Gender differences in ACS and CAD

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Ph Gabriel Steg – Disclosures

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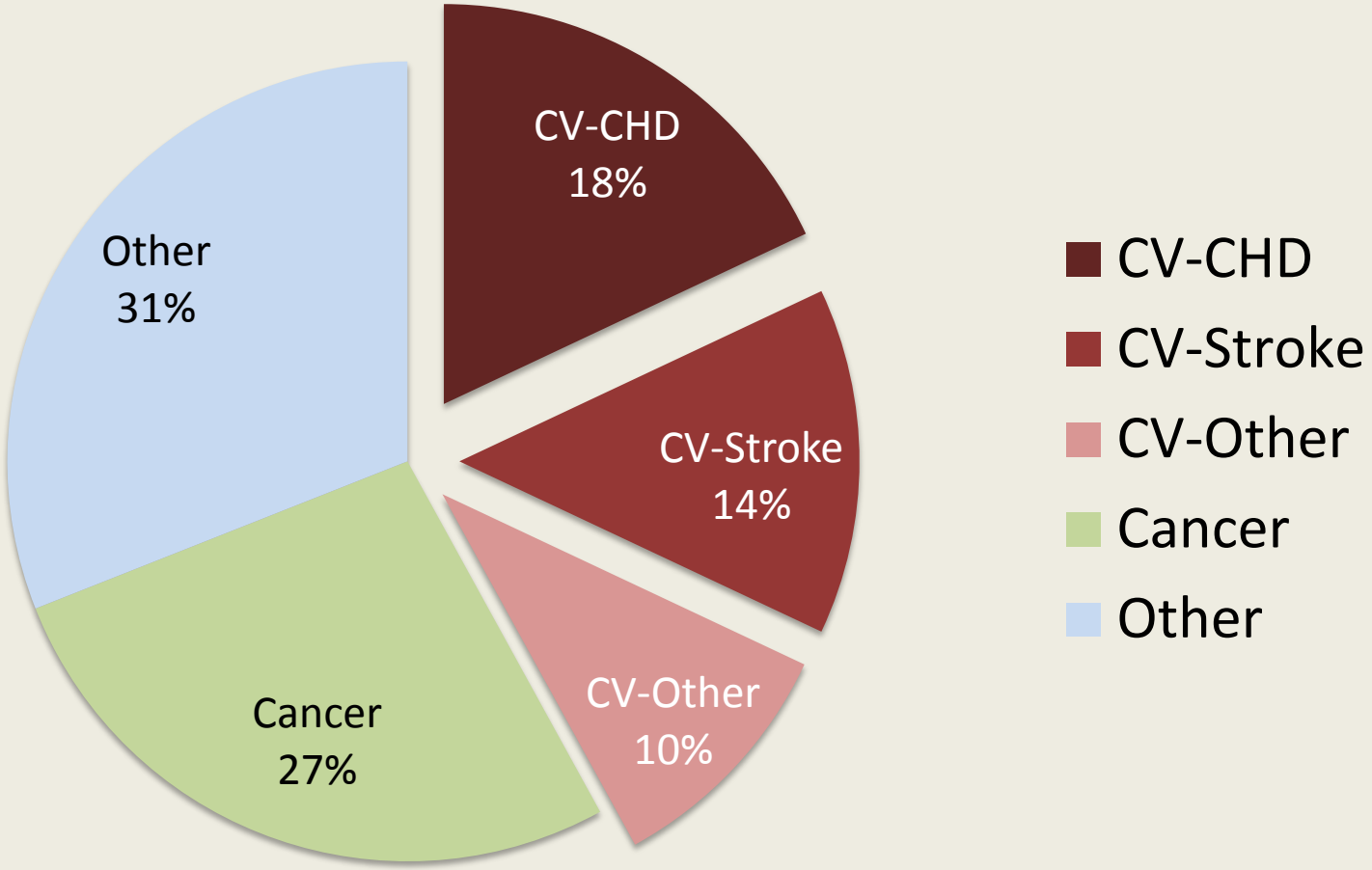
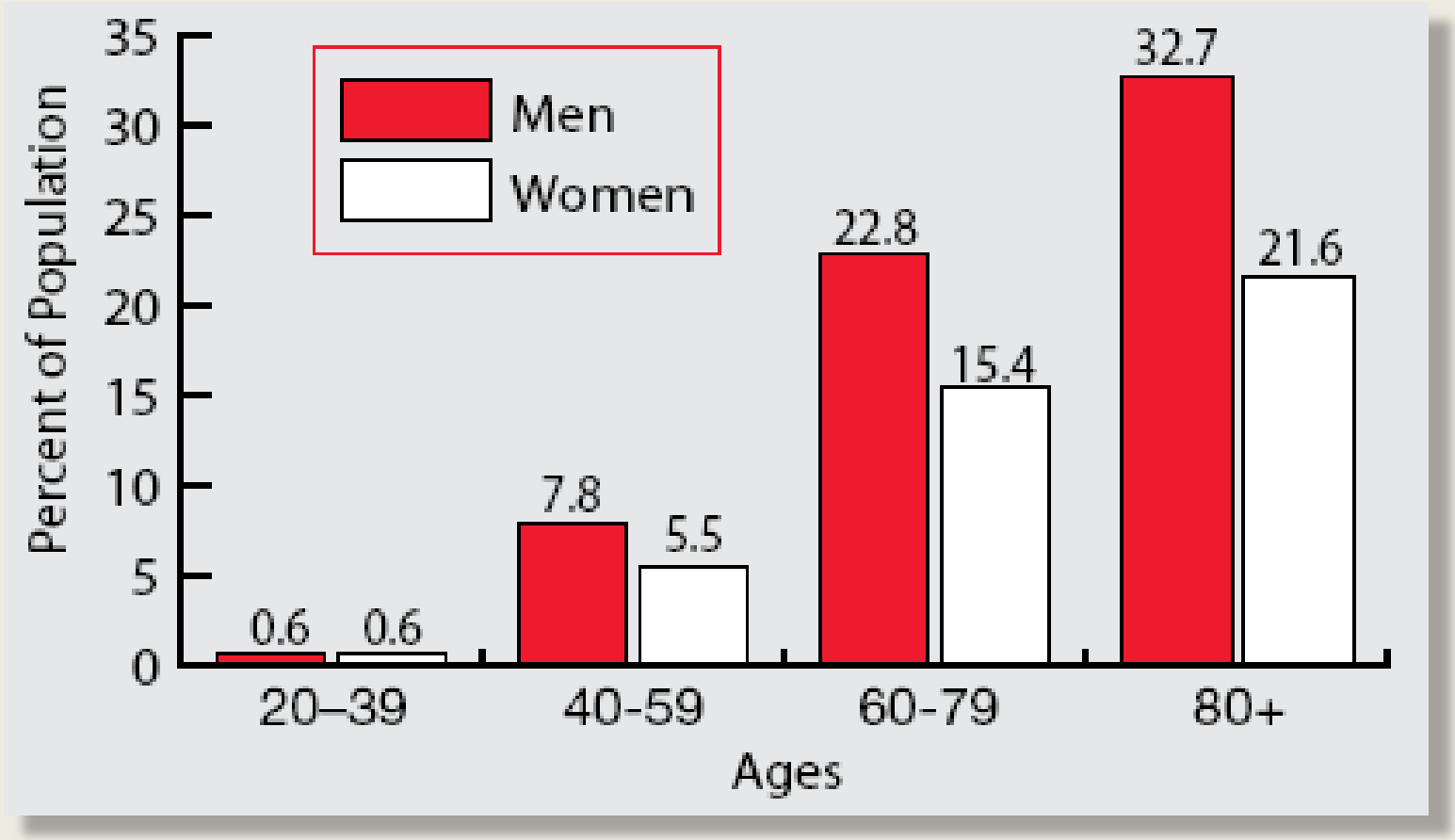
Causes of death in women < 75 years in Europe



Adapted from www.ehnheart.org/cdv-statistics.html,

Maas A H et al. ***Eur Heart J*** 2011;32:1362-1368

Prevalence of CAD among US adults by age and sex



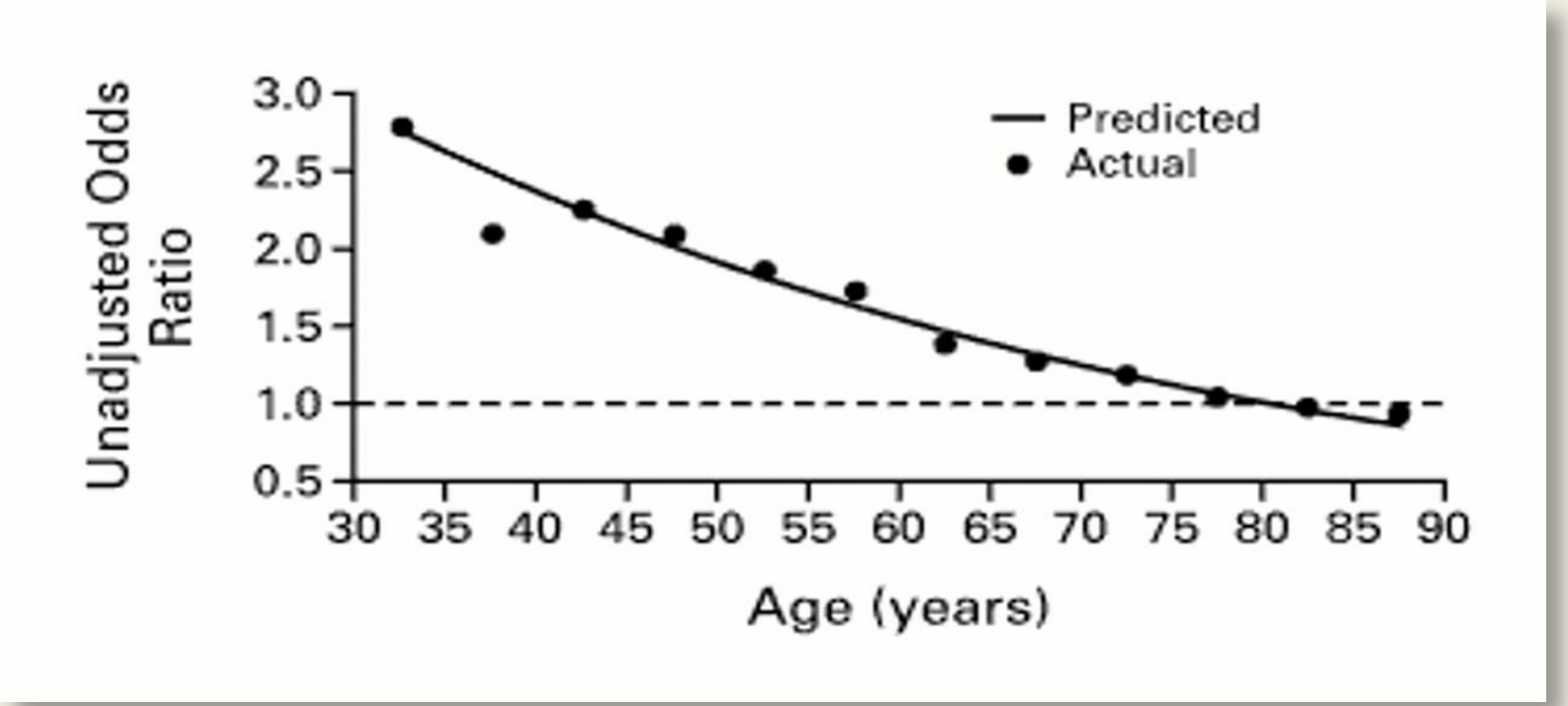
NHANES 1999-2004

Gender differences

- In AMI

Excess hospital mortality after AMI in women

Odds Ratios for Death during Hospitalization for Myocardial Infarction in Women as Compared with Men, According to Age in NRMI-2



Unadjusted ORs were derived from the model that included sex, age, the interaction between sex and age, and the year of discharge.

The NEW ENGLAND JOURNAL of MEDICINE

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

Hypothetical mechanisms of higher AMI mortality in women than men

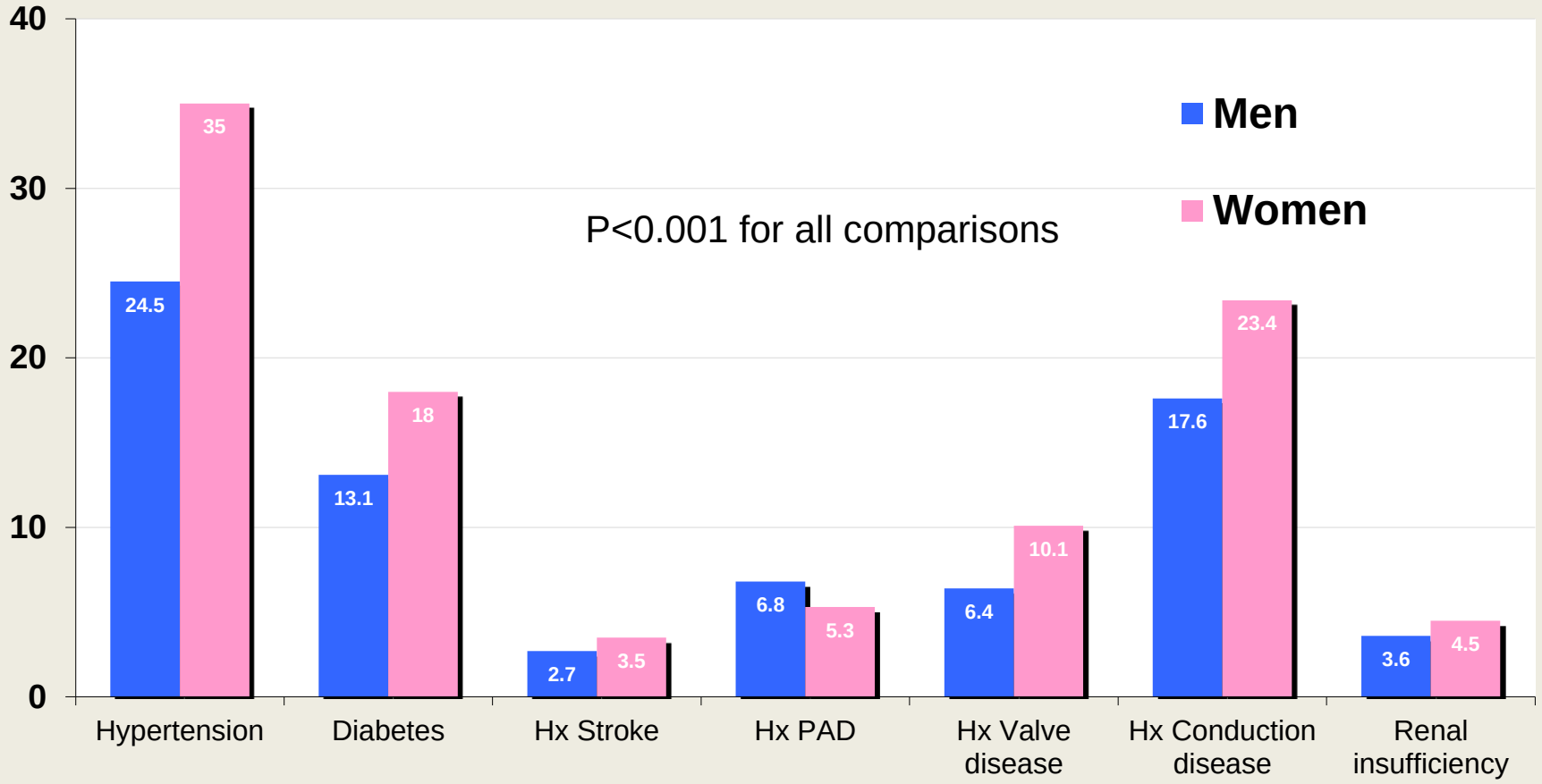
Biological differences

- **Women are older with more comorbidities**

Behavioural differences

Comorbidities are more frequent in women than men with AMI

74,038 hospital AMI admissions – 1999 - France



Milcent, C. et al. ***Circulation*** 2007;115:833-839

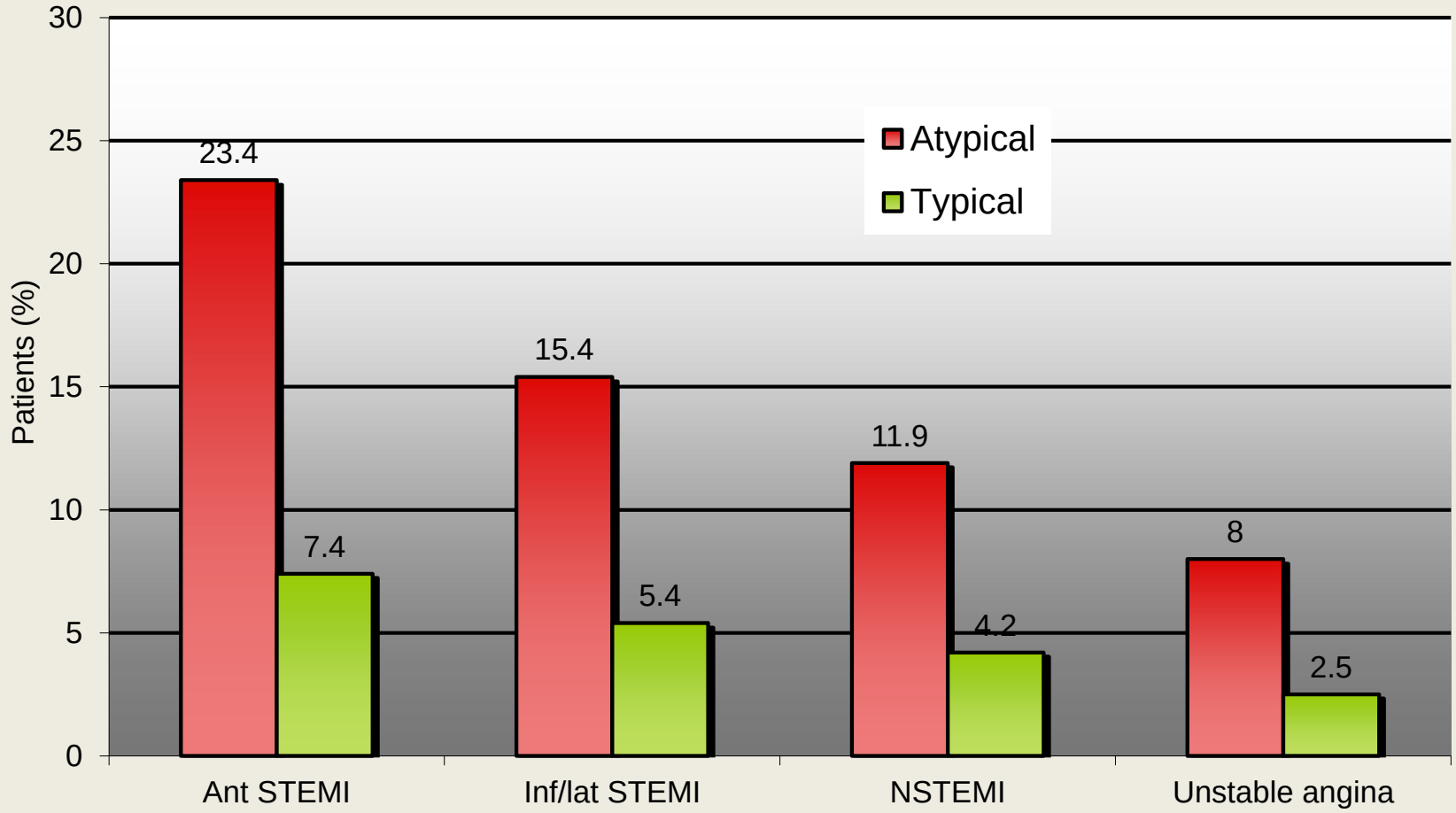
Hypothetical mechanisms of higher AMI mortality in women than men

Biological differences

- Women are older with more comorbidities
- **More frequent atypical symptoms**

Behavioural differences

In-hospital mortality in ACS according to presenting symptoms



Brieger et al ***Chest*** 2004;126:461-9

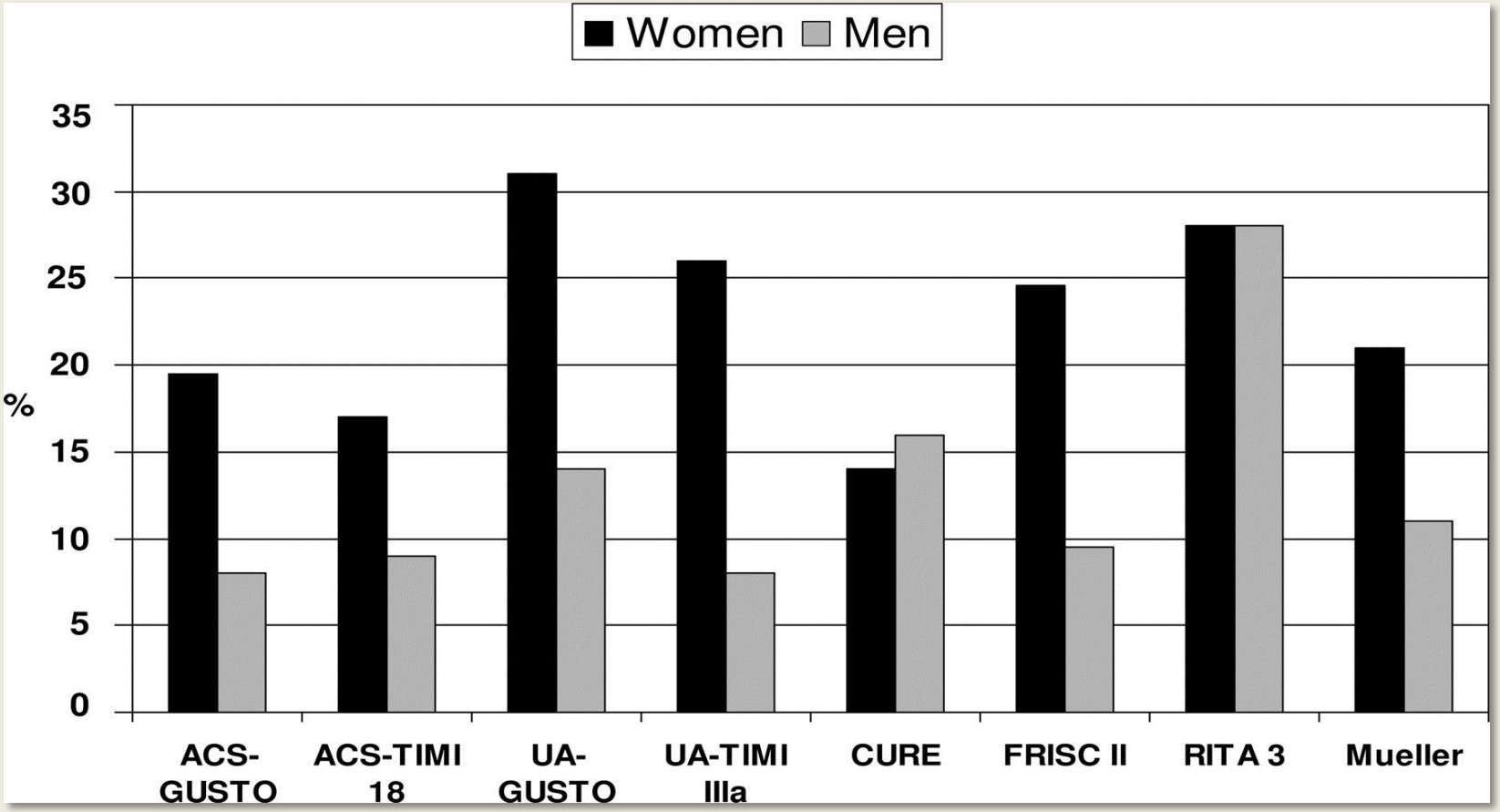
Hypothetical mechanisms of higher AMI mortality in women than men

Biological differences

- Women are older with more comorbidities
- More frequent atypical symptoms
- **Frequent non obstructive CAD**

Behavioural differences

Prevalence of normal or nonobstructive coronary arteries by gender on early angiography in recent ACS trials



Anderson RD. and Pepine CJ. ***Circulation*** 2007;115:823-826

Hypothetical mechanisms of higher AMI mortality in women than men

Biological differences

- Women are older with more comorbidities
- More frequent atypical symptoms
- Frequent non obstructive CAD
- Smaller arteries
- Lower rates of PCI success

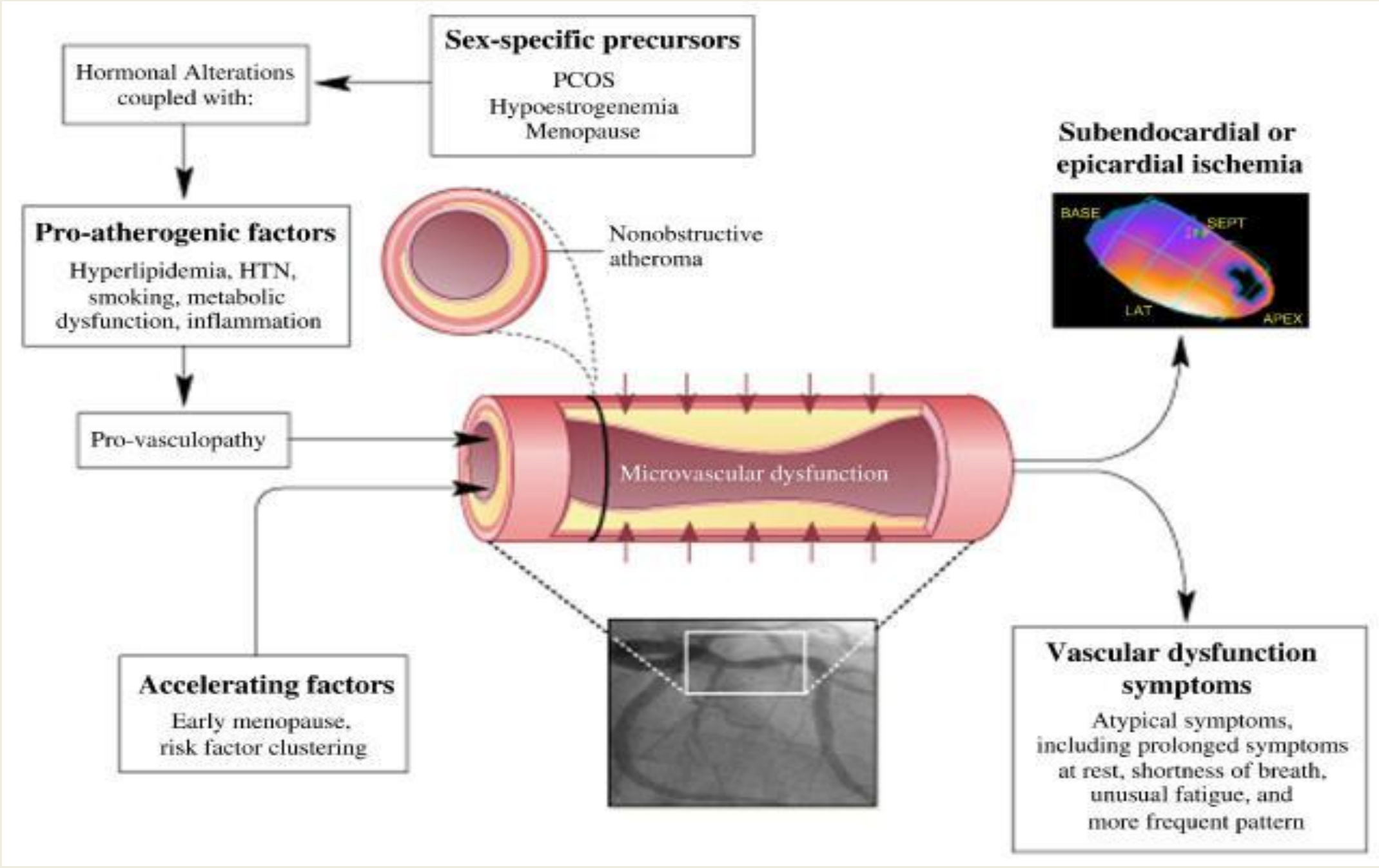
Behavioural differences

Hypothetical mechanisms of higher AMI mortality in women than men

Biological differences

- Women are older with more comorbidities
- More frequent atypical symptoms
- Frequent non obstructive CAD
- Smaller arteries
- Lower rates of PCI success
- A different disease process ?

Behavioural differences


Sex-specific precursors
PCOS
Hypoestrogenemia
Menopause
Hormonal Alterations coupled with:
Pro-atherogenic factors
Hyperlipidemia, HTN, smoking, metabolic dysfunction, inflammation
Nonobstructive atheroma
Pro-vasculopathy
Microvascular dysfunction
Accelerating factors
Early menopause, risk factor clustering
Subendocardial or epicardial ischemia
BASE
SEPT
LAT
APEX
Vascular dysfunction symptoms
Atypical symptoms, including prolonged symptoms at rest, shortness of breath, unusual fatigue, and more frequent pattern

Hypothetical mechanisms of higher AMI mortality in women than men

Biological differences

- Women are older with more comorbidities
- More frequent atypical symptoms
- Frequent non obstructive CAD
- Smaller arteries
- Lower rates of PCI success
- A different disease process ?

Behavioural differences

- By the patient
  - Longer delay to call
  - Lower adherence to Rx
- By the physician
  - Higher threshold for diagnosis
  - Less invasive approach
  - Less intensive treatment

Excess hospital mortality after AMI in women may be explained by undertreatment

Information abstracted from the charts of 138,956 Medicare beneficiaries (49 % of them women) who had an AMI in 1994 or 1995

30-Day Mortality and Hazard Ratio for Death among Women and Men with Acute Myocardial Infarction. The CCP project

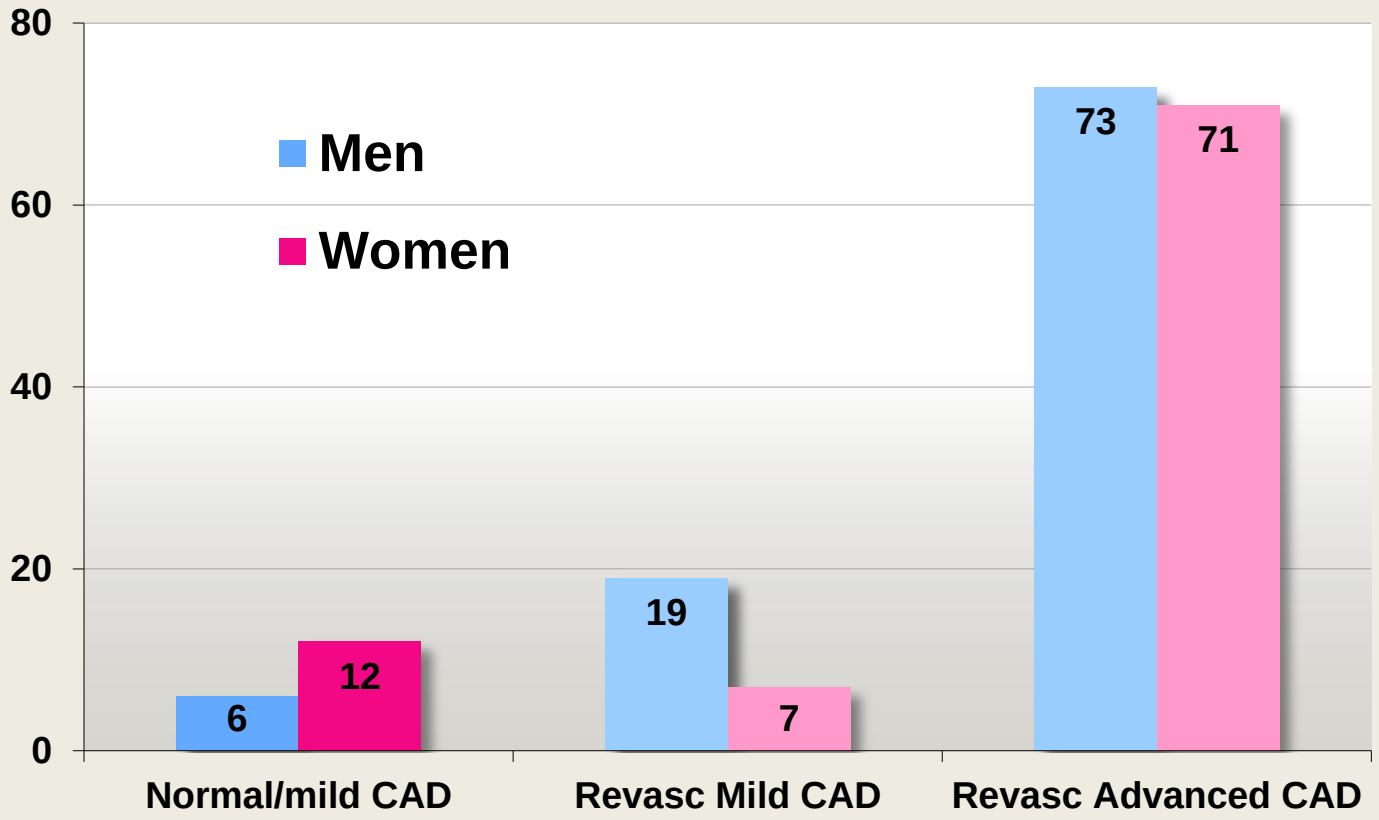
VARIABLE	WOMEN (N=68,108)	MEN (N=70,848)
30-Day mortality — % (no.)	21.0 (14,274)	17.2 (12,211)
Unadjusted HR (95% CI)	1.24 (1.21–1.28)	1.00
Adjusted HR (95% CI) in model not including treatments†	1.04 (1.01–1.07)	1.00
Adjusted HR (95% CI) in model including early treatments‡	1.02 (0.99–1.04)	1.00

The NEW ENGLAND JOURNAL of MEDICINE

Gan SC et al. ***N Engl J Med*** 2000;343:8-15

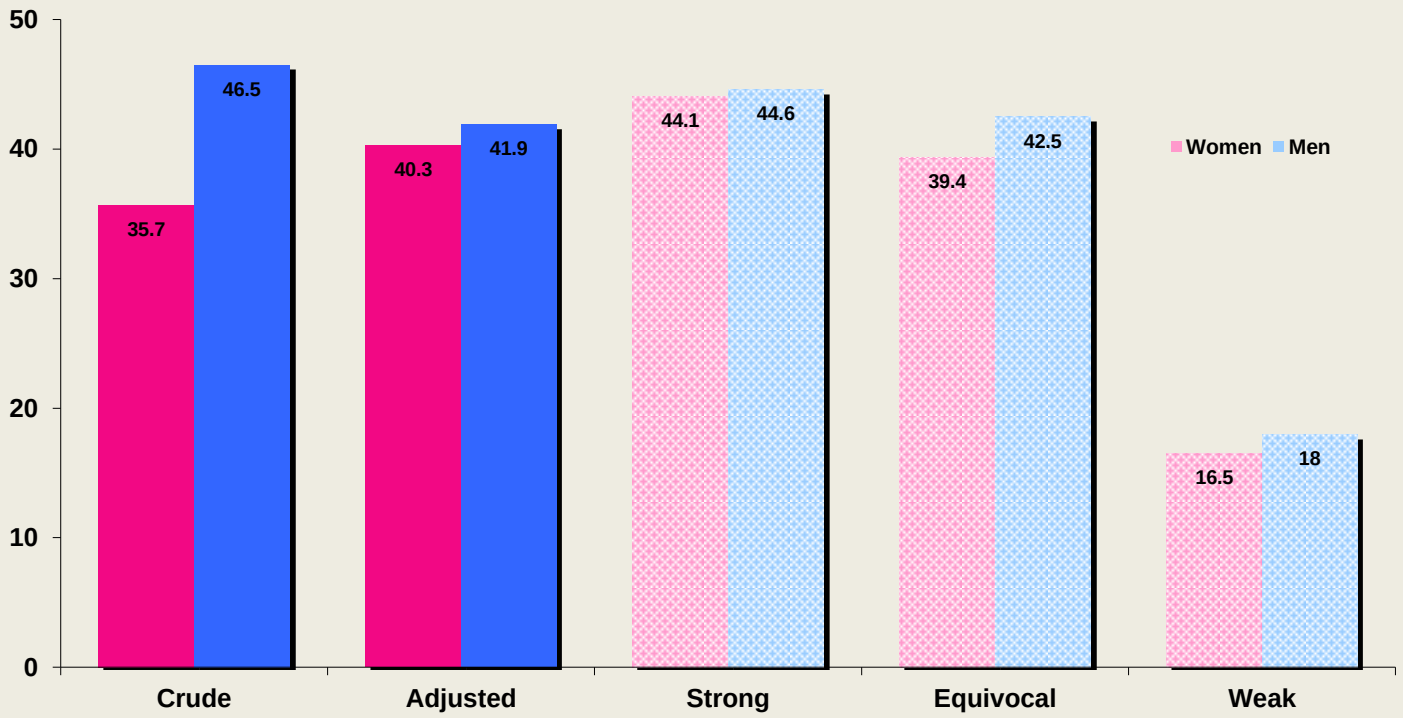
Impact of differences in CAD severity on use of revascularization in ACS

Data from 2579 pts with coronary angiography in the GRACE registry



Dey S et al. ***Heart*** 2009;95:20-6

Sex differences in cardiac catheterization within 60 days after AMI: the role of procedure appropriateness



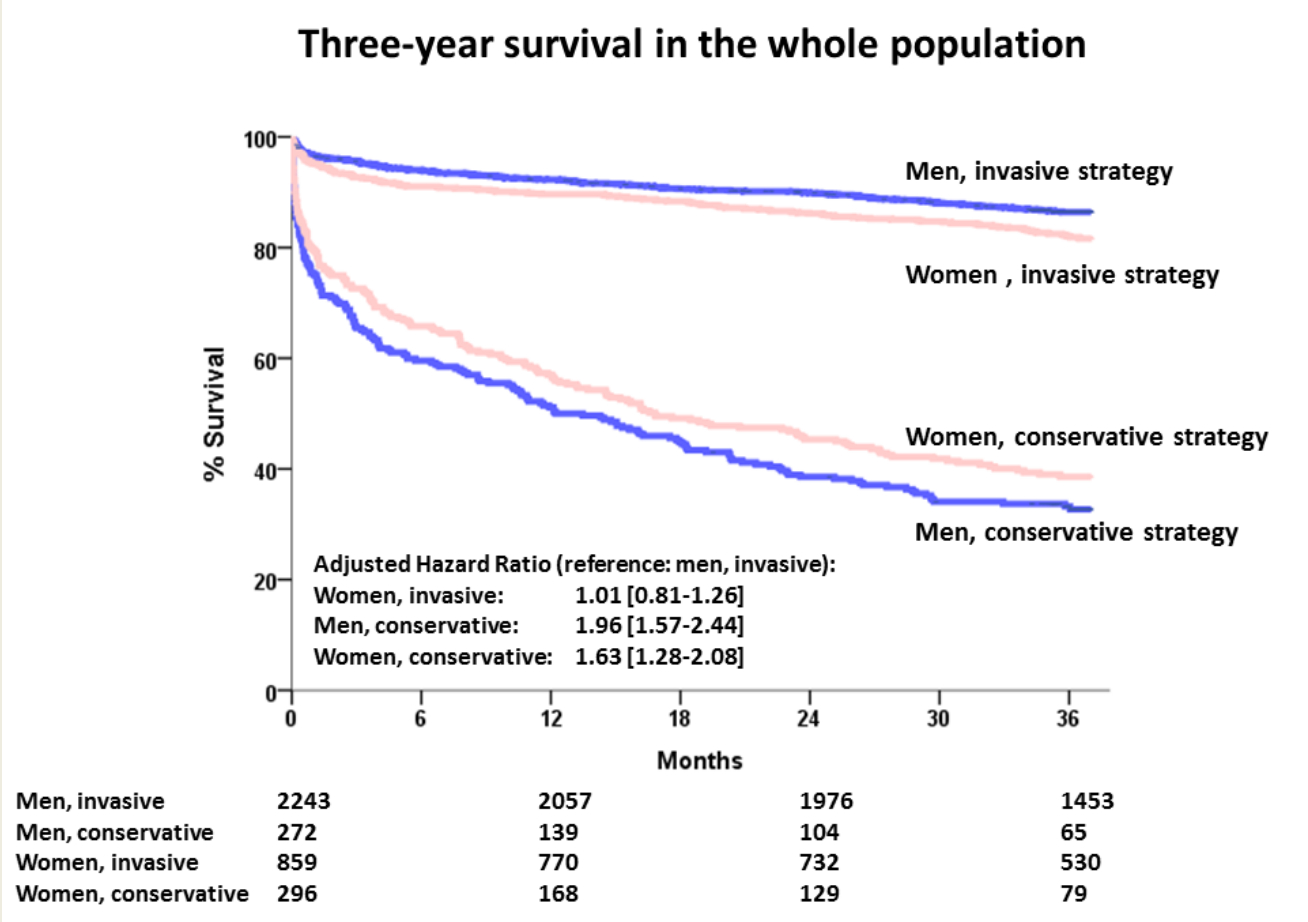
143 444 Medicare patients hospitalized for AMI between 1994 and 1996

Rathore SS et al. ***Ann Intern Med***. 2002;137:487-93

The Yentl Syndrome

Lower use of invasive strategy in ACS accounts for higher mortality in women

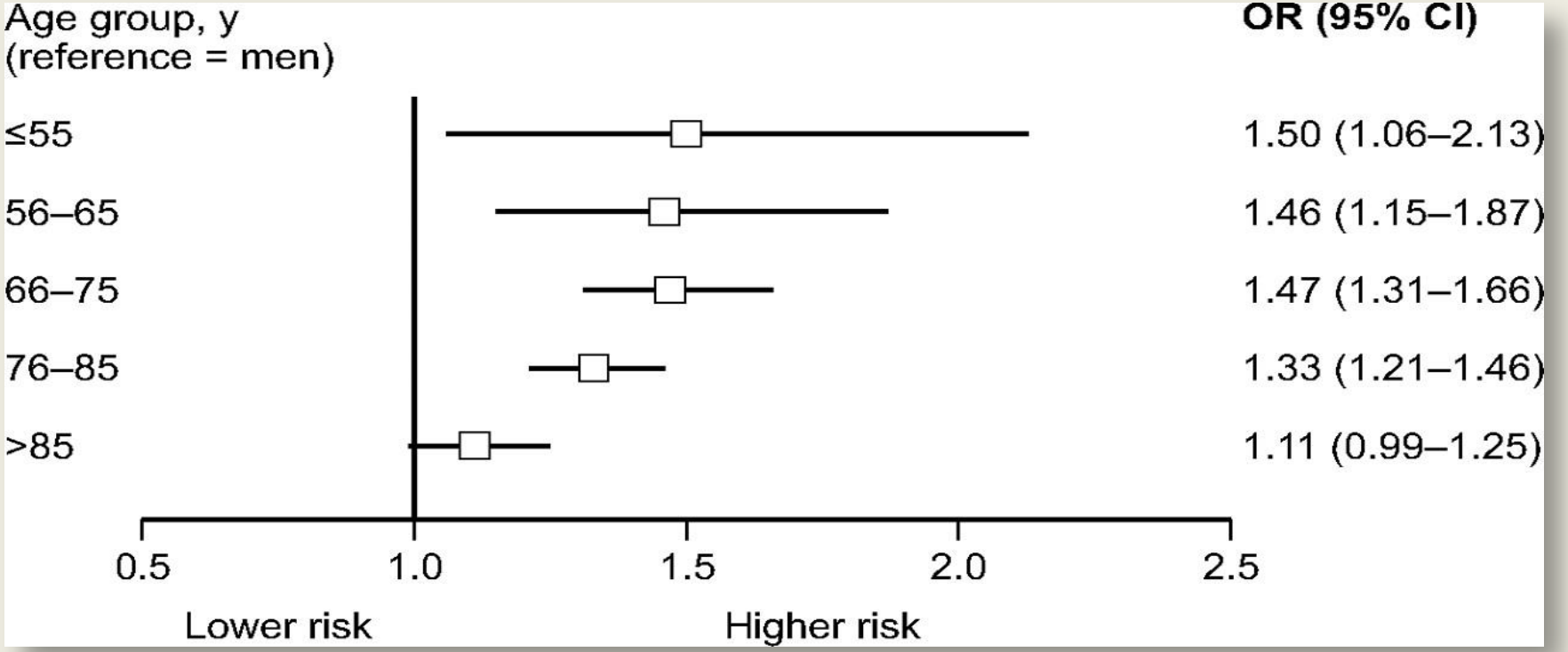
Data from the FAST MI 2005 nationwide french registry



Donataccio et al. Submitted

AMI mortality is higher in younger women compared to younger men, even after accounting for comorbidities and interventions

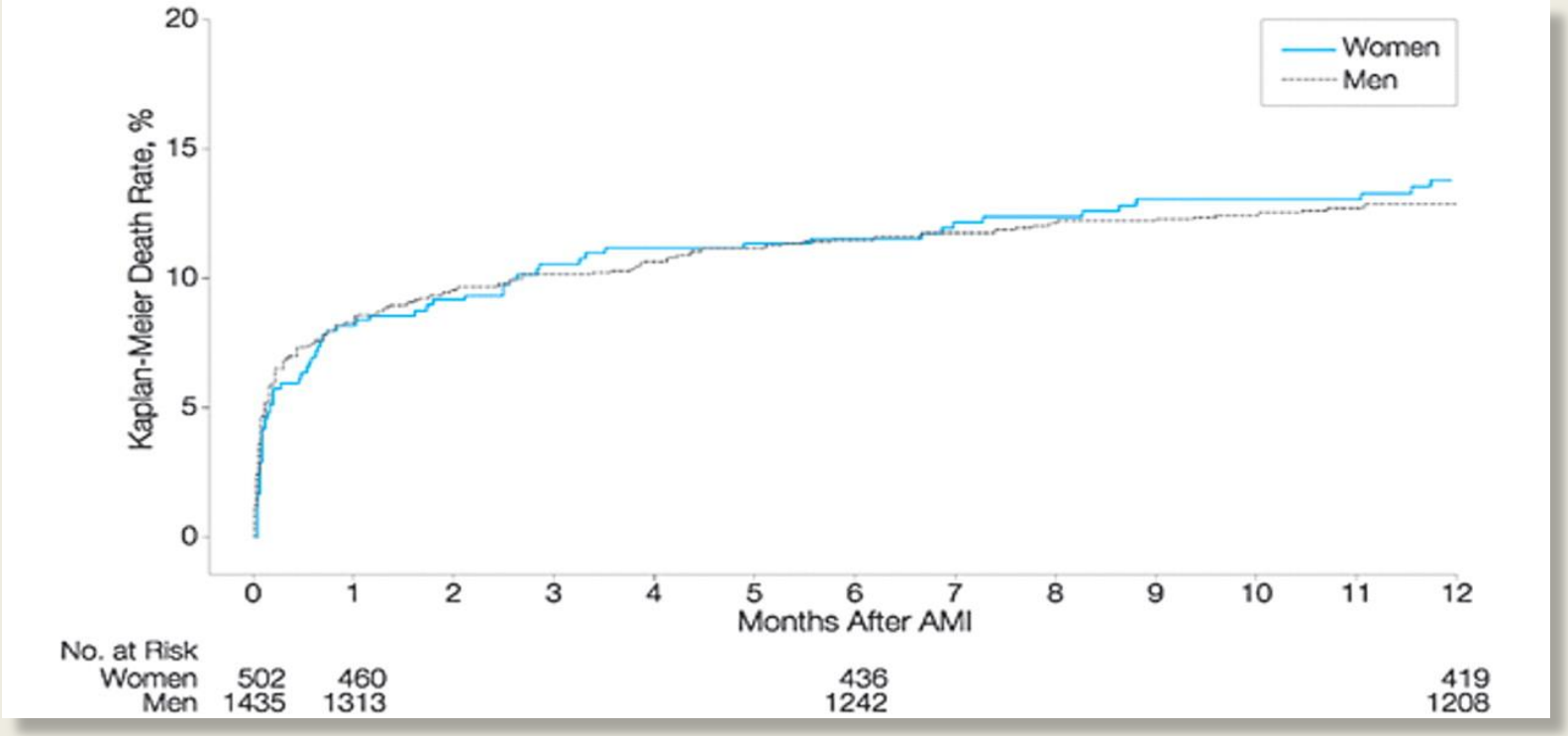
Impact of gender on hospital AMI mortality rates across age categories after adjustment for comorbidities and use of coronary interventions. French national database.



Milcent, C. et al. ***Circulatio***n 2007;115:833-839

Excess mortality in women is not observed when AMI is Treated Predominantly With PCI

One-Year Cumulative Incidence of Death



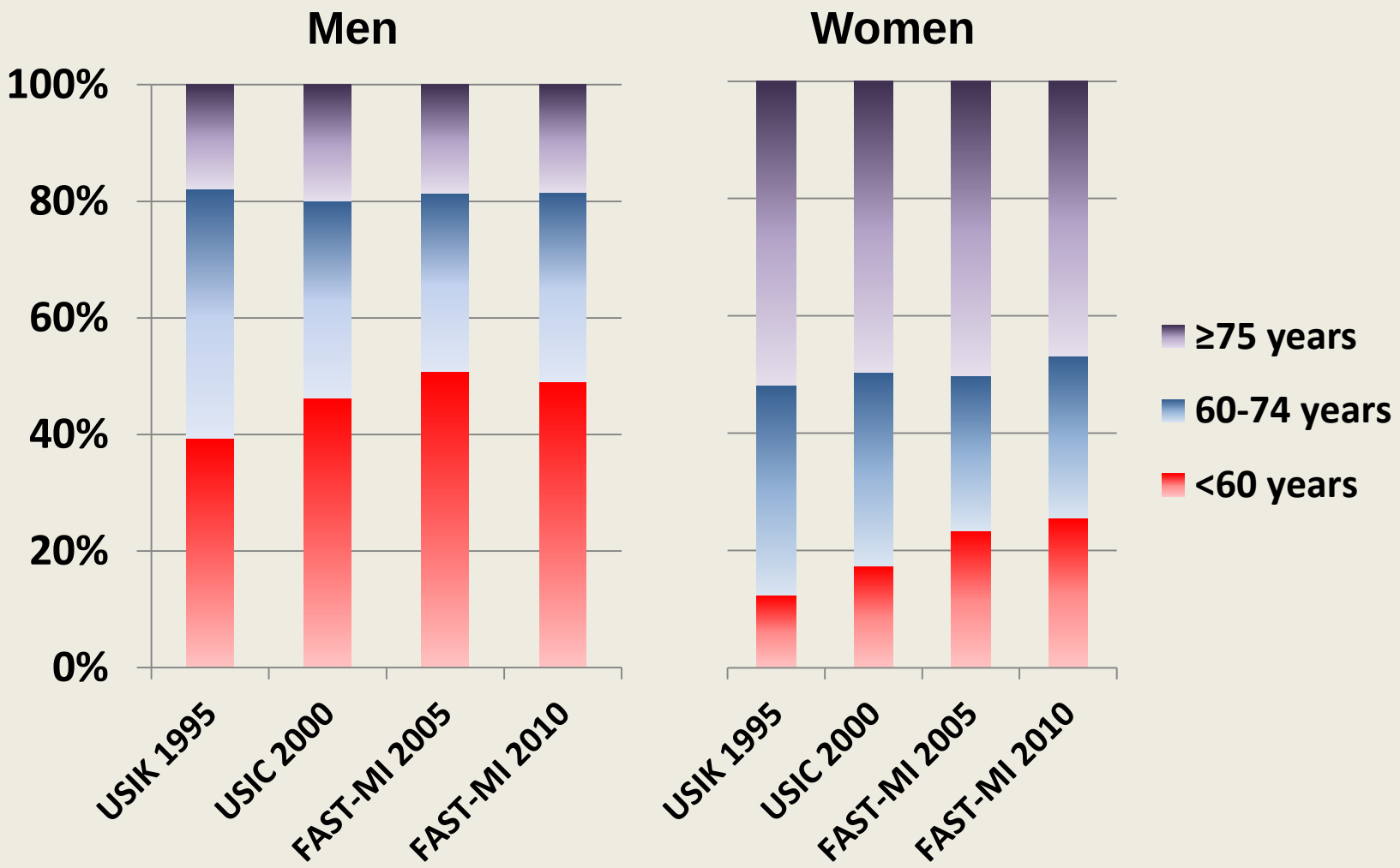
1937 patients (502 women and 1435 men) admitted with a diagnosis of AMI to a tertiary referral institution between January 1995 and December 2000

Mehilli, J. et al. ***JAMA*** 2002;287:210-215.

JAMA

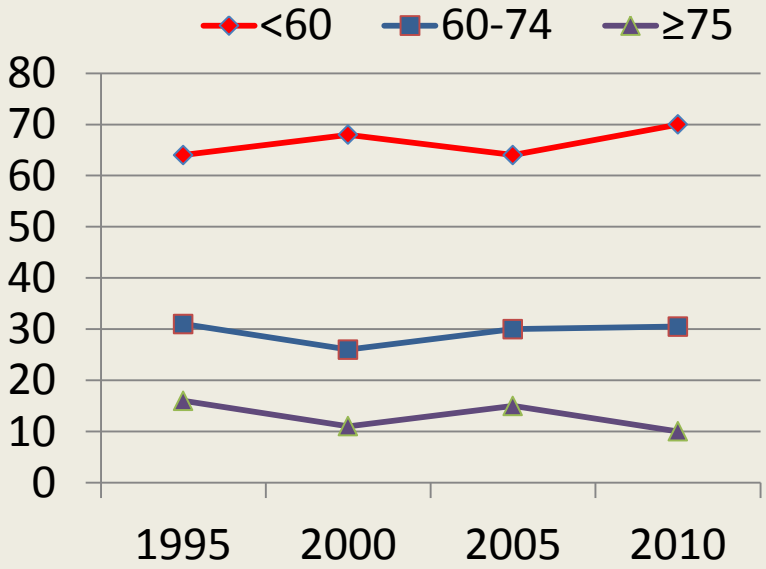
Increased proportion of younger women among french patients with AMI

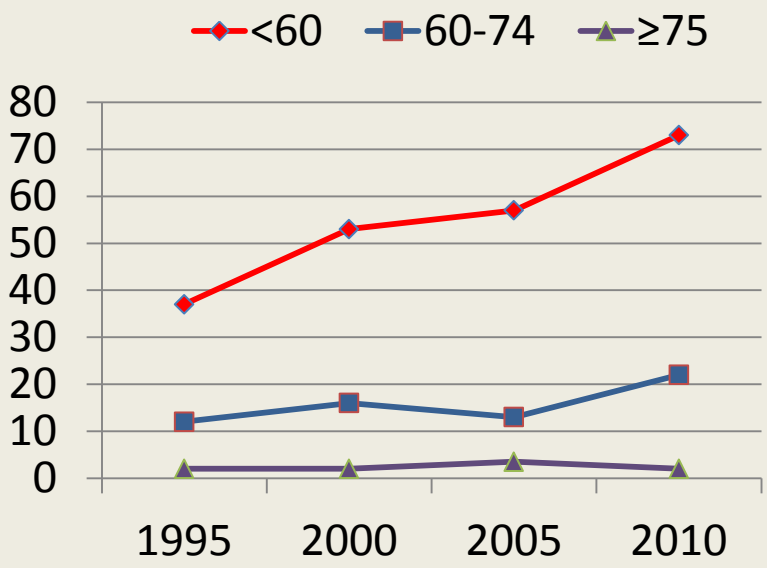
The french AMI registries 1995-2005



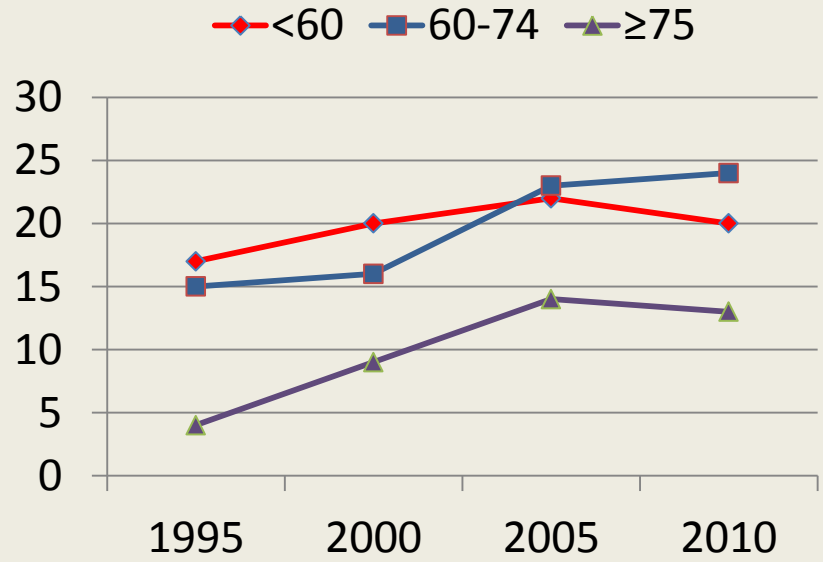
Puymirat et al ***JAMA*** 2012

Current smoking

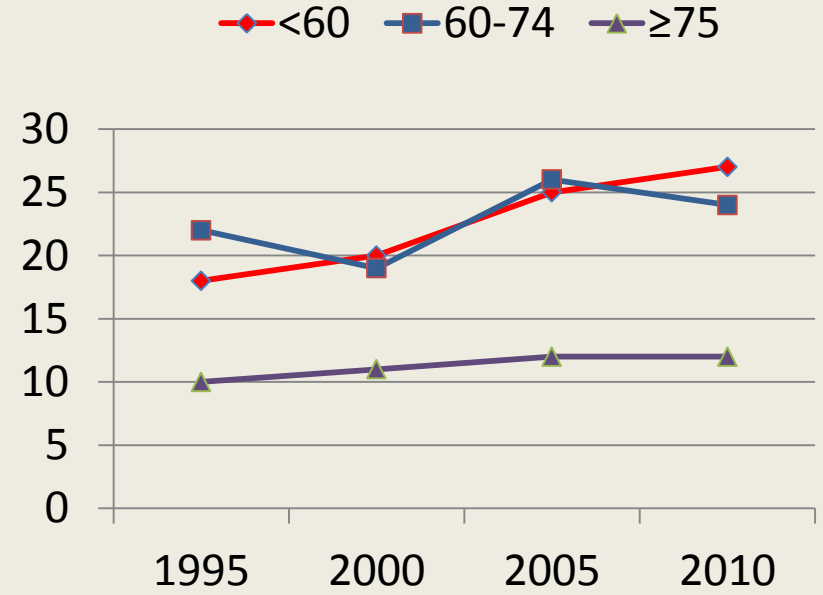




Obesity



Men

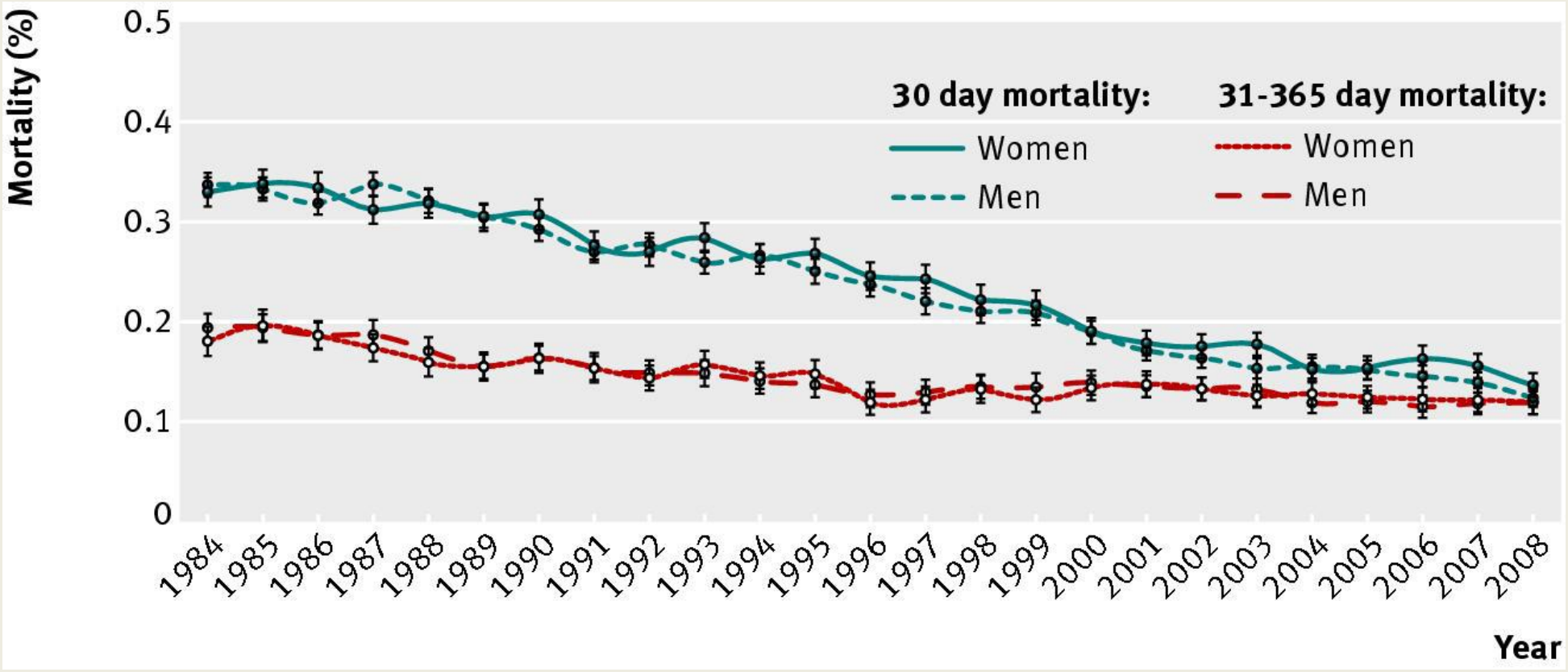


Women

Puymirat et al ***JAMA*** 2012

Ongoing reduction in incidence and lethality of AMI in both men and women

Standardised 30 day and 31–365 day mortality after first time hospitalisation for myocardial infarction among men and women between 1984 and 2008



Schmidt 2012 ***BMJ***

Gender differences

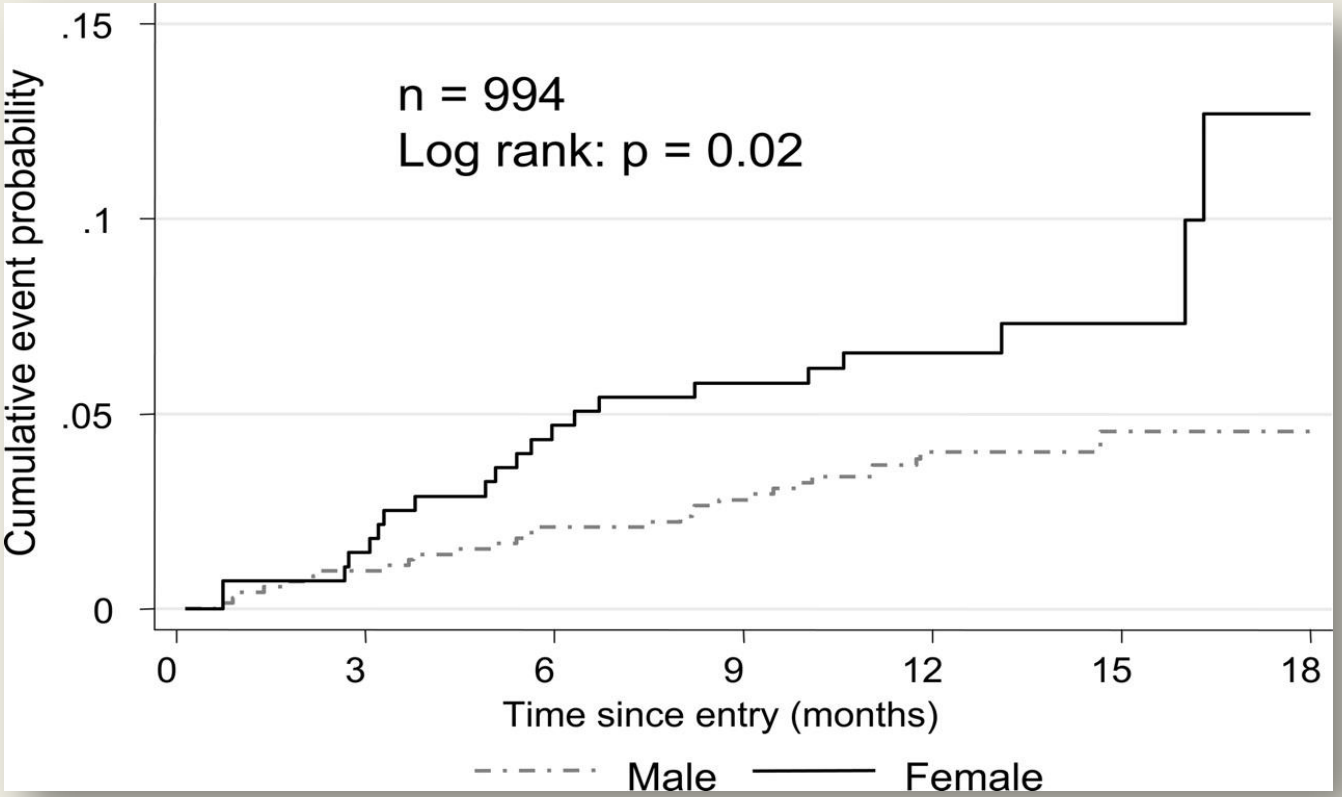
- In AMI

- **In stable CAD**

Higher risk of death/MI in women vs men with stable angina

Data from the Euro Heart Survey on stable angina

Cumulative probability of death or MI in pts with confirmed CAD and stable angina



Daly C et al. ***Circulation*** 2006;113:490-498

Impact of female gender on outcomes in the EHS on stable angina

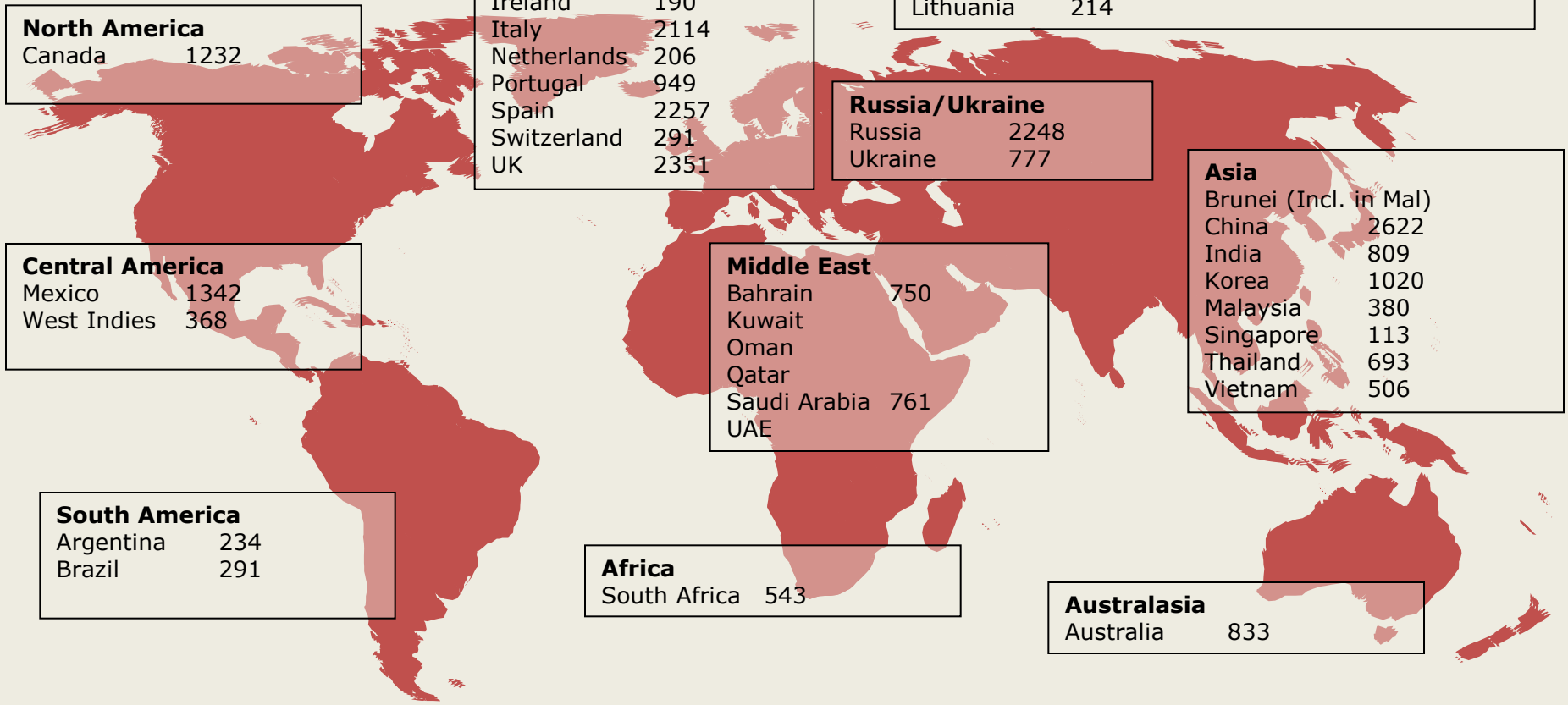
Hazard of Death or MI Associated With Female Gender in Individuals With Proven Coronary Disease From the Euro Heart Survey of Stable Angina

	HR	95% CI	P
Death or MI	2.07	1.16–3.72	0.01
Death or MI, adjusted for age, diabetes, LV function, and severity of CAD	2.09	1.14–3.85	0.02
Death or MI, adjusted for age and use of statin and antiplatelet therapy	2.07	1.14–3.74	0.02
Death or MI, adjusted for age and revascularization	2.20	1.22–3.98	0.009

Daly C et al. ***Circulation*** 2006;113:490-498

The CLARIFY registry

Data on 30977 stable CAD Pts (23% women)



Western Europe

Austria	425
Belg/Luxem	577
Denmark	133
France	2428
Germany	2250
Greece	559
Ireland	190
Italy	2114
Netherlands	206
Portugal	949
Spain	2257
Switzerland	291
UK	2351

Central/Eastern Europe

Bulgaria	172	Poland	1004
Czech Rep	393	Romania	502
Hungary	344	Slovakia	183
Latvia	120	Slovenia	81
Lithuania	214		

North America

Canada	1232

Russia/Ukraine

Russia	2248
Ukraine	777

Asia

Brunei (Incl. in Mal)	
China	2622
India	809
Korea	1020
Malaysia	380
Singapore	113
Thailand	693
Vietnam	506

Central America

Mexico	1342
West Indies	368

Middle East

Bahrain	750
Kuwait	
Oman	
Qatar	
Saudi Arabia	761
UAE	

South America

Argentina	234
Brazil	291

Africa

South Africa	543

Australasia

Australia	833

Primary Outcome

CV death, MI and stroke

- 407 events in men (1.7%)
- 122 events in women (1.8%)

Odds ratios & 95% CI:

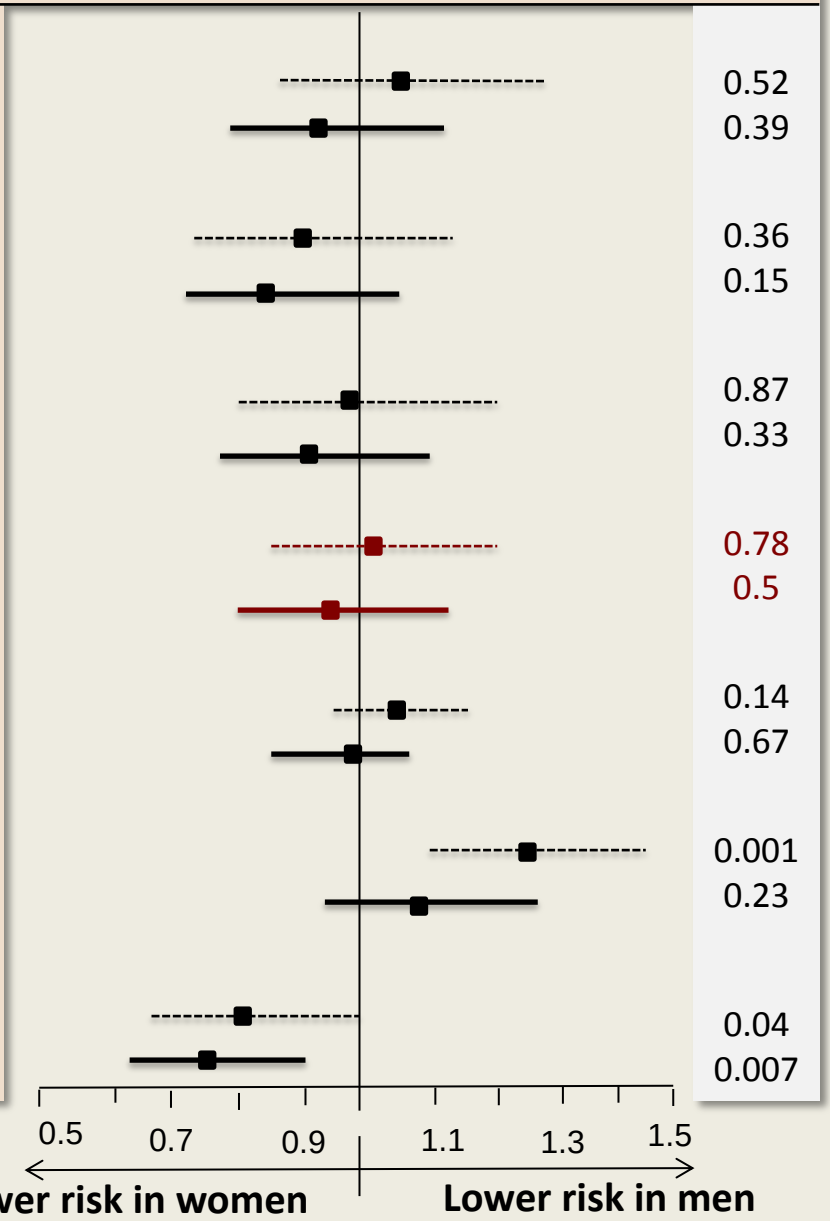
– Crude:	1.03 (0.84-1.26)	p = 0.78
– Adjusted*:	**0.93 (0.75-1.15)**	**p = 0.5**

* Adjusted on age, presence and severity of angina, diabetes, hypertension, MI, PAD, HR, and SBP

Major 1 year outcomes

Event	Men	Women	OR	P
All cause death	1.5%	1.6%		
Unadjusted			1.07	0.52
Adjusted			**0.91**	0.39
Fatal or non-fatal MI	1.0%	0.9%		
Unadjusted			0.88	0.36
Adjusted			**0.81**	0.15
CV death or non-fatal MI	1.4%	1.4%		
Unadjusted			0.98	0.87
Adjusted			**0.89**	0.33
CV death, non-fatal MI or non-fatal stroke	1.7%	1.8%		
Unadjusted			1.03	0.78
Adjusted			**0.93**	0.5
All coronary events*	5.8%	6.2%		
Unadjusted			1.09	0.14
Adjusted			**0.98**	0.67
Unstable angina	3.8%	4.7%		
Unadjusted			1.24	0.001
Adjusted			**1.09**	0.23
Revascularization (PCI or CABG)	2.6%	2.1%		
Unadjusted			0.83	0.04
Adjusted			**0.77**	0.007

*: MI, revascularization or unstable angina



Special subsets

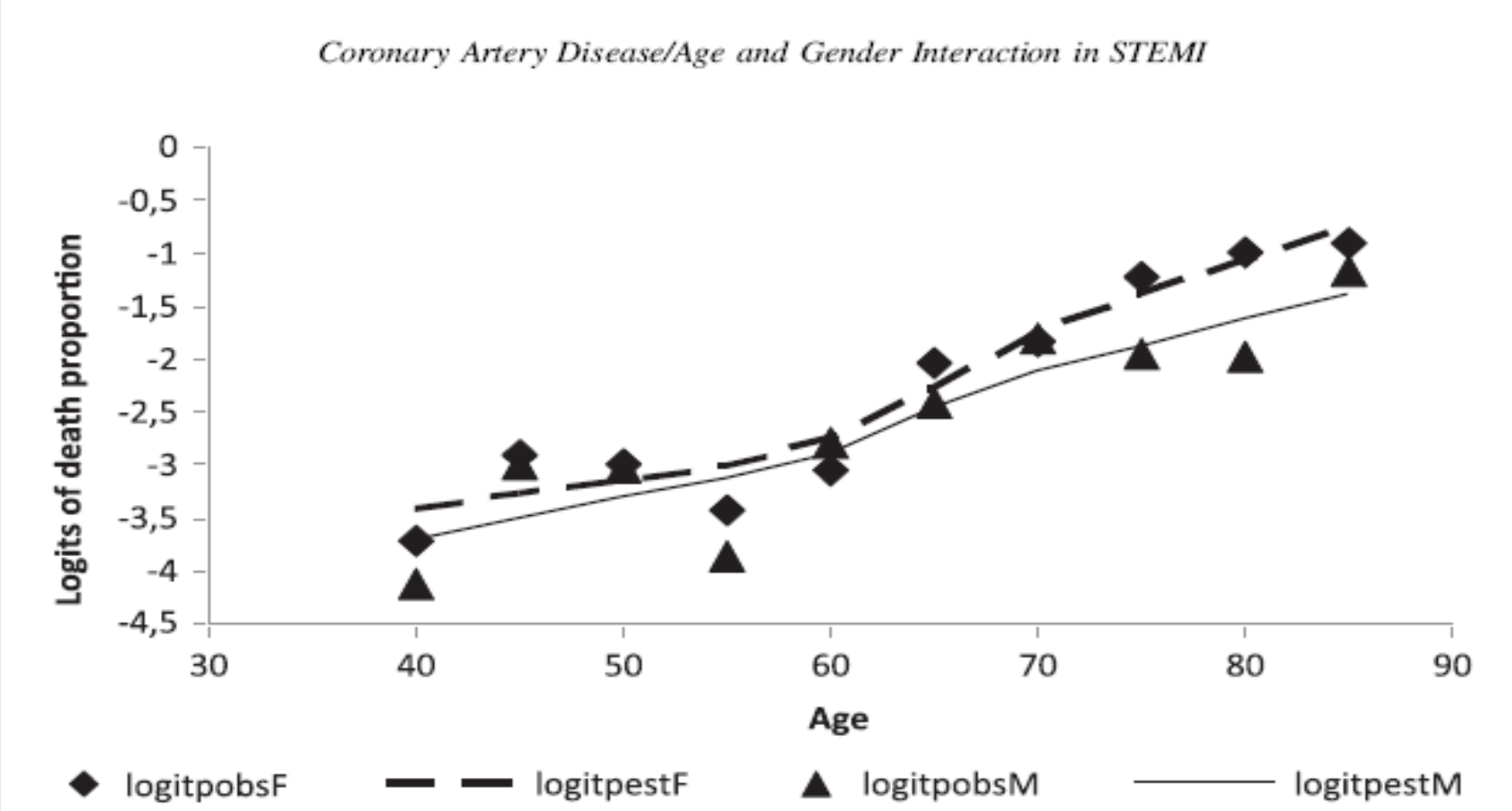
Recommendations	Class	Level
Both genders must be managed in a similar fashion.	I	C
A high index of suspicion for myocardial infarction must be maintained in women, diabetics, and elderly patients with atypical symptoms.	I	B
Special attention must be given to proper dosing of antithrombotics in elderly and renal failure patients.	I	B

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs215

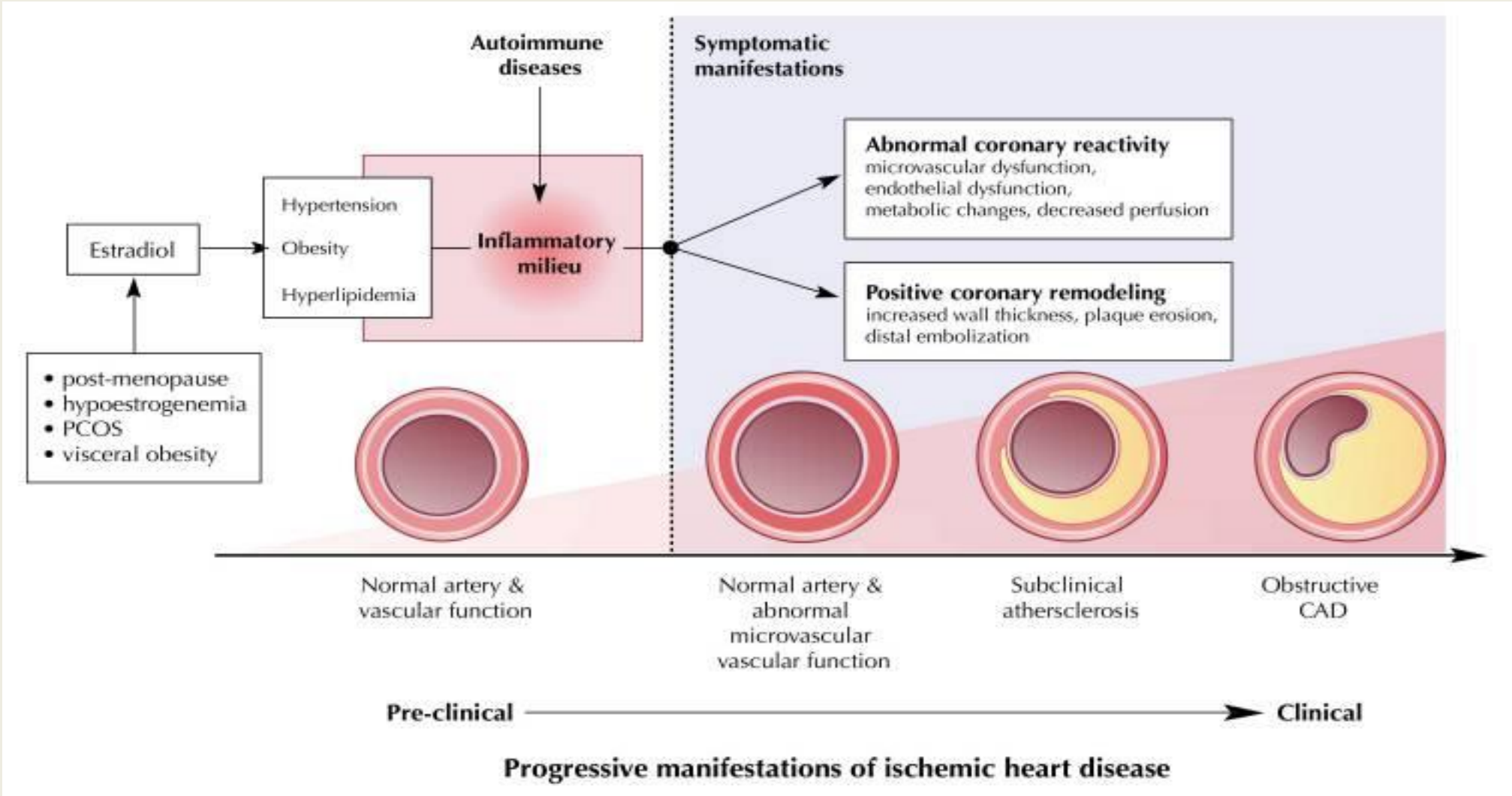
Conclusions

- There are important differences between men and women, in AMI, ACS and stable CAD presentation and management.
- Women tend to receive less intensive therapy and be referred less frequently and later for invasive management
- With increasing use of revascularization, and improved outcomes sex differences in lethality tend to vanish.
- But the proportion of younger women with AMI increases, presumably because of the increased prevalence of smoking and obesity in women
- Future research should address
  - Behavioral differences in management of AMI and CAD (patients and physicians).
  - Exploration of biological differences
- In the interim, women should not be deprived of the same management as men (particularly interventions) and we must close the “gender gap”

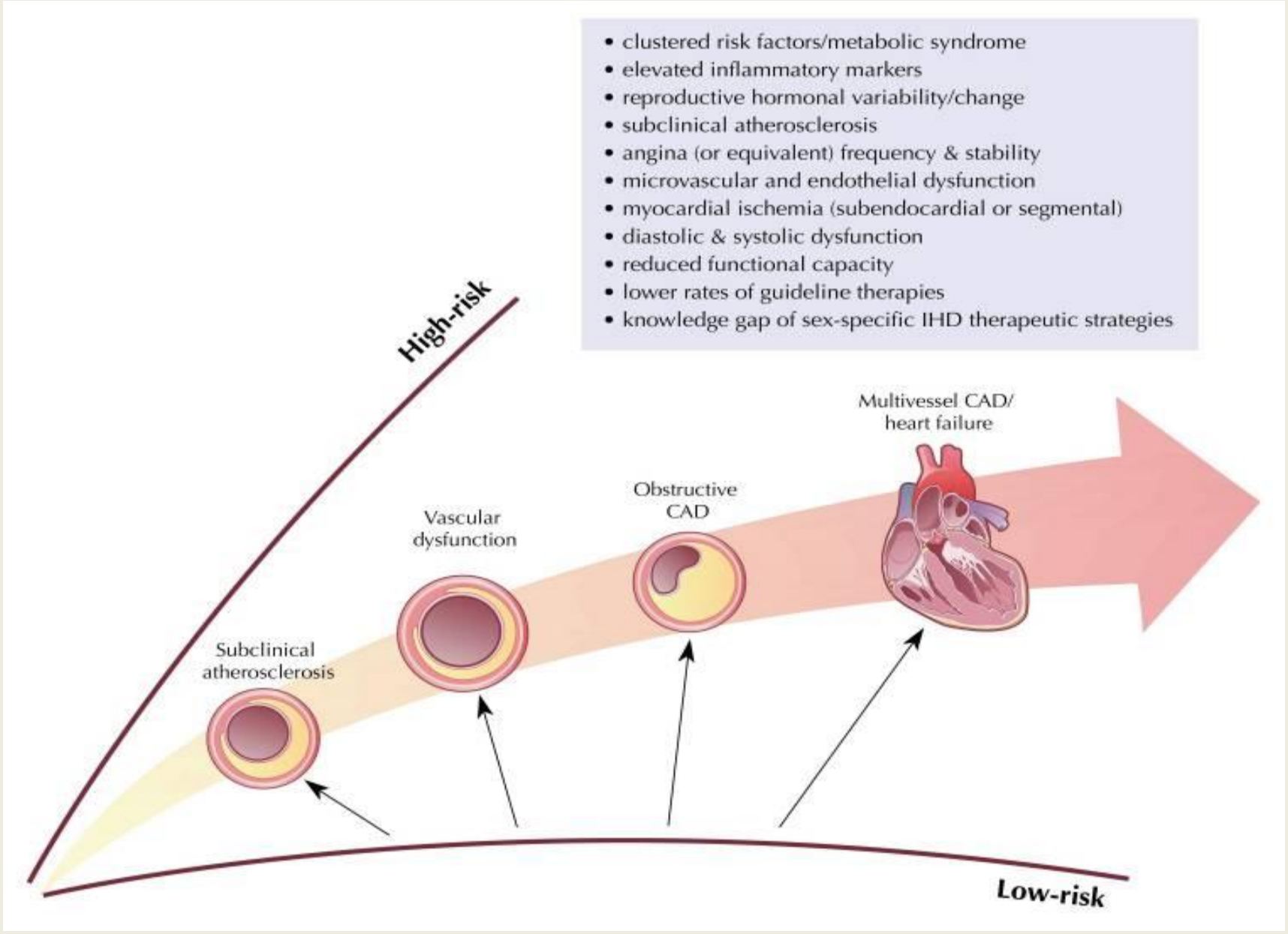
Gender and probability of death after primary PCI for STEMI



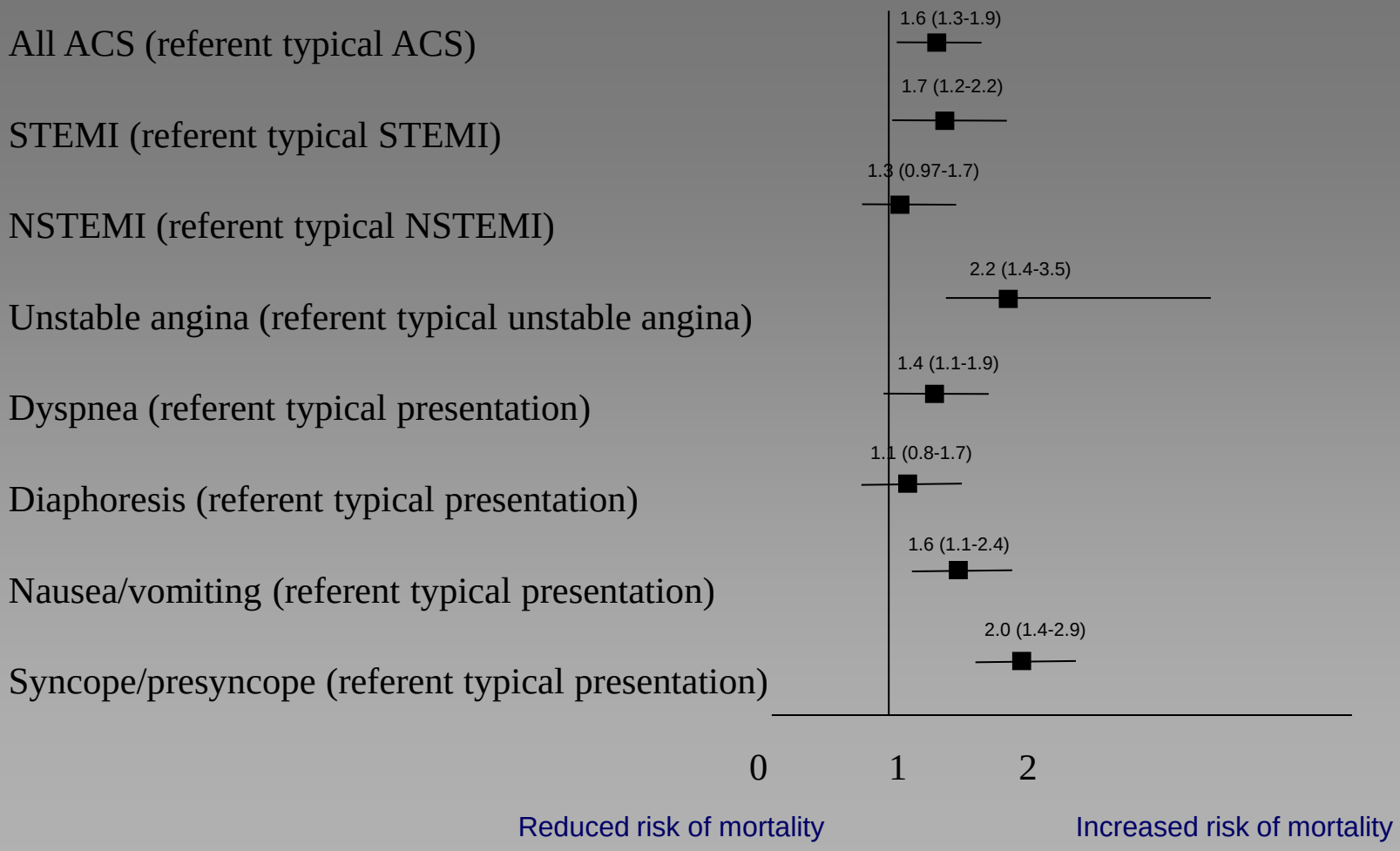
Juliard JM et al. ***Am J Cardiol*** 2013



Progressive manifestations of ischemic heart disease


• clustered risk factors/metabolic syndrome
• elevated inflammatory markers
• reproductive hormonal variability/change
• subclinical atherosclerosis
• angina (or equivalent) frequency & stability
• microvascular and endothelial dysfunction
• myocardial ischemia (subendocardial or segmental)
• diastolic & systolic dysfunction
• reduced functional capacity
• lower rates of guideline therapies
• knowledge gap of sex-specific IHD therapeutic strategies
High-risk
Multivessel CAD/
heart failure
Obstructive
CAD
Vascular
dysfunction
Subclinical
atherosclerosis
Low-risk

Atypical presentation: impact on hospital mortality



Brieger et al ***Chest*** 2004;126:461-9