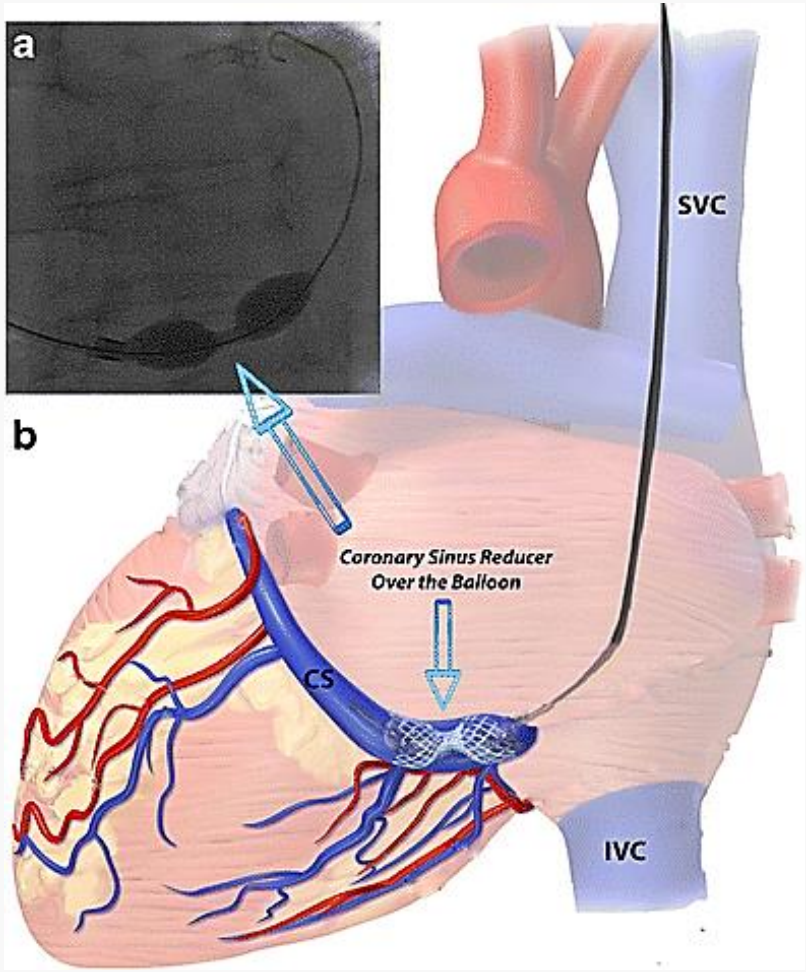
Background

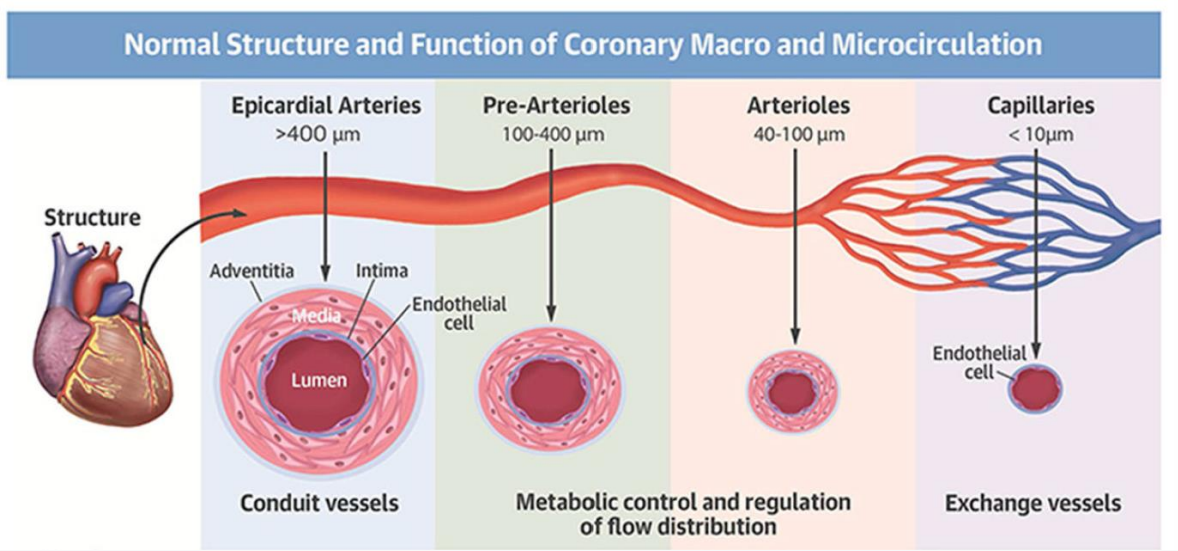
Refractory angina (RA) refers to long-lasting symptoms (> 3 months) due to documented reversible ischemia in the presence of obstructive CAD, which cannot be controlled by escalating anti-anginal medications, PCI or BPAC, including the treatment of CTO.

Coronary Sinus Reduction has been indicated for patients with refractory symptoms despite revascularization of obstructive CAD and OMT[1].



Background

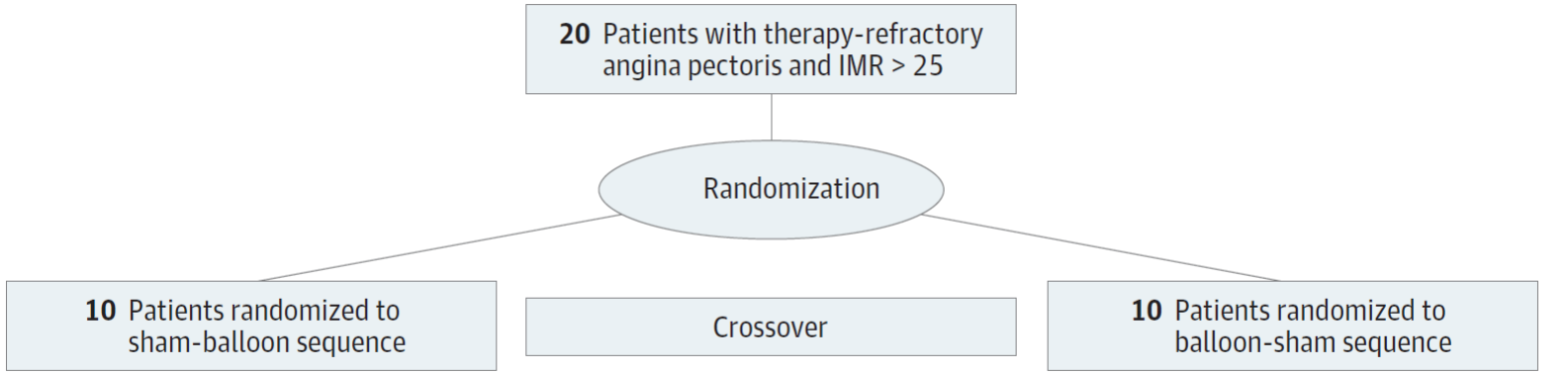
However, refractory angina in the absence of obstructive CAD also exists, and an important shift in the understanding of RA relates to the additional role of **microvascular dysfunction** in perpetuating this process.



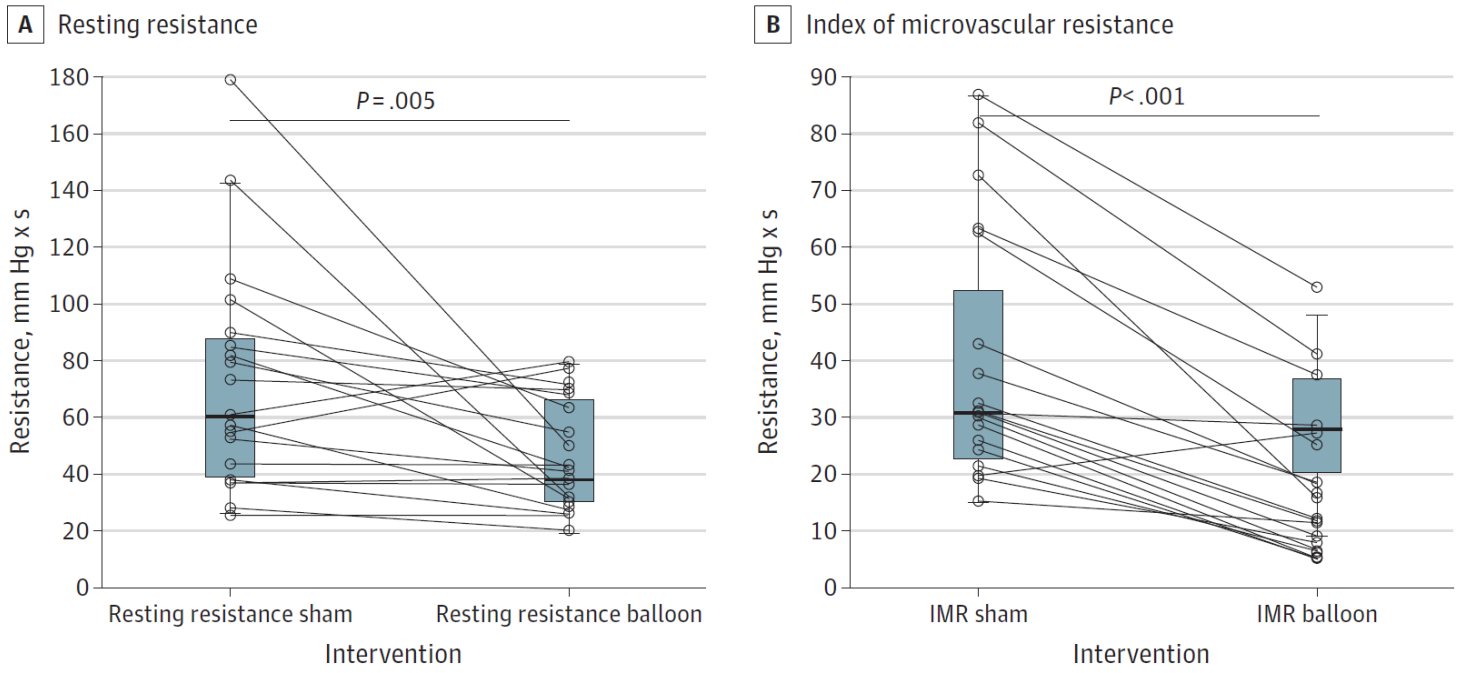
Some reports have suggested positive effects of Reducer implantation in patients with refractory symptoms secondary to disorders of the **coronary microcirculation**[2]**.**

Nevertheless, the mechanisms underlying the observed clinical benefits remain unclear, and there is lack of data describing the effect of coronary sinus reduction on coronary microcirculation function.

Gori et al.



Hemodynamic variable	Sham Median (IQR)	Balloon Median (IQR)	*P* value[b]
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



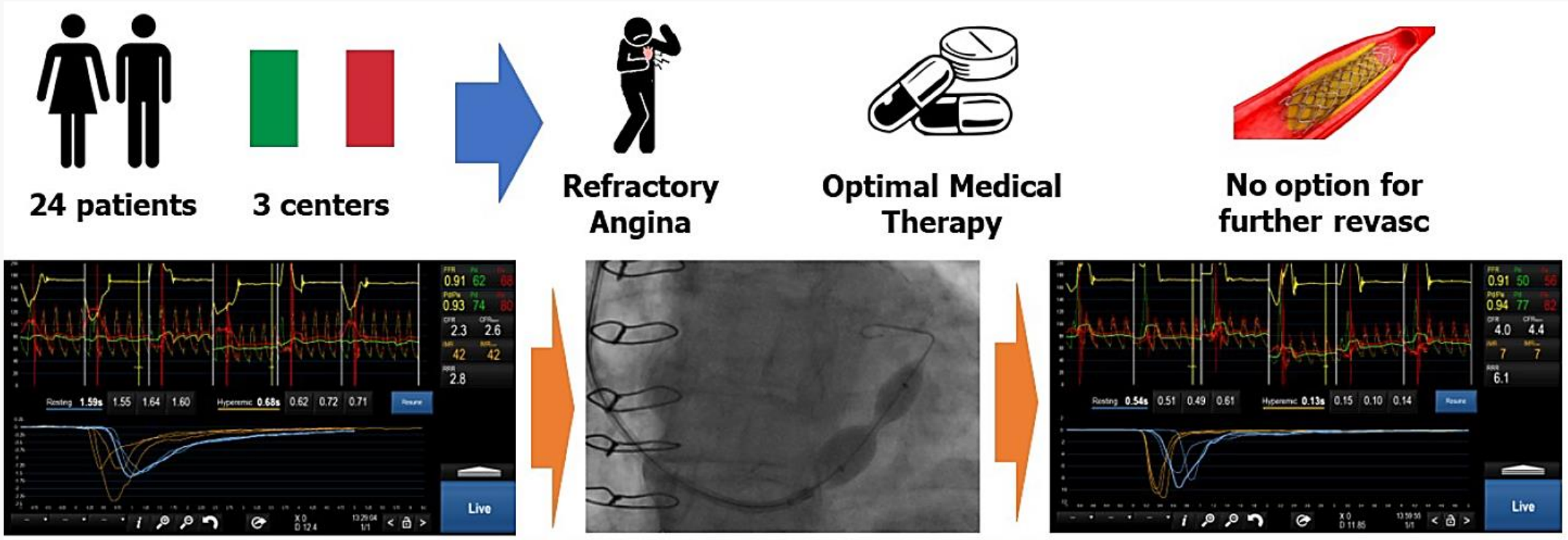
Research question

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

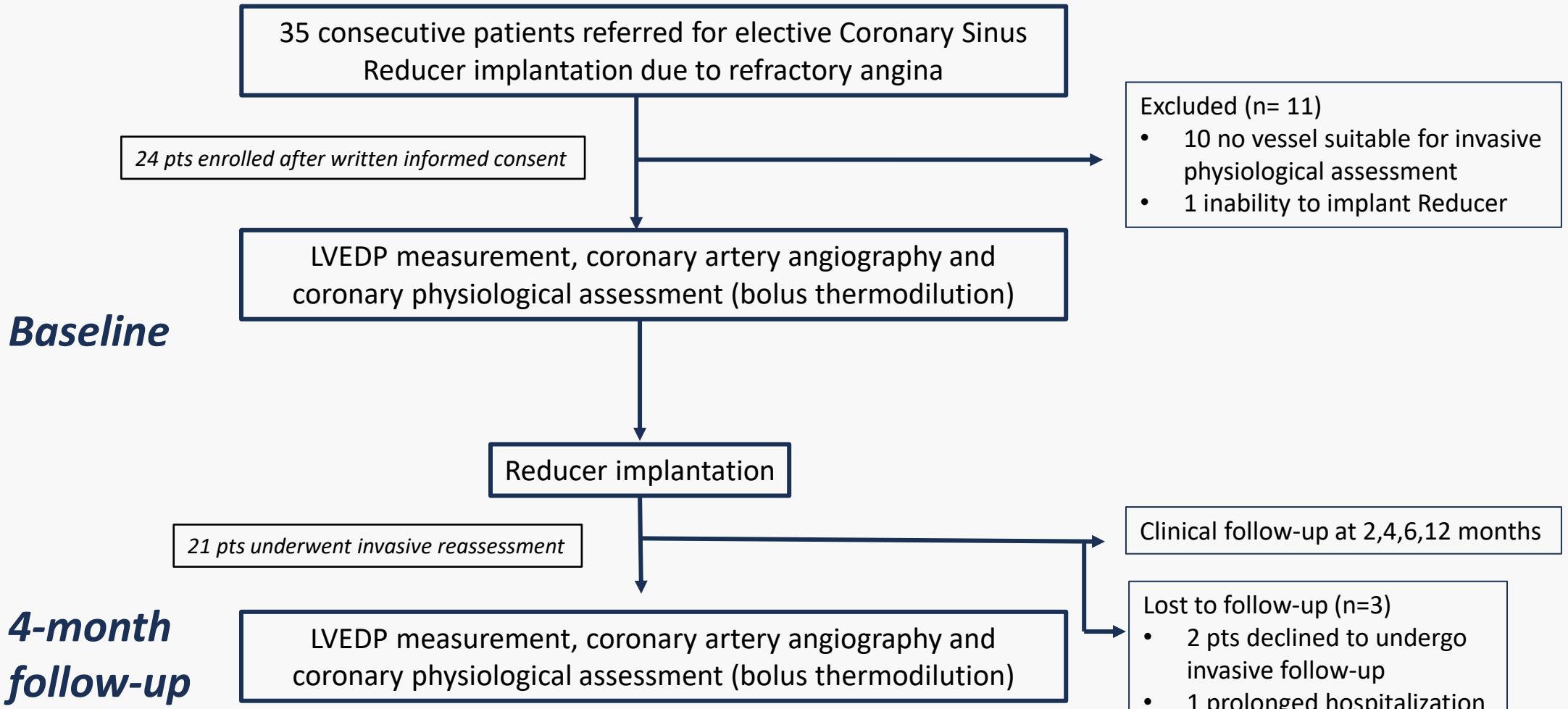
Exclusion criteria

- 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-month 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)
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)
CKD	12 (50.0)

Characteristic	Patients (n=24)
LVEF (%)	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 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)
Pd/Pa	0.93 ± 0.02
RFR	0.94 ± 0.03
FFR	0.89 ± 0.04
CFR	2.36 ± 1.45
CFR < 2, no. (%)	13 (54)
RRR	2.71 ± 2.18
RRR < 3.5 (%)	18 (75)

Results – PRIMARY ENDPOINT

	Baseline (n=21)	4-month (n=21)	Mean difference (95% CI) from baseline to 4-month	P
Invasive coronary physiology				
IMR	33.35 ± 19.88	15.42 ± 11.36	-17.90 (from -26.16 to -9.64)	< 0.001
IMR ≥ 25, no (%)	12 (57)	4 (19)	NA	0.016
Pd/Pa	0.93 ± 0.02	0.93 ± 0.03	-0.001 (from -0.016 to 0.013)	0.843
RFR	0.94 ± 0.03	0.93 ± 0.03	-0.001 (from 0.017 to 0.016)	0.907
FFR	0.89 ± 0.04	0.89 ± 0.03	-0.001 (from -0.020 to 0.011)	0.538
CFR	2.46 ± 1.52	4.20 ± 2.52	1.73 (from 0.51 to 2.96)	0.007
CFR < 2, no (%)	11 (52)	4 (19)	NA	0.039
RRR	2.81 ± 2.31	4.75 ± 2.88	1.93 (from 0.67 to 3.2)	0.004
RRR < 3,5, no. (%)	15 (71)	8 (38)	NA	0.092

	Baseline (n=21)	4-month (n=21)	Mean difference (95% CI) from baseline to 4-month	P
LVEDP	1.94 ± 2.54	10.53 ± 2.16	- 1.42 (from -2.61 to -0.22)	0.023
CCS angina class, no. (%)				
I	0 (0)	12 (57)	NA	< 0.001
II	6 (28)	6 (28)	NA	< 0.001
III	14 (67)	3 (15)	NA	< 0.001
IV	1 (5)	0 (0)	NA	< 0.001
SAQ				
Angina frequency	51.42 ± 21.22	56.34 ± 19.47	4.92 (from 2.41 to 7.42)	< 0.001
Angina stability	40.95 ± 19.06	48.76 ± 16.64	7.81 (from 2.87 to 12.70)	0.003
Physical limitation	55.10 ± 2.74	53.81 ± 22.57	-1.28 (from -3.90 to 1.33)	0.317
Treatment satisfaction	55.95 ± 26.28	54.56 ± 24.03	-1.39 (from -3.49 to 0.71)	0.183
Quality of life	43.84 ± 20.22	48.81 ± 15.87	4.96 (from 1.58 to 8.33)	0.006
Summary Score	49.45 ± 16.28	52.46 ± 14.54	3.01 (from 1.39 to 4.61)	< 0.001

Results – PRIMARY ENDPOINT

	Baseline (n=21)	4-month (n=21)	Mean difference (95% CI) from baseline to 4-month	P
Invasive coronary physiology				
IMR	33.35 ± 19.88	15.42 ± 11.36	-17.90 (from -26.16 to -9.64)	< 0.001
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RRR < 3,5, no. (%)	15 (71)	8 (38)	NA	0.092

	Baseline (n=21)	4-month (n=21)	Mean difference (95% CI) from baseline to 4-month	P
LVEDP	1.94 ± 2.54	10.53 ± 2.16	- 1.42 (from -2.61 to -0.22)	0.023
CCS angina class, no. (%)				
I	0 (0)	12 (57)	NA	< 0.001
II	6 (28)	6 (28)	NA	< 0.001
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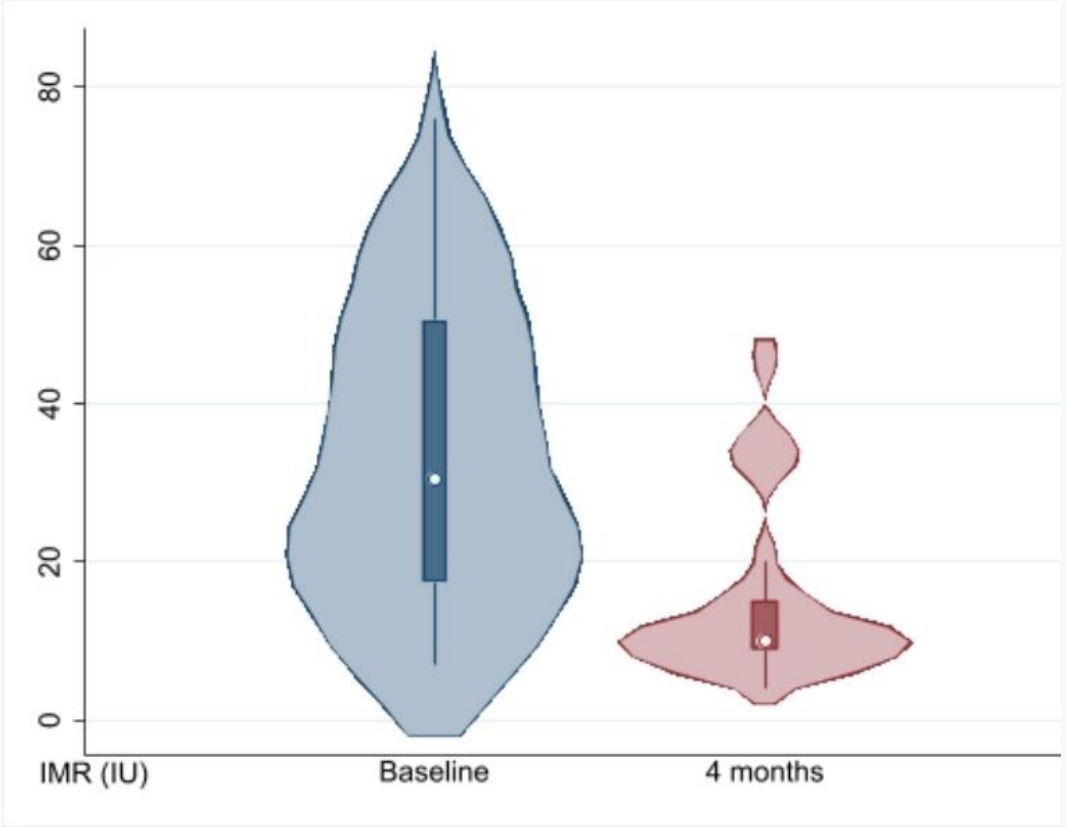
Quality of life	43.84 ± 20.22	48.81 ± 15.87	4.96 (from 1.58 to 8.33)	0.006
Summary Score	49.45 ± 16.28	52.46 ± 14.54	3.01 (from 1.39 to 4.61)	< 0.001

Results – PRIMARY ENDPOINT

Figure 1. Violin plot of the index of microcirculatory resistance values

IMR: index of microcirculatory resistance



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

Results – SECONDARY ENDPOINTS

	Baseline (n=21)	4-month (n=21)	Mean difference (95% CI) from baseline to 4-month	P
Invasive coronary physiology				
IMR	33.35 ± 19.88	15.42 ± 11.36	-17.90 (from -26.16 to -9.64)	< 0.001
IMR ≥ 25, no (%)	12 (57)	4 (19)	NA	0.016
Pd/Pa	0.93 ± 0.02	0.93 ± 0.03	-0.001 (from -0.016 to 0.013)	0.843
RFR	0.94 ± 0.03	0.93 ± 0.03	-0.001 (from 0.017 to 0.016)	0.907
FFR	0.89 ± 0.04	0.89 ± 0.03	-0.001 (from -0.020 to 0.011)	0.538
CFR	2.46 ± 1.52	4.20 ± 2.52	1.73 (from 0.51 to 2.96)	0.007
CFR < 2, no (%)	11 (52)	4 (19)	NA	0.039
RRR	2.81 ± 2.31	4.75 ± 2.88	1.93 (from 0.67 to 3.2)	0.004
RRR < 3,5, no. (%)	15 (71)	8 (38)	NA	0.092

	Baseline (n=21)	4-month (n=21)	Mean difference (95% CI) from baseline to 4-month	P
LVEDP	1.94 ± 2.54	10.53 ± 2.16	- 1.42 (from -2.61 to -0.22)	0.023
CCS angina class, no. (%)				
I	0 (0)	12 (57)	NA	< 0.001
II	6 (28)	6 (28)	NA	< 0.001
III	14 (67)	3 (15)	NA	< 0.001
IV	1 (5)	0 (0)	NA	< 0.001
SAQ				
Angina frequency	51.42 ± 21.22	56.34 ± 19.47	4.92 (from 2.41 to 7.42)	< 0.001
Angina stability	40.95 ± 19.06	48.76 ± 16.64	7.81 (from 2.87 to 12.70)	0.003
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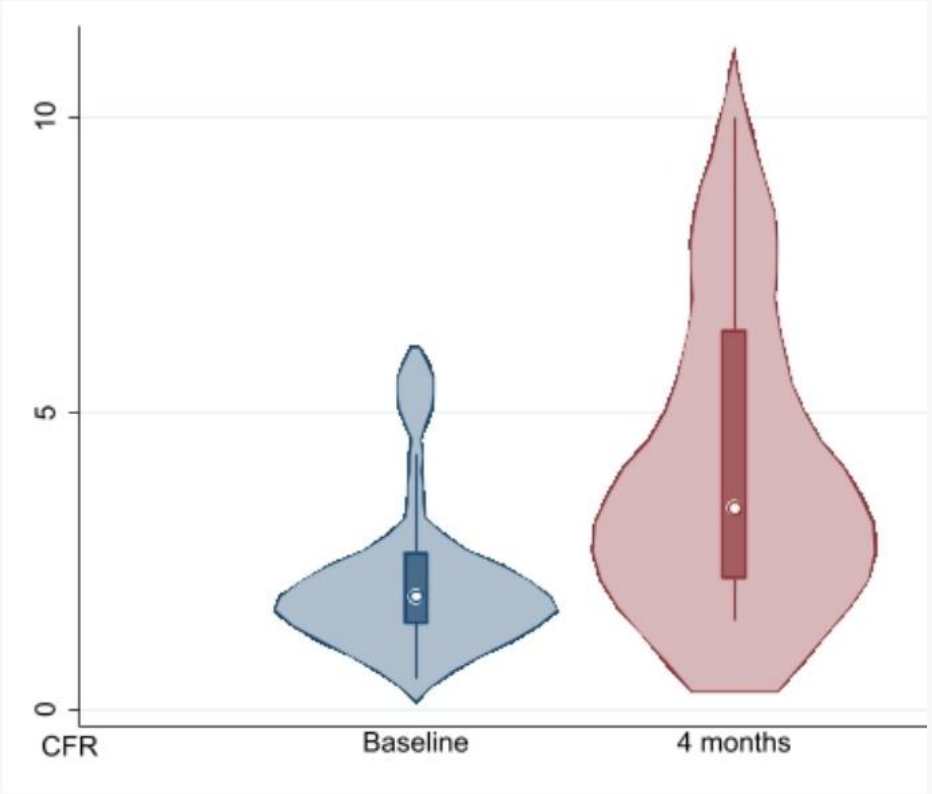
Quality of life	43.84 ± 20.22	48.81 ± 15.87	4.96 (from 1.58 to 8.33)	0.006
Summary Score	49.45 ± 16.28	52.46 ± 14.54	3.01 (from 1.39 to 4.61)	< 0.001

INROAD Study: Results

Figure 2. Violin plot of the coronary flow reserve values

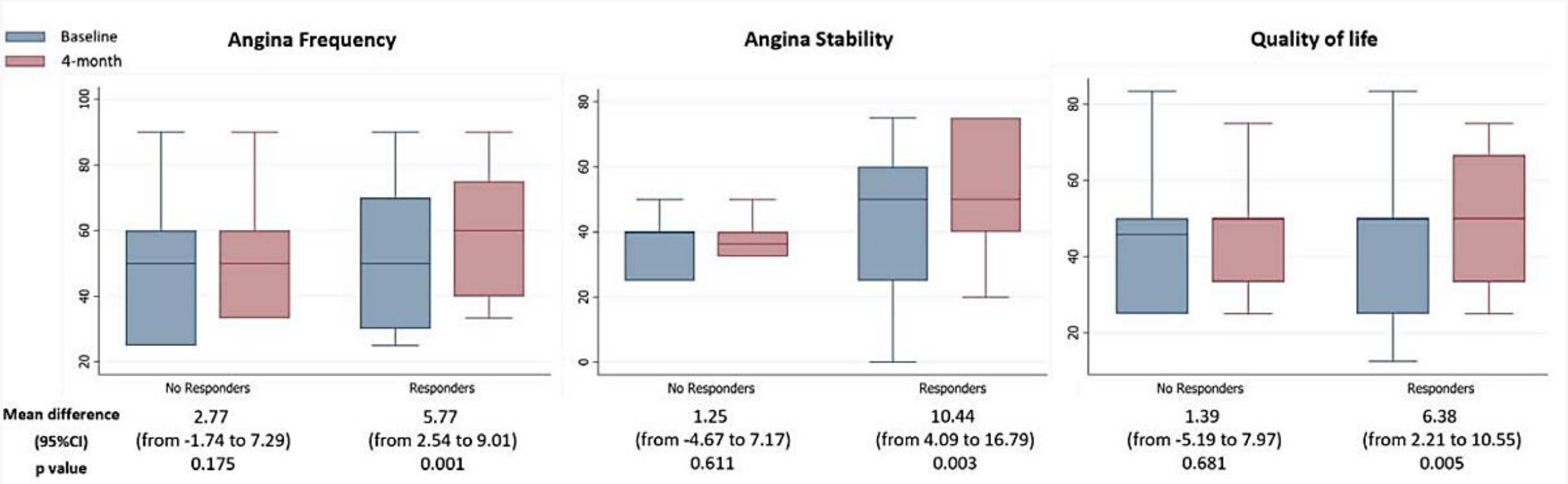
CFR: coronary flow reserve



CFR, RRR, CCS, SAQ

INROAD Study: Results

IMR responders VS IMR non-responders



	Angina Frequency		Angina Stability		Quality of life	
Mean difference	2.77	5.77	1.25	10.44	1.39	6.38
(95%CI)	(from -1.74 to 7.29)	(from 2.54 to 9.01)	(from -4.67 to 7.17)	(from 4.09 to 16.79)	(from -5.19 to 7.97)	(from 2.21 to 10.55)
p value	0.175	0.001	0.611	0.003	0.681	0.005

4 points SAQ in IMR Responders

INROAD Study: Conclusions

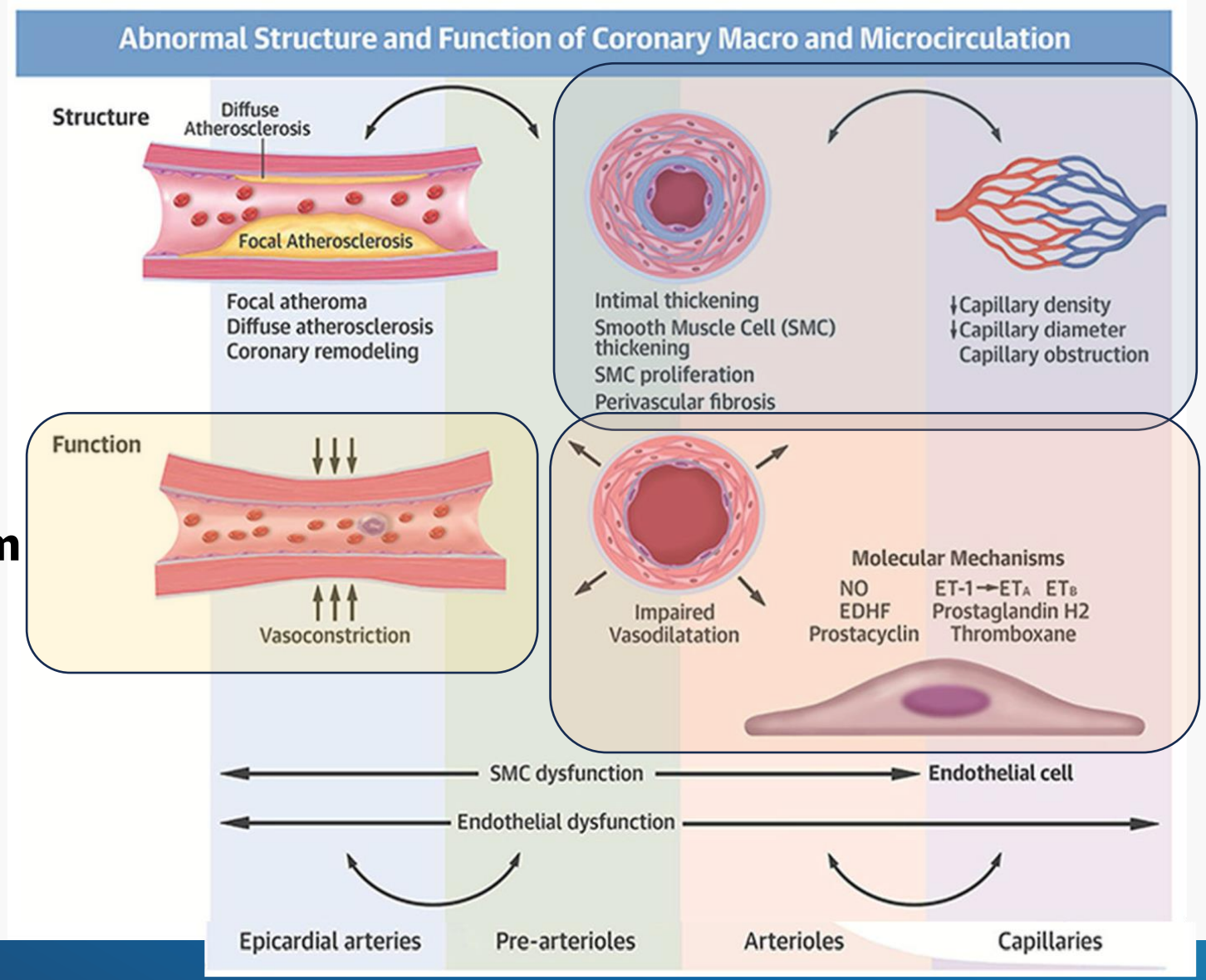
CMD represents an important **unmet clinical need** in daily practice affecting patients with no obstructive CAD (ANOCA) as well as those with epicardial disease treated with successful coronary revascularization.

Reducer implantation positively modulates coronary microvascular function. Of note, clinical benefits were seen only in **IMR responders**. Although improvements were more pronounced in patients with higher baseline IMR values, benefit was consistent in the whole cohort.

First study showing a **positive correlation** between an improvement in **microvascular function indexes** and angina related **symptoms** and **quality of life**.

Although our findings are preliminary, they suggest that coronary microvascular function may be a reversible condition, indicating that **Reducer implantation could be considered as an effective interventional therapy for CMD**.

#FullPhysiology: Microvascular Dysfunction



Vasospasm

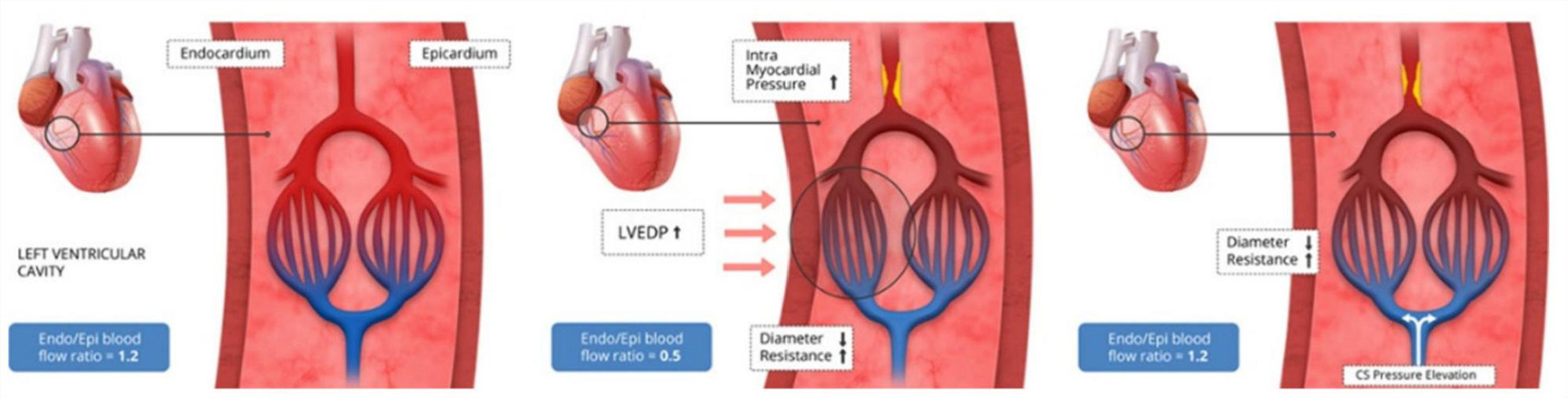
Structural CMD

Ischemic Heart Disease
Arterial Hypertension
Diabetes Mellitus

Functional CMD

Aortic stenosis
Dilated CMP (?)

INROAD trial



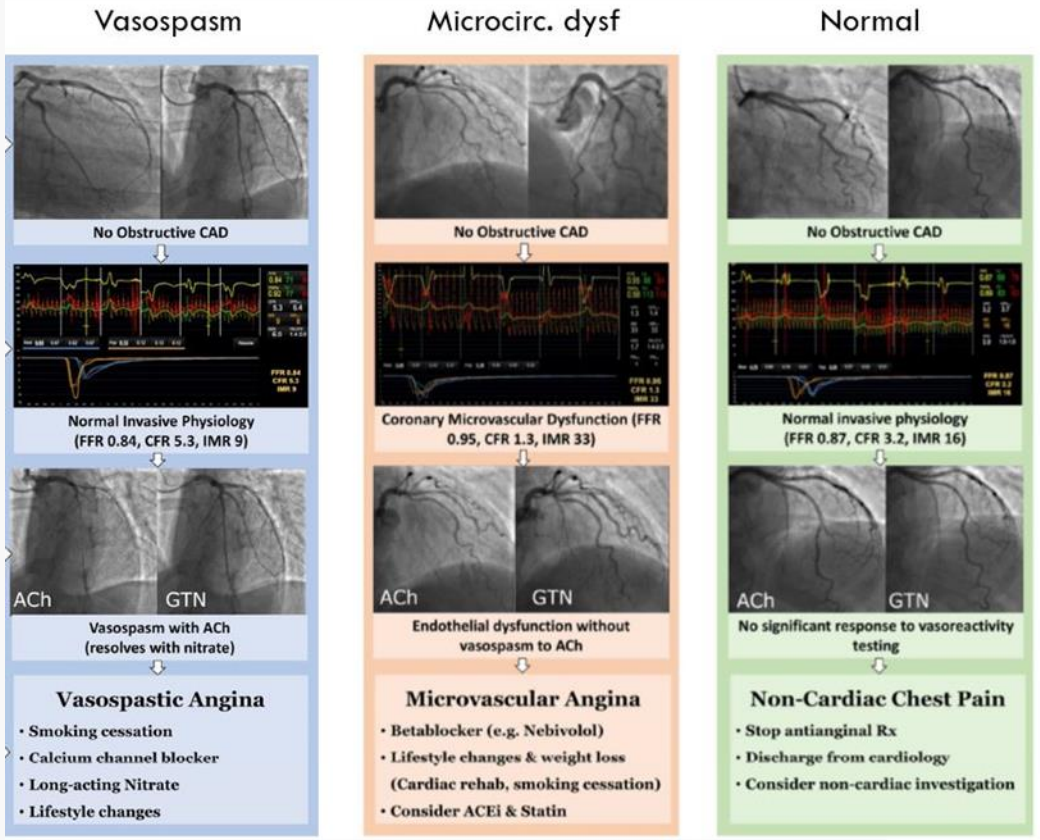
- **Elevation in backward pressure in the coronary venous system**
- **Slight dilation of the venules, capillaries and arterioles**
- **Subsequent reduction of the resistance to flow**
- **Improvements in IMR, CFR and RRR values.**

Skeletons in the closet

Patient with CMD diagnosis

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

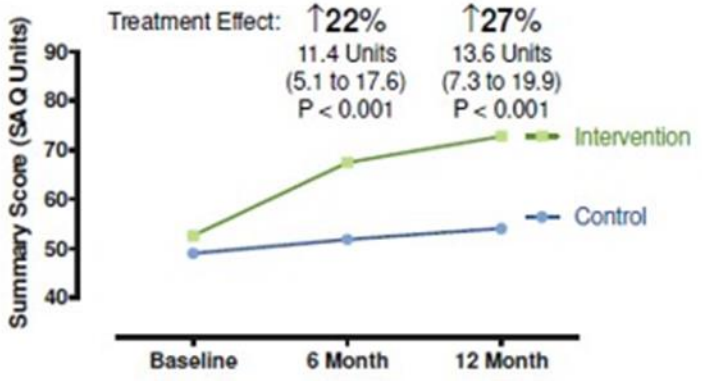
CorMIcA trial



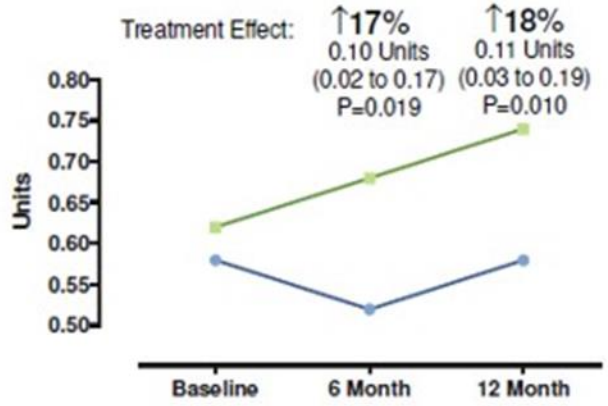
CB. 16.11.2019

CorMIcA

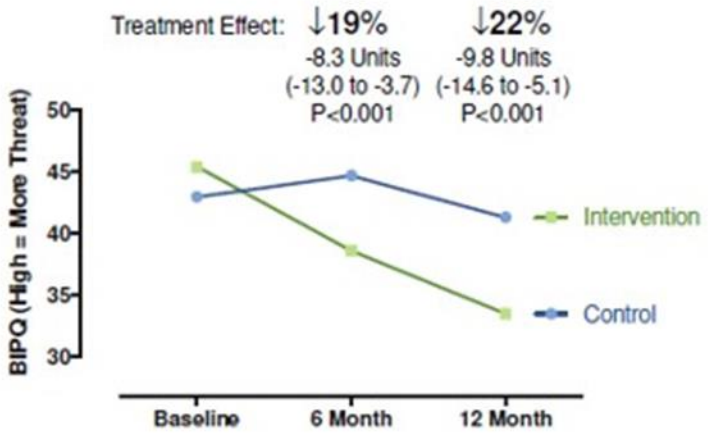
Primary endpoint: SAQ



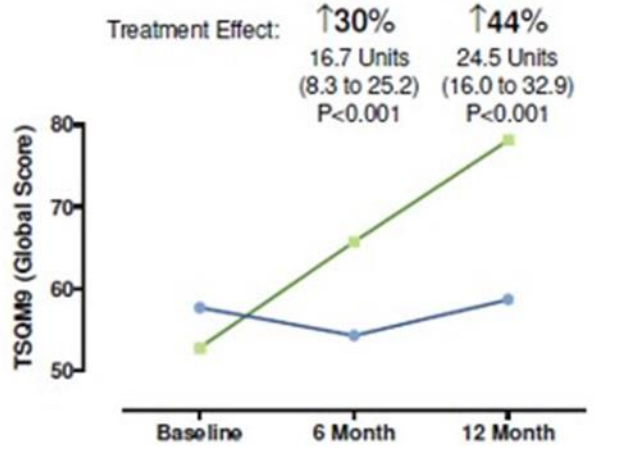
EQ5D



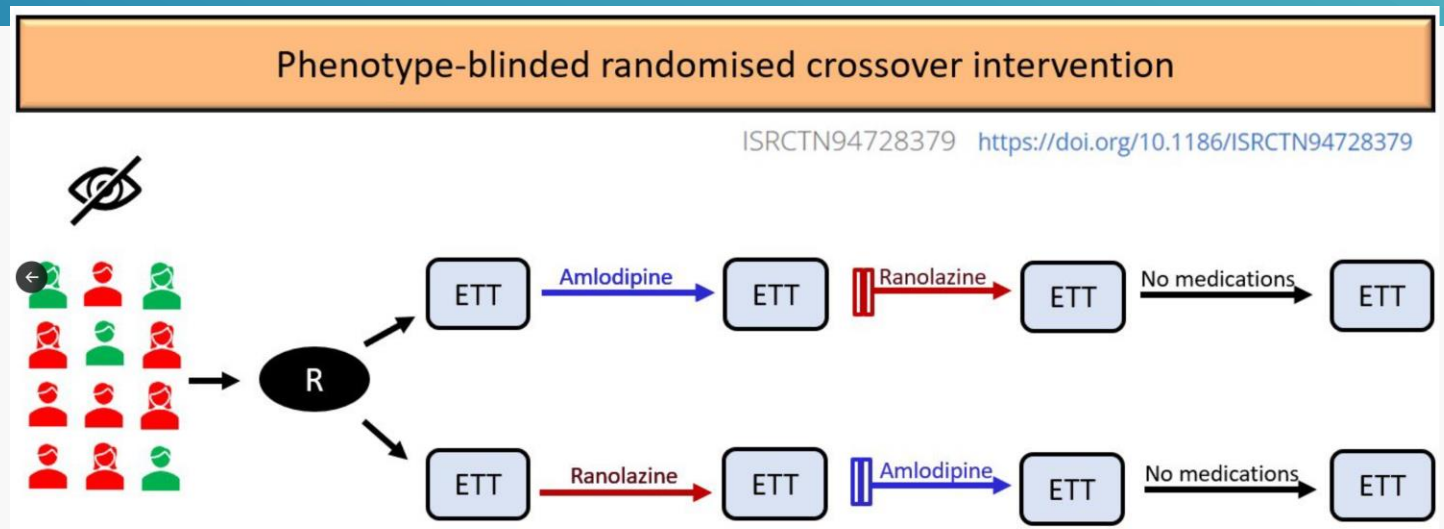
Illness Perception



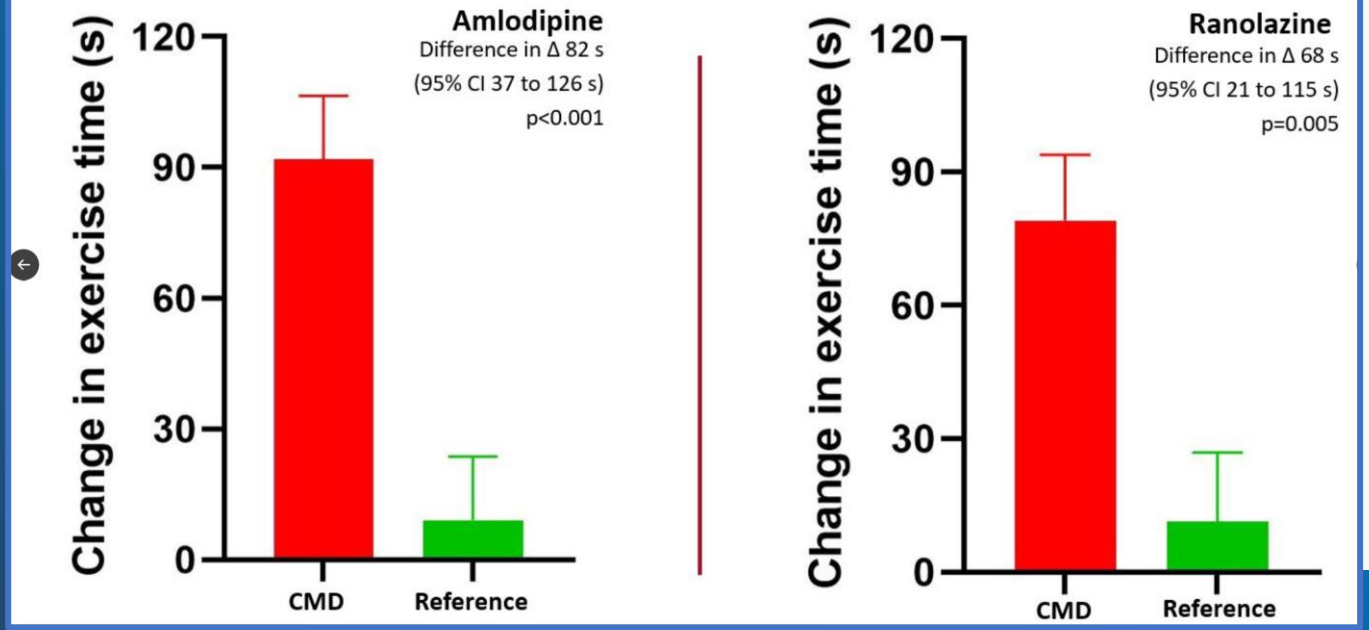
Treatment Satisfaction

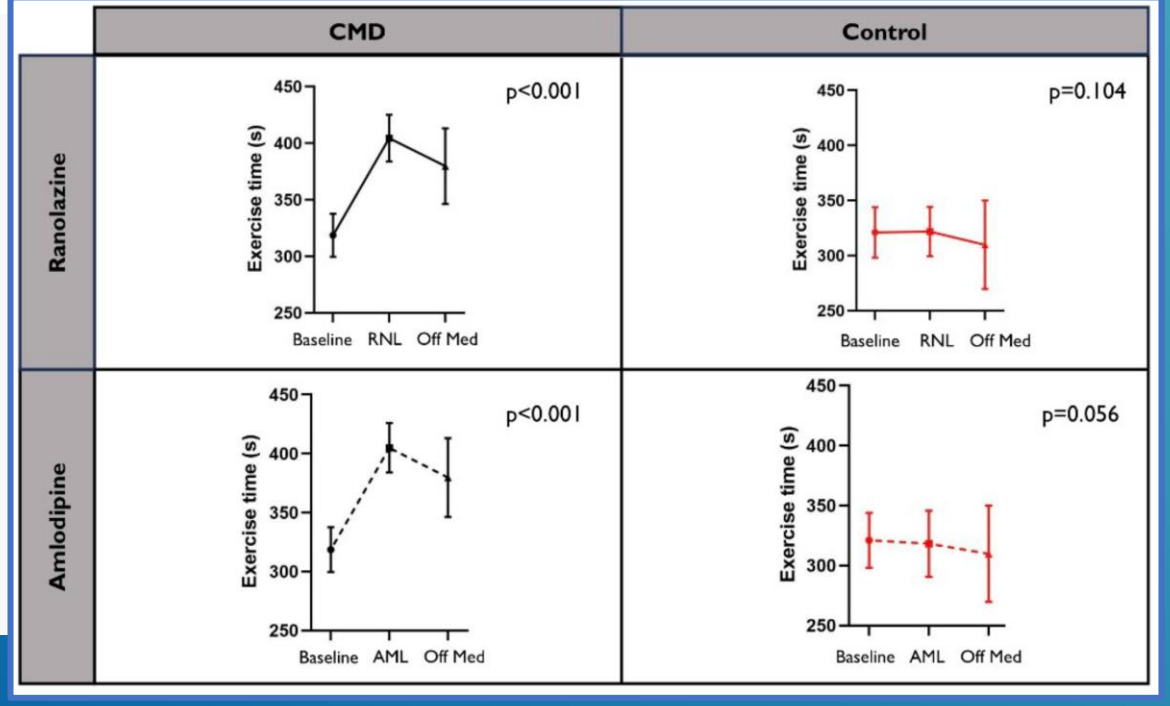


ChaMP-CMD trial



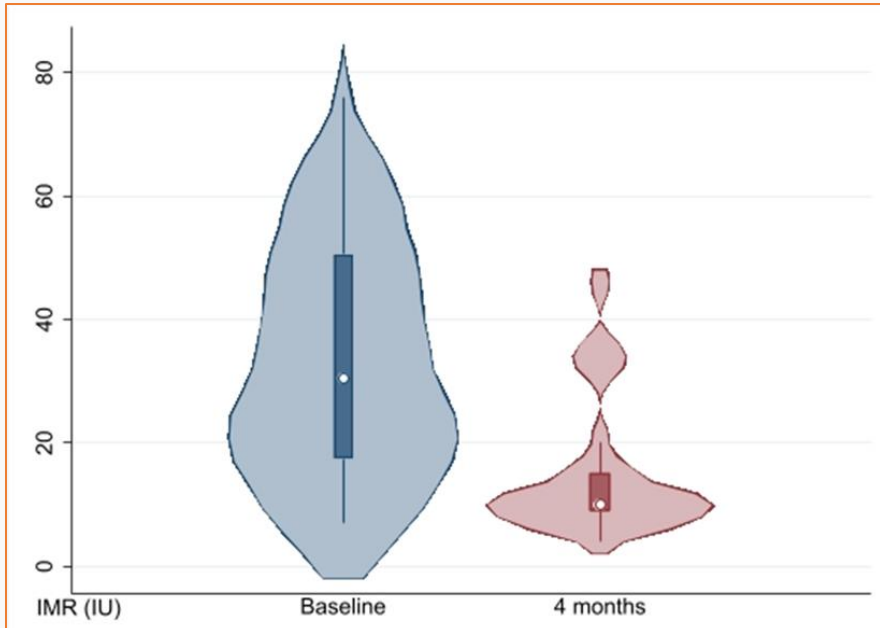
H_1: Does CFR predict change in exercise time in response to therapy?



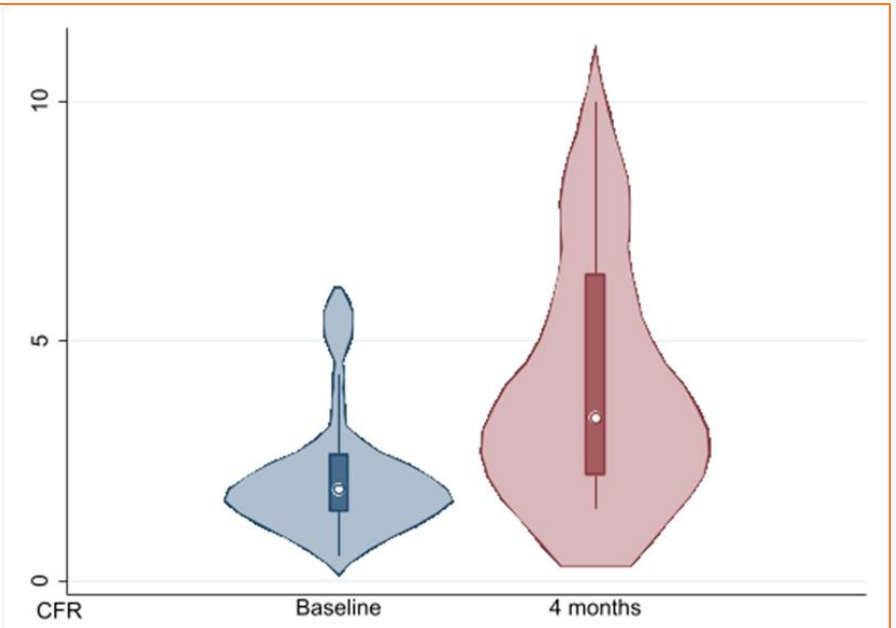


INROAD trial

	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 prevoius 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)



IMR before/after Reducer



CFR before/after Reducer