Coronary artery disease in women: no reason for gender-specific treatment

Professor Michael S Marber
Department of Cardiology, KCL, St Thomas' Hospital, Lambeth Place Road, London SE1 7EH, UK (mike.marber@kcl.ac.uk)

This issue of our quarterly is dedicated to the management of women with, or at risk of developing, coronary artery disease. The traditional view has been that the female menopause represents a watershed in cardiovascular risk. Since before the menopause overt coronary artery disease is rare. The question of whether the relationship between reduced estrogen/progestogen and increased risk is associative or causative is the theme pervading the contributions to this issue.

Within this issue Dr's Clanachan and Fraser present numerous lines of evidence that suggest the male and female cardiovascular systems differ. These differences, as Dr's Holdright and Hayward and Collins point out, contibute to a chronological delay of approximately 20 years in the incidence of cardiovascular complications in women compared with men. This means that the incidence of cardiovascular disease increases sharply in women after the menopause. The question has been whether this temporal association between reduction in estrogen levels and increase in manifestations of ischaemic heart disease is causal? This issue is critical since estrogen replacement therapy (ERT) is the only cardiovascular intervention that is unique to women.

The use of ERT to reduce cardiovascular risk is addressed in this issue within the article by Dr Wenger. On the basis of observational studies women who choose to take ERT, with or without progestogens, have a reduced risk of coronary heart disease but it is also possible they are better educated, more compliant and have healthier lifestyles. Observational and other data from small randomised trials supported the concept that the risk of developing ischaemic heart disease after the menopausal could be reduced by ERT. However the Heart and Estrogen/Progestin Replacement Study (HERS)[1] has radically altered this view. This study, was the first large-scale (n=2763), randomised trial of ERT (0.625mg conjugated equine estrogens with 2.5mg medroxyprogesterone acetate) versus placebo, in older (mean age 66.7yr) postmenopausal women with confirmed ischaemic heart disease adopting "hard" clinical cardiovascular endpoints of nonfatal MI or death attributable to ischaemic heart disease. After an average of 4.1 years follow up, no significant difference existed for any cardiovascular end point.

As a result of this trial most recent guidelines do not support the initiation of ERT in women with established ischemic heart disease.[2] However since, within the HERS trial, ERT was perhaps associated with an early hazard (up to year 3), but then late benefit, (years 4 and 5) therapy continuation is probably reasonable until longer term follow-up of the HERS cohort and results from other ERT trials become available.

The question of ERT therapy to reduce events in women without overt ischaemic heart disease is a complex issue. No randomised data are available to support efficacy. Moreover, there are many examples of interventions effective in a secondary setting which later prove of value in primary prevention, whereas I'm not aware of an example of an intervention failing in secondary prevention but succeeding in primary prevention. These factors, together with other possible risks of ERT such as increased incidence of thromboembolic disease, breast cancer, endometrial cancer and gallbladder disease, means their use in primary prevention of ischaemic heart disease is likely to remain contentious.

The important point made in this issue is that although ERT is of unproven benefit, other interventions, that reduce the complications of ischaemic heart disease in whole populations, are increasingly becoming proven in women as they are better represented in trial populations.[3] This is particularly the case in women with diabetes. The worrying feature however is that evidence suggests that women are being denied beneficial advice and treatment. For example in a recent ambulatory care survey in the US, women were counselled less often that men about exercise, nutrition and weight reduction[2] whilst in England and Wales the prevalence of smoking is falling much more rapidly in men than in women.[4] The cause for this complacency is uncertain but may relate to guidelines that are driven by absolute risk together with a lower absolute risk of ischaemic heart disease in women. However once ischaemic heart disease is established intervention to reduce risk should no longer be gender-specific, yet in the HERS study 90% of women had LDL-cholesterol levels above 100mg/dl.[2]

These, and other issues raised in this quarterly, have opaque solutions. However one thing is clear; the reasons to treat men and women differently are becoming harder to find. Vive la difference? Perhaps not.

REFERENCES

1. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E, for the Heart and Estrogen/progestin Replacement Study (HERS) research group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-613.
2. Mosca L, Grundy SM, Judelson D, King K, Limacher M, Oparil S, Pasternak R, Pearson TA, Redberg RF, Smith SC, Winston M, Zinberg S. AHA/ACC scientific statement:Consensus panel statement. Guide to preventative cardiology for women. Circulation 1999;99:2480-2484.
3. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, Ramipril, on cardiovascular events in high risk patients. NEJM 2000;342:145-153.
4. Saving lives: Our Healthier Nation. http://www.ohn.gov.uk/ohn/ohn.htm

Gender differences in myocardial structure, function and metabolism

Dr. A.S. Clanachan[1], Dr. H. Fraser[2]
[1]Department of Pharmacology, Cardiovascular Research Group,
Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta T6G 2H7, Canada,
and [2]Division of Cardiology, Johns Hopkins University, Baltimore, MD, USA

Gender differences in cardiac function and metabolism are attracting considerable interest, particularly in relation to mechanisms responsible for the relative resistance of premenopausal females to ischemic heart disease. The delay in onset of cardiovascular disease in women before the menopausal years suggests that female sex hormones might possess cardioprotective properties. However, it is still unclear whether cardioprotection is due to circulating estrogen or to an inherent ability of female hearts to resist damage. Nevertheless, the potential benefit of estrogen has prompted its widespread clinical use and has stimulated numerous experimental investigations into the putative beneficial actions of estrogen replacement therapy. There is considerable evidence that physiologic concentrations of estrogen elicit a number of effects on function and metabolism that may contribute to the ability of the female heart to resist ischemic damage.

Introduction

Examination of the incidence of a broad spectrum of cardiovascular diseases has indicated that female gender is a protective factor.[1,2] Moreover, cardiovascular mortality rates are lower in premenopausal women than in males of equivalent age. The lack of any specific behavioral effect to account for such cardioprotection and the similarity in cardiovascular events between older men and menopausal women suggest that female sex hormones might possess cardioprotective properties.[3] Gender-dependent protection is also observed in patients with heart failure. However, it is still unclear if the resistance of the female heart is due to estrogen or to an inherent ability of the female heart to resist injury.

Cardiac structure

Premenopausal women have smaller hearts, but relative to total body mass, there is no difference when compared with men.[4] Left ventricular (LV) wall thickness, but not LV wall mass, increases after menopause,[5] whereas increases in LV mass during hormone replacement therapy (HRT) have been noted in some[6] but not all studies.[7] Cardiac fibroblasts, which contribute to structural remodeling associated with myocardial infarction and reperfusion injury, comprise ~60% of the total heart cells. Cardiac fibroblasts possess estrogen receptors, and both increases[8] and decreases[9] in fibroblast proliferation have been reported with estrogen replacement therapy (ERT). The survival advantage in women may also be related to gender-related differences in the degree of myocardial hypertrophy and a preserved systolic function.[10]

Cardiac dysfunction

Impairment of cardiac function may arise as a consequence of the loss of cardiomyocytes by necrosis and/or apoptosis. There are marked differences in the rates of necrosis and apoptosis between male and female hearts, particularly following the onset of cardiac failure.[11] Gender differences are also manifest during acute coronary occlusion when females have a greater vagal activation and fewer cardiac dysrhythmias.[12] Thus, while it is conceivable that the female heart resists injury by some, as yet unidentified, inherent property, considerable attention has focused on the cardioprotective properties of estrogen.

ERT is considered to reduce the risk of cardiovascular disease in menopausal females,[1,3] although recent evidence from a large (n = 2763) randomized trial indicated that HRT

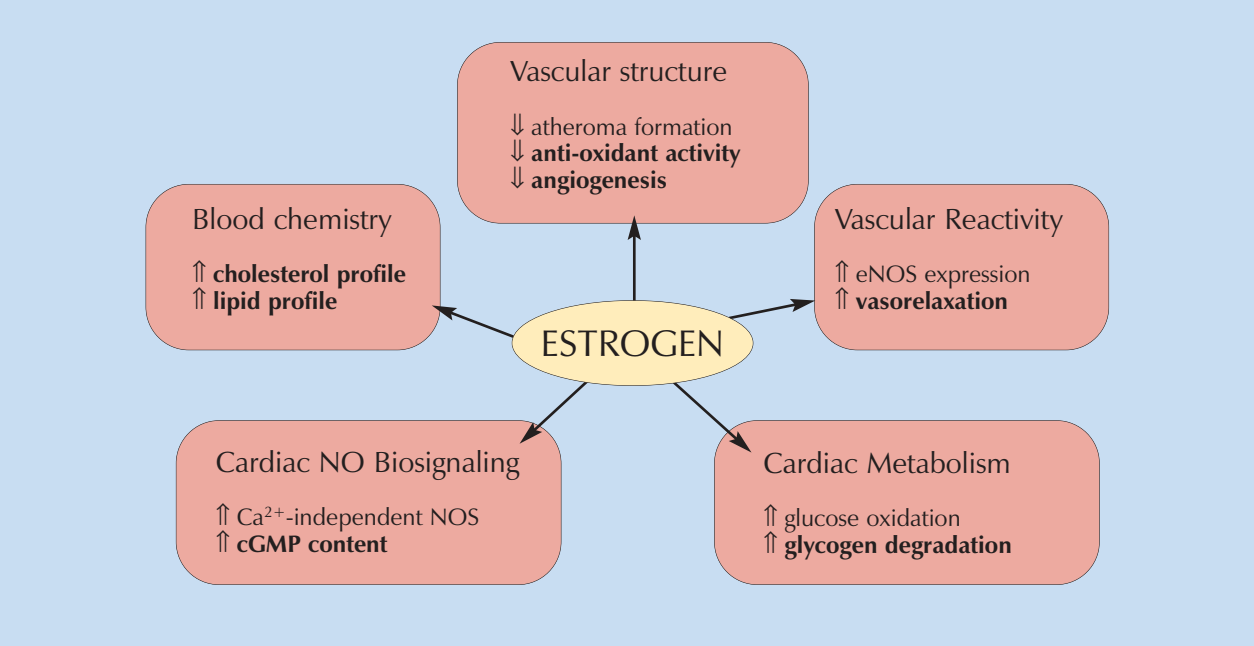

Figure 1. Cardioprotective mechanisms of estrogen

consisting of a combination of conjugated estrogens and medroxyprogesterone exerts no significant beneficial actions.[13] While the cardioprotective efficacy of estrogen *per se* was not assessed, reports of improved cholesterol profiles,[14] decreased insulin resistance and enhanced glucose tolerance[15] by ERT provide evidence that estrogen may offer protection against coronary heart disease. Moreover, experimental data that demonstrate a reduction in myocardial necrosis after ischemia and reperfusion by chronic 17β-estradiol[16] and an improved recovery of post-ischemic contractile function in hearts perfused *ex vivo*[17,18] suggest that mechanisms occurring directly in the heart also contribute to estrogen-induced cardioprotection. While most experimental models of estrogen-induced cardioprotection require chronic therapy, rapid non-genomic actions of estrogen may also be involved.

Indirect protective mechanisms of estrogen

Indirect (non-cardiac) mechanisms proposed for the cardioprotective actions of estrogen include reduced responses to vascular injury arising, in part, from alterations in lipid metabolism that improve the ratio of HDL to LDL. Indeed, this has been considered the principal mechanism of protection.[19] Estrogen also inhibits LDL oxidation and so limits atherosclerotic plaque formation.[20] Moreover, estrogen may exert an additional protective action on the circulation by virtue of an antioxidant activity.[21] Similar reduction in cardiovascular risk factors has been observed with raloxifene, a selective estrogen receptor modulator.[22]

Vasodilator properties of estrogen have been described, including increased blood flow in the carotid and coronary arteries.[23,24] While inhibition of L-type Ca^{2+} channels occurs with 17β-estradiol concentrations much higher than those associated with ERT,[23] there is considerable evidence for enhanced nitric oxide (NO) biosignaling by clinical concentrations of estrogen[25] that can exert an array of beneficial effects on blood-borne cellular elements (inhibition of platelet aggregation and neutrophil adhesion) as well as vascular smooth muscle (vasorelaxation and inhibition of proliferation). Key findings include an estrogen-induced increase in the expression and activity of NO synthases that facilitate endogenous NO production.[26] Female vascular endothelium has an enhanced capacity to produce NO and reduce smooth muscle tone,[27] and there is a similar enhanced endothelial-dependent (NO-

mediated) relaxation in 17β-estradiol-treated male rats.[27] Finally, estrogen-induced release of vascular endothelium growth factor may stimulate coronary angiogenesis.[28]

Direct protective mechanisms of estrogen
A direct cardioprotective effect of estrogen is also demonstrable. While enhanced NO biosignaling in the vasculature has been implicated in many of the cardiovascular changes arising from estrogen, several cell types in the myocardium, including endothelial cells[29] and cardiomyocytes,[30] possess the various isoforms of NO synthase and can generate endogenous NO that may benefit cardiac function. Estrogen upregulates NO synthase[25,26,31] in cardiomyocytes, and a recent study that discovered enhanced myocardial NO biosignaling (NO synthase activity and cGMP content) in hearts from estrogen-treated rats provides strong evidence for a role of NO in the direct cardioprotective actions of 17β-estradiol.[32]

Myocardial metabolism

Myocardial energy is generated mainly from the oxidation of fatty acids and carbohydrates. Although the beta-oxidation of fatty acids is the more important source of ATP production, glucose metabolism, particularly the relative rate of glycolysis and glucose oxidation, is an important consideration during periods of sympathetic activation or post-ischemic reperfusion. The rate of glycolysis greatly exceeds that of glucose oxidation, a condition that leads to considerable proton production and intracellular acidosis. Accumulation of Na^+ (via the Na^+-H^+ exchanger) and Ca^{2+} overload (via the Na^+-Ca^{2+} exchanger) impair recovery of mechanical function and myocardial efficiency upon reperfusion.[33] Overexpression of the Na^+-Ca^{2+} exchanger in male, but not in female, animals worsens recovery of post-ischemic function, presumably by promoting greater Ca^{2+} overload. Interestingly, bilateral ovariectomy prevents this gender difference and suggests that estrogen may protect by mechanisms that ultimately affect Ca^{2+} overload.[34]

No direct examinations of gender differences in overall myocardial energy substrate metabolism are available, but estrogen-induced regulation of glucose metabolism is demonstrable. Estrogen increases glycogen deposition in heart[35] and improves exercise tolerance and prevents depletion of myocardial glycogen.[36] Estrogen signaling pathways have also been implicated in the translational control of enzymes in fatty acid and glucose metabolism by the nuclear receptor, peroxisome proliferator-activated receptor-alpha.[37]

Direct assessment of rates of myocardial glycolysis and glucose oxidation in hearts removed from rats treated chronically with 17β-estradiol revealed an acceleration of glucose oxidation both during aerobic perfusion and during post-ischemic reperfusion.[18] These data, in combination with the well-documented benefits elicited by the optimization of myocardial glucose metabolism,[38,39] suggest that changes in glucose metabolism arising from chronic 17β-estradiol treatment may indeed contribute to the direct cardioprotective efficacy of estrogen.

Conclusion

There are important gender-based differences that affect cardiovascular function and resistance to injury, including direct estrogen-mediated changes in cardiac function and metabolism, as well as indirect factors that alter the coronary and systemic vasculature and the generation of atherosclerosis. Ongoing clinical and basic research aims to identify more carefully the mechanisms underlying such gender-related differences and to exploit pharmacologically these effects so that the full cardioprotective efficacy of estrogen and selective estrogen receptor modulators can be realized for both male and female patients. ■

REFERENCES

1. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1991; 20: 47–63.
2. Adams KF Jr, Sueta CA, Gheorghiade M et al. Gender differences in survival in advanced heart failure. Insights from the FIRST study. Circulation 1999; 99: 1816–1821.
3. Grady D, Rubin SM, Petitti DB et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992; 117: 1016–1037.
4. Hutchinson PL, Cureton KJ, Outz H, Wilson G. Relationship of cardiac size to maximal oxygen uptake and body size in men and women. Int J Sports Med 1991; 12: 369–373.
5. Pines A, Fisman EZ, Drory Y et al. The effects of sublingual estradiol on left ventricular function at rest and exercise in postmenopausal women: an echocardiographic assessment. Menopause 1998; 5: 79–85.
6. Sites CK, Tischler MD, Blackman JA et al. Effect of short-term hormone replacement therapy on left ventricular mass and contractile function. Fertil Steril 1999; 71: 137–143.
7. Snabes MC, Payne JP, Kopelen HA et al. Physiologic estradiol replacement therapy and cardiac structure and function in normal postmenopausal women: a randomized, double-blind, placebo-controlled, crossover trial. Obstet Gynecol 1997; 89: 332–339.
8. Lee HW, Eghbali-Webb M. Estrogen enhances proliferative capacity of cardiac fibroblasts by estrogen receptor- and mitogen-activated protein kinase-dependent pathways. J Mol Cell Cardiol 1998; 30: 1359–1368.
9. Dubey RK, Gillespie DG, Jackson EK, Keller PJ. 17β-estradiol, its metabolites, and progesterone inhibit cardiac fibroblast growth. Hypertension 1998; 31: 522–528.
10. Carroll JD, Carroll EP, Feldman T et al. Sex-associated differences in left ventricular function in aortic stenosis of the elderly. Circulation 1992; 86: 1099–1107.
11. Guerra S, Leri A, Wang X et al. Myocyte death in the failing human heart is gender dependent. Circ Res 1999; 85: 856–866.
12. Airaksinen KE, Ikaheimo MJ, Linnaluoto M et al. Gender difference in autonomic and hemodynamic reactions to abrupt coronary occlusion. J Am Coll Cardiol 1998; 31: 301–306.
13. Hully S, Grady D, Bush T et al., for the Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. J Am Med Assoc 1998; 280: 605–613.
14. Godsland IF, Wynn V, Crook D, Miller NE. Sex, plasma lipoproteins, and atherosclerosis: prevailing assumptions and outstanding questions. Am Heart J 1987; 114: 1467–1503.
15. Bailey CJ, Ahmed-Sorour H. Role of ovarian hormones in the long-term control of glucose homeostasis. Effects of insulin secretion. Diabetologia 1980; 19: 475–481.
16. Hale SL, Birnbaum Y, Kloner RA. β-Estradiol, but not alpha-estradiol, reduced myocardial necrosis in rabbits after ischemia and reperfusion. Am Heart J 1996; 132: 258–262.
17. Kolodgie FD, Farb A, Litovsky SH et al. Myocardial protection of contractile function after global ischemia by physiologic estrogen replacement in the ovariectomized rat. J Mol Cell Cardiol 1997; 29: 2403–2414.
18. Fraser H, Davidge ST, Clanachan AS. Enhancement of post-ischemic myocardial function by chronic 17β-estradiol treatment: role of alterations in glucose metabolism. J Mol Cell Cardiol 1999; 31: 1539–1549.
19. Stevenson JC, Crook D, Godsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. Atherosclerosis 1993; 98: 83–90.
20. Williams JK, Adams MR, Klopfenstein HS. Estrogen modulates responses of atherosclerotic coronary arteries. Circulation 1990; 81: 1680–1687.
21. Delyani JA, Murohara T, Nossuli TO, Lefer AM. Protection from myocardial reperfusion injury by acute administration of 17β-estradiol. J Mol Cell Cardiol 1996; 28: 1001–1008.
22. de Valk-de Roo GW, Stehouwer CD, Meijer P et al. Both raloxifene and estrogen reduce major cardiovascular risk factors in healthy postmenopausal women: a 2-year, placebo-controlled study. Arterioscler Thromb Vasc Biol 1999; 19: 2993–3000.
23. Hugel S, Neubauer S, Lie SZ et al. Multiple mechanisms are involved in the acute vasodilatory effect of 17β-estradiol in the isolated perfused rat heart. J Cardiovasc Pharmacol 1999; 33: 852–858.
24. Berman M, Gewirtz H. Acute effects of 17β-estradiol on the coronary microcirculation: observations in sedated, closed-chest domestic swine. Coron Artery Dis 1997; 8: 351–361.
25. Weiner CP, Lizasoain I, Baylis SA et al. Induction of calcium-dependent nitric oxide synthases by sex hormones. Proc Nat Acad Sci USA 1994; 91: 5212–5216.
26. Kleinert H, Wallerath T, Euchenhofer C et al. Estrogens increase transcription of the human endothelial NO synthase gene: analysis of the transcription factors involved. Hypertension 1998; 31: 582–588.
27. Kauser K, Rubanyi GM. Gender difference in bioassayable endothelium-derived nitric oxide from isolated rat aortae. Am J Physiol 1994; 267: H2311–H2317.
28. Agrawal R, Prelevic G, Conway GS et al. Serum vascular endothelial growth factor concentrations in postmenopausal women: the effect of hormone replacement therapy. Fertil Steril 2000; 73: 56–60.

29. Wever RM, Luscher TF, Cosentino F, Rabelink TJ. Atherosclerosis and the two faces of endothelial nitric oxide synthase. Circulation 1998; 97: 108–112.
30. Schulz R, Nava E, Moncada S. Induction and potential biological relevance of a Ca^{2+}-independent nitric oxide synthase in the myocardium. Br J Pharmacol 1992; 105: 575–580.
31. Grohe C, Kahlert S, Lobbert K, Vetter H. Expression of oestrogen receptor α and β in rat heart: role of local oestrogen synthesis. J Endocrinol 1998; 156: R1–7.
32. Fraser H, Davidge ST, Clanachan AS. Activation of Ca^{2+}-independent nitric oxide synthase by 17β-estradiol in post-ischemic rat heart. Cardiovasc Res. 2000; 46: 11–118.
33. Liu B, Clanachan AS, Schulz R, Lopaschuk GD. Cardiac efficiency is improved after ischemia by altering both the source and fate of protons. Circ Res 1996; 79: 940–948.
34. Cross HR, Lu L, Steenbergen C et al. Overexpression of the cardiac Na^{+}/Ca^{2+} exchanger increases susceptibility to ischemia/reperfusion injury in male, but not female, transgenic mice. Circ Res 1998; 83: 1215–1223.
35. Carrington LJ, Bailey CJ. Effects of natural and synthetic estrogens and progestins on glycogen deposition in female mice. Horm Res 1985; 21: 199–203.
36. Kendrick ZV, Steffen CA, Rumsey WL, Goldberg DI. Effect of estradiol on tissue glycogen metabolism in exercised oophorectomized rats. J Appl Physiol 1987; 63: 492–496.
37. Djouadi F, Weinheimer CJ, Saffitz JE et al. A gender-related defect in lipid metabolism and glucose homeostasis in peroxisome proliferator-activated receptor alpha-deficient mice. J Clin Invest 1998; 102: 1083–1091.
38. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic, and reperfused ischemic rat hearts. Circulation 1996; 93: 135–142.
39. Lopaschuk GD, Stanley WC. Glucose metabolism in the ischemic heart. Circulation 1997; 95: 313–315.

Incidence, aetiology and prognosis of coronary artery disease in women

Dr Diana R. Holdright
Department of Cardiology, The Middlesex Hospital (UCL Hospitals),
Mortimer St, London W1N 8AA, UK

Introduction

The earlier ignorance amongst the medical profession of the importance of coronary artery disease in women has been virtually dispelled due to the ever-increasing number of publications in this area. Although the message has yet to be fully received and understood by the general public, all current and proposed studies in coronary artery disease also address potential gender differences which previously were generally not even considered in trial concept or design, many studies being conducted exclusively in the typical middle-aged male population. We are now able to paint a detailed picture of the woman at risk of ischaemic heart disease.

Incidence

Generally speaking, a 50-year-old woman has a lifetime risk of developing coronary artery disease of 31%. The Framingham data show that women are more likely to present with angina (47%) than either myocardial infarction (32%), unstable angina (7%) or cardiac death (14%).[1] Nearly one-half of first presentations in men are due to myocardial infarction (46%), followed by angina (32%), death (16%) and unstable angina (6%).

More than 236,000 women die each year in the US from myocardial infarction. Approximately one-quarter of all deaths in women in industrialized nations are due to coronary artery disease.[2] Before the age of 75, the proportion of deaths from coronary artery disease is far less in women than in men. Whereas the death toll from breast cancer is the same as that from ischaemic heart disease in women aged less than 65, the overall mortality for all ages is 23% from ischaemic heart disease and only 5% from breast cancer (*Table 1*). Mortality rates rise rapidly with increasing age for both men and women. The male excess, although particularly pronounced at younger ages, lessens with increasing age to approximately 1.5:1 in the over-75s.

Worldwide there are marked geographical differences in coronary mortality rates for men and women. There are remarkable differences between countries (*Figure 1*), with the highest rates in Eastern Europe and the lowest in Japan and China, yet the ratio of men to women

Table 1. Deaths in women in the UK (1992) and the US (1990).[2]

	All ages		<75 Years		<65 Years	
	n	%	*n*	%	*n*	%
UK						
All causes	325,703	100	105,921	100	44,286	100
Ischaemic heart disease	6,366	23	21,843	21	5815	13
Breast cancer	15,221	5	9275	9	5690	13
Cervical cancer	1863	<1	1368	1	902	2
USA						
Total deaths	1,035,046	100	417,805	100	215,923	100
Ischaemic heart disease	236,574	23	63,051	15	20,956	10
Breast cancer	43,391	4	29,933	7	18,609	9
Cervical cancer	4627	<1	3647	1	2777	1

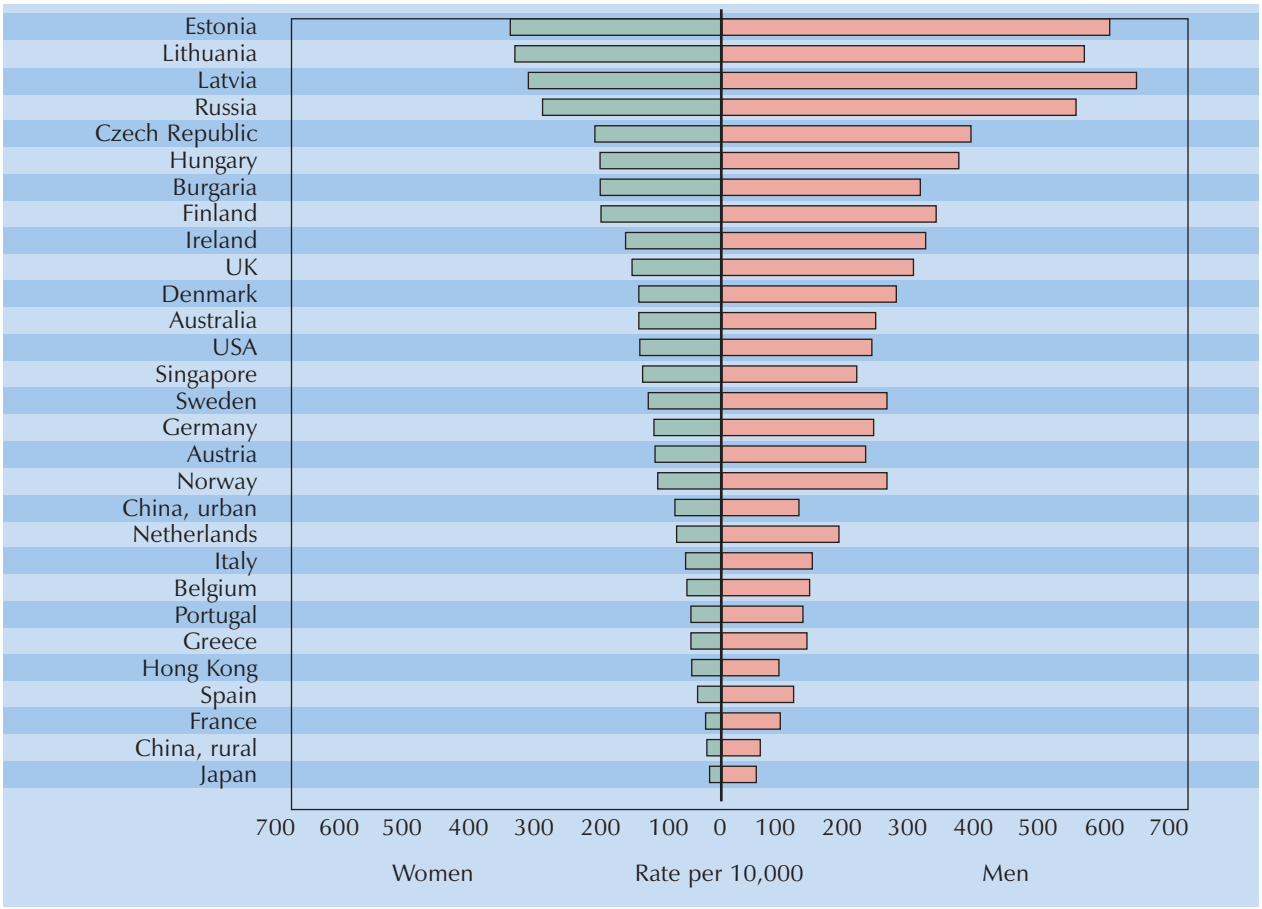

Figure 1. Ischaemic heart disease. Age-standardized (to European Standard population) mortality rates for women and men, 1991–1993.[2]

remains similar. Changes in mortality rates over the last few decades have been most impressive in the USA, which had the highest rate in the 1950s but has shown the most dramatic decline in the last two decades for both men and women. Increasing mortality rates are seen for both sexes in many Eastern European countries.

The latest WHO MONICA publication[3] showed changes in coronary event rates and survival among 37 populations in 21 countries over a 10-year period, beginning in the early 1980s. Overall mortality rates fell by –2.7% per year in men and by –2.1% per year in women. Coronary event rates fell more (by –2.1% and –1.4% per year, respectively) than case fatalities (–0.6% and –0.8% per year, respectively). Most rates fell and were similar for men and women across populations (*Figure 2*). The male populations with the greatest increases were predominantly Central and Eastern Europe and Asia, with similar findings in women. Case fatality trends were more consistent geographically in men than in women. The overall fall in mortality was driven more by a change in event rates than by case fatalities. This was seen for both sexes but there was less consistency in women due to the smaller numbers.

Aetiology

Changes in coronary event rates in men and women are correlated within the different countries, suggesting that whatever factors influence or determine coronary risk, they affect men and women similarly. Most classical cardiovascular risk factors operate similarly in men and women although the absolute risk is typically lower in women.[4] The exception is

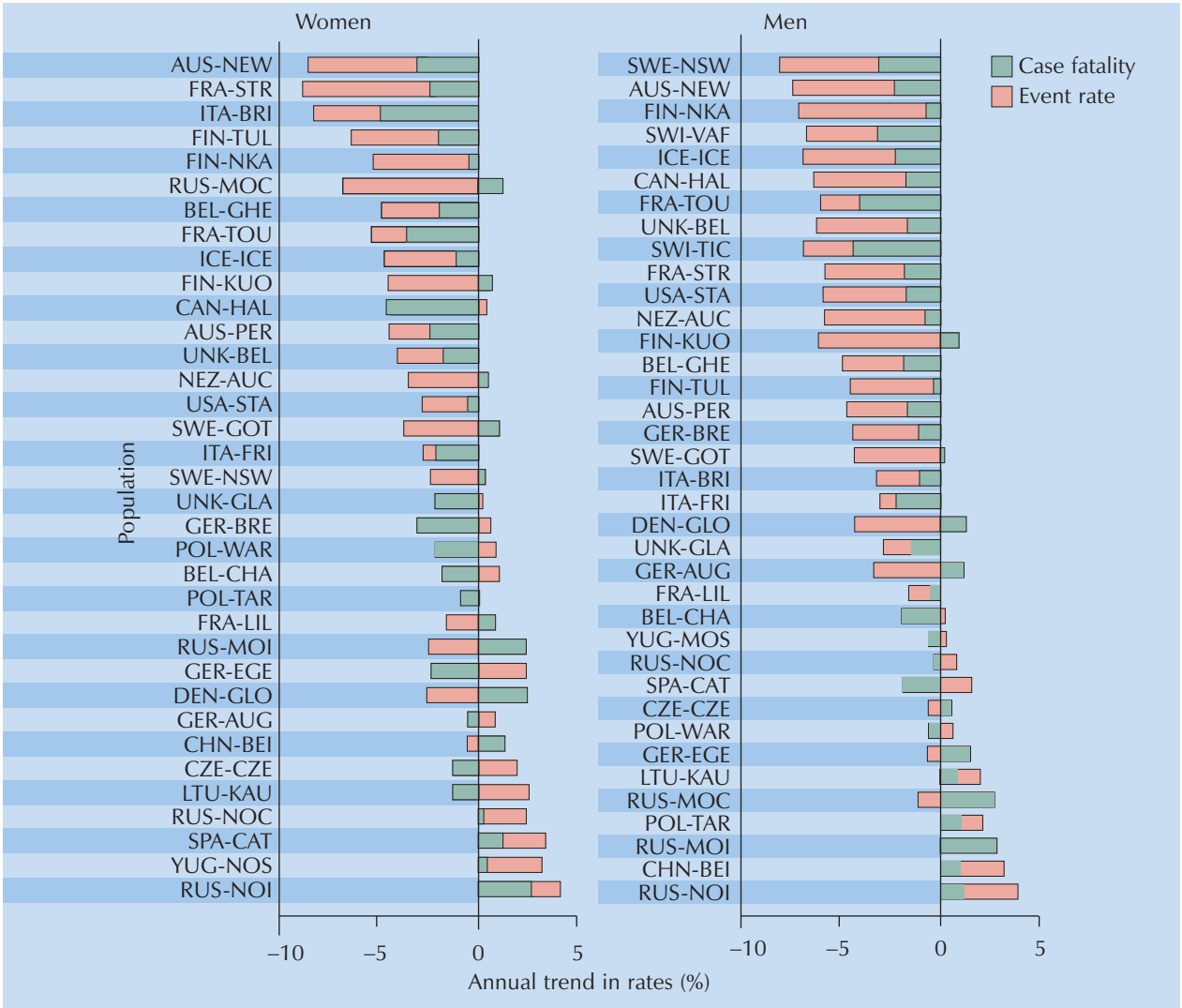

Figure 2. Population rankings, by sex, of trends in MONICA CHD mortality rate showing contribution of trends in coronary-event rate and in case fatality.[3]

diabetes mellitus, which negates the female advantage: mortality rates are three to seven times higher in diabetic *vs* non-diabetic women compared with a two- to fourfold difference between diabetic and non-diabetic men. Oestrogen deficiency, whether premature or natural, is an important and exclusive risk factor. Cigarette smoking, which is increasing particularly in young women, quadruples the risk of coronary artery disease.

Generally speaking, women tend to have a better risk factor profile at younger ages in comparison with men until older age when the opposite is true. There is compelling evidence from clinical trials of the benefit in women of lowering serum cholesterol levels and reducing blood pressure. The relative risk reductions are generally similar but the absolute risk reductions are less in women. A 15-year follow-up of over 15,000 adults (>50% women) from Scotland[5] showed that women were more likely to have high cholesterol, to be obese and to come from lower social classes than men, but they smoked less and had similar blood pressures. Relative risks of coronary death were similar in men and women for cholesterol but absolute risks were far lower in women: women in the top quintile for cholesterol had lower mortality than men in the bottom quintile (*Figure 3*). The relative risks in women were similar, but the

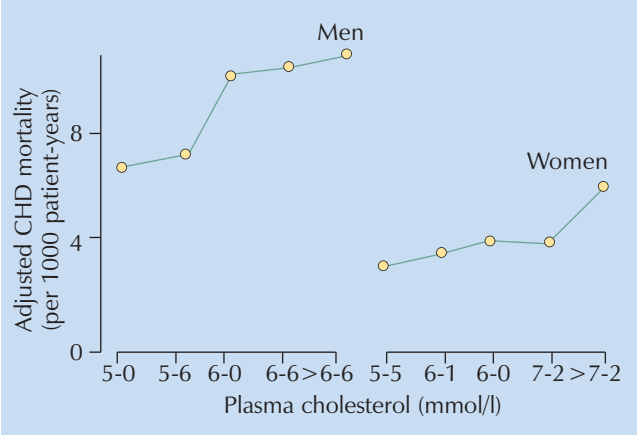

Figure 3. Adjusted mortality from coronary heart disease (CHD) in deaths per 1000 patient-years by quintile of plasma cholesterol.[5]

absolute and attributable risks were also lower than in men for smoking and diastolic blood pressure (*Table 2*).

A recent comparison of 27 different potential risk factors for coronary artery disease in men and women indicated that the classical risk factors scored more strongly in both sexes for predicting cardiovascular risk than new ones.[6] Total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure and previous angina all ranked within the top six risk factors for coronary artery disease in men and women. Diabetes ranked 7th in women and 21st in men.

The oestrogen status of a woman is a unique and highly important factor with regard to coronary risk. Premature menopause, natural or surgical, is associated with a marked increase in risk. How much the increased cardiovascular risk with natural menopause is due to oestrogen deficiency and how much is due to the other effects of age is uncertain, since the two are inextricably linked. There is only a small attributable risk associated with oral contraception, since the group of women using it are relatively young with low rates of coronary artery disease.

Old trials of hormone replacement therapy (HRT) suggested a significant protective effect[7] but it is impossible to dissect out the 'healthy cohort' effect, since women likely to use HRT are generally speaking at lower cardiovascular risk in any case.[8] The HERS study,[9] which is the only reported study of secondary prevention using HRT, showed no overall effect on the occurrence of non-fatal myocardial infarction or coronary heart disease death but there was a time trend towards benefit in years 4 and 5. There was a significant, but hardly surprising, increased risk of thromboembolic disease and gallbladder disease. Consequently, HRT is no longer recommended for secondary prevention of coronary artery disease. However, the trial can be criticized on several counts, which is beyond the scope of this article, and some would argue that the HERS study has simply created more confusion on this issue than it has answered any fundamental questions.

Table 2. Relative and attributable risk of coronary death in men and women.[5]

	Relative risk (95% CI)	Deaths saved in the study population
Men		
Cholesterol	1.56 (1.32–1.85)	211
Smoking	2.03 (1.64–2.52)	351
Diastolic blood pressure	2.19 (1.74–2.75)	272
Women		
Cholesterol	1.77 (1.45–2.16)	103
Smoking	2.38 (1.92–2.96)	181
Diastolic blood pressure	2.62 (1.92–3.58)	191

Prognosis

The Framingham database provides insight into the prognosis of women given a diagnosis of coronary artery disease, broken down according to the mode of presentation (angina, myocardial infarction, etc).[1] In subjects with angina, which was the most common presentation in women, men experienced a higher myocardial infarction rate than did women during follow-up. The male:female hazard risk for subsequent myocardial infarction was 2.2, for coronary death it was 2.1 and for total mortality it was 1.6. After a recognized myocardial infarction, women had a worse prognosis, although the sex difference diminished, but did

Table 3. Sex differences in risk for outcome events according to initial coronary heart disease (CHD) presentation: 10-year follow-up in men vs women.[1]

Outcome	Age- and RF-adjusted[a] (95% CI)
Angina as the initial CHD presentation	
MI	2.20 (1.45–3.34)
CHD death	2.11 (1.32–3.36)
Total mortality	1.59 (1.14–2.24)
Coronary insufficiency as the initial CHD presentation	
MI	1.43 (0.45–4.52)
CHD death	1.05 (0.32–3.46)
Total mortality	1.35 (0.60–3.02)
Recognized MI as the initial CHD presentation	
MI	0.80 (0.43–1.51)
CHD death	0.88 (0.57–1.37)
Total mortality	0.75 (0.53–1.08)
Unrecognized MI as the initial CHD presentation	
MI	1.28 (0.61–2.68)
CHD death	1.75 (0.92–3.31)
Total mortality	2.01 (1.28–3.15)

RF, risk factor; MI, myocardial infarction.
[a]Risk factors: cholesterol, diabetes, hypertension and smoking.

not disappear, after adjustment for age and other risk factors (*Table 3*).

The better outcome for women with angina has been found in numerous studies and undoubtedly relates to the difficulty in establishing whether chest pain in a woman is cardiac in origin.[10] Angiographic studies have shown that women with 'angina' are far more likely to have angiographically normal coronary arteries compared with men. Hence, a significant proportion of women are erroneously given a label of coronary artery disease. It is hardly surprising, therefore, that women with 'angina' have a better prognosis than men.

Outcome after myocardial infarction was extensively investigated in the GUSTO IIb study,[11] which enrolled more than 12,000 patients (>25% women) with acute coronary syndromes. Women were older and sicker at presentation (with higher rates of diabetes, hypertension and prior heart failure). Women also had more complications in hospital and a higher 30-day mortality (6 *vs* 4% in men). To a great extent the worse outcome in women could be accounted for by baseline variables. Women with unstable angina had a better outcome, undoubtedly related in part to less severe coronary artery disease; indeed, 30.5% of women were subsequently shown to have no significant disease at angiography, compared with 13.9% of men.

The worse outcome in women following myocardial infarction probably has several explanations. As well as having greater comorbidity at presentation, studies have shown that women are treated less aggressively than men and are less likely to be admitted to a coronary care unit, to receive thrombolysis and to proceed to coronary angiography and revascularization.[12] Women are also older at presentation, raising the possibility of ageism, particularly where coronary care units have upper age limits, denying older patients the benefit of careful monitoring and thrombolysis, which is not usually administered outside the coronary care unit.[13]

Many earlier studies showed that women with suspected or presumed coronary artery disease were less likely to undergo invasive testing with a view to revascularization.[14] One of several possible explanations was that women were generally thought to fare less well

after PTCA and bypass surgery, with a greater incidence of periprocedural complications and a poorer symptomatic result during follow-up. More recent reports, incorporating contemporary practice and recent technological and pharmaceutical advances show that this is no longer likely to be true, particularly when baseline differences in clinical status are taken into account.[15]

Conclusions

Compared with men, coronary artery disease is less common in women but it remains the major cause of mortality in developed societies. Coronary risk factors are similar, although attributable risks are generally lower in women than in men. The role of HRT remains uncertain. The prognosis of women with coronary artery disease differs according to the mode of presentation and is partly explained by the accuracy of diagnosis and differing risk factor profiles, particularly age, at presentation. ■

REFERENCES

1. Murabito JM, Evans JC, Larson MG, Levy D. Prognosis after the onset of coronary heart disease. An investigation of differences in outcome between the sexes according to initial coronary disease presentation. Circulation 1993; 88: 2548–2555.
2. World Health Statistics Annuals 1982–1994. Geneva: World Health Organization, 1982–1994.
3. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M et al., for the WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project. Contributions of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. Lancet 1999; 353: 1547–1557.
4. Holdright DR. Risk factors for cardiovascular disease in women. J Hum Hypertens 1998; 12: 667–673.
5. Isles CG, Hole DJ, Hawthorne VM, Lever AF. Relation between coronary risk and coronary mortality in women of the Renfrew and Paisley survey: comparison with men. Lancet 1992; 339: 702–706.
6. Tunstall-Pedoe H et al. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. Br Med J 1997; 315: 722–729.
7. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1991; 20: 47–63.
8. Posthuma WFM, Westendorp RGJ, Vandenbroucke JP. Cardioprotective effect of hormone replacement therapy in postmenopausal women: is the evidence biased? Br Med J 194; 308: 1268–1269.
9. Hulley S et al., for the Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. J Am Med Assoc 1998; 280: 605–613.
10. Collins P. Metabolic imaging — diagnosis of CAD in women vs men.
11. Hochman JS et al., for the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. Sex, clinical presentation and outcome in patients with acute coronary syndromes. N Engl J Med 1999; 341: 226–232.
12. Wilkinson P, Laji K, Ranjadayalan K et al. Acute myocardial infarction in women: survival analysis in first six months. Br Med J 1994; 309: 566–569.
13. Adams JN, Jamieson M, Rawles JM et al. Women and myocardial infarction: ageism rather than sexism. Br Heart J 1995; 73: 87–91.
14. Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary heart disease. N Engl J Med 1991; 325: 221–225.
15. Jacobs AK et al. Better outcome for women compared with men undergoing coronary revascularization. A report from the Bypass Angioplasty Revascularization Investigation (BARI). Circulation 1998; 98: 1279–1285.

Does hormone replacement therapy enhance or reduce cardiovascular event rate?

Dr Nanette K. Wenger
Professor of Medicine (Cardiology), Division of Cardiology, Emory University School of Medicine, Atlanta, GA 30303, USA; Chief of Cardiology, Grady Memorial Hospital; and Consultant, Emory Heart and Vascular Center, Atlanta, GA, USA

Epidemiologic data suggest the potential of postmenopausal hormone replacement therapy (HRT) to confer cardioprotection. These observations include the preponderance of coronary heart disease (CHD) in postmenopausal women[1] and the accelerated appearance of CHD in women with premature natural menopause or bilateral oophorectomy. The almost doubled risk of CHD in the latter is abolished by estrogen therapy.[2]

Population-based observational studies of both estrogen and estrogen/progestin use in women not known to have CHD, and meta-analyses of these studies, almost uniformly suggest a 35–50% reduction in CHD risk[3] (*Figures 1 and 2*). However, observational data can be confounded by selection bias, in that HRT is typically prescribed to healthy women.

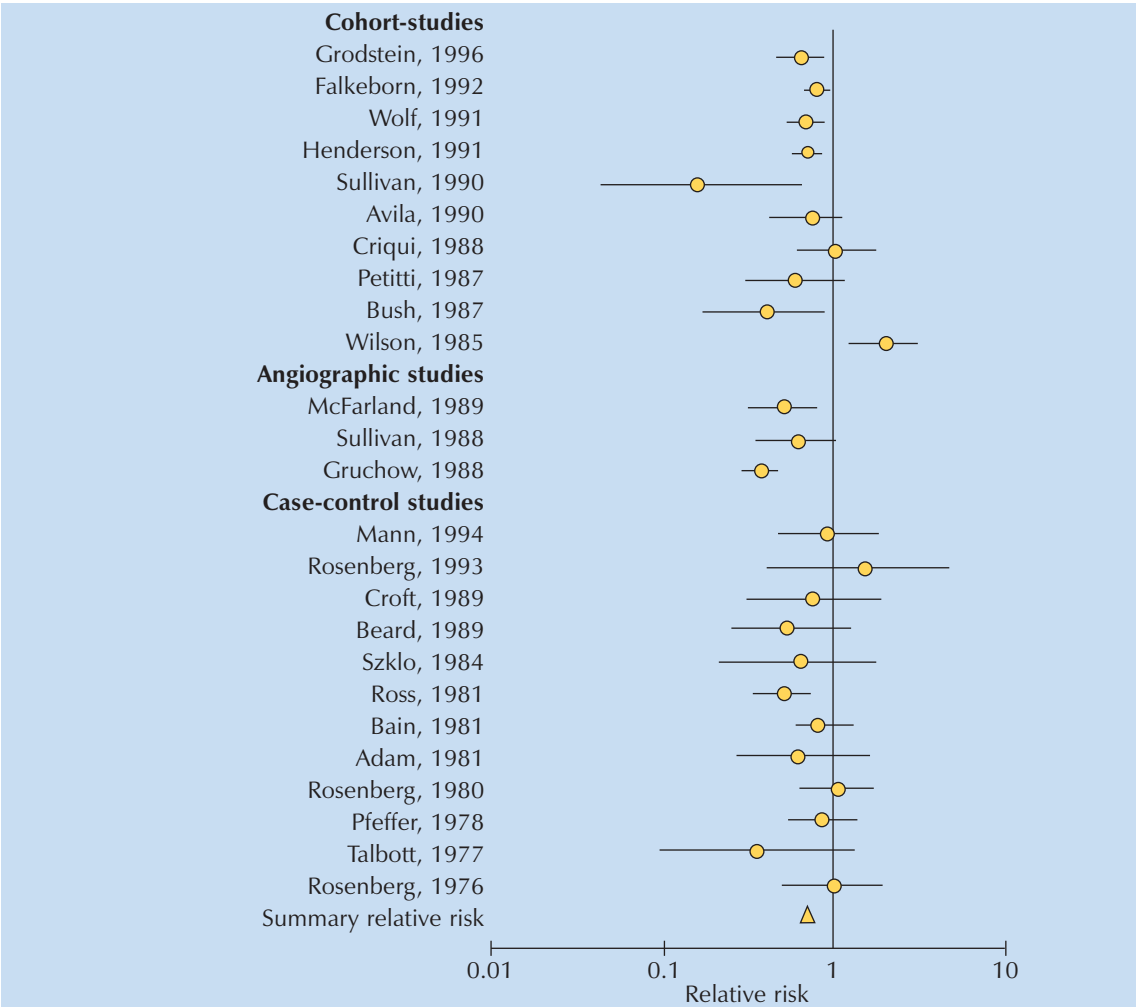

Figure 1. Meta-analysis of studies investigating the risk for CHD in estrogen users compared with non-users. (Reproduced with permission from the Annual Review of Public Health, volume 19, ©1998 by Annual Reviews www.AnnualReviews.org).[3]

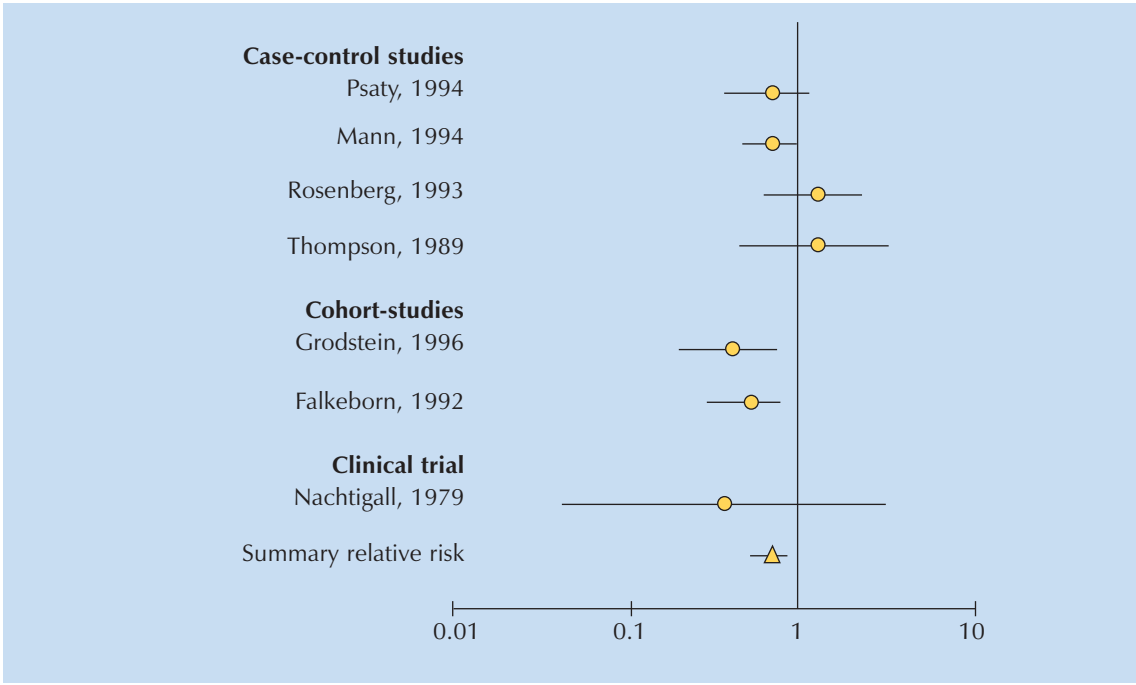

Figure 2. Meta-analysis of seven studies of estrogen plus progestin in CHD. (Reproduced with permission from the Annual Review of Public Health, volume 19, ©1998 by Annual Reviews www.AnnualReviews.org).[3]

An additional concern is compliance bias, such that women compliant with HRT are likely to exhibit other favorable health-related behaviors. In contrast, a recent meta-analysis of CHD adverse events in 22 small trials of HRT suggests an increased relative risk of 1.4 for hormone users.[4] An intermediate outcomes, randomized, controlled clinical trial, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, documented an overall favorable effect on coronary risk factors in healthy postmenopausal women taking several estrogen and estrogen/progestin regimens.[5] Whether HRT-related improvement in coronary risk factors will translate into reduced coronary event rates remains to be ascertained.

Observational data for women with documented CHD have also shown a decrease in death or myocardial infarction in estrogen users compared with non-users following PTCA.[6,7] Data regarding the estrogen effect on restenosis following PTCA remain conflicting.[6,7] Also, among a small cohort of women taking estrogen after CABG surgery (with only 3% of estrogen users also receiving a progestin), survival was greater in estrogen users than in non-users.[8]

The Heart and Estrogen/Progestin Replacement Study (HERS) significantly altered the landscape of HRT information.[9] HERS is the sole randomized, double-blind, placebo-controlled clinical trial of HRT in postmenopausal women with established CHD reported to date. During an average follow-up of 4.1 years, 2763 such women aged <80 years with an intact uterus were randomized to receive daily 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate in one tablet versus an identical placebo. Despite an average 11% decrease in LDL cholesterol levels and a 10% increase in HDL cholesterol levels, there was no overall reduction in the primary endpoint of coronary death and non-fatal myocardial infarction (*Figure 3*); nor was there benefit for a variety of secondary cardiovascular endpoints, including coronary revascularization, hospitalization for unstable angina, hospitalization for heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, peripheral arterial disease and all-cause mortality. Within this overall null effect was a puzzling trend: of concern was a statistically significant time trend of an early increase in the risk of coro-

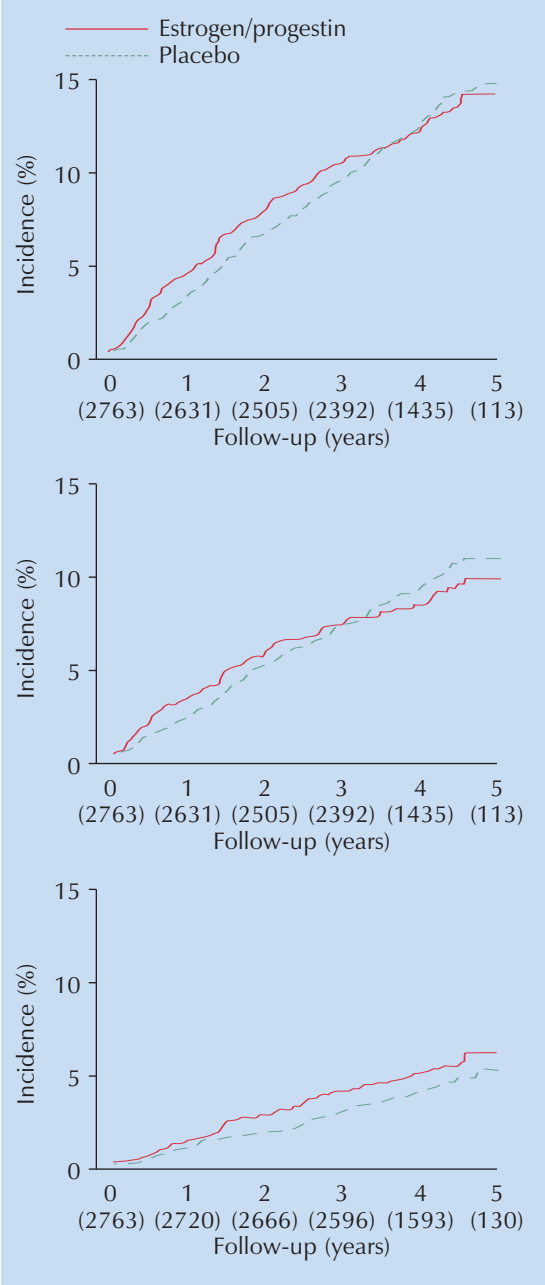

Figure 3. Kaplan-Meier estimates of the cumulative incidence of primary CHD events (left) and its constituents: non-fatal myocardial infarction (center) and CHD death (right). The number of women observed at each year of follow-up and still free of an event is given in parentheses, and the curves become fainter when this number drops below half of the cohort. Log-rank P-values are 0.91 for primary CHD events, 0.46 for non-fatal myocardial infarction and 0.23 for CHD death. (Reproduced with permission from the JAMA 1998; 280: 605–613, © 1998, American Medical Association).

nary events in the first year of HRT (relative hazard 1.52), but a favorable pattern of CHD events after several years of therapy (relative hazard 0.67 in years 4 and 5). The HERS recommendations are that women with established CHD should not initiate this hormone regimen for cardioprotection, but that it could be appropriate for women with CHD who are already taking HRT to continue therapy for the potential of late protection. The increased occurrence of venous thromboembolism (VTE) with HRT is addressed below.

It is not appropriate to extrapolate HERS data to unopposed estrogen therapy or other estrogen/progestin regimens, nor should they be extrapolated to healthy women. Nonetheless, the HERS results highlight the need for clinical trial data to ascertain whether HRT confers benefit or risk in other populations. Among HRT trials currently underway in predominantly healthy women are the US Women's Health Initiative (WHI)[10,11] and the UK Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) trial.[12] The 27,000 predominantly healthy postmenopausal women in the WHI randomized to estrogen plus progestin, estrogen (for women with hysterectomy), or placebo were notified in April 2000 of an early increase in cardiovascular events in hormone-treated women involving about 1% of the women. Because the period of risk had passed when these preliminary 2-year data were reviewed, the Data Safety and Monitoring Board recommended continuation of the study to evaluate potential late benefit. Secondary prevention trials in progress supported by the US National Institutes of Health include WAVE (Women's Angiographic Vitamin and Estrogen trial), WELL-HART (Women's Estrogen/Progestin and Lipid-Lowering Hormone Atherosclerosis Regression Trial) ERA (Estrogen Replacement and Atherosclerosis trial). Results were reported at the 2000 Scientific Sessions of the American College of Cardiology. In this angiography trial, 30% of postmenopausal women with documented CHD were randomized to estrogen, estrogen plus progestin, or placebo. Comparing baseline and mean 3.2-year angiograms, there was no difference in angiographic lesion

changes between the hormone regimens and placebo.

Although the increased risk of VTE with oral contraceptive use has been well documented,[13,14] only recently has there been evidence that the far lower dose HRT is associated with an increased risk of VTE.

Data from recent observational studies suggest a two- to fourfold increase in the risk of spontaneous deep vein thrombosis and pulmonary embolism.[15–19] In HERS, randomized controlled trial data from older women with documented CHD revealed a relative hazard of 2.7 (95% CI 1.4–5.0) for idiopathic and non-idiopathic VTE in HRT-treated women.[20] Women with lower extremity fractures had a relative hazard of 18.1, with cancer 3.9, in the first 90 days after inpatient surgery 4.9, in the first 90 days after non-surgical hospitalization 5.7, and in the first 90 days after myocardial infarction 5.9 (even after adjustment for hospitalization, with 80% of women taking daily aspirin). The increased risk was similar with idiopathic (relative hazard 3.1) and non-idiopathic (relative hazard 2.5) VTE, and the risks were similar for women with and without other risk factors for VTE. This increased risk of VTE must be addressed when counseling women about the risks and benefits of HRT.

Despite biologically plausible mechanisms for estrogen's cardioprotective benefit[21] and observational data suggesting such benefit, randomized controlled trial data from HERS are contradictory. Of particular concern is the early increased coronary risk in HERS as well as the increased risk of venous thromboembolism. Given these uncertainties, clinical outcome randomized trial data are clearly requisite using varied HRT regimens in healthy women and in women with CHD.

Until the results of such trials become available, the decision to initiate HRT for cardioprotection must be individualized. Relevant variables include the individual woman's risk of CHD, as well as her risks for osteoporosis, VTE and breast cancer, the severity of her menopausal symptoms and her individual preferences. ■

REFERENCES

1. Wenger NK. Coronary heart disease in women: an older woman's major health risk. Br Med J 1997; 315: 1085–1090.
2. Colditz GA, Willett WC, Stampfer MJ et al. Menopause and the risk of coronary heart disease in women. N Engl J Med 1987; 316: 1105–1110.
3. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. Annu Rev Public Health 1998; 19: 55–72.
4. Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. Br Med J 1997; 315: 149–153.
5. The Writing Group for the PEPI trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. J Am Med Assoc 1995; 273: 199–208.
6. Abu-Halawa SA, Thompson K, Kirkeeide RL et al. Estrogen replacement therapy and outcome of coronary balloon angioplasty in postmenopausal women. Am J Cardiol 1998; 82: 409–413.
7. O'Keefe JH Jr, Kim SC, Hall RR et al. Estrogen replacement therapy after coronary angioplasty in women. J Am Coll Cardiol 1997; 29: 1–5.
8. Sullivan JM, El-Zeky F, Zwaag RV, Ramanathan KB. Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. Am J Cardiol 1997; 79: 847–850.
9. Hulley S, Grady D, Bush T et al., for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. J Am Med Assoc 1998; 280: 605–613.
10. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials 1998; 19: 61–109.
11. Rossouw JE, Finnegan LP, Harlan WR et al. The evolution of the Women's Health Initiative: perspective from the NIH. J Am Med Women Assoc 1995: 50: 50–55.
12. Vickers MR, Meade TW, Wilkes HC. Hormone replacement therapy and cardiovascular disease: the case for a randomized controlled trial. Ciba Found Symp 1995; 191: 150–154.
13. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of an international multicentre case-control study. Lancet 1995; 346: 1575–1582.
14. Carr B, Ory H. Estrogen and progestin components of oral contraceptives: relationship to vascular disease. Contraception 1997; 55: 267–272.
15. Daly E, Vessey MP, Hawkins MM et al. Risk of venous thromboembolism in users of hormone replacement therapy. Lancet 1996; 348: 977–980.

16. Jick H, Derby LE, Myers MW et al. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. Lancet 1996; 348: 981–983.
17. Grodstein F, Stampfer MJ, Goldhaber SZ et al. Prospective study of exogenous hormones and risk of pulmonary embolism in women. Lancet 1996; 348: 983–987.
18. Gutthann SP. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. Br Med J 1997; 314: 796–800.
19. Varas-Lorenzo C, Garcia-Rodriguez L, Cattarazzi C et al. Hormone replacement therapy and the risk of hospitalization for venous thromboembolism: a population-based study in southern Europe. Am J Epidemiol 1998; 147: 387–390.
20. Grady D, Wenger NK, Herrington D et al. Post-menopausal hormone therapy increases risk of venous thromboembolic disease: the Heart and Estrogen/progestin Replacement Study (HERS). Ann Intern Med. In press.
21. Wenger NK. Cardiovascular disease in menopausal women: the benefits of HRT are not restricted to improving lipid profiles. Medicographica 1999; 21: 223–228.

Diagnosis of coronary artery disease in women vs men

Dr Christopher S. Hayward, Dr Peter Collins
Department of Cardiac Medicine, National Heart and Lung Institute,
Imperial College School of Medicine, London, UK (peter.collins@ic.ac.uk)

Introduction

Epidemiological studies suggest that women lag behind men by approximately 20 years with respect to cardiovascular disease.[1] Gender differences exist at each stage of cardiovascular disease: in its presentation, investigation, treatment outcome and prognosis. This review focuses on gender differences in the interpretation of investigations used in the diagnosis of coronary artery disease. While differences do exist, most studies have found that the same diagnostic tests remain valid for both sexes.

Symptoms

A number of studies have found that men and women react differently in response to coronary occlusion. In a study of 1360 subjects which examined symptoms due to definite myocardial infarction, men were less likely to have neck, jaw and back pain, and were more likely to complain of diaphoresis or sweating compared with women.[2] Description of actual chest pain was similar between the sexes. In a further prospective study of a cohort of patients undergoing angioplasty for single vessel disease, women were more likely than men to have vagal activation (manifested as decreased heart rate and blood pressure) in association with chest pain, as well as having greater associated ST-segment change in response to a standardized protocol of coronary occlusion.[3] Another significant feature concerning presentation with symptoms of a cardiac event, is that women tend to seek medical care later than men.[4] In the Scottish MONICA population, women were more likely to present to their local doctor with myocardial infarction, contributing to the delay in their presentation to hospital care.[5]

Electrocardiography

While baseline 'ischaemic ECG' abnormalities (in apparently disease-free subjects) are more prevalent in women, the difference is due to mainly ST-T-wave changes.[6] After correction for risk factors, however, the 10-year prognostic value of an ischaemic ECG was found to be similar to that of men.[6] Thus, the relative risk for women with an ischaemic ECG (compared with the remaining women) was similar to the relative risk for men with resting ECG abnormalities (when compared with the remaining men). A myocardial perfusion study found, however, that ST-T abnormalities in women were not associated with increased perfusion defects on diagnostic scanning, whereas men with baseline ST-T abnormalities did have a significantly higher rate of perfusion defects.[7] It is well recognized that the diagnosis of left ventricular hypertrophy on ECG is less reliable in women, even when appropriate adjustments are performed.[8,9]

Exercise testing

It has been recognized for many years that treadmill exercise testing in women is associated with a greater number of false-positive ECG changes. It continues to be used, however, because it remains a cost-effective test in women who have at least 'probable angina'.[10] Women typically have lower exercise capacity and total workload, in association with more symptoms at the time of index stress testing.[11] In a meta-analysis of 19 studies which included at least 50 women and compared exercise testing with coronary angiography, Kwok et al.[12] found the specificity of exercise testing to be significantly lower in women compared with men (70 *vs* 77%). The reason for this is still unknown, but differences in electrical repolarization are likely to play a role. It has

been suggested that this difference could be improved using gender-specific ST/heart rate slope partitions.[13] In clinical practice, therefore, it is not surprising that women are more likely to undergo a further non-invasive test (usually perfusion imaging) before coming to angiography.[14] Shaw et al.[15] found that despite a similar rate of positive treadmill testing or reversible thallium defect, women were still less likely than men to undergo subsequent invasive procedures, even in the presence of similar risk factors. In that cohort, men were more likely to undergo subsequent revascularization procedures.

An important variable available from exercise testing, independent of ECG findings, is the exercise capacity, which has been shown to give valuable prognostic information independent of gender.[16]

Isotope scanning

Nuclear scanning has been shown to have superior accuracy to exercise testing in both men and women.[12,17] An early meta-analysis found both lower sensitivity and specificity of exercise thallium scanning in women compared with men,[18] possibly related to breast attenuation artefact in women.[19] Despite this, a large prospective study using rest thallium in combination with sestamibi SPECT scanning showed that low-risk patients of either gender were classified appropriately, but that patients were classified to a high-risk category with greater accuracy in women.[20] The use of technetium 99m sestamibi and ECG gating has recently been shown to improve the specificity of nuclear scanning in women, without any decrement in sensitivity.[21]

Stress echocardiography

A meta-analysis comparing exercise echocardiography with exercise SPECT found similar sensitivity (85 and 87%, respectively), but higher specificity for exercise echocardiography (77%) compared with exercise thallium (64%).[22] A recent meta-analysis found slightly better accuracy for exercise echocardiography over exercise thallium (sensitivity and specificity 0.86 and 0.79 *vs* 0.78 and 0.64, respectively).[12] While stress echocardiography has been suggested as the investigation of choice for women undergoing cardiac assessment,[23] a large study of 2748 consecutive subjects (1209 women) found lower sensitivity in women compared with men both for single and multivessel disease.[24] In that series, a low specificity in both men and women was found and attributed to post-test referral bias.

Smaller studies have less consistent results. In a smaller study of 306 subjects (96 women), dobutamine stress echocardiography was found to have higher accuracy in women (82 *vs* 74% in men).[25] Pilot data ($n = 92$) from the Women's Ischemia Syndrome Evaluation (WISE) project showed that dobutamine stress echocardiography reliably detected multivessel disease (sensitivity of 82% with adequate heart rate response), but was usually negative in single vessel disease.[26] While cavity obliteration in response to dobutamine is more common in women and impairs the visualization of wall motion abnormalities,[27] it has been shown to be a negative predictive factor with respect to subsequent cardiac events.[28]

Cardiac catheterization

Whether there is a systematic under-referral or gender bias against women has been examined in a number of studies. Some have found such a bias,[29,30] while others have been able to account for the differences on the basis of differences in comorbidities and age.[31]

It has been suggested that the difference exists when symptoms (angina) are the basis for angiography, rather than infarction.[32] In the USA National Hospital Discharge Survey, the lower angiography rate contributed to the subsequent lower utilization of invasive procedures for women such as cardiac surgery and PTCA.[30,33]

A significant role for physician bias in limiting referral of women for angiography is suggested by a recent study which used actors of varying age, sex and race to describe symptoms of chest pain.[34]

A likely contributor to the persistently lower

catheterization rate in women compared with men is the marked difference in likelihood of significant coronary disease at angiography with reported rates of non-significant coronary disease of 25–41% in women compared with only 8–14% in men.[33,35] A significant proportion of these women will have syndrome X (the triad of chest pain, a positive stress test and no significant angiographic coronary artery disease).[36] Various theories have been proposed to account for syndrome X, with microvascular dysfunction a favoured possibility.[37]

The lack of simple non-invasive measures of detection means that the number of women undergoing coronary angiography with non-obstructive disease is likely to remain significantly greater than the number of men.

Newer technologies

The roles of newer technologies such as cardiovascular MRI and electron beam CT have not been defined.[38] MRI, in particular, shows promise with greater resolution of perfusion defects even in patients with poor acoustic windows for echocardiography, though there remains a small percentage (5%) in whom it cannot be satisfactorily completed.[39] Further improvements in resolution with imaging of coronary anatomy and plaque may make MRI an attractive option in the future.

Electron beam CT has been shown to be very sensitive in predicting coronary disease although there is a wide scatter in the degree of coronary calcification both in the absence as well as the presence of coronary artery disease.[40] While coronary calcification in women lags approximately 10 years behind that in men, in a small group of women with triple vessel disease, Kajinami et al.[40] found greater calcification compared with men with triple vessel disease. These findings need to be confirmed in larger series.

Choice of investigation

The optimal choice of investigation for the diagnosis of coronary artery disease remains a clinical decision based on the likelihood of actual disease. Non-invasive tests increase or decrease that likelihood, but only coronary angiography remains definitive. In patients with a high pre-test probability of coronary disease, even angiography without prior investigation may be cost-effective.[41] Differences in the sensitivity and specificity of the various tests need to be considered particularly in light of local experience. ■

Acknowledgments

Dr Hayward is supported by an Overseas Research Fellowship from the National Heart Foundation of Australia.

REFERENCES

1. Kannel WB, Wilson PWF. Risk factors that attenuate the female coronary disease advantage. Arch Intern Med 1995; 155: 57–61.
2. Goldberg RJ, O'Donnell C, Yarzebski J et al. Sex differences in symptom presentation associated with acute myocardial infarction: a population-based perspective. Am Heart J 1998; 136(2): 189–195.
3. Airaksinen KE, Ikaheimo MJ, Linnaluoto M et al. Gender difference in autonomic and hemodynamic reactions to abrupt coronary occlusion. J Am Coll Cardiol 1998; 31(2): 301–306.
4. Lambrew CT, Bowlby LJ, Rogers WJ et al. Factors influencing the time to thrombolysis in acute myocardial infarction. Time to Thrombolysis Substudy of the National Registry of Myocardial Infarction-1. Arch Intern Med 1997; 157(22): 2577–2582.
5. Tunstall-Pedoe H, Morrison C, Woodward M et al. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women. Circulation 1996; 93(11): 1981–1992.
6. De Bacquer D, De Backer G, Kornitzer M et al. Prognostic value of ischemic electrocardiographic findings for cardiovascular mortality in men and women. J Am Coll Cardiol 1998; 32(3): 680–685.
7. Elhendy A, van Domburg RT, Bax JJ, Roelandt JR. Gender differences in the relation between ST-T-wave abnormalities at baseline electrocardiogram and stress myocardial perfusion abnormalities in patients with suspected coronary artery disease. Am J Cardiol 1999; 84(8): 865–869.
8. Okin PM, Roman MJ, Devereux RB, Kligfield P.

Gender differences and the electrocardiogram in left ventricular hypertrophy. Hypertension 1995; 25(2): 242–249.
9. Casiglia E, Maniati G, Daskalakis C et al. Left-ventricular hypertrophy in the elderly: unreliability of ECG criteria in 477 subjects aged 65 years or more. The Cardiovascular Study in the Elderly (CASTEL). Cardiology 1996; 87(5): 429–435.
10. Kim C, Kwok YS, Saha S, Redberg RF. Diagnosis of suspected coronary artery disease in women: a cost-effectiveness analysis. Am Heart J 1999; 137(6): 1019–1027.
11. Roger VL, Jacobsen SJ, Pellikka PA et al. Gender differences in use of stress testing and coronary heart disease mortality: a population-based study in Olmsted County, Minnesota. J Am Coll Cardiol 1998; 32(2): 345–352.
12. Kwok Y, Kim C, Grady D et al. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999; 83(5): 660–666.
13. Okin PM, Kligfield P. Gender-specific criteria and performance of the exercise electrocardiogram. Circulation 1995; 92(5): 1209–1216.
14. Lauer MS, Pashkow FJ, Snader CE et al. Sex and diagnostic evaluation of possible coronary artery disease after exercise treadmill testing at one academic teaching center. Am Heart J 1997; 134 (5 part 1): 807–813.
15. Shaw LJ, Miller DD, Romeis JC et al. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. Ann Intern Med 1994; 120(7): 559–566.
16. Roger VL, Jacobsen SJ, Pellikka PA et al. Prognostic value of treadmill exercise testing: a population-based study in Olmsted County, Minnesota. Circulation 1998; 98(25): 2836–2841.
17. Morise AP, Diamond GA, Detrano R, Bobbio M. Incremental value of exercise electrocardiography and thallium-201 testing in men and women for the presence and extent of coronary artery disease. Am Heart J 1995; 130(2): 267–276.
18. Detrano R, Janosi A, Lyons KP et al. Factors affecting sensitivity and specificity of a diagnostic test: the exercise thallium scintigram. Am J Med 1988; 84(4): 699–710.
19. Grover-McKay M. Gender-related imaging issues in assessment of coronary artery disease by nuclear techniques. Am J Card Imaging 1996; 10(1): 54–64.
20. Hachamovitch R, Berman DS, Kiat H et al. Effective risk stratification using exercise myocardial perfusion SPECT in women: gender-related differences in prognostic nuclear testing. J Am Coll Cardiol 1996; 28(1): 34–44.
21. Taillefer R, DePuey EG, Udelson JE et al. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. J Am Coll Cardiol 1997; 29(1): 69–77.
22. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. J Am Med Assoc 1998; 280(10): 913–920.
23. Tong AT, Douglas PS. Stress echocardiography in women. Cardiol Clin 1999; 17(3): 573–582.
24. Secknus MA, Marwick TH. Influence of gender on physiologic response and accuracy of dobutamine echocardiography. Am J Cardiol 1997; 80(6): 721–724.
25. Elhendy A, Geleijnse ML, van Domburg RT et al. Gender differences in the accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery disease. Am J Cardiol 1997; 80(11): 1414–1418.
26. Lewis JF, Lin L, McGorray S et al. Dobutamine stress echocardiography in women with chest pain. Pilot phase data from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). J Am Coll Cardiol 1999; 33(6): 1462–1468.
27. Khanal S, Daggubati R, Gaalla A et al. Left ventricular cavity obliteration during dobutamine stress echocardiography is associated with female sex and left ventricular size and function. J Am Soc Echocardiogr 1998; 11(10): 957–960.
28. Secknus MA, Niedermaier ON, Lauer MS, Marwick TH. Diagnostic and prognostic implications of left ventricular cavity obliteration response to dobutamine echocardiography. Am J Cardiol 1998; 81(11): 1318–1322.
29. Behar S, Gottlieb S, Hod H et al. Influence of gender in the therapeutic management of patients with acute myocardial infarction in Israel. The Israeli Thrombolytic Survey Group. Am J Cardiol 1994; 73(7): 438–443.
30. Giles WH, Anda RF, Casper ML et al. Race and sex differences in rates of invasive cardiac procedures in US hospitals. Data from the National Hospital Discharge Survey. Arch Intern Med 1995; 155(3): 318–324.
31. Krumholz HM, Douglas PS, Lauer MS, Pasternak RC. Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: is there evidence for a gender bias? Ann Intern Med 1992; 116(10): 785–790.
32. Maynard C, Beshansky JR, Griffith JL, Selker HP. Influence of sex on the use of cardiac procedures in patients presenting to the emergency department. A prospective multicenter study. Circulation 1996; 94 (9 suppl): II93–98.
33. Scirica BM, Moliterno DJ, Every NR et al. Differences between men and women in the management of unstable angina pectoris (The GUARANTEE Registry). The GUARANTEE Investigators. Am J Cardiol 1999; 84(10): 1145–1150.
34. Schulman KA, Berlin JA, Harless W et al. The effect of race and sex on physicians' recommendations for cardiac catheterization. N Engl J Med 1999; 340(8): 618–626.

35. Sullivan AK, Holdright DR, Wright CA et al. Chest pain in women: clinical, investigative, and prognostic features. Br Med J 1994; 308(6933): 883–886.
36. Kaski JC, Rosano GMC, Collins P et al. Cardiac syndrome X: clinical characteristics and left ventricular function. Long term follow up study. J Am Coll Cardiol 1995; 25: 807–814.
37. Reis SE, Holubkov R, Lee JS et al. Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease. Results from the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study. J Am Coll Cardiol 1999; 33(6): 1469–1475.
38. Hunink MG, Kuntz KM, Fleischmann KE, Brady TJ. Noninvasive imaging for the diagnosis of coronary artery disease: focusing the development of new diagnostic technology. Ann Intern Med 1999; 131(9): 673–680.
39. Hundley WG, Hamilton CA, Thomas MS et al. Utility of fast cine magnetic resonance imaging and display for the detection of myocardial ischemia in patients not well suited for second harmonic stress echocardiography. Circulation 1999; 100(16): 1697–1702.
40. Kajinami K, Seki H, Takekoshi N, Mabuchi H. Noninvasive prediction of coronary atherosclerosis by quantification of coronary artery calcification using electron beam computed tomography: comparison with electrocardiographic and thallium exercise stress test results. J Am Coll Cardiol 1995; 26(5): 1209–1221.
41. Kuntz KM, Fleischmann KE, Hunink MG, Douglas PS. Cost-effectiveness of diagnostic strategies for patients with chest pain. Ann Intern Med 1999; 130(9): 709–718.

Microvascular angina: a new potential target for trimetazidine?

Dr Pierre Sabouret
Department of Cardiology, Hôpital Pitié-Salpétrière, Paris, France

A 66-year-old female patient presented to the hospital with 18 min of chest pain and was admitted to the cardiac emergency ward.

The patient had a history of non-insulin-dependent diabetes mellitus, diagnosed 8 years earlier, and type 2b dyslipidemia (hypercholesterolemia with elevated low-density and very-low-density lipoproteins associated with hypertriglyceridemia,), discovered 7 years earlier. She was currently being treated with an oral sulfonylurea and fenofibrate.

On arrival, the patient received intravenous nitroglycerin, aspirin, low molecular weight heparin and an oral beta-blocker. Her chest pain resolved, and, on physical examination, this mildly/moderately obese patient was in no apparent distress.

The 12-lead ECG showed a pattern of ST-segment elevation in the anteroseptal and apical regions. The creatinine phosphokinase-MB peak was 460 UI/l and troponin Ic was 2 mg/l (normal value <0.5). Over 4 days, the ST-segment and T-wave abnormalities resolved.

On coronary angiography, moderate anteroseptal and apical hypokinesis were seen, consistent with the electrocardiographic diagnosis of a non-Q-wave infarction. However, the patient had no significant coronary stenosis. The ergotamine test was negative. Despite this, the etiology of the myocardial infarction was presumed to be vasospastic in origin and atenolol was replaced by sustained-release verapamil 240 mg.

Before discharge, an exercise stress test was found positive and accompanied by exercise-limiting chest pain at 150 W with a maximal heart rate of 154 bpm (100% of the MPHR) *(Figure 1)*.

To improve the persistent and activity-limiting anginal symptoms and improve the patient's exercise tolerance, she was started on trimetazidine 20 mg t.i.d.

At the follow-up visit 1 month later, the patient described a marked decrease in the frequency of her anginal attacks. A second exercise stress test carried out the same day showed no ischemic ST-T changes. The patient had no chest pain even at a maximal workload of 150 W and a peak heart rate of 143 bpm (93% of MPHR) *(Figure 2)*.

Discussion

Epidemiology of coronary heart disease (CHD) in women

Although young women are relatively immune to cardiovascular disease (CVD), at least in part because of their hormonal status, CVD has become the major cause of death in women in developed countries.[1] Coronary heart disease (CHD) accounts for much of this and occurs on average 7–10 years later in women than in men.[2,3] Although the frequency of CHD increases exponentially with age, the rates observed in women are still lower than those in men. This trend may change somewhat in the future in light of the increasing number of young female smokers.[4,5]

Although the principal risk factors are the same in both sexes, the prevalence differs somewhat and the absolute mortality risk associated with each risk factor is generally lower in women than in men, with the exception of diabetes mellitus.[6–8]

Diagnosis and clinical pattern of CHD in women

The clinical presentation and natural history of angina pectoris often differ between women and men, and the diagnosis in women may be more difficult to make.[7,9] The Framingham study reported that women are more likely than men to experience an unrecognized, or silent, myocardial infarction (MI).[7]

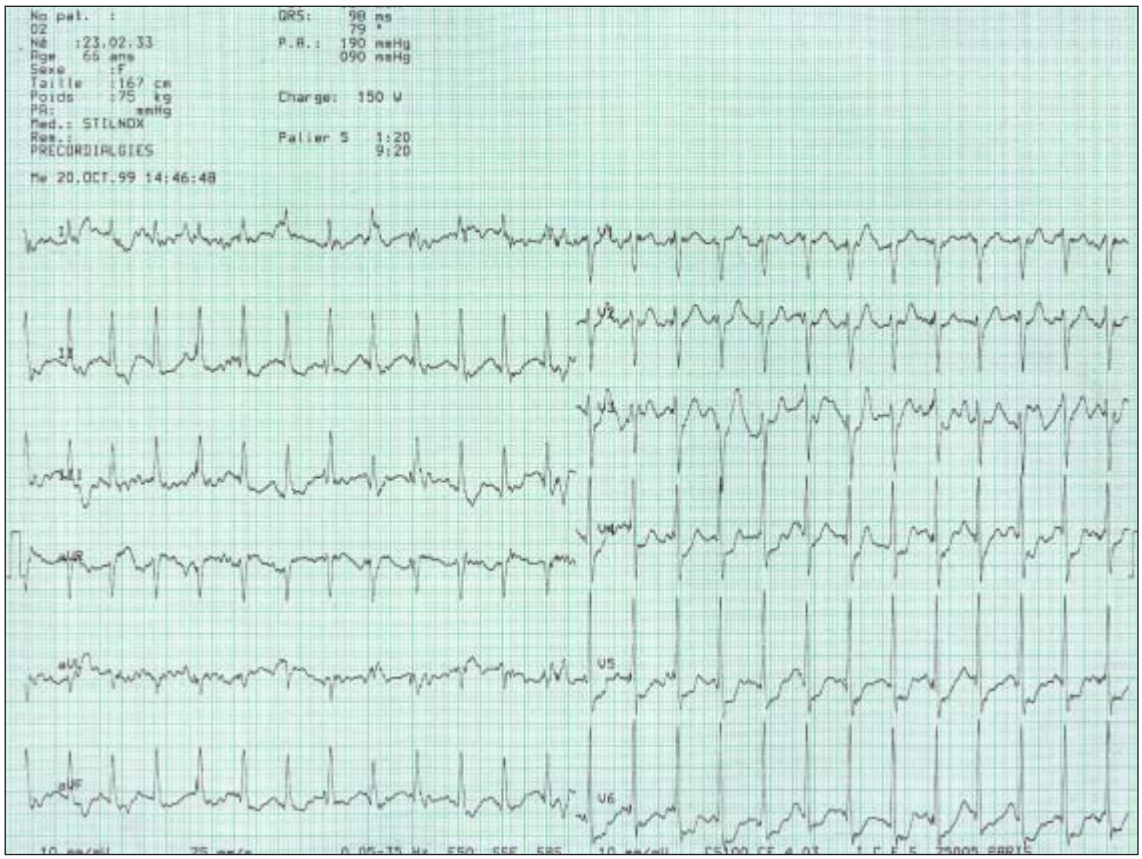

Figure 1. Treadmill test no. 1 (treatment with verapamil alone).

The exercise stress test has been shown to have a lower accuracy for the identification of coronary artery disease in women than in men, although the basis for this remains unclear.[10,11] Myocardial perfusion imaging has also been found to be less specific for the diagnosis of coronary artery disease in women than in men, largely due to breast attenuation.[12,13]

Furthermore, women are more likely to have syndrome X, defined as the presence of clinically typical anginal chest pain, as well as evidence of ischemia on the exercise stress test, in the absence of significant coronary artery disease.[14] Such was the case for the patient in this report.

Syndrome X

The increased prevalence of syndrome X in women, as well as its reported association with the menopause, has led to the theory of a hormonal trigger, possibly estrogen deficiency, which could in turn lead to an imbalance in vasomotor tone involving the coronary arteries. However, syndrome X is likely a clinical entity of diverse etiologies and pathophysiological mechanisms. A subset of patients may have coronary artery disease limited to only small arteries, so-called microvascular angina. On the initial studies using electron microscopy of coronary biopsies in patients with syndrome X,[14] many endothelial nuclei in capillaries were found to be swollen, with an irregular narrowing of the arterioles and small vessels and proliferating and deformed smooth muscle cells. Although the pathophysiology of syndrome X is unclear, it is a common problem for which therapies are needed. One approach to therapy, which we used with success in this patient, is the metabolic approach using a metabolic agent.

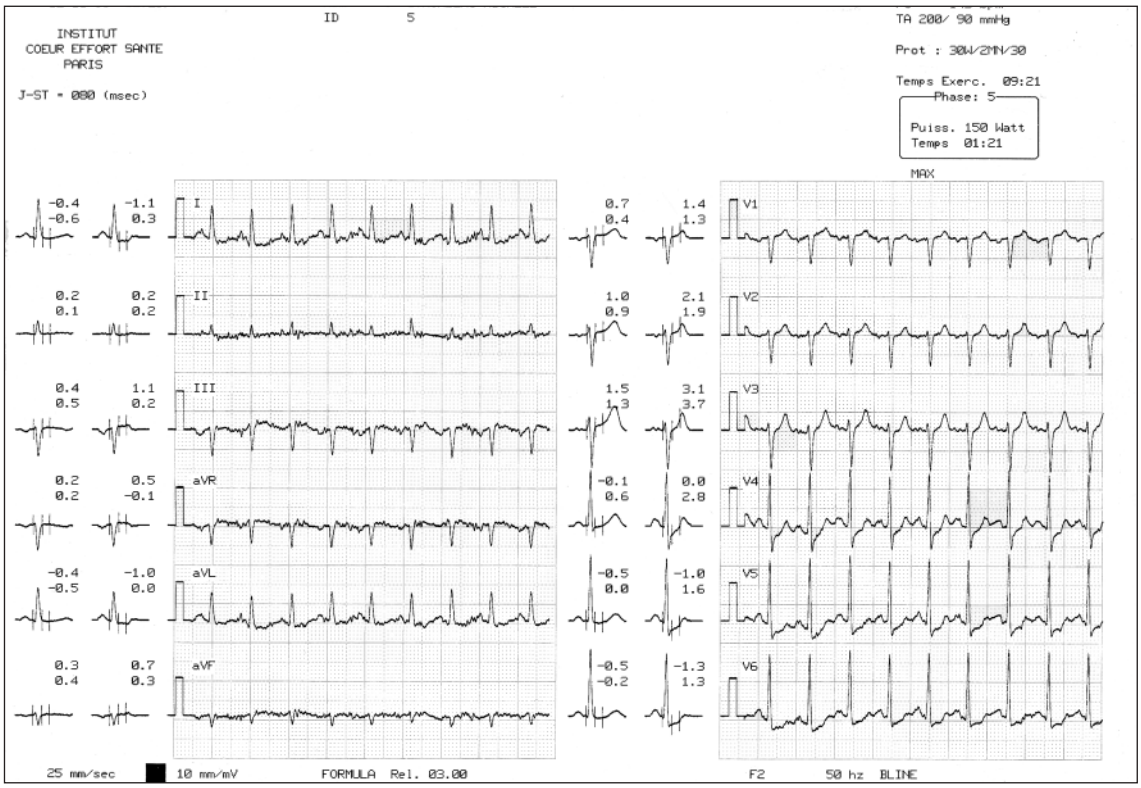

Figure 2. Treadmill test no. 2 (treatment with verapamil and trimetazidine).

The metabolic approach in stable angina and syndrome X

A number of recent studies have shown that the metabolic agent, trimetazidine, is an effective treatment for stable angina pectoris.[15–21] By specifically inhibiting the long-chain 3-ketoacyl-coenzyme A thiolase, trimetazidine causes a partial inhibition of fatty acid beta-oxidation.[22] This leads to an optimization of cardiac metabolism during ischemia and reperfusion, reducing acidosis and preserving energy production for contractility.

The metabolic approach with trimetazidine in monotherapy has been shown to be as effective as a beta-blocker (propranolol) in patients with chronic stable angina.[15] Other studies have demonstrated the value of adding trimetazidine to another agent (beta-blocker, calcium channel blocker or long-acting nitrate).[17–21] For example, in combination with a beta-blocker, trimetazidine has been shown to be more effective than the combination of a beta-blocker and a long-acting nitrate (isosorbide dinitrate).[17] The association of trimetazidine with diltiazem is also useful and well tolerated.[18,19] Such an additive benefit could be anticipated from the distinct mechanism of action of trimetazidine from the hemodynamic drugs. Furthermore, this benefit occurs without incurring any unwanted hemodynamic side effects.

Thus, the efficacy of trimetazidine in stable angina pectoris has been well documented in controlled studies. Trimetazidine may also be beneficial in the setting of syndrome X, as was the case for this patient. Two recent studies have reported positive results.

The first study included 35 patients with microvascular angina.[23] Microvascular angina was defined as typical exertional chest pain and positive exercise test results (>1 mm ST-segment depression and typical chest pain) with a completely normal coronary angiogram. None of the patients had hypertension, left ventricular hypertrophy, cardiomyopathy, coronary artery spasm or conduction disturbances.

The effects of trimetazidine (60 mg daily) were investigated in a double-blind study comprising two 4-week treatment periods. After a 1-week washout period, patients received placebo for 4 weeks; after another week of washout, patients received trimetazidine for 4 weeks. No other drug was prescribed. Exercise testing was performed at the end of the placebo and trimetazidine treatment periods. Patients were also studied with the ambulatory ECG monitoring test before treatment and at the end of both treatment periods. The number of anginal attacks at the second week and thereafter was significantly decreased with trimetazidine compared with placebo ($P < 0.0001$). On treadmill testing, the time to 1 mm ST-segment depression and total exercise time were significantly longer in the trimetazidine group, and the maximum ST depression was significantly less ($P < 0.0001$, $P < 0.0001$, $P < 0.0005$, respectively). Rogacka and colleagues[24] found similar benefit with trimetazidine on clinical symptoms and exercise tolerance in 28 patients with syndrome X.

The exact role of trimetazidine in patients with syndrome X remains to be determined, but there is evidence that trimetazidine may be as beneficial in these patients as it is in patients with chronic stable angina and coronary artery disease.

CONCLUSION

Even if the precise pathophysiology of microvascular angina remains unclear and without consensus on its treatment, many investigators believe that coronary microvascular dysfunction and intracellular metabolic changes are the main etiologic factors. The metabolic approach with trimetazidine, which is highly effective in reducing symptoms and improving exercise capacity in chronic stable angina, may also be useful in certain patients with syndrome X. ■

REFERENCES

1. World Health Statistics Annuals 1982–1994. Geneva: World Health Organization, 1982–1994.
2. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M et al. for the WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project. Contributions of trends in survival and coronary event-rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. Lancet 1999; 353: 1547–1557.
3. Holdright DR. Risk factors for cardiovascular disease in women. J Hum Hypertens 1998; 12: 667–673.
4. Murabito JM, Evans JC, Larson MG, Levy D. Prognosis after the onset of coronary heart disease. An investigation of differences in outcome between the sexes according to initial coronary presentation. Circulation 1993; 88: 2548–2555.
5. Isles CG, Hole DJ, Hawthorne VM, Lever AF. Relation between coronary risk and coronary mortality in women of the Renfrew and Paisley survey: comparison with men. Lancet 1992; 339: 702–706.
6. Kuhn FE, Rackley CE. Coronary heart disease in women. Risk factors, evaluation, treatment and prevention. Arch Intern Med 1993; 153: 2626–2636.
7. Stokes JS, Kannel WB, Wolf PA et al. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years' follow-up in the Framingham study. Circulation 1987; 75 (suppl V): 65–73.
8. Tunstall-Pedoe H et al. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. Br Med J 1997; 315: 722–729.
9. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med 1996; 334: 1311–1315.
10. Sketch NH, Mohiuddin SM, Lynch JD et al. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. Am J Cardiol 1975; 36: 169–173.
11. Detry JMR, Kapita BM, Cosyns J et al. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary heart disease. Circulation 1977; 56: 756–761.
12. Friedman D, Green AC, Ishandrian DS et al. Exercise thallium-201 myocardial scintigraphy in women. Correlation with coronary arteriography. Am J Cardiol 1982; 49: 1623.
13. Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary heart disease. N Engl J Med 1991; 325: 221–225.
14. Schlant RC, Alexander RW. Diagnosis and management of patients with chronic ischemic heart dis-

ease. In: Alexander W, Schlant R, Fuster V, eds. Hurst's the heart. 9th ed. New York: McGraw-Hill, 1998; 1275–1305.
15. Detry JM, Sellier P, Pennaforte S et al. Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina. Br J Clin Pharmacol 1994; 37: 279–288.
16. Lu C, Dabrowski P, Fragasso G, Chierchia SL. Effects of trimetazidine on ischemic left ventricular dysfunction in patients with coronary artery disease. Am J Cardiol 1998; 82: 898–901.
17. Michaelides AP, Spiropoulos K, Dimopoulos K et al. Antianginal efficacy of the combination of trimetazidine-propranolol compared with isosorbide dinitrate-propranolol in patients with stable angina. Clin Drug Invest 1997; 13: 8–14.
18. Manchanda SC, Krishnaswami S. Combination treatment with trimetazidine and diltiazem in stable angina pectoris. Heart 1997; 78: 353–357.
19. Levy S, and the group of South France Investigators. Combination of trimetazidine with diltiazem in patients with coronary artery disease. Am J Cardiol 1995; 76: 12B–16B.
20. Szwed H, Pachocki R, Domzal-Bochenska M et al. Efficacy and tolerance of trimetazidine in combination one of the antianginal drugs in patients with stable effort angina. Diagnostyka i Leczenie w Kardiologii 1997; 4: 237–247.
21. Szwed H, Sadowski Z, Pachocki R et al. Trimpol II — multicenter study. Efficacy and safety of trimetazidine in patients with stable angina pectoris under beta-blocker therapy. Preliminary results. Eur Heart J 1999; 20: 478.
22. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res 2000; 86: 580–588.
23. Nalbangtil S, Altintig A, Yilmaz H et al. The effect of trimetazidine in the treatment of microvascular angina. Int J Angio 1999; 8: 40–43.
24. Rogacka D, Guzik P, Dziamaga M et al. The influence of trimetazidine therapy on clinical symptoms and exercise tolerance in patients with syndrome X. A pilot study.