

## Atherosclerotic Risk Factors— Are There Ten or Is There Only One?

In the January 1988 publication of the National Cholesterol Education Program on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, the expert panel listed 10 risk factors, hereafter termed “atherosclerotic risk factors,” which were predictive of coronary arterial atherosclerotic events.<sup>1</sup> The 10 atherosclerotic risk factors were the following:

1. *Serum (or plasma) total cholesterol >200 mg/dl (>5.2 mmol/liter) and low density lipoprotein (LDL)-cholesterol >130 mg/dl (>3.4 mmol/liter).*
2. *Definite clinical evidence of coronary artery disease (either myocardial infarction or ischemia [angina pectoris]).*
3. *Male sex.*
4. *History of either myocardial infarction or sudden death before 55 years of age in a parent or sibling.*
5. *Cigarette smoking (>10 cigarettes a day).*
6. *Systemic hypertension (undefined).*
7. *High density lipoprotein (HDL)-cholesterol <35 mg/dl.*
8. *Diabetes mellitus.*
9. *Cerebrovascular or peripheral vascular disease (by history).*
10. *Severe obesity (>30% overweight).*

This piece examines each of these 10 risk factors to ask if each is an independent atherosclerotic risk factor or if it is not.

**Serum (or plasma) total cholesterol or low density lipoprotein-cholesterol level:** In my view, the only absolute, unequivocal, independent atherosclerotic risk factor is an elevated serum total or LDL-cholesterol level. What constitutes an *elevated* level is debatable. If an elevated level is that minimal level above which atherosclerotic events occur, then that level in my view would be 150 mg/dl (3.9 mmol/liter). If it is the level where the risk of atherosclerotic events is substantially increased compared to lower levels, then that level would be 200 mg/dl. Irrespective of which level is chosen, the higher the level the greater the risk of an atherosclerotic event. From study of >350,000 men, Stamler et al<sup>2</sup> have clearly demonstrated that the higher the serum total cholesterol level, the greater the risk of an atherosclerotic event. The Framingham study, involving approximately 5,000 residents of that Massachusetts community, also has shown that the higher the total and LDL-cholesterol levels and the lower the HDL-cholesterol level, the greater the risk of having an atherosclerotic event.<sup>3</sup> International epidemiologic studies also have shown that populations having serum total cholesterol levels <150 mg/dl for decades have a virtual absence of atherosclerotic events.<sup>4</sup> A certain critical serum total cholesterol level is necessary before an atherosclerotic event can occur and this critical level appears to be

approximately 150 mg/dl. As the level increases above this value, the risk of an atherosclerotic event increases roughly proportional to the level. Thus, the only absolute prerequisite for a fatal or nonfatal atherosclerotic event is a serum total cholesterol level >150 mg/dl.

**Male sex:** Fatal and nonfatal atherosclerotic events are more common in men than women by a ratio of 2:1.<sup>5</sup> At least half of the atherosclerotic events in men occur before their sixtieth birthday, whereas atherosclerotic events in women are relatively infrequent before their sixtieth year.<sup>5</sup> After age 70, atherosclerotic events in women are as frequent as in men, but by age 70, over 75% of men destined to have a fatal atherosclerotic event have already had it. The average age of death in men in the USA from atherosclerotic coronary artery disease is 60, whereas the average age of women is 68.<sup>5</sup> Men have higher total and LDL serum cholesterol levels earlier in life than do women, but later in life women have higher levels than do men.<sup>6</sup> Neither men nor women, however, have atherosclerotic events unless the total cholesterol level is >150 mg/dl, and the higher the level the greater the chance of an event and the earlier the event occurs irrespective of sex. Thus, it is the person's blood cholesterol level, not the sex, that determines whether an atherosclerotic event occurs. Male sex, in my view, cannot be viewed as an independent atherosclerotic risk factor.

**Family history:** When atherosclerotic events occur in persons <55 years of age, it generally means (1) that the affected individuals have serum total cholesterol levels considerably higher than persons of similar age and sex without atherosclerotic events, and (2) that the affected individuals have total cholesterol levels much higher than those found in older individuals with atherosclerotic events. In persons with untreated familial hypercholesterolemia of the heterozygous type, the serum total cholesterol level is usually 300 to 400 mg/dl, and these individuals usually have atherosclerotic events when they are 31 to 55 years of age. In untreated individuals with familial hypercholesterolemia of the homozygous variety, the serum total cholesterol is usually >800 mg/dl and these individuals usually have atherosclerotic events before they are 20 years of age. Thus, individuals having atherosclerotic events before age 55 generally have higher total cholesterol levels than do individuals having atherosclerotic events later in life, and the genetic forms of hyperlipidemia are in these younger groups. A young age of an atherosclerotic event simply denotes very high serum to-



tal cholesterol levels and it is the cholesterol level, not the patient's age or the presence of atherosclerotic events in other family members, that is the villain.

**Cigarette smoking:** Although it is incompatible with good health, cigarette smoking, in my view, does not, in and of itself, produce atherosclerotic plaques. In populations where serum total cholesterol levels are <150 mg/dl, atherosclerotic events are rare even when cigarette smoking is widespread. In Japan, cigarette smoking is common, but atherosclerotic events are relatively uncommon. The average serum total cholesterol in adults in Japan is about 160 mg/dl, not a level associated with a high frequency of atherosclerotic events. Many Japanese adults have serum total cholesterol levels <150 mg/dl. In populations where the average serum total cholesterol in adults is >200 mg/dl—such as the USA—smoking cigarettes appears to accelerate atherosclerosis. In the USA, only 5% of the population >40 years of age have serum total cholesterol <150 mg/dl.<sup>6</sup> Therefore, in 95% of the USA population, cigarette smoking does appear to be associated with an increased frequency of atherosclerotic events, but this acceleration appears to be a cholesterol-dependent phenomenon. Thus, cigarette smoking is not an independent atherosclerotic risk factor.

**Systemic hypertension:** In nonhuman experimental animals given atherogenic diets (high fat-high cholesterol), those previously made hypertensive develop more atherosclerotic plaques than do the normotensive animals.<sup>7</sup> Hypertensive persons with total and LDL-cholesterol levels similar to those in normotensive persons have a higher frequency of atherosclerotic events compared to normotensive subjects.<sup>7</sup> These 2 facts have supported the contention that systemic hypertension is an atherosclerotic risk factor. Most studies describing benefits of anti-hypertensive therapy have not demonstrated a reduction in coronary or peripheral atherosclerotic events by such therapy. There is no evidence that systemic hypertension accelerates atherosclerosis if the serum total cholesterol level is <150 mg/dl.

In the late 1960s I spent a week in Kampala, Uganda, where I examined several hundred hearts. Many of them were severely hypertrophied without ventricular cavity dilatation or associated valvular disease. I learned that systemic hypertension was by far the most common cardiovascular condition in adults in Uganda. Yet, examination of hundreds of coronary arteries in these hypertrophied adult hearts disclosed virtually no atherosclerotic plaques. I also learned that most adults in Kampala at the time had serum total cholesterol levels ranging from 90 to 140 mg/dl. Thus, despite the high frequency of systemic hypertension, there was a low frequency of atherosclerosis. It appears that systemic hypertension also is a cholesterol-dependent risk factor in that the serum total cholesterol must be >150 mg/dl before hypertension has the ability to accelerate atherosclerosis and, therefore, hypertension is not an independent atherosclerotic risk factor.

In persons with serum total cholesterol levels >150 mg/dl, elevation of the pulmonary arterial pressure clearly causes the development of atherosclerotic plaques in the major pulmonary arteries. Whether these plaques

develop in the extrapulmonary pulmonary arteries in patients with severe chronic elevation of pulmonary arterial pressures associated with low serum total cholesterol levels is unclear to me.

Although the evidence is lacking, in my view, implicating systemic hypertension as a direct atherosclerotic risk factor, it clearly is the major risk factor for development of stroke and aortic dissection.<sup>7</sup> These 2 lesions are not atherosclerotic dependent. The prime effect of hypertension is on the media of arteries causing this arterial layer to tear, dissect or rupture. Atherosclerosis is an intimal process and only indirectly is the media affected.

**Diabetes mellitus:** Juvenile diabetic patients clearly have more atherosclerotic plaques and a higher frequency of atherosclerotic events than do nondiabetics of similar age and sex.<sup>8</sup> But the juvenile diabetics have higher serum total and LDL-cholesterol levels than do their nondiabetic counterparts.<sup>8</sup> Likewise, adult-onset diabetics have more atherosclerosis and a higher frequency of atherosclerotic events than do nondiabetics of similar age and sex. Moreover, the adult-onset diabetics have higher serum total and LDL-cholesterol levels than do their nondiabetic counterparts. Thus, diabetes mellitus appears to be an atherosclerotic risk factor because these individuals have higher total and LDL-cholesterol levels than do their nondiabetic counterparts. There is no evidence that diabetics who have serum total cholesterol levels <150 mg/dl have an increased frequency of atherosclerotic events compared to nondiabetic counterparts with similar cholesterol levels. Indeed, there is no evidence that diabetics with low serum total cholesterol levels have atherosclerosis of any significance. Thus, diabetes mellitus also appears to be a cholesterol-dependent risk factor.

**Severe obesity:** In general, obese persons have higher total and LDL-cholesterol levels than do nonobese persons of similar age and sex. This fact is, of course, not surprising because obese persons eat more fat than do nonobese persons. Usually about a third of the fat eaten is of the saturated variety and most of the saturated fat once absorbed is converted into cholesterol. Although few exist to study, I am not aware that obese adults with serum total cholesterol levels <150 mg/dl have any risk to development of atherosclerotic events. Thus, obesity is a cholesterol-dependent risk factor, not an independent risk factor.

**Low levels of serum high density lipoprotein-cholesterol:** In adults in the USA the mean plasma HDL level in men is 45 mg/dl and in women it is 55 mg/dl.<sup>6</sup> Data, especially from Framingham, Massachusetts, have shown that high levels of HDL are associated with decreased risk and that low levels, with increased risk of atherosclerotic events.<sup>3,9</sup> Although there are some doubters about the beneficial effects of high HDL levels and the harmful effects of low HDL levels, the evidence is convincing, in my view, that high HDL is good and low HDL is bad. But what is the risk of a serum HDL level of 20 mg/dl if the LDL-cholesterol is only 100 mg/dl and the serum total cholesterol is <150 mg/dl? The answer is no risk. Is an HDL of 100 mg/dl protective when the LDL is 200 mg/dl? The answer is no. Whether the HDL-

cholesterol is an independent risk factor, i.e., independent of the LDL-cholesterol level, is, in my view, not yet clear. I believe it best to view a low HDL-cholesterol as an additive atherosclerotic risk factor if the LDL-cholesterol is elevated, but not as an additive atherosclerotic risk factor if the LDL-cholesterol is low. Whichever is proper, the HDL-cholesterol is a type of cholesterol, and, therefore, consistent with the thesis that the blood cholesterol is the only direct atherosclerotic risk factor.

**Definite clinical evidence of coronary artery disease:**

An atherosclerotic risk factor is a predictor of an atherosclerotic event, not necessarily in a single individual, but certainly in groups of individuals. Therefore, if an atherosclerotic risk factor is a predictor of an atherosclerotic event, how can the atherosclerotic event itself be an atherosclerotic risk factor? On the other hand, the presence of one atherosclerotic event is highly predictive of another atherosclerotic event. The person most prone to an atherosclerotic event is the person who has already had an atherosclerotic event. I believe it inappropriate, however, to include an atherosclerotic event as an atherosclerotic risk factor. By doing so, no distinction is made between primary and secondary prevention.

**History of peripheral or cerebrovascular disease:** Most peripheral vascular events are atherosclerotic events and many cerebrovascular events are atherosclerotic events. Therefore, the same aforementioned argument concerning a definite coronary event is applicable here. An atherosclerotic event is best not considered to be synonymous with an atherosclerotic risk factor (predictor).

In summary, in my view there are not 10 atherosclerotic risk factors, there is only 1—and that is an elevated (>150 mg/dl) serum total cholesterol level and specifically an elevated serum LDL-cholesterol level. A low (<35 mg/dl) HDL-cholesterol level in the presence of an elevated LDL-cholesterol level probably should be viewed as an additive atherosclerotic risk factor. Male sex, family history of coronary events before age 55 in a parent or sibling, cigarette smoking, systemic hypertension, diabetes mellitus, and severe obesity are best viewed as cholesterol-dependent atherosclerotic risk factors and not in themselves atherogenic in the absence of a serum

total cholesterol level >150 mg/dl. Atherosclerotic events (coronary, cerebrovascular and peripheral), although predictive of future atherosclerotic events, are not by definition true atherosclerotic risk factors and they should not be viewed as such. Nevertheless, all of the aforementioned cholesterol-dependent atherosclerotic risk factors take effect when the serum total cholesterol level is >150 mg/dl, and because 95% of Americans >40 years of age have total cholesterol levels >150 mg/dl, these indirect risk factors need to be dealt with and managed accordingly.



**William Clifford Roberts, MD**  
Editor in Chief

1. The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Arch Intern Med* 1988;148:36-69.

2. Stamler J, Wentworth D, Neaton JD, for the MRFIT Research Group. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenings of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256:2823-2828.

3. Castelli WP, Garrison RJ, Wilson PWF, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham study. *JAMA* 1986;256:2835-2838.

4. Keys A. Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease. Cambridge, Massachusetts: Harvard University Press, 1980.

5. Roberts WC, Potkin BN, Solus DE, Reddy SG. Modes of death, frequency of healed and acute myocardial infarcts, numbers of major epicardial coronary arteries severely narrowed by atherosclerotic plaque, and heart weight in fatal atherosclerotic coronary artery disease: analysis of 889 patients studied at necropsy. *JACC*, in press.

6. The Lipid Research Clinics Program Epidemiology Committee: Plasma lipid distributions in selected North American populations: the Lipid Research Clinics Program Prevalence Study. *Circulation* 1979;60:427-439.

7. Roberts WC. Frequency of systemic hypertension in various cardiovascular diseases. *Am J Cardiol* 1987;60:1E-8E.

8. Crall FV Jr, Roberts WC. The extramural and intramural coronary arteries in juvenile diabetes mellitus. Analysis of nine necropsy patients aged 19 to 38 years with onset of diabetes before age 15 years. *Am J Med* 1978;64:221-230.

9. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. *Am J Med* 1977;62:707-714.