Future Innovations - COVADIS
Coronary Microvascular Dysfunction: Procedure and Diagnostic Coding (U.S. Approach)

Puja K. Mehta, MD FACC FAHA
Director, Women's Translational Cardiovascular Research
Assistant Professor, Emory Women's Heart Center
Emory Clinical Cardiovascular Research Institute (ECCRI)
August 29, 2018

EMORY UNIVERSITY SCHOOL OF MEDICINE

Objectives

- Determine the role of coronary reactivity testing (CRT) in chest pain with no obstructive CAD.
- Identify pathways of CRT and prognosis
- Identify diagnostic/billing codes
- Discuss challenges and future directions

Coronary Vascular Disorders

- Heterogeneous disorders
- Various pathophysiologic mechanisms
- Clinical presentation varies
  - Rest angina
  - Emotional-stress angina
  - Typical, exertional angina
  - Dyspnea, etc
- Target treatment based on pathophysiology (ideally)

Diagnosis

- Non-Invasive
  - Cardiac PET with CFR
  - Doppler Echo with CFR
  - Cardiac stress MRI – Myocardial perfusion reserve index

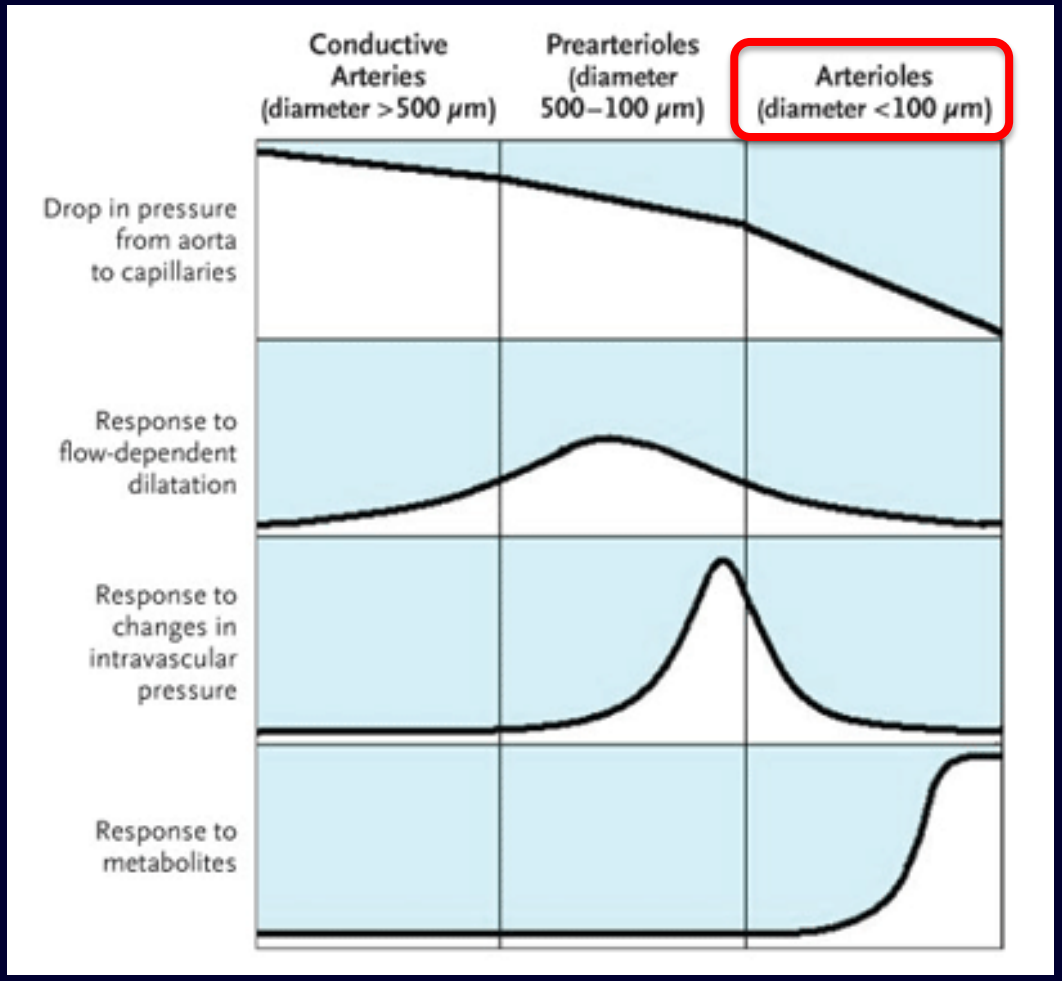
- invasive
  - Coronary reactivity testing (functional angiogram)

Pharmacologic Agents For Coronary Reactivity Testing

	Epicardial Vessels	Microcirculation
Endothelium-dependent vascular function	Acetylcholine	Acetylcholine
	Salbutamol	Salbutamol
	Serotonin	Bradykinin
	Substance P	
	Calcitonin gene-related peptide	
Endothelium-independent vascular function	Nitroglycerin	Adenosine
	Nitroprusside	Dipyridamole
	Papaverine	Nitroprusside
		Papaverine

Flammer AJ, Circulation. 2012;126:753-767

Normal Non-Endothelial Dependent Function



Adenosine

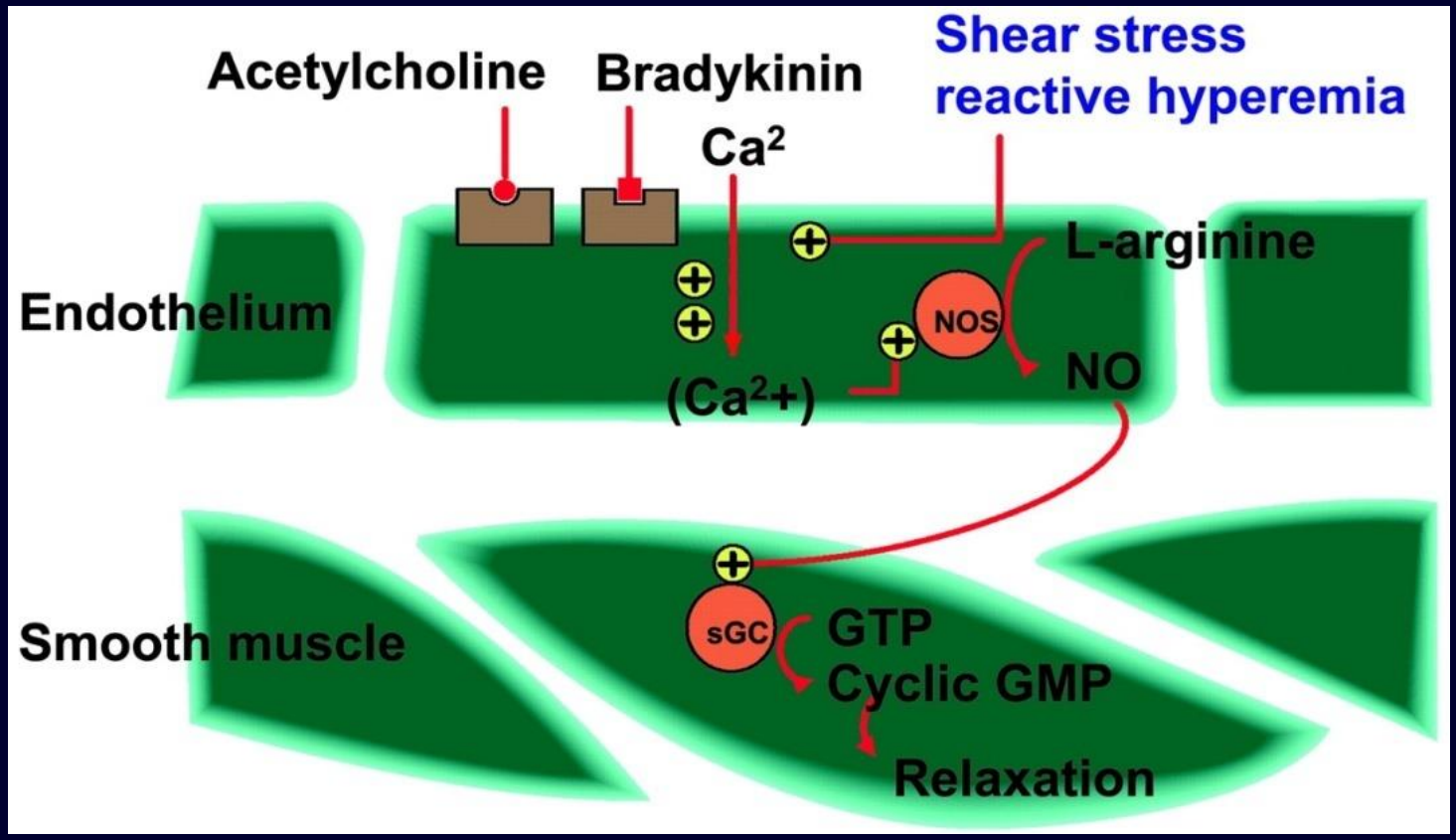
- Arteriole smooth muscle vasodilatation via A2A receptors

Coronary Flow Reserve (CFR)

- ratio of hyperemic-to-basal coronary flow velocity

Camici PG, and Crea F. N Engl J Med. 2007;356:830-40

Normal Endothelial Function

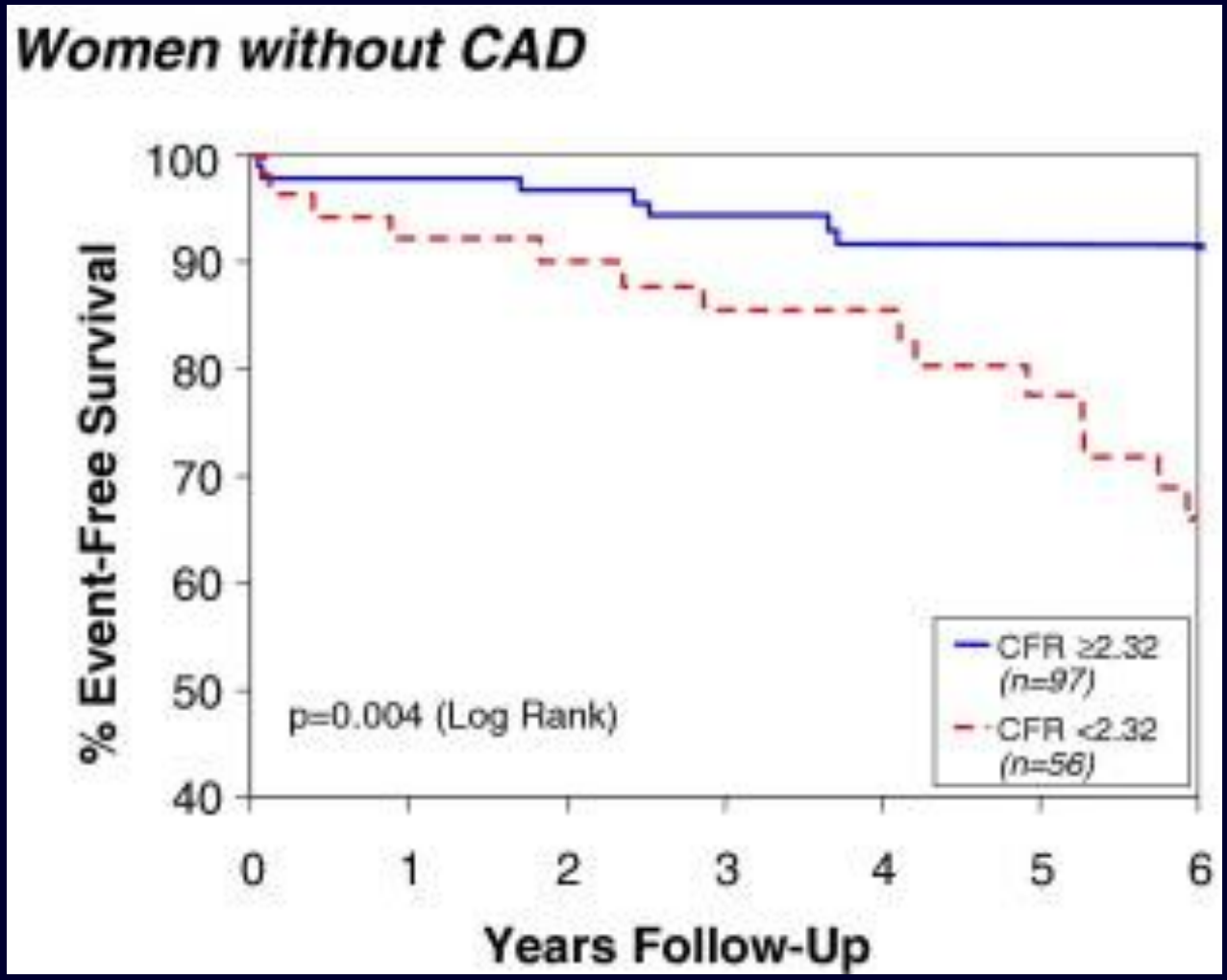


– Releases nitric oxide (NO) in response to increase in flow, shear stress, acetylcholine

– Allows 3- to 4-fold increase in coronary blood flow (CBF)

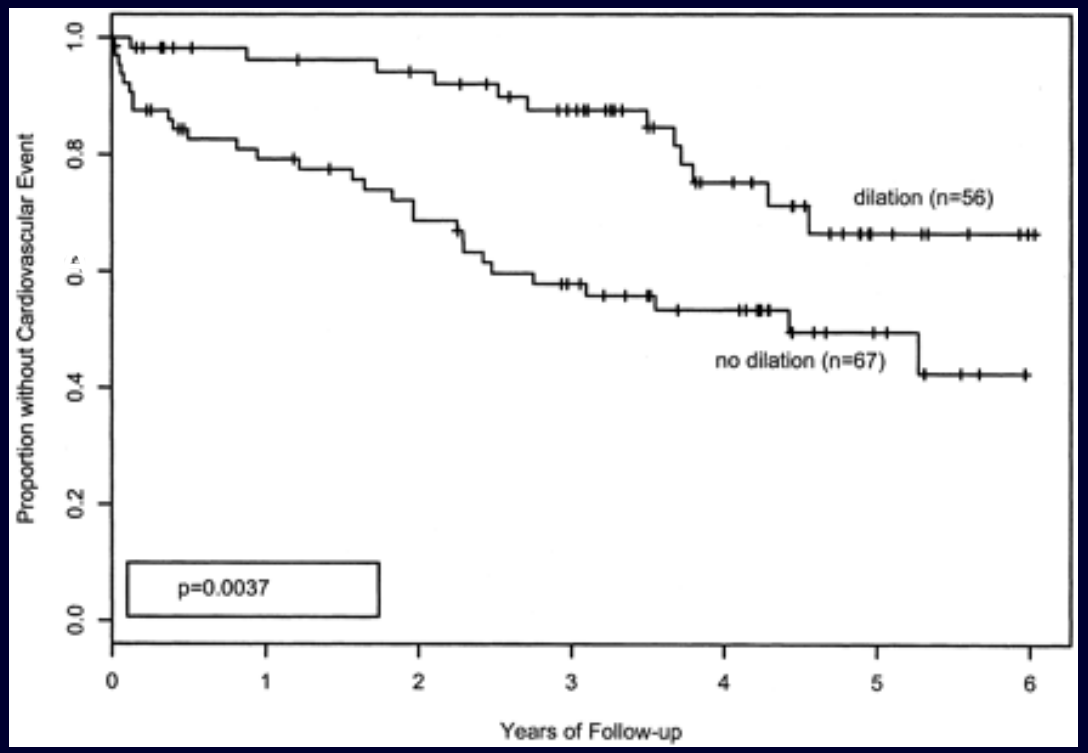
Lerman A et al. Circulation. 2005;111:363-368

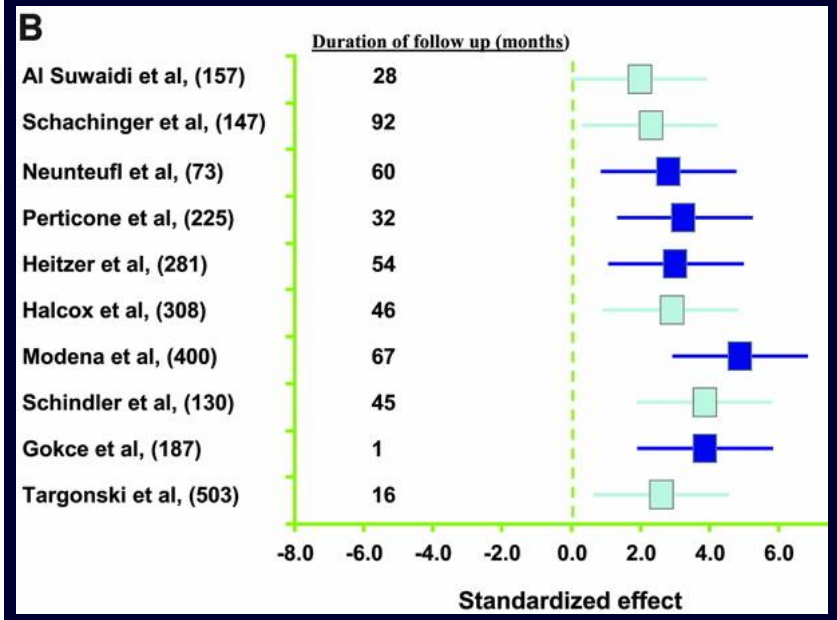
Coronary Flow Reserve (CFR) Predicts Adverse Cardiovascular Outcomes



Pepine CJ et al. J Am Coll Cardiol. 2010;55:2825-2832

Endothelial Dysfunction Predicts Cardiovascular Events





Von Mering GO et al. Circulation. 2004;109:722-725
Lerman A, et al. Circulation. 2005;111:363-368

Indications For Invasive Coronary Reactivity Testing

Evidence of ischemia

+

No obstructive CAD

+

Persistent chest pain

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

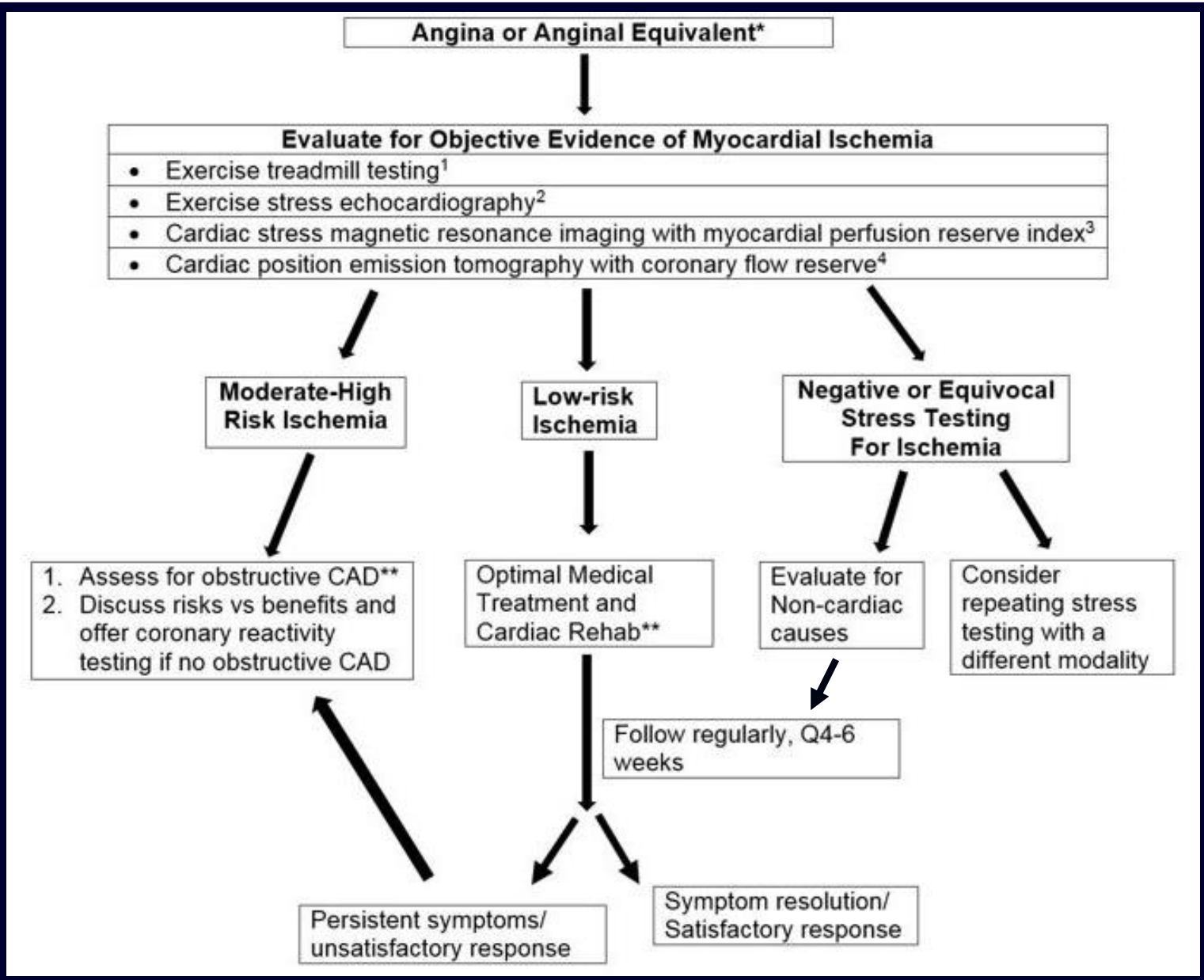
Negative Non-invasive Test Does Not Rule Out Coronary Vascular Dysfunction

Test	N	% (+)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
Exercise Echocardiogram	99	40.4	38(26–51)	55(38–71)	36(24–49)	58(41–73)
Dobutamine Echocardiogram	21	33.3	29(8–58)	57(18–90)	29(8–58)	57(18–90)
Exercise SPECT	131	38.2	40(29–51)	65(49–78)	38(28–50)	66(51–79)
Vasodilator SPECT	64	50.0	51(35–68)	52(31–72)	41(24–59)	63(44–79)
Vasodilator PET	33	36.4	35(16–57)	60(26–88)	29(11–52)	67(35–90)
All imaging	365	41.4	41(34–47)	57(49–66)	36(30–43)	62(54–70)
Exercise ECG	242	16.1	18(12–25)	80(71–88)	41(33–48)	69(52–83)
All imaging + ECG	365	6.3	6(3–10)	90(83–94)	37(32–43)	61(39–80)

- No vasoconstrictive stimulus for clinical non-invasive testing (such as mental stress, cold pressor, hyperventilation, etc)

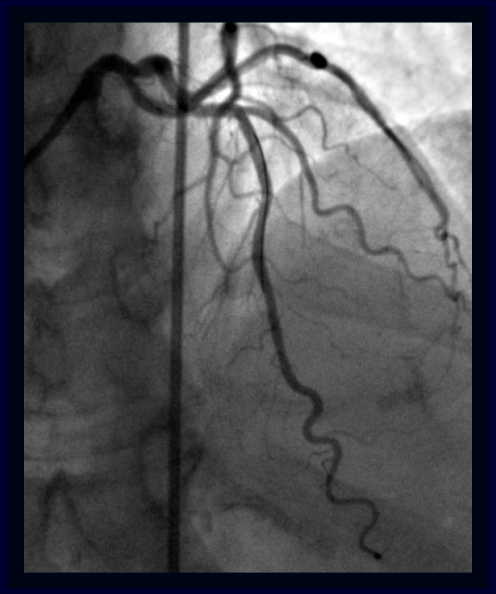
Cassar A et al. Circ Cardiovasc Interv. 2009;2(3): 237–244

Diagnostic Algorithm - Suggested Approach



Mehta PK, Wei J, Bairey Merz CN. Chronic Coronary Artery Disease, A Companion to Braunwald's Heart Dz, 2018.

WISE Study Coronary Reactivity Testing Protocol



ADO	18 mcg	18 mcg	36 mcg
ACH	0.364 mcg	36.4 mcg	108 mcg
NTG	200 mcg		

Spasm Testing Dose

**Not done in the setting of ACS

**Higher ACH doses are used in other countries

Bairey Merz CN et al. Circulation. 2017;135(11):1075-1092

Components of Coronary Reactivity Testing

	Microvascular Dysfunction	Macrovascular Dysfunction
Non-Endothelial Dependent	CFR <2.5 to Adenosine	Coronary dilation <20% to Nitroglycerin
Endothelial Dependent	ΔCBF <50% to Acetylcholine	Coronary dilation ≤0% to Acetylcholine
Coronary Spasm	Chest pain + ECG changes + significant constriction to Acetylcholine	

Bairey Merz CN et al. Circulation. 2017;135(11):1075-1092

Final Assessment

- ? Normal appearing epicardial coronary arteries (confirm no obstructive atherosclerosis)
- ? Luminal irregularities, ? Slow flow, ? Myocardial bridging
- LVEDP
- 4 pathways:
  - non-endothelium dependent microvascular function
  - endothelium dependent microvascular function
  - endothelium dependent macrovascular function
  - smooth muscle dysfunction/spasm
- ? Cardiac nociceptive abnormality (sedation)

Coronary Microvascular Dysfunction is Frequent in Women with Chest Pain

Non-endothelial-dependent CMD Coronary Flow Reserve (CFR) ≤ 2.5 to adenosine	138/293 (47%)
Endothelial-dependent CMD Δ Coronary Blood Flow (CBF) ≤ 50% to acetylcholine	112/220 (51%)
Endothelial-dependent macrovascular dysfunction	127/220 (58%)
Macrovascular smooth muscle dysfunction	136/225 (60%)

Women's Ischemia Syndrome Evaluation (WISE) Study

Wei J et al. JACC Interventions 2012;5(6):646-53

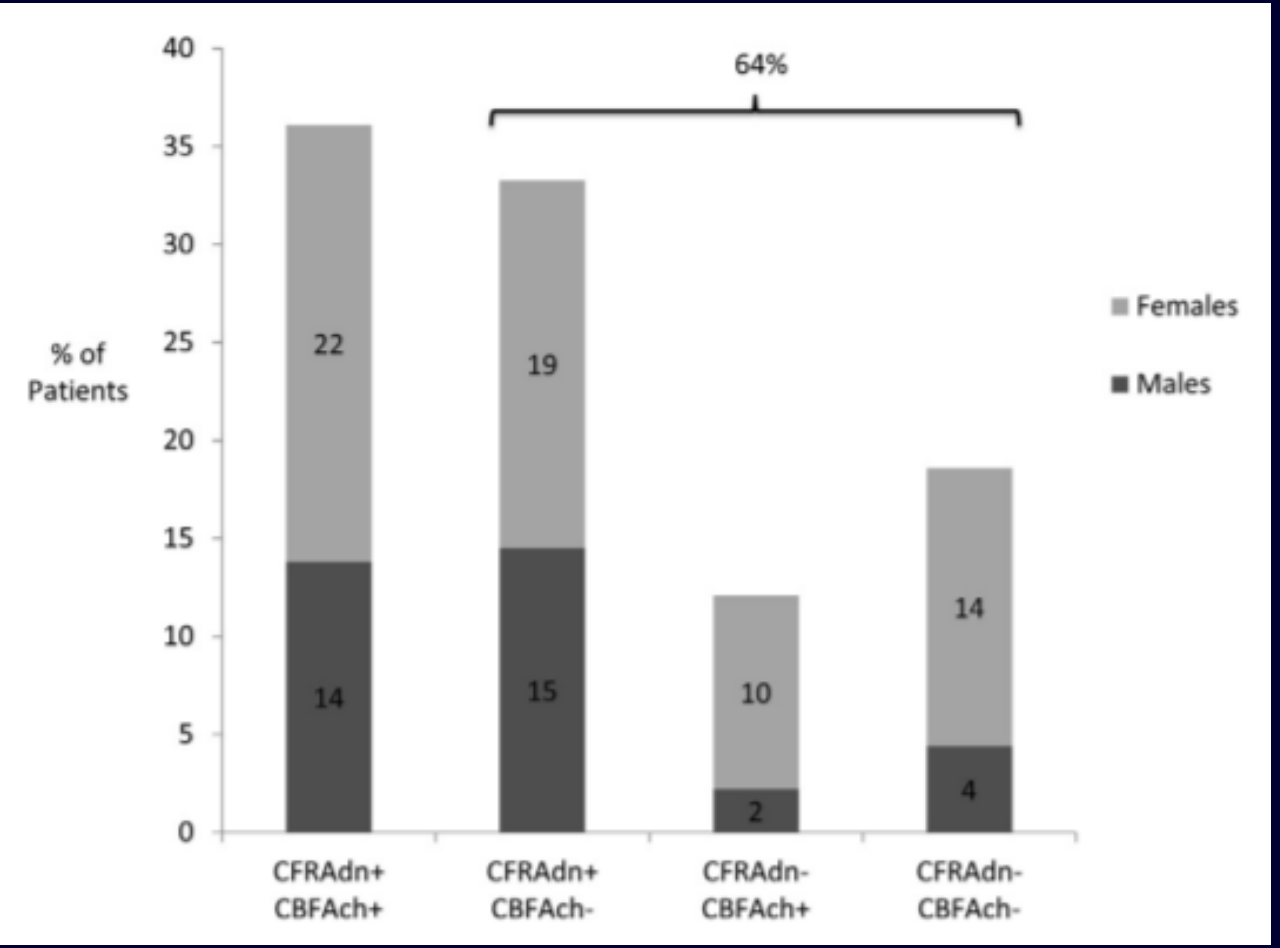
High Prevalence of Coronary Microvascular Dysfunction in Both Sexes

Mayo Clinic:

1,439 patients
- Mean age 51.9 years
- 34.9% male

Men: 60% with CMD

Women: 66% with CMD



Sara JD et al. JACC Interventions. 2015;8:1445–53

Coronary Reactivity Testing Safety

1) **WISE** (n=293, 100% women):
   - 0.7% SAE: 1 coronary dissection, 1 MI from coronary spasm
   - MACE rate after 5.4 years: 8.2%

2) **Mayo** (n= 470, 68% women):
   - 0.6% SAE: 3 coronary dissection
   - MACE rate after 9.7 years: 13%

3) **Germany and UK** (n= 921, 61% women):
   - 1% minor complications with acetylcholine: 1 NSVT, 1 fast paroxysmal atrial fibrillation, 6 symptomatic bradycardia

Wei J et al. JACC Interventions. 2012;5(6):646-53
Reriani M et al. Coronary Artery Disease. 2015;27(3):213-20
Ong P et al. Circulation. 2014;129(17):1723-30

Diagnostic Procedure Coding (U.S.)

- The Current Procedural Terminology (CPT) was developed by the American Medical Association (AMA) - updated every year
- Meant to communicate uniform information and to simplify medical claims
- Use of CPT codes is mandated by all health insurance companies and federal agencies such as Centers for Medicare and Medicaid Services (CMS)

	CPT® Code
Coronary angiography with left heart catheterization	93456
Pharmacological agent administration with hemodynamic assessment	93463
Intravascular CFR measurement, initial vessel with interpretation	93571
Intravascular CFR measurement, each additional vessel	93572

Billing Codes - Diagnosis (U.S.)

- International Statistical Classification of Diseases and Related Health Problems (ICD)
  - Current version – ICD-10

	ICD Code
Endothelial dysfunction of coronary artery	199.8
Cardiac microvascular disease	I20.9
Mild CAD	I25.10
Vasospastic angina	I20.1
Coronary vasospasm	I20.1
Chronic chest pain	R07.9
Other forms of angina pectoris	I20.8
Atherosclerotic heart disease of native coronary artery with angina pectoris	I25.11

Therapy

Coronary Endothelial Dysfunction

ACE-I, statins, L-arginine, aerobic exercise, EECP

Abnormal CFR

beta-blockers/alpha-beta blockers, ACE-I

Abnormal Smooth Muscle/ Vasospasm

calcium channel blockers, nitrates, rho kinase inhibition

Anti-Anginal/Anti-Ischemic

ranolazine, ivabradine, xanthine derivatives, nicorandil

Abnormal Cardiac Nociception

Low dose tricyclic, spinal cord stimulation, stellate ganglion block, cognitive behavioral therapy

Mehta PK, Wei J, Bairey Merz CN. Chronic Coronary Artery Disease, A Companion to Braunwald's Heart Disease, 2018.

Coronary Reactivity Testing: Challenges

- Repeating an invasive test (sometimes prior 2-3 angiograms already)
- Need support staff to obtain prior authorization from insurance company for this specialized testing
- Withdrawal of vasoactive meds
- Radial vs. femoral – and impact of using CCBs for radial artery spasm (prior to beginning of physiologic assessment)
- Sedation vs. no sedation
- Cath lab staff training
- Interventional fellow training
- Time – at least additional 20 minutes per case for full physiologic testing

Coronary Reactivity Testing: Conclusions

- CRT is a safe, prognostic procedure in symptomatic subjects to clarify diagnosis and can guide treatment of CMD.
- In the U.S., procedure and diagnostic codes are available for billing CRT.
- However, there are challenges that limit more widespread implementation of CRT.

Future Innovations for COVADIS

- Outline a systematic approach for a complete coronary physiology study
  - ? White paper with a general overview followed by a technical paper for methods
  - ? Video live case demonstrations at ACC/AHA/ESC
- Suggest specific patient groups where CRT should be considered
  - Who should undergo a functional study vs. PET first?
  - Case series
- Develop expert consensus algorithms (i.e. MINOCA, etc)