

Handbook of Clinical Gender Medicine

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Coronary Heart Disease

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Abstract

Cardiovascular disease (CVD) is the most common cause of death in both sexes. There are sex and gender differences in the disease; that is, the epidemiology, pathophysiology, diagnostics, treatment response, and prognosis, as well as how women and men experience the disease in their sociocultural setting, may differ. CVD presents later in women, who are therefore older and more likely to suffer from comorbidities such as diabetes and hypertension. Women have smaller vessels, including the coronaries, and they also present more often with acute coronary syndrome including myocardial infarction with normal coronaries. Women do not always have the typical symptoms of myocardial infarction and therefore may seek help later. Prevention is as important in men as it is in women since 6 of 10 deaths due to CVD may be prevented. It is therefore very important that all health professionals as well as women themselves are aware of and know about CVD. The profession must also participate in disseminating knowledge about female CVD. This paper aims to get the reader to realize the importance of taking sex and gender into account when treating female or male patients with heart problems.

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Cardiovascular disease (CVD) includes coronary heart disease (CHD) and stroke. CHD involves ST elevation myocardial infarction, acute coronary syndrome (ACS) and stable angina pectoris. This paper deals with gender considerations in CHD.

CVD has traditionally been perceived as a male illness, but it ends the lives of as many women as men. Women's health has traditionally been focused on matters related to sexual and reproductive health. However, CVD is the most common cause of female death in most countries except for Africa. It is in many countries more common than cancer, HIV/AIDS, malaria, and tuberculosis combined. However, according to the World Heart Federation, CVD is indisputably the most serious neglected health problem for women in both developing and developed economies. The lack of awareness among both clinicians and women is especially alarming in countries of low or middle income where public health policy has been largely focused on infectious disease in general and maternal and reproductive health for women specifically. The other

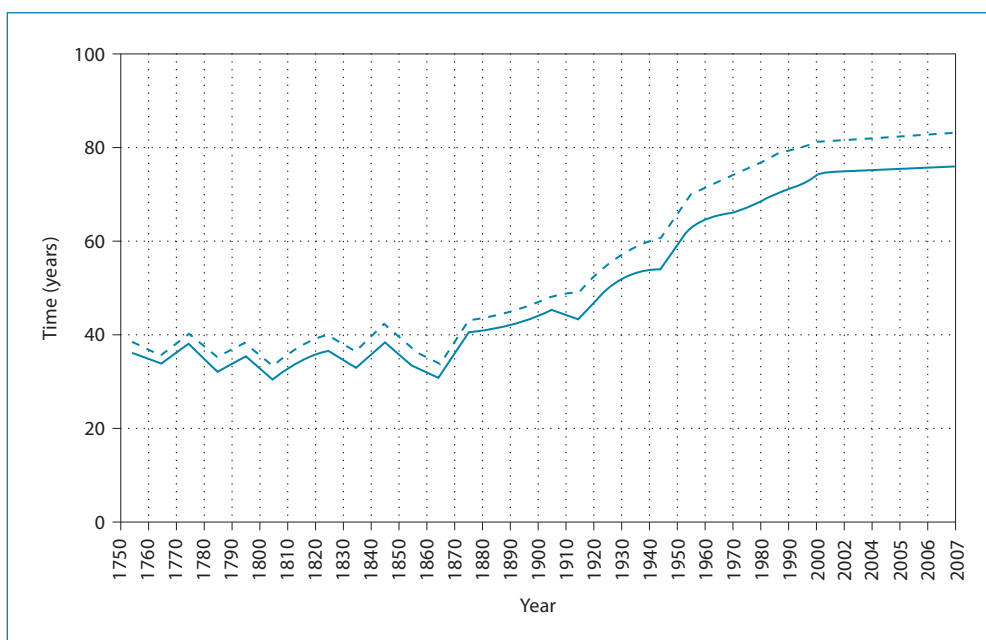


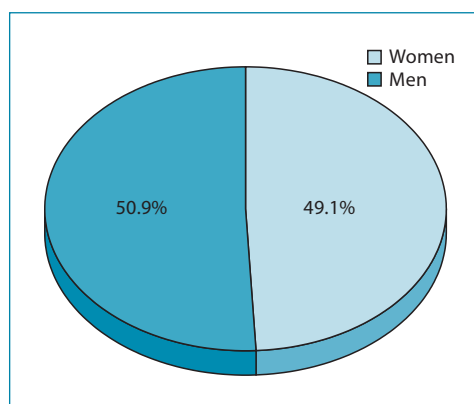
Fig. 1. In Sweden, women live longer than men since 1750. Dashed line represents women; solid line represents men. Source: Statistiska centralbyran [24].

alarming statistic is that 6 out of 10 deaths from CVD can be prevented also in women. It is therefore critically important that we increase the awareness of gender aspects of CVD among healthcare providers and the general public since gender differences exist in the impact of conventional risk factors as well as in the presentation of myocardial infarction and ACS. Unfortunately, as confirmed by two recent meta-analyses from Europe and the USA [1, 2], the evidence to support the treatment of heart disease in women remains incomplete and is an area that requires further work.

Epidemiology

In Sweden, women have lived longer than men since 1750 (fig. 1), but lately after 2007 the gender gap has begun to decrease. This decrease is also seen in many other countries. However, CVD is the most common cause of death in Sweden as in most countries in the world. Worldwide over 8.6 million women die from CVD each year (fig. 2); this is almost equal to the number of deaths seen in men [3]. The case fatality for both men and women is falling in most Northern, Southern, and Western European countries and recently also in the USA. Within Central and Eastern Europe, the fatality is either constant or rising. Mortality has changed little in premenopausal women. In Europe overall 23% of women are dying of ischemic heart disease versus 21% of men.

Fig. 2. CVD death (based on WHO estimations of 17.5 million total CVD deaths and 8.6 million female CVD deaths). Chronic diseases: CVD, cancer, chronic respiratory disease, and diabetes. Source: WHO [25].



This is in contrast to only 3% of European women dying from breast cancer. CVD presents about 10 years later in women than in men; therefore, older women are more likely to suffer from comorbidities such as diabetes and hypertension. The difference in age at first myocardial infarction may be largely explained by the greater presence of risk factors at younger ages in men compared to women [4]. With respect to women, polycystic ovary syndrome, early menopause, gestational diabetes or hypertension, and a history of preeclampsia are important risk factors.

Clinical Considerations

Risk Factors

When addressing clinical aspects of CVD, it is important to discuss risk factors. This is especially relevant in women who may in some cases present nonclassical clinical symptoms, and the assessment of risk factors may need to be taken into account. The most important preventable risk factors for developing CVD are diet, including the possible role of the degree of alcohol use, the degree of physical activity, and the use of tobacco. Related to these risk factors is the presence of comorbidity including dyslipidemia, hypertension, diabetes, obesity, and stress [5].

Diet and Alcohol Use. In women as in men the association between cholesterol and low-density lipoprotein (LDL) cholesterol with increased cardiac risk is beyond dispute as are the benefits of reduction in high-risk individuals. The association between LDL cholesterol and increased cardiac risk has been well documented. Evidence shows the beneficial effects of the Mediterranean diet, which has a high proportion of fruits and vegetables, on total cholesterol, LDL cholesterol, blood pressure, and myocardial infarction. In the secondary prevention Lyon Heart Study, 600 women and men were randomized to Mediterranean food or to a control group, and after 27 months a significant difference in both sexes was found in mortality and morbidity due to CVD as well as in

total mortality in favor of the Mediterranean food group [6]. The mechanisms behind these beneficial effects are multiple, and diet should always be combined with other lifestyle changes like exercise as well as – when necessary – medication. With regard to alcohol, the beneficial effects are probably the same in both men and women, but few gender analyses have been performed. While a moderate intake may be protective, too much alcohol is deleterious. The grade of evidence is poor because of the problems in undertaking placebo-controlled studies. Also, the control group may include ex-alcoholics who are now ‘teetotalers’. The type of alcohol is not as important as the when and how. A low-to-moderate daily dose can be protective while binge drinking can be harmful to the heart and the liver. Recommendations are difficult but there is no reason to ask people to stop moderate drinking after a myocardial infarction. Conversely, it is not necessary to advise people to start drinking in order to prevent ischemic heart disease or further myocardial infarction if they do not wish to drink. Light-to-moderate alcohol intake is defined as 1 standard glass daily for women and 2 for men; women metabolize alcohol more slowly than men do and therefore need half the dose. A standard glass is defined as 1.2 g alcohol which is equivalent to 15 cl of wine.

Physical Activity. Women’s bodies seem to react differently than men’s to the metabolic effects of exercise. Female bodies have a biological need to maintain energy stores for reproduction, so exercise for many women (and for some men) increases the desire to eat. In a study from 2009 [7] overweight men and women walked on treadmills in multiple sessions while either eating enough that day to replace the calories burned during exercise or not. Afterward, the men displayed little or no changes in their energy-regulating hormones or their appetites, much as in other studies. The women, however, showed increased blood concentrations of acylated ghrelin and decreased concentrations of insulin after the sessions in which they had eaten less than they had burned. Their bodies were directing them to replace the lost calories, consistent with the paradigm that mechanisms to maintain body fat are more effective in women. In a huge prospective observational study in both sexes, a lower fitness level was found to be associated with a 4.7-fold increased risk of myocardial infarction and stroke, independently of other vascular risk factors. The overall reported beneficial effects of exercise on the CVD risk profile are, however, less marked in women compared with men, with a smaller increase in high-density lipoprotein (HDL) and less weight loss resulting from similar exercise training. Nevertheless, in the Nurses’ Health Study [8], two aspects were particularly important: brisk walking conferred the same benefit as vigorous exercise, and sedentary women who became active late in life achieved similar benefits as those who remained active throughout life. The recommended dose of physical activity is a minimum of 30 min of brisk walking daily (for younger persons often more). It is the same for men and women.

Tobacco Use. That smoking predisposes to CVD is not disputed, and it affects women to a higher extent than men. Whether mechanisms underlying the sex difference are biological or related to differences in smoking behavior between men and women is unclear.

A systematic review and meta-analysis of prospective cohort studies published between January 1, 1966, and December 31, 2010, with measures of relative risk (RR) and associated variability, for CHD and current smoking compared with not smoking was published in *Lancet* in 2011 [9]. In 75 cohorts (2.4 million participants) the pooled adjusted female-to-male RR ratio of smoking compared with not smoking for CHD was 1.25 (95% CI 1.12–1.39, $p < 0.0001$). The increased risk for women has also been confirmed in other studies.

In the Nurses' Health Study including over 120,000 healthy nurses, only 4–5 cigarettes daily almost doubled the risk and 20 cigarettes increased the risk 6 times. Also, in the Copenhagen City Heart Study, women were more damaged by smoking [10]. The reduction in male smokers has been a public health achievement; sadly, the number of female smokers (initially lower than the number of male smokers) has not declined to the same extent. This is particularly true of younger women who may be storing up significant vascular problems for later life [11]. Regular exposure to secondhand smoke is estimated to increase the risk of CVD by about 25%. The INTERHEART case-controlled study estimated that 29% of heart attack cases in Western Europe are due to smoking, and smokers and former smokers are at almost twice the risk of a heart attack compared to never-smokers. Women are said to find it more difficult to stop smoking, one reason being a concern about weight gain. Cigarette smoking decreases the endogenous levels of estrogens in women; this will lead to premature menopause, which in itself is predisposing for future CVD. The same dose of tobacco for both men and women might induce more harmful effects in females because of the smaller anatomical dimensions and different circulatory physiology.

High Blood Pressure. A meta-analysis of prospective data on over 1 million adults (aged 40–69 years) has shown that an increase of 20 mm Hg systolic or 10 mm Hg diastolic blood pressure doubles the incidence of death from CHD for both men and women. A 3-fold increase in stroke and ischemic heart disease is found in women with a systolic blood pressure over 185 mm Hg as compared to women with a blood pressure over 135 mm Hg. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure VII recommends a blood pressure below 140/90 mm Hg in all hypertensive patients and a blood pressure below 130/80 mm Hg in diabetics or other groups with a high cardiovascular risk, a target agreed upon by most national societies.

Diabetes Mellitus. Cardiovascular events are the leading cause of death, especially in type 2 diabetes mellitus. Diabetic women have a 3- to 5-fold increased risk of developing CVD compared to men. The INTERHEART study estimated that 15% of heart attacks in Western Europe and 9% of heart attacks in Central and Eastern Europe are due to diagnosed diabetes. In the Nurses' Health Study, women with diabetes alone had a coronary mortality 8.7 times higher than that of nondiabetics, and those who had a known ischemic heart disease history in addition had a relative risk (RR) of fatal coronary artery disease of 25.8. In the Copenhagen City Heart Study, over a 20-year period in 7,198 women, the RR of new myocardial infarction was 1.5–4.5

among diabetics compared to nondiabetics [12]. Also, diabetic women develop CVD earlier, at the same age as men. The reason for this is still unknown and intriguing. The frequency and severity of atherosclerotic disease in diabetes have led the Adult Treatment Panel III of the US National Cholesterol Education Project to classify the condition as a CHD equivalent justifying aggressive intervention.

Obesity. Worldwide, 30% of women are now overweight compared to 40% of men, and 27% of women are obese compared to 24% of men. One of the outcomes noted in the Nurses' Health Study was that there is a gradient of coronary risk, with the heaviest category of women having a 3-fold risk for CVD compared with lean-built women [13]. Much evidence has focused on the fat distribution. The recommended target body mass index is 18.5–24.9 and the recommended waist circumference is below 82 cm for women and below 98 cm for men.

Stress. The general public has long associated psychosocial stress and acute stress with myocardial infarction or stroke. Also, the saying that she/he died of a broken heart has increased in popularity because of the increasing amount of almost only women referred to the hospital with severe heart failure after having experienced an extremely stressful event (so-called broken heart syndrome or Tako-tsubo syndrome). Compared with other CVD risk factors, psychosocial variables are more difficult to define and to measure objectively.

In spite of that, there are several dimensions within the broader definition of psychosocial factors that are now associated with the risk of myocardial infarction. Stress at work and in the family, negative life events, lack of control, poorly functioning social networks, low socioeconomic status, and depression are some of these factors, with an impact on the risk of ischemic heart disease as well as the prognosis. Several studies show a clear relation between stress and CVD. In women, family stress including marital stress has been shown to increase the risk of ischemic heart disease [14]. In the INTERHEART study, stress at work as well as stress at home were more common among the patients with myocardial infarction than their controls, and stress represented 30% of the total risk. Depression is one face of psychosocial stress, and more women than men get depressed after myocardial infarction. Also, depression is a more important risk factor for ischemic heart disease in women compared to men. In conclusion, stress can induce ischemic heart disease and also worsen it, probably via influencing atherosclerosis, endothelial function, fibrinolysis and coagulation, inflammation, and vessel function.

Symptoms

Myocardial Infarction and Acute Coronary Syndrome

The typical symptoms of myocardial infarction are: pressure, burning, or squeezing in the center of the chest for 20 min; sometimes discomfort in one or both arms or shoulders or the neck, jaw, stomach, or back; shortness of breath; fatigue; cold sweat; nausea, and weakness. Central breast pain is the most dominant symptom. No matter what

the sufferer does to try to alleviate the symptoms (e.g. taking a deep breath, getting fresh air, drinking something, or altering the body position) the chest pain remains constant. Symptoms of myocardial infarction in men and women are in most cases the same but in 1 of 5 women the symptoms may be different. There is no chest pain but instead shortness of breath, pain in the upper back, jaw, or neck, flu-like symptoms, fatigue or weakness, feelings of anxiety, loss of appetite, or discomfort may be the predominant features among females. Of course, some of these female symptoms are very general, and therefore it should be stressed that the suspicion of myocardial infarction should also be based upon the presence of cardiovascular risk factors. The Acute Coronary Syndrome Registry at the University of Michigan, comprising 1,940 patients, showed that men were more likely to present with chest pain, left arm pain, or diaphoresis. While nausea was more common in women, there were no gender differences in the symptom of dyspnea. In that study, it was shown that the chest pain symptoms decreased with age in both sexes. Chest pain was more common in men but the difference in chest pain occurrence could be explained by the women's older age and diabetes mellitus being more common in younger women. Other symptoms like jaw pain, neck pain, back pain, and emesis were more common in women. In a meta-analysis [15], the overall findings suggest that the typical chest pain symptoms are the strongest predictors of ACS in women but women experience other symptoms more frequently than men. Women had significantly more back and jaw pain, nausea and/or vomiting, dyspnea, indigestion, and palpitations. This was also confirmed by other studies of patients with ACS. After simultaneously controlling for age, medical history, and acute myocardial infarction characteristics by regression modeling, men were significantly less likely to complain of neck pain, jaw pain, and nausea than were women. A Swedish study from 2010 observed that it is much more common in women than in men to have chest pain together with several other symptoms like dizziness, back pain, or tachycardia [16]. According to the US myocardial registry of 2012, 41% of the women did not have chest pain but higher hospital mortality compared to men.

Angina Pectoris

The typical anginal attack is characterized by chest pain induced by physical or mental effort and will persist for a couple of minutes and disappear promptly during rest. It is also diagnostic that if nitroglycerin is taken, the pain will stop immediately or within a few minutes. The chest pain in women might appear differently, for example as in stable angina pectoris, being induced more by mental stress than by physical stress and more at rest than during physical effort compared to men. The typical features of unstable angina are stable angina pectoris accelerating for the last 3 or 4 weeks or newly debuted angina pectoris for 3–4 weeks with symptoms increasing every day.

Delays

The delay in seeking care is greater in women than in men with acute myocardial infarction. Some studies report that most women have prodromal symptoms, like

unusual fatigue, sleep disturbance, and shortness of breath, long before the ACS event. Only 1/3 report chest discomfort, and the most frequent acute symptoms are shortness of breath, weakness, and fatigue. These symptoms might be more important than CVD risk factors. The time between presentation to the emergency department and the acute coronary intervention is significantly longer in women, probably due to multiple factors from the women themselves to the health professionals in the ambulance and at the hospitals. However, according to the latest statistics from the Swedish Heart Registry (RIKSHIA) the gender gap in delays has shortened and, overall, the delay times in general have become shorter both for ACS and for stroke.

Differential Diagnoses

The most common differential diagnoses for ACS are the same in men and women, i.e. spinal problems, gastric pain, esophageal pain, lung disease, pericarditis, and other infections.

Diagnostic Considerations

Risk Factor Assessment Models

Levels of lipoprotein (a), C-reactive protein, amyloid A, homocysteine, interleukin-6, and intercellular adhesion molecule-1 as well as socioeconomic status should be considered when evaluating risks. In Europe the Systematic Coronary Risk Evaluation system is used to evaluate CVD risk. Although this system is considered to be superior to prior models, it only extends to 65 years of age and does not take into account that women may present with CVD later than their male counterparts. Further, while guidelines are based on traditional risk factors, cardiac events in women can occur in their absence and in women with the traditional risk factors cardiac events do not necessarily occur. The same risk factors for both sexes have been used in risk calculations during the last 40 years in spite of the increasing knowledge about gender differences. In 2007, Ridker et al. [17] suggested using the Reynolds score system for women. This is based on 10-year data of CVD events in 25,558 women aged over 45 years from the Women's Health Study. The clinically simplified model contains age, systolic blood pressure, hemoglobin A1c if diabetic, smoking, total and HDL cholesterol, high-sensitivity C-reactive protein, and parental history of myocardial infarction before the age of 60 years. This scoring system reclassified 40–50% of women at intermediate risk into higher or lower risk categories. It was concluded that this new scoring system predicted the CVD risk in women much better than the classical instruments.

Female patients with myocardial infarction, ACS, or angina pectoris have a lower degree of atheromatosis and stenosis compared to male patients, they have more disturbances in the microvasculature and endothelial function, and they are more

prone to spasm in their vessels. However, women have a lower degree of enzyme leakage of both troponins and other ischemic markers. The question has therefore been asked whether women have been underdiagnosed in relation to myocardial infarction or ACS. Silent myocardial infarction includes an infarct detected a long period of time after an event where the patient had some type of symptom but received no hospital care or did not have any symptoms at all, perhaps via a routine electrocardiogram (ECG) where Q waves are present indicating a previous infarct or a magnetic resonance or positron emission tomography scan indicating old infarcts. Old infarct scars can also be detected by an autopsy without any known hospital care for heart problems. Silent myocardial infarction in women has been reported to represent about 20–30% of the infarcts in a study from Rotterdam. About 38,000 ECG analyses in the healthy women cohort of the WHI (Women's Health Initiative) were studied, and an unexpectedly high degree of Q waves was detected. This indicated that old myocardial infarctions were present as a sign of previous not known myocardial damage.

Exercise Stress Testing

Exercise stress testing on a bicycle or treadmill is not always as reliable in women as in men, especially when it comes to the ST depression indicating ischemia. Women can have 'pathological' ST depressions during exercise but a 'normal' coronary angiography. This might be due to more frequent repolarization abnormalities on baseline ECG or even estrogen having a digitalis-like effect. Digitalis is known to induce ST depression on ECG. The products of pulse and blood pressure at baseline and the exercise maximum seem to be better predictors of ischemia than the degree of ST depression, especially in younger women. In the Stockholm Female Coronary Risk Study, typical angina symptoms during an exercise test were induced in women to the same degree whether they had 3-vessel disease or an almost normal coronary angiography. The exercise test is a cheap and easy test, so it should be used also in women but with awareness of its drawbacks.

Nuclear Stress Testing

Both sensitivity and specificity for thallium scintigraphy or tests with other isotope techniques are much better than those of the exercise test for women and as good in women as in men. Therefore, a normal scintigraphy in a woman with chest pain almost always excludes ischemic heart disease. Presumably, the investigating laboratory is of good quality and is aware of artifacts caused by women's smaller left ventricular chamber sizes and soft tissue attenuation from breast tissue. In a meta-analysis and in recommendations from the American Heart Association, it was concluded that the diagnostics of stenosis seem to be rather gender neutral but that women with diabetes, metabolic syndrome, and polycystic ovary syndrome need special attention and should be investigated extra carefully.

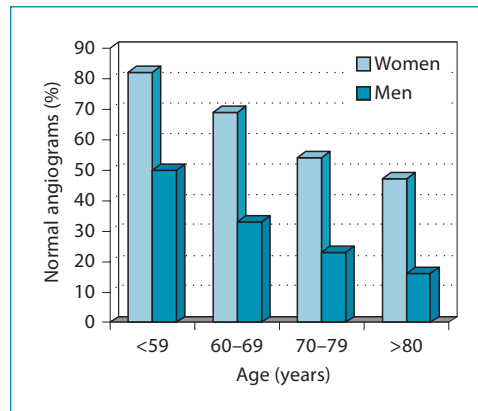


Fig. 3. Percentage of normal angiograms by age. Source: Johnston et al. [18].

Coronary Angiography

Women have smaller dimensions of the coronary vessels. Women more than men have a lower prevalence of coronary stenosis and atheromatosis as seen in coronary angiography when presenting with ischemic heart disease. Normal coronary angiographies in women with chest pain do not mean the absence of ischemic heart disease. There might be endothelial dysfunction due to uncontrolled hypertension, vasospasm, or microvascular disturbances. In a recent Swedish study of 12,000 coronary angiograms performed as part of a clinical chest pain evaluation, it turned out that women in all age groups showed a high rate of so-called normal findings, much more so than men. Especially women under 60 years had up to 80% normal angiograms. Was the investigation perhaps unnecessary? [18] (fig. 3).

This indicates that we have poor diagnostic instruments for women with chest pain. The problem has recently been reviewed and is also well illustrated in the Women's Ischemia Syndrome Evaluation studies funded by the National Institutes of Health and by findings of the Stockholm Female Coronary Risk Factor Study. In general, both in chronic and acute coronary artery disease, women are less likely to be referred to coronary angiography. Whether this is right or wrong must be evaluated given the new knowledge that women can contract ischemic heart diseases without significant coronary stenosis.

Treatment Options

Guidelines

Guidelines with sex and gender aspects are slowly emerging. Some examples are separate guidelines in the prevention of CVD in women published by the American Heart Association, as well as Australian ACS guidelines. However, most clinical guidelines so far do not contain information about sex and gender aspects.

Hyperlipidemia. Swedish national guidelines suggest for total cholesterol a target of less than 5 mmol/l for primary prevention and one of less than 4.5 mmol/l for secondary prevention; for LDL the suggested target is below 2 mmol/l. In the UK, the National Service Framework for CHD suggests a cholesterol target of less than 5 mmol/l both for primary and secondary prevention and a target below 2 for LDL. US guidelines even suggest a target of less than 4 mmol/l of total cholesterol, and for LDL the suggested target is below 1.8 mmol/l in the secondary prevention setting. In epidemiological studies, low HDL levels have been found to have a greater impact in women than men, but intervention studies independently focused on HDL are difficult to design. However, there are some ongoing clinical trials with drugs which increase HDL. A newly designed synthetic HDL with gold nanoparticles has been shown to be capable of irreversibly binding cholesterol. This synthetic HDL is similar to HDL in size and mimics its general surface composition. Most recent guidelines recommend treatment for those with concentrations below 1 mmol/l. An increase in HDL of 1% is associated with a 3–5% decrease in risk for women but only a 2% decrease for men. In women hypertriglyceridemia is an independent risk factor for coronary artery disease while among men this remains an ongoing debate.

In the two major secondary prevention trials involving significant numbers of women, lipid-lowering therapy benefited women to an even greater extent than men. In the simvastatin arm of the Heart Protection Trial, there was a significant reduction in all-cause mortality and a 24% reduction in vascular events. The Heart Protection Trial is one of the few lipid studies where a power calculation was performed before the study start and the numbers needed of both genders were calculated.

The treatment of dyslipidemia consists of a combination of dietary improvement, increased exercise, and medication (with statins being the mainstay medication). Early concerns about the safety of these agents, particularly with respect to carcinoma of the breast, have proven to be unfounded. Other agents include bile acid binders, ezetimibe, and fibric acid derivatives (gemfibrozil and fenofibrate), but gender-specific outcomes with these agents have not been reported. A 2011 Cochrane report confirms this [19].

Hypertension. The treatment of hypertension is currently the same in both genders; in most cases it comprises pharmacotherapy together with lifestyle changes. In secondary hypertension sometimes surgically interventions are needed.

The first-line drugs are angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), diuretics, and calcium channel blockers. If the response is insufficient, doses can be increased, the actual medications can be replaced, or new medication can be added. Compared to men, women report more cough with angiotensin-converting enzyme inhibitors and peripheral edema with calcium channel blockers.

Smoking Cessation. Smoking cessation is more difficult but as important for women compared to men. Women's fear of weight gain is one reason for their difficulty quitting. There are some programs combining weight reduction with smoking cessation which have been especially suitable for women. Tobacco control programs should consider women, particularly in those countries where smoking among young women is increasing in prevalence.

Diabetes Mellitus. Women are better at following recommendations and attending 'diabetes schools' than men are. The treatment is probably the same in both sexes (in both diabetes types 1 and 2) but so far there is too little evidence.

Obesity. Women more than men are on weight-reducing diets periodically. Practically all previously registered weight-reducing pills have now been withdrawn by the medical product agencies because of serious adverse side effects. They are illegally marketed on the web. Weight-reducing surgery like gastric bypass is the best evidence-based method so far and has the best long-term results. As far as is known, the same results are achieved in men and women but more women than men want to be operated. Cognitive behavioral therapies are currently being discussed as therapies for obesity, but so far gender differences have not been studied.

Stress. Modern stress management in primary and secondary prevention of CVD might be effective, and there are many sex and gender issues. However, little evidence exists as a basis for guidelines.

Alcohol. Certainly, the management of alcohol abuse may differ between men and women since there are well-known sex and gender differences behind alcoholism. However, there are few studies in this area and therefore sparse evidence as a basis for guidelines.

Myocardial Infarction and Acute Coronary Syndrome. The evidence from clinical trials is less robust when applied to women as they are usually included in too small a proportion. This is often due to age limitations or exclusions based on comorbidities. There is a reliance on registry data as clinical trial data are relatively sparse and outcomes for women are usually derived from post hoc subgroup analysis or gender-specific outcomes may not be reported. The small numbers mean that studies are likely to be underpowered; real differences may not achieve statistical significance. Clinical CVD trial data on postadmission drug therapy after cardiac events show equal efficacy for the long-term use of aspirin, β -blockers, statins, and angiotensin-converting inhibitors in men and women.

In conclusion, ACS including myocardial infarction should be managed with the same pharmacological therapy in women and men both in the hospital and for prevention.

With regard to antiplatelet and anticoagulant doses, these should be based on weight and renal function. Doses of drugs mostly renally cleared should be based on the estimated creatinine clearance.

Recommended indications for noninvasive and invasive testing in women are similar to those for men; patients with ACS and with high-risk features benefit

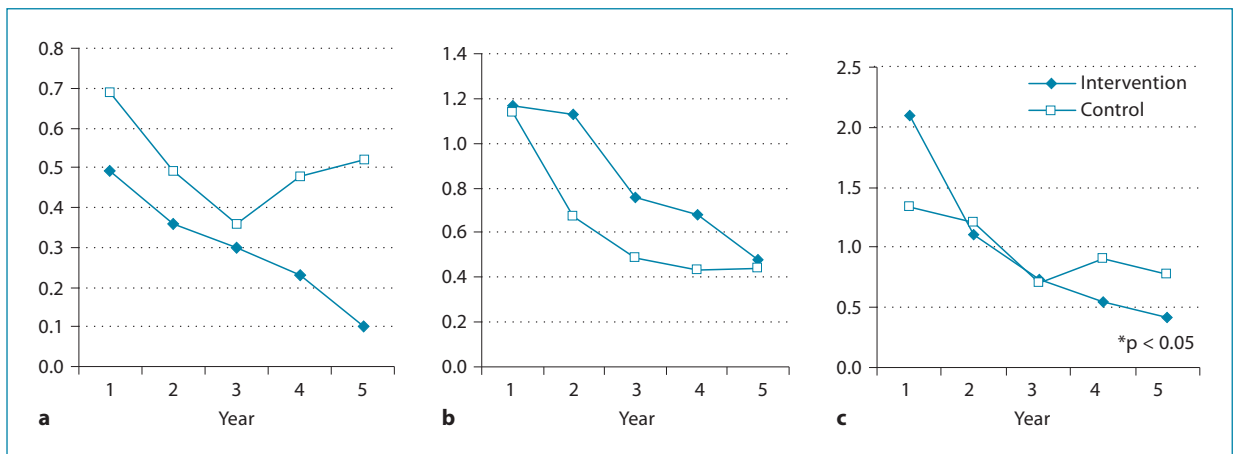


Fig. 4. Emergency (a) and scheduled doctor (b) visits to the hospital and number of in-patient days (c) (means) during 5 years by group assignment. Source: Andersson et al. [21].

from an early invasive strategy (intervention within 48 h) with stenting and an adjunctive glycoprotein IIb/IIIa inhibitor. Women with ACS are at a lower risk, and those with negative troponin levels tend to have an excess of complications with an invasive strategy. In ST elevation myocardial infarction, timely primary angioplasty improved outcomes as compared with fibrinolysis also in women. Women also benefit from early revascularization for cardiogenic shock. The CRUSADE prospective registry which included 17,926 patients with ACS supported the use of an early invasive strategy in women, but they were less likely to receive early invasive treatment. Therefore women had significantly higher in-hospital mortality [20].

Rehabilitation

In a recent Swedish rehabilitation study in women [21], the program combined stress management with life style changes during 5 years and reduced the need for hospital care (fig. 4). Perhaps women need specially designed rehabilitation programs since cardiac rehabilitation was originally developed in the 1970s with special regard for the needs of middle-aged men to promote return to work post-myocardial infarction [22]. Despite the preponderance of evidence on the numerous benefits of cardiac rehabilitation, it remains largely underutilized in women. A Cochrane review reported that 3–11% of the patients enrolled were women [23]. Studies of the effectiveness of rehabilitation have generally revealed no major differences between men and women. However, female-specific data on the effect on mortality and morbidity are lacking.

Future Options and Research

Presently, evidence regarding the treatment of CVD in women is not complete; few guidelines exist where sex and gender are taken into account and the majority of the publications have not performed a sex and gender analysis.

Women have generally been either excluded or underrepresented in cardiovascular trials, and thus the evidence base is rather unsatisfactorily drawn either from observational cohorts or from small numbers within larger randomized trials. This is evident from the European Heart Surveys in angina and heart failure as well as in randomized controlled trials funded by the US National Heart, Lung and Blood Institute, as confirmed in a follow-up from 2008. A task force within the European Society of Cardiology wrote a policy document in 2006 on CVD in women, with recommendations for the future management of the problem of forgetting women in research. As a follow-up, a working group in the European Society of Cardiology and World Heart Federation in collaboration with Euro Heart Health, EU Workpackage, went through all publications between 2006 and 2010 in the areas of lipids, ACS, heart failure, stroke, atrial fibrillation, antithrombotic therapy, hypertension, and diabetes [1]. A total of 380,891 patients were analyzed in 62 prospective, randomized, placebo-controlled clinical studies in these areas. Of the patients, 127,716 were women (i.e. 33.5%); the mean age was 66.3 years, and the mean follow-up was 2.7 years. The proportions of women included were between 15 and 60%, and in most cases the numbers of women included were too small in relation to the prevalence of the disease. Only in 31 of 62 studies, i.e. 50%, were the results analyzed according to gender and sex. This study resulted in a letter to the DG SANCO of the EU with a recommendation of an action plan to solve the situation. An American review [2], also from 2010, of 156 randomized clinical studies on CVD from 1970 to 2006 showed that the inclusion rate of women had increased from 9% in 1970 to 41% in 2006. More women were included in non-American studies than in American studies (33 vs. 27%, respectively). The largest proportions of women were found in the secondary preventive studies: 43 versus 27% in the primary preventive studies. Most of the women were included in studies on hypertension (44%), diabetes (40%), and stroke (38%), and the fewest were again found in studies on heart failure (29%), coronary artery disease (25%), and lipids (28%). Sex and gender were not discussed in 70% of the primary preventive studies. It was concluded that there were still too few women included in relation to the disease prevalence. Hardly one third of the studies had a sex- and gender-specific analysis of the results, which is not optimal at all. More campaigns such as the World Heart Federation's (former American Heart Association's) 'Go Red for Women' are needed to spread the knowledge about CVD in women. The project is now running globally in 30 countries; Sweden was one of the first in Europe to start (2006).

There is therefore a pressing need to ensure that cardiovascular trials are specifically designed to include sufficient numbers of women to allow sex- and gender-specific analyses. It is a huge but important task to encourage more properly designed

studies to obtain evidence-based guidelines. Active initiative should be taken by the medical authorities. More research is needed in the areas of pathophysiology, mechanisms, the role of sex hormones, the impact of hormone-related risk factors, broken heart syndrome, treatment response, and many others.

References

- 1 Stramba-Badiale M: Women and research on cardiovascular diseases in Europe: a report from the European Heart Health Strategy (Euro Heart) project. *Eur Heart J* 2010;31:1677–1681.
- 2 Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, et al: Representation of women in randomized clinical trials of cardiovascular disease prevention. *Circ Cardiovasc Qual Outcomes* 2010;3:118–119.
- 3 World Health Organization: WHO Statistical Information System, 2008. <http://www.who.int/whosis>.
- 4 Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, et al: Risk factors of myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J* 2008;29:932–940.
- 5 Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al: Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case control study. *Lancet* 2004;364:937–952.
- 6 Kris-Etherton P, Eckel RH, Howard BV, St Jeor S, Bazzarre TL, Nutrition Committee Population Science Committee and Clinical Science Committee of the American Heart Association: Benefits of a Mediterranean-style: National Cholesterol Education Program/American Heart Association step I dietary pattern on cardiovascular disease. *Circulation* 2001;103:1823–1825.
- 7 Hagobian TA, Sharoff CG, Stephens BR, Wade GN, Silva JE, Chipkin SR, Braun B: Effects of exercise on energy-regulating hormones and appetite in men and women. *Am J Physiol Regul Integr Comp Physiol* 2009;296:R233–R242.
- 8 Lee IM, Rexrode KM, Cook NR, Manson JE, Buring JE: Physical activity and coronary heart disease in women: is ‘no pain, no gain’ passé? *JAMA* 2001;285:1447–1454.
- 9 Huxley RR, Woodward M: Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet* 2011;378:1297–1305.
- 10 Prescott E, Scharling H, Osler M, Schnohr P: Importance of light smoking and inhalation habits on risk of myocardial infarction and all cause mortality: a 22 year follow up of 12,149 men and women in the Copenhagen City Heart Study. *J Epidemiol Community Health* 2002;56:702–706.
- 11 Nilsson S, Carstensen JM, Pershagen G: Mortality among male and female smokers in Sweden: a 33 year follow-up. *J Epidemiol Community Health* 2001;55:825–830.
- 12 Almdal T, Scharling H, Jensen JS, Vestergaard H: The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Arch Intern Med* 2004;164:1422–1426.
- 13 Li TY, Rana JS, Manson JE, Willett WC, et al: Obesity as compared with physical activity in predicting risk of coronary heart disease in women. *Circulation* 2006;113:499–506.
- 14 Orth-Gomér K, Wamala SP, Horsten M, Schenck-Gustafsson K, Schneiderman N, Mittleman MA: Marital stress worsens prognosis in women with coronary heart disease: the Stockholm Female Coronary Risk Study. *JAMA* 2000;284:3008–3014.
- 15 Arslanian-Engoren C, Patel A, Fang J, Armstrong D, et al: Symptoms of men and women presenting with acute coronary syndromes. *Am J Cardiol* 2006;98:1177–1181.
- 16 Berg J, Björck L, Dudas K, Lappas G, et al: Symptoms of a first acute myocardial infarction in women and men. *Gend Med* 2009;6:454–462.
- 17 Ridker PM, Buring JE, Rifai N, Cook NR: Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;297:611–619.
- 18 Johnston N, Schenck-Gustafsson K, Lagerqvist B: Are we using cardiovascular medications and coronary angiography appropriately in men and women with chest pain? *Eur Heart J* 2011;32:1331–1336.
- 19 Kostis WJ, Moreyra AE, Cheng JQ, Dobrzynski JM, Kostis JB: Continuation of mortality reduction after the end of randomized therapy in clinical trials of lipid-lowering therapy. *J Clin Lipidol* 2011;5:97–104.

- 20 Tavriss D, Shoaibi A, Chen AY, Uchida T, Roe MT, Chen J: Gender differences in the treatment of non-ST-segment elevation myocardial infarction. *Clin Cardiol* 2010;33:99–103.
- 21 Andersson A, Sundel KL, Unden AL, Schenck-Gustafsson K, Eriksson I: A five-year rehabilitation programme for younger women after a coronary event reduces the need for hospital care. *Scand J Public Health* 2010;38:566–573.
- 22 Limacher MC: Exercise and rehabilitation in women: indications and outcomes. *Cardiol Clin* 1998;16:27–36.
- 23 Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S: Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2001:CD001800.
- 24 Statistiska centralbyran. Statistics Sweden, 2008. <http://www.scb.se>.
- 25 World Health Organization: Preventing Chronic Diseases: A Vital Investment. Geneva, WHO, 2005.

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