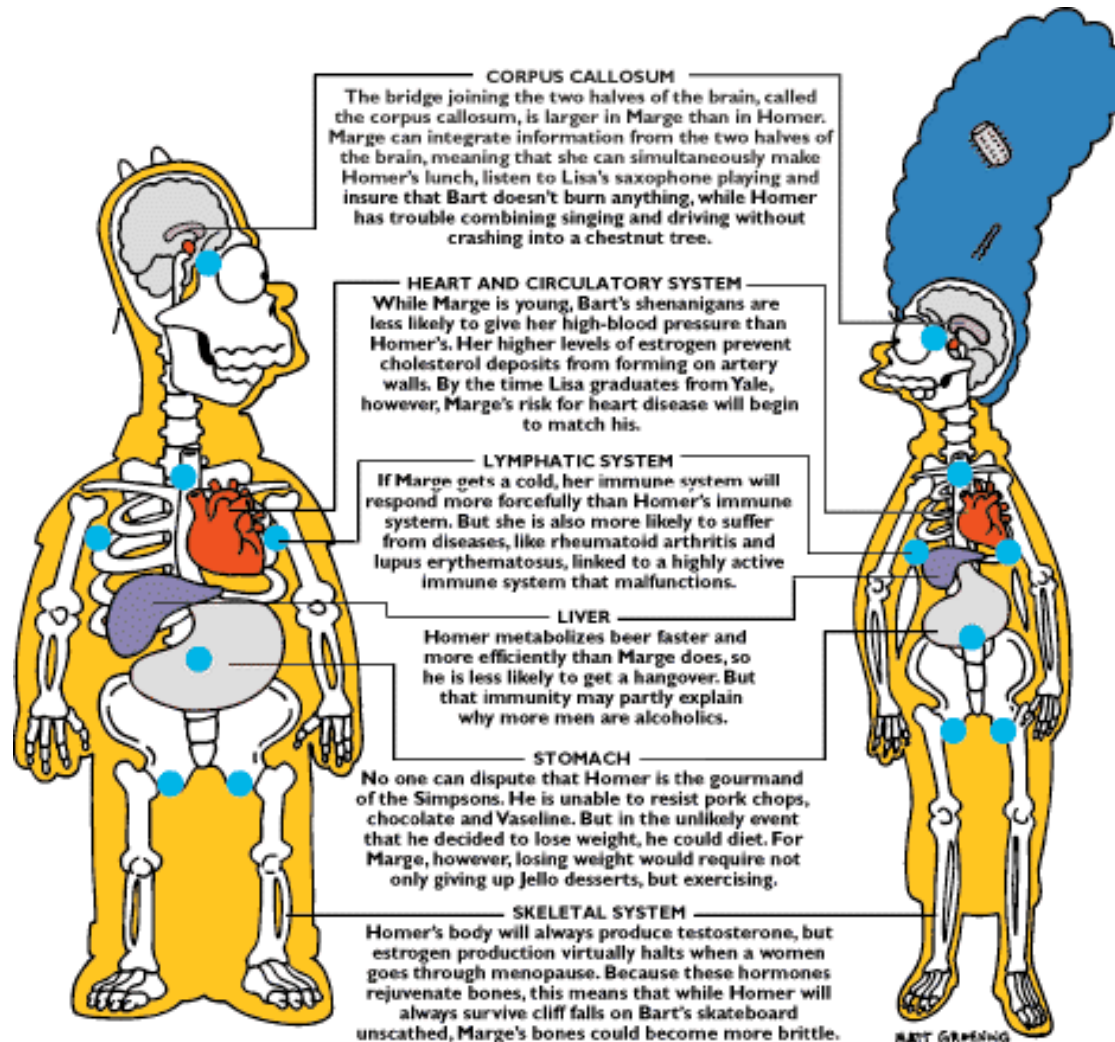# Gender Differences in Clinical Practice

Gender related differences in patient presentation, management and outcome across different manifestations of cardiovascular disease

Dr Caroline Daly, MB PhD
Cardiologist, Dublin

Gender Differences: Historical Male Focus

Sex differences in CV disease in 1990's

1991 NEJM

Ayanian & Epstein

- Women presenting with coronary disease less likely to have invasive investigation, PTCA or surgery

SAVE Study

- Less angiography in women post infarction

Wenger editorial

- "Yentl Syndrome"
- Reproach to "bikini" approach to womens' health, ignoring cardiovascular disease

Professional Society Support

- 2005 Women at Heart Initiative of ESC

- 2005 Go Red For Women by AHA

Scope of the problem

- Cardiovascular risks/1° and 2° prevention
  - Hypertension
  - Hyperlipidaemia
- Coronary Heart Disease
  - Angina
  - Acute coronary Syndrome/MI
- Heart Failure
- Arrhythmia
- Congenital Heart Disease

Scope of the problem

- Epidemiology/Natural History

- Morbidity and mortality (incl temporal trends)

- Access to services

- Investigation

- Pharmacological treatment

- Other treatments eg revasculatisation

Euro Heart Survey Programme

- Programme of surveys launched 1999 by ESC

Aims

- Applicability of evidence based medicine
- How clinical practice match guidelines
- Process and outcome associated with cardiac conditions in "real world", outside RCT's

Euro Heart Survey Programme

	1996	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Prevention Euro Aspire	+	+							+		
Heart Failure			+				+				
Acute Coronary Syndromes (ACS)		+				+					+
Valvular HD				+							
Revascularisation			+					+			
Angina					+						
Diabetes					+						
Atrial Fibrillation						+					
Adult Congenital Heart Disease						+					

Scope of the problem

- Cardiovascular risks/Primary prevention
  - Hypertension
  - Hyperlipidaemia
- Coronary Heart Disease
  - Angina
  - Acute coronary Syndrome/MI
- Heart Failure
- Arrhythmia
- Congenital Heart Disease

Age-Adjusted and Age-Specific Hypertension Awareness, Treatment, and Control in the U.S. Population Aged 60 and Older with Hypertension: National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES 1999–2004

	NHANES III			NHANES 1999–2004		
	Aware	Treated	Control in Treated	Aware	Treated	Control in Treated
			Percent			
Total	70	58	36	74	67	43
Sex						
Male	65	52	39	74	68	51
Female	74	62	35	74	67	37

EUROASPIRE I, II & III 1995/6, 1999/2000 & 2006/7

	Raised blood pressure			Raised cholesterol			Reported diabetes		
	I	II	III	I	II	III	I	II	III
Men	1345/2388 (56·3%)	1270/2223 (57·1%)	1106/1835 (60·3%)	1686/1794 (94·0%)	1554/2078 (74·8%)	756/1747 (43·3%)	388/2389 (16·2%)	411/2222 (18·5%)	476/1822 (26·1%)
Women	502/790 (63·5%)	460/746 (61·7%)	346/550 (62·9%)	582/605 (96·2%)	568/688 (82·6%)	293/526 (55·7%)	164/791 (20·7%)	187/748 (25·0%)	188/549 (34·2%)

Mean age 59, 25% female

Kotseva Lancet 2009

EUROASPIRE I, II & III
Proportion of pts achieving target BP

	No blood pressure lowering Tx			Blood Pressure Lowering Tx		
	I	II	III	I	II	III
Men	182/393 (46·3%)	104/219 (47·5%)	32/62 (51·6%)	861/1995 (43·2%)	849/2004 (42·4%)	693/1761 (39·4%)
Women	47/99 (47·5%)	28/60 (46·7%)	8/12 (66·7%)	241/691 (34·9%)	258/686 (37·6%)	196/535 (36·6%)

Mean age 59, 25% female

Kotseva Lancet 2009

Scope of the problem

- Cardiovascular risks/Primary prevention
  - Hypertension
  - Hyperlipidaemia
- Coronary Heart Disease
  - Acute coronary Syndrome/MI
  - Angina
- Heart Failure
- Arrhythmia
- Congenital Heart Disease

Meta-analysis of RCT data on ACS
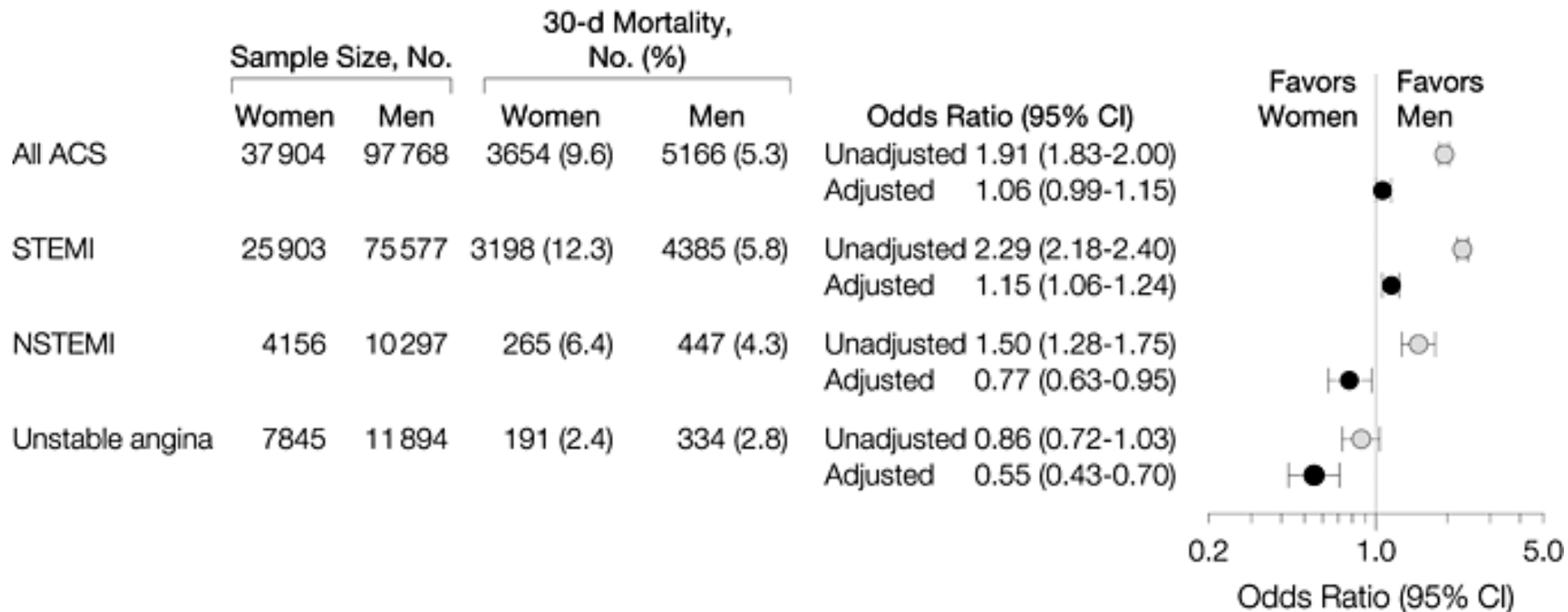
Table 1. Summary of Trials Used in the Study

Source	No./Total No. (%) of Patients Enrolled		Type of ACS Evaluated	Intervention
	Women	Men		
GUSTO I,[25] 1993	10 315/40 968 (25.2)	30 653/40 968 (74.8)	STEMI	Streptokinase and subcutaneous heparin, streptokinase and intravenous heparin, accelerated tissue plasminogen activator and intravenous heparin, or a combination of streptokinase plus tissue plasminogen activator with intravenous heparin
GUSTO IIb,[26] 1996	3661/12 140 (30.2)	8479/12 140 (69.8)	STEMI, NSTEMI, unstable angina	Heparin; hirudin
GUSTO III,[27] 1997	4124/15 059 (27.4)	10 935/15 059 (72.6)	STEMI	Tissue plasminogen activator; reteplase
ASSENT II,[28] 1999	3930/17 004 (23.1)	13 074/17 004 (76.9)	STEMI	Tissue plasminogen activator; tenecteplase
ASSENT III,[29] 2001	1438/6116 (23.5)	4678/6116 (76.5)	STEMI	Full-dose tenecteplase and heparin; full-dose tenecteplase and enoxaparin; half-dose tenecteplase and abciximab
ASSENT III+,[30] 2003	378/1639 (23.1)	1261/1639 (76.9)	STEMI	Full-dose tenecteplase and heparin; full-dose tenecteplase and enoxaparin
HERO 2,[31] 2001	4850/17 087 (28.4)	12 237/17 087 (71.6)	STEMI	Bivalirudin; heparin; streptokinase
PURSUIT,[32] 2000	3857/10 947 (35.2)	7090/10 947 (64.8)	NSTEMI, unstable angina	Placebo; low-dose eptifibatide; high-dose eptifibatide
PARAGON A,[33] 1998	776/2262 (34.3)	1486/2262 (65.7)	NSTEMI, unstable angina	Low-dose lamifiban with and without heparin; high-dose lamifiban with and without heparin
PARAGON B,[34] 2000	1789/5225 (34.2)	3436/5225 (65.8)	NSTEMI, unstable angina	Lamifiban; heparin
GUSTO IV,[35] 2001	2930/7800 (37.6)	4870/7800 (62.4)	NSTEMI, unstable angina	Heparin; 24-h abciximab; 48-h abciximab
Total	**38 048/136 247** (27.9)	**98 199/136 247** (72.1)		

Abbreviations: ACS, acute coronary syndromes; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Berger, J. S. et al. JAMA 2009;302:874-882.

JAMA

Unadjusted and Multivariable-Adjusted 30-Day Mortality Models in Women vs Men Across the Spectrum of ACS (n = 136 247)

	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	25 903	75 577	3198 (12.3)	4385 (5.8)	Unadjusted	2.29 (2.18-2.40)
					Adjusted	1.15 (1.06-1.24)
NSTEMI	4156	10 297	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)

Favors Women | Favors Men

Odds Ratio (95% CI) 0.2 1.0 5.0

Berger, J. S. et al. JAMA 2009;302:874-882.

JAMA

Euro Heart Survey of Acute Coronary Syndromes I

- Pan European Survey of patients with acute coronary syndromes presenting to hospitals across Europe

- Diagnosis of ACS at presentation assessed

- Use of investigations and treatments surveyed

- In hospital outcome assessed in this analysis

Enrollment: September 2000 to May 2001

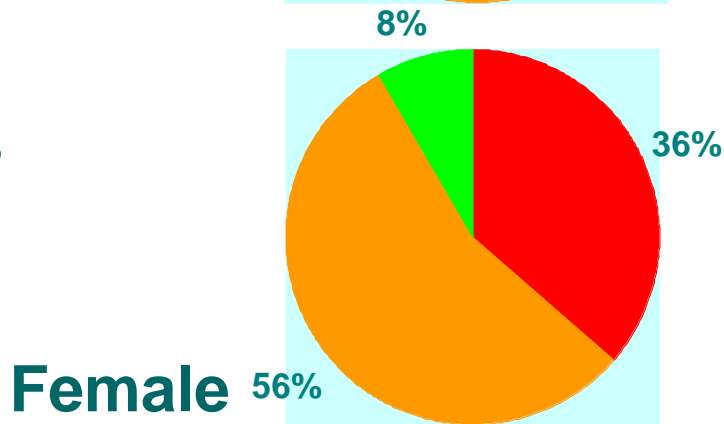# EHS ACS I   n=10,253
Initial Diagnosis

< 65 yrs

4%
39%
57%
(Female, <65 yrs)

3%
51%
46%
(Male, <65 yrs)

> 65 yrs

8%
36%
Female 56%

10%
38%
Male 52%
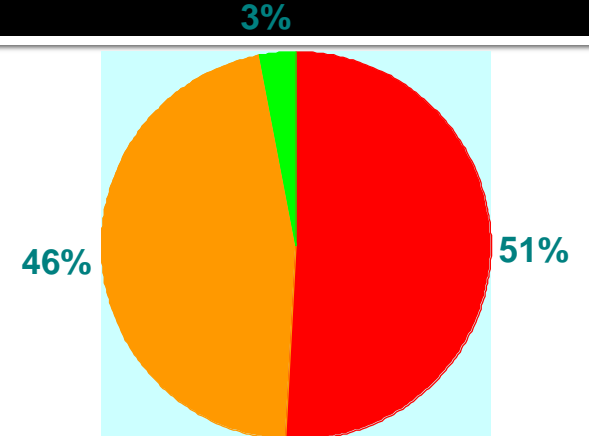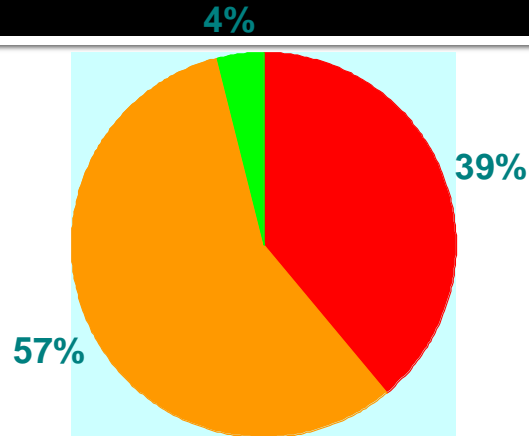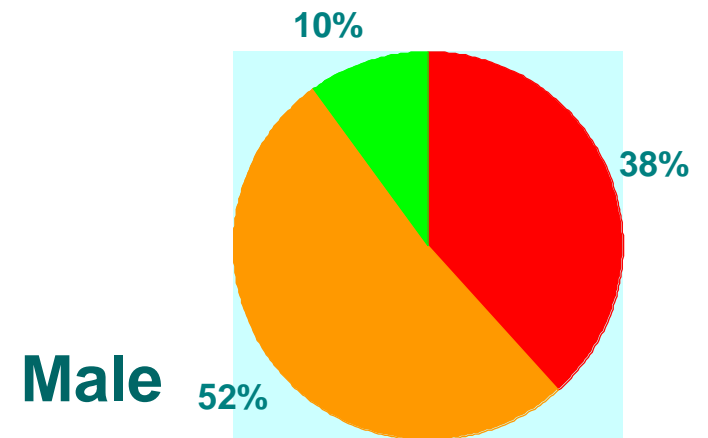
ST elevation MI   Non ST elevation ACS   Undetermined

Gender differences at presentation

➢ Women are older, more likely to have a history of diabetes or hypertension and less likely to smoke

Women less than 65

- More atypical chest pain OR 1.7 (1.3-2.2)

- More normal ECG's OR 1.3 (1.1-1.5)

- Higher HR and Systolic BP

Women over 65

- Symptoms and ECG findings similar

- Higher HR and Systolic BP

- Greater severity of Killip Class. p=0.009

"Normal" coronary angiography
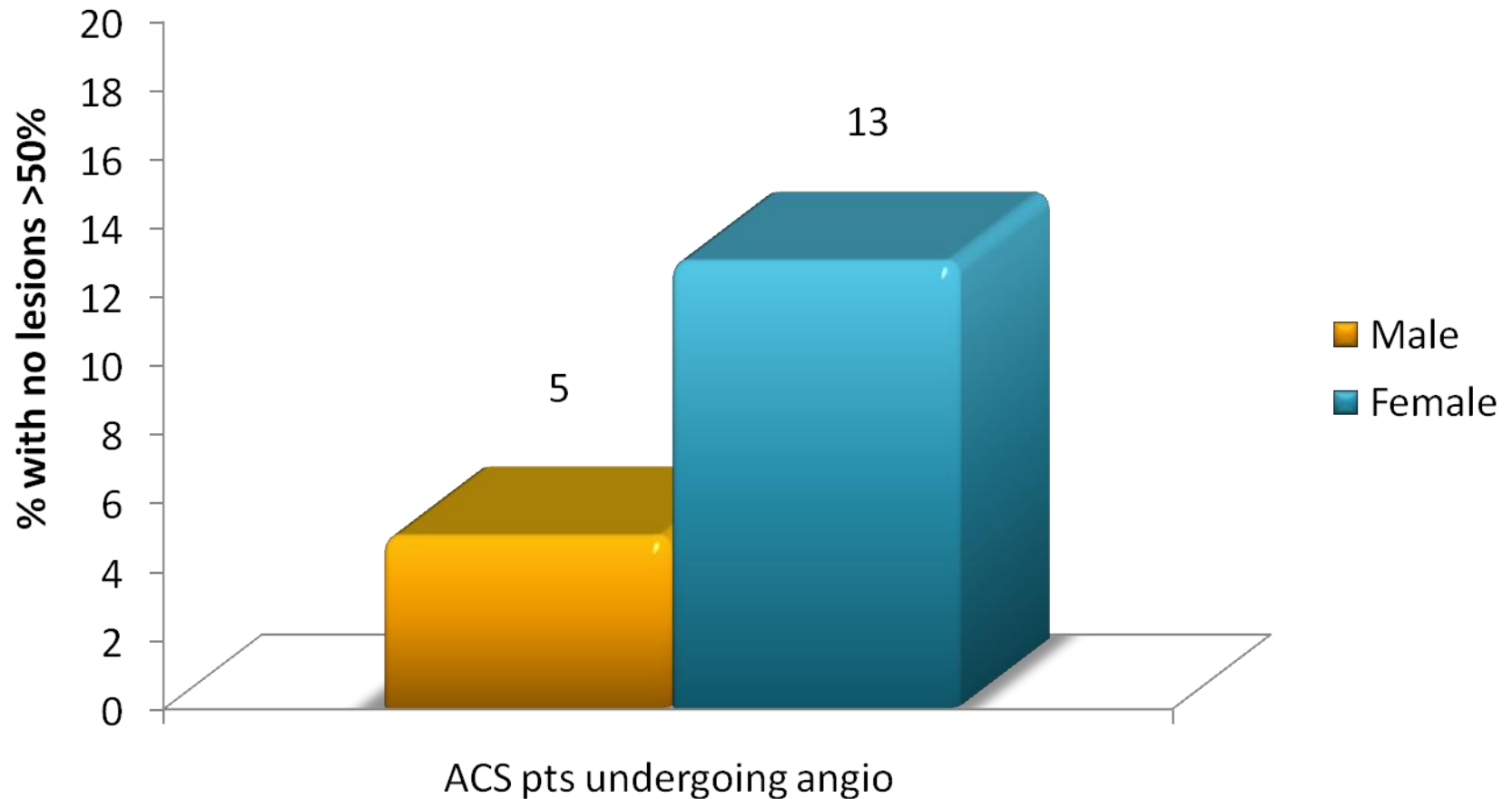
Variation in Spectrum of ACS

- Discharge diagnosis of "Unstable Angina" more likely in younger women OR 1.56 (1.35-1.79), not so in older age group

- Hochman et al, NEJM 1999 (GUSTO IIb)

- ? Different pathophysiological process at play

- Finding confirmed in unselected population and found to be significantly age dependent
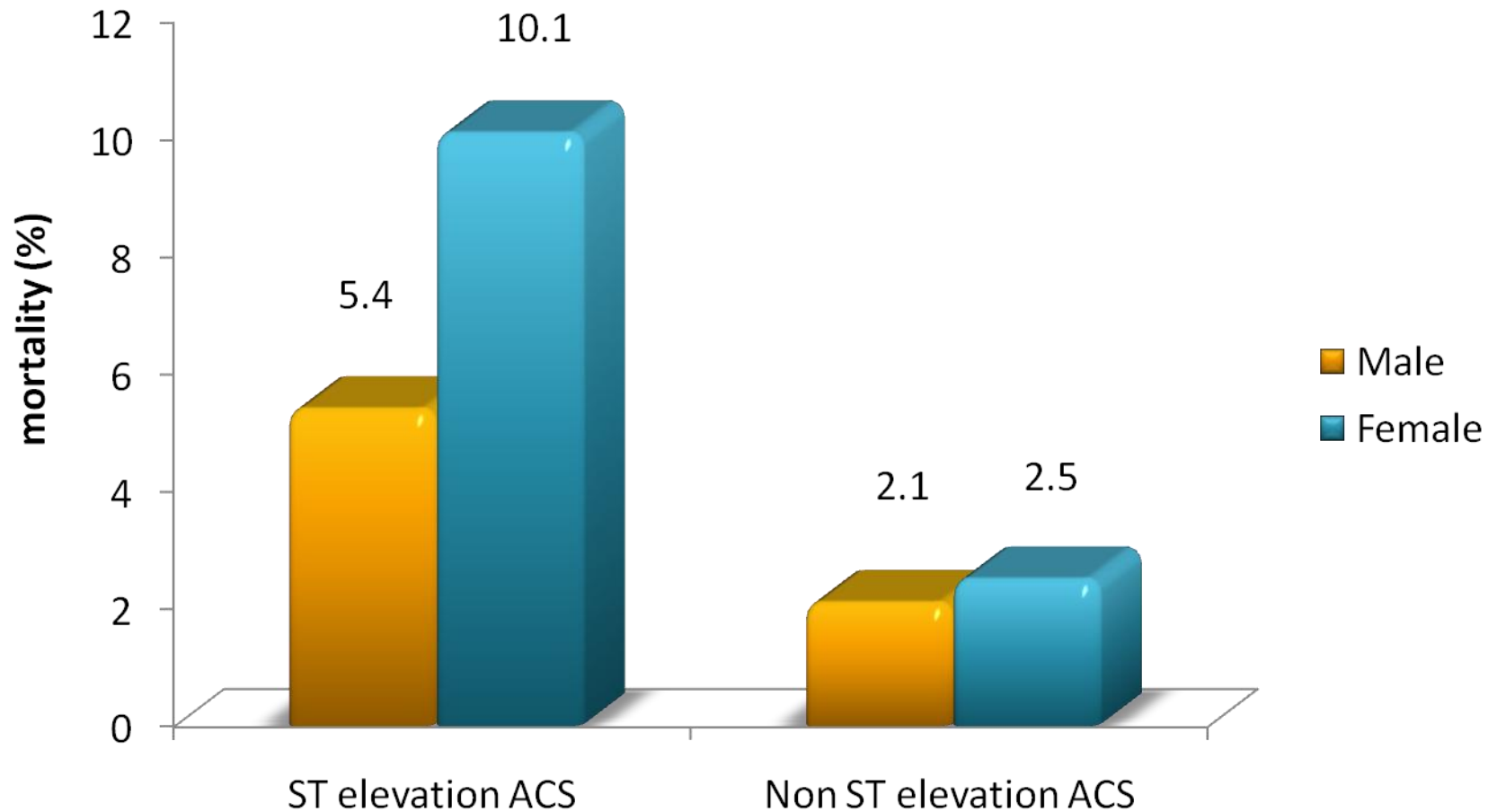
Reperfusion therapy (ST elevation MI only)
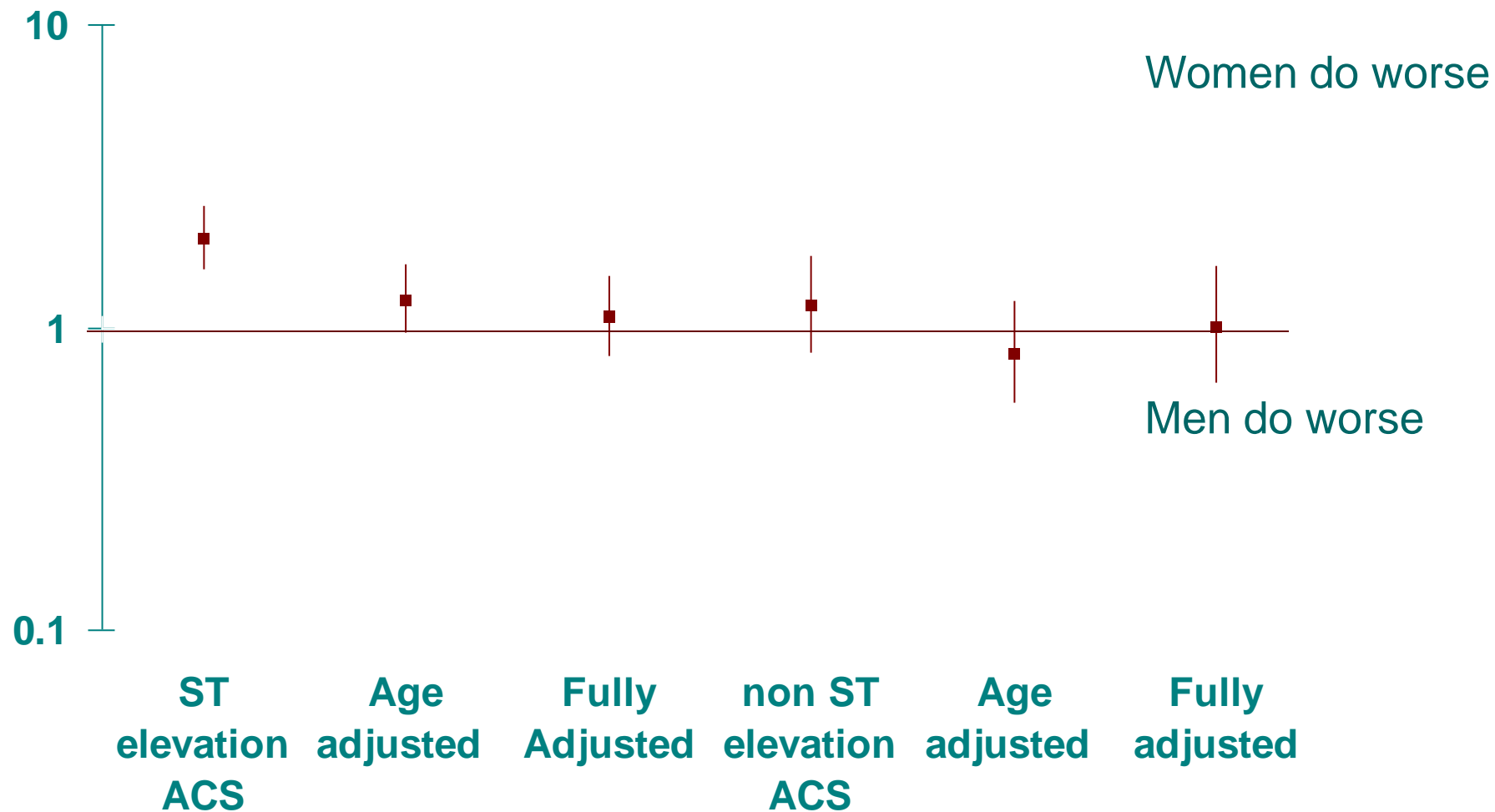

< 65 yrs

ns
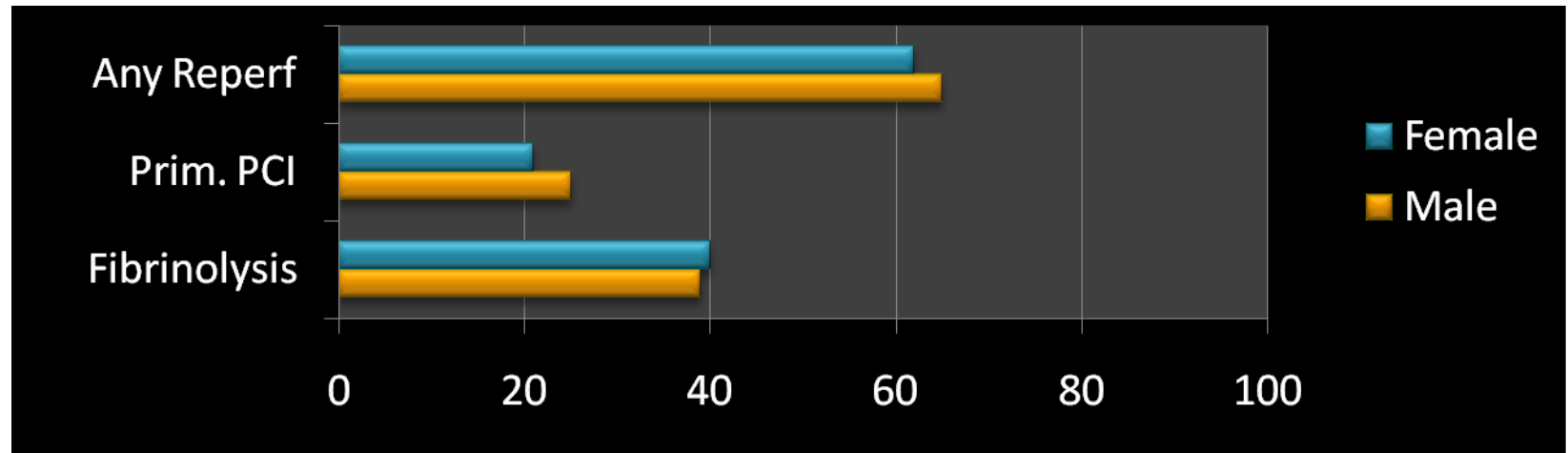
> 65 yrs

OR 0.66 (0.55-0.78)
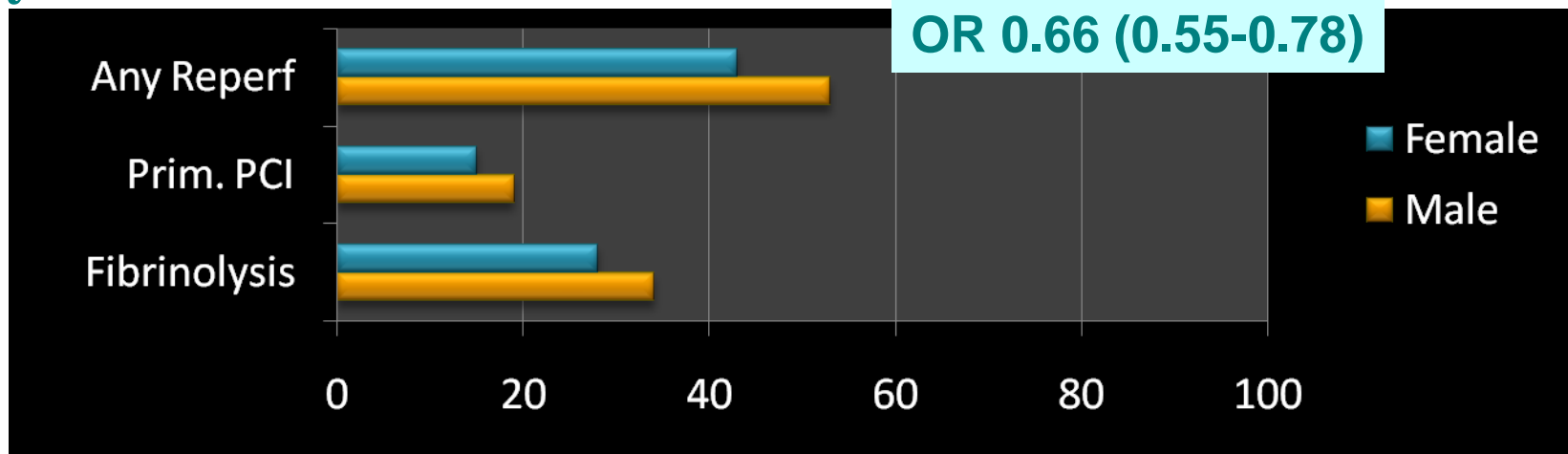
In-Hospital mortality

In-Hospital mortality

Women do worse

Men do worse

10

1

0.1

ST elevation ACS

Age adjusted

Fully Adjusted

non ST elevation ACS

Age adjusted

Fully adjusted

NB not adjusted for differences in reperfusion therapy

EHS PCI survey (2005):
Predictors of in-hospital MACCE in STEMI patients
Baseline data and angiographic information (n=2621)
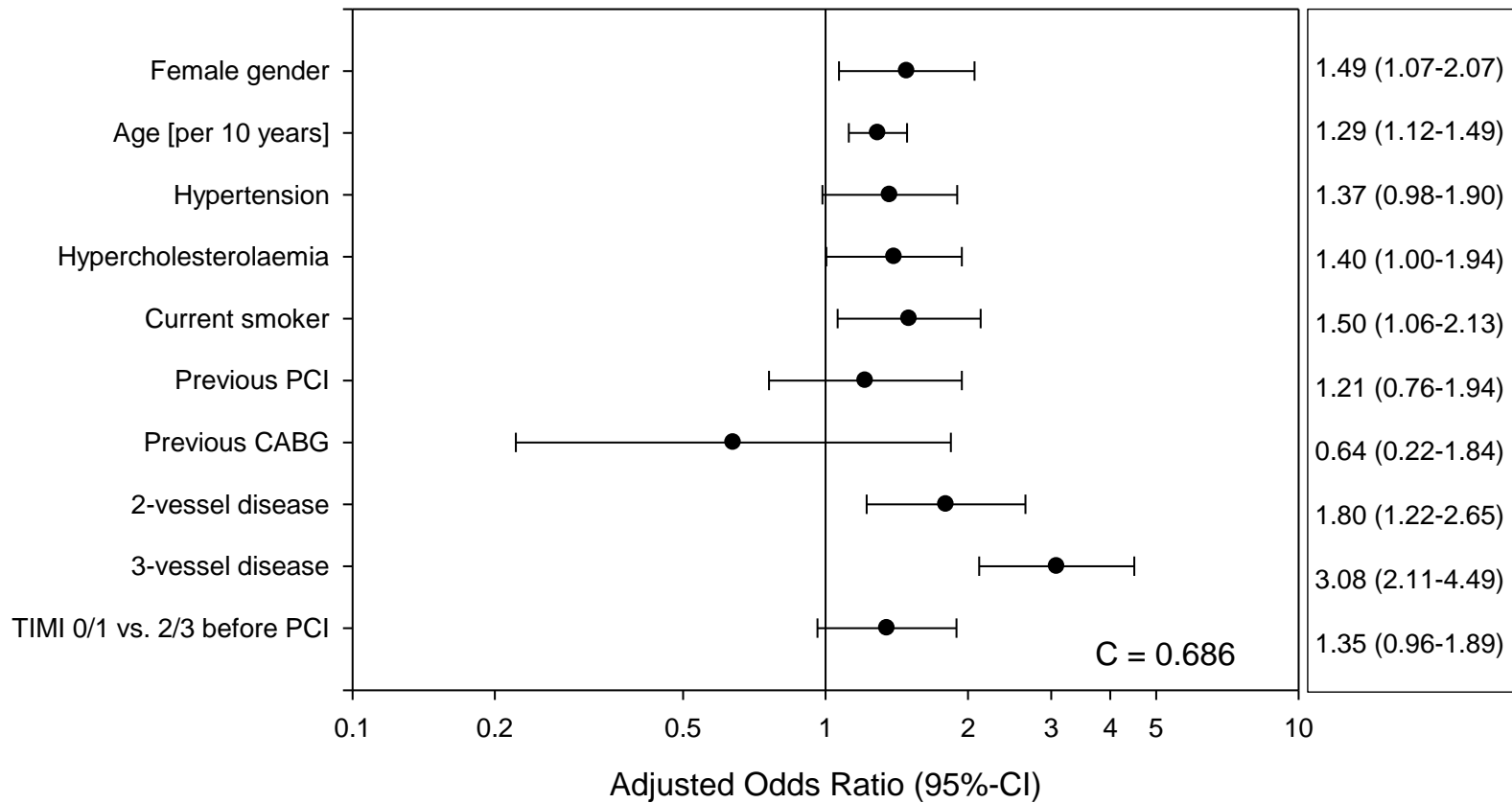
Summary of gender differences in ACS I

- Women are more likely to present with non ST elevation MI or have unstable angina than men

- Women have more adverse baseline characteristics and older women present with more worse clinical predictors (Killip Class etc)

- Women with ST elevation are 1/3 less likely than men to receive reperfusion

- Crude in-hospital mortality for women is twice that of men, but after adjustment differences not significant

Gender related coronary disease manifestations

First manifestations of CHD by sex from 26 year
follow-up of Framingham *(Lerner & Kannel 1986)* **Finnish Data**
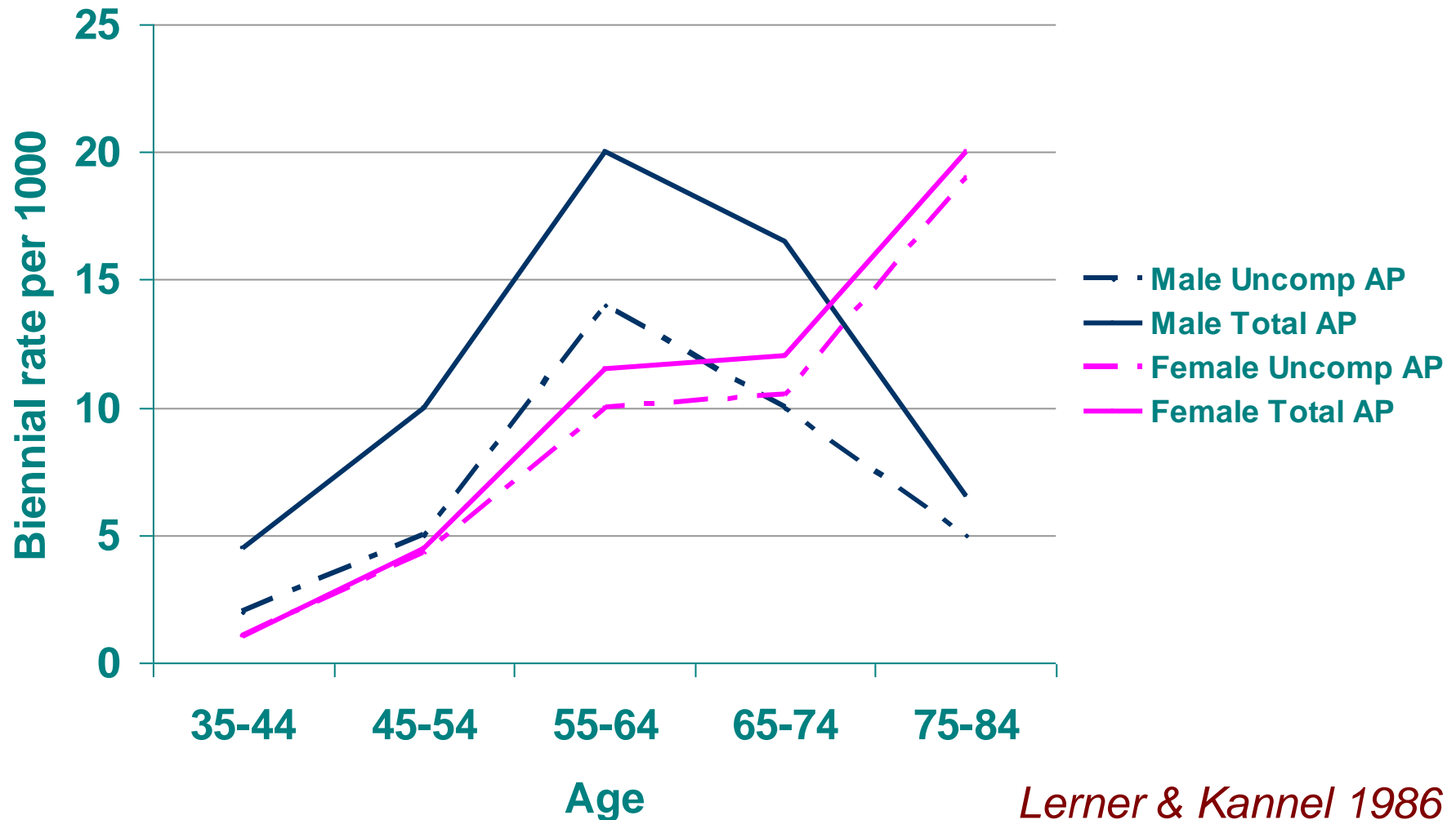*Reunanen et al '85*

Men
- MI   43%
- followed by Angina   26%   **29%**
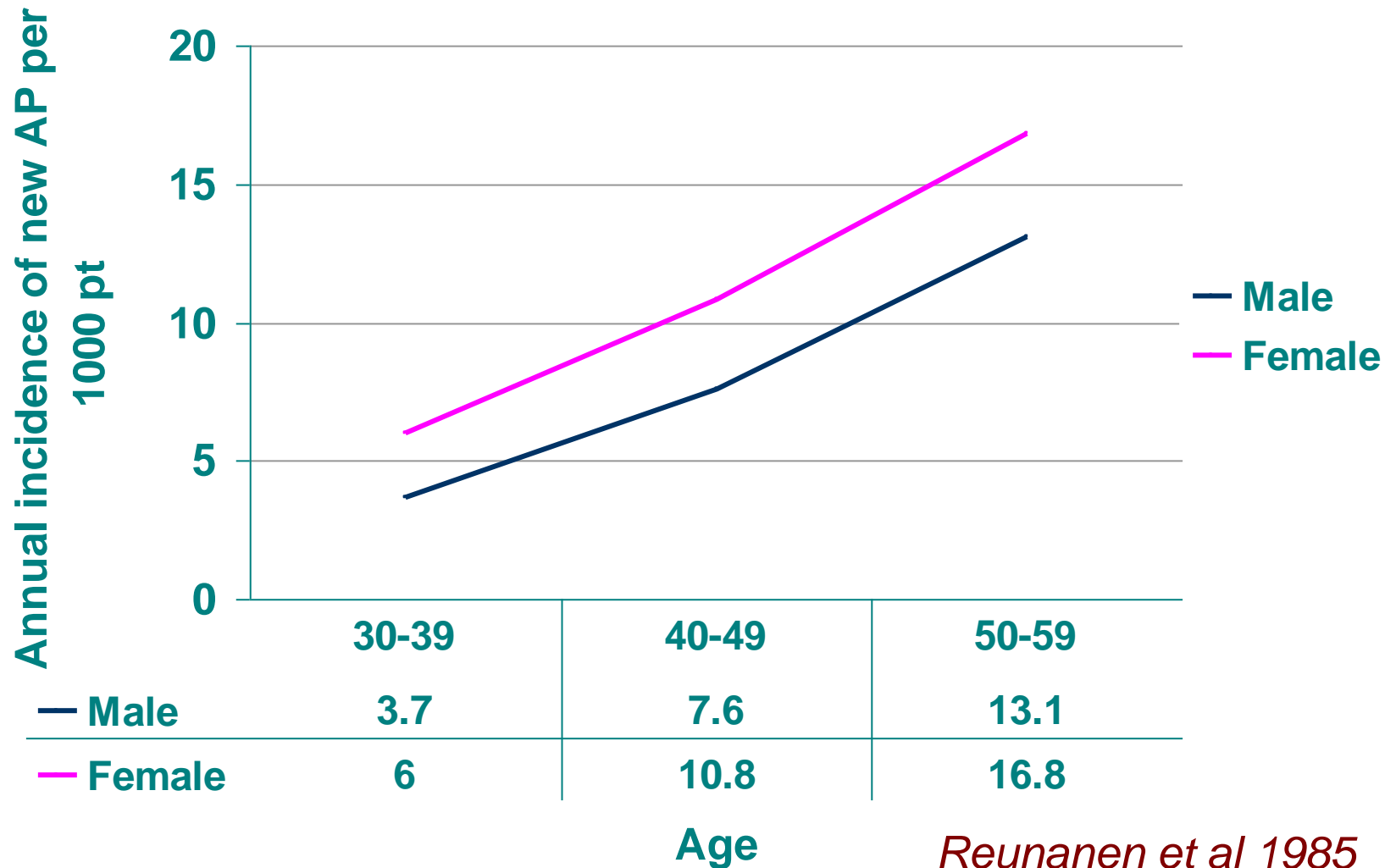- then sudden death   10%

In Women the distribution of events is changed
- MI   29%
- Angina   47%   **50%**
- sudden death   7 %

Age and sex specific incidence of Angina

Lerner & Kannel 1986

Age and sex specific incidence of Angina

Reunanen et al 1985

	30-39	40-49	50-59
Male	3.7	7.6	13.1
Female	6	10.8	16.8

Prevalence of Stable Angina

Study	Country	Years	Age	Definition	Male	Female
	Wales	1967	30-74	Rose		17.8%
9 Comm	Italy	1978-79	30-69	Rose	2.3%	3.1%
SHS	Scotland	1979-80	40-59	Rose	6.3%	8.5%
BRHS	UK	1978-80	40-59	Rose	4.8%	
EPES	USA	1981-83	>65	Rose	3-4%	4-6%
CVHS	USA	1989-90	>65	Confirmed self-report	16%	10%
NHANES	USA	1988-94	40-65	Rose	5.2%	6.2%
PANES	Spain	1990's	30-69	Rose	7.3%	7.8%
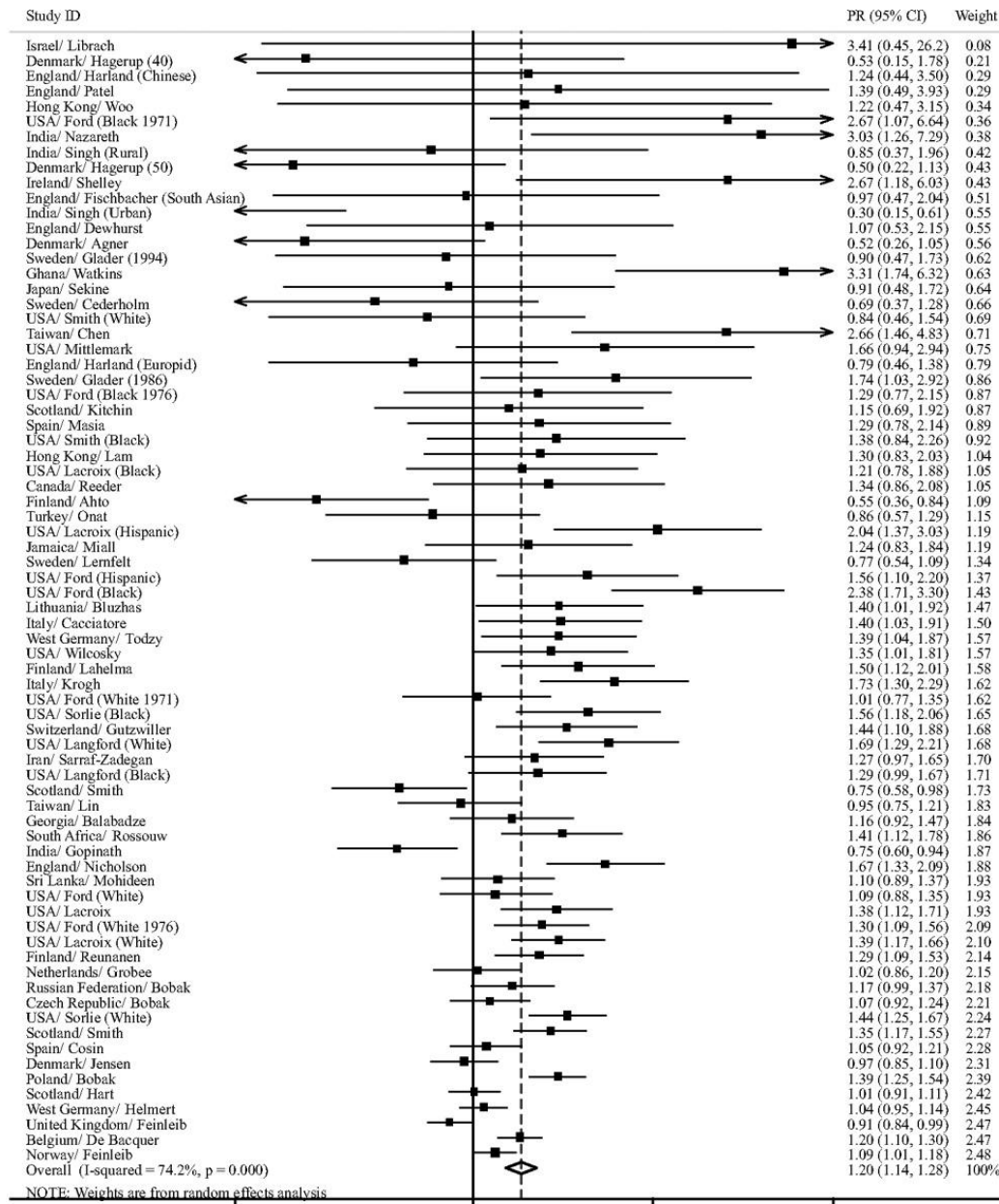
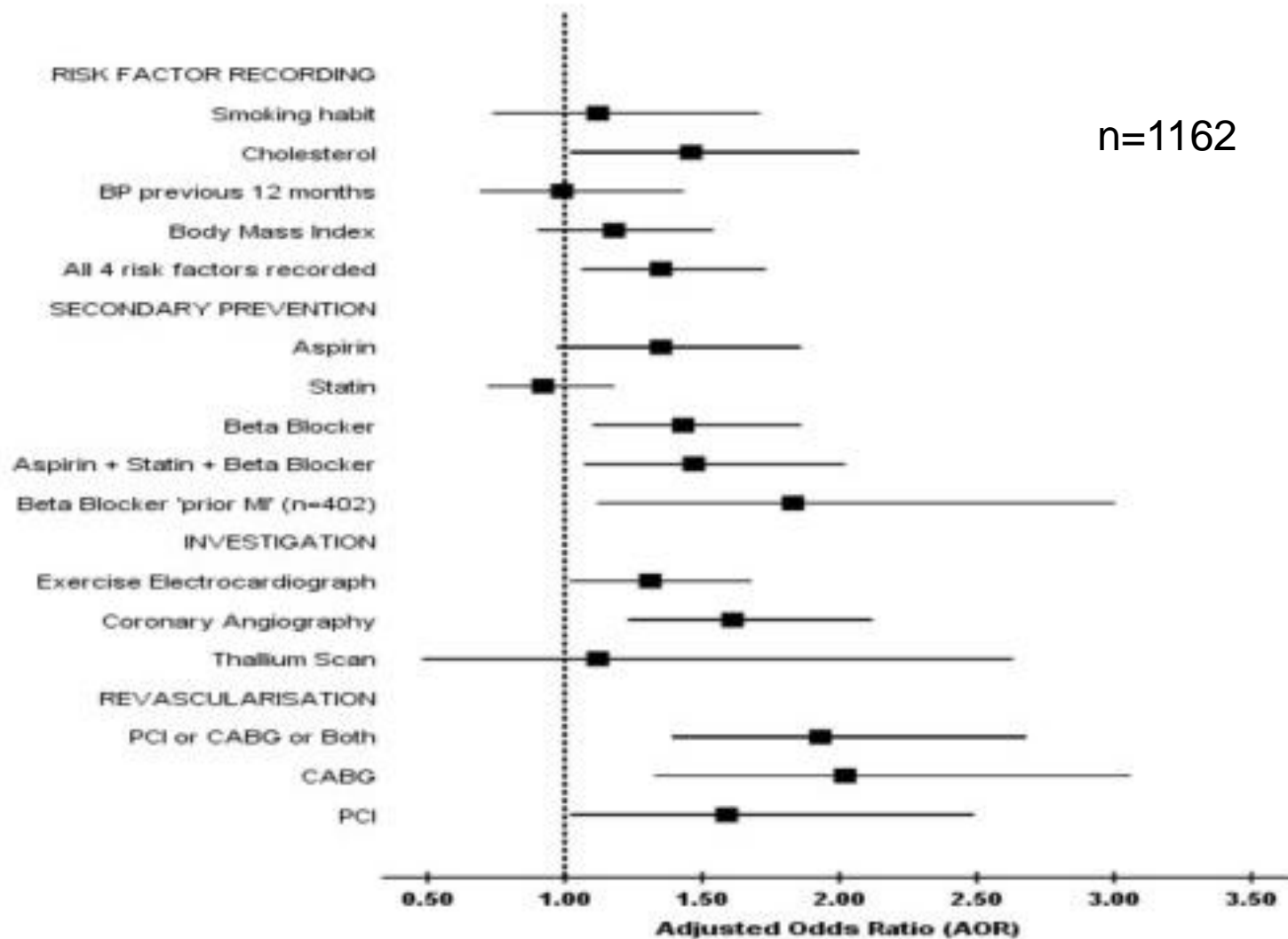# Sex ratios in Rose angina prevalence ([PR] 95% CIs)

Hemingway, H. et al. Circulation 2008;117:1526-1536

# Liverpool Primary Care Study 2001


n=1162

Liverpool Primary Care Study 2001

n=1162

RISK FACTOR RECORDING
- Smoking habit
- Cholesterol
- BP previous 12 months
- Body Mass Index
- All 4 risk factors recorded

SECONDARY PREVENTION
- Aspirin
- Statin
- Beta Blocker
- Aspirin + Statin + Beta Blocker
- Beta Blocker 'prior MI' (n=402)

INVESTIGATION
- Exercise Electrocardiograph
- Coronary Angiography
- Thallium Scan

REVASCULARISATION
- PCI or CABG or Both
- CABG
- PCI

Adjusted Odds Ratio (AOR)
0.50 1.00 1.50 2.00 2.50 3.00 3.50

Temporal Changes in Rates of Cardiac Stress tests without imaging per 1000, by Gender, Adjusted for Age, Medicare, 1993–2001

Annual decrease

Males   -1.1%
Females -0.5%
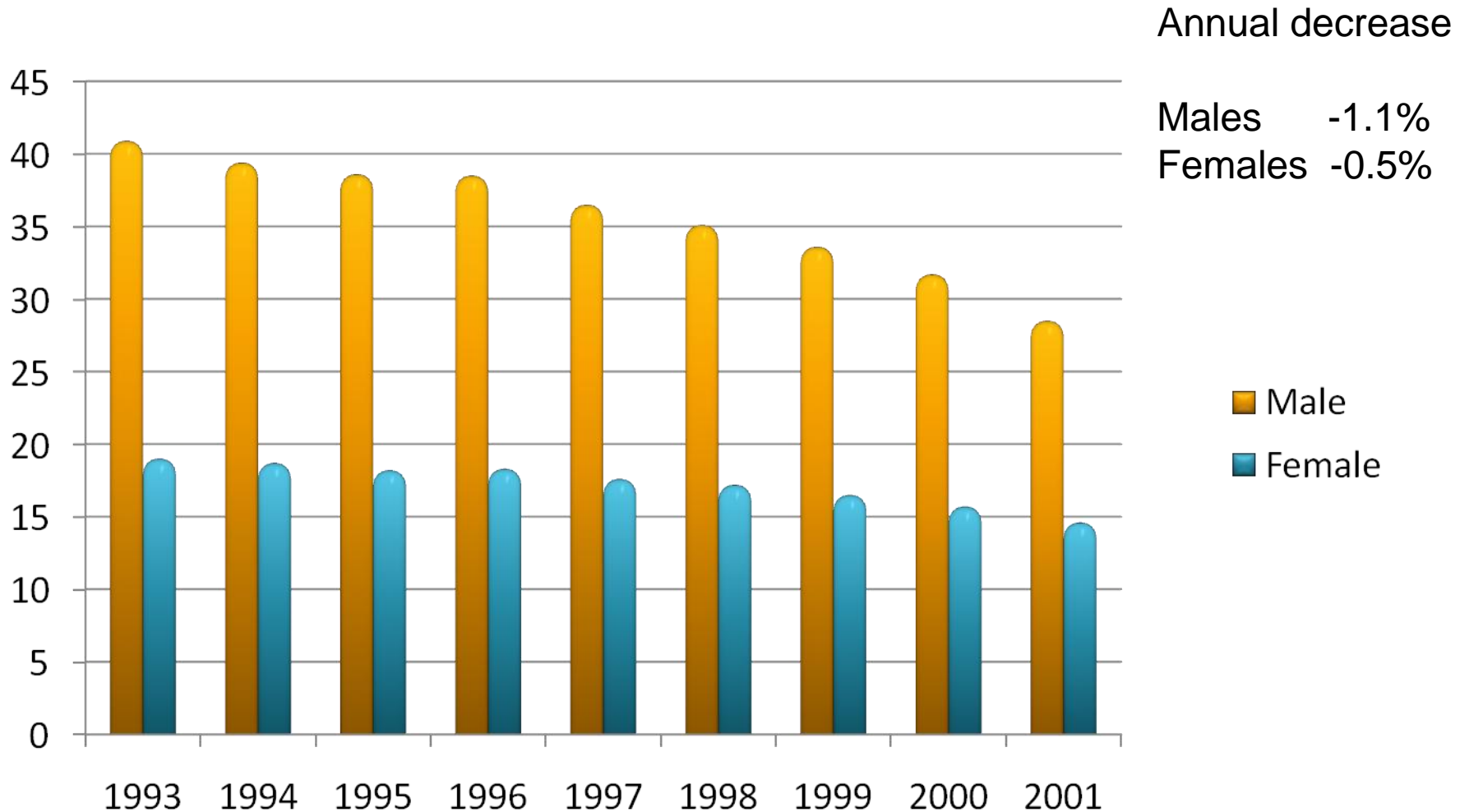
Temporal Changes in Rates of Cardiac Stress Imaging Procedures per 1000, by Gender, Adjusted for Age, Medicare, 1993–2001

Annual increase
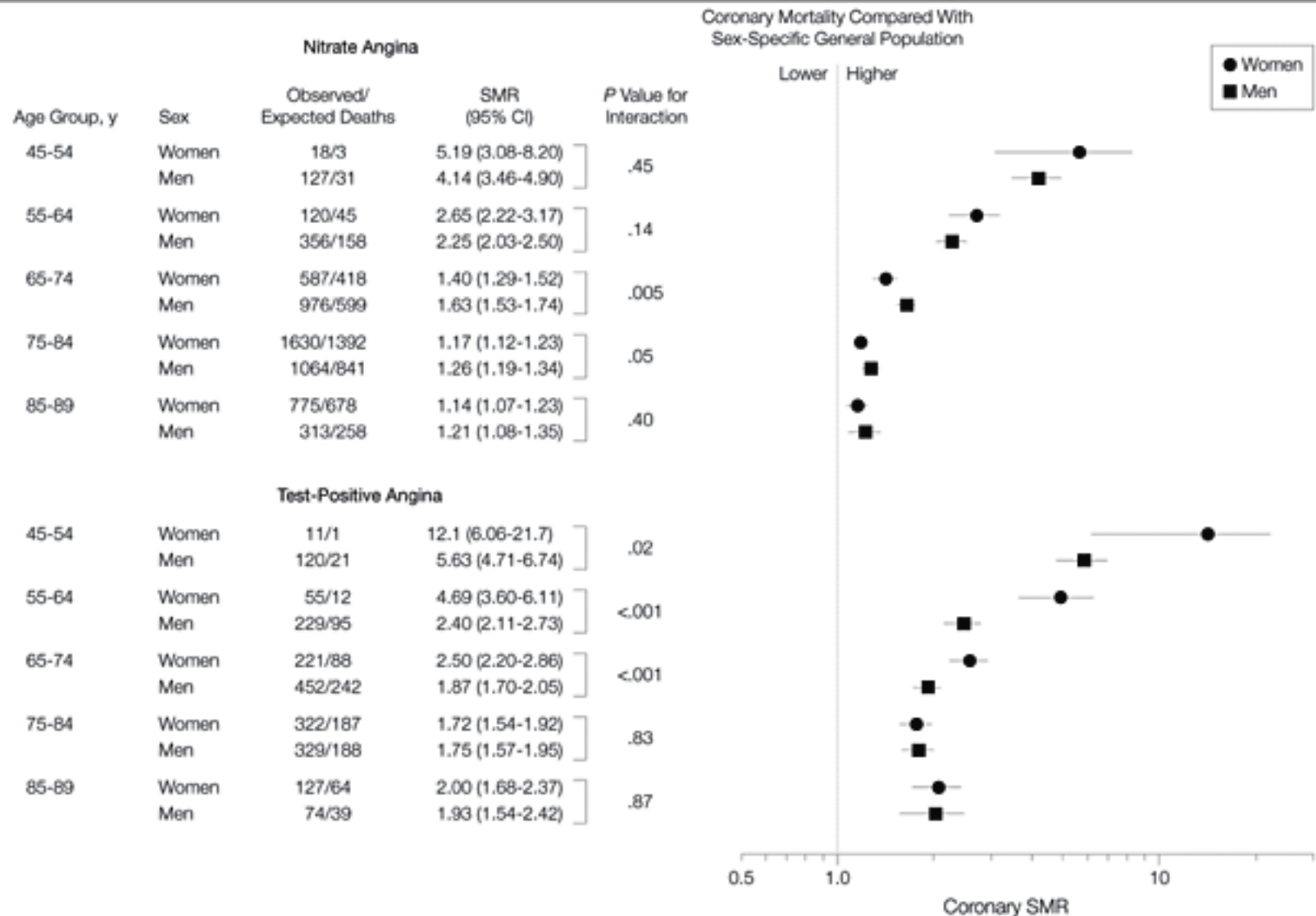
Males   7.8%
Females 5.7%
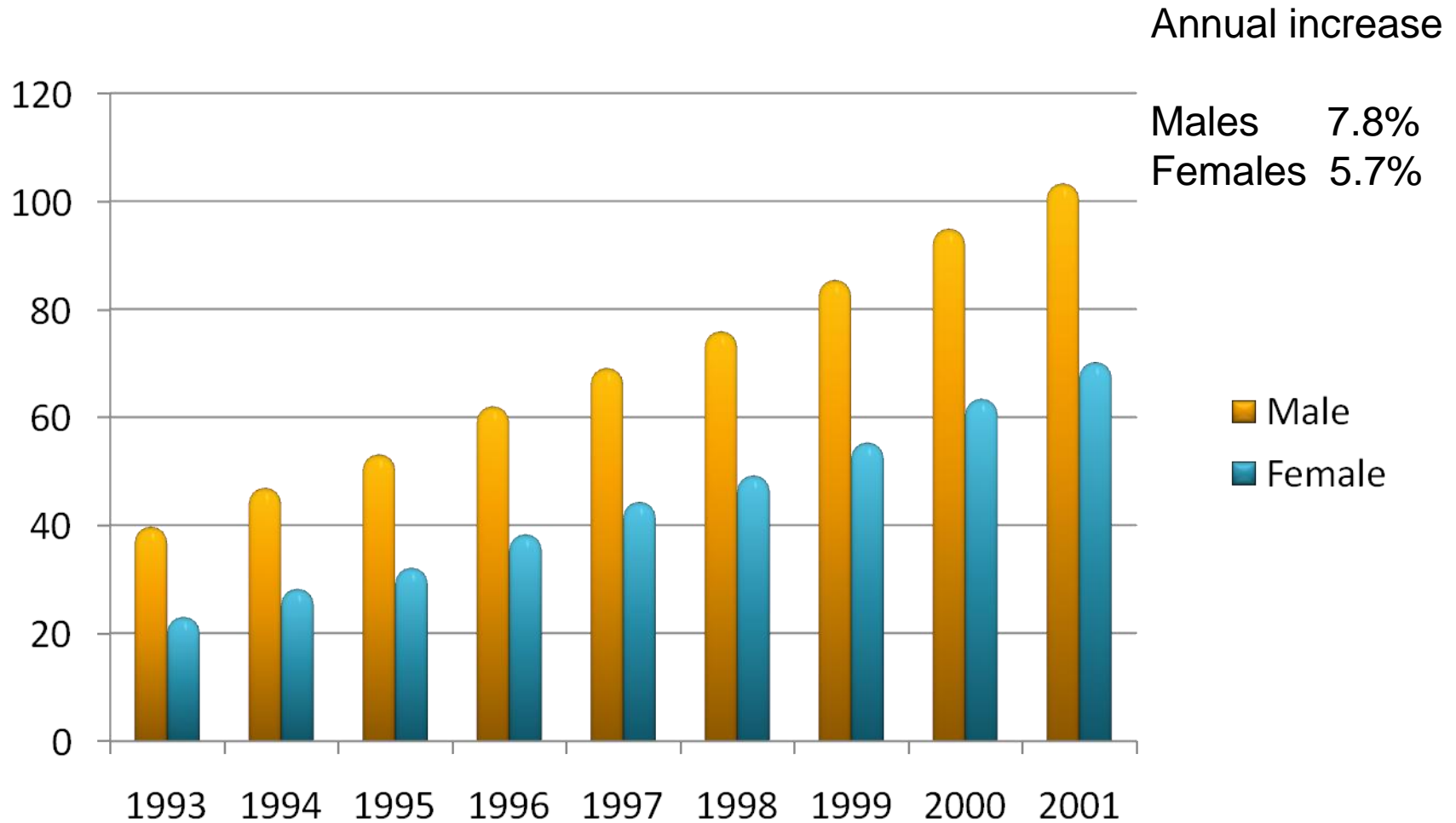
Temporal Changes in Rates of Cardiac Catheterisation Procedures per 1000, by Gender, Adjusted for Age, Medicare, 1993–2001

Annual increase

Males   2.4%
Females 1.6%
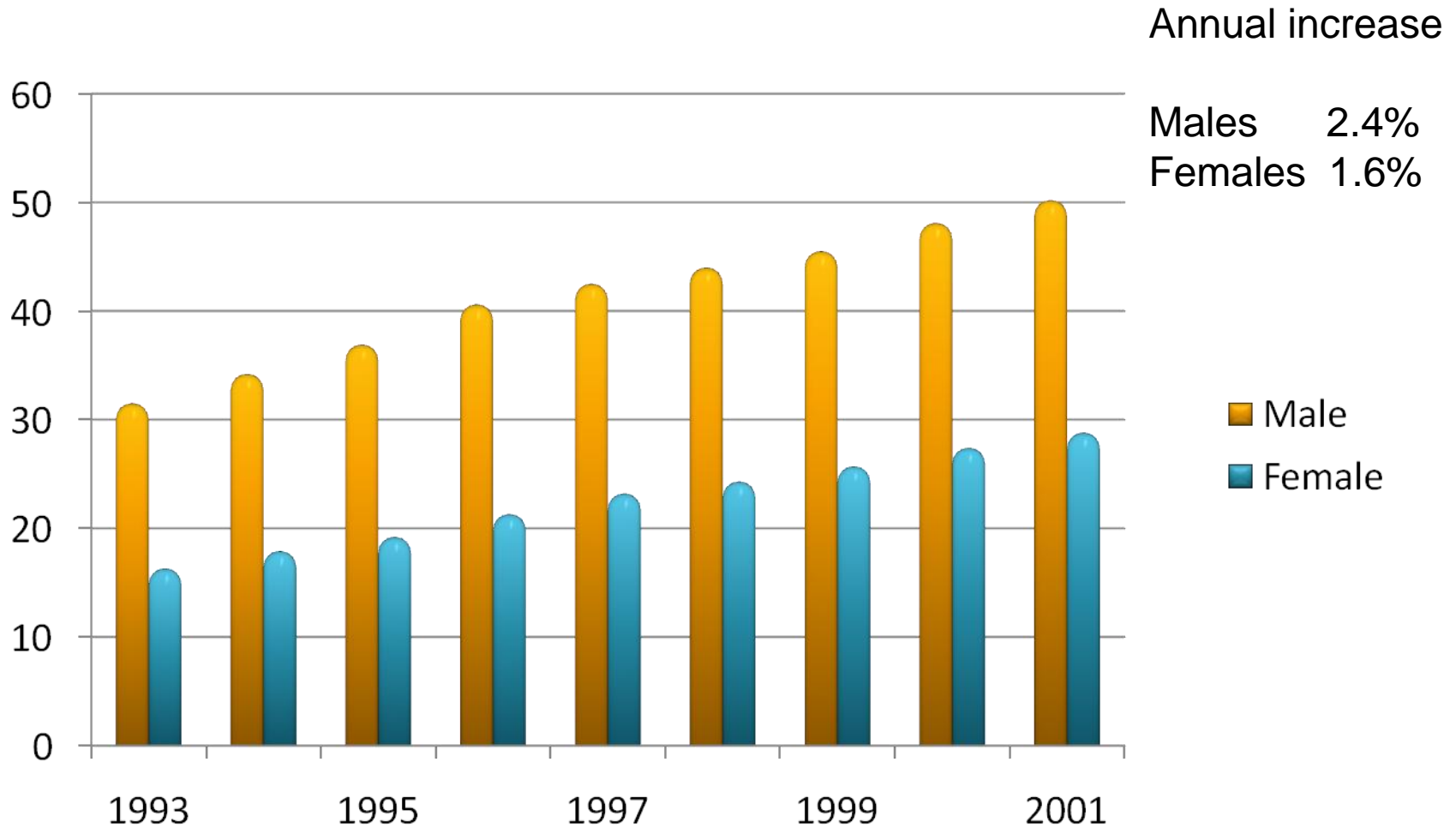
Standardised Mortality Rates in Angina
Hemingway JAMA 2007

Gender Differences in Angina

Euro Heart Survey of Stable Angina

Daly et al Circulation 2006

Euro Heart Survey of Angina

- Pan European Survey of patients with **stable angina** presenting to cardiologists in Europe, with one year follow-up

- Based on ambulatory, non hospitalised patients

- Full complement of investigations and treatments surveyed across countries, also clinical outcome

Initial survey: March 2002 to December 2002

Follow up: March 2003 to January 2004

Definition

- <u>Out-patient</u> at a <u>new presentation</u> to a <u>cardiologist</u>
- in whom <u>diagnosis is made, on clinical assessment</u>,
- of <u>stable angina</u> caused by myocardial ischaemia
- <u>due to coronary disease</u>,
- and who <u>does not have unstable angina</u>.

Excluding patients with Class IV symptoms, those admitted to hospital within 24 hrs, those with prior revascularisation, or MI within 1 year

	Male n=2196	Female n=1582	p	Overall
Mean age ($\pm$ sd)	60 (11)	62 (11)	<0.0001	61 (11)
Diabetic	17%	19%	0.17	18%
Hypertensive	58%	66%	<0.0001	62%
Hyperlipidaemia	57%	59%	0.24	59%
Ever Smoked	69%	30%	<0.0001	57%
Periph. Vasc. Dis	7%	7%	0.32	7%
Prior CVA/TIA	6%	4%	0.02	5%
Prior MI (>1 year)	5%	3%	0.004	4%
CCS Class I	39%	32%		36%
CCS Class II	43%	47%	<0.0001	45%
CCS Class III	12%	11%		12%
Signs of HF	8%	8%	0.81	8%

Completeness of follow up   EHS Angina
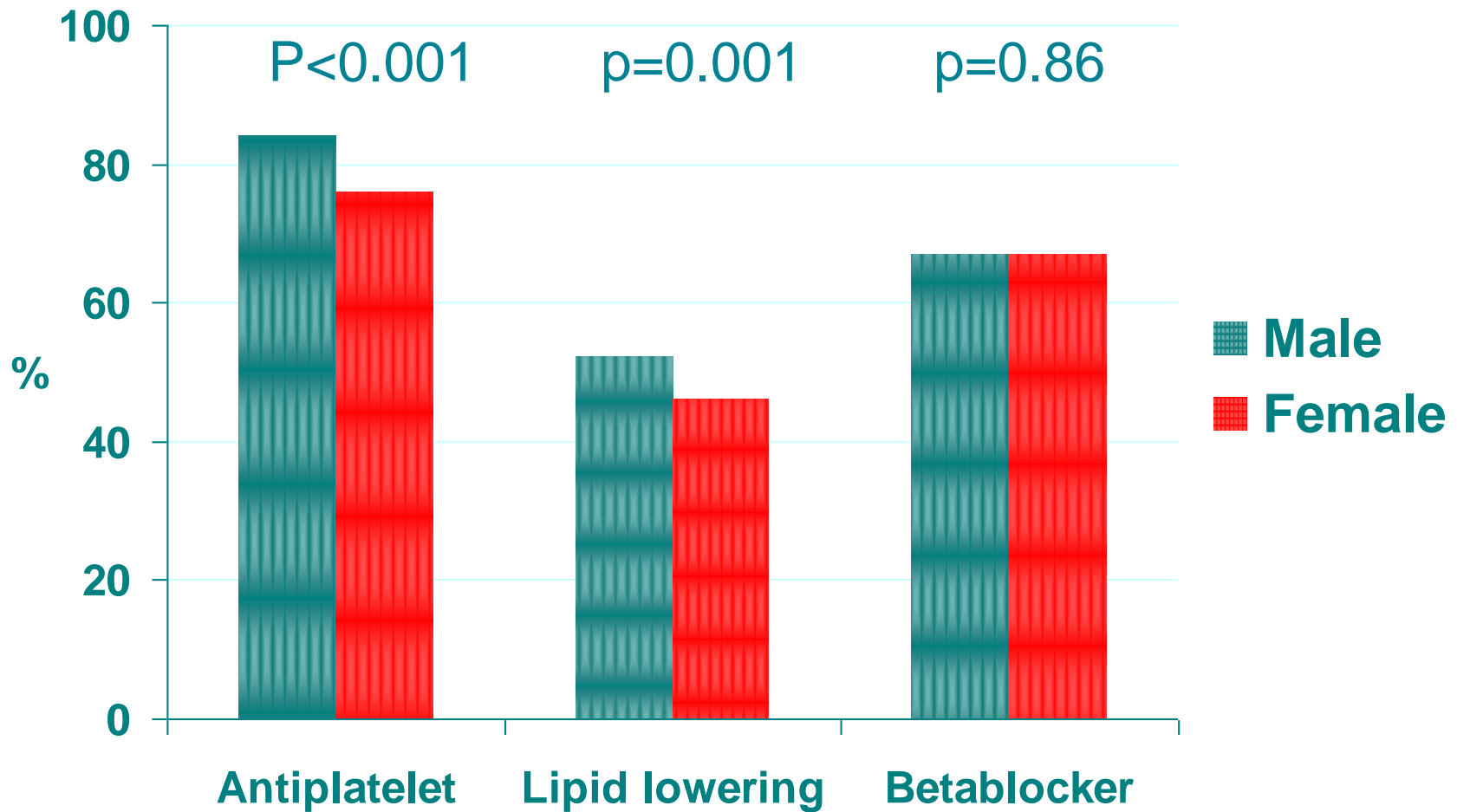
- Initial survey   n=3779

- Total Follow up   94%

- Suitable for analysis   n=3031

- Final Follow   up   80%

Effect of sex on use of investigations: Initial 4wks
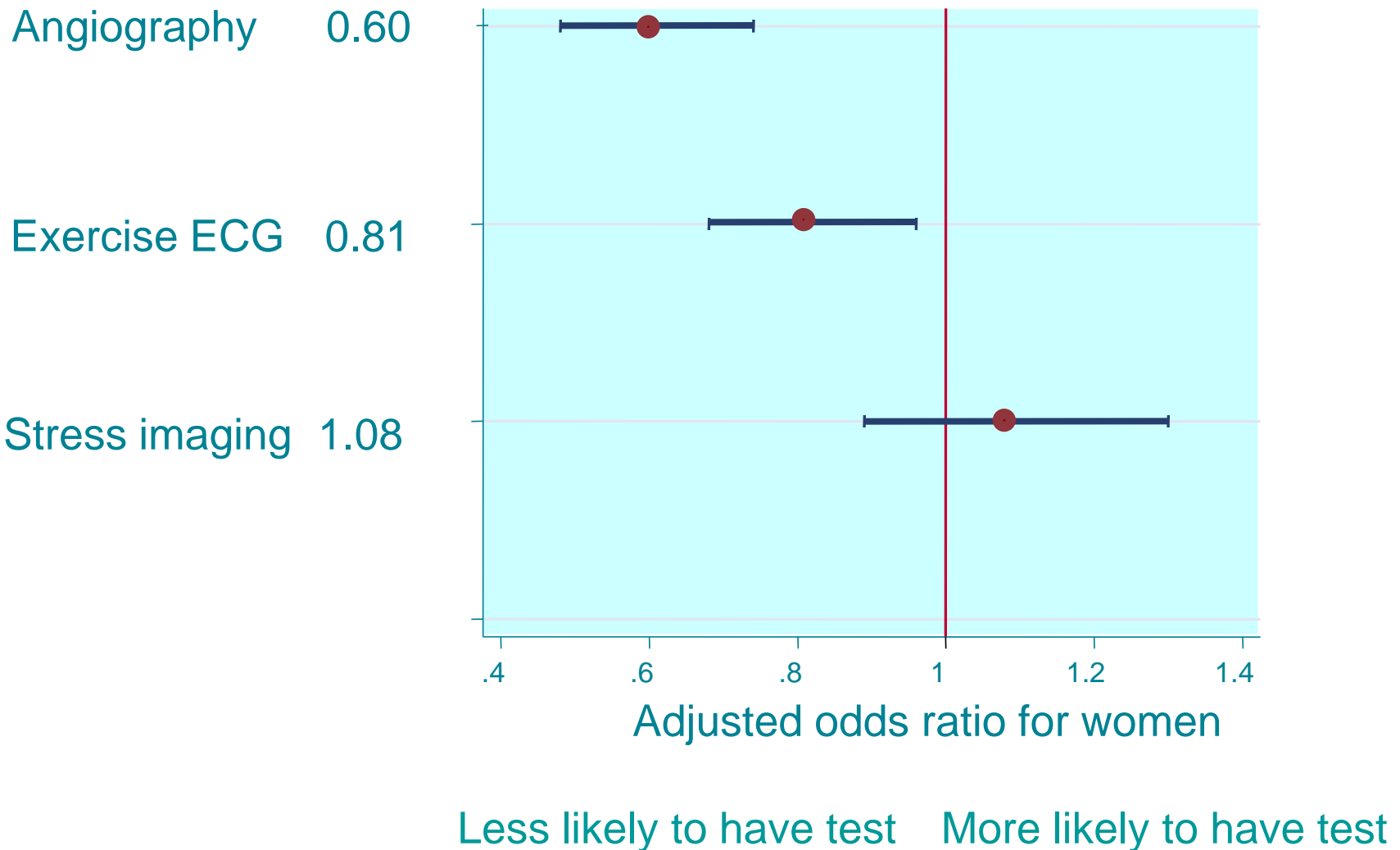
Angiography 0.60

Exercise ECG 0.81

Stress imaging 1.08

Adjusted odds ratio for women

Less likely to have test   More likely to have test

Investigations performed in 1 yr   EHS Angina

	Male	Female	p value	Overall
Echo	64%	65%	0.37	64%
Ex ECG	78%	73%	0.001	76%
Stress Echo	4%	4%	0.14	4%
Perfusion	13%	15%	0.35	14%
Angiography	47%	34%	<0.001	41%

Coronary Disease Status at 1 year   EHS Angina

Male

Female

Confirmed CAD

Positive non-invasive tests

Negative tests

Inconclusive or no tests
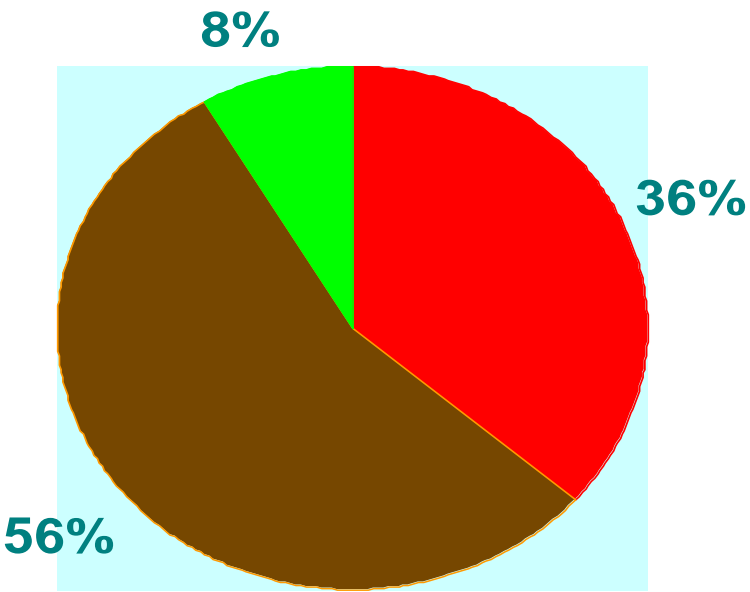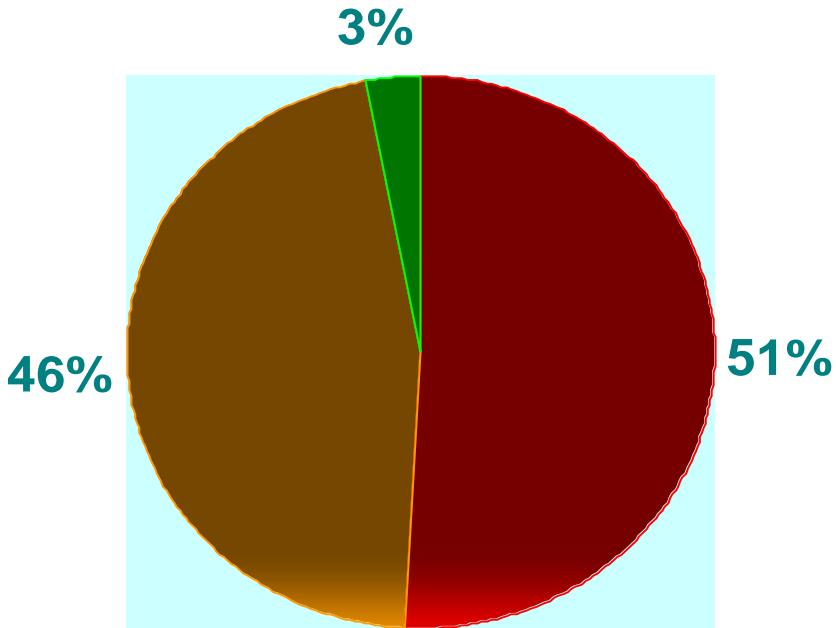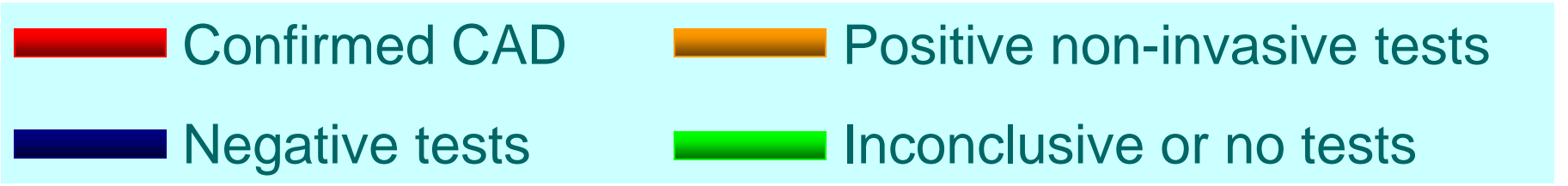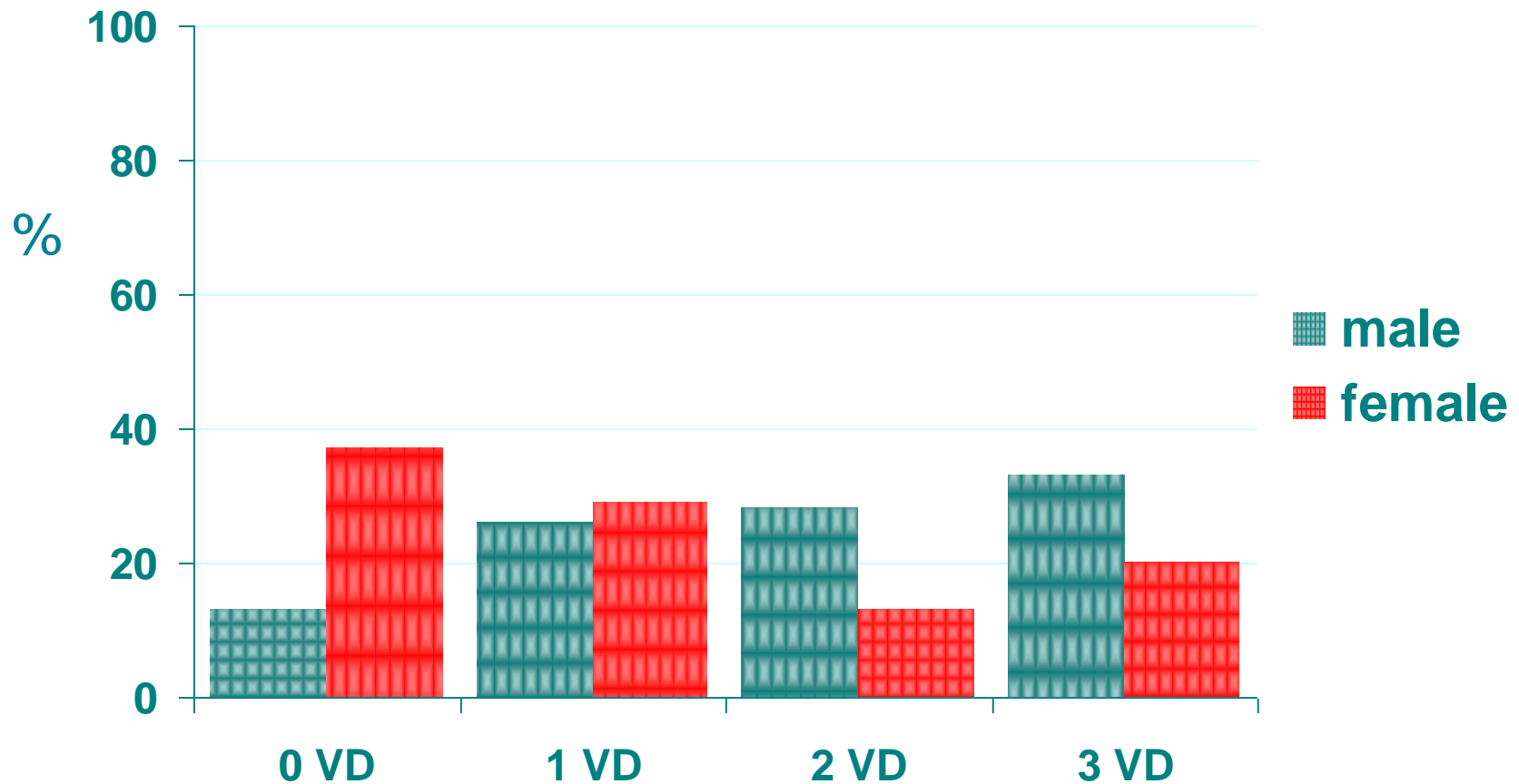
Results of angiography   EHS Angina

n = 1253   males = 821   females= 432

Meds at 1 year in those with <u>confirmed CAD</u>

	Male	Female	p value	Overall
Antiplatelet	94%	92%	0.156	93%
Lipid lowering	82%	76%	0.057	80%
Antiplatelet & lipid low.	78%	71%	0.013	76%
B Blocker	77%	82%	0.141	78%

Effect of sex on revascularisation   EHS Angina

	*Adj. OR F vs M	p value
Revascularisation planned/performed within 4 wks	**0.56**	<0.001
Revascularisation at 1 year	**0.19**	<0.001
Revascularisation at 1 year in women with CAD	**0.68**	0.002

*Adjusted for age, symptom severity and other factors predictive at univariate level

Effect of sex on risk of death/MI   EHS Angina

	*MV HR	95% CI	p value
Female vs Male	**2.08**	1.13-3.83	0.01
Abnormal LV Fxn.	**2.03**	1.04-3.94	0.04

Multivariate HR adjusted for age, DM, LV function and severity of CAD

- Significantly less use of antiplatelet and lipid lowering therapy in women even after CAD has been confirmed

- Women with angina are significantly less likely to receive either non-invasive or invasive investigation, even after adjustment for age, comorbidity, symptom severity or the results of preliminary investigation.

- Women significantly less likely to receive revascularisation than men, even in the presence of confirmed CAD

- Women with angina and confirmed CAD have a significantly worse prognosis than men
- more than twice as likely to suffer death or MI during follow up, independent of the effects of age, diabetes, LV function or severity of CAD

Conclusions of EHS Angina

Women with stable angina are

- Under-investigated
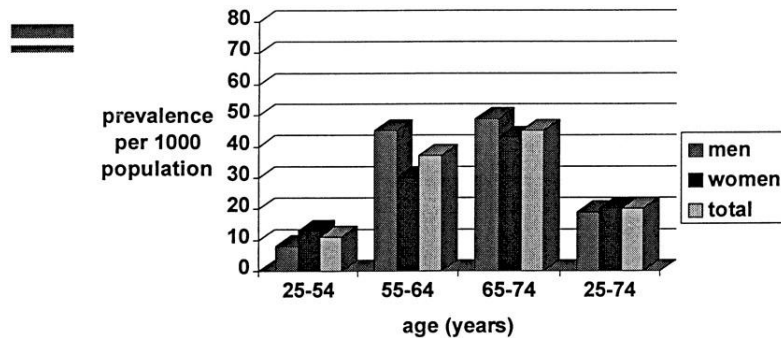
- Under-treated

even though

- Symptoms more severe

- Women with proven CAD have worse prognosis
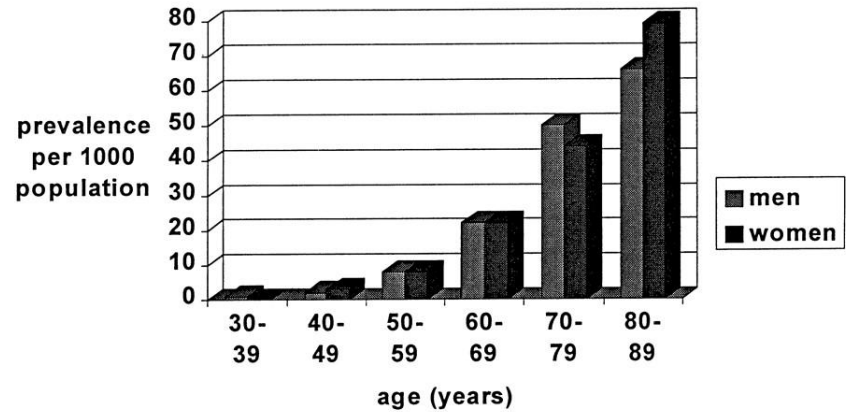
Scope of the problem

- Cardiovascular risks/Primary prevention
  - Hypertension
  - Hyperlipidaemia
- Coronary Heart Disease
  - Angina
  - Acute coronary Syndrome/MI
- Heart Failure
- Arrhythmia
- Congenital Heart Disease
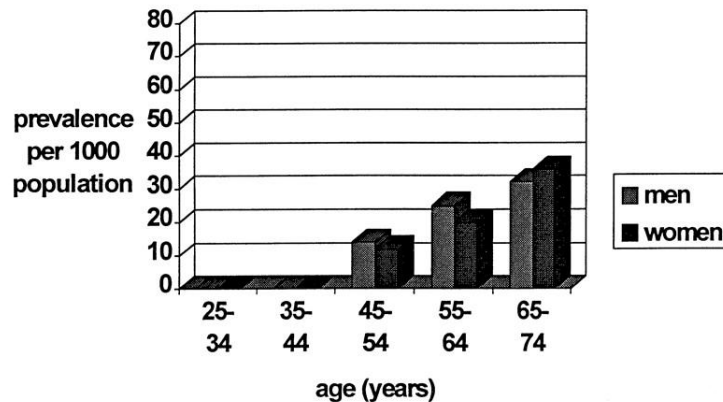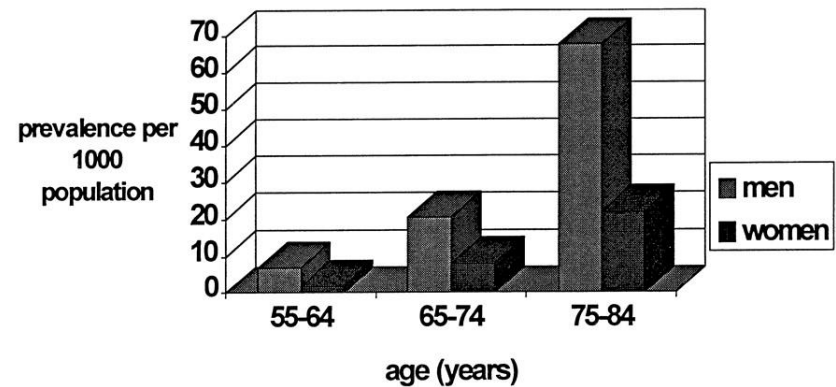
Population prevalence

1) *NHANES-I[2]

2) *Framingham[3]

3) **Glasgow[4]

4) **Rotterdam[5]

*based on clinical criteria
**based on echocardiography

Gender differences in care of Heart Failure- UK data, primary care

|	Median age (yr)	F/M
All patients on diuretics *(n = 505)*	73	60/40
Patients with heart failure *(n = 281)*	76	47/53
Patients referred to hospital *(n = 230)*	71	48/52
Patients treated by GP *(n = 275)*	80	70/30

Clarke et al, Br Heart J 1994

Euro Heart Survey of Heart Failure I

- N= 11304 patients from across Europe

- 116 hospitals

- Suspected or confirmed Heart Failure

- Mean age 71years, 53% male

- First diagnosis on index admission in 27%

EF in women (2048; 41% of total enrolled) and men (3249; 57% of total enrolled) in EHS Heart Failure I
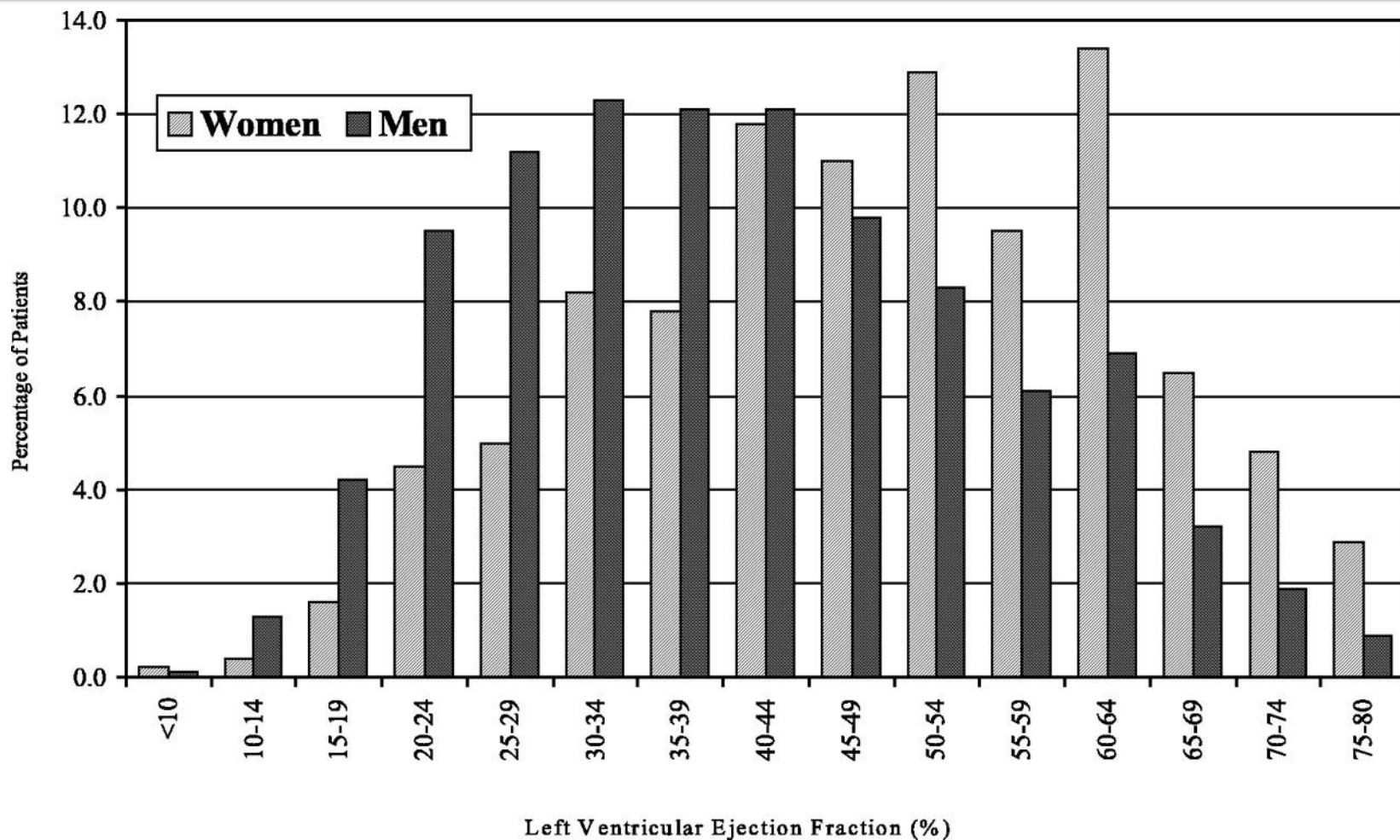
51% of men but only 28% of women had a left ventricular EF <40%

OR (adj) of use of medication for men v women in EHS Heart Failure I

	Odds ratio (95% CI)
B Blockers	1.16 (1.05 to 1.29)*
CCB	0.79 (0.71 to 0.88)*
Anti thrombotic	1.19 (1.00 to 1.40)
ACE i	1.34 (1.22 to 1.48)*
Spironolactone	1.28 (1.15 to 1.43)*
Aspirin	1.34 (1.23 to 1.46)*

Montreal multidisciplinary HF clinics 2000-02

N= 765, 27% female, mean age 65 yrs

Hospital admissions with CHF: 3006 men 2890 women

|	All, %	Men, %	Women, %	P
Beta-blockers	78	81	71	0.003
ACE inhibitors	74	77	66	0.001
ARBs	21	20	25	0.138
ACE or ARBs	88	90	82	0.002
Nitrates	50	51	46	0.173
Cardiac glycoside	69	69	67	0.477
Antiplatelet agents	56	57	51	0.129
Diuretics	89	91	86	0.040
Antiarrhythmic	24	27	17	0.006

Montreal Study: use of meds

Use of medications	OR	CI
BB	0.58	0.32-0.78
ACE or ARB	0.50	0.32-0.78
	Adjusted OR	**CI**
BB (adjusted for Systolic Function)	0.77	0.50-1.19
ACE or ARB (adjusted for Systolic Function)	0.80	0.44-1.44

Use According to Canadian Guidelines	Men	Women	p
BB	87%	82%	0.21
ACE	84%	75%	0.06
ACE or ARB	97%	95%	ns

Euro Heart Survey Heart Failure II

- 133 hospitals in 30 European countries

- October 2004 to August 2005

- Patients admitted to hospital with dyspnoea and verification of HF (new-onset AHF or ADCHF) based on (i) symptoms and signs of HF and (ii) lung congestion on chest X-ray.

- n=3580 patients

Euro Heart Survey Heart Failure II
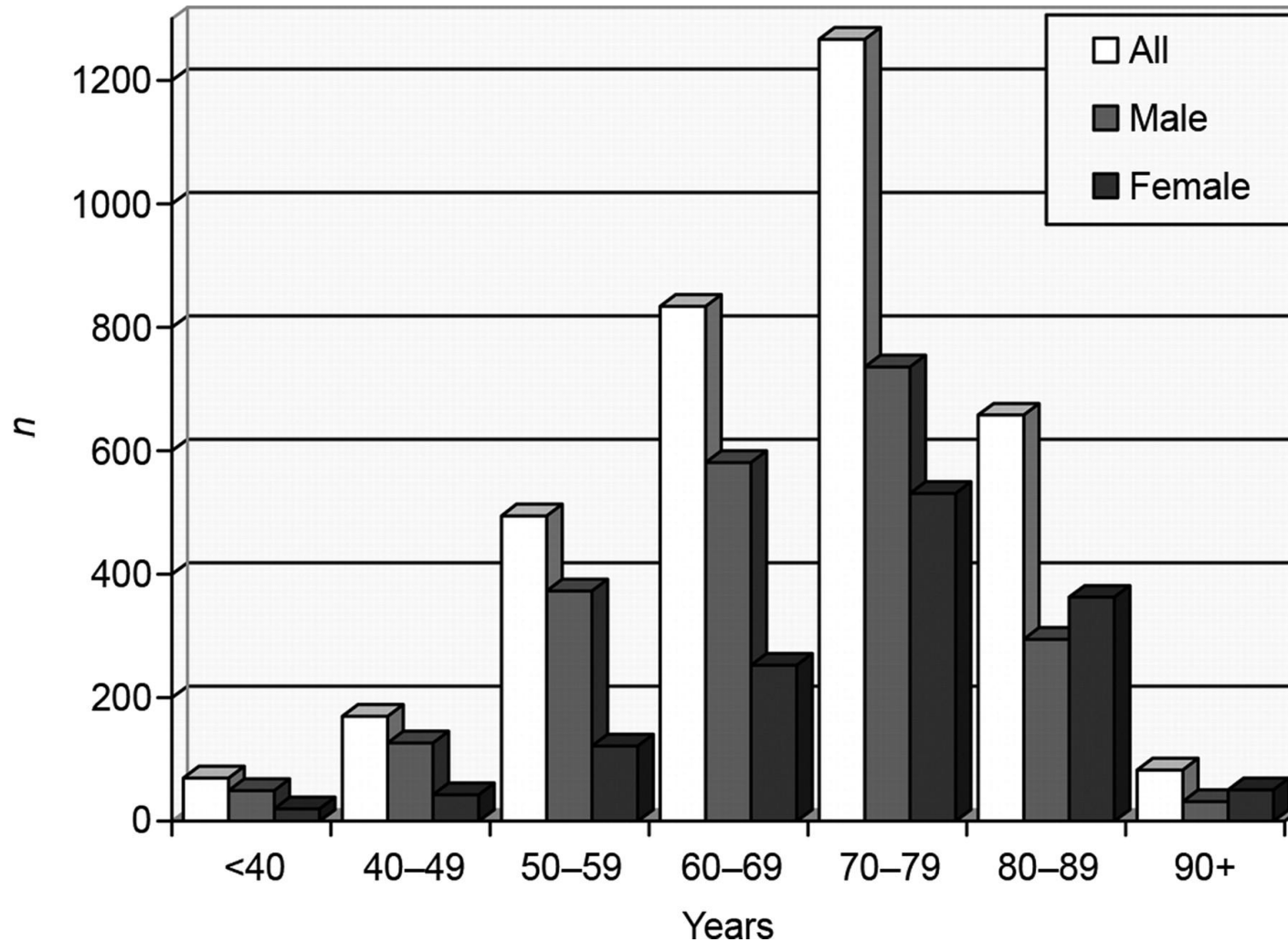
Gender differences EHS Heart Failure II

- Diuretics
- Aldosterone antagonists
- ACE inhibitors (ACEI)
- Angiotensin receptor blockers (ARB)
- Beta-blockers
- Digitalis compounds
- Anti-arrhythmic drugs
- Calcium channel blockers
- Oral nitrates
- Aspirin
- Vitamin K antagonist
- Lipid regulating drugs
- Insulin
- Oral antidiabetics

- Echocardiography
- Exercise testing
- Holter monitoring
- Arterial line
- Pulmonary artery catheter
- IABP
- Thrombolysis
- Coronary angiography
- PCI/CABG
- Heart transplantation
- BNP/NT-proBNP tested
- Length of stay (days)
- Admission to ICU/CCU
- In hospital Mortality
- Death, MI or stroke

# NO Gender differences EHS Heart Failure II

- Diuretics
- Aldosterone antagonists
- ACE inhibitors (ACEI)
- Angiotensin receptor blockers (ARB)
- Beta-blockers
- Digitalis compo...
- Anti-arrhyth... ...ugs
- Calcium ch... ...blockers
- Oral nit...
- Aspir...
- Vit... K antagonist
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- Echocardiography
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- Thrombol...
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- H... ...ansplantation
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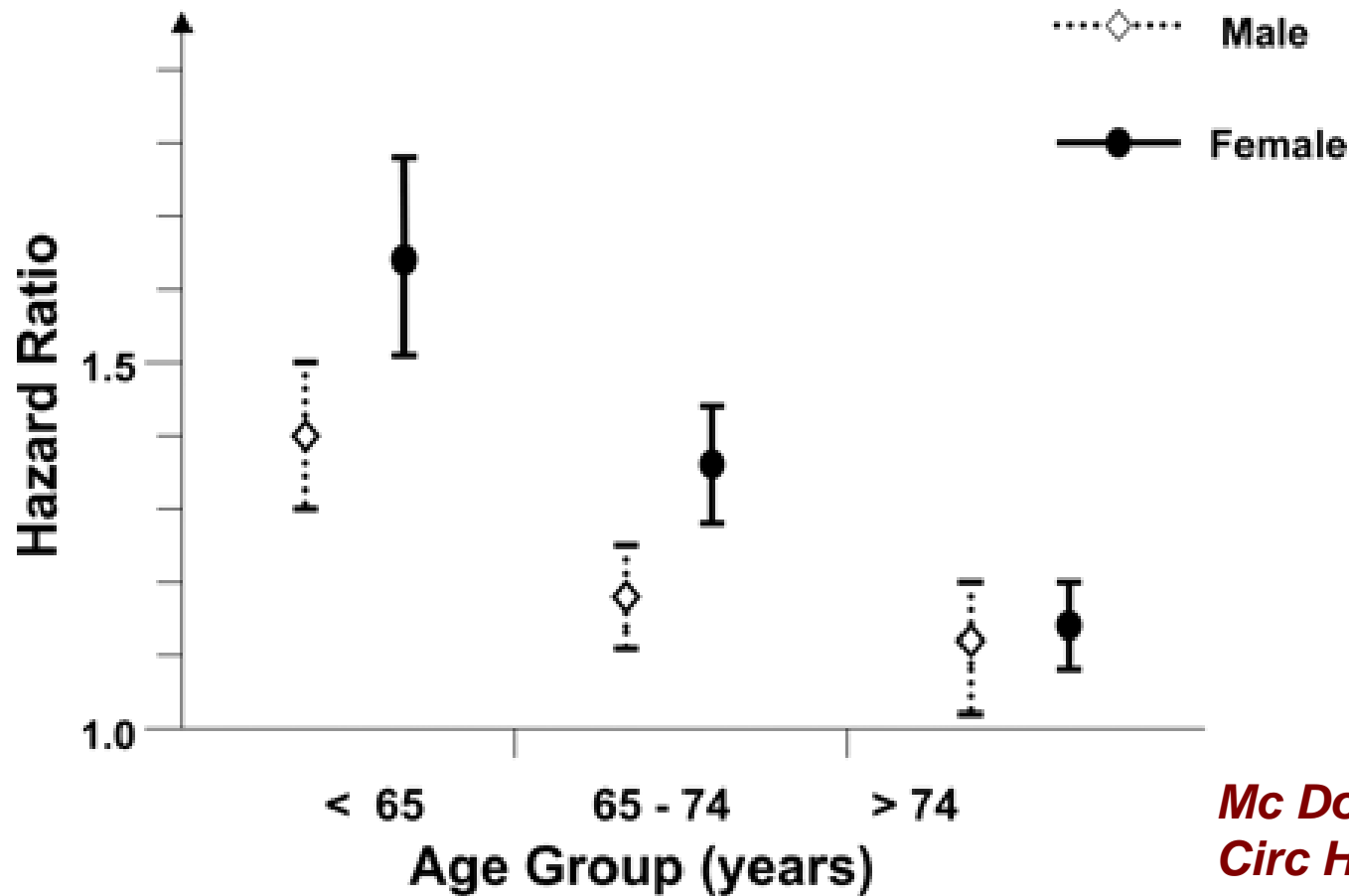No significant differences

No significant differences

Expected survival curves for 60 and 80 year old men and women hospitalised for acute heart failure
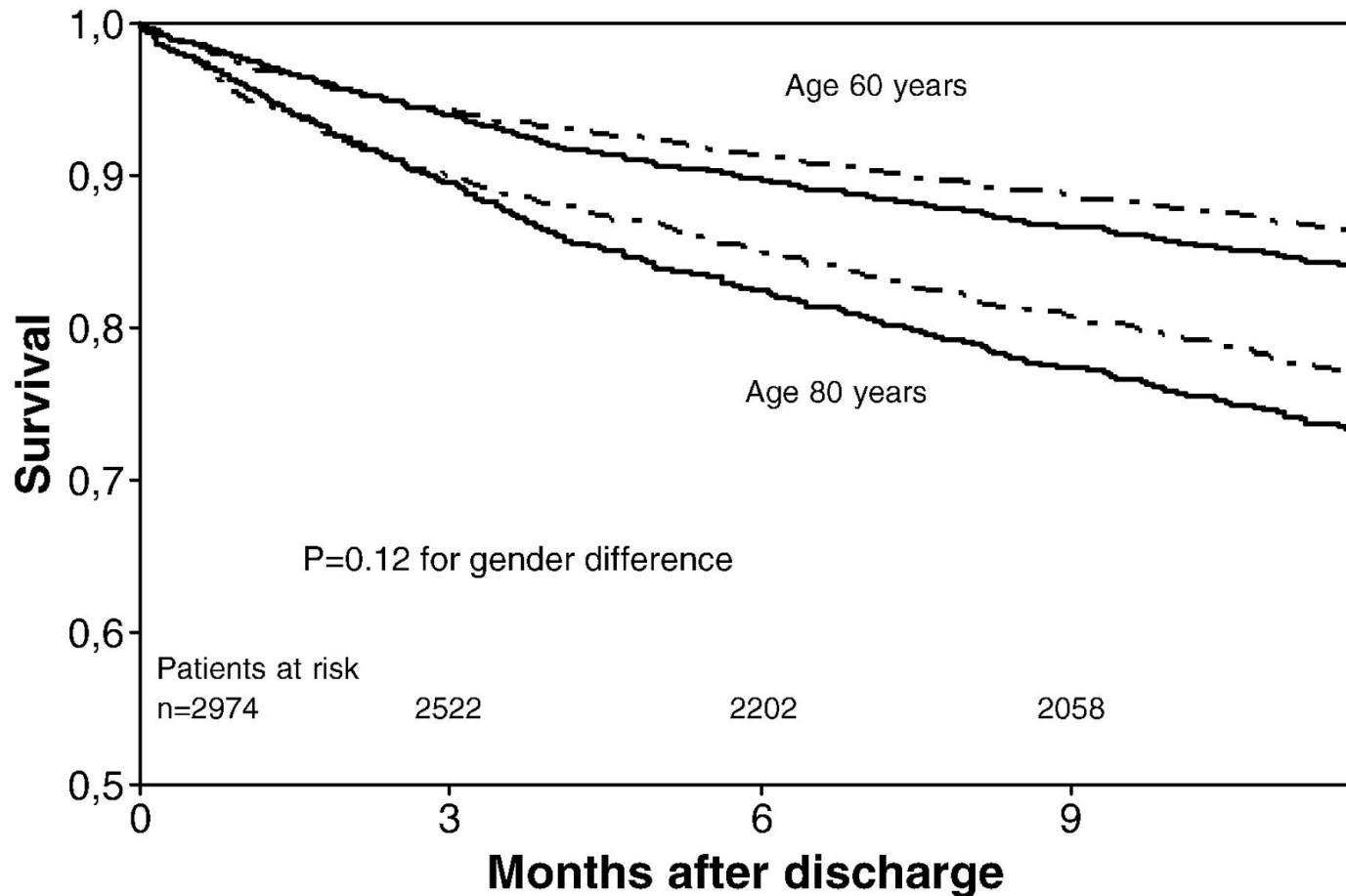
*Nieminen, M. S. et al. Eur J Heart Fail 2008 10:140-148;*

Adjusted risk of death at 5 years in men and women (diabetics v non diabetics). Excluding patients who died in the first 30 days.

Mc Donald
Circ Heart Failure 2008

Patients discharged from hospital in Scotland (n=116 556) from 1986 to 2003 with a diagnosis of HF analysed by diabetes and sex

NHANES I, II and III: Diabetes And CVD mortality

Diabetic Men
Mortality rate reduction -13.6%

Diabetic Women
Mortality rate reduction -1.1%
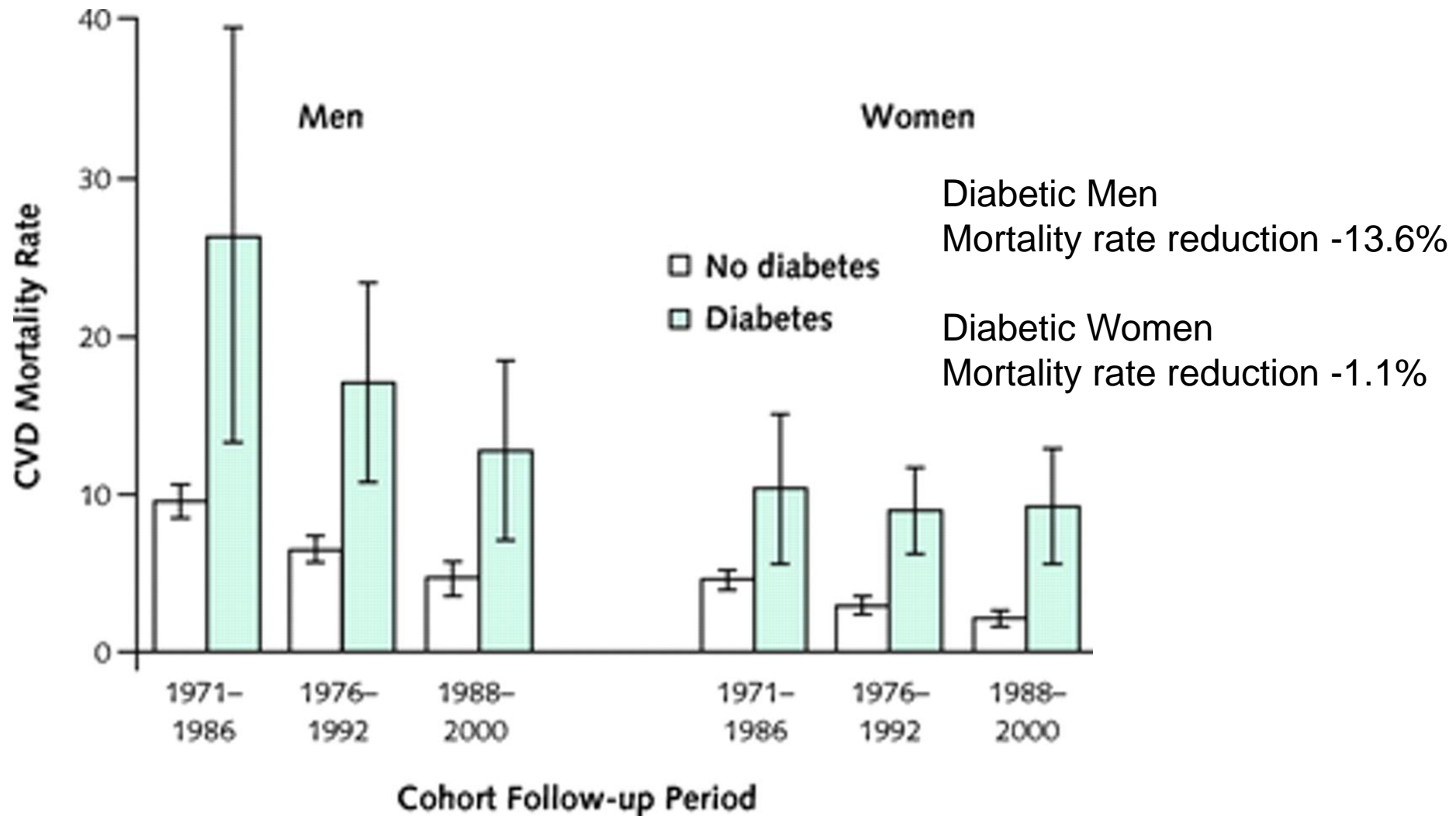
Conclusions

- Systematic bias in the use of investigations and treatment across range of indications

- Lack of improvement in age standardised CVD mortality rates for women

- Early signs that awareness and vigilance can improve discrepancies, await impact on morbidity and mortality