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Review

Risk factors for coronary heart disease: implications of gender

Jeanine E. Roeters van Lennep[a], H. Tineke Westerveld[b], D. Willem Erkelens[b], Ernst E. van der Wall[a,*]

[a]*Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands*
[b]*Department of Internal Medicine, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands*

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Abstract

It has been recognized over the past years that women form a distinct subpopulation within patients with coronary heart disease. This phenomenon should be acknowledged in the management and in the assessment of coronary heart disease. Over the past years remarkable progress has been made concerning our knowledge of cardiovascular risk factors related to gender. For instance, diabetes, high density lipoproteins and triglycerides levels have been found to have a greater impact on coronary heart disease risk in women compared to men. On the other hand, evidence showing that lipoprotein (a) is a cardiovascular risk factor seems to be stronger in men than in women. For optimal treatment and prevention of coronary heart disease it is necessary to acknowledge that it is not self-evident that women and men show simular responses to risk factors or to treatment. This review article addresses the role of cardiovascular risk factors focusing on the differential impact they might have on men and women.

Keywords: Coronary disease; Epidemiology; Gender

1. Introduction

Traditionally, coronary heart disease (CHD) has been considered as a disease predominantly affecting men and for a long time women were not included in cardiovascular research programs. Although the life-time risk of CHD is one in three for women [1], they are still not fully aware of their risk of CHD and perceive the chance of dying of breast cancer as far more likely than of CHD [2,3]. In the early 1990s more attention was focused on women with CHD. Since then an increasing number of studies have been published concerning women's cardiovascular health. Several studies reported the existence of a gender difference in the use of diagnostic and therapeutic procedures for CHD. Women were less likely to be referred for diagnostic and therapeutic procedures [4–6]. Also the prognosis for women with CHD was worse than for men [7–9]. Although most risk factors contribute to CHD in both men and women [10,11], the impact of individual risk factors might be different. The influence of the menopause on both cardiovascular risk factors and CHD is unique for women. Hence, women form a distinct subpopulation within patients with CHD. This should be acknowledged in the management and assessment of CHD. In the past years remarkable progress has been made concerning our knowledge of cardiovascular risk factors. In this review we discuss the role of cardiovascular risk factors focusing on the differential impact they have on men and women (Table 1).

2. Epidemiology

CHD is the leading cause of death worldwide [12]. The lifetime risk of developing CHD at age 40 years is 50% for men and 33% for women [1]. Over the past decades there seems to be a trend towards a decrease in cardiovascular mortality in North America and Western Europe [13]. Most studies [13–15] found that this change in mortality

*Corresponding author. Building 1, C5-P 28, PO Box 9600, Leiden University Medical Center, Albinusdreef 2, 2300 RC Leiden, The Netherlands. Tel.: +31-71-526-2038; fax: +31-71-524-8116.

E-mail address: e.e.van_der_wall@lumc.nl (E.E. van der Wall).

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Table 1
Risk factors for men and women

Risk factor	Men	Women
Total cholesterol	+++	+++
LDL	+++	+++
HDL	++	+++
Triglycerides	+	++
Apo A-I	+++	+++
Apo-B	+++	+++
Apo(a)	++	+(+)
Smoking	++	++(+)
Diabetes	++	+++
Obesity		
BMI	++	++
WHR	+++	+++
Hypertension	++	++
Family History	++	++(+)
Hormones		+++
Homocysteine	+	+
Fibrinogen	++	++
Inflammation (CRP)	+	++
Infection (HP, ChP)	–	–
Psychosocial factors	+	+

Apo(a), apolipoprotein (a); Apo A-I, apolipoprotein A-I; Apo B, apolipoprotein B; BMI, body mass index; ChP, *Chlamydia pneumoniae*; CRP, C-reactive protein; HDL, high density lipoprotein cholesterol; HP, *Helicobacter pylori*; LDL, low-density lipoprotein cholesterol; WHR, waist hip ratio.

was similar for men and women, although other reports showed that mortality trends are more favorable in women than in men [15–19]. Controversy exists about the causes of this decline in mortality. Several studies [13,20] showed no decline in the incidence of hospitalization for a first myocardial infarction, suggesting an important contribution of improvement in medical treatment and secondary prevention of myocardial infarction. On the other hand, data from the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (WHO MONICA) project indicate that the decline in case fatality of acute myocardial infarction can be explained by an absolute reduction in the incidence of this disease [16,19]. This effect might be the result of primary prevention and the modification of risk factors.

3. Risk factors

3.1. Lipids

3.1.1. Total cholesterol and low-density lipoprotein cholesterol

Total cholesterol and low-density lipoprotein cholesterol (LDL) levels in men and women are similar up to ~20 years of age [21]. In the third and fourth decades, cholesterol levels increase more sharply in men than in women [22]. Total cholesterol and LDL levels in women rise or even exceed the levels in men following the menopause [23–25]. Estrogens are potent LDL receptor-upregulating agents [26]. In the presence of low endogenous estrogen levels, LDL receptor activity is reduced. This leads to the elevated LDL concentration observed in postmenopausal women [27]. Elevated total cholesterol and LDL levels are major risk factors for CHD in both men and women [28,29]. Recent studies included a sufficient number of women to show that they respond at least as well as men to cholesterol lowering therapy [30–33]. The Scandinavian Simvastatin Survival Study (4S) showed that a reduction of high cholesterol level (range 5.5–8.0 mmol/l) in patients with CHD reduced major coronary events by 34% in both men and women [33]. In the Cholesterol And Recurrent Events (CARE) trial [34], which addressed the effect of pravastatin in patients with average cholesterol levels (6.2 mmol/l), women had a risk reduction of major coronary events which was twice as large as that in men (46 vs. 20%, $P=0.048$). Most of the primary prevention trials included only middle-aged men. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) is the only study with a considerable number of women [35]. This study assessed the effect of lipid lowering therapy in men and women without clinically evident cardiovascular disease and with average cholesterol (mean total cholesterol 5.71 mmol/l) and LDL levels (mean LDL 3.89 mmol/l), but below-average high-density lipoprotein cholesterol (HDL) levels (0.94 mmol/l for men and 1.03 mmol/l for women). This study included 997 women (15% of the study population). After a follow-up period of 5.2 years, the incidence of first acute major coronary events was reduced by 37% in the group who received lovastatin compared to those who received placebo. Although the beneficial effect of treating elevated levels of cholesterol and LDL in both genders is well established in secondary prevention, the use of lipid lowering drugs in primary prevention will probably be reserved for high-risk patients for economic reasons.

3.1.2. High-density lipoprotein cholesterol

High-density cholesterol (HDL) levels are reported to correlate closely and inversely with the risk of CHD [36–38]. HDL levels are higher in women than in men from young adulthood onwards [24,39,40]. Some studies [41,42], but not all [24,25,43], have described a decrease in HDL levels following the menopause. The loss of protection from HDL is considered to be a major factor for the increased coronary risk in postmenopausal women. It has been suggested that low levels of HDL are more predictive of coronary artery disease in women than in men [38]. Because of the higher level of HDL in women, a modification of the current National Cholesterol Education Program (NCEP) guidelines has been proposed with more aggressive targets for HDL in women [44]. Although it was initially presumed that low HDL levels pose no risk in the absence of elevated LDL cholesterol, total cholesterol or elevated triglyceride levels, several studies have recently shown that an ‘isolated low HDL’ level represents a

significant risk of CHD [45–47]. The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) showed that a modest increase in HDL levels in men with CHD and normal LDL levels ($\leq$3.6 mmol/l) resulted in a significant reduction in the risk of major cardiovascular events [46]. So far, similar data for women are not available. In conclusion, the HDL level is an important factor affecting atherosclerosis. It might be appropriate to apply a gender specific approach in interpreting HDL levels because of the higher absolute levels and possible greater impact of HDL in women.

3.1.3. Triglycerides

Elevated levels of triglycerides have been associated with an increased risk of CHD in men and women [48,49]. However, the role of plasma triglycerides as an independent risk factor is still elusive. First, there are methodological difficulties in interpreting triglyceride levels because of high biologic intra- and inter-individual variability. Second, strong interactions exist between triglycerides and other lipid factors. Elevated triglycerides are often seen with lower HDL levels and this combination has been associated with increased CHD risk [50]. A meta-analysis including more than 46 000 men and nearly 11 000 women showed for men and women, respectively, a 32 and 76% increase in cardiovascular risk associated with a 1-mmol/l increase in triglycerides. After adjustment for HDL and other risk factors, these risks were decreased to 14% in men and 37% in women, but this remained statistically significant for both genders [51]. It seems that elevated triglycerides increase cardiovascular risk more in women than in men, implying a gender difference in the role of triglycerides in atherosclerosis [52]. Therefore, analogous to the gender-specific approach for HDL, the latest NCEP guidelines have suggested that that the optimal levels for triglycerides may be lower for women [44]. There is accumulating evidence that postprandial triglyceride levels are of major importance in determining cardiovascular risk [53–55] and that premenopausal women have lower triglyceride levels than men and postmenopausal women [56–58].

3.1.4. Apolipoproteins A-I and B

Apolipoprotein A-I (apo A-I) is the major apolipoprotein of HDL. Apo A-I has previously been reported to be a better marker for CHD than HDL [59–61]. Biologically, this finding is plausible because not all HDL particles are equal in size. Two subclasses of HDL can be recognized, HDL particles that only contain apo A-I, lipoprotein A-I, and particles that contain both apo A-I and apo A-II, lipoprotein A-I/A-II. In general, lipoprotein A-I is considered to be more protective against CHD than lipoprotein AI/A-II [62]. Therefore, apo A-I levels may be a better marker for functional reverse cholesterol transport than HDL. Because HDL appears to be a less adequate predictor for CHD for men than for women, apo A-I measurement might be particularly valuable for men. This was supported by data from Kwiterovich et al. who found that the level of apo A-I but not the level of HDL was an indicator of future CHD in 99 men and 104 women [59].

Atherogenic lipoproteins including LDL particles, very low density lipoprotein (VLDL) particles, and remnants of triglyceride-rich particles each contain one molecule of apo B [63]. Consequently, apo B gives an accurate estimation of the total number of atherogenic particles [64]. The composition of LDL particles, each containing one molecule of apo B, is heterogeneous because of the variable content of cholesterol. Smaller and denser LDL particles are more atherogenic than larger, more buoyant ones [65,66]. Therefore, apo B could be superior compared to LDL in determining CHD risk. This impression has been supported by a number of studies in both women and men [59,67,68].

Former problems with measuring these apolipoproteins have been overcome with the standardization of apo A-I and apo B [69,70]. In conclusion, both apo A-1 and apo B might be better predictors for CHD in men and women and may therefore be more suitable for cardiovascular risk assessment than traditional lipid factors.

3.1.5. Lipoprotein(a)

Lipoprotein(a) consists of an LDL particle bound by a disulfide bridge to apolipoprotein(a) that has a structure resembling plasminogen. Lipoprotein(a) levels are independent of other lipid parameters [71]. In women, circulating lipoprotein(a) levels increase after the menopause just like the other lipid parameters (triglycerides, LDL and total cholesterol) [72].

Most cross-sectional, case-control studies and prospective studies show that lipoprotein(a) is a risk factor for CHD. Prospective studies have reported that elevated levels of lipoprotein(a) (in particular of lipoprotein(a) levels of $>$0.30 g/l) are associated with an increase in CHD even after adjustment for other cardiovascular risk factors in men [73–75] and in women [73,76]. Other data indicate that lipoprotein(a) is not as strong a risk factor for CHD in women as in men [77,78] The results of these studies might have been biased because of the low CHD event rate in women. Elevated lipoprotein(a) levels are difficult to treat. The only drugs that lower lipoprotein(a) levels are nicotinic acid, and, as recently shown, hormone replacement therapy (HRT) [79]. The reports on the effect of fibrate therapy on the synthesis of lipoprotein(a) are conflicting [80–82]. In conclusion, lipoprotein(a) can be regarded as a cardiovascular risk factor, but the evidence in women is not as strong as in men. More data are necessary to determine whether gender-related differences are clinically relevant.

3.2. Smoking

Smoking is the most important preventable cause for the development of CHD among men and women [83]. In the United States 23.9% of women and 27.3% of men older than 18 years are current smokers [84]. A clear dose–response relationship exists between the number of cigarettes smoked and the increase of risk of CHD [85,86]. Fortunately, smoking cessation can considerably reduce the risk of CHD in both genders [87,88]. After 2–3 years of abstinence the level of risk of ex-smokers is similar to that of never smokers regardless of the amount or duration of cigarettes smoked or the age at which they stopped smoking [87]. This beneficial effect is sustained at an older age [89,90]. A number of studies [10,85,91] showed that smoking appears to be a stronger risk factor for myocardial infarction in middle-aged women than in men. Smoking has also been associated with an early menopause [92–94]. A recent study showed that current smoking decreased the age of the natural menopause by 2 years and past smoking by 1 year [94]. In both men and women smoking has an unfavorable affect on plasma lipoproteins, in particular a decrease in HDL [10,91,95]. Some studies have suggested that this harmful effect on HDL is more pronounced in female smokers than in male smokers [10,95]. In conclusion, smoking is a very important modifiable risk factor that seems to have at least a similar impact in women and men.

3.3. Hypertension

Elevated systolic blood pressure is, as risk factor, at least as powerful as diastolic blood pressure [96,97]. Isolated systolic hypertension, defined as a systolic blood pressure $\geq$160 mmHg and a diastolic blood pressure $<$90 mmHg [98], is associated with an increased risk of cardiovascular disease, stroke and all-cause mortality in men and women independent of other risk factors [99,100]. Isolated systolic hypertension is an indication of loss of arterial elasticity, and its prevalence increases with age for both sexes [101]. However, the rise in prevalence of isolated systolic hypertension is steeper for women than for men $\geq$55 years of age [102]. Isolated systolic hypertension is a common finding in elderly women, with a prevalence of 30% in women over 65 years of age [103]. The Systolic Hypertension in the Elderly Program (SHEP) [98] has shown that both men and women with isolated systolic hypertension benefit from blood pressure control. Antihypertensive treatment reduced the incidence of stroke and non-fatal myocardial infarction (36 and 27%, respectively). Large long-term clinical trials have included both men and women and a meta-analysis of these studies did not show significant gender differences in blood pressure and clinical outcome [104]. The current guidelines recommend antihypertensive therapy for a heterogeneous population including pregnant women or women on oral contraceptives, elderly individuals and persons with isolated hypertension [105]. However, with the large number of persons who are now considered for anti-hypertensive treatment, risk stratification is necessary for this treatment to remain cost-effective. In conclusion, hypertension is a highly prevalent risk factor, especially in the elderly. Because of the tendency of risk factor clustering in the presence of elevated blood pressure, hypertension is an important marker for patients with a high-risk profile. The current guidelines for the treatment of hypertension have incorporated this view and emphasize risk factor intervention [105,106].

3.4. Diabetes

Diabetes is a powerful risk factor for CHD. Up to 75–80% of adult diabetic patients die of cardiovascular diseases, and 75% of these deaths are caused by CHD [107]. Compared to diabetic men, who have a two-fold to three-fold increased risk of CHD, diabetic women are reported to have a three-fold to seven-fold increased risk [108–111]. Thus, diabetes seems to eliminate the premenopausal 'female advantage' in the prevalence of CHD [112]. Mortality from myocardial infarction is significantly higher in diabetic women than in non-diabetic women and in men with or without diabetes [113]. Lipid abnormalities frequently found in patients with diabetes type II are elevated triglycerides, low HDL levels and small dense LDL [114]. Goldschmidt et al. [108] showed that decreased HDL and very low-density lipoprotein levels predict CHD mortality in diabetic women but not in non-diabetic women or diabetic and non-diabetic men. Because of the poor prognosis for women with diabetes, aggressive treatment of cardiovascular risk factors, such as dyslipidemia, should be a high priority.

3.5. Obesity

Obesity is an independent risk factor for CHD in women as well as in men [115,116]. Willet and colleagues [115] showed in data from the Nurses' Health Study that even women with a modestly increased body mass index ($>$25 and $<$29 kg/m^2) had twice the risk of CHD as the leanest women (body mass index $<$21 kg/m^2). Independent of overall obesity, the distribution of body fat is a determinant of cardiovascular risk. It has been shown that truncal obesity, the so-called android habitus, confers a far higher risk than the peripheral or 'gynecoid' body fat distribution [117–119]. Waist-hip ratio and waist circumference are highly correlated to the risk of CHD [117]. Rexrode and colleagues showed that women with a waist-hip ratio of 0.76 or higher or waist circumference of $\geq$76.2 cm had a markedly increased cardiovascular risk even after adjustment for hypertension, diabetes and elevated cholesterol levels [117]. Weight reduction was associated with an improvement in risk factors and favorable changes in

triglycerides, high and low-density lipoprotein levels and blood pressure [120,121]. These observations suggest a beneficial effect of weight reduction, but direct evidence that weight loss reduces the risk of CHD is currently not available. Because of the difficulty of achieving and maintaining weight loss, the prevention of obesity is of utmost importance.

3.6. Family history

Familial aggregation of CHD has been studied in both women and men [122–124]. Research on family history as a cardiovascular risk factor is complicated by methodological factors such as identification and the definition of a positive family history and endpoints. These factors can act as confounding elements in comparing study results. Also, the interaction between known risk factors and family history is evident. Therefore, the underlying mechanism of how family history acts as a risk factor and the separate impact of genetic and environmental factors is still controversial. Several studies showed that a parental history of CHD increases the chance of premature onset of CHD in men [125]. As with most risk factors, results in women became available much later. An early study showed that an independent effect on cardiovascular death was only present in men of <60 years but not in women [126]. This study, however did not include a sufficient enough number of women to detect a significant relationship between family history and risk of CHD. More recent studies have reported that a family history of CHD is also a risk factor for women [122–124,127,128]. The Nurses' Health Study showed an age-adjusted risk of non-fatal CHD of 2.8 and an age-adjusted risk of fatal CHD of 5.0 in women with a parental history of myocardial infarction before 60 years of age [127]. Recently, some studies showed that the risk of premature CHD was higher in women compared to men [122,124,129]. A Finnish study showed that 76% of the women and 62% of the men who survived a myocardial infarction had first degree relatives with CHD at <65 years of age. In particular, the sisters of female patients were at risk for CHD [124]. Jousilahti et al. [122] showed that the adjusted risk of a first coronary event was markedly higher for women than for men (relative risk 2.64 vs. 1.64, respectively). However, the practical implications of identifying a positive family history as a risk factor are uncertain. At this moment the only application is identifying individuals who are at risk. In the future genetic research may be able to identify different subtypes in the familial risk and this could be used for targeted counseling and therapy to prevent CHD.

In conclusion, women and men with a positive family history have an increased risk of premature coronary events. Recent results indicated that this risk might be higher in women compared to men. To date, neither the evaluation nor the interpretation of family history as a risk factor for CHD are completely established.

3.7. Homocysteine

Over the past 10 years many studies have demonstrated a relationship between elevated levels of total plasma homocysteine and increased risk of CHD [130]. For a long time data in women were scarce. When women were included, they often formed a small percentage of the population. In addition, in most cases estimations of vascular disease risk were given for the pooled sexes [131]. Several studies that did include women have shown that the risk of vascular disease associated with elevated homocysteine levels was at least as strong in women as in men [131–134]. Meta-analysis showed that the summary odds ratio, based on a 5-μmol/l increment in plasma homocysteine, was 1.6 for men and 1.8 for women [134]. Homocysteine levels rise with age, and fasting homocysteine levels appear to be generally lower in women than in men [131]. Higher homocysteine levels in men might be due to both their larger muscle mass since most plasma homocysteine is formed in conjunction with creatine-creatinine synthesis. Furthermore, a homocysteine-lowering effect of estrogens has been reported in some studies [135,136]. This latter mechanism might also explain why some studies found that the levels of homocysteine in postmenopausal women were higher than in premenopausal women and even men of a similar age [137,138]. It has been suggested that the lower levels of homocysteine in premenopausal women contribute to the lower incidence of vascular disease [139]. However, controversy still exists as to whether elevated homocysteine is a cause or a consequence of CHD. The majority of prospective studies in individuals initially free of CHD failed to show a significant association between elevated homocysteine and CHD incidence [140]. On the other hand, recent evidence suggests that hyperhomocysteinemia is an independent risk factor for arterial endothelial dysfunction and might therefore act as pathogenic factor in the development of vascular disease [141].

3.8. Fibrinogen

The haemostatic system plays an important role in the pathogenesis of atherosclerosis. Several studies have demonstrated a significant association of fibrinogen level and cardiovascular disease in men and women [142–144]. Plasma fibrinogen levels are higher in women and increase with smoking, age, post-menopausal status, obesity and use of oral contraceptives [145–147]. Smoking cessation, alcohol use and weight loss have a lowering effect on fibinogen levels [145,146]. In the Framingham study, the risk for CHD associated with fibrinogen diminished with age in women but not in men [148]. After the menopause, levels of fibrinogen increase, but as antithrombotic factors like antithrombin III and plasminogen increase, the net effect of the menopause is unclear [149]. Several drugs including fibrates, propranolol, nislodipine and ticlopidine

[150] and HRT have been reported to lower fibinogen levels [151]. In conclusion, fibrinogen is an important cardiovascular risk factor that can be modified by external factors (e.g. drug therapy), life style and the female hormonal status.

3.9. Infections

The possible role of chronic infections and CHD has been investigated in a number of studies. Most of these studies relate to *Helicobacter pylori* and *Chlamydia pneumoniae*. A great number of studies found evidence for an association between *C. pneumoniae* antibodies and CHD [152]. More recently, *C. pneumoniae* studies have been published both supporting [153,154] and refuting [155–157] its role in the pathogenesis of CHD. Most of these studies have only included men or did not consider women separately. Two studies carried out a separate analysis for men and women. One study found a possible association between circulating *C. pneumoniae* DNA and CHD in men only [153]. The other study found that serological evidence of an *C. pneumoniae* infection was associated with an atherogenic lipid profile in men but not in women [158]. However, because of the relatively small number of women included, these results might be coincidental and lack statistical power. Therefore, further research is needed to investigate these associations. Of the five prospective studies [159–163] which examined whether *H. pylori* was associated with cardiovascular disease, three studies [159,161,163] included women. None of these prospective studies found any statistically significant evidence for a relationship between CHD and *H. pylori* infection. In summary, data are not available to show that infective agents are of major importance as risk factors for CHD in either men or women.

3.10. Inflammation

Inflammation as assessed by C-reactive protein (CRP) levels has been demonstrated to predict cardiovascular events in healthy middle-aged [164,165] and elderly [166] men. Recently, the predictive value of CRP has been investigated in middle-aged and elderly women [166,167]. Interestingly, both studies found that the relative risks associated with CRP were higher for women than for men. It remains to be investigated whether these results reflect true sex differences or whether they are chance. In a recent study, Ridker et al. [168] raised the possibility of adding CRP measurements to the standard lipid screening, since CRP was the most significant and strongest risk factor for cardiovascular events in healthy middle-aged women compared to measurements of homocysteine, lipids and apolipoproteins. In conclusion, evidence of the importance of CRP as marker for future CHD is becoming more convincing for women.

3.11. Psychosocial factors

Psychosocial factors such as socio-economic status and social support have been frequently linked to CHD in both men and women [169–172]. Although initially data for women were scarce and inconclusive, several studies have addressed the role of psychosocial issues for women [169,172,173]. A low education level has been associated with an increased incidence of CHD, mainly because of the strong inverse correlation of atherogenic risk factors and education attainment. It is a consistent finding that men and women with lower education have a higher incidence of elevated blood pressure, total cholesterol, body mass index and current smoking [174–176]. The psychosocial work environment also seems predictive for future CHD. The Whitehall II study showed that men and women with low job control, either self-reported or independently assessed, had a higher risk of newly diagnosed CHD [177]. Subjects with low job control had an odds ratio for any subsequent coronary event of 1.93 compared to subjects with high job control. This association could not be explained by employment grade or classic coronary risk factors [177]. In conclusion, these findings support the significance of psychosocial factors for CHD for both men and women.

3.12. Estrogens

Unique to women is the influence of their hormonal status on CHD. In comparison with men of a similar age and postmenopausal women, the incidence of CHD is significantly lower in premenopausal women suggesting that endogenous estrogens have a protective effect on the development of CHD [94,178,179]. Estrogens affect the atherosclerotic process through a variety of mechanisms. Estrogens have been reported to have a lowering effect on total cholesterol and LDL [23,25,180], lipoprotein(a) [72] and homocysteine [135,136] levels. HDL levels are increased [181–184] and postprandial lipid metabolism improved by estrogens [185]. Moreover, estrogens have an acute vasodilatory effect on the vessel wall and an atheroprotective effect involving inhibition of smooth-muscle cell proliferation [186]. The role of exogenous estrogens is controversial. Meta-analyses of multiple observational studies suggested a 35–50% reduction of CHD associated with the use of estrogens after the menopause [187]. However, two double blind randomized trials [181,184] addressing this topic both failed to demonstrate a favorable effect of HRT for the secondary prevention of CHD. The Hormone Estrogen Replacement Study (HERS) [184], which compared HRT consisting of estrogen plus progestin with placebo in women with CHD showed no overall benefit of HRT on coronary death and non-fatal myocardial infarction, despite an 11% decrease in LDL and a 10% increase in HDL. Moreover, an increase was seen in the relative risk of venous thrombotic events and

gallbladder disease of 2.89 and 1.38, respectively. Interestingly, a time trend was seen with more coronary events in the 1st year with HRT, and fewer in years 4 and 5. Therefore, the HERS investigators recommended not initiating this hormone regiment for secondary prevention of CHD, but given the late benefit of long-term use, it could be appropriate to continue HRT for women who already use this therapy. Recently a double-blind placebo controlled trial examined the effect of estrogen, estrogen with progesterone or placebo on the progression of coronary atherosclerosis in women with CHD [181]. No effect was found for estrogen alone or estrogen in combination with progesterone on the progression of coronary atherosclerosis. Despite these landmark studies, many issues concerning hormone use in postmenopausal women are still unresolved. Estrogen therapy might be more protective in preventing atherosclerosis than in slowing down the progression of established disease. No data for estrogen therapy in primary prevention are currently available. The Women's Health Initiative has randomized 27 500 postmenopausal women to conjugated equine estrogen with continuous progestin in a primary prevention trial; results are awaited in 2005 [188]. A new therapeutic approach is the use of Selective Estrogen Receptor Modulators (SERMs), non-hormonal agents which share the effects of estrogen that are favorable on bone and the cardiovascular system but not in other tissues such as the breast and endometrium [189]. In healthy menopausal women raloxifen had a favorable effect on cardiovascular risk by decreasing LDL, fibrinogen and lipoprotein(a) levels [189]. Currently ongoing is the RUTH (Raloxifen Use for the Heart) trial which aims to enroll 10 000 post-menopausal women, with a scheduled follow-up period of ~5 years [190]. In conclusion, at this time the benefit of exogenous estrogens for the prevention of CHD is unconvincing. Therefore, the use of HRT is as yet not recommended, particularly since there are other agents (e.g. statins) that have been indisputably proven to be beneficial in risk factor management. However, it should be realized that in the decision whether or not to prescribe HRT, cardiovascular issues are only one factor among others such as osteoporosis, peri-menopausal symptoms and cancer concerns.

4. Conclusions

In this review an update is provided on the role of a number of risk factors with emphasis on possible differences between men and women. Except for female hormonal status, no risk factor has been recognized as acting on one gender but not on the other. This finding indicates that the pathogenesis of CHD is very similar for men and women. Yet, diabetes, HDL and triglycerides levels have been found to have a greater impact on CHD risk in women compared to men. In addition, there are indications that risk factors such as smoking, family history and inflammation characterized as C-reactive protein, have a more negative influence on CHD in women than in men. On the other hand the evidence showing that lipoprotein(a) is a cardiovascular risk factor seems to be stronger in men than in women. The majority of cardiovascular risk factors show no important differences between the genders. For optimal treatment and prevention of CHD it is necessary to acknowledge that it is not self-evident that women and men show a similar response to risk factors or to treatment. Therefore, it is essential that studies present results according to gender, in order to comprehend to what extent CHD prevention measures are similar for men and women.

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