



# Looking into a Woman's Heart: Acute Coronary Syndrome and Gender

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Disclosures: None



# Learning Objectives

- Understand that ACS affects both women & men
- Review sex differences in ACS symptoms
- Explore the spectrum of ACS pathophysiology & etiologies in women
- Become aware of MINOCA, and understand the significance, especially in women
- Learn about sex-based differences in ACS prognosis and treatment
- Recognize the needs for sex-based CV research

# Institute of Medicine Definitions:

**Sex:** -male/female classification according to reproductive organs/functions  
-assigned by chromosomal complement

**Gender:** -person's "self-representation"  
-"rooted in biology, shaped by environment & experience"

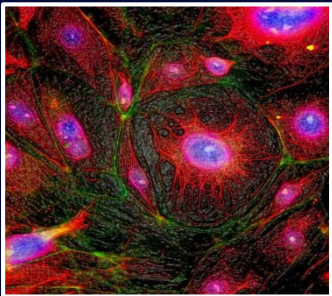
Every cell has a sex—including cardiac-related cells

Cells

Animals

Human  
subjects

Medical  
practice



# Startling Stats on Sex and ACS

- More women than men have died of ACS since 1984
- Within 5 years of an initial MI
  - 15% of men and **22%** of women 45 – 64 yo will suffer a recurrent MI or fatal coronary heart event
- Women (and minorities) are significantly more likely to die within 5 yrs after a first MI compared with white male patients

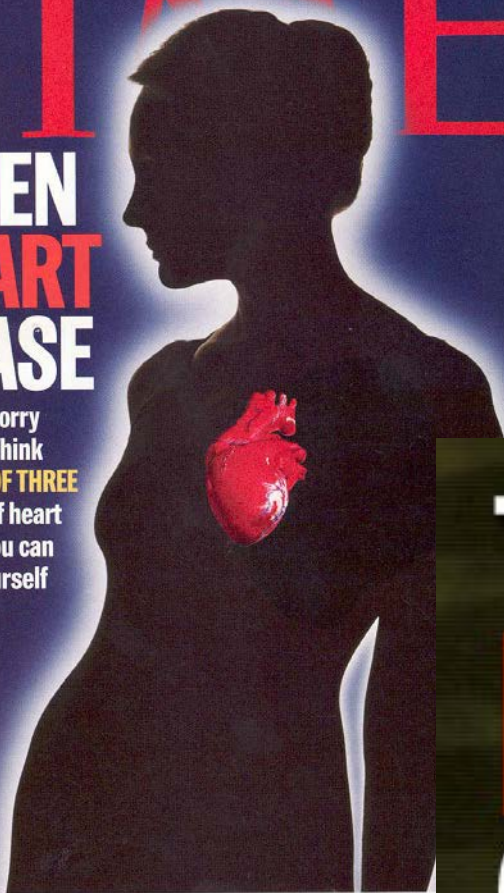


IRAQ: INSIDE THE OCCUPATION / THE SEARCH FOR SADDAM

# TIME

## WOMEN & HEART DISEASE

Is your biggest worry breast cancer? Think again. **ONE OUT OF THREE** women will die of heart disease. What you can do to protect yourself



April 28, 2003

# Heart Disease: An Equal Opportunity Killer

# THE NO. 1 KILLER OF WOMEN

► One out of three women will die of HEART DISEASE. What you can do to **protect yourself** ►



# ACS in Women: Age Matters



**Sofia Vergara, Age 43**

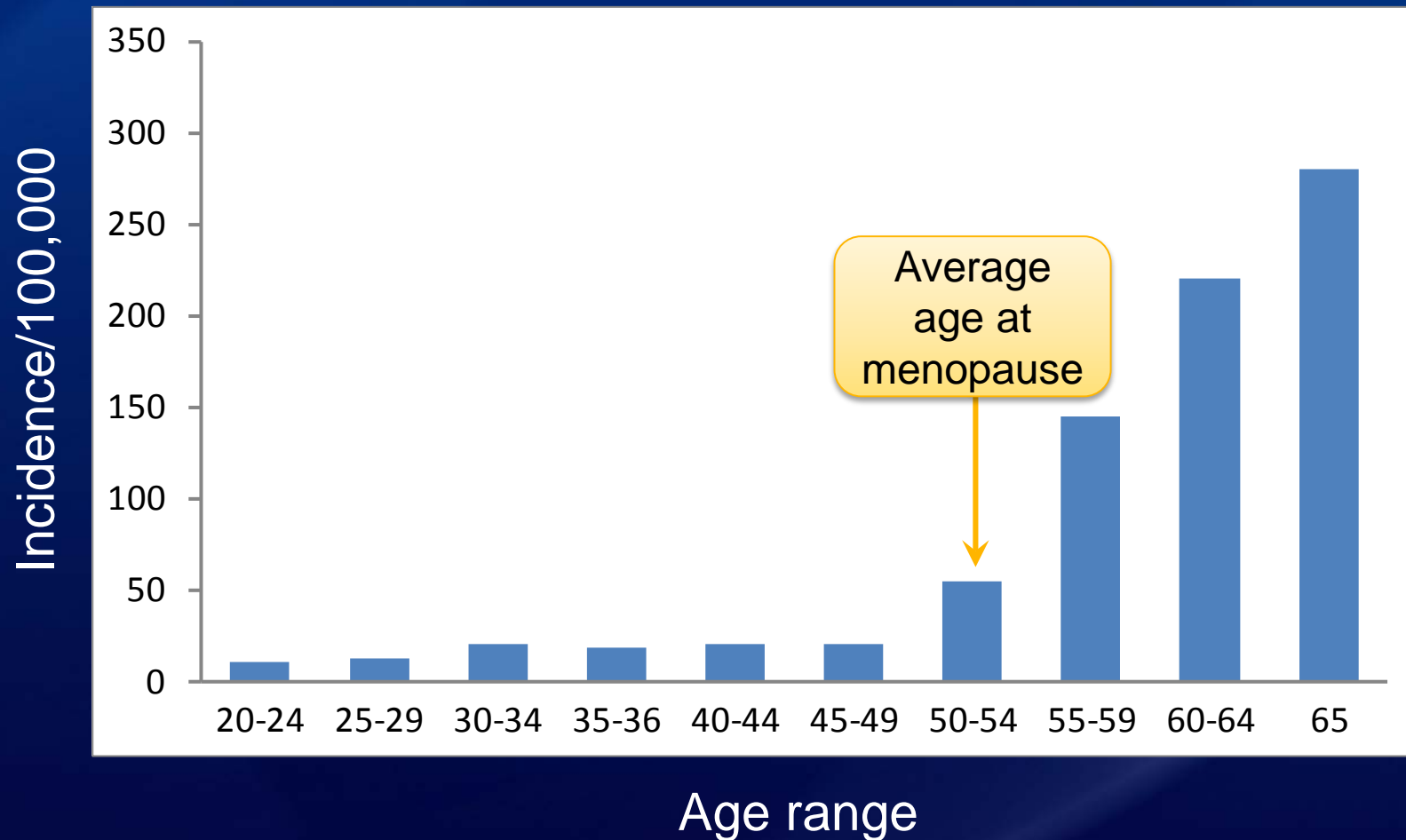
≠



**Sophia Loren, Age 81**

*Courtesy of Dr. Harmony Reynolds, NYU*

# Incidence of Cardiovascular Events in Women Before and After Menopause



Hu FB et al: New Engl J Med 343:530, 2000

# Heart disease risks unique to Women



**Pregnancy:  
“ a stress test for the heart”**

**-Pregnancy induced high blood pressure: Preeclampsia, toxemia**

**↑ 2-3 X**

**-Gestational diabetes:**

**↑ ~2X**

Ray JG et al. *Lancet*, 2005

Mosca L, *Circulation* 2011



# ACS in Women: More to Think About

***VIRGO (Variation In Recovery: role of Gender on Outcomes of Young (<55) AMI Patients) --Taxonomy***

**Class I MI (plaque rupture/epicardial vessel obstruction)**  
**95% of men; 82% women**

**1 in 8 of AMI's in women:**

**“unclassified” (by Universal Definition of MI)**  
**4X more than in men**

**Women more likely to have:**

**Supply-Demand-Mismatch, SCAD, vasospasm,  
embolism, “undetermined” (?CMD/MVD)**

# ACS in Women

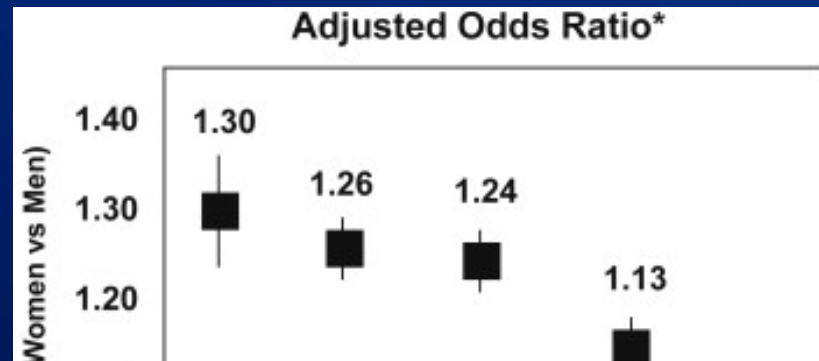
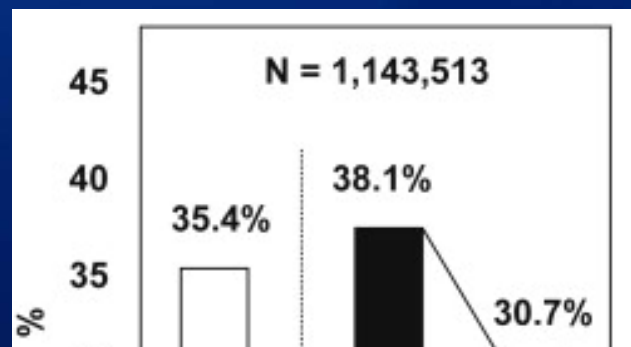


- **Presentation**
- **Pathophysiology**
- **Prognosis**
- **Treatment**

# Sex and ACS Presentation:

## Are “atypical symptoms” more common in women?

### Presentation *without* chest pain



**Women are more likely to experience shortness of breath, nausea/vomiting, back or jaw pain, and excessive fatigue than men**

# AMI Trends in the USA for Young Women & Men 2001 to 2010 [230,684 hospitalizations (of total 1,129,949)]



Young women <55  
years with AMI

- > Comorbidities
- < AMI Hospitalization Rate
- > Length-of-Stay
- > In-hospital Mortality



Young men <55  
years with AMI

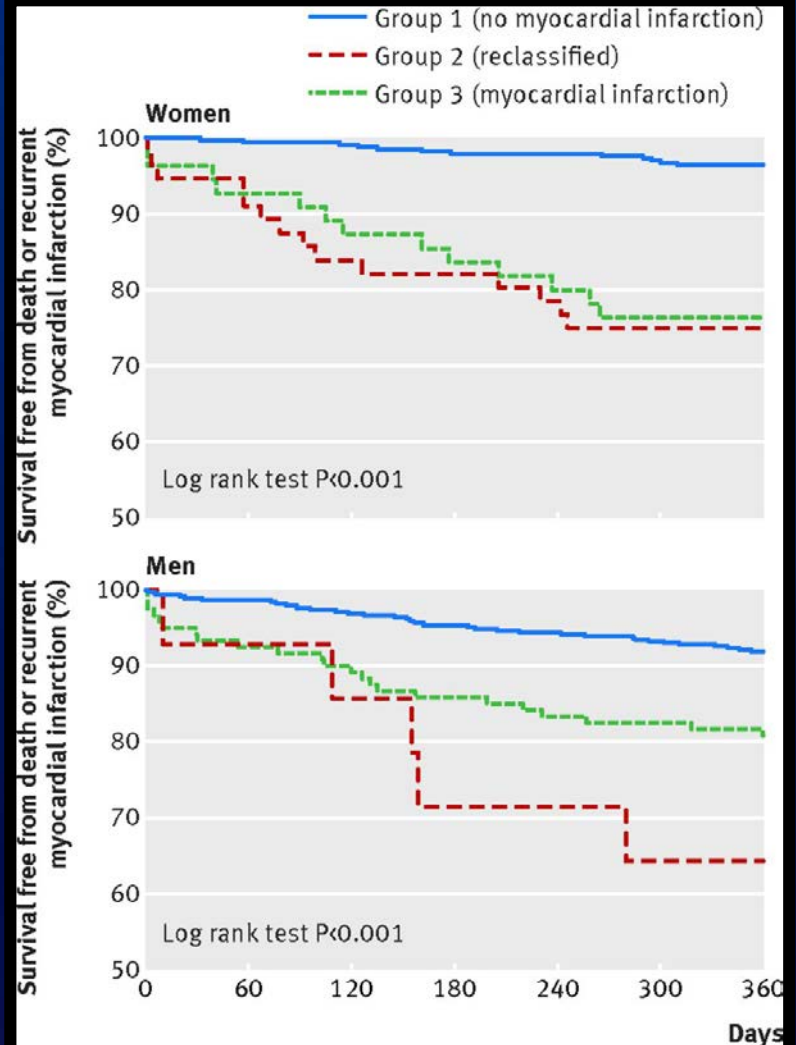
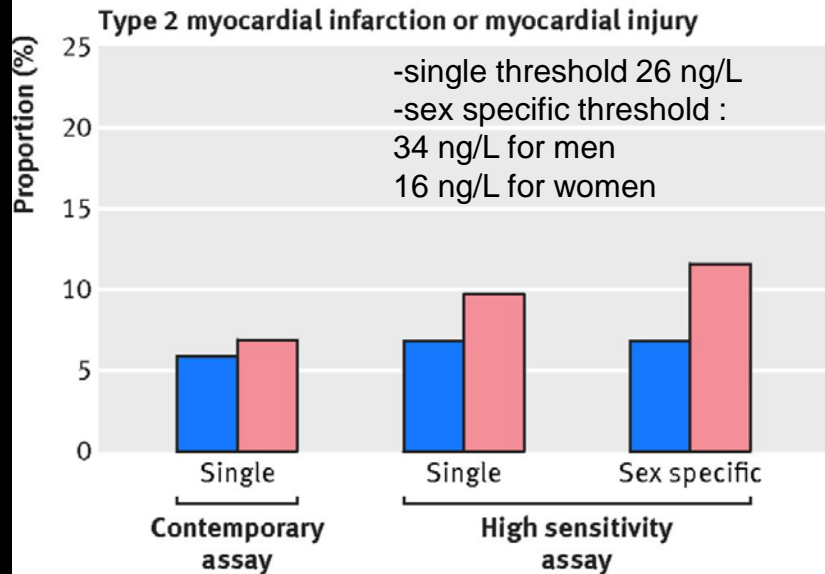
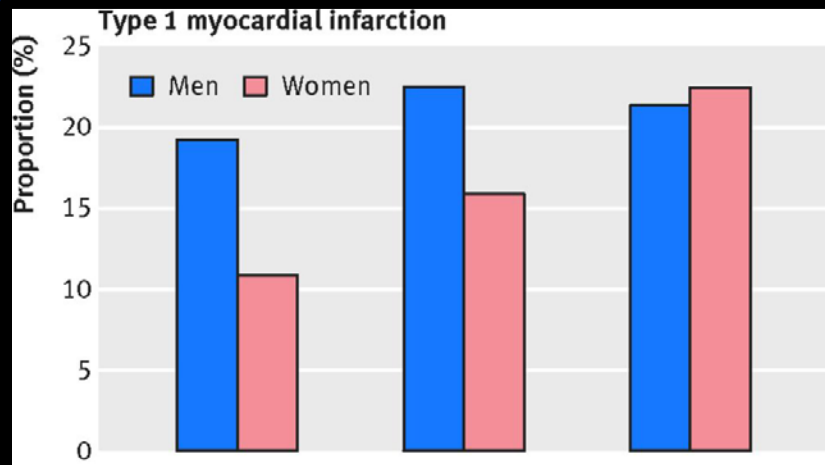
**CONCLUSIONS:** AMI hospitalization rates for young people have not declined over the past decade. Young women with AMIs have more comorbidity, longer LOS, and higher in-hospital mortality than young men, although their mortality rates are decreasing

# Sex differences in ACS pathophysiology

- Biomarkers
- Angiographic findings
- Underlying etiology

# High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study

BMJ 2015 ; 350 doi: <http://dx.doi.org/10.1136/bmj.g7873> (Published 21 January 2015)



single threshold 50 ng/L

Shah AS *BMJ* 2015;350:g7873

# “Inconvenient” Angiographic Truths

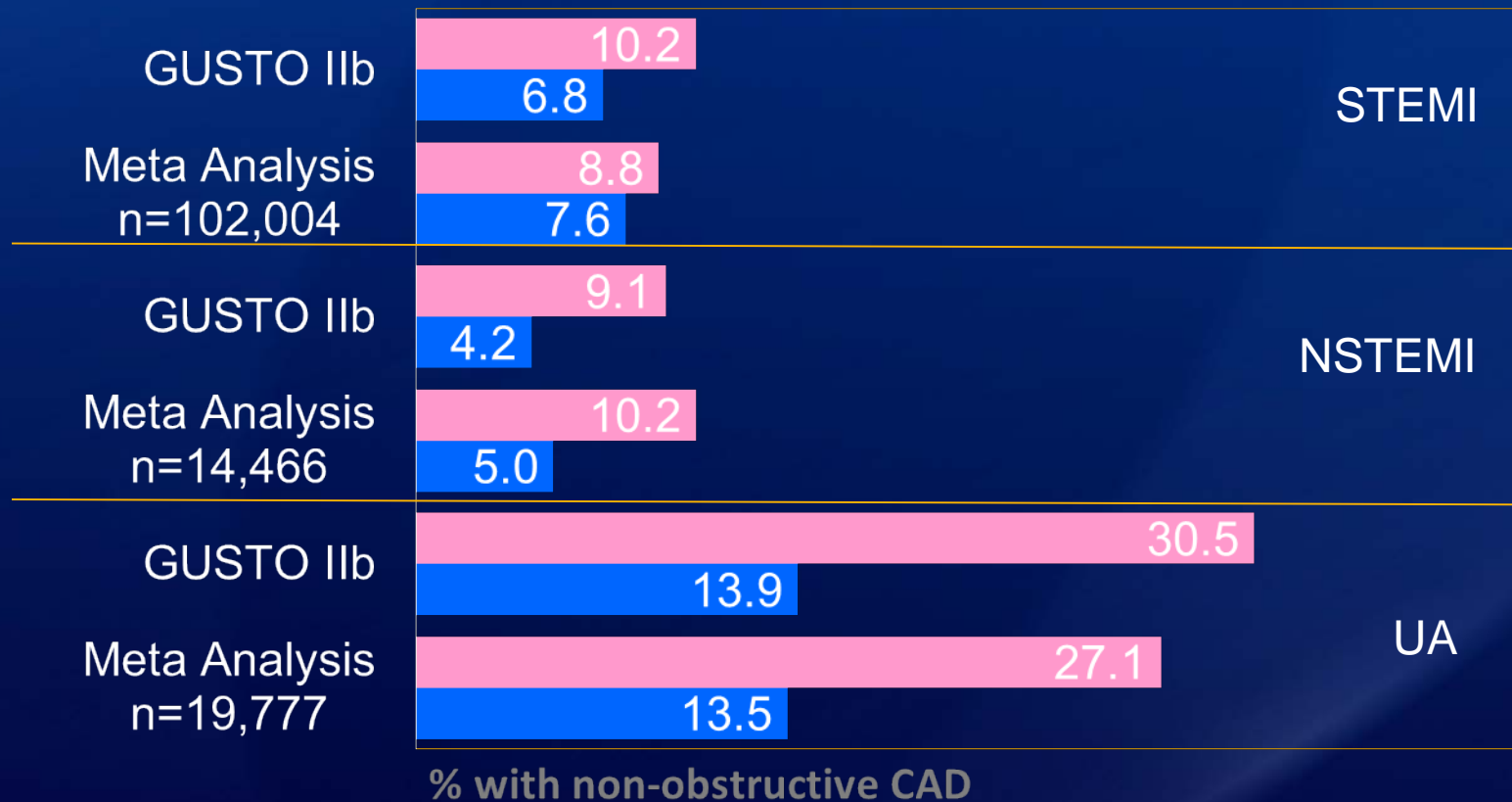
- Men are ~3X more likely to have obstructive CAD
- Women are ~2-3X more likely to have no or non-obstructive CAD

## BUT

- Women *with* chronic persistent angina, and *without* obstructive CAD have a worse prognosis than women with no angina

Patel MR, N Engl J Med 2010; 362:886-895  
(ACC National Cardiovascular Data Registry)  
Johnson BD Eur Heart J. 2006 Jun;27(12):1408-15  
Gulati M, Arch Intern Med 2009; 843–850

# ACS and Non-Obstructive CAD at Cor Arterio: More common in Women



p<0.02 for all comparisons

Hochman JS et al. NEJM 1999

Berger JS et al. JAMA 2009



# How can it be ACS if no significant angiographic stenosis?

- For decades it has been recognized that angiography may identify no “significantly” diseased artery in some patients with MI, and more patients with unstable angina
- “Significant” typically defined as  $\geq 50\%$  --arbitrary
- Uniform terminology: “MINOCA” = MI with Non-Obstructive CAD at Angiography
- Recognized in Third Universal definition of MI

# Coronary Heart Disease

## Systematic Review of Patients Presenting With Suspected Myocardial Infarction and Nonobstructive Coronary Arteries

Sivabaskari Pasupathy, BSc(Hons); Tracy Air, BA (Hons), M.Biostatistics;  
Rachel P. Dreyer, BSc(Hons), PhD; Rosanna Tavella, BSc(Hons), PhD;  
John F. Beltrame, BSc, BMBS, PhD

**Background**—Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a puzzling clinical entity with no previous evaluation of the literature. This systematic review aims to (1) quantify the prevalence, risk factors, and 12-month prognosis in patients with MINOCA, and (2) evaluate potential pathophysiological mechanisms underlying this disorder.

**Methods and Results**—Quantitative assessment of 28 publications using a meta-analytic approach evaluated the prevalence, clinical features, and prognosis of MINOCA. The prevalence of MINOCA was 6% [95% confidence interval, 5%–7%] with a median patient age of 55 years (95% confidence interval, 51–59 years) and 40% women. However, in comparison with those with myocardial infarction associated with obstructive coronary artery disease, the patients with MINOCA were more likely to be younger and female but less likely to have hyperlipidemia, although other cardiovascular risk factors were similar. All-cause mortality at 12 months was lower in MINOCA (4.7%; 95% confidence interval, 2.6%–6.9%) compared with myocardial infarction associated with obstructive coronary artery disease (6.7%, 95% confidence interval, 4.3%–9.0%). Qualitative assessment of 46 publications evaluating the underlying pathophysiology responsible for MINOCA revealed the presence of a typical myocardial infarct on cardiac magnetic resonance imaging in only 24% of patients, with myocarditis occurring in 33% and no significant abnormality in 26%. Coronary artery spasm was inducible in 27% of MINOCA patients, and thrombophilia disorders were detected in 14%.

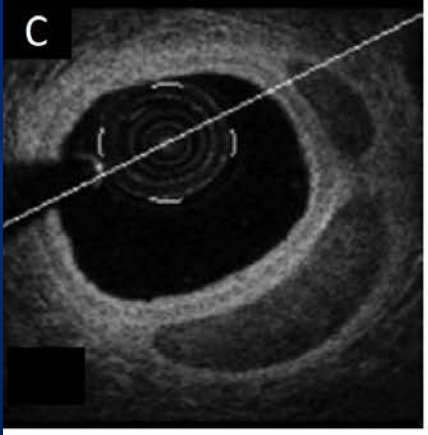
**Conclusions**—MINOCA should be considered as a working diagnosis with multiple potential causes that require evaluation so that directed therapies may improve its guarded prognosis. (*Circulation*. 2015;131:861-870. DOI: 10.1161/CIRCULATIONAHA.114.011201.)

# What do women with MI and No Obstructive Coronary Artery (MINOCA) disease have?

- Non-obstructive CAD, *plaque rupture/erosion*
- Coronary vasospasm (Syndrome X)
- Microvascular disease/ Endothelial dysfunction
- Supply/demand Mismatch (imbalance)
- Stress-induced cardiomyopathy (Takotsubo)
- Spontaneous coronary artery dissection (SCAD)
- Intracoronary thromboembolism
- myocarditis

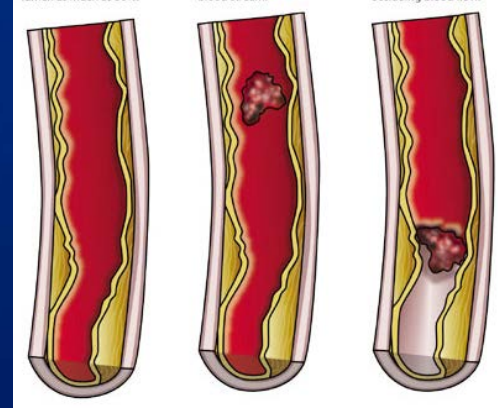
# ACS & Sex Differences

## Dissection (SCAD)



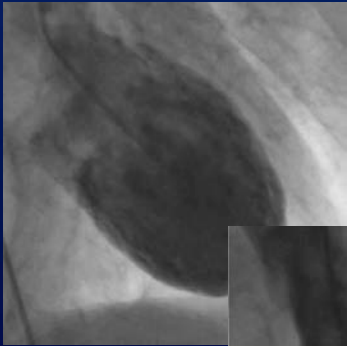
*More common in younger women*

## Embolism



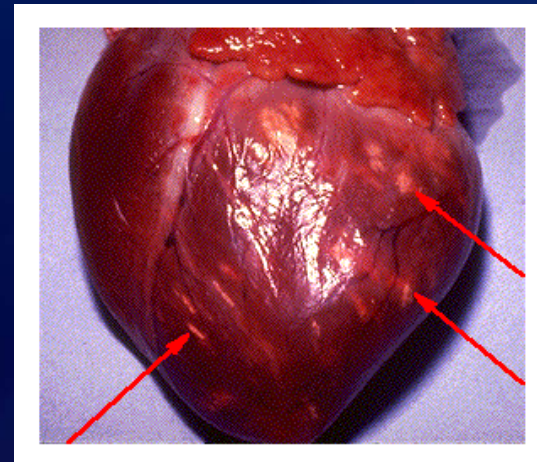
*Can be missed – look carefully*

## Takotsubo cardiomyopathy (ABS/Stress CM)



*More common in older women; 1.2% of all ACS*

## Myocarditis



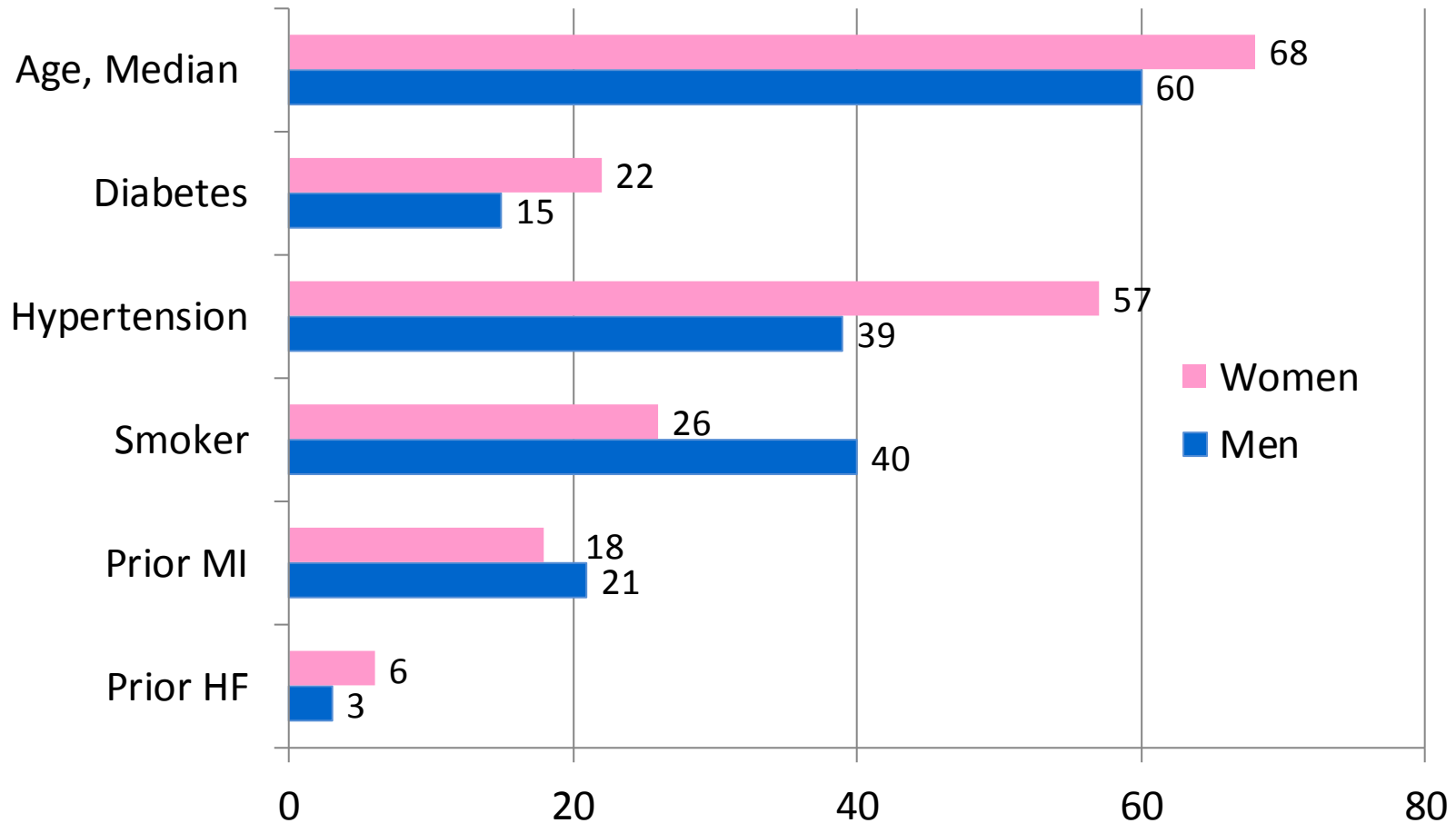
*More common in men*

# Sex differences in ACS: Prognosis

*Are women at higher risk for adverse outcomes after ACS?*



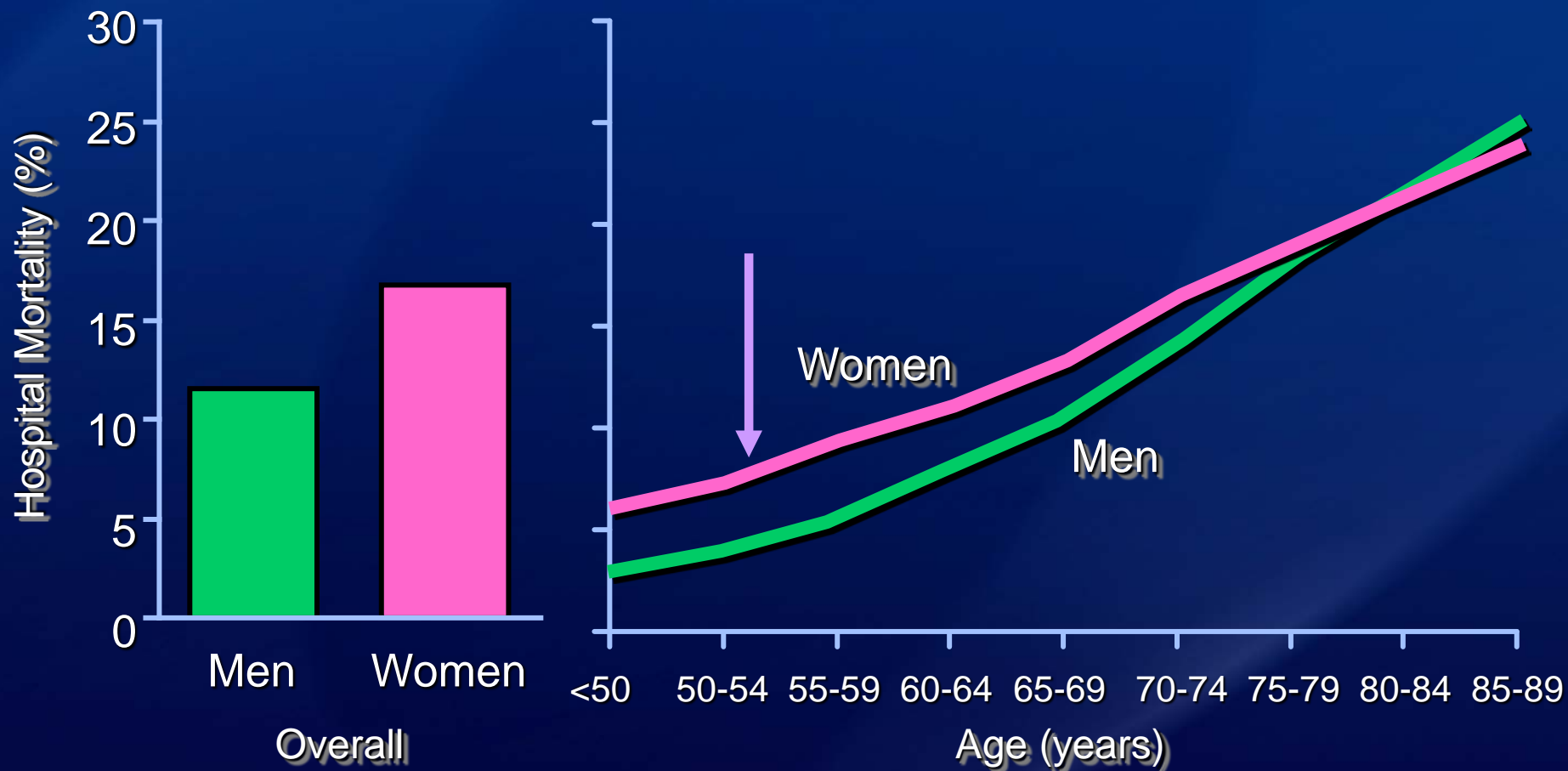
# Older Age and Greater Burden of Risk Factors Place Women at Higher Risk



**Data pooled from 11 randomized ACS trials  
N=136,247**

Berger JS et al. JAMA 2009;302:874-882

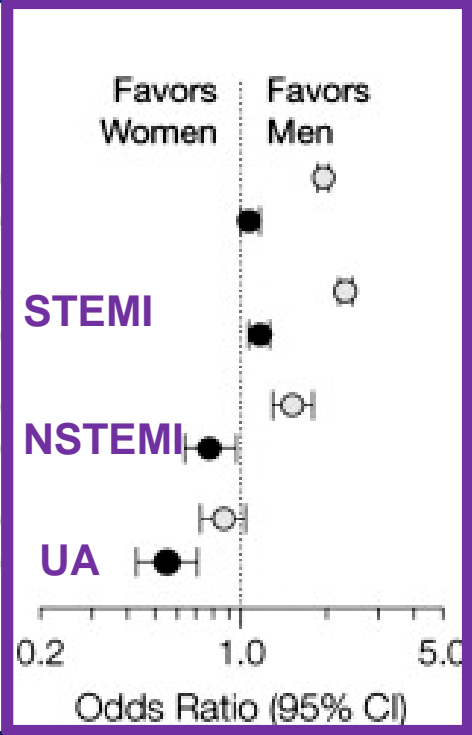
# Sex and Myocardial Infarction (MI) Mortality: Largest Gaps in Young Women



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

# Are women at higher risk for adverse outcomes after ACS?

	Sample Size, No.		30-d Mortality, No. (%)		Odds Ratio (95% CI)
	Women	Men	Women	Men	
All ACS	37 904	97 768	3654 (9.6)	5166 (5.3)	Unadjusted 1.91 (1.83-2.00) Adjusted 1.06 (0.99-1.15)
STEMI	25903	75577	3198 (12.3)	4385 (5.8)	Unadjusted 2.29 (2.18-2.40) Adjusted 1.15 (1.06-1.24)
NSTEMI	4156	10297	265 (6.4)	447 (4.3)	Unadjusted 1.50 (1.28-1.75) Adjusted 0.77 (0.63-0.95)
Unstable angina	7845	11 894	191 (2.4)	334 (2.8)	Unadjusted 0.86 (0.72-1.03) Adjusted 0.55 (0.43-0.70)



Women *are* at higher risk of early death after ACS, if a STEMI  
 After adjustment for comorbidities, women with STEMI remain at higher risk of death, but women with NSTEMI are at *lower* risk

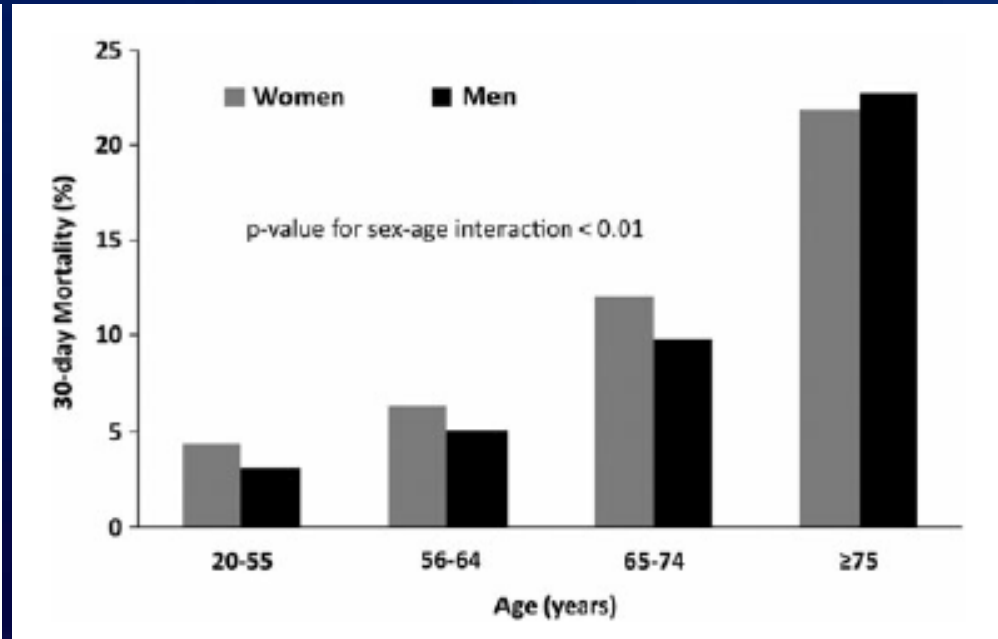
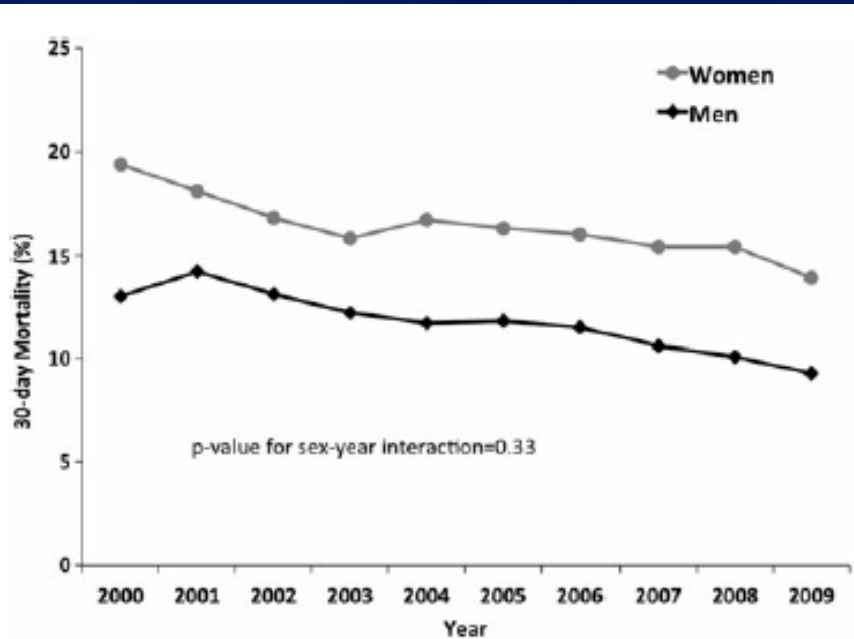


# Do Younger Women Fare Worse? Sex Differences in Acute Myocardial Infarction Hospitalization and Early Mortality Rates Over Ten Years

JOURNAL OF WOMEN'S HEALTH  
Volume 23, Number 1, 2014

Mona Izadnegahdar, PhD,<sup>1,2</sup> Joel Singer, PhD,<sup>1</sup> May K. Lee, MSc,<sup>2</sup> Min Gao, PhD,<sup>1,2</sup>  
Christopher R. Thompson, MD,<sup>3</sup> Jacek Kopec, MD, PhD,<sup>1</sup> and Karin H. Humphries, DSc<sup>2,3</sup>

-70,628 AMI hospitalizations in adults aged >20 years, in British Columbia, Canada  
-contemporary, sex-specific, population-based data



# Sex differences in ACS: Treatment

# Rx Recommendations for ACS In Women

2014 ACC/AHA guidelines for the management of pts with NSTEMI and STEMI:

**women should be treated similarly to men**

***But are they?***

# ACS-NSTEMI : Treatment for Women

- 35,835 pts with NSTEMI: 41% women
- Women with NSTEMI tend to be older than men and have more comorbidities
- Women had:
  - ↑ DM, HTN, age; ↓ CAD events
  - ↓ Early ASA, heparin, GPIIb-IIIa, ACE-I
  - ↓ Catheterization: 42% vs 49% in men
  - ↓ Revascularizations: PCI- ( 44% vs 52% in men)
  - ↓ Discharge ASA, beta blocker, ACE-I, statins (Four Magic Pills)\*
  - ↑ Death, MI, CHF ( after adjustment, rates were similar to men)

\* **Associated with a 90% reduction in recurrent major adverse cardiac events**

# Coronary Heart Disease

## Sex Differences in Reperfusion in Young Patients With ST-Segment–Elevation Myocardial Infarction

### Results From the VIRGO Study

Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients

Gail D'Onofrio, MD; Basmah Safdar, MD; Judith H. Lichtman, PhD; Kelly M. Strait, MS; Rachel P. Dreyer, PhD; Mary Geda, MSN; John A. Spertus, MD; Harlan M. Krumholz, MD

- 1238 pts (age:18 to 55, 695 women) w/ STEMI
- Women (vs. men) were:
  - less likely to receive reperfusion (4% vs 9%)
  - More likely to exceed door-to-needle time (67% vs. 37%)
- sex was an important factor in exceeding reperfusion guidelines - odds ratio 1.72 (95% CI 1.28–2.33)

# THE LANCET

## Safety and efficacy of drug-eluting stents in women: a pooled analysis of randomised trials

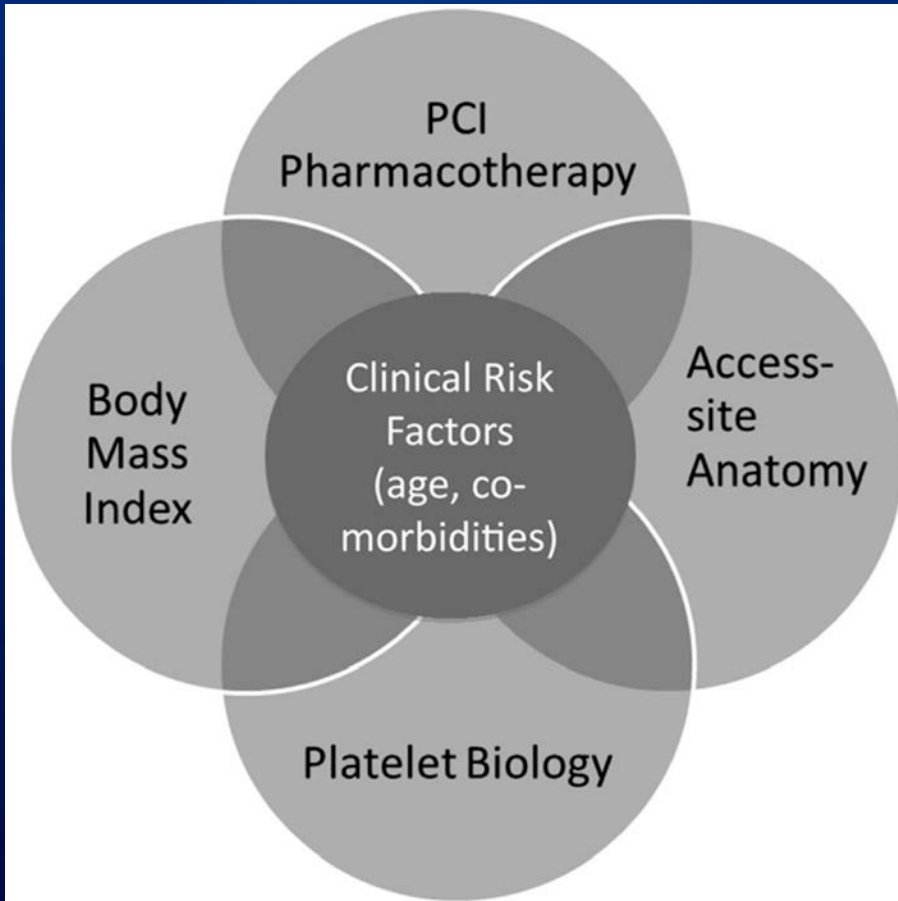
*Giulio G Stefanini\*, Usman Baber\*, Stephan Windecker, Marie-Claude Morice, Samantha Sartori, Martin B Leon, Gregg W Stone, Patrick W Serruys, William Wijns, Giora Weisz, Edoardo Camenzind, Philippe G Steg, Peter Smits, David Kandzari, Clemens Von Birgelen, Søren Galatius, Raban Jeger, Takeshi Kimura, Ghada Mikhail, Dipti Itchhaporia, Laxmi Mehta, Rebecca Ortega, Hyo-Soo Kim, Marco Valgimigli, Adnan Kastrati, Alaide Chieffo, Roxana Mehran*

-26 Randomized Trials , global  
-11,557 Women (~25%); 3 yr f/u  
-~45% ACS

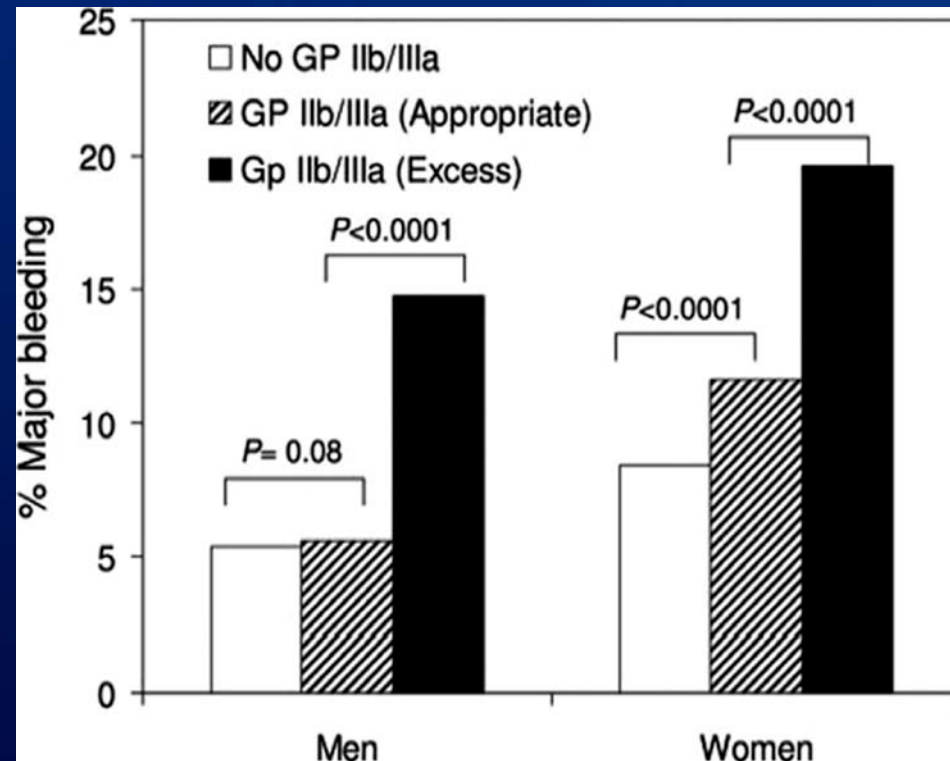
- The **use of DES in women is safe and effective** compared with BMS during long-term follow-up
- **Newer-generation DES** are associated with an **improved safety profile** compared with early-generation DES in women

# The female predisposition to bleeding

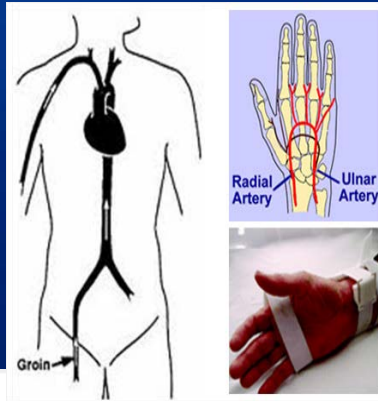
Women have more bleeding than men  
-Anti-plt agents typically not dosed based on body wt  
-Avoid Effient if you are less than <60kg)



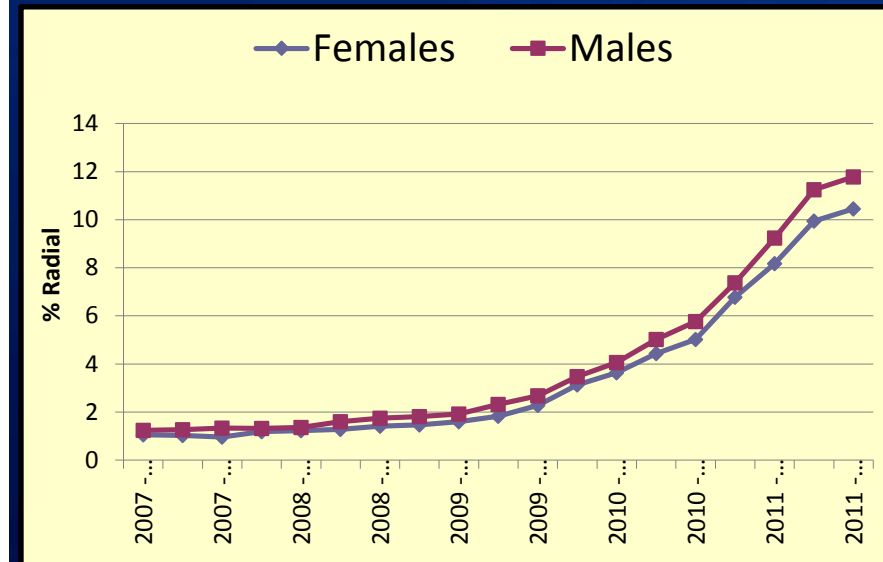
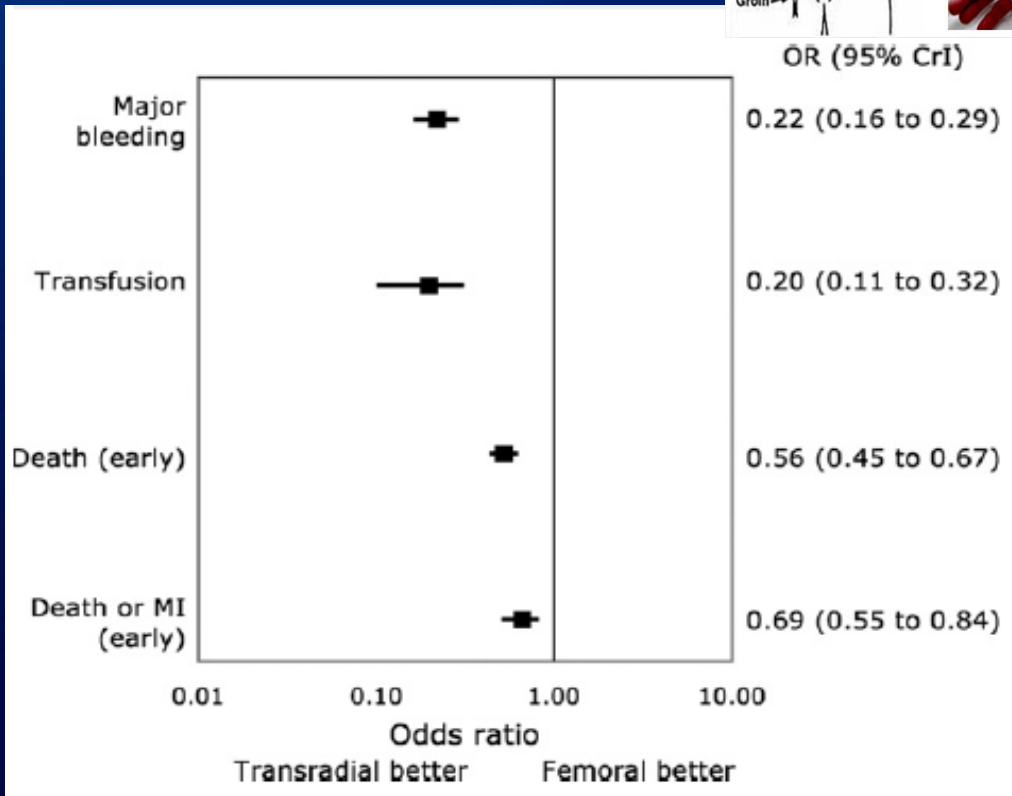
## Glycoprotein (GP) inhibitor (GPI) therapy and bleeding



# Is the Answer: A Radial Approach?



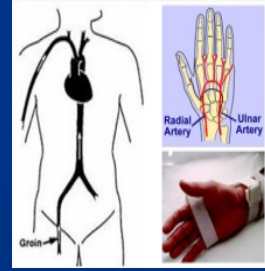
Radial approach in men vs. women  
From the NCDR CathPCI Registry®



Bertrand OF, et. al. *AHJ* 2012  
Feldman DN, et. al. *Circ* 2013



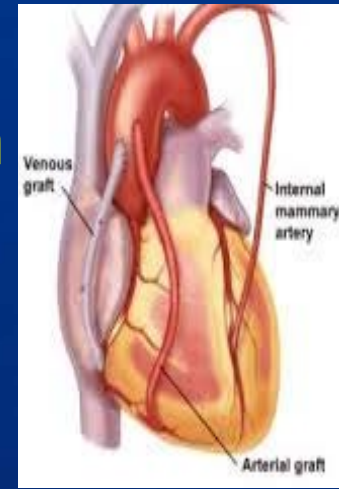
# Study of Access site For Enhancement of PCI for Women (SAFE-PCI for Women) Trial



- **First RCT comparing interventional strategies in women**
  - **To determine efficacy/feasibility of transradial PCI in women**
  - 1,787 women (691 undergoing PCI) were randomized at 60 sites
  - radial access significantly reduced bleeding & vascular complications (0.6% vs. 1.7%; OR: 0.32; 95% CI: 0.12 to 0.90)
- **Conclusions**
  - **Radial preferred** over femoral approach by majority of women undergoing PCI
  - conversion to femoral access in ~6% of cases
  - The SAFE-PCI for Women trial suggests an initial strategy of radial access is reasonable
  - May be preferred by some operators for women undergoing cardiac catheterization or PCI

Rao S et al JACC Cardiovasc Interv 2014;7:857-67

# Invasive Procedures & Women



- even after adjustment for baseline differences, have different pattern of access to revascularization
- **With risk adjustment, women are *nearly as likely* as men to undergo coronary angioplasty or stenting but women are *less likely to undergo CABG***
- Unclear if this represents bias or appropriate medical therapy given higher mortality following CABG in women

# Improving the inclusion of sex and gender in *CV Research*

- Clarify terms (sex, gender)
- Increase research in women (funding)
- Monitor compliance for female participation
- Require sex-specific analysis and reporting
- EDUCATION (med school onwards)
- WOMEN'S HEART CENTERS OF EXCELLENCE

Pilote L, Humphries KH; and Arthur H. 2014: Canadian J Cardiology

# Summary: ACS, Sex and Gender

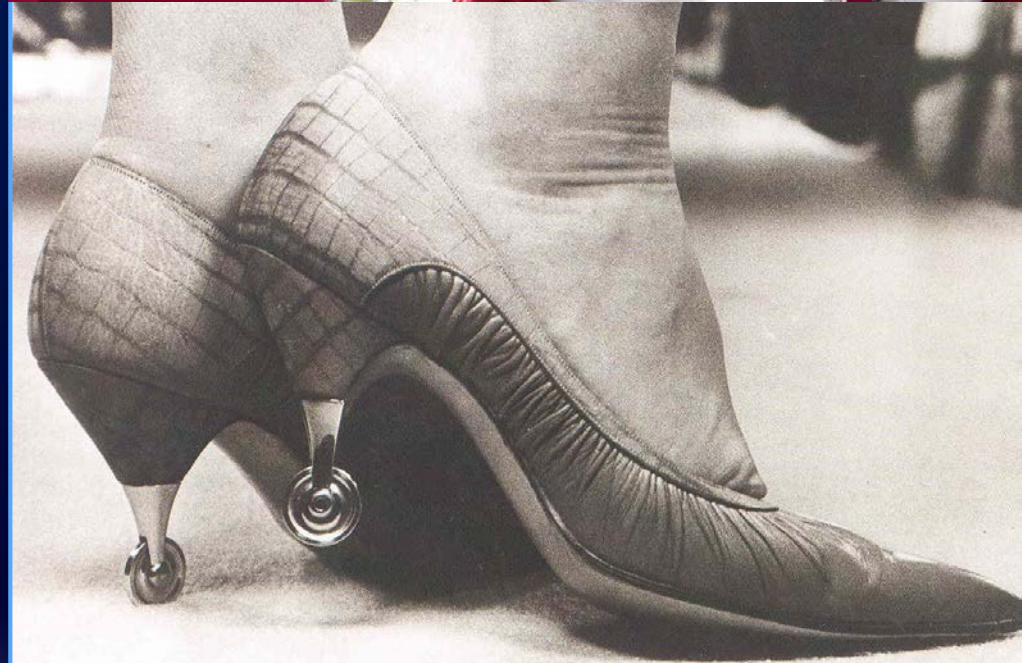


- Diagnosis of ACS in women can be challenging: ....both sex & age matter!
- ACS affects both women & men, but symptomatic presentations, biomarkers, and underlying etiologies may differ
- Women are less likely to have chest pain, and less likely to have Class I MI (think about less common causes...MINOCA)
- Women have greater mortality after MI
- NSTEMI/STEMI Rx- same for both sexes; **both** need to be Rx'd
- Radial approach for cor angio/PCI may be preferred in women
- Impact of hs-troponin (assay, sex-specific thresholds) on outcomes?
- Additional research is needed to better understand sex-based differences in ACS pathophysiology, and develop optimal diagnosis and treatment strategies

## **In Summary**

***Major differences exist in the diagnosis, management, and outcomes of men and women with acute coronary syndromes***

**We need to acknowledge this,  
and ACT!**



# Thank You

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[@HeartDocSharon](https://twitter.com/HeartDocSharon)