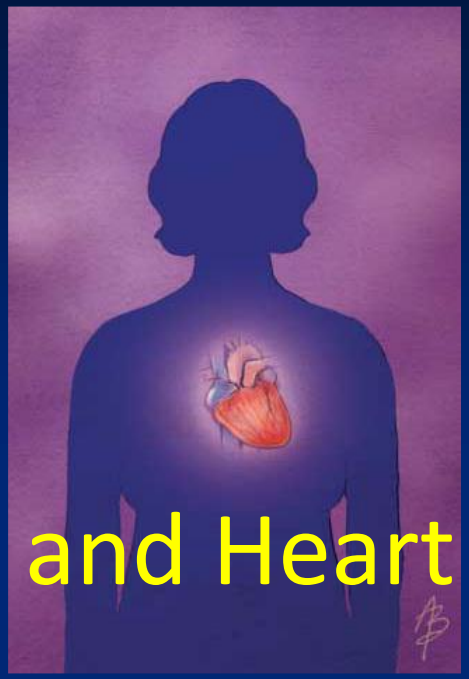


Women and Heart Disease

J. Susie Woo, MD FACC

Virginia Mason Heart Institute

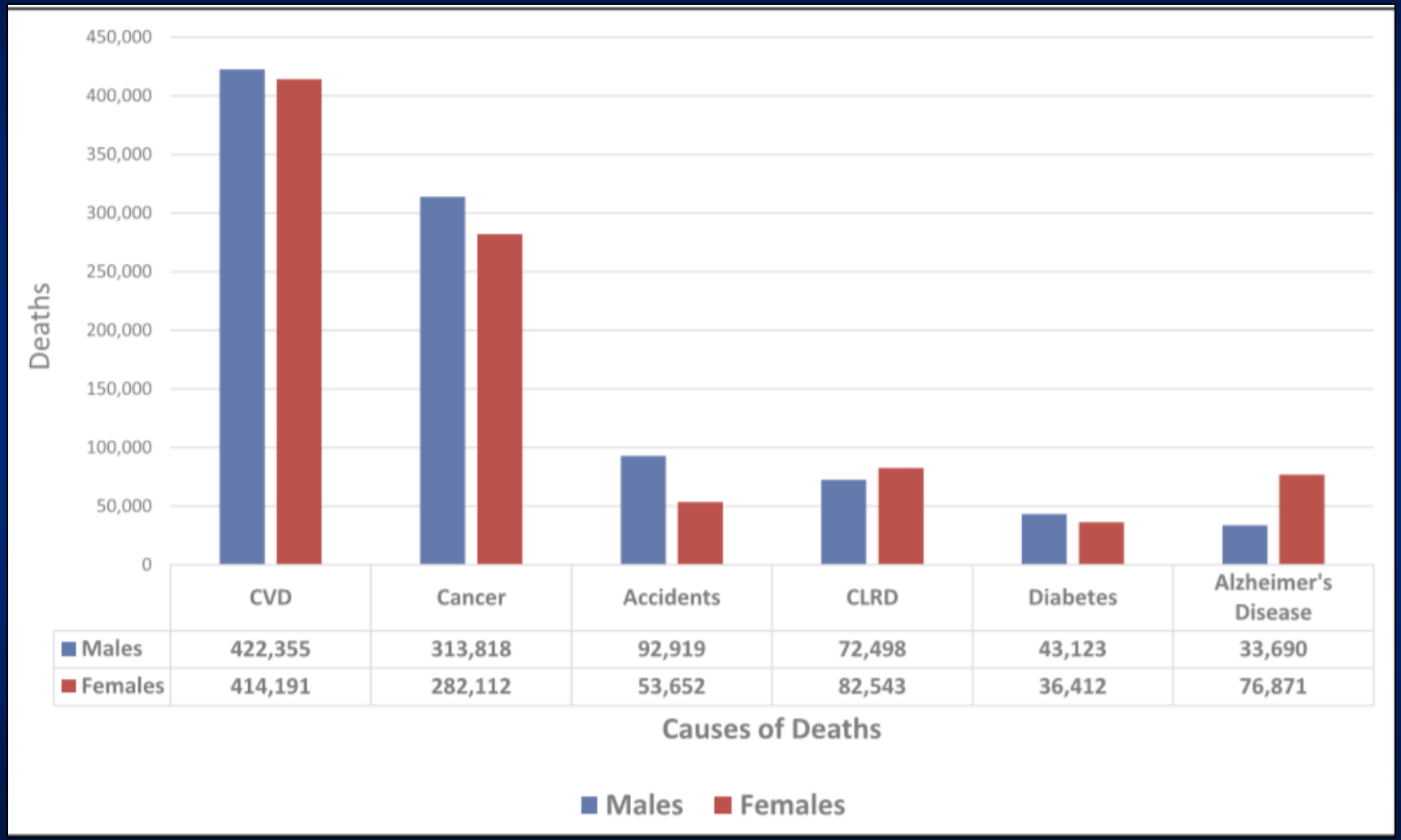
October 11, 2019

Virginia Mason™

Disclosures

- None

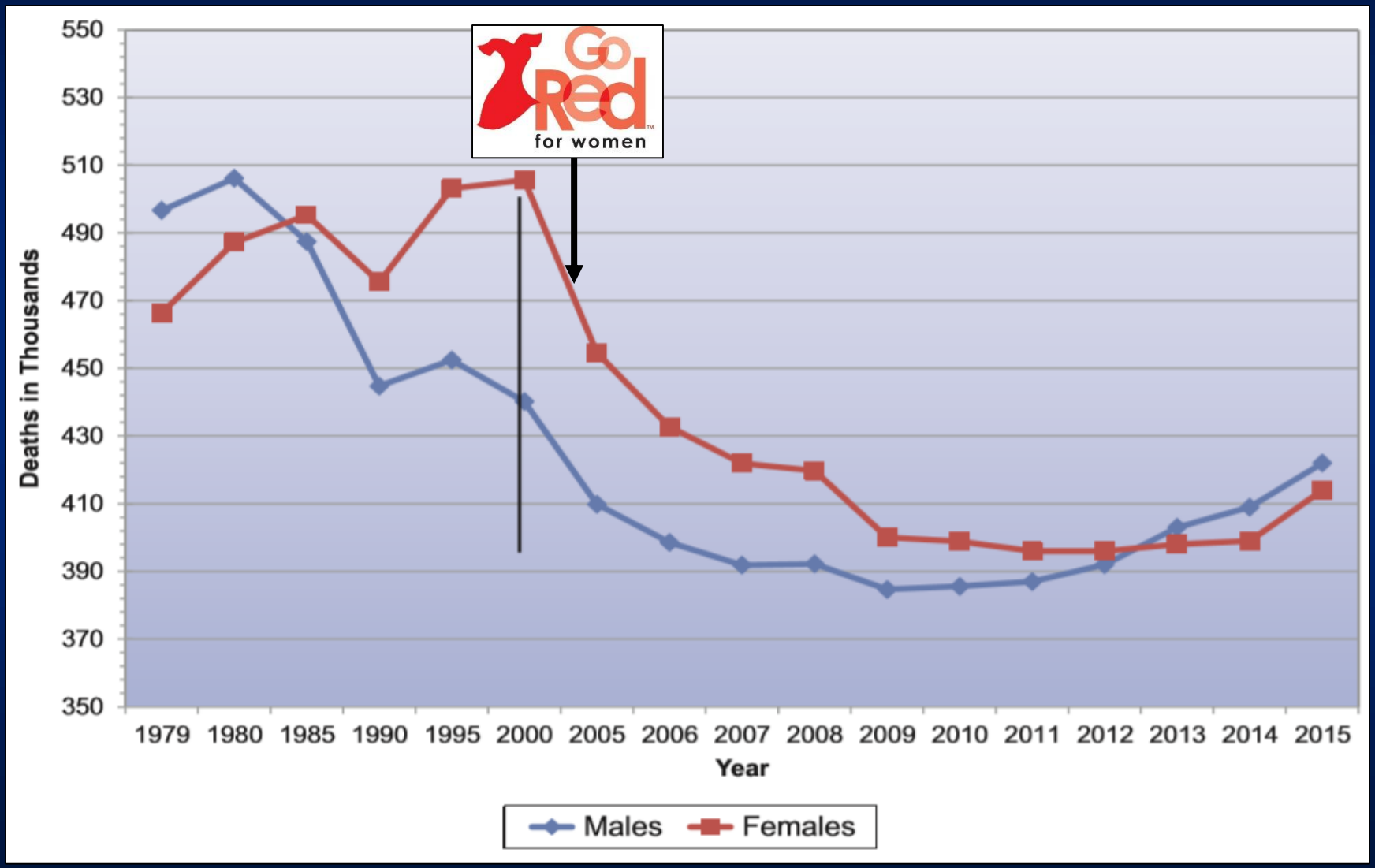
Major Causes of Death, 2015



	CVD	Cancer	Accidents	CLRD	Diabetes	Alzheimer's Disease
Males	422,355	313,818	92,919	72,498	43,123	33,690
Females	414,191	282,112	53,652	82,543	36,412	76,871

AHA Statistical Update, 2018.

CVD Mortality



Women's Perception of the Leading Cause of Death

	2009	2003	1997
Breast cancer	11	15	15
Cancer	23	20	35
Heart Disease	54	46	30

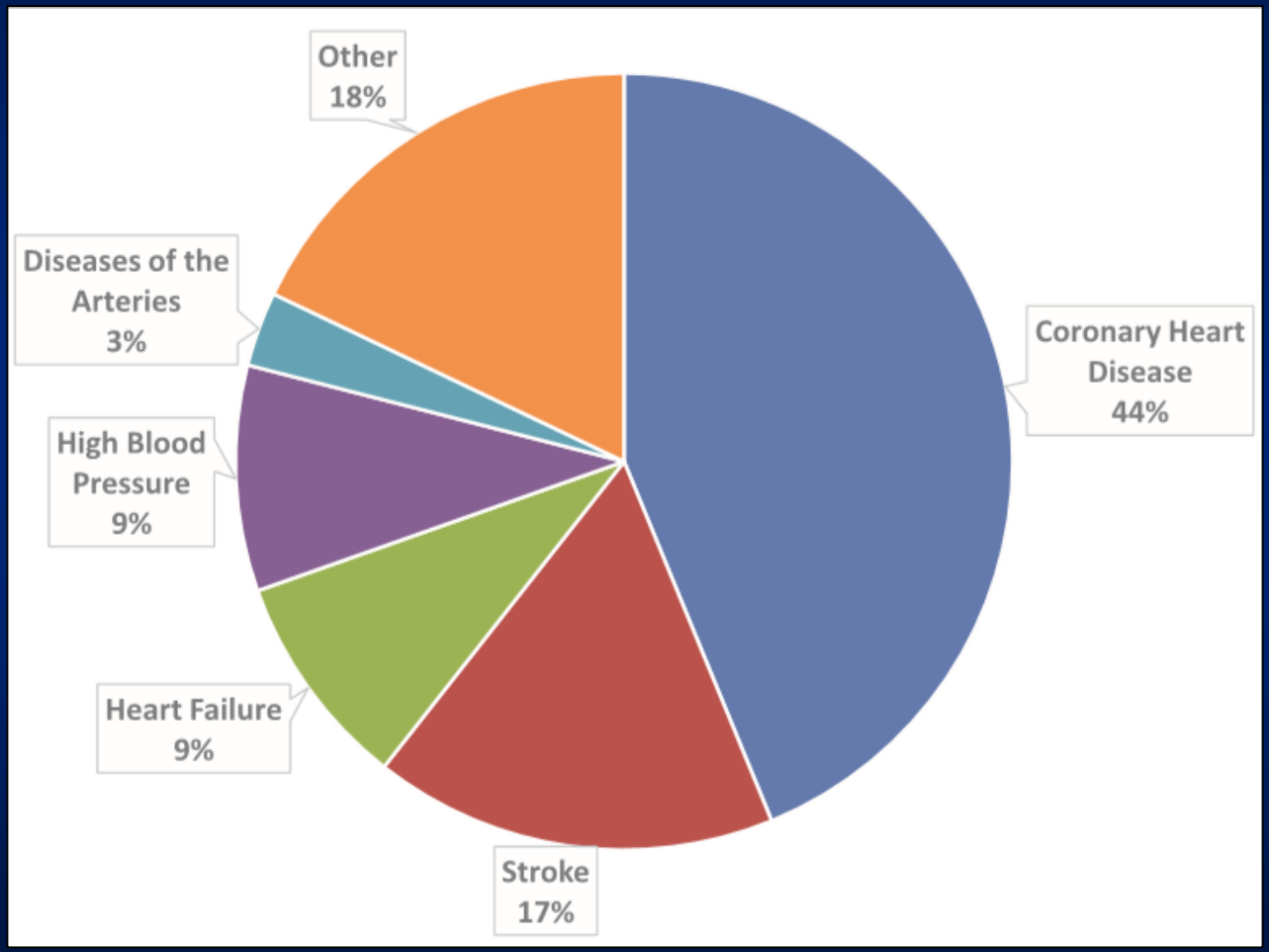
AHA National Awareness Survey, Mosca *Circ* 2010: 120.

Women's perception of THEIR OWN greatest health risk

	2009	2003	1997
Breast cancer	28	35	34
Cancer	18	16	27
Heart disease	16	13	7

AHA National Awareness Survey, Mosca *Circ* 2010: 120.

Deaths from CVD



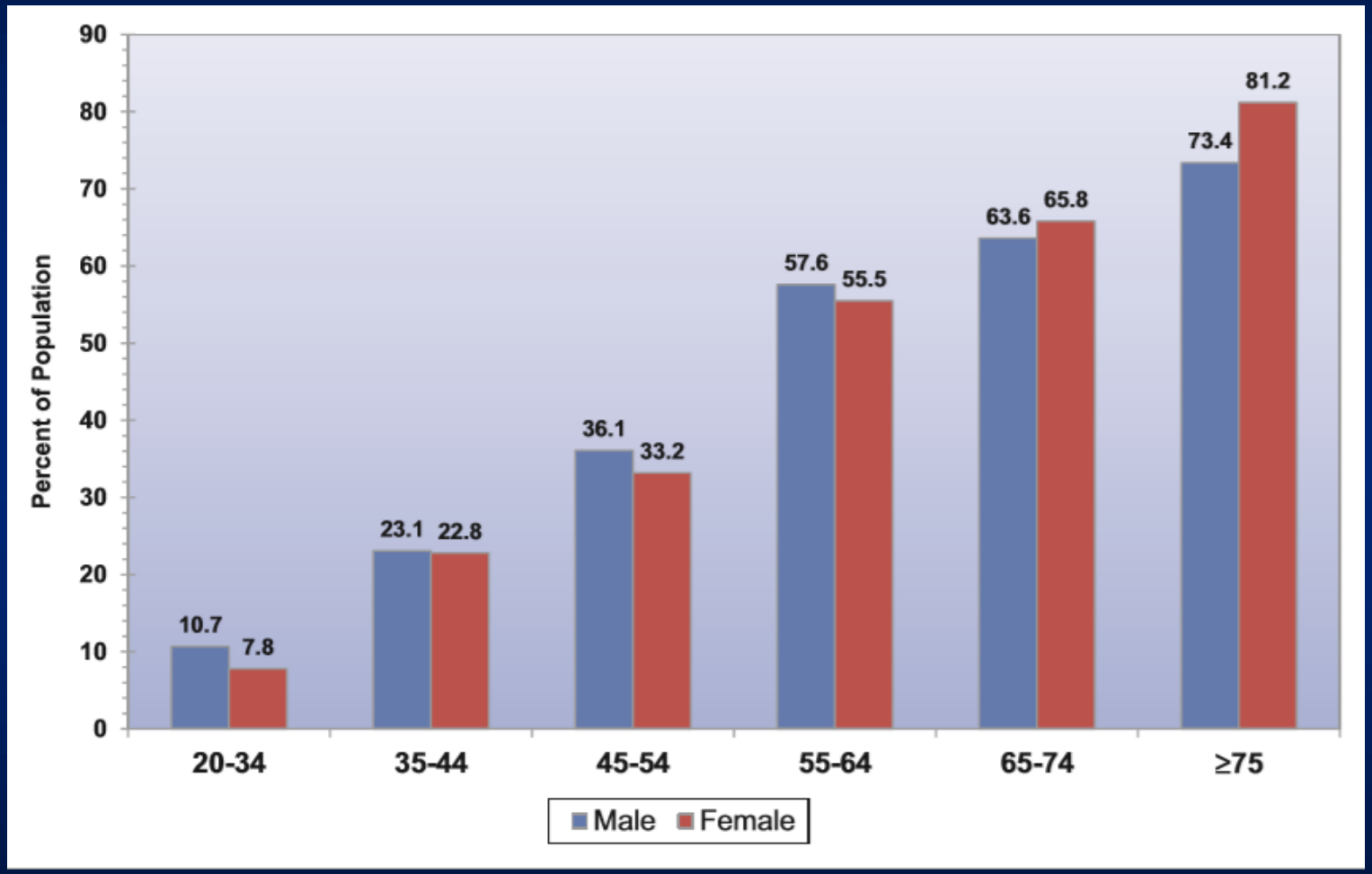
Coronary Heart Disease

- Differences between men and women
  - Risk Factors
  - Presentation
  - Evaluation
  - Treatment

Risk Factors

- Traditional risk factors still apply:
  - blood pressure, cholesterol
  - smoking, lifestyle
  - diabetes, obesity
  - family history
- Age: “10-yr lag” of CAD incidence & mortality
- HDL: higher in women

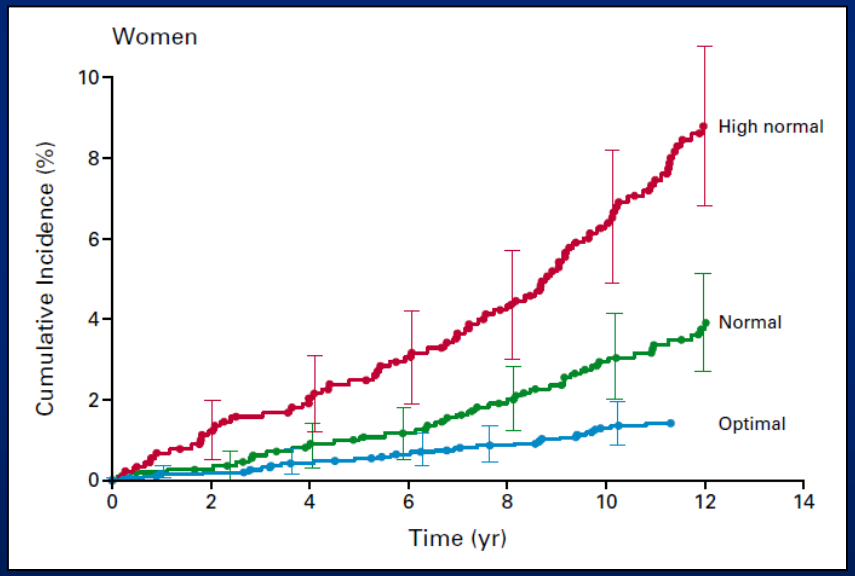
Prevalence of Hypertension

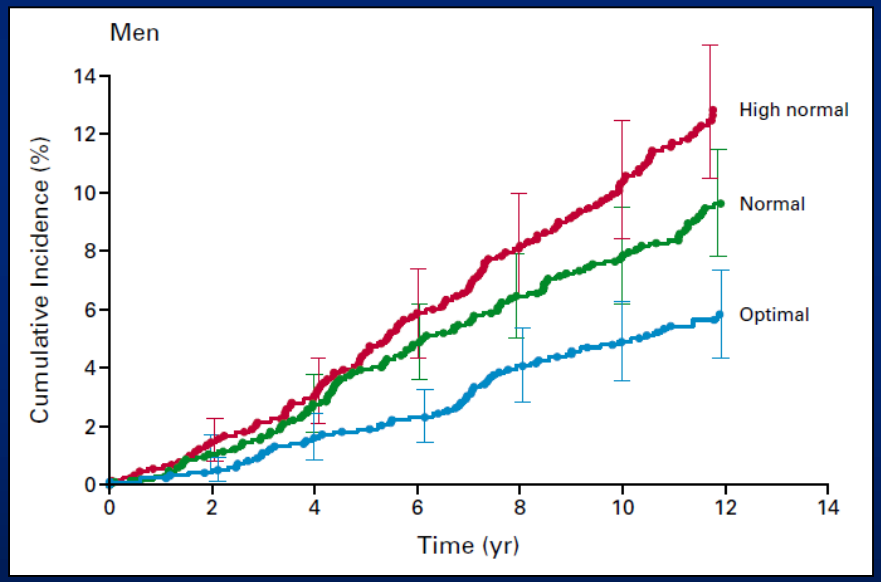


NHANES (2011-2014); AHA Statistical Update 2018.

High-normal BP and CVD risk

Framingham Heart Study: n=6859
High Normal = 130-139/85-89
Normal = 120-129/80-84
Optimal = <120/80

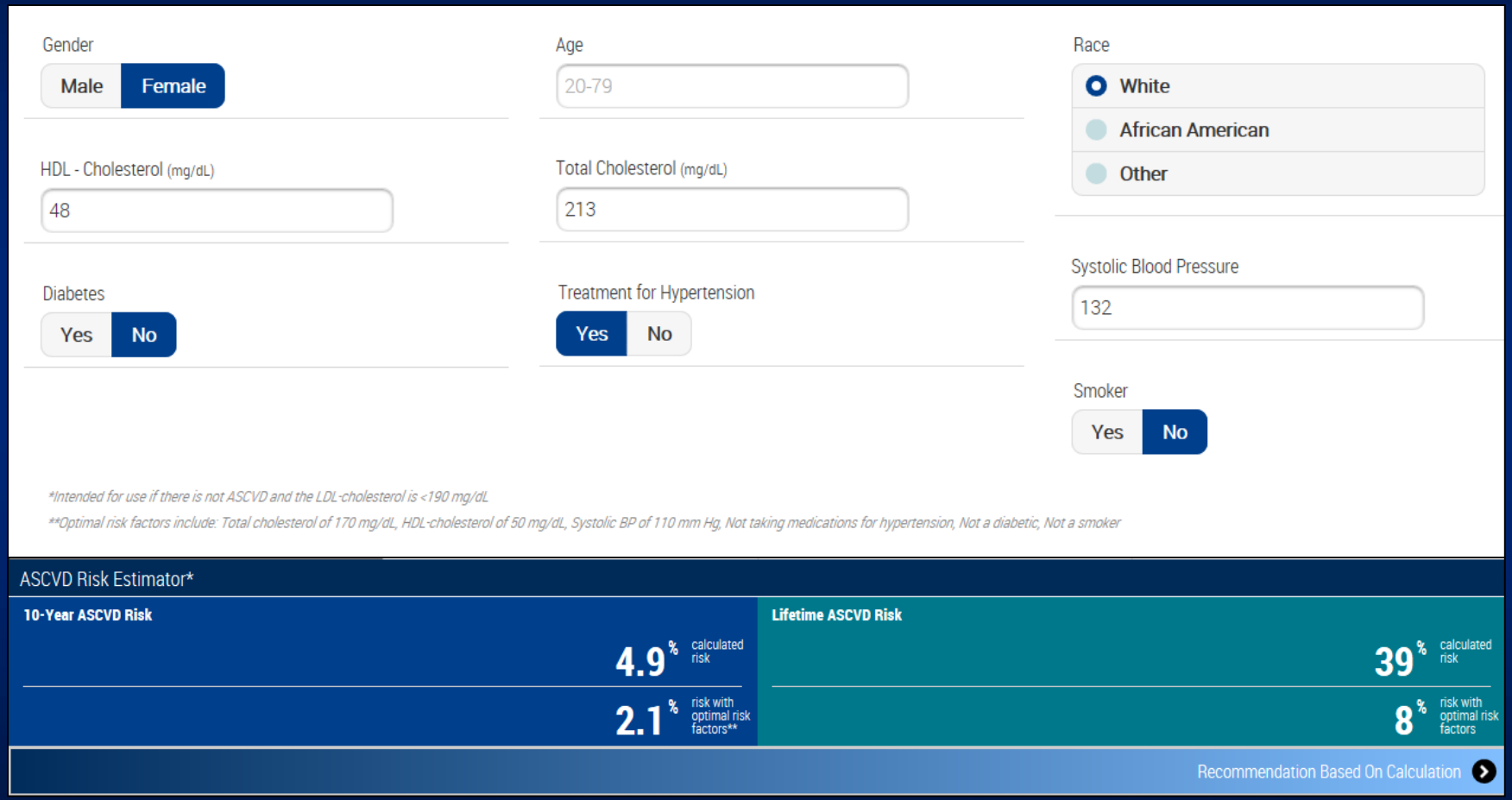




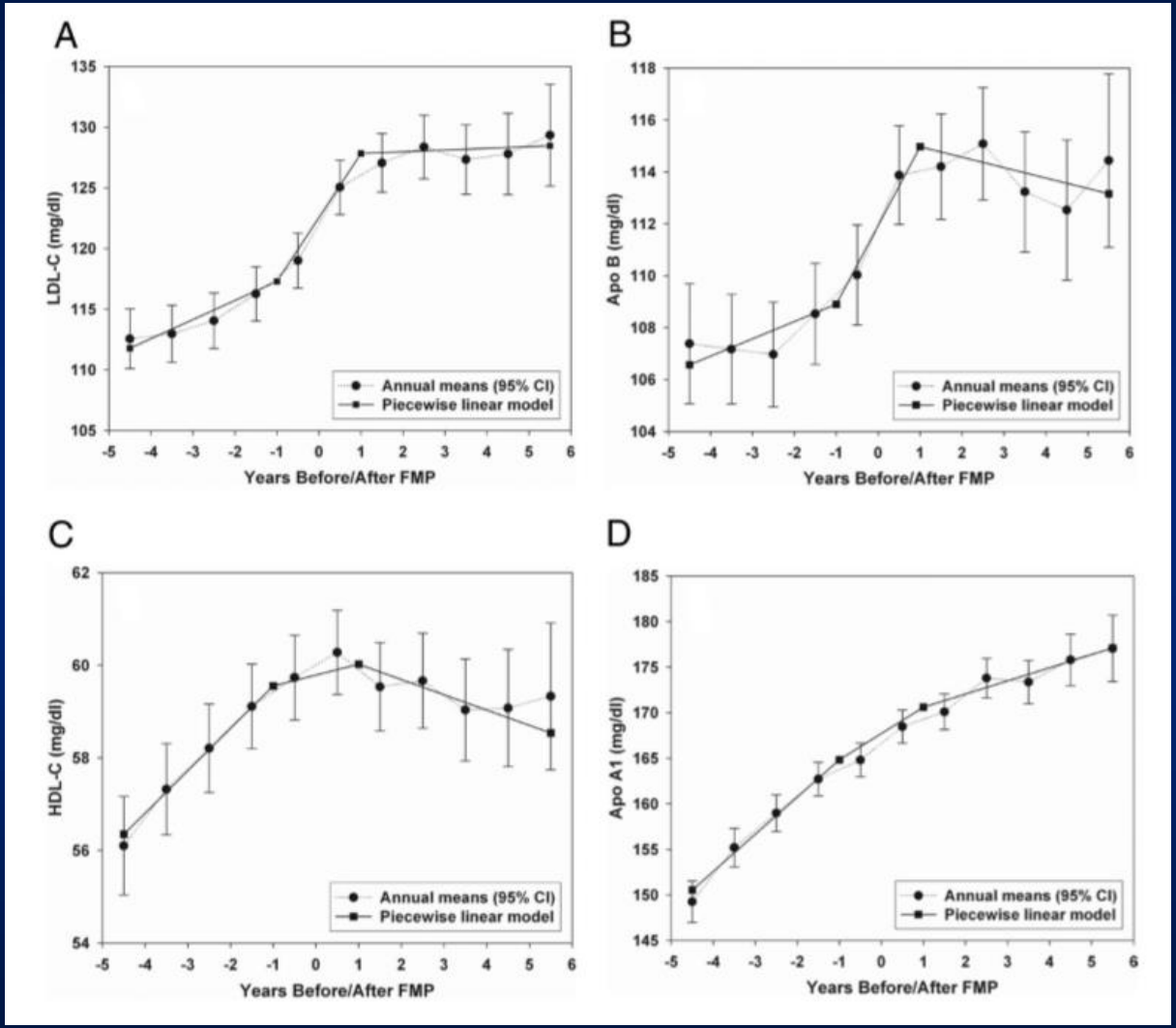
Risk-adjusted HR 2.5 for women, 1.6 for men

Vasan et al., *NEJM* 2001;345: 1291-7.

http://tools.acc.org/ASCVD-Risk-Estimator/

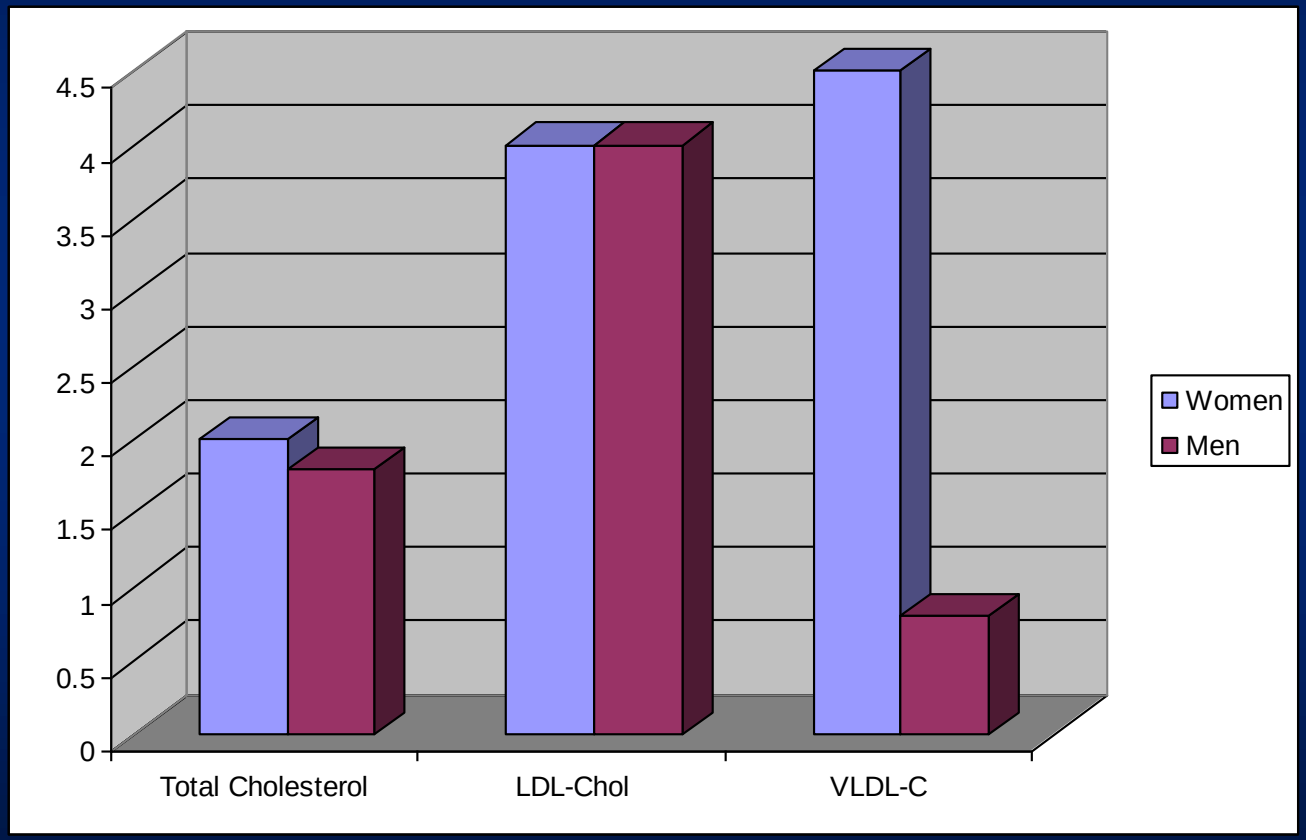


Changes in cholesterol at menopause



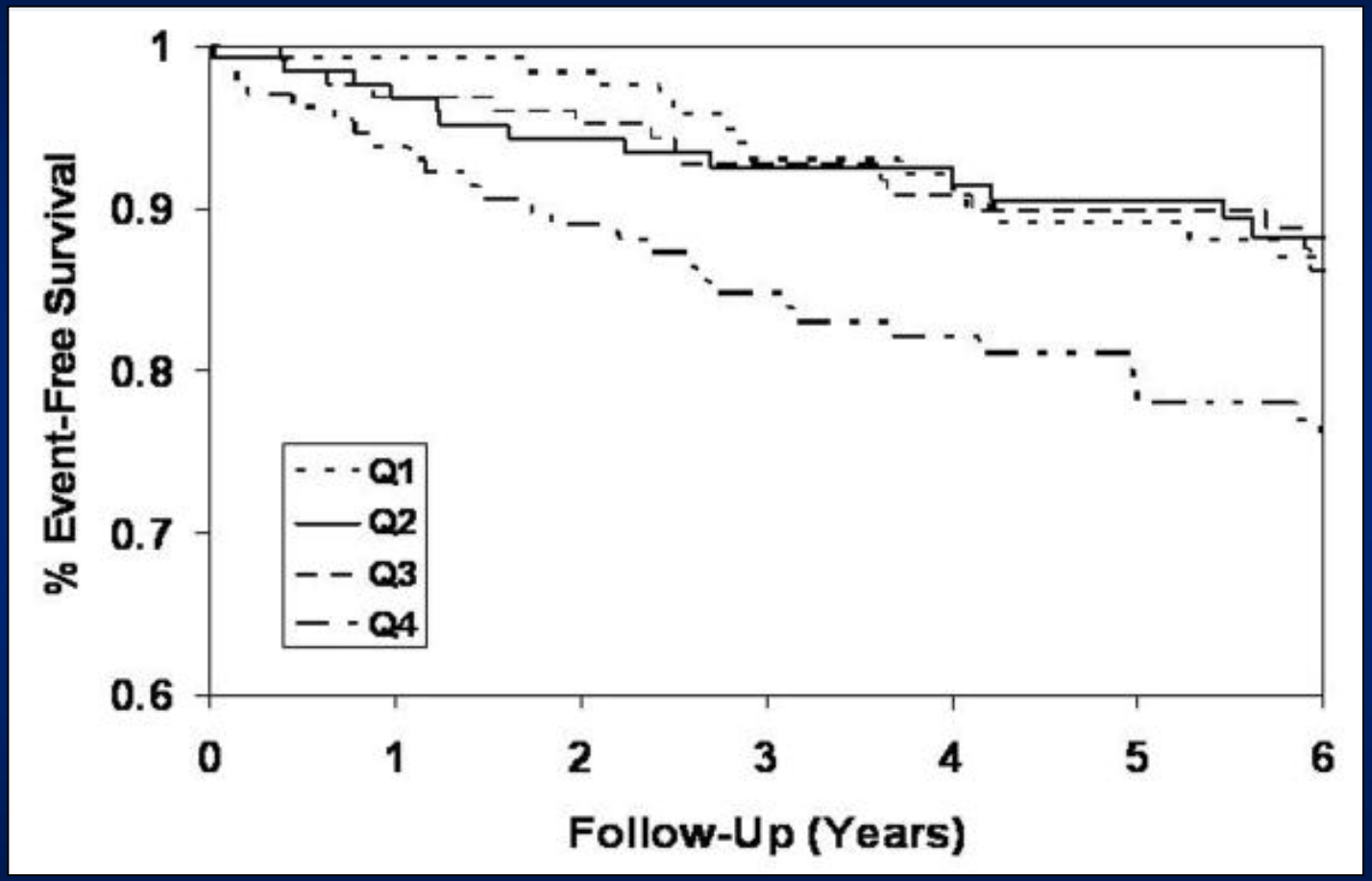
Matthews KA et al., *JACC* 2009;54:2366-73.

Triglycerides are a more significant risk factor for women



Framingham Heart Study

TG/HDL ratio predicts outcome in women



Q4 = TG/HDL ratio > 3.66

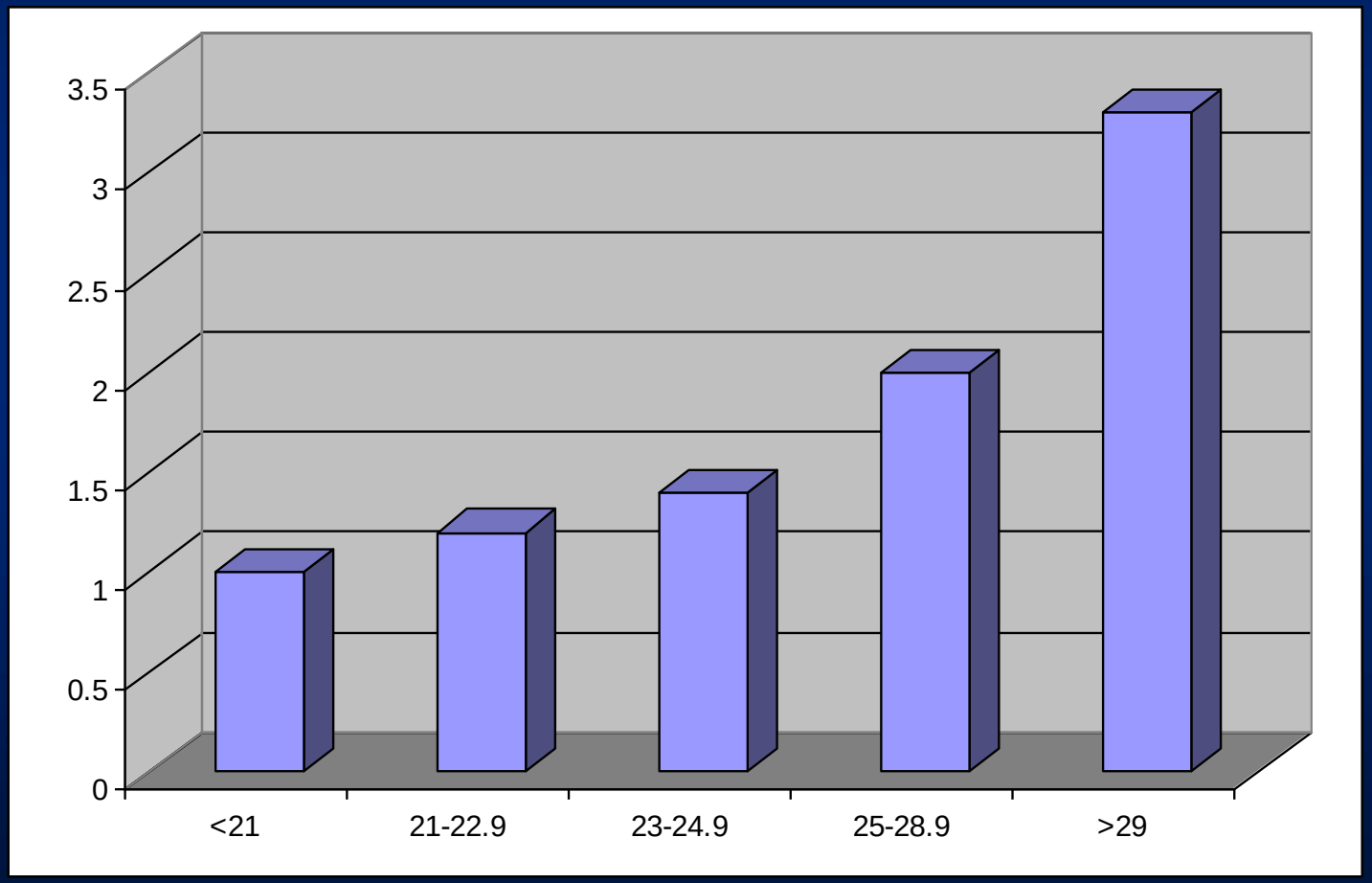
Bittner et al, *Am Heart J* 2009, 548.

Diabetes and CHD in women

- Approximately 75% of all diabetics will die from heart attack or stroke
- Women with diabetes are 3-4 times more likely than men with diabetes to develop heart disease
- Higher CVD mortality rate than diabetic men

NHLBI Healthy Heart Handbook for Women, 2003.

BMI and Relative Risk of CHD: Nurses Health Study 14 yr results



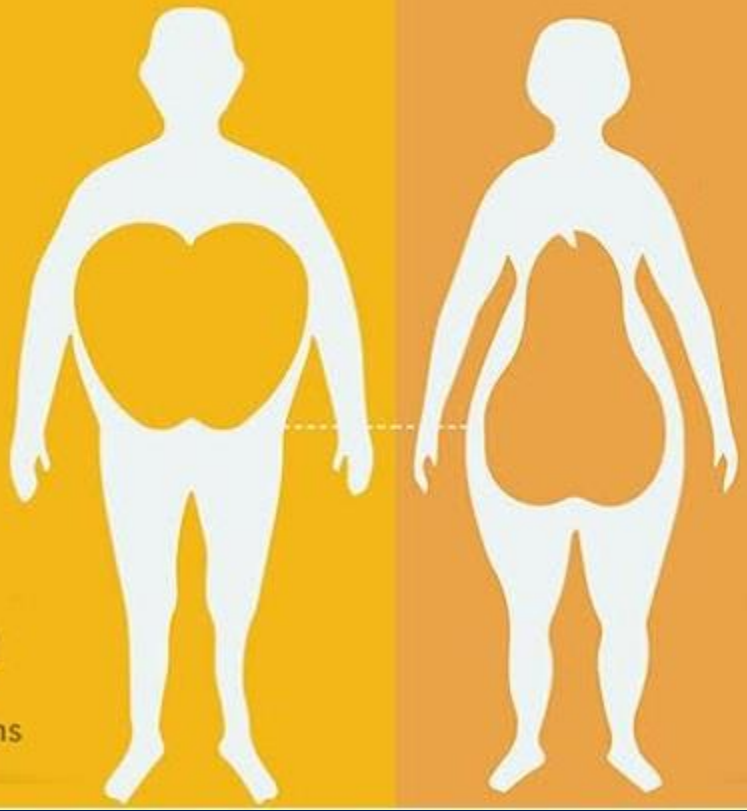
APPLE SHAPED OBESITY

Excess amount of fat is accumulated **above waist line** i.e. in belly region

Associated with excess visceral and subcutaneous (somatic) fat

Abdominal girth is bigger than hip circumference

Most commonly associated with metabolic syndrome and related health problems



PEAR SHAPED OBESITY

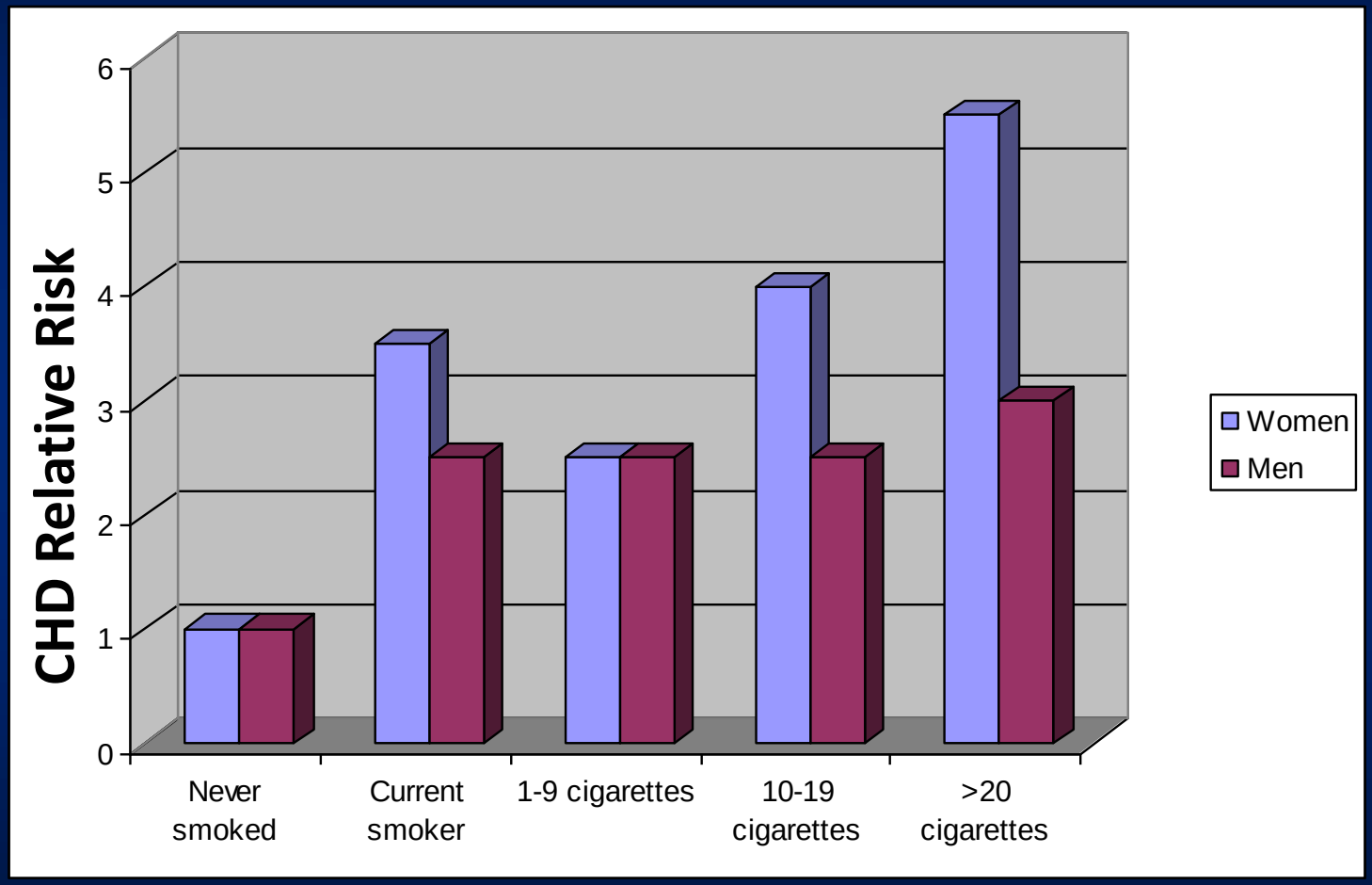
Excess amount of fat is accumulated **below waist line** i.e. around hips and thighs

Waist is relatively thinner as compared to apple shaped obesity but has large hips

More commonly associated with subcutaneous fat

Associate less commonly with metabolic syndrome related health issues

Smoking



Njolstad I et al., *Circ* 1996;93:450-456.

Smoking and CVD

- Leading cause of MI in younger women
- Risk accentuated by OCP use
- Associated with early menopause
- Decrease in HDL is more pronounced in women

- Clear dose-response with risk of CHD
- Risk equals non-smokers after 2-3 yrs of abstinence

Taylor KG et al., *Atherosclerosis* 1981;38:11-18.

Novel risk factors

- Unique or more common in women
  - Hypo-estrogenemia
  - Polycystic ovarian syndrome
  - Peripartum disorders
  - Increased autoimmune disease and vasculitis
- CRP higher in women

Risk Enhancers

ASCVD Risk Enhancers:

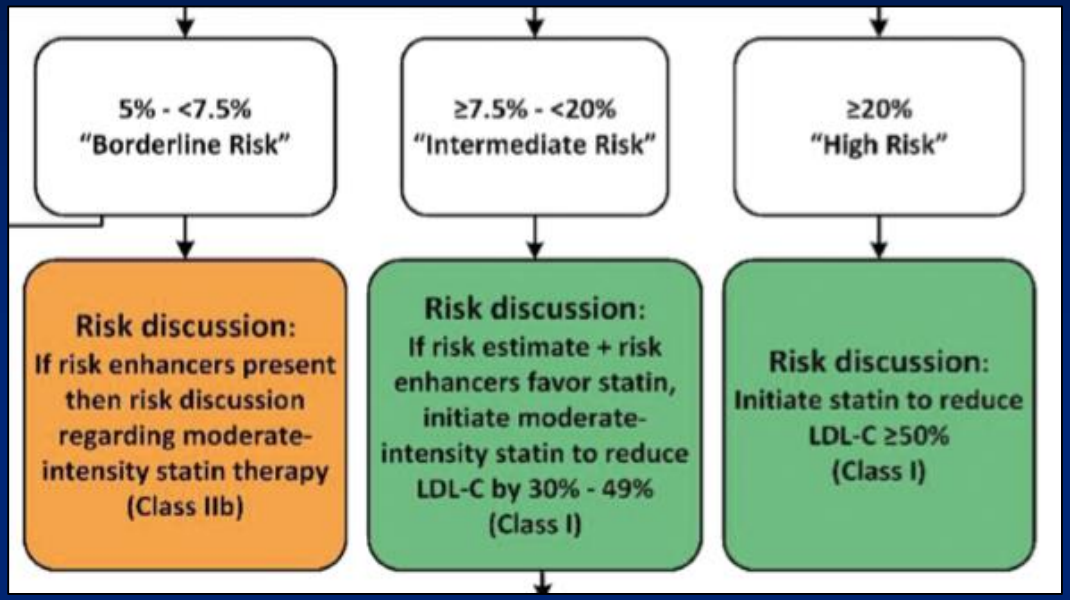
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

<u>Lipid/Biomarkers:</u>

- Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))

<u>In selected individuals if measured:</u>

- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9



2018 Cholesterol Clinical Practice Guidelines, *Circ* 2019;139:e1082–e114.

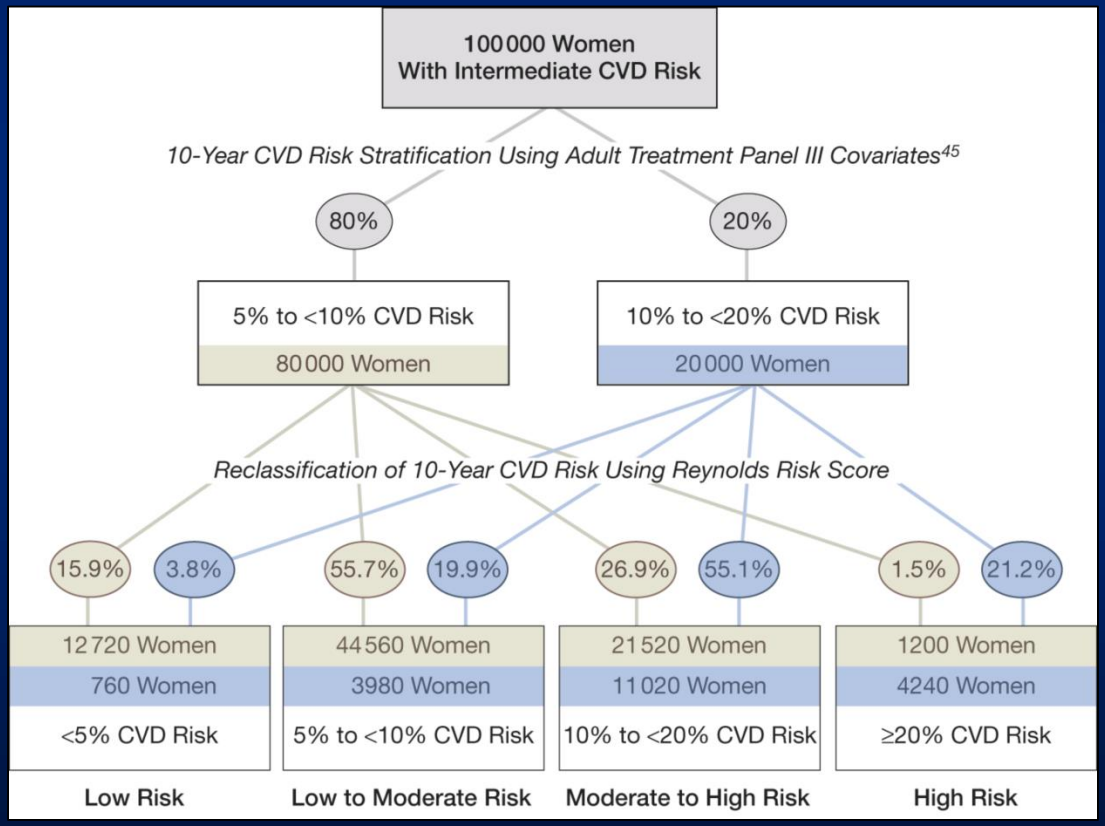
4.5.3. Issues Specific to Women

Recommendations for Issues Specific to Women Referenced studies that support recommendations are summarized in Online Data Supplements 33 to 35.		
COR	**LOE**	**Recommendations**
I	B-NR	1. Clinicians should consider conditions specific to women, such as premature menopause (age <40 years) and history of pregnancy-associated disorders (hypertension, preeclampsia, gestational diabetes mellitus, small-for-gestational-age infants, preterm deliveries), when discussing lifestyle intervention and the potential for benefit of statin therapy.[S4.5.3-1–S4.5.3-6]
I	C-LD	2. Women of childbearing age who are treated with statin therapy and are sexually active should be counseled to use a reliable form of contraception.[S4.5.3-7–S4.5.3-12]
I	C-LD	3. Women of childbearing age with hypercholesterolemia who plan to become pregnant should stop the statin 1 to 2 months before pregnancy is attempted, or if they become pregnant while on a statin, should have the statin stopped as soon as the pregnancy is discovered.[S4.5.3-7–S4.5.3-12]

2018 Cholesterol Clinical Practice Guidelines, *Circ* 2019;139:e1082–e114.

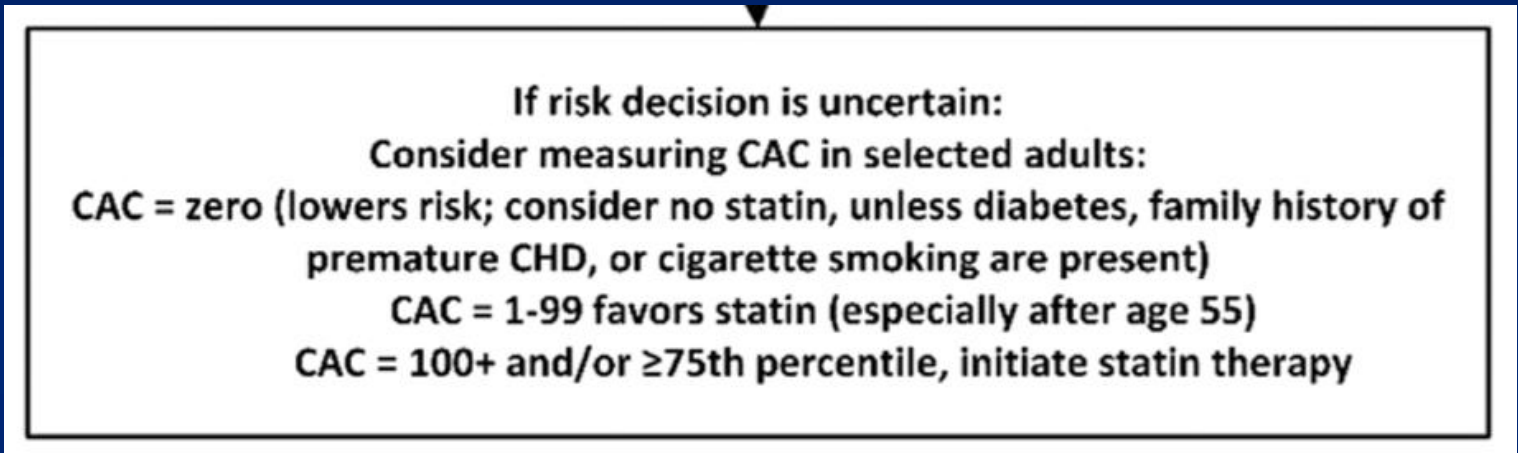
Reynolds Risk Score

- Adds hs-CRP and family history to traditional risk factors
- Reclassified ~50% of intermediate risk women



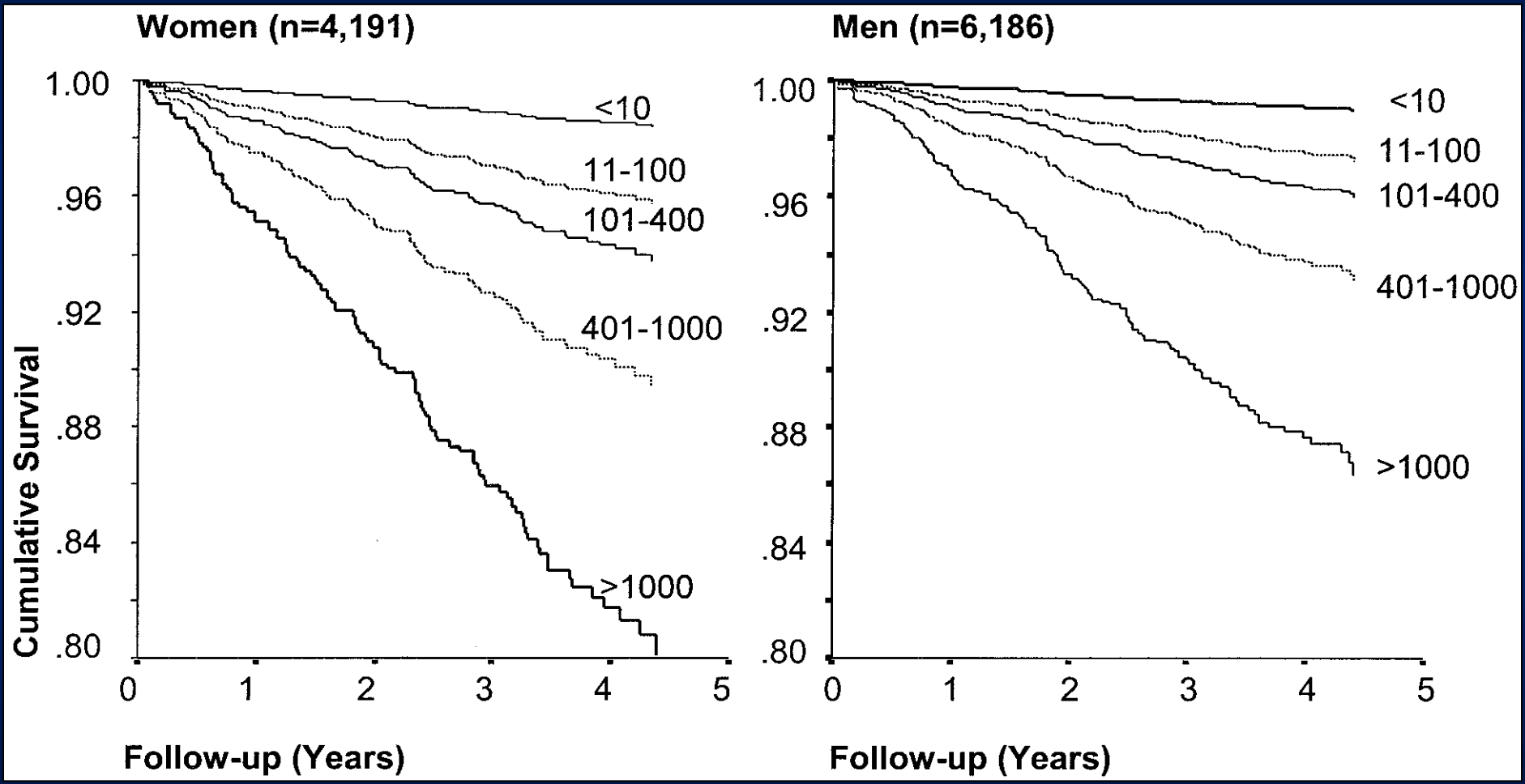
Ridker et al, *JAMA* 2007;297(6):611-619.

Additional Assessment



2018 Cholesterol Clinical Practice Guidelines, *Circ* 2019;139:e1082–e114.

Prognostic Value of CACS

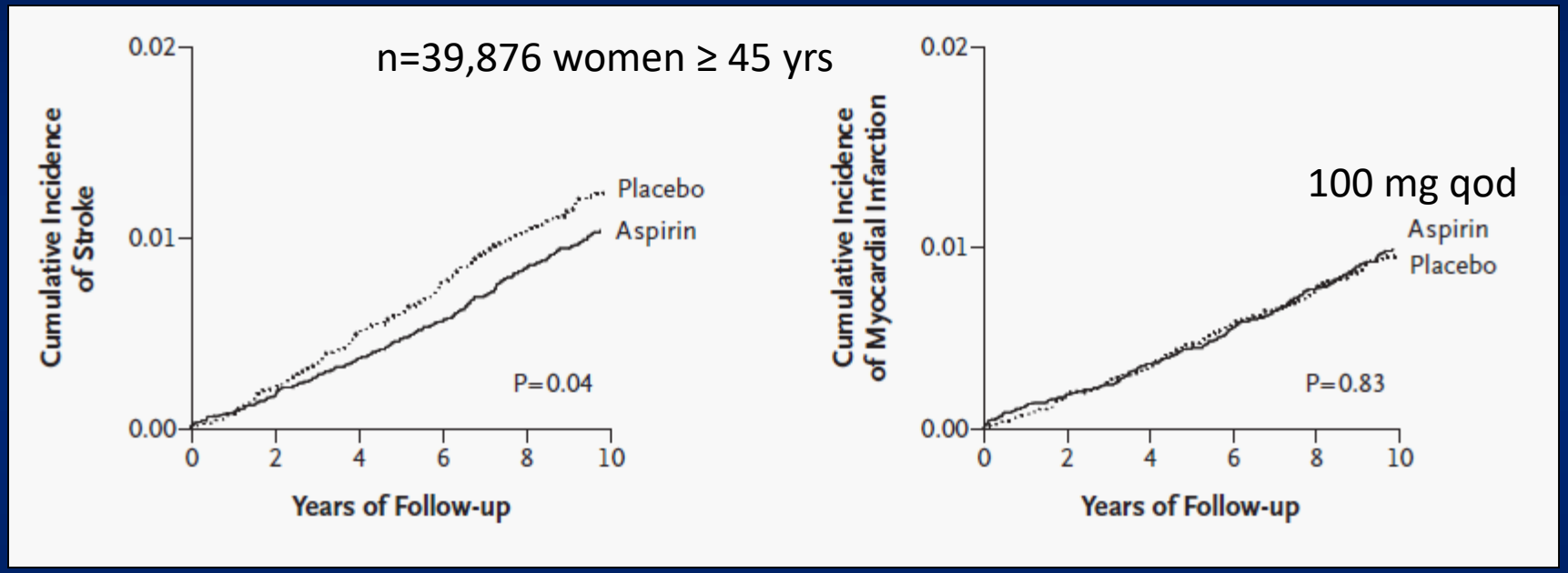


Raggi et al, *J Womens Health* 2004;13(3):273-283.

Risk factor	Men	Women
Total cholesterol	+++	+++
LDL	+++	+++
HDL	++	+++
Triglycerides	+	++
Apo A-I	+++	+++
Apo-B	+++	+++
Apo(a)	++	+(+)
Smoking	++	++(+)
Diabetes	++	+++
Obesity		
BMI	++	++
WHR	+++	+++
Hypertension	++	++
Family History	++	++(+)
Hormones		+++
Homocysteine	+	+
Fibrinogen	++	++
Inflammation (CRP)	+	++
Infection (HP, ChP)	–	–
Psychosocial factors	+	+

Lennep, *CV Research* 2002;53:538-549.

Aspirin for Primary Prevention



- 17% decrease in risk of stroke
- ASA 81 mg qd in women 55-79 yrs if benefit > risk

Women's Health Study: Ridker, *NEJM* 2005;352:1293-304.

USPSTF

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I

Gender and CHD

- Differences between men and women
  - Risk Factors
  - Presentation
  - Evaluation
  - Pathophysiology
  - Treatment

WOMAN WITH A COLD

MAN WITH A COLD

Symptoms

- Women <65 are *twice* as likely to die from a heart attack
- More likely to die of cardiac arrest prior to hospital arrival, die within 1 yr, become disabled from CHF

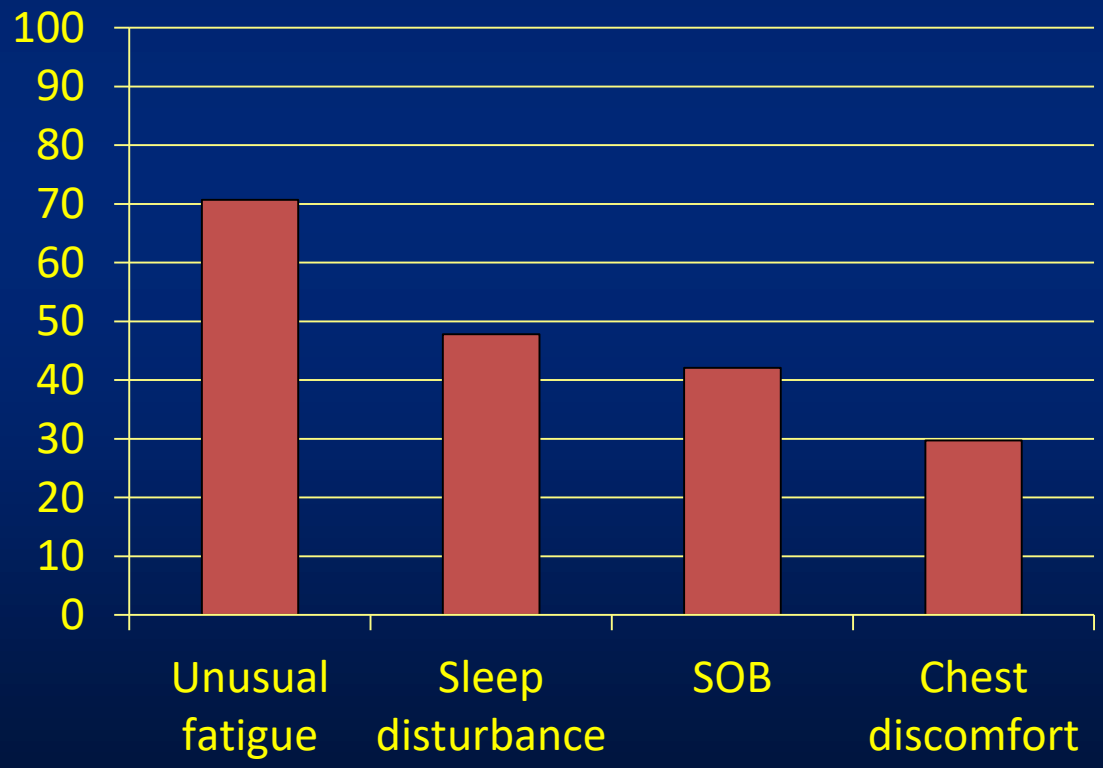
Shaw LJ et al, *JACC* 2006;47:4S-20S.

Why do women have higher morbidity/mortality?

- Delay in presentation & diagnosis
- Advanced age and comorbidities in women
- Underutilization of guideline care
- Tests are not as accurate in women
- Therapies are not as effective in women
- Lack of trial data specific to women
- Different pathophysiology of disease

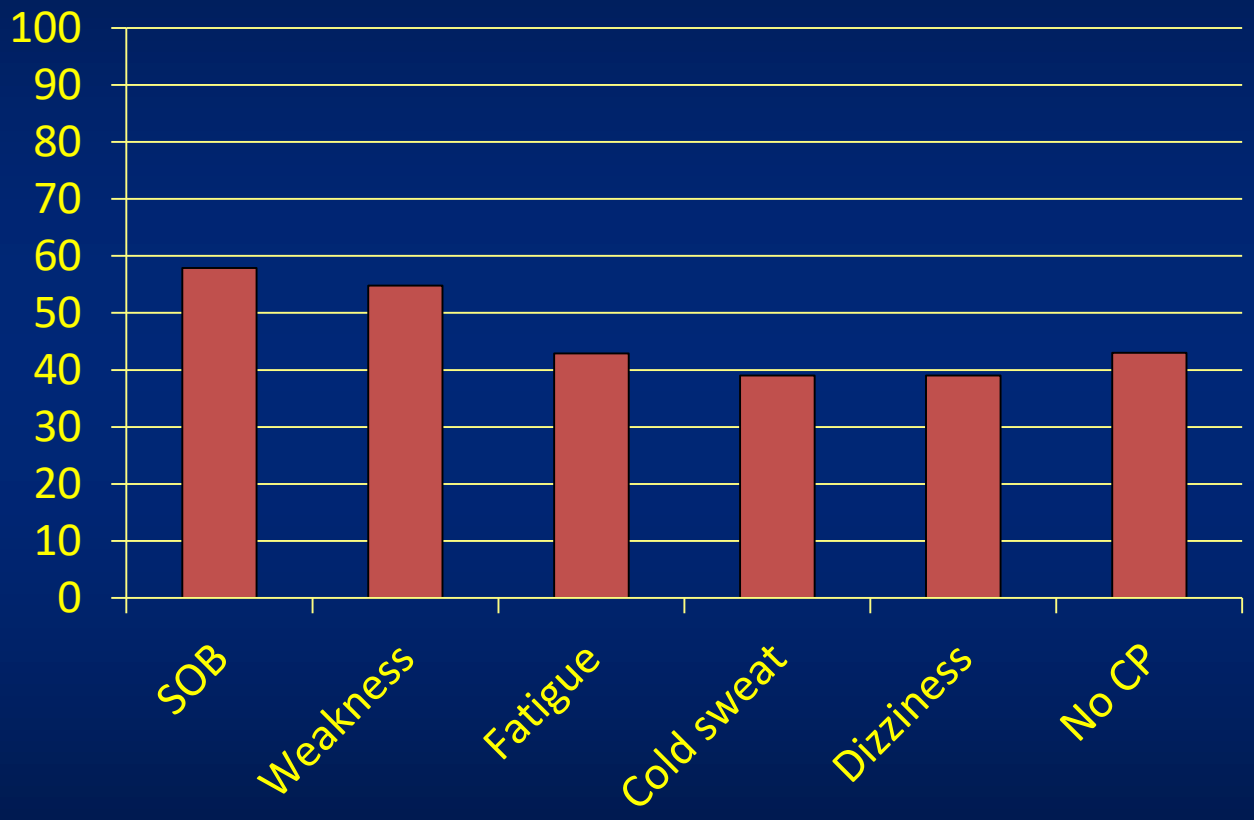
Early warning symptoms of Acute MI

- 515 women surveyed 4-6 months post-event
- 95% reported prodromal symptoms



McSweeney, *Circ* 2003, 2619.

Acute Symptoms



McSweeney, *Circ* 2003, 2619.

Gender and CHD

- Differences between men and women
  - Risk Factors
  - Presentation
  - Evaluation
  - Pathophysiology
  - Treatment

Stress testing

Age (years)	Gender	Typical/Definite angina pectoris	Atypical/Probable angina pectoris	Nonanginal chest pain	Asymptomatic
<39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
>60	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

High: >90% pretest probability; **Intermediate:** Between 10% and 90% pretest probability; **Low:** Between 5% and 10% pretest probability; **Very low:** <5% pretest probability.
*Modified from the ACC/AHA Exercise Testing Guidelines to reflect all age ranges.

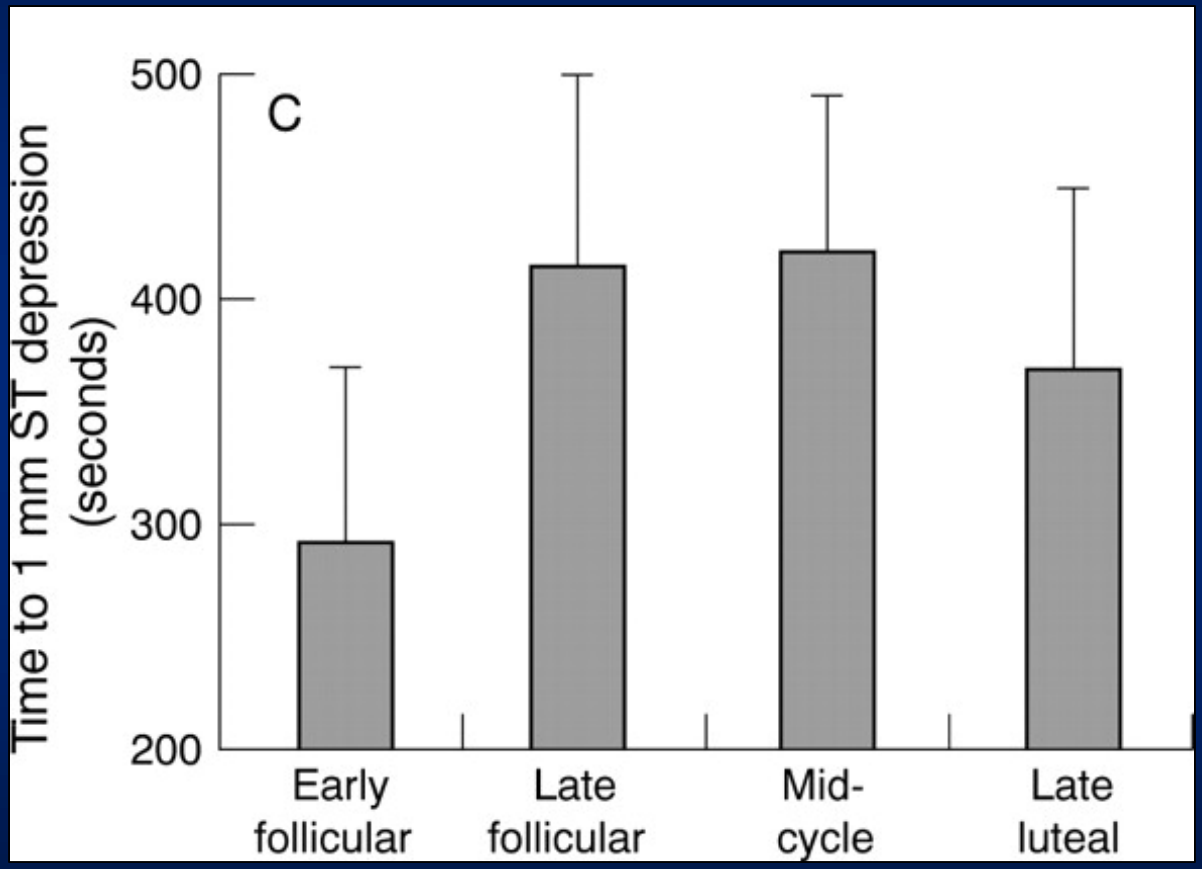
1) Substernal chest discomfort
2) Provoked by exertion or emotional stress
3) Relieved by rest or NTG

Diagnosis of CAD in women

- ECG less reliable to diagnose a heart attack
- Lesser degree of ST elevation
- ETT with lower sensitivity/specificity
  - 61%/70% vs. 68%/77% in men
  - PPV 47% vs. 77% (more false + tests)
- Baseline ECG
- ST depression does not predict prognosis

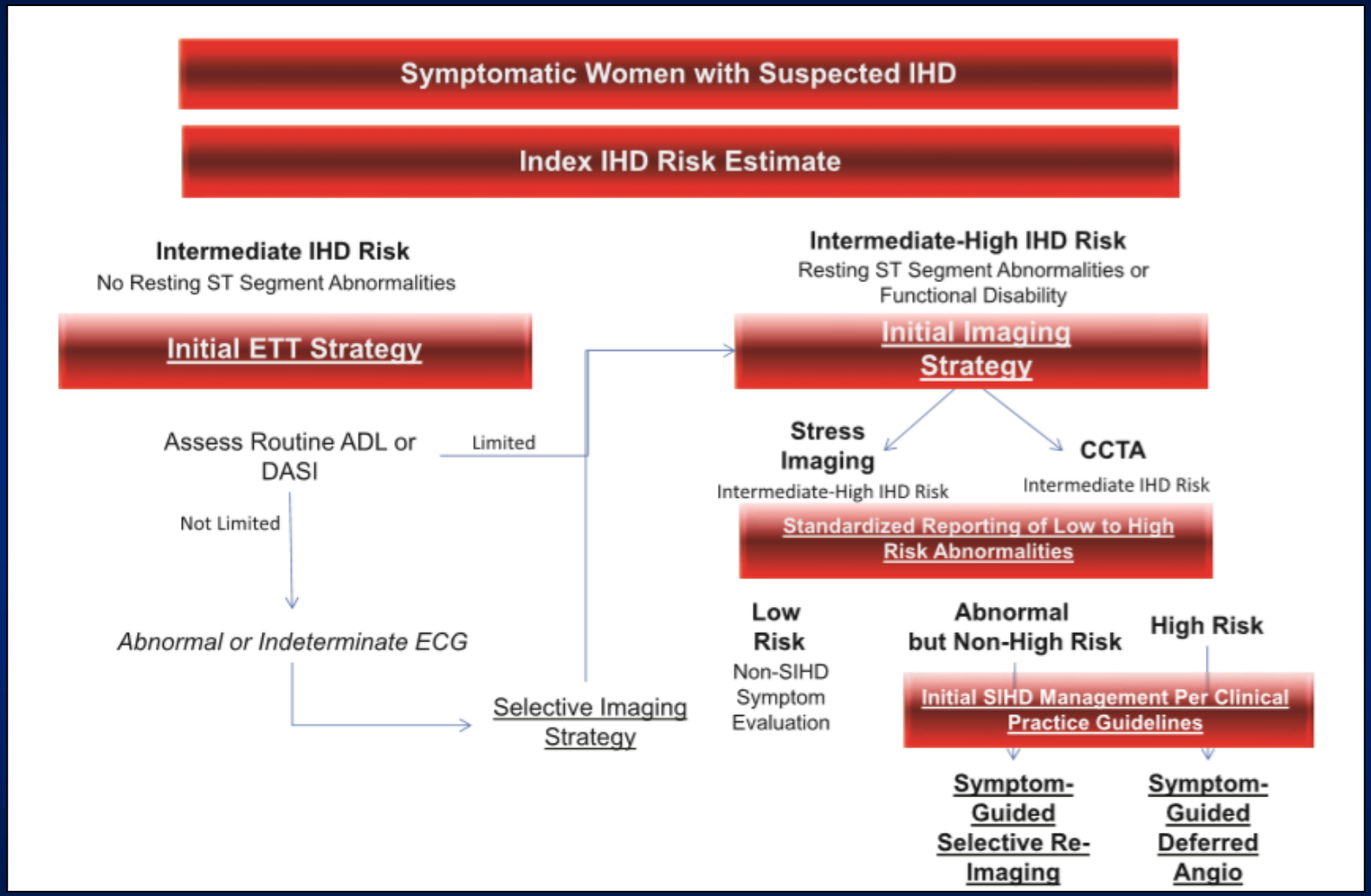
Rev Esp Cardiol. 2009;62:23-30.
Kohli & Gulati, *Circ* 2010;122:2570-2580.

Cyclic variation in ETT results in women



Lloyd, *Heart* 2000:189.

AHA Consensus Statement: Diagnostic Algorithm



Mieres, JH et al. *Circ* 2014;130:350-379.

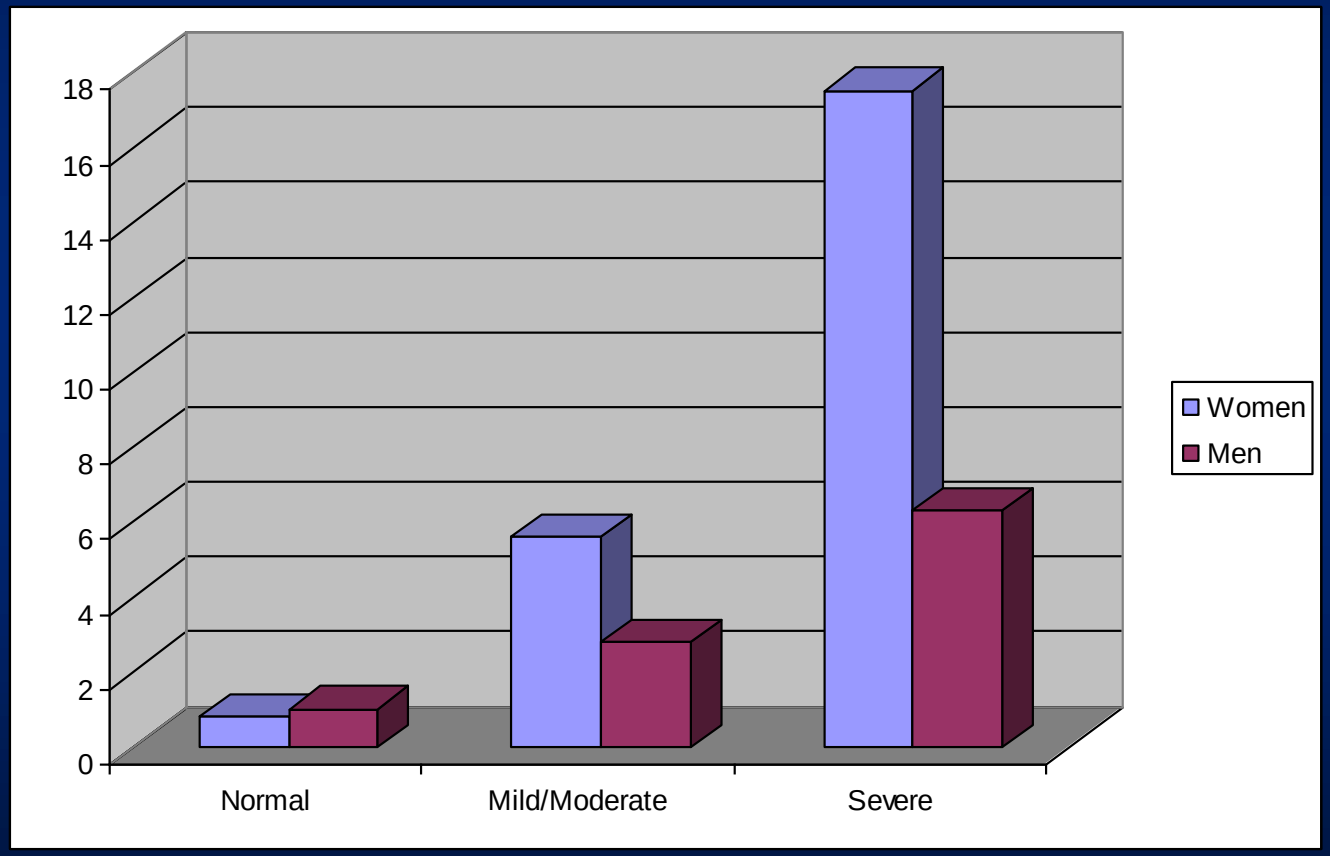
Diagnostic Testing in Women

Stress Modality	Sensitivity	Specificity	NPV	PPV
Exercise Echo	86%	90%	98	74
Exercise SPECT	80%	92%	99	87

- No significant gender differences in diagnostic accuracy of exercise echo and nuclear studies
- Breast attenuation, small LV size

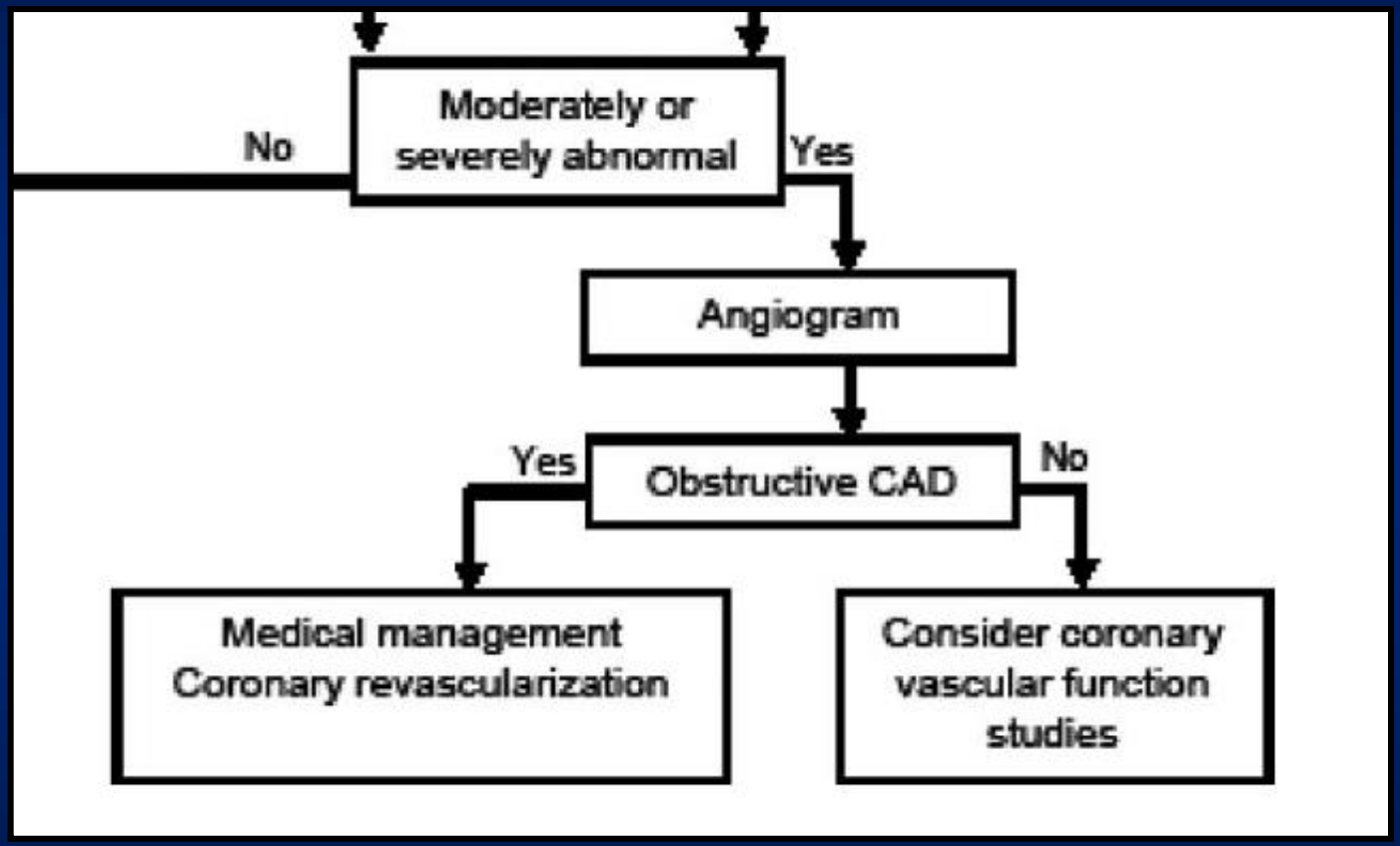
Modified from Kwok *Am J Cardiol*.1999
with data added from *JACC* 1997.

Risk stratification with exercise MPI



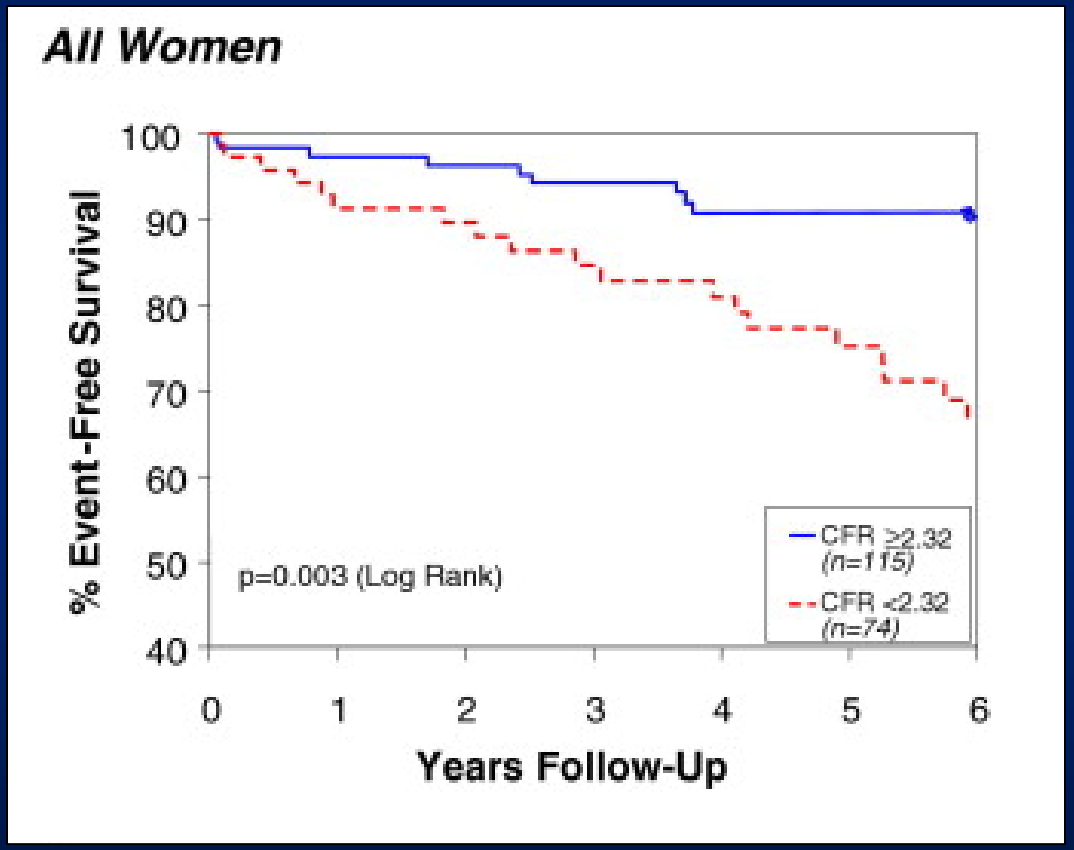
Hachamovitch *JACC* 1996;28(1):34-44.

Further studies



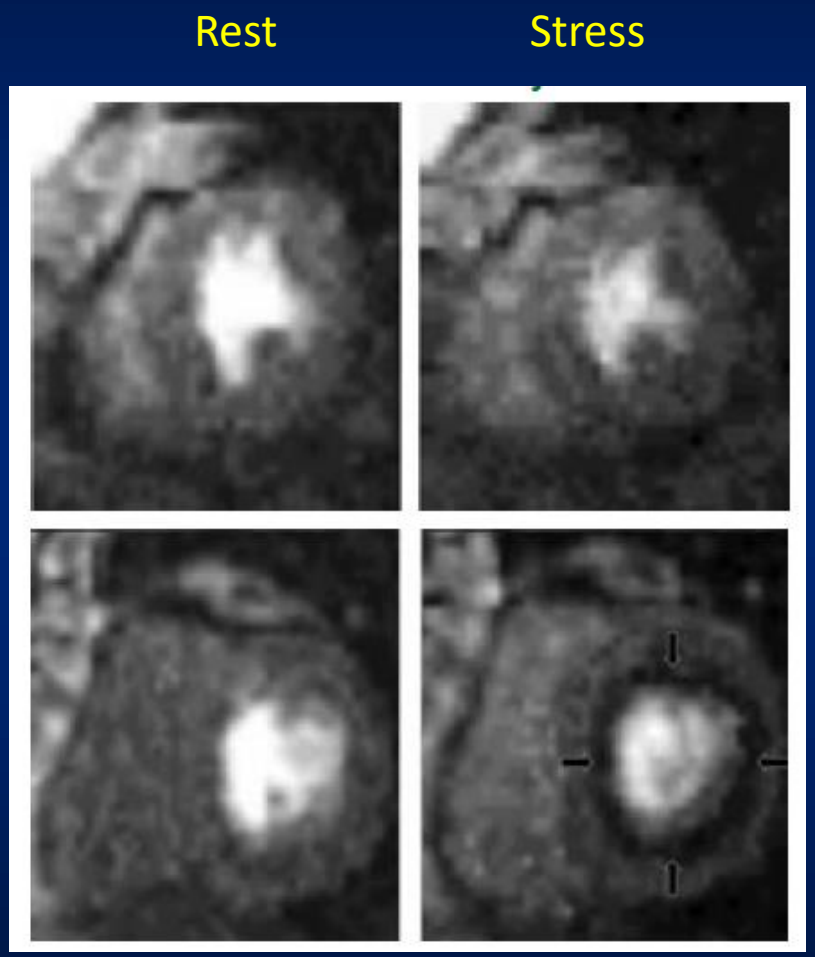
Kohli & Gulati, *Circ* 2010;122:2570-2580.

Coronary Flow Reserve Predicts Outcome in Women



Pepine et al, *JACC* 2010;55(25):2825-2832.

Stress CMR

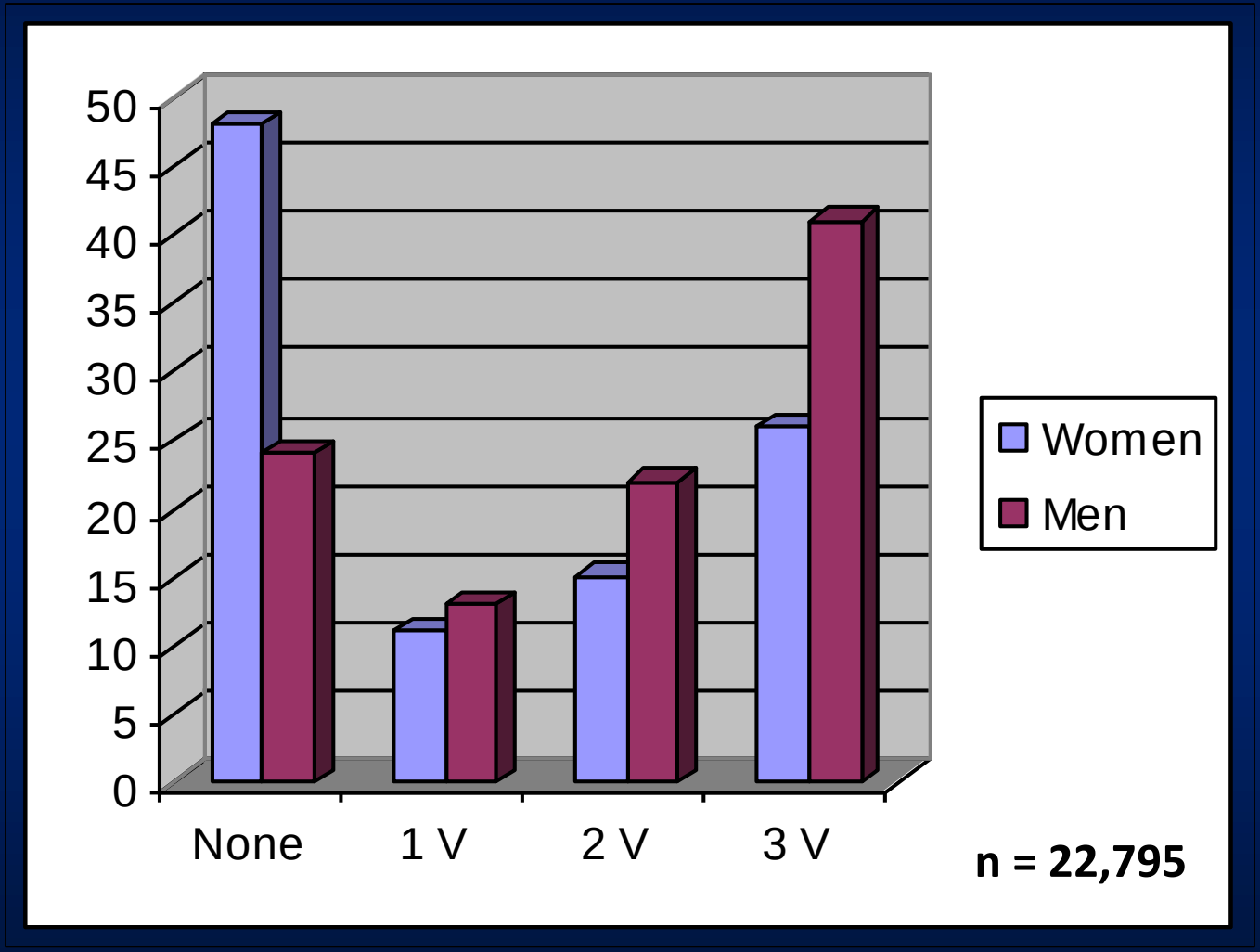


NEJM 2002;346:1948-1953.

Gender and CHD

- Differences between men and women
  - Risk Factors
  - Presentation
  - Evaluation
  - Pathophysiology
  - Treatment

Obstructive CAD



Bell, *JACC* 1995: 1650

CAD (IHD) in women

Lower:

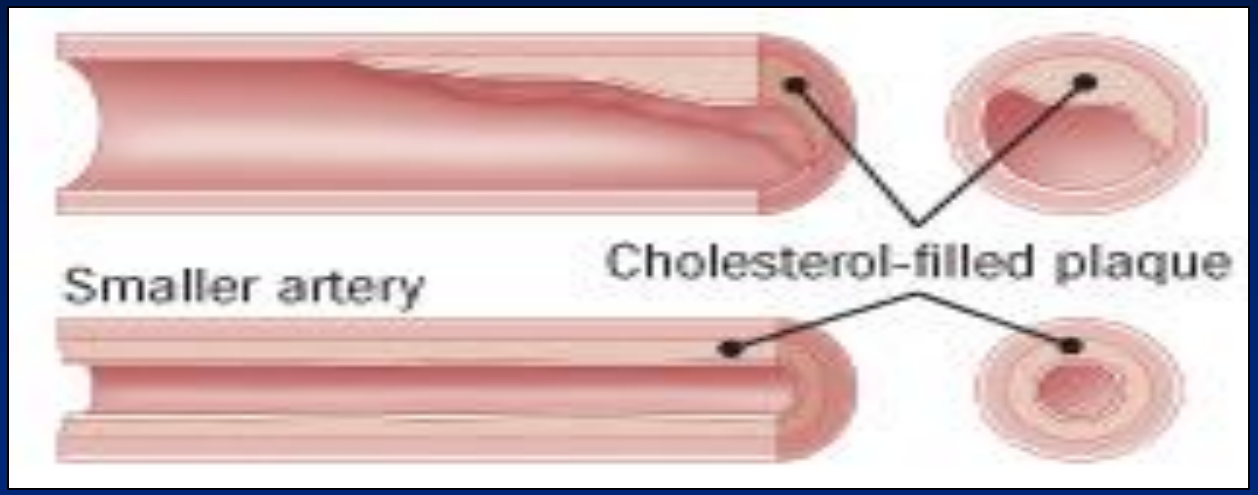
- Extent and severity of obstructive disease
- Systolic dysfunction compared to men

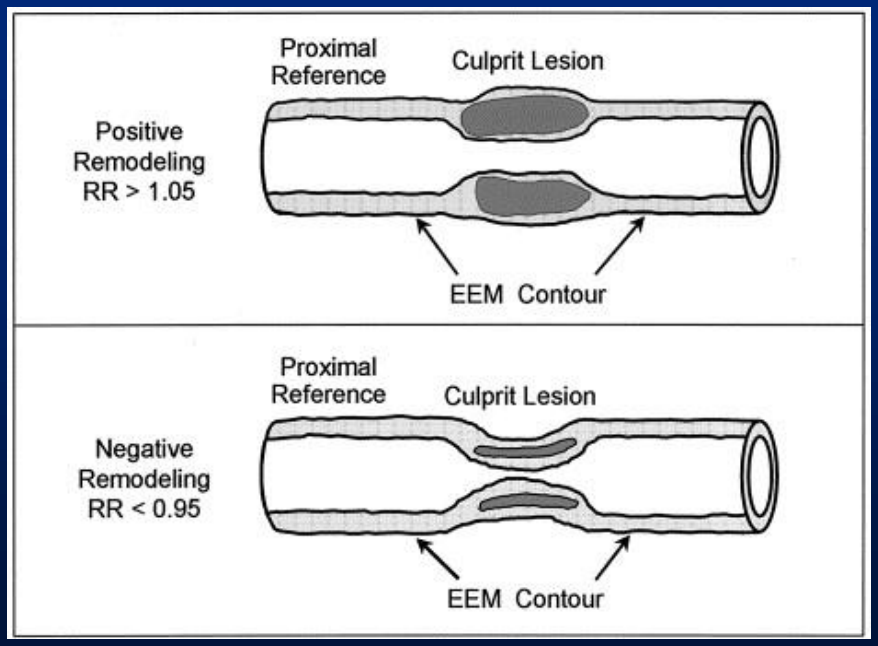
Higher:

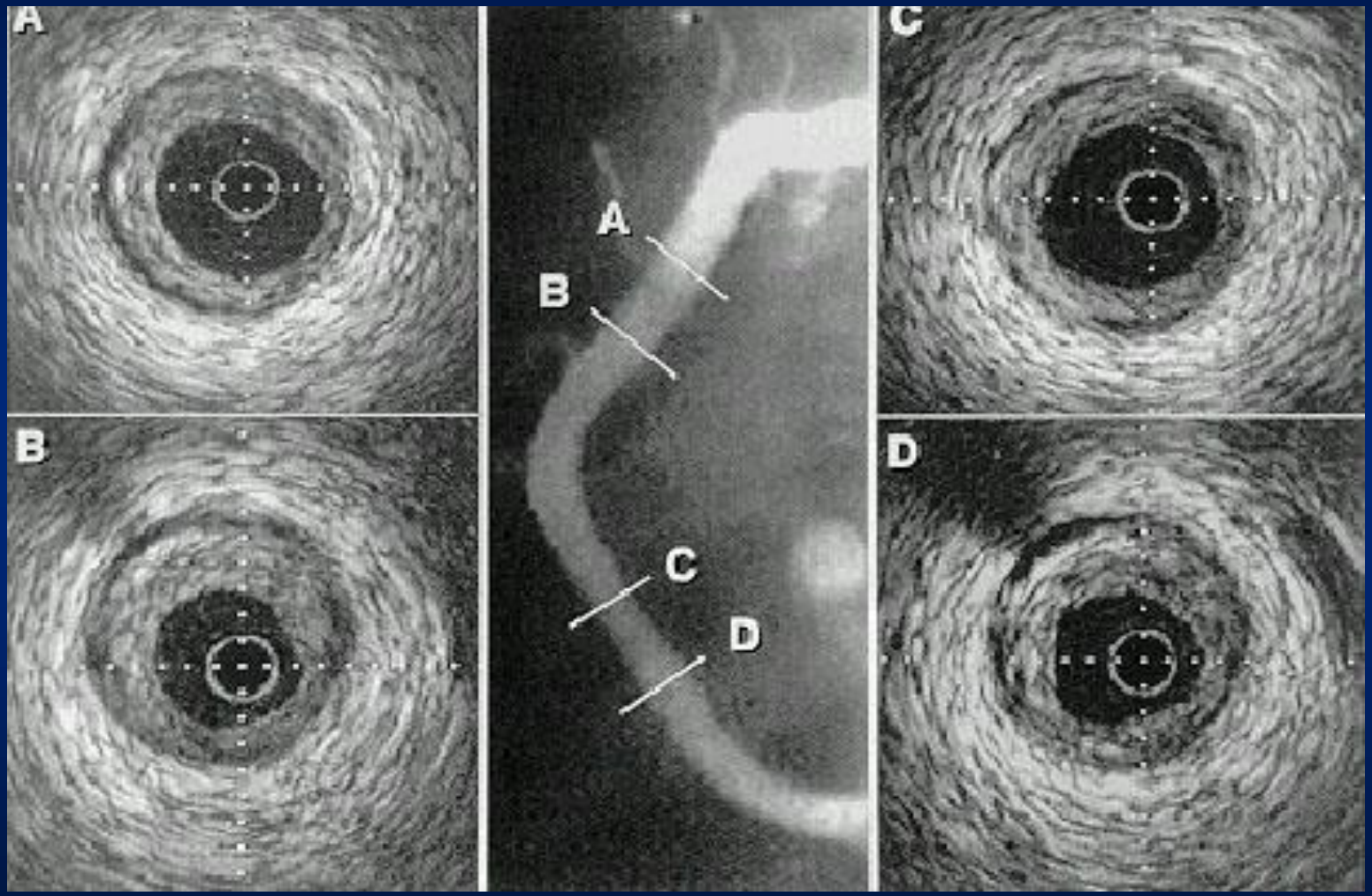
- Symptom burden
- Functional disability
- Health care needs (office visits, hospitalizations)
- Adverse outcomes

Shaw, *JACC* 2009;54:1561–75.

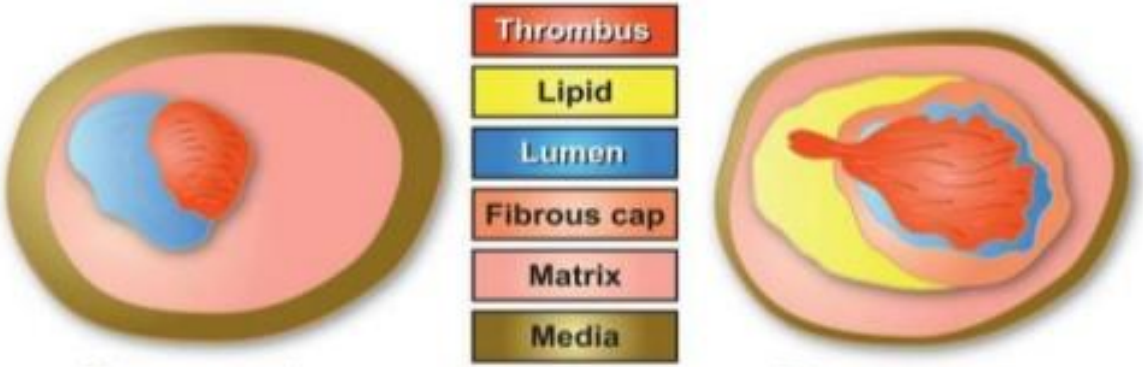
Coronary pathophysiology






A
B
C
D
A
B
C
D

Plaque Rupture and Erosion



Plaque erosion

Lipid poor
Proteoglycan and glycosaminoglycan rich
Non-fibrillar collagen breakdown
Few inflammatory cells
Endothelial cell apoptosis
Secondary neutrophil involvement
Female predominance
High triglycerides

Plaque rupture

Lipid rich
Collagen poor, thin fibrous cap
Interstitial collagen breakdown
Abundant inflammation
Smooth muscle cell apoptosis
Macrophage predominance
Male predominance
High LDL

Cardiac Syndrome X

- Different from insulin resistance syndrome X
- Aka “chest pain with normal coronary arteries” (CPNA), INOCA or microvascular angina
- Noncardiac causes of CP must be excluded
- Longer duration of chest pain
- During daily activities or mental stress
- Autonomic abnormalities
- Enhanced pain sensitivity

INOCA Mechanisms

- Hypertension
- Aortic stenosis
- Severe anemia
- Coronary spasm (Prinzmetal angina)
- Myocarditis
- Coronary anomalies
- Myocardial bridging
- Coronary microvascular dysfunction (CMD)

Bairey Merz CN et al., *Circ* 2017;135:1075-1092.

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 CN et al., *Circ* 2017;135:1075-1092.

CMD

- Abnormal endothelial function
  - ACE-I, statins, L-arginine 3 g tid or 4.5 g bid, metformin
  - Aerobic exercise, EECP
- Antianginals
  - Beta-blockers, CCBs and nitrates
  - Ranolazine, ivabradine, xanthine derivatives
- Abnormal cardiac nociception
  - Imipramine 50 mg qhs
  - Cognitive behavioral therapy, meditation

Lerman, A et al., *Circ* 1998;97:2123-8.
Pizzi C et al., *Circ* 2004;109:53-8.


Man
ON
OFF
Woman
ON
OFF

Gender and CHD

- Differences between men and women
  - Risk Factors
  - Presentation
  - Evaluation
  - Pathophysiology
  - Treatment

Gender differences & disparities

- ↓ Early ASA, beta-blockers, heparin, GPIIb-IIIa
- ↓ Catheterization and revascularization
- ↑ Vascular complications and mortality after PCI
- ↑ Operative complications with CABG
- ↑ Mortality after CABG
- ↓ Discharge ASA, β-blocker, ACE-I, statins
- ↑ Hospital stay, in-hospital mortality with MI in women vs. men (age 18-59)

Rathore SS et al., *JAMA* 2001;286:2849-56.
Jneid H et al.,*Circ* 2008;118:2803-10.
Sahil K et al, JACC 2015; 65(10S).

CVD care disparity

	Unadjusted		Adjusted*	
Exposure	OR (95% CI)	*P*	OR (95% CI)	*P*
Women vs men†	0.92 (0.89, 0.95)	<0.0001	0.92 (0.88, 0.95)	<0.0001
Black vs white‡	0.97 (0.92, 1.03)	0.29	0.95 (0.89, 1.03)	0.20
Hispanic vs white‡	1.00 (0.91, 1.10)	0.98	0.97 (0.86, 1.08)	0.53
Asian vs white‡	0.94 (0.79, 1.11)	0.46	0.90 (0.74, 1.10)	0.29

		3-Year Mortality			
		Unadjusted		Adjusted	
Exposure	Events/Person	OR (95% CI)	*P*	OR (95% CI)	*P*
Men	7807/25 989	Reference		Reference	
Women vs men*	8323/23 369	1.20 (1.15, 1.24)	<0.0001	0.99 (0.95, 1.03)	0.72

Excess mortality was modified by quality of care received

69% of the sex-mortality disparity could potentially be reduced by providing universally high-quality care

Circ Cardiovasc Qual Outcomes 2016;9:S36-S44.

Heart Disease

Conditions that present differently in women:

- Coronary artery disease
- Peripheral arterial disease

Conditions and risk factors that exclusively affect women:

- Peripartum cardiomyopathy
- Polycystic ovarian syndrome
- menopause

Conditions that disproportionately affect women:

- Microvascular angina (CMD)
- Coronary artery dissection (SCAD)
- Apical ballooning (Takotsubo's)
- Heart failure with preserved EF
- Postural orthostatic tachycardia

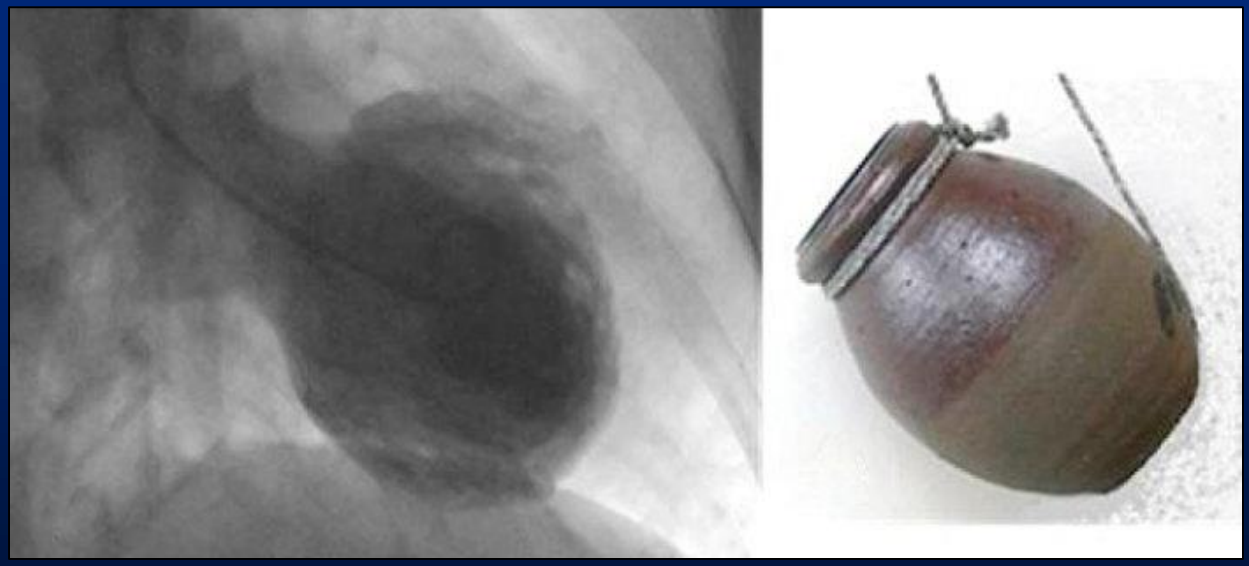
Other CVD more prevalent in women

Spontaneous Coronary Artery Dissection (SCAD)

- Presents as ACS/MI (or cardiac arrest)
- Can be difficult to dx
- “normal coronaries” or spasm
- Associated with systemic fibromuscular dysplasia (FMD)

Takotsubo Cardiomyopathy

- Aka stress-induced cardiomyopathy, apical ballooning or broken heart syndrome
- ACS or CHF, ECG changes, troponin elevation
- Complete recovery within 1 month



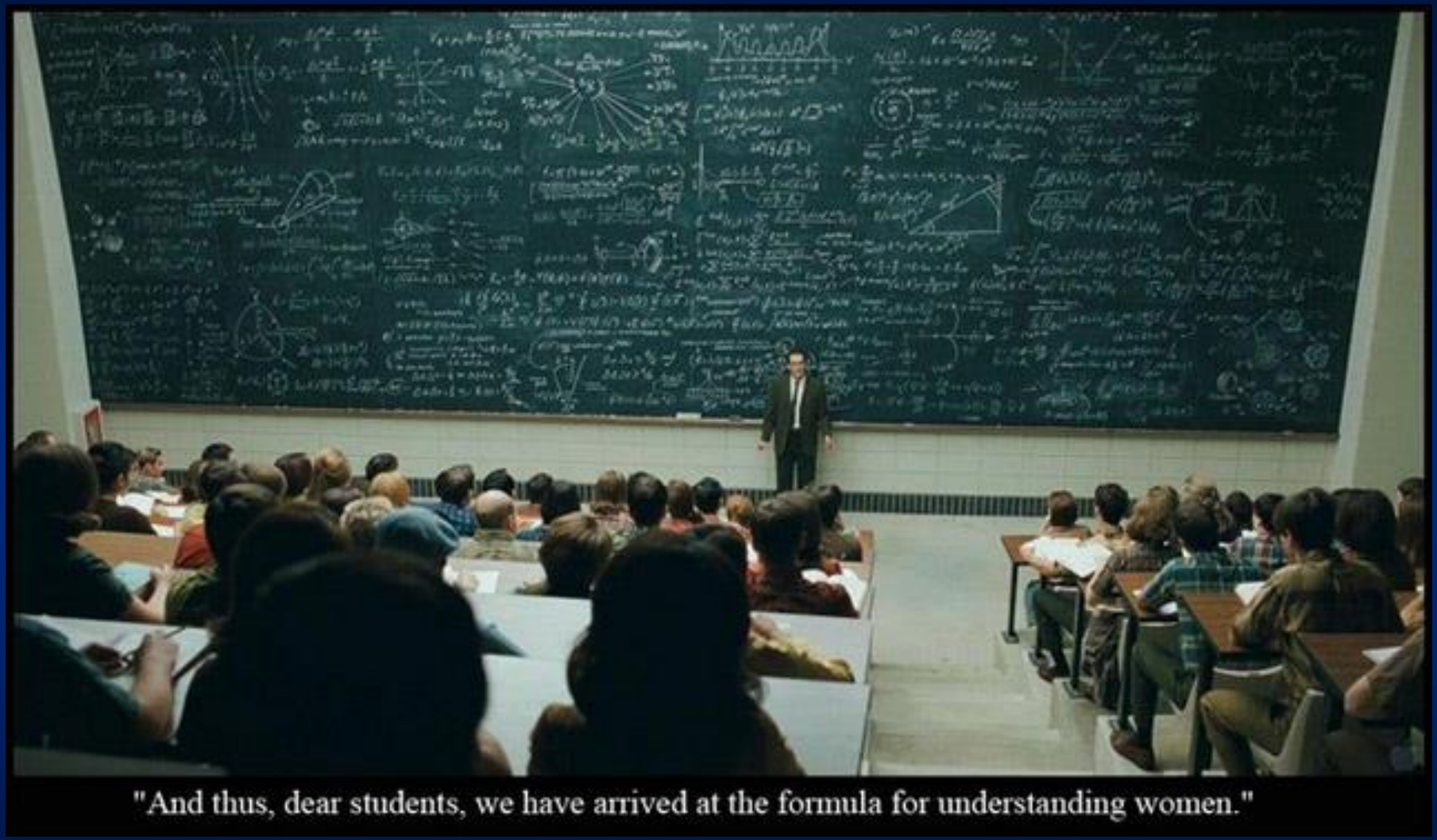
HFpEF

- Women are ~2x more likely to develop HFpEF
- Increase in ventricular and vascular stiffness with age is more dramatic in women
- Higher prevalence of hypertension
- More concentric LV remodelling and less ventricular dilatation in response to HTN than men

Curr Opin Cardiol 2011 Nov;26(6):562-8.

Conclusions

- Women have different risk factors and clinical CVD syndromes
- Traditional evaluation focuses on detection of focal stenosis and may fail to identify women at risk
- New algorithms and non-invasive tests may help improve risk stratification and diagnosis
- Outcomes may be improved simply by universal application of proven therapies
- More research is critical to better understand and treat heart disease in women


"And thus, dear students, we have arrived at the formula for understanding women."

Thank you

Susie.Woo@virginiamason.org
Virginia Mason Medical Center
Heart Institute