

Ischemic Heart Disease in Women

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Disclosures

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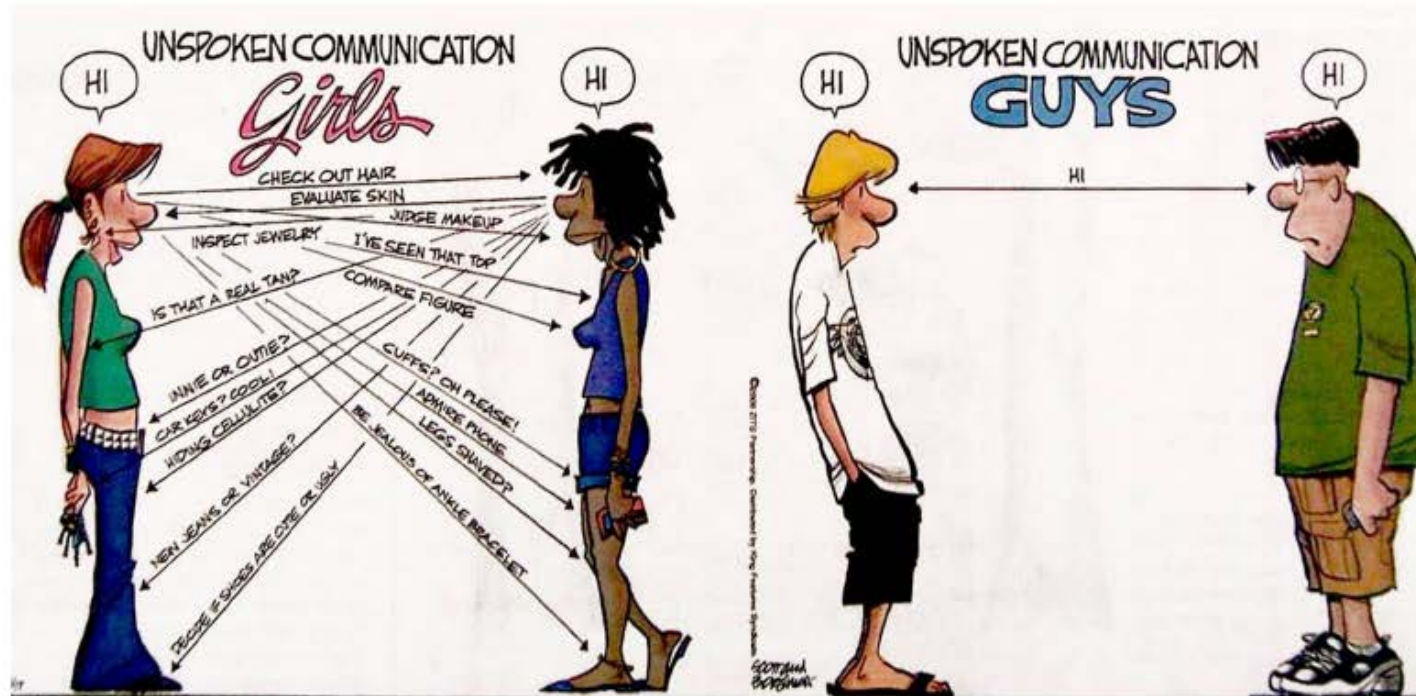
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<u>Presenter</u>	<u>Disclosure</u>
Cindy Grines MD	Advisory boards Abiomed and Philips

Women are very different than men

- ◆ **Different cardiovascular risks and benefits**
- ◆ **Different mechanisms of angina and AMI**
- ◆ **Different drug pharmacokinetics**
- ◆ **More side effects to medications**
- ◆ **More bleeding complications**
- ◆ **Diagnosis often missed until advanced disease**
- ◆ **Less likely to receive guidelines based therapy**
- ◆ **Worse outcomes**

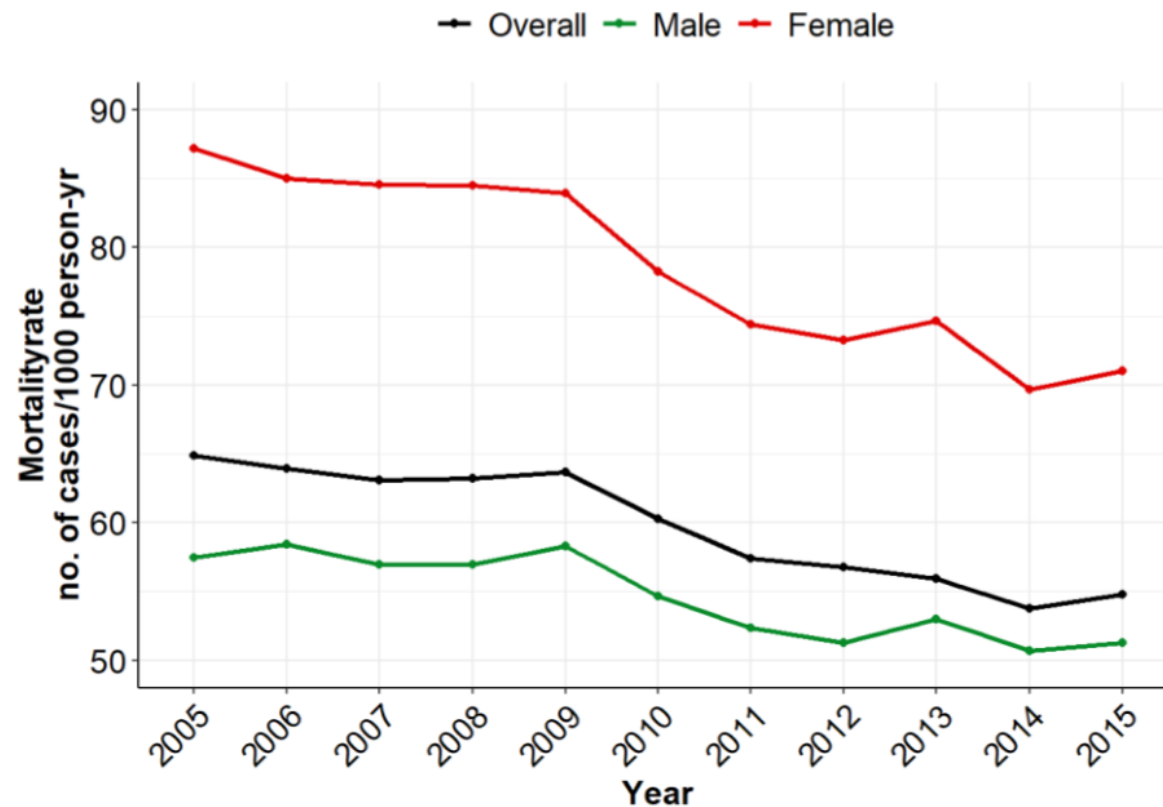
ACS in Women: More to Think About



Less common ACS etiologies preferentially affect women

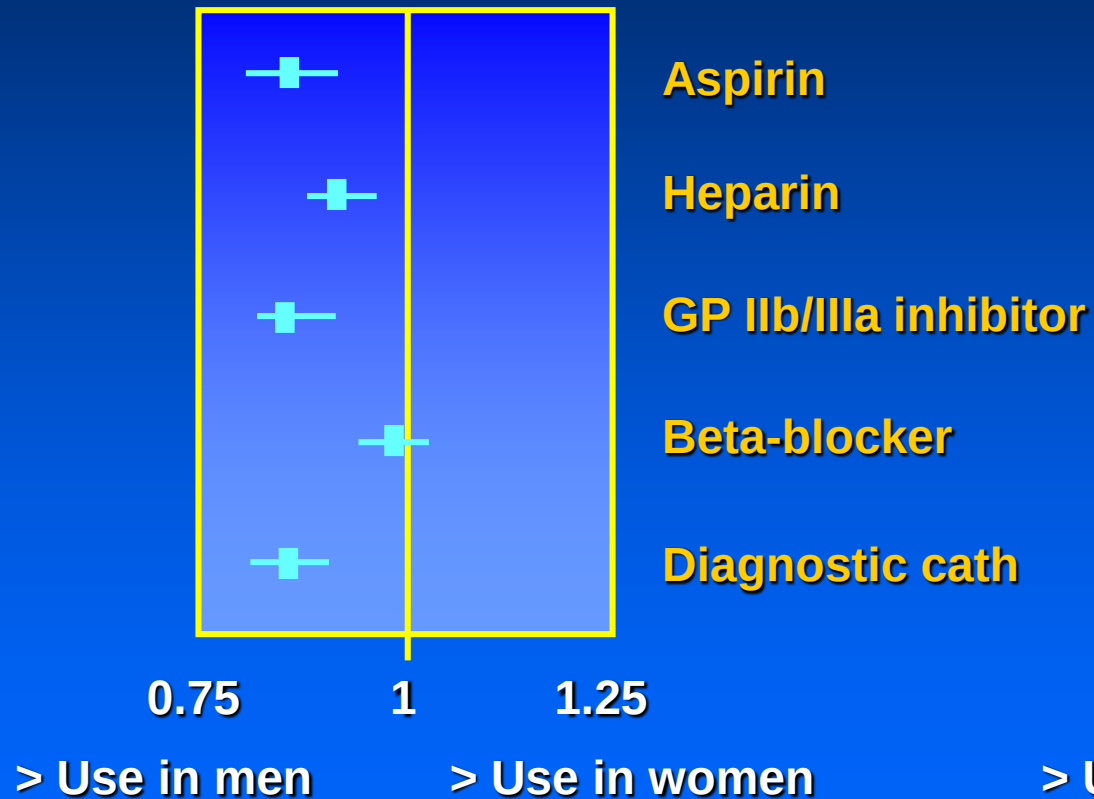
German ACS Registry: Higher Mortality in Women

Adjusted incidence rates of in-hospital mortality cases per 1,000 person-years ranging from 2005 to 2015.

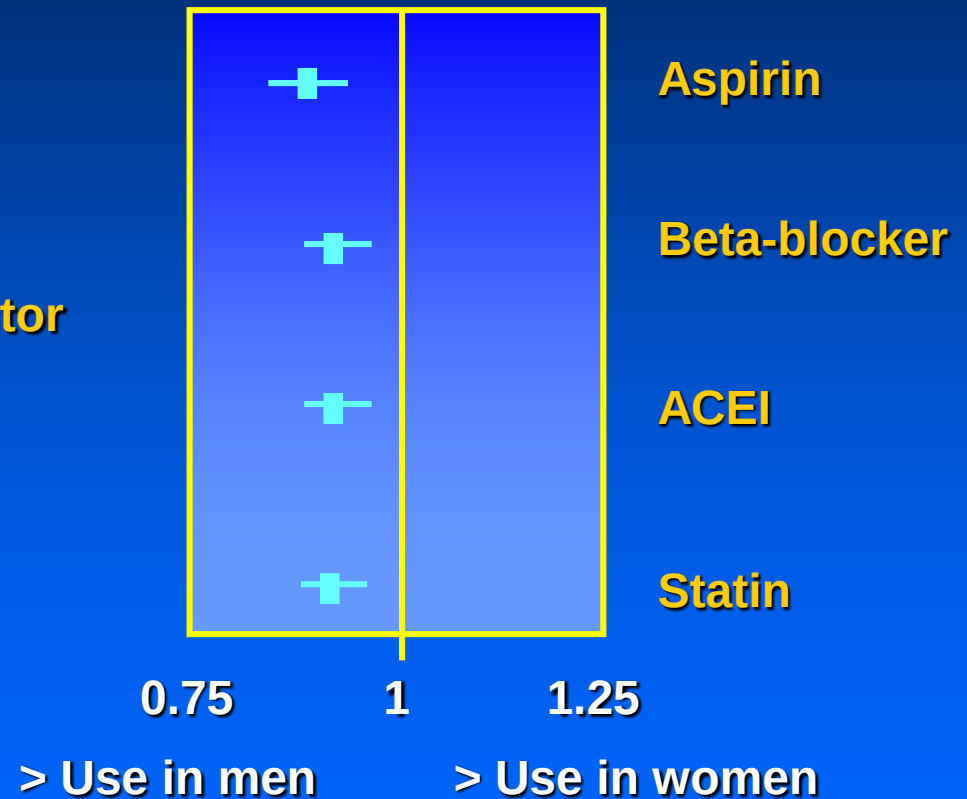


Use of Recommended Rx Among Women vs Men with Acute Coronary Syndrome

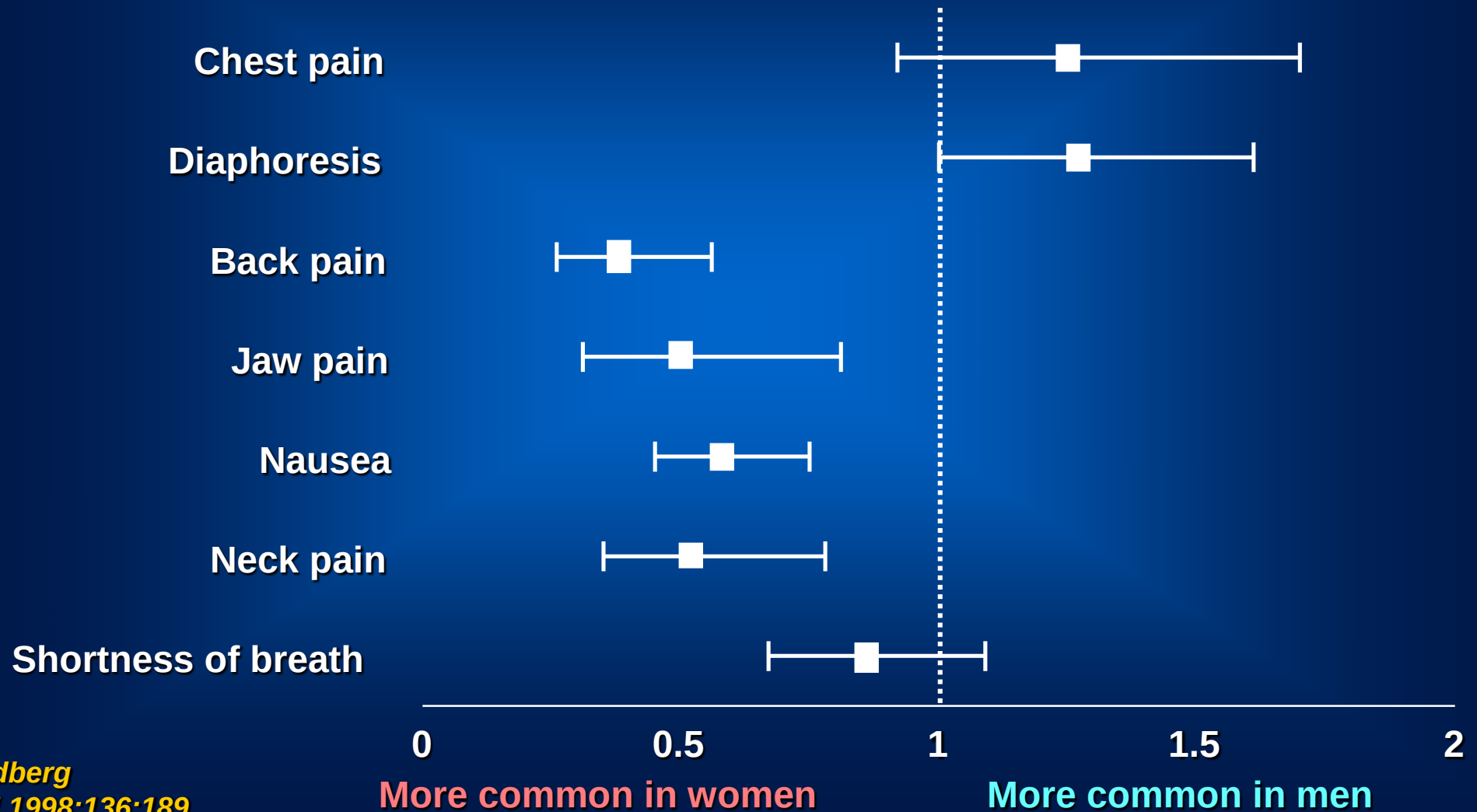
Acute Therapy



Discharge Therapy



Differences in Symptom Presentation Associated with AMI in Men Compared with Women

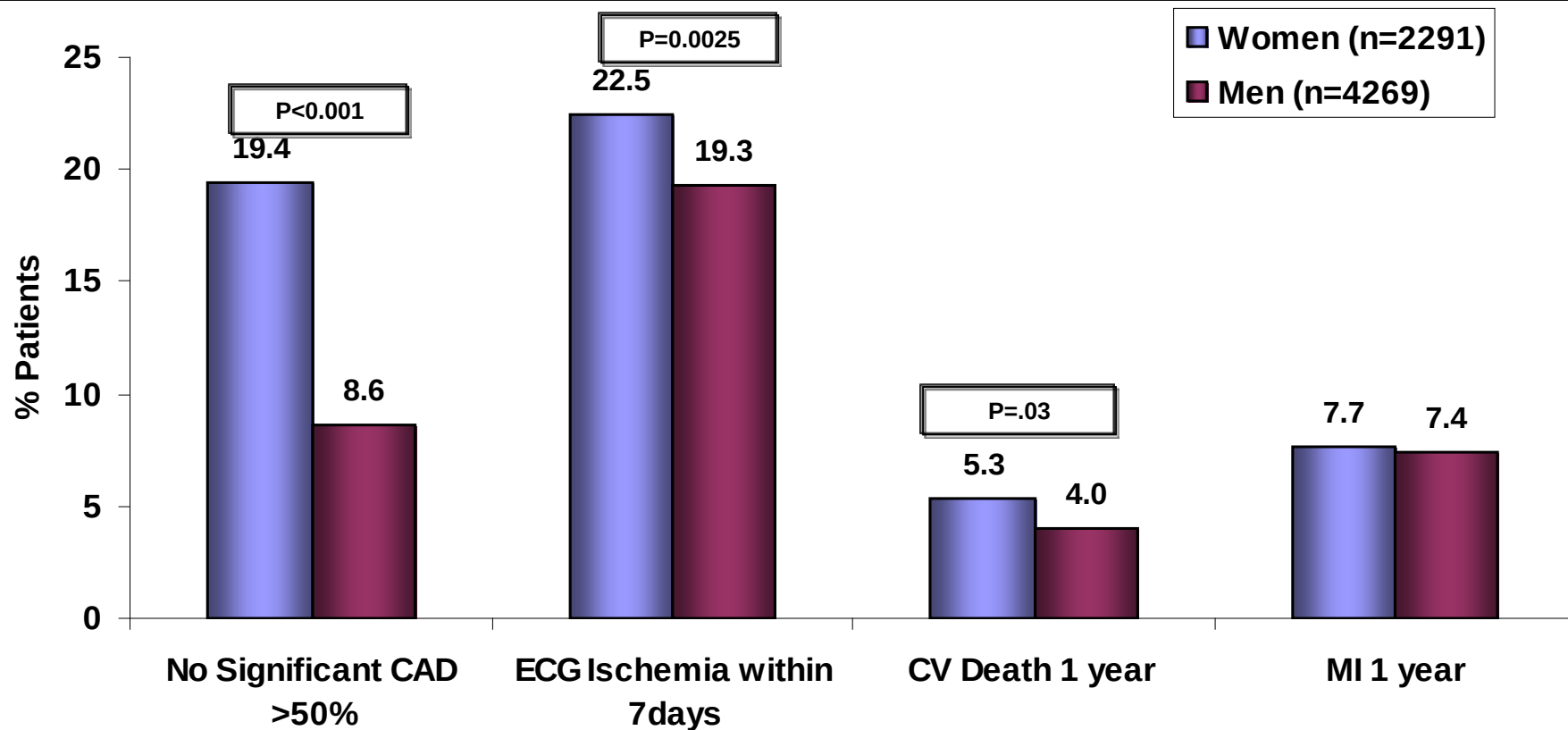


Absence of Chest Pain is associated with Increased Mortality in Women with AMI

Hospital Mortality

Age, y	Men with Chest Pain (%)	Women with Chest pain (%)	Women without Chest pain (%)
<45 (n= 66 540)	1.3	2.0	15.3
45 - 54 (n= 132,777)	1.7	2.7	14.5
55 - 64 (n= 201,019)	3.3	4.7	16.8
65 - 74 (n= 267,480)	6.9	8.6	19.3
≥ 75 (n= 475,697)	13.7	15.2	21.8
Adjusted OR (95% CI)			
<45		1.26 (1.16 - 1.49)	5.51 (4.63 - 6.56)
45 - 54		1.33 (1.20 - 1.47)	4.37 (3.92 - 4.87)
55 - 64		1.26 (1.18 - 1.34)	3.22 (3.02 - 3.44)
65 - 74		1.13 (1.09 - 1.18)	2.23 (2.14 - 2.32)
≥ 75		0.99 (0.97 - 1.02)	1.43 (1.39 - 1.46)

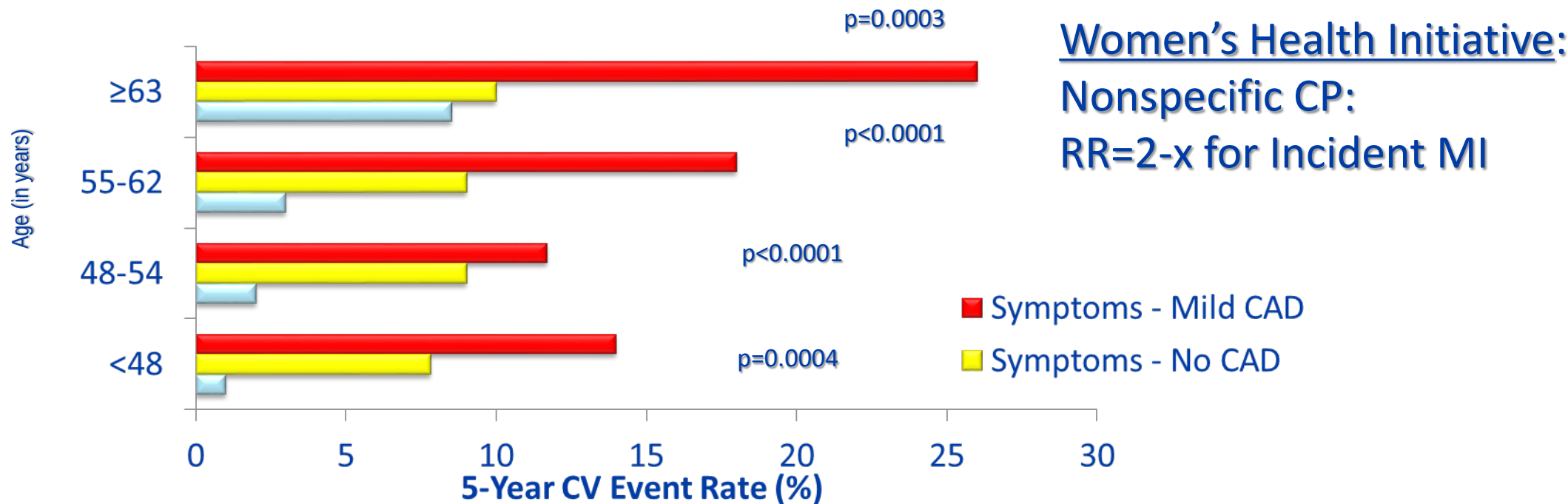
Despite Less Critical CAD in Women with ACS, more Ischemia and Worse Prognosis: TIMI-36 (MERLIN) Study



Ischemia on monitor doubled the 1 year risk of CV death (9.6 vs 4.1%, P<.001) or MI 10.0% vs 6.81% P=.02

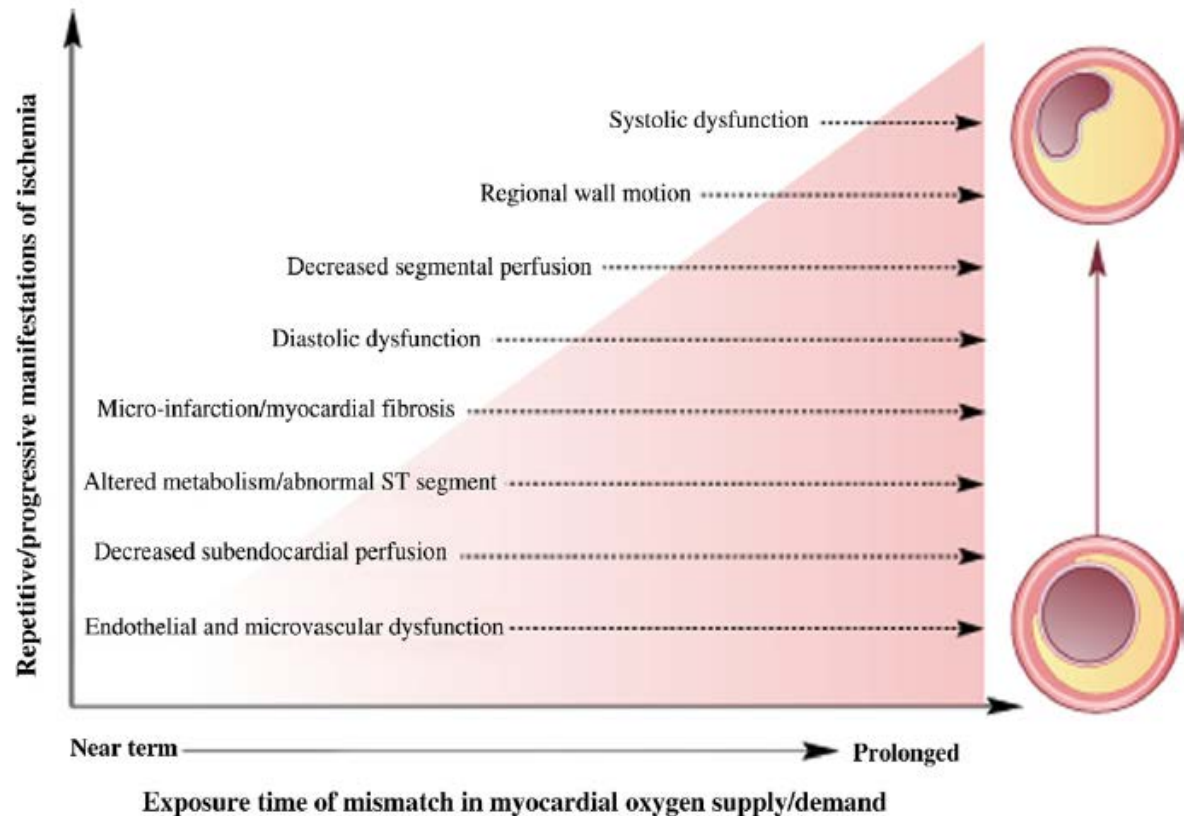
NIH-NHLBI WISE Study:

Symptoms in Women are NOT Benign (Even Atypical Sx, Mild or No CAD)



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**

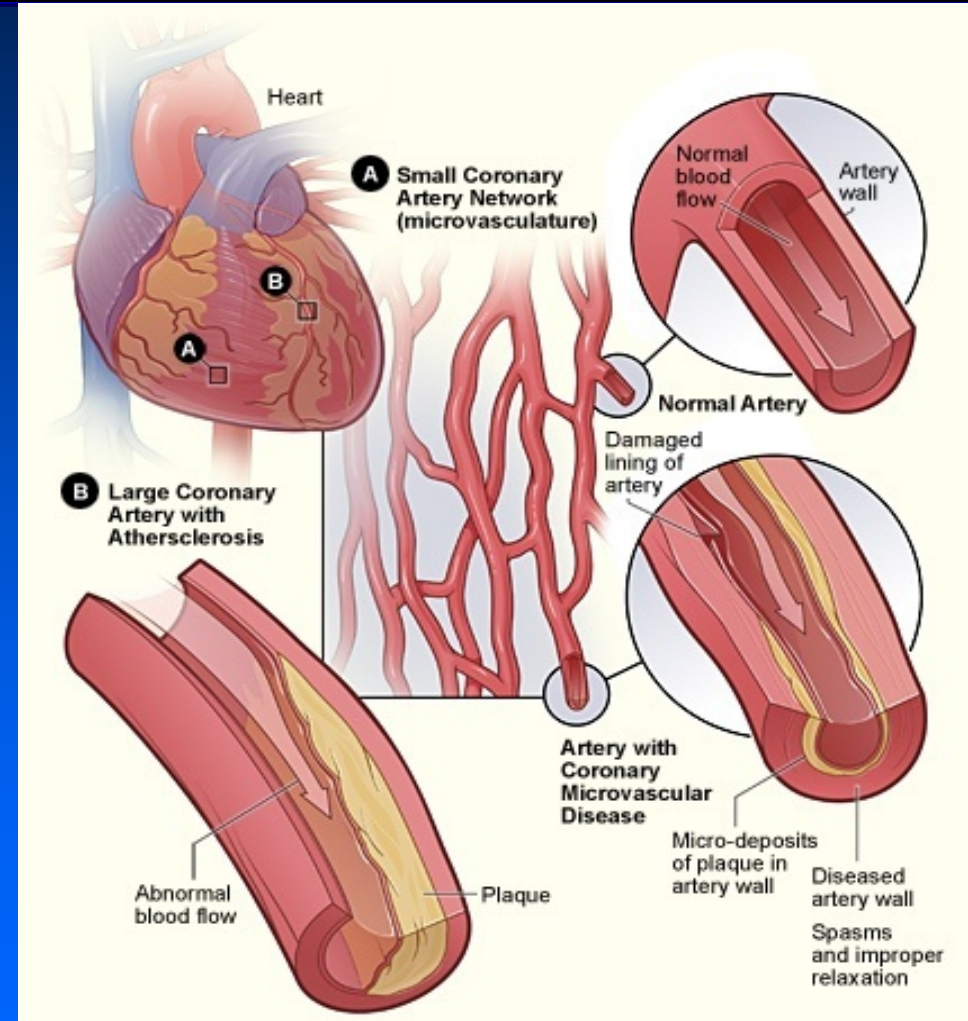


Source: Shaw, L. J.; et al J Am Coll Cardiol (2009) 54:1561-1575

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

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 US



Potential 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

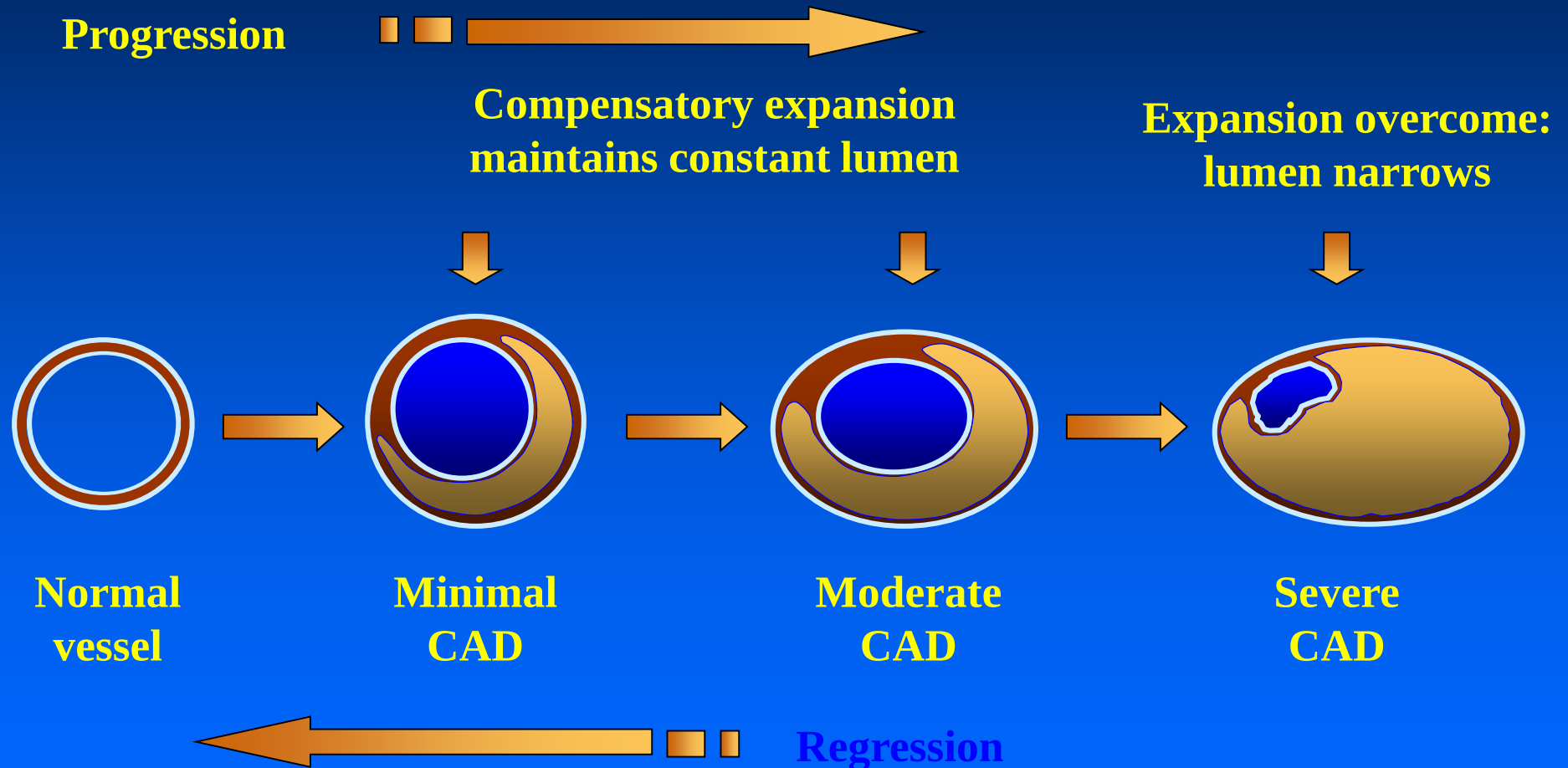
- Lipid-lowering effects
- Improve endothelial function
- Improve CFR and exercise tolerance
- Reduce angina

Low dose aspirin

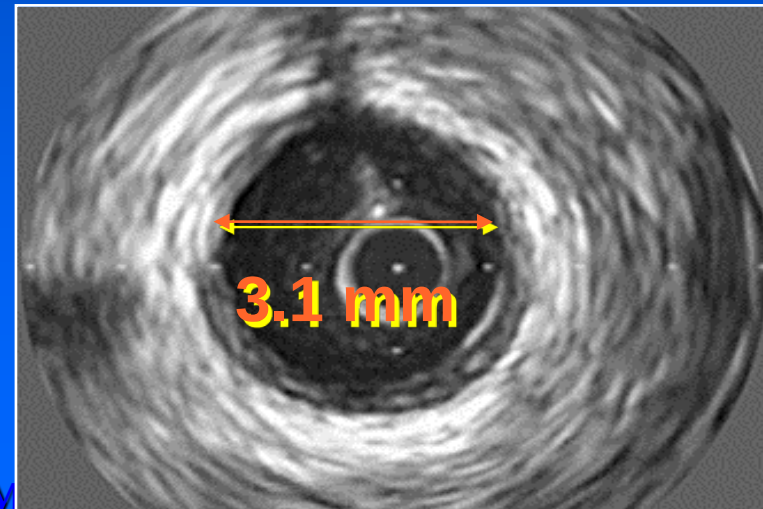
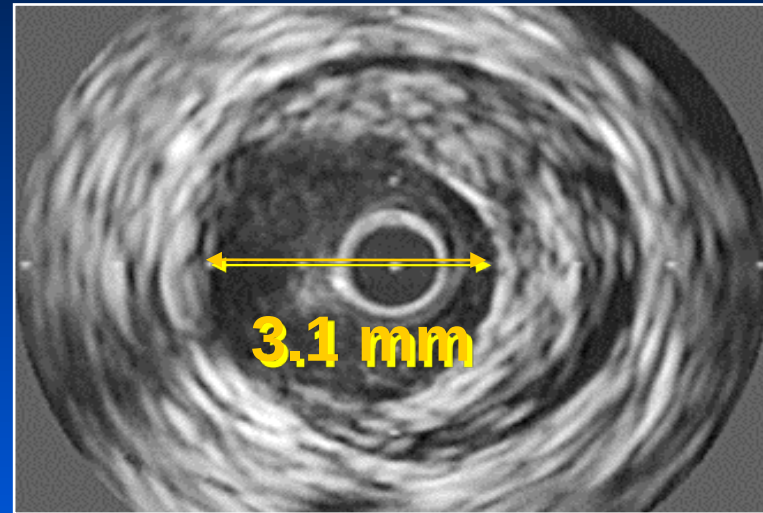
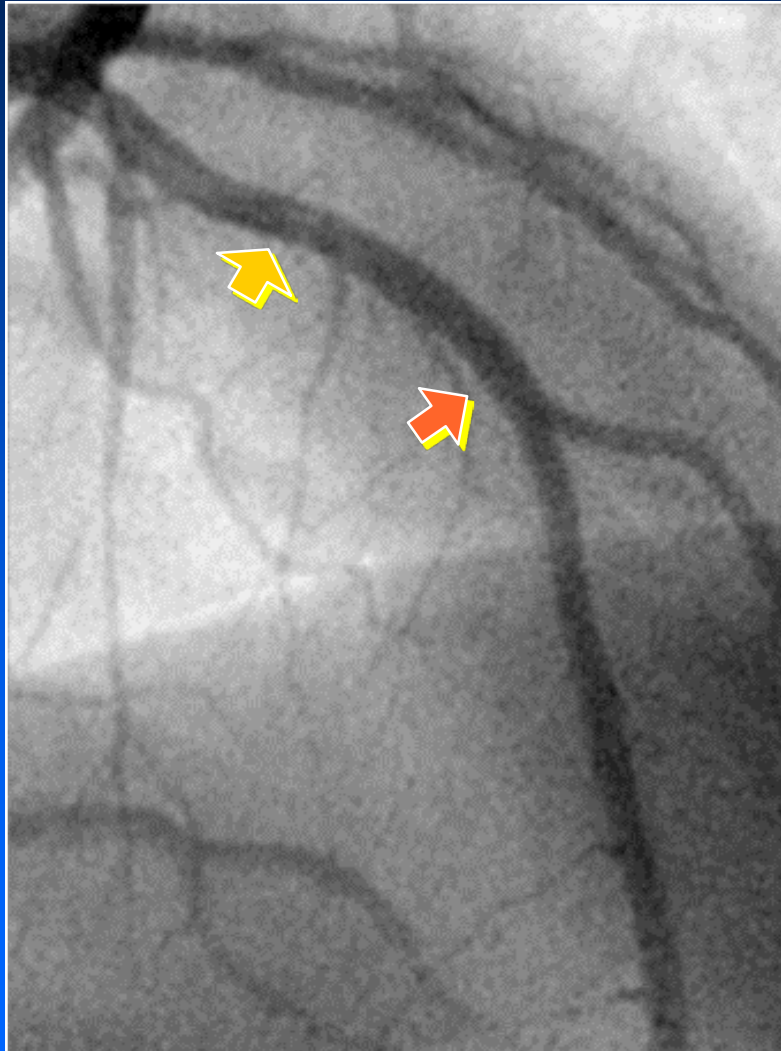
- Secondary prevention of cardiovascular events

Atherosclerosis is a Diffuse Process





Angiography Fails to Depict Coronary Arterial Remodeling



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Implementation

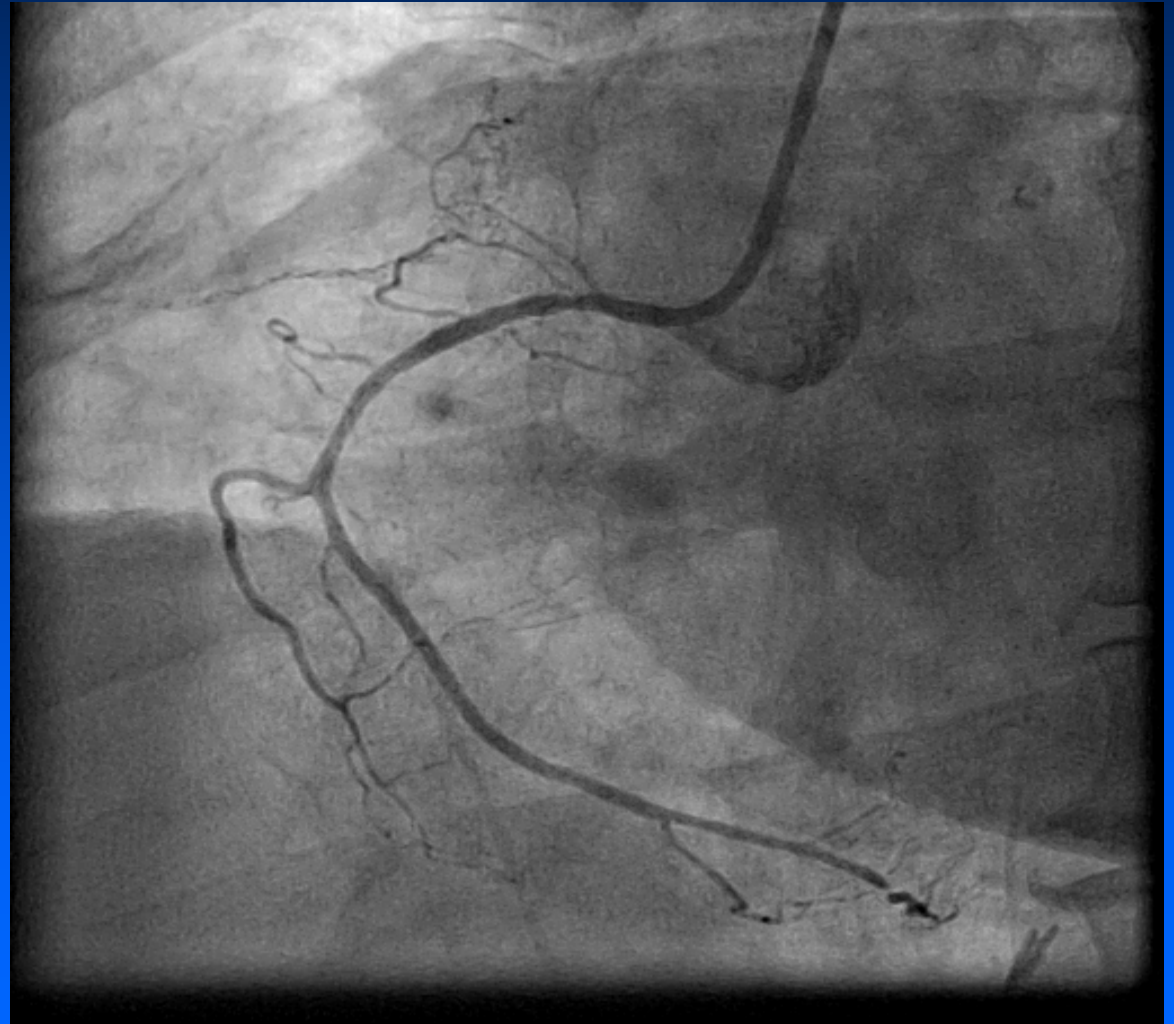
Cardiac Cath may miss Diffuse Atherosclerosis

- ◆ 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

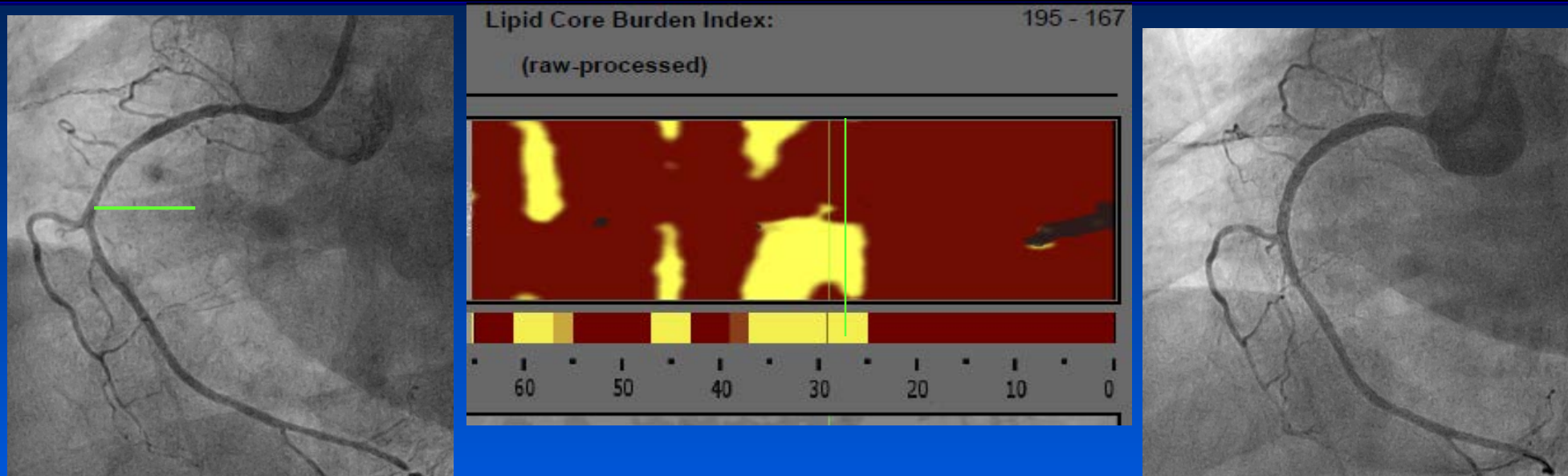
Right Coronary Artery “Small”

51 year old female, History of obesity, HTN, Hyperlipidemia

Angina, abnormal stress test (inferior distribution)



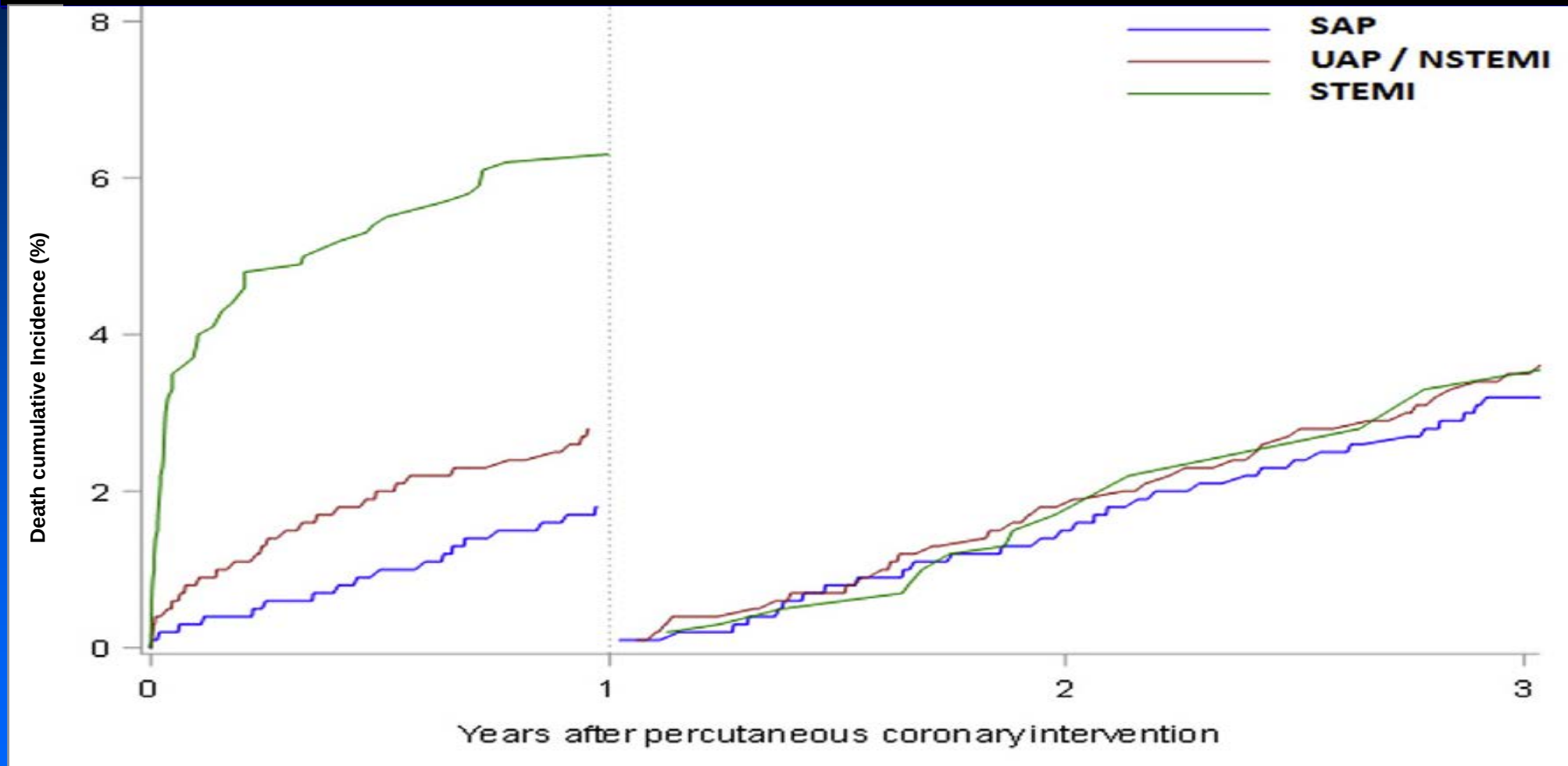
RCA Imaging



- ◆ RCA Angio – “Small” vessel, mild diffuse disease
- ◆ IVUS Large amount of plaque prox and mid, 70% stenosis
- ◆ NIR imaging: Huge amount of soft lipid
- ◆ Drug Eluting Stents 3.0x15mm and 2.5x28mm with resolution of chest pain

Use of Percutaneous Coronary Intervention (PCI) in Women with Significant Coronary Disease

DES in 10,133 Women Enrolled in Randomized Stent Trials: Mortality Based on Presenting Symptoms



SAP	5760	5243	3570	2640
UAP/NSTEMI	3594	3108	2039	1469
STEMI	779	695	245	102

Gender Differences in Bleeding and Vascular Complications in ACS Population: NCDR

	Men (n= 131 664)	Women (n= 68 026)	<i>p</i>
Bleeding			
Blood products transfused after laboratory visit	3.55	7.62	<.01
Percutaneous entry site	0.80	1.85	<.01
Retroperitoneal bleed	0.23	0.84	<.01
GI	0.52	0.85	<.01
GU	0.21	0.13	0.0002
Others/unknown	0.45	1.01	<.01
Vascular			
Access site occlusion	0.03	0.11	<.01
Peripheral embolization	0.05	0.12	<.01
Dissection	0.54	0.64	<.01
Pseudoaneurysm	0.29	0.73	<.01
AV fistula	0.06	0.09	<.01

Radial Approach is still Associated with More Bleeding in Women

- 1348 ACS patients pretreated with ASA, clopidogrel → radial PCI using 70 u/kg uFH and abciximab (EASY trial of early discharge)

	Women	Men	<i>p</i> value
Sheath size – 5F	57%	44%	0.0003
– 6F	43%	55%	
Hb drop	1.7%	0.4%	0.059
Hematoma	22%	5.8%	0.001
Final ACT (sec)	322	308	0.003

Gender Differences in Response to Anticoagulants

- Among drug applications submitted to FDA between 1994 and 2000, 20% had gender differences in pharmacokinetics
 - gender differences in gastric emptying
 - more hepatic cytochrome CYP3A in women
 - more dietary supplements taken by women
 - more accumulation in fat
 - less renal excretion
- Increased risk of HIT in women compared to men (*Blood 2006;108:2937-410*)

AHA Scientific Statement

Acute Myocardial Infarction in Women

A Scientific Statement From the American Heart Association

Laxmi S. Mehta, MD, FAHA, Chair; Theresa M. Beckie, PhD, FAHA, Co-Chair;
Holli A. DeVon, PhD, RN, FAHA; Cindy L. Grines, MD; Harlan M. Krumholz, MD, SM, FAHA;
Michelle N. Johnson, MD, MPH; Kathryn J. Lindley, MD; Viola Vaccarino, MD, PhD, FAHA;
Tracy Y. Wang, MD, MHS, MSc, FAHA; Karol E. Watson, MD, PhD;
Nanette K. Wenger, MD, FAHA; on behalf of the American Heart Association Cardiovascular
Disease in Women and Special Populations Committee of the Council on Clinical Cardiology,
Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing,
and Council on Quality of Care and Outcomes Research

Abstract—Cardiovascular disease is the leading cause of mortality in American women. Since 1984, the annual cardiovascular disease mortality rate has remained greater for women than men; however, over the last decade, there have been marked reductions in cardiovascular disease mortality in women. The dramatic decline in mortality rates for women is attributed partly to an increase in awareness, a greater focus on women and cardiovascular disease risk, and the increased application of evidence-based treatments for established coronary heart disease. This is the first scientific statement from the American Heart Association on acute myocardial infarction in women. Sex-specific differences exist in the presentation, pathophysiological mechanisms, and outcomes in patients with acute myocardial infarction. This statement provides a comprehensive review of the current evidence of the clinical presentation, pathophysiology, treatment, and outcomes of women with acute myocardial infarction. (*Circulation*. 2016;133:00-00. DOI: 10.1161/CIR.0000000000000351.)

Risk Factors for Intracranial Hemorrhage with Lytic therapy

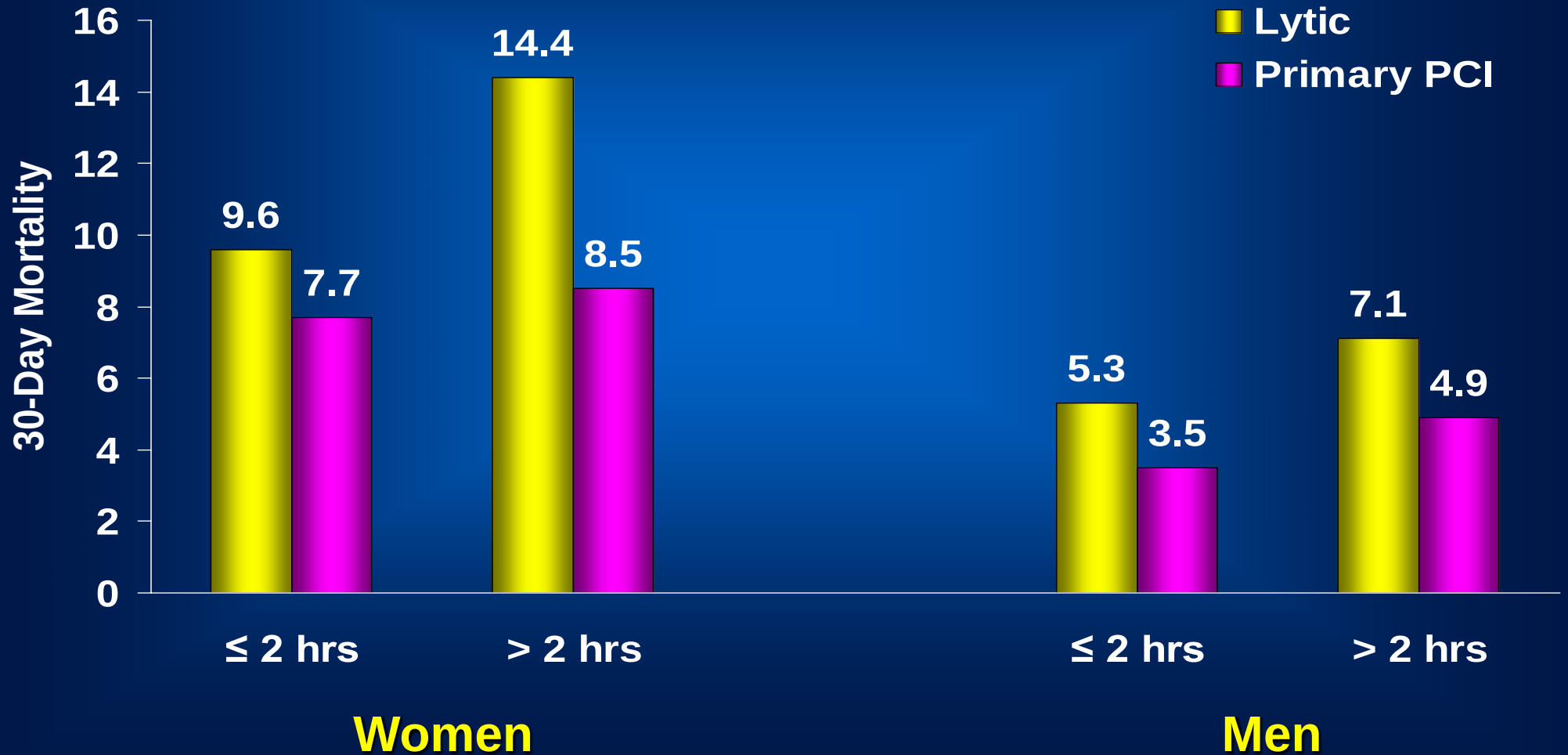
- ◆ Age > 75 years
- ◆ Black race
- ◆ Female sex
- ◆ Prior history of stroke
- ◆ Systolic BP > 160mmHg
- ◆ Weight < 65kg women < 80kg for men
- ◆ INR >4 or PT >24
- ◆ Use of alteplase (versus other lytic agent)

◆ Risk Score : %Rate of ICB

- | | |
|-------|-------|
| ◆ 0-1 | 0.69% |
| ◆ 2 | 1.02% |
| ◆ 3 | 1.63% |
| ◆ 4 | 2.49% |
| ◆ 5 | 4.11% |

Primary PCI is Superior to Lytics in Women

Meta-Analysis of 23 Randomized Trials (PCAT-2)



AMI in Women:
Later Presentation and Delay in Treatment
- CADILLAC Primary PCI Trial-

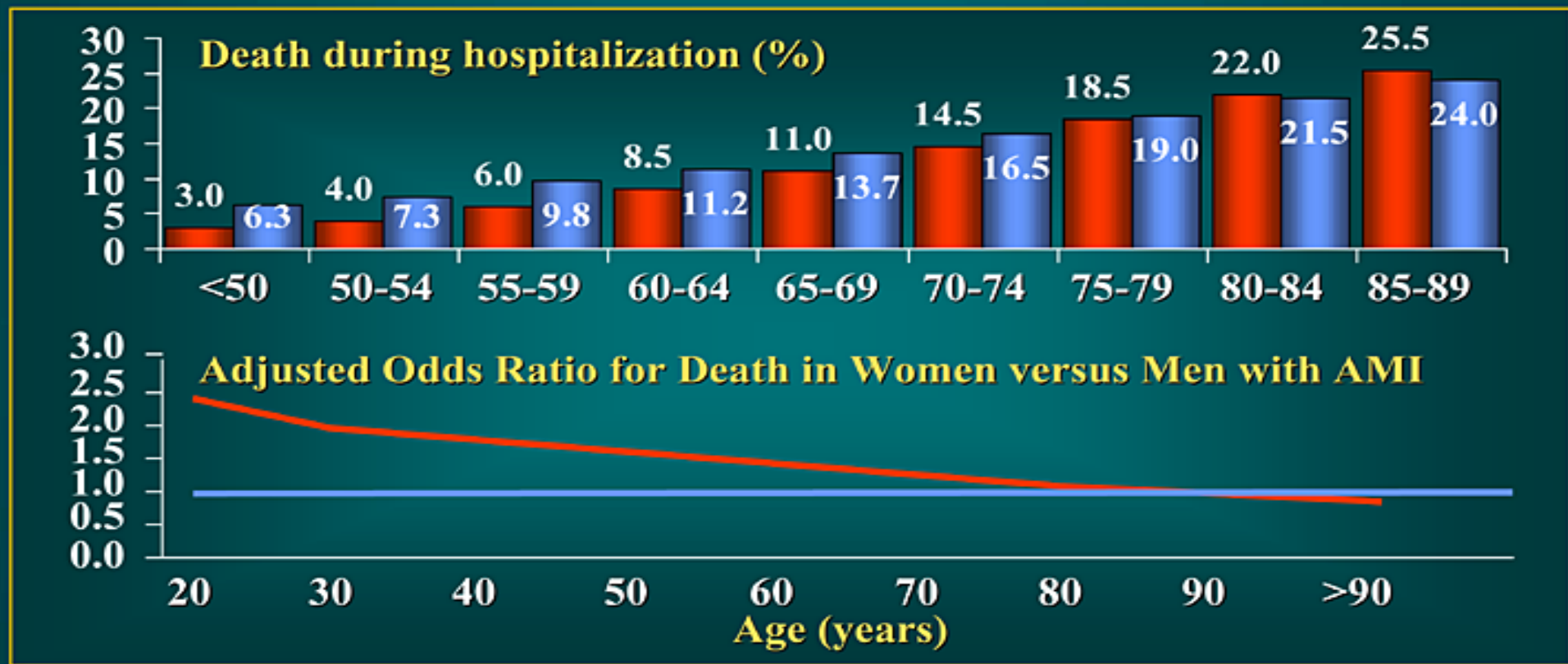
	Men	Women	<i>p</i> Value
N	1520	562	-
Chest pain to ER (hrs)	2.6 ± 2.5	3.0 ± 2.6	< 0.001
ER to procedure (hrs)	1.9 ± 2.2	2.1 ± 2.3	< 0.001
Stent use	57%	57%	NS
Abciximab use	54%	51%	NS

Although the Increased Mortality in Women has been attributed to advanced age and comorbidities,

Young Women with AMI have a Very Poor Prognosis

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

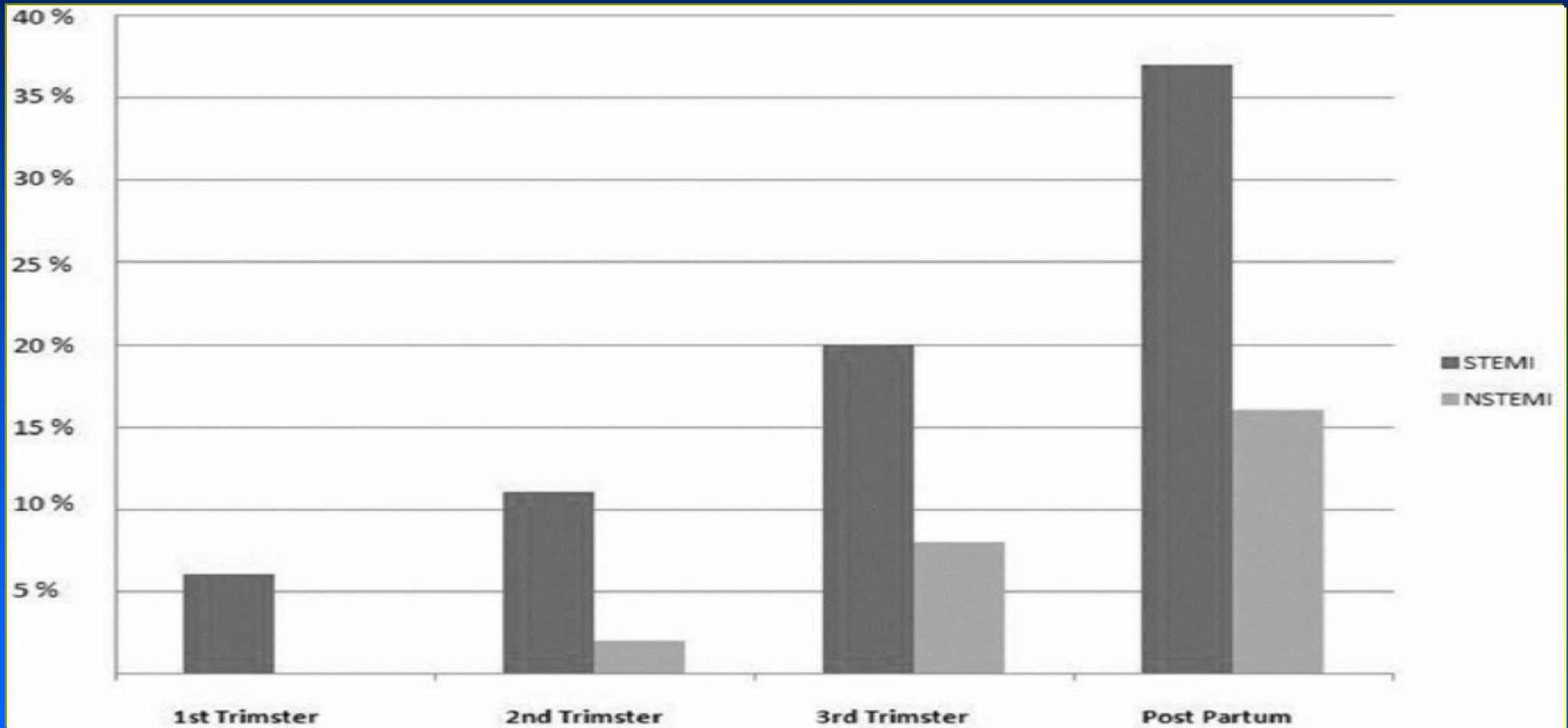
Mechanism of MI May be Different in Women

- ◆ **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**

Pregnancy-Associated MI

- ◆ Rare: ~6/100,000 (3-4 X age matched controls)
- ◆ Mortality high (>7% - maternal, >5% fetal)
- ◆ AGE: 30-fold ↑MI risk age > vs. <20 yrs
- ◆ Conventional CVD risks common:
 - HTN (15%), smoking (45%), DM (11%) infection, preeclampsia
 - Black women's ↑risk due to ↑RF's (not race)
- ◆ Spontaneous coronary dissection (SCAD) in majority (35-45%); Athero (20-30%); Clot (~20%)

Type, Timing of Pregnancy Associated MI



Physiology of Normal Pregnancy may Increase risk of MI

- ◆ **↑ Blood volume, cardiac output (30-40%)**
- ◆ **Stroke volume and HR increase**
- ◆ **↓ SVR in 2nd trimester**
- ◆ **↓ BP**
- ◆ **Hypercoagulability (4-5X ↑VTE rate)**
- ◆ **Insulin resistance**
- ◆ **Immune modulation**

Spontaneous Coronary Artery Dissection

◆ NOT atherosclerosis!

- Average age 42 yrs (P-SCAD ~ 36 yrs)
- Few/no CVD risk factors
- ~80% women, ~10-20% of women peripartum

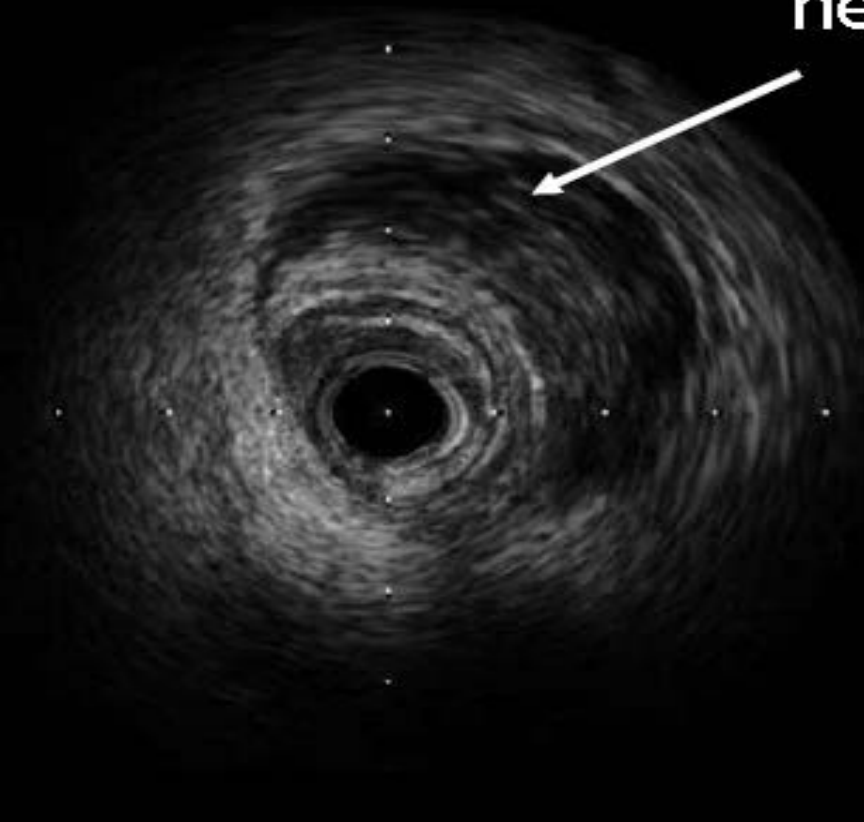
◆ Importance/difficulty diagnosing SCAD

- Index of suspicion often lacking
- Angiographic uncertainty
- Excess complications with PCI
- Uncertainties of post-SCAD management

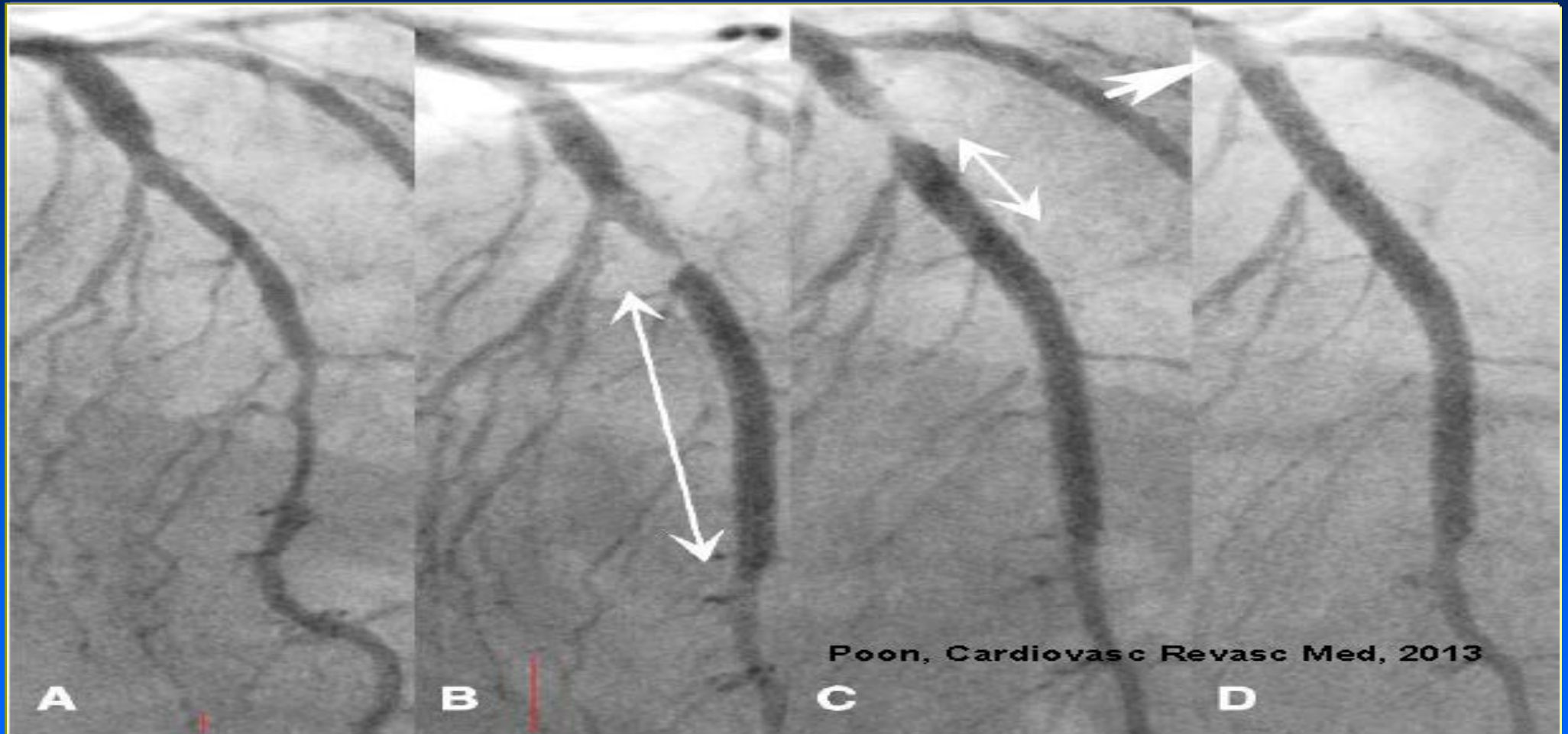
IVUS (Intravascular Ultrasound)

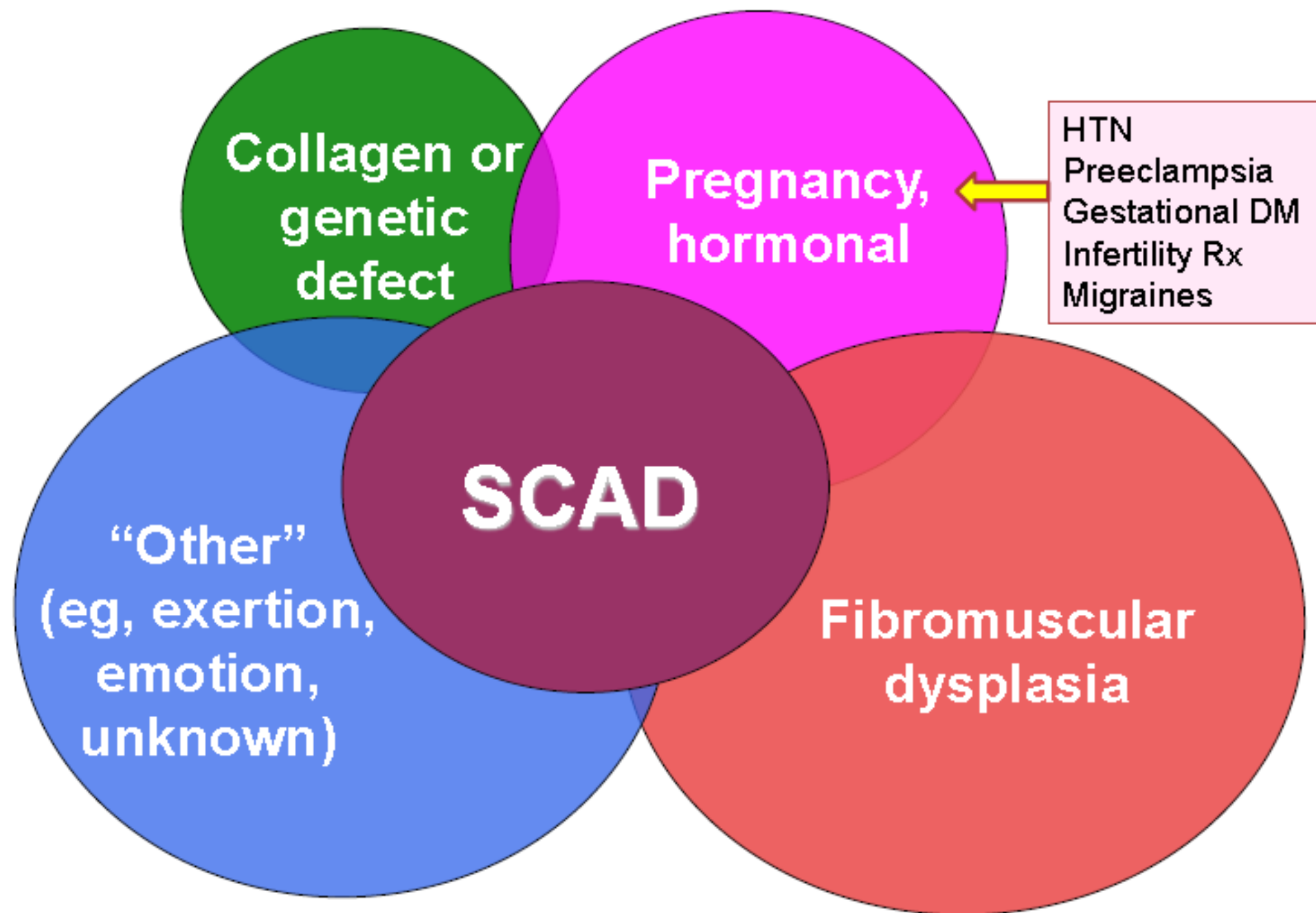
OCT (Optical Coherence Tomography)

Intramural
hematoma



Dissection Propagation with PCI





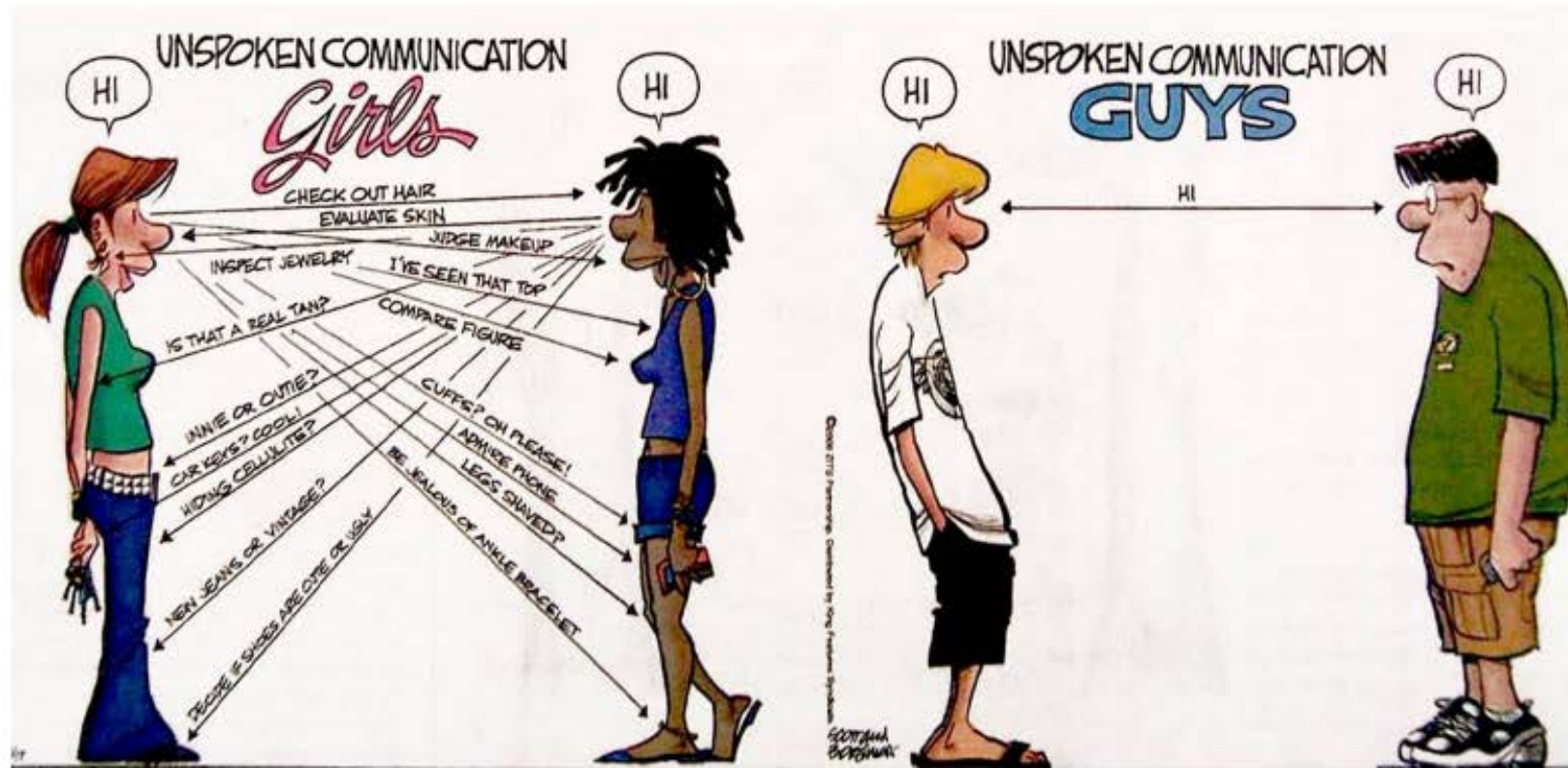
ACS in Women: Conclusions

- ◆ **The risk factor profile in women presenting with ACS, AMI or CAD 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 very atypical – even in the midst of AMI! Have a high level of suspicion/frequent ECGs.**
- ◆ **Younger woman? Think spontaneous dissection**

Cardiovascular Disease in Women

- ◆ In ACS and AMI women benefit from early invasive strategy; but 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
 - Potential role of advanced imaging and hemodynamic measurements to detect diffuse atherosclerosis or plaque erosion

ACS in Women: More to Think About



Less common ACS etiologies preferentially affect women

***MEN*strual Cramps**

***MEN*opause**

***MEN*tal Anxiety**

***MEN*tal Breakdown**

Ever notice how all problems

begin with MEN ? ! ? ! ? ! ?