Chapter 51
Risk Factors for Atherosclerosis in the Elderly

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Coronary artery disease (CAD), peripheral arterial disease (PAD), atherothrombotic brain infarction (ABI), and extracranial carotid arterial disease (ECAD) are more common in old individuals than in middle-aged ones. CAD is the leading cause of death in old persons, especially those with PAD, ABI, or ECAD. This chapter discusses risk factors for CAD, PAD, ABI, and ECAD in old persons.

Cigarette Smoking

Coronary Artery Disease

The Chicago Stroke Study demonstrated that current cigarette smokers, age 65–74, had a 52% higher mortality from CAD than nonsmokers, ex-smokers, and pipe and cigar smokers [1]. Ex-smokers who had stopped smoking for 1–5 years had similar mortality from CAD as nonsmokers. The Systolic Hypertension in the Elderly Program pilot project found that smoking was a predictor of a first cardiovascular event and myocardial infarction (MI)/sudden death [2]. During a 30-year follow-up of subjects 65 years of age and older in the Framingham Heart Study, cigarette smoking was not associated with the incidence of CAD but was associated with mortality from CAD [3].

During a 12-year follow-up of men aged 65–74 in the Honolulu Heart Program, cigarette smoking was an independent risk factor for nonfatal MI and fatal CAD [4]. The absolute excess risk associated with cigarette smoking was 1.9 times higher in old men than in middle-aged men. At 5-year follow-up of old subjects (age ≥ 65) in three communities, cigarette smokers were shown to have a higher incidence of cardiovascular mortality than nonsmokers [5]. The relative risk for cardiovascular mortality was 2.0 in male smokers and 1.6 in female smokers. The incidence of cardiovascular death in former smokers was similar to those who had never smoked [5].

At 40-month follow-up of 664 old men (mean age 80 years) and 48-month follow-up of 1,488 old women (mean age 82 years), cigarette smoking was demonstrated by multivariate analysis to increase the relative risk of new coronary events 2.2 and 2.0 times, respectively (Table 51.1) [6]. During a 42-month mean follow-up of 410 old Blacks and Whites with hypertension (mean age 81), the odds ratio for developing new coronary events was 2.0 in cigarette smokers [7]. It has also been observed that cigarette smoking aggravates angina pectoris and precipitates silent myocardial ischemia in old persons with CAD.

In the Coronary Artery Surgery Study (CASS) Registry, subjects over the age of 65 who continued smoking had an increased risk of developing MI or sudden death compared with those who stopped smoking during the year before enrolling in the study [8]. Furthermore, increasing age did not decrease the beneficial effects of smoking cessation.

In the Bronx Longitudinal Aging Study (BAS), whose cohort consisted of subjects 75–85 years of age at study onset, 10% of the cohort were smoking at study onset, and 46% reported having smoked in the past [8]. In the various BAS multivariate analyses, cigarette smoking history was shown to be an independent predictor of both cardiovascular morbidity and mortality and the development of MI.

Peripheral Arterial Disease

Numerous studies have shown that cigarette smoking is a risk factor for PAD in men and women [9–17]. In a study of 1,911 old subjects (mean age 81 years), current cigarette smoking was shown to increase the prevalence of symptomatic PAD 2.6 and 4.6 times in old men and women, respectively (Table 51.1) [9]. At 43-month follow-up of 291 old subjects (mean age 82 years) with PAD, multivariate analysis demonstrated that cigarette smoking was an independent predictor of new coronary events, with a relative risk of 1.6 [18].

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Table 51.1 Association of cigarette smoking with new coronary events, peripheral arterial disease, new atherothrombotic brain infarction, and extracranial carotid arterial disease in elderly men and women

	Elderly men			Elderly women		
Study	No. of patients	Mean follow-up (months)	Relative risk	No. of patients	Mean follow-up (months)	Relative risk
Incidence of new coronary events [6]	664	40	2.2	1,488	48	2.0
Prevalence of PAD [9]	467	–	2.6	1,444	–	4.6
Incidence of new ABI [23]	664	42	1.5	1,488	48	1.9
Prevalence of 40–100% ECAD in 1,063 men and women [24]			4.0			

PAD peripheral arterial disease, *ABI* atherothrombotic brain infarction, *ECAD* extracranial carotid arterial disease

Atherothrombotic Brain Infarction

A meta-analysis of 32 studies showed that cigarette smoking is a risk factor for ABI in men and women and carries a relative risk of 1.9 [19]. In the Medical Research Council (MRC) Trial, the incidence of strokes was 2.3 times higher in smokers than in nonsmokers [20]. Moreover, nonsmokers who received propranolol as antihypertensive therapy had a reduction in the incidence of stroke that cigarette smokers did not have. In the Framingham Heart Study, during a 26-year follow-up, cigarette smoking increased the incidence of new ABI 1.6 and 1.9 times in men and women, respectively [21]. Furthermore, the incidence of stroke in smokers who used >40 cigarettes daily was twice as high as in those who used <10 cigarettes daily. The impact of cigarette smoking did not diminish with increasing age. The risk of stroke was substantially decreased within 2 years of quitting smoking, with the incidence of stroke returning to the level of nonsmokers 5 years after smoking cessation. Although elderly individuals who quit smoking have higher cerebral perfusion levels than old persons who continue to smoke, their cerebral perfusion levels are lower than those who have never smoked [22].

At 42-month follow-up of 664 old men (mean age 80) and 48-month follow-up of 1,488 old women (mean age 82), cigarette smoking was demonstrated by multivariate analysis to increase the relative risk for ABI 1.5 and 1.9 times in men and women, respectively (Table 51.1) [23].

Extracranial Carotid Arterial Disease

Numerous studies have demonstrated that cigarette smoking is a strong risk factor for ECAD [24–29]. In a study of 1,063 old subjects (mean age 81 years), cigarette smoking was found by multivariate analysis to increase the prevalence of 40–100% ECAD 4.2 times (Table 51.1) [24].

On the basis of the available data, old men and women who smoke should be strongly encouraged to stop. In these individuals, cigarette smoking is a risk factor for CAD, PAD, ABI, and ECAD, as well as for other disorders including pulmonary disease and lung cancer. Smoking cessation should reduce mortality due to CAD, stroke, and other cardiovascular diseases and all-cause mortality in elderly persons.

Approaches to smoking cessation include the use of nicotine patches or nicotine polacrilex gum, which are available over the counter [30]. If this therapy is unsuccessful, nicotine nasal spray or treatment with the antidepressant buproprion and/or varenicline should be considered [30–32]. A nicotine inhaler may also be used [32]. The dosage and duration of treatment of each of these pharmacotherapies are discussed in detail elsewhere [32]. Concomitant behavioral therapy may also be needed [33]. Repeated physician advice is very important in the treatment of smoking addiction.

Hypertension

Coronary Artery Disease

Increased peripheral vascular resistance is the cause of systolic and diastolic hypertension in old persons. *Systolic hypertension* is diagnosed if the systolic blood pressure is 140 mmHg or higher on three occasions, and *diastolic hypertension* is diagnosed if the diastolic blood pressure is 90 mmHg or higher on three occasions [34]. *Isolated systolic hypertension* is diagnosed when the systolic blood pressure is 140 mmHg or higher on three occasions but diastolic blood pressure is normal [34].

In 1,414 old subjects (mean age 82 years), the prevalence of systolic or diastolic hypertension was higher in Blacks than in Hispanics or Whites [35]. In a study of 1,051 old individuals with hypertension, isolated systolic hypertension occurred in two-thirds of the persons [36]. Although both diastolic and isolated systolic hypertension are associated with increased cardiovascular morbidity and mortality in old individuals, increased systolic blood pressure is the greater risk factor [37].

The higher the systolic or diastolic blood pressure, the greater the morbidity/mortality from CAD in old men and

women. During a 30-year follow-up of subjects 65 years and older in the Framingham Heart Study, systolic hypertension correlated with the incidence of CAD in men and women [3]. Diastolic hypertension correlated with CAD in old men but not in old women. At 40-month follow-up of 664 old men and 48-month follow-up of 1,488 old women, systolic or diastolic hypertension was demonstrated by multivariate analysis to increase the relative risk of new coronary events 2.0 and 1.6 times, respectively (Table 51.2) [6].

In the BAS [38], no relation was found between hypertension and the development of fatal MI, but a relation did exist for the development of clinically unrecognized MI, especially among hypertensives not on medication. Antihypertensive drugs have been shown to reduce new coronary events in the elderly hypertensive population [39–44]. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends diuretics or β-blockers as initial drug therapy because these drugs have been demonstrated to reduce cardiovascular morbidity and mortality in controlled clinical trials [35]. The particular antihypertensive agent selected as monotherapy should depend on the associated medical conditions. For example, old individuals with hypertension who have had an MI or who have angina pectoris, myocardial ischemia, or complex ventricular arrhythmias should be treated initially with a β-blocker [44]. Old hypertensive persons with congestive heart failure associated with abnormal or normal left ventricular ejection fraction should receive a diuretic, an angiotensin-converting enzyme (ACE) inhibitor, and a β-blocker [45–53]. Old persons with hypertension who have diabetes mellitus or left ventricular hypertrophy (LVH) should initially be treated with an ACE inhibitor [35, 54].

Old persons with hypertension and a prior MI should be treated with both β-blockers and ACE inhibitors [35, 55–58].

Peripheral Arterial Disease

Numerous studies have demonstrated that hypertension is a risk factor for PAD [10–12, 14–18]. In a study of 1,911 old persons (mean age 81 years), systolic or diastolic hypertension was observed to increase the prevalence of PAD 2.2 times in men and 2.8 times in women (Table 51.2) [10]. At 43-month follow-up of 291 old subjects with PAD (mean age 82), new coronary events developed in 165 patients (57%) [19].

Hypertension should be adequately controlled to decrease cardiovascular mortality and morbidity in persons with PAD. The blood pressure should be reduced to <140/90 mmHg and to <130/80 mmHg in patients with diabetes mellitus or chronic renal insufficiency, respectively [35, 55]. Among persons with PAD in the Appropriate Blood Pressure Control in Diabetes Trial, the incidence of cardiovascular events in persons treated with antihypertensive drug therapy with enalapril or nisoldipine was 13.6% if the mean blood pressure was reduced to 128/75 mmHg versus 38.7% if the mean blood pressure was reduced to 137/81 mmHg [59].

Atherothrombotic Brain Infarction

Numerous studies have documented that both systolic and diastolic hypertension increase the incidence of stroke in old persons [24, 39–43, 60–62]. Indeed, the higher the systolic or diastolic blood pressure, the greater the incidence of stroke. During a 30-year follow-up of men and women of age 65–94 years in the Framingham Heart Study, systolic blood pressure was the single risk factor most strongly correlated with ABI or transient cerebral ischemic attack [63]. At 42-month follow-up of 664 old men and 48-month follow-up of 1,488 old women, systolic or diastolic hypertension was demonstrated by multivariate analysis to increase the relative risk of ABI 2.2 times in men and 2.4 times in women (Table 51.2) [24].

In the BAS, subjects with measured hypertension had a significantly increased incidence of stroke (1.9/100 person-years) compared with that in controls (0.6/100 person-years) [9]. Previous studies have used a definition of hypertension as systolic blood pressure >160 mmHg, diastolic blood pressure >95 mmHg, or both to show an increased risk of stroke [24, 39–43, 60–62]. The findings in the BAS extended the risk of stroke to this oldest-old age group; [9] and considering the strict study values used, it suggested that the risk exists even

Table 51.2 Association of systolic or diastolic hypertension with new coronary events, peripheral arterial disease, and new atherothrombotic brain infarction in elderly men and women

	Elderly men			Elderly women		
Study	No. of patients	Mean follow-up (months)	Relative risk	No. of patients	Mean follow-up (months)	Relative risk
Incidence of new coronary events [6]	664	40	2.0	1,488	48	1.6
Prevalence of PAD [9]	467	–	2.2	1,444	–	2.8
Incidence of new ABI [23]	664	42	2.2	1,488	48	2.4

at levels of blood pressure not previously uniformly considered to be elevated by others. The BAS also showed an association between blood pressure elevation and the risk of vascular dementia [9], suggesting that some dementias could be prevented by blood pressure lowering [64].

Antihypertensive drug therapy has been shown to reduce the incidence of new ABI in old individuals [39–43, 61]. A systolic blood pressure of 140–160 mmHg causes an increased risk for cardiovascular disease that is equivalent to a diastolic blood pressure of 95–105 mmHg [38]. Consequently, the clinician should consider the treatment of old persons with systolic blood pressures in this range. Although nonpharmacologic interventions are indicated [65], there are currently no data showing that drug therapy for systolic blood pressures of 140–160 mmHg reduces the incidence of stroke in old persons. Nevertheless, the presence of LVH, target organ damage, and other risk factors for stroke would cause the authors to treat these individuals with antihypertensive drug therapy [66, 67].

Extracranial Carotid Arterial Disease

Numerous studies have demonstrated by univariate analysis that hypertension is a risk factor for ECAD [25–27, 29, 68]. According to multivariate analysis, however, hypertension is a risk factor in some studies [26, 68] but not in others [25, 26]. In a study of 1,283 old subjects (mean age 81), LVH was more prevalent in those with systolic or diastolic hypertension and ECAD than in those with systolic or diastolic hypertension alone [69].

Left Ventricular Hypertrophy

Coronary Events

LVH caused by hypertension or other cardiovascular disease is not only a marker of but also a contributor to cardiovascular morbidity and mortality in the elderly population. Indeed, old persons with electrocardiographic (ECG) and echocardiographic evidence of LVH have an increased risk of developing new coronary events [7, 70–75].

During a 4-year follow-up of 406 old men and 735 old women in the Framingham Heart Study, echocardiographic LVH was 15.3 times more sensitive for predicting new coronary events in men and 4.3 times more sensitive in women than ECG LVH [73]. The relative risk for new coronary events per 50 g/m increases in LV mass/height was 1.67 and 1.60 for old men and women, respectively [73].

At a 37-month follow-up of 360 old subjects (mean age 82 years) with hypertension or CAD, echocardiographic LVH was 4.3 times more sensitive for predicting new coronary events than ECG LVH [71]. Multivariate analysis of 472 old hypertensive subjects followed for 45 months showed that echocardiographic LVH was an independent risk factor for new coronary events, with a relative risk of 3.2 [75].

In the BAS a multivariate analysis showed that baseline ECG LVH is an independent predictor of MI and overall mortality. Those subjects who developed new LVH on ECG during follow-up had a 3.4 times higher total death rate and a 6.6-fold greater relative risk of cardiovascular death [9].

Atherothrombotic Brain Infarction

Elderly persons with ECG [7, 70–72] and echocardiographic [7, 71, 74–77] LVH have an increased risk of developing a new ABI. During an 8-year follow-up of 447 old men and 783 old women in the Framingham Heart Study, the hazard ratio for new cerebrovascular events was 1.45 for each quartile increase in the LV mass/height ratio after adjustments were made for age, sex, and cardiovascular disease [76]. At the 37-month follow-up of 360 old persons with hypertension and CAD, echocardiographic LVH was 4.0 times more sensitive for predicting a new ABI than ECG LVH [71]. Multivariate analysis of 472 old subjects with hypertension followed for 45 months revealed that echocardiographic LVH was an independent risk factor for a new ABI, with a relative risk of 2.9 [75]. Among 1,482 old persons (mean age 82 years) followed for 45 months, multivariate analysis also showed that echocardiographic LVH was an independent risk factor for a new ABI, with a risk ratio of 2.3 [77].

Physicians should try to prevent LVH from developing or progressing in persons with hypertension or other cardiovascular disease. The effect of various antihypertensive drugs on reducing LV mass is discussed elsewhere [78, 79]. A meta-analysis of 109 treatment studies showed that ACE inhibitors are more effective than other antihypertensive drugs in decreasing LV mass [79].

Reduction of LV mass with antihypertensive agents does not cause deterioration of LV systolic function and may improve LV diastolic function. Data from the Framingham Heart Study have shown a decrease of cardiovascular events in patients with the regression of LVH [80]. In patients with uncomplicated hypertension followed for 10.2 years, the Cornell group found that the development of LVH increases and the regression of LVH decreases the incidence of new cardiovascular events [81]. Regression of ECG LVH by antihypertensive treatment was associated with a 30% significant reduction in sudden cardiac death independently of

treatment modality, blood pressure reduction, prevalent CAD, and other cardiovascular risk factors in hypertensive patients with LVH [82]. In addition, the BAS demonstrated that old subjects who developed new ECG LVH had a higher incidence of cardiovascular morbidity and mortality than old persons without ECG LVH [72] based on a 10-year follow-up. Old persons in whom the ECG pattern of LVH disappeared over time had a lower incidence of cardiovascular morbidity and mortality than old persons with persistent LVH [72].

Dyslipidemia

Serum Total Cholesterol and Coronary Artery Disease

Serum total cholesterol was an independent risk factor for CAD in old men and women in the Framingham Heart Study [83]. Among subjects with prior MI in this study, serum total cholesterol was most strongly related to death from CAD and to all-cause mortality in persons of age ≥65 years [84]. Many other studies have demonstrated that a higher serum total cholesterol level is a risk factor for new coronary events in old men and women [2, 6, 85, 86].

During a 9-year follow-up of 350 men and women with a mean age of 79 years, the BAS demonstrated that a consistently elevated low-density lipoprotein (LDL) cholesterol was associated with the development of MI in women [87]. In the Established Populations for Epidemiologic Studies of the Elderly study, serum total cholesterol was a risk factor for CAD-associated mortality in old women but not in old men [88]. At 40-month follow-up of 664 old men and 48-month follow-up of 1,488 old women, there was a 1.12 times higher probability of developing new coronary events in men and women for each 10 mg/dl increase in serum total cholesterol (Table 51.3) [6].

During a 5.4-year median follow-up of 1,021 old men and women with CAD and hypercholesterolemia in the Scandinavian Simvastatin Survival Study (4S), patients treated with simvastatin had a 34% reduction in mortality, a 43% reduction in CAD mortality, a 34% reduction in major coronary events, a 33% reduction in nonfatal MI, a 33% reduction in any acute CAD-related event, a 34% reduction in any atherosclerosis-related endpoint, and a 41% reduction in coronary revascularization [89]. The absolute risk reduction for both all-cause mortality and CAD mortality was approximately twice as great in older persons as in those younger than 65 years of age.

In the Cholesterol and Recurrent Events (CARE) Trial, 4,159 men and women with MI, serum total cholesterol levels <240 mg/dl, and serum LDL cholesterol ≥115 mg/dl were followed over a 5-year period [90]. The trial showed a 27% reduction in major coronary events in subjects 60–75 years of age who were randomized to pravastatin at study event; a 20% reduction in major coronary events was observed in subjects <60 years of age who were randomized to pravastatin. Furthermore, the reduction in coronary events was greater in women (46%) than in men (20%). On the basis of these data, old men and women with CAD and elevated total or LDL cholesterol should be treated with a statin drug.

At 6.1-year mean follow-up of 9,014 men and women (3,514 of whom were aged 65–75 years) with MI (64%) or unstable angina pectoris (36%) and serum total cholesterol levels of 155–271 mg/dl in the Long-Term Intervention With Pravastatin in Ischemic Disease Study (LIPID), compared with placebo, pravastatin 40 mg daily significantly reduced all-cause mortality by 22%, death from CAD by 24%, fatal and nonfatal MI by 29%, death from cardiovascular disease by 25%, need for coronary artery bypass surgery by 22%, need for coronary angioplasty by 19%, hospitalization for unstable angina pectoris by 12%, and stroke by 19% [91]. The absolute benefits of treatment with pravastatin were greater in groups of persons at higher absolute risk for a major coronary event such as older persons, those with a higher serum LDL-cholesterol level, those with a lower serum high-density lipoprotein (HDL)-cholesterol level, and those with a history of diabetes mellitus or smoking.

At 5-year follow-up of 20,536 British men and women (10,697 of whom were aged 65–80 years) with either CAD, occlusive arterial disease of non-coronary arteries, diabetes mellitus or treated hypertension and no serum lipid requirement in the Heart Protection Study, compared with placebo, simvastatin 40 mg daily significantly reduced all-cause mortality by 13%, any vascular mortality by 17%, major coronary events by 27%, any stroke by 25%, any revascularization procedure by 24%, and any major vascular event by 24% [92]. In the 1,263 persons aged 75–80 years at study entry

Table 51.3 Association of abnormal serum lipids with new coronary events and with new atherothrombotic brain infarction in 664 old men and 1,488 old women

	New coronary events		New antithrombotic brain infarction	
	Relative risk			
	Men	Women	Men	Women
Serum total cholesterol	1.12[a]	1.12[a]	NS	1.06[a]
Serum HDL cholesterol	1.70[b]	1.95[b]	NS	1.14[b]
Serum triglycerides	NS	1.02[c]	NS	NS

HDL high-density lipoprotein, *NS* nonsignificant
Source: Adapted from Aronow et al. [6, 23], with permission from Elsevier
[a]For an increment of 10 mg/dl of serum total cholesterol
[b]For a decrement of 10 mg/dl of serum HDL cholesterol
[c]For an increment of 10 mg/dl of serum triglycerides

and 80–85 years at follow-up, any major vascular event was significantly reduced 28% by simvastatin. Lowering serum LDL cholesterol from <116 to <77 mg/dl by simvastatin caused a 25% significant reduction in vascular events.

In the Heart Protection Study, 3,500 persons had initial serum LDL-cholesterol levels <100 mg/dl [92]. Decrease of serum LDL cholesterol from 97 to 65 mg/dl by simvastatin in these persons caused a similar decrease in risk as did treating patients with higher serum LDL-cholesterol levels. The Heart Protection Study Investigators recommended treating persons at high risk for cardiovascular events with statins, regardless of the initial levels of serum lipids, age, or gender [92].

On the basis of these data and other data [92–96], the American College of Cardiology/American Heart Association (ACC/AHA) guidelines [55] and the updated National Cholesterol Education Program III guidelines [97] state that in very high-risk persons, targeting a serum LDL-cholesterol level of <70 mg/dl is a reasonable clinical strategy. When a high-risk person has hypertriglyceridemia or low HDL cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL cholesterol-lowering drug [55, 97].

Serum HDL Cholesterol and Coronary Artery Disease

A low level of serum HDL cholesterol is a risk factor for new coronary events in old men and women [2, 6, 83, 87, 88, 98, 99]. In the Framingham Heart Study [83] and in the Established Populations for Epidemiologic Studies of the Elderly study [88], a low serum HDL was a more powerful predictor of new coronary events than was the total cholesterol.

During a 9-year follow-up of 350 men and women in the BAS, a consistently low HDL-cholesterol level was independently associated with the development of MI, cardiovascular disease, or death in men [87]. At a 40-month follow-up of 664 old men and 48-month follow-up of 1,488 old women, multivariate analysis showed that there was a 1.7 times higher probability of developing new coronary events in men and 1.95 times higher probability in women for each 10 mg/dl decrement in serum HDL cholesterol (Table 51.3) [6].

Serum Triglycerides and Coronary Artery Disease

High-serum triglycerides have been reported to be a risk factor for new coronary events in old women but not in old men [6, 83]. At a 40-month follow-up of 664 old men and 48-month follow-up of 1,488 old women, multivariate analysis showed that serum triglyceride levels were not a risk factor for new coronary events in the men and were a weak risk factor in the women (Table 51.3) [6].

Serum Lipids and Peripheral Arterial Disease

Some studies have shown an association between increased serum total cholesterol and PAD [10, 11, 14–18, 100, 101] but other studies have not [102]. A low serum HDL-cholesterol level, however, has been shown to be associated with PAD [10, 11, 14–18, 100, 101]. In a study of 559 old men and 1,275 old women (mean age 81 years), an inverse association was found between serum HDL cholesterol and PAD [101]. Multivariate analysis demonstrated a 1.24 times higher probability of having PAD for each 10 mg/dl decrement of serum HDL cholesterol.

Increased serum triglycerides have been associated with PAD in some studies [13, 14] but not in others [10, 11, 100, 101]. In a study of 559 old men and 1,275 old women, serum triglycerides were associated with PAD in both men and women according to univariate analysis but not according to multivariate analysis [101].

Treatment of hypercholesterolemia with statins has been demonstrated to reduce the incidence of cardiovascular events and mortality in older persons with PAD [92, 103]. Three double-blind, randomized, placebo-controlled studies have also demonstrated that statins improve walking performance in persons with PAD [104–106].

Serum Lipids and Atherothrombotic Brain Infarction

The Framingham Study found that serum total and HDL-cholesterol levels were not associated with new ABIs in old men or women [107]. However, the serum total cholesterol HDL-cholesterol ratio was associated with new ABIs in the women but not in the men. Very low-density lipoprotein (VLDL) levels were not associated with new ABIs in older men or women [107].

The Multiple Risk Factor Intervention Trial revealed an association between serum total cholesterol and death from nonhemorrhagic stroke in men [108]. Bihari-Varga et al. [109] demonstrated an inverse relation between serum HDL cholesterol and ABIs in men and women. At 42-month follow-up of 664 old men and 48-month follow-up of 1,488 older women, multivariate analysis showed no association between serum lipids and new ABIs in the men. There was an association between serum total cholesterol and an inverse association between HDL cholesterol and new ABIs in the

women (Table 51.3) [24]. In this population, there was a 1.06 times higher probability of developing a new ABI for each 10 mg/dl increment in serum total cholesterol. Likewise, there was a 1.14 times higher probability of developing a new ABI for each 10 mg/dl decrement in serum HDL cholesterol.

In the Scandinavian Simvastatin Survival Study, patients treated with simvastatin had a 27% reduction in new ABIs [89]. In the Cholesterol and Recurrent Events Trial, patients treated with pravastatin had a 31% reduction in new ABIs [90]. A meta-analysis of four primary prevention trials and eight secondary prevention trials of CAD that used simvastatin, pravastatin, or lovastatin to reduce serum total cholesterol levels demonstrated a 27% reduction in new ABIs [110]. Many other studies reported since then have also demonstrated a significant reduction in ischemic stroke in patients treated with statins [91, 92, 111–114].

At 3-year follow-up of 1,410 patients, mean age 81 years, with prior MI and a serum LDL cholesterol of 125 mg/dl or higher, use of statins significantly reduced stroke by 60% [112]. Decreasing serum LDL cholesterol to less than 90 mg/dl was associated with a 7% incidence of new stroke, whereas decreasing serum LDL cholesterol to 90–99 mg/dl was associated with a 16% incidence of new stroke. The lower the serum LDL cholesterol in elderly persons treated with statins, the greater was the reduction in new stroke [112] and in new coronary events [95]. In 4,731 patients, mean age 63 years, with stroke or transient ischemic attack, reduction of serum LDL cholesterol at least 50% by atorvastatin caused a significant reduction in stroke of 31% and in major coronary events of 37% at 4.9-year follow-up [114]. These data support the use of statins to reduce elevated serum total and LDL-cholesterol levels in old men and women to prevent new thrombotic and/or embolic strokes and new coronary events.

A meta-analysis by our group has shown an increased risk of cerebral hemorrhage in patients receiving statins compared with those individuals not receiving statins. The mechanism for this finding is not known, and the data would suggest that patients with a history of cerebral hemorrhage or those individuals with a cerebral hemorrhage on a statin did not receive this therapy for cholesterol lowering [115].

Serum Lipids and Extracranial Carotid Arterial Disease

Elevated serum total cholesterol [25, 116, 117] and decreased serum HDL cholesterol [25, 27, 29, 32, 116, 117] are risk factors for ECAD. In 1,189 persons of age 66–93 years in the Framingham study, there was a strong association between the severity of ECAD and the serum total cholesterol, as measured 8 years before the carotid studies [116]. In women, but not in men, there was a strong inverse association between the severity of ECAD and the serum HDL cholesterol level measured 8 years before the carotid studies and concurrently [116].

In a study of 1,063 old persons, increased total cholesterol and decreased HDL cholesterol, but not serum triglycerides, were found to be risk factors for ECAD [25]. There was a 1.17 times higher probability of having 40–100% ECAD for each 10 mg/dl increment of serum total cholesterol and a 1.66 times higher probability of having 40–100% ECAD for each 10 mg/dl decrement of serum HDL cholesterol. Many studies have demonstrated the beneficial effects of lipid-lowering drug therapy on carotid atherosclerosis and on coronary events [118–121]. At 21-month follow-up of 449 patients with severe carotid arterial disease who did not undergo revascularization, use of statins caused a 87% significant reduction in the incidence of new stroke or new MI or death [121].

Diabetes Mellitus

Coronary Artery Disease

Diabetes mellitus is a risk factor for new coronary events in old men and women [6, 122]. At a 40-month follow-up of 664 old men and 48-month follow-up of 1,488 old women, diabetes mellitus was shown by multivariate analysis to increase the relative risk of new coronary events 1.9 and 1.8 times in men and women, respectively (Table 51.4) [6]. In the BAS diabetes mellitus, by history or a fasting blood glucose level

Table 51.4 Association of diabetes mellitus with new coronary events, peripheral arterial disease, new atherothrombotic brain infarction, and new extracranial carotid arterial disease in old men and women

	Older men			Older women		
Study	No. of patients	Mean follow-up (months)	Relative risk	No. of patients	Mean follow-up (months)	Relative risk
Incidence of new coronary events [6]	664	40	1.9	1,488	48	1.8
Prevalence of PAD [9]	467	–	2.4	1,444	–	3.0
Incidence of new ABI [23]	664	42	1.5	1,488	48	1.5
Prevalence of 40–100% ECAD in 1,063 men and women [24]			1.7			

PAD peripheral arterial disease, *ABI* atherothrombotic brain infarction, *ECAD* extracranial carotid arterial disease

of >140 mg/dl was associated with an increased incidence risk of all-cause mortality and cardiovascular disease [9].

Diabetic patients are more often obese and have higher serum LDL- and VLDL-cholesterol levels and lower serum HDL-cholesterol levels than do nondiabetics. Diabetics also have a higher prevalence of hypertension and LVH. These risk factors contribute to their higher incidence of new coronary events and new ABIs and the higher prevalence of PAD and ECAD. The drug of choice for treating hypertension in diabetics is an ACE inhibitor or angiotensin receptor blocker [35, 54]. The blood pressure should be lowered to <130/80 mmHg. The serum LDL cholesterol should be reduced to <70 mg/dl by a statin in diabetics [55, 97].

Diabetics with microalbuminuria have more severe angiographic CAD than diabetics without microalbuminuria [123]. Diabetics also have a significant increasing trend of hemoglobin A_{1c} levels over the increasing number of vessels with CAD [124]. Diabetics have a higher prevalence of unrecognized MI and a higher prevalence of silent myocardial ischemia without a history of angina pectoris than nondiabetics [125]. The hemoglobin A_{1c} level should be reduced to <7% in patients with diabetes mellitus [55].

Peripheral Arterial Disease

Diabetes mellitus is a risk factor for PAD in men and women [10–18]. In a study of 467 old men and 1,444 old women, diabetes mellitus was found to increase the prevalence of PAD 2.4 times in men and 3.0 times in women (Table 51.4) [10]. The higher the hemoglobin A_{1c} levels in diabetics with PAD, the higher the prevalence of severe PAD [126].

Atherothrombotic Brain Infarction

Diabetes mellitus is a risk factor for new ABIs in old men and women [23, 107, 127]. At a 42-month follow-up of 664 old men and a 48-month follow-up of 1,488 old women, diabetes was found by multivariate analysis to increase the relative risk for new ABIs 1.5 times in both men and women (Table 51.4) [24].

Extracranial Carotid Arterial Disease

Some studies [25, 128] have shown an association between diabetes mellitus and ECAD, whereas other studies [27] have not. In a study of 1,063 old men and women, diabetes mellitus was demonstrated by multivariate analysis to increase the prevalence of 40–100% ECAD 1.7 times [25].

Obesity

In the Framingham Heart Study, obesity was demonstrated to be a risk factor for new coronary events in old men and women [122]. A disproportionate distribution of fat to the abdomen, as assessed by the waist/hip circumference ratio, has also been shown to be a risk factor for cardiovascular disease, mortality due to CAD, and total mortality [129, 130]. At a 40-month follow-up of 664 old men and a 48-month follow-up of 1,488 old women, obesity was shown to be a risk factor for new coronary events in both men and women by univariate but not multivariate analysis [6].

In the BAS, body surface area was also not predictive. There were no subjects with major obesity problems [9]. In elderly subjects, maintenance of weight and appetite is a sign of health. Indeed, when old subjects lose weight and have reductions in their cholesterol, it may signify starvation, an occult malignancy, or a major cognitive problem.

The Framingham Heart Study showed that relative weight, according to Metropolitan Life Insurance criteria, was not associated with intermittent claudication in women but was inversely associated with intermittent claudication in men [63]. In a study of 244 old men and 625 old women, obesity did not significantly increase the prevalence of PAD in the men, but it did increase the prevalence of PAD 1.8 times in the women [11].

The Framingham Heart Study showed that relative weight was not a risk factor for new ABIs in old men but was a weak risk factor in old women [107]. Barrett-Connor and Khaw [127] observed no association between body mass index and new ABIs in old men and women. At a 42-month follow-up of 664 old men, obesity was not a risk factor for new ABIs [24]. At a 48-month follow-up of 1,488 old women, obesity was a risk factor for new ABIs by univariate analysis but not multivariate analysis [24]. Obesity is not a risk factor for ECAD [23, 27].

Physical Inactivity

Physical inactivity is associated with obesity, hypertension, dyslipidemia, and hyperglycemia. Paffenbarger et al. [131] found that individuals of age 65–79 years with a physical activity index >2,000 kcal/week have a better survival rate than those with an index <2,000 kcal/week. Wenger [132] discussed physiologic bases for the decrease in habitual physical activity with age and noted studies suggesting that physical activity is beneficial in preventing CAD. The relation of physical inactivity to ABI is unclear [107, 133].

Moderate exercise programs suitable for old persons include walking, climbing stairs, swimming, and bicycling.

Table 51.5 Association of gender with incidence of new coronary events, prevalence of peripheral arterial disease, incidence of new thromboembolic stroke, and prevalence of 40–100% extracranial carotid arterial disease in old men and women

	Old men			Old women		
Study	No. of patients	Mean follow-up (months)	Incidence or prevalence (%)	No. of patients	Mean follow-up (months)	Incidence or prevalence (%)
Incidence of new coronary events [135]	1,160	46	46	2,464	46	44
Prevalence of peripheral arterial disease [135]	1,160	–	32*	2,464	–	26
Incidence of new thromboembolic stroke [135]	644	46	23	2,464	46	21
Prevalence of 40–100% ECAD [24]	435	–	18	1,057	–	15

ECAD extracranial carotid arterial disease
*$p=0.0001$

Exercise training programs are not only beneficial for preventing CAD [132], but have also been demonstrated to improve endurance and functional capacity in old men with CAD [134].

Age

The incidence of new coronary events increases with age in old men and women [6, 122]. The incidence of PAD [10, 63] and ABI [24, 107] also increased with age. In the BAS, age was the strongest independent predictor of total mortality, cardiovascular mortality, MI, stroke, and dementia [9].

Gender

At a 46-month follow-up of 1,160 old men (mean age 80 years) and of 2,464 old women (mean age 81 years), the incidence of new coronary events was not significantly different in the men (46%) and the women (44%) (Table 51.5) [135]. The prevalence of PAD in the old men (32%) was higher than in the old women (26%) ($p=0.0001$) (Table 51.5). The incidence of new thromboembolic stroke was not significantly different between the men (23%) than in the women (21%) (Table 51.5) [135]. The prevalence of 40–100% ECAD was not significantly different for 435 old men (18%) and 1,057 old women (15%) with a mean age of 82 years. In the BAS, the incidence of MI was higher in women than in men [9].

Race

Black men are 2.5 times more likely to die of stroke than white men, and black women are 2.4 times more likely to die of stroke than white women [136]. Table 51.6 shows the prevalence of CAD, PAD, and ABI in 268 elderly Blacks (mean age 81), 71 elderly Hispanics (mean age 81), and 1,310 elderly Whites (mean age 82) [137]. The prevalence of CAD was not significantly different among the Blacks, Hispanics, and Whites. However, the prevalence of PAD was significantly higher in the Blacks than in Whites. Likewise, the prevalence of ABI was significantly higher in the Blacks than in either Hispanics or Whites.

Prior Coronary Artery Disease, Peripheral Arterial Disease, and Atherothrombotic Brain Infarction

At a 40-month follow-up of 664 old men and a 48-month follow-up of 1,488 old women, prior CAD was shown by multivariate analysis to increase the relative risk of new coronary events 1.7 times in men and 1.9 times in women [6]. At a 43-month follow-up of 291 old persons (mean age 82) with PAD, prior CAD was shown to be an independent risk factor for new coronary events, with a relative risk of 2.7 [19].

In the BAS, over an average range of 5–8 years of follow-up, the incidences of cardiovascular disease and mortality in subjects with evidence of infarct at baseline were 8.8 and 5.9 per 100 person-years versus 4.7 and 3.9 per 100 person-years in controls, respectively. The rates of development of unrecognized MI (Q-wave) were 2.4 and 3.2 per 100 person-years, respectively, for recognized MI. The rate of development of either a recognized or unrecognized MI was three times more likely in those with a history of a prior infarct [9].

Old persons with prior ABI or transient cerebral ischemic attacks have a higher incidence of ABI [7, 24, 138]. At a 42-month follow-up of 664 old men and a 48-month follow-up of 1,488 old women, multivariate analysis showed that a prior ABI increased the relative risk of a new ABI 2.6 times in men and 2.9 times in women [24].

Table 51.6 Prevalence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in elderly Blacks, Hispanics, and Whites

	Prevalence (%)		
Disorder	Blacks ($n=268$)	Hispanics ($n=71$)	Whites ($n=1,310$)
CAD	46	34	41
PAD	29*	24	23
ABI	47**	31	22

Source: Adapted from Aronow [137]
*$p<0.05$ comparing Blacks with Whites
**$p<0.001$ comparing Blacks with Whites and <0.02 comparing Blacks with Hispanics

Coexistence of Coronary Artery Disease, Peripheral Arterial Disease, and Atherothrombotic Brain Infarction

Persons with PAD [15, 19, 139–143] or cerebrovascular disease [144–146] are at increased risk for developing new coronary events. The Framingham Heart Study demonstrated that the age-adjusted incidence of stroke was more than doubled in patients with CAD [107]. In a study of 110 old persons (mean age 82) with chronic atrial fibrillation, logistic regression analysis revealed that a prior MI was an independent predictor of thromboembolic stroke, with an odds ratio of 4.8 [147].

Table 51.7 shows the prevalence of coexistence of CAD, PAD, and ABI in a study of 1,886 old persons (580 men and 1,306 women) whose mean age was 81 years [148]. If CAD was present, 33% had coexistent PAD and 32% had coexistent ABI. If PAD was present, 58% had coexistent CAD and 34% had coexistent ABI. If ABI was present, 53% had coexistent CAD and 33% had coexistent PAD.

Table 51.8 shows the prevalence of coexistence of CAD, PAD, and ischemic stroke in a study of 1,802 old persons (474 men and 1,328 women) whose mean age was 80 years [149]. If CAD was present, 26% had coexistent PAD and 32% had coexistent ischemic stroke. If PAD was present, 68% had coexistent CAD and 42% had coexistent ischemic stroke. If ischemic stroke was present, 56% had coexistent CAD and 28% had coexistent PAD.

Conclusion

Many of the risk factors and markers for atherosclerosis complicated by CAD, cerebrovascular disease, and PAD seen during middle age continue to be operative in the elderly (Table 51.9) [9].

Table 51.7 Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in 1,886 elderly persons

	Prevalence (%)		
Condition	CAD	PAD	ABI
ABI present	53	33	–
PAD present	58	–	34
CAD present	–	33	32

Source: Adapted from Aronow and Ahn [148], with permission from Elsevier

Table 51.8 Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and ischemic stroke in 1,802 older persons in an academic geriatrics practice

	Prevalence (%)		
Condition	CAD	PAD	ABI
Stroke present	56	28	–
PAD present	68	–	42
CAD present	–	26	32

Source: Adapted from Ness and Aronow [149], with permission from John Wiley & Sons, Inc.

Table 51.9 Factors associated with increased independent risk of incident morbidity or cardiovascular disease in the oldest old[a]: Bronx Longitudinal Aging Study

Age
Smoking history
Diabetes mellitus
History of past MI (clinically apparent or silent) documented on ECG
LVH by ECG (including new onset)
Cardiomegaly by chest radiography (including new onset)
Nonsustained ventricular tachycardia on 24-h Holter ECG
Persistent HDL cholesterol ≤30 mg/dl in men; persistent LDL cholesterol ≥171 mg/dl in women
Hypertension, both combined systolic and diastolic and isolated systolic
Prolongation of the RR interval on resting ECG
Nonspecific ST and T-wave abnormalities on resting ECG (unrelated to LV or past MI)
Digoxin use
Unfavorable baseline self-rated health assessment
Development of dementia
High vitamin B_{12} level

MI myocardial infarction, *ECG* electrocardiography, *LVH* left ventricular hypertrophy
Source: Reprinted from Frishman et al. [38], with permission from Elsevier
[a]Age: 75–85 years

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