The care of patients with ischaemic heart disease from a gender perspective

Introduction

For many years, women have been excluded from studies of cardiovascular disease [1,2]. It is difficult to find the reason for this neglect, since cardiovascular disease is one of the major causes of death among women, but is probably due to notions that have existed, and may still exist, in the world of medical care. One such notion is that coronary artery disease primarily afflicts men and when women are afflicted, the disease is of a more benign character. This emerged in a publication from the Framingham study [3], where it was shown that women who had angina pectoris generally had a good prognosis whereas angina in men more often led to myocardial infarction. Nevertheless, this study also showed that the prognosis for women with myocardial infarction was worse than that for men. Another notion which may explain why women are referred for further diagnostic examinations such as coronary angiography [4] more seldom than men, is that certain earlier studies [5,6] have shown a much higher risk of serious side-effects for women in connection with bypass operations or percutaneous transluminal coronary angioplasty (PTCA).

In order to make further progress concerning knowledge of cardiovascular disease among women, it is necessary to understand the unique aspects of cardiovascular disease and chest pain in women. In addition, it is important to understand the physical differences between the sexes, such as smaller body size, a smaller heart, the presence of breast tissue etc. in women, all of which can influence the effects of treatment as well as diagnostic options.

Incidence and prevalence

Cardiovascular disease is a common ailment among both men and women over 50 and is responsible for approximately half of all deaths in the western world. The total mortality in this panorama of diseases is the same for men as for women, even if the prevalence among women is lower. A total of 27 000 people diagnosed with acute myocardial infarction were admitted to hospital in Sweden during 1989. Since then, the numbers have decreased by 3–5% per year. Approximately 15% of these patients are under 60 years of age; thus the majority are men and women who are not of working age. Until the age of 65, the prevalence of cardiovascular disease among women is much less than among men, but between the ages of 65 and 70 the prevalence of cardiovascular disease in the female population changes rapidly. In fact, among women over 60 myocardial infarction is the most common cause of death. The infarction incidence for women aged 60 to 70 corresponds to that for men who are 10 years younger. Sex differences in mortality due to myocardial infarction have been reduced owing to a greater reduction in mortality among men than among women [7,8]. In North America and western and northern Europe the number of deaths from cardiovascular disease has decreased by approximately 30% since the early 1970s. The greatest decrease has occurred during the latter half of the 1980s across all age groups and in both sexes.

Prognosis

In Sweden, 10 000 myocardial infarction patients die outside hospital each year. Using the patient registers for in-patient hospital treatment for 1987–1991, Hannerz [9] has analysed care time, mortality and risk of death as a function of the care day and length-of-life tables of patients receiving hospital care for acute myocardial infarction. This analysis reveals that women with myocardial infarction are an average of 6 years older than men. Furthermore, it shows that the median care time for myocardial infarction has decreased by 2 days (from 9 to 7) for men and by 1 day (from 9 to 8) for women. The risk of death for 75-year-old-men and women has decreased by 2-5%, and a further analysis shows that both the risk of death and the reduction of the risk do not depend on sex at this particular age. Because of greater age when women experience their myocardial infarction, their chance of survival is lower than that of men relative to the population. Unfortunately, the register for these years does not permit a longer follow-up of the prognoses because it was not possible to identify individual persons. Other sources show a survival rate of 72% for at least a year among 30–54 year-olds with myocardial infarction. In older age groups survival is lower; for those between 65 and 79 the one-year
survival rate is 46%. Women and all patients >70 have a generally higher mortality due to myocardial infarction than do men and younger patients[8]. In a study from Gothenburg, Sweden, in which women with myocardial infarction were followed up for 12 years (1968–1981), a mortality of 45% was found. No comparative study of men was made[10].

In long-term follow-ups in other countries[3,11], women of advanced age, and especially those who had had a myocardial infarction, were seen to have a higher case-fatality rate than men (32% vs 27%)[12]. Moreover, in recently published material from Ontario, Canada, it has been seen once again that women, independent of age and other contributory factors, have a 2–3% higher hospital mortality than men[13]. This study states however, that this is only valid for the first 30 days after the onset of disease[12].

Risk factors

A number of metabolic atherogenic factors have been identified which increase the risk of developing cardiovascular disease. Among these metabolic factors are the blood lipid pattern, carbohydrate tolerance, coagulation factors and obesity.

Plasma lipid levels, and in particular HDL and LDL cholesterol, are considered to be the most significant determinators of risk of developing cardiovascular disease. In women, it has been found that the ratio of total cholesterol/HDL cholesterol, in addition to lipoprotein(a), is the most strongly associated with cardiovascular disease. Lipoprotein(a) is of particular interest as the concentration of this protein is hereditary and remains stable from early childhood. This lipoprotein is also considered to have both atherogenic and thrombogenic properties owing to its special molecular structure. The pattern of the other lipids and lipoproteins changes during a lifetime in a way that is unfavourable to the development of atheroma. This is especially true in the case of women, where these changes begin at the onset of the menopause. At this point the level of LDL cholesterol increases while that of HDL cholesterol decreases[14–17]. The role of triglycerides in the development of cardiovascular disease has not yet been fully established. Many epidemiological studies have displayed a relationship between serum-triglyceride levels and mortality with respect to cardiovascular disease. The relationship weakens and disappears, however, when other risk factors are taken into account. Most such studies have been performed on men, but among studies including women, triglycerides have appeared as an independent risk factor[18,19] which seems to be unique for women. The mechanisms behind this remain however unexplained.

Cardiovascular disease associated with hypertension is common. As early as the 1920s[20] it was demonstrated that serious cardiovascular disease was 10 times more common in autopsies of patients with high blood pressure than in a normotensive group. It is indisputable that hypertension is a definite risk factor even for women and the incidence of hypertension in women with cardiovascular disease is clearly higher than that of men with the same disease[11,21]. A systolic blood pressure of >160 mmHg, or a diastolic pressure of ≥85 mmHg, increases the risk 2–3 times for both sexes[22].

Other unfavourable changes can take place in the carbohydrate metabolism. Diabetes greatly increases the risk of cardiovascular disease in women and places them, regardless of age, in the same, or even worse, risk group as men with diabetes[23]. The interaction between insulin and androgenous hormones has been discussed in this context. Non-insulin dependent women with diabetes have been found to have hyperinsulinaemia, insulin resistance and male central obesity (‘pot belly’) [24]. Furthermore, it has been found that both sex and waist–hip ratio correlate to HDL-2, although the sex correlation disappears in a regression analysis[25].

Obesity in itself also leads to unfavourable metabolic changes. The lipid profile changes, with raised triglycerides, lower HDL cholesterol and a worse LDL/HDL ratio. Glucose tolerance declines, sensitivity to insulin is reduced and blood pressure increases. These changes increase the risk of cardiovascular diseases in both sexes, even if obesity as a sole factor does not contribute independently to an increased risk among women. On the other hand, it has been found that central obesity, even among women, predisposes them more to hypertension, diabetes and cardiovascular disease than general obesity (see above)[26].

Smoking is a significant risk factor for the development of cardiovascular disease in both men and women. The risk increases with the number of cigarettes smoked per day and is approximately four-fold in general[27]. Certain studies have shown that young women (<55 years old) who are heavy smokers (>25 cigarettes/day) run a tenfold increased risk of developing myocardial infarction. Ex-smokers, on the other hand, run the same risk as those who have never smoked. Smokers experience their first infarct about a decade earlier than non-smokers, while heavy smokers have infarctions two decades earlier. Women who smoke experience earlier menopause, which is a
further reason why smoking entails such a great risk of women.

Type A behaviour and its relation to cardiovascular disease in women was first described in the Framingham study. Tests showed that, above all, hostility and anger were components that were significantly related to cardiovascular disease in both sexes. These findings, however, must be interpreted cautiously as many of the studies are methodologically weak.

The variations in the age pattern between men and women with respect to contracting cardiovascular disease suggest that the endogenous ovarian hormones are of importance. Lack of oestrogen, as in the case of long-term amenorrhoea in pre-menopausal women, early menopause or oophorectomy are associated with an enhanced risk of cardiovascular disease. It is likely that there are several mechanisms behind this. Changes in total cholesterol levels have been observed, as has the pattern of HDL cholesterol and LDL cholesterol, which changes in an atherosclerotic direction after the menopause. In addition to this, there are also changes in levels of haemostasis factors, glucose, insulin and hypertension, and a predisposition towards cardiovascular disease. A further explanation as to why the fertile woman is protected against atherosclerotic vascular changes may be the direct beneficial effect of oestrogen on the endothelium. Initial studies on monkeys indicate this.

With successively diminishing oestrogen levels, the post-menopausal woman is exposed to an increasing number of recognised risk factors or, to put it another way, over the years she becomes more like a man with respect to the vascular system.

These observations show a clear connection between the endogenous ovarian hormones and women’s developing cardiovascular disease. There is, however, no scientific evidence to prove that this hormonal difference leads to a distinct pathogenesis.

Symptomatology

The symptoms of angina and myocardial infarction are to a great extent the same for both sexes i.e. chest pain triggered by effort, with or without radiation to part of the thorax, arms or head. In clinical practice, however, it is often found that women express their symptoms differently. Common expressions are ‘discomfort, unease in the chest, breathlessness, fatigue, weakness’ etc. To my knowledge, no studies have been made of whether this is due to their having a different experience of pain or that they communicate in another way. Nor is there any support for this in the literature. This ‘feeling’ of a different anamnesis for women compared to that we are used to from dealing with men needs to be studied scientifically. Otherwise there is a great risk that those who describe their angina symptoms in an unusual way will be misinterpreted, and their disease overlooked. The result of such a phenomenon would be that female patients would receive the correct care later and, consequently, would have a poorer prognosis.

What has been established is that women with typical symptoms of angina and obvious changes in their ECG at rest and after exercise tests do not display atherosclerotic changes in the coronary arteries to the same extent as men, at least not in the epicardial vessels which appear in coronary angiography.

Diagnostics

The correct diagnosis for women is often established late, which may be due to the fact that our normal diagnostic methods have difficulties in detecting cardiovascular disease before it is manifested in an obvious myocardial infarction.

Studies have shown that women with typical angina have a high prevalence of coronary artery disease, whereas the prevalence among those with atypical symptoms was low. Once again, however, age is significant, as pre-menopausal women with typical angina manifest a prevalence of 50% as opposed to 90% in older women with the same symptoms. The prevalence of chest pain on its own is not especially sensitive in identifying women who have significant coronary artery stenoses upon coronary angiography.

The number of false-positive ECG reactions among women at rest and during exercise tests is higher than that for men, a phenomenon which has been known for a long time and which makes the diagnosis uncertain. This has often led to women being excluded from studies of coronary artery disease. The low specificity can be explained partly by the higher prevalence of changes in resting ECGs among women and which the diagnostic certainty of the test, however, depends on the prevalence of the disease in the population studied. Women have a lower age-related prevalence of coronary artery disease than men, which most likely explains a major part of the diagnostic uncertainty of rest and exercise ECGs among women, even if it does not account for the phenomenon in its entirety. In studies of older women, the FRISC study, results suggest that the ordinary exercise test can be used predictively, especially if parameters other than changes in
the ECG are measured e.g. heart rate, maximum work capacity and chest pain. On the other hand, studies of mixed populations with similar prevalence have shown that, despite this, the positive predictive value of the exercise test is lower for women\textsuperscript{[40]}. As opposed to this, the negative predictive value of an exercise test is the same for both sexes. There is no obvious explanation for these findings.

A number of studies using isotope techniques have shown that these methods are more sensitive and specific than the ordinary exercise test in diagnosing coronary artery disease. Unfortunately, the number of women in these studies, if the gender distribution has been given at all, has been very small, therefore the value of nuclear medical methods for women cannot be said to be fully investigated. Nevertheless, at present there is nothing to suggest that the diagnostic certainty of these methods should be worse for women than for men. Certain gender-specific characteristics have crystallized, among which perfusion artefacts owing to women’s breasts are one. In women with large breasts, attenuation varies more than in men or among women with small breasts. The breasts can also vary in position in exercise and rest diagrams, respectively, several hours later. These artefacts make it difficult to interpret the analysis of the perfusion defects and therefore reduce the specificity of the test for women\textsuperscript{[41–44]}. Exercise echocardiography was first described by Wann \textit{et al.} in 1979\textsuperscript{[45]}. During the pre-digital era, promising results had been achieved, but difficult technical problems made it hard to use the method. Armstrong and Feigenbaum\textsuperscript{[46]} were pioneers in the field of digital computerized technology. In studies where men have predominated, a sensitivity of between 61 and 86\% has been found, in addition to a high specificity of 75–100\%. The prevalence of coronary artery disease was high in these studies, up to 84\%. There are few studies of echocardiography among women. In a study from 1989\textsuperscript{[47]}, however, where 57 women were investigated, it was concluded that, for detecting coronary artery disease, exercise echocardiography reached a clinically valuable level of both sensitivity and specificity which was fully comparable to the male material. Gender differences in echocardiography and simultaneous pharmaceutical provocation in the form of dipyridamole and dobutamine have given rise to even fewer studies involving women, and at present there are no reports which show gender differences with respect to dobutamine echocardiography. In summary, it can be said that both exercise echocardiography and stress echocardiography with pharmaceuticals can be useful for female patients. At the moment, however, very few data have been published on their reliability and there is no information whatsoever on the prognostic value of the methods\textsuperscript{[48]}. Gender differences in the use of diagnostic tests and therapeutic measures

In recent years, several centres have reported gender differences in the diagnosis and medical treatment of cardiovascular disease to the detriment of women. An imbalance in the former creates an imbalance in the latter.

Already in the emergency ward, women are treated differently with respect to care and examination. A study from the U.S.A. in 1992\textsuperscript{[49]} demonstrated that women wait longer than men for examination and ECGs and that women, as compared to men, with infarction were more often placed in an ordinary ward, not in intensive care (56\% as against 83\%). In 1987 it was reported\textsuperscript{[50]} that a far greater number of men than women (six times higher chance) were referred for coronary artery angiography after positive findings on a thallium scan. The difference remained after corrections for such variables as previous infarction and the degree of severity of the angina. In the same study it was found that, although women had more symptoms than men, the examining doctor believed that the symptoms could be explained in terms of non-cardiac causes, especially among women with pathological test results. Despite this, no difference was observed in the prescription of anti-anginal medication. In several other studies from the U.S.A., England, Ireland and Canada, these findings have been verified both for the investigation of suspected coronary artery disease and after hospital care for manifest disease\textsuperscript{[51–55]}. To my knowledge, no similar study has been carried out in Scandinavia. In a publication by King \textit{et al.} in 1992\textsuperscript{[56]}, it was made evident that patients’ symptoms were interpreted differently depending on their sex. After a bypass operation, women’s psychological symptoms were more often interpreted as emotional and were treated with sedatives; similar symptoms among men were to be considered organic in origin. Thus fewer women were referred to coronary artery angiography. However, with manifest atherosclerosis of the coronary arteries, women are revascularized to the same extent as men\textsuperscript{[57]}. Another aspect which has been highlighted in recent years is gender differences with respect to medical treatment. British studies\textsuperscript{[12,58]} have shown that far more men than women receive nitroglycerin infusions while hospitalized, and on discharge
significantly more than men were prescribed beta-blockers and acetylsalicylic acid (aspirin). It also emerged from the same studies that women were less frequently given thrombolysis. Several other studies have revealed that even in the absence of contra-indications for thrombolysis, it is available to women to a lesser extent than to men. The investigation of Maynard et al.\textsuperscript{[59]} observed that only 55\% of the women for whom thrombolysis was indicated actually received it, compared with 78\% in the case of men. The authors found this difficult to explain.

In a well-planned and carefully implemented study (SAVE)\textsuperscript{[60]} it was found that, although women reported more disabling angina than men, they were more seldom referred to invasive investigations, even though it is known that such procedures can alleviate symptoms and improve function. In Sweden, female coronary artery disease has been focused upon in studies in Gothenburg\textsuperscript{[10,19,22,61]}. In 1993\textsuperscript{[62]} an investigation from Gothenburg was published in which symptoms and well-being after myocardial infarction were studied in both sexes. Its findings are along the same lines as in other studies. It was also found that women displayed a higher degree of psychological and psychosomatic symptoms, including sleep disturbance, which are known to be risk factors for serious occurrences after infarction, at least in men. Thus, the attitudes, treatment methods and rehabilitation goals of doctors differ with respect to men and women. In part, this less aggressive treatment of women’s disease can be explained by the early results\textsuperscript{[5]} from bypass operations, where a five-fold increased risk of death was found among women. In a number of studies it has been possible to credit the reason for this to the higher age of the women\textsuperscript{[6,63–67]}, less body surface and thus smaller coronary arteries\textsuperscript{[64,65]}, more diabetes\textsuperscript{[63–67]}, high blood pressure\textsuperscript{[65–67]}, cardiac failure\textsuperscript{[6,66]}, more widespread changes in the coronary arteries\textsuperscript{[63]} and acute operations owing to unstable angina\textsuperscript{[6,63,64,66]}.

Rahimtoola, et al. however, point out in a report from 1993\textsuperscript{[68]} that a bypass operation is an effective form of treatment for angina (at a follow-up of 15–20 years) in both women and men. This is also indicated by Ståhle in an article in \textit{Läkartidningen} (the Swedish medical journal) in 1995\textsuperscript{[69]} after examining material from Uppsala, Sweden.

Studies of revascularization have shown a higher peri-operative mortality among women\textsuperscript{[63]}, while the long-term results have been comparatively similar between the sexes\textsuperscript{[63,70]}. Nevertheless, one must bear in mind that of the three major prospective randomized studies carried out in the 1970s comparing the effects of bypass operations with those of medical treatment, two studies\textsuperscript{[71,72]} included only men and the third\textsuperscript{[73]}, about 10\% women. Thus, about 2000 men have been studied and 76 women. It is therefore difficult to draw conclusions about women from these randomized data.

In a fairly recent national register of open heart surgery in Sweden (initiated in 1992), which includes information on a total of approximately 9000 interventions per year, it can be seen that men comprise 73\% of the total and that 30-day mortality is higher for women than for men (3.6\% and 1.8\%, respectively). Divided according to coronary artery surgery, the figures are 3.1\% and 1.4\%, respectively. On average, men have a higher number of vessels implanted (3.7) than do women (3.5). Thus far, however, no deeper analysis of these differences between the sexes has been made.

In the same manner, previous studies\textsuperscript{[70]} of PTCA have produced similar peri-operative results to those from bypass operations, i.e. women display more complications and a higher procedure-related mortality than men. As in previous studies, this has been explained partly by the women’s higher age, cardiac failure, severe vascular disease, smaller coronary arteries etc. A less advantageous vascular anatomy can therefore be a significant factor primarily because of the larger balloons that were used in the early stages of the PTCA era\textsuperscript{[74]}. Better techniques may have laid the foundations for the better results presented in latter years\textsuperscript{[75]}, from which it can be concluded that the safety and results are the same for women as for men. The long-term results of PTCA during this period, however, have been equal to those displayed by men\textsuperscript{[70,76]}.

Preliminary results from the Swedish register for coronary angioplasty (initiated in 1990), with information on approximately 3000 interventions per year, show that 73\% of the interventions are performed on men and that the success rate is 90\% for both sexes. No differences in immediate complications have been observed either. What is seen, however, is that women are significantly older at the time of intervention and the time spent in hospital is longer. The men have often had an infarction or undergone revascularizing interventions previously. Primary PTCA upon acute myocardial infarction was more often performed on men, as were stent implants and atherectomy.

As women get older, the frequency of cardiovascular disease increases, and in very old women, it exceeds that of men. It is quite natural to associate this development of cardiovascular disease in women with the post-menopausal state of oestrogen deficiency. Accordingly, oestrogen substitution might be able to reverse this trend, resulting in lower morbidity and mortality from cardiovascular disease. This has
also been studied in 28 epidemiological studies of varying design[77]. These studies have taken place in the U.S.A. for the most part and with conjugated oestrogen, without added progesterone. A few studies have been performed in Europe, most often with oestradiol[77]. Most of these epidemiological studies have shown that hormone supplements reduce the risk of cardiovascular disease[78] by 40–50%. Nevertheless, the value of these studies has been questioned as the protective effect can be explained by methodological errors, such as selecting healthy women who choose hormones. Hence, prospective, randomized, double-blind studies to verify the epidemiological results are very desirable[79]. At present, no such study has been published, thus it is not possible to prescribe post-menopausal hormone treatment on this indication. There is, however, no evidence to support withholding hormone treatment from women with cardiovascular diseases if it is needed for other indications.

**Summary**

In summary, there are gender and age differences in prevalence, prognosis and manifestation of cardiovascular disease, a phenomenon which has been known for a long time. Nevertheless, it is only since the end of the 1980s that this has been generally discussed and that research has been commenced with specific reference to female coronary artery disease, not only in Sweden but internationally as well. The reason for this gender difference is not known, but it has been suggested that women are cared for and treated differently. In recent years, reports have been received from different centres which indicate that there are gender differences in the use of diagnostic and therapeutic measures in cardiovascular disease.

Because of this gender difference in prognosis, investigation and treatment, special measures need to be applied in the care of female cardiovascular patients. It is also very important that randomized studies include a sufficient number of women in order to be able to answer gender-specific questions.

The good prognosis for women with angina shown in the Framingham study most likely reflected a high prevalence of women with chest pain originating from disease other than that affecting the coronary arteries. This created the impression that women tolerated angina better; thus, angina in women has been given less attention. It is likely that this has led to incorrect decisions concerning investigation and treatment alternatives, resulting in an inability to identify the high-risk woman in time. When she is finally admitted to proper care, she is older, has concomitant diseases and revascularization often has to be performed at an acute, unstable stage, which leads to higher mortality and morbidity in connection with the intervention. This phenomenon has been described as the so-called ‘Yentl syndrome’[80] i.e. a woman has to masquerade as a man in order to receive the same treatment.

More medical research needs to be done on women’s health to come to terms with this problem. Hitherto, major efforts have been made to obtain homogenous groups in research studies, which is why there are lots of results containing data on middle-aged white men. Even in tests on rats the females are excluded. The results of studies performed exclusively on men cannot be generalized to apply to women without evidence that the results can be used safely and effectively on both sexes. Research on health problems that are common to both sexes must include both men and women, preferably of all ages. It is also important to point out that unnecessarily restrictive inclusion criteria diminish the ability to generalize the results. Moreover, the chance increases of being able to detect a difference in the effects of treatment in a population with an increased risk, such as the elderly and women with a high frequency of recurring coronary artery disease.

There are still many questions to be answered before we can treat women with coronary artery disease properly.

E. SWAHN

University Hospital, Linköping, Sweden

**References**


