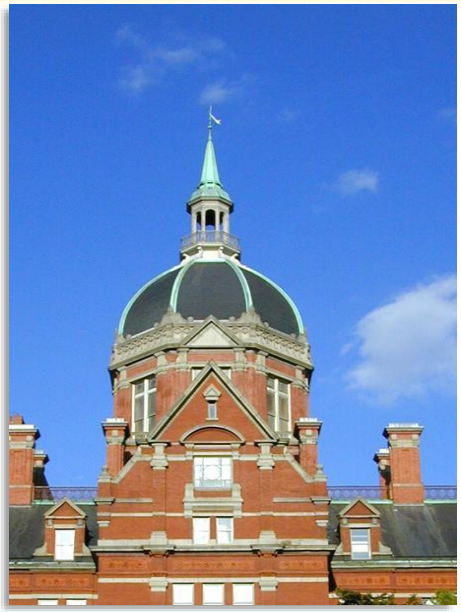

Cardiovascular Disease in Women

Erin D. Michos, MD, MHS, FACC, FAHA
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Associate Director of Preventive Cardiology
Associate Faculty, Welch Center for Prevention, Epidemiology, & Clinical Research
Johns Hopkins University School of Medicine

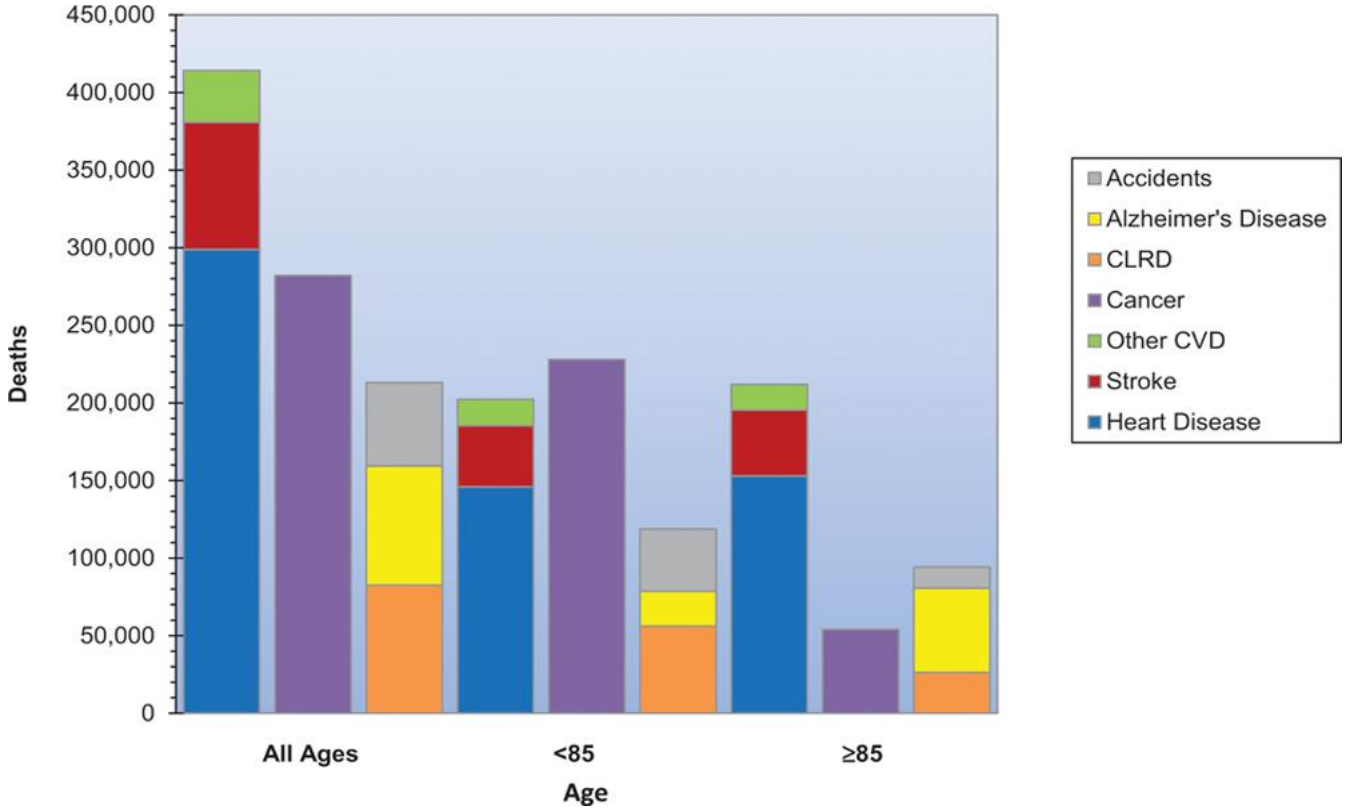
American College of Osteopathic Internists, May 9 2019

@ErinMichos

Take-Home Points

- CVD Kills Women
  - Women are at increased CVD risk, most notably at older ages
  - young women <50 more likely to incur fatality after MI and after CABG compared to younger men
- CVD can be different in women
  - Symptoms and presentations differ by sex
  - Disparity exists in the risk conferred by traditional CVD risk factors
  - Unique risks posted by pregnancy and hormones
  - Some “unusual” types of CVD more common in women

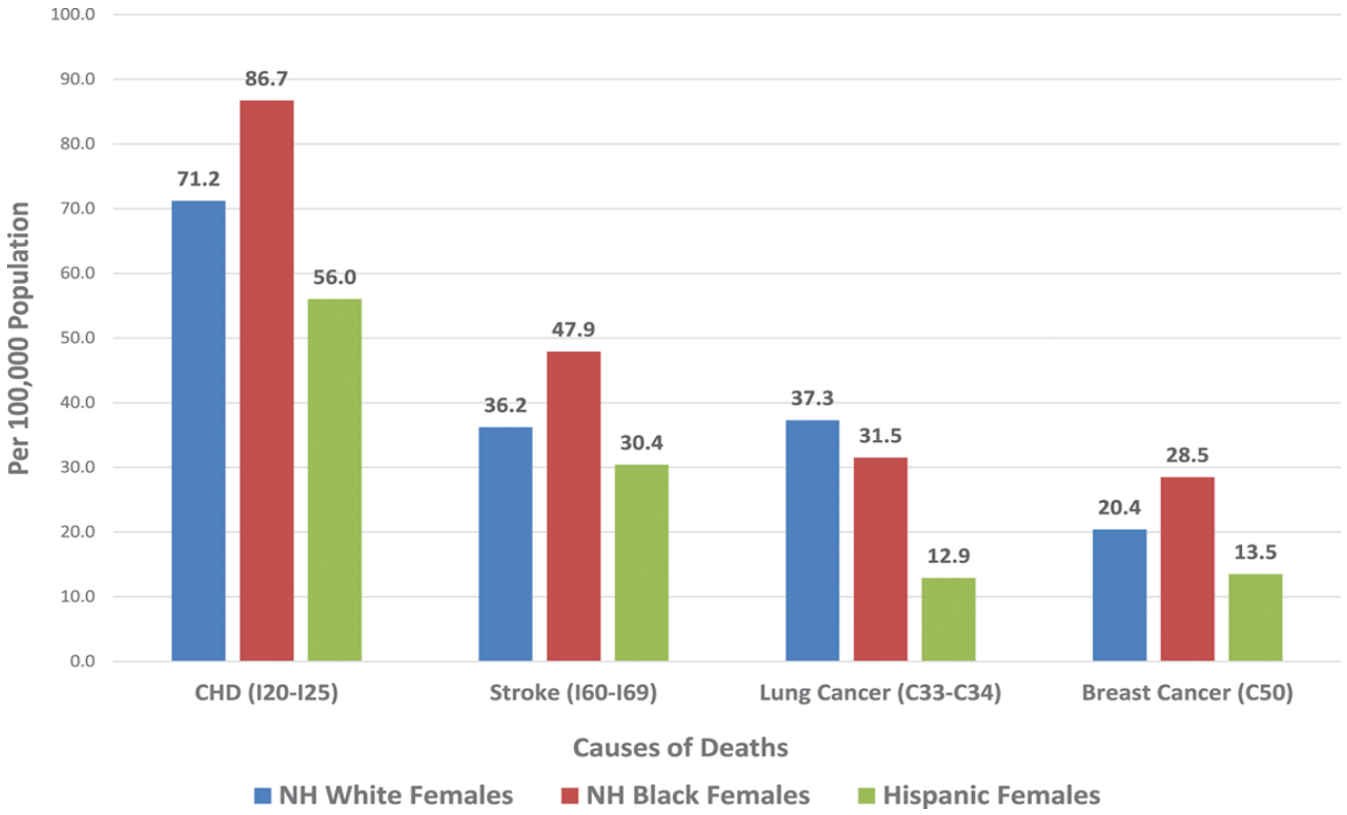
CVD is leading cause of death in women



Cardiovascular disease (CVD) and other major causes of death in females: total, <85 years of age, and ≥85 years of age., through 2015

Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association, Volume: 137, Issue: 12, Pages: e67-e492, DOI: (10.1161/CIR.0000000000000558)

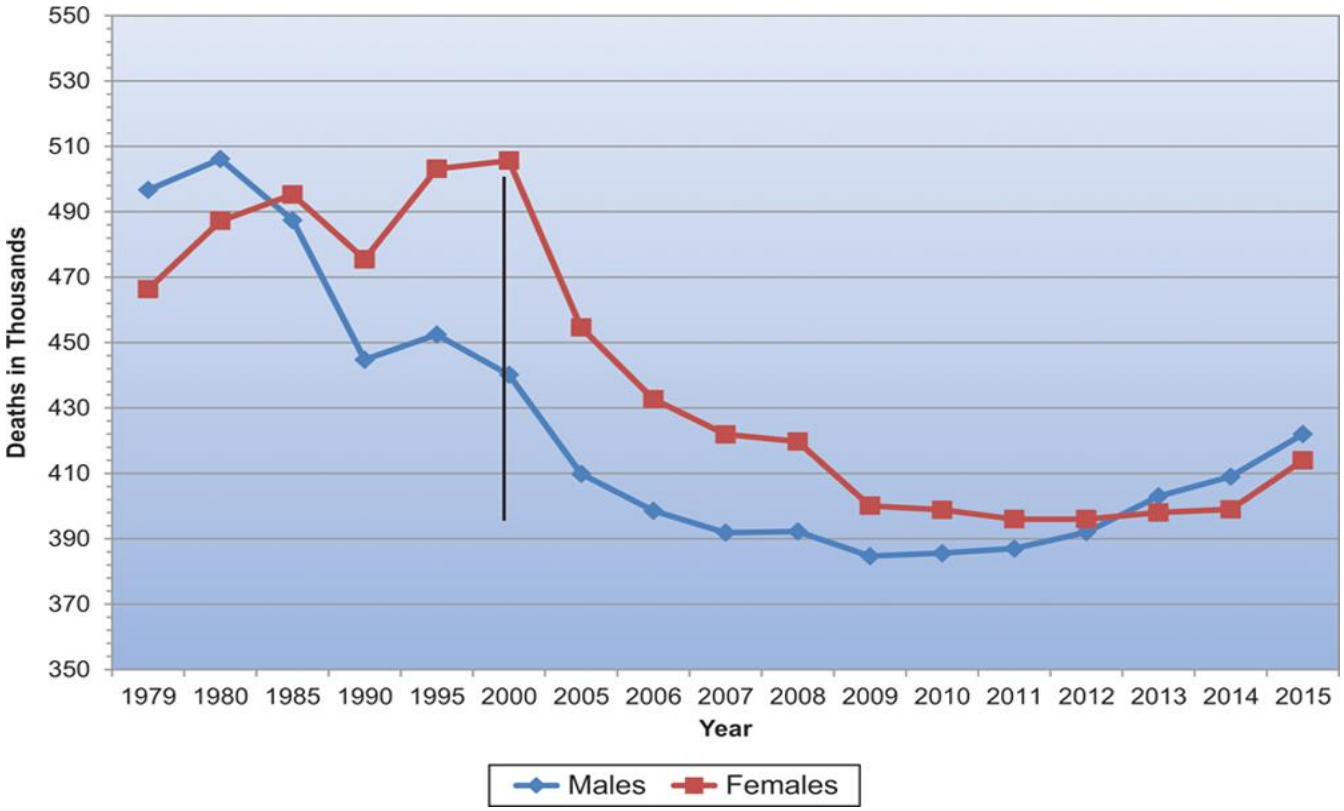
Racial disparities in CVD outcomes



Age-adjusted death rates for coronary heart disease (CHD), stroke, and lung and breast cancer for white, black, of Hispanic females (United States: 2015).

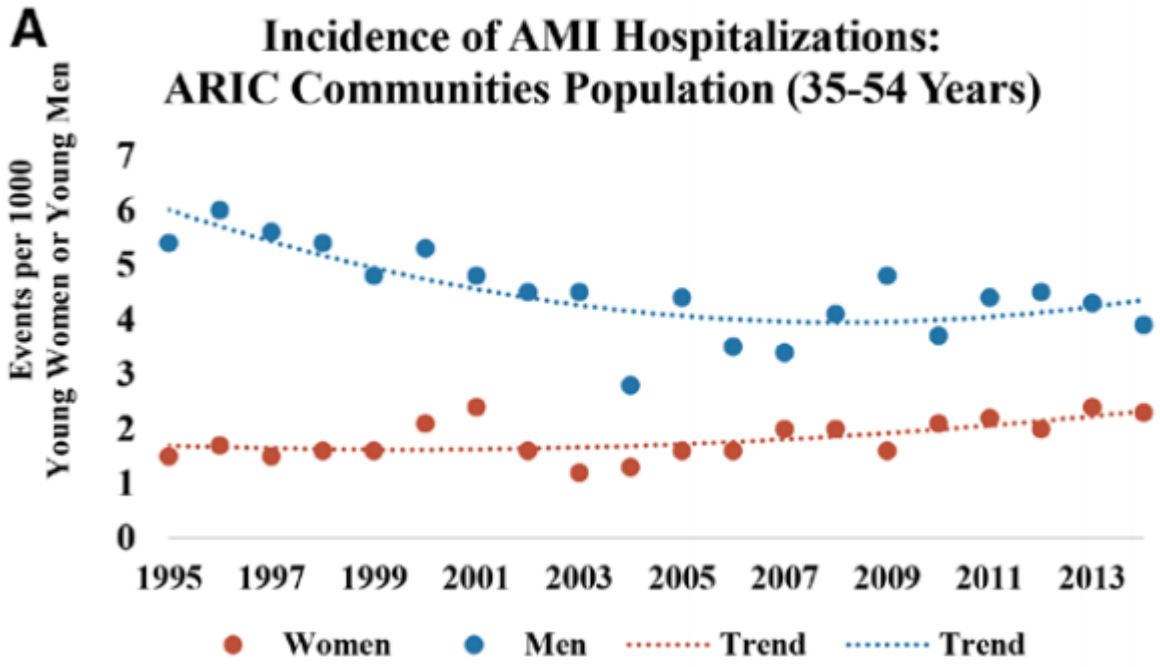
Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association, Volume: 137, Issue: 12, Pages: e67-e492, DOI: (10.1161/CIR.0000000000000558)

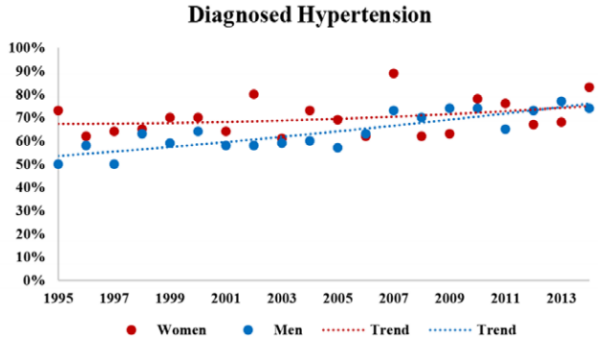
CVD mortality gap between men and women is narrowing

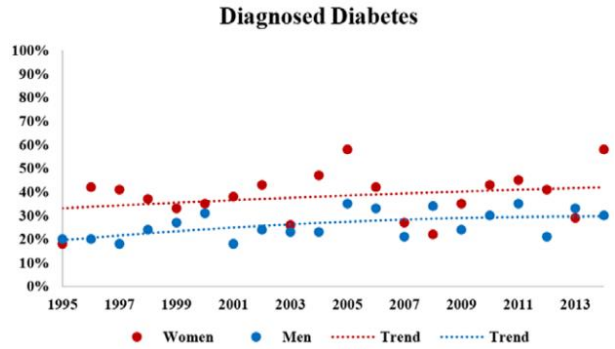


Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association, Volume: 137, Issue: 12, Pages: e67-e492, DOI: (10.1161/CIR.0000000000000558)

Incidence of Acute MI Rising in Young Women

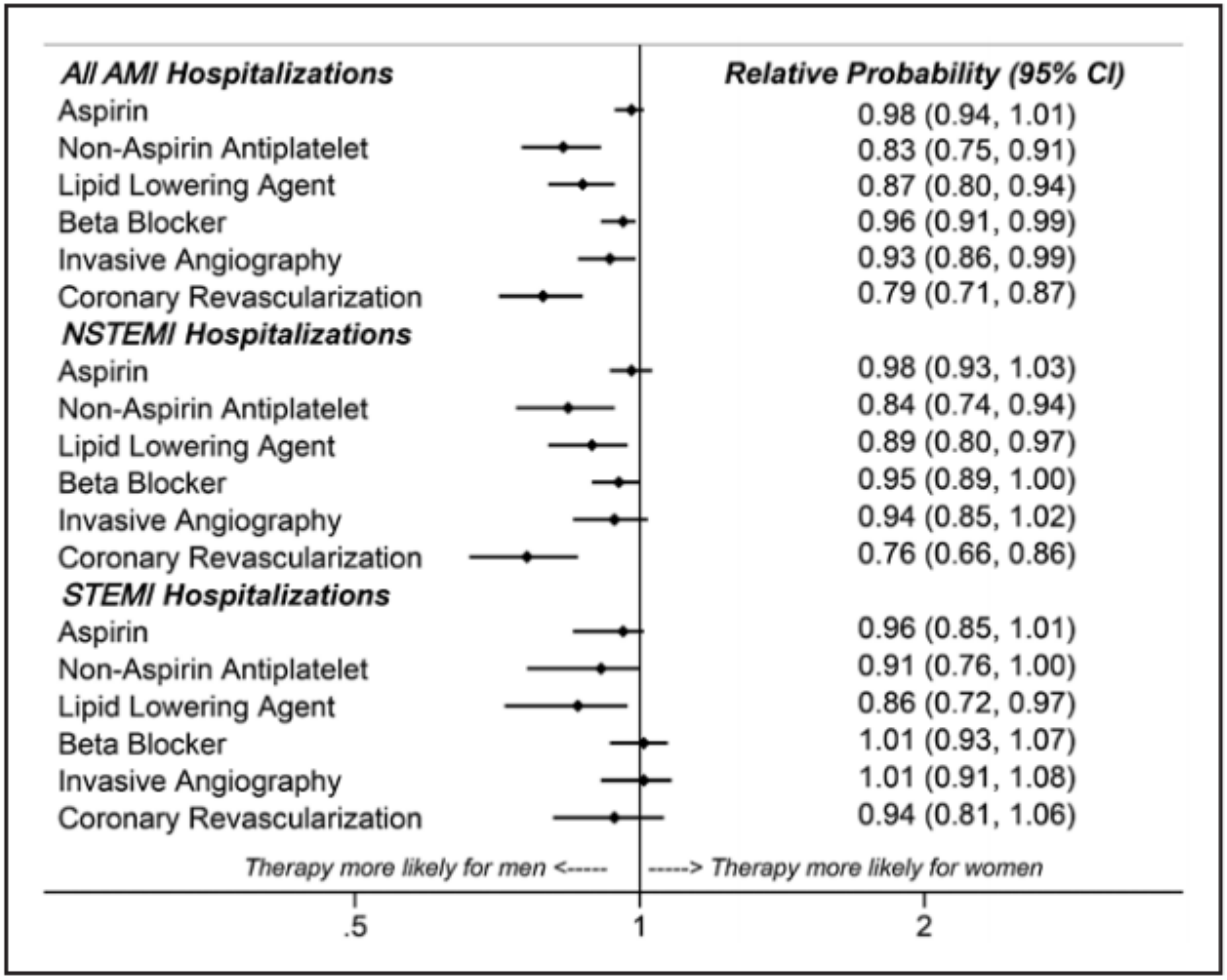






Arora S et al. Twenty Year Trends and Sex Differences in Young Adults Hospitalized With Acute Myocardial Infarction, Volume: 139, Issue: 8, Pages: 1047-1056, DOI: (10.1161/CIRCULATIONAHA.118.037137)

Young Women with MI are Undertreated vs Young Men



- Probabilities of young women vs young men receiving guideline directed therapies for acute MI.
- ARIC Surveillance, 1995 to 2014.
- Model adjusted for race, geographic location, and year of hospital admission.

Arora S et al. Twenty Year Trends and Sex Differences in Young Adults Hospitalized With Acute Myocardial Infarction, Volume: 139, Issue: 8, Pages: 1047-1056, DOI: (10.1161/CIRCULATIONAHA.118.037137)

Dr. Bernadine Healy, the NIH, and the Yentl Syndrome

THE NEW ENGLAND JOURNAL OF MEDICINE July 25, 1991

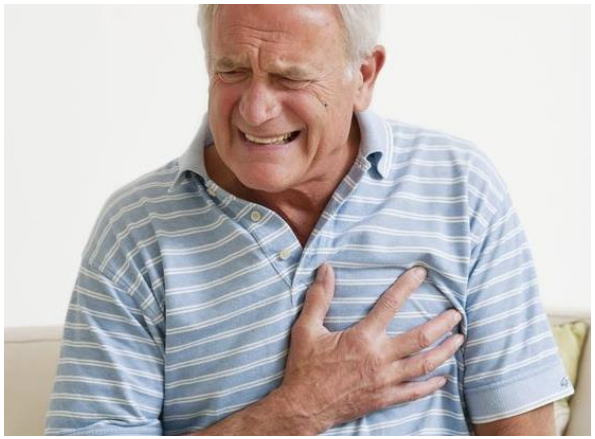
THE YENTL SYNDROME

YENTL, the 19th-century heroine of Isaac Bashevis Singer's short story,[1] had to disguise herself as a man to attend school and study the Talmud. Being "just like a man" has historically been a price women have had to pay for equality. Being different from men has meant being second-class and less than equal for most of recorded time and throughout most of the world. It may therefore be sad, but not surprising, that women have all too often been treated less than equally in social relations, political endeavors, business, education, research, and health care.

Dr. Bernadine Healy
-first woman to join Hopkins Cardiology faculty
-first woman director at NIH (1991-1993)
-died in 2011 at age 67 of brain cancer

Face of Cardiovascular Disease

Google Stock Images – “Heart Attack”

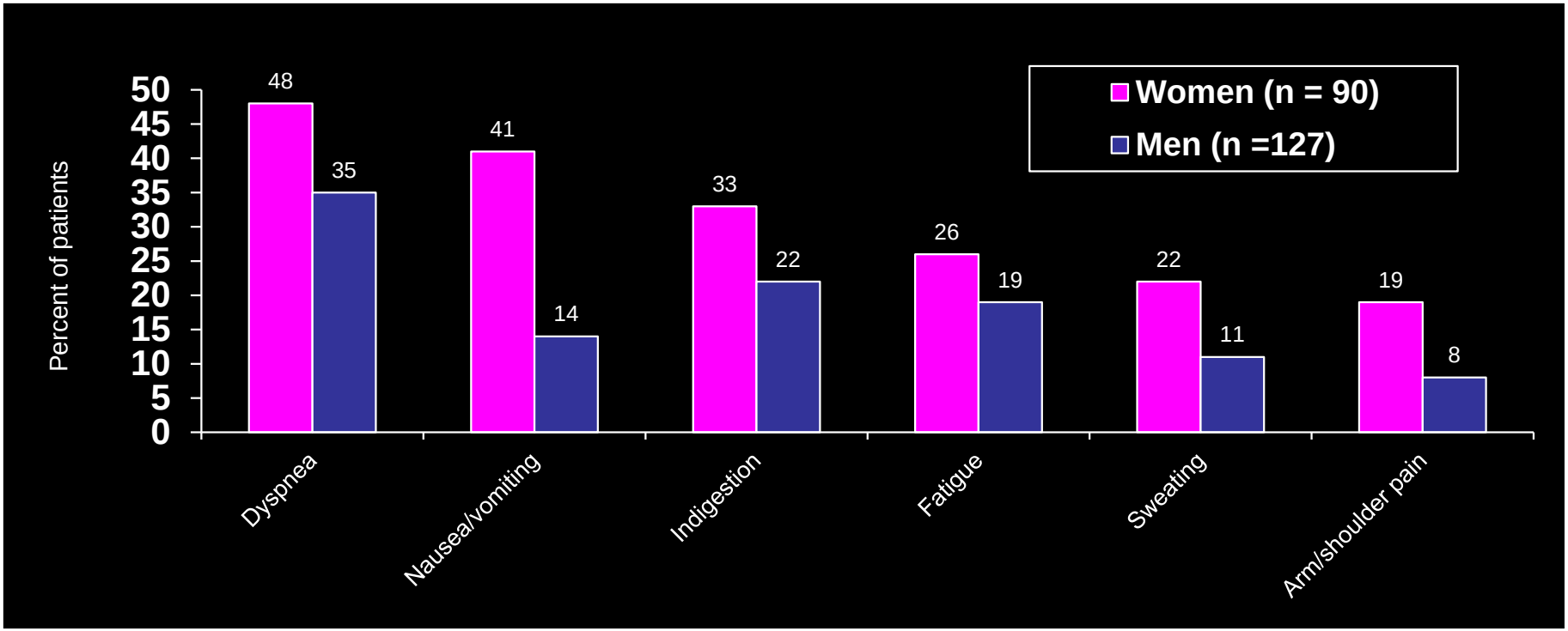


Real life heart attack survivor

Julia Brokmeyer was diagnosed by cardiologists with a very rare heart condition called **SCAD,** or spontaneous coronary artery dissection.

Article from the Richmond Observer

Sex Differences in Emergency Department Presentation for CAD Without Chest Pain



Milner KA, et al. *Am J Cardiol.* 1999

Make the Call
Don't Miss a Beat

- Only **53%** of women said they would call 911 if **they** were experiencing the symptoms of a heart attack
- However **70%** said they would call 911 if **someone else** was having a heart attack
- Lack of "expected symptoms" leads to delay in care

Delays in Medical Care for STEMI by sex

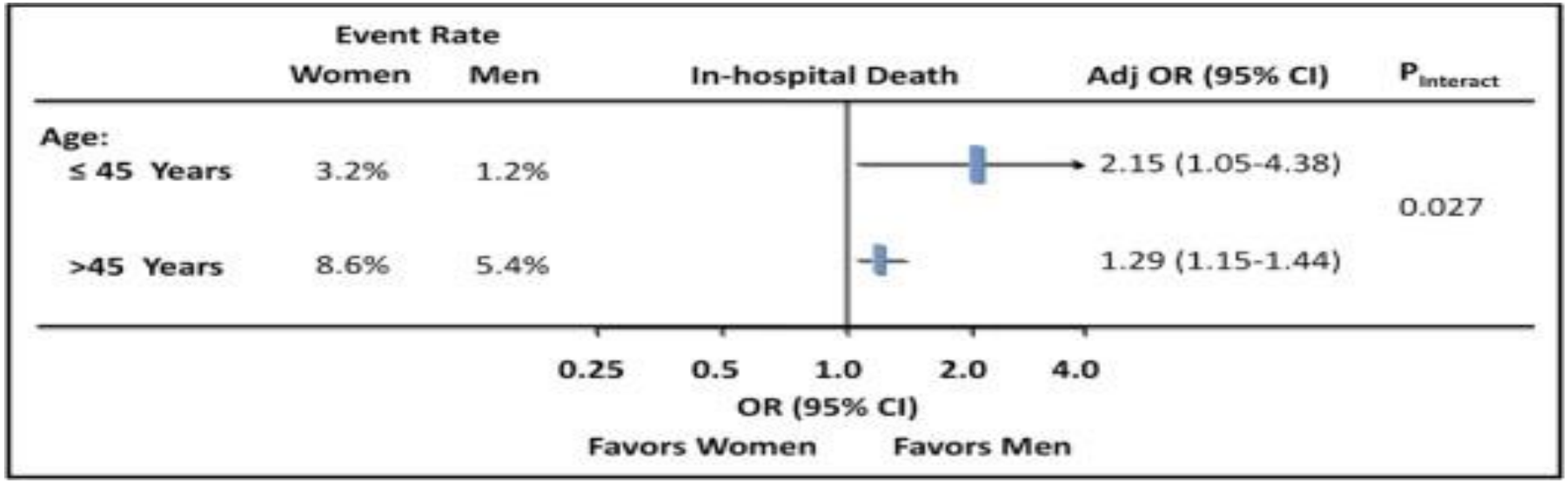
In a cohort of ST-Elevation Myocardial Infarction (**STEMI**) patients presenting to a large metropolitan region, after multivariable adjustment, female sex was associated with both patient and system delay

- **Time from Sx to 1st medical contact**
  - **34% (27-min) increase in time**
- **Time from medical contact to reperfusion therapy**
  - **23% (or 13-min) increase in time**

Kaul P et al. Am Heart J 2011;161:91-7

Sex disparities in MI mortality

Women after STEMI have higher mortality than men, particularly younger women



31,544 patients presenting with ST-segment elevation myocardial infarction who were enrolled in the American Heart Association's Get With the Guidelines Coronary Artery Disease registry

Bangalore et al. Age and Gender Differences in Quality of Care and Outcomes for Patients with ST-segment Elevation Myocardial Infarction. The American Journal of Medicine 2012.

Sex Disparities in Pharmacologic Treatment post MI

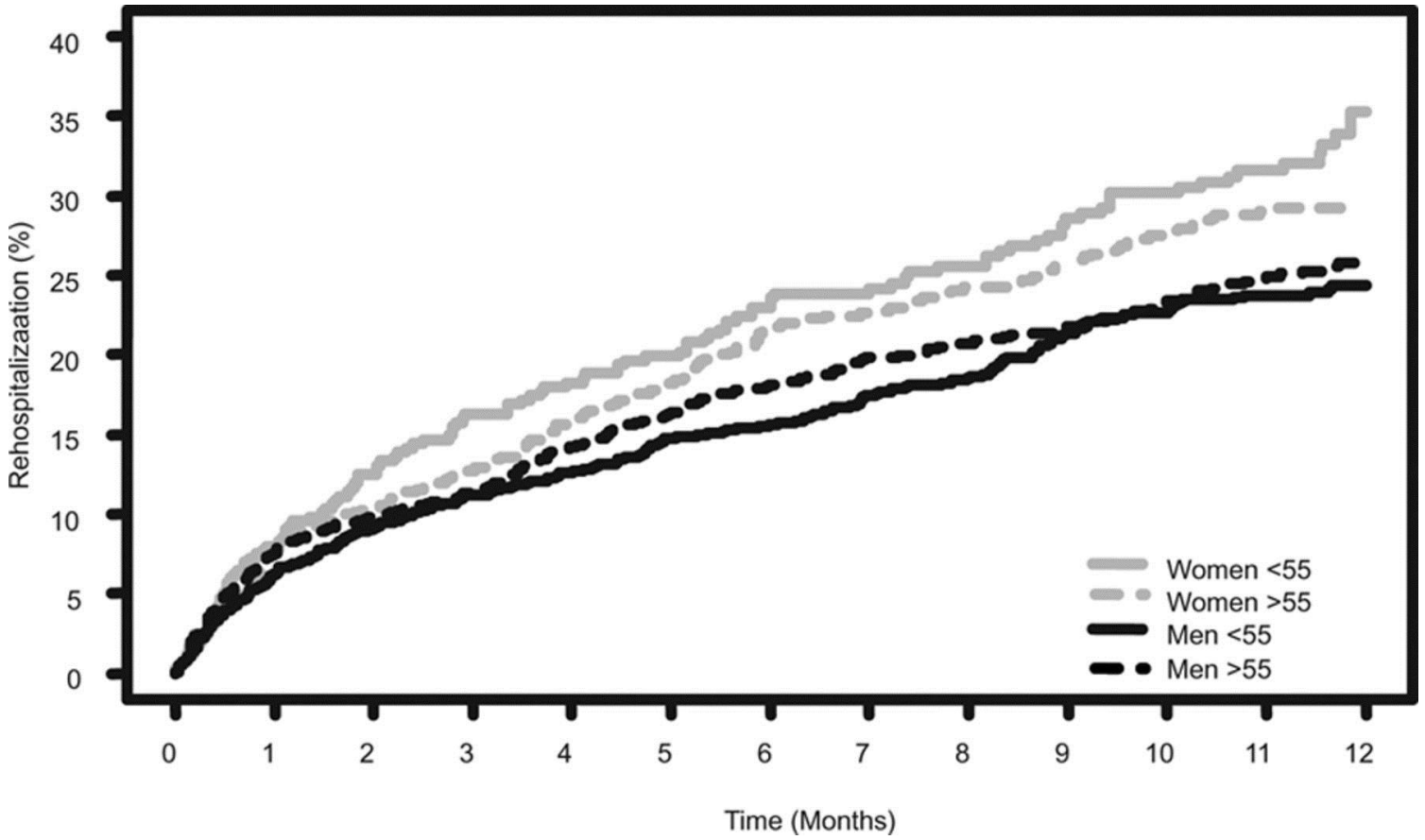
ACE/ARB, β-blockers, and statins

- After Myocardial Infarction (MI), women were less likely to
  - Be initiated on preventive pharmacotherapies
  - Have adherence to treatment >80%
  - Be on Optimal Medical Therapy 1 year after discharge
  - **Disparity greatest for younger women age 20-54 years**

(analyses were adjusted for age, race, income, pre-MI medication use, type of MI, and comorbidities)

Smolina K et al. Sex Disparities in Post-Acute Myocardial Infarction Pharmacologic Treatment Initiation and Adherence, Circ Cardiovasc Qual Outcomes. 2015 Nov;8(6):586-92. doi: 10.1161/CIRCOUTCOMES.115.001987.

Women more likely to be re-hospitalized within 1 year after MI



Rachel P. Dreyer et al. Circulation. 2017;135:521-531

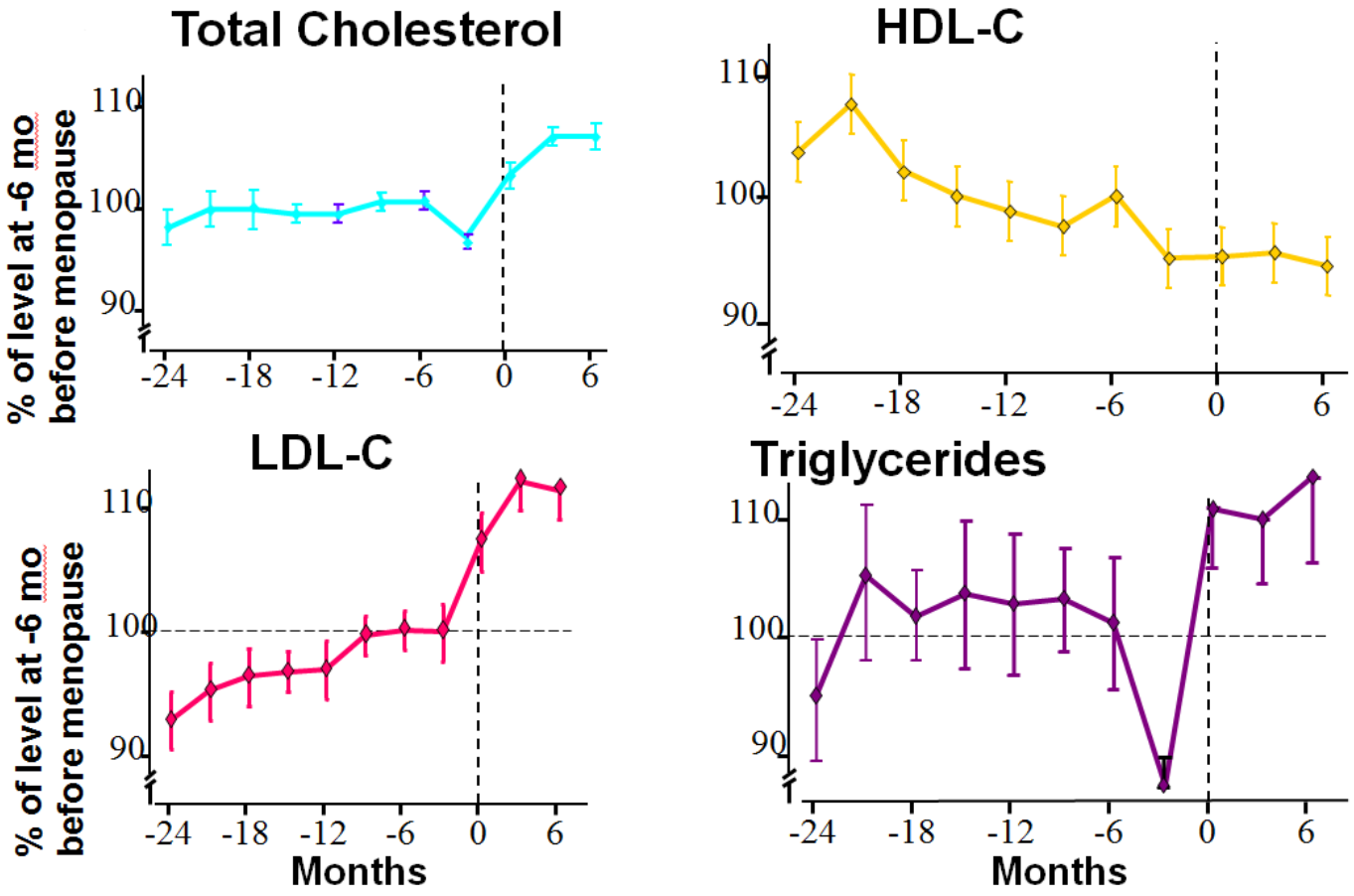
Traditional CVD Risk Factors

- **Modifiable Risk Factors**:
  - Abnormal cholesterol
  - Tobacco smoking
  - Hypertension
  - Diabetes mellitus, obesity, metabolic syndrome
  - Lack of physical exercise
- **Non-modifiable risk factors:**
  - Advanced age
  - Family history of early coronary artery disease

Traditional Risk Factors: Gender Disparities

- **Diabetes**
  - 4–6x increased risk of developing coronary artery disease in women compared to 2–3x increased risk in men
- **Smoking**
  - 6x increased risk in women vs. 3 x increased risk in men
- **Hypertension**
  - Over age 65, hypertension prevalence is higher in women than men
  - less than half receive adequate treatment

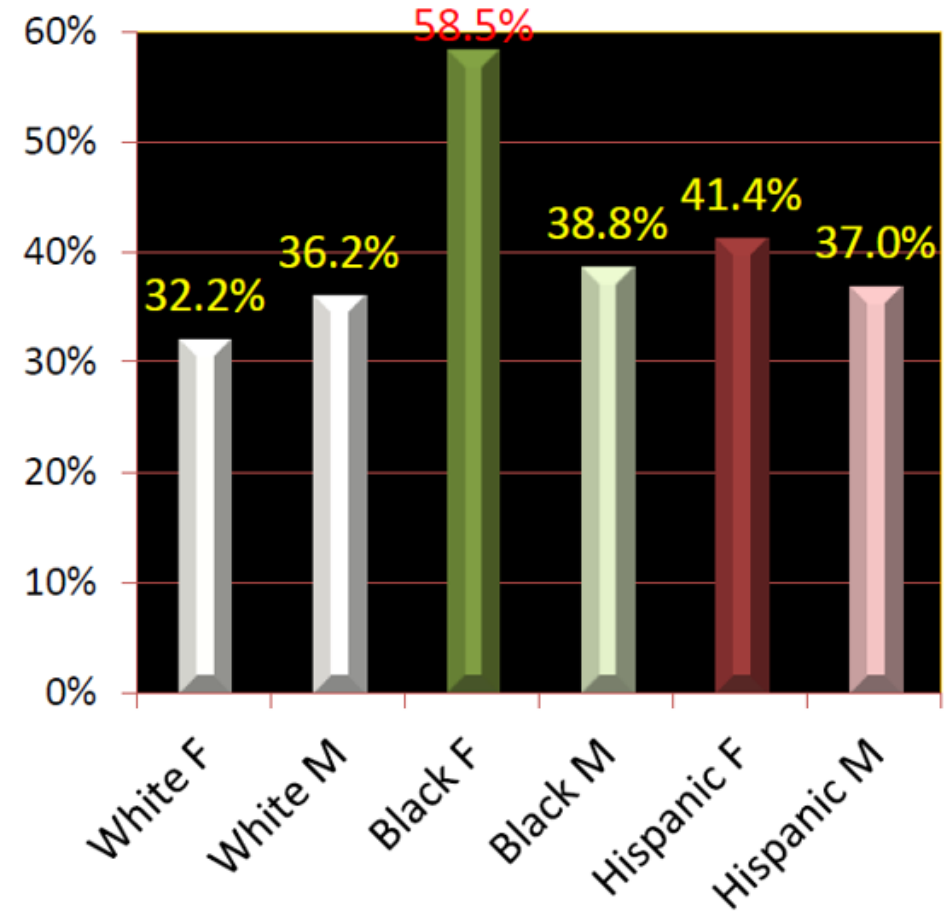
Change in Lipids After Menopause



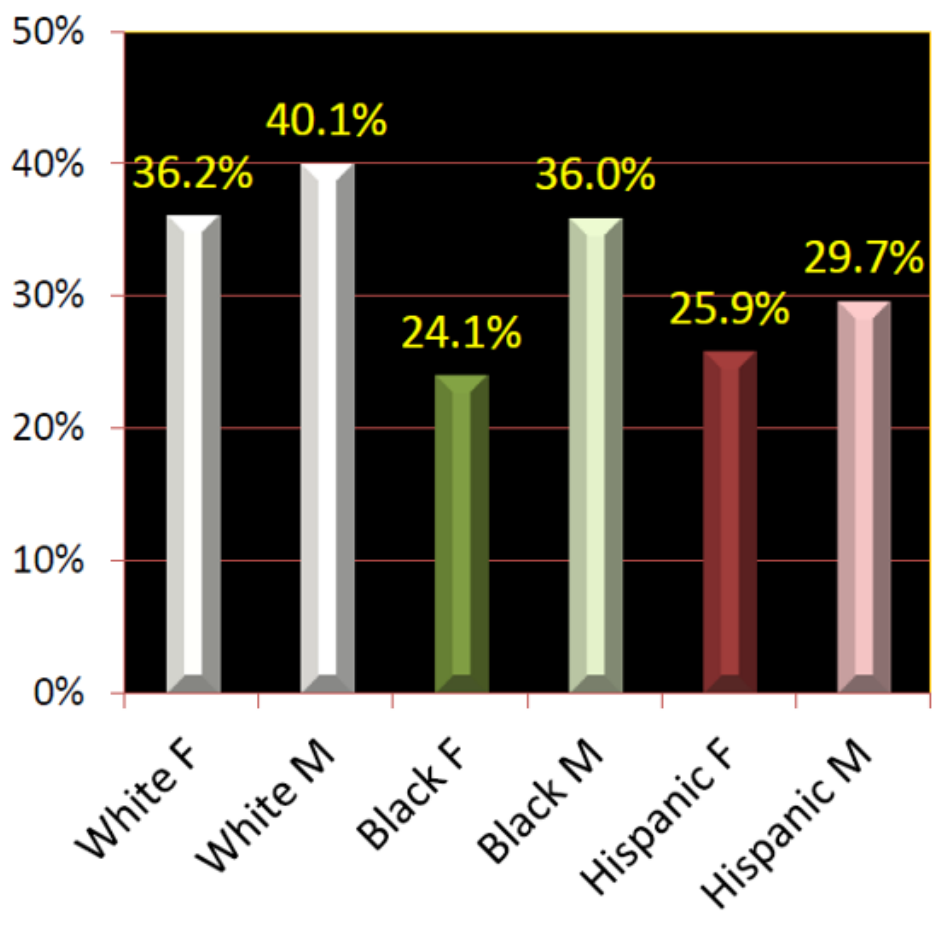
Jensen J et al. Maturitas 1990;12:321-31.

Obesity, Physical activity

Obesity age ≥20yr



Physical activity age ≥18 y



EDITORIAL

Encouraging Young Women to Move More

Linking Physical Activity in Young Adulthood to Coronary Risk in Women

Nurses Health Study

- 97 230 women aged 27 to 44 yrs
- Followed 20 years
- Women with at least **two and half hours** of leisure time each week being active had **25% reduced risk of incident CHD**
- Brisk walking alone also had lower CHD risk

Article, see p 290

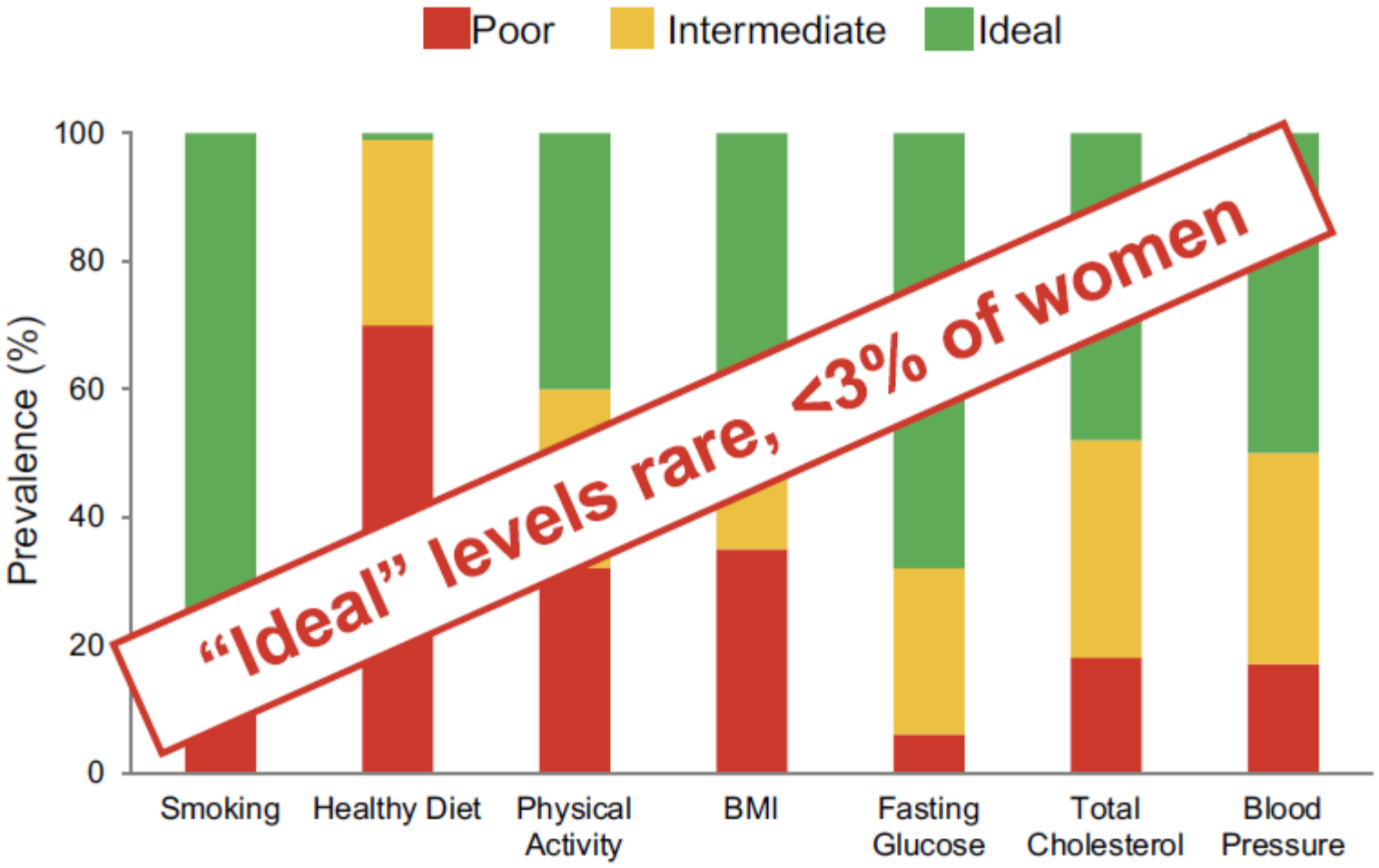
"In the long run, we shape our lives, and we shape ourselves. The process never ends until we die. And the choices we make are ultimately our own responsibility."

-Eleanor Roosevelt

Erin D. Michos, MD, MHS
Michael J. Blaha, MD, MPH

Circulation. 2016;134:300–303. DOI: 10.1161/CIRCULATIONAHA.116.023400

Ideal Cardiovascular Health
AHA Life Simple 7 in Women



American Heart Association statistics

Risk Factors Unique to Women

- Age at Menarche
- Polycystic Ovarian Disease
- Pregnancy history
  - Parity
  - Gestational diabetes
  - Preeclampsia/ gestational hypertension
  - Pre-term delivery
- Reproductive health questions
  - Infertility
  - Menopause
  - Oophorectomy

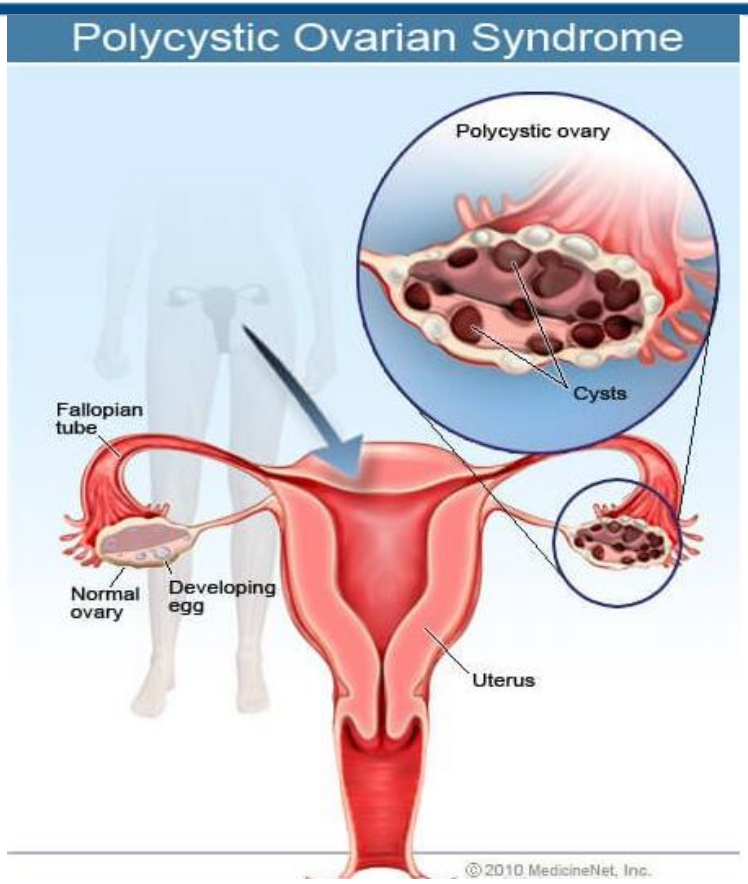
PCOS

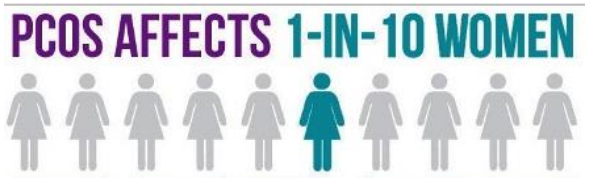
Polycystic Ovarian Syndrome

JOHNS HOPKINS MEDICINE

CHD=coronary heart disease
DM = diabetes mellitus

- **2-fold CVD risk** (CHD +stroke)
- Diabetes, obesity, hypertension, & metabolic syndrome more prevalent
  - **5x risk of type 2 DM** than age and weight matched controls
  - 70% with **dyslipidemia**
- Elevated coronary artery calcium (**atherosclerosis**) compared to healthy matched controls
- Weight management & exercise can improve their cardiac risk.





Gestational Diabetes

- **Gestational Diabetes**
  - 1 in 10 pregnancies
  - Up to 70% will develop Type 2 diabetes within 5 years

Mother's Diabetes Leads to Obesity in Their Children

Pregnant diabetic women's children grow up to be heavier adults

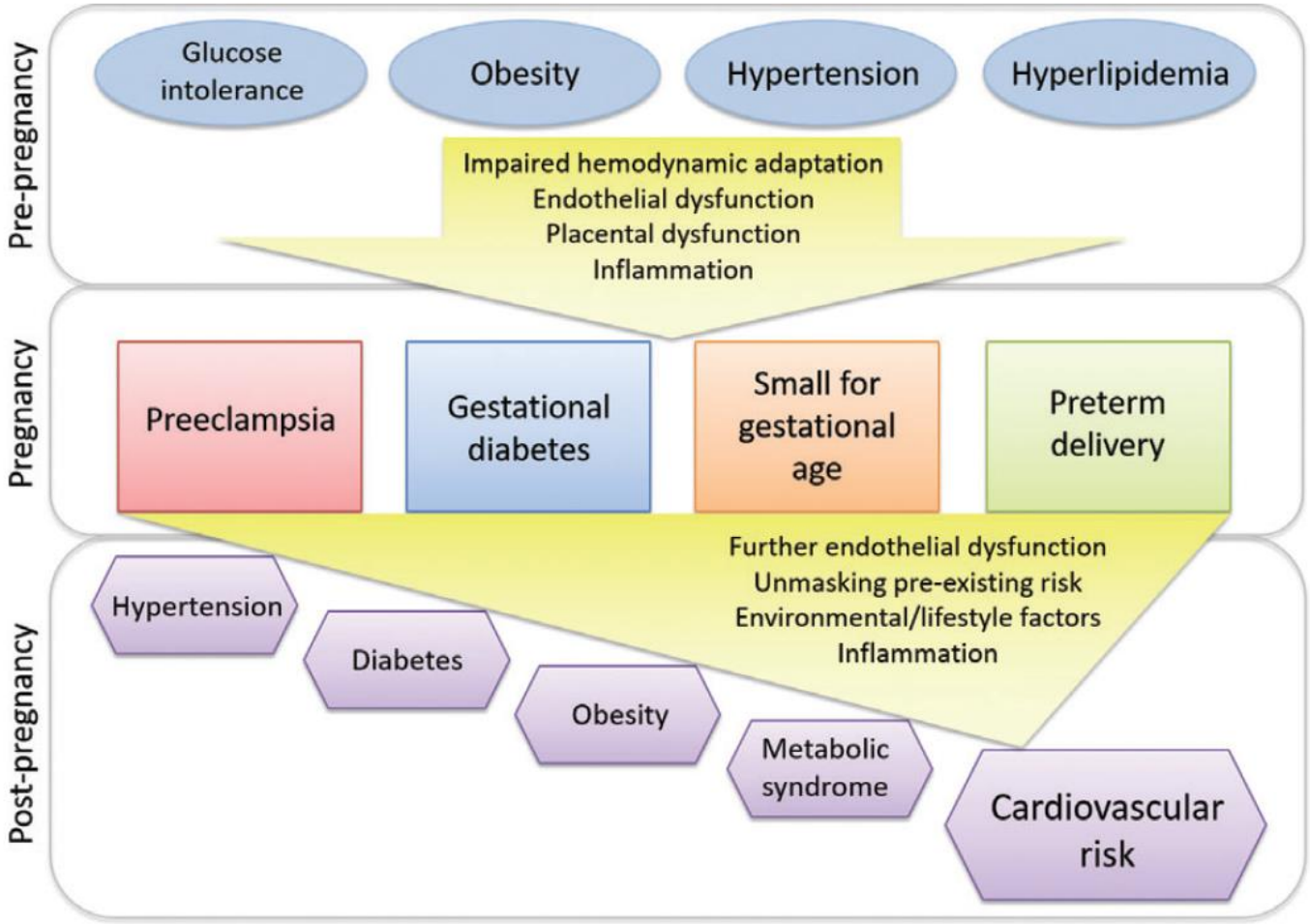
Pre-Eclampsia, Pre-term Delivery and Subsequent Maternal CVD: Meta-analysis

- >20 studies, with ~6 million women including >25,8000 with preeclampsia & 338 000 with previous Pre-term Delivery
- **Preeclampsia** is associated with a **4-fold increase in incident HF** and a **2-fold increased risk in CHD, stroke, and CVD death**
- **Pre-Term Delivery** is associated with an increase in future maternal adverse CV outcomes, including a **2- fold increase in deaths caused by CHD**
  - **highest risks** occurred when the PTD occurred **before 32 weeks gestation** or were medically indicated.

Wu P et al. Circ CQO 2017;10:e003497. DOI: 10.1161/CIRCOUTCOMES.116.003497

Wu P et al. J Am Heart Assoc. 2018;7:e007809. DOI: 10.1161/JAHA.117.007809

Adverse pregnancy outcomes and future maternal CVD risk

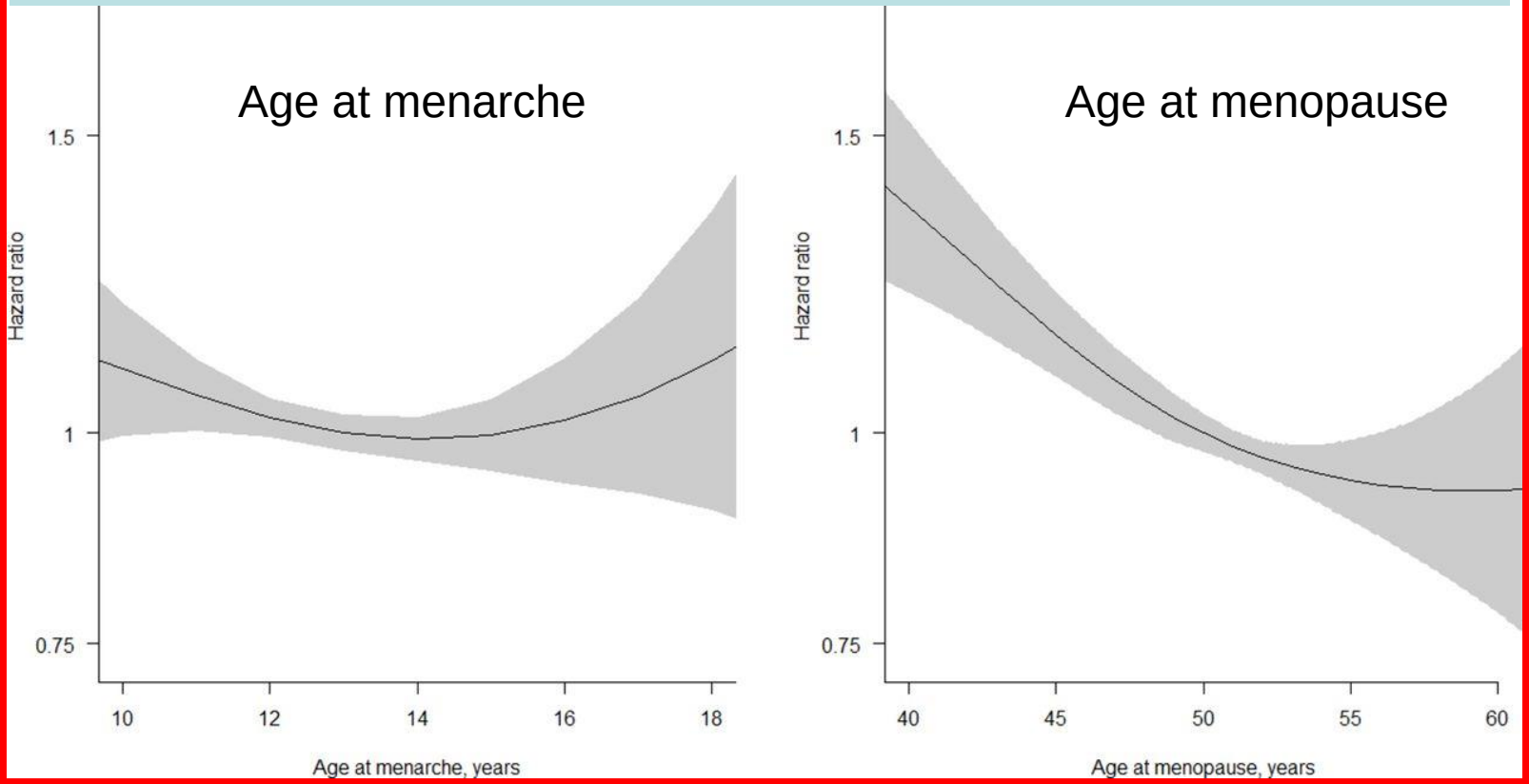


Hauspurg A, Ying W, Hubel CA, **Michos ED**, Ouyang P. Clin Cardiol 2018

Women's reproductive factors and incident CVD in the UK Biobank

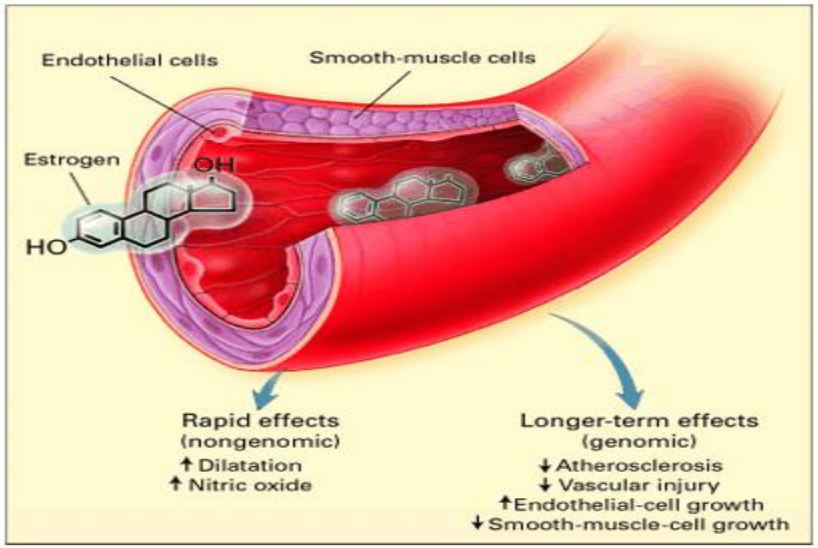
Analyses are adjusted for age, Townsend deprivation index, smoking status, systolic blood pressure, history of diabetes and body mass index.

HR for CVD



Sanne AE Peters, and Mark Woodward Heart 2018;104:1069-1075

Negative and Positive Effects of Estrogen

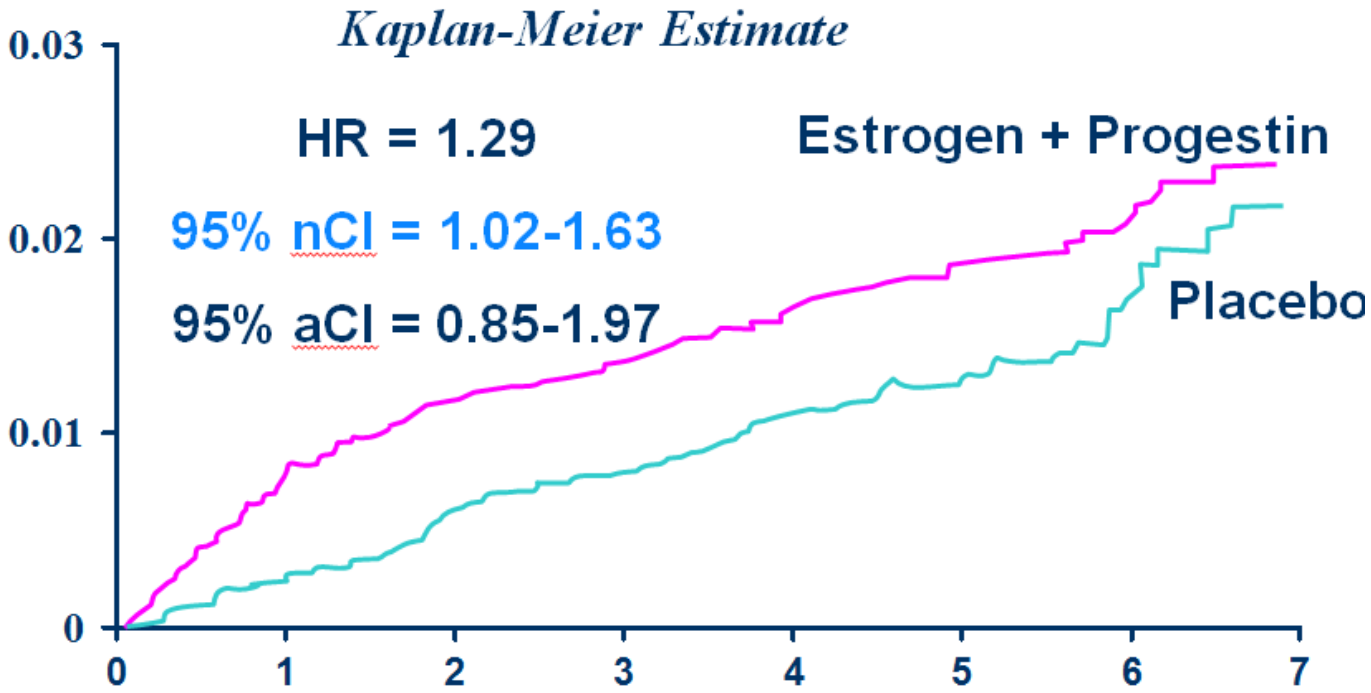


- Favorable
  - decreases LDL (bad chol)
  - increases HDL (good chol)
  - dilates blood vessels via NO
- Negative
  - increases CRP
  - increases prothrombin
  - decreases antithrombin III
  - increases triglycerides

Hormone therapy after menopause

- **not been shown to reduce CVD events**
- **not recommended to be prescribed for the purpose of CVD prevention**

Hormone Therapy Does Not Decrease Risk for CHD: WHI Results



- 18 year f/u data

No increase in mortality with hormone therapy

Manson JE, JAMA 2017

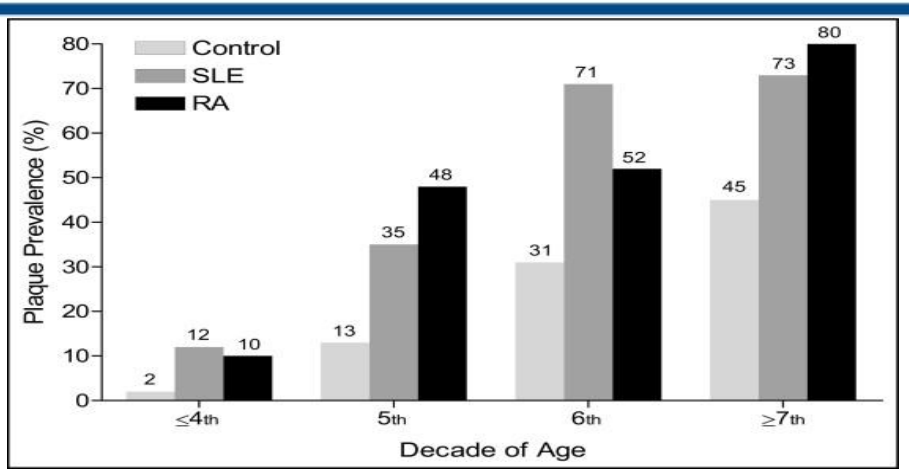
HR = hazard ratio; aCI = adjusted confidence interval; nCI = nominal confidence interval.

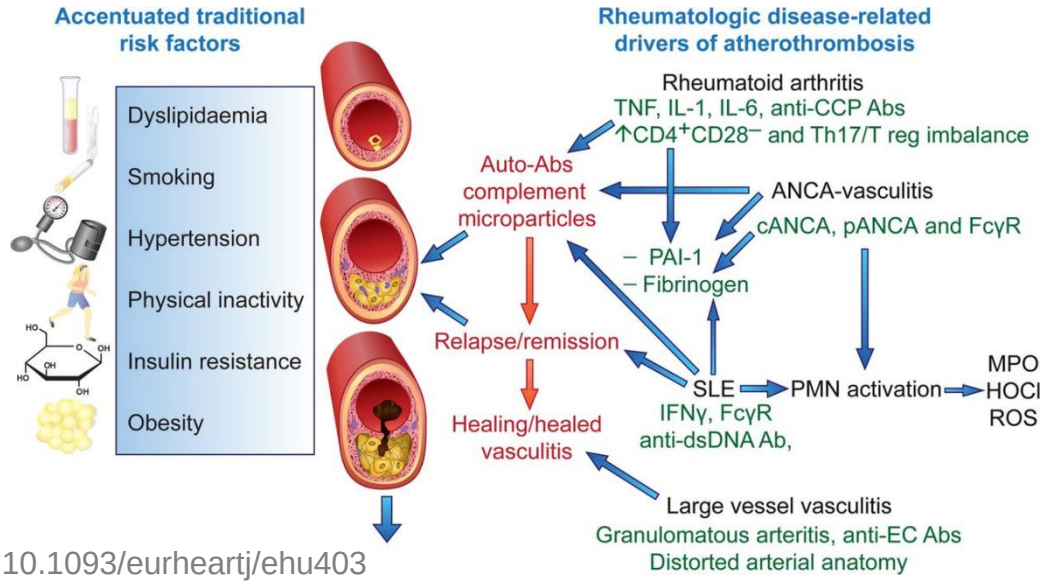
Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

Lupus, Rheumatoid Arthritis: Risk Factors for CVD

Salmon JE. Am J Med 2008

- Autoimmune disease more prevalent in women
- Women with SLE were 50x more likely to have acute MI than women of same age without SLE
- Considered a major CVD risk factor in the AHA Women's Guidelines





Eur Heart J. 2014;36(8):482-489. doi:10.1093/eurheartj/ehu403

Types of CVD in Women

JOHNS HOPKINS MEDICINE

Men and Women

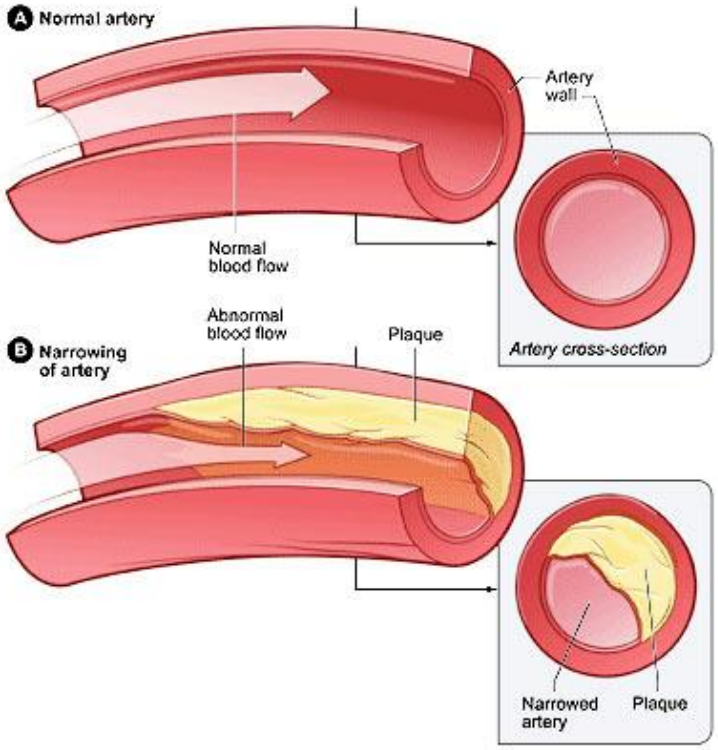
- Atherosclerosis
  - CHD
  - Stroke
  - PAD
- Valvular disease
- Arrhythmias
- Heart failure

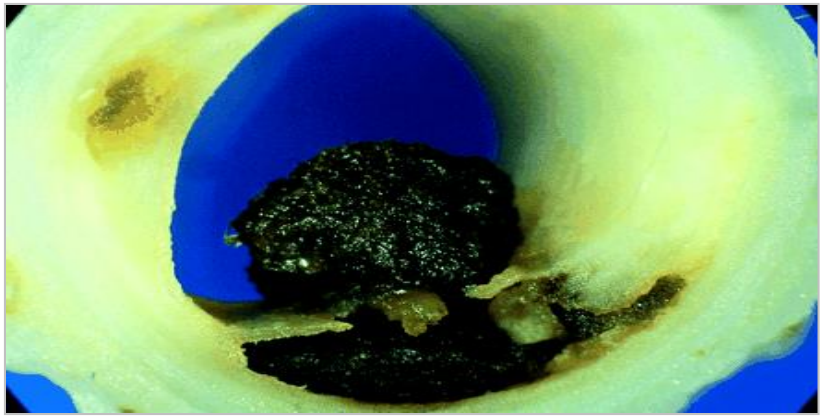
More common in women or only women*

- Microvascular angina
- Coronary Vasospasm
- SCAD
- Stress Cardiomyopathy
- Peripartum Cardiomyopathy*
- Heart failure with preserved ejection fraction

Atherosclerotic CVD

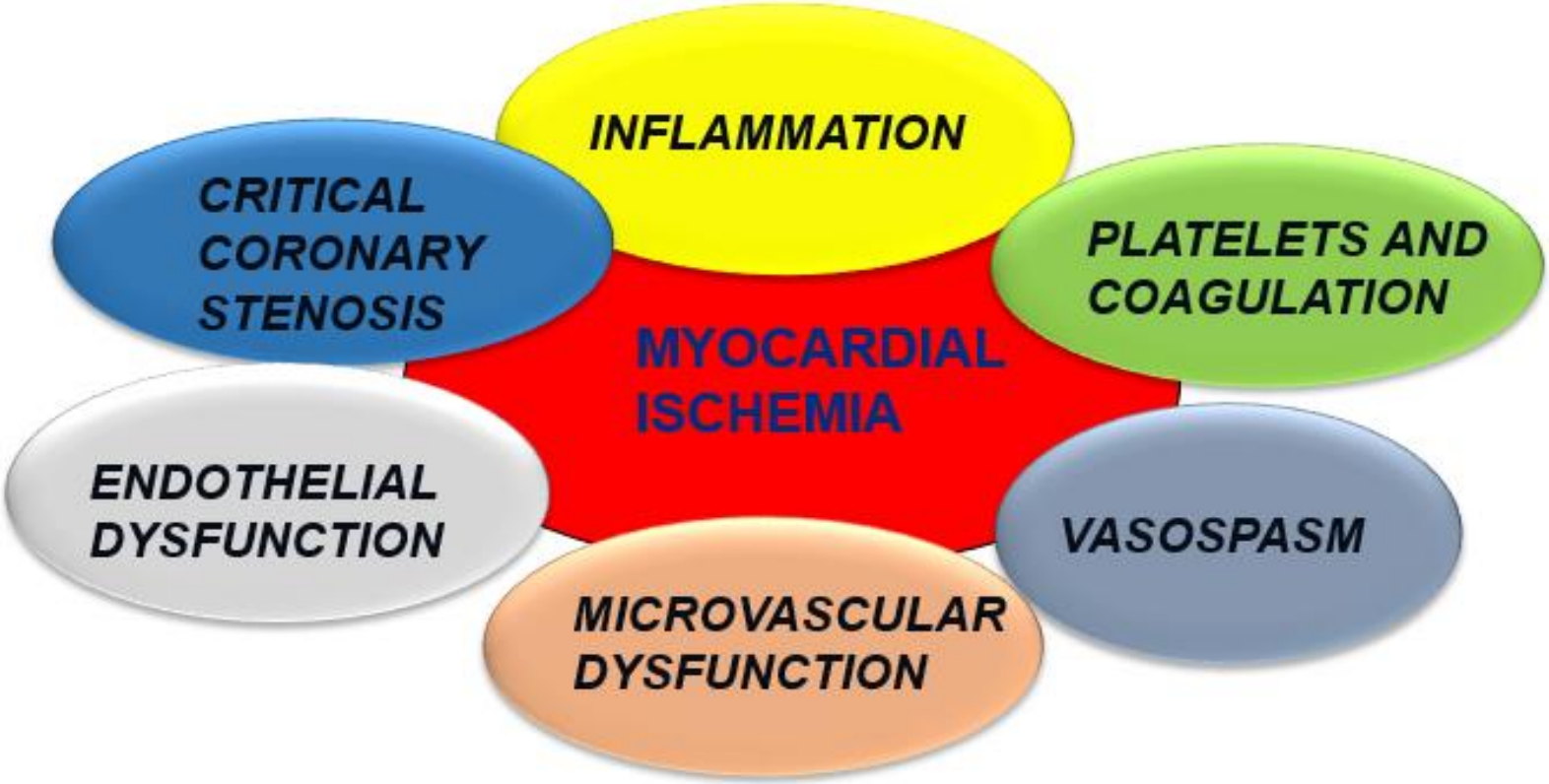
Leading cause of death in Women





MINOCA and INOCA

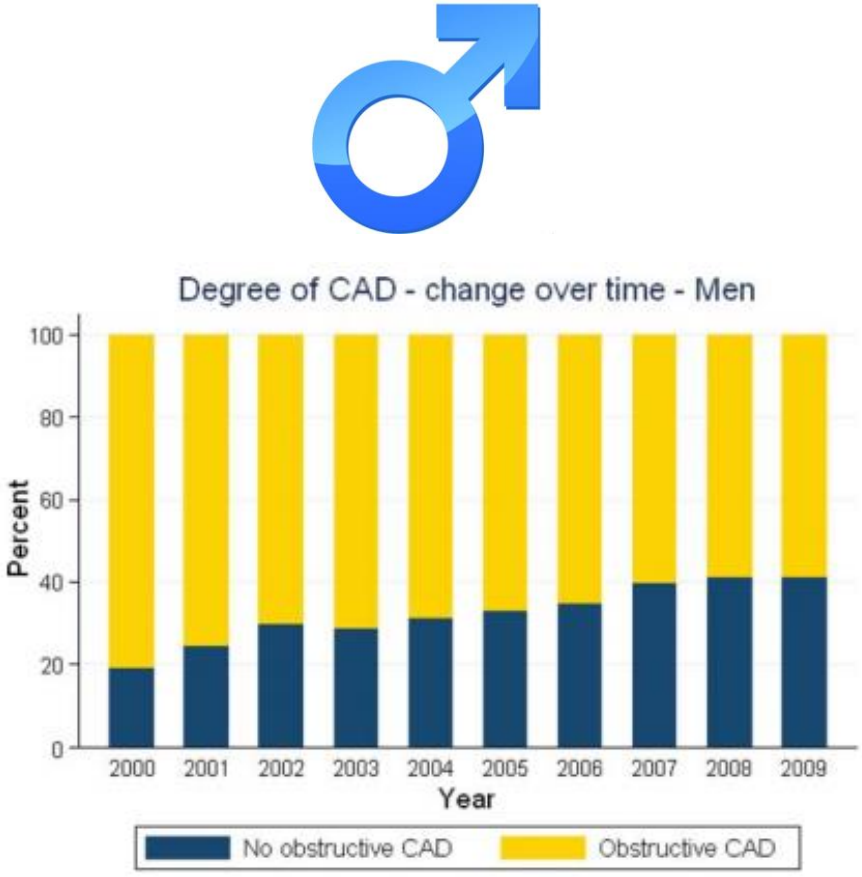
- Myocardial Infarction with Non-Obstructed Coronary Arteries
- Ischemia with Non-obstructed Coronary Arteries

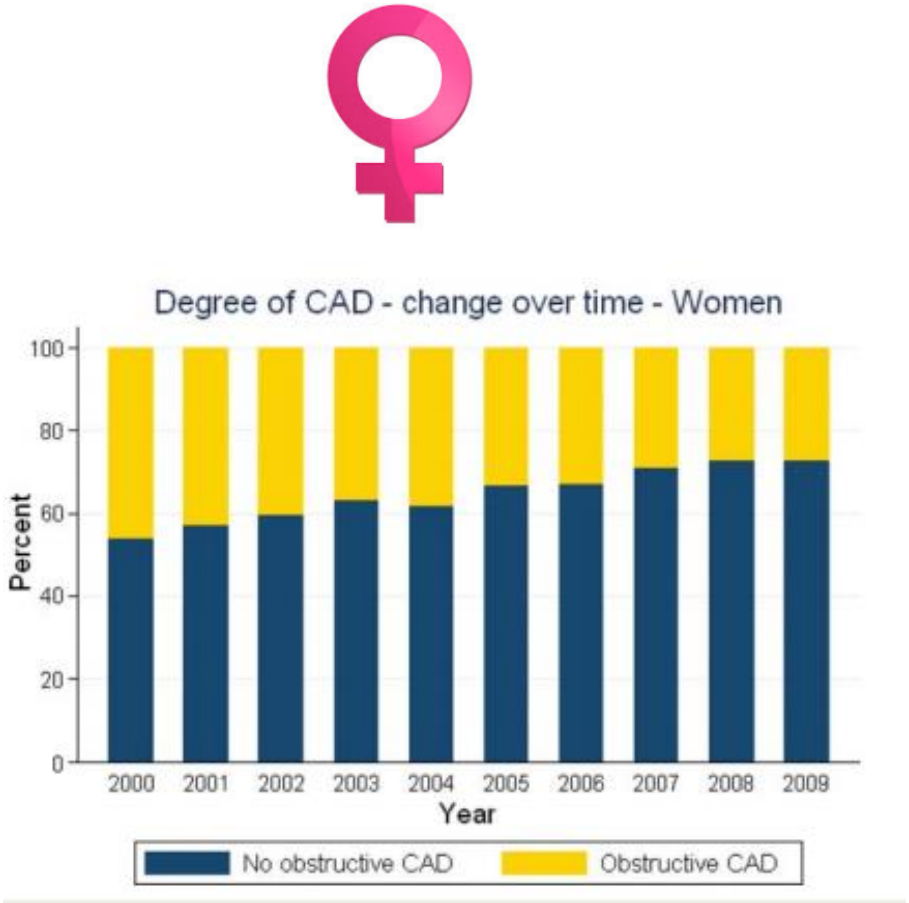


Pathobiological Contributors to Ischemic Heart Disease: *Not Just Epicardial Stenosis*

Marzilli M et al. *J Am Coll Cardiol*. 2012;60:951-956.

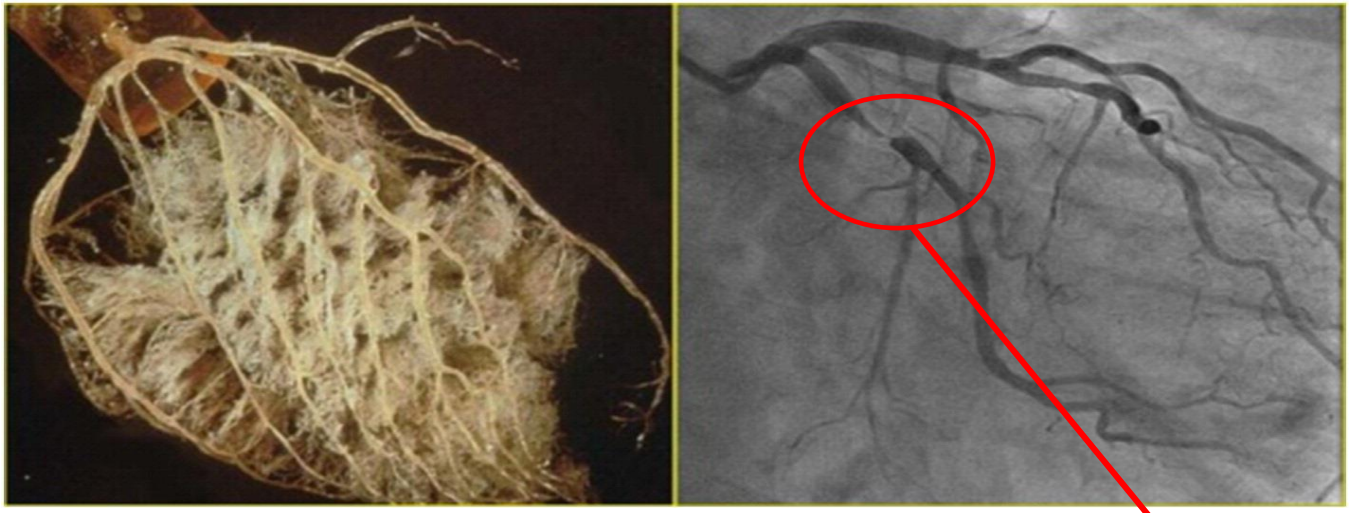
Women have more angina than men without obstructive CAD





Jespersen L et al. *Eur Heart J.* 2012;33:734-744.

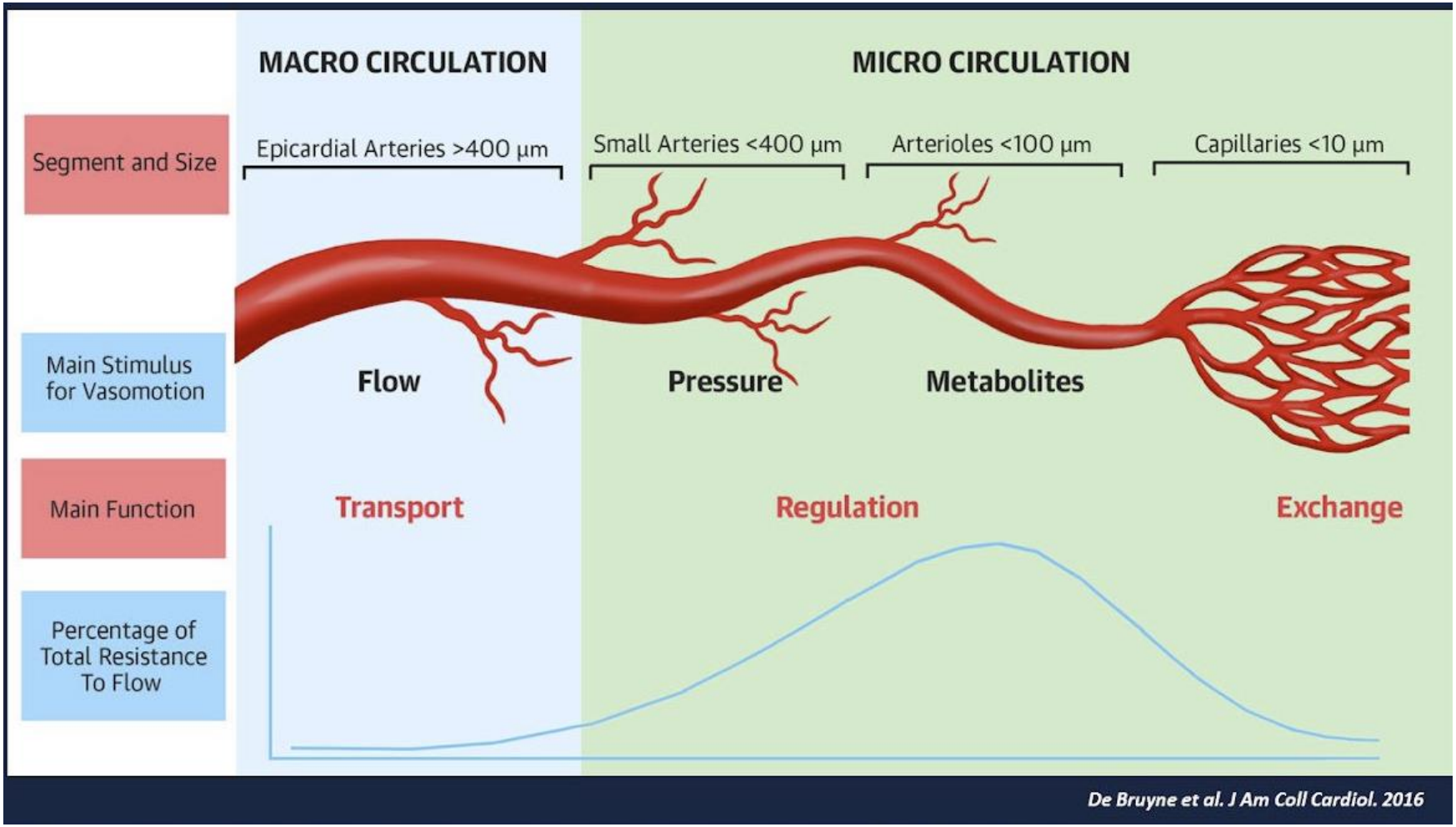
Microvascular angina



Microvascular disease
more often seen in women

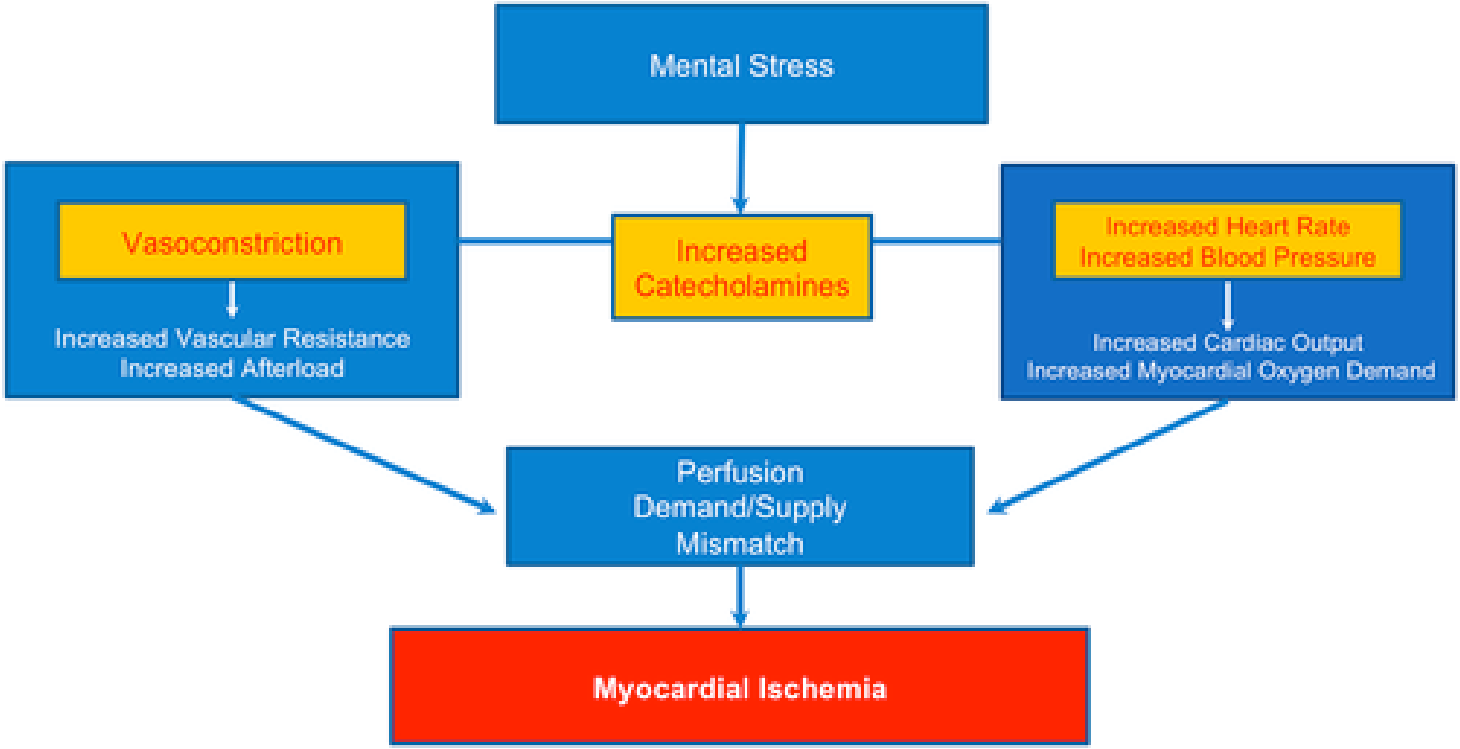
Obstructive
Epicardial CAD

Microvascular Circulation



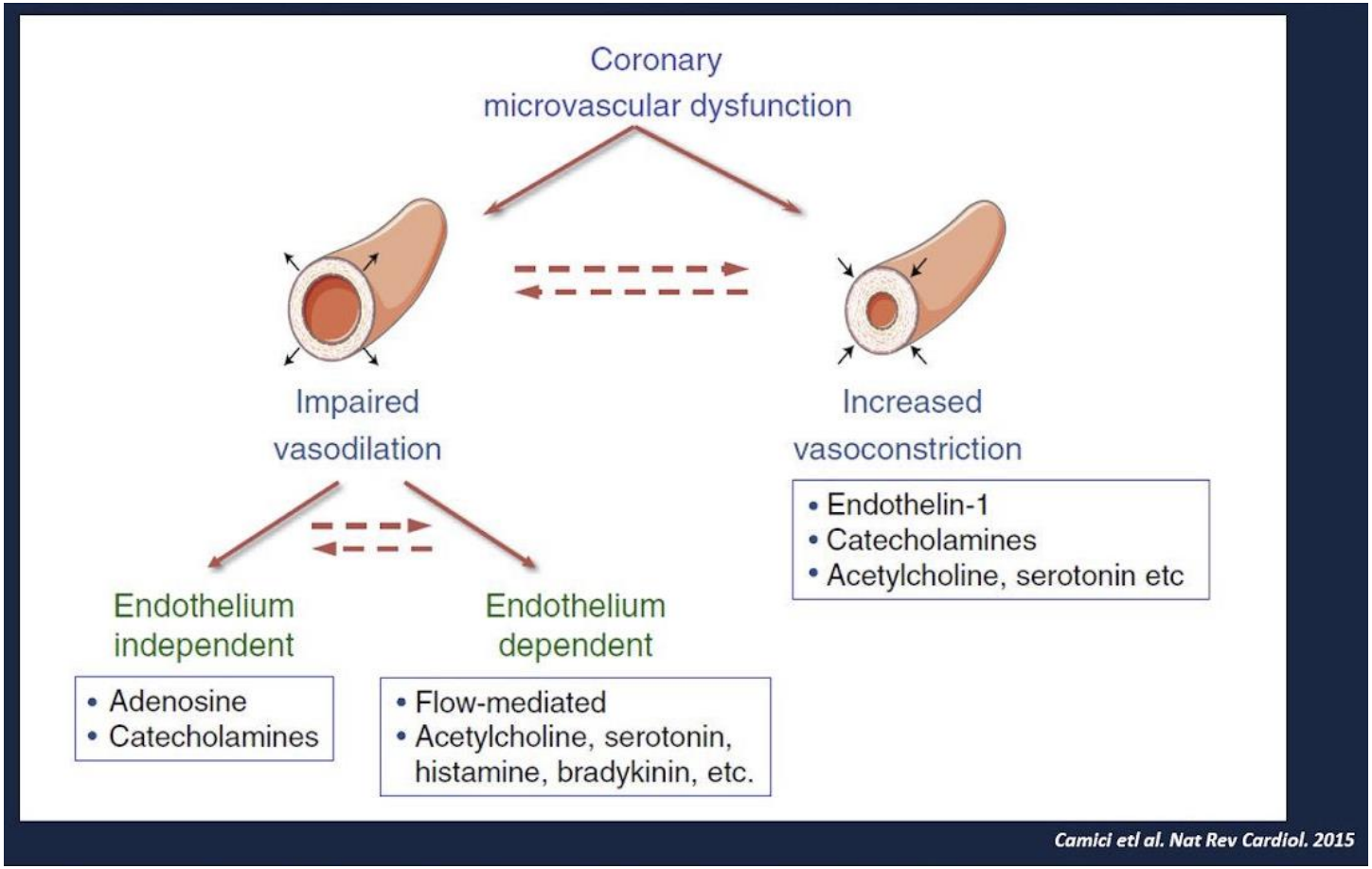
Microvascular Angina

- Due to coronary microvascular dysfunction (CMD) and/or micro coronary vasospasm
- Can be brought on by both physical and mental/emotional exertion



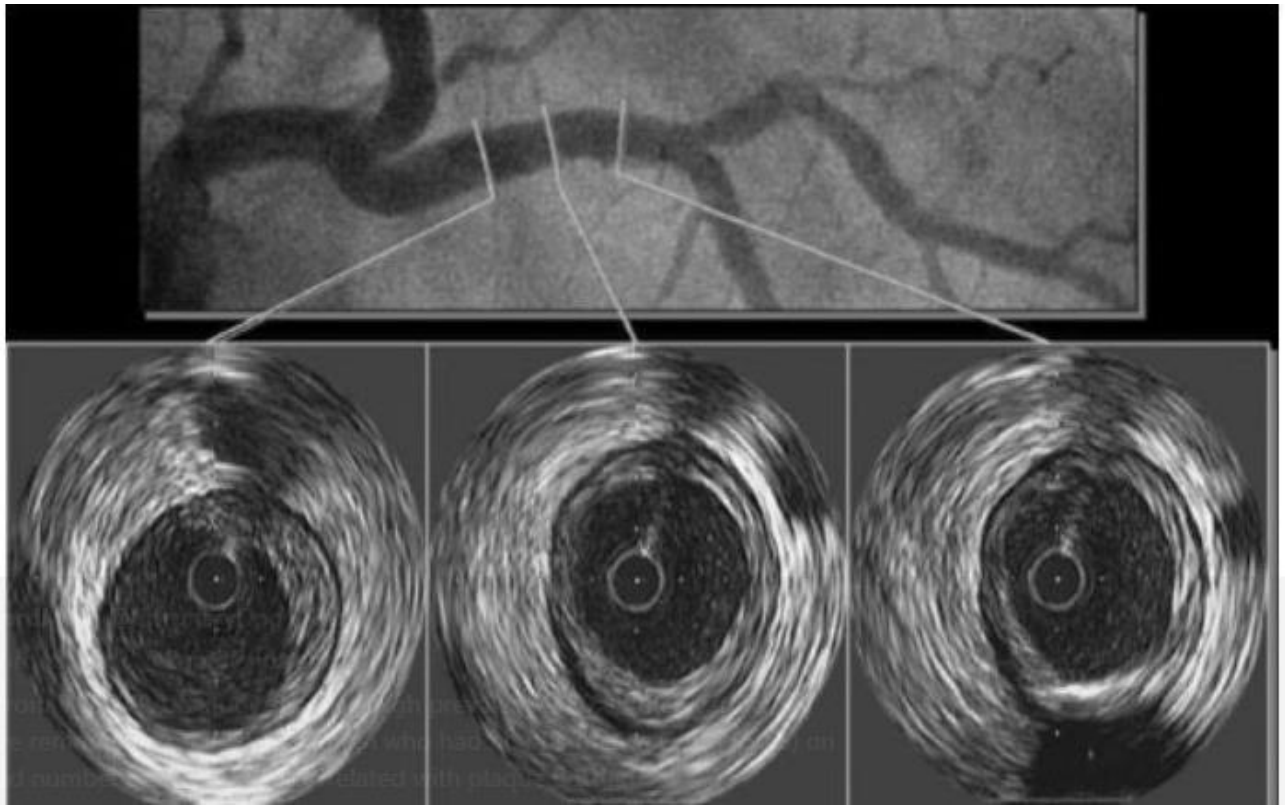
Bullock-Palmer RP et al. Clinical Cardiology, First published: 21 February 2019, DOI: (10.1002/clc.23165)

Coronary Microvascular Dysfunction (CMD)



CMD is functional & structural abnormalities of microcirculation resulting in impairment of myocardial perfusion & ischemia

Significant overlap between atherosclerosis and CMD



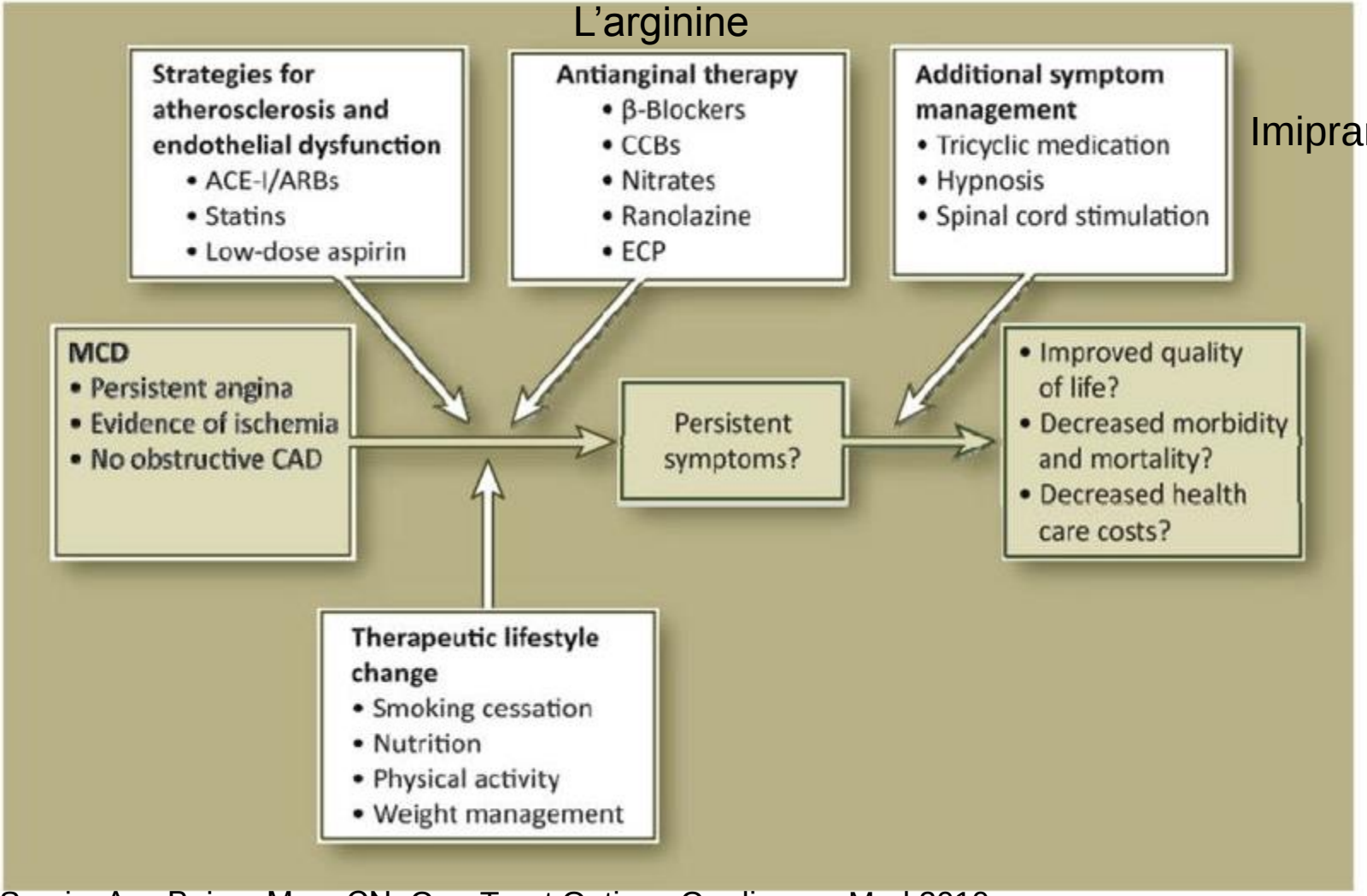
Among women in WISE that underwent IVUS, 80% with no obstructive CAD had some atherosclerosis

Conclusions: *In symptomatic women without significant luminal obstructive CAD, we observed a high prevalence of atherosclerosis with positive remodeling and preserved lumen size. These findings may help explain increased risk and emphasize need for improved diagnostic and treatment options for women with concealed CAD.* (J Interven Cardiol 2010;23:511–519)

Treatments for Microvascular Angina

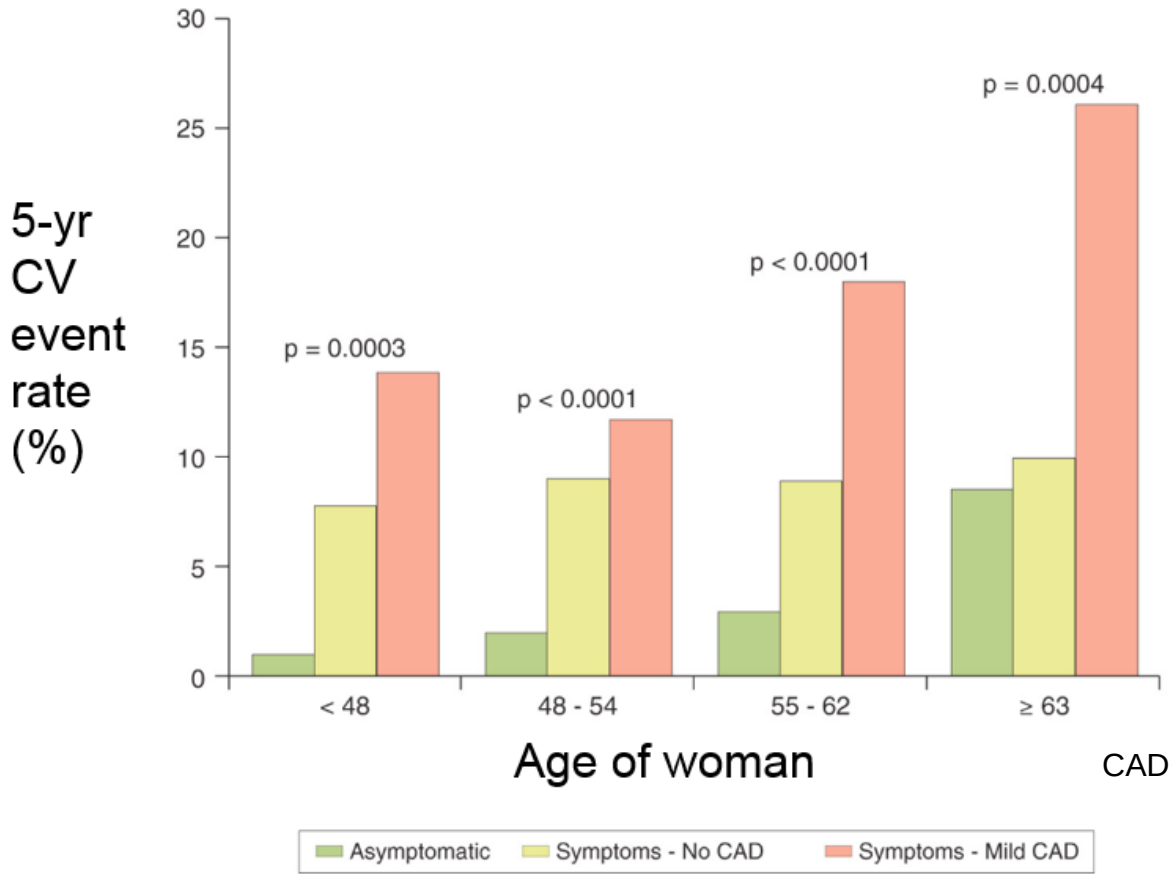
L'arginine

Imipramine



Samim A….Bairey Merz CN. Curr Treat Options Cardiovasc Med 2010

NHLBI-WISE data: Ischemic symptoms, even atypical, are not benign, in women



CAD = coronary artery disease

All suspected Ischemic Heart Disease symptoms, even atypical chest pain are associated with 5-year CVD events compared with the lower risk noted for asymptomatic women

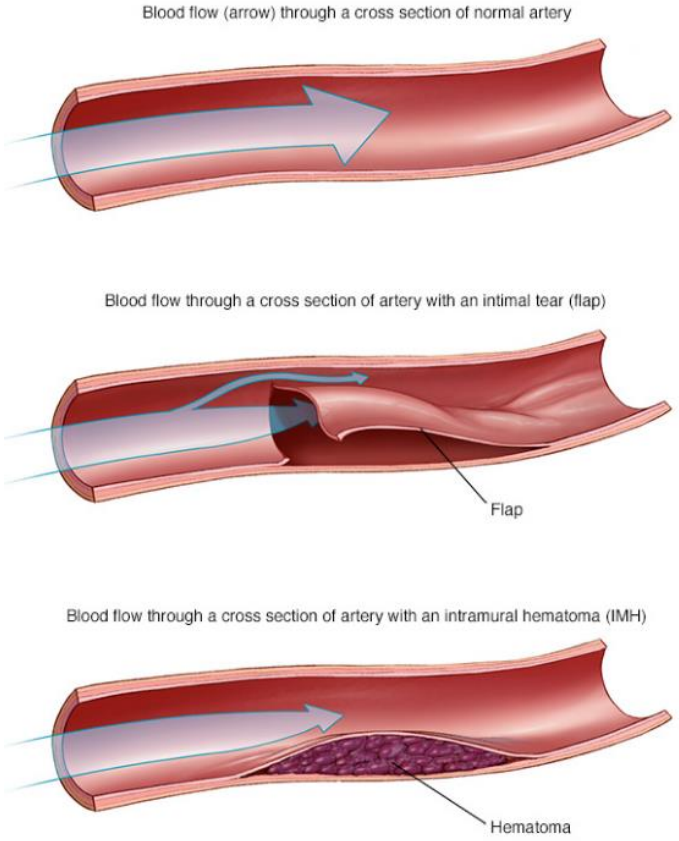
Shaw LJ. JACCi 2016

SCAD

Spontaneous Coronary Artery Dissection

JOHNS HOPKINS MEDICINE

- Cause of 3-4% of acute coronary syndromes (ACS)
- ~80% SCAD are women
- Mean age 35 to 45
- Up to 25% of ACS cause in women <50yrs
- 10-15% peripartum
- Recurrence (de novo) in ~10%



SCAD: Predisposing Factors and Management

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TABLE 4 Potential Predisposing Factors

	Patients (N = 327)
FMD	205 (62.7)
Systemic inflammatory condition	39 (11.9)
Connective tissue disorder	16 (4.9)
On hormonal therapy	38 (11.6)
Postpartum	7* (2.4)
Multiparous (≥4 births)	25* (8.8)
Grand multiparity (≥5 births)	7* (2.4)
Grand multigravida (≥5 pregnancies)	39* (11.9)
Idiopathic	91 (27.8)

- MI in patients with SCAD is often precipitated by physical or emotional stress.
- Think about SCAD in young women with ACS presentation

- Given the relatively poor outcomes of PCI, **conservative management** is generally preferred.
- PCI indicated only if isolated LM SCAD or if there are symptoms that are recurrent/refractory to medRx or flow limiting dissection.
- If no stent, use and duration of antiplatelet therapy is controversial
  - Most say 1 year
- Statin use – Not routine. Only if additional indication beyond SCAD

Saw J Am Coll Cardiol 2017;70:1148–58

SCAD: Management

Hypertension increases risk of recurrence, beta-blockers appear to reduce risk

FIGURE 3 Survival Free of Recurrent SCAD: Hypertension

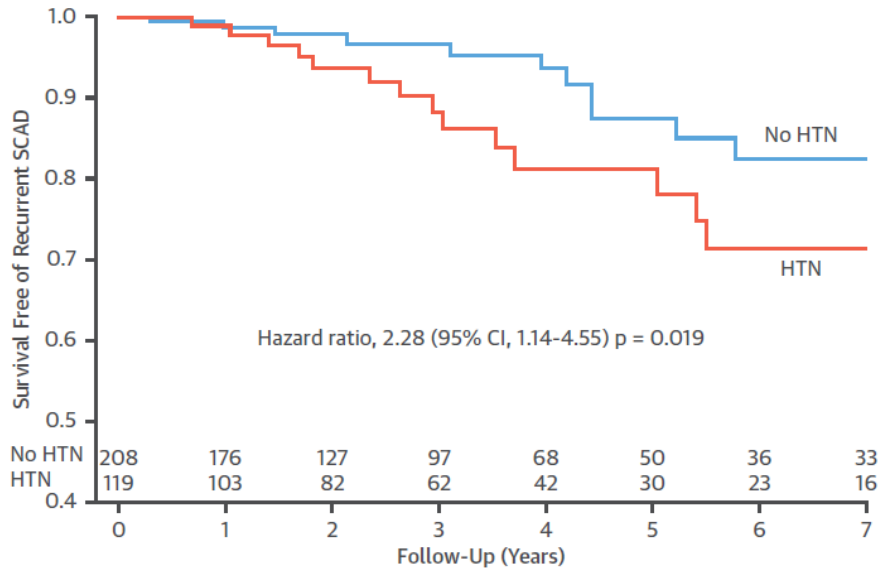
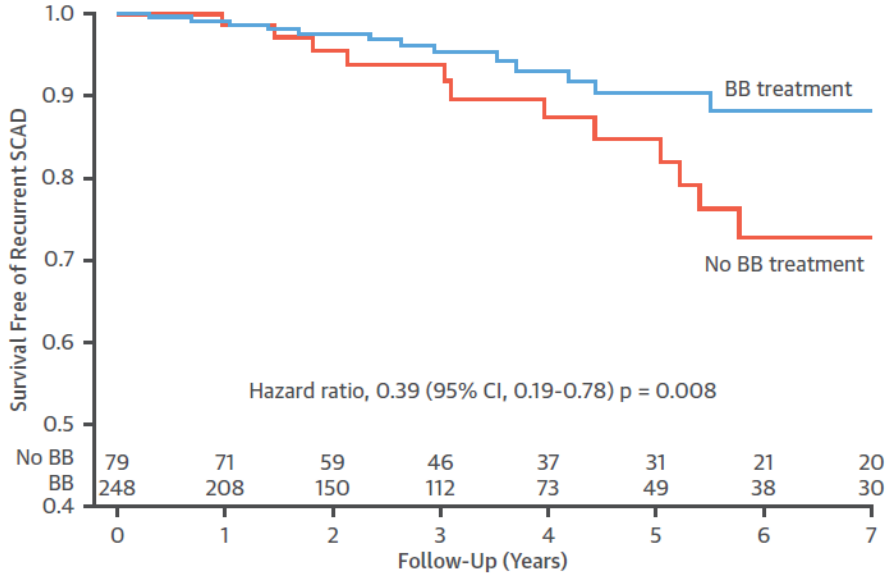


FIGURE 4 Survival Free of Recurrent SCAD: Beta-Blocker Treatment

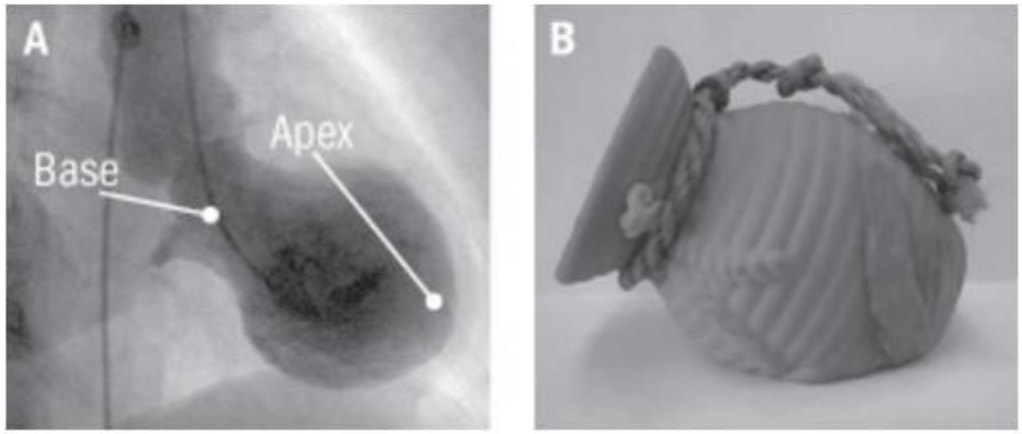


Saw J Am Coll Cardiol 2017;70:1148–58

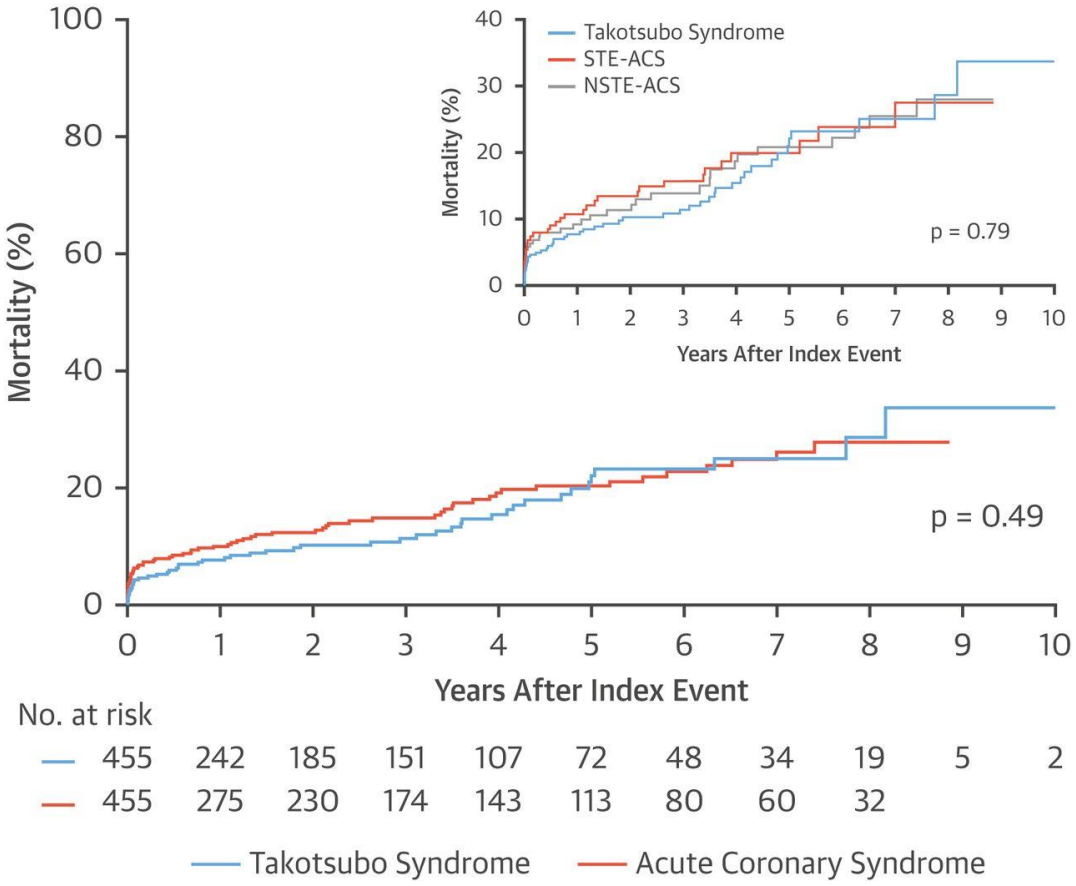
Stress Cardiomyopathy

- Acute LV dysfunction, mimicking an MI, but w/o angiographic evidence of obstructive CAD or plaque rupture
- Usually the result of severe emotional or physical stress
- More than 90% of reported cases are in women ages 58 to 75
- Most recover back to normal functioning

Apical ballooning and the tako-tsubo



Long-Term Prognosis of Takotsubo Syndrome



Jelena R. Ghadri et al. JACC 2018;72:874-882

NOT BENIGN

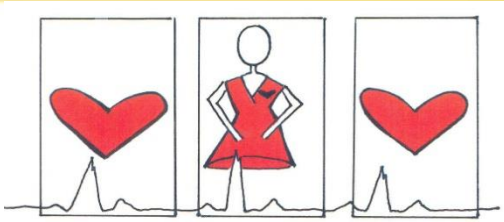
Long-term prognosis for Takotsubo Syndrome is similar to age and sex matched ACS patients

Peripartum Cardiomyopathy

Diagnostic criteria for PPCM

- New onset LV systolic dysfunction/heart failure in peripartum (last month of pregnancy or in the first 5 months postpartum)
- Absence of other cause of cardiac failure or heart disease before the last month of pregnancy

- Rare (1 in 4000 of pregnancies)
- Increased risk: Maternal age, African Americans, pre-eclampsia/HTN, multiple gestations
- Can result in serious HF morbidity
- ~70% of women recover LVEF to >50% by 6 mo.
- Prognosis is variable, depends on recovery of LVEF
- Risk of relapse much higher in patients w/ persistent LV dysfunction than in those w/ normalized LVEF



Pharmacologic Treatment of CVD: Statins and Asprin

Aspirin in Women

- There is good evidence for the use of aspirin in secondary prevention in women – it reduces subsequent MI, stroke, and death from CVD by 25% in women with established disease.

- In healthy women (primary prevention), not generally recommended for most
  - ACC/AHA Guidelines IIB indication (may be considered selective)

Statins: Similar CVD risk reduction in men and women

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Meta-analysis of Statin Therapy

- 18 randomized clinical trials of statins with sex-specific outcomes
  - N = 141,235; 40,275 women; 21,468 cardiovascular events
- Overall 19% Reduction in CVD in Women
  - **OR: 0.81, 95% CI: 0.75 to 0.89; p < 0.0001**
- Benefit seen in both Primary and Secondary Prevention
- All-cause mortality also lower in both Women and Men with statin therapy
- No interaction of treatment effect by sex

Implication: Statin therapy should be used in appropriate patients without regard to sex

Kostis et al. JACC 2012;59:572-82.

2018 Cholesterol Guidelines Refining Risk Estimates for Individual Patients

JOHNS HOPKINS MEDICINE

Risk-Enhancing Factors for Clinician–Patient Risk Discussion

- **Family history of premature ASCVD**; (males, age <55 y; females, age <65 y)
- **Primary hypercholesterolemia** (LDL-C, 160-189 mg/dL [4.1- 4.8 mmol/L]; non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L])*
- **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
- **Chronic kidney disease** (eGFR 15-59 mL/min/1.73 m^2 with or without albuminuria, not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS

- **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as pre-eclampsia**

- **High-risk race/ethnicities** (e.g. South Asian ancestry)
- **Lipid/biomarkers**: Associated with increased ASCVD risk
  -Persistently* elevated, primary hypertriglyceridemia (≥175mg/dL);
  -If measured:
  - **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L
  - **Elevated Lp(a)** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL or ≥125 nmol/L constitutes a risk enhancing factor especially at higher levels of Lp(a)
  - **Elevated apoB** ≥130 mg/dL - A relative indication for its measurement would be triglyceride ≥ 200 mg/dL. A level ≥ 130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk enhancing factor
  - **ABI (ABI)** <0.9

Grundy SM et al. J Am Coll Cardiol. 2018 Nov 8. doi: 10.1016/j.jacc.2018.11.003.

Gender Disparities in Patient-Provider Communication

Medical Expenditure Panel Survey (MEPS) data 2006-2015
Represents ~11 million women in U.S.

Patient Healthcare Experience (in women compared to men)	OR* (95% CI)
Patient-provider communication	
Poor Patient-Provider Communication (summary score)	**1.25 (1.11-1.41)**
Individual Components of Patient-Provider Communication	
Doctor Never/Sometimes listened to you	**1.23 (1.07-1.42)**
Doctor Never/Sometimes explained so you understood	1.07 (0.92-1.25)
Doctor Never/Sometimes showed respect	**1.20 (1.04-1.38)**
Doctor Never/Sometimes spent enough time with you	**1.36 (1.20-1.54)**
Patient satisfaction with healthcare	
Poor patient satisfaction	**1.12 (1.02-1.24)**
All models (which compare women to men) were adjusted for age, race/ethnicity, level of income, region, health insurance, educational status, modified charlson comorbidity index (without the cardiovascular component), and cardiovascular risk factors.	

Okunrintemi V…..Michos ED. J Am Heart Assoc 2018;7:e010498
https://doi.org/10.1161/JAHA.118.010498

Women vs Men with ASCVD

Medical Expenditure Panel Survey (MEPS) data 2006-2015

	[Yes vs. No; OR* (95% CI)]
Surrogate Measures for Clinical Outcomes (in women compared to men)	
Statin usage	**0.55 (0.48-0.62)**
Aspirin usage	**0.65 (0.58-0.72)**
≥ 2 ED visits/yr	**1.28 (1.11-1.46)**
≥ 2 Hospitalizations visits/yr	1.05 (0.88-1.25)
*Odds ratios compare women to men and were adjusted for age, race/ethnicity, level of income, region, health insurance, educational status, modified charlson comorbidity index (without the cardiovascular component), and cardiovascular risk factors.	

Okunrintemi V…..Michos ED. J Am Heart Assoc 2018;7:e010498
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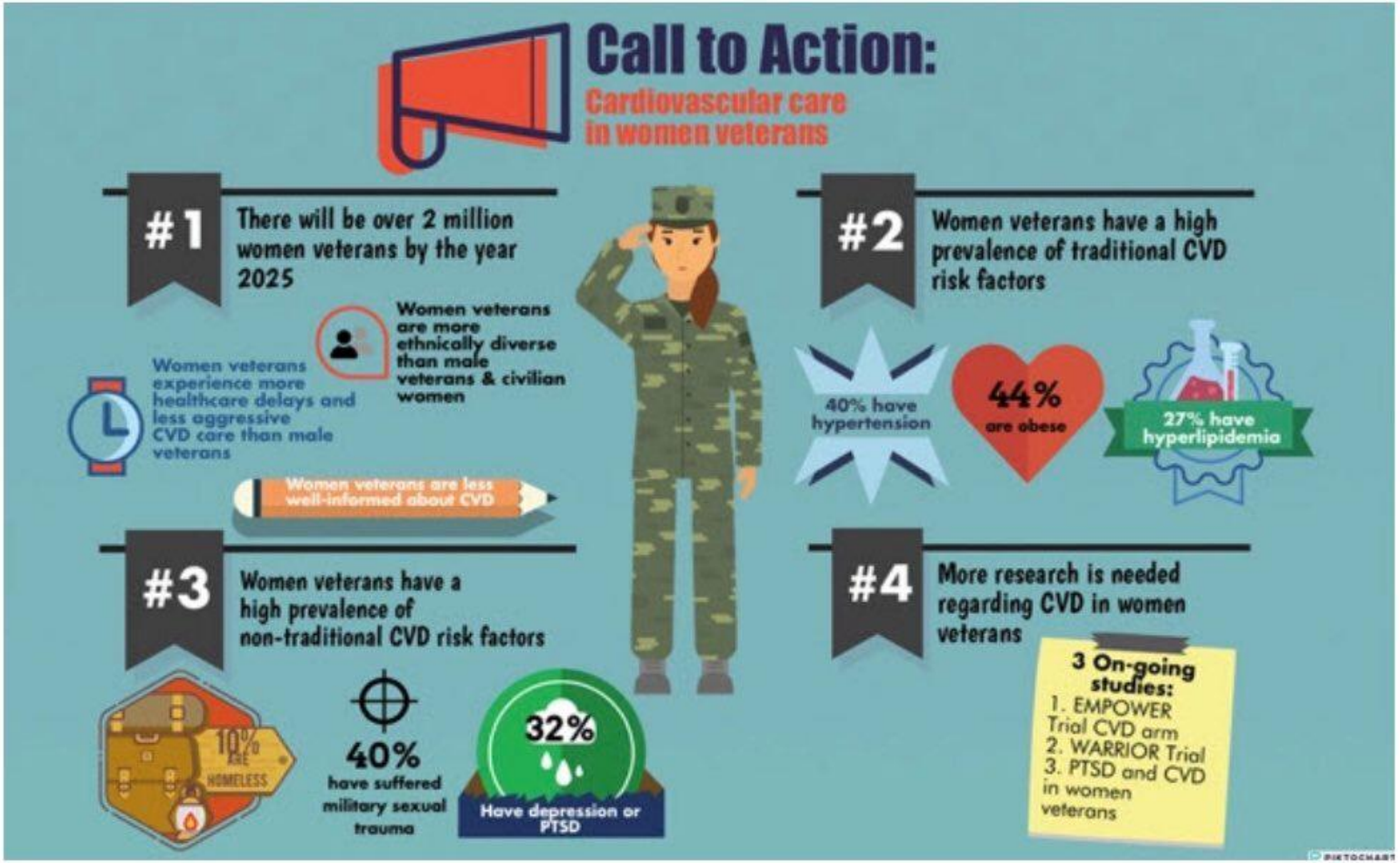
CVD in Women Veterans



Cardiovascular Care in Women Veterans, Volume: 139, Issue: 8, Pages: 1102-1109, DOI: (10.1161/CIRCULATIONAHA.118.037748)

Improving CV Health in Women

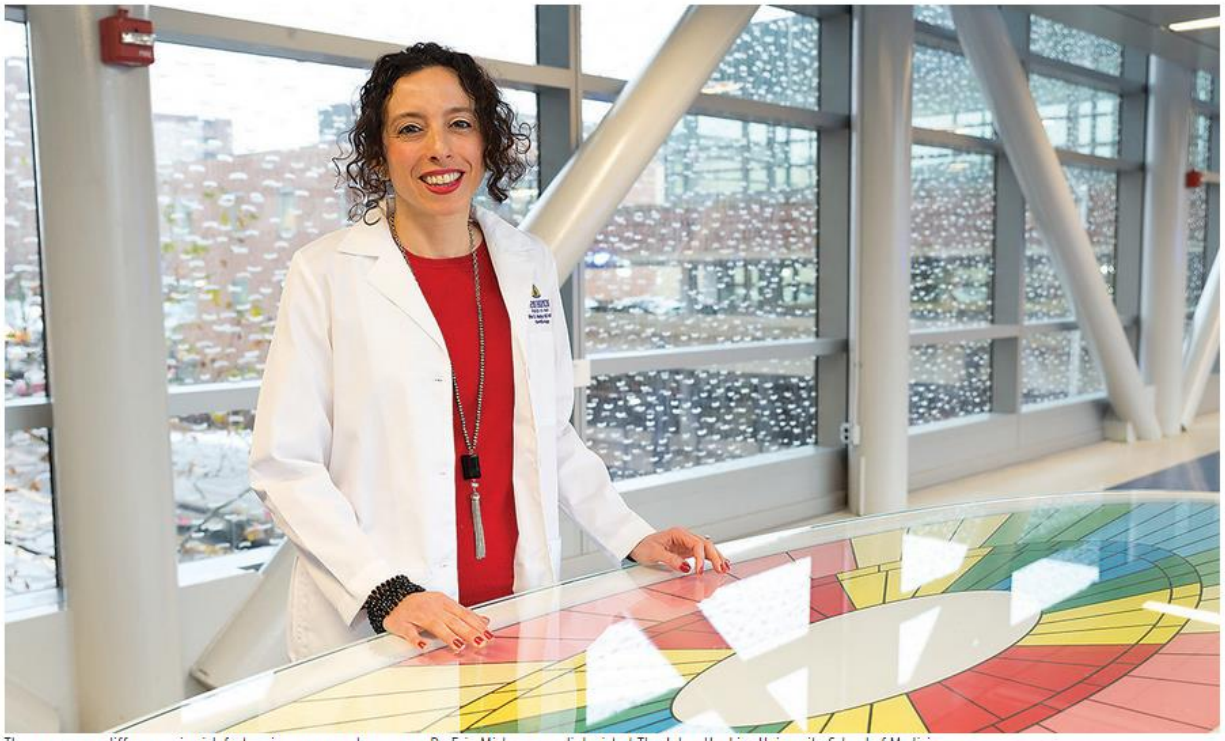
- Recognize and address sex and gender differences in traditional CVD risks and novel risk factors
- **Raise awareness**: especially minority women
- Universal **lifestyle counseling**
- MI symptoms: "**Make the Call! Don't miss a beat**!
- Assess and Address Barriers
- Families, children, and communities benefit from improving women's CVD health

Listen To Your Heart

JOHNS HOPKINS MEDICINE

Feel something, say something; Here's why women's heart disease is so dangerous.

By Rebecca Kirkman - *February 2016*



There are some differences in risk factors in women and men, says Dr. Erin Michos, a cardiologist at The Johns Hopkins University School of Medicine.

Thanks! Questions??

Go Red for Women

Johns Hopkins Ciccarone Center for the Prevention of Heart Disease

CVD Prevention In women

http://www.baltimoremagazine.net/promotions/listen-to-your-heart-why-womens-heart-disease-is-so-dangerous

@ErinMichos