



The Impact of Gender On the Experience of Coronary Artery Disease.



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How Important is CAD for Women?



- Coronary artery disease kills 233,000 American women annually: all cancers combined kill 246,000.
- 1 in 9 women between 45 and 60 and 1 in 3 women over 60 have the disease.
- 24% of all deaths in women is due to CAD.
- **Age adjusted mortality in women** after acute MI: women younger than 75 showed 2X higher mortality as men in same age group. *



What Do Women Know About Their Risk for CAD?*

- **Overall, 76% of women surveyed knew**
 - CAD was leading cause of death in middle aged men; 67% knew that cancer kills most middle aged women.
 - 59% knew CAD was leading cause of death in older men; 45% knew that this is also the case for older women.
- **Only 1 in 3 of older women** knew that CAD is the leading cause of death in their age range. (After age 65, men and women have an equal likelihood of dying of CAD).
- **More than half of the group** believed breast cancer was the leading cause of death in women aged 55 to 64; four out of five did not know that lung cancer is the deadliest cancer for women of that age; colon cancer is the most deadly for the oldest women.

*Wilcox S and Stefanick ML. Health Psychology. 1999.18(4).



Men, Women and CAD:

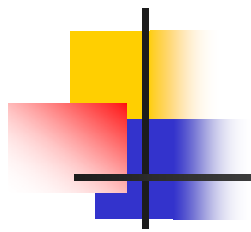
Is There a Gender-Specific Pathogenesis of CAD?

- **Initial symptoms** 10 years later in women.
- Most common **initial presentation** of CAD:
 - Women: unstable angina
 - Men: acute MI
- When there is an episode in CAD, including AMI, women have **less extensive** coronary arteriosclerosis than men and develop smaller infarcts than men. Coronary *spasm* may be an important mechanism for myocardial ischemia and damage in women.



How much reliable data do we have about women and coronary artery disease?

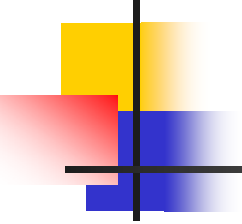
Excluding 2 large single sex trials focusing on primary prevention of CAD, between 1965 and 1998 **there was no increase in the proportion of women enrolled** in clinical trials funded by NHLBI.*



Findings of the Evidence- based Practice Center at UCSF/Stanford*

- **Much of research in last 20 years has excluded women or included only limited numbers.**
- **Only 20% of articles reviewed provided separate findings on women, even when women were included in the study.**

*Grady D et al. Agency for Healthcare Research and Quality.
Publication No.03-0035. 2003



“Even though funding agencies appear to have succeeded in ensuring that some women and minorities are included in randomized trials, data about these populations often are not made clear in the published findings.”

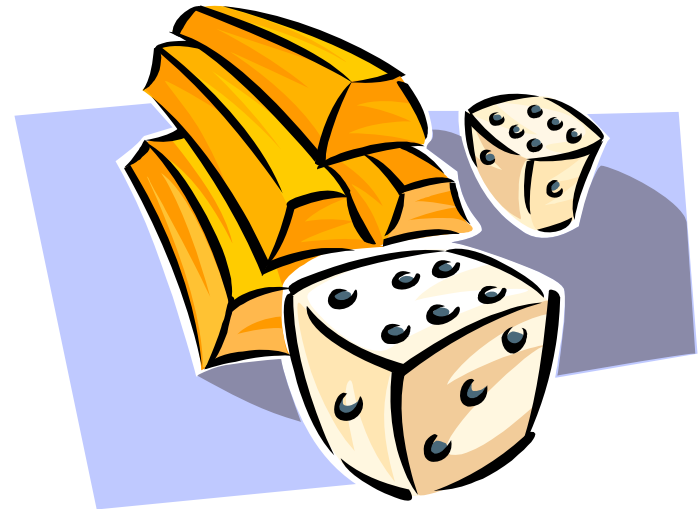


Risk Factors:

**Impact Quantitatively Different
In Men and Women**

Risk Factors: What Can't Be Changed.

- Age
- Family history
- Menopause





AGE

- Women are 10 years older than men at initial manifestation of the disease and 20 year older at the time of their first MI.
- There is a 40-fold increase in CAD in women at 75-84. The incidence is equal in the sexes by age 80.
- The increase in incidence is gradual, **with no abrupt acceleration at menopause.**



Family History

- A parent with an **MI before age 60** increases women's RR of MI to 2.8 and RR of fatal CAD to 5.0.*
- Death of a **first degree relative** of CAD before the age of 55 significantly increases risk for women, particularly if the decedent is a female.



Menopause:

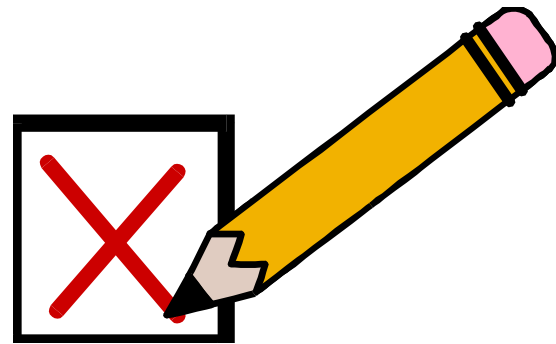
*An Endocrinopathy For Which
Estrogen Is The Cure?*



Risk Factors:

What Can Be Treated.

- **HYPERTENSION**
- **DIABETES**
- **DYSLIPIDEMIA**
- **OBESITY**





HYPERTENSION

- **High normal** (c/w optimal) BP 130-139 mm/85-89 increases RR for CVD of 2.5 for women, 1.6 for men. (Vasan RS et al. N Engl J Med. 2001. 345: 1291.)
- **Isolated systolic hypertension** (loss of elasticity in large arteries) affects 37% of women 55 and older. Rx reduces stroke incidence by 30% and CAD incidence by 23% in women. (Stasson JA wet al. Lancet 1997.350:757.) No gender difference in benefit from treatment.
- **Treatment of severe hypertension** benefits both sexes alike. (Gueyffier F et. Al. Ann Intern Med. 1997. 126:761.)



What's The Best Way To Assess Blood Pressure?*

- LV mass is a better measure of blood pressure over time than standard readings of peripheral blood pressure.
- Risk for CVA:
 - For highest quartile of LV mass to height ratio:
Men: 18.4%
Women: 12.2%
 - For lowest quartile:
Men: 5.2%
Women: 2.9%

*Devereux RB. JAMA.1994;272:71-72 (editorial) and Bikina M et al. JAMA.272:33-36.



DIABETES

- **Increases risk 5-7 fold in women c/w 2-4 fold in men. (Diabetes accelerates CAD more in women than in men.)***
- Risk for fatal MI increases sharply for women as duration of diabetes increases (RR 16-25 for diabetes of over 25 years' duration).
- 50% of increased risk is due to dyslipidemia, **particularly a low HDL** in diabetic women.***
- Diabetes may impair estrogen binding and raise testosterone levels, negating advantage of premenopausal state.
- Diabetic women who **smoke have an additional 3-fold** increase in risk**

*Perthman JA et al. Am J Obstet Gynecol 1988.158.1568

**Manson JE; Arch Intern Med.1991.1511.1141

***Vital Statistics. Alexandria, VA. ADA. 1991

Intriguing (and unanswered) Questions

- What accounts for the **greater impact** of diabetes on women as a risk factor for CAD?
- Why is a **low HDL** a greater risk factor for CAD in women than in men?





How to Protect the Diabetic Against CAD Risk?

- **No evidence that tight glycemetic control is effective in risk reduction.**
- **Intensive treatment of Type I diabetes such that weight increased actually increased risk of CAD:** heavier patients had higher levels of small, dense LDL particles. Measurement of LDL particle size may be particularly important; niacin, fibrates and metformin may be better in these patients than statins, which do not impact LDL particle size. (Purnell JO et al. JAMA.1998.280:140-146.)
- **Best treatment is to modify other risk factors: obesity, smoking, hypertension and dyslipidemia all act synergistically with diabetes to increase CAD risk. (Manson JE et al. Arch Intern Med. 1991. 151:1141-1147.)**



Dyslipidemia

- TC increases with age; plateaus in men at age 45-50, in women, increases until 60-65. (Jousilahi P et al. Ann Intern Med.1996.125:713.)
- For women under 65, TC >240 associated with RR of 2.44; LDL>160 associated with RR of 3.27. **For women over 60, high levels of TC and LDL had much lower RR: 1.12 and 1.13 respectively.** (Manolio TA et al. Ann Epidemiol.1992.2:161.)
- **HDL** a special risk factor for women: with less than 50, risk doubled. Risk higher after age 65 for women (1.75) compared with men (RR 1.09). (Ibid)
- **Hypertriglyceridemia** : RR of 4.7 in women, 2.1 in men.



Lipoprotein (a)

- An independent risk factor for CAD in men.
- Age as a factor in vulnerability: in older (>72 years) adults, elevated Lp(a) is a predictor of stroke, death from vascular disease and any cause *in men but not in women.* *
- In the HERS study: **
 - Women in highest baseline quartile of Lp(a) had 54% high RR for CAD death or first nonfatal MI.
 - HT (Premarin + MPA) lowered Lp(a) significantly by year 1; those with greatest decrease had significantly lower risk for CAD.

** Shlipak MG et al. JAMA.2000.283:1845-1852

* Ariyo AA et al. NEngl J Med.2003.349:22.



How Does HDL Work? (Differently in Men and Women)

- **Reverse cholesterol transport:** HDL transports cholesterol from peripheral tissues to the liver, binding to a “scavenger receptor” (**SR-B1**) in the liver and delivers the sterol to hepatocytes for excretion in bile or incorporation into other lipoprotein particles.
- **Female HDL –associated estradiol stimulates NO release by endothelial cell in premenopausal and postmenopausal women on HT. ***
 - SR-B1 is also expressed in endothelial cells; HDL binds to this receptor to deliver estrogen to the endothelial cell and promotes release of nitrous oxide.
 - HDL from premenopausal women or postmenopausal women receiving HT stimulated NO release with vessel dilatation; **male-derived HDL did not promote NO release.**



Significance of Gong Paper

- Provides **mechanism** for how female HDL in the presence of physiologic amounts of estrogen protects premenopausal woman and postmenopausal woman on HT from CAD.
- Male derived HDL has no such effect *unless it is enriched with estrogen*. Only estrogen-associated HDL stimulates eNOS.
- The mechanism of action is **not transcriptional**; isolated membrane caveolae and isolated plasma membranes showed the effect of HDL-estrogen on eNOS stimulation.



NCEP III:

JAMA 2001; 285.2486-2509

- ***New concept of diabetes:*** Elevates diabetes to CAD risk equivalent, even without established CAD.
- ***Targeting patients with multiple risk factors.*** Uses Framingham system to identify patients with multiple risk factors for more intensive treatment. (Separate tables for men and women.)
- ***LDL cholesterol:*** primary target is <100 mg/dL
- ***HDL cholesterol:*** raises baseline from 35 to 45 mg/dL for both men and women.
- ***Triglycerides:*** recommends treatment beyond LDL lowering for trigs >200 mg/dL.



Obesity and the WHR

- Being **30% over ideal** body weight increases RR to 3.3. For women*
- **Increased WHR** (over 0.9 for men and 0.8 for women) predicts elevated triglyceride and low HDL levels.
- Central obesity correlates with **hypertension** and in men, with insulin resistance.
- **WHR** is a more accurate predictor of risk than BMI or total weight and explains the gender difference in incidence of MI.
- **Low BMI** is protective: BMI < 21 = RR 1 (Nurses' Study).



Why Obesity Increases Risk

- Association with hypertension, dyslipidemia, glucose intolerance and insulin resistance.
(Rexrode KM et al. Curr Opin Cardiol 1996.490-495.)
- Obesity is associated with elevation in
 - **thrombotic markers** like fibrinogen and plasminogen activator inhibitor-1.
(Duncan BB et al. Obes Res.2000. 8:279-286.)
 - **inflammatory markers** (interleukin-6 and C-reactive protein)
(Visser M. et al. JAMA 1999.272:2131.).



Newer Markers of Risk

- **C-reactive protein:** a predictor of risk for cardiovascular events in women (Ridker et al. N Engl J Med 2000;342:836-43) and in men (Rodker PM et al. Circulation.1998.97:2000-2002).
 - More important marker in women, in whom the increase in LDL with age is not as significant a risk as that in men.
 - Statins are effective in lowering CRP
- **Homocysteine:** ?a cause or a marker for CAD?; can be lowered by treatment with folate, B6 and B12. Elevated levels are independently associated with all cause and CVD in elderly. (Bostom AG et al. Arch Intern Med.1999.159:1077-1080.)



LIFESTYLE

- **Exercise**
- **Smoking**
- **Stress**
- **Alcohol**





WHI Data: Walking Compared With Vigorous Exercise*

- 73,743 women ages 50-79
- Walking and vigorous exercise were associated with similar risk reductions: **data did not change as a function of BMI, age or race.**
- Women in increasing quintiles of energy expenditure (measured in METS) had a decreasing RR for CAD: 1.00, 0.73, 0.69, 0.68 and 0.47.
- **First quantification of risk of a sedentary lifestyle:** Women who spent 12-15 hours/day lying down or sleeping and women who spent 16 hours/day sitting had RR of 1.38

*Manson JE et al. N Eng J Med 2002. 347:716-725.



Sedentary Behavior: What's the Risk?*

- **Time spent viewing TV**: For each 2 hours/day increase, obesity rose 23%, diabetes risk by 14%.
- **Walking significantly reduced risks** for obesity and diabetes: 30% of new obesity cases and 43% of new diabetes cases can be prevented by limiting TV viewing to less than 10 hours/week and by walking vigorously for more than 30 minutes/day.

SMOKING:

The leading preventable cause of death
in both sexes.

- One of strongest **predictors** of premature CAD and premature death from CAD in women: 40% of all deaths from CAD are directly attributed to smoking.
- Myocardial blood supply **reduced by 21%** in smokers. (Kaufman PA et al. Circulation.2000;102:1233-1238.)
- Nurses' Study: Effect is dose dependent: even 1-4 cigarettes a day double vulnerability.
- Smokers and **perception**: only 29% believe they are at increased risk for heart disease. (Ayanian JZ and Cleary PD. JAMA.1999.281:1019-1021)



Alcohol

- Nurses' Health Study: 10-15 gm alcohol/day reduces risk by 40% over a 4 year follow-up period.*
- 50% of risk reduction is due to changes in HDL.**
- Other beneficial effects;
 - Increase in tissue-type plasminogen activator
 - Reduced platelet aggregation
- With **higher levels** of consumption: women are more susceptible to alcoholic liver disease and alcoholic cardiomyopathy compared with men.

*Fuchs et al. N Engl J Med.1995.332:1245.

**Sess HD et al. Curr Opi Nephrol Hypertens.1999.8:353.



STRESS AND CAD IN WOMEN: *What Do We Know?*

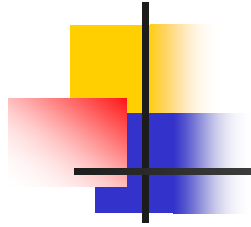
- Reactivity to **stress**
 - Men have more pronounced cardiovascular reactivity than women
 - Oxytocin (release enhanced by estrogen) promotes “tend and befriend” reflex in women, decreases BP and increases pain threshold.
 - Men with sustained anxiety have a higher risk of plaque occurrence; women show no such increase. *
- Impact of **work**: Framingham data
- Repressed **hostility**: women are more likely to repress hostility than men and to be angry longer. **
- **Depression**: in women with CAD, prevalence of major depression is 3X that of other persons. **
- **Stockholm Female Coronary Risk Study**: marital stress=2.9 fold increased risk of recurrent events in women. *Work stress did not significantly predict recurrent coronary events.* ***

*Paterniti S et al. Arterioscler Thromb Vasc Biol.2001.21:136-141.

**Thomas SP. Women and Anger. NY Springer. 1993

**Rozanski et a. Circulation .1999.99:2192.

*** Orth-Gomer K et al. JAMA.2000.284:3008-3014.



Symptoms



Presentation

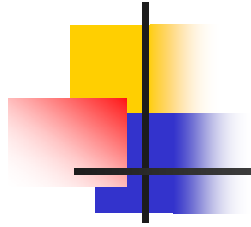
Compared with men,
women have a higher incidence of

- angina
- atypical chest pain
- silent MI
- death from MI
- sudden death
- false positive exercise tests
- angina predictive of MI



WOMEN AND SYMPTOMS

- **Chest pain:** angina or non-coronary chest pain?
- **MI:** initial manifestation in 39% of men and 31% of women.
- **Unrecognized MI:** 35% in women, 27% in men.
- **15-20% of women:** epigastric or back pain, dyspnea, nausea and diaphoresis.



Testing for CAD



Women and Testing For CAD

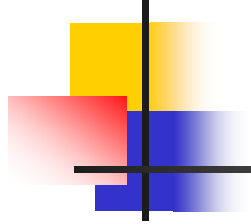
- **Exercise radionuclide angiography**: sensitivity for peak EF lower in women.
- **Stress test**: 54% false positive rate in women. Significantly less specificity (36%) in presence of abnormal resting EKG in women compared with men (54%).
- **Stress-echocardiography**: specific value for women.
- **Thallium-210** scintigraphy: no gender difference in S/S with correction for breast artifact.



Electron Beam CT Coronary Screening

- EBCT scores have **similar predictive values** for men and women.*
- Similar calcium scores are diagnostic of similar overall atherosclerotic plaque burdens regardless of age & gender. **Other factors like age and gender must be considered, however, in interpreting the scores.**
- Total calcium area is about 20% of total plaque area.
- Number of plaques identified as calcified by EBCT is roughly proportional to the number of non-calcified plaques identified by intravascular ultrasound.***

•Rumberger JA et al. Am J Cardiol.1993.73:1169-1173 and Rumberger JA. Circulation.1995.91:1363-1367.
•** Rumberger JA et al. May Clin Proc. 1999.74:243-252).
•***Schmermund A et al. Am J Cardiol.1998;81:141-146.



The Myocardial Infarction





Outcome

Compared with men
women have more:

- MI morbidity
- MI mortality
- CABG mortality



After the AMI

- Women have more **complications**:
 - More likely to present in CHF and cardiogenic shock
 - More likely to undergo major clinical events during hospitalization (cardiac rupture, arrest, AV block, reinfarction, systaine hypotension, atrial arrhythmias and stroke.) even after correction for older age.
- Women have **higher mortality** in most studies in the short term. (No difference in long term mortality 1 month post hospitalization.)



Treatment of AMI in Women: Less Aggressive Than in Men*

- **Women take 12.5 minutes longer to arrive at the hospital after onset of symptoms.**
- **93% of men received ASA acutely; 87.8% of women did.**
- **Thrombolysis: door-to-needle time: 90 minutes for women, 78 minutes for men.**
- **Beta blockers after an MI: 31.6% prescribed for women, 44.9% of men.**
- **Estimated survival one month after MI: 78.4% for women, 88.0% for men.**

Gender and Outcome From Myocardial Infarction

- **Women's overall mortality after first MI**
 - 45% c/w 10% in men (Framingham)
 - 36% c/w 21% in men (MILIS)
 - 23% c/w 16% in men (Israel)
- **Women:**
 - 2X more likely to die as men in first few weeks.
 - 39% c/w/ 31% of men die in year one.
 - 20% c/w 15% of men will have a second attack in 4 years.

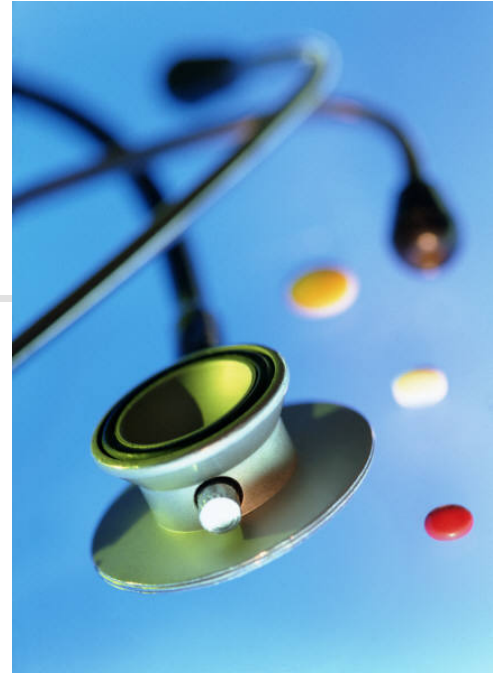
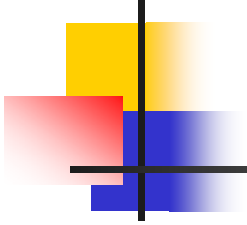




Gender and Access to Care: 2002*

- Women are still less likely to be offered therapeutic cardiac procedures than men.. The reason is unknown.
- Women are less likely than men to have a revascularization process in the year after cardiac catheterization; **this is related to a difference in the extent of disease.**
- Women are less likely to receive
 - beta blockers (1/3 of women received them)
 - cholesterol lowering drugs (1/2 of women used them)
 - aspirin (only 80% used them).

*Ghali WA. An Intern Med. 2002.136:723.



Treatment



Women and Treatment

- **Health care professionals counsel women less often than men about exercise, nutrition and weight reduction.***
- **Prevalence of obesity in women is increasing.**
- **25% of women report no regular sustained physical activity and smoking rates are declining less for women than for men.**

Women and Cardiac Catheterization: How Big a Factor is Patient Refusal?



- 74,745 Medicare beneficiaries in the Cooperative Cardiovascular Project.*
- White (3.29%) and black (3.6%) women and black men (3.49%) refused CC more than white men (2.46%): **patient refusal is not the only reason for observed race (3%) and sex (7%) differences in cardiac catheterization.**

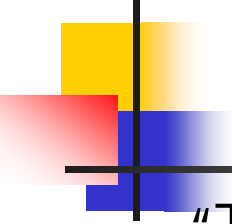
*Rathore SS et al. Am Heart J.2002.144:1052.



Do Women Benefit from Early Invasive Management with Acute Coronary Syndromes?*

- TACTICS-TIMI 18 randomized trial 1997-1999 in 169 centers in 9 countries in North American & Europe: 757 women and 1463 men.
- Early invasive strategy: cardiac cath 4-48 hours and revascularization when appropriate.
- Conservative management: medical treatment with CC and revascularization only if they met specific criteria.
- Men and women had a **similar benefit** from early invasive strategy: 28% odds reduction in primary end point in spite of important *differences in baseline characteristics and presentation:*
 - Women older, more had hypertension
 - Women had less previous MI, CABG, elevated cardiac markers.
 - Women had less severe coronary artery disease, including no critical lesions in 17% of women vs 9% of men.

Glaser R et al. JAMA.2002.288:3124.



“The hypothesis that higher procedural complications, comorbidities and less severe disease at angiography in women may favor conservative therapy is not supported by our data.”





Women and PTCA: The NHLBI Experience

- **Women were older by 4.5 Yrs and sicker than men.**
- **Mortality: 2.6% for women c/w 0.3% for men, but 95.7% of women survived the procedure.**
- **Equal rates of four year survival**
- **Women less likely to restenose.**

Kelsey SF et al. Circulation 1993.87.720



Gender, Stenting and Outcome*

- Compared to men, women were:
 - Older (mean age 69 vs. 63)
 - More likely to be diabetic, have hypertension, dyslipidemia and diabetes
- Women likely to have an excess risk (3.1% vs. 1.8%) in men for death *only in first 30 day period after stenting*. Outcome essentially the same after a year.

*Mehilli J et al. JAMA.2000.284:1799-1805.



Women, PCI *, 1994-1999

Northern New England**

- 22,689 men, 10,977 women; underwent PCI from 1994 through 1999.
- Women: 5-6 years older than men (80 or older)
- For **both genders**:
 - Stent use increased from 4% to 80%
 - Clinical success rates increased, emergency CABG decreased significantly
 - Rates for any bypass surgery declined by 72%
 - **Mortality was similar.**

*PCI: Percutaneous Coronary Intervention

**Malenka DJ et al. J Am Coll Cardiol.2002.40:2092.



Mortality Rates After PCI *

- Database: **National Cardiovascular Network** (49,699 women and 101,249 men who underwent angioplasty and/or stenting between 1993 and 1999.)
- Women *younger than 50* were 78% more likely to die after PCI than same aged men.
- In this same age group, *absolute mortality rates* were lowest of all patients in the data base (0.8% for women and 0.4% for men).

*Abramson JL et al. Am J Cardiol 2003.91:968-971.



Referral for CABG:

Does Gender Make a Difference?

- **New England:** men referred more frequently than women.*
- **CASS:** men had a higher referral rate than women.**
- **Duke:** lower risk women referred less frequently than lower risk men.***

- Ayanian JZ. N Engl J Med.1991.125.221
- **Davis KBJ AmJ Cardiol 1995.25.1000
- ***Bickel NA AnnIntern Med 1992.116.791.



Women and CABG

- **Meta-analysis: women's RR of death 2.19 c/w men.**
- **Difference due to greater severity of disease and smaller vessel size.**
- **Women have less relief of symptoms, but similar 5-10 year survival rates compared with men.**



Prevention of CAD in Women: What's New and/or Most Important?*

- **First line of therapy for dyslipidemia in postmenopausal women: statin or other cholesterol-lowering drug.**
- **Target HDL for women should be higher than national recommendations (greater than 45 mg/dL).**
- **Diabetes increases women's risk for CAD 3-7 times c/w men, in whom increase in risk is 2-3 fold.**

Mosca L. et al. AHA/ACC scientific statement: consensus panel statement: guide to preventive cardiology for women. J Am Coll Cardiol 1999;22:1751-55.