

Women and coronary disease

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Heart disease is the leading cause of death and morbidity in Western countries, and ischaemic heart disease (IHD) accounts for most cardiac deaths in both sexes.¹ This review focuses on gender-related issues concerning the epidemiology, pathogenesis, presentation and treatment of IHD.

EPIDEMIOLOGY

The prevalence and the incidence of IHD at all ages are higher in males than in females, increasing with age in both genders (fig 1 and tab 1).^{w1}

Table 1. Age-adjusted prevalence and incidence of myocardial infarction and angina in American men and women.

MI	Prevalence (%)	ARIC (45-64 yrs)		CHS (>70 yrs)		FHS (35-84 yrs)	
		MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
		6.3	1.9	17.7	9.0	7.8	2.6
	Incidence (cases/1000 person yrs)	ARIC (45-84 yrs)		CHS (>65 yrs)		FHS (>35 yrs)	
		MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
		5.8	3.3	18.2	9.0	7.8	3.0
ANGINA	Prevalence (%)	ARIC (45-64 yrs)		CHS (>70 yrs)		FHS (35-84 yrs)	
		MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
		3.8	6.0	31.0	22.7	8.0	3.7
	Incidence (cases/1000 person yrs)	ARIC (45-74 yrs)		CHS (>65 yrs)		FHS (>35 yrs)	
		MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
		10.8	13.4	29.9	18.2	5.9	2.2

Prevalence in % of population. Incidence in cases/1000 person years. In *ARIC* (Atherosclerosis Risk in Communities), prevalence of MI based on ECG, physician diagnosis, or self-reported hospitalisation; prevalence of angina based on Rose questionnaire; incidence of MI by expert committee diagnosis. In *CHS* (Cardiovascular Health Study), MI based on death certificates, medical records, interview with physician, next-of-kin or witnesses, or symptoms + ECG; prevalence of angina based on medications, coronary surgery or angioplasty, physician diagnosis, or hospital record; incidence of angina based on physician diagnosis and treatment, chest pain plus surgery, obstruction at angiography, or Rose questionnaire. In *FHS* (Framingham Heart Study) MI based on ECG, hospital or autopsy records; angina based on physician diagnosis. The less restrictive criteria for angina in ARIC may justify differences from FHS and CHS. Data extrapolated from ref. 17.

However, since the elderly female population is larger than that of males, beyond 75 years of age the absolute number of women discharged for IHD overcomes the number of males (364000 vs 326000 per year in the USA).¹ At the time of a first coronary event, women are approximately 10 years older than men.^{2,w2} In the Framingham Heart Study (FHS), angina was the initial diagnosis of IHD in 61% of women but only in 38% of men; in contrast, men more often exhibit myocardial infarction (MI) or sudden death as first manifestations.^{2,w3} Among patients with suspected acute coronary syndrome (ACS), the discharge diagnosis in women is more commonly unstable angina compared to men.^{3,4} Over the past 3 decades, the relative risk (RR) of coronary death has declined similarly in both genders.^{w4} Thus, in women compared to men the overall prevalence of IHD is lower and the age at presentation is delayed; however, among the elderly, women outnumber men, so that the absolute number of elderly female IHD patients is greater than that of men.

RISK FACTORS

In the case-control INTERHEART study of 15152 patients with MI and 14820 controls, 90% of the population-attributable risk (PAR) for MI in both genders was accounted for by the presence of 9 modifiable risk factors: namely, raised serum lipoprotein apoB/A1 ratio, smoking, diabetes,

psychosocial stress, hypertension, high waist-to-hip ratio, low fruit and vegetable intake, lack of regular exercise, and lack of regular alcohol intake (fig 2).⁵

Diabetes and hypertension

The prevalence of hypertension in the general population >60 years of age is reported to be higher among women compared to age-matched men,^{1,w5} although a possible survival bias cannot be excluded.

In women, diabetes and hypertension appear to confer a higher risk of coronary events compared to men.⁵ A possible explanation is that diabetes and hypertension promote IHD more aggressively in women than in men, perhaps in relation to the smaller coronary size. Alternatively or additionally, we propose that women - who *per se* are relatively protected against IHD - may require a greater risk factor-burden compared to men before developing IHD. Consistent with the latter is the lower likelihood of disease in women than in men for a similar combination of risk factors (see American and European risk charts shown in fig 3 and fig 4).^{w6, w7}

A meta-analysis of studies specifically enrolling diabetic and control subjects, with an average follow-up of 14 years, found no significant gender-related difference in the risk of coronary death (2.9 for diabetic vs non diabetic women vs 2.3 for diabetic vs non diabetic men, $p=0.19$) or nonfatal MI related to diabetes (1.7 for diabetic vs non diabetic women compared to 1.6 for diabetic vs non diabetic men, $p=0.68$).⁶ Population-based studies, instead, found that women who develop a first coronary event have a 2 to 3 fold adjusted risk of having diabetes compared to men.^{w8,w9}

Overall, these findings suggest that diabetes and hypertension *per se* may not increase the risk of IHD more in women than in men,⁶ but simply that women who develop IHD are more frequently diabetic and hypertensive compared to men^{5,w8,w9} ("higher risk factor burden" hypothesis).

Lipids and metabolic syndrome

Beyond 65 years of age, the prevalence of hypercholesterolemia (≥ 240 mg/dl or ≥ 6.2 mmol/l) is more than twofold greater in women compared to men;¹ as for hypertension, a possible survival bias cannot be excluded. The OR and PAR for MI associated with a raised lipoprotein apoB/apoA1 ratio are similar in the two sexes⁵ (fig 2). LDL cholesterol lowering by statins is associated with similar reductions in coronary and cerebral ischaemic events and in overall mortality in men and women.⁷ Whether the presence of metabolic syndrome confers a higher risk of IHD in women than in men is not clear.^{w10} The INTERHEART study found similar OR for MI associated with a high waist-to-hip ratio in the two genders.⁵

Smoking and stress

The prevalence of never smokers in the general population is higher in women than in men (53% vs 29%).^{w11} In the ARIC (Atherosclerosis Risk In Communities) study, current female smokers had a RR of coronary disease of 2.95 vs 1.55 in men,^{w11} in line with our hypothesis that women require a larger cluster of risk factors before reaching the threshold of IHD. Perceived high levels of mental stress, compared to low levels, have been associated with an increased risk of fatal IHD in women, but not in men.^{w12} The INTERHEART study, on the other hand, found similar OR for MI in men and women who smoked or in association with psychosocial stress.⁵

Family history

The Physicians' and Women's Health Studies (totalling 534154 subject-years) assigned to a maternal history of MI, especially if premature, a higher RR of cardiovascular disease compared with a paternal history.^{w13} Given the lower prevalence of MI among females (tab 1), a maternal history of MI may signal a more unfavourable background.

PATHOPHYSIOLOGY

Women with IHD have less obstructive and less extensive epicardial disease than men, suggesting that other mechanisms - such as impaired microcirculation, impaired vasomotion, erosion, dissection, and thrombophilia - may contribute to ischaemia more frequently than in men.

Atherosclerosis

Autopsy data indicate that, in the general population, the severity of coronary stenoses is lesser in women than in men, a difference that is lost in the very elderly.^{w14} Women admitted to hospital for all forms of ACS have fewer diseased epicardial arteries compared to men (tab 2).^{3,8,w15,w16}

Table 2. Prevalence of “normal” or nonobstructive coronary arteries in women and men with acute coronary syndromes. Modified with permission from ref. 8.

	No./Total (%)		P
	Women	Men	
Acute coronary syndrome			
GUSTO ³	343/1768 (19.4)	394/4638 (8.5)	<0.001
TIMI 18 ^{w15}	95/555 (17.1)	99/1091 (9.1)	<0.001
Unstable angina			
GUSTO ³	252/826 (30.5)	220/1580 (13.9)	<0.001
TIMI IIIa ^{w16}	30/113 (26.5)	23/278 (8.3)	<0.001
Non-ST elevation MI³	41/450 (9.1)	55/1299 (4.2)	0.001
ST elevation MI³	50/492 (10.2)	119/1759 (6.8)	0.02

Women with a fatal ACS, compared to men, are more likely to have plaque erosion, rather than plaque rupture.^{w17} Among women, plaque erosion has been associated with smoking and younger age.^{w18} Similarly, spontaneous coronary artery dissection appears to be more prevalent in women than in men, particularly if young and without significant coronary atherosclerosis.^{w19} Thus, on average, women have less obstructive and less extensive epicardial disease than men.

Thrombophilia

In a general Scottish population of 8824 subjects (40-60 yrs, 4309 women), plasma fibrinogen levels were higher in women than in men for all age strata.^{w20} In patients with obstructive coronary disease, women again showed higher age-adjusted plasma levels of fibrinogen, in addition to higher plasminogen activator inhibitor-1 antigen and factor VII:C, compared to men.^{w21} Interestingly, during the first 24 hours after trauma or injury, young/middle-aged women are more hypercoagulable than men.^{w22} Overall, the evidence suggests a greater haemostatic potential in women than in men; whether this may be finalized at limiting post-partum bleeds is a matter of speculation.

Endothelial and microvascular dysfunction

Endothelial dysfunction can predict adverse coronary events in men and women, independently of coronary disease severity,⁸ but appears to occur later in women compared to men.⁹ Patients with angina, normal epicardial arteries and a positive exercise test (cardiac syndrome X), as well as Japanese patients with microvascular angina, are more often women than men.^{w23,w24} Conversely, epicardial vasospastic disease (variant angina) does not show a female predilection.

Estrogens and menopause

Estrogens have potential protective cardiovascular effects through HDL and LDL-cholesterol modulation, inhibition of smooth-muscle proliferation, enhanced synthesis of nitric oxide, of prostacyclin and of vascular endothelial growth factor, and progenitor cell stimulation,⁹ but also

potential detrimental effects (increasing tryglicerides and inflammatory and prothrombotic markers). Whether the lower prevalence of IHD among pre-menopausal women compared to age-matched men can be attributed specifically to a protective role of endogenous estrogens is still not clear. Randomised trials testing exogenous estrogens for the prevention of IHD showed no benefit or even harm in preventing cardiovascular events.^{w25,w26} To explain these findings, a “timing hypothesis” has been proposed, whereby estrogens may be cardioprotective only before the development of advanced atherosclerotic lesions.^{w27} Other possible biases may concern the type of estrogen, concomitant progestins, route of administration, and age and risk factors of enrolled women. Currently, however, the evidence does not support the use of estrogens for the primary or secondary prevention of IHD.

The impact of menopause *per se* on IHD is difficult to unravel from the concomitant increase in traditional risk factors.^{10, w28} In the Nurses’ Health Study, each one year decrease in age of onset of natural menopause was associated with a small, smoke-related, increase in the RR of IHD: 1.03 (95%CI 1.01-1.05).^{w29} Bilateral oophorectomy carries an adjusted RR of cardiovascular disease of 4.55 (95%CI 2.56-8.01).¹⁰ The overall rate of coronary deaths, however, remains lower in women than in men up to 4 decades beyond the average time of menopause (50-54 years).^{w28}

Autonomic balance

Women, unlike men, have a prevailing parasympathetic autonomic cardiac tone.^{w30} This is consistent with a higher female rate of syncope, hypotension, and bradycardia after MI, and, conversely, with more malignant post-MI tachyarrhythmias and a higher incidence of sudden cardiac death among men.^{2,w31,w32}

PREVENTION

The most important strategy to prevent female IHD is to avoid an underestimation of the risk of disease.

In primary prevention, in both genders, the use of aspirin is limited to subjects at high cardiovascular risk.^{w33} High risk subjects can be defined as those with an absolute 10-yr probability of a fatal cardiovascular event $\geq 5\%$ when extrapolated to age 60 or above,^{w7} or of MI and coronary death $>20\%$.^{w6,w11} This risk should be weighed against that of major bleeds with aspirin intake, of approximately 1-2% over 10 years.^{w33} Similarly, lipid-lowering therapy is currently recommended in both male and female subjects at high cardiovascular risk,^{11,w34} who have a total cholesterol >190 mg/dl (>5 mmol/l) and/or an LDL cholesterol >115 mg/dl (>3 mmol/l), despite life-style changes.^{w7} The prevention of IHD events by blood pressure control is of similar degree in the two sexes, as shown by the ALLHAT (Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial) during 6 years of follow-up.¹²

For the secondary prevention of IHD, the evidence-based benefits of several cardiovascular drugs (aspirin, thienopyridines, statins, inhibitors of the renin-angiotensin system, beta-blockers) are similar in both genders,^{11,13} despite sex-specific differences in pharmacokinetics and pharmacodynamics.^{w35}

NON INVASIVE DIAGNOSTIC TESTS

The lower pre-test likelihood of IHD in women compared to men is associated with a higher probability of false-positive results and thus a lower specificity of noninvasive diagnostic testing in women (Bayes’ theorem).

Additionally, the sensitivity of exercise ECG is lower in women compared to men.¹⁴ The inclusion of a multiparametric evaluation (e.g., the Duke treadmill score), particularly in women, may improve the diagnostic accuracy of exercise ECG.^{w36} Exercise Thallium SPECT shows a higher sensitivity, but not specificity, compared to exercise ECG in women,¹⁵ although the overall sensitivity remains lower compared to men.^{w37} Technetium-99m sestamibi SPECT yields a higher specificity compared to Thallium SPECT in women,^{w38} with similar results in both sexes after correction for referral bias.^{w39} Stress echocardiography is reported to be the most accurate provocative test in women (with a higher specificity and sensitivity compared to SPECT and

exercise ECG)¹⁵ and the most specific test in both genders.^{w40} Coronary calcium score, in both sexes, may be an important diagnostic tool to rule out disease, given its high specificity, although its sensitivity is low.^{w41}

As in men, the appropriate diagnostic strategy in women should be based on the pre-test probability of IHD.^{14,w42} Women with an intermediate-high pre-test likelihood of IHD should undergo non-invasive testing (fig 5).¹⁴ An intermediate-high likelihood of IHD can be defined as women \geq 50 years of age with typical or atypical chest pain, or women $<$ 50 years of age with typical angina, or women with symptoms plus diabetes or other multiple risk factors.¹⁴

CORONARY ANGIOGRAPHY, PERCUTANEOUS INTERVENTION (PCI) AND BYPASS SURGERY

Women undergo cardiac catheterization less frequently than men even after MI.^{w43} At coronary angiography, women are older and more frequently diabetic and hypertensive.^{w44} Early studies on balloon angioplasty showed more frequent adverse outcomes and higher dissection rates in women, probably related to comorbidities and smaller coronary size.^{w45-w47} In the stent era, several, though not all,^{w48-w50} studies show similar adjusted in-hospital and long term mortality in the two sexes.^{16,w51-w53} Long term rates of other major coronary events and of restenosis are also similar in both genders.^{w47,w54-w57} Vascular complications after PCI remain more common in women than in men.^{w47,w52} Current indications for PCI or bypass surgery in the acute and stable patient do not differ according to gender.^{13,w58,w59} Short term mortality is reported to be worse, but long term mortality better, after bypass surgery in women compared to men.^{13,w60}

STABLE ANGINA

Epidemiology and presentation

The CHS (Cardiovascular Health Study) and FHS reported a lower prevalence and incidence of angina (defined mostly by physician interview) in women compared to men (tab 1).^{2,17} A large Finnish study confirmed a slightly lower, age-standardized, annual incidence of angina (assessed by nitrate prescription or by invasive or non-invasive testing) in women, with a male to female ratio of 1.07 (95%CI 1.06-1.09).¹⁸ On the contrary, the ARIC study reported a higher prevalence and incidence of angina, defined by less restrictive criteria, in women than in men (tab 1).¹⁷

In the FHS, angina was the most common first clinical diagnosis of IHD in women but not in men.² Female patients with angina, compared to men, are older, more often hypertensive, less frequently smokers or with prior MI, and report a higher intensity of pain on a visual analogue scale.^{19,w3,w61} On average, the available data indicate lower prevalences and incidences of stable angina in women than in men.

Management and prognosis

In the Euro Heart Survey of 3779 patients with angina, women compared to men were less likely to receive non invasive and invasive diagnostic procedures, or to be treated by coronary revascularization and appropriate medical therapy (including the combination of antiplatelet and lipid-lowering drugs) even in presence of significant angiographically-documented coronary disease.¹⁹

Several reports indicate a better or similar age- and risk factor-adjusted prognosis in women than in men with diagnosed angina.^{18,w3,w62,w63} An important limitation of these studies,^{w3,w62,w63} however, is the absence of angiography, that is known to show less extensive coronary disease in women with angina compared to men.^{w64} In a cohort of 1457 patients with stable angina undergoing coronary stenting (32% female), women exhibited similar 1-yr RR of death, nonfatal MI and cardiac rehospitalisation compared to men, even after adjustment for the extent of coronary disease.^{w64} The Euro Heart Survey also found no gender difference in the outcome of the overall population, but assigned an adjusted 2-fold *worse* prognosis (death/non fatal MI at 1-yr follow-up) to the subgroup of women with angiographically-documented disease compared to men; this subgroup, however, may have selected women at particularly high risk.¹⁹ Thus, on balance, the

available data suggest similar outcomes for men and women with stable angina, despite a degree of female undertreatment.

ACUTE CORONARY SYNDROMES

Epidemiology and presentation

The prevalence and incidence of MI are consistently lower in women than in men, across all classes of age¹⁷ (tab 1). Among patients with ACS, women present more frequently with unstable angina (UA) and non-ST elevation MI (NSTEMI) and less frequently with ST elevation MI (STEMI) compared to men.^{3,4}

Women with ACS report a similar incidence of chest pain compared to men, but more often an “atypical” location (back, jaw, neck), a higher intensity, and additional nausea, fatigue, dizziness, dyspnea, and anxiety/fear.^{20,w65} Thus, symptoms considered “atypical” for men may be “characteristic” for women, although not necessarily the most prevalent. Nonetheless, typical, rather than atypical, symptoms remain the strongest predictor of ACS in both women and men.²⁰ Women hospitalised for MI are older, and more often hypertensive and diabetic compared to men.^{w66-w67} The prevalence of ‘normal’ or nonobstructive coronary arteries is roughly twofold higher in women with ACS than in men, particularly for those with NSTEMI ACS (tab 2).⁸

Non-ST elevation acute coronary syndromes (UA / NSTEMI)

A recent study showed a significant underuse of medical therapy on admission and even after discharge in women compared to men with NSTEMI ACS,^{w68} despite a higher risk factor profile and the lack of gender-differences in treatment guidelines.^{w69,w70} For both genders, the ACC/AHA and ESC UA/NSTEMI guidelines recommend an early invasive strategy (particularly coronary angiography within 48 hours) for patients at high cardiovascular risk.^{w69,w70} The latter may be defined by the presence of recurrent, rest or low threshold ischaemia, dynamic ST segment changes, elevated troponin levels, signs of heart failure, malignant arrhythmias, recent PCI, and prior CABG.^{w69,w70} Although not all studies show a significant benefit of an invasive vs a non-invasive strategy for women with NSTEMI ACS,¹⁶ it is important to consider the lower representation of women than men in all trials, and the differences across trials in baseline risk, in timing and type of revascularization (CABG vs PCI), and in the use of GPIIb/IIIa inhibitors.

The impact of gender on the outcome of NSTEMI ACS is debated. Women have a higher prevalence of nonobstructive coronary disease compared to men, and this subpopulation, in both genders, has a better in-hospital prognosis compared to those with significant disease.^{w71} At least 4 studies found male gender independently associated with long term risk of death and MI,^{w72,w73} even after adjustment for angiographic features,²¹ and despite the lesser access of women to invasive and non invasive diagnostic procedures.^{w74} No differences in long term prognosis were found in other reports of NSTEMI²² or NSTEMI ACS.^{w67,w75} Finally, one investigation found a worse prognosis in the subgroup of women with NSTEMI ACS and significant coronary stenoses undergoing PCI compared to men.^{w64} None of these studies, however, directly compared patients with NSTEMI to those with UA. This comparison was performed within the GUSTOIIb trial³ that showed a similar adjusted risk of death and reinfarction at 30 days among women and men admitted for NSTEMI, but an independent protective effect of female gender in patients with UA (OR 0.65, 95%CI 0.49-0.87, p=0.003). Thus, the available data suggest that the differences in outcome for men and women with UA/NSTEMI largely depend on clinical diagnosis and extent of coronary disease.

ST elevation myocardial infarction

Women with STEMI compared to men are more likely to present to hospital later,^{w66,w76} with atypical symptoms,²⁰ leading to a more difficult recognition of MI, a greater delay in obtaining a first 12-lead ECG, and a more frequent missed diagnosis.²³ On average, women have a more frequent history of angina or heart failure and a higher Killip class.^{w66} Even after adjustment for comorbidities and age, women more frequently than men experience in-hospital shock, pulmonary oedema, AV-block, stroke, cardiac rupture, and major bleeds.^{w66,w77,w78} In contrast, the incidence of early malignant tachyarrhythmias and sudden cardiac death are more common in men.^{2,w32}

When STEMI is diagnosed, women less often receive appropriate treatment,^{w79} including admission to a coronary care unit^{w80-w82} and thrombolysis.^{w79} If rapidly feasible, primary PCI is the better revascularization strategy in women as in men,^{w83-w85} although vascular complications occur more often in women.²⁴ Women experience longer door-to-balloon delays after diagnosis.^{w86} Primary PCI seems to offer better myocardial salvage in women,^{w87} suggesting greater myocardial tolerance to hypoxia than in men.

Following thrombolysis, several^{25,26,w2,w66,w88-w91} but not all^{3,27,28,w92-w95} studies report higher adjusted in-hospital and 30-day mortality in women than in men. The apparent discrepancies among these investigations may stem from heterogeneity in statistical adjustments, examined populations, and observed time periods (e.g., pre-hospital vs in-hospital). Indeed, the MONICA study, that took into account pre-hospital deaths, found a *lower pre-hospital* but a *higher in-hospital* mortality rate in women compared to men,^{29,w89} without significant gender differences in overall 28-day mortality. This observation (that men are more likely to die before reaching the hospital) has been confirmed by others.^{w96,w97} Most studies do not find gender differences in the adjusted long term mortality rates after STEMI.^{27,w90,w95,w96,w98,w99}

Several^{25,30,w96,w100,w101} but not all²⁶ studies also report a significant interaction between age and gender-related outcome after STEMI, with higher mortality rates after hospitalisation in younger women compared with age-matched men, but better outcomes among older women.^{w100,30} Again, however, when pre-hospital deaths are taken into account, the higher 30-day mortality in younger (<55 years) hospitalised women, compared to age-matched men, disappears, turning into a female advantage.^{w96} The adjusted mortality rates after primary PCI in women compared to men are reported to be significantly higher^{w102} or no different²⁴ during hospitalisation, but similar at 30-days^{w103} and long term.^{24,w76} Taken together, the above data suggest that overall outcome post STEMI in the two sexes may not differ substantially, but that early pre-hospital deaths occur more often in men, especially if young.^{w96}

CONCLUSION

In Figure 6 we have tried to summarize the peculiar features of coronary disease in women. As in men, IHD constitutes a major cause of death and morbidity in women, and this fact is underestimated by both women and cardiologists. Educational initiatives specifically tailored to the female population and to the medical community^{w104} will enhance awareness and contribute to reduce undertreatment of women in the acute setting and in the primary and secondary prevention of disease. Cardiologists must pay particular attention to women hospitalised for IHD because, on average, they are older, with multiple risk factors and comorbidities, and therefore at high risk. Nonetheless, the lower overall prevalence of coronary disease in women and its occurrence at a more advanced age suggest a protective effect of female gender on the development of IHD. Thus, Elizabeth I (1533-1603) might well have cherished her heart of a queen when she humbly said: "I have the body of a weak and feeble woman, but the heart of a king."^{w105}

COMPETING INTEREST STATEMENT

All authors declare that the answer to the questions on your competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore have nothing to declare.

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Figure legends

- Fig 1** **Prevalence of ischaemic heart disease in the United States by age and gender.** The prevalence of ischaemic heart disease is lower in women than in men in all classes of age. Reproduced with permission from the Heart Disease and Stroke Statistics—2007 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee.^{w1}
- Fig 2** **Risk for myocardial infarction in men and women in the INTERHEART study.*** The odds and population attributable risks for myocardial infarction associated with diabetes and hypertension were significantly greater in women than in men (*adjusted for age and geographic region). Reproduced with permission from Lancet 2004;**364**:937–52.⁵
- Fig 3** **10-year relative and absolute risk of ischaemic heart disease endpoints* estimated from the Framingham data.** For all combinations of coronary risk factors, US women have a lower 10-yr risk of ischaemic endpoints than men. (*Total: stable and unstable angina, myocardial infarction, and coronary death; hard: myocardial infarction, and coronary death). Reproduced with permission from Circulation 1999;**100**:1481-92.^{w6}
- Fig 4** **Estimated 10-year risk of fatal cardiovascular disease in European countries at high* and low† risk.** For a similar combination of risk factors, women throughout Europe have a lower 10-yr risk of cardiovascular death than men. (†=Belgium, France, Greece, Italy, Luxembourg, Portugal, Spain and Switzerland; *other European countries). Reproduced with permission from Eur Heart J 2003;**24**:1601-10.^{w7}
- Fig 5** **A proposed algorithm for the non-invasive evaluation of symptomatic women at intermediate-high likelihood of ischaemic heart disease.** See text for definition of intermediate-high likelihood. Modified with permission from reference 14.
- Fig 6** **Coronary disease by gender: similarities and differences.** ACS = acute coronary syndromes. IHD = ischaemic heart disease. MI = myocardial infarction. NSTEMI = non-ST elevation MI. STEMI = ST elevation MI. UA = unstable angina.

WOMEN AND CORONARY DISEASE: KEYPOINTS

- **The prevalence and incidence of all forms of IHD are lower in women compared to men and the age at presentation is delayed. However, beyond 75 yrs of age, women outnumber men, so that the absolute number of elderly female IHD patients is greater than that of men.**
- **Compared to men:**
 - **women, who are relatively protected against coronary disease, may require a greater risk factor-burden before developing IHD;**
 - **women with all forms of IHD are older, have more vascular risk factors and more comorbidities and thus represent a high-risk group;**
 - **on average, however, women with IHD have less obstructive and less extensive epicardial disease.**
- **Women with ACS, more often than men, have atypical symptoms. Nonetheless, typical rather than atypical symptoms remain the strongest predictor of disease in both genders.**
- **As in men, the appropriate diagnostic strategy should be based on the pre-test probability of IHD.**
- **International guidelines do not suggest gender-differences in the management of IHD. Nonetheless, women with all forms of IHD are substantially undertreated compared to men.**
- **The adjusted prognosis of stable angina is similar in women and men. The outcome of non-ST elevation ACS depends on the clinical diagnosis and on the extent of coronary disease.**
- **After MI, the overall adjusted mortality is similar in both genders, although men are more likely to die before reaching the hospital.**

WOMEN AND CORONARY DISEASE: QUESTIONS (each true or false)**1. Regarding the epidemiology of IHD:**

- In women the prevalence and incidence are lower compared to men
- At the time of first presentation women are older
- The gender differences in prevalence disappear with age
- Beyond 75 years of age the absolute number of women with IHD is lower compared to men
- Women are at lower risk of events compared to men with similar risk factors

2. Regarding the diagnosis of IHD in women:

- Non invasive tests yield a lower specificity than in men
- Exercise ECG has similar specificity and sensitivity than in men
- Tc99 scintigraphy has improved specificity
- Stress echocardiography is reported to be the most accurate test
- A pre-test probability guided approach is recommended

3. Women with IHD compared to men:

- Have more diabetes and hypertension
- Have less comorbidities
- Have more extensive epicardial atherosclerotic disease
- Have more often normal or nonobstructive coronary disease
- Experience more often angina as first clinical manifestation

4. Women compared to men admitted for NSTEMI ACS:

- Are older
- Present atypical symptoms less frequently
- Undergo diagnostic procedures more often than men
- Have worse adjusted clinical outcomes
- Receive less medical and invasive therapy

5. In women hospitalized for STEMI compared to men:

- Medical care is delayed
- The rate of missed diagnoses is similar
- Haemodynamic complications are less frequent
- Long term outcome is unquestionably worse than in men even after adjustment for baseline characteristics
- Younger age has been related to lower mortality

- 1) T, T, F, F, T
- 2) T, F, T, T, T
- 3) T, F, F, T, T
- 4) T, F, F, F, T
- 5) T, F, F, F, F

Figure 1

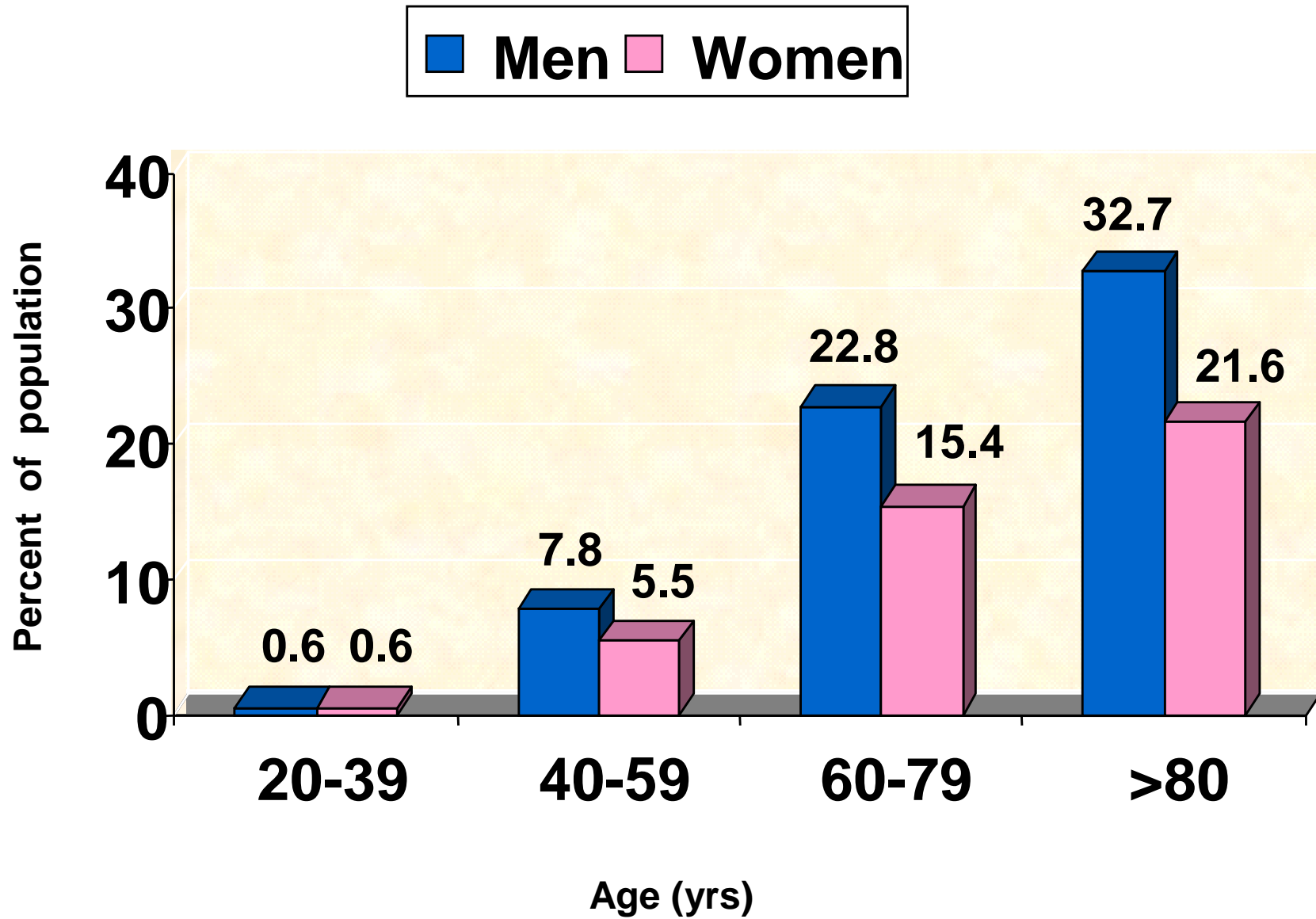


Figure 2

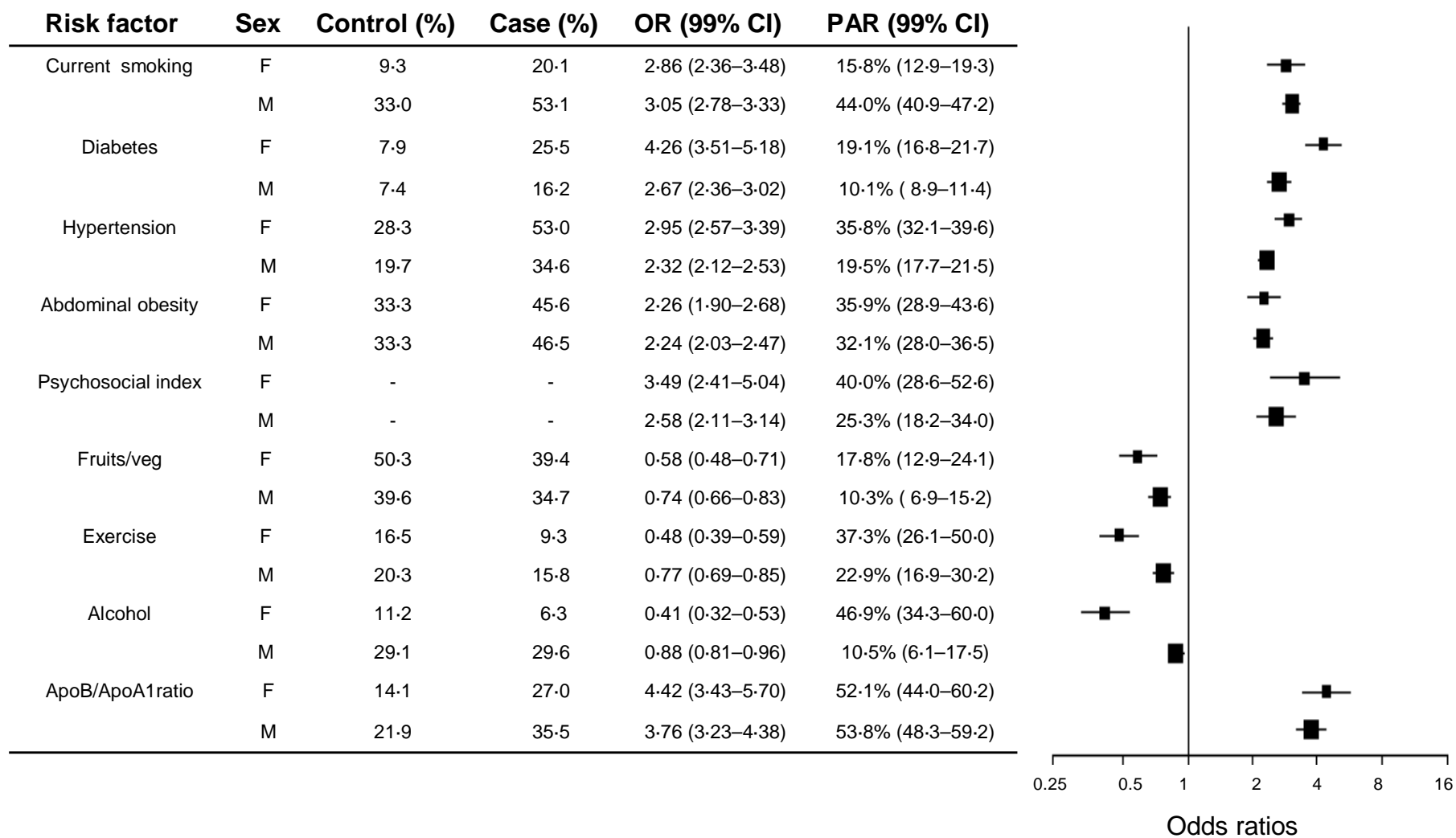


Fig 3

Men

Age (Low-risk level)*	30-34 (2%)	35-39 (3%)	40-44 (3%)	45-49 (4%)	50-54 (5%)	55-59 (7%)	60-64 (8%)	65-69 (10%)	70-74 (13%)	Absolute Risk	Absolute Risk†
Points †										Total CHD‡	Hard CHD§
0	1.0									2%	2%
1	1.5	1.0	1.0							3%	2%
2	2.0	1.3	1.3	1.0						4%	3%
3	2.5	1.7	1.7	1.3	1.0					5%	4%
4	3.5	2.3	2.3	1.8	1.4	1.0				7%	5%
5	4.0	2.6	2.6	2.0	1.6	1.1	1.0			8%	6%
6	5.0	3.3	3.3	2.5	2.0	1.4	1.3	1.0		10%	7%
7	6.5	4.3	4.3	3.3	2.6	1.9	1.6	1.3	1.0	13%	9%
8	8.0	5.3	5.3	4.0	3.2	2.3	2.0	1.6	1.2	16%	13%
9	10.0	6.7	6.7	5.0	4.0	2.9	2.5	2.0	1.5	20%	16%
10	12.5	8.3	8.3	6.3	5.0	3.6	3.1	2.5	1.9	25%	20%
11	15.5	10.3	10.3	7.8	6.1	4.4	3.9	3.1	2.3	31%	25%
12	18.5	12.3	12.3	9.3	7.4	5.2	4.6	3.7	2.8	37%	30%
13	22.5	15.0	15.0	11.3	9.0	6.4	5.6	4.5	3.5	45%	35%
>14	26.5	>17.7	>17.7	>13.3	>10.6	>7.6	>6.6	>5.3	>4.1	>53%	>45%

Women

Age (Low-risk level)*	40-44 (2%)	45-49 (3%)	50-54 (5%)	55-59 (7%)	60-64 (8%)	65-69 (8%)	70-74 (8%)	Absolute Risk	Absolute Risk
Points †								Total CHD‡	Hard CHD§
0	1.0							2%	1%
1	1.0							2%	1%
2	1.5	1.0						3%	2%
3	1.5	1.0						3%	2%
4	2.0	1.3						4%	2%
5	2.0	1.3						4%	2%
6	2.5	1.7	1.0					5%	2%
7	3.0	2.0	1.2					6%	3%
8	3.5	2.3	1.4	1.0				7%	3%
9	4.0	2.7	1.6	1.1	1.0	1.0	1.0	8%	3%
10	5.0	3.3	2.0	1.4	1.3	1.3	1.3	10%	4%
11	5.5	3.7	2.2	1.6	1.4	1.4	1.4	11%	7%
12	6.5	4.3	2.6	1.9	1.6	1.6	1.6	13%	8%
13	7.5	5.0	3.0	2.1	1.9	1.9	1.9	15%	11%
14	9.0	6.0	3.6	2.6	2.3	2.3	2.3	18%	13%
15	10.0	6.7	4.0	2.9	2.5	2.5	2.5	20%	15%
16	12.0	8.0	4.8	3.4	3.0	3.0	3.0	24%	18%
≥ 17	>13.5	>9.0	>5.4	>3.9	5.4	5.4	5.4	>27%	>20%

Green	Violet	Yellow	Red
Below Average risk	Average risk	Moderately above average risk	High risk

	Age	Men	Women
	<34	-1	-9
	35-39	0	-4
	40-44	1	0
	45-49	2	3
	50-54	3	6
	55-59	4	7
	60-64	5	8
	65-69	6	8
	70-74	7	8
Total cholesterol, mg/dL			
	<160	-3	-2
	169-199	0	0
	200-239	1	1
	240-279	2	2
	>280	3	3
HDL cholesterol, mg/dL			
	<35	2	5
	35-44	1	2
	45-49	0	1
	50-59	0	0
	>60	2	3
Syst Blood Pressure			
	<120	0	-3
	120-129	0	0
	130-139	1	1
	140-159	2	2
	>160	3	3
	Diabetes		
	yes	0	0
	no	2	4
	Smoker		
	yes	0	0
	no	2	2

Fig 4

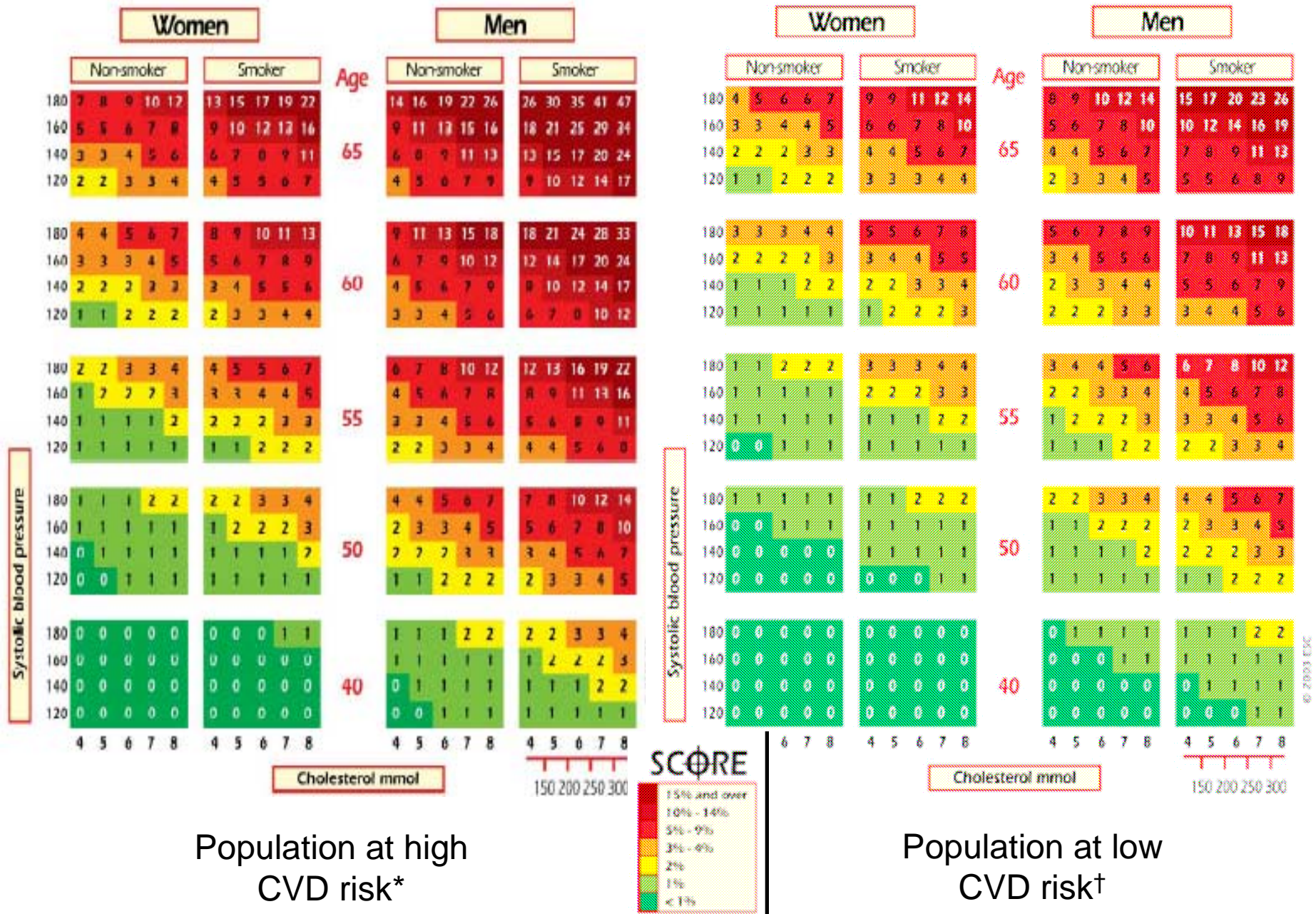


Fig 5

Women at Intermediate-High Likelihood of IHD

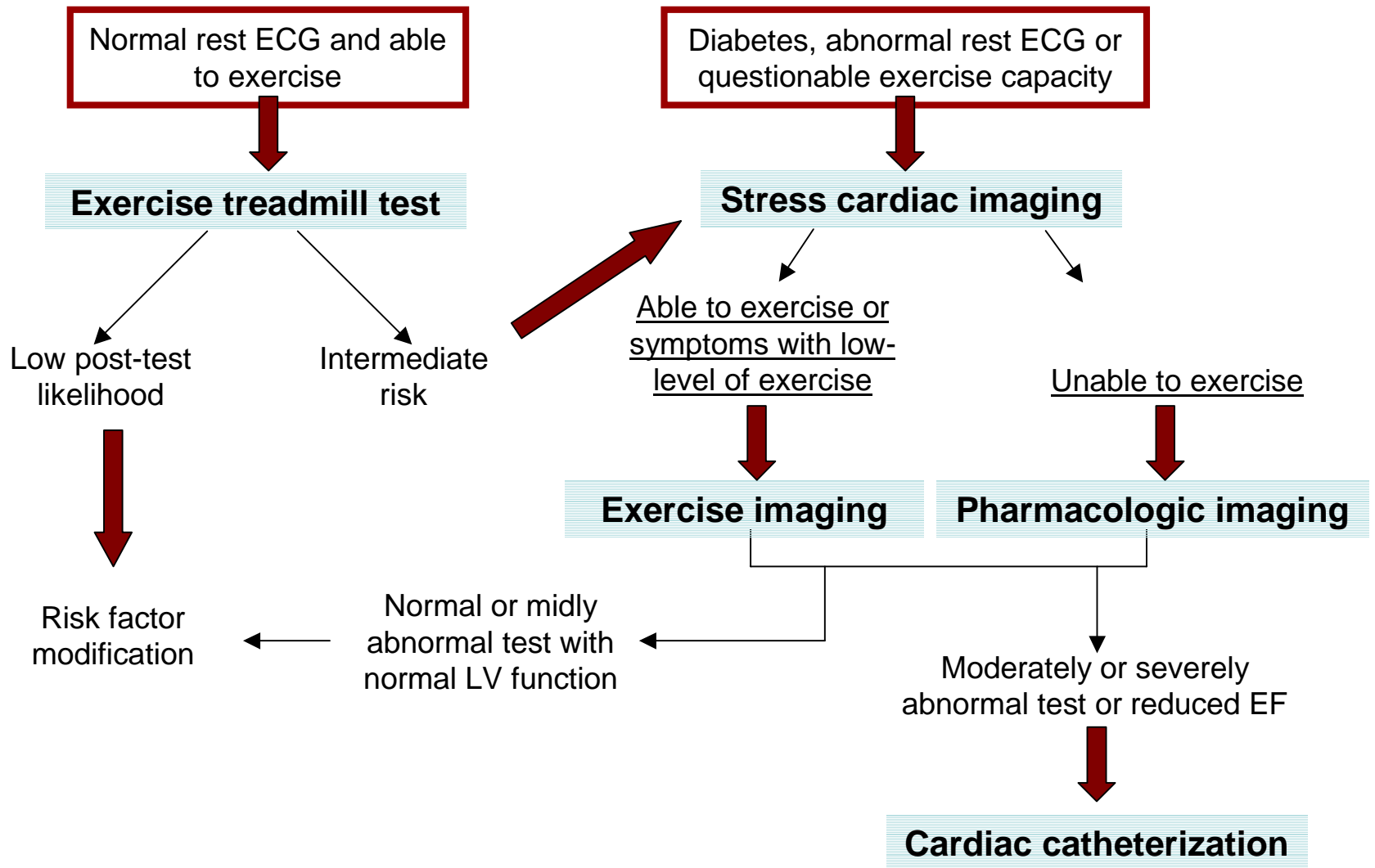


Fig 6

	Similarities	Peculiarities of women
Epidemiology	<ul style="list-style-type: none"> • IHD is a major cause of death • Increasing prevalence of IHD with age • Decline of IHD mortality rate over recent decades 	<ul style="list-style-type: none"> • Later occurrence of IHD • Lower prevalence and incidence of IHD at all ages
Risk Factors	<ul style="list-style-type: none"> • The presence of 9 modifiable risk factors account for more than 90% of the population attributable risk for myocardial infarction • Preventive drug interventions equally effective in men and women 	<ul style="list-style-type: none"> • Lower risk of events for a given combination of risk factors • Among patients with IHD, higher prevalence of diabetes and hypertension • 'Heavier' burden of risk factors may be required before developing IHD
Pathogenesis	<ul style="list-style-type: none"> • Atherosclerosis and thrombosis main causes of stable and unstable coronary syndromes 	<ul style="list-style-type: none"> • Less obstructive and less extensive epicardial disease • Impaired microcirculation, impaired vasomotion, erosion, dissection, and thrombophilia may contribute to IHD more than in men
Clinical features	<ul style="list-style-type: none"> • Typical angina most frequent clinical presentation • No gender-specific recommendations in IHD guidelines 	<ul style="list-style-type: none"> • Lower pre-test probability of IHD • Among ACS patients: <ul style="list-style-type: none"> - more frequent UA, "atypical" symptoms, older age, and comorbidities - delays and underuse of diagnostic and therapeutic procedures
Prognosis	<ul style="list-style-type: none"> • Overall similar adjusted short and long term outcomes after NSTEMI and STEMI 	<ul style="list-style-type: none"> • Lower pre-hospital mortality after MI • Better 30-day outcome after UA