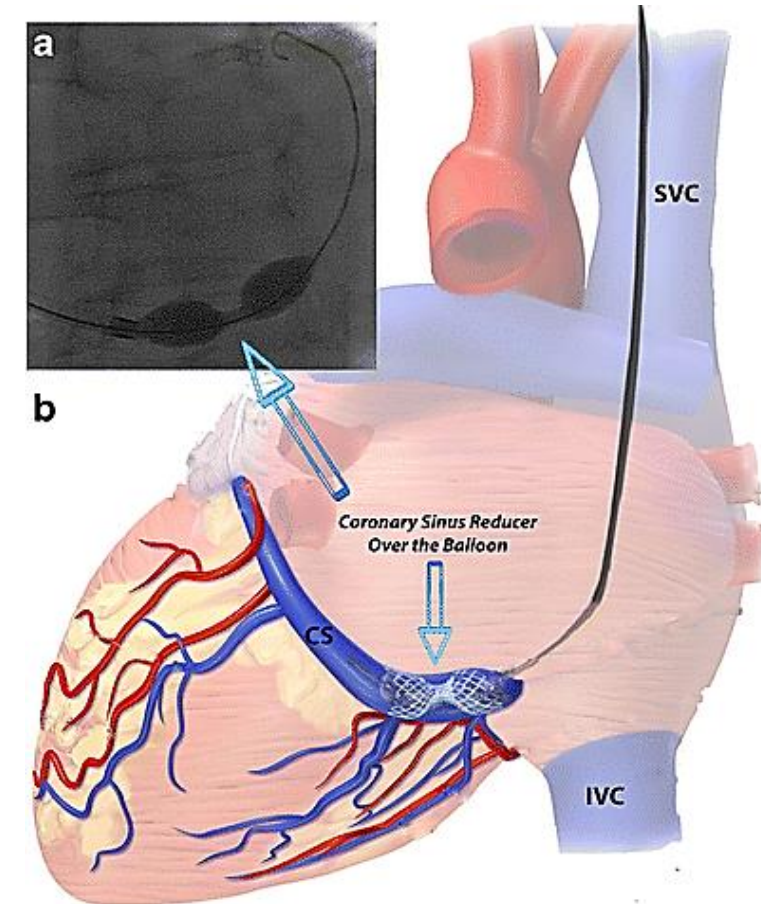


Background – INROAD

Refractory angina (RA) refers to long-lasting symptoms (> 3 months) due to documented reversible ischemia in the presence of obstructive CAD, which cannot be controlled by escalating anti-anginal medications, PCI or BPAC, including the treatment of CTO.



Coronary Sinus Reduction has been indicated for patients with refractory symptoms despite revascularization of obstructive CAD and OMT¹

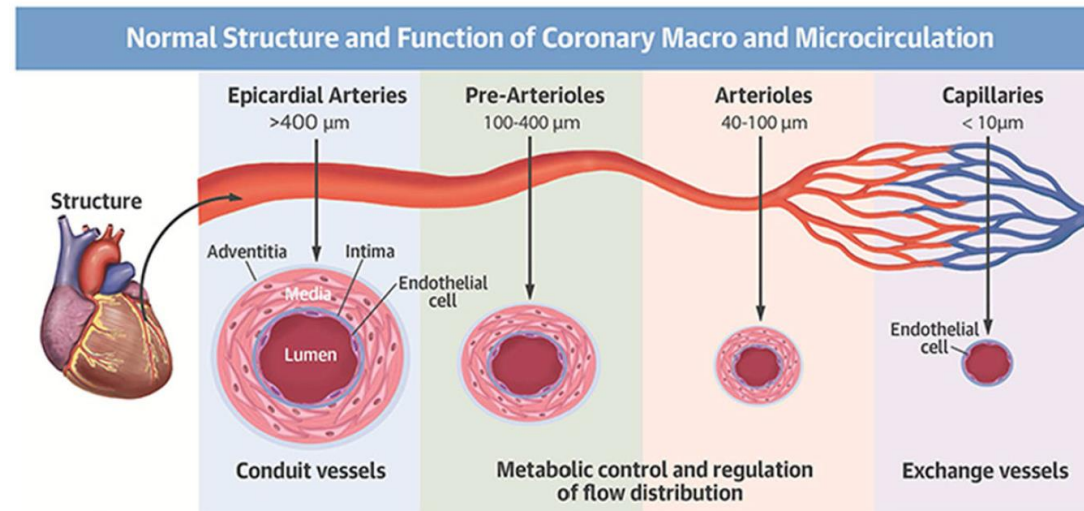


¹ Verheye S, Banai S. Efficacy of a device to narrow the coronary sinus in refractory angina. COSIRA trial. N Engl J Med. 2015;372:519-27.



Background

Refractory angina in the absence of obstructive CAD:
what is the role of **microvascular dysfunction**?

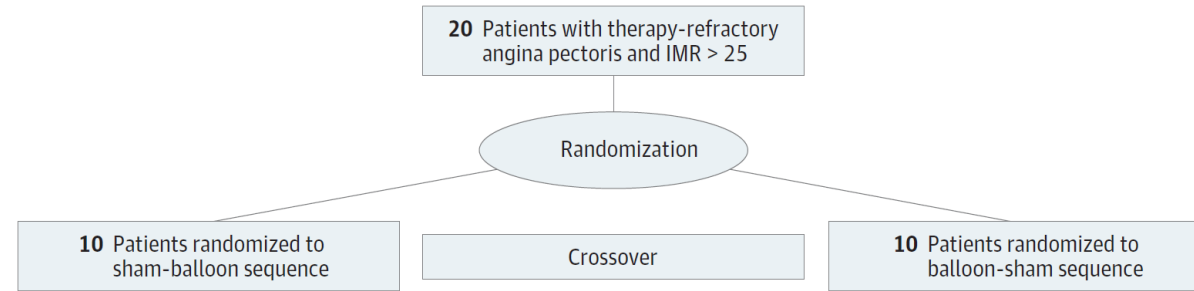


Some reports have suggested positive effects of Reducer implantation in patients with refractory symptoms secondary to disorders of the **coronary microcirculation**²

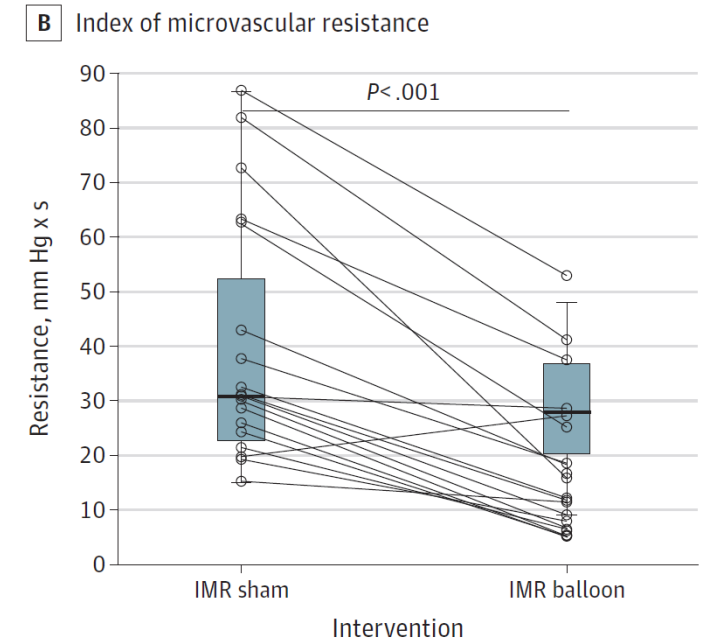
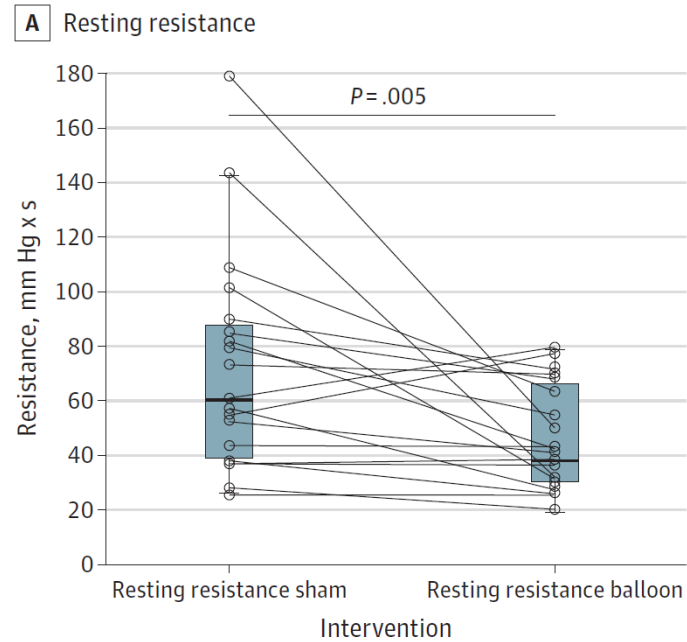
² Giannini F, Colombo A. JACC Cardiovasc Interv. 2017;10:1901-1903.



Mechanicistic study



Hemodynamic variable	Sham	Balloon	P value ^b
	Median (IQR)	Median (IQR)	
Primary end point			
IMR, mm Hg × s	31 (23-53)	14 (7-26)	<.001
Secondary end points			
Rest			
Pa, mm Hg	103 (93-110)	101 (89-111)	.28
Pd, mm Hg	98 (85-101)	89 (84-102)	.21
Tmn, s	0.69 (0.43-1.14)	0.58 (0.44-0.82)	.37
Pcs, mm Hg	5 (2-9)	20 (13-29)	<.001
Pra, mm Hg	4 (2-7)	3 (2-8)	.63
Resistances, mm Hg × s	59 (37-87)	42 (31-68)	.005
Hyperemia			
Pa, mm Hg	92 (80-100)	89 (84-102)	.05
Pd, mm Hg	98 (88-110)	79 (75-93)	.01
Tmn, s	0.39 (0.23-0.62)	0.26 (0.17-0.46)	.008
Pcs, mm Hg	6 (3-9)	25 (13-36)	<.001
Pra, mm Hg	6 (3-8)	5 (3-8)	>.99
FFR	0.87 (0.82-0.94)	0.94 (0.88-0.94)	.003
CFR	1.70 (1.4-2.3)	2.1 (1.3-4.1)	.18
MRR	2.0 (1.4-2.7)	2.7 (1.4-5.3)	.06





Research question

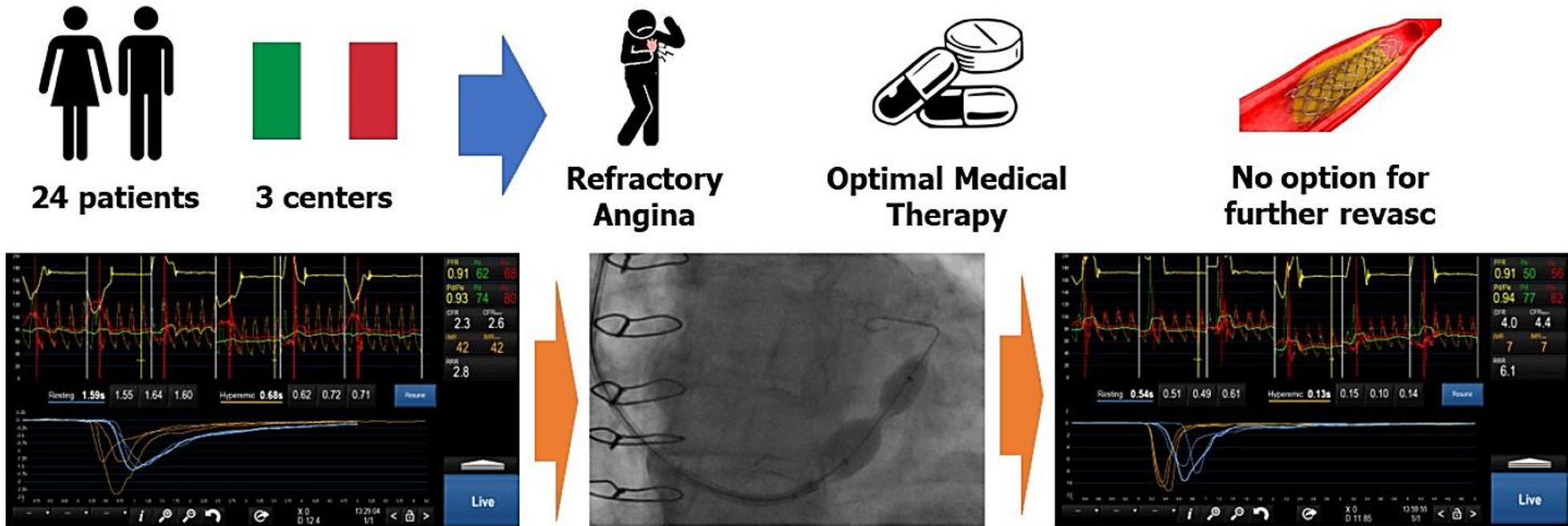
To evaluate the impact of Reducer on coronary microvascular function indexes invasively assessed by measuring **IMR, CFR, RRR** in patients with RA and previous coronary revascularization.



INROAD Study

Prospective, multicenter, single-cohort, investigator-driven clinical trial

Hypothesis In patients with refractory angina, CS narrowing will improve microvascular function.





Study Design

Patients

Patients with refractory angina with history of obstructive CAD and prior coronary revascularization assuming antianginal medications at maximum tolerated dose.

Inclusion criteria

- Age > 18 y.o.
- Diagnosis of refractory angina
- One open coronary artery (excluded RCA) where to perform invasive coronary physiology assessment
- Ability to provide informed written consent

Exclusion criteria

- Recent (≤ 3 months) ACS or PCI/BPAC
- LVEF < 30%
- Severe VHD
- Inability to undergo invasive coronary physiological assessment or Reducer implantation.



Study Design

Primary Endpoint

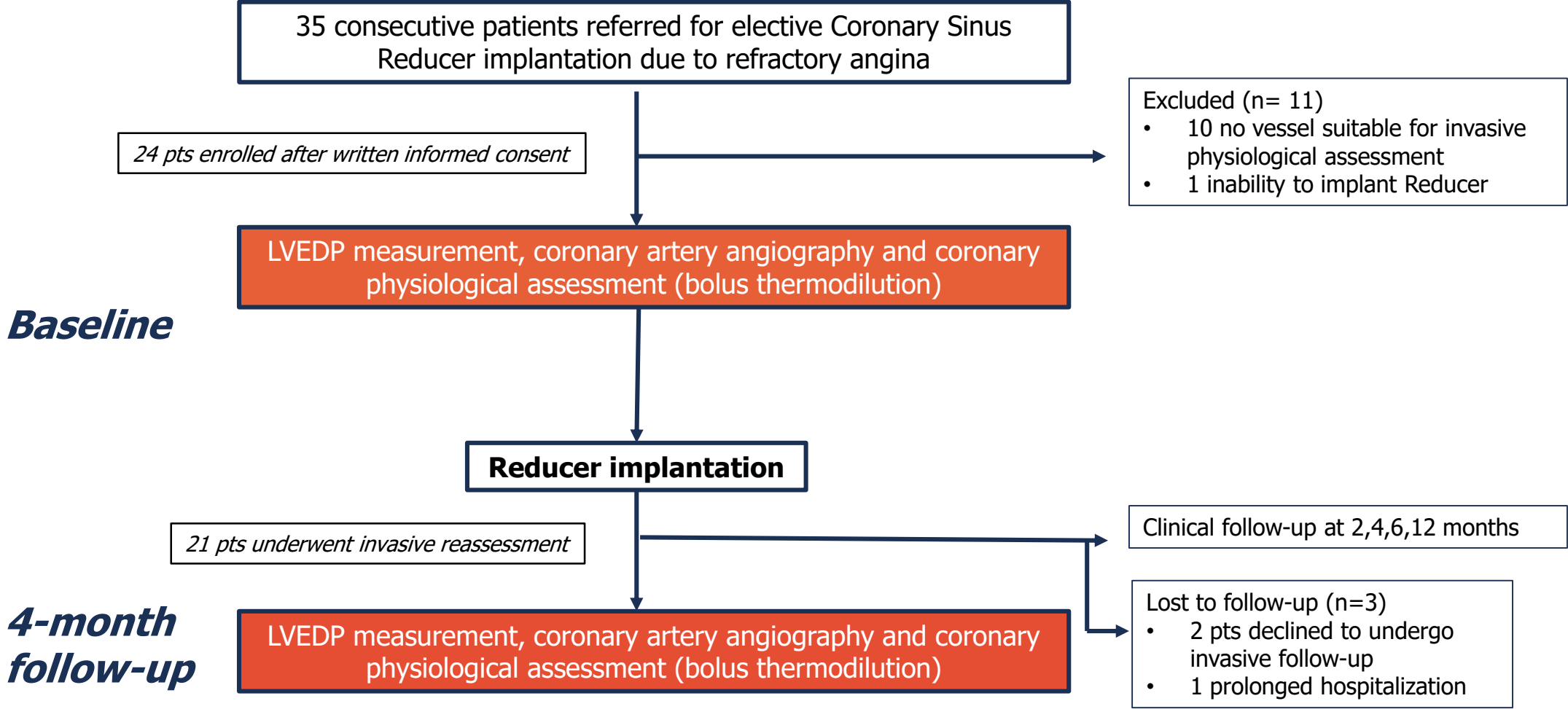
- Change in IMR values from baseline to 4-m follow-up.

Secondary Endpoints

- Change in CFR and RRR values
- Change in LVEDP
- Change in angina status as assessed by CCS class and the Seattle Angina Questionnaire (SAQ)
- Change in depression severity as assessed by Beck Depression Inventory (BDI).



Study Design





INROAD Study: Population

Characteristic Patients (n=24)

CCS angina class, no. (%)

I	0 (0)
II	7 (29.2)
III	16 (66.6)
IV	1 (4.2)

Antianginal medication, no. (%)

Beta-blockers	21 (87.5)
Calcium-channel blockers	16 (66.6)
Nitrates	12 (50)
Ranolazine	19 (79.1)
Ivabradine	5 (20.8)
≥ 3 antianginal medications	17 (70.8)

Characteristic Patients (n=24)

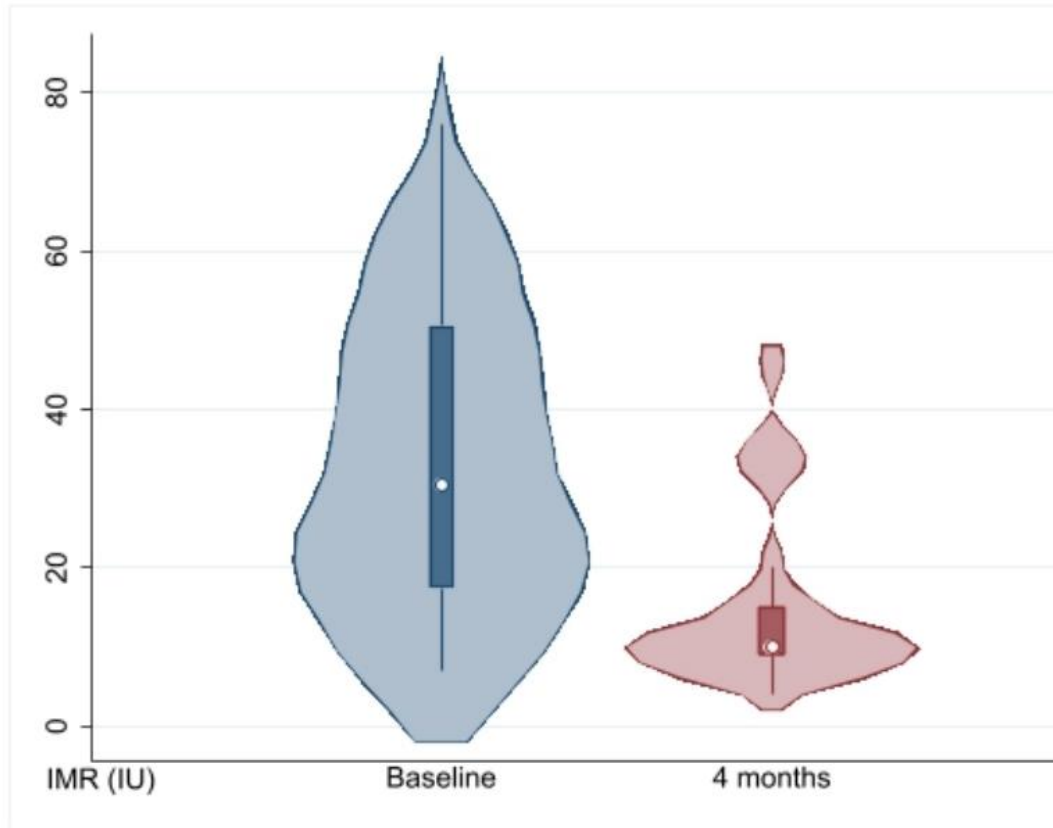
Invasive coronary angiography

IMR	33.58 ± 19.18
IMR ≥ 25, no. (%)	14 (58)
FFR	0.89 ± 0.04
CFR	2.36 ± 1.45
CFR < 2, no. (%)	13 (54)



Results – PRIMARY ENDPOINT

IMR Violin plot



↓ **IMR in 15 (71%)
patients, mainly in pts
with higher baseline
IMR values**



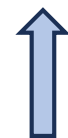
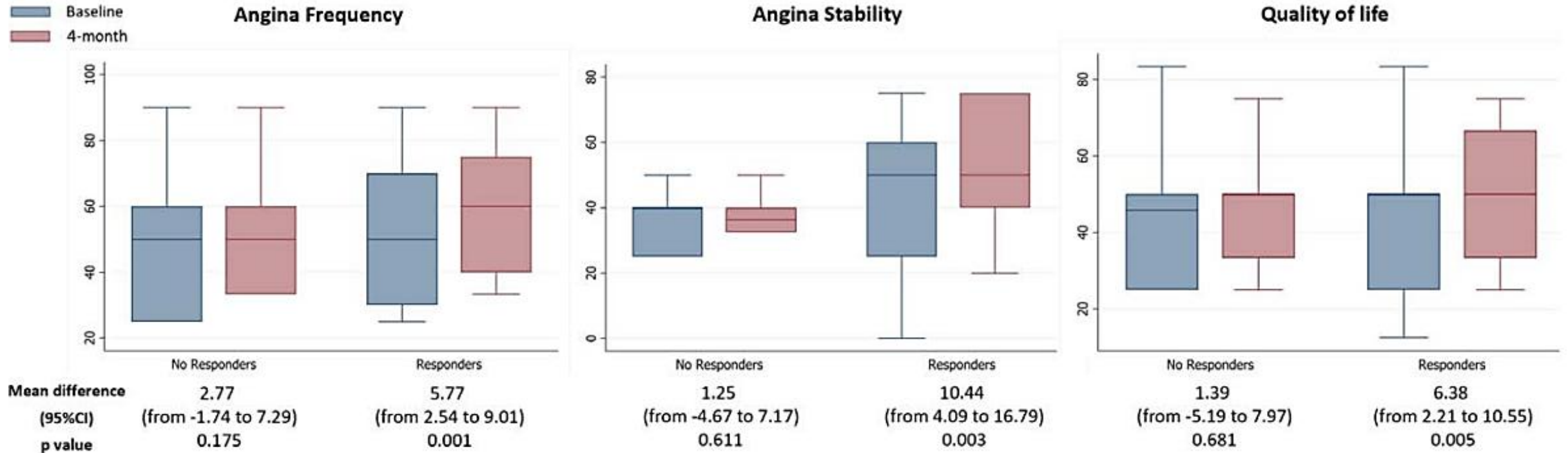
Results – SECONDARY ENDPOINTS

	Baseline (n=21)	4-month (n=21)	P		Baseline (n=21)	4-month (n=21)	P
Invasive coronary physiology				LVEDP	1.9 ± 2.5	10.5 ± 2.2	0.023
				CCS			
				I	0 (0)	12 (57)	< 0.001
				II	6 (28)	6 (28)	< 0.001
IMR	33.3±19.9	15.4±11.4	< 0.001	III	14 (67)	3 (15)	< 0.001
IMR ≥ 25	12 (57)	4 (19)	0.016	IV	1 (5)	0 (0)	< 0.001
CFR	2.5±1.5	4.2±2.5	0.007	SAQ			
CFR < 2	11 (52)	4 (19)	0.039	Angina frequency	51.4 ± 21.2	56.3 ± 19.5	< 0.001
				Angina stability	40.9 ± 19.1	48.8 ± 16.6	0.003
				Quality of life	43.8 ± 20.2	48.8 ± 15.9	0.006
				Summary Score	49.5 ± 16.3	52.5 ± 14.5	< 0.001



INROAD Study: Results

IMR responders VS IMR non-responders



4 points SAQ in IMR Responders

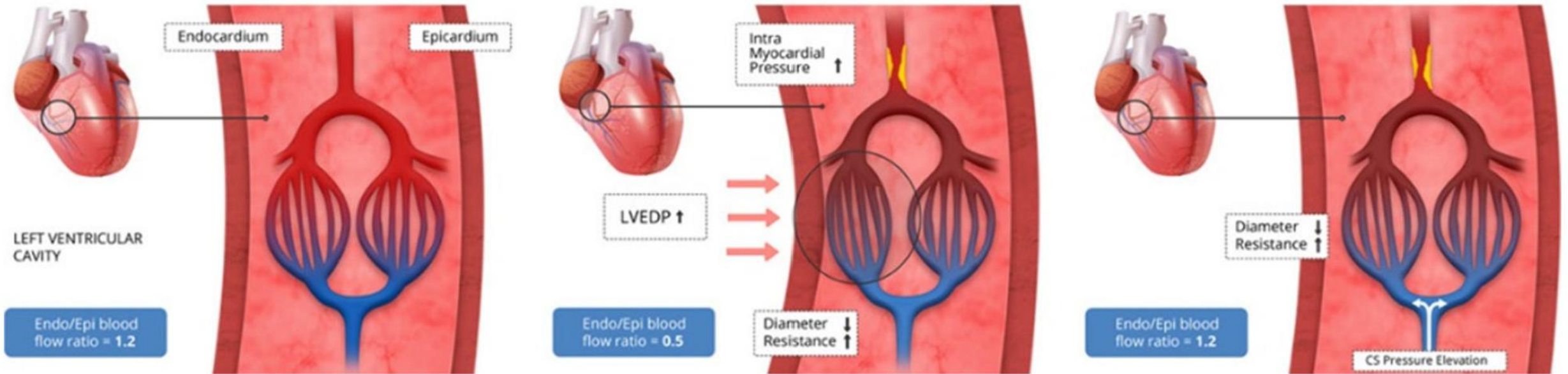


INROAD Study: Conclusions

- **Reducer implantation** positively modulates coronary microvascular function.
- **Positive correlation** between improvement in **microvascular function** and angina related **symptoms** and **quality of life**.
- Coronary microvascular function may be a reversible condition, indicating that **Reducer implantation could be considered as an effective interventional therapy for CMD.**



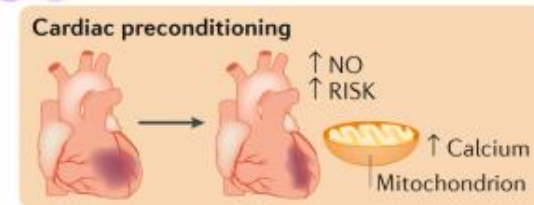
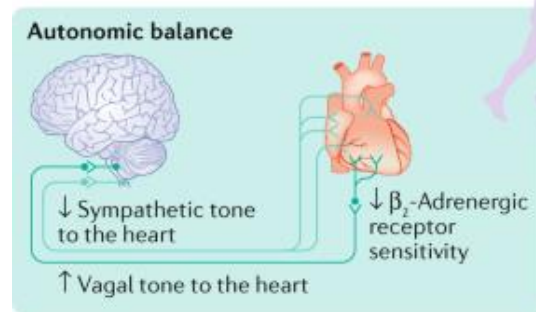
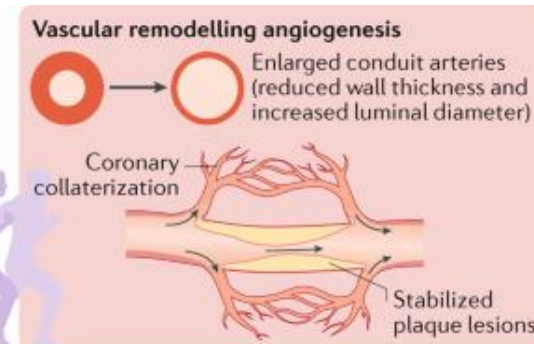
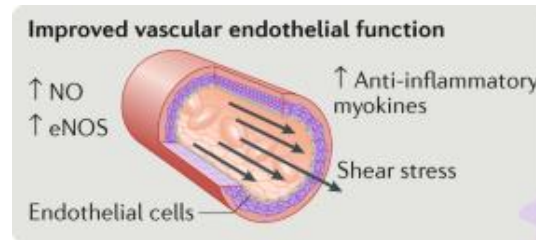
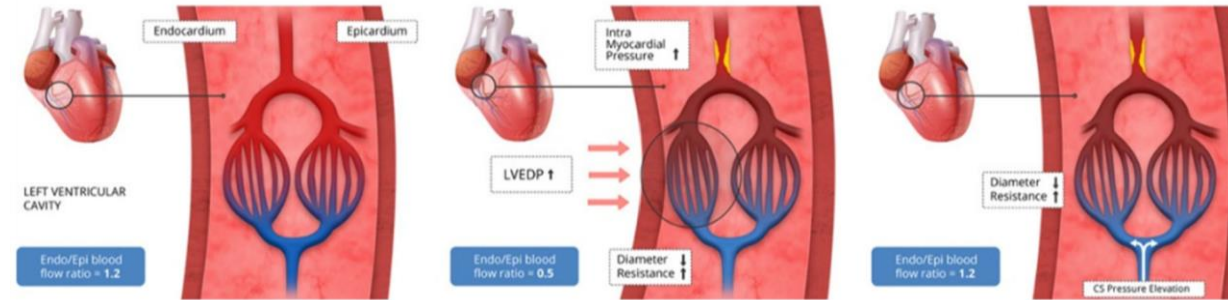
INROAD trial



- **Elevation in backward pressure in the coronary venous system**
- **Slight dilation of the venules, capillaries and arterioles**
- **Subsequent reduction of the resistance to flow**
- **Improvements in IMR, CFR and RRR values.**

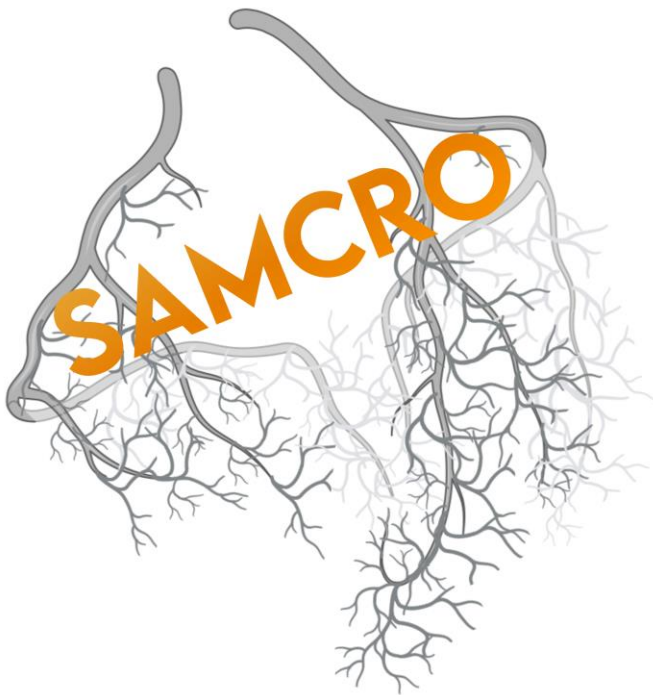


The natural Reducer





Standardizing the Management of patients with coronary microvascular dysfunction



The SAMCRO trial



Background

- ❑ **ANOCA patients:**
 - higher MACE compared with normal subjects
 - poor quality of life (QoL) with functional disability and limitations in activities of daily living

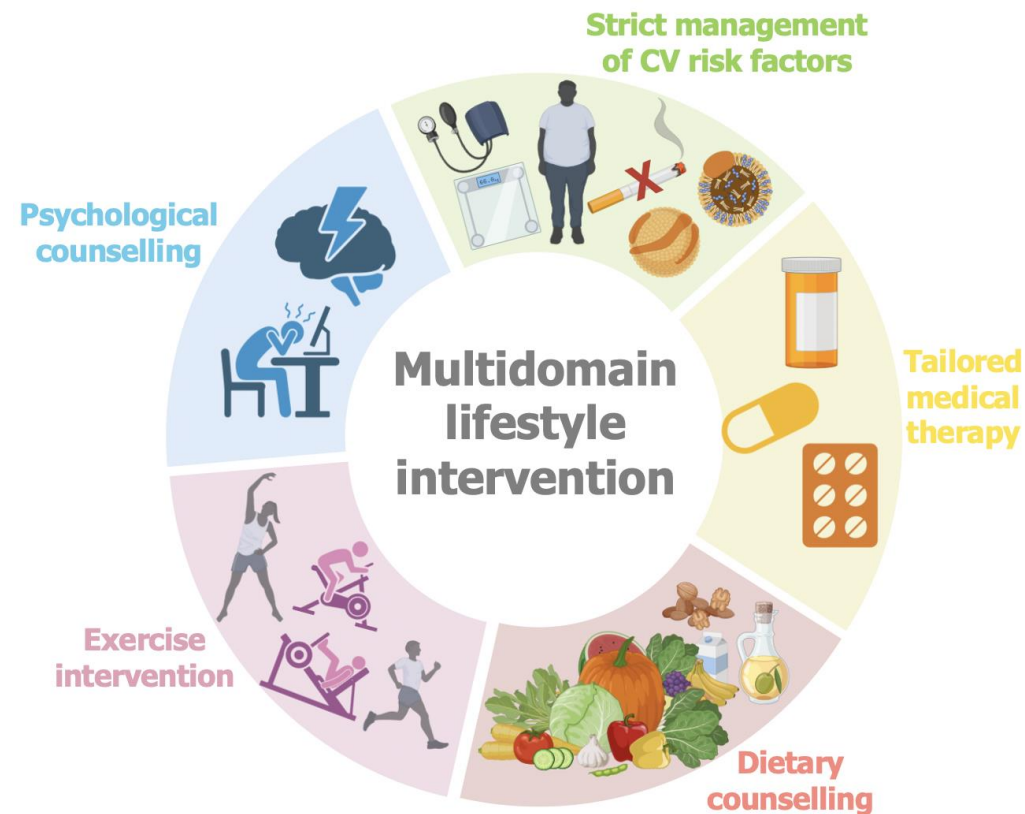
- ❑ **The main investigations were focused on:**
 - prevalence of ANOCA condition
 - contributing factors
 - impact on QoL
 - ANOCA diagnostic workflow and medical treatment

- ❑ **Data regarding how to improve physical limitation, depression and overall QoL beyond the medical treatment are lacking**



Aim

The aim of the SAMCRO trial is to investigate if a multidomain lifestyle intervention, based on 5 different domains, improves angina status and quality of life in ANOCA patients as compared to current standard of care





Endpoints

Primary

Seattle Angina Questionnaire (SAQ) summary score at 1 year

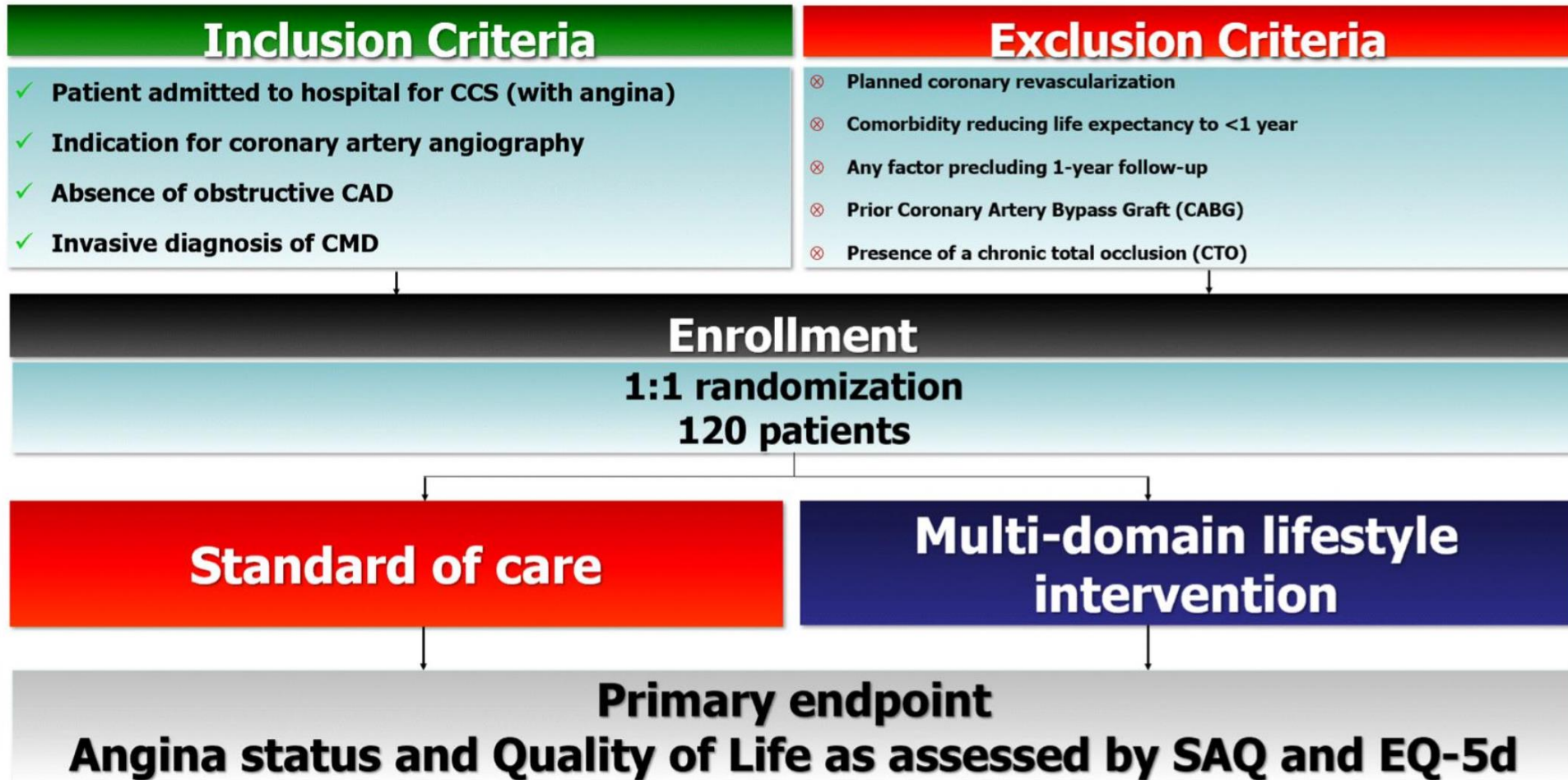
Secondary

SAQ angina frequency & stability, treatment satisfaction, physical limitation, QoL domain
EQ-5D: mobility, self-care, usual activities, pain/discomfort, anxiety/depression
EQ visual analogue scale (**EQ-VAS**)
Beck Depression Inventory (**BDI**)
Compliance to the multidomain lifestyle intervention
All-cause death
Cardiovascular death
Hospital admission for any cause



Study Design

All comers, prospective, randomized, multicenter, open-label study with blinded adjudicated evaluation of outcomes (PROBE)





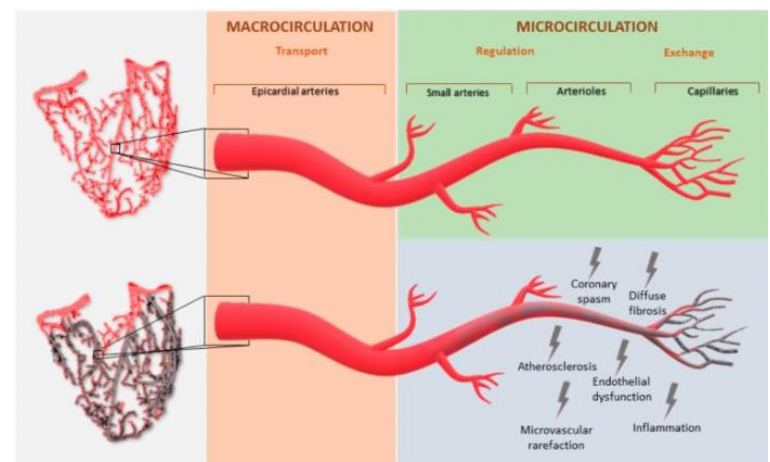
CMD

Inclusion Criteria

- ✓ Patient admitted to hospital for CCS (with angina)
- ✓ Indication for coronary artery angiography
- ✓ Absence of obstructive CAD
- ✓ Invasive diagnosis of CMD

Based on invasive coronary physiology and defined as:

- **FFR > 0.80**
and
- **CFR < 2**
and/or
- **IMR > 25**
and/or
- Positive vasoreactivity test with **Ach**



- Three ANOCA subtypes:**
- 1. Coronary microvascular dysfunction**
 - 2. Coronary vasospasm (epicardial and/or microvascular)**
 - 3. Mixed forms**



Experimental arm

Multi-domain lifestyle intervention with 5 different kinds of interventions:

i) strict management of CV and metabolic risk factors

ii) tailoring of medical therapy on the basis of the assessment of CMD endotype

iii) dietary counselling

[2 visits within the 1st month with a nutritionist where personal dietary goals and patient's daily diet]

iv) psychological counselling

[2/3 sessions of individual supportive-expressive psychotherapy focused on 4 areas related to depression in CAD: coping with illness, dealing with emotions, change of lifestyle, shaping of social relationship]



Experimental arm

v) exercise intervention

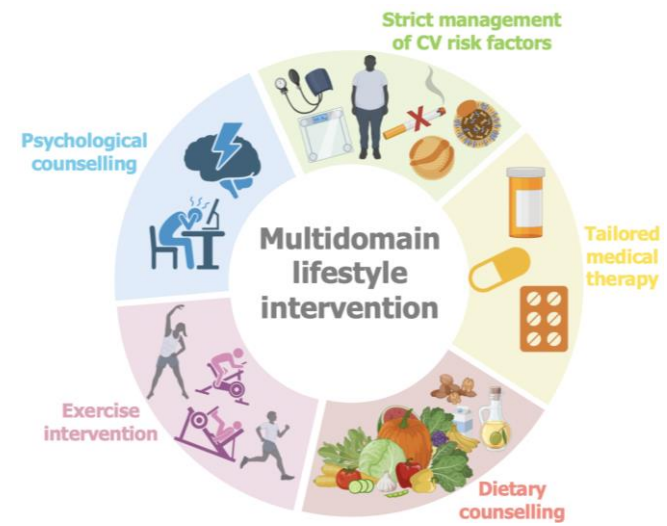
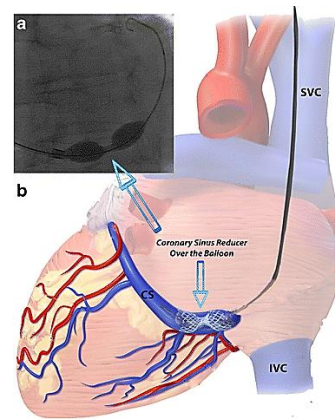
[early, tailored mixed program with 6 supervised physical activity sessions and a series of exercises to be performed at home, along with at least 20 mins of moderate walking]

First supervised session	Home-based sessions	Subsequent supervised session
<p>Pre-test:</p> <ul style="list-style-type: none">• measure of blood pressure• positioning RS100 Polar heart rate monitor to constantly evaluate heart rate• Calisthenics exercises <p>Start: walking on the level at 2.0 km/h</p> <p>Every 30 s: increases of 0.3 km/h up to reach a walking speed corresponding to a perceived exertion of 11–13 on the Borg scale for 1 km^a.</p> <p>Post-test:</p> <ul style="list-style-type: none">• Measure of blood pressure.• Counselling on physical activity and daily activities, such as gardening, or household work	<ul style="list-style-type: none">• 30 to 60 min of continuous moderate walking a day, at least 3 to 4 and preferably 7 days a week• Calisthenics exercises^b	<p>Pre-test:</p> <ul style="list-style-type: none">• Measure of blood pressure• Positioning RS100 Polar heart rate monitor to constantly evaluate heart rate. <p>• Calisthenics exercises^b</p> <p>Start: walking at an updated intensity established according to reached results in the previous activity session</p> <p>Every 30 s: increases of 0.3 km/h up to reach a walking speed corresponding to a perceived exertion of 11–13 on the Borg scale for 1 km^a.</p> <p>Post-test:</p> <ul style="list-style-type: none">• Measure of blood pressure• Counselling on physical activity and daily activities, such as gardening, or household work



Patient with CMD diagnosis

"Oh no! There is so much to be done!!!"





Thanks for your attention!

If you want to know more about the **Element study group**, please go

to **elementrials.org**

