Cardiac Disease in Women

Update in Internal Medicine 2019

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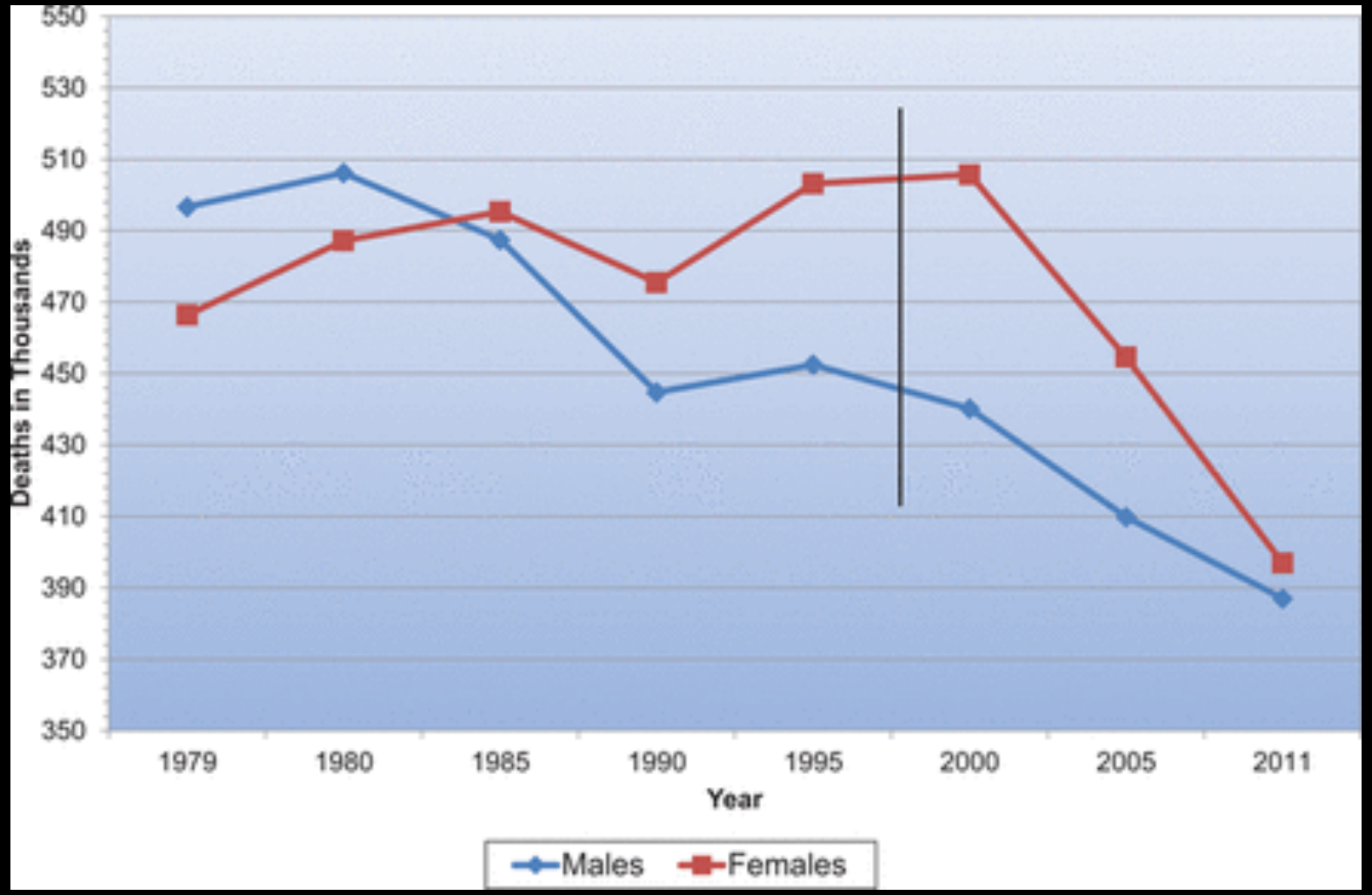
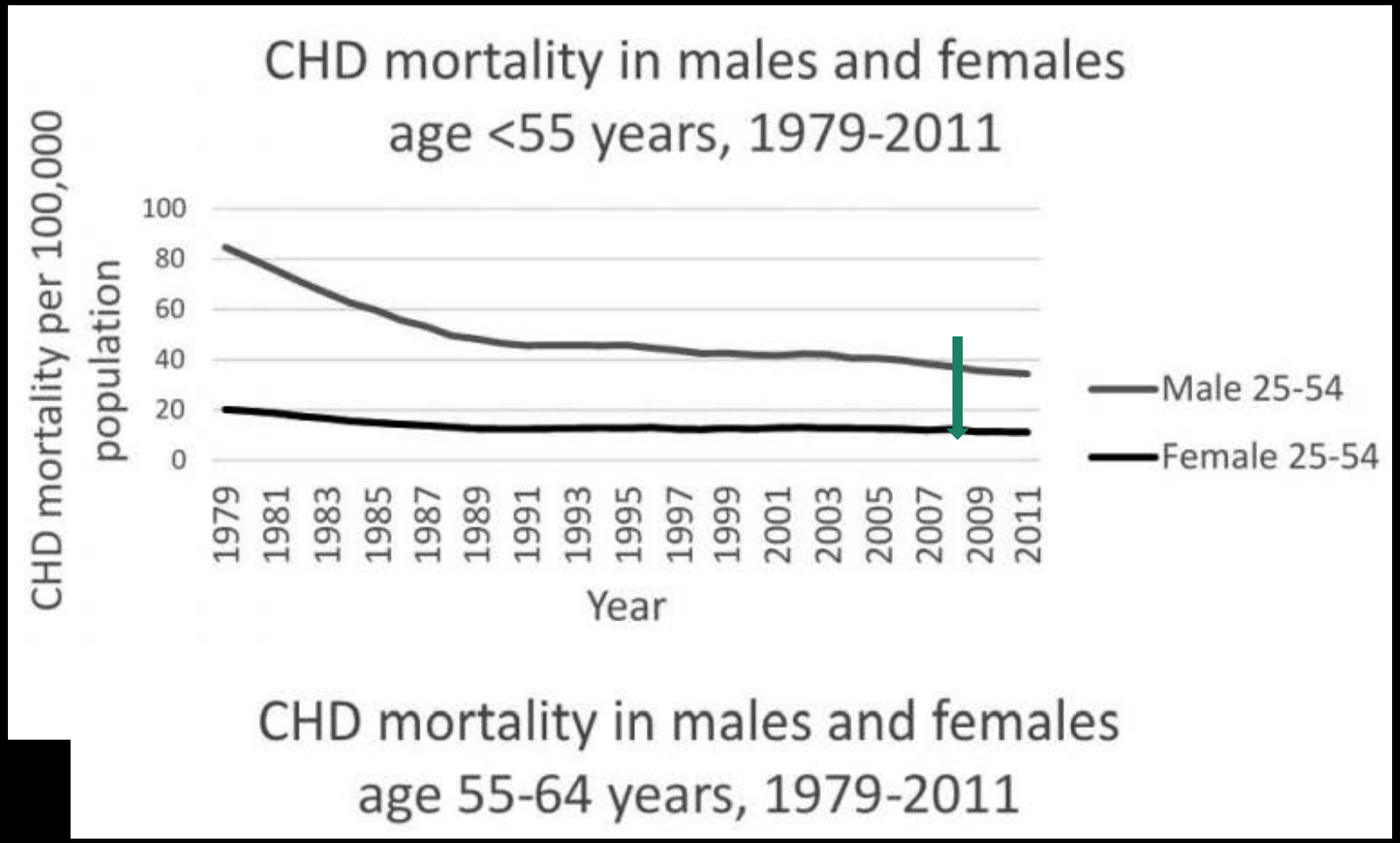
I have no disclosures.



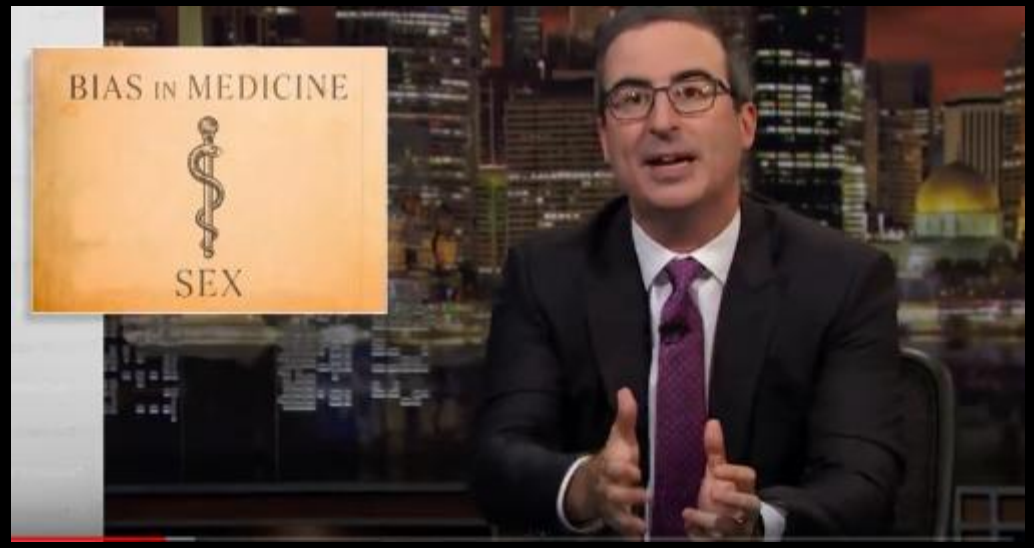
CVD Is the Leading Cause of Death among Women

Mozaffarian et al., *Circulation*, 2015

Improvement in CVD mortality among younger women is stagnant



Wilmot et al., *Circulation*, 2015



Last Week Tonight, John Oliver on HBO

Objectives

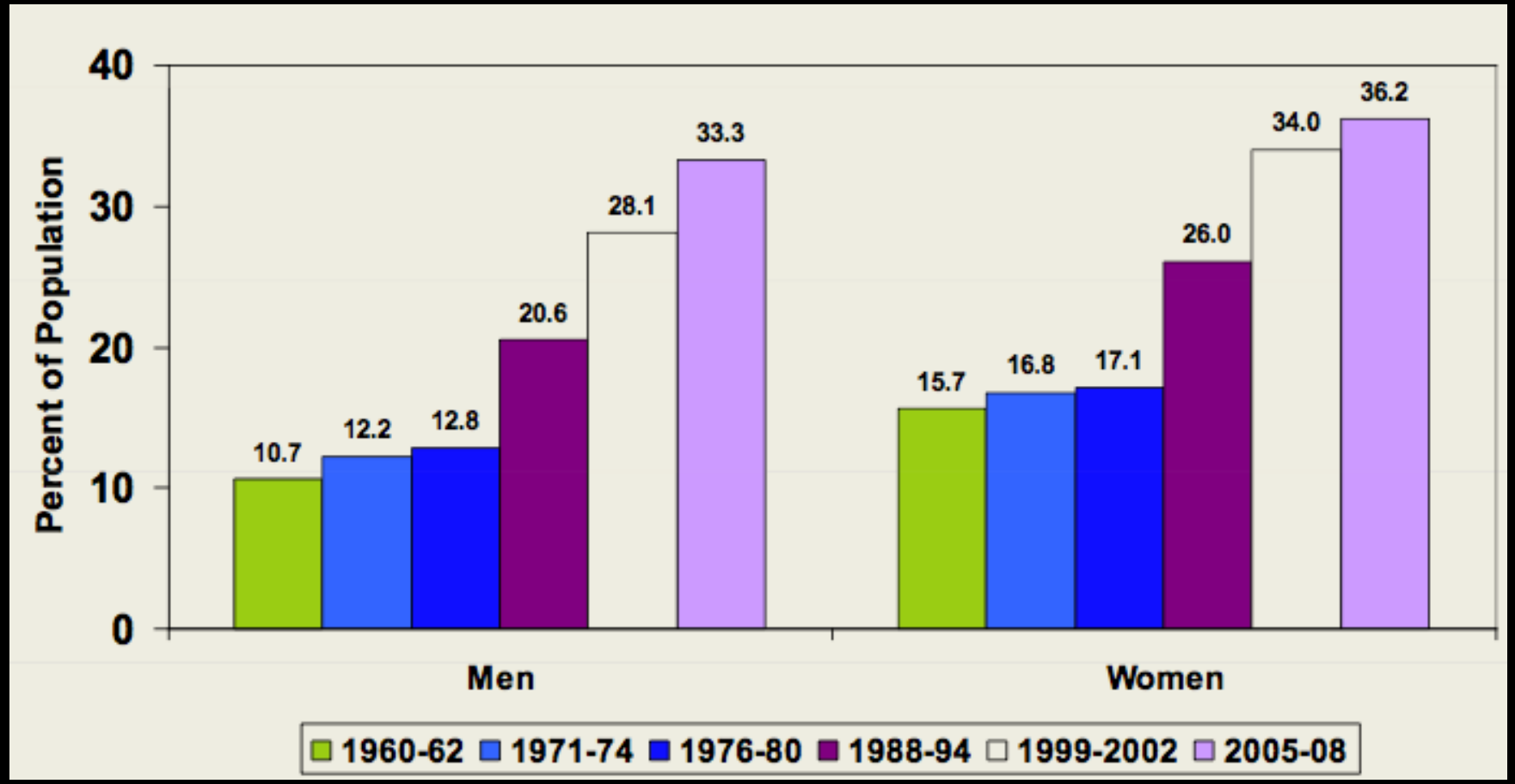
- Identify non traditional risk factors for CAD in women
- Describe presentation of patient with spontaneous coronary artery dissection
- Name three barriers that contribute to disparity in cardiovascular care and outcomes for women

CV Risk Factors in Women

Women and Risk Factors

- 80% of women have more than one risk factor at presentation of heart disease.
- Obesity is prevalent in >1/3 women.
- Women with diabetes have more of a risk for acute infarction when compared to men with diabetes.

Obesity in America



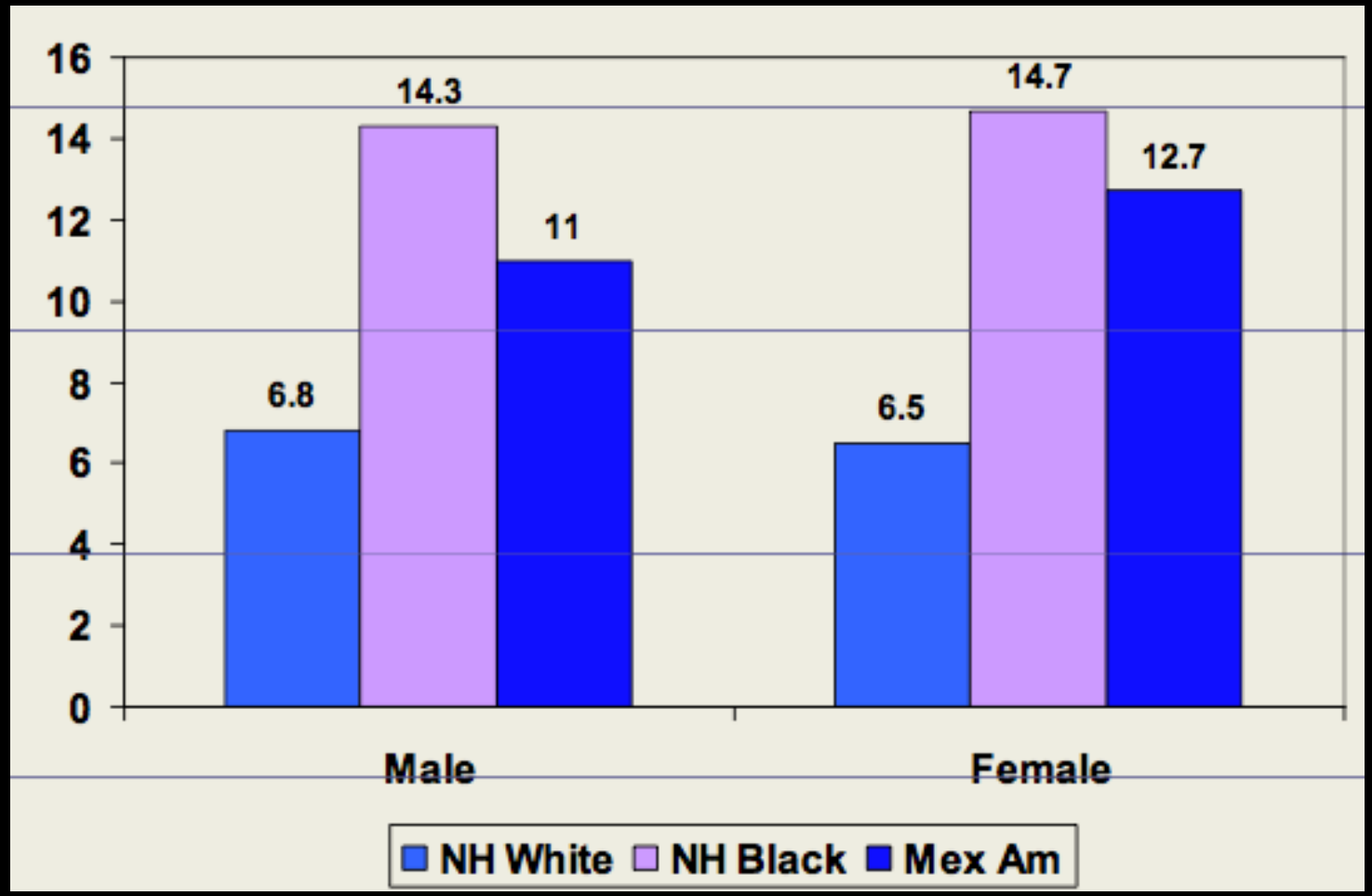
Roger VL et al AHA Heart and Stroke Facts 2012 update. Circulation. Dec 2011.

Women and Diabetes

- Women have a higher prevalence of DM than men.

- Diabetes is a stronger risk factor for heart disease in women than men.
  - 3-5x higher risk of heart disease in women with DM.

Prevalence of Type II DM



MEN = 7.2%

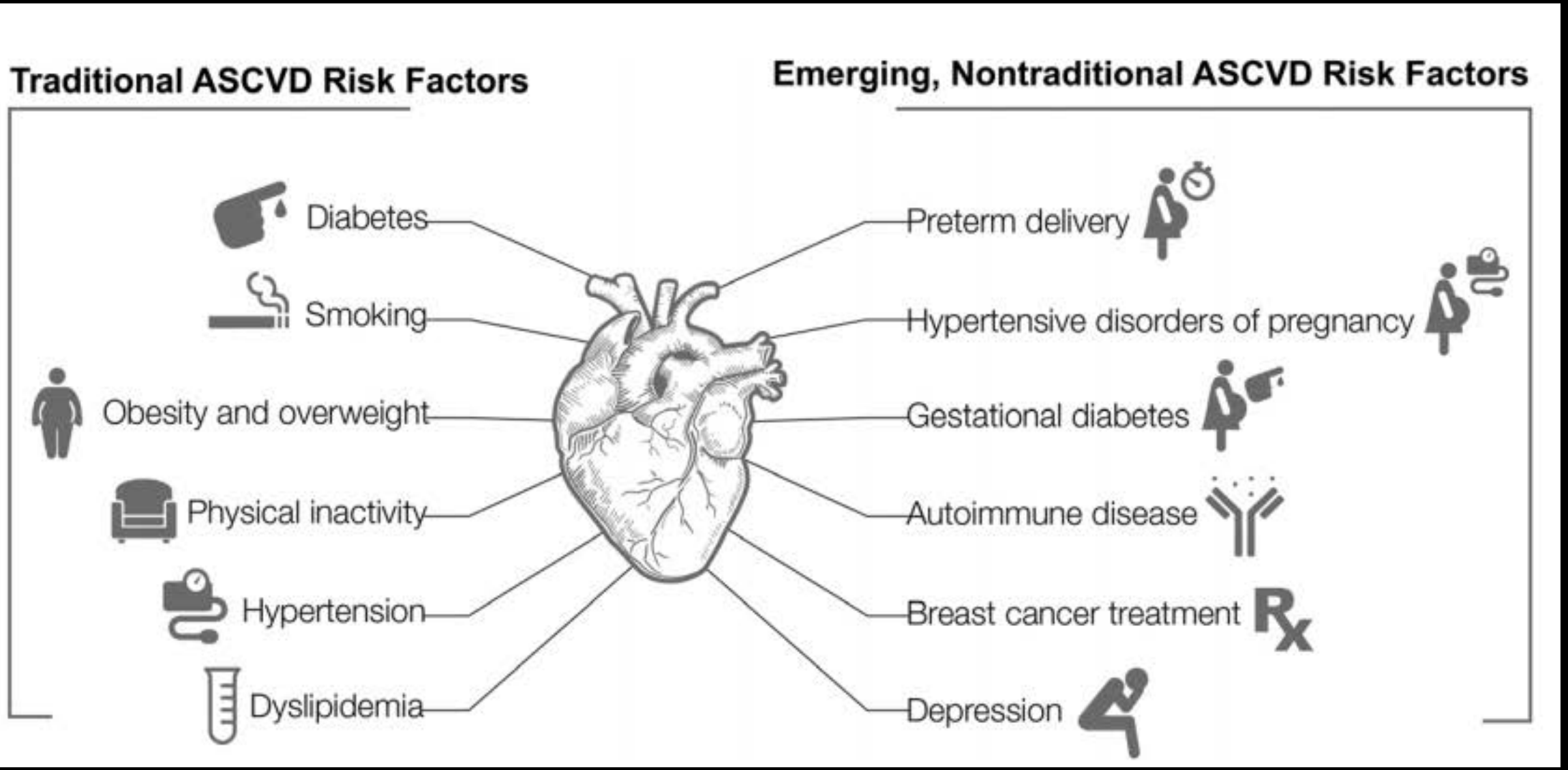
WOMEN = 8.3%

Assessing CVD Risk in Women

Framingham Risk Score

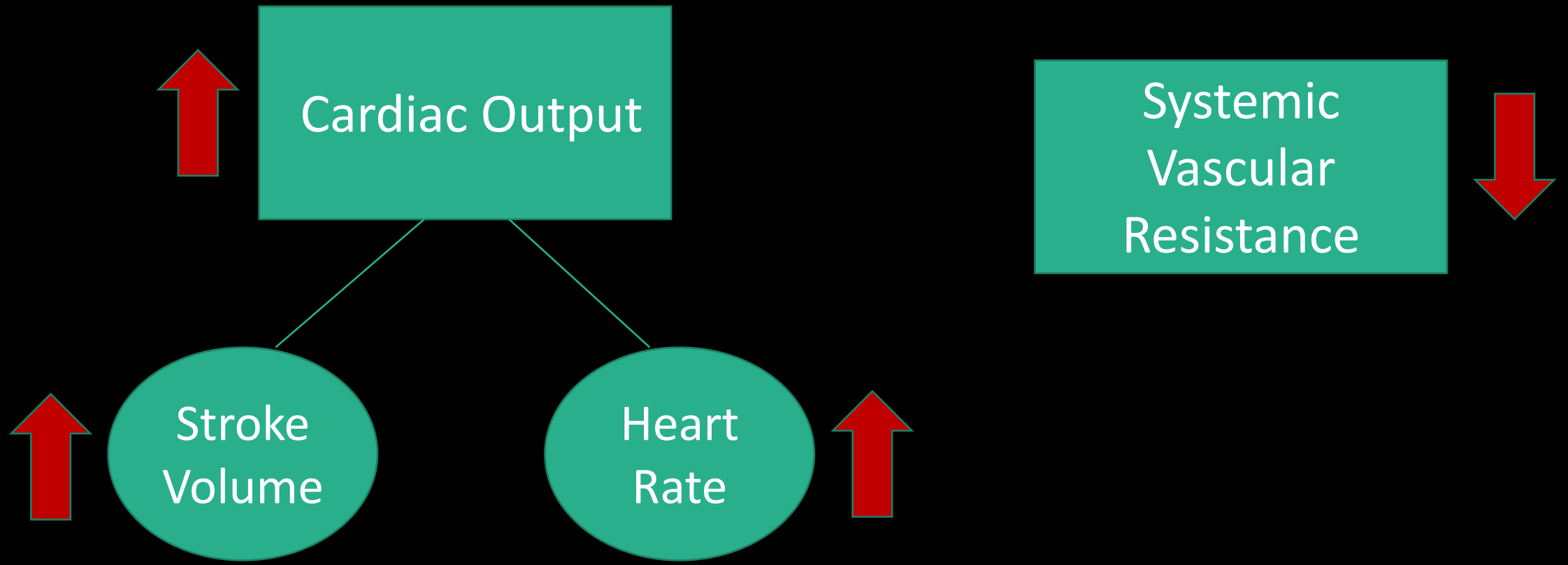
Reynold's Risk Score

ASCVD Risk Score



Garcia et al., *Circulation Research*, 2016

Pregnancy as a Stress Test



Hypertensive Disorders of Pregnancy

Gestational Hypertension (6-7% of pregnancies)

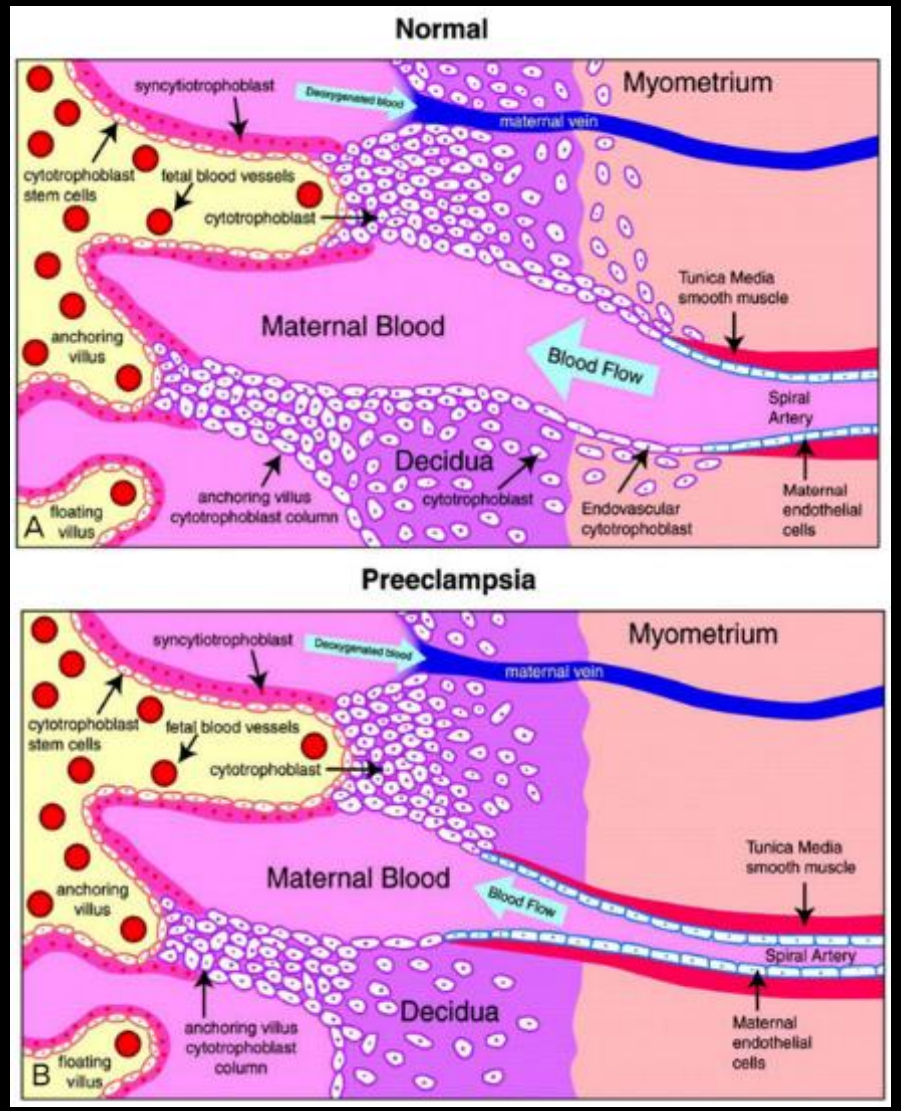
- BP 140/90mmHg
- >20wks gestation
- Treat with CCB or BB
- Resolves within 42d postpartum

Preeclampsia (2-5% of pregnancies)

- BP 140/90mmHg
- >20wks gestation
- Proteinuria

  and/or
- End organ dysfunction

Preeclamptic Pregnancy



Later Life

Unmasks Underlying Predisposition for CVD

Vascular changes result in permanent damage

Preeclampsia – Who's at Risk?

- >40yo
- Black race
- Nulliparity
- Previous PE or GH
- Chronic HTN
- Obesity, HLD, DM2
- CKD

Preeclampsia and CVD Risk

Outcome	Mean weighted f/u (years)	RR
HTN	14.1	3.70 (2.70 to 5.05)
Ischemic heart disease	11.7	2.16 (1.86 to 2.52)
Stroke	10.4	1.81 (1.45 to 2.27)
VTE	4.7	1.79 (1.37 to 2.33)

41% of women with severe preeclampsia have HTN just 1 year after delivery.

Bellamy et al. *BMJ*. 2007
Benschop et al. *Hypertension*. 2018

Preterm Delivery < 34 weeks

- ❑ 1.5x risk of coronary heart disease
- ❑ 1.8x risk of CV mortality

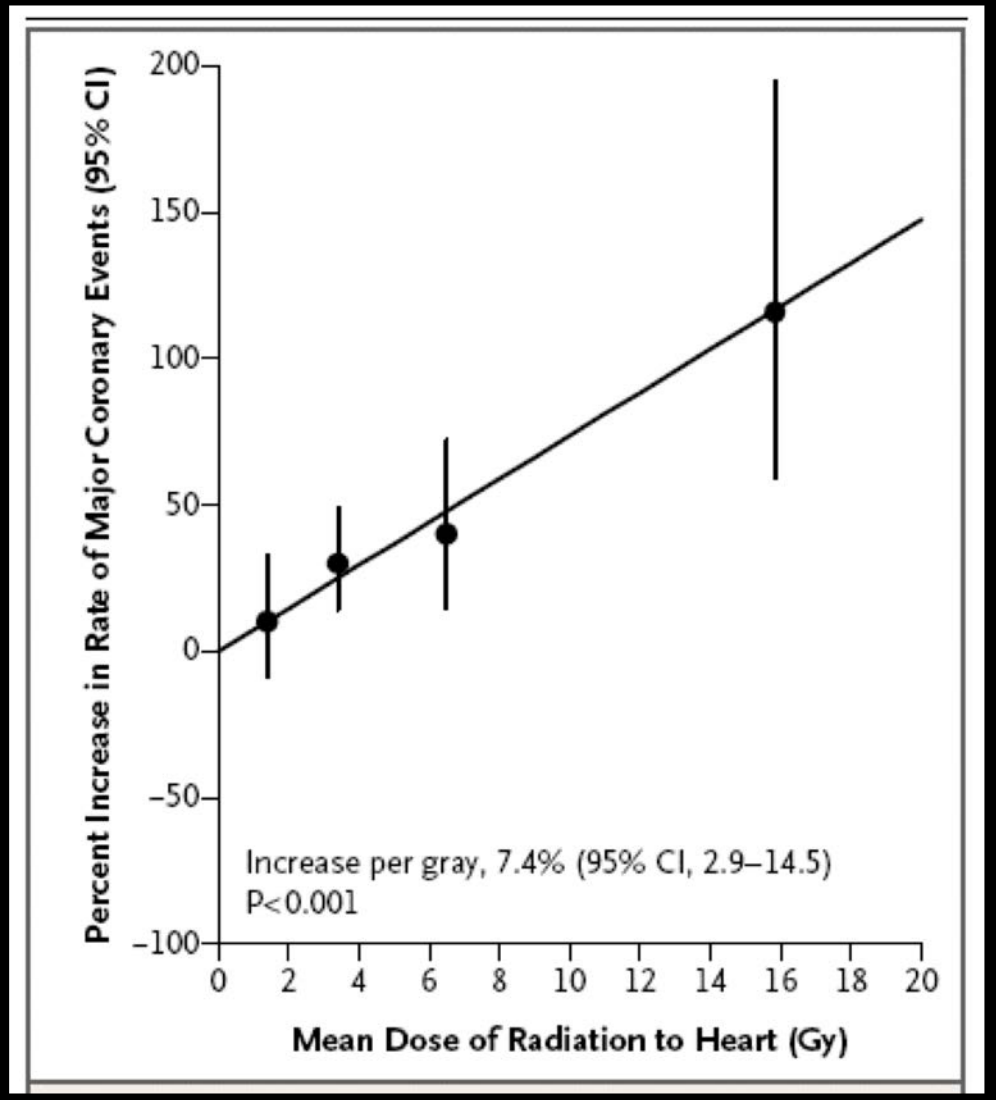
Wu et al. *JAHA*. 2018

https://i.ytimg.com/vi/Vwhee8jVPnc/maxresdefault.jpg

Radiation and CVD

- NEJM March 2013, Darby et al
- Population-based control study of major coronary events in women who had thoracic radiation for breast cancer between 1958 and 2001.
- 963 women with events; 1205 controls.
- **Results:**
  - Left sided radiation had higher rates of events
  - Rate of events increased by 7.4% for each increase of 1 gray in the mean radiation dose to the heart

Rate of Major Coronary Events according to Mean Radiation Dose to Heart



Consider asking your patients about radiation when assessing risk for CAD.

What does this mean for providers?

Case follow up

Clinical Presentation of ACS

- Chest pain
- Fatigue
- Nausea/vomiting
- Dyspnea
- Neck or jaw pain
- Weakness

https://www.sharecare.com/health/heart-disease/slideshow/top-5-heart-attack-signs-in-women

ACS Presentations

- Chest pain is the most common symptom for BOTH women and men.
- Women are more likely to have *atypical* symptoms, including:
  - Arm, back, shoulder, neck, jaw pain
  - Shortness of breath
  - Nausea
  - Unexplained fatigue
  - Palpitations

What Happens to Women with CHD?

- Women are more likely to die from heart attacks: 44% of women vs. 27% of men at one year
- 50% of men and **64% of women** who die suddenly of CHD have no previous symptoms.
- Women develop more angina, heart failure, arrhythmias after heart attack.

Women Have Worse Outcomes

- 1 year after first AMI:
  - <45 yo, 19% men and **26% women** die.
  - 45 – 64 yo, 5% white men, **9% white women**, **14% black men**, 8% black women die.
  - ≥65 yo, 25% white men, **30% white women**, 25% black men, **30% black women** die.
- 5 years after first AMI:
  - <45 yo, 36% men and **47% women** will die.
  - 45 - 64 yo, 11% white men, **18% white women**, 22% black men, **28% black women** will die.
  - ≥65 yo, 46% white men, **53% white women**

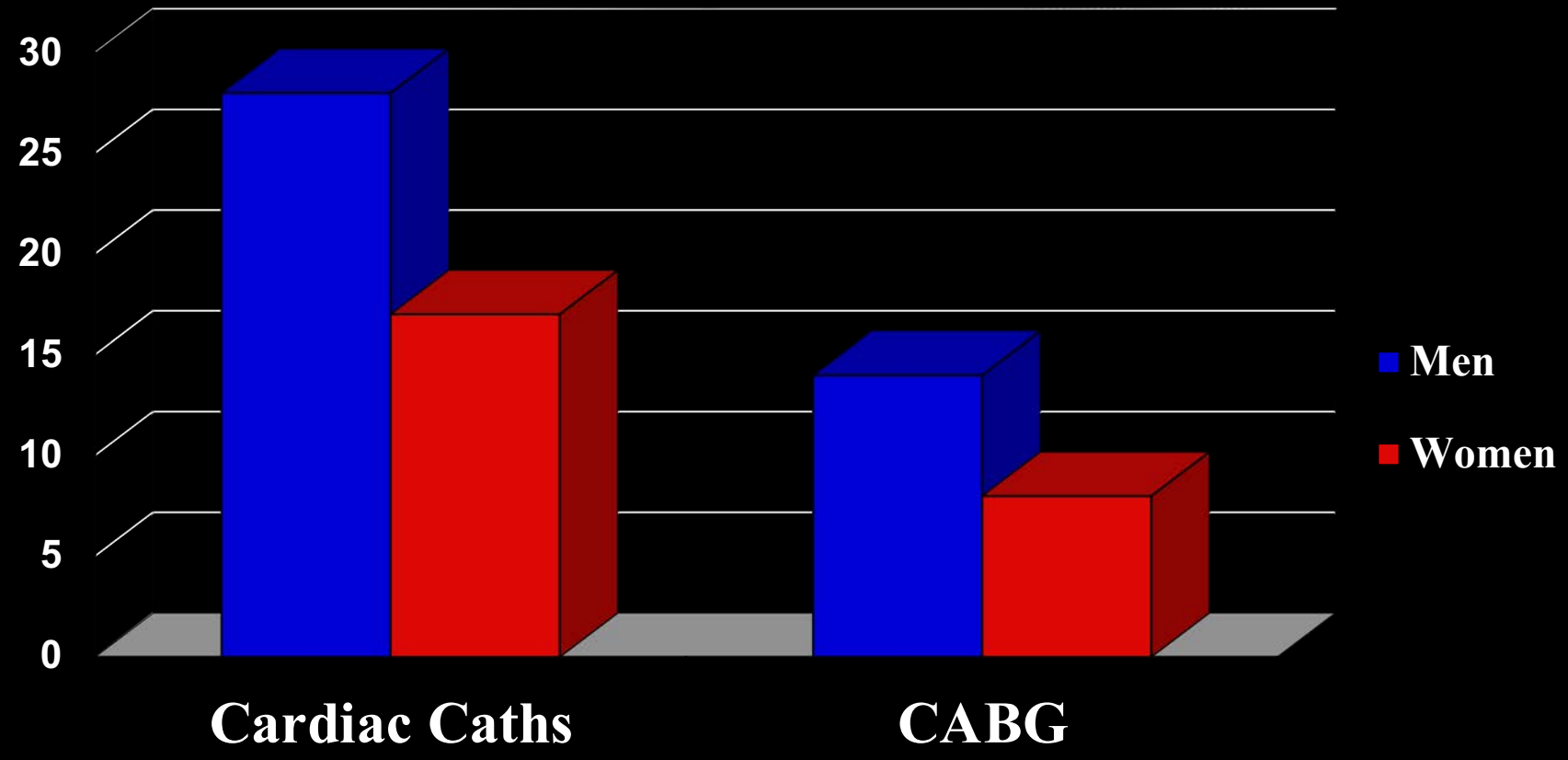
Pooled data from the NHLBI

Women Receive Less Intervention

- Less cholesterol screening and therapies
- Less use of heparin, beta-blockers and aspirin during AMI
- Less antiplatelet therapy for secondary prevention
- Fewer referrals to cardiac rehabilitation
- Fewer ICDs compared to men with the same recognized indications

Chandra 1998, Nohria 1998, Scott 2004, O'Meara 2004, Hendrix 2005, Chou 2007, Hernandez 2007, Cho 2008

Referral for Invasive Procedures

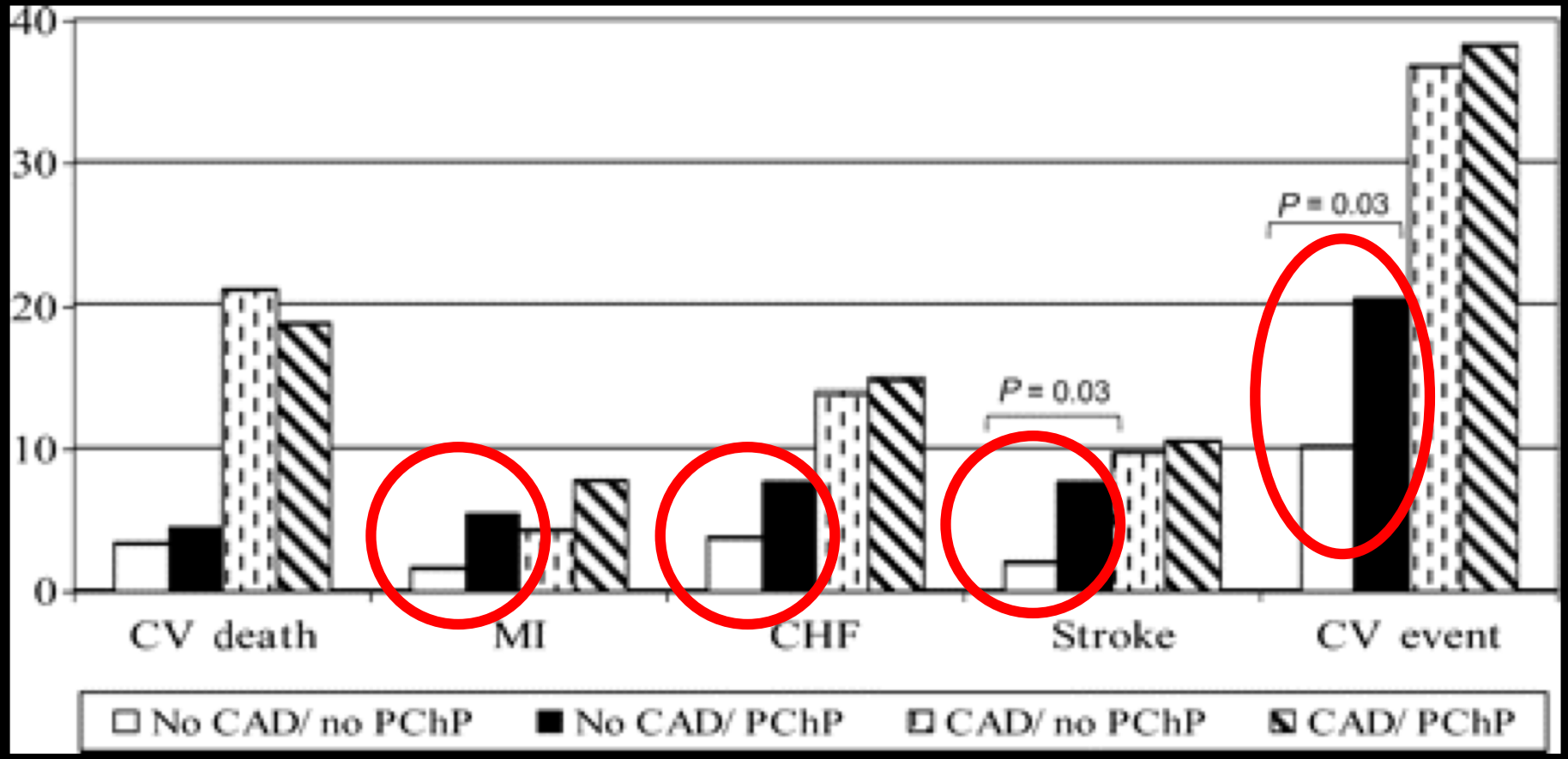


Daly C, et al. Circulation 2006;113:490-498

Women's Ischemia Syndrome Evaluation

- Johnson BD et al in Eur Heart J, 2006
- Subset of WISE study
- 673 women with chest pain who had a catheterization for suspected ischemia
- Persistent chest pain (PChP) defined as 1 year after cath
- Compared events after one year in women with and without CAD and women with and without PChP.
- Median age 58, 39% had obstructive CAD, 45% had PChP

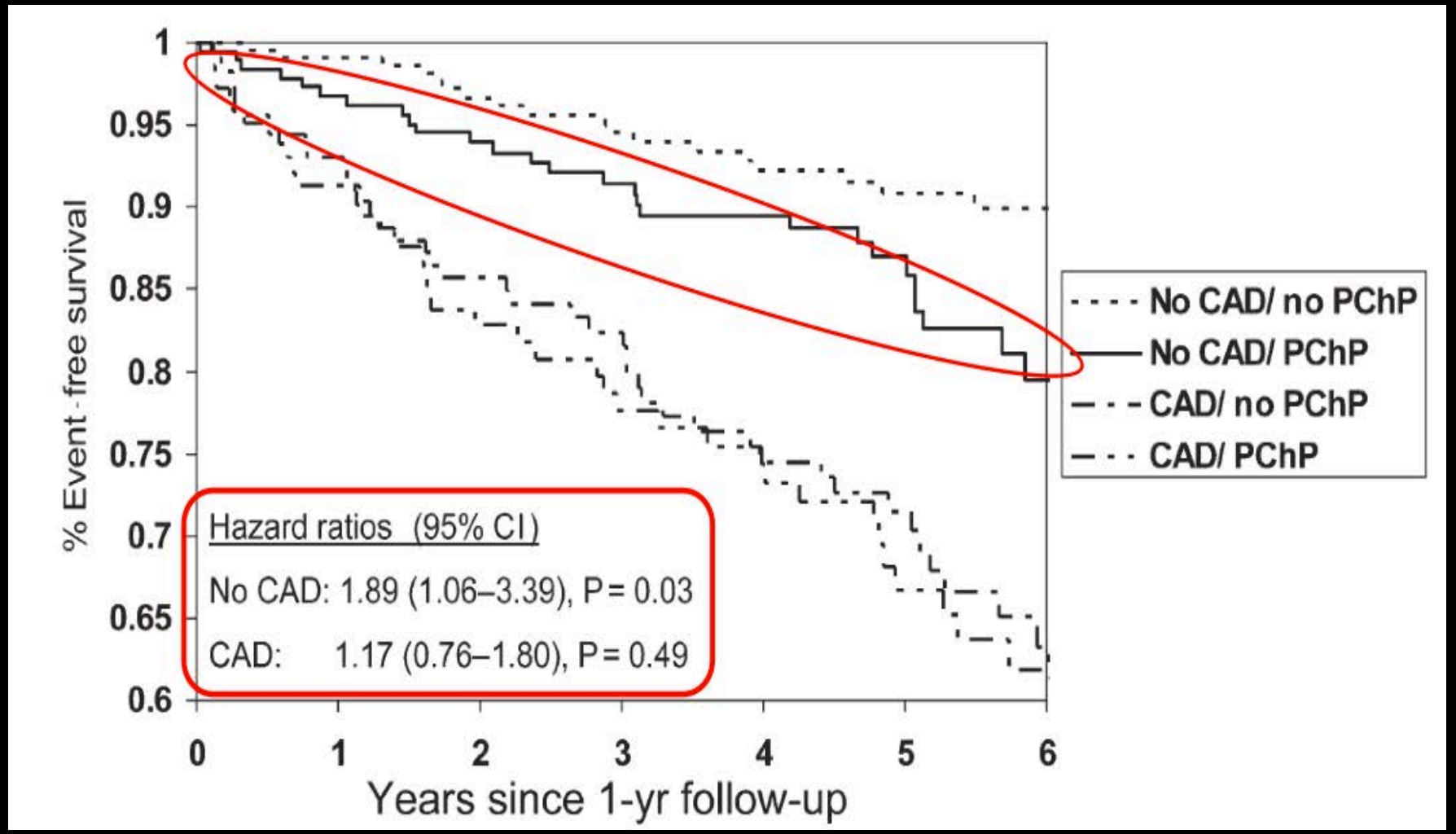
Women's Ischemia Syndrome Evaluation



6 year event rates by coronary artery disease (CAD) and persistent chest pain (PChP). Note the difference between no CAD/no PChP and no CAD/PChP.

Johnson BD, EHJ, 2006;27:1408-15

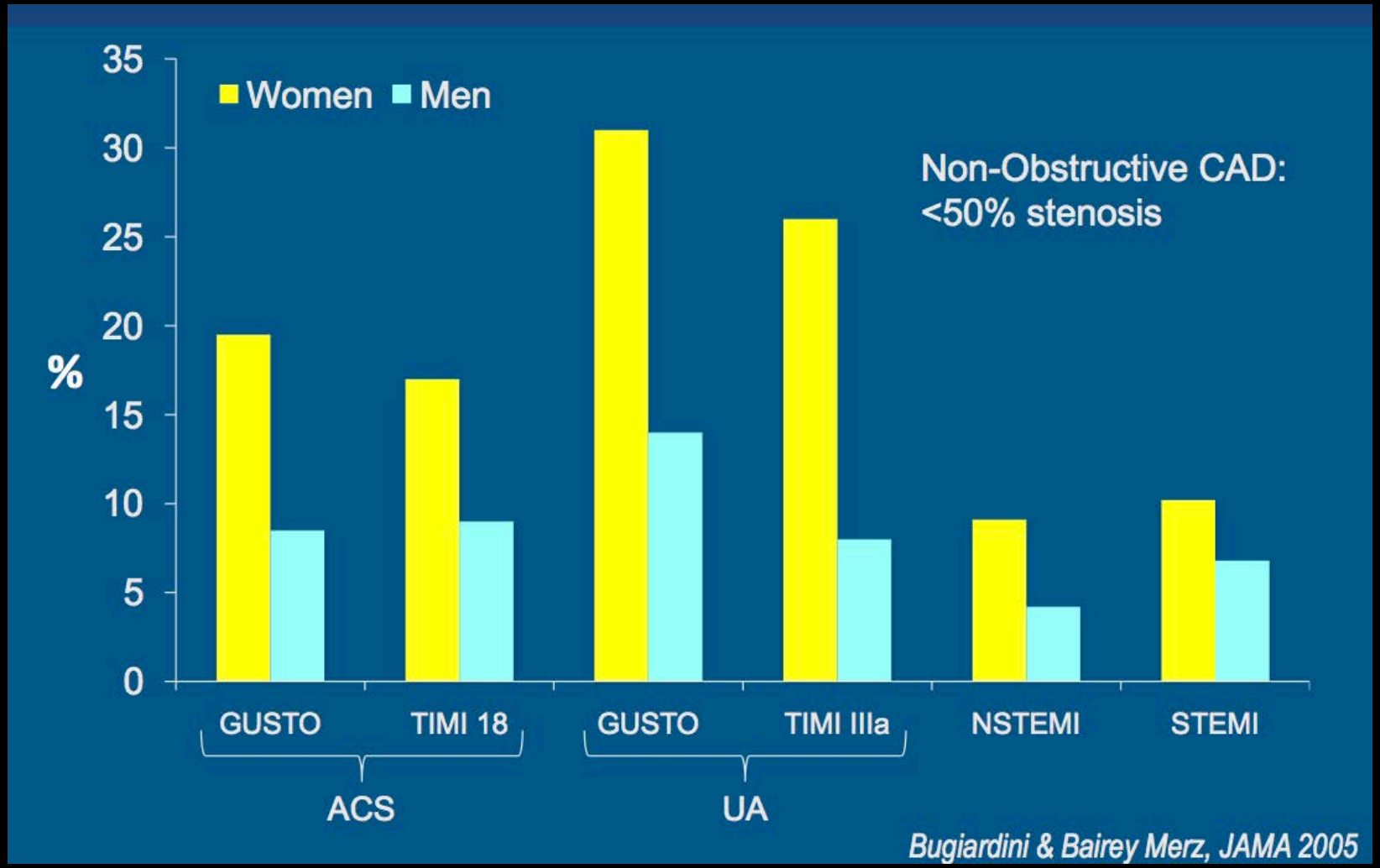
Persistent CP with no CAD predicts cardiac events.



Up to 50% of women who have chest pain undergoing catheterization are ***not*** found to have significant coronary artery obstruction.

(as compared to ~20% of men)

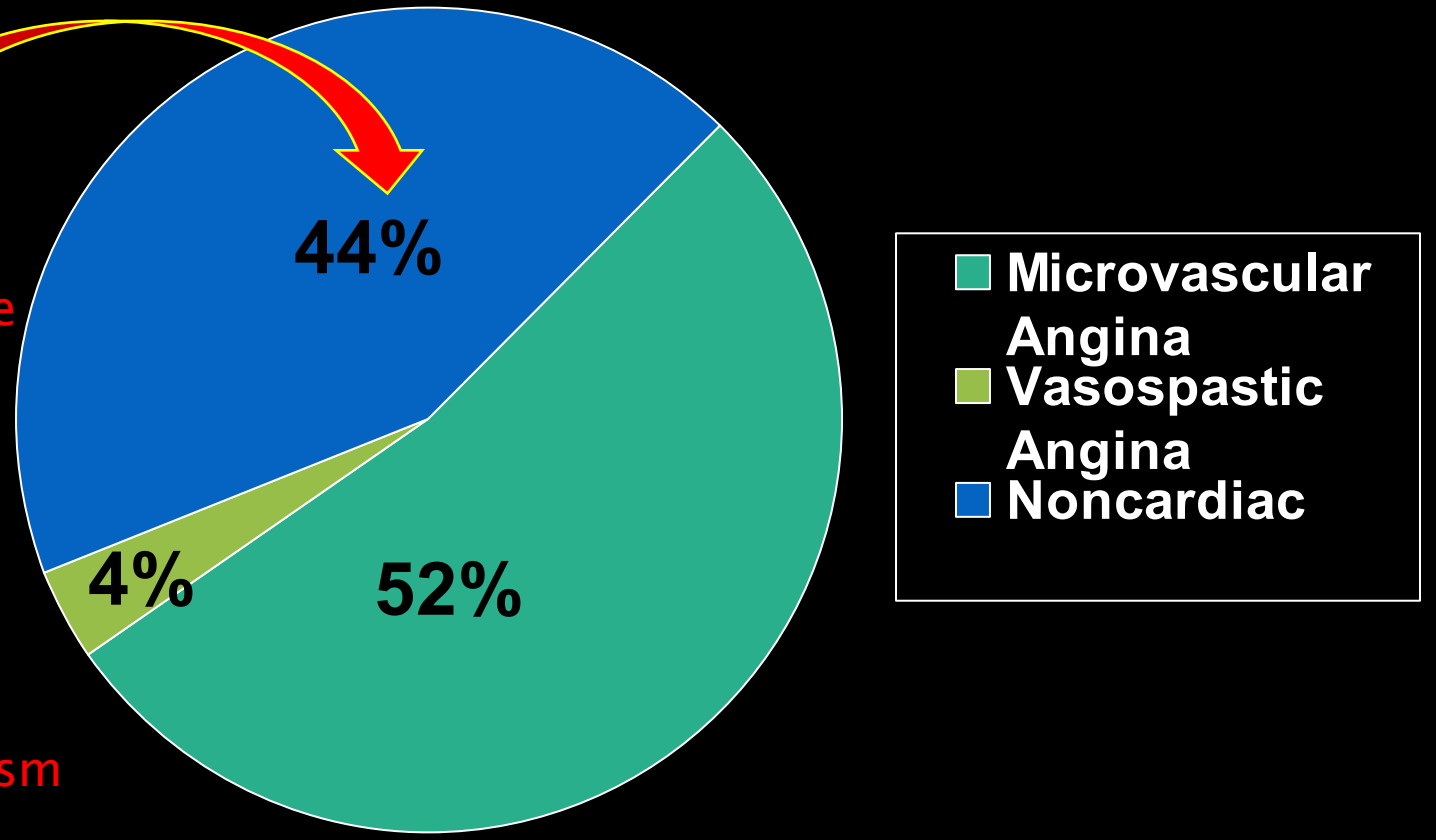
Rates of non-obstructive coronary disease in ACS trials

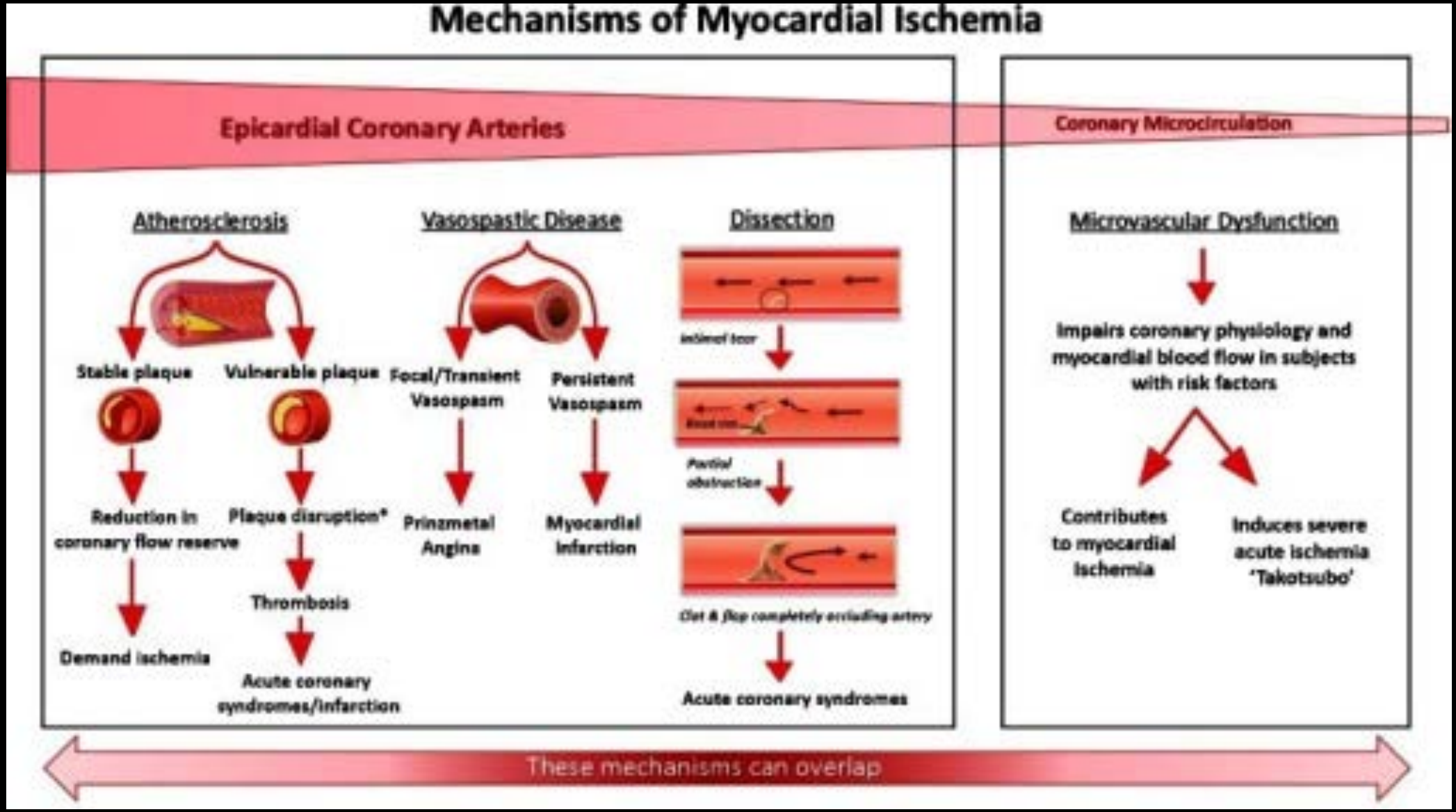


Bugiardini and Merz, JAMA 2005.

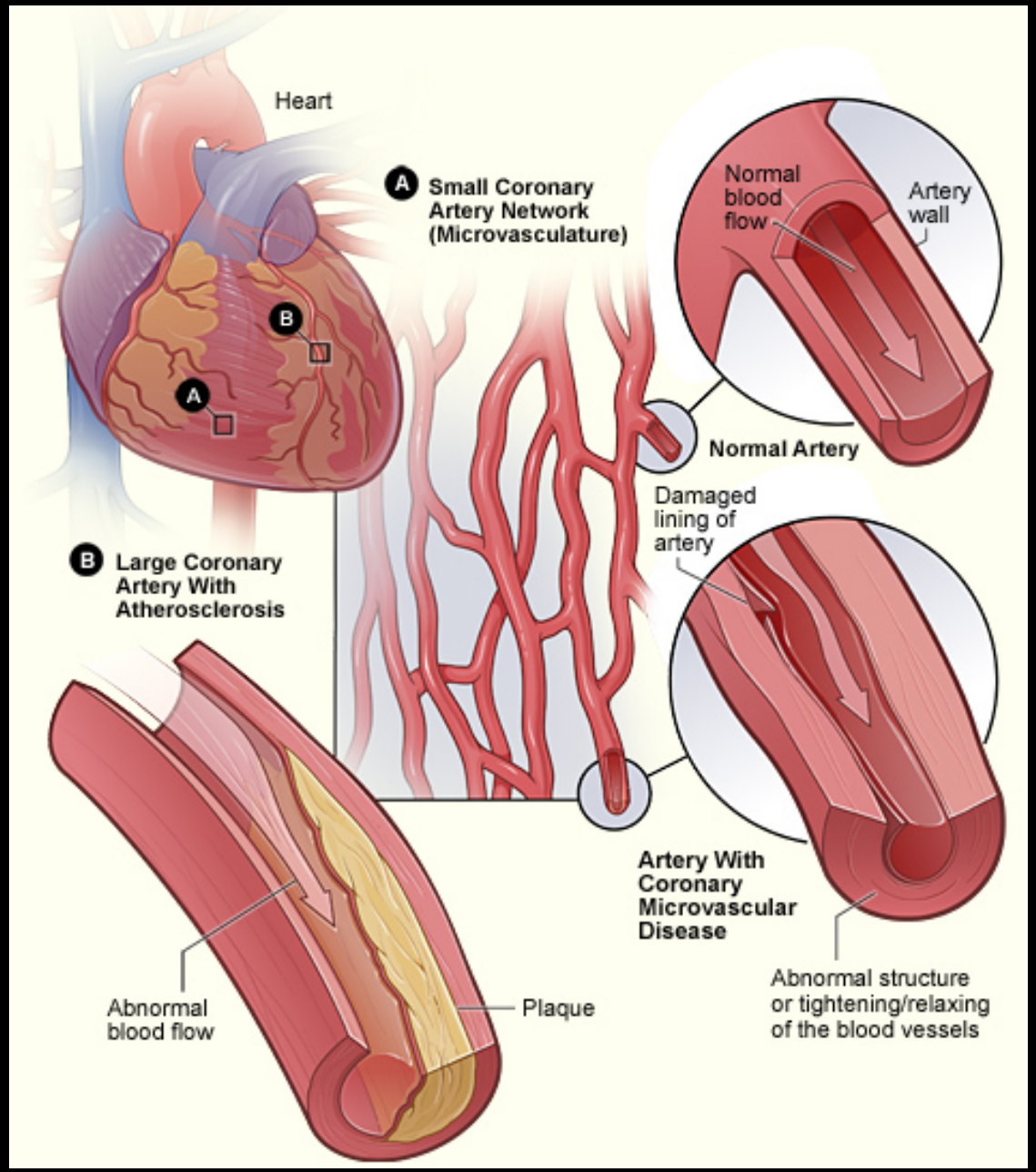
Mechanisms of Chest Pain when Coronary Arteries are “Normal”

Esophageal spasm
Acid reflux disease
Hernia
Zoster
Radiculopathy
Costochondritis
Fibromyalgia
Depression
Anxiety
Pulmonary embolism
Pleurisy
Pneumonia





Sanghavi and Gulati. *Curr. Ather. Reports*. 2015



Microvascular Dysfunction

https://www.nhlbi.nih.gov/health/health-topics/topics/cmd

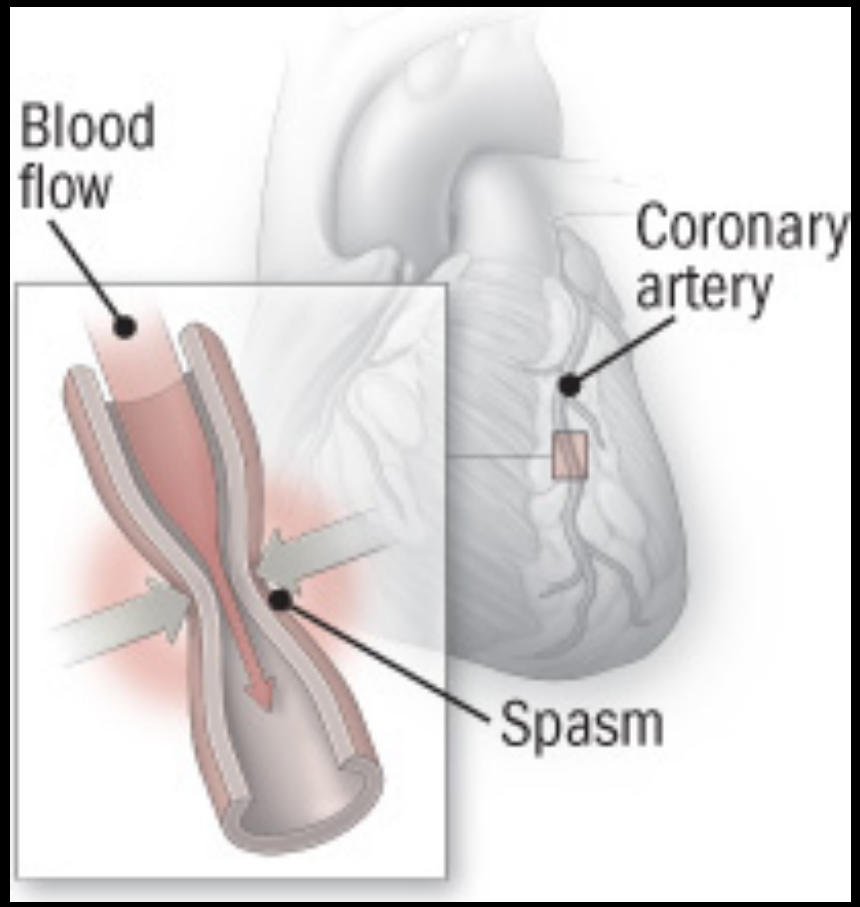
Coronary Microvascular Dysfunction

Diagnosis

- Left Heart Catheterization
  - With CFR measurement
- PET
- Cardiac MRI
- Contrast echocardiography

Treatment

- ACE-I
- Calcium channel blockers
- Beta Blockers
- ASA
- Statins
- Nitrates
- Lifestyle modifications

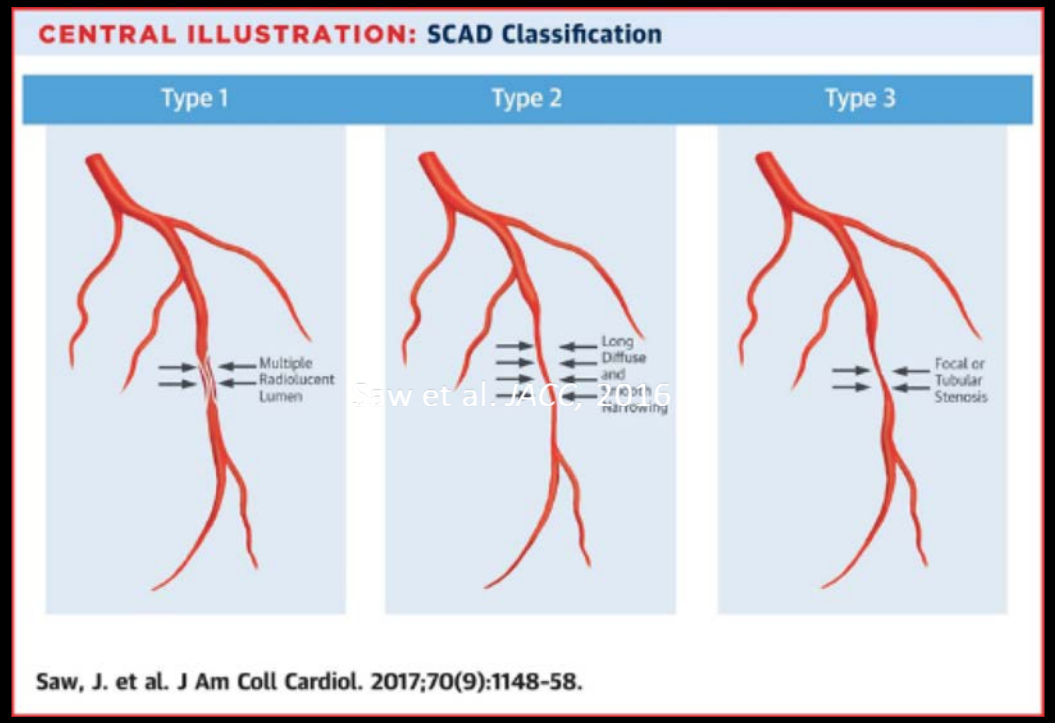


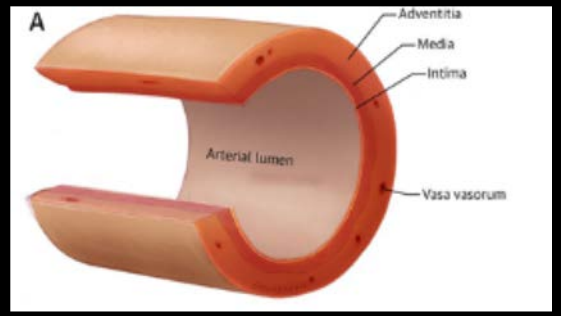
Vasospastic Disease

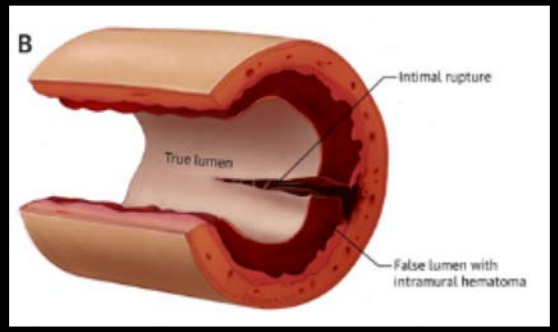
- Difficult to diagnose
- Calcium channel blockers
- Long-acting nitrates
- Smoking cessation
- Statin

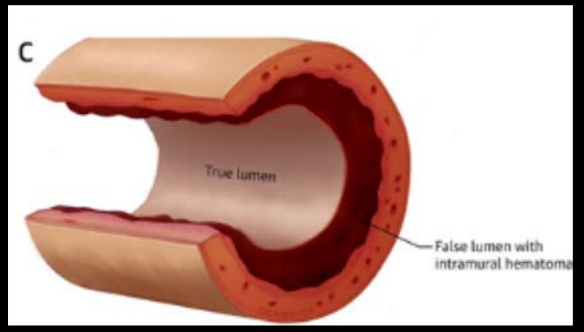
https://www.health.harvard.edu/newsletter/images/H0610c-1.jpg

Spontaneous Coronary Artery Dissection (SCAD)









Other theories of pathophysiology

Autonomic Abnormalities

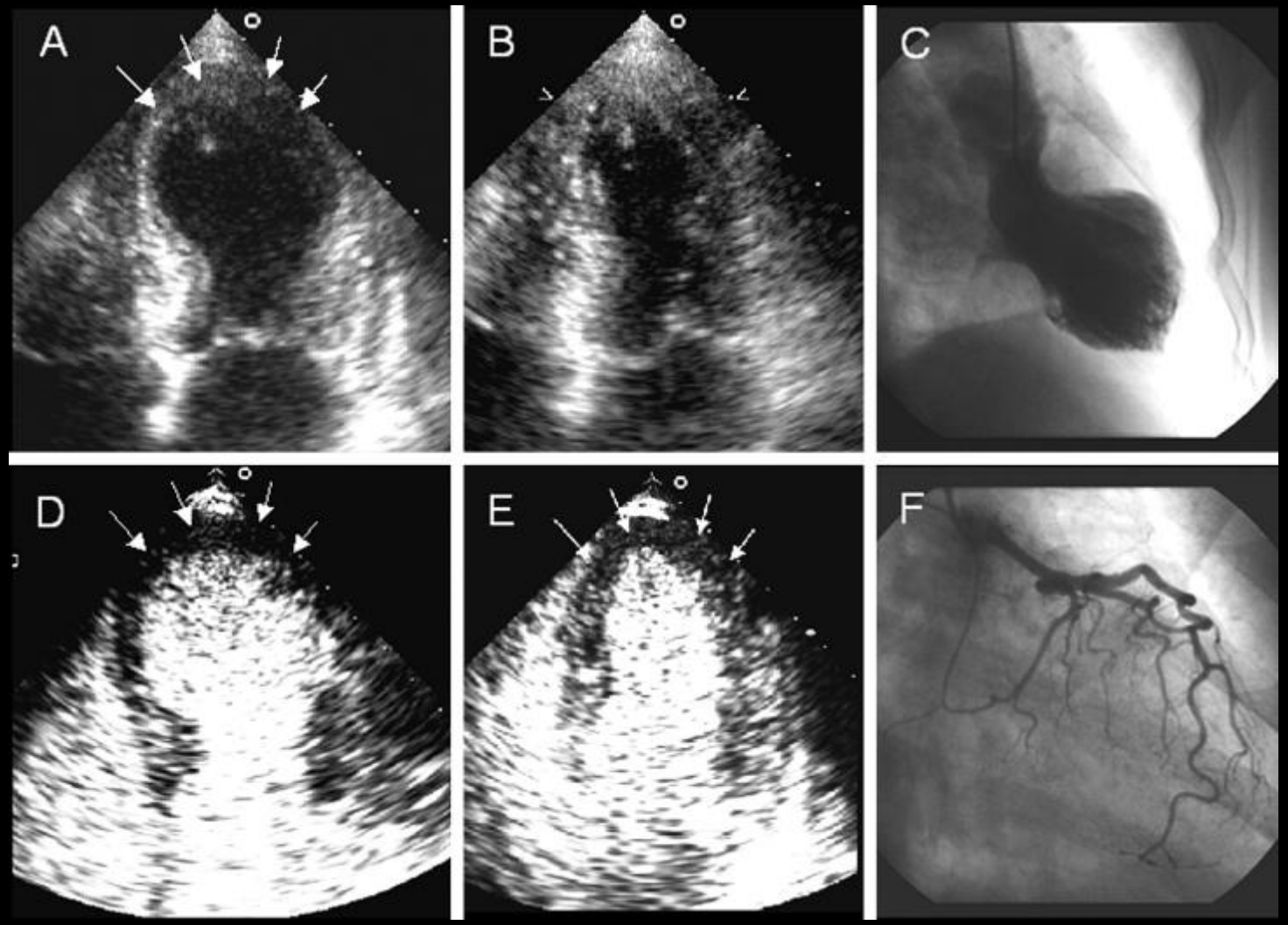
- Increased sympathetic tone leading to small vessels that are sensitive to vasoconstriction and/or vasospasm

Enhanced Pain Sensitivity

- Chest pain provoked by electrical stimulation of atrium and ventricle
- Injection of contrast media into LAD reproduced pain
- Increased activation of regional cerebral cortex during dobutamine stress echo

Estrogen Deficiency

- Impaired endothelial dysfunction
- Poor pain modulation

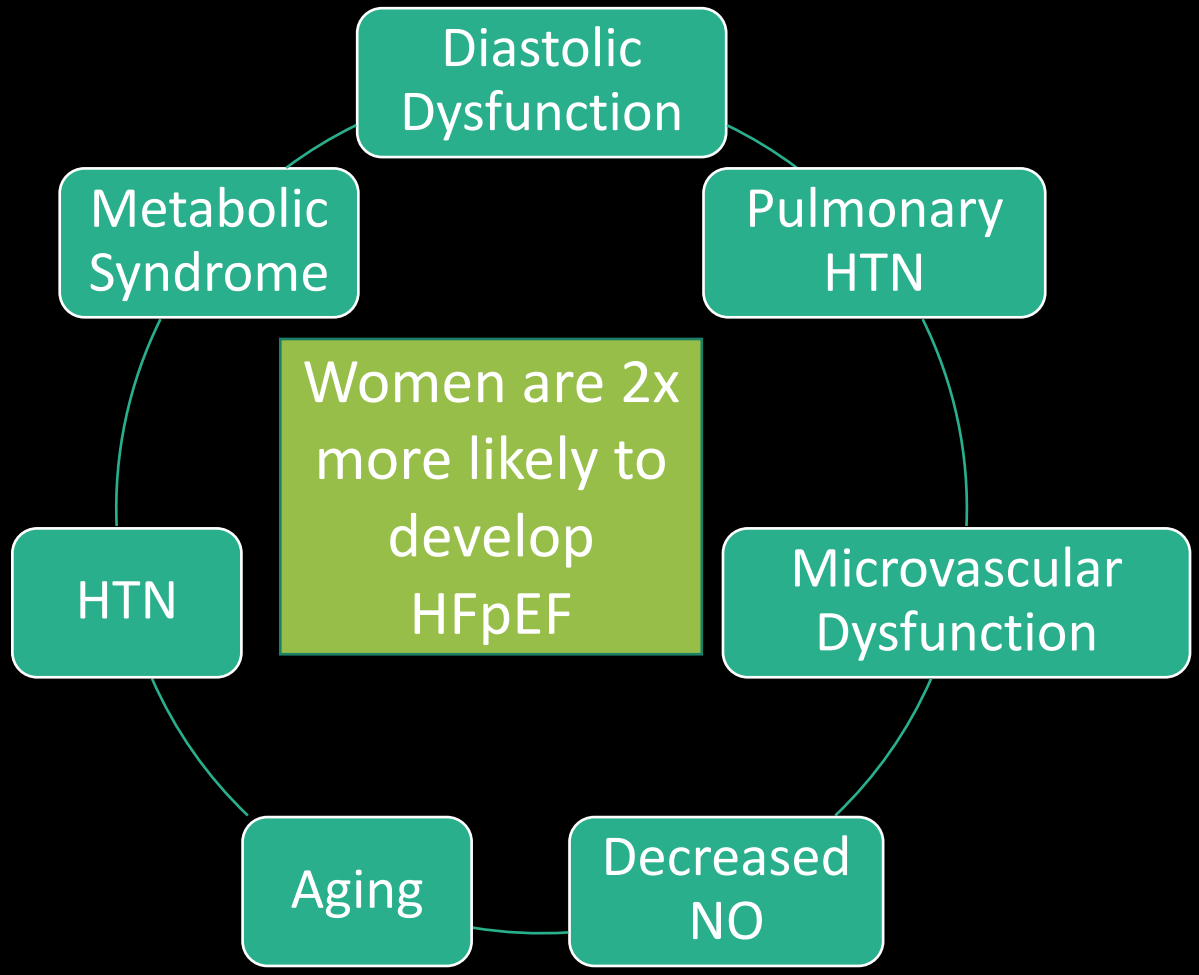


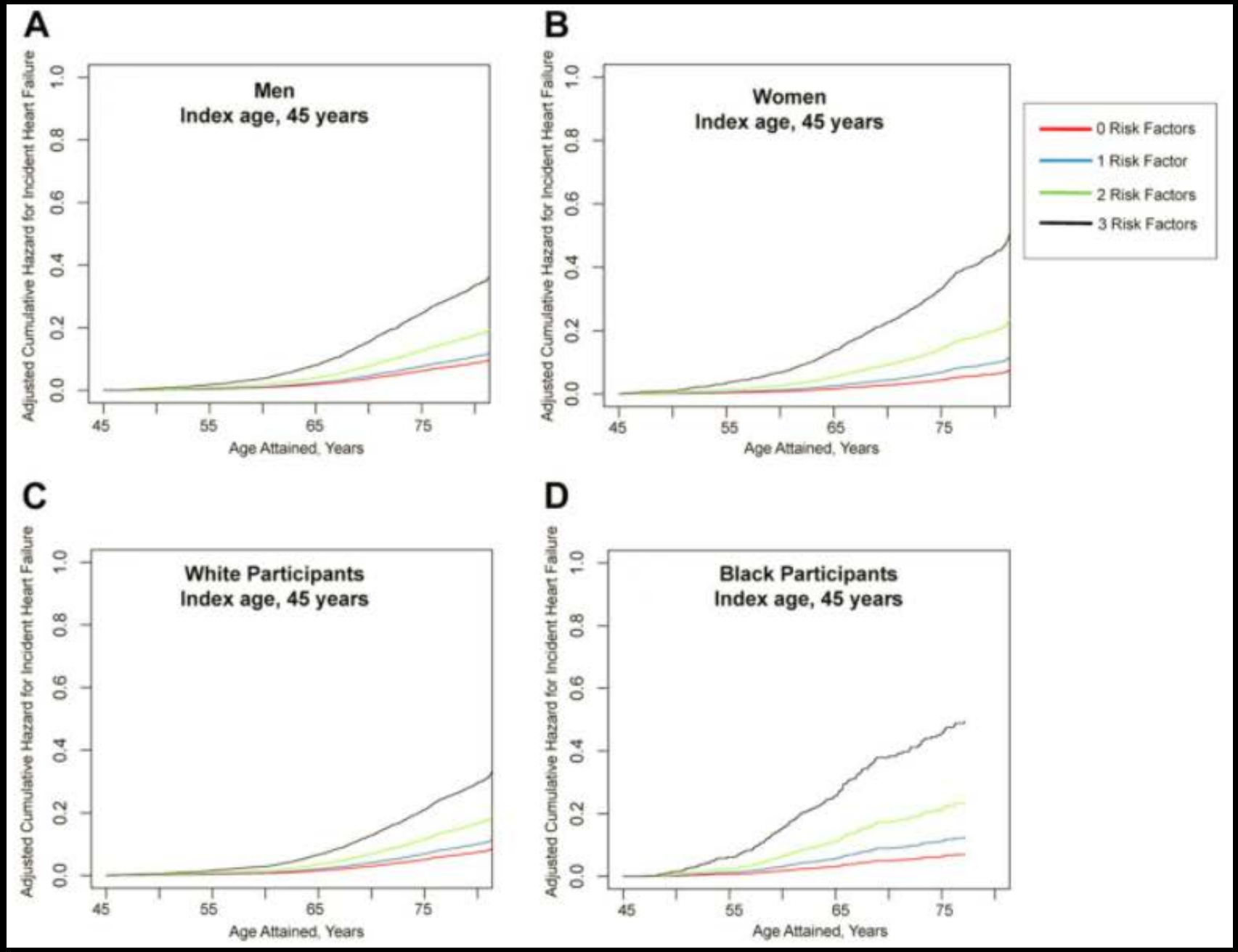
Stress-Induced Cardiomyopathy (Takotsubo's)

- - Acute drop in EF that preferentially involves apical walls
- - Can mimic anterior MI
- - Often precipitated by emotional or physical stress
- - More prevalent in women
- - Generally transient

Shah et al. *Circulation,* 2006

HF with Preserved Ejection Fraction (HFpEF)

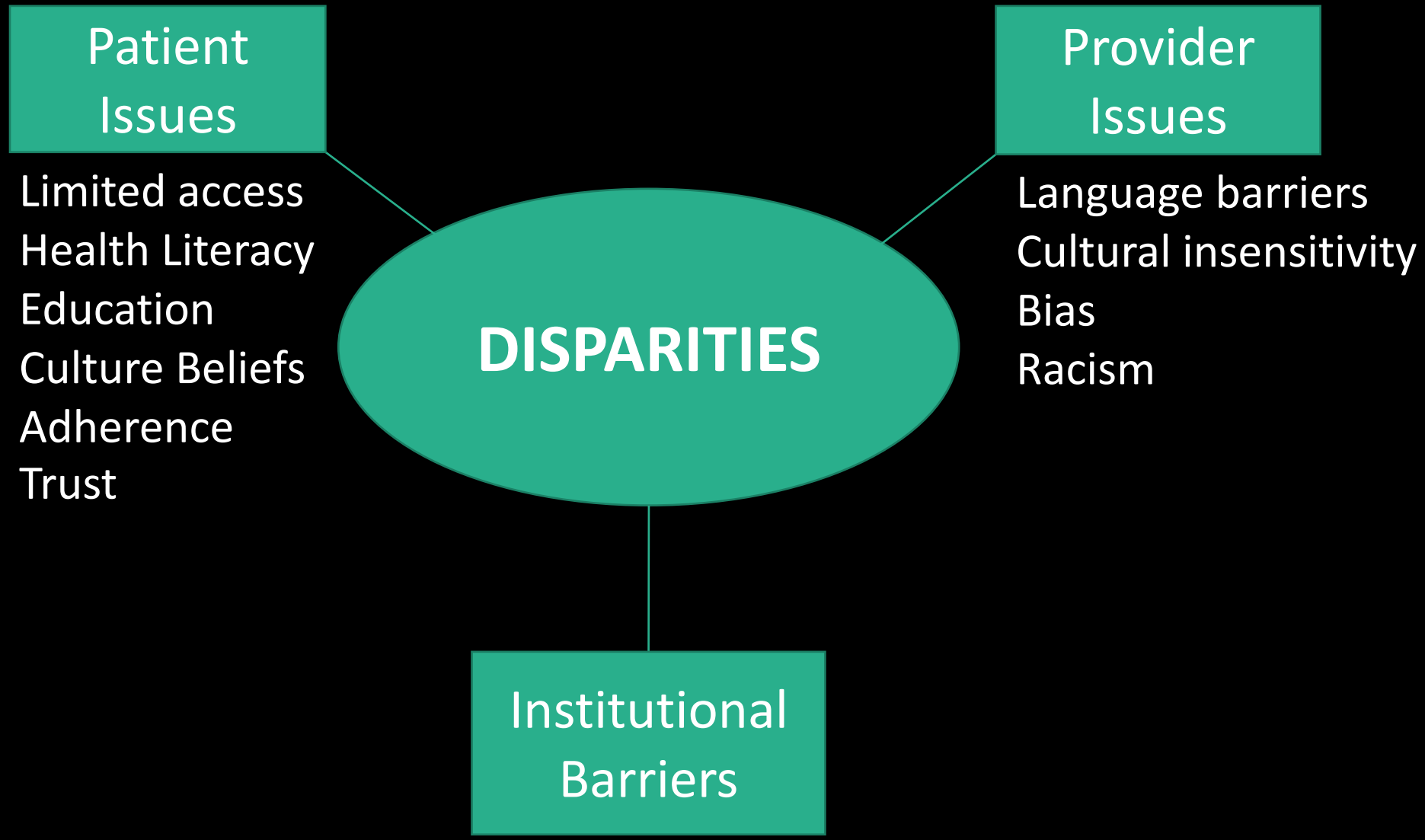




Risk Factor Burden and Incident HF

Ahmad et al. *JACC HF*. 2016

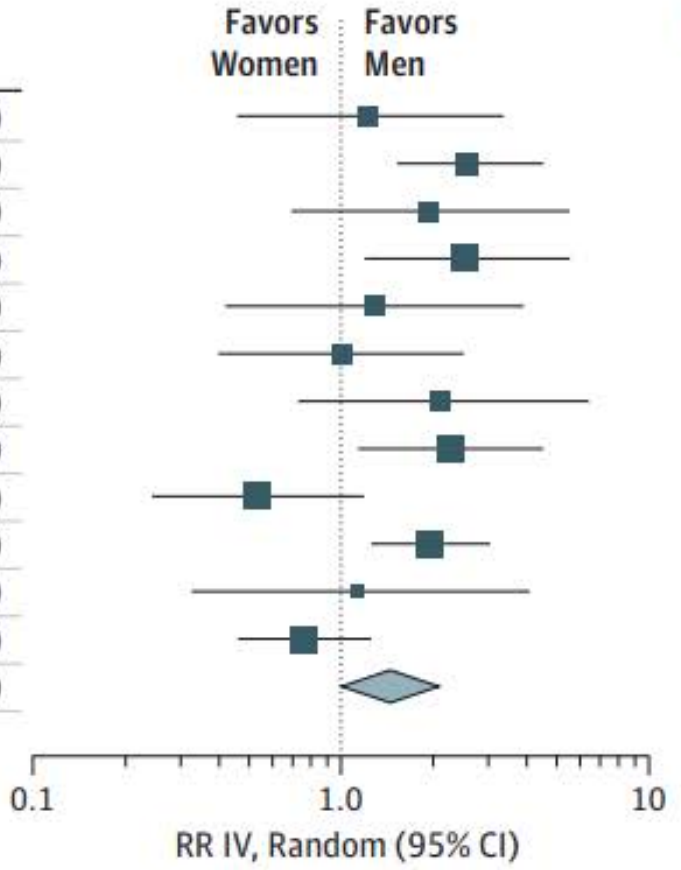
Gender Disparities in CVD


Patient Issues
Limited access
Health Literacy
Education
Culture Beliefs
Adherence
Trust
Provider Issues
Language barriers
Cultural insensitivity
Bias
Racism
DISPARITIES
Institutional Barriers

Women have worse outcomes after STEMI: Adjusted Meta-analysis

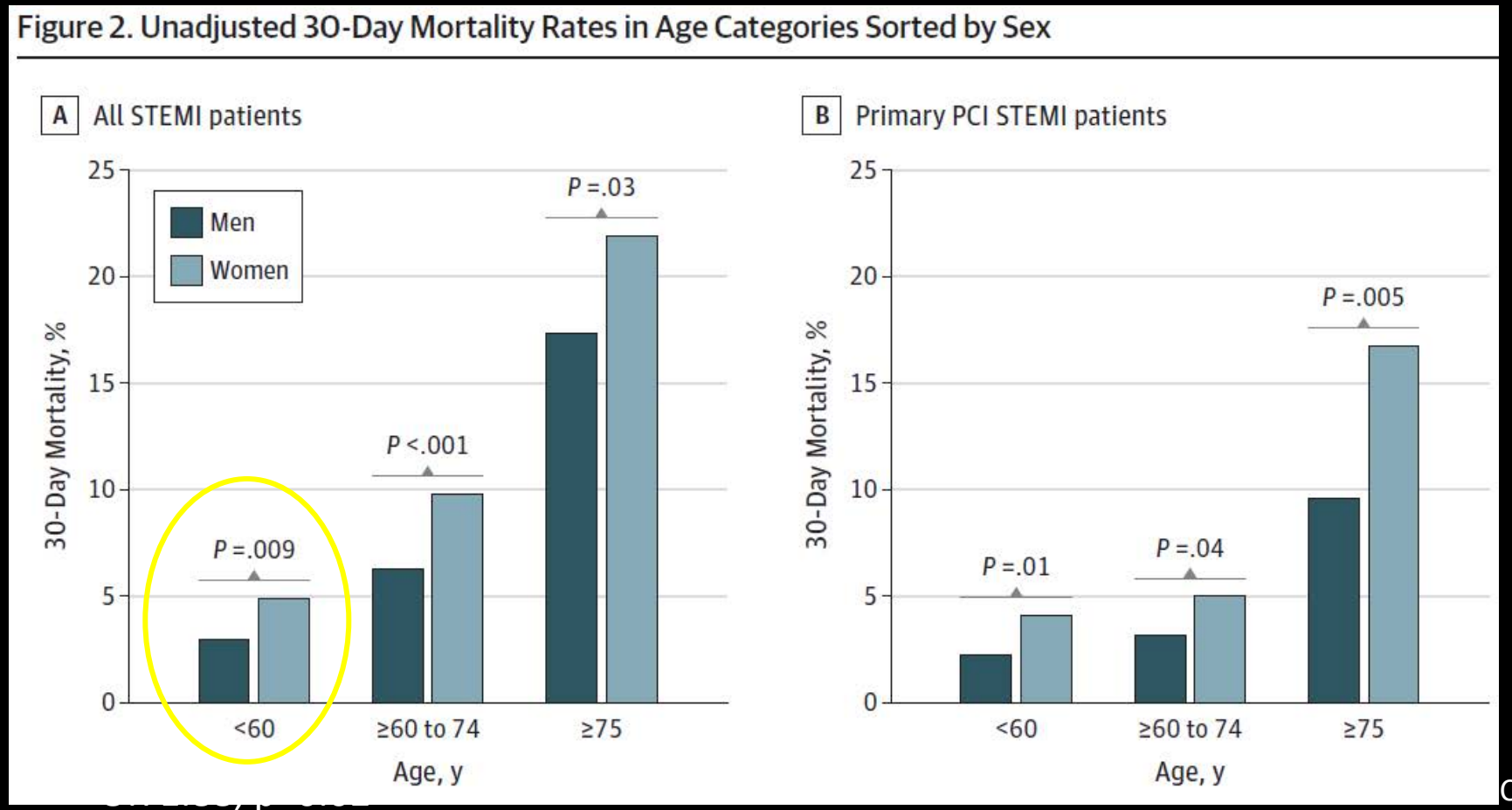
Source	log (RR)	SE	RR IV, Random (95% CI)	Weight %
Berger and Brown,[6] 2006	0.223	0.48	1.25 (0.49-3.20)	6.9
De Luca et al,[9] 2004	0.95	0.27	2.59 (1.52-4.39)	11.3
Eitel et al,[10] 2012	0.66	0.51	1.93 (0.71-5.26)	6.4
Hurtado-Martinez et al,[16] 2006	0.92	0.38	2.51 (1.19-5.28)	8.8
Jackson et al,[17] 2011	0.26	0.56	1.30 (0.43-3.89)	5.7
Kosuge et al,[18] 2006	0.0099	0.46	1.01 (0.41-2.49)	7.2
Srimahachota et al,[22] 2004	0.765	0.55	2.15 (0.73-6.32)	5.8
Vakili et al,[24] 2001	0.83	0.343	2.29 (1.17-4.49)	9.6
Valente et al,[27] 2012	-0.612	0.39	0.54 (0.25-1.16)	8.5
Yamane et al,[28] 2011	0.667	0.21	1.95 (1.29-2.94)	12.9
Zanchi et al,[25] 2009	0.14	0.63	1.15 (0.33-3.95)	4.8
Zhang et al,[26] 2010	-0.26	0.24	0.77 (0.48-1.23)	12.1
Total			1.48 (1.07-2.05)	100.0

Heterogeneity: $\tau^2 = 0.17$; $\chi^2_{11} = 25.28$, ($P = .008$); $I^2 = 56\%$
Test for overall effect: $Z = 2.38$ ($P = .02$)



Pancholy et al. *JAMA IM*. 2014

Younger Women have Worse Outcomes after STEMI



Cenko et al, *JAMA IM*. 2018

Why do we see higher mortality in women?

- Higher prevalence of risk factors: HTN, DM2, HLD, ? Pregnancy
- Lack of awareness of symptoms
- Delay in presentation and diagnosis
- Men may be more likely to die before arrival
- Pathophysiology differences
- Differences in treatment
  - Not on optimal medical therapy
  - Lower use of revascularization

Women are less likely to receive optimal preventative treatment

- ❑ BP at goal ⬇
- ❑ Treated with statins (esp women with DM) ⬇
- ❑ Cardiac rehab ⬇

Gu et al, *Am J HTN*. 2008

Chou et al. *Wmns Hlth Iss*. 2007

Ghisi et al. *Clin. Cardiol*. 2013

Women Receive Less Aggressive Treatment for ACS

Table 3. Use of In-Hospital Procedures by Gender With Odds Ratios for Use in Women Relative to Men

Variable	Male (n = 21,323)	Female (n = 14,552)	Unadjusted OR	Adjusted* OR (95% CI)
Noninvasive stress testing	11.7%	13.2%	1.10	1.07 (1.00–1.14)
Diagnostic catheterization	71.1%	60.1%	0.70	0.86 (0.82–0.91)
Catheterization ≤24 h of arrival	48.7%	42.1%	0.69	0.87 (0.82–0.92)
Arrival to catheterization (h)†	22.6 (7.2, 45.9)	26.5 (12.4, 53.9)	1.16	1.08 (1.02–1.14)
Percutaneous coronary intervention (PCI)	40.4%	31.4%	0.73	0.91 (0.86–0.96)
PCI ≤24 h of arrival	51.9%	44.3%	0.64	0.85 (0.79–0.91)
Arrival to PCI, (h)†	21.0 (4.7, 44.2)	25.2 (9.0, 52.8)	1.17	1.06 (0.99–1.19)
Coronary artery bypass grafting	14.0%	9.0%	0.62	0.59 (0.54–0.64)

*Variables in the model are same as in Table 2. Data are presented as percentages except arrival to catheterization and arrival to percutaneous coronary intervention = median (25th, 75th percentile). †For continuous variables, data presented are unadjusted or adjusted estimate and 95% CI for adjusted estimate.
Abbreviations as in Table 2.

Blomkalns et al, *JACC*. 2004

Women with ischemic heart disease are less likely to be on OMT

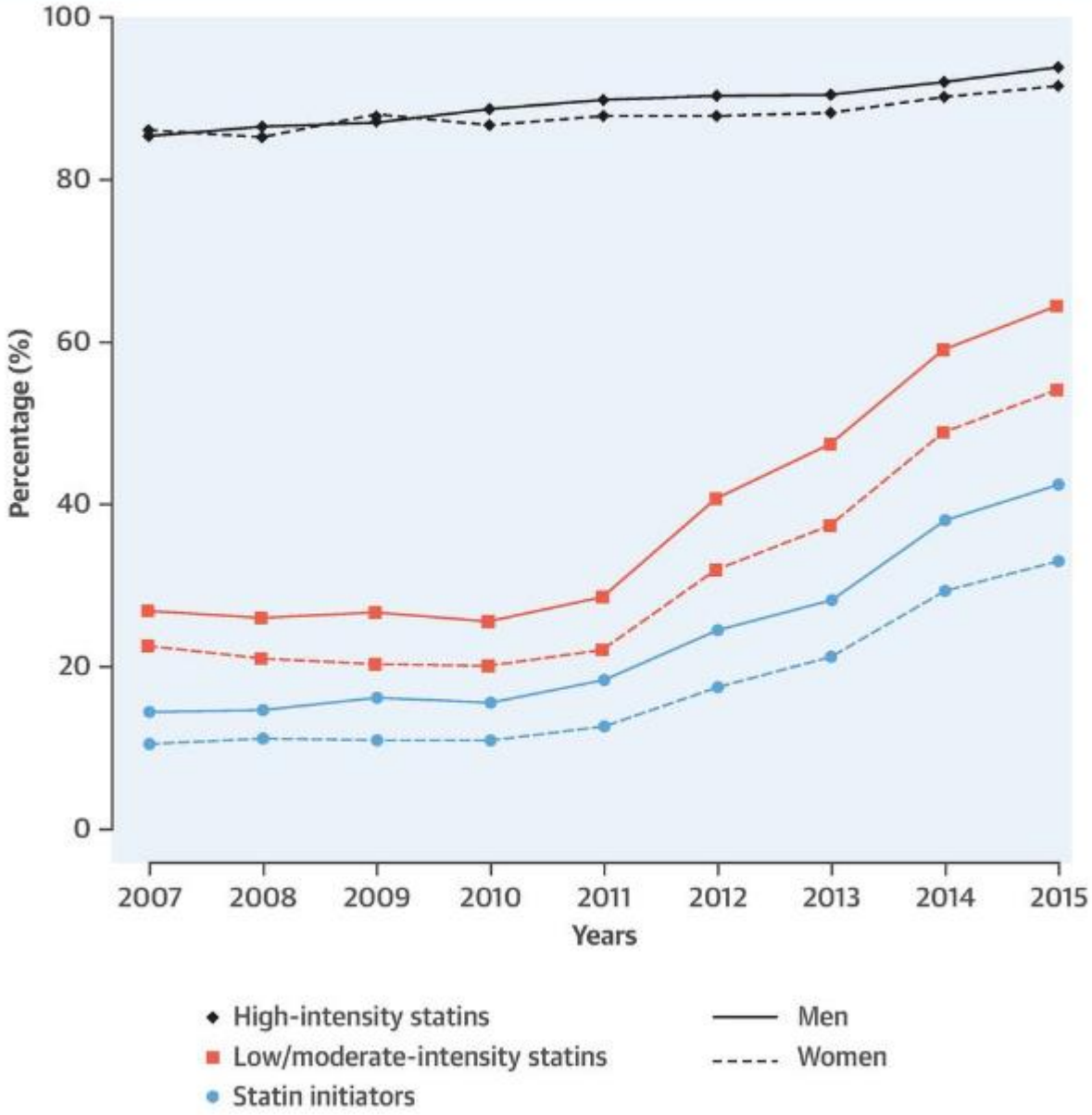
	ASA for IHD and CVA n=788	Beta Blocker for IHD n=605
Female, %	20.7	31.9
Male, %	35.5	44.5
Adjusted OR (95% CI)*	0.43 (0.27-0.67)	0.60 (0.36-0.99)

*Adjusted for insurance, race, Hispanic ethnicity, smoking, CVD, CHF, HLD, DM2, IHD, HTN, obesity

Keyhani et al, *Hypertension*. 2008

Women are Less Likely to Fill Statin Prescriptions after MI

CENTRAL ILLUSTRATION: Trends in the Percentage of Women and Men Filling a High-Intensity Statin Prescription After Hospital Discharge for Myocardial Infarction Between 2007 and 2015



The New England Journal of Medicine

THE EFFECT OF RACE AND SEX ON PHYSICIANS' RECOMMENDATIONS FOR CARDIAC CATHETERIZATION

- Physician estimates of probability of CAD differed according to sex, age, level of risk, and type of chest pain

- Women 40% less likely to be referred for cath
  - Referral rate 85% vs 91% (p=0.02)
- Black pts also less likely to be referred for cath

Schulman & Excarce et al, *NEJM*, 1999

Overcoming Gender Disparities in CVD

https://aapsblog.aaps.org/2017/04/27/is-funding-subject-to-gender-bias/

Addressing Knowledge Gaps: Patient Education

- National Initiatives, ie. “Know Your Numbers” and “Go Red”
- Behaviorally-based individualized counseling
- Self-monitoring
- Group sessions
- Electronic communication and reminders

Overcoming Implicit Bias

- Recognize that bias exists
- Consider unconscious bias training
- Treat patients with empathy and compassion
- Follow guideline-based care

Conclusions

- CVD in women is under-recognized and undertreated
- Women have both traditional and unique risk factors for CVD
- Women have difference phenotypes of CVD
- More research is needed in optimal therapies for CVD in women
- We are part of the solution

Tell your grandmothers, mothers, aunts, sisters, daughters, friends.

Heart disease is the leading cause of death in women.

Women and men have different physiology and different risk factors.

Women may not present with their heart attack the same way the movies show it.

Persistent chest pain, even when there is no significant coronary artery disease, confers worse cardiovascular outcomes. Don’t ignore this.

Thank you!!

Resources and Citations

Roger VL et al, AHA Heart Disease and Stroke Update 2012; *Circulation* 2011

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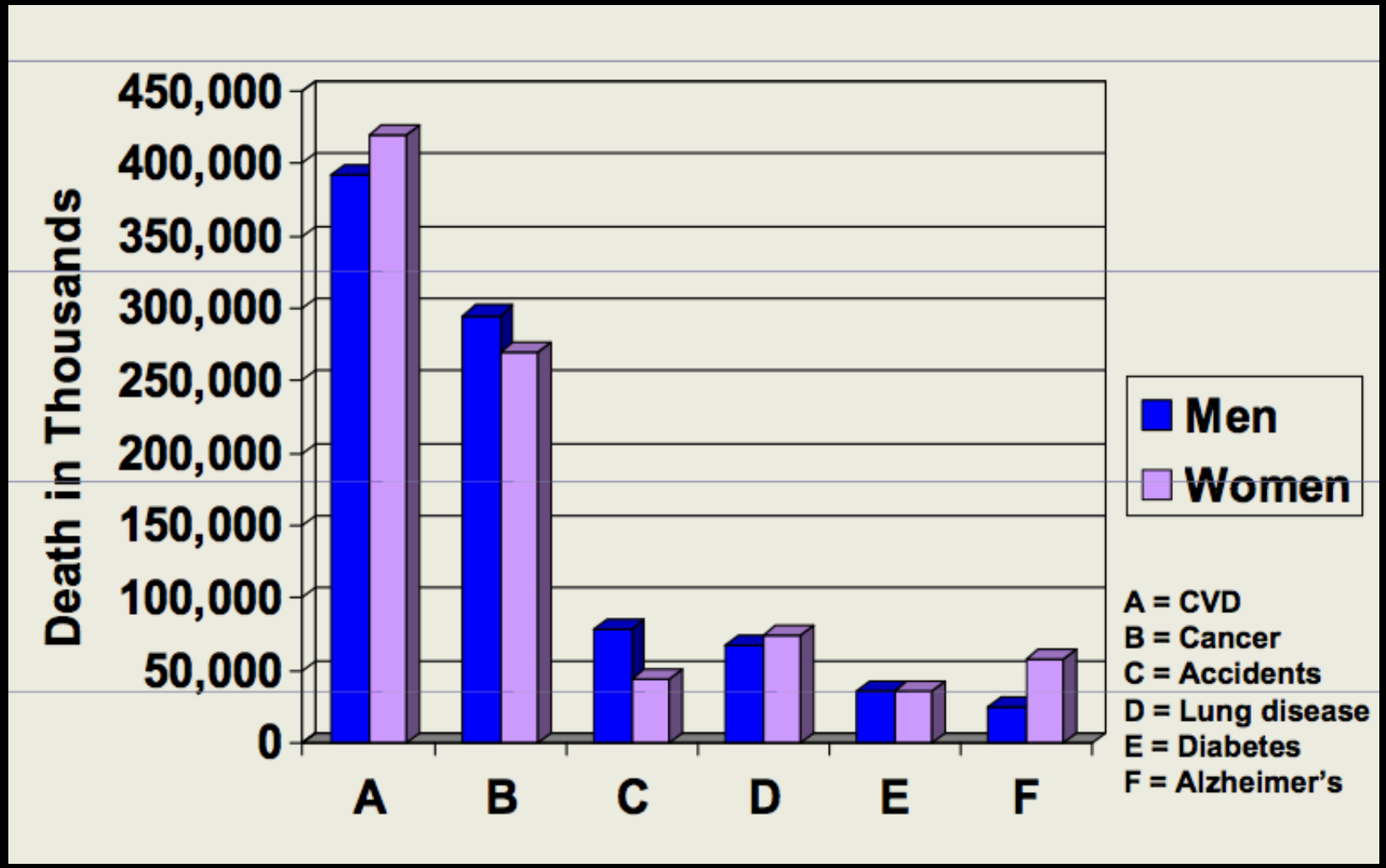
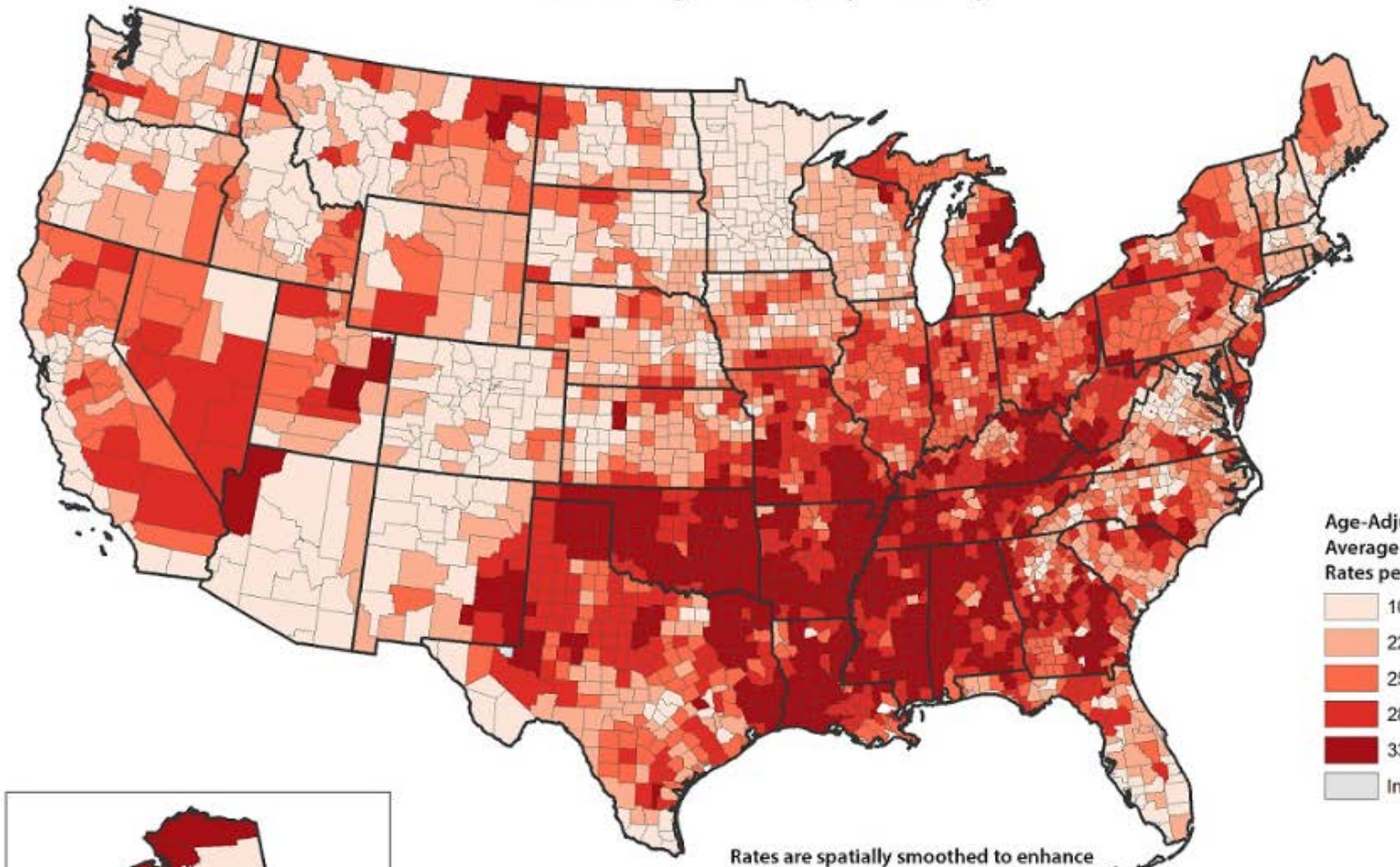
Daly C, et al. Gender differences in the management and clinical outcome of stable angina. Circulation 2006;113:490-498.

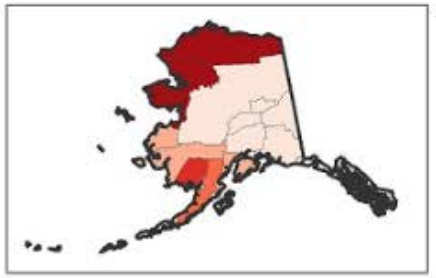
Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries. JAMA 2005; 4:477-84.

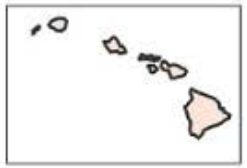
CVD is the leading cause of death for all women (and men)



Heart Disease Death Rates, 2015-2017
Women Ages 35 +, by County







Age-Adjusted
Average Annual
Rates per 100,000

- 102.0 - 221.6
- 221.7 - 254.1
- 254.2 - 285.3
- 285.4 - 335.1
- 335.2 - 900.5
- Insufficient Data

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics

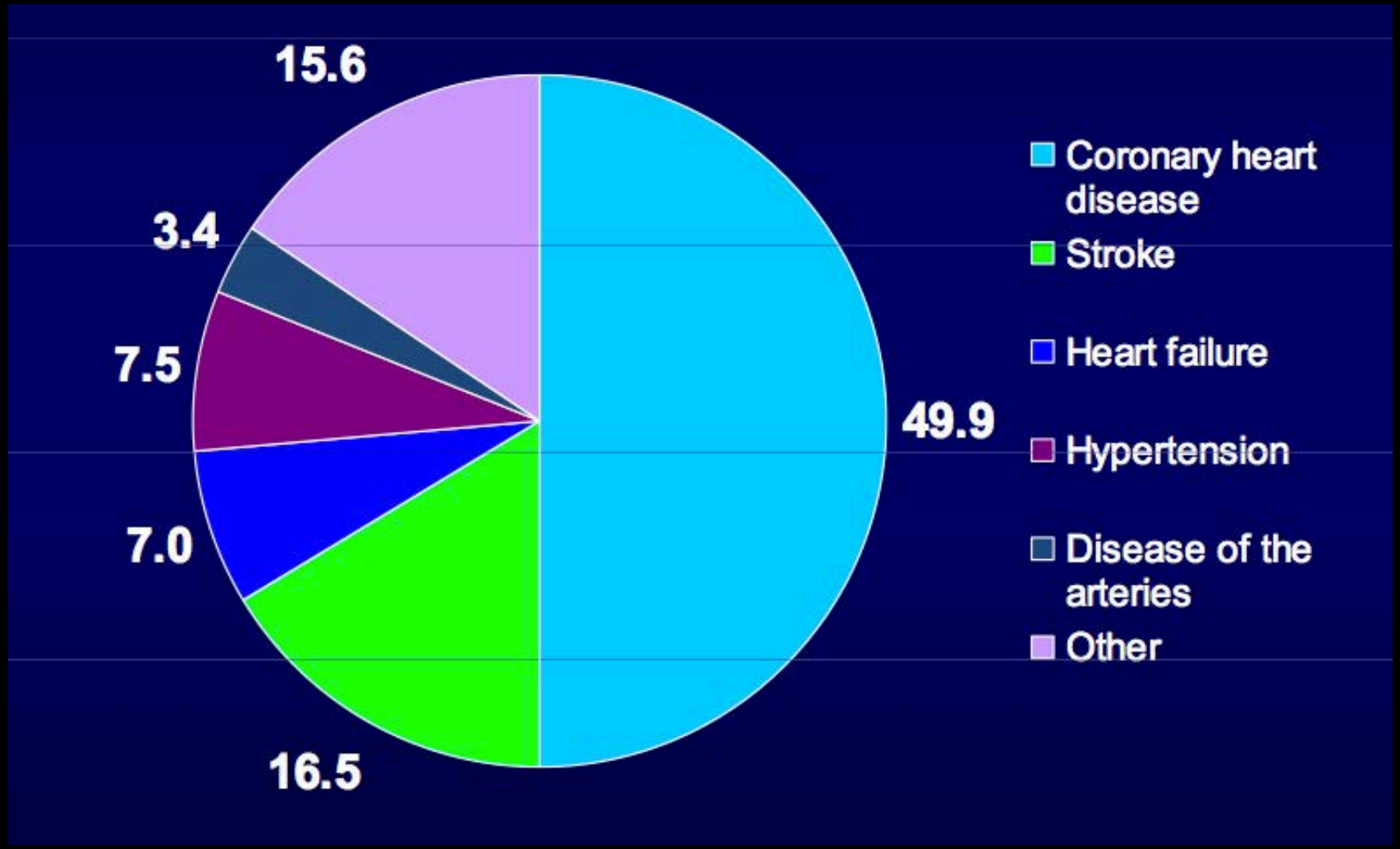
www.cdc.gov/dhdsp/maps

CDC

Heart Disease in Women

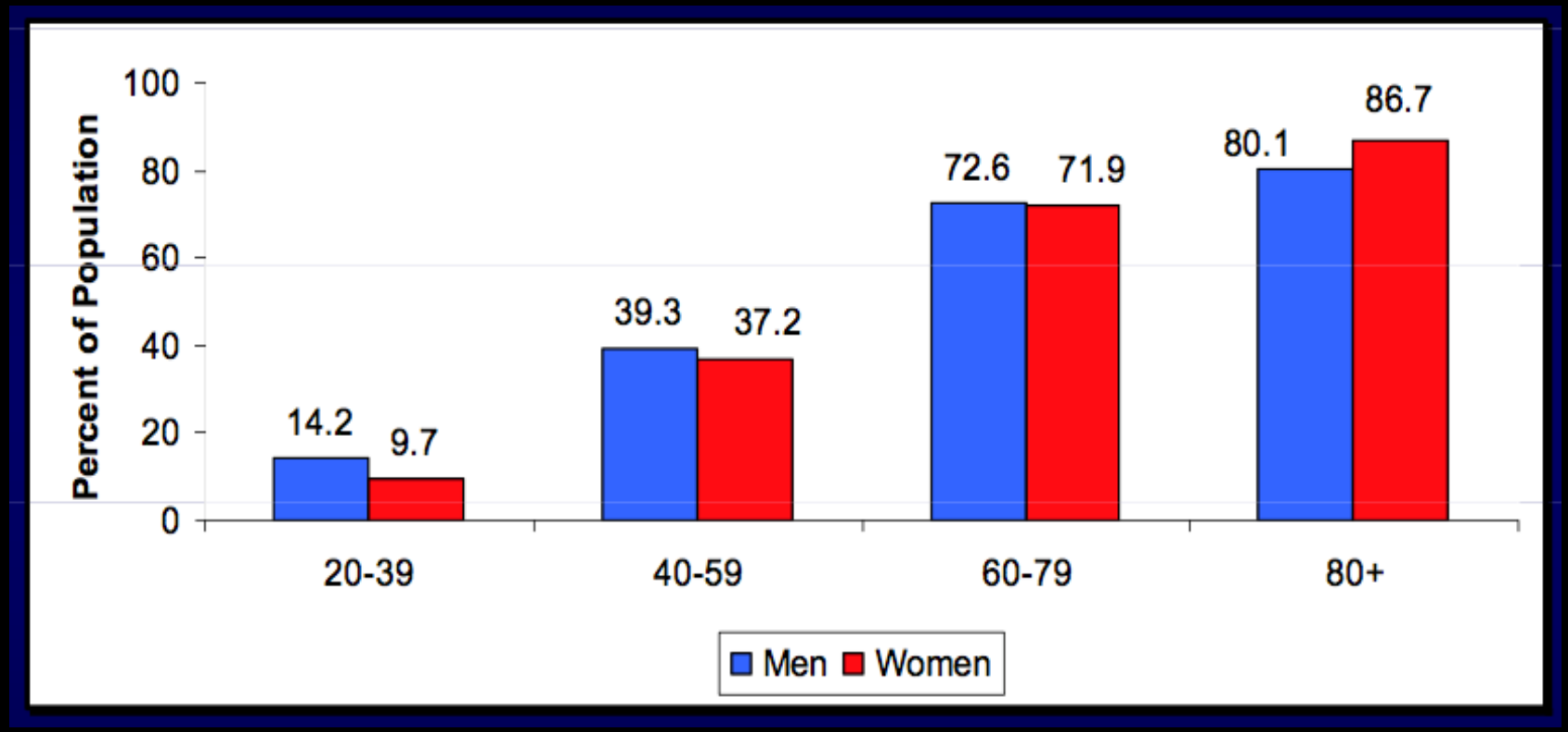
- Leading cause of death
- Accounted for ~280,000 deaths in women per year
- **1 in 4** women will die from it
- A woman is **6 times** more likely to die of heart disease than of breast cancer

Breakdown of Deaths due to CVD



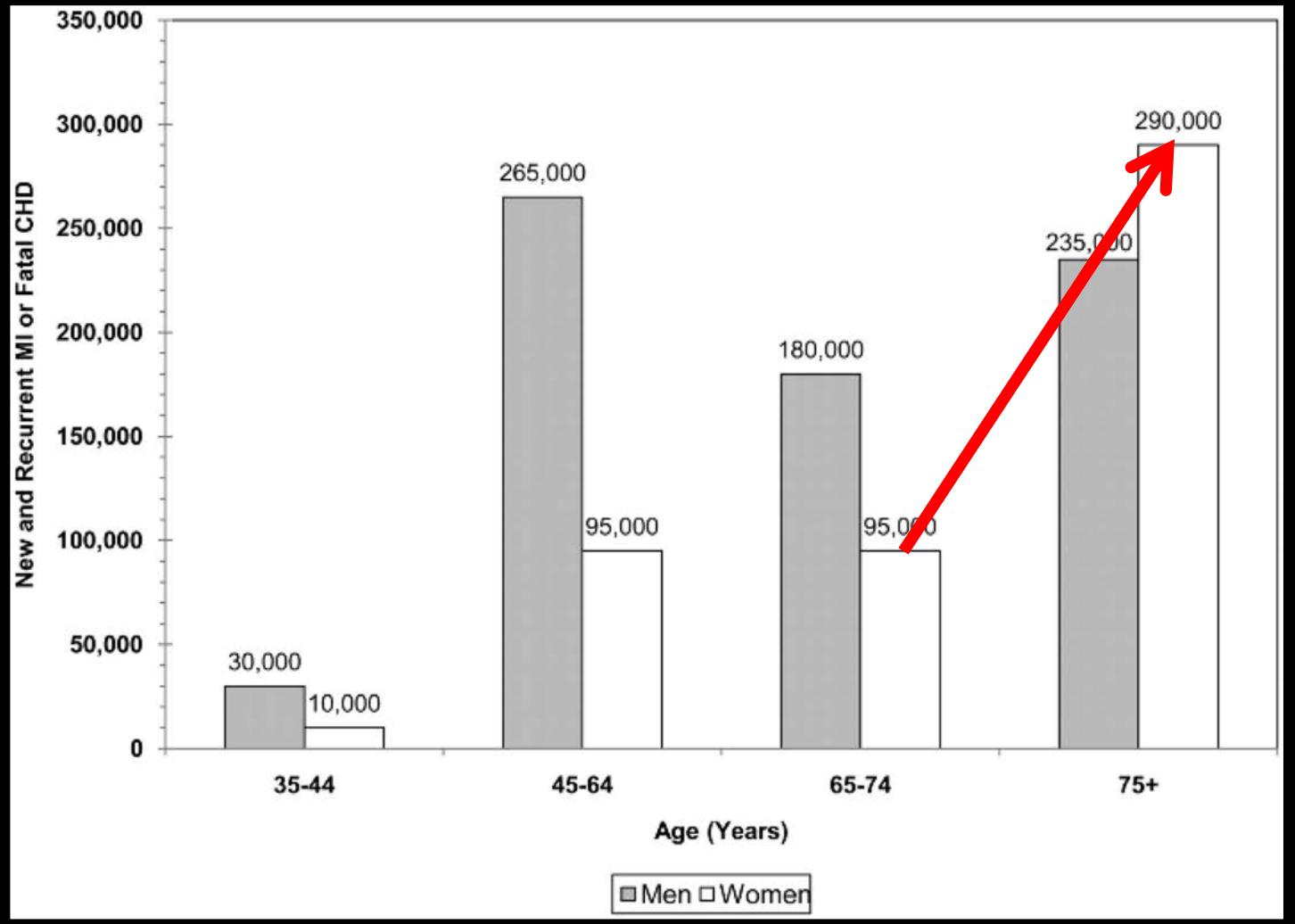
Roger VL et al, AHA Heart Disease and Stroke Update 2012; *Circulation* 2011

CVD Prevalence by Age and Sex



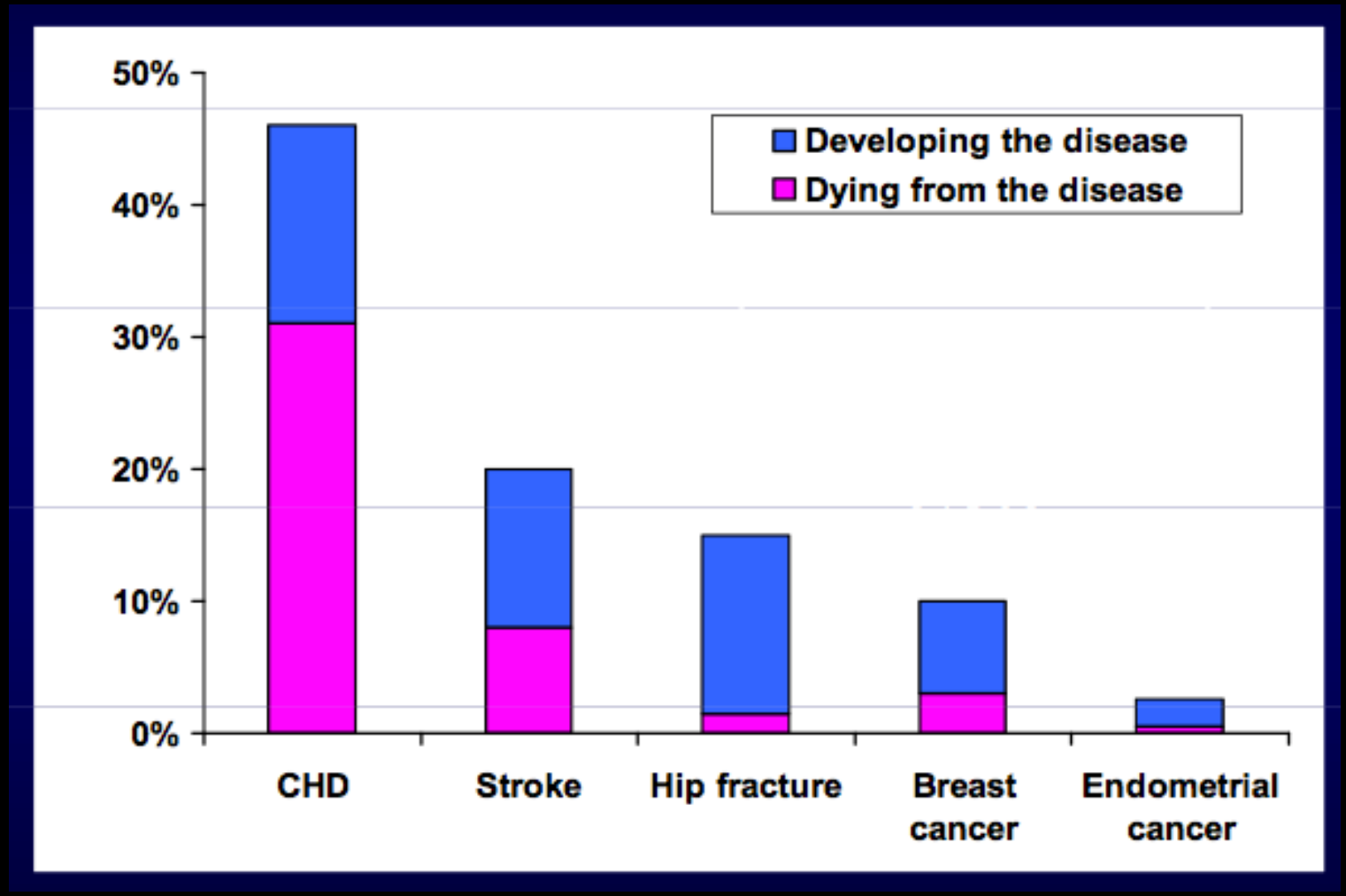
Roger VL et al, AHA Heart Disease and Stroke Update 2012; *Circulation* 2011

Annual # of Adults with AMI or Fatal Heart Disease



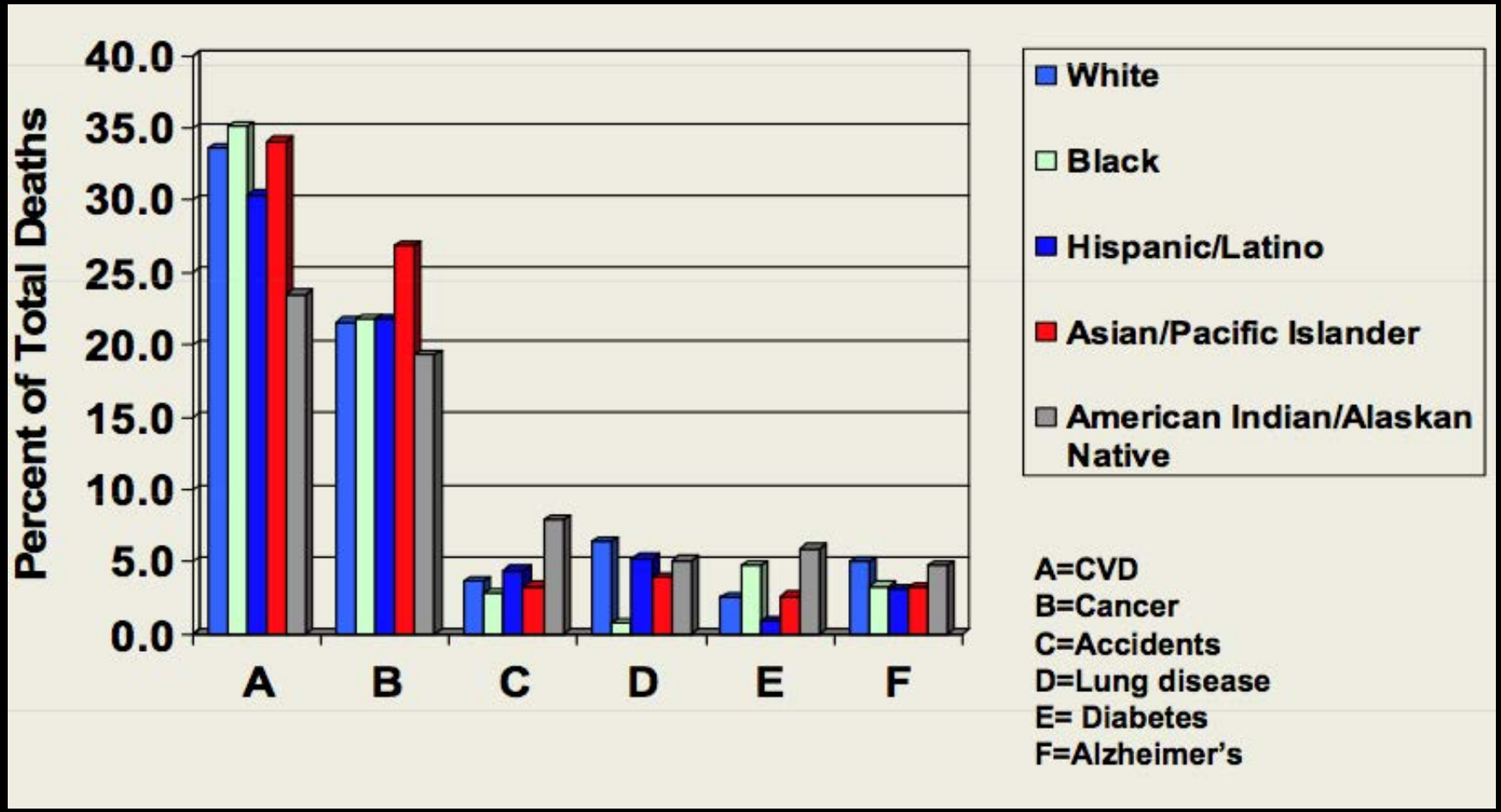
Atherosclerosis Risk in Communities Surveillance: 1987–2004 and Cardiovascular Health Study: 1989–2004

Probability of US Women *Developing* vs *Dying* from Disease

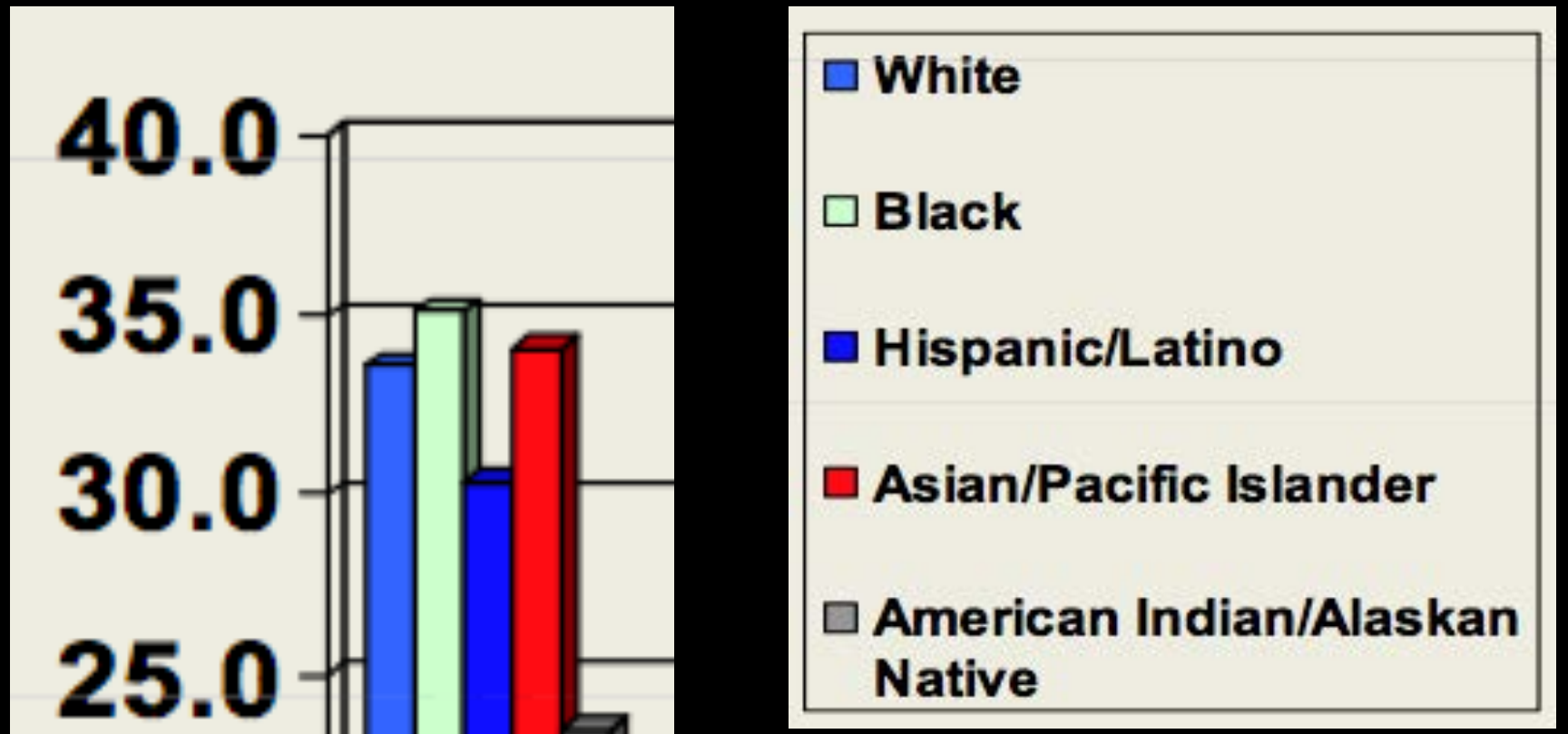


AHA Heart Disease and Stroke Stat 2009 Update. Circulation 2009.
Grady et al. Ann Intern Med 1992; 117; 1016-1030

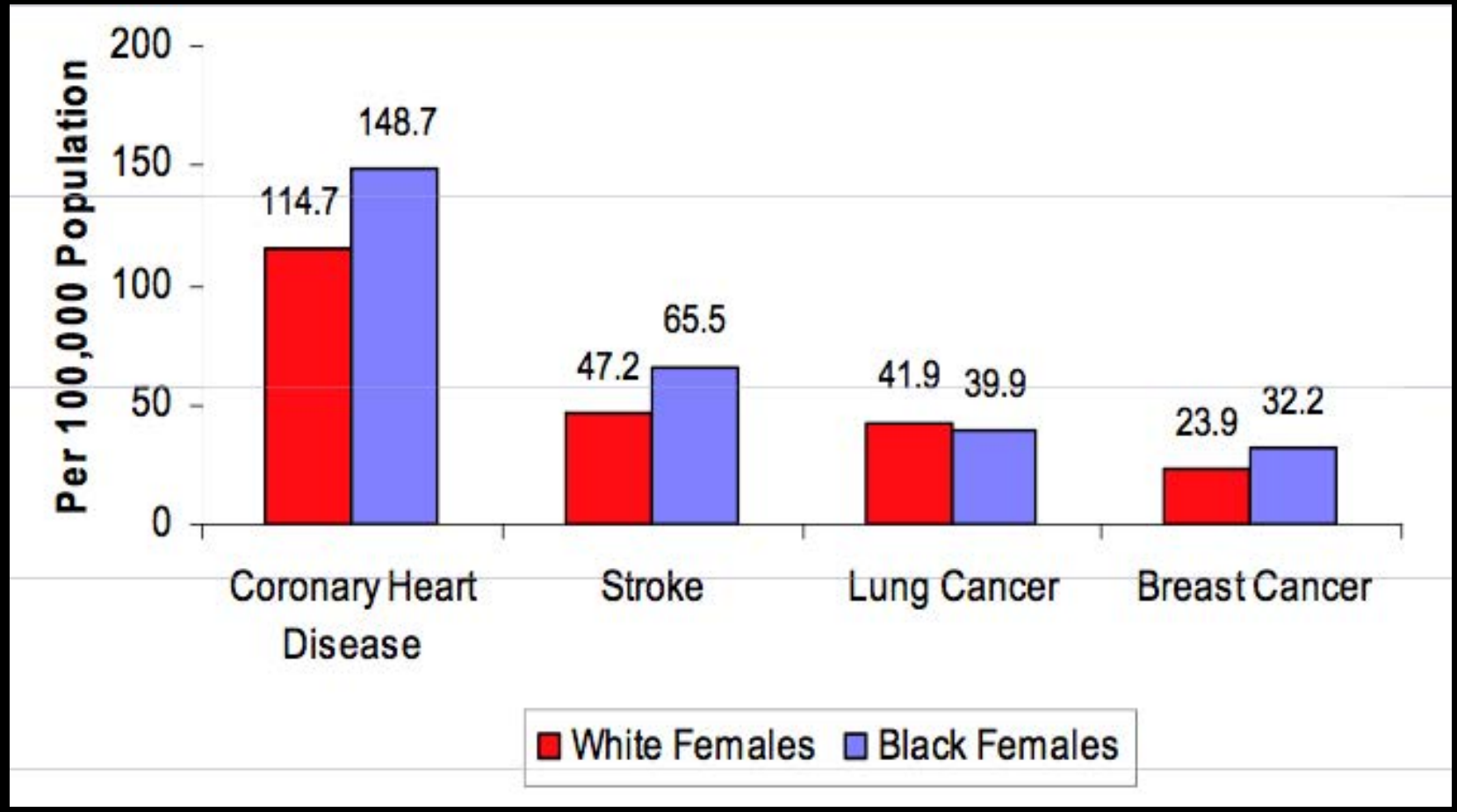
Causes of Death in Women by Race



Let’s look at that a little closer…



Age-Adjusted Death Rates in White and Black Women



NCHS and NHLBI, 2004, US statistics

General Differences of Women

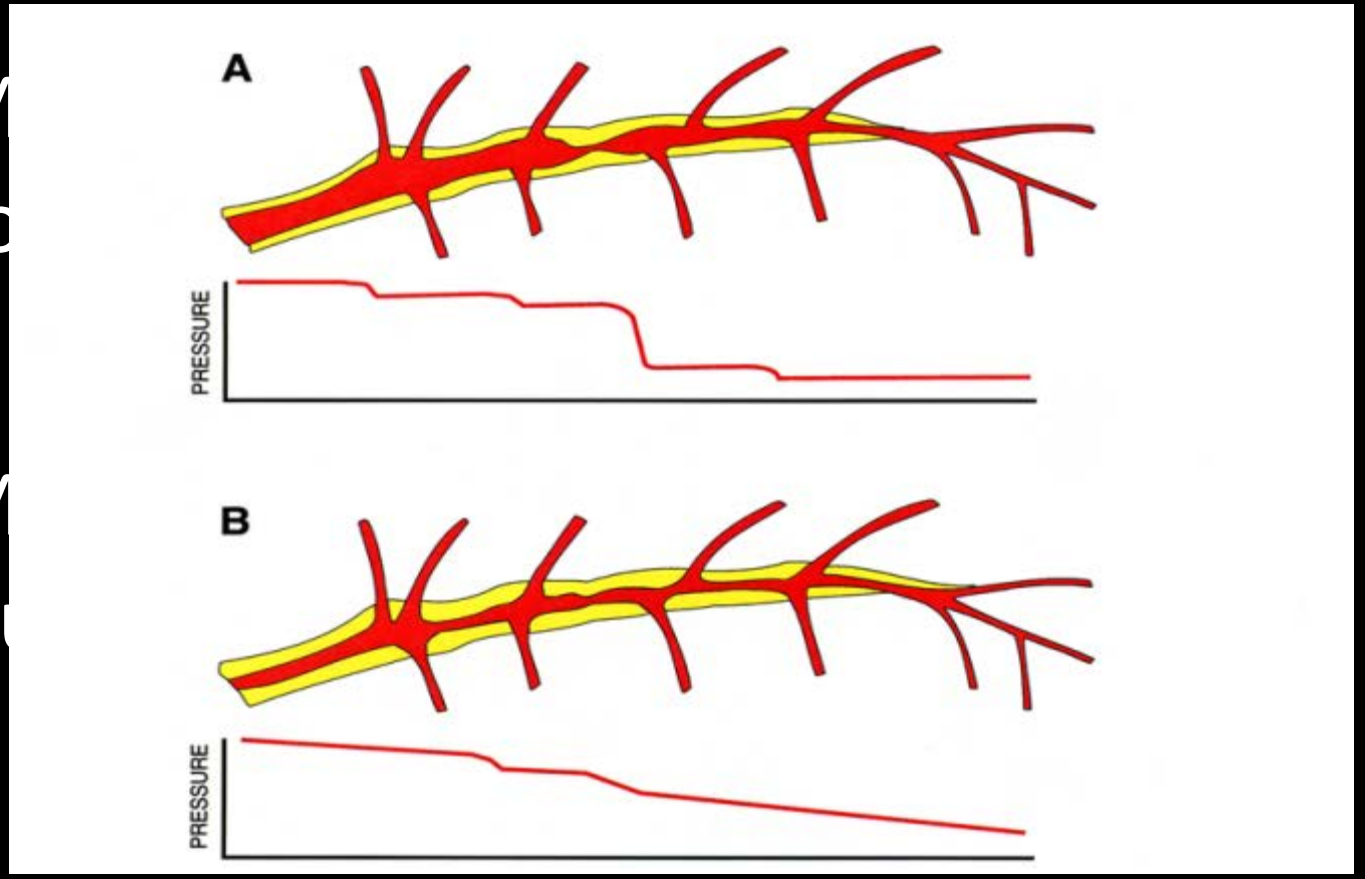
- Cardiac Anatomy
  - Smaller left ventricular mass, wall thickness, left atrial dimension, left end diastolic size.
- Cardiac Function
  - Stroke volume is ~10% less
  - Ejection fraction slightly higher
  - Pulse 3-5 beats/min faster
- Physiology
  - Reduced sympathetic activity
  - Enhanced parasympathetic activity
  - Decreased levels of norepinephrine

Huxley V, Adv Phys Edu; 2007.

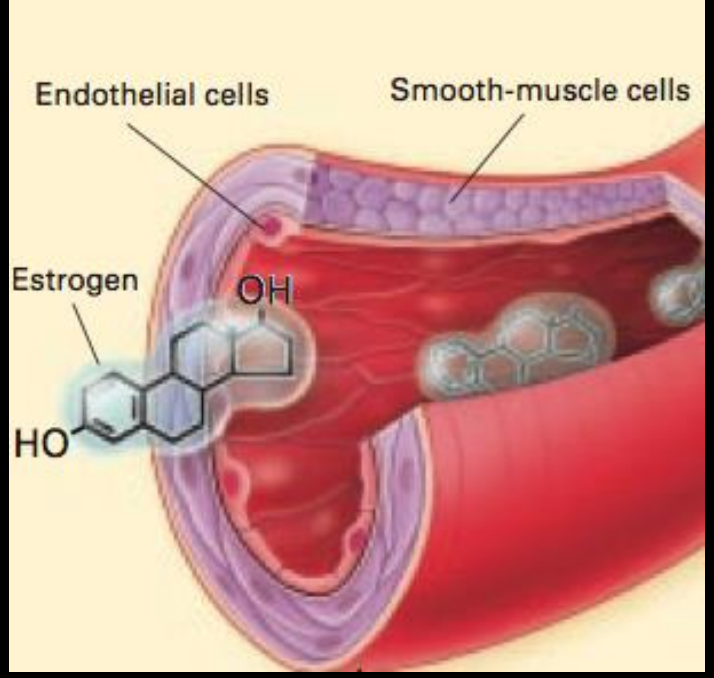
Gender Differences in Plaque Distribution

M
fo

WOM
diff



Effects of Estrogen



- Decreased LDL
- Increased HDL
- Increased Triglycerides
- Enhanced endothelial function
  - Increased vasodilation by increasing nitric oxide availability
  - Inhibition of response to vessel injury by increasing endothelial growth and decreasing smooth muscle growth