

# RISKS AND GENDER-SPECIFIC DIFFERENCES OF WOMEN'S HEART HEALTH

American Heart Association  
Kansas City Cardiac Symposium  
November 5, 2020



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# OBJECTIVES

- Understand disparities of diagnosis and management of cardiovascular disease in women
- Raise awareness of unique risk of cardiovascular disease affecting women
- Identify potential social barriers, biochemical and physiological differences
- Identify emerging treatment and therapeutic options

# American Heart Association®

- Designed to spread awareness cardiovascular (CV) disease impact on women
- Only 55% of women realize heart disease is most likely cause for death
- CV disease claims 1 in 3 deaths
- Encourages involvement in outreach through education and research

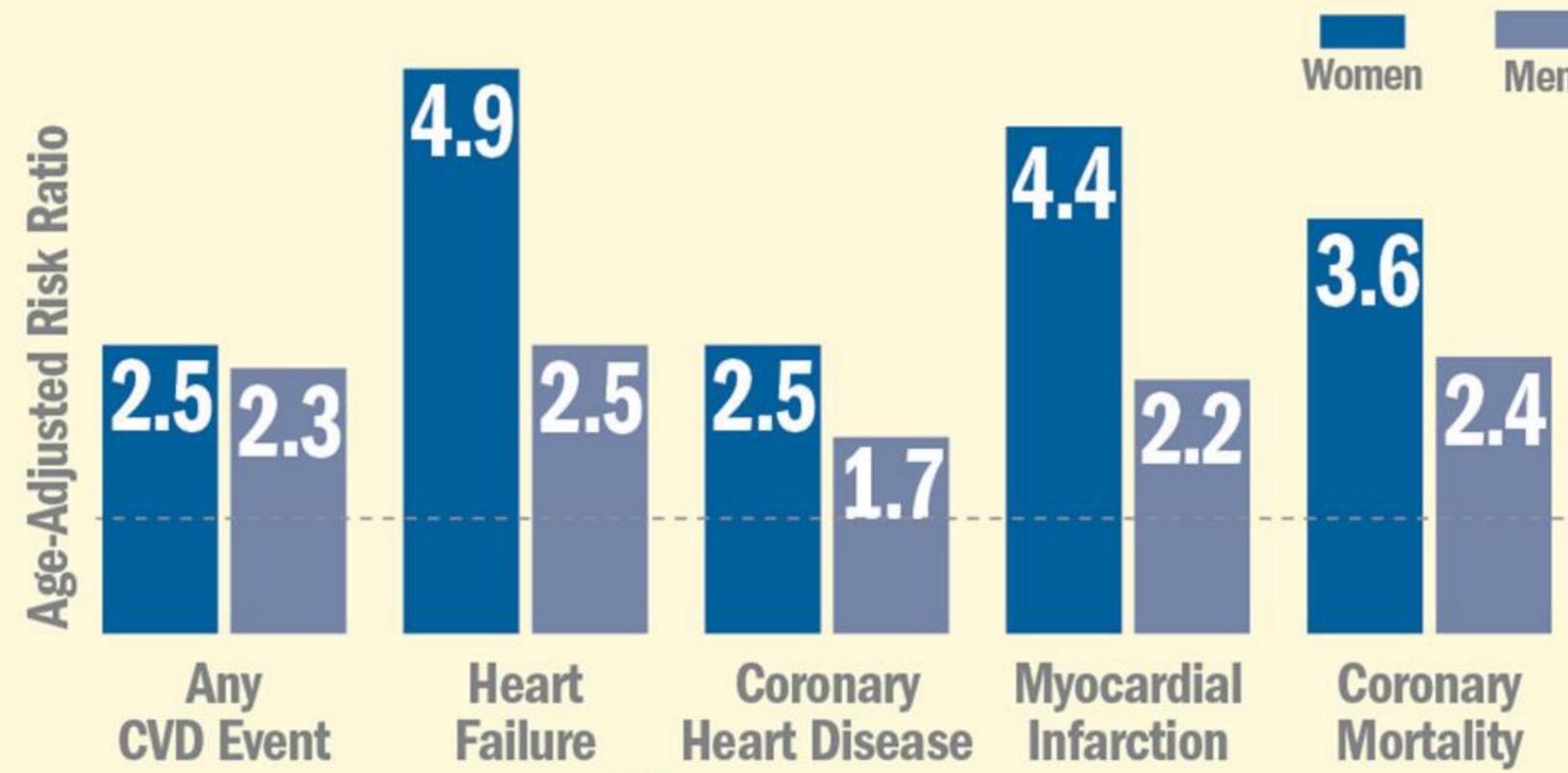


# 1 in 3 deaths

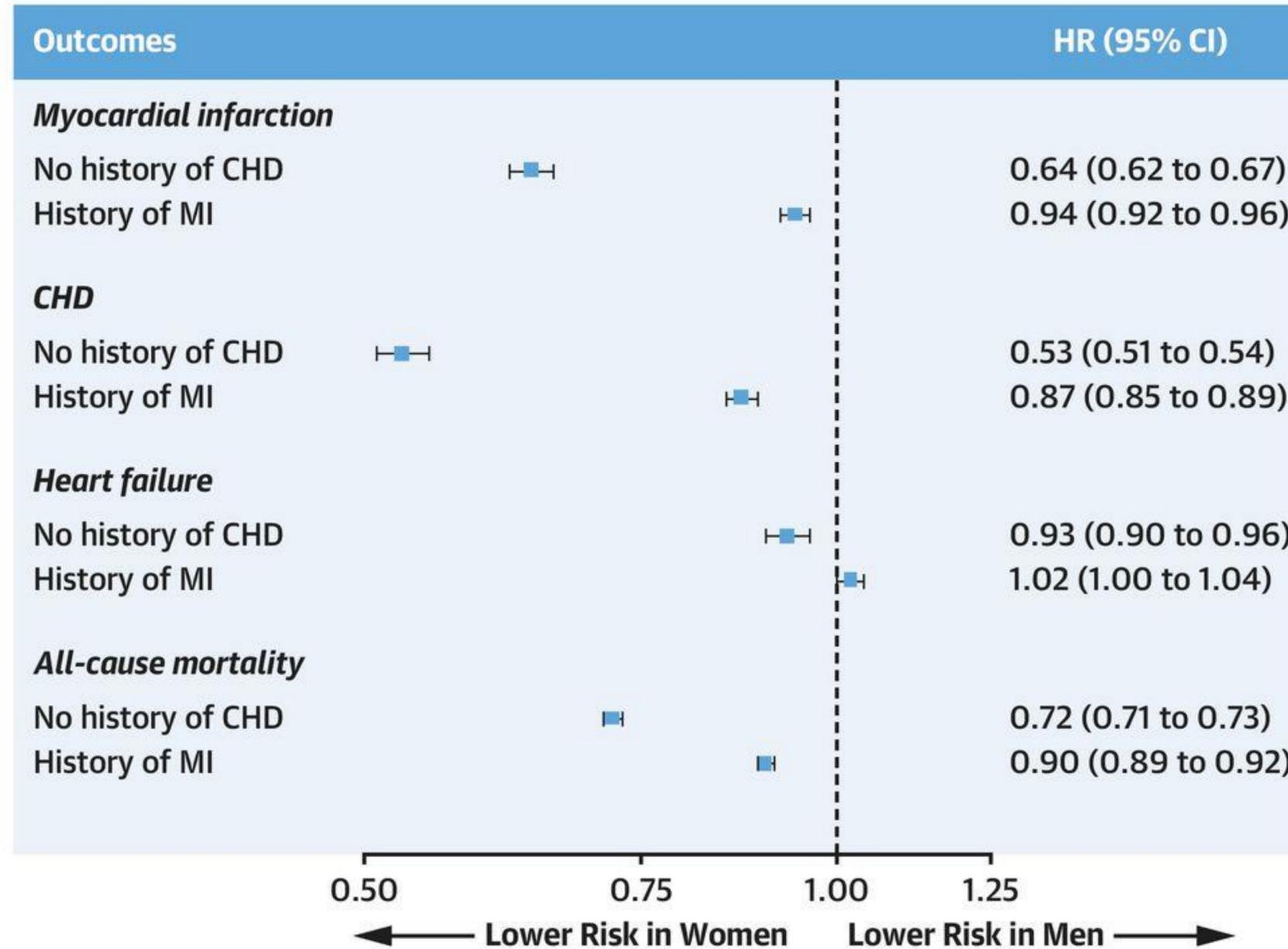
- Cardiovascular disease claims 1 in 3 women in the United States
  - More deaths from cardiovascular disease than all cancers combined
- Historically, women under represented in cardiovascular research and drug trials
- Unique factors contribute to healthcare disparity
  - Biochemical/anatomical
  - Socioeconomic
  - Different health/disease states

**FIGURE 2**

## Relative Risk of Cardiovascular Events in Men and Women With Diabetes

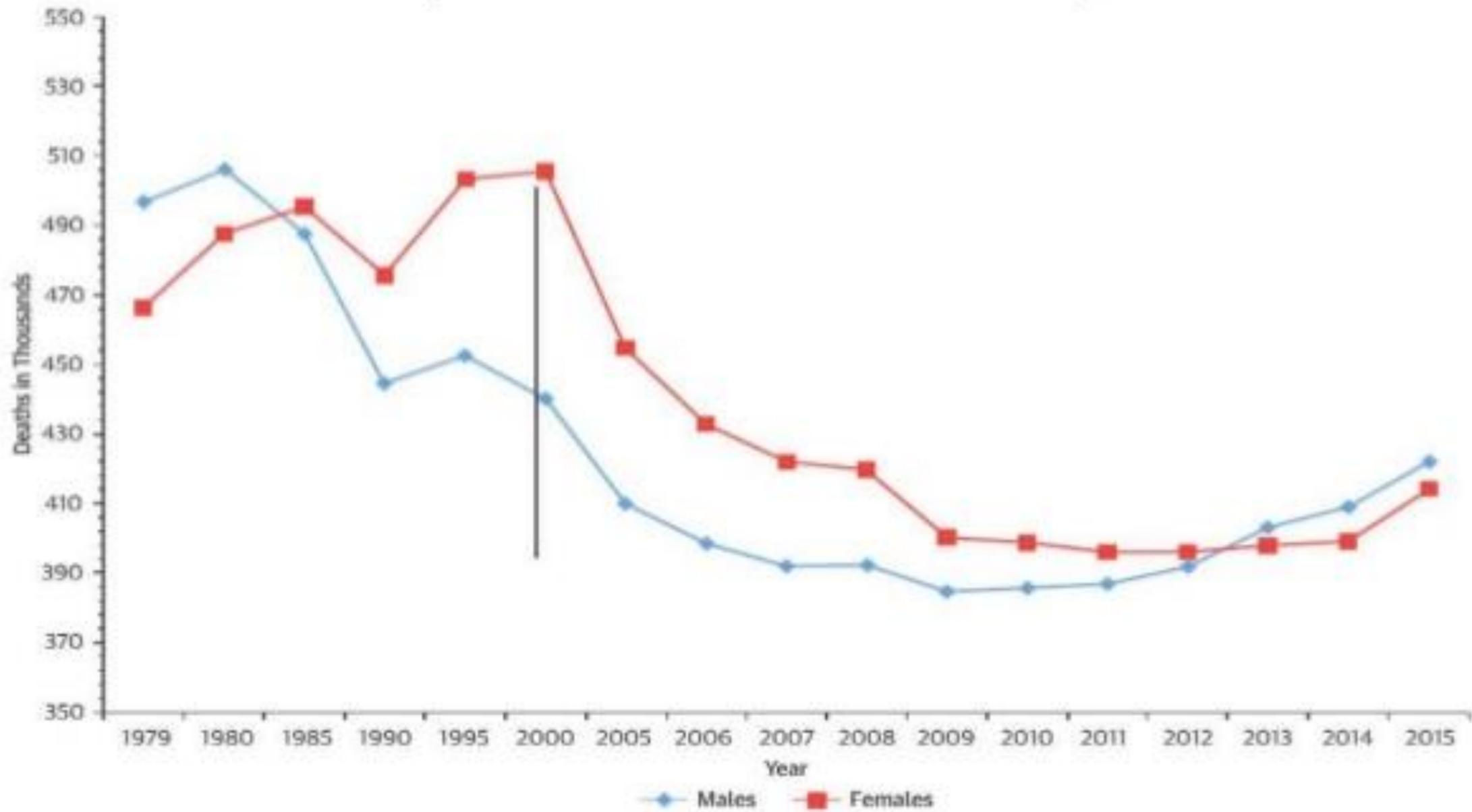


**CENTRAL ILLUSTRATION: Women-to-Men Hazard Ratios for Myocardial Infarction, Coronary Heart Disease, Heart Failure, and All-Cause Mortality Among Beneficiaries Without a History of Coronary Heart Disease and Among Beneficiaries With a Previous Myocardial Infarction**



Peters, S.A.E. et al. J Am Coll Cardiol. 2020;76(15):1751-60.

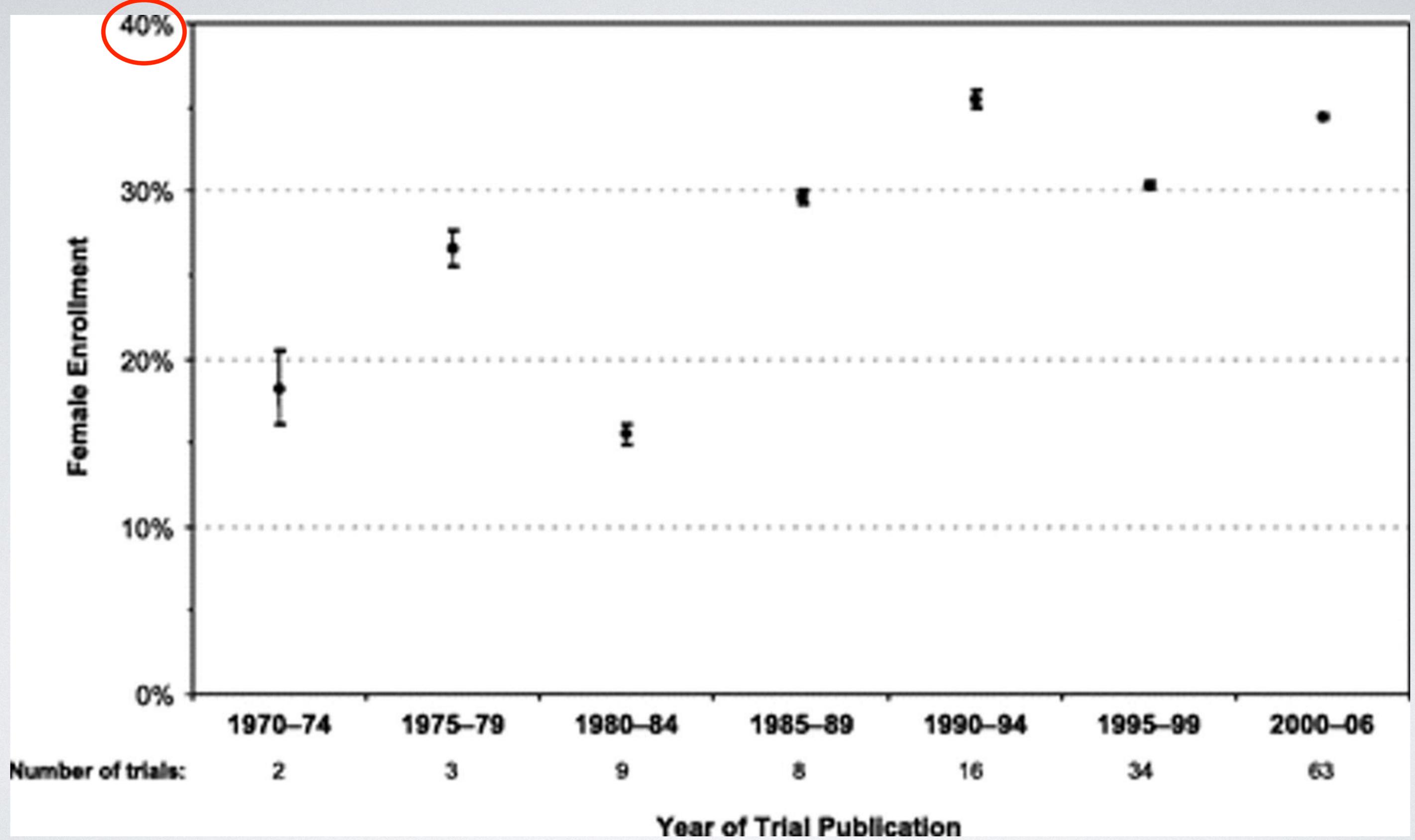
## CVD Mortality Trends for Males and Females (United States 1979-2015)

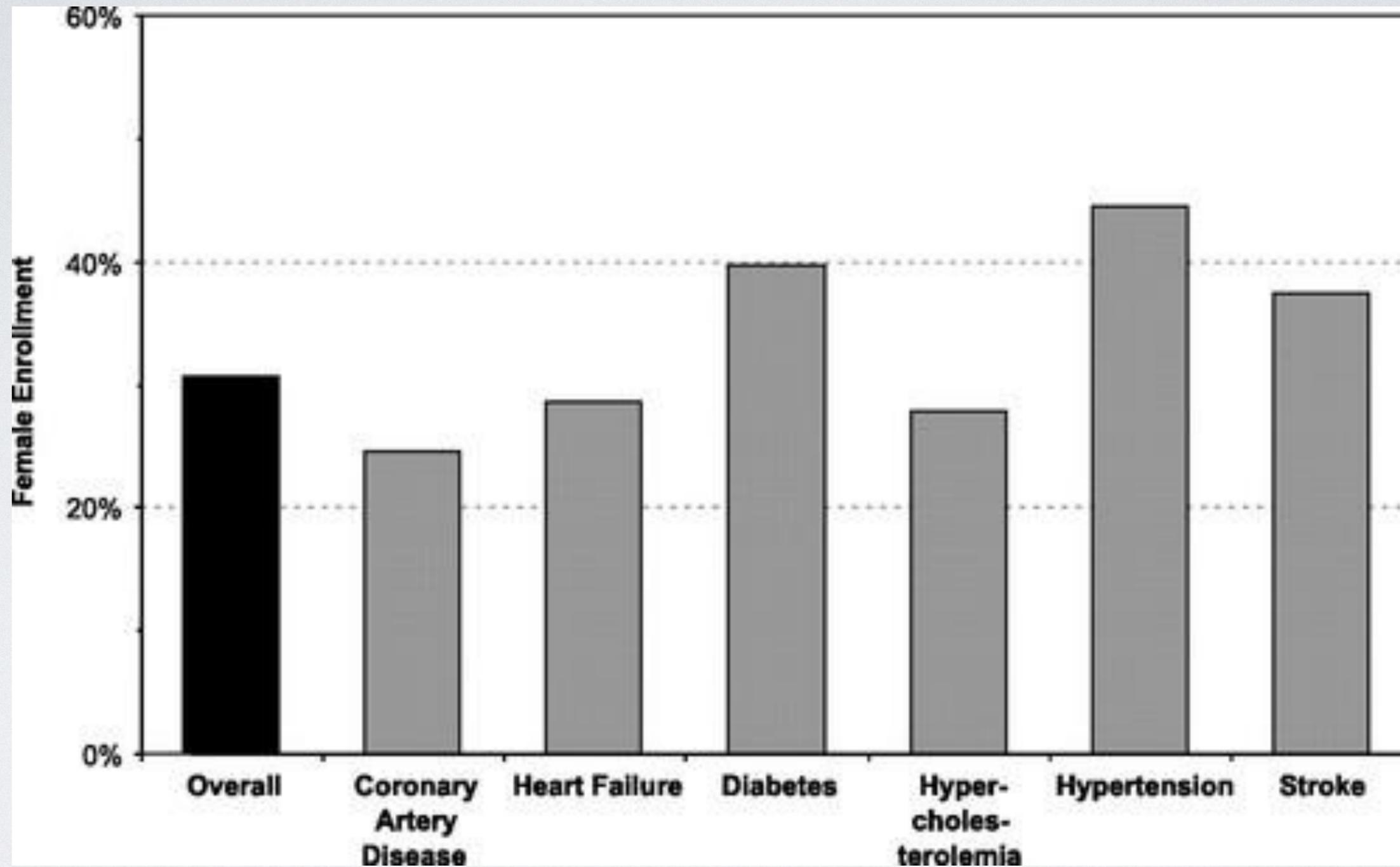


Benjamin, et al. Heart disease and stroke statistics - 2018 update. Circulation. 2018;129:e67-492

# INITIATIVES AFFECTING WOMEN AND CARDIOVASCULAR DISEASE

- (1948: Framingham Heart Study commissioned by Congress)
- 1986: NHLBI publishes proceedings of Coronary Heart Disease in Women: Reviewing the Evidence, Identifying the Needs
- 1992: American Heart Association publishes the first scientific statement on women and CVD
- 1994: NIH guidelines state that women are to be included in all human subject research and that valid analyses of differences in intervention effects are to be conducted; cost is not an allowable reason for exclusion, and recruitment outreach programs are initiated and supported
- 1999: AHA publishes the first women-specific clinical recommendations for prevention of CVD, “A Guide to Preventive Cardiology in Women”
- 2004: AHA publishes first evidence-based guidelines for preventing CVD in women



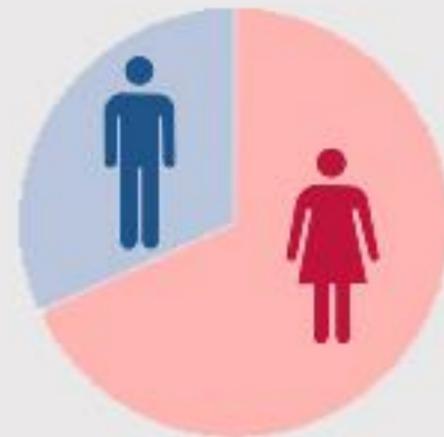


# NHLBI Heart Research: Fiscal Year 2013

*The NHLBI's research portfolio supports a range of research on women's health and ensures that women are represented in clinical trials.*



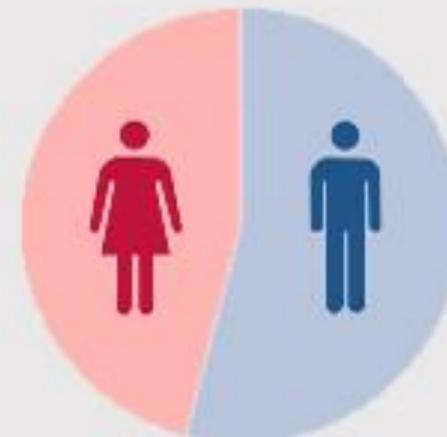
## Percent of Men and Women Enrolled in NHLBI Cardiovascular Trials



Including the Women's  
Health Initiative

**68.2% Women**

**31.8% Men**



Excluding the Women's  
Health Initiative

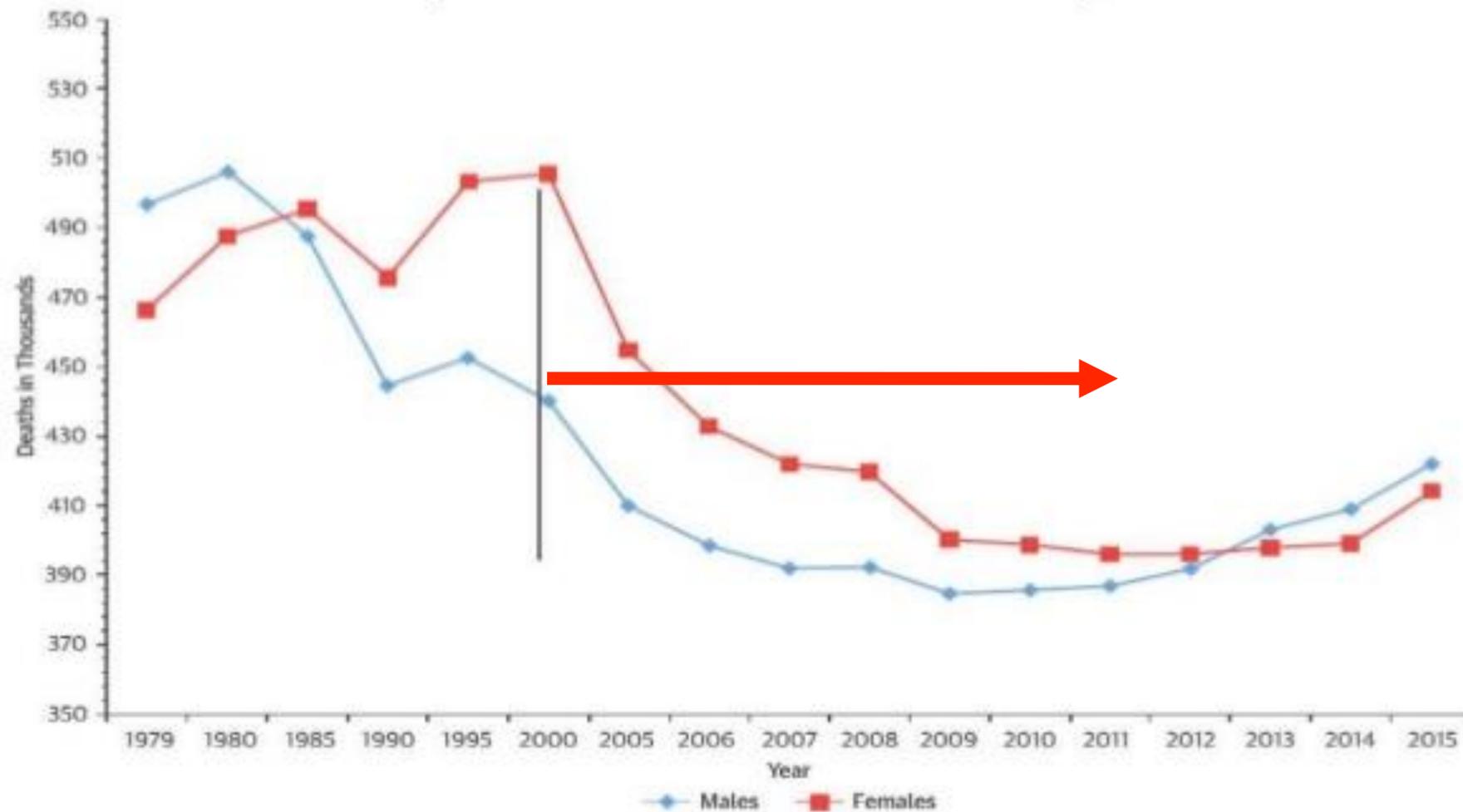
**45.9% Women**

**54.1% Men**

**CENTRAL ILLUSTRATION: Participation of Women of CVD Clinical Trial: Prevalence-Corrected Estimate**

Acute Coronary Syndrome  
 Atrial Fibrillation  
 Atrial Fibrillation\*  
 Coronary Artery Syndrome  
 Heart Failure  
 Heart Failure†  
 Hypertension  
 Pulmonary Hypertension

**CVD Mortality Trends for Males and Females (United States 1979-2015)**



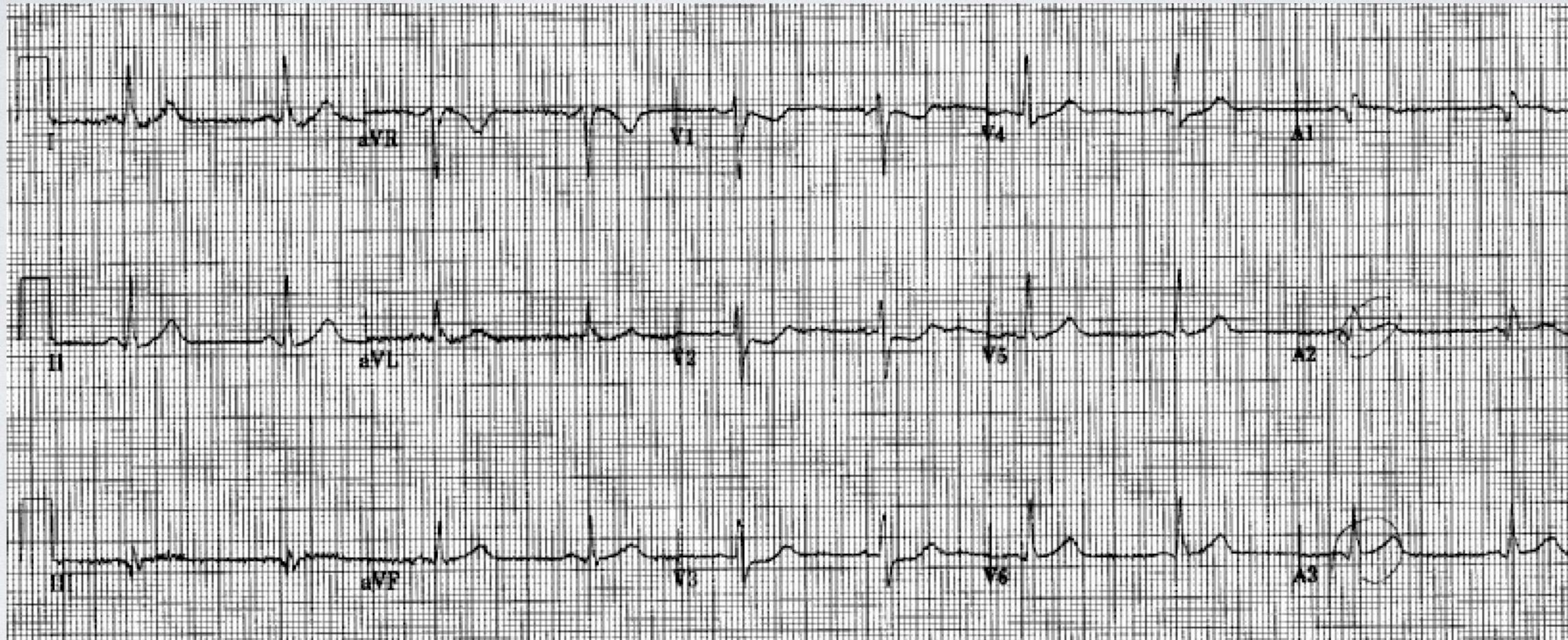
Benjamin, et al. Heart disease and stroke statistics - 2018 update. Circulation. 2018;129:e67-492

Scott, P.E. et al. J Am Coll Cardiol. 2018;71(18):1960-9.

# CASE 1: 68 YEAR OLD F

- 65 YEAR OLD FEMALE WITHOUT PRIOR KNOWN HISTORY OF CORONARY DISEASE PRESENTS TO ED AFTER MVA FOR EVALUATION
  - DENIED ACUTE SYMPTOMS ASIDE FROM BEING “SHOOK UP” AFTER ACCIDENT
    - NAGGING HEARTBURN, NO NAUSEA, NO CHEST PAIN. “BURNING QUALITY” TO EPIGASTRIUM
  - INSISTENT ON DISMISSAL FROM ED TO CARE FOR HUSBAND
  - REPORTS BEING TREATED WITH PANTOPRAZOLE BY PCP IN LAST 2 WEEKS FOR INTERMITTENT REFLUX WITH SIMILAR QUALITY DISCOMFORT

# CASE 1: 68 YEAR OLD F

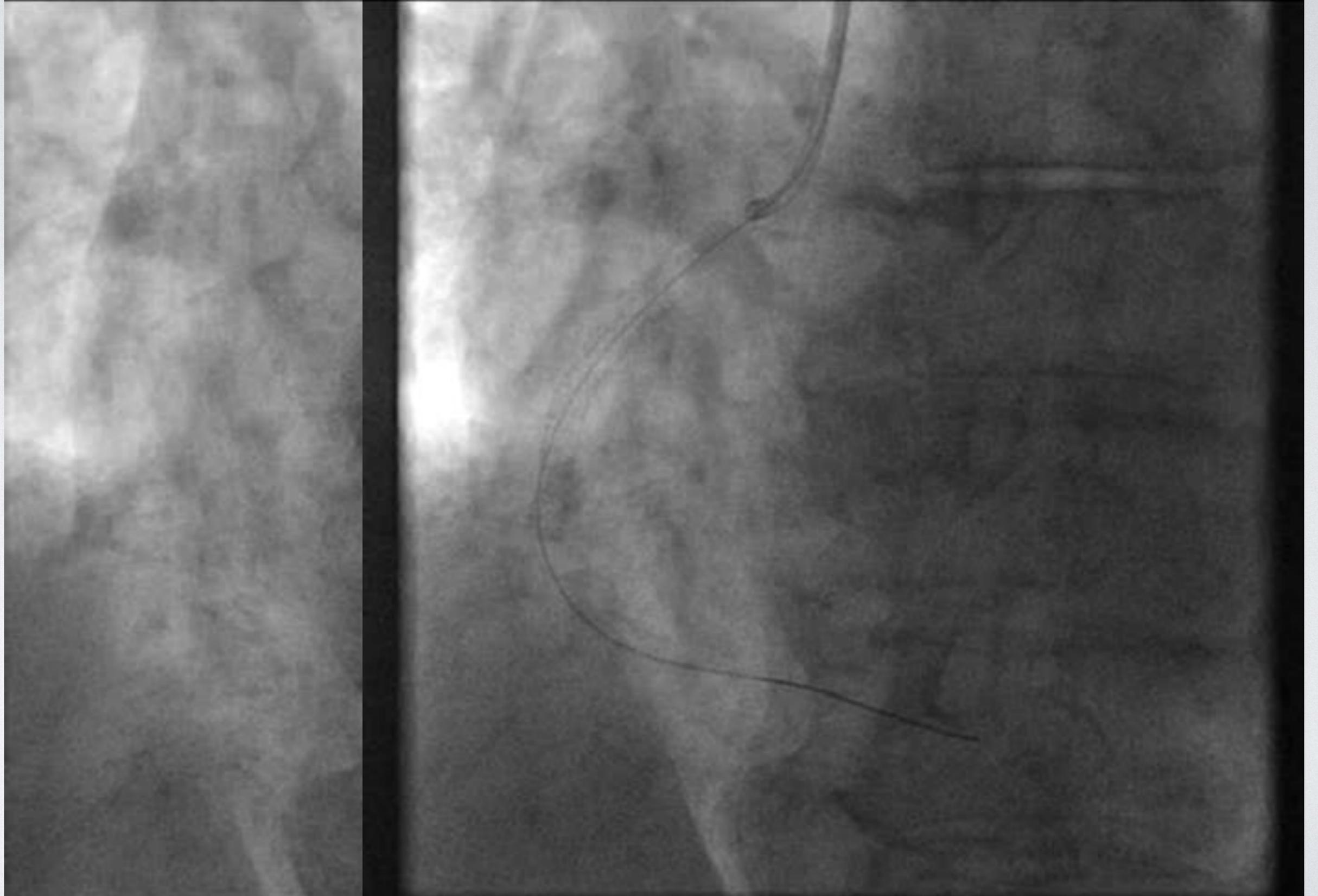


	16:07	17:44	22:19	00:00	04:58	13:17
<b>Cardiac Markers</b>						
<input type="checkbox"/> Troponin T QuaNT High Sensitivity	* C 508	* C 621	* C 715	* C 809	* C 876	* C 898
<input type="checkbox"/> pro BNP	* H 5548					

Lossy compression - not intended for diagnosis



Lossy compression - not intended for diagnosis



# REPRESENTATION

- Through more inclusive research studies and promotion of cardiovascular event risk, women's heart disease process better represented
  - “Unique” physiological differences
- Allows for alternate symptom identification during acute coronary syndrome and stroke
- Results in better treatment, outcomes, and recognition of disparity in disease management

# GENDER DIFFERENCES: PRESENTATION

- Chest pain (“classic angina”) less likely in women
  - More common: shoulder or jaw pain, arm or back pain, nausea, or breathlessness
- Stroke
  - Nonfocal symptoms
- Result
  - Delayed diagnosis
  - Increased morbidity and mortality

# SYMPTOM PRESENTATION

**Heart Attack**  
Signs and Symptoms

*Heavy chest pain*

*Cold and sweaty*

*Pain in neck or left arm*

*Nausea*

*Sudden onset of symptoms*

*Short of breath*

*More tired than usual*

*Flu-like symptoms*

*Feelings of indigestion or heartburn*

*Symptoms for a number of days*

*Heartburn*

Men and Women

Women

# STROKE SYMPTOMS: WOMEN VS. MEN

Men and women share a common set of stroke symptoms. But women also can experience more subtle warning signs.

## WOMEN

Face drooping



Arm weakness



Speech difficulty



Vision problems



Trouble walking  
or lack of  
coordination



Severe headache  
without a  
known cause



General weakness



Disorientation &  
confusion or  
memory problems



Fatigue



Nausea or  
vomiting



## MEN

Face drooping



Arm weakness



Speech difficulty



Vision problems



Trouble walking  
or lack of  
coordination



Severe headache  
without a  
known cause



American Heart Association®



**Table 1. Acute Coronary Syndrome Presentation Without Chest Pain or Discomfort According to Sex—Summary of Studies From Large Cohorts**

Source	Study Characteristic							Proportion Without Chest Pain, %		
	Study Description	Patient Population	Study Years	Sample Size	Mean Age, y	Age Adjusted	Race Adjusted	Proportion Without Chest Pain, %		
								Men	Women	All
Brieger et al, <sup>37</sup> 2004	GRACE Registry	ACS	1999-2002	20 881	65.8	Yes	No	7.3	10.6	8.4
Canto et al, <sup>8</sup> 2000	National MI Registry	MI	1994-1998	434 877	69.3	Yes	Yes	28.6	38.6	32.7
Canto et al, <sup>38</sup> 2002	Alabama UA Registry	UA	1993-1999	4167	72.3	Yes	Yes	50.2	53.0	51.7
Culi et al, <sup>39</sup> 2002	CCUs Croatia	MI	1990-1995	1996	58.8	Yes	No	12.4	20.3	14.8
Dorsch et al, <sup>7</sup> 2001	United Kingdom	MI	1995	2096	70.6	Yes	No	17.6	24.6	20.1
Goldberg et al, <sup>40</sup> 1998	Worcester MI Study	MI	1986-1988	1360	67.7	Yes	No	18.0	23.0	20.0
Milner et al, <sup>41</sup> 2004	Worcester MI Study	MI	1997-1999	2073	70.2	Yes	No	30.9	45.8	37.3
Roger et al, <sup>42</sup> 2000	Olmsted County, Minnesota	UA	1985-1992	2271	63.0	Yes	No	25.0	19.0	22.0
Stern et al, <sup>43</sup> 2004	26 Hospitals, CCU, Israel	ACS	2000	2113	64.9	Yes	No	18.7	29.7	21.7
Cumulative	...	...	...	...	...	...	...	27.4 (76 036 of 276 933)	37.5 (73 003 of 194 797)	31.6 (149 039 of 471 730)

Abbreviations: ACS, acute coronary syndrome; CCU, coronary care unit; MI, myocardial infarction; UA, unstable angina.

# DIFFERENCES: MYOCARDIAL INFARCTION

- Women with STEMI have significant delays in presentation and revascularization with a higher 30-day mortality compared with men
  - Symptom to door time was 4x higher in women
  - Door to balloon time was longer in women
  - 30 day mortality was higher for women

# DIFFERENCES: MYOCARDIAL INFARCTION

- Post-ACS (NSTEMI, STEMI) observational studies show consistent underuse of guideline-recommended therapies among women compared with men
  - Women with nonobstructive CAD and MI are less likely to be prescribed medications for secondary prevention of MI
  - Results in increased rates of readmission, reinfarction, and death in the first year after MI

# DIFFERENCES: MYOCARDIAL INFARCTION

- Although referral to CARDIAC REHAB is designated as a performance measure of healthcare quality after AMI, 307,308 CR has failed to reach >80% of eligible women in the last 3 decades!
- Eligible women more likely to include uninsured, unmarried, socioeconomically disadvantaged, smokers, depressed, obese, sedentary, elderly, and nonwhite, less education, less social support, and competing family obligations
- Depressive symptoms are linked to suboptimal CR attendance
- Evidence suggests that CR exercise training improves depression in women

# DIFFERENCES: STROKE

- Increased stroke severity and mortality in women
  - Poorer functional outcome after acute ischemic stroke (22.7% of women are fully recovered by 6 months vs. 26.7% of men)
  - Women are less likely than men to be discharged home after a stroke admission (40.9 vs. 50.6%)
  - Women 10% less likely to be admitted to the hospital within the first 3 h of stroke onset than men
  - Women 13% less likely to receive tPA

# DIFFERENCES: HEART FAILURE

- Meta-analysis of 10 years, 43 studies
- Women less likely to undergo invasive procedures like heart catheterization
- Less use of aspirin, statins, and ACE-inhibitors
- More likely to undergo therapy or testing for secondary prevention

# DIFFERENCES: HEART FAILURE

Heart failure trials: number and percent of women enrolled in each and LVEF for entry

Study	% Women	No. of Women	LVEF
A-HeFT	40	420	≤35%
CHARM–Overall	32	2400	Any
CHARM–Preserved	40	1212	>40%
CIBIS II	19	515	≤35%
COMPANION	32	493	≤35%
CONSENSUS	30	75	Unknown
COPERNICUS	20	469	<25%
DIG	22	1520	≤45%
ELITE-I	33	240	≤40%
ELITE-II	31	966	≤40%
MADIT II	16	192	≤30%
MERIT-HF	23	898	≤40%
MIRACLE	32	145	≤35%
PARADIGM	22	1832	≤40%
RALES	27	446	≤35%
SCD HeFT	23	588	≤35%
SOLVD-Prevention	11	484	≤35%

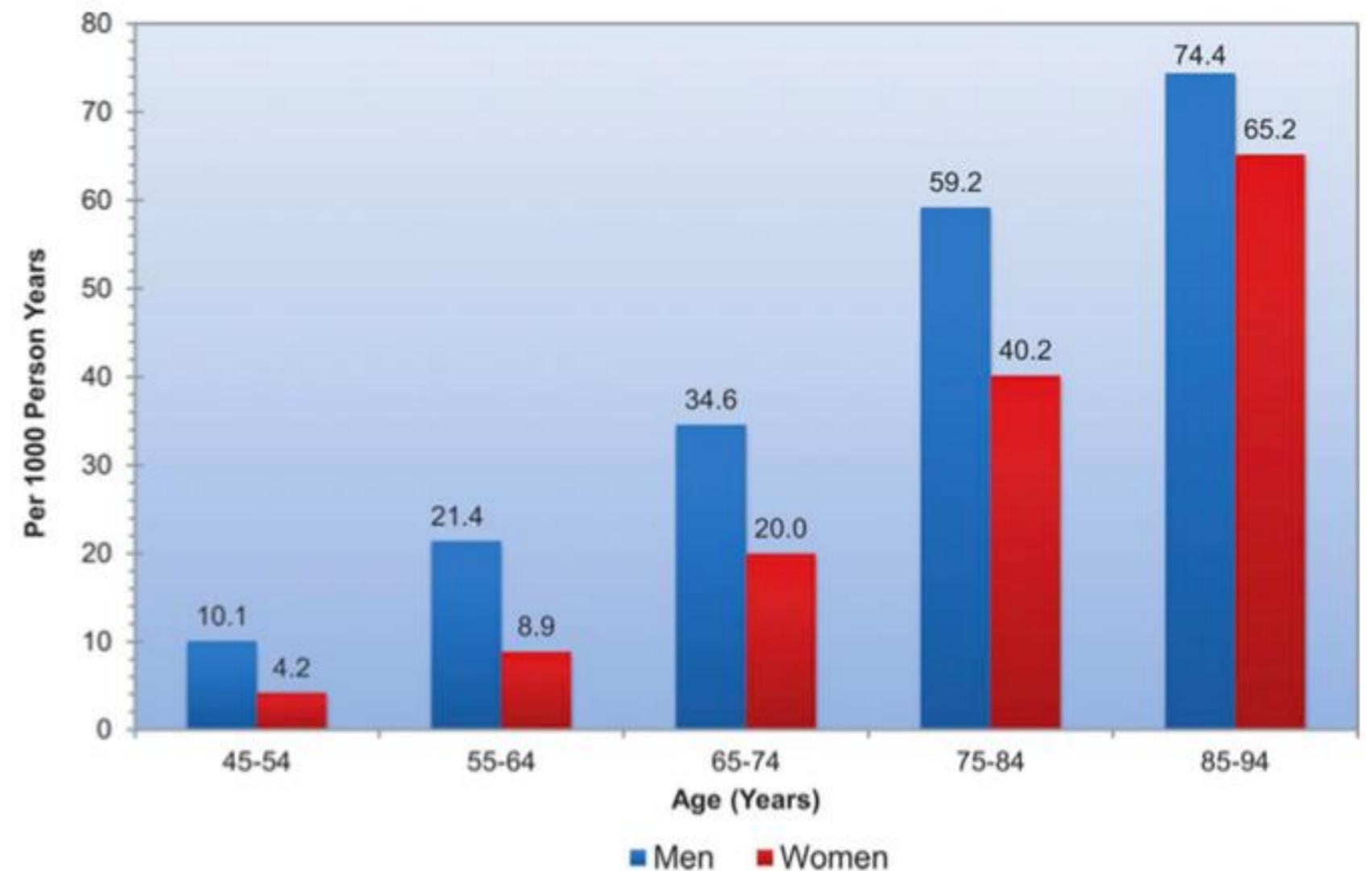
# DIFFERENCES: HEART FAILURE

- Women account for 40% of all patients with HFrEF
- Women 60% less likely to undergo left ventricular assist device (LVAD) implantation for severe heart failure
- Women higher risk of mortality and adverse events after LVAD
  - Younger women undergoing LVAD as bridge to transplant
    - Men more likely to receive transplant

# HORMONAL DIFFERENCES

- Women believed to have “protective” benefit of estrogen
- Not seen with replacement therapy
- After age 65, risk of CV event accelerates, comparable to men

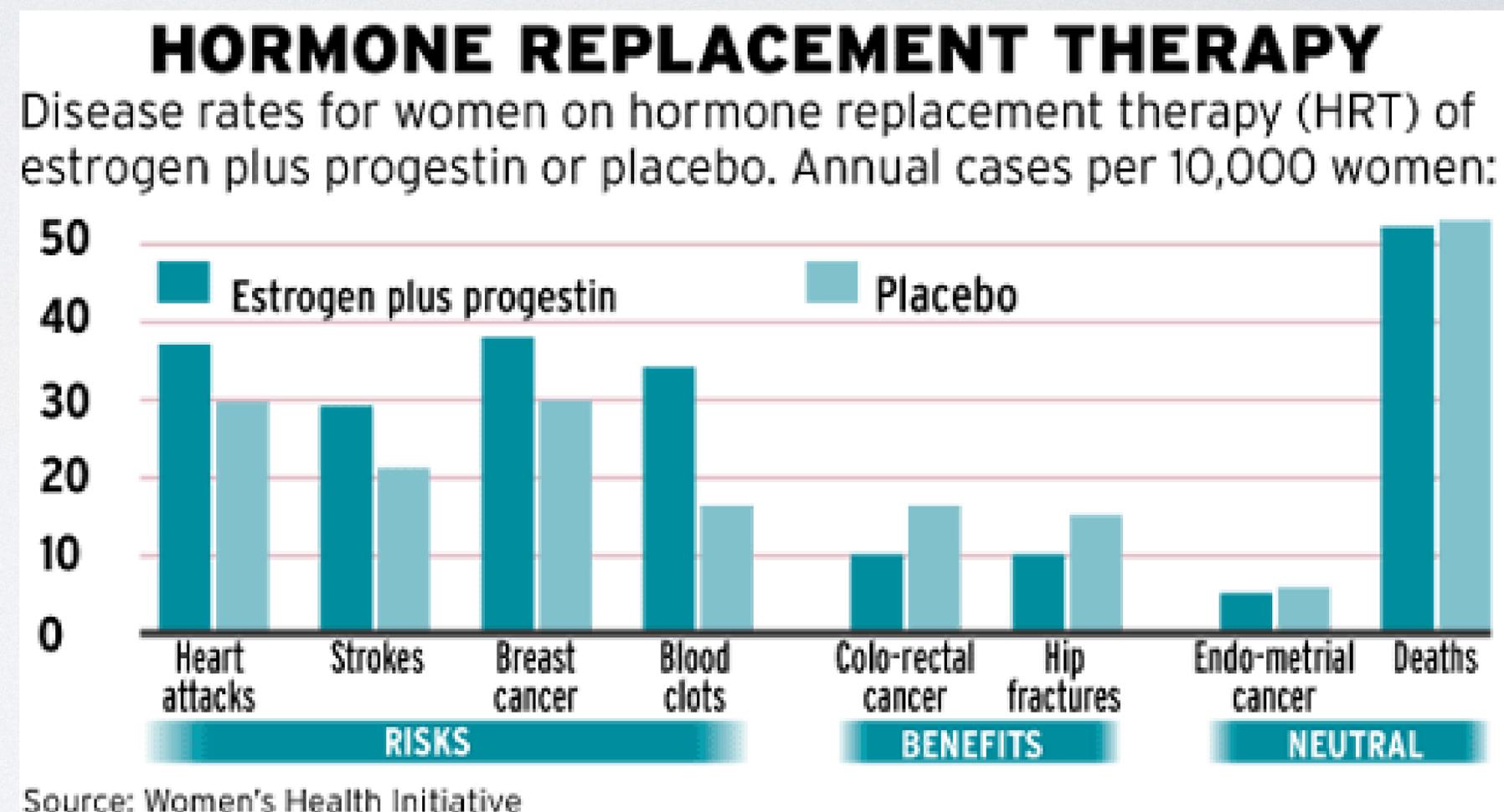
**Incidence of cardiovascular disease (coronary heart disease, heart failure, stroke, or intermittent claudication; does not include hypertension alone) by age and sex**



Framingham Heart Study, 1980–2003.

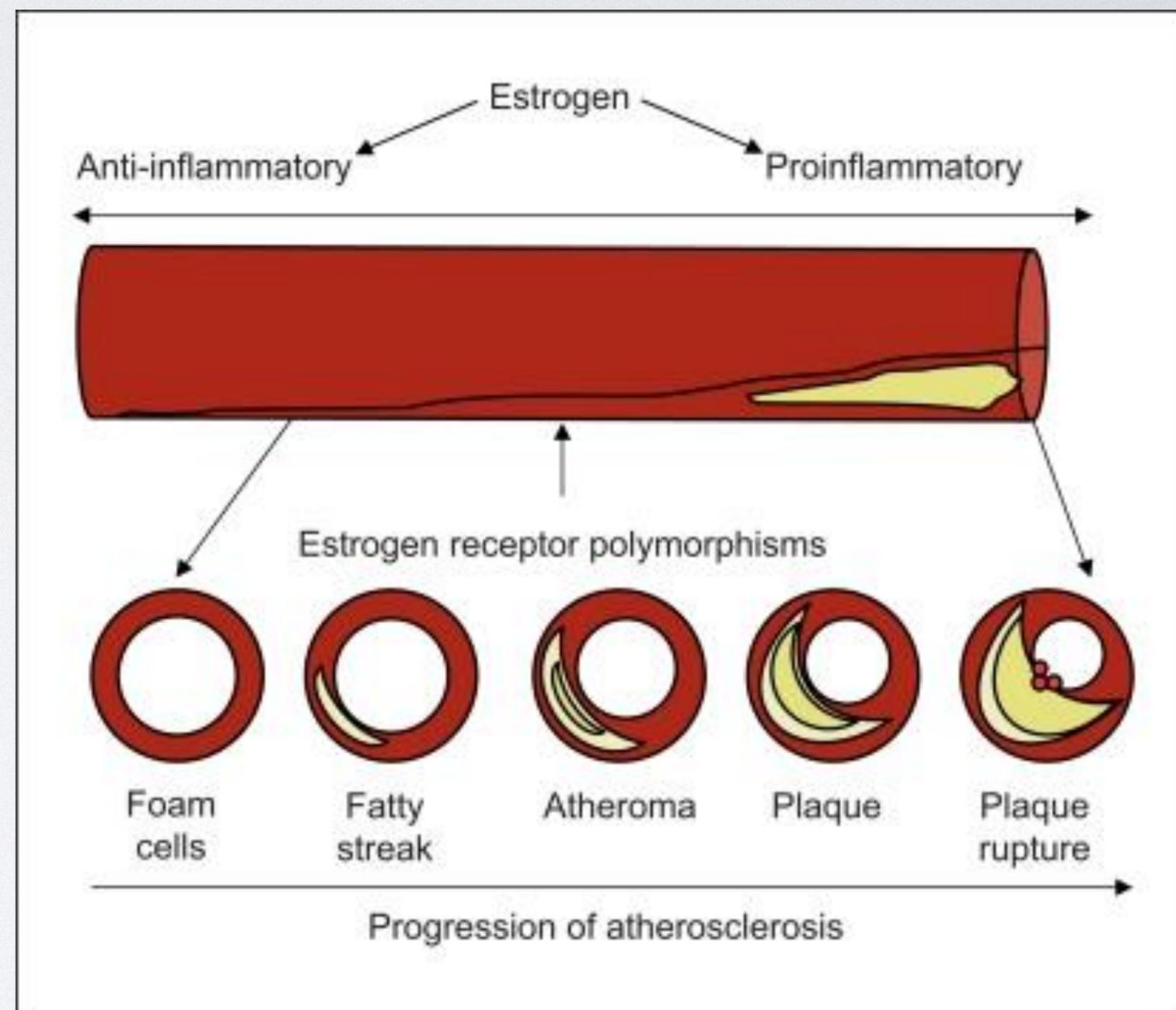
# HORMONE REPLACEMENT

- HRT (estrogen + progestin or estrogen alone) should not be started in postmenopausal women after AMI for secondary prevention of coronary events
- Women who are already taking HRT at the time of their MI should discontinue taking these agents



# HORMONE REPLACEMENT

- Estrogen imparts anti-inflammatory effect in healthy vessels before contributing to pro-inflammatory changes after atherosclerotic changes





[Back to MESA CAC](#)

Input your age, select your gender and race/ethnicity, input (optionally) your observed calcium score and click "Calculate".

Age (45-84):

Gender:

Race/Ethnicity:

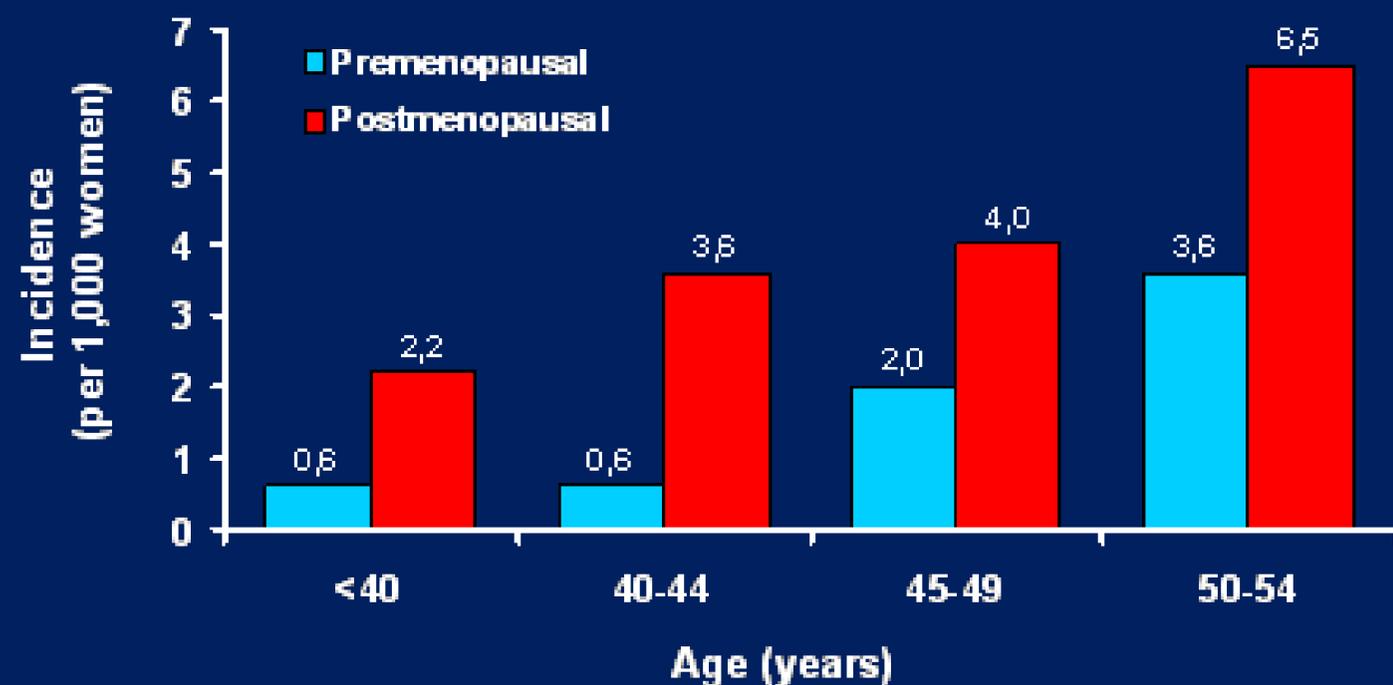
Observed Agatston Calcium Score (optional):

Calculate

The estimated probability of a non-zero calcium score for a white female of age 70 is **59 %**.

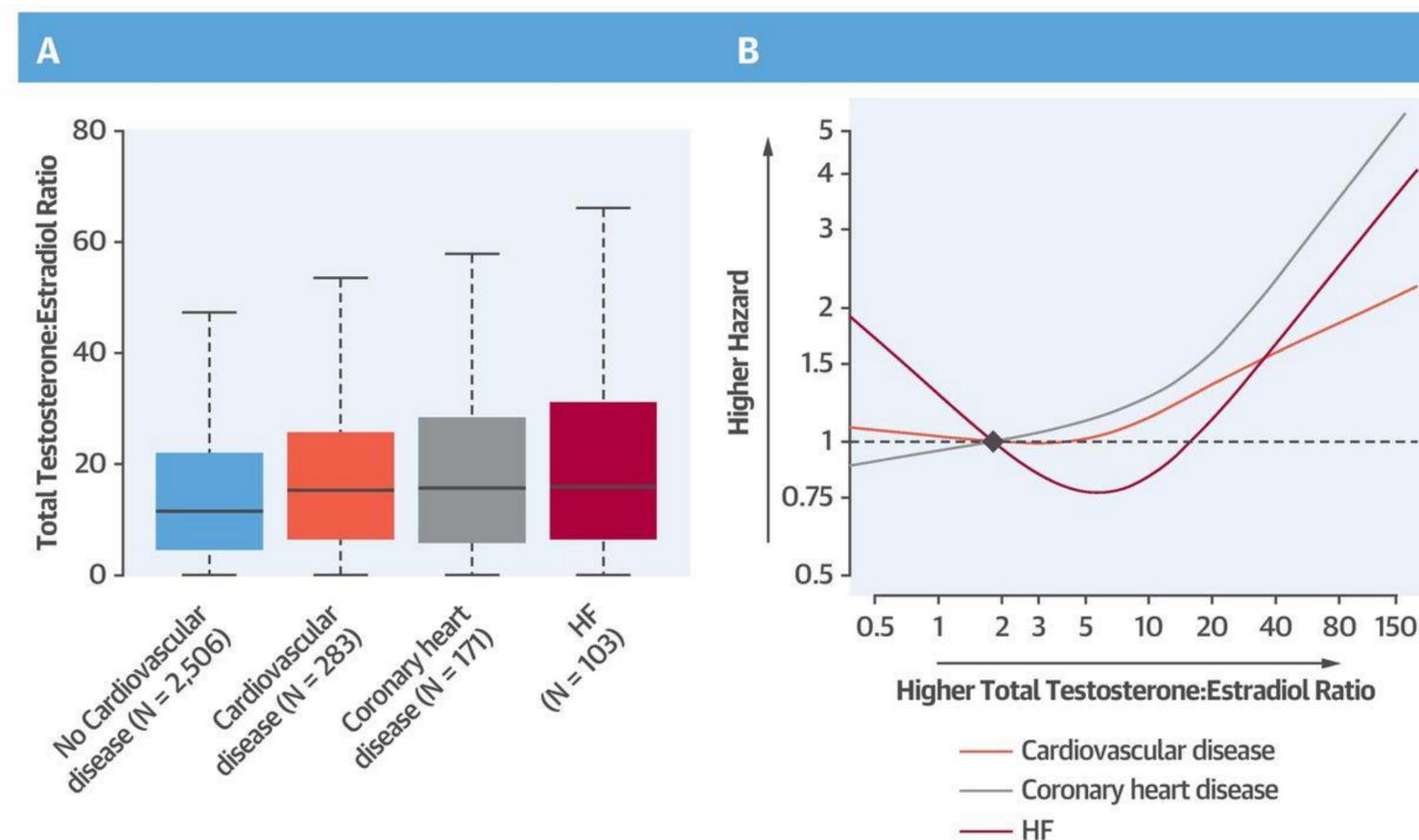
# HORMONAL DIFFERENCES

## Incidence of Cardiovascular Disease Relation to Menopause Status



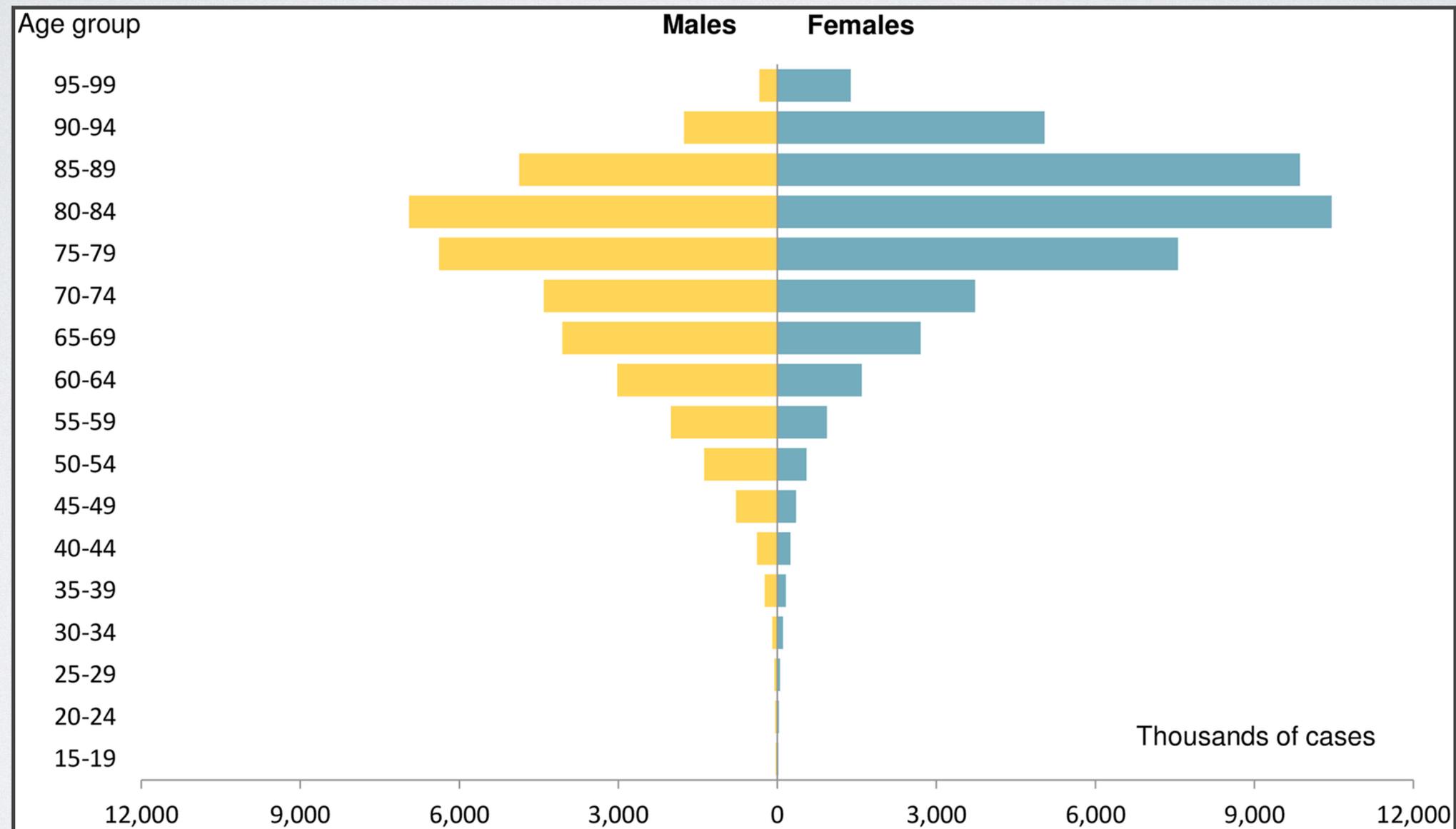
Kannel W, et al. *Ann Intern Med.* 1976;85:447-52.

## CENTRAL ILLUSTRATION: Testosterone/Estradiol Ratio and the Risk of Incident CVD, CHD, and HF in Post-Menopausal Women: MESA



Zhao, D. et al. *J Am Coll Cardiol.* 2018;71(22):2555-66.

# HORMONAL DIFFERENCES

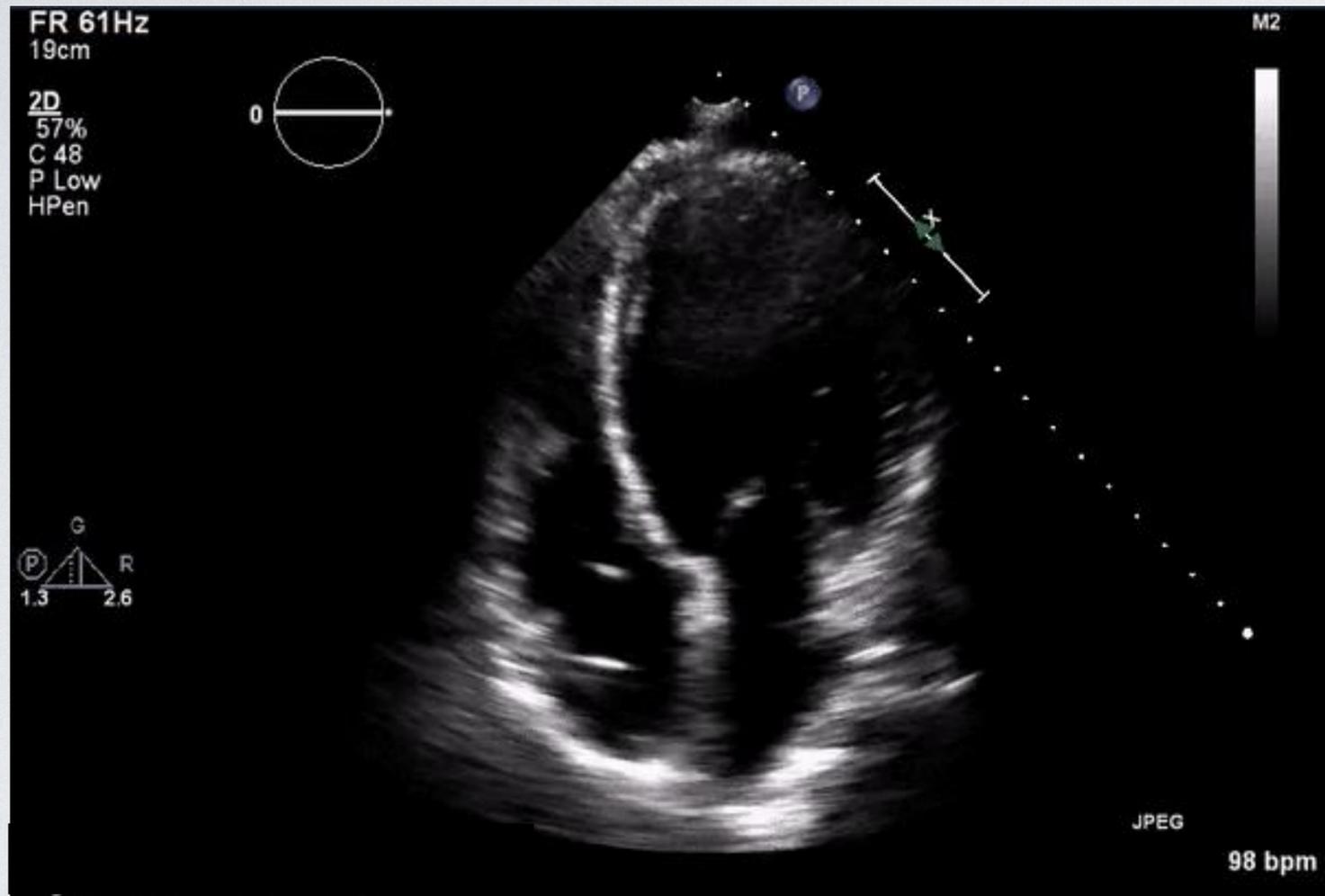


- Post-menopausal women exhibit an exponential increase in the incidence of HFpEF



# CASE 2

- 39 year old female presents one week after c-section delivery for twin infants
  - Post-delivery course was unremarkable
  - Prenatal course notable for pregnancy induced hypertension
    - Managed successfully with oral nifedipine until time of delivery
  - Prior to delivery, noted persistent mild pitting edema to feet (“shoes were tight”)
    - Moderate dyspnea on exertion- more restful periods needed
    - Symptoms worsened after returning home



# PREGNANCY

- Emerging evidence identifies unique factors during or as result of pregnancy
  - Peripartum cardiomyopathy
  - Preeclampsia/Eclampsia
  - Vascular complications and latent cardiovascular risk

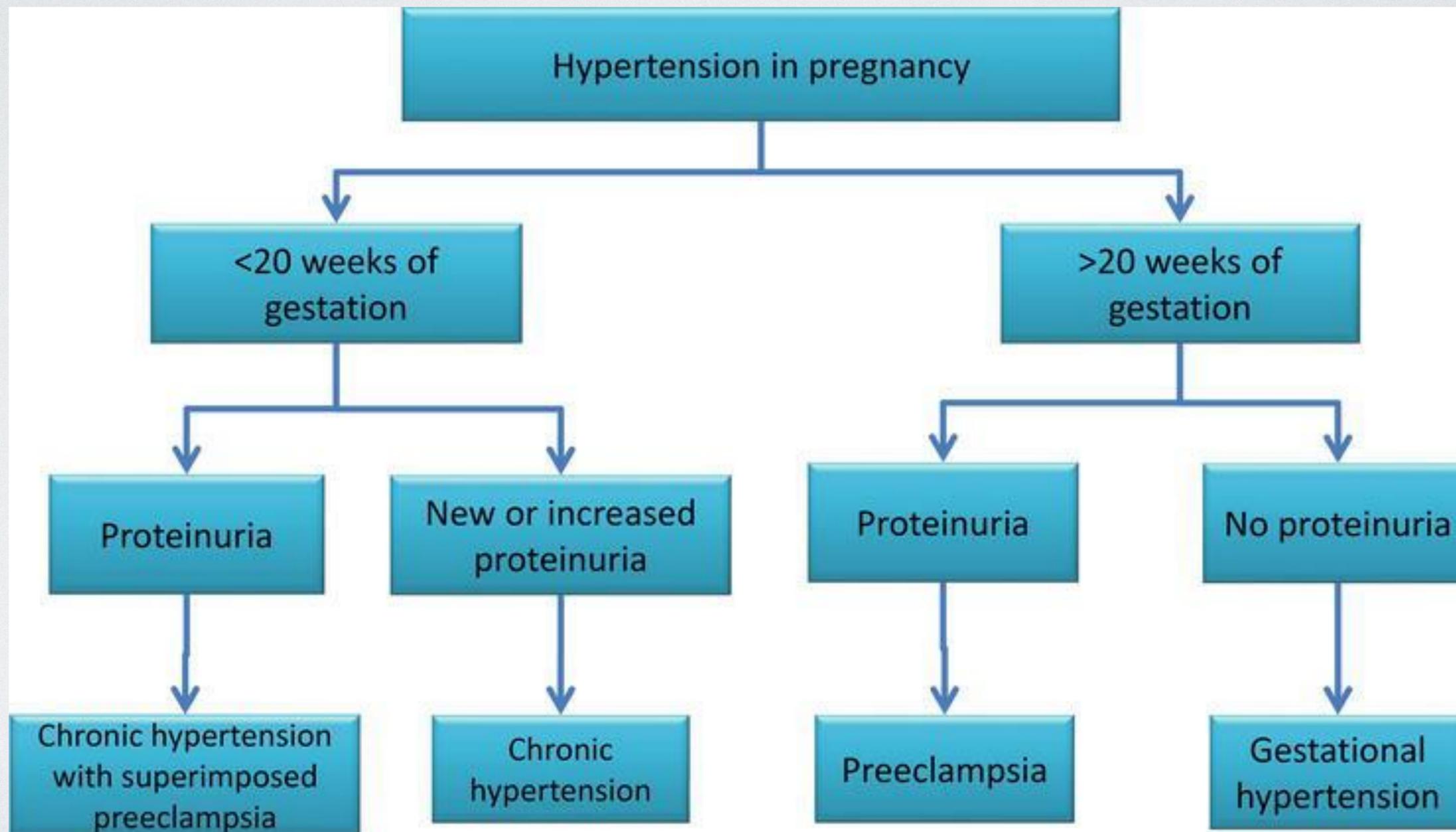
# PERIPARTUM CARDIOMYOPATHY

- Cause uncertain
- Incidence (in US): 1 in 1500 to 1 in 4000
  - Worldwide: 1 in 100 (Nigeria) to 1 in 20,000 (Japan)
- Tendency to effect older mothers or multiparid patients
- Potentially related to history of pregnancy related hypertension or preeclampsia

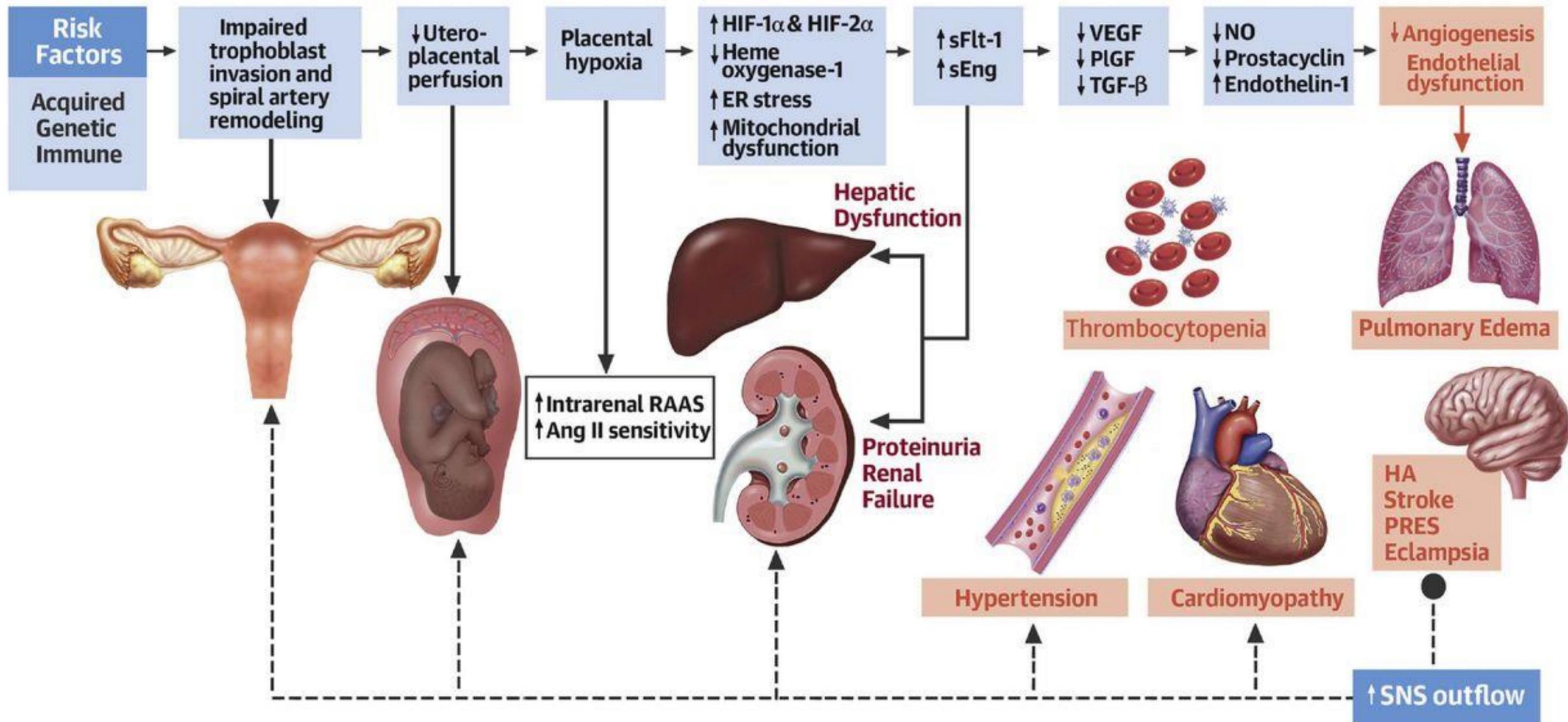
# PERIPARTUM CARDIOMYOPATHY

- Prognosis variable
  - Most studies show variability in tendency for recovery
- Risk of recurrence with future pregnancies
- Duration of treatment uncertain
  - Risk of future pregnancy and fetal complications

# HYPERTENSION IN PREGNANCY



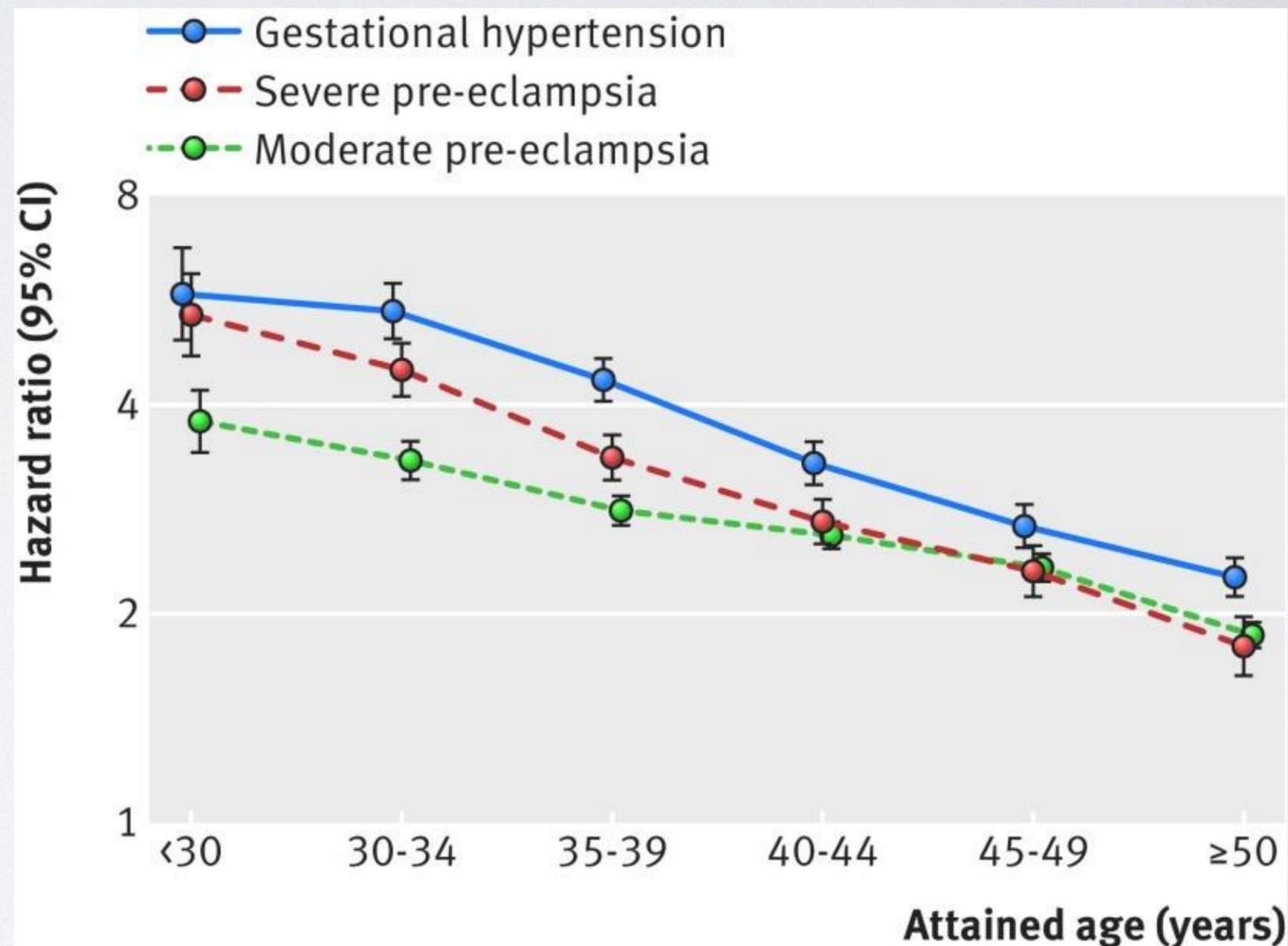
# CENTRAL ILLUSTRATION: Pathogenesis of Preeclampsia



Ives, C.W. et al. J Am Coll Cardiol. 2020;76(14):1690-702.

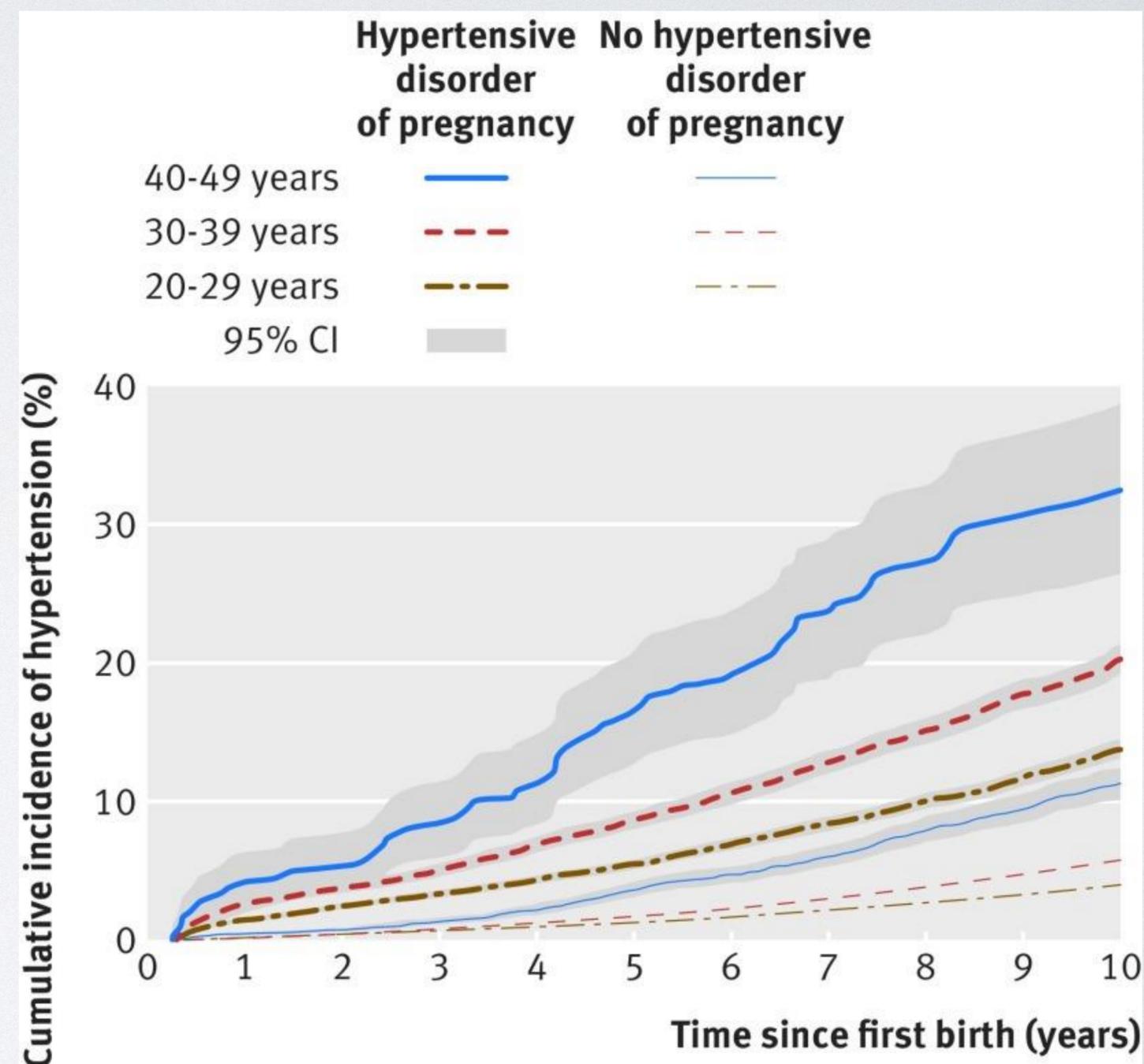
# HYPERTENSION IN PREGNANCY

- Latent effects can last decades
- Increases risk for stroke, essential hypertension, renal disease and other end-organ damage



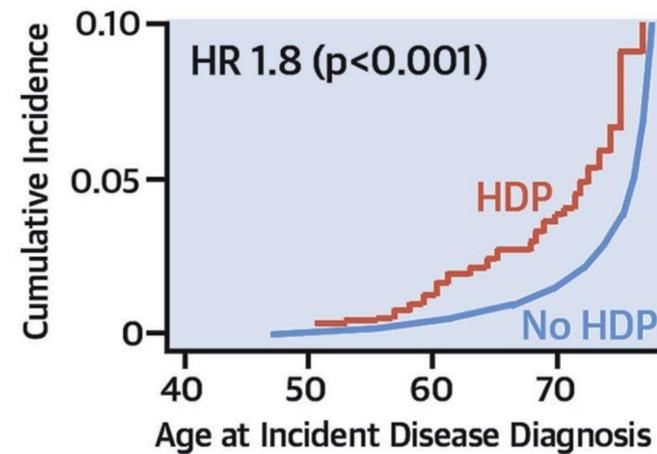
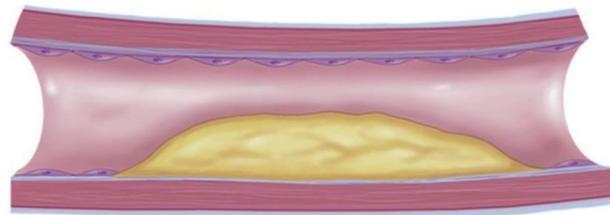
# HYPERTENSION IN PREGNANCY

- Incidence of hypertensive disorder during pregnancy influences long term cardiovascular health

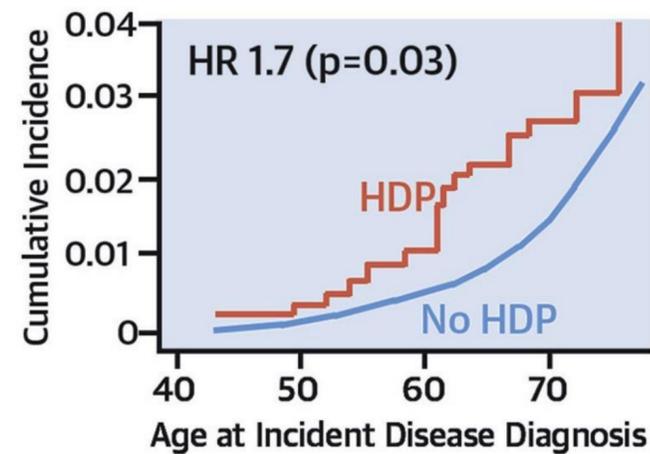
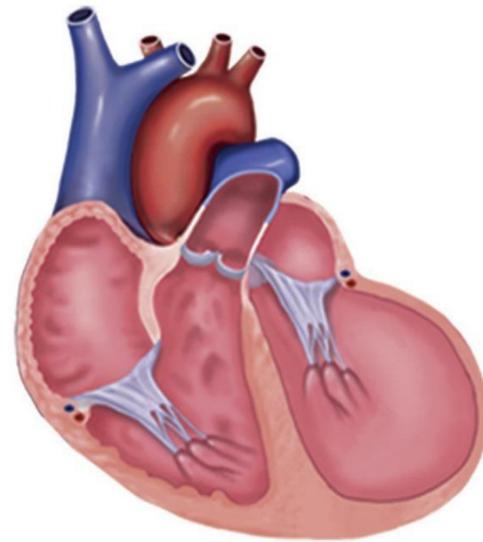


# CENTRAL ILLUSTRATION: Hypertensive Disorders of Pregnancy Are Associated With Long-Term Risk of Diverse Cardiovascular Diseases

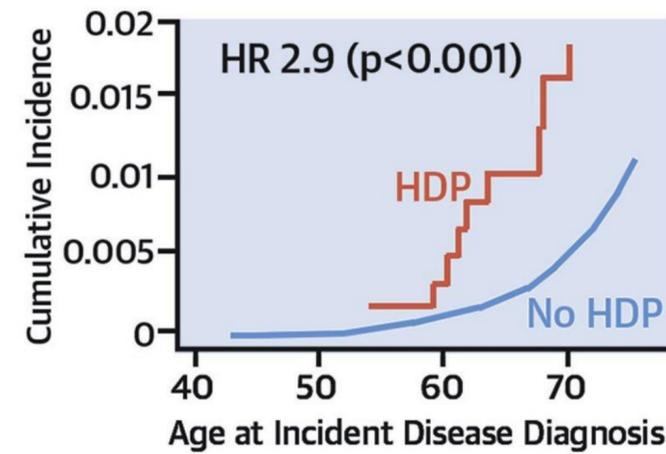
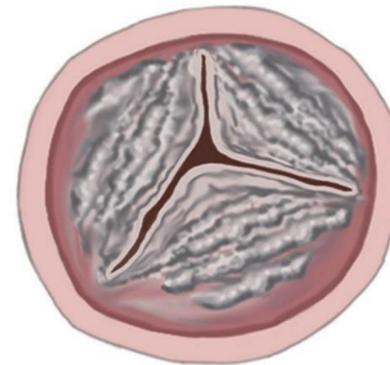
## Coronary Artery Disease



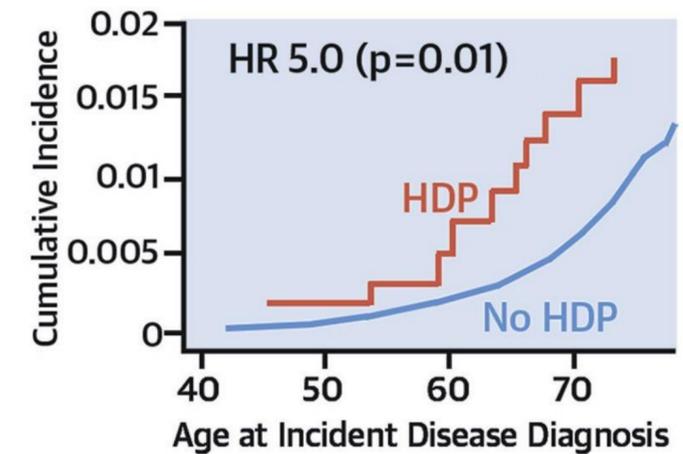
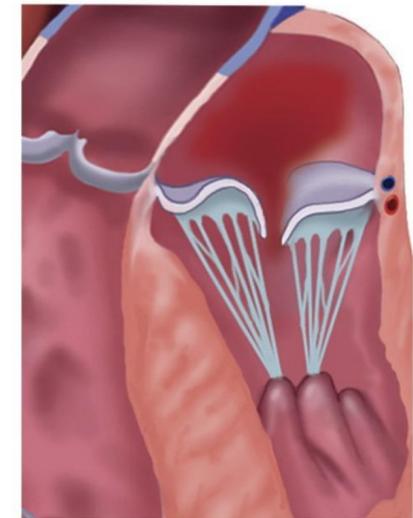
## Heart Failure



## Aortic Stenosis



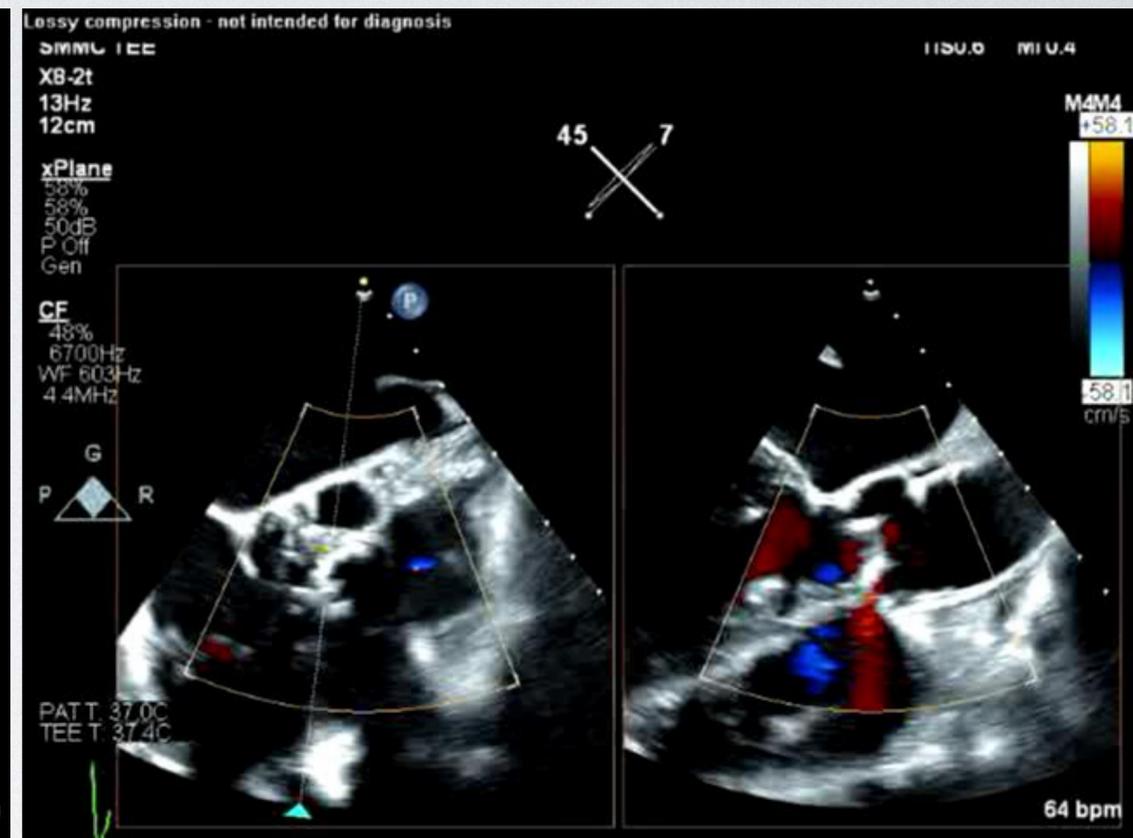
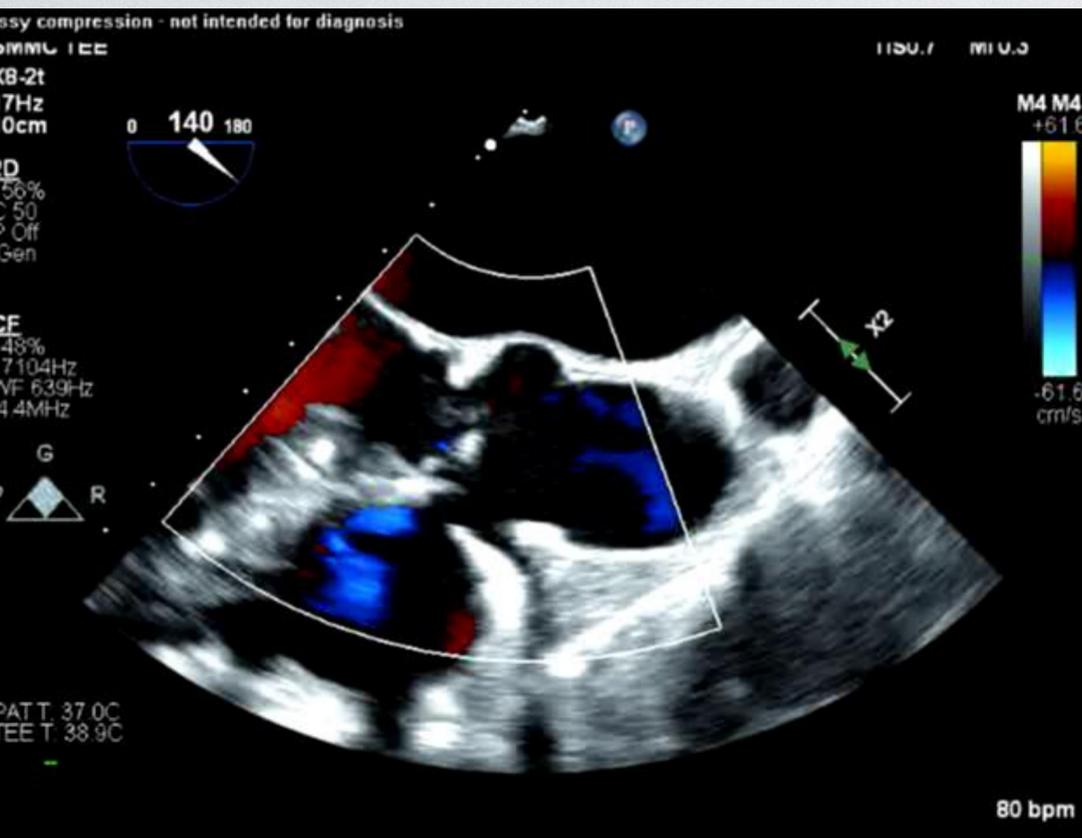
## Mitral Regurgitation



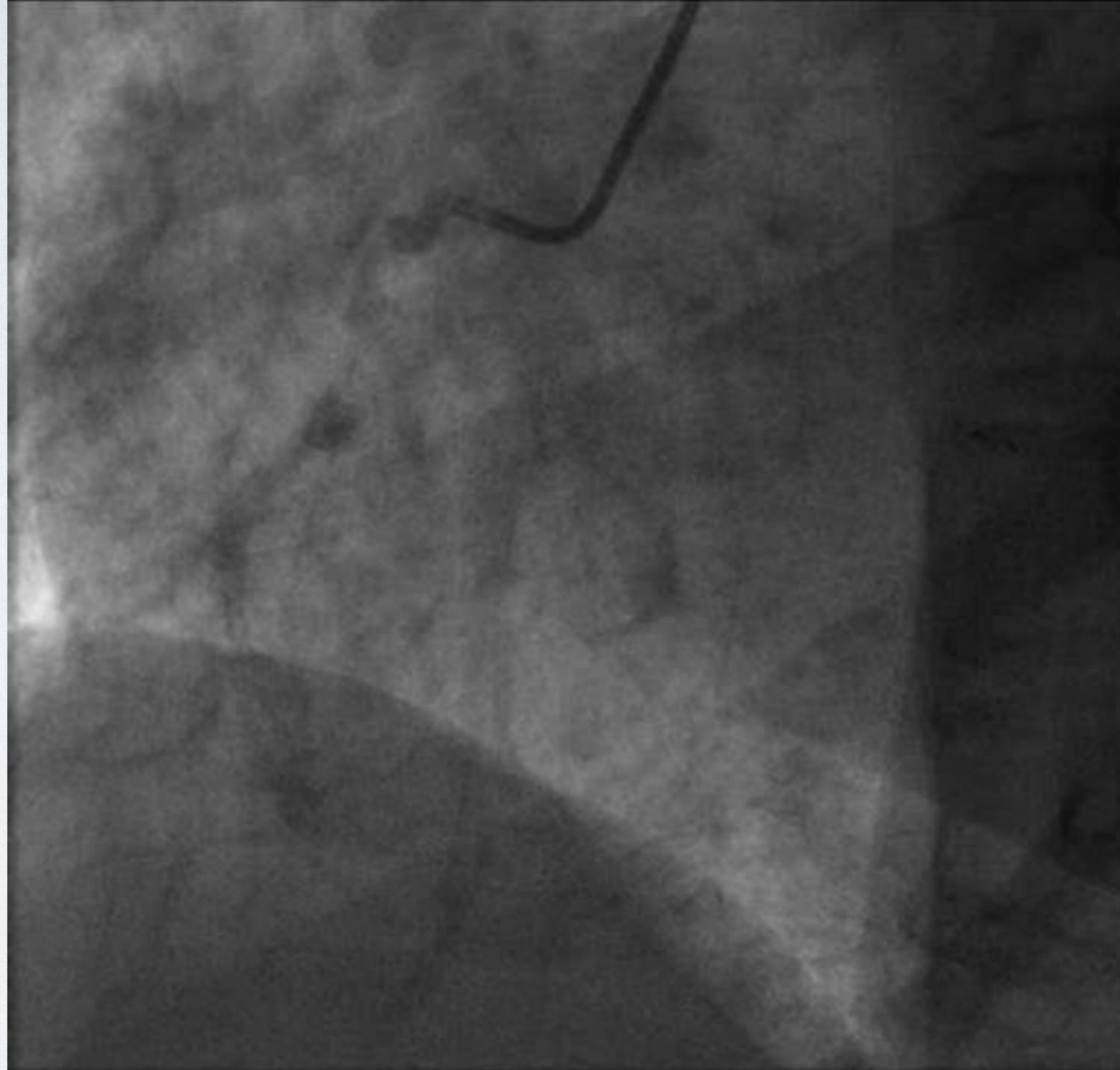
Honigberg, M.C. et al. J Am Coll Cardiol. 2019;74(22):2743-54.

# CASE 3

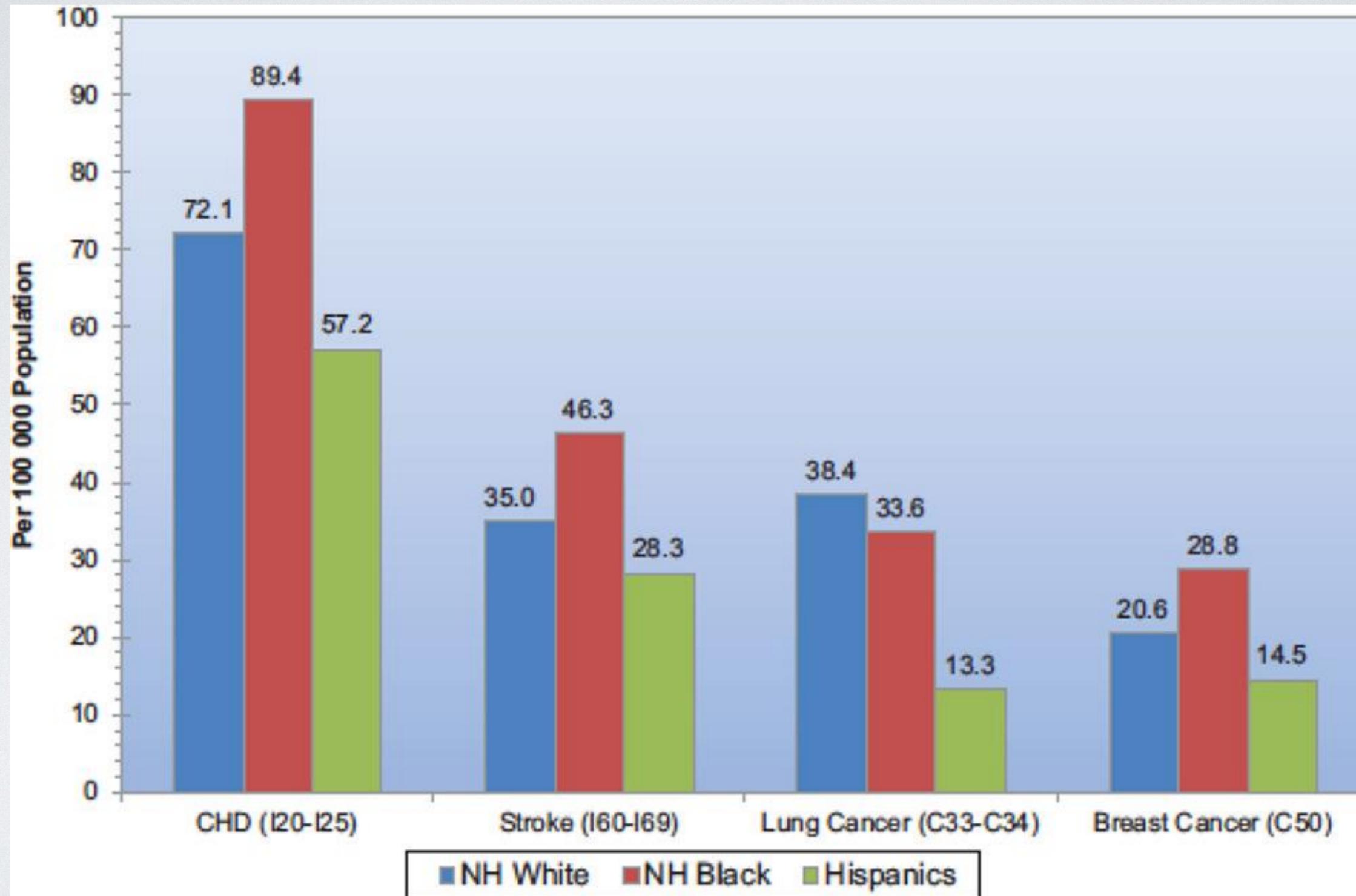
- 68 year old female, previously seen for risk management and history of heart murmur returns in follow up after completing chemotherapy
- Diagnosed one year ago with undifferentiated lymphoma
  - treated with radiation, RCHOP chemotherapy
    - rituximab, cyclophosphamide, doxorubicin, vincristine prednisolone
- After completing chemotherapy, feels persistently weak, short of breath, two episodes of near syncope during yard work.



Lossy compression - not intended for diagnosis

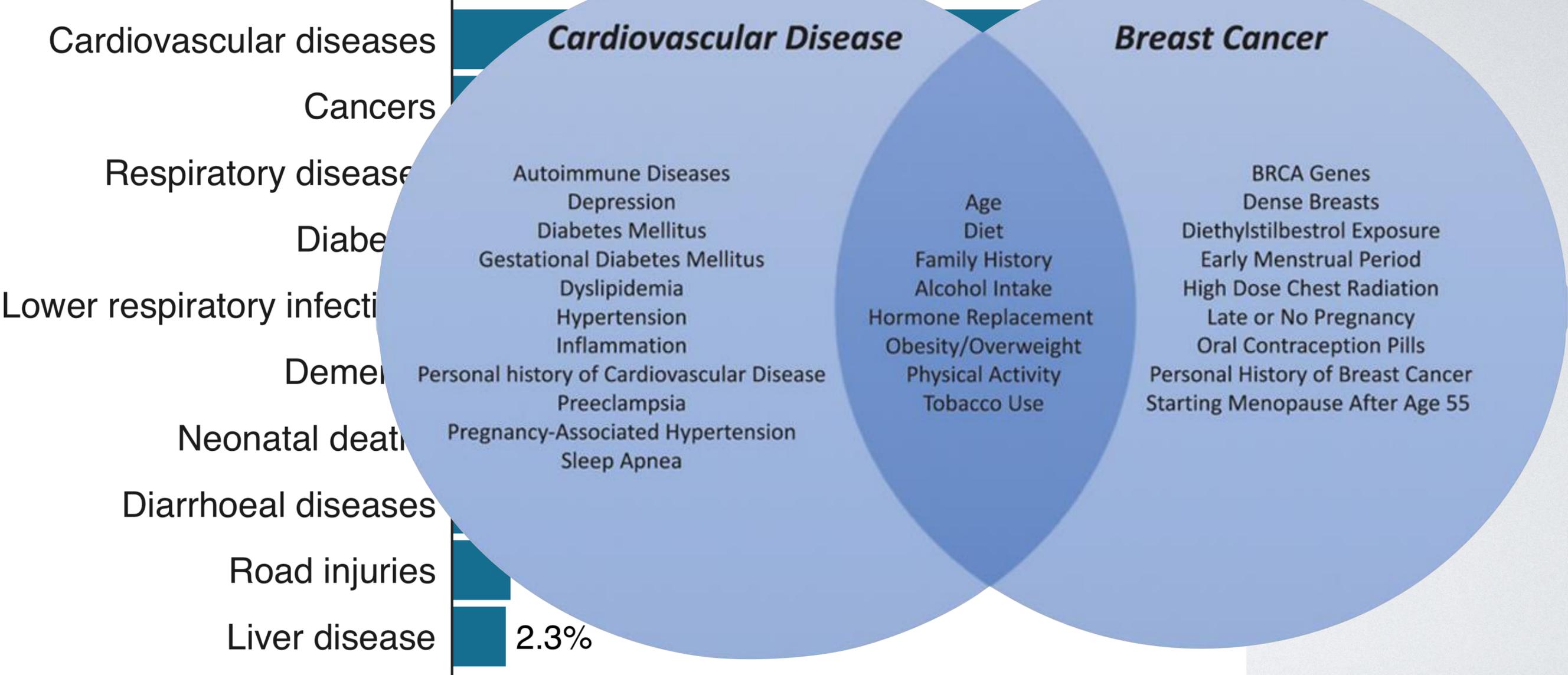


# Rates of cardiovascular disease and breast cancer in women



# Leading causes of death

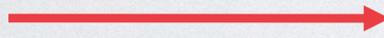
World, 2016



Source: IHME, Global Burden of Disease, Our World in Data

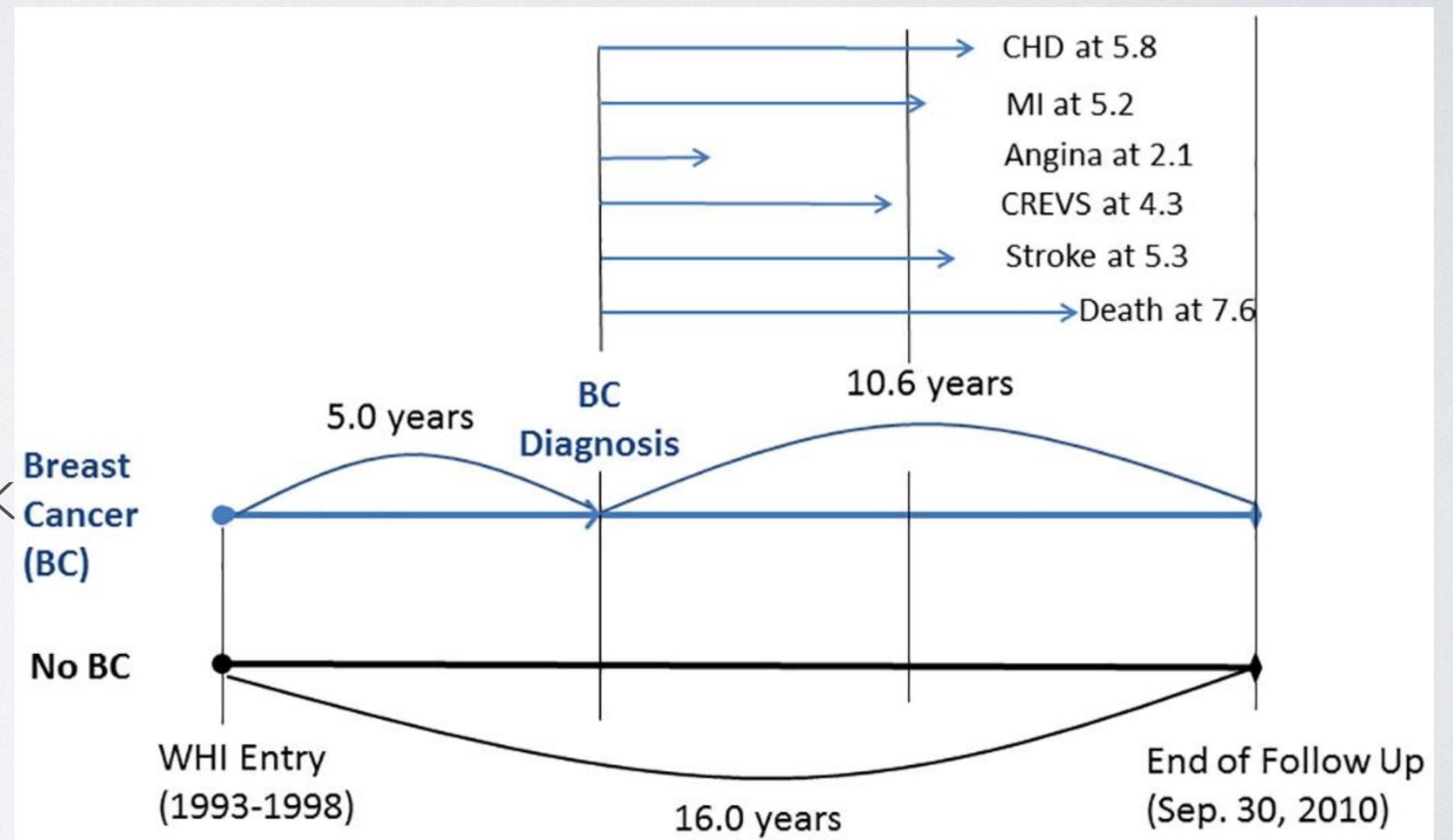


	Risk of CVD	Risk of Breast Cancer
Healthy Diet	↓	↓
Western Diet	↑	↑
Light-Moderate Alcohol Intake	↓	↑
Red/Processed Meat	↑	↑
Physical Activity	↓	↓
Sedentary Lifestyle	↑	↑
Premenopausal Obesity	↑	↓
Smoking	↑	↑
Early Menarche	↑	↑
Early Menopause	↑	↓
Hormone Replacement Therapy	↑	↑



# BREAST/GYNECOLOGICAL CANCER

- Strong correlation between diagnosis of breast or ovarian/uterine cancer and subsequent risk of major adverse cardiovascular events



	Invasive Breast Cancer Diagnosis at Age 70–79			
	Localized	Regional	Distant	All
Survival status	n (%)	n (%)	n (%)	n (%)
Alive	938 (80.6)	214 (68.6)	2 (33.3)	1,154 (77.9)
Dead	226 (19.4)	98 (31.4)	4 (66.7)	328 (22.1)
<b>Total (%)</b>	<b>1,164 (78.5)</b>	<b>312 (21.1)</b>	<b>6 (0.4)</b>	<b>1,482 (100)</b>
Causes of death	Localized	Regional	Distant	All
Causes of death	n (%)	n (%)	n (%)	n (%)
Breast Cancer	39 (17.3) ←	43 (43.9)	4 (100)	86 (26.2) ←
Other Major Cancers <sup>a</sup>	14 (6.2)	8 (8.2)	0 (0.0)	22 (6.7)
Other Cancer Death	26 (11.5)	5 (5.1)	0 (0.0)	31 (9.5)
<b>Total CVD</b>	<b>49 (21.7) ←</b>	<b>14 (14.3)</b>	<b>0 (0.0)</b>	<b>63 (19.2) ←</b>
Coronary heart disease	21 (9.3)	9 (9.2)	0 (0.0)	30 (9.1)
Stroke	9 (4.0)	2 (2.0)	0 (0.0)	11 (3.4)
Other CVD	19 (8.4)	3 (3.1)	0 (0.0)	22 (6.7)
<b>Others<sup>b</sup></b>	<b>98 (43.4)</b>	<b>28 (28.6)</b>	<b>0 (0.0)</b>	<b>126 (38.4)</b>

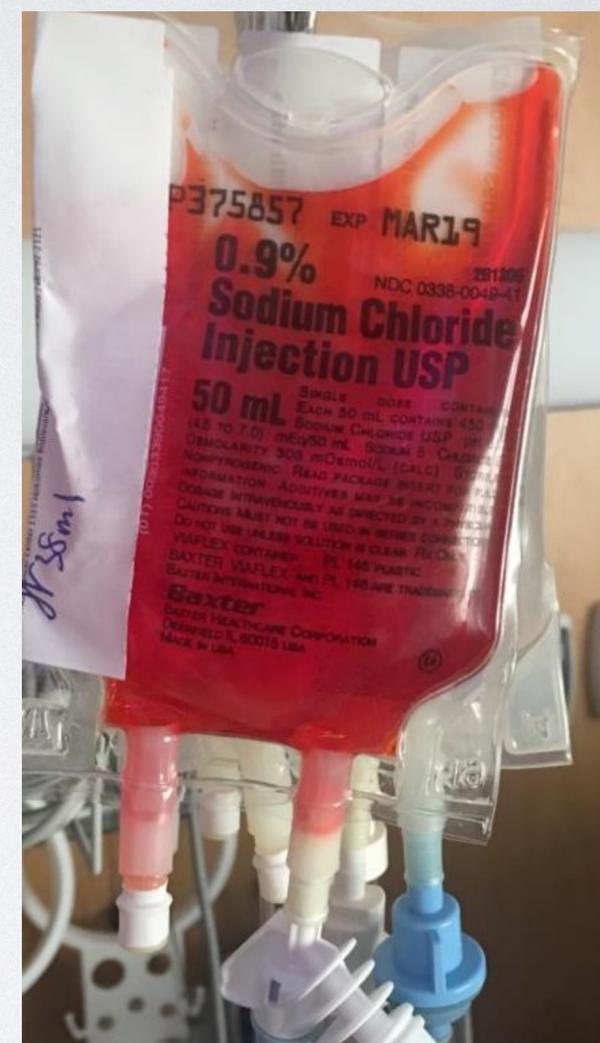
CVD indicates cardiovascular disease.

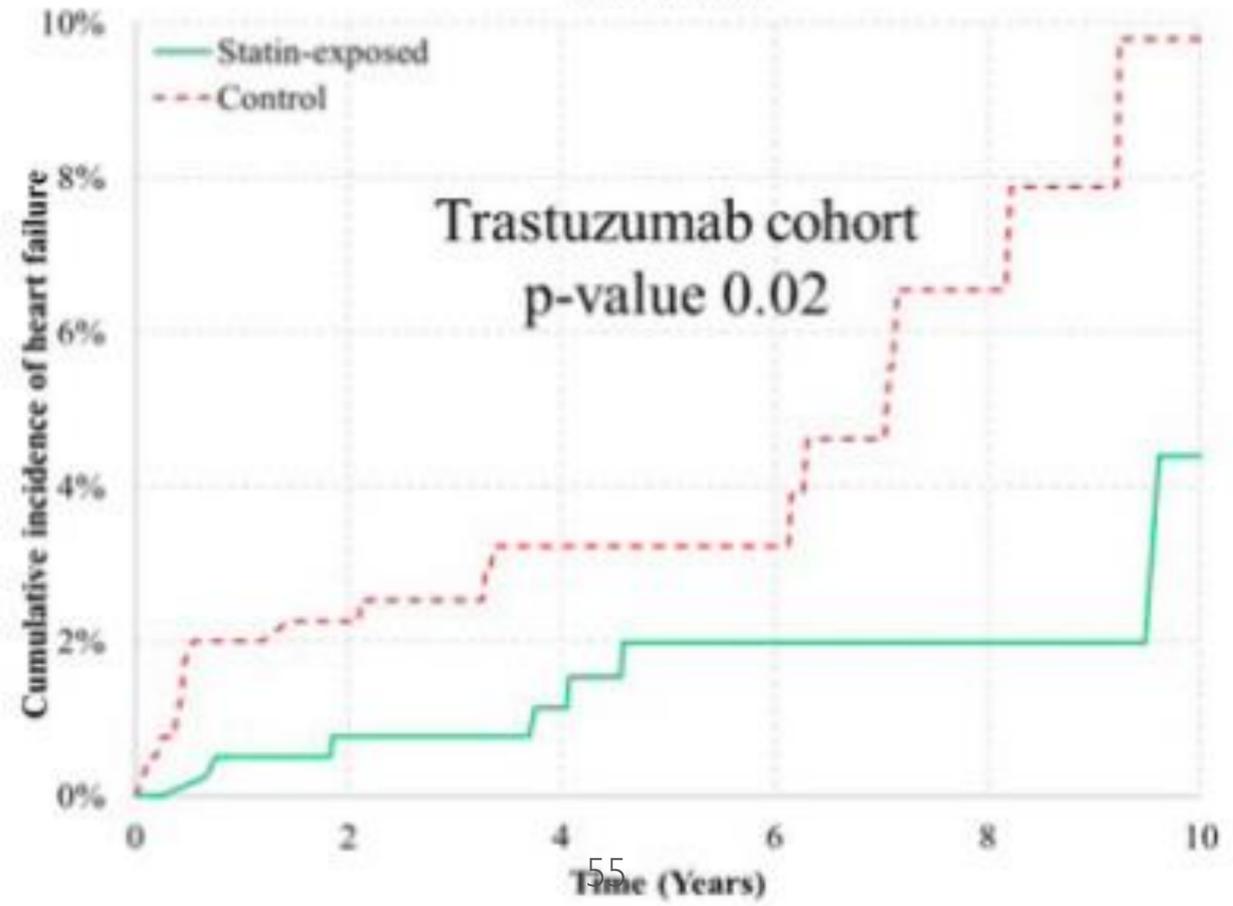
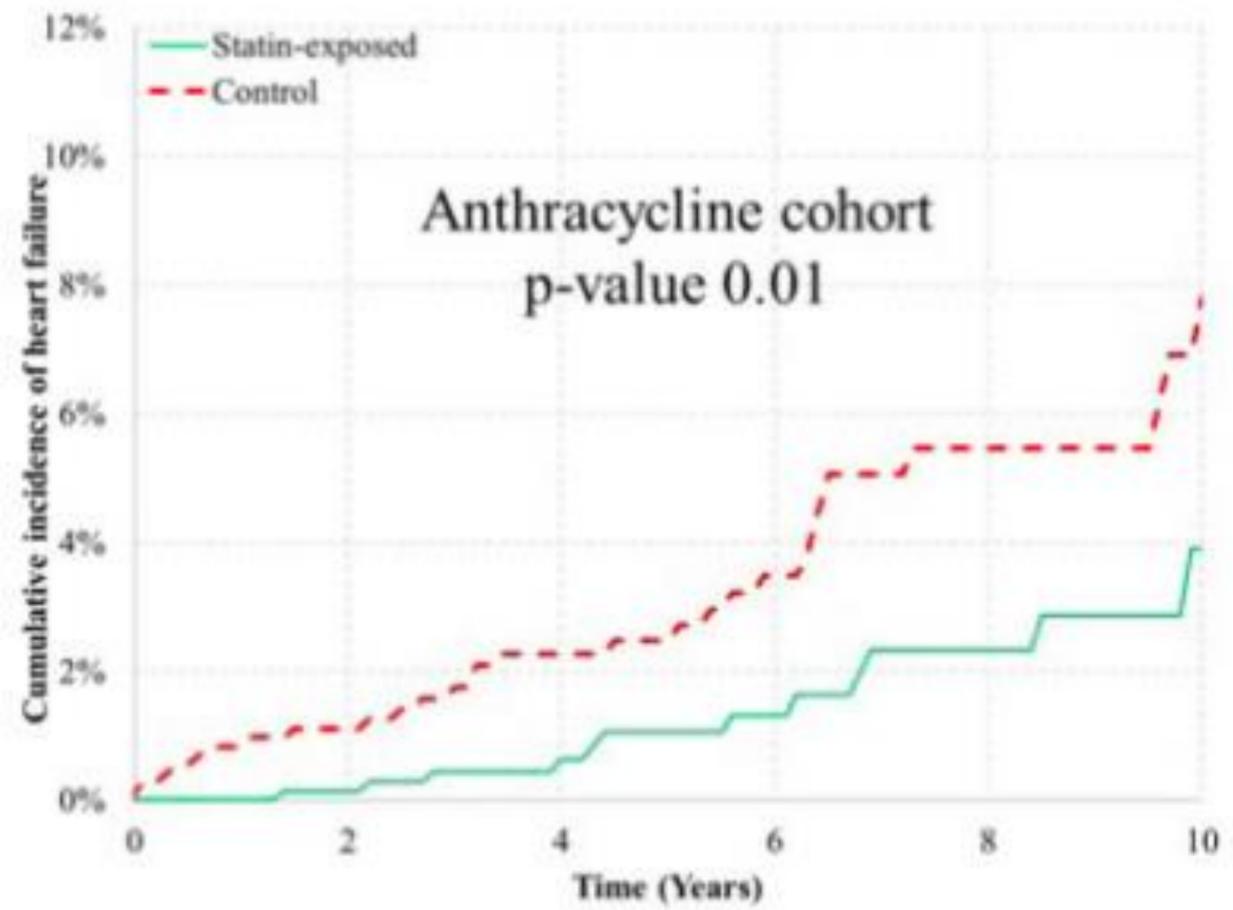
<sup>a</sup> Major cancers include lung, ovarian, and colon cancers.

<sup>b</sup> Other causes of death include COPD, pneumonia, sepsis, accident, Alzheimer's disease, etc. For more details, see [S5 Table](#).

# BREAST/GYNECOLOGICAL CANCER

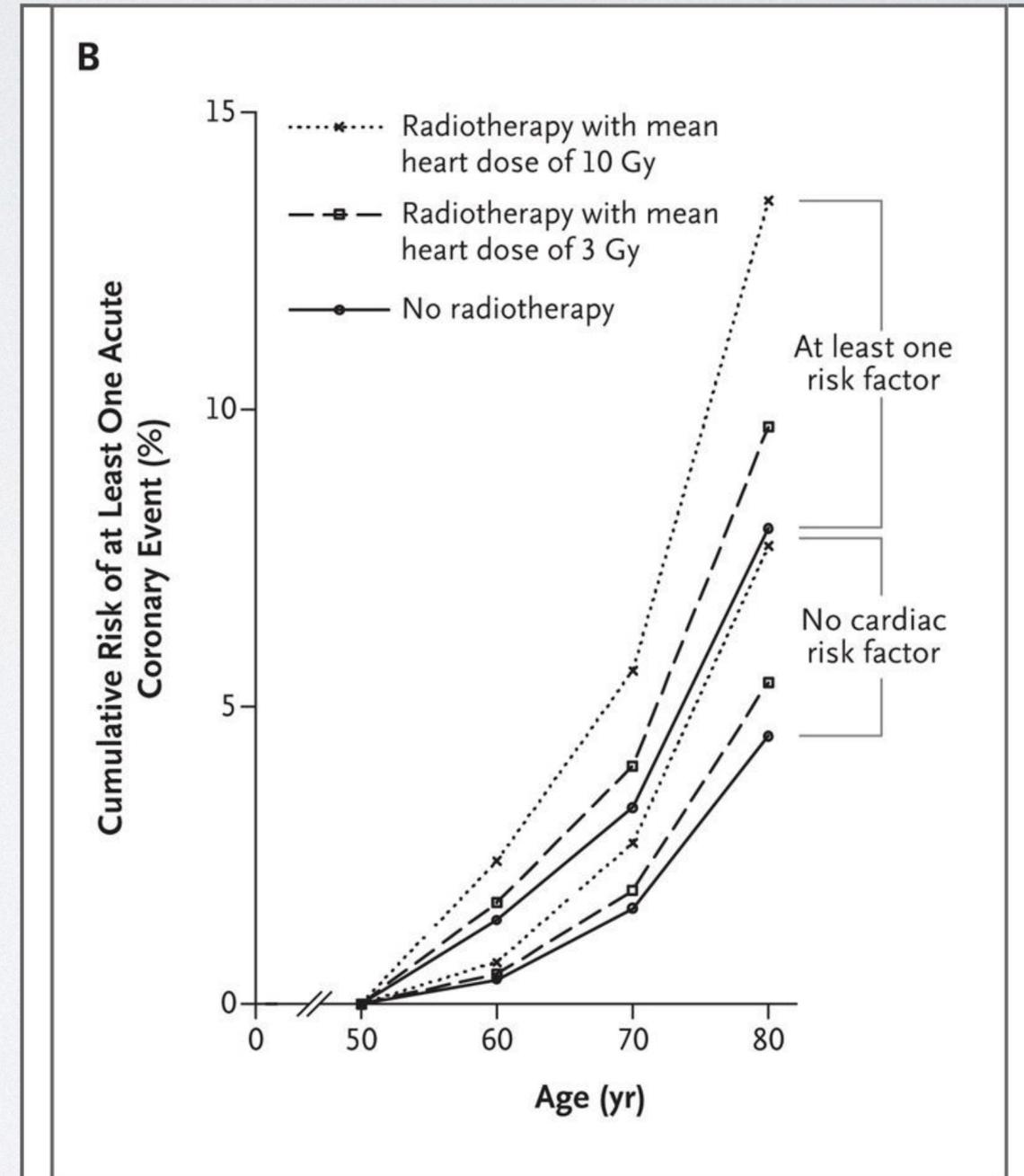
- Treatment: chemotherapy
  - Anthracyclines (ex, doxorubicin): heart failure
    - Risk occurs at 240 mg/m<sup>2</sup>
  - Taxanes (paclitaxel): arrhythmias
    - Bradycardia, non sustained VT
  - Monoclonal antibodies (trastuzumab): heart failure
    - 5% monotherapy, up to 27% when used with anthracyclines





# BREAST/GYNECOLOGICAL CANCER

- Adjuvant radiation therapy
  - Pericarditis
  - Valvular disease
  - Coronary disease
    - More commonly involves LAD
  - Dose dependent effect
  - Independent of side/location





## Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

- Case control study of 963 women with major coronary events compared to 1205 controls
- 44% of coronary events occurred less than 10 years after breast cancer was diagnosed
  - 33% occurred 10-19 years afterward, 23% occurred 20+ years afterward.
- 54% of case patients were known to have died from ischemic heart disease
- Higher mortality with history of left sided radiation

# PHARMACOLOGICAL TREATMENT

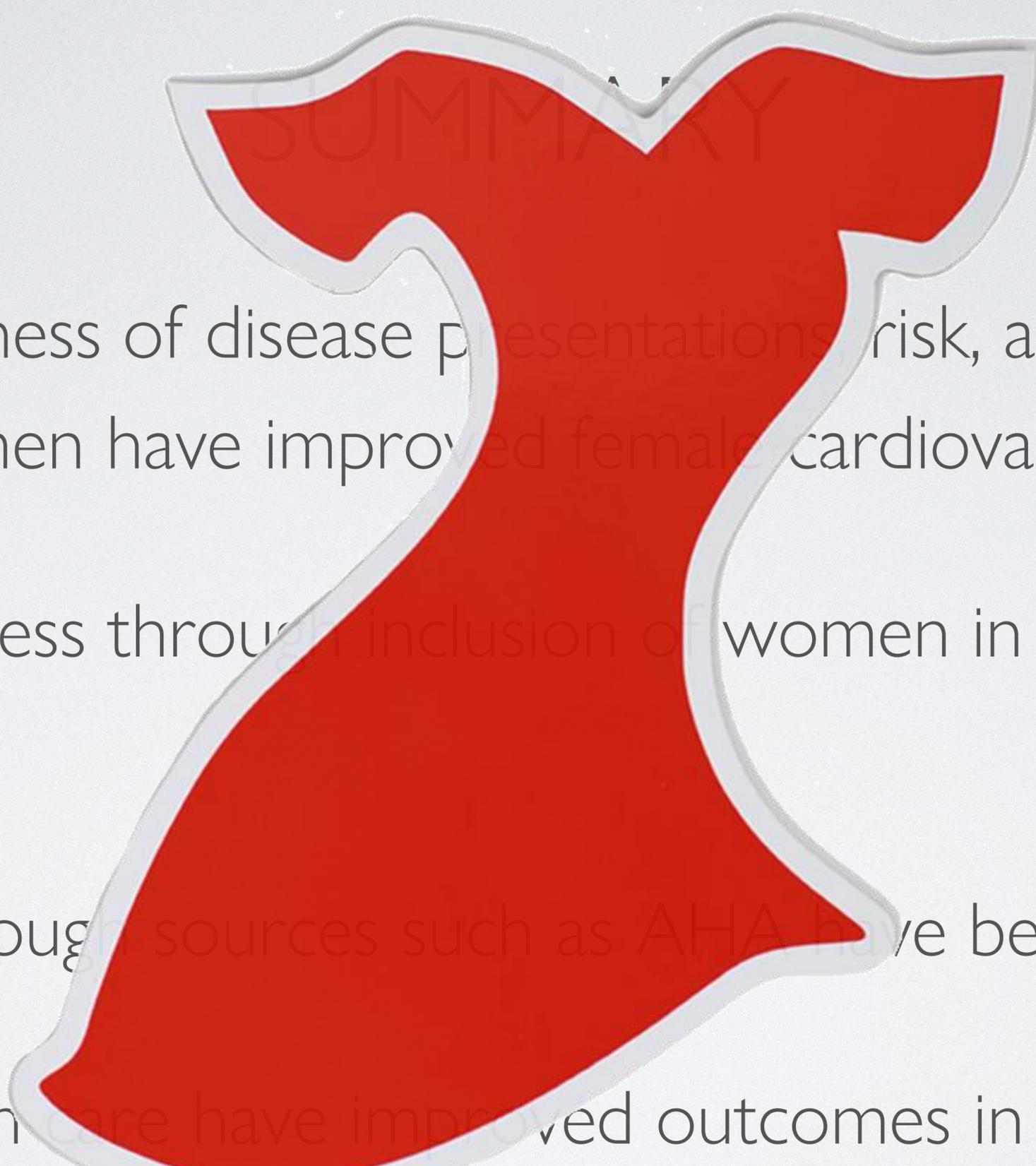
- Unique variables
  - Breastfeeding/pregnancy
  - Potential for childbearing, risk of fetal development or demise
    - Existing treatment, potential needs, anticoagulation
- Pharmacokinetics

# PHARMAKOKINETIC DIFFERENCES

## Variations in PK properties of drugs in women

<b>PK</b>		
<b>Property</b>	<b>Effect in Women</b>	<b>Cause</b>
Absorption	Less oral drug absorption	Less gastric acid secretion Slower GI motility and transit time
Distribution	Larger for lipophilic drugs Smaller for hydrophilic drugs	Greater body fat Lower total body water
Metabolism	Phase I  Increased activity of CYP2B6, CYP2D6, CYP3A4  Decreased activity of CYP1A2, CYP2E1  Phase II  Increased activity of xanthine-oxidases  Decreased activity of N- acetyltransferases, sulfotransferases, methyltransferases	Variations in enzyme activity due to pregnancy, menopause, OC use and menstruation
Excretion	Lower but marginal difference when normalized for body weight	Decreased renal blood flow, GFR, and tubular secretion and reabsorption



- 
- Increasing awareness of disease presentations, risk, and physical attributes in women have improved female cardiovascular management
  - Greatest progress through inclusion of women in medical studies and research
  - Promotion through sources such as AHA have been paramount
  - Identifiable gaps in care have improved outcomes in women

THANK YOU!

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