

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

American Heart Association
Kansas City Cardiac Symposium
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OBJECTIVES

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

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- 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

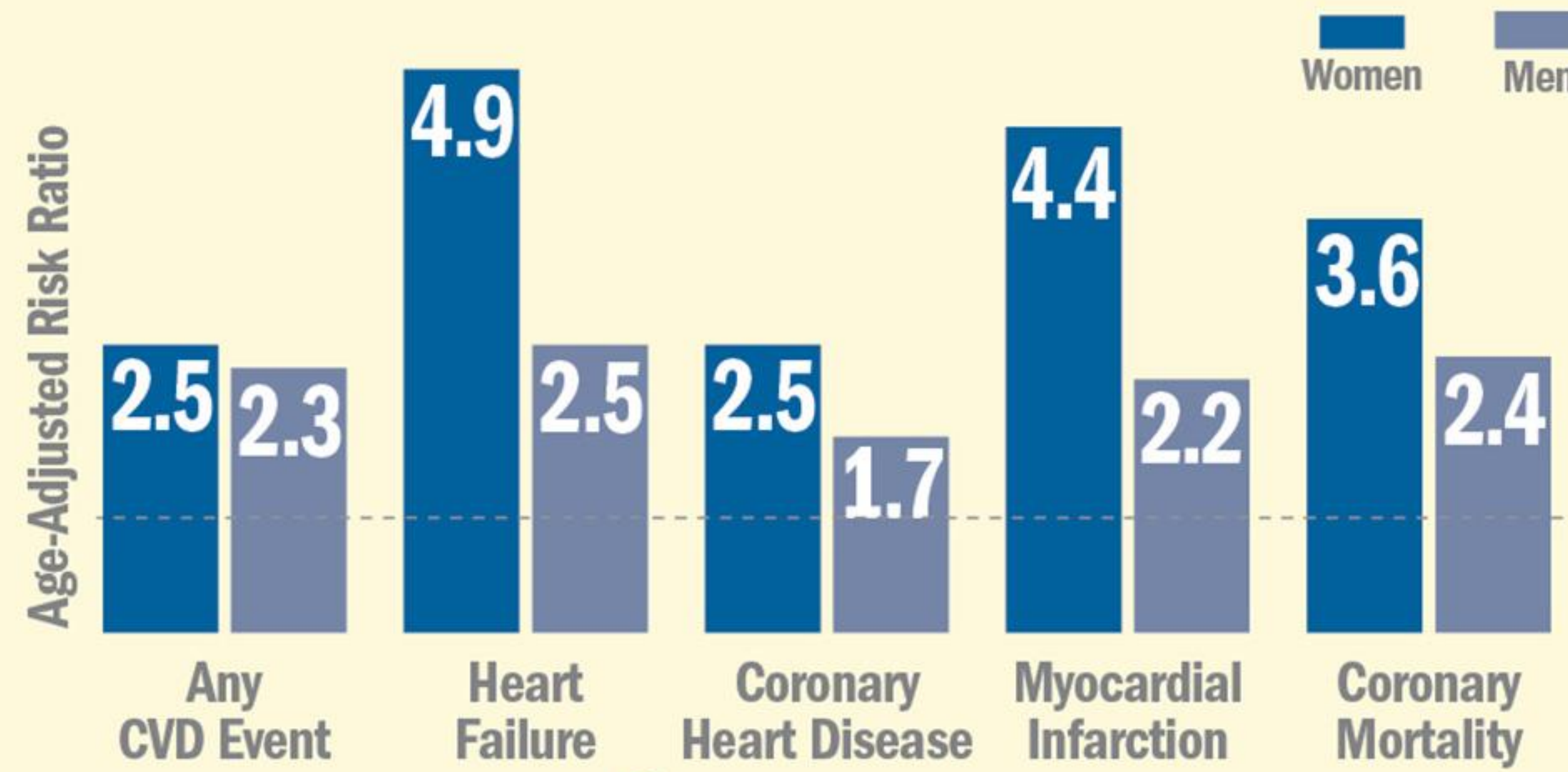


1 in 3 deaths

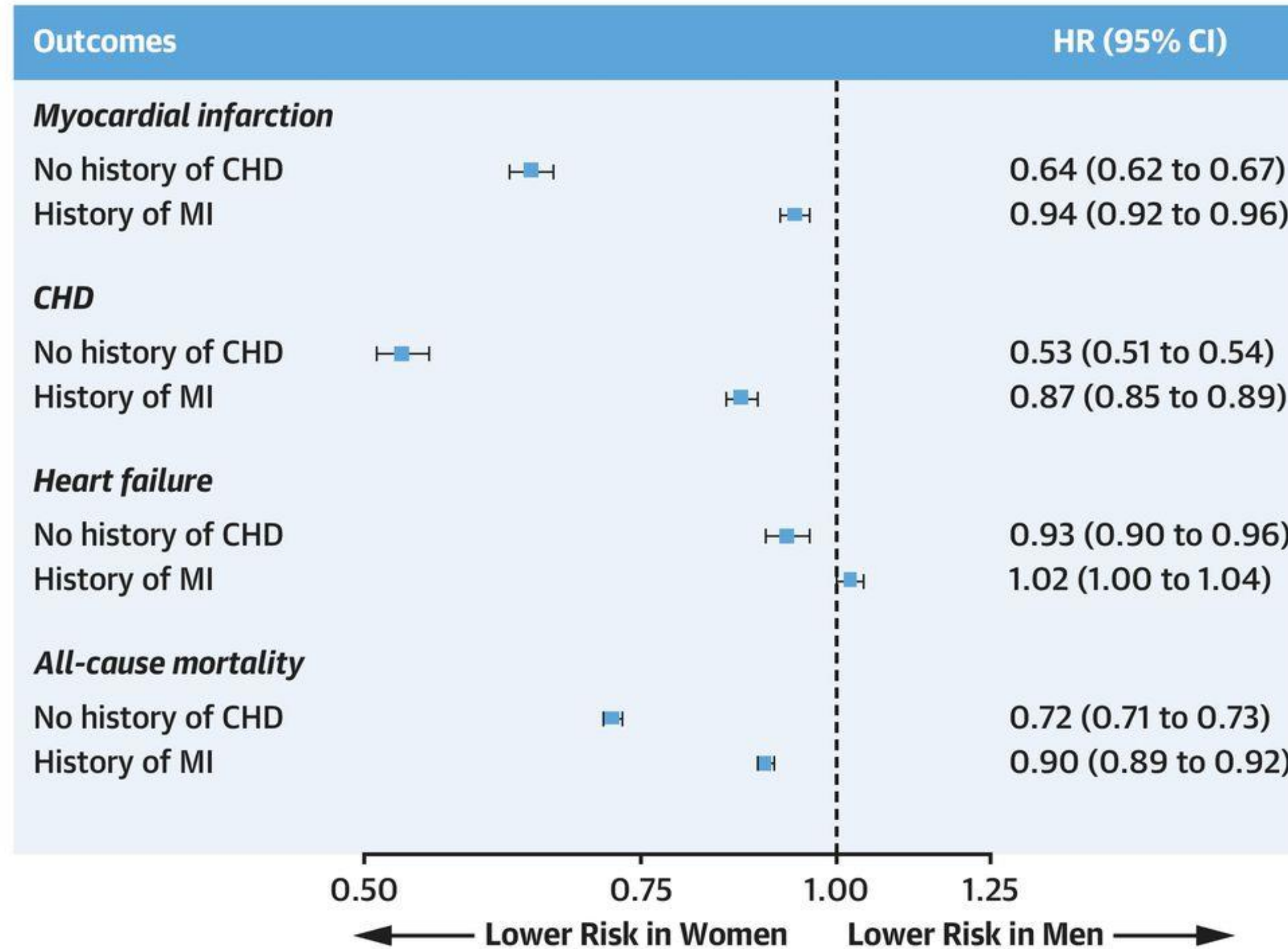
- Cardiovascular disease claims 1 in 3 women in the United States
 - More deaths from cardiovascular disease than all cancers combined
- Historically, women under represented in cardiovascular research and drug trials
- Unique factors contribute to healthcare disparity
 - Biochemical/anatomical
 - Socioeconomic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

FIGURE 2

Relative Risk of Cardiovascular Events in Men and Women With Diabetes

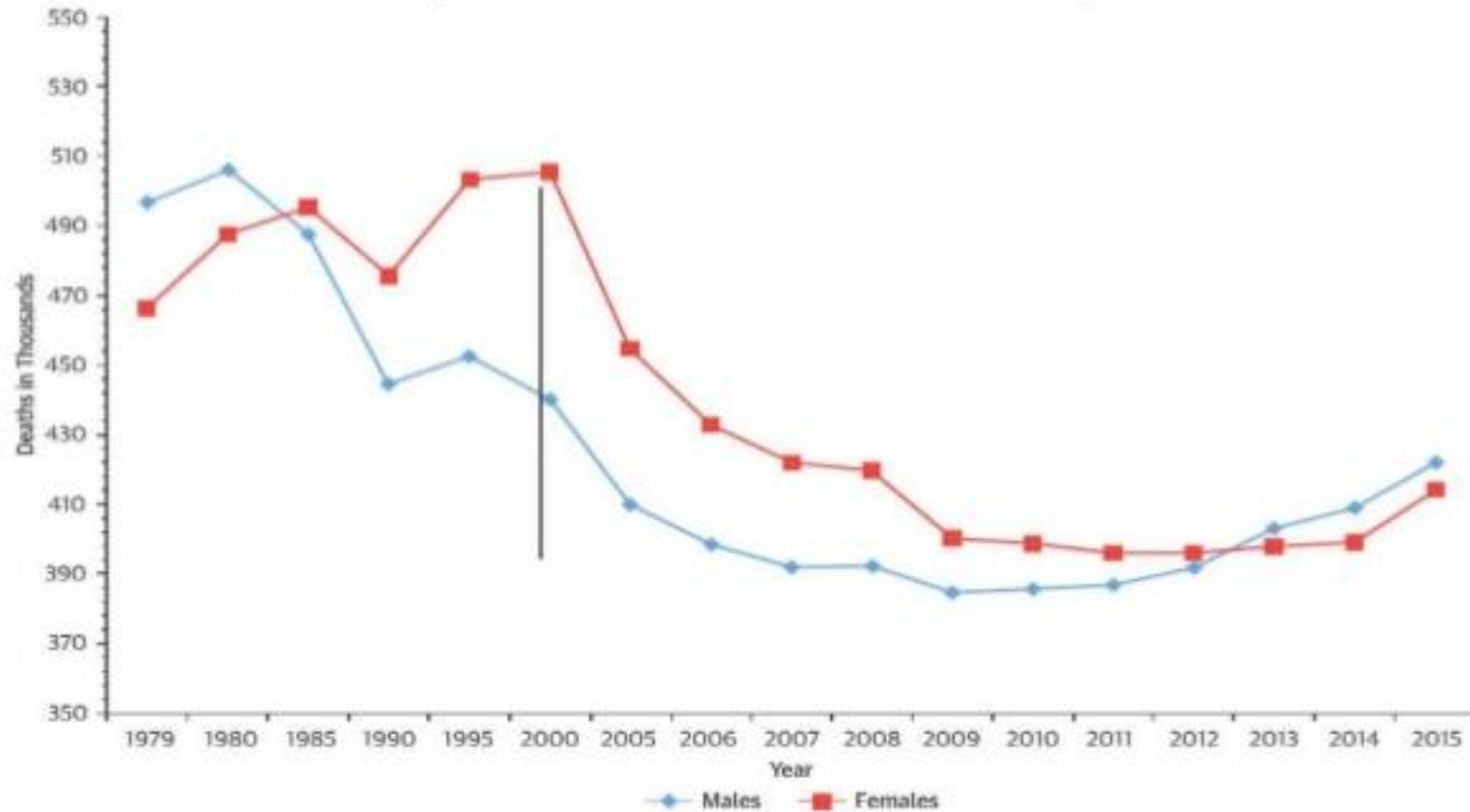


CENTRAL ILLUSTRATION: Women-to-Men Hazard Ratios for Myocardial Infarction, Coronary Heart Disease, Heart Failure, and All-Cause Mortality Among Beneficiaries Without a History of Coronary Heart Disease and Among Beneficiaries With a Previous Myocardial Infarction



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

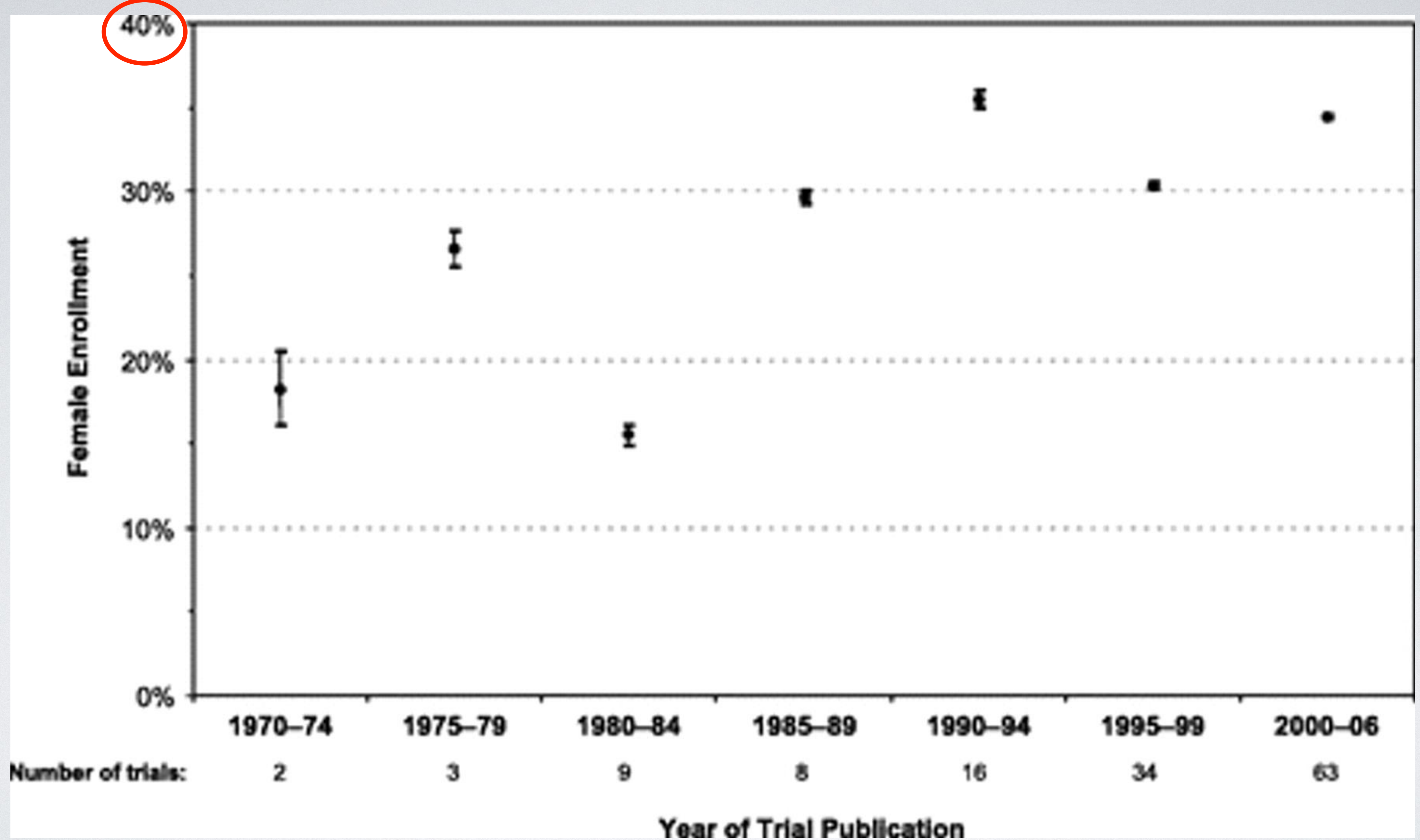
CVD Mortality Trends for Males and Females (United States 1979-2015)

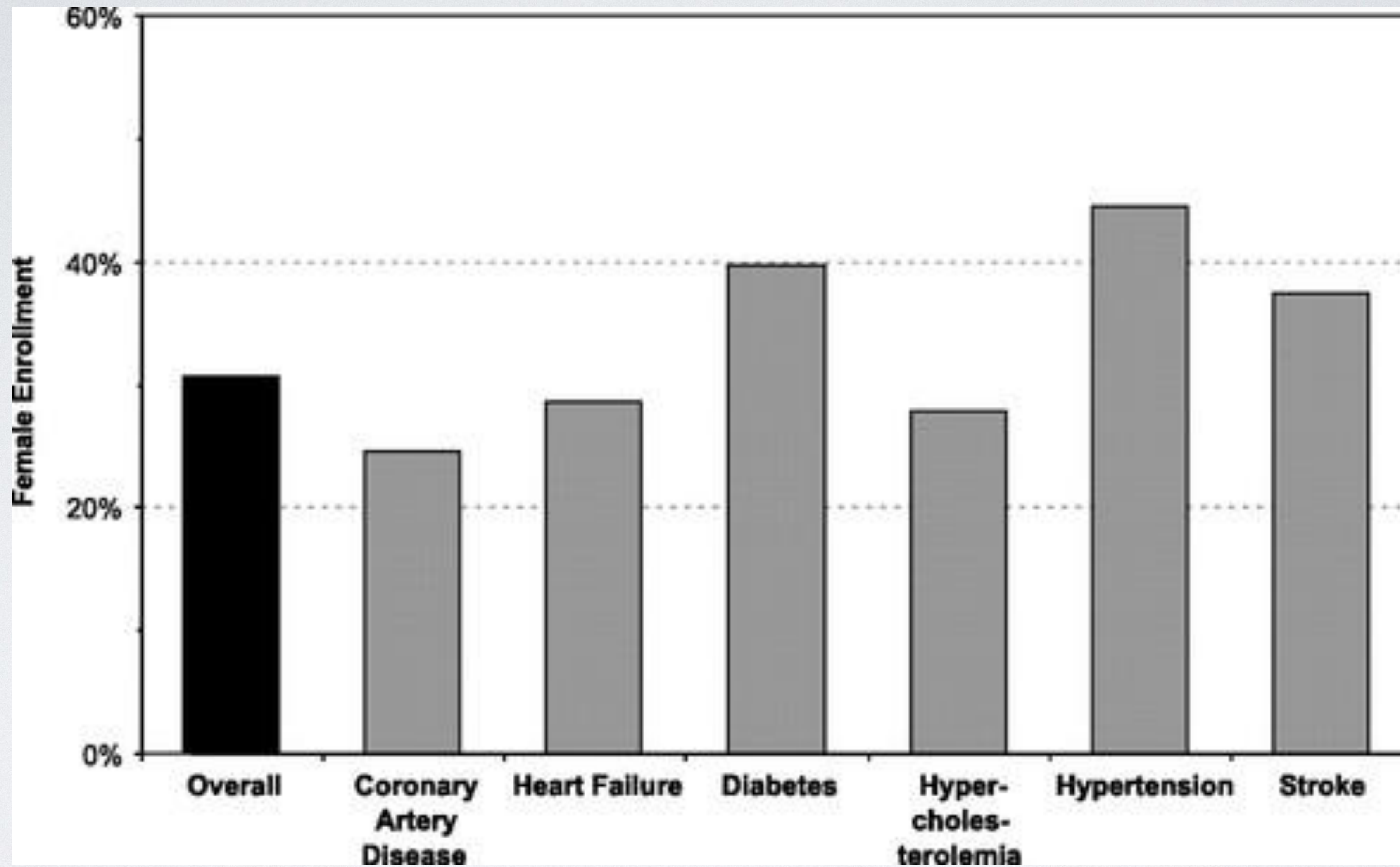


Benjamin, et al. Heart disease and stroke statistics -
2018 update. Circulation. 2018;129:e67-492

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



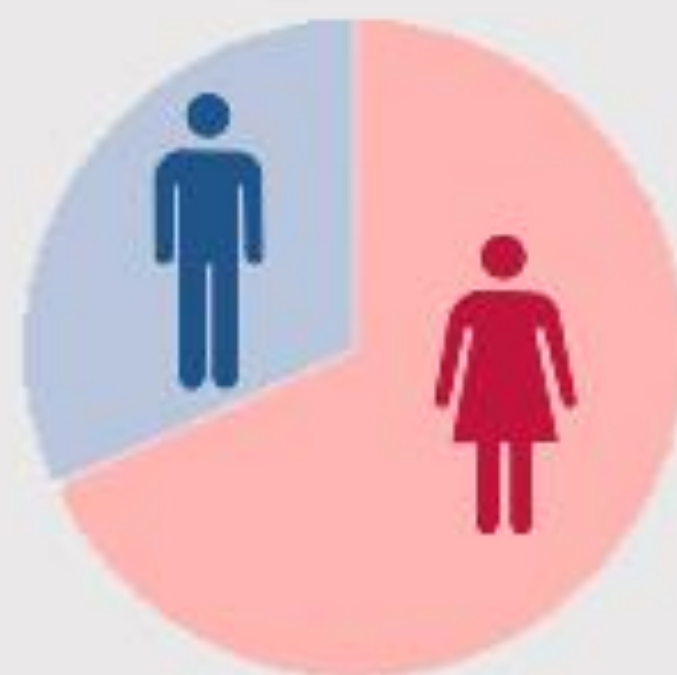


NHLBI Heart Research: Fiscal Year 2013

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



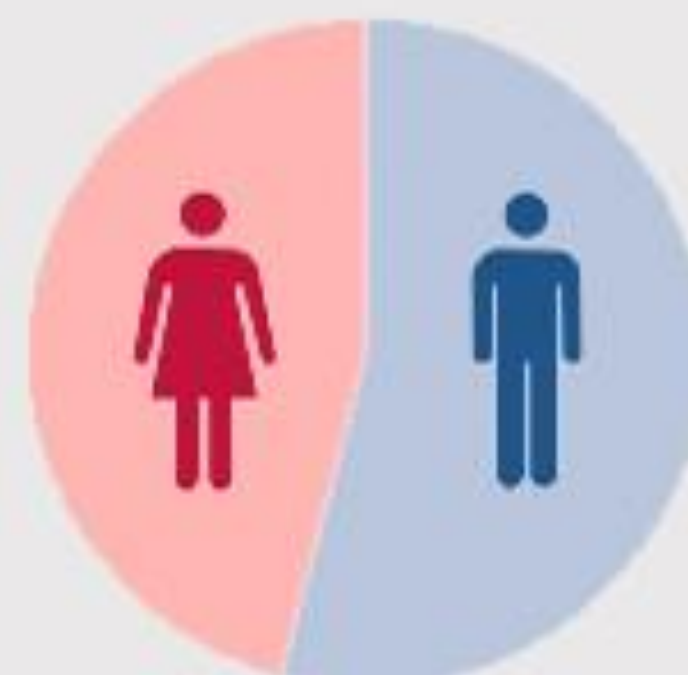
Percent of Men and Women Enrolled in NHLBI Cardiovascular Trials



Including the Women's
Health Initiative

68.2% Women

31.8% Men



Excluding the Women's
Health Initiative

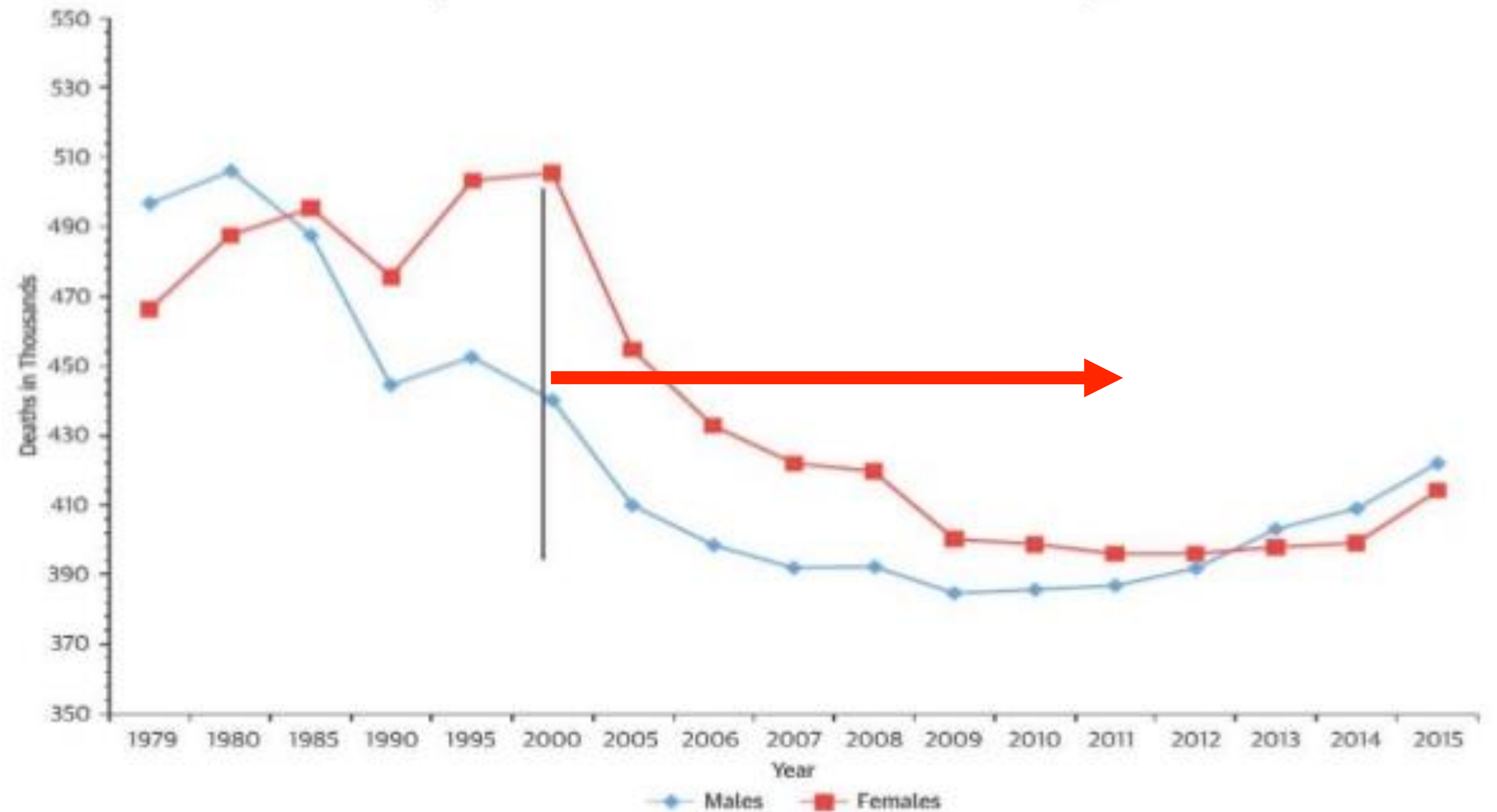
45.9% Women

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)



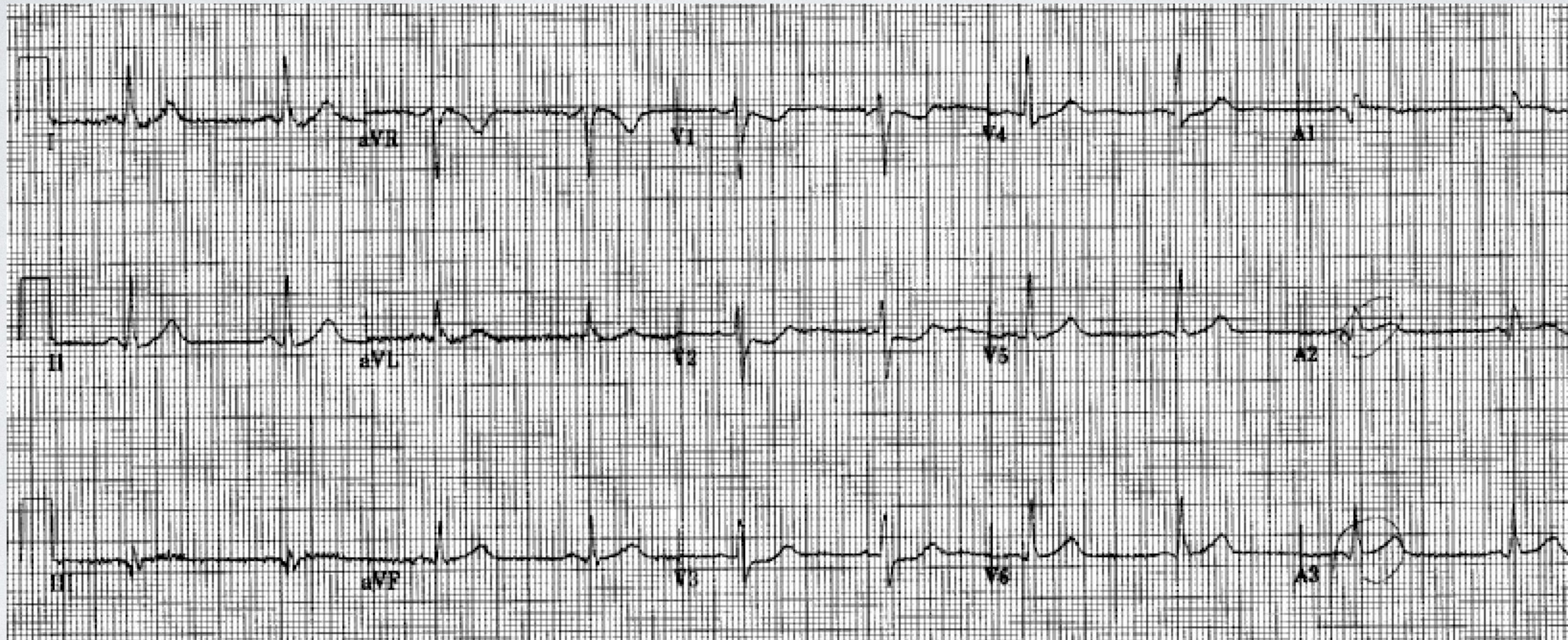
Benjamin, et al. Heart disease and stroke statistics - 2018 update. Circulation. 2018;129:e67-492

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

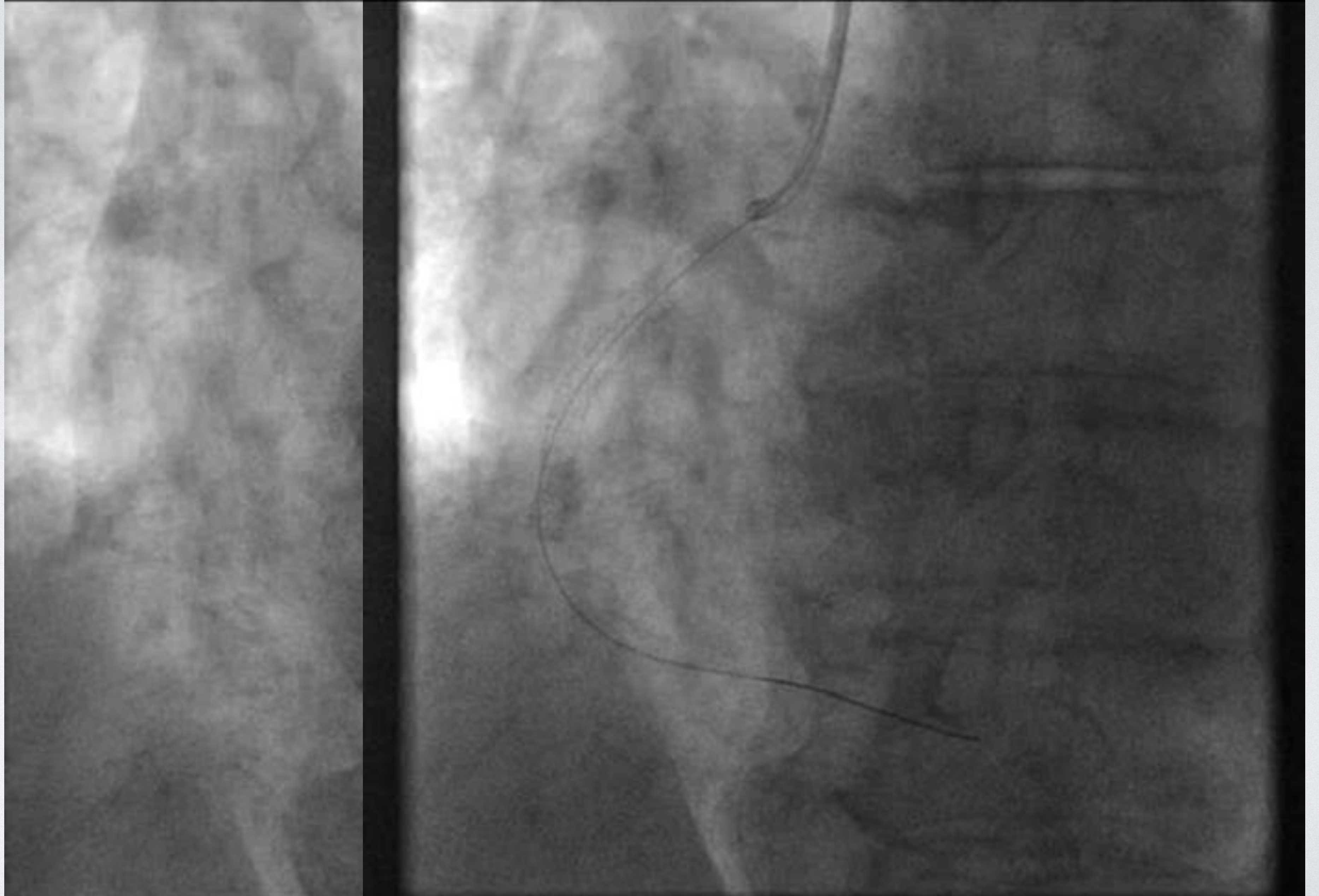


| | 16:07 | 17:44 | 22:19 | 00:00 | 04:58 | 13:17 |
|--|----------|---------|---------|---------|---------|---------|
| Cardiac Markers | | | | | | |
| <input type="checkbox"/> Troponin T QuaNT High Sensitivity | * C 508 | * C 621 | * C 715 | * C 809 | * C 876 | * C 898 |
| <input type="checkbox"/> pro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



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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, ³⁷ 2004 | GRACE Registry | ACS | 1999-2002 | 20 881 | 65.8 | Yes | No | 7.3 | 10.6 | 8.4 |
| Canto et al, ⁸ 2000 | National MI Registry | MI | 1994-1998 | 434 877 | 69.3 | Yes | Yes | 28.6 | 38.6 | 32.7 |
| Canto et al, ³⁸ 2002 | Alabama UA Registry | UA | 1993-1999 | 4167 | 72.3 | Yes | Yes | 50.2 | 53.0 | 51.7 |
| Culi et al, ³⁹ 2002 | CCUs Croatia | MI | 1990-1995 | 1996 | 58.8 | Yes | No | 12.4 | 20.3 | 14.8 |
| Dorsch et al, ⁷ 2001 | United Kingdom | MI | 1995 | 2096 | 70.6 | Yes | No | 17.6 | 24.6 | 20.1 |
| Goldberg et al, ⁴⁰ 1998 | Worcester MI Study | MI | 1986-1988 | 1360 | 67.7 | Yes | No | 18.0 | 23.0 | 20.0 |
| Milner et al, ⁴¹ 2004 | Worcester MI Study | MI | 1997-1999 | 2073 | 70.2 | Yes | No | 30.9 | 45.8 | 37.3 |
| Roger et al, ⁴² 2000 | Olmsted County, Minnesota | UA | 1985-1992 | 2271 | 63.0 | Yes | No | 25.0 | 19.0 | 22.0 |
| Stern et al, ⁴³ 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% |

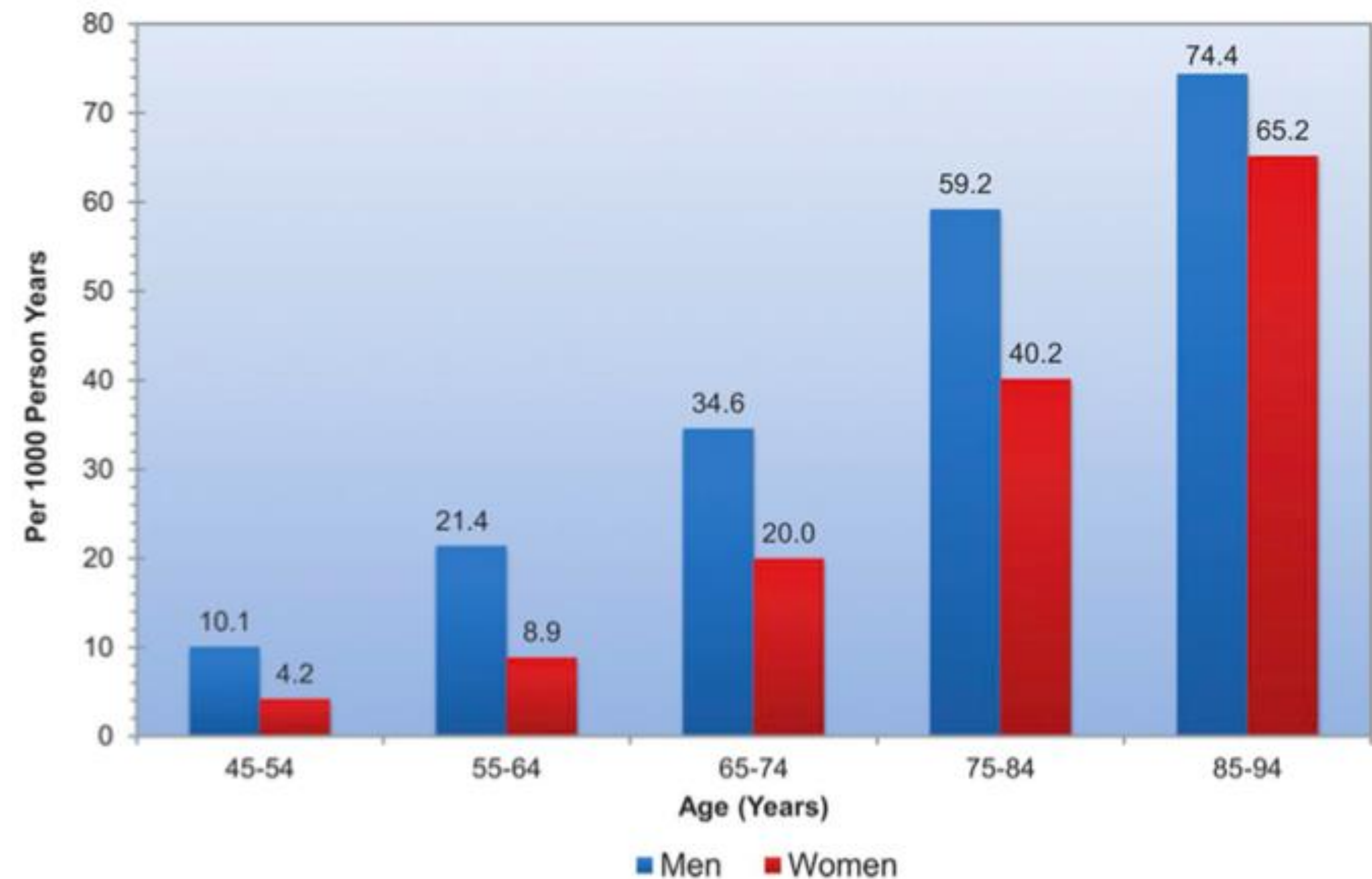
DIFFERENCES: HEART FAILURE

- 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

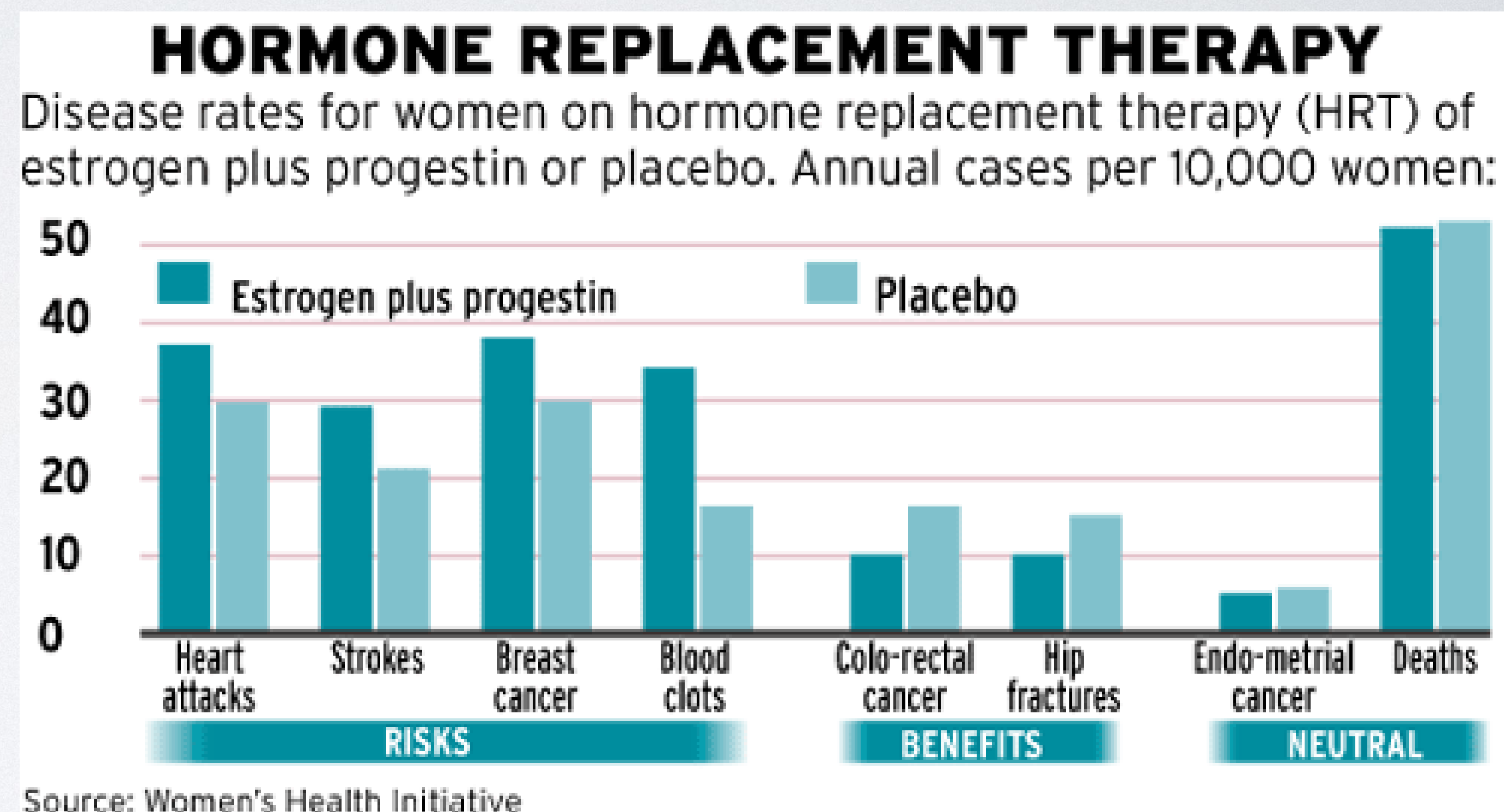
Incidence of cardiovascular disease (coronary heart disease, heart failure, stroke, or intermittent claudication; does not include hypertension alone) by age and sex



Framingham Heart Study, 1980–2003.

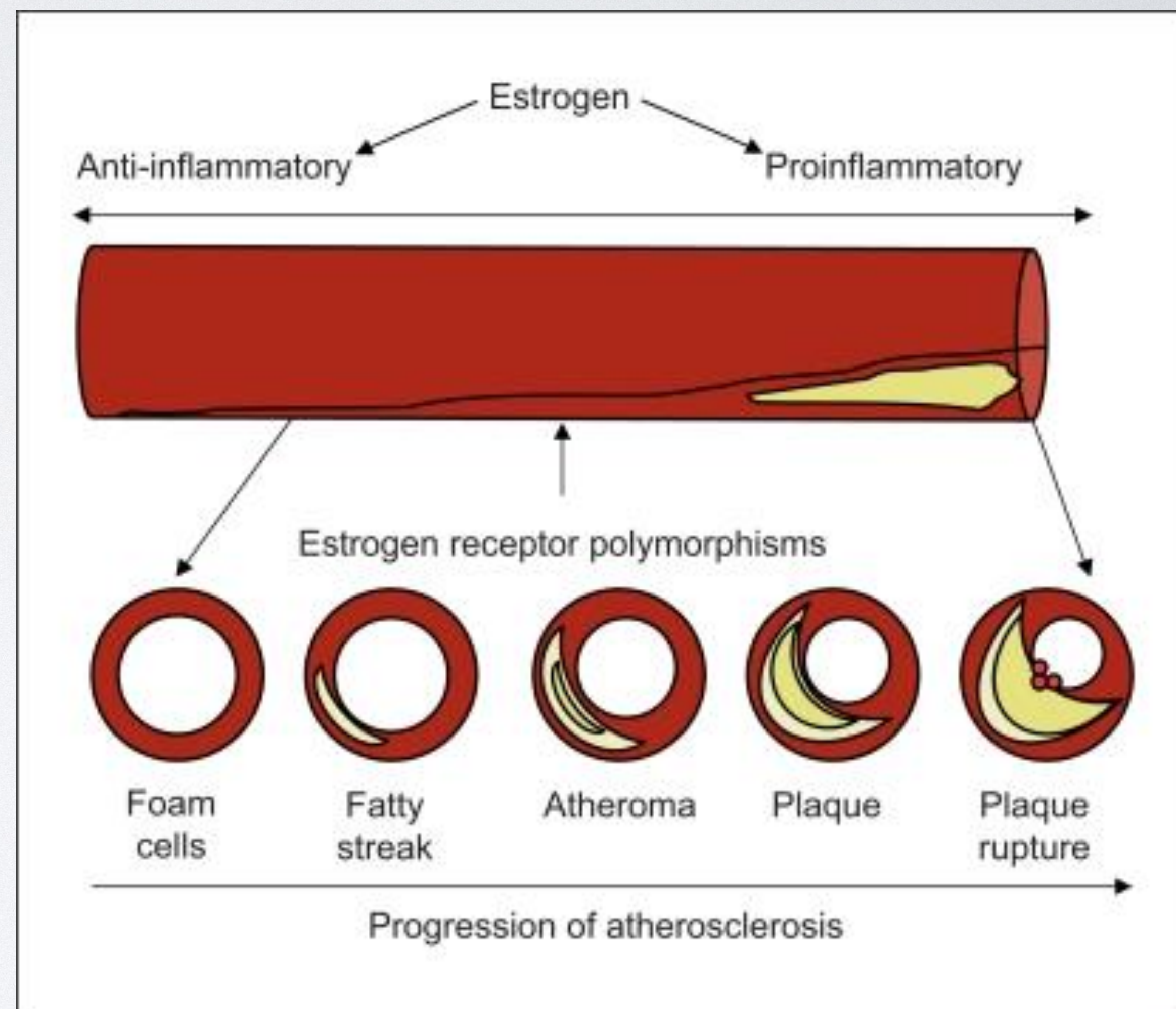
HORMONE REPLACEMENT

- 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:

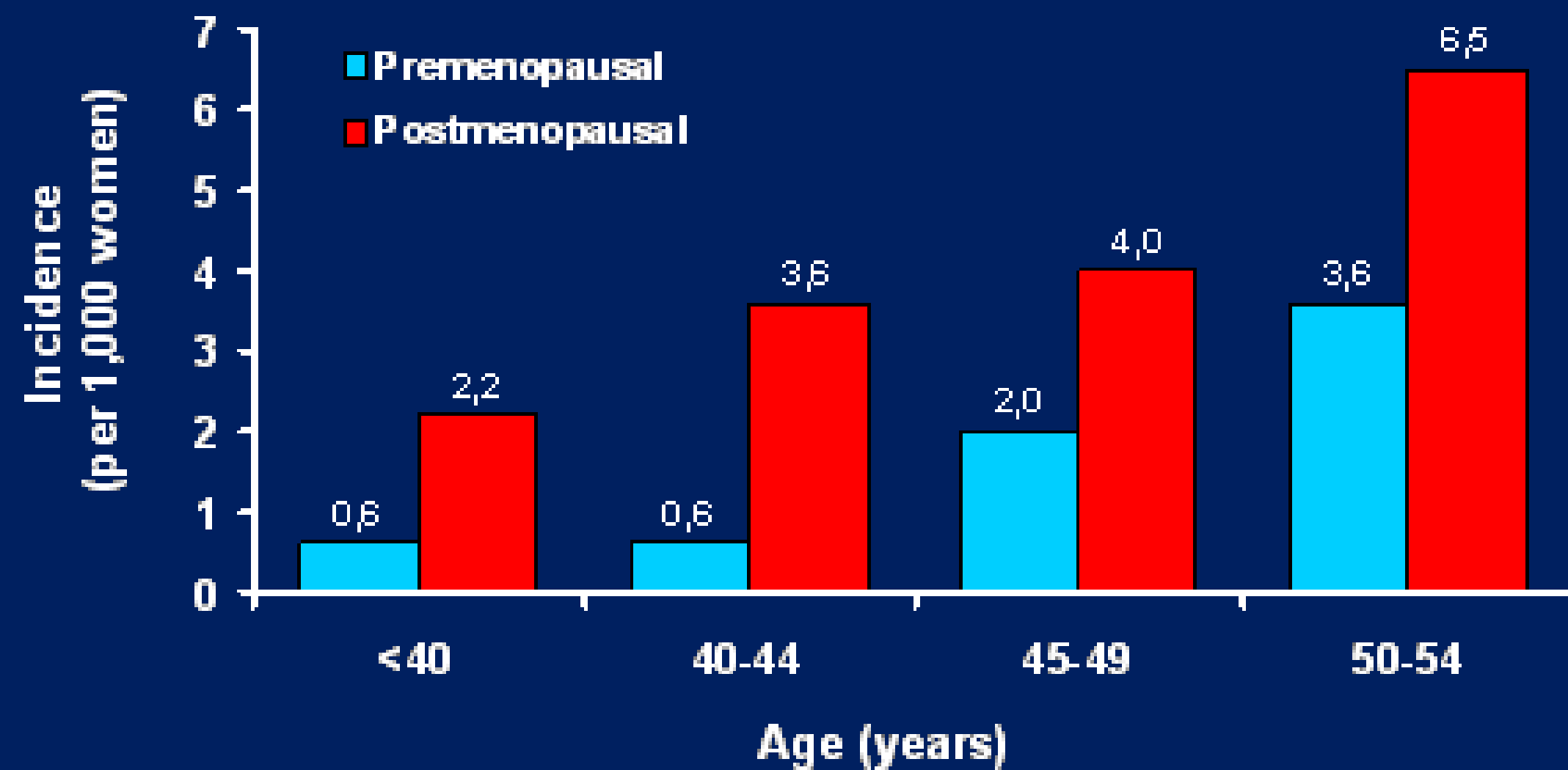
Observed Agatston Calcium Score (optional):

Calculate

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

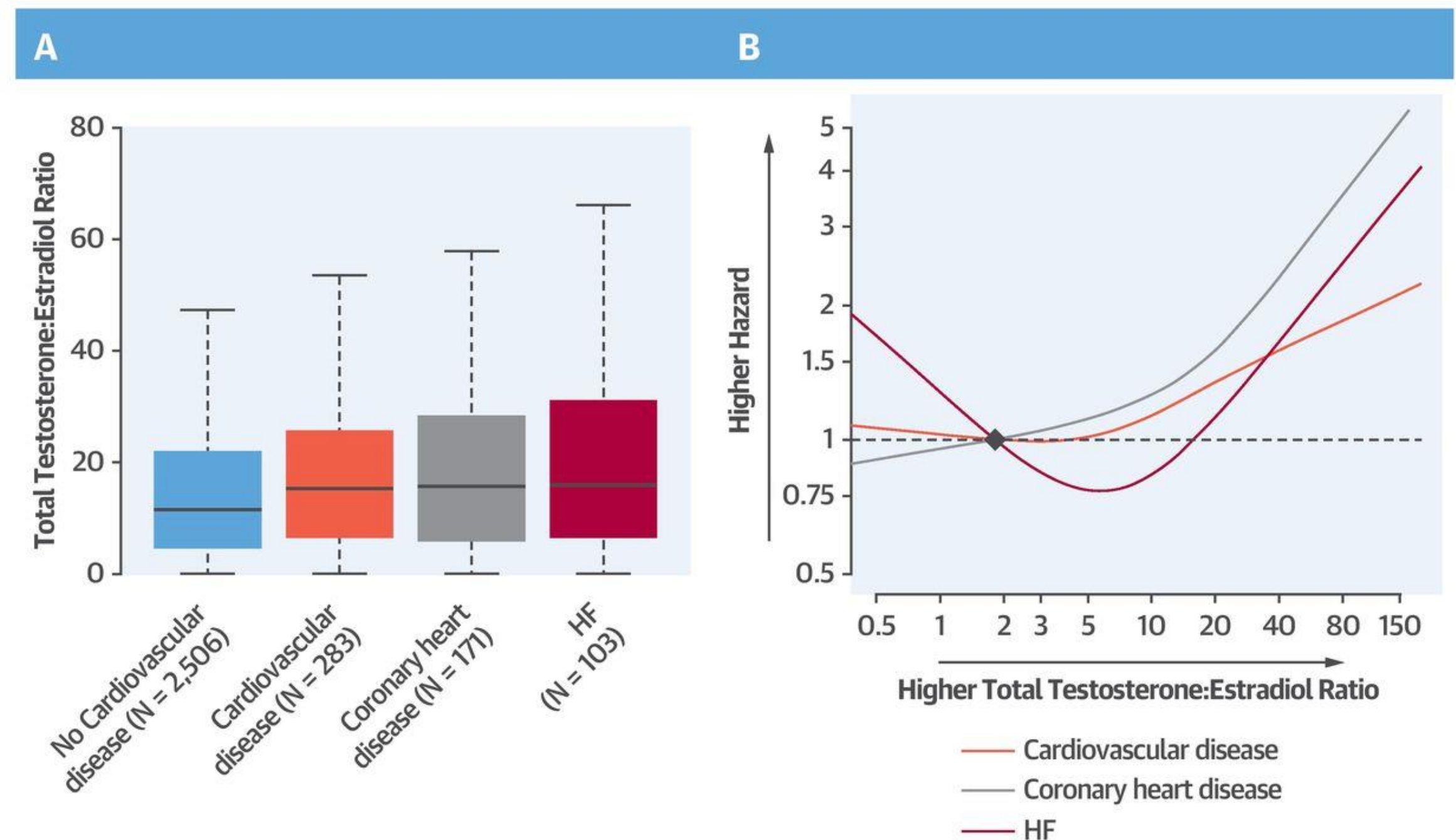
HORMONAL DIFFERENCES

Incidence of Cardiovascular Disease Relation to Menopause Status



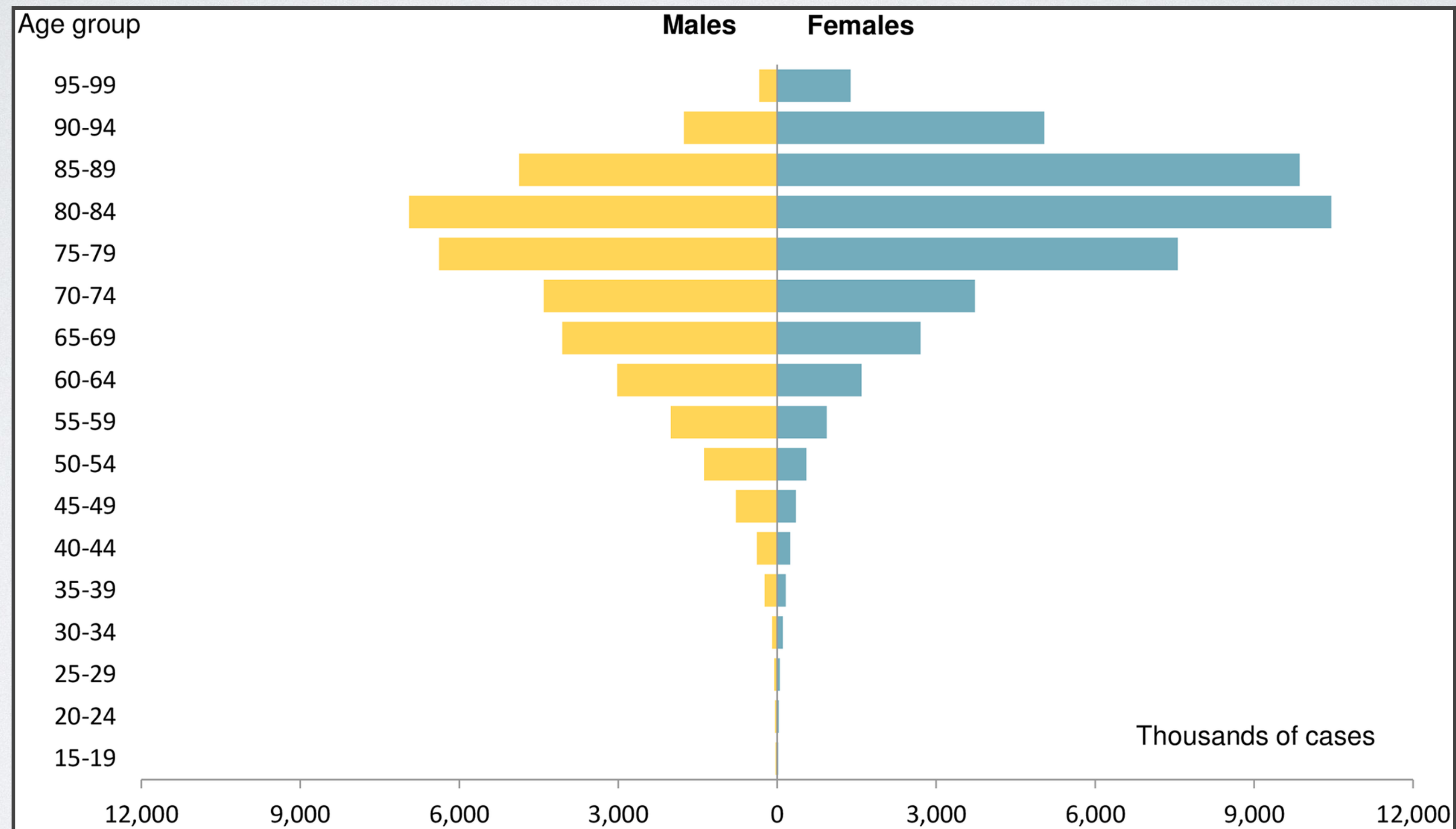
Kannel W, et al. *Ann Intern Med.* 1976;85:447-52.

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



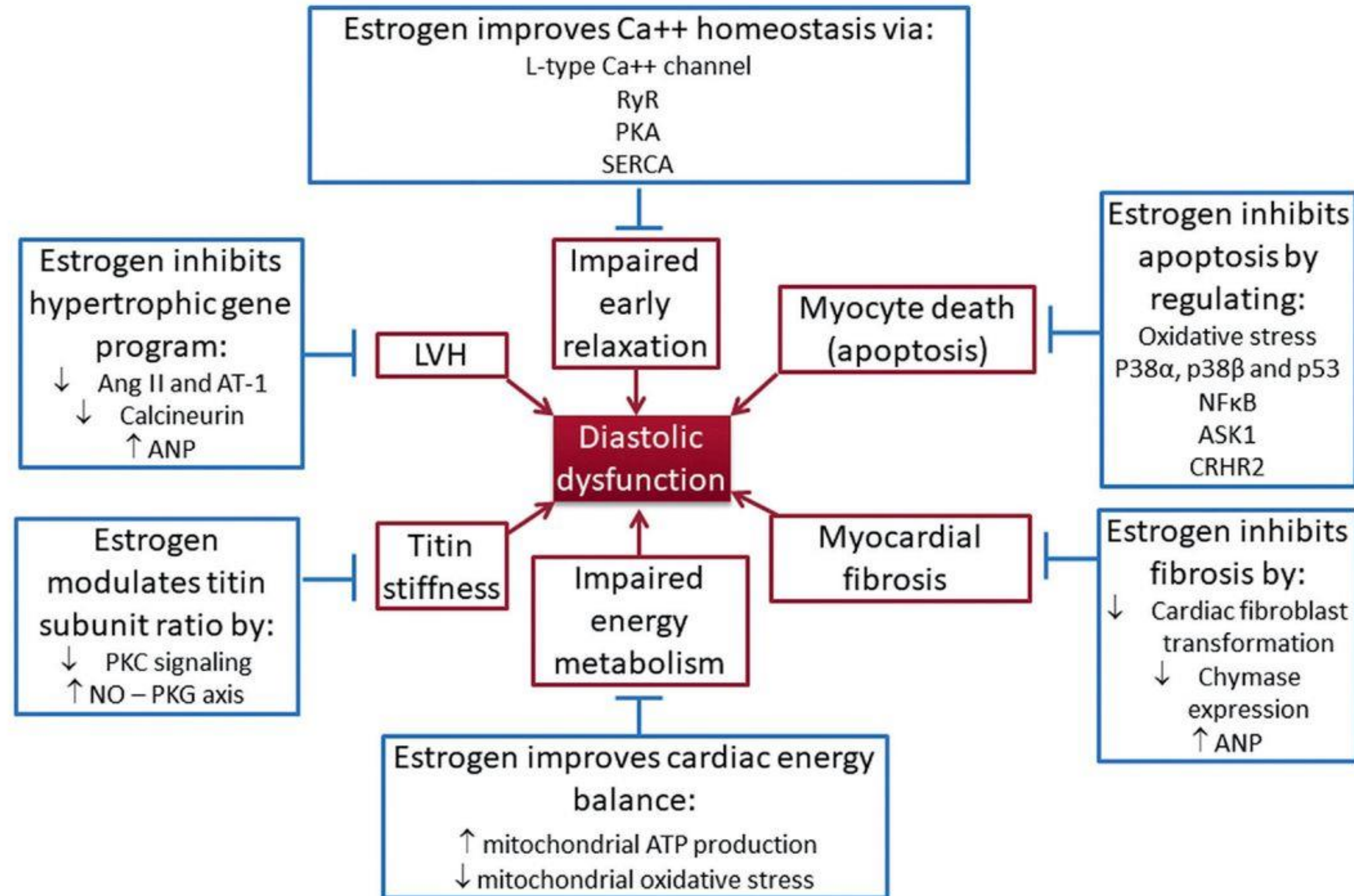
Zhao, D. et al. *J Am Coll Cardiol.* 2018;71(22):2555-66.

HORMONAL DIFFERENCES



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

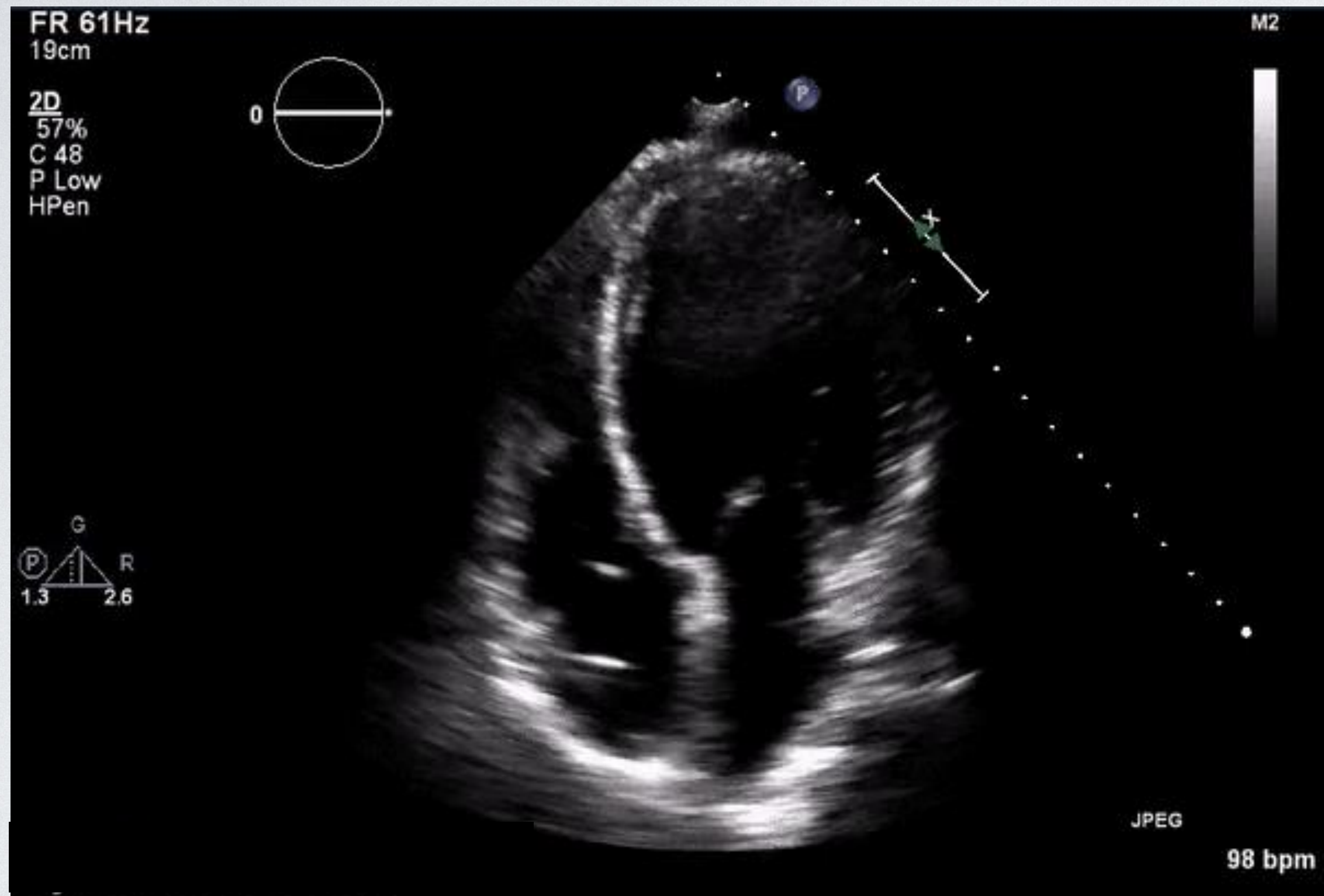
CENTRAL ILLUSTRATION: The Role of Estrogen in Regulation of Titin Isoform Switch



Maslov, P.Z. et al. J Am Coll Cardiol HF. 2019;7(3):192-203.

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

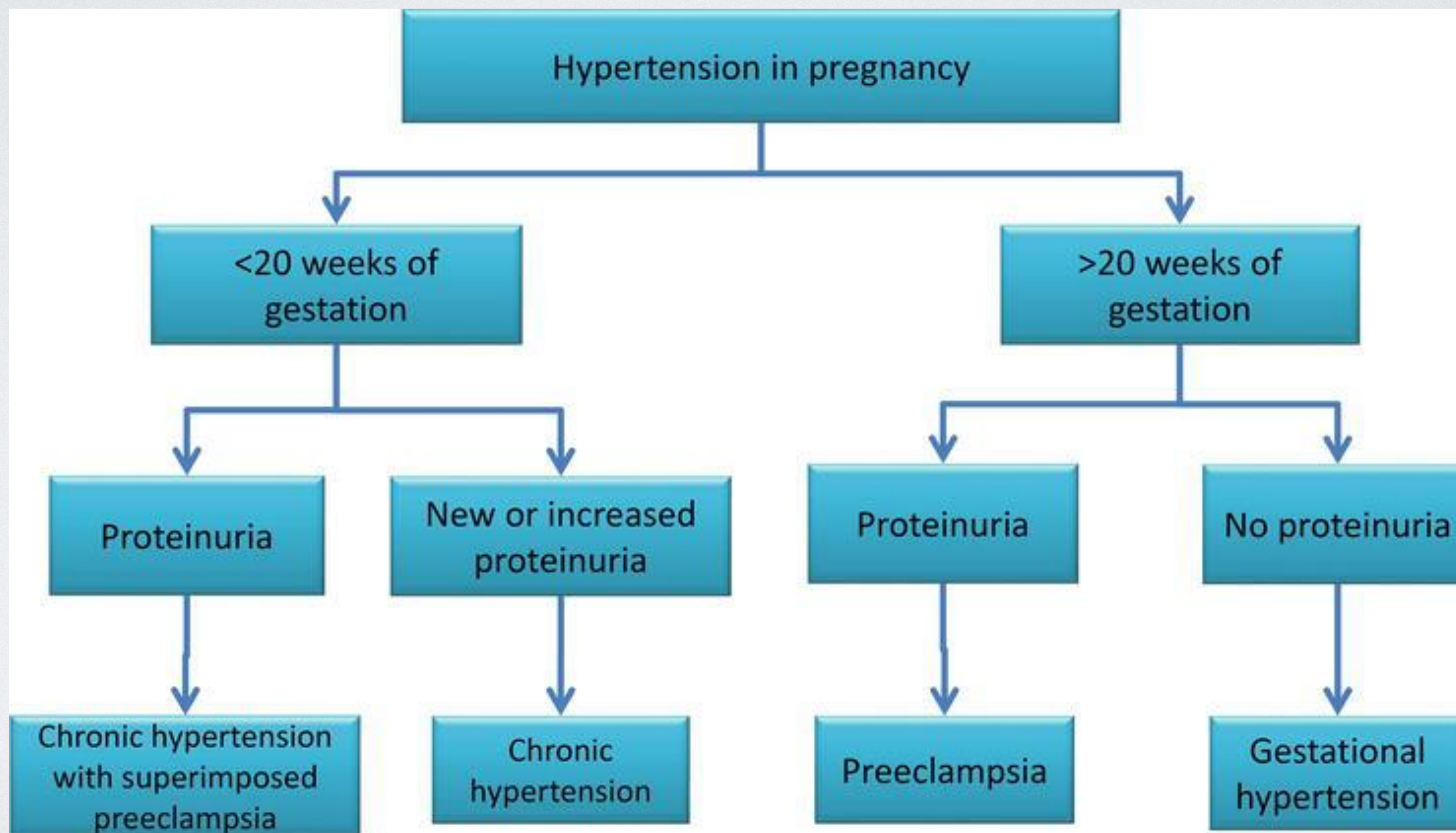
PERIPARTUM CARDIOMYOPATHY

- 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

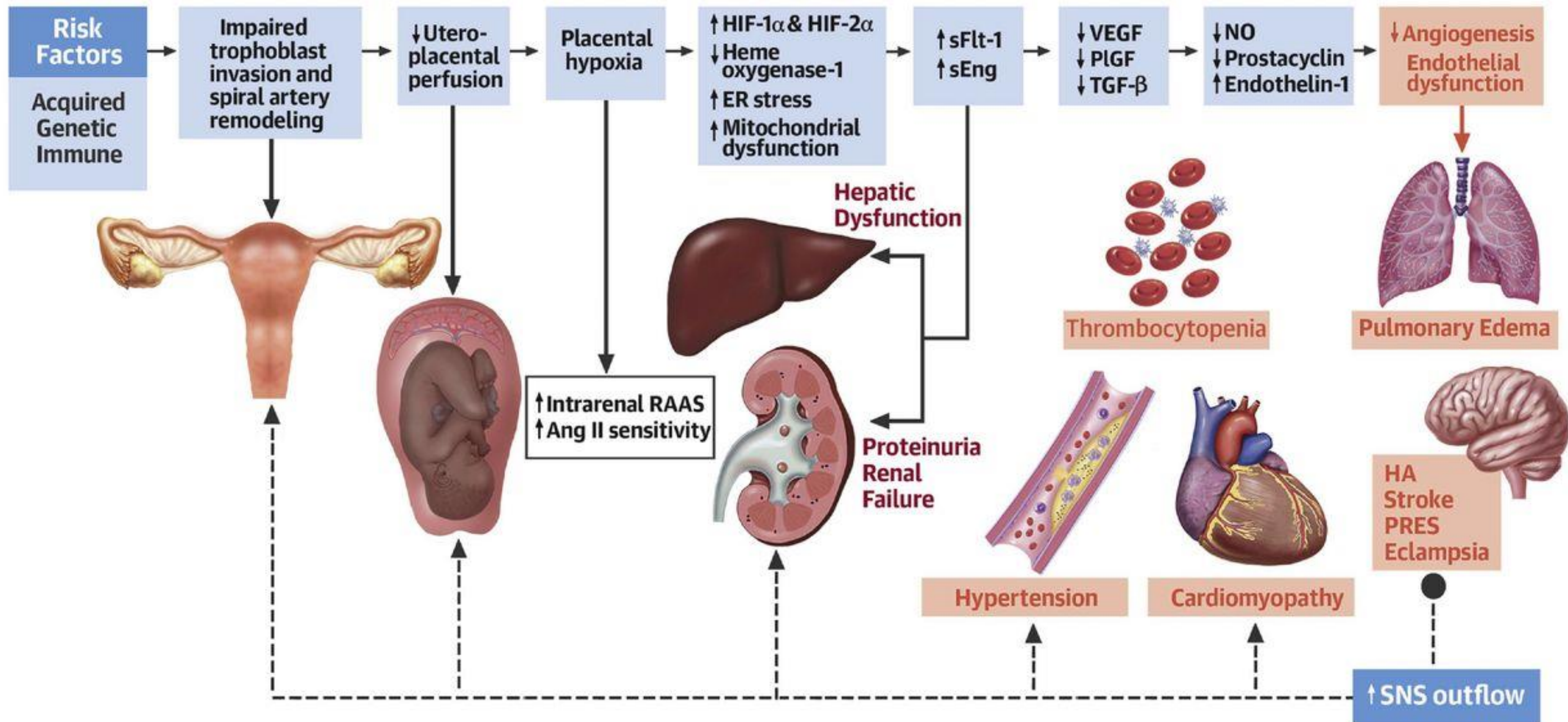
PERIPARTUM CARDIOMYOPATHY

- 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



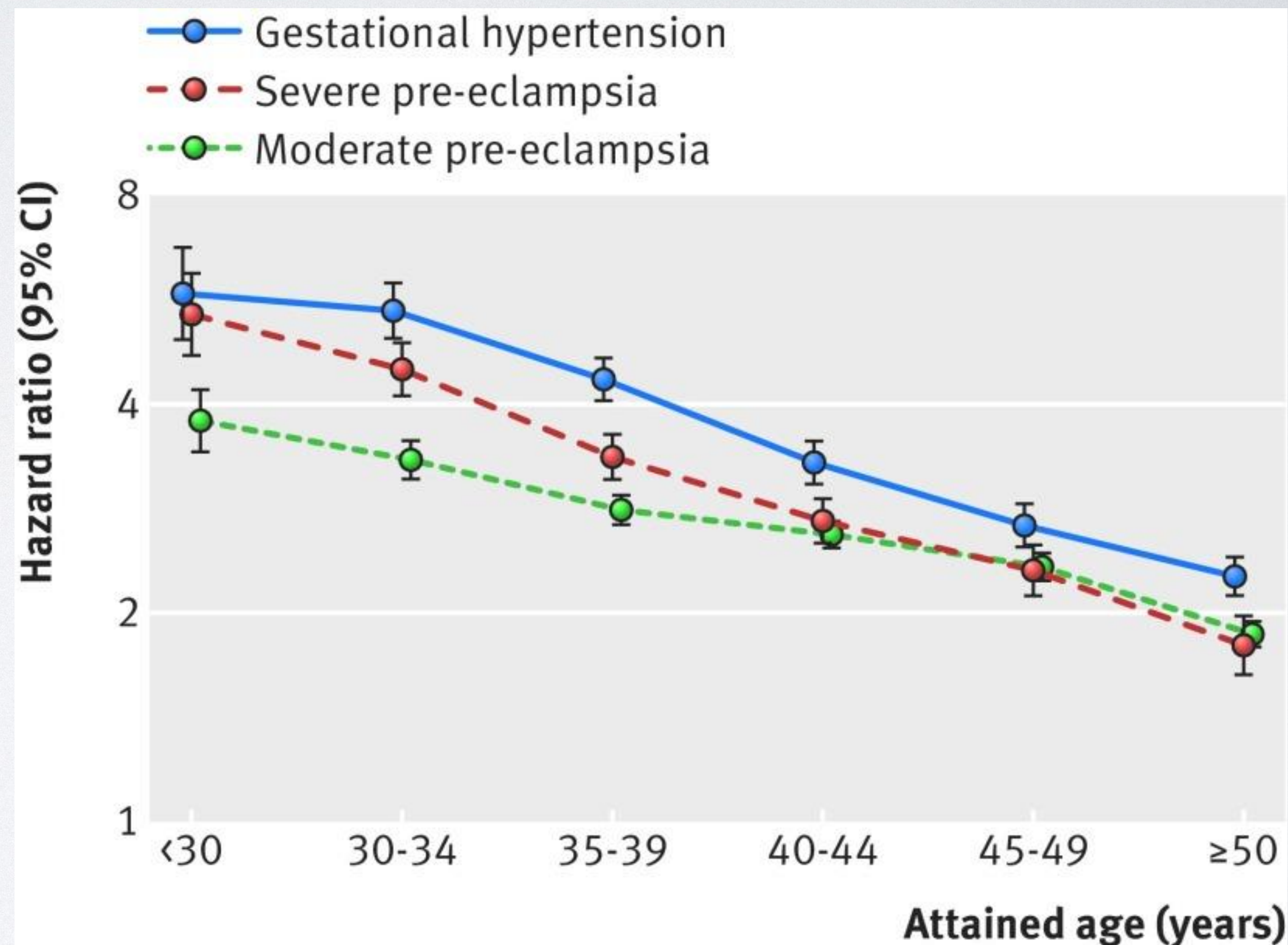
CENTRAL ILLUSTRATION: Pathogenesis of Preeclampsia



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

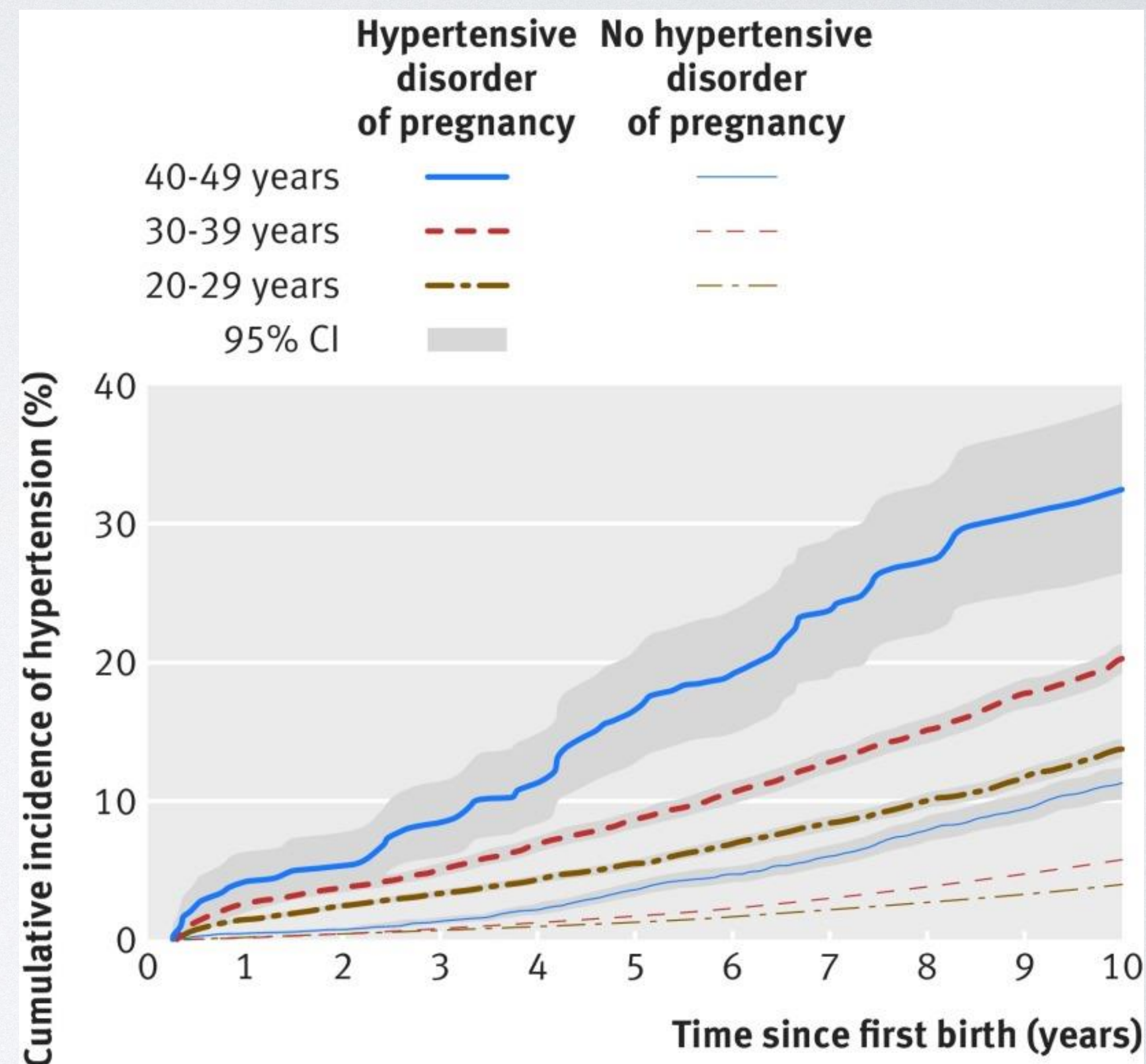
HYPERTENSION IN PREGNANCY

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



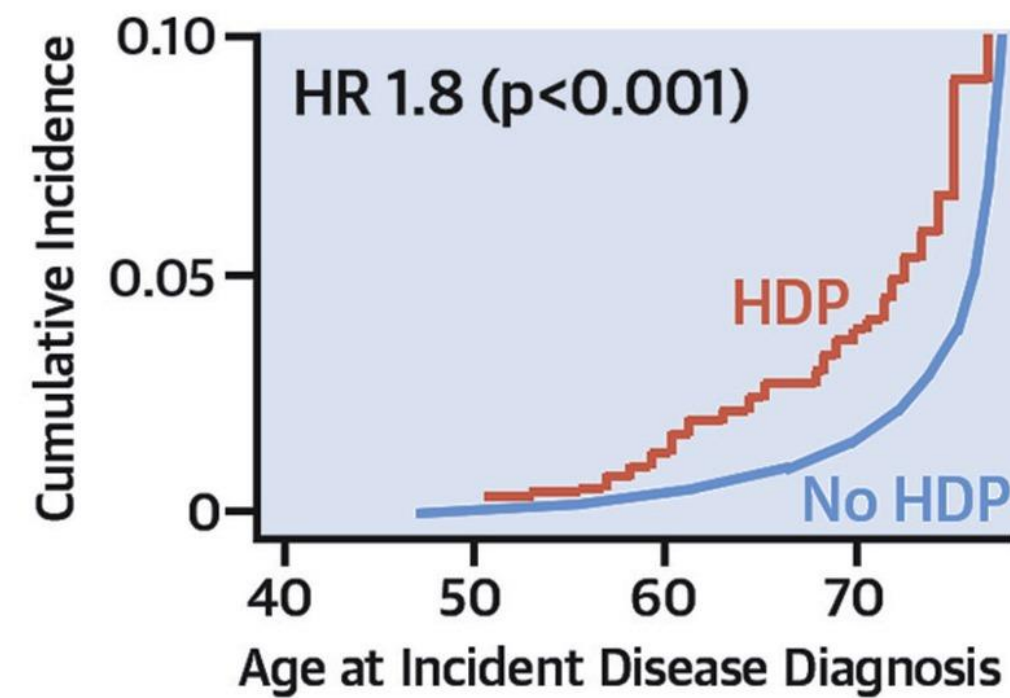
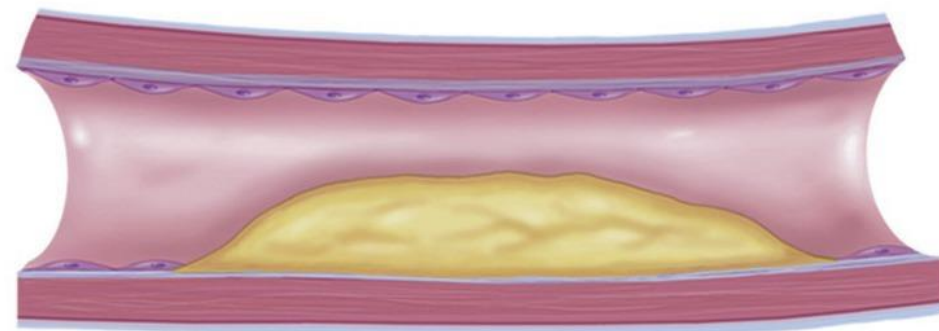
HYPERTENSION IN PREGNANCY

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

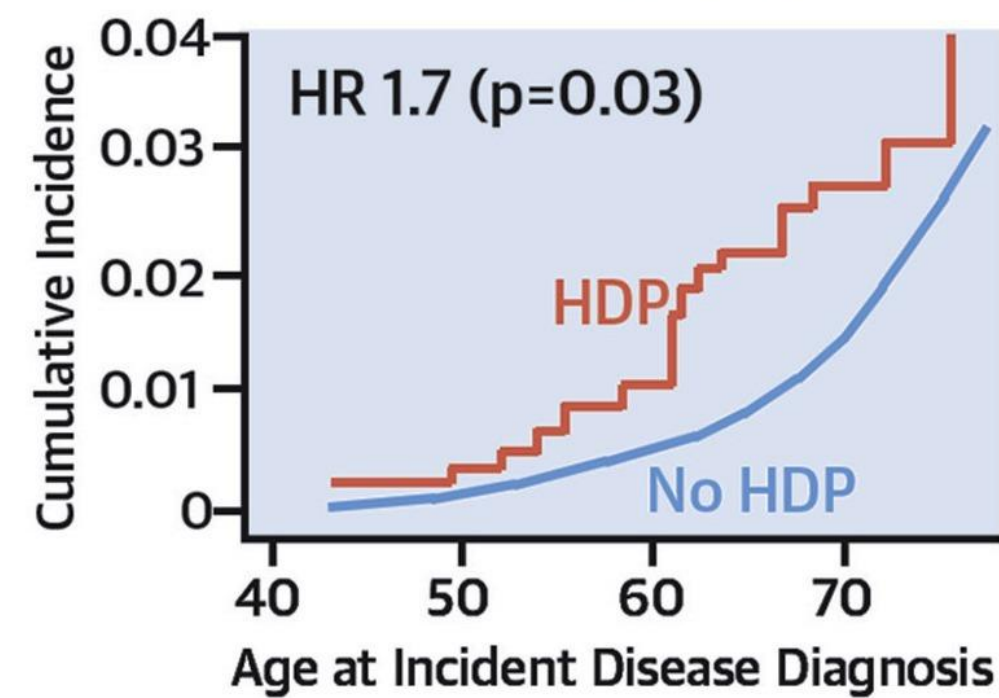
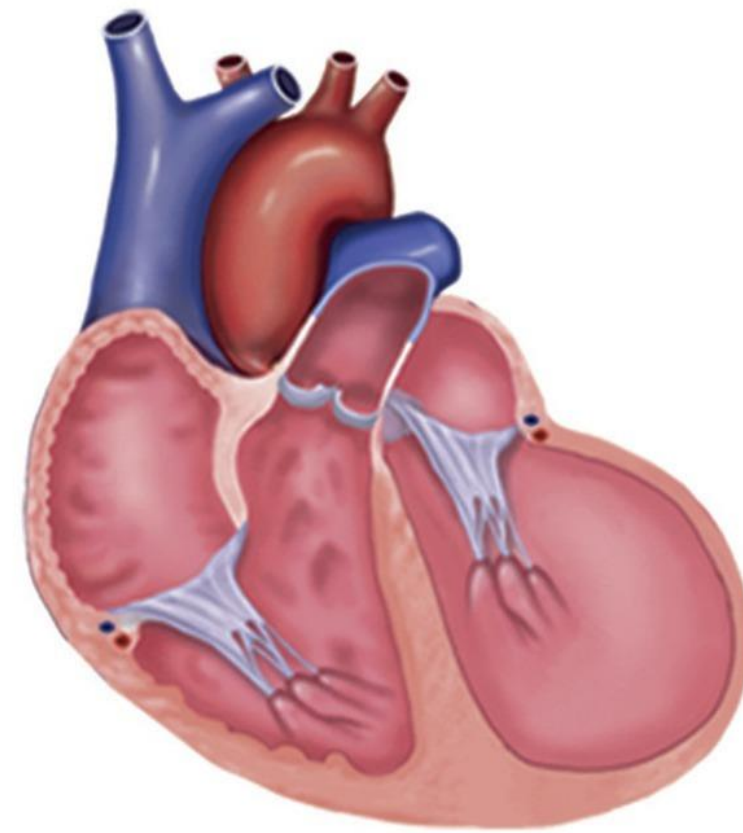


CENTRAL ILLUSTRATION: Hypertensive Disorders of Pregnancy Are Associated With Long-Term Risk of Diverse Cardiovascular Diseases

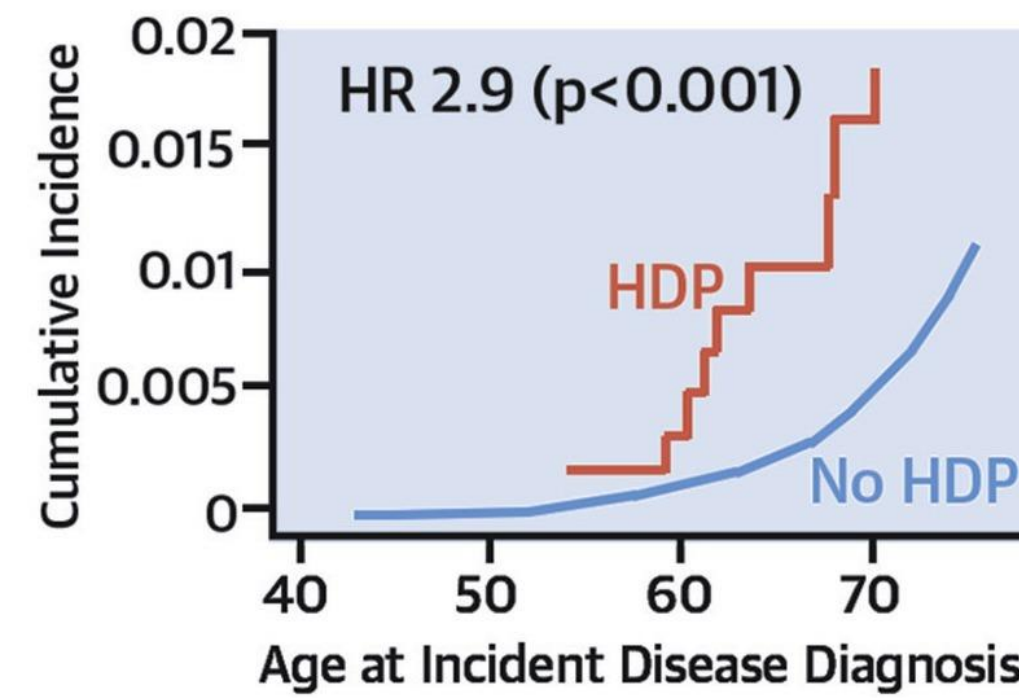
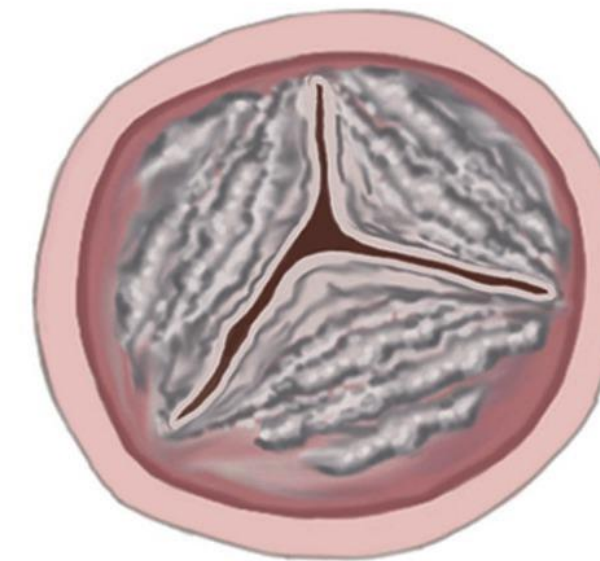
Coronary Artery Disease



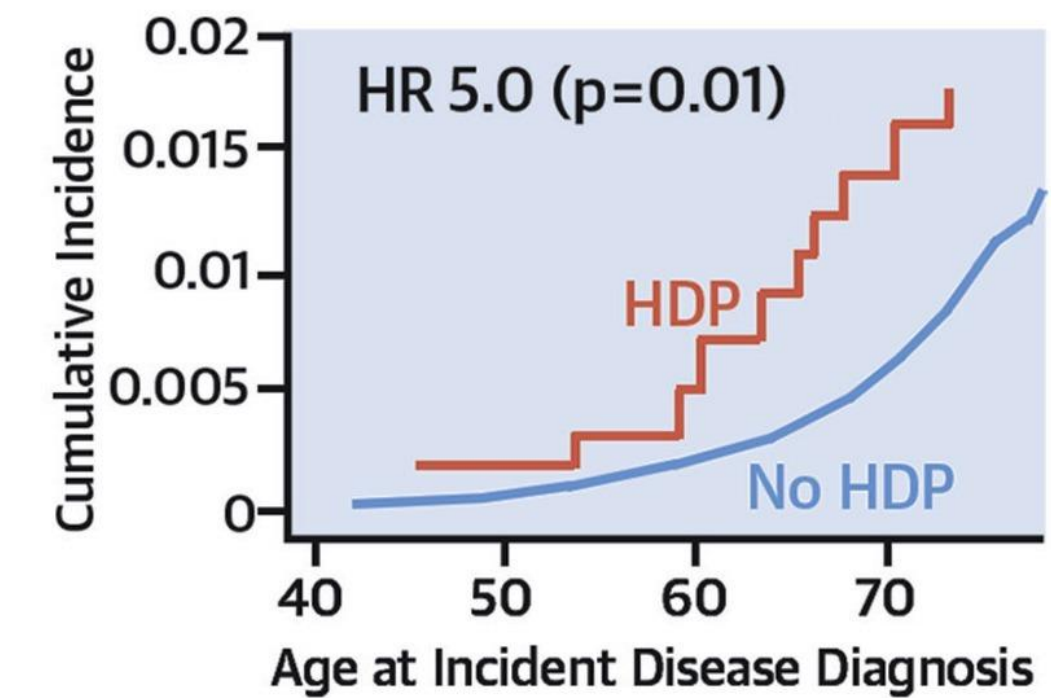
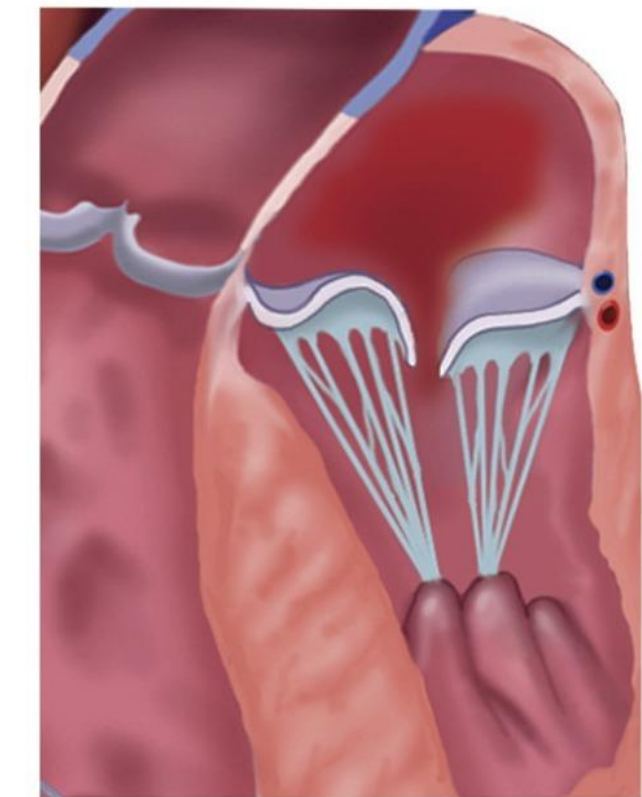
Heart Failure



Aortic Stenosis



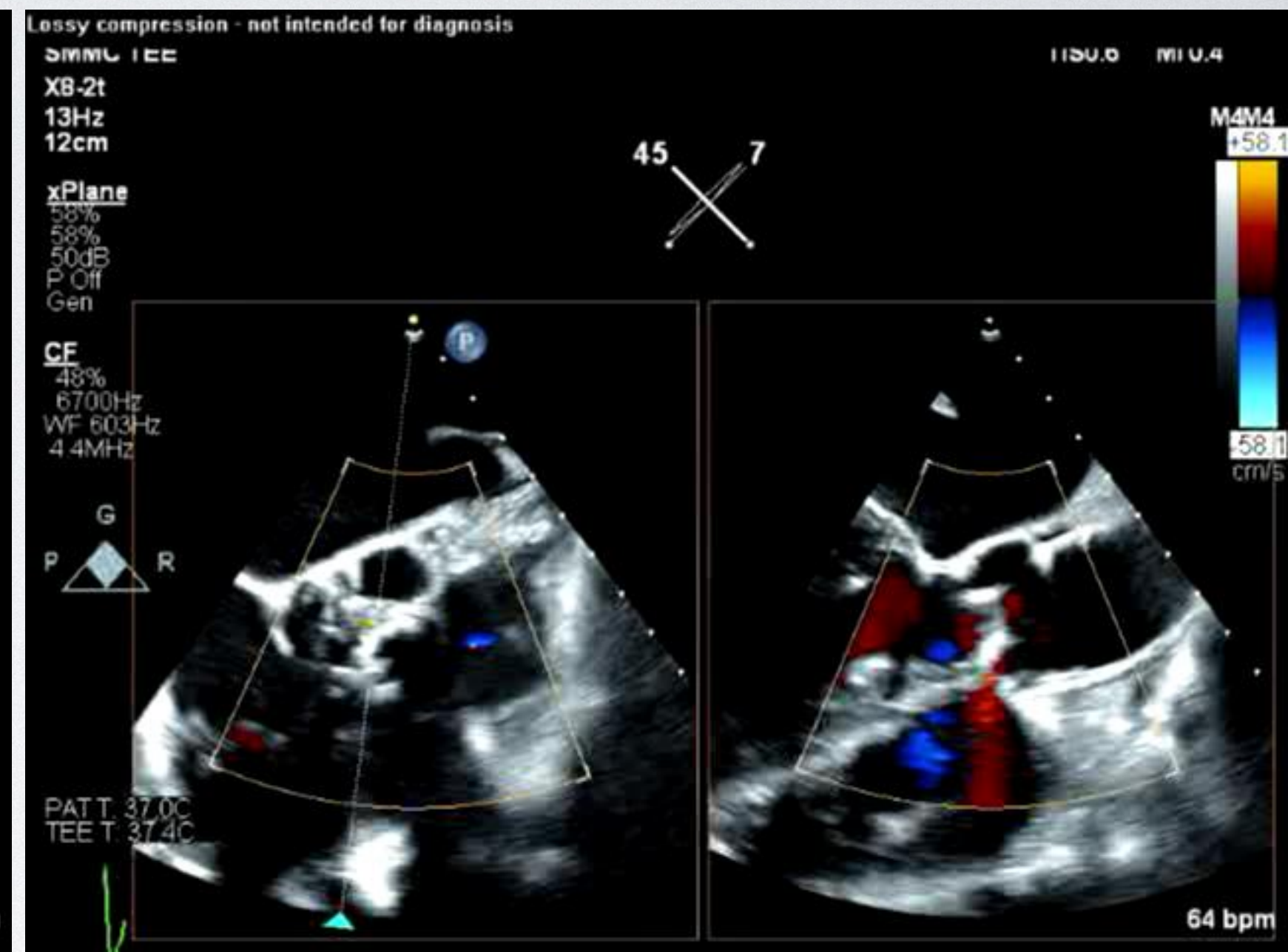
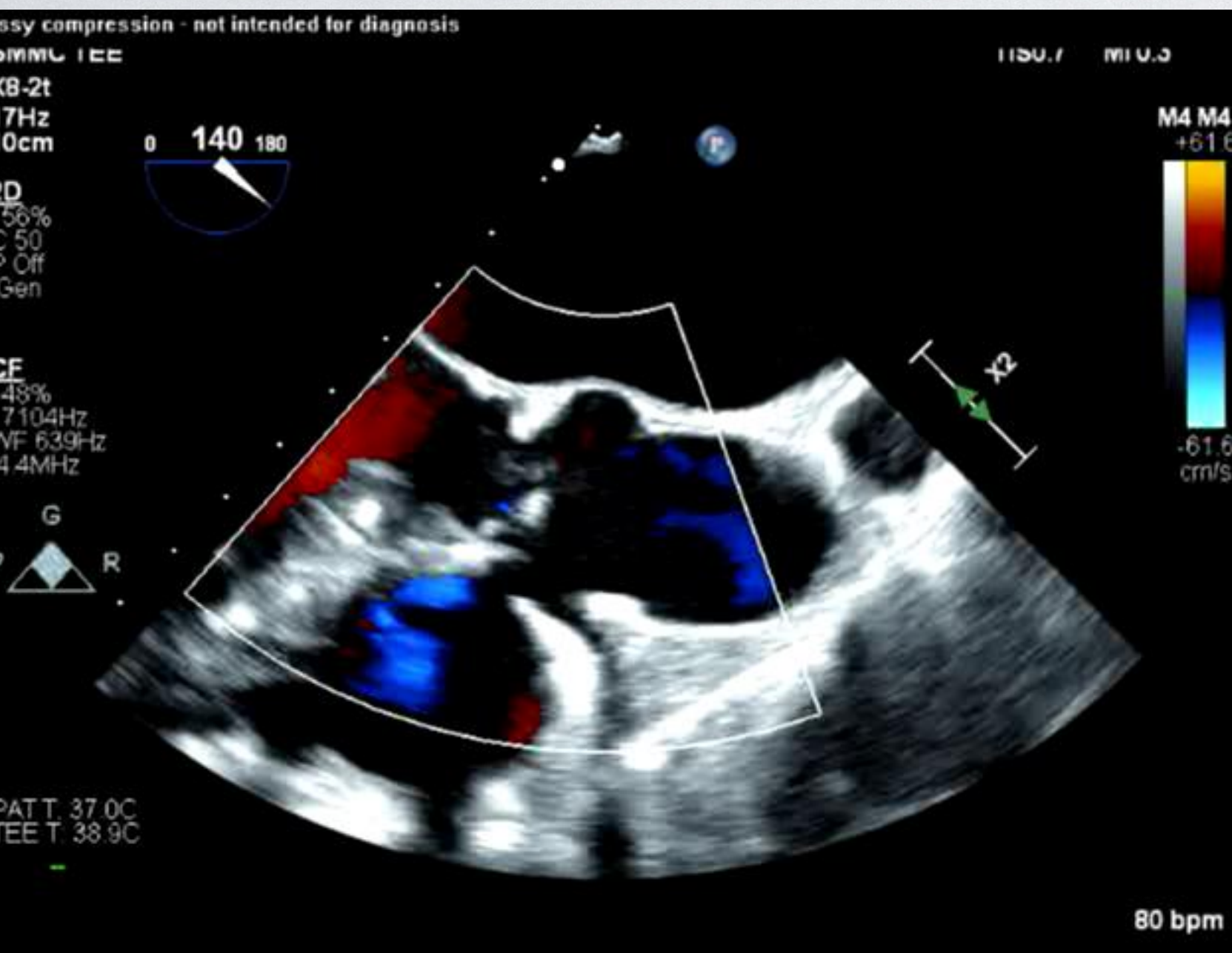
Mitral Regurgitation



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

CASE 3

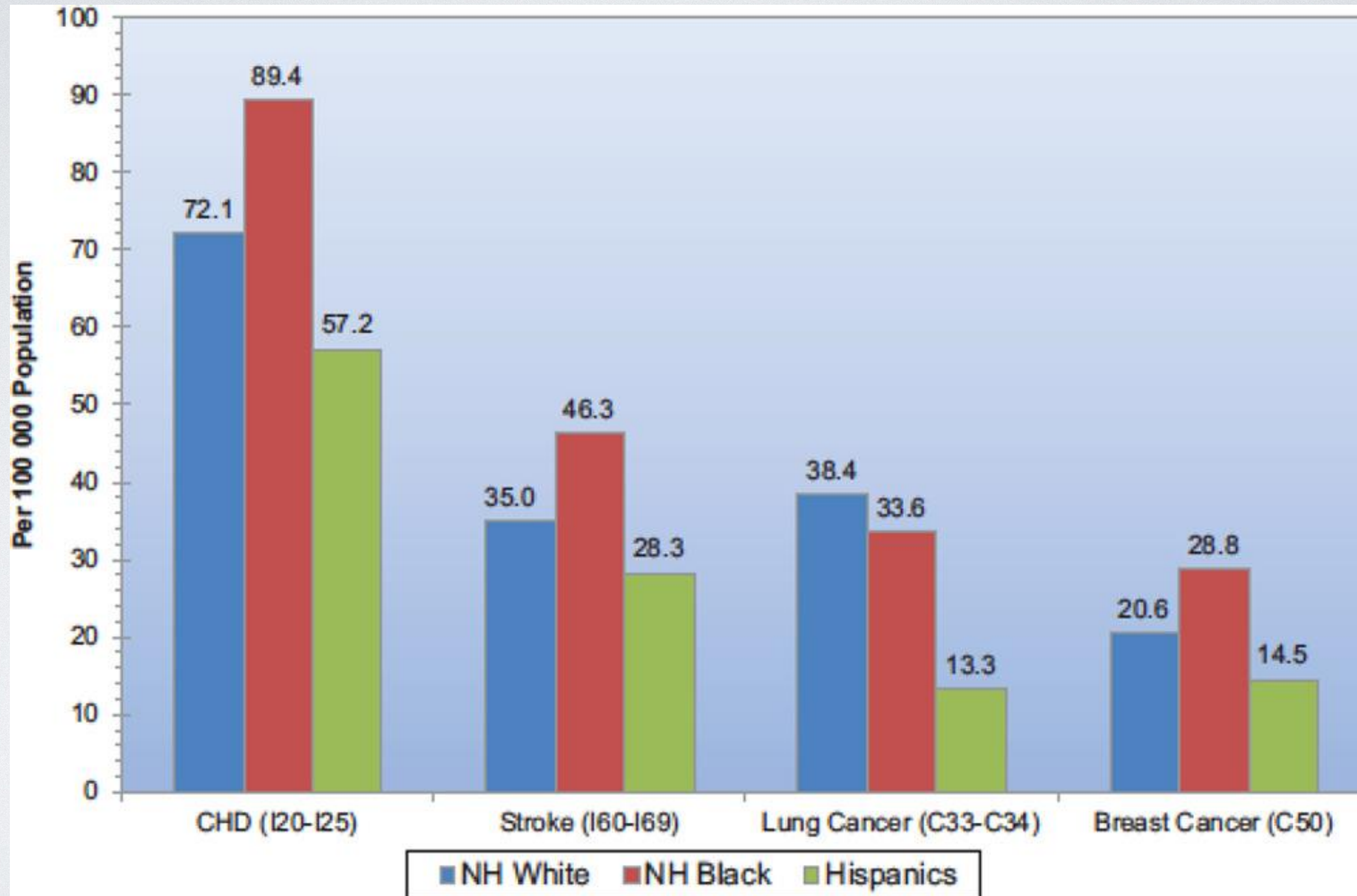
- 68 year old female, previously seen for risk management and history of heart murmur returns in follow up after completing chemotherapy
- Diagnosed one year ago with undifferentiated lymphoma
 - treated with radiation, RCHOP chemotherapy
 - rituximab, cyclophosphamide, doxorubicin, vincristine prednisolone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



Lossy compression - not intended for diagnosis

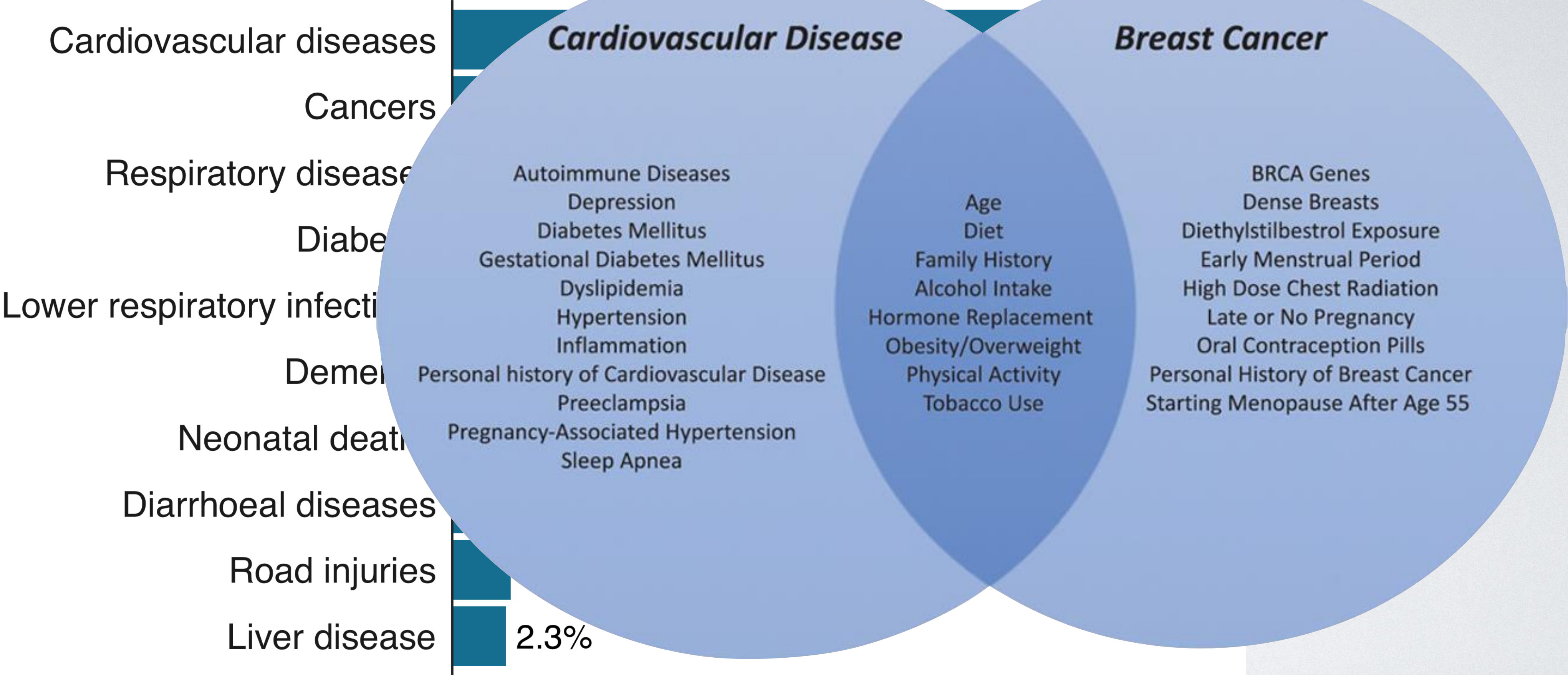


Rates of cardiovascular disease and breast cancer in women



Leading causes of death

World, 2016



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

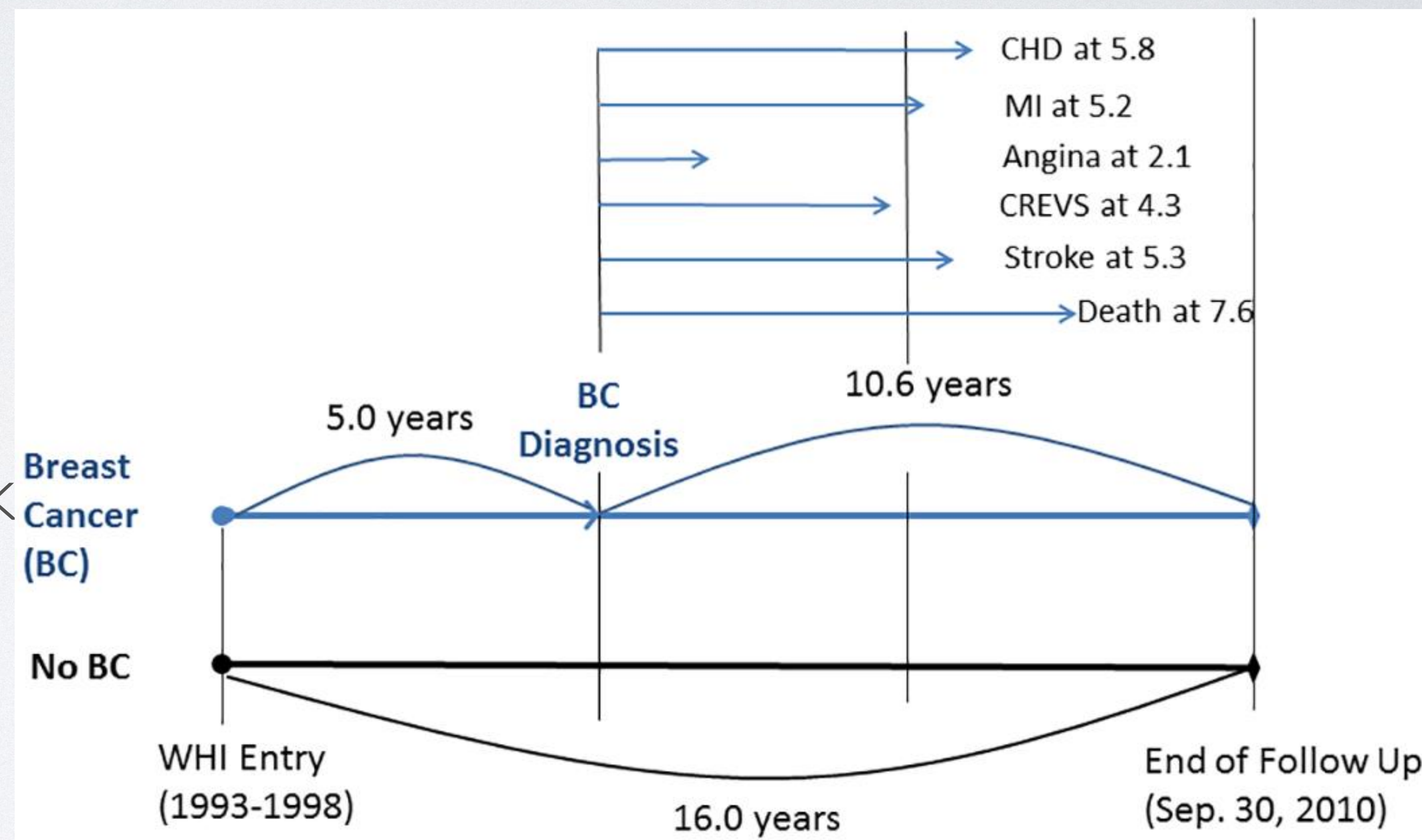


| | Risk of CVD | Risk of Breast Cancer |
|-------------------------------|-------------|-----------------------|
| Healthy Diet | ↓ | ↓ |
| Western Diet | ↑ | ↑ |
| Light-Moderate Alcohol Intake | ↓ | ↑ |
| Red/Processed Meat | ↑ | ↑ |
| Physical Activity | ↓ | ↓ |
| Sedentary Lifestyle | ↑ | ↑ |
| 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) |
| Total (%) | 1,164 (78.5) | 312 (21.1) | 6 (0.4) | 1,482 (100) |
| 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 ^a | 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) |
| Total CVD | 49 (21.7) ← | 14 (14.3) | 0 (0.0) | 63 (19.2) ← |
| 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) |
| Others^b | 98 (43.4) | 28 (28.6) | 0 (0.0) | 126 (38.4) |

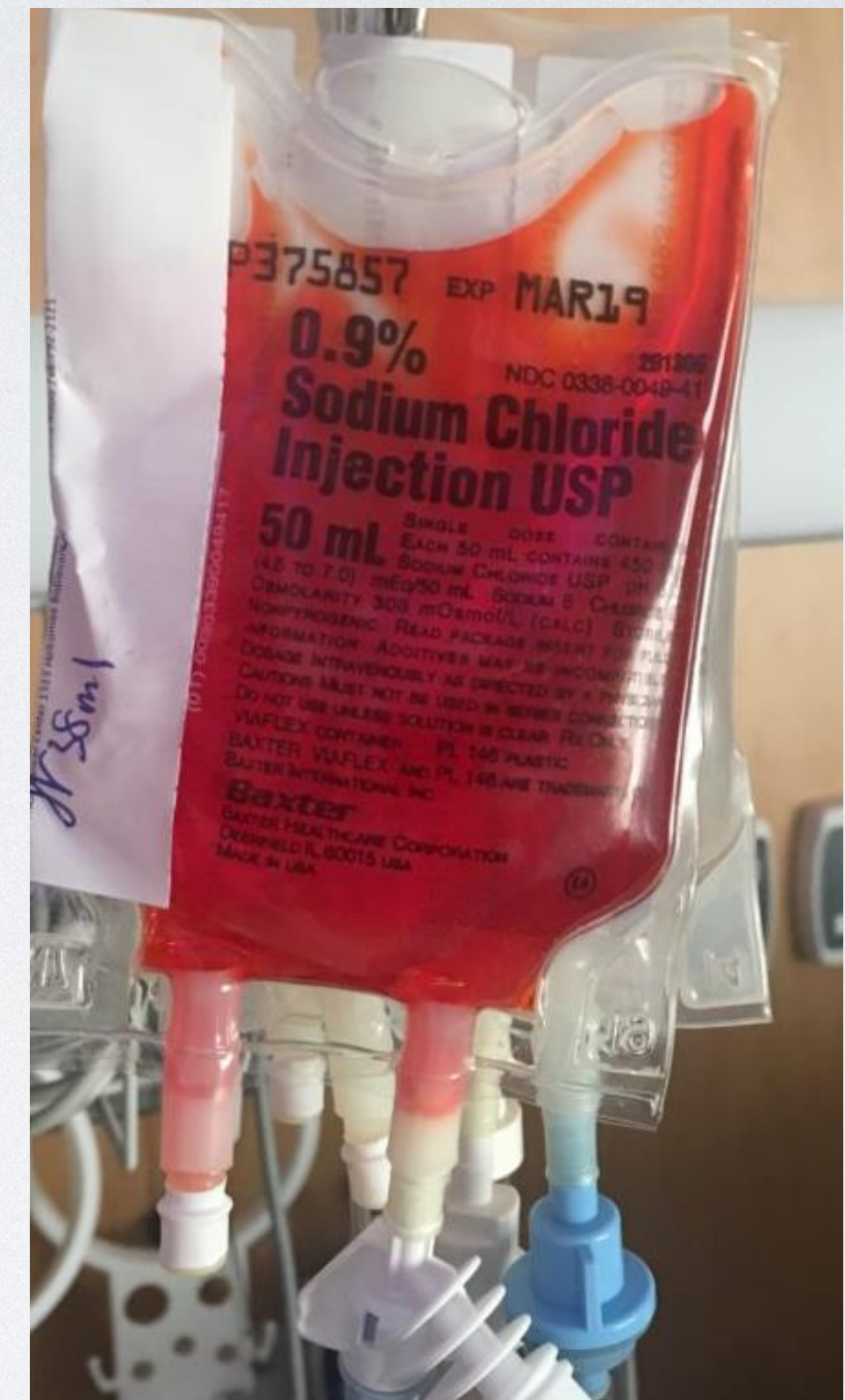
CVD indicates cardiovascular disease.

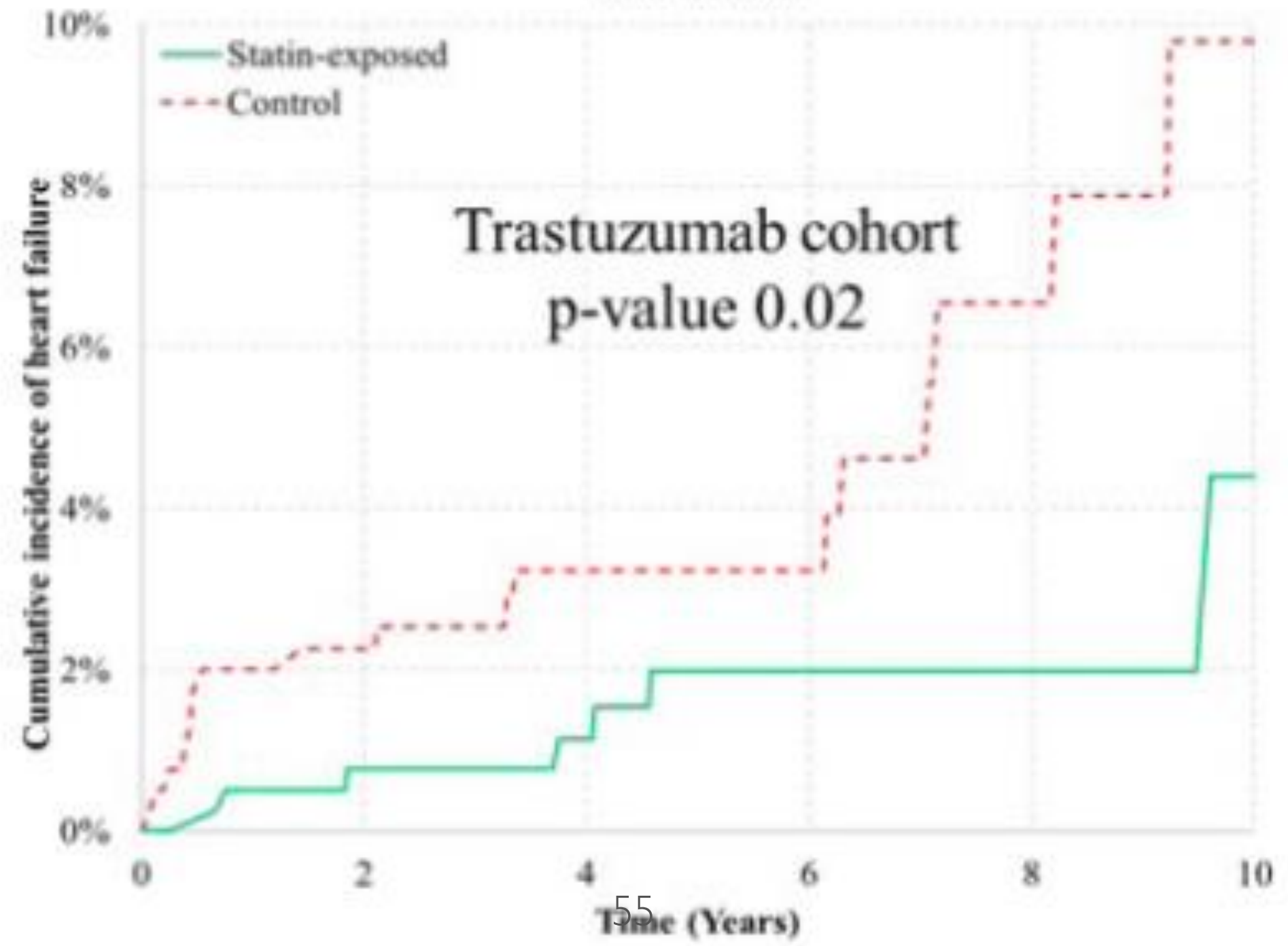
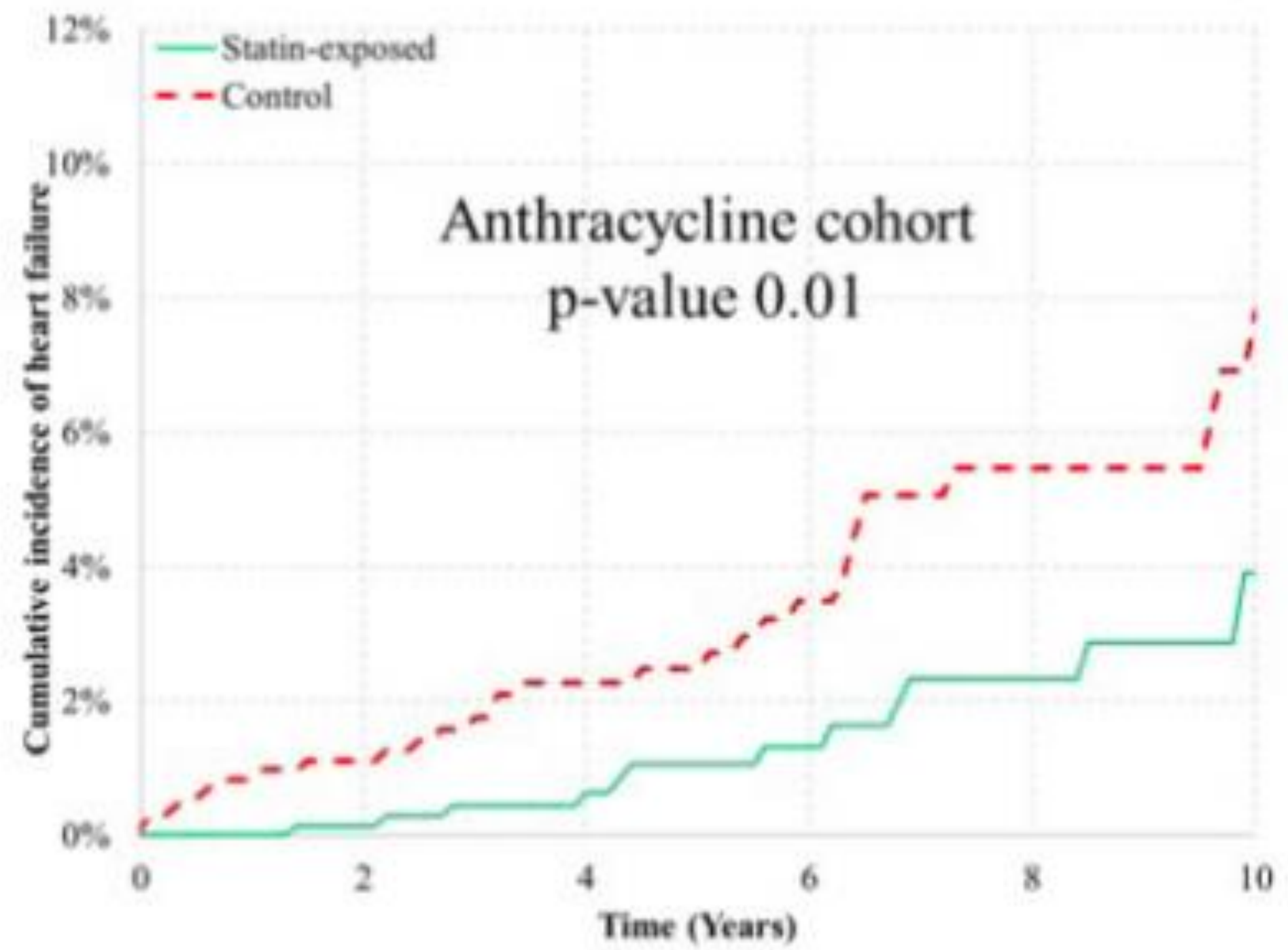
^a Major cancers include lung, ovarian, and colon cancers.

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

BREAST/GYNECOLOGICAL CANCER

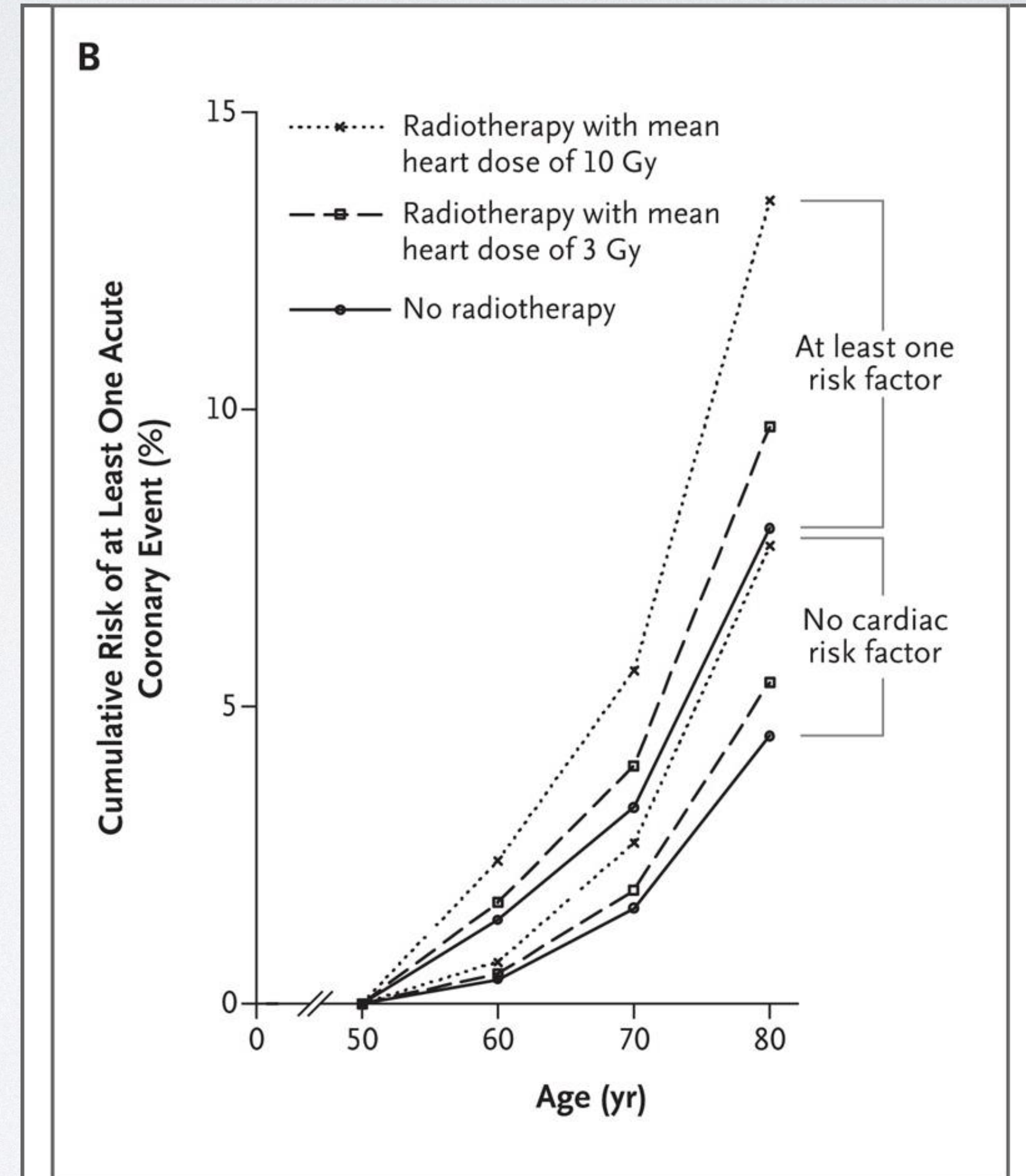
- Treatment: chemotherapy
 - Anthracyclines (ex, doxorubicin): heart failure
 - Risk occurs at 240 mg/m²
 - Taxanes (paclitaxel): arrhythmias
 - Bradycardia, non sustained VT
 - Monoclonal antibodies (trastuzumab): heart failure
 - 5% monotherapy, up to 27% when used with anthracyclines





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

| PK | | |
|-----------------|--|--|
| Property | Effect in Women | Cause |
| 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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