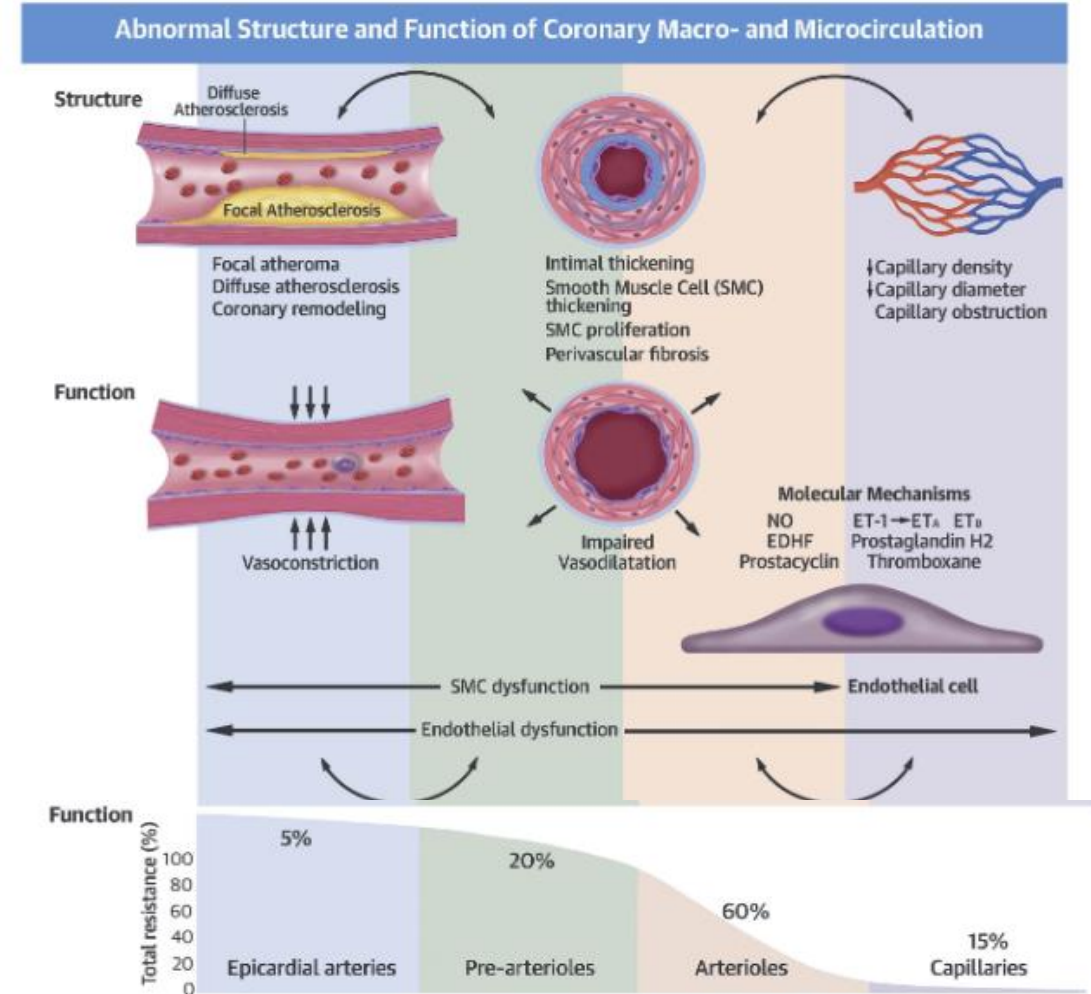
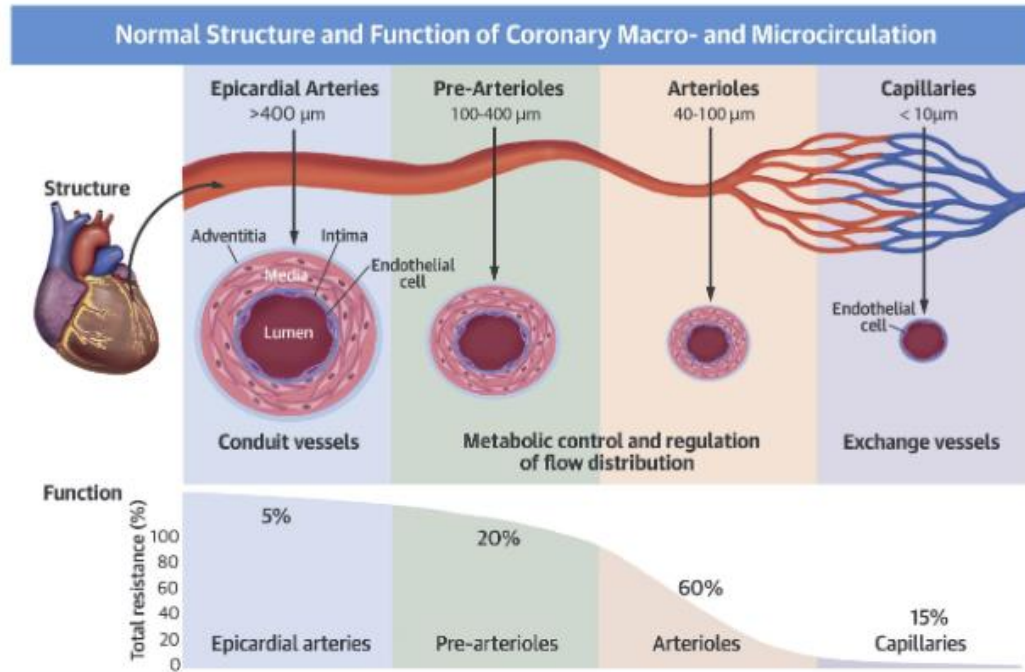


# THERAPEUTICS: TARGETING VESSEL REACTIVITY WITH MEDICATION

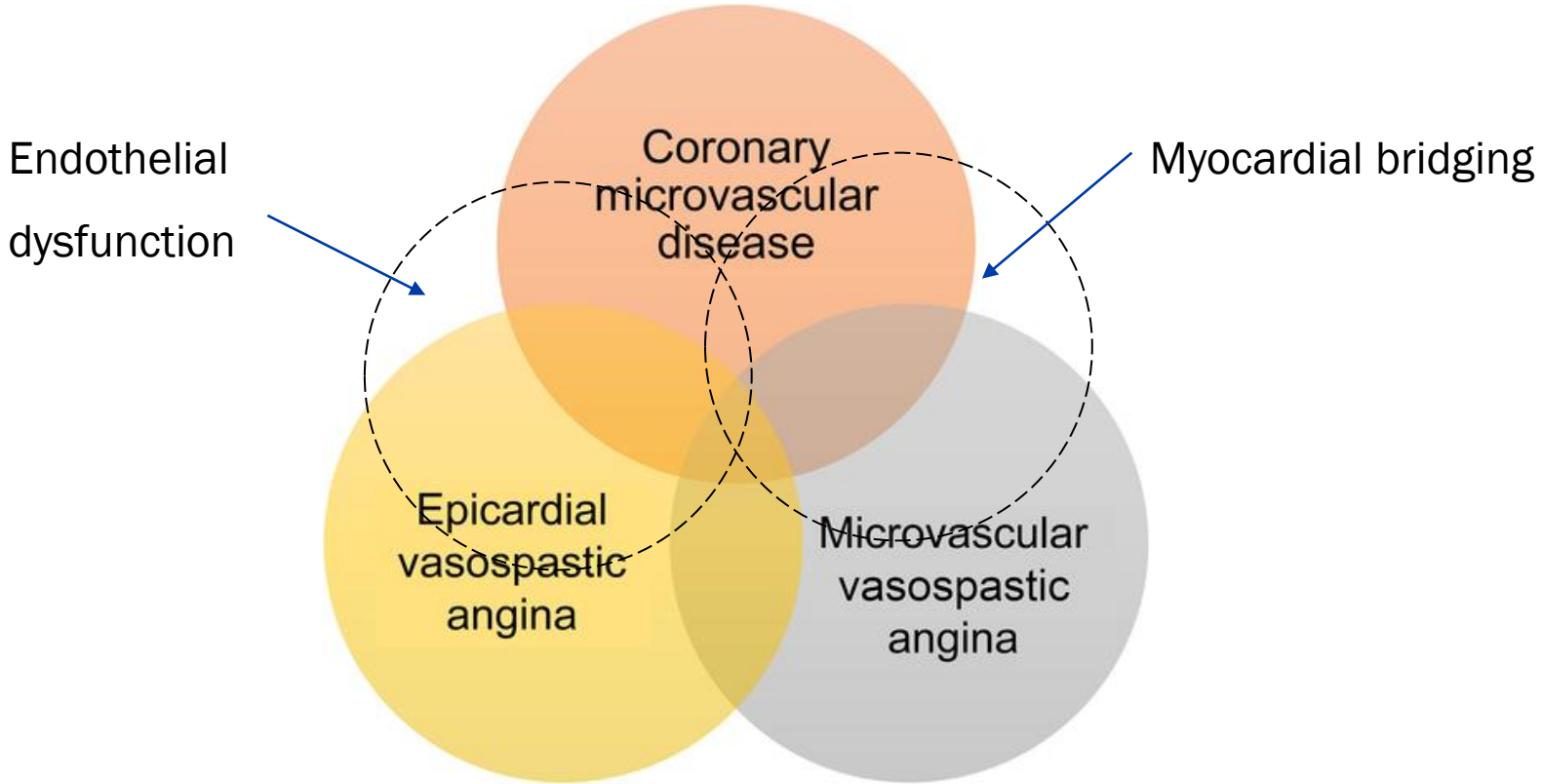
Nisha I. Parikh MD MPH  
System Director, Women's Heart  
Cardiovascular Institute  
Director of Cardiovascular Diseases,  
Katz Institute of Women's Health

# ANOCA ENDOTYPES IN TERMS OF CORONARY ARTERY ANATOMY




## CENTRAL ILLUSTRATION: Normal and Abnormal Structure and Function of the Coronary Macrocirculation and Microcirculation



# OVERLAP OF ANOCA ENDOTYPES



Doyeon Hwang et al. *JACC: Asia* 2023; 3:169-184.

 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

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)			

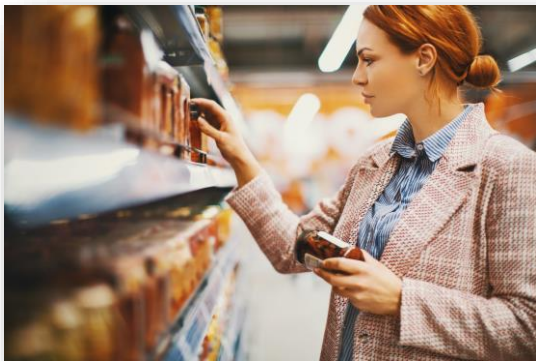
Ranolazine	Long-Acting Nitrates	CCB (DHP/non-DHP)	Long-Acting Nitrates	Ivabradine
CCB (DHP/non-DHP)	Ranolazine		Cilostazol	
Ivabradine				

TCA/SSRI	TCA/SSRI		Cyproheptadine	Surgical Unroofing
L-Arginine	L-Arginine		Hormone Therapy	
PDE-5-Inhibition	Hormone Therapy			
Adenosine Antagonists	Metformin/GLP-1			
Hormone Therapy	EECP			
Metformin/GLP-1				
EECP				

# MICROVASCULAR ANGINA- GOALS OF TREATMENT

1. Prevent and treat angina
2. Get patients to their desired level of exercise tolerance
3. Prevent long-term atherosclerotic cardiovascular disease and related adverse outcomes

**Coronary  
Microvascular  
Disease**



# AUDIENCE QUESTION #1

What is the initial step to treat confirmed coronary microvascular dysfunction?

1. Imdur
2. EECp
3. Cilostazol
4. Betablocker
5. Exercise, weight loss, SL NTG, BP control



# TREATMENT OF MICROVASCULAR ANGINA- INITIAL STEPS

## Sublingual nitroglycerin



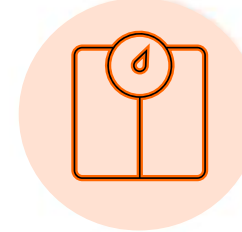
## Lifestyle modification



Nutrition



Exercise



Weight management



Smoking cessation



Coping with stress

## Risk factor management



Hypertension



Dyslipidaemia



Diabetes mellitus

## Secondary prevention

\* *Aspirin*

\* *Statin*

*Ace-inhibitor preferred*



# TREATMENT OF MICROVASCULAR ANGINA- CLASSIFY ANGINA

Effort angina



Rest angina



1

- Start beta-blocker\*
- Nitro patch prior to exercise

- Start calcium channel blocker
- Titrate to symptom relief

2

Reassess at 1 month  
Persistent angina or medication intolerance?

3

Switch to calcium channel blocker

Switch to beta blocker

\*Preferably BB with vasodilatory, not sympathomimetic effect, eg nebivolol

# TREATMENT OF MICROVASCULAR ANGINA- UNACCEPTABLE ANGINA AFTER 1 MONTH

\* therapies for refractory angina that have mixed/ little supportive evidence

1 Add/ titrate **ranolazine**

2 Persistent symptoms?  
Switch to/ add **ivabradine**

3 Persistent symptoms?

1. Assess comorbidities
  - a. Depression/hyperalgesia: add **imipramine**
  - b. Metabolic syndrome/prediabetes: add **metformin**
2. Try **sildenafil**

4 Persistent symptoms:

- Confirm diagnosis with functional testing
- Refer for possible **spinal cord stimulation\***
- Less evidence: **EECP, coronary sinus reduction\***

# SUMMARY OF EVIDENCE OF EFFICACY FOR MICROVASCULAR ANGINA THERAPIES

Therapy	CMD increase?	Symptom improvement?
Weight loss (exercise, diet, bariatric surgery)	--	+
Stress reduction (relaxation, meditation)	?	+

Therapy	CMD increase?	Symptom improvement?
Ace-inhibitor	+	+
Betablocker	?	+
Statin	-	?
Ranolazine	?	+/--
Calcium Channel blockers	--	+/--
Long acting nitrates	?	+
Ivabradine	--	+
L-arginine	--	+
Sildenafil	+	?

# AUDIENCE QUESTION #1: ANSWER

What is the initial step to treat confirmed coronary microvascular dysfunction?

1. Imdur
2. EECp
3. Cilostazol
4. Betablocker
5. **Exercise, weight loss, SL NTG, BP control**

# Epicardial Artery Vasospasm



# AUDIENCE QUESTION

Following smoking cessation counseling, SL nitroglycerin, and ASCVD risk factor modification, what typically the next treatment for coronary artery vasospasm?

1. PCI of affected vessel
2. IV magnesium
3. Hormone replacement therapy
4. Propanolol
5. Diltiazem

# TREATMENT OF CORONARY VASOSPASM

1

## Initial therapy

- SL nitroglycerin
- Smoking cessation (smoking is a trigger, can decrease episode frequency)
- ASCVD risk factor modification (ASCVD and coronary vasospasm often co-exist)



# TREATMENT OF CORONARY VASOSPASM- CALCIUM CHANNEL BLOCKERS

2

- Diltiazem 240 to 360 mg daily or amlodipine 5 to 10 mg daily.  
[Higher doses (eg, diltiazem up to a dose of 960 mg per day) can be used in patients with refractory angina].
- Long-acting nifedipine (30 to 90 mg daily) is less used (*long-acting nifedipine can cause severe hypotension and reflex tachycardia*).
- Short-acting formulations of nifedipine *should not* be used because may cause rebound symptoms.

# TREATMENT OF CORONARY VASOSPASM- SUBSEQUENT THERAPY FOR PERSISTENT SYMPTOMS (UP TO 15%)

3

Add **long-acting nitrate** (eg, imdur 60 mg once daily, titrated up to 120 mg once daily). Note: *nitrate tolerance can occur, and long-acting nitrates may trigger endothelial dysfunction.*

*Others:*

- **Statins**– addition of fluvastatin showed efficacy in small open label trial
- Addition of **guanethidine, clonidine, or cilostazol** have reported benefit

*Not enough data, possibly helpful:*

- **Magnesium** supplementation in those deficient
- **PCI/CABG** for those with concomitant obstructive disease
- **Surgical sympathetic denervation**
- **Fasudil** (rho kinase inhibitor) studied in Asia in subarachnoid hemorrhage surgical patients.

# EVIDENCE OF EFFICACY FOR SPASM-FOCUSED THERAPIES

Therapy	Symptom improvement	Microvascular spasm treatment
Calcium-channel blockers*	+	+
Short acting nitrates	+	+/--
Statins	+	?
Long-acting nitrates	?	?
Cilastozol	?	?

\*EDIT-CMD Study

*Smilowitz et al, JACC 2023*

# AUDIENCE QUESTION #2- ANSWER

Following smoking cessation counseling, SL nitroglycerin, and ASCVD risk factor modification, what typically the next treatment for coronary artery vasospasm?

1. PCI of affected vessel
2. IV magnesium
3. Hormone replacement therapy
4. Propanolol
5. **Diltiazem**

# EFFICACY OF THIRD LINE THERAPIES FOR UNDIFFERENTIATED ANOCA (SMALL OR MIXED STUDIES)

Therapy	Symptom improvement	Comments
Antidepressants	+	Pain, psych sx.
Glycemic control	+	Duke treadmill score, peripheral
Hormone therapy	+	No improvement in noninvasive ischemia (CMR)
Adenosine agonists	+	Targets nociception

*Smilowitz et al, JACC 2023*

# PROCEDURE AND DEVICE-BASED THERAPY FOR ANOCA

Therapy	Symptom improvement	Comments
Nerve stimulation	+	N=8 ANOCA patients
EECP	?/+	Nonrandomized study
Coronary sinus reducer	?	CMD study underway
Stellate ganglion block	+	Only in refractory patients

*Smilowitz et al, JACC 2023*

**THANK YOU**

