Getting Ahead of Cardiovascular Disease – Applying what we know

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Financial conflicts of interests

- The following relationships exist related to this presentation (*paid to Cedars-Sinai Medical Center):
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- **Consulting:** NIH CSR and NIH ORWHAB*, iRhythm, SHL Telemedicine
- **Honorarium*:**
- **Stocks:** iRhythm

Getting Ahead of Cardiovascular Disease – Applying what we know

1. An epidemic of death in women and men
2. Gender and secondary prevention
3. Gender and primary prevention
4. Policy and our future

Following a heart attack, women age 50 and younger are:

a. More likely to die than men of the same age

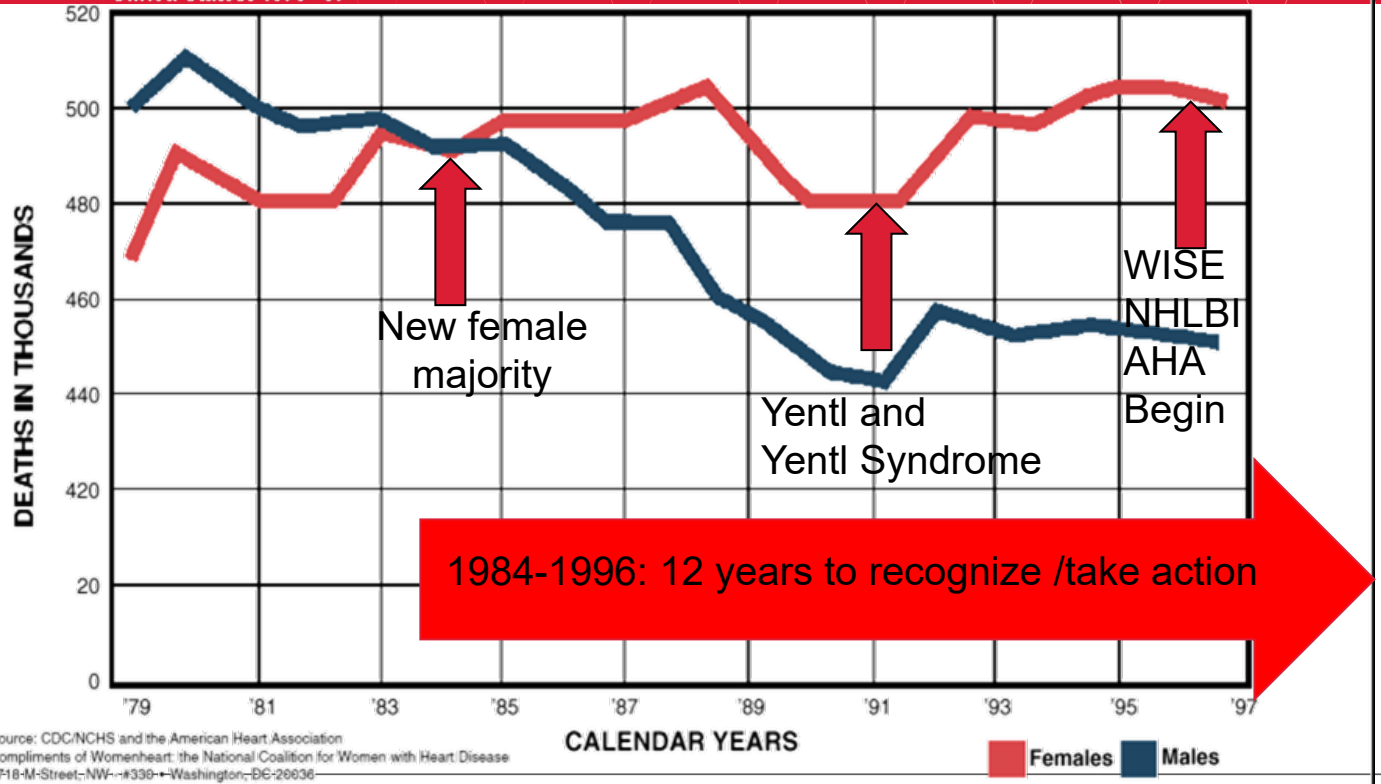
b. Less likely to die than men of the same age

c. Equally likely to die than men of the same age

Women and Heart Disease Deaths

An Alarming Trend...

Cardiovascular Disease Mortality Trends for Males and Females
United States: 1979–97



Source: CDC/NCHS and the American Heart Association
Compliments of Womenheart: the National Coalition for Women with Heart Disease
1718 M Street, NW • #336 • Washington, DC 20036
(www.womenheart.org)

The Yentl Syndrome 1991

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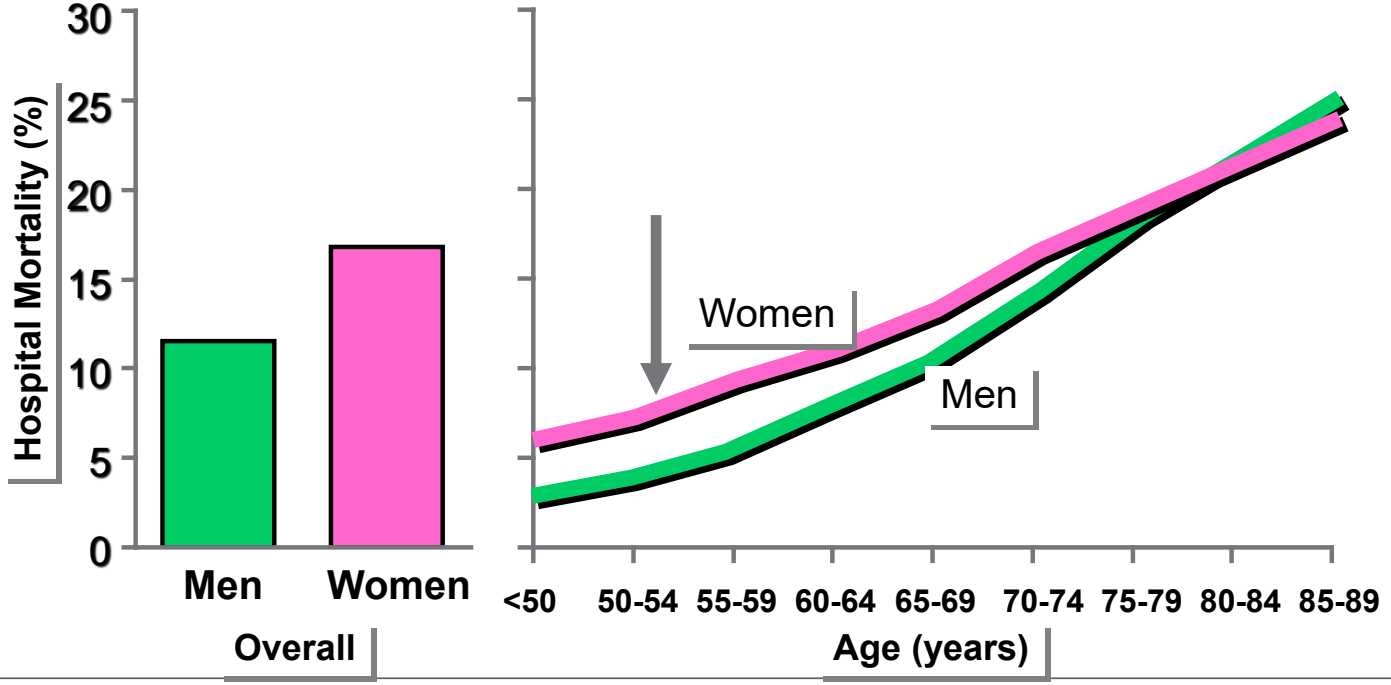
Sex and Myocardial Infarction (MI) Mortality: Does Age Explain the Disparity?

Largest Mortality Gaps are Young Women



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Vaccarino V et al. NRMI. *N Engl J Med*. 1999;341:217-225.

Paradox: Women have a two-fold increase in "normal" Coronary arteries in the setting of ACS, NSTEMI and STEMI

Table. Prevalence of "Normal" and Nonobstructive Coronary Arteries in Women Compared With Men

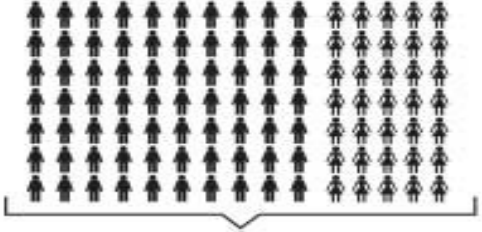
	No./Total (%)		
	Women	Men	*P* Value
Acute coronary syndrome			
GUSTO[2]	343/1768 (19.4)	394/4638 (8.4)	<.001
TIMI 18[3]	95/555 (17)	99/1091 (9)	<.001
Unstable angina[2]	252/826 (30.5)	220/1580 (13.9)	<.001
TIMI IIIa[6]	30/113 (26.5)	27/278 (8.3)	<.001
MI without ST-segment elevation[2]	41/450 (9.1)	55/1299 (4.2)	.001
MI with ST-segment elevation[2]	50/492 (10.2)	119/1759 (6.8)	.02

Abbreviations: GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MI, myocardial infarction; TIMI, Thrombosis In Myocardial Infarction.

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

Angina/
ACS

Bairey Merz EHJ 2011



Coronary
Angiography

Obstructive CAD
Male-pattern

Microvascular CAD
Female-pattern

More men receive
treatment

More women
die

RX:
ASA,
BB,
ACE,
STATIN

DEATH/MI
FOLLOWUP

Summary: An Epidemic of Death in Women

1. There is a significant adverse gender gap in CHD-MI mortality

2. Women, particularly younger women, face a more adverse CHD prognosis

3. Adjustment for disease severity, comorbidity and treatment does not fully account for the gap

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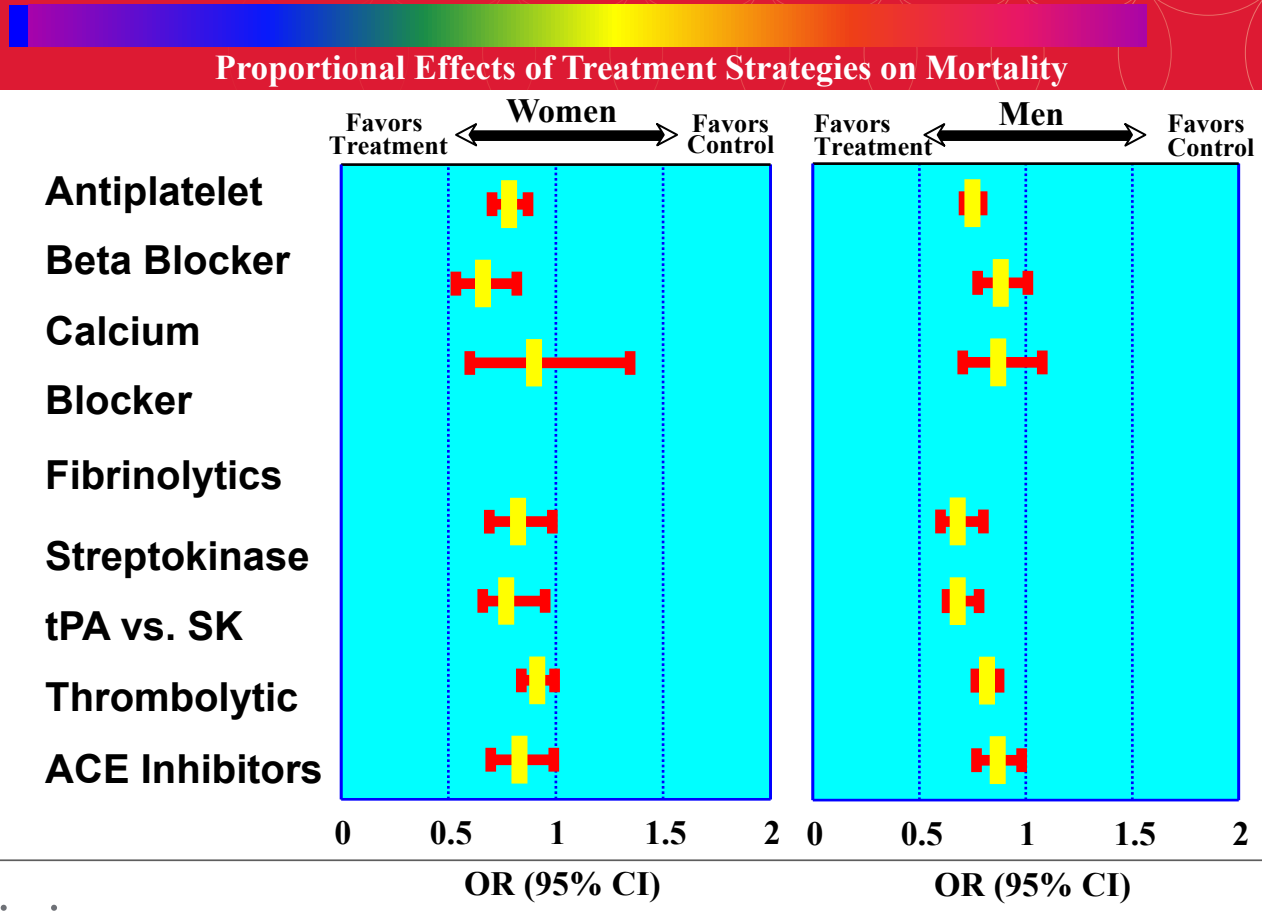
Disparities in ACS Treatment for Women and Men

- 35,835 pts with NSTEMI: 41% women
- Women had:
  - ↑ DM, HTN, age; ↓ CAD events
  - ↓ Early ASA, heparin, GPIIb-IIIa, ACE-I
  - ↓ Revascularizations: CABG ↓41%
  - ↓ Discharge ASA, beta blocker, ACE-I, statins (Four Magic Pills)*
  - ↑ Death, MI, CHF

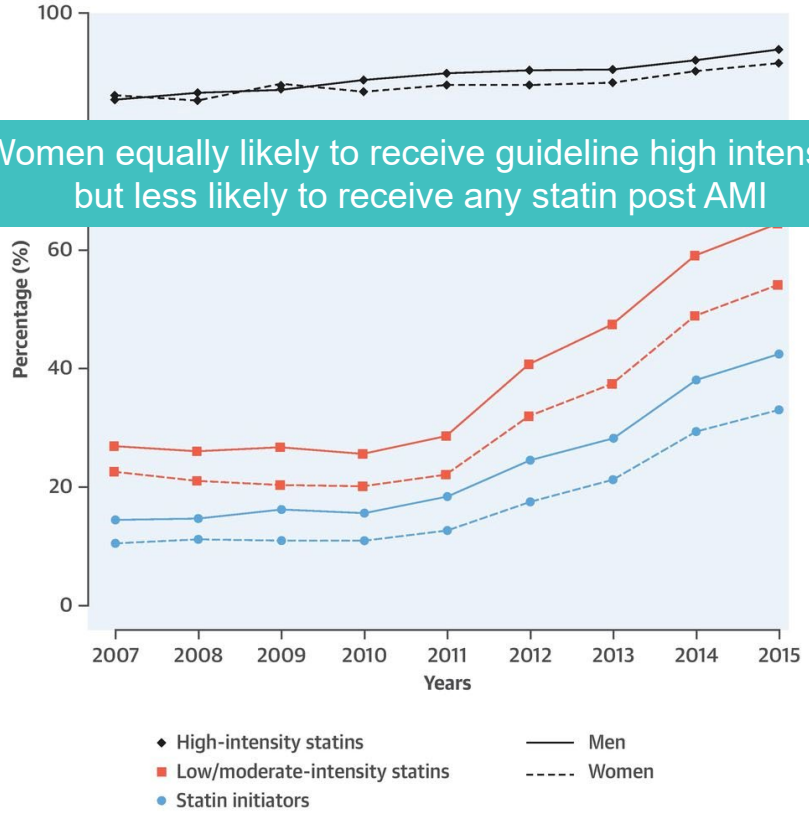
* Associated with a 90% reduction in recurrent major adverse cardiac events, AMI Guidelines Therapy

Blomkalns AL et al. CRUSADE NSTEMI database. *J Am Coll Cardiol*. 2005;45:832-837.

AMI Treatment: women and men have similar risk benefit



CENTRAL ILLUSTRATION: Trends in the Percentage of Women and Men Filling a High-Intensity Statin Prescription After Hospital Discharge for Myocardial Infarction Between 2007 and 2015



Women equally likely to receive guideline high intensity but less likely to receive any statin post AMI

Peters, S.A.E. et al. J Am Coll Cardiol. 2018;71(16):1729-37.

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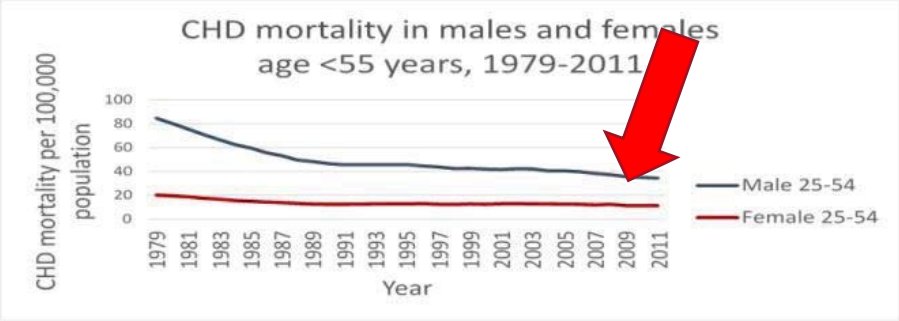
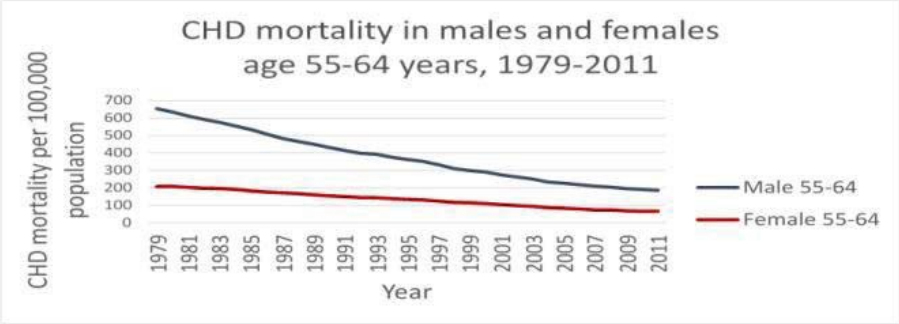
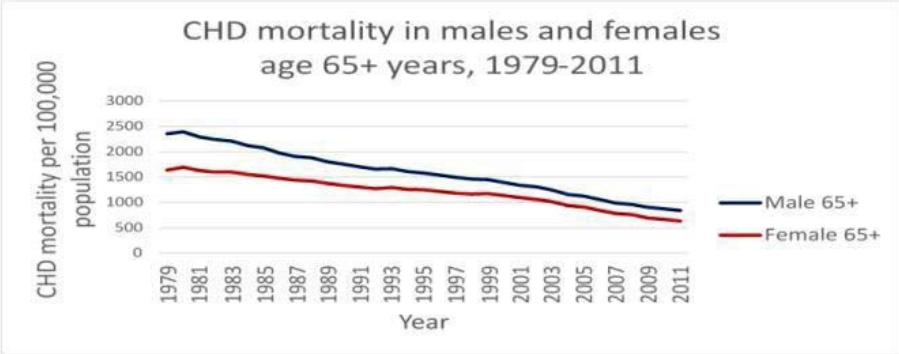
Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011: Evidence for Stagnation in Young Adults, Especially Women

Vaccarino V, et al
CIRCULATIONAHA.115.015293
Published online before print August 24, 2015, doi: 10.1161/CIRCULATIONAHA.115.015293







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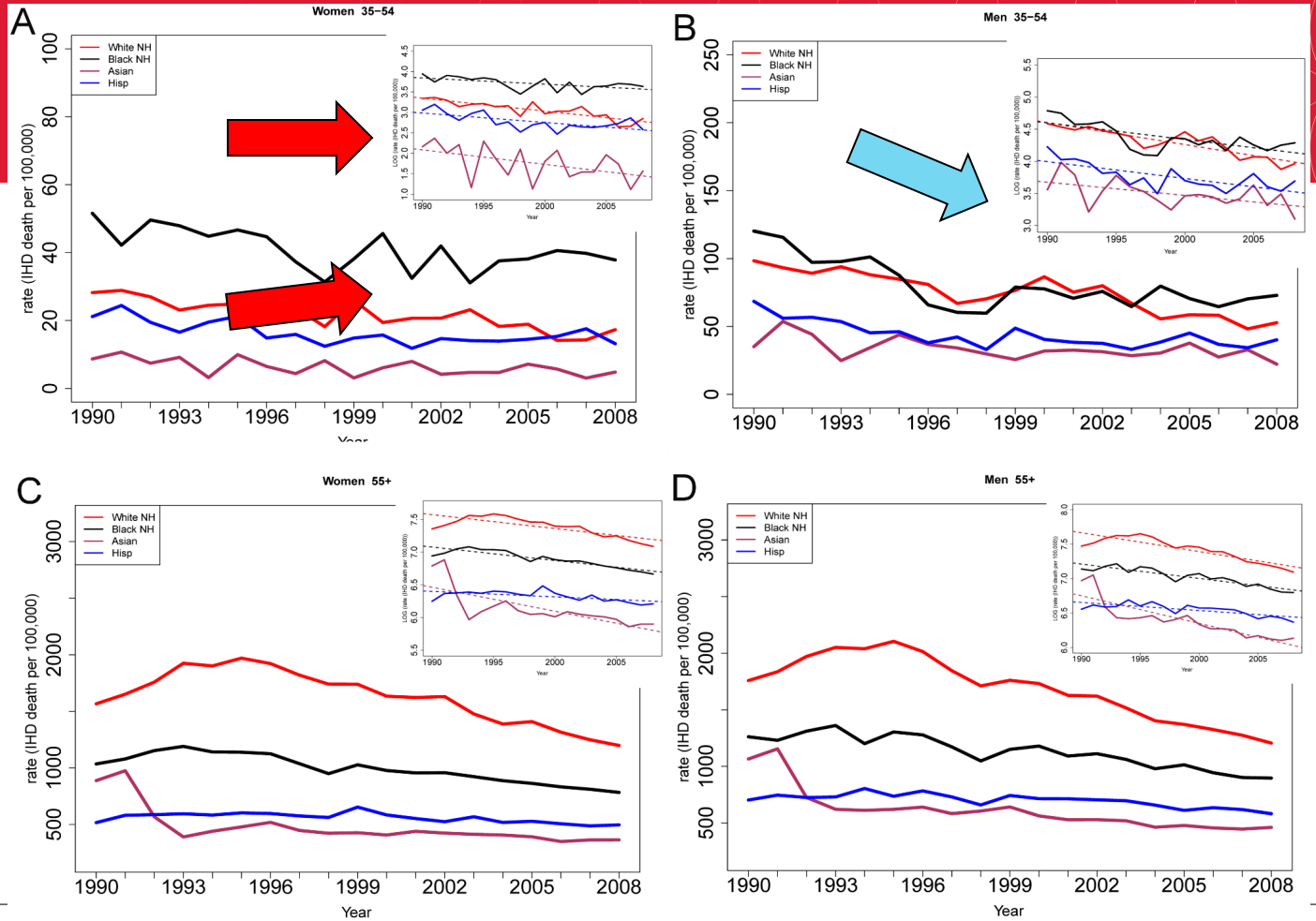

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Adverse Trends in Ischemic Heart Disease Mortality among Young New Yorkers, Particularly Young Black Women
Nathaniel R. Smilowitz Gil A. Maduro Jr. Iryna V. Lobach Yu Chen Harmony R. ReynoldsPublished: February 16, 2016
https://doi.org/10.1371/journal.pone.0149015

Guideline Implementation and ACS and the Sex Survival Gap

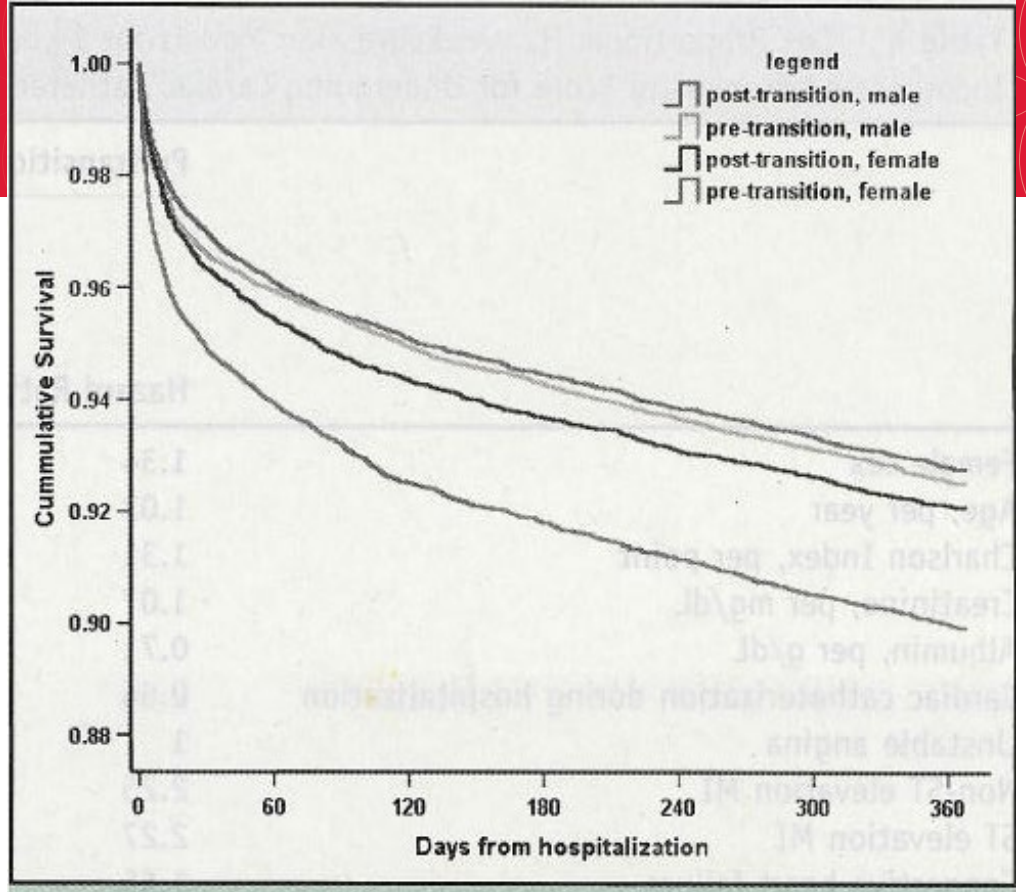

Figure Cox proportional hazard functions for 1-year survival at mean of covariates pre- and post-transition stratified by women vs men.

Novak et al Am J Medicine 2008;121:602.

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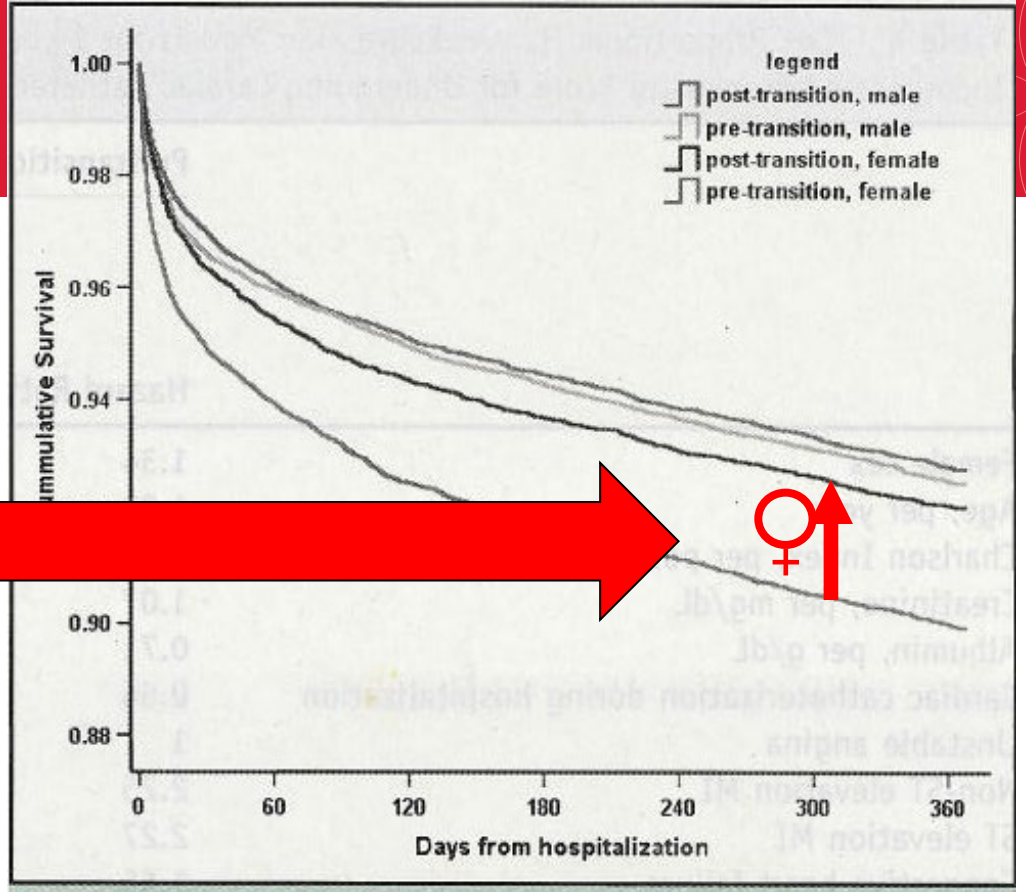
Guideline Implementation and ACS and the Sex Survival Gap

Following guideline implementation, mortality for women improves and the sex gap narrows (RED)



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Guideline Implementation and ACS and the Sex Survival Gap

Following guideline implementation, mortality for women improves and the sex gap narrows (RED)

Persistent sex gap (BLUE) suggests more work still needed to understand sex-specific pathophysiology to improve outcomes for women and men

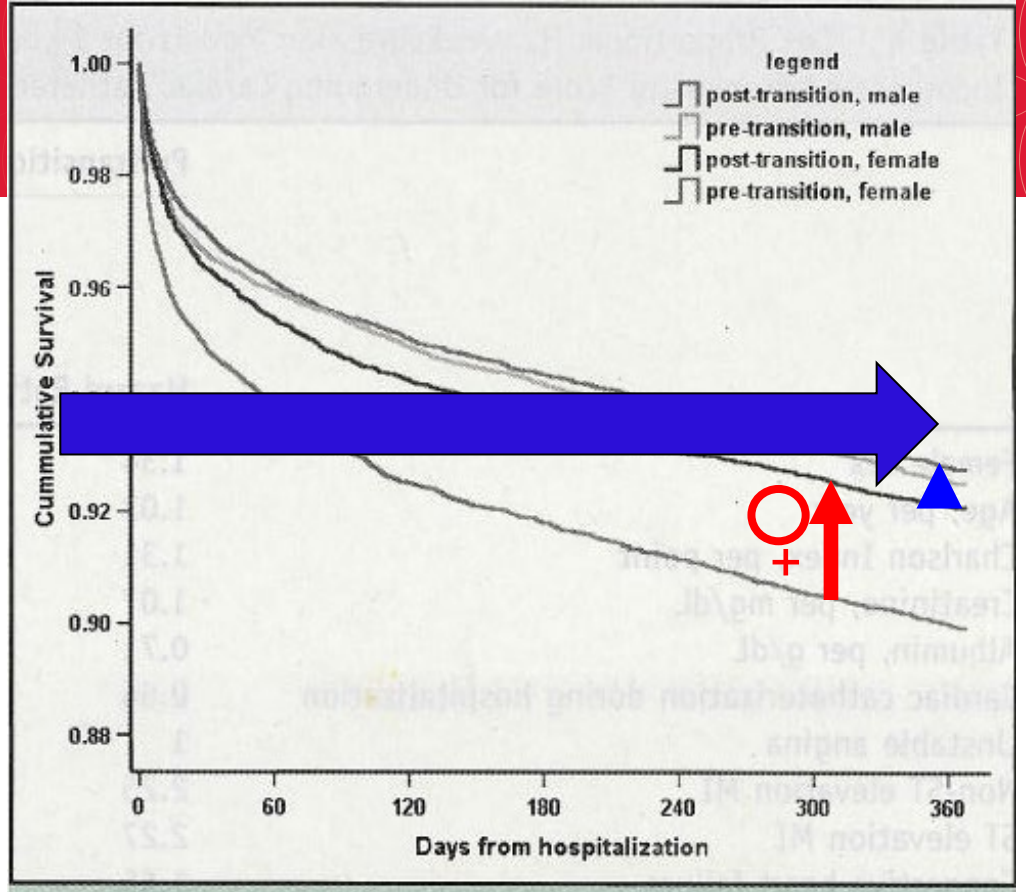

Figure Cox proportional hazard functions for 1-year survival at mean of covariates pre- and post-transition stratified by women vs men.

Novak et al Am J Medicine 2008;121:602.

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Summary: Gender and Secondary Prevention

1. AMI guidelines therapy works equally well in women and men
2. Application of AMI guidelines preferentially saves women's lives
3. Can we routinely deploy guidelines to save women's lives?

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Women with diabetes or similarly elevated CVD risk are:

a. More likely to be treated with statin than men of the same age

b. Less likely to be treated with a statin than men of the same age

c. Equally likely to be treated with a statin than men of the same age

Coronary Heart Disease Mortality Among Young Adults in the US: 1980-2002 (Ford et al JACC 2007;50:2128)

- **Included women and men aged 35 and older using ICD-9 codes in US Census data**
- **Mortality from CHD fell 52% in men and 49% in women**
- **Improved mortality each decade from 1980s, 1990s until the 2000s**
- **Age analysis demonstrates:**

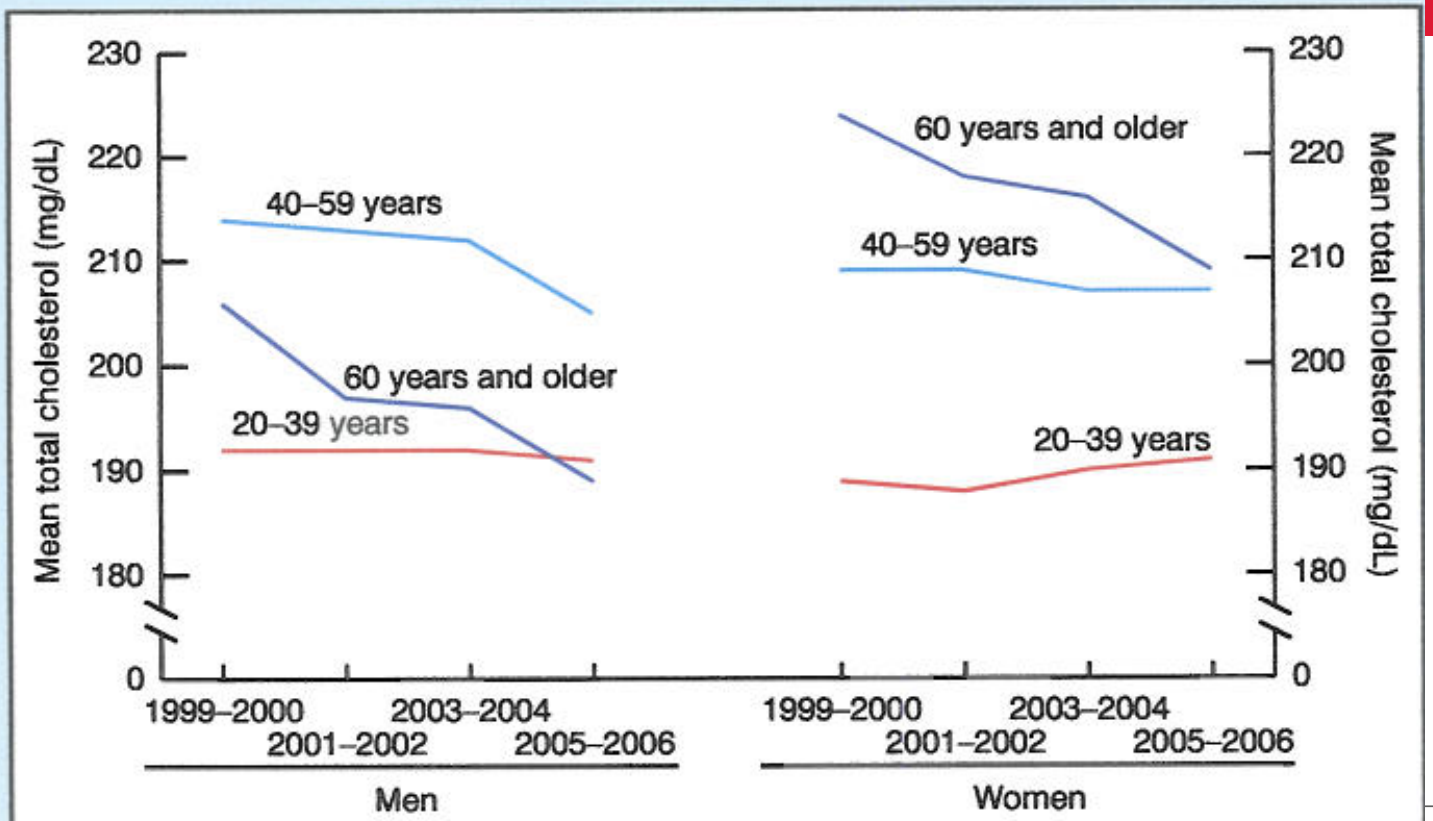
Leveling off of mortality decline in men 35-54 yrs in the 2000s

Actual *increase* in mortality in women 35-54 yrs, and specifically among women 35-44 yrs ($p<0.05$)

Results are consistent with a UK study (O'Flahrty et al Heart 2007:10:1136.

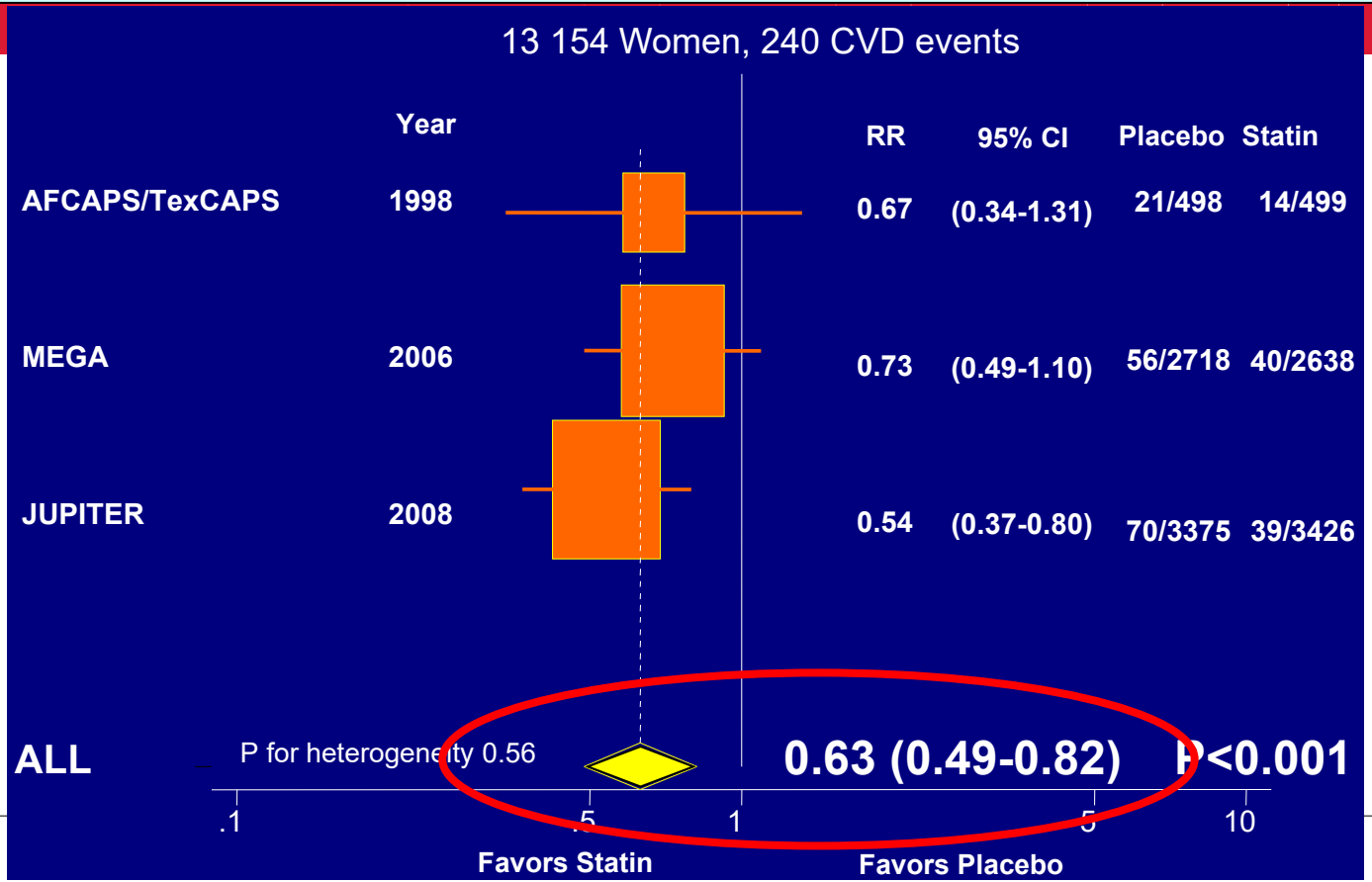
Concomitant with increased use of thrombolysis, PCI, statins and antithrombotics (ASA), yet adverse nutrition, physical acitivity, obesity and smoking trends.

Figure 1. Mean serum total cholesterol levels of adults aged 20 years and older by age and sex, United States, 1999–2006



SOURCE: CDC/NCHS, National Health and Nutrition Examination Surveys, 1999–2006.

Meta-analysis of Exclusively Primary Prevention Statin Trials in Women



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Mora S et al Circulation 2010; 1069

JUPITER
Primary Trial Endpoint : Number Needed to Treat (5-years)

Mora S et al Circulation 2010; 1069

	Rosuva	Placebo	
	No. (Rate)	No. (Rate)	NNT*
Women	39 (0.56)	70 (1.04)	36
Men	103 (0.88)	181 (1.54)	22
All	142 (0.77)	251 (1.36)	25

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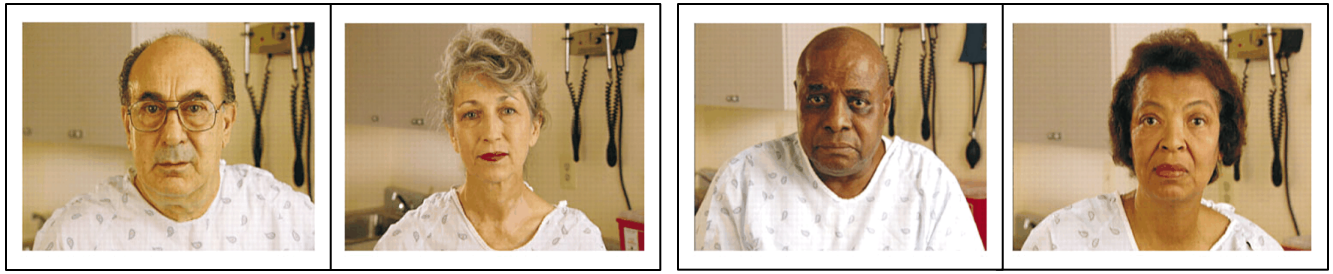
* Calculated based on the method of Altman and Andersen

The Effect of Race and Sex on Physicians' Recommendations for Treatment



Despite full risk and history adjustment:

- Men are twice as likely as women to be treated than women
- Caucasians are twice as likely to be treated than non-causasians

Schulman et. al N Engl J Med. 1999;340:14

Sex and Gender Disparities – The VIRGO Registry

- The VIRGO registry matched young (<50 yrs) AMI women to age-matched AMI men (2:1)
- JACC manuscript identifies that women compared to men prior to AMI are:
  - More DM (by Rx of DM meds)
  - Less dyslipidemic (by Rx of statin)
  - More overweight (by physician advisement to “lose weight”), but less overweight!
- JACC Editorial contrasts sex and gender differences:
  - DM is a more potent AMI RF for women – why are guidelines of statin Rx not followed?
  - Overweight/obesity are not AMI risk factors – why are women are more “objectified” and given non-evidenced based guidelines therapy to lose weight?

Bairey Merz CN, et al… the Sexism of Obesity. JACC 66:1958-60.


Difference between
men and women

Summary: Gender and Primary Prevention

1. Primary prevention works equally in women and men relative to risk.
2. Calculate ASCVD risk scores for women and men
3. Act on scores not on intuition or physical appearance – avoid the gender disparity gap!

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The Number Needed to Treat (NNT) magnitude for primary and secondary prevention of CVD for statin therapy is:

a. Similar for women and men

b. Higher for women than men

b. Lower for women than men

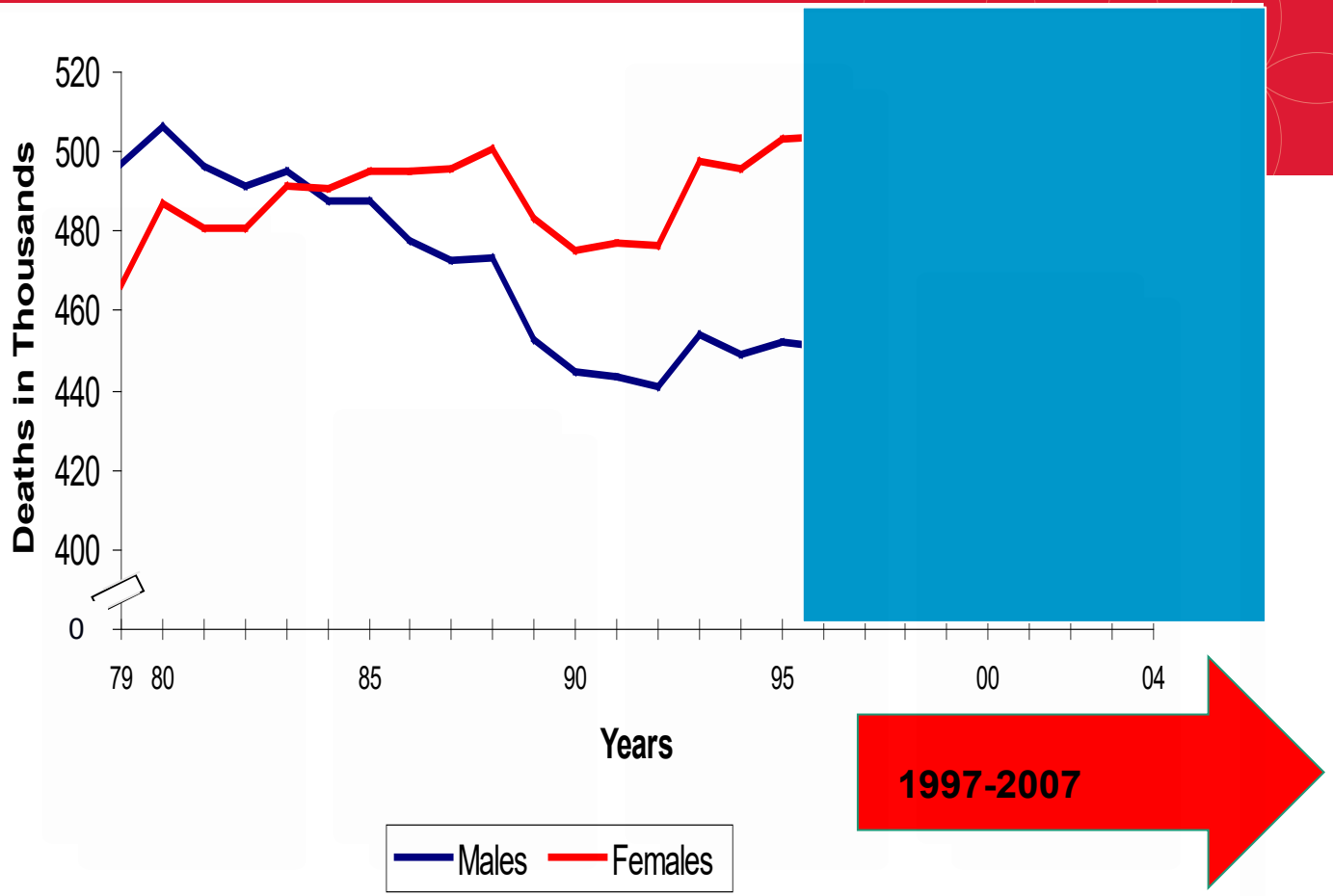
Clinical Practice Guidelines

This slide set was adapted from the following 2004-6 ACC/AHA guidelines:

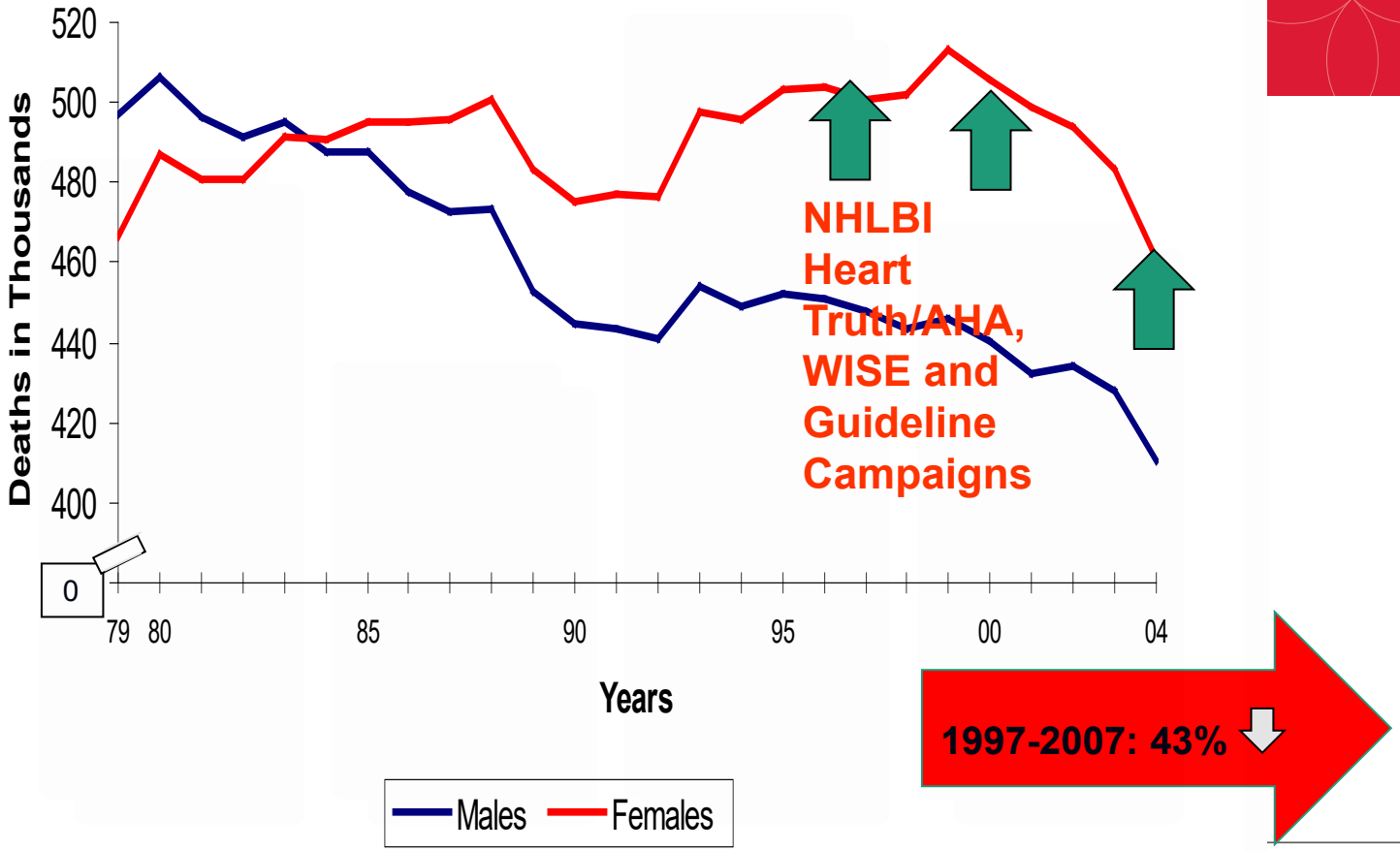
- ***Cardiovascular Disease Prevention in Women 2004, 2007, 2010***
- ***Management of Patients With ST-Elevation Myocardial Infarction***
- ***Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction***
- ***Preventing Heart Attack and Death in Patients with Atherosclerotic Cardiovascular Disease***
- ***Management of Patients with Chronic Stable Angina***
- ***Update for Coronary Artery Bypass Graft Surgery***
- ***Evaluation and Management of Chronic Heart Failure in the Adult***

- **The full-text guidelines and executive summaries are also available on the ACC and AHA websites at www.acc.org and www.americanheart.org**

ACC=American College of Cardiology, AHA=American Heart Association

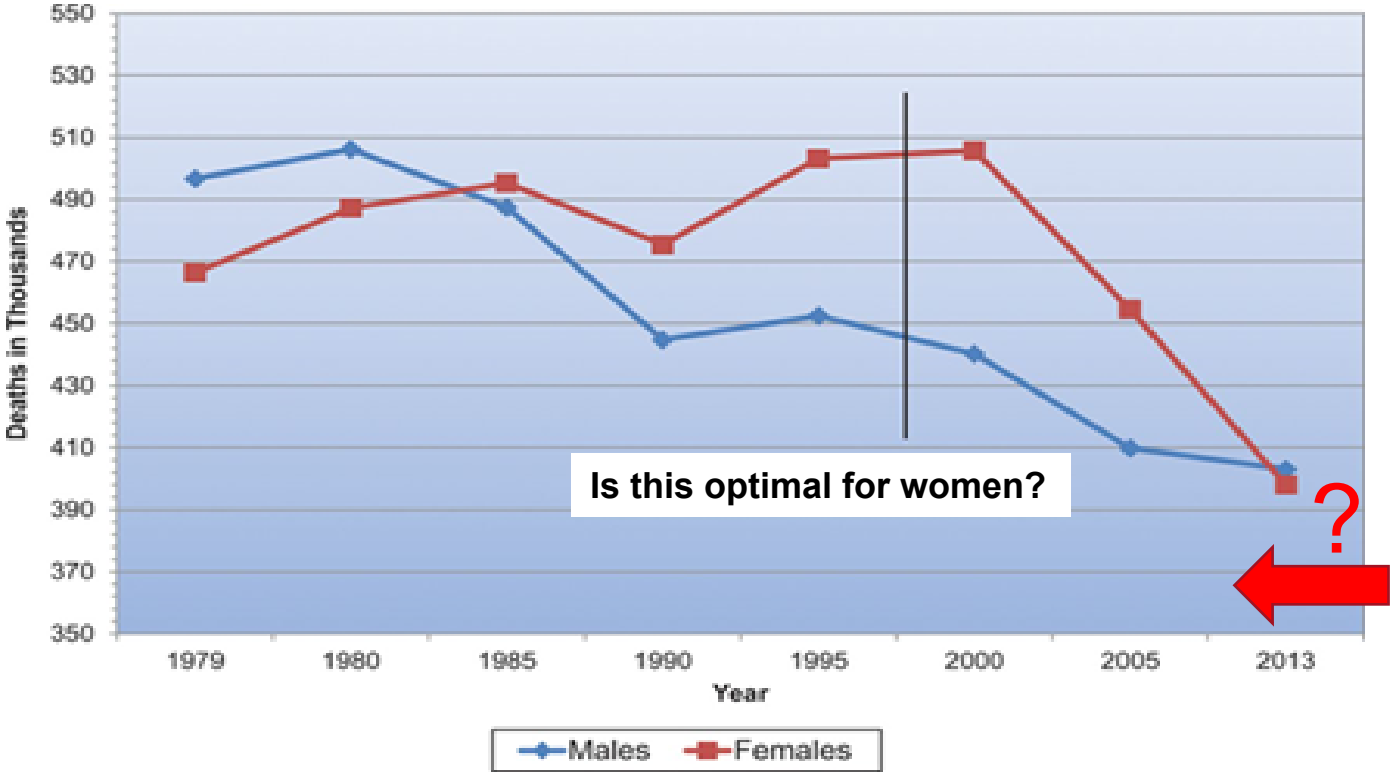


Source: NCHS and NHLBI



Source: NCHS and NHLBI

Cardiovascular disease mortality trends for males and females (United States: 1979–2013).



Darlush Mozaffarian et al. Circulation. 2016;133:e38-e360

American Heart Association.

Getting Ahead of Cardiovascular Disease – Applying what we know

Policy and our future:

- Investigate – increase research funding
- Educate – sex and gender in curriculum
- Translate – guidelines and guidelines care
- Advocate – health policy for all

Following a heart attack, women age 50 and younger are:

a. More likely to die than men of the same age

b. Less likely to die than men of the same age

c. Equally likely to die than men of the same age

Younger women with diabetes or similarly elevated CVD risk are:

a. More likely to be treated with statin than men of the same age

b. Less likely to be treated with a statin than men of the same age

c. Equally likely to be treated with a statin than men of the same age

The Number Needed to Treat (NNT) magnitude for primary and secondary prevention of CVD for statin therapy is:

a. Similar for women and men

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Thank you to the Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center – participants, research staff, faculty and collaborators!

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