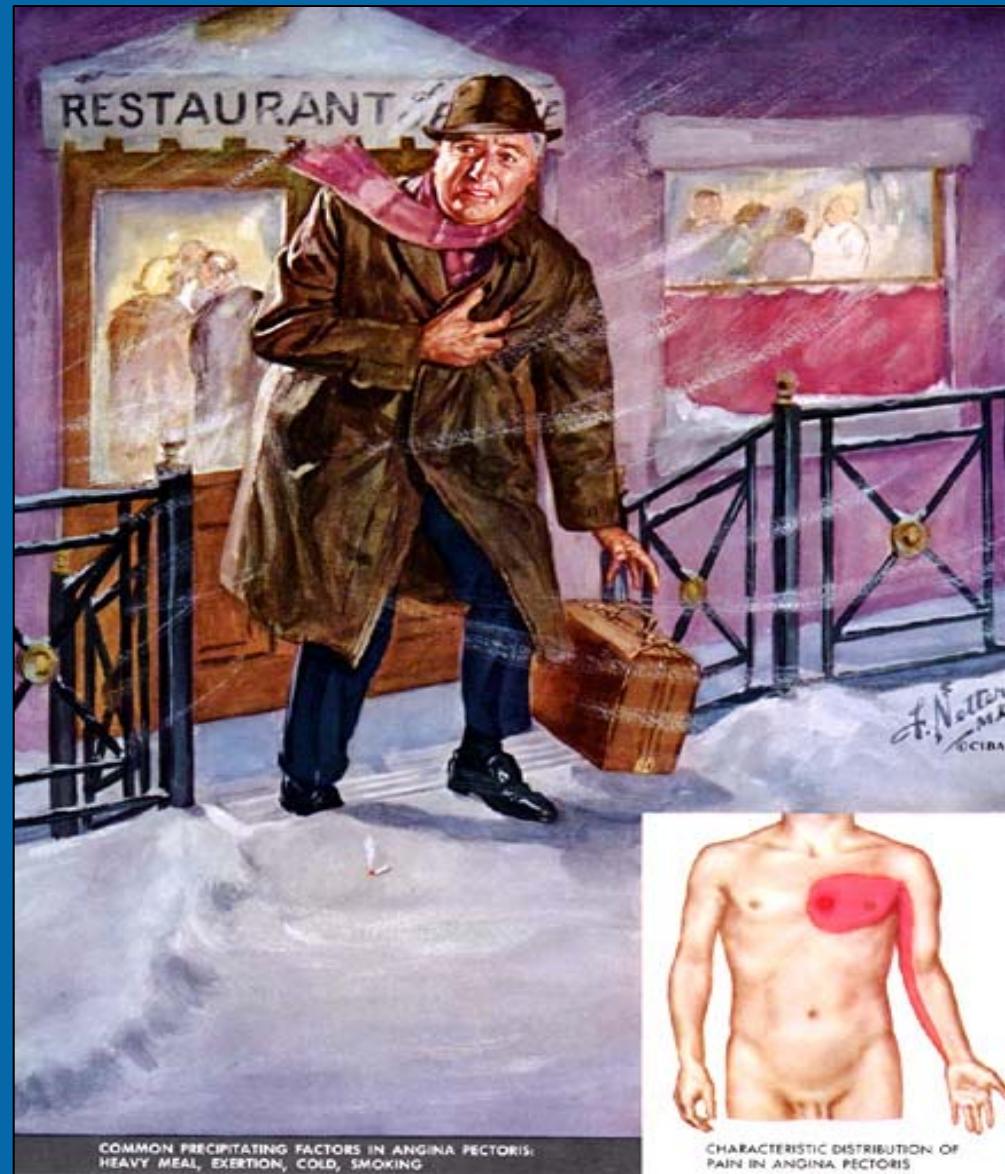




Women and Heart Disease

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Angina Pectoris



Epidemiology

- 500,000 US women die annually from CV disease
- 250,000 US women die annually of CAD
- 1 in 2.4 women die of a cardiovascular event
- 1 in 30 women die of breast cancer

Epidemiology

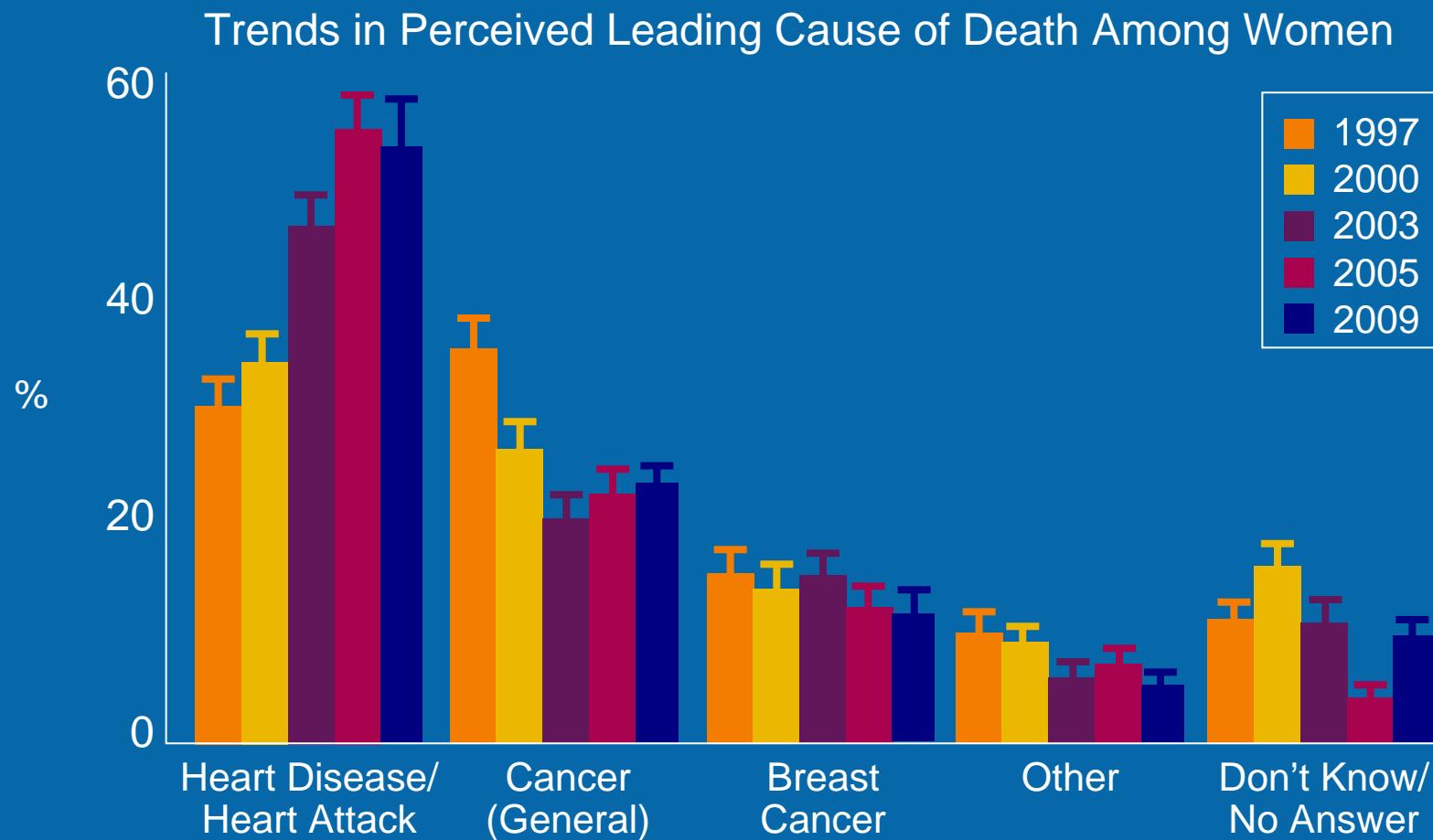
- Women typically 10 years older than men at first manifestation of CAD
- 1 in 8 women age 45-64 years has clinical evidence of CAD
- 1 in 3 women age > 65 years has clinical evidence of CAD
- Impact of CVD greater for African American women (67% greater mortality rate)

2004 - A Year of Changing Attitudes

- New emphasis on educating women
 - AHA's "Go Red for Women" campaign
 - NHLBI's "The Heart Truth" campaign
 - February 2004- AHA's first evidence based Guidelines for Cardiovascular disease Prevention in Women (Mosca et al *Circ* 109:672-693). *Guidelines most recently updated March 2011. (*Circulation*.123 (11): 1243-62)

Women's Perception of Risk of Heart Disease

Does education make a difference?



Mosca et al. Circ Outcomes 2010;109:120-127

Awareness of Leading Cause of Death

Response (unaided)	All (n=1142)	White (n=660)	Black (n=128)	Hispanic (n=200)	Asian (n=29)
Breast cancer, %	11	10	16	14	7
Cancer (general), %	23	20	43	44	20
Heart disease/ heart attack, %	54	60	43	44	34
Other, %	4	3	3	7	12
Don't know/ no answer, %	8	7	6	10	18

Mosca et al., Circ Outcomes. 2010;109:120-127

Perceptions & Effects on Preventive Action

- Majority of women - NOT aware of healthy levels of risk factors
- Women who perceived themselves at high risk -more likely to see a health care provider in past year compared to those at moderate or low risk.
- Women who had seen, heard or read info about heart disease in prior 12 months- significantly more likely to increase physical activity, decrease intake of unhealthy foods, and lose weight.

AHA Guidelines

- Guidelines tailored for a patient's individual risk
- Women are divided into 3 categories:
 - High Risk
 - At Risk
 - Optimal Risk
- Recommendations rated on strength of evidence

Classification of CVD Risk in Women:

- High Risk Established CAD, Cerebrovascular Disease, PVD, AAA, end-stage or chronic renal disease, DM, 10 year Framingham global risk > 10%
- At Risk \geq 1 major risk factors for CVD including: smoking, poor diet, physical inactivity, obesity (esp central), FHx of premature CVD, HTN, dyslipidemia, evidence of subclinical vascular disease (eg. coronary calcification), metabolic syndrome, poor exercise capacity on treadmill test or abnormal heart rate recovery p exercise
- Optimal Risk-Framingham global risk < 10% and a healthy lifestyle, with no risk factors

Prevalence of Traditional Risk Factors in Women

- Data from 2008 for U.S. women > 18 yrs of age:
 - > 1/3 HTN
 - > 1/3 with LDL > 130 mg/dL
 - ~ 1/5 are smokers
 - ~ 2/3 are overweight or obese
 - > 2/3 led a sedentary lifestyle
- These risk factors are more prevalent in socio-economically and educationally disadvantaged women

Diabetes and Women

- Diabetes is the most powerful risk factor for CAD in women: Stronger risk factor for CAD incidence and mortality in women
- Diabetes increases risk of MI x2 and increases risk of CAD x 5 from nondiabetic women of same age
- Eliminates the 10 year gender gap
- DM women are more likely to have CHF after MI

Cardiac Risk Factors

- Lipids
 - Total Cholesterol/HDL-C predictive of presence of CAD in women (TC alone not predictive)
 - T Chol/HDL should be ≤ 4
 - HDL-C : 20% higher in pre-menopausal women than men
 - Effect of loss of estrogen with menopause:
 - \uparrow Total Cholesterol, LDL-C, TRG
 - \downarrow HDL
- Low HDL and high TRG risk factor for older women.

Hyperlipidemia and Women

- Secondary prevention:
 - CARE trial - 46% ↓ CV events with Pravastatin in women after MI
 - 4S trial- 35% ↓ CV events with simvastatin in women post MI
 - LIPID trial – 24% ↓ relative risk of CV events in patients with prior MI or unstable angina with low to moderate cholesterol Rx with pravastatin

Hyperlipidemia and Women

- Primary Prevention:
 - AFCAPS/TexCAPS- 46% reduction in incidence 1st major acute CAD event with long-term lipid lowering therapy in postmenopausal women with average T-cholesterol and LDL-C, but below average HDL-C (vs 37% in men)
- No data, however, for aggressive lipid lowering in premenopausal women without risk factors

Hypertension

- 50 million people in US with HTN - 60% Women
- Etiology : pregnancy, OCPs & HRT (1^oly older agents) and renal artery stenosis (fibromuscular dysplasia) 8:1
- Women benefit with anti-HTN Rx- with reduction in total mortality, CV death, and CVA
- Women more likely to have side effects on anti HTN medications
 - Hyponatremia
 - Hypokalemia
 - ACE-inhibitor induced cough
 - Peripheral edema from Ca++channel blockers
 - Hirsuitism from monoxidil

Hypertension- Choice of agents

- Rx: thiazides vs β blockers and ACE inhibitors. Perry et al-No difference between anti-HTN agents
- Women's Health Initiative (WHI) - diuretics as monotherapy associated with better BP control than other drug classes
- Pregnancy: methyldopa is preferred. ACE-inhibitors and angiotensin receptor blockers are contraindicated
- Elderly: thiazide diuretics helpful to reduce hip fractures

Smoking and Women

- Smoking is associated with half of all CV events in women
- Smoking is a more potent risk factor for MI in women than in men.
- CV risk associated with smoking compounded by simultaneous use of oral contraceptives.
- The Nurse's Health Study cohort showed a strong causal relation between smoking and stroke in women

AHA Guidelines- Lifestyle interventions

- Encourage ALL women to stop smoking and avoid second hand smoke
- Perform minimum of 30 minutes of moderate intensity activity on most, preferably all days (those to lose wt-minimum 60-90 minutes/day)
- Consume heart healthy diet.
- BMI goal between 18.5 and 24.9kg/m² and waist circumference < 35 in.
- Consider omega 3 fatty acid supplementation
- Evaluate for depression in women with CVD

AHA Guidelines- Risk Factor Interventions

- Blood Pressure-Target BP: < 120/80 mmHg.
 - Rx indicated if BP > 140/90 mmHg or if end organ damage from HTN or DM
 - Thiazide diuretics recommended (high risk women-Rx with β blocker and/or ACE/ARBs, add thiazides as needed for BP goal)
- Lipids-Optimal Levels: LDL-C < 100 mg/dL, HDL-C > 50 mg/dL, total-C - HDL-C < 130 mg/dL, triglycerides <150mg/dL.

Guidelines- Risk Factor Modification- Lipids

- Diet-for **High Risk** women or when LDL-C is elevated:
 - Fat intake < 7% calories, cholesterol < 200 mg/day, and trans fatty acids reduced
- Pharmacotherapy- **High Risk** - initiate Rx if LDL-C >100mg/dL simultaneous with lifestyle changes. Rx with niacin or fibrate when HDL-C is low (**Very High Risk** - consider reduction to < 70mg/dL)
- Rx **At Risk**:
 - Rx if LDL-C > 130 mg/dL on lifestyle changes and there are multiple risk factors and 10 year absolute risk is 10-20%
 - Rx if LDL-C > 160 mg/dL on lifestyle changes and multiple risk factors even if absolute risk <10%.
 - Rx if LDL-C > 190 mg/dL regardless of presence or absence of risk factors on lifestyle changes.
- Consider niacin or fibrate Rx when HDL-C is low or non HDL-C is elevated after LDL goal is reached with multiple risk factors and 10 year risk 10-20%.

Guidelines- Preventive Drug Interventions

- Aspirin- (75-325mg/day) or clopidogrel if ASA intolerant
 - for women with CHD unless contraindicated
 - Reasonable for women with DM unless contraindicated
- Aspirin 81 mg/day or 100 mg qod
 - Consider for At Risk women \geq 65yrs if BP controlled and benefit(MI and CVA) outweigh risk of GI side effects
 - Consider for At Risk women < 65yrs when benefits for ischemic CVA likely outweighs adverse effects
- Aspirin should NOT be used in healthy women < 65 years of age to prevent MI
- Beta-blockers- for 2° prevention post MI or if chronic ischemic syndromes unless contraindicated

Guidelines- Preventive Drug Interventions

- ACE Inhibitors- in high risk women unless contraindicated
- ARBs- in high risk women with clinical evidence of heart failure or EF < 40% and intolerant to ACE inhibitors
- Aldosterone blockade- post MI in women with no significant renal dysfunction or hyperkalemia receiving therapeutic doses of ACE inhibitors and β blockade and have LVEF \leq 40% with sx of heart failure.

Guidelines – Preventive Drug Interventions.

- Warfarin in Atrial Fibrillation-(INR 2.0-3.0)- in women with chronic AF or PAF unless low risk for stroke (<1%/yr) or if high risk of bleeding. Use aspirin 75-325 mg for chronic AF or PAF if low risk for stroke (<1%/yr or CHADS2 score <2).
- Dabigatran –possible alternative to warfarin for AFib if no prosthetic valves or significant valvular disease, no severe renal failure or advanced liver disease.
- Antioxidants should NOT be used to prevent CVD in women
- Hormone Replacement Therapy should NOT be used for CVD prevention
- Folic Acid +/- B6 or B12 should NOT be used for primary or secondary prevention of CVD

CAD presentation in Women

- Most common presentation of CAD in women is Angina
- Women are more likely than men to have
 - Atypical symptoms (fatigue, dyspnea)
 - Hypertension, diabetes, heart failure and be older than men
 - False positive ETT (stress EKG)
 - Single vessel disease and nonobstructive CAD than men

Women and thrombolytics

- Equivalent benefit as men (12-14% ↓ death)
- Risk of hemorrhagic stroke is equivalent after adjusting for age and BMI (GUSTO I, ISIS III)
- Higher bleeding complications
- Higher rates of shock, CHF, rupture, VF, AF, and reinfarction

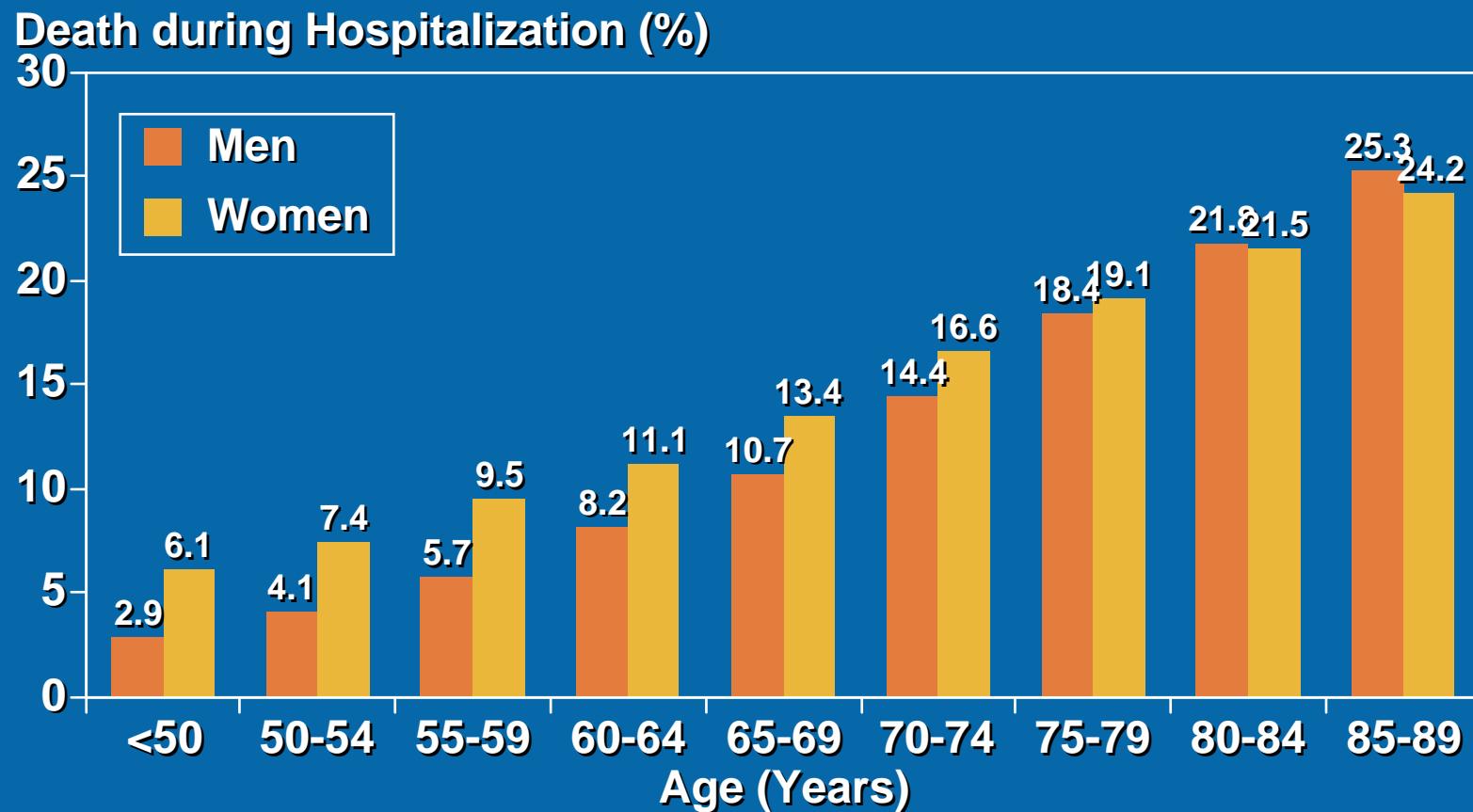
PCI in Women

- Women more likely to be older, have more advanced disease and have more comorbidities
- No lesion difference between men and women
- Outcomes between men and women similar
- Women have higher vascular complication rates
- Women less likely to have state of the art treatment using stent and abciximab
- Previously women with abnl noninvasive testing - less likely to be referred for angiography, but now comparable referral rates as men with abnl nuclear stress tests. Also similar referral rates for revascularization based on anatomy.

CABG and Women

- Women more likely to be older, have more advanced disease and more comorbidities
- Less complete revascularization and less use of IMA in women
- More angina after CABG in women
- More bleeding after CABG in women

Gender Based Differences in Mortality post MI



Vaccarino, NEJM 1999 Jul22; vol 341 (4)217-25.

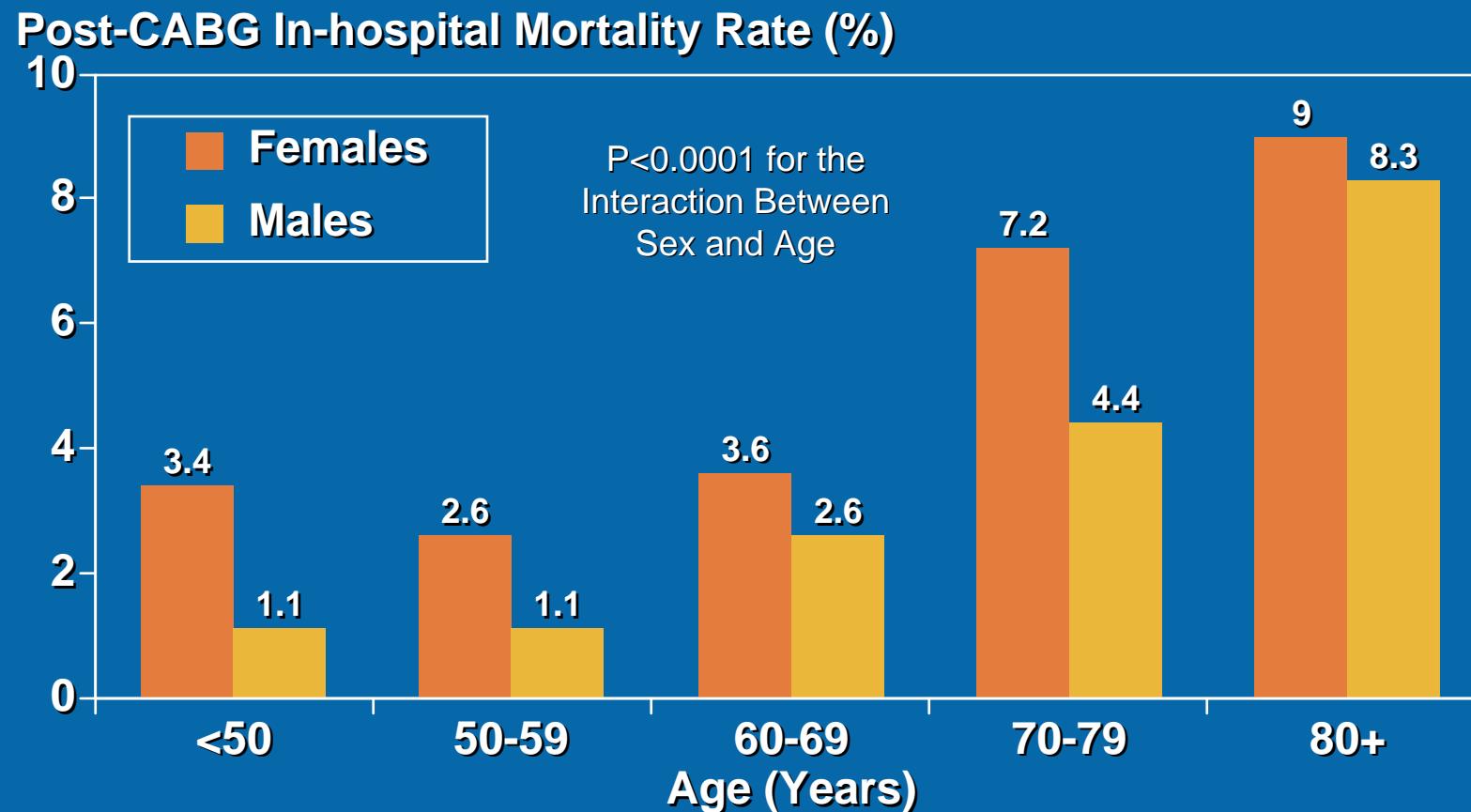
Gender based differences in mortality post MI

National Registry of MI 2 participants

- Overall in hospital mortality rates:
 - 16.7% in women vs 11.5% in men
- There was a significant interaction between age and gender:
 - Younger women post MI had significantly higher in hospital mortality rates compared to men of same age, however there was no difference in mortality rates between men and women older than 75.
- Differences in medical history, clinical severity of infarction and early management, accounted for 1/3 of the difference in risk

Gender Differences in Hospital Mortality post CABG

N = 51,187 patients in the National Cardiovascular Network database



Vaccarino: Circulation, vol 105(10). March 12, 2002, 1176-1181

Gender Differences in Hospital Mortality after CABG

- Conclusions: Compared with men
 - Fewer women were white
 - Women had more risk factors and more comorbidities
 - Women had higher LVEF and fewer diseased vessels
 - Women had higher in hospital mortality rates, but gender differences were more marked among younger patients
 - *Therefore younger women undergoing CABG were at higher risk than age matched men, but this difference in risk decreased with advancing age.

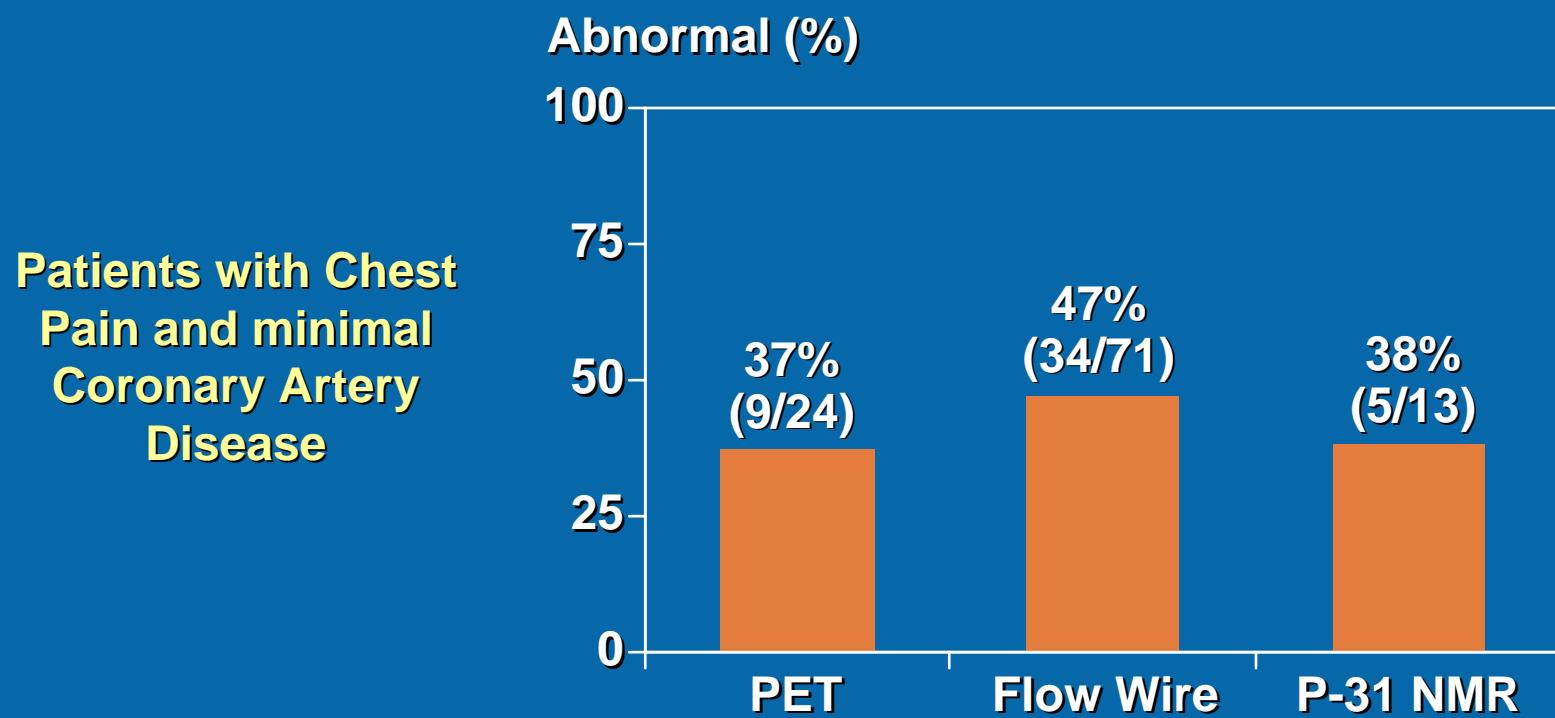
Paradox - Although worse outcomes for women with ACS, have double the rates of “Normal Coronary Arteries”

	No/Total (%) Women	No/Total (%) Men	P value
GUSTO	343/1768 (19.4)	394/4638 (8.4%)	< 0.001
TIMI 18	95/555 (17)	99/1091 (9)	< 0.001
Unstable angina	252/826 (30.5)	220/1580 (13.9)	< 0.001
TIMI IIIa	30/113 (26.5)	27/278 (8.3)	< 0.001
MI without ST elevation	41/450 (9.1)	55/1299 (4.2)	0.001
MI with ST elevation	50/492 (10.2)	119/1759 (6.8)	0.02

Bugardini and Bairey Merz JAMA 2005; 293:477-84

Lessons learned from WISE study (Women's Ischemic Syndrome Evaluation Study)

- >80% of patients with normal angiograms had plaques > 0.5mm by IVUS.
- Approximately 1/3 of women with Chest pain and “Minimal Coronary Artery Disease” had vascular dysfunction



Women may have Epicardial Coronary Artery Disease or Microvascular Coronary Disease

- Epicardial Disease - as seen in men- amenable to percutaneous or surgical revascularization
- Microvascular Coronary Disease -
 - Classic exertional anginal sx
 - Inducible ischemia on nuclear stress testing
 - Minimal coronary disease on angiography
 - Abnormal flow reserve with intracoronary adenosine
 - Plaque noted on IVUS
 - Responds to aggressive risk factor modification and medical therapy

Lessons from the WISE study (Women's Ischemic Syndrome Evaluation Study)

- Initial presentation of Ischemic Heart Disease in women = acute MI or sudden cardiac death in 60% cases
- Post mortem - men and older women with plaque rupture with large necrotic core and disrupted fibrous cap infiltrated by macrophages and lymphocytes. Vs Younger women with plaque erosions and absent fibrous cap, and more frequent distal embolization.
- Younger women presenting with acute MI have worse prognosis

Ischemic Syndromes in Women

- Acute Coronary Syndromes vs Chronic Stable Chest Pain
 - Survival in women with chronic chest pain symptoms superior to men, however women with acute MI have higher 1-year death and reinfarction rates compared to men.
- Women with Chest Pain –
 - Greater symptom burden, lower quality of life, but more often have non-obstructive coronary disease
 - Smaller vessels and endothelial dysfunction
 - Decades of higher levels of inflammation, with clustering of risk factors may be associated with more frequent endothelial dysfunction, loss of arterial compliance and dysfunction of microvasculature

Do we need an Alternative strategy for Women with Chest pain?

- Women with greater prevalence of non-obstructive coronary disease but higher frequency of myocardial ischemia
- Rely more on measures of functional capacity, plaque burden, extent and severity of perfusion abnormalities and global ventricular function and inflammatory markers to identify patients at risk, and less on looking for “culprit lesions”
- Aggressively treat women at risk with risk factor modification and medical therapy.

Summary

- Cardiovascular Disease is the leading cause of death in American women
- Guidelines for prevention can empower women to take control of their healthcare and reduce their risk
- Education does cause behavioral changes, and can be effective in disease prevention
- Future research on risks and treatments of heart disease must focus on women as well as men

Estrogen and Coagulation Factor

Increases

Factor VII

Factor X

F 1+2

Protein C

Plasminogen

Decreases

Fibrinogen

Antithrombin III

Protein S

MI Complications by Gender

