Cardiovascular Disease in Women

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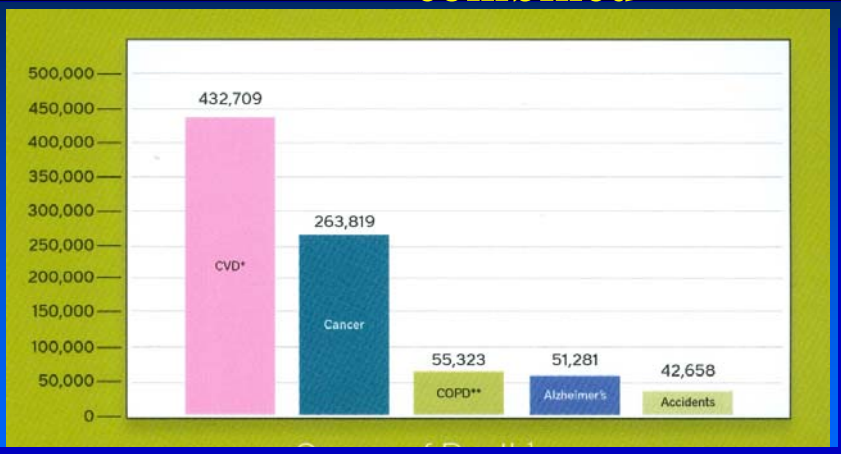
Learning Objectives

- Compare differences between men and women in risk factors, incidence and treatment of cardiovascular disease
- Define the terms endothelial dysfunction and microvascular disease

Cardiovascular disease kills more women each year than the next four causes of death combined

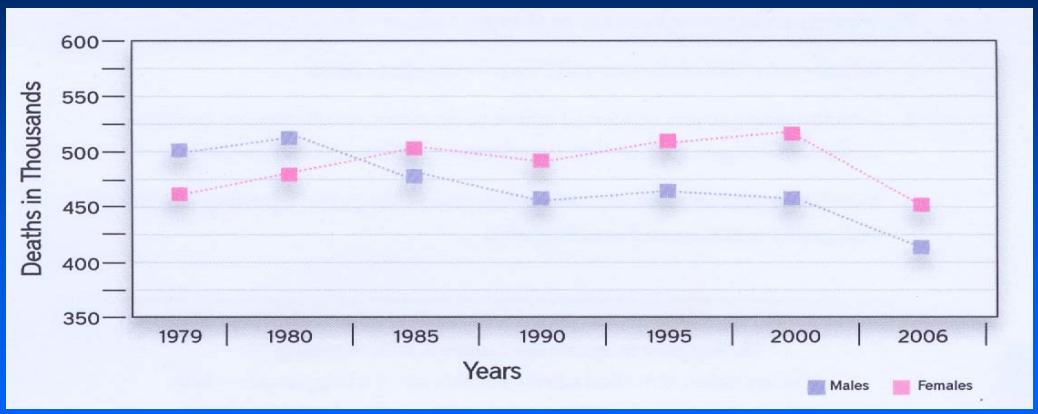


Causes of Death:
* Cardiovascular Disease
** Chronic Obstructive Pulmonary Disease

Since 1984 more women than men have died of heart disease each year and yet much of the medical community still largely considers it a "men's disease."

Source: Aha 2010 Statistics Update

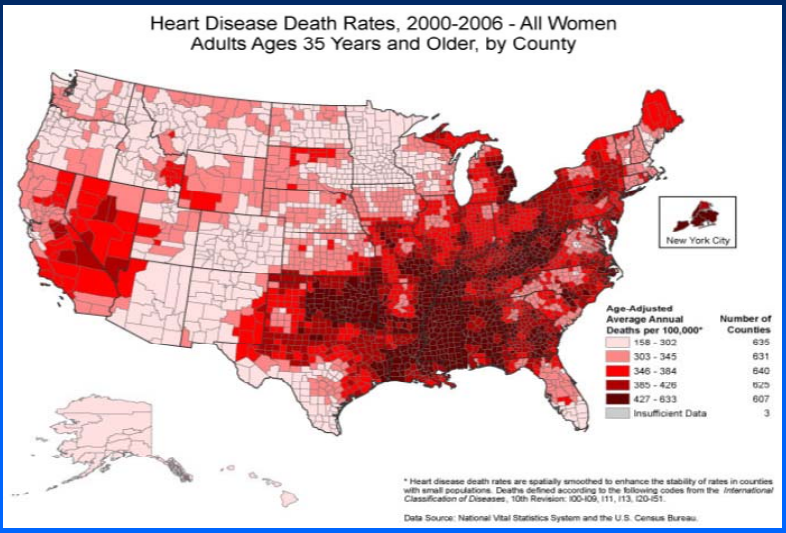
Gender Differences in Symptoms, Prevention and Treatment of CVD Contribute to a High Number of Fatalities in Women



Trends in Deaths from Cardiovascular Disease for Males and Females (US: 1979-2006).

Source: NCHS and National Heart, Lung, and Blood Institute

Women and Heart Disease: US Prevalence



Women are very different than men

- Different cardiovascular risks and benefits
- Hypercoagulable: platelets and thrombin
- Different drug pharmacokinetics
- More side effects to medications
- More bleeding complications
- Less likely to receive guidelines based therapy

Hormonal Influences on cardiovascular disease

- Oral contraceptives associated with 2-3 fold increase in HTN, ↑MI, ↑CVA.
- Gestational diabetes and pre-eclampsia ↑cardiovascular risk
- Spontaneous coronary dissection
  - women>>>men
  - ↑prevalence within a few months of childbirth

Other CV Risk Factors in Women

- ↑CRP – greater risk in women than men
- Autoimmune disorders (Rheumatoid arthritis)
- Carrier of HPV (human papilloma virus) 2-3x ↑risk of MI and CVA
- Radiation for Breast cancer - ↑higher risk of CAD

Traditional Risk Factors for CAD may affect women differently than men

- Smoking –
  - incidence of CAD women > men (Lancet 2011;378.1297)
  - incidence of PVD in smokers: women >>> men
  - women who smoke are twice as likely to have MI compared to men who smoke
- Diabetes –
  - causes 50% ↑risk of MI in men, but 150% ↑risk in women
  - metabolic syndrome, insulin resistance > risk in women compared to men

Diagnosis and Treatment of Cardiovascular Disease in Women

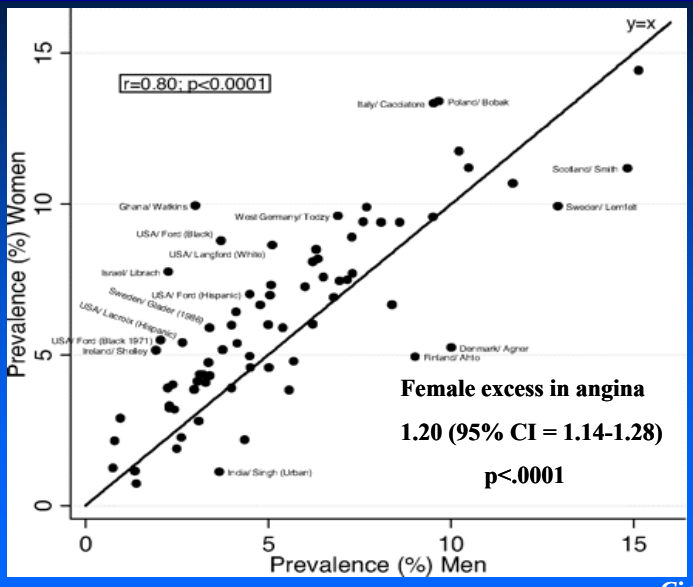
- Atypical symptoms
- False positive and false negative stress tests
- Different response to treatments
- More complications from invasive procedures
- More side effects from medications

Top heart attack symptoms in women

One month before a heart attack	During a heart attack
Unusual fatigue (71%)	Shortness of breath(58%)
Sleep disturbance (48%)	Weakness (55%)
Shortness of breath (42%)	Unusual fatigue (43%)
Indigestion (39%)	Cold sweat (39%)
Anxiety (36%)	Dizziness (39%)
Heart racing (27%)	Nausea (36%)
Arms weak/heavy (25%)	Arms weak/heavy (35%)

Source: *Circulation* **2003, Vol. 108, p. 2621.**

Women have higher Prevalence of Angina compared to Men



Circ 2008; 117:1526

Effect of sex, age and race on Angina Prevalence

Subgroup	No. of Populations	Crude Prevalence Women/Men	Pooled Sex Ratio (95% CI)
Mean age of participants, y			
<45	15	3.8/3.2	1.11 (0.92-1.34)
45-54	33	7.1/5.9	1.27 (1.17-1.38)
55-64	13	8.2/6.7	1.26 (1.12-1.41)
65-74	9	6.2/6.9	1.02 (0.85-1.23)
≥ 75	4	7.1/8.8	0.95 (0.53-1.71)
P_{trend}			0.12
Ethnicity			
White	8	6.8/5.3	1.26 (1.10-1.44)
Nonwhite	10	7.2/4.5	1.58 (1.35-1.86)
$P_{interaction}$			0.03

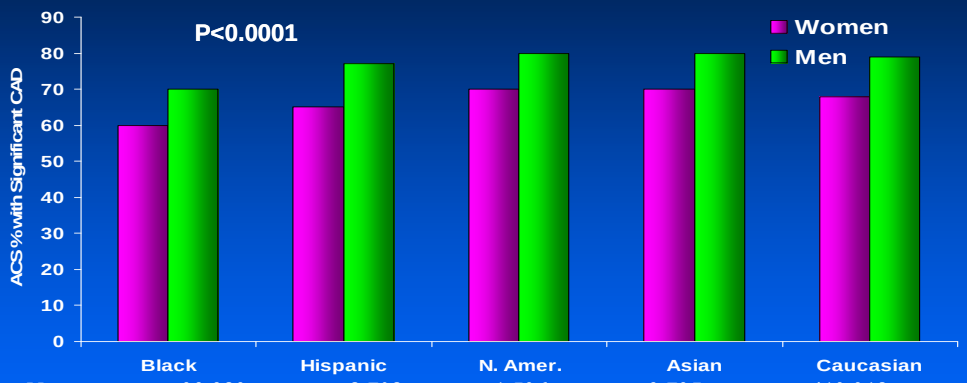
Circ 2008; 117:1526

Diagnostic Accuracy of Noninvasive Evaluation of CAD in Women

	Exercise ECG		Stress Echo		Stress SPECT	
Reference	Sens.	Spec.	Sens.	Spec.	Sens.	Spec.
Fleischmann et al 1998	--	--	85%	77%	87%	64%
Kwok et al., 1999	61%	70%	86%	79%	78%	64%
Beattie et al., 2003	--	--	81%	73%	77%	69%
Average	61%	70%	84%	76%	81%	66%

JACC 2006;47:450-456

Gender Differences in CAD Significance after Diagnostic Cath for ACS



	Black	Hispanic	N. Amer.	Asian	Caucasian
N =	23,382	8,708	1,596	3,725	412,918
% Female	50.2	39.1	37.6	39.4	38

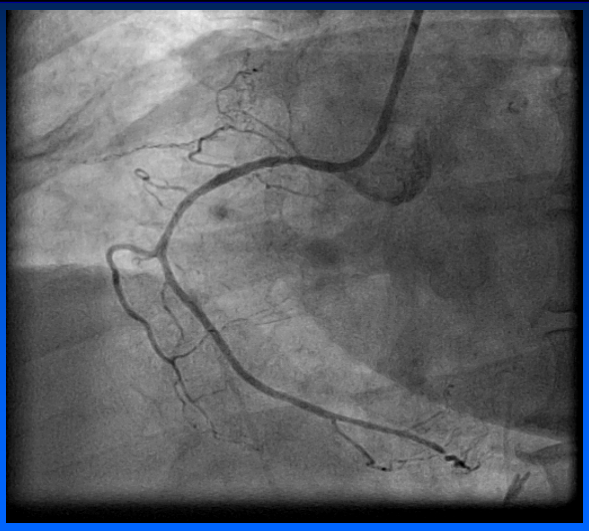
ACC/NCDR database

Circ 2008;117:1792

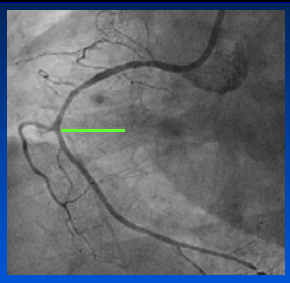
Cardiac Cath may miss Atherosclerosis

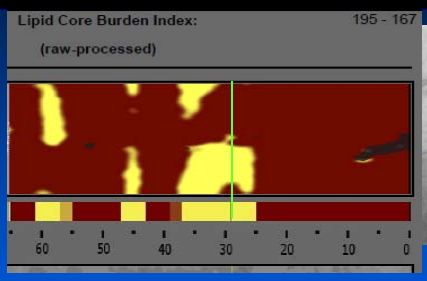
- 51 year old female, History of obesity, HTN, Hyperlipidemia
- S/P Stent in Circumflex 2 years ago
- Angina, abnormal stress test (inferior distribution)
- Cardiac Cath

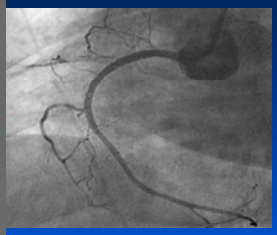
Right Coronary Artery "Small"



RCA Imaging





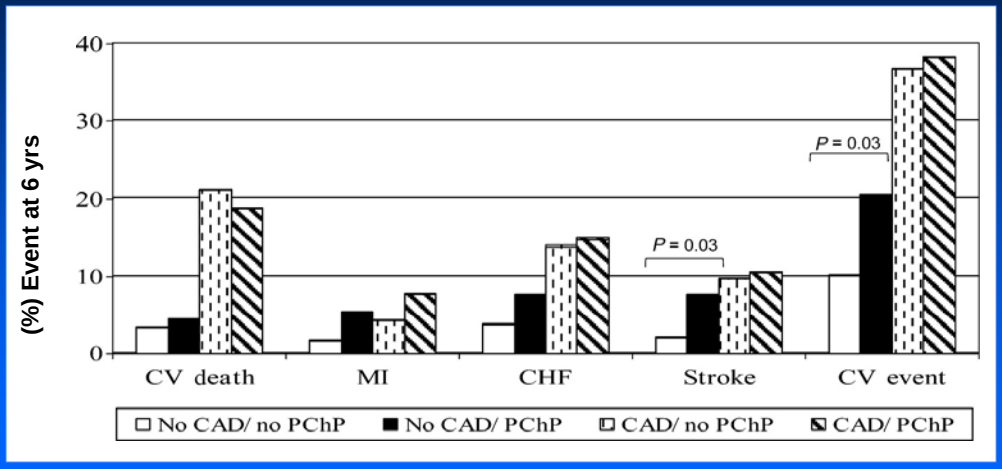


- RCA Angio – Small vessel, mild diffuse disease
- IVUS Large amount of plaque prox and mid, 70% stenosis
- NIR Huge amount of soft lipid
- Drug Eluting Stents 3.0x15mm and 2.5x28mm

Persistent Chest Pain in Women is a Poor Prognostic Sign,

Even in the Absence of Significant Epicardial CAD

WISE Study: CV Events Based on CAD or Persistent Chest Pain



EHJ 2006;27:1408

Non-Obstructive CAD is Not Benign

Symptomatic women with non-obstructive CAD have high 5 year cardiovascular event rates

Cardiovascular event rate increases with number of risk factors present

Women with non-obstructive disease and CFR <2.32 had significantly more major adverse outcomes

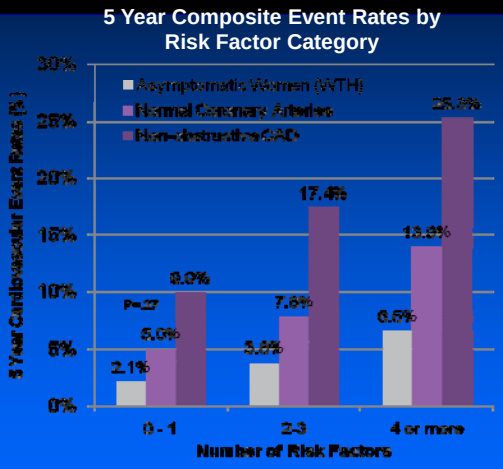


Chart adapted from Gulati, M.; et al Arch Intern Med (2009) 169: 843-850

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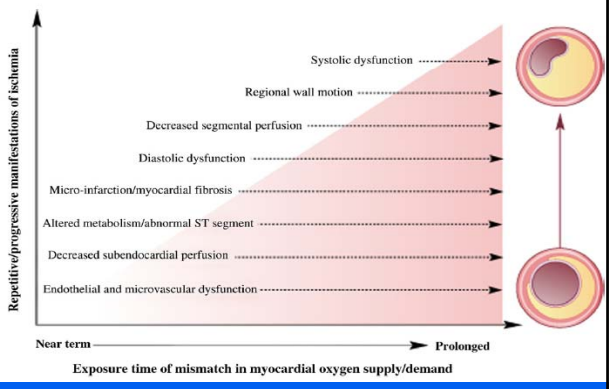
Sources: Johnson, B. D.; et al European Heart Journal (2006) 27:1408-1415; Gulati, M.; et al Arch Intern Med (2009) 169:843-850 ; Pepine, C. J.; et al J Am Coll Cardiol (2010) 55: 2825-2832

Endothelial Dysfunction

- **Abnormal flow-mediated dilation (or paradoxical vasoconstriction) of epicardial coronaries - associated with increased risk**
- **Impaired in hypertensive, smoking, hyperlipidemic or diabetic women**
- **Exacerbated after onset of menopause**



Source: Shaw, L. J.; et al J Am Coll Cardiol (2009) 54:1561-1575

Figure illustration by Rob Flewell. Reprinted from Shaw L.J. et al J Am Coll Cardiol (2009) 54:1561-1575 with permission from Elsevier.

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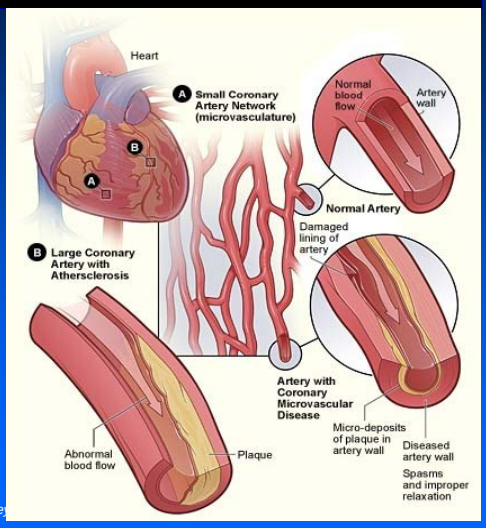
What is Microvascular Disease?

- Dysfunction in small coronary arterioles <500 microns in diameter
  - Main determinants of vascular resistance
  - Major etiological factor for ischemic heart disease in women
  - Potential precursor of obstructive CAD
- 2-3 million women with microvascular coronary dysfunction in the U.S.
  - ~90,000 new cases annually



Sources: NHLBI; Vaccarino V.; et. al Cardovascular Research (Dec. 14, 2010 [e-pub]); Bairey Merz, CN.; et al Journal of Women's Health 19(2010):1059-1072

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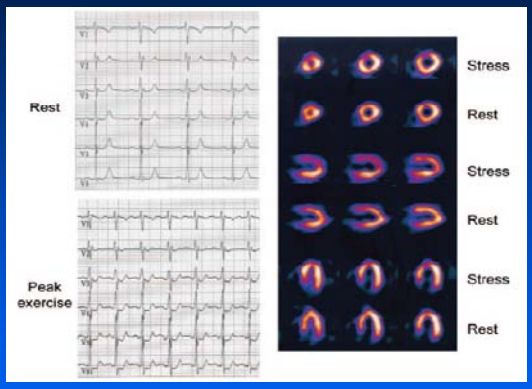
Graphic courtesy of NHLBI, National Institutes of Health, U.S. Department of Health and Human Services

Clinical Presentation of Microvascular Ischemia

- Angina – stable and unstable
- ST segment depression
- Abnormal SPECT
- Non-obstructive CAD angiographically
- Abnormal coronary flow reserve (CFR) by intracoronary doppler and elevated LVEDP



Graphics from Lanza, G. A. and Crea, F. Circulation (2010) 121:2317-2325

Sources: Noel Bairey Merz "Women and Heart Disease: A Changing Paradigm" Presentation; Khuddus, M.: et al J Interv Cardiol. (2010) 23:511-519; Lanza, G. A. and Crea, F. Circulation (2010) 121:2317-2325

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Strategies for Atherosclerosis & Endothelial Dysfunction

ACE Inhibitors

- Lower blood pressure, improve endothelial function
- Improve exercise duration and CFR in patients with microvascular coronary ischemia

Statins

- Lipid-lowering effects
- Improve endothelial function
- Improve CFR and exercise tolerance
- Reduce angina

Low dose aspirin

- Secondary prevention of cardiovascular events

Source: Samim, A.; et al Current Treatment Options in Cardiovascular Medicine (2010)12:355-364

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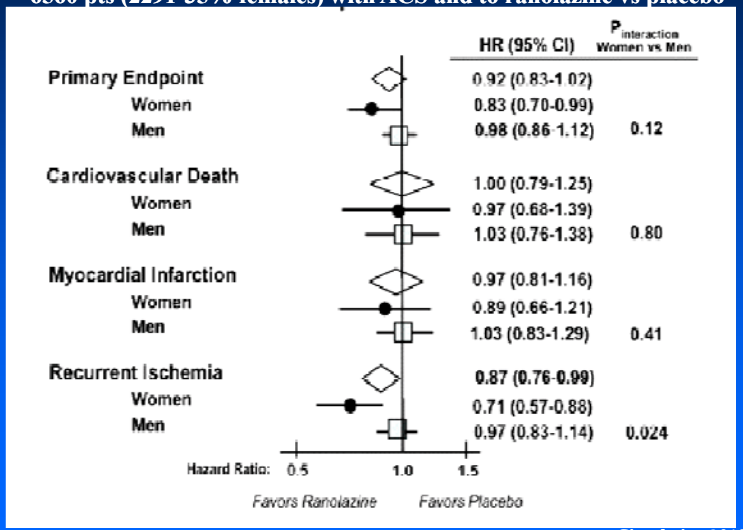
Possible Role of Ranolazine? Gender specific results of MERLIN-TIMI 36 Trial

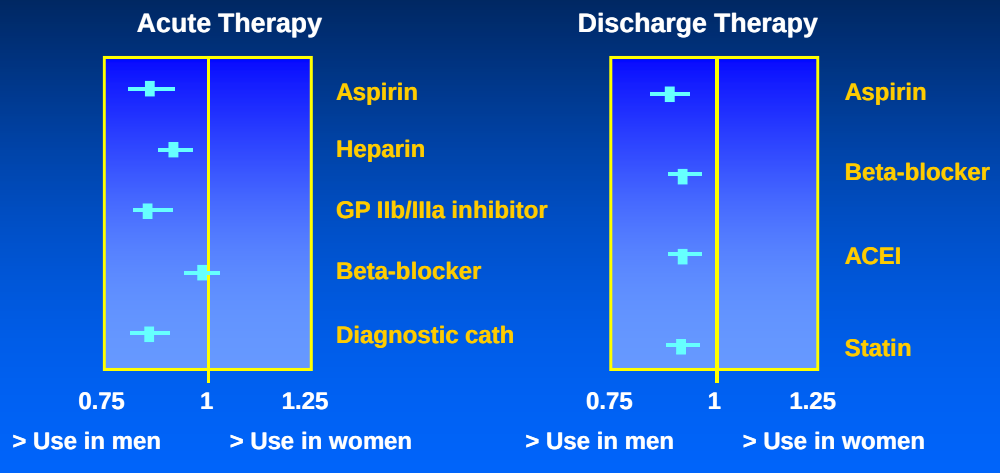
- 6560 pts (2291-35% females) with ACS and to ranolazine vs placebo



Circulation 2010;121:1809-1817

Treatment of Women with Coronary Disease

Use of Recommended Rx Among Women vs Men with Acute coronary syndrome



Crusade registry JACC 2005;45:832

A Systematic Review of Gender Differences in Mortality after CABG and PCI

- Review of randomized trials of CABG (n=23) and PCI (n= 48) reporting outcomes based on gender
- Women have a greater number of co-morbidities – older, more diabetes, HTN, CHF and severe non-cardiac disease
- Anatomic differences - women have smaller BSA, smaller coronaries, smaller LV chamber size (low SV and cardiac output)
- Higher early mortality in women – not consistently eliminated after adjustment for co-morbidities

ClinCardiol 2007;30:491-5

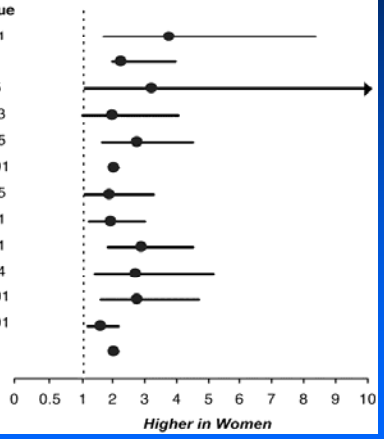
A Systematic Review of Gender Differences in Mortality after CABG and PCI: Differences in Treatment

- Late referrals
  - more advanced CAD
  - more urgent/emergent procedures
  - longer DTB times in STEMI cases
- Lower rates of IMA grafts in women even after adjustment for age, extent of disease and urgent surgery
- Similar benefits from GP IIb/IIIa agents and stents
- Improved PCI mortality over time in both men and women

ClinCardiol 2007;30:491-5

Women Have Higher Rate of Vascular Complications After PCI

Study	N	Vascular Complications: Women	Vascular Complications: Men	P-Value
Alfonso[19]	981	11/157 (7.0%)	16/824 (2.0%)	<0.01
Antoniucci[38]	1019	14/234 (6.0%)	24/785 (3.0%)	0.01
BOAT[40]	989	6/237(2.5%)	6/752 (0.8%)	0.05
CAVEAT[138]	512	14/128 (10.8%)	22/384 (5.8%)	0.003
NACI[30]	2855	39/971 (4.0%)	28/1884 (1.5%)	<0.05
NCN[32]	109708	1955/36204 (5.4%)	1985/73504 (2.7%)	<0.001
NHLBI[45]	2136	24/555 (4.4%)	36/1581(2.3%)	<0.05
NHLBI[13]	2524	44/883 (5.0%)	43/1641(2.6%)	≤0.01
STARS[95]	1965	44/570 (7.8%)	39/1395 (2.8%)	<0.01
Trabatoni[26]	1100	15/165 (9.3%)	33/935 (3.5%)	0.004
Welty[33]	5989	34/2096 (1.6%)	23/3893 (0.6%)	<0.001
WHC[18]	7372	78/2064 (3.8%)	125/5308 (2.4%)	<0.001
Combined	**137150**	**2278/44264 (5.1%)**	**2380/92886 (2.6%)**	



Circ 2005;III;940-953

AMI in Women: Later Presentation and Delay in Treatment

- CADILLAC Primary PCI Trial-

	Men	Women	*p* Value
N	1520	562	-
Chest pain to ER (hrs)	2.6 ± 2.5	3.0 ± 2.6	< 0.001
ER to procedure (hrs)	1.9 ± 2.2	2.1 ± 2.3	< 0.001
Stent use	57%	57%	NS
Abciximab use	54%	51%	NS

Why do women present late during STEMI?

- Only 53% of women said they would call 9-1-1 if experiencing the symptoms of a heart attack
- However, 79% said they would call 9-1-1 if someone else was having a heart attack
- For themselves, 46% of women would do something other than call 9-1-1—such as take an aspirin, go to the hospital, or call the doctor

Source: Mosca 2010.

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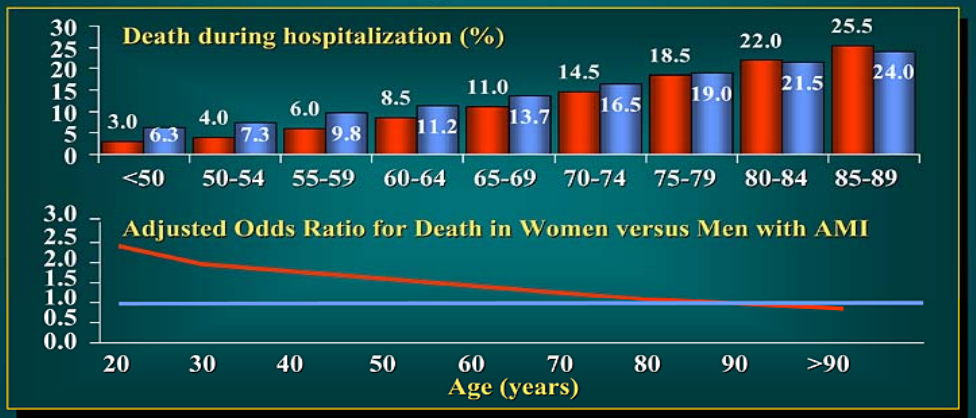
Higher Mortality in Women with AMI: NRMI 2 (N=384,878)

" The younger the age of the patients, the higher the risk of death among women relative to men"



Vaccarino et al, NEJM 1999; 341:217

Mechanism of MI May be Different in Women

- Atherosclerotic: plaque erosion: women > men; plaque rupture: men > women
- Spontaneous coronary dissection: women > men
- Spasm (migranes, Raynauds): women > men
- Non-STEMI: women > men (subendocardial ischemia due to LVH, microvascular disease, endothelial dysfunction)
- Takotsubo (high circulating levels of catecholamines): women >>>> men

CAD in Women: Conclusions

- The risk factor profile in women presenting with ACS and AMI is distinctive compared to men. Women are older, have more HTN, DM, but also unique risk factors related to hormonal influences and inflammation
- Despite having less extensive CAD and better LV function, prognosis is worse than in men – late diagnosis and inadequate treatment
- Symptoms may be atypical – even in the midst of AMI! Have a high level of suspicion.

Cardiovascular Disease in Women

- In ACS and AMI women benefit from early invasive strategy; take caution to reduce bleeding and vascular complications.
- Women are more likely to have endothelial dysfunction, microvascular disease and angina due to left ventricular hypertrophy and subendocardial ischemia.
  - "Non-obstructive" CAD does not signify low risk
  - Ranolazine may be useful in women with angina

***MEN*strual Cramps**

***MEN*opause**

***MEN*tal Anxiety**

***MEN*tal Breakdown**

Ever notice how all problems begin with MEN ? ! ? ! ? ! ?