Evolving Progress of Cardiovascular Imaging

Redefining its Role in Biomedical Research and Clinical Practice

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- Research grant from Spectrum Dynamics
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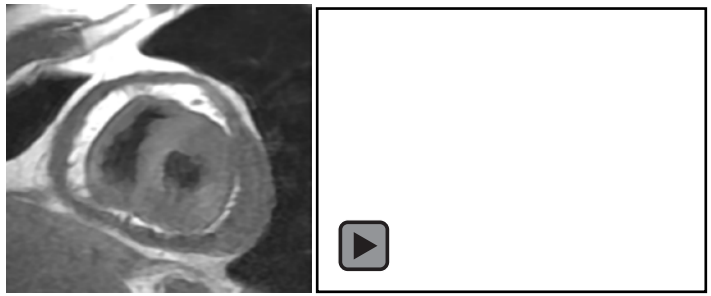
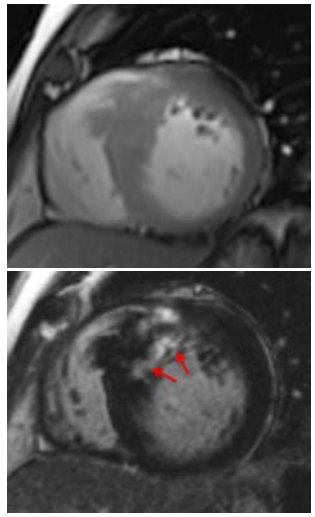
The increasing power of imaging in diagnosis and management of CV disease

- Non-invasive
- High resolution
- Targeted
- Quantitative

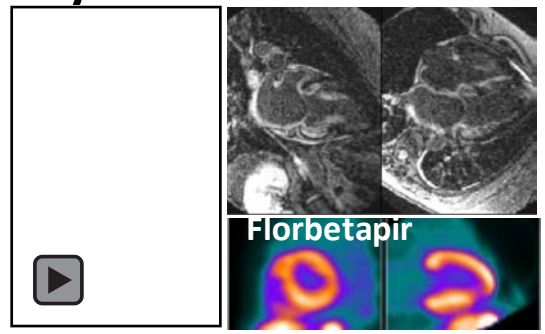
Pericardial disease



HCM

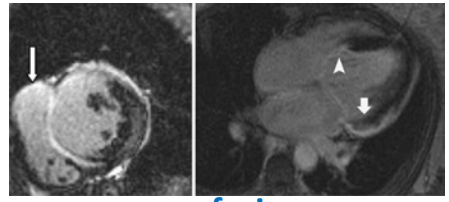


Amyloidosis



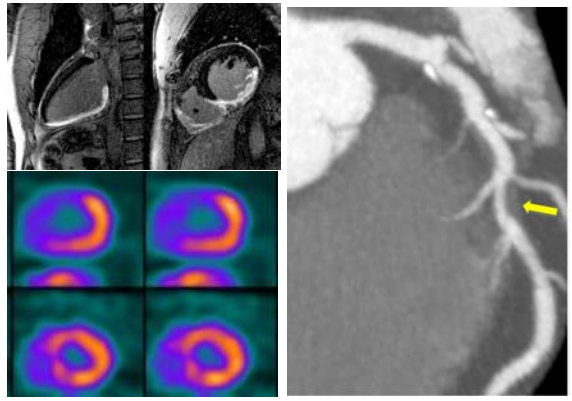
PAH

Sarcoidosis



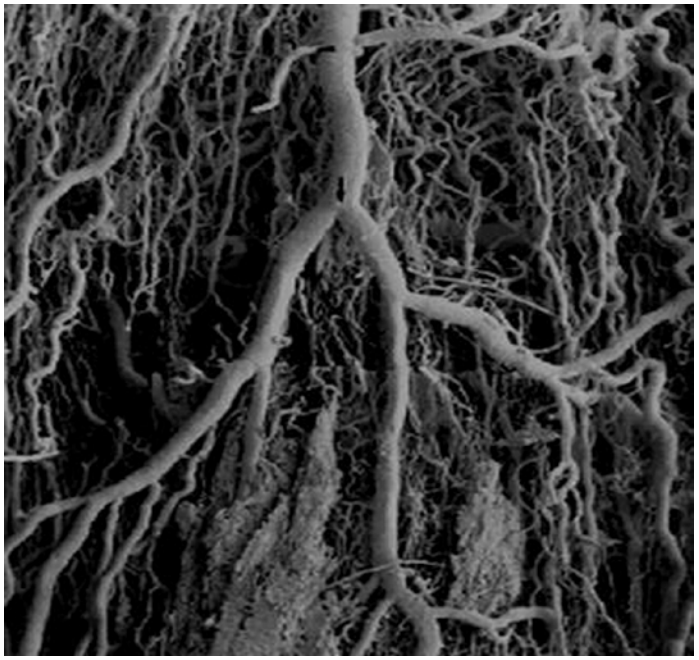
Vasculitis

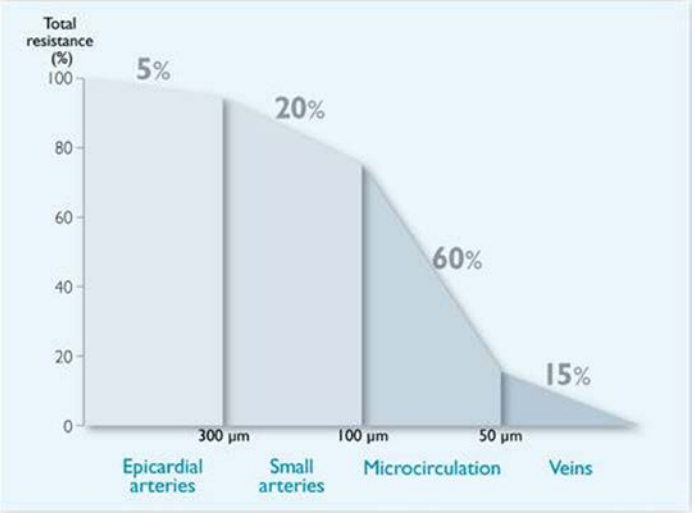
CAD



Evolving Progress of Imaging Across the Continuum of Biomedical Research and Clinical Practice

Coronary microvasculature disease





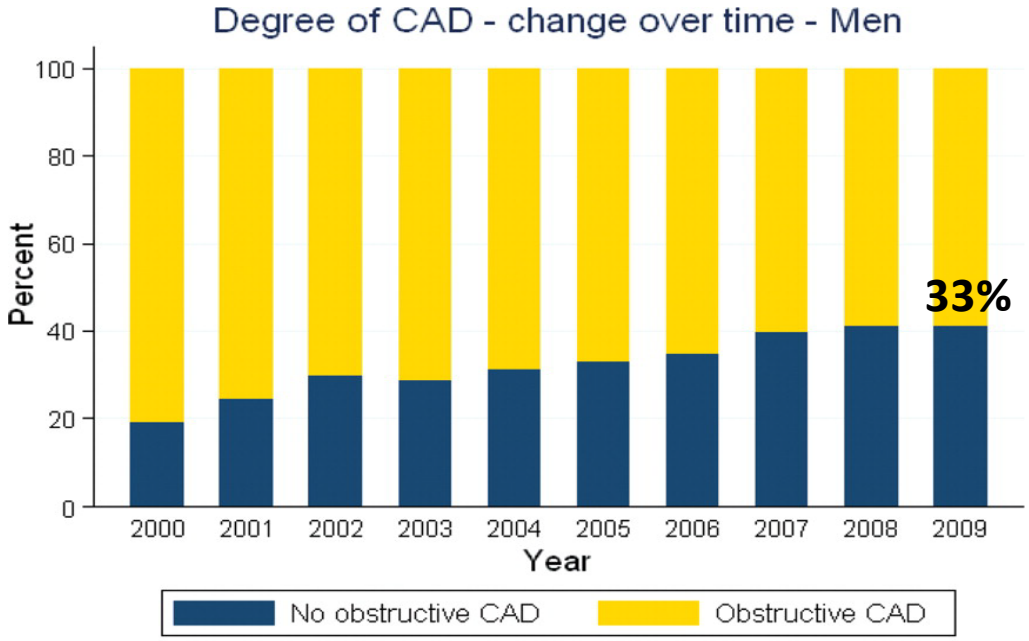
CMD is implicated in the pathophysiology and manifestations of a broad spectrum of CV disease

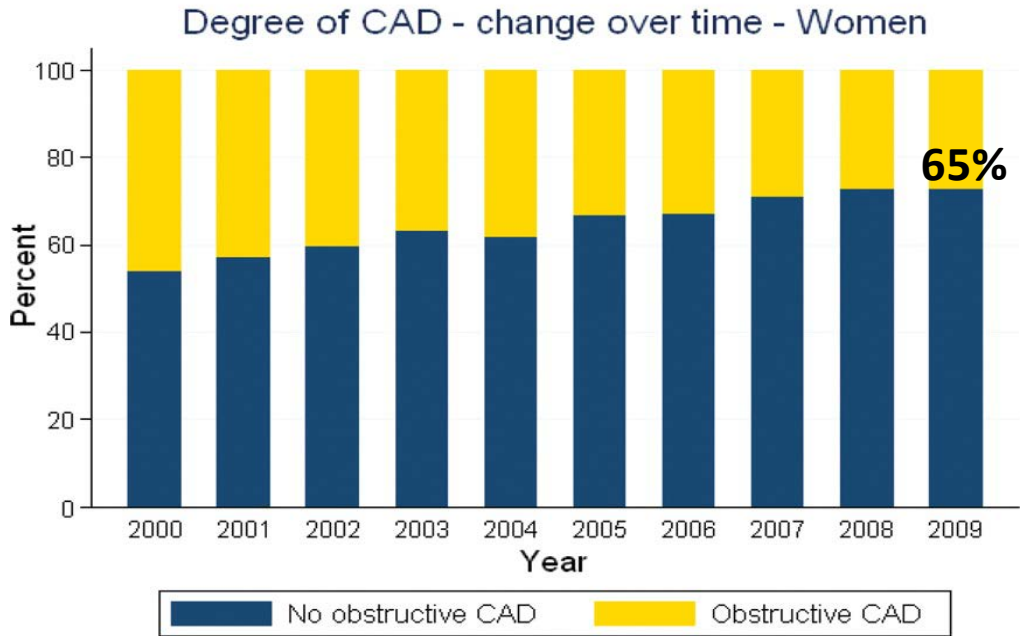
- Ischemic heart disease
- HFpEF
- Valvular heart disease
- Cardiomyopathies

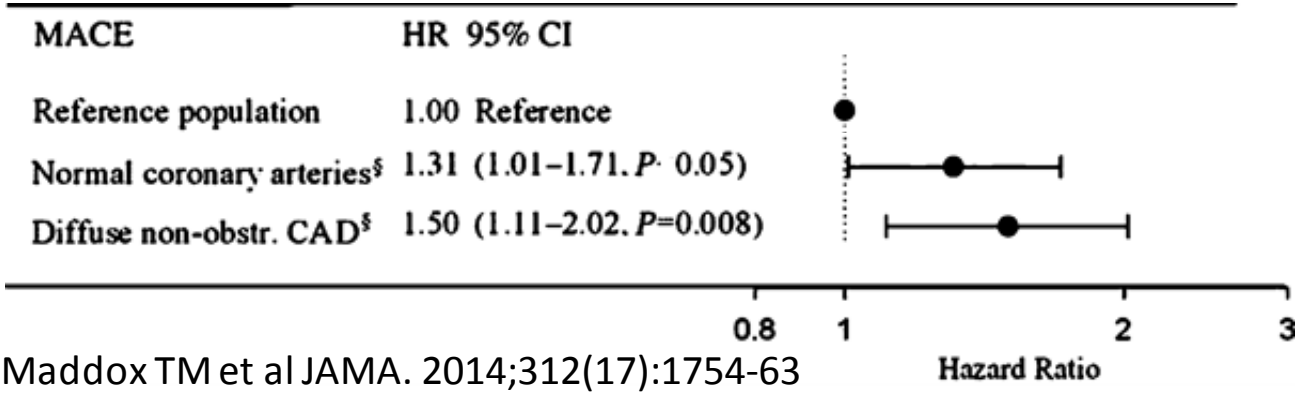
Source: Chilian WM. J Nucl Cardiol 2001;8:599-605

The absence of obstructive stenosis fails to explain symptoms or risk in many patients with stable chest pain

11,223 patients referred for coronary angiography between 1998–2009



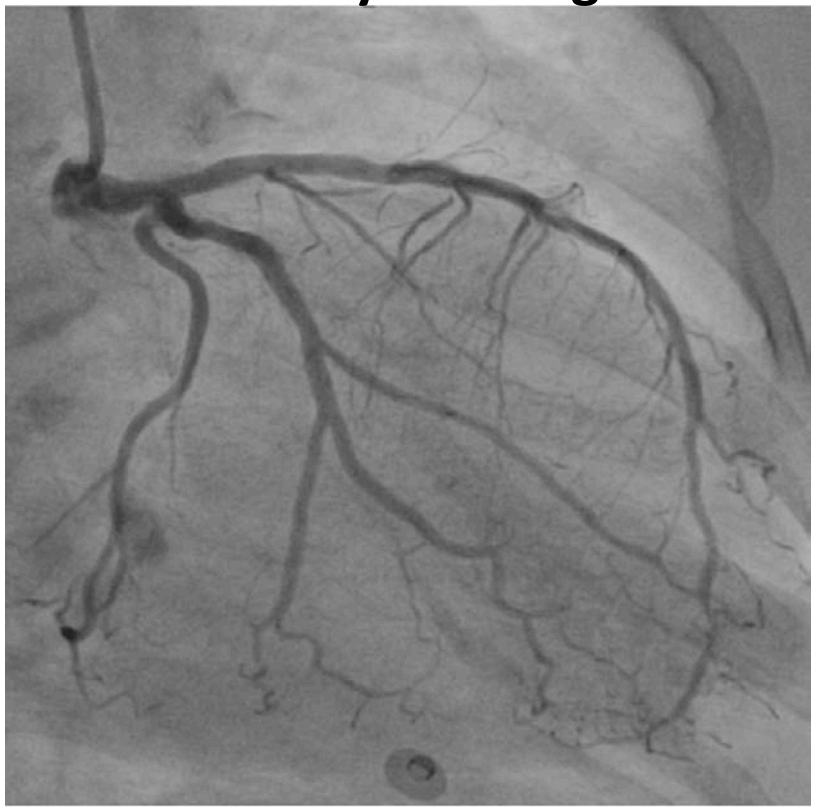




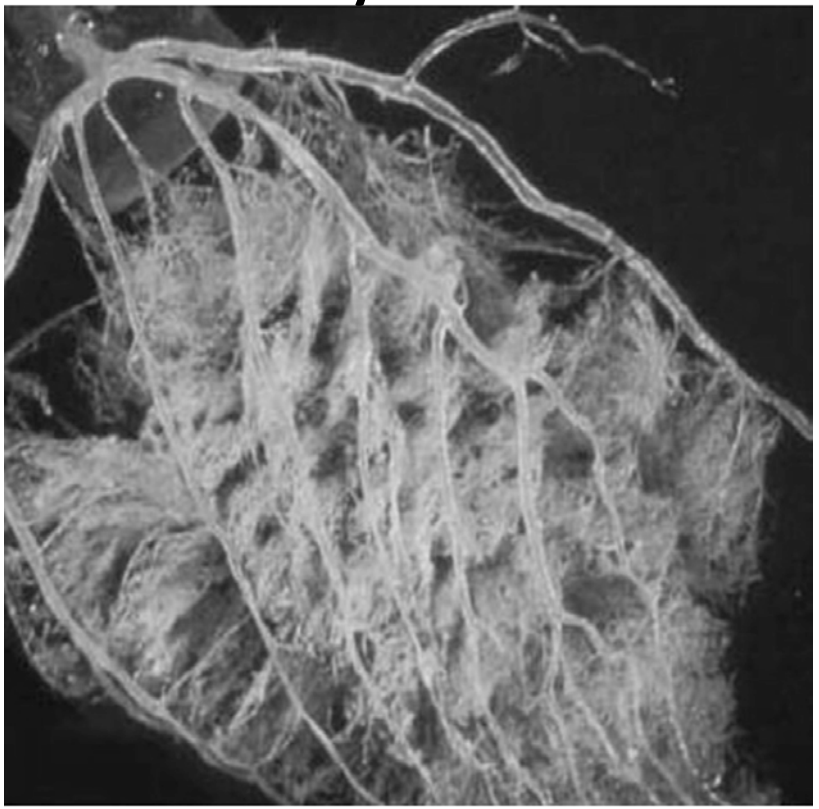
Sources: Jespersen L et al. EHJ 2012;33:734-44; Maddox TM et al JAMA. 2014;312(17):1754-63

We can no longer assume that a normal coronary angiogram implies a normal coronary vasculature

Coronary Arteriogram



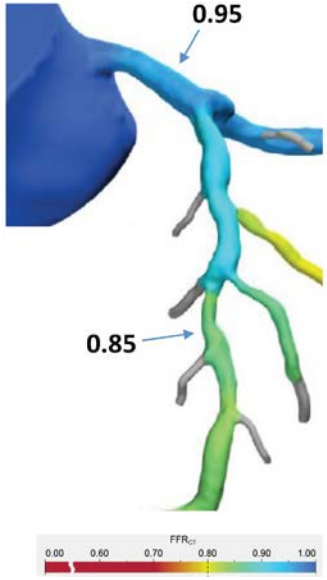
Coronary Vasculature

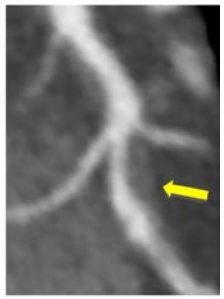


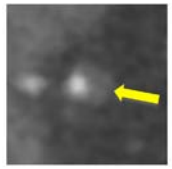
Courtesy of M. Gibson

Imaging based phenotyping of CMD in atherosclerosis

atherosclerosis

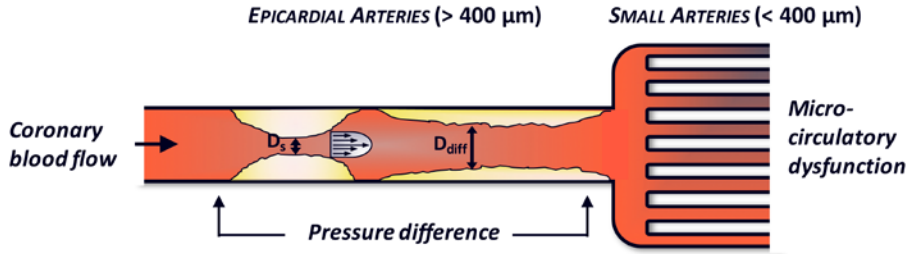






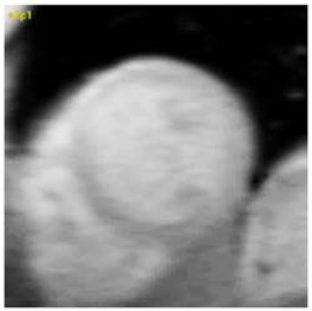
microvascular dysfunction

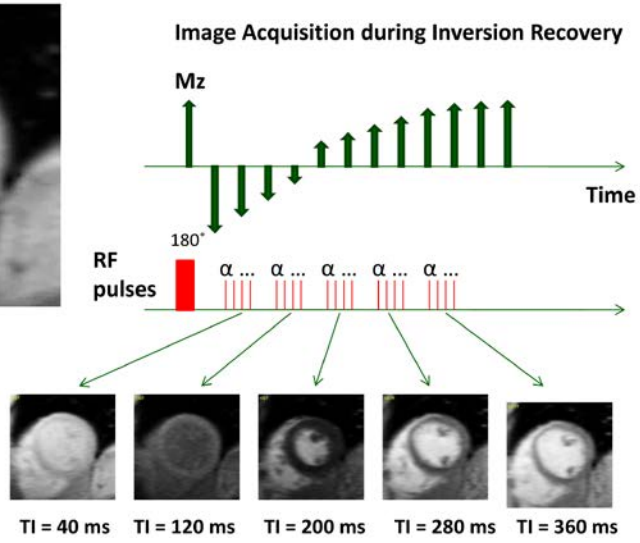
➔ Measures *integrated* hemodynamic effects of epicardial CAD, diffuse atherosclerosis and vessel remodeling, and micro-circulatory dysfunction (*endothelial dysfunction, obstruction, and rarefaction*) on myocardial tissue perfusion



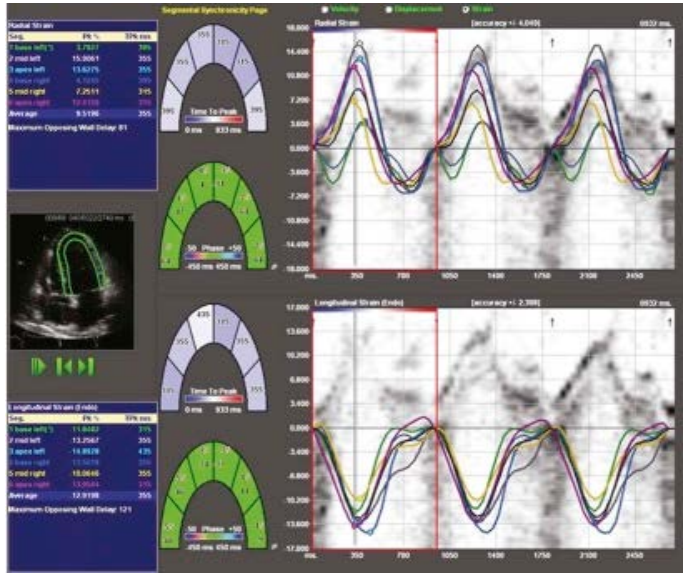
$$CFR = \frac{MBF_{\text{peak hyperemia}}}{MBF_{\text{rest}}}$$

myocardial fibrosis





diastolic dysfunction



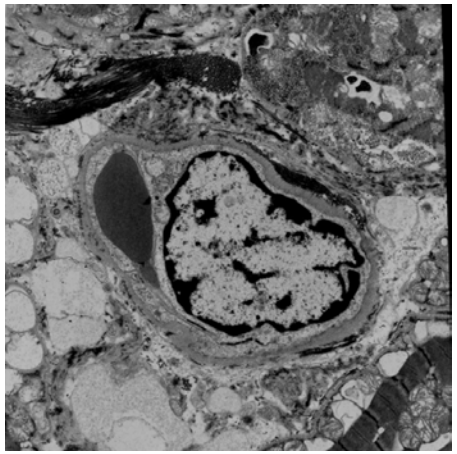
New developments about CMD in atherosclerosis

1. **Definition, pathophysiology and clinical presentation**
2. Diagnosis and prevalence
3. A marker of ischemia and clinical risk
4. A target for therapy?

Definition and Pathophysiology of CMD

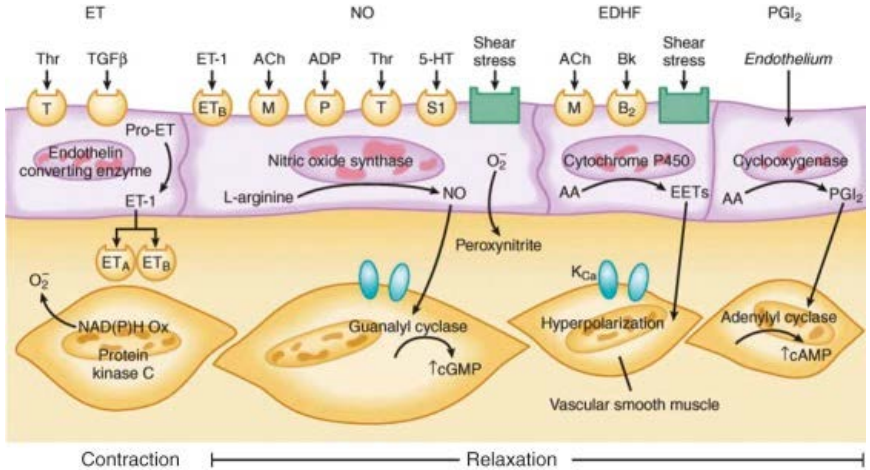
→ Coronary microvascular disease is heart disease that affects the structure and function of the small coronary artery vessels.

Structural abnormalities



- Arteriolar remodeling (SMC thickening)
- ↓ capillary diameter and density (rarefaction)
- ↑ endothelial swelling and capillary obstruction

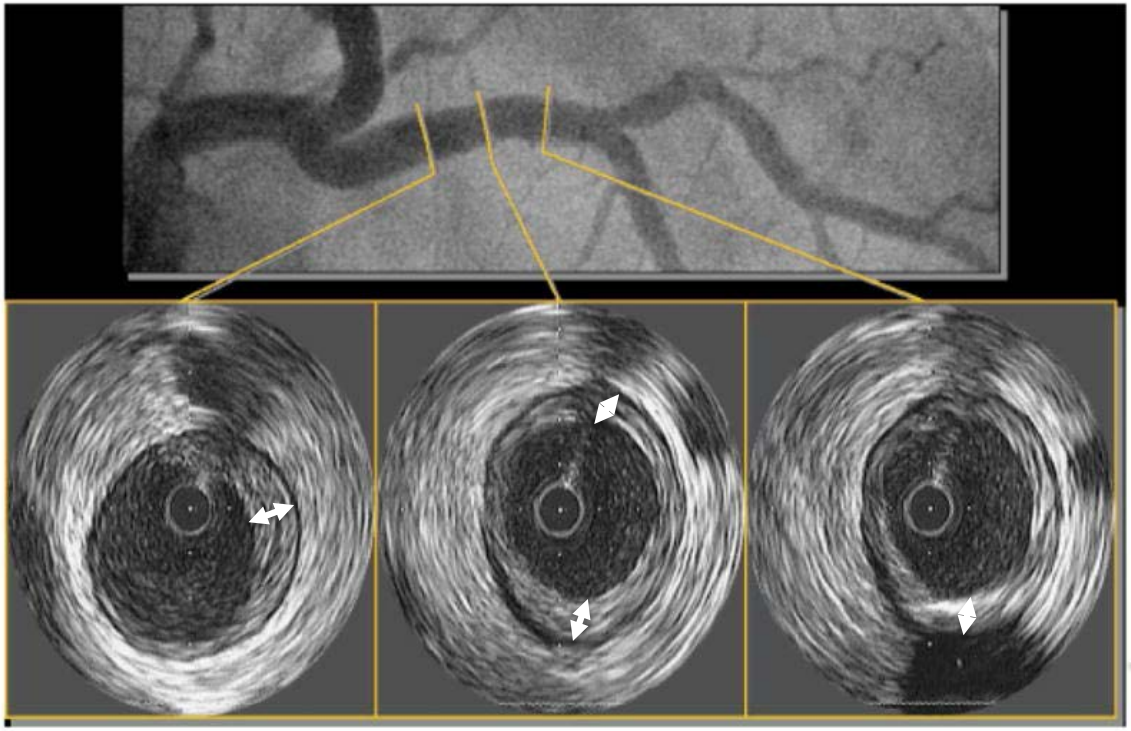
Functional abnormalities

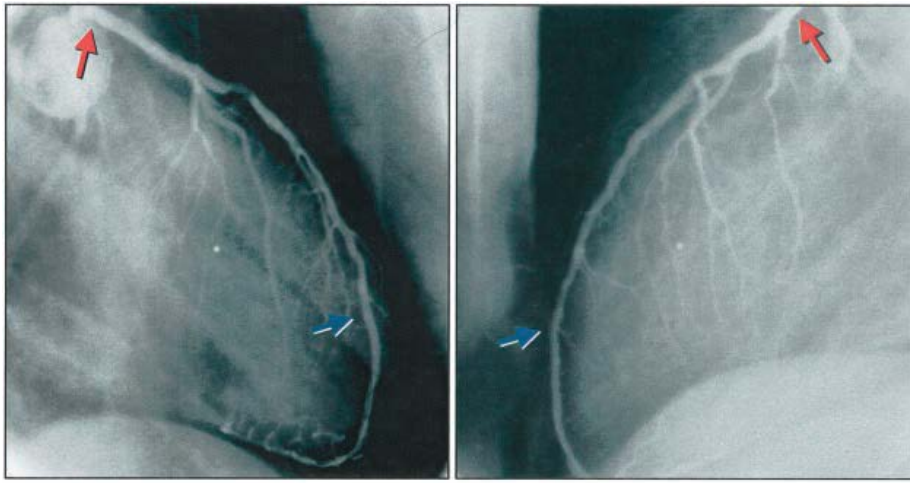


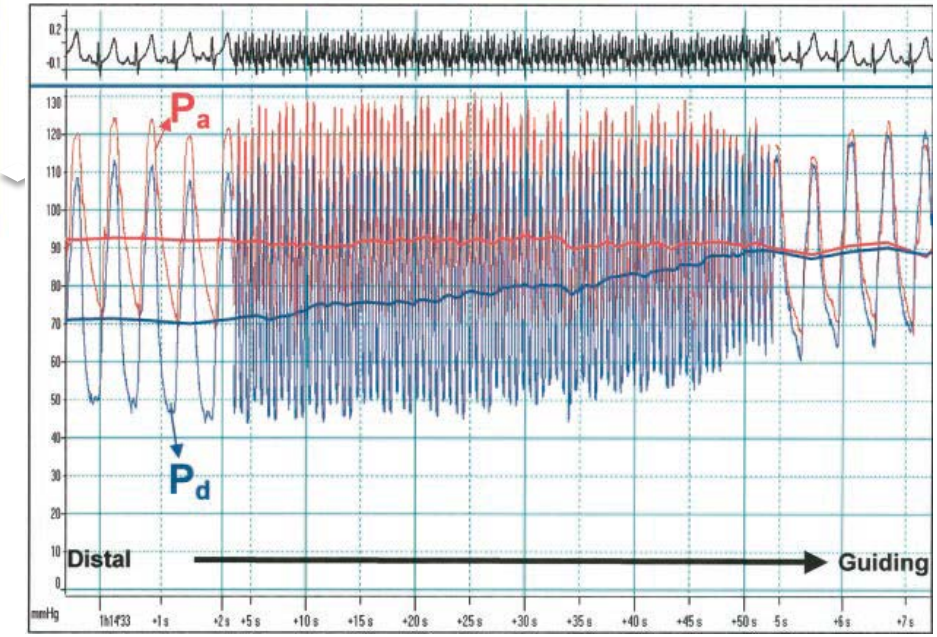
- Vascular EC dysfunction
- SMC dysfunction
- MCV spasm

Sources: Asghar O, et al. Clinical Science 2009;116:741–60; Amann K, et al. JASN 1998;9:1018-22; Tanaka M, et al. Circulation. 1987;75:1130–9; Ong P, et al. JACC 2012;59:655-62

Diffuse Atherosclerosis: A common finding in patients with chest pain without obstructive stenosis







Sources: Khuddus MA, et al. J Interv Cardiol 2010;23(6):511-9; De Bruyne B, et al. Circulation 2001;104:2401–6

CMD - Clinical Manifestations

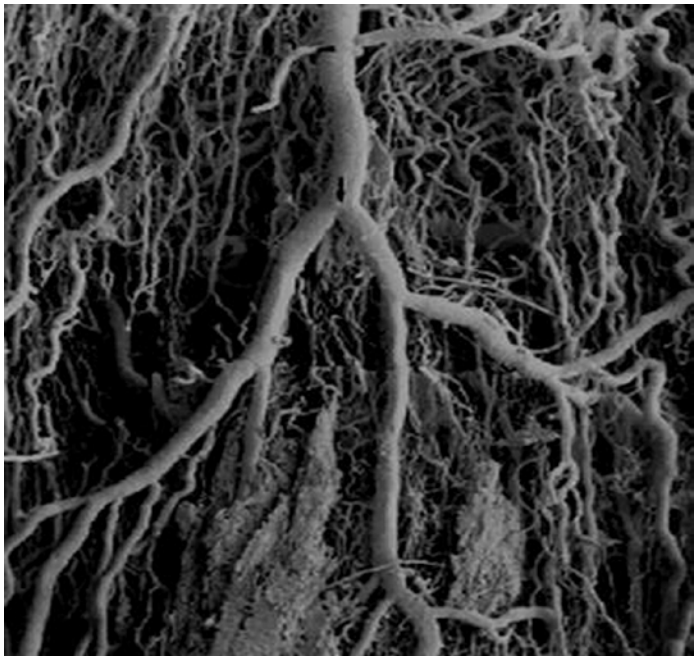
- Asymptomatic
- Angina pectoris
- Dyspnea
- Heart failure

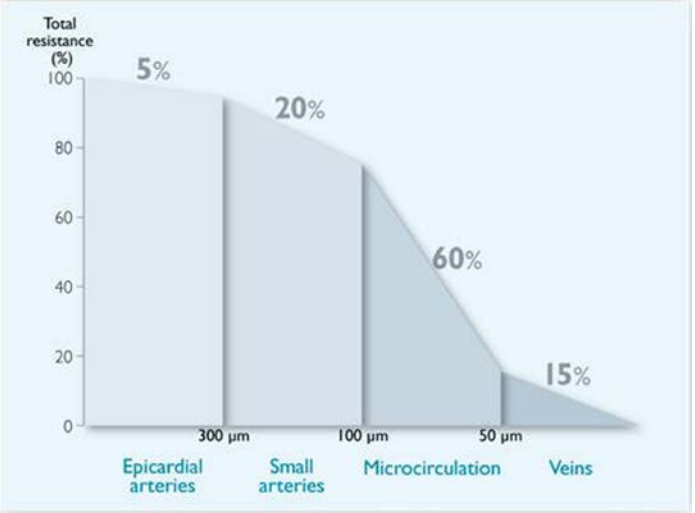
Source: Crea, Camici, Bairey Merz. EHJ 2014;35: 1101–11

New developments about CMD in atherosclerosis

1. Definition, pathophysiology and clinical presentation
2. **Diagnosis and prevalence**
3. A marker of ischemia and clinical risk
4. A target for therapy?

Diagnosis of CMD



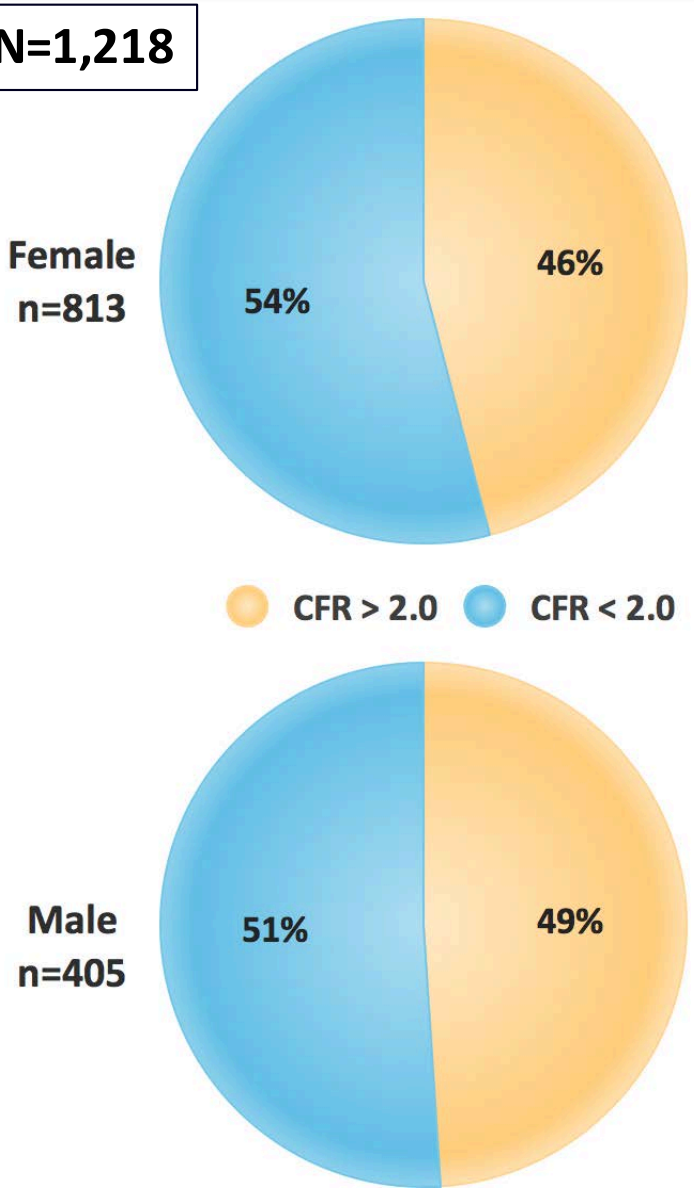


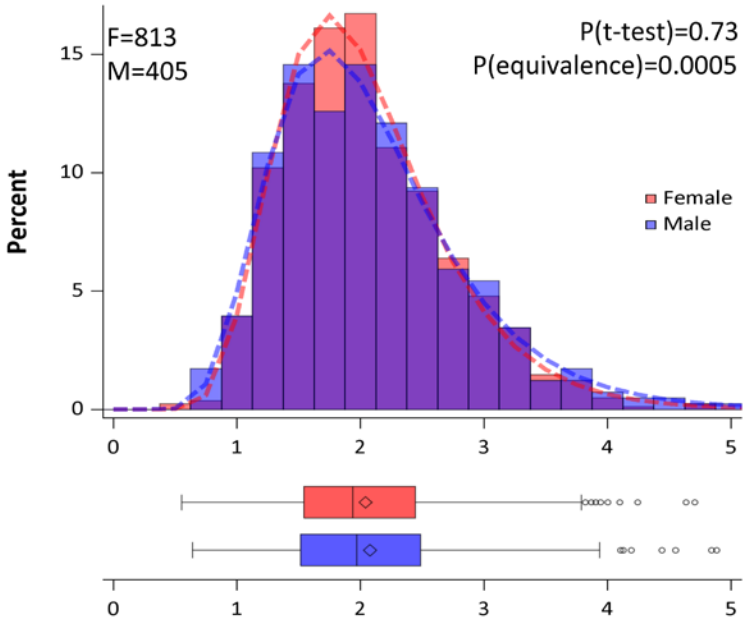
1. Symptoms (w/o obstructive CAD)
2. Signs of ischemia (ECG)
3. Direct measurement of coronary flow (PET, CMR, Echo)

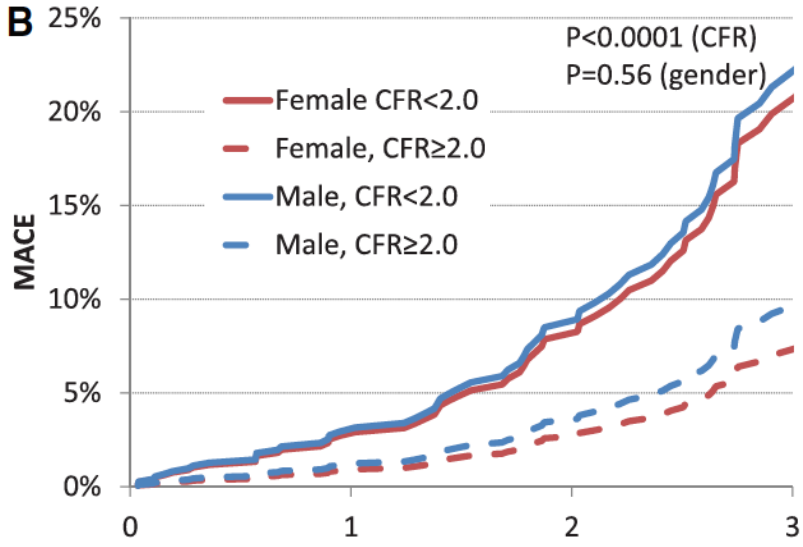
Source: Chilian WM. J Nucl Cardiol 2001;8:599-605

High prevalence of CMD in symptomatic patients without obstructive CAD

N=1,218

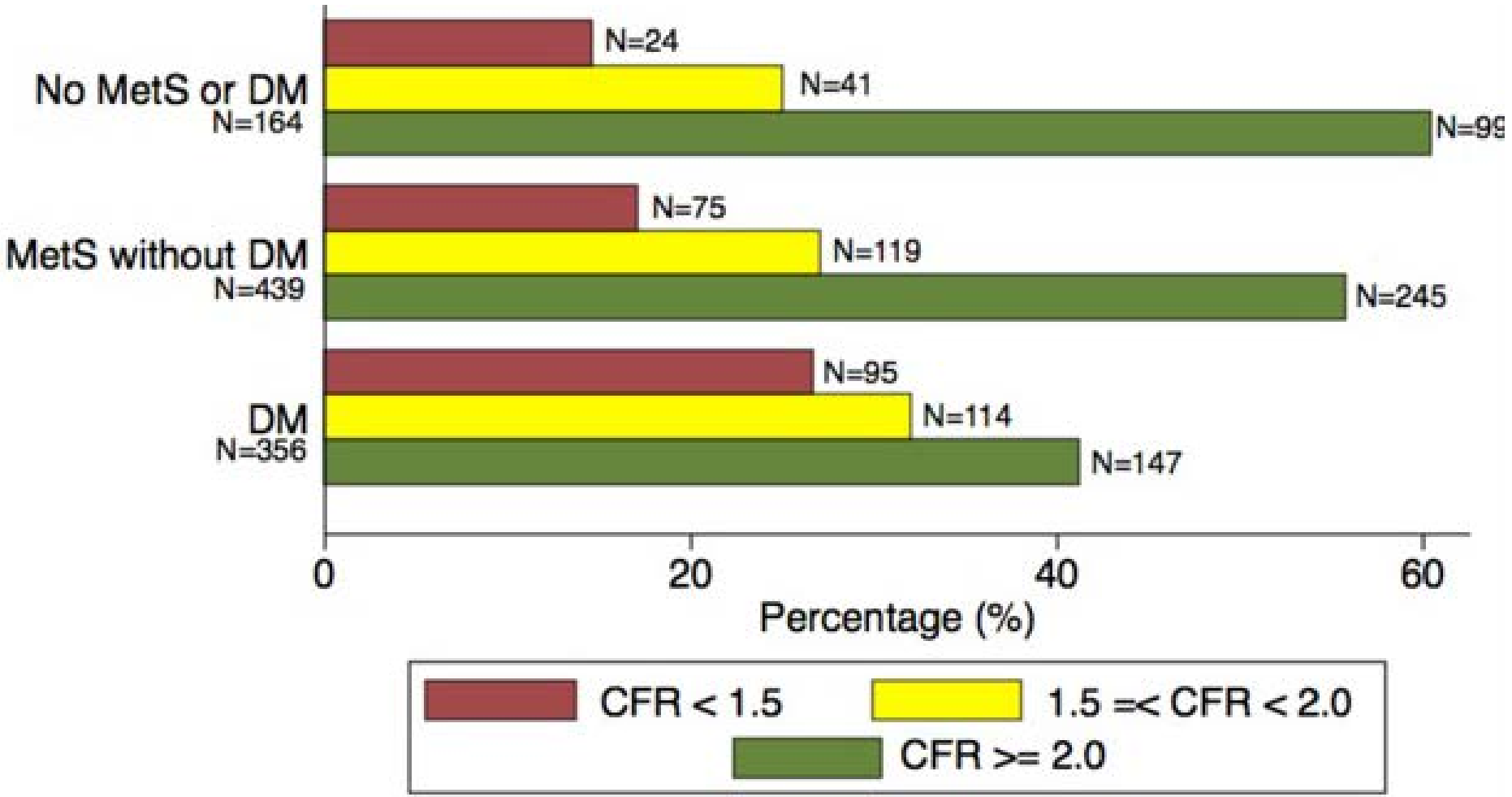






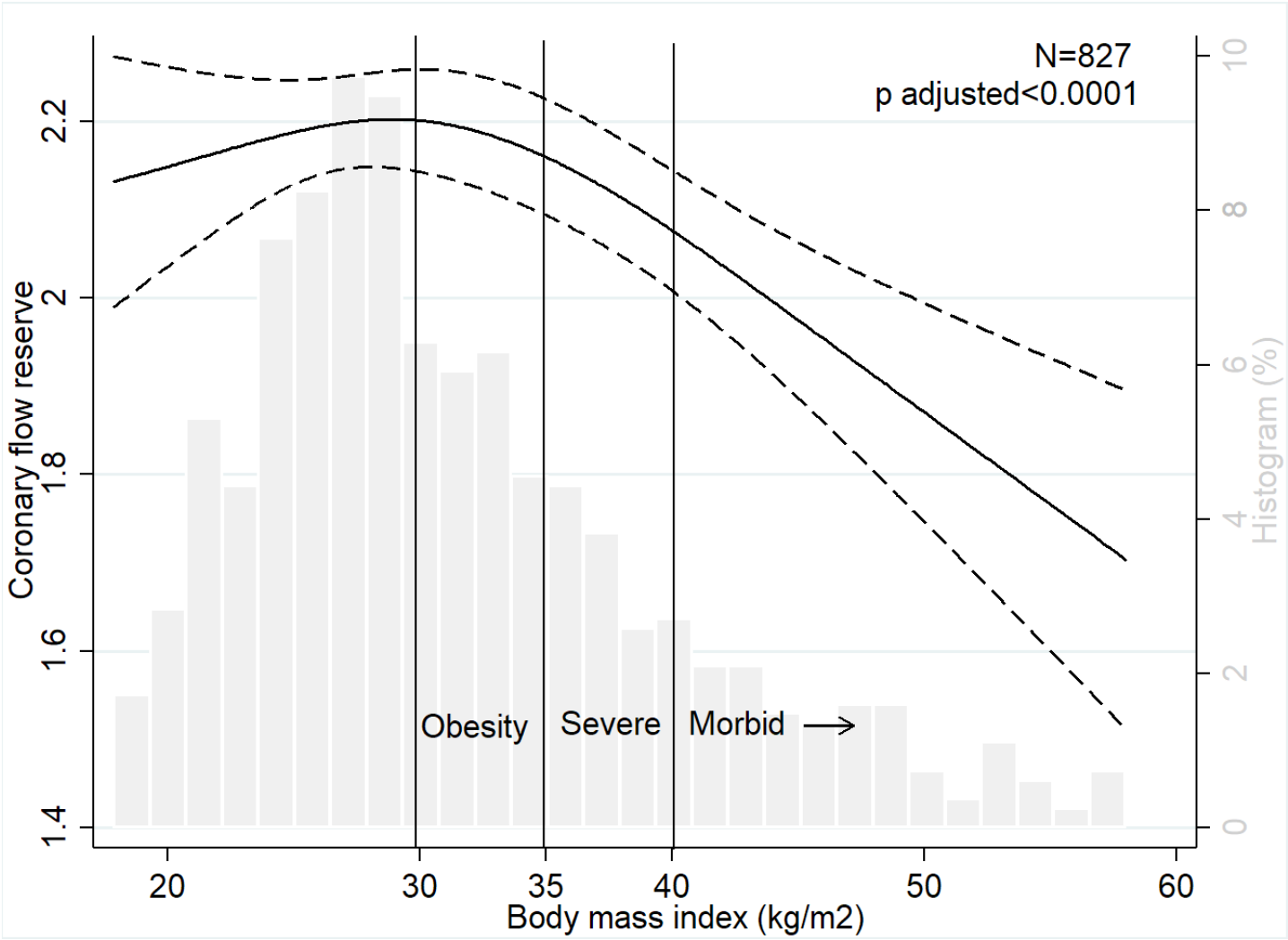
Source: Murthy V…Di Carli M. Circulation 2014;129:2518-2527

Prevalence of CMD across the spectrum of cardiometabolic risk



Source: Osborne M…Di Carli M. JACC 2017, Dec 5;70(22):2835-37

High prevalence of CMD in obese patients

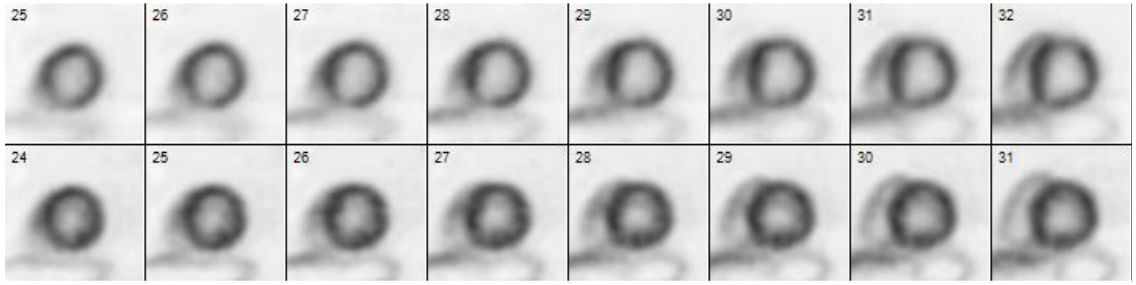


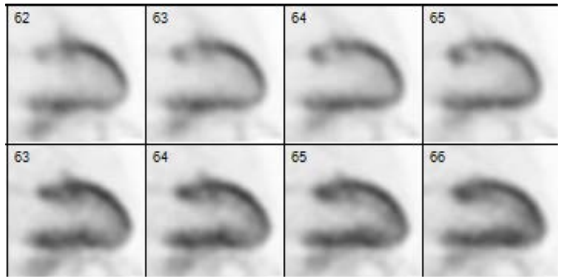
Source: Bajaj N… Di Carli M, Taqueti V. 2017, under review

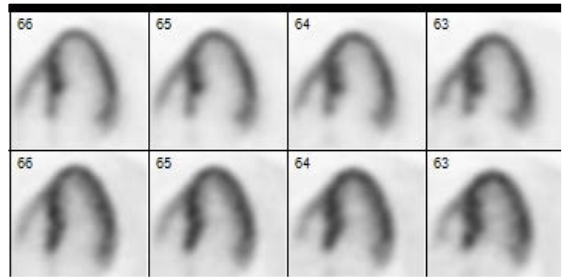
New developments about CMD in atherosclerosis

1. Definition, pathophysiology and clinical presentation
2. Diagnosis and prevalence
3. **A marker of ischemia and clinical risk**
4. A target for therapy?

51 yo M with CAD, recent STEMI and DES to pLAD in 2/16, HTN, Type 1 DM, diabetic nephropathy s/p renal transplant in 2008, p/w several hours of chest pain and dyspnea.

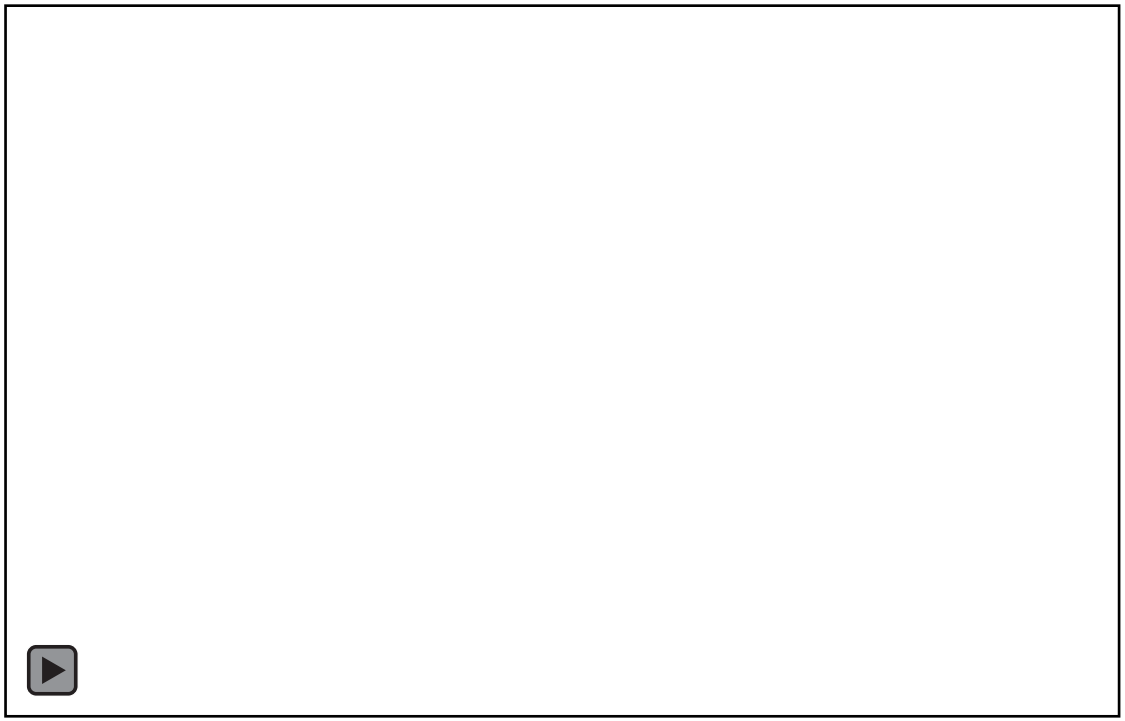


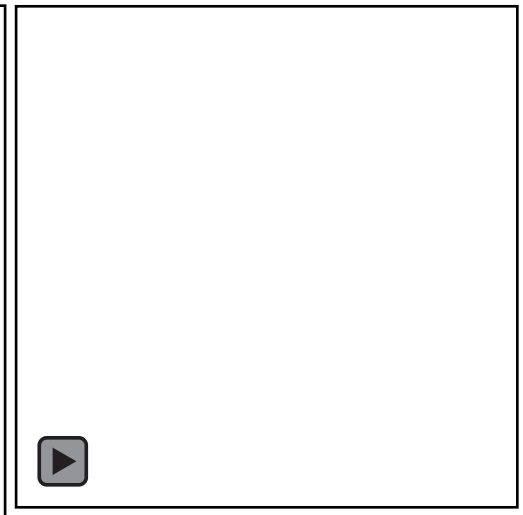


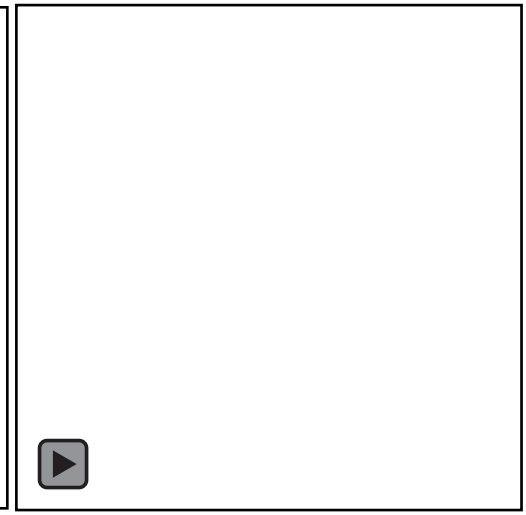


Quantitative myocardial blood flow and CFR

	Rest	Stress	CFR
LAD	0.82	1.23	1.50
LCX	0.83	1.34	1.62
RCA	0.81	1.13	1.39
Global LV	0.82	1.23	1.50

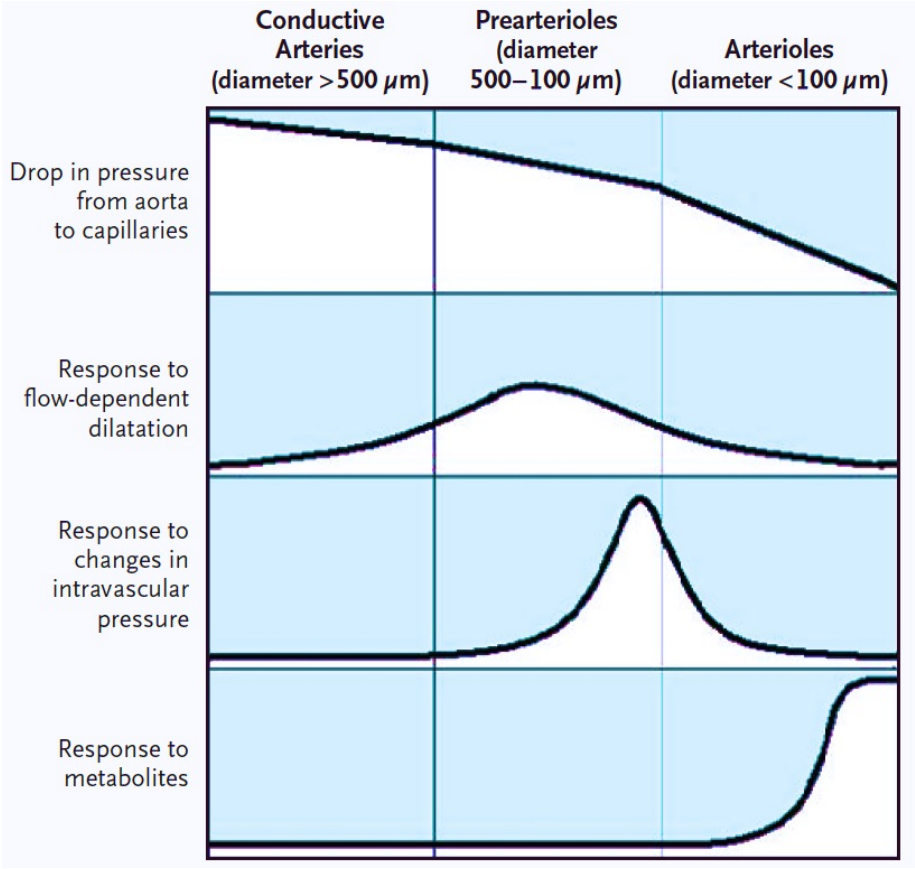




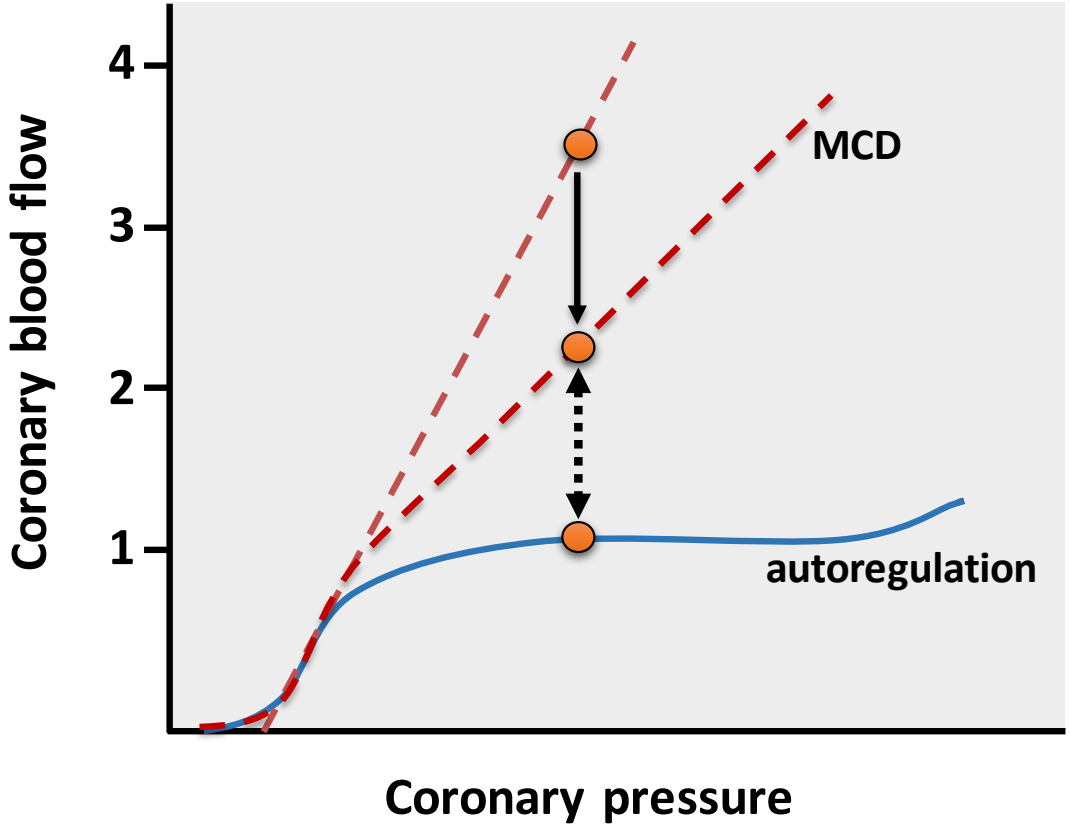


RCA FFR=0.78

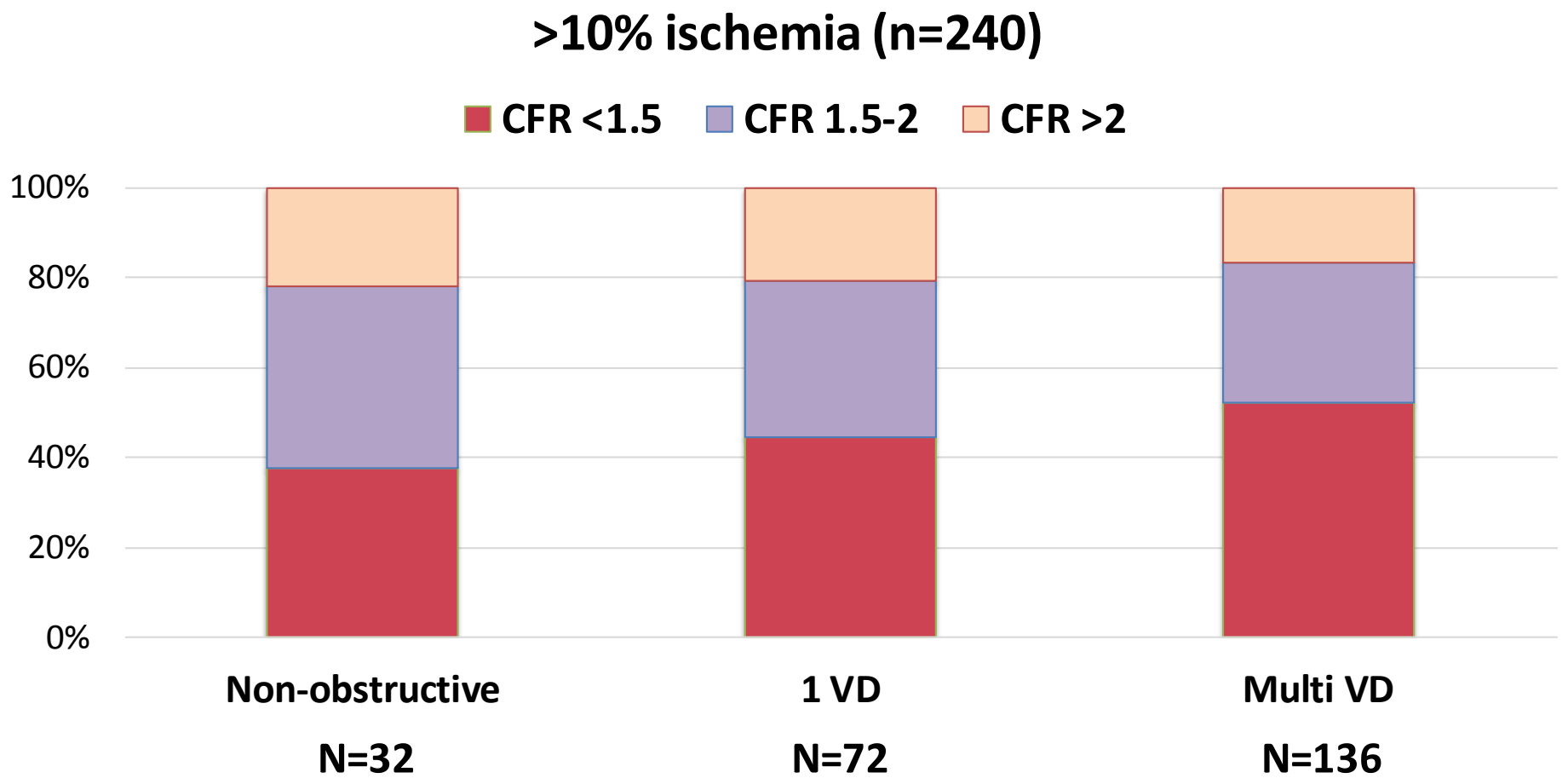
CMD affects the severity of myocardial ischemia even in the absence of epicardial stenosis



Source: Camici P, et al. NEJM 2007;356:830-40

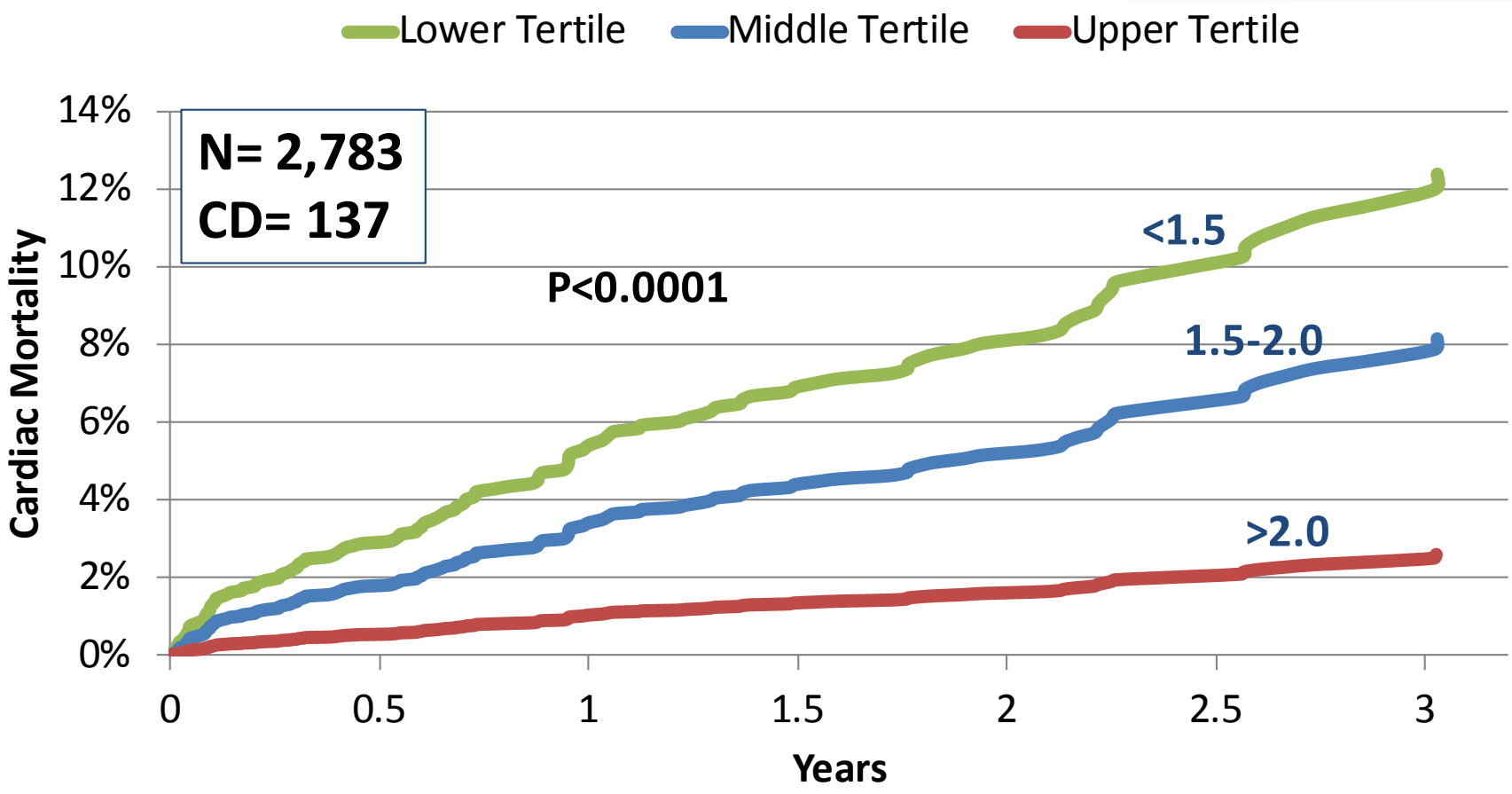


Severe ischemia is only partially accounted for by the extent/severity of angiographic stenosis



Source: Christensen T…Di Carli M. 2017, under review

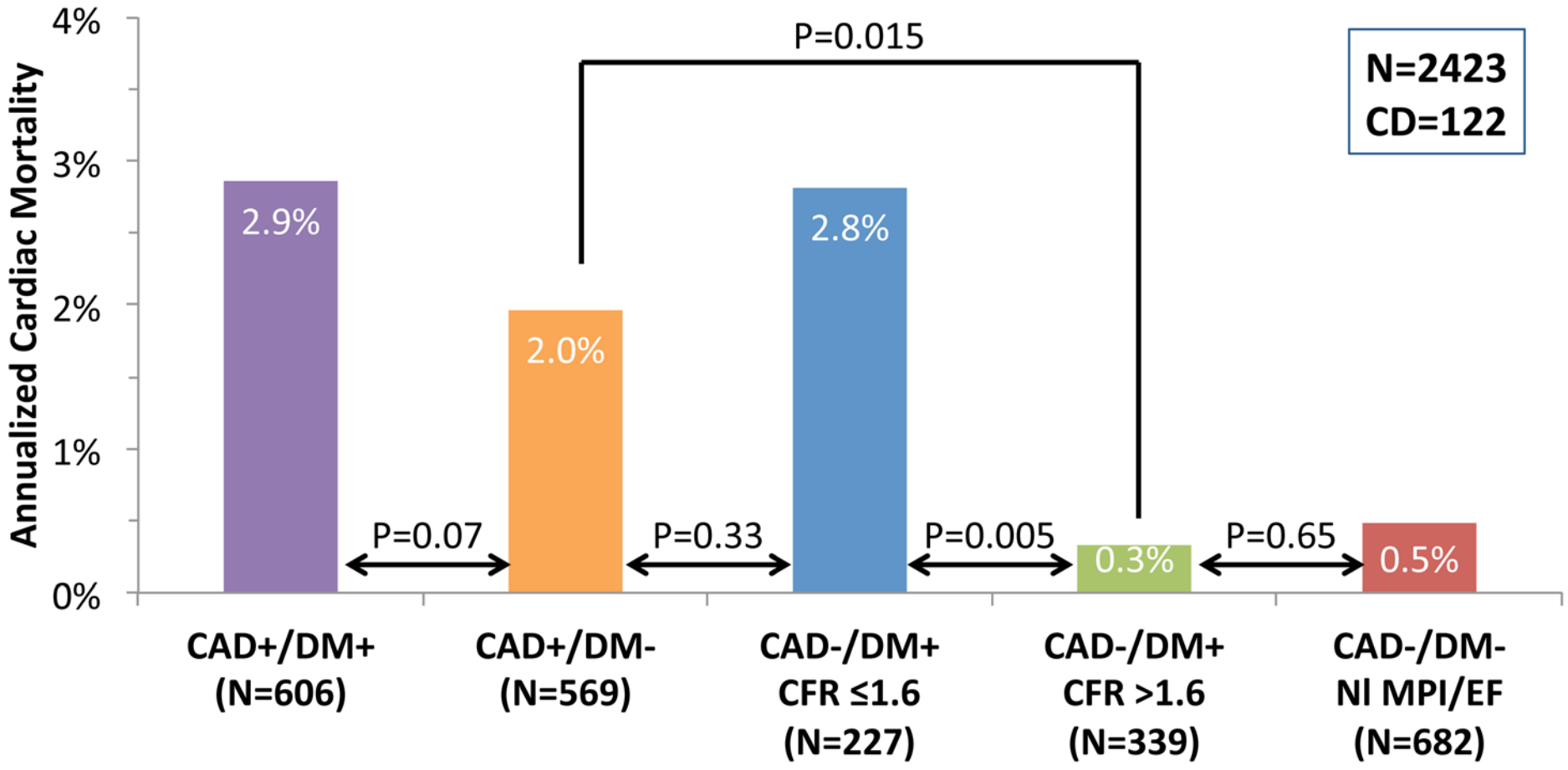
Adjusted cardiac mortality by severity of CFR impairment



Lower vs. Upper	**HR 5.6 [2.5-12.4]**	**p<0.0001**
Middle vs. Upper	**HR 3.4 [1.5-7.7]**	**p=0.003**

Sources: Murthy VL, et al. Circulation. 2011;124:2215-24; Herzog et al. JACC 2009;54:150; Ziadi et al. JACC 2011;58:740; Fukushima et al. J Nucl Med 2011;52:726

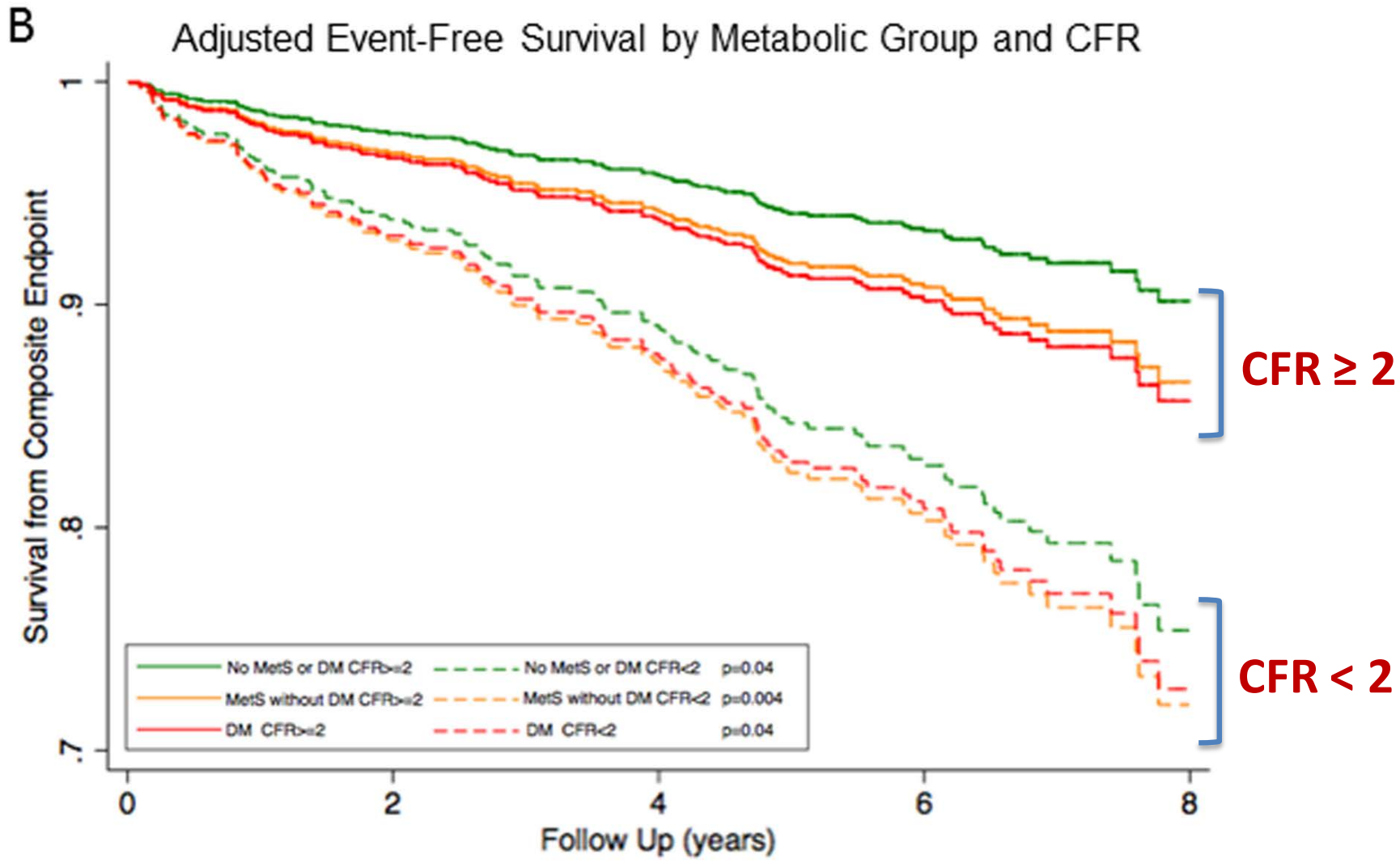
CFR Reclassifies Risk of Cardiac Death in Diabetics



***Adjusted for Duke score, ischemia + scar, rest LVEF and early revascularization**

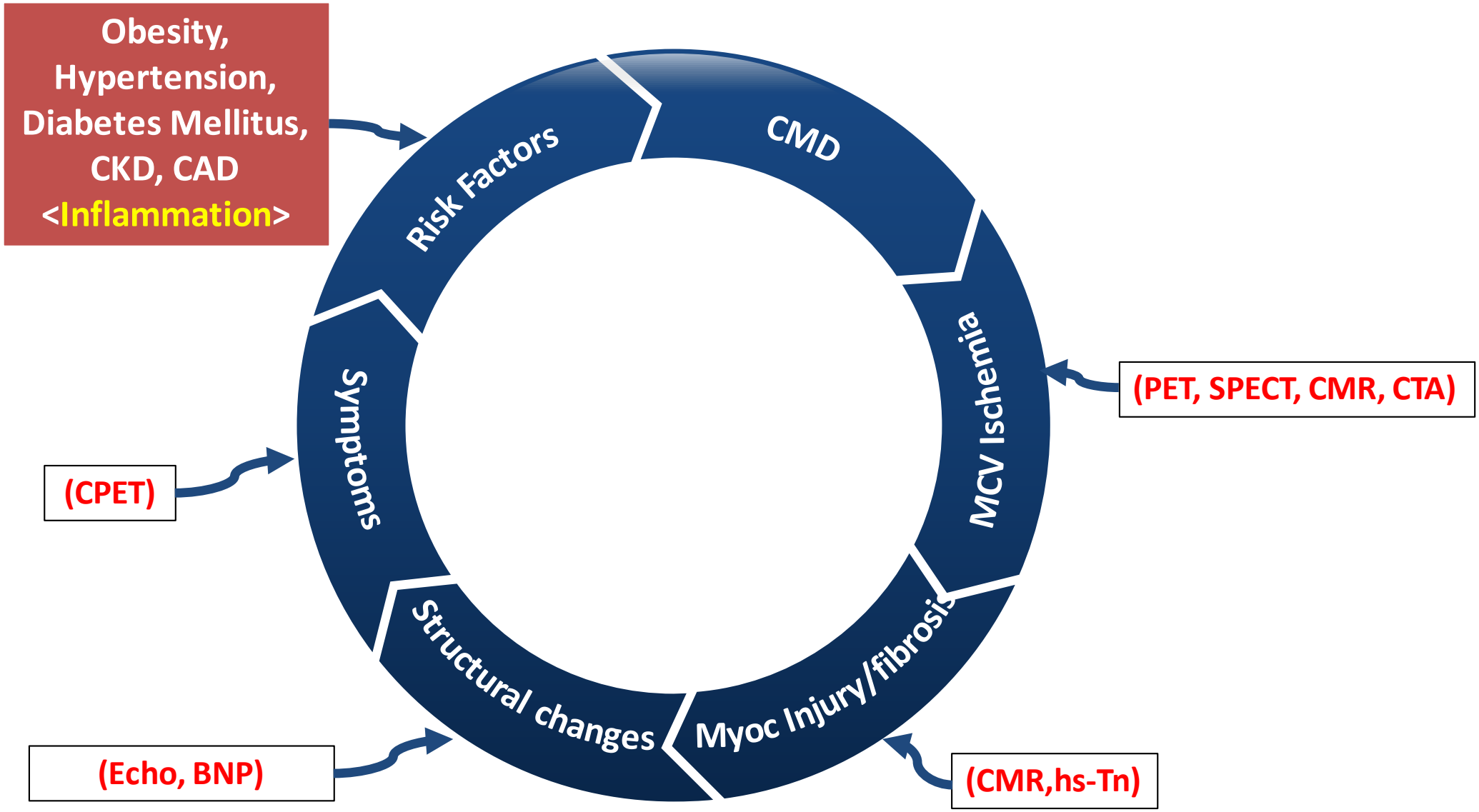
Source: Murthy VL…Di Carli M. Circulation. 2012;126:1858-1868

CMD and risk stratification across the spectrum of cardiometabolic risk



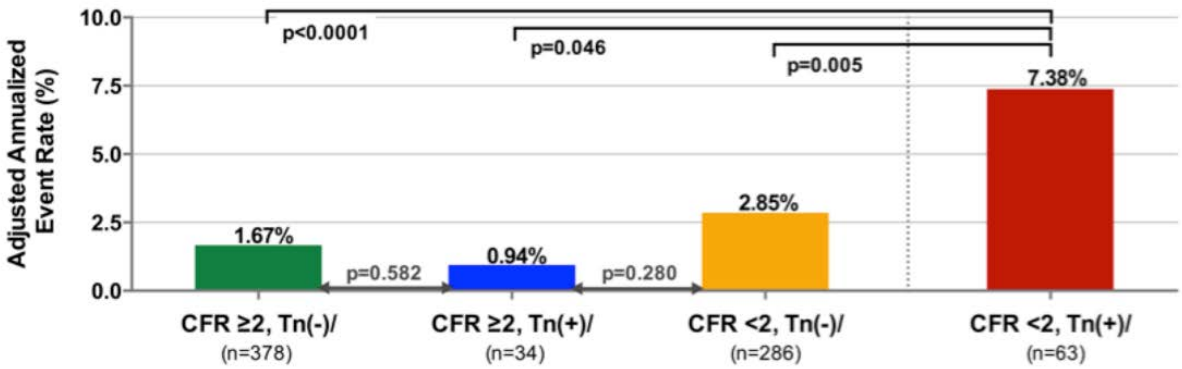
Source: Osborne M…Di Carli M. JACC 2017, Dec 5;70(22):2835-37

Proposed pathophysiologic link between CMD and clinical outcomes and role of imaging and serum biomarkers



Association between CMD, myocyte injury, and outcomes in patients w/o obstructive CAD

N=761



Annualized event rates adjusted for pretest clinical score, LVEF, and estimated glomerular filtration rate <60 mL.min^{-1}.1.73 m^{-2}.

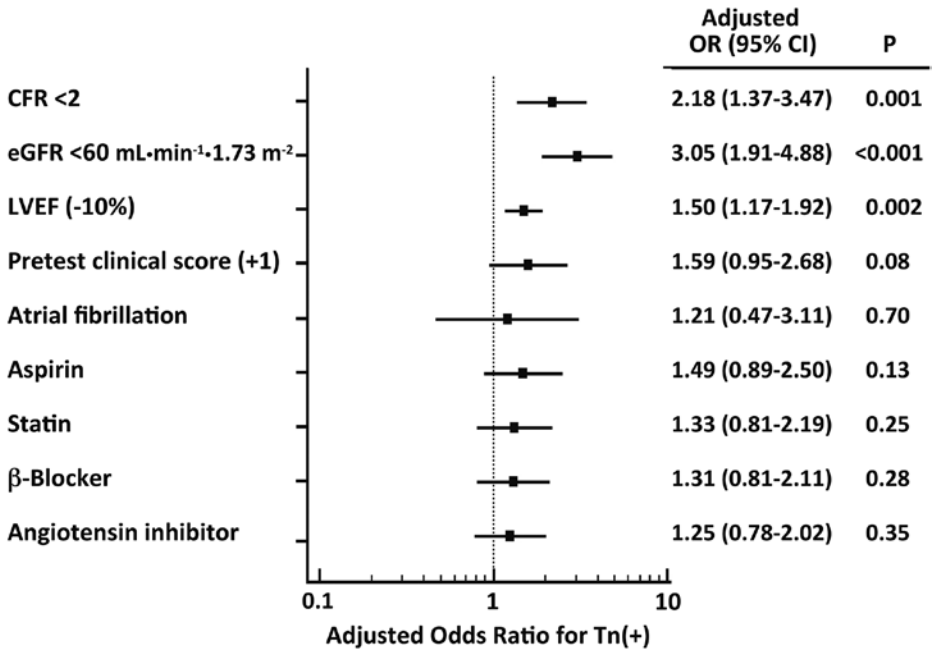


Table 2. Association Between CFR and Positive Troponin

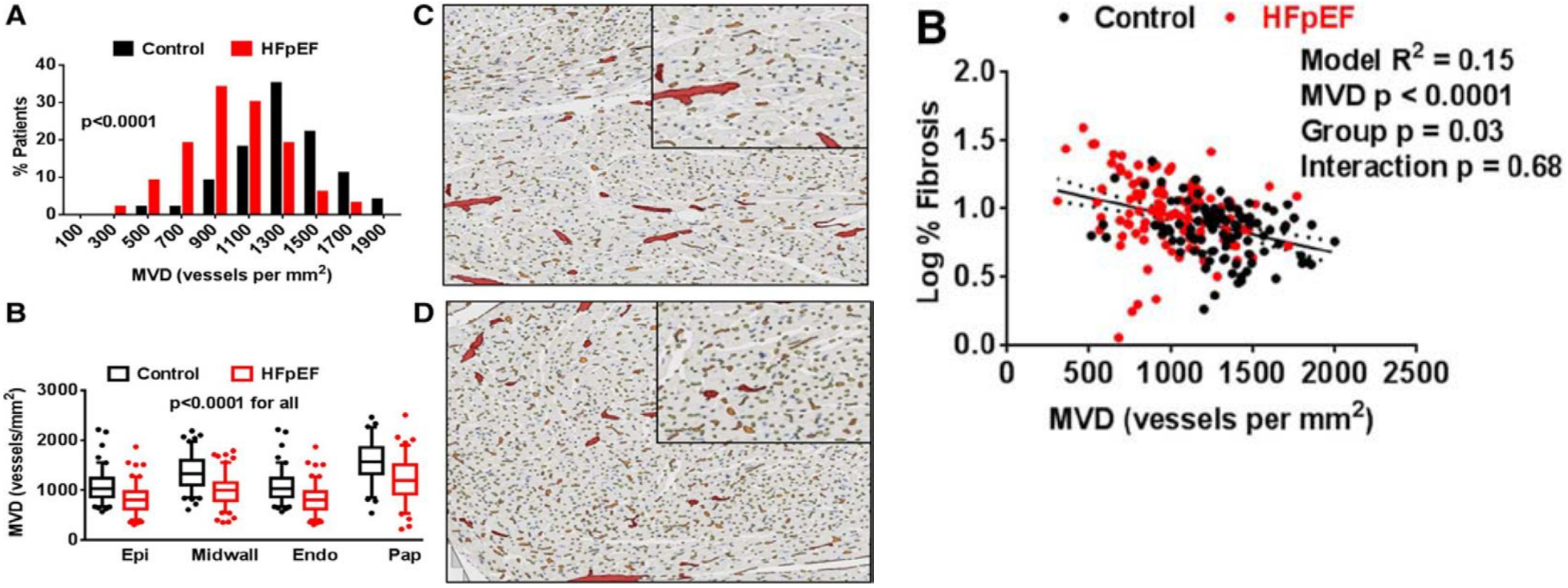
	Univariable Model		Multivariable Model*	
Covariate	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
CFR_{binary}†	2.45 (1.57–3.82)	<0.0001	2.18 (1.37–3.47)	0.001
$CFR_{continuous}$‡	1.80 (1.34–2.43)	0.0001	1.62 (1.19–2.20)	0.002

CFR indicates coronary flow reserve; CI, confidence interval; and OR, odds ratio.

*Adjusted for pretest clinical score, left ventricular ejection fraction, estimated glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2}, history of atrial fibrillation, and use of aspirin, β-blocker, statin, or angiotensin inhibitor.

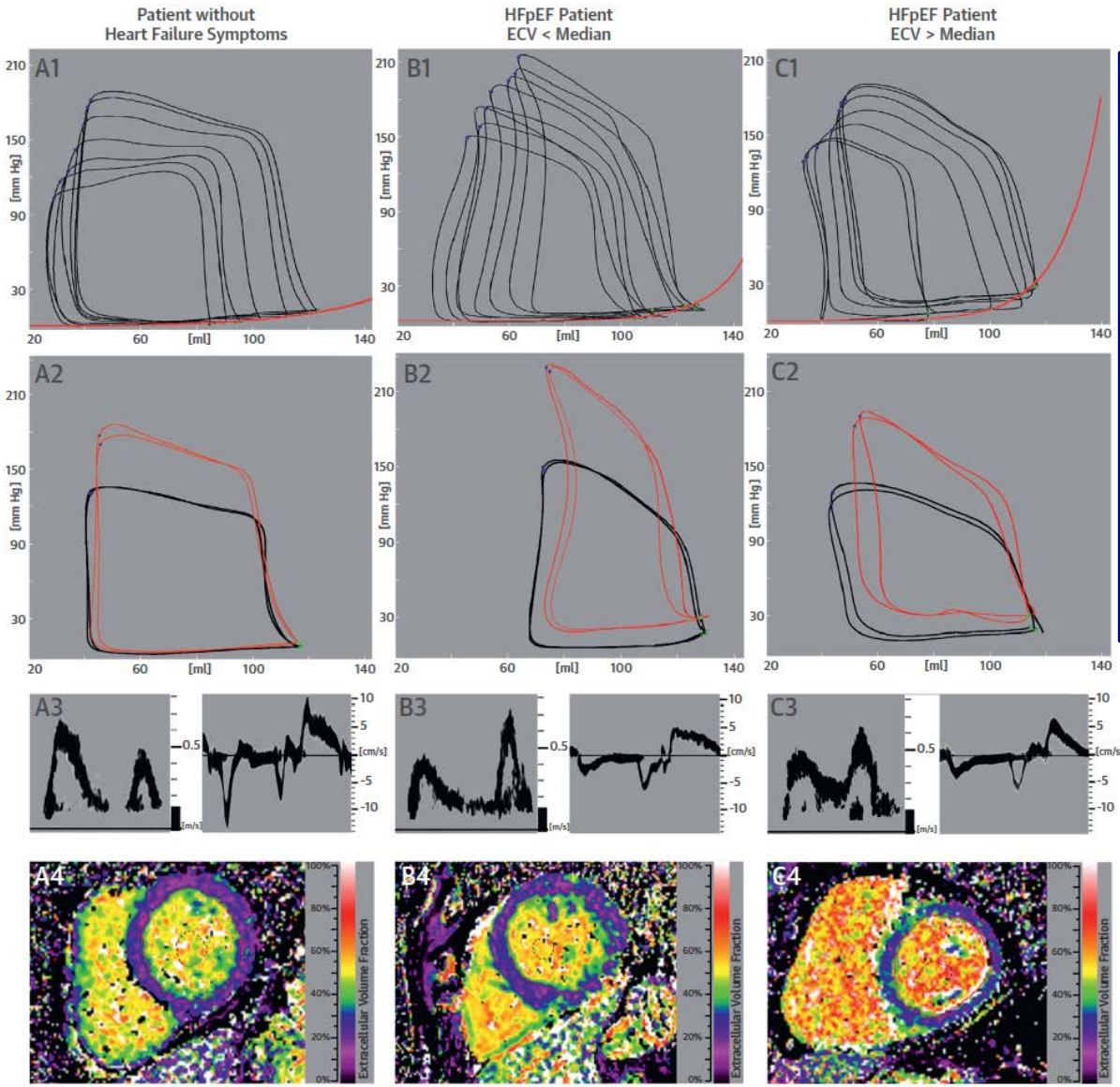
Source: Taqueti VR…Di Carli M. Circulation. 2015 Feb 10;131(6):528-35

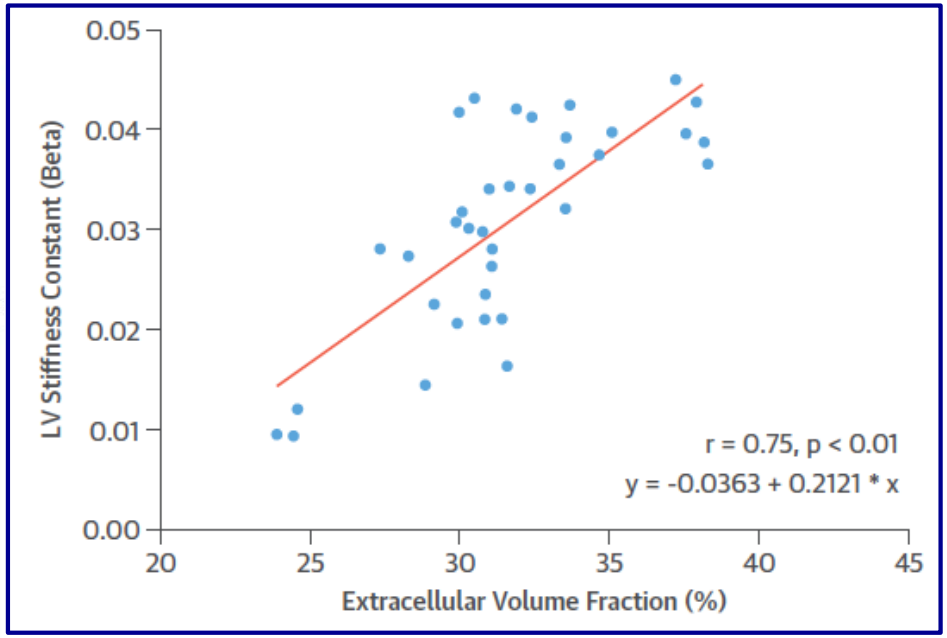
Reduced coronary microvascular density associates with fibrosis in HFpEF



Source: Selma F. Mohammed et al. Circulation. 2015;131:550-559

Interstitial fibrosis and LV diastolic dysfunction

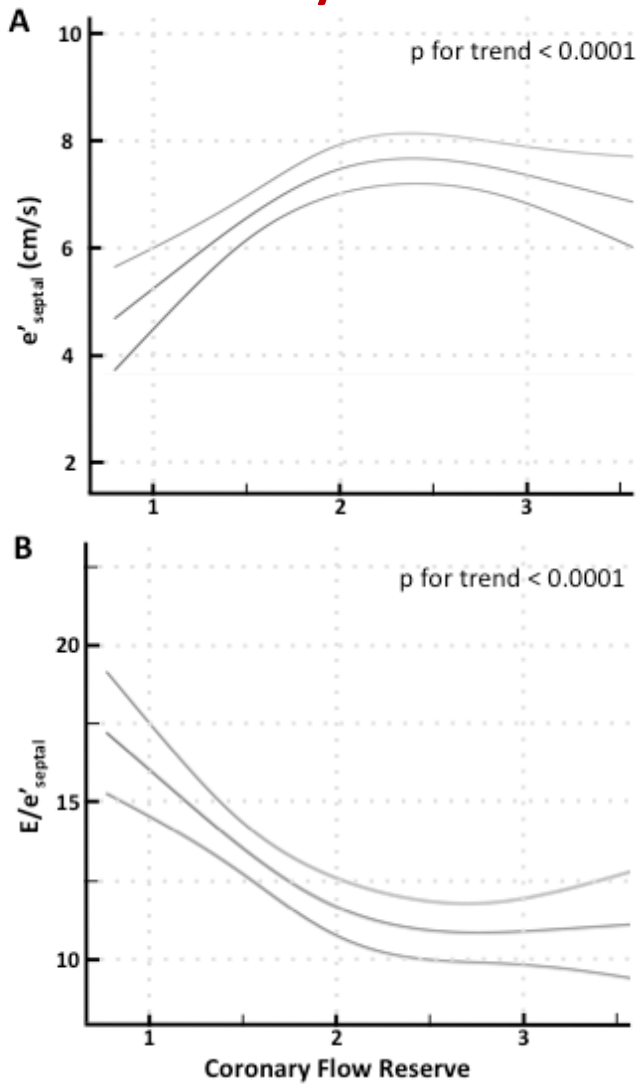




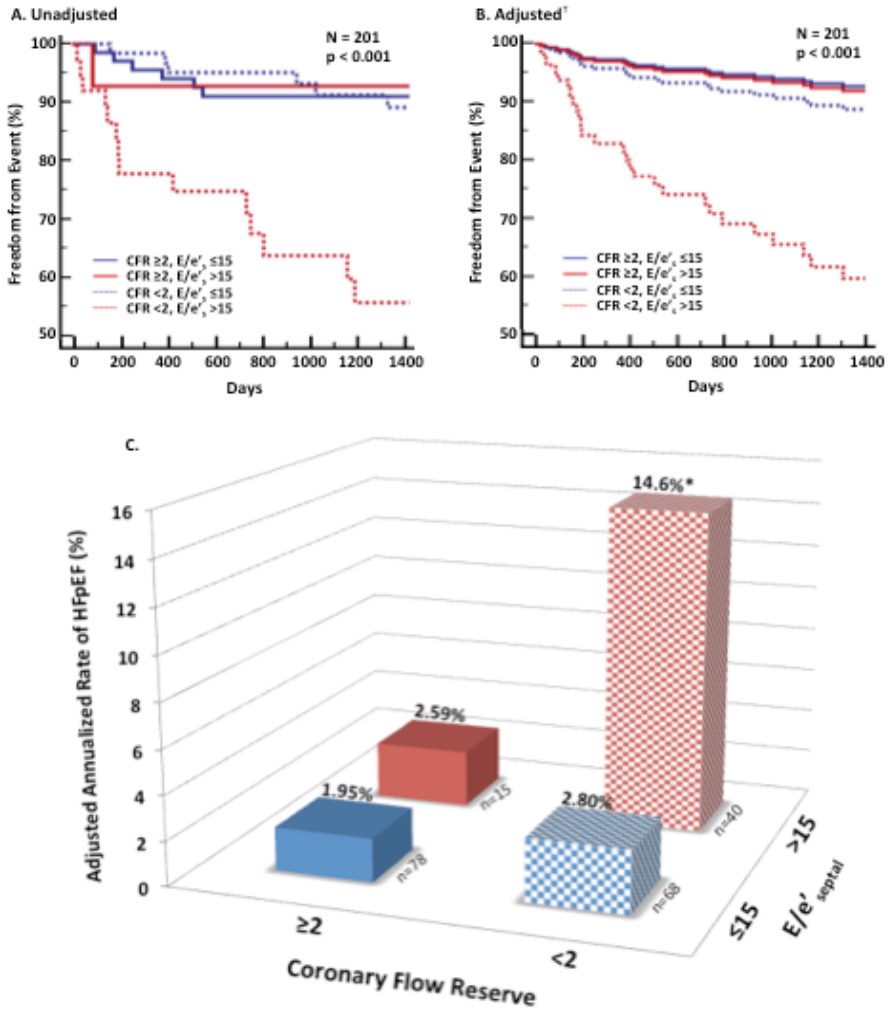
Source: Rommel K-P, et al. J Am Coll Cardiol 2016;67:1815–25

CMD, diastolic dysfunction, and HF hospitalizations

CFR and markers of diastolic dysfunction



Freedom from Hospitalization for HF by CFR and E/e'



*'E/e'$_0$' refers to E/e'$_{septal}$
†Adjusted for pretest clinical score and detectable troponin

Source: Taqueti VR…Di Carli M. EHJ 2017, in press

New developments about CMD in atherosclerosis

1. Definition, pathophysiology and clinical presentation
2. Diagnosis and prevalence
3. A marker of ischemia and clinical risk
4. **A target for therapy?**

Medical management of MCD

Treatment	Baseline CFR <2.5	No CAD ≥50% Stenosis	Mode of Assessing CFR or MPR	Patients (n)	Findings	First Author, Year (Ref. #)
Renin/angiotensin/aldosterone inhibitors						
Eplerenone 25 mg	No	Yes	IC Doppler	25	Angina ↔, CFR ↔	Bavry et al., 2014 (44)
Candesartan 4–8 mg	NA	No	IC Doppler	14	CFR ↑	Iino et al., 2012 (74)
Enalapril 5 mg 2× daily	No	Yes	IC Doppler	10	Angina ↑, CFR ↑	Chen et al., 2002 (75)
Enalapril 10–20 mg/day	No	Yes	Argon dilution	15	Symptoms ↑, CFR ↑	Motz et al., 1996 (43)
Enalapril 5 mg 2× daily	No	Yes	PET	10	Exercise capacity ↑	Kaski et al., 1994 (42)
Statins						
Fluvastatin 40 mg	Yes	Yes	TTDE	23	Angina ↑, CFR ↑	Zhang et al., 2014 (50)
Atorvastatin 80 mg	No	No	IC Doppler	20	CFR ↔	Eshtehardi et al., 2012 (51)
Atorvastatin 20 mg	Yes	Yes	TTDE	20	CFR ↑	Caliskan et al., 2007 (52)
Nitric oxide modulators						
L-arginine 1-time infusion	No	Yes	IC Doppler	11	CBF ↓	Gellman et al., 2004 (58)
Tetrahydrobiopterin 1-time infusion	No	No	IC Doppler	23	CBF ↑	Setoguchi et al., 2001 (76)
L-arginine infusion 3 g 3× daily	No	No	IC Doppler	13	Angina ↑, CFR ↔	Lerman et al., 1998 (59)
L-arginine 1-time infusion	No	No	IC Doppler	8	CBF ↑	Egashira et al., 1996 (57)
Calcium-channel blockers						
Diltiazem 90 mg	No	Yes	TTDE	23	Angina ↑, CFR ↑	Zhang et al., 2014 (50)
Lidoflazine 240–360 mg	No	Yes	Thermodilution	11	Angina ↔, MBF ↑, Arrhythmias*	Cannon et al., 1990 (48)
Verapamil 80 mg 4× daily	No	Yes	Thermodilution	17	Angina ↑	Cannon et al., 1985 (47)
Nifedipine 10 mg 4× daily	No	Yes	Thermodilution	9	Angina ↑	Cannon et al., 1985 (47)
Alpha-blockers						
Doxazosin 2 mg	No	Yes	PET scan	11	Angina ↔, CBF ↔,	Rosen et al., 1999 (61)
Antianginal agents and nitrates						
Ivabradine 5 mg	Yes	Yes	TTDE	16	Angina ↑, CFR ↔	Villano et al., 2013 (68)
Isosorbide dinitrate 5 mg (SL)	NA	Yes	TTDE	29	Stress testing ↔	Russo et al., 2013 (69)
Ranolazine 500–1,000 mg	No	Yes	CMR	20	Angina ↑, CFR ↔	Mehta et al., 2011 (67)
Isosorbide dinitrate 10 mg (SL), 2 mg (IV)	NA	Yes	Thermodilution	11	Angina ↓, CBF ↓	Bugiardini et al., 1993 (70)
Estrogens						
17β-estradiol 1 mg + drospirenone 2 mg	No	NA	PET	27	MPR ↑	Knuuti et al., 2007 (63)
Devices						
EECP	Yes	Yes	TTDE	24	Angina ↑, CFR ↑	Luo et al., 2012 (65)
TENS	NA	Yes	IC Doppler	13	CBF ↓	Sanderson et al., 1996 (66)
Other						
Bariatric surgery	Yes	NA	TTDE	50	CBF ↑	Nerla et al., 2012 (72)
Cognac	No	NA	TTDE	18	CFR ↔	Kiviniemi et al., 2008 (77)
Vitamin C 3 g infusion	No	N/A	PET	19	CFR ↑ in asymptomatic smokers	Kaufmann et al., 2000 (78)
Exercise training	No	No	PET	13	CFR ↑	Czernin et al., 1995 (71)

Source: Marinescu MA, et al. J Am Coll Cardiol Img 2015;8:210–20

Potential role of novel therapies

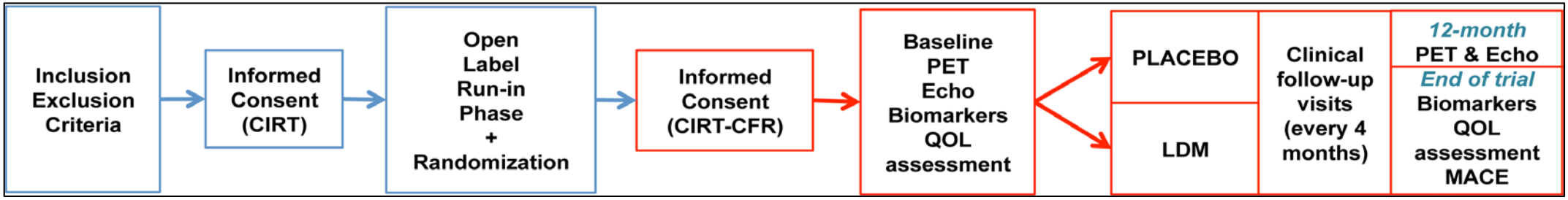
- Inflammation reduction (CIRT-CFR)
- Lipid management
- Metabolic modulators
- Neurohormonal inhibition
- MR receptor antagonists (SPIN-D)
- Rho kinase inhibition (ANOCA)

CIRT | CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

NHLBI-funded multicenter RCT allocating 7,000 pts with prior MI and T2DM or MS to LDM vs. placebo, primary outcome MACE (CD, MI, stroke) target follow-up 3 yrs

CIRT-CFR trial

- Does reduction in systemic inflammation improve CFR?
- Is the improvement in CFR associated with improved LV function?



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Summary

- We have seen fantastic progress
- Quantitative imaging is helping us advance:
  - Mechanisms of disease
  - Early diagnosis
  - Drug discovery
  - Improving clinical trials
    - Enrich cohorts
    - Mechanistic insights into how drugs work