

# Cardiovascular Disease in Women

Christopher Bianco D.O.

4/20/2016

# Outline

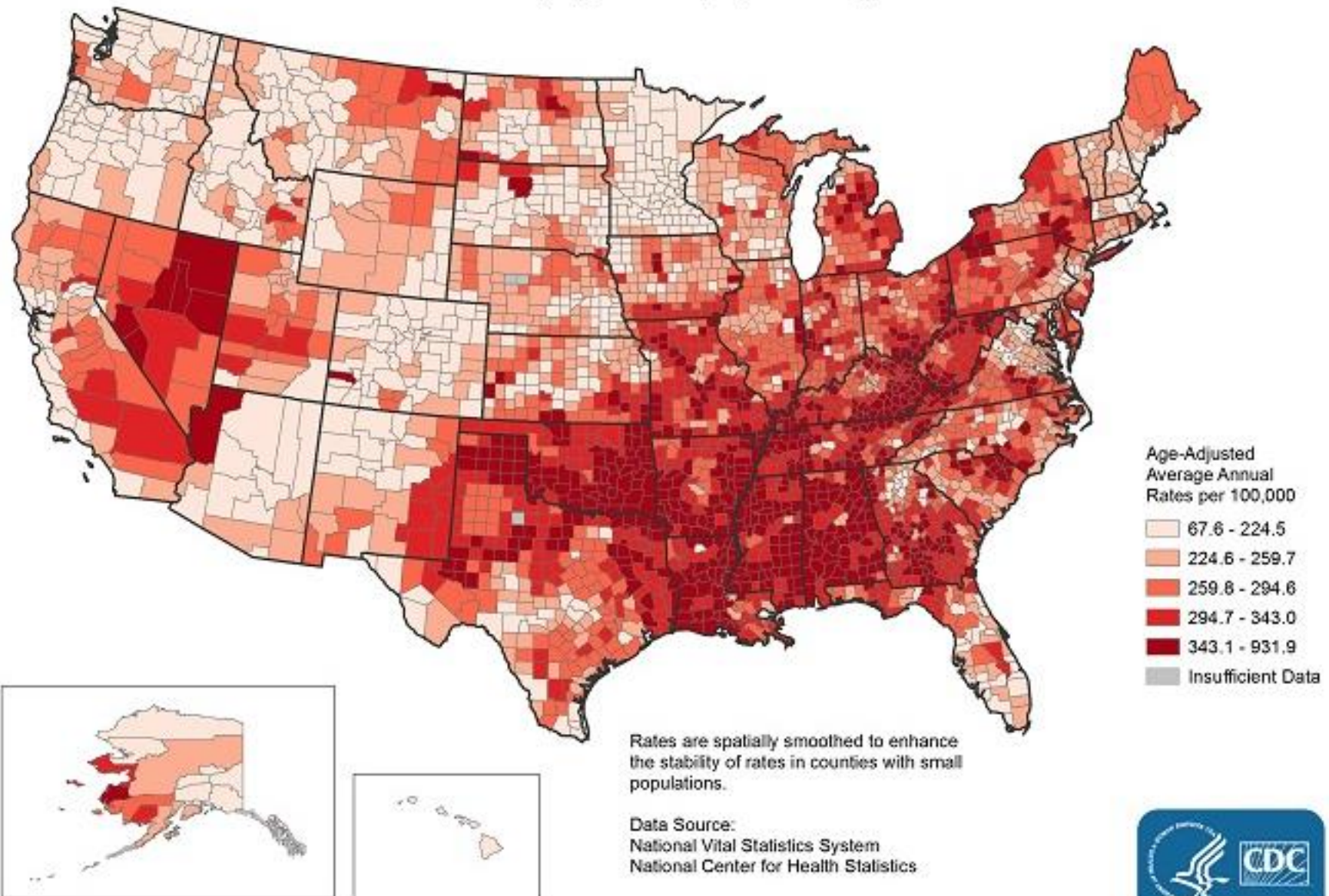
- Challenges to CVD Care in Women
- Gender Specific Risk Factor Management
- Diagnosis and Treatment of CAD in Women
- Mechanisms of Non-Atherosclerotic Vascular Disease in Women
- Gender Differences in Heart Failure

# Challenges to CVD Care in Women

# “A Man’s Disease”

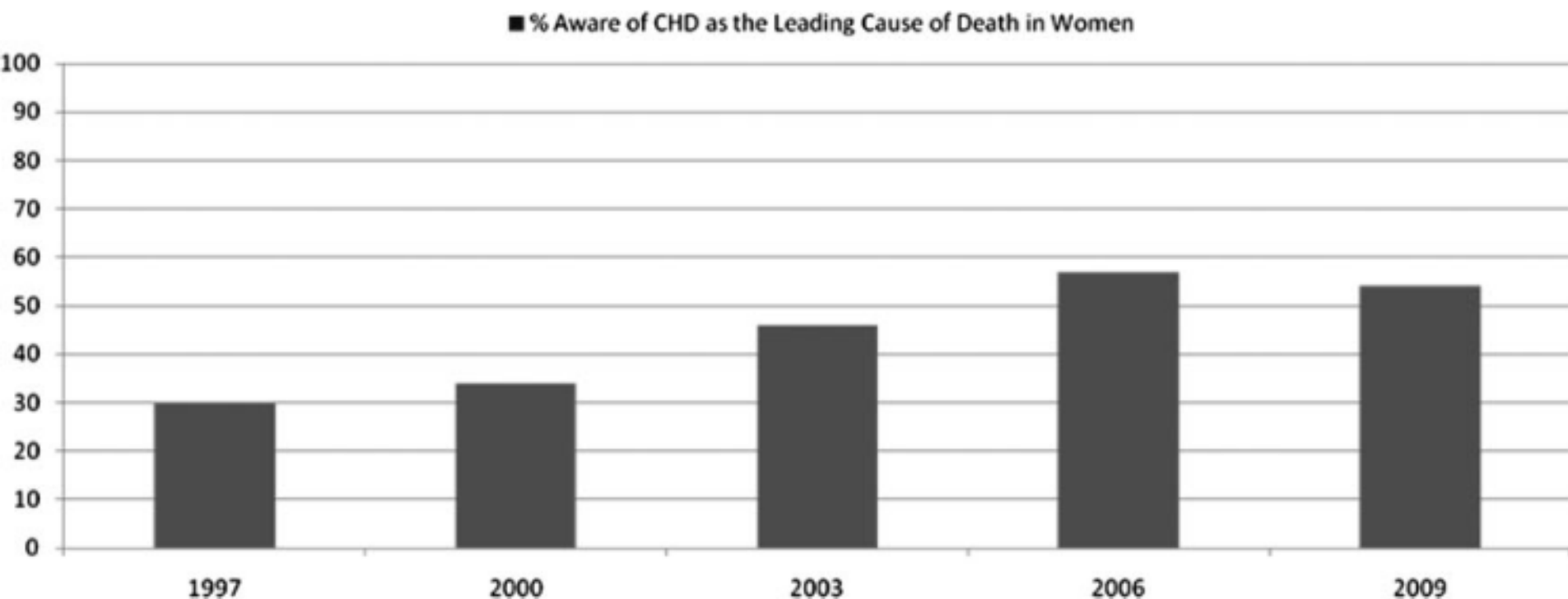
- The same number of women and men die each year of heart disease in the United States
- Heart disease is the leading cause of death for women in the United States, killing 292,188 women in 2009—that’s 1 in every 4 female deaths

## Heart Disease Death Rates, 2011-2013 Women, Ages 35+, by County



## Twelve-Year Follow-Up of American Women's Awareness of Cardiovascular Disease Risk and Barriers to Heart Health

Lori Mosca, MD, MPH, PhD; Heidi Mochari-Greenberger, MPH, RD; Rowena J. Dolor, MD, MHS;  
L. Kristin Newby, MD, MHS; Karen J. Robb, MBA



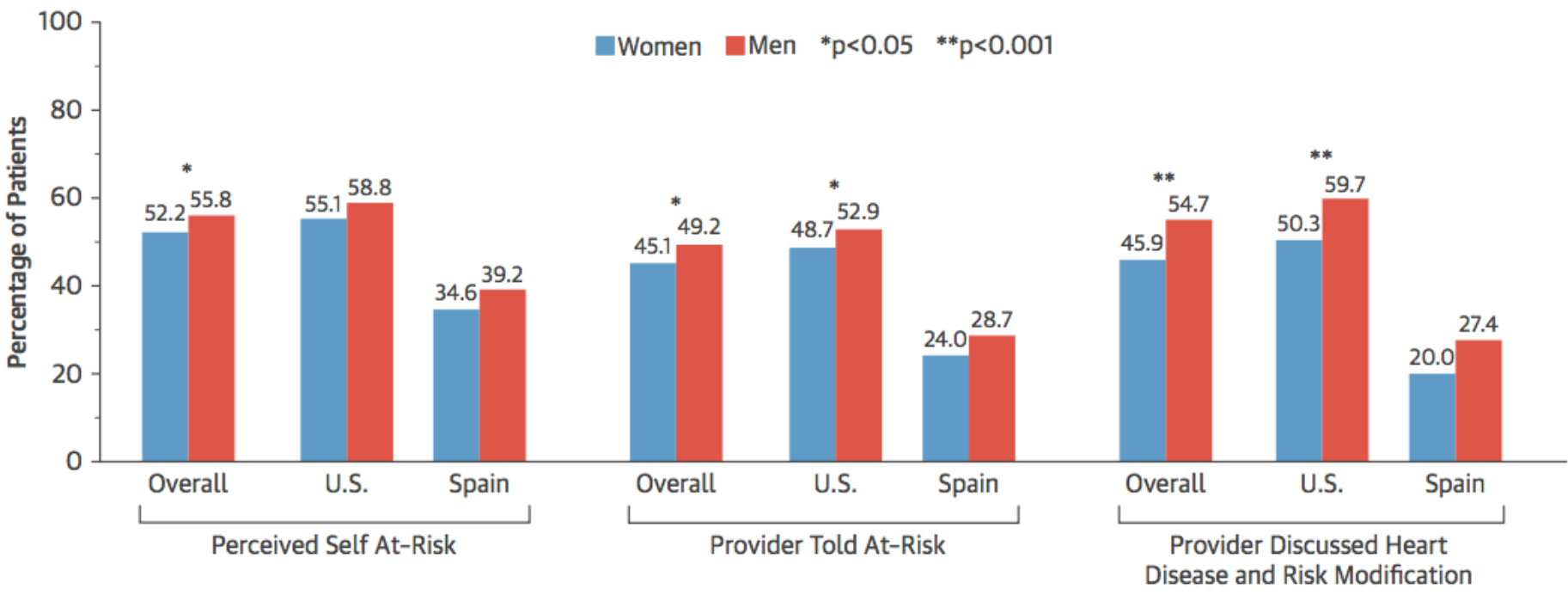
**Figure.** Overall trends in awareness that coronary heart disease is the leading cause of death in women.



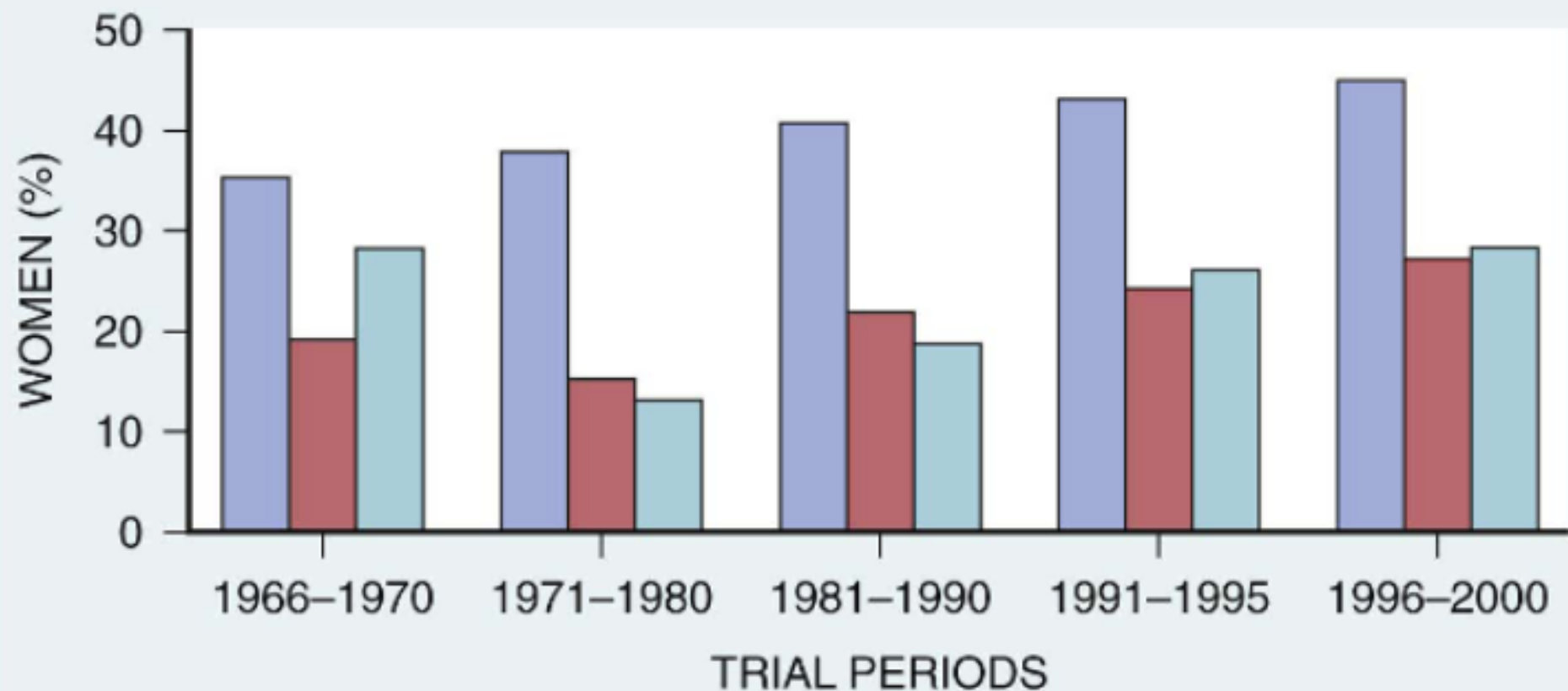
# Sex Differences in Cardiac Risk Factors, Perceived Risk, and Health Care Provider Discussion of Risk and Risk Modification Among Young Patients With Acute Myocardial Infarction

The VIRGO Study

**FIGURE 1** Perceptions and Discussions of Risk by Sex and Country



Percentage of women and men reporting that before their index acute myocardial infarction event, they considered themselves at risk for heart disease, were told by a health care professional that they were at risk, or had a health care provider talk to them about heart disease and ways to modify their risk. p Values for comparisons by sex within the overall, U.S., and Spanish cohorts were calculated with chi-square tests.



- Proportion of all patients with MI in the United States
- Proportion enrolled in RCTs of MI
- Proportion enrolled in U.S. RCTs of MI



# Established Risk Factors

# Age

- The prevalence of CVD increases with age in both sexes, but IHD events in women occur on average approximately 10 years after those in men.
- IHD increases in women >60 years, with 1 in 3 women >65 years having evidence of IHD, in contrast to 1 in 8 women 45 to 64 years of age.
- Nonetheless, **the highest sex difference in IHD mortality is observed in young/middle-aged women**, in whom mortality from AMI is twice that of age-matched men.

# Family History

- The AHA guidelines for the prevention of CVD in women define a family history of premature IHD as a first-degree relative with CHD before 65 years of age for women and before 55 years for men.
- Premature IHD in **first-degree female relatives** is a relatively more potent family history risk factor than is premature IHD in male relatives.
- Women classified as being at low risk for IHD (using the Framingham Risk Score) but having a sister with premature IHD are more likely to have evidence of subclinical IHD by CT based coronary calcium scoring.

# Hypertension

- From 45 to 64 years of age, men and women have a similar prevalence of HTN, but at >65 years old, women have a higher prevalence of hypertension.
- The NHANES survey from 1999 to 2004 demonstrated that hypertensive women were more likely to be treated than men but were **less likely to achieve blood pressure control.**

# Hypertension

- HTN is associated with increased risk for the development of congestive HF ... but this risk appears to be greater in women.
  - From the Framingham Heart Study and Framingham Offspring Study, risk for development of HF in those with HTN versus normotensive subjects was x2 in men and x3 in women
- Women with strokes are more likely than men to have HTN.
- In women taking **oral contraceptives**, HTN is x 2 to 3 times more common than in women not taking them, and use raises blood pressure 7 to 8 mm Hg on average.

# Diabetes

- Diabetes is a relatively greater risk factor for IHD in women than in men; it increases a woman's risk for IHD by **threefold to sevenfold**, with only a twofold to threefold increase in diabetic men.
- Per ADA recommendations: women with a history of gestational diabetes, screening for diabetes should occur 6 to 12 weeks postpartum and then every 1 to 2 years thereafter.

# Dyslipidemia

- **HDL-C** predicts CVD in both men and women, perhaps more so in women.
  - Framingham study: Men in the lowest quartile for HDL-C (<36 mg/dL) had a 70% greater risk for MI than those in highest HDL-C quartile (>53 mg/dL).
  - Women in the lowest HDL-C quartile (<46 mg/dL) had a **x6-7** higher rate of coronary events than those in highest HDL-C quartile (>67 mg/dL)
- Adverse changes in the lipid profile accompany menopause and include increased levels of total cholesterol, LDL-C, and TGs and decreased levels of HDL-C.

# Emerging Risk Factors



# Metabolic Syndrome

- NHANES data from 2003 to 2006 indicate that 32.6% of women met the criteria for metabolic syndrome.
- In addition, those with metabolic syndrome have an increased risk for the development of CVD, and this association is strongest in women, with a relative risk for CHD of 2.63 as compared with 1.98 in men.

# Autoimmune Disease

- Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have been associated with a significantly increased relative risk for CVD.
- Women 18 to 44 years of age with SLE (vs without SLE)
  - X 2.27 more likely AMI
  - X 3.80 more likely HF
  - X 2.05 more likely CVA
- Women 35 to 44 years of age with SLE in the Framingham Offspring Study were **50 times more likely to have an AMI** than were women of the same age without SLE.

# Polycystic Ovarian Syndrome

- Women with PCOS have an increased prevalence of impaired glucose tolerance (insulin resistance), metabolic syndrome, and diabetes when compared with women without PCOS.
- PCOS has not been independently proven associated with IHD although above clearly mediate significant risk.

# Functional Hypothalamic Amenorrhea

- FHA can cause premenopausal ovarian dysfunction and occurs when gonadotropin-releasing hormone increases, thereby increasing luteinizing hormone in a pulse frequency and causing amenorrhea and hypoestrogenemia.
- In a large cohort study, women with menstrual irregularities had a **50% increased risk for nonfatal and fatal IHD** when compared with women who had regular menstrual cycling.
- Additional data from women undergoing coronary angiography indicate that FHA is associated with premature coronary atherosclerosis.

# Preeclampsia and Pregnancy HTN

- Women with preeclampsia have a 3.6- to 6.1-fold greater risk for the development of hypertension and a 3.1- to 3.7-fold higher risk for the development of diabetes.
- Women with a history of preeclampsia have approximately **double the risk** for subsequent IHD, stroke, and venous thromboembolic events over the 5 to 10 years following the pregnancy.

# Hormone Therapy

- For most women who are healthy and free of CVD and cardiovascular risk factors, the use of combination estrogen-progestin oral contraceptives is associated with low relative and absolute risks for CVD.
- **Smokers**, those with **uncontrolled hypertension, IHD, and obesity** may have an unacceptable level of risk associated with oral contraceptives.
- Even though postmenopausal hormone therapy was hypothesized to reduce the incidence of CVD, multiple randomized trials did **not** find hormone therapy or selective estrogen receptor modulators (SERMs) to primarily or secondarily prevent CVD.

# CAD Evaluation in Women

# Diamond-Forrester Classification

THE NEW ENGLAND JOURNAL OF MEDICINE

June 14, 1979

## ANALYSIS OF PROBABILITY AS AN AID IN THE CLINICAL DIAGNOSIS OF CORONARY-ARTERY DISEASE

GEORGE A. DIAMOND, M.D., AND JAMES S. FORRESTER, M.D.



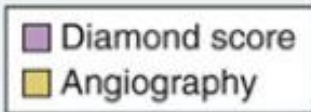
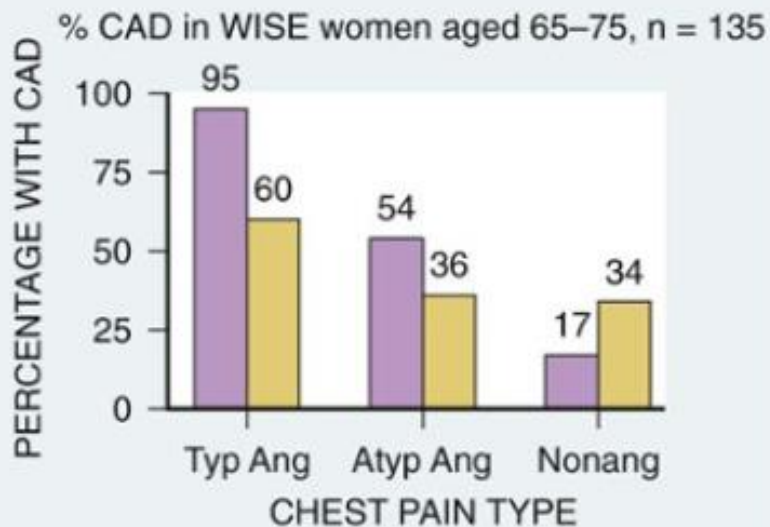
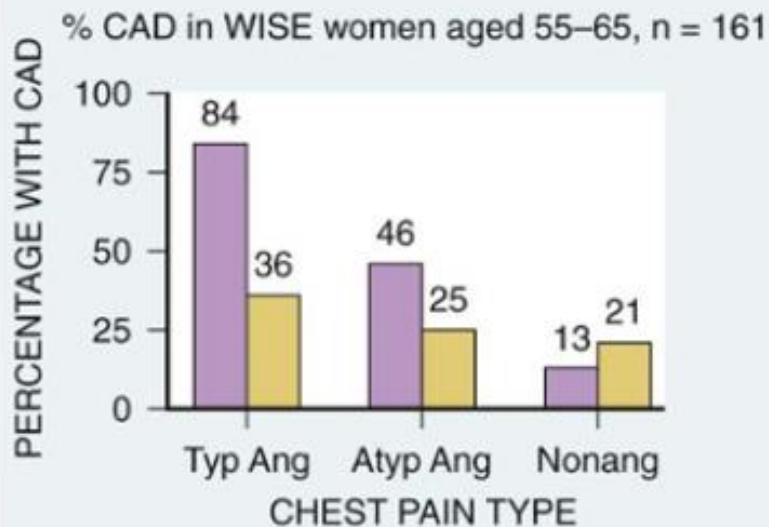
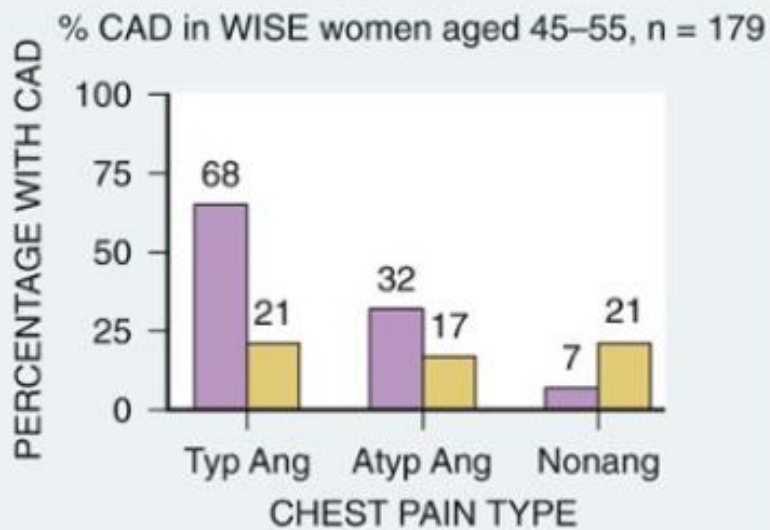
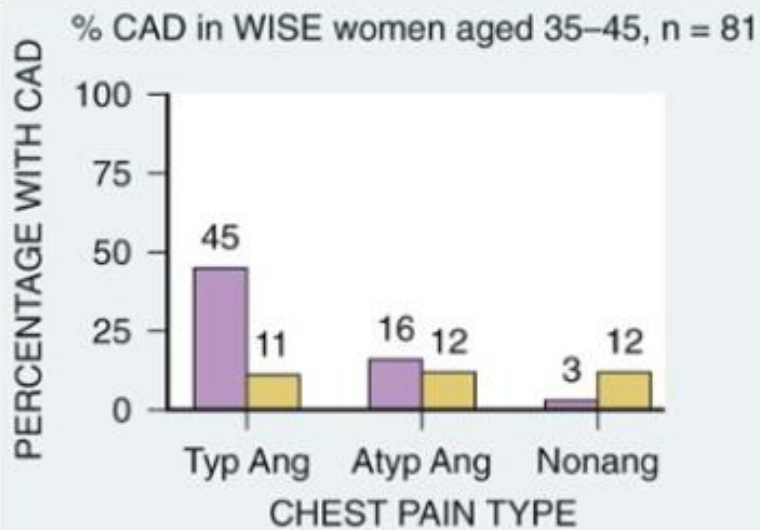
**Table A. Pretest Probability of CAD by Age, Gender, and Symptoms\***

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 (20a) to reflect all age ranges.





# Pretest Probability

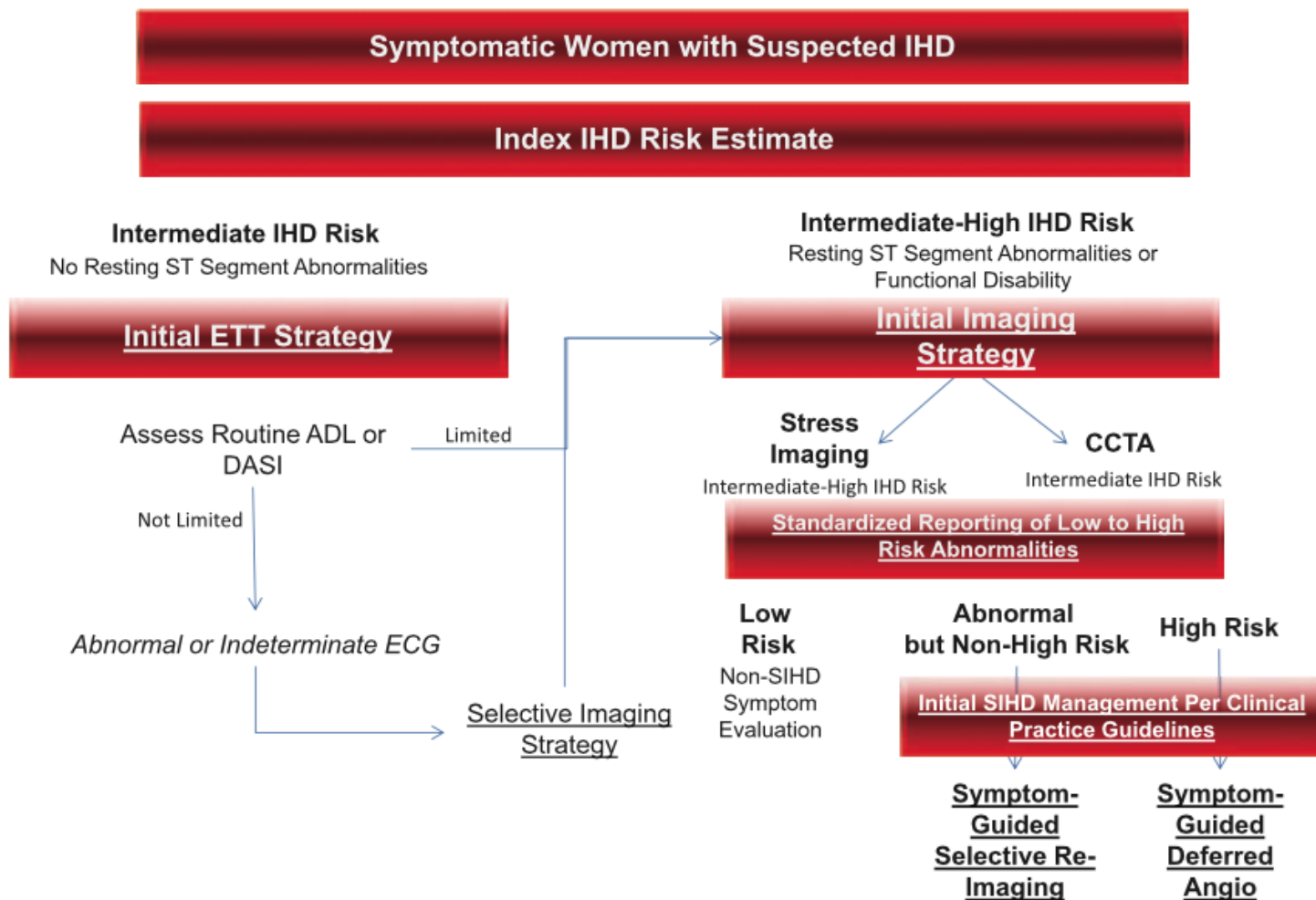
- Symptomatic women in **fifth decade** of life should be considered at **low** to **intermediate** risk for CAD if they are capable of performing routine activities of daily living (ADLs).
  - If performance of **routine ADLs** is **compromised**, a woman in her **50s** is elevated to the **intermediate** CAD risk category.
- Women in their **60s** are also generally considered to be at **intermediate** risk for IHD.
- Women 70 years and older are considered to be at high risk for CAD.

## Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Ischemic Heart Disease

A Consensus Statement From the American Heart Association

- Women with low CAD risk are not candidates for diagnostic evaluation; in exceptional cases, an exercise ECG.
- Women at **low** or **intermediate** risk are candidates for an exercise ECG if they have an **estimated** functional capacity of **5 METs** or greater.
- Women at **intermediate** to **high risk** with **abnormal** findings on **resting ECG** should be referred for a noninvasive **imaging modality**, including stress myocardial perfusion imaging (MPI), stress echocardiography, cardiovascular magnetic resonance imaging, or coronary computed tomographic angiography (CCTA).
- Women at high risk for CAD with stable symptoms may be referred for a stress imaging modality for functional assessment of their ischemic burden and to guide post-test anti-ischemic therapies

**Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Ischemic Heart Disease**  
**A Consensus Statement From the American Heart Association**



# ECG Response to Exercise

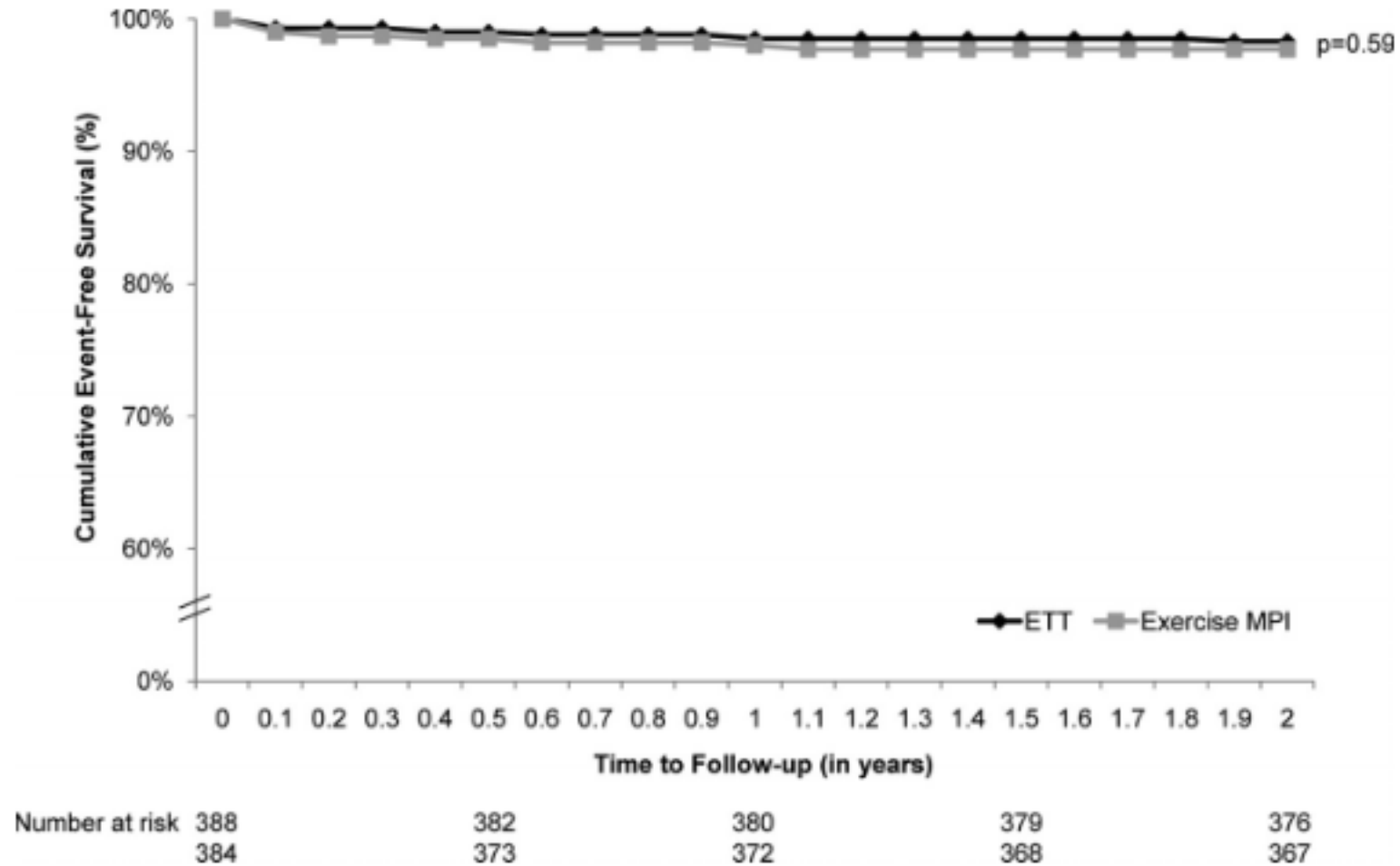
- The diminished accuracy of the ECG response to exercise may result from more frequent resting ST-T wave changes, lower ECG voltage, and hormonal factors.
- Sensitivity and specificity for the diagnosis of obstructive CAD in women range from 31% to 71% and from 66% to 86%, respectively.
- Nevertheless, a negative exercise ECG stress test has considerable diagnostic value.

# ECG Response to Exercise

- Women have a lower positive predictive value of ST-segment depression with exercise testing for obstructive CAD than men do (47% versus 77%,  $P < 0.05$ )
- Symptomatic women and men have a similar **negative predictive value** of ST-segment depression (78% versus 81%).
- So although women may be more likely to have a false-positive exercise ECG, a negative exercise stress test is useful to exclude obstructive CAD.
- **A woman with a negative exercise ECG and normal exercise ability has an excellent event-free survival and a low risk for obstructive CAD.**

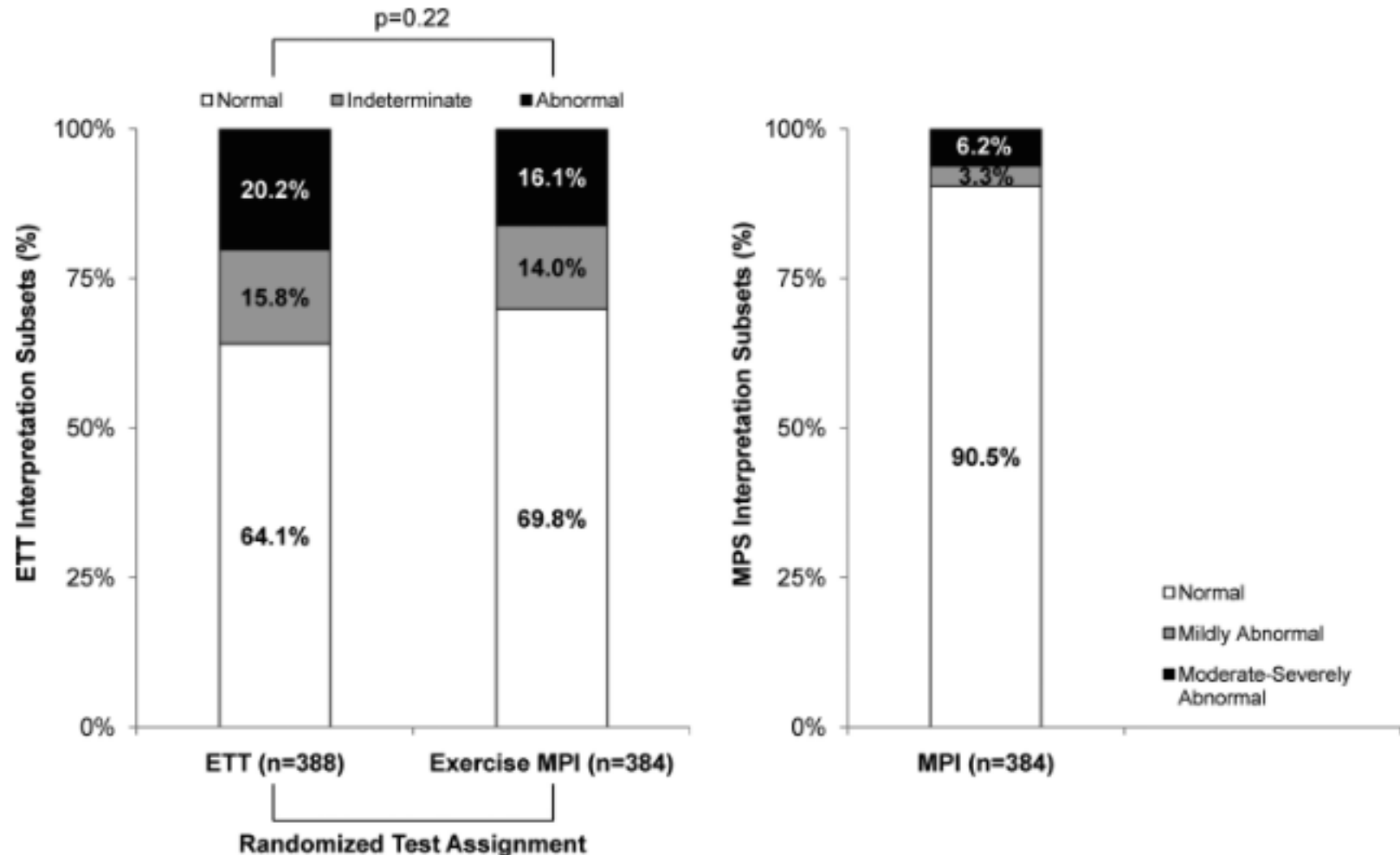
# Comparative Effectiveness of Exercise Electrocardiography With or Without Myocardial Perfusion Single Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease

Results From the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) Trial



# Comparative Effectiveness of Exercise Electrocardiography With or Without Myocardial Perfusion Single Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease

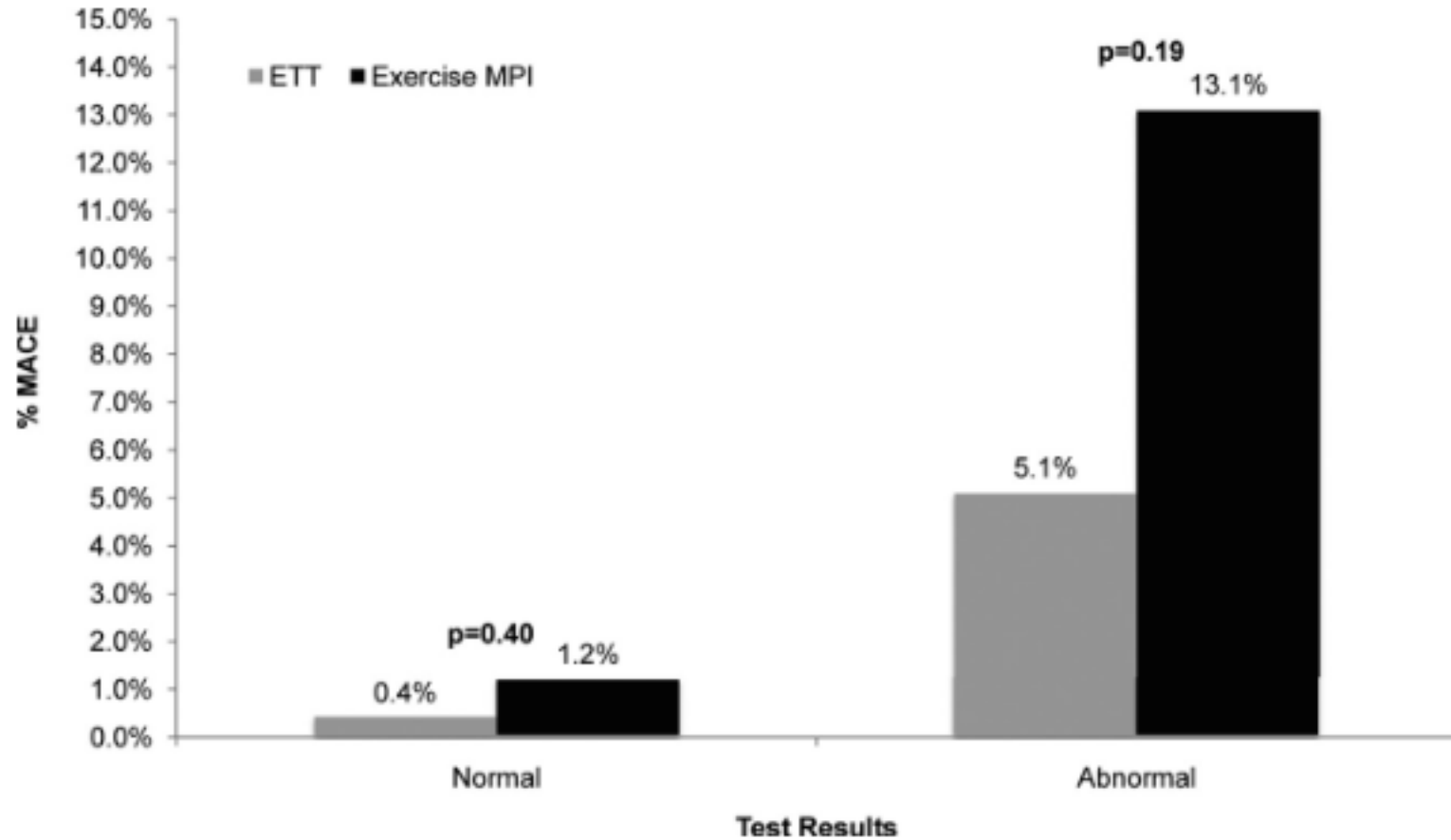
Results From the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) Trial





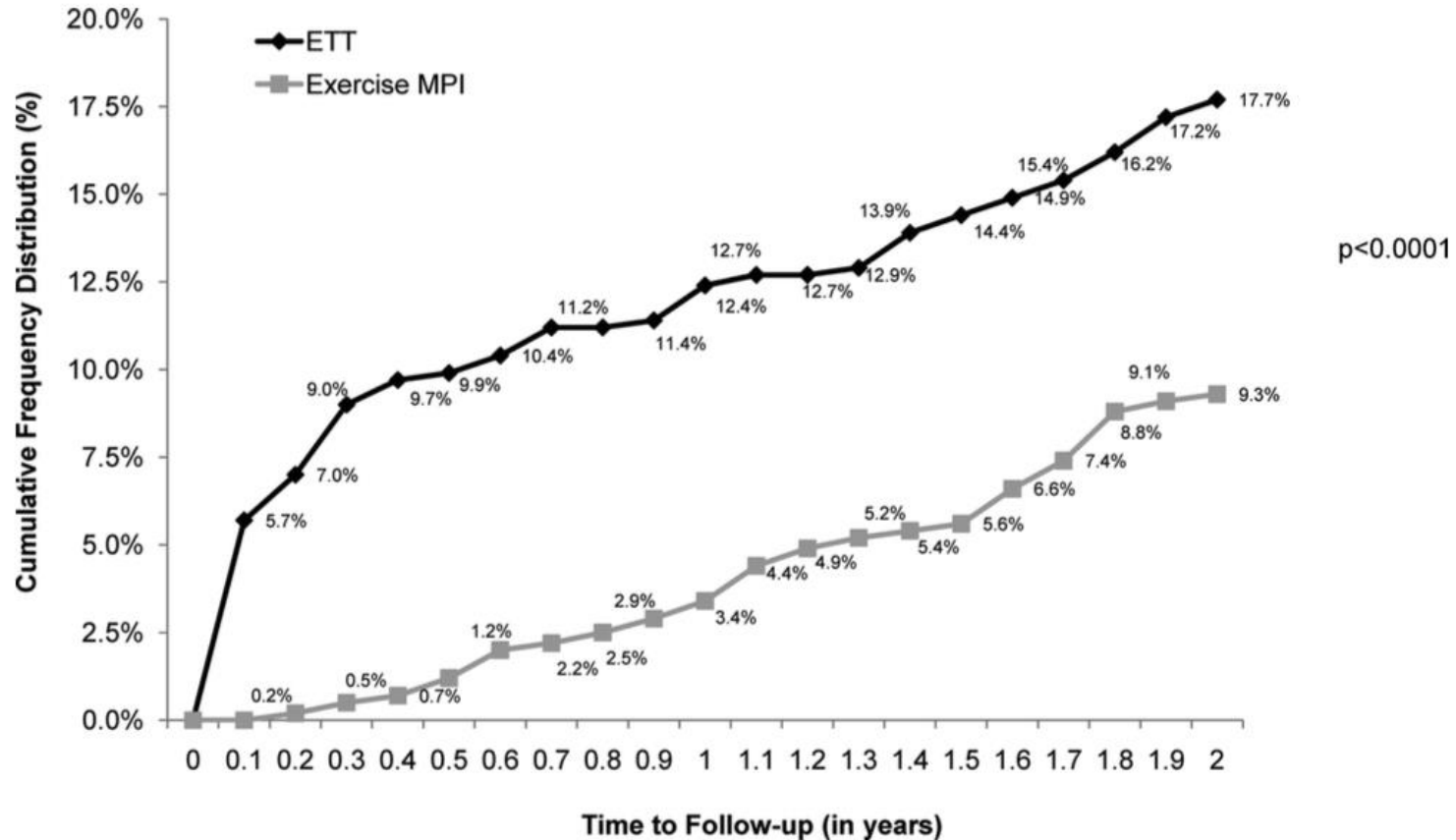
# Comparative Effectiveness of Exercise Electrocardiography With or Without Myocardial Perfusion Single Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease

Results From the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) Trial



# Comparative Effectiveness of Exercise Electrocardiography With or Without Myocardial Perfusion Single Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease

Results From the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) Trial



**Figure 6.** Cumulative frequency of crossover or repeat stress myocardial perfusion imaging (MPI) after randomization to an exercise treadmill test (ETT) vs exercise MPI.

# Comparative Effectiveness of Exercise Electrocardiography With or Without Myocardial Perfusion Single Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease

Results From the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) Trial

**Table 3. Diagnostic Workup Costs for Exercise ECG Compared With Single Photon Emission Computed Tomographic Myocardial Perfusion Imaging**

Randomized Test Strategy	Index Testing	Follow-Up Testing	Total Costs
<b>ETT</b>			
Mean (SD)	\$154.28 (\$30.42)	\$179.97 (\$413.64)	\$337.80 (\$416.26)
Median (25th, 75th percentile)	\$169.86 (\$111.57, \$178.22)	\$0 (\$0, \$0)	\$174.14 (\$169.86, \$182.29)
<b>Exercise MPI</b>			
Mean (SD)	\$495.24 (\$8.54)	\$144.77 (\$407.75)	\$643.24 (\$411.51)
Median (25th, 75th percentile)	\$492.67 (\$87.95, \$508.68)	\$0 (\$0, \$0)	\$492.67 (\$487.95, \$508.68)
Wilcoxon <i>P</i>	<0.001	0.0008	<0.001

ETT indicates exercise treadmill test; MPI, myocardial perfusion imaging.

# Comparative Effectiveness of Exercise Electrocardiography With or Without Myocardial Perfusion Single Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease

Results From the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) Trial

- Inclusion Criteria
  - typical/atypical chest pain or ischemic equivalents (eg, dyspnea)
  - interpretable baseline ECG (ie, no significant resting ST-segment changes  $\geq 0.5$  mm)
  - aged  $\geq 40$  years or postmenopausal
  - capable of performing  $\geq 5$  metabolic equivalents (METs) on the Duke Activity Status Index (DASI) questionnaire
  - intermediate pretest CAD likelihood
- 12 - 14% Diabetes
- Women reported median METs of  $\approx 12$  on the DASI
- Women exercised to an average 8.4 METs or into stage III of the Bruce protocol

# Women and ACS

# Challenges to ACS Care

- ACS presentation may be under appreciated
- Women are having ACS at earlier ages than historically seen
  - ? More sensitive biomarkers
  - ? Western Metabolic Syndrome Epidemic
  - ? Women Smokers
- Women may suffer from non-atherosclerotic mechanism ACS
- Women are more susceptible to bleeding complications of ACS therapy
- Women are often prescribed less intense secondary preventative therapies

# “Female-pattern” IHD

- Characterized by a relatively lower obstructive CAD burden and preserved left ventricular ejection fraction (LVEF)
- Women are relatively less likely to be recognized and treated than men with “male-pattern” IHD.



# Sex-Specific Trends in Midlife Coronary Heart Disease Risk and Prevalence

Amytis Towfighi, MD; Ling Zheng, PhD; Bruce Ovbiagele, MD

JAMA Internal Medicine

**Background:** While recent data indicate that stroke prevalence in women at midlife is double that of similarly aged men in the United States, little is known about current sex-specific trends in symptomatic cardiovascular disease. This study aimed to determine sex-specific midlife prevalence of myocardial infarction (MI) and risk of future coronary heart disease.

**Methods:** We assessed the sex-specific MI prevalence and the Framingham coronary risk score (FCRS) among US adults aged 35 to 54 years who participated in the National Health and Nutrition Examination Surveys (NHANES), cross-sectional, nationally representative surveys, during 1988 to 1994 and 1999 to 2004.

**Results:** In both epochs, men aged 35 to 54 years had a higher prevalence of MI than similarly aged women, but the gap narrowed in recent years as MI prevalence decreased among men and increased among women (2.5% vs 0.7% in NHANES 1988-1994 [ $P < .01$ ] and 2.2% vs

1.0% in NHANES 1999-2004 [ $P < .01$ ]). Among men, the mean FCRS showed an improving trend (8.6% in NHANES 1988-1994 vs 8.1% in NHANES 1999-2004 [ $P = .07$ ]), while among women, the mean FCRS worsened (3.0% in NHANES 1988-1994 vs 3.3% in NHANES 1999-2004 [ $P = .02$ ]). Temporal trends in FCRS components revealed that men had more improvements in vascular risk factors than women, but diabetes mellitus prevalence increased in both sexes.

**Conclusions:** Over the past 2 decades, MI prevalence has increased among midlife women, while declining among similarly aged men. Also, although the risk of future hard cardiovascular events remains higher in midlife men compared with midlife women, the gap has narrowed in recent years. Greater emphasis on vascular risk factor control in midlife women might help mitigate this worrisome trend.

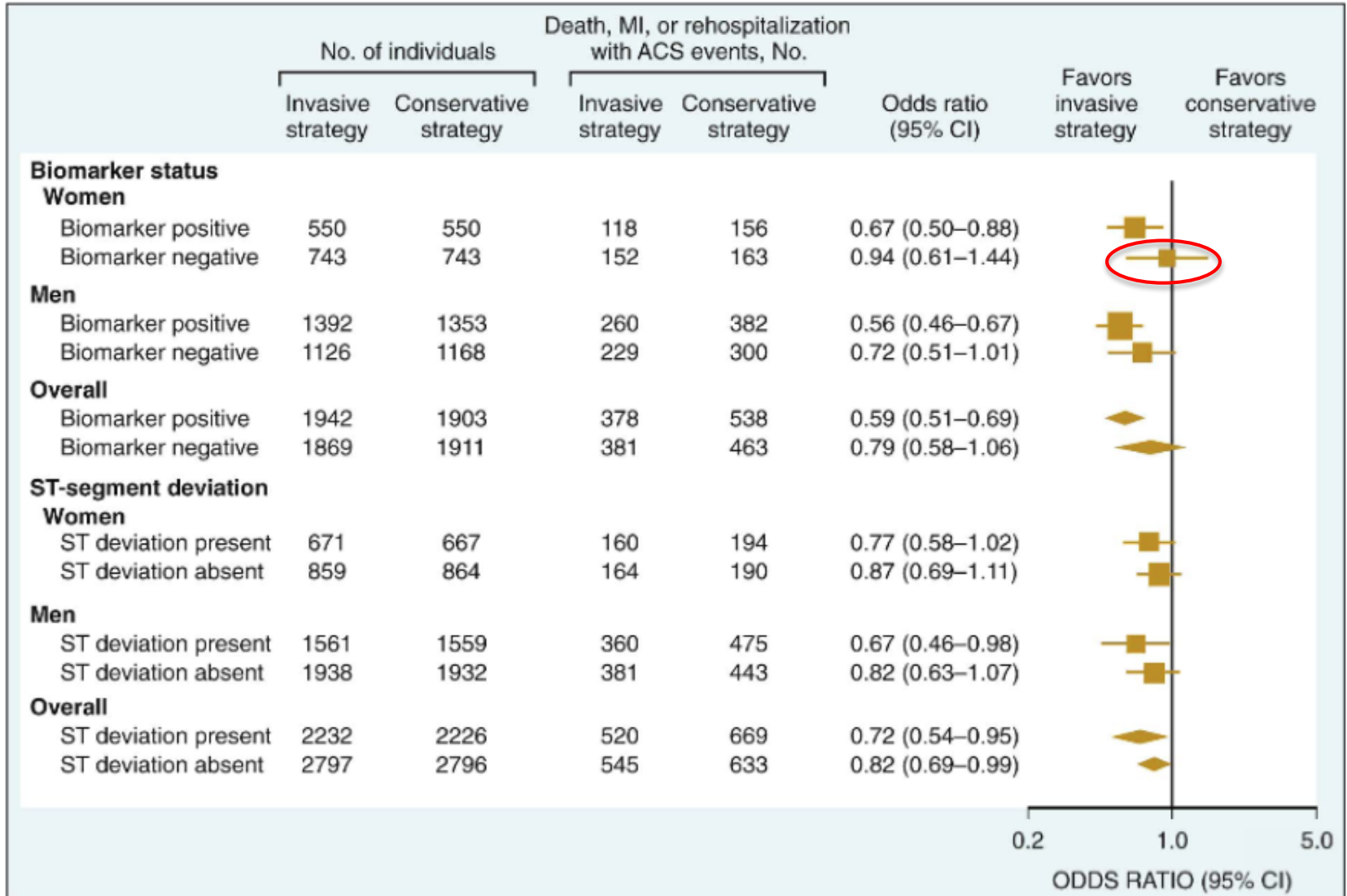
*Arch Intern Med.* 2009;169(19):1762-1766



# Sex Differences in ACS GDMT

- Women with AMI are less likely to receive
  - ACEI or ARBS at discharge
  - lipid-lowering therapy
  - to have blood pressure lower than 140/90 mm Hg at discharge
  - to receive stents
  - to have a door-to-balloon time of 90 minutes or less or a door-to-thrombolytic time of 30 minutes or less
- Sex disparity is greater in younger cohort than older cohort.

# Early Invasive Strategy ?



# Non-Obstructive Epicardial CAD

- The WISE study (Outpt Eval or ACS) demonstrated that 57% of women with symptoms and signs of ischemia had no obstructive CAD evident on coronary angiography.
- ACS registries show that women have non-obstructive CAD more frequently than men (10% to 25% of women versus 6% to 10% of men)
- Women with chest pain and no obstructive CAD have higher mortality and adverse cardiovascular events than asymptomatic women
  - Prognosis in women with symptoms and signs of ischemia is not benign, even when they have no obstructive CAD or have angiographically “normal” coronary arteries

# ACS related to Non-ASCVD Mechanism

# Microvascular Disease

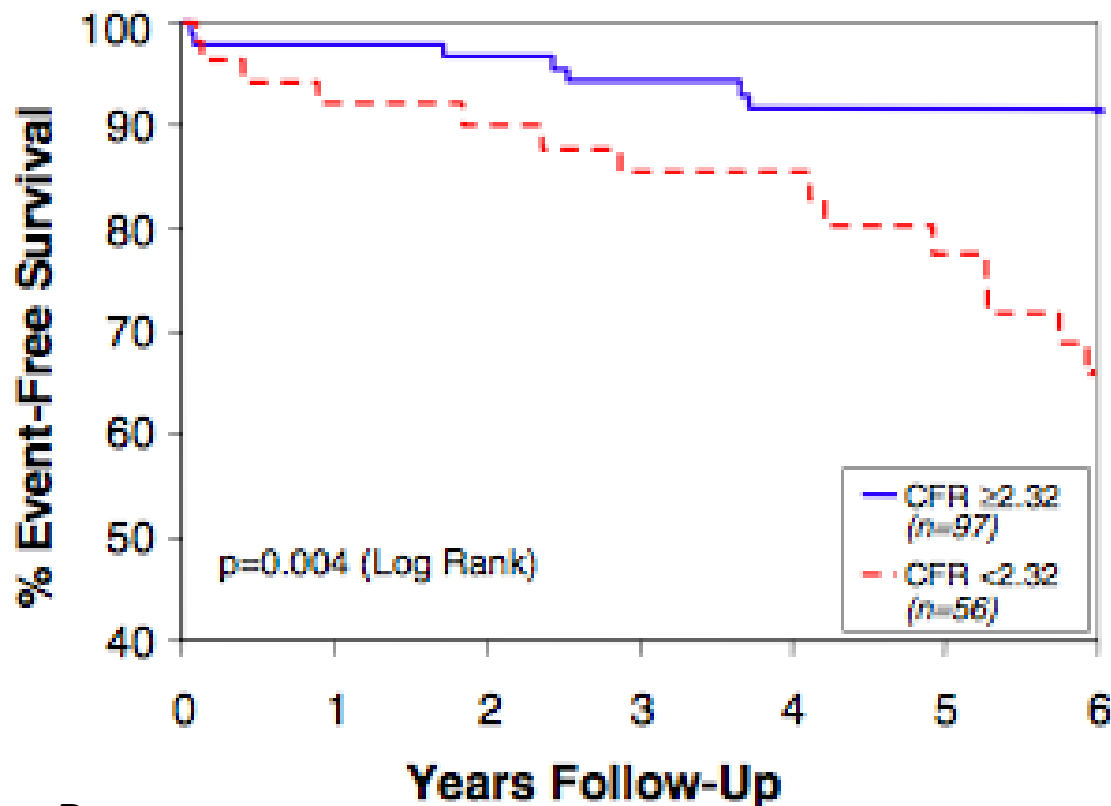
## Cardiac Syndrome X

- Associations:
  - Estrogen deficiency (in women)
  - Insulin resistance
  - Dysautonomic imbalance
  - Common CVD risk factors
- Presentation: Stable microvascular angina or ACS
- Therapy: ??? BB, CCB, NTG, ACEI/ARBs, Statin,
  - ?estrogen replacement

# Coronary Microvascular Reactivity to Adenosine Predicts Adverse Outcome in Women Evaluated for Suspected Ischemia

Results From the National Heart, Lung and Blood  
Institute WISE (Women's Ischemia Syndrome Evaluation) Study

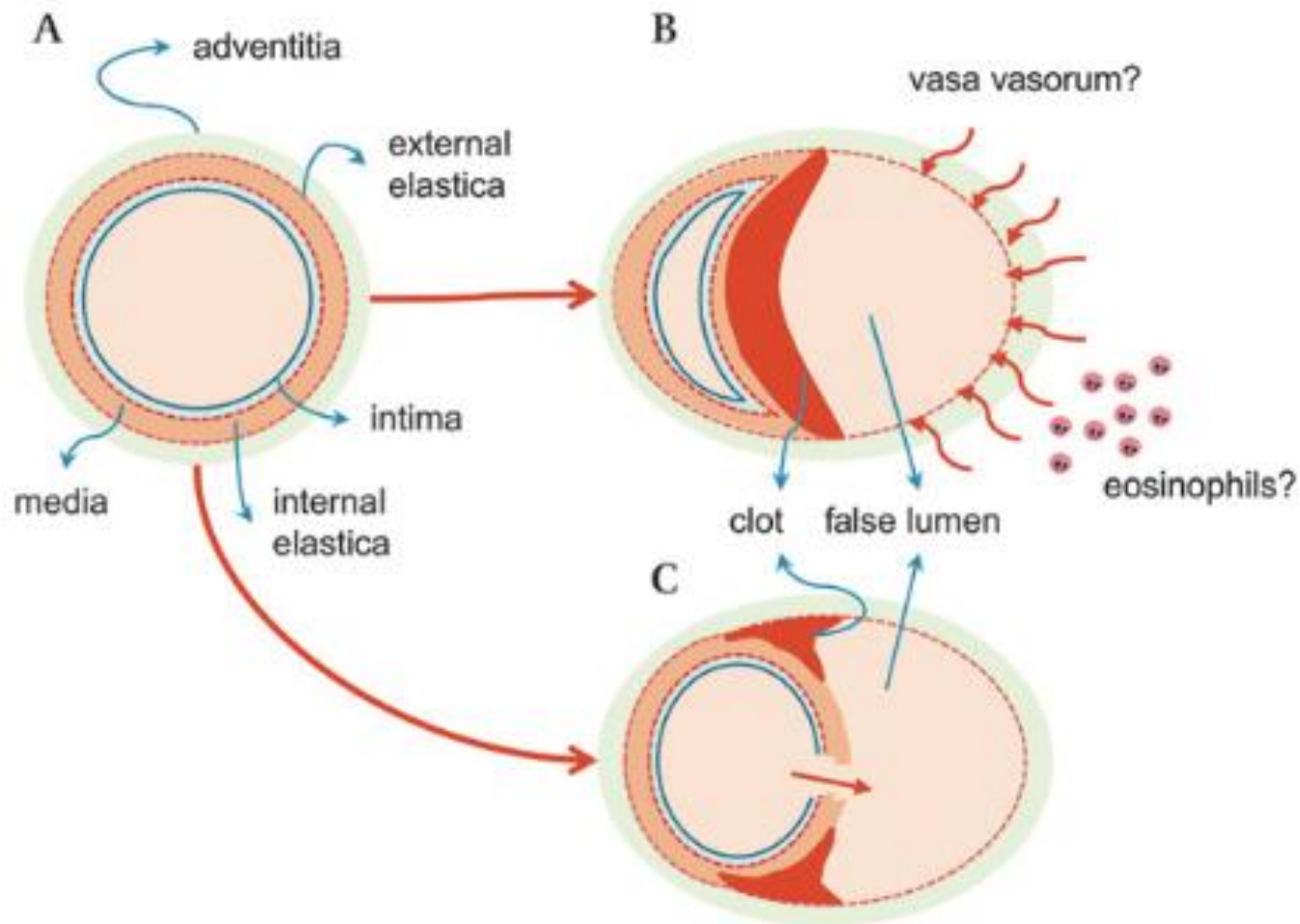
## Women without CAD



CFR = Coronary Flow Reserve

... measure of coronary microvascular reactivity

# Spontaneous Coronary Artery Dissection (SCAD)



# Spontaneous Coronary Artery Dissection (SCAD)

- More than 70% of SCAD cases are women
  - approximately 30% occurs during peripartum period (pk incidence is 2 weeks postpartum)
  - incidence of SCAD highest in women below 40 yo
- Limited Series suggest that up to 10% of AMI cases in Women < 50 yo are related to SCAD



# Spontaneous Coronary Artery Dissection (SCAD)

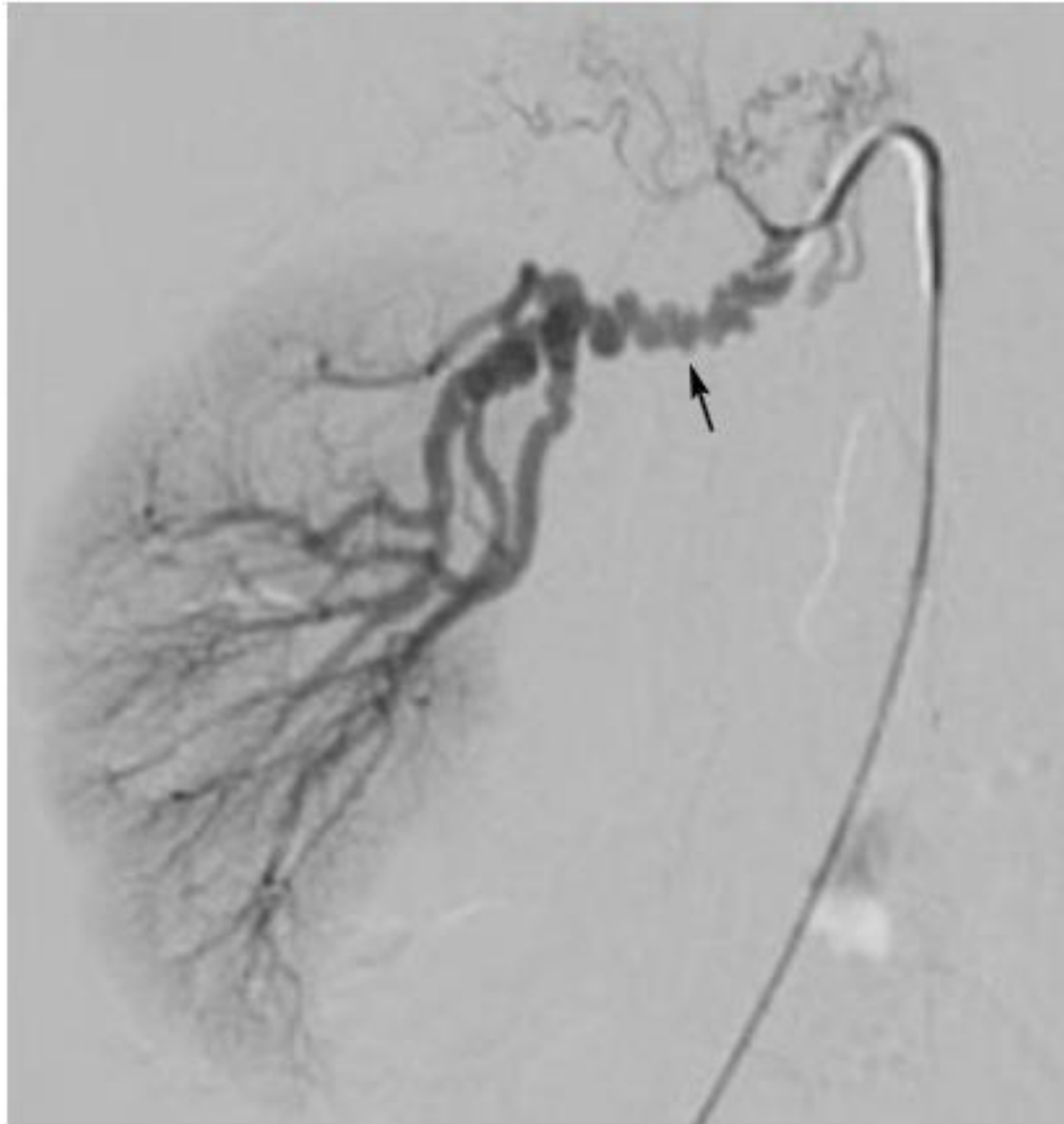
## SCAD Associated with:

- ASCVD
  - Peripartum Vascular Changes
  - Fibromuscular Dysplasia \*\*\*
  - Autoimmune Disease: SLE, Vasculitis
  - Connective Tissue Disease
  - Cocaine Use
  - HRT/OCP
  - Vigorous Exercise
- 
- Treatment decisions are complex but are largely conservative in absence of ongoing ischemia

# Fibromuscular Dysplasia (FMD)

- Nonatherosclerotic, Noninflammatory vascular disease that primarily affects women from age 20 to 60
- Most commonly affects the renal and carotid arteries but has been observed in almost every artery in the body
- Nonatherosclerotic SCAD – 86% have FMD

## Medial fibroplasia: Angiographic appearance



# FMD of the Coronary Arteries

On coronary angiogram, histopathology manifestation of FMD may be seen as

- classic string-of-beads appearance (rare)
  - diffuse tubular stenosis in mid-distal vessels (might be due to obliterative disease, dissection, or healed dissection)
  - **More likely as “normal”** (subsequently labeled as microvascular disease).
- Therapy for Coronary Manifestation: ???  
Conservative, PCI precipitates dissection, only performed if acute ischemia

# Takotsubo Cardiomyopathy

- Estimated 1% to 2% of patients with ACS
- Women in more than 90% of cases
  - Most commonly post-menopausal
- Precipitant: ~ 1/3 Physical (ex Asthma exacerbation), ~ 1/3 Emotional, ~ 1/3 Idiopathic
- Mayo Clinic Criteria:
  - Transient wall motion changes of LV mid +/- apical segments extending beyond a single coronary bed. Preceding physical or emotional stressor is often present
  - No obstructive CAD or acute plaque rupture
  - New ECG changes (STE, TWI, or both) or modest elevation troponin
  - No pheochromocytoma or myocarditis.

# Takotsubo Cardiomyopathy

- ST Elevation (1/3), deep TWI, long QTc, arrhythmias common
- Majority + biomarkers but under-proportion to WMA
- If hypotensive consider pump failure +/- RV failure vs dynamic LVOT obstruction (“HOCCM like”)
- Therapy ???
  - Acute setting avoid inotropes or IABP if LVOTO
  - ??? BB / ACEI

# Heart Failure

# Heart Failure

- The lifetime risk for the development of HF in a 40-year-old individual without a preceding MI is 1 in 6 for women versus 1 in 9 for men
- Women with acute decompensated HF are twice as likely as men to have preserved left ventricular function or HF with a preserved ejection fraction (HFpEF)
- Generally women with HF have a lower quality of life, lower functional capacity, more hospitalizations for HF, and more frequent depression



# Prevalence and Population-Attributable Risk Factors for Developing Heart Failure

RISK FACTOR		AGE- AND RISK FACTOR-ADJUSTED HAZARD RATIO	% PREVALENCE	POPULATION-ATTRIBUTABLE RISK
Hypertension (BP $\geq$ 140/90 mm Hg)	Men	2.1	60	39
	Women	3.4	62	59
Myocardial infarction	Men	6.3	10	34
	Women	6.0	3	13
Angina	Men	1.4	11	5
	Women	1.7	9	5
Diabetes	Men	1.8	8	6
	Women	3.7	5	12
Left ventricular hypertrophy (EKG)	Men	2.2	4	4
	Women	2.9	3	5
Valvular heart disease	Men	2.5	5	7
	Women	2.1	8	8

# Peripartum Cardiomyopathy

- Impaired LVEF in the last month of pregnancy or within 5 months postpartum, with no preexisting cardiac disease and no identifiable cause
- 1 in 4000 pregnancies
- Risk factors:
  - Advanced maternal age
  - African descent
  - High parity
  - Twin pregnancy
  - Tocolytics
  - Poverty

# Peripartum Cardiomyopathy

- LVEF recovers in approximately half within 6 months
  - 20% deteriorate and either die or require heart transplantation.
- Recovery appears to be related to a less severe decline in LVEF.
- The risk during subsequent pregnancies is not entirely clear, but recent evidence suggests that LVEF declines in subsequent pregnancies in both those who originally recovered LV function and those with persistent impairment.

# Conclusion

- Perception and Study of CVD in Women Must Change
- Consider Gender Specific and Emerging Risk Factors in Preventative Efforts and Assessment of PTP
- Presentation and Diagnostic Evaluation for IHD in Women is Nuanced
- Consider Non-Atherosclerotic Vascular Disease in Women
- Gender Differences in Heart Failure Exist

Fin