

Coronary Artery Disease in Women:

A Review of Emerging Cardiovascular Risk Factors

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Abstract

Coronary heart disease is the leading cause of death and disability in both men and women in industrial nations. From 1988 to 1998, the death rate from coronary heart disease actually declined 26.3%, resulting to some extent from the recognition and treatment of modifiable risk factors. The clinical observation that traditional risk factors for atherosclerosis cannot account for all patients who develop coronary heart disease or stroke has stimulated interest in reevaluating these factors and considering other determinants of pathogenesis. Our understanding of atherogenesis has evolved from a focus on lipid deposition within the arterial wall causing obstruction to the broader view of an inflammatory process which involves specific cellular and molecular responses to endothelial dysfunction. As a consequence, “emerging” cardiovascular risk factors and preventive strategies have been proposed. For example, there is an increasing understanding of the pathology of hypercholesterolemia and the benefits of lipid-lowering medications (specifically statins), the role of oxidative stress, and antioxidant, homocysteine, and hypercoagulable states.

This review examines the data for these and other emerging risk factors, with specific attention to gender differences.

Key Words: Coronary artery disease, coronary heart disease, women, atherosclerosis, pathophysiology.

Introduction

CORONARY HEART DISEASE (CHD) remains the leading cause of death and disability in both men and women in industrial nations. In 1997, a total of 466,101 deaths in the United States were attributed to CHD. Approximately half of them were women (1). However, the common misperception that CHD is a “man’s disease” remains. A survey by the American Heart Association reported that only 8% of the women questioned recognized that heart disease and strokes are the leading cause of death among women, and that cardiovascular disease kills more women each year than the next 16 causes of death combined. One in two women dies of heart disease or stroke, while only one in 25 dies of breast cancer (2).

During the decade 1988–1998, the death rate from CHD actually declined 26.3% (1). This resulted in part from the recognition and treatment of modifiable risk factors such as diabetes, hypertension and tobacco use. While most traditional risk factors are similar in men and women, there are differences in risk factors between the two sexes, as well as differences in the magnitude of the effects of these risk factors. For example, diabetes, a known risk factor for CHD, is a stronger risk factor in women than in men. CHD mortality rates are approximately 3–7 times greater for diabetic women than for non-diabetic women. In comparison, the mortality rate is only 2–3 times greater for diabetic men than for non-diabetic men (3).

The clinical observation that traditional risk factors for atherosclerosis cannot account for all patients who develop CHD or stroke has stimulated interest in reevaluating the risk factors and considering other determinants of pathogenesis. Our understanding of atherogenesis has evolved from a focus on lipid deposition within the arterial wall causing obstruction, to the broader view of an inflammatory process which involves specific cellular and molecular responses to endothelial dysfunction. As a con-

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Pathogenesis

One of the earliest events in the development of atherosclerosis is thought to be endothelial dysfunction (4), the causes of which are thought to include elevated and oxidized low-density lipoproteins (LDL), free radicals from tobacco, hypertension, diabetes mellitus, acquired and genetic hypercoagulable states, and infectious organisms. These factors may also act in synergy. Endothelial dysfunction in turn results in a series of compensatory responses that alter the homeostatic properties of the endothelium (4–6). The atherosclerotic lesion progresses from the early fatty streak to plaque rupture if the insult is not removed and the inflammatory response continues unabated.

Endothelial dysfunction is characterized by a number of changes. Cell surface markers involved in adhesion — such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) — are up-regulated, and production of cytokines, chemokines and other growth factors is increased. As a result, there is increased adhesiveness of platelets and leukocytes to the endothelium, increased vascular permeability and a local procoagulant state. These factors contribute to the recruitment from the circulation of mononuclear leukocytes and their migration into the subendothelial space. Foam cells are formed when monocyte-derived macrophages take up LDL. Both the macrophages and T lymphocytes in turn produce cytokines, including interleukin-1 (IL-1) and interleukin-6 (IL-6), which increase cellular recruitment and promote smooth muscle cell proliferation. The fatty streak progresses into an intermediate lesion, which is characterized by a fibrous cap that forms over the atheroma and separates the cells, lipids and necrotic cell debris from the vascular lumen. The artery wall thickens and attempts to compensate by dilatation. Continued inflammation results in increased recruitment of activated in-

flammatory cells, causing the release of enzymes such as metalloproteinases, and the manufacture of tissue factor. Ultimately, further damage of the arterial wall occurs, and in some cases rupture of a vulnerable plaque and thrombus formation, causing what is known today as the acute coronary syndrome (7). Other factors that may contribute to the unstable coronary syndrome include a hypercoagulable state and impaired responsiveness to endothelium-dependent vasodilators in diseased portions of the coronary arteries.

Markers of Inflammation

These new insights into the role of inflammation in the pathophysiology of atherosclerosis have led several investigators to examine mediators and markers of inflammation in patients with coronary heart disease. A number of studies have shown elevations in the levels of high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA) protein, fibrinogen, cellular adhesion molecules-1 (ICAM-1), and cytokines (IL-6, tumor necrosis factor- α). One of the hurdles in performing these studies has been the difficulty in developing standardized assays. Because of the availability of a reliable and sensitive assay, C-reactive protein (CRP) has been the most studied of the inflammatory markers.

It has been demonstrated that high-sensitivity C-reactive protein (hs-CRP) levels may be useful in predicting CHD as well as other vascular events, e.g., stroke and peripheral vascular disease (8). This has been validated by findings in a number of different populations, ranging from patients at low risk for CHD to those with overt CHD, as well as in women and in the elderly. A prospective, nested case-control study of the Women’s Health Study (WHS) assessed the risk of cardiovascular events associated with levels of markers of inflammation among 122 apparently healthy postmenopausal women (9). The markers of inflammation included hs-CRP, SAA, IL-6, and soluble ICAM-1. This study demonstrated that women with the highest hs-CRP at baseline had a 5-fold increase in the risk of any vascular event and a 7-fold increase in risk of myocardial infarction (MI) or stroke. Similarly, hs-CRP levels were also measured in the Physician’s Health Study (PHS), a primary prevention study that randomized male physicians to aspirin vs. placebo (10). In the more than 8 years of follow-up, individuals who went on to have coronary events or

stroke had higher levels of hs-CRP than did those who did not have a vascular event. Those with the highest hs-CRP levels had three times the risk of myocardial infarction and twice the risk for stroke compared to those with the lowest hs-CRP. As in the WHS, the risk estimates were independent of other traditional cardiovascular risk factors. Importantly, CRP has also been shown to add to the predictive value of lipid parameters in determining the risk of a first MI. In the PHS, baseline levels of CRP, total cholesterol, and high-density lipoproteins (HDL) correlated with myocardial events. Multivariate analysis models incorporating CRP and lipid parameters provided a significantly better method of predicting risk than did models using lipids alone (11).

Additional studies have shown the prognostic value of hs-CRP in men and women with coronary disease. In a small prospective study of 32 patients (26 men and 6 women), Liuzzo et al. demonstrated that patients with unstable angina and elevated hs-CRP (>0.3 mg/dL) had a higher incidence of ischemic episodes and more adverse outcomes, including death, myocardial infarction and/or emergent revascularization, compared to patients with lower levels of hs-CRP (12). Furthermore, Ferreiros et al. showed a strong relationship between elevated CRP, especially levels at time of discharge, and 90-day outcome (defined as death from any cause, myocardial infarction and/or refractory angina) compared to patients with lower levels of CRP (13).

The role of hs-CRP as a marker has also been examined in the context of therapeutic interventions. A nested case-control study of Cholesterol and Recurrent Events (CARE), a secondary prevention trial that randomized patients to pravastatin vs. placebo, suggested that treatment with pravastatin decreases the level of hs-CRP in both men and women. This supports the theory that hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors have benefits beyond lipid-lowering effects (14). An analysis of the PHS found that the use of aspirin was associated with a significant reduction in the risk of first myocardial infarction in patients with the highest levels of CRP, perhaps reflecting its anti-inflammatory effects (10).

Interestingly, the median levels of hs-CRP in the WHS were slightly higher than those in the PHS, and the absolute risk associated with the elevated levels of hs-CRP in this study of women was greater than that observed in prior studies of men (15). Estrogen appears to in-

crease CRP levels. Four markers of inflammation (CRP, soluble E-selectin, von Willebrand factor antigen, and coagulation factor VIIIc) were studied in 365 postmenopausal women from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study, a randomized, placebo-controlled trial that examined the effects of four hormone preparations on cardiovascular risk factors. All four of the hormone preparations were associated with an increase in CRP levels (16). Similarly, in another study of 493 healthy postmenopausal women with mean age of 51 years, median CRP levels were twice as high among women taking hormone replacement therapy (HRT) (17). Neither study was designed to assess clinical endpoints. These studies may help explain the results of the Heart and Estrogen/Progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis (ERA) trials. The HERS trial found no reduction in risk of nonfatal myocardial infarction and death from coronary heart disease among women with established CHD (average age 65 years) who were treated with conjugated estrogen plus medroxy-progesterone acetate (18). The ERA trial demonstrated that although HRT produced significant reductions in LDL cholesterol and increases in HDL cholesterol, there was no effect on the progression of CHD by coronary angiogram (19). This raises the possibility that pro-inflammatory effects of HRT may cause plaque instability that offset the benefits of HRT on lipids. Further investigation needs to be done to determine the significance of this gender difference.

The exact mechanism by which a stable plaque converts into an unstable lesion and the role of CRP in the acute coronary syndrome are both unclear. It is hypothesized that CRP can act as a procoagulant or even as an inducer of the immune system. Conversely, CRP could simply be an inflammatory marker that is the result of whatever inflammatory process is occurring. Whatever the case might be, based on epidemiological studies, inflammatory parameters like hs-CRP level may help determine which clinically stable patients are at risk for future cardiac events, and guide future treatment strategies.

Risk Factors

Hyperlipidemia

The association between hypercholesterolemia and CHD was first noted in the 1930s

by Muller et al. (20), who reported premature coronary heart disease in patients with hereditary xanthomatosis. Since then, a number of large epidemiological studies have confirmed the relationship between high cholesterol and CHD in men and women. However, gender differences exist in the patterns of cholesterol associated with increased risk. For example, the level of total cholesterol that correlates with increased risk for CHD may be higher in women than in men, in part secondary to higher HDL levels seen in women (21).

While the Framingham Heart Study (21) demonstrated that low levels of HDL cholesterol predict an increased incidence of CHD in men and women, it is independent of other CHD risk factors, including LDL (22). Several studies have shown that increasing HDL lowered CHD events in men and women, independent of LDL (The Lipid Research Clinics Coronary Primary Prevention Trials using cholestyramine, Helsinki Heart Study using gemfibrozil, and The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group also using gemfibrozil) (23–25). As in the male population, a particularly strong relationship between low HDL cholesterol and CHD risk is also found in women. A National Heart, Lung, and Blood Institute workshop pooled data on different lipoproteins from several cohort studies of a total of approximately 86,000 women from different populations. Among younger women (< 65 years) there was an increased relative risk associated with elevated total and LDL cholesterol, and low HDL. However, in older women (> 65 years, and therefore a group at higher risk for CHD), only low HDL of < 50 mg/dL was significantly associated with increased CHD mortality (26). This was confirmed in a study by Corti et al. of 2,527 women who were 71 years of age or older (27). In those individuals whose HDL cholesterol levels were less than 35 mg/dL, the relative risk of CHD mortality was twice that of women with HDL cholesterol levels greater than 60 mg/dL, in the 4.4 years of follow-up (27). In men whose HDL levels were less than 35 mg/dL, the relative risk of CHD mortality was close to 5 times that of men with HDL greater than 60 mg/dL.

HDL is thought to exert its positive effects via its role as a reverse cholesterol transporter and antioxidant, its maintenance of endothelial function, and its protection against thrombosis (28). Low HDL cholesterol is affected by such factors as heredity, tobacco smoking, obesity,

lack of exercise and certain medications such as beta-blockers. Estrogen appears to elevate HDL cholesterol levels, which may explain why premenopausal women have higher levels than men and exhibit a lower incidence of CHD before the age of 50. Treatment of low HDL includes niacin, gemfibrozil and estrogen.

Triglycerides

More support for high triglycerides as an independent CHD risk factor has accumulated in recent years. There is some evidence to suggest that triglycerides are an important risk factor in women 50–69 years of age and in patients with non-insulin-dependent diabetes (29, 30). In one analysis of 17 studies (46,413 men and 10,864 women), elevated triglyceride levels were associated with an increased cardiovascular risk of 76% in women and 32% in men (31). After adjustment for HDL and other risk factors, the increased risks were decreased but remained statistically significant (37% in women, 14% in men). Another study of myocardial infarction survivors showed that the risk of MI was 6.8 times higher in those with the highest triglyceride levels. The risk was even more significant (16-fold) in those with the highest triglycerides-to-HDL ratio (32). High triglycerides also seem to be more important in women with non-insulin-dependent diabetes mellitus. Diabetic women in the highest tertile of triglyceride levels have a 200-fold increase in CHD prevalence, in contrast to diabetic men whose risk increases 3-fold (33). Current treatment strategies for high triglycerides include non-pharmacologic therapy, in particular, diet, exercise, weight control, and alcohol reduction. Pharmacologic approaches that have been effective in reducing high triglycerides include niacin, fibrates, and to a lesser extent statins.

Clinical Trials

Several clinical trials have demonstrated that lowering cholesterol decreases coronary artery disease morbidity and mortality, slows the progression of atherosclerotic lesions and perhaps leads to their regression. The degree to which these results can be extrapolated to women is unknown, since most studies either excluded women or had too few women to be statistically significant. Review of primary prevention trials that included women yielded four studies. Two studies (the Finnish Mental Hospital Study and the Minnesota Coronary Sur-

vey) examined dietary intervention in reducing total cholesterol levels. The other two (the Upjohn Colestipol Study and the Air Force/Texas Coronary Atherosclerosis Prevention Study — AFCAPS/TexCAPS) examined pharmacologic intervention. The Finnish Mental Hospital Study (34) randomized 6,435 women in mental institutions who were older than 15 years of age to a cholesterol-lowering diet or a control diet. Women in the treated group had a 12% reduction in their serum cholesterol, but there were no statistically significant reductions in CHD deaths in the treated group. The Minnesota Coronary Survey (35) randomized 4,664 women to a low-saturated-fat, high-polyunsaturated-fat, low-cholesterol diet or a regular control diet. Serum cholesterol decreased by 15% in the treated group, but there were no significant differences in events such as acute myocardial infarctions, sudden deaths and silent myocardial infarctions between the two groups. The Upjohn Colestipol Study (36) randomized 1,184 women to colestipol or placebo and followed them for up to three years. Total cholesterol decreased in the treated group; however, there was no significant difference in the mortality rates between the two groups. More recently, the AFCAPS/TexCAPS (37), the first trial to demonstrate the efficacy of primary prevention in women, randomized 6,605 patients (997 women) with “average” cholesterol and no history of CHD to placebo vs. lovastatin. This study showed that the effect of treatment with lovastatin on the rate of first acute major coronary events was greater in women than in men (46% vs. 37% reduction in relative risk).

Secondary prevention trials appear to show benefits of lipid lowering in women. The CARE trial randomized 4,159 CHD patients (3,583 men, 576 women) with cholesterol levels of less than 240 mg/dL to receive either 40 mg/day of pravastatin or placebo. The women had twice the reduction in risk of recurrent cardiovascular events, including reduction in CHD death or nonfatal MI, coronary artery bypass grafting (CABG), or angioplasty (PTCA), and combined cardiovascular events, when compared to men (46% reduction rate for women vs. 20% for men) (38). The Scandinavian Simvastatin Survival Study (4S) randomized 4,444 patients (827 women) with angina pectoris or prior myocardial infarction and elevated cholesterol (213–310 mg/dL) to simvastatin vs. placebo. There was a 34% reduction for major coronary events in women vs. 42% for men (39).

Mechanism of Treatment Benefits

It is not entirely clear how therapy with statins improves outcome. The decrease in incidence of events is far more significant than the degree of plaque regression, as evaluated by coronary angiogram (40). Furthermore, the benefit of lipid lowering, which must occur before significant regression can occur, is seen in as little as six months. The beneficial effects of statins on clinical events, in addition to their role in the regression of coronary lesions, may involve a therapeutic role in inflammation. Possible nonlipid mechanisms include plaque stabilization, reversal of endothelial dysfunction, inhibition of monocyte recruitment, inhibition of smooth muscle proliferation, decrease in thrombogenicity and reduction in inflammation after MI (40). There is even some evidence that statins may have an antioxidant effect (41).

Lipoprotein (a)

Lipoprotein a (Lp(a)) is a modified form of LDL, in which a large glycoprotein, apolipoprotein (a), is covalently bound to apo B by a disulfide bridge. The apo (a) chain shares partial homology with plasminogen, a plasma protein that dissolves blood clots when activated. Because of this structural similarity to plasminogen, it is hypothesized that Lp(a) interferes with fibrinolysis by competing with plasminogen binding to molecules and cells (42). This causes impairments in plasminogen activation, plasmin generation, and fibrinolysis. Lp(a) also binds to macrophages via a high-affinity receptor that promotes foam cell formation and deposition of cholesterol in atherosclerotic plaques. Lp(a) is increased in renal disease. Its levels also fluctuate in states of hormonal change, such as that which occurs in diabetes, after menopause, and with pregnancy.

There is conflicting evidence as to whether Lp(a) is an independent risk factor for CHD. A positive association between Lp(a) and CHD has been shown in many retrospective trials, but the data in prospective trials have not been as convincing. For example, the Physicians' Health Study, Helsinki Heart Study, and the Quebec Cardiovascular Study showed no evidence of a positive association between baseline plasma concentration of Lp(a) and future vascular events (43). This contrasts with findings in the Lipid Research Study, the British United Provident Association and the Stanford Five City Project, which did show positive

graded associations between Lp(a) and risk for CHD. The Framingham Heart Study, a major study of 3,103 women, did find Lp(a) to be an independent predictor of MI and cardiovascular disease (44). In this study, Lp(a) was measured at baseline by electrophoresis. At a mean follow-up of 12 years, multivariate-adjusted relative risk (RR) estimates were 2.37 for MI, 1.61 for CHD, and 1.44 for total cardiovascular disease.

Lp(a) has also been studied as a risk factor for restenosis after PTCA as well as CABG, with conflicting results. In one angiographic study of 71 patients (23 women) who underwent successful PTCA, the incidence of restenosis was significantly higher in patients with Lp(a) of more than 30 mg/dL, than in those with Lp(a) of less than 30 mg/dL (65% vs. 26%; $p < 0.01$) (45). This was confirmed in another angiographic study of 80 patients (22 women). Serum Lp(a) levels in the restenosis group were significantly higher than in the nonrestenosis group (29 mg/dL vs. 17 mg/dL) (46). This correlation, however, was not seen in other studies. In an angiographic study of 305 patients (58 women), no significant association was determined between serum levels of lipoproteins and luminal loss (47). Similar conflicting results were seen in patients who underwent CABG with vein grafts. In a study by Hoff et al. of 167 patients (18 women), 92% of the patients with Lp(a) levels of 31.6 mg/dL or above demonstrated vein graft stenosis (48). A more recent study of 353 patients (56 women), however, did not show that serum Lp(a) level correlated with vein graft occlusion five years after CABG surgery (49). Because of the inconsistency of prospective data, screening for Lp(a) is usually done only in specific high-risk settings (i.e., premature CHD or a family history of CHD) or in patients without apparent traditional risk factors. Drugs used to treat Lp(a) are niacin and estrogen.

Oxidative Stress — The Role of Antioxidants

As stated previously, oxidative modification of LDL is an important step in the pathogenesis of atherosclerosis. Several animal models have demonstrated that antioxidants decrease oxidation of LDL and reduce plaque formation (50). There is also evidence that antioxidants inhibit monocyte adhesion, protect against the cytotoxic effects of oxidized LDL, inhibit platelet activation, and protect against endothelial dysfunction associated with atherosclerosis, by preserving endothelium-derived

nitric oxide activity. Epidemiological studies have reported that increased intake of antioxidants, specifically vitamins E and C, via diet or supplements, is associated with decreased morbidity and mortality of coronary artery disease.

There is conflicting evidence for vitamin E supplementation in the prevention of CHD. In the Nurse Health Study, increased vitamin E intake was associated with less cardiovascular disease (51). The study was a prospective cohort study that assessed intake of vitamin E (along with vitamins A and C) in 34,486 women with no history of CHD. Intake of vitamins A and C did not have a significant association with risk of death from CHD. The Cambridge Heart Antioxidant Study (CHAOS) was a secondary prevention study that randomized 2,002 patients with coronary atherosclerosis to vitamin E 800 IU or 400 IU daily, or to placebo (52). This study reported marked reductions in nonfatal myocardial infarction and in the combined endpoint of nonfatal MI and cardiovascular death of any major cardiovascular event after one year of treatment. No effect on cardiovascular death was observed. However, this trial had many methodological problems (e.g., the study groups were not balanced at baseline and there was a short duration of follow-up).

Conversely, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) design trial, another secondary prevention trial, did not show statistically significant reductions in clinical events when patients were treated with 300 mg/day of vitamin E (53). Recently, the Heart Outcomes Prevention Evaluation Study (HOPE) randomized 9,541 patients (2,545 women and 6,996 men) who were at high risk for cardiovascular disease to vitamin E 400 IU/day, ramipril 10 mg/day, both, or none (placebo). There was no clear benefit to patients treated with vitamin E for a mean of 4.5 years in reduction of the incidence of cardiovascular death, myocardial infarction, and stroke (54).

Other antioxidants have been evaluated, with equally conflicting results. A number of epidemiological studies have evaluated the influence of supplemental vitamin C intake in the primary prevention of CHD. The Atherosclerosis Risk in Communities Study (ARIC Study) noted an inverse relationship between vitamin C intake and the average carotid artery wall thickness in more than 4,000 patients who were 55 years of age or older (55). The National Health and Nutrition Examination Survey (NHANES) (56) showed that men with the

highest vitamin C intake (> 50 mg/day) had significantly lower all-cause mortality and cardiovascular mortality rates. In women there was an insignificant all-cause mortality reduction, but cardiovascular deaths were significantly less frequent (56). On the other hand vitamin C supplementation did not affect the risk of myocardial infarction or coronary death in the Nurses' Health Study or in the PHS (57, 58). The role of vitamin C in secondary prevention has not been well studied, but the available data do not support its use. For example, in the Cholesterol Lowering Atherosclerosis Study (CLAS), supplemental vitamin C use did not improve angiographically determined lesion progression (59).

Homocysteine

Homocysteine is an intermediary amino acid formed by the conversion of methionine to cysteine. Elevations of plasma homocysteine have been associated with increased age, menopause, genetic defects in the enzymes involved in homocysteine metabolism (e.g., methylene tetrahydrofolate reductase deficiencies), nutritional deficiencies in vitamin co-factors (e.g., folate, vitamin B12), and other systemic diseases (e.g., renal failure, liver disease) (60). The proposed pathophysiologic mechanisms of hyperhomocysteinemia include endothelial injury and dysfunction followed by platelet activation and thrombus formation (60).

In most prospective and case-control studies of men and women, hyperhomocysteinemia appears to be an independent risk factor of atherothrombotic vascular disease. In a case-control study of the PHS, men with homocysteine levels above the 95th percentile had a 3-fold increase in the risk of myocardial infarction compared to those in the lower 90th percentile (61). The authors estimated that 7% of the observed myocardial infarctions could be attributed to hyperhomocysteinemia. One population-based, case-control study compared 79 women younger than 45 years of age who had a myocardial infarction, with 386 normal controls. This study showed that myocardial infarct patients had a higher mean plasma homocysteine level (13.4 $\mu\text{mol/L}$ vs. 11.1 $\mu\text{mol/L}$) and lower mean folate level (12.4 nmol/L vs. 16.1 nmol/L) (62). Similarly a prospective, nested case-control study of 122 WHS participants who had experienced cardiovascular disease showed that case subjects had a higher baseline homocysteine level (14.1 $\mu\text{mol/L}$ vs.

12.4 $\mu\text{mol/L}$) (63). A meta-analysis of 27 non-randomized studies demonstrated that each 5 $\mu\text{mol/L}$ increment increase in homocysteine levels was associated with 1.6- and 1.8-fold increased CHD risks in men and women, respectively (64). In one study of 587 patients (approximately 20% women) with documented CHD who were followed for 4.6 years, mortality increased in patients with homocysteine levels greater than 15 $\mu\text{mol/L}$ (65). A graded effect has also been demonstrated between homocysteine concentrations and the risk of coronary artery disease or cerebrovascular accident as well as mortality from CHD (61, 66–68).

Gender differences in circulating homocysteine concentrations have been reported (69). In the Third National Health and Nutrition Examination Survey, total homocysteine level was compared among population subgroups differing in estrogen status. Premenopausal women (17–54 years old) had lower mean homocysteine levels when compared to similarly aged men (8.1 $\mu\text{mol/L}$ vs. 8.9 $\mu\text{mol/L}$). Women aged 17–44 years who were pregnant had lower mean homocysteine levels than did those who were not pregnant and not using oral contraceptives (6.0 $\mu\text{mol/L}$ vs. 8.1 $\mu\text{mol/L}$). The homocysteine levels of estrogen-using women older than 55 years of age was slightly decreased when compared to nonestrogen users of similar age (9.5 $\mu\text{mol/L}$ vs. 10.7 $\mu\text{mol/L}$). Men in the same age group also had slightly elevated homocysteine levels (10.4 $\mu\text{mol/L}$). The authors suggested that higher estrogen status is associated with a decreased homocysteine level.

Treatment of hyperhomocysteinemia varies with the underlying cause, but generally is related to vitamin supplementation with folic acid, pyridoxine, and vitamin B12. Although there are some data that suggest that treatment with folic acid can improve arterial endothelial function in adults with hyperhomocysteinemia, the effect on cardiovascular and venous thromboembolic disease of lowering homocysteine remains unknown (70). More studies will have to be performed to evaluate the clinical efficacy of therapeutic interventions before widespread screening and treatment of patients with atherosclerotic vascular disease can be recommended.

Obesity

The Framingham data has documented that obesity is an independent risk factor for CHD for both sexes (71, 72). Traditionally, women are defined as obese when their bone mass

index (BMI) exceeds 27 kg/m². Different patterns of obesity appear to correlate to CHD incidence. An analysis of the data of the Nurses' Health Study showed that higher waist:hip ratio and greater waist circumference were associated with increased risk of CHD. If waist:hip ratio was 0.88, the adjusted relative risk (RR) of CHD death or myocardial infarction was 3.25 (vs. waist:hip ratio < 0.72). A waist circumference of 38 inches was associated with an adjusted RR of CHD death and myocardial infarction of 3.06 (73). The Iowa Women's Health Study was a cohort study of 31,702 women aged 55–69 years who were free of cancer, heart disease, and diabetes. Abdominal obesity as measured by waist:hip ratio appeared to be an independent risk factor for total mortality. Abdominal obesity when combined with high body mass index was found to be an important risk factor for CHD-related mortality or incident. Abdominal obesity appeared to be associated with hyperinsulinemia, dyslipidemia, hypertension and impaired fibrinolytic capacity, all of which increase the risk of CHD (74). Higher BMI was also found to be associated with higher CRP levels among 16,161 participants (8,678 women) 17 years of age or older, suggesting a state of low-grade systemic inflammation in overweight persons. Both overweight (BMI 25–29.9 kg/m²) and obese (BMI > 30 kg/m²) participants were more likely to have elevated CRP levels than their normal-weight counterparts (BMI < 25 kg/m²). After adjustment for potential confounders, including smoking and health status, the odds ratio of elevated CRP was 6.21 (95% CI: 4.94–7.81) for obese women compared with 2.13 (95% CI: 1.56–2.91) for obese men (75). These data are of great concern, given the trend in increasing body weight in the United States over the past decade, especially among women (76). Currently, it is estimated that more than one-third of all American women can be classified as obese.

Sedentary lifestyle is a known risk factor for CHD. In a meta-analysis, there was a 2-fold increase in risk in CHD mortality in persons with sedentary vs. active occupation (77). An observational cohort study of 32,421 patients (22% women) showed that among women, low fitness and tobacco use were independent mortality predictors (78). This was supported in the recently published analysis of the Nurses' Health Study, in which women who adhered to a lifestyle involving diet, exercise, and abstinence from tobacco use had a very low risk of

CHD (79). In a cohort study of the same Nurses' Health Study, brisk walking was associated with fewer coronary events (80). This underscores the importance of behavior modification in addition to pharmacological approaches in the prevention of CHD.

Hypercoagulable States

Rupture of an unstable plaque with formation of an occlusive thrombus is an important component in the pathogenesis of the acute coronary syndrome. In recent years, several studies have examined alterations in coagulation and fibrinolysis as risk factors for CHD. The largest body of evidence of an association between a hemostatic factor and CHD has been accumulated for fibrinogen. Fibrinogen increases plasma viscosity, promotes platelet aggregation, and stimulates smooth muscle proliferation. All of these properties may explain the mechanisms by which fibrinogen is thought to mediate its pro-atherogenic effects.

A meta-analysis of six prospective epidemiological studies that included a total of 92,147 persons demonstrated that an increase in the fibrinogen level was associated with an increased risk of subsequent MI or stroke (81). Persons with fibrinogen levels in the highest tertile had 2.3 times the relative risk of those in the lowest tertile. Of the six studies, only one, the Framingham Heart Study, included women. For women, the fibrinogen risk ratio was greatest only for CHD. In contrast, the risk ratio was greatest for stroke, intermediate for myocardial infarction, and smallest for peripheral vascular disease in men. The Atherosclerosis Risk in Communities (ARIC) Study followed 14,477 patients (> 50% of the participants were women) in the 45–64-year-old range without history of CHD for approximately 5 years. Increased fibrinogen was associated with a higher likelihood of CHD; in men the RR was 1.48 and in women it was 1.21. The highest versus lowest quintile RR's were 3.66 in men and 3.50 in women. In a multivariate analysis, factor VIII, von Willebrand factor and white blood cell count, as well as fibrinogen, were associated with total mortality (82). A more recent meta-analysis of 18 prospective fibrinogen studies indicated that, in comparing the fibrinogen levels of the highest and lowest tertiles, the CHD risk ratio was 1.8 (83). High fibrinogen levels in patients with chronic stable angina also predicted subsequent acute coronary events (84).

Fibrinogen levels appear in part to be genetically determined (85). Women tend to have higher levels than do men. Plasma fibrinogen increases with menopause, pregnancy, and the use of oral contraceptives; treatment with hormone replacement therapy (HRT) lowers this rise (86). Tobacco users have consistently been found to have high fibrinogen levels. Diabetics also appear to have elevated levels of fibrinogen as well as factor VII and anti-thrombin III. A prospective cohort study of 1,676 middle-aged persons (57% were women) with diabetes and no history of CHD showed that levels of albumin, fibrinogen, von Willebrand factor, factor VIII activity and leukocyte count were predictors of CHD (87). Pharmacologic intervention with ticlopidine, a drug that inhibits the adenosine diphosphate (ADP)-induced aggregation of blood platelets, has been shown to reduce fibrinogen level in patients with CHD, stroke, and peripheral vascular disease (88–90).

The fibrinolytic system is responsible for the removal of fibrin from the circulation. It consists of plasminogen, which is converted to its active form, plasmin, by plasminogen activators, including tissue plasminogen activator (tPA). Inhibitors of the system include plasminogen activator inhibitor type I (PAI-1). Since most of the tPA antigen measured is complexed with PAI-1 and is inactive, high levels of tPA antigen in association with high levels of PAI-1 reflect impairment of the fibrinolytic system. This impaired fibrinolytic system has been studied as a possible risk factor for CHD. High levels of plasma PAI-1 and tPA have been associated with CHD (91). In a prospective nested case-control study in which 78 cases and 156 controls were matched for age, sex, and sampling time, patients with a history of myocardial infarction had significantly higher PAI-1 and tPA levels (92). In a subset of the ARIC cohort, high levels of PAI-1, tissue-tPA, and D-dimer were associated with increased thickness of the carotid artery, which was used as an index of early atherosclerosis (93). This was supported by the European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study on the role of fibrinolysis and MI. The study included 3,043 patients with angina pectoris and angiographically verified coronary arteriosclerosis. It provided substantial documentation of an association between high plasma concentration of tPA and the risk of acute coronary syndromes (94).

Lifestyle modifications such as tobacco cessation and exercise appear to help improve the

fibrinolytic profile. In addition, several studies have shown that HRT decreases PAI-1. In a double-blind, randomized, placebo-controlled trial, the short-term effects of oral 17-beta-estradiol were assessed in 40 postmenopausal women with non-insulin-dependent diabetes mellitus (NIDDM). Both total PAI-antigen and active PAI-1 antigen concentration decreased significantly during HRT compared with the placebo group (95). This reduction in PAI-1 has also been shown in non-diabetic, postmenopausal women (96). In another study using 143 participants from the Framingham Offspring Study (a long-term, prospective evaluation of risk factors of cardiovascular disease), levels of plasminogen activator inhibitor (PAI-1) antigen and tissue plasminogen activator antigen were measured. Fibrinolytic parameters for subjects with high estrogen status (premenopausal women and postmenopausal women receiving HRT) were compared with those for subjects with low estrogen status (men and postmenopausal women not on HRT). The results showed that the presence of estrogen, either naturally in premenopausal women or as a result of HRT in postmenopausal women, was associated with lower levels of PAI-1 and tPA antigen compared with those subjects expected to have low estrogen status (97). Other pharmacologic interventions that may modulate the fibrinolytic system include angiotensin-converting enzyme inhibitors and gemfibrozil (98, 99).

Conclusion

Coronary heart disease is the leading cause of morbidity and mortality in the United States. It affects both men and women. While women share many of the traditional risk factors with men, there are many significant differences (e.g., diabetes is a stronger risk factor in women than in men). New insights into the pathogenesis of atherogenesis underscore the fact that CHD is more than the consequence of arterial obstruction secondary to lipid deposition; it is an inflammatory process that occurs in response to endothelial dysfunction. As a result, “emerging” cardiovascular risk factors have been proposed. These include dyslipidemia, Lp(a), hyperhomocysteinemia, hypercoagulable states, and oxidative stress. Understanding these “emerging” risk factors has led to the development of new strategies to treat CHD. Gender differences are apparent in these “emerging” risk factors. For example, a high triglycerides

level is a greater CHD risk factor in women than in men, especially those with diabetes, and decreased homocysteine level is associated with increased estrogen status. Women also have higher levels of fibrinogen, which has been associated with increased risk of CHD. Further investigations into gender differences will help influence the management of CHD in women and thus help prevent a disease that is the leading killer of women.

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