Multifactorial Approach to the Primary and Secondary Prevention of Atherosclerosis

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We review data regarding the importance of various conventional and evolving atherosclerosis risk factors. In addition, we discuss a multifactorial approach to the primary and secondary prevention of major vascular events, including stroke.

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There is currently great enthusiasm in the cardiovascular arena for the prevention and treatment of stroke due to cardiogenic emboli, including the use of transesophageal echocardiography as a diagnostic tool (for detecting thrombi in the left atrium and left atrial appendage, as well as complicated aortic arch plaques), antithrombotic therapy for atrial fibrillation and patients with cardiac thrombi, as well as for the identification and management of patients with atrial septal defects, including patent foramen ovale (1). However, it must be recognized that the leading cause of cardiovascular events, including stroke, continues to be due to atherosclerosis. Therefore, reducing progression, stimulating regression, and reducing the risk of acute events in patients with known atherosclerosis remains the leading focus in the primary and secondary prevention of most cardiovascular diseases, including stroke.

We will briefly review the leading conventional and evolving atherosclerosis risk factors (Table 1) as well as a multifactorial approach to the primary and secondary prevention of major vascular events.

CONVENTIONAL RISK FACTORS

Cigarette smoking

Cigarette smoking remains a major risk factor for developing carotid artery disease (CAD) and stroke, and is attributed to more than 430,000 deaths in the US each year, including 40,000 nonsmokers who die as a result of exposure to environmental smoke (2-4). Smoking is responsible for one in five US deaths and costs the US economy at least $100 billion in health care costs and lost productivity each year. Recent data suggest that about half of all regular cigarette smokers die of smoking-related diseases (2-4).

The benefits to quitting smoking, even after many years of active tobacco abuse, are significant. Whereas it takes nearly 20-25 years after smoking cessation for the risk of lung cancer to fall to the risk level of one who has never smoked, quitting smoking reduces the risk of subsequent myocardial infarction (MI) and other major cardiovascular events generally within 2 years. Persons with known atherosclerosis experience as much as a 50% reduction in the risk of major morbidity and mortality soon after quitting smoking (4,5). Furthermore, a pack-a-day smoker can expect to save more than $1000 per year in tobacco costs by quitting. Nicotine substitution has been the most promising pharmacological method studied to date and has been demonstrated to be two to three times more effective than placebo in maintaining smoking cessation (6). In our experience, nicotine therapy, often combined with welbutrin therapy and regular exercise training, has helped the majority of our atherosclerosis patients to successfully quit and maintain smoking cessation.

Table 1: Risk factors for atherosclerosis.

Conventional	Unconventional
• Cigarette Smoking • Hypertension • Dyslipidemia - High LDL - High triglycerides - Low HDL • Diabetes • Obesity • Physical Inactivity	• Inflammation (HSCRP) • Homocysteine • Lipoprotein(a) • Psychological Stress - Depression - Hostility - Anger - Distress

Hypertension

There is a strong positive and continuous correlation between blood pressure (BP) and the risk of cardiovascular diseases (including MI, but more so chronic heart failure [CHF] and stroke), which is even true within the normotensive range (6-8). This correlation is more robust with systolic than diastolic BP and is highly correlated with pulse pressure. Not only is hypertension established as a risk factor for vascular disease, the results of intervention trials have provided evidence that lowering BP can substantially reduce the risk of cardiovascular events (9,10). Although most of the original antihypertensive trials, particularly with diuretic agents, produced only minimal reductions in CAD events, all of these studies have demonstrated impressive reductions (often in the 30% - 50% range) in the risk of stroke. In the Heart Outcomes and Prevention Evaluation (HOPE) study, one antihypertensive agent (angiotensin converting enzyme [ACE]-inhibition with ramipril) was even shown to reduce the risk of stroke by 32% (despite minimal reductions in BP) in patients who were not even hypertensive at study entry (11, 12). In the Losartan Intervention For Endpoint Reduction in Hypertention (LIFE) trial of patients with hypertension and echocardiogram (ECG) evidence of left ventricular hypertrophy, an angiotensin receptor blocker (ARB, losartan) produced a 25% reduction in the risk of stroke compared with a beta blocker (atenolol), despite both drugs having equal and substantial reductions in BP (average 30/17 mmHg) (13).

Lipids

Various lipid fractions, including high LDL cholesterol, high triglycerides, and, particularly low levels of HDL, are potent predictors of atherosclerosis, especially CAD events (14-17). However, most studies demonstrate that cholesterol is a relatively weak predictor of stroke. Despite this, numerous statin trials, including a meta-analysis of 21,303 patients (18), a meta-analysis of three pravastatin studies (Pravastatin Pooling Project) (19), the recent Myocardial Ischemial Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (20), and the Heart Protection Study (21) all show very powerful effects of these agents on the risk of major ischemic stroke: an average of a 30% reduction.

Diabetes

Diabetes has long been recognized as an extraordinarily potent risk factor for vascular disease, and in most epidemiologic studies it appears to double or triple the risk of major vascular disease events (22, 23). The very high risk associated with diabetes is further evident since the recent publication of the Adult Treatment Panel (ATP) III guidelines (24). These guidelines recognize diabetes as a CAD risk equivalent (as opposed to merely a risk factor), indicating that a diabetic patient without known vascular disease is at higher risk than a nondiabetic with known vascular disease, so the patient with diabetes must be vigorously assessed and treated aggressively. In addition, the new ATP III guidelines have fully recognized the importance of the insulin resistance syndrome and have now defined the metabolic syndrome. We have recently demonstrated that the metabolic syndrome is present in nearly 60% of our patients with CAD and is associated with a highly inflammatory state characterized by a > 2-fold elevation in high-sensitivity C-reactive protein (HSCRP) compared with CAD patients without the metabolic syndrome (25).

Obesity

Obesity is the second leading cause of preventable death in the US and represents a major and growing public health concern that raises the risk of mortality from hypertension, dyslipidemia, type 2 diabetes, CAD, and stroke, as well as a number of noncardiovascular diseases (26-28). Higher body weights are also associated with increased all-cause mortality. There is strong evidence that even modest weight loss in overweight and obese individuals reduces risk factors for major vascular disease (29,30). Nonrandomized trials have also suggested significant mortality reductions associated with weight reduction (31, 32).

Physical Inactivity

We have recently reviewed the effects of regular exercise and high levels of fitness on overall cardiovascular health, and, clearly, physical inactivity has various adverse effects on many of the vascular disease risk factors. Most studies demonstrate inactivity to be an independent predictor of vascular disease and overall mortality (33).

UNCONVENTIONAL RISK FACTORS

Inflammation

Atherosclerosis is certainly a chronic inflammatory disease, and acute vascular events involve acute plaque inflammation. Although many inflammatory markers have been studied and correlated with the risk of vascular events, by far the greatest enthusiasm recently has been with the data regarding HSCRP (34). Many studies demonstrate that HSCRP is a potent predictor of cardiovascular events in men and even more so in women. Recent data indicate that it is a much better predictor of vascular disease than is LDL cholesterol and adds considerably to the established Framingham Risk Score to accurately predict the risk of major vascular events (34).

At the present time, we believe that HSCRP should be measured in patients felt to be at intermediate risk of vascular disease events (e.g., patients with 10-year risk of 5%-15%). HSCRP values would not likely be very useful in patients with very low risk (e.g., those with a 10-year risk of < 5%). Likewise, HSCRP value may not be very helpful in patients with known significant vascular disease or those with a 10-year risk of > 15%-20% who already have evidence that more vigorous treatment is needed.

Homocysteine

Many studies have indicated that homocysteine has adverse effects on endothelial function and is a procoagulant thereby increasing risks of major vascular events (35, 36). A recent meta-analysis indicates that elevated homocysteine values are at least a modest independent predictor of both CAD events and stroke (37). At the present time, there are only two established ways to reduce homocysteine: folic acid therapy and exercise training (35,36). We generally measure homocysteine levels in patients who present with atherosclerosis prematurely, or those who have atherosclerosis out of proportion to their risk factor profile.

Lipoprotein (a) or Lp(a)

Lp(a) values are very genetically determined by autosomal dominant transmission, play a role in foam cell formation (an early step in the atherosclerosis process), and act as a competitive inhibitor of fibrinolysis (36,38). Not surprisingly, many studies indicate that Lp(a) is related to CAD and stroke, and a recent meta-analysis indicates that elevated Lp(a) increases the risk of vascular events by 30% in secondary prevention studies and by 70% in primary prevention studies (38).

Currently only two therapies safely reduce Lp(a). Niacin therapy reduces Lp(a) values by 20%-70% (39) and estrogen therapy reduces Lp(a) by 15%-30%. Estrogen therapy has currently been criticized due to adverse effects noted in both the Heart and Estrogen/Progestin Replacement Study (HERS) (40) and the Women's Health Initiative (41). However, even in the HERS trial, estrogen therapy reduced levels of Lp(a) in women with CAD and high baseline levels of Lp(a) and was associated with significant reductions in cardiovascular events and cardiovascular mortality in this group. Otherwise, there are no intervention studies demonstrating that reducing Lp(a) is associated with risk reduction, although most experts would expect this to be the case. On the other hand, therapy to reduce LDL cholesterol without reducing Lp(a) has reduced the progression of CAD in coronary patients with elevated Lp(a).

We currently recommend measuring Lp(a) in patients who present with atherosclerosis prematurely or who have atherosclerosis out of proportion to their risk factor profile. We also recommend measuring Lp(a) in patients who meet borderline criteria for drug lipid treatment, patients who need lipid treatment but who are good candidates for either statin therapy or niacin therapy (e.g., patients with only mild elevations of LDL and triglycerides and mildly low HDL), as well as in patients who are compliant with statin therapy but who seem to be having only suboptimal lipid improvements with this usually potent therapy. We are generally very enthusiastic regarding the use of niacin therapy (approximately 2 g/d) for patients with elevated Lp(a), especially if they have vascular disease, are considered to be at high risk, and also have low HDL and/or high triglycerides (42).

Psychological Stress

Although somewhat controversial, we believe that psychological stress, including depression, hostility, and anxiety, is a risk factor for vascular disease and affects recovery following vascular events. We have published on the benefits of cardiac rehabilitation and exercise training for improving the atherosclerosis risk profiles in patients with these disorders (43-46).

To estimate a patient's 10-year risk of major cardiovascular disease, the Framingham Score is generally utilized, as recommended by ATP. Recent evidence suggests that this can be further improved by also incorporating HSCRP (34). We have incorporated several of these unconventional risk factors in our risk assessment, available on our website at www.myheartrisk.com.

Therapy

A recent meta-analysis suggests that for primary prevention of stroke, adequate BP reduction, treatment of hyperlipidemia, and use of antithrombotic therapy in patients with atrial fibrillation and antiplatelet therapy in patients with MI are effective and supported by evidence from randomized trials (47). Effective strategies for secondary prevention of stroke include treatment of hypertension and hyperlipidemia, antithrombotic therapy for patients with atrial fibrillation, antiplatelet therapy, and carotid endarterectomy in patients with severe carotid artery stenoses. We will briefly discuss this and other modalities in the primary and secondary prevention of atherosclerosis, including ischemic stroke (Table 2).

Antiplatelet Therapy

Substantial evidence indicates that low-dose aspirin therapy ($\leq$ 325 mg/d) is indicated in patients with known atherosclerosis, high risk of atherosclerosis, and for the primary and secondary prevention of stroke (48,49). More potent antiplatelet therapy (e.g., clopidogrel 75 mg/d) would be indicated for high-risk patients who cannot take aspirin and patients with aspirin resistance. Based on data from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) (50) and Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) (51) studies, this therapy can also be strongly considered for patients who continue to have vascular events despite aspirin therapy. However, the cost-effectiveness of using this therapy in all patients with atherosclerosis has recently been questioned (52).

Table 2. Primary and secondary prevention of atherosclerosis.

A. Antiplatelet Therapy
1. Aspirin
2. Clopidogrel
B. Antihypertensive Therapy
C. Lipid Therapy
D. Fish Oils
E. Exercise Training

Antihypertensive Therapy

Antihypertensive therapy is indicated for the primary and secondary prevention of most atherosclerosis events, but particularly for stroke (9,10). The goal of BP reduction should be levels less than 130/85 mmHg, but overzealous BP reduction (e.g., to levels <100-110/70 mmHg) may be difficult and could cause orthostatic hypotension and cerebral hypoperfusion in patients with severe cerebral vascular disease. Based on considerable evidence, we believe that most patients with atherosclerosis should be treated with an ACE inhibitor or an ARB for vascular protection (11-13). Although ACE-inhibitors (or ARBs) may particularly be beneficial for patients with severe hypertension, left ventricular dysfunction following acute MI, or CHF, we believe that many patients (more so those with diabetes) would benefit from this therapy, even if they do not need additional BP lowering.

Lipid Therapy

Based on the ATP III guidelines, most patients with established atherosclerosis, as well as other high-risk patients, need dietary and pharmacologic treatment of lipids. Although we frequently use niacin therapy for patients with very low levels of HDL cholesterol and elevated Lp(a), as well as fibrates, niacin, or high-doses of omega-3 fatty acids for those with hypertriglyceridemia, the mainstay of lipid therapy is the statin family of medications. Based on 13 published clinical event trials and an unequalled safety profile (including being hydrophilic and not metabolized by the cytochrome p 450 3A4 system), we prefer pravastatin for most patients with mild-moderate LDL elevations. However, as reviewed previously, the evidence now exists for stroke reduction with simvastatin and atorvastatin, and high doses of these agents may be indicated in patients with moderate-severe elevations in LDL cholesterol.

Omega-3 Fatty Acids (Fish Oils)

The potential benefits of omega-3 fatty acids, or fish oil therapy, have been touted for almost 30 years (53,54), and we have recently reviewed the benefits of this therapy in preventive cardiology (55), particularly for the prevention of sudden cardiac death, but also against CAD events and stroke (56). At the present time, we recommend dietary or supplemental omega-3 fatty acids at doses of approximately 1000 mg/d of EPA/DHA for our patients with known atherosclerosis or high vascular disease risk.

Exercise Training

The benefits of regular physical exercise and increasing levels of overall physical fitness have been reviewed extensively elsewhere (33). We have also recently demonstrated that our cardiac rehabilitation and exercise training program (which includes instruction on a Mediterranean-type of diet) led to a nearly 50% reduction in levels of HSCRP (57) and produced marked improvements in the metabolic syndrome (25), leading to a "cure" of this syndrome in many of our CAD patients. These benefits are in addition to the benefits that we have previously published, including marked benefits on exercise capacity, lipids, obesity indices (58), homocysteine (36), viscosity and blood rheology (59), and autonomic function (60) in our patients. Patients may obtain substantial benefit from three or four 30-45 minute exercise sessions per week; however, because obesity is such a tremendous and growing problem for our patients, we generally recommend moderate-intensity exercise for 45 min/d on most days (preferably 5 or 6 per week). Although recent evidence indicates that greater benefits may be achieved with higher intensity and longer duration exercise, many studies clearly point out that even a few days per week of light exercise is associated with substantial health benefits.

CONCLUSION

As specialists in cardiovascular diseases, we often direct our major efforts in patients with established CAD. However, the process of atherosclerosis affects not only the coronary arteries but also other vascular beds (including the arterial system to the kidneys, legs, and brain). Therefore, a major emphasis needs to be placed on a generalized approach to primary and secondary prevention of atherosclerosis, which will lead to broad reductions in all areas of cardiovascular diseases, including ischemic stroke.

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