Prevention of atherosclerosis progression in asymptomatic healthy elderly

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ABSTRACT
This review focuses on the role of lipid-lowering, blood pressure-lowering, antithrombotic drugs and diet and their place in the prevention and treatment of atherosclerosis in middle-aged and elderly men and women. The major emphasis is on noninvasive assessment of the extent of atherosclerotic plaque and the importance of following plaque progression or regression by use of noninvasive ultrasound. With these data, we can demonstrate to both patients and physicians the value, at any age, of treating hypertension and abnormal blood lipids. Am J Clin Nutr 2007;86(suppl):1569S–71S.

KEY WORDS Blood lipids, cholesterol-lowering drugs, HDL-raising drugs, antithrombotic drugs, carotid ultrasound, plaque regression

INTRODUCTION
In the past several decades, a great deal of clinical research has been focused on the prevention of atherosclerosis and its sequelae. Multiple trials with lipid-lowering drugs, in men and women, in several countries, have shown drug-related lowering of heart attack and stroke incidence (1). Unfortunately, for many persons, the significant question is not prevention, but rather whether appropriate treatment is available to halt progression, and even cause regression, of atherosclerosis. The answer to the question is a definite “yes.” The data make clear that middle-aged men and women, with or without clinically evident disease, benefit greatly from lowering blood cholesterol, blood sugar, blood pressure, and hypercoagulability. Effective treatments are available for all the risk factors listed above. Current methods for noninvasive assessment of atherosclerosis burden are now safely, painlessly, and inexpensively available. The importance in motivating patients to follow their treatment regimen on a regular basis is obvious.

THE ROLE OF DIET
Diet plays an important role in resistance, or in susceptibility, to atherosclerosis and its sequelae, most commonly coronary heart disease and stroke. Both the composition and the amount of food consumed have profound effects on the risk of heart disease and stroke. In women, as in men, the risk of early onset of these diseases is directly related to the composition and the amount of diet consumed.

A major aspect of food composition is the nature, as well as the quantity, of the food fat. A normal diet should have a moderate amount of fat, most of it as mono- or di-unsaturated fatty acid glycerides. Food fats in milk, cream, butter, and meat are mostly fully saturated, whereas fats ingested from vegetables and vegetable oils are mono- or di-unsaturated. Olive oil, for example, consists almost entirely of triolein, which is entirely monounsaturated. In contrast, fats and oils from many fish and other marine animals that eat predatory fish, that in turn eat lake and oceanic grasses, are rich in polyunsaturated fatty acids and other lipids. Some of these lipids, which are in the human diet by way of eating fish and other aquatic animals, eg, oysters, clams, and other shellfish, have a significant LDL-lowering effect in humans (2). The beneficial effects have included not only changes in plasma lipids, but also inhibition of atherosclerotic progression in animals (3) and in human subjects (4). In contrast, the current trend of hydrogenating food fat is unfortunate, because hydrogenated fats raise total plasma cholesterol (5) and may very well be atherogenic.

Although men usually develop atherosclerosis before women do, both sexes are at much higher risk if they are overweight. In a recent study, a randomly accrued group of healthy but obese women were found to have a highly significant correlation of common carotid intimal media thickness, a sensitive and reliable parameter of generalized atherosclerotic plaque burden (6), with the extent of the patient’s body weight (7). As is the case with medications, middle-aged and elderly persons who switch to a healthy diet, both qualitatively and quantitatively, can achieve major reduction in risk. The role of diet in the control of atherosclerosis in diabetics is critical and is discussed in more detail in the next section.

DIABETES
Diabetes mellitus is a major cause of atherosclerosis, not only in Europe and North America, but worldwide. It is discussed separately because both its presentation and its treatment are somewhat different from those of non-diabetes-related hyperlipidemia and hypertension. In addition, type 1 (juvenile diabetes)
and type 2 (adult-onset diabetes) diabetes are significantly different from each other in both their time of onset and their relation to atherosclerosis. Type 1, the juvenile form, as the name suggests, appears in childhood and is characterized by low circulating insulin concentrations and not usually by obesity. In my limited experience, maintenance of normal body weight and blood pressure, normal glucose concentrations, and especially maintenance of plasma glycerides as low and HDL as high, as feasible with appropriate drug treatment, markedly reduces the risk of early atherosclerosis.

Type 2 diabetes is quite different from type 1. Patients are usually characterized by high blood insulin concentrations, marked insulin resistance, and obesity. Hypertension and hyperlipemia are also usually present. Total plasma cholesterol and triacylglycerols may vary widely, but HDL cholesterol is almost always low. This presentation, often called the metabolic syndrome, is accompanied by a high incidence of atherosclerosis. Unless treated, it is almost uniformly accompanied by early onset of clinically evident atherosclerosis, manifested by peripheral vascular disease, coronary heart disease, or stroke. Strict dietary control, weight reduction to normal levels, and appropriate lipid-lowering drug therapy with fibrates and statins, as appropriate, are the keys to successful treatment. Such treatment may reduce the symptoms of coronary and peripheral atherosclerosis. The major challenge is that of motivating the patient to comply with strict attention to calorie control and drug therapy. In my experience, patients who have followed this regimen have often been rewarded with stability, or even regression, of their coronary and peripheral vascular disease. Usually, when they notice the difference, they stick to their regimen. In obese children, type 2 diabetes and hyperlipidemia may be seen in adolescence and even earlier. In these patients, dietary control, albeit difficult, is the first step in preventing early onset of atherosclerotic disease.

LIPID-LOWERING DRUGS

An early meta-analysis of lipid-lowering treatment in women with coronary disease showed that multiple different lipid-lowering treatments decreased the likelihood of heart attack and death (8). A later study of pravastatin, a widely prescribed cholesterol-lowering drug, on coronary events after myocardial infarction in patients with average cholesterol concentrations (9) showed that both men and women, who were on average aged 59 y, treated with pravastatin had fewer subsequent cardiac events and stroke. Women had a greater decrease in events than did men, and the reduction in cardiovascular events was greater in subjects who had higher initial plasma LDL-cholesterol concentrations. In a later study of 253 men in their 60s, who had low HDL, treatment with gemfibrozil, a drug of the fibrate class, which raises plasma HDL, significantly reduced the occurrence of stroke (10). Interestingly, the lower the initial HDL value, the greater was the benefit. In that regard, niacin is one of the most potent anti-atherosclerotic drugs in the armamentarium. Unlike other drugs, niacin simultaneously raises HDL and lowers LDL. It is inexpensive, and has a large body of data attesting to its efficacy. Other drugs that lower triacylglycerols almost all decrease the plasma concentration of small, dense LDLs, which are generally thought to be more atherogenic than LDL particles of normal size (11).

The jury is still out, however, because the treatments, including diet control and drug therapy, change several factors, all of which are related to atherogenesis. Obesity and diabetes are both associated with elevated plasma LDL and VLDL. The inevitable effects of treatment with weight reduction or appropriate drug therapy are to reduce plasma triacylglycerols and concomitant large LDL and VLDL and to increase plasma HDL and small dense LDL concentrations. Unfortunately, accurate sizing of LDL particles is an expensive project. Fortunately, the surrogates, lowering plasma triacylglycerol concentrations and measuring total plasma cholesterol, are fairly reliable (11). Most important, however, is to follow the progression, and hopefully regression, of the status of major arteries. As noted above, this can be measured accurately, noninvasively, and at low cost with ultrasound (4–9).

ANTITHROMBOTIC DRUGS

In addition to lipid-lowering drugs and LDL apheresis, patients, young and old, with symptomatic atherosclerosis, chiefly angina pectoris or transient cerebral ischemic attacks, usually benefit markedly by treatment with anticoagulants or antiplatelet drugs. Aspirin has a long history of reducing thromboembolic events, as have anticoagulants. As long ago as 1985, I and a colleague treated patients who had severe, symptomatic, nonoperable cardiovascular disease with simultaneous administration of aspirin and warfarin (12). The patients showed marked clinical improvement, and at the end of the 6-y follow-up, only 3 of 20 subjects had died, statistically many fewer than were expected. Nevertheless, this treatment modality is recommended only for patients whose symptoms are serious and otherwise uncontrollable. It requires very close and careful monitoring of the prothrombin time and clinical status and should be continued only if the patient improves both symptomatically and objectively. Interestingly, the results with a new antithrombotic drug, clopidogrel (Plavix; Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, New York, NY) (8–9), seem to be little different from those with the aspirin-warfarin regimen. Only time and further experience will allow us to compare the usefulness of these 2 regimens, and, likely, one or more others.

APHERESIS

Patients with intractable familial hypercholesterolemia and those with sitosterolemia (a rare sterol disorder that is more atherogenic than hypercholesterolemia), who characteristically have plasma sitosterol concentrations of >300 mg/dL (normal is <25 mg/dL), may be successfully treated with LDL apheresis. This technique is costly, but is life-saving. Its use is restricted to a relatively small number of patients, but its ability to prevent early death in otherwise fully functional children and adults makes it an important part of our armamentarium. LDL apheresis is beneficial in both the elderly and the young. For example, a 59-y-old nurse with known coronary disease had a cardiac arrest in the hospital, was resuscitated, and was sent to us for further care. She has been treated with LDL apheresis since about 1 mo after her event and every 2 wk thereafter for >3 y at this writing. At her request, she returned to all aspects of bedside nursing care 6 wk after the cardiac arrest and continues to do so.
The critical role of noninvasive assessment of disease progression and regression

One of the most important aspects of the care of men and women with hyperlipidemia, in particular, children and elderly individuals, from both a medical and a motivational point of view, is the monitoring, at appropriate intervals, of the progression or regression of the subject’s atherosclerosis. The methods used must be painless, harmless, and relatively inexpensive. They must also be completely noninvasive. Our practice is to show all patients the results of their treatment. As noted above, hardly any persons deviate from their regimen when they see the results of treatment. Furthermore, children aged 8 to 21 are often neglected for testing of blood cholesterol and triacylglycerol concentrations and for evidence of early, and sometimes not so early, atherosclerosis. In my experience, the incidence of detectable, early carotid atheroma in these children is high.

The accepted site for noninvasive assessment of plaque burden is the carotid bifurcation, because there is a high correlation between the carotids and other large arteries. The carotid ultrasound technique is noninvasive, painless, takes only a few minutes to perform, and is both reliable and reproducible. The same techniques may be used to detect and follow other important arteries, including the femorals at the groin and the dorsalis pedis in the feet.

The noninvasive assessment of disease has its own interesting history. More than 20 y ago, my colleagues and I followed in the footsteps of Dr Eugene Strandness and his colleagues (6). They used ultrasound to measure both blood flow and arterial wall thickness. We used audible sound analysis to analyze blood flow (13), along with ultrasound imaging, to provide discomfort-free, accurate, and reproducible assessment of carotid artery wall thickness as well as lumen diameter (13).

A pharmaceutical company, Bristol-Myers Squibb, demonstrated the importance of noninvasive assessment of disease by supporting 2 parallel clinical trials of plaque regression with the cholesterol-lowering drug Pravachol. The 2 trials were essentially identical, except that one trial (PLAC II) chose plaque size measured by noninvasive carotid ultrasound as the endpoint for the lipid-lowering drug (9), whereas the other trial (PLAC I) used coronary angiography, a highly invasive technique, as the endpoint (14). The results were essentially identical. The only differences were that the noninvasive trial was painless, risk-free, far less expensive, and gave a statistically significant result months before the invasive trial results reached statistical significance.

The implication of this, and many subsequent studies, is that men and women of middle age, with risk factors, family history of atherosclerosis, and other indicators of risk should be treated with the appropriate anti-atherosclerotic drug. Patients should be able to see their own quantitative progress with ease, and at low cost, to motivate them to prolong their health and life. Until quite recently, this approach, to our knowledge, has not been widely applied. It should have profound positive effects on patient compliance, and thus on the efficacy of therapy.

REFERENCES