Northwestern Medicine®

Coronary Microvascular Disease:
The Small but Mighty Vessels

Cardiovascular Symposium India

January 21, 2023

Sadiya S. Khan, MD, MSc, FACC, FAHA
Assistant Professor of Medicine and Preventive Medicine
Associate Program Director, CVD Fellowship
Director of Research, Section of Heart Failure
Northwestern University Feinberg School of Medicine
Associate Editor, *JAMA Cardiology*
@HeartDocSadiya

DISCLOSURES

No relevant COI/RWI

Grant support

- AHA
- NIH

CASE PRESENTATION

- 40-year-old woman who presented to clinic after multiple episodes of squeezing chest pain. She has had multiple visits to the ER and had a coronary angiogram with “normal” coronary arteries
- Vitals: HR 90, BP 124/70
- Exam: RRR, nl s1, s2, no murmurs
- Echo: LVEF 55%, no significant wall motion abnormality at rest

CASE PRESENTATION

- 40 year old woman who presented to clinic after multiple episodes of squeezing chest p… …l” c…
- V…
- Exam: RRR, nl s1, s2, no murmurs
- E…

At this point, should additional diagnostic testing be pursued?

What potential therapeutic options are available to manage her angina?

CMD LEARNING OBJECTIVES

1. Define coronary microvascular disease (CMD) as an important cause of angina
2. Determine the role of non-invasive perfusion imaging to detect and associated prognosis in CMD
3. Discuss management strategies and prevention in populations at high-risk for CMD

CMD LEARNING OBJECTIVES

1. Define coronary microvascular disease (CMD) as an important cause of angina
2. Determine the role of non-invasive perfusion imaging to detect and associated prognosis in CMD
3. Discuss management strategies and prevention in populations at high-risk for CMD

HISTORICAL PERSPECTIVE: 1988 REPORT

ORIGINAL ARTICLE ARCHIVE

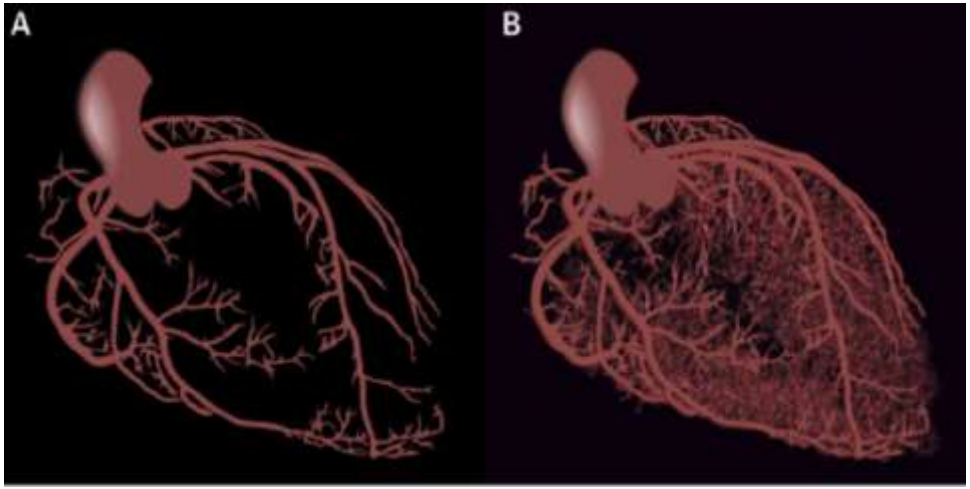
Angina Due to Coronary Microvascular Disease in Hypertensive Patients without Left Ventricular Hypertrophy

John E. Brush, Jr., M.D., Richard O. Cannon, III, M.D., William H. Schenke, B.A., Robert O. Bonow, M.D., Martin B. Leon, M.D., Barry J. Maron, M.D., and Stephen E. Epstein, M.D.

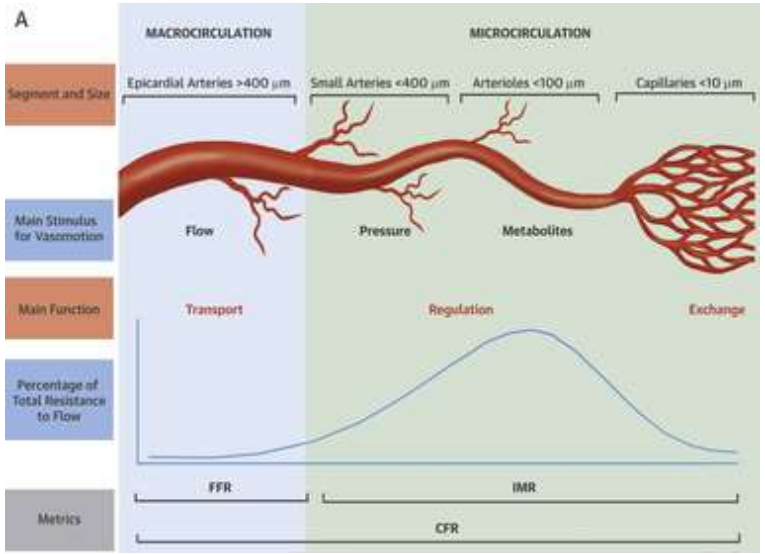
"Thus, angina in hypertensive patients without epicardial coronary disease may be caused by myocardial ischemia, which appears to be due to an abnormally elevated resistance of the coronary microvasculature."

CORONARY CIRCULATION: STRUCTURE/FUNCTION

Coronary Macro- and Micro-Circulation



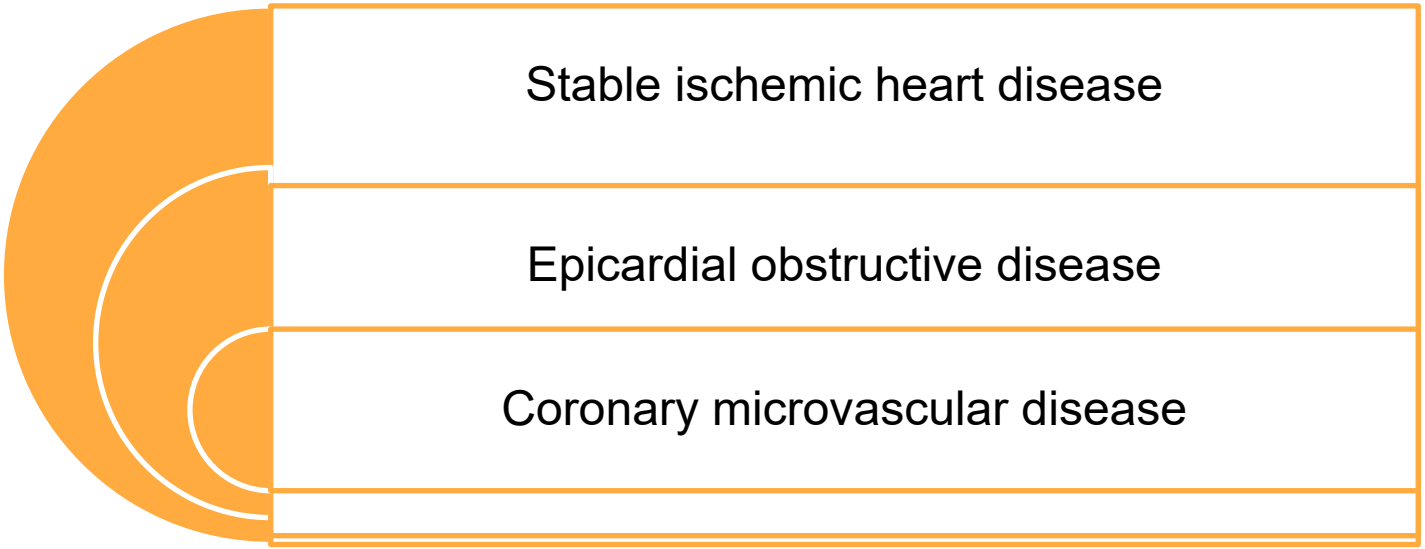
Functional Roles of Arterial Bed and CFR



Magnitude of increase in coronary flow (per unit of time) with maximum coronary vasodilation (ratio of blood flow during hyperemia [vasodilator stress] to rest)

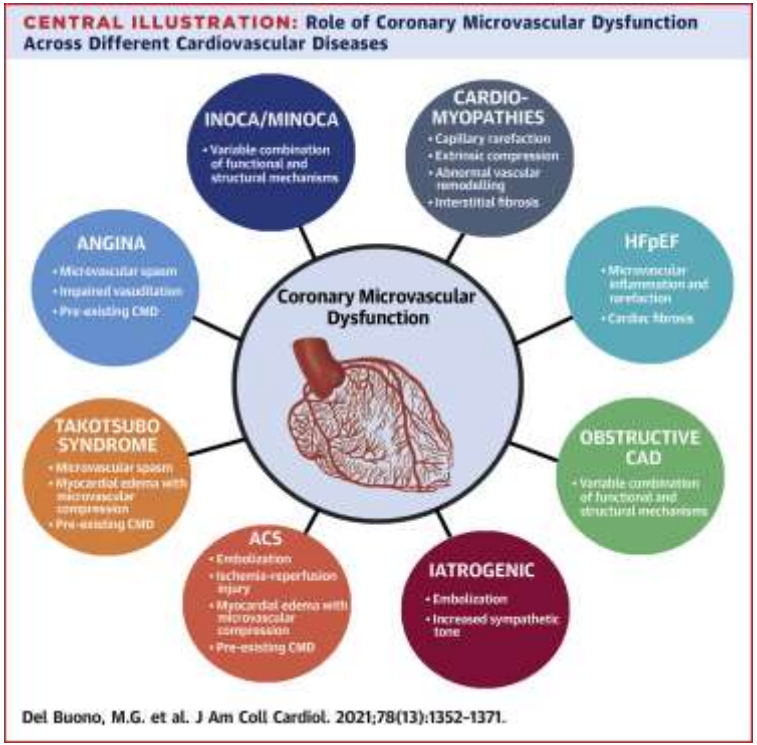
Taqueti V and Di Carli M. *JACC* 2018

WHAT IS CORONARY MICROVASCULAR DISEASE?



- **Other names** include Coronary syndrome X, MINOCA/INOCA, microvascular angina, chest pain with normal coronary arteries

WHO IS AFFECTED BY CMD?



RF

Obesity

Insulin resistance

HTN

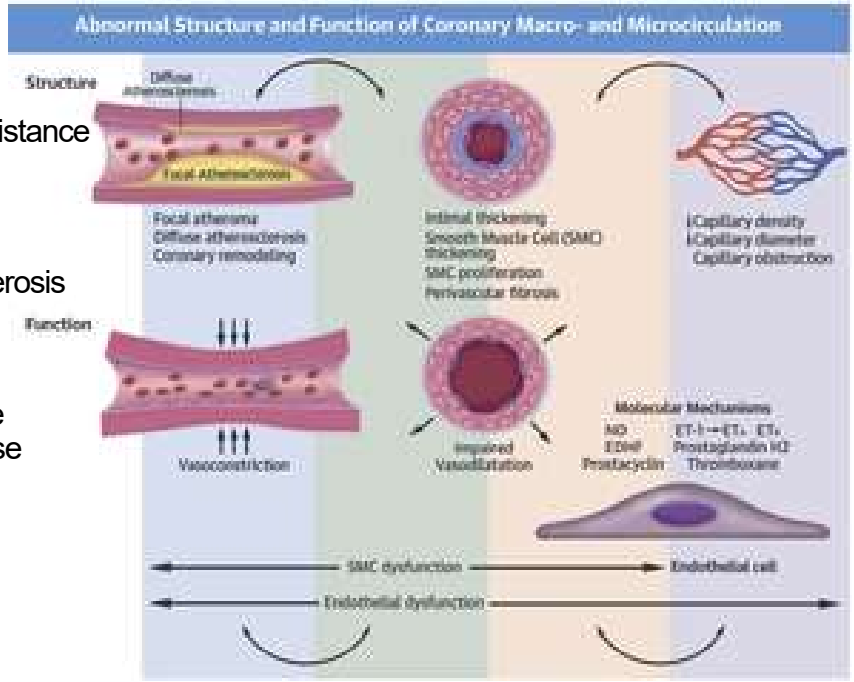
CKD

Atherosclerosis

REF

Premature menopause

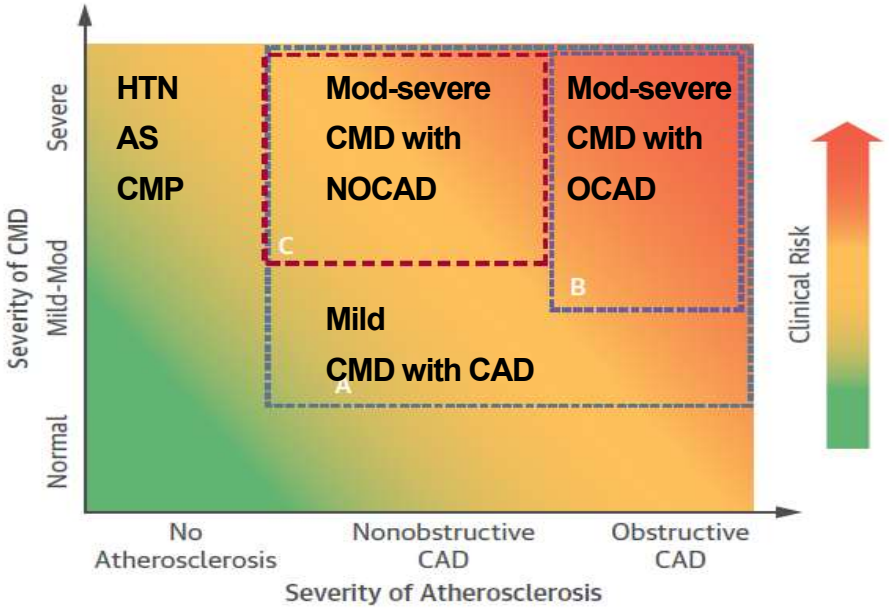
APOs



Taqueti V and Di Carli M. *JACC* 2018

WHY DOES CMD MATTER TO DETECT?

- Difficult to diagnose (in comparison with epicardial CAD) due to prior limitations in non-invasive imaging techniques
- Occurs overwhelmingly in patients with atherosclerosis and cardiometabolic disorders – obesity, insulin resistance, CKD, ASCVD
- MINOCA and INOCA are not benign conditions despite the lack of significant epicardial stenosis
- CMD may play a large role in patients with persistent anginal/equivalent symptoms, and HFpEF – for which we have therapies

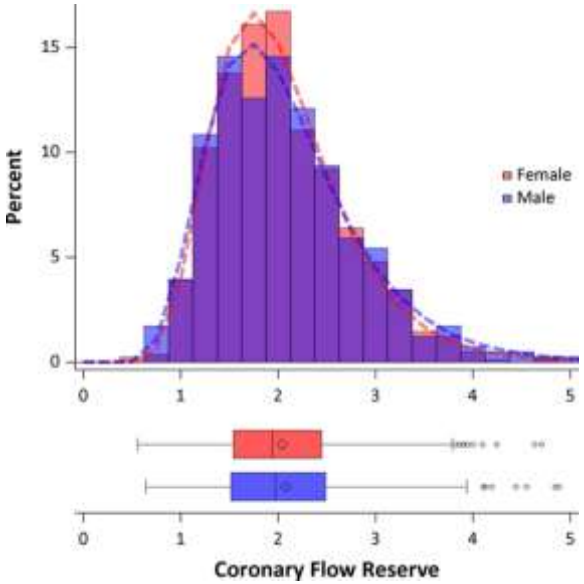


CMD occurs in the presence of CAD and confers excess risk

Taqueti V and Di Carli M. *JACC* 2018

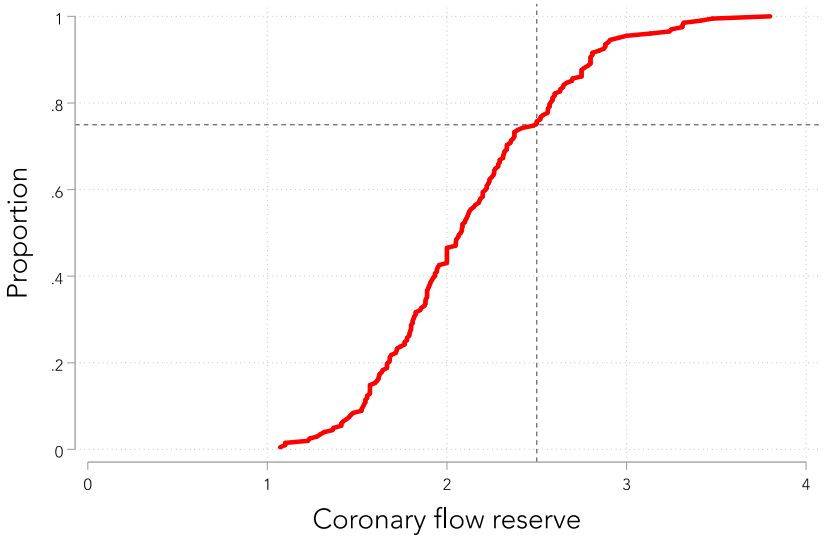
CMD IS HIGHLY PREVALENT WITHOUT OCAD OR HF

Ischemia without OCAD



- N=405 men and 813 women referred for PET
- CMD present in 51% of men and 54% of women
- HR 0.80 (0.75-0.86) per 10% higher CFR for MACE

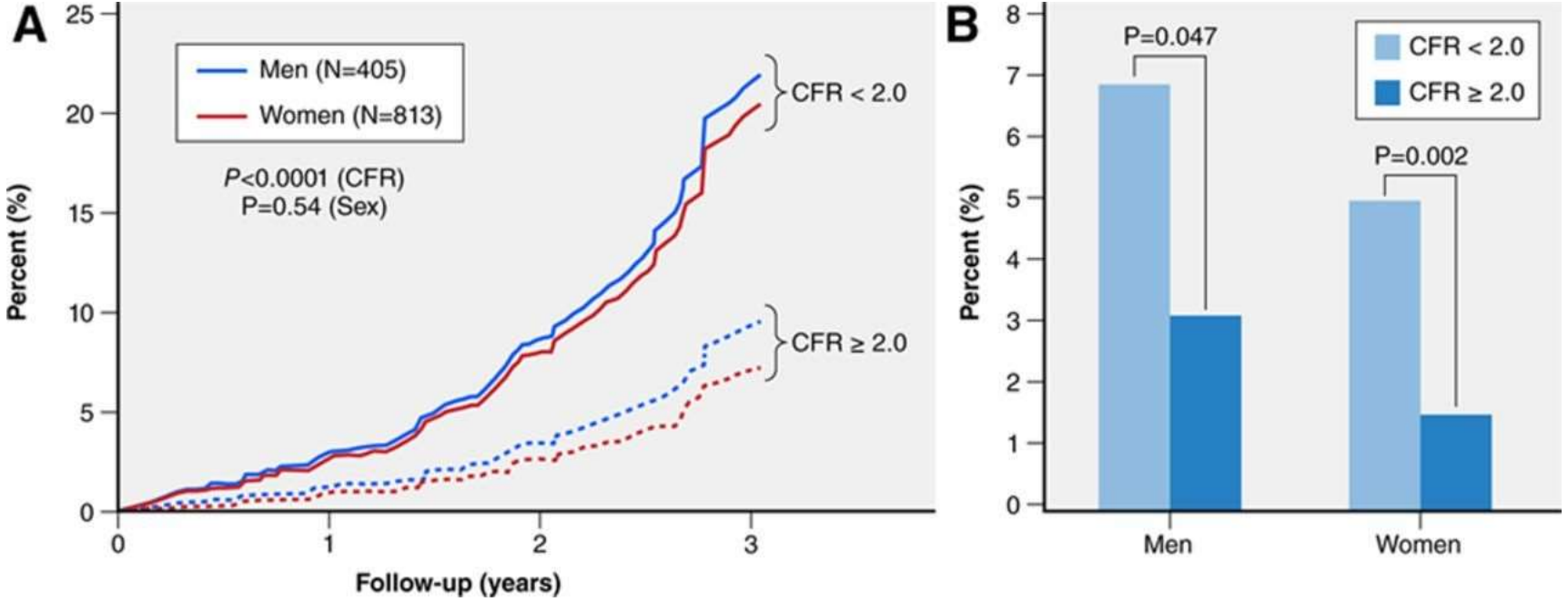
PROMIS-HFpEF



- N=202 patients with HFpEF from 5 sites
- CMD present in 75% (69-81%)
- CMD was associated with systemic endothelial dysfunction (UACR) and HF biomarkers (NTproBNP)

Murthy VL et. al. *Circulation 2014*
Shah SJ et. al. *Eur Heart J* 2018

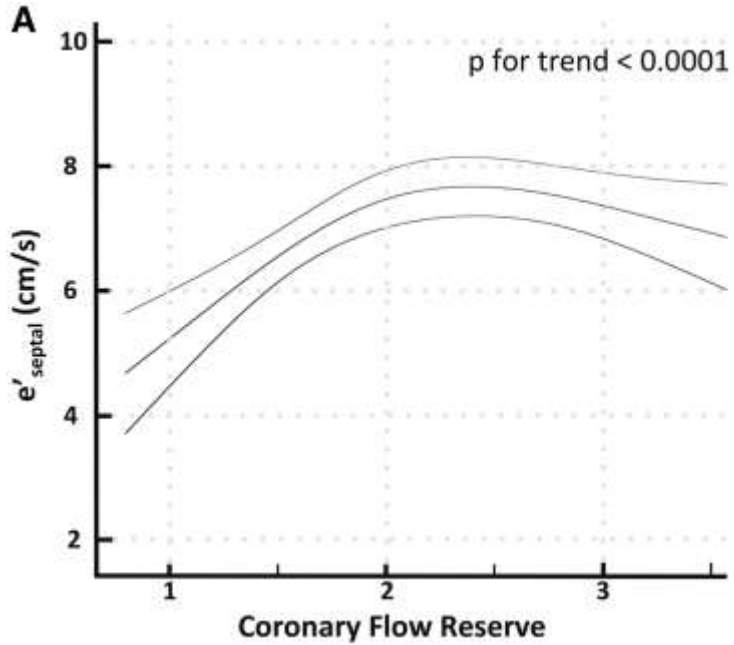
IMPAIRED CFR WORSE IN WOMEN



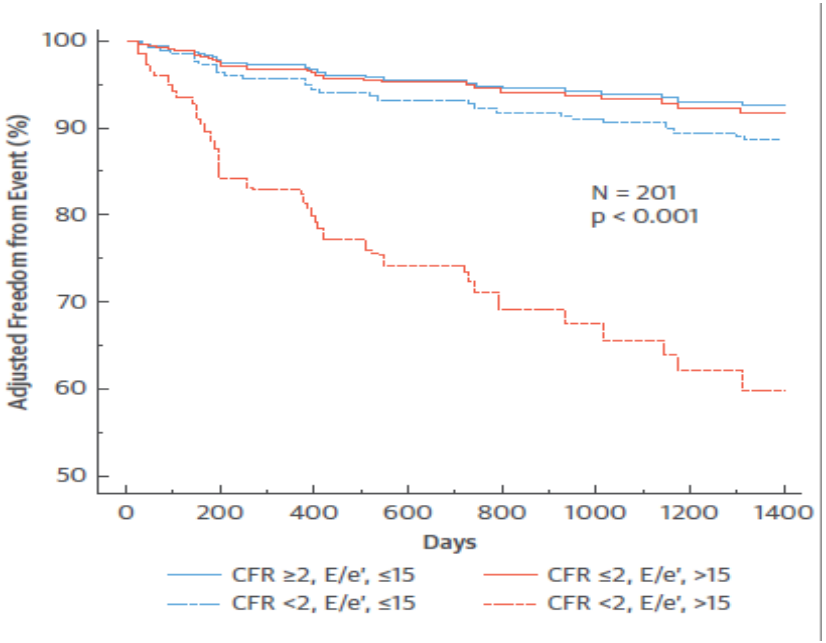
Murthy VL et. al. *Circulation* 2014

PROGNOSIS WITH CMD AND DD IS WORSE

Association Between CFR and e'

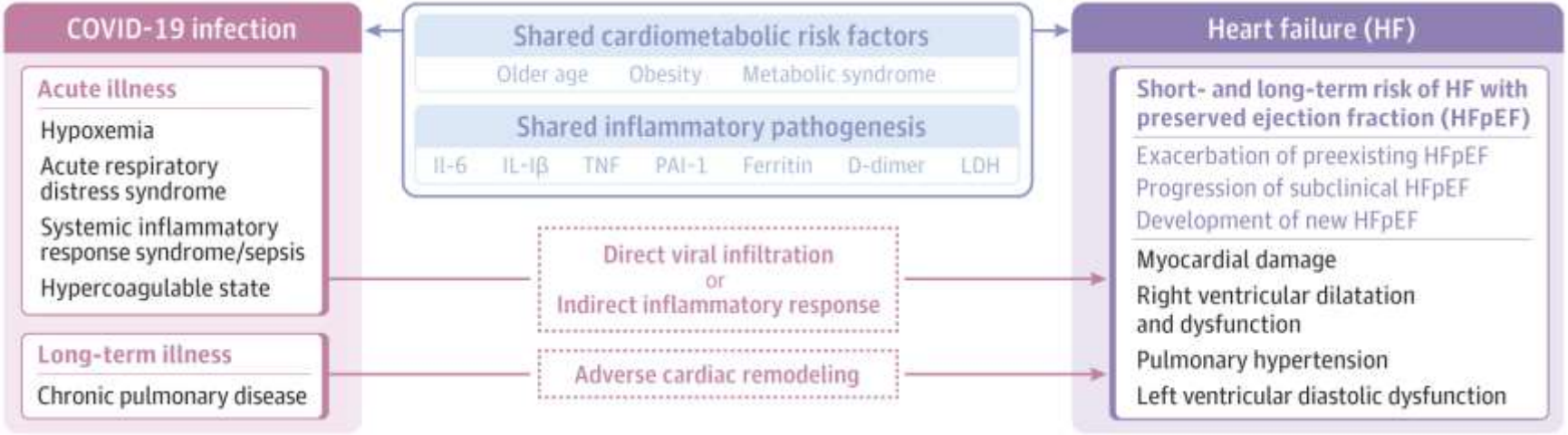


CFR and Diastolic Dysfunction



Taqueti V et al. *Eur Heart J* 2018

COVID-19 PERSPECTIVE: INCREASE IN CMD + HFPEF



Microvascular dysfunction

Freaney P…Khan SS. *JAMA* 2020

CMD LEARNING OBJECTIVES

1. Define coronary microvascular disease (CMD) as an important cause of angina
2. Determine the role of non-invasive perfusion imaging to detect and associated prognosis in CMD
3. Discuss management strategies and prevention in populations at high-risk for CMD

DIAGNOSTIC CRITERIA FOR CMD

Coronary Vasomotor Disorders International Study (COVADIS) Diagnostic Criteria

- ☐ Symptoms of myocardial ischemia with effort or rest angina
- ☐ Absence of obstructive CAD (<50% diameter reduction or FFR>0.80) by coronary CTA or invasive coronary angiography
- ☐ Objective evidence of myocardial ischemia by presence of reversible defect, abnormality or flow reserve on a functional imaging test
- ☐ Evidence of coronary dysfunction with impaired coronary flow reserve (cut-off≤2.0 or ≤2.5 depending on methodology), invasive or non-invasively determined
  Coronary microvascular spasm
  Abnormal coronary microvascular resistance indice (e.g., IMR≥25)
  Coronary slow flow phenomenon, defined as TIMI frame count >25

DIAGNOSTIC CRITERIA FOR CMD: DEFINITE

Coronary Vasomotor Disorders International Study (COVADIS) Diagnostic Criteria

- ☑ Symptoms of myocardial ischemia with effort or rest angina
- ☑ Absence of obstructive CAD (<50% diameter reduction or FFR>0.80) by coronary CTA or invasive coronary angiography
- ☑ Objective evidence of myocardial ischemia by presence of reversible defect, abnormality or flow reserve on a functional imaging test
- ☑ Evidence of coronary dysfunction with impaired coronary flow reserve (cut-off≤2.0 or ≤2.5 depending on methodology), invasive or non-invasively determined
  Coronary microvascular spasm
  Abnormal coronary microvascular resistance indice (e.g., IMR≥25)
  Coronary slow flow phenomenon, defined as TIMI frame count >25

DIAGNOSTIC CRITERIA FOR CMD: SUSPECTED

Coronary Vasomotor Disorders International Study (COVADIS) Diagnostic Criteria

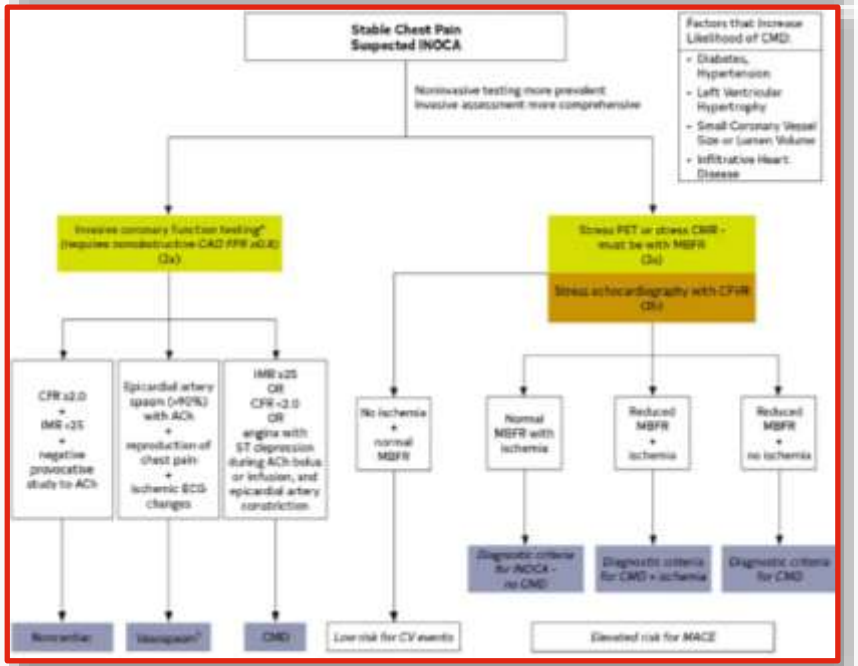
- [x] Symptoms of myocardial ischemia with effort or rest angina
- [x] Absence of obstructive CAD (<50% diameter reduction or FFR>0.80) by coronary CTA or invasive coronary angiography
- [ ] Objective evidence of myocardial ischemia by presence of reversible defect, abnormality or flow reserve on a functional imaging test
- [ ] Evidence of coronary dysfunction with impaired coronary flow reserve (cut-off≤2.0 or ≤2.5 depending on methodology), invasive or non-invasively determined
  Coronary microvascular spasm
  Abnormal coronary microvascular resistance indice (e.g., IMR≥25)
  Coronary slow flow phenomenon, defined as TIMI frame count >25

2021 ACC/AHA Chest Pain Guidelines emphasize the need to consider INOCA in stable and unstable chest pain syndromes and outline a clinical decision pathway

Circulation
Volume 144, Issue 22, 30 November 2021; Pages e336-e367
https://doi.org/10.1161/CIR.0000000000001030

AHA/ACC CLINICAL PRACTICE GUIDELINE

2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines



2021 ACC/AHA Chest Pain Guidelines emphasize the need to consider INOCA in stable and unstable chest pain syndromes and outline a clinical decision pathway

Recommendations for Patients With Suspected INOCA
Referenced studies that support the recommendations are summarized in Online Data Supplements 36 and 37.

COR	LOE	Recommendations
2a	B-NR	1. For patients with persistent stable chest pain and nonobstructive CAD and at least mild myocardial ischemia on imaging, it is reasonable to consider invasive coronary function testing to improve the diagnosis of coronary microvascular dysfunction and to enhance risk stratification.[348-351]
2a	B-NR	2. For patients with persistent stable chest pain and nonobstructive CAD, stress PET MPI with myocardial blood flow reserve is reasonable to diagnose microvascular dysfunction and enhance risk stratification.[272,331-334,344,345]
2a	B-NR	3. For patients with persistent stable chest pain and nonobstructive CAD, stress CMR with the addition of myocardial blood flow reserve measurement is reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE.[326,346,347]
2b	C-EO	4. For patients with persistent stable chest pain and nonobstructive CAD, stress echocardiography with the addition of coronary flow velocity reserve measurement may be reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE.

ECHO/SPECT IMAGING FOR CMD

Modality	Accuracy	Reproducibility	Prognostic Validation	Availability	Pros/Cons
Contrast echo	+++	?	?	++++	+ Low cost + Low risk/no radiation - Tech-dependent - Difficult imaging - Not FDA approved
Doppler echo of prox LAD	++ (Corr with wire, not PET)	++	++	++++	+ Low cost + Low risk/no radiation - Tech-dependent - Difficult imaging
SPECT for MBF	?	?	?	+++	- Requires new generation cameras/lower resolution - High radiation - Minimal validation

Mathew R. et. al.. *J Am Coll Cardiol Img* 2020

CT/MR IMAGING FOR CMD

Modality	Accuracy	Reproducibility	Prognostic Validation	Availability	Pros/Cons
CMR	+++	+++	++	++	+ No radiation + Excellent spatial resolution - High cost - Difficult for patients - Not for renal failure - Intensive post-processing
Dynamic CT	+++	+++	?	+	+ Anatomy and perfusion in one study + CTA-derived FFR - Iodinated contrast - High radiation - Limited validation

Mathew R. et. al.. *J Am Coll Cardiol Img* 2020

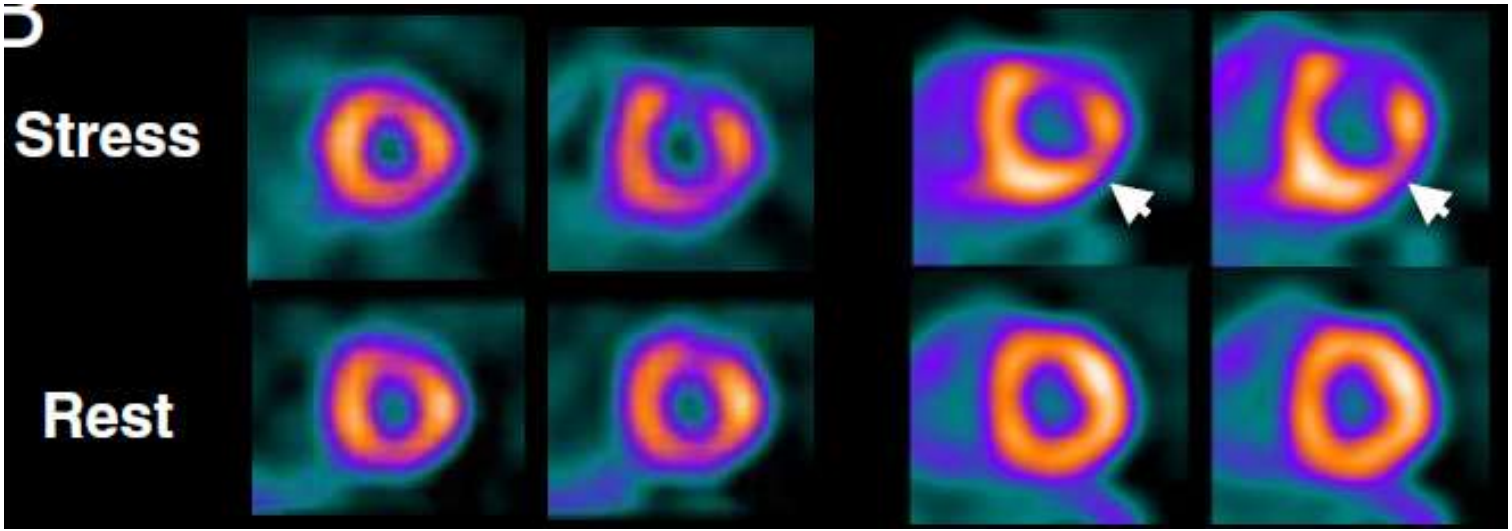
CT/MR IMAGING FOR CMD

Modality	Accuracy	Reproducibility	Prognostic Validation	Availability	Pros/Cons
PET/PET-CT*	++++	++++	++++	++	+ High spatial resolution + Most well validated + Most prognostic data + Not affected by CKD = Low radiation - High cost
*Gold standard for non-invasive assessment of CMD					

Mathew R. et. al.. *J Am Coll Cardiol Img* 2020

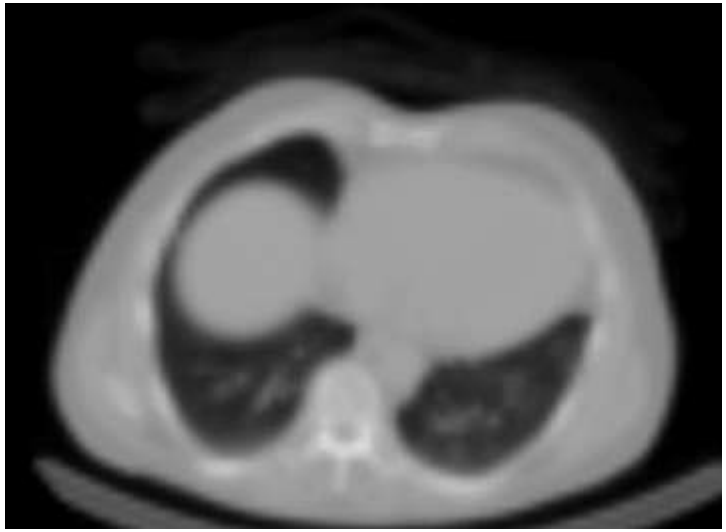
PET/PET-CT IS GOLD STANDARD

^{99m}Tc-MIBI SPECT | ^{82}Rb PET



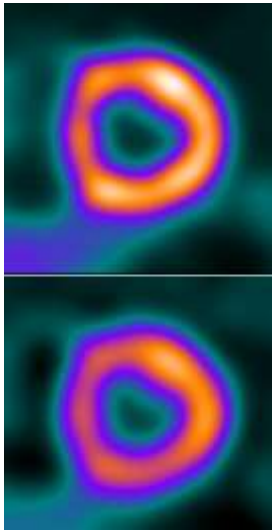
Higher Extraction = Better Defect Resolution

PET/PET-CT IS GOLD STANDARD



Attenuation correction

No attenuation correction



CT Attenuation Correction = Better Image Quality

PET/PET-CT IS GOLD STANDARD

Ideal Population for PET MPI Stress Imaging

- No contraindications based on:
- Body habitus (significant obesity → excellent quality images)
- Renal function
- Lung disease (regadenoson is safe except with active wheezing)
- Age
- Any functional capacity
- Complex coronary disease
- Prior non-diagnostic ischemic evaluation
- CCTA, stress echo, SPECT

Advantages of Cardiac PET

- Better diagnostic accuracy
- Less radiation
- Faster imaging time
- Quantitative blood flow analysis
- Additional diagnostic & prognostic information
- Peak-stress evaluation of LVEF
- Coronary artery calcium scoring

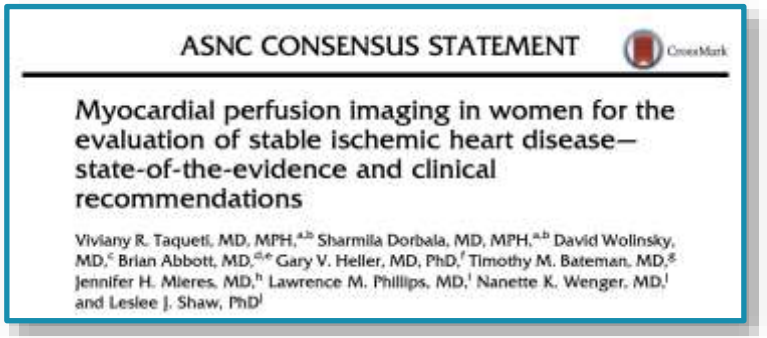
PET/PET-CT IS GOLD STANDARD

Ideal Population for PET MPI Stress Imaging

- No contraindications based on:
- Body habitus (significant obesity → excellent quality images)
- Renal function
- Lung disease (regadenoson is safe except with active wheezing)
- Age
- Any functional capacity
- Complex coronary disease
- Prior non-diagnostic ischemic evaluation
- CCTA, stress echo, SPECT

Advantages of Cardiac PET

- Better diagnostic accuracy
- Less radiation
- Faster imaging time
- Quantitative blood flow analysis
- Additional diagnostic & prognostic information
- Peak-stress evaluation of LVEF
- Coronary artery calcium scoring


ASNC CONSENSUS STATEMENT

Myocardial perfusion imaging in women for the evaluation of stable ischemic heart disease—state-of-the-evidence and clinical recommendations

Viviany R. Taqueti, MD, MPH,[a,b] Sharmila Dorbala, MD, MPH,[a,b] David Wolinsky, MD,[c] Brian Abbott, MD,[d,e] Gary V. Heller, MD, PhD,[f] Timothy M. Bateman, MD,[g] Jennifer H. Mieres, MD,[h] Lawrence M. Phillips, MD,[i] Nanette K. Wenger, MD,[j] and Leslee J. Shaw, PhD[j]

CMD LEARNING OBJECTIVES

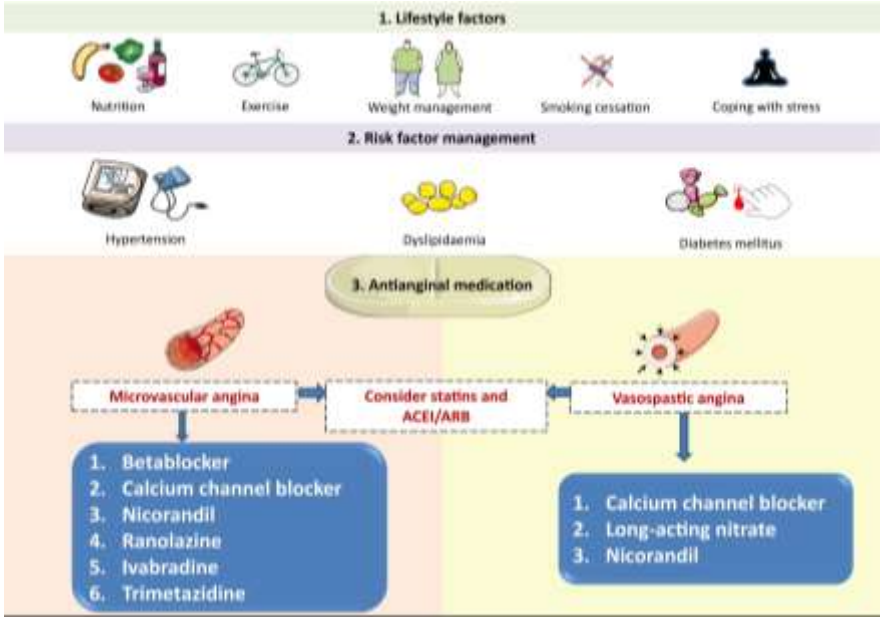
1. Define coronary microvascular disease (CMD) as an important cause of angina

2. Determine the role of non-invasive perfusion imaging to detect and associated prognosis in CMD

3. Discuss management strategies and prevention in populations at high-risk for CMD

TREATMENT OPTIONS ARE LIMITED

Therapeutic Options



Prevention of CMD

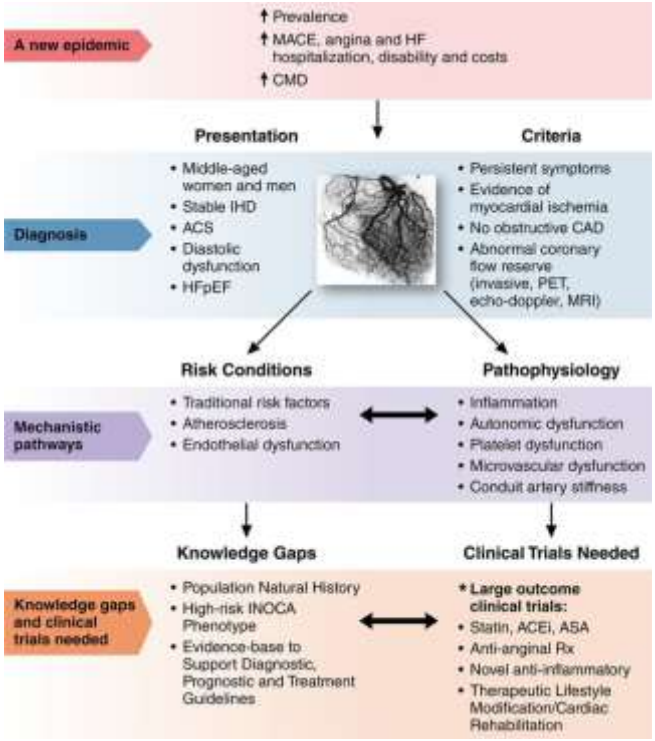
Kunadian et. al. *Eur Heart J* 2020
Lloyd-Jones DM et. al. *Circulation* 2022

POTENTIAL THERAPIES FOR CMD

Pharmacologic	Non-Pharmacologic
• Nitrates • Statins • ACE-I • ACE-I + Aldosterone blockade • Calcium antagonists • Low-dose tricyclic antidepressants • Estrogens • PDE-5 inhibitors • Exercise • L-arginine • Ranolazine • Ivabradine • Ranolazine + Ivabradine • Metformin • Rho-kinase inhibitors • Endothelin receptor blockers	• Exercise • Cognitive behavioral therapy • Transcendental meditation • Transcutaneous electrical nerve stimulation

Bairey Merz et. al. *Circulation* 2017

FUTURE RESEARCH IN CMD



WARRIOR

Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD

STUDY OVERVIEW

ABSTRACT

The WARRIOR (Women's Ischemia Trial to Reduce Events In Non-Obstructive CAD) trial is a multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) evaluating Intensive Medical Therapy vs. Usual Care in 4,422 symptomatic women with ischemia but no obstructive CAD. The hypothesis is that IMT will reduce MACE 20% vs. Usual Care. The primary outcomes are first occurrence of death, MI, Stroke/TIA, Hospitalization for chest pain or heart failure. Secondary outcomes include quality of life, health resource consumption, angina, CV death and primary outcome components. Follow-up will be 5-years using 50 sites: including VA sites, hospitals and private practices across the United States.

ELIGIBILITY

Enrolled women will be clinically stable, with angina or equivalent symptoms of sufficient severity to seek, or have sought, referral for coronary angiography or coronary CT angiogram within the previous 5 years.

INCLUSION CRITERIA

- Signs and symptoms of suspected ischemia prompting referral for further evaluation by cardiac catheterization or coronary CT angiogram last 5 years
- Non-obstructive CAD defined as 0 to 49% diameter reduction of a major epicardial vessel or a FFR>0.80
- Age ≥18 yrs.

Bairey Merz et. al. *Circulation* 2017

KEY TAKEAWAYS FOR CMD IN SIHD

1. Assessment for obstructive CAD alone is inadequate among people with chest pain syndromes

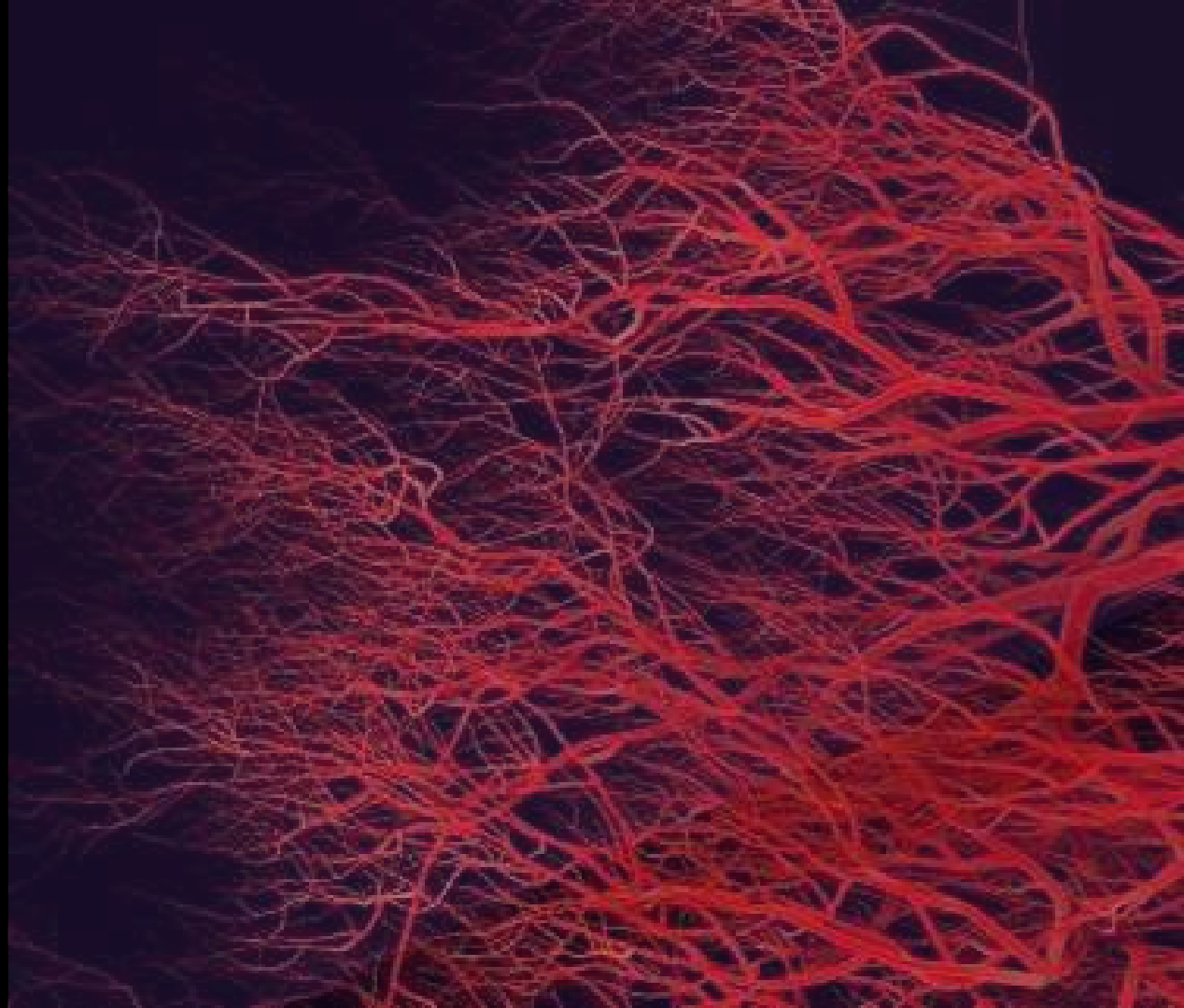
2. Diagnostic testing with perfusion imaging (PET/MRI) is important in identifying CMD, which is highly prevalent in patients with CP

3. Future research should focus on underlying pathogenesis to identify novel targeted therapies in at-risk groups (e.g., women, HFpEF)

Thank you.

Questions?

@HeartDocSadiya



Northwestern Medicine®

Coronary Microvascular Disease:
The Small but Mighty Vessels

Cardiovascular Symposium India

January 21, 2023

Sadiya S. Khan, MD, MSc, FACC, FAHA
Assistant Professor of Medicine and Preventive Medicine
Associate Program Director, CVD Fellowship
Director of Research, Section of Heart Failure
Northwestern University Feinberg School of Medicine
Associate Editor, *JAMA Cardiology*
@HeartDocSadiya