

Potential New Cardiovascular Risk Factors: Left Ventricular Hypertrophy, Homocysteine, Lipoprotein(a), Triglycerides, Oxidative Stress, and Fibrinogen

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The 1996 Bethesda Conference acknowledged left ventricular hypertrophy, hyperhomocysteinemia, lipoprotein(a) excess, hypertriglyceridemia, oxidative stress, and hyperfibrinogenemia as possible new cardiac risk factors. This review summarizes the current literature that supports these conditions as cardiac risk factors. Left ventricular hypertrophy is an independent risk factor for vascular disease. Improvement or progression of left ventricular hypertrophy influences subsequent cardiovascular complications. Clinical trials are under way to assess the potential benefit of decreasing homocysteine levels. The role of lipoprotein(a) excess in vascular disease is controversial. The atherogenic potential of lipoprotein(a) seems to be neutralized by effective reduction of low-density lipoprotein cholesterol levels. Increasing evidence supports an independent role of hypertriglyceridemia in cardiovascular disease and a possible clinical benefit from decreasing triglyceride levels. Among antioxidant micronutrients, supplementation with vitamin E has been shown to be beneficial in primary and secondary prevention studies. Data supporting the use of other antioxidants are much weaker. Preliminary evidence suggests that reducing fibrinogen levels in patients with high baseline levels and coronary disease may be beneficial. Despite the potential relation between new risk factors and cardiovascular disease, routine clinical application of these conditions as cardiovascular risk factors would be premature. Evidence is needed that these conditions extend prognostic ability beyond conventional risk factors and that modification of these conditions can reduce the risk for cardiovascular events.

Risk factor modification is an integral part of the management of patients who have or are at risk for cardiovascular disease. In addition to established cardiovascular risk factors, clinical research has identified more than 100 other conditions that may be associated with an increased risk for cardiovascular disease. **Table 1** provides an abbreviated list of these new risk factors. Clinicians who care for patients with cardiovascular disease should be aware of new risk factors. Almost 25% of patients with premature cardiovascular disease do not have any established risk factors (1). As a result of reductions in morbidity and mortality attributable to hypertension, smoking, and dyslipidemia (2–4), the relative contribution of new risk factors to the total burden of cardiovascular disease is likely to increase. Significant associations exist between established and new risk factors (**Table 2**), and better understanding of new risk factors may shed light on the pathogenetic mechanisms of established risk factors.

On the basis of a growing body of evidence, the 1996 Bethesda Conference acknowledged left ventricular hypertrophy, hyperhomocysteinemia, lipoprotein(a) excess, hypertriglyceridemia, hyperfibrinogenemia (among other thrombogenic factors), and oxidative stress as possible risk factors for coronary disease (1). This review covers the role of these selected new risk factors in cardiovascular disease. Other potential new risk factors, such as infectious agents, inflammatory markers, and procoagulant substances, are not discussed.

Methods

The MEDLINE database was searched by using the terms *cardiovascular disease* or *coronary artery disease* combined with each of the following terms: *left ventricular hypertrophy*, *homocysteine*, *lipoprotein(a)*, *antioxidants*, *triglycerides*, and *fibrinogen*. Only English-language articles published between 1988 and 1997 and selected cross-references were considered for inclusion. During the peer review process, selected articles published in 1998 and 1999 were added. Articles were screened for their relevance on the basis of information in the title and abstract. The primary criterion for including studies

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Table 1. New Cardiovascular Risk Factors

Left ventricular hypertrophy*
Hyperhomocysteinemia*
Lipoprotein(a) excess*
Hypertriglyceridemia*
Oxidative stress*
Hyperfibrinogenemia*
Infectious agents (such as <i>Chlamydia pneumoniae</i> , <i>Helicobacter pylori</i> , and cytomegalovirus)†
Markers of inflammation (such as C-reactive protein and serum amyloid A)†
Procoagulant substances (such as plasminogen, factor VII, plasminogen activator inhibitor-1, and von Willebrand factor)†

* Factors discussed in this review.

† Substantial evidence exists for a relation between infectious agents, inflammatory markers, and procoagulant substances and vascular disease, but these are not covered in this review.

in this review was the author's judgment regarding their relevance to the clinician involved in the care of patients with cardiovascular diseases.

Left Ventricular Hypertrophy

Left ventricular hypertrophy is the response of the heart to chronic pressure or volume overload. It is defined as left ventricular mass exceeding 131 g/m² of body surface area in men and 100 g/m² in women (12). Echocardiography is the method of choice for estimating left ventricular mass (13).

In the Framingham Heart Study (5), 16% of men and 19% of women had left ventricular hypertrophy. In a subgroup of the Systolic Hypertension in the Elderly Program, left ventricular hypertrophy was present in 26% of patients with hypertension compared with 10% of age-matched controls (14). Age, blood pressure, obesity, valve disease, and myocardial infarction are independently associated with left ventricular hypertrophy (5). Sodium intake (15), hereditary factors (16), and neurohumoral factors (17) are also thought to play a role in determining left ventricular mass.

Three patterns of left ventricular hypertrophy have been identified. These patterns depend on left ventricular mass index (expressed in g/m²) and relative wall thickness (2 × posterior wall thickness/left ventricular end-diastolic diameter) (Figure) (18).

Left ventricular hypertrophy is independently associated with increased incidence of cardiovascular disease, cardiovascular and all-cause mortality (19), and stroke (20). In a quantitative analysis of 17 studies involving 20 000 patients, the adjusted odds ratios for morbid events among patients with left ventricular hypertrophy compared with those without this condition ranged from 1.4 to 5.4 (21). Among patients with essential hypertension, the risk for death and morbidity is higher among those with concentric left ventricular hypertrophy than among those with eccentric hypertrophy or concentric remodeling (22). In a pooled analysis of 1145 patients in four studies, the incidence of morbid events in

patients with progression of left ventricular hypertrophy was 13% to 59% compared with 7% to 12% in patients with regression of left ventricular hypertrophy (21). Diminished coronary vasodilator reserve, increased myocardial oxygen demand, subendocardial ischemia, lethal arrhythmias, and diminished ventricular performance may explain the increased risk associated with left ventricular hypertrophy (23).

Nonpharmacologic interventions, such as weight reduction, sodium restriction, and aerobic physical exercise (24), can reduce left ventricular mass. In patients with essential hypertension, effective blood pressure control is the most important intervention to reduce left ventricular mass (25). It is suspected that different antihypertensive medications have disparate effects on left ventricular mass, independent of reduction of blood pressure. In a meta-analysis of 39 clinical trials performed through June 1995, the use of angiotensin-converting enzyme inhibitors, calcium-channel blockers, diuretics, or β -blockers was associated with respective reductions in left ventricular mass of 13%, 9%, 7%, and 6% (25). In a recent trial, patients whose blood pressure was adequately controlled while receiving monotherapy with captopril, hydrochlorothiazide, or atenolol showed reduction in left ventricle mass, but those receiving diltiazem, clonidine, or prazosin did not (26). In a subset analysis of 104 patients from the Systolic Hypertension in the Elderly Program, a diuretic-based regimen significantly reduced left ventricular mass index (27).

The lack of standard, universally accepted elec-

Table 2. Associations between New and Established Risk Factors*

New Risk Factor	Association with Established Risk Factors
Left ventricular hypertrophy	Incidence of left ventricular hypertrophy increases with age, blood pressure, and obesity (5)
Homocysteine	Higher homocysteine levels are seen in older persons, men, and postmenopausal women (6)
Lipoprotein(a)	Lipoprotein(a) levels are higher among postmenopausal women
Hypertriglyceridemia	Hypertriglyceridemia is frequently seen with diabetes mellitus; low levels of HDL cholesterol; high levels of small, dense, LDL cholesterol and intermediate-density lipoprotein particles; obesity; smoking; and postmenopausal state (1, 7-9)
Oxidative stress	The susceptibility of LDL cholesterol to oxidation is increased in the presence of hypertriglyceridemia; smoking; hypertension; diabetes; low levels of HDL cholesterol; and predominance of small, dense LDL cholesterol
Fibrinogen	Higher fibrinogen levels are associated with increased age, hypertension, diabetes, hypertriglyceridemia, high levels of LDL cholesterol, low levels of HDL cholesterol, obesity, smoking, and family history of premature coronary artery disease (10, 11)

* HDL = high-density lipoprotein; LDL = low-density lipoprotein.

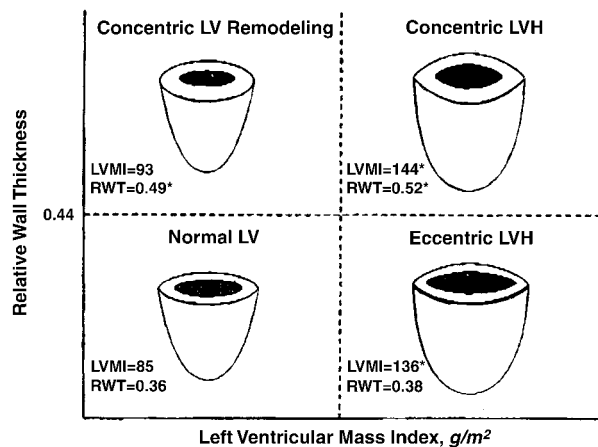


Figure. Geometric patterns of left ventricular hypertrophy. * $P = 0.001$ compared with normal persons. LV = left ventricle; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index, calculated as left ventricular mass divided by body surface area; RWT = relative wall thickness. Reprinted with permission from the American College of Cardiology (18).

trocardiographic criteria for left ventricular hypertrophy and the absence of definitive prospective evidence that reversing left ventricular hypertrophy will improve clinical outcomes over and above that achievable with blood pressure control alone have limited the application of this risk factor in routine clinical practice. For these and other reasons, left ventricular hypertrophy does not yet have a place in simplified coronary disease prediction algorithms, such as the Framingham model (28). The Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement is testing the hypothesis that reduction of left ventricular mass, independent of decreasing blood pressure, will improve cardiovascular outcomes (29).

Hyperhomocysteinemia

Homocysteine, an intermediate compound derived from methionine, is metabolized by two pathways: vitamin B₆-dependent transsulfuration and vitamin B₁₂-dependent and folate-dependent remethylation (30). Fasting total homocysteine levels of 5 to 15 mmol/L are considered normal. Some patients with normal fasting homocysteine levels have a latent abnormality of homocysteine metabolism, which can be diagnosed by measuring homocysteine levels after methionine loading (31).

The association of hyperhomocysteinemia with atherosclerotic and thrombotic vascular disease was first seen in patients with homocystinuria, a rare autosomal recessive disease caused by deficiency of cystathionine β -synthetase. The disease is characterized by exceedingly high blood levels of homocysteine and the presence of homocysteine in urine, along with skeletal defects, mental retardation, and lens dislocation (32). In recent investigations, mild to

moderate hyperhomocysteinemia was independently associated with coronary artery disease, myocardial infarction, peripheral vascular disease, cerebrovascular disease, stroke, cardiac allograft vasculopathy, and death from coronary artery disease (33–36). The relation between homocysteine levels and vascular disease is suspected to be graded. Each increase of 5 mmol/L in the fasting homocysteine level is estimated to increase the incidence of coronary disease by 1.6-fold to 1.8-fold (37). In the Physicians' Health Study, the adjusted relative risk for subsequent myocardial infarction among participants with homocysteine levels in the top 5th percentile (>15.8 mmol/L) was 3.4 compared with those with homocysteine levels in the bottom 90th percentile (33).

In contrast to findings from cross-sectional studies, results from prospective studies have been less consistent. Only two (33, 38) of five prospective studies (33, 38–41) found a positive relation between homocysteine levels and coronary disease. Furthermore, when one of these studies was extended by 2.5 years, it no longer showed an association between homocysteine level and coronary artery disease (42). Similarly, in the Atherosclerosis Risk in Communities Study (41), women (but not men) with homocysteine levels in the top 10th percentile had a higher incidence of coronary disease; however, with adjustment for other risk factors, homocysteine level was not significantly associated with coronary disease.

Several effects of homocysteine may contribute to its role in vascular disease. Homocysteine promotes endothelial dysfunction (43), endothelial cell injury (44, 45), and proliferation of smooth-muscle cells (46). In addition, it enhances thromboxane A₂ formation and platelet aggregation (47), reduces the protective effect of endothelium-derived relaxing factor (48), increases binding of lipoprotein(a) to fibrin (49), and has procoagulant effects (6).

Genetic, nutritional, and other factors are involved in the development of hyperhomocysteinemia. Up to 80% of patients with hyperhomocysteinemia have low cystathionine β -synthase activity (34). A thermolabile variant of methylenetetrahydrofolate reductase with reduced enzymatic activity has been seen in 5% of the general population, in about 17% of patients with coronary artery disease, and in 28% of patients with premature vascular disease who have hyperhomocysteinemia (37). Low levels of folate, vitamin B₁₂, and vitamin B₆ are commonly seen in patients with hyperhomocysteinemia (50). Whether nutritional deficiency of these vitamins by itself can increase homocysteine levels or whether this response occurs only in persons with a genetic predisposition to hyperhomocysteinemia is unknown.

In patients with hyperhomocysteinemia, supplementation with folate, vitamin B₁₂, and vitamin B₆ decreases homocysteine levels. Folate is the most powerful agent for reducing homocysteine levels and is effective in dosages as low as 0.65 mg/d. Higher doses are required in patients with renal insufficiency (51). The exact dose and duration of folate therapy remain to be defined, especially in view of the recent folate fortification of cereal-grain products in the United States, which may help increase plasma folate levels and decrease homocysteine levels in the population (52). The concern that folate therapy may unmask underlying vitamin B₁₂ deficiency in elderly persons can be addressed by additional supplementation with 1 mg of vitamin B₁₂ daily (37). Administration of vitamin B₁₂ alone is less effective than folate therapy, except in patients with vitamin B₁₂ deficiency (53). Vitamin B₆ supplementation does not decrease fasting homocysteine levels, but it may reduce homocysteine levels after methionine loading (54). Combined supplementation with these vitamins reduces homocysteine levels in elderly patients irrespective of serum vitamin concentrations (55). In small studies, the use of oral estrogen in men and postmenopausal women is associated with a 11% to 14% reduction in fasting homocysteine levels (56, 57).

Despite the potential relation between hyperhomocysteinemia and vascular disease seen in epidemiologic and observational studies, no prospective data support benefit from reduction in homocysteine levels. Large randomized clinical trials addressing the impact of decreasing homocysteine levels on vascular risk are under way.

Lipoprotein(a) Excess

The lipoprotein(a) molecule is structurally similar to low-density lipoprotein (LDL) cholesterol, with the addition of a large glycoprotein, designated as apolipoprotein(a) (58). Lipoprotein(a) competes with plasminogen for binding sites, resulting in decreased synthesis of plasmin and inhibition of fibrinolysis (59). Other effects of lipoprotein(a) include increased cholesterol deposition in the arterial wall (60), enhanced foam-cell formation (61), generation of oxygen free radicals in monocytes (62), promotion of smooth-muscle-cell proliferation (63), and induction of monocyte chemotactic activity in endothelial cells (64).

Substantial controversy surrounds the role of elevated levels of lipoprotein(a) as a risk factor for vascular disease. Prospective and retrospective studies have suggested an independent association between high levels of lipoprotein(a) (>1.07 $\mu\text{mol/L}$ [>30 mg/dL]) and presence and extent of coronary

artery disease (65–70), premature coronary artery disease (71–74), myocardial infarction (75, 76), restenosis after balloon angioplasty (77), cerebrovascular disease (78–80), saphenous vein bypass graft disease (81), and cardiac allograft vasculopathy (82). This association has been documented in men and women (65–67, 70, 83) and in white persons, African Americans, and Asian Indians (84–87). Up to 20% of patients with premature coronary artery disease have elevated lipoprotein(a) levels (88), making lipoprotein(a) excess the most common inherited lipoprotein disorder in these patients.

Other studies have shown no association between lipoprotein(a) levels and vascular disease. In the Physicians' Health Study, which involved 14 916 predominantly white, middle-aged men, serum lipoprotein(a) level did not correlate with future risk for myocardial infarction or stroke (89, 90). In the Helsinki Heart Study, baseline lipoprotein(a) levels were similar in patients who developed coronary events over 5 years of follow-up and in those who did not (91). A 5-year prospective follow-up study of 2156 French Canadian men showed that elevated lipoprotein(a) level was not an independent risk factor for coronary artery disease, but it seemed to enhance the deleterious effect of increased total and LDL cholesterol levels and to counteract the beneficial effect of elevated levels of high-density cholesterol (92). In a study of 140 African-American patients, plasma lipoprotein(a) levels were similar in those with and in those without coronary disease (93).

Conflicting results from previous studies may relate to several factors, including acquisition of samples during acute illness, inadequate sample storage temperature or prolonged storage, lack of standardized assays, and vague definitions of end points (94–96). On the basis of current evidence, the value of screening for and treating lipoprotein(a) excess is debatable, especially given the many other risk factors for which modification is known to be beneficial. Treatment of lipoprotein(a) excess should be considered for patients with a history of premature vascular disease that is not attributable to other risk factors, but only with the clear understanding that no trial data show clinical benefit from reducing lipoprotein(a) levels. In men with high LDL cholesterol and lipoprotein(a) levels, the atherogenic potential of lipoprotein(a) is neutralized by effective reduction of LDL cholesterol levels (97). Most dietary interventions (98), antilipid drugs (96), and exercise (99) do not affect lipoprotein(a) levels; recent evidence suggests that a fish diet may reduce lipoprotein(a) levels (100). Of the available antilipid measures, only estrogens (in postmenopausal women) and nicotinic acid (3 to 4 g/d) are associated with reductions in lipoprotein(a) levels (101,

102). Other promising agents include angiotensin-converting enzyme inhibitors (103), neomycin sulfate (102), and *N*-acetylcysteine (104).

Hypertriglyceridemia

The exact role of hypertriglyceridemia as a risk factor for atherosclerosis remains elusive (105). Although high fasting triglyceride levels are generally predictive of cardiovascular risk, multivariate adjustment for other risk factors diminishes this association (1, 7). Furthermore, significant intra-individual variation exists in fasting plasma triglyceride levels, which probably leads to substantial bias in epidemiologic studies (106).

Nevertheless, a growing body of evidence supports hypertriglyceridemia as an independent cardiac risk factor. In a meta-analysis of 17 population-based, prospective studies involving more than 57 000 patients (107), each increase in serum triglyceride level by 1 mmol/L (88.6 mg/dL) was associated with crude relative risks for cardiovascular disease of 1.32 in men and 1.76 in women. After adjustment for other risk factors, the relative risks remained significant at 1.14 in men and 1.37 in women. Other recent studies concluded that fasting (108) and non-fasting triglyceride levels (109) are significant, independent predictors of the future risk for myocardial infarction. Furthermore, in the Copenhagen Male Study, the independent relative risks for coronary artery disease over 8 years of follow-up among participants with the middle and highest thirds of triglyceride levels were 1.5 and 2.2, respectively, compared with participants with levels in the lowest third (110). In addition, triglyceride-rich lipoproteins have been shown to have an important, independent role in the angiographic progression of coronary artery disease, particularly for lesions with less than 50% diameter stenosis (111, 112).

Hypertriglyceridemia frequently coexists with low levels of high-density lipoprotein (HDL) cholesterol (8) and high levels of atherogenic lipids, such as small, dense LDL particles (9). Hypertriglyceridemia may represent a procoagulant state mediated by increased levels of factors I, VII, VIII, and X and plasminogen activator inhibitor-1, as well as by reduced tissue plasminogen activator activity (7). Triglyceride-rich lipoproteins may also be directly atherogenic (9).

Although definitive data are lacking, clinical studies suggest a beneficial effect from reducing triglyceride levels. The Bezafibrate Infarction Prevention Study enrolled 3122 patients (serum total cholesterol level, 4.66 to 6.48 mmol/L [180 to 250 mg/dL]; LDL cholesterol level \leq 4.66 mmol/L [\leq 180 mg/dL]; HDL cholesterol level \leq 1.17 mmol/L [\leq 45 mg/dL]; and triglyceride level \leq 3.39 mmol/L [\leq 300

mg/dL]) with coronary artery disease to evaluate the efficacy of bezafibrate-induced reduction in serum triglyceride levels and increases in HDL cholesterol levels on the incidence of fatal and nonfatal myocardial infarction and sudden death (113). Among patients with high baseline triglyceride levels (>2.26 mmol/L [>200 mg/dL]), bezafibrate reduced the incidence of study end points. In the Bezafibrate Coronary Artery Intervention Trial, which involved patients with coronary artery disease, bezafibrate decreased angiographic disease progression and acute coronary events (114). The magnitude of benefit was similar to that seen in trials using simvastatin and pravastatin (115). Because LDL cholesterol levels were essentially unchanged in the Bezafibrate Coronary Artery Intervention Trial, benefit from bezafibrate probably relates to other effects of this drug, such as reduction in triglyceride levels. However, patients receiving bezafibrate also had reductions in fibrinogen levels and increases in HDL cholesterol levels, which may explain some of the benefit from this drug.

A case for decreasing triglyceride levels has also been made on the basis of comparison of patient outcomes in two large primary prevention studies (7). In the Lipid Research Clinics Study (116), reducing LDL cholesterol levels by 21% without a significant change in triglyceride levels was associated with a 19% reduction in fatal and nonfatal myocardial infarction. The Helsinki Heart Study (117), in which levels of LDL cholesterol and triglycerides were decreased by about 10% and 43%, respectively, showed a greater reduction (34%) in the incidence of myocardial infarction. Even if a comparison between two different studies is valid, the greater benefit in the Helsinki Heart Study may have been secondary to greater improvement in HDL cholesterol levels (10% compared with 3%).

Thus, the benefit of reducing triglyceride levels remains largely indirect. However, it may be reasonable to attempt reduction of triglyceride levels in hypertriglyceridemic patients at high risk for atherosclerosis or in those with documented disease. Such measures as weight loss, caloric restriction, physical activity, decreased alcohol consumption, and cessation of smoking, all of which decrease triglyceride levels, may also reduce cardiovascular risk independent of their effect on triglyceride levels.

Oxidative Stress

Oxidative modification of LDL cholesterol plays a central role in atherogenesis (118, 119). Oxidized LDL acts as a chemoattractant for T lymphocytes and monocytes, immobilizes macrophages within the cell wall (120), increases LDL uptake by the macrophages, and promotes the formation of foam cells

(121). In addition, oxidized LDL is directly cytotoxic to subendothelial and smooth-muscle cells (122). Oxidative stress, although not a readily measured entity, underlies the current enthusiasm for antioxidant therapy in preventive cardiology.

Primary Prevention Studies

Epidemiologic and observational studies have suggested that high intakes of vitamins E, C, and A may provide primary protection against cardiovascular disease (123–125). The first National Health and Nutrition Examination Survey (126), which involved more than 11 000 participants, suggested that daily intake of vitamin C was inversely related to cardiovascular and all-cause mortality. In a study of almost 40 000 middle-aged male health professionals in the United States, consumption of supplemental vitamin E (≥ 100 IU/d) for 2 years or longer was associated with a 37% reduction in the incidence of coronary disease. Supplemental β -carotene reduced the risk for coronary artery disease in smokers and ex-smokers only (124). In contrast to the First National Health and Nutrition Examination Survey (126), high intake of vitamin C in this study did not provide protection from coronary disease. In the Nurses' Health Study, supplemental vitamin E was associated with a 41% reduction in the incidence of coronary disease over 8 years of follow-up, after adjustment for conventional risk factors (125). In the Iowa Women's Study, high dietary intake of vitamin E was associated with a lower risk for death from coronary disease, but intake of supplemental vitamin E did not show any beneficial effect (127). However, because details relating to the dose and duration of vitamin E supplementation were not available, these results cannot be compared directly with those of the Nurses' Health Study. In the Lipid Research Clinics Coronary Primary Prevention Trial and Follow-up Study (122), a high level of serum carotenoids was associated with decreased risk for coronary disease among men with preexisting hyperlipidemia.

Optimism about the role of antioxidant vitamins in primary prevention was blunted by the results of placebo-controlled, primary prevention trials. In the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study (128), the use of vitamin E (50 mg/d) was associated a slight reduction in deaths from coronary disease (crude relative risk reduction, 5%) but with more deaths from cancers and hemorrhagic stroke, resulting in a nonsignificant 2% higher mortality rate among participants who received vitamin E. Among participants who received β -carotene, an increased incidence of deaths from lung cancer, coronary disease, and ischemic and hemorrhagic stroke was seen, resulting in a significant 8% increase in total mortality over 5 to 8 years of follow-up. Sim-

ilarly, in the Beta-Carotene and Retinol Efficacy Trial (129), a double-blind, placebo-controlled trial of daily therapy with 30 mg of β -carotene and 25 000 IU of retinyl palmitate in more than 18 000 participants, a higher incidence of lung cancer and mortality from this disease were seen in the active intervention group (129). In the Physicians' Health Study, supplementation with β -carotene (50 mg given on alternate days) produced no significant change in the incidence of malignant neoplasms, cardiovascular disease, or death from all causes (130). Similar results were seen in a subset analysis of current and former smokers. Differences between outcomes in large studies may relate to several factors, including varied study designs (observational studies that assessed nutritional intake or serum levels of antioxidants compared with randomized clinical trials), use of different doses of antioxidants, and different primary study end points (cardiovascular compared with cancer protection). The Women's Health Study (131) is an ongoing primary prevention trial that aims to randomly assign 40 000 women to therapy with aspirin, β -carotene, and vitamin E (600 IU every other day) in a 2×2 factorial, double-blind manner.

Secondary Prevention Studies

In the Cambridge Heart Antioxidant Study (132), more than 2000 patients with documented coronary disease were randomly assigned to receive placebo or vitamin E (400 IU/d or 800 IU/d). Over a median follow-up of 1.4 years, patients who received vitamin E had a 77% reduction in the risk for nonfatal myocardial infarction but no reduction in cardiovascular deaths. In the Cholesterol-Lowering Atherosclerosis Study (133), administration of supplemental vitamin E (≥ 100 IU/d) led to a decrease in the rate of progression of angiographically diagnosed coronary disease. In a recent analysis of patients in this study, an inverse association was found between self-reported supplementation of vitamins E and C and rate of progression of carotid arterial intima-media thickness (134). Enrollment is under way in the Women's Antioxidant and Cardiovascular Study, a placebo-controlled secondary prevention trial of antioxidant vitamins (vitamins E and C and β -carotene) among 8000 women with preexisting cardiovascular disease (135).

It is hoped that definitive results from ongoing prospective clinical trials (131, 135) will clarify the ambivalence regarding the use of vitamin supplements. In the meantime, a case could be made for daily supplementation with vitamin E (400 IU/d) in patients with documented coronary artery disease, with the caveat that such treatment may reduce the incidence of nonfatal myocardial infarction but does

Table 3. Evidence Supporting the Pathogenetic Role of New Cardiovascular Risk Factors

Risk Factor	Evidence of Association with Cardiovascular Disease	Evidence of Benefit from Risk Factor Modification
Left ventricular hypertrophy	In pooled analysis, the odds ratio for morbid cardiovascular events in patients with ventricular hypertrophy compared with those without this condition ranged from 1.4 to 5.4 (21)	In pooled analysis, the incidence of morbid events in patients with progression of left ventricular hypertrophy was 13% to 59% compared with 7% to 12% in those with regression of left ventricular hypertrophy (21)
Hyperhomocysteinemia	In a meta-analysis, each increase of 5 $\mu\text{mol/L}$ in serum homocysteine increased the risk for coronary artery disease by 1.6- to 1.8-fold (37)	Large randomized clinical trials addressing the impact of reducing homocysteine levels on vascular risk are under way
Lipoprotein(a) excess	Some studies suggest an independent association between high levels of lipoprotein(a) ($>1.07 \mu\text{mol/L}$ [$>30 \text{ mg/dL}$]) and vascular disease (65–76); other large-scale trials have not confirmed this relation (89–92)	No data from prospective clinical trials exist to indicate independent benefit from decreasing lipoprotein(a) levels
Hypertriglyceridemia	In a meta-analysis, each increase in serum triglyceride level of 1 mmol/L was associated with an adjusted relative risk of 1.14 in men and 1.37 in women for cardiovascular disease (107)	Among patients with high baseline triglyceride levels ($>2.26 \text{ mmol/L}$ [$>200 \text{ mg/dL}$]) in the Bezafibrate Infarction Prevention Study (113), bezafibrate reduced the incidence of fatal and nonfatal myocardial infarction
Oxidative stress	Oxidative modification of low-density lipoprotein cholesterol plays a central role in atherogenesis (118, 119)	Among patients with coronary disease, vitamin E (400 or 800 IU/d) led to a 77% reduction in the risk for nonfatal myocardial infarction (132)
Hyperfibrinogenemia	The odds ratio for coronary artery disease for the highest compared with the lowest tertile of fibrinogen level is estimated to be 2.3 (147)	In patients with high baseline fibrinogen levels and coronary artery disease, reduction of fibrinogen with bezafibrate therapy reduced the incidence of cardiac death and ischemic stroke (154)

not reduce cardiovascular mortality. Data supporting the use of vitamins A and C are much weaker.

Oxidative stress can also be modified by specific dietary measures. Two diets that have received attention are the “Mediterranean diet,” which is rich in oxidation-resistant monounsaturated fat (136), and a diet rich in ω -3 fatty acids (137). The beneficial effects of these diets may be related to their antioxidant properties (138). In addition, the flavonoids present in red wine, fruits, vegetables, and tea have strong antioxidant properties and may have cardioprotective effects (139). Antioxidant medications, such as probucol, may have cardioprotective properties (140, 141).

Hyperfibrinogenemia

Several studies have established the association of plasma fibrinogen levels with cardiovascular disease (142–146). In one pooled analysis (147), the odds ratio for coronary disease for the highest compared with the lowest tertile of fibrinogen level was 2.3. In patients with established coronary disease, fibrinogen levels are associated with angiographic severity of disease (148, 149), recurrent ischemic events (150), and risk for restenosis after coronary angioplasty (151). In male nonsmokers, fibrinogen levels show a strong association with all-cause and cardiovascular mortality (152). In patients presenting with unstable angina or non-Q-wave infarction,

hyperfibrinogenemia is associated with a higher chance of death or myocardial infarction (153). Preliminary results of the Bezafibrate Infarction Prevention Study suggest that reduction of plasma fibrinogen levels in patients with high levels at baseline and preexisting coronary artery disease decreases the incidence of cardiac death and ischemic stroke (154).

In addition to its role in the coagulation cascade, fibrinogen stimulates smooth-muscle-cell migration and proliferation, promotes platelet aggregation, and increases blood viscosity (150) and may have mitogenic and angiogenic properties (155). Furthermore, fibrin binds to lipoprotein in the vascular intima (155, 156) and may enhance accumulation of extracellular lipid in fibrous plaques. Hyperfibrinogenemia may also be a marker of the inflammatory activity associated with the atherosclerotic process.

High fibrinogen levels are associated with increased age, female sex, high levels of LDL cholesterol and triglycerides, low levels of HDL cholesterol, obesity, smoking, physical inactivity, family history of premature coronary disease, and personal history of hypertension or diabetes (10, 11). However, these associations explain only part of the interindividual variation in fibrinogen levels (157). Socioeconomic factors, such as lower social and educational class; lack of control over work; shorter body height; and acute mental stress are also associated with higher fibrinogen levels (158, 159). In addition, substantial variability in fibrinogen level

exists within patients (160), and it has been suggested that a single fibrinogen reading is not adequate for prediction of vascular risk.

Smoking cessation, weight loss, regular exercise, and moderate alcohol consumption (161) are known to reduce plasma fibrinogen levels. Therapy with bezafibrate, ciprofibrate, and fenofibrate, but not gemfibrozil, may reduce fibrinogen levels by up to 40% (162–166). In postmenopausal women and elderly men, estrogen replacement is associated with significant reduction of plasma fibrinogen levels (56, 101). Ticlopidine, but not aspirin, is known to reduce fibrinogen levels (167).

The lack of a single standardized assay, the presence of intra-individual variability in fibrinogen levels, and lack of conclusive evidence that reduction in fibrinogen levels improves cardiovascular risk have limited the wide application of fibrinogen levels as a risk factor in clinical practice.

Implications

In an effort to better predict the development of vascular disease, recent studies have identified several potential new risk factors. The success of preventive measures against established risk factors (hypertension, hypercholesterolemia, and smoking) seen in the last three decades and the sheer magnitude of vascular disease burden justify the enthusiasm surrounding new risk factors. For several reasons, however, definite recommendations for screening and modification of new risk factors cannot yet be made. First, despite the abundance of data associating new risk factors with cardiovascular disease (Table 3), definitive information is lacking about the impact of modifying new risk factors on the course of cardiovascular disease. Second, we need evidence that assessment of new risk factors will extend our prognostic ability beyond strategies using established risk factors alone (168). Third, measurement techniques for some new risk factors, such as lipoprotein(a) and fibrinogen, need standardization. Finally, the cost implications of screening for and modifying new risk factors, including those discussed in this review as well as other promising risk factors (such as inflammatory markers, infectious agents, and prothrombotic states), must be determined (168). Clinical trials that address the effect of modifying new risk factors on cardiovascular outcomes will help in selecting risk factors with potential for routine clinical use.

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