Coronary heart disease- men and women are really different?

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Faculty/Presenter Disclosure

- **Faculty: Olga Toleva**

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  - **Other:**

Mitigating Potential Bias

- Not Applicable

Objectives
Cardiac Ischemic Syndromes in Women
Demystifying "Normal" Coronaries

- Chest pain and ischemia syndromes in women
- Steps in the diagnosis, treatment and follow up
- Coronary Micro Vascular Dysfunction (CMD) a new paradigm in angina without significant coronary artery disease

Clinical presentations of Chest Pain

- Acute coronary syndrome unstable angina
- NSTEMI
- STEMI
- Sudden cardiac death VT/VF
- Stable Angina
- “Chest pain NYD”- non cardiac or non ischemic chest pain

Symptoms and Signs

Men

- Crushing chest pain
- Severe shortness of breath
- Chest pain radiating to the arms
- Jaw pain
- Profuse sweating

Women

- Chest pressure
- Shortness of breath
- Arm pain / burning only
- Nausea or stomach pain
- Back, neck, jaw pain
- Fatigue
- Sweating

Chest pain and MI

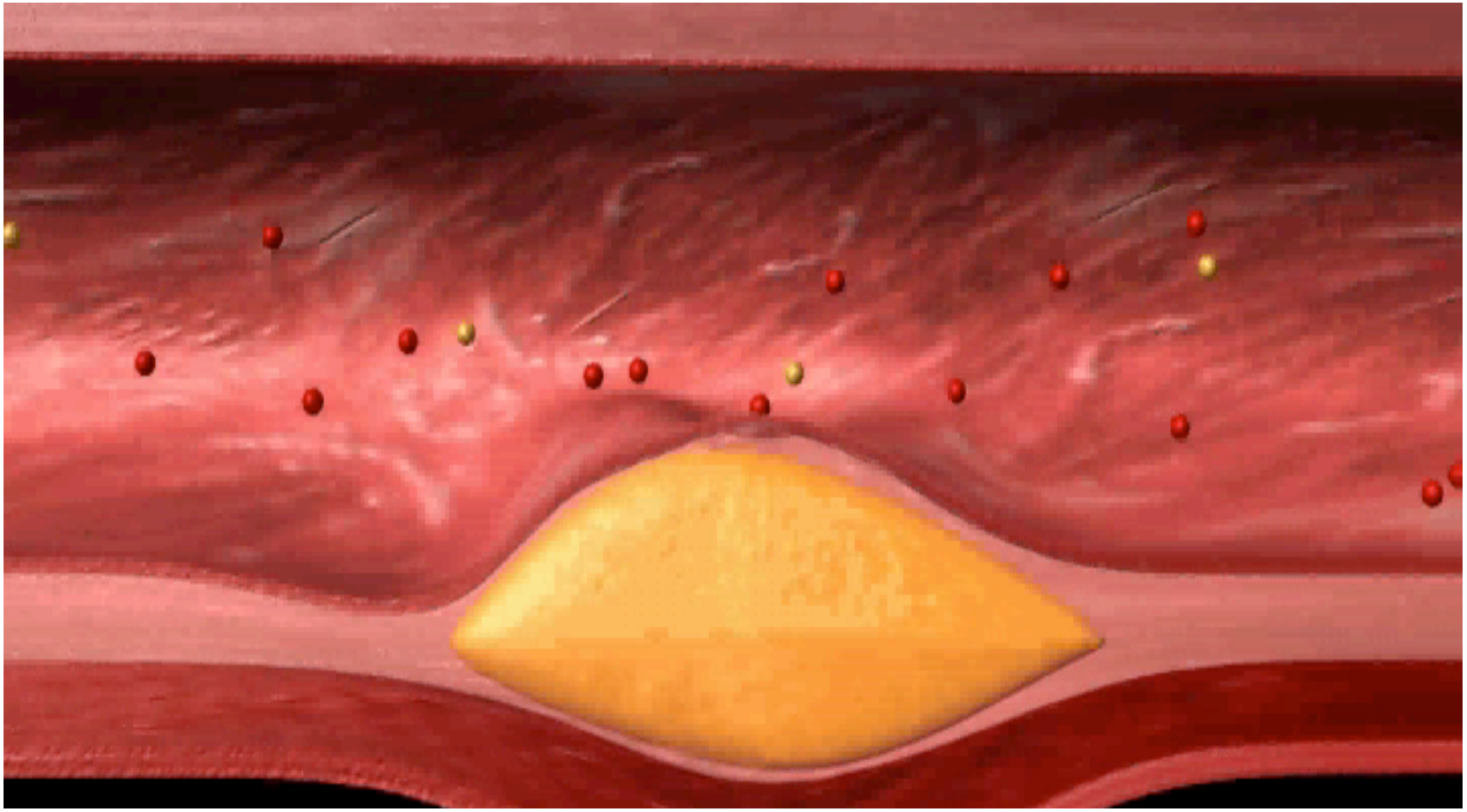
Atherosclerosis

- Smoking
- High cholesterol
- Diabetes
- Hypertension
- Family history of MI
- Postmenopausal

“Normal“ coronaries

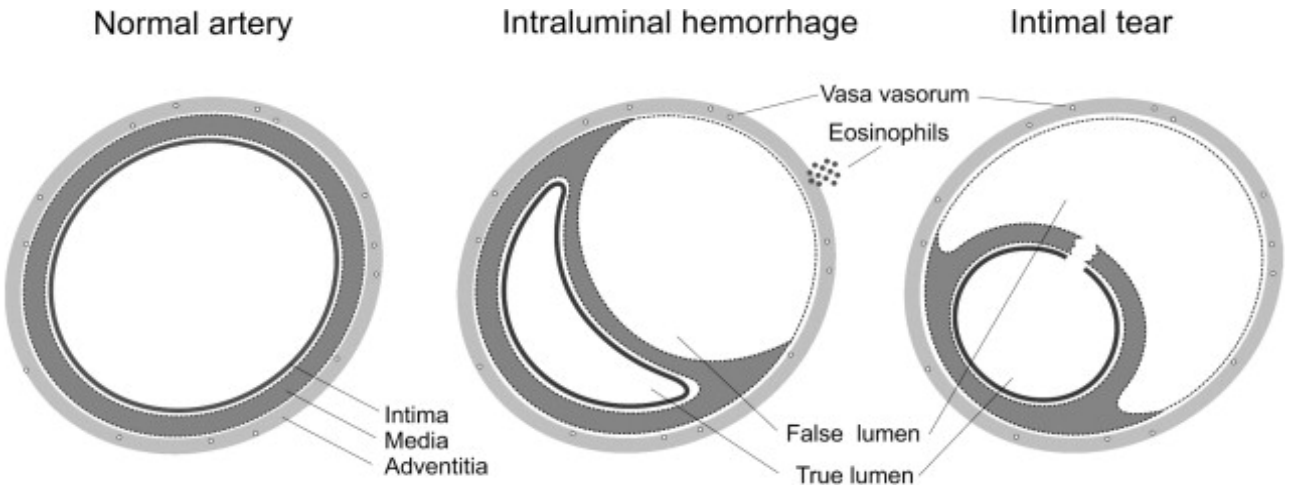
- Spontaneous coronary dissection SCAD
- Epicardial coronary spasm Prinzmetal
- Broken heart syndrome Takotsubo
- MI Non Obstructive Coronary arteries MINOCA
- MI Normal Coronary Arteries MINCA
- Ischemia with Normal Coronary arteries INCA
- Muscle bridge
- Syndrome Y slow flow
- Syndrome X CMD

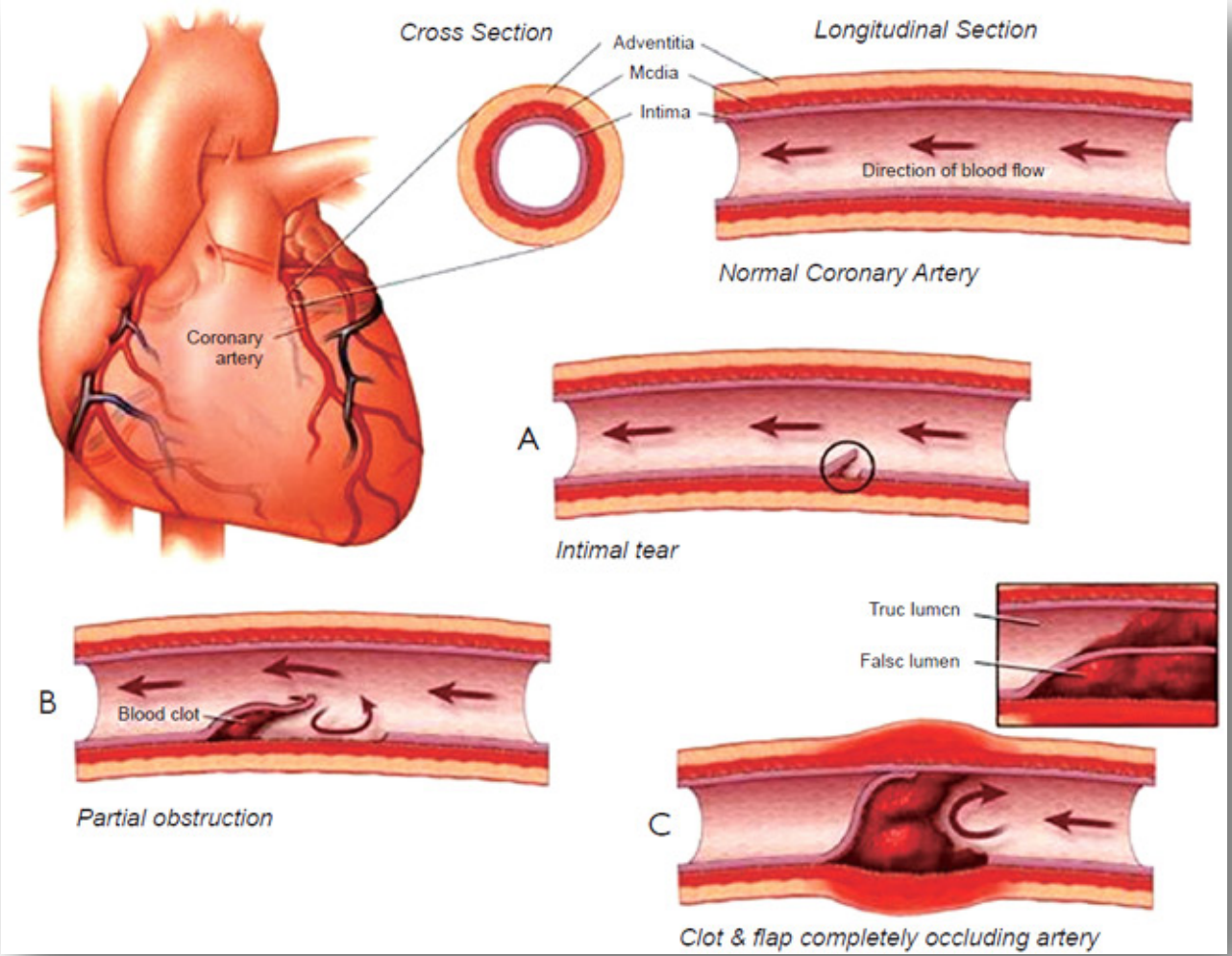
Acute MI with Atherosclerosis



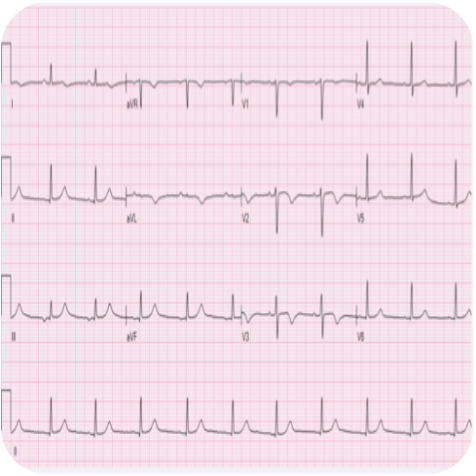
Acute MI with SCAD

- In SCAD we have narrowing of the lumen of the coronary artery due to expansion of the intramural hematoma which could lead to partial narrowing (NSTEMI) or complete occlusion of the vessel (STEMI).



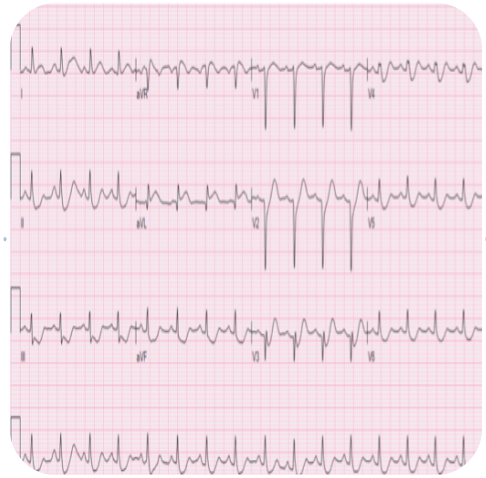

Cross Section
Adventitia
Media
Intima
Longitudinal Section
Direction of blood flow
Normal Coronary Artery
Coronary artery
A
Intimal tear
True lumen
False lumen
B
Blood clot
Partial obstruction
C
Clot & flap completely occluding artery

Spectrum of SCAD presentation

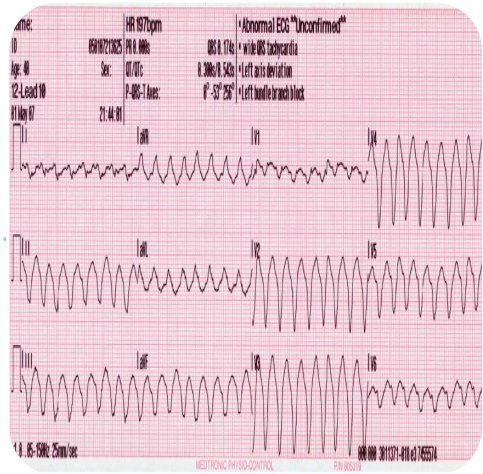


NSTEMI

STEMI



Shock



VT/VF

Clinical features associated with SCAD

- Myocardial infarction in women younger 50 years of age
- Absence of traditional cardiac risk factors
- No evidence of coronary atherosclerosis on angiography
- Peripartum state
- Hx of fibro muscular dysplasia
- Hx of connective tissue disorder (Ehler Danlos, Lois Deitz, Cystic medial necrosis)
- Hx of Systemic inflammatory condition – PAN, Churg-Strauss, Rheumatoid arthritis, Sarcoidosis
- Recent intensive exercise or emotional stress

Coronary Angiogram Classification of Spontaneous Coronary Artery Dissection J. Saw Catheterization and Cardiovascular Interventions 84:1115–1122 (2014)

History and Predisposing factors

- Emotional triggers- stressful situations
- Physical triggers- resistance or high intensity training
- Pregnancy and peripartum state
- Hormonal triggers
- Genetic predisposition connective tissue disorders or inflammatory condition

CanSCAD cohort study J. Saw et al, EHJ 2019; 40 1188-1197

Angiography and intravascular imaging

- Type 1 SCAD mostly staining
- Type 2 SCAD smooth edges with narrowing of the lumen
- Type 3 SCAD mimics atherosclerosis
- IVUS- intramural hematoma (IMH), extent of false and true lumen
- OCT- features of intimal tear, intraluminal thrombi, false lumen and Intramural hematoma

Coronary Angiogram Classification of Spontaneous Coronary Artery Dissection J. Saw Catheterization and Cardiovascular Interventions 84:1115–1122 (2014)

Can SCAD

median (Q1, Q3), or n (%)	N=750
Acute Coronary Syndrome	
STEMI	223 (29.7%)
NSTEMI	524 (69.9%)
Unstable angina	3 (0.4%)
Presenting main symptom	
Chest discomfort	686 (91.5%)
Back discomfort	15 (2.0%)
Shoulder or arm discomfort	10 (1.3%)
Dyspnea	7 (0.9%)
Arrhythmia	8 (1.1%)
Other	24 (3.2%)
Troponin Levels	
Elevated Troponin	732 (97.6%)
Troponin not elevated	3 (0.4%)
Troponin value not available	15 (2.0%)
Emotional stress (high or severe)	377 (50.3%)
Unusually intense physical stress	216 (28.9%)
Isometric stress >50lb	74 (9.8%)

median (Q1, Q3), or n (%)	N=750
ECG changes	
Normal ECG	170 (22.7%)
Non-specific changes	81 (10.8%)
T inversion	138 (18.4%)
ST depression	47 (6.3%)
ST elevation <1mm	85 (11.3%)
ST elevation >1mm	187 (24.9%)
Q waves	11 (1.5%)
LBBB	5 (0.7%)
Other	26 (3.5%)
Ventricular Tachycardia or Fibrillation	61 (8.1%)
Left ventricular function assessment	
Ejection fraction assessed	737 (98.2%)
Angiogram	491 (65.5%)
Echocardiogram	243 (32.4%)
Initial ejection fraction (%)	55 (50, 60)
Ejection fraction <50%	188/734 (25.6%)
Ejection fraction <35%	28/734 (3.8%)
Wall motion abnormality	
No abnormality	114 (15.2%)
Hypokinesis	359 (47.9%)
Akinesis	215 (28.7%)
Dyskinesis	43 (5.7%)
Not assessed	19 (2.5%)

CanSCAD cohort study J. Saw et al, EHJ 2019; 40 1188-1197

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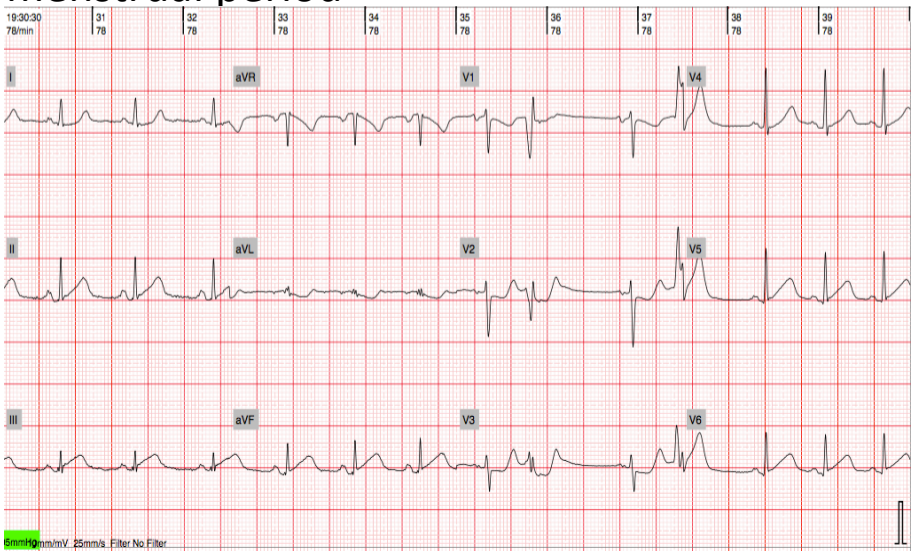
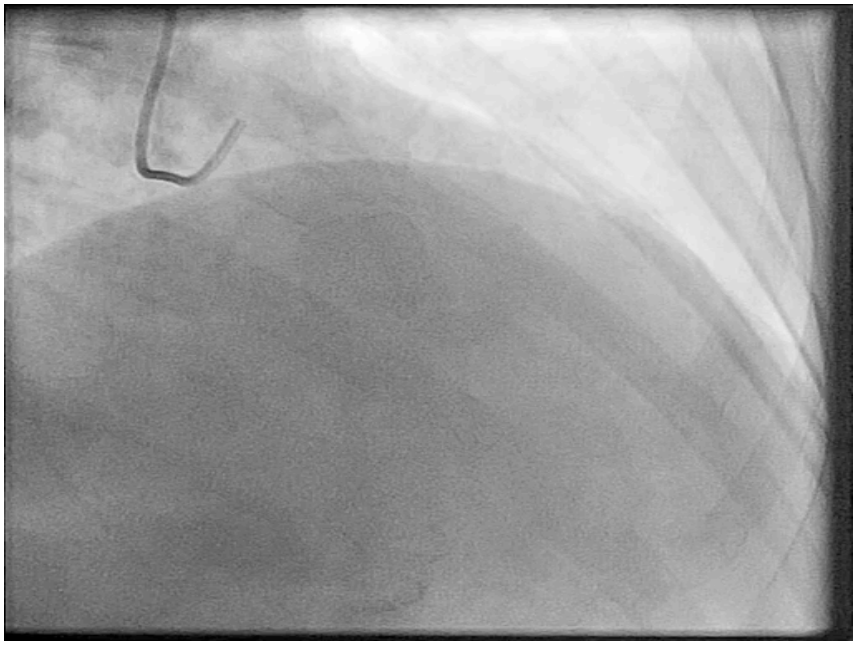
Case of SCAD with STEMI

- 49 year old woman with sudden onset chest pain after lifting heavy crockpot. Inferior STEMI.
- Long distance runner. No cardiac risk factors.
- Past history: heavy menstrual bleeding
- Medications: tranexamic acid for heavy menstrual period





SCAD was suspected in the OM and LAD. Possible clot in the OM and likely culprit lesion due to poor flow.
The LAD lesion had long segment of narrowing

Life post SCAD - what to advice your patient

- To stent or not to stent in SCAD
- Chest pain and ongoing symptoms
- Need for angiographic or CT- angiographic follow up
- Ischemia testing post SCAD
- Exercise prescription
- What is the risk of reoccurrence of SCAD and how to prevent it

SCAD clinic and Cardiac Rehabilitation Program

Strategies to Prevent Recurrent SCAD

- Beta-blockers to reduce arterial shear stress (dP/dT)
- Optimal management of hypertension
- Reduce potential precipitating triggers:
  - Emotional stress: psychosocial support, peer-group support
  - Physical stress: avoid heavy weight lifting (<30-50 pounds), avoid competitive sports, participate in Cardiac Rehab Program
- **Avoid** hormonal therapies, sympatho-mimetic drugs, intense coughing/ retching/vomiting/bowel straining (Valsalva-type activities), future pregnancy

TABLE 6 In-Hospital and Follow-Up MACE

	Patients (N = 327)
Long-term events (Median FU 3.1yr)	(%/yr)
Death	0.3
MI	4.8
Recurrent de novo SCAD	2.8
Stroke/TIA	0.3
Revascularization	1.5
Overall MACE	5.8
Angina hospitalization	2.0

Saw J, et al. JACC 2017 Aug;70(9):1148-58. Saw J, et al. JACC 2016;68:297-312. Hayes et al, Circulation 2018;137:e523-e557.

Long term predictors for recurrence

TABLE 8 Univariate and Multivariate Predictors of Recurrent SCAD

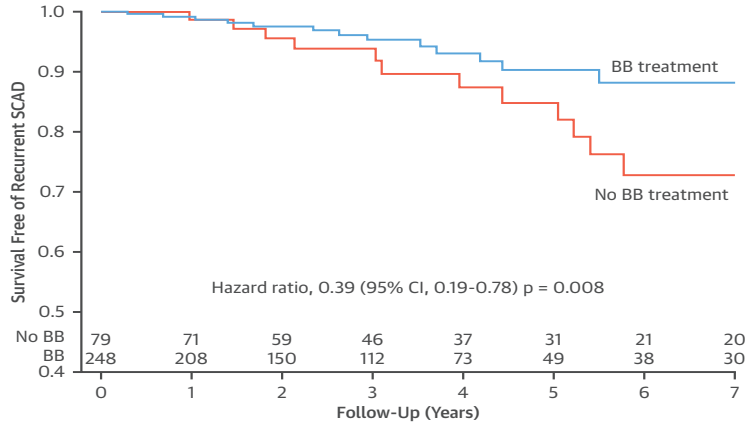
Predictor	Univariate Model		Multivariate Model	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Hypertension	2.28 (1.14–4.55)	0.019	2.46 (1.23–4.93)	0.011
Beta-blocker	0.39 (0.19–0.78)	0.008	0.36 (0.18–0.73)	0.004
Calcium-channel blocker	2.57 (1.25–5.31)	0.011		
Aspirin	0.36 (0.18–0.73)	0.004		

CI = confidence interval; SCAD = spontaneous coronary artery dissection.

Saw J, et al. JACC 2017 Aug;70(9):1148-58.

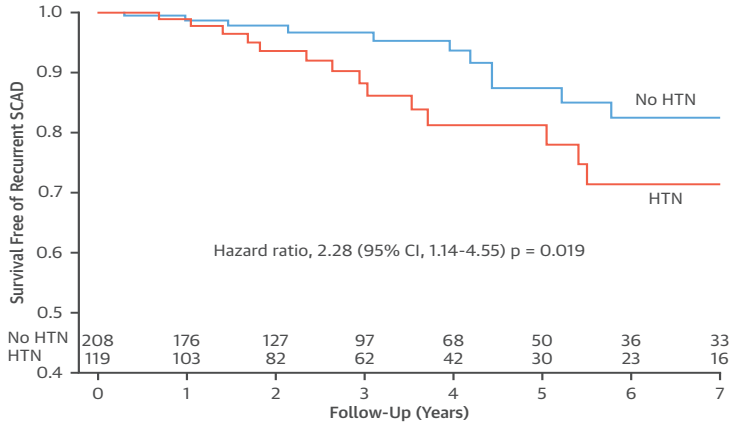
Survival free of SCAD

FIGURE 4 Survival Free of Recurrent SCAD: Beta-Blocker Treatment



BB treatment reduced the risk of recurrent SCAD. BB = beta-blocker; other abbreviations as in Figure 3.

FIGURE 3 Survival Free of Recurrent SCAD: Hypertension



Presence of HTN increased the risk of recurrent SCAD. CI = confidence interval; HTN = hypertension; SCAD = spontaneous coronary artery dissection.

Saw J, et al. JACC 2017 Aug;70(9):1148-58.

Summary SCAD

- SCAD in-hospital event rates are relatively low
- PCI success rate is 64-91% with high risk of potential complications (iatrogenic dissection, extension of dissection, stent thrombosis)
- Conservative management is the first choice of treatment unless high risk features
- Natural progression of SCAD healing is overall 86.3% healed and at ≥30d: 95% healed. And at 6 months 96.7-100% are healed

Summary SCAD

- Recurrent SCAD has been reported in up to 30% of cases with a 4- to 10-year follow-up in different series
- Recurrent SCAD is accounting for the majority of recurrent MI at long-term follow-up that is unrelated to PCI
- Recurrent MI in the 30 day and up to 3 years FU is 4-6%
- Recurrent de novo SCAD 2.8%
- Regular Cardiology follow up is important in the management and reduction of events

Micro Vascular dysfunction post SCAD

- 10-20% of patients post SCAD have chest pain >3 months post event despite healing of the SCAD
- Coronary Reactivity Testing (CRT) was measured in SCAD patients post healing
- CRT was performed in the SCAD and non - SCAD artery
- 82% of patients had abnormal Coronary Flow Reserve<2.5
- 72% had abnormal Intra-Myocardial Resistance>25

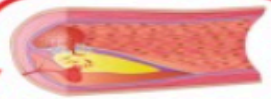
Suggestive of MVD playing a role in the post SCAD angina

Sedlak et al CCC abstract 2017

Mechanisms of myocardial ischaemia

Epicardial coronary arteries

Atherosclerotic disease



- Stable plaque
  - Reduction in CFR
    - Demand ischaemia ± angina
- Vulnerable plaque
  - Plaque rupture
    - Thrombosis
      - Acute coronary syndromes/infarction

Vasospastic disease

- Focal/transient vasospasm
  - Prinzmetal angina
- Persistent vasospasm
  - Myocardial infarction

Coronary microcirculation

Microvascular dysfunction

- Impairs coronary physiology and myocardial blood flow in subjects with risk factors
  - Contributes to myocardial ischaemia in CAD and CMP
  - Induces severe acute ischaemia 'Takotsubo'

These three mechanisms can overlap

Functional CAD

- Umbrella term used to describe dysfunction in the behaviour of the epicardial and microvascular coronary arteries.
  - Coronary microvascular disease (CMVD)
  - Syndrome X
  - Syndrome Y: Slow flow syndrome
  - Epicardial Vasospasm /Prinzmetal Angina/
  - Takotsubo Cardiomyopathy
  - No re-flow phenomena
  - MINOCA- MI with no obstructive CAD
  - INOCA- Ischemia with no obstructive CAD

Demystifying "Normal" Coronaries

Coronary micro-vascular dysfunction CMD

- **MINOCA** MI with non-obstructive coronary arteries
- **MINCA** MI with normal coronaries

- **INOCA** ischemia with non-obstructive coronaries
- **INCA** ischemia with normal coronaries

Exertional Angina
Abnormal stress test
Angiogram appears normal or only mild disease or slow flow

- More commonly diagnosed in women

- Debilitating symptoms - repeated diagnostic evaluations and hospitalizations

Reis et al Am Heart J 2001;141:735-41. WISE study

Why Should We Care?

- Impaired coronary vascular function is associated with adverse outcomes: MI, CHF, arrhythmias, stroke, and death.
- Significant burden on the health care system (recurrent ER visits, multiple angiograms, repeat cardiac investigations, numerous specialists-GI, respirology)
- Patients suffer from debilitating symptoms
- High prevalence of anxiety and depression
- Limited exercise tolerance
- Lower quality of life
- Patients are given false reassurance
- Microvascular dysfunction occurs in up to 50% of patients with STEMI contributing to worse clinical outcomes
- Optimal treatment strategies are undefined

(Kothawade & Merz, 2011) (Jaskanwal et al. 2015) (Bulluck, et al, 2017)

	Clinical setting	Main pathogenetic mechanisms
Type 1: in the absence of myocardial diseases and obstructive CAD	Risk factors Microvascular angina	Endothelial dysfunction SMC dysfunction Vascular remodelling
Type 2: in myocardial diseases	Hypertrophic cardiomyopathy Dilated cardiomyopathy Anderson-Fabry's disease Amyloidosis Myocarditis Aortic stenosis	Vascular remodelling SMC dysfunction Extramural compression Luminal obstruction
Type 3: in obstructive CAD	Stable angina Acute coronary syndrome	Endothelial dysfunction SMC dysfunction Luminal obstruction
Type 4: iatrogenic	PCI Coronary artery grafting	Luminal obstruction Autonomic dysfunction

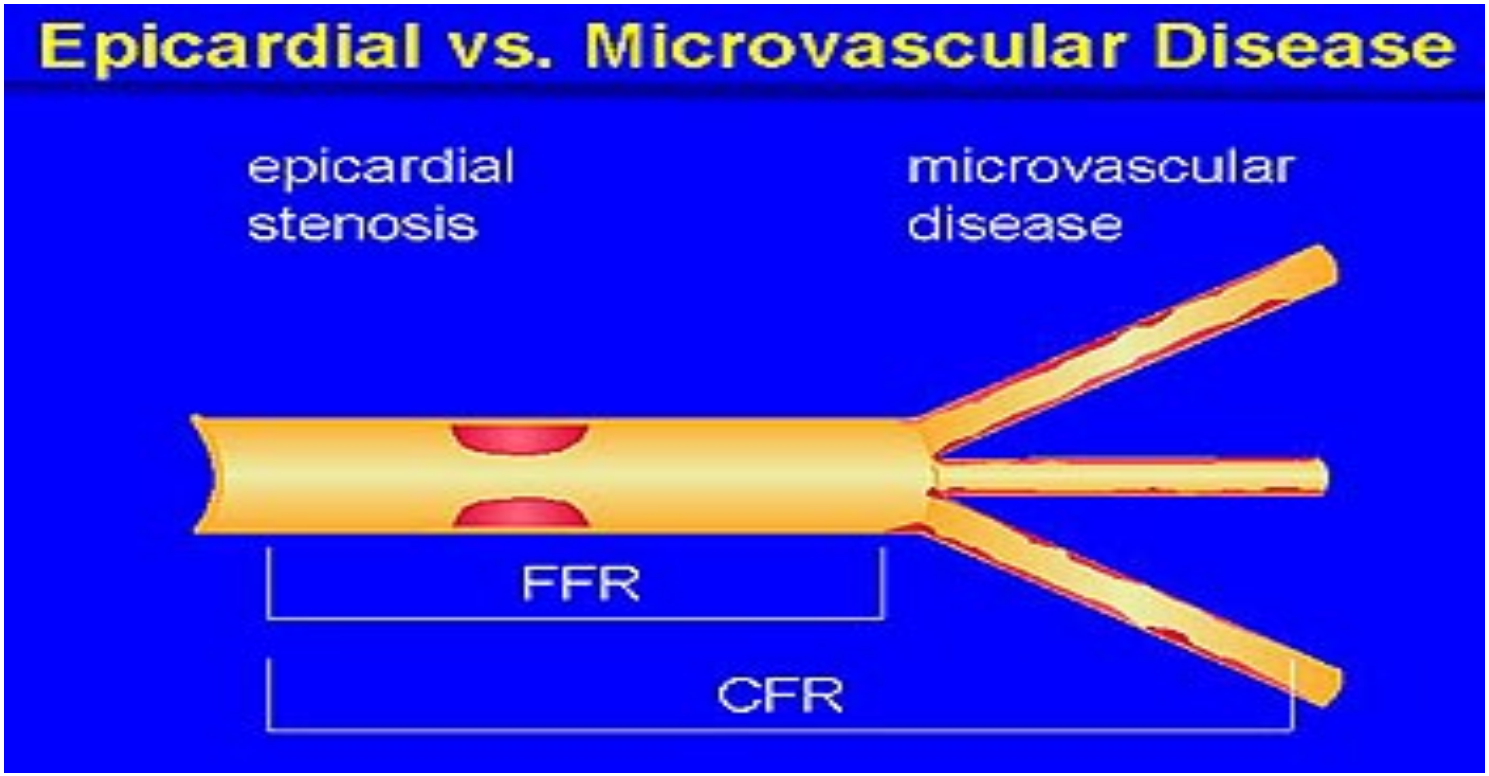
Crea et al Eur Heart J. 2014 May 1; 35(17): 1101–1111.
doi: 10.1093/eurheartj/eht513

When Should Functional CAD be Suspected?

- Anyone who has ACS with no obstructive CAD/SCAD
- Recurrent CP, abnormal non-invasive testing, normal angiogram
- Slow flow documented on angiogram TIMI >40
- Takotsubo CMP
- Recurrent CP sounding ischemic, no other cause of CP identified

Invasive Physiology Study

- Assesses patients for physiological mechanisms contributing to coronary ischemia other than severe flow-limiting stenoses
- Unable to directly visualize coronary microvasculature
- Microvasculature is indirectly tested via measurement of coronary flow and resistance down arteries
- Epicardial arteries reactivity are also tested
- Invasive, guidewire-based measurement of coronary flow reserve and resistance via thermodilution method or Doppler flow



Fractional flow reserve and coronary flow reserve are complementary measures that inform about the physiology and microvascular disease. Pijls 2000

Coronary Microvascular Reactivity to Adenosine Predicts Adverse Outcome in Women Evaluated for Suspected Ischemia

Results From the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) Study

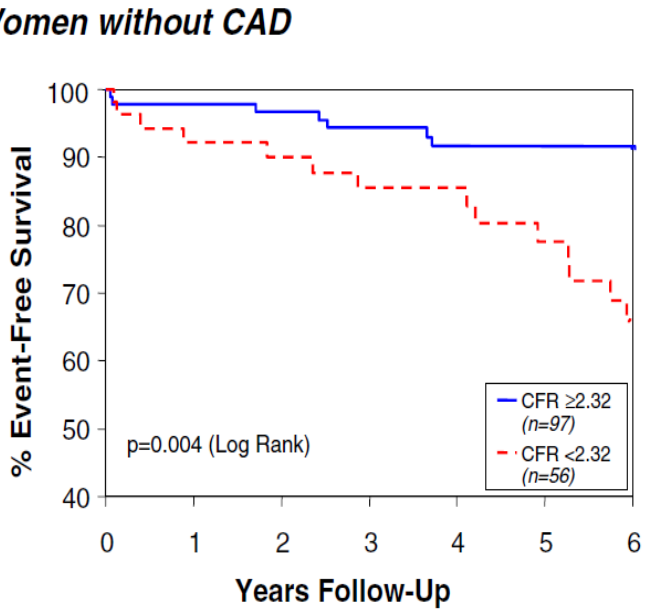
Carl J. Pepine, MD,* R. David Anderson, MD,* Barry L. Sharaf, MD,† Steven E. Reis, MD,‡
Karen M. Smith, MD,* Eileen M. Handberg, PHD,* B. Delia Johnson, PHD,‡
George Sopko, MD, MPH,§ C. Noel Bairey Merz, MD‖

Gainesville, Florida; Providence, Rhode Island; Pittsburgh, Pennsylvania; and Los Angeles, California

Abnormal CFR independently predicts cardiac events in women with non obstructive CAD

The WISE study at 9.7 year follow-up demonstrated more adverse events:

MI, Death, Stroke, New onset heart failure in women with reduced coronary flow reserve and assessed by adenosine and acetylcholine

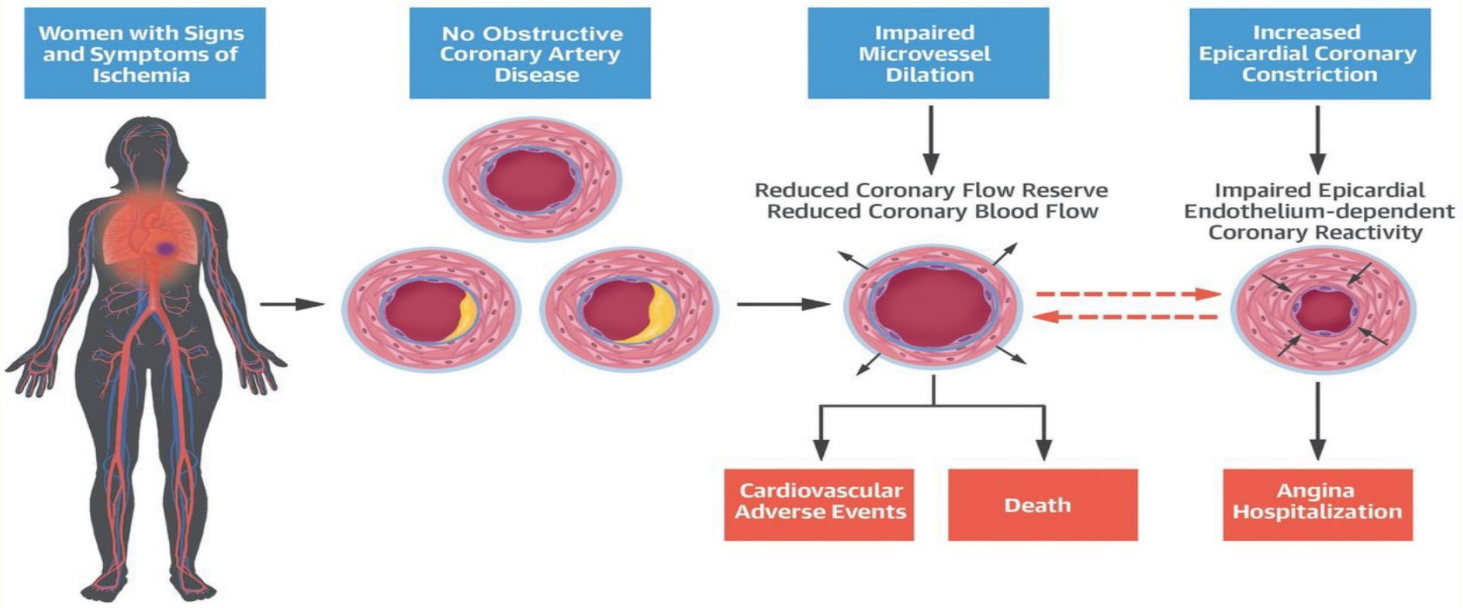


12%

26%

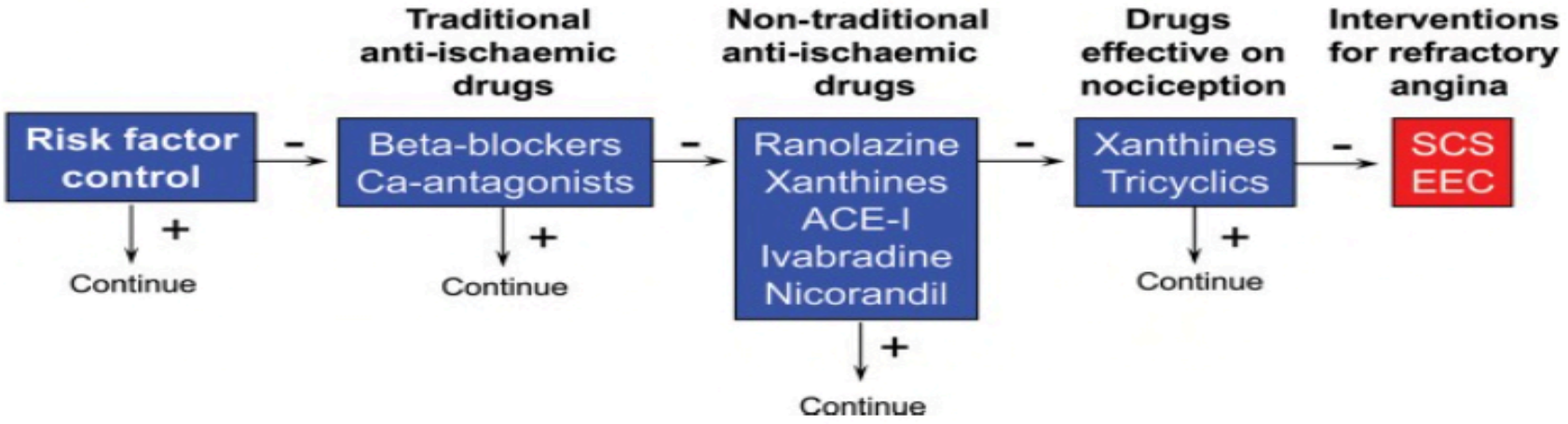
Pepine et al J Am Coll Cardiol. 2010;55:2825–2832.
Al Bardi et al J Am Coll Cardiol, 2019, Feb 6Vol 73 issue 6

CENTRAL ILLUSTRATION: Women With Signs and Symptoms of Ischemia With No Obstructive Coronary Artery Disease and the Potential Role of Coronary Reactivity Testing



AlBadri, A. et al. J Am Coll Cardiol. 2019;73(6):684–93.

Treatment algorithm for patients with microvascular angina



Crea et al Eur Heart J. 2014 May 1; 35(17): 1101–1111.
doi: 10.1093/eurheartj/eht513

Statins: reduce vascular inflammation and improve endothelial function / CFR

Beta blockers: (Nebivolol) improve endothelial function, reduce symptoms increases CFR

ACE-I: Modulate vascular tone, improve CFR and reduce symptoms

Metformin: improve microvascular endothelial function and decreasing myocardial ischemia in non-diabetics

Allopurinol: Xanthine oxidase inhibitor reduces oxidative stress and improves endothelial function

Theophylline: adenosine blocker used in patients with increased sensitivity to adenosine

SSRI: used for other vasospastic disorders (Raynaud's)

Exercise and Smoking cessation