ROLE OF THE MICROVASCULATURE WITH FOCUS ON ANOCA AND MINOCA

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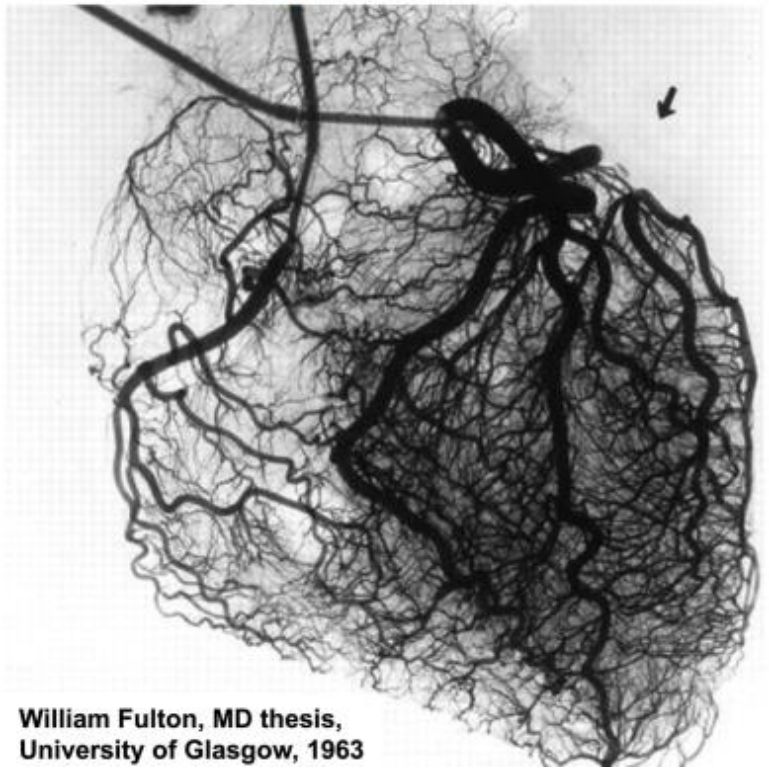
Coronary Microvascular System: What you don't see on an Angiogram

Stereo-arteriogram **Coronary angiogram**

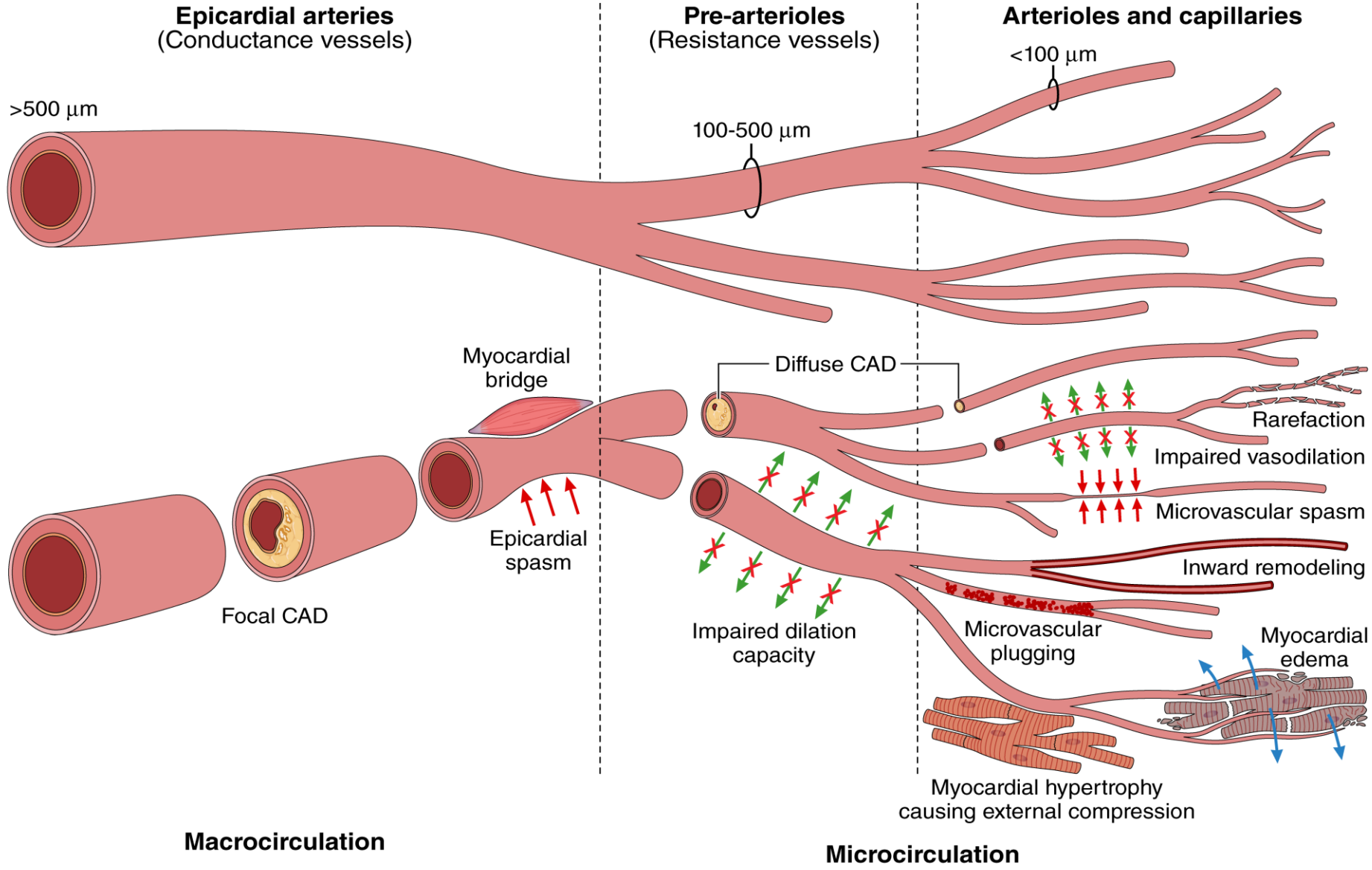
Imaging resolution

30 µm **300 µm +**



William Fulton, MD thesis,
University of Glasgow, 1963

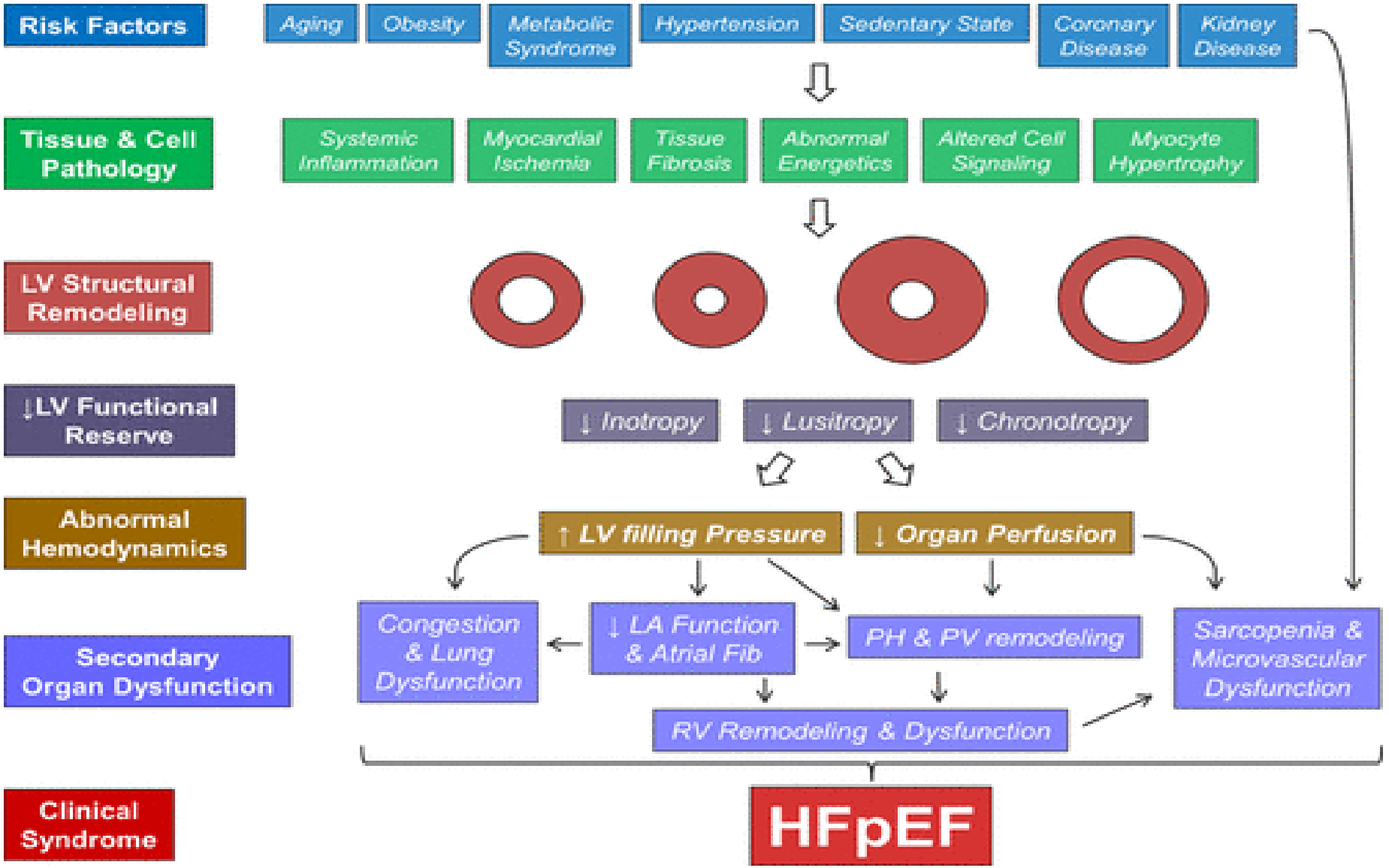
Coronary Microvascular Dysfunction and Vasomotor Diseases



Smilowitz NR, Toleva O et al. Circ Cardiovasc Interv. 2023;16:e012568.

Microvasculature Plays a Key Role

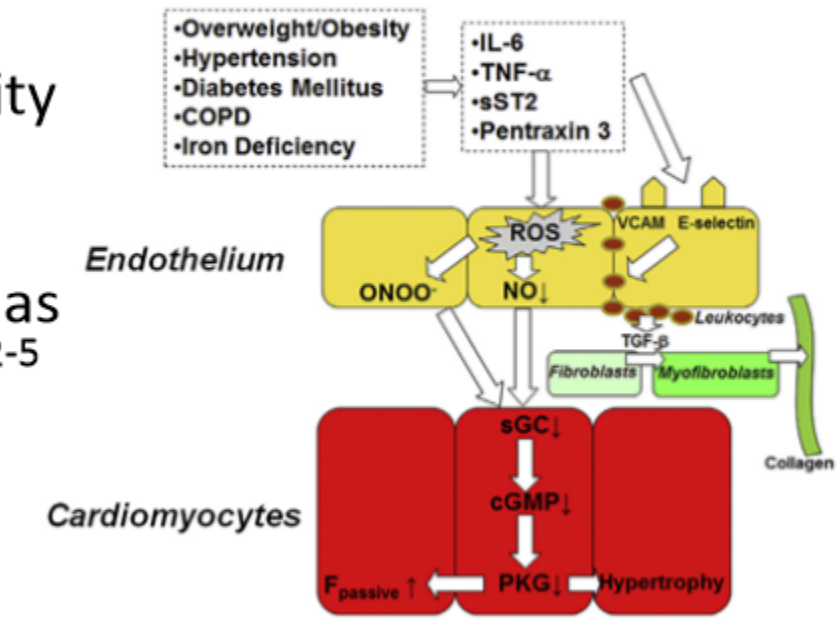
- Microvascular Dysfunction
- Heart Failure with Preserved EF
- STEMI/NSTEMI
- Post-PCI angina
- Post-CTO angina
- Refractory angina



Marc A. Pfeffer. Circulation Research. Heart Failure With Preserved Ejection Fraction In Perspective, Volume: 124, Issue: 11, Pages: 1598-1617, DOI: (10.1161/CIRCRESAHA.119.313572)

Background

- No treatment yet shown to reduce morbidity and mortality in HFpEF[1]
- Coronary microvascular dysfunction (CMD) proposed as a novel mechanism in HFpEF[2-5]
- Clinical evidence of CMD in HFpEF limited to selected referral samples[6-10]



[1]Eur Heart J 2016;37:2129, [2]J Am Coll Cardiol 2013;62:263, [3]JACC Heart Fail 2016;4:312, [4]Heart 2016;102:257, [5]Eur Heart J 2018 doi: 10.1093/eurheartj/ehy301, [6]Microcirculation 2015;22:528, [7]Eur Heart J 2018;39:840, [8]Am J Physiol Heart Circ Physiol 2018;314:H1033, [9]JAHA 2016;5.pii: e002649, [10]Circ HF 2016;9.pii: e002562

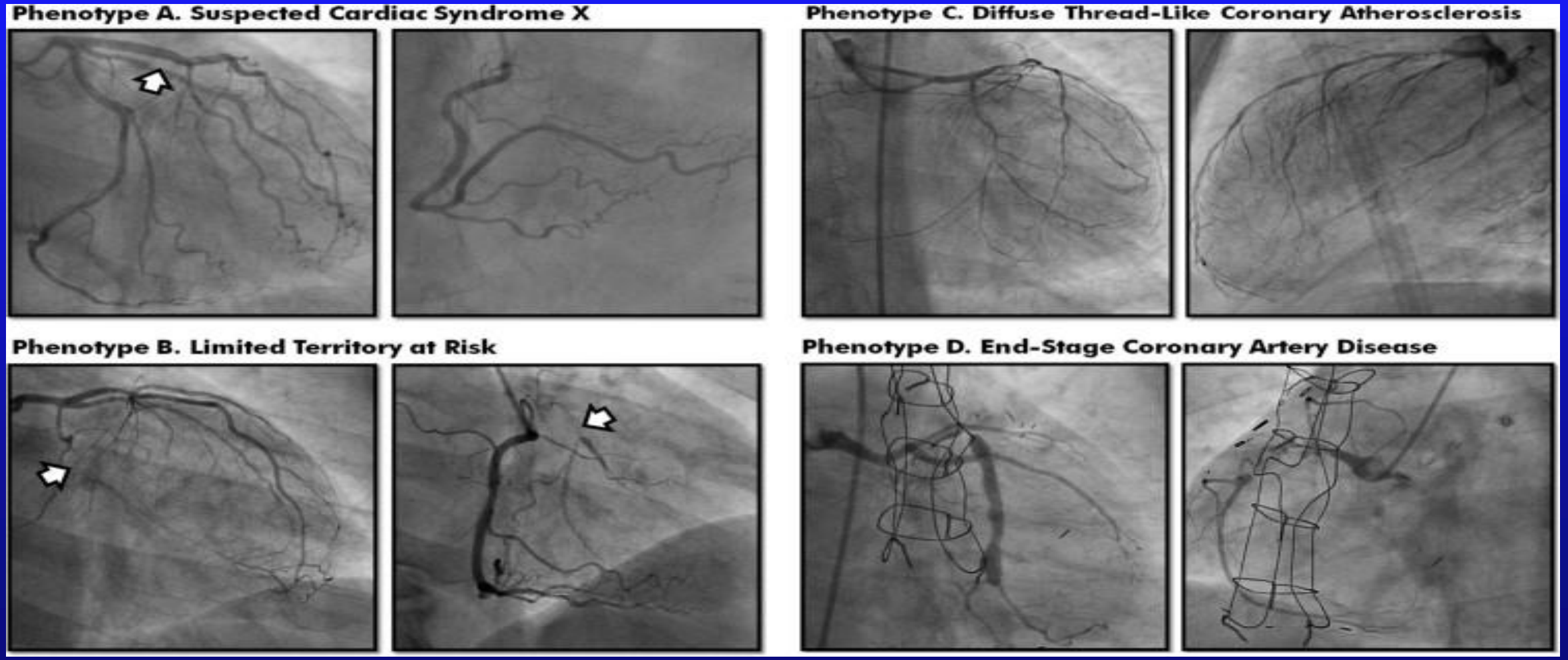
PROMIS-HFpEF: Conclusions

- Largest prospective multicenter study of CMD in HFpEF
- High (75%) prevalence of CMD in HFpEF in the absence of unrevascularized macrovascular CAD
- CMD is associated with HF severity (↑NT-proBNP), systemic endothelial dysfunction (↓ EndoPAT RHI, ↑UACR), and cardiac dysfunction (↓LV, LA, RV strain)
- Microvascular dysfunction may be a promising composite risk marker and therapeutic target in HFpEF

Refractory Angina

- Increasing number of patients as CAD mortality decreases and population ages
- 10-12 million patients in the US with chronic angina
- 10-15% of patients undergoing coronary angiography have myocardial ischemia with anatomy not ideal for CABG/PCI
- Chronic total occlusion, degenerated SVG, diffuse disease, poor distal targets, comorbidities and angina
- Angina in the COURAGE trial at 1 year: 42% for medical treatment vs. 34% for PCI ($p<0.001$)

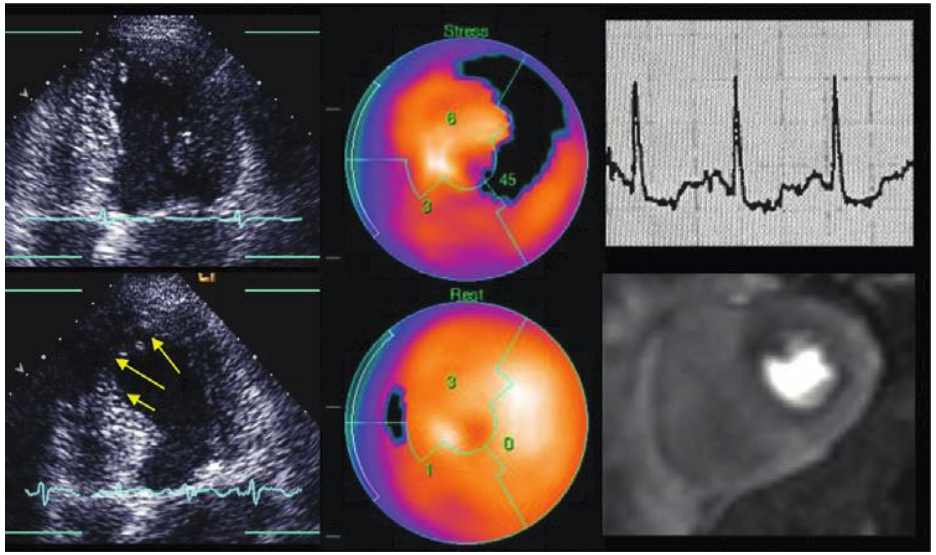
Refractory Angina Classification Scheme



Henry and Jolicoeur, Nature Reviews Cardiology 2014;11:78

INOCA: insights from the ISCHEMIA Trial

8,518 ISCHEMIA Enrolled Participants

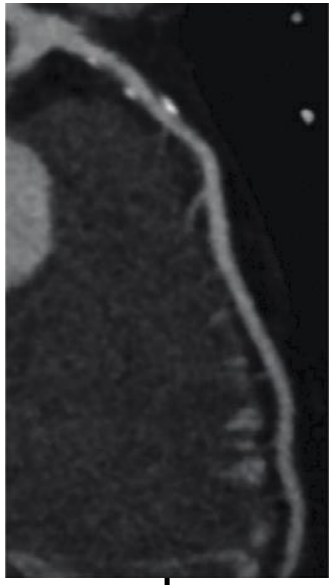


Moderate or severe ischemia

Core lab-verified

Exclusion of prior PCI, CABG, uninterpretable CCTA or no CCTA

13% INOCA



Ischemia severity not associated with extent of nonobstructive CAD on CCTA

INOCA associated with:

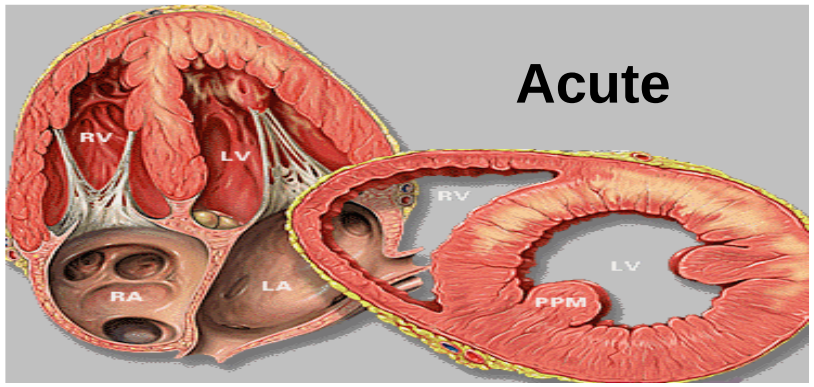
- Female sex
- Younger age
- Relatively less severe ischemia

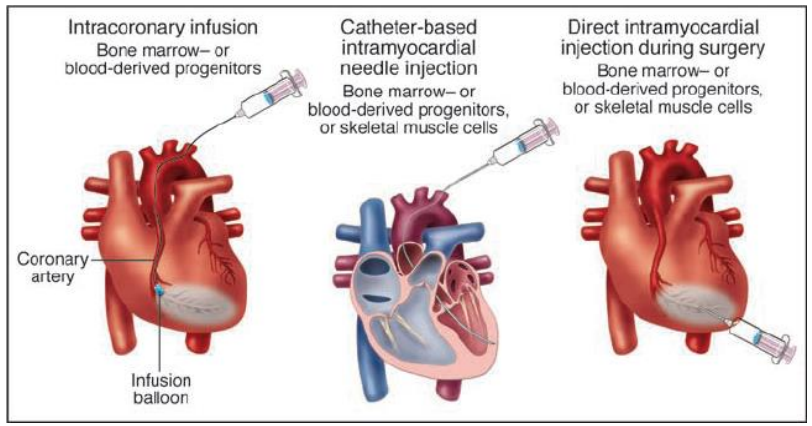
Women >4-fold odds of INOCA vs men on multivariate analysis

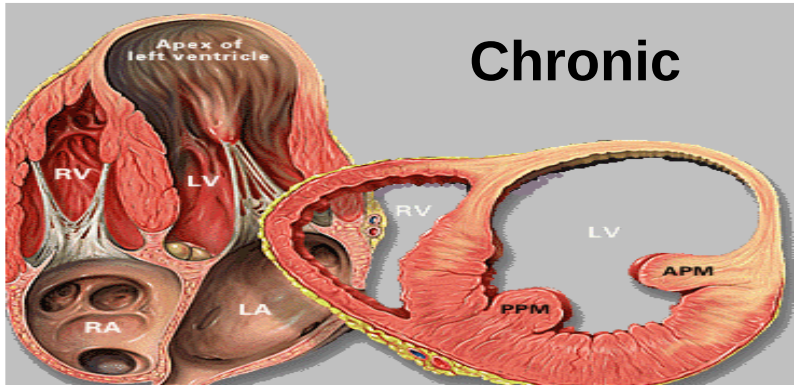
Reynolds HR et al. JACC Cardiovascular Imaging. 2023;16(1):63-74

STEMI/NSTEMI

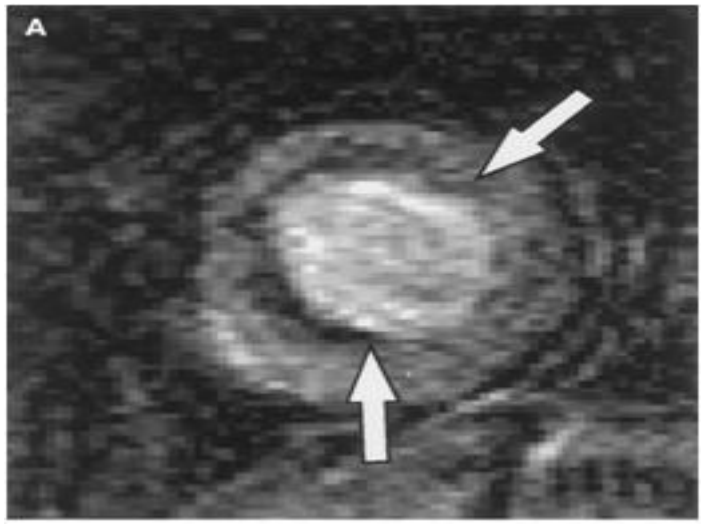
- Identification of high risk patients
- Selection for novel early treatments ?

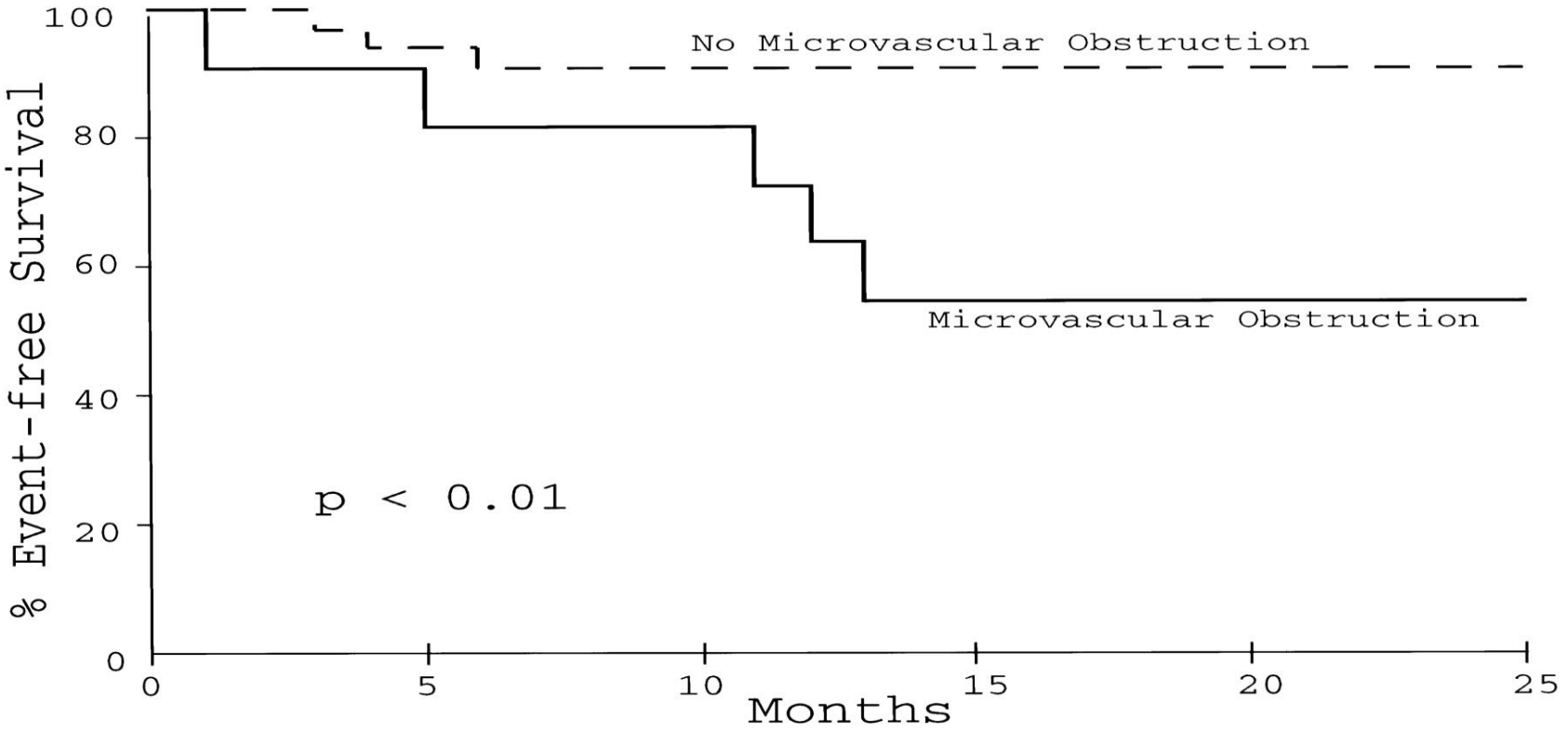






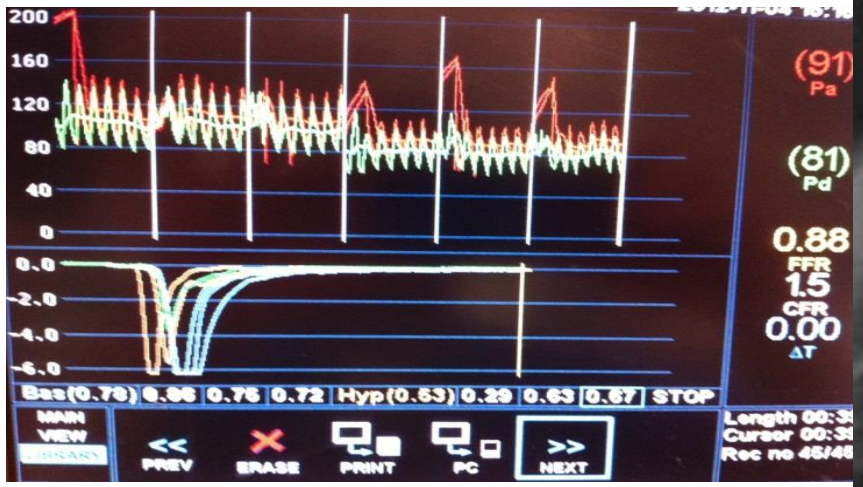
MVO and Risk

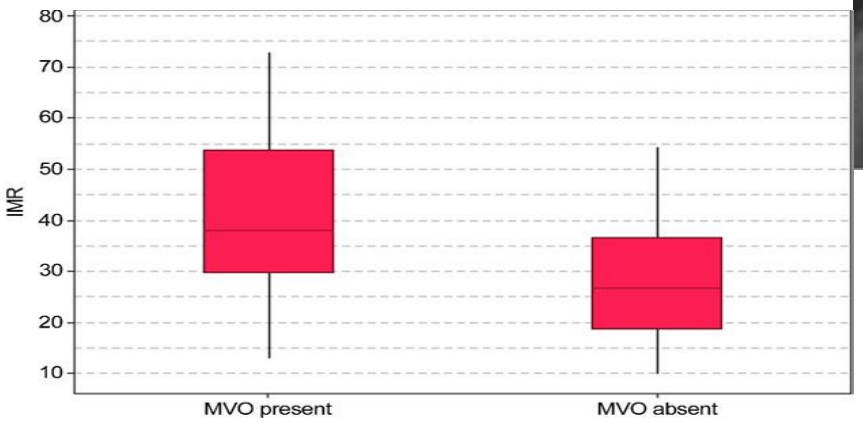


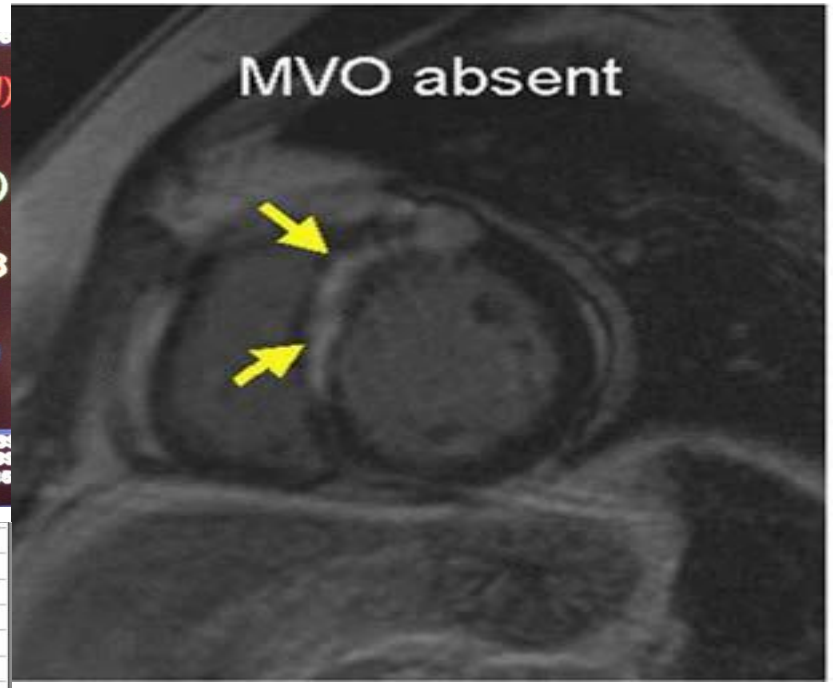


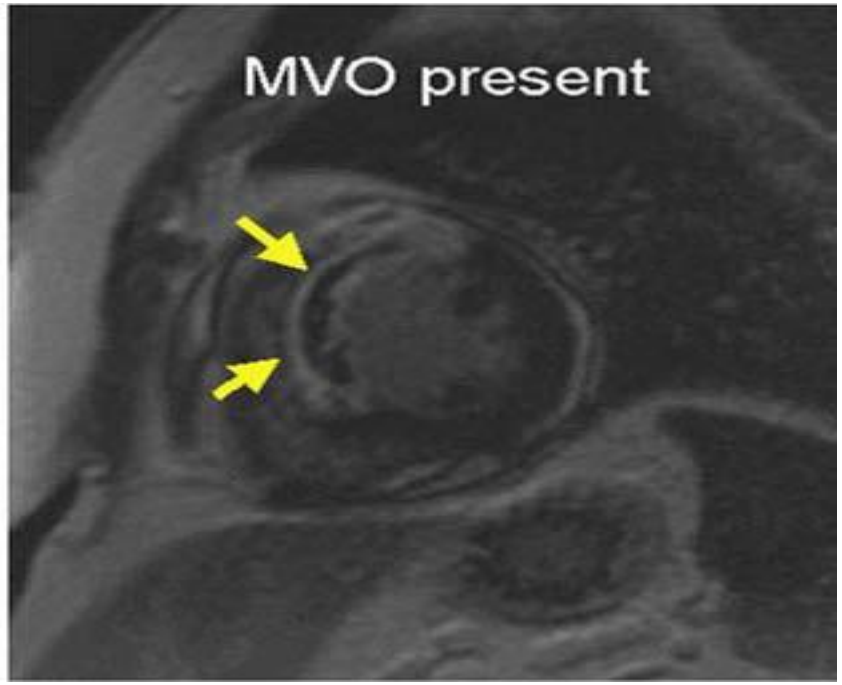
Wu K C et al. Circulation. 1998;97:765-772

IMR correlates to presence of MVO



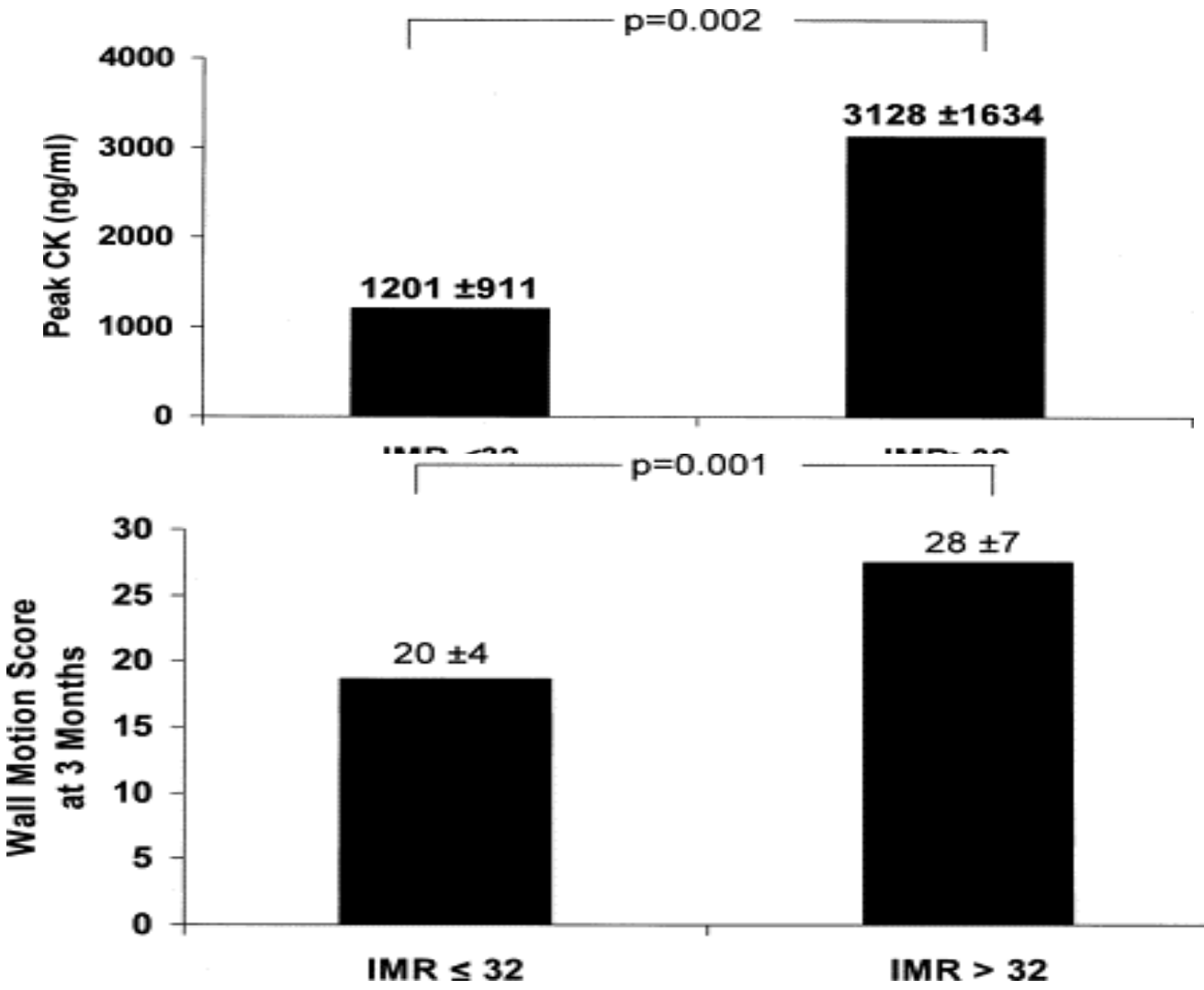


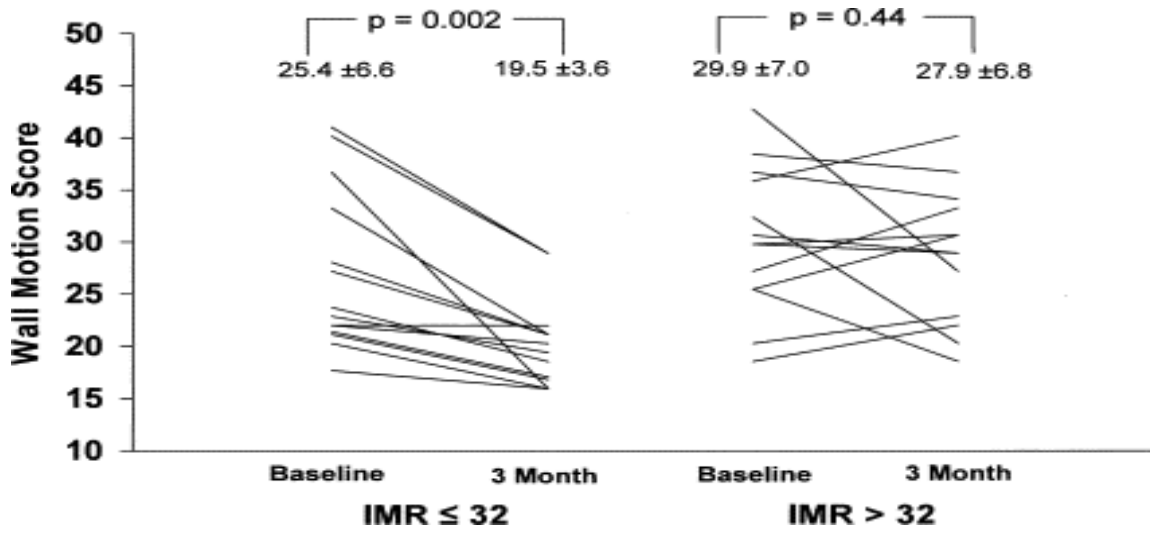




McGeoch et al. JACC: CARDIOVASCULARINTERVENTIONS, VOL.3, NO.7, 2010: 715–22

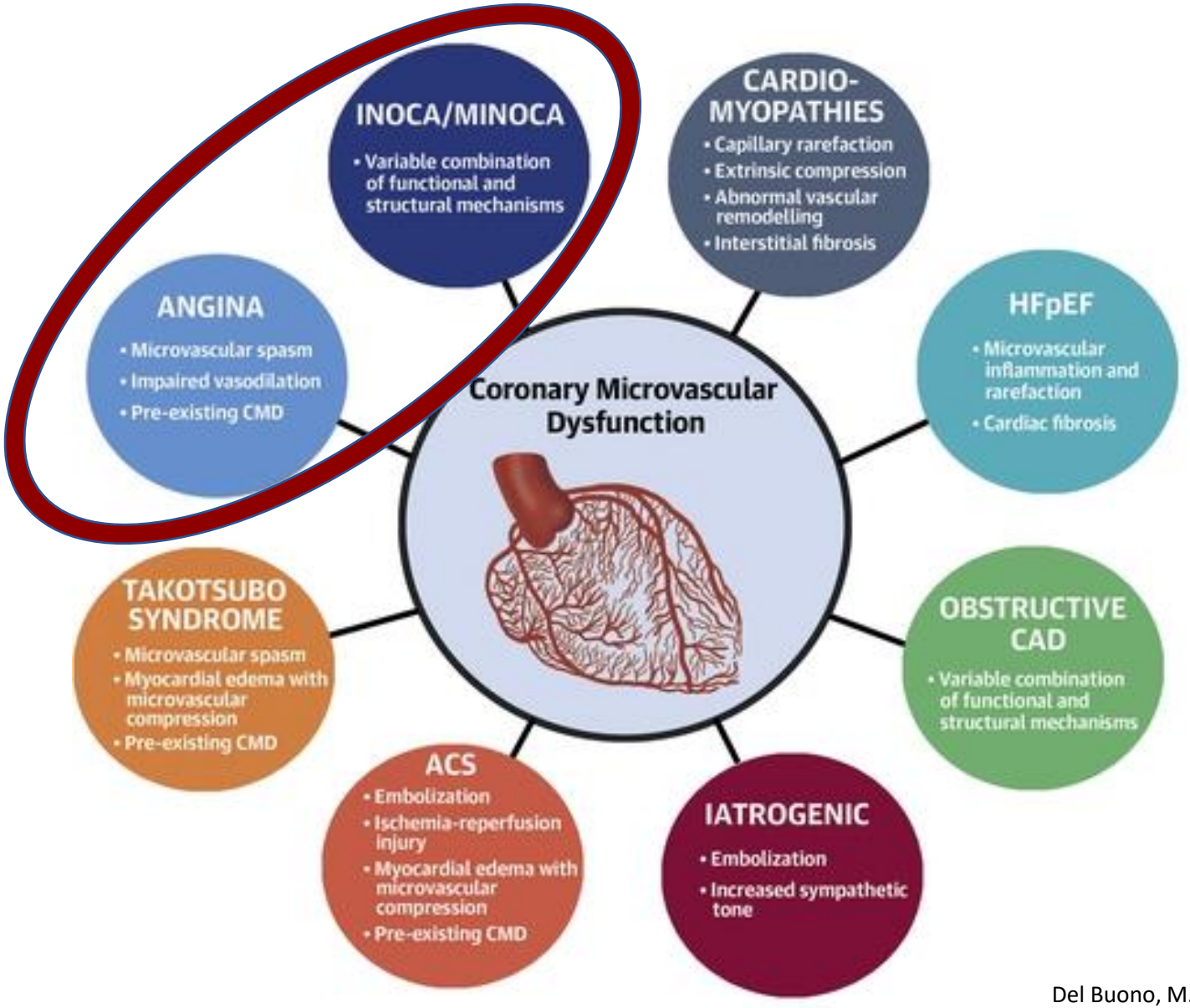
Infarct size, recovery and IMR





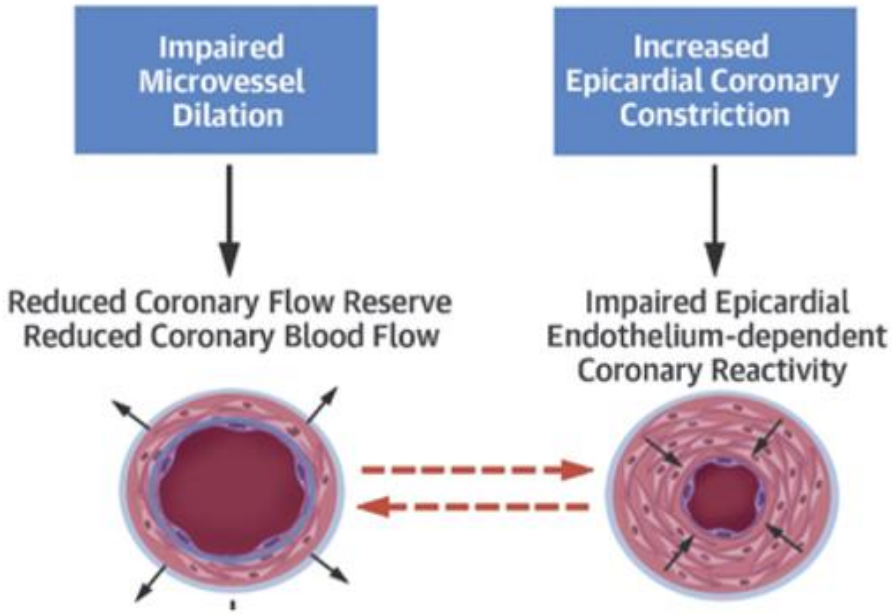
Fearon et al. JACC 51, 5, 2008, 560 - 565

Coronary Microvascular Dysfunction Across CVD



Del Buono, M.G et al. J Am Coll Cardiol. 2021;78(13):1352-1371

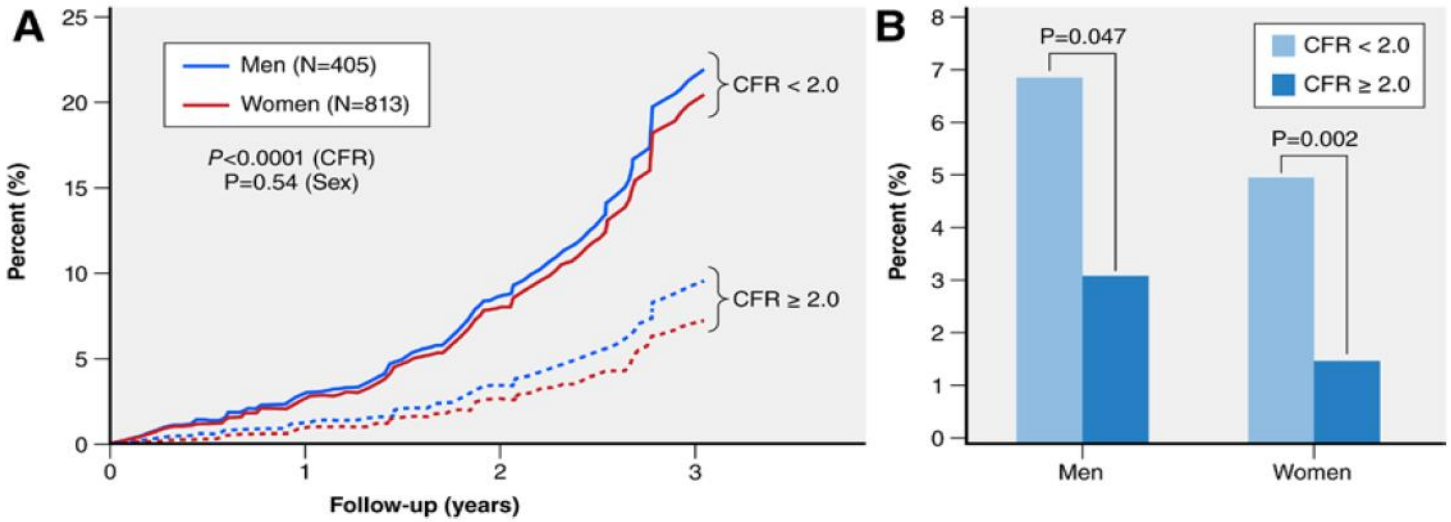
INOCA (ISCHEMIA & NON-OBSTRUCTIVE CORONARY ARTERY DISEASE) & CORONARY MICROVASCULAR DYSFUNCTION (CMD)

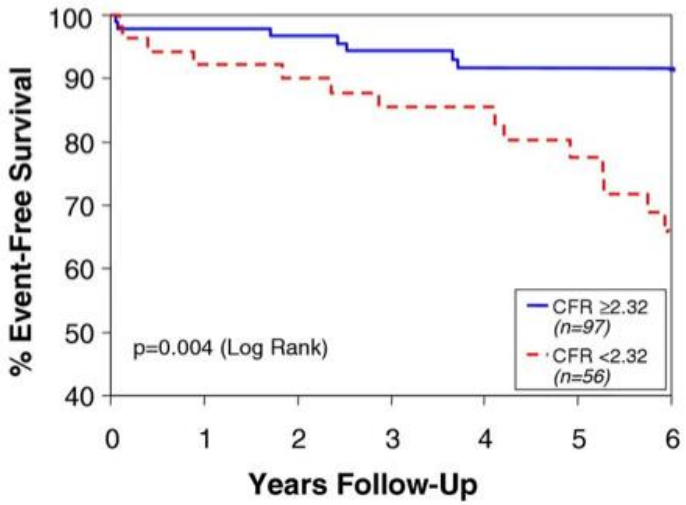


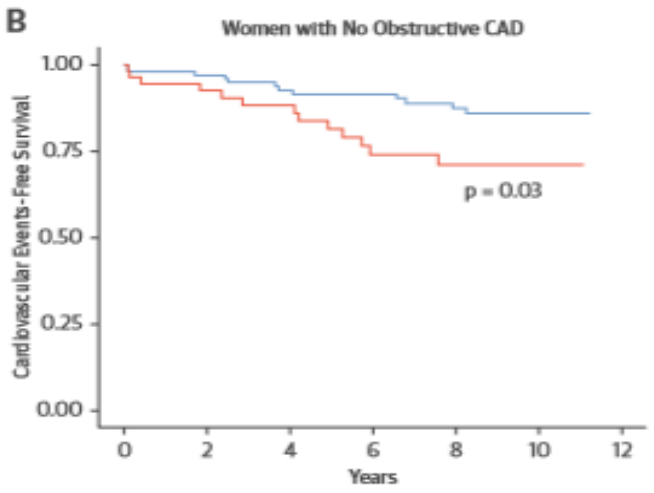
- INOCA is increasingly recognized
  - Estimated prevalence of 3 to 4 million
  - Women make up about 70% of INOCA population in the US
- CMD is present in ~50% INOCA

Long-term Outcomes in INOCA

Non-endothelial Dependent CMD predicts MACE



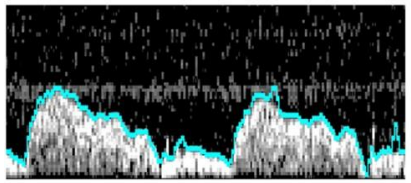


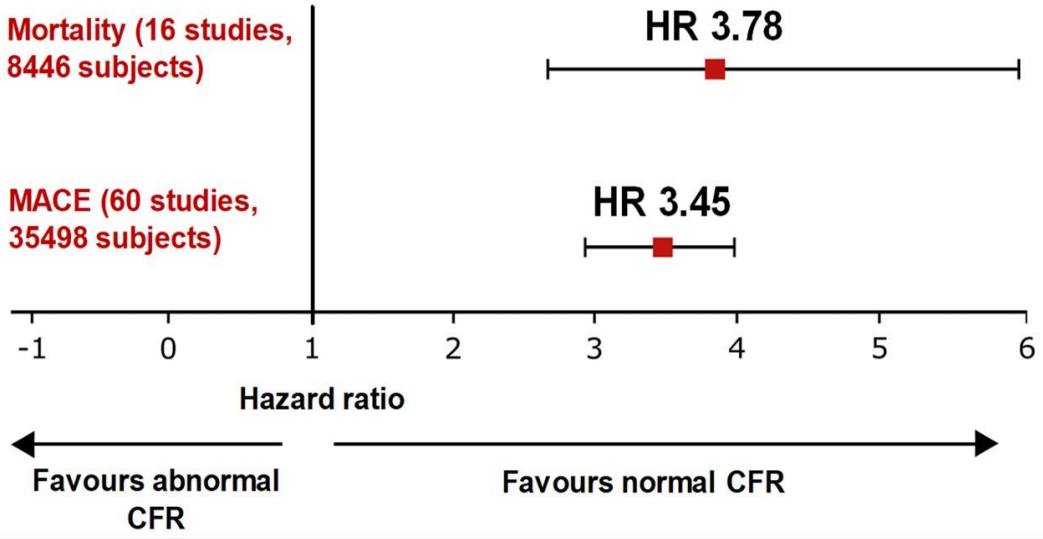


Murthy VL, et al. Circulation. 2014 Jun 17;129(24):2518-27
Pepine C, et al. J Am Coll Cardiol. 2010 Jun 22;55(25):2825-32.
AlBadri A, et al. J Am Coll Cardiol. 2019 Feb 19;73(6):684-693.

CFR Predicts MACE and Mortality

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



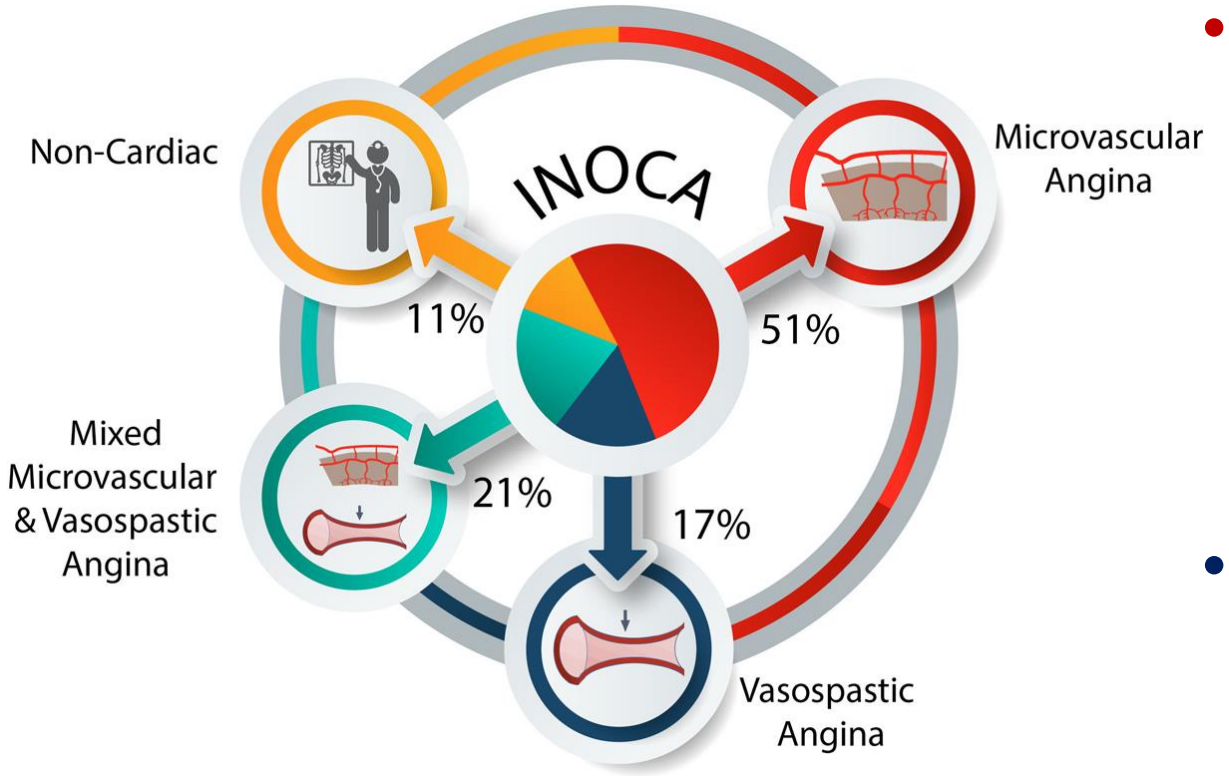


A systematic review and meta-analysis of 79 studies and 59740 individuals across multiple modalities of CFR measurement.

- 1 in 4 patients with abnormal CFR will die in 3 years
- CFR was predictive not only in patient with acute and chronic coronary syndromes but in diseases like HF, AS, systemic sclerosis
- CFR was predictive of outcomes across all modalities (invasive, PET, TTE)
- IMR was prognostic only in transplant patients
- CFR as a tool to risk stratify patients

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

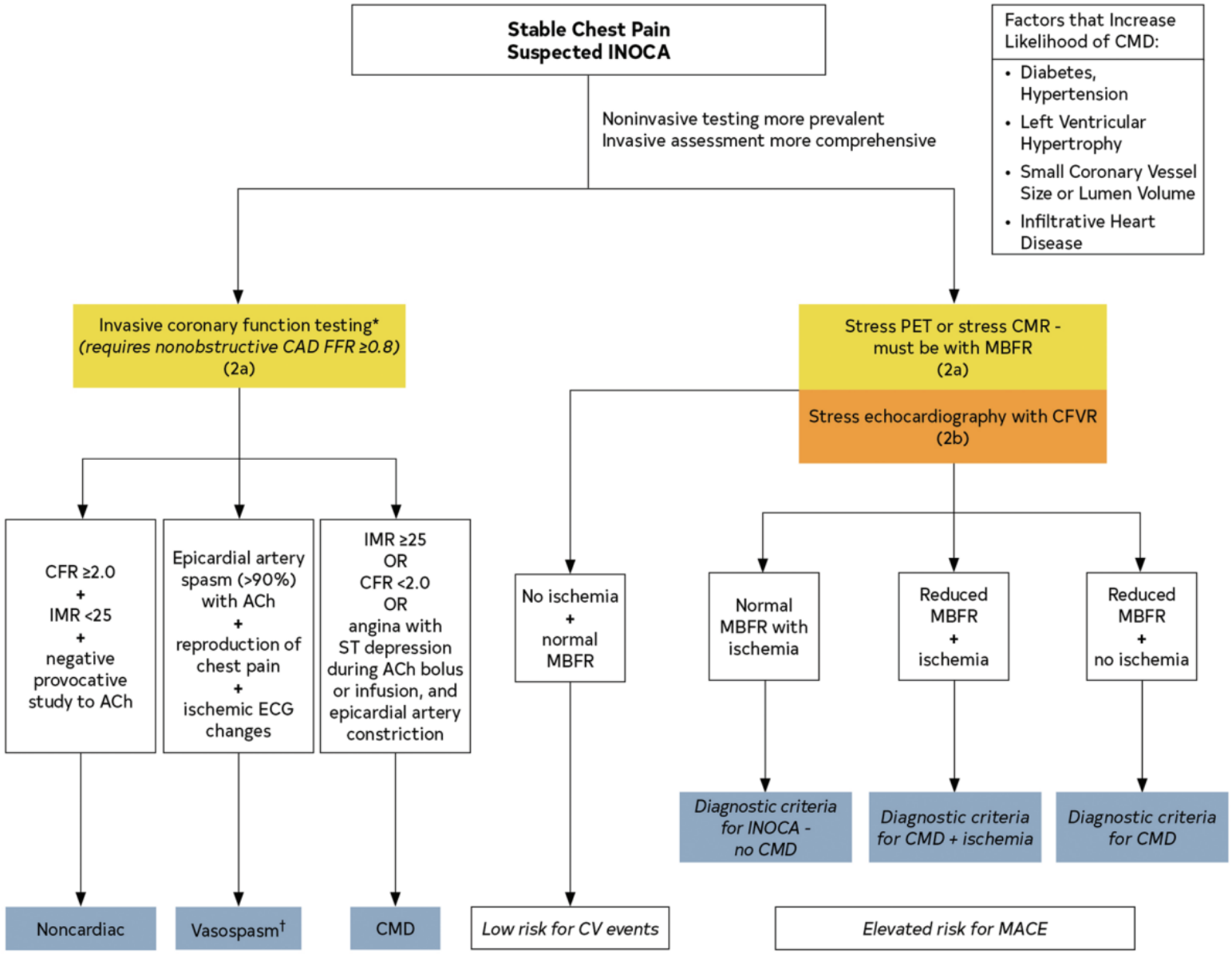
Coronary Vasomotor Disorders International Study (COVADIS) INOCA Endotypes



- **Microvascular Angina (MVA):**
  - *Non-endothelial dependent CMD*
    - ↓ Vasorelaxation
  - *Endothelial Dependent Dysfunction*
    - ↑ Vasoconstriction
  - *Microvascular spasm*
- **Vasospastic angina (VSA)**
  - Vascular smooth muscle hyperactivity

Ford TJ, et al. Circ Cardiovasc Interv. 2019 Dec;12(12):e008126.

2021 ACC/AHA Chest Pain Guidelines - INOCA



Gulati M., et al. Circulation. 2021 Nov 30;144(22):e368-e454.

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–71
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

Investigations in patients with suspected coronary micro-vascular 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

2019

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1—71
doi:10.1093/eurheartj/ehz425

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

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

Stress Tests Predict Obstructive CAD NOT INOCA

Predicting Obstructive CAD

Test	Sensitivity, %	Specificity, %
Exercise echocardiogram	88	72
Dobutamine echocardiogram	97	65
Exercise/Vasodilator SPECT	98*	13†
Vasodilator PET	96‡	34§
Exercise ECG	53 to 69	69 to 74

After correction for referral bias: *67%, †75%, ‡82%, §73%.

Predicting Non-Endothelium Dependent CMD

Test	n	% (+)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	NPV, % (95% CI)	PPV, % (95% CI)
Exercise echocardiogram	101	40.6	42 (25 to 61)	60 (48 to 72)	70 (57 to 81)	32 (18 to 48)
Dobutamine echocardiogram	21	33.3	33 (4 to 78)	67 (38 to 88)	71 (42 to 92)	29 (4 to 71)
Exercise SPECT	134	38.8	51 (34 to 68)	66 (56 to 75)	78 (68 to 86)	37 (24 to 51)
Vasodilator SPECT	66	48.5	41 (18 to 67)	49 (34 to 64)	71 (53 to 85)	22 (9 to 40)
Vasodilator PET	33	36.4	50 (23 to 77)	74 (49 to 91)	67 (43 to 85)	58 (28 to 85)
All imaging	372	41.4	46 (37 to 56)	61 (54 to 67)	73 (67 to 79)	32 (25 to 40)
Exercise ECG	237	15.2	16 (8 to 27)	75 (68 to 81)	71 (64 to 77)	31 (16 to 48)
All imaging+ECG	372	6.2	6 (3 to 13)	89 (85 to 93)	71 (66 to 76)	30 (13 to 53)

Predicting Endothelium-Dependent CMD

Test	n	% (+)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	NPV, % (95% CI)	PPV, % (95% CI)
Exercise echocardiogram	100	40.0	42 (28 to 57)	62 (47 to 75)	52 (38 to 65)	53 (36 to 68)
Dobutamine echocardiogram	21	38.1	18 (2 to 52)	40 (12 to 74)	31 (9 to 61)	25 (3 to 65)
Exercise SPECT	131	38.2	37 (26 to 50)	61 (48 to 73)	48 (37 to 60)	50 (36 to 64)
Vasodilator SPECT	63	50.8	61 (42 to 78)	59 (41 to 76)	61 (42 to 78)	59 (41 to 76)
Vasodilator PET	33	36.4	20 (4 to 48)	50 (26 to 74)	43 (22 to 66)	25 (5 to 57)
All imaging	365	41.6	41 (34 to 49)	58 (50 to 65)	49 (42 to 56)	50 (42 to 58)
Exercise ECG	233	15.5	18 (12 to 27)	78 (69 to 85)	51 (43 to 59)	61 (43 to 77)
All imaging+ECG	365	6.3	8 (4 to 12)	90 (85 to 94)	50 (45 to 56)	61 (39 to 80)

Cassar et al. Circ Cardiovasc Interv 2009 Jun;2(3):237-44

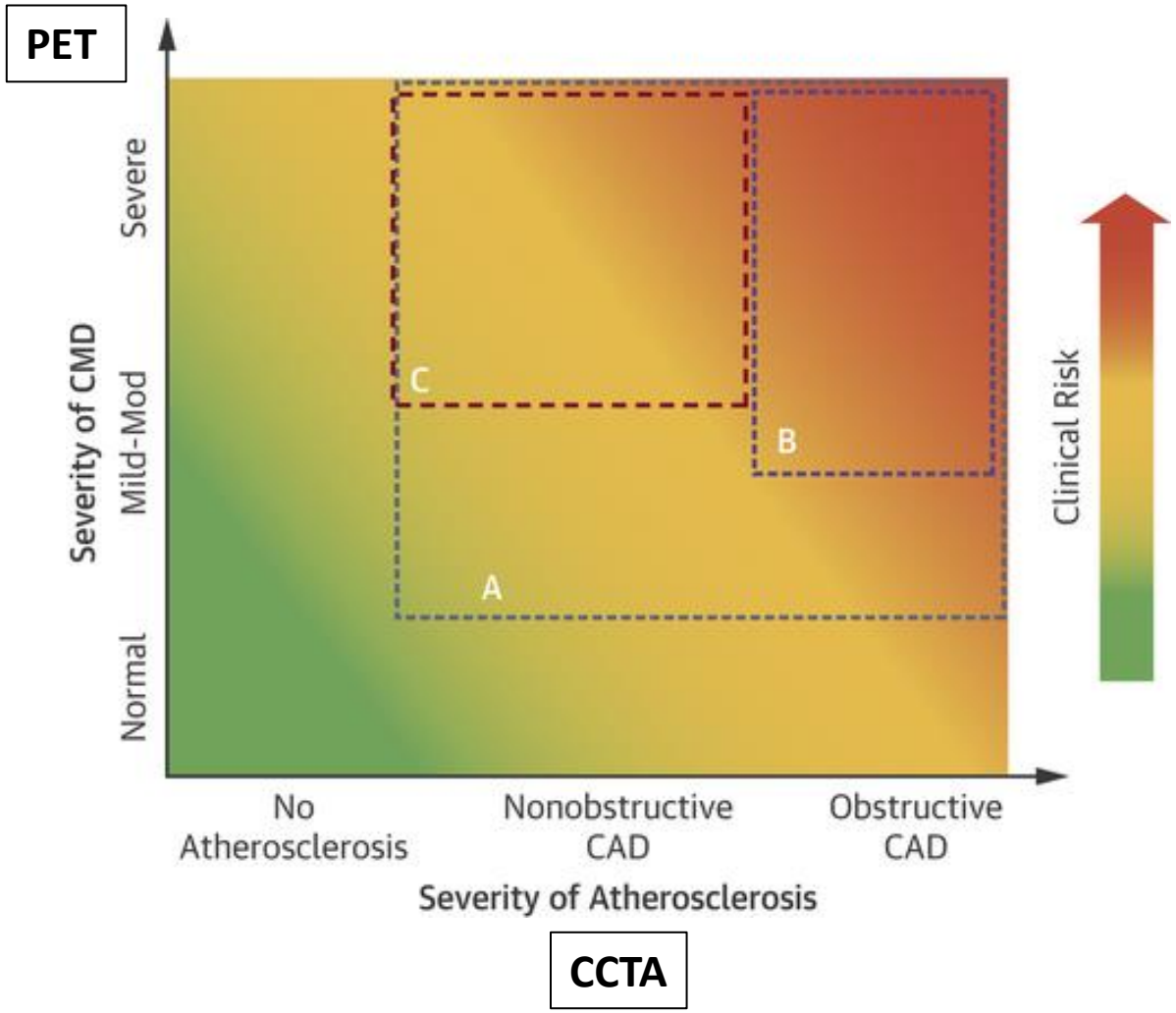
Diagnostic Techniques for Evaluation of CMD

	Accuracy	Reproducibility	Diagnostic Threshold	Prognostic Validation	Availability	Cost
Noninvasive*						
PET	++++	++++	CFR <2	++++	++	$$$
CMR	+++	+++	MPRI <2	++	++	$$$
Doppler echocardiography	++	+++	CFVR <2	+++	++++	$
Invasive*						
CFR	++++	++++	<2.3	+++	++++	$$$$
IMR	++++	+++	>25 U	++	++	$$$$

*Endothelial Dependent CMD and Coronary Vasospasm can only be tested with invasive coronary functional angiography

Taqueti VR, et al. J Am Coll Cardiol. 2018 Nov 27;72(21):2625-2641.

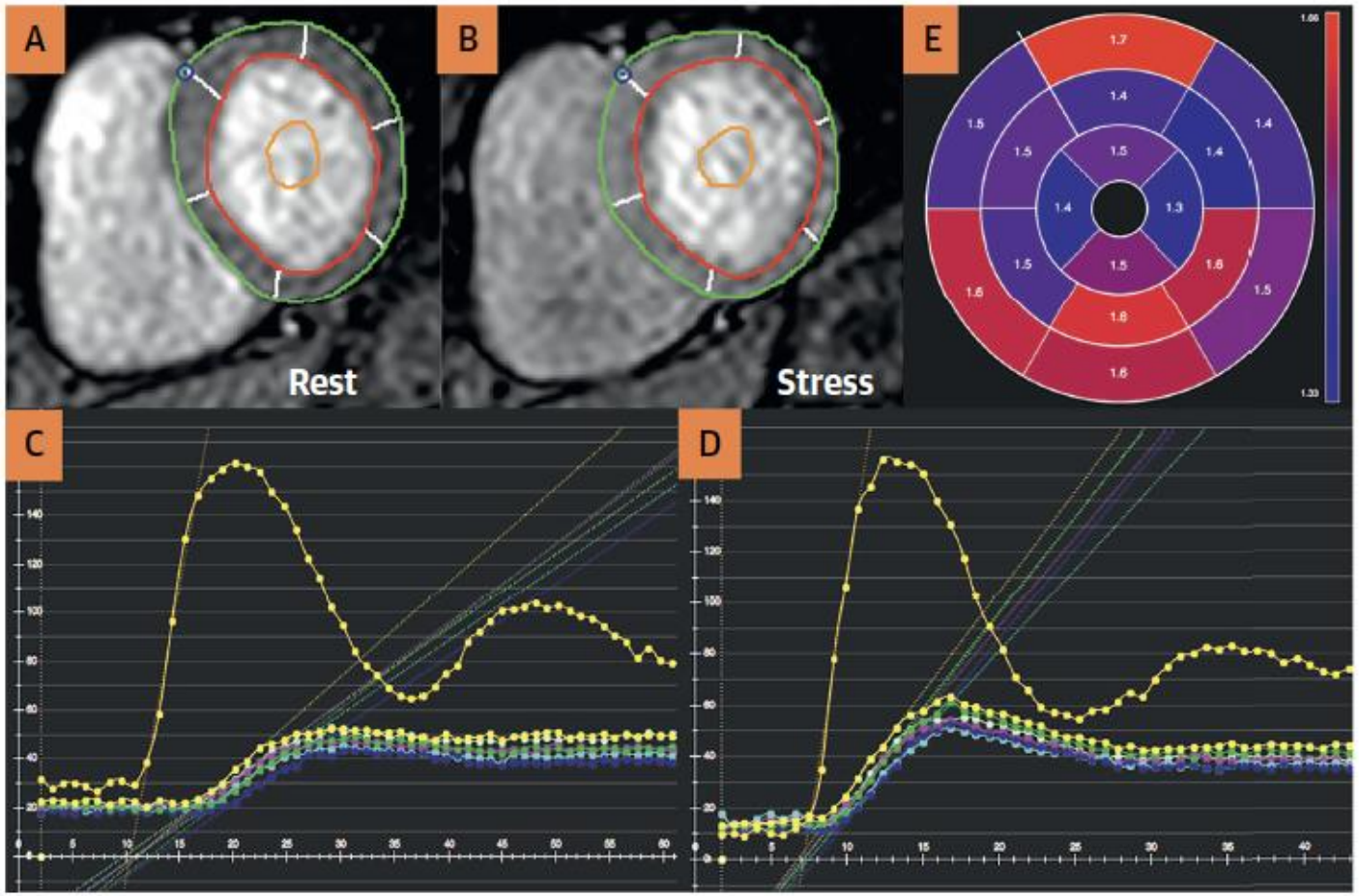
Role Of PET and CCTA in CMD Evaluation & Risk Stratification



- PET and CCTA have complementary roles for anatomical and functional imaging
- Most patients undergoing evaluation for CMD have some degree of atherosclerosis
- Atherosclerotic burden and CMD are independent prognostic markers of clinical risk

Taqueti VR, et al. J Am Coll Cardiol. 2018 Nov 27;72(21):2625-2641.

Stress Cardiac MRI

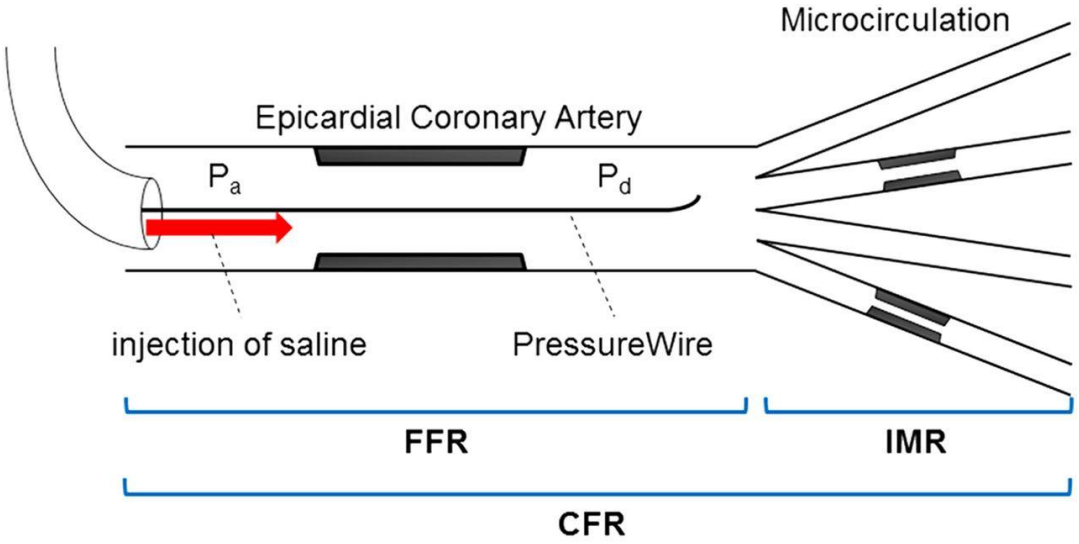


- Myocardial perfusion Reserve Index
  - MPRI = (RU at stress) / (RU at rest)
  - Relative upslope (RU) = (Maximum upslope of the myocardial signal intensity curve)/ (maximum upslope of the LV cavity curve)
- MPRI < 1.84 predicts ≥1 abnormal pathway on CFA
  - Sensitivity 73%
  - Specificity 74%

Thomson et al. Circ CV imaging 2015

Invasive Coronary Functional Angiography (CFA)

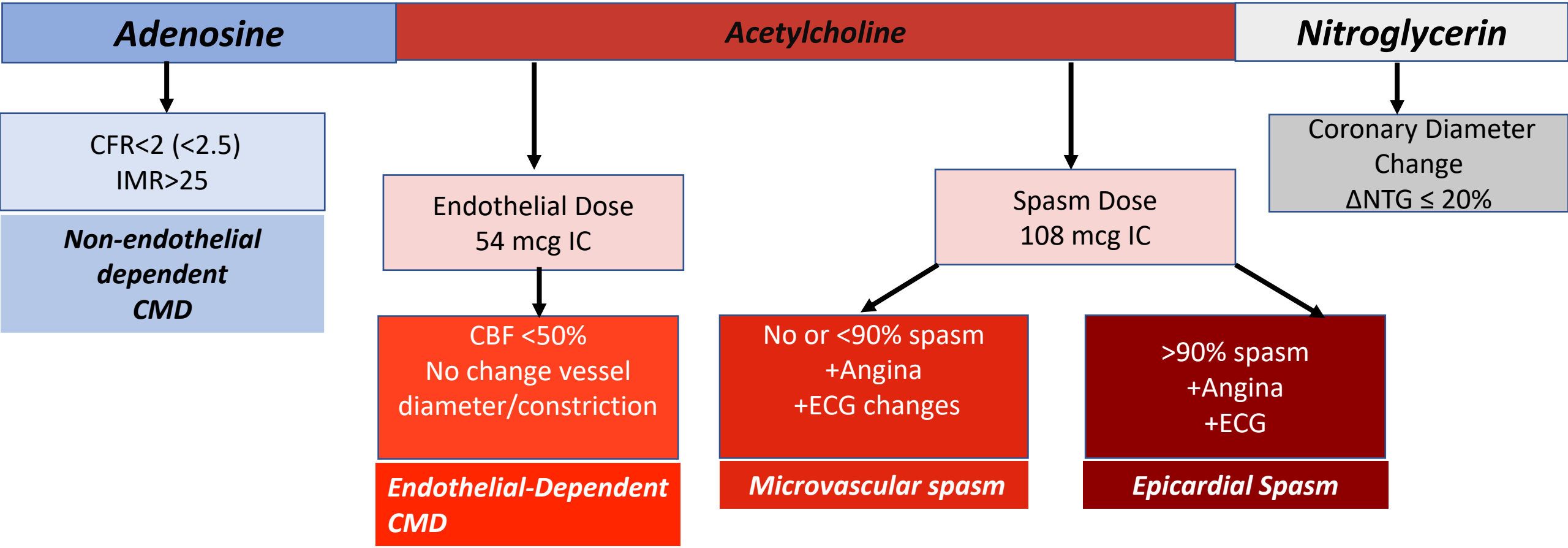
- Coronary microvasculature is indirectly tested via measurement of coronary flow and resistance down epicardial arteries
- Invasive, guidewire-based measurement of coronary flow reserve and resistance via Doppler flow (Volcano) & Thermodilution method (Coroflow)
- IC Adenosine is used to reach hyperemic state



- **FFR** $=P_d/P_a$ at maximal hyperemia
- **CFR** =hyperemic coronary flow ÷ resting coronary flow
  $=1/\text{hyperemic } T_{mn} \div 1/\text{resting } T_{mn}$
  $=\text{resting } T_{mn}/\text{hyperemic } T_{mn}$
- **IMR** $=P_d$ at maximal hyperemia ÷ $1/\text{hyperemic } T_{mn}$
  $=P_d$ at maximal hyperemia × $\text{hyperemic } T_{mn}$

(T_{mn}: an inverse correlate to absolute coronary flow)

Invasive Assessment: Coronary Functional Angiography



Adapted Ford TJ, et al. *Heart* 2018;**104**:284–292.
Kissel et al. Consensus document (COVADIS)

Invasive Testing: Doppler vs TD

- CFR overestimated by bolus TD: different normal
- Doppler: Classically in the Proximal LAD with IC adenosine
- Bolus TD: Typically in the mid-distal LAD with IV adenosine
- Very poor correlation between IMR (TD) and HMR (doppler)
- Testing pre or post IC NTG??
- Continuous TD and other novel techniques on the way, Doppler will be back within the year
- Pts don’t fit in neat little boxes…
- Complex pts requiring thoughtful study
- An inaccurate dx may be worse than NO diagnosis!!

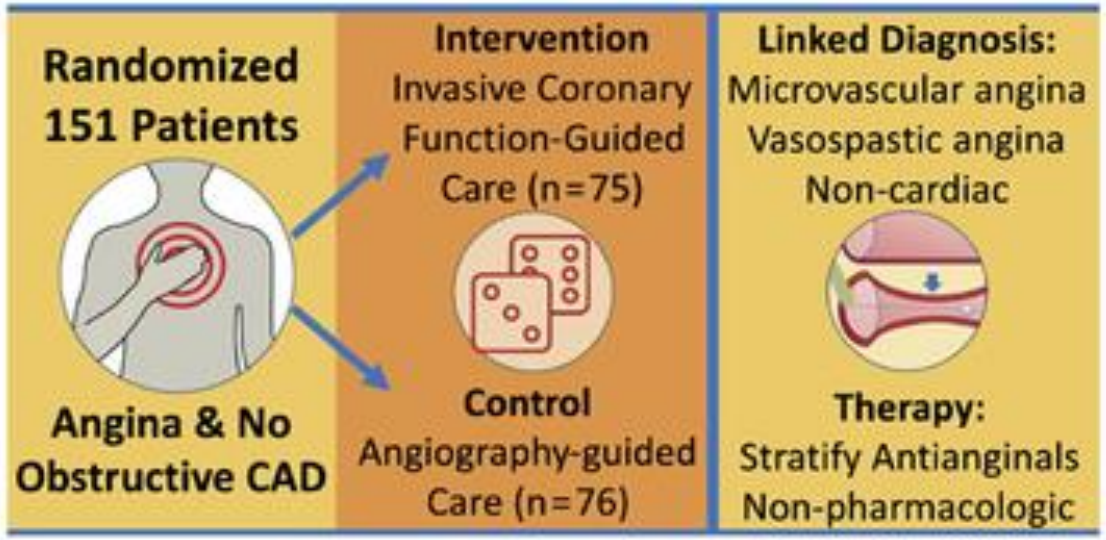
Treatment Approach Based on Abnormal CMD Pathway

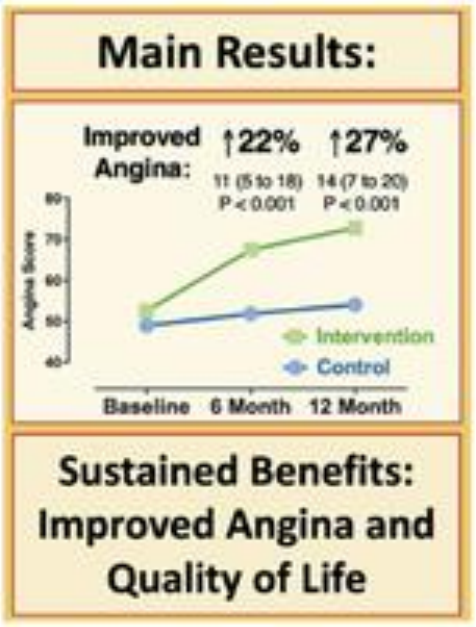
Microvascular Angina		Vasospastic Angina
Non-endothelial Dependent Dysfunction ↓ Vasorelaxation Adenosine: ↓ CFR &/or ↑ IMR	**Endothelial Dependent Dysfunction** ↑ Vasoconstriction ACh: vasoconstriction, impaired vasodilation	**Coronary Vasospasm** Vascular smooth muscle hyperactivity Ach: vasoconstriction

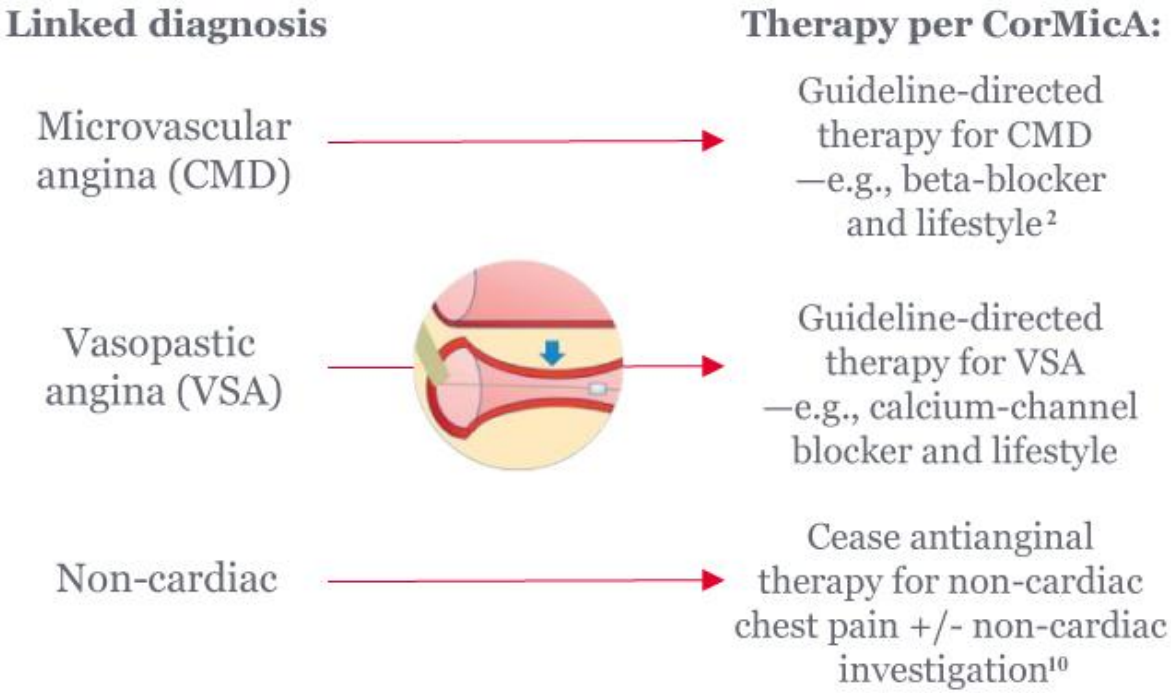
• ACEI/ARB
  • ↑ CFR, ↓ workload, ?improve microvasculature remodeling
• Statins
  • ↑ CFR
• BB
  • ↓ myocardial oxygen consumption
• Ranolazine
  • Improve MPRI in MVA
	• ACEI/ARB
	  • Improve endothelial vasomotor dysfunction
	• Statins
	  • Improve endothelial function; pleotrophic effects (reduced vascular inflammation)
	• CCB
	  • Vascular smooth muscle relaxation; ↓ myocardial oxygen consumption
		• CCB
		  • ↓spontaneous and inducible coronary vasospasm via vascular smooth muscle relaxation & ↓ oxygen demand
		• Nitrates
		  • ↓spontaneous and inducible coronary vasospasm via epicardial vasodilation, ↓ oxygen demand

Avoid Nitrates		Avoid BB
Exercise training-Cardiac Rehabilitation		

Invasive Coronary Function Testing Angina (CorMICA): 1-Year RCT Outcomes





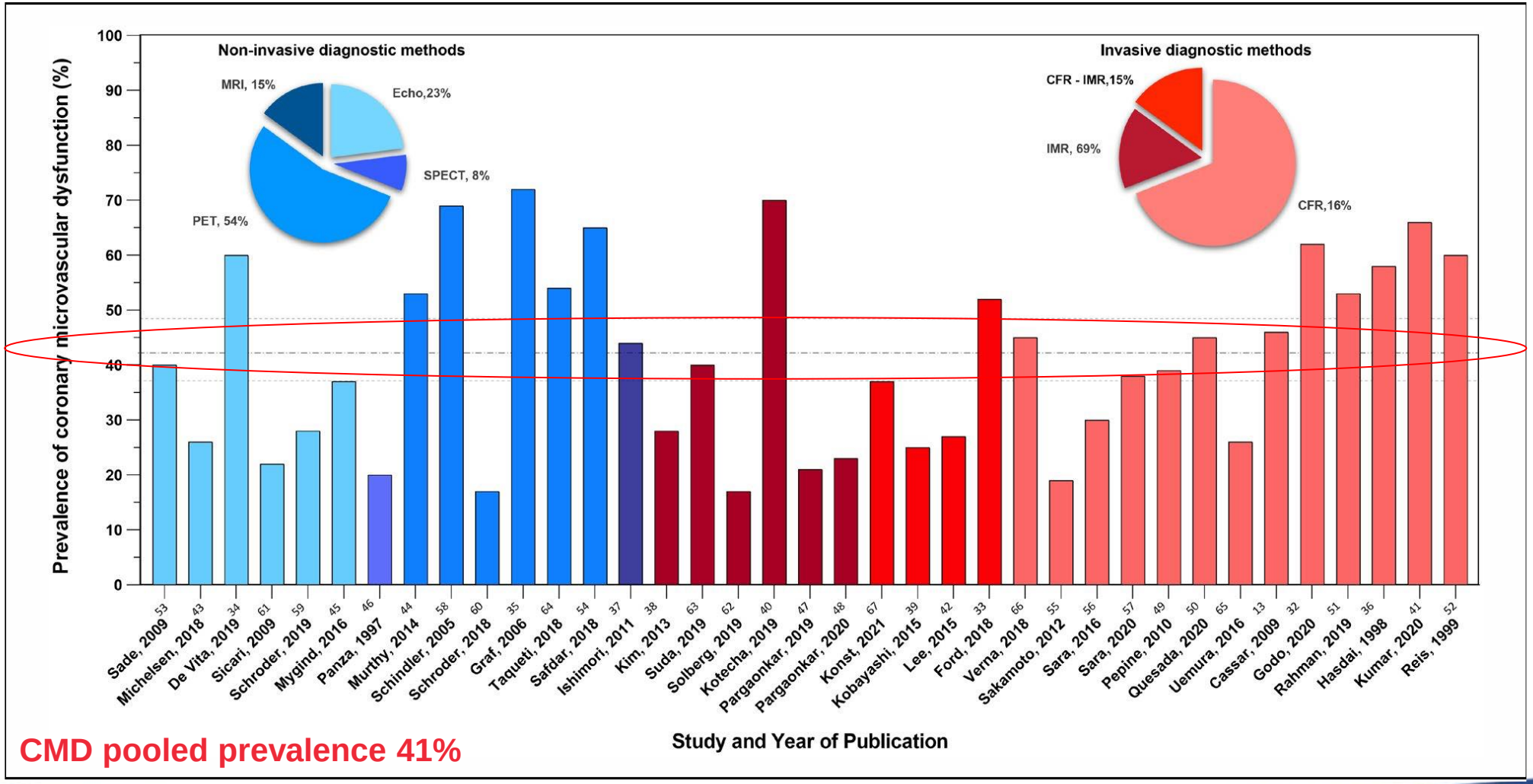


Ford TJ, et al. JACC Cardiovasc Interv. 2020 Jan 13;13(1):33-45.

Prevalence of CMD among patients with non obstructive CAD

14 Non-invasive

23 Invasive

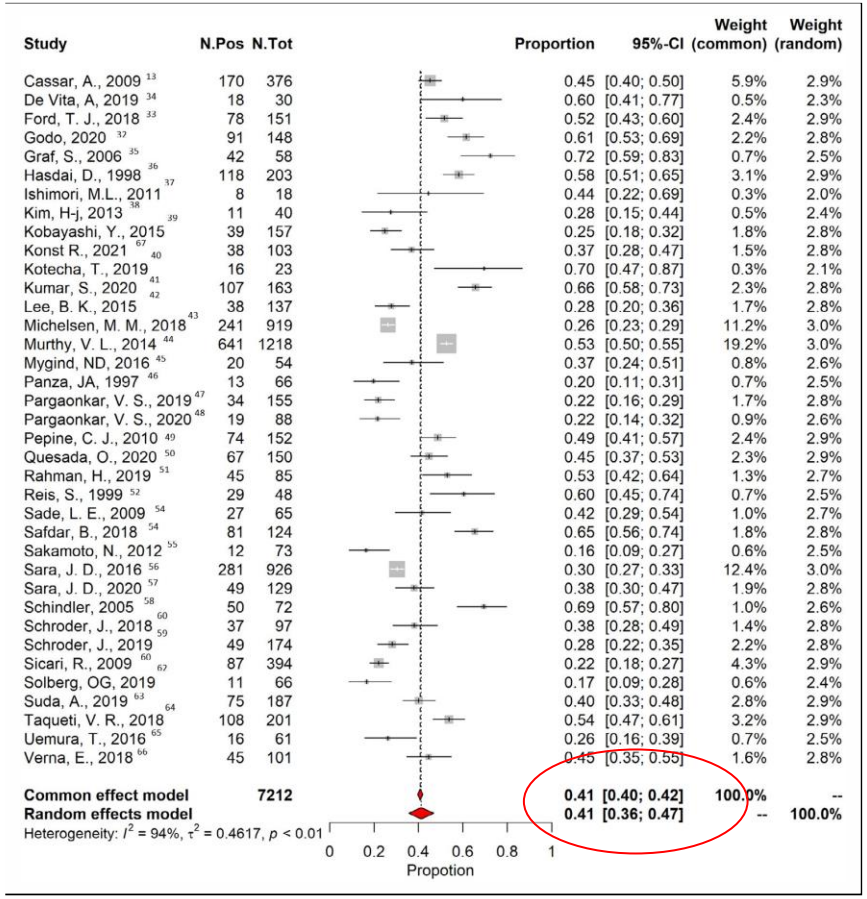


CMD pooled prevalence 41%

Mileva N, et al. J Am Heart Assoc. 2022 Apr 5;11(7):e023207.

Prevalence of CMD vs. Coronary Epicardial and Microvascular spasm

CMD pooled prevalence 41%



Study	N.Pos	N.Tot	Proportion	95%-CI	Weight (common)	Weight (random)
Cassar, A., 2009 [13]	170	376	0.45	[0.40; 0.50]	5.9%	2.9%
De Vita, A, 2019 [34]	18	30	0.60	[0.41; 0.77]	0.5%	2.3%
Ford, T. J., 2018 [33]	78	151	0.52	[0.43; 0.60]	2.4%	2.9%
Godo, 2020 [37]	91	148	0.61	[0.53; 0.69]	2.2%	2.8%
Graf, S., 2006 [35]	42	58	0.72	[0.59; 0.83]	0.7%	2.5%
Hasdai, D., 1998 [36]	118	203	0.58	[0.51; 0.65]	3.1%	2.9%
Ishimori, M.L., 2011 [37]	8	18	0.44	[0.22; 0.69]	0.3%	2.0%
Kim, H-j, 2013 [38]	11	40	0.28	[0.15; 0.44]	0.5%	2.4%
Kobayashi, Y., 2015 [39]	39	157	0.25	[0.18; 0.32]	1.8%	2.8%
Konst R., 2021 [67]	38	103	0.37	[0.28; 0.47]	1.5%	2.8%
Kotecha, T., 2019 [40]	16	23	0.70	[0.47; 0.87]	0.3%	2.1%
Kumar, S., 2020 [41]	107	163	0.66	[0.58; 0.73]	2.3%	2.8%
Lee, B. K., 2015 [42]	38	137	0.28	[0.20; 0.36]	1.7%	2.8%
Michelsen, M. M., 2018 [43]	241	919	0.26	[0.23; 0.29]	11.2%	3.0%
Murthy, V. L., 2014 [44]	641	1218	0.53	[0.50; 0.55]	19.2%	3.0%
Mygind, ND, 2016 [45]	20	54	0.37	[0.24; 0.51]	0.8%	2.6%
Panza, JA, 1997 [46]	13	66	0.20	[0.11; 0.31]	0.7%	2.5%
Pargaonkar, V. S., 2019 [47]	34	155	0.22	[0.16; 0.29]	1.7%	2.8%
Pargaonkar, V. S., 2020 [48]	19	88	0.22	[0.14; 0.32]	0.9%	2.6%
Pepine, C. J., 2010 [49]	74	152	0.49	[0.41; 0.57]	2.4%	2.9%
Quesada, O., 2020 [50]	67	150	0.45	[0.37; 0.53]	2.3%	2.9%
Rahman, H., 2019 [51]	45	85	0.53	[0.42; 0.64]	1.3%	2.7%
Reis, S., 1999 [52]	29	48	0.60	[0.45; 0.74]	0.7%	2.5%
Sade, L. E., 2009 [54]	27	65	0.42	[0.29; 0.54]	1.0%	2.7%
Safdar, B., 2018 [54]	81	124	0.65	[0.56; 0.74]	1.8%	2.8%
Sakamoto, N., 2012 [55]	12	73	0.16	[0.09; 0.27]	0.6%	2.5%
Sara, J. D., 2016 [56]	281	926	0.30	[0.27; 0.33]	12.4%	3.0%
Sara, J. D., 2020 [57]	49	129	0.38	[0.30; 0.47]	1.9%	2.8%
Schindler, 2005 [58]	50	72	0.69	[0.57; 0.80]	1.0%	2.6%
Schroder, J., 2018 [59]	37	97	0.38	[0.28; 0.49]	1.4%	2.8%
Schroder, J., 2019 [60]	49	174	0.28	[0.22; 0.35]	2.2%	2.8%
Sicari, R., 2009 [67]	87	394	0.22	[0.18; 0.27]	4.3%	2.9%
Solberg, OG, 2019 [63]	11	66	0.17	[0.09; 0.28]	0.6%	2.4%
Suda, A., 2019 [64]	75	187	0.40	[0.33; 0.48]	2.8%	2.9%
Taqueti, V. R., 2018 [65]	108	201	0.54	[0.47; 0.61]	3.2%	2.9%
Uemura, T., 2016 [66]	16	61	0.26	[0.16; 0.39]	0.7%	2.5%
Verna, E., 2018 [66]	45	101	0.45	[0.35; 0.55]	1.6%	2.8%
Common effect model		**7212**	**0.41**	**[0.40; 0.42]**	**100.0%**	--
Random effects model			**0.41**	**[0.36; 0.47]**	--	**100.0%**

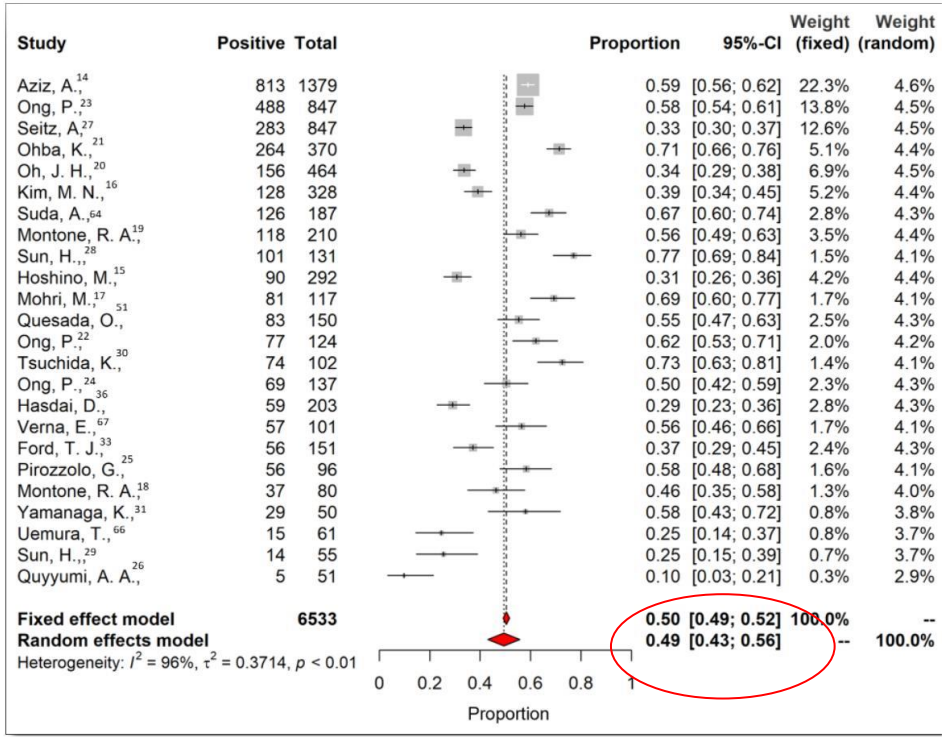
Heterogeneity: I^2 = 94%, τ^2 = 0.4617, p < 0.01

0 0.2 0.4 0.6 0.8 1

Propotion

Pooled Prevalence spasm 49%

Epicardial or Microvascular Spasm



Study	Positive	Total	Proportion	95%-CI	Weight (fixed)	Weight (random)
Aziz, A.,[14]	813	1379	0.59	[0.56; 0.62]	22.3%	4.6%
Ong, P.,[23]	488	847	0.58	[0.54; 0.61]	13.8%	4.5%
Seitz, A,[27]	283	847	0.33	[0.30; 0.37]	12.6%	4.5%
Ohba, K.,[21]	264	370	0.71	[0.66; 0.76]	5.1%	4.4%
Oh, J. H.,[20]	156	464	0.34	[0.29; 0.38]	6.9%	4.5%
Kim, M. N.,[16]	128	328	0.39	[0.34; 0.45]	5.2%	4.4%
Suda, A.,[64]	126	187	0.67	[0.60; 0.74]	2.8%	4.3%
Montone, R. A.,[19]	118	210	0.56	[0.49; 0.63]	3.5%	4.4%
Sun, H.,,[28]	101	131	0.77	[0.69; 0.84]	1.5%	4.1%
Hoshino, M.,[15]	90	292	0.31	[0.26; 0.36]	4.2%	4.4%
Mohri, M.,[17]	81	117	0.69	[0.60; 0.77]	1.7%	4.1%
Quesada, O.,[51]	83	150	0.55	[0.47; 0.63]	2.5%	4.3%
Ong, P.,[22]	77	124	0.62	[0.53; 0.71]	2.0%	4.2%
Tsuchida, K.,[30]	74	102	0.73	[0.63; 0.81]	1.4%	4.1%
Ong, P.,[24]	69	137	0.50	[0.42; 0.59]	2.3%	4.3%
Hasdai, D.,[36]	59	203	0.29	[0.23; 0.36]	2.8%	4.3%
Verna, E.,[67]	57	101	0.56	[0.46; 0.66]	1.7%	4.1%
Ford, T. J.,[33]	56	151	0.37	[0.29; 0.45]	2.4%	4.3%
Pirozzolo, G.,[25]	56	96	0.58	[0.48; 0.68]	1.6%	4.1%
Montone, R. A.,[18]	37	80	0.46	[0.35; 0.58]	1.3%	4.0%
Yamanaga, K.,[31]	29	50	0.58	[0.43; 0.72]	0.8%	3.8%
Uemura, T.,[66]	15	61	0.25	[0.14; 0.37]	0.8%	3.7%
Sun, H.,,[29]	14	55	0.25	[0.15; 0.39]	0.7%	3.7%
Quyyumi, A. A.,[26]	5	51	0.10	[0.03; 0.21]	0.3%	2.9%
Fixed effect model		**6533**	**0.50**	**[0.49; 0.52]**	**100.0%**	--
Random effects model			**0.49**	**[0.43; 0.56]**	--	**100.0%**

Heterogeneity: I^2 = 96%, τ^2 = 0.3714, p < 0.01

0 0.2 0.4 0.6 0.8 1

Proportion

Epicardial Spasm 40%

Microvascular Spasm 24%

Female higher risk of CMD vs male (RR, 1.45 [95% CI, 1.11-1.90])

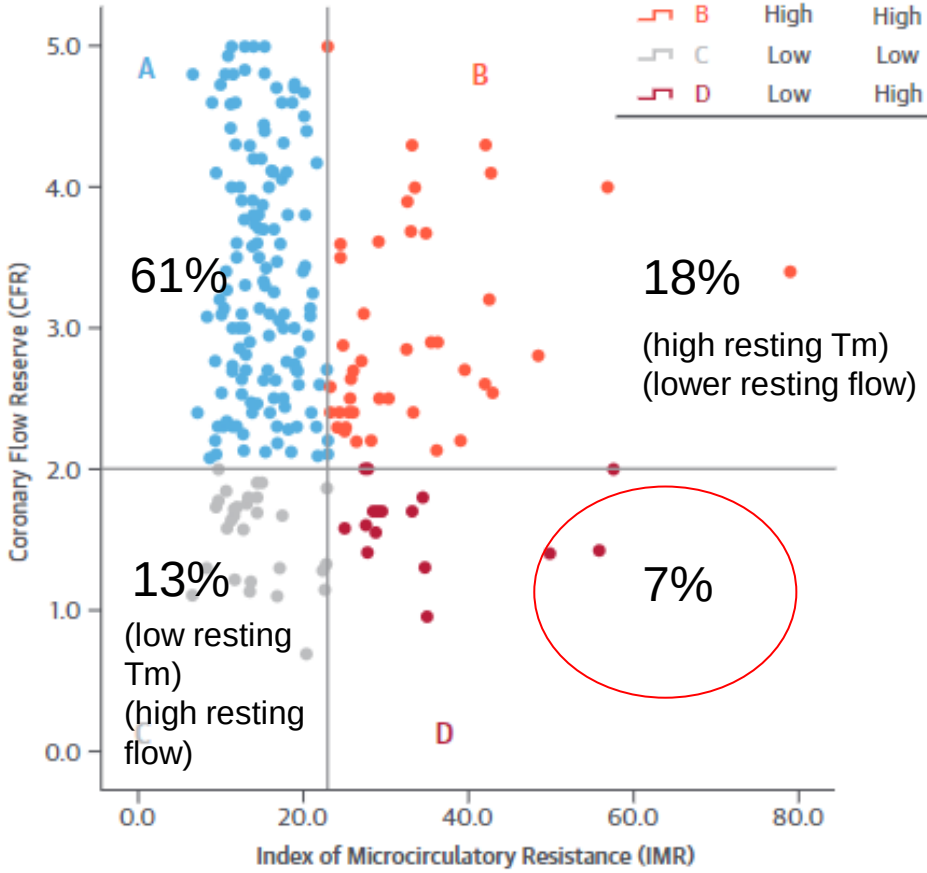
3 studies / 541 patients evaluated for CMD and Spasm
Coexistent CMD and coronary spasm 23%

Mileva N, et al. J Am Heart Assoc. 2022 Apr 5;11(7):e023207.

CFR/IMR patterns and outcomes in non obstructive CAD

Four CFR/IMR Patterns

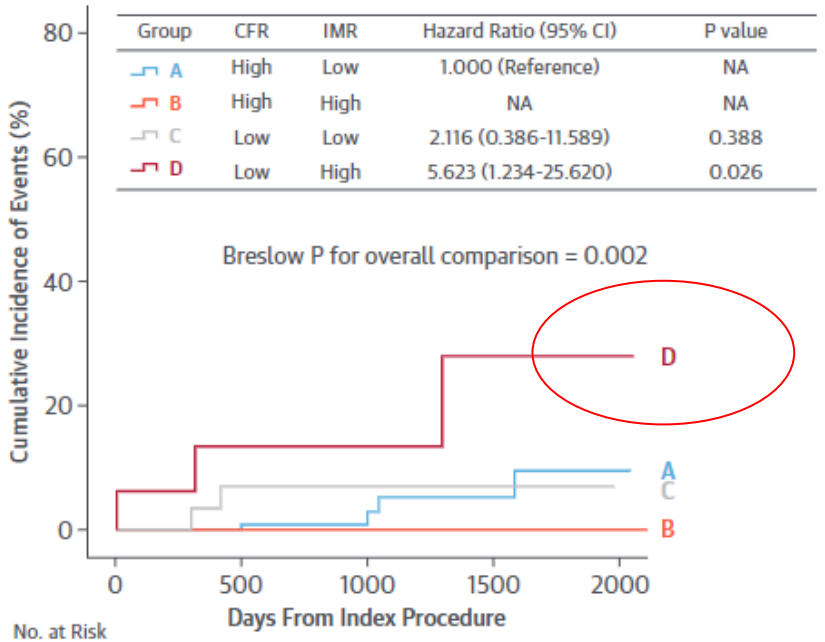
Group	CFR	IMR
A	High	Low
B	High	High
C	Low	Low
D	Low	High



Clinical Outcomes by CFR/IMR Pattern

Events: all-cause mortality, any MI, any revascularization

Group	CFR	IMR	Hazard Ratio (95% CI)	P value
A	High	Low	1.000 (Reference)	NA
B	High	High	NA	NA
C	Low	Low	2.116 (0.386-11.589)	0.388
D	Low	High	5.623 (1.234-25.620)	0.026



No. at Risk

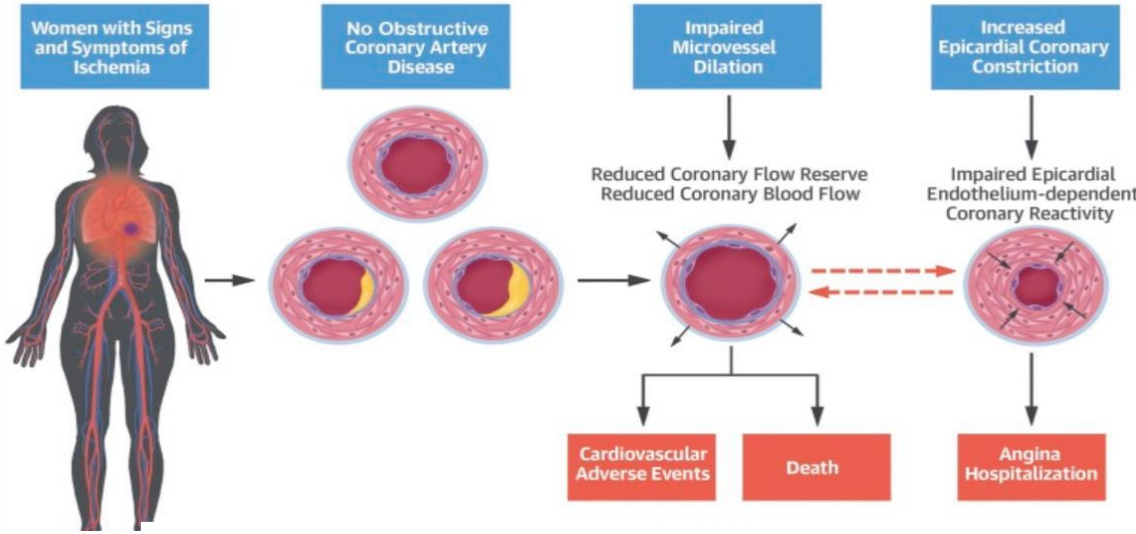
Group A	141	114	47	26	3
Group B	42	26	12	5	1
Group C	31	25	13	4	4
Group D	16	10	8	5	3

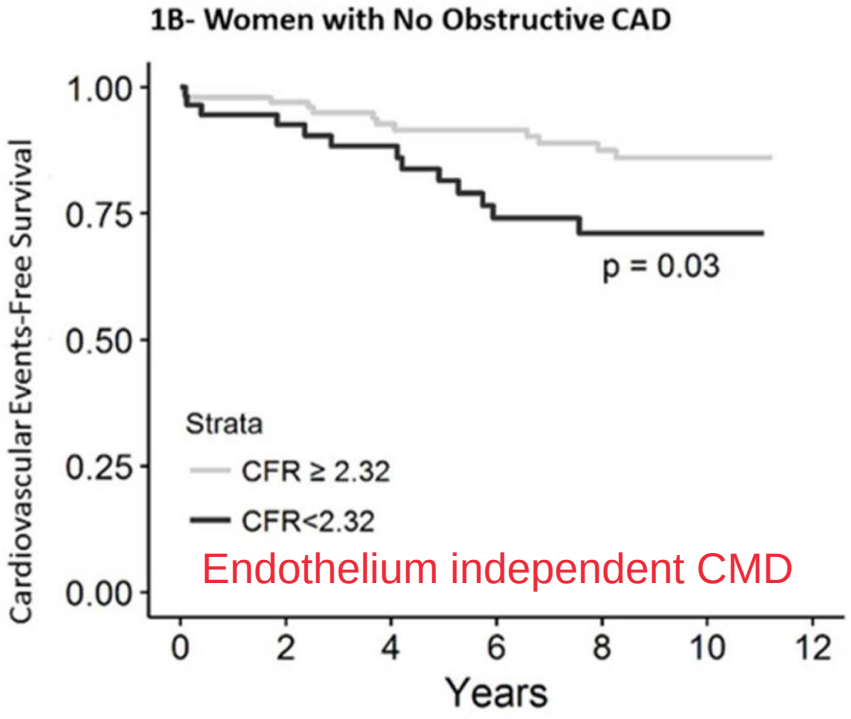
Lee et al. J Am Coll Cardiol. 2016;67:1158–69

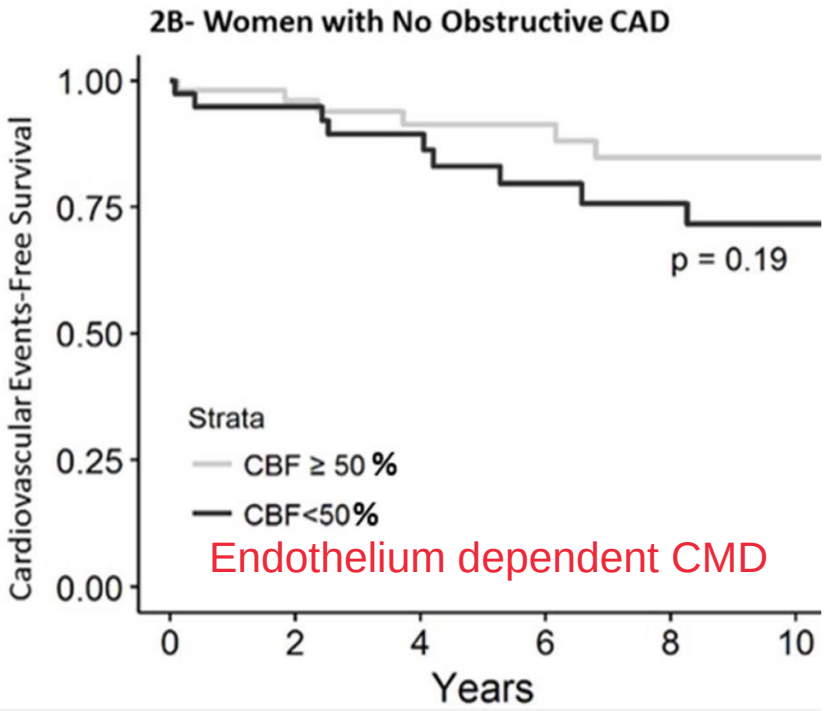
Prognosis of CMD and Spasm from Women's Ischemia Syndrome Study

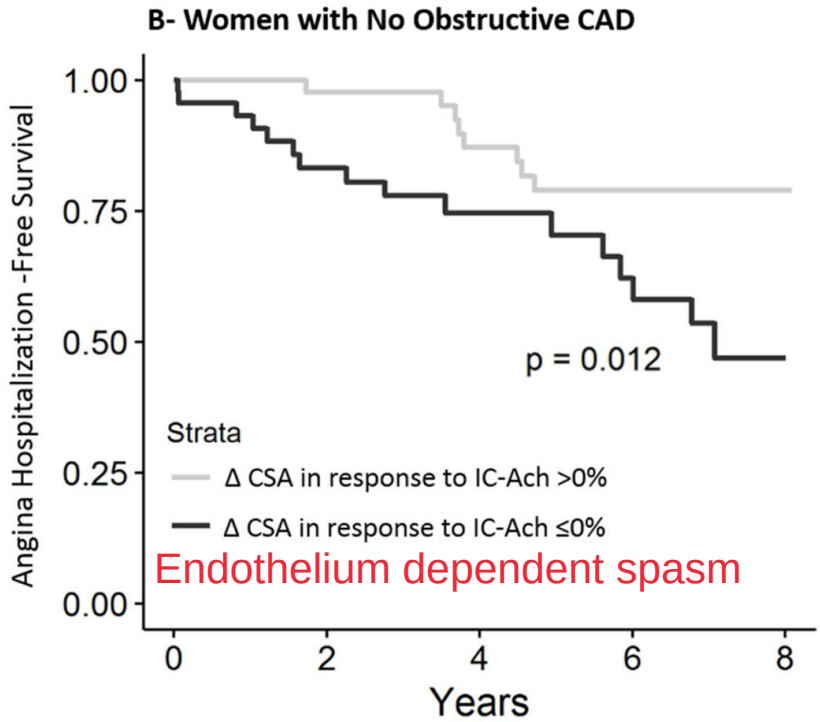
N=224

Median follow-up of 9.7 years





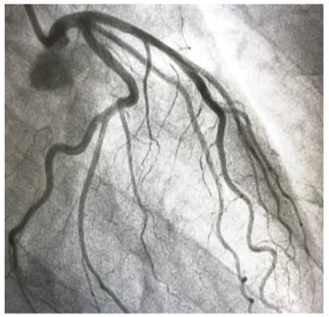


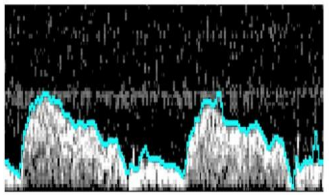


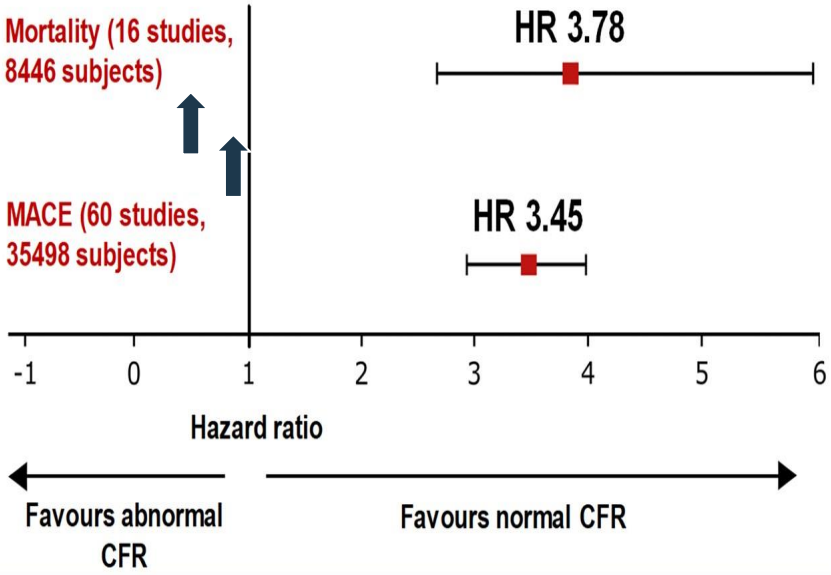
AlBadri A et al. JACC. 2019;73(6):684-93

Prognosis of CMD measured by low CFR

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



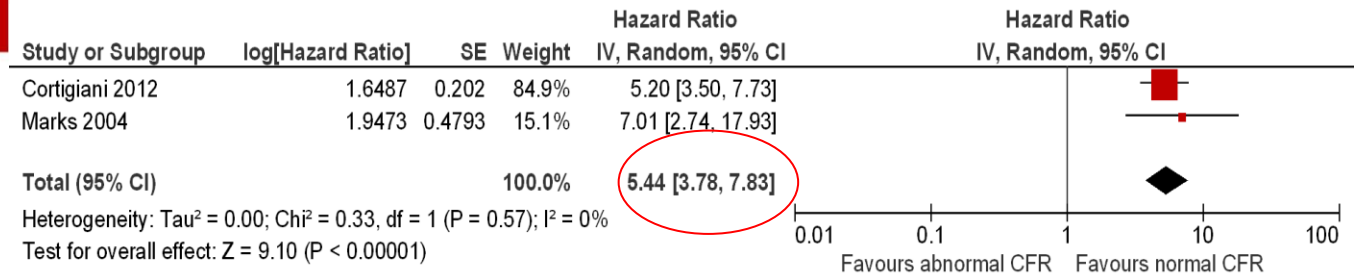




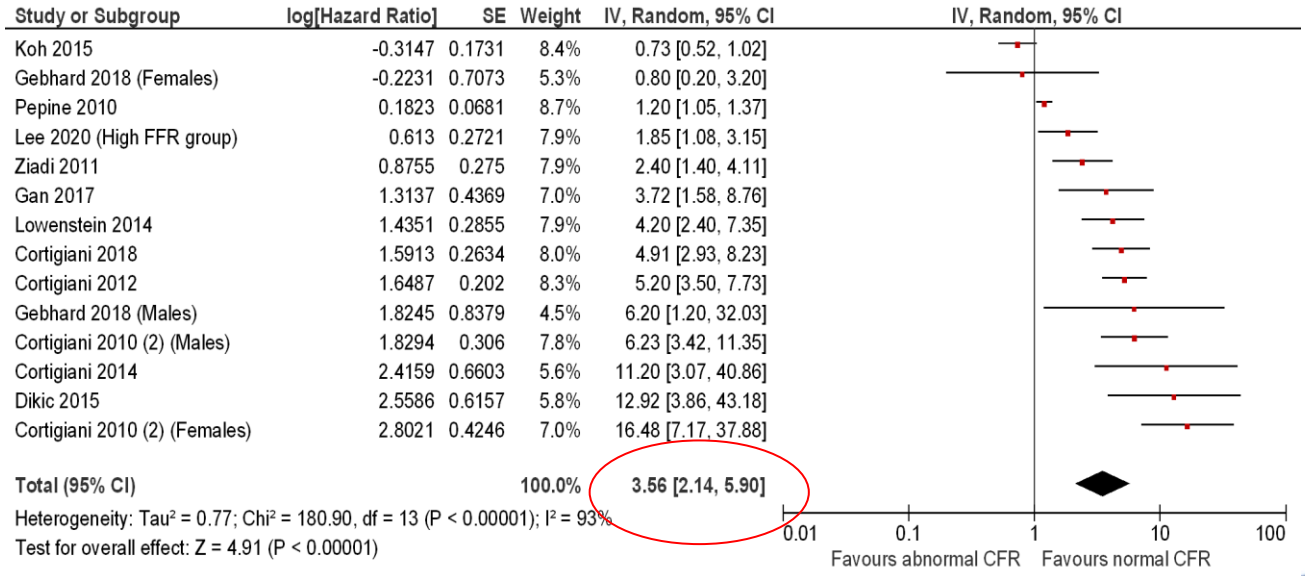
A systematic review and meta-analysis of 79 studies and 59740 individuals across multiple modalities of CFR measurement.

Each 0.1- unit ↓CFR was associated with a proportional
↑Mortality (per 0.1 CFR unit HR: 1.16, 95% CI: 1.04–1.29)
↑MACE (per 0.1 CFR unit HR: 1.08, 95% CI: 1.04–1.11)

Isolated CMD overall mortality with low CFR



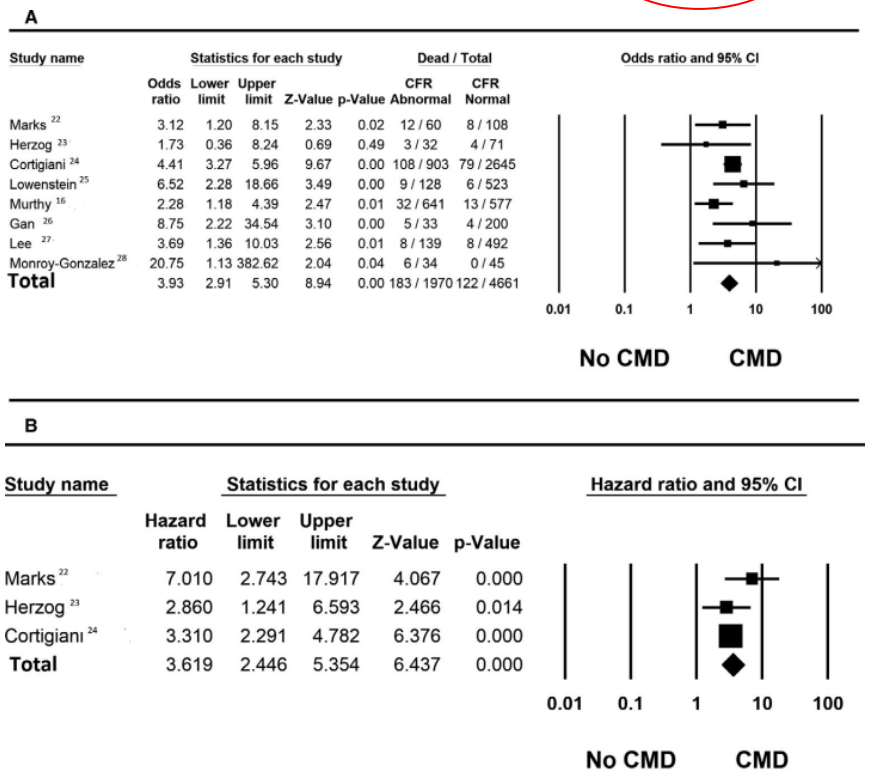
Isolated CMD overall MACE with low CFR



Kelshiker M et al. European Heart Journal (2022)43, 1582–1593

Prognosis of CMD vs No CMD based on low CFR

Odds Ratio for Mortality: 3.93



A

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Dead / Total CFR Abnormal	CFR Normal
Marks [22]	3.12	1.20	8.15	2.33	0.02	12 / 60	8 / 108
Herzog [23]	1.73	0.36	8.24	0.69	0.49	3 / 32	4 / 71
Cortigiani [24]	4.41	3.27	5.96	9.67	0.00	108 / 903	79 / 2645
Lowenstein [25]	6.52	2.28	18.66	3.49	0.00	9 / 128	6 / 523
Murthy [16]	2.28	1.18	4.39	2.47	0.01	32 / 641	13 / 577
Gan [26]	8.75	2.22	34.54	3.10	0.00	5 / 33	4 / 200
Lee [27]	3.69	1.36	10.03	2.56	0.01	8 / 139	8 / 492
Monroy-Gonzalez [28]	20.75	1.13	382.62	2.04	0.04	6 / 34	0 / 45
Total	3.93	2.91	5.30	8.94	0.00	183 / 1970	122 / 4661

Odds ratio and 95% CI: 0.01, 0.1, 1, 10, 100

No CMD CMD

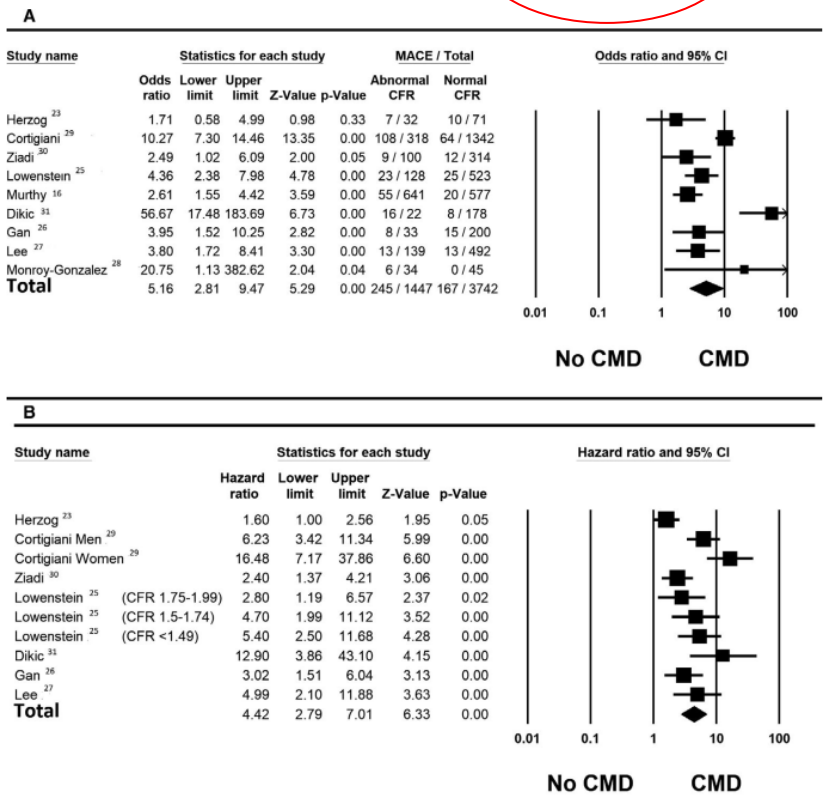
B

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Marks [22]	7.010	2.743	17.917	4.067	0.000
Herzog [23]	2.860	1.241	6.593	2.466	0.014
Cortigiani [24]	3.310	2.291	4.782	6.376	0.000
Total	3.619	2.446	5.354	6.437	0.000

Hazard ratio and 95% CI: 0.01, 0.1, 1, 10, 100

No CMD CMD

Odds Ratio for MACE: 5.16



A

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	MACE / Total Abnormal CFR	Normal CFR
Herzog [23]	1.71	0.58	4.99	0.98	0.33	7 / 32	10 / 71
Cortigiani [29]	10.27	7.30	14.46	13.35	0.00	108 / 318	64 / 1342
Ziadi [30]	2.49	1.02	6.09	2.00	0.05	9 / 100	12 / 314
Lowenstein [25]	4.36	2.38	7.98	4.78	0.00	23 / 128	25 / 523
Murthy [16]	2.61	1.55	4.42	3.59	0.00	55 / 641	20 / 577
Dikic [31]	56.67	17.48	183.69	6.73	0.00	16 / 22	8 / 178
Gan [26]	3.95	1.52	10.25	2.82	0.00	8 / 33	15 / 200
Lee [27]	3.80	1.72	8.41	3.30	0.00	13 / 139	13 / 492
Monroy-Gonzalez [28]	20.75	1.13	382.62	2.04	0.04	6 / 34	0 / 45
Total	5.16	2.81	9.47	5.29	0.00	245 / 1447	167 / 3742

Odds ratio and 95% CI: 0.01, 0.1, 1, 10, 100

No CMD CMD

B

Study name		Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Herzog [23]		1.60	1.00	2.56	1.95	0.05
Cortigiani Men [29]		6.23	3.42	11.34	5.99	0.00
Cortigiani Women [29]		16.48	7.17	37.86	6.60	0.00
Ziadi [30]		2.40	1.37	4.21	3.06	0.00
Lowenstein [25]	(CFR 1.75-1.99)	2.80	1.19	6.57	2.37	0.02
Lowenstein [25]	(CFR 1.5-1.74)	4.70	1.99	11.12	3.52	0.00
Lowenstein [25]	(CFR <1.49)	5.40	2.50	11.68	4.28	0.00
Dikic [31]		12.90	3.86	43.10	4.15	0.00
Gan [26]		3.02	1.51	6.04	3.13	0.00
Lee [27]		4.99	2.10	11.88	3.63	0.00
Total		4.42	2.79	7.01	6.33	0.00

Hazard ratio and 95% CI: 0.01, 0.1, 1, 10, 100

No CMD CMD

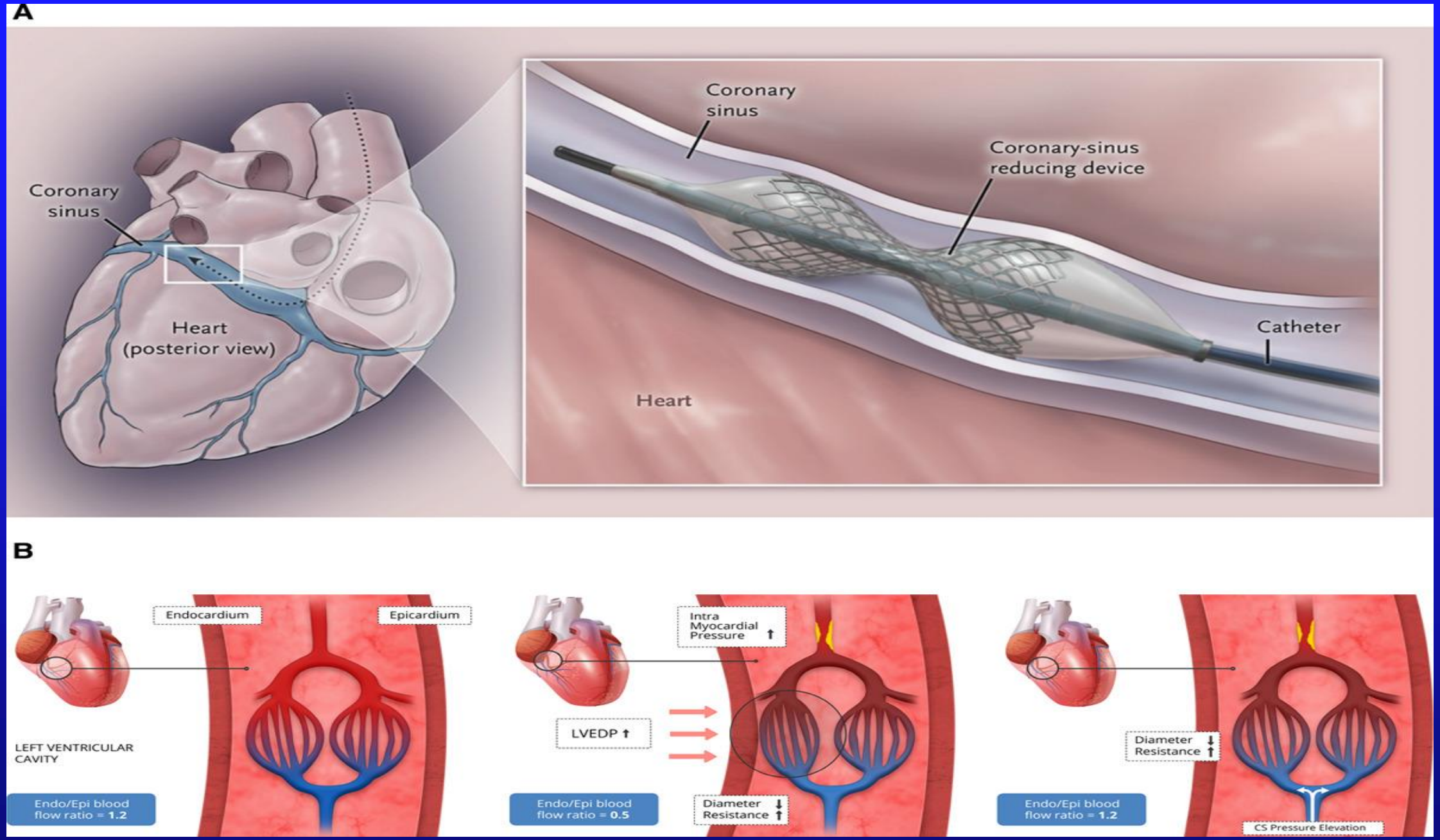
Crude mortality in 4661 non- CMD 2.6%(122) vs CMD 9.3% (183) in 1970 patients

Crude MACE in 3742 non- CMD 4.5%(167) vs CMD 16.9 % (245) in 1447 patients

Gdowski MA et al. J Am Heart Assoc. 2020;9:e014954.

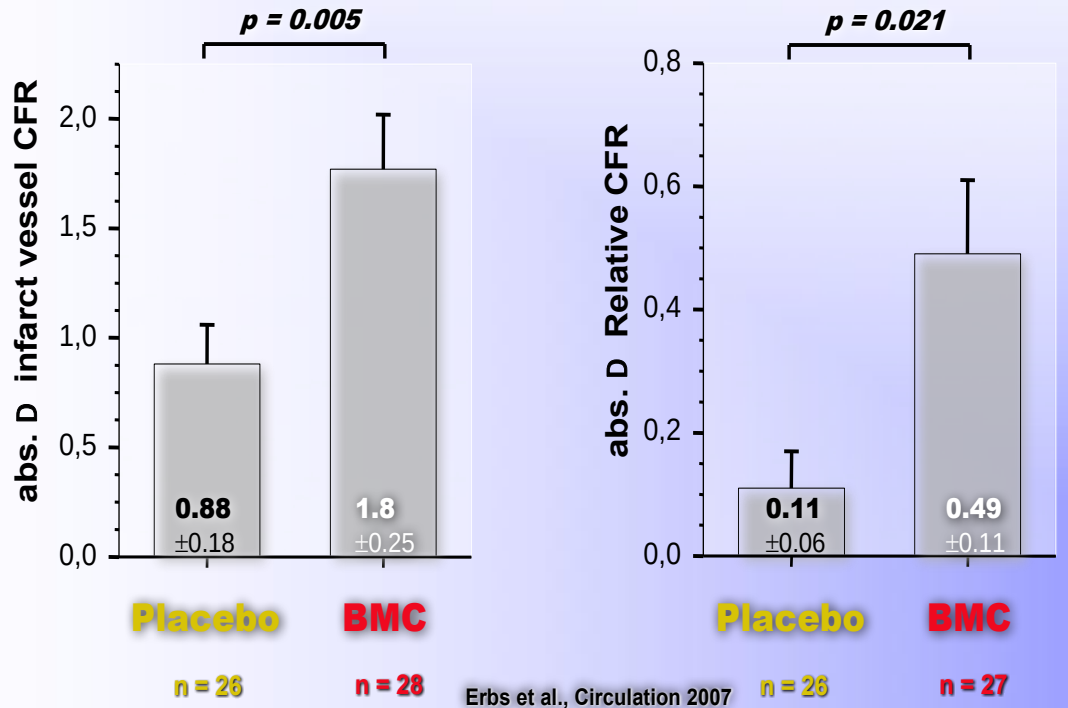
Novel Therapies for Microvascular Dysfunction

- Coronary Sinus Reducer
- Stem Cell Therapy
- Novel therapeutics



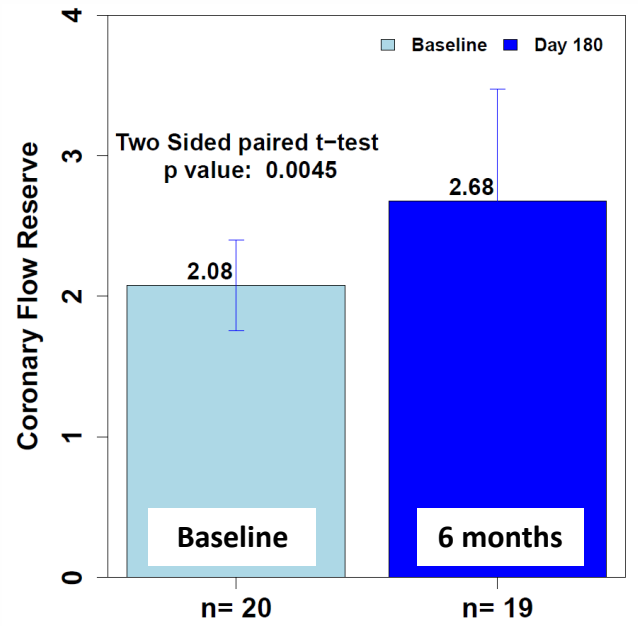
Povsic TJ, Henry TD, Ohman EM. Therapeutic Approaches for the No-Option Refractory Angina Patient. Circ Cardiovasc Interv. 2021 Feb;14(2):e009002.

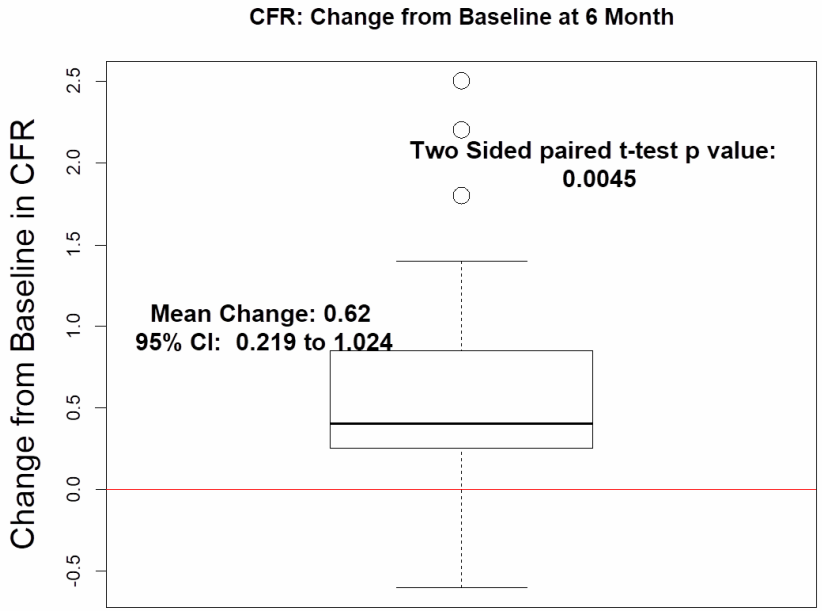
Intracoronary BMC Administration Normalizes Coronary Flow Reserve



Erbs et al., Circulation 2007

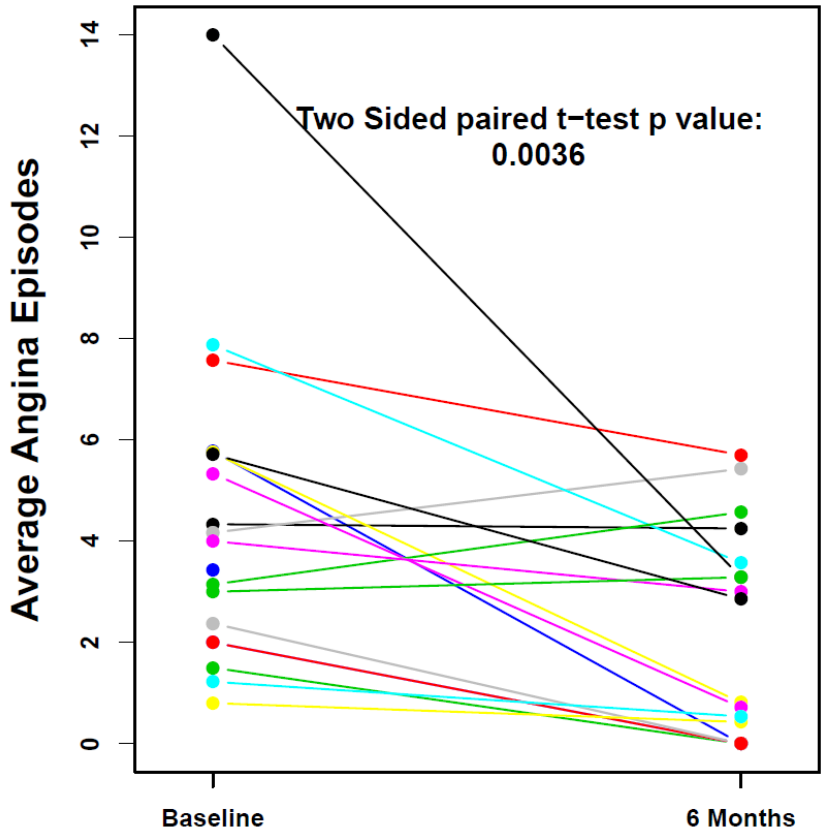
ESCAPE-CMD INCREASES CFR AT 6 MONTHS IN CMD

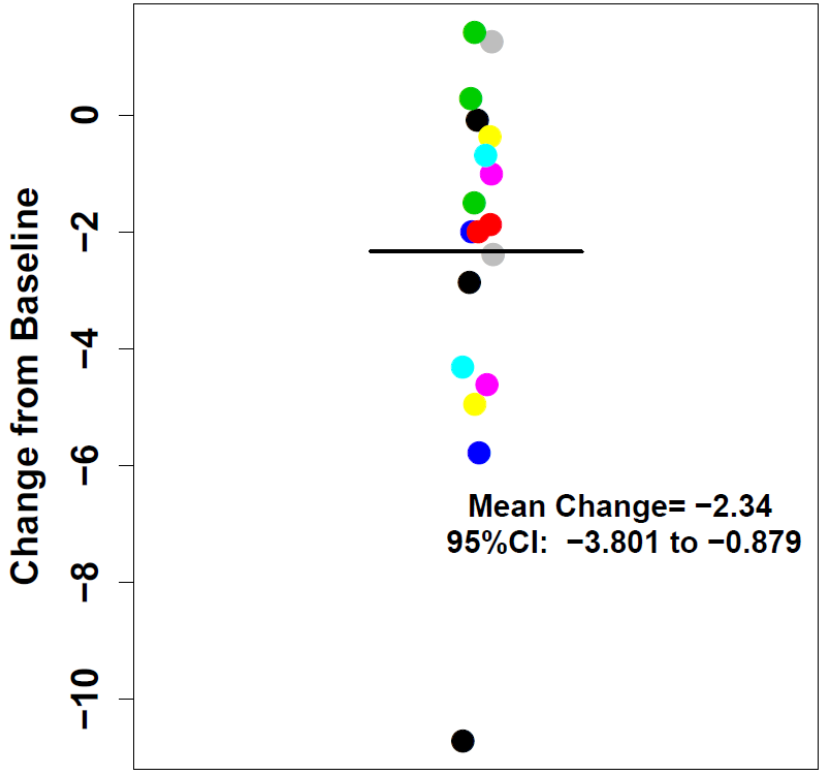




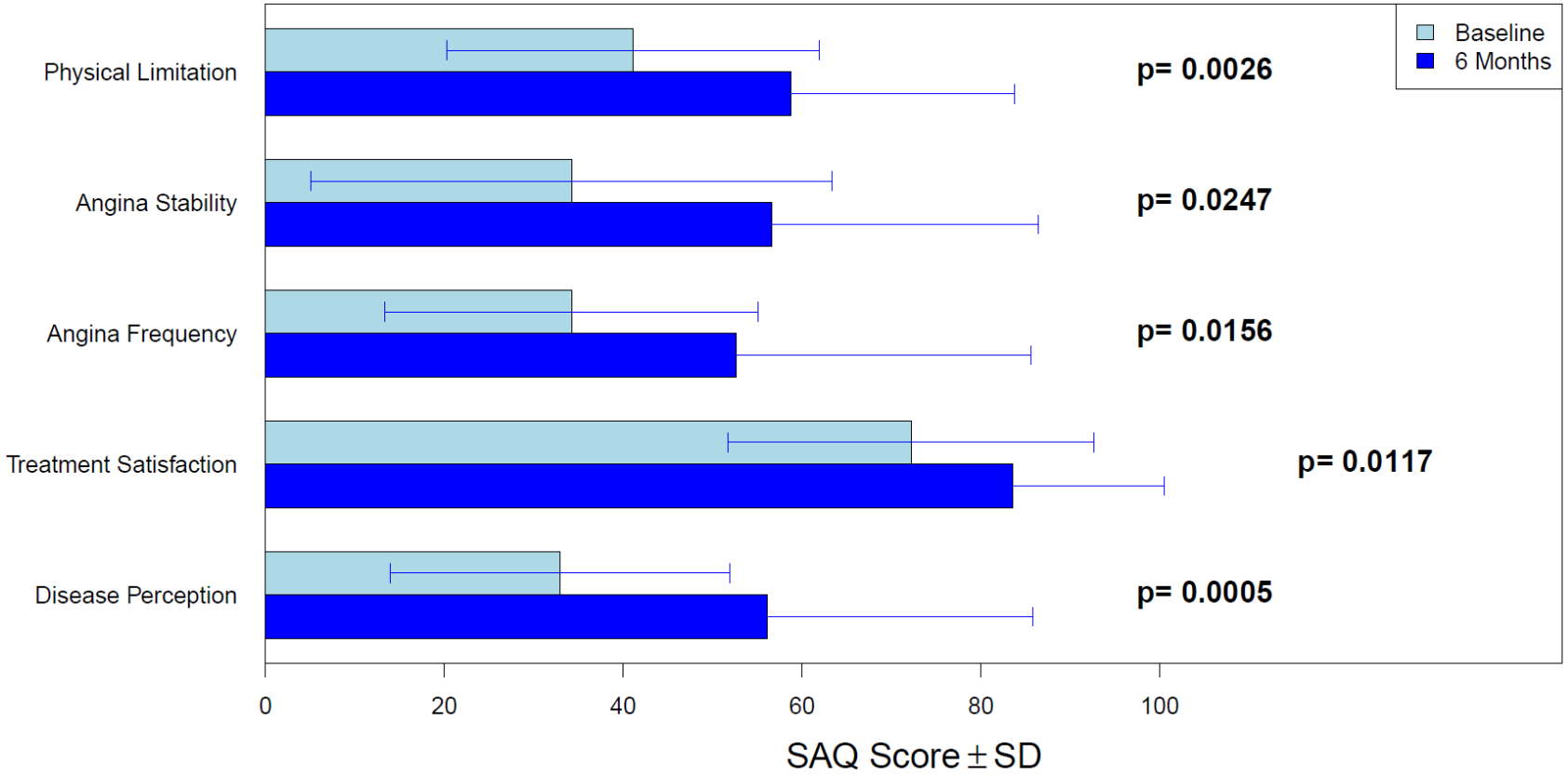
SCAI
Society for Cardiovascular Angiography & Interventions

ESCAPE-CMD DECREASES ANGINA FREQUENCY AT 6 MONTHS





ESCAPE-CMD IMPROVES SEATTLE ANGINA QUESTIONNAIRE SCORES AT 6 MONTHS



AHA Diagnostic Criteria for MINOCA

1. Acute myocardial infarction

- Modified from the "Fourth Universal Definition of Myocardial Infarction" Criteria)
- Detection of a rise or fall of cTn
- Clinical evidence of infarction evidenced by at least 1 of the following:
  - Symptoms of myocardial ischemia
  - New ischemic ECG changes
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic cause
  - Identification of a coronary thrombus by angiography or autopsy

2. No Obstructive CAD

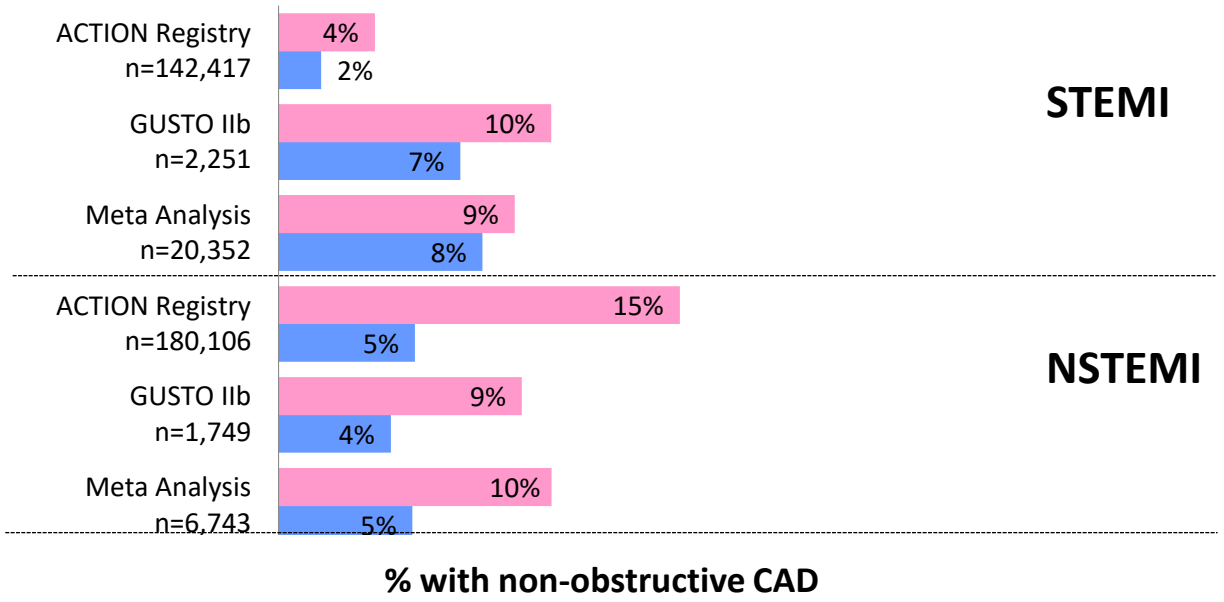
- Defined as the absence of obstructive disease on angiography (ie, no coronary artery stenosis ≥50%) in any major epicardial vessel

3. No specific alternate diagnosis for the clinical presentation

- Alternate diagnoses include but are not limited to nonischemic causes such as sepsis, pulmonary embolism, and myocarditis

Tamis-Holland JE, et al. Circulation. 2019 Apr 30;139(18):e891-e908.

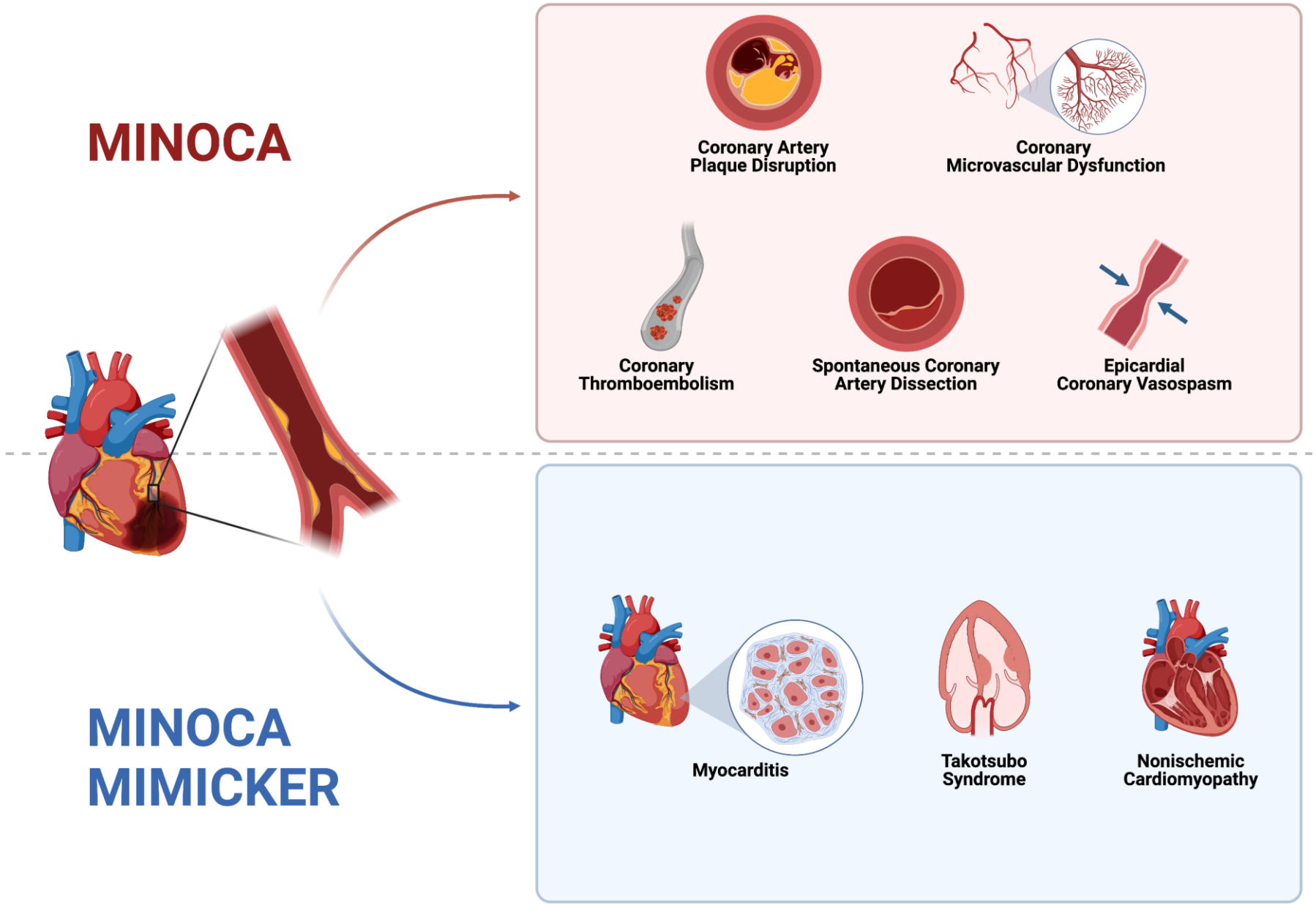
Prevalence of MINOCA



1/3 ACS in women angiogram shows no obstructive CAD

Marzilli M, et al. J Am Coll Cardiol. 2012 Sep 11;60(11):951-6.

MINOCA is a Syndrome NOT a Diagnosis



ESC Guidelines - MINOCA

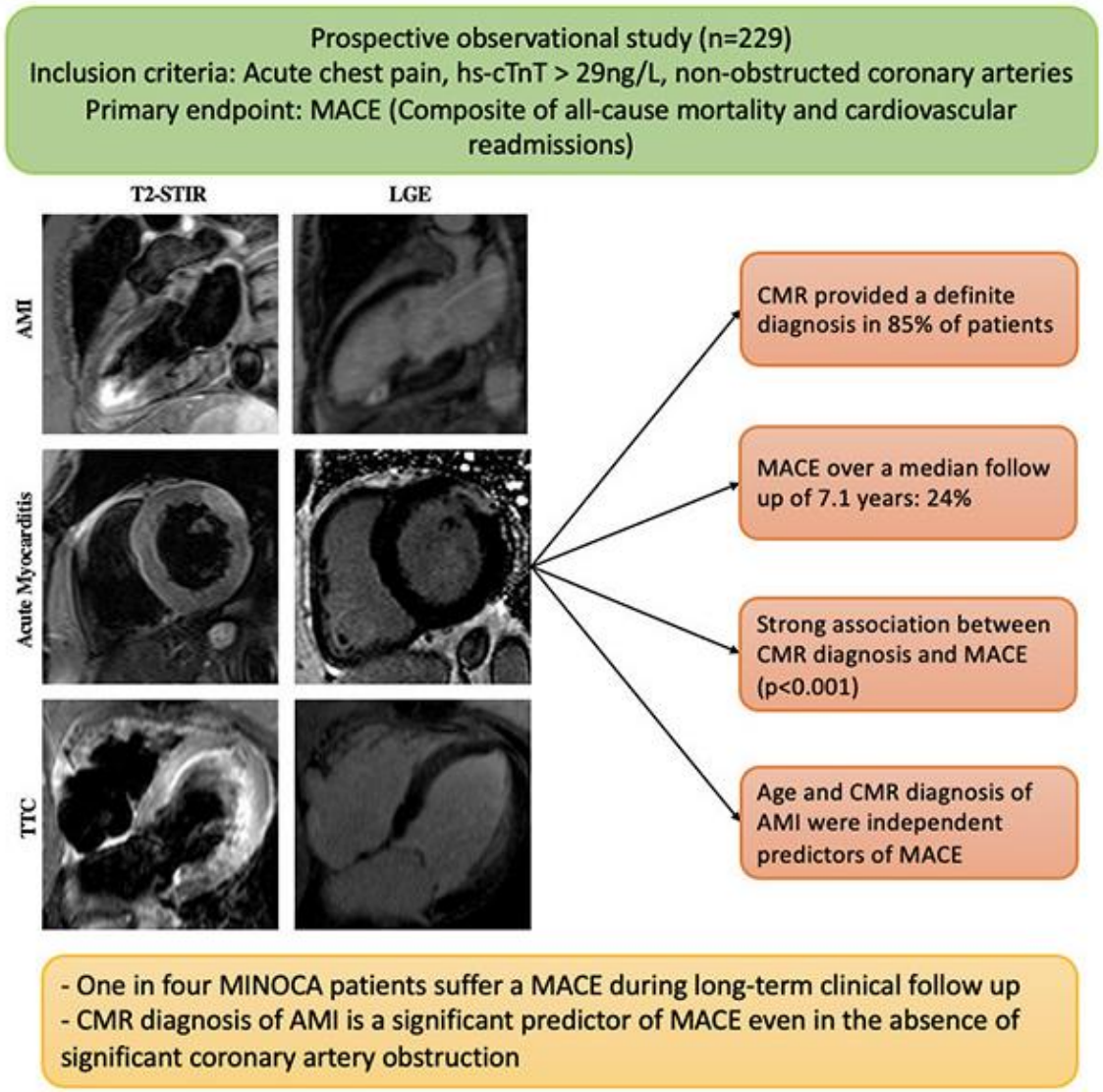
Recommendations for myocardial infarction with non-obstructive coronary arteries

Recommendations	Class[a]	Level[b]
In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to differentiate true MINOCA from alternative diagnoses.	I	C
It is recommended to perform CMR in all MINOCA patients without an obvious underlying cause.[370]	I	B
It is recommended to manage patients with an initial diagnosis of MINOCA and a final established underlying cause according to the disease-specific guidelines.	I	C
Patients with a final diagnosis of MINOCA of unknown cause may be treated according to secondary prevention guidelines for atherosclerotic disease.	IIb	C

CMR = cardiac magnetic resonance; MINOCA = myocardial infarction with non-obstructive coronary arteries.
[a]Class of recommendation.
[b]Level of evidence.

Collet JP, et al. Eur Heart J. 2021 Apr 7;42(14):1289-1367.

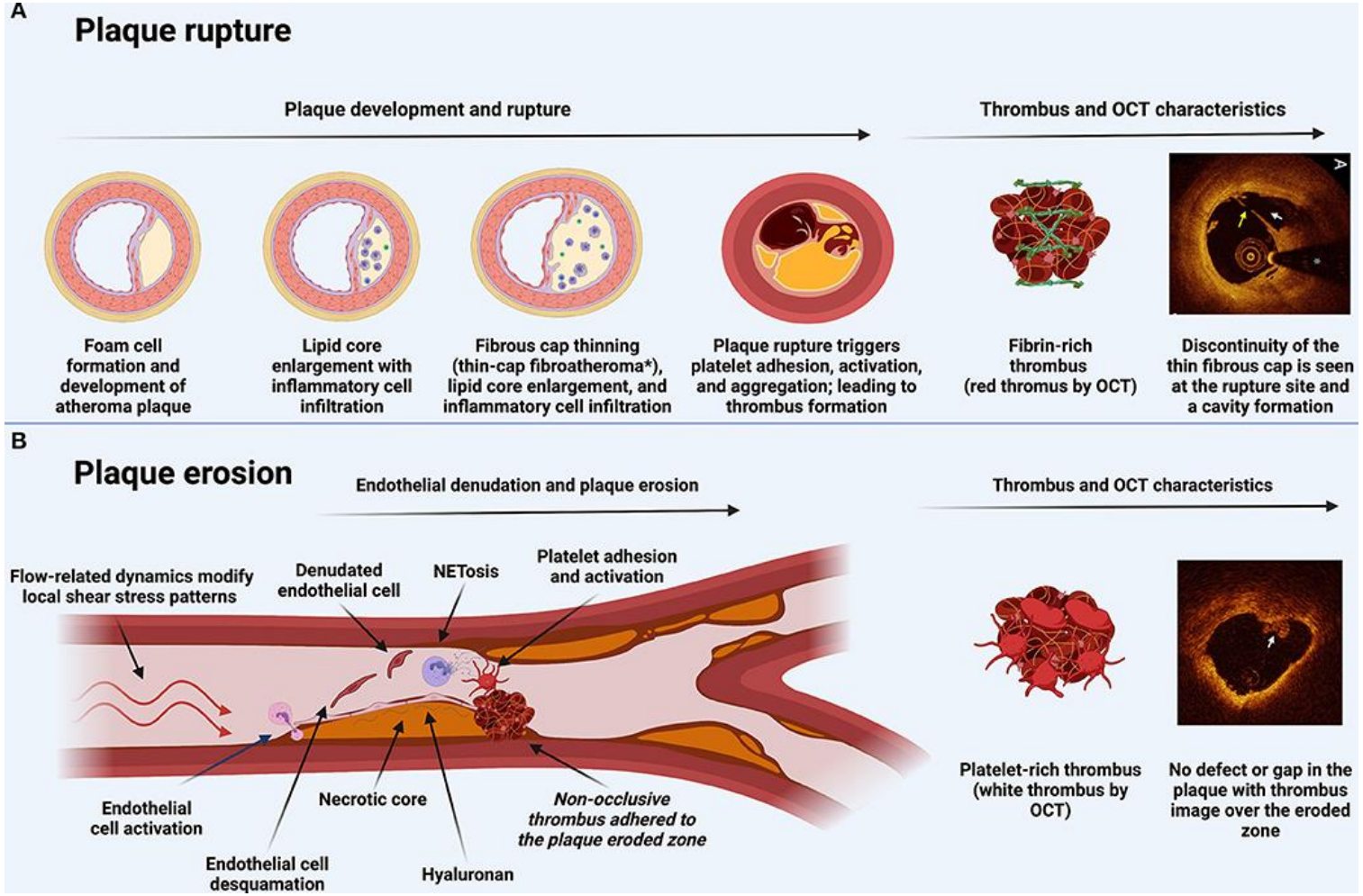
CMRI for Prognostication in MINOCA



- CMRI also carries not only diagnostic but also prognostic value.
- CMRI confirmed MI was an independent predictor of long-term cardiovascular events.

Ananalthakrishna R, et al. Int J Cardiol. 2022 Feb 15;349:12-17.

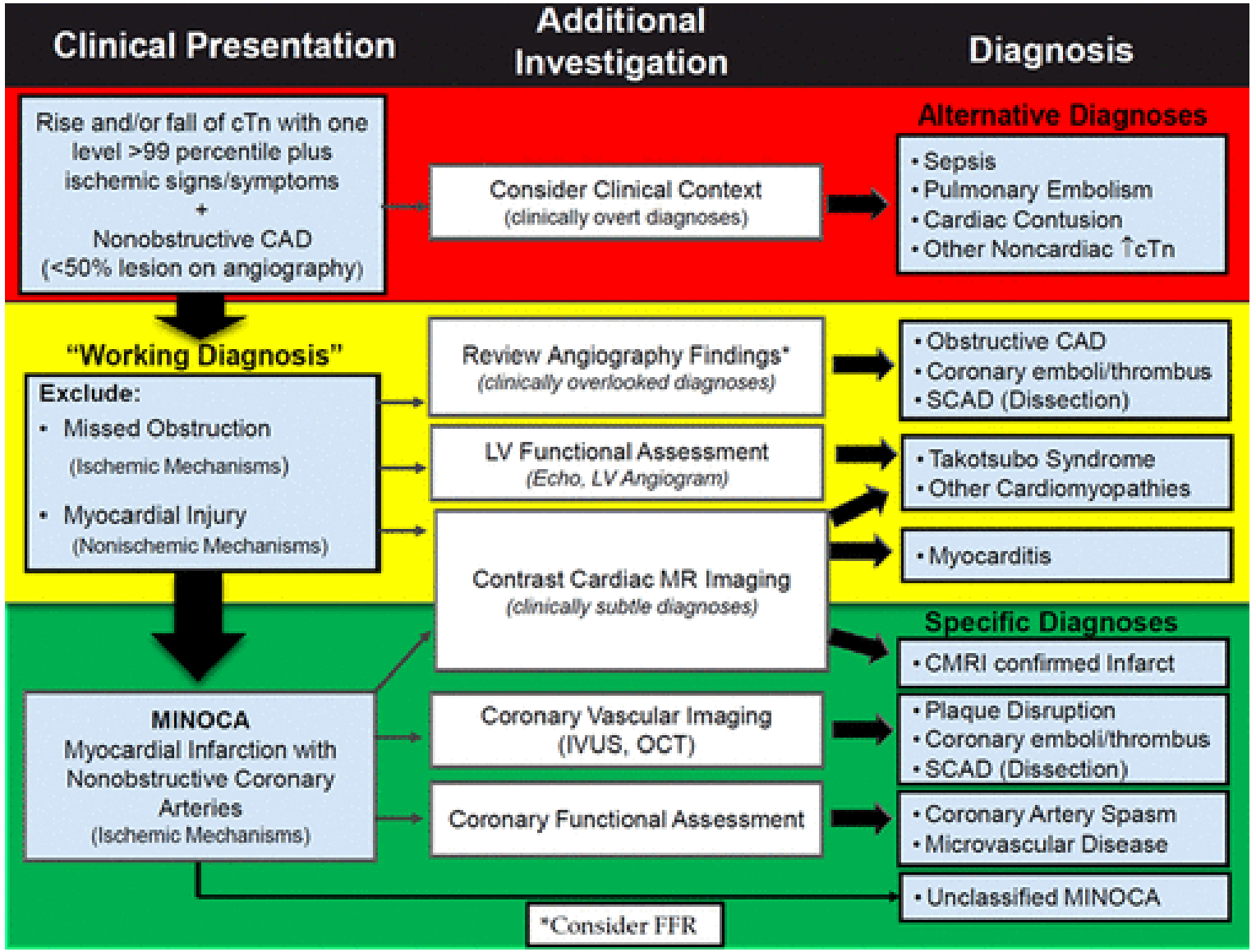
MINOCA: Coronary Artery Plaque Disruption



- The HARP study plaque disruption was the most common cause of NSTEMI MINOCA
- 43.4% of females with MINOCA who underwent OCT had plaque disruption:
  - 8 plaque rupture
  - 5 plaque erosion
  - 38 intra-plaque cavity
  - 19 layered plaque

Front. Cardiovasc. Med., 14 February 2022

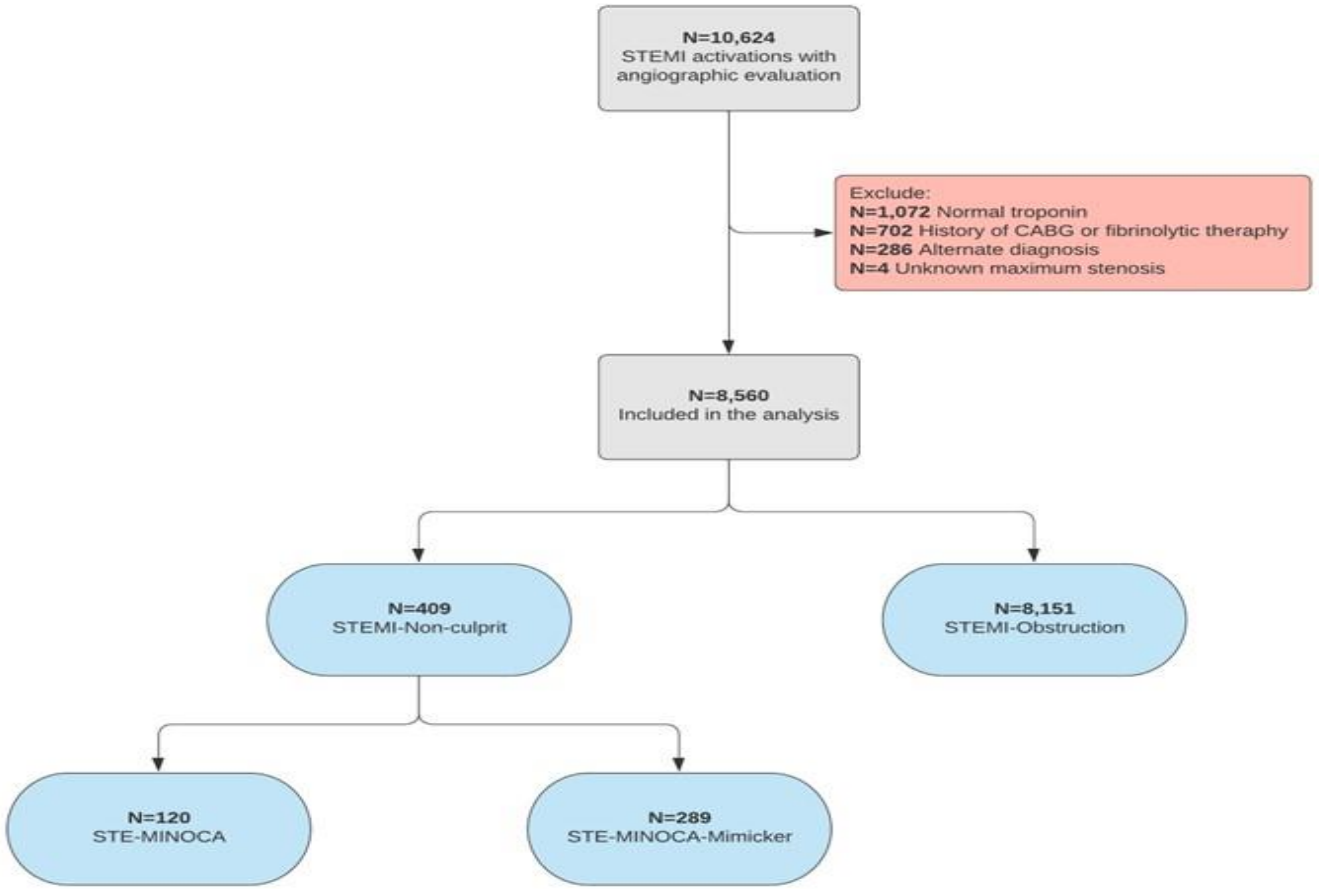
MINOCA Algorithm



*The diagnostic performance of **cMRI** decreases significantly from **77%** at **3 days** to **47%** at **12 days** after hospital admission.

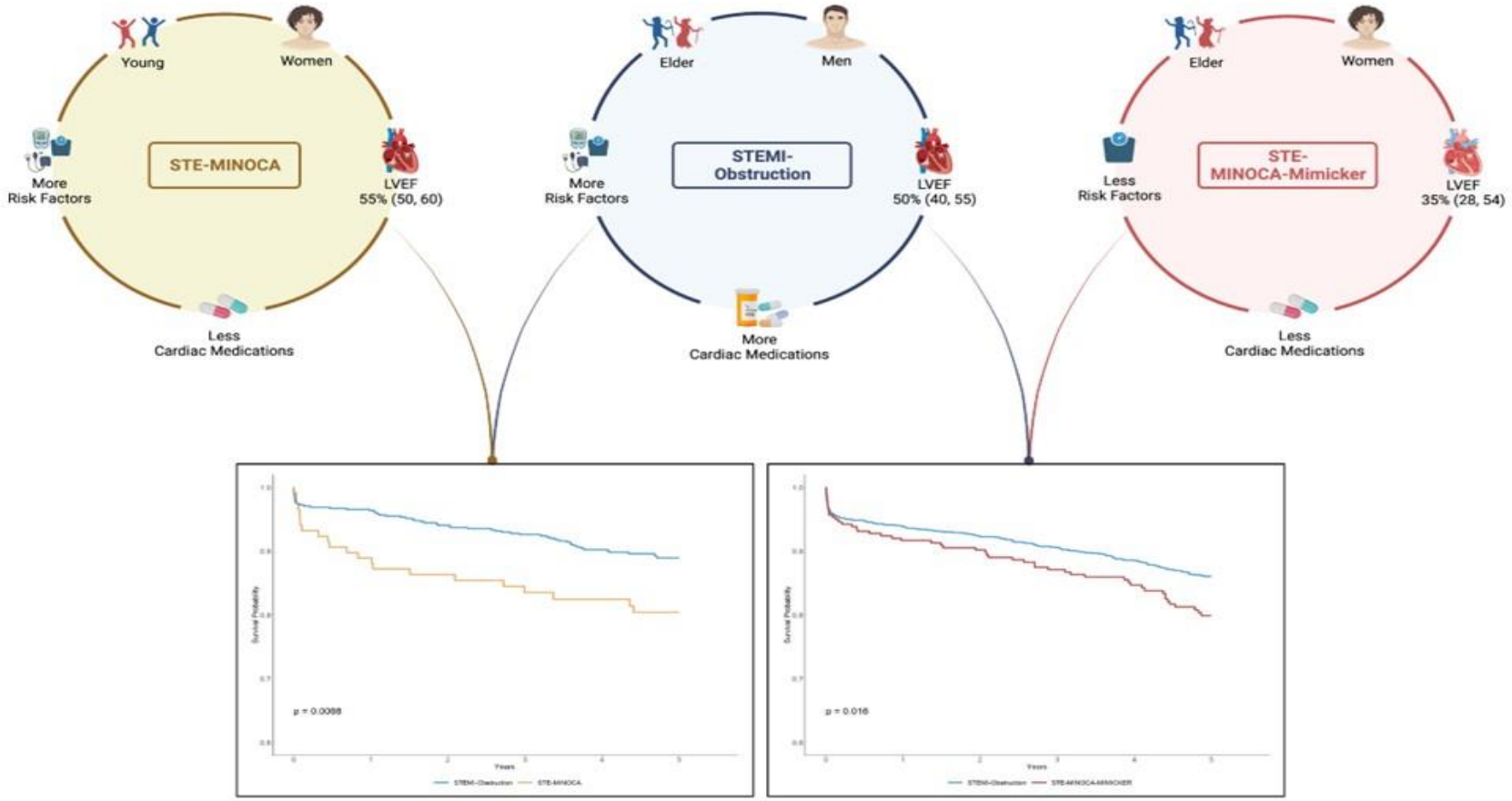
Tamis-Holland JE, et al. Circulation. 2019 Apr 30;139(18):e891-e908.
Sörensson P, et. *JACC: Cardiovascular Imaging*. 2021;14(9):1774-1783.

MSC MINOCA STEMI

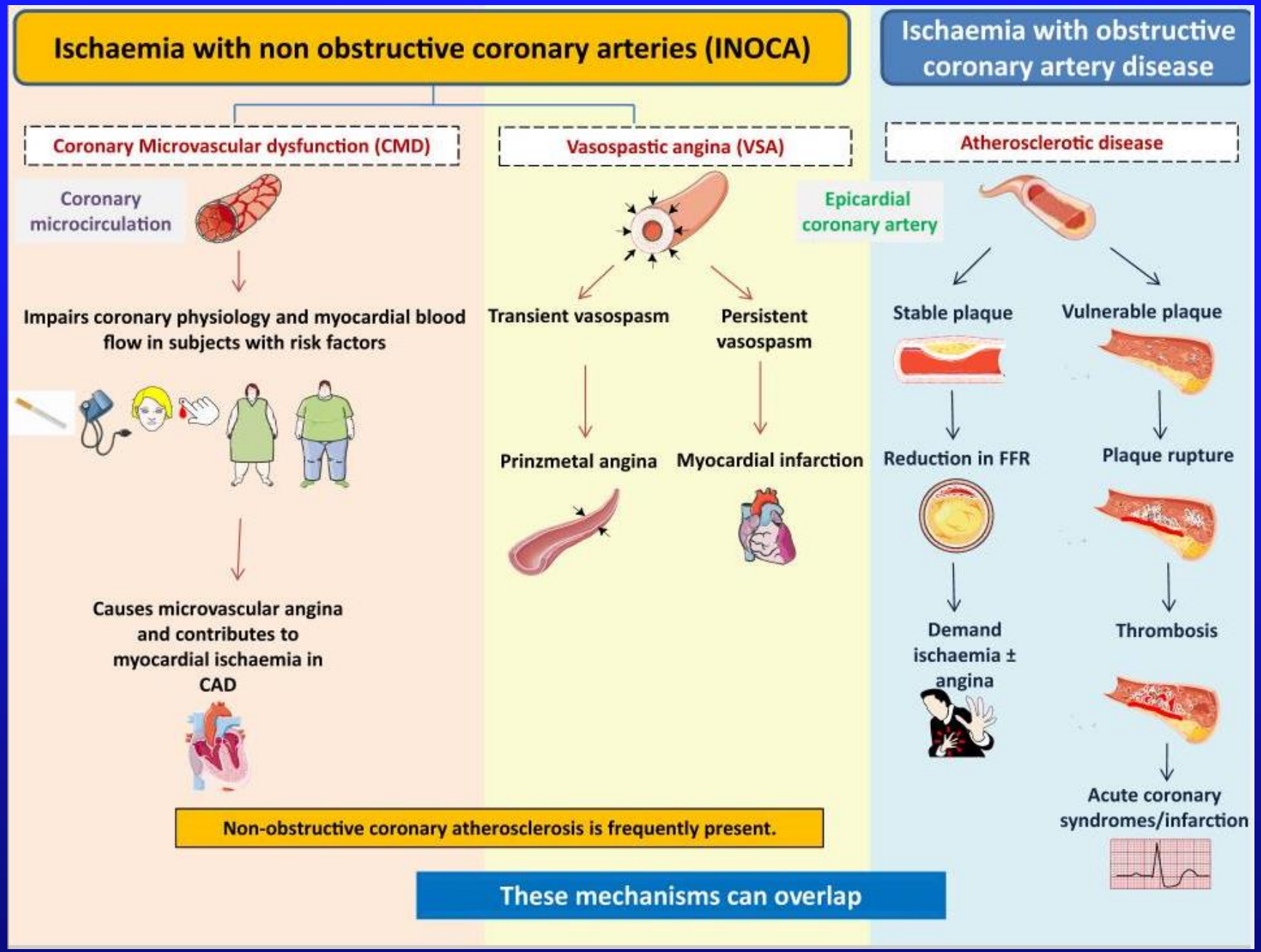


Quesada O, et al. Characteristics and Long-term Mortality in Patients with ST-Segment Elevation Myocardial Infarction with Non-Obstructive Coronary Arteries (STE-MINOCA): A High Risk Cohort. medRxiv [Preprint]. 2023 Feb 7:2023.02.05.23285502.

MINOCA STEMI



Quesada O, et al. Characteristics and Long-term Mortality in Patients with ST-Segment Elevation Myocardial Infarction with Non-Obstructive Coronary Arteries (STE-MINOCA): A High Risk Cohort. medRxiv [Preprint]. 2023 Feb 7:2023.02.05.23285502.



Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, Prescott E, Karam N, Appelman Y, Fraccaro C, Louise Buchanan G, Manzo-Silberman S, Al-Lamee R, Regar E, Lansky A, Abbott JD, Badimon L, Duncker DJ, Mehran R, Capodanno D, Baumbach A. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. Eur Heart J. 2020 Oct 1;41(37):3504-3520.

Thank you!

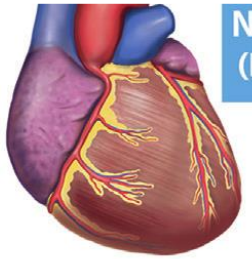
The Christ Hospital™ Health Network

Women's Heart Center

www.TheChristHospital.com/Womens-Heart

Lindner Center phone number: 513-585-1737

Coronary Function Testing (CFT)



Diagnostic Testing: Nonobstructive Epicardial Coronary Arteries (Diameter Stenosis <50%, FFR >0.8, NHPR >0.89)

Coronary Function Testing

IVUS + Coronary Physiology

Coronary Flow Reserve & Hyperemic Resistance (endothelium-independent)

Acetylcholine Coronary Reactivity Testing (endothelium-dependent)

Endothelium independent

Endothelium dependent

Coronary Microvascular Dysfunction	Microvascular Spasm	Endothelial Dysfunction	Epicardial Coronary Spasm	Myocardial Bridging
CFR <2-2.5 and/or IMR ≥25 and/or HMR ≥2-2.5	Angina and ischemic ECG changes with acetylcholine, but without epicardial spasm	>0% to ≤90% narrowing and/or <50% Δ in coronary blood flow with acetylcholine	>90% spasm with acetylcholine with angina and ECG changes	Half-moon sign / ≥10% systolic compression by IVUS + dobutamine dFFR/iFR/RFR ≤0.76

Treatment:

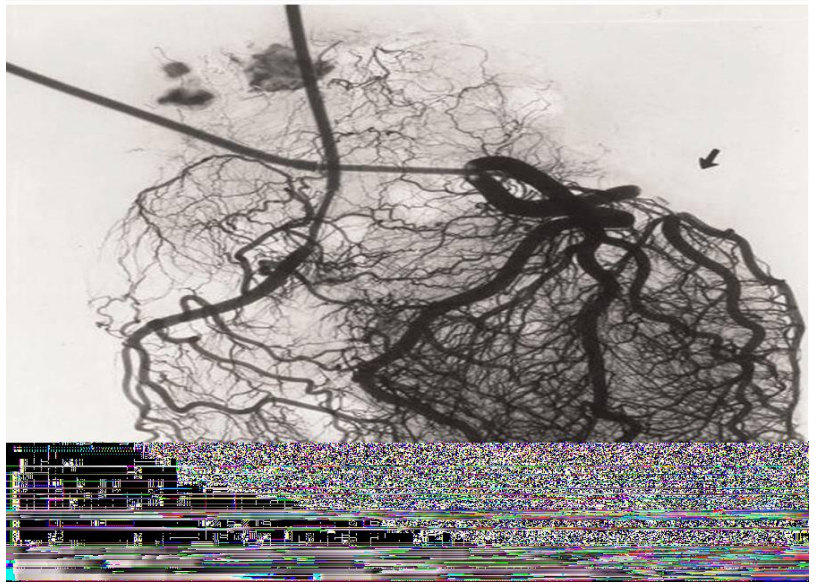
Statin, Exercise, Weight Loss	Statin, Exercise, Weight Loss	Statin, Exercise, Weight Loss	Statin, Exercise, Weight Loss	Beta-Blocker
prn SLNTG	prn SLNTG	prn SLNTG	prn SLNTG	CCB (non-DHP)
ACE Inhibitor	ACE Inhibitor	Long-Acting Nitrates	CCB (DHP/non-DHP)	
Beta-Blocker	CCB (DHP/non-DHP)			

Smilowitz NR, et al. J Am Coll Cardiol. 2023;82(12):1264–1279.

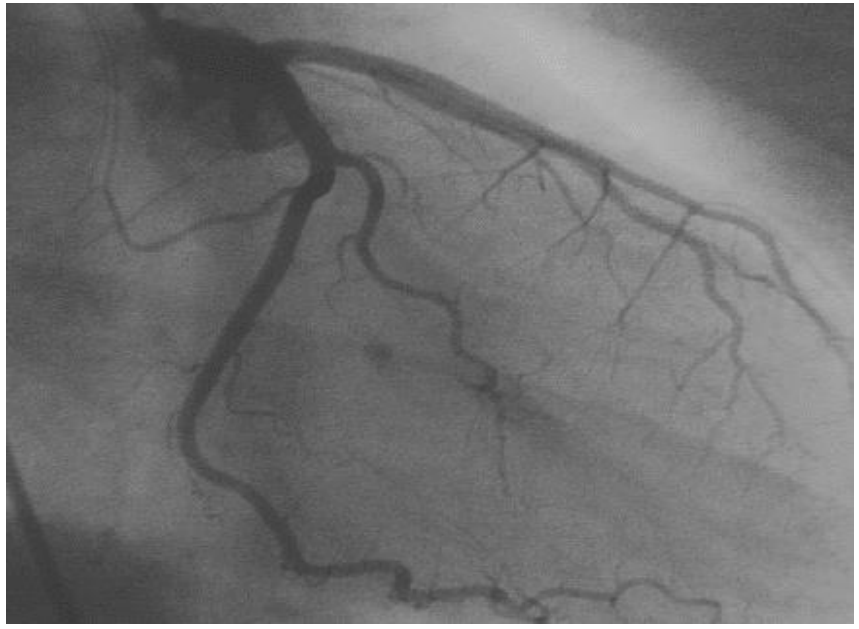
What you see . . .

The tip of the iceberg
Resolution >500 µm

What you don't see . . .

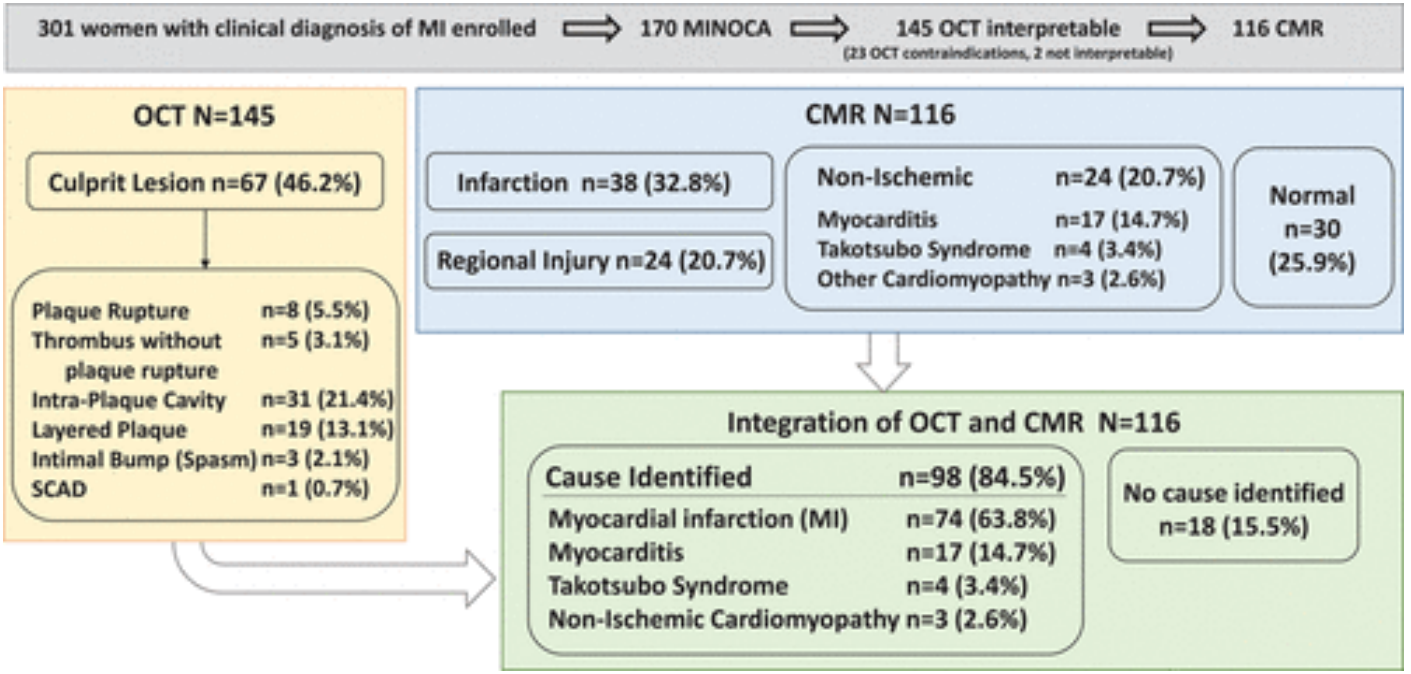


The hidden side of the iceberg
Resolution <500 µm



Microvascular Disease?

Multi-modality Imaging to Identify Underlying Diagnosis in MINOCA: HARP Study



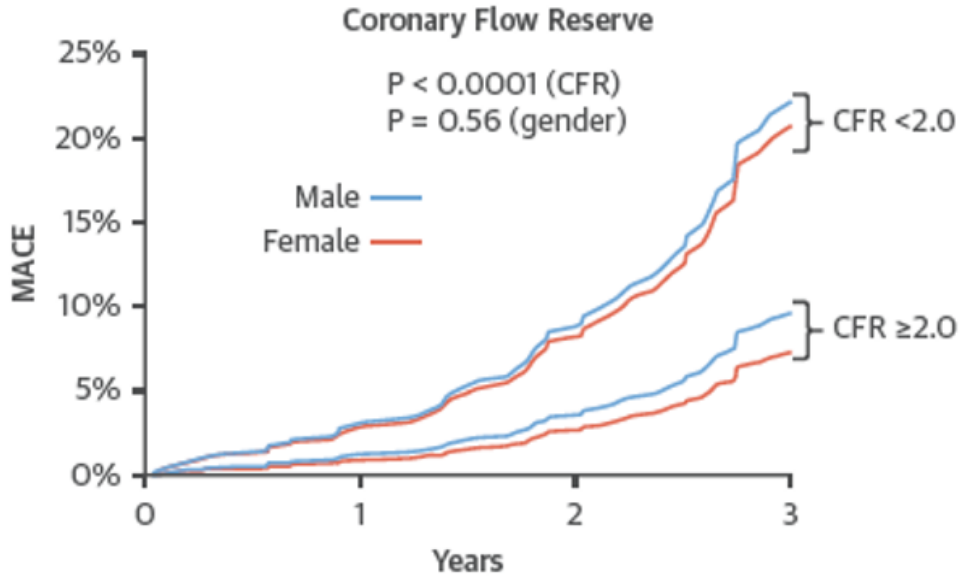
*MINOCA in HARP was predominantly NSTEMIs

- OCT culprit → CMR evidence of infarction or regional ischemic injury in 69%
- Ischemic CMR findings (LGE or regional injury) → 44% no OCT culprit
- Multi-modality imaging (OCT+CMR) → 85% with cause identified
  - OCT alone: 46% ($p<0.001$)
  - CMR alone: 74% ($p=0.001$)

Reynolds HR, et al. Circulation. 2021 Feb 16;143(7):624-640.

Future of Interventional Cardiology: Does it reach a plateau or limit?

BACKGROUD: REDUCED CORONARY FLOW RESERVE IS ASSOCIATED WITH SIGNIFICANTLY INCREASE RISK OF MACE



Murthy et al, Circulation, 2014

GUIDELINES ARE MOVING: WHO AND WHAT IS NEXT?

Timothy D. Henry, MD

Medical Director, The Carl and Edyth Lindner Center for Research and Education

The Carl and Edyth Lindner Center Distinguished Chair in Clinical Research

Director of Programmatic and Network Development Heart and Vascular Service Line

The Christ Hospital™ Health Network

Diagnosis of Coronary Microvascular Disease: Invasive Imaging

Indications for Invasive Coronary Function Testing (CFT)

Evidence of ischemia
+
No obstructive CAD
+
Persistent chest pain

- Chest pain refractory to medical management
- Preference for definitive diagnosis

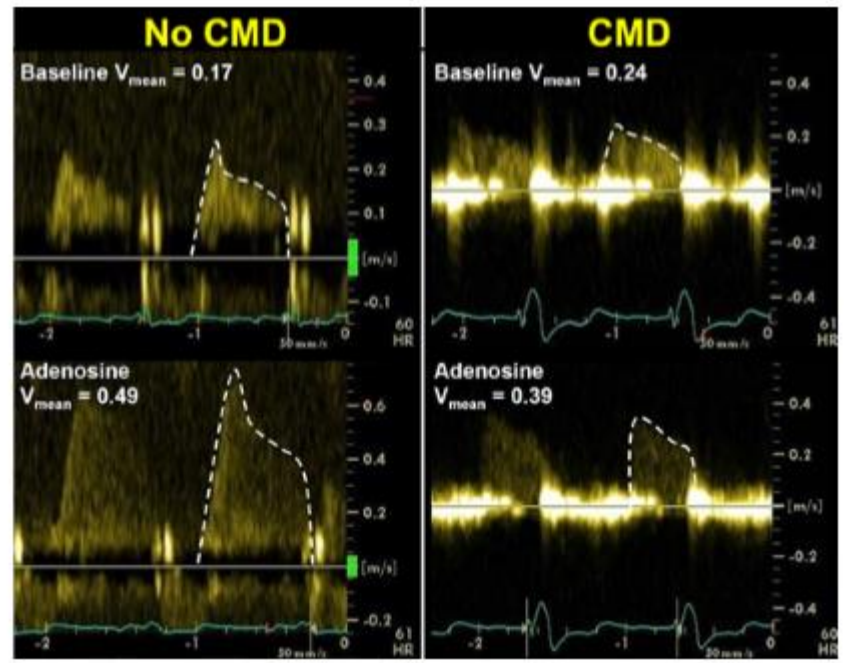
Safety data:

<0.6-0.7% serious adverse event (coronary dissection, MI)

Wei J et al. *JACC Interventions*. 2012;5:646-53;
Reriani M et al. *Coronary Artery Disease*. 2015;27:213-20;
Ong P et al. *Circulation.* 2014;129:1723-30

Methods

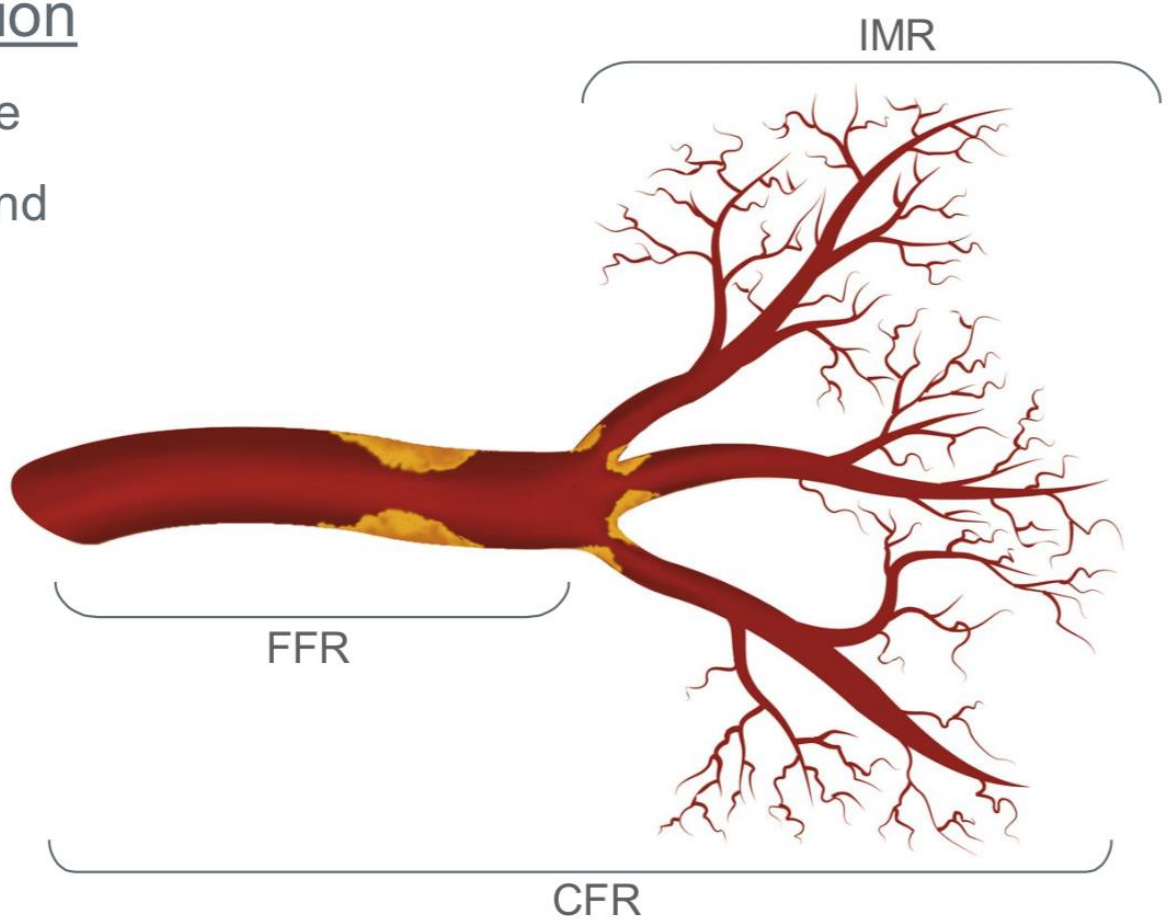
- Coronary flow reserve (CFR) by transthoracic Doppler echo coronary flow velocity at rest and with adenosine
  - Read by core lab
  - CMD defined as CFR<2.5
- Systemic microvascular function by peripheral arterial tonometry (EndoPAT) reactive hyperemia index (RHI)
- Myocardial function by echo tissue Doppler and speckle-tracking



Index of Myocardial Resistance: IMR

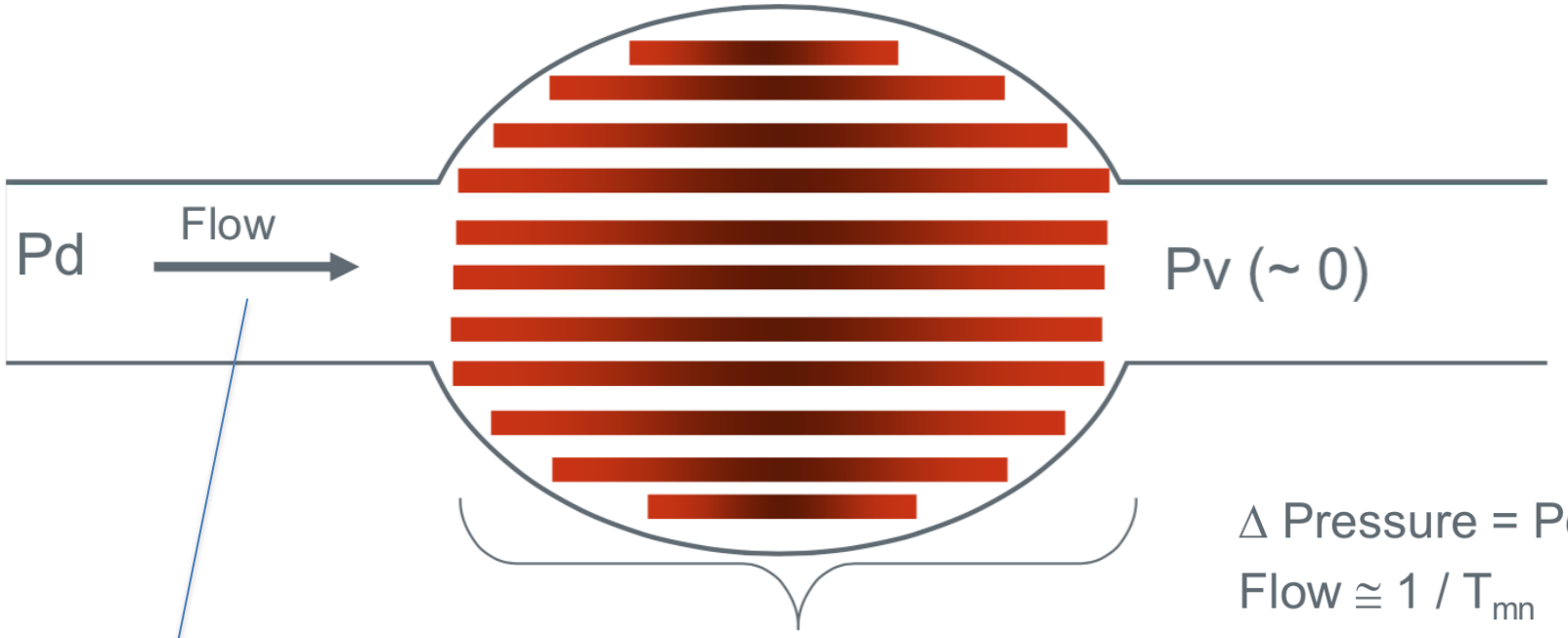
Invasive and quantitative method for evaluating the microcirculation

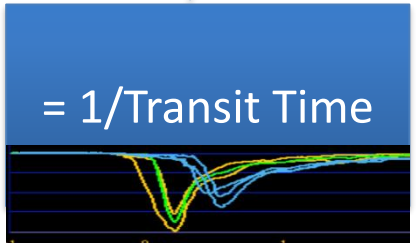
- FFR: Specific for epicardial disease
- CFR: Affected by both epicardial and microcirculatory disease (cannot distinguish between the two)
- IMR: Specific for microcirculatory disease



IMR

Myocardial resistance = pressure drop across the myocardium divided by flow





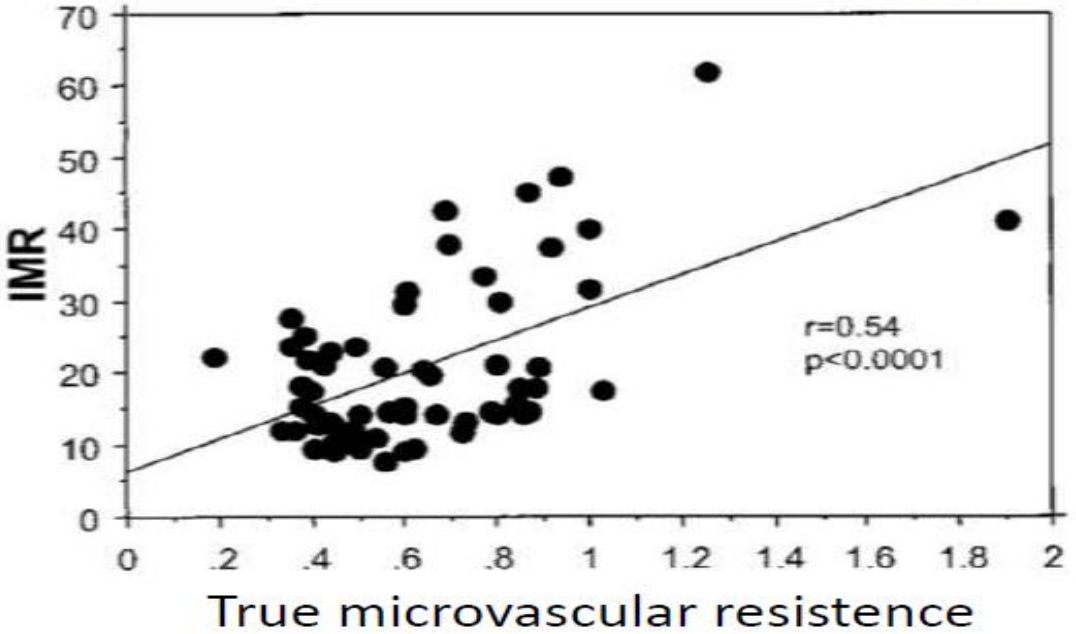
Δ Pressure = Pd - Pv = Pd (assuming Pv = 0)

Flow $\cong 1 / T_{mn}$

IMR = Pd / $(1 / T_{mn})$

IMR = Pd x T_{mn} (at maximal hyperemia)

Index of microcirculatory resistance (IMR)



$$IMR = P_d \times T_{mn\ hyperemic}$$

- IMR assesses the status of microcirculation independent of both, epicardial stenosis and changes in hemodynamics.
- Collateral flow contribution should be taken into account in case of severe stenoses.

Fearon et al. Circulation. 2003;107:3129-3132
Yong et al.Circ Cardiovasc Interv. 2012;5:103-108

"It sort of makes you stop and think, doesn't it."

Long term prognosis of epicardial and microvascular spasm

847 patients with **angina + unobstructed coronary arteries** → **Intracoronary acetylcholine spasm provocation testing** → **Long-term follow-up:** 7.2 (6.5-7.9) years

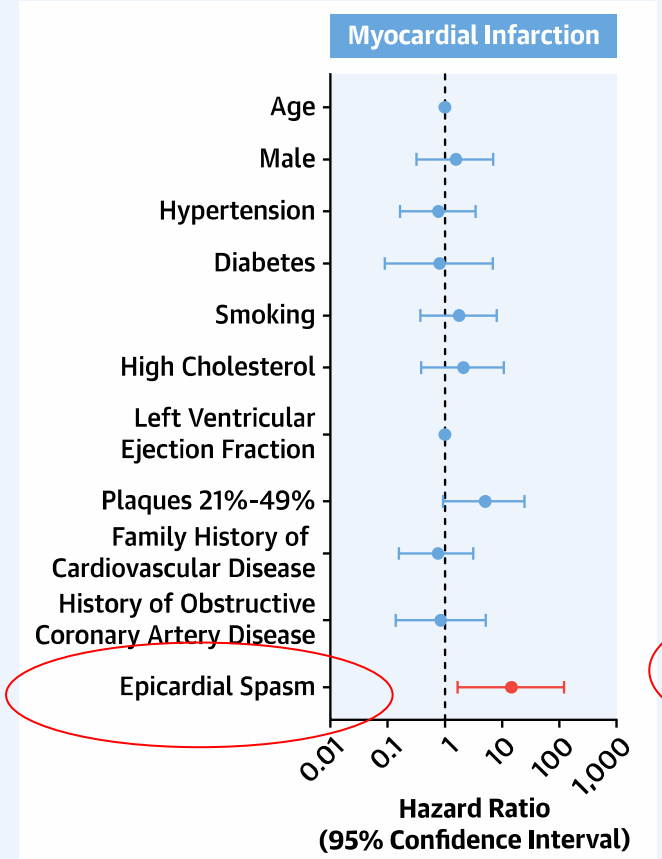
Mortality

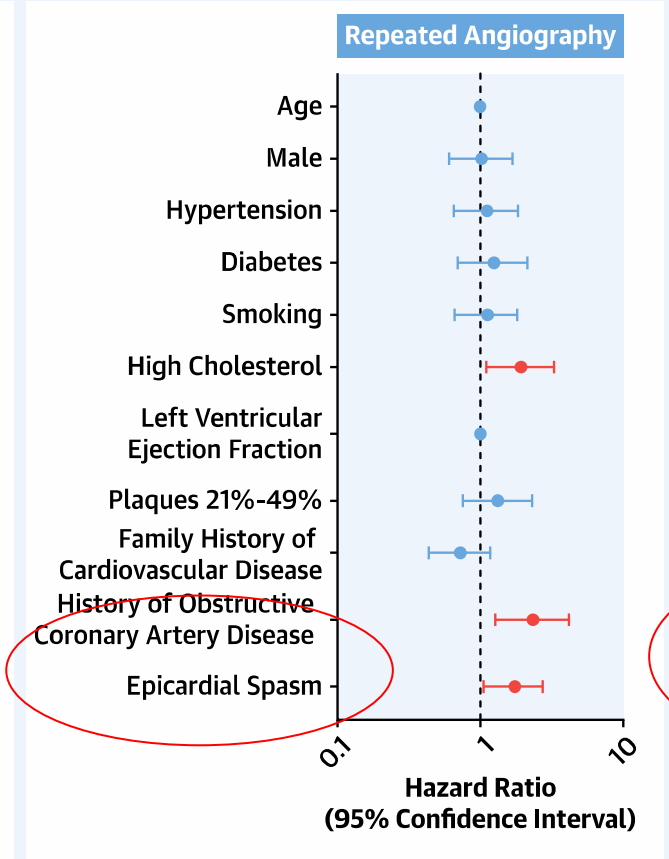
All-Cause Mortality
7.5% in 7 years
(≈1.0% per year)

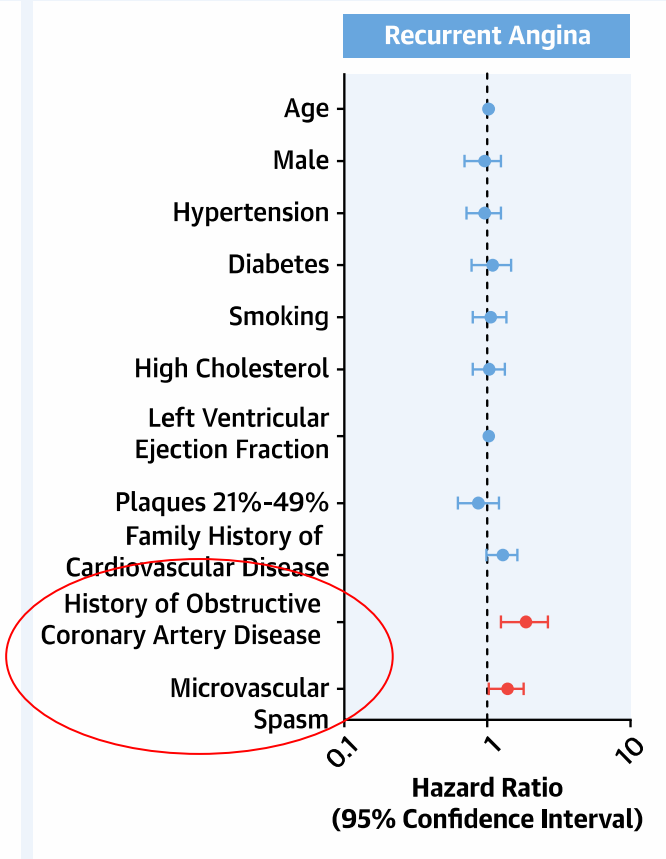
Cardiac Mortality
0.9% in 7 years
(≈0.1% per year)

Low Mortality independent of coronary spasm

Predictors of Morbidity

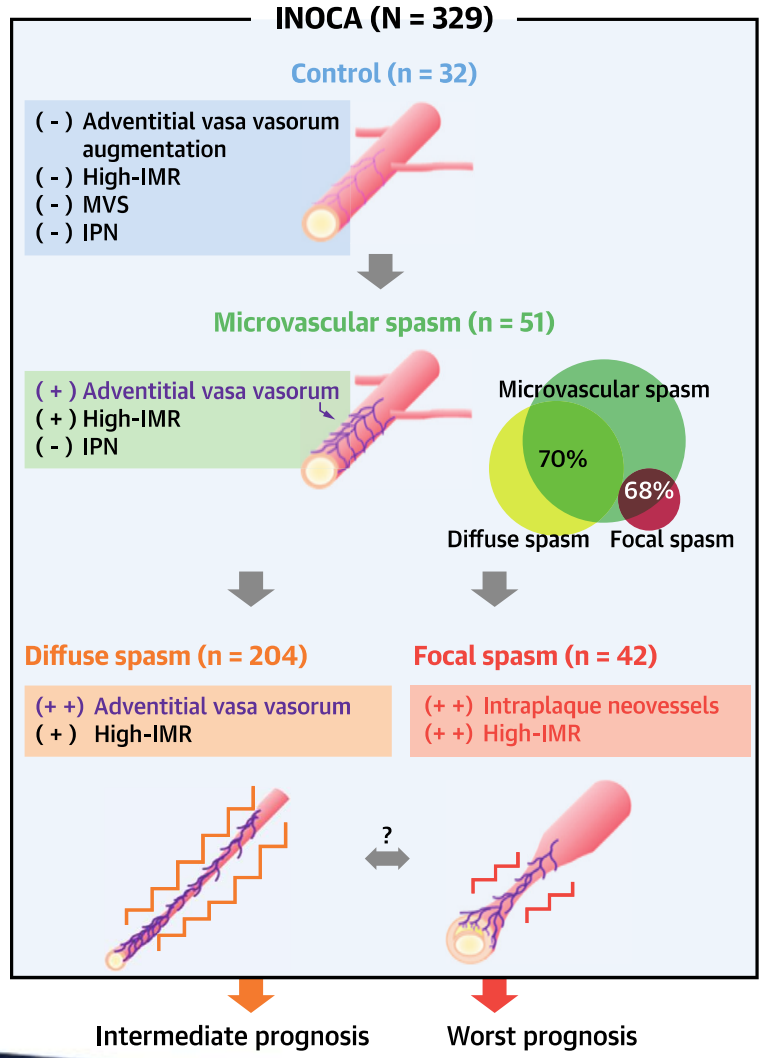


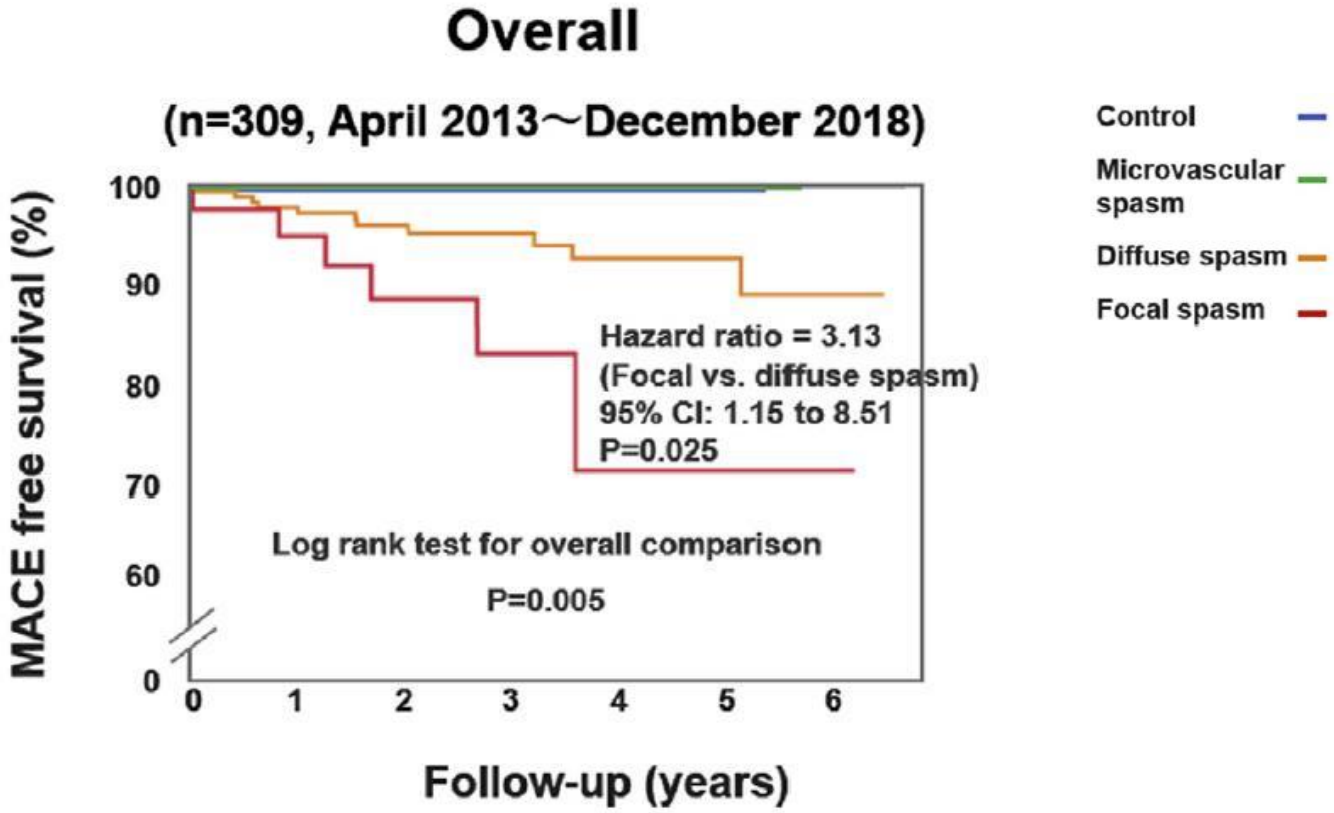




Seitz A et al. J Am Coll Cardiol Intv. 2020 Aug, 13 (16) 1865–1876

Coronary morphology by OCT and outcomes in focal vs diffuse spasm





Nishimiya K et al. JACC Interventions. 2021;14:606–18

Conclusions

- In patients with no obstructive CAD, half present with vasomotor abnormality - CMD or spasm
- CMD is more prevalent in women, but men are affected in significant proportion
- Prevalence of CMD is similar between methods and techniques used
- CMD is associated with increased risk of MACE, mortality and hospitalization, whereas spasm has more hospitalization and repeat angiograms but lower MACE and death rates

EMORY UNIVERSITY

What we could do for coronary microvascular disease?

Timothy D. Henry, MD

Medical Director, The Carl and Edyth Lindner Center for Research and Education
The Carl and Edyth Lindner Family Distinguished Chair in Clinical Research
Director of Programmatic and Network Development

International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches (ISCHEMIA):

Primary Report of Clinical Outcomes

Funded by the National Heart, Lung and Blood Institute

Judith S. Hochman, MD

NYU School of Medicine

On behalf of the ISCHEMIA Research Group