Coronary atherogenic risk factors in women

V. Stangl, G. Baumann and K. Stangl

Medizinische Klinik mit Schwerpunkt Kardiologie, Angiologie, Pneumologie, Charité, Campus Mitte, Humboldt-Universität Berlin, Germany

Introduction
Cardiovascular disease, primarily coronary heart disease (CHD), remains the most frequent cause of death in Western industrialized nations: nearly one in every two deaths are currently attributable to CHD. Since the 1980s, gender-specific trends have become apparent in these statistics: whereas coronary–vascular mortality has appreciably decreased among men, women have conversely experienced a continuous rise in rates of death from CHD. In 1998 in Germany, for example, there were 94 700 deaths from coronary vascular disease among women (225·3 per 100 000), but only 84 015 among men (210·1 per 100 000)

One explanation of this trend may lie in the fact that modern medicine over the past 30 to 40 years has considered CHD a ‘male disease’, and that classical epidemiological studies have consequently concentrated primarily on men. Fortunately for men, this phenomenon, its associated preventive measures, and improved therapeutic approaches have signified a decrease in mortality among men. The contrary development among females may be attributed to two factors: that insights gained in research for men are not automatically applicable to women, and/or that women less often enjoy application of advances in possibilities for diagnosis and therapy resulting from these insights. Since the 1980s, moreover, changes have taken place in the risk factor profile in women and men. Although the overall prevalence of risk factors such as hypertension, overweight, and smoking remains greater for men, the total increase in such risk factors has in recent decades been greater among women to a pronounced degree. This development has become especially apparent in smoking, which has increased among young women in contrast to a decreasing trend among men.

Dyslipidaemias
Cholesterol is predominantly transported in the plasma in three major apolipoprotein-B-containing lipoprotein classes: LDL-cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), and high density lipoprotein cholesterol (HDL-C). Lipoprotein (Lp) (a) is another apo-B-containing lipoprotein involved in the atherogenic process. There are highly apparent gender-specific differences in lipid status, depending on menopausal circumstances. Before the menopause, total cholesterol (TC) and LDL-C are generally lower in women than in men. HDL-C, however, is as a rule higher among women before menopause. After menopause, TC and LDL-C increase in women and achieve their maxima between the ages of 55 and 65 years: approximately a decade later than among men.

Key Words: Atherosclerosis, coronary heart disease, risk factor, female, gender.
National Heart, Lung and Blood Institute (NHLBI), with data collected in 1995 from 86,000 women under 65 years disclosed that women with TC values over 240 mg. dl\(^{-1}\) suffered a risk of CHD 2.4 times greater than that of control group women (below 200 mg. dl\(^{-1}\)). For women above 65, however, the relative risk was only 1.12, and therefore barely evident\[2\]. The overall significance of TC levels for atherogenic development among women is evidently slight. Neither the Framingham Study nor the MONICA Study revealed a significant relationship between the level of TC and atherogenic risk, or between TC and the severity of CHD\[3–5\]. It was only in the group of 40- to 50-year-old women that a closer correlation became apparent\[6\]. Although the CHD risk for TC levels among women above 204 mg. dl\(^{-1}\) at the beginning of the study was also greater than among control persons with normal cholesterol levels, this risk was appreciably less than among likewise hypercholesterolaemic men for any elevated TC value selected\[6\]. Better prediction is reliably be assumed for a TC/HDL-C ratio greater than 4.5\[7,8\].

In severe forms of familial hypercholesterolaemia, e.g. with various homozygous variants of LDL receptor deficiency, and with excessively elevated TC levels (between 600–1200 mg. dl\(^{-1}\)), gender-specific differences are hardly evident between male and female cases in which CHD is manifested for both genders at a very early age. In contrast, however, the myocardial infarction rate with heterozygous forms is appreciably lower among women (12%) than among men (50%)\[9\].

**HDL cholesterol (HDL-C)**

According to National Health And Nutrition Examination Surveys (NHANES), the HDL-C level among women over 20 years is about 10 mg. dl\(^{-1}\) higher than among men (56 mg. dl\(^{-1}\) vs 47 mg. dl\(^{-1}\))\[9\]. This difference may be considered a gender-specific protective factor. As total fraction, HDL-C in all probability remains extensively constant after the menopause as well\[10\], although smaller studies have described postmenopausal decreases\[11,12\]. There is evidence, however, that the HDL2 subtraction, considered especially cardioprotective, does in fact diminish after menopause\[12\]. LDL-C and Lp(a), on the other hand, rise. Studies conducted by Gordon et al. have demonstrated the great significance of HDL-C for women. Their analyses have computed data from four major prospective studies: the Framingham Study, the Lipid Research Prevalence Mortality Follow-Up Study, the Coronary Primary Prevention Study, and the Multiple Risk Factor Intervention Trial. These results revealed that, among white participants, an increase in HDL-C by 1 mg. dl\(^{-1}\) reduces CHD risk by 2% for men, but by 3% for women\[9,13\].

In addition to the absolute HDL-C value, the ratio of TC to HDL-C is likewise highly significant. The Framingham Study disclosed a definite positive correlation between the TC/HDL-C quotient and coronary risk: over an observation period of 8 years, the risk was less than 7% for a quotient less than five; 12% for quotients between five and seven; and 20% for quotients greater than seven\[14,15\]. Findings in the Prospective Established Populations for Epidemiologic Studies of the Elderly (EPESE) on 2527 women over 71 years (with a follow-up over 4.5 years) revealed that an increase in the TC/HDL-C quotient by one unit signifies a 17% increase in CHD risk\[16\].

Low HDL-C values (i.e. below 35 mg. dl\(^{-1}\)) must be considered an independent, relevant atherogenic risk factor for women. The prevalence of HDL-C values below 35 mg. dl\(^{-1}\) is estimated at 5% among non-fasting women in the U.S.A.\[9\]. Low HDL-C values among men are an even more definite risk predictor of CHD\[17\]. This applies especially to older women: data from the EPESE Study have shown that women with HDL-C values below 35 mg. dl\(^{-1}\) are subject to CHD risk twice as high as that for female controls with values ≥60 mg. dl\(^{-1}\)\[16\].

**LDL cholesterol (LDL-C)**

In contrast to peri- and postmenopausal alterations in the HDL-C level (slight in any case), LDL-C increases by about 2 mg. dl\(^{-1}\) year\(^{-1}\) between the fifth and seventh decades of life. LDL-C values can accordingly lie above those of men of the same age\[10,15,18\]. The NHLBI analysis published in 1992 compared women with LDL-C values over 160 mg. dl\(^{-1}\) with those with LDL-C less than 140 mg. dl\(^{-1}\)\[19\]. These findings disclosed that relatively young women (under 65 years) with elevated LDL-C values had a CHD risk 3.3 times that of women with normal levels, whereas women over 65 with elevated LDL-C were no longer subject to such excess risk\[9\].

LDL is a heterogeneous category of lipoproteins consisting of at least four major subspecies according to molecular properties, size and density: LDL-I is the largest and least dense, and LDL-IV is the smallest and most dense. An abundance of small, dense LDL particles, also termed pattern B, is associated with an atherogenic milieu and includes features of the insulin resistance syndrome. LDL pattern B contrasts with large buoyant LDL, termed LDL pattern A, without association to the atherogenic milieu of pattern A\[20–23\].

LDL pattern B, in which small dense LDL is predominant, is reported in 25% of the population but is less frequent in women\[24,25\]. However, comparison of pre- and post-menopausal women demonstrated more small dense LDL in postmenopausal women indicating that menopausal transition is associated with an increase in this LDL subtraction\[26\]. Beside the association of small dense LDL with features of the insulin resistance syndrome, the potential atherogenicity of this LDL subtraction may be explained by the fact that it is more easily oxidised and its smaller size facilitates penetration of the arterial wall\[27\]. There is evidence that small, dense...
Lipoprotein (a)

During recent years, lipoprotein (Lp(a)) has attracted increased attention as a cardiovascular risk factor. Lp(a) consists of an LDL particle linked by a disulfide bond to apoprotein B-100. Lp(a) possesses great structural homology with the fibrinolytic proenzyme plasminogen. This has led to the hypothesis that Lp(a) competes in endothelial cells for plasminogen bonds. Reports of in vitro findings have furthermore demonstrated that Lp(a) blocks plasminogen activation by tissue plasminogen activators and, in turn, prevents elimination of fibrin by the vessel wall as a result of inhibition of the local thrombolytic activity. Lp(a) furthermore evidently accelerates the phenotype change of macrophages in foam cells. These effects allow the assumption that Lp(a) could play a causal role both in atherogenesis as well as in thrombogenesis.

A number of studies conducted for women and men have produced substantial evidence that Lp(a) represents an independent risk factor for CHD. These findings have described associations of high Lp(a) with the progression, extent, and severity of CHD, as well as with poorer prognosis after myocardial infarction.

Elevated Lp(a) values (>0.3 mg·ml\(^{-1}\)) among women represent an independent atherogenic risk factor in both pre- as well as post-menopausal cases. The CHD risk appears to worsen if high Lp(a) values occur in combination with unfavourable changes in the lipid profile. For women under 60 years the combination of elevated Lp(a) (>0.55 mg·dl\(^{-1}\)) and a TC/HDL-C ratio >5.85, for example, was associated with dramatic CHD excess risk (>100). Another study revealed excess risk among women who, in addition to already elevated Lp(a) (>0.55 mg·dl\(^{-1}\)), demonstrated either excessive LDL-C (>5 mmol·l\(^{-1}\)) or abnormally low HDL-C (<1.15 mmol·l\(^{-1}\)). There is some evidence that elevated Lp(a) levels among premenopausal women are associated with a 5-fold increase in risk for acute coronary events.

Hypertension

Arterial hypertension afflicts up to 20-40% of the adult population in Western industrialized nations. With this degree of endemic prevalence, it represents a political health challenge of the greatest order of magnitude. For both genders, hypertension is one of the most serious atherogenic risk factors, in which (according to the Framingham Study) the systolic blood pressure plays a more significant role than does the diastolic.

The prevalence of hypertension is rare among young women, but substantially increases after menopause. Women with hypertension experience a risk of developing CHD that is 3-5 times that of female controls with normal blood pressure. However, data from the Framingham Study have evidenced that hypertensive women enjoy a better prognosis than do hypertensive men, and that they more rarely develop CHD.
New data from the Framingham Study have revealed that elevated blood pressure — even if it is still formally within the normal range — is associated with cardiovascular risk greater than that for women with low-normal values. In concurrence with these findings, Nanchanal et al. disclosed in a cross-sectional study conducted on no fewer than 14,000 healthy women between 30 and 64 that the risk of developing CHD during the following 10 years of their lives was closely related to blood pressure level, beginning even in the so-called normotensive range. The risk for women in the high-normal blood-pressure range, for example, was already four times that of women in the low-normal range — whereas hypertensive women, even those under unsatisfactory blood pressure medication, were exposed to CHD risk eight times higher. For women with inadequate therapy, the risk was almost 19-fold.

A major problem is related to the fact that hypertension as an isolated phenomenon is rare, and that it frequently occurs in concert with further factors of risk. In the Framingham Study less than 20% of the hypertensive women suffered from high blood pressure that was not combined with high TG and LDL-C levels, glucose intolerance, hyperinsulinaemia, abdominal fat distribution patterns, or left-ventricular hypertrophy. These findings clearly reveal that the number of risk factors in addition to hypertension exerts crucial influence on cardiovascular risk. Among men, coronary events have been related to clusters of two or more additional risk factors in 30% of cases; among women, the proportion is much higher: 70%.

The use of oral contraceptives must be considered critical among female smokers. In a study published during the 1980s (a period in which hormone dosage in oral contraceptives, to be sure, was presumably higher than today), the combination of oral contraception and consumption of up to 15 cigarettes per day was associated with a 3-5-fold increase in coronary risk; for women who smoked more than 15 per day, the increase rose to 20-fold.

Despite widespread attempts to ignore evidence, the insight has by now gained general acceptance that passive smoking also must be considered a coronary risk factor for women and men: one associated with a 30% excess risk. In the U.S.A. it is believed that passive smoking represents the third most frequent preventable cause of death.

Smoking

Smoking is indisputably an important atherogenic risk factor, especially for peripheral arterial occlusive disease, in which it increases the risk by seven-fold. In addition, smoking exacerbates the risk of coronary vascular disease by at least a factor of two. Tobacco smoke is directly and indirectly atherogenic as a result of many and various mechanisms. It may induce coronary spasms, for example, and it has prothrombotic properties. Strong evidence exists for the assumption that tobacco smoke is likewise responsible for alterations in blood rheology, increased LDL-cholesterol oxidation, platelet aggregation, elevation in fibrinogen levels, as well as impairment of endothelial functions and of the lipid status, with reduction in HDL-C. Among women, moderate nicotine abuse is responsible for 1-7-fold elevation of myocardial infarction risk; for heavy smoking, the elevation is four-fold. The most recent data from the Nurses’ Health Study (NHS) have also shown a definite dose relationship between nicotine consumption and coronary risk among women. Data collected over a period of 25 years revealed a 1·5-fold greater CHD risk for former female smokers, a three-fold risk for women who smoked one to 14 cigarettes per day, and a 5·5-fold risk for over 14 per day.

Not least the result of antismoking campaigns, the percentage of smokers, including women, in the population has decreased over the past three decades in Western industrialized countries: a prime example is in the U.S.A., with 25% less smoking. Nevertheless, various trends must be differentiated here, according to a number of social, educative, and ethnical factors. The Coronary Artery Risk Development in Young Adults (CARDIA) study, for example, has reported that smoking has decreased among young white women and men between 18 and 30 years, regardless of their level of education, during the study period between 1986 and 1996. There was no change reported for black women, however, and smoking actually increased among black men. In contrast, another publication has reported an alarming increase in smoking among the subgroup of female teenagers.

Diabetes

Type II diabetes mellitus is a first degree cardiovascular risk factor. A recent Finnish study has emphasized its significance by the following report: among type-II diabetics studied, although they had not manifested CHD at the beginning of the investigation, cardiovascular mortality during the seven years of follow-up was seven times higher than for controls. Their mortality is furthermore at the same level as for non-diabetic patients with manifested CHD and with previous myocardial infarction. Among women, diabetes mellitus is one of the most eloquent predictors of CHD, and is associated with more severe consequences than for men. Men and women tend to manifest diabetes at the same age. As reported by Laakso et al., diabetic women, however, suffer from CHD risk that is up to eight times that of non-diabetic controls; among men, this factor is only as high as three. A recent meta-analysis has carefully compiled data of ten prospective studies, primarily with type II diabetics, with respect to...
their coronary mortality. These results have somewhat placed the pronounced Laakso findings into context by reporting the relative risk for women at 2·58 and for men, at 1·88[14]. These latter results, however, confirm the basically greater CHD risk for diabetic women.

There is less reported data on type I diabetes as an atherogenic risk factor. Its significance as a predictor of a definitely increased coronary vascular risk has been confirmed, however[79,80]. The recently published British Diabetic Association Cohort Study with more than 23 000 patients over an observation period of 21 years again confirmed, analogously to type II, greater risk for the type-I female diabetic. In comparison to the cardiovascular mortality of age- and gender-adjusted controls, the CHD risk of diabetic women was seven times greater in the first two decades of life, 11·3 times greater in the third and fourth decades, and 7·8 times greater in the fifth and sixth decades. The respective factors for men were significantly lower: 3·9, 5·7, and 4·7[80]. As a result, no other risk factor so dramatically demonstrates such gender-specific differences to the disadvantage of women, nor so severely attenuates their premenopausal advantages.

**Obesity**

Overweight among adults is defined as a body-mass index (BMI = weight in kg divided by square of height in m) greater than 25 but less than 30, obesity as BMI greater than 30 but less than 40, and severe obesity as over 40[81,82]. Based on this definition, there is a rising tendency toward overweight and obesity in the U.S.A. and in a number of other Western industrialized countries[83]. Also according to this definition, most recent data classify 17% of white women in the U.S.A. as obese[84]. Owing not least to its pronounced association with hypertension, insulin resistance, compensatory hyperinsulinaemia, diabetes, elevated TG levels, diminished HDL-C levels, and elevated small dense LDL-C[61,85], there is no doubt that obesity must be seen as a coronary risk factor[17,82,85].

The NHS, with almost 116 000 women studied over a period of 14 years, revealed the positive association between BMI and CHD: the coronary risk for women rises monotonically with BMI, up to a factor of 3·6 in women with BMI greater than 29 in comparison with BMI less than 21[86]. Similarly, the Buffalo Health Study found a risk for women in the top BMI quintile that was three times that of women in the bottom quintile[87]. It must be noted, however, that results of prospective studies on this topic are not uniform. The PROCAM study, for example, with no fewer than 7300 women and with a follow-up period of 8 years, disclosed that conditions revealed by the BMI do not represent an independent risk factor[88].

In addition to the BMI as an absolute figure, weight gain during development toward obesity should receive special scrutiny. In the NHS, coronary risk again rose monotonically with weight gain. Women who had gained enough weight to achieve a BMI of over 23·3, in addition, lived under coronary risk six times greater than otherwise[89].

Repeated weight loss and weight gain — weight cycling — is a well-known phenomenon. The Women’s Ischemia Syndrome Evaluation Study (WISE) revealed that 27% of women reported weight cycling[89]. The coronary significance of weight cycling is not clear. On the one hand, studies have attributed a protective effect to weight loss alone for obese patients[90]. On the other, weight fluctuations are associated with increased coronary risk[91]. Indirect indications of this phenomenon are contained in the WISE Study, which reported relevantly lower HDL-C levels for female weight cyclers with high fluctuations (over 20 lb).

In addition to excess weight measured as increased BMI, body fat composition likewise plays a special role in CHD. Certain abdominal patterns can represent independent factors associated with particularly high risks[17,92]. The atherogenic potency arising from omental fat is explained by the fact that, in addition to facilitated lipolysis, abdominal obesity is linked to features of the insulin resistance syndrome, including elevated TG, hyperinsulinaemia, hypertension, and diabetes[91,95]. Abdominal obesity is clinically expressed in terms of waist–hip ratio (WHR), or as waist circumference (the latter advocated as simpler measure)[94–96]. The NHS, as the largest study conducted heretofore on the significance of WHR and waist circumference, classified these two parameters in six categories. In comparison to a reference value of WHR less than 0·72, women with WHR only as much as over 0·76 were subject to CHD risk 2·3 times as great. For WHR over 0·88, the risk was five times greater. In comparison to the waist circumference reference category that includes values less than 71·1 cm, values over 76·2 cm were associated with risk 1·8 times as great; for more than 96·5 cm, the factor was 3·2[96]. The IOWA Health Study, which included almost 32 000 women from 55 to 69 years of age, likewise investigated WHR and waist circumference as predictors of coronary events. Women in the top WHR quintile demonstrated coronary mortality that was elevated by a factor of 2·5, and those in the highest waist circumference quintile, by 2·6. In combination with high BMI values (i.e. in the highest quintile), the prevalence of other risk factors such as diabetes mellitus was dramatically elevated by a factor of 1·9[95].

**Physical inactivity**

Physical inactivity must be considered as an atherogenic risk factor. A major meta-analysis showed that physically active persons were 50 to 70% less probable than inactive persons of developing CHD[97]. Most recent data have provided good evidence that even slight to moderate physical activity among women can achieve
favourable preventive effects. A cohort study that included almost 40 000 women over 45 between 1992 and 1995, and that followed-up on them until 1999, found that brisk walking alone for up to 1 h per week resulted in a 15% reduction in risk. Brisk walking of over 1 h weekly enabled no less than 50% reduction of coronary risk[98]. A recently published analysis in NHS 1 h weekly enabled no less than 50% reduction of resulted in a 15% reduction in risk. Brisk walking of over 1 h per week found that brisk walking alone for up to 1 h per week could reduce cardiovascular risk substantially: that any form of physical activity improves the lipid profile[101], insulin sensitivity[102], and coronary endothelial function as an integral parameter[103]. Several randomized studies on the influence of various intensities of exercise on blood pressure have revealed, furthermore, that light forms of exercise primarily reduce the systolic value, whereas moderate to strenuous exercise contributes more toward lowering diastolic pressure[104]. The Insulin Resistance Atherosclerosis Study reported on an additional positive aspect of exercise: that any form of physical activity is effective in enhancing insulin sensitivity. This report also contains evidence that exercise enhances feelings of well-being and reduces stress and anxiety[104].

C-reactive protein (CRP)

With increasing realization of atherosclerosis as an inflammatory process[105], increased investigation has taken place of the predictive value of inflammation markers such as high-sensitivity CRP (hs-CRP). Hs-CRP is a systemic inflammation marker that is hepatically synthesized and that is up-regulated by; inter alia, interleukins such as IL-1 and IL-6[106]. There is significant correlation between CRP and fibrinogen levels: a finding explained by the fact that both substances are acute-phase proteins that are synthesized in the liver. Atherogenic significance for CRP could lie in procoagulatory effects, as a result of tissue factor induction in monocytes and in complement activation[107,108]. CRP levels rise with increasing age and are higher in smokers[106,109].

An increasing number of studies have pointed out an important atherogenic role played by elevated CRP levels[106,109-111]. The Women’s Health Study disclosed elevated CRP levels among post-menopausal women who developed cardiovascular events[111,112]. In a prospective case-control study conducted throughout 3 years with over 28 000 at the beginning healthy, post-menopausal women, the same authors identified, in addition to hs-CRP, three additional inflammation markers as predictors of cardiovascular events: serum amyloid A, IL-6, and sICAM-1. Among these, hs-CRP clearly demonstrated the best predictive value[112]. Hs-CRP enabled classification of women into high- and low-risk groups, even for women who had low LDL-cholesterol values (i.e. below 130 mg . dl⁻¹). There is evidence, furthermore, that the CRP level rises with the severity of CHD[106].

These findings have several implications. First, they emphasize the importance of inflammatory markers as risk predictors for future cardiovascular events among women. Second, they indirectly support the viewpoint that the inflammatory reaction has important pathogenetic significance for atherogenesis. Within the context of early action taken in the form of primary prevention, assay of hs-CRP may facilitate the identification of patient groups that could especially benefit from such therapy. The Study Cholesterol And Recurrent Event (CARE) has presented an interesting aspect here with respect to the pleiotropic effects of statins: independently of lowering the cholesterol level, pravastatin reduced the hs-CRP level[113]. Interestingly, those patients with the highest hs-CRP levels at baseline experienced the greatest reduction in cardiovascular events[111,113,114]. It remains to be elucidated whether the inflammation occurring here further accelerates atherogenesis within the context of its development, or whether the inflammation should be considered a repair process. In this context, the repeated attention called to the CRP-reducing effects of statins (e.g., in the CARE study) is important: i.e. the antiinflammatory effects of these inhibitors, regardless of their effects on lipid metabolism.

The Postmenopausal Estrogen/Progestin Intervention study (PEPI) — a randomized, placebo-controlled study on the effects of post-menopausal hormone therapy on lipid status — included a subgroup analysis that determined CRP values among 365 women: basal, after 12 months, and after 36 months[115,116]. The findings are especially interesting in that hormone therapy very quickly raised the serum concentration of the inflammatory factor CRP, but other inflammatory markers did not change under hormone therapy (factor VIIIc and von Willebrand factor), or in fact decreased (i.e. E-selectin). It is of course necessary to interpret these results with caution, since the study was not designed for this endpoint. Nevertheless, these results allow one to consider whether the hormone-induced CRP elevation could — by exacerbation of the inflammatory reaction among female patients with previously existing CHD — represent a possible explanation for the unfavorable effects of hormone-replacement therapy during the first year of the Heart and Estrogen/progestin Replacement Study (HERS)[117].

Homocyst(e)ine (Hcy)

Increased discussion has taken place of whether elevated Hcy levels (>15 μmol . l⁻¹) in fact represent a cardiovascular risk factor. Elevated Hcy levels are not rare in Western industrialized nations: the Framingham Study has shown that 21% of the older participants in the study had Hcy levels >15.8 μmol . l⁻¹. It is safe to
assume that 5 to 7% of the total population suffers from hyperhomocyst(e)inaemia\textsuperscript{118,119}. Causes of hyperhomocyst(e)inaemia are primarily defects in key enzymes of Hcy metabolism: e.g. cystathionine-B-synthase and methylene tetrahydrofollic acid reductase (the latter being involved in the remethylation of Hcy to methionine).

Possible mechanisms for the atherogenic effects of Hcy include impairment of the endothelial function by promotion of activation of LDL cholesterol, procoagulatory activation, and proliferation induction of the smooth vascular muscle cells\textsuperscript{119–121}.

Results from cross-sectional and case control studies suggest that hyperhomocyst(e)inaemia is an atherogenic risk factor. Data from prospective studies, to be sure are less consistent, and positive findings\textsuperscript{122–124} as well as negative results\textsuperscript{125–127} tend to balance each other. A recently published meta-analysis by Christen covered 43 studies that examined a possible association of elevated Hcy levels and cardiovascular risk\textsuperscript{128}. The analysis of these cross-sectional and case control studies (included in this meta-analysis) revealed that persons with cardiovascular diseases consistently had Hcy levels that were higher than those of healthy controls. The evaluation of the prospective studies covered by the meta-analysis, however, eliminated the possibility of association between hyperhomocyst(e)inaemia and atherogenic risk\textsuperscript{126,127,129}, or, any still remaining association was weakened. Studies that have described an association between Hcy levels and cardiovascular risk have included only patients with already existing vascular disease\textsuperscript{123}.

But does hyperhomocyst(e)inaemia in fact play a significant role for women as a risk factor for CHD? Hcy plasma levels are consistently lower in women than in men; they are lower during premenopausal years than in postmenopausal years\textsuperscript{129–131}. Ridker et al. have prospectively studied the association of Hcy levels with CHD among women who were healthy when included in the Women’s Health Study. These results disclosed that women with elevated basal Hcy levels also demonstrated a heightened, independent risk for future cardiovascular events. This risk was, to be sure, only moderate in comparison to other established risk factors\textsuperscript{132}. The subgroup analysis in the study Atherosclerosis Risk In Communities (ARIC) produced a similar result: it found an association between high Hcy levels and CHD among women, but not among men\textsuperscript{127}. A recently published review that summarized 12 epidemiological studies found evidence that high Hcy levels represent a greater atherogenic risk factor for women than men. To be sure, only one study included significant findings\textsuperscript{129}; and it is not clear until now whether these findings truly represented gender-related effect modification, or merely reported a coincidence.

These results show that essential questions concerning the standing of hyperhomocyst(e)inaemia as an atherogenic risk factor must for the time being remain open. Controlled, randomized studies are necessary for the clarification of questions as to whether screening and the treatment of hyperhomocyst(e)inaemia are in fact advisable.

### Coagulation factors

Several epidemiological studies suggest an association between coronary risks and plasma levels and/or the activity of coagulation factors: i.e. such as fibrinogen\textsuperscript{109,133–138} and plasminogen activator inhibitor-1 (PAI-1)\textsuperscript{139–141}. These factors play a significant role in procoagulatory activation and fibrinolysis. They contribute to the formation of atherosclerotic plaques and, in cases of plaque rupture, to acute vascular occlusion by virtue of thrombus formation.

There is evidence that coagulation factors, as well as endothelial function, are particularly significant in conjunction with thrombogenesis and CHD, especially among women\textsuperscript{142}. The following observation may serve as indirect evidence of this significance: women who have suffered myocardial infarction manifest — much more often than do men — no pathological substrate during subsequent coronary angiography. This phenomenon in turn suggests a dominating thrombotic event in the infarct development\textsuperscript{143}.

### Fibrinogen

Currently, the mechanisms are not fully understood by which fibrinogen is involved in atherothrombosis. In addition to stimulatory action on proliferative vascular wall processes and cell migration, fibrinogen leads to alterations in blood rheology, increased fibrin formation, more pronounced platelet aggregation, and, in turn, to a procoagulant situation that can assume an important role in acute coronary syndromes\textsuperscript{144,145}.

Numerous studies conducted during recent years have emphasized that fibrinogen should be considered an independent cardiovascular risk factor for men. These studies have evidenced an association between high fibrinogen levels and morbidity and mortality with CHD among men. Also reported was fibrinogen association with the extent of coronary atherosclerosis\textsuperscript{109,133,135,137}.

Although the significance of high fibrinogen levels for the development of CHD is not generally so well documented for women, a number of investigations, such as the ARIC Study, and the Scottish Heart Health Study, have likewise described an association among women of high plasma fibrinogen levels not only with CHD prevalence, but also with overall mortality\textsuperscript{146–148}. A Swedish case control study conducted on younger women (<65 years) recently identified elevated plasma fibrinogen levels as eloquent independent predictors of CHD risk: especially among pre-menopausal women (odds ratio (OR) 7·0), and also among postmenopausal women (OR 2·1)\textsuperscript{149}. The authors hypothesized that the appreciably elevated risk among women before menopause is the consequence of a highly pronounced inflammatory process of the vascular wall. Another interesting finding of this study was that the prognostic value of the fibrinogen
levels is especially enhanced when the significance of other risk determinants is low.

**Plasminogen activator inhibitor-1 (PAI-1)**

As an antagonist of the tissue plasminogen activator, PAI-1 represents a central factor in the adjustment of equilibrium between coagulation and fibrinolysis. Mutations in the coding gene, as well as environmental factors, play key roles in influencing PAI-1 activity\[^{150}\]. High PAI-1 plasma levels occur in conjunction with reduced fibrinolytic activity, and consequently lead to prothrombotic activation\[^{140,151}\]. Several cross-sectional studies have described similar PAI-1 levels for men and women\[^{152,153}\]. Healthy women with high oestrogen levels and women undergoing hormone therapy have lower PAI-1 levels than women not taking hormones\[^{154}\].

Diabetic women manifest higher PAI-1 values than do diabetic men\[^{155}\]. There have been numerous reports that PAI-1 is associated, especially among women, with CHD and with acute coronary events\[^{139,153,156,157}\]. In cases in which CHD is already manifest, PAI-1 values are higher among women than among male patients\[^{109,153}\]. Since elevated PAI-1 levels occur not infrequently in conjunction with insulin resistance\[^{158}\], however, discussion is certainly justified as to whether PAI-1 in fact plays a causal role as an atherogenic risk factor, or whether elevated PAI-1 levels are merely an indicator of the more pronounced insulin resistance syndrome among women\[^{158}\].

**Factor VII (FVII)**

Factor VII, the first enzyme in the cascade of the extrinsic coagulation system, has during recent years been the subject of discussion as a potential cardiovascular risk factor. To be sure, epidemiological studies have resulted in inconsistent findings. Various investigations conducted in men have disclosed an association between plasma levels of FVIIc and heightened cardiovascular risk\[^{154,159–161}\]. In contrast, others have discovered no significant relationship between FVIIc and the occurrence of CHD\[^{140,146,162,163}\]. These contradictory findings are partially the result of methodological problems in the assays of FVII concentrations and activity\[^{164,165}\]. It has until now not been definitely elucidated as to whether there is in fact an association between this coagulation factor and CHD among men.

For women, available data are meagre and no less inconsistent. Both of the studies Atherosclerosis Risk in Communities (ARIC) and European Concerted Action on Thrombosis and disabilities (ECAT) reported higher FVIIc levels for women with angina pectoris and/or cardiovascular diseases, than was the case for men. A recent case control study carried out on women \(\leq 65\) years, on the other hand, determined no significant correlation between FVIIa levels and CHD\[^{163,165}\].

**Menopause**

The fact that the prevalence of CHD among women up to the age of 50 years is appreciably less than that among men, and that the occurrence of cardiovascular diseases significantly increases after the menopause, suggest that the natural oestrogen deficit is involved in a causal relationship, and that the menopause accordingly merits discussion as an atherogenic risk factor\[^{166,167}\]. A number of studies have revealed that there is heightened CHD risk among women with premature natural menopause, as well as among female patients with premature menopause surgically induced by bilateral oophorectomy\[^{167–171}\]. The greater risk of developing cardiovascular diseases for increasingly premature menopause is furthermore evidently increasing. Every year by which the menopause is delayed signifies a reduction in cardiovascular risk by 2%\[^{167,171}\].

The menopause is accompanied by a number of metabolic, biochemical, and physiological alterations. TC, LDL-C, and TG rise; HDL-C apparently decreases slightly\[^{12,172–175}\]. Furthermore, glucose metabolism worsens in the sense of higher blood glucose and a decrease in insulin sensitivity (for review see\[^{167}\]). An additional change is procoagulatory activation, with increase in fibrinogen and PAI-1 values\[^{154,167,176}\]. On the whole, endothelial dysfunction seems to develop during the menopause: a process which can be partly reversed by administration of oestrogen\[^{177}\].

As described above, these menopause-associated alterations are almost exclusively considered to be atherogenic risk factors; they are evidently and for the most part, the result of oestrogen deficiency. Hormone therapy after the menopause is capable to a certain degree of countering these disadvantageous alterations. There is solid evidence that oestrogens improve the lipid profile. The prospective PEPI study\[^{116}\], with 875 healthy postmenopausal women between 45 and 64, investigated hormone substitution therapy, and verified experimental and clinical findings that oestrogens lead to significant reduction in LDL-C and to increase in HDL-C\[^{19,178}\]. Lipid-independent protective effects of oestrogen arise through improvement of glucose metabolism, of haemostasis (i.e. reduction of fibrinogen and increased activity of fibrinolysis), and of endothelial function, by virtue of induction of increased production of NO and prostacyclin, and of diminished production of endothelin and thromboxan A\(_2\)\[^{179–181}\].

A great number of epidemiologic non-randomized studies on primary and secondary prevention have almost unanimously suggested that postmenopausal women undergoing hormone therapy develop fewer cardiovascular events than women without hormone substitution. The largest study on primary prevention,
the NHS, reported that the risk of severe coronary events with women undergoing hormone therapy is 39% less than among women who have never taken hormones\textsuperscript{[170]}. There are no prospective data on primary prevention by means of hormone substitution therapy. Two most recent prospective studies available on secondary prevention — i.e. the Heart and Estrogen/Progestin Replacement Study (HERS), and the Estrogen Replacement and Atherosclerosis trial (ERA), surprisingly report no atheroprotective effects of hormone therapy\textsuperscript{[117,182]}. Vigorous discussion has ensued on why these clinical studies have reported negatively in this sense, despite the experimental evidence of the anti-atherogenic effects of oestrogens.

In addition to the well-known methodological limitations of these studies, more recent findings could provide an explanation: i.e. that hormone therapy leads to significant increase in CRP. This inflammation marker has recently been identified as an independent cardiovascular risk factor for women (see above). It has further been speculated that hormones in the menopause induce proinflammatory effects as a result of CRP. It is also believed that accelerated arteriosclerosis, plaque destabilization, and thrombosis can in this way offset the well-known anti-atherogenic mechanisms of oestrogens\textsuperscript{[111,183]}. The significance of the great majority of polymorphisms as inherited risk factors has not yet been conclusively elucidated, and there has been much controversy in this field. It is even less certain whether there are gender differences involved in the importance of individual polymorphisms. The literature contains regular mention of certain polymorphisms alleged to play a role among women. The platelet glycoprotein Ibalpha, a Kozak sequence polymorphism, may serve as an illustration example here; studies have indeed (paradoxically) attributed a protective role to it\textsuperscript{[197]}. Recent results from the Women’s Health Study analysing almost 40 000 female health professionals older than 45 years indicated that only maternal myocardial infarction history confers a relative risk for cardiovascular events of 1.46, only paternal a relative risk of 1.15, and both maternal and paternal history a relative risk of 2.05. Moreover, history of premature myocardial infarction manifestation was even more predictive: among women, maternal age of myocardial infarction manifestation <50 years conferred a relative risk of 2.57, in joint association with paternal myocardial infarction history a relative risk of five\textsuperscript{[192]}. Other studies have likewise described an association with parental history among women who suffer myocardial infarction at an early age.

Estimates of the impact of inheritance on susceptibility to arterial thrombosis and consecutive myocardial infarction range from 20 to 80%\textsuperscript{[150]}. Even if the figure of 80% appears exaggerated, the genetic risk for relatively young women is evidently elevated. In a major twin study including 21 004 Swedish twins, the relative risk factor for coronary death among the men whose twin had died of CHD before the age of 55 was 8.1 for the 3298 monozygotic twins covered in the investigation. In contrast, the excess risk factor was 15 for the 4012 monozygotic female twins whose twin had died of CHD before the age of 65\textsuperscript{[193]}. In addition to the evident aspects of sole family history, new developments in molecular biology and the possibilities of emerging techniques in high-throughput sequencing and DNA array technology have directed research of CHD to its genetic basis and now allow targeted screening of variations in disease candidate genes\textsuperscript{[184]}. The complexity of CHD results from numerous physiologic systems involved in the athero-genic process, including haemostasis, inflammation, regulation of blood pressure and vascular wall homeostasis, cholesterol and carbohydrate metabolism, and others. Many genes regulate these systems, and one study has estimated that more than 400 are involved in these processes\textsuperscript{[195]}. Except for familial hypercholesterolaemia, in which single gene variations are major determinants of the disease, it has until now been believed that most genes involved have only subtle impact on the clinical phenotype. This, however, does not lessen their importance, and a number of polymorphisms with modest effects in various genes will in any case converge to CHD\textsuperscript{[150,196]}. Studies on the association between single candidate gene polymorphisms and CHD risk are common in the literature, but a detailed treatment would exceed the context of the present presentation.

The significance of the great majority of polymorphisms as inherited risk factors has not yet been conclusively elucidated, and there has been much controversy in this field. It is even less certain whether there are gender differences involved in the importance of individual polymorphisms. The literature contains regular mention of certain polymorphisms alleged to play a role among women. The platelet glycoprotein Ibalpha, a Kozak sequence polymorphism, may serve as an illustrative example here; studies have indeed (paradoxically) attributed a protective role to it\textsuperscript{[197]}. Caution is certainly advised in the interpretation of these results, and sight should not be lost of the principal problems of association studies, such as selection bias and insufficient numbers of cases. Typically, several hundred or more participants are required to
effectively preclude chance and to attain narrow confidence intervals. Many studies do not go so far as to satisfy this basic prerequisite: not even in their total sample size, much less in the number of women included.

However, if prospective investigations are successful in confirming the findings of such hypothesis-generating studies, and in establishing functional roles for specific gene variants, consideration of inherited markers together with common risk-factor assessment will surely improve both diagnosis and treatment options for both women and men.

Psychosocial influences

Evidence has now accumulated for years that psychosocial influences may represent relevant risk factors for the development and progress of CHD. Chronic work-related stress is evidently associated with an elevated incidence of cardiac events, and with more pronounced progression of already manifest atherosclerosis. Work-related stress may include pressing demands, insufficient decision-making responsibility, or lack of recognition. Little data is available on the association of psychosocial stress with CHD among women. The Framingham Study was the first to describe the relationship between Type A behaviour and cardiovascular disease. Evidence exists that hostility and anger are significantly associated with cardiovascular disease in both genders. Other studies, however, have not detected a relationship between behavior types and elevated CHD risk among women. Depression, to be sure, is evidently associated with elevated risk among men and, to an even more pronounced degree, among women.

New results published by the Stockholm Female Coronary Risk Study (FemCorRisk) suggest that low socio-economic position and work-related stress exacerbate CHD risk among women as well. Marital stress, at the same time, appears to be one of the primary factors in worsening prognosis among women with CHD.

Summary

We may summarize by stating that the same cardiovascular risks principally apply to both men and women. There are, nevertheless, pivotal gender-related differences with respect to the relative weight and the significance of these risks. The reasons behind these differences, for the most part unknown, may to some degree be explained by the effects or the cessation of steroid hormones. Satisfactory monitoring and therapy of cardiovascular risk factors among women necessitates knowledge not only of the various differences between the genders in manifestation of these risk factors, but also of their similarities. Although many CHD risk factors have in fact been identified in women, there is less evidence than for men that modifying most of these factors would decrease the risk of CHD. For this reason, further randomized studies are essential, in efforts toward the possibility of achieving results that could be used to enhance prophylaxis and therapy.

We may conclude by again stating the following findings of our review:

- The increase in prevalence of cardiovascular risk factors is greater among women.
- The significance of total cholesterol is less than for men and of HDL-C, greater. Low HDL-C is an independent risk factor among women. High HDL-C values are associated with greater protection.
- Triglycerides represent a major risk factor in women.
- Hypertension is a risk factor for both genders, with probably less impact on CHD in women.
- Cigarette smoking is the leading preventable cause of CHD in both sexes; women’s rate of smoking cessation still lower than men’s.
- Diabetes is an appreciably more serious risk factor among women.
- CRP is a cardiovascular risk factor in both genders, with an increase in risk during hormone replacement therapy.
- The menopause is considered a cardiovascular risk factor. Hormone replacement therapy has not a proven benefit in primary and secondary prevention of CHD.

References

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