ACC Latin America Conference 2017

MEXICO CITY

JUNE 22 – 24, 2017

GLOBAL EXPERTS, LOCAL LEARNING

ACC Latin America Conference 2017

Looking into the Heart of Women: Insights into the Future of Ischemic Heart Disease (IHD)

(How to Recognize Female-Pattern IHD)

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Presenter Disclosure Information

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DISCLOSURE INFORMATION

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Honorarium*: Practice Point, Pri-Med, VBWG

Stocks: None

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Monet or Manet?

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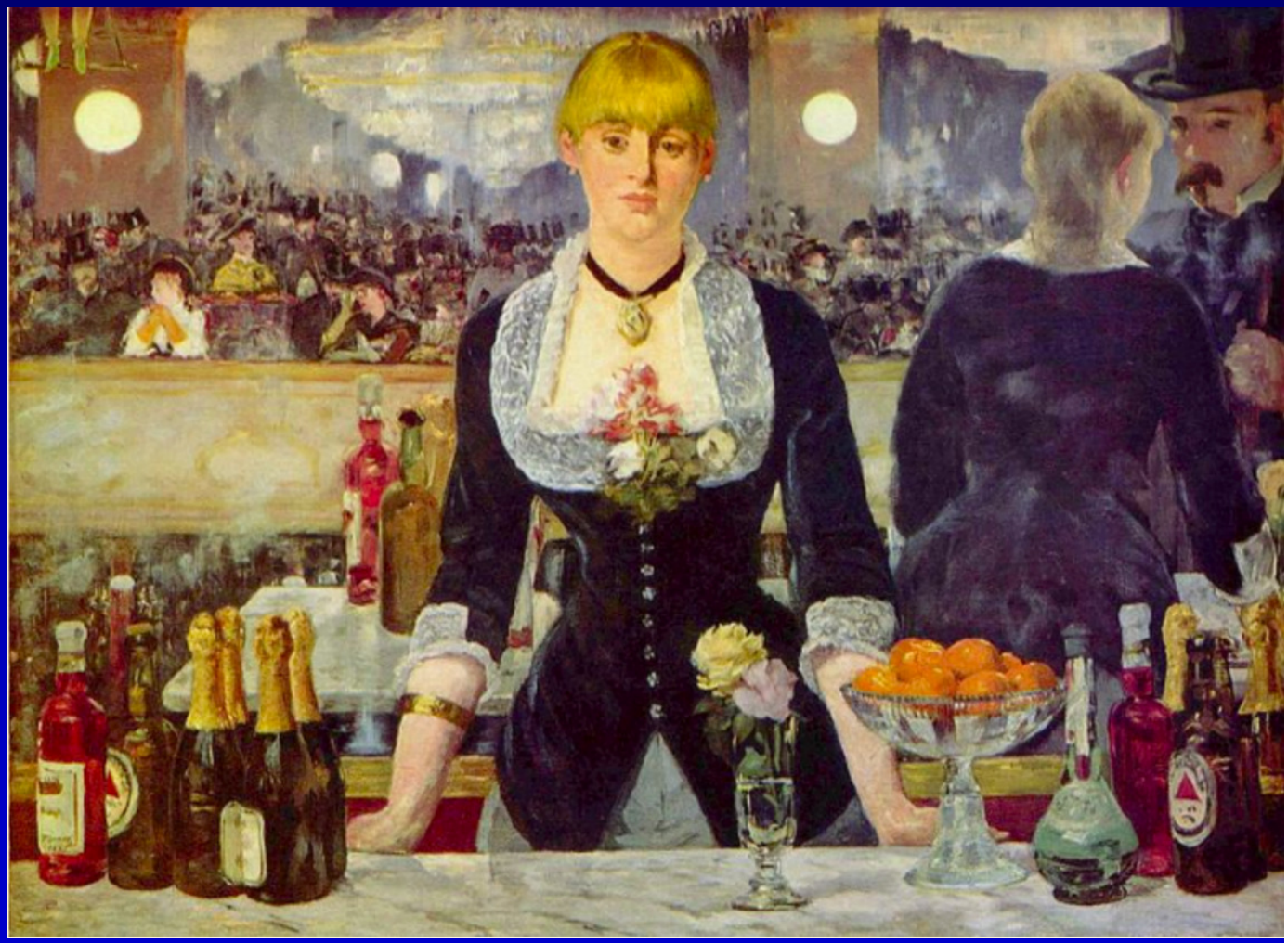
Monet or Manet?



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Claude Monet

Madame Monet in a Japanese Costume, 1875

Edouard Manet

A Bar at the Folies-Bergere, 1882

Female-pattern Ischemic Heart Disease:
(or why women have more adverse IHD outcomes)

1. An epidemic of death in women
2. Low hanging fruit - gender
3. Critical investigation - sex
4. Results of our labor
5. Policy and our future

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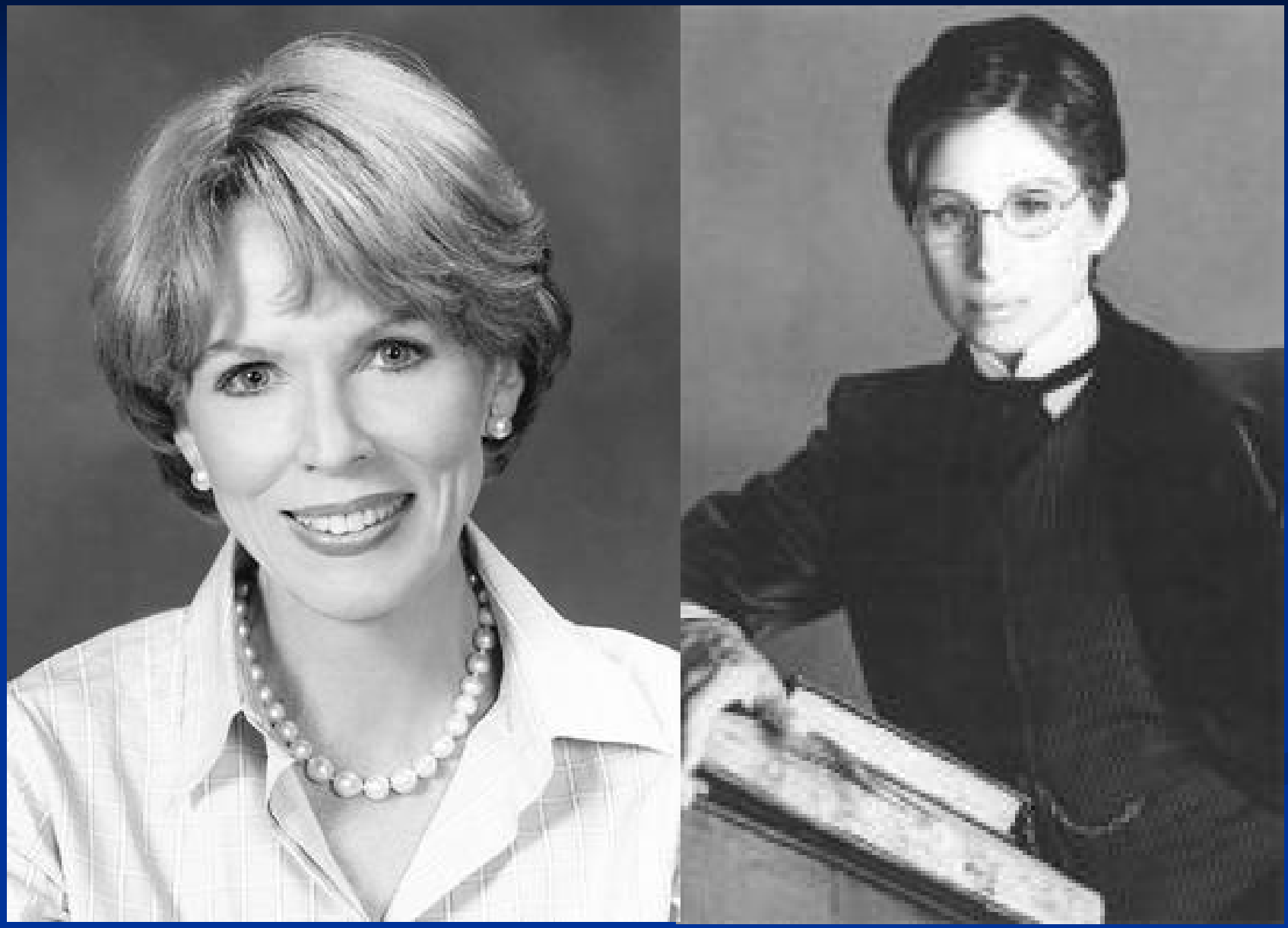
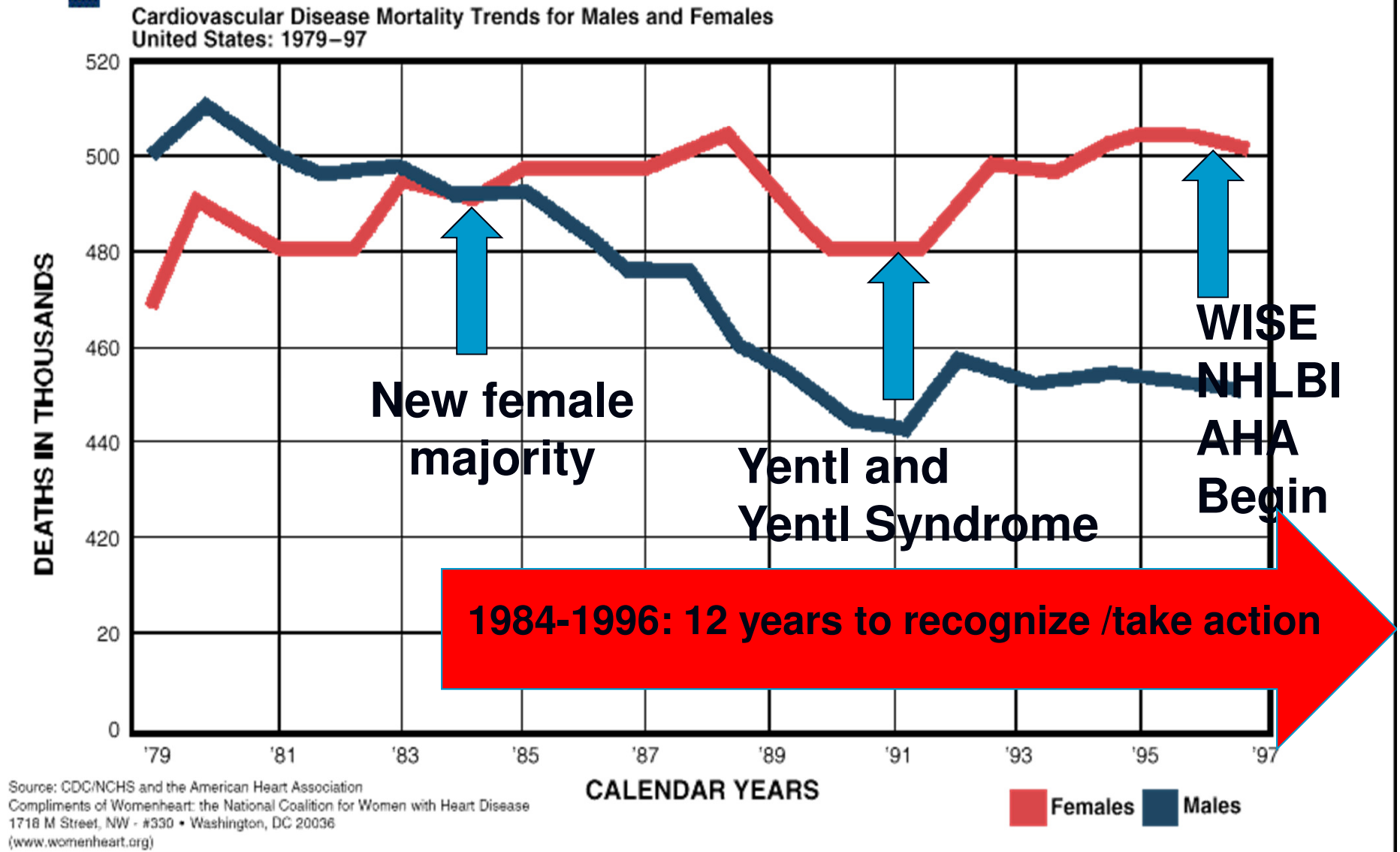
The Yentl Syndrome 1991



Women and Heart Disease Deaths

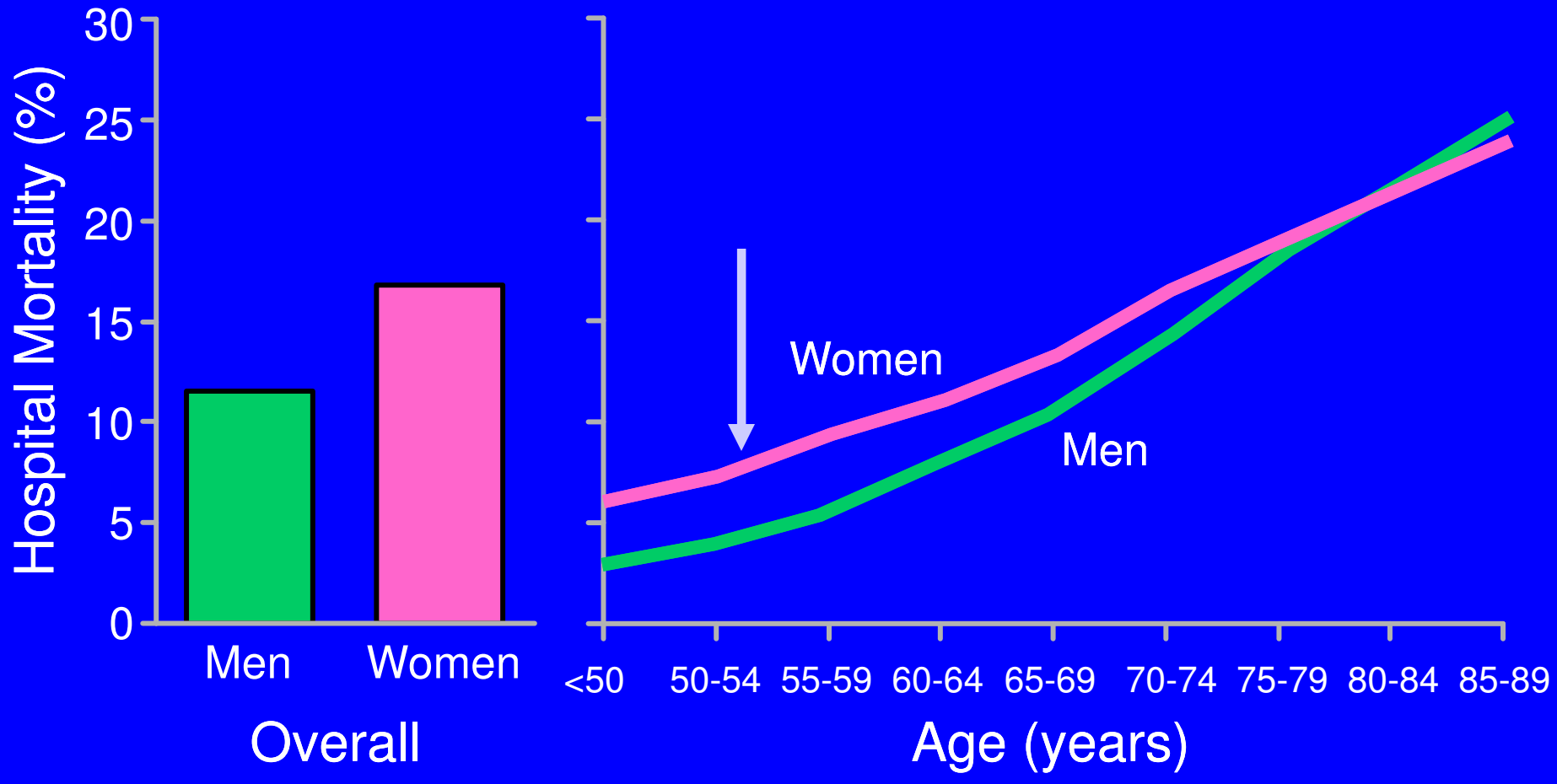
An Alarming Trend...



Source: CDC/NCHS and the American Heart Association
Compliments of Womenheart: the National Coalition for Women with Heart Disease
1718 M Street, NW - #330 • Washington, DC 20036
(www.womenheart.org)

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

Largest Mortality Gaps are Young Women



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

Summary: An Epidemic of Death in Women

1. There is a significant national 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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Sex and Gender Differences in CVD

Terminology:

- *Sex* = biological sexual differentiation, (e.g. women have ovaries, men have testes)
- *Gender* = socio-cultural attributes of the biological sex, e.g. women have complex social networks, men have wives

Gender Differences in CVD

- *Gender differences in reporting* = women are more comfortable discussing feelings with friends and reporting symptoms to physicians[1], possibly due to gender-related acculturation

- *Gender differences in physician response to symptoms* = physicians are more likely to evaluate men compared to women and minorities[2], possibly due to gender-related presentation styles, and/or cultural sexism/racism biases

[1] Stoverink J Fam Pract 1996;43:567; [2] Schulman NEJM 1999;340:618-626

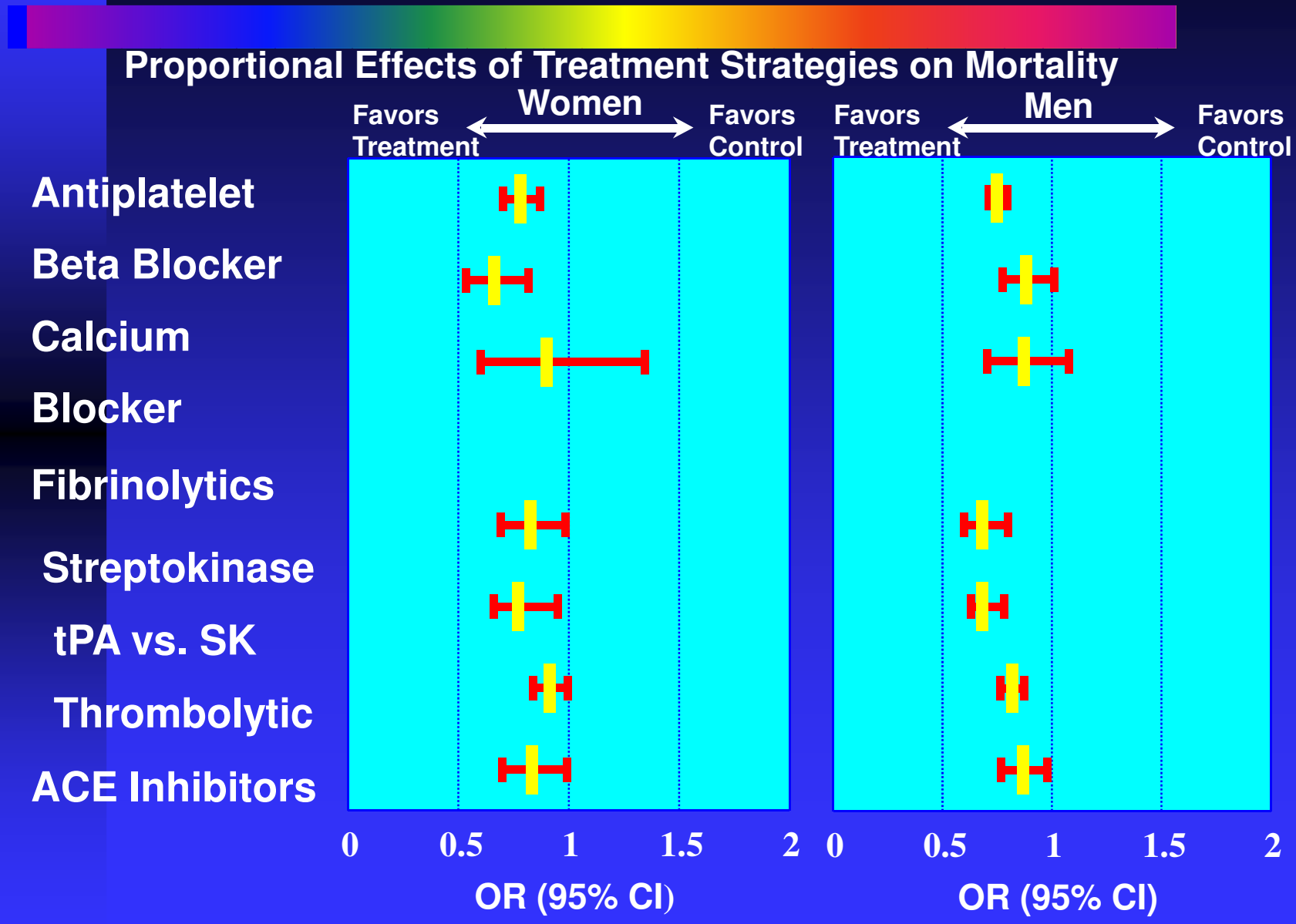
Disparities in ACS Treatment for Women

- 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.

MI Treatment: Women and Men have similar risk benefit



Guideline Implementation and ACS and the Sex Survival Gap

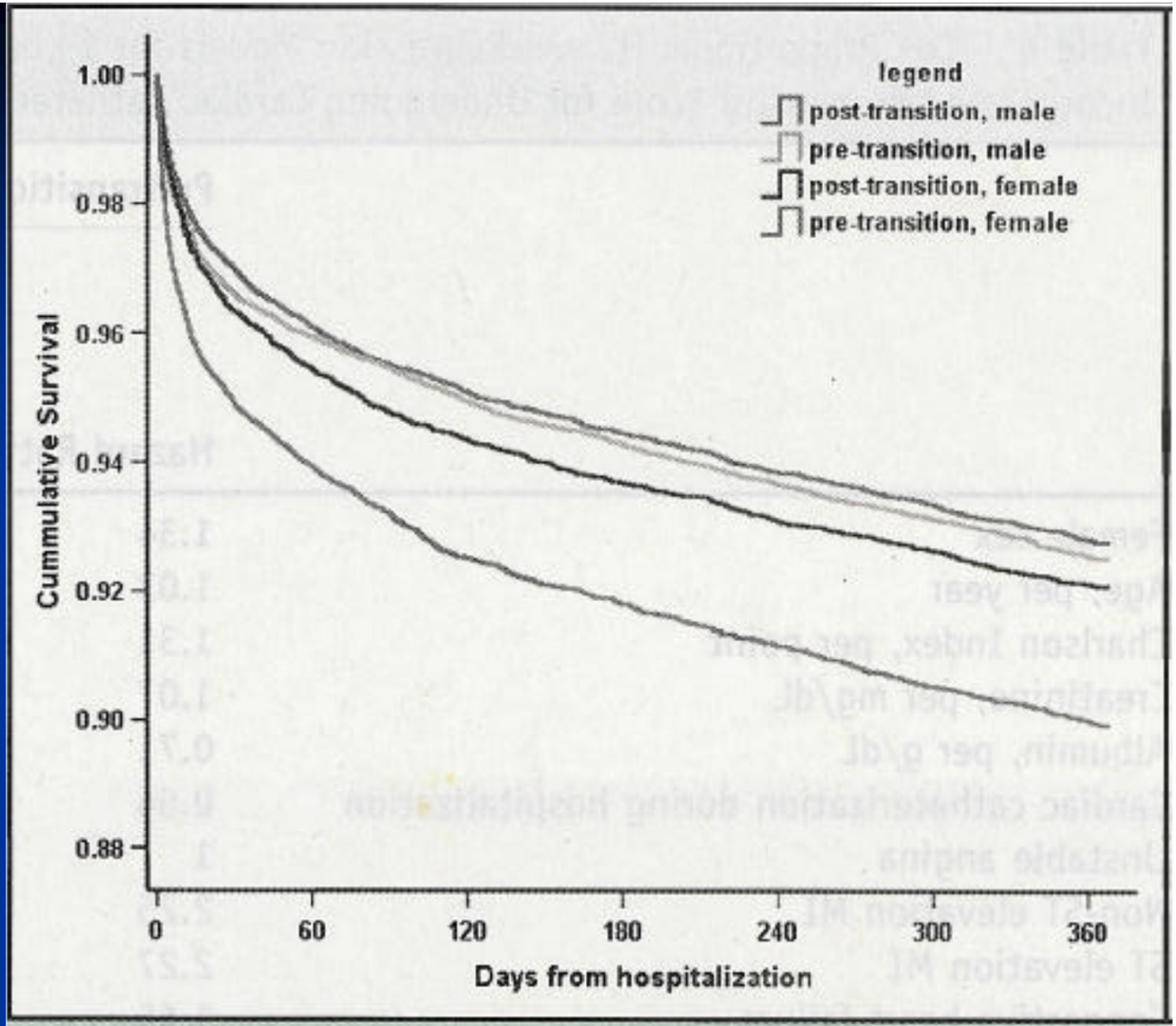
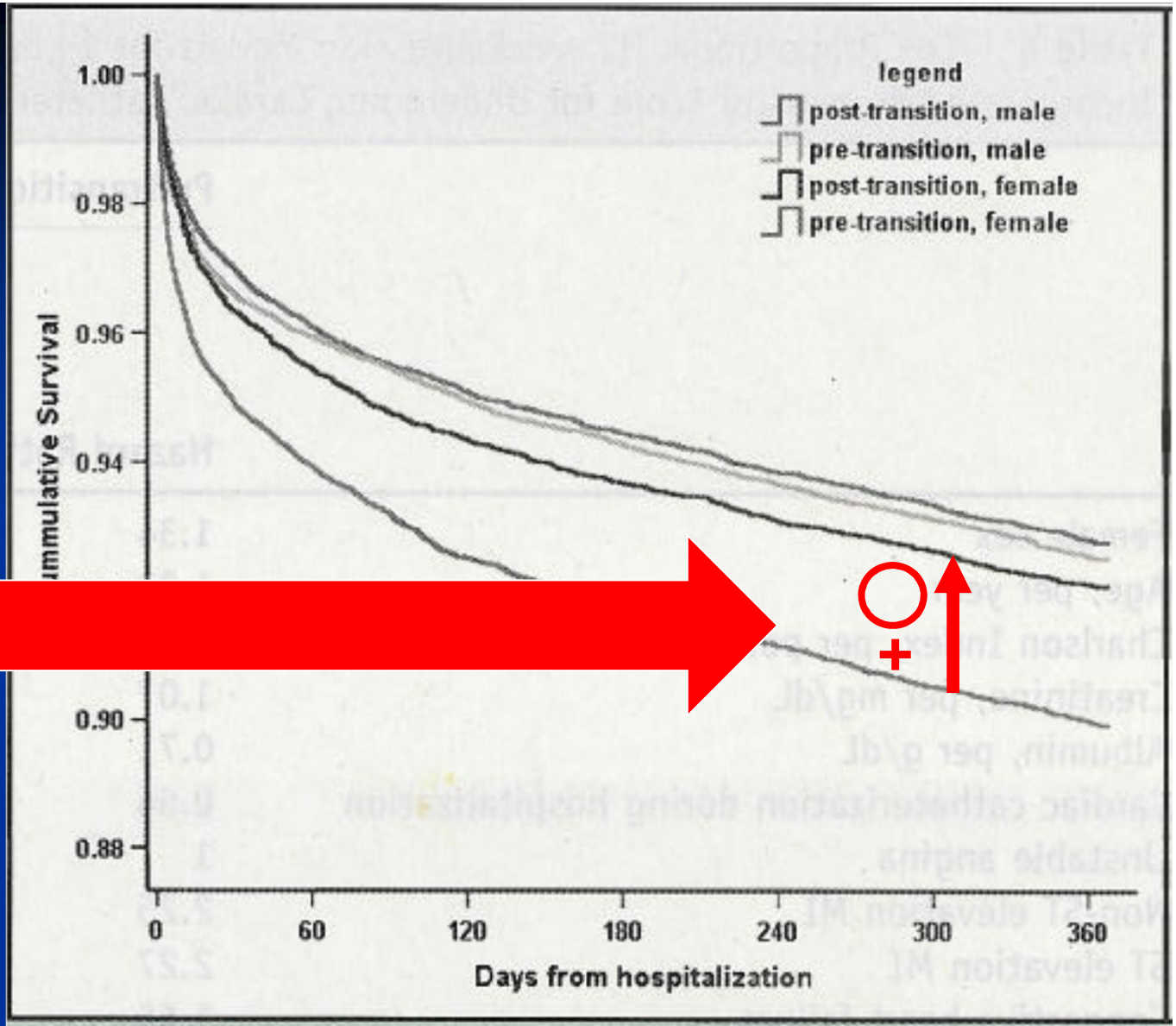


Figure Cox proportional hazard functions for 1-year survival at mean of covariates pre- and post-transition stratified by women vs men.

Novak et al Am J Medicine 2008;121:602

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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Novak et al Am J Medicine 2008;121:602

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

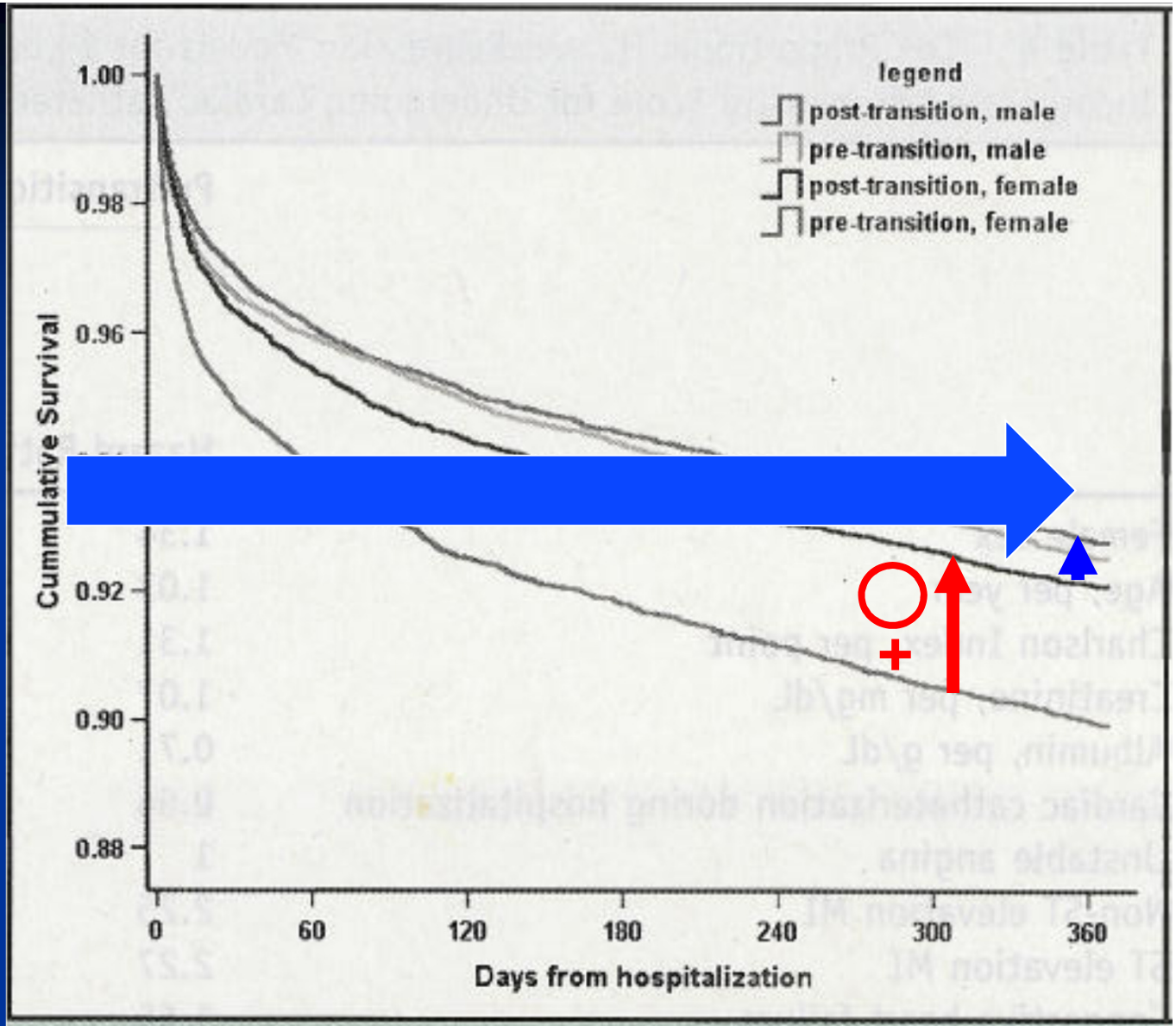

Figure Cox proportional hazard functions for 1-year survival at mean of covariates pre- and post-transition stratified by women vs men.

Novak et al Am J Medicine 2008;121:602

Summary: Low hanging fruit - gender

1. AMI guidelines therapy works equally well in women and men
2. Application of AMI guidelines preferentially saves women's lives
3. Lack of AMI guidelines management (gender) is insufficient to fully explain the adverse outcomes

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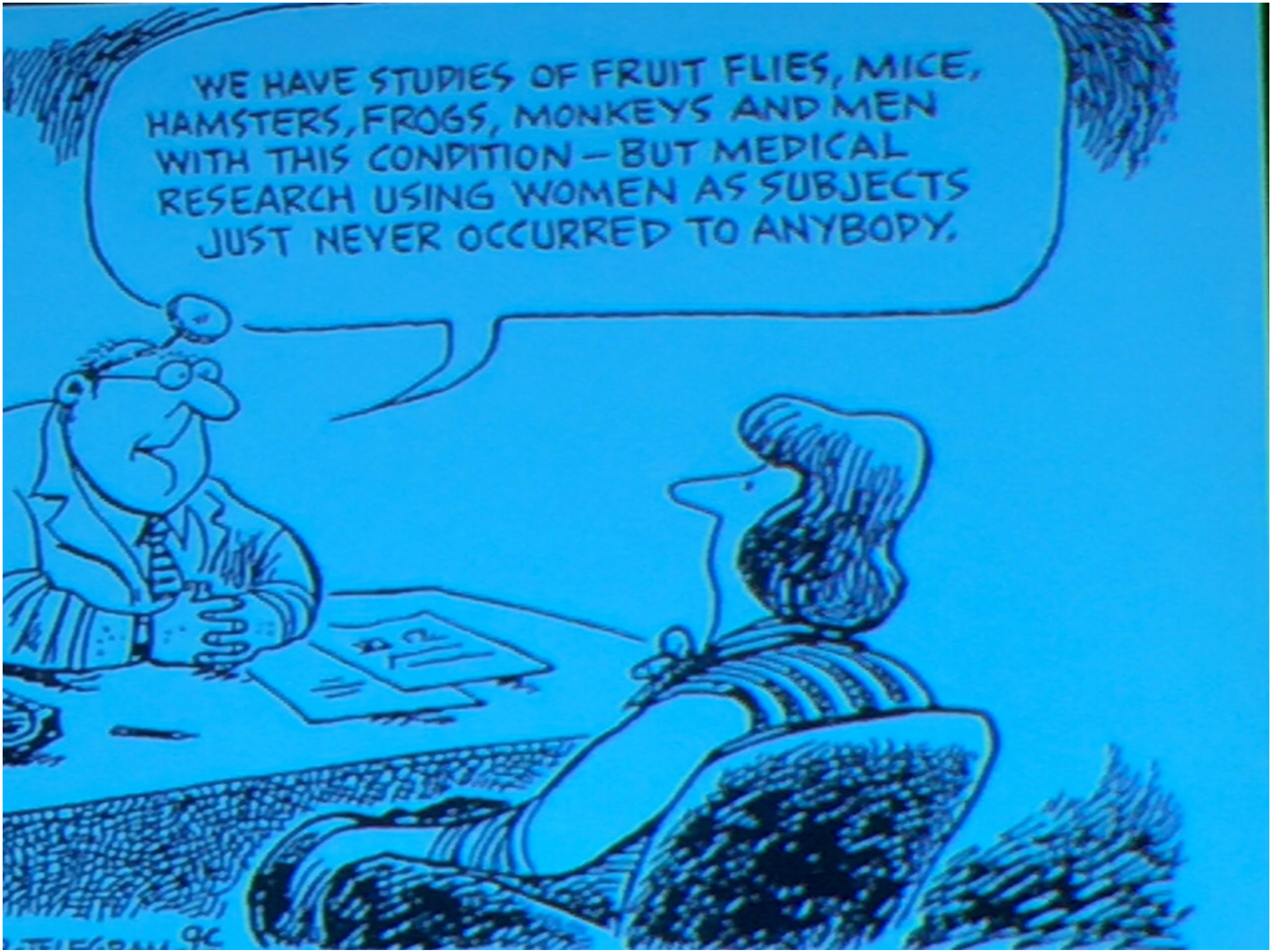
WE HAVE STUDIES OF FRUIT FLIES, MICE, HAMSTERS, FROGS, MONKEYS AND MEN WITH THIS CONDITION – BUT MEDICAL RESEARCH USING WOMEN AS SUBJECTS JUST NEVER OCCURRED TO ANYBODY.

Sex Differences in CVD

- *Sex differences in perception* = women have greater perception (high frequency non-auditory brain testing). Gay men are intermediate between women (higher perception) and men (lower perception), suggesting that this may be genotypic[1]
- *Sex differences in pain* = women have lower thermal pain thresholds compared to men. Thresholds appear mediated by estrogen levels, with higher E2 levels associated with enhanced pain, suggesting that this may be phenotypic[2]

[1]Shaywitz et al, Nature 1995;373:607; [2] Fillingim et al, Pain Forum 1995;4:209

The WISE Study: continuous NHLBI funding for 20 years

Clinical Translational Research

1. A systematic approach to an identified problem
2. T1 (bench ↔ bed), T2 (bed ↔ clinic), T3 (clinic ↔ community)
3. Four steps –
    1. Observation
    2. Mechanisms
    3. Intervention
    4. Translation

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Observation:

Phenotype - *Microvascular Coronary Disease*

Exertional angina

Abnormal SPECT

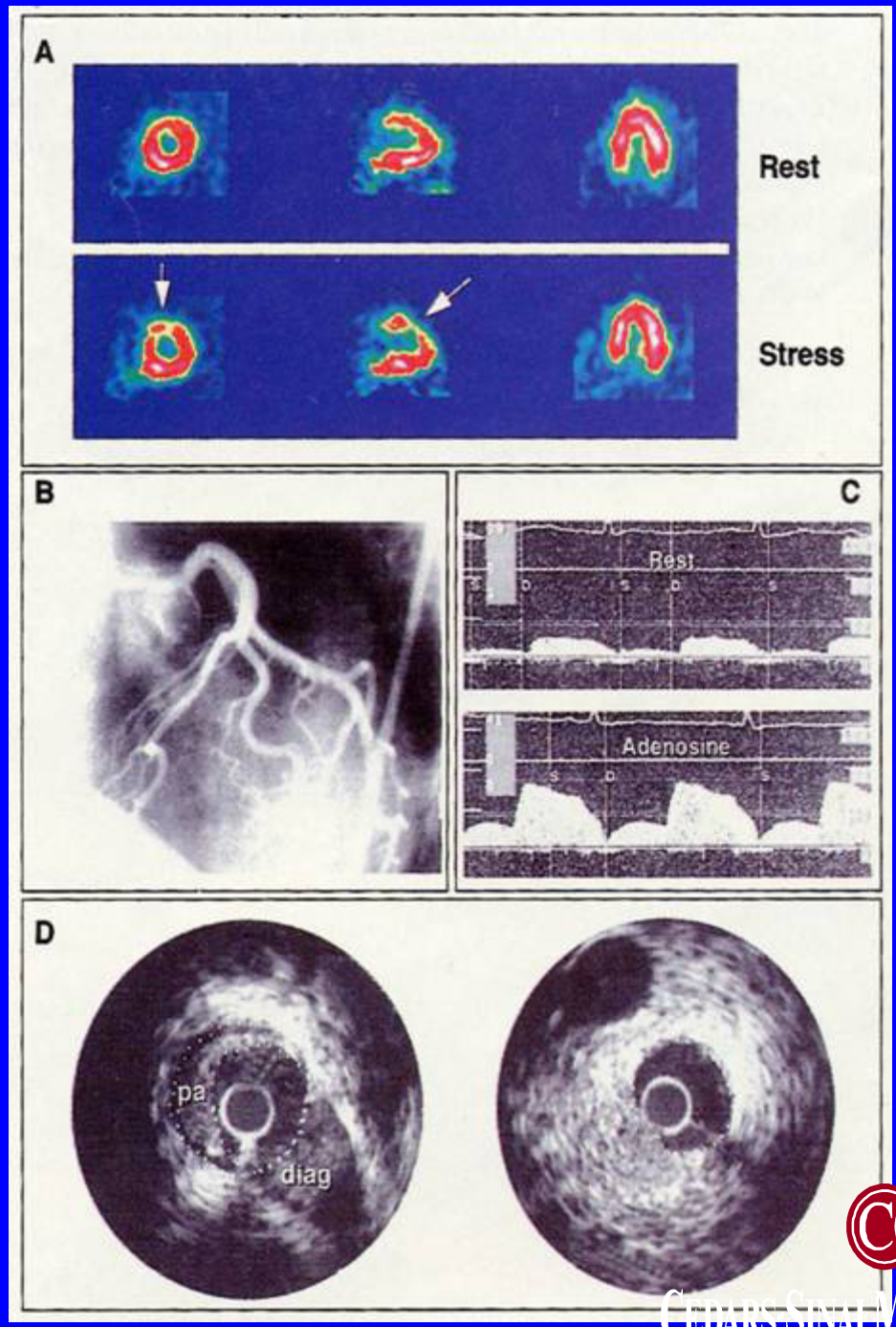
No obstructive CAD

Abnormal coronary flow reserve and elevated LVEDP

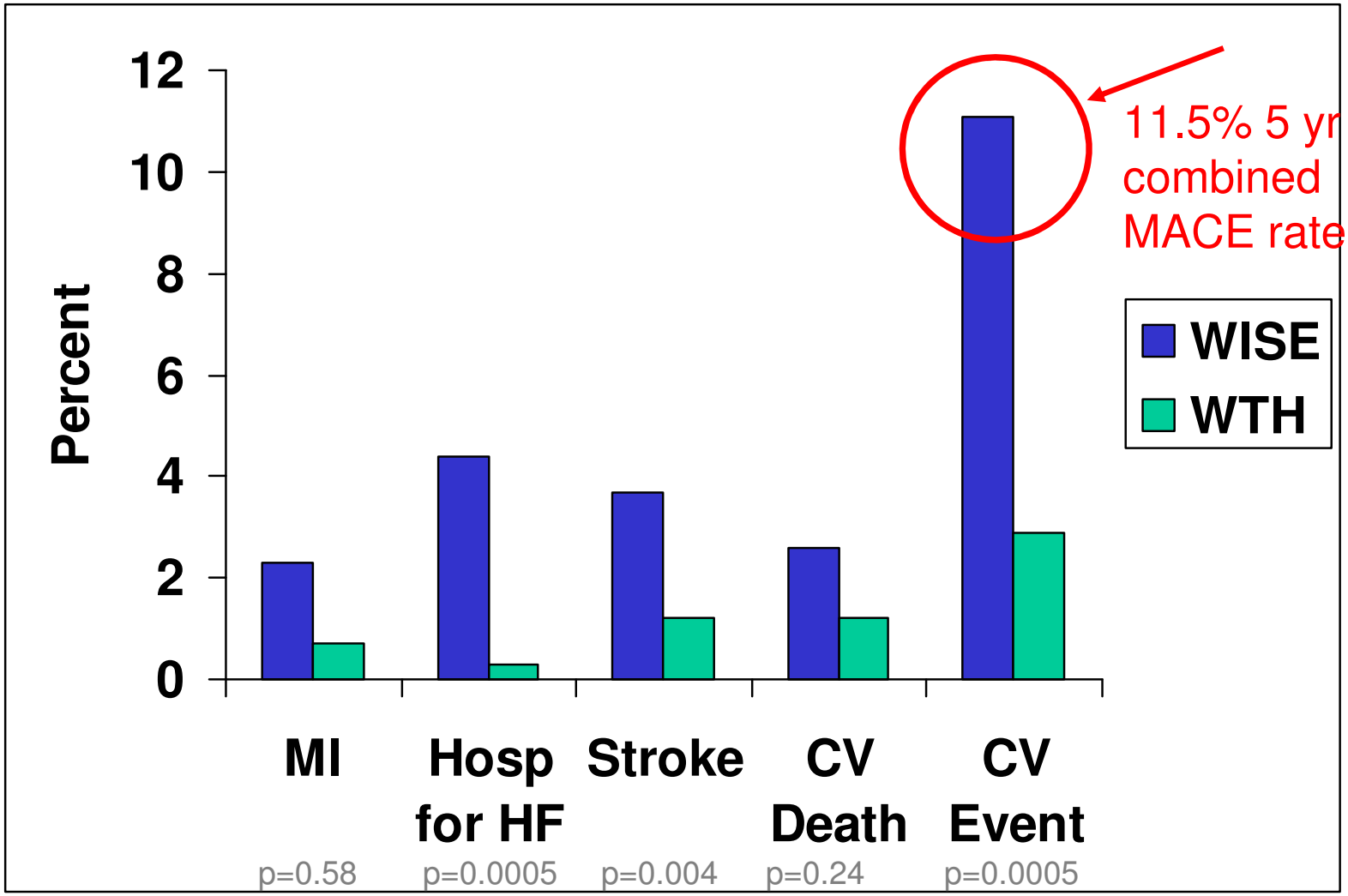
Diffuse atherosclerosis by IVUS

NCDR estimate 3 million women in the US – a larger problem than breast cancer.

Circulation. 1999;99:1774



WISE Patients with signs and symptoms of ischemia have elevated MACE compared to asymptomatic Women Take Heart (WTH) with no ischemia by ETT



All comparisons adjusted for age, race, BMI, history of hypertension, diabetes, education, employment, family history of CAD, menopausal status, smoking history and metabolic syndrome.

Gulati et al Arch Int Med 2010

Clinical Translational Research

1. Observation
2. Mechanisms
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4. Translation

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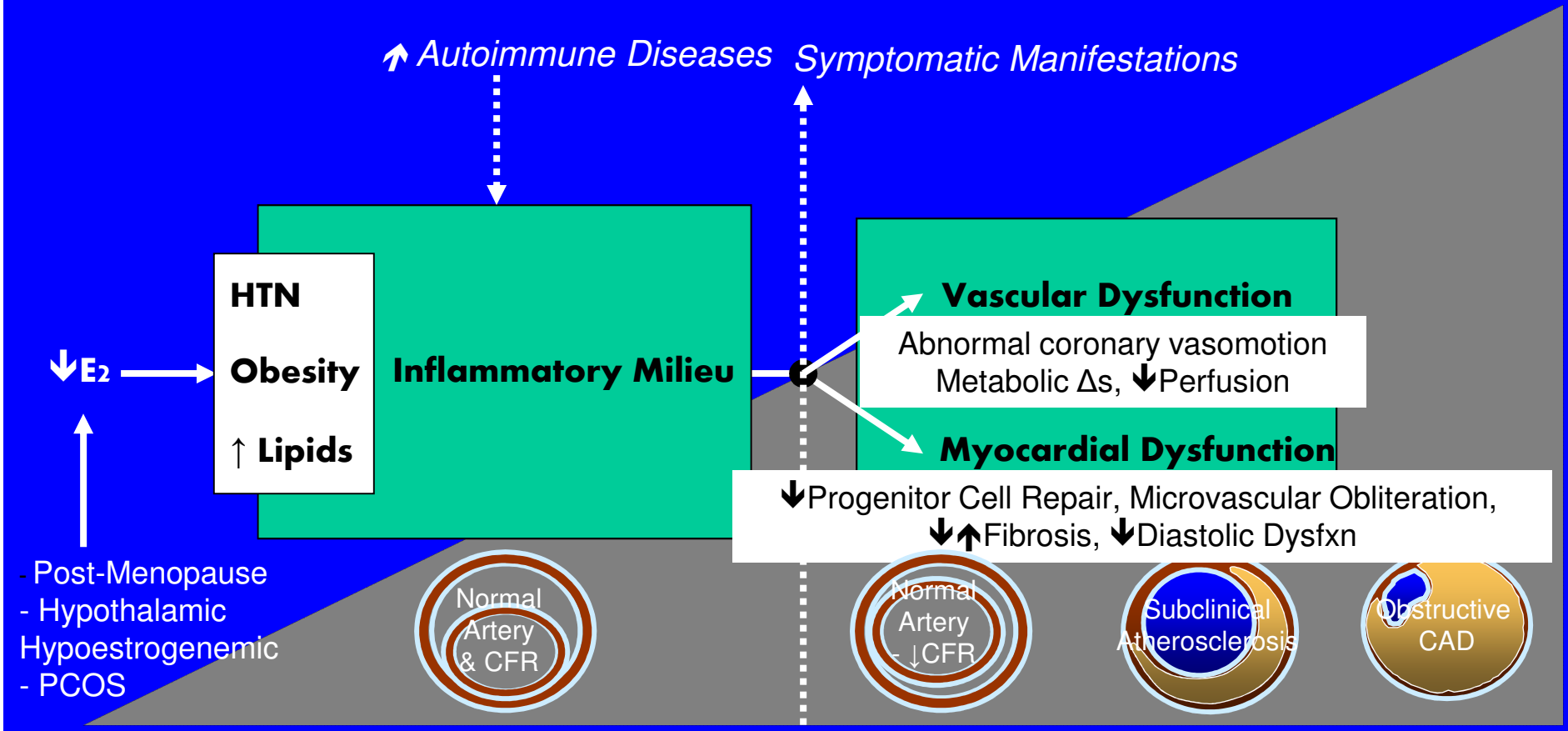
Hypothetical New Understanding of Ischemic Heart Disease in Women (Bairey Merz and Shaw JACC 2009)



Progressive Manifestations of Demand Ischemia

Exposure Time of Mismatch in Myocardial Oxygen Supply / Demand

Near Term ----------▶ *Prolonged*

Coronary Reactivity Testing

- Interventional cardiologist
- PTCA setup
- FloMed Doppler
- 1/600 SAE

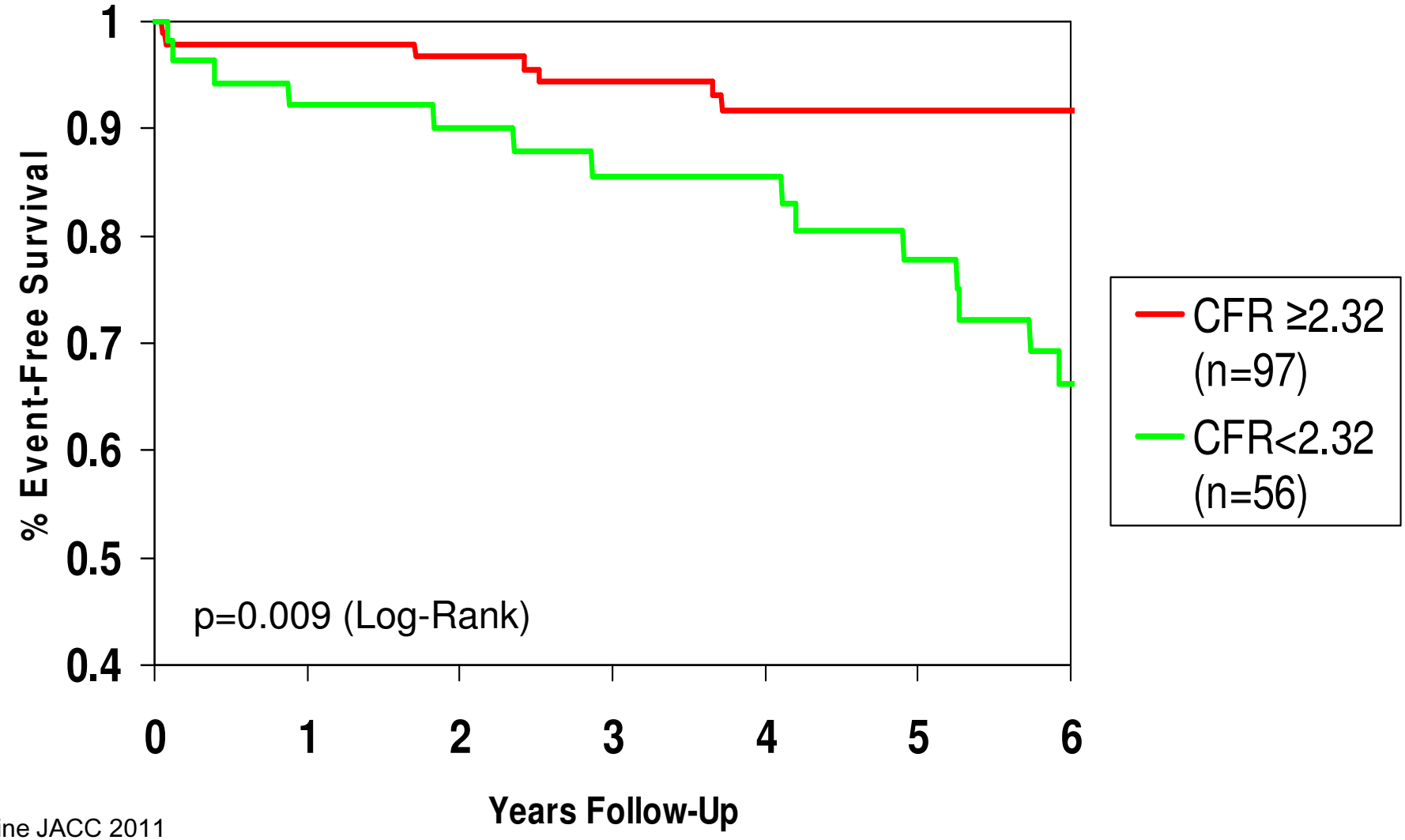
Intracoronary:
- Adenosine
- Acetylcholine
- NTG

1. CFR (micro fxn)
2. Endo fxn
3. Non-endo fxn
4. Micro-endo fxn

OBESE, HYPERTENSIVE, NIDDM, BLACK, 57 yo, FEMALE

with HYSTERECTOMY at AGE 21

Mechanisms: MACE by CFR with adenosine: *Women without CAD* (Death, MI, Stroke, CHF)



Pepine JACC 2011

Clinical Translational Research

1. Observation
2. Mechanisms
3. Intervention
4. Translation

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WISE CMD pharmacologic probe trials

Trial (n)	Intervention	Results
QWISE[1] (n=78)	**quinipril**	↑ CFR; ↓ angina
FemHRT-WISE [2](n=35)	**ethinyl estradiol and norethindrone acetate**	→ MRS; ↓ angina
EWISE[3] (n=41)	**eplenerone**	→CFR; →angina
SWISE[4] (n=23)	**sildenafil**	→CFR; →angina
RWISE Pilot[5] (n=20)	**ranolazine**	↗MPRI; ↓angina
RWISE[6] (n=128)	**ranolazine**	→MPRI; →angina

CFR = coronary flow reserve, MRS = magnetic resonance spectrosopy; myocardial perfusion reserve index; WISE = Women's Ischemia Syndrome Evaluation. 1. Pauley AHJ 2011; 2. Bairey Merz AHJ 2010; 3. Bavry AHJ 2014; Denardo Clin Card 2011; 5. Mehta JACC Imaging; 6. Bairey Merz EHJ 2015

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Clinical Translational Research

1. Observation
2. Mechanisms
3. Intervention
4. Translation
    2. ESC Guidelines

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Summary: Critical investigation - sex

1. Ischemia in the absence of obstructive coronary disease is prevalent, and has an adverse prognosis and cost.
2. Mechanistic pathways include atherosclerosis, and coronary endothelial and microvascular dysfunction.
3. Existing guidelines focus on symptom management and current clinical practice is reassurance.
4. A practical therapeutic clinical trial is needed.

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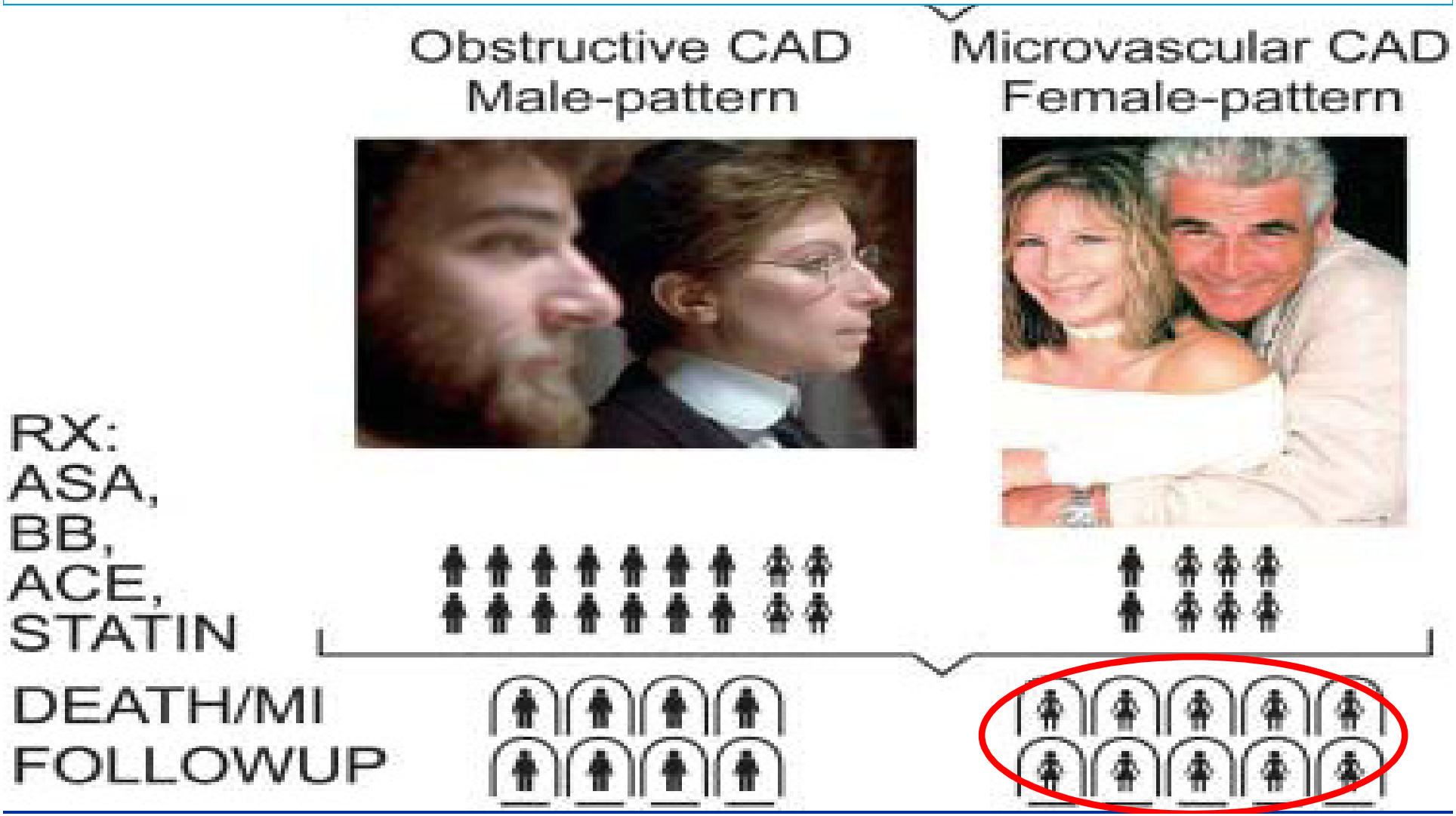
Monet vs Manet?

More men receive treatment

More women die

Bairey Merz EHJ 2011



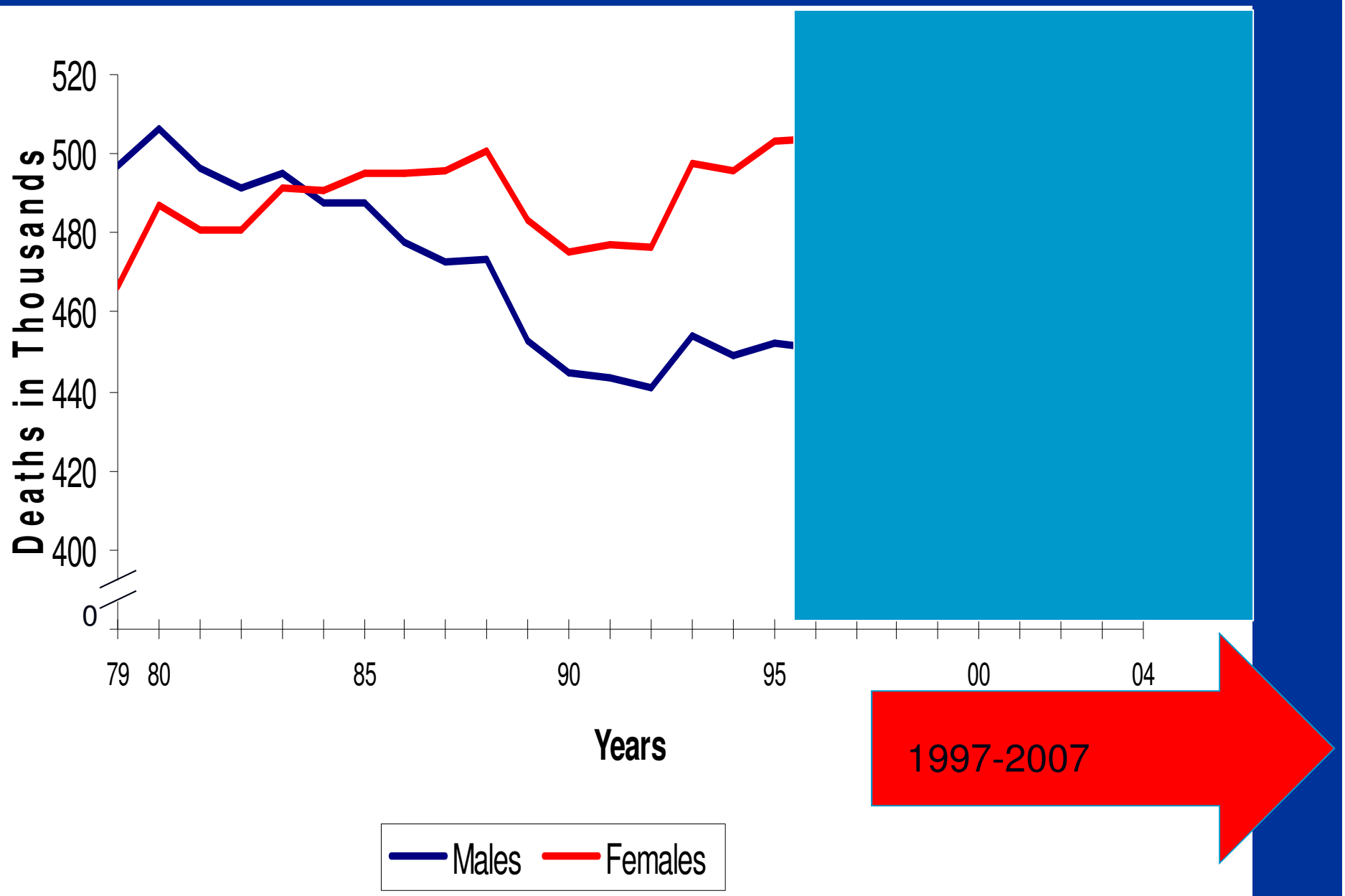
Clinical Practice Guidelines

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

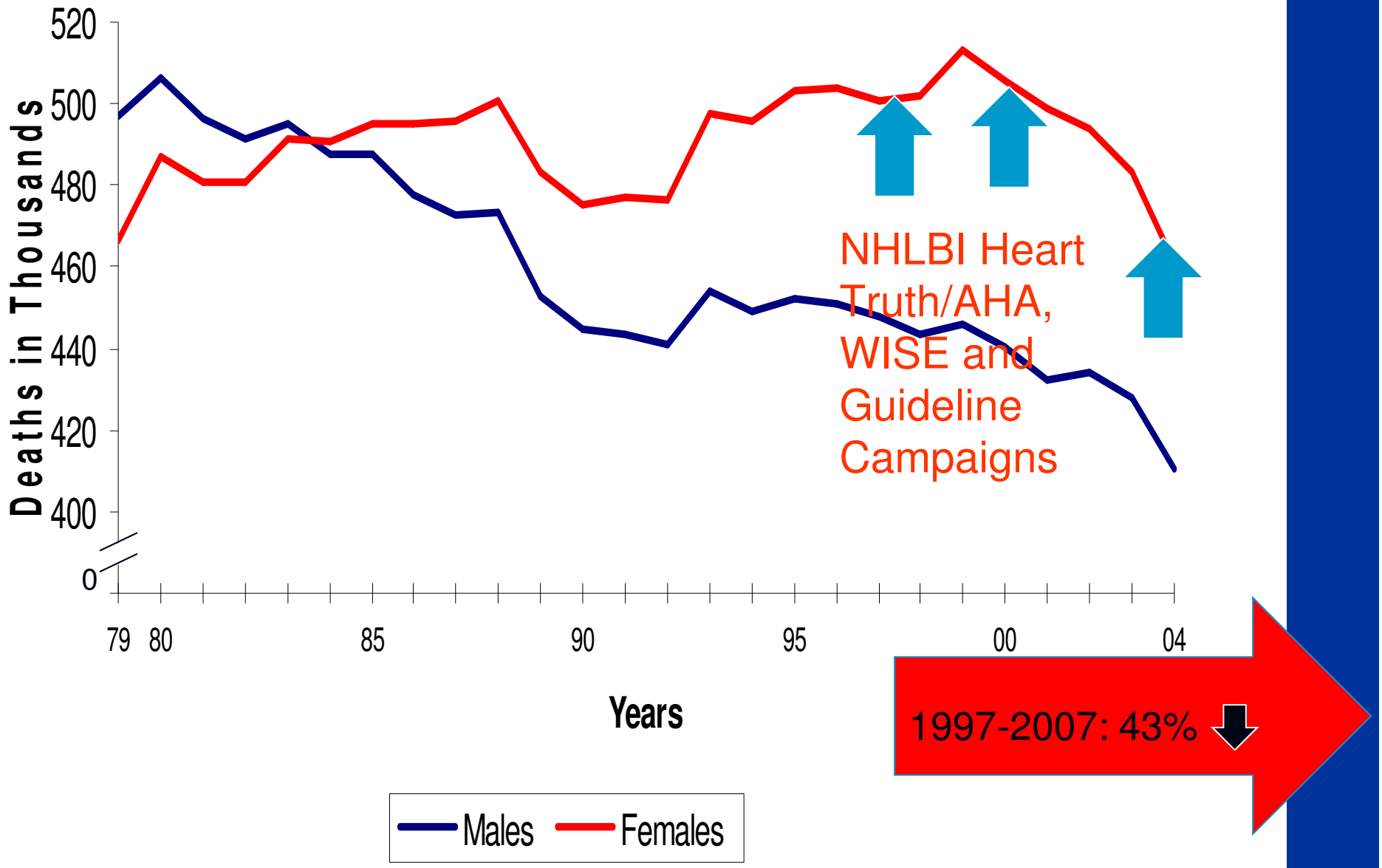
- *Cardiovascular Disease Prevention in Women 2004, 2007, 2010*
- *Management of Patients With ST-Elevation Myocardial Infarction*
- *Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction*
- *Preventing Heart Attack and Death in Patients with Atherosclerotic Cardiovascular 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

Summary: Results of our labor

1. CAD/CHD renamed to IHD to improve recognition of women (and small men)
2. Guidelines campaigns are effective for improving quality of care and outcomes
3. Female mortality has substantially fallen

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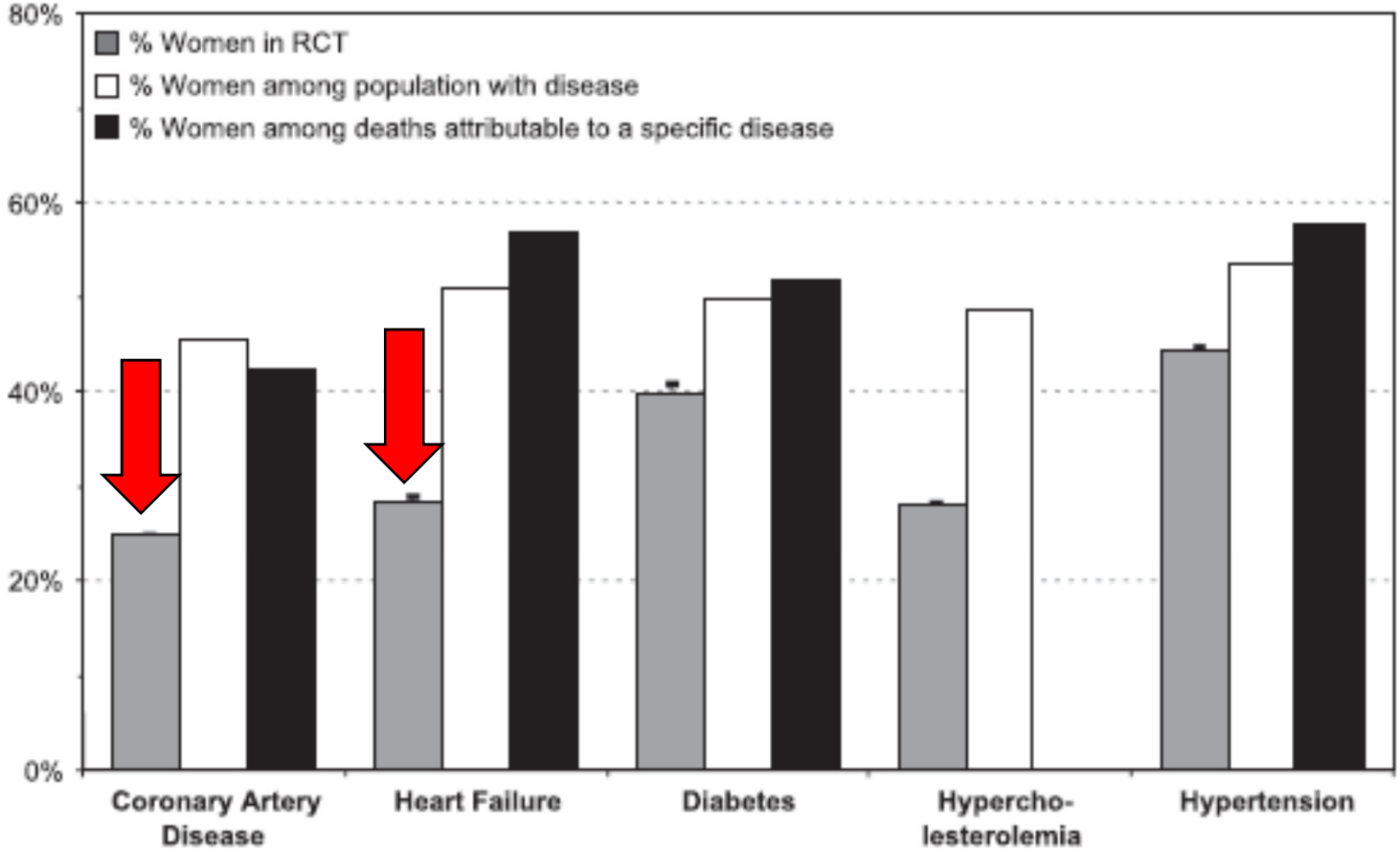
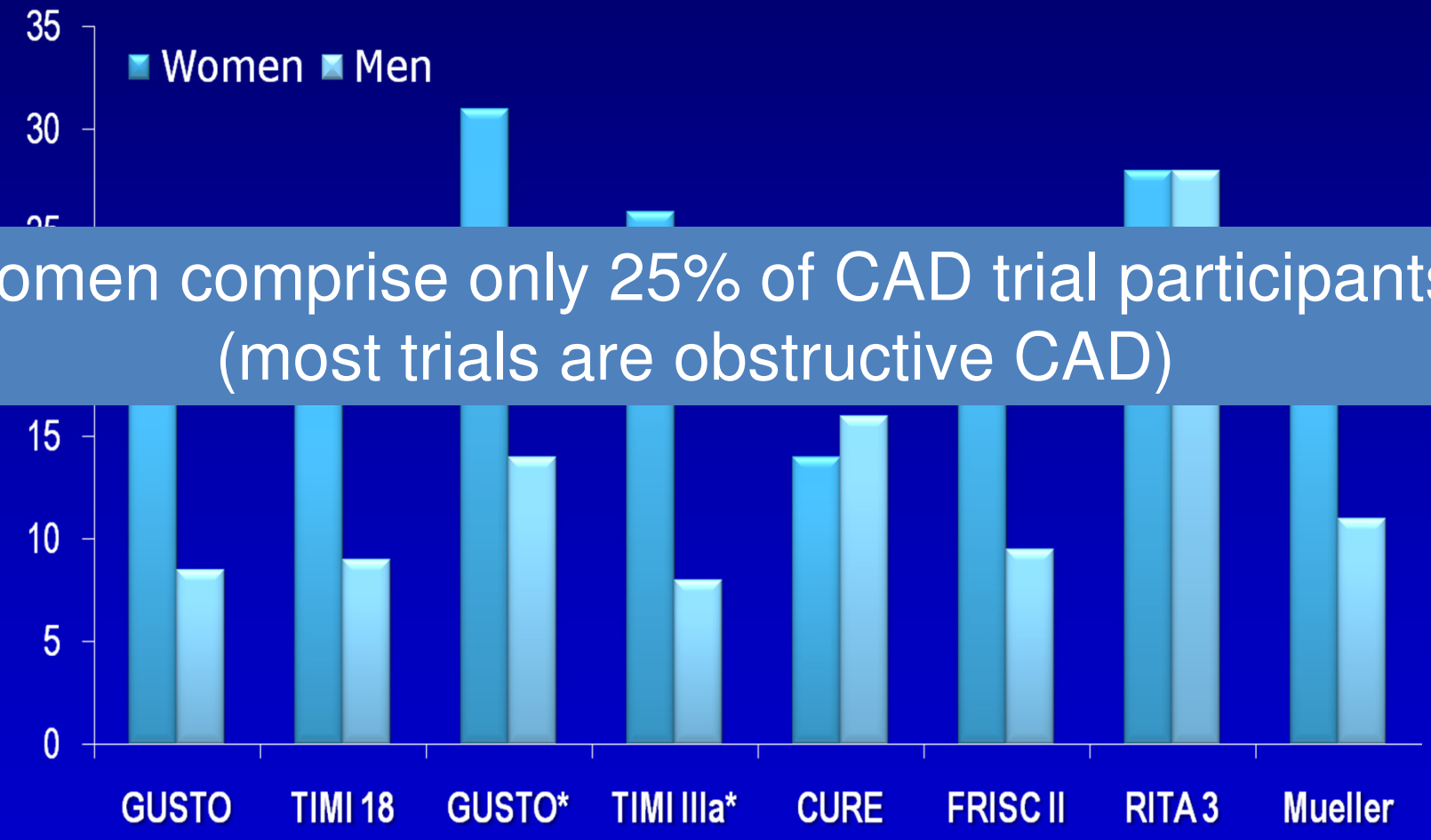
Under-representation of Women in Cardiovascular Clinical Trials

Remains low compared to disease prevalence and death rates - Largest gaps in CAD and HF due to phenotype inclusion criteria (e.g. obstructive CAD, troponin, and reduced ejection fraction)



Melloni, et al, Circ Cardiovasc Qual Outcomes 2010

Non-obstructive CAD Rates in ACS Trials



Women comprise only 25% of CAD trial participants (most trials are obstructive CAD)

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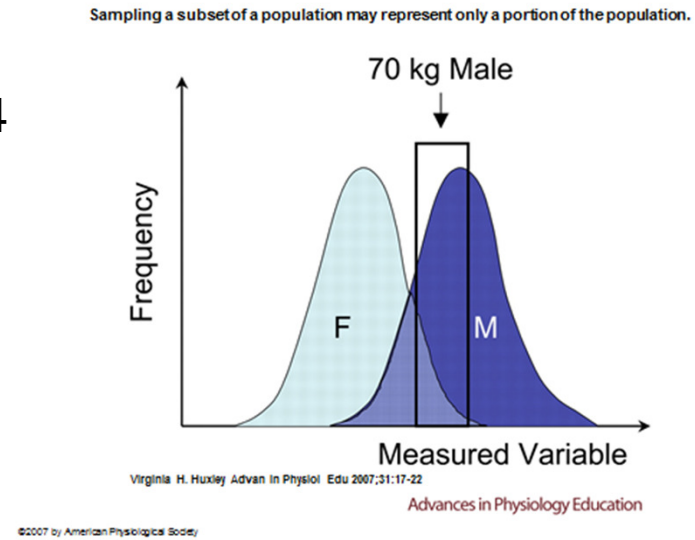
*UA

Source: Anderson Circulation 2007;115:823-826.

Sex Differences in Cardiovascular Disease Biomarkers
(Van Eyk, Bairey Merz, submitted)

Despite their current widespread use, cardiac troponin assays lack sex specific reference value reporting, even for widely used commercial assays that indicate 99th percentile cutoffs or ranges 1.2-2.4 fold higher in males than females[22]. The same is true for CPK-MB[16]

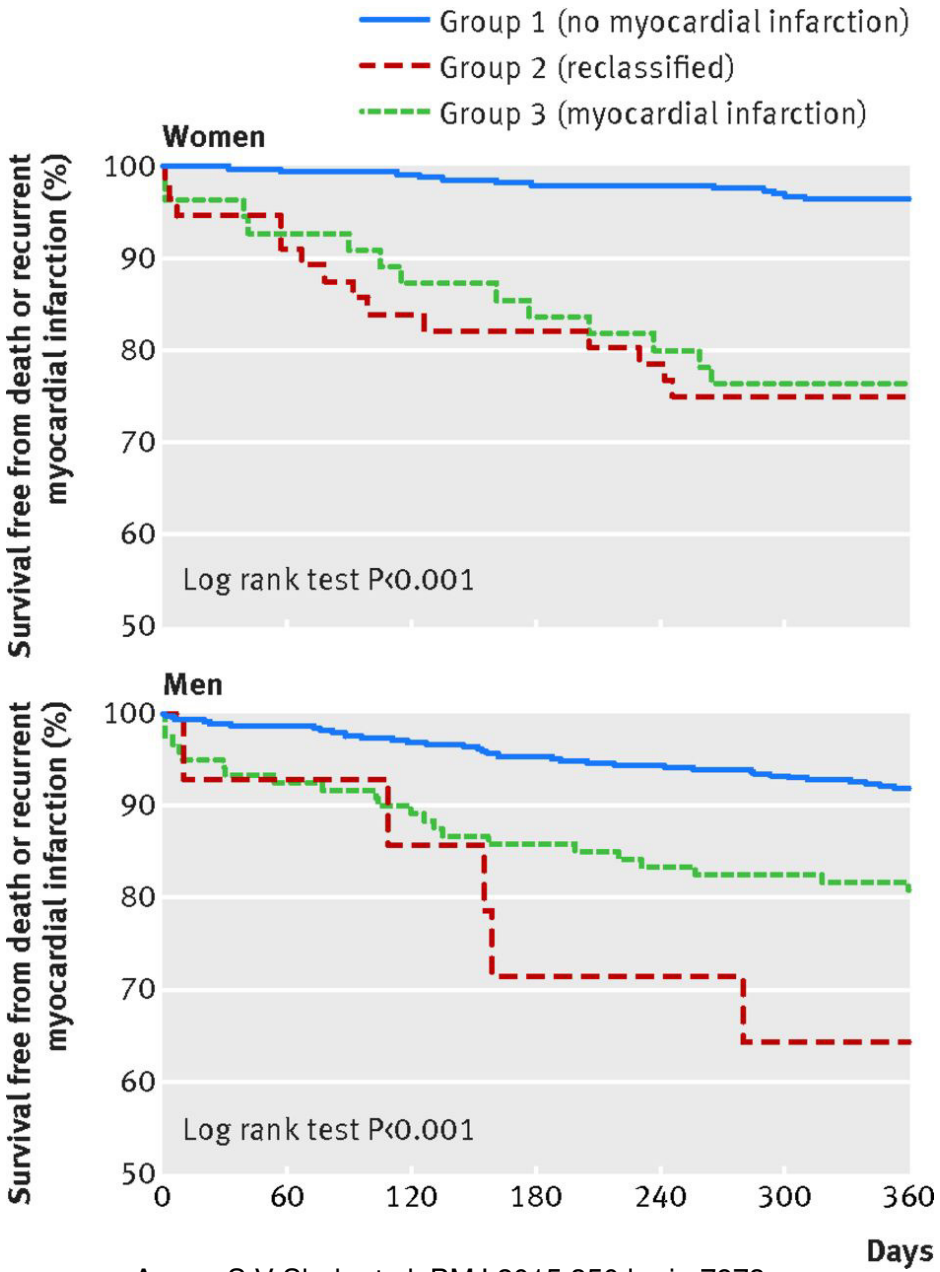


Overall, these data suggest that at-risk women can be missed using the standard male sex-specific threshold, and that those women that meet standard AMI troponin criteria have suffered a greater degree of myocardial damage[26]

[22]Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem. 2012;58(11):1574-1581.
[16] Apple FS, Quist HE, Doyle PJ, Otto AP, Murakami MM. Plasma 99th percentile reference limits for cardiac troponin and creatine kinase MB mass for use with European Society of Cardiology/American College of Cardiology consensus recommendations. Clin Chem. 2003;49(8):1331-1336.
[26] Slagman A, Searle J, Vollert JO, et al. Sex differences of troponin test performance in chest pain patients. Int J Cardiol. 2015;187:246-251.

Undiagnosed MIs are untreated MIs with a 25-35% 1 yr death/MI rate

Fig 4 Survival free from death or recurrent myocardial infarction in women and men with suspected acute coronary syndrome.



Back to 1970s AMI mortality!

Anoop S V Shah et al. BMJ 2015;350:bmj.g7873

Table 1. Percentage of women's population in HF trials

Trial	Total population	Female population	Percentage of females
CONSENSUS [58] (Enalapril)	253	75	30
SOLVD [59] (Ramipril)	4228	486	11.5
ATLAS [60] (Lisinopril)	3164	648	20
COPERNICUS [61] (Carvedilol)	2289	469	20
MERIT HF [62] (Metoprolol)	3991	898	22.5
CIBIS II [63] (Bisoprolol)	2647	515	19
SENIORS [64] (Nebivolol)	2061	785	38
VAL-HeFT [70] (Valsartan)	5010	1003	20
CHARM Added [71] (Valsartan vs Candesartan vs placebo)	2548	542	21.3
ELITE II [72] (Losartan vs Captopril)	3152	966	31
HEEAL [73] (Losartan vs Lisinopril)	3846	1155	29.5
VALIANT [74] (Valsartan)	14703	4570	31.1
OPTIMAAL [75] (Losartan vs Captopril)	20573	5925	28.8
SHIFT [76] (Ivabradine)	6558	1171	17
BEAUTIFUL [77] (Ivabradine)	10917	1870	17
MADIT II [78] (ICD)	720	192	26
SCD- HeFT [79] (ICD)	2521	588	23
COMPANION [80] (CRT)	1520	493	32
CARE HF [81] (CRT)	813	215	26

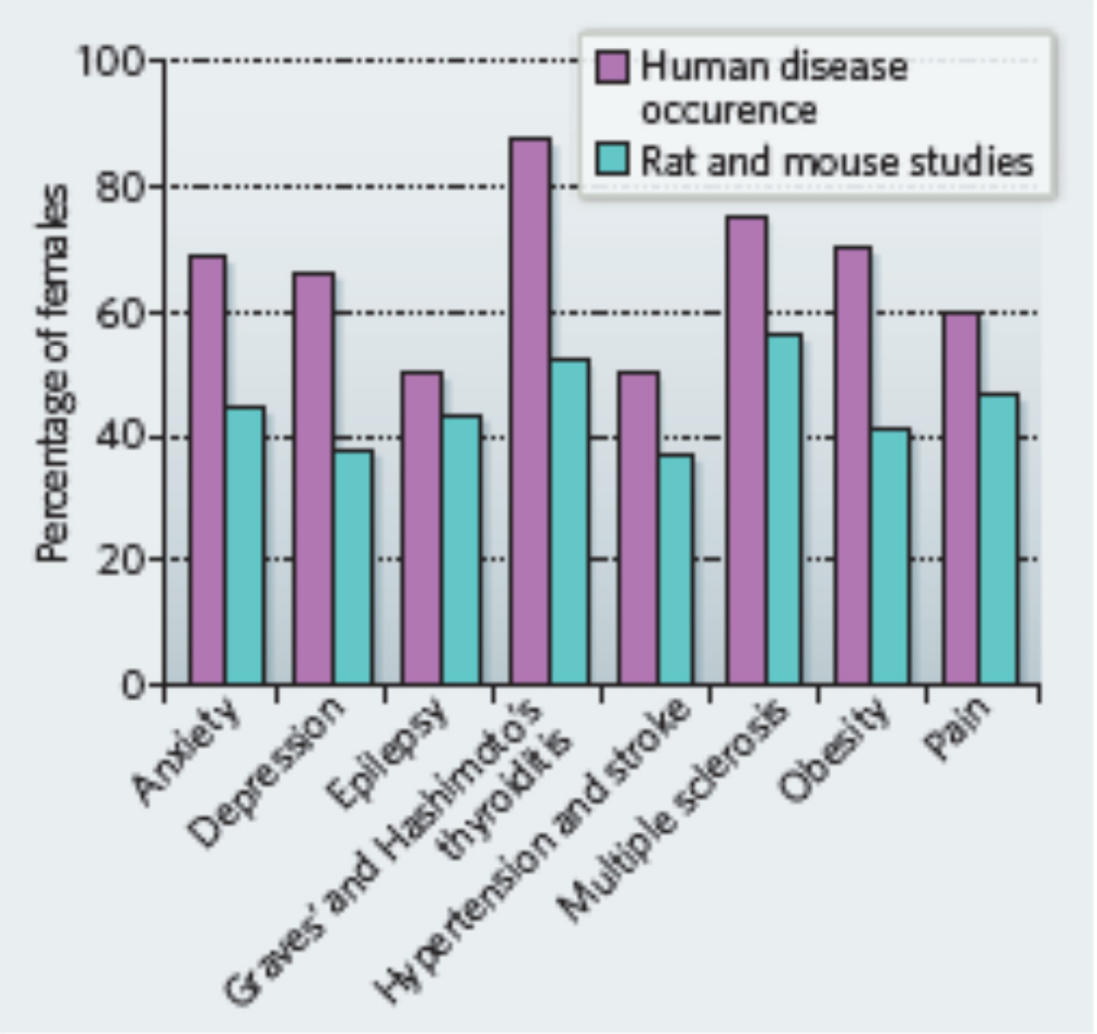
Women comprise only 6-38% of HF trial participants (because most trials are HFrEF)

Giulia D'Agostini et al. Heart Failure in Women: A Disease with Peculiar Pathophysiological Mechanisms and Clinical Presentation. American Journal of Cardiovascular Disease Research, 2013, Vol. 1, No. 1, 1-6. doi:10.12691/ajcdr-1-1-1

Historical Policy Actions

- Clinical studies and trials must include both men and women when the condition being studied affects both sexes (NIH Healy)
- Women's Health Initiative (WHI)(Healy)
- Women's Health Centers of Excellence (WH CoE) – 20 centers funded (Clinton)
- WH CoE centers *defunded (*GW Bush)
- National Institute of Minority Health, and Precision Medicine (but no plans for a Women's or Gender Institute)(Obama)
- Basic science studies must include male and female cells, animals when the condition being studied affects both sexes (NIH Collins)

Status Quo: Male animals used to study female disease



Gender gap. The percentage of women in the total population presenting with a disease (purple; see ref. 1) outstrips the percentage of females in rat and mouse models of that disease (green; data from Web of Science). Only studies with 'female' or 'male' as keywords were captured, so the chart underestimates male bias relative to a survey of individual articles by field.

www.charite.de/gender

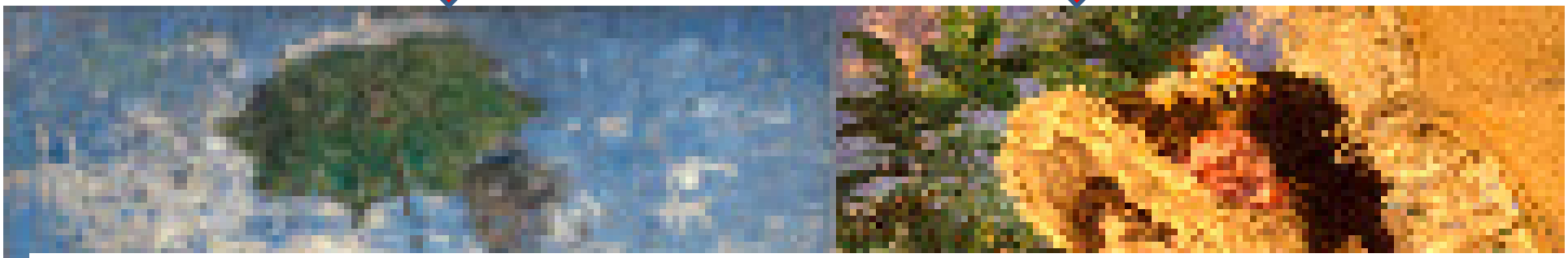
Zucker I, Beery A, Nature, 465; June 2010

Female cells and animals are important for drug and device development

- **Sex-specific response to therapy**
  - **Pharmacokinetics:**
    - **GFR in women is 10% below those of men after correction for BMI; increased difference with age (40%)**
    - **Cytochrom P450 system is sex-specific**
  - **Pharmacodynamics:**
    - **Digitalis; ACEI, antiarrhyhtmic drugs, anticoagulants**
    - **SSRI (Selective Serotonin re-uptake inhibitors), ambien**
  - **Sex-specific adverse: effects 15-17 % higher in women**
  - **7/10 medications withdrawn by the FDA are due to unanticipated adverse events in women**

Sex and Gender Differences in Pharmacology, Editors: Regitz-Zagrosek, Vera (Ed.)

Monet or Manet?



Okay maybe Monet and Manet are kind of similar. They use the same kind of brushstrokes, use a mix of en plein air and alla prime, and both love color. But the subjects are usually different and Manet is more realistic. But we won't forgive anyone who confuses who made what masterpiece.

WHAT CAN THIS TEACH US ABOUT CVD SEX AND GENDER DIFFERENCES?

Conclusions and Clinical Pearls

Female-pattern Ischemic Heart Disease:
Monet vs Manet
(or why women have more
adverse IHD outcomes)

Policy and our future

a. Science – advocacy, philanthropy

b. Policy – research, publication, guidelines

c. Education – disparities, technology

AMERICAN COLLEGE *of* CARDIOLOGY


THE BARBRA STREISAND
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